Adaptation to chronic hypoxia involves immune cell invasion and increased expression of inflammatory cytokines in rat carotid body

Frank L. Powell

Department of Medicine and White Mountain Research Station, University of California, San Diego, La Jolla, California

NEURAL PLASTICITY IS CURRENTLY a “hot topic” in the literature on the control of breathing. This is largely because such rapid progress is being made on the molecular and cellular mechanisms of ventilatory acclimatization to challenges such as chronic hypoxia. The potential significance of this research is huge given the pervasive problem of chronic hypoxemia a wide range of heart, lung, and vascular diseases. Understanding the consequences of chronic intermittent hypoxia from sleep-disordered breathing could have an even larger impact considering estimates that it affects 2–4% of adults (6). In this issue of AJP-Lung, Liu and colleagues from the University of Utah School of Medicine (4) report experiments demonstrating that immune cells and inflammatory cytokines play a critical role in the increased O2 sensitivity of carotid body chemoreceptors during adaptation to chronic hypoxia. Hence, neural plasticity in arterial chemoreceptors involves much more than just neurons, neurotransmitters, and ion channels.

Liu et al. (4) demonstrated that chronic hypoxia recruits macrophages to the carotid bodies and increases gene expression for chemokines and proinflammatory cytokines in the carotid body. mRNA for IL-6 remained elevated for 4 wk of sustained hypoxia, whereas mRNA for IL-1β and TNF-α increased during the initial exposure to hypoxia and then returned to control levels. The increased cytokine expression was not restricted to immune cells. Chronic sustained hypoxia also increased IL-6 expression in both the chemosensitive type I glomus cells and the type II glia-like cells of the carotid body. Most importantly, the investigators showed that anti-inflammatory drugs (ibuprofen and dexamethasone) blocked the increased O2 sensitivity normally observed in carotid bodies during chronic hypoxia as well as blocked immune cell invasion and significantly reduced increases in cytokine expression. Other laboratories have reported increased cytokines in the carotid body with chronic sustained hypoxia (3), but Liu and coworkers are the first to demonstrate the physiological significance of this, in terms of chemoreception, as well as the first to demonstrate immune cell invasion.

Increased sensitivity in sensory systems caused by a neural-immune interaction is not a new idea and, in fact, is a very well-developed concept in somatosensory physiology for pain. Hyperalgesia (increased pain sensation to a noxious stimulus) depends on a number of cytokines (e.g., IL-1, IL-6, and TNF-α) that are released from activated immune cells and glia, which act on both sensory nerve endings and synaptic transmission between primary afferents and integrative neurons in the central nervous system (CNS) (12). Changes in the CNS are referred to as “central sensitization” and involve both presynaptic and postsynaptic changes. Such sensitization may also occur in the carotid body because O2-sensitive type I glomus cells transmit their sensory information to the CNS via synapses with afferent fibers of the carotid sinus nerve in the carotid body. Glia cells appear to be especially important in central sensitization as a source of cytokines that act in a paracrine fashion (10). Also, glia cells are linked by gap junctions in widespread networks and can distribute their influence beyond a local synapse, which is characteristic of plasticity in pain pathways (12). Some experts in the field propose that therapies designed for chronic neuropathic pain frequently fail because they target changes in the neurons instead of glia. This suggests that it will be important to sort out the role of type I vs. type II cells in immune mechanisms of carotid body sensitization to chronic hypoxia (12).

“Neurogenic inflammation” is another neural-immune mechanism of plasticity in pain pathways that increases sensory fiber sensitivity to painful stimuli. Neurogenic inflammation does not require nerve trauma but the release of neuropeptides (e.g., substance P) by nonmyelinated nociceptors into their own receptive field; this is in addition to the normal synaptic release of these cotransmitters centrally (12). The neuropeptides trigger inflammatory responses and induce immune cells to release proinflammatory cytokines, which sets up a positive feedback loop between substance P and cytokines. Such neurogenic inflammation was hypothesized to contribute to airway hypersensitivity in lung diseases such as asthma or chronic obstructive pulmonary disease (COPD) based on the discovery of nonmyelinated nerve fibers that released neuropeptides (e.g., substance P) and neuropeptide receptors in the airways of experimental animals (1). However, clinical trials designed to test the efficacy of neuropeptide receptor antagonists were disappointing. This might have been predicted if researchers knew then that substance P is rare in the nerves of human airways, in contrast to rodents (1). It is worth noting that there is still strong evidence for central sensitization in airway reflexes (5). However, this points out the importance of accounting for well-known species differences in neurotransmitters and neuromodulators (9), as well as the distribution of myelinated vs. unmyelinated fibers, in animal models used to study plasticity in the carotid body.

The material above supports the general importance of neural-immune mechanisms for plasticity in sensory systems and reflexes. The new work by Liu and coworkers (4) provides another model to start testing which of these mechanisms are universal and which are specific to individual systems. Other questions include: What is the role of the resident macrophages in the carotid body vs. infiltrating macrophages? Are chemokines and infiltration essential for the response, and how do the macrophages move into the carotid body? Is it relevant that the carotid body has the highest blood flow per unit mass of any organ in the body, or is there a specific role for the fenestrations in carotid body capillaries? Cytokines enter the CNS by carrier-mediated transport or directly at sites where the blood brain barrier is absent (13). What is the role of cytokine expression...
from carotid body type I and II cells vs. migrating immune cells? An important issue for clinical medicine may be determining the effects of anti-inflammatory drugs on carotid body function in patients with chronic hypoxemia.

Perhaps the most fundamental question raised by this study is, how does chronic hypoxia trigger an innate immune response? Recent work has shown that NF-κB (a major transcription factor for cytokines) links innate immunity to the hypoxic responses through transcriptional regulation of hypoxia-inducible factor-1α (HIF-1α; Ref. 11). HIF-1α increases the expression of glycolytic enzymes and angiogenic factors, which can support the host-defense responses that consume energy in infected and inflamed tissues (14). Conditional deletion of HIF-1α in myeloid cells blocks the normal inflammatory response (2) and HIF-1α increases TNF-α by a nitric oxide (NO)-dependent mechanism (7). NO also modulates carotid body activity (9), which adds another layer of complexity. Innate immunity and hypoxia are two evolutionarily ancient responses to stress that may be coupled because there is survival value in their synergistic actions, for example, during trauma or infection. Alternatively, both responses may be based on a common and even more ancient mechanism such as O2-sensitive prolyl hydroxylases. Hence, understanding the molecular, cellular, and integrative mechanisms of plasticity in the carotid body during chronic hypoxia has the potential to explain even more than the different time domains of the hypoxic ventilatory response (cf., Ref. 8).

GRANTS
This work was supported by National Heart, Lung, and Blood Institute Grant R01-HL-081823 and the University of California White Mountain Research Station.

REFERENCES