Morphine-Induced Acetylcholine Release at the Hypoglossal Motor Nucleus: Implications for Opiate-Induced Respiratory Suppression

Comment on Skulsky EM, Osman NI, Baghdoyan HA, Lydic R; Microdialysis Delivery of Morphine to the Hypoglossal Motor Nucleus of Wistar Rat Increases Hypoglossal Acetylcholine Release. SLEEP 2007;30(5):566-573

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Morphine and other analgesic drugs derived from opium exert their physiological effects by mimicking the action of endogenous opioid peptides, the natural ligands for opioid receptors. Opioid drugs have been used for the management of acute and chronic pain for hundreds of years, and they remain the basis of pain management in clinical medicine today. In addition to their analgesic actions, opiate drugs also significantly affect mood and emotion, induce drowsiness and alter respiratory, cardiovascular, gastrointestinal, and neuroendocrine functions. The suppression of breathing is a well-known and potentially serious side effect when opiate drugs are administered clinically; this can be a major problem when these drugs are abused because of the risk of respiratory arrest.

The significant suppression of breathing produced by opiate drugs has stimulated efforts to determine the basic mechanisms underlying this suppression, as well as efforts to devise pharmaceutical strategies to avoid the adverse respiratory effects but preserve the analgesic actions. The study by Skulsky and colleagues in this issue of SLEEP is significant because it reveals in anesthetized rats a novel morphine-induced acetylcholine release at the hypoglossal motor nucleus. This release of acetylcholine was dose-dependent, and blocked by μ but not κ opioid receptor antagonists. This increase in acetylcholine release elicited by morphine at the hypoglossal motor nucleus is in direct contrast to the decreased acetylcholine release observed with morphine at other more rostral brain regions, particularly those associated with REM sleep and electrocortical arousal. The effect of decreased acetylcholine release in brain regions modulating arousal may contribute to the drowsiness and decreased REM sleep with opiate drugs. Although the functional consequences of the morphine-induced increase in acetylcholine release at the hypoglossal motor nucleus was not studied by Skulsky et al, it has been shown previously that increased endogenous acetylcholine at this motor pool leads to decreased genioglossus muscle activity in anesthetized rats. This suppression of genioglossus muscle activity is mediated by an inhibitory muscarinic receptor effect that overwhelms background nicotinic receptor-mediated excitation. Whether morphine at the hypoglossal motor nucleus leads to decreased genioglossus muscle tone mediated, at least in part, by muscarinic receptor mechanisms remains to be determined.

The study by Skulsky and colleagues focused on the hypoglossal motor nucleus because this nucleus is the source of motor outflow to the genioglossus muscle of the tongue. The genioglossus, in conjunction with the other pharyngeal muscles also innervated by the hypoglossal motor nucleus, helps maintain an open airspace for effective breathing and prevent obstructive apneas. Determining the effects of opioid drugs on the neurochemical environment at the hypoglossal motor nucleus and genioglossus muscle activity is directly relevant to understanding the predisposition to airway obstructions in sleep with these analgesic medications, and to understanding the vulnerability of breathing during recovery from surgical levels of anesthesia when opiate drugs are also present. In this respect, the implication that the morphine-induced increase in acetylcholine at the hypoglossal motor nucleus may contribute to suppression of respiratory motoneuron activity independent of opiate receptor mechanisms is significant. This significance is further increased because previous attention has largely focused on the effects of opiates directly on central respiratory neurons rather than on motoneurons, which are the final common output pathway that directly activate respiratory muscle. The physiological effects of opiate drugs on the mechanisms controlling respiratory motoneurons has been little studied despite the obvious clinical relevance.

In general, opioid drugs cause dose-dependent suppression of breathing by decreasing both respiratory rate and tidal volume, and by decreasing the ventilatory responses to hypoxia and hypercapnia. Morphine and most other clinically used opioids exert their effects via μ opioid receptors which are expressed widely in the brainstem structures comprising the respiratory network. Determining the effects of opiates on central respiratory neurons is of interest from the clinical perspective of understanding the basis for the respiratory suppression; it is also of interest because the apparent differential sensitivity of specific central respiratory neurons to opiate drugs has generated insight into the mechanisms underlying the fundamental rhythm of breathing and the ability to maintain breathing despite a surge in endogenous opiates at birth.

Detailed electrophysiological studies in animals have shown that many brainstem respiratory neurons are sensitive to the application of μ receptor agonists, and these effects can contribute to reduced respiratory rate, decreased inspiratory neural drive, and decreased tidal volume. In particular, a small region of

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The study by Skulsky et al is an important step in characterizing opioid effects locally at respiratory neurons and motoneurons. Further characterization of the effects of central opioid administration on breathing, pharyngeal and respiratory pump muscle activities, and involvement of neurotransmitters such as acetylcholine will be a fruitful and clinically important avenue for future research. Such research may lead to identification of pharmacological methods to reduce the respiratory suppressant effects of opiate drugs but preserve their analgesic activity. Such knowledge may improve the postoperative care of individuals prone to upper airway obstructions, such as children undergoing adenotonsillectomy for obstructive sleep apnea who have a higher sensitivity to μ-opioid receptor agonists and in whom postoperative difficulty in breathing is higher than in children without obstructive sleep apnea.

REFERENCES