Commentaries on Viewpoint: Central chemoreception is a complex system function that involves multiple brain stem sites

CENTRAL CHEMORECEPTION IS A COMPLEX SYSTEM FUNCTION THAT INVOLVES MULTIPLE BRAIN SITES

TO THE EDITOR: Amniote vertebrates adjust the acid-base status of the blood through ventilatory alterations of PaCO2 and, to some degree, by renal modulation of bicarbonate concentration. Receptor systems for the ventilatory acid-base regulation has been studied mainly in mammals, in which the ventrolateral surface of the medulla oblongata that faces the cerebrospinal fluid of the forth ventricle has been historically taken as the primary receptor site. The earliest evidence for the existence of central chemoreceptor drive to breathing in vertebrates was obtained in 1958 by Loeschcke and colleagues (4) who perfused the fourth ventricle of cats with mock cerebrospinal fluid of different pH values and measured its effect on pulmonary ventilation. Fifty years latter, Nattie and Li (5) bring us to the frontiers of respiratory physiology related to central chemoreception and shows that it involves multiple sites within the hindbrain, and different neuronal types. According to this notion, 1) glutamatergic neurons in the retrotrapezoid nucleus (3), 2) serotoninergic neurons of the medullary raphe (2), and 3) noradrenergic neurons of the locus ceruleus (1) have all been proposed as putative central chemoreceptors. The authors hypothesize that these multiple receptor sites involved in central chemoreception provide stability in a closed-loop control system. The progress related to our knowledge of this area has amazingly increased over the last 50 years but it is even more amazing how little we currently know. Further research remains urgent.

REFERENCES


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IS CENTRAL CHEMOREFLEX A WIDESPREAD PROPERTY?

TO THE EDITOR: According to Dr. Nattie neurons that pass any or all the following tests qualify as putative central chemoreceptors: their destruction attenuates the central chemoreflex, they are acid-sensitive in vitro, and topical acidification of these neurons in vivo activates breathing. On that basis, Dr. Nattie proposes that central chemoreception involves elements of the central pattern generator (CPG; e.g. pre-Bötzinger complex) plus a selection of neurons that regulate the CPG (noradrenergic and serotoninergic neurons, the retrotrapezoid nucleus). Many other neurons could have been added to the list (motoneurons, solitary tract nucleus, fastigial nucleus, orexinergic neurons), and the resulting picture is that chemoreception is a widespread property. The trouble is that the selected criteria are far too lax (3). Lesions do not prove that the targeted neurons detect CO2, only that their integrity is needed for the chemoreflex. The chemoreflex measured in rodents is not perfectly relevant to the homeostatic regulation of CO2 since the high CO2 levels used to trigger the reflex would be perceived as aversive in humans and therefore presumably also elicit some form of enteroceptive stress. Neurons that are highly acid sensitive in vitro may respond poorly or not at all to changes in arterial PCO2 in vivo (reviewed in 2), perhaps because they reside in regions where ISF pH is buffered against changes in arterial PCO2 by the blood brain barrier (1). If this notion is correct, topical brain acidification may be a questionable experimental paradigm if the targeted region is normally protected against blood CO2-induced acidification.

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TO THE EDITOR: The Viewpoint (3) that there are multiple brain stem locations where CO2/pH-sensitive chemoreceptors adjust ventilation to meet metabolic demand is consistent with the results of in vivo (1–3) as well as in vitro (5) studies. The three sites Nattie and Li (3) single out for discussion (see their Viewpoint Refs. 1, 2, 6) each express CO2/pH-sensitive neurons that, presumably, evoke distinctive downstream respiratory motor effects through different neurotransmitter and neuromodulator substances. In the retrotrapezoid nucleus (RTN), the chemoreceptor neurons are glutamatergic (2), and their destruction (1) reduces tidal volume (VT). Lesions of noradrenergic neurons in locus ceruleus (LC) and serotoninergic neurons in raphe magnus (RM) also depress VT (1,3), whereas a nonselective lesion in RM depresses both VT and breathing frequency (3). Breathing frequency increases when chemoreceptor neurons in the medullary raphe are activated by CO2 during microdialysis but only during sleep; there is no ventilatory effect during wakefulness (5). In the RTN, CO2 elevation increases VT during wakefulness but not sleep. Collectively, these results suggest a high degree of neurotransmitter- and state-dependent plasticity in central chemoreceptor control of ventilation, which remains to be explained in neuroanatomical and neurochemical terms. State-dependant modulation by LC and raphe regions might be anticipated on the basis of

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Letter To The Editor

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studies of other types of motor behavior that they influence, but the wiring of chemoreceptor neurons into the respiratory network and the neurochemical mechanisms through which they differentially affect VT and breathing frequency are surprising and should be particularly interesting topics for future research.

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CHEMORECEPTION LIKELY INVOLVES A COMPLEX DISTRIBUTED NETWORK THROUGHOUT DEVELOPMENT TO THE EDITOR: The recent Viewpoint article by Nattie and Li (3) is a welcome addition to the debate about whether central chemoreception arises from a complex distributed network of sensory elements or is restricted to a single region containing specialized neurons (1). Nattie and Li (3) properly focus the debate on defining chemoreceptive regions based on data derived from conscious animals (focal acidosis and lesioning studies) and not on defining chemoreceptive neurons based largely on their response to acidosis (1). Evidence for the involvement of glutamatergic neurons from the retrotrapezoid nucleus, serotoninergic neurons from the medullary raphe, and noradrenergic neurons from the locus ceruleus (LC) in central chemoreception is reviewed as support for a distributed chemosensitive network. Work from my laboratory suggests that there is also a neonatal form of chemoreception that transitions to an adult form during development (4). We recently found that a high percentage of LC neurons from neonatal rats younger than day 10 are intrinsically chemosensitive (respond to CO2 with electrical and chemical synapses blocked) and exhibit a large firing rate increase in response to hypercapnia. Interestingly, rat adrenal chromaffin cells have likewise been shown to be CO2 sensors up to neonatal day 10, releasing catecholamines in response to peripheral hypercapnia (2). These findings suggest that neonatal chemoreception is strongly dependent on CO2-induced release of catecholamines, both peripherally and centrally. If true, this would indicate that chemoreception is even more complex, involving peripheral sites as well as central sites and varying with development.

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TO THE EDITOR: Drs. Nattie and Li (2) address a fundamental issue in how the central chemoreceptor system is organized:
To the Editor: Nattie and Li review data suggesting that the central respiratory chemosensitivity is a complex system function that involves multiple brain stem sites. This is supported by the evidence that in conscious states lesions of glutamatergic neurons in the retrotrapezoid nucleus, serotonergic neurons in the medullary raphe, locus ceruleus NA neurons, or NK-1 receptor expressing cells in the ventral medulla reduce (albeit to a different degree) the ventilatory responses to CO2. The existence of functional respiratory chemosensors in several brain stem sites makes a lot of sense to ensure redundancy and stability within this “high-gain” system (1 mmHg increase in arterial PCO2 may lead to a 2 l/min increase in lung ventilation). This, however, greatly complicates studies of the underlying cellular mechanisms as these could be quite distinct in chemosensory neurons at different locations. We found that on the ventral surface of the medulla CO2 chemosensory transduction involves release of ATP, which is acting at downstream neurons to increase respiratory activity (2, 3). ATP may also play a role at other sites as all of them are equipped with ATP receptors, which are expressed by brain stem catecholaminergic neurons among other cell types (4). Finally, we should not forget about the peripheral chemoreceptors (in the carotid and aortic bodies), which contribute about 1/3 of the overall response to CO2 and play a predominant role in controlling arterial PCO2 during eupnic breathing (1). This is particularly important considering that most of the studies discussed by Nattie and Li were performed in animals with intact peripheral chemoreceptors.

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