On the opiate trail of respiratory depression

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Agonists at μ-opiate receptors are very important clinically in the alleviation of pain. A well known and unwanted side effect is the marked depression of breathing that complicates their clinical administration and is potentially life threatening when opiates are abused. Neuronal μ-opiate receptors are widespread in the ventrolateral medulla including on neurons in the region of the ventral respiratory column. Their activation reduces breathing frequency and tidal volume, as well as the respiratory response to chemoreceptor stimulation elicited by an elevation in arterial carbon dioxide. Many brain stem respiratory neurons are known to be sensitive to the application of μ-opiate agonists, but the specific neuronal targets causing respiratory depression are relatively poorly understood.

In a technical tour de force in the cat, Lalley (8) in this issue of the American Journal of Physiology—Regulatory, Integrative and Comparative Physiology identifies specific classes of respiratory neurons whose activity is directly influenced by drugs with activity at central nervous system μ-opiate receptors and demonstrates that the respiratory effects of these opiates are not dependent on any concurrent anesthetic agents.

Neurons important for the generation of respiratory rhythm and pattern are concentrated in the ventrolateral medulla. Extending the entire length of the ventrolateral medulla these neurons form the ventral respiratory area (VRC; 1) consisting of neurons that discharge bursts of action potentials with fixed temporal relationships to the breathing cycle. Within the VRC, neurons exhibit various degrees of segregation with respect to their hypothesized roles in generating respiratory rhythm (i.e., breathing frequency) or breathing pattern (i.e., the intensity and the temporal pattern of activation of different respiratory muscles such as the diaphragm and intercostal muscles).

Opiate effects on respiratory rhythm generation. One VRC subregion, termed the pre-Bötzinger complex (pBC), contains propriobulbar neurons postulated to play an essential role in respiratory rhythm generation (14). Consistent with this view, in vitro pharmacological experiments have implicated pBC neurons that coexpress μ-opiate and neurokinin-1 receptors (i.e., receptors for substance P) as probable respiratory rhythmogenic neurons (4, 5). These neurons are likely candidates for explaining the effects of μ-opiate agonists on respiratory rhythm. Lalley (8) demonstrates that μ-opioid receptor agonists directly inhibit a subset of inspiratory neurons found within this region.

This view of the role of the pBC in respiratory rhythm generation was recently expanded after identification of a second group of rhythm-generating neurons that are μ-opioid insensitive (12) and located rostroventral to the pBC (12). They synaptically interact with pBC neurons to form a circuit consisting of coupled oscillators, each capable of independently generating rhythmic firing in the absence of the other (11, 12). Agonists for μ-opiate receptors appear to selectively disrupt inspiratory rhythm generation by pBC neurons while sparing an expiratory rhythm generated in the more rostral area (11, 16). This rhythm does not appear to be transmitted to many of the respiratory muscles innervating the chest wall as Lalley (8) showed that the premotor input to these muscles began discharging tonically after suppression of inhibitory synaptic potentials. Interestingly, however, an opiate-insensitive expiratory rhythm persists at least on a subset of lumbar motoneurons innervating abdominal muscles (7, 11). The detailed functional consequences of this postulated dual oscillator system for the in vivo regulation of normal adult respiration (eupnea) has yet to be incorporated into computational models of respiratory rhythm generation.

Opiate effects on respiratory pattern generation. In addition to depression of respiratory frequency, μ-opiate receptor activation also decreases chemoreceptor drive and tidal volume as well as altering pulmonary mechanics (13). Agonists at μ-opiate receptors also directly depress the activity of ventral medullary respiratory neurons likely to be involved in the control of respiratory motor pattern (3). Central to this role are the bulbo spinal premotor neurons innervating spinal respiratory motoneurons including phrenic, intercostal, and abdominal motoneurons. Both inspiratory and expiratory bulbo spinal neurons were clearly inhibited by μ-opiate agonists in the study of Lalley (8). Of particular note, he describes a potential mechanism for the decreased chest wall compliance that accompanies opiate administration. Suppression of expiratory phase synaptic inhibition causes expiratory bulbo spinal neurons to discharge continuously, leading to a low-level tonic activation of spinal expiratory muscles.

Interestingly, although phrenic premotor neurons are glutamatergic (6, 10, 15), the majority of these also appears to be enkephalinergic (15), so that direct actions of opiates at the phrenic nucleus may also contribute to the regulation of respiratory motor pattern. Agonists at μ-opiate receptor agonists also inhibit cholinergergic neurotransmission at airway smooth muscle.
and by this means can contribute to airway obstruction (2). However, a central mechanism of action is also implicated by Lalley’s (8) observations that vagal motoneurons promoting dilation of the vocal folds are directly inhibited by μ-opiate agonists. Drugs acting at μ-opiate receptors are important clinical tools but are also widely abused. In either case, depression of breathing is a dangerous side effect. This complicates its beneficial application as an analgesic and has engendered pharmacological efforts to separate these two effects (9). Whatever the problems related to exogenous applications of μ-opiates, it is clear that endogenous opiate transmitters are intimately involved in the neuronal organization of normal respiration. Characterization of the multiple levels at which these neuromodulators contribute to the control of respiration has clearly become an important avenue for respiratory research and the present detailed observations of opiate actions at individual respiratory neurons described by Lalley (8) are an important contribution to this progress.

REFERENCES