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PHYSIOLOGICAL REVIEW

The role of high loop gain induced by intermittent hypoxia in the pathophysiology of obstructive sleep apnoea

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SUMMARY

Intermittent hypoxia and unstable breathing are key features of obstructive sleep apnoea (OSA), the most common pathological problem of breathing in sleep. Unstable ventilatory control is characterised by high loop gain (LG), and likely contributes to cyclical airway obstruction by promoting airway collapse during periods of low ventilatory drive. Potential new strategies to treat OSA include manipulations designed to lower LG. However, the contribution of inherent versus induced LG abnormalities in OSA remains unclear. Hence, a better understanding of the mechanisms causing high LG in OSA is needed to guide the design of LG based treatments. OSA patients exhibit abnormal chemoreflex control which contributes to increased LG. These abnormalities have been shown to normalise after continuous positive airway pressure treatment, suggesting induced rather than inherent trait abnormalities. Experimental intermittent hypoxia, 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. This review outlines the evidence to support that a key component of high LG in OSA is induced by intermittent hypoxia, and is reversed by simply preventing this inducing stimulus.

Introduction

Obstructive sleep apnoea (OSA) is characterised by repeated partial (hypopnoea) or complete (apnoea) collapse of the airway during sleep resulting in bouts of combined hypercapnia and hypoxia. OSA is the most common sleep disorder and is estimated to affect between 10% of men and 3% of women aged 30–49 y, and 17% of men and 9% of women aged 50–70 y [1]. OSA is associated with increased mortality and morbidities including cardiovascular disease [2], diabetes [3], cognitive impairment [4], pathological daytime sleepiness [5] and increased frequency of driving and other accidents [6]. Continuous positive airway pressure (CPAP) is the main treatment for OSA, however long term adherence is poor, with ≤50% of patients accepting and tolerating CPAP long term [7]. Consequently there is a strong ongoing need for the development of alternative treatments. OSA pathophysiology is now understood to involve multiple interacting factors including increased airway collapsibility (typically measured from airway critical closing pressure), a propensity to wake to airway obstruction (low arousal threshold), poor upper airway muscle recruitment responses and unstable ventilatory control (high loop gain, LG), with variable combinations producing differing OSA phenotypes between individuals [8]. Wellman and colleagues have recently proposed new diagnostic methods designed to quantify these causal factors in each patient, thus allowing treatments to be tailored to each individual [8]. High LG has been reported in 36% of CPAP treated patients [9], and could play a significant pathogenic role in a greater proportion of previously untreated OSA patients. Given the prevalence of LG disturbances, a key part of this individualised treatment approach could include pharmacological or non-pharmacological manipulation of LG [10]. However it remains unclear if high LG is an inherent causal trait in OSA and/or an induced effect exacerbating OSA and contributing to disease progression. A greater understanding of the inherent versus induced mechanisms underpinning high LG in OSA is therefore needed to effectively guide treatments designed to reduce LG.

LG includes “plant” (respiratory apparatus) and “controller” (chemoreflex) gain components, both of which can be abnormal in OSA. Increased plant gain may predominantly reflect obesity effects

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Abbreviations

AIH	acute intermittent hypoxia
AHI	apnoea hypopnoea index
CIH	chronic intermittent hypoxia
CPAP	continuous positive airway pressure
HCVR	hypercapnic ventilatory response
hLTF	hypoglossal long term facilitation
HVR	hypoxic ventilatory response
IH	intermittent hypoxia
LTF	long term facilitation
LG	loop gain
OSA	obstructive sleep apnoea
$PaCO_2$	arterial CO_2 partial pressure
PaO_2	arterial O_2 partial pressure
$P_{ET}CO_2$	end tidal partial pressure of CO_2
pLTF	phrenic long term facilitation
PA	progressive augmentation
ROS	reactive oxygen species
sLTF	sensory long term facilitation
$_{UA}$LTF	upper airway long term facilitation
V_I	minute ventilation
V_T	tidal volume
$_V$LTF	ventilatory long term facilitation

on lung volume that may normalise while using CPAP [11]. However, OSA patients also exhibit abnormally elevated controller gain independent of BMI [12–14]. These chemoreflex control abnormalities have been shown to normalise following ≥1 mo of CPAP use [13,15,16], supporting that high controller gain is predominantly induced rather than an intrinsic trait in OSA.

Several stimuli experienced during obstructed breathing events have been shown to induce lasting changes in ventilatory neural responses. Intermittent hypoxia (IH) induces neuroplastic changes in the carotid bodies [17], brainstem [18], and cervical spinal cord [19], inducing increased hypoxic sensitivity [17] and long term facilitation (LTF) of various ventilatory nerves, manifesting as a sustained increase in neural output to a given stimulus [20]. LTF of ventilatory neural output has been studied and demonstrated in a variety of species including humans [21], dogs [22], cats [23], goats [24], rats [25] and avian species such as ducks [26]. LTF is thus highly conserved across phylogenetically distant species suggesting an important adaptive mechanism in ventilatory neural control. However, as with many physiological processes in disease states, LTF could play both adaptive and maladaptive roles in OSA pathophysiology and both have been posited [27,28]. On the one hand hypoglossal LTF may augment upper airway dilator muscle activity to help prevent airway collapse [27]. However, experimental IH also induces the same abnormalities in chemoreflex control that are seen in OSA patients [21,29,30], which increase controller and therefore overall LG, suggesting IH induced neuroplasticity may worsen OSA. These neuroplastic changes appear to gradually decay following return to room air breathing for several days [17,31–33], much the same as chemoreflex abnormalities in OSA normalise with CPAP use [13,15,16]. These data support that normalisation of LG may simply require prevention of IH and allowing sufficient time for chemoreflex control, and therefore controller gain, to readjust. Although lowering LG may not cure OSA given other contributory factors, IH induced high LG likely exacerbates OSA in a feed-forward manner. Neuroplasticity effects on LG have several treatment implications; including lowered pressures over time that could improve long-term CPAP adherence, the development of drug therapies targeting the cellular mechanisms contributing to raised LG, and future combination treatments where LG lowering may be achieved with short term conventional treatments such as CPAP by simply preventing the inducing IH stimulus.

This review summarises the evidence to support a pathogenic role for abnormal chemoreflex control and high LG in OSA, and further evidence to support that these effects are predominantly induced by OSA and reverse with treatment. The main focus is on animal and human studies supporting that IH induced neuroplasticity is the main causal mechanism inducing high controller gain and therefore overall LG in OSA. Implications for treatment and future research are also discussed.

Sleep chemoreflex control

Resting end-tidal CO_2 (end tidal partial pressure of CO_2 ($P_{ET}CO_2$), an indirect estimate of arterial CO_2 partial pressure ($PaCO_2$)) determines the position of eupnoea on the so called metabolic hyperbola, which governs the relationship between changes in CO_2 when ventilation changes at a given rate of metabolic CO_2 production. During sleep, ventilation below eupnoea decreases linearly with reducing $P_{ET}CO_2$ until an "apnoeic threshold" 3–6 mmHg below eupnoea is reached, where ventilation is totally suppressed [34]. Above eupnoea, ventilation increases linearly with $P_{ET}CO_2$ and the slope of this relationship indicates CO_2 chemoreflex sensitivity. Following hypocapnic central apnoea during sleep or anaesthesia (e.g., after withdrawal of mechanical hyperventilation to induce central apnoea), $PaCO_2$ must rise several mmHg above not only the level of CO_2 which induced apnoea, but also to a level above the resting eupnoeic level called the ventilatory recruitment threshold, before rhythmic breathing is reinitiated [35,36]. This contrasts with wakefulness, where hypocapnia does not induce central apnoea, and ventilation is maintained at a stable baseline level below a CO_2 chemoreflex threshold [37], above which ventilation rises linearly with increasing $P_{ET}CO_2$ [38].

During hypoxaemia mammals exhibit a characteristic biphasic hypoxic ventilatory response (HVR). Initially, there is an acute HVR during which ventilation increases with decreasing arterial O_2 (PaO_2). If hypoxia is sustained the acute response is followed by a decrease in ventilation called hypoxic ventilatory decline [39]. The HVR modulates ventilation via the combined effects of O_2 and CO_2 on peripheral chemoreflex responses [38,40], with hypoxia increasing the sensitivity to CO_2 unless $PaCO_2$ is below the chemoreflex threshold, below which the HVR is suppressed [41]. Increased minute ventilation (V_I) during hypoxia results in a reduction of $P_{ET}CO_2$ which tends to constrain the HVR. During sleep, hypoxia does not alter the apnoeic threshold, therefore the point of eupnoea moves closer to the apnoeic threshold, reducing the CO_2 reserve and increasing the slope of the ventilatory response to CO_2 below eupnoea [42].

Ventilatory control stability – loop gain

Loop gain is an engineering concept usefully applied in many negative feedback control systems, such as the chemoreflex control of breathing, to quantify the overall stability of the feedback control system. LG is the ratio of a control systems response relative to the magnitude of the disturbance eliciting the response, and incorporates three main components; controller gain, plant gain and the feedback delay between the controller and plant. In ventilatory control, controller gain reflects chemoreflex sensitivity ($\Delta V/\Delta PaCO_2$ and/or ΔPaO_2), plant gain reflects the magnitude of change in blood