The role of intermittent hypercapnic hypoxia in the induction of high loop gain in obstructive sleep apnoea pathophysiology

by

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABSTRACT

Intermittent hypoxia (IH) and unstable breathing are key features of obstructive sleep apnoea (OSA), the most common respiratory sleep disorder. Unstable ventilatory control is characterised by high loop gain (LG), and likely contributes to the propagation of apnoeas by promoting airway collapse during periods of low ventilatory drive. Currently, the contribution of inherent versus induced traits causing high LG in OSA remains unclear. OSA patients exhibit abnormal chemoreflex control which contributes to increased LG. These abnormalities normalise with continuous positive airway pressure (CPAP) treatment, suggesting induced rather than inherent trait abnormalities. Experimental IH, mimicking OSA, increases hypoxic chemosensitivity and induces long-term facilitation; a sustained increase in ventilatory neural output which outlasts the original stimulus. These neuroplastic changes induce the same abnormalities in chemoreflex control as seen in OSA patients, suggesting that high LG in OSA is largely induced by IH, and is reversible.

IH protocols are typically conducted on a background of poikilocapnia or isocapnia, in contrast to combined hypoxia and hypercapnia experienced in OSA. The level of concomitant CO_2 is thought to be critical for both the induction and expression of IH induced neuroplasticity. To more accurately mimic OSA, the effects of intermittent hypercapnic hypoxia (IHH) on ventilatory neuroplasticity and LG were investigated in the first two experiments contained within this thesis. The effect of CPAP treatment on LG in untreated OSA patients was investigated in the third and final study of this thesis.

In the first study, whether IHH during sleep induces LTF or increases chemosensitivity in healthy males was investigated. A randomised, separate day of intermittent medical air served as control. Unlike previous reports using isocapnic IH during sleep in healthy males, IHH did not induce LTF of ventilation or genioglossal muscle activity. Also, there was no change in the magnitude or slope of the ventilatory response to IHH from the first exposure to the last, to indicate any change in chemosensitivity. These findings suggest the effects of IHH differ to those of IH during sleep in healthy males.

During wakefulness LTF in humans is only expressed during mild hypercapnia. In the second study, the effect of IHH on LG was investigated in healthy males during wakefulness using a CO_2 pseudorandom binary stimulation technique to measure LG on a background of mild hypercapnia. There was no change in chemosensitivity during IHH or ventilatory LTF following IHH. There was no change in LG and although there was a trend towards a change in the ventilatory impulse response to a sudden change in CO_2 following IHH, this was not statistically significant. These findings further support that the effects of IHH during wakefulness differ to those of IH in healthy males.

In the third study, the effect of 6 weeks CPAP treatment on LG in previously untreated OSA males was investigated. Participants matched for age, sex, height, weight and BMI were also studied as controls. Helium dilution was used to assess supine functional residual capacity (FRC) and LG was compared prior to

commencing CPAP treatment and at 2 and 6 weeks after starting treatment, and at the same time points but without CPAP treatment in controls. LG was higher in the OSA patients versus matched controls, but there was no effect of CPAP treatment on LG. There was also no difference between patients and controls in FRC or controller or plant gain components of LG, although given that LG is the product of controller and plant gains, this could reflect a type II error. Patients exhibited reduced FEV1 and FVC and also higher supine abdominal height which positively correlated with AHI. Thus, this study confirmed that LG is higher in OSA patients versus matched controls, and supported previous work suggesting that central adiposity contributes to upper airway collapse. However, given no effect of CPAP on LG, larger cohorts and potentially alternative measures may be required to determine mechanisms driving elevated LG in OSA patients.

Although IH has previously been shown to induce neuroplastic changes to chemoreflex control that mirror abnormalities associated with high LG in OSA patients, the findings in this thesis suggest the effects of acute IHH differ to those of IH, both during sleep and wakefulness in healthy males. Potential causes for this disparity, and relevance of experimental findings to OSA pathophysiology are discussed. The effects of CPAP treatment on LG and implications for treatment options and CPAP adherence outcomes are also discussed.

PUBLICATIONS

Publications arising from this thesis

1. **Deacon, N.L.,** Catcheside, P.G. The role of high loop gain induced by intermittent hypoxia in the pathophysiology of obstructive sleep apnoea. *Sleep Med Rev.,* http://dx.doi.org/10.1016/j.smrv.2014.10.003.

   Editorialised: Mateika JH, The role of high loop gain induced by intermittent hypoxia in the pathophysiology of obstructive sleep apnea. *Sleep Med Rev.,* http://dx.doi.org/10.1016/j.smrv.2015.02.001.

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2. **Deacon, N.,** McEvoy, D., Stadler, D., Catcheside, P. The effects of intermittent hypercapnic hyopoxia during sleep in healthy males on long-term facilitation, respiratory and upper airway control. Sleep and Biological Rhythms (2010) 8(Suppl): OP19, A25.

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1. **Deacon, N.L.,** Arnould, J.P.Y. Terrestrial apnoeas and the development of cardiac control in Australian fur seal *(Arctocephalus pusillus doriferus)* pups. *J Comp Physiol B* (2009) **179:**287-295.

2. Atul Malhotra, **Naomi Deacon,** Frank Powell, Eliot Katz. Adaptive responses using obstructive sleep apnea as the paradigm. *Physiology*. (2014) **29**(3): 153-155

DECLARATION

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

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Naomi Louise Deacon

Date: Monday, 21 December 2015

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GLOSSARY OF ABREVIATIONS

AG	abdominal girth
AHI	apnea hypopnea index (events·hr^{-1} sleep)
AIH	acute intermittent hypoxia
$PaCO_2$	arterial CO_2 partial pressure
F_B	breathing frequency
CIH	chronic intermittent hypoxia
CPAP	continuous positive airway pressure
CG	controller gain
EMGdia	diaphragm electromyogram
diaLTF	diaphragm long-term facilitation
ECG	electrocardiogram
EEG	electroencephalogram
EMG	electromyogram
$P_{ET}CO_2$	end tidal partial pressure of CO_2
Pepi	epiglottic pressure
T_E	expiratory time
FRC	functional residual capacity
FEV1	forced expiratory volume in the first second
FVC	forced vital capacity
EMGgg	genioglossal electromyogram
ggLTF	genioglossal long-term facilitation
HH	hypercapnic hypoxia
HCVR	hypercapnic ventilatory response
hLTF	hypoglossal long-term facilitation
HVR	hypoxic ventilatory response

T_I	inspiratory time
P_ICO_2	inspiratory partial pressure of CO_2
IHH	intermittent hypercapnic hypoxia
IH	intermittent hypoxia
LTF	long-term facilitation
LG	loop gain
P_{MASK}	mask pressure
MAP	mean arterial pressure
V_I	minute ventilation
OSA	obstructive sleep apnoea
PIF	peak inspiratory flow
pLTF	phrenic long-term facilitation
PG	plant gain
PSG	polysomnography
PRBS	pseudorandom binary stimulation
PA	progressive augmentation
SaO_2	saturation of oxygen
sLTF	sensory long-term facilitation
V_T	tidal volume
T_{TOT}	total breath time
$_{UA}$LTF	upper airway long-term facilitation
R_{UA}	upper airway resistance
$_V$LTF	ventilatory long-term facilitation
ROS	reactive oxygen species
SAH	supine abdominal height