Hypercapnia, largely through the direct influence of CO₂ on proton production, but possibly also via a direct effect of molecular CO₂, is the primary chemical stimulus for alveolar ventilation. Small deviations in arterial CO₂ in either direction elicit integrated cardio-respiratory reflexes that quickly restore CO₂ levels in various tissue and cellular compartments, thereby providing the body with its most rapid physiological mechanism for pH regulation and homeostasis. A reduction in arterial oxygenation under normocapnic conditions, by contrast, does not stimulate alveolar ventilation significantly until it drops below 60 Torr and begins endangering oxygen uptake by hemoglobin in the pulmonary circulation. Thus, understanding how CO₂ and pH levels are monitored in the body and regulated provides insight to the fundamental control mechanism that sets alveolar ventilation and pH homeostasis during wakefulness and sleep. Congenital and adult-onset abnormalities of the CO₂ chemoreceptors are
thought to contribute to onset of disordered breathing patterns and various chronic central hypoventilation syndromes that lead to chronic acid-base imbalance, redox stress and nitrosative stress that produce additional neurological deficits.

The peripheral CO₂ chemoreceptors that monitor the partial pressure of CO₂ (PCO₂) and pH in plasma are located unequivocally within the carotid bodies. The anatomical isolation of these small but well vascularized and perfused structures lends them to easy visualization and experimental manipulation while simultaneously measuring ventilation to confirm their function in CO₂/H⁺ chemoreception. The intracranial chemoreceptors, by contrast, which are the focus of this “Highlighted Topic” series, are more difficult to isolate and the extent of their distribution in the brain stem is still being debated (1, 10, 16, 18). The first intracranial chemoreceptor area was identified in 1963 by Mitchell and colleagues (13) on the ventrolateral medullary (VLM) surface. They proposed that this was the sole site of CO₂ chemoreception in the brain stem, a theory that would be embraced by nearly all cardio-respiratory neurophysiologists for the next two decades. In 1983, Miles (12) and later, others (3, 5), challenged this idea and suggested that neurons in the caudodorsal medulla in the vicinity of the nucleus tractus solitarius (NTS) also functioned in CO₂/H⁺ chemoreception. Over the next two decades, several independent laboratories using a variety of in vivo and in vitro methodologies, reported that CO₂ chemosensitivity was distributed across additional brain stem nuclei, including the locus coeruleus (LC), medullary raphe (MR), retrotrapezoid nucleus (RTN), rostroventrolateral medulla (RVLM), preBötzinger complex (PBC), and cerebellar fastigial nucleus.

In recent years, the VLM surface theory has been “resurrected” with particular importance assigned to the RTN (8). This has reignited the debate as to which region(s) of the CNS is/are the principle sites of intracranial CO₂ chemoreception. This ongoing debate has
reinvigorated the field and, in the process, provided the rationale for this highlighted topic series on “Central CO2-Chemoreception in Cardio-respiratory Control”. While the series does not focus on the debate of central CO2 chemoreceptor location per se, it does address it to a certain extent by including summaries of studies done at multiple chemosensitive areas for the readers’ consideration. The primary topics covered can be roughly categorized as follows: cellular mechanisms of chemoreceptor signaling and the role of pH and other stimuli (4, 6, 11, 14, 17); mechanisms of neural integration of central chemoreceptors with peripheral chemoreceptor afferents and cardiovascular circuits (7, 9); factors and conditions that modulate central chemoreceptor activity (4, 15); and the contribution of central chemoreceptor dysfunction to central hypoventilation syndromes (2).

The first review “Contributions of central and peripheral chemoreceptors to the ventilatory response to CO2/H+” (7) summarizes the evidence from studies using anesthetized, decerebrate, and awake animals that addresses the issue of whether the integrated neural signal to breathe produced by carotid and intracranial chemoreceptors during hypercapnic acidosis is additive, hyperadditive or hypoadditive. The authors conclude that chemosensitivity of the central chemoreceptors is “critically dependent” on input from the peripheral chemoreceptors, and that the majority of the evidence supports the notion of hypoadditive interactions. The second review, “Central CO2-chemoreception and integrated neural mechanisms of cardiovascular and respiratory control” (9), addresses the fundamental question of why blood pressure and sympathetic nerve activity increases during stimulation of central CO2 chemoreceptors. Two fundamental mechanisms of integration are postulated for future testing; one that involves central chemoreceptor stimulation of the central pattern generator and results in respiratory modulation of sympathetic nerve activity in the caudal ventrolateral medulla.
(CVLM), RVLM, NTS and spinal cord; and another that occurs independently of the central pattern generator and is dependent on the relative level of hypercapnia. Under normocapnic conditions, PCO₂-dependent activation of chemoreceptors in RTN activate a central sympathetic chemoreflex via RVLM and CVLM neurons, whereas under abnormal hypercapnic conditions, arousal is triggered by activation of wake-promoting and/or stress-related circuits including orexinergic, noradrenergic and serotonergic neurons in NTS, VLM and preganglionic neurons.

In the third review, “Hypoventilation syndromes with autonomic dysregulation”, a clinical framework for the consequences of chemoreceptor dysfunction is provided using three cases of hypoventilation syndromes that are characterized by impaired respiratory control with autonomic dysfunction. One of these, congenital central hypoventilation syndrome, has been identified with mutations of the *PHOX2B* gene. Recommendations are made by the authors for future basic science research that incorporates the necessary clinical relevance in experimental design and animal model so that important genotype-phenotype relationships can be established for making the next translational step to diagnosis and treatment.

The second set of reviews highlight the issue of central chemoreceptor locations and their functions in specific aspects of respiratory control. The review, “Central chemoreception in wakefulness and sleep: evidence for a distributed network and a role for orexin” (15), summarizes studies using focal mild acidosis to stimulate breathing in unanesthetized, intact animals and how CO₂ responsiveness of a given area is modulated by arousal state. The authors propose that central chemoreception is linked to arousal state via orexinergic neurons in the hypothalamus that project onto central chemoreceptors. The authors also provide a concisely written summary of the evidence for and against a single dominant central chemoreceptor site in the RTN, which is of interest to the ongoing debate on chemoreceptor location and hierarchy.
The next review, “The role of medullary serotonin (5-HT) neurons in respiratory control: contributions to eupneic ventilation, CO₂ chemoreception and thermoregulation” (11), examines the functional roles of serotonergic neurons in the MR in the context of central chemoreception and other processes such as providing tonic excitatory drive for eupnea in normocapnia and thermoregulation. The third review in the second set, “Current ideas on central chemoreception by neurons and glial cells in the retrotrapezoid nucleus” (14), summarizes the characteristics of pH-sensitive neurons and the possible role of pH-sensitive glial cells as a source of purinergic drive for chemosensitive neurons and, moreover, as regulator of cerebral vascular tone and thus blood flow, CO₂ removal, and local brain tissue pH.

The third and final set of reviews focuses primarily on stimuli of the central chemoreceptors. The first two papers discuss the role of CO₂-induced pH on neurons and glia in chemosensitive areas. In the review, “Role of pH in cellular CO₂ chemosensitivity” (17), the mechanisms of intracellular pH (pHᵢ) regulation in chemosensitive areas are summarized. Electrophysiology studies in LC neurons indicate that firing rate is stimulated by decreased pHᵢ or extracellular pH (pHₑ), but not in response to molecular CO₂ alone. A number of potassium channels and other channels are involved in LC chemosensitivity; however, more pharmacological studies are needed of pH-sensitive ionic current expressed by neurons in other chemosensitive areas. The role of pHₑ is expanded further in the review “Glia modulation of the extracellular milieu as a factor in central CO₂ chemosensitivity and respiratory control” (6). The authors summarize mechanisms of pHᵢ regulation in astrocytes and the evidence supporting their hypothesis that astrocytic pHᵢ regulation during hypercapnia lowers pHₑ and thus amplifies the hypercapnic stimulus that modulates chemoreceptor neurons. The final review, “Hypercapnia causes cellular oxidation and nitrosation in addition to acidosis: implications for CO₂-
chemoreceptor function and dysfunction” (4), examines the possible role of CO$_2$- and pH-induced reactive oxygen and nitrogen species produced under physiological and pathological conditions as additional stimuli of central chemoreceptors that work in tandem with cellular acidosis.

This collection of nine mini-reviews shows clearly the emergence of broad views on central CO$_2$ chemoreception. From the historical relatively simple idea that central chemoreception involves one site on the VLM surface there is now considerable support for the involvement of many sites, cell types and molecular signaling mechanisms. Central chemoreception is evolving into a richly complex subject. Why is there so much diversity in this function? Perhaps it is because of the importance of CO$_2$/pH as a signal that determines the level of alveolar ventilation at rest as well as the varying sensitivity of the system to changes in CO$_2$ that occurs as arousal state varies from sleep to wakefulness to increased vigilance to outright ‘defense reaction’ responses. A full understanding of the physiological relevance of the complexity of the chemoreceptor system and all of its parts will require the combination of ingenious in vitro and in vivo experiments that must, in part, include study of specific cell types, molecules, locations and their synaptic interactions, as well as animal models that can express the range of normal arousal state behaviors.

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References


