Consciousness, awareness, and the clinician

Ira Rampil MD

UNTIL recently, general anesthesia was considered by many to be an emergent phenomenon due to generalized suppression of neuronal electrical function. The mechanism of this action was thought related to lipophilicity, and hence due to some effect on the lipid bilayer of the neuronal cell membranes.¹ That once prevalent unitary hypothesis of anesthetic mechanism (anesthesia is created by a common effect on all neurons)^{2,3} has now been displaced by an understanding that the state of general anesthesia is composed of several (semi) independent behaviours mediated at specific loci by (apparently) disparate mechanisms. Current research suggests that lipophilic sections of proteins may be the dominant sites of anesthetic action.⁴

This author considers that the state of general anesthesia is comprised of at least two major behavioural effects. Patients require oblivion, which at a minimum must include amnesia. Physicians require unresponsiveness, which must include at least surgical immobility and suppression of the reflexes that cause hemodynamic fluctuation due to noxious stimulation. As will be elaborated below, anesthesia-induced surgical immobility appears to be mediated at a spinal level, whereas learning and suppression of learning (amnesia) appear to require specific components of the cerebral hemispheres.

Surgical immobility

For decades, *sine qua non* of adequate general anesthesia was surgical immobility, i.e., that the patient did not move when surgical noxious stimulation began. As late as ten years ago, little was known about the way in which anesthetic drugs prevented somatic movements, aside from the Meyer-Overton relationship to lipophilicity,⁵ and that a general anesthetic had but minimal effects on axonal transmission⁶ or the neuromuscular junction at clinically relevant concentrations. Although inadvertent, Saidman and Eger's definition of the minimum alveolar concentration (MAC) response as "purposeful" movement⁷ probably biased subsequent investigators into the upper central ner-

vous system as the general area in which anesthetics acted. This hypothesis was supported by Angel who observed that afferent traffic from peripheral stimulation passed undiminished rostrally within the central nervous system up to the level of thalamus where the impulses were first suppressed by anesthetic agents then further suppressed in transmission to the sensory cortex.^{8,9} However, the electrical activity within the cerebral cortex also underlies the generation of the electroencephalogram (EEG). If both motor control and EEG activity derive from this same source, one might reasonably hypothesize that some aspect of the EEG should correlate with surgical immobility. Despite numerous attempts, no useful correlation has been reliably identified.^{10,11} Even during profound EEG depression, animals¹² and humans¹³ can have vigorous somatic motor activity in response to noxious stimulation. The question then naturally arises about the role of the cerebral cortex in modulating surgical immobility. A series of independent experiments suggests that, indeed, the spinal cord alone is necessary and sufficient to demonstrate anesthetic-induced suppression of somatic movement. Rampil *et al.* removed both cerebral hemispheres in anesthetized rats and found that potency (MAC) of isoflurane did not change due to the lesion.¹⁴ A second lesion study found no difference in isoflurane-induced suppression of movement, either above or below a T1 spinal transection.¹⁵ Todd *et al.* independently found that cerebral ischemic lesions of the cerebrum did not alter MAC of isoflurane in rats.¹⁶ Antognini *et al.* developed a model with isolated brain perfusion of the goat and found that isoflurane delivered only to the brain was remarkably impotent in preventing somatic movement in response to noxious peripheral stimulation.¹⁷ Taken together, these findings suggest that the "purposeful" movements classically taken as a positive response to the MAC test are spinal reflexes and that anesthetics can act solely at spinal sites to provide this component of general anesthesia. Having localized anesthetic-induced immobility to the spinal cord, it is possible to begin to define the neural circuits which underlie this phenomenon.

From the Department of Anesthesiology and Neurological Surgery, University of Stony Brook, New York, USA.

Address correspondence to: Dr. Ira Rampil, Department of Anesthesiology and Neurological Surgery, University of Stony Brook, L4-060 Health Sciences Center, Stony Brook, New York 11794-8480, USA. Phone: 631-444-2975; Fax: 631-444-2907; E-mail: ira.rampil@sunysb.edu

The simplest nocifensive spinal reflex is the withdrawal reflex, which may be as simple as a monosynaptic connection between an afferent dorsal root ganglion neuron and an a-motor neuron. This simple two-neuron circuit is elaborated with interneurons from central spinal pattern generators (which can coordinate multiple muscle groups and create more "purposeful" response movements) and descending inhibitory medullary (e.g., from the periaqueductal grey and nucleus raphe magnus) control fibres, as well as recurrent feedback synapses. Still, it is instructive to examine the effects of general anesthetics on the simple, two-neuron circuit. Clinically relevant concentrations of inhaled anesthetics do not significantly suppress axonal transmission of action potentials;⁶ therefore anesthesia is a perisynaptic phenomenon. The monosynaptic reflex response can be quantified *in vivo* using an electrophysiologic test known as the H (after Hoffmann) reflex. In this test, a mixed peripheral nerve is electrically stimulated and the electromyogram generated by muscles in the ipsilateral dermatome is recorded. With an intact monosynaptic reflex, an electrical stimulus will emulate the equivalent of a patellar tap, resulting in a muscle jerk, detected by its electrical signature in the corresponding muscle. Volatile anesthetics and nitrous oxide are known to depress this H reflex in humans.¹⁸ Sensation begins in large, fast conducting, Aδ nociceptive afferent fibres with soma in the dorsal root ganglia. Available evidence suggests that while parenteral anesthetics (e.g., thiopental or propofol) depress dorsal root ganglion neurons,¹⁹ volatile anesthetics have a variable effect (depending on the model), at least through the level of generating and conducting impulses from peripheral noxious stimuli to the dorsal horn of the spinal cord.^{20,21} Likewise, motor axons are little affected by anesthetics. Transmission across the neuromuscular junction is only slightly effected by clinically relevant concentrations of general anesthetics.²²

These observations point to the motor neuron and its synaptic connection to the afferent neuron as a likely substrate for anesthetic-induced surgical immobility. In *in vitro* excised rat spinal cord, it is possible to stimulate dorsal rootlets and tease apart several electrical responses based on the speed of the response. For example, the monosynaptic response has the shortest latency and a C-fibre nociceptive response is relatively delayed. Nociceptive afferents have been associated with many neurotransmitters and neuromodulators including a variety of peptides. However, the synapse to the motor neurons appears to use glutamate with excitatory AMPA type ionophores on the motor neuron.²³ The *in vitro* spinal monosynaptic reflex is blocked by the AMPA specific antagonist

NBQX and also by enflurane²⁴ or ethanol,²³ but not by propofol or barbiturates. Systemic,²⁵ but not lumbar intrathecal²⁶ blockade of AMPA reduces the MAC of inhaled general anesthetics by up to 60% in rats. Concurrent block of N-methyl-D-aspartate and AMPA receptors synergistically reduces MAC.²⁷ Blockade of metabotropic glutamate receptors does not seem to alter anesthetic potency.²⁸ Another possible mechanism for depressing the monosynaptic reflex might be an anesthetic-induced increase in inhibitory post-synaptic activity. Patch clamp experiments have demonstrated that the GABA_A and glycine gated ion channels (the major inhibitory channels in the spinal cord) are sensitive to volatile anesthetics. These agents increase the inward chloride current during each gated cycle, thus increasing the degree of hyperpolarization in the motor neurons. Lumbar intrathecal administration of glycine and GABA_A antagonists increases MAC by about 50%. Interestingly, altering a single specific amino acid in the transmembrane component of a subunit of either the glycine receptor, or the homologous location in the GABA_A receptor dramatically alters the sensitivity of these channels to inhaled anesthetics without necessarily altering the response to the native ligands, or to propofol or barbiturates. Studies are now underway to test the anesthetic sensitivity of transgenic animals with modified GABA_A or glycine receptors. Finally, another possible mechanism of action of anesthetics in inducing surgical immobility is a direct depression of the a-motor neurons.

Until recently, the effects of anesthetics on spinal motor neurons have received little attention. A seminal observation by Nicholl *et al.* found that frog spinal motor neurons were hyperpolarized by ether or halothane anesthesia.²⁹ The hyperpolarization was thought to be due to an increase in potassium ion conductance across the motor neuron membrane. This finding did not resonate, however, until after the demonstrations noted above that the spinal cord was the site of anesthetic-induced immobility. The excitability of a-motor neurons can be assessed non-invasively with the F-wave test. This test does not rely on any neuron-to-neuron synapse. In rats^{30,31} and humans,^{32,33} volatile anesthetics reduce the excitability of motor neurons, and the ED₅₀ is approximately 1.0 MAC. In tissue slices, ethanol³⁴ and enflurane²⁴ have been shown to reduce glutamate-induced ionophore currents with a post-synaptic mechanism. This reduction in excitability is independent of the inhibitory effects of GABA_A or glycine.²⁴ This reduced efficacy of excitatory ionophores may be due to a direct effect of anesthetics on the pore protein,^{35,36} analogous to the effects of anesthetics on inhibitory channels.³⁷

Finally, the anesthetic-induced potassium conductance noted by Nicoll *et al.*²⁹ has renewed currency. Other investigators have also observed neuronal hyperpolarization by general anesthetics.^{38,39} Franks and Lieb first identified a novel, anesthetic-sensitive background potassium "leak" channel (i.e., insensitive to neurotransmitters or membrane voltage) in mollusks.^{40,41} These channels have since been identified and cloned from the human genome⁴² and would seem to explain both presynaptic and post-synaptic suppression. These leak channels appear to contribute to hyperpolarization and depressed excitability of rat motor neurons by halothane⁴³ and by their presence in the locus coeruleus to analgesia and sedation.⁴⁴

Surgical amnesia

Consciousness and memory are functions of our nervous system, of which we have a meager knowledge. At present, we have some fragmentary knowledge of some of the simplest forms of learning. One such form of learning, Pavlovian conditioning, is conveniently studied in small animals. For example, animals exposed to a particular sound followed by an electrical shock quickly learn to associate the two, and will become anxious hearing that sound for weeks afterward. If however, the animals are exposed to a sub-MAC of anesthetic during the initial training, they develop less recall and anxiety in later testing. Perhaps this auditory memory is a very primitive version of a patient recalling intraoperative, distasteful conversations?

Elegant studies by Ledoux, and by Fanselow and others suggest that auditory associations with painful stimuli are formed in the basolateral amygdala (in rats at least), which then projects to the sites that mediate the components of the fear/anxiety response. Investigations of anesthetic effects in the amygdala and other parts of the limbic system are ongoing.

Intraoperative awareness

Between the strident sensationalist media coverage and the absolute denial expressed by many practitioners, it is difficult to gauge the true prevalence of intraoperative awareness. Many patients do not come forth out of fear for being labeled crazy. Several recent prospective studies place incidence of intraoperative awareness at approximately 0.2%. A recent prospective survey of patients at the author's institution detected two probable cases of awareness in approximately 1,600 patients. The literature provides several risk factors for awareness including gender, the use of muscle relaxants and/or opioids, the absence of volatile agents, and the type of surgery. Probably related to the widespread use of opioids, episodes of intraoperative awareness are seldom

reflected by changes in the patient's vital signs. In fact, vital signs have never been validated as a monitor for intraoperative awareness. Severe psychological consequences (e.g., post-traumatic stress disorder) following awareness is relatively rare, but may be exacerbated by recall of pain or of paralysis. In the United States, awareness claims constitute less than 2% of cases in the closed malpractice claims database. The relatively small number of cases may be due to the historically low median payout of \$18,000.

Unlike its failure to correlate with patient movement, the EEG or evoked potentials may prove to be useful monitors for level of sedation or "hypnosis." A multicenter trial is currently underway to test the hypothesis that bispectral EEG monitoring reduces the incidence of awareness. Until the results are available, several simple guidelines will reduce the incidence of awareness: keep the vaporizer or infusion system full of anesthetic agent, do not use neuromuscular blockade unnecessarily, use opioids as analgesics, not as hypnotics, and minimize disrespectful conversations during surgery.

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