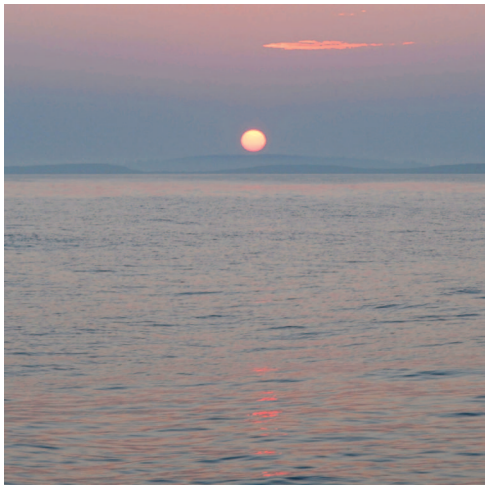
Sleep and Anesthesia

The Histamine Connection

SLEEP is essential for survival in mammals. However, the relationship of sleep to anesthesia and coma is not clear. The tuberomamillary nucleus (TMN) of the posterior hypothalamus has an established role in natural sleep and recently has been implicated in anesthesia. This nucleus contains the cell bodies of neurons that release histamine, an excitatory neurotransmitter that plays a major role in the regulation of sleep-wake cycles and arousal.[1] Interestingly, Luo and Leung have shown that enhancement of excitatory histamine H1 receptor-mediated transmission in the nucleus basalis magnocellularis (a nucleus involved in sleep-wake regulation) induces electroencephalographic arousal and facilitates emergence from isoflurane anesthesia in rats.[2] In an experimental study published in this issue of ANESTHESIOLOGY, these authors provide additional evidence for a role of histaminergic TMN neurons in the maintenance of anesthesia. They report that depletion of histamine content by selective targeted neurotoxic lesions of the TMN or pharmacologic blockade of central H1 receptor-mediated histaminergic transmission facilitates anesthesia by isoflurane but not by several intravenous anesthetics.[3]



"… reactivation of brain arousal systems, such as the histaminergic TMN neuron pathways, appears to account in part for maintenance and emergence from anesthesia."

Anesthesia is often considered to be pharmacologically induced artificial sleep, but it is clinically more akin to a reversible drug-induced coma because the anesthetized patient is unrousable compared with the sleeping patient. Enhancement of inhibitory γ-aminobutyric acid–mediated (GABAergic) neurotransmission has been established as an important molecular mechanism for many anesthetic agents.[4] Considerable evidence suggests that specific GABAergic pathways in various brain regions converge and contribute to anesthesia. TMN histamine neurons send dense excitatory projections to the basal forebrain and participate in the state of wakefulness.[5] The TMN receives important GABAergic projections that inhibit the activity of the histaminergic neurons during sleep. Blockade of GABAergic transmission locally in the TMN in rats *in vivo* attenuates the anesthetic response to intravenous anesthetics that act as positive modulators of γ-aminobutyric acid type A receptors. This suggests a role for reduced activity of TMN histaminergic neurons in the production and/or maintenance of anesthesia.[6]

The authors examined the impact of selective stereotaxic lesions of histaminergic neurons in the TMN and pharmacologic manipulation of central histamine H1 and H2 receptors on loss of righting reflex (a gross measure of anesthesia in rodents) induced by isoflurane or the intravenous anesthetics propofol, pentobarbital, or ketamine. Rats with selective destruction of TMN histaminergic neurons produced by local administration of orexin-saporin lost their righting reflex at significantly lower concentrations of isoflurane. In lesioned animals, the time to onset of loss of righting reflex was unchanged, but the recovery time was significantly prolonged compared with sham lesioned rats. Intracerebroventricular delivery of the histamine H1 receptor antagonist triprolidine, but not of the H2 histamine receptor antagonist cimetidine, also decreased isoflurane requirements for the loss of righting reflex. In contrast, sensitivity to pentobarbital, propofol, or ketamine was unaffected by any of these manipulations of histaminergic signaling.

A number of potential molecular targets of anesthetics in the central nervous system have been identified, such as certain γ-aminobutyric acid type A receptor subtypes, but recent attention has focused on how modulation of neuronal networks leads to the state of anesthesia. This elegant study, together with the authors' previous work, represents an important step forward in understanding how anesthetics act on specific brain nuclei to produce their effects. It demonstrates a role for TMN histaminergic neurons in modulating both maintenance and emergence from isoflurane anesthesia. These two phenomena appear to involve distinct networks and mechanisms, with emergence no longer considered a passive reversal of anesthesia relying solely

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on pharmacokinetic elimination of the anesthetic.[7] Histaminergic TMN neurons send dense excitatory projections to the basal forebrain. The authors hypothesize that reduced activity of TMN neurons, which is associated with reduced arousal, facilitates anesthesia, whereas restoration of TMN activity, which is critical for brain arousal, is an important signal for emergence from anesthesia. The time to onset of loss of righting reflex induced by isoflurane was not affected by histaminergic neuron depletion in the TMN or by acute central histamine H1 receptor blockade. As emphasized by the authors, this suggests that neuronal pathways involved in the control of sleep-wakefulness other than the excitatory histaminergic TMN system (the noradrenergic neurons of locus ceruleus, for example) contribute to the induction of isoflurane anesthesia.

The absence of a major influence of TMN histaminergic neurons on induction of anesthesia by isoflurane, and possibly other halogenated anesthetics, might be common to other systems involved in the control of sleep-wakefulness.[7] Thus, reduced activity of other arousal pathways, such as the orexinergic system, does not account for halothane-induced anesthesia.[8] Conversely, a role for activation of orexinergic neurons in promoting emergence from halothane or sevoflurane anesthesia has been suggested.[9] Because orexins are devoid of an arousal effect in histamine H1 receptor knockout mice, histaminergic signaling is required for the arousal state produced by orexin.

Another important finding reported by Luo and Leung is that anesthetic sensitivity to intravenous anesthetic agents was unaffected by modulation of the TMN histamine system. Based on these findings, it is tempting to conclude that histaminergic neurons do not contribute to the anesthetic mechanisms of the γ-aminobutyric acid type A receptor-modulating agents pentobarbital and propofol, in contrast to isoflurane. This is consistent with the greater involvement of GABAergic mechanisms in anesthesia produced by propofol compared with isoflurane,[10] which is known to interact with multiple molecular and cellular targets at clinical concentrations.[1] From the current findings, it might also be speculated that antihistamine H1 receptor blockers (which frequently are given as preanesthetic medications) may attenuate a patient's emergence from anesthesia preferentially when volatile, rather than intravenous, anesthetics are used for maintenance of anesthesia. However, it is premature to conclude that the role played by histaminergic TMN neurons in anesthesia is agent-specific because other inhaled anesthetics have not been tested. Limitations inherent to stereotaxic lesions must also be considered, as nicely discussed by the authors. It is difficult to compare directly the effects of muscimol (an agonist of the γ-aminobutyric acid type A receptors) and orexin-saporin injections into the TMN because diffusion of these agents beyond the TMN could lead to effects on nearby nonhistaminergic neurons and because of possible compensatory mechanisms occurring days after the neurolytic TMN injections.

There are several important limitations to the experimental approach used in addition to those discussed by the authors. Loss of righting reflex is an imperfect measurement of loss of consciousness that importantly depends on the spinal component of anesthesia. Although the differences observed in isoflurane anesthesia between lesioned and sham animals were statistically significant, they were modest in magnitude, emphasizing that neuronal pathways in addition to the TMN histaminergic pathway contribute to isoflurane anesthesia. Clearly more work needs to be done, but the authors are to be congratulated for undertaking this sophisticated and elegant approach to anesthetic neuropharmacology. Although anesthesia and natural sleep exhibit significant differences in their mechanisms,[7] endogenous sleep-wake mechanisms might provide important points of convergence for anesthetic effects on neuronal networks regulating arousal. Reduced activity followed by reactivation of brain arousal systems, such as the histaminergic TMN neuron pathways, appears to account in part for maintenance and emergence from anesthesia.

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