Invited Editorial on “Ventilatory effects of glial dysfunction in a rat brain stem chemoreceptor region”

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STUDIES FROM ABOUT 1955 TO 1990 led to major conclusions on the anatomic site and physiological role of intracranial CO₂/H⁺ chemoreceptors (5, 11). These chemoreceptors were thought to be restricted to discrete areas near the rostral (Mitchell’s area) and caudal (Loeschke's area) ventrolateral medullary (VLM) surface. Supposedly, between these areas were neurons (Schlaefke’s area) that “integrated” intracranial chemoreceptor activity. There has been controversy over the role of these chemoreceptors, with one dominant view maintaining that the chemoreceptors provided the major drive for eupneic breathing and changes in ventilatory drive during metabolic acidosis and alkalosis and high-altitude acclimatization. Moreover, in the anesthetized state, breathing appeared to be critically dependent on VLM areas of intracranial chemoreception.

Studies over approximately the last five years suggest that these views require modification. First, in anesthetized reduced preparations, chemoreceptors have been identified at widespread sites within the brain, including the VLM, nucleus tractus solitarii, midline raphe, and locus coeruleus (1–3, 9, 12). Second, the effect on breathing of neuronal dysfunction is state dependent; lesioning a chemoreceptor VLM area causes terminal apnea in the anesthetized state but only a slight reduction in breathing during physiological wakefulness (7). These recent findings raise several questions.

Do all neurons with chemoreceptor properties stimulate breathing? Dysfunction of neurons near the VLM surface in awake goats reduces CO₂ sensitivity at most by 60%, which suggests that chemoreceptors at other sites can stimulate breathing (7). However, it is conceivable that not all chemoreceptor neurons stimulate breathing, as some decrease firing with acidosis/hypercapnia (9). It is also conceivable that some chemoreceptors serve functions other than altering breathing, such as eliciting and maintaining an “aroused” state (12). Finally, the intrinsic membrane properties may change with changes in state, preparation, and/or other causes, which may mean that all neurons can display chemoreceptor properties given the right condition. Thus it may not be a valid assumption that chemoreceptors at widespread sites are continually active and only function to stimulate breathing.

How and where is chemoreceptor activity integrated or processed? There are several possibilities, including that the activity of individual receptors could be algebraically summed or that there could be some form of synergism among the inputs. On the other hand, there might be occlusion among the inputs and/or a hierarchy in the importance of the individual inputs. The concept of integration seems intuitive, and the absence of CO₂ sensitivity in the clinical condition known as congenital central alveolar hypoventilation seems consistent with a lesion of a chemoreceptor integrative site (15). If such a site exists, it does not seem to be Schlaefke’s area in the awake state because lesioning this area in the awake state reduces CO₂ sensitivity no more than 60% in goats (7).

Is intracranial chemoreceptor responsiveness per se regulated? Through efferent innervation and/or changes in neurotransmitters/neuromodulators, carotid chemoreceptor responsiveness can be altered (10). A similar process or other mechanisms may exist to alter global, regional, or individual intracranial chemoreceptor activity. Such a system could be a means by which only a portion of all the chemoreceptors has an influence on breathing at any point in time.

Why is breathing critically dependent on surface VLM chemoreceptor sites in the anesthetized but not the awake state? It is conceivable that chemoreceptors have minimal influence on breathing in the awake state or they may normally provide a major contribution; however, because of redundancy and plasticity, eupneic breathing is minimally affected by attenuated chemoreceptor activity at any given site (7, 8). If the latter is true, then redundancy and plasticity of chemoreception must be less in the anesthetized than in the awake state.

Published in this issue of the Journal are the results of the study by Erlichman et al. (6) on the “Ventilatory effects of glial dysfunction in a rat brain stem chemoreceptor region.” This study shows that continual unilateral administration for 60 min of a low dose of the gliotoxin fluoroacetate into the retrotrapezoid nucleus of an anesthetized rat results in acidification of the surrounding extracellular fluid (ECF) and an increase in phrenic nerve activity (PNA). These changes were reversible, and the temporal patterns of ECF pH and PNA were similar during both the period of fluorocitrate perfusion and recovery. These findings demonstrate that glial cell function is important in intracranial chemoreception and the regulation of breathing.
Relevant is the present state of knowledge regarding the function of glia. Recently it was stated that "glial cells are no longer viewed as simply a scaffolding around which the nervous system is built." (14). It was emphasized that glial cells are strategically located in the brain to detect and correct changes in neuronal microenvironment (14). For example, when neural activity increases, ECF K⁺ concentration ([K⁺]) also increases, but glial cells buffer this effect by K⁺ uptake, thereby minimizing the alterations in several physiological functions (such as neuronal excitability) that occur with altered ECF [K⁺]. Changes in ECF H⁺ are another important determinant of neural excitability. Indeed, when increased neural activity increases ECF [K⁺], glial cells extrude H⁺, which then depresses neural activity (13). In addition, glial cells possess several mechanisms to modulate ECF H⁺, which provide for fast-acting local control of ECF H⁺ concentration and thus neuronal excitability (4). Glial cells also affect neural activity through uptake, synthesis, and release of neurotransmitters (14) and they express neurotransmitter receptors that may serve as transducers in a neuron-to-glial cell signaling system (14). Accordingly, glial cells "may participate in most of the sophisticated functions that were previously believed to be reserved for neurons alone" (14).

It seems reasonable then to postulate that glial cells are important determinants of stimulus level and excitability of intracranial chemoreceptors. Glial cells may indeed "regulate" chemoreceptor activity that could be local; thus, under any specific condition, only a few of the widespread chemoreceptors may stimulate breathing. In addition, if chemoreceptor activity is attenuated in one brain region, the network of glial communication provides a signaling mechanism whereby other chemoreceptors become active to stimulate breathing. Such a system or other aspects of glial function might be state dependent; thus the apparent redundancy in the awake state is limited in the anesthetized state.

The work by Erlichman et al. (6) suggests the above and offers additional hypotheses to direct future studies that may provide insight into the earlier stated questions. Ransom and Sontheimer (14) caution, however, that progress will be slow “due in part to the necessity of moving from the convenience of studying glial cells in relative isolation to the more forbidding circumstances associated with pursuing questions of their function in more intact tissue.” Erlichman et al. (6) met this challenge and conclude that further study be "preferable in an unanesthetized animal model in which the depressant effects of anesthesia are absent."

An additional issue in the study of Erlichman et al. (6) is precise identification of neurons affected when substances are microinjected into the brain. Clearly, coinjection of dyes or fluorescent microbeads only identifies the injection site, as these will not diffuse in the same pattern as a neurotoxin or a gliotoxin. The authors have recognized this problem and have reported on their efforts in using DEAD red (ethidium homodimer-1) as a marker of neuronal or glial cell damage. This agent offers advantages in acute studies over other markers, but its rapid clearance suggests that it will not provide precise identification. Moreover, it seems that for chronic studies DEAD red would not be a valid marker. This aspect of their publication is important in emphasizing the problem, which hopefully will stimulate research that may lead to precise identification of lesioned neurons.

REFERENCES