Neurophysiological Mechanisms Underlying Elevated Blood Pressure and Sympathetic Activation in Sleep Apnea

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Introduction

Sleep apnea is a common respiratory disorder characterized by transient, repetitive cessations in breathing during sleep. Because each cessation can last for tens of seconds, the disorder is often accompanied by an intermittent decrease in blood oxygen levels (i.e. hypoxia). There are two clinically distinct phenotypes of sleep apnea: obstructive sleep apnea (OSA), which is characterized by the partial or complete obstruction of the upper airways, and central sleep apnea (CSA), which arises due to the generation of defective respiratory rhythm by the central nervous system. Both phenotypes are associated with an increased risk of developing cardiovascular disorders such as hypertension (Floras, 2013). Although both OSA and CSA can co-occur, OSA is the most prevalent phenotype of sleep apnea, and is therefore the focus of this review. Previous studies have demonstrated that both neuronal and metabolic mechanisms are involved in the development of sleep apnea-induced hypertension, and that the resulting elevation of blood pressure is a risk factor for the development of stroke and heart failure (Narkiewicz et al., 1997; Aurora et al., 2013). During sleep, recurring episodes of hypoxia, normoxia and hypercapnia (elevated blood CO₂ levels) act through various mechanisms to alter sympathetic drive in sleep apnea patients. In the long term, such alterations to the body’s homeostasis can have severe cardiovascular consequences. The objective of this review is to illustrate the neurophysiological mechanisms by which sleep apnea promotes the development and progression of elevated blood pressure, as well as to emphasize the increased cardiovascular risk present in patients with the disorder.
Sleep apnea augments sensory activity of peripheral chemoreceptors in response to hypoxia

Carotid and aortic bodies are peripheral sensory chemoreceptors that detect changes in blood oxygen levels. During hypoxia, these chemoreceptors increase sensory discharge to the medulla oblongata, where specialized neurons process the afferent traffic and respond by increasing sympathetic and ventilatory activity (Teppema & Dahan, 2010). The resulting increase in sympathetic activity ultimately leads to an elevation in blood pressure.

Little controversy exists that intermittent hypoxia (IH), the recurring exposure to alternating periods of hypoxia and normoxia, is the major pathophysiological concomitant of sleep apnea responsible for blood pressure dysregulation (Aurora et al., 2013). Consequently, to elucidate the mechanisms involved in the pathogenesis and progression of sleep apnea, researchers often induce chronic IH in animal models to mimic the disorder (Pamidi et al., 2012). A suggested mechanism by which sleep apnea leads to elevated blood pressure is by augmenting the sensory activity of peripheral chemoreceptors in response to hypoxia (Fig. 1; Prabhakar, 2000). In support of this suggestion, a study by Rey et al. (2004) revealed that inducing chronic IH in cats resulted in an enhanced sensitivity of carotid bodies to hypoxia. This enhanced hypoxic sensitivity is thought to be attributable, at least in part, to an IH-induced increase in oxidative stress (Prabhakar & Kumar, 2010).

Oxidative stress refers to a state in which the production of reactive oxygen species (ROS) exceeds the body’s antioxidant defences. Previous research has shown that ROS, which are generated during the reoxygenation phase of IH, mediate the cellular responses of carotid body chemoreceptors to chronic IH (Prabhakar, 2001). This may occur via a ROS-induced elevation of Ca^{2+} levels in glomus cells of carotid bodies, which enhances the release of neurotransmitters, ultimately leading to increased hypoxic sensitivity of carotid body...
chemoreceptors (Fig. 2; Prabhakar, 2001). Alternatively, ROS might act at the level of oxygen-sensitive K\(^+\) channels to alter the sensitivity of glomus cells to oxygen levels in the blood (Peng et al., 2003). Although further experiments are needed to test these possibilities, it has been demonstrated that ROS levels are elevated in the carotid bodies of rats chronically treated with IH, as evidenced by reduced aconitase enzyme activity, a common marker for ROS (Peng et al., 2003).

![Diagram](image)

**Fig. 1.** Schematic illustration showing the mechanisms involved in chronic intermittent hypoxia (IH)-induced increase in blood pressure. ET-1 = Endothelin-1; ET\(_A\) = Endothelin receptor A; 5-HT = 5-hydroxytryptamine; sLTF = sensory long-term facilitation of the carotid body activity. CA = catecholamines; Ang II = angiotensin II; SNA = sympathetic nerve activity; BP = Arterial blood pressure. (Adapted from Prabhakar & Kumar, 2010.)

Furthermore, the increased hypoxic sensitivity of carotid bodies, seen in chronic-IH induced animals, has been shown to be associated with an increase in expression of endothelin-1 (ET-1; Rey et al., 2006). ET-1 is a vasoactive peptide that acts as an excitatory modulator of carotid body chemoreception. Therefore, an increase in ET-1 expression can lead to an increase in carotid body activity. Indeed, a study by Rey et al. (2006) showed that an increased expression
of ET-1 is partly responsible for carotid body hyperactivity seen in chronic-IH treated cats. This finding was supported by that of Pawar et al. (2009), which revealed that the chronic IH-induced increase in the hypoxic response of carotid bodies involves a ROS-mediated upregulation of ET-1 in rats. Collectively, these findings suggest that chronic IH-induced increase in ET-1 expression is partly responsible for the hypersensitivity of carotid body chemoreceptors in sleep apnea patients (Prabhakar & Kumar, 2010). However, whether ET-1 receptor antagonist drugs may be beneficial in the treatment of sleep apnea remains to be explored.

![Schematic illustration showing the involvement of reactive oxygen species (ROS) in chronic IH-induced short- and long-term changes in carotid body sensitivity and gene expression. (Adapted from Prabhakar et al., 2001.)(Fig. 2)](image)

In addition to its effects on ET-1 expression, chronic IH has also been demonstrated to elicit a form of respiratory plasticity known as sensory long-term facilitation (LTF) of the carotid body (Peng et al., 2003). Sensory LTF is the progressive and continuous increase in the baseline sensory activity of carotid bodies. Because sensory LTF has been shown to be elicited by chronic IH-treatment in rats, this may also contribute to the long lasting elevation of sympathetic activity seen in sleep apnea patients (Peng et al., 2003). However, the intermediate signaling mechanisms involved in evoking sensory LTF are different from those mediating carotid body sensitization to the hypoxic response. Of note, one difference is that 5-hydroxytryptamine, not ET-1, mediates
the development of sensory LTF in chronic IH-treated carotid bodies (Fig. 1; Peng et al., 2006). Additionally, chronic IH is thought to activate specific genes and transcriptional factors that potentiate the long-term adaptation of carotid bodies to chronic IH (Fig. 2; Prabhakar, 2001). However, the mechanisms involved in this process remain unclear and understudied, although they are thought to likely involve the contribution of ROS (Fig. 2; Prabhakar, 2001).

**Sleep apnea promotes blood pressure elevation by attenuating baroreceptor activity**

Baroreceptors are blood vessel mechanoreceptors that sense and relay blood pressure information to the central nervous system to maintain homeostasis. If there is a rise in blood pressure, arterial baroreceptors relay this information to the nucleus of the solitary tract (NTS) in the brainstem, where a reflex (i.e. baroreflex) is generated to suppress sympathetic nervous activity (SNA) and lower blood pressure (Fig. 4).

In sleep apnea patients, the presence of functional baroreflex activity would likely counter the effects of an exaggerated chemoreceptor reflex (i.e. chemoreflex) on the sympathetic nervous system. However, the elevated SNA and blood pressure seen in sleep apnea patients is also partly attributable to a simultaneous suppression of baroreflex sensitivity, as evidenced by attenuated heart rate and vascular resistance responses to activation of baroreceptors in these patients (Abboud et al., 2014). In a study by Peng et al. (2012), investigators examined the effects of chronic IH on the activity of carotid baroreceptors by measuring the baroreceptor activity of rats treated with chronic IH in response to stepwise increases in carotid sinus pressure. The study found that the magnitude of increase in baroreceptor activity at higher pressures was markedly attenuated in chronic IH-treated rats, as evidenced by a decrease in saturation and threshold pressures of carotid baroreceptors, compared with controls (Fig. 3; Peng et al., 2012).
This finding suggests that the attenuation of baroreflex function in sleep apnea patients is at least partly due to the effects of chronic IH on baroreceptor activity.

Fig. 3. Carotid baroreceptor activity in response to 20 mmHg increases in sinus pressure is attenuated in chronic-IH treated rats (B) compared with control rats (A). (Adapted from Peng et al., 2012.)

The significance of the chronic IH-induced homeostatic imbalance generated by the simultaneous upregulation of chemoreceptor reflex and downregulation of baroreceptor reflex, has been subject to some hypotheses. Although not yet proven, it is plausible that this imbalance is mediated by elaborate interactions between baroreceptor and chemoreceptor signals in the central nervous system. Notably, a study by Silva et al. (2011) revealed an interaction between baroreceptor and chemoreceptor signals in neurons of the caudal ventrolateral medulla (CVLM) in rats. However, future studies are needed to elucidate whether this interaction is altered by sleep apnea-associated chronic IH, and what cardiovascular effects, if any, such an alteration might have on patients with sleep apnea.

Furthermore, the ET-1 peptide, which is involved in mediating hypoxic sensitivity in chemoreceptors, is also associated with downregulating baroreceptor sensitivity in chronic IH-treated rats (Fig. 1; Peng et al., 2012). This suggests that chronic IH may also mediate the attenuation of baroreceptor activity via an ET-1-dependent pathway in sleep apnea patients. It is
remarkable that the same peptide, ET-1, is able to exert diametrically opposing effects on chemoreceptors and baroreceptors, in that it enhances the activity of the former, and decreases activity of the latter. This finding is only further complicated by the fact that ET-1 is a major vasoconstrictor hormone that can itself contribute to the elevation of blood pressure seen in patients with sleep apnea (Prabhakar & Kumar, 2010).

**Sleep apnea alters chemoreflex and baroreflex sensitivity by increasing leptin levels in the circulation**

Chronic IH, in addition to its effects on baroreceptor and chemoreceptor activity, has been shown to be associated with an elevation of leptin levels in the circulation (Harsch et al., 2003). Leptin is a satiety-inducing adipokine that is produced and released into the circulation by adipocytes in proportion to adiposity (Ciriello & Moreau, 2012). In healthy humans, leptin acts on specific regions of the central nervous system to decrease food intake and increase energy expenditure. However, in sleep apnea patients, leptin exerts negative effects on both chemoreflex and baroreflex function, which may contribute to the development or progression of hypertension and cardiovascular risk in these patients (Ciriello, 2013).

Recent studies have identified long form of leptin receptors (Ob-Rb) in the caudal regions of the NTS, where baroreceptor afferents predominantly terminate in the brainstem (Ciriello, 2013). In addition, it has been demonstrated that injecting leptin into the caudal NTS leads to a decrease in the spontaneous discharge rates of NTS neurons that project to sympathoinhibitory sites of the CVLM (Ciriello, 2013). Since the CVLM inhibits sympathetic outflow by projecting inhibitory neurons to the rostral ventro-lateral medulla (RVLM; Fig. 4), suppressing the sympathoinhibitory activity of the CVLM results in a decrease in baroreflex sensitivity. Therefore, it is possible that leptin contributes to the attenuation of baroreflex
sensitivity by suppressing the activity of NTS neurons that mediate the projection of baroreceptor afferent information to the CVLM. In turn, the CVLM decreases its inhibition of sympathoexcitatory RVLM neurons, thereby leading to increased sympathetic activity, and, ultimately, elevated blood pressure in sleep apnea patients (Fig. 4). This hypothesis is supported by the presence of fenestrated capillaries, enlarged perivascular spaces, and high capillary permeability in the caudal NTS, which supports the possibility of leptin being transported through the blood-brain barrier to access Ob-Rb-containing NTS neurons in the brainstem (Gross et al., 1990; Shaver et al., 1991). However, it is also possible that leptin exerts its effects on other Ob-Rb-containing neurons, which send projections to the NTS to alter the brain’s response to increased baroreceptor activity evoked by high blood pressure (Barnes et al., 2010).

![Diagram](image)

**Fig. 4.** The central baroreceptor pathway showing neural projections from arterial baroreceptors to the brainstem, and associated baroreflex responses to maintain homeostasis. Chronic IH leads to a decrease in the spontaneous discharge rates of NTS neurons that project to the CVLM, thereby attenuating baroreflex sensitivity and enhancing sympathetic activity. NTS = nucleus of the solitary tract, CVLM = caudal ventrolateral medulla; RVLM = rostral ventrolateral medulla; IML = intermedial lateral cell column; AMB = nucleus ambiguous. (Adapted from a lecture by Dr. John Ciriello.)
Leptin has also been demonstrated to exert effects on the cardiovascular responses evoked by the activation of the chemoreflex (Ciriello & Moreau, 2012). Ciriello & Moreau (2012) showed that injecting leptin into the NTS of anesthetized rats resulted in a dose-dependent increase in mean arterial pressure (MAP), heart rate (HR), and renal SNA (Fig. 5). Interestingly, the increase in MAP was attributable to an overall increase in SNA, as evidenced by the complete abolition of the MAP response by a peripheral ganglionic blockade; whereas the increase in HR was attributable to both an inhibition of parasympathetic nervous activity, and an activation of SNA, as a total autonomic blockade was required to completely abolish this response (Ciriello & Moreau, 2012). This suggests that, in addition to enhancing sympathetic activity, elevated levels of leptin also suppress parasympathetic activity by attenuating vagal responses to increased chemoreceptor activity. Collectively, these findings suggest that increased leptin levels may contribute to the elevated MAP and SNA seen in sleep apnea patients, by altering the sensitivity of the chemoreflex at the level of the NTS (Ciriello & Moreau, 2012). However, the exact cellular and subcellular mechanisms by which leptin alters the activity of NTS neurons remain unclear.

**Fig. 5.** Bar charts summarizing the effects of injecting different concentrations of leptin into the caudal NTS of rats on (A) MAP, (B) HR (C) renal SNA. MAP = mean arterial pressure; HR = heart rate; RSNA = renal sympathetic nervous activity. (Adapted from Ciriello & Moreau, 2012.)
**Sleep apnea augments synthesis/release of vasoconstrictor hormones**

In addition to its effects on chemoreflex and baroreflex regulation of blood pressure, sleep apnea is also linked to an increase in synthesis/release of several vasoactive hormones, which act directly on resistance vessels to elevate blood pressure. In sleep apnea patients, these hormones are primarily derived from the kidney, adrenal gland, and vascular endothelium (Prabhakar & Kumar, 2010).

Catecholamines are a family of vasoactive hormones mostly derived from the adrenal medulla, that show elevated levels of synthesis/secretion in sleep apnea patients (Marrone et al., 1993). Two important catecholamines that affect blood pressure regulation in sleep apnea patients are epinephrine and norepinephrine, both of which are vasoconstrictor hormones released in response to the chronic IH-induced elevation of sympathetic activity (Marrone et al., 1993; Peng et al., 2006). However, a study by Kuri et al. (2007) revealed another mechanism by which chronic IH is able to evoke the secretion of elevated levels of norepinephrine and epinephrine in the adrenal medulla of mice. In normal mice, chromaffin cells of the adrenal medulla release catecholamines via the Ca\(^{2+}\)-mediated fusion of secretory granules to the cell surface. However, inducing chronic IH in mice led to an increase in the readily releasable pool of secretory granules in adrenal chromaffin cells, independent of sympathetic input (Kuri et al., 2007). A likely mechanism by which this occurs is via the ROS-mediated activation of protein kinase C (PKC), which triggers an increase in recruitment of reserve granules to the readily releasable pool in adrenal chromaffin cells. As these granules contain catecholamines, this finding suggests that chronic IH facilitates elevated catecholamine secretion from the adrenal medulla, via a ROS-mediated signaling pathway (Kuri et al., 2007). Since norepinephrine and epinephrine are able to act directly on resistance vessels to increase blood pressure, an increase
in catecholamine secretion likely contributes, at least in part, to the elevated blood pressure seen in sleep apnea patients (Prabhakar & Kumar, 2010).

Another vasoconstrictor hormone that exhibits increased levels in sleep apnea patients is angiotensin II (Ang II), which is involved in the renin-angiotensin system (RAS; Prabhakar & Kumar, 2010). An increase in sympathetic activity stimulates the secretion of renin from the juxtaglomerular cells of the kidneys, which in turn cleaves angiotensinogen to form angiotensin I, which is then converted to Ang II (Fig. 6). In addition to its vasoactive effects, Ang II has been demonstrated to increase SNA and blood pressure by activating vasomotor glutamatergic sympathetic neurons in the RVLM of rats (Hu et al., 2002). In an epidemiological study by Moller et al. (2003), researchers measured 24-hour plasma Ang II levels in patients with OSA, and examined whether this was associated with changes in blood pressure. The study revealed a strong correlation between sleep apnea severity, Ang II production, and blood pressure (Moller et al., 2003). This suggests that sleep apnea promotes the development of hypertension, at least in part, by evoking an increased activation of the RAS. However, future studies are needed to better elucidate the cellular mechanisms involved in the association between sleep apnea and elevated RAS activity.

Fig. 6. Schematic illustrating the classic renin-angiotensin system cascade. (Adapted from Speth & Geise, 2014.)
Conclusion

Overall, this review highlights the various mechanisms by which sleep apnea results in sustained sympathetic activation and elevated blood pressure. Previous studies on both sleep apnea patients and chronic IH-treated animal models have provided crucial insights into the mechanisms underlying the development and progression of elevated blood pressure in sleep apnea patients. Notably, such studies have shown that sleep apnea is able to alter the activity of the sympathetic nervous system and elevate blood pressure by: (1) augmenting the chemoreflex, (2) attenuating the baroreflex, (3) increasing leptin levels in the circulation, and (4) promoting the synthesis/release of vasoconstrictor hormones. Altogether, the interplay between sympathetic activation, leptin production, and vasoactive hormones is able to trigger hypertension, which is a risk factor for the development of several cardiovascular diseases including stroke and heart failure (Floras, 2013). An increase in blood pressure is also associated with increased heart rate, and is a strong predictor of coronary heart disease in humans across all ages (Franklin et al., 2012). Additionally, sleep apnea is prevalent in patients with stroke, heart failure, and atrial arrhythmias, thus highlighting its association with increased cardiovascular risk (Floras, 2013).

Although understanding the physiological mechanisms involved in sleep apnea-induced hypertension has led to the development of newer, more effective interventions for sleep apnea, there is as yet no clinical trial evidence that treating sleep apnea significantly alters the rates of cardiovascular events (Floras, 2013).
REFERENCES


