

https://dspace.org/

Selective dopamine agonists In man and the mptp-treated primate model.

Temlett, James Alexander

1991
https://hdl.handle.net/10539/26793

Downloaded from a DSpace repository. https://dspace.org/

7.9.2

Results of pre-treatment with sulpiride or SCH 23390 on the response to CY 208-243 in MPTP-treated marmosets. (Table 7.2 and Fig. 7.8 and 9).

Administration of SCH 23390 (2,0 mg/kg ip. 60 minutes previously) markedly inhibited the ability of CY 208-243 (1,0 mg/kg sc.) to correct parkinsonian deficit and improve motor hyperactivity compared to the effect of SCH 23390 vehicle proceeding CY 208-243 (1,0 mg/kg sc.). The effect of SCH 23390 was apparent over the entire 3 hour period of observation.

Administration of sulpiride (20 mg/kg ip.; 60 minutes previously) followed by CY 208-243 (1,0 mg/kg sc.) attenuated the locomotor hyperactivity produced by sulpiride vehicle and CY 208-243 (1,0 mg/kg sc.) alone (Fig 7.9). The effect of sulpiride inhibition of locomotor activity was most evident in the second and third hours following CY 208-243 administration. Sulpiride did not appear to alter the disability scores at 30 minutes following CY 208-243 administration, but by 60 minutes had increased their motor deficits (Fig 7.8).

Table 7.2

The effect of CY 208-243 alone on the marmoset motor disability score and then with pretreatment either with SCH 23390 or sulpiride 1 hour previously. Treatment with SCH 23390 and vehicle and sulpiride plus vehicle 1 hour later are also shown.

Drug treatment	Scores	Range
MPTP	9.9±0.4	8-11.5
CY 208-243 alone	6.8±1.3*	3-9
SCH 23390 alone	12.4±0.3*	11-13
Sulpiride alone	11.6±0.6*	9-13
SCH 23390 + CY 208-243 (1hr)	9.9±0.5**	8-12
Sulpiride + CY 208-243 (30min)	4.5±0.6	2-6
Sulpiride + CY 208-243 (1hr)	11.0±0.8**	9-13

*$p < 0.05$ compared to MPTP treatment alone.
**$p < 0.05$ compared to CY 208-243 treatment alone.

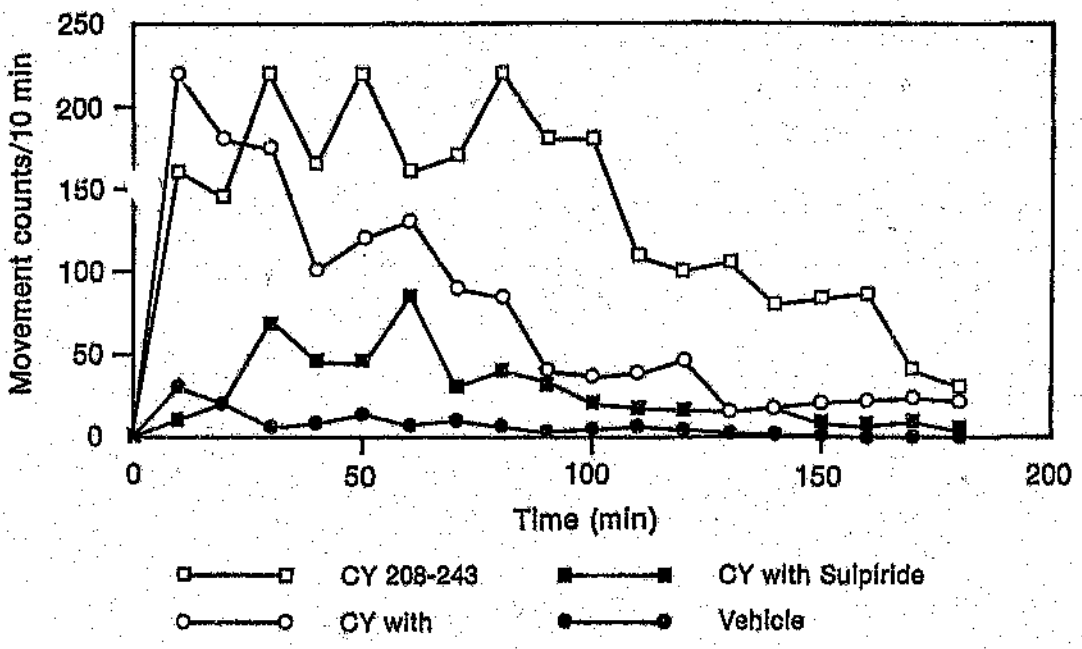


Fig 7.8

The effect of pretreatment with SCH 23390 or Sulpiride, 1 hour previously, on the time course of subsequent CY 208-243 (1mg/kg sc) in stable MPTP-treated marmosets. The SEM's varied between 18-39% of the mean movement counts, in 8 animals over 3 hours. The solid lines with closed circles represents animal mobility in the same MPTP-treated animals who received vehicle control injections.

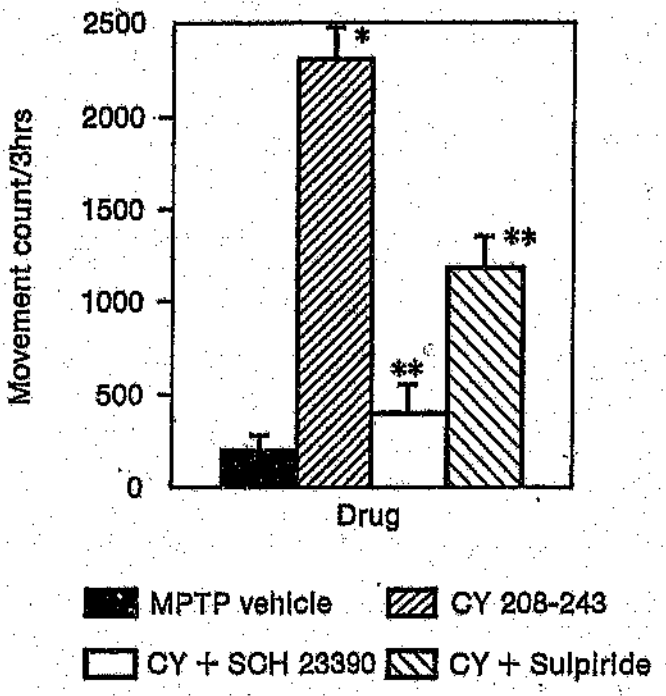


Fig 7.9

The effect of pretreatment cumulated over 3 hours of SCH 23340 or sulpiride upon CY 208-243 (1 mg/kg sc) an hour later in MPTP-treated marmosets. Statistical significance at *$p<0.05$ CY compared to vehicle and **$p<0.05$ compared SCH or sulpiride plus CY to CY 208-243 alone in MPTP-treated animals.

7.10 Experiment 4: Effects of CY208-243 to drug naive animals pre and post-treatment

7.10.1

Method of administration of CY 208-243 to drug naive marmosets before and after treatment.

A second and completely different group of 8 adult, aged, common marmosets were given CY 208-243 vehicle injections after 30 minutes acclimatisation and their locomotor motility recorded for 180 minutes, while the animals were video-taped and rated. Careful attention not to give this group of animals any other drugs was enforced.

MPTP-treatment similar to the previous group was administered and the animals allowed 6 weeks to recover. Once persistent and stable parkinsonism deficit remained, the animals were once again given the vehicle injection, introduced into the photocell cages, and after 10 minutes their motility recorded for 180 minutes. Without allowing any D-2 receptor priming these animals received CY 208-243 (1,0 mg/kg sc.) and their activity was recorded over the following 180 minute period. Thereafter these animals received L-Dopa (12,5 mg/kg ip.) plus carbidopa (12,5 mg/kg po. in 1% methylcellulose or (+)-PHNO (4 ug/kg sc.). Activity as previously described was video-taped and recorded after 10 minutes; for a total of 180 minutes.

7.10.2

Results of the administration of CY 208-243 to drug naive marmosets before and after MPTP-treatment. (Fig. 7.10).

The drug naive animals, when given CY 208-243 vehicle injections and then on a different day CY 208-243 (1,0 mg/kg sc.) did not increase their normal locomotor activity. No other motor changes or nausea and vomiting was noted (Fig 7.10).

Following MPTP treatment, administration of CY 208-243 (1,0 mg/kg sc.) led to reversal of akinesia within a few minutes, the animals being restored to normal motor activity. Vocalisation spontaneously increased, the animals moved freely from perch to perch, demonstrated normal balance and their posture improved. The maximal effect on CY 208-243 occurred 30-40 minutes following drug administration and lasted 120 minutes before the animals once again became bradykinetic, developed a flexed posture and became unstable while on perches (Fig. 7.10). Nausea and vomiting did not occur at any stage following CY 208-243.

Administration of L-dopa (12,5 mg/kg ip.) plus carbidopa (12,5 mg/kg ip.) 30 minutes previously similarly improved animal locomotor activity and reversed motor deficits, as did (+)-PHNO (4 ug/kg sc.). Activity began within 10 min-

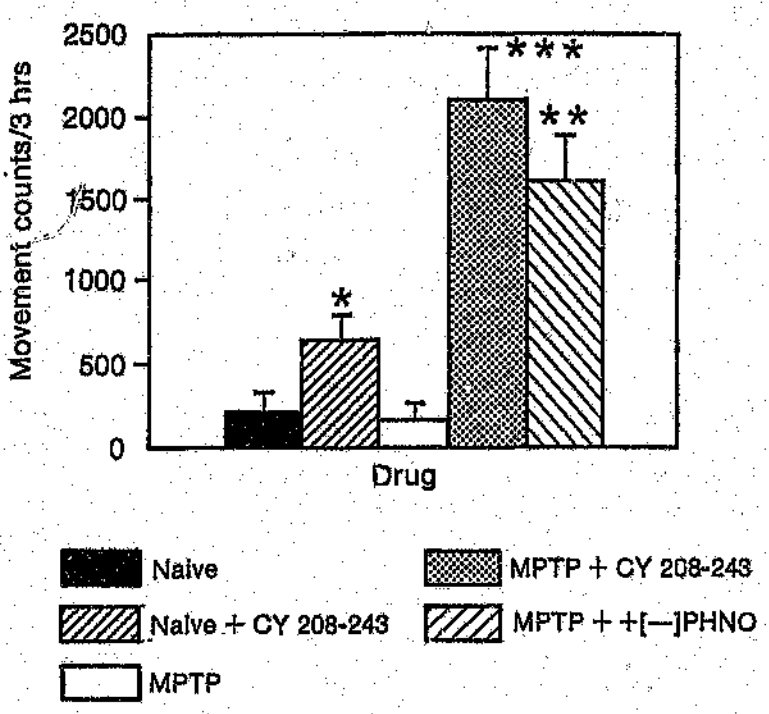


Fig 7.10

The effect of the administration of CY 208-243 (1 mg/kg sc) to drug naive normal marmosets, then following MPTP-treatment once stable and Parkinsonian. Six animals were recorded over 10 minute segments for 180 minutes. SEM's using the paired student test were significant at *$p<0.05$ compared to drug naive normal animals, **$p<0.05$ compared to MPTP-treated animals, ***$p<0.001$ compared to MPTP-treated animals

utes and lasted 180 minutes following L-dopa and 120 minutes following (+)-PHNO administration. Nausea and vomiting was only noted following (+)-PHNO. All the above animal experiments were published in the European Journal of Pharmacology, (see Appendix V).

7.11 Experiment 5: Effects of CY208-243 and (+)-PHNO combinations to MPTP-treated marmosets

7.11.1 Methods of the administration of CY 208-243 and (+)-PHNO in combination to MPTP-treated marmosets

Eight marmosets, treated with MPTP 3 months previously and still grossly parkinsonian were given two vehicle injections, 30 minutes apart and introduced into the photocell cages for locomotor activity monitoring for 180 minutes. Sub-therapeutic doses of the D-2 agonist (+)-PHNO (1,0 ug/kg sc.) or the D-1 agonist CY 208-243 (0,25 or 0,5 mg/kg sc.) were given 30 minutes before or after the respective vehicle injections. The method used was to allow the animals 30 minutes of acclimatisation, administer the D-1 agonist or vehicle injections and then 30 minutes later the D-2 agonist or vehicle injection. Thereafter at least

180 minutes photocell monitoring was conducted. Once a suitable drug free interval of 5 days had been allowed, the same animals received both CY 208-243 (0,25 or 0,5 mg/kg sc.) and 30 minutes later (+)-PHNO (1.0 or 2 ug/kg sc.) invariable combinations. Activity was video-taped was for 180 minute periods. Finally CY 208-243 (0,5 mg/kg sc.), followed 30 minutes later by (+)-PHNO (2 ug/kg sc.) was administered, recording over 180 minutes in the photocell cages.

7.11.2

Results of CY 208-243 and (+)-PHNO combinations in MPTP-treated marmosets. (Fig. 7.11)

Administration of two vehicle injections, 30 minutes apart did not increase locomotor activity, over 180 minutes in the photocell cages. (Fig. 7.11b).

Administration of CY 208-243 (0,25 or 0,5 mg/kg sc.), followed by (+)-PHNO vehicle 30 minutes later, did increase animal motility slightly as expected following two injections, but not significantly (Fig 7.11 b). These doses were chosen on what appeared a sub-maximal dose (Fig. 7.11 c & d), to prime the animals for the D-2 agonist (+)-PHNO.

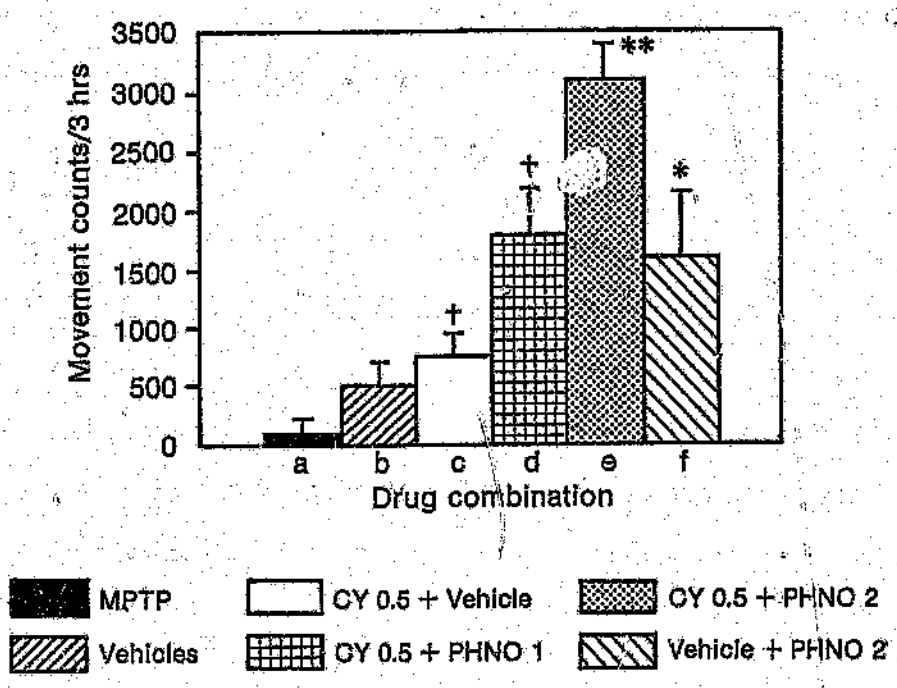


Fig 7.11

The effect of spontaneous movement in MPTP-treated marmosets
(a) over 3 hours, then
(b) following one or two vehicle injections.

The effect following sub-therapeutic doses of dopamine agonist drugs:
(c) CY 208-243 (< 0.25 mg/kg sc) (N/S compared to vehicle injections)
(d) or PHNO (< 1 ug/kg ip)(N/S compared to vehicle injections).

The administration of combinations of:
(e) CY 208-243 (0.25 mg/kg sc) and PHNO (1 ug/kg ip)(**$p<0.005$ compared to *c* and *d* but $p<0.001$ compared to *b* and N/S compared to *f*).
(f) CY 208-243 vehicle plus PHNO 2 ug/kg sc (*$p<0.05$ compared to *d*) are shown in all 8 animals monitored over 3 hours.

Administration of CY 208-243 vehicle and 30 minutes later (+)-PHNO (1 or 2 ug/kg sc.) was similarly considered a sub-maximal dosage of the D-2 agonist drug. Administration of CY 208-243 (0,25 mg/kg sc.) and 30 minutes later(+)-PHNO (1 ug/kg sc.) had no effect on motor activity or motor deficit scores. Administration of CY 208-243 (0,25 mg/kg sc.) followed 30 minutes later by (+)-PHNO (2 ug/kg sc.) produced very marked locomotor hyperactivity and full reversal of motor deficits (Fig. 7.11 e). This effect lasted 180 minutes. This was much greater than the effects of (+)-PHNO at the same dose alone (Fig. 7.11 e & f).

Administration of CY 208-243 (0,5 mg/kg sc.) and 30 minutes later (+)-PHNO (1 ug/kg sc.) produced significant increase in locomotor activity and reversed motor deficits (Fig 7.11 g). The dose of CY 208-243 alone did not produce much increase in locomotor activity but once combined with a sub-therapeutic dose of D-2 agonist (+)-PHNO the animals became markedly mobile.

Finally, after a 2 week drug free interval and rest, repeat administration of CY 208-243 vehicle and 30 minutes later (+)-PHNO (2 ug/kg sc.) produced increased locomotor activity, lasting 120 minutes, but statistically significantly less than that observed following additional CY 208-243 drug priming (Fig 7.11 f).

7.12 Statistical methods in the analysis of the animal experiments

In all the animal motility experiments, the two tailed students t-test for paired samples was employed to assess differences in accumulative counts between different drug treatments. Motor scores of the animals recorded upon the video-tape were compared using the Mann-Whitney test for non-parametric data analysis. Significance was taken at $p<0,05$.

7.13 Discussion of the animals experiments

MPTP-treated common marmosets are a good model to assess drug efficacy and potential drug interactions. Biochemically and histologically the common marmoset brain shows similar nigrostriatal dopamine depletion, substantia nigra compacta dopamine cell death and striatal dopamine receptor hypersensitivity. Hence, although not perfect, the MPTP-treated primate model was thought best to analyse new dopamine receptor modifying drugs prior to their being tested in man.

Antiparkinsonian drugs with proven efficacy were administered in these MPTP-treated marmosets to validate the model. Experiment 1 showed that L-dopa (with PDI) and (+)-PHNO fully reversed the akinetic-rigid states of the primate and in dose responsive fashion these drugs being able to increase motor motility and restore normal behaviour. The motility could be quantitatively measured by the infrared motility cages and the animal behaviour could be assessed directly undisturbed, or upon video-taped review. The clinical score correlated consistently with overall motility. Disturbing the animals, however, clearly affected their behaviour and motility, hence where possible animals were left undisturbed throughout the monitoring period.

L-dopa plus carbidopa has known D-1 and D-2 dopamine receptor influence. It remains the best drug in man and MPTP-treated primates, consistently reversing parkinsonism. L-dopa (plus PDI) was thus selected to test predictable improvement and all animals showed good levodopa responsiveness. Hence it was considered a suitable model.

Many D-2 selective agents have been recently studied, some of which have been successful in man. The relatively new D-2 agonist (+)-PHNO was chosen to test the MPTP-marmoset model due to its potency, availability and relative ease to

inject either subcutaneously or intraperitoneally. This D-2 agonist produced nausea and vomiting as expected but not dyskinesias or stereotipy in the marmoset. Vomiting associated with oral drug ingestion may lead to less predictable dosage, thereby invalidating data.

The D-1 agonist SKF 38393 did not produce hypermotility or improve behaviour which confirmed earlier observations in the same model (Nomoto et al., 1985; Close et al., 1985). Hence the MPTP-treated marmoset showed responsiveness to mixed D-1 and D-2 agonist (levodopa) and D-2 agonists ((+)-PHNO) but not SKF 38393 (a D-1 agonist).

Another putative selective D-1 partial receptor agonist CY 208-243 did, to our surprise, reverse MPTP-induced parkinsonism. The effects were identical to L-dopa and (+)-PHNO regarding behaviour and motility, except no nausea or vomiting was found. While stereotypic behaviour and dyskinesias were not observed in doses of CY 208-243 below 1,25 mg/kg sc., greater administered doses produced hyperexcitability, cataplexy and even frank seizures. Animals may injure themselves with greater doses due to hypermotility and self inflicted injury upon the cages.

Why does CY 208-243, but not SKF 38393, reverse MPTP-induced parkinsonism? This remains unclear and will have to await the production and testing of other D-1 selective

agonist drugs. A number of possible differences between SKF 38393 and CY 208-243 have emerged.

Firstly, while both drugs produce contralateral rotation in 6OHDA rodents it has been suggested the SKF 38393 penetrates poorly into the brain (Clarke and White, 1987) and especially so in the primates compared to the rat. Secondly, the drugs differ in their actions upon the D-1 receptor. Both pharmacologically possess partial D-1 agonist potential (Setler et al., 1978) but a breakdown product of SKF 38393 could antagonise the dopamine receptor. Thirdly, that CY 208-243 or its metabolite, may possess D-2 receptor agonist properties, is a possibility that cannot be ignored. The chemical structure of CY 208-243 looks very similar to other ergolines. However rodent pharmacological data suggest clearly D-1 receptor selectivity with a failure to induce stereotipy and nausea. In vitro studies to decrease acetylcholine release in striatal tissue slices and to suppress prolactin release are all recognised D-2 drug actions.

Furthermore, in the marmoset the lack of D-2 effects was strengthened by lack of D-1 stimulation in animals with normal nigrostriatal dopaminergic pathways. In contrast D-2 agonists, including (+)-PHNO, produce marked hypermobility in drug naive normal animals. The observation that SCH 23390 fully inhibits the action of CY 208-243

was expected, since SCH 23390 is a potent and selective D-1 receptor antagonist. This drug SCH 23390 produces a parkinsonian state in normal animals without MPTP-induced parkinsonism and certainly aggravated the MPTP-lesioned group by making them completely akinetic. This implies that some endogenous levodopa is still present in MPTP-treated primates and that some striatal receptors have the capacity to respond. What was surprising was the fact that the D-2 selective antagonist sulpiride also attenuated the CY 208-243 induced increase in motility. This was not as dramatic as that observed following SCH 23390 priming but nevertheless indicated CY 208-243 possesses some as yet undetected direct D-2 agonist properties or alternately that some functional interdependence exists between the D-1 and D-2 receptor population. In addition to this possible functional linkage, CY 208-243 affects opiate receptors, 5-HT(1A) receptors and possibly alpha-adrenergic and 5-HT(2) sites (Foote et al., 1982). These receptors may have antiparkinsonian effects themselves and the neurochemical cascade that interlinks cell neurotransmitters may be altered in some way independently of the dopamine receptors themselves. Special note should be made of the dose response curve of CY 208-243 in the MPTP-treated primate and thereafter the effect of CY 208-243 on normal nigrostriatal systems. An expected increase in motility occurs with greater motility correlating with greater administered D-2 agonist drug dosage (Nomoto et

al., 1988). However following incremental doses of CY 208-243 (Fig. 8.5) one noted a plateau at 0,75 to 1,25 mg/kg sc. Why motility was not steadily increased from 0,75 to 1 mg/kg sc. of drug is unknown but could reflect a saturation of the D-1 receptors, the best antiparkinsonian dose at moderate dosage or ı.nally that at doses greater than 0.75 mg/kg sc., other receptors became operational adding their contribution toward increased mobility. The alternate receptor possibility is strengthened by the observation that hyperexcitability and self inflicted trauma plus seizures occurred at not much greater than 1,25 mg/kg sc. The importance of little CY 208-243 increase in mobility (in contrast to D-2 agonist drugs) in drug naive animals stems from 6OHDA rodent experiments suggesting D-1 agonist induced rotation is dependant upon prior priming with D-2 agonist drugs (Marcelli and Di Chiari, 1987). CY 208-243, without any prior D-2 agonist drug exposure, was clearly able to increase MPTP-treated marmoset motility. This increase in mobility following MPTP-treatment was far greater than vehicle or even when the same dose of CY 208-243 was given prior to MPTP therapy. Hence this D-1 agonist drug alone would appear to possess functional antiparkinsonian activity without concomitant D-2 receptor priming by other agents.

What would the best state of the D-1 dopamine receptor be that would allow the D-2 receptor to maximally express

itself? Clinically the benefit of levodopa (mixed D-1 and D-2 drug) in unrivalled, but when loss of benefit occurs dopamine agonists may still restore some benefit. Animal studies suggested a D-1 or D-2 functional linkage similarly when it was reported that the unilateral 6OHDA rotating rat increased maximal D-2 expression when primed with SKF 38393 (Carlson et al., 1987).

Experiment five addressed the functional benefit of submaximal doses of levodopa and (+)-PHNO following a small and insignificant in itself D-1 priming dose of CY 208-243. Clearly the MPTP-treated marmoset showed maximal amplification of D-2 expression, following (+)-PHNO and L-dopa (plus PDI) administration once the D-1 receptors were activated with CY 208-243.

The effects of D-1 and D-2 drugs may be additive but data suggests a synergistic response that is similar to maximal D-2 expression alone following much larger doses of D-2 agonists. Additional complexities arise when the D-1 and D-2 dopamine receptors function in the normal striatal state compared with the depleted nigrostriatal state (Arnt, 1985). Further studies utilising different models of parkinsonism and multiple drugs in each dopamine receptor group are required to answer more definitively these possible functional linkages.

7.14 Relevance of non-human primate data to human idiopathic Parkinson's disease

Having confirmed the above concepts of D-1 and D-2 functional interaction and possible receptor synergism to man with IPD, the question arose - do these drugs work in man? Most advanced patients with IPD suffered motor fluctuations and dyskinesias when mobile and it was decided that this group would be denied levodopa the day of novel drug testing. Should these compounds (both CY 208-243 and CQA 206-291) be efficacious, confirm what the MPTP monkeys had shown, then patients should become mobile. The long term effects of CQA 206-291 would then subsequently be tested, in addition to levodopa maintenance, in the same type of patient.

CHAPTER 8

FURTHER HUMAN STUDIES

The MPTP-primate marmoset model has shown that (+)-PHNO, CQA 206-291, both D-2 selective agonists and CY 208-243 a D-1 dopamine agonist are effective in reversing MPTP parkinsonism. Having established the need for new dopamine agonists, we administered these same agents to man with IPD, once full ethical approval was obtained. The remaining studies in this thesis set out to examine these same antiparkinsonian agents in man, initially an open study alone while "off" levodopa and then double-blind compared with placebo as adjuvant therapy to levodopa.

8.1 Trial 3: CQA 20[illegible]-291 in advanced Parkinson's disease

Methods

Six patients with IPD in an advanced stage, all suffering unpredictable "on-off" fluctuations and on long-term levodopa therapy were hospitalised while their usual levodopa was

withheld overnight (Table 8.1). Upon waking the following day an anti-emetic domperidone (20 mg po.) was given at breakfast. This drug, while also a dopamine antagonist but does not cross the blood brain barrier. A single dose of CQA 206-291 was then given and their parkinsonian status was monitored utilising the Unified Parkinsons Disease Rating Scale (UPDRS) (Appendix II) at baseline and half-hourly for 2 hours, hourly for 6 hours or until the benefit of CQA 206-291 had subsided. If no benefit was noted after 3 hours, the usual morning dose of levodopa was given, the patient allowed a day to recover and the next incremental dose of CQA 206-291 administered the next day following similar levodopa withdrawal. Patients were given 0,1, 0,2, 0,5, 2,5, 5, 10 and a maximum of 20 mg po. Since the first 3 patients did not respond to doses below 2,5 mg the final 3 were started at this dose. At each time interval "on-off" status, side-effects, blood pressure recumbent and standing and heart rate were recorded in addition to the motor components of the UPDRS.

Biochemistry, prolactin levels, haematology and electrocardiograms were recorded daily. Four subjects taking other medications (Table 8.1) were continued unchanged throughout the trial.

Table 8.1

Patient characteristics at trial entry to receive CQA 206-291 (0.1 - 20 mg po) following levodopa withdrawal overnight.

Patient	Sex	Age (yrs)	Disease duration	Levodopa dose	Other drugs	(mg/day)
RE	M	49	9	375	Amantadine	(300)
DS	M	74	16	1750	Amantadine	(200)
JG	M	63	12	700	-	-
RB	F	52	16	600	Benzhexol	(8)
GK	F	61	12	400	Amantadine	(300)
BG	F	71	15	1000	-	-

Results

Three males and 3 females, aged 49-77 years (median 62) all Hoehn and Yahr stage 3 or 4 off medication were studied. Disease duration was 9-16 years (median 13.5) and patients were taking oral levodopa plus PDI in doses ranging 375-1750 mg po. (median 650 mg) per day. All patients were "off" rigid and akinetic and clearly different from their "on" mobile status following levodopa ingestion.

Figure 8.1 shows the patient's individual baseline scores preceding each days CQA 206-291 ingestion (indicated by B) and their response following their usual levodopa (indicated by LD). This is then compared to incremental doses of CQA 206-291 which indicates doses below 2,5 mg po. (n=3 patients) had no effect; after 2,5 mg po. (n=6) 1 patient partially turned "on"; after 5,0 mg po. (n=6) 1 patient partially and 2 fully "on"; after 10mg po. (n=6) 3 patients fully "on"; and finally following 20mg po. (n=3) all 3 patients turned fully "on". The "on" response was usually accompanied by dyskinesia similar to those induced by levodopa. The tendency toward dose responsiveness is shown in Figure 8.2 which accumulates all the patients' scores versus the incremental CQA 206-291 dosage, indicating most patients turning "on" in the highest dosages employed. Latency to turn "on" was 60-140 minutes

(mean 90), the duration of the "on" response 30-450 minutes (mean 70).

Side effects were noted following single oral CQA 206-291 doses including drowsiness (n=5), nausea (n=3) with vomiting (n=2), postural dizziness (n=1) and transient confusion (n=1). No lasting side-effects or significant biochemical, haematological or electrocardiographic abnormalities were attributed to the drug.

Discussion

The ergoline derivative CQA 206-291 has now been employed more widely in double-blind studies to test its efficacy against placebo, and other D-2 dopamine agonists, particularly bromocriptine (Rascol, 1988; Jaton, 1988). This trial suggests that dose for dose it is 3 to 4 times more potent than its predecessor bromocriptine, is well tolerated but does have similar side effects. It was hoped that less postural hypotension and neuropsychiatric side-effects suggested by this study compared to bromocriptine would be confirmed in larger studies, and hence the double-blind placebo matched study was initiated.

The rigid akinetic state in advanced IPD may be converted to a mobile "on" phase sometimes accompanied by dyskine-

sias. The latency to the "on" response is similar to bromocriptine reflecting rapid intestinal absorption, carriage by plasma proteins and transport across the blood-brain barrier to the striatal dopaminergic receptors. The duration the patients turn "on" and the quality of the "on" response are both dose related and long lasting.

This study was published in Clinical Neuropharmacology, (see Appendix VI).

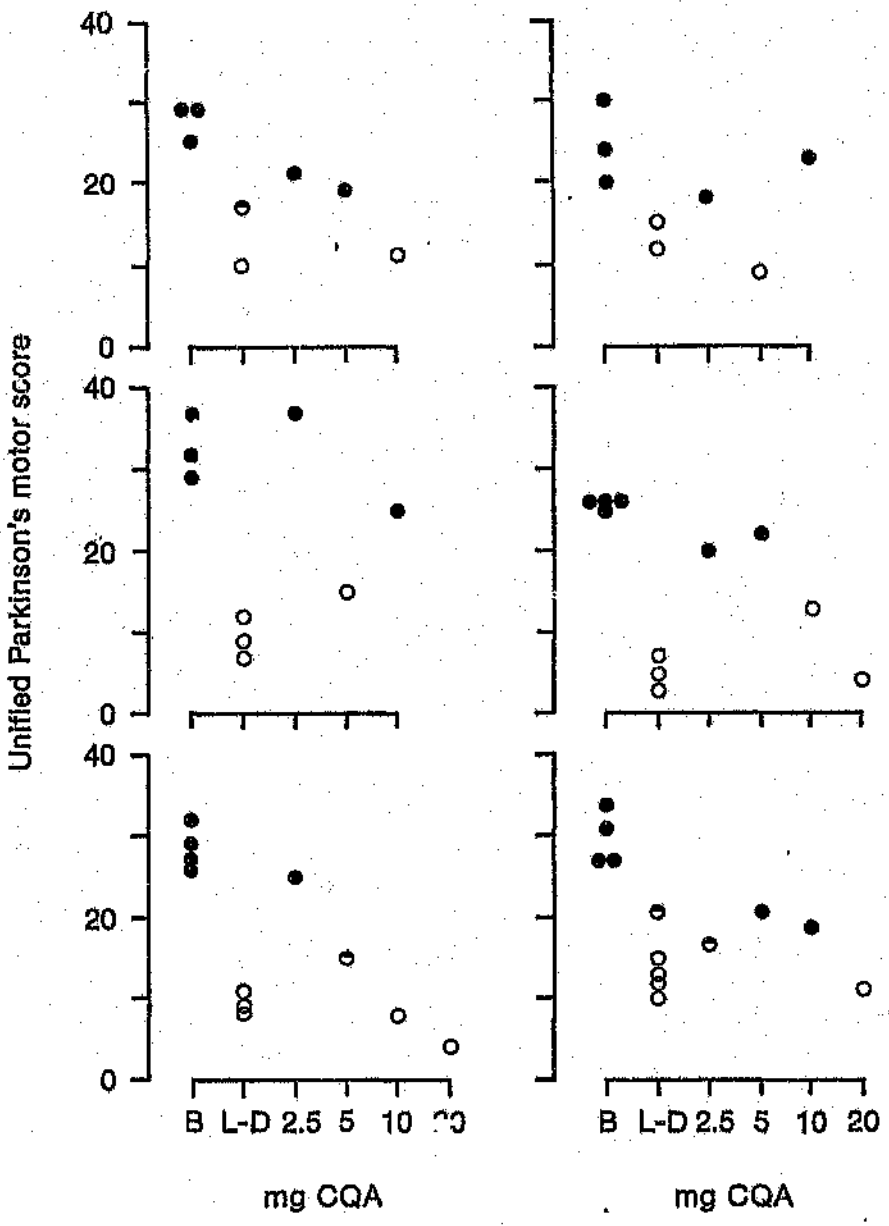


Fig 8.1

Motor disability scores using section 3 of the UPS (Version 3, 1987) in six patients prior to drug administration (B), at the time of maximal usual levodopa response (L-D) and then following a single CQA 206-291 dose (2.5 - 20 mg po). Open circles (O) represent the 'on' mobile state whereas closed circles (●) represent the 'off' rigid and immobile state and semi-open circles (◓) the inbetween state.

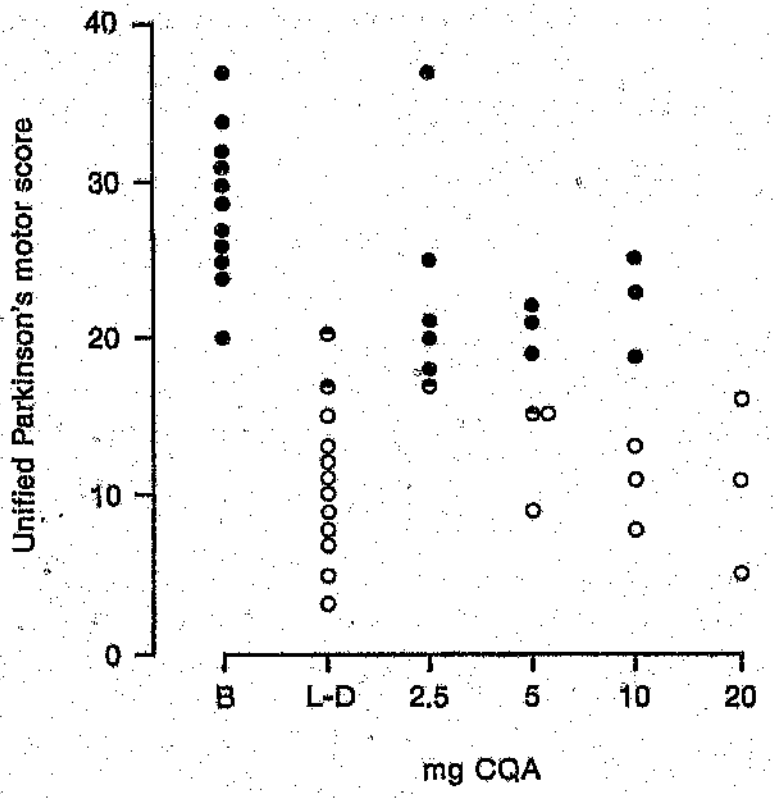


Fig 8.2

Motor disability scores (using section 3 of the UPS) in all patients grouped together following CQA 206-291 (2.5 - 20 mg po). Open circles (O) represent the 'on' mobile state whereas closed circles (●) represent the 'off' rigid and immobile state and semi-open circles (◓) the inbetween state.

8.2 Trial 4: CQA 206-291, a double blind study with adjuvant levodopa in advanced Parkinson's disease

Methods

Patients: Ten patients with idiopathic Parkinson's disease were entered into a double-blind and randomised study which was performed over 4 months (Table 8.2). After giving informed consent patients received either placebo or CQA 206-291 in progressively increasing doses ranging from 2,5 mg to 30 mg/day po. The increment occurred during the first 3 months of the trial. Previously, patients with advanced IPD "off" levodopa turned "on" at a CQA 206-291 dose of 10-20mg po.

Simultaneously an attempt was made to lower the dose of levodopa from week 3 of therapy in all patients, provided stable clinical status was maintained. The patients were evaluated using the Unified Parkinson's Disease Rating Scale (UPDRS) on visits at baseline and weeks 1,2,3,4,6,8,12 and 16.

Patients were included provided they had idiopathic Parkinson's disease, Hoehn and Yahr stage 2 to 4, scoring more than the minimum in 2 of 3 major IPD features:

Table 8.2

Patient characteristics in 10 patients with advanced PD at baseline before being given CQA 206-291 as adjuvant therapy to maintenance levodopa.

PATIENT DATA AT BASELINE

Patient No.	Age (yrs)	Sex	Disease duration (yrs)	Hoehn & Yahr Stage	Current L-dopa dose(mg/d)
1	78	F	19	3	750
2	61	M	4.5	3	750
3	74	M	15	3	1000
4	56	F	7	4	450
5	72	F	1	3	400
6	71	M	10	4	625
7	60	M	10	4	1125
8	60	M	3	4	400
9	67	M	1	2.5	1000
10	77	M	9	2.5	750
Mean n=10	67.6	7:2	8	2-4	725

tremor, rigidity or bradykinesia. Either sex, aged 40 - 80 years, on stable levodopa (Sinemet or Madopar) dose, for more than two months were entered, all experiencing levodopa induced adverse effects, or decline in levodopa efficacy. Patients were not on selegiline at any stage and had not been given an alternate dopamine agonist for more than 3 months.

Exclusion criteria included end stage IPD (Hoehn and Yahr stage 5), continuance of dopamine agonist drug, active or past psychosis history; evidence of hepatic, renal or cardiac dysfunction; other neurologic illness; or secondary causes of parkinsonism such as drugs, trauma or multiple system degeneration.

Drug trial safety precluded nursing or pregnant females as well as patients thought to abuse alcohol. All patients once screened and agreed to participate, were examined medically and neurologically and then considered for the study.

Following recruitment, individuals were randomised to receive placebo or CQA 206-291 in identical capsules as an adjunct to their levodopa. Both groups were monitored in parallel without a levodopa change from baseline (week 0) to week 2 where they received a fixed titration of CQA 206-291 from 0.5 mg/day to a maximum of 10 mg/day po.

Thereafter from weeks 2 to 10, while maintaining clinical stability, the dose of levodopa was reduced where possible while simultaneously increasing the CQA 206-291 dose from 10 to 40 mg/day po. The study aim was where possible to reduce levodopa while increasing CQA 206-291 and at the same time maintain constant motor stability.

Should this fail the patient would report deterioration, diarise it, and if clinical evaluation concurred the levodopa dose was then increased. An attempt was made to plateau the optimal combination of levodopa plus trial compound at the final 4 weeks of the study period. Compliance and understanding of medication was checked by tablet counts each visit. Patients were evaluated twice before the first dose of trial medication, thereafter at weeks 1,2,3,4,6,8,12 and 16. Other medication was continued unchanged through the study. Patients underwent full general neurological and parkinsonian evaluation at baseline and the end of the study. Between these visits, the UPDRS was employed to evaluate drug efficacy. In addition, lying and standing blood pressure, weight, pulse rate, review of patient diaries, and specific questions relating to dyskinesia, dystonia, "on-off" motor fluctuations or any neuropsychiatric side effects were documented. Evaluation was made at the same time of day, usually with patients "on" two to three hours after the early morning dose of medication.

Prior to, at week 8 and following the study all patients had blood taken for serum biochemistry, full blood counts and ESR, liver function tests, random blood glucose; and also had urine analysis, ECG's and chest X-rays.

A paired students t-test was employed to assess significance between data, not only between placebo versus active drug at each interval, but also between baseline and each subsequent visit.

Results

Six patients received CQA 206-291 and 4 placebo. Of the 10 patients there were 3 females and 7 males with a mean age of 67,6 years (range 56-78) and a mean disease duration of 8 years (range 1 to 19). The Hoehn and Yahr stage in an "off" period was at least 2 and the mean dose of levodopa at baseline was 725 mg per day (range 400-1125 mg/day). The motor activities which encompass tremor, bradykinesia, rigidity and postural stability showed an improvement in all patients receiving CQA 206-291 and in 1 patient on placebo. The motor scores of the CQA 206-291 and placebo groups are shown as a percentage of the baseline score (Fig.8.3). An improvement is indicated by a decrease in the percentage or a fall in the motor score.

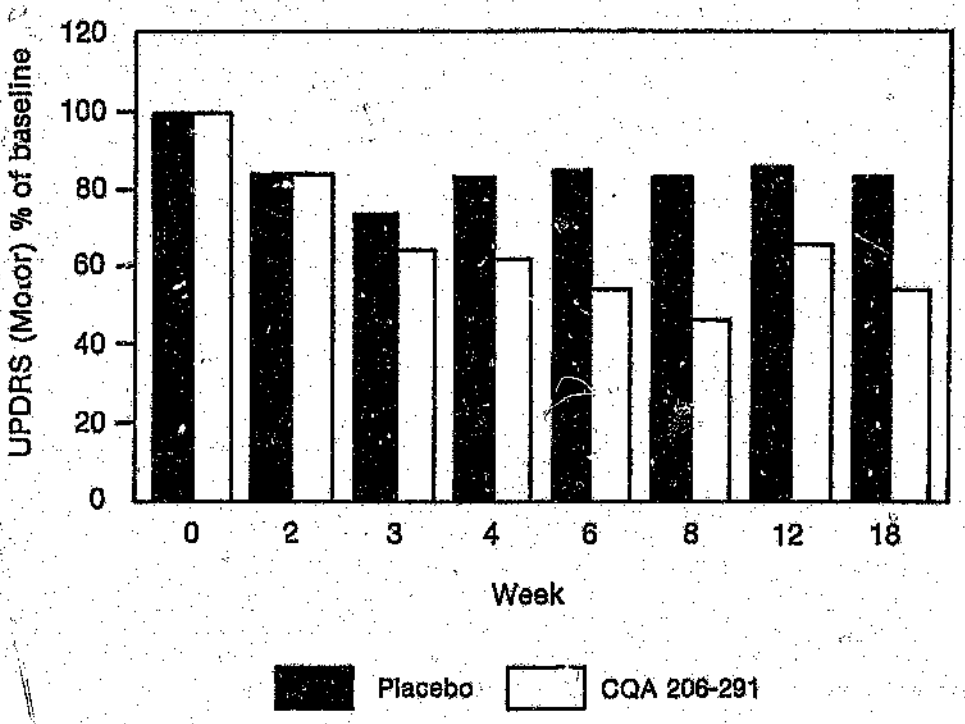


Fig 8.3

Mean motor score of 10 patients who either received CQA 206-291 (open) or placebo (solid bars) from baseline to 16 weeks at the end of the double blind study ($p < 0.01$).

At baseline the groups were statistically comparable. Although the scores for the placebo and the CQA 206-291 groups both fell, the decrease for the placebo group was not significant while that for the CQA 206-291 group was statistically significant ($p<0,01$). The overall motor score improved in the active group by 45%.

Fig.8.4, represents the dose of levodopa in both groups as a percentage of the baseline dose. A reduction in dose is evidenced by a decrease in the column height. The baseline doses of the groups were comparable. The patients receiving placebo were unable to tolerate a significant reduction in levodopa dose while maintaining adequate motor scores; however the dose of levodopa was reduced by 35% in the patients receiving CQA. This was statistically significant compared to baseline dosage ($p<0,005$).

Involuntary movements in the form of dyskinesias were present in 2 of the placebo patients at baseline which improved with reduction in levodopa dose. However 3 of the CQA 206-291 patients developed dyskinesias during the trial. Dystonia, present in a single patient receiving placebo, remained unchanged over the 4 months. A marked effect in terms of "on-off" motor fluctuations was noticed with a single patient in the placebo group deteriorating while 5 of the 6 patients in the active group improved significantly. There were no side-effects in the placebo

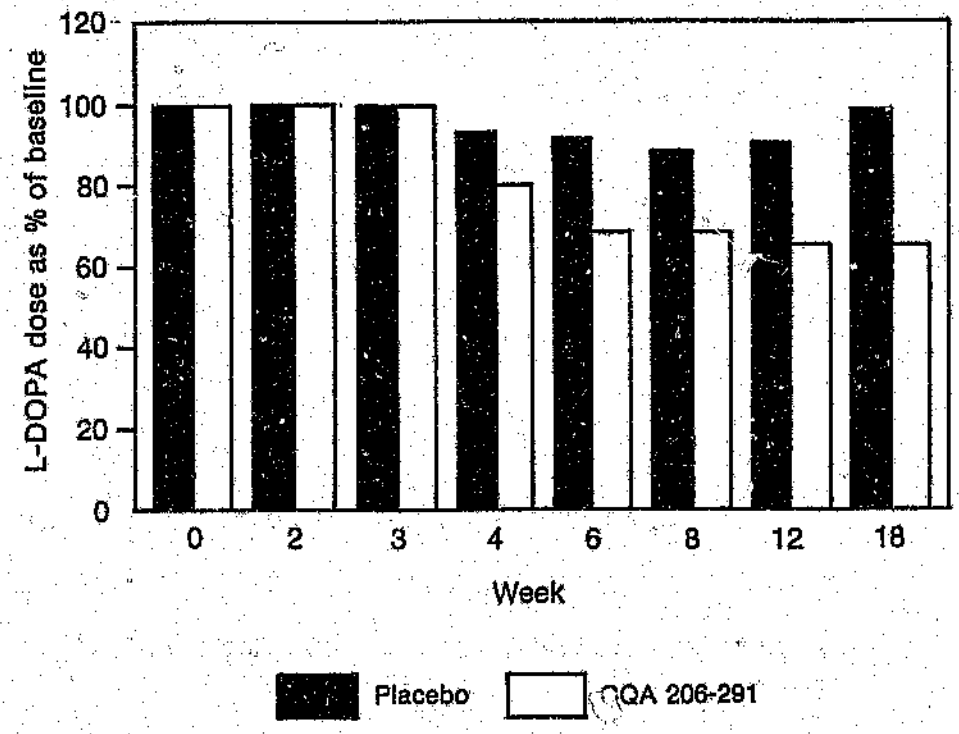


Fig 8.4

The mean dose of levodopa in 10 patients who were allocated to receive either CQA 206-291 (open) or placebo (solid bars) over 16 weeks follow-up ($p < 0.005$).

group. Neuropsychiatric adverse events in the form of severe hallucinations occurred in 2 of the CQA 206-291 patients. Postural hypotension in a single CQA 206-291 patient remained unchanged from baseline to termination of study. No nausea - vomiting was reported.

Discussion

This double-blind parallel study demonstrates that CQA 206-291 compared with placebo match is an effective antiparkinsonian agent as an adjunct to levodopa in moderate IPD. Statistically significant improvements in all aspects of the UPDRS were seen, in addition patients were able to be maintained on less levodopa. Any reduction in the overall levodopa dose is beneficial in the long term, an overall reduction of 35% is of great advantage. The addition of 25 mg/day CQA 206-291 allowed a 35% levodopa reduction over baseline requirements.

As could be expected, because of experience with other D-2 dopamine agonists, more dyskinesias were encountered. While 2 patients in each group had dyskinesias at recruitment, these generally were more severe both in duration and degree particularly those of the CQA 206-291 group. The increased dyskinesia was always accompanied by increased overall mobility. However in contrast to other

D-2 dopamine agonists little nausea, vomiting, orthostatic hypotension, neuropsychiatric episodes, or other motor fluctuations were noted.

Clearly CQA 206-291 is an effective antiparkinsonian agent and hopefully other D-2 agents of the 8-α ergoline group will be produced in future to better supplement levodopa or even possibly manage patients de novo.

8.3 Trial 5: CY 208-243 in advanced Parkinson's disease

Methods

Eight patients with idiopathic Parkinson's disease, 7 male and 1 female, aged 50 - 73 years (median 61) were studied after giving informed consent (Table 8.3). They were Hoehn and Yahr stage 3 or 4 off medication, had a disease duration for 9-18 years (median 12), and were receiving levodopa therapy ranging 400-2400 (median 800) mg per day (plus PDI). All were experiencing long term levodopa complications and motor fluctuations. Levodopa was withdrawn overnight before each study day but other drugs continued unchanged.

Table 8.3

The patient characteristics of 6 patients (the remaining 2 having being studied in Paris) of the 8 reported to receive CY 208-243 (2.5 - 40 mg po) following overnight levodopa withdrawal.

Patient	Sex	Age (yrs)	Disease duration (yrs)	Levodopa dosage (mg/day)	Other drugs (mg/day)
RE	M	49	9	375	Amantadine (300)
RB	F	52	16	600	Benzhexol (8)
EC	F	74	11	500	Amantadine (200)
LN	M	60	18	2050	-
WM	M	73	10	850	-
GR	M	64	12	1500	Dissipal (100)

CY 208-243 was given in open fashion, by mouth, each alternate morning after breakfast in single doses of 5 (n=5), 10 (n=7), 20 (n=8) and 40 (n=7) mg po. respectively. Motor disability using the Unified Parkinsons Disease Rating Scale (Version 3) blood pressure and pulse was measured at baseline, half hourly for 2 hours, and then hourly for the next 4 hours. If no clinical improvement was present by 3 hours, or if any benefit lasted less than 3 hours, patients was given their usual morning dose of levodopa. The response of each patient to his usual dose of levodopa was assessed at least once in each patient and all demonstrated markedly different UPDRS scores when "on" compared to when "off". A full general and neurological examination was performed prior to and after the study. Serum biochemistry, haematology and ECG were monitored before and within 24 hours of each dose administered.

Results

All 8 patients showed improvement in parkinsonian motor disability following administration of their usual morning dose of levodopa (Fig 8.5). This "on" score was associated with the mobile, reduced or absent tremor, good postural balance and minimal bradykinesia state often associated with dyskinesias. Following overnight levodopa withdrawal

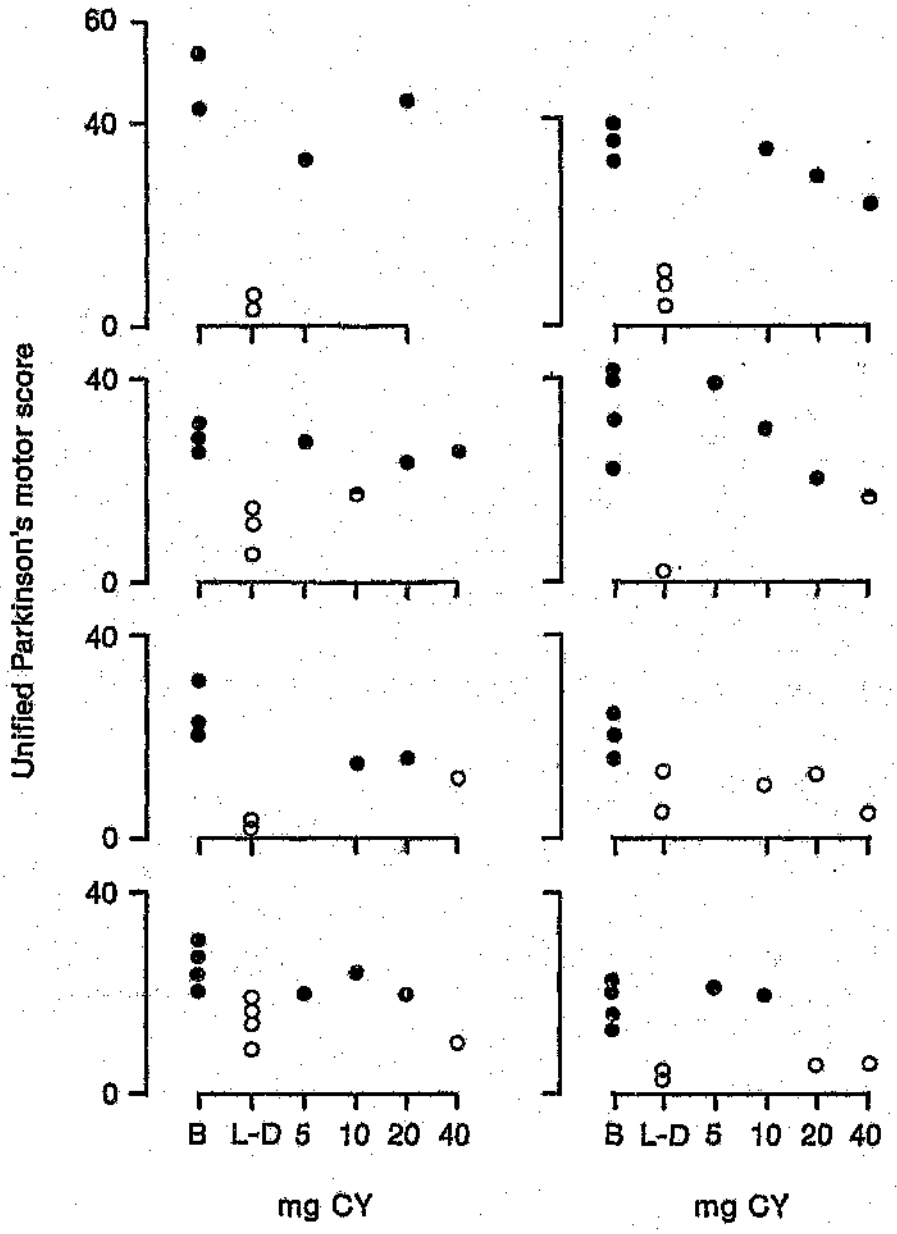


Fig 8.5

Motor disability scores (using section 3 of the UPS) in 8 patients prior to drug administration (B), at the time of maximum response to levodopa (L-D),or at the time of maximal response to single doses of CY 208-243 (5-40 mg po). Open circles (O) represent the 'on' mobile state, closed circles (●) represent the 'off' immobile state and semi-open circles (◓) the inbetween state.

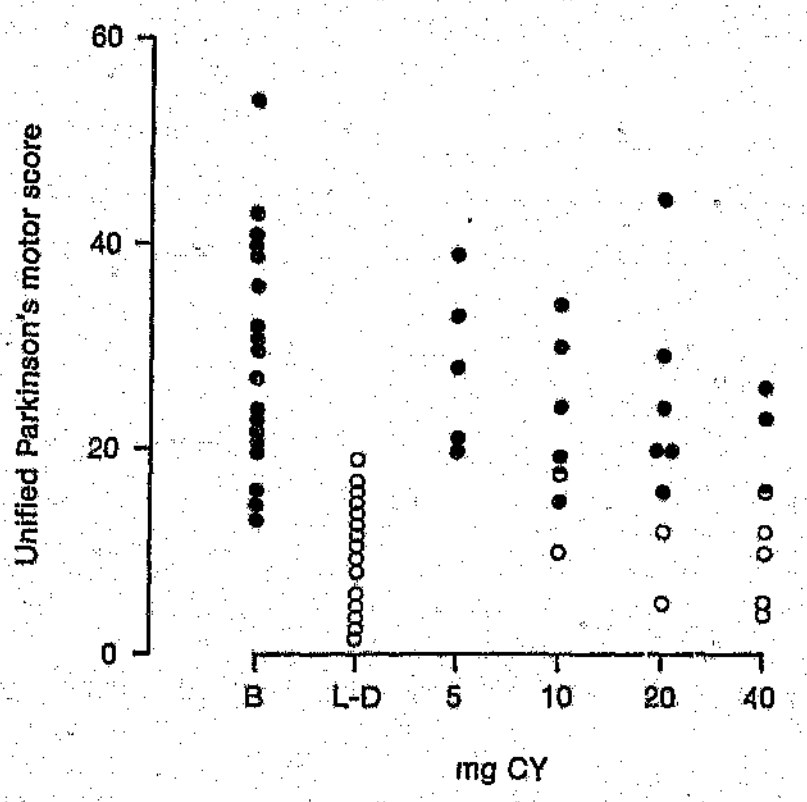


Fig 8.6

Motor disability scores in 8 patients grouped together following CY 20[illegible]243 (5-40 mg po) administration. Open circles (O) represent the 'on' mobile state, closed circles (●) the 'off' immobile state and semi-open circles (◓) the inbetween state.

all patients were rigid and akinetic, unable to walk alone and "off". Figure 8.5 and 6 shows the clinical response, judged by the motor disability scores of the UPDRS following each dose of CY 208-243 compared to their usual response to levodopa. After 10 mg po., one patient turned "on" fully and another patient partially "on".

Hence following doses less than 40 mg CY 208-243 po., only occasional improvements was noted. The full on response following 40 mg CY 208-243 po., occurred after 30-90 (median 2,5) minutes and lasted 30-150 (median 150) minutes after drug ingestion (Fig 8.6).

Dyskinesias occurred in two patients, in one exactly the same pattern as that following levodopa or D-2 dopamine receptor agonists. Nausea only occurred in two patients and drowsiness was noted in one case. No postural hypotension, neuropsychiatric complications, vomiting, significant laboratory or ECG abnormalities were found.

This study was published in the journal, Movement Disorders, (see Appendix VII).

Discussion

The novel D-1 selective agonist CY 208-243 has the capacity, in correct dosage, to turn advanced IPD patients "on" following levodopa withdrawal. It is safe, produced no serious side-effects attributable to the compound, but unfortunately has been withdrawn from further clinical studies in longer term use because hepatotoxicity has been noted in some patients. Animal models suggest the drug is a dopamine receptor selective and a partial agonist. It has exciting potential in advanced Parkinson's disease since this group of patients are often resistant to levodopa and D-2 selective agents. If able to correct Parkinsonian motor deficits alone, or by interacting with other agents the therapeutic prospects of a new group of drugs, namely the D-1 dopamine receptor modulators, will emerge. This study suggests that CY 208-243 is able to reverse fully advanced parkinsonism and in two instances actually produce dyskinesia hitherto thought to be a D-2 receptor mediated behavioural manifestation. The duration of the "on" response was short lived at 150 minutes, while a longer levodopa duration of benefit occurred in the same patients.

8.4 Discussion of the human trials in this thesis and the treatment of Parkinson's disease

Dopamine agonists are an important development in the treatment options facing Parkinsonian patients. While originally employed in advanced illness as adjuvant therapy, dopamine agonists are also being successfully employed early in the progression of the disease. Their efficacy combined with the absolute need to eventually supplement levodopa, has stimulated the development of multiple dopamine agonists that have not only been tested in animal models but also in man.

Advanced Parkinson's disease patients are difficult to manage since while patients become symptomatic with greater than 80% dopamine cell loss (Bernheimer et al., 1973), continued decline in nigrostriatal input causes the remaining SNc dopamine cells to work harder to increase their dopaminergic output (Agid et al., 1973). This excessive workload is limited and ultimately will fail. Also the striatal dopamine receptors multiply and become more receptive to endogenous dopaminergic input (Ungerstedt, 1971). This progression is inevitable and eventually so little dopamine output occurs that diminishing input into the striatum results in increasing symptoms in spite of exogenous levodopa supplementation. Hence patients become

less responsive to levodopa with disease progression. Another problem is the emergence of problems that are thought to be aggravated by exogenous levodopa itself. Clues that these problems could be attributed to levodopa therapy is that they are rarely reported prior to 1967 when levodopa was introduced into clinical practice.

Dyskinesias, "on-off" motor fluctuations, wearing-off phenomena and some forms of dystonia all occur with greater frequency in patients with earlier and larger doses of levodopa. Hence, whatever the reason, whether deterioration, disease progression or levodopa related limitations, a great need for alternate medication to supplement or even supersede levodopa is present. Dopamine agonists are one such option. While many adjuvant therapies exist, including monoamine oxidase inhibitors, amantadine, anticholinergics, tricyclic antidepressants, lithium, gaba-aminobutyric acid agonists, serotoninergic agents, baclofen, catechocol-O-methyltransferase inhibitors, or the various dopamine agonists, the latter remain the best option available.

At least two things are clear when analysing large cumulative experiences in multiple centres. Firstly patient groups vary regarding their responsiveness to different dopamine agonists initially employed and as they progress within themselves their responsiveness to drugs

will eventually change (Lieberman, 1988). Some patients respond better to different dopamine agonists. Similarly only some develop side-effects on one type but not other types of drugs. Secondly, the amount of supplementary levodopa required will influence the results of all dopamine agonists.

Hence an attempt to standardise the dose equivalents of the different drugs within the ergoline class is important. Comparisons could then be made with similar patient groups at similar stages of progression of the disease.

It is also evident that the D-1 and D-2 dopamine receptors are important both individually and in combination, when examining their function. Crucial to this interaction is the influence of levodopa, which is known to act at both receptor sites. Levodopa supplementation is thought to be beneficial because theoretically the levodopa that crosses the blood-brain barrier may be taken up by nigral neurones to re-establish nigrostriatal input. Dopamine is decreased at striatal dopamine receptors in advanced parkinsonism since patients have fewer and fewer remaining nigral cells. Hence levodopa efficacy declines. Dopamine agonists may circumvent this problem by acting directly at the postsynaptic receptor site. A theoretical danger of excessive chronic levodopa ingestion is the possibility

that levodopa itself may cause striatal dopamine receptors to become subsensitive (Markham et al., 1981 and Lesser et al., 1979). This will then physiologically blunt a valuable attempt of the brain to compensate. What then is the place of dopamine agonists and when would they be employed? Since two types of DA receptors exist, called D-1 and D-2, stimulation of either postsynaptic receptor will influence the striatum. Any molecule simulating dopamine at the receptor site theoretically will compete with dopamine to biochemically exert its influence. The ergoline group of drugs does this very effectively.

When dealing with end-stage disease with receptors have become unresponsive to declining dopamine, and theoretically this would not be the best time to initiate dopamine agonists. This is confirmed by patients who at end-stage illness do not respond to any pharmacological intervention, including dopamine agonists. Similarly destruction of the striatal receptors themselves such as occurs in dementia pugilstica, striatal degeneration or Wilson's disease, the benefit from dopamine agonists, or for that matter, levodopa is limited. Hence the best time to employ dopamine agonists would appear to be moderate stage illness and the trend today should be toward earlier utilisation. The possibility that early dopamine agonist use may delay the emergence of or prevent levodopa complications has also accelerated early utilisation of

dopamine agonists.

Unfortunately de novo dopamine agonists such as bromocriptine are insufficient in most patients. Many feel that dopamine agonists may be effective in mild IPD but cannot be employed indefinitely alone, since all eventually require levodopa in addition. However many useful years may be gained by sensible early use of dopamine agonists alone, thus delaying levodopa related problems.

Dopamine agonists are mainly of the D-2 type, but it may well be that simultaneous stimulation of both the D-1 and D-2 dopamine receptor is needed for maximal antiparkinsonian effects. The concept that D-1 receptor stimulation within itself may reverse parkinsonism is still to be further substantiated. Improvement in motor deficit may be mainly related to the D-2 receptor stimulation by D-2 agonists alone or perhaps greatest when empyoyed in combination with D-1 receptor agonists.

Bromocriptine was initially used in hyperprolactinaemic states since it was shown to reduce prolactin levels effectively (Corrodi et al., 1973). Successfully tested in animals, then man (Calne et al, 1974) it became the most widely used dopamine agonist to date. It was found particularly useful in patients who have developed limiting levodopa effects or in patients who cannot tolerate

levodopa. Bromocriptine was studied in this thesis to assess the overall ability to reduce overall levodopa requirements (Trial 1). While keeping patients in the same clinical stage, bromocriptine was successively built up from 20-50 mg/day, while simultaneously reducing levodopa. The best combination occurred at a mean of 26 mg/day bromocriptine with a consistent 30% reduction of levodopa. Bromocriptine usage may arbitrarily be subdivided into "low dose" and "high dose" the cut off being 30 mg/day (Lieberman, 1987). Therefore low dose bromocriptine was shown to improve the majority of patients since their overall levodopa requirements fell while mantaining stable clinical status. Lieberman (1987) reviewed the double-blind studies available, which indicate 58% of the patients improved while 9% patients experienced adverse effects. This leads to drug withdrawal in those on bromocriptine alone, but 71% of patients improve when bromocriptine is added to maintenance levodopa. Of the latter group, 26% developed side-effects. Overall, at least 61% of 706 patients improved. The suggestion is made that low dose bromocriptine be reserved for mild disease and high dose for moderate to advanced disease. Most patients in Trial 1 were moderate IPD patients and little improvement was seen in their states beyond a mean of 26 mg/day. Larger doses were not effective in obtaining mobility in the more advanced disease patients. In agreement with other investigators

the slow introduction of bromocriptine with incremental build up of the dose to 30 mg/day with levodopa is well tolerated. Very few could not complete this part of the trial.

Regarding the adverse effects encountered more dyskinesias and dystonia occurred, but non-significantly, in the placebo controlled phase compared to levodopa alone. In the open part of the trial, when levodopa was reduced, dyskinesias and dystonias were markedly reduced. Hence, if tolerated, bromocriptine added to less overall levodopa maintained mobility but with fewer involuntary movements. Bromocriptine, even in higher dosage, however was rarely sufficient to allow complete levodopa drug withdrawal. The only time this occurred was in mild and early disease.

Slow release levodopa administration Sinemet CR4 is advantageous compared with conventional Sinemet. The pharmacological slow release improves the "pulse" mode release, which is not the method by which endogenous dopamine stimulates the dopamine striatal receptors. Clearly CR4 pharmacokinetics offer a slower and more sustained release profile. Two main problems have emerged however. Firstly, the slower action of drug leaves patients distressed and immobile early in the day. Secondly, patients require increased overall levodopa administration. Unacceptable patient discomfort results,

reflected by the few that elected to stay upon CR4.

More worrying, however, is the possibility that excessive overall levodopa requirement may in itself be harmful in the long term. These assumptions remain hypothetical since they stem from observations of the patients with established levodopa complications and not from observations following early administration of slow release compounds. Given as a more continuous and sustained plasma levodopa concentration, it is posssible that slow release compounds may exert maximum benefit upon the dopamine receptors which may best respond, because of continuous (rather than intermittent) stimulation, in spite of higher overall levodopa dosage. The aim that once or twice daily levodopa administration will be sufficient, has not been reached (Ashkog et al., 1988: Cedarbaum et al., 1989). This study has shown that CR4 is well tolerated and a reduced dose frequency is possible compared to conventional Sinemet.

Limitation in the currently available D-2 dopamine agonists have led to research being conducted upon alternate D-2 and some D-1 compounds.

8.5 Discussion of novel dopamine agonists

CQA 206-291, a selective D-2 dopamine receptor agonist, has shown that it is effective in advanced IPD with motor fluctuations (Trial 3). In addition CQA 206-291 is effective in moderate disease and double-blind placebo matched studies (Trial 4). Our study showed CQA 206-291 able to reduce levodopa requirements by 35%. Keeping levodopa constant the double-blind study showed a steady improvement in the UPDRS score. While side effects are common, they are dose related and temporary. The efficacy compared to bromocriptine is yet to be established. This new D-2 ergoline is an effective and apparently safe anti-parkinsonian drug. It has a longer half-life than bromocriptine which in turn is longer lasting than levodopa. The capacity to turn advanced parkinsonian patients with fluctuations "on" and the duration of action, is dose related. No hepatic toxic effects were observed in animal models or man. Other preliminary studies communicate early efficacy and encouraging data but the long term effects and the possible long term side-effects are unknown.

CY 208-243, a D-1 selective partial agonist, given as a single morning dose to advanced parkinsonian fluctuating patients following levodopa withdrawal, clearly demonstrated its efficacy. CY 208-243 turned immobile, rigid, "off"

patients to mobile, less rigid state very similar to that obtained following their usual levodopa. While well tolerated in this trial (Trial 5) longer term studies at higher dose, 60 mg/day po., showed hepatotoxicity which has halted further human clinical studies. However CY 208-243 was well tolerated, produced no emesis or postural hypotension and supported animal data to suggest it has intrinsic anti-parkinsonian effects.

If confirmed that CY 208-243 is a D-1 'pure' agonist, the observation that it produced dyskinesias in two patients would be most interesting and important, since to date all dyskinetic movements are dose related to D-2 active drugs. However levodopa (D-1 and D-2 actions) produces dyskinesia. Either the drug has some as yet to be explained D-2 activity or dyskinesias may be not only a D-2 phenomenon but rather a D-1 receptor priming other dopamine receptor (possibly the D-2 receptor) effect.

8.6 The role of dopamine agonists in the therapy of Parkinson's disease

The best treatment of IPD today remains levodopa and when appropriate the introduction of supplementary drug therapy. Dopamine receptor agonist drugs provide a useful levodopa sparing effect, are efficacious in their own right

alone in de novo therapy of early IPD and are continually being improved upon. The functional role of the D-1 receptor, while unclear, has led to the development of many D-1 specific drugs and this in turn has created many exciting therapeutic options. Which functional combination of D-1 and D-2 dopamine receptor status is the best remains controversial. Hence the ultimate combination drug is not yet available, but appears closer to being developed. The possibility of D-3, and other dopamine receptors being discovered with the development of safe agonists and antagonists, will possibly answer many of these questions.

Antiparkinsonian drugs currently researched variably interact with D-1 sites, but have been thought to exert their major effect by acting upon D-2 sites. The concept that the D-2 receptor was the receptor to analyse antiparkinsonain drug efficacy came from an era prior to the introduction of D-1 specific drugs. Hence a re-examination of ideas and data is necessary to define better the role of the D-1 receptor alone and probably more importantly in concert with the D-2 receptors. Whether the D-1 receptor remains coupled to the D-2 receptor or acts independently, the D-1 receptor agonist drugs apparently may be potentially helpful in treating IPD. There are many more D-1 than D-2 receptors in the human striatum and what happens in human IPD regarding D-1 and D-2 receptors, in the primate models remains unclear. Because one finds

supersenitivity of both receptor populations, dopamine agonists remain potentially useful especially when combined with levodopa, in both the MPTP-treated primate and man.

After 15 years of bromocriptine usage the indications to supplement levodopa have emerged. In an attempt to reduce levodopa side-effects many prescribe bromocriptine early in the illness, some even suggest initial therapy with a dopamine agonist (Rinne 1989). Once levodopa side-effects occur even then bromocriptine may be useful to restore mobility, but with less dyskinesias, dystonia, "on-off" motor fluctuations and end-of-dose deterioration. Clearly it is wise to avoid these levodopa related problems by administering the lowest dose of levodopa that will restore function. The optimal dose of 20-30 mg/day, if tolerated, and the fact that in moderately severe IPD that bromocriptine alone cannot maintain functional mobility is clear (Rinne 1987). Also confirmed by other studies is the impression that less dyskinesias, dystonias, "on-off" and end-of-dose deterioration occur at the same level of mobility on the combination of bromocriptine plus levodopa versus levodopa alone. Bromocriptine is well tolerated in the long term and while relatively safe, still does produce side-effects which limit dosage.

Other D-2 agonists such as lisuride, pergolide, apomorphine, meselergine, terguride, CQ 32-084, CM 29-712,

(+)-PHNO and CQA 206-291 are all variably beneficial as antiparkinsonian agents. CQA 206-291 is attractive in that along with antiparkinsonian effects the drug does not drop the blood pressure or produce as many neuropsychiatric episodes as bromocriptine. It however, is more potent and in higher doses should be used with an anti-emetic, such as domperidone. Efficacy was established both in open phase dose ranging studies and in placebo matched longer term double-blind studies. Aside from fewer side-effects the agent is a similar antiparkinsonian agent to bromocriptine.

Slow release Sinemet CR4, an advanced generation matrix designed to release levodopa slowly with a prolonged half life, was disappointing in that the long latency effect reduced patient acceptability. However in those needing nocturnal mobility it produced clear benefit and potentially combined with conventional Sinemet may produce a better combination.

CY 208-243 was the first D-1 agonist employed in IPD. In advanced IPD the D-1 agonist clearly showed its ability to switch a patient "on" but this was shown against a back-ground of levodopa maintenance therapy. Patients were selected carefully as those easily differentiating "on" versus "off" and hence responded entirely to the CY 208-243 alone. What was even more interesting was that in at least 2 of them dyskinesias accompanied the "on" response,

suggesting that the D-1 receptor may also be important in the mechanisms contributing towards adverse side-effects.

All the above compounds have provided safe and effective antiparkinsonian activity and once more widely available may provide more acceptable alternatives when considering the best therapeutic option available to treat IPD today. The MPTP-treated primate marmoset has proved a useful model to employ in drug development. The model is sound regarding current theories of aetiology of Parkinson's disease - indeed it has added much useful information to the mechanisms of nigral dopaminergic cell death. Biochemically, histologically, electrophysiologically and even electromicroscopically the MPTP-treated primate has demonstrated consistent and reliable results to ensure this model will continue to be used to study parkinsonism. Utilising this behavioural model the effects of SKF 38393, CY 208-243, SCH 23390 and levodopa have been explored paying particular attention to the D-1 receptor. D-2 active agents in this thesis have included bromocriptine, (+)-PHNO, CQA 206-291, sulpiride and haloperidol either alone or in combination with D-1 active drugs. As a prelude to clinical application in humans with IPD, these agents demonstrated their benefit in the MPTP marmosets thus complimenting rodent preclinical data. CY 208-243 differs from the alternative partial D-1 agonist SKF 38393, in that the latter does not correct MPTP-induced parkinsonism or human IPD (Chase et

al., 1988). This agent, only the second D-1 selective agonist available has, thus stimulated further development of similar compounds. These new D-1 selective agonists are required to confirm data obtained with CY 208-243. Of interest was the fact that not only did CY 208-243 express antiparkinsonian effects in man with advanced disease but also in primates. The primates, both D-2 agonist naive and those who had had prior exposure to D-2 agonists, were in an ideal position to test D-1 responsiveness. Hence, as judged by the drug naive MPTP-treated marmoset, CY 208-243 would appear to possess intrinsic antiparkinsonian effects. This was only observed in the damaged nigrostriatal tract since the animals prior to receiving MPTP did not respond to CY 208-243. That CY 208-243 possessed mainly D-1 receptor activity was demonstrated by the attenuated response following SCH 23390. Whether any inadvertent D-2 agonist activity is part of CY 208-243's antiparkinsonian activity as suggested by its chemical structure being similar to other ergolines, and the partial attentuation of CY 208-243 activity by sulpiride priming, remains unknown.

(+)-PHNO administered subcutaneously, intraperitoneally, orally or even transdermally to marmosets showed it to be a potent and useful D-2 selective agonist. Its use in humans (Coleman et al., 1988) and the potential use of long term slow release plasters is now a reality. Interaction

studies utilising CY 208-243 and either levodopa or (+)-PHNO demonstrated a potentiation of low dosage and otherwise sub-therapeutic effects of the D-2 agonist drug.

This benefit is yet to be further tested in man, but suggestions that bromocriptine potentiate levodopa response indicate that functional interactions could exist (Rinne 1987; Calne, 1978). The role of the D-1 receptor may be permissive, additive or synergistic to maximal D-2 receptor expression.

CHAPTER 9

FINAL DISCUSSION

The ideal treatment of idiopathic Parkinson's disease is not yet available. While fetal transplantation remains experimental the best pharmacotherapy of the illness remains a crucial research objective.

Clues to the ultimate causes of dopamine cell death in the SNc are emerging and any step that retards cell death will delay the emergence of progressive symptoms. It is crucial to understand dopamine receptors, mainly D-2, but also D-1 and others (Todd et al., 1989; Schwartz et al., 1990; Monsma et al., 1989; Anderson et al., 1990; Van Tol et al., 1991; Sunahara et al., 1991), thereby allowing better drug manipulation and treatment.

This thesis set out to establish three principles:

1. How to best utilise levodopa, its long acting forms and bromocriptine to their maximal advantage. Patients with idiopathic Parkinson's disease were examined to place into perspective levodopa limitations, side-effects and how one

could possibly avoid them.

2. Novel selective D-1 and D-2 agonists were successfully tested in MPTP-treated marmosets. Methodology is discussed, the evaluation of the MPTP primate model has been considered and results derived from animal data used to facilitate testing of CQA 206-291 and CY 208-243 in man.

The D-2 agonists, as predicted from the MPTP-treated primate data, demonstrated potent antiparkinsonian motor benefit.

One D-1 agonist, CY 208-243 but not SKF 38393, also demonstrated antiparkinsonian motor benefit both in MPTP-treated primates and man with advanced Parkinson's disease. It remains to be confirmed if the antiparkinsonian efficacy and indeed the dyskinesias seen, are D-1 mediated, or whether CY 208-243 has some as yet unknown other dopamine receptor effects.

3. Combination experiments utilising selective D-1 and D-2 dopamine agonists were initiated in the MPTP-treated primates, in attempt to identify the most suitable antiparkinsonian state. This has long been examined with levodopa and adjuvant D-2 agonist therapy in man, both to potentiate levodopa benefit and reduce levodopa related side-effects. The most suitable D-1, D-2 , D-3 and other

receptor combination with maximal antiparkinsonian motor effects plus the least side-effects has yet to be established.

Development of other selective dopamine receptor agonists and antagonists, especially D-3, D-4, D-5 and other dopamine receptor subsets as yet not available, hopefully will stimulate further research, understanding and ultimately offer better treatment strategies in the treatment of idiopathic Parkinson's disease.

BIBLIOGRAPHY

Adams R D, Salam-Adams M. Striatonigral degeneration. In: Vinken P J, Bruyn C W, Klawans H L, eds. Handbook of Clinical Neurology Vol 5 (49): Extrapyramidal disorders. Amsterdam: Elsevier Science Publishers B V, 1986: 205-212.

Adams R D, van Bogaert L, van der Eecken H. Striato-nigral degeneration. J Neuropathol Exp Neurol 1964; 23: 584-608.

Aghajanian G K, Bunney B S. Dopamine 'autoreceptors': pharmacological characterization by microiontophoretic single cell recordings studies. Arch Pharm 1977; 297: 1-7.

Agid Y, Pollak P, Bonnet A M, Signoret J L, Lhermitte F. Bromocriptine associated with peripheral dopamine blocking agent in the treatment of Parkinson's disease. Lancet 1979; i: 570-572.

Agid Y, Javoy-Agid F, Ruberg M. Biochemistry of neurotransmitters in Parkinson's disease. In: Marsden C D, Fahn S, eds. Movement disorders 2. London: Butterworth, 1987: 166-230.

Agid Y, Javoy F, Glowinski J. Hyperactivity of remaining dopaminergic neurons after partial destruction of the nigrostriatal dopaminergic system in the rat. Nature 1973; 245: 150-151.

Agid Y, Javoy-Agid F. Peptides and Parkinson's disease. Trends Neurosci 1985; 8: 30-35.

Agid Y, Ruberg M, Dubois B, Javoy-Agid F. Biochemical substrates of mental disturbances in Parkinson's Disease. Adv Neurol 1984; 40:211-218.

Ahlquist R P. A study of the adrenotropic receptors. Am J Physiol 1948; 153: 586-600.

Ahlskog J E, Manfred M D, Muenter M D, McManis P G, Bell G N, Bailey P A. Controlled-release Sinemet (CR-4): A double-blind crossover study in patients with fluctuating Parkinson's disease. Mayo Clin Proc 1988; 63: 876-886.

Alander T, Andén N-E, Grabowska-Andén M. Metoclopramide and sulpiride as selective blocking agents of pre-and postsynaptic dopamine receptors. Arch Pharm 1980; 312: 145-150.

Albanese A, Bentivoglio M. The organization of dopaminergic and non-dopaminergic mesencephalocortical neurons in the rat. Brain Res 1982; 238: 421-425.

Albanese A, Minciacchi D. Organization of the ascending projections from the ventral tegmental area: a multiple fluorescent retrograde tracer study in the rat. J Comp Neurol 1983; 216: 406-420.

Alexander G E, De Long M R, Strick P L. Parrallel organisation of functionally segregated circuits linking basal ganglia and cortex. Ann Rev Neurosci 1986; 9: 357-381.

Allen G S, Burns R S, Tulpan N B, Parker R A. Adrenal medullary transplantation to the caudate nucleus in

Parkinson's disease: initial clinical results in 18 patients. Arch Neurol 1989; 46: 487-491.

Andén N E, Carlsson A, Dahlström A, Fuxe K, Hillarp N A, Larsson K. Demonstrating and mapping out of nigro-neostriatal dopamine neurons. Life Sci 1964; 3: 523-530.

Andén N E, Dahlström A, Fuxe K, Larsson K. Mapping out of catecholomine and 5-hydroxytryptamine neurons innervating the telencephalon and diencephalon. Life Sci 1965; 4: 1275-1279.

Andén N E, Dahlström A, Fuxe K, Larsson K, Olson L, Ungerstedt U. Ascending monoamine neurons to the telencephalon and diencephalon. Life Sci 1966; 67: 313-326.

Andén N E, Fuxe K, Hamberger B, Hökfelt T. A quantitative study on the nigro-striatal dopamine neuron system in the rat. Acta Physiol Scand 1966; 67: 306-312.

Andersen P. Brain slices - a neurobiological tool of increasing usefullness. Trends Neurosci 1981; 4: 53-56.

Anderson P H, Gingrich J A, Bates M D, et al. Dopamine receptor subtypes: beyond the D1/D2 classification Trends Pharm Sci 1990: 11: 231-236.

Andrews C D, Woodruff G N. Turning behaviour following nigral injections of dopamine agonists and glycine. Eur J Pharmacol 1982; 84: 169-175.

Arbuthnott G, Dunnett S B, Macleod N. Electrophysiological properties of single units in dopamine-rich mesencephalic transplants in rat brain. Neurosci Lett 1985; 57: 205-210.

Armstrong P W, Armstrong J A, Marks G S. Pharmacokinetic-hemodynamic studies of nitroglycerin ointment in congestive heart failure. Am J Cardiol 1980; 46: 670-676.

Arnt J, Christensen A V. Differential reversal by scopolamine and THIP of the antistereotypic and cataleptic effects of neuroleptics. Eur J Pharmacol 1981; 69: 107-111.

Arnt J, Christensen A V, Hyttel J. Differential reversal by scopolamine of effects of neuroleptics in rats. Relevance for evaluation of therapeutic and extrapyramidal side-effect potential. Neuropharmacology 1981; 20: 1331-1334.

Arnt J. Pharmacological specificity of conditioned avoidance response inhibition in rats. Inhibition by neuroleptics and correlation to dopamine receptor blockade. Acta Pharmacol Toxicol 1982; 51: 321-329.

Arnt J. Differential effects of neuroleptics on 3-PPP and amphetamine induced circling behaviour in 6-hydroxy-dopamine lesioned rats. Br J Pharmacol 1982; 77: 308.

Arnt J, Bogeso K P, Christensen A V, Hyttel J, Larsen J-J, Svendsen O. Dopamine receptor agonistic and antagonistic effects of 3-PPP enantiomers. Psychopharmacology 1983; 81: 199-207.

Arnt J. Neuroleptic inhibition of 6,7-ADTN-induced hyperactivity after injection into the nucleus accumbens. Specificity and comparison with other models. Eur J Pharmacol 1983; 90: 47-55.

Arnt J. Differential behavioural effects of dopamine agonists in developing rats: A study of 3-PPP enantiomers. Eur J Pharmacol 1983; 91: 273-278.

Arnt J, Bogeso K P, Hyttel J, Larsen J-J, Svendsen O. Effects of S(+)-3-phenethyl-PP, a putative dopamine autoreceptor agonist with greater autoreceptor selectivity than 3-PPP enantiomers. Eur J Pharmacol 1984; 102: 91-99.

Arnt J, Hyttel J. Differential inhibition by dopamine D1 and D2 antagonists of circling behaviour induced by dopamine agonists in rats with unilateral 6-hydroxy-dopamine lesions. Eur J Pharmacol 1984; 102: 349-354.

Arnt J, Hyttel J. Postsynaptic dopamine agonistic effects of 3-PPP enantiomers revealed by bilateral 6-hydroxy-dopamine lesions and by chronic reserpine treatment in rats. J Neural Trans 1984; 60: 205-223.

Arnt J. Antistereotypic effects of dopamine D1 and D2 antagonists after intrastriatal injection in rats. Pharmacological and regional specificity. Arch Pharm 1985; 330: 97-104.

Arnt J. Behavioural stimulation is induced by separate D1 and D2 receptor sites in reserpine-pretreated but not in normal rats. Eur J Pharmacol 1985; 113: 79-88.

Arnt J. Hyperactivity induced by stimulation of separate dopamine D1 and D2 receptors in rats with bilateral 6-OHDA lesions. Life Sci 1985; 37: 717-723.

Arnt J, Hyttel J. Differential involvement of dopamine D1 and D2 receptors in the circling behaviour induced by apomorphine, SK & F 38393, pergolide and LY171555 in 6-hydroxydopamine-lesioned rats. Psychopharmacol 1985; 85: 346-352.

Arnt J. Independent dopamine D1 and D2 receptor regulation of dopamine agonist-induced hyperactivity in

6-OHDA-lesioned, but not in normal rats. In: Woodruff G N ed. Dopamine Systems and Their Regulations. London: MacMillan, 1986: 449-450.

Arnt J. Behavioural studies of dopamine receptors: Evidence for regional selectivity and receptor multiplicity. Dopamine Receptors 1987; 199-231.

Asher I M, Aghajanian G K. 6-hydroxydopamine lesions of olfactory tubercles and caudate nuclei: Effects on amphetamine-induced stereotyped behavior in rats. Brain Res 1984; 82: 1-12.

Backlund E-O, Granberg P O, Hamberger B, et al. Transplantation of adrenal medullary tissue to striatum in parkinsonism: First clinical trials. J Neurosurg 1985; 62: 169-173.

Backlund E-O, Olson L, Seiger A, Lindvall O. Toward a transplantation therapy in Parkinson's disease: a progress report from continuing clinical experiments. Ann NY Acad Sci 1987; 495: 658-673.

Bakay R A E, Fiandaca M S, Barrow D L, Schiff A, Collins D C. Preliminary report on the use of fetal tissue transplantation to correct MPTP-induced Parkinson-like syndrome in primates. Appl Neurophysiol 1985; 48: 358-361.

Bakay R A E, Barrow D L, Fiandaca M S, Iuvone P M, Schiff A, Collins D C. Biochemical and behavioral correction of MPTP Parkinson-like syndrome by fetal cell transplantation. Ann N Y Acad of Sci 1987; 495: 623-638.

Ballard P A, Langston J W, Tetrud J W, Burns R S. Chemically induced chronic parkinsonism in young

adults: clinical and neuropharmacologic aspects. Neurology 1983; 33: 90.

Ballard P A, Tetrud J W, Langston J W. Permanent human parkinsonism due to 1-methyl-4-phenyl-1,2,3,6-tetra-hydropyridine (MPTP): seven cases. Neurology 1985; 35: 949-956.

Bannister R, Oppenheimer D R. Degenerative diseases of the nervous system associated with autonomic failure. Brain 1972; 95: 457-474.

Barbeau A. Preliminary observation on abnormal catecholamine metabolism in basal ganglia disease. Neurology 1960; 10: 446-451.

Barbeau A. Biochemistry of Parkinson's Disease. International Congress Series 1961; 38: 152-153.

Barbeau A, Murphy G F, Sourkes T L. Excretion of dopamine in diseases of basal ganglia. Science 1961; 133: 1706-1707.Barbeau A, Sourkes T L, Murphy G F. Les Catécholamines dans la maladie de Parkinson. In: Ajuriaguerra J, ed. Monoamines et Système Nerveux Central, Symposium Bel-Air. Geneva: Georg & Co., 1962: 247-262.

Barbeau A. L-Dopa therapy in Parkinson's disease: A critical review of nine years experience. Can Med Ass J 1969; 101: 59-68.

Barbeau A. Long term side effects of levodopa. Lancet 1971; i: 395.

Barbeau A, Pourcher E. New data on the genetics of Parkinson's disease. Can J Neurol Sci 1982; 9: 53-60.

Barbeau A, Roy M. Familial subsets in idiopathic Parkinson's disease. Can J Neurol Sci 1984; 11: 144-150.

Barbeau A, Roy M, Langston J W. Neurological consequence of induxtrial exposure to 1-methyl-4-phenyl-1,2,3,6-tetra-hydropyridine. Lancet 1985; i: 747.

Barbeau A, Roy M, Pari S, Clou , Plasse L, Poirier J. Ecogenetics of Parkinson's disease: 4-hydroxylation of debrisoquine. Lancet 1985; ii: 1213-1216.

Barbeau A, Dallaire L, Buu N T, Veilleux F, de Boyer H, Lanney L E, Irwin I, Langston E B, Langston J W. New amphibian models for the study of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Life Sci 1985; 36: 1125-1134.

Barone P, Davis T A, Braun A R, Chase T N. Dopaminergic mechanisms and motor function: characterisation of D-1 and D-2 dopamine receptor interactions. Eur J Pharmacol 1986; 123: 109-114.

Battista A, Fuxe K, Goldstein M, Ogawa M. Mapping of central monoamine neurons in the monkey. Experientia 1972; 28: 688-690.

Bawa R, Siegel R A, Marasca B, et al. An explanation for the controlled release of macromolecules from polymers. J Controlled Release 1985; 1: 259-267.

Beaulieu M. Clinical importantce of D1 and D2 receptors. Can J Neurol Sci 1987; 14(3)(suppl): 402-406.

Beckstead R M. Convergent prefrontal and nigral projections to the striatum of the rat. Neurosci Lett 1979; 12: 59-64.

Berger B, Tassin J P, Blanc B, Moyne M A, Thierry A M. Histochemical confirmation for dopaminergic innervation of the rat cerebral cortex after destruction of the noradrenergic ascending pathways. Brain Res 1974; 81: 332-337.

Bernheimer H, Birkmayer W, Hornykiewicz O, Jellinger K, Seitelberger F. Brain dopamine and the syndromes of Parkinson and Huntington - Clinical, morphological and neurochemical correlations. J Neurol Sci 1973; 20: 415-455.

Bernheimer H, Birkmeyer W, Hornykiewicz O, et al. Brain dopamine and the syndromes of Parkinson and Huntington. J Neurol Sci 1973; 20: 415-445.

Bernheimer H, Birkmayer W, Hornykiewicz O. Verhalten der monoaminoxydase im gehirn des menschen nach therapie mit monoaminoxydase hemmern. Wien Klin Wochenschr 1962; 74: 558-559.

Bernheimer H, Hornykiewicz O. Das verhalten einiger enzyme im gehirn normaler und Parkinson-kranker menschen. Archiv für Experimentelle Pathologie und Pharmakologie 1962; 243: 295-299.

Berridge M J, Irvine R F. Inositol trisphosphate, a novel second messenger in cellular signal transduction. Nature 1984; 312: 315-321.

Bertler A, Falck B, Gottfries C G, Ljunggren L, Rosengren E. Some observations on adrenergic connections between the mesencephalon and the cerebral hemispheres. Acta Pharmacol Toxicol 1964; 21: 283-289.

Biket-Smith E, Bottcher J, Dupont E. Dopaminergic agonist RO8,4650 in Parkinson's disease: Patients treated with dopa. Acta Neurol Scand 1978; 58: 74-76.

Billard W, Ruperto V, Crosby G, Iorio L C, Barnett A. Characterization of the binding of ^{3}H-SCH 23390, a selective D-1 receptor antagonist ligand, in rat striatum. Life Sci 1984; 35: 1885-93.

Birkmayer W, Riederer P, Youdin M B H, Linauer W. The potentiation of the anti-akinetic effect after L-dopa treatment by an inhibitor of MAO-B, Deprenil. J Neural Transm 1975; 36: 303-326.

Birkmayer W, Riederer P, Ambrozi L, Youdim M B H. Implications of combined treatment with Madopar and L-deprenyl in Parkinson's disease. Lancet 1977; i: 439-443.

Birkmayer W, Hornykiewicz O. Der L-3,4-dioxyphenyl-alanin (L-Dopa) - Effekt bei der Parkinson-Akiniese. Wien Klin Wochenschr 1961; 73: 787-788.

Birkmayer W, Riederer P. Parkinson's disease: Biochemistry, Clinical Pathology and Treatment. Berlin: Springer-Verlag 1980.

Birkmayer W, Knoll J, Riederer P, et al. Increased life expectancy resulting from addition of L-deprenyl to madopar treatment in Parkinson's disease: A longterm study. J Neural Transm 1985; 64(2): 113-127.

Bischoff S, Bittiger H, Delini-Stula A, Ortman R. Septo-hippocampal system: Target for substituted benzamides. Eur J Pharmacol 1982; 79(3-4): 225-232.

Bischoff S, Heinrich M, Kraus J, Sills M A, Williams M, Vassout A. Interaction of the D-1 receptor antagonist SCH 23390 with the central 5-HT system: radioligand binding studies, measurements of biochemical parameters and effects on L-5-HTP syndrome. J Recept Res 1988; 8: 107-112.

Bizière K, Gueudet C, Worms P. Turning induced by intrastriatal injections in conscious mice: A useful screening model for dopaminomimetic drugs. Br J Pharmacol 1985; 85: 385-387.

Björklund A, Nobin A. Fluorescence histochemical and microspectrofluorometric mapping of dopamine and noradrenaline cell groups in the rat diencephalon. Brain Res 1973; 51: 193-205.

Björklund A, Lindvall O, Nobin A. Evidence of an incertohypothalamic dopamine neurone system in the rat. Brain Res 1975; 89: 29-42.

Björklund A, Divac I, Lindvall O. Regional distribution of catecholamines in monkey cerebral cortex, evidence for a dopaminergic innervation of the primate prefrontal cortex. Neurosci Lett 1978; 7: 115-119.

Björklund A, Stenevi U. Reconstruction of the nigrostriatal dopamine pathway by intracerebral nigral transplants. Brain Res 1979; 177: 555-560.

Björklund A, Schmidt R H, Stenevi U. Functional reinnervation of the neostriatum in the adult rat by use of intraparenchymal grafting of dissociated cell suspensions from the substantia nigra. Cell Tissue Res 1980; 212: 39-45.

Björklund A, Dunnett S B, Stenevi U, Lewis M E, Iversen S D. Reinnervation of the denervated striatum by substantia nigra transplants: functional consequences as revealed by pharmacological and sensorimotor testing. Brain Res 1980; 199: 307-333.

Björklund A, Stenevi U, Dunnett S B, Iversen S D. Functional reactivation of the deafferented neostriatum by nigral transplants. Nature 1981; 298: 497-499.

Björklund A, Stenevi U, Dunnett S B, et al. Cross species neural grafting in a rat model of Parkinson's disease. Nature 1982; 298: 652-654.

Björklund A, Stenevi U, Schmidt R H, Dunnett S B, Gage F H. Intracerebral grafting of neuronal cell suspensions. I. Introduction and general methods of preparation. Acta Phys Scand 1983; 522 (suppl): 1-10.

Björklund A, Stenevi U, Schmidt R H, Dunnett S B, Gage F H. Intracerebral grafting of neuronal cell suspensions. II Survival and growth of nigral cell suspensions implanted in different brain sites. Acta Phys Scand 1983; 522 (suppl): 9-18.

Björklund A, Lindvall O. Dopamine-containing systems in the CNS. In: Björklund A, Hökfelt T, eds. Handbook of chemical neuroanatomy, Vol 2. Classical transmitters in the CNS, Part I. Amsterdam: Elsevier, 1984: 55-122.

Björklund A, Stenevi U. Intracerebral neural implants: Neuronal replacement and reconstruction of damaged circuitries. Ann Rev Neurosci 1984; 7: 279-308.

Björklund A, Lindvall O. Dopamine-containing brainstem regulatory systems. In: Bloom F E, ed. Handbook of Physiology Vol 4. Integrative systems. Baltimore: Williams and Wilkins, 1984.

Björklund A, Gage F H. Neural grafting in animal models of neurodegenerative disease. Ann NY Acad Sci 1985; 457: 53-76.

Björklund A, Lindvall O, Isacson O, et al. Mechanisms of action of intracerebral neural implants: studies on nigral and striatal grafts to the lesioned striatum. Trends Neurosci 1987; 10: 509-515.

Björklund A, Brundin P, Isacson O. Neuronal replacement by intracerebral neural implants in animal models of neurodegenerative disease. Adv Neurol 1988; 47: 455-493.

Bohn M C, Cupit L, Marciano F, Gash D J. Adrenal medulla grafts enhance recovery of striatal dopaminergic fibres. Science 1987; 237(4817): 913-916.

Bokobza B, Ruberg M, Scatton B, Javoy-Agid F, Agid Y. [^{3}H]spiperone binding, dopamine and HVA concentrations in Parkinson's disease and supranuclear palsy. Eur J Pharm 1984; 99: 167-175.

Bolam J P. Synapses of identified neurons in the neostriatum. In: Functions of the Basal Ganglia. Ciba Foundation Symposium Pitman, London 1984; 107: 30-47.

Boyce S, Kelly E, Reavill C, Jenner P, Marsden C D. Repeated administration of n-methyl-4-phenyl-1,2,3,6-tetrahydropyridine to rats is not toxic to striatal dopamine neurons. Biochem Pharmacol 1984; 33: 1747-1752.

Bradbury A J, Costall B, Naylor R J. Inhibition and facilitation of motor responding of the mouse by actions of dopamine agonists in the forebrain. Neuropharmacology 1984; 23: 1025-1031.

Bradbury A J, Costall B, Domeney A M, et al. 1-Methyl-4-phenylpyridine is neurotoxic to the nigrostriatal dopamine pathyway. Nature 1986; 319: 56-57.

Brain R. Diseases of the Nervous System. London: Oxford University Press, 1955; 538-550.

Braun A, Barone P, Chase T N. Interaction of D-1 and D-2 dopamine receptors in the expression of dopamine

agonist induced behaviours. In: Breese G R, Creese I, eds. Neurobiology of Central D-1 Dopamine Receptors. New York: Plenum Press, 1986: 151-166.

Braun A, Fabbrini G, Mouradian M M, Serrati G, Barone P and Chase T N. Selective D-1 dopamine receptor agonist treatment of Parkinson's disease. J Neural Transm 1987; 68: 41-50.

Bridges T E, Hillhouse E W, Jones M T. The effect of dopamine on neurohypophyseal hormone release in vivo and from the rat neural lobe and hypothalamus in vitro. J Physiol 1976; 260: 647-666.

Brooks D J, Frackowiak R. PET and movement disorders. J Neurol Neurosurg Psychiatry 1989; 52 (Suppl): 68-77.

Brown J H, Makman M H. Influence of neuroleptic drugs and apomorphine on dopamine-sensitive adenylate cyclase of retina. J Neurochem 1973; 21: 477-479.

Brown G, Seeman P, Lee T. Dopamine/neuroleptic receptors in basal hypothalamus and pituitary. Endocrinology 1976; 99: 1407 - 1410.

Brown E M, Carroll R J, Aurbach G D. Dopaminergic stimulation of cyclic AMP accumulation and parathyroid hormone release from dispersed bovine parathyroid cells. Proc N Acad Sci USA 1977; 74: 4210-4213.

Brown R M, Crane A M. Goldman P S. Regional distribution of monoamines in the cerebral cortex and subcortical structures of the rhesus monkey: concentrations and in vivo synthesis rates. Brain Res 1979; 168: 133-150.

Brown L L, Makman M H, Wolfson L I, Dvorkin B, Warner C, Katzman R. A direct role of dopamine in the rat subthalamic nucleus and an adjacent intrapeduncular area. Science 1979; 206: 1416-1418.

Brown R G, Marsden C D. How common is dementia in Parkinson's disease? Lancet 1984; ii: 1262-1265.

Browning M D, Huganir R, Greengard O. Protein phosphorylation and neuronal function. J Neurochem 1985; 45: 11-23.

Brun A, Englund E. Regional pattern of degeneration in Alzheimer's disease: neuronal loss and histopathological grading. Histopathology 1981; 5: 549-564.

Brundin P, Nilsson O G, Gage F H, Björklund A. Cyclosporin A increases survival of cross-species intrastriatal grafts of embryonic dopamine-containing neurons. Exp Brain Res 1985; 60: 204-208.

Brundin P, Björklund A. Survival growth and function of dopaminergic neurons grafted to the brain. Prog Brain Res 1987; 71: 293-308.

Brundin P, Isacson O, Björklund A. Monitoring of cell viability in suspensions of embryonic CNS tissue and its use as a criterion for intracerebral graft survival. Brain Res 1985; 331: 251-259.

Brundin P, Nilsson O G, Strecker R E, et al. Behavioural effects of human fetal dopamine neurones grafted in a rat model of Parkinson's disease. Exp Brain Res 1986; 65: 235-240.

Brundin P, Strecker R E, Widner H, et al. Human fetal dopamine neurones grafted in a rat model of Parkinson's disease: immunological aspects, spontaneous and drug-induced behaviour, and dopamine release. Exp Brain Res 1988; 70: 192-208.

Bunney B S, Walters J R, Roth R H, Aghajanian G K. Dopaminergic neurons: effect of antipsychotic drugs and amphetamine on single cell activity. J Pharmacol Exp Ther 1973; 185: 560-571.

Burke R, Fahn S. Pharmacokinetics of trihexyphenidyl after acute and chronic administration. Ann Neurol 1982; 12:94-97.

Burns R S, Chiueh C C, Markey S P, Ebert M H, Jacobowitz D M, Kopin I J. A primate model of parkinsonism: selective destruction of dopaminergic neurons in the pars compacta of the substantia nigra by N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. Proc Natl Acad Sci USA 1983; 80: 4546-4550.

Burns R S, Le Witt P A, Ebert M H, Pakkenberg H, Kopin I J. The clinical syndrome of striatal dopamine deficency. Parkinsonism induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. New Engl J Med 1985; 312: 1418-1421.

Burns R S, Gopinathan G, Humpel M et al. The pharmacokinetics of lisuride in parkinsonian patients. Neurology 1981; 31: 49-50.

Burns R S, Allen G S, Tulipan N B. Adrenal medullary transplants as a treatment for Parkinson's disease: A review Adv Neurol 1990; 53: 571-576.

Burton K, Larsen T A, Robinson G. Mesulergine for Parkinson's disease: a comparison with bromocriptine. Neurology 1984; 34(suppl): 159-165.

Bush D F, Liss C L, Morton A, and the Sinemet CR Multicenter Study Group. An open multicentre long-term treatment evaluation of Sinemet CR. Neurology 1989; 39(suppl 2): 101-104.

Calne D B, Williams A C, Neophytides A. Long-term treatment parkinsonism with bromocriptine. Lancet 1978; i: 735-738.

Calne D B, Langston J W, Martin W R W, Stoessl A J, Ruth T J, Adam M J, Pate B D and Schulzer M. Positron emission tomography after MPTP: Observations relating to the cause of Parkinson's disease. Nature 1985; 317: 246-248.

Calne D B, Teychenne P F, Claveria L E, Eastman R, Greenacre J K, Petrie A. Bromocriptine in parkinsonism. Br Med J 1974; 4: 422-444.

Calne D B, Duvoisin R C, McGeer E. Speculations on the etiology of Parkinson's disease. Adv Neurol 1983; 40: 353-360.

Calne D B, Langston J W. Hypothesis: Aetiology of Parkinson's disease. Lancet 1983; i: 1457-1459.

Calne D B, Eisen A, McGeer E, Spencer P. Alzheimer's disease, Parkinson's disease, and motor neurone disease: Abiotrophic interaction betw en ageing and environments? Lancet 1986; ii: 1067-70.

Calne S, Schoenberg B, Martin W, Utti R J, Spencer P, Calne D B. Familial Parkinson's disease: possible role of environmental factors. Can J Neurol Sci 1987; 14(3): 303-305.

Cannon J G, Costall B, Laduron P M, Leysen J E, Naylor R J. Effects of some derivatives of 2-aminotetralin on dopamine-sensitive adenylate cyclase and on the binding of ^{3}H-haloperidol to neuroleptic receptors in the rat striatum. Biochem Pharmacol 1978; 27: 1417-1420.

Cannon J G, Hsu F-L, Long J P, Flynn J R, Costal B, Naylor R J. Preparation and biological actions of some symmetrically N,N-di-substituted dopamines. J Med Chem 1978; 21: 248-253.

Cannon J G, Lee T, Ilhan M, Koons J, Long J P. 6-Hydroxy-4-[2-(di-n-propylamino)ethyl)]-indole: Synthesis and dopaminergic actions. J Med Chem 1984; 27: 386-389.

Canter G J, de la Torre R, Mier M. A method for evaluating disability in patients with Parkinson's disease. J Nerv Ment Dis 1961; 7: 133-143.

Caraceni T, Giovannini P, Girotti F, Pederozoli M, Scigliano G. Long term evaluation of combined treatment of Parkinson's Disease with L-dopa, peripheral decarboxylase inhibitors and bromocriptine. Ital J Neurol Sci 1981; 2: 337-342.

Carlsson A, Lindquist M, Magnusson T. 3,4-Dihydroxy-phenyl-alanine and 5-hydroxytryptophan as reserpine antagonists. Nature 1957; 180: 1200-1204.

Carlsson A, Lindquist M, Magnusson T, Waldeck B. On the presence of [^{3}H]-hydroxytyramine in brain. Science, 1958; 127: 471.

Carlsson A. Receptor-mediated control of dopamine metabolism. In: Usdin E, Bunney E, eds. "Pre and Postsynaptic Receptors. New York: Marcel Dekker, 1975: 49-63.

Carlsson A. Dopamine receptor agonists: Intrinisic activity vs. state of receptor. J Neural Transm 1983; 57: 309-315.

Carlson J H, Debra A, Bergstrom D A, Walters J R. Stimulation of both D1 and D2 dopamine receptors

appears necessary for full expression of postsynaptic effects of dopamine agonist; a neurophysiological study. Brain Res 1987; 400: 205-218.

Caron M G, Beaulieu M, Raymond V, Gagne B, Drouin J, Lefkowitz R J, Labrie F.
Dopaminergic receptors in the anterior pituitary gland. Correlation of [^{3}H dihydroergocryptine binding with the dopaminergic control of prolactin release.
J Biol Chem 1978; 253(7): 2244-2253.

Carpenter M B, Batton R R, Carleton S C, Keller J T.
Interconnections and organization of pallidal and subthalamic nucleus neurons in the monkey. J Comp Neurol 1981; 197: 579-603.

Carpenter M B, Batton R R , Carleton S C, Keller J T.
Interconnections and organization of pallidal and subthalamic nucleus neurons in the monkey. J Comp Neurol 1981; 197: 579-603.

Carpenter M B, Carleton S C, Keller J T, Conte P.
Connections of the subthalamic nulceus in the monkey. Brain Res 1981; 224: 1-29.

Casey D E. Amantadine intoxication reversed by physostigmine. N Engl J Med 1978; 298: 516.

Cash R, Ruberg M, Raisman R, Agid Y. Adrenergic receptors in Parkinson's disease. Brain Res 1984; 322: 269-275.

Cedarbaum J M, Breck L, Kutt H, McDowell F H. Controlled-release levodopa/carbidopa. I. Sinemet CR3 treatment of response fluctuations in Parkinson's disease. Neurology 1987; 37: 233-241.

Cedarbaum J M, Breck L, Kutt H, McDowell F H.
Controlled-release levodopa/carbidopa. II. Sinemet CR4

treatment of response fluctuations in Parkinson's disease. Neurology 1987; 37: 1607-1612.

Chapman L J, Peters H A, Mathews C C, Levine R L. Parkinsonism and industrial chemicals. Lancet 1987; i: 332-333.

Charcot J M. On paralysis agitans. (Lecture V). In: G Sigerson (trans): ed. Lectures on the diseases of the Nervous System. London: New Sydenham Society, 1877: 129-156.

Charcot J M. Cinquième lecon: De la paralysie agitant. Maladies de système Nerveux 1880; 1: 155-188.

Chase T N. Parkinson's disease - Modification by 5-hydroxytryptophan. Neurology 1972; 22: 479-484.

Chase T N, Woods A C, Glaubiger G A. Parkinson's disease treated with a suspected dopamine receptor agonist. Arch Neurol 1974; 30: 383-386.

Chase T N. Pharmacokinetics of controlled-release formulations: Moderator's Summary. Neurology 1989; 39: 59.

Chaudhuri K R, Critchley P, Abbott R J, Pye I F, Millac P A H. Subcutaenous apomorphine for on-off oscillations in Parkinson's disease. Lancet 1988; ii: 1260

Cheramy A, Leviel V, Glowinski J. Dendritic release of dopamine in the substantia nigra. Nature 1981; 289: 537-542.

Chiba K, Trevor A, Castagnoli N. Metabolism of the neorotoxic tertiary amine, MPTP, by brain monoamine oxidase. Biochem Biophys Res Commun 1984; 120: 574-578.

Chiueh C, Markey S P, Burns R S, Johannessen J, Pert A, Kopin I J. Neurochemical and behavioural effects of systemic and intranigral administration of N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine in the rat. Eur J Pharmacol 1984; 100: 189-94.

Chivers J K, Gommeren W, Leysen J E, Jenner P, Marsden C D. Comparison of the in vitro receptor selectivity of substituted benzamide drugs for brain neurotransmitter receptors. J Pharmacol 1988; 40: 415.

Christensen A V, Arnt J, Hyttel J, Larsen J-J, Svendsen O. Pharmacological effects of a specific dopamine D1 antagonist SCH23390 in comparison with neuroleptics. Life Sci 1984; 34: 1529-1540.

Christensen A V, Arnt J, Hyttel J, Svendsen O. Behavioural correlates to the dopamine D1 and D2 antagonists. Pol J Pharmacol Pharm 1984; 36: 249-264.

Clark D and White F J. Review: D1 dopamine receptor - the search for a function: A critical evaluation of the D1/D2 dopamine receptor classification and its functional implications. Synapse 1987; 1: 347-388.

Clark D, Hjorth S, Carlsson A. Dopamine receptor agonists: Mechanisms underlying autoreceptor agonists: Mechanisms underlying autoreceptor selectivity. I. Review of the evidence. J Neural Transm 1985; 62: 1-52.

Clark D, Hjorth S, Carlsson A. Dopamine receptor agonist: Mechanisms underlying autoreceptor selectivity. II. Theoretical considerations. J Neural Transm 1985; 62: 171-207.

Clark D, Hjorth S, Carlsson A. (±)-and(-)3PPP exhibit different intrinsic activity at striatal dopamine autoreceptors controlling dopamine synthesis. Eur J Pharmacol 1985; 106: 185-189.

Clarke D J, Brundin P, Strecker R E, Nillson O G, Björklund A, Lindvall O. Human fetal dopamine neurons grafted in a rat model of Parkinson's disease: ultrastructural evidence for synapse formation using tyrosine hydroxylase immunocytochemistry. Exp Brain Res 1988; 73: 115-126.

Clement-Cormier Y C, Kebabian J W, Petzold G L, Greengard P. Dopamine-sensitive adenylate cyclase in mammalian brain: A possible site of action of antipsychotic drugs. Proc Natn Acad Sci, USA 1974; 71: 1113-1117.

Close S P, Marriott A S, Pay S. Failure of SKF 38393-A to relieve parkinsonian symptoms induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine in the marmoset. Br J Pharm 1985; 85: 320-2.

Cohen G, [illegible] M B. Deprenyl suppresses the oxidant stress associated with increased dopamine turnover. Ann Neurol 1989; 26: 689-690.

Coleman R J, Lange K W, Quinn N P, et al. The antiparkinsonian actions and pharmacokinetis of transdermal (+)-4-propyl-9-hydroxynapthoxazine (PHNO): preliminary results. Movement Disorders 1989; 4: 129-138.

Coleman R J, Temlett J A, Quinn N P, Stahl S M, Marsden C D. A strategy for measuring the therapeutic properties of new antiparkinsonian drugs, such as (+)-PHNO, in patients with on-off fluctuations. Clin Neuropharm 1989; 12: 37-45.

Coleman R J, Quinn N P, Traub M, Marsden C D. Nasogastric and intravenous infusions of (+)-4-propyl-9-hydroxy-naphthoxazine (PHNO) in Parkinson's disease. J Neurol Neurosurg Psychiatry 1990; 53: 102-105.

Colpaert F C, Leysen J E M F, Niemegeers C J E, Janssen P A J. Blockade of apomorphine's discriminative stimulus properties: Relation to neuroleptic activity in neuropharmacological and biochemical assays. Pharmacol Biochem Behav 1976; 5: 671-679.

Conte-Devolx B, Grino M, Nieoullon A, et al. Cortico-liberin, somatocrinin, and amine contents in normal and parkinsonian human hypothalamus. Neurosci Lett 1985; 56: 217-222.

Cools A R, Van Rossum J M. Excitation-mediating and inhibition-mediating dopamine receptors: A new concept towards a better understanding of electrophysiological, biochemical, pharmacological, functional and clinical data. Psychopharmacol 1976; 45: 243-254.

Cools A R, Van Rossum O. Multiple receptors for brain dopamine in behaviour regulation: concept of dopamine-E and dopamine-I receptors. Life Sci 1980; 27: 1237-1253.

Cooper I S. Chemopallidectomy: an investigative technique in geriatric parkinsonians. Science 1955; 121: 217-218.

Cooper I S. Cryogenic surgery of basal ganglia. JAMA 1962; 181: 600-604.

Corrodi H, Fuxe K, Hokfelt T, Lidbrink P, Ungerstedt U. Effect of ergot drugs on central catecholamine neurons: evidence for a stimulation of central dopamine neurons. J Pharmac 1973; 25: 409-411.

Costall B, Naylor R J. Neuroleptic antagonism of dyskinetic phenomena. Eur J Pharmacol 1975; 33: 301-312.

Costall B, Naylor R J. A comparison of circling models for the detection of antiparkinson activity. Psychopharmacol 1975; 41: 57-64.

Costall B, Naylor R J. A comparison of the abilities of typical neuroleptic agents and of thioridazine, clozapine, sulpiride and metoclopramide to antagonise the hyperactivity induced by dopamine applied intracerebrally to areas of the extrapyramidal and mesolimbic systems. Eur J Pharmacol 1976; 40: 9-19.

Costall B, Marsden C D, Naylor R, Pycock C J. The relationship between striatal and mesolimbic dopamine dysfunction and the nature of circling responses following 6-hydroxydopamine and electrolytic lesions of the ascending dopamine systems of rat brain. Brain Res 1976; 11: 87-113.

Costall B, Naylor R J, Pycock C J. Non-specific supersensitivity of striatal dopamine receptors after 6-hydroxydopamine lesion of the nigrostriatal pathway. Eur J Pharm 1976; 35: 275-283.

Costall B, Marsden CD, Naylor RJ, Pycock CJ. Stereotyped behaviour patterns and hyperactivity induced by amphetamine and apomorphine after discrete 6-hydroxydopamine lesions of extrapyramidal and mesolimbic nuclei. Brain Res 1977; 123: 89-111.

Costall B, Naylor R J. Studies on the dopamine agonist properties of 8-amino-2-methyl-4-(3,4-dihydroxyphenyl) -1,2,3,4-tetrahydroisoquinoline, a derivative of nomifensine. J Pharm Pharmacol 1978; 30: 514-516.

Costall B, Fortune D H, Naylor R J, Nohria V. A study of drug action on normal and denervated striatal mechanisms. Eur J Pharmacol 1979; 56: 207-216.

Costall B, Naylor R J. Behavioural aspects of dopamine agonists and antagonists. In: Horn AS, Korf J, Westerink BHC, eds. The Neurobiology of Dopamine. London: Academic Press, 1979: 555-576.

Costall B, Naylor R J. Assessment of the test procedures used to analyse neuroleptic action. Rev Pure Appl Pharmacol Sci 1980; 1: 3-83.

Costall B, Fortune D H, Hui-S-CG, Naylor R J. Neuroleptic antagonism of the motor inhibitory effects of apomorphine within the nucleus accumbens: Drug interaction at presynaptic receptors? Eur J Pharmacol 1980; 63: 347-358.

Costall B, Lim S K, Naylor R J. Characterisation of the mechanisms by which purported dopamine agonists reduce spontaneous locomotor activity of mice. Eur J Phamacol 1981; 73: 175-188.

Costall B, Naylor R J. The hypothesis of different dopamine receptor mechanisms. Life Sci 1981; 28: 215-229.

Costall B, Eniojukan J F, Naylor R J. Spontaneous climbing behaviour of mice, its measurement and dopaminergic involvement. Eur J Pharmacol 1982; 85: 125-132.

Costall B, Kelly M E, Naylor R J. The production of asymmetry and circling behaviour following unilateral, intrastriatal administration of neuroleptic agents: A comparison of abilities to antagonise striatal function. Eur J Pharmacol 1983; 96: 79-86.

Costall B, Kelly M E, Naylor R J. Does contralateral circling involve action of drugs on hyposensitive striatal dopamine receptors in the hemisphere contralateral to denervation? Neuropharmacol 1983; 22: 295-302.

Costall B, Eniojukan J F, Naylor R J. D1 and D2 dopamine agonist-antagonist action in the nucleus accumbens to modify mouse spontaneous climbing behaviour. Br J Pharmacol 1984; 81: 115.

Costall B, Kelly M E, and Naylor R J. Unilateral striatal dopamine denervation: Reduced motor inhibitory effects of dopamine antagonists revealed in models of asymmetric and circling behaviour. Arch Pharm 1984; 326: 29.

Cote T, Munemura M, Kebabian J. Lisuride hydrogen maleate: An ergoline with beta-adrenergic antagonist activity. Eur J Pharmacol 1979; 59: 303-306.

Cote T E, Munemura M, Eskay R L, Kebabian J W. Biochemical identification of the beta-adrenoceptor and evidence for the involvement of an adenosine 3', 5'-monophosphate system in the beta-adrenergically induced release of alpha-melanocyte-stimulating hormone in the intermediate lobe of the rat pituitary gland. Endocrinology 1980; 107(1): 108-116.

Cotler S, Holazo A, Boxenbaum H G, Kaplan S A. Influence of route of administration on physiological availability of levodopa in dogs. J Pharm Sci 1976; 65: 822-827.

Cotzias G C, Van Woert M H, Schiffer L M. Aromatic amino acids and modification of parkinsonism. N Engl J Med 1967; 276: 374-378.

Cotzias G C, Papavasiliou P S, Gellene R. Modification of parkinsonism - chronic treatment with L-dopa. N Eng J Med 1969; 280: 337-345.

Cotzias G C. Levodopa in the treatment of Parkinsonism. JAMA 1971; 218: 1903.

Cotzias G C, Papavasiliou P S, Tolosa E S, Mendez J S, Bell-Midura M. Treatment of Parkinson's disease with apomorphines. Possible role of growth hormones. New Engl J Med 1976; 294(11): 567-572.

Coward D M. Apomorphine-induced biphasic circling behaviour in 6-hydroxydopamine-lesioned rats. Arch Pharm 1983; 323: 49-53.

Creese I, Burt D R, Snyder S H. Dopamine receptor binding predicts clinical and pharmacological potencies of antischizophrenic drugs. Science 1976; 192: 481-483.

Creese I, Prosser T, Snyder S H. Dopamine receptor binding: specificity, localization and regulation by ions and guanyl nucleotides. Life Sci 1978; 23: 495-500.

Creese I, Snyder S H. Nigrostriatal lesions enhance striatal [^{3}H]apomorphine and [^{3}H]spiroperidol binding. Eur J Pharm 1979; 56; 277-281.

Creese I. Dopamine receptors explained. Trends Neurosci 1982; 5: 40-43.

Creese I, Sibley D R, Leff S. Classification of dopamine receptors. In: Mandel P, DeFendis eds., Pharmacology to behaviour. New York: Raven Press 1983; 255-262.

Creese I, Chen A. Selective D-1 dopamine receptor increase following chronic treatment with SCH 23390. Eur J Pharm 1985; 109: 127-128.

Critchley P, Parkes D. Transdihydrolisuride in Parkinsonism. Clin Neuropharmacol 1987, 10: 57-64.

Crossman A R, Clarke D E, Boyce S, Roberson R G, Sambrook M A. MPTP-induced parkinsonism in the monkey: Neurochemical pathology, complications of treatment and pathophysiology mechanisms. Can J Neurol Sci 1987; 14: 428-435.

Cuello A C, Horn A S, Mackay A V P, Iversen L L. Catecholomines in the median eminence: new evidence for a major noradrenergic input. Nature 1973; 243: 465-467.

Curtis L, Lees A J, Stern G M, Marmot M G. Effect of l-dopa on the course of Parkinson's disease. Lancet 1984; ii: 211-212.

Dahlström A, Fuxe K. Evidence for the existence of monoamine-containing neurons in the central nervous system. I. Demonstration of monoamines in the cell bodies of brain stem neurons. Acta Physiol Scand 1964; 62 (suppl) 232: 1-55.

D'Amato R J, Benhan D F, Snyder S H. Characterisation of the binding of N-methyl-4-phenylpyridine, the toxic metabolite of the parkinsonian neurotoxin N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine to neuromelanin. J Neurochem 1987; 48: 653-658.

Dandridge P A, Kaiser C, Brenner M et al. Synthesis, resolution, absolute stereochemistry and enatioselectivity of 3' 4'-dihydroxynomofensine. J Med Chem 1984; 27(1): 28-35.

Davis G C, Williams A C, Markey S P, et al. Chronic parkinsonism secondary to intravenous injection of meperidine analogues. Psychiatry Res 1979; 1: 249-254.

Debono A G, Marsden C D, Parkes J D. Alpha and Beta Dopamine receptors. Acta Neurol Belg 1976; 76 (5-6): 315-317.

De Camilli P, Macconi D, Spada A. Dopamine inhibit adenylate cyclase in human prolactin-secreting pituitary adenomas. Nature 1979; 278: 252-254.

De Lean A, Kilpatrick B F, Caron M G. Dopamine receptor of the porcine anterior pituitary gland. Evidence for two affinity states discriminated by both agonists and antagonists. Mol Pharmacol 1982; 22: 290-297.

Delini-Stula A, Baumann P, Büch O. Depression of exploratory activity by clonidine in rats as a model for the detection of relative pre- and postsynaptic central noradrenergic receptor selectivity of adrenolytic drugs. Arch Pharm 1979; 307: 115-122.

Del Poso E, Maclay W P. Gastrointestinal bleeding in patients on bromocriptine. Lancet 1976; ii: 906 -907.

Demonet J F, Rostin M, Dueymes M, Ioualalen A, Montastruc J L, Rascol A. Retroperitoneal fibrosis and treatment of Parkinson's disease with high doses of bromocriptine. Clin Neuropharmacol 1986; 9(2): 200-201.

Deny R M, Fritz R R, Patel N T, Abell C W. Human liver MAO-A and MAO-B separated by immunoaffinity chromotography with MAO B-specific monoclonal antibody. Science 1982; 215: 1400-1403.

De Smet Y, Ruberg M, Serdaru M, Dubois B, Lhérmitte F, Agid Y. Confusion, dementia and anticholinergics in Parkinson's disease. J Neurol Neurosurg and Psychiatry, 1982; 45: 1161-1164.

Dettmar P W, Lynn A G, Tulloch I F. Neuropharmacological studies in rodents on the action of RX781094, a new selective adrenoceptor antagonist. Neuropharmacology 1983; 22: 729-737.

Dexter D T, Carter C, Agid F, et al. Lipid peroxidation as a cause of nigral cell death in Parkinson's disease. Lancet 1986; ii: 639-640.

Dexter D T, Wells F R, Agid F, Lees A J, Jenner P, Marsden C D. Increased nigral iron content in post-mortem parkinsonian brain. Lancet 1987; ii: 1219-1220.

Dexter D T, Carayon A, Vidaihet M, Ruberg M, Agid F, Agid Y, Lees A J, Wells F R, Jenner P, Marsden C D. Decreased ferritin levels in brain in Parkinson's disease. J Neurochem 55; 1: 16-20.

Dexter D T, Carter C, Wells F R, et al. Basal Lipid Peroxidation in Substantia Nigra is Increased in Parkinson's disease. J Neurochem 1989; 52(2): 381-389.

Dexter D T, Wells F R, Lees A J, et al. Increased Nigral Iron Content and alterations in other Metal Ions occurring in the brain in Parkinson's disease. J Neurochem 1989; 52: 1830-1836.

Diamond S G, Markham C H, Treciokas LJ. Long-term experience with L-Dopa: Efficacy, progression and mortality. Advances in Parkinsonism, Roche, Basle: 1975; 444-455.

Diamond S G, Markham C H. Present mortality in Parkinson's disease: the ratio of observed to expected deaths with a method to calculate expected deaths. J Neural Transm 1976; 36: 259-269.

Diamond S G, Markham C H. Mortality of Parkinson patients treated with Sinemet. In: Poirier L J, Sourkes T L, Bédard P J, eds. Adv Neurol Vol.24, New York: Raven Press, 1979: 489-497.

Dick J P, Cantello R, Buruma O, et al. The Bereitschafts-potential, L-Dopa and Parkinson's disease. Electroencephalogr Clin Neurophysiol 1987; 66: 263-274.

DiFiglia M, Aronin N. Ultrastructural features of immunoreactive somatostatin neurons in the rat caudate nucleus. J Neurosci 1982; 2: 1267-1274.

Divac I, Lindvall O, Björklund A, Passingham R E. Converging projections from the mediodorsal thalamic nucleus and mesencephalic dopaminergic neurons to the neocortex in three species. Exp Brain Res 1975; 23: 58.

Divac I, Björklund A, Lindvall O. Converging projections from the mediodorsal thalamic nucleus and mesencephalic dopaminergic neurons to the neocortex in three species. J Comp Neurol 1978; 180: 59-72.

Dowling J E, Watling K J. Dopaminergic mechanisms in the teleost retina. II.Factors affecting the accumulation of CAMP in pieces of corp retina. J Neurochem 1981; 36(2): 569-579.

Drachman D A. Memory and cognitive function in man: does the cholinergic system have a specific role? Neurology 1977; 27: 783-790.

Dray A, Gonye T J, Oakley N R. Effects of fluperthixol on dopamine and 5-hydroxytryptamine responses of substantia nigra neurons. Neuropharmacology 1976; 15: 793-796.

Drew G M, Gower A J, Hilditch A, Marriott A S. A pharmacological comparison of dopamine receptors in the cat heart and those mediating emesis in the dog. Br J Pharmacol 1982; 75: 145-147.

Drucker-Colin R, Madrazo I, Ostrosky-Solis F, Shkurovich M, Franco R, Torres C. Adrenal medullary tissue transplants in the caudate nucleus of Parkinson's patients. Prog Brain Res 1988; 78: 567-574.

Dubois B, Hauw J J, Ruberg M, Serdaru M, Javoy-Agid F, Agid Y. Demence et maladie de Parkinson: correlations biochimiques et anatomo-cliniques. Revue Neurologique (Paris) 1985; 141(3): 184-193.

Dubois B, Mayo W, Agid G, Le Moal M, Simon H. Profound disturbances of spontaneous and learned behaviors following lesions of the nucleus basalis magnocellularis in the rat. Brain Res 1985; 338: 249-258.

Dubois B, Ruberg M, Javoy-Agid F, Ploska A, Agid Y. A subcortico-cortical cholinergic system is affected in Parkinson's disease. Brain Res 1983; 288: 213-218.

Duby S E, Cotzias C C, Papavasiliou P S, Lawrence W H. Injected apomorphine and orally administered levodopa in parkinsonism. Arch Neurol 1972; 27: 474-480.

Duncan M W, Kopin I J, Garruto R M, Lavine L, Markey S P. 2-amino-3(methylamino)-propionic acid in cycad-derived foods is an unlikely cause of amyotrophic lateral sclerosis/parkinsonism. Lancet 1988; ii, 631-632.

Dunnett S B, Björklund A, Stenevi U, Iversen S D. Behavioural recovery following transplantation of substantia nigra in rats subjected to 6-OHDA lesions of the nigrostriatal pathway. I. Unilateral lesions. Brain Res 1981; 215: 147-161.

Dunnett S B, Björklund A, Stenevi U, Iversen S D. Behavioural recovery following transplantations of substantia nigra in rats subjected to 6-OHDA lesions of the nigrostriatal pathway. II. Bilateral lesions. Brain Res 1981; 229: 457-470.

Dunnett S B, Björklund A, Stenevi U, Iversen S D. Grafts of embryonic substantia nigra reinnervating the

ventrolateral striatum ameliorate sensorimotor impairments and akinesia in rats with 6-OHDA lesions of the nigrastriatal pathway. Brain Res 1981; 229: 209-217.

Dunnett S B, Björklund A, Stenevi U, Iversen S D. CNS transplantation: structural and functional recovery from brain damage. In: Buijs R M, Pévet P. Swaab D F, eds. Chemical transmission in the Brain. Prog Brain Res 1982; 55: 431-443.

Dunnett S B, Björklund A, Schmidt R H, Stenevi U, Iversen S D. Intracerebral grafting of neuronal cell suspensions. IV. Behavioural recovery in rats with unilateral 6-OHDA lesions following implantation of nigral cell suspensions in different forebrain sites. Acta Phys Scand 1983; 522 (suppl): 29-37.

Dunnett S B, Whishaw I Q, Jones G H, et al. Effects of dopamine-rich grafts on conditioned rotation in rats with unilateral 6-OHDA lesions. Neurosci Lett 1986; 68: 127-133.

Dunstan R, Broekkamp C L, Lloyd K G. Involvement of caudate nucleus, amygdala or reticular formation in neuroleptic and narcotic catalepsy. Pharmacol Biochem Behav 1981; 14: 169-174.

During M J, Freese B, Sabel B A, et al. Controlled release of dopamine from a polymeric brain implant: In vivo characeterization. Ann Neurol 1989; 25(4), 351-356.

Duvoisin R C. The evaluation of extrapyramidal disease. In: Monoamines: Noyaux Gris Centraux et Syndrome de Parkinson de Ajuriagena J, ed. Paris: Masson, 1970: 313-325.

Duvoisin R C, Eldridge R, Williams A, Nutt J, Calne D. Twin study of Parkinson's disease. Neurology 1981; 31: 77-80.

Duvoisin R C. Is Parkinson's disease acquired or inherited? Can J Neurol Sci 1984; 11: 151-155.

Duvoisin R C. Etiology of Parkinson's disease: current concepts. Clin Neuropharmacol 1986; 9: 3-21.

Duvoisin R C. New strategies in dopaminergic therapy of Parkinson's disease: The use of a controlled-release formulation. Neurology 1989; 39: 4-6.

Duvoisin R C. Therapeutic profile of Sinemet CR: Closing remarks. Neurology 1989; 39(suppl 2): 106.

Editorial. Brain transplant for Parkinson's disease. Lancet 1987; i: 1012-1013.

Editorial: Embryos and Parkinson's disease. Lancet 1988; i: 1087.

Ehringer H, Hornykiewicz O. Verteilung von Noradrenalin und Dopamin 3-Hydroxytyramin) im Gehirn des Menschen und ihr Verhalten bei Erkrankungen des extrapyramidalen System. Wien Klin Wochenschr, 1960; 38: 1236-1239.

Eisler T, Hall R P, Kalaver K, Calne D B. Erythromyelalgia-like eruption in parkinsonian patients treatment with bromocriptine. Neurology (NY) 1981; 31: 1368 - 1370.

Eisler T, Teravainen H, Nelson R, et al. Deprenyl in Parkinson's disease. Neurology 1981; 31: 19-23.

Eldridge R, Ince S E. The low concordance rate for Parkinson's disease in twins: A possible explanation. Neurology 1984; 34: 1354-1356.

Elizan T S, Yahr M D, Moros D A, Mendoza A, Pang S, Bodian C A. L-Deprenyl, a MAO-B inhibitor, as an adjuct to conventional L-Dopa therapy in Parkinson's disease: Experience in 200 patients. Adv Neurol 1990; 53: 431-435.

Elsworth J D, Glover V, Reynolds G P, Sandler M, Lees A J, Phuapradit P, Shaw K M, Stern G M, Kumar P. Deprenyl administration in man: a selective monoamine oxidase B inhibitor without the "cheese effect". Psychopharmacology, 1978; 57: 33-38.

England A C, Schwab R S. Post-operative evaluation of selected patients with Parkinson's disease. J Am Geriat Soc 1956; 4: 1219-1232.

Eriksson E, Modigh K, Carlsson A, Wikström H. Dopamine receptors involved in prolactin secretion pharmacologically characterized by means of 3-PPP enantiomers. Eur J Pharmacol 1983; 96: 29-36.

Euvrard C, Ferland L, Dipaolo M, et al., Activity of two new potent dopaminergic agonists at the striatal and anterior pituitary levels. Neurophamacol 1980; 19(4): 379-386.

Evarts E V, O'Connor M, eds. Function of the basal ganglia, Ciba Foundation Symposium Pitman, London 1984; 107.

Evarts E V, Wise S P. Basal ganglia outputs and motor control. In: Evarts E V, O'Conner M eds. Functions of the Basal Ganglia. Ciba Foundation Symposium Pitman, London 1984; 107: 83-102.

Fabre N, Rascol O, Senard J M, et al. Clinical evaluation of CQA206-291 in levodopa treated parkinsonian patients. 9th International Symposium on Parkinson's Disease, Jerusalem, Israel 1988.

Fahn S, Libsch L R, Cutler R W. Monoamines in the human neostriatum: Topographic distribution in normals and in Parkinson's disease and their role in akinesia, rigidity, chorea and tremor. J Neurol Sci 1971; 14: 427-455.

Fahn S. On-off phenomenon with levodopa therapy in parkinsonism: clinical and pharmacologic correlations and the effect of intramuscular pyridoxine. Neurology 1974; 24: 431-441.

Fahn S. Regional distribution of GABA and other putative neurotransmitters and their enzymes. In: Roberts E, Chase T N, Tower D B, eds. GABA in Nervous System Function, New York, Raven 1976; 169-186.

Fahn S, Calne D B. Considerations in the management of Parkinsonism. Neurology 1978; 28: 5-7.

Fahn S. Fluctuationss of disability in Parkinson's disease: Pathophysiology. Marsden C D and Fahn S, eds: In: Movement disorders. London: Butterworth Scientific, 1982: 123-145.

Fahn S, High dosage antocholinergic therapy in dystonia. Adv Neurol 1983; 37: 177-188.

Fahn S, Bressman S B. Should levodopa therapy for Parkinsonism be started early or late? Evidence agianst early treatment. Can J Neurol Sci 1984; (suppl 1): 200-205.

Fahn S, Marsden C D, Jenner P, Teychenne P F. eds. Recent Developments in Parkinson's disease. New York: Raven Press, 1986.

Fahn S, Elton R L, and members of the UPDRS development Committee. The unified Parkinson's disease Rating

Scale. In: Fahn S, Marsden C D, Calne D, Goldstein M, eds: Recent developments in Parkinson's disease. New Jersey: Macmillan Healthcare Information, 1987; 2: 153-64.

Falck B, Hillarp N A, Torp A. Some observations on the history and histochemistry of the chromaffin cells probably storing dopamine. J Histochem 1959; 7: 323-328.

Fallon J H, Moore R Y. Catecholamine innervation of the basal forebrain. III. Olfactory bulb, anterior olfactory nuclei, olfactory tubercle and periform cortex. J Comp Neurol 1978; 180: 533-544.

Fallon J H, Moore R Y. Catecholamine innervation of the basal forebrain. IV. Topography of the dopamine projection to the basal forebrain and neostriatum. J Comp Neurol 1978; 180: 545-580.

Farley I J, Hornykiewicz O. Noradrenaline in subcortical brain regions of patients with Parkinson's disease and control subjects. In: Birkmayer W, Hornykiewicz O, eds. Advances in Parkinsonism. Basel: Roche, 1976: 178-185.

Fellman J H, Roth E S. Inhibition of tyrosine amino-transferase activity by L-3,4-dihydroxyphenyl-alanine. Biochemistry 1971; 10: 408-414.

Felten D L, Laties A, Carpenter M. Monoamine-containing cell bodies in the squirrel monkey brain. Am J Anat 1974; 139: 153-166.

Fenton H M, Leszczak E, Gerhardt S, Liebman J M. Evidence for heterogenous rotational responsiveness to apomorphine, 3-PPP and SKF38393 in 6-hydroxydopamine-denervated rats. Eur J Pharmacol 1985; 106: 363-372.

Fermaglich J. Effect of gastric motility on levodopa. In: O'Doherty D S. ed. Diseases of the Nervous System 1972; 33: 624-625.

Fibiger H C, Phillips A G. Dopamine and the neural mechanisms of reinforcement. In: Horn A S, Korf J, Westerink B H C, eds. The Neurobiology of Dopamine. London: Academic Press, 1979: 597-615.

Fine A, Hunt S P, Oertel W H, et al. Transplantation of embryonic marmoset dopaminergic neurons to the corpus striatum and marmosets rendered parkinsonian by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. Prog Brain Res 1988; 78: 479-489.

Fink J S, Smith G P. Relationships between selective denervation of dopamine terminal fields in the anterior forebrain and behavioural responses to amphetamine and apomorphine. Brain Res 1980; 201: 107-127.

Fishman P S. Neural transplantation; scientific gains and clinical perspectives. Neurology 1986; 36: 389-392.

Fog R. On stereotypy and catalepsy: Studies on the effect of amphetamines and neuroleptics in rats. Acta Neurol Scand 1972; 48(suppl); 50: 3-66.

Fonnum F, Gottesfeld Z, Grofova I. Distribution of glutamate decarboxylase, choline acetyltransferase and aromatic amino acid decarboxylase in the basal ganglia of normal and operated rats. Evidence for striatopallidal, striatoentopeduncular and striatonigral Gabaergic fibers. Brain Res 1978; 143: 125-138.

Foote R W, Buscher H H, Romer D, et al. CY208-243: A unique combination of atypical opioid antinociception and D-1 dopaminomimetic properties, Life Sci 1988; 42: 137.

Forno L S. Pathology of Parkinson's disease. In: Marsden C D, S Fahn S, eds. Movement Disorders. London: Butterworths Scientific, 1981: (2):25-40.

Forno L S. The Lewy body in Parkinson's Disease. Adv Neurol 1986; 45: 35-43.

Forno L S, De Lanney L E, Irwin I, Langston J W. Neuropathology of MPTP-treated monkeys: Comparison with the neuropathology of human idiopathic Parkinson's disease. In: Markey S P, Castagnoli N Jr, Trevor A J, Kopin I J, eds. MPTP: a neurotoxin producing a parkinsonian syndrome. New York: Academic Press, 1986: 119-140.

Forno L S, Langston J W, De Lanney L E, Irwin I, Ricaurte G A. Locus ceruleus lesions and eosinophilic inclusions in MPTP-treated monkeys. Ann Neurol 1986; 20: 449-455.

Forno L S, Langston J W, De Lanney L E, Irwin I. An electron microscopic study of MPTP-induced bodies in an old monkey. Brain Res 1988; 448: 150-157.

Frankel J P, Lees A J, Kempster P A, Stern G M. Subcutaneous apomorphine in the treatment of Parkinson's disease. J Neurol Neurosurg Psychiatry 1990; 53: 96-101.

Freed C R, Robert M D, Breeze R E, et al. Transplantation of Human Fetal Dopamine Cells for Parkinson's Disease. Arch Neurol 1990; 47: 505-512.

Freed W J, Karoum F, Spoor H E, Morihisa J M, Olson L, Wyatt R J. Catecholamine content of intracerebral adrenal medulla grafts. Brain Res 1983; 269: 184-189.

Freed W J, Ko G N, Niehoff D L, et al. Normalization of spiroperidol binding in the denervated rat striatum by

homologous grafts of substantia nigra. Science 1983; 222: 937-939.

Freed W J, Morihisa J M, Spoor E, Hoffer B J, Olson L, Seiger A, Wyatt R J. Transplanted adrenal chromaffin cells in rat brain reduce lesion-induced rotational behaviour. Nature 1981; 292: 351-352.

Freed W J, Perlow M J, Karoum F, et al. Restoration of dopaminergic function by grafting of foetal rat substantia nigra to the caudate nucleus: long-term behavioural, biochemical, and histochemical studies. Ann Neurol 1980; 8: 510-519.

Freed C R. Tansplantation of fetal substantia nigra and adrenal medulla to the caudate nucleus in two patients with Parkinson's disease. N Engl J Med 1988; 319: 370-371.

Freedman S B, Wait C P, Woodruff G N. Effects of dopamine receptor agonists and antagonists in the rat nucleus accumbens. Br J Pharmacol 1979; 67: 430-431.

Freese A, Bernhard A, Sabel B A, Saltzman W M, During M J, Langer R. Controlled release of dopamine from a polymeric brain implant: In vitro characterization. Exp Neurol 1989; 103: 234-238.

Freund T F, Bolam J P, Björklund A, Stenevi U, Dunnett S B, Powell J F, Smith A D. Efferent synaptic connections of grafted dopaminergic neurons reinnervating the host neostriatum: a tyrosine hydroxylase immunocytochemical study. J Neurosci 1985; 5: 603-616.

Fuxe K, Hökfelt T, Ungerstedt U. Distribution of monoamines in the mammalian central nervous system by histochemical studies. In: Hooper G, Ed. Metabolism of Amines in the Brain. London: Macmillan, 1969: 10-22.

Fuxe K, Hökfelt T, Johansson O, Jonsson G, Lidbrink P, Ljungdahl A. The Origin of the dopamine nerve terminals in limbic and frontal cortex. Evidence for mesocortical dopamine neurons. Brain Res 1974; 82: 349-355.

Gage H, Dunnett S B, Stenevi U, Björklund A. Aged rats: recovery of motor impairments by intrastriatal nigral grafts. Science 1983; 221: 966-969.

Gage F H, Dunnett S B, Stenevi U, Björklund A. Intracerebral grafting of neuronal cell suspentions: VIII: Survival and growth of implants of nigral and septal cell suspensions in intact brains of aged rats. Acta Physiol Scand 1983; 522(suppl): 67-75.

Gage F H, Wolff J A, Rosenberg M B, et al. Implantation of genetically engineerd cells to the brain. Prog Brail Res 1988; 78: 651-658.

Garau L, Govoni S, Stefanini E, Trabucchi M and Spano P F. Dopamine receptors: pharmacological and anatomical evidence indicated two distinct dopamine receptor populations are present in rat striatum. Life Sci. 1987; 23: 1745-1750.

Garver D L, Sladek J R. Monoamine distribution in primate brain. I: Catecholamine-containing perikarya in the brain stem of macaca speciosa. J Comp Neurol 1975; 159: 289-305.

Geffen L B, Jessell T M, Cuello A C, Iversen L L. Release of dopamine from dendrites in rat substantia nigra. Nature 1976; 260: 258-260.

George S R, Watanabe M, Seeman P. Dopamine D2 receptor in the anterior pituitary: A single population without reciprocal agonist/antagonist states. J Neurochem 1985; 44: 1168-1177.

Gerfen C R, Staines W A, Arbuthnot G W, Fibiger H C. Crossed connections of the substantia nigra in the rat. J Comp Neurol 1982; 207: 283-303.

Gershanik O, Heikkila R E, Duvoisin R C. Effects of dopamine depletion on rotational behavior to dopamine agonists. Brain Res 1983; 261: 358-360.

Gessa G L, Porceddu M L, Collu M, et al. Sedation and sleep induced by high doses of apomorphine after blockade of D1 receptors by SCH23390. Eur J Pharmacol 1985; 109: 269-274.

Gibb W R G, Lees A J. The significance of the Lewy body in the diagnosis of idiopathic Parkinson's disease. Neuropathol Appl Neurobiol 1989; 15: 27-44.

Gibb W R G, Lees A J. The [illegible]evance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. J Neurol Neurosurg Psychiatry 1988; 51: 745-752.

Glick S D. Heritable differences in turning behaviour of rats. Life Sci 1985; 36: 499-503.

Glover V, Sandler M, Owen F, Riley G J. Dopamine is a monoamine oxidase B substrate in man. Nature 1977; 265: 80-81.

Goetz C G, Tanner C M, Glantz R H, Klawans H L. Chronic agonist therapy for Parkinson's disease: A five year study of bromocriptine and pergolide. Neurol 1985; 35: 749-751.

Goetz C G, Tanner C M, Klawans H L, Shannon K M, Carroll V S. Parkinson's disease and motor fluctuations: long-acting carbidopa/levodopa (CR-4-Sinemet). Neurol 1987; 37: 875-878.

Goetz C G, Tanner C M, Gilley D W, Klawans H L. Development and progression of motor fluctuations and side effects in Parkinson's disease: Comparison of Sinemet CR versus carbidopa/levodopa. Neurol 1989; 2(suppl): 63-66.

Goetz C G, Olanow C W, Koller W C, et al. Multicentre study of autologous adrenal medullary transplantation to the corpus striatum in patients with advanced Parkinson's disease. N Engl J Med 1989; 320: 337-341.

Goldberg L I, Glock D, Kohli J D, Barnett A. Seperation of peripheral dopamine receptors by a selective DA1 antagonist, SCH 23390. Hypertension 1984; 6(2): 25-30.

Goldstein M, Battista A F, Anagnoste B, Nakatani S. Tremor production and strial amines in monkeys. In: Gillingham F J, Donaldson I L M, eds. Third Symposium on Parkinson's Disease. London: E & S Livingstone, 1969: 37-40.

Goldstein M, Lieberman A, Lew J Y. Interaction of pergolide with central dopaminergic receptors. Proc Natl Acad Sci USA, 1980; 77: 3725-3738

Goldstein M, Lieberman A M, Battis A F. The therapeutic potential of centrally acting dopamine agonists. Trends Pharmocol Sci 1984; 5: 227-230.

Goldstein M, Lieberman A, Meller E. A possible molecular mechanism for the anti-parkinsonian action of bromocriptine in combination with levodopa. Trends in Pharm Sci 1985; 6: 436-437.

Goodwin-Austen R B, Smith N J. Comparison of the effects of bromocriptine and levodopa in Parkinson's disease. J Neurol Neurosurg Psychiatry 1977; 44: 4479-4482.

Goodwin-Austen R B, Lee P N, Marmot M G, Stern G M. Smoking and Parkinson's disease. J Neurol Neurosurg Psychiatry 1982; 45: 577-581.

Gopinathan G, Lieberman A N, Nelson J, et al. Mesulergine (CU 32-085) in Parkinson's disease. Neurology 1984; 34(suppl 1):270-272.

Gower A J, Marriott A S. Pharmacological evidence for the subclassification of central dopamine receptors in the rat. Br J Pharmacol 1982; 77: 185-194.

Gower A J, Berendsen H H G, Princen M M, Broekkamp C L E. The yawning-penile erection syndrome as a model for purative dopamine autoreceptor activity. Eur J Pharmacol 1984; 103: 81-89.

Gowers W R. A manual of diseases of the nervous system. London: Churchill, 1888: 589-607.

Grandas F, Quinn N, Critchley P, Rohan A, Marsden C D, Stahl S M. Antiparkinsonian activity of a single dose of PHNO. Movement Disorders 1987; 2: 47-51.

Graybiel A M, Ragsdale C W. Fiber connections of the basal ganglia. Prog Brain Res 1979; 51: 239-283.

Graybiel A M, Ragsdale C W. Histochemically distinct compartments in the striatum of human, monkey and cat demonstrated by acetylcholinersterase staining. Proc Natl Acad Sci USA 1979; 75: 5723-5726.

Graybiel A M, Ragsdale C W. Clumping of acetylcholinesterase activity in the developing striatum of the human fetus and young infant. Proc Natl Acad Sci USA 1980; 77: 1214-1218.

Graybiel A M, Pickel V M, Joh T H, Reis D J, Ragsdale C W. Direct demonstration of a correspondence between the dopamine islands and acetylcholinesterase patches in the developing striatum. Proc Natl Acad Sci USA 1981; 78: 5871-5875.

Graybiel A M, Ragsdale C W Jr. Biochemical anatomy of the striatum. In: Emson P C, ed. Chemical neuroanatomy. New York: Raven Press, 1983: 427-504.

Graybiel A M, Chesselet M-F, Wu J-Y, Eckenstein F, Joh T E. The relation of striosomers in the caudate nucleus of the cat to the organization of early-developing dopaminergic fibres, GAD-positive neuropil, and CAT-positive neurons. Neurosci 1983; 9: 14.

Graybiel A M, Ragsdale C W Jr, Yoneoka E S, Elde R P. An immunohistochemical study on enkephalins and other neuropeptides in the striatum of the cat with evidence that the opiate peptides are arranged to form mosaic patterns in register with the striosomal compartments visible by acetylcholinersterase staining. Neurosci 1981; 6: 377-397.

Green A R, Heal D J. The effects of drugs on serotonin-mediated behavioural model. In: Green A R, ed. Neuropharmacology of Serotonin. Oxford: Oxford University Press, 1985: 326-365.

Grewe C W, Frey E A, Cote T E, Kebabian J W. YM-09151-2 a potent antagonist for a peripheral D-2-dopamine receptor. Eur J Pharmacol 1982; 81(1): 149-152.

Grigoriadis D, Seeman P. The dopamine/neuroleptic receptor. Can J Neurol Sci 1984; 11: 108-113.

Grimes J D, Delgado M R. Bromocriptine: problems with low dose de novo therapy in Parkinson's disease. Clin Neuropharmacol 1985; 8: 73-77.

Grimes J D, Hassan M. Bromocriptine in the long term management of advanced Parkinson's disease. Can J Neurol Sci, 1983; 10 (2): 86-90.

Guerin B, Silice C, Mouchet P, Feuerstein C, Demenge P. Changes of the striatal [^{3}H]spiperone binding 3-6 weeks after nigrostriatal denervation and after two years. Life Sci 1985; 37: 955-961.

Guttman, M. and Seeman,P. L-Dopa reverses the elevated density of D2 dopamine receptors in Parkinson's diseased striatum. J Neural Trans 1985; 64: 93-103.

M, Seeman P, Reynolds G P, Riederer P, Jellinger K, tte W W. Dopamine D_2 receptor density remains in treated Parkinson's disease. Ann Neurol 487-492.

Guttman M, Seeman P. Dopamine D2 receptor density in parkinsonian brain is constant for duration of disease, age, and duration of L-Dopa therapy. Adv Neurol 1986; 45: 51-57.

Guttman M. Receptors in the basal ganglia. Can J Neurol Sci 1987; 14(3)(suppl): 395-401.

Häggendal J, Malmfors T. Evidence of dopamine-containing neurons in the retina of rabbits. Acta Physiol Scand 1963; 59: 295-296.

Halasz N, Johansson O, Hökfelt T, Ljungdahl A, Goldstein M. Immunohistological identification of two types of dopamine neuron in the rat olfactory bulb as seen by serial sectioning. J Neurocytol 1981; 10: 251-259.

Halliwell B, Gutteridge J M C. Free radicals in Biology and medicine. Oxford: Clarendon Press, 1985.

Hamblin M W, Leff S E, Creese I. Interactions of agonists with D-2 dopamine receptors: evidence for a single receptor population existing in multiple agonist affinity-states in rat striatal membranes. Biochem Pharm 1984; 33: 877-887.

Hardie R J, Lees A J, Stern G M. On-off fluctuations in Parkinson's disease. A clinical and neuropharmacological study. Brain 1984; 107: 487-506.

Harding R K, Hugenholtz H, Keaney M, Kucharczyk J. Discrete lesions of the area postrema abolish radiation-induced emesis in the dog. Neurosci Lett 1985; 5[illegible]95-100.

Hardy J, Adolfsson R, Alafuzoff I, et al. Transmitter deficits in Alzheimer's disease. Neurochemistry International, 1985; 7(4): 545-563.

Hargraves R, Freed W J. Chronic intrastriatal dopamine infusions in rats with unilateral lesions of the substantia nigra. Life Sci 1987; 40: 959-966.

Hassan M N, Thakar J H. Dopamine receptors in Parkinson's disease. Prog Neuropsychopharmacol Biol Psychiatry 1988; 12: 173-182.

Hassler R. Zur Pathologie der Paralyse agitans und des postencephalitischen parkinsonism. J Psychol Neurol 1938; 48: 387-476.

Hassler R. Extrapyramidal-motorische systeme und erkrankungen. In:Handbuch der Innerin Medezin. Berlin: Springer Verlag, 1953; 3: 676-904.

Hayashi T, Tadokoro S. Parallelism between avoidance-suppressing and prolactin-increasing effects of antipsychotic drugs in rats. Jpn J Pharmacol 1984; 35: 451-456.

Hefti F, Melamed E, Wurtman R J. Partial lesions of the dopaminergic nigrostriatal system in rat brain: Biochemical characterization. Brain Res 1980; 195: 95-101.

Hefti F, Kartikka J, Schlumph M. Implantation of PC12 cells into the corpus striatum of rats with lesions of the dopaminergic nigrostriatal neurons. Brain Res 1985; 348: 283-288.

Heikkila R E, Manzino L, Cabbat F S, Duvoisin R C. Protection against the neurotoxicity of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine by monoamine oxidase inhibitors. Nature 1984; 311: 467-469.

Heikkila R E, Hess A, Duvoisin R C. Dopaminergic neurotoxicity of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine in mice. Science 1984; 224: 1451-1453.

Heikkila R E, Manzino L, Cabbat F S, Duvoisin R C. Studies on the oxidation of the dopaminergic neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine by monoamine oxidase. Br J Neurochem 1985; 45: 1049-1054.

Heikkila R E, Nicklas W J, Duvoisin R C. Dopaminergic toxicity after the stereotaxic administration of the 1-methyl-4-phenylpyridinium ion (MPP+) to rats. Neurosci Lett 1985; 49: 135-140.

Heikkila R E, Hess A, Duvoisin R C. Dopaminergic neurotoxicity of ..-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in the mouse: Relationships between monoamine oxidase, MPTP Metabolism and neurotoxicity. Life Sci 1985; 36: 231-236.

Heikkila R E. Differential neurotoxicity of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in

Swiss-Webster mice from different sources. Eur J Pharmacol 1985; 117: 131-133.

Heimer L, Wilson R D. The subcortical projections of the allocortex; similarities in the neural associations of the hippocampus, the piriform cortex, and the neocortex. In: Santini M, Ed. Golgi Centennial Symposium: Perspectives in Neurobiology. 1975: 177-193.

Hemmings H C Jr, Greengard P, Lim Tung H Y, Cohen P. DARP-32, a dopaminergic -regulated neuronal phosphoprotein, is a potent inhibitor of protein phosphetase-1. Nature 1984; 310: 503-505.

Herrera-Marschitz M, Hyttel J, Ungerstedt U. The dopamine D1 antagonist SCH 23390 inhibits apomorphine but not pergolide induced rotation. Acta Physiol Scand 1984; 122: 427-428.

Herrera-Marschitz M, Ungerstedt U. Evidence that striatal efferents relate to different dopamine receptors. Brain Res 1984; 323: 269-278.

Hess E J, Battaglia G, Normal A B, Ioria L C and Creese I. Guanine nucleotide regulation of agonist interactions at [^{3}H]SCH 23390-labelled D1 dopamine receptors in rat striatum. Eur J Pharm 1986; 121: 31-38.

Hinterberger H, Andrews C J. Catecholamine metabolism during oral administration of levodopa. Arch Neurol 1972; 26: 245-252.

Hirsch E, Graybiel A M, Agid Y A. Melanized dopaminegic neurons are differentially susceptable to degeneration in Parkinson's disease. Nature 1988; 334: 345-348.

Hitchcock E R, Clough C, Hughes R, Kenny B. Embryos and Parkinson's disease. Lancet 1988; i: 1274.

Hjorth S, Carlsson A, Clark D, et al. Central dopamine receptor agonist and antagonist actions of the enantiomers of 3-PPP. Psychopharmacol 1983; 81: 89-99.

Hoehn M M, Yahr M D. Parkinsonism: onset, progression and mortality. Neurology 1967; 17: 427-442.

Hoehn M M. Bromocriptine and its uses in parkinsonism. J Am Geriatr Soc 1981; 29: 251-258.

Hoehn M M. Progression and mortality. J Neural Transm 1983; 19(suppl): 253-284.

Hoehn M M. The result of chronic levodopa therapy and its modification by bromocriptine in Parkinson's disease. Acta Neurol Scand 1985; 71: 97-106.

Hökfelt T, Fuxe K. Effects of prolactin and ergot alkaloids on the tuberoinfundibular dopamine neurons. Neuroendocrinology 1972; 9: 100-122.

Hökfelt T, Fuxe K, Johansson O, Ljungdahl A. Pharmacohistochemical evidence of the existence of dopamine nerve terminals in the limbic cortex. Eur J Pharm 1974; 25: 108-112.

Horn A A. Structure-activity relations for neurotransmitter receptor agonists and antagonists. In: Handbook of Psychopharm. Iversen L L, Iversen S D, Snyder S H, eds. New York: Plenum Press, 1975; 2: 179-243.

Horn A S, Tepper P, Kebabian J W, Beart P M. N-0434 a very potent and specific new D-2 dopamine receptor agonist. Eur J Pharmacol 1984; 99(1): 125-126

Horn A S, Tepper P, Van Der Weide J, Watanabe M, Grigoriadis D, Seeman P. Synthesis and radioceptor bindings activity of N-0437, a new, extremely potent

and selective D2 dopamine receptor agonist. Pharm Weekblad Sci 1985; 7: 208-211.

Hornykiewicz O. Die topische Lokalization und das Verhalten von Noradrenalin und Dopamin (3-Hydroxytyramin) in der Substantia nigra des normalen und Parkinsonkranken Menschen. Wiener Klin Wochenschrift 1963; 75: 309-312.

Hornykiewicz O. Dopamine (3-Hydroxytyramine) and brain function. Pharmacol Rev 1966; 18: 925-964.

Hornykiewicz O. Neurochemistry of parkinsonism. In:Lajtha ed., Handbook of Neurochemistry New York: Plenum Press 1972; 7: 465-501.

Hornykiewicz O. Dopamine in the basal ganglia. Its role and therapeutic implications (including the clinical use of L-Dopa). Br Med Bull 1973; 29(2): 172-178.

Hornykiewicz O. Brain dopamine in Parkinson's disease and other neurological disturbances. In: Neurobiology of Dopamines. Horn A S, Korf J, Westerink B H C, eds. London: London Academic Press, 1979: 633-654.

Hornykiewicz O. Compensatory biochemical changes at the striatal dopamine synapse in Parkinson's disease - Limitation of L-Dopa therapy. Adv Neurol 1979; 24: 275-281.

Hornykiewicz O, Lloyd K G, Davidson L. The GABA system, function of the basal ganglia and Parkinson's disease. In: Roberts E, Chase T N, Tower D B, eds. GABA in Nervous System Function. New York: Raven Press, 1976: 479-485.

Hornykiewicz O, Kish S J. Biochemical pathophysiology of Parkinson's Disease. Adv Neurol 1986; 45: 19-34.

Hyttel J. Effects of neuroleptics on (3)H-haloperidol and (3)H-cis (Z)-fluphenthixol binding and on adenylate cyclase activity in vitro. Life Sci 1978; 23: 551-556.

Hyttel J. Further evidence that ^{3}H-cis(Z)-flupenthixol binds to the adnylate cyclase-associated dopamine receptor (D1) in rat corpus striatum. Psychopharmacol 1980; 67: 107-109.

Hyttel J. Similarities between the binding of (3)H-piflutixol and (3)H-flupentixol to rat striatal dopamine receptors in vitro. Life Sci 1981; 28: 563-569.

Hyttel J. SCH 23390: The first selective dopamine D-1 antagonist. Eur J Pharm 1983; 91: 153-154.

Hyttel J, Christensen A V, Arnt J. Neuroleptic classification: Implications for tardive dyskinesia. Mod Probl Pharmacopsychiat 1983; 21: 49-64.

Hyttel J. Functional evidence for selective dopamine D1 receptor blockade by SCH 23390. Neuropharmacol 1984; 23: 1395-1401.

Hyttel J, Arnt J. Characterisation of dopamine D-1 and D-2 recepors. In: Breese G R, Creese I, eds. Neurobiology of Central D-1 Dopamine Receptors. New York: Plenum Press, 1986: 15-28.

Ilson J, Fahn S, Mayeux R. Pergolide treatment in parkinsonism. In: Lisuride and Other Dopamine Agonists. Calne D B Ed. New York, Raven Press, 1983: 443-457.

Iorio L C, Houser V, Korduba C A, Leitz F, Barnett A. SCH 23390, a benzazepine with atypical effects on dopaminergic systems. Pharmacologist 1981; 23: 137.

Iorio L C, Barnett A, Leitz F H, Houser V P, Korduba C A. SCH 23390, a potential benzazepine antipsychotic with unique interactions on dopaminergic systems. J Pharmacol Exp Ther 1983; 226: 462-8.

Irwin I, Langston J W. Selective accumulation of MPP^+ in the substantia nigra: a key to neurotoxicity? Life Sci 1985; 36: 207-212.

Isacson O, Brundin P, Kelly P A T, Gage F H, Björklund A. Functional neuronal replacement by grafted striatal neurons in the ibotenic acid-lesioned striatum. Nature 1984; 311: 458-460.

Iversen L L. Dopamine receptors in the brain. Science 1975; 188: 1084-1089.

Iversen L L, Miller R J. Biochemical pharmacology of dopamine receptors in mammalian central nervous system. In: Bradford H F, Marsden C D, eds. Biochemistry and Neurology. New York: Academic Press, 1976: 35-45.

Iversen S D. Neural substrated mediating amphetamine responses. In: Ellinwood E H, Kilbey M M, eds. Cocaine and Other Stimulants. New York: Plenum Press, 1977: 31-45.

Iversen S. Behavioural effects of manipulation of basal ganglia neurotransmitters. In: Evarts E V, ed. Functions of the Basal Ganglia. Ciba Foundation Symposium London: Pitman, 1984; 107: 183-195.

Jackson D M, Andén N-E, Dahlstöm A. A functional effect of dopamine in the nucleus accumbens and in some other dopamine-rich parts of the rat brain. Psychopharmacol 1975; 45: 139-149.

Jackson D M, Ahlenius S, Andén N-E, Engel J. Antagonism by locally applied dopamine into the nucleus accumbens or the corpus striatum of α-methyltyrosine-induced disruption of conditioned avoidance behaviour. J Neural Transm 1977; 41: 231-239.

Jackson E A, Kelly P H. Effects of intranigral injections of dopamine agonists and antagonists, glycine, muscimol and N-Methyl-D, L-aspartate on locomotor activity. Brain Res Bull 1984; 13: 309-317.

Jackson D M and Hashizume M. Bromocriptine induces marked locometer stimulation in dopamine-depleted mice when D-1 dopamine receptors are stimulated with SKF 38393. Psychopharm 1986; 90: 147.

Jankovic J, Orman J, Jansson B. Placebo-controlled study of mesulergine in Parkinson's disease. Neurol 1985; 35: 161-165.

Jankovic J. Long-term study of pergolide in Parkinson's disease. Neurology 1985; 35: 296-299.

Jaton A L, Enz A, Vigouret J M, Pfaffle P and Markstein R. CQA 206-291, an ergot derivative with biphasic dopaminergic action. Experientia 1987; 43: 705.

Jaton A L, Enz A, Vigouret J M, Markstein R. CQA206-291, an ergot derivative with a biphasic dopaminergic pharmacologic profile. 9th International Symposium on Parkinson's Disease, Jerusalem, Israel, 1988.

Javitch J A, D'Amato R J. Strittmatter S M, Snyder S H. Parkinsonism-inducing neurotoxin, N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. Uptake of the metabolite N-methyl-4-phenylpyridine by dopamine neurons explains selective toxicity. Proc Natl Acad Sci USA 1985; 82: 2173-2177.

Javoy-Agid F, Agid Y. Is the mesocortical dopaminergic system involved in Parkinson's disease? Neurology 1980; 30: 1326-1330.

Javoy-Agid F, Grouselle D, Tixier-Vidal A, Agid Y. Thyrotropin releasing hormone in brain of patients with Parkinson's disease. Neuropeptides 1983; 3: 405-410.

Javoy-Agid F, Ploska A, Agid Y. Microtopography of TH, CAT, and GAD activity in the substantia nigra and ventral area of control and parkinsonian human brain. Neurochemistry 1982; 37: 1221-1227.

Javoy-Agid F, Ruberg M, Hirsch E, et al. Recent progress in the neurochemistry of Parkinson's disease. In: Fahn S, ed. Recent Developments in Parkinson's Disease. New York: Raven Press, 1986: 67-83.

Javoy-Agid F, Ruberg M, Pique L, Bertagna X, Taquet H, Studler J M, et al. Biochemistry of the hypothalamus in Parkinson disease. Neurology 1984; 34: 672-676.

Javoy-Agid F, Ruberg M, Taquet H, et al. Biochemical neuropathology of Parkinson's disease. Adv Neurol 1984; 40: 189-198.

Javoy-Agid F, Taquet H, Ploska A, Cherif-Zahar C, Ruberg M Agid Y. Distribution of catecholamines in the ventral mesencephalon of human brain with special reference to Parkinson's disease. J Neurochem 1981; 36: 2102-2105.

Jellinger K, Danielczyk W. Striato-nigral degeneration. Acta Neurol 1968; 10: 242-257.

Jellinger K. Adjuvant treatment of Parkinson's disease with dopamine agonists. Open trial with bromocriptine and CU 32-085. J Neurol 1982; 227: 75-88.

Jellinger K. Pathology of parkinsonism. In: Marsden C D, Fahn S, Jenner P, Teychenne P, eds. Recent Developments in Parkinson's Disease. New York: Raven Press 1986: 33-66.

Jellinger K. The pathology of parkinsonism. In: Marsden C D, Fahn S, eds. Movements disorders Vol 2: London: Butterworths, 1987: 124-165.

Jenner P, Rupniak N M J, Rose S, et al. 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced parkinsonism in the common marmoset. Neurosci Lett 1984; 50: 85-90.

Jenner P, Marsden C D. The actions of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine in animals as a model of Parkinson's disease. J Neural Trans 1986; (suppl XX): 11-39.

Jenner P, Marsden C D, Nomoto H, Stahl S M. Antiparkinsonian activity of (+)-PHNO in the MPTP-treated marmoset following subcutaneous infusion or skin application. Br J Pharmacol 1986; 89: 626.

Jenner P. Clues to the mechanism underlying dopamine cell death in Parkinson's disease. J Neurol Neurosurg Psychiatry 1989; 52 (suppl): 22-28.

Jenner P, Taquet H, Mauborgne A, et al. Lack of change in basal ganglia neuropeptide content following subacute 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine treatment of the common marmoset. J Neurochem 1986; 47(5): 1548-1551.

Joyce J N, Sapp D W, Marshall J F. Human striatal dopamine receptors are organized in compartments. Proc Natl Acad Sci USA 1986; 83: 8002-8006.

Joynt R J, Gash D M. Neural transplantation: are we ready? Ann Neurol 1987; 22: 455-456.

Kaiser C, Dandridge P A, Garvey E, et al. Absolute stereochemistry and dopa-minergic activity of enantiomers of 2,3,4,5-tetrahydro-7,8-dihydroxy-1-phenyl-1H-3-benzazepine. J Med Chem 1982; 25: 697-703.

Kaiser C, Jain T. Dopamine receptors: Function, subtypes and emerging concepts. Medicinal Res Rev 1985; 5: 145-229.

Kaplan G P, Hartman B K, Creveling C R. Immunohistochemical demonstration of catechol-O-methyltransferase in mammalian brain. Brain Res 1979; 167: 241-250.

Karlsson G, Jaton A-L, Vigouret J-M. Dopamine D1 and D2 receptor interaction in turning behaviour induced by dopamine agonists in 6-hydroxydopamine-lesioned rats. Neurosci Lett 1988; 88: 69-74.

Karobath M and Leitich H. Antipsychotic drugs and dopamine-stimulated adenylate cyclase prepared from corpus striatum of rat brain. Proc Natl Acad Sci USA 1974; 71: 2915-2918.

Kebabian J W, Petzold G L, Greengard P. Dopamine-sensitive adenylate cyclase in caudate nucleus of rat brain, and its similarity to the "dopamine receptor". Proc Natl Acad Sci USA 1972; 69: 2145-2149.

Kebabian J W, Kebabian P R, Munemura M, Calne D B. In: Fuxe K, Calne D B, eds. Dopaminergic Ergot Derivatives and Motor Flunction. New York: Pergamon Press, 1979.

Kebabian J W and Calne D B. Multiple receptors for dopamine. Nature 1979; 277: 93-96.

Kebabian J W, Agui T, van Oene J C, Shigematsu K, Saavedra J M. The D1 dopamine receptor: new perspectives. Trends in Pharmacol Sci 1986; 7: 96-99.

Kelly P H, Seviour P W, Iversen S D. Amphetamine and apomorphine responses in the rat following 6-OHDA lesions of the nucleus accumbens septi and corpus striatum. Brain Res 1975; 94: 507-522.

Kelly P H. Drug-induced motor behaviour. In: Iverson L L, Iverson S D, Snyder S H, eds: Handbook of Psychopharmacology. New York: Plenum Press, 1977; (8): 295-331.

Kelly P H, Moore K E. Mesolimbic dopamine neurons: Effects of 6-hydroxydopamine-induced destruction and receptor blockade on drug-induced rotation of rats. Psychopharmacol 1977; 55: 35-41.

Kelly E, Nahorski S R. Endogenous dopamine functionally activates D-1 and D-2 receptors in the striatum. J Neurochem 1987; 49(1): 115 - 120.

Kelly E, Jenner P, Marsden C D. Behavioural effects mediated by unilateral nigral dopamine receptor stimulation in the rat. Exp Brain Res 1984; 55: 243-252.

Kelly E and Nahorski S R. Endogenous dopamine functionally activates D-1 and D-2 receptors in striatum. J Neurochem 1987; 49: 115.

Kempster P A, Gibb W R G, Lees A J, Stern G M. Asymmetry of substantia nigra loss in Parkinson's disease and its relevance to the mechanisms of motor fluctuations. J Neurol Neurosurg Psychiatry 1989; 52: 72-76.

Kish S J, Shannak K S, Rajput A H, Gilbert J J, Hornyckiewicz O. Cerebellar norepinephrine in patients with Parkinson's disease and control subjects. Arch Neurol 1984; 41: 612-614.

Kish S J, Morito C, Hornykiewicz O. Glutathione peroxidase activity in Parkinson's disease brain. Neurosci Lett 1985; 58: 343-346.

Kish S J, Rajput A, Gilbert J, Rozdilsky B, Chang L J, Shannak K, Hornykiewicz O. GABA is elevated in striatal but not extrastriatal brain regions in Parkinson's disease: correlation with striatal dopamine loss. Ann Neurol 1986; 20: 26-31.

Kish S J, Shannak K, Hornykeiwicz O. Uneven pattern of dopamine loss in the striatum of patients with idiopathic Parkinson's disease: pathophysiologic and clinical implications. N Engl J Med 1988; 318: 876-880.

Klawans H L, Goetz C G, Völkman D. Lergotrile in the treatment of Parkinsonism. Neurology 1978; 28: 699-702.

Knoll J. The possible mechanisms of action of (-)deprenyl in Parkinson's disease. J Neural Transm 1978; 43: 177-198.

Koob G F, Simon H, Herman J P, Le Moal M. Neuroleptic-like disruption of the conditioned avoidance response requires destruction of both the mesolimbic and nigrostriatal dopamine systems. Brain Res 1984; 303: 319-329.

Kopin I J, Markey S P, Burns R S, Johannessen J N, Chiueh C C. Mechanisms of neurotoxicity of MPTP. In: Fahn S, ed. Recent developments in Parkinson's disease. New York: Raven Press, 1986: 165-173.

Korf J, Zielman M, Westerink B H C. Dopamine release in substantia nigra? Nature 1976; 260: 257-258.

Kuhar M J. Autoradiographic localization of drug and neurotransmitter receptors in the brain. Trends In Neurosci 1981; 4: 60-64.

Kurkland L T. Epidemiology: incidence, geographic distribution and genetic considerations. In: Field W J, Thomas C C, eds. Pathogenesis and treatment of Parkinsonism. Springfield: 1958.

Laaksonen H, Riekkinen P, Rinne U K, Sonninen V. Brain glutamic acid decarboxylase and gamma-aminobutyric acid in Parkinson's disease. In: Birkmayer W, Hornykiewicz O eds. Advances in Parkinsonism. Basal: Roche, 1975; 205-210.

Laduron P M. Criteria for receptor sites in binding studies. Biochem Pharm 1984; 33: 833-839.

Lang A E, Quinn N, Brincat S, Marsden C D, Parkes J D. Pergolide in Late-stage Parkinson disease. Ann Neurol 1982; 12: 243-247.

Lang A E. Treatment of Parkinson's disease with agents other than Levodopa and dopamine agonists: controversies and new approaches. Can J Neurol Sci 1984; 11: 210-220.

Landau W M. Artificial intelligence: The brain transplant cure for parkinsonism. Neurology 1990; 40: 733-740.

Langer S Z, Starke K, Dubocovich M L. Presynaptic Receptors. Oxford: Pergamon Press, 1979

Langston J W, Ballard P A. Parkinson's disease in a chemist working with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. N Engl J Med 1983; 309: 310.

Langston J W, Ballard P A, Tetrud J W, Irwin I. Chronic parkinsonism in humans due to a product of meperidine-analog synthesis. Science 1983; 219: 979-980.

Langston J W, Forno L S, Rebert C S. Irwin I. 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine causes selective damage to the zona compacta of the substantia nigra in the squirrel monkey. Brain Res 1984; 292: 390-394.

Langston J W, Irwin I, Langston E B, Forno L S. Pargyline prevents MPTP-induced parkinsonism in primates. Science 1984; 225: 1480-1482.

Langston J W, Irwin I, Langston E B, Forno L S. 1-Methyl-4-phenylpyridinium ion (MPP+): Identification of a metabolite of MPTP, a toxin selective to the substantia nigra. Neurosci Lett 1984; 48: 87-92.

Langston J W, Irwin I, Langston E B, Forno L S. The importance of the '4-5' double bond for neurotoxicity in primates of the pyridine derivative MPTP. Neurosci Lett 1984; 50: 289-294.

Langston J W. MPTP and Parkinson's disease. Trends in Neurosci 1985; 80: 79-83.

Langston J W, and Irwin I. MPTP: Current concepts and controversies. Clin Neuropharmacol 1986; 9: 485-507.

Langston J W, Irwin I, Ricaurte G A. Neurotoxins, Parkinsonism and Parkinson's Disease. Pharmacol Ther 1987; 32: 19-49.

Lee R G. Physiology of the Basal Ganglia and Pathophysiology of Parkinson's Disease. Can J Neurol Sci 1987; 14(3): 373-380.

Lee R G, Tatton W G. Motor response to sudden limb displacements in primates with specific CNS lesions and in human patients with motor system disorders. Can J Neurol Sci 1975; 2: 285-293.

Lee T, Seeman P, Rajput A, Farley I J, Hornykiewicz O. Receptor basis for dopaminergic supersensitivity in Parkinson's disease. Nature 1978; 273: 59-61.

Leenders K L, Palmer A J, Quinn N, et al. Brain dopamine metabolism in patients with Parkinson's disease measured with positron emission tomography. J Neurol Neurosurg Psychiatry 1986; 49: 853-860.

Lees A J, Lander C M, Stern G M. Tiapride in levodopa-induced involuntary movements. J Neurol Neurosurg Psych 1979; 42(4): 380-383.

Lees A J, Kohout L J, Shaw K M, Stern G M, Elsworth J D, Sandler M. Deprenyl in Parkinson's disease. Lancet 1977; ii: 791-795.

Lees A J, Haddad S, Shaw K M, Kohout L J, Stern G M. Bormocriptine in Parkinsonism. Arch Neurol 1978; 35: 503-505.

Lees A J. Monoamine axidase inhibitors.In:Koller W Ed. Handbook of Parkinson's Disease. New York: Marcel Dekker 1987; 403-419.

Lees A J, Stern G M. Sustained bromocriptine therapy in previously untreated patients with Parkinson's disease. J Neurol Neurosurg Psychiatry 1981; 44: 1020-1023.

Lees A J, Smith E. Cognitive deficits in the early stages of Parkinson's disease. Brain 1983; 257-270.

Lees A J. L-Dopa treatment and Parkinson's disease. Q J Med 1986; 59: 535-547.

Leff S E, Creese I. Dopamine receptors re-explained. Trends Pharmacol Sci 1983; 4: 463-467.

Leff S E, Creese I. Dopaminergic D-3 binding sites are not presynaptic autoreceptors. Nature 1984; 306: 586-589.

Lehmann J, Langer S Z. The striatal cholinergic interneuron: synaptic target of dopaminergic terminals? Neuroscience 1983; 10: 1105-1111.

Lemberger L, Crabtree R, Callaghan J T. Pegolide, a potent long acting dopamine receptor agonist. Clin Pahrmacol Ther 1980; 27: 642-651.

Lemberger L, Crabtree R, Clemens J. The inhibitory effect of an ergoline derivative, lergotrile, compound 83,636 on prolactin secretion in man. J Endocrinol Metab 1974; 39: 579-584.

Lesser R P, Fahn S, Sneider S R, Cote L J, Isgreen W P, Barrett R E. Analysis of the clinical problems in parkinsonism and the complications of long term levodopa therapy. Neurology 1979; 29: 1253-1260.

Lewin R. Environmental hypothesis for brain diseases strengthened by new data. Science 1987; 237: 483-484.

Lewin R. Trail of ironies to Parkinson's disease. Science 1984; 224: 1083-1085.

Lewin R. Brain enzyme is the target of drug toxin. Science 1984; 225: 1460-1462.

Lewin R. Parkinson's disease: An environmental cause? Science 1985; 229: 257-258.

LeWitt P A, Calne D B. Recent advances in the treatment of Parkinson's Disease: The role of Bromocriptine. J Neural Transm 1981; 51: 175-184.

LeWitt P A, Gopinathan G, Ward C D, et al. Lisuride versus bromocriptine treatment in Parkinson's disease: A double-blind study. Neurology (NY) 1982; 32: 69-72.

LeWitt P A, Ward C D, Larsen T A, et al. Comparisons of pergolide and bromocriptine therapy in parkinsonism. Neurology 1983; 33: 1009-1014.

LeWitt P A, Calne D B. Experience with dopamine agonists in Parkinson's Disease and related disorders. In:Calne D B, Horowski R, McDonald R J, Wittke W, eds. Lisuride and other dopamine agonists. New York: Raven Press, 1983: 473-480.

LeWitt P A, Burns R S, Newman R P. Dystonia in untreated Parkinsonism. Clin Neuropharmacol 1986; 9(3): 293-297.

LeWitt P, Pintar J E, Breakfield X O. Immunocytochemical demonstration of monoamine oxidase B in brain astrocytes and serotonergic neurons. Proc Nat Acad Sci USA. 1982; 79: 6385-6389.

Leysen J E, Gommereu W, Van Gompel P. Demonstration of a complex subunit composition of a unitary dopamine receptor: effects of lesions and proteolytic enzymes on stereo- specific binding. Adv Biochem Psychopharmacol 1983; 36: 147-162.

Leysen J E, Niemegeers C J E, Tollenaere J P, Laduron P M. Serotonergic component of neuroleptic receptors. Nature 1978; 272: 168-171.

Lieberman A N, Goldstein M, Leibowitz M. Long-term treatment with pergolide: decreased efficacy with time. Neurology 1984; 34: 223-226.

Lieberman A N, Kupersmith M, Casson I. Bromocriptine and lergotrile comparative efficacy in Parkinson disease. Adv Neurol 1979; 24: 461-473.

Lieberman A N, Gopinathan G, Neophytides A. Bromocriptine and lisuride in Parkinson's disease. Ann Neurol 1983; 13: 44-47.

Lieberman A N, Neophytides A, Liebowitz A, et al. Comparitive efficacy of pergolide and bromocriptine in patient's with Parkinson's disease. Adv Neurol 1983; 37: 95-108.

Lieberman A, Goldstein M, Leibowitz M, et al. Treatment of advanced Parkinson's disease with pergolide. Neurology (NY) 1981; 131: 675-682.

Lieberman A, Koslow M. Adrenal grafts for Parkinson's disease. N Engl J Med 1987; 317: 1091-1092.

Lieberman A, Kupersmith M, Estey E, Goldstein M. The treatment of Parkinson's disease with bromocriptine. New Engl J Med 1976; 295: 1400-1404.

Lieberman A N, Gopinathan G, Estey E. Lergotrile in Parkinson's disease: Further studies. Neurology 1979; 29: 267-272.

Lieberman A, Miyamoto T, Battista A, Goldstein M. Studies on the antiparkinsonian efficacy of lergotrile. Neurology 1975; 25: 459-462.

Lieberman A N, Gopanathan G, Neophytides A, et al. Pergolide and lisuride in advanced Parkinson's disease. Adv Neurol 1984; 40: 503-507.

Lieberman A N, Gopinathan G, Nelson J. Mesulergine (CU 32-085) in Parkinson's disease. Neurology 1984; 34 (suppl 1): 270.

Lieberman A, Kupersmith M, Neophytides A. Long-term efficacy of bromocriptine in Parkinson's disease. Neurology 1980; 30: 518-523.

Lieberman A N, Zolfaghari M, Boal D. The antiparkinson efficacy of bromocriptine. Neurology 1976; 26: 405-409.

Lieberman A N, Kupersmith M, Neophytides A. Bromocriptine in Parkinson's disease: Report on 106 patients treated for up to 5 years. In: Goldstein M. ed: Ergot Compounds and Brain Function: Neuroendocrine and Neuropsychiatric Aspects. New York, Raven Press, 1982: 45-53.

Lindvall O, Björklund A. The organization of the ascending catecholamine neuron systems in the rat brain as revealed by the glyoxylic acid fluorescence method. Acta Physiol Scand 1974; 412 (suppl): 1-48.

Lindvall O, Björklund A. The glyoxylic acid fluorescence histochemical method: a detailed account of the methodology for the visualization of central catecholamine neurons. Histochem 1974; 39: 97-127.

Lindvall O, Björklund A. Organization of catecholamine neurons in the rat central nervous system. In: Iversen L L, Iversen S D, Snyder S H, eds. Handbook of Psychopharm, Amsterdam, Elsevier, 1978; 9: 139-231.

Lindvall O, Backlund E-O, Farde L, et al. Transplantation in Parkinson's disease: two cases of adrenal medullary grafts to the putamen. Ann Neurol 1987; 22: 457-468.

Lindvall O, Dunnett S B, Brundin P, Björklund A. Transplantation of catecholamine-producing cells to the basal ganglia in Parkinson's disease: experimental and clinical studies. In: Rose F C, ed. Parkinson's Disease: Clinical and Experimental Advances. London: John Libbey, 1987: 189-206.

Lindvall O, Rehncrona S, Gustavii B, et al. Fetal dopamine-rich mesencephalic grafts in Parkinson's disease. Lancet 1988; ii: 1483-1484.

Lindvall O, Rehncrona S, Brundon P, et al. Human fetal dopamine neurons grafted into the striatum in two patients with severe Parkinson's Disease. Arch Neurol 1989; 46: 615-631.

Lindvall O. Transplantation into the human brain: present status and future possibilities. J Neurol Neurosurg Psychiatry 1989; 52 (suppl): 39-54.

Lindvall O, Brundin P, Widner H, et al. Grafts of foetal dopamine neurons survive and improve motor function in Parkinson's disease. Science 1990; 247: 574-577.

List S J, Seeman P. Resolution of the dopamine and serotonin receptor components of ^{3}H-spiperone binding to rat brain regions. Proc Natl Acad Sci USA 1981; 78: 2620-2624.

List S, Seeman P. ^{3}H-Dopamine labeling of D_3 dopaminergic sites in human, rat and calf brain. J Neurochem 1982; 39: 1363 - 1373.

Lloyd K G, Davidson L, Hornykiewicz O. The neurochemistry of Parkinson's disease: effect of L-Dopa therapy. J Pharmacol Exp Ther 1975; 195: 453-464.

Lloyd K G, Mohler H, Heits P, Bartholini G. Distribution of choline-acetyltransferase and glutamate decarboxylase within the substantia nigra and in other brain regions from control and parkinsonian patients. J Neurochem 1975; 25: 789-795.

Lloyd K G, Shemen L, Hornykiewicz O. Distribution of high affinity sodium-independent [^{3}H]gamma-aminobutyric acid ([^{3}H]gaba) binding in the human brain: alterations in Parkinson's disease. Brain Res 1977; 127: 269-278.

Longoni R, Spina L, Di Chiara G. Permissive role of D-1 receptor stimulation by endogenous dopamine for the expression of postsynaptic D-2 mediated behavioural responses. Yawning in rats. Eur J Pharmacol 1987; 134: 163.

Luef G, Poewe W, Kleedorfer B, Gerstenbrand F, et al. Effectiveness of monotherapy with a novel ergoline (CQA 206-291) in previously untreated patients with Parkinson's disease. 9th International Symposium on Parkinson's disease, Jerusalem, Israel: 1988.

Lund R D, Rao K, Hankin M H, Kunz H W, Gil T J. Transplantation of retina and visual cortex to rat brains of different ages. Maturation, connection patterns, and immunological consequences. Ann NY Acad Sci 1987; 495: 227-240.

Lyrenas S, Carlström K, Bäckström T, Von Schoultz B. A comparison of serum oestrogen levels after percutaneous and oral administration of oestradiol-17β. Br J Obstet Gynaecol 1981; 88: 181-187.

Madrazo I, Drucker-Colin R, Diaz V, Martinez-Mata J, Torres C, Bocerril J J. Open microsurgical autograft of adrenal medulla to the right caudate nucleus in two patients with intractable Parkinson's disease. N Engl J Med 1987; 316: 831-834.

Madrazo L, Léon V, Torres C, et al. Transplantation of fetal substantia nigra and adrenal medulla to the caudate nucleus in two patients with Parkinson's disease. N Engl J Med 1988; 318: 51.

Mahalik T J, Finger T E, Strömberg I, Olson L. Substantia nigra transplants into denervated striatum of the rat: ultrastructure of graft and host interconnections. J Comp Neurol 1985; 240: 60-70.

Mahowald M B. Neural fetal tissue transplantation. Should we do what we can do? Neurol Clin 1989; 7(4): 745-757.

Maj J, Przewlocka B, Kukulka L. Sedative action of low doses of dopaminergic agents. Pol J Pharmacol 1977; 29: 11-21.

Manyam N V B. Low CSF gamma-aminobutyric acid levels in Parkinson's disease, effect of levodopa and carbidopa. Arch Neurol 1982; 39: 391-392.

Markey S P, Johannessen J N, Chiueh C C, Burns R S, Herkenham M A. Intraneuronal generation of a pyridinium metabolite may cause drug-induced parkinsonism. Nature 1984; 311: 464-467.

Markham C H, Diamond S G. Evidence to support early levodopa therapy in Parkinson's disease. Neurology 1981; 31: 125-131.

Markham C H, Diamond S G. Long-term follow-up of early dopa treatment in Parkinson's disease. Ann Neurol 1986; 19: 365-372.

Markstein R, Herrling P L, Büki H R, Asper H, Ruch W. The effect of bromocriptine on rat striatal adenylate cyclase and rat brain monoamine metabolism. J Neurochem 1978; 31: 1163-1172.

Markstein R. Mesulergine and its 1,20-N,N-bidemethylated metabolite interact directly with D1 and D2-receptors. Eur J Pharmacol 1983; 95: 101-107.

Markstein R, Seiler M P, Vigouret J M, Urwyler S, Enz A, Dixon K. In: Sandler M, ed. Progress in catecholamine research, central aspects. New York: Alan Liss, 1989.

Markstein R, Seiler N P, Vigouret J M, Urwyler S, Enz A, Dixon K. Pharmacological properties of CY208-243 and normal D-1 agonists. In: Sandler M, ed. XIth International Catecholamine Symposium. Jerusalem, 1986:

Mars H. Modification of levodopa effect by systemic decarboxylase inhibition. Arch Neurol 1973; 28: 91-95.

Marsden C D, Parkes J D. Success and problems of long-term levodopa therapy in Parkinson's disease. Lancet 1977; i: 345-349.

Marsden C D, Parkes J D. On-off effects in patients with Parkinson's disease on chronic levodopa therapy. Lancet 1976; i: 292-296.

Marsden C D. The mysterious motor function of the basal ganglia: The Robert Wartenberg lecture. Neurology 1982; 32: 514- 539.

Marsden C D, Schachter M. Assessment of extrapyramidal disorders. Br J Clin Pharmacol 1981; 11: 129-151.

Marsden C D. Neurotransmitter and CNS disease: basal ganglia diseases. Lancet 1982; ii: 1141-1147.

Marsden C D, Parkes J D, Quinn N. Fluctuations of disability in Parkinson's disease - clinical aspects. In: Marsden C D, Fahn S, eds. Movement Disorders. London: Butterworth Scientific, 1982: 96-122.

Marsden C D. Parkinson's disease: Review article. Lancet 1991; 335: 948-952.

Marshall J F, Ungerstedt U. Supersensitivity to apomorphine following destruction of the ascending dopamine neurons: Quantification using the rotational model. Eur J Pharmacol 1977; 41: 361-367.

Martin G E, Haubrich D R, Williams M. Pharmacological profiles of the putative dopamine autoreceptor agonists 3-PPP and TL-99. Eur J Pharmacol 1981; 76: 15-23.

Martin G E, Wiliams M, Haubirich D R. A pharmacological comparison of 6,7-dihydroxy-2-dimethylaminotetralin (TL-99) and N-n-propyl-3-(3-hydroxy-phenyl)piperidine (3-PPP) with selected dopamine agonists. J Pharmacol Exp Ther 1982; 223: 298-304.

Martin G E, Bendensky R J. Mouse locomotor activity: An in vivo test for dopamine autoreceptor activation. J Pharmacol Exp Ther 1984; 229: 706-711.

Martin G E, Williams M, Pettibone D J, Yarbrough G G, Clineschmidt B V, Jones J H. Pharmacological profile of a novel potent directly-acting dopamine agonist, (+)-4-propyl-9-hydroxynaphthoxazine [(+)-PHNO]. J Pharmacol Exp Ther 1986; 230: 569-576.

Marttila R J, Rinne U K. Changing epidemiology of Parkinson's disease: Predicted effects of levodopa treatment. Acta Neurol Scand 1979; 59: 80-87.

Marttila R J. Epidemiology. In: Koller W C, ed. Handbook of Parkinson's disease. New York: Marcel Dekker Inc, 1987: 35-50.

Mashurano M and Waddington J L. Stereotyped behaviour in response to the selective D-2 dopamine receptor agonist RU 24213 in enhanced by pretreatment with the selective D-1 agonist SK&F 38393. Neuropharmacology 1986; 25: 947.

Mason D W, Charlton H M, Jones A J, Lavy C B D, Puklavec M, Simmonds S J. The fate of allogeneic and xenogeneic neuronal tissue transplanted into the third ventricle of rodents. Neuroscience 1986; 19: 685-694.

Mattock C, Marmot M, Stern G. Could Parkinson's disease follow intra-uterine influenza? a speculative hypothesis. J Neurol Neurosurg Psychiatry 1988; 51: 753-756,

Mauborgne A, Javoy-Agid F, Legrand J C, Agid Y, Cesselin F. Decrease of substance P-like immunoreactivity in the substantia nigra and pallidum of parkinsonian brains. Brain Res, 1983; 268: 167-170.

Mayeux R, Stern Y. Intellectual dysfunction and dementia in Parkinson's Disease. In: Mayeux R, Rosen W G, eds. The Dementias. New York: Raven Press, 1983: 211-227.

Mayeux R, Stern Y, Rosen J, Benson D F. Is "subcortical dementia" a reconizable clinical entity? Ann Neurol 1983; 14: 278-283.

McGeer P L, McGeer E G, Wada J A. Glutamic acid decarboxylase in Parkinson's disease and epilepsy. Neurology (Min) 1971; 21: 1000-1007.

McGeer P L, McGeer E G. Evidence for Glutamic acid decarboxylase containing interneurons in the neostriatum. Brain Res 1975; 91: 331-335.

McGeer P L, McGeer E G. [illegible] associated with the metabolism of catecholamines, acetylcholine and GABA in human controls and patients with Parkinson's disease and Huntington chorea. J Neurochem 1976; 26: 65-76.

McGeer P L, McGeer E G, Suzuki J S. Aging and extrapyramidal function. Arch Neurol 1977; 34: 33-35.

McGeer E G, Staines W A, McGeer P L. Neurotransmitters in the basal ganglia. Can J Neurol Sci 1984; 11: 89-99.

McGeer P L, McGeer E G, Scherer U, Singh K. A glutamatergic corticostriatal path? Brain Res 1977; 128: 369-373.

McGeer P L, McGeer E G, Nagai T. GABAergic and Cholinergic indices in various regions of rat brain after intracerebral injections of folic acid. Brain Res 1983; 260: 107-116.

McRae-Degueurce A, Hjorth S, Dillon D L, Mason D W, Tice T R. Implantable microencapsulated dopamine (DA): a new approach for slow-release DA delivery into brain tissue. Neurosci Lett 1988; 92: 303-309.

Melamed E, Hefti F, Wurtman R J. Nonaminergic striatal neurons convert exogenous l-dopa to dopamine in parkinsonism. Ann Neurol 1980; 8: 558-563.

Melamed E, Hefti F, Wurtman R J. Compensatory mechanisms in the nigrostriatal dopaminergic system in Parkinson's disease: studies in an animal model. Isr J Med Sci 1982; 18(1): 159-163.

Melamed R W, Rosenthal J, Cohen O, Globus M, Uzzan A. Dopamine but not norepinephrine or serotonin uptake inhibitors protect against neurotoxicity of MPTP. Eur J Pharmacol 1985; 116: 179-181.

Melamed E. Initiation of levodopa therapy in Parkinsonian patients should be delayed until the advanced stages of the disease. Arch Neurol 1986; 43: 402-405.

Melamed E, Bitton V, Zelig D. Episodic unresponsiveness to single doses of L-dopa in Parkinsonian fluctuations. Neurology 1986; 36: 100-103.

Mena I, Cotzias G C. Protein intake and treatment of Parkinson's disease with levodopa. N Eng J Med 1975; 292: 181-184.

Mendlewicz J, Youdin M B H. L-deprenyl monoamine oxidase type B inhibitor in the treatment of depression. A double blind evaluation. Br J Psychiatry 1983; 142: 508-511.

Miller R J, Horn A H and Iversen L L. The action of neuroleptic drugs on dopamine-stimulated adenosine cyclic 3,5-monophosphate production in rat neostriatum and limbic forebrain. Mol Pharmacol 1974; 10: 759-766.

Miller R J and Iversen L L. Effects of chlorpromazine and some of its metabolites on the dopamine-sensitive adenylate cyclase of rat brain striatum. J Pharm Pharmacol 1974; 26: 142-144.

Mitchell I J, Cross A J, Sambrook M A, Crossman A R. Sites of the neurotoxic action of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine in the macaque monkey include the ventral tegmental area and the locus ceruleus. Neuroscience 1985; 61: 195-200.

Mogilnicka E, Klimek V. Drugs affecting dopamine neurons and yawning behaviour. Pharmacol Biochem Behav 1977; 7: 303-305.

Molloy A G, Waddington J L. Dopaminergic behaviour stereospecifically promoted by the D1 agonist R-SK&F 38393; and selectively blocked by the D1 antagonist SCH 23390. Psychopharmacology (Berlin) 1984; 82: 409.

Molloy A G, O'Boyle K M, Waddington J L. The D1 dopamine recepto. and ageing: Behavioural and neurochemical studies. In: Winlow W, Markstein R, eds. The Neurobiology of Dopamine Systems. Manchester: Manchester University Press, 1985.

Molloy A G, O'Boyle K M, Pugh M T, Waddington J L. Locomotor behaviours in response to new selective D1 and D2 dopamine receptor agonists, and the influence of selective antagonists. Pharmacol Biochem Behav. 1986; 25: 249-253.

Monfort J C, Javoy-Agid F, Hauw J J, Dubois B, Agid Y. Brain glutamate decarboxylase and 'premortem severity index', with a special reference to Parkinson's disease. Brain 1985; 108(2): 301-313.

Montagu K A. Catechol compounds in rate tissues and in brain of different animals. Nature 1975; 180: 224-245.

Monsma F J, McVittie L D, Gerfen C R, Mahan L C, Sibley D R. Multiple D2 dopamine receptors produced by alternative RNA splicing. Nature 1989; 342: 926-929.

Morelli M, Di Chiara G. Homologous and heterologous sensitization to D-1 and D-2 receptors after dopaminergic agonists administration in 6-OHDA denervated rats. Xth International Congress of Pharmacology, Sydney, Australia: 1987.

Morgan J P, Bianchine J R, Spiegel H E, Rivera-Calilim L, Hersey R M. Metabolism of levodopa in patients with Parkinson's disease. Arch Neurol 1971; 25: 39-44.

Mouradian M M, Heuser I J E, Baronti F, Chase T N. Modification of Central Dopaminergic Mechanisms by continuous levodopa therapy for advanced Parkinson's Disease. Ann Neurol 1990; 27: 18-23.

Mouradian M M, Juncos J L, Fabbrini G, Chase T N. Motor fluctuations in Parkinson's disease: pathogenetic and therapeutic studies. Ann Neurol 1987; 22: 475-479.

Muenter M D, Sharpless N S, Tyce G M. 3-0-methyldopa in Parkinson's disease. Adv Neurol 1974; 5: 309-315.

Muenter M D, Sharpless N S, Tyce G M, Darley F L. Patterns of dystonia ("I-D-I" and "D-I-D") in response to L-dopa therapy for Parkinson's disease. Mayo Clin Proc 1977; 52: 163-174.

Muenter M D, Tyce G M. L-dopa therapy of Parkinson's disease: plasma L-dopa concentration, therapeutic response, and side effects. Mayo Clin Proc 1971; 46: 231-239.

Muenter M D. Should levodopa therapy be started early or late? Can J Neurol Sci 1984; 11 (suppl): 195-199.

Muenter M P, Ahlskog J E, Bell G, McManis P. PHNO [(+-)-4-propyl-9-hydroxynaphthoxazine]: A new and

effective anti-Parkinson's disease agent. Neurology 1988; 38: 1541-1545.

Mytilineou C, Cohen G, Heikkila R E. 1-Methyl-4-phenyl-pyridine (MPP+) is toxic to mesencephalic dopamine neurons in culture. Neurosci Lett 1985; 57: 19-24.

Nagai T, McGeer P L, McGeer E G. Distribution of GABA-T-intensive neurons in the rat forebrain and midbrain. J Comp Neurol 1983; 218: 220-238.

Nagatsu T, Kanamori T, Kato T, Iizuka R, Narabayashi H. Dopamine stimulated adenylate cyclase activity in the human brain changes in Parkinsonism. Biochem Med 1978; 19: 360-365.

Nakano I, Hirano A. Parkinson's disease: neuron loss in the nucleus basalis without concomitant Alzheimer's disease. Ann Neurol 1984; 15: 415-418.

Nauta H J W, Cole M. Efferent projections of the subthalamic nucleus: an autoradiographic study in monkey and cat. J Comp Neurol 1978; 180: 1-16.

Nauta H J W, Pritz M B, Lasek R J. Afferents to the rat caudoputamen studied with horseradish peroxidase: an evaluation of a retrograde neuroanatomical research method. Brain Res 1974; 67: 219-238.

Nauta W J H, Smith G P, Faull R L M, Domesick V B. Efferent connections and nigral afferents of the nucleus accumbens septi in the rat. Neuroscience 1978; 3: 385-401.

Nestler E J, Greengard P. Protein phosphorylation in the brain. Nature 1983; 305: 583-588.

Nicklas W J, Vyas I, Heikkila R E. Inhibition of NADH-linked oxidation in brain mitochondria by 1-methyl-4-phenylpyridine, a metabolite of the neurotoxin, 1-methyl -4-phenyl-1,2,3,6-tetrahydropyridine. Life Sci 1985; 36: 2503-8.

Nielsen E B, Jepsen S A. Antagonism of the amphetamine cue by both classical and atypical antipsychotic drugs. Eur J Pharmacol 1985; 111(2): 167-176.

Nielsen E B, Scheel-Krüger J. Cueing effects of amphetamine and LSD: Elicitation by direct microinjection of the drugs into nucleus accumbens. Eur J Pharmacol 1986; 125: 85-92.

Niemegeers C J E, Janssen P A J. A systematic study of the pharmacological activities of dopmaine antagonists. Life Sci 1979; 24: 2201-2216.

Nieoullon A, Cheramy A, Glowinski J. Release of dopamine in vivo from cat substantia nigra. Nature 1977; 266: 375-377.

Nobin A, Björklund A. Topography of the monoamine neuron systems in the human brain as revealed in fetuses. Acta Physiol Scand 1973; 388(suppl): 1-40.

Nomoto M, Jenner P, Marsden C D. The dopamine D2 agonist LY141865, but not the D1 agonist SKF 38393, reverses parkinsonism induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in the common marmoset. Neurosci Lett. 1985; 57: 37-41.

Nomoto M, Stahl S, Jenner P and Marsden C D. Antiparkinsonian activity of (+)-PHNO in the MPTP-treated common marmoset. Mov Disord 1987; 2: 37-45.

Nomoto M, Jenner P, Marsden C D. The D1 agonist SKF38393 inhibits the antiparkinsonian activity of the D2 agonist LY171555 in the MPTP-treated marmoset. Neurosci Lett 1988; 93(2-3): 275-280.

Northup J K, Smigel M D, Gilman A G. The guanine nucleotide activating site of the regulatory component of adenylate cyclase: identificatin by ligand binding. J Biol Chem 1982; 257: 11416-11423.

Nutt J G, Fellman J H. Pharmacokinetics of levodopa. Clin Neuropharm 1984; 7: 35-50.

Nutt J G, Woodward W R, Hammerstad J P, Carter J H, Anderson J L. The on-off phenomenon in Parkinson's disease. Relation to levodopa absorption and transport. N Engl J Med 1984; 310: 483-488.

Nutt J G, Woodward W R, Anderson J L. The effect of carbidopa on the pharmacokinetics of intravenously administered Levodopa: the mechanism of action in the treatment of parkinsonism. Ann Neurol 1985; 18: 537-543.

Nutt J G, Woodward W R. Levodopa pharmacokinetics and pharmacodynamics in fluctuating parkinsonian patients. Neurology 1986; 36: 739-744.

Oberlander C, Euvrard C, Dumont C, Boissier J R. Circling behaviour induced by dopamine releasers and/or uptake inhibitors during degeneration of the nigrostriatal pathway. Eur J Pharmacol 1979; 60: 163-170.

Oberlander C, Boissier J R. Postsynaptic striatal dopamine agonist of antagonist actions of (+) or (-) 3-PPP and modification after receptor deafferentation. J Physiol (Paris) 1983; 14: 401-404.

Obeso J A, Luquin M R, Martinez Lage J M. Intravenous lisuride corrects motor oscillations in Parkinson's disease. Ann Neurol 1986; 19: 31-35.

Obeso J A, Luquin M R, Martinez-Lage J M. Lisuride infusion pump: a device for the treatment of motor fluctuations in Parkinson's disease. Lancet 1986; i: 467-470.

Obeso J, Grandas F, Vaamonde J, Luquin M R, Martinez-Lage J M. Apomorphine infusion for motor fluctuations in Parkinson's disease. Lancet 1987; i: 1376-1377.

Obeso J A, Rothwell J C, Quinn N P, et al. Cortical reflex myoclonus response to intravenous lisuride. Clin Neuropharmacol 1983; 6: 231-240.

Obeso J A, Martinez-Lage J M, Luquin M R. Lisuride infusion for Parkinson's disease. Ann Neurol 1983; 14: 134-137.

O'Boyle K M, Pugh M, Waddington J L. Stereotypy induced by the D2 agonist RU 24213 is blocked by the D2 agonist Ro 22-2586 and the D1 antagonist SCH 23390. Br J Pharmacol 1984; 82: 242.

O'Boyle K M, Waddington J L. Selective and stereospecific interactions of R-SK&F 38393 with [^{3}]piflutixol but not [^{3}H]spiperone binding to striatal D1 and D2 dopamine receptors: comparisons with SCH 23390. Eur J Pharmacol 1984; 98: 433-436.

Ohye C, Bouchard R, Boucher R, Poirier L J. Spontaneous activity of the putamen after chronic interruption of the dopaminergic pathway: effect of L-Dopa. J Pharmacol Exp Ther 1970; 175: 700-708.

Olanow L W, Alberts M J. Double blind controlled study of pergolide mesylate in the treatment of Parkinson's

disease. In: Fahn S, Marsden C D. Jenner P, Teychenne P F, eds. Recent developments in Parkinson's disease. New York: Raven Press, 1986: 315-322.

Olson R, Roos B E. Concentrations of 5-Hydroxyindolacetic and homovanillic acid in the cerebrospinal fluid after treatment with probenecid in patients with Parkinson's disease. Nature 1968; 219: 502-503.

Olson L, Backlund E O, Freed W, Marschitz M H, Hoffer B, Seiger A, Strömberg I. Transplantation of monoamine-producing cell systems in oculo and intracranially: Experiments in search of a treatment for Parkinson's disease. Ann NY Acad Sci 1985; 105-123.

Ordenstein L. Sur la Paralysie Agitante et la Sclérose en Plaque Généralisé. Paris, Martinet 1867.

Ouimet C C, Miller P E, Hemmings H C, Walaas S I, Greengard P. DARPP-32, a dopamine- and adenosine 3'5'-monophosphate- regulated phosphoprotein enriched in dopamine- innervated brain regions III: Imunocytochemical localisation. J Neurosci 1984; 4(1): 111-124.

Pardridge W M. Kinetics of competitive inhibition of neutral amino acid transport across the blood-brain barrier. J Neurochem 1977; 28:103-108.

Pardridge W M, Oldendorff W H. Transport of metabolic substrates through the blood-brain barrier. J Neurochem 1977; 28: 5-12.

Parent A, Gravel S, Boucher R. The origin of forebrain afferents to the habenula in rat, and monkey. Brain Res Bull 1981; 6: 23-38.

Parisi J E, Burns R S. MPTP-induced parkinsonism in man and experimental animals. J Neuropathol Exp Neurol 1985; 44: 325.

Parkes J D. Bromocriptine in the treatment of parkinsonism. Drugs 1969; 17: 365-382.

Parkes J D, Baxter R C, Marsden C D, Rees J E. Comparative trial of benzhexol, amantadine and levodopa in the treatment of Parkinson's disease. J Neurol Neurosurg Psychiatry 1974; 37: 422-425.

Parkes J D, Marsden C D, Donaldson I. Bromocriptine treatment in Parkinson's disease. J Neurol Neurosurg Psychiatry 1976; 39: 184-193.

Parkes J D, Schachter M, Marsden C D. Lisuride in parkinsonism. Ann Neurol 1981; 9: 48-52.

Parkes J D. Amantadine. Adv Drug Res 1974; 5: 11-81.

Parkinson J. An Essay on the Shaking Palsy. London: Sherwood, Neely and Jones, 1817.

Pearce L B, Roth J A. Monoamine oxidase: separation of the type A and B activities. Biochem Pharmacol 1984; 33: 1809-1811.

Pearson J, Goldstein M, Markey K, Brandeis L. Human brainstem catecholamine neuronal anatomy as indicated by immunocytochemistry with antibodies to tyrosine hydroxylase. Neuroscience 1983; 8: 3-22.

Pendleton R G, Samler L, Kaiser C, Ridley P T. Studies on renal dopamine receptors with SK&F 38393, a new agonist. Eur J Pharmacol 1978; 51: 19.

Penn R D, Goetz C G, Tanner C M, et al. The adrenal medullary transplant operation for Parkinson's disease: clinical observations in five patients. Neurosurg 1988, 22: 999-1004.

Penney J B Jr, Young A B. Speculations on the functional anatomy of basal ganglia disorders. Ann Rev Neurosci 1983; 6: 73-94.

Perlow M J, Freed W J, Hoffer B J, Seiger A, Olson L, Wyatt R J. Brain grafts reduce motor abnormalities produced by destruction of nigrostriatal dopamine system. Science 1979; 204: 643-647.

Perry T L, Godin D V, Hansen S. Parkinson's disease: A disorder due to nigral glutathione deficiency. Neurosci Lett 1982; 33: 305-310.

Perry T, Yong V W. Idiopathic Parkison's disease, progressive supranuclear palsy and glutathione metabolism in the substantia nigra of patients. Neurosci Lett 1986; 67: 269-274.

Perry E K, Curtis M, '' D J, et al. Cholinergic correlates of cognitive impairment in Parkinson's disease; comparisons with Alzheimer' disease. J Neurol Neurosurg Psychiatry 1985; 48: 413-421.

Perry E K, Perry R H, Candy J M, et al. Cortical serotonin-S2 receptor binding abnormalities in patients with Alzheimer's disease: comparisons with Parkinson's disease. Neurosci Lett 1984; 51: 353-357.

Perry E K, Tomlinson B E, Blessed G, Bergmann K. Gibson P H, Perry R H. Correlation of cholinergic abnormalities with senile plaques and mental test scores in senile dementia. Br Med J 1978; 2: 1457-1459.

Perry R H, Tomlinson B E, Candy J M, et al.Cortical cholinergic deficit in mentally impaired parkinsonian patients. Lancet 1983; ii: 789-790.

Perry T L, Javoy-Agid F, Agid Y, Fibiger H C. Is striatal GABAergic neuronal activity reduced in Parkinson's disease? J Neurochem 1983; 40: 1120-1123.

Peterson D I, Price L, Small C S. Autopsy findings in a patient who had an adrenal-to-brain transplant for Parkinson's disease. Neurol 1989; 39: 235-238.

Pezzoli G, Fahn S, Dwork A, et al. Non-chromaffin tissue plus nerve growth factor reduces experimental parkinsonism in aged rats. Brain Res 1988; 45: 398-403.

Pfeiffer R F, Wilken K, Glaeske C. Mesulergine (CU 32-085) in the treatment of Parkinson's disease. Ann Neurol 1985; 17: 334-336.

Pickel V M, Specht L A, Sumal K K, Joh T H, Reis D J, Hervonen A. Immunocytochemical localization of tyrosine hydroxylase in the human fetal nervous system. J Comp Neurol 1980; 194: 465-474.

Pimoule C, Schoemaker H, Reynolds G P, Langer S Z. [^{3}H]SCH 23390 labelled D-1 dopamine receptors are unchanged in schizophrenia and Parkinson's disease. Eur J Pharmacol 1985; 114: 235-237.

Poewe W, Kleedorfer B, Gerstenbrand F, Oertel W. Subcutaneous apomorphine in Parkinson's disease. Lancet 1988; i: 943.

Porrino L J, Goldman-Rakic P S. Brainstem innervation of prefrontal and anterior cingulate cortex in the rhesus monkey revealed by retrograde transport of HRP. J Comp Neurol 1982; 205: 63-76.

Price K S, Farley I J, Hornykiewics O. Neurochemistry of Parkinson's disease: relation between striatal and limbic dopamine. Adv Biochem Psychopharmacol 1978; 19: 293-300.

Price N M, Schmitt L G, McGuire J, Shaw J E, Trobough G. Transdermal scopolamine in the prevention of motion sickness at sea. Clin Pharmacol Ther 1981; 29: 414-419.

Protais P, Costentin J, Schwartz P C. Climbing behaviour induced by apormorphine in mice: A simple test for the study of dopamine receptors in the striatum. Psychopharmacol 1976; 50: 1-6.

Protais P, Dubuc I, Costentin J. Pharmacological characteristics of dopamine involved in the dual effect of dopamine agonists on yawning behaviour in rats. Eur J Pharmacol 1983; 94: 271-280.

Pycock C J. Turning behaviour in animals. Neuroscience 1980; 5: 461-514.

Pycock C J, Marsden C D. The rotating rodent: A two component system? Eur J Pharmacol 1978; 47: 167-175.

Quinn N, Illas A, Lhermitte F, Agid Y. Bromocriptine and Domperidone in the treatment of Parkinson's disease. Neurology 1981; 31: 662-667.

Quinn N P, Marsden D C, Parkes J D. Complicated response fluctuations in Parkinson's disease. Lancet 1982; 412-415.

Quinn N, Parkes J D, Marsden C D. Control of on/off phenomenon by continuous intravenous infusion of levodopa. Neurology 1984; 34: 1131-1136.

Quinn N P, Lang A E, Sheehy M P, Marsden C D. Lisuride in dystonias. Neurology 1985; 35: 766-769.

Quinn N, Rossor M N, Marsden C D. Dementia and Parkinson's disease - Pathological and neurochemical considerations. Br Med Bull 1986; 42(1): 86-90.

Quinn N P. New strategies in dopaminergic therapy of Parkinson's disease: The use of a controlled-release formulation. Neurology 1989; 39: 72.

Raisman R, Cash R, Ruberg M, Javoy-Agid F, Agid Y. Binding of [^{3}H]SCH 23390 to D-1 receptors in the putamen of control and parkinsonian subjects. Eur J Pharmacol 1985; 113: 467-468.

Rajput A H. Etiology of Parkinson's disease: environmental factor(s). Neurology 1984; 34(suppl): 207-211.

Rajput A H, Stern W, Laverty W H. Chronic low-dose levodopa therapy in Parkinson's disease: an argument for delaying levodopa therapy. Neurology 1984; 34: 991-996.

Ramon y Cajal S. Histologie du Système Nerveux de l'Homme et Vertèbrès. In: Ramon y Cajal, ed. Consejo Superior de Investigaciones Cientificas, Vol 2: Madrid 1955; Inst. Ramon y Cajal, 1955: 275-278.

Ramsay R R, Salach J I, Dadgar J, Singer T P. Inhibition of mitochondrial NADH dehydrogenase by pyridine derivatives and its possible relation to experimental and idiopathic parkinsonism. Biochem Biophys Res Commun 1986; 135: 269-275.

Rascol A, Guiraud B, Montastruc J L, David J, Clanet M. Long-term treatment of Parkinson's disease with bromocriptine. J Neurol Neurosurg Psychiatry 1979; 42: 143-150.

Rascol A, Montastruc J L, Rascol O. Should dopamine agonists be given early or late in the treatment of Parkinson's disease? Can J Neurol Sci 1984, 11(suppl): 229-232.

Rascol O, Fabre N, Senard J M, et al. CQA 206-291 in the management of de novo parkinsonian patients. 9th International Symposium on Parkinson's Disease, Jerusalem, Israel 1988.

Rascol O, Fabre N, Terävänen H, Poewe W, Lücking C, Rinne U, Dupont E, Hirt D, Hoyer M, Lataste X. CQA 206-291: A novel dopamine agonist in the treatment of Parkinson's disease. Clin Neuropharmacol 1990; 13: 303-311.

Redmond D E Jr, Sladek J R Jr, Roth R H, et al. Transplants of primate neurons. Lancet 1986; ii: 1046.

Redmond D E Jr, Sladek J R J, Roth R H, et al. Fetal neuronal grafts in monkeys given methylphenyltetrahydropyridine. Lancet 1986; i: 1125-1127.

Redmond D E Jr, Naftolin F, Collier T J, et al. Cryopreservation, culture, and transplantation of human fetal mesencephalic tissue into monkeys. Science 1988; 242: 768-771.

Reef H E. Prevalence of Parkinson's disease in a multiracial community. In:, den Hartog Jager W A, Bruyn W A, Heijstee A P J, eds. 11th World Congress of Neurology. Amsterdam: Excerpta Medica: 1977.

Reid J L, Calne D B, Vakil S D, Allen J G, Davies C A. Plasma concentration of levodopa in parkinsonism before and after inhibition of peripheral decarboxylase. J Neurol Sci 1972; 17: 45-51.

Reisine T D, Fields J Z, Yamamura H I, Bird E D, Spokes E, Schreiner P S, Enna S J. Neurotransmitter receptor alterations in Parkinson's disease. Life Sci 1977; 21: 335-344.

Reubi J C, Iversen L L, Jessell T M. Dopamine selectively increases ^{3}H-GABA release from slices of rat substantia nigra in vitro. Nature 1977; 268: 652-654.

Reynolds G P, Elsworth J D, Blau K, Sandler M, Lees A J, Stern G M. Deprenyl is metabolised to methamphetamine and amphetamine in man. Br J Clin Pharmacol 1978; 6: 542-544.

Riederer P, Birkmayer W, Seemann D, Wuketich S. Brain-noradrenaline and 3-methoxy-hydroxyphenylglycol in Parkinson's syndrome. J Neural Transm 1977; 41: 241-251.

Riederer P, Rausch W D, Birkmayer W, Jellinger K, Danielczyk W. Dopamine-sensitive adenylate cyclase activity in the caudate nucleus and metabolic encephalopathies. J Neural Transm 1978; 14:(suppl) 153-159.

Riederer P, Reynolds G P, Danielczyk W, Jellinger K, Seemann D. Desensitization of striatal spiperone-binding sites by dopaminergic agonists in Parkinson's disease. In: Calne D B, ed. Lisuride and Other Dopamine Agonists. New York: Raven Press, 1983: 375-381.

Riederer P, Wuketich S. Time course of nigrostriatal degeneration in Parkinson's disease. J Neural Transm 1976; 38: 277-301.

Rinne U K, Skirtola T, Sonninen V. L-deprenyl treatment of on-off phenomena in Parkinson's disease. J Neural Transm 1978; 43: 253-262.

Rinne U K, Koskinen V, Lonnberg P. Neurotransmitter receptor in the parkinsonian brain. In: Rinne U K, Klinger M, Stamm G, eds. Parkinson Disease. Amsterdam: Elsevier, 198.: 93-107.

Rinne U K. Treatment of Parkinson's disease. Problems with a progressing disease. J Neural Transm 1981; 51: 161-174.

Rinne U K. Problems associated with long term levodopa treatment of Parkinson's disease. Acta Neurol Scand 1983; 68 (suppl 95): 19-26.

Rinne U K. Dopamine agonists in the treatment of Parkinson's disease. Adv Neurol 1983; 37: 141-149.

Rinne U K. Combined bromocriptine - levodopa therapy early in Parkinson's disease. Neurology 1985; 35: 1196-1198.

Rinne J O, Rinne J K, Laakso K, Lönnberg P, Rinne U K. Dopamine D-1 receptors in the parkinsonian brain. Brain Res 1985; 359: 306-310.

Rinne U K. Early combination of Bromocriptine and Levodopa in the treatment of Parkinson's disease. In: Fahn S, Marsden C D, Jenner P, Teychenne P F, eds. Recent developments in Parkinson's Disease. New York: Raven Press, 1986: 267-272.

Rinne U K. Early combination of bromocriptine and levodopa in the treatment of Parkinson's disease: a 5-year follow-up. Neurology 1987; 37: 826-828.

Rinne U K. Lisuride, a dopamine agonist in the treatment of early Parkinson's disease. Neurology 1989; 39: 336-339.

Rinne U K, Rinne J O. Treatment of early Parkinson's disease with controlled-release levodopa preparations. Neurology 1989; 39: 78.

Rinne U K. New strategies in dopaminergic therapy of parkinson's disease: The use of a controlled-release formulation. Neurology 1989; 39: 95.

Rinne U K, Koskinen V, Laaksonen H, Lönnberg P, Sonninen V. GABA receptor binding in the parkinsonian brain. Life Sci 1978; 22: 2225-2228.

Rinne U K. New ergot derivatives in the treatment of Parkinson's disease. In: Lisuride and Other Dopamine Agonists, ed. Calne D B, New York, Raven Press, 1983; 431-442.

Rinne U K, Laaksonen H, Riekkinen P, Sonninen V. Brain glutamic acid decarboxylase activity in Parkinson's disease. Eur J Neurol 1974; 12: 13-19.

Rinne U K, Lönnberg P, Koskinen V. Dopamine receptors in the parkinsonian brain. J Neural Transm 1981; 51: 97-106.

Rinne U K, Sonninen V, Laaksonen H. Responses of brain neurochemistry to levodopa treatment in Parkinson's disease. Adv Neurol 1979; 24: 259-274.

Rinne U K. Early dopamine agonist therapy in Parkinson's disease. Adv Neurol 1990; 53: 417-420.

Rinvik E, Grofova I, Ottersen O P. Demonstration of nigrotectal and nigroreticular projections in the cat

by axonal transport of proteins. Brain Res 1976; 112: 338-394.

Rivera-Calimlim L, Dujovne C A, Morgan J P, Lasagna L, Bianchine J R. L-dopa treatment failure: explanation and correction. Br Med J 1970; 4: 93-94.

Robbins T W, Everett B J. Functional studies of the central catecholamines. Int Rev Neurobiol 1982; 25: 303-366.

Robertson G S, Robertson H A. Synergistic effects of D1 and D2 dopamine agonists on turning behaviour in rats. Brain Res 1986; 384: 387-390.

Robertson G S, Robertson H A. D1 and D2 dopamine agonist synergism: separate sites of action? Trends Pharm Sci 1987; 8: 295-299.

Robertson J A. The ethical acceptability of fetal tissue transplants. Transplant Proc, 1990; 22(3): 1025-1027.

Robinson D S, Nies A, Davis J N, et al. Ageing, monoamines, and monoamine-oxidase levels. Lancet 1972; i: 290-291.

Rondot P, Ziegler M, Aymard N, Teinturier A. Session IV: Therapy with controlled-release levodopa. Effect of controlled-release carbidopa/levodopa on motor performance in advanced Parkinson's disease. Neurology 1989; 39: 74.

Rose G, Gerhardt G, Strömberg I, Olson L, Hoffer B. Monoamine release from dopamine-depleted rat caudate nucleus reinnervated by substantia nigra transplants: an in vivo electrochemical study. Brain Res 341: 92-100.

Rosenstein J M. Neocortical transplants in the mammalian brain lack a blood barrier to macromolecules. Science 1987; 235: 772-774.

Rosengarten H, Schweitzer J W, Friedhoff A J. Induction of oral dyskinesias in naive rats by D1 stimulation. Life Sci 1983; 33: 2479-2482.

Rossetti Z L, Sotgiu A, Sharp D, Hadjic stantinou M, Neff N H. 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and free radicals in vitro. Biochem Pharmacol 1988; 37; 4573-4574.

Rossor M N, Garrett N J, Johnson A L, Mountjoy C, Roth M, Iversen L L. A postmortem study of the cholinergic and GABA systems in senile dementia. Brain 1982; 105: 313-330.

Ruberg M, Ploska A, Javoy-Agid F, Agid Y. Muscarinic binding and choline acetyltransferase activity in Parkinson subject with reference to dementia. Brain Res 1982; 232: 129-139.

Ruberg M, Rieger F, Villageois A, Bonnet A M, Agid Y. Acetylcholinesterase and butyrylcholinesterase in frontal cortex and cerebrospinal fluid of demented and non-demented patients with Parkinson's disease. Brain Res 1986; 362: 83-91.

Ruffieux A, Schultz W. Dopaminergic activation of reticulata neurones in the substantia nigra. Nature 1980; 285: 240-241.

Rupniak N M J, Tye S J, Jennings C A, et al. Antiparkinsonian efficacy of a novel transdermal delivery system for (+)-PHNO in MPTP-treated squirrel monkeys. Neurology 1989; 39: 329-335.

Sacks O. Awakenings. London: Picador, 1982.

Sadeh M, Brahim J, Modan M. Effects of anticholinergic drugs on memory in Parkinson's disease. Arch Neurol 1982; 39: 666-667.

Saltzman W M, Pasternak W M S, Langer R. Recent advances in controlled release technology. In: Lee P I and Good W R, eds. ACS Symposium, Washington (DC). Amer Chem Soc, 1987; 348: 17-33.

Sandler M, Johnson R D, Ruthven C R J, Reid J L, Calne D B. Transaminatation is a major pathway of L-dopa metabolism following peripheral decarboxylase inhibition. Nature 1974; 247: 364-366.

Sasahara K, Nitanai T, Habara T, Moroika T, Nakajima E. Dosage form design for improvement of bioavailability of levodopa. IV: Possible causes of low bioavailability of oral levodopa in dogs. J Pharm Sci 1981; 70: 730-733.

Sasahara K, Nitanai T, Habara T, Moroika T, Nakajima E. Dosage form design for improvement of bioavailability of levodopa. V: Absorption and metabolism of levodopa in intestinal segments of dogs. J Pharm Sci 1981; 70: 1157-1160.

Scapagnini, Clement G, Fiore L, Marcchetti B, Prato A, Fonzo G, Nistico G, Germana G, Bronzetti B. Sulpiride and other Benzamides. In: Spano P F, Trabucchi M, Corsini C U, Gessa G L, eds. Italian Brain Research Foundation Press, 1979: 193-205.

Scatton B, Dennis T, L'Heureux R, Monfort J C, Duyckaerts C, Javoy-Agid F. Degeneration of noradrenergic and serotoninergic but not dopaminergic neurons in the

lumbar spinal cord of parkinsonian patients. Brain Res 1986; 380(1): 181-185.

Scatton B. Brain 3,4-dihydroxyphenyl ethyleneglycol levels are dependent on central noradrenergic neuron activity. Life Sci 1982; 31(5): 495-504.

Scatton B, Javoy-Agid F, Rouquier L, Dubois B, Agid Y. Reduction of cortical dopamine, noradrenaline, serotonin and their metabolites in Parkinson's disease. Brain Res 1983; 275: 321-328.

Scatton B, Monfort J C, Javoy-Agid F, Agid Y. Neurochemistry of monoaminergic neurones in Parkinson's disease.In: Catecholamines: Neuropharmacology and Central Nervous System. Therapeutic Aspects, New York: Alan R. Liss Inc, 1984: 43-52.

Schachter M, Bédard P, Debono A G, et al. The role of D-1 and D-2 receptors. Nature 1980; 286: 157-159.

Schachter M, Marsden C D, Parkes J D, Jenner P, Testa B. Deprenyl in the management of response fluctuations in patients with Parkinson's disease on levodopa. J Neurol Neurosurg Psychiatry 1980; 43: 1016-1021.

Schapira A H V, Cooper J M, Dexter D, Jenner P, Clark J B, Marsden C D. Mitochondrial complex I deficiency in Parkinson's disease. Lancet 1989; i: 1269.

Scheel-Krüger J, Arnt J. New aspects on the role of dopamine, acetylcholine and GABA for the development of tardive dyskinesia. In: Casey D, Chase T N, Christensen A V, Gerlach J, eds. Dyskinesia-Research and Treatment. Pharmacology Berlin: Springer-Verlag, 1985; (suppl 2): 46-57.

Schmidt R H, Björklund A, Stenevi U. Intracerebral grafting of dissociated CNS tissue suspensions: a new approach for neuronal transplantation to deep brain sites. Brain Res 1981; 218: 347-356.

Schmidt R H, Björklund A, Stenevi U, Dunnett S B, Gage F H. Intracerebral grafting of neuronal cell suspensions. III: Activity of intrastriatal nigral suspension implants as assessed by measurements of dopamine synthesis and metabolism. Acta Phys Scand 1983; 522(suppl): 19-28.

Schneider J S, Yuwiler A, Markham C H. Production of a Parkinson-like syndrome in the cat with n-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP): behaviour, histology, and biochemistry. Exp Neurol 1986; 91: 293-307.

Schoemaker H, Pimoule C, Arbilla S, Scatton B, Javoy-Agid F, Langer S.Z. Sodium dependent [^{3}H]cocaine binding associated with dopamine uptake sites in the rat striatum and human putamen decrease after dopaminergic denervation and in Parkinson's disease. Arch Pharmacol 1985; 329: 227-235.

Schoenberg B S, Anderson D W, Haerer A F. Prevalence of Parkinson's disease in the biracial population of Copiah Country, Mississipi. Neurology 1985; 35: 841-845.

Schoenberg B S. Environmental risk factors for Parkinson's disease: the epidemiologic evidence. Can J Neurol Sci 1987; 14 (Suppl 3): 407-413.

Schultz W. Depletion of dopamine in the striatum as an experimental model of Parkinsonism: Direct effects and adaptive mechanisms. Prog Neurobiol 1982; 18: 121-166.

Schultzberg M, Dunnett S B, Björklund A, et al. Dopamine and cholecystokinin immunoreactive neurones in mesencephalic grafts reinnervating the neostriatum: evidence for selective growth regulation. Neurosci 1984; 12: 17-32.

Schwab R S, England A C Jr. Amantadine HCL (Symmetrel) and its relation to levo-dopa in the treatment of Parkinson's disease. Trans Am Neurol Assoc 1969; 94: 85-90.

Schwab R S, Poskanzer D C, England A C, Young R R. Amantadine in Parkinson's disease. Review of more than two years experience. JAMA 1972; 222: 792-795.

Schwab R W. Progression and prognosis in Parkinson's disease. J Nerv Ment Dis 1960; 130: 556-566.

Schwab R S, England J C Jr: Projection technique for evaluating surgery in Parkinson's disease. In: Gillingham F H, Donaldson M C, eds. Third Symposium on Parkinson's disease. Edinburgh: Livingstone, 1969: 152-157.

Schwarcz R, Fuxe K, Agnati L F, Hökfelt T, Coyle J T. Rotational behaviour in rats with unilateral striatal kainic acid lesions: A behavioural model for studies on intact dopamine receptors. Brain Res 1979; 170: 485-495.

Seeman P, Chau-Wong M, Tedesco JL, Wong K. Brain receptors for antipsychotic drugs and dopamine: Direct binding assays. Proc Natl Acad Sci USA 1975; 72: 4376-4380.

Seeman P, Lee T, Chau-Wong M, Wong K. Antipsychotic drug doses and neuroleptic/dopamine receptors. Nature 1976; 261: 717-9.

Seeman P. Brain dopamine receptors. Pharmacol Rev 1980; 32: 229-313.

Seeman P. Nomenclature of central and peripheral dopaminergic sites and receptors. Biochem Pharmacol 1982; 31: 2563-2568.

Seeman P, Ulpian C, Bergeron C,et al. Bimodal distribution of dopamine receptor densities in brains of schizophrenics. Science 1984; 225: 728-731.

Seeman P, Grigoriadis D. Dopamine D-2 receptor dissociation constant for spiperone: Identical values using ^{3}H-labeled agonist or ^{3}H-Labeled antagonist. Biochem Pharm 1985; 34: 4065-4066.

Seeman P, Ulpian C, Grigoriadis D, Pri-Bar I, Buchman O. Conversion of dopamine D-1 receptors from high to low affinity for dopamine. Biochem Pharmacol 1985; 34: 151-154.

Seeman P, Grigoriadis D, George S R, Watanabe M, Ulpian C. Functional states of dopamine receptors. In: Woodruff G N, Poat J A, Roberts P J, eds. Dopaminergic Systems and Their Regulation. London: MacMillan Press, 1986: 97-109.

Seeman P, Grigoriadis D. Biochemistry of dopamine receptors in brain and periphery. Neurochem Int 1987; 10: 1-25.

Seeman P. The absolute density of Neurotransmitter Receptors in the Brain. Example for dopamine receptors. J Pharmacol Methods 1987; 17: 347-360.

Seeman P. Dopamine Receptors and the Dopamine Hypothesis of Schizophrenia. Synapse 1987; 1: 133-152.

Seeman P. Human Brain D1 and D2 dopamine receptors in Schizophrenia, Alzheimer's, Parkinson's, and Huntington's Diseases. Neuropsychophamacol 1987; 1: 5-15.

Seeman P. The absolute density of neurotransmitter receptors in the brain: Example for dopamine receptors. J Pharmacol Methods 1987; 17(4): 347-360.

Sethy V H. Regulation of striatal acetylcholine concentration by D-2 dopamine receptors. Eur J Pharmacol 1979; 60(4): 397-398.

Setler P E, Sarau H M, Zirkle C L, Saunders H L. The central effects of a novel dopamine agonist. Eur J Pharmacol 1978; 50: 419-430.

Setler P E, Malesky M, McDevitt J, Turner K. Rotation produced by administration of dopamine and related substances directly into the supersensitive caudate nucleus.Life Sci 1978; 23(12) : 1277-1284.

Shalaby I A, Spear L P. Psychopharmacological effects of low and high doses of apomorphine during ontogeny. Eur J Pharmacol 1980; 67: 451-459.

Sharpless N S, Muenter M D, Tyce G M, Owen C A. 3-Methyoxy-4-hydroxyphenylalanine (3-O-methyldopa) in plasma during oral L-dopa therapy of patients with Parkinson's disease. Clin Chemica Acta 1972; 37: 359-369.

Shaw J E, Urquhart J. Programmed, systemic drug delivery by the transdermal route. Trends Pharmacol Sci 1980; 1: 208-211.

Shaw K M, Lees A J, Stern G M. The impact of treatment with levodopa in Parkinson's disease. Q J Med 1980; 195: 283-293.

Shaw J E, Urquhart J. Transdermal drug administration - a nuisance becomes opportunity. Br Med J 1981; 283: 875-876.

Sherman A D, Petty F, Sacquitne J L. Regional aspects of the delay of acquisition conditioned avoidance responding by chlorpromazine. Life Sci 1982; 30: 1811-1815.

Shibuya M. Dopamine sensitive adenylate cyclase activity in the striatum of Parkinson's disease. J Neural Transm 1979; 44: 287.

Shoulson I, and the Parkinson Study Group. DATATOP: A multicentre controlled clinical trial in early Parkinson's disease. Arch Neurol 1989; 46: 1052-1060.

Shoulson I, and the Parkinson Study Group. Effect of deprenyl on the progression of disability in early Parkinson's disease. N Engl J Med 1989; 321: 1364-1371.

Shoulson I, Glaubiger G A, Chase T N. "On-off" response: clinical and biochemical correlations during oral and intravenous levodopa administration in p..rkinsonian patients. Neurology 1975; 25: 1114-1148.

Shy G M, Drager G A. A neurologic syndrome associated with orthostatic hypotension. Arch Neurol 1960; 2: 511-527.

Sibley D R, Leff S E, Creese I. Interactions of novel dopaminergic ligands with D-1 and D-2 dopamine receptors. Life Sci 1983; 31(7): 637-654.

Sibley D R, Creese I. Interactions of ergot alkaloids with anterior pituitary D-2 dopamine receptors. Mol Pharmacol 1983; 23: 585-593.

Singer T P, Salach J I, Crabtree D. Reversible inhibition and mechanism-based irreversible inactivation of monoamine oxidases by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Biochem Biophys Res Commun 1985; 127: 707-712.

Singer T P, Castagnoli N Jr, Ramsay R R, Trevor A J. Biochemical events in the development of parkinsonism induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. J Neurochem 1987; 49: 1-8.

Skirboll L R, Grace A A, Bunney B S. Dopamine auto-and postsynaptic receptors: Electrophysiological evidence of differential sensitivity to dopamine agonists. Science 1979; 206: 80-82.

Sladek J R Jr, Collier T J, Haber S N, Roth R H. Redmond D E Jr. Survival and growth of fetal catecholamine neurons transplanted into primate brain. Brain Res Bull 1986; 17: 809-818.

Sladek J R Jr, Redmond D E Jr, Collier T J, et al. Transplantation of fetal dopamine neurons in primate brain reverses MPTP induced parkinsonism. Prog Brain Res 1987; 71: 309-323.

Sladek J R Jr, Collier T J, Haber S N, et al. Reversal of parkinsonism by fetal nerve cell transplants in primate brain. Ann NY Acad Sci 1987; 495: 641-657.

Sladek J R Jr, Redmond D E Jr, Collier T J, et al. Fetal dopamine neural grafts: extended reversal of methylamphetamine in N-methyl 1,2,3,6 tetrahydropyri-

dine-induced parkinsonism in monkeys. Prog Brain Res 1988; 78: 497-596.

Sladek J R, Redmond D E, Roth R H. Transplantation of fetal neurones in primates. Clin Res 1988; 36: 200-204.

Sladek J R Jr, Shoulson S. Neural transplantation: a call for patience rather than patients. Science 1988; 240: 1386-1388.

Snyder S H. Neurotransmitter receptors in the brain molecular approaches. Trends Neurosci 1978; 1: 123-125.

Snyder S H, D'Amato R J. MPTP: a neurotoxin relevant to the pathophysiology of Parkinson's disease. Neurology 1986; 36: 250-258.

Sokoloff P, Martes M P, Schwartz J C. Three classes of dopamine receptor (D-2, D-3, D-4) identified by binding studies with ^{3}H-apomorphine and ^{3}H-domperidone. Arch Pharmacol 1980; 315: 89-112.

Sokoloff P, Brann M, Redouane K, et al. The use of [(3)H] (-)-DO 710 as selective dopaminergic ligand for binding and autoradiographic studies. Eur J Phar 1985; 107(2): 243-251.

Spano P F, Govoni S, and Trabucchi M. Dopamine receptors in various areas of the central nervous system. Adv Biochem Psychopharm 1978; 19: 155-165.

Spano P F, Stefanini E, Trabucchi M, Fresia P. Sulpiride and other Benzamides. In: Spano P F, Trabucchi M, Corsini G U, Gessa G L, eds. Milan: Italian Brain Research Foundation Press, 1979: 11-31.

Spencer P S, Nunn P B, Hugon J, Ludolph A C, Ross S M, Roy D N, Robertson R C. Guam amyotrophic lateral sclerosis-parkinsonism-dementia linked to a plant excitant neurotoxin. Science 1978; 237: 517-522.

Spencer S E, Wooten G F. Altered pharmacokinetics of L-dopa metabolism in rat striatum deprived of dopaminergic innervation. Neurology 1984; 34: 1105-1108.

Spencer P S. Nun P B, Hugon J, et al. Motorneurone Disease on Guam: Possible role of a food neurotoxin. Lancet 1986; i: 965.

Spencer P. Guam ALS/Parkinsonism-Dementia: a long-term latency neurotoxic disorder caused by 'slow-toxin(s)' in food? Can J Neurol Sci 1987; 14, 3(suppl) 347-357.

Spiegel E A, Wycis H T, Freed H. Stereoencephalotomy. Thalamotomy and related procedures. JAMA 1952; 148: 446-451.

Staal-Schreinemachers A L, Wesselring H, Kamphuis D J, v d Burg W, Lakke J P W. Low dose bromocriptine therapy in Parkinson's disease: Double blind placebo-controlled study. Neurology 1986; 36: 291-293.

Starke K, Spaeth J D, and Adelung C. Further functional in vitro comparison of pre- and post-synaptic dopamine receptors in the rabbit caudate nucleus. Arch Pharmacol 1983; 323: 298-306.

Starr M S, Summerhayes M. Multifocal brain sites for apomorphine-induced circling and other stereotyped motor behaviour in the 6-hydroxydopamine-lesioned rat. Neurosci Lett 1982; 34: 277-282.

Steinbusch H W M. Serotonin-immunoreactive neurons and their projections in the CNS. In: Björklund A, Hökfelt

T, Kuhar M J, eds. Classical Transmitters and Transmitter Receptors in the CNS. Part II. Handbook of Chemical Neuroanatomy, Vol 3. Amsterdam: Elsevier, 1984: 68-126.

Steinsland O S, Hieble J P. Dopaminergic inhibition of adrenergic neurotransmission as a model for studies on dopamine receptor mechanisms. Science 1978; 199: 443-445.

Stern G M, Lees A J, Sandler M. Recent observations on the clinical pharmacology of (-)deprenyl. J Neural Transm 1978; 43: 245-251.

Stern Y, Mayeux R, Rosen J, Ilson J. Perceptual motor dysfunction in Parkinson's disease: A deficit in sequential and predictive movement. J Neurol Neurosurg Psychiatry 1983; 46: 145-151.

Stern G M, Lees A J. Sustained bromocriptine therapy in 50, previously untreated patients with Parkinson's disease. Adv Neurol 1983; 37: 17-21.

Stern G. Role of Bromocriptine. In: Fahn S, Marsden C D, Jenner P, Teychenne P F, eds. Recent developments in Parkinson's disease. New York: Raven Press, 1986: 259-262.

Stern Y, Langston J W. Intellectual changes in patients with MPTP-induced parkinsonism. Neurology 1985; 35: 1506-1509.

Stern G M. A long-term comparative trial of three treatment regimens in previously untreated patients with Parkinson's disease: Research Group of the United Kingdom. IX International Symposium on Parkinson's Disease. 1988: 67.

Sternberger L A, Joseph F A. The unlabelled antibody method of paired pituitary hormone without antibody removal. J Histo Cytochem 1979; 29: 1424-1429.

Stibe C, Lees A, Stern G. Subcutaneous infusion of apomorphine and lisuride in the treatment of parkinsonian on-off fluctuations. Lancet 1987; i: 871.

Stibe C M H, Kempster P A, Lees A J, Stern G M. Subcutaneous apomorphine in parkinsonian on-off oscillations. Lancet 1988; i: 403-406.

Stoessl A J, Mak E, Calne D B. (+)-4-Propyl-9-hydroxy naphthoxazine (PHNO), a new dopaminimimetic, in treatment of parkinsonism. Lancet 1985; ii: 1330-1331.

Stoof J C, Kebabian J W. Opposing roles for D-1 and D-2 dopamine receptors in efflux of cyclic AMP from rat neostriatum. Nature 1981; 294: 366-368.

Stoof J C. Dopamine receptors in the neostriatum: biochemical and physiological studies. In: Kaiser C, Kebabian J W, eds. Dopamine Receptors. Washington (DC): American Chemical Society, 1983: 117-145.

Stoof J C, Kebabian J W. Two dopamine receptors: Biochemistry, physiology and pharmacology. Life Sci 1984; 35: 2281-2296.

Stoof J C, Kebabian J W. Opposing roles for D-1 and D-2 dopamine receptors in efflux of cyclic AMP from rat neostriatum. Nature 1981; 294: 366-8.

Strecker R E, Sharp T, Brundin P, Zetterström T, Ungerstedt U, Björklund A. Autoregulation of dopamine release and metabolism by intrastriatal nigral grafts as revealed by intracerebral dialysis. Neuroscience, 1987; 22: 169-178.

Stricker E M, Zigmond M J. Recovery of function after damage to central catecholamine-containing neurons: a neurochemical model for the lateral hypothalamic syndrome. In: Sprague J M, Epstein A N, eds. Progress in Psychobiology and Physiological Psychology. New York: Academic Press, 1976; 121-188.

Strömberg I, Herrera-Marshitz M, Ungerstedt U, et al. Chronic implants of chromaffin tissue into the dopamine-denervated striatum: effects of NGF on graft survival, fiber growth and rotational behaviour. Exp Brain Res 1985; 60: 335-349.

Studler J M, Javoy-Agid F, Cesselin F, Legrand J C, Agid Y. CCK-8 immunoreactivity distribution in human brain: selective decrease in the substantia nigra from parkinsonian patients. Brain Res 1982; 243: 176-179.

Sumners C, De Vries J B, Horn A S. Behavioural and neurochemical studies on apomorphine-induced hypomotility in mice. Neuropharmacol 1981; 20: 1203-1208.

Sunahara R K, Guan H-C, O'Dowd B F. et al. Cloning of the gene for a human dopamine D5 receptor with higher affinity for dopamine than D1. Nature 1991; 350: 614-619.

Swanson L W. The projections of the ventral tegmental area and adjacent regions: a combined fluorescent retrograde tracer and immunofluorescence study in the rat. Brain Res Bull 1982; 9: 321-353.

Sweet R D, Wasterlain C G, McDowell F H. Piribedil, a dopamine agonist, in Parkinson's disease. Clin. Pharmacol Ther., 1974; 16: 1077-1082.

Sweet R, McDowell F H. Five years treatment of Parkinson's disease with levodopa. Therapeutic results and survival of 100 patients. Ann Int Med 1975; 83: 456-463.

Tanner C M, Chhabiani R, Goetz C G, Klawans H L. Pergolide mesylate: Lack of cardiac toxicity in patients with cardiac disease. Neurology 1985; 35: 918-921.

Tanner C M. The role of environmental toxins in the etiology of Parkinson's disease. Trends Neurosci 1989; 12: 49-54.

Taquet H, Javoy-Agid F, Hamon M, Legrand J C, Agid Y, Cesselin F. Parkinson's disease affects differently Met and Leu-enkephalin in the human brain. Brain Res 1983; 280: 379-382.

Taquet H, Javoy-Agid F, Giraud P, Legrand J C, Agid Y, Cesselin F. Dynorphin levels in parkinsonian patients: Leu-enkepahlin production from either proenkephalin A or prodynorphin in human brain. Brain Res 1985; 341: 390-392.

Tatton W G, Bedingham W, Verrier M C, et al. Characteristic alterations in responses to imposed wrist displacements in parkinsonian rigidity and dystonia musculorum deformans. Can J Neurol Sci 1984; 11: 281-287.

Temlett J A, Quinn N P, Jenner P G, Marsden C D, et al. Anti-parkinsonian activity of CY208-243, a partial D-1 dopamine receptor agonist, in MPTP-treated marmosets and patients with Parkinson's disease. Mov Disord 1989; 4(3): 261-265.

Temlett J A, Quinn N P, Marsden C D, Lataste X, Jaton A L. The antiparkinsonian activity of CQA206-291, a new D2 dopamine receptor agonist. Clin Neuropharmacol 1989; 12(1): 55-59.

Temlett J A, Chong P N, Oertel W H, Jenner P, Marsden C D. The D-1 dopamine receptor partial agonist, CY208-243, exhibits antiparkinsonian activity in the MPTP-treated marmoset. Eur J Pharmacol 1988; 156(2): 197-206.

Teräväinen H. Selegiline in Parkinson's disease. Acta Neurol Scand 1990; 81: 333-336.

Terry R D, Peck A, Deteresa R, Schechter R, Horoupian D.S. Some morphometric aspects of the brain in senile dementia of the Alzheimer type. Ann Neurol 1981; 10: 184-192.

Testa B, Naylor R, Costall B, Jenner P, Marsden C D. Does an endogenous methylpyridinium analogue cause Parkinson's disease. J Pharm Pharmacol 1985; 37: 679-680.

Tetrud J W, Langston J W. The effect of deprenyl (selegiline) on the natural history of Parkinson's disease. Science 1989; 245: 519-522.

Tetrud J W, Langston J W. L-deprenyl as a possible protective agent in Parkinson's disease. J Neural Transm 1987; (Suppl 25): 1-20.

Teychenne P F, Pfeiffer R, Bern S M, Calne D B. Experiences with new ergolene (CF25397) in parkinsonism. Neurology 1977; 27: 1140-1143.

Teychenne P F, Pfeiffer R F, Bern S M. Comparison between lergotrile and bromocriptine in parkinsonism. Ann Neurol 1978; 3: 319-324.

Teychenne P F, Ziegler M G, Lake R C, Enna S J. Low CSF GABA in parkinsonian patients who respond poorly to therapy or suffer from the 'on-off' phenomenon. Ann Neurol 1982; 11: 76-79.

Teychenne P F, Bergsrud D, Racy A. Bromocriptine: Low dose therapy in parkinsonism. Neurology (NY) 1982; 32(6): 577-583.

Teychenne P F, Bergrud D, Racy A. Subcategories of Parkinsonian patients treated with Bromocriptine. In: Fahn S, Marsden C D, Jenner P, Teychenne P F, eds. Recent Developments in Parkinson's Disease, New York: Raven Press, 1986: 303-314.

Thierry A M, Stinus L, Blanc G, Glowinski J. Some evidence for the existence of dopaminergic neurons in the rat cortex. Brain Res 1973; 50: 230-234.

Todd R D, Khurana T S, Sajovic P, Stone K R, O'Malley K L. Cloning of ligand specific cell lines via gene transfer: Identification of a D2 dopamine receptor subtype. Proc Natl Acad Sci(USA) 1989; 86: 10134-10138.

Tolosa E S, Martin W E, Cohen H P. Value of plasma dopa determinations in the management of Parkinson's disease. Lancet 1973; i: 942.

Tsui J K C, Wolters E, Peppard R F, Calne D B. A double-blind, pacebo-controlled, dose-ranging study to investigate the safety and efficacy of CY 208-243 in patients with Parkinson's disease. Neurol 1989; 39: 856-858.

Tsuruta K, Frey E A, Grewe C W, Cote T E, Eskay R L, Kebabian J W. Evidence that LY-141865 specifically stimulates the D-2 dopamine receptor. Nature 1981; 292: 463-465.

Tyce G M. Metabolism of 3,4-dihydroxyphenylalanine by isolated perfused rat liver. Biochem Pharmacol 1971; 20: 3447-3462.

Tyce G M, Owen C A. Administration of L-3,4-dihydroxy-phenylalanine to rats after complete hepatectomy. I: Metabolites in tissue. Biochem Pharmacol 1979; 28: 3271-3276.

Uhl G R, Hedreen J C, Price D L. Parkinson's disease: loss of neurons from the ventral tegmental area contralateral to therapeutic surgical lesions. Neurology 1985; 35: 1215-1218.

Ulm G. Experiences with lisuride in the treatment of Parkinson's disease. In: Calne D B, ed. Lisuride and other Dopamine Agonists. New York, Raven Press, 1983: 463-472.

Ungerstedt U, Arbuthnott G W. Quantitative recording of rotational behaviour in rats after 6-hydroxydopamine lesions of the nigrostriatal dopamine system. Brain Res, 1970; 24: 485-493.

Ungerstedt U. Stereotaxic mapping of the monoamine pathways in the rat brain. Acta Physiol Scand 1971; 367(suppl): 1-48.

Ungerstedt U. Striatal dopamine release after amphetamine or nerve degeneration revealed by rotational behavior. Acta Physiol Scand 1971; 367 (suppl): 49-68.

Ungerstedt U. Postsynaptic supersensitivity after 6-hydroxydopamine induced degeneration of the nigrostriatal dopamine system. Acta Physiol Scand 1971; 367 (suppl): 69-93.

Ungerstedt U. Adipsia and aphagia after 6-hydroxy-dopamine induced degeneration of the nigrostriatal dopamine system. Acta Physiol Scand 1971; 367 (suppl): 95-122.

Ungerstedt U. Brain dopamine neurons and behavior. In: Schmidt F O, Worden F G, eds. The Neurosciences Third Study Program. Cambridge Mass:MIT Press, 1974: 695-703.

Ungerstedt U, Herrera-Marschitz M, Ståhle L, Tossman U, Zetterström T. Dopamine receptor mechanisms studied by correlating transmitter release and behaviour. Acta Pharmacol Sci 1983; 1 (suppl): 165-181.

Ungerstedt U, Herrera-Marschitz M, Ståhle L, Tossman U, Zetterström T. Functional classification of different DA receptors. In: Casea D, Chase T N, Christensen A V, Gerlach J, eds. Dyskinesia-Research and Treatment. Pharmacology (suppl 2). Berlin: Springer-Verlag, 1985; 19-30.

Urquhart J, Farra J W, Wilis K L. Rate-controlled delivery systems in drug and hormone research. Ann Rev Pharmacol 1984; 24: 199-236.

Usdin E, Bunny W E Jr. Pre and Postsynaptic Receptors. New York: Marcel Dekker, 1975.

Van der Heyden J A M, Venema K, Korf J. Biphasic and opposite effects of dopamine and apomorphine on endogenous GABA release in the rat substantia nigra. Neurochem 1980; 34: 119-125.

Van Noorden S. Tissue preperation and immunocytochemistry techniques for light microscopy. In: Polak J M, Van Noorden S eds. Immunocytochemistry: Modern methods and applications Bristol: J Wright and sons, 1986; 26-53.

Van Praag H M. Depression. Lancet, 1982; ii: 1259-1264.

Van Tol H M M, Bunzow J B, Guan H-C. Cloning of the gene for a human dopamine D4 receptor with high affinity for the antipsychotic clozapine. Nature 1991; 350: 610-614.

Ungerstedt U. Brain dopamine neurons and behavior. In: Schmidt F O, Worden F G, eds. The Neurosciences Third Study Program. Cambridge Mass:MIT Press, 1974: 695-703.

Ungerstedt U, Herrera-Marschitz M, Stähle L, Tossman U, Zetterström T. Dopamine receptor mechanisms studied by correlating transmitter release and behaviour. Acta Pharmacol Sci 1983; 1 (suppl): 165-181.

Ungerstedt U, Herrera-Marschitz M, Stähle L, Tossman U, Zetterström T. Functional classification of different DA receptors. In: Casea D, Chase T N, Christensen A V, Gerlach J, eds. Dyskinesia-Research and Treatment. Pharmacology (suppl 2). Berlin: Springer-Verlag, 1985; 30.

Ur... J, Farra J W, Wilis K L. Rate-controlled delivery systems in drug and hormone research. Ann Rev Pharmacol 1984; 24: 199-236.

Usdin E, Bunny W E Jr. Pre and Postsynaptic Receptors. New York: Marcel Dekker, 1975.

Van der Heyden J A M, Venema K, Korf J. Biphasic and opposite effects of dopamine and apomorphine on endogenous GABA release in the rat substantia nigra. Neurochem 1980; 34: 119-125.

Van Noorden S. Tissue preperation and immunocytochemistry techniques for light microscopy. In: Polak J M, Van Noorden S eds. Immunocytochemistry: Modern methods and applications Bristol: J Wright and sons, 1986; 26-53.

Van Praag H M. Depression. Lancet, 1982; ii: 1259-1264.

Van Tol H M M, Bunzow J B, Guan H-C. Cloning of the gene for a human dopamine D4 receptor with high affinity for the antipsychotic clozapine. Nature 1991; 350: 610-614.

Veening J G, Corneliussen F M, Lieven P A J M. The topical organization of the afferents to the caudatoputamen of the rat. A horseradish peroxidase study. Neuroscience 1980; 5: 1253-1268.

Vyas I, Heikkila R E, Nicklas W J. Studies on the neurotoxicity of 1-methyl-4-phenyl-1,2,3,6-tetra hydropyridine. Inhibition of NAD-linked substrate oxidation by its metabolite 1-methyl-4-phenyl pyridinium. J Neurochem 1986; 46: 1501-1507.

Waddington J L. Bromocriptine, selective D-2 dopamine receptor and D-1 dopaminergic tone. Trends Pharmacol Sc 1986; 7: 223-224.

Waddington J L, O'Boyle K M. The D-1 Dopamine receptor and the search for its functional role: from neurochemisty to behaviour. Rev Neurosci 1987; 1, 3 & 4: 157-184.

Waddington J L. Therapeutic potential of selective D-1 dopamine receptor agonists and antagonists in psychiatry and neurology. Gen Pharmacol 1988; 19: 55-60.

Wade D N, Mearrick P T, Morris J L. Active transport of L-dopa in the intestine. Nature 1973; 242: 463-465.

Wade L A, Katzman R. 3-O-Methyldopa uptake and inhibition of L-dopa at the blood-brain barrier. Life Sci 1975; 17: 131-136.

Wade L A, Katzman R. Synthetic amino acids and the nature of L-dopa transport at the blood-brain barrier. J Neurochem 1975; 25: 837-842.

Walaas S I, Asward D W, Greengard P. A dopamine and cyclic AMP-regulated phosphoprotein enriched in dopamine innervated brain regions. Nature 1983; 301: 69-71.

Walaas S I, Greengard P. DARP-32 a dopamine and adonosine 3' 5'-monophosphate-regulated phosphoprotein enrighed in dopamine innervated brain regions. I: Regional and cellular distribution in the rat brain. J Neurosci 1984; 4(1): 84-98.

Walters J R, Bergstrom D A, Carlson J H, Chase T N, Braun A R. D1 dopamine receptor activation required for postsynaptic expression of D2 agonist effects. Science 1987; 236: 719-22.

Ward C D, Duvoisin R C, Ince S E, Nutt J D, Eldridge R, Calne D B. Parkinson's disease in 65 pairs of twins and in a set of quadruplets. Neurology 1983; 33: 815-824.

Wass J A H, Thorner M O, Besser G M. Digital vasospasm with bromocriptine. Lancet 1976; i: 1135.

Wassef M, Bérod A, Sotelo C. Dopaminergic dendrites in the pars reticula of the rat substantia nigra and their striatal input. Combined immunocytochemical localization of tyrosine hydroxylase and anterograde degeneration. J Neuroscience 1981; 6: 2125-2139.

Waszczak B L, Walters J R. Dopamine modulation of the effects of gamma-aminobutyric acid on substantia nigra pars reticulata neurons. Science 1983; 220: 218-221.

Webster D D. Critical analysis of the disability in Parkinson's disease. Modern Treatment 1968; 5: 257-282.

Weil-Malherbe H, Van Buren J M. The excretion of dopamine and dopamine metabolites in Parkinson's disease and the effect of diet thereon. J Lab Clin Med 1969; 74: 305-318.

Weiner W J, Factor S A, Sanchez-Ramos J R. The efficacy of (+)-4-propyl-9-hydroxynaphthoxazine as adjunctive therapy in Parkinson's disease. J Neurol Neurosurg Psychiatry. 1989: 52: 732-735.

Weiss P A. The deplantation of fragments of nervous system in amphibians. I: Central reorganization and the formation of nerves. J Exp Zoo 1950; 113: 397-462.

Widner H, Brundin P. Immunological aspects of grafting in the mammalian central nervous system. A review and speculative synthesis. Brain Res 1988; 13: 287-324.

Widner H, Brundin P, Björklund A, Möller E. Survival and immunogenicity of dissociated allogeneic fetal neural dopamine-rich grafts implanted into the brains of adult mice. Exp Brain Res 1989; 76: 187-197.

Williams A. Cell implantation in Parkinson's disease. Br Med J 1990; 301: 301-302.

Wilson S A K. Neurology. A N Bruce, ed. London: Williams and Wilkens, 1940: 787-805.

Winn P, Robbins T W. Comparative effects of infusions of 6-hydroxydopamine into nucleus accumbens and anterolateral hypothalamus induced by 6-hydroxydopamine on the responses to dopamine agonists. Body Weight, locomotor activity and measures of exploration in the rat. Neuropharmacol 1985; 24: 25-31.

Wong D T, Bymaster F P, Reid I R, Fuller R W, Perry K W, Kornfield E C. The effect of a stereospecific D-2 dopamine agonist on acetylcholine concentration in Corpus Striatum of Rat Brain. J Neural Transm 1983; 58(1-2): 55-67.

Woolverton W L, Goldberg L I, Ginos J Z. Intravenous self-administration of dopamine receptor agonists by rhesis monkeys. J Pharmacol Exp Ther 1984; 230: 678-683.

Wright J M, Wall R A, Perry T L, Paty D W. Chronic parkinsonism secondary to the intranasal administration of a product of meperidine-analogue synthesis. New Engl J Med 1984; 310: 325.

Yahr M D, Duvoisin R C, Shear M J, Barret R E, Hoehn M M. Treatment of parkinsonism with levodopa. Arch Neurol 1969; 21: 343-354.

Yahr M D. Levodopa. Diagnosis and treatment. Drugs five years later. Ann Int Med 1975; 83: 677-682

Yahr M D. Evaluation of long term therapy in Parkinson's disease. Mortality and therapeutic efficacy. In: Birkmayer W, Hornykiewics O, eds. Advances in Parkinsonism. Basle: Roche; 1976: 435-443.

Yahr M D. Long-term levodopa in Parkinson's disease. (letter) Lancet 1977; i(8013): 706-707.

Yahr M D. Overview of present treatment of Parkinson's disease. J Neural Transm 1978; 43: 227-238.

Yamamoto B K, Freed C R. The trained circling rat: a model for inducing unilateral caudate dopamine metabolism. Nature 1982; 298: 467.

Youdim M B H, Collins G G S, Sandler M, Jones Bevan A B, Pare C M B, Nicholson W J. Human brain monoamine oxidase, multiple forms and selective inhibitors. Nature 1972; 236: 225-8.

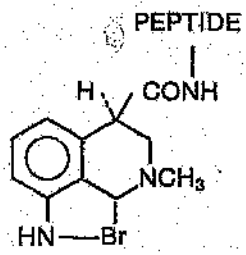
Zigmond M J, Acheson A L, Stachowiak M K, Stricker E M. Neurochemical compensation after nigrostriatal bundle injury in an animal model of preclinical parkinsonism. Arch Neurol 1984; 41: 856-861.

APPENDICES

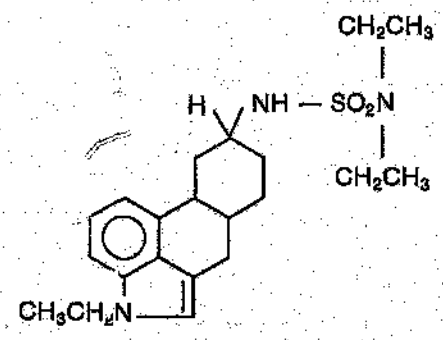
APPENDIX I

DOPAMINE D-2 RECEPTOR AGONISTS

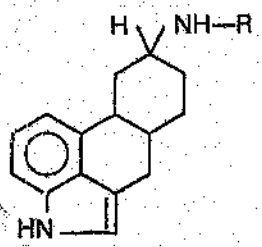
BROMOCRIPTINE



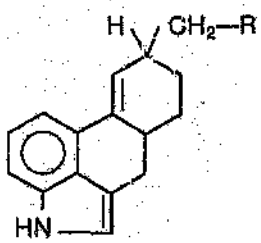
CQA 206-291



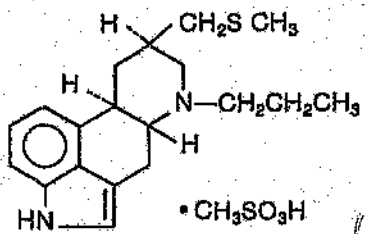
LISURIDE



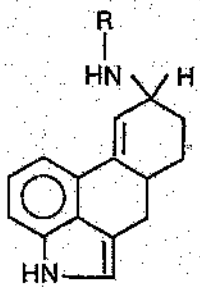
LEGOTRILE



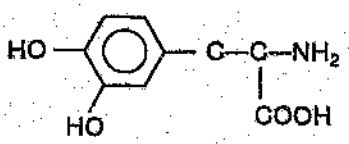
PERGOLIDE



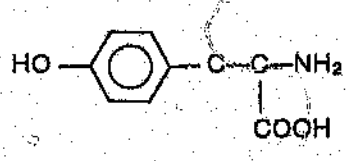
MESULGERINE



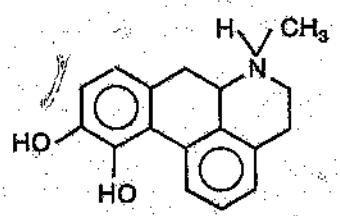
DOPAMINE



LEVODOPA

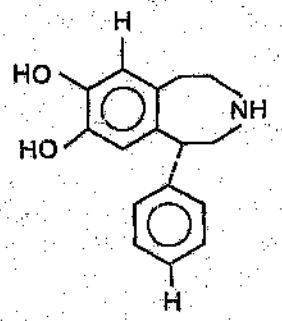


APOMORPHINE (A)

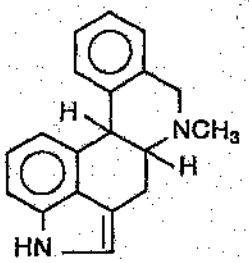


DOPAMINE D-1 RECEPTOR AGONISTS

SKF 38393

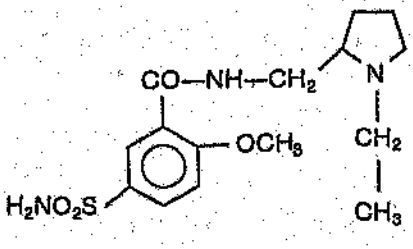


CY 208-243

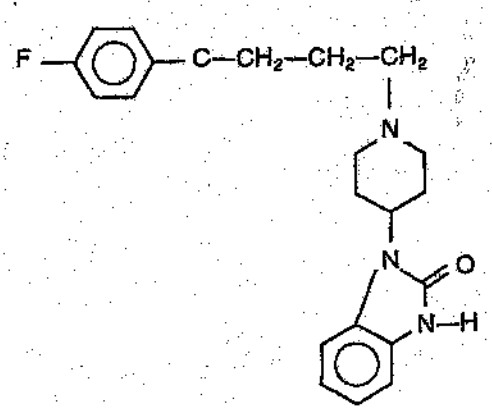


DOPAMINE RECEPTOR ANTAGONISTS

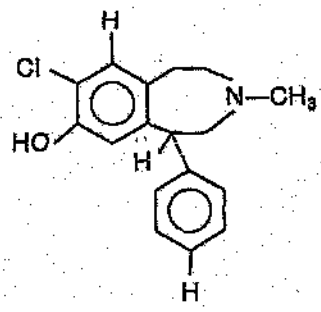
SULPIRIDE



DOMPERIDONE



SCH 23390



APPENDIX II

Unified Parkinson's Disease Rating Scale
Version 3.0—February 1987
Definitions of 0-4 Scale

I. MENTATION, BEHAVIOR AND MOOD

1. *Intellectual impairment:*
   - 0=None.
   - 1=Mild. Consistent forgetfulness with partial recollection of events and no other difficulties.
   - 2=Moderate memory loss, with disorientation and moderate difficulty handling complex problems. Mild but definite impairment of function at home with need of occasional prompting.
   - 3=Severe memory loss with disorientation for time and often to place. Severe impairment in handling problems.
   - 4=Severe memory loss with orientation preserved to person only. Unable to make judgments or solve problems. Requires much help with personal care. Cannot be left alone at all.

2. *Thought disorder:* (DUE TO DEMENTIA OR DRUG INTOXICATION)
   - 0=None.
   - 1=Vivid dreaming.
   - 2="Benign" hallucinations with insight retained.
   - 3=Occasional to frequent hallucinations or delusions; without insight; could interfere with daily activities.
   - 4=Persistent hallucinations, delusions, or florid psychosis. Not able to care for self.

3. *Depression:*
   - 0=Not present.
   - 1=Periods of sadness or guilt greater than normal, never sustained for days or weeks.
   - 2=Sustained depression (1 week or more).
   - 3=Sustained depression with vegetative symptoms (insomnia, anorexia, weight loss, loss of interest).
   - 4=Sustained depression with vegetative symptoms and suicidal thoughts or intent.

4. *Motivation/Initiative:*
   - 0=Normal.
   - 1=Less assertive than usual; more passive.
   - 2=Loss of initiative or disinterest in elective (nonroutine) activities.
   - 3=Loss of initiative or disinterest in day-to-day (routine) activities.
   - 4=Withdrawn, complete loss of motivation.

II. ACTIVITIES OF DAILY LIVING (DETERMINE FOR "ON/OFF")

5. *Speech:*
   0=Normal.
   1=Mildly affected. No difficulty being understood.
   2=Moderately affected. Sometimes asked to repeat statements.
   3=Severely affected. Frequently asked to repeat statements.
   4=Unintelligible most of the time.

6. *Salivation:*
   0=Normal.
   1=Slight but definite excess of saliva in mouth; may have nighttime drooling.
   2=Moderately excessive saliva; may have minimal drooling.
   3=Marked excess of saliva with some drooling.
   4=Marked drooling, requires constant tissue or handkerchief.

7. *Swallowing:*
   0=Normal.
   1=Rare choking.
   2=Occasional choking.
   3=Requires soft food.
   4=Requires NG tube or gastrotomy feeding.

8. *Handwriting:*
   0=Normal.
   1=Slightly slow or small.
   2=Moderately slow or small; all words are legible.
   3=Severely affected; not all words are legible.
   4=The majority of words are not legible.

9. *Cutting food and handling utensils:*
   0=Normal.
   1=Somewhat slow and clumsy, but no help needed.
   2=Can cut most foods, although clumsy and slow; some help needed.
   3=Food must be cut by someone, but can still feed slowly.
   4=Needs to be fed.

10. *Dressing:*
   0=Normal.
   1=Somewhat slow, but no help needed.
   2=Occasional assistance with buttoning, getting arms in sleeves.
   3=Considerable help required, but can do some things alone.
   4=Helpless.

11. *Hygiene:*
   0=Normal.
   1=Somewhat slow, but no help needed.
   2=Needs help to shower or bathe; or very slow in hygienic care.

3=Requires assistance for washing, brushing teeth, combing hair, going to bathroom.
4=Foley catheter or other mechanical aids.

12. *Turning in bed and adjusting bedclothes:*
0=Normal.
1=Somewhat slow and clumsy, but no help needed.
2=Can turn alone or adjust sheets, but with great difficulty.
3=Can initiate, but not turn or adjust sheets alone.
4=Helpless.

13. *Falling (unrelated to freezing):*
0=None.
1=Rare falling.
2=Occasionally falls, less than once per day.
3=Falls an average of once daily.
4=Falls more than once daily.

14. *Freezing when walking:*
0=None.
1=Rare freezing when walking; may have start-hesitation.
2=Occasional freezing when walking.
3=Frequent freezing. Occasionally falls from freezing.
4=Frequent falls from freezing.

15. *Walking:*
0=Normal.
1=Mild difficulty. May not swing arms or may tend to drag leg.
2=Moderate difficulty, but requires little or no assistance.
3=Severe disturbance of walking, requiring assistance.
4=Cannot walk at all, even with assistance.

16. *Tremor:*
0=Absent.
1=Slight and infrequently present.
2=Moderate; bothersome to patient.
3=Severe; interferes with many activities.
4=Marked; interferes with most activities.

17. *Sensory complaints related to parkinsonism:*
0=None.
1=Occasionally has numbness, tingling, or mild aching.
2=Frequently has numbness, tingling, or aching; not distressing.
3=Frequent painful sensations.
4=Excruciating pain.

III. MOTOR EXAMINATION

18. *Speech:*
    0=Normal.
    1=Slight loss of expression, diction and/or volume.
    2=Monotone, slurred but understandable; moderately impaired.
    3=Marked impairment, difficult to understand.
    4=Unintelligible.

19. *Facial expression:*
    0=Normal.
    1=Minimal hypomimia, could be normal "Poker Face".
    2=Slight but definitely abnormal diminution of facial expression.
    3=Moderate hypomimia; lips parted some of the time.
    4=Masked or fixed facies with severe or complete loss of facial expression; lips parted 1/4 inch or more.

20. *Tremor at rest:*
    0=Absent.
    1=Slight and infrequently present.
    2=Mild in amplitude and persistent. Or moderate in amplitude, but only intermittently present.
    3=Moderate in amplitude and present most of the time.
    4=Marked in amplitude and present most of the time.

21. *Action or postural tremor of hands:*
    0=Absent.
    1=Slight; present with action.
    2=Moderate in amplitude, present with action.
    3=Moderate in amplitude with posture holding as well as action.
    4=Marked in amplitude; interferes with feeding.

22. *Rigidity:* (Judged on passive movement of major joints with patient relaxed in sitting position. Cogwheeling to be ignored.)
    0=Absent.
    1=Slight or detectable only when activated by mirror or other movements.
    2=Mild to moderate.
    3=Marked, but full range of motion easily achieved.
    4=Severe, range of motion achieved with difficulty.

23. *Finger taps:* (Patient taps thumb with index finger in rapid succession with widest amplitude possible, each hand separately.)
    0=Normal.
    1=Mild slowing and/or reduction in amplitude.
    2=Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
    3=Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
    4=Can barely perform the task.

24. *Hand movements: (Patient opens and closes hands in rapid succession with widest amplitude possible, each hand separately.)*
    0=Normal.
    1=Mild slowing and/or reduction in amplitude.
    2=Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
    3=Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
    4=Can barely perform the task.

25. *Rapid alternating movements of hands:* (Pronation-supination movements of hands, vertically or horizontally, with as large an amplitude as possible, both hands simultaneously.)
    0=Normal.
    1=Mild slowing and/or reduction in amplitude.
    2=Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
    3=Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
    4=Can barely perform the task.

26. *Leg agility:* (Patient taps heel on ground in rapid succession, picking up entire leg. Amplitude should be about 3 inches.)
    0=Normal.
    1=Mild slowing and/or reduction in amplitude.
    2=Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
    3=Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
    4=Can barely perform the task.

27. *Arising from chair:* (Patient attempts to arise from a straight-back wood or metal chair with arms folded across chest.)
    0=Normal.
    1=Slow; or may need more than one attempt.
    2=Pushes self up from arms of seat.
    3=Tends to fall back and may have to try more than one time, but can get up without help.
    4=Unable to arise without help.

28. *Posture:*
    0=Normal erect.
    1=Not quite erect, slightly stooped posture; could be normal for older person.
    2=Moderately stooped posture, definitely abnormal; can be slightly leaning to one side.

3=Severely stooped posture with kyphosis; can be moderately leaning to one side.
4=Marked flexion with extreme abnormality of posture.

29. *Gait:*
0=Normal.
1=Walks slowly, may shuffle with short steps, but no festination or propulsion.
2=Walks with difficulty, but requires little or no assistance; may have some festination, short steps, or propulsion.
3=Severe disturbance of gait, requiring assistance.
4=Cannot walk at all, even with assistance.

30. *Postural stability:* (Response to sudden posterior displacement produced by pull on shoulders while patient erect with eyes open and feet slightly apart. Patient is prepared.)
0=Normal.
1=Retropulsion, but recovers unaided.
2=Absence of postural response; would fall if not caught by examiner.
3=Very unstable, tends to lose balance spontaneously.
4=Unable to stand without assistance.

31. *Body bradykinesia and hypokinesia:* (Combining slowness, hesitancy, decreased armswing, small amplitude, and poverty of movement in general.)
0=None.
1=Minimal slowness, giving movement a deliberate character; could be normal for some persons. Possibly reduced amplitude.
2=Mild degree of slowness and poverty of movement which is definitely abnormal. Alternatively, some reduced amplitude.
3=Moderate slowness, poverty or small amplitude of movement.
4=Marked slowness, poverty or small amplitude of movement.

IV. COMPLICATIONS OF THERAPY(In the past week)

A. *Dyskinesias*

32. *Duration: What proportion of the waking day are dyskinesias present?* (Historical information)
0=None
1=1-25% of day.
2=26-50% of day.
3=51-75% of day.
4=76-100% of day.

33. *Disability: How disabling are the dyskinesias? (Historical information; may be modified by office examination.)*
0=Not disabling.
1=Mildly disabling.

2=Moderately disabling.
3=Severely disabling.
4=Completely disabled.

34. *Painful dyskinesias: How painful are the dyskinesias?*
0=No painful dyskinesias.
1=Slight.
2=Moderate.
3=Severe.
4=Marked.

35. *Presence of early morning dystonia: (Historical information)*
0=No
1=Yes

B. *Clinical Fluctuations*

36. *Are any "off" periods predictable as to timing after a dose of medication?*
0=No
1=Yes

37. *Are any "off" periods unpredictable as to timing after a dose of medication?*
0=No
1=Yes

38. *Do any of the "off" periods come on suddenly, e.g., over a few seconds?*
0=No
1=Yes

39. *What proportion of the waking day is the patient "off" on average?*
0=None
1=1-25% of day.
2=26-50% of day.
3=51-75% of day.
4=76-100% of day.

C. *Other Complications*

40. *Does the patient have anorexia, nausea, or vomiting?*
0=No
1=Yes

41. *Does the patient have any sleep disturbances, e.g., insomnia or hypersomnolence?*
0=No
1=Yes

42. *Does the patient have symptomatic orthostasis?*
0=No
1=Yes

RECORD THE PATIENT'S BLOOD PRESSURE, PULSE AND WEIGHT ON THE SCORING FORM.

V. MODIFIED HOEHN AND YAHR STAGING

Stage 0 =No signs of disease.
Stage 1 =Unilateral disease.
Stage 1.5=Unilateral plus axial involvement.
Stage 2 =Bilateral disease, without impairment of balance.
Stage 2.5=Mild bilateral disease, with recovery on pull test.
Stage 3 =Mild to moderate bilateral disease; some postural instability; physically independent.
Stage 4 =Severe disability; still able to walk or stand unassisted
Stage 5 =Wheelchair bound or bedridden unless aided.

VI. MODIFIED SCHWAB AND ENGLAND ACTIVITIES ON DAILY LIVING SCALE

100%-Completely independent. Able to do all chores without slowness, difficulty or impairment. Essentially normal. Unaware of any difficulty.
90%-Completely independent. Able to do all chores with some degree of slowness, difficulty, and impairment. Might take twice as long. Beginning to be aware of difficulty.
80%-Completely independent in most chores. Takes twice as long. Conscious of difficulty and slowness.
70%-Not completely independent. More difficulty with some chores. Three to four times as long in some. Must spend a large part of the day with chores.
60%-Some dependency. Can do most chores, but exceedingly slowly and with much effort. Errors; some impossible.
50%-More dependent. Help with half, slower, etc. Difficulty with everything.
40%-Very dependent. Can assist with all chores, but few alone.
30%-With effort, now and then does a few chores alone or begins alone. Much help needed.
20%-Nothing alone. Can be a slight help with some chores. Severe invalid.
10%-Totally dependent, helpless. Complete invalid.
0%-Vegetative functions such as swallowing, bladder, and bowel functions are not functioning. Bedridden.

APPENDIX III

Adjunctive therapy with bromocriptine in Parkinson's disease

J. A. TEMLETT, A. MING, M. SALING, V. U. FRITZ, A. BLUMENFELD, T. R. BILCHIK, A. L. BECKER, P. B. FOURIE, H. E. REEF

Summary

Patients with moderately severe Parkinson's disease complicated by the adverse effects of chronic levodopa use benefited from the addition of bromocriptine (Parlodel; Sandoz) in doses up to 26 mg daily, which allowed an approximate 30% reduction of levodopa dose. This resulted in a significant decrease in the amount of levodopa side-effects while maintaining or improving the original parkinsonian clinical stage. Increased effectiveness in these patients was not associated with increased dosage beyond 25 - 30 mg daily. When the doses of bromocriptine were increased slowly, the adverse reactions were minor and usually transient.

S Afr Med J 1980; 78: 680-685.

Neurology Unit, Johannesburg Hospital and University of the Witwatersrand, Johannesburg
J. A. TEMLETT, M.B. B.CH., D.A. (S.A.), F.C.P. (S.A.), M.MED. (NEUROL.)
A. MING, M.B. B.CH., F.C.P. (S.A.), F.C.P. (S.A.) (NEUROL.)
V. U. FRITZ, M.B. B.CH., F.C.P. (S.A.), PH.D. (MED.)
A. BLUMENFELD, M.B. B.CH.
T. R. BILCHIK, M.B. B.CH.
H. E. REEF, M.B. B.CH., F.R.C.P.
School of Psychology, University of the Witwatersrand, Johannesburg
M. SALING, PH.D.
Past Medical Advisor, Sandoz Ltd, Johannesburg
A. L. BECKER M.B. B.CH., D.P.M.
Institute for Biostatistics of the South African Medical Research Council, Pretoria
P. B. FOURIE, M.SC., PH.D. (MED.)

Reprint requests to: Dr J. A. Temlett, Neurology Unit Dept of Medicine, Medical School, 7 York Road, Parktown, 2193 RSA.

Despite the initial successful experiences with levodopa therapy, disabling motor disturbances have emerged among parkinsonian patients during chronic levodopa treatment. Reduction of responsiveness to levodopa over years and associated long-term adverse effects, including abnormal involuntary movements (dyskinesia), dystonia, psychiatric disturbances and the development of severe 'on-off' fluctuations should be taken into consideration in the therapeutic strategy of Parkinson's disease.[1-7]

The efficacy of bromocriptine (Parlodel; Sandoz) as an antiparkinsonian agent has been established in many clinical trials.[8-10] There is, however, still controversy about the role of bromocriptine as a single first-line agent and the ideal dosage ratio of levodopa to bromocriptine if both drugs are used. In addition, the ideal time to add bromocriptine to existing levodopa therapy is not well established. Should this be before or after the long-term drug side-effects of levodopa have manifested themselves?

The assessment of these problems with drug therapy in Parkinson's disease depends largely on subjective patient and doctor evaluation of the patient's clinical status. The disability associated with Parkinson's disease is difficult to quantify and a number of rating scales have been published. These scales have emphasised the physical aspects of the disability, to the almost complete exclusion of the mental status changes. In order to evaluate therapeutic regimens for Parkinson's disease effectively, a comprehensive and sensitive procedure for assessing the disability is essential.

The development of such a comprehensive disability scale depends upon a number of factors. Firstly, a comparative assessment of the value of the existing scales must be made. Secondly, a determination of the relative contributions of the various items of these scales to overall ratings of the disability of Parkinson's disease should be evaluated. Finally, determination of the relative contributions of physical and mental status changes to the overall ratings of the disability in Parkinson's disease should be assessed.

In order to evaluate further the role of bromocriptine as an adjunctive agent to levodopa in the management of Parkinson's disease, a study was designed at the Neurology Unit of Johannesburg Hospital in conjunction with the School of Psychology at the University of the Witwatersrand. The study also planned to assess the various accepted motor rating scales used in Parkinson's disease at present. In addition, a battery of neuropsychological tests was included for the purpose of monitoring mental status during the course of the trial.

The aims of the study were to: (*i*) determine whether bromocriptine could partially replace dopamine therapy used by patients while at least maintaining their original clinical response on levodopa alone; (*ii*) determine the dosage ratio for combining levodopa with bromocriptine; (*iii*) confirm the therapeutic efficacy and tolerance of bromocriptine in patients with Parkinson's disease already controlled on levodopa; and (*iv*) monitor mental status and to explore the possibility of including a practical mental status assessment to complement the standard motor scales.

Patients and methods

Forty-four patients of both sexes, mean age of 64,8 years (range 30 - 75 years), who fulfilled the inclusion criteria of idiopathic Parkinson's disease with a disease rating of Hoehn and Yahr stages 2 - 4 were entered into the trial. All patients were outpatients and were excluded if they had features of severe systemic disease (cardiovascular, gastro-intestinal, renal, hepatic or psychiatric) or musculoskeletal disease causing significant disability.

Informed consent was obtained and patients were stabilised for a minimum period of 2 months on levodopa. Thereafter they were admitted to the trial, which was conducted in two phases — a double-blind phase and an open parallel-group design phase. There were 4 patients in whom results could not be analysed owing to lack of compliance. Thus a total of 40 patients completed the trial and were evaluated.

In the double-blind phase, which lasted 5 weeks (designated weeks 1 - 5, the daily dose of levodopa (determined in the initial 2 months) was kept constant in all patients. These patients were randomly allocated to receive either increasing doses of bromocriptine or matching placebo. The bromocriptine group (22 patients) received an initial dose of 2,5 mg daily, which was then increased incrementally to a total dose of 20 mg bromocriptine daily by the end of the 5-week period. The increments were supervised weekly, increasing by 2,5 - 5 mg total daily dose each week.

In the open phase of the study, the patients who had received placebo in the first phase (18 patients) were unblinded and given bromocriptine in incremental aliquots of 2,5 - 5 mg weekly in the same way as those who had been randomly allocated bromocriptine in the double-blind phase. Thus by the end of a further 5 weeks all 40 patients were receiving their initial levodopa dosage and 20 mg of bromocriptine. This strategy allowed a comparison between a placebo baseline and bromocriptine efficacy. At this stage (designated weeks 6 - 11) the 40 patients, including those who had received bromocriptine in the first 5 weeks, entered a phase in which levodopa was progressively reduced, at weekly intervals where possible, until the therapy failed to control symptoms. The reduced dose of levodopa was then maintained and the bromocriptine dosage, which had remained at 20 mg in all patients, was increased by 5 mg/d each week until the parkinsonism was once again controlled. Once the patient was stabilised, further reduction of levodopa with further increases of bromocriptine was again attempted in a similar manner. If bromocriptine was tolerated without side-effects an attempt was made to increase this dosage to a maximum of 50 mg/d by mouth in divided doses in order to further improve the parkinsonian status. This procedure continued for weeks 6-11, i.e. 6 weeks in the open phase.

Throughout the trial, patients were seen weekly and underwent full clinical assessment. Parkinson's disease symptomatology and response to treatment was assessed by subjective enquiry and completion of the Hoehn and Yahr,[11] Webster,[12] Columbia[13] and North Western University[14] scales. Biochemical profiles were performed at trial entry and at the end of the trial. In addition, full psychological evaluations were carried out by trained psychometrists at the beginning and end of the trial. Psychological tests used were the Beck Depression Inventory, Vocabulary and Similarity sub-tests and the Wechsler Adult Intelligence Scale, Benton's Controlled Word Association Test, Rey's Auditory Verbal Learning Test, Rey's Complex Figure, and the Mini Mental State Examination. The Beck test was also repeated on weeks 6 and 9 and the Mini Mental State Examination was carried out on weeks 1, 6, 8, 10 and the end of the trial. However, on the first and final weeks an expanded version of the Mini Mental State Examination was used (maximum score of 80). Concomitant medication was not changed during the trial. Adverse reactions and compliance were monitored continuously.

Statistical computations were carried out with the Statistical Analyser System (SAS) version 5 package installed on an IBM mainframe computer. In all tests differences were regarded significant at the 5% level. The associations upon trial entry between treatment groups (bromocriptine and placebo/levodopa) and personal attributes, clinical status, disability ratings and Hoehn and Yahr stage were assessed by the chi-square test. Intragroup comparisons of Hoehn and Yahr stage or patient status at the beginning and end of the double-blind phase employed the McNemar chi-square test for non-independence samples with Yates' correction for continuity. For sparse 2×2 tables Fisher's exact test was used. For larger contingency tables the Mantel-Haenzel test of significance was used. Comparison of means was by *t*-test procedure and for time trends in vital signs, dosage requirements and mean disability scores by analysis of co-variance and multiple regression.

Results

For analytical purposes, discontinuations were classified into premature interruptions (related to drug therapy, and including therapeutic failure/inefficacy as well as intolerance/adverse reaction to treatment) and drop-outs unrelated to test medications.

Double-blind phase

The two randomised groups (levodopa and bromocriptine v. levodopa and placebo) were fully comparable in terms of personal attributes (Table I), clinical status (Table II) and disability ratings (Table III) at the onset of the study. Thus, with the groups being comparable and with no changes in the dosage of levodopa (640 mg/d on average in all patients), during the first 5 weeks, and a constant increase of bromocriptine (up to 20 mg/d) in one subgroup v. placebo in the other, it was possible to compare changes in clinical status of treatment efficacy in the two groups objectively.

Bromocriptine was well tolerated in the first phase of the study, with only 2 patients being withdrawn prematurely from this phase of the trial because of persisting adverse effects of confusion and postural hypotension. Table IV demonstrates that the mean patient scores did not deviate significantly throughout the 11-week period of the study no matter which of the 4 methods of assessment were used. This suggested that

TABLE I. PERSONAL ATTRIBUTES AT TRIAL ENTRY

	Bromocriptine	Placebo	Total
No. of patients	22	18	40
Mean age (yrs) (SE)	64,3 (1,6)	65,3 (1,8)	64,0 (1,2)
Sex			
M	13	8	21
F	9	10	19
Mean disease duration (yrs) (SE)	13,4 (1,4)	13,3 (2,1)	13,4 (1,2)
Mean levodopa dosage (mg/d) (SE)	669,3 (66,6)	622,2 (69,9)	666,0 (68,1)
Smoking habit			
No. of smokers	3	1	4
No. stopped smoking	10	8	18
No. never smoked	9	9	18
Tremor in family			
Yes	1	1	2
No	21	17	38
Surgical treatment			
No	21	14	35
Yes, no effect	0	1	1
Yes, slight	0	0	0
Yes, moderate	0	3	3
Yes, good	1	0	1
Yes, very good	0	0	0

TABLE II. CLINICAL STATUS AT TRIAL ENTRY

Symptom	Degree	No. of patients on bromocriptine	No. of patients on placebo	Total
Dystonia				
Intensity	None	11	12	23
	Mild	6	4	10
	Moderate	4	1	5
	Severe	1	1	2
Frequency	None	11	14	23
	Occasional	6	4	10
	Frequent	5	0	5
	Continuous	0	0	0
Freezing episode				
Intensity	None	13	12	25
	Mild	1	4	5
	Moderate	3	0	3
	Severe	5	2	7
Frequency	None	13	12	25
	Occasional	3	4	7
	Frequent	6	2	8
	Continuous	0	0	0
Dyskinesia				
Type	None	13	13	26
	Face	1	1	2
	Trunk	0	0	0
	Arms	2	0	2
	Legs	1	2	3
	Multiple	5	2	7
Intensity	None	13	13	26
	Mild	2	1	3
	Moderate	4	3	7
	Severe	3	1	4
Frequency	None	13	13	26
	Occasional	3	1	4
	Frequent	3	4	7
	Continuous	3	0	3
On-off phenomena				
Intensity	None	20	17	37
	Mild	2	1	3
	Moderate	0	0	0
	Severe	0	0	0
Frequency	None	19	17	36
	Occasional	2	1	3
	Frequent	1	0	1
	Continuous	0	0	0

bromocriptine dosage could be increased and levodopa dosage decreased without significantly altering the clinical disability status of the patients.

In terms of adverse events, these two groups were similar with reference to freezing, 'on-off' phenomena and dystonias. As expected, the bromocriptine group demonstrated more dyskinesias — both peak-dose and biphasic (or complex) type patterns. This, however, improved in the next phase of the trial once levodopa could be reduced.

Open phase

The primary objective of this phase was to establish whether bromocriptine could partially replace levodopa while maintaining at least the original clinical response that was achieved on levodopa alone. If this was feasible, this phase then aimed to determine the optimal dosage ratio for maximum therapeutic effect with minimal risk of adverse events. Fig. 1 shows increases in bromocriptine dosage from 2,5 mg/d to 20 mg/d in the first 5 weeks, and then from 20 mg to 40 mg in the latter 6 weeks. These dosage changes were achieved while levodopa dosage was decreased by approximately 30% of the original dose. This was accomplished while keeping the clinical status stable (Table IV).

The stability of the mean rating scale scores during the open phase emphasises the ability of a reduced levodopa and increased bromocriptine regimen to maintain a relatively stable clinical response. From Table IV it can also be seen that patients were at their best clinical stage between week 5 and week 8, where the average dose of bromocriptine was 26 mg/d and the original levodopa dose (640 mg/d in all patients) had been decreased by approximately 30%. It was observed that the patient's clinical stage did not improve with further increases of bromocriptine beyond week 8 (i.e. above approximately 26 mg/d).

Dyskinesia, hypotension and dystonia were the most common adverse events related to the trial medications and individual patients frequently experienced more than one type of adverse events at different times (Table V). In the majority of these patients, the adverse effects lessened or disappeared as the dose of levodopa was decreased and/or the bromocriptine dose was increased. Some of the side-effects attributable to increased dosages of bromocriptine, such as dizziness, hypotension and confusion, seemed to lessen or even disappear with time. As these effects occurred while levodopa dosage was kept constant and bromocriptine dosage was increased, it appears that certain patients develop tolerance to, or overcome some of the side-effects of bromocriptine, with time.

The therapeutic efficacy in terms of the clinical stage and adverse effects at the various doses is reflected in Tables VI and VII. Two groups emerged, one with side-effects at some stage of the study and one with no side-effects at any stage.

In the first group (25 patients), where adverse events were experienced at some stage, it was found that maximal adverse

TABLE III. DISABILITY RATINGS AT TRIAL ENTRY

	No. of patients on bromocriptine	No. of patients on placebo	Total
Hoehn and Yahr clinical stage			
1	0	0	0
2	9	6	15
3	11	10	21
4	2	2	4
5	0	0	0
Webster total scores*			
0	0	2	2
1	13	11	24
2	9	5	14
3	0	0	0
Columbia total scores*			
0	6	6	12
1	6	4	10
2	6	5	11
3	3	2	5
4	1	1	2
NWU total scores*			
0	0	0	0
1	0	0	0
2	1	1	2
3	0	1	1
4	0	2	2
5	1	2	3
6	6	2	8
7	9	6	15
8	5	4	9
9	0	0	0
10	0	0	0

* Total scores computed by summing frequencies within same rating category across all scale items. Scores were then weighted according to sample size and averaged to the nearest integer.

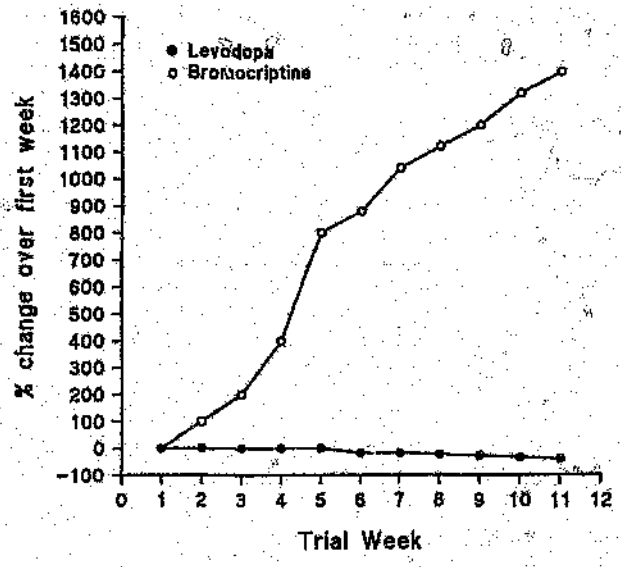


Fig. 1. Mean percentage change in dosage of drug.

events were experienced in 11 men and 14 women at a mean dose of 10 mg/kg/d of levodopa (802 mg in men, 537 mg in women) in combination with a dose of 18 mg bromocriptine per day (Table VI). This included patients in both the open and double-blind phase of the trial. Most side-effects occurred when the levodopa dosage was at its highest in the earlier part of the study and bromocriptine had not reached adequate therapeutic levels. When the dose of levodopa was decreased by approximately 30% (542 mg in men, 348 mg in women) and the bromocriptine dosage increased to about 26 mg per day the adverse events were at minimum and in most cases were entirely absent, while maintaining the clinical stage (Table VII). Twenty-two of these 25 patients (9 men and 13 women) became symptom free ($P < 0{,}0001$). In the remaining 3 patients, symptoms persisted despite adjustment in medication.

The patients in the second group (the remaining 10 men and 5 women) experienced no adverse events at any stage while the drugs were being interchanged. In addition, their clinical stage also remained constant and did not, in fact, improve as the dose of bromocriptine was increased beyond 26 mg/d. They were able to tolerate bromocriptine doses of up to 39 mg/d by the end of the study with an accompanying mean levodopa dosage of 522,5 mg (7,3 mg/kg) in men and 370 mg (6,6 mg/kg) in women. Further increases in bromocriptine dosage were not carried out because of the limited duration of the study.

Psychological tests were used to monitor mental status. When the neuropsychological test scores of each individual patient were compared at the beginning and end of the study,

TABLE IV. RATING SCALES (MEAN SCORES) AT EACH WEEK OF THE STUDY

Week	Hoehn and Yahr (SD 0,6 - 0,9)	Webster (SD 0,4 - 0,5)	NWU (SD 1,0 - 1,3)	Columbia (SD 0,5 - 0,9)
1	2,75	1,19	6,52	1,27
2	2,61	1,16	6,59	1,19
3	2,61			
4	2,50	1,07	6,74	1,05
5	2,54			
6	2,50	1,09	6,71	1,05
7	2,42	1,09	6,71	1,09
8	2,44	1,12	6,77	1,08
9	2,42	1,13	6,70	1,08
10	2,45	1,08	6,82	1,12
11	2,53	1,12	6,71	1,11

NWU = North Western University

TABLE V. TYPE AND FREQUENCY OF ADVERSE EVENTS (OPEN PHASE)

Events	No. of patients	No. of events
Dystonia		
Severe	1	3
Dyskinesia		
Mild	4	5
Moderate	3	4
Severe	5	9
Hypotension		
Mild	6	6
Moderate	5	6
Severe	2	3
Dizziness		
Mild	2	2
Moderate	5	5
Severe	2	3
Hallucinations		
Mild	1	2
Moderate	1	2
Severe	1	2
Confusion		
Mild	1	4
Moderate	2	10
Other		
Associated with hypotension/dizziness*	4	5
Not associated with other adverse events†	3	4

* Nausea and vomiting — mild; syncope — mild; multiple falls — severe; difficulty in concentrating — mild; dry mouth — mild.
† Balance impairment — mild; nausea — moderate; increased sexual drive — moderate.

no statistical differences emerged. This mental status finding paralleled the relative stability of the motor rating scales throughout the study. The mean Expanded Mini Mental State Examination scores in the 40 patients were 64,4 (SE = 2,4) in week 1 and 66,1 (SE = 1,4) in week 12 out of a possible maximum score of 80. The following neuropsychological profile was consistently seen throughout the trial: good presentation of vocabulary and verbal fluency; marked disturbances in constructional function as measured by Rey Complex Figure Test occurred consistently; and normality of memory was observed throughout the study.

Although this profile was seen to a greater or lesser extent in all patients, it should also be noted that there were marked individual variations in cognitive integrity; approximately 50% of patients obtaining a Mini Mental State score of < 25 out of 30, indicating consistently poor overall cognitive function.

Discussion

Levodopa has been the mainstay of therapy in Parkinson's disease since its introduction to clinical use in 1969.[15] However, following nearly two decades of experience with this agent, it has become apparent that patients who have used levodopa for 6 years may begin to develop problems of dyskinesias, freezing and 'on-off' fluctuation in response to the ever-increasing levodopa dosage that is necessary to maintain mobility.[16-18] For this reason, new agents have been developed, the most promising of which are the dopamine agonists. Bromocriptine is a predominantly D-2 receptor agonist but in addition appears to have D-1 receptor antagonist properties. When bromocriptine is employed in advanced Parkinson's disease in patients who have levodopa-induced complications, studies have shown its efficacy.[19-21] Unfortunately, bromocriptine may also produce dyskinesias and, in addition, neuropsychiatric problems emerge — all of which limit increasing the dosage. The equivalent oral dosage of bromocriptine in place of levodopa is still unknown but we have shown that when combining this dopamine agonist (in approximately 25 mg/d total dosage) with levodopa it is possible to reduce overall levodopa requirements by 30% without compromising clinical scores. Although bromocriptine has been tolerated at up to 150 mg/d,[23] sometimes combined with levodopa, we suggest that little additional benefit is seen beyond 25 mg/d in moderately severely affected patients.

With the low dosages of bromocriptine used, adverse events usually attributed to bromocriptine such as hypotension, confusion and dizziness were usually mild and transient. Only 2 patients (5%) in our study were withdrawn because of persistent adverse effects, which disappeared on removal of bromocriptine. In the majority of our patients the adverse effects either settled as the levodopa dose was decreased or disappeared spontaneously after sustained use of the same dosage of bromocriptine, the levodopa dose being kept constant. These findings confirm other studies[24-27] showing that bromocriptine is well tolerated at low dosages. In only 37% of our patients, the majority of whom had mild disease and who had no fluctuations in response or other effects of chronic levodopa use, it was possible to increase bromocriptine to fairly high levels (approxi-

TABLE VI. DRUG DOSAGE WHEN MAXIMUM ADVERSE EVENTS OCCURRED (25/40 PATIENTS*)

No. of patients	Sex	Mean body weight (kg)	Mean dosage levodopa (mg)	Mean dosage bromocriptine (mg)
11	M	71,1	802,3 ± 116,9	18,4 ± 3,6
14	F	55,6	537,5 ± 45,4	22,1 ± 2,6

* 15 patients not included in this Table did not develop adverse events throughout all phases of study.

TABLE VII. DRUG DOSAGE WHEN OPTIMAL CLINICAL STATUS OCCURRED RESULTING IN NO SIDE-EFFECTS (25/40 PATIENTS*)

No. of patients	Sex	Mean body weight (kg)	Mean dosage levodopa (mg)	Mean dosage bromocriptine (mg)
9	M	71,1	541,7 ± 111,5	25,6 ± 2,1
13	F	55,6	346,1 ± 67,5	26,5 ± 1,7

* 15 patients not included in this Table did not develop adverse events throughout all phases of the study.

mately 39 mg/d with concurrent levodopa therapy) without them developing side-effects. However, the clinical stage of this group was already optimal at a dose of bromocriptine of less than 26 mg/d and further increases of bromocriptine beyond this dose did not continue to improve their clinical status.

In this study, attempts were made to compare rating scales and to establish which was the most efficient scale and which features in each scale were most useful. Despite numerous statistical comparisons, which are not reported in detail, no single scale was found to be superior. The most likely explanation is that his study was not designed to evaluate changes in individual aspects of the rating scales. Patients motor deficits were being stabilised at optimum doses of therapy concomitant with minimal adverse effects. Thus no significant changes in the clinical status of patients or their rating scales were achieved in the study.

The major neuropsychological finding was the stability of mental status throughout the trial, which did not fluctuate with the introduction or change in bromocriptine therapy. The neuropsychological features observed were typically those of Parkinson's disease, namely a marked dissolution of constructional skills in the face of preserved verbal function and memory.

In conclusion, this study demonstrated that, while maintaining a stable clinical state, the addition of bromocriptine in a group of patients with moderately severe Parkinson's disease could reduce the levodopa requirements by approximately 30%. Since individual differences occur in the mental status of individual patients with Parkinson's disease, it appears advisable to include a Mini Mental State score in the motor rating scales.

We would like to acknowledge the support and sponsorship of Sandoz Products (Pty) Ltd.

REFERENCES

1. Barbeau A. Long term side effects of levodopa. *Lancet* 1971; 1: 395.
2. Marsden CD, Parkes JD. On-off effects in patients with Parkinson's disease on chronic levodopa therapy. *Lancet* 1976; 1: 129-151.
3. Rinne UK. Treatment of Parkinson's disease: problems with a progressing disease. *J Neural Transm* 1981; 51: 161-174.
4. Rinne UK. Problems associated with long term levodopa treatment of Parkinson's disease. *Acta Neurol Scand* 1983; 68: suppl. 95, 19-26.
5. Yahr MD. Evaluation of long term therapy in Parkinson's disease: mortality and therapeutic efficacy. In: Birkmayer W, Hornykiewicz O, eds. *Advances in Parkinsonism*. Basle: Roche, 1976: 435-443.
6. Lesser RP, Fahn S, Snider SR, Cote LJ, Isgreen WP, Barrett RE. Analysis of the clinical problems in parkinsonism and the complications of long term levodopa therapy. *Neurology* 1979; 29: 1253-1260.
7. Shaw KM, Lees AJ, Stern GM. The impact of treatment with levodopa in Parkinson's disease. *Q J Med* 1980; 195: 283-293.
8. Caine DB, Teychenne PF, Claveria LE, Eastman R, Greenacre JK, Petrie A. Bromocriptine in parkinsonism. *Br Med J* 1974; 4: 422-444.
9. Parkes JD. Bromocriptine in the treatment of parkinsonism. *Drugs* 1979; 17: 365-382.
10. Quinn N, Illas A, Lhermitte F, Agid Y. Bromocriptine and domperidone in the treatment of Parkinson's disease. *Neurology* 1981; 31: 662-667.
11. Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. *Neurology* 1967; 17: 427-442.
12. Webster DD. Critical analysis of the disability in Parkinson's disease. *Mod Treatment* 1968; 5: 257-282.
13. Duvoisin RC. The evaluation of extrapyramidal disease. In: De Ajuriguerra J, ed. *Monoamines: Noyaux Gris Centraux et Syndrome de Parkinson*. Paris: Masson, 1970. 313-325.
14. Canter GJ, De la Torre R, Mier M. A method for evaluating disability in patients with Parkinson's disease. *J Nerv Ment Dis* 1961; 7: 133-143.
15. Cotzias GC, Papavasiliou PS, Gellene R. Modification of parkinsonism — chronic treatment with L-dopa. *N Engl J Med* 1969; 280: 337-345.
16. Fahn S. 'On-off' phenomenon with levodopa therapy in parkinsonism. *Neurology* 1974; 24: 431-441.
17. Hoehn MM. Extrapyramidal disorders: progression and mortality. *J Neural Transm* 1983; 19: suppl. 253-284.
18. Marsden CD, Parkes JD. Success and problems of long-term levodopa therapy in Parkinson's disease. *Lancet* 1977; 1: 345-349.
19. Hoehn MM. Bromocriptine and its uses in parkinsonism. *J Am Geriatr Soc* 1981; 29: 251-258.
20. Rinne UK. Dopamine agonists in the treatment of Parkinson's disease. *Adv Neurol* 1983; 37: 142-146.
21. Rinne UK. Combined bromocriptine-levodopa therapy early in Parkinson's disease. *Neurology* 1985; 35: 1196-1198.
22. Parkes JD, Marsden CD, Donaldson I. Bromocriptine treatment in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1981; 39: 184-189.
23. Agid Y, Pollak P, Bonnet AM, Signoret JL, Lhermitte F. Bromocriptine associated with a peripheral dopamine blocking agent in the treatment of Parkinson's disease. *Lancet* 1979, 1: 570-572.
24. Curaceni T, Giovannini P, Girotti F, Pederzoli M, Scigliano G. Long-term evaluation of combined treatment of Parkinson's disease with L-dopa, peripheral decarboxylase inhibitors and bromocriptine. *Ital J Neurol Sci* 1981; 2: 337-342.
25. Grimes JD, Hassan M. Bromocriptine in the long-term management of advanced Parkinson's disease. *Can J Neurol Sci* 1982; 10: 86-90.
26. Rascol A, Guiraud B, Montastruc JL, David J, Clanet M. Long-term treatment of Parkinson's disease with bromocriptine. *J Neurol Neurosurg Psychiatry* 1979; 42: 143-150.
27. Lees AJ, Stern GM. Sustained bromocriptine therapy in previously untreated patients with Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1981; 44: 1020-1023.

APPENDIX IV

Sinemet (CR4): an open-label study in moderately severe Parkinson's disease

A. MING, J. A. TEMLETT & V. U. FRITZ

From the Neurology Unit, University of the Witwatersrand and Johannesburg Hospital, Johannesburg, South Africa

Abstract. Ming A, Temlett JA, Fritz VU (Neurology Unit, University of the Witwatersrand and Johannesburg Hospital, Johannesburg, South Africa). Sinemet (CR4): an open-label study in moderately severe Parkinson's disease. *Journal of Internal Medicine* 1991; 230: 113–117.

Almost all patients with idiopathic Parkinson's disease respond to levodopa and progress steadily, requiring an increased overall dosage with time. Sinemet CR4 offers a theoretically attractive method of achieving gradual sustained release of levodopa over time which may be more physiological to striatal dopamine receptors in the early stages of the disease. This study evaluated 20 patients with moderate to severe Parkinson's disease who were treated with Sinemet CR4 over a 1-year period. Eleven patients completed the full year on therapy, and nine subjects withdrew. Of the withdrawals, two subjects died from non-Parkinson's disease-related illness, three showed no therapeutic benefit, and four responded well for a minimal 6-month period, but then lost therapeutic benefit and developed more severe dystonias. A higher overall levodopa dosage was required by all patients, and side-effects of levodopa were still present in most patients. However, the nocturnal benefit of this long-acting preparation was observed by all the patients in the study. Slow onset of action of Sinemet CR4 resulted in early-morning immobility. Sinemet CR4 cannot replace standard Sinemet, but appears to be a useful form of adjunct therapy in selected patients.

Keywords: Parkinson's disease, Sinemet CR4.

Introduction

The combination of levodopa and peripheral decarboxylase inhibitors (Sinemet and Madopar) remains the most effective medication available for treatment of Parkinson's disease. Initially, there are few side-effects and the clinical benefits are sustained, necessitating a dosing frequency of only two or three times daily. However, with prolonged use of these compounds for 3 years or more, the duration of benefit is reduced, requiring an increased dosing frequency. Many patients also experience motor fluctuations, despite the increased number of doses and overall amount of levodopa [1–3].

There is evidence that plasma levodopa concentrations are correlated with motor fluctuations in many patients [4–6]. Short-term studies involving intravenous infusions of levodopa suggest that constant plasma levels can reduce these motor fluctuations [7, 8]. Hence a long-acting oral formulation of levodopa was developed in combination with carbidopa, initially Sinemet CR3 [9], and improved upon and now called Sinemet CR4 (Merck, Sharp and Dohme, Montreal, Canada), the fourth generation of a controlled-release preparation [10]. This study reports on the effects of Sinemet CR4 in an open-label study protocol to test its advantages over conventional Sinemet.

Patients and methods

Drugs

Each Sinemet CR4 tablet contains 200 mg levodopa and 50 mg carbidopa suspended in an erodible polymeric matrix. *In-vitro* studies have shown that the levodopa in Sinemet CR4 is released over a period of approximately 2.5 h in 0.1 N HCl, as compared to the standard Sinemet formulation, which is released over 1.1 h in the same acid medium [11].

Table 1. Criteria used in study for diagnosis of Parkinson's disease

Major criteria	Minor criteria
Bradykinesia	Seborrhoea
Rigidity	Facial hypomimia
Tremor	Speech impairment
Loss of postural reflexes	Dysphagia
Gait disturbance	

Study subjects

Twenty patients who fulfilled the trial's inclusion criteria were recruited to this study after their informed consent had been obtained. Patients were of either sex, they had to be ≥ 35 years of age, and had to have established Parkinson's disease, as indicated by at least two major or one major and two minor manifestations of the disease (Table 1). Patients who exhibited motor fluctuations as a consequence either of the disease itself or of anti-Parkinsonian medication were included. Patients with unstable clinical or laboratory indications of any significant medical illness (other than Parkinson's disease), concomitant use of medication that may potentially induce Parkinsonism, likelihood of becoming pregnant, known hypersensitivity to Sinemet, history of melanoma or undiagnosed skin lesions, or narrow angle glaucoma were excluded from the study.

Protocol

The study was conducted in an open manner and was divided into two phases. Initially, there was a 4-week baseline period during which the patients' Parkinsonian status was optimized using standard Sinemet. Other anti-Parkinsonian medication, i.e. Bromocriptine, anti-cholinergics and Amantadine, was continued if the patients were already taking these drugs. During this period, the patients underwent routine detailed general physical and neurological clinical examinations, electrocardiology, urinalysis, biochemical analysis and complete blood counts. The Parkinsonian status was scored according to the Hoehn and Yahr [12], North Western University [13] and a Modified Neurological Sign and Symptom Parkinson's Disease Score, which included a four-point rating scale for rigidity, tremor, bradykinesia, balance and gait during the 'on' phase.

The patients were subsequently entered into a 52-week phase of treatment with Sinemet CR4. Conventional Sinemet was changed to an equivalent dose of Sinemet CR4 at a dosing frequency equivalent to 50% of their usual Sinemet dose. During the ensuing 52 weeks, the doses and frequency of Sinemet CR4 were adjusted to achieve an optimal therapeutic response. Other anti-Parkinsonian agents used during the baseline period remained unchanged during this Sinemet CR4 treatment phase. Patients were screened for the same parameters as those assessed in the baseline period at weeks 1, 2, 4, 8, 12, 24, 36 and 52. Patients were also asked to complete diaries on one day of each week throughout the study.

Results

Twenty patients were recruited to the study (12 men and eight women), of age range 46–76 years (mean age 64 years). The duration of Parkinson's disease ranged from 1.5–40 years (mean duration 14.1 years). All patients showed some form of motor fluctuation over a mean period of 4.5 years. All 20 patients experienced 'wearing off', 12 patients experienced dyskinesias and five experienced 'on-off' phenomena. All patients had a Hoehn and Yahr clinical stage of 2–4, and a North West University score of 6–18 at baseline on standard Sinemet. This indicated moderate to severe Parkinson's disease. The mean daily requirement of Sinemet was 706 mg administered in 5.6 doses d^{-1} to all 20 patients prior to the onset of the study.

Withdrawals

Over the 52-week period, only eleven of the 20 subjects who were originally recruited were able to complete the study and to remain exclusively on Sinemet CR4 therapy.

Of the nine patients who did not complete the study, two died and three were withdrawn by week 12. Four patients withdrew from the study after 24–50 weeks in order to add an early-morning dose of standard Sinemet to overcome a problem of early-morning immobility (Table 2).

The two deaths were not due to Parkinson's disease but to unrelated causes; one individual died from an acute myocardial infarction at week 22, and one from pneumonia and septicaemia at week 50. Both of these patients had shown a favourable response to Sinemet CR4 prior to death. Three of the nine patients who were unable to complete the year of Sinemet CR4 treatment showed a poor therapeutic response to Sinemet CR4, virtually from the time of

Table 2. Data for the nine patients who were withdrawn from the study

Cause	Stage of withdrawal (week no.)	Baseline L-Dopa dose (mg)	L-Dopa dose at withdrawal (mg)	Reason for withdrawal
Poor effect	8	1375	1800	Dystonia worse, poor therapeutic benefit
	8	1250	1600	No therapeutic effect
	12	750	800	Poor therapeutic benefit
Death	22	750	1000	Died of myocardial infarction
	50	500	900	Died of septicaemia
Early morning immobility, worsening dystonia	24	400	600	Loss of therapeutic benefit
	24	600	800	Loss of therapeutic benefit, dystonia worse
	49	1200	1800	Loss of therapeutic effect, hallucinations
	50	550	1000	Loss of therapeutic effect, dystonia worse, confusion

entry to the trial, and had to return to conventional Sinemet by week 12. All had been on high daily doses of Sinemet (more than 1200 mg daily) at baseline, and had required frequent doses of conventional Sinemet. Although they all experienced fewer 'on-off' motor fluctuations and peak-dose dyskinesias, their mobility was constantly reduced and they were never truly 'on'. Bradykinesia became more prominent compared to the baseline period when the patients were on conventional Sinemet treatment. Two of these three patients also developed more marked nocturnal dystonias compared to those they experienced on conventional Sinemet treatment. One of the patients with increased dystonias also developed intermittent nocturnal confusion. All these increased adverse effects subsided when Sinemet CR4 was stopped and patients returned to conventional Sinemet treatment.

The remaining four withdrawals occurred between weeks 24 and 50 of the Sinemet CR4 treatment phase. These four patients had all benefited from treatment on Sinemet CR4 over the first 24 weeks, in that they experienced fewer motor fluctuations and their Parkinsonian status remained stable. Single-dose failures did occur during this period, but were infrequent. However, after the initial period, during weeks 24 to 50, similar problems to those noted in the earlier 'dropout' group were observed. The complaint was again made that, although true 'off' periods occurred uncommonly, high-quality 'on' time decreased as well. Early-morning immobility was specifically a problem, and single-dose failures increased in frequency, sometimes up to 5 episodes per week. In addition, three of these four patients experienced more early-morning dystonias, and two of them developed episodic confusion as doses of Sinemet CR4 were increased in an attempt to maintain the baseline Parkinsonian status. These four individuals were therefore withdrawn from the study, making it possible to add conventional Sinemet to the daily Sinemet CR4 medication regimen. This improved early-morning mobility and reduced single-dose failures, thus allowing a reduction in the total levodopa dose in that the Sinemet CR4 dosage was simultaneously reduced. The dose-related side-effects of dystonia and confusion also improved. These four patients continued to take Sinemet CR4 throughout the 52-week period, but could not be included in the final analysis because standard Sinemet therapy additions did not form part of the original protocol.

Patients who completed the trial

Eleven patients completed all the requirements of the 52-week study. Details of the subjects who completed the study and their clinical status and dosage patterns are listed in Table 3.

It is evident from the Parkinson's disability scales that most of these 11 patients were clinically at their best between weeks 12 and 24. However, no

Table 3. Data for the 11 patients who completed the entire 52-week study

	Baseline	Week 12	Week 24	Week 36	Week 52
Hoehn & Yahr					
Stage 1	0	0	0	0	0
Stage 2	1	1	1	1	1
Stage 3	7	10	10	9	8
Stage 4	3	0	0	1	2
North Western University score	10.27	7.63	7.72	8.54	9.18
Mean L-Dopa dose (mg)	4.95	6.91	7.00	7.00	7.05
Mean number of doses d^{-1}	4.28	3.04	3.91	4.09	4.18
Mean interval between doses (h)	5.61	7.89	6.14	5.86	5.74

persistent benefit was maintained as scores approached the original baseline scores during the 52-week period. While maintaining the Parkinsonian clinical status, the levodopa dosage had to be increased from a mean value of 495 mg daily in conventional Sinemet to 705 mg daily in Sinemet CR4, indicating a 42% increase in levodopa requirements over the 52-week period. Over the initial 2 weeks, fewer doses per day were required, declining from a mean value of 4.28 doses per day to 3.04 doses per day. Thus the interval between doses increased from 5.61 to 7.89 h. Unfortunately this benefit was not maintained, and more frequent dosing became necessary with time. After 52 weeks, the number of doses per day was 4.18, which was similar to that for baseline.

Since all patients experienced 'wearing off', dyskinesia, dystonia or 'on-off' motor fluctuations, it was encouraging to note that, with the introduction of Sinemet CR4, all subjects experienced a definite benefit for up to 24 weeks. Fewer episodes of 'wearing off' were noted, and 'on-off' fluctuations, peak dose dyskinesias and dystonias improved significantly. The patients noted a more sustained clinical response both during the day and at night. It was significant that 11 patients reported increased and sustained mobility in bed and relative ease in getting out of bed. The only problem noted by the 24-week stage was the slower onset of action of Sinemet CR4. Patients who were taking their first morning dose of Sinemet CR4 took longer to become mobile.

During the 24–36 week period, further problems arose, since it became necessary to increase the dose and frequency of Sinemet CR4 in order to maintain stable baseline Parkinsonian status. Again dyskinesias became more significant in two of the four patients, both of whom had suffered early-morning dystonias. Early-morning dystonia became more severe in four patients. Although 'wearing-off' phenomena still occurred less frequently than at baseline, seven of the 11 patients complained of having fewer true 'on' periods, and they regarded Sinemet CR4 as being less potent than conventional Sinemet.

Single-dose failures with Sinemet CR4, which had been uncommon during the first 24 weeks, appeared. Five of the 11 patients experienced on average at least one single-dose failure per week, and the remaining six experienced up to 5 episodes per week. Four of these 6 patients had suffered from Parkinsonian symptoms for more than 8 years. The other dose-related side-effects observed after week 24 were increased constipation (2 cases), neuropsychiatric disturbances (4 cases) and hypersomnolence (1 case). No significant ECG, blood test or urinary abnormalities could be attributed to Sinemet CR4 during the study period.

Thus the only sustained benefit experienced by all patients up to week 52 was improved nocturnal mobility. In this study of 20 patients, one subject died and three withdrew within 12 weeks. Fifteen patients remained on Sinemet CR4 treatment, but four of them withdrew from the study in order to be able to use standard Sinemet combined with Sinemet CR4 to overcome the problem of early-morning immobility.

Discussion

A major impetus behind the development of a slow-release levodopa formulation has been the theoretical possibility that 'pulse-like' levodopa administration of drugs may in fact be detrimental to dopamine receptor status and function [14]. Sinemet CR4 pharmacokinetics offer a slower, more sustained and probably more physiological levodopa release profile. However, problems have emerged in long-standing Parkinsonian patients. First, the slower action of the drug leaves the patients distressed and immobile early in the day. This problem produces unacceptable patient discomfort, reflected by the minority of patients who elected to stay on Sinemet CR4 treatment alone. Secondly, the patients generally appeared to require increased levodopa administration.

It is possible that an excessive levodopa requirement may in itself be harmful in the long term [15]. This remains hypothetical, however, because such assumptions arise in connection with patients with established levodopa complications, and not with early administration of slow-release compounds. It is possible that, if slow-release compounds are administered at an early stage, a more continuous and sustained plasma levodopa concentration will result. Dopamine receptors may respond more favourably despite the higher overall dosage, and long-term levodopa-related problems may theoretically be avoided.

The expectation that levodopa administration once or twice daily is sufficient to control Parkinsonian symptoms has not been confirmed [11].

This study has shown that Sinemet CR4 reduces the dose frequency compared to conventional Sinemet by approximately 30% within the first 12 weeks, and extends the duration of efficacy from a mean period of 5.61 to 7.89 h. This benefit was not sustained after 52 weeks. However, all patients derived a sustained nocturnal benefit throughout the 52-week period. We remain concerned, as do others [16], that unpredictable 'off periods' and single-dose 'failures' generate lack of confidence of patients in the Sinemet CR4 preparation.

With advanced idiopathic Parkinson's disease, the striatal dopamine receptors require constant levodopa delivery due to negligible endogenous central dopamine [17]. Sinemet CR4 compounds represent an attempt to fulfil this ideal, but unfortunately oral therapy is subject to many possible interruptions, including maldigestion, malabsorption of levodopa, altered carrying protein in the plasma, variable passage of levodopa across the blood-brain barrier and, finally, the responsiveness of the D-2 dopamine receptors themselves [4, 17, 18]. Hence it is not surprising that constant intravenous levodopa infusions are more efficacious than the slow-release preparations. However, the Sinemet CR4 compound does take us one step closer to optimal drug treatment. Further trials in which Sinemet CR4 is used in combination with faster acting Sinemet to achieve mobility, started more actively and earlier in the morning, are warranted, as are studies to treat single dose failures and to test patients with an earlier stage of the illness.

References

1 Yahr MD. Limitations of long-term use of anti-Parkinsonian drugs. *Can J Neurol Sci* 1984; 11: 191–4.

2 Barbeau A. *Long term side-effects of levodopa. Lancet* 1971; 1: 395.

3 Marsden CD, Parkes JD. 'On-off' effects in patients with Parkinson's disease on chronic levodopa therapy. *Lancet* 1976; 1: 292–6.

4 Nutt JG, Woodward WR, Hammerstad JP *et al.* The 'on-off' phenomena in Parkinson's disease. Relation to levodopa absorption and transport. *N Engl J Med* 1984; 310: 483–8.

5 Hardie RJ, Lees AJ, Stern GM. 'On-off' fluctuations in Parkinson's disease. *Brain* 1984; 107: 487–506.

6 Swart RD, McDowell FH. Plasma dopa concentrations and the 'on-off' effect after chronic treatment of Parkinson's disease. *Neurology* 1974; 24: 953–6.

7 Quinn N, Marsden CD, Parkes JD. Complicated response fluctuations in Parkinson's disease: a response to intravenous infusion of levodopa. *Lancet* 1982; ii: 412–5.

8 Shoulson I, Glaubiger GA, Chase TN. 'On-off' response. Clinical and biochemical correlations during oral and intravenous levodopa administration in Parkinsonian patients. *Neurology* 1975; 25: 1144–8.

9 Hutton JT, Dippel RL, Blanchine JR *et al.* Controlled-release Carbidopa/Levodopa in the treatment of Parkinsonism. *Clin Neuropharmacol* 1984; 7: 135–9.

10 Goetz CG, Tanner CM, Klawans HL *et al.* Parkinson's disease and motor fluctuations: long-acting carbidopa/levodopa (CR-4 Sinemet). *Neurology* 1987; 37: 875–8.

11 Cedarbaum JM, Breck J, Kutt H *et al.* Controlled-release levodopa/carbidopa. Sinemet CR4 treatment of response fluctuations in Parkinson's disease. *Neurology* 1987; 37: 1607–12.

12 Hochman MM, Yahr MD. Parkinsonism: onset, progression and mortality. *Neurology* 1967; 17: 427–42.

13 Canter GJ, de la Torre J, Meir M. A method for evaluating disability in patients with Parkinson's disease. *J Nerv Ment Dis* 1961; 7: 133–43.

14 Chase TN, Juncos J, Serratic *et al.* Fluctuations in response to chronic levodopa therapy: pathogenesis and therapeutic considerations. *Adv Neurol* 1986; 45: 477–80.

15 Fahn S, Bressman SR. Should levodopa therapy for parkinsonism be started early or late? Evidence against early treatment. *Can J Neurol Sci* 1984; 11 (Suppl. 1): 200–205.

16 Ahlskog JE, Meunter MD, McManis PG. Controlled-release Sinemet (CR4): a double-blind crossover study in patients with fluctuating Parkinson's disease. *Mayo Clin Proc* 1988; 63: 876–86.

17 Juncos JL, Serrati C, Fabbrini G *et al.* Fluctuating Levodopa concentrations and Parkinson's disease. *Lancet* 1985; 2: 440–43.

18 Fabbrini G, Juncos J, Mouradain MM *et al.* Levodopa pharmacokinetic mechanisms and motor fluctuations in Parkinson's disease. *Ann Neurol* 1987; 21: 370–76.

Received 19 March 1990, accepted 31 January 1991.

Correspondence: Dr A. Ming, Neurology Unit, Area 455, Johannesburg Hospital, Private Bag X39, Johannesburg 2000, South Africa.

APPENDIX V

The D-1 dopamine receptor partial agonist, CY 208-243, exhibits antiparkinsonian activity in the MPTP-treated marmoset

James A. Temlett, Piang Ngok Chong, Wolfgang H. Oertel, Peter Jenner *
and C. David Marsden [1]

MRC Movement Disorders Research Group, University Department of Neurology and Parkinson's Disease Society Research Centre, Institute of Psychiatry and King's College Hospital Medical School, Denmark Hill, London SE5, U.K.

Received 21 April 1988, revised MS received 13 July 1988, accepted 26 July 1988

Administration of L-DOPA plus carbidopa, or the D-2 agonist (+)-PHNO, to MPTP-treated common marmosets caused motor hyperactivity and a reversal of the parkinsonian syndrome. In contrast, administration of the putative D-1 agonist SKF 38393 was without effect on movement or motor disability. The subsequent administration of another putative selective D-1 partial agonist CY 208-243 produced a dose-related improvement in motor activity and reversal of parkinsonian motor deficits in MPTP-treated animals. The effect of CY 208-243 was inhibited by pretreatment with the D-1 antagonist SCH 23390 and, to a lesser extent, by the D-2 antagonist sulpiride. In another group of normal drug naive marmosets, the administration of CY 208-243 produced only a small increase in motor activity. Following treatment with MPTP and without other drug administration, administration of CY 208-243 produced a marked reversal of motor deficits and locomotor hyperactivity. Thus, CY 208-243, suggested to be a partial D-1 agonist exhibits antiparkinsonian activity in MPTP-treated marmosets which does not require prior or concurrent exposure to D-2 agonists.

MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine); Common marmoset; Parkinsonism; CY 208-243; Dopamine D-1 receptor agonists

1. Introduction

The role of dopamine D-1 receptors in the control of motor behaviour remains unclear. In normal rats, a functional linkage exists between D-1 and D-2 sites. D-2 receptor activation may inhibit D-1 receptor-mediated stimulation of cyclic AMP formation in striatal slices (Stoof and Kebabian, 1981). On the other hand, behavioural experiments suggest that D-1 receptors gate the level of response to D-2 receptor activation. For example, the D-1 agonist SKF 38393, which does not induce stereotyped behaviour itself, potentiates the ability of the D-2 agonist RU 24213 to induce stereotypy (Mashurano and Waddington, 1986). Other data also supports a positive role for D-1 receptor agonists. For example, in rats the inhibition of pallidal cell firing produced by the D-2 agonist LY 171555 (quinpirole) is potentiated by pretreatment with the D-1 agonist SKF 38393 (Carlson et al., 1987). These data suggest that concurrent D-1 and D-2 receptor stimulation is necessary for the full expression of postsynaptic dopamine receptor-mediated events. Whether such a functional interaction exists in man or other primate species is not known.

Linkage between D-1 and D-2 receptors appears dependent on intact dopamine function in brain at least in rodents. Following depletion of brain dopamine content by reserpine, or destruc-

* To whom all correspondence should be addressed.
[1] Present address: University Department of Clinical Neurology, Institute of Neurology, The National Hospital, London WC1, U.K.

tion of nigro-striatal dopamine fibres, this linkage is lost and D-1 and D-2 receptors appear to act independently. Thus, the inhibitory effect of D-2 receptor occupation on cyclic AMP formation disappears following reserpine treatment (Kelly and Nahorski, 1987). Behaviourally, the D-2 agonist pergolide, but not the D-1 agonist SKF 38393, induces hypermotility in normal rats, whereas in reserpine-treated animals both drugs are effective (Arnt, 1985). The stimulant effect of pergolide in reserpinised rats is prevented by the D-2 antagonist clebopride, but not by the D-1 antagonist SCH 23390. In contrast, the effect of SKF 38393 is blocked by SCH 23390, but not by clebopride. In addition, the effects of bromocriptine in producing locomotor activity in mice are reduced by prior treatment with reserpine plus AMPT, but are restored by combined administration with SKF 38393 (Jackson and Hashizume, 1986). This implies that in normal animals the effects of bromocriptine are dependent on the stimulation of D-1 sites by endogenous dopamine. Indeed, depletion of brain dopamine by reserpine or α-methyl-p-tyrosine inhibits yawning in intact rats or circling behaviour in rats with a unilateral quinolinic acid-induced striatal lesion produced by the selective D-2 agonist LY 171555; an effect reversed by coadministration of SKF 38393 (Barone et al., 1986; Longoni et al., 1987).

Such findings have implications for the treatment of Parkinson's disease. Drugs acting predominantly on D-2 sites (e.g., (+)-PHNO or bromocriptine) or drugs affecting both D-1 and D-2 sites (e.g., L-DOPA or apomorphine) are effective in reversing the motor deficits of this disorder. However, the pharmacological findings in animals suggest that D-1 agonists might enhance the effect of D-2 drugs if linkage between receptors is present, or that a D-1 agonist would itself be effective in treating Parkinson's disease if D-1 and D-2 receptors were acting independently of one another.

To date, SKF 38393 is the only suggested selective D-1 agonist which has been studied extensively. SKF 38393 only produces non-stereotyped grooming and sniffing in normal rats, but induces marked contraversive circling in rats with unilateral 6-OHDA lesions (Setler et al., 1978; Molloy and Waddington, 1984; Costall et al., 1984). This latter finding implies a potential use for the drug in the treatment of Parkinson's disease. However, in MPTP-treated marmosets SKF 38393 does not reverse the motor deficits, and can inhibit the positive effects of the D-2 agonist LY 171555 (Nomoto et al., 1985; in press; Close et al., 1985). Indeed, in Parkinson's disease itself, SKF 38393 alone or in combination with intravenous L-DOPA does not alter parkinsonian disability (Braun et al., 1987). These findings might suggest that D-1 agonists are not of use in treating Parkinson's disease. However, SKF 38393 does not readily penetrate into brain, it has a short half-life, and it may be metabolised to another compound which has D-2 antagonist properties. So, SKF 38393 may not be ideal for examining the role of D-1 receptors in motor function.

Recently, another putative D-1 agonist, the benzergoline CY 208-243, has been described (Markstein et al., in press). CY 208-243 displaces [^{3}H]dopamine binding in nanomolar concentration, but only displaces [^{3}H]spiperone in micromolar amounts. CY 208-243 stimulates cyclic AMP formation, but does not produce a maximal effect and can inhibit the actions of dopamine. So CY 208-243 appears to be a selective D-1 receptor partial agonist. The D-1 receptor selectivity of CY 208-243 is indicated by its failure to alter striatal dopamine turnover in vivo or in vitro, or to inhibit electrically stimulated acetylcholine release. Also, CY 208-243 does not decrease serum prolactin levels or induce emesis. In behavioural tests, CY 208-243 in high doses does not induce stereotypy or produce other behavioural effects, with the exception of non-stereotyped sniffing. However, in rats with a unilateral 6-OHDA lesion, CY 208-243 produces contraversive rotation.

We now report the effect of CY 208-243 in MPTP-treated marmosets. We find evidence for potential antiparkinsonian activity independent of prior or concurrent D-2 receptor stimulation.

2. Materials and methods

The experiments to be described were divided into two parts involving two separate groups of

common marmosets. In initial experiments (Group A), the response to a variety of D-1 or D-2 agonist drugs (including CY 208-243) was tested in MPTP-treated animals. In a second set of experiments (Group B), the effect of CY 208-243 was assessed in drug naive animals which were then treated with MPTP and subsequently received CY 208-243 again.

2.1. Experiment 1

2.1.1. MPTP treatment of Group A animals

Adult common marmosets of either sex (aged 3-8 years; weight range 290-360 g) received MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) (2 mg/kg s.c.) daily for 5 days, to a cumulative dose of 10 mg/kg. MPTP hydrochloride (Research Biochemicals Inc.) was dissolved in sterile 0.9% saline. On the second treatment day all animals became tremulous, rigid and sometimes dystonic, for a period up to 1 h. Subsequently, animals developed persistent motor deficits comprising marked bradykinesia, flexed posture, rigidity and intermittent postural tremor. At this time all animals were reluctant to eat or drink spontaneously and were hand fed from a syringe with Mazure marmoset jelly. After 3 weeks the animals had recovered from the acute effects of MPTP treatment and were subsequently able to feed and groom themselves. Over the following 6 weeks a further improvement in motor disability was observed, but all animals remained parkinsonian over the following 6 month period.

2.1.2. Assessment of locomotor activity

Individual animals were placed in a novel cage identical to that in which the animals were normally housed. The cage was fitted with eight infrared photocells. Four were focussed horizontally across the width of the cage floor and one along the width of each of the two perches. One beam was directed from front to back of the cage above each perch. This arrangement allowed assessment of movement in all directions. An acclimatization period of between 30-120 min was allowed prior to drug treatment. Motility counts were accumulated over 10 min periods for at least 180 min following drug administration.

2.1.3. Assessment of motor deficits

The extent of motor disability was assessed by observer rating of video tapes of the animals. These were recorded in the environment simultaneously used to record locomotor activity. In experiments designed to assess the effects of MPTP treatment or to assess locomotor activity following drug administration to MPTP-treated marmosets, animals were only scored for motor disability when undisturbed. The following components of behaviour were scored. (a) *Eyes*: Attention focussed towards the observer, the amount of blinking, eye movement and general alertness. Normal (0); abnormal (1). (b) *Posture*: Normal (0); abnormal trunk (+1); tail (+1) or limbs (+1); grossly abnormal animals flexed on the floor of the cage (4). (c) *Balance*: Normal (0); unstable (1); spontaneous falls (2). (d) *Motility*: Normal (0); mild slowing (1); moderate bradykinesia (2); akinesia (3). (e) *Vocalisation*: Normal (0); reduced (1). (f) *Tremor*: Absent (0); present (1). (g) *Fur condition*, indicating the animal's ability to groom: Normal (0); dirty (1). Assessment of these items gives a score of 0 for normal marmosets and a maximal disability score of 13.

2.1.4. Administration of L-DOPA, (+)-PHNO or SKF 38393 to Group A MPTP-treated marmosets

Sterile solutions of L-DOPA were prepared immediately prior to each experiment. L-DOPA for injection (4.0 ml; 5 mg/ml; pH 2.5; Hoffmann La Roche, Basle) was mixed with 0.5 M sodium phosphate buffer (0.864 ml; pH 7.4) and an aqueous solution of 10% Tween 80 (0.364 ml; pH 6.5). The final pH of the solution was 6.0. Solutions were sterilised by filtration through a 0.2 μm bacterial filter. Animals were pretreated orally with carbidopa (12.5 mg/kg α-methyldopa hydrazine; Merck Sharp & Dohme) suspended in 1% methylcellulose and immediately introduced into the activity cages. After 1 h L-DOPA (12.5 mg/kg i.p.) was administered and activity monitored over the following 3 h period.

(+)-PHNO ((+)-propyl-9-hydroxynapthoxazine; Merck Sharp & Dohme) was dissolved in sterile 0.9% saline and the pH adjusted to 7.0 immediately before the experiment. Eight days following the L-DOPA challenge animals were

placed into the photocell monitoring cages and, after 30 min acclimatization, (+)-PHNO (4 μg/kg s.c.) was administered. Activity was monitored over the following 3 h period.

SKF 38393 (2,3,4,5-tetrahydro-7,8-dihydroxy-1-phenyl-1H-3-benzazepine hydrochloride; Smith Kline & French) was dissolved in 0.9% sterile saline in a darkened container and filtered using a 20 μm bacterial filter immediately prior to the experiment (final pH 6.5). Two weeks following the previous drug challenge group A animals were introduced into the photocell monitoring cages and after 30 min acclimatisation SKF 38393 (10 mg/kg i.p.) was administered and activity monitored for the subsequent 3 h period.

Video assessment of the animals behaviour was made following administration of L-DOPA, (+)-PHNO and SKF 38393.

2.1.5. Administration of CY 208-243 to Group A MPTP-treated marmosets

CY 208-243 ((−)-(6aR)(12bR)-4,6,6a,7,8,12b-hexahydro-7-methylindolo[4,3-ab]-phenanthridine; Sandoz, Basle) was mixed with an equal weight of tartaric acid and dissolved in 0.9% sterile saline (pH 4.0) and the pH adjusted with 0.1 M NaOH to 5.5. After a drug free period of two weeks control vehicle injections were administered (0.2 ml sterile tartaric acid and NaOH pH 5.5 s.c.) following a 30 min acclimatisation in the photocell cages. Thereafter activity was monitored over a 3 h period. Over the following two weeks Group A animals were placed into the activity cages, acclimatised for 30 min, and administered 0.5, 0.75, 1.0, 1.25 mg/kg s.c. of CY 208-243 in a random dose sequence. Activity was monitored for 3 h periods. Animals were allowed at least 48 h to recover between administrations of CY 208-243.

2.1.6. Effects of pretreatment with sulpiride or SCH 23390 on the response to CY 208-243 in Group A MPTP-treated marmosets

The effects of CY 208-243 alone and following pretreatment with sulpiride or SCH 23390 were also assessed by rating of video tapes. In these experiments it was only possible to utilize one dose of each antagonist. The dose of the D-2 antagonist sulpiride chosen was that previously shown to totally inhibit the effects of the D-2 agonist LY 141865 in MPTP-treated marmosets (Nomoto et al., 1985). Sulpiride does not interact with D-1 sites or other neuronal receptors even at high concentrations (Chivers et al., 1988). The high dose of the D-1 antagonist SCH 23390 employed will not interact with D-2 sites (see Hyttel 1983; Bischoff et al., 1988) but may act on 5HT-2 sites.

SCH 23390 (1-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1H-3-benzazepin-7-ol hemimaleate; Schering) was dissolved in 0.9% sterile saline (final pH 6.5). Animals received SCH 23390 (0.5 mg/kg i.p.) and were immediately introduced into the photocell cages. One hour later CY 208-243 (1 mg/kg s.c.) was administered and activity recorded for the following 3 h period.

Sulpiride (Delagrange, France) was dissolved in a minimum quantity of 2% sulphuric acid and diluted to volume with 0.9% sterile saline. The pH of the final solution was adjusted to 7.0 using 0.1 M HCl. Sulpiride (20 mg/kg i.p.) was administered 1 h prior to the administration of CY 208-243 (1 mg/kg s.c.). Activity was recorded over the following 3 h period.

2.2. Experiment 2

2.2.1. Administration of CY 208-243 to Group B drug naive animals

Adult common marmosets of either sex (aged 2-5 years; weight range 260-365 g) were placed into the photocell motility cages, allowed 30 min to acclimatise and spontaneous activity recorded for a 3 h period. This was repeated on the following day. The next day animals received vehicle control injections (tartaric acid plus NaOH; 0.2 ml; pH 5.5; s.c.) and were immediately placed into the photocell cages for a 3 h period. On the fourth day the animals received CY 208-243 (1 mg/kg s.c.) and were immediately placed into the photocell cages for a 3 h period.

2.2.2. MPTP treatment of Group B marmosets

MPTP (2 mg/kg s.c.) was administered daily for 8-10 days to induce motor deficits. After 6 weeks the animals exhibited stable motor deficits

which remained unaltered throughout the period of the experiments. Animals were placed in the photocell cages and assessed for motor activity.

2.2.3. Administration of CY 208-243 to Group B marmosets following MPTP treatment

CY 208-243 was administered to Group I animals who until then had received no other drugs other than MPTP. Following 30 min acclimatisation the animals received CY 208-243 (1 mg/kg s.c.) and were placed back into the photocell cages for a 3 h period. Subsequently, these animals also received L-DOPA (12.5 mg/kg i.p.) plus carbidopa (12.5 mg/kg p.o.) or (+)-PHNO (4 μg/kg s.c.). Activity was recorded over the following 3 h period.

2.3. Statistics

Student's t-test for paired samples was employed to assess differences in cumulative movement counts between different drug treatments. Motor disability scores were compared using the Mann-Whitney test for non-parametric data.

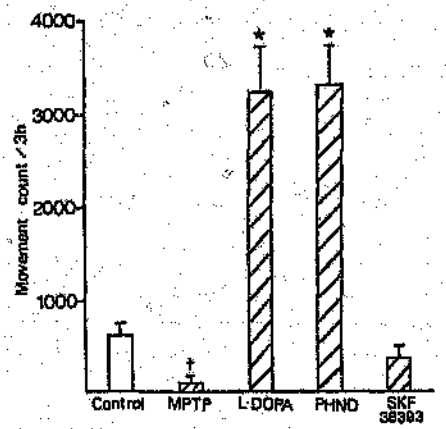


Fig. 1. The effect of administration of L-DOPA (12.5 mg/kg i.p.) plus carbidopa (12.5 mg/kg p.o.) or (+)-PHNO (4 μg/kg s.c.) or SKF 38393 (10 mg/kg i.p.) on cumulative movement counts in common marmosets rendered parkinsonian by prior treatment with MPTP. Values are the means (±1 S.E.M.) of movement counts obtained for eight individual animals recorded in 10 min segments and summed over a 3 h period. Open columns represent normal animals and hatched columns the same animals following MPTP treatment and drug or vehicle administration. Group differences were assessed by a paired Student's t-test. $^{+}$ $P < 0.05$ compared to activity in animals prior to MPTP treatment. * $P < 0.05$ compared to activity in MPTP-treated animals receiving drug vehicle.

3. Results

3.1. Experiment 1

3.1.1. MPTP-induced motor deficits in Group A marmosets

Immediately prior to the start of the experiments MPTP-treated animals exhibited obvious akinesia, a flexed posture, poor balance, loss of vocalisation and blink reflex when observed in their home cage. At this time assessment of locomotor activity in the photocell cages showed MPTP-treated marmosets to exhibit decreased motility with the animals spending most of the time on the floor of the cage or in one place on the lower of the two perches. Retrospective blind assessment of video tapes confirmed that the animals remained in an akinetic and flexed state for the duration of monitoring. The animals remained parkinsonian over the period of the experiments.

3.1.2. Administration of L-DOPA, (+)-PHNO or SKF 38393 to Group A MPTP-treated marmosets (table 1; fig. 1)

Administration of the vehicle solutions of L-DOPA, (+)-PHNO or SKF 38393 had no effect on motor activity or parkinsonian disability scores (data not shown).

Administration of L-DOPA (12.5 mg/kg i.p.) plus carbidopa (12.5 mg/kg p.o.) caused a rapid reversal of motor deficits and induced locomotor hyperactivity which lasted for approximately 3-4 h. Similarly, administration of (+)-PHNO (4 μg/kg s.c.) also produced a reversal of motor deficits in MPTP-treated animals. The action of (+)-PHNO was of approximately 2 h duration. The behavioural changes produced by L-DOPA and (+)-PHNO were identical. Nausea and sometimes vomiting was noted following (+)-PHNO, but not following administration of L-DOPA plus carbidopa.

TABLE 1

The effect of prior treatment with MPTP and the subsequent administration of L-DOPA (12.5 mg/kg i.p.) plus carbidopa (12.5 mg/kg p.o.) (+)-PHNO (4 μg/kg s.c.) or SKF 38393 (10 mg/kg i.p.) on the motor disability scores of common marmosets. The results are expressed as the mean (±1 S.E.M.) scores for six to eight individual animals. Scores were taken at the time of peak drug actions. The maximum parkinsonian score obtainable was 13. Differences between groups were assessed using a Mann-Whitney test for non-parametric data.

Treatment status	Score	Range
Normal (n = 8)	0 ±0	0
MPTP (n = 8)	12.8±0.2 [a]	11–13
+L-DOPA (n = 8)	3.6±0.6 [b]	2– 6.5
+(+)-PHNO (n = 8)	5.6±1.3 [b]	2–10.5
+SKF 38393 (n = 6)	11.0±0.9	8–13

[a] $P < 0.05$ compared to before MPTP. [b] $P < 0.05$ compared to MPTP treatment alone.

Administration of SKF 38393 (10 mg/kg i.p.) did not alter motor deficits in MPTP-treated marmosets. All animals remained akinetic over the 3 h period of observation. No other behavioural changes were observed. Nausea and vomiting were not evident.

3.1.3. Administration of CY 208-243 to Group A MPTP-treated marmosets (table 2; fig. 2)

Administration of the vehicle used for CY 208-243 had no effect on motor activity or motor deficit scores.

Administration of CY 208-243 (0.5-1.25 mg/kg s.c.) to MPTP-treated marmosets produced a reversal of motor deficits within a few minutes of drug administration which reached a peak within 30 min. The reversal of motor deficits and accompanying locomotor hyperactivity lasted for approximately 2 h. The motor effects produced by CY 208-243 were identical to those produced by (+)-PHNO or L-DOPA. The effects of CY 208-243 were dose-related in the range employed. Higher doses of CY 208-243 were not used in these studies since preliminary investigations showed these to induce hyperexcitability in the animals. CY 208-243 did not cause nausea or vomiting in any animal.

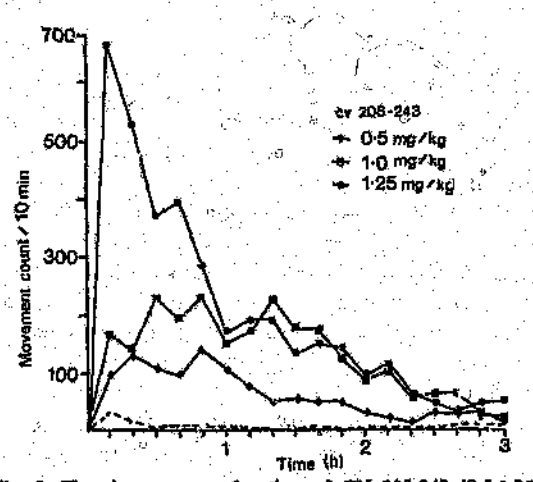


Fig. 2. The time course of action of CY 208-243 (0.5-1.25 mg/kg s.c.) in producing locomotor hyperactivity in MPTP-treated marmosets. The values shown are the mean for eight individual animals. Movement counts were accumulated over 10 min periods. The S.E.M.'s varied between 18-26% of the mean movement counts. The dashed line indicates the movement counts shown by the MPTP-treated animals when receiving the vehicle used for CY 208-243.

TABLE 2

The effect of pretreatment with SCH 23390 (2 mg/kg i.p. 1 h previously) or sulpiride (20 mg/kg i.p. 1 h previously) alone and in combination with CY 208-243 (1 mg/kg s.c.) on the motor disability scores of MPTP-treated common marmosets. Results are expressed as the mean (±1 S.E.M.) scores for eight individual animals. Motor disability scores were assessed 1 h after CY 208-243 administration with or without SCH 23390 or sulpiride. In addition, scores were obtained 30 min after CY 208-243 following pretreatment with sulpiride. The maximum parkinsonian score possible was 13. Differences between groups were assessed using a Mann-Whitney test.

Drug treatment	Scores	Range
MPTP	9.9±0.4	8–11.5
CY 208-243 alone	6.8±1.3 [a]	3– 9
SCH 23390 alone	12.4±0.3 [a]	11–13
Sulpiride alone	11.6±0.6 [a]	9–13
SCH 23390 +CY 208-243 (1 h)	9.9±0.5 [b]	8–12
Sulpiride +CY 208-243 (30 min)	4.5±0.6	3– 6
Sulpiride +CY 208-243 (1 h)	11.0±0.8 [b]	9–13

[a] $P < 0.05$ compared to MPTP treatment alone. [b] $P < 0.05$ compared to CY 208-243 treatment alone.

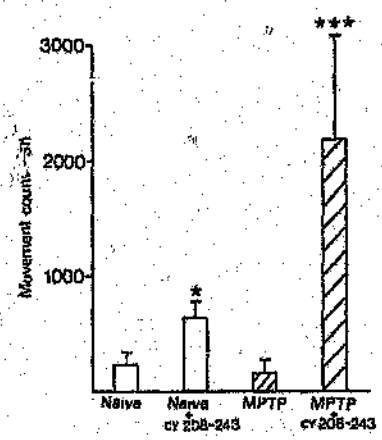


Fig. 5. The effect of administration of CY 208-243 (1.0 mg/kg s.c.) to drug naive normal marmosets and following treatment with MPTP on cumulative movement counts. Values are the means (±1 S.E.M.) of movement counts obtained for six individual animals recorded in 10 min segments and summed over a 3 h period. Open columns represent normal animals and hatched columns the same animals following MPTP treatment. Group differences were assessed using a paired Student's t-test. * $P < 0.05$ compared to drug naive normal animals. *** $P < 0.001$ compared to MPTP-treated animals.

activity prior to and following MPTP administration.

Administration of the vehicle for CY 208-243 had no effect on motor activity or motor deficit scores.

Administration of CY 208-243 (1.0 mg/kg s.c.) led to a reversal of akinesia within a few minutes. The animals exhibited an increase in locomotor activity and restoration of normal motor function. The animals vocalised, blinked and moved freely from perch to perch, showing normal balance. The effect of CY 208-243 was maximal 30 min following drug administration and lasted for 2 h before the animals again became bradykinetic and adopted a flexed posture. Nausea or vomiting were not observed.

The subsequent administration of (+)-PHNO and L-DOPA to MPTP-treated Group B animals produced an identical reversal of motor deficits and induction of motor hyperactivity (data not shown).

4. Discussion

MPTP-treated primates respond to the administration of known antiparkinsonian agents, which cause reversal of parkinsonian motor deficits and locomotor hyperactivity. In this study MPTP-treated marmosets showed a typical response following administration of L-DOPA plus the peripheral decarboxylase inhibitor carbidopa, or following (+)-PHNO treatment. As expected, the D-2 agonist (+)-PHNO also induced nausea and vomiting in some animals. The acute administration of L-DOPA or (+)-PHNO did not induce stereotypy or dyskinesias. In contrast, and as previously reported, the administration of the D-1 agonist SKF 38393 did not induce a reversal of MPTP-induced motor deficits (Nomoto et al., 1985; Close et al., 1985). So, the group of animals used in this investigation showed a response to mixed D-1/D-2 drugs, or to selective D-2 agents, but not to D-1 receptor stimulation at least as judged by the effects of SKF 38393.

However, administration of another putative D-1 partial receptor agonist CY 208-243 to this same group of MPTP-treated marmosets did produce a reversal of motor deficits and initiated motor hyperactivity. The effects observed were identical to those produced by L-DOPA or (+)-PHNO, except nausea and vomiting were not observed. Again, stereotypy or dyskinesias were not apparent on acute administration of CY 208-243. CY 208-243 was only examined in a limited dose range. Higher doses than those reported produced hyperexcitability in the animals, the cause of which is not apparent. The maximum increase in activity produced by CY 208-243 was comparable to that seen following administration of L-DOPA or (+)-PHNO. Recently, Markstein and colleagues have shown a similar antiparkinsonian activity of CY 208-243 in MPTP-treated squirrel monkeys (Markstein et al., in press).

So, CY 208-243 possesses antiparkinsonian activity in MPTP-treated primates not observed with SKF 38393. What are the differences between the drugs? Both compounds are described as selective partial D-1 agonists. Both SKF 38393 and CY 208-243 produce contraversive rotation in 6-OHDA lesioned rats. It has been speculated that

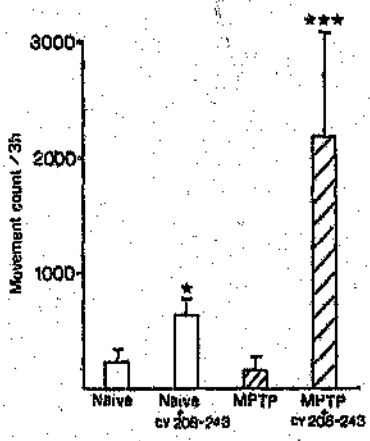


Fig. 5. The effect of administration of CY 208-243 (1.0 mg/kg s.c.) to drug naive normal marmosets and following treatment with MPTP on cumulative movement counts. Values are the means (±1 S.E.M.) of movement counts obtained for six individual animals recorded in 10 min segments and summed over a 3 h period. Open columns represent normal animals and hatched columns the same animals following MPTP treatment. Group differences were assessed using a paired Student's t-test. * $P < 0.05$ compared to drug naive normal animals. *** $P < 0.001$ compared to MPTP-treated animals.

activity prior to and following MPTP administration.

Administration of the vehicle for CY 208-243 had no effect on motor activity or motor deficit scores.

Administration of CY 208-243 (1.0 mg/kg s.c.) led to a reversal of akinesia within a few minutes. The animals exhibited an increase in locomotor activity and restoration of normal motor function. The animals vocalised, blinked and moved freely from perch to perch, showing normal balance. The effect of CY 208-243 was maximal 30 min following drug administration and lasted for 2 h before the animals again became bradykinetic and adopted a flexed posture. Nausea or vomiting were not observed.

The subsequent administration of (+)-PHNO and L-DOPA to MPTP-treated Group B animals produced an identical reversal of motor deficits and induction of motor hyperactivity (data not shown).

4. Discussion

MPTP-treated primates respond to the administration of known antiparkinsonian agents, which cause reversal of parkinsonian motor deficits and locomotor hyperactivity. In this study MPTP-treated marmosets showed a typical response following administration of L-DOPA plus the peripheral decarboxylase inhibitor carbidopa, or following (+)-PHNO treatment. As expected, the D-2 agonist (+)-PHNO also induced nausea and vomiting in some animals. The acute administration of L-DOPA or (+)-PHNO did not induce stereotypy or dyskinesias. In contrast, and as previously reported, the administration of the D-1 agonist SKF 38393 did not induce a reversal of MPTP-induced motor deficits (Nomoto et al., 1985; Close et al., 1985). So, the group of animals used in this investigation showed a response to mixed D-1/D-2 drugs, or to selective D-2 agents, but not to D-1 receptor stimulation at least as judged by the effects of SKF 38393.

However, administration of another putative D-1 partial receptor agonist CY 208-243 to this same group of MPTP-treated marmosets did produce a reversal of motor deficits and initiated motor hyperactivity. The effects observed were identical to those produced by L-DOPA or (+)-PHNO, except nausea and vomiting were not observed. Again, stereotypy or dyskinesias were not apparent on acute administration of CY 208-243. CY 208-243 was only examined in a limited dose range. Higher doses than those reported produced hyperexcitability in the animals, the cause of which is not apparent. The maximum increase in activity produced by CY 208-243 was comparable to that seen following administration of L-DOPA or (+)-PHNO. Recently, Markstein and colleagues have shown a similar antiparkinsonian activity of CY 208-243 in MPTP-treated squirrel monkeys (Markstein et al., in press).

So, CY 208-243 possesses antiparkinsonian activity in MPTP-treated primates not observed with SKF 38393. What are the differences between the drugs? Both compounds are described as selective partial D-1 agonists. Both SKF 38393 and CY 208-243 produce contraversive rotation in 6-OHDA lesioned rats. It has been speculated that

SKF 38393 penetrates poorly into brain (see Clark and White, 1987), an effect which may be more pronounced in the primate than in the rat. So at least in the marmoset this might explain the failure of SKF 38393 to reverse MPTP-induced parkinsonism.

The two drugs also differ in their actions on D-1 sites. Both SKF 38393 and CY 208-243 have the properties of partial agonists. Thus, they only produce a partial stimulation of adenylate cyclase activity, and inhibit the ability of dopamine to produce maximal stimulation (Setler et al., 1978; Markstein et al., in press). However, the maximum stimulation of adenylate cyclase activity produced by CY 208-243 is less than that achieved by SKF 38393. So, it might have been expected that CY 208-243 would be less, rather than more, effective in inducing motor activity than SKF 38393.

An alternative explanation is that CY 208-243 has some unexpected D-2 receptor activity. In rodents the acute pharmacological profile of CY 208-243 clearly demonstrates D-1 receptor selectivity. In particular, the failure of CY 208-243 to induce stereotypy, to decrease acetylcholine release, and to inhibit prolactin levels argues against D-2 actions (Markstein et al., in press). In normal marmosets CY 208-243 did not induce stereotyped behaviour and only produced a small increase in motor activity. In contrast, administration of (+)-PHNO to normal marmosets induced a profound hyperactivity syndrome (Nomoto et al., 1987). A further argument against D-2 actions of CY 208-243 in marmosets was its failure to induce nausea or vomiting in either normal or MPTP-treated animals.

The effects of selective dopamine receptor inhibitors on the actions of CY 208-243 in the common marmoset might have been expected to explain its site of action. The D-1 antagonist SCH 23390 certainly produced a marked inhibition of the motor response to CY 208-243. So, D-1 systems may be involved. However, the D-2 antagonist sulpiride also produced some reversal of the actions of CY 208-243. The effect of sulpiride was most marked 2-3 h following administration of CY 208-243. Motor activity and motor disability scores taken 30 min following CY 208-243 administration indicated no effect of sulpiride at the time of peak effect of CY 208-243. Since sulpiride was administered only 1 h prior to CY 208-243, the slow penetration of the former drug into brain may have contributed to its lack of effect early on. Indeed, by 1 h following CY 208-243 administration (and 2 h following sulpiride treatment) a worsening of motor deficits was observed. However, the dose of sulpiride and the timing employed was previously shown to produce an almost total inhibition of the actions of the D-2 agonist LY 141865 (Nomoto et al., 1985). Interestingly, both sulpiride and SCH 23390 increased the basal motor disability scores of the MPTP-treated marmosets. This suggests the effects of residual endogenous dopaminergic activity on both D-1 and D-2 systems can continue to provide some protection against parkinsonian motor deficits. Indeed, the apparent effect of sulpiride on the activity of CY-208-243 may have been due to the removal of residual D-2 tone rather than pharmacological antagonism.

Whatever the reason for the time course of effect of sulpiride, the results indicate some involvement of both D-1 and D-2 sites in the actions of CY 208-243. Whether this is because CY 208-243 possesses some activity at D-2 sites, hitherto unrecognised, or whether this is the result of some complex interactions between D-1 and D-2 activation in the MPTP-treated marmoset remains to be established.

Finally, it should be remembered that CY 208-243 does not act specifically on brain dopamine receptors. CY 208-243 possesses atypical opioid agonist activity, interacts with high affinity at $5HT_{1A}$ binding sites and shows weak α-adrenergic and $5HT_2$ activity (Foote et al., 1988). Whether these actions of CY 208-243 contribute to its antiparkinsonian effects is unknown.

The studies in drug naive animals indicate that CY 208-243 has little effect in normal animals and that its action are considerably potentiated following destruction of nigrostriatal dopamine systems by MPTP administration. Also, the results of these experiments show that the effects of CY 208-243 are not dependent on prior D-2 agonist exposure of animals. In contrast, in rats with unilateral 6-OHDA lesions, the ability of a D-1 agonist to cause rotation seems dependent on prior priming

with a D-2 agonist (Morelli and Di Chiara, 1987). Clearly, the ability of CY 208-243 alone to reverse the motor disabilities in MPTP-treated monkeys without D-2 priming has implications for the clinical use of such drugs in Parkinson's disease.

Acknowledgements

This study was supported by the Medical Research Council, the Parkinson's Disease Society and the Research Funds of the Bethlem Royal and Maudsley Hospitals and King's College Hospital. A.T. is an MRC (R.S.A.) post-doctoral fellow.

References

Arnt, J., 1985, Behavioural stimulation is induced by separate dopamine D-1 and D-2 receptor sites in reserpine-pretreated but not normal rats, European J. Pharmacol. 113, 79.

Barone, P., T.A. Davis, A.R. Braun and T.N. Chase, 1986, Dopaminergic mechanisms and motor function: characterisation of D-1 and D-2 dopamine receptor interactions, European J. Pharmacol. 123, 109.

Bischoff, S., M. Heinrich, J. Krauss, M.A. Sills, M. Williams and A. Vassout, 1988, Interaction of the D1 receptor antagonist SCH 23390 with the central 5-HT system: radioligand binding studies, measurements of biochemical parameters and effects on L-5-HTP syndrome, J. Rec. Res. 8, 107.

Braun, A., G. Fabbrini, M.M. Mouradian, C. Serrati, P. Barone and T.N. Chase, 1987, Selective D-1 dopamine receptor agonist treatment of Parkinson's disease, J. Neural Transm. 68, 41.

Carlson, J.H., D.A. Bergstrom and J.R. Walters, 1987, Stimulation of both D1 and D2 dopamine receptors appears necessary for full expression of postsynaptic effects of dopamine agonist; a neurophysiological study, Brain Res. 400, 205.

Chivers, J.K., W. Gommeren, J.E. Leysen, P. Jenner and C.D. Marsden, 1988, Comparison of the in vitro receptor selectivity of substituted benzamide drugs for brain neurotransmitter receptors, J. Pharm. Pharmacol. 40, 415.

Clark, D. and F.J. White, 1987, Review: D1 dopamine receptor - the search for a function: A critical evaluation of the D1/D2 dopamine receptor classification and its functional implications, Synapse 1, 347.

Close, S.P., A.S. Marriott and S. Pay, 1985, Failure of SKF 38393-A to relieve parkinsonian symptoms induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine in the marmoset, Br. J. Pharmacol. 85, 320.

Costall, B., M.E. Kelly and R.J. Naylor, 1984, Unilateral striatal dopamine denervation: Reduced motor inhibitory effects of dopamine antagonists revealed in models of asymmetric and circling behaviour, Naunyn-Schmiederb. Arch. Pharmacol. 326, 29.

Foote, R.W., H.H. Buscher, D. Romer, R. Maurer, A. Enz, A., B.H. Gahwiler, G.T. Shearman, M.P. Seiler and H. Wuthrich, 1988, CY 208-243: A unique combination of atypical opioid antinociception and D-1 dopaminomimetic properties, Life Sci. 42, 137.

Hyttel, J., 1983, SCH-23390 – The first selective dopamine D-1 antagonist, European J. Pharmacol. 91, 153.

Jackson, D.M. and M. Hashizume, 1986, Bromocriptine induces marked locomoter stimulation in dopamine-depleted mice when D-1 dopamine receptors are stimulated with SKF 38393, Psychopharmacology 90, 147.

Kelly, E. and S.R. Nahorski, 1987, Endogenous dopamine functionally activates D-1 and D-2 receptors in striatum, J. Neurochem. 49, 115.

Longoni, R., L. Spina and G. Di Chiara, 1987, Permisive role of D-1 receptor stimulation by endogenous dopamine for the expression of postsynatpic D-2 mediated behavioural responses. Yawning in rats, European J. Pharmacol. 134, 163.

Markstein, R., N.P. Seiler, J.M. Vigouret, S. Urwyler, A. Enz and K. Dixon, Pharmacological properties of CY 208-243, and normal D-1 agonists, Proceedings of XIth International Catecholamine Symposium, Jerusalem 1986, ed. M. Sandler (in press).

Mashurano, M. and J.L. Waddington, 1986, Stereotyped behaviour in response to the selective D-2 dopamine receptor agonist RU 24213 is enhanced by pretreatment with the selective D-1 agonist SK&F 38393, Neuropharmacology 25, 947.

Molloy, A.G. and J.L. Waddington, 1984, Dopaminergic behaviour stereospecifically promoted by the D1 agonist R-SK&F 38393 and selectively blocked by the D1 antagonist SCH 23390, Psychopharmacology 82, 409.

Morelli, M. and G. Di Chiara, 1987, Homologous and heterologous sensitization to D-1 and D-2 receptors after dopaminergic agonists administration in 6-OHDA denervated rats. Presented at the XIth International Congress of Pharmacology, Sydney, Australia.

Nomoto, M., P. Jenner and C.D. Marsden, 1985, The dopamine D2 agonist LY [illegible], but not the D1 agonist SKF 38393, reverses parkinsonism induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in the common marmoset, Neurosci. Lett. 57, 37.

Nomoto, M., P. Jenner and C.D. Marsden, The D-1 agonist SKF 38393 inhibits the antiparkinsonian activity of the D-2 agonist LY 171555 in the MPTP-treated marmoset, Neurosci. Lett. (in press).

Nomoto, M., S. Stahl, P. Jenner and C.D. Marsden, 1987, Antiparkinsonian activity of (+)-PHNO in the MPTP-treated common marmoset, Movement Dis. 2, 37.

Seiler, P.E., H.M. Sarau, C.L. Zirkle and H.L. Saunders, 1978, The central effects of a novel dopamine agonist, European J. Pharmacol. 50, 419.

Stoof, J.C. an J.W. Kebabian, 1981, Opposing roles for D-1 and D-2 dopamine receptors in efflux of cyclic AMP from rat neostriatum Nature, 294, 366.

APPENDIX VI

Clinical Neuropharmacology
Vol. 12, No. 1, pp. 53–59
© 1989 Raven Press, Ltd., New York

The Antiparkinsonian Activity of CQA 206-291, a New D_2 Dopamine Receptor Agonist

J. A. Temlett, N. P. Quinn, C. D. Marsden, *X. Lataste, and *A. L. Jaton

*University Department of Clinical Neurology, Institute of Neurology, National Hospital for Nervous Diseases, London, England; and *Sandoz Ltd., Basle, Switzerland*

Summary: CQA 206-291, a new D_2 dopamine receptor agonist with a biphasic dopaminergic profile, was given to six patients with idiopathic Parkinson's disease after overnight drug withdrawal. With incremental single oral doses of CQA, a dose-related, clinically significant, and prolonged antiparkinsonian effect was observed. Most subjects experienced drowsiness after the drug while a minority of subjects experienced nausea and/or vomiting or postural hypotension. Further study of this drug in humans is indicated. Key Words: CQA 206-291—Parkinson's disease.

[5*R*(5β, 8α, 10α)]-*N*′,*N*-Diethyl-*N*-(1-ethyl-6-methyl-ergoline-8-yl) sulfamide hydrochloride (CQA 206-291; Sandoz, Ltd., Basle, Switzerland) is an ergot derivative. The parent drug is a weak D_2 antagonist. It is metabolized to CQ 32-084, which is a potent D_2 and D_1 combined agonist (1,2). We here report the effects of a single oral dose of CQA 206-291 in patients with idiopathic Parkinson's disease (PD) experiencing motor fluctuations on long-term levodopa therapy. In each subject, the effect of increasing doses of the drug was compared with their usual response to administration of levodopa.

PATIENTS AND METHODS

Six patients with idiopathic PD, three men and three women aged 49–77 years (median, 62 years), were studied in the hospital after giving informed consent. They were all at Hoehn and Yahr Stage 3 (n = 4) or 4 (n = 2) off medication. Their disease duration was 9–16 years (median, 13.5 years), and they had been receiving levodopa preparations for 9–15 years (median, 12 years). Current levo-

Address correspondence and reprint requests to Prof. C. D. Marsden at University Department of Clinical Neurology, Institute of Neurology, National Hospital for Nervous Diseases, Queen Square, London WC1N 3BG, England.

dopa dosage (plus peripheral decarboxylase inhibitor) ranged from 375 to 1,750 mg/day (median, 650 mg/day). All were experiencing motor fluctuations with "on" period dyskinesias. Four subjects were also taking other antiparkinsonian medications (amantadine in three, benzhexol in one), which were continued unchanged throughout the study period (Table 1).

The patients' motor response to their usual morning dose of levodopa was assessed on two occasions in two cases, three times in three cases, and five times in the oth· · CQA 206-291 was given on alternate days, with usual treatment on the intervening days. Levodopa was stopped the evening before each study day, and the patient fasted overnight. On waking the following morning, domperidone 20 mg was given by mouth, followed shortly by breakfast. A single dose of CQA 206-291 was then given orally, beginning in the first three patients with 0.1 mg on the first study day and increasing through 0.25, 0.5, 1, 2.5, 5, and 10 mg, up to a maximum of 20 mg. Because doses below 2.5 mg had no effect, the second three patients started with 2.5 mg as their first dose. Parkinsonian motor disability was rated using the motor score (section 3) of the Unified Parkinson's Scale (3) prior to drug administration and at 0.5, 1, 1.5, 2, 3, 4, 5, and 6 h after the drug. Sitting and standing blood pressure, pulse, and any side effects were also recorded at each of the time intervals. If a patient failed to improve within 3 h after dosing or if benefit had worn off by that time, then the usual morning dose of levodopa was given and the antiparkinsonian response to the latter drug monitored. A full general and neurological examination was performed prior to the study and also following the final dose. Serum biochemistry, hematology, and electrocardiogram were monitored before and within 24 h after each dose administered.

RESULTS

All six patients showed improvement in parkinsonian motor disability as measured by the Unified Parkinson's Scale when given their usual morning dose of levodopa. The effect of levodopa was to switch these fluctuating patients from an akinetic-rigid state ("off") to mobility with dyskinesias ("on"). This change was reflected in a considerable reduction in their motor disability scores.

Doses of CQA 206-291 below 2.5 mg had no effect. The 2.5-, 5-, and 10-mg doses were received by all six subjects and 20 mg by three. The best scores achieved by each subject after each dose are shown in Fig. 1, which also indicates the range of baseline scores and scores after levodopa for each subject. After 2.5

TABLE 1. *Patient characteristics*

Patient initials	Sex	Age (yrs)	Disease duration (yrs)	L-Dopa dose (mg/day)	Other drugs (mg/day)
RE	M	49	9	375	Amantadine 300
DS	M	74	16	1,750	—
JG	M	63	12	700	Amantadine 200
RB	F	52	16	600	Benzhexol 8
GK	F	61	12	400	Amantadine 300
BG	F	71	15	1,000	—

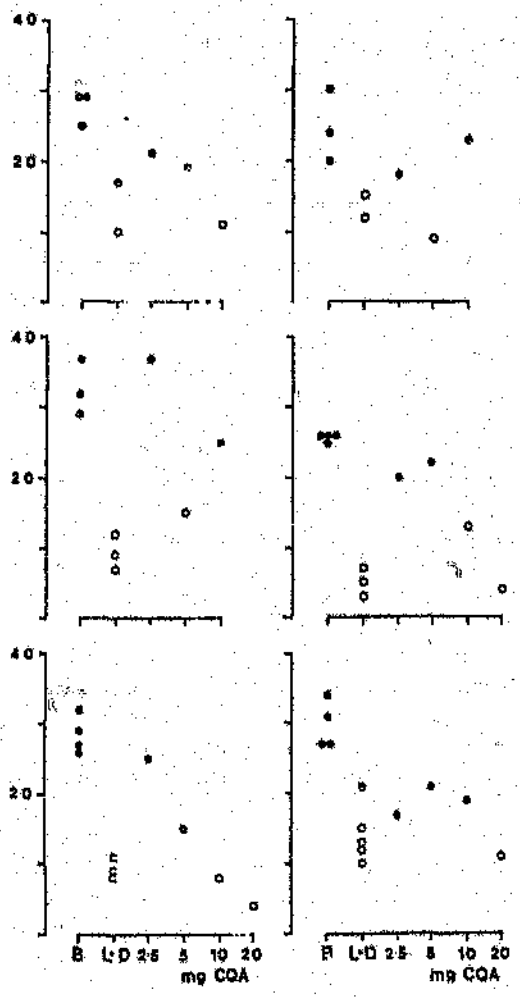


FIG. 1. Motor disability scores (on section 3 of the Unified Parkinson's Scale) in six patients off therapy (baseline) prior to drug administration (B), at the time of maximum response to their usual dose of levodopa (100–225 mg with a peripheral decarboxylase inhibitor) (L-D), or at the time of their maximum response to single doses of CQA 206-291 (2.5–20 mg orally). Filled circles indicate scores at times when the patients were judged by their attending doctor to be "off." Open circles are scores when the patients were clearly "on." Half-filled circles indicate scores at times when patients were intermediate between "on" and "off."

mg (n = 6), one patient turned partially "on"; after 5 mg (n = 6), one patient turned partially and two fully "on"; with 10 mg (n = 6), three subjects turned fully "on"; and all three subjects receiving 20 mg turned fully "on" (Table 2).

Motor disability scores for all the patients are shown together in Fig. 2, which shows a dose-response tendency to turn "on" at oral single doses of 10–20 mg CQA. This full "on" response was accompanied by dyskinesias similar to those provoked by levodopa in the same subjects. Latency to turn "on" was 60–140 min (median, 90 min), and time "on" lasted 30–450 min (median, 70 min). Latency from CQA ingestion to turning "off" again was 120–510 min (median, 167 min).

Five subjects experienced drowsiness, three nausea (two of whom vomited), and one each postural faintness and transient confusion. There were no significant

TABLE 2. *No. of patients turning "on," or partially "on," after each dose of CQA 206-291*

Dose of CQA 206-291 (mg)	n	"On"	Half "on"	"Off"
2.5	6	0	1	5
5	6	2	1	3
10	6	3	0	3
20	3	3	0	0

biochemical, hematological, or electrocardiographic changes attributable to the drug.

DISCUSSION

This study has shown that CQA 206-291, given as a single morning oral dose to patients with fluctuating PD withdrawn from levodopa overnight, is capable of reversing parkinsonian disability. The capacity of the drug to turn patients "on," and the duration of the "on" response, are both dose related. On average, patients turned "on" some 90 min after an effective dose of CQA 206-291, and benefit lasted for ~70 min. The duration of action of the 20-mg dose in one subject deserves special mention. This woman turned "on" 1 h after CQA and remained "on" for 7.5 h, turning "off" at 5 h after the dose.

Side effects were common, but usually mild. Pretreatment with a single oral dose of domperidone 20 mg did prevent nausea in three subjects, two of whom vomited.

We conclude that CQA 206-291, given alone and at adequate dosage, produces clinically useful and long-lasting motor improvement in patients with PD to an equivalent degree, but perhaps of longer duration, than can be obtained with standard levodopa preparations, in agreement with preliminary results obtained

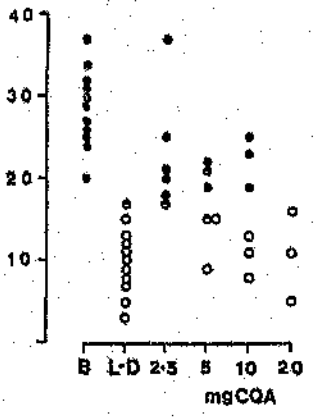


FIG. 2. Motor disability scores (on section 3 of the Unified Parkinson's Scale) in all six patients. Filled circles indicate scores at times when the patients were judged to be "off" by the attending doctors. Open circles represent scores when patients were judged clinically to be "on." Half-filled circles indicate scores when patients were intermediate between "on" and "off." See Fig. 1 for abbreviations.

with chronic administration of CQA 206-291 (4–6). Further studies of CQA 206-291 are required to define its value in the treatment of PD.

Acknowledgment: J.A.T. is a Medical Research Council (R.S.A.) postdoctoral fellow.

REFERENCES

1. Jaton AL, Enz A, Vigouret JM, Markstein R. CQA 206-291, an ergot derivative with a biphasic dopaminergic pharmacologic profile. Presented at 9th International Symposium on Parkinson's Disease, Jerusalem, Israel, 1988.
2. Jaton AL, Enz A, Vigouret JM, Pfaffle P, Markstein R. CQA 206-291, an ergot derivative with biphasic dopaminergic action. *Experientia* 1987;43:705.
3. Fahn S, Elton RL, et al. The unified Parkinson's disease rating scale. In: Fahn S, Marsden CD, Calne DB, Goldstein M, eds. *Recent developments in Parkinson's disease, vol 2*. New Jersey: Macmillan Healthcare Information, 1987:153–64.
4. Rascol O, Fabre N, Senard JM, et al. CQA 206-291 in the management of de novo parkinsonian patients. Presented at 9th International Symposium on Parkinson's Disease, Jerusalem, Israel, 1988.
5. Fabre N, Rascol O, Senard JM, et al. Clinical evaluation of CQA 206-291 in levodopa treated parkinsonian patients. Presented at 9th International Symposium on Parkinson's Disease, Jerusalem, Israel, 1988.
6. Lucf G, Poure W, Kleedorfer B, et al. Effectiveness of monotherapy with a novel ergoline (CQA 206-291) in previously untreated patients with Parkinson's disease. Presented at 9th International Symposium on Parkinson's Disease, Jerusalem, Israel, 1988.

APPENDIX VII

Movement Disorders
Vol. 4, No. 3, 1989, pp. 261–265
© 1989 Movement Disorder Society

Antiparkinsonian Activity of CY 208-243, a Partial D-1 Dopamine Receptor Agonist, in MPTP-Treated Marmosets and Patients with Parkinson's Disease

J. A. Temlett, *N. P. Quinn, P. G. Jenner, *C. D. Marsden, †E. Pourcher, †A.-M. Bonnet, †Y. Agid, ‡R. Markstein, and ‡X. Lataste

*University Department of Neurology, Institute of Psychiatry and King's College School of Medicine and Dentistry, *The Institute of Neurology, Queen Square, London, England; †Clinique de Neurologie et Neuropsychologie, INSERM U-289, Hopital de la Salpetriere, Paris, France; and ‡Sandoz Ltd, Basle, Switzerland.*

Summary: The effect of stimulation of cerebral dopamine D-1 receptors by CY 208-243 on motor disability was tested in MPTP-treated parkinsonian marmosets and patients with Parkinson's disease. CY 208-243 (0.5–1.25 mg/kg s.c.) produced a dose-related reversal of akinesia and rigidity in the marmosets, lasting some 2 h. Single morning doses of CY 208-243 (5–40 mg) were compared with the usual morning dose of levodopa in eight patients with Parkinson's disease on long-term levodopa therapy who had developed motor fluctuations from immobility with akinesia and rigidity (off) to mobility often with dyskinesias (on). CY 208-243 alone was capable of switching such patients from off to on; five of the eight patients responded to the highest dose (40 mg), sometimes with dyskinesias. The response to CY 208-243 was comparable to that produced by levodopa in these cases. Drugs designed to stimulate both dopamine D_1 and D_2 receptors in the brain may improve the therapy of Parkinson's disease. Key Words: Parkinson's Disease—D-1 Agonist Drugs—CY 208–243.

Large numbers of both dopamine D_1 and D_2 receptors are present in human striatum. Hitherto, all dopamine-active drugs used in the treatment of Parkinson's disease have possessed D_2 agonist activity (1), but only some have exhibited additional D_1 receptor agonism. As a result, the role of D_1 receptor stimulation in the treatment of this disease is unknown. CY 208-243: (−)-(6aR) (12bR)-4,6,6a,7,8,12b-hexahydro-7-methylindolo[4,3-ab]-phenanthridine (Sandoz,

Address correspondence and reprint requests to Dr. C. D. Marsden at the Institute of Neurology, Queen Square, London WC1N 3BG, England.

Basle), is a new selective dopamine D_1 receptor partial agonist. In vitro, it stimulates adenylate cyclase in rat striatum and bovine retina (D_1 effect) and fails to inhibit electrically evoked acetylcholine release in striatal slices (D_2 effect) (2). Nor does it produce D_2 action in vivo in animals. Thus, it does not cause emesis in dogs, lower prolactin in rats and humans, or increase tyrosine hydroxylase activity and dopamine turnover in rat striatum. Studies of circling behavior in unilaterally 6-OH-dopamine–lesioned rats indicate motor stimulant effects, which can be blocked by the selective D_1 antagonist SCH 23390, but not by the selective D_2 antagonist sulpiride (3).

We, therefore, have investigated the antiparkinsonian activity of CY 208-243 in MPTP-treated parkinsonian marmosets and in patients with Parkinson's disease.

STUDIES IN MPTP TREATED MARMOSETS

Adult common marmosets were given MPTP 2 mg/kg s.c., daily for 5 days, to a cumulative dose of 10 mg/kg. After this treatment, all animals developed persistent motor deficits comprising marked bradykinesia, flexed posture, rigidity, and intermittent rest tremor. After 9 weeks, the animals had improved sufficiently from the acute effects to feed and groom themselves, but remained stable and grossly parkinsonian over the following 6 months.

Individual animals were placed in a new cage, identical to their usual one, but fitted with seven infrared photocells. Three were focused horizontally across the width of the cage floor and one along the width of each of two perches. One beam was directed from front to back of the cage above each perch. This arrangement allowed assessment of movement in all directions. An acclimatization period of 30 min was allowed prior to drug treatment. Movement counts were accumulated over 10-min periods for at least 180 min following drug administration. Cumulative counts over a given period could be subanalyzed to show whether the animal spent time on the perches or on the cage floor.

CY 208-243 was mixed with an equal weight of tartaric acid and dissolved in 0.9% sterile saline, and then the pH was adjusted with 0.1 M NaOH to 5.5. After a drug-free period of 2 weeks, control vehicle injections or CY 208-243 (0.5, 1.0, and 1.25 mg/kg s.c.) were administered in a random dose sequence following a 30-min acclimatization period in the photocell cages. Thereafter, activity was monitored over a 3-h period. Animals were given 48–72 h to recover between doses. Student's *t* test for paired samples was employed to assess differences between different drug treatments.

Prior to drug administration, all the MPTP-treated marmosets had markedly decreased motility, spending most of the time on the floor of the cage or in one place on the lower of the two perches, and remained akinetic and flexed.

Administration of the vehicle alone had no effect on motor activity. Administration of CY 208-243 produced a dose-related reversal of the motor deficits within a few minutes of drug administration, which reached a peak within 30 min (Fig. 1). The reversal of motor deficits and the accompanying locomotor hyperactivity lasted for ~2 h. Higher doses of CY 208-243 were not used in these studies since preliminary investigations showed these to induce hyperexcitability.

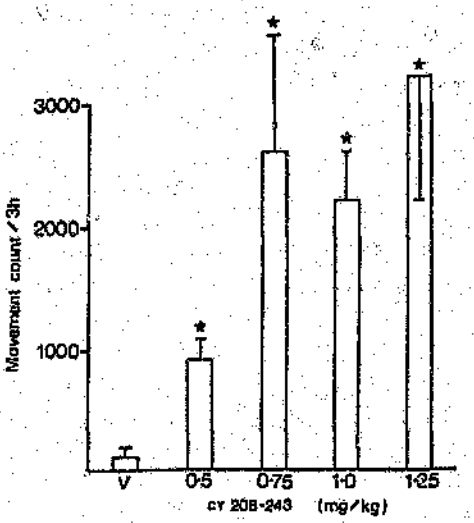


FIG. 1. The effect of CY 208-243 (0.5–1.25 mg/kg s.c.) compared with vehicle (V) on locomotor activity in MPTP-treated marmosets. The values shown are the means (± 1 SE) for eight individual animals. Movement counts were accumulated over 10-min periods for 3 h. *$p < 0.05$ or greater, Student's t test for paired samples.

CLINICAL STUDIES

The effects of CY 208-243 were investigated in eight inpatients with idiopathic Parkinson's disease (seven men and one woman, aged 50–73 years, with a median of 61 years), who gave informed consent to enter the study, which was approved by the Hospital Ethical Committee. They were at Hoehn and Yahr stage III or IV off medication, and had the disease for 9–18 (median of 12) years. All were experiencing motor fluctuations in response to long-term levodopa therapy (dose range of 400–2,400 mg/day, median of 800 mg/day, plus a peripheral decarboxylase inhibitor), which was withdrawn overnight before each study day. Other drugs were continued unchanged.

CY 208-243 was given in open fashion by mouth on alternate mornings after breakfast in single doses of 5 (n = 5), 10 (n = 7), 20 (n = 8), and 40 (n = 7) mg, respectively (Table 1). Blood pressure and pulse, and a score of motor disability [section 3 of the Unified Parkinson's Scale (4)] were measured at time 0, half-hourly for the first 2 h, and then hourly for the next 4 h. If no clinical benefit was apparent after 3 h or if any improvement lasted less than 3 h, the patient was given their usual morning dose of levodopa. The response of each patient to their usual dose of levodopa also was assessed on one occasion in one patient, twice in four patients, and three times or more in the remaining three patients.

TABLE 1. *The number of patients turning on, or partially on, after each dose of CY 208-243*

Dose of CY 208-243 (mg)	n	On	1/2 On	Off
5	5	0	0	5
10	7	1	1	5
20	8	2	0	6
40	7	4	1	2

Figure 2 shows the clinical response, judged by motor disability scores, of the patients to each dose of CY 208-243 and their usual response to levodopa. All eight patients turned on in response to their usual morning dose of levodopa; they rapidly switched from severe akinesia and rigidity (off) to near normal mobility, often with dyskinesias (on). With doses of CY 208-243 <40 mg, only occasional improvement was noted. After 10 mg, one patient turned fully on and another partially on (although he subsequently failed to turn on after 20 and 40 mg). After 20 mg, two patients turned on. However, with 40 mg, four of seven patients turned on and one partially on. The full on response with 40 mg occurred after 30–90 (median of 42.5) min and lasted 30–150 (median of 85) min; the patients turned off again 75–180 (median of 150) min after drug ingestion.

Mild dyskinesias in two patients who turned fully on, nausea in two subjects, and drowsiness in one were encountered. No postural hypotension, confusion or vomiting was noted, and no significant laboratory electrocardiogram (ECG) abnormalities were found.

DISCUSSION

The studies in the MPTP-treated marmoset showed CY 208-243 to reverse akinesia in this animal model of Parkinson's disease in dose-related fashion. This confirms similar observations in squirrel monkeys (R. Markstein, unpublished observations). In the clinical study of CY 208-243, the drug clearly produced an on response comparable to that achieved with levodopa in four of eight patients. Of the four patients who turned on following the 40 mg dose of CY 208-243, two had dyskinesias similar to those produced by levodopa. Previous studies with another putative partial D_1 agonist SKF 38393 showed no effect of the drug on either parkinsonian motor signs in marmosets (5,6) or humans (7), or on levodopa-induced dyskinesias in patients with Parkinson's disease (7). The failure of SKF 38393 to affect parkinsonian marmosets or patients with Parkinson's disease might be due to relatively poor penetration into brain or weak cerebral D_1 agonist

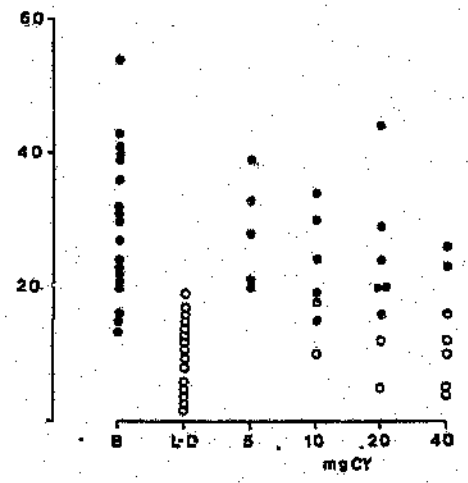


FIG. 2. Motor disability scores (on part 3 of the Unified Parkinson's Scale—ordinate) in eight patients off therapy (baseline) prior to drug administration (left hand column, B), at the time of maximum response to their usual morning dose of levodopa (100–225 mg with a peripheral decarboxylase inhibitor) (next column; L-D), or at the time of their maximum response to single doses of CY 208-243 (5–40 mg orally). Solid circles indicate scores at times when the patients were judged by their attending doctor to be off (i.e., akinetic and rigid). Open circles are scores when the patients were clearly on (i.e., mobile). The half-circles for two patients indicate a score at a time when the patient was intermediate between on and off.

activity. In addition, the formation of metabolites that interfere with dopamine receptors might account for the lack of efficacy of SKF 38393.

CY 208-243 is not known to possess significant D_2 receptor agonist activity. The present results of administration of CY 208-243 to parkinsonian marmosets and humans suggests that D_1 receptor stimulation can reverse the akinetic-rigid syndrome. If optimum antiparkinsonian treatment requires an appropriate balance between D_1 and D_2 receptor stimulation, further studies with CY 208-243 may indicate methods of improving the clinical response to drug treatment of Parkinson's disease.

REFERENCES

1. Schachter M, Bedard P, Debono AG, et al. The role of D-1 and D-2 receptors. *Nature* 1980;286:157–9.
2. Starke K, Spaeth JD, Adelung C. Further functional in vitro comparison of pre- and post-synaptic dopamine receptors in the rabbit caudate nucleus. *Naunyn Schmiedebergs Arch Pharmacol* 1983;323:298–306.
3. Markstein R, Seiler MP, Vigouret JM, Urwyler S, Eng A, Dixon K. In: Sandler M, ed. *Progress in catecholamine research, central aspects.* New York: Allan Liss (in press).
4. Fahn S, Elton RL, et al. The unified Parkinson's disease Rating Scale. In: Fahn S, Marsden CD, Calne D, Goldstein M, eds. *Recent developments in Parkinson's disease. Vol. II.* New Jersey: Macmillan Healthcare Information, 1987:153–64.
5. Close SP, Marriott AS, Pay S. Failure of SKF 38393A to relieve parkinsonian symptoms induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine in the marmoset. *Br J Pharmacol* 1985;85:320–2.
6. Nomoto M, Jenner P, Marsden CD. The dopamine D-2 agonist LY 141865, but not the D-1 agonist SKF 38393, reverses parkinsonism induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in the common marmoset. *Neurosci Lett* 1985;57:37–41.
7. Braun A, Fabbrini G, Mouradian MM, Serratt C, Barone P, Chase TN. Selective D-1 dopamine receptor agonist treatment of Parkinson's disease. *J Neural Transm* 1987;68:41–50.

Author:Temlett JA
Name of thesis:Selective dopamine agonists in man and the MPTP-Treated primate model

PUBLISHER:
University of the Witwatersrand, Johannesburg
©2015

LEGALNOTICES:

Copyright Notice: All materials on the University of the Witwatersrand, Johannesburg Library website are protected by South African copyright law and may not be distributed, transmitted, displayed or otherwise published in any format, without the prior written permission of the copyright owner.

Disclaimer and Terms of Use: Provided that you maintain all copyright and other notices contained therein, you may download material (one machine readable copy and one print copy per page)for your personal and/or educational non-commercial use only.

The University of the Witwatersrand, Johannesburg, is not responsible for any errors or omissions and excludes any and all liability for any errors in or omissions from the information on the Library website.