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Update on Chemoreception: Influence On Cardiorespiratory Regulation And Patho-Physiology

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INTRODUCTION

The past decade has provided major advances in our understanding of chemoreception—its basic mechanisms of transduction, its role in cardiorespiratory regulation in wakefulness, sleep, and exercise and its contributions to the “sensory hyper-reflexia” and aberrant afferent tonic¹ known to exist in such chronic diseases as hypertension, heart failure, COPD and sleep apnea. Our brief essay updates these topics with emphasis on key feedback influences on cardiorespiratory control emanating from carotid and medullary chemoreceptors and their interdependence, as well as from group III – IV metabo- and mechano-receptors in skeletal muscle.

PERIPHERAL/CENTRAL CHEMORECEPTION

Peripheral Chemoreception

The location and function of two distinct sets of chemoreceptors have been identified that play key roles in regulating both ventilation and sympathetic nerve activity. The primary oxygen sensors, the carotid body (CB) chemoreceptors, have the primary function of sensing PO₂, CO₂/H⁺ in arterial blood. They are polymodal receptors which also sense a number of factors including but not limited to K⁺, temperature, osmolarity, glucose, and insulin². Hypoxia is thought to be transduced by CO-modulated production of H₂S which in turn promotes Ca₂⁺ release via mitochondrial and membrane pathways resulting in neurotransmitter release and increased neural activity in the carotid sinus nerve which is then transmitted to the central nervous system via the nucleus tractus solitarius (NTS) (see Fig. 1). Transduction of CO₂/H⁺ at the carotid chemoreceptor occurs via a fall in glomus

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cell intracellular pH which inhibits K⁺ channels leading to membrane depolarization and a voltage gated increase in intracellular [Ca²⁺] which triggers neurotransmitter release and increased neural activity in the carotid sinus nerve³. The carotid sinus nerve and ventilatory and sympathetic responses to hypoxia/hypercapnic combinations (i.e., asphyxia) is powerful and hyperadditive—with the site of this hyperaddition occurring almost exclusively at the level of the carotid chemoreceptor⁴. The carotid chemoreceptor response to hypoxia, per se, is curvilinear with respect to a falling PaO₂ and—owing to the HbO₂ dissociation curve sigmoid shape—fairly linear with respect to arterial HbO₂ percent saturation.

The ventilatory response to carotid chemoreceptor CO₂—in the absence of concomitant changes in PaO₂—appears to be relatively sluggish (vs. PaO₂), as best demonstrated in awake goats and awake or sleeping dogs using extracorporeal perfusion of the isolated carotid chemoreceptor. In these animals the raising of the isolated carotid chemoreceptor PCO₂ more than 15 – 20mmHg above eupneic air breathing levels was required to elicit a significant hyperventilatory response^{5,6}. The hypoventilatory response to hypocapnic blood delivered to the isolated carotid chemoreceptor was more sensitive, requiring reductions in P_{CB} CO₂ of 10-15mmHg below normal eupneic levels⁷. Similarly, the sympathetic nervous system responds more sensitively to hypoxemia than to carotid body hypercapnia.

Central Chemoreception

Sufficient evidence now exists to support the medullary retrotrapezoid nucleus (RTN) as the primary and most sensitive site of “central” chemoreception of CO₂/H⁺ in its environment of the brain extracellular fluid. Several unique features distinguish the RTN from the surrounding glia and remainder of the lower brain stem respiratory network including glutaminergic neurons characterized by expression of Phox2b and NK1 receptors⁸. Recent findings have shown that in contrast to the highly sensitive vascular reactivity of most of the cerebral vasculature to hypercapnic-induced vasodilation and hypocapnic-induced vasoconstriction, the RTN vasculature appears to be non-responsive to changes in PCO₂ in its local environment⁹. Given that the vascular reactivity is intended to minimize changes in brain ECF CO₂/H⁺ for any given change in arterial PCO₂¹⁰, this lack of RTN CO₂ vasoreactivity means that RTN H⁺ homeostasis would be sacrificed while preserving a hypersensitive RTN chemoresponsiveness.

Central nervous system (CNS) Hypoxia

Contrary to what has been commonly assumed from the results of studies in anesthetized animals, in the unanesthetized state CNS hypoxia is stimulatory—rather than inhibitory—to ventilatory drive and sympathetic nerve activity. This stimulatory effect of CNS hypoxia is not always evident following carotid body denervation but is consistent in awake or sleeping animals when selective CNS hypoxia is produced (via inhalation of hypoxic concentrations) simultaneous with preserving tonic input from the isolated carotid chemoreceptor perfused with normoxic normocapnic blood (see Fig. 2)^{11,12}. The CNS hypoxic ventilatory response is dose-dependent and about one-third the magnitude of that obtained when both carotid body and CNS are exposed to hypoxia as in the intact animal. This ventilatory response is entirely driven by an increase in breathing frequency as opposed to increases in both tidal

volume and frequency in the intact animal. Hyperventilation with CNS hypoxia first appears within 15-20 seconds following the onset of alveolar hypoxia, i.e., in close proximity to the response time in the intact animal. CNS hypoxia, per se, also elicits a sympatho-excitatory response, although this response required quite severe levels of hypoxia—at least in the anesthetized animal¹³.

Although some medullary respiratory neurons have been shown to be directly stimulated via hypoxia in their immediate environment, recent evidence suggests a “non-neural” mechanism¹⁴. First, brain astrocytes are capable of sensing even small reductions in PO₂ via inhibition of mitochondrial respiration and subsequent release of ATP in close proximity to the brain stem respiratory network. Secondly, given that specific CNS hyperoxia – with maintained tonic input from the isolated carotid body or following carotid body resection (CBX) – also stimulates ventilation, then increased reactive oxygen species are also likely to be a significant mechanism in this signaling cascade¹⁵ (see Fig. 2). Thus, while carotid chemoreceptor tonic input appears to be required for a stimulatory response to CNS hypoxia, in the intact hypoxic animal both the carotid body (primarily) and the CNS (to a lesser extent) would be expected to contribute to the total cardiorespiratory response.

HYPERADDITIVE INTERDEPENDENCE IN THE EXPANDED CHEMORECEPTOR PATHWAY

Phox2b, a key gene product proliferating in early embryonic development of the autonomic nervous system, is strongly expressed in neurons which are part of an uninterrupted chain in a circuit which includes the carotid body and their afferents as well as the NTS projection to the RTN. Carotid chemoreceptor input also has a direct pathway from NTS to the central respiratory pattern generator (CPG) and even higher to the paraventricular nucleus (PVN) in the hypothalamus⁸ (see Fig. 1). As outlined below, this entire “expanded” interdependent chemoreceptor pathway comes into play to explain the ventilatory and sympathetic vasomotor responses when carotid bodies are stimulated or inhibited via changes in arterial PO₂ or CO₂...or even when “tonic” carotid chemoreceptor activity is withdrawn under normoxic conditions during eupneic air breathing.

Figure 3 in the awake canine reveals the importance of these interdependencies throughout the chemoreceptor pathway and especially the influence of carotid chemoreceptor input on “central” CO₂ chemosensitivity. Note in Figure 3:A that with CB inhibition achieved via perfusion of the isolated CB with hyperoxic hypocapnic blood, eupneic air-breathing ventilation falls immediately and reaches a nadir of about 60% below control after about 30 seconds of exposure on average. Beyond 30 seconds of continued carotid body inhibition, $\dot{V}/E$ rises to about 35% below control and remains at this level for 25+ minutes despite the substantial sustained systemic and CNS hypercapnic acidosis. That carotid body inhibition was markedly suppressing the central CO₂ chemosensitivity is further evidenced in the 30% ventilatory overshoot apparent immediately upon termination of the carotid body hyperoxic hypocapnia¹⁶. This critical dependence of carotid body input on responses to central CO₂ accumulation was also shown via the hyperadditive effects of CB stimulation/inhibition on the ventilatory response slope to “central” CO₂, as illustrated in the awake canine with

extracorporeal perfusion of the carotid chemoreceptor. These hyperadditive effects occurred whether carotid body excitation/inhibition was accomplished via changes in oxygen, CO₂, or their combination⁶. These hyperadditive influences are also consistent with the effects of bilateral carotid body denervation in several species—including humans^{17,18}—which resulted in a 40-70% reduction in the steady-state ventilatory response to hyperoxic hypercapnia (see Fig. 3:B) and in a reduced response to focal cerebral acidosis¹⁹.

Guyenet et al.^{20,21} questioned whether the marked hypoventilation/CO₂ retention accompanying CBX could be interpreted to mean that carotid body afferents contribute significantly to the drive to breathe under control (normoxic) conditions. These authors critiqued use of the CBX approach to this question by raising the possibility that the surgical deafferentation procedure—with accompanying potential collateral damage to baroreceptors and sympathetic innervation, along with inflammation and synaptic rearrangement—was *not* equivalent to merely silencing the CBs. To the contrary we argue that CB inhibition using the isolated perfused chemoreceptor preparation (see Figure 3:A) provides clear evidence that carotid chemoreceptors do indeed provide a substantial tonic input to the eupneic drive to breathe. This effect is likely due to the silencing of direct afferent input to the CPG as well as to a marked diminution in central CO₂ chemosensitivity achieved via inhibition of the CB afferent input.

The chemoreceptor pathway involves integrative regulation of cardiorespiratory control extending from the carotid chemoreceptor to the hypothalamus.

The carotid chemoreceptor exerts a marked tonic input on the normal, eupneic drive to breathe even in health through its “direct” effect on the medullary respiratory pattern generator plus its significant hyperadditive influence on the central chemoreceptor sensitivity to CO₂.

This interdependence of chemoreceptor function also means that the common practice of assessing “central” chemosensitivity, *per se*, in intact humans and animals via the use of hyperoxic/hypercapnic inhalation is not justified.

To what extent tonic CB input in normoxia also influences sympathetic nerve activity is less clear. For example, transient inhibition of CBs in the healthy dog (using close carotid body injection of dopamine or hyperoxic saline) or in healthy humans with transient hyperoxia has no discernable effect on limb vascular conductance or on MSNA at rest, but does cause significant MSNA inhibition and enhanced limb vascular conductance and blood flow during even mild intensity exercise^{22,23}. These sympathetic vasomotor responses were prevented via sympathetic blockade in the canine²³. In many disease states (see below) excessive chemosensitivity is manifested in chronically elevated sympathetic vasomotor activity.

Is the Rodent Model Exceptional/Appropriate?

Like other species, the rodent expresses a substantial and sustained hypoventilation and CO₂ retention following carotid body denervation, but unlike other mammals shows no reduction in the slope of the ventilatory response to CO₂²⁴⁻²⁶. We have no explanation for this puzzling dissociation between the marked effects of CBX on eupneic air breathing ventilation and

CO₂ retention in the absence of coincident changes in (superimposed) CO₂ sensitivity... other than they suggest an absence of any hyperadditive effects of carotid body input on the “central” CO₂ response sensitivity in this species. Despite these puzzling species differences the anesthetized rodent does show a significant effect of systemic hypoxemia on the activity of CO₂ sensitive RTN neurons which is prevented via CBX²⁶ i.e., a CB – RTN functional link does exist. Further, the rodent has provided all of the evidence thus far supporting CO₂ sensitive neurons in the RTN as an integrative site in the medulla whose output and cardiorespiratory effects are influenced by inputs from the vagally-mediated stretch receptors from the lung as well as from locomotor areas of the hypothalamus⁸ (Fig. 1). Finally, recent studies in the awake rodent showed that obliteration of almost all neurons in the RTN will cause acute alveolar hypoventilation and CO₂ retention, similar to that achieved via CBX, but the alveolar hypoventilation was caused by an increase in breathing frequency and dead space ventilation with a reduced VT and no change in overall ventilation ($\dot{V}_E$)²⁰. Given the almost exclusive use of the rodent currently for mechanistic studies of chemoreceptor-driven cardiorespiratory regulation, these differences between species limit generalization of findings. Similar concerns in assessing chemoreceptor characteristics in the rodent and other small mammals stem from the marked reductions in their metabolic rate elicited upon acute exposure to hypoxia^[1]. Since CO₂ production (and/or pulmonary exchange of CO₂) is an important drive to breathe it must always be measured and accounted for in quantifying hypoxic cardio-respiratory responsiveness²⁸.

The rodent is the mammal currently used almost exclusively for the study of mechanisms underlying chemoreception in health and disease. However, there are several fundamental differences between rodents and larger mammals in such factors as chemoreceptor interdependence and metabolic plasticity that need clarification before generalizations from rodents to humans are accepted.

HYPERSENSITIZATION OF CHEMORECEPTION/MUSCLE AFFERENT FEEDBACK EFFECTS ON BREATHING AND SYMPATHETIC NERVE ACTIVITY

Substantial evidence now exists to support a susceptibility to sensitization of such key autonomic afferent regulators as chemoreception and metabo- and mechanoreceptor muscle afferents. For chemoreceptors, variations in the amount and “pattern” of O₂ supply are critical regulators of chemosensitivity as shown in the following examples:

- Upon exposure to even moderate levels of constant hypoxia, carotid chemoreceptors begin to increase sensitivity within a few hours and continue to increase for several days eliciting time-dependent hyperventilation, increased MSNA, and systemic hypertension—all of which persist for some days upon return to normoxic environments following cessation of hypoxia. These time

¹Hypoxic stimulation of arterial chemoreceptor afferents coincides with a reduction in sympathetic outflow to brown adipose tissue which, in turn inhibits non-shivering thermogenesis, thereby contributing to hypoxia-induced reductions in body temperature and metabolic rate²⁷.

dependent ventilatory changes occur even in the presence of a persistent hypocapnia and alkalosis. Proliferation of type 1, hypoxic-sensing glomus cells in the CB begins to appear early in the hypoxic exposure²⁹.

- The intermittent hypoxemia (IH) attending sleep apnea is especially sensitizing to the entire chemoreceptor pathway as the pro-oxidant transcriptional regulator HIF1 (HIF-1 α) is fully expressed without the accompanying upregulation of the opposing anti-oxidant HIF-2 α ³⁰ (see Fig. 4). This results in sustained oxidative stress and pro-inflammatory molecules distributed to neuronal structures throughout the chemoreceptor pathway and to the systemic resistance vessels. The very fast reoxygenation phase following each apnea in the obstructive sleep apnea (OSA) patient is a key element in the deleterious widespread, excessive inflammatory response triggered by IH³¹.
- CHF in animal models and humans is characterized by increased chemosensitivity with accompanying autonomic imbalance in the form of increased SNA, renal vasoconstriction, cardiac arrhythmias, and unstable breathing. The enhanced chemosensitivity usually occurs in the absence of arterial hypoxemia. Rather, it has been attributed to a reduced carotid body blood flow leading to a reduced expression of a sheer-stress-induced mechano-sensitive transcription of target genes which in turn determine NO availability, and anti-oxidant defenses in the CB³².
- Carotid bodies are sensitized and tonically active in the spontaneously hypertensive rat accounting for excessive levels of renal SNA and high vascular resistance. The precise source of CB sensitization in this hypertensive model has not been completely elucidated—although reduced carotid body flow and sheer stress could occur via excessive sympathetic vasoconstriction of the carotid body vasculature¹. Increased renal afferent activity has also been identified as another source of excessive SNA in chronic hypertension.
- A coupling of high central respiratory drive to sympathetic output has been shown in reduced rodent preparations and suggested as an important source for excessive SNA in chronic hypertension³³. Whether this link is an important source of excessive SNA in intact humans is confounded by the following evidence: a) MSNA is *inhibited* during most of inspiration and the onset of inhibition during inspiration is dependent upon the absolute level of lung inflation and in part mediated by lung afferents³⁴; b) changing central respiratory motor output, per se, (either increased via voluntary efforts or reduced via mechanical ventilation) was without significant effect on MSNA³⁵ (see Fig. 5); and c) steady state—as opposed to within breath—MSNA levels are not influenced by substantial voluntary increases or decreases in breathing frequency, tidal volume, and $\dot{V}_E$ ^{36,37}. Guyenet has emphasized the importance of chemoreceptor mediated “direct” activation of pre-sympathetic medullary neurons that operate via a pathway from the NTS independently of the CPG²¹.
- Thinly myelinated and unmyelinated skeletal muscle afferents are also highly sensitized in animal models of CHF and hypertension, leading to excessive

sympatho-excitation and vasoconstriction and exaggerated pressor and ventilatory responses to exercise^{38,39} (also see below).

Hypersensitization of carotid chemoreception occurs via exposure to hypoxia and especially to intermittent hypoxemia with its rapid restoration to normoxia attending cyclical sleep apneas...and also to the reduced CB blood flow and sheer stress attending CHF and chronic hypertension.

This hypersensitivity is manifested as chronically high levels of sympathetic vasomotor activity as well as breathing instability and periodic breathing.

VENTILATORY VS. SYMPATHETIC REGULATION VIA CHEMOSENSITIZATION

Although chemoreceptor activation certainly stimulates both phrenic nerve activity and ventilation as well as SNA with accompanying vasoconstriction, there are important instances where chemoreceptor stimulation might elicit quite different outcomes. For example, following several minutes of intermittent hypoxemia or intermittent asphyxia in humans SNA stays elevated for up to two hours or more upon return to room air, whereas ventilation returns immediately to control values⁴⁰. It has also been suggested that the carotid chemoreceptor sensitization accompanying CIH or CHF is sufficient to increase SNA and its cardiovascular sequelae in the resting air-breathing state but has little effect on ventilation. Apparently this dichotomy may occur because the baroreflex countervailing influence on SNA is reduced with increasing chemoreceptor activity and therefore will not oppose the increased SNA, whereas the RTN countervailing influence on ventilatory control will be “silenced” by the cerebral alkalosis accompanying carotid chemoreceptor stimulation⁴¹. However, not to be overlooked is the substantial evidence that chemosensitization in chronic states has significant effects on ventilatory control. Consider in CHF the periodic breathing during wakefulness and sleep, the failure of $\dot{V}_E$ to decrease and PaCO_2 to increase upon transition from rest to sleep thereby sensitizing the hypocapnic-induced apneic threshold⁴² and the tachypneic hyperventilatory response to even mild intensity exercise in CHF⁴³. Even the supposed silencing of the RTN CO_2 sensitive neurons with CB stimulation⁴¹ must derive from some significant degree of respiratory alkalosis and in turn this must stem from hyperventilation-induced hypocapnia, even of a mild degree. Further, in the face of marked carotid chemoreceptor stimulation and systemic alkalosis the central chemoreceptors remain highly sensitive to small changes in the CO_2 in their environment⁶.

ROLE OF HYPERSENSITIZED CHEMORECEPTOR AND MUSCLE AFFERENTS IN CYCLICAL SLEEP APNEA PATHOGENESIS, DYSPNEA AND HYPERTENSION

Obstructive Sleep Apnea

A case has been made for an important role for instability of central motor output in cyclical sleep apnea—both central and obstructive sleep apnea^{44,45}. The link of central instability to obstructive apnea occurs at the nadir of the oscillatory central drive to breathe in patients with a collapsible upper airway⁴⁴. In turn the causes of ventilatory under- and overshoot with central respiratory instability are deeply rooted in the excessive chemosensitivity underlying increases in “loop gain”—see Figure 6⁴⁶. In brief, sleep unmasks a critical dependence of ventilatory control on CO₂ and in particular an apneic threshold which occurs just a few mmHg PaCO₂ below eupnea. Carotid body denervation studies in rats and dogs show that carotid chemoreceptors are required for apneas to occur following a brief ventilatory overshoot—but use of the isolated carotid chemoreceptor perfusion preparation in sleeping dogs shows that transient hypocapnia at *both* the level of the carotid chemoreceptor as well as the level of the medullary chemoreceptors is required to cause apnea—again demonstrating the functional importance of peripheral central chemoreceptor interdependence^{44,47}. In addition, use of a sleeping canine preparation with reversible vagal blockade showed that vagal inhibitory feedback influences via lung stretch during the ventilatory overshoot phase were also important contributors to subsequent apneas⁴⁸. Another key element underlying repeated ventilatory overshoots and undershoots is the patient’s arousal threshold in response to chemoreceptor driven sensory input during an apnea⁴⁵. Transient arousals will augment the accompanying transient ventilatory overshoot at apnea termination, thereby enhancing the hypocapnia and tidal volume achieved before returning to sleep and perpetuating repeated apneas.

Congestive Heart Failure

Many CHF patients present a “perfect storm” for high loop gain and periodic breathing in sleep as their high chemosensitivity sensitizes both their ventilatory overshoot and apneic threshold (see Figure 6). In addition, their high pulmonary vascular pressures also lead to sensitization of the apneic threshold and the high drive to breathe emanating from both chemoreceptor and pulmonary vascular receptor stimulation constrains the hypoventilation normally accompanying sleep onset and reduces the CO₂ “reserve,” i.e., the differences in PaCO₂ between eupnea and the apneic threshold⁴². Further, the blunted CO₂ cerebrovascular responsiveness commonly accompanying CHF means that cerebral ECF PCO₂ is less well “protected” from accompanying changes in arterial PCO₂—again leading to a reduced CO₂ reserve and sensitized apneic threshold. Finally, the prolonged circulation time means longer apneas and cycle times and more blood gas disturbances accompanying each apnea, thereby exacerbating the ventilatory overshoot.

Periodic breathing with cyclical central apneas occur primarily because of increased “loop gain,” wherein transient perturbations in breathing result in exaggerated hyper- and/or hypo-ventilatory responses and continued instability. Chemosensitivity is a major

source of loop gain and is one of several key contributors to the periodic breathing of heart failure. Cyclical obstructive sleep apneas are often dependent on the presence of both a collapsible airway, excessive chemosensitivity, and a sensitized arousal threshold, leading to sustained oscillations in central respiratory motor output, with obstructions occurring at the nadir of the central motor drive.

Muscle Afferents

Hypersensitized muscle metaboreceptor/mechanoreceptor afferents also play a significant role in the cardiorespiratory response to exercise and to exercise limitation. This was best demonstrated by the effect of locomotor muscle afferent partial blockade during exercise in CHF, COPD, and hypertensive patients achieved via intra-theal administration of the opiate agonist Fentanyl⁴⁹. In all of these cases major effects of blockade on cardiorespiratory responses to exercise occurred as: a) breathing frequency, dead space ventilation and dyspnea were markedly reduced and exercise performance prolonged in COPD⁵⁰; b) in CHF marked hypoventilation occurred and limb muscle vascular conductance blood flow and cardiac output increased^{23,51}; and c) in chronically hypertensive patients the excessive pressor response to exercise was normalized⁵². These cardiorespiratory effects of muscle afferent blockade were also reported in young healthy exercising subjects⁴⁹, but appear to be significantly greater in CHF, COPD and hypertensive patients in whom sympathetic vasomotor activity and the drive to breathe during exercise are excessive.

Excessive feedback from sensitized muscle afferent group III-IV mechano- and metabo receptors during exercise precipitates excessive ventilatory drive, hyperinflation and dyspnea in COPD, high cardiac output, muscle vasoconstriction and hyperventilation in CHF and excessive pressor responses in chronic hypertension...all of which negatively impact locomotor muscle O₂ transport and fatigue, dyspnea, exercise performance and quality of life.

TREATMENT IMPLICATIONS OF “SENSORY HYPERREFLEXIA”

There are some limited but promising findings recently in both animal models and in humans in support of attempts to modify excessive sensitivities of feedback pathways in treating/rehabilitating patients with OSA, CHF, COPD and hypertension.

Obstructive Sleep Apnea (OSA)

CPAP is clearly the preferred, effective treatment of sleep-induced cyclical obstruction and its accompanying intermittent hypoxemia. The problem is that many OSA patients either refuse CPAP treatment or underutilize it less than four hours per night—a level of usage which is inadequate for effectively treating the cardiovascular sequelae attending OSA⁵³. Alternatively, reductions in loop gain can be achieved through the use of supplemental O₂ (to reduce chemoreceptor gain) or ventilatory stimulation (acetazolamide, to reduce plant gain) (see Figure 6). If these approaches are applied to those patients with high loop gain and moderate degrees of airway collapsibility they may often be effective in significantly

reducing sleep-disordered breathing^{44,54}. Any residual apneas are commonly prolonged with supplemental O₂ but hypoxemia does not occur. Combination therapies of supplemental O₂ plus hypnotics used to reduce the arousal threshold have also shown promise – again in selected OSA patients⁵⁵. Phenotyping the patient for high loop gain is important in determining the feasibility of these approaches and this might be accomplished by examining patterns of ventilatory overshoot or a high prevalence of “mixed” apneas in the routine polysomnogram or even by simple breath hold or CO₂ chemosensitivity tests in wakefulness⁵⁶. Some claims that continuous positive airway pressure (CPAP) effects on selected cardiovascular outcomes in OSA patients exceeded those of supplemental O₂, were based on studies which applied these treatments for < 5 hours per night and in OSA patients with very minimal sleep time spent below 90% HbO₂ saturation⁵⁷. Again there is a need to tailor treatment to individual patient characteristics⁵⁴.

Cyclical Central Sleep Apnea (CSA)

CSA is common in heart failure with its accompanying intermittent hypoxemia and resulting hyperadrenergic state⁵³. CPAP is usually not effective or only partially effective in treating central apneas and therefore may even be harmful to those whose CSA is not suppressed⁵⁸. In animal models of CHF, CBX or pharmacologic blockade of carotid body excitatory neurotransmitters effectively prevents unstable breathing⁴⁴. Systematic studies in humans using nocturnal supplemental oxygen show substantial improvement in CSA, reduced sympathetic activity and arrhythmias and improved cardiac function⁵³. Importantly, only supplemental O₂ in quantities sufficient to prevent HbO₂ desaturation and CSA should be used, as determined via titration during sleep. Inducing hyperoxia for sustained periods has been shown to increase vasoconstriction and impair ventricular function. A strong case has been made for clinical trials to determine the role of supplemental O₂ in treating CSA in CHF⁵³.

Attention should also be paid to the use of acetazolamide to reduce plant and loop gain via moderate reductions in PaCO₂⁵³. Clearly, lowering steady state PaCO₂ and plant gain moves the apneic threshold PCO₂ further away—not closer—to the eupneic PaCO₂ (see Figure 6). In CHF patients who develop obstructive as well as central apneas secondary to excess fluid accumulation around the upper airway, a diuretic therapy might be combined with these measures to lower loop gain. Finally there may even be ways to address the underlying mechanism of CB sensitization in CHF by enhancing carotid body blood flow: a) statin use in a post-infarction CHF rodent model upregulated CB blood flow, enhanced endothelial NO synthase within the CB, and reduced chemosensitivity—resulting in less ventilatory instability and fewer cardiac arrhythmias⁵⁹; and b) exercise training in CHF rodents and human patients augmented cardiac output and blood flow in moderate amounts, apparently sufficient to reduce CB hypersensitivity^{60,61}.

Chemosensitivity and Systemic Hypertension

In the rodent chronic hypertensive model the hypersensitized carotid body is tonically active during normoxic, air breathing conditions. CBX lowers BP and renal SNA and improves baroreflex and renal function⁶². How might this be accomplished in humans who are resistant to anti-hypertensive medications and show enhanced chemosensitivity? Limited

numbers of hypertensive patients have undergone single or even bilateral carotid body denervation with a number of the “responders” showing significant reductions in BP—but such approaches are non-reversible and could elicit serious consequences in circumstances of sleep apnea or exposure to hypoxic environments. Other approaches to reduce CB hypersensitivity include exercise training and statin use (see above). Another exciting recent idea identifies a pure adrenergic receptor P₂X₃ mRNA expression in chemoreceptive petrosal sensory neurons as a source of enhanced CB tonic drive and hyperreflexia in the CHF rodent model. Specific pharmacologic antagonists of these neurons might provide a means of reducing high tonic activity from the CB while preserving its emergency function⁶³. Stay tuned!

Exertional Dyspnea/Increased Respiratory Drive

An abnormally high drive to breathe during exercise is commonly encountered in COPD and CHF patients leading to flow limitation, hyperinflation, dyspnea, limb fatigue and exercise limitation. Significant sources of these high drives are to be found in sensitized afferents in both the CBs and muscle group III-IV afferents (see above). Accordingly, rehabilitation efforts which target these muscle afferent hypersensitivities will allow these patients to train at higher intensities and experience more beneficial training effects in their markedly fatigueable locomotor muscles and improve exercise performance and quality of life. These approaches would include: a) the use of O₂ supplementation during training sessions to enhance O₂ transport and reduce the ventilatory response and dyspnea – thereby raising work output; and b) exercise training of single limbs which will upregulate the low aerobic capacity in limb muscles via increased mitochondrial volume and capillarization, thereby reducing metabolite accumulation and sensory input from muscle metaboreceptors and reducing the ventilatory drive and its negative sequelae during exercise⁵⁰. Respiratory muscle unloading studies have also revealed the high sensitivity of respiratory muscle metaboreceptors in CHF and COPD patients causing sympathoexcitation, redistribution of blood flow and exacerbating limb fatigue during exercise⁶⁴. Accordingly, specific respiratory muscle training studies have been shown to delay the onset of diaphragm fatigue and metabolite accumulation during exercise thereby delaying the metaboreflex-induced sympathoexcitation, improving blood flow distribution, and reducing locomotor muscle fatigue⁶⁴. (Box 1)

SUMMARY

Recent research has unraveled many of the mechanisms underlying central and peripheral chemoreception and revealed a highly interdependent chemoreceptor pathway extending from carotid chemoreceptors to the hypothalamus. Thus in physiologic preparations, input from the carotid chemoreceptor exerts hyperadditive effects on central CO₂ ventilatory responsiveness and central chemoreceptor CO₂ sensitive neurons are also influenced by input from both the hypothalamus and lung stretch. Hyperchemosensitivity results from sustained hypoxic exposure, intermittent hypoxemia, and reduced blood flow, resulting in unstable breathing and enhanced tonic vasomotor sympathetic activity and its cardiovascular sequelae. Hypersensitivity of group III-IV muscle afferents have also been documented, especially in sedentary, deconditioned patient populations, resulting in excessive pressor,

ventilatory and dyspneic responses to exercise and exercise limitation. These states of “hyper-reflexia” occur in OSA, CHF, COPD and chronic hypertension. Specific targeting of the sensitized reflexes may provide effective alternate treatments in selected patient populations.

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Abbreviations

CB	carotid body
CBX	carotid body resection
CHF	chronic heart failure
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CPG	central respiratory pattern generator
CPAP	continuous positive airway pressure
CSA	central sleep apnea
HbO₂	oxyhemoglobin
IH	intermittent hypoxemia
NTS	nucleus tractus solitarius
OSA	obstructive sleep apnea
Pa	arterial partial pressure
PVN	paraventricular nucleus
RTN	retrotrapezoid nucleus
SNA	sympathetic nerve activation
VE	ventilation

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Box 1:**Treatment implications targeting hypersensitive chemoreceptors and/or muscle afferents**

Treatment implications targeting hypersensitive chemoreceptors and/or muscle afferents, include reducing their sensitivity via:

- a.** use of supplemental O₂ during sleep to treat central apnea and even obstructive apneas in some OSA patients with high chemosensitivity and moderately collapsible airways
- b.** exercise training of single limbs plus supplemental O₂ to increase training intensity, thereby leading to improved aerobic capacity of locomotor muscles and reduced muscle metabolite accumulation and afferent stimulation in COPD
- c.** use of physical training and statin therapy in CHF to enhance chemoreceptor blood flow;
- d.** ongoing research to selectively reduce excessive *tonic* carotid chemoreceptor activity in drug resistant hypertension without sacrificing chemoreceptor emergency function.

KEY POINTS

- Peripheral chemoreceptor stimulation has marked hyperadditive influences on central chemoreceptor responsiveness and CNS hypoxia is stimulatory to ventilation in physiologic preparations.
- Peripheral and central chemoreceptors and their interdependence as well as muscle metaboreceptors exert tonic influences on ventilatory drive and sympathetic vasomotor activity in health at rest and/or exercise.
- States of hyper-reflexia occur in OSA, COPD, CHF and hypertension and effective treatment of the resultant hyperadrenergic state, sleep apnea, and exertional dyspnea should require targeting of these hypersensitivities.

SYNOPSIS

We examine recent findings which have revealed interdependence of function within the chemoreceptor pathway regulating breathing and sympathetic vasomotor activity and the hypersensitization of these reflexes in chronic disease states. Recommendations are made as to how these states of hyper-reflexia in chemoreceptors and muscle afferents might be modified in treating sleep apnea, drug-resistant hypertension, CHF-induced sympathoexcitation and the exertional dyspnea of COPD.

Fig. 1.

Simplified functional schema of known and potential interdependencies in chemoreceptor driven cardio-respiratory control systems. Yellow shading indicates structures known to be chemosensitive. Arrows indicate reported pathways; solid arrows indicate pathways known to show interdependence. See text for details. Abbreviations: BAROs = baroreceptors; CB = carotid body; CMR = caudal medullary raphé; CPG = central respiratory pattern generator; LC = locus ceruleus; LH = lateral hypothalamus; NTS = nucleus tractus solitarius; PVN = paraventricular nucleus; RMR = rostral medullary raphé; RTN = retrotrapezoid nucleus; RVLM = rostral ventrolateral medulla; SAR = lung slowly adapting receptors.

Fig. 2.

Steady-state ventilatory responses to central nervous system (CNS) hypoxia/hyperoxia alone (open diamonds) vs. CNS plus carotid body (CB) hypoxia/hyperoxia (filled squares) in awake canines. The CNS hypoxic data were obtained using a perfused carotid body canine preparation to isolate the CNS from the CB with the CB held at normoxic and normocapnic levels via perfusion during inhalation of hypoxic gases (N=11). The CNS hyperoxia data were obtained in bilaterally carotid body denervated dogs (N=5). Note that when the CNS was exposed to hypoxia with CB held normoxic, dose-dependent hyperventilatory responses occurred which were about one-third of the response obtained in the intact animal when both CB and CNS were hypoxic. With CNS hyperoxia, a moderate hyperventilation occurred. The hyperventilation with CNS hypoxia was due entirely to a progressive increase in breathing frequency whereas the hyperventilation in CNS hyperoxia was due primarily to an increase in VT.

Data from Curran AK, Rodman JR, Eastwood PR, Henderson KS, Dempsey JA, Smith CA. Ventilatory responses to specific CNS hypoxia in sleeping dogs. J Appl Physiol (1985). 2000;88(5):1840-1852 and Rodman JR, Curran AK, Henderson KS, Dempsey JA, Smith CA. Carotid body denervation in dogs: eupnea and the ventilatory response to hyperoxic hypercapnia. J Appl Physiol (1985). 2001;91(1):328-335

Fig. 3:

a Effects of carotid chemoreceptor inhibition on breath-by-breath $\dot{V}_E$ and $P_{ET}CO_2$ in normoxia in the awake canine. At time zero the isolated and perfused carotid body was inhibited by suddenly reducing perfusate PCO_2 from 40 to 20 mmHg and increasing perfusate PO_2 from 90 to ~500 mmHg. Normal CB blood gases were abruptly restored at the +25 minute mark. The persistent hypoventilatory response to CB inhibition despite the continued systemic and CNS hypercapnic acidosis consisted of a reduced V_T , fb, V_T/T_i and EMG_{di} and prolonged T_E .

Adapted from Blain GM, Smith CA, Henderson KS, et al. Contribution of the carotid body chemoreceptors to eupneic ventilation in the intact, unanesthetized dog. *J Appl Physiol* (1985). 2009;106(5): 1564-1573; with permission.

b. Thirty-five to seventy percent reduction in the slope of the hyperoxic CO_2 ventilatory response in the awake canine (left) and human (right) resulting from bilateral CB denervation. In canines the response slopes are shown pre-CBX and at 1-4 days post-CBX (adapted with permission from Rodman et al., 2001¹⁸). In the human the plotted ventilatory response slope values represent those obtained early (less than 15 seconds) (“peripheral chemoreceptor”) and later (“central chemoreceptor”) in the CO_2 exposure period. The gradual rise in the “central chemoreceptor” CO_2 response slope after 6 months post CBX shows the long term plasticity of the CO_2 response following CBX.

Adapted from Dahan A, Nieuwenhuijs D, Teppema L. Plasticity of central chemoreceptors: effect of bilateral carotid body resection on central CO_2 sensitivity. *PLoS Med*.

2007;4(7):e239.

Daytime CV Effects of Sleep Apnea-Induced Intermittent Hypoxemia (CIH)

Figure 4.

Summary of effects of chronic intermittent hypoxemia induced via cyclical sleep apnea characterized by a rapid reoxygenation phase at apnea termination following each O₂ desaturation.

Data from Semenza GL, Prabhakar NR. Neural regulation of hypoxia-inducible factors and redox state drives the pathogenesis of hypertension in a rodent model of sleep apnea. *J Appl Physiol* (1985). 2015;119(10):1152-1156 and Lim DC, Brady DC, Soans R, et al. Different cyclical intermittent hypoxia severities have different effects on hippocampal microvasculature. *J Appl Physiol* (1985)

Fig. 5.

Within-breath modulation of MSNA in the healthy human. Note the increase in MSNA modulation with increased VT above spontaneous eupnea (PETCO₂ maintained normocapnic), but with no further modulating effect of increases or decreases in central respiratory motor output. For example, contrast high central drive (voluntary hyperventilation and inspiration against high resistance) vs. no or reduced central drive (passive or assisted mechanical ventilation).

From St Croix CM, Satoh M, Morgan BJ, Skatrud JB, Dempsey JA. Role of respiratory motor output in within-breath modulation of muscle sympathetic nerve activity in humans. *Circ Res.* 1999;85(5):457-469; with permission.

Figure 6.

Diagrammatic representation of the relationships in the alveolar gas equation ($\text{PaCO}_2 = \dot{V}\text{CO}_2 / \dot{V}\text{A} \times K$) at an isometabolic $\dot{V}\text{CO}_2$ of 250ml/min, illustrating the effects of changes in plant gain (top) and controller gain (or chemosensitivity – bottom) on susceptibility to apnea/instability. Note: Owing to the hyperbolic $\dot{V}\text{E}:\text{PaCO}_2$ relationship, as PaCO_2 is reduced via steady state hyperventilation (e.g., acetazolamide therapy) the reduced plant gain means that a transient ventilatory overshoot much larger than that under control conditions is required to reach the apneic threshold. Conversely with steady state hypoventilation (e.g., metabolic alkalosis or NREM sleep) a much smaller ventilatory overshoot is required to reduce PaCO_2 to the apneic threshold. In bottom panel note increased propensity for apnea and destabilization of breathing with increases in CO_2 sensitivity (e.g., hypoxia, CHF), because the hypocapnic-induced apneic threshold resides much closer to eupneic PaCO_2 than in control conditions plus the ventilatory overshoot response to increases in chemical stimuli is exaggerated. Stabilization of breathing occurs with reduced chemosensitivity (e.g., hyperoxia) because ventilatory overshoots are reduced

and reaching the apneic threshold PaCO_2 requires a much greater increase in ventilation and reduction in PaCO_2 .

Data from Khoo MC, Kronauer RE, Strohl KP, Slutsky AS. Factors inducing periodic breathing in humans: a general model. *J Appl Physiol Respir Environ Exerc Physiol.* 1982;53(3):644-659.

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