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Expressions of angiotensin and cytokine receptors in the paracrine signaling of the carotid body in hypoxia and sleep apnea

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ABSTRACT

Arterial chemoreceptors in the carotid body are central to the chemical control of breathing in the chemotransduction of physiological stimuli in the arterial blood for eliciting the chemoreflex, which mediates the respiratory, cardiovascular and autonomic responses to hypoxia, hypercapnia and acidosis. Recent evidence suggests that signaling molecules locally produced in the carotid body, including angiotensin II and pro-inflammatory cytokines play an important role in the modulation of the activity of carotid chemoreceptors, via the angiotensin and cytokine receptors expressed in the chemosensitive cells in an autocrine–paracrine manner. The carotid chemoreceptor activity is augmented in subjects at high altitude and in patients with sleep-disordered breathing. Maladaptive responses of the paracrine signaling to hypoxia in the carotid body have been proposed to play a pathogenic role in sleep apnea. Specifically, recent findings show significant increases in expressions of angiotensin receptors and components of a local angiotensin-generating system in the carotid body in sustained or intermittent hypoxia, which augments the chemoreceptor activity and also mediates the inflammatory response of the carotid body to hypoxia. In addition, inflammation of the carotid body involves an increased local expression of cytokine receptors and pro-inflammatory cytokines in sustained or intermittent hypoxia. This review aims to summarize the evidence supporting that the upregulated expression of the angiotensin receptors and cytokine pathways in the carotid body leads to augmented activities of the carotid chemoreceptor in hypoxic conditions, which could play a role in the pathophysiology of sleep apnea.

1. Introduction

Arterial chemoreceptors in the carotid body, located bilaterally at the bifurcation of the carotid artery, are responsive to chemical changes in the arterial blood, which are essential to elicit the chemoreflex for the maintenance of the blood gases and pH homeostasis. The carotid body is innervated by chemoafferent fibers of the carotid sinus nerves, which project the sensory activity via the glossopharyngeal nerve to the medullary neurons in the nucleus tractus solitary for eliciting the central efferent outputs of the chemoreflex. Increased central respiratory activities and altered autonomic activities are responsible for the ventilatory and circulatory responses to hypoxia, including but not limited to hyperventilation, bradycardia and redistribution of blood flow to vital organs. Thus, resection of the carotid body greatly diminishes the ventilatory response to hypoxia in human subjects (Teppema and Dahan, 2010).

The carotid chemoreceptor is composed of chemosensitive glomus (type-I) cells apposed to nerve endings of petrosal ganglionic neurons. The glomic clusters are also encompassed by sustentacular (type-II) cells and are proximal to highly dense capillaries supplied with blood perfusion far exceeding the metabolic rate of the carotid body (Gonzalez et al., 1994; Lahiri et al., 2001). Thus, chemical stimuli in the arterial blood and signaling molecules locally produced in the carotid body are within a diffusing distance of equilibrium effecting on the chemosensory component of the carotid body. Chemotransduction is mainly mediated by type-I cells which biosynthesize and release a number of neurotransmitters including acetylcholine, ATP, catacholamines, and also neuromodulators including neuropeptides and adenosine in responding to physiological stimuli including hypoxia, hypercapnia and acidosis (Nurse, 2010). More recently, type-II cells are also believed to play an active role in the local regulation of the chemosensory process, mediated by the ATP release from these cells as a paracrine signal to modulate the activity of type-I cells via purinergic pathways (Nurse, 2014).

Moreover, the carotid chemoreceptor is responsive to circulating hormones including angiotensin II, inflammatory and

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immunogenic signaling molecules including pro-inflammatory cytokines and lipopolysaccharides (LPS) because the corresponding receptors are expressed in the carotid body. In addition, recent findings suggest that a number of vasoactive peptides, including angiotensin II and endothelin-1, and pro-inflammatory cytokines, including interleukin (IL)-1β, IL-6 and tumor necrosis factor (TNF)-α, are produced locally in the carotid body. Evidence suggests that these signaling molecules modulate the activity of the carotid chemoreceptor in a paracrine–autocrine manner (Fung et al., 2014). More importantly, these local mechanisms are regulated by hypoxia, as in sustained hypoxia relevant to the physiological acclimation to altitudes and also in intermittent hypoxia relevant to sleep apnea in disease conditions. Thus it has been recently proposed that alterations of the expression of the receptors of these paracrine–autocrine signaling molecules by hypoxia play roles in the inflammatory response of the carotid body to hypoxia and also in the augmented activity of the carotid chemoreceptor, which could be functionally important in the ventilatory acclimation to hypoxia and also in the pathophysiology of sleep apnea (Fung et al., 2014). This review aims to summarize recent findings in the literature focusing on the hypoxic regulation of the expression of angiotensin and cytokine receptors in the paracrine signaling of the carotid body under hypoxic conditions relevant to sleep apnea.

2. Expression of angiotensin receptors in the carotid body

Carotid chemoreceptors are responsive to angiotensin II because angiotensin (AT) receptors are expressed in the carotid body. Morphological studies have demonstrated that the AT receptor–ligand binding is present in the carotid body with or without sympathetic or afferent denervation, suggesting the expression of AT_1 receptors in the chemosensory component of the carotid body (Allen, 1998). Positive AT_1-immunoreactivity is found in the rat carotid body although it is not ubiquitously expressed under physiological conditions (Fung et al., 2001). The AT_1 receptor is co-localized with type-I cells containing tyrosine hydroxylase (Leung et al., 2000; Fung et al., 2002). Functionally, exogenous angiotensin II at nanomolar concentrations significantly increases the discharge activity of carotid chemoreceptors by up to 2 folds in a superfused rat carotid body, although there is a brief inhibitory effect prior to the excitatory response and not all the single-fiber recordings are responsive to angiotensin II under physiological conditions (Allen, 1998; Leung et al., 2000). The chemoreceptor response to angiotensin II is mediated by AT_1 receptors because losartan, an AT_1 receptor antagonist ($C_{22}H_{23}ClN_6O$), blocks the effect of angiotensin II (Allen, 1998; Leung et al., 2000). Also, angiotensin II elevates the intracellular calcium level in the fura-2 loaded chemosensitive type-I cells, which is sensitive to losartan but not to AT_2 receptor antagonist PD-123319; about 40% of type-I cells are responsive to angiotensin II under physiological conditions (Fung et al., 2001). In addition, it has been shown that angiotensin II increases the sensitivity of the potassium current to hypoxia in the type-I cell of the rabbit carotid body (Li and Schultz, 2006; Li et al., 2006).

Besides AT_1 receptors, AT_2 receptors are expressed in the carotid body although its functional role remains unclear (Leung et al., 2000; Fung et al., 2002). In addition, AT_4 receptors have been reported in the carotid body (Fung et al., 2007). AT_4 receptors contain high-affinity binding sites for angiotensin IV which is a metabolite of angiotensin II containing the 3–8 fragment of the octapeptide (Chai et al., 2004). The immunoreactivity of AT_4 receptors is localized in the tyrosine hydroxylase-containing type-I cells in the rat carotid body (Fung et al., 2007). High concentration (10 μM) of angiotensin IV elevates the intracellular calcium level of the chemosensitive glomus cells, suggesting a functional role of Ang IV-binding of the AT_4 receptor in the modulation of chemoreceptor activities (Fung et al., 2007). Thus, evidences strongly support that angiotensin receptors expressed in the carotid body mediate the excitatory response of the carotid chemoreceptor to angiotensin peptides via AT_1 and AT_4 receptors.

Angiotensin II in the arterial blood is at picomolar concentrations under physiological conditions, depending on the bioavailability of the precursor angiotensinogen and enzymatic activities of renin and angiotensin-converting enzyme (ACE). The plasma level of angiotensin II elevates to nanomolar concentrations in responding to alterations in extracellular fluid volume, osmolarity, blood volume or sodium depletion, which stimulates the cardiovascular and renal responses to maintain the blood pressure, electrolyte and fluid homeostasis (Reid et al., 1978; Huang et al., 1989). It has been known that activation of the chemoreflex pathway elevates renal sympathetic activities contributing to the renal secretion of renin, which increases sodium reabsorption and water intake (Honig, 1989; Marshall, 1994). Thus, the excitatory effect of angiotensin II on the carotid chemoreceptor activity mediates an increase in the respiratory, circulatory and autonomic activities via the chemoreflex for the maintanence of blood gases and blood volume and flow under pathophysiological or disease conditions for instances hypovolemia or hemorrhage.

In addition to the circulating renin–angiotensin system (RAS), components of the RAS are expressed in numerous local tissues and organs (Campbell, 2003). In the carotid body, the mRNA and protein expressions of angiotensinogen are found in the type-I cells containing tyrosine hydroxylase (Lam and Leung, 2002). Also the mRNA transcript of ACE, but not renin, is present in the rat carotid body. These evidences suggest a locally expressed renin-independent pathway for an intrinsic generation of angiotensin peptides in the carotid body. In effect, the local RAS could increase the tissue concentration of angiotensin II above the circulating level in the carotid body, which effects as a paracrine–autocrine signaling molecule via the activation of angiotensin receptors expressed in the carotid body.

3. Expression of receptors of pro-inflammatory cytokines in the carotid body

The carotid chemoreceptor is responsive to pro-inflammatory cytokines because of the expression of cytokine receptors in the carotid body, which plays a role in the immune-to-brain communication of the inflammatory and infective status (Zapata et al., 2011; Porzionato et al., 2013). It has been shown that IL-1 receptor type I (IL-1r1) is expressed in the type-I cells of the carotid body (Wang et al., 2002; Lam et al., 2008, 2012). The receptor is functional because the outward potassium current in type-I cells is significantly decreased by exogenous application of IL-1β (Shu et al., 2007). Also, the discharge of the carotid sinus nerve is increased by application of IL-1β to the carotid body in rats (Shu et al., 2007). In addition, IL-1β induces an elevated level of intracellular calcium response to hypoxia in the type-I cell (Lam et al., 2008, 2012). Furthermore, intraperitoneal injection of IL-1β increases the IL-1r1 expression in the carotid body (Zhang et al., 2007), suggesting that the cytokine receptors in the carotid body are regulated by inflammatory cytokines, which could modulate the chemosensory activity and its response to proinflammatory cytokines and hypoxia under inflammatory or disease conditions.

Besides the expression of IL-1 receptors, IL-6 receptors, namely IL-6 receptor alpha chain (IL-6Rα) and gp130, are found in the type-I, type-II and vascular cells in the carotid body in rats (Wang et al., 2006; Lam et al., 2008, 2012). Exogenous application of IL-6 increases the secretion of catecholamines (Fan et al., 2009) and the intracellular calcium response to hypoxia in the type-I cell in rats (Lam et al., 2012). Moreover, TNF receptors TNF-r1 and TNF-r2