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Ion Channels Take Center Stage

Twin Spotlights on Two Anesthetic Targets

ONE of the fundamental ideas behind the science of anesthesiology throughout the majority of the twentieth century was the idea that there exists a "unitary site" of action for all general anesthetics.[1] As our knowledge of the underlying neurobiology has grown, together with the database of potential anesthetic target sites, it has become increasingly obvious that this simplistic notion is incorrect.[2] It now seems unlikely that general anesthetics interact with a single common target site because the function of a variety of membrane proteins has been shown to be altered within the clinically relevant range of anesthetic concentrations.[3] Not only do multiple potential anesthetic targets exist, but the array of susceptible targets varies among different classes of anesthetic (review of Krasowski and Harrison[4]). For example, clinical concentrations of pentobarbital inhibit depolarization mediated *via* AMPA- and kainate-type glutamate receptors, enhance and prolong γ-aminobutyric acid (GABA)-mediated inhibition *via* an action at $GABA_A$ receptors, and inhibit the function of neuronal nicotinic acetylcholine receptors (n-nAChRs), whereas ketamine has no effect at $GABA_A$ receptors, but inhibits the function of the *N*-methyl-D-aspartate (NMDA) subtype of glutamate receptors (reviews of Franks and Lieb[3] and Krasowski and Harrison[4]).

As the century draws to a close, this "multiple alternate target" hypothesis gains further support from a study published in this issue of ANESTHESIOLOGY.[5] In this study,

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Sara de Sousa *et al.*,[5] from Nick Franks' laboratory in London, compare the synaptic actions of the everyday inhaled anesthetic isoflurane with those of the more exotic noble gas xenon. Although isoflurane is easy to obtain and study, the expense and lack of potency of xenon have long been obstacles to the study of its mechanism of action. Yet, in evaluating the various hypotheses of anesthetic mechanism, it is desirable to study a variety of anesthetic structures to test the general applicability of a potential mechanism. Xenon is a monoatomic inert gas and therefore seems like an unpromising substance for which to seek selective actions. Remarkably, Franks *et al.* has shown that xenon, applied at approximately 80% atm to cultures of rat hippocampal neurons, inhibits currents through the NMDA receptor, but fails to alter the function of $GABA_A$ receptors.

In the de Sousa *et al.* article,[5] the authors point out the stark contrast between the actions of isoflurane and xenon. Isoflurane, at 1 minimum alveolar concentration (MAC), was found to increase the duration of inhibitory postsynaptic currents, while causing a small decrease in the amplitude of excitatory postsynaptic currents. The increase in inhibitory postsynaptic currents duration is consistent with the actions of isoflurane on postsynaptic $GABA_A$ receptors, whereas the decrease in amplitude of excitatory postsynaptic currents probably reflects presynaptic actions of the volatile anesthetics.[6,7] Conversely, xenon had no effect on the inhibitory postsynaptic current, but selectively reduced the slow component of the excitatory postsynaptic current that is mediated by NMDA receptors.[5]

These differences between two simple anesthetic gases at the level of molecular and cellular targets may seem surprising at first and are certainly at odds with the unitary models that dominated thinking in this field for so long. In fact, the discrepancy is less surprising when one considers the pharmacologic profile of the two anesthetics. Isoflurane produces hypnosis and unconsciousness and depresses spinal reflexes, yet confers little analgesia. Xenon, however, is an excellent analgesic and has the ability to produce hypnosis and amnesia. The pharmacologic profile of xenon anesthesia is very similar to that of ketamine, another known antagonist of glutamate at NMDA receptors. The analgesic and amnestic actions of xenon and ketamine are shared by other NMDA receptor antagonists and fit well with what is known about the anatomic distribution and physiologic functions of this ligand-gated ion channel.[5]

So much for the cellular and synaptic pharmacology of isoflurane and xenon. But what about the molecular level? How can such selectivity between ligand-gated ion channels be exhibited by simple gaseous anesthetics? The answer may lie in the differences of molecular structure between the four transmembrane domain $GABA_A$ receptor subunits and the three transmembrane domain NMDA receptor subunits (which appear to be members of a distinct gene superfamily among the receptor molecules) and in the existence of anesthetic-binding pockets or cavities within these target molecules. Recent work using site-directed mutagenesis has shown that specific mutations at serine 270 in the $GABA_A$ receptor α subunit can alter the sensitivity of the receptor to enflurane and isoflurane.[8,9] A new article suggests that serine 270 might be part of a hypothetical binding pocket of defined volume for anesthetic ethers,[10] located between adjacent transmembrane domains within each receptor subunit polypeptide.

Are anesthetic binding pockets merely fanciful inventions of molecular pharmacologists? Apparently not, because the existence and precise location and dimensions of an anesthetic binding cavity has been demonstrated using X-ray crystallography in firefly luciferase.[11] The binding of anesthetics within such pockets, although necessarily of low affinity, would be driven by a combination of enthalpic and entropic free-energy changes and hence be governed by the customary laws of thermodynamics.[12]

If one accepts for the moment the premise that such binding pockets exist within these ion channels, it follows that xenon does not bind well within the anesthetic ether pocket associated with the $GABA_A$ receptor. This might reflect the inappropriate size or shape of the xenon atom, or perhaps an inability to participate in hydrogen-bonding interactions. Apparently the NMDA receptor is also selective, admitting xenon but excluding isoflurane. The search surely will now be on for the molecular determinants of the actions of xenon on the NMDA receptor, and for further clues concerning the lack of interaction of the noble gas with the $GABA_A$ receptor.

The study by de Sousa *et al.*[5] therefore provides a satisfying conclusion to the discussions concerning unitary mechanisms of anesthesia. The unitary hypothesis has clearly outlived its usefulness; but all is not lost in terms of understanding. The illumination provided by this monochromatic concept has indeed been diffracted across a rainbow of molecular targets in recent years, but may now be refocussed to throw the spotlight onto two molecular stars of the synaptic stage: the $GABA_A$ and NMDA receptors.

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Neil L. Harrison, Ph.D.
Professor and Director
C. V. Starr Laboratory of Molecular Neuropharmacology
Department of Anesthesiology
Weill Medical College of Cornell University
New York, New York 10021
neh2001@mail.med.cornell.edu

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