

Galloping in Full Pursuit of the Mechanism of Anesthetic Immobility

THE pharmacology of general anesthetics is the essence of anesthesiology, and the quest to understand how volatile anesthetics work has occupied anesthetic pharmacologists for more than a century. Immobility in response to a painful stimulus, usually an incision in the clinic or a tail clamp in the laboratory, is used as a measurable endpoint for quantifying anesthetic potency that is much more accessible than complex endpoints such as amnesia or unconsciousness. Understanding immobility has therefore become the focus of most investigations into the fundamental mechanisms of this pharmacologic conundrum. However, efforts to determine the mechanisms of volatile anesthetic drugs have been stymied by the complexity of the neural networks that underlie behavior. Now-classic studies from the early 1990s^{1,2} showed that the spinal cord is the principal anatomical locus for volatile anesthetic-induced immobility in response to a noxious stimulus as defined by the minimum alveolar concentration (MAC) of anesthetic required to suppress movement.³ This has focused attention on the underlying neurobiologic mechanisms of the relatively simple pathways involved in spinal cord reflexes. A critical question in this regard has been the relative role of anesthetic effects on dorsal nociceptive inputs *versus* ventral motor outputs in the suppression of movement. Jinks *et al.*⁴ have now taken a large step toward solving the mystery of MAC by isolating anesthetic actions on motor responses that originate in the ventral horn of the spinal cord from anesthetic effects on activation of dorsal horn neurons by peripheral nociceptors involved in the withdrawal reflex.

Locomotion results from a spinal neuronal circuit or central pattern generator capable of generating the basic locomotor pattern.⁵ Using a decerebrate rat model that eliminates cortical effects (and that does not significantly change MAC, as shown previously for isoflurane²), Jinks *et al.* have cleverly removed the requirement for activation of the dorsal horn by a noxious mechanical stimulus to elicit a motor response. Locomotion (four-limb galloping) is induced through a descending pathway by direct electrical microstimulation of the mesencephalic locomotor region (MLR). This midbrain region contains the

cuneiform and pedunculopontine nuclei, which send axons to reticulospinal neurons in the ventromedial medulla. These medullary neurons project to the spinal cord to activate ventral central pattern generating networks that produce rhythmic locomotor activity in motoneurons (fig. 1 in Jinks *et al.*⁴). MLR stimulation also inhibits activation of dorsal horn neurons by noxious stimuli, adding to the specificity of ventral mechanisms in MLR-evoked locomotion. Normally, a noxious stimulus excites dorsal horn neurons, which in turn activate the central pattern generator to produce rhythmic movement. This response is blocked by volatile anesthetics at MAC. By comparing the anesthetic requirement to block MLR-elicited movement, which is independent of dorsal horn activation, with that for noxious stimulus-evoked movement in decerebrate rats, the relative importance of dorsal and ventral spinal cord involvement in anesthetic-induced immobility could be resolved independent of descending pathways. Both isoflurane and halothane inhibited movement induced by direct activation of the MLR at concentrations only slightly higher (10% for isoflurane and 21% for halothane) than those required to inhibit movement in response to the classic supramaximal tail clamp (MAC). This indicates that the impact of dorsal horn effects on anesthetic suppression of movement in response to a painful stimulus is relatively limited. These technically challenging experiments, making use of intact neuronal networks critical to the immobilizing effects of anesthetics, support a recent article from the Antognini group,⁶ which showed that responses of ventral horn neurons to nociceptive stimuli are more sensitive to isoflurane and halothane than dorsal horn neurons.

These results should not be confused with simple direct inhibition of motor neuron excitability. Stimulation of the MLR activates central pattern generators to evoke stepping behavior. These are complex multisynaptic spinal networks that are responsible for complex motor reflexes and could be subject to anesthetic inhibition at multiple levels. The results of the current experiments do suggest that the targets critical for immobility are in ventral regions of the spinal cord. This suggests that a close examination of the links between central pattern generators and motor neurons might be fruitful in the search for the cellular molecular mechanisms of volatile anesthetic-induced immobility. Although these data strongly suggest that the immobilizing properties of halothane and isoflurane are independent of dorsal horn actions, some caution is necessary in this interpretation. Anesthetic concentrations significantly higher than MAC were required for inhibition of MLR-evoked locomotion, consistent with the existence of a

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slightly more sensitive site in anesthetic suppression of noxious stimulus-induced movement. Because MLR stimulation also inhibits dorsal horn responses and produces behavioral analgesia to tail clamp, it could mask a potential dorsal horn-mediated analgesic effect of the anesthetics. The observations that halothane requirements for MLR-induced galloping were greater than those for isoflurane, coupled with the greater dorsal horn depression by halothane than by isoflurane,⁷ are consistent with at least a small dorsal horn contribution to halothane-induced immobility. These issues will require higher resolution studies of anesthetic effects on this fascinating neural network, in particular the relative contributions of locomotor network *versus* direct motoneuron effects. Further studies of these and other neuronal networks promise to provide a useful bridge between studies of the molecular and behavioral effects of anesthetics.

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