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Review

Chronic intermittent hypoxia affects integration of sensory input by neurons in the nucleus tractus solitarii☆

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ABSTRACT

The autonomic nervous and respiratory systems, as well as their coupling, adapt over a wide range of conditions. Chronic intermittent hypoxia (CIH) is a model for recurrent apneas and induces alterations in breathing and increases in sympathetic nerve activity which may ultimately result in hypertension if left untreated. These alterations are believed to be due to increases in the carotid body chemoreflex pathway. Here we present evidence that the nucleus tractus solitarii (nTS), the central brainstem termination site of chemoreceptor afferents, expresses a form of synaptic plasticity that increases overall nTS activity following intermittent hypoxia. Following CIH, an increase in presynaptic spontaneous neurotransmitter release occurs under baseline conditions. Furthermore, during and following afferent stimulation there is an augmentation of spontaneous transmitter release that occurs out of synchrony with sensory stimulation. On the other hand, afferent evoked synchronous transmitter release is attenuated. Overall, this shift from synchronous to asynchronous transmitter release enhances nTS cellular discharge. The role of the neurotransmitter dopamine in CIH-induced plasticity is also discussed. Dopamine attenuates synaptic transmission in nTS cells by blockade of N-type calcium channels, and this mechanism occurs tonically following normoxia and CIH. This dopaminergic pathway, however, is not altered in CIH. Taken together, alterations in nTS synaptic activity may play a role in the changes of chemoreflex function and cardiorespiratory activity in the CIH apnea model.

1. Introduction

The cardiovascular and respiratory systems are vital in maintaining physiological homeostasis. Heart rate and blood pressure are maintained within normal limits by precise beat-to-beat control of the autonomic nervous system. Likewise, the respiratory system maintains typical arterial oxygen, carbon dioxide and pH within the body. These systems do not work in isolation but are coordinated through afferent and efferent pathways as well as central nuclei. These systems are also tightly coupled in that respiratory rhythms are observed in sympathetic nerve activity and changes in blood pressure influence respiration. The cardiorespiratory systems, and their coupling, exhibit an amazing degree of adaptation under physiological [e.g., exercise (Michelini and Stern, 2009), deconditioning (Hasser and Moffitt, 2001), pregnancy (Kvochina et al., 2007)] and pathophysiological [e.g., heart failure (Patel, 2000)] conditions.

Commonly observed is exposure to periods of low oxygen, either environmentally influenced or due to disease states. Decreases in arterial oxygen (hypoxia) are sensed by peripheral chemoreceptors in the carotid body located in the bifurcation of the common carotid artery. Hypoxia increases carotid body chemoreceptor sensory activity within the carotid sinus nerve, which joins the glossopharyngeal nerve, and this afferent activity is sent to the central nervous system (Mifflin, 1992; Vardhan et al., 1993). Ultimately, hypoxic episodes activate the carotid body chemoreflex and robustly increase breathing, sympathetic nerve activity and their coupling to maintain proper perfusion of the lungs, brain and kidney and to compensate for the direct vasodilating response of hypoxia. Several key central nuclei are important for integrating sensory information and increasing activity of the cardiovascular and respiratory system. One such area is the nucleus tractus solitarii (nTS), which is the first site for sensory termination in the brain (Andresen and Kunze, 1994), the focus of this short review.

2. Recurrent apneas induce alterations in the cardiorespiratory system

Epidemiologically, up to 24% of males and 9% of females from several racial and ethnic groups have mild hypoxic episodes from

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recurrent apneas throughout the night (Bradley and Floras, 2009). A prominent example is obstructive sleep apnea in which the upper airway periodically collapses (Bradley and Floras, 2009). With the occurrence of each apneic episode, there is an increase in arterial pressure and sympathetic nerve activity (Kato et al., 2009). The persistence of recurrent apneas induces daytime elevations in blood pressure and sympathetic nerve activity which eventually leads to hypertension. Clinical case studies suggest that the carotid body chemoreflex is one of the primary components of obstructive sleep apnea-induced alterations in the cardiovascular system (Narkiewicz et al., 1998, 1999b). Sleep apnea patients, even when studied without the influence of other confounding factors, exhibit increased chemoreflex sensitivity and hypertension (Spicuzza et al., 2006). Ventilatory depression caused by brief hyperoxia, a measure of peripheral chemosensitivity, is also more pronounced in sleep apnea patients (Tafil-Klawe et al., 1991). Last, apneic patients who have had their carotid bodies removed for unrelated purposes do not develop hypertension (Somers and Abboud, 1993). Untreated, recurrent apneas elevate the mortality rate. With the use of continuous airway positive pressure therapy, a successful reduction in nocturnal respiratory events, elevated sympathetic nerve activity and cardiovascular morbidity can occur (Narkiewicz et al., 1999a; Doherty et al., 2005; Spicuzza et al., 2006). Moreover, treatment is associated with a return to near normal of the elevated chemosensitivity (Spicuzza et al., 2006). In summary, sleep apnea is associated with an elevated chemoreflex.

3. Chronic intermittent hypoxia

Chronic intermittent hypoxia (CIH) is a common rodent model for recurrent apneas. This model was designed to mimic hypoxic episodes during apneas by subjecting animals to brief periods of acute hypoxia interspersed with normal room air, or normoxia (Fletcher et al., 1992). The pattern of CIH exposure, however, varies widely among laboratories (Fletcher and Bao, 1996; Greenberg et al., 1999; Ling et al., 2001; Peng et al., 2003; Kline et al., 2007; de Paula et al., 2007; Almado et al., 2008; Huang et al., 2009). The time of each hypoxic episode occurs between ~30 s to a few minutes, with the hypoxic-normoxic cyclic periods ranging from hours to months. This is an important consideration because the pattern and duration of the hypoxic challenge can determine the final cardiorespiratory output (Prabhakar and Kline, 2002).

Similar to sleep apnea, during and following CIH exposure in animal models, cardiorespiratory reflexes are amplified compared to those observed during brief hypoxia; this is believed to be due to changes in the chemoreflex. For instance, after CIH exposure, the ventilatory response to hypoxia is augmented in the rat (Peng et al., 2004), mouse (Peng et al., 2006) and cat (Rey et al., 2004). The sympathoexcitatory response to peripheral chemoreflex activation is also increased after CIH in anesthetized (Braga et al., 2006) and conscious (Huang et al., 2009) rats. Furthermore, intermittent hypoxia also induces an increase in baseline arterial pressure of 10–30 mm Hg (Kumar et al., 2006; Zoccal et al., 2007; Lin et al., 2007). Last, sectioning of the carotid sinus nerve carrying chemoafferent fibers ablates CIH-induced hypertension (Fletcher et al., 1992). Thus, the chemoreflex plays a prominent role in the augmentation of hypoxic ventilatory response, sympathetic nerve activity and blood pressure in CIH, similar to individuals inflicted with sleep apnea.

In addition to the chemoreflex pathway, the baroreceptor reflex is also altered following CIH. While ten days of CIH increases the gain of the baroreflex (Zoccal et al., 2009a), longer exposures to CIH (1–3 months) significantly blunt the baroreflex in mice (Lin et al., 2007) and rats (Gu et al., 2007). This occurs despite an increase in aortic depressor nerve activity (Gu et al., 2007) which may result from structural changes of baroreceptor terminal fields in the aortic arch (Ai et al., 2009). In short, CIH can significantly alter sensory reflexes such as the chemo- and baroreflex. The site and mechanism of these alterations has received considerable attention.

4. The central nervous system contributes to CIH-induced alterations of sensory reflexes

The chemoreflex arc that is responsible for increases in breathing and sympathetic activity during hypoxia consists of afferent sensory axons, central brainstem and forebrain nuclei, and motor and autonomic efferent axons. The augmented reflexes seen in CIH animal models are due, in part, to enhanced chemosensory afferent discharge during hypoxia (Peng et al., 2003; Peng and Prabhakar, 2004). In addition, several studies suggest CIH induces alterations in the processing of sensory information within the central nervous system. Following seven days of CIH, an increase in the gain of the central component of chemoreceptor processing has been demonstrated (Ling et al., 2001). In those studies, carotid sinus nerve stimulation, which bypasses the carotid body and thereby avoids the potential influence of differences in afferent activity, was more effective in inducing phrenic nerve discharge in CIH-conditioned rats compared to normoxic rats. In contrast, CIH decreases the central component of the baroreflex. After 35–50 days of CIH, the reflex fall in heart rate and blood pressure due to directly stimulating the aortic depressor nerve was reduced when compared to their normoxic controls (Gu et al., 2007). The reduced baroreflex response in CIH to depressor nerve stimulation was not due to an attenuation in the activity of efferent pathways to the heart or blood vessels as direct stimulation of the vagus nerve resulted in a potentiated fall in heart rate and blood pressure (Gu et al., 2007). These studies would suggest a central component is involved in both the alterations of the chemo- and baroreflex.

The central site for reflex modifications in CIH may involve several cardiorespiratory nuclei. The induction of the immediate early gene protein Fos, a marker for neuronal activation, may lend some insight into the nuclei affected. CIH induces Fos expression in the raphé, intermediate reticular nuclear zone, and along the rostral to caudal ventral lateral medulla cell column (Greenberg et al., 1999). Another key region is the nTS where Fos was observed in the medial and commissural subregions of this nucleus.

5. Sensory afferent processing is altered in the nTS following CIH

The nucleus tractus solitarii is the first site of chemoreceptor and baroreceptor integration in the central nervous system (van Giersbergen et al., 1992; Andresen and Kunze, 1994). A loose viscerotopic organization of afferent integration has been suggested, with baroafferents primarily terminating in the medial subnucleus and chemoafferents terminating in the medial and commissural subnucleus (Finley and Katz, 1992; Andresen and Kunze, 1994). Chemo- and barosensory afferent axons enter the brainstem and travel along the sensory bundle of the solitary tract before exiting and forming synapses with cells in the nTS (Housley et al., 1987; Finley and Katz, 1992; Andresen and Kunze, 1994). In addition to second-order cells that directly receive afferent information, the nTS possesses a large number of interneurons, receives projections from many brain regions that influence cardiorespiratory control, and contains a multitude of neurotransmitters and neuromodulators (Andresen and Kunze, 1994). Thus, the nTS is well suited for cardiorespiratory integration.

The nTS receives baroreceptor and chemoreceptor afferent signals in a continuous manner and processes this incoming information to modulate the autonomic and respiratory systems. This central nucleus is crucial to the integration of afferent signals and is