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The Nervous Mechanism of Sympathetic over Activity Induced by Chronic Intermittent Hypoxia

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Abstract

Hypertension is concerned to be a common complication in Chronic Intermittent Hypoxia (CIH) conditions which mimic the state of Obstructive Sleep Apnoea (OSA) in clinic. Sympathoexcitation is a crucial origin in the process of high blood pressure and the mechanisms involved in the sympathoexicitatory changes after CIH exposure are complex referring to chemoreflex, baroreflex, neurotransmitters, and central nuclei and so on. In this review we predominantly expound the effect of CIH-induced potentiated Carotid Body (CB) chemoreceptor sensitivity to hypoxia stimulation which results in the enhancement of RSNA and Endothelin (ET) is mentioned due to its expression in CB and the fact that ET is thought to be a significant chemoreceptor-excitatory transmitter. Previously studies have shown expression of ET and ET receptors in the CB chemoreceptor glomus cells and vessel system, and CIH obviously increased the expression which indicated a possible effect of ET to the potentiated ventilatory and cardiovascular responses to acute hypoxia probably via increased inward Ca^{2+} currents, inflammatory response or Acid-Sensitive Ion Channels (ASICs) in chemoafferent neurons in the petrosal ganglion. However we also display the effect of enhanced central respiratory-sympathetic coupling which also participated in the increase in sympathetic activity. The other mechanism introduced in this review is the role of the Nucleus Tractus Solitarius (NTS) after CIH exposure. Neurotransmitters like ET and Glutamate act on the cerebroventricle and the NTS elicit significantly increase of RSNA in CIH group. The sympathetic nerve originated site Rostral Ventrolateral Medulla (RVLM) also makes adaptive changes after CIH to copes the hypoxia stimulation and induces RSNA responses. At last we raise the phenomenon that depressed baroreflex sensitivity emerged after a long time CIH exposure and is involved in the process of sustained high blood pressure.

Keywords: Chronic intermittent hypoxia; Hypertension; Chemoreceptor-sensitivity; Sympathetic nerve activity

Introduction

Obstructive Sleep Apnoea (OSA), which was a common respiratory system disease, affects between 5% and 20% of the population with a high morbidity and mortality. Among all of these complications, hypertension has obtained more and more attention due to its complex mechanism which elucidating the procedure of increasing of artery pressure. A deal of laboratory focus on OSA—correlated hypertension used Chronic Intermittent Hypoxia (CIH) mimics the state of OSA, aimed at establishing integrity etiology of hyperpiesia consisting of central nervous system, vascular activity , neurotransmitter ,and other influential factors. Protocols of CIH were developed by Fletcher, who exposed adult rats to 30 days of CIH during their sleep period and found a sustained increase in mean arterial pressure [1]. Fletcher et al. demonstrated that CIH-induced sustained systemic hypertension was partly mediated by the sympathetic nervous system [2]. A study exposed healthy subjects between the ages of 20 and 34 yr to 28 days of CIH showing an increased muscular sympathetic nerve activity and forearm vascular resistance, indicating a relationship between increased blood pressure following prolonged exposure to CIH in healthy humans and sympathetic activation and augmented forearm blood flow [3].

Renal Sympathetic Nerve Activity (RSNA) and baroreflex or chemoreflex sympathetic activity pertaining to central nervous system lay on a critical position with regard to hypertension; nevertheless its exact contribution is still equivocal and is required further investigation. Previous studies emerged variant consequence of SNA and reflex-related SNA after CIH exposure, which alike or opposite. Therefore, we conclude all of these findings and observe their disparity, determine whether these diversities were based on variant species, experiment condition and other factors, compare different mechanisms in these studies. This will provide allround and intimate prehension for further research.

Resting RSNA after CIH Exposure

Exposure of rats to CIH increased arterial pressure combined with enhanced sympathetic nerve activity (SNA). Rats had higher SNA after exposure to CIH in anesthetic conditions compared with control rats (1.9 ± 0.2 vs. 0.9 ± 0.2 μV, $P<0.05$) [4]. Healthy humans subjects demonstrated an increase in mean muscle sympathetic nerve activity (MSNA) that was expressed as either burst frequency (bursts/min) or burst incidence (bursts/100 hb) after 4wk of intermittent cyclic hypoxia [9.94 ± 2.0 to 14.63 ± 1.5 bursts/min ($P<0.05$); 16.89 ± 3.2 to 26.97 ± 3.3 bursts/100 hb ($P=0.01$)] [3]. Study previously shown that sympathectomy chemically caused by 6-OH-dopamine prior to CIH restricted the increase in arterial pressure [5]. Bao et al. in another experiment observed similar results using renal sympathetic denervation [6]. Therefore, the integrity of the sympathetic nervous system to the kidneys was essential to the increase of arterial pressure in CIH rodents. Kumar et al. reported an enhanced secretion from adrenal medulla during hypoxia if only the rodents were prior exposure to CIH which indicating an augmented chemoreflex-sympathetic hypoxia sensitivity [7].

Guild et al. have pronounced another index of total sympathetic activity by administration of ganglionic blockade [8]. The fall in MAP in

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response to hexamethonium (a ganglionic blockade) after injection of losartan (AT1 receptor antagonist) was higher in CIH than in normoxic rats and the MAP was decreased to similar levels in both groups, despite the fact that losartan or hexamethonium alone produced no significant changes [9]. This indicated that the increase in baseline arterial pressure of CIH is maintenanced by an augmentation in sympathetic outflow to vascular beds.

The Sympathetic Nerve Response to Acute Hypoxia after CIH

Several lines of evidence concerning the involvement of the sympathetic nervous system in the sustained hypertension after exposure to CIH observed in adult rats were definitely certified. The responsiveness of the sympathetic nerve activity to a new acute episode of hypoxia after exposure to CIH also demand completely characterized. Exposed 3-weeks-old rats to CIH conditions presented a significant increase in tSNA (thoracic Sympathetic Nerve Activity), frequency of the PND and a greater bradycardic in response to new chemoreflex activation by potassium cyanide [10].

The Effect of Peripheral Chemoreflex on Sympathoexcitation after CIH

A potentiated sympathetic chemoreflex is a hallmark of exposure to CIH and has been attributed to enhanced responsiveness of carotid body afferents to the brain [11]. The increase of sympathetic nerve activity after CIH exposure was attenuated when the animals were prior undertook carotid sinus denervated [12]. Patients with OSA or exposure to CIH, all could exhibit tonic chemoreflex activation which may enhance sympathetic activity and then induced increase in blood pressure [13]. It was introduced that the effects of CIH on the CB are similar to that of ischemia-reperfusion response in other tissue, which is characterized to enhance superoxide anion production and oxidative stress, since administration of superoxide scavenger could completely abolish the effects of CIH on CB afferent activity [14].

The mechanisms that involved in the augmented sympathetic-chemoreflex hypoxic responses after CIH were complicated and referred to multiple modulators and pathways.

The Role of ET-1 on Carotid Body Chemoreceptor

Arterial chemoreceptors located in the aortic and CBs respond to hypoxemia and hypercapnia. CBs acted as a primarily component of chemoreflex response attracted greatest attention recently. Its potentiated chemosensory response to hypoxia was verified to contribute to the CIH-induced hypoxic ventilatory and cardiovascular responses [15]. ET was confirmed to be the merely clearly excitatory peptide modulator of CB function [16]. ET-1 through two types of heptahelicoidal G protein-coupled transmembrane receptors which were ET_A-R and ET_B-R [17].

Rey et al. [18] found a 10-fold increase of ET-1 immunoreactivity in the CB from CIH cats and administration of bosentan, ET receptor type A and B antagonists, significantly reduce the increased CB discharge and chemosensory responses to acute hypoxia [18]. The authors previously have confirmed that ET-1 immunoreactivity was found in blood vessels of the CB vascular pole, suggesting that ET-1 plays a relevant role in the regulation of the CB vascular tone [19]. Previously studies showing a relationship between ET-1 and CB oxygen-sensing process. *In situ* or vitro preparation, ET-1 generated a potent dose-dependent chemosensory excitation [20]. Some literatures found that ET-1 was bound with ^{125}I in blood vessels and chemoreceptor (glomus) cells in rat and cat CBs [21]. Using immunohistochemistry method, Chen et al. also found the presence of ET_A-R in rat glomus cells and interlobular vasculature and chronic sustained hypoxia increases ET-like immunoreactivity and ET_A-R expression in the rat CB, accompanied with an augmented rat CB chemosensory response to acute hypoxia in a time-dependent manner and ET_A-R antagonist BQ-123 reversed this change [22]. Western Blot analysis showed a significant increase in ET_B-R expression in CB after 4 days exposure to CIH, but with no differences in ET_A-R [23]. In this literature, the authors also used immunohistochemistry to determine that the ET_A-R and ET_B-R staining were found in both control and CIH-treated CBs while distributed differently. ET_A-R immunoreactivity was localized in the cytoplasm of TH-positive cells that the latter was a marker for glomus cells [24] but with no significance in both groups. However the ET_B-R was present a conspicuous increase in the glomus cells of the CIH-treated group. They did not detect any qualitative difference in staining intensity of ETA-R and ETB-R within the blood vessels when we compared CBs from control and CIH-treated cats. Double-positive staining for ET-1 and TH was abundant within the cell clusters located in the CB parenchyma and scarce in the peripheral zones close to the vascular pole indicating that cat glomus cells express ET peptides in normoxia and after CIH exposure [24]. It is known that ETB-R increases nitric oxide (NO) synthesis through endothelial NO synthase upregulation. NO is a tonic inhibitory modulator of CB chemoreception. Gardner et al. found that the ET_B-R agonist sarafotoxin 6c could dose-dependently inhibited high extracellular potassium- induced ATP release [25]. It is worth mentioning that ATP seems to be an excitatory neurotransmitter in the hypoxic response of the mammalian CB [26]. Therefore, ETB-R upregulation in the CIH-exposed CB may be a compensatory inhibitory mechanism by increasing the NO synthesis and counteracting the chemoexcitatory effect of ET-1 [23].

Carotid body type 1 chemoreceptive cells displayed inward Ca^{2+}-currents which induced an increase of $[Ca^{2+}]_i$. Whole-cell patch clamp investigation revealed that the Ca^{2+} inward currents were potentiated in the presence of ET in normoxic condition [27]. Hypoxia-induced increase of intracellular Ca^{2+} levels was augmented after superfusion of ET. The role of ET in the potentiated inward Ca^{2+} currents was concerned to patiticipate in the process of phosphorylation of protein like Ca^{2+}-channel protein. Type 1 O2-sensitive cells [18] depolarization after hypoxia and then enhance Ca^{2+}-currents which leading to an increase of intracellular Ca^{2+}, however this step was thought to be prior to the phosphorylation of Ca^{2+}-channel protein. Therefore, in this study, superfusion of ET alone without hypoxia stimulation was not able to induce any changes in the intracelluar Ca^{2+} levels, nor basal carotid sinus nerve activity. Nevertheless, perfusion CB preparation with ET produced long-lasting dose-dependent increase in Carotid Sinus Nerve (CSN) in normoxic and hypoxic conditions [28]. With this in mind, ET may participate the increase of inward Ca^{2+} currents posterior to the stimulation of hypoxia and the effect of ET-related chemosensory responses were dependent the presence of vascular control.

In addition to the contribution of ET on inward Ca^{2+} currents, inflammation that related to ET and ET receptors may also associated with carotid body chemoafferent neuron adaptation process. Previous studies have demonstrated elevated levels of ET-A receptors in resident and invasive CD45+ immune cells distributed in tissue surrounding carotid body chemosensory cell lobules after Chronic Hypoxia (CH) exposure and bosentan, a nonselective ET-A/B receptor antagonist, could blocked the invasion of immune cells and attenuated the upregulation of proinflammatory cytokines consisting of interleukin-1β (IL-1β), interleukin-6 (IL-6), tumor necrosis factor α (TNFα),

and monocyte chemoattractant protein-1 (MCP-1) [29]. However, Rio shown that CIH-releated potentiation of the CB chemosensory and ventilatory responses to hypoxia and the hypertension were attributed critically to the oxidative stress whereas TNFα and IL-1β were responsible for the cardio-ventilatory alterations [30]. Reactive Oxygen Species (ROS) were the production of oxidative stress and reports have suggested that ET-1 generated ROS by activating NADPH oxidase [31]. Nevertheless, whether ET-induced generation of ROS could contribute to the enhanced Hypoxic Sensory Response (HSR) in Intermittent Hypoxia (IH) group needs further investigation. What have been confirmed was the fact that ROS play a critical role in IH-induced augmentation of HSR and an increase of basal ET-1 release and upregulation of ETA receptor mRNA in the carotid body which may via ROS-dependent Ca2+ signaling pathways [32].

CIH upregulated the expression of Acid-Sensitive Ion Channels (ASICs) in chemoafferent neurons in the petrosal ganglion [29], which was a new discovered cation channels that related to $[Ca^{2+}]_i$ in central and peripheral neuronal system [33]. The author also showed that treatment with bosentan blocked the ASICs overexpression, which indicated a possible pathway that was ET involved in the responses to hypoxia conditions [29].

Peng et al. [34] at have shown a long time facilitation of sensory nerve discharge (sLTF) of the carotid body in rodents exposed to CIH [34], which seemed to be responsible for the elevation of RSNA and hypertension after CIH exposure [35]. The mechanisms that interpreted the change of the CB sensory nerve discharge were complicated; however upregulation of ET in the CIH carotid body was not contributed to sLTF despite its effect on augmented hypoxic sensitivity [36]. Previous studies have confirmed that the sLTF was mediated by Angiotensin II [37] or 5-HT [38] via the common NADPH oxidase-generated ROS system.

The Role of Respiration in the Sympathetic Over Activity after CIH

Daniel B Zoccal et al. [39] observed a significantly increase of tSNA in late expiration period in CIH rats compared with normoxic rats [39], and the increase of tSNA was in accordance with an increase of Abdominal Nerve Activity (AbN) at late expiration (late-E) whereas a decrease of cervical nerve and AbN at post-inspiration period. The increasing response of tSNA during inspiration was similar both in CIH and normoxia animals.

Similar respiration response after CIH was also demonstrated in several studies such as enhanced long-term facilitation of respiratory motor activity [40] and an augmented ventilatory response to hypoxia which indicating changes in brainstem respiratory network function after CIH . As we know, cardiovascular sympathetic activity is predominantly regulated through central respiratory activity [41]. Some scholars have discovered that brainstem, where containing neurons involving respiratory-sympathetic coupling and generating respiratory rhythm, related sympathetic nerve activity lasting despite the absence of vagus nerve [42]. A lot of scholars introduced that sympathetic nerve activity emerged accompanied with respiratory cycle [39].

These findings lend credence to the possibility that there present a relationship between sympathetic nerve activity and respiratory action and any stimulation like hypoxia change respiratory rhythm and then alter SNA. As we know, the respiratory response was mainly regulated by chemoreflex that contains peripheral and central components. The cardiorespiratory systems, and their coupling, exhibit an amazing degree of adaptation under physiological e.g. exercise [43], deconditioning [44], and pathophysiological e.g. heart failure [45] conditions. Herein, any alteration in respiratory activity may lead to sympathetic outflow change.

When any chemical stimulation acts on peripheral chemoreceptor, such as hypoxic condition, glomus cells in the CB depolarize and release multiple putative neurotransmitters, including acetylcholine, serotonin, ATP, substance P and so on [46], then the afferent information along the carotid body sinus nerve is sent to brainstem firstly integration station, the Nucleus Tractus Solitarius (NTS) [47], activating primary neurons and then the secondary, reaching to other regulating areas such as the RVLM [48], in which containing sympathetic vascular-activated and cardio-sympathetic neurons, inducing contraction in the skin, the kidney, and other vessels but relaxation in important tubes to assure heart and brain possess sufficient blood flow. In this scenario, sympathetic nerve may present overactivity resulting from increased chemoreceptor sensitivity.

Central Respiratory-sympathetic Couples Involved In the Sympathoexcitation

Central coupling of respiratory and sympathetic neurons may occur at the level of the ventrolateral medulla, where many of the neurons involved in the generation of respiratory and sympathetic activities are located on these domains [49]. Specifically in this region, the inspiratory and expiratory neurons of the Ventral Respiratory Column (VRC) interact with the presympathetic neurons in the RVLM as well as with inhibitory interneurons in the Caudal Ventrolateral Medulla (CVLM) [49]. Sun et al. showing that in sight of anatomical degree, expiratory neurons of ventral respiratory column, which originates from BötC, were projected closely opposed to pre-sympathetic neurons of RVLM along its axon [50]. The pons was also shown to play a significant role in the respiratory modulation of sympathetic nerve activity, since pontine transection conspicuously attenuated this accommodation [51]. In addition, the activities of many medullary and pontine neurons involved in sympathorespiratory functions are modulated by central chemoreceptors located in the RTN/pFRG [52]. RTN/pFRG appears to be an important source of excitation to bulbospinal expiratory neurons located in caudal ventral respiratory column that relay excitatory drive to the lumbar abdominal motoneurons that drive late-E bursting in the AbN and also to presympathetic RVLM neurons, culminating result in an increase of sympathetic activity correlated with late-E bursts in abdominal motor activity [53]. In a latest study, Moraes et al. [54] shown that the respiratory-modulated RVLM presympathetic neurons may contribute to the increased sympathetic outflow in CIH rats, which mechanisms involve enhanced respiratory synaptic inputs, probably from expiratory neurons.

With respect to the relationship between respiratory action and sympathetic nerve activity, Simms et al. documented that sympathetic overactivity which results from enhanced respiratory-sympatheic coupling was observed in spontaneously hypertensive rats [55]. Central chemoreceptors may be sensitized after CIH exposure and contribute to the development of active expiratory pattern as well as an augmented sympathetic activity observed in CIH rats in normoxic/normocapnic conditions [56]. The same authors in this literature also showing that CIH-evoked increase in the neuronal excitability or CO2 sensitivity results in a lowering of the CO2 threshold for generation of late-E activity within the RTN/pFRG.

Peripheral-central chemoreceptor interaction may be involved in the development of plastic changes in the excitability of central chemoreceptors after CIH conditioning via activation of

neuromodulators that enhance the activity of RTN chemosensitive neurons, such as serotonin [57], ATP [58], or locally produced oxidative stress [59].

Silva et al. [60] at 2011 have documented that in addition to chemoreflex, other reflexes such as nasopharyngeal and somatosympathetic reflexes also promotes augmented sympathoexcitatory responses after exposured to CIH conditions [60]. These data indicating that CIH-induced lasting central nervous system changes utilized similar pathways among these reflexes. Maybe these reflexes terminated at RVLM level by activation of glutamatergic neurons, since microinjection of glutamate directly activated RVLM and then evoked exaggerated increases in SNA in rats exposed to CIH [61].

The Changes of Transmitters on Cerebral Nuclei

L-glutamate is suggested be the neurotransmitter that released by these viscerosensory primarily afferents in the NTS including those related to cardiovascular baroreceptor and chemoreceptor afferents [62]. Costa et al. [63] manifested the fact that respiratory-sympathetic coupling were mediated by glutamatergic inputs in the caudal and intermediate NTS which were activated by chemoreflex [63]. Microinjection L-glutamate into the commissural nucleus tractus solitarius (cNTS) induced thoracic sympathetic nerve (tSN) and central vagus nerve (cVN) activities increase and phrenic nerve (PN) activity decrease, with the changes higher in control than in CIH group [64]. When administrating KYN (a glutamatergic receptor antagonism), the reversing responses compared with L-glutamate were encountered the same tendency in both groups. At the same time, KYN induced decrease in sympathoexcitatory response to peripheral chemoreflex activation in control group but not in CIH group. With the Western blot analysis showing a significant increase of NMDAR-1 and glutamate receptor 2/3receptor in cNTS, the author conjecture that CIH inducing sympathetic and respiratory coupling changes partly resulted from the increased glutamatergic transmission in this position.

Huang et al. [65] demonstrated that CIH significantly increase renal sympathetic nerve response to intracerebroventricular injection of ET-1 and associated with a higher expression of ETA protein in the subfornical organs [65]. However, whether these changes directly contributed to the sympathic-overactivity after CIH was needed further investigation.

CIH in rats promotes increased expression of c-fos, a marker of neuronal activation, in several brainstem regions that are critical for normal regulation of SNA, such as the nucleus of the solitary tract and the ventrolateral medulla [66].

The Role of Baroreflex on the CIH-related Sympathoexcitation

In addition to peripheral chemoreflex, other reflex that may ultimately influence sympathetic activity involving arterial baroreflex, cardiopulmonary reflex, metaboreflex and so on, coordinated with its central system, produced accommodative changes during CIH regimen. Baroreflex as a complex regulatory mechanism exhibited unequal responses after CIH exposure.

Zoccal et al. [67] utilized the sigmoidal analysis found that juvenile rats submitted to CIH for 10 days exhibited an increased cardiac baroreflex gain [67]. With respect to human patients with obstructive sleep apnea, depressed baroreflex sensitivity was confirmed [68]. A recent study exposed adult rats to CIH conditions 7 days showing that baroreflex control of RSNA was not attenuated while ABP was increased [69]. Another considerable discovery focused on CIH for 7 days shifts the baroreflex stimulus-response curves of SNA rightward with the midpoint pressure increased 10mmHg, which was in similar magnitude to the increase in resting MAP. These differences were formed possible due to the strain, the use of anesthesia, and the time that exposure to CIH conditions. However what confirmed was that 7 even 10 days of CIH induced increased in ABP was not secondary to reductions in the baroreflex sensitivity and there was a time lag between the development of hypertention and the impairment of baroreflex. Lin et al. demonstrated that after ninety days of CIH, baroreflex-heart response were attenuated, yet heart rate response to cervical vagus nerve electrical stimulus was increased, indicating that the efferent component did not contribute to the impaired baroreflex-heart response [70]. These results indicate a possibility that the baroreflex control of SNA may be reduced after a long term exposure of CIH [71]. Taken together, mechanisms participate in onsetting of hypertention during frontal days of CIH and the long term sustained increase in ABP induced by CIH were different.

The Role of NTS and RVLM in CIH Condition

As previously proposed, the NTS, RVLM and other cerebral organ make adaptive changes and lead to sympathetic-related response ultimately after CIH.

The afferents of baroreceptor and chemoreceptor integration were terminated at the medial and medial or commissural site of central nervous system. Other previously studies have demonstrated that lesions or inhibition of commissural subnuclei of the nucleus tractus solitarii in the medulla, where CB chemoreceptors project, reduce blood pressure in spontaneously hypertensive rats [72].

The NTS sends reciprocal projections to several nuclei within the forebrain, brainstem and spinal cord. Prominent areas for innervation include the paraventricular nucleus of hypothalamus, rostral and caudal ventrolateral medulla, and raphé. It is the coordinated activity of the NTS with these other central nuclei that modulates the cardiorespiratory system during hypoxic stress [73].

Kline et al. [74] used caudal NTS cells in the vitro brainstem preparation showing that CIH augments chemosensory afferent fiber activity, which then contributes to the increased overall activity in NTS cells and the central processing of afferent information accompanied with its associated reflexes [74]. And these enhanced responses were time-dependent and reversible.

RVLM neurons are critical for the maintenance of resting arterial pressure and are important to the sympathoexcitatory response of the chemoreflex. Anatomical and imunohistochemical studies have suggested the existence of a direct excitatory projection from the NTS to the RVLM [75], which may convey peripheral chemoreceptor signals. When peripheral chemoreceptors are stimulated, the RVLM neurons project to the intermediolateral cell column in the spinal cord. Moraes used electrophysiological technique demonstrated that a specific subpopulation of non-cathecholaminergic C1 respiratory-modulated RVLM presympathetic neurons presented enhanced excitatory synaptic inputs from the respiratory network after CIH which may contribute to the increased sympathetic activity observed in CIH rats [54]. Further study will be necessary to delineate the basis and cellular mechanisms of changes to RVLM neurones induced by exposure to CIH.

Several studies in the literature previously support the concept that in the first weeks of life, CIH is more effective in producing changes in the central nervous system. Ling et al. showed that the long-term facilitation of ventilatory responses is greater in 1-month-old rats than

in 2-month-old rats [76]. And the initial 4 weeks of life are important for the maturation of the carotid body and chemoreflex responses, since previously exposure to hyperoxia throughout the period of 1-4 weeks of age result in an attenuation of the ventilatory and phrenic responses to acute hypoxia [77]. Reeves et al. demonstrated that exposure to CIH during the first 30 days of life exhibited a decrease in the number of neurons that receiving vagal and glossopharyngeal projections in the NTS and nucleus ambiguus in accompany with an augmentation in the number of neurones receiving projections in the RVLM [78]. These crucial anatomical lines of proof underline the concept that alterations within selected brainstem nuclei may develop after CIH and early postnatal environmental exposures, including CIH, may lead to long-term alterations in cardiorespiratory control [11].

Above all, what definitely is that CIH-induced hypertension is associated with sympathetic nerve system overactivity, and the latter is regulated by several different ways which include peripheral chemoreflex, baroreflex, central system and other regulatory factors like ET-1 and glutamate, notwithstanding these analyses are insufficient to underlie the whole mechanisms that behind the process of CIH-related sympathetic nerve changes. The increased of peripheral chemoreflex sensitivity result in central respiratory activity changes which is characterized by enhanced expiratory response in late expiratory period and increased sympathetic nerve activity during the same period. These changes are adaptive to the hypoxia. With respect to baroreflex, we suppose that long time CIH may impair its sensitivity whereas several days of exposure exhibit diverse response.

Our laboratory is mainly focus on the role of ET-1 in hypertension after CIH exposure. In addition to it directly effect on vessel and smooth muscle cell, ET-1 is also involved in oxidize stress response at carotid body or brain. Though the precisely effect of ET-1 on central system that influence sympathetic nerve activity is not absolutely determined, its pressor effect in brain organs is supposed to similar to angiotensin.

CIH-induced sympathetic nerve system changes are diverse with allround mechanisms, attracting a great deal of attention among scholars. The intimate regulatory mechanisms of sympathetic alteration and how these principles interact with each other need further investigation.

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