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Oxidative Stress in the Carotid Body: Implications for the Cardioventilatory Alterations Induced by Obstructive Sleep Apnea

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1. Introduction

The obstructive sleep apnea (OSA) syndrome is recognized as an independent risk factor for systemic hypertension. The OSA syndrome is characterized by cyclic episodes of oxygen desaturation due to the partial or complete obstruction of the air flow during sleep. Among the disturbances produced by OSA, the chronic intermittent hypoxia is considered the main factor for developing hypertension. Oxidative stress, inflammation, and sympathetic hyperactivity have been proposed as pathogenic mechanisms involved in the hypertension. However, evidence for a single mechanism has been difficult to establish in OSA patients, because of concomitant comorbidities. Since OSA patients show augmented reflex sympathetic, cardiovascular and ventilatory responses to acute hypoxia, it has been proposed that an enhance carotid body responsiveness to hypoxia is involved in the pathological alterations induced by OSA. This proposal has received further support, since studies performed in animals have shown that intermittent hypoxia selectively enhances the carotid body chemosensory and ventilatory responses to acute hypoxia, producing long-term potentiation of the motor ventilatory and sympathetic discharges. The mechanisms underlying the enhanced carotid body chemosensory reactivity to hypoxia induced by intermittent hypoxia are not completely known. Nevertheless, the available evidence indicates that the repeated episodes of hypoxia-reoxygenation produce local oxidative stress in the carotid body due to the accumulation of reactive oxygen species. In this chapter, we will review and discuss the new evidence supporting the essential role played by the carotid body chemoreceptors, and the contribution of the oxidative stress, endothelin-1 and pro-inflammatory cytokines to the progression of the cardioventilatory alterations induced by chronic intermittent hypoxia.

2. The carotid body chemoreceptors

Most of the mammalian cells respond to hypoxia modifying the expression of genes and proteins, which induce a physiological response to recover the tissue oxygen levels (i.e.

angiogenesis). However, gene expression induction is not fast enough to counteract a rapid drop in systemic oxygen levels. Only the peripheral chemoreceptors located in the carotid and aortic bodies are capable to evoke fast systemic adjustments to overcome a hypoxic episode. The carotid body located in the bifurcation of the carotid arteries is the main arterial chemoreceptor in terms of its contribution to the reflex ventilatory responses to hypoxia (Gonzalez et al., 1994). In humans and mammals, the carotid body initiates the hyperventilatory response induced by hypoxia and activates the sympathetic nervous system. The carotid body is a complex chemoreceptor organ with a high blood flow formed by different types of cells. The glomus cells are considered the oxygen sensors in the carotid body. Glomus cells establish synaptic contacts with the nerve terminals of the primary sensory neurons, whose soma are located in the petrosal ganglion (Gonzalez et al., 1994, Iturriaga & Alcayaga, 2004, Iturriaga et al., 2007). The current model for oxygen chemoreception in the carotid body states that low oxygen induced the inhibition of a voltage-independent potassium TASK-like current, leading to the depolarization of the glomus cells, followed by the entry of Ca^{2+} through L-type Ca^{2+} channels and the subsequent release of one or more excitatory transmitters, which in turn increase the discharges of action potentials in the nerve endings of the chemosensory neurons (Iturriaga & Alcayaga 2004, Iturriaga et al., 2007). The glomus cells contain several molecules proposed as putative excitatory transmitters, such as dopamine, acetylcholine, adenosine nucleotides and peptides. Among these molecules present in glomus cells, acetylcholine and adenosine triphosphate fulfill most of the criteria to be considered as the excitatory transmitters between the glomus cells and petrosal nerve ending (Iturriaga et al., 2007). However, other molecules such as dopamine, histamine, nitric oxide and endothelin-1 acts as modulators of the chemosensory process, acting on the glomus cells or controlling the vasomotor tone of the blood vessel (Iturriaga et al., 2007). More recently, it has been proposed that pro-inflammatory cytokines, such as tumor necrosis factor-α (TNF-α), interleukin 6 (IL-6) and interleukin 1β (IL-1β) are excitatory modulators of the chemoreception process in the rat carotid body (Lam et al., 2008, Liu et al., 2009, Shu et al., 2007).

3. Cardiovascular alterations in patients with obstructive sleep apnea and animals exposed to intermittent hypoxia

The OSA syndrome, a highly prevalent sleep-breathing disorder is now recognized as an independent risk factor for systemic hypertension. Approximately 50% of the OSA patients develop systemic diurnal hypertension and 30% of the hypertensive patients have OSA. The OSA syndrome is also associated with stroke, pulmonary hypertension, coronary artery disease and atrial fibrillation (Garvey et al., 2009, Parati et al., 2007, Somers et al., 2008). The OSA syndrome affect up to 5% worldwide adult population, but according to the report of the American Heart Association in collaboration with the National Heart, Lung, and Blood Institute National Center on Sleep Disorders Research (Somers et al., 2008) "85% of patients with clinically significant and treatable OSA have never been diagnosed, and referral populations of OSA patients represent only the *tip of the iceberg* of OSA prevalence". OSA is characterized by recurrent episodes of partial or complete obstruction of the air flow during sleep produced by the collapse of the pharyngeal airway. The interruption of the air flow produces hypoxia and hypercapnia, negative intrathoraxic pressure, sleep fragmentation

and arousal. During the airway occlusion, hypoxia and hypercapnia stimulate the carotid body chemoreceptors increasing the respiratory muscle effort, the vascular sympathetic tone and the arterial blood pressure. Finally, the stimulation of the carotid body chemoreceptors and probably the pulmonary mechanoreceptors elicit arousal and restores the ventilation. Among the disturbances produced by OSA, the exposure to intermittent hypoxia is considered the main factor for developing hypertension. Oxidative stress, inflammation and sympathetic overflow have been proposed as potential pathogenic mechanisms involved in the onset of the hypertension and cardiovascular diseases (Arnardottir et al., 2009, Garvey at al., 2009, Lavie 2003, Somers et al., 2008). However, conclusions from studies performed in humans are conflictive, because of concomitant effects of comorbidities (obesity, cardiovascular diseases, diabetes, etc) associated with OSA (Gozal & Kheirandish-Gozal, 2008, Somer et al., 2008). Thus, animal models of chronic intermittent hypoxia (CIH), which simulate the hypoxic-reoxygenation cycles observed in OSA patients, reproduce several pathologic cardiovascular features of OSA (Fletcher et al., 1992, Pack 2009; Schulz et al., 2008). The hypoxic-reoxygenation episodes in OSA patients enhance the cardiorespiratory and sympathetic responses to acute hypoxia (Carlson et al., 1993; Narkiewicz et al., 1998a, 1998b, 1999); impair the autonomic regulation of the heart rate and the arterial blood pressure (Narkiewicz et al., 1999b, Shiomi et al., 1996) and exacerbate the renin-angiotensin system (Fletcher et al., 2002, Moller et al., 2003). Similarly, animals exposed to intermittent hypoxia show potentiated sympathetic discharges and vascular responses to hypoxia, and develop systemic hypertension (Dick et al., 2007; Fletcher et al., 1992, Greenberg et al., 1999, Zoccal et al., 2008). The autonomic hyperactivity is associated with a reduction of the efficiency of the baroreflex control of heart rate and alterations of heart rate variability in OSA patients (Narkiewicz et al., 1998b, Shiomi et al., 1996) and animals exposed to intermittent hypoxia (Lai et al., 2006; Lin et al., 2007; Rey et al., 2004, 2008). Thus, it is likely that the enhanced sympathetic activity along with the reduction of the baroreflex efficiency would impair the regulation of heart rate and the vasomotor tone of blood vessels eliciting hypertension. Besides that, it has been found that intermittent hypoxia produces parasympathetic withdrawal, attributed in part to neuronal loss in the vagal ambiguous nucleus (Lin et al., 2007, Yan et al., 2008).

4. Contribution of the carotid body to the cardiorespiratory alterations in obstructive sleep apnea and animal exposed to intermittent hypoxia

Patients with recently diagnosed OSA show enhanced ventilatory, sympathetic and vasopressor responses to acute hypoxia, attributed to a potentiated hypoxic chemoreflex (Cistulli & Sullivan, 1994). Narkiewicz et al., (1999) studied the ventilatory, tachycardic and hypertensive responses to acute hypoxia in untreated normotensive OSA patients, and found that the hypoxic stimulation evokes higher ventilatory, tachycardic, and blood pressor responses in OSA patients than control subjects, but the ventilatory and blood pressor responses induced by hypercapnia and by the cold pressor tested in OSA patients were not different from control subjects. Loredo et al., (2001) reported that OSA hypertensive patients present higher basal tidal volumes, suggesting an enhanced carotid body chemosensory drive. Leuenberger et al., (2007) measured changes in sympathetic discharges recorded from the peroneal nerve of normal humans in response to acute

hypoxic stimulation before and after the exposure to 30 episodes of apnea. The episodes of apnea do not only increased sympathetic discharges and produced mild increases in arterial blood pressure, but also enhanced the sympathetic neural response to acute hypoxia, indicating that short-term intermittent hypoxia produces a facilitation of the hypoxic chemoreflex in normal humans. Thus, the available evidence supports the proposal that the enhanced oxygen chemoreflex response in OSA patients is produced by the intermittent hypoxia. Similarly, rats and cats exposed to chronic intermittent hypoxia show enhanced hypoxic ventilatory responses to acute hypoxia (Iturriaga et al., 2009, Rey et al., 2004; Reeves et al., 2003) and long-term facilitation of respiratory motor responses (McGuire et al., 2003, Dick et al., 2007, Prahbakar et al., 2005). The long-term potentiated ventilatory responses to acute hypoxia observed in animals exposed to intermittent hypoxia has been attributed to a central facilitation of the serotonin-mediated motor ventilatory output (McGuire et al., 2003). Although, Narkiewicz et al., (1998a, 1998b) found that sympathetic, pressor and ventilatory responses to acute hypoxia were enhanced in OSA patients, and Fletcher et al., (1992) reported that the bilateral carotid body denervation prevents the hypertension in rats exposed to intermittent hypoxia, the idea that carotid body chemoreceptors are involved in the progression of the hypertension did not receive much attention. However, new evidence obtained in the last decade have shown that an abnormal potentiated carotid chemosensory reactivity to hypoxia is crucial to potentiate the sympathetic activity (Iturriaga et al., 2005, 2009, Feng et al., 2008, Garvey at al., 2009; Prabhakar et al., 2005, Rey et al., 2004; Smith & Pacchia, 2007).

5. Intermittent hypoxia enhanced the carotid body chemosensory responses to acute hypoxia

Recording of chemosensory discharges from the carotid sinus nerve have shown that chronic intermittent hypoxia produces long-term potentiation of the carotid body chemosensory responses to acute hypoxia. Indeed, exposure of cats and rats to intermittent hypoxia for 4 to 10 days increases the basal carotid body chemosensory discharges measured in normoxia and enhances the chemosensory responses to acute hypoxia (Peng et al., 2003, Rey et al., 2004, Del Rio et al., 2010). Peng et al., (2003) found that the baseline carotid discharge and the chemosensory responses to acute hypoxia were higher in rats exposed to short cyclic hypoxic episodes followed by normoxia, applied during 8 hrs for 10 days. Similarly, we found that cats exposed to intermittent hypoxia during 8 hrs for 4 days showed enhanced CB chemosensory and ventilatory responses to acute hypoxia (Rey et al., 2004). In rats, we found that intermittent hypoxia for 7 days potentiates the carotid chemosensory responses to acute hypoxia, effect that persisted until 21 days of intermittent hypoxia when animals developed hypertension (Del Rio et al., 2011). Figure 1 illustrates representative recordings of carotid chemosensory responses induced by short hypoxic challenges in a sham rat and in one carotid body from a rat exposed to 5% O_2, 12 times/hr during 8 hrs for 21 days. As is shown in fig. 1, chronic intermittent hypoxia increased the baseline carotid chemosensory discharges measured in normoxia and induced a potentiation of chemosensory responses to acute hypoxia. Since these alterations in the carotid chemosensory function occurred without significant elevation of the arterial blood pressure until 21 days of intermittent hypoxia, the hypertension was preceded by an early potentiation of the carotid body chemosensory and ventilatory responses to hypoxia.

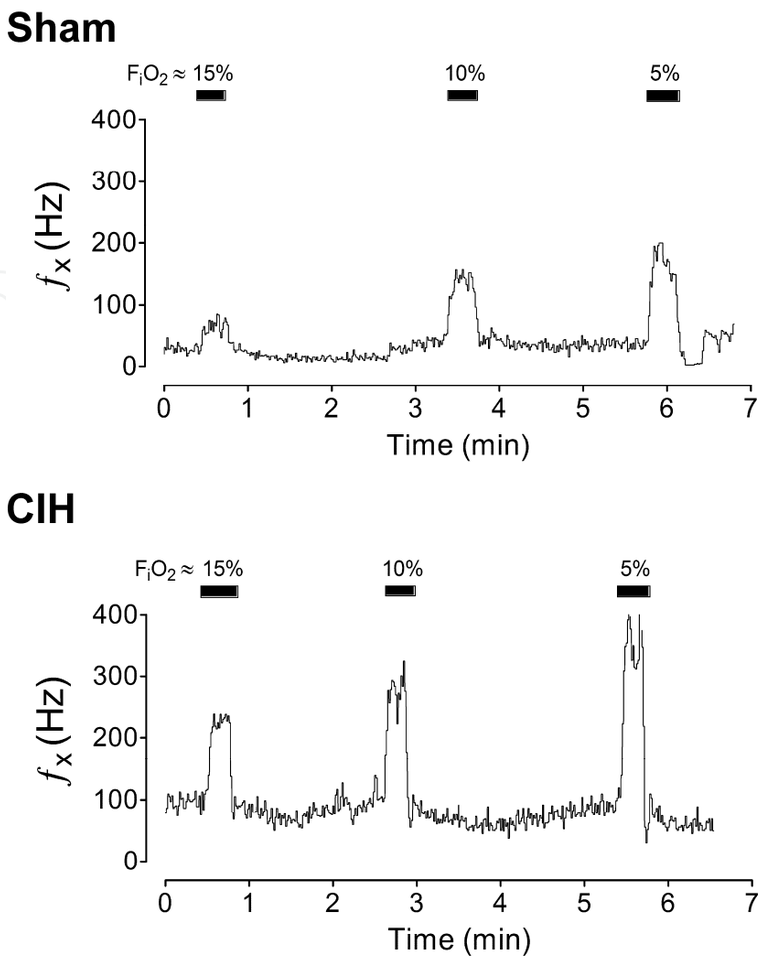

Fig. 1. Carotid body chemosensory potentiation induced by intermittent hypoxia in the rat. The carotid chemosensory discharges in response to various levels of inspired O_2 (FiO_2 ~15 to 5%) were measured from the carotid sinus nerve of a sham rat exposed to air to air cycles and a rat exposed to chronic intermittent hypoxia (CIH) for 21 days. f_x, frequency of carotid chemosensory discharges, expressed in Hz.

6. Mechanisms underlying the potentiation of carotid body chemosensory responses to hypoxia induced by chronic intermittent hypoxia

The enhance carotid chemosensory responses to hypoxia has been associated to increased levels of reactive oxygen species (Peng et al., 2003, Iturriaga et al., 2009, Del Rio et al., 2010) and endothelin-1 within the CB (Rey et al., 2006, Pawar et al., 2009), but it is possible that pro-inflammatory cytokines, which increased in the plasma of OSA patients (Lavie 2003, Jelic et al., 2008) may also contributes to the enhanced carotid body chemosensory responses to acute hypoxia (Iturriaga et al., 2009; Del Rio et al., 2011). Although some studies addressed the effects of intermittent hypoxia on transmitter production and release in the carotid body, very little is known on the functional significance of the role played by the neurotransmitters in the carotid body chemosensory potentiation induced by intermittent hypoxia (See for review Kumar, 2011).

6.1 Reactive oxygen and nitrogen species

Reactive oxygen species (ROS) and reactive nitrogen species (RNS) have been proposed as mediators of the cardiovascular and cognitive morbidities in several diseases including the OSA syndrome (Christou et al., 2003; Gozal & Kheirandish-Gozal, 2008, Lavie 2003) and in pathological consequences of intermittent hypoxia in animal models (Chen et al., 2005, Del Rio et al., 2010, Peng et al., 2003, Peng et al., 2009). Studies performed in OSA patients and animals exposed to chronic intermittent hypoxia have shown that the cyclical episodes of hypoxia-reoxygenation produces systemic oxidative stress due to the accumulation of ROS and RNS, which are well known potential sources of cellular damage. Peng et al., (2003) found evidence that the superoxide radical participates in the potentiation of the rat carotid chemosensory responses to hypoxia induced by intermittent hypoxia. They found that pre-treatment of rats for 10 days before the exposure to intermittent hypoxia with the superoxide dismutase mimetic, manganese (III) tetrakis (1-methyl-4-pyridyl) porphyrin pentachloride (MnTMPyP) prevents the potentiation of the carotid body chemosensory response to hypoxia. In addition, they found that intermittent hypoxia decreases the activity of the ROS sensitive enzyme aconitase in the whole carotid body, as well as the activity of the complex I of the mitochondrial electron transport chain, suggesting that the mitochondria is one of the sources of ROS (Peng & Prabhakar, 2003). More recently, Peng et al., (2009) tested the hypothesis that ROS generated by NADPH oxidase (NOX) mediate the intermittent hypoxia-induced carotid body potentiation. They found that acute hypoxia produced a larger increase in NOX activity in carotid body of rats exposed to intermittent hypoxia for 10 days than that of control carotid bodies. The carotid body chemosensory potentiation was prevented by NOX inhibitors and was not observed in NOX2 deficient mice. On the other hand, MacFarlane and Mitchell (2008) found that application of MnTMPyP into the intrathecal space of the cervical spinal cord abolished the phrenic long-term potentiation induced by acute intermittent hypoxia in rats, suggesting that ROS production is needed for enhancing the phrenic nerve ventilatory discharge. Consequently, ROS formation seems to be necessary for respiratory plasticity induced by intermittent hypoxia, at the level of the carotid body and respiratory motor output. Recently, we tested the hypothesis that oxidative stress contributes to the carotid chemosensory potentiation and the progression of the hypertension in rats exposed to intermittent hypoxia (Del Rio et al., 2010). We hypothesized that oral supplementation of the common antioxidant ascorbic acid (vitamin C) may prevent the carotid chemosensory potentiation and the cardioventilatory alterations including the hypertension induced by the intermittent hypoxic exposure. Accordingly, we studied the effects of ascorbic acid supplementation in the drinking water (1.25 g/l) on plasma lipid peroxidation, arterial blood pressure, and carotid chemosensory responses to acute hypoxia in rats exposed to short hypoxic episodes (5% O_2, 12 times/hr for 8 hrs) for 21 days (Del Rio et al., 2010). We found that exposure of the rats to intermittent hypoxia increased the plasma lipid peroxidation and the formation of 3-nitrotyrosine in the carotid body, the arterial blood pressure and enhanced the carotid chemosensory and ventilatory responses to hypoxia. Ascorbic acid treatment reduced the increased plasma lipid peroxidation and the formation of 3-nitrotyrosine in the carotid body, the potentiation of carotid body chemosensory responses (See Fig. 2), the ventilatory responses to acute hypoxia, as well as the hypertension.

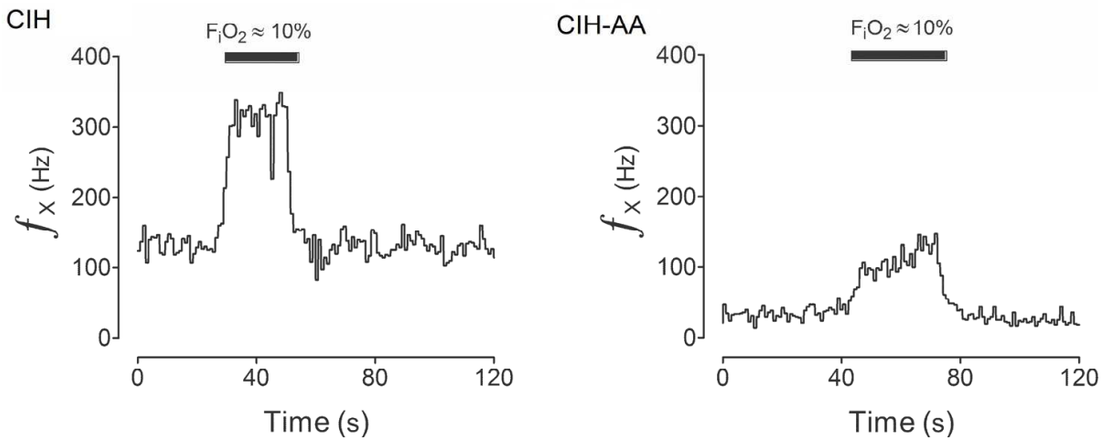

Fig. 2. Effect of ascorbic acid on the potentiated carotid body chemosensory responses to hypoxia induced by intermittent hypoxia. CIH, rat exposed to intermittent hypoxia. CIH-AA, rat exposed to intermittent hypoxia and treated with ascorbic acid. Note that ascorbic acid reduced both the baseline and the chemosensory response to 10% O_2. f_x, frequency of carotid chemosensory discharges, expressed in Hz.

Although the current information suggests that an increased local oxidative stress contributes to the carotid body chemosensory potentiation induced by intermittent hypoxia, the direct participation of ROS on the oxygen chemotransduction process is matter of debate, because no chemosensory excitatory effects of ROS have been observed (Gonzalez et al., 2007). A possible explanation is that an increased level of the superoxide radical in the carotid body may reacts with nitric oxide generating peroxynitrite, a powerful oxidizing agent that nitrates tyrosine residues forming 3-nitrotyrosine. We already found the excessive formation of 3-nitrotyrosine in glomus cells and blood vessels from carotid bodies harvested from rats exposed to intermittent hypoxia (Del Rio et al., 2010, 2011), as is shown in fig. 3. The increased formation of 3-nitrotyrosine indicates that the carotid body tissue is continuously exposed to oxidative stress during the intermittent hypoxic exposure. In addition, we found that a correlation between the marked increase of 3-nitrotyrosine immunoreactivity in the carotid body exposed to intermittent hypoxia and the enhanced carotid chemosensory responses to acute hypoxia (Del Rio et al., 2011), supporting and extending the idea that oxidative-nitrosative stress plays a critical role in the CB chemosensory potentiation (Iturriaga et al., 2009, Peng & Prabhakar, 2003). In OSA patients, Jelic et al., (2008) found that the expression of 3-nitrotyrosine in endothelial cells was greater than controls subjects, indicating that the oxidative stress contributes to the endothelial dysfunction caused by the intermittent hypoxia. In addition to the formation of nitrotyrosine residues, peroxynitrites may also modify iron sulfur clusters, zinc thiolates and other residues. Moreover, peroxynitrites may react with inorganic molecules such as CO_2 producing other free radicals that may modify DNA, lipids or proteins.

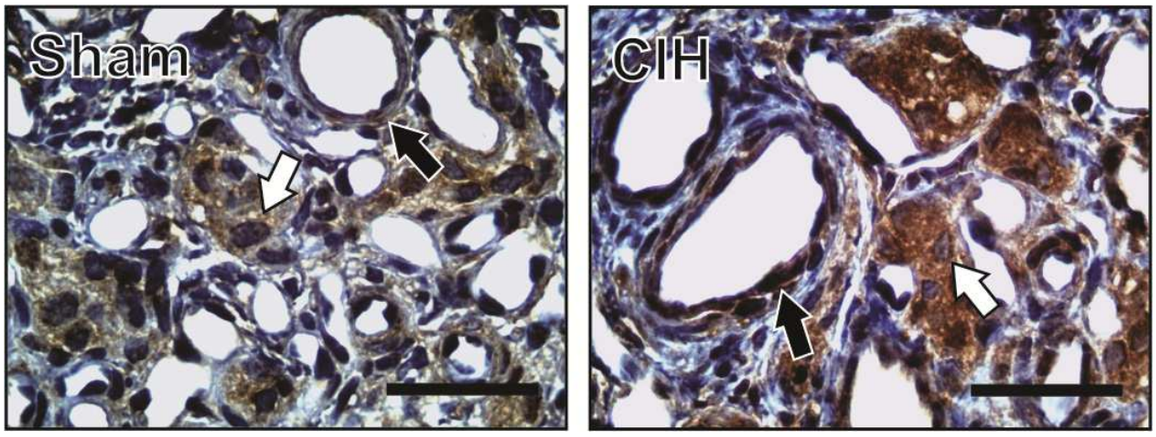

Fig. 3. Exposure to CIH increased 3-nitrotyrosine formation in the glomus cells (white arrows) and endothelial cells (black arrows) from rat carotid bodies. Scale bar, 20 μm.

6.2 Vasoactive molecules

An interesting molecule, which may mediate the carotid body chemosensory potentiation induced by intermittent hypoxia, is endothelin-1 (ET-1). It is known that the plasmatic ET-1 level increases in rats exposed to intermittent hypoxia (Kanagy et al., 2001) and OSA patients (Phillips et al., 1999). This potent vasoconstrictor peptide is expressed in the endothelium, blood vessels and glomus cells of the carotid body (Rey et al., 2007). The application of ET-1 produces chemosensory excitation in both *in situ* and *in vitro* carotid body perfused preparations, but not in the superfused preparation devoid of vascular effects (Rey & Iturriaga, 2004). We found that ET-1 was increased locally in the carotid body of cats exposed to 4 days to intermittent hypoxia by ~10-fold, while ET-1 plasma levels remains unchanged (Rey et al., 2006). The enhanced carotid body chemosensory responses to hypoxia were reduced by the ET receptor blocker bosentan in the intermittent hypoxic - treated cats, but have no effects on the carotid body chemosensory activity in control animals (Rey et al., 2006), indicating that a local increase of ET-1 contributes to enhance the carotid chemosensory responses. Pawar et al., (2009) tested the hypothesis that ET-1 induced by ROS plays a role in intermittent hypoxia induced chemosensory potentiation in the rat neonatal carotid body. They found that intermittent hypoxia enhanced the release of ET-1 and the expression of the ET-A receptor in response to intermittent hypoxia. Systemic administration of MnTMPyP, which prevent the elevation of ROS, reduced the increased basal release of ET-1, the overexpression of ET-A receptor mRNA and the enhanced carotid body chemosensory response to acute hypoxia. These results support the idea that a ROS-induced increase of ET-1 release is involved in the potentiation of carotid body chemosensory response elicited by intermittent hypoxia. Increased plasmatic levels of ROS and ET-1 have been also implicated in the hypertension induced by intermittent hypoxia. Troncoso-Brindeiro et al., (2007) reported that the concurrent treatments of rats exposed to intermittent hypoxia with the SOD mimetic, 4-hydroxy-2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPOL), prevents the increased ROS plasmatic level and the hypertension. However, it is worth noting that intermittent hypoxia increases the expression of ET-1 in the rat CB during the first week of hypoxia, and later the ET-1 levels returned back to the control levels (Del

Rio et al., 2011), suggesting that ET-1 may contribute to the enhanced carotid body responsiveness to hypoxia in the early phase of the intermittent hypoxic exposures. In addition to the transient changes in ET-1 expression, we found a significant decrease in the eNOS expression in the rat carotid body at 7 days of intermittent hypoxia (Del Rio et al., 2011), suggesting that chronic intermittent hypoxia may decrease the nitric oxide (NO) levels within the carotid body. Since NO at low concentration is an inhibitory modulator of the carotid chemosensory activity (Iturriaga et al., 2000), a reduced NO level may contribute to enhance the carotid body chemosensitivity, as well as to amplify the vasoconstrictor effect of ET-1. This interpretation is supported by the finding that intermittent hypoxia decreases the expression of the neuronal NO synthase in the rat carotid body (Marcus et al., 2010), suggesting that the removal of the inhibitory NO effects may also contribute to enhance the carotid chemosensory responses to hypoxia. Our results also showed that carotid body iNOS immunorreactive levels increased after 21 days of intermittent hypoxic exposure. Since iNOS produce higher amounts of NO, it is plausible that the NO levels in the carotid body will increase during long-term intermittent hypoxic exposure. It is worth noting that NO has a dual effect on carotid chemosensory discharges. Indeed, Iturriaga et al., (2000) found that at low levels NO is predominantly an inhibitor of the chemosensory discharges, whereas at high concentration NO increases carotid body chemosensory discharges. Thus, it is plausible that high NO levels in the carotid body following long-term intermittent hypoxia may partially contribute to maintain the carotid body chemosensory potentiation.

6.3 Pro-inflammatory cytokines

Endothelial dysfunction has been related to the progression of hypertension in OSA patients and animals exposed to intermittent hypoxia due to the increased plasmatic levels of pro-inflammatory cytokines (Biltagi et al., 2008, Jelic et al., 2008, Jun et al., 2008, Tam et al., 2007, Williams & Scharf, 2007). It is likely that an increased production of ROS induced by the hypoxia-reoxygention cycles may evoke the expression of genes and the synthesis of pro-inflammatory cytokines, mediated by the activation of transcription factors such as the nuclear factor kappa B (NF-κB), the activator protein 1 and HIF-1α (Semenza & Prahbakar, 2007). In response to oxidative stress, HIF-1α induces the expression of several genes including ET-1 and iNOS, but ROS also produces the translocation of NF-κB to the nucleus, increasing the expression of several inflammatory genes such as IL-1β, IL-6, TNF-α, adhesion molecules, iNOS and ET-1 (Janseen-Heininger et al., 2000). Recently, we found that intermittent hypoxia increased the levels of TNF-α and IL-1β in the rat carotid body after 21 days of exposure (Del Rio et al, 2011). We found that glomus cells constitutively expresses TNF-α and IL-1β in the cell bodies and that chronic intermittent hypoxia up-regulates the expression of both TNF-α and IL-1β, without inducing carotid body tissue infiltration with macrophages or changes in TNF-α and IL-1β plasmatic levels (Del Rio et al., 2011). Our results showed that exposure to intermittent hypoxia enhances the rat carotid chemosensory responses to acute hypoxia, and progressively increase the immunorreactive TNF-α and IL-1β expression in the carotid body, suggesting a potential role for this cytokines in modulating the enhanced carotid body chemosensory activity after exposure to intermittent hypoxia.

7. Proposed targets of the effects of ROS in the carotid body

The available evidence indicates that oxidative stress mediated the potentiation of the carotid body chemosensory responses to acute hypoxia, induced by the exposure to intermittent hypoxia. However, the nature of the molecular mechanism by which ROS induced chemosensory potentiation is not known. Based on the presented evidences, we hypothesized that chronic intermittent hypoxia may increase the expression of pro-inflammatory cytokines and other chemosensory modulators, such as ET-1 and NO, which may potentially contribute to enhance the carotid body chemosensory responses to hypoxia. Figure 4 summarized the possible targets of the effects of ROS on oxygen chemoreception in the carotid body. It is plausible that excessive amounts of free radicals may modify the O_2-sensitive K^+ channels, increasing the intracellular Ca^{2+} levels, which in turn evokes the release of excitatory transmitters, but a direct participation of ROS on the O_2 chemotransduction process in the carotid body is not clear (Gonzalez et al., 2007). ROS or other molecules, produced downstream of the ROS signal, which act upon the mitochondria, membrane channels or the gene expression machinery may modify the oxygen sensing in the carotid body. Further studies are required to determine which protein or enzyme complexes involved in the carotid body chemosensory process are affected by ROS or ROS-dependent molecules induced by intermittent hypoxia.

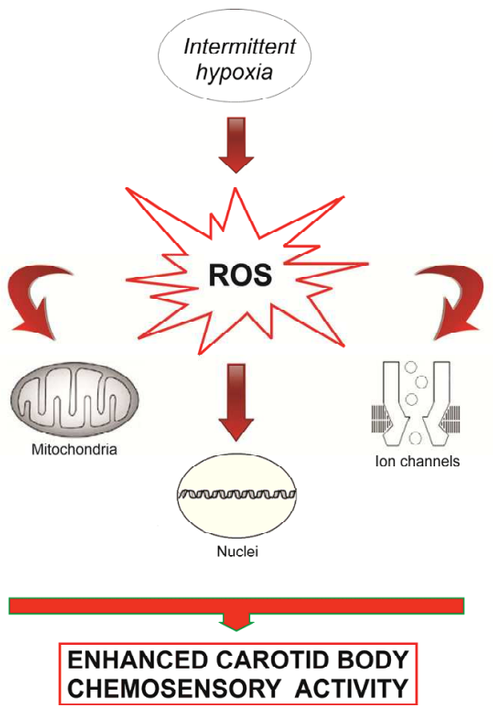

Fig. 4. Proposed targets of the effects of ROS on the potentiation of the carotid body induced by intermittent hypoxia.

8. Integrative model

Figure 5 shown a diagram of the proposed mechanisms involved in the potentiation of the carotid body chemosensory responses to hypoxia induced by intermittent hypoxia, which

finally contributes to the development of the hypertension. We postulate that cyclic episodes of hypoxia-reoxygenation enhance the carotid body chemosensitivity to hypoxia, which in turn contributes to elicit a persistent facilitation of the sympathetic neural output. The enhanced sympathetic activity along with a reduction of the baroreflex efficiency should impair the regulation of the heart rate variability and the vasomotor tone of blood vessels, resulting in an elevation of arterial blood pressure. On the other hand, systemic oxidative stress and the inflammation *per se* may contribute to the endothelial dysfunction, leading to the hypertension.

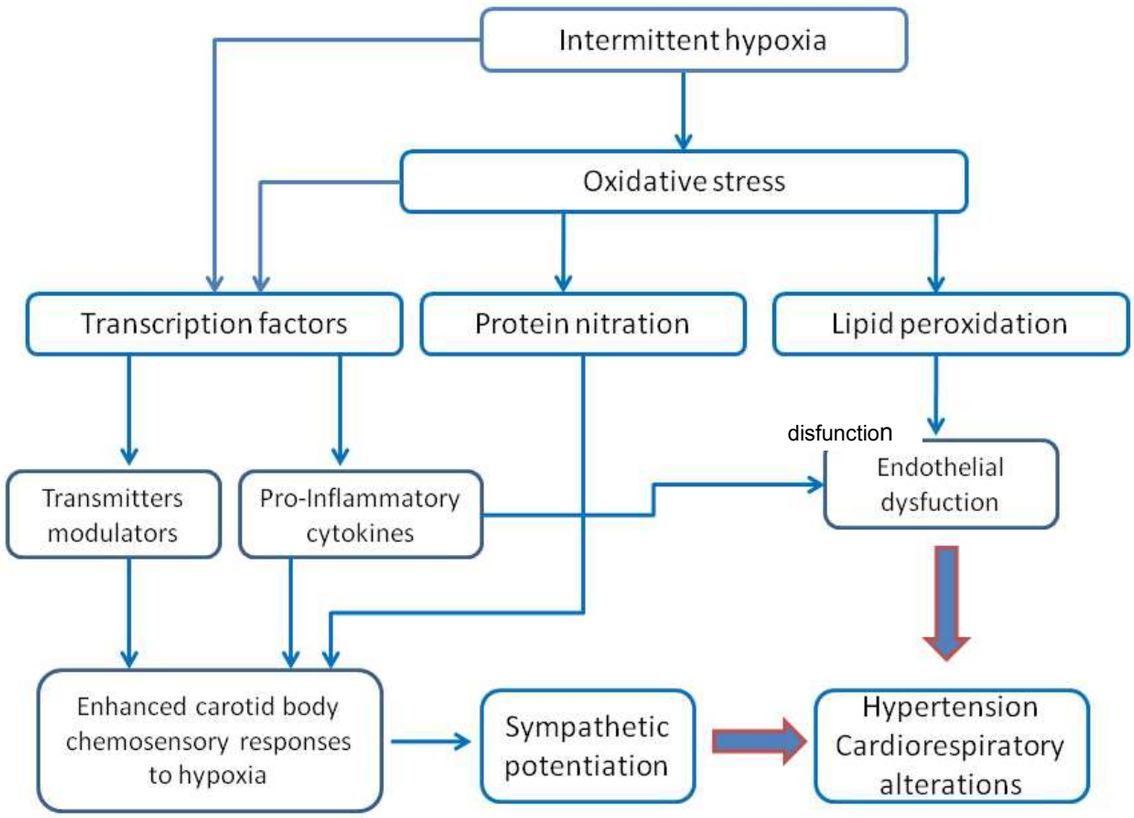

Fig. 5. Proposed mechanisms involved in the hypertension induced by the potentiation of the carotid body chemosensory responses to hypoxia induced by intermittent hypoxia, and the systemic oxidative stress.

9. Conclusion

Autonomic dysfunction has been associated to exposure to chronic intermittent hypoxia in animal models, and is thought to be involved in the increased risk of hypertension and cardiovascular mortality in OSA patients. The cyclic hypoxic episodes in OSA patients potentiate cardiovascular and sympathetic responses induced by hypoxic stimulation of peripheral chemoreceptors, and impair the regulation of arterial blood pressure and the renin–angiotensin system. Intermittent hypoxia enhances the ventilatory and cardiovascular responses to acute hypoxia, suggesting a major role of the carotid body in the pathological

cardiorespiratory consequences of intermittent hypoxia. New evidences indicate that intermittent hypoxia induced oxidative stress in the carotid body, which contributes to potentiate the carotid body chemosensory responses to acute hypoxia. Understanding how the oxidative stress interacts with the carotid body chemoreceptor system will provide new insights into the pathophysiological cardiovascular consequences of OSA. Thus, upcoming new knowledge in the field will serve to propose new therapies to moderate the severity of the cardiovascular alterations induced by OSA. We believe that is possible to ameliorate or prevent the hypertension using antioxidants, which will reduced the systemic oxidative stress as well as the carotid body potentiated chemosensitivity to hypoxia.

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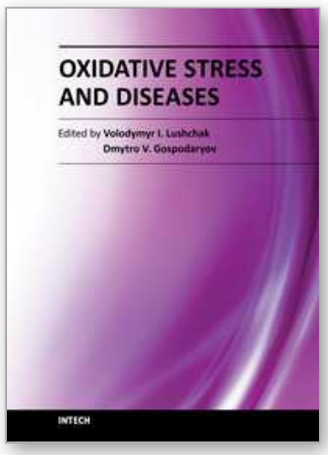

Oxidative Stress and Diseases

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The development of hypothesis of oxidative stress in the 1980s stimulated the interest of biological and biomedical sciences that extends to this day. The contributions in this book provide the reader with the knowledge accumulated to date on the involvement of reactive oxygen species in different pathologies in humans and animals. The chapters are organized into sections based on specific groups of pathologies such as cardiovascular diseases, diabetes, cancer, neuronal, hormonal, and systemic ones. A special section highlights potential of antioxidants to protect organisms against deleterious effects of reactive species. This book should appeal to many researchers, who should find its information useful for advancing their fields.

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