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Overview: The Neurochemistry of Respiratory Control

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This Special Issue reviews important neurochemical aspects of the neural system controlling breathing. In recent decades substantial progress has accumulated identifying neurotransmitters, modulators, receptors, and trophic or modulatory proteins associated with specific neuroanatomical circuits. This work has been fueled, in part, by dramatic advances in molecular neuroscience, including improved techniques for determining the neurochemical constituents of individual cells and of the networks in which they participate.

Multiple approaches have been used to unite the physiology of respiration with a rapidly expanding catalog of relevant neurochemicals and these approaches are highlighted in the papers presented in this Special Issue. In the papers presented by Alheid and McCrimmon, Doi and Ramirez, Horner, Kubin and Volgin, Pilowsky, and by Stornetta, neurotransmitters, and their varied receptors are considered in the context of those found within specific classes of respiratory neurons, including those participating in sensory processing, rhythm generation and motor pattern formation.

One remarkable aspect of the respiratory control system is its adaptability and the extent to which neurotransmitters, their associated receptors, and their postsynaptic targets, change throughout early life. Contributions specifically focused on neurochemical modifications during development are presented by Dutschmann et al., Fregosi and Pilarski, Kubin and Volgin, Montandon et al., and by Wong-Riley and Liu. A remarkable observation is that neurochemical changes in development exhibit critical periods where respiratory function may be particularly vulnerable to disruption. For human infants the interaction of such a window of instability with compromised respiratory development of genetic or environmental origins are manifestly life-threatening in devastating disorders such as sudden infant death syndrome (SIDS).

In closely related, and in part, overlapping papers, mutations associated with genetic disorders of breathing are described. The papers by Gallego and Dager, Ogier and Katz, and by Weese-Meyer et al. address the severely disrupted respiratory phenotypes associated with specific genetic mutations that may underlie SIDS, congenital central hypoventilation syndrome (CCHS) and Rett syndrome.

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The lifelong demand to maintain homeostasis in arterial P_{O_2} and P_{CO_2} , requires plasticity in respiratory control in order to accommodate environmental (*e.g.* altitude) or physiological changes (*e.g.* changes in body mass, activity, or the onset of lung pathology). Neurochemical changes that underlie plasticity in respiratory control are addressed in papers by Dutschmann et al., Kline, Golder, and Mantilla and Sieck. Additional papers by Ling, MacFarlane et al, Kumar and Prabhakar, Nanduri et al., and Powell and Fu focus on respiratory neuroplasticity in response to intermittent or sustained hypoxia.

Breathing is influenced by vigilance state. Respiration is typically highest during wakefulness and particularly susceptible to disruption during sleep. Accordingly, neurochemical changes occurring over the sleep-wake cycle are addressed by Carley and Radulovacki, Horner, Kubin and Volgin, and by Kuwaki.

Many investigations concerning the neurochemical control of respiration focus on defining the neurochemical phenotypes of identified respiratory cells groups of the brainstem and spinal cord. One common approach to this question is the pharmacological activation or blockade of post-synaptic receptors on respiratory neurons, and identification of the afferent neurons targeting these receptors. The impact of specific neurotransmitter receptors on breathing are reviewed in papers by Doi and Ramirez, Funk et al., Gargaglioni et al., Hodges and Richerson, Kuwaki, Lalley et al., Ling, Reeves et al., Viemari, and by Wilson and Cummings. Further, while hormonal influences on breathing are evident, this topic has not been extensively investigated. Sex hormone effects on respiratory motoneurons are described in the paper by Behan and Wenninger, however, the respiratory effects of many other hormone systems await investigation.

Finally, one of the most critical clinical aspects of the neurochemical control of respiration is the interaction of analgesia and anesthesia with respiratory circuits. Their impact on synaptic transmission in respiratory circuits is discussed by Lalley and by Stuth et al., including the effects of anesthetics on the gain (magnitude) of activity on respiratory nerves.

The neurochemical control of breathing is a broad topic, as illustrated by the reviews contained in this Special Issue of *Respiratory Physiology & Neurobiology*. Given the rapid advances in this area, it is hardly possible to claim that any review, or small collection of reviews, will adequately cover this field. Thus, this Special Issue can be regarded as the “tip of the iceberg.” We applaud the authors for contributing their time and energy to the success of this Special Issue. Given the excitement in the field and its rapid expansion, we anticipate that the coming decade will witness astonishing progress in understanding the neurochemical control of respiration.

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