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Review

Baroreflex and chemoreflex controls of sympathetic activity following intermittent hypoxia

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ABSTRACT

There is a large amount of evidence linking obstructive sleep apnea (OSA), and the associated intermittent hypoxia that accompanies it, with the development of hypertension. For example, cross-sectional studies demonstrate that the prevalence of hypertension increases with the severity of OSA (Bixler et al., 2000; Grote et al., 2001) and an initial determination of OSA is associated with a three-fold increase for future hypertension (Peppard et al., 2000). Interestingly, bouts of intermittent hypoxia have also been shown to affect sympathetic output associated with the baroreflex and chemoreflex, important mechanisms in the regulation of arterial blood pressure. As such, the possibility exists that changes in the baroreflex and chemoreflex may contribute to the development of chronic hypertension observed in OSA patients. The aim of the current article is to briefly review the response of the baroreflex and chemoreflex to intermittent hypoxic exposure and to evaluate evidence for the hypothesis that modification of these autonomic reflexes may, at least in part, support the comorbidity observed between chronic hypertension and OSA.

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1. Introduction

Obstructive sleep apnea (OSA) is characterized by brief repeated bouts of hypoxia during the night as a result of periodic blockage of the respiratory airway. Patients suffering from OSA are at a greater risk for a number of cardiac pathologies including heart failure (Malone et al., 1991; Tkacova et al., 1998), coronary artery disease (Mooe et al., 2001), and stroke (Dyken et al., 1996; Mohsenin, 2001). In addition, evidence indicates that OSA also contributes to the development of hypertension. For example, cross-sectional studies demonstrate that the prevalence of hypertension increases with the severity of OSA (Bixler et al., 2000; Grote et al., 2001) and an initial determination of OSA is associated with a three-fold increase for future hypertension (Peppard et al., 2000). Although the exact mechanisms are currently unclear, such data suggests that OSA may not only affect blood pressure acutely but may also alter regulatory mechanisms involved in the sympathetic nervous system to produce chronic effects on blood pressure and allow for the development of maladaptive states such as hypertension.

Acute or chronic intermittent hypoxia models are most frequently used to experimentally emulate the neurocirculatory changes associated with OSA due to the fact that intermittent hypoxia is a prominent feature of OSA (i.e., patients with OSA experience brief and repeated episodes of hypoxia) and that acute intermittent hypoxia (AIH) is capable of inducing phrenic long-term facilitation (LTF) in which progressive and

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sustained increase in phrenic motor output develops independent of changes in chemo-afferent input (Mitchell et al., 2001). It is well known that respiration markedly modulates the sympathetic nervous system (Adrian et al., 1932) and it is possible that respiratory LTF may induce sympathetic LTF (Zoccal et al., 2008) and contribute to the development of hypertension.

An important mechanism in the regulation of arterial blood pressure is the baroreflex. Stretch-sensitive baroreceptors in the afferent arm of the reflex monitor changes in arterial pressure and transmit the information centrally to modulate efferent sympathetic activity to numerous end-target organs (e.g., the heart and vascular beds) to adjust arterial pressure. Impairment of the baroreflex has been associated with hypertension and OSA (Bonsignore et al., 2002; Carlson et al., 1996; Vitela et al., 2005) suggesting that this reflex may be altered following repeated hypoxic exposure. However, direct evidence for the modulation of baroreflex function by acute or chronic hypoxia is limited, and moreover, whether the modulation of baroreflex function by hypoxia contributes to sympathetic LTF and hypertension remains unclear.

Highly integrated with the baroreflex is the chemoreflex which monitors PO_2, PCO_2, and pH in the blood via central and peripheral mechanisms. Activation of the chemoreflex alters respiratory rate, at least in part, by the modulation of sympathetic nerve activity and, together, the baroreflex and the chemoreflex contribute to adequate perfusion and oxygenation of the body and maintain homeostatic balance through control of sympathetic output. In OSA, muscle sympathetic nerve activity is increased through the stimulation of chemoreceptors and OSA augments resting sympathetic activity in awake patients (Imadojemu et al., 2007; Narkiewicz et al., 1999; Waradekar et al., 1996). As such, the possibility exists that the activation of the baroreflex and chemoreflex by intermittent bouts of hypoxia in disorders such as OSA alters the interaction and function of these autonomic reflexes and contributes to the hypertension observed in these pathologies.

The current review will focus on the response and modulation of the baro- and chemo-reflexes by intermittent hypoxia, as well as the hypothesis that hypoxia-induced changes in these reflexes contribute to the development of hypertension. It is well known that the chemoreflex responds to intermittent hypoxic exposure with an increase in sympathetic activity (Dick et al., 2007; Xing and Pilowsky, 2010), although studies evaluating the net effect on ventilation have produced conflicting results; some demonstrate an increase (Del Rio et al., 2010; Ling et al., 2001) while others a decrease (Kimoff et al., 1997; Osanai et al., 1999). The baroreflex, however, responds to intermittent hypoxia (specifically the increased sympathetic activity, released vasoconstrictors, and increased total peripheral resistance) in a manner that buffers the chemoreflex response (i.e., works to decrease sympathetic activity and blood pressure); in addition, evidence also suggests that the baroreflex may directly interact with the chemoreflex to alter its function (Lee et al., 1964; Somers et al., 1991). As such, repeated bouts of hypoxia appear to create an antagonistic relationship between the chemoreflex and baroreflex, at least in terms of control of sympathetic outflow. With sustained exposure to chronic intermittent hypoxia (CIH), preservation of the chemoreflex may become paramount at the expense of baroreflex sympathetic control. Indeed, the chemoreflex becomes sensitized to future bouts of hypoxia (Marcus et al., 2010; Prabhakar et al., 2010) while the threshold of the baroreflex resets to operate at higher pressure levels (Monahan et al., 2006; Prabhakar and Kumar, 2010).

In sum, intermittent hypoxia modulates baro- and chemoreflexes, as well as interactions between these two reflexes. This review will explore the evidence, and suggest that modulations of the baro- and chemo-reflexes, as well as maladaptive interactions between the two reflexes may contribute to the dysregulation of the control of sympathetic output and, at least partially, form the basis of the chronic hypertension observed in OSA patients.

2. The baroreflex regulates sympathetic activity as a function of arterial blood pressure

The arterial baroreflex is an important autonomic reflex that stabilizes arterial blood pressure on a moment-to-moment basis. Stretch-sensitive baroreceptors located in the carotid sinus and aortic arch monitor changes in arterial pressure and transmit the information via myelinated (A-fiber) and unmyelinated (C-fiber) projections to the nucleus of the tractus solitarius (NTS) in the medulla (Davies and Kalia, 1981; Fan and Andresen, 1998; Fan et al., 1999; Housley et al., 1987). Excitatory neurons in the NST then project to sympathoinhibitory neurons in the caudal ventrolateral medulla (cVLM) (Kubo et al., 1991; Somogyi et al., 1989) which, consequently, inhibit activity in the rostral ventrolateral medulla (rVLM) (Agarwal and Calaresu, 1991; Cravo and Morrison, 1993; Jeske et al., 1995). The rVLM contains sympathoexcitatory neurons which project to the intermediolateral cell column (IML) in the thoraco-lumbar spinal cord and synapse with sympathetic preganglionic neurons (SPGN) (Bernstein-Goral and Bohn, 1989; Deuchars et al., 1997; Minson et al., 1997; Morrison et al., 1989; Oshima et al., 2006). SPGN innervates numerous end organ targets (i.e., heart, vasculature, etc) and decreased SPGN activity lowers arterial blood pressure (Janig and Habler, 2003; Sved et al., 2001). As such, the baroreflex works through a system of negative feedback in which increased arterial pressure increases baroreceptor, NTS, and cVLM activities which, in turn, decreases rVLM activity. The decrease in sympathetic output results in decreased blood pressure which limits subsequent baroreflex activity.

Activation of the baroreceptors also modulates sympathetic activity through a respiratory-dependent pathway that includes respiratory pattern generator nuclei. This pathway is responsible for the respiratory rhythmicity observed in sympathetic nerve activity (Adrian et al., 1932; Barman and Gebber, 1980) and provides a critical role in the maintenance of optimal ventilation, circulation, and gas exchange through the coupling of respiratory and cardiovascular activities (Habler et al., 1994). In addition to sympathoinhibitory neurons, the cVLM also contains a group of excitatory respiratory neurons known as the pre-Bötzinger complex (pre-BötC) (Pilowsky, 1995; Smith et al., 1991). Conversely, the sympathoexcitatory neurons in the rVLM are adjacent to a population of inhibitory respiratory neurons known as the Bötzinger complex (BötC) (Lipski and Merrill, 1980). Evidence indicates that the pre-BötC and BötC neuron populations are critical for the generation of respiratory rhythmicity and its effects on sympathetic output (Habler et al., 1994; Ramirez et al., 1998; Smith et al., 1991). Specifically, pre-BötC neurons are a pacemaker source of inspiratory rhythmic activity while the BötC is a source of expiratory rhythmic activity (Smith et al., 1991). In addition, recent evidence also indicates that the activation of the baroreceptors activates the ventral respiratory column (which contains the pre-BötC and BötC) and inhibits the rVLM (Baekey et al., 2010).

Finally, although the baroreflex is traditionally considered a short-term regulator of blood pressure, evidence indicates that repeated activation of the baroreflex can have long-term effects on blood pressure. While the mechanisms are still unclear, it is believed that the renin–angiotensin system and other humoral and/or hormonal factor may be involved (Lohmeier, 2001; Nishida et al., 2012). In addition, it has been shown that prolonged stimulation of the baroreceptors can produce decreases in blood pressure that last for up to a week (Lohmeier et al., 2004, 2005). Such data support the hypothesis that the baroreflex is not only important in moment-to-moment regulation, but may be involved in long-term regulation as well and, as such, may influence more chronic maladaptations.

3. The chemoreflex regulates sympathetic activity as a function of pH and gas concentration in the blood

Another important autonomic reflex that regulates sympathetic activity is the chemoreflex. The chemoreflex consists of peripheral