

https://dspace.org/

The effects of chronic intermittent hypoxia on insulin and leptin homeostasis in the rat

Romain, Heidi Shira

2006-11-16T08:37:37Z
http://hdl.handle.net/10539/1770

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

THE EFFECTS OF CHRONIC INTERMITTENT HYPOXIA ON INSULIN AND LEPTIN HOMEOSTASIS IN THE RAT

Heidi Shira Romain

A dissertation submitted to the Faculty of Science, University of the Witwatersrand, in fulfillment of the requirements for the degree of Master of Science, 2005.

Johannesburg, 2005

I declare that this dissertation is my own, unaided work. It is being submitted for the Degree of Master of Science in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination in any other University.

_____

Heidi Shira Romain

_____ day of _____ 2005

ABSTRACT

There is a high prevalence of insulin and leptin resistance and increased cortisol concentrations in sleep apnoea patients, independent of obesity. Chronic intermittent hypoxia is used an experimental animal model to simulate the hypoxia occurring in sleep apnoea patients. The aim of this study was to measure plasma insulin and leptin concentrations and hypothalamic-pituitary-axis activity in rats exposed to either intermittent hypoxia (CIH) or sham hypoxia (SH) for fourteen days. To induce CIH plexiglass cylinders were flushed with 100% nitrogen for nine seconds every 90 seconds, seven hours/day. The rats were weighed each day during the exposure period. Venous blood samples for insulin and leptin were collected on days one, three, five, eight and fifteen. Faecal samples were collected to measure glucocorticoid metabolites. There was no significant difference in the daily change in body weight between the rats exposed to CIH compared to the rats exposed to SH (unpaired t-test). Plasma insulin concentrations were not affected by CIH. In both groups of rats plasma leptin concentrations were significantly higher on day fifteen compared to day five ($p=0.03$, unpaired t-test). Glucocorticoid metabolites were significantly increased in the intermittent hypoxia group on day two ($p=0.003$ one-way ANOVA). In conclusion, exposing normal weight rats to CIH for fourteen days resulted in a transient

increase in HPA axis activity on day two and an elevation in plasma leptin levels, in both groups of rats, at day fifteen.

ACKNOWLEDGEMENTS

Dr Alison Bentley and Dr Irné Du Plessis

Dr Kennedy Erlwanger for his assistance with surgery

Dr Neville Pitts for his technical advice

This project was funded by the Wits Dial·a·Bed Sleep Laboratory and the Medical Research Council

CONTENTS **Page**

DECLARATION……ii

ABSTRACT……iii

ACKNOWLEDGEMENTS……v

LIST OF FIGURES……...viii

LIST OF ABBREVIATIONS……..……ix

CHAPTER ONE- INTRODUCTION

1.1 General Introduction……1

1.2 Literature Review……4

1.2.1 Obstructive sleep apnoea……..4

1.2.2 Physiological abnormalities associated with obstructive sleep apnoea……6

1.2.2a Sleep disruption……7

1.2.2b Hypoxic effects of obstructive sleep apnoea……8

1.2.3 HPA axis activity and obstructive sleep apnoea……9

1.2.4 Obesity and obstructive sleep apnoea……..…11

1.2.5 Insulin resistance and obstructive sleep apnoea……..…14

1.2.6 Leptin resistance and obstructive sleep apnoea……...18

1.2.6a Leptin and respiratory depression……19

1.2.6b The relationship between leptin and sympathetic nervous system activity……20

1.2.6c The relationship between leptin and HPA axis activity……..21

1.2.7 Interactions between insulin and leptin……21

1.2.8 Cytokines and obstructive sleep apnoea……23

1.2.9 An animal model for obstructive sleep apnoea…....……26

1.3 Objectives……..……..……...28

CHAPTER TWO

2.1 Methods and materials……..…..…..…29

2.1.1 Animals……..……..…29

2.1.2 Surgery……..……..…30

2.1.3 Pilot study……31

2.1.4 Experimental protocol……..…...32

2.1.5 Sample collection……..……33

2.1.6 Data analysis……..……..…39

2.2 Results……..……....41

2.2.1 Pilot study……...…..41

2.2.2 Body weights……..……..41

2.2.3 Plasma insulin concentrations……..…42

2.2.4 Plasma leptin concentrations……....42

2.2.5 Faecal glucocorticoid metabolites……....43

2.3 Discussion……..…56

CHAPTER THREE- CONCLUSION

3.1 Conclusion……..…..64

REFERENCES……..……..……67

LIST OF FIGURES **Page**

Figure 1: 24-hour profile of the plasma insulin levels of a single rat …….45

Figure 2: 24-hour profile of the plasma leptin levels of a single rat……47

Figure 3: Mean change in body weight……..49

Figure 4: Plasma insulin concentrations……..……51

Figure 5: Plasma leptin concentrations……..53

Figure 6: Excreted glucocorticoid metabolite concentrations……....55

LIST OF ABBREVIATIONS

ACTH - adrenocorticotropic hormone

AHI - apnoea-hypopnoea index

BS - before surgery

CIH - chronic intermittent hypoxia

CPAP - continuous positive airway pressure

CRH - corticotropin releasing hormone

F_iO_2 - fraction inspired oxygen

HPA - axis hypothalamic-pituitary-adrenal axis

IL-6 - interleukin 6

IU - international units

NaCl - sodium chloride

$PaCO_2$ - partial pressure of arterial carbon dioxide

PaO_2 - partial pressure of arterial oxygen

SH - sham hypoxia

T_a - ambient temperature

TNF-α - tumor necrosis factor alpha