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Neonatal exposure to streptococcus pneumoniae in rat pups and its consequences on cognitive functionning in adolescence

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ABSTRACT

Pneumococcal meningitis, an infection caused by the *Streptococcus pneumoniae* (*S. pneumoniae*) bacterium, is a leading cause of serious illness in children and when it is experienced during critical periods of neurodevelopment, particularly in males, it appears to be associated with decreased cognitive functioning later in life. Studies, which have investigated the long-term sequelae of bacterial meningitis, do not separate *S. pneumoniae*-induced sequelae from those sequelae caused by other bacteria. Therefore, using a rat model of neonatal haematogenous meningitis I aimed to determine if neonatal haematogenous meningitis induced by *S. pneumoniae* would affect cognitive functioning in adolescent rats in a gender-specific manner.

Postnatal day (P) 4 rat pups received an intra-peritoneal (i.p.) injection of either *S. pneumoniae* (mean ± SD: 46 ± 35 colony forming units (CFU) in 250 ul) or 0.9% sterile saline. Calibrated microchips were used to obtain skin temperature measurements to evaluate the progression of disease. Cerebral spinal fluid (CSF) and tail blood were collected between 16 and 24 hours after infection once the pups showed signs of illness. A bacterial load of $1x10^7$ CFU/ml was detected in the blood and $1x10^5$ CFU/ml was found in the CSF. Infected pups were treated with ceftriaxone (100 mg/kg, intramuscularly). No gender-specific differences were found in the spread of disease.

Learning and memory of pups was tested on P30 using two behavioural models: the Morris water maze and contextual fear conditioning. In the Morris water maze, both male and female pups that received either saline or *S. pneumoniae* learned to find the location of the platform equally well. In the probe test, both genders of pups that received either saline or *S. pneumoniae* found the location of the platform significantly faster than the cut-off time of 30 seconds. Freezing behaviour during contextual fear testing did not differ between gender or intervention groups.

Results from my study appear to suggest that an acute episode of severe neonatal haematogenous meningitis may not affect hippocampal-dependent spatial, or associative, learning and memory in adolescence. My findings are contradictory to existing literature which suggests that an early life infection leads to an overproduction of pro-inflammatory cytokines which may cause the cognitive impairments seen in later life. To confirm that the *S. pneumoniae* used in my study does indeed activate the immune system and induce pro-inflammatory cytokine release I stimulated micro-cultures of the rat hippocampus with ethanol-treated *S. pneumoniae* ($5x10^3$, $5x10^4$, $5x10^5$ and $5x10^6$ CFU/ml) to determine the effect of *S. pneumoniae* on nuclear factor- interleukin 6 (NF-IL6) activation. NF-IL6 is a transcription factor which regulates the expression of pro-inflammatory cytokines.

NF-IL6 immunoreactivity was increased in hippocampal cells that were stimulated with alcohol-treated *S. pneumoniae* in a dose dependant manner. Neonatal hippocampal cells exposed to high concentrations (5×10^6 CFU/ml) of alcohol-treated *S. pneumoniae* expressed NF-IL6 particularly in astrocytes and microglia. Therefore the presence of a greater number of *S. pneumoniae* CFU in the brain during neonatal life could result in a greater activation of astrocytes and microglia. This increased activation of astrocytes and microglia could then lead to an overproduction of pro-inflammatory cytokines that is capable of inducing hippocampal damage and long-lasting hippocampal-dependant memory impairment.

In conclusion my results suggest that an acute episode of severe neonatal haematogenous meningitis induced by *S. pneumoniae* does not affect hippocampal-dependant memory in adolescent Sprague-Dawley rats. However, my results cannot be directly applied to human cases of pneumococcal meningitis. To fully understand the impact of pneumococcal meningitis on neurocognitive function in humans, a longitudinal case-control based study is needed. There is a high prevalence of bacterial meningitis caused by *S. pneumoniae* in the South African population therefore it is imperative that research continues in the field.