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Potential Contribution of Carotid Body-Induced Sympathetic and Renin-Angiotensin System Overflow to Pulmonary Hypertension in Intermittent Hypoxia

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Abstract

Purpose of Review Obstructive sleep apnea (OSA), featured by chronic intermittent hypoxia (CIH), is an independent risk for systemic hypertension (HTN) and is associated with pulmonary hypertension (PH). The precise mechanisms underlying pulmonary vascular remodeling and PH in OSA are not fully understood. However, it has been suggested that lung tissue hypoxia, oxidative stress, and pro-inflammatory mediators following CIH exposure may contribute to PH.

Recent Findings New evidences obtained in preclinical OSA models support that an enhanced carotid body (CB) chemosensory reactiveness to oxygen elicits sympathetic and renin-angiotensin system (RAS) overflow, which contributes to HTN. Moreover, the ablation of the CBs abolished the sympathetic hyperactivity and HTN in rodents exposed to CIH. Accordingly, it is plausible that the enhanced CB chemosensory reactivity may contribute to the pulmonary vascular remodeling and PH through the overactivation of the sympathetic-RAS axis. This hypothesis is supported by the facts that (i) CB stimulation increases pulmonary arterial pressure, (ii) denervation of sympathetic fibers in pulmonary arteries reduces pulmonary remodeling and pulmonary arterial hypertension (PAH) in humans, and (iii) administration of angiotensin-converting enzyme (ACE) or blockers of Ang II type 1 receptor (ATR1) ameliorates pulmonary remodeling and PH in animal models.

Summary In this review, we will discuss the supporting evidence for a plausible contribution of the CB-induced sympathetic-RAS axis overflow on pulmonary vascular remodeling and PH induced by CIH, the main characteristic of OSA.

Keywords Carotid body · Intermittent hypoxia · Pulmonary remodeling · Systemic and pulmonary hypertension · Obstructive sleep apnea

Abbreviations

ACE	Angiotensin-converting enzyme
AHI	Apnea/hypopnea index
Ang II	Angiotensin II
ATR1	Angiotensin II receptor type 1
ATR2	Angiotensin II receptor type 2
BP	Arterial blood pressure
BRS	Baroreceptor reflex sensitivity
CB	Carotid body
CIH	Chronic intermittent hypoxia
CPAP	Continuous positive airway pressure
CSN	Carotid sinus nerve
CVO	Circumventricular organs
ET-1	Endothelin-1
ETB	Endothelin type B receptor
HTN	Systemic hypertension
HIFs	Hypoxia-induced factors
IL-6	Interleukin 6
IL-1β	Interleukin 1β
ICAM	Intercellular adhesion molecule 1
MnSOD	Manganese-dependent superoxide dismutase
MCP-1	Monocyte chemoattractant protein-1
MSNA	Muscle sympathetic nerve activity
NA	Nucleus ambiguous
NF-kB	Transcription nuclear factor κB
NTS	Nucleus of the tractus solitarious
NADPH	Nicotinamide adenine dinucleotide phosphate

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NOX2	NADPH oxidase 2
NOX4	NADPH oxidase 4
3-NT	3-Nitrotyrosine
OSA	Obstructive sleep apnea
PASMC	Pulmonary arterial smooth muscle cells
PAH	Pulmonary arterial hypertension
PH	Pulmonary hypertension
PVN	Paraventricular nucleus
RAS	Renin-angiotensin system
ROS	Reactive oxygen species
RVSP	Right ventricular systolic pressure
RVH	Right ventricular hypertrophy
RVLM	Rostral ventrolateral medulla
SFO	Subfornical organ
SHR	Spontaneous hypertensive rats
TNF-α	Tumor necrosis factor
VCAM	Vascular cell adhesion molecule

Obstructive Sleep Apnea and Pulmonary Hypertension

OSA is a leading sleep breathing disorder associated with sleep fragmentation, somnolence, and cognitive dysfunction [1]. However, OSA is also recognized as an independent risk factor for developing systemic hypertension (HTN) and is associated with pulmonary hypertension (PH), stroke, coronary artery disease, and arrythmias [2•, 3, 4, 5•]. Indeed, 50% of OSA patients develop HTN, with a positive association between the apnea/hypopnea index (AHI) and the prevalence of resistant HTN [6, 7]. OSA is diagnosed when patients show an AHI > 10 events/h, affecting up to 10% of adult men and 5% of women worldwide population [5•, 8]. OSA is characterized by repeated episodes of complete or partial airflow stop during sleep caused by the upper airway collapse, eliciting intermittent hypoxia and hypercapnia, respiratory efforts, negative thorax pressure, and micro-arousals. During an apneic episode, hypoxia and hypercapnia stimulate the carotid body (CB) chemoreceptors eliciting ventilatory and sympathetic responses, and transient increases in arterial blood pressure (BP). Among these alterations, chronic intermittent hypoxia (CIH) is considered the main factor for HTN [2•, 4, 5•]. Moreover, CIH is sufficient to elicit autonomic alterations and HTN in rodent OSA models [9–11]. In addition to the well-known relationship with HTN, OSA is associated with mild PH. According to the World Health Organization (WHO), sleep breathing disorders are recognized as a cause of PH Group 3 [12], with an incidence ranging from 20 to 50% [13•, 14–16]. Imran et al., using a meta-analysis determine whether continuous positive airway pressure (CPAP) therapy may reduce pulmonary blood pressure in OSA patients without cardiac or lung disease [17]. Their meta-analysis, which included 222 OSA patients with PH (~ 39.3 ± 6.3 mmHg), showed that CPAP therapy was associated with a decrease in pulmonary arterial pressure of 13.3 mmHg, indicating that CPAP produces a significantly lower pulmonary blood pressure in patients with OSA. It is worth to note that PH correlates positively with several comorbidities in OSA patients such as obesity, daytime hypoxia and hypercapnia, obstructive airway disease, and nocturnal oxygen desaturation [18–20]. We used the term pulmonary hypertension (PH) to refer to animal models of PH, clinical PH associated with OSA, or other forms of hypoxia, while the term pulmonary arterial hypertension (PAH) is used to designate the heritable, idiopathic, and associated pulmonary hypertension in patients.

Contribution of Oxidative Stress, Inflammatory Mediators, and Hypoxia-Inducible Factors on CIH-Mediated Pulmonary Hypertension

Acute hypoxia vasodilates systemic vessels but contracts pulmonary arteries, a transient response called "hypoxic pulmonary vasoconstriction," which redistributes arterial blood flow from poorly to well-ventilated lung areas to optimize the ventilation/perfusion ratio [21•]. The maintenance of the hypoxic stimulus triggers vascular remodeling characterized by hyperplasia and/or hypertrophy of pulmonary arterial smooth muscle cells (PASMC), persistent vasoconstriction, augmented pulmonary vascular resistance, and PH [22, 23••]. Similar to sustained hypoxia, CIH produces vascular remodeling and PH (Table 1). Indeed, rats and mice exposed to CIH developed vascular lung remodeling, right ventricular systolic pressure (RVSP > 30 mmHg), and in some cases causes to right ventricular hypertrophy (RVH), which has been attributed to the activation of reactive oxygen species (ROS) and inflammatory signaling pathways [24, 26–30]. High ROS levels increase intracellular Ca^{2+} in PASMC, a key process in the vascular remodeling and PH [23••, 31–33]. Exposure of rodents to CIH for 28 days increased lung lipid peroxidation, 3-nitrotyrosine (3-NT) levels, and pro-oxidant enzymes and decreased manganese superoxide dismutase (MnSOD) and catalase levels [24, 25, 27]. In addition, Jin et al. reported that the administration of grape seed procyianidin, an extract with antioxidant properties, prevents the development of PH and vascular remodeling in a CIH rat model [25]. On the other hand, several studies have shown that PAH patients and animal PH models exhibit inflammatory responses [34–36]. The transcription nuclear factor κB (NF-κB) plays a key role in the inflammatory responses and its activity is regulated by hypoxia. In fact, NF-κB controls the expression of pro-

inflammatory genes [37]. Furthermore, exposure of rodents to CIH for 28 days increased lung protein levels of NF-κB and the pro-inflammatory cytokines TNF-α, IL-6, MCP-1, IL-1β, and the cell adhesion proteins ICAM and VCAM [30, 38, 39]. These findings suggest that CIH activate ROS or/and inflammatory signaling pathways in the lung tissue and both factors may have a role in the development of the PH induced by CIH. CIH increased ROS in the lung by decoupling of complex III from the mitochondrial electron transport chain and by increasing pro-oxidant enzyme levels [40, 41]. Indeed, exposure of rodents to CIH for 28 days increased lipid peroxidation, protein nitration, and levels of pro-oxidants (NOX2 and NOX4), and decreased the activity of antioxidant enzymes such as MnSOD, catalase, and homoxygenase-1 (HO-1) [24, 25, 27, 38, 42, 43].

The hypoxia-inducible factors (HIFs) are also involved in the progression of PH induced by sustained hypoxia [44]. A reasonable hypothesis is that the activation of HIFs and ROS-downstream signaling pathways may increase lung levels of endothelin 1 (ET-1) and pro-inflammatory cytokines, which contribute to the development of the CIH-induced vasoconstriction and PH. Several studies have demonstrated the participation of HIF-1α and HIF-2α in the development of pulmonary vascular remodeling and PH. HIF-2α is abundantly expressed in the pulmonary tissue [45]. Abud et al. found that digoxin, an inhibitor of HIFs, attenuates both PH and RVH in rats exposed to hypoxia sustained for 3 weeks [46]. Furthermore, HIF-2α transgenic deficient mice exposed to sustained hypoxia show a reduction in RVSP and pulmonary vascular remodeling compared to the wild controls [47, 48•, 49, 50].

Renin-Angiotensin System in Pulmonary Remodeling and Pulmonary Hypertension

The kidney renin-angiotensin system (RAS) regulates the electrolytes, body fluid balance, and systemic arterial blood pressure. Renin cleaves the liver-derived angiotensinogen peptide into Ang I, which is processed by ACE into Ang II in the pulmonary and renal endothelium. In addition, RAS components are present in several tissues, including the brain, the CB, and lung [51–53]. RAS is involved in pulmonary remodeling and PH [54–56, 57•, 58]. Ang II signaling through ATR1 produces vasoconstriction, oxidative stress, inflammation, fibrosis, and vascular dysfunction, while signaling via ATR2 produces vasodilation and vascular protection [59, 60]. In addition, the enzyme ACE2 cleaves Ang I and II into Ang (1–7), which activates the MAS receptor producing vasodilatation. High levels of circulating Ang II and high renin activity have been found in PAH patients [55, 61]. In the lung, Ang II activates oxidative stress-signaling pathways increasing pro-inflammatory cytokines, promoting cell proliferation and migration, and leading to extracellular matrix remodeling and fibrosis [54]. Sustained hypoxia increases the expression and activity of ACE and Ang II in rat pulmonary vessels, while Ang II upregulates AT1R and produces proliferation of PASMC [57•, 58]. In addition, PAH patients show increased levels of ACE in the endothelial cells of small pulmonary arteries [62]. Furthermore, Morell et al. found that the ACE blocker captopril and the ATR-1 blocker losartan reduces pulmonary BP and right ventricular hypertrophy in hypoxic rats [57•]. The RAS-aldosterone axis plays an important role in modulating pulmonary vascular NO synthesis, which

Table 1 Pulmonary vascular remodeling and PH induced by CIH

Animal model	CIH exposition	Alterations	Refs.
Sprague-Dawley rat	4% O_2 8 h/day × 28 days	↑RVSP (~37.5 mmHg) ↑Fulton index Arterial remodeling	[24]
Sprague-Dawley rat	10% O_2 10 h/day × 28 days	↑RVSP (~35 mmHg) ↑Fulton index Arterial remodeling ↑Lung SM-α-actin	[25]
Sprague-Dawley rat	10% O_2 10 h/day × 28 days	↑RVSP (~35 mmHg) ↑Fulton index Arterial remodeling	[26]
Sprague-Dawley rat	6% O_2 8 h/day × 35 days	↑MPAP (~27 mmHg)	[27]
Mice	5% O_2 12 h/day × 28–56 days	↓Ejection fraction Arterial remodeling	[28]
Mice	10% O_2 8 h/day × 56 days	↑RVSP (32 mmHg) ↑Fulton index Arterial remodeling	[27]

Fulton index right ventricle/septum + left ventricle. *RVSP* right ventricular systolic pressure, *MPAP* mean pulmonary artery pressure, *SM-α-actin* smooth muscle actin

level is reduced in PH [63]. The NO production in lung endothelial cells is mediated by the ETB-induced activation of eNOS. The ETB contains an intracellular cysteinyl thiol that regulates the signal transduction of NO. Maron et al. reported that aldosterone modulates the effect of ET-1 in a rat monocrotaline PH model. They found that ET-1 levels were associated with elevated aldosterone levels in plasma and lung tissue and reduced NO metabolites in the lung. Aldosterone increased ROS production altering the cysteinyl thiols in the eNOS-activating region of the ETB receptor, which in turn reduced lung endothelium-derived NO and promoted PH [64].

Sympathetic and RAS overflow plays a crucial role in the progression of PH [6, 14, 55, 65–68]. In rats, lung sympathetic noradrenergic innervation is predominant in large central arterial vessels and decreases toward the periphery [69]. Electrical stimulation of the stellate ganglion or sympathetic nerves increases pulmonary blood pressure in dogs and cats, an effect mediated by the activation of adrenergic receptors [70], although non-adrenergic and non-cholinergic agents and peptides are also involved in the regulation of lung vessel contractility. The sympathetic noradrenergic fibers are activated by the distension of the main pulmonary arteries or superior airways, or by the hypoxic activation of the CB chemoreceptors [71]. The hypoxia-induced sympathetic response acts on central vessels, which are closely coupled to the clinical consequences of PAH in patients, and it is different from the vasocontraction that occurs more distally in response to alveolar hypoxia [69]. Shirai et al. studied the alterations of pulmonary sympathetic activity following CIH by recording sympathetic pulmonary fibers and measuring vascular remodeling in 42-day CIH-treated rats, and found that CIH increased sympathetic baseline discharge and exacerbated the responses to acute hypoxia [66]. Velez-Roa et al. measured muscle sympathetic nerve activity (MSNA) with microneurography in PAH patients and control subjects, and found that PAH patients showed higher MSNA, while the unloading of the CB-mediated chemoreflex with by 100% FiO2 (Dejours Test) decreased MSNA and partially reduced the increased sympathetic discharge [68]. Those observations suggest that sympathetic hyperactivity in PAH patients is partially mediated by tonic increases in CB chemoreflex drive. Chen et al. tested the safety and efficacy of pulmonary artery sympathetic denervation in patients with idiopathic PAH, which did not respond to medical therapy [72•]. This first-in-man pulmonary artery denervation for treatment of PAH showed that at 3 months of follow-up, patients who underwent sympathetic denervation showed a significant reduction of pulmonary arterial pressure from 55 ± 5 to 36 ± 5 mmHg, highlighting the importance of the sympathetic activation in PAH [72•]. Liu et al. performed renal denervation 24 h and 2 weeks after monocrotaline injection in rats to test if sympathetic activation of RAS contributes to PH. After 35 days, they found beneficial effects of this procedure on the lung and cardiac alterations, which better results when the sympathetic neurotomy was performed sooner during the development of PH [73].

Contribution of the CB of Systemic and Pulmonary Hypertension Induced by CIH

The sympathetic hyperactivation and cardiorespiratory alterations found in OSA patients [5•, 74] and animals exposed to CIH [9, 75–79] suggest that CIH enhances the CB hypoxic chemoreflex. Furthermore, carotid sinus nerve recordings of chemosensory discharges in rats and cats have shown that CIH selectively increases CB baseline discharge in normoxia and enhances chemosensory responses to hypoxia, providing direct evidence that CIH enhanced CB chemoreceptor responsiveness to low oxygen [75, 78, 80]. Fletcher et al. obtained the first evidence for the critical role played by CB in the CIH-induced HTN. They found that carotid sinus denervation prevented the development of HTN in rats exposed to CIH for 35 days [9]. Oxidative stress, ET-1, and pro-inflammatory molecules are involved in the autonomic alterations and HTN in OSA patients [81, 82] and animal exposed to CIH [83–85]. The hypoxia-reoxygenation cycles produce oxidative stress by increasing the superoxide radical, which contribute to enhance the CB chemosensory discharge and evokes HTN [75, 77, 78, 85–87]. The treatment with antioxidants normalizes the enhanced CB chemosensory discharge and prevents or reverts HTN in CIH-treated rats [75, 78, 85, 88, 89]. The cellular response to hypoxia is driven by HIF-1α and HIF-2α [44]. In the CB, CIH modified the balance between HIF-1α/HIF-2α; promoting the upregulation of pro-oxidant enzymes (i.e., NADPH) and the downregulation of antioxidant enzyme levels [87]. Ascorbic acid abolished the CIH-induced increases of TNF-α and IL-1β immunoreactivity in the CB, suggesting that inflammation depends on oxidative stress in the CB [90]. These findings indicate that oxidative stress is the key mediator of the enhanced CB chemosensory responses to hypoxia and HTN induced by CIH. Since antioxidant treatment prevents or reverses both the enhanced CB discharge and HTN, it is impossible to probe any causal relationship between them. Therefore, we tested whether autonomic and CIH-induced HTN depended on the enhanced CB chemosensory discharge by eliminating the CB input to the brainstem [91]. On day 21 of CIH exposure, hypertensive rats underwent bilateral CB ablation and then were exposed to CIH for 1 week more. The ablation of the CBs normalized the elevated BP (mean 10 mmHg), restored heart rate variability, and baroreflex sensitivity, but did not reduce the systemic oxidative stress. Our results showed that HTN and autonomic alterations induced by CIH depended critically on the enhanced CB discharge, supporting a main role for the CB on the onset and maintenance of HTN [91, 92].

The up-to-date model of carotid chemoreception proposes that hypoxia produces chemoreceptor (glomus, type I) cell depolarization and Ca^{2+}-dependent release of excitatory transmitters, which in turn increases the neural discharge of axons that projects through the carotid sinus nerve to the nucleus of the tractus solitarius (NTS), where second- and third-order neurons integrates visceral inputs [93]. The NTS projects to the paraventricular nucleus (PVN) and to the rostral ventrolateral medulla (RVLM), where the pre-sympathetic neurons are located. During CIH, the enhanced CB discharge potentiates the chemoreflex pathway, activating neurons in the NTS, PVN, and RVLM [94–96]. The CIH-induced CB chemosensory potentiation produces sympathetic and RAS hyperactivation, which contributes to HTN [9–11, 97]. Indeed, renal artery sympathetic denervation [83] and administration of losartan [98] prevent HTN induced by CIH. Interestingly, CB chemoreceptor cells express functional AT1R, which are overexpressed in CIH [52]. Indeed, Ang II increases intracellular Ca^{2+} in chemoreceptor cells, an effect blocked by losartan, suggesting that local Ang II may play a role in the enhanced CB chemosensory discharge during CIH [52]. Recently, Kim et al. proposed that circulating Ang II may stimulate the CB during intermittent hypoxia. They found that acute exposure to intermittent hypoxia increases renal sympathetic discharge, which was prevented by losartan [99]. The CB denervation and the pharmacological inhibition of the subfornical organ (SFO) partially

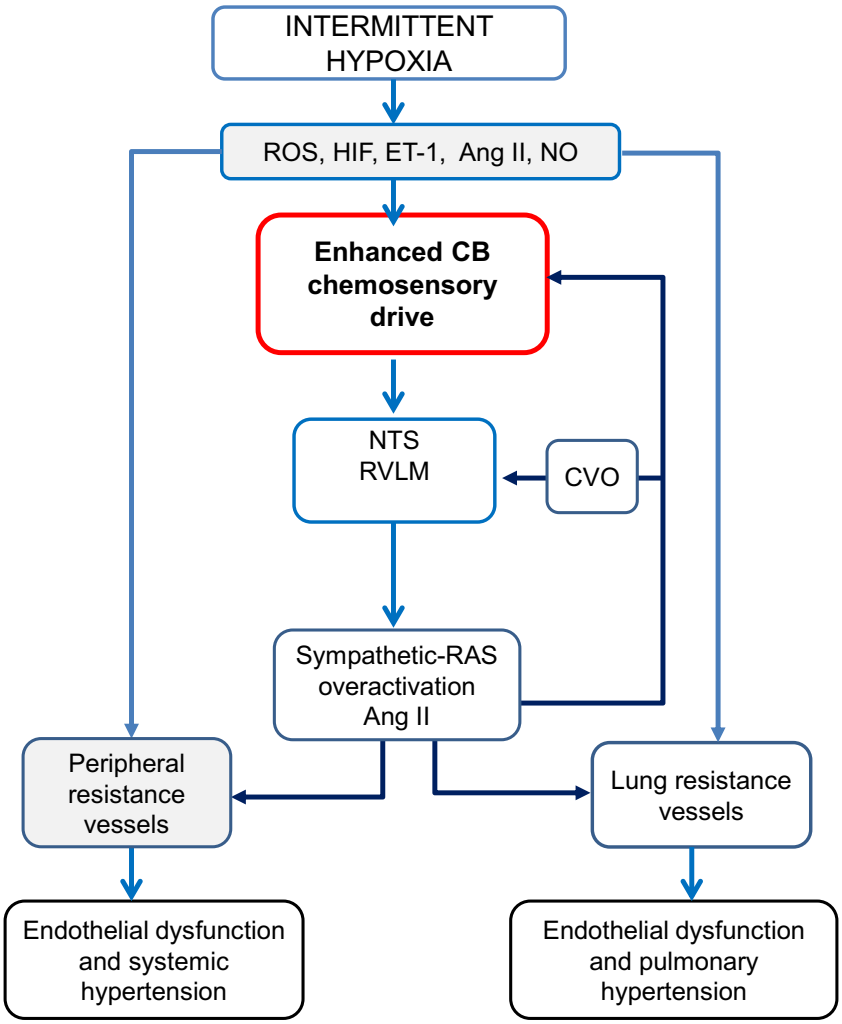

Fig. 1 Proposed model for the carotid body contribution to PH following CIH. Obstructive sleep apnea, features by chronic intermittent hypoxia (CIH), is associated with systemic and pulmonary arterial hypertension. Oxidative stress, inflammation, and sympathetic overflow are involved in the progression of systemic and pulmonary hypertension in OSA patients. CIH produces cyclic episodes of hypoxia-reoxygenation that increase reactive oxygen species (ROS) production and stabilizes hypoxia-inducible factors (HIFs), which in turn augment pro-inflammatory cytokines and endothelin-1 (ET-1), and reduce nitric oxide (NO) levels. The up-to-date evidence shows that an enhanced carotid body (CB) chemosensory discharge potentiates sympathetic and renin-angiotensin systems (RAS), increasing circulating levels of angiotensin II (Ang II). Ang II elicits vasoconstriction acting directly on pulmonary and systemic arterial vessels but may also contribute to the maintenance of cardiovascular alterations in CIH by a positive feedback mechanism involving Ang II-activation of the CB and central cardiovascular regulatory nuclei (NTS) through the circumventricular organs (CVO)

reduces the sympathetic renal discharge, while the combined CB denervation and SFO inhibition eliminates the increased sympathetic discharge following acute intermittent hypoxia. These results reinforced the idea that the CIH-mediated potentiation of the CB chemoreflex pathway increases circulating Ang II, which may act not only at the pulmonary and systemic arteries producing vasoconstriction but also on the CB and CVO neurons that command sympathetic activation (see Fig. 1: Proposed model for the CB contribution to pulmonary vascular remodeling and PH during CIH). However, direct evidence that Ang II potentiates the CB chemosensory discharge during CIH is missing. Thus, recording of CB chemosensory discharges during ATR1 blockade in CIH rats would help to understand the role play by RAS.

Fletcher et al. found that CIH for 35 days increased plasma renin activity 4-fold compared with CIH rats with bilateral renal neurotomy [76]. Moreover, Marcus et al. found that administration of losartan prevents HTN induced by CIH [98]. Thus, CIH produces a progressive increase in BP-mediated in part by the activation of renal sympathetic system that increase Ang II. Recently, da Silva et al. demonstrate in a rat model of combined sustained hypoxia and monocrotaline that renal sympathetic denervation delayed the progression of PH, reduced the pulmonary vascular remodeling, and reduced the right ventricular hypertrophy [65]. These beneficial effects were associated with a partial suppression of RAS signaling through downregulation of AT1R in the pulmonary vasculature [65]. The increased Ang II elicits vasoconstriction acting directly on pulmonary and systemic arterial vessels, but Ang II may also contribute to the maintenance of the adverse cardiovascular outcome in CIH by a positive feedback mechanism involving Ang II-activation of the CB and central cardiovascular regulatory neurons through the CVO regions (SFO and area postrema). Circulating Ang II cannot effectively activate AT1R in the NTS and RVLM of healthy subjects, because these receptors are protected by the blood-brain barrier, but Ang II may access the brain through the CVO regions with weak blood-brain barrier and a high density of AT1R. Saxena et al. studied the contribution of Ang II on the sustained BP increase and FosB activation in the median preoptic nucleus and the PVN in rats with AT1R knockdown in the SFO [100]. They found that CIH increased BP during the hypoxic exposure in both control and AT1R-knockdown rats. However, during the normoxic dark phase, only CIH rats showed HTN. AT1R-knockdown rats showed a decrease in FosB in the median preoptic nucleus and the PVN. Thus, the evidence suggests that SFO contributes to the HTN elicited by elevated circulating levels of Ang II.

The feasibility that CB stimulation increases pulmonary BP was provided by Sugito et al. They found that selective rat CB stimulation with NaCN in normoxia, produced a fast and transient increase in pulmonary BP [101•]. The denervation of the CBs completely abolished the rise in pulmonary BP, indicating that the activation of the CB chemoreflex contributes to the regulation of pulmonary vasculature in rats [101•]. In addition, Shinoda et al. reported that CB ablation improved the survival in monocrotaline-induced-PH rats. In addition, ablation of the CBs restores the normal heart rate variability and decreased 24-h urinary norepinephrine, suggesting that CB contributes to the increase in sympathetic outflow and PH [102].

Perspectives and Conclusions

In summary, the enhanced CB chemoreceptor discharge may contribute to the pulmonary vascular remodeling and PH through the activation of the sympathetic-RAS axis. This idea is supported by the facts that (i) stimulation of the CB increases pulmonary BP, (ii) pulmonary remodeling and PAH in humans is reduced by sympathetic denervation of pulmonary arteries, and (iii) administration of angiotensin-converting enzyme (ACE) or AT1R blockers reduces pulmonary remodeling and PH in animal models. Besides that, Ang II may stimulate the CB and the neurons in circumventricular organs leading to a further sympathetic-RAS axis overflow. Whereas these two processes may occur in tandem or as separate events remain to be determined. Accordingly, we hypothesized whether the enhanced CB chemosensory drive following CIH exposure may contribute to trigger PH through the activation of the sympathetic nervous system and RAS.

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Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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