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General Anesthesia and Ascending Arousal Pathways

THE ability to produce a reversible loss of consciousness is the defining characteristic of general anesthetics. It is also the most fascinating and elusive. Although the molecular targets of many anesthetics have been identified, they are widely distributed in the central nervous system. Therefore, identifying the locus of action of these drugs in the brain represents a major challenge. The neuronal mechanisms of sleep, a physiologic state that involves a loss of consciousness, provide one obvious avenue of enquiry.[1] Brain imaging and electroencephalographic studies give a broad characterization of the anesthetic state and show clear similarities with the sleeping brain. However, natural sleep and wakefulness are controlled by multiple arousal pathways, as well as by the intimate connectivity between the thalamus and cortex. Anesthetics could cause a loss of consciousness by pressing a switch in any (or all) of these regions, for example by disrupting intracortical connectivity[2] by directly triggering burst firing in the thalamus[3,4] or by inhibiting ascending arousal pathways.[5–7] An interesting study presented by Luo and Leung in this issue of ANESTHESIOLOGY is the latest evidence that the ascending control of natural sleep-wake cycles may be targeted in drug-induced loss of consciousness.[8]

Luo and Leung investigate whether the histaminergic system contributes to the neural mechanism of isoflurane anesthesia. The tuberomammillary nucleus is the sole source of histamine in the brain, and has been previously implicated in the actions of γ-aminobutric acid–mediated anesthetics such as propofol and pentobarbital[5,7] and the α_2 adrenoceptor agonist dexmedetomidine.[6] Centrally active histamine receptor antagonists are known to cause sedation, and histamine levels are reduced during both natural sleep and anesthesia. However, the tuberomammillary nucleus sends projections to the entire brain, so exactly how histamine release produces behavioral and electroencephalographic arousal needs further investigation. The new study focuses on the possible role of histaminergic excitation of the basal forebrain, a structure implicated in the control of arousal largely because of its widespread cholinergic innervation of the cerebral cortex.

The authors take an *in vivo* approach, studying the effects of histamine and histamine receptor antagonists on cortical (and hippocampal) recordings from anesthetized rats, using power spectral analysis and the burst suppression ratio to quantify the electroencephalography under isoflurane anesthesia.

In the first part of the study, histamine was locally infused into the nucleus basalis magnocellularis (NBM) of the basal forebrain during burst suppression caused by isoflurane (at 1.4%). The electroencephalography shows a pronounced shift to increased delta and theta power, equivalent to the pattern recorded at lower concentrations of isoflurane. The respiratory rate was also increased, which the authors cite as a measure of behavioral arousal. Behavioral arousal itself was not observed, but this was presumably because of the high concentrations of isoflurane used. Future studies on the effects of histamine in the NBM at a concentration of isoflurane just above that required for loss of righting reflex would be informative in terms of the correlation between behavioral and electroencephalographic measures of anesthetic depth. However, they do show that histamine infusion into this region speeds up emergence from isoflurane anesthesia.

Luo and Leung do not study induction, and it remains an open question whether these two processes are caused by separate neuronal mechanisms as recently suggested by Kelz *et al.*[9] In studies of induction and emergence there is an intrinsic asymmetry in both the arousal state of the animal and the experimental design. For induction, the animal is in a state of high arousal during equilibration with the anesthetic before loss of righting reflex. During emergence the animal is awakening from a quiescent state, with the anesthetic being slowly cleared by the animal. Perhaps this inevitable asymmetry does mean that some anesthetic targets are more important than others during induction *versus* emergence, but it is hard to see why a pathway that clearly mediates one should not be able to impact the other.

Of course, just because the infusion of histamine into the NBM *can* elicit cortical arousal and reduce emergence time, this does not necessarily mean that this phenomenon plays a role in anesthetic action. First, direct cortical or thalamic projections of the tuberomammillary nucleus may be just as important. Second, and perhaps more importantly, agonists for a wide range of excitatory neurotransmitter systems have been shown to counteract the effects of anesthetics. Enhancing cholinergic,[10,11] orexinergic[7,9,12] and serotonergic[13] drive have all been shown to attenuate anesthesia; histamine is not unique in this respect. This probably reflects the redundancy of brain arousal systems, that is, the multiple parallel pathways through which the cortex can be excited. The application of exogenous neurotransmitters

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will alter the baseline arousal against which the anesthetic effect is being measured. Pinning down which neurotransmitter systems are the real anesthetic targets and which are merely able to overcome anesthesia through a physiologic excitation is therefore fraught with difficulties. The authors attempt to address this issue by showing that an antagonist (triprolidine) specific to the histamine H1 receptor can affect measures of isoflurane anesthesia.

Triprolidine alone did not produce loss of righting reflex or reverse the burst suppression caused by higher doses of isoflurane, but it did produce a significant increase in emergence time. However, centrally acting H1 antagonists are well known sedatives. Therefore, even experiments with antagonists can be problematic because of their effects on arousal in the control state. In isolation, the effect of triprolidine on emergence could be because of its sedative properties, independent of whether the tuberomammillary nucleus was inhibited by isoflurane. Having said this, neurotransmitter antagonists can also be a powerful tool. The authors show that although applying triprolidine alone to the NBM did not affect burst suppression, it could block histamine-induced activation, suggesting that at sufficiently high isoflurane concentrations histaminergic tone in the NBM is completely inhibited. The effects of triprolidine on emergence time are consistent with the reactivation of the histaminergic system and specifically histamine release in the NBM as a physiologic component of arousal from anesthesia. It would be interesting to compare these local effects of triprolidine to a systemic (*e.g.*, intracerebroventricular) application of the drug; the ceiling effect would inform whether the NBM is the sole target of histaminergic activation or whether behavioral arousal is also because of the excitation of other structures, such as the thalamus or cerebral cortex.

This study adds some weight to the idea that anesthetic-induced depression of arousal pathways is a part of the mechanism by which these drugs cause a loss of consciousness. It also draws attention to the difficulty of attributing the actions of anesthetics to a specific pathway, because altering baseline arousal can affect susceptibility to anesthesia. Therefore, investigating (ideally through unit recordings) how anesthetics actually affect neuronal activity will be fundamental in determining whether the various neurotransmitter systems are mechanistically involved in causing loss of righting reflex, or whether they merely modulate this state because of actions on parallel arousing or sedating pathways.

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