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Through the Eye of the Channel: Considerations of a Reductionist View of General Anesthesia

FROM A CLINICAL PERSPECTIVE, general anesthesia is assessed as a behavioral phenomenon. The anesthesiologist administers a broad variety of drugs by several routes to produce behavioral states characterized by varying degrees of amnesia, agnosia and analgesia. Although we describe the "anesthetic state" according to these three criteria, their relative interdependence is unclear. For example, if a person is devoid of perception, is there any experiential remnant to recall; does agnosia obligate amnesia?

General anesthesia may be analyzed at different levels of resolution. We may ask if the same parts of the brain are modified in the same way by all anesthetics, or if thematic differences underlie the similar but nonidentical behavioral end-points of halogenated hydrocarbons as compared to barbiturates. Further analysis seeks to determine whether the essential anesthetic-induced alterations occur through interactions among different parts of the brain or independently at affected regions. Do these alterations require that groups of cells (neurons and glia) act in concert, or do the anesthetic effects on isolated single cells *in vitro* describe what occurs at the individual cell level in intact brain?

At still finer magnification, we examine which of the many cellular processes contribute to the anesthetic state. Despite the well-known correlations by Meyer and by Overton concerning anesthetic potency and lipoid solubility,[1] much of the subsequent early work on general anesthesia focused on changes in brain metabolism.[2] This was the thrust of neurochemical investigation in 1930–1940, when the role of cytoplasmic proteins was enthusiastically studied. Then cell membranes were advanced in status from mere inanimate dividers that enclosed or compartmentalized cytoplasm to dynamic structures of intriguing transport capability. Recently, the cytoplasm has received renewed attention with the recognition of complex relations within the cell. Both the nature of cytoskeletal: membrane associations in cellular dynamics[3] and the mediation of ion conductances and hormone and transmitter actions by cellular metabolism, such as protein phosphorylation,[4] reveal the interactions between cytosol, organelles, and plasma membrane.

The history of investigations on general anesthesia records repeated "unified theories," yet none of these has withstood numerous experimental inconsistencies, which are the true criteria of theoretical validity. Recurringly, the complexity of the problem has been disclosed, then subsequently ignored as new unifying theories emerged. Reductionism is again in vogue, and we are both easily attracted to and seduced by the power and elegance of experiments on single cells, membranes, and molecules. A more integrated approach seems improbable; indeed, if we do not know how the brain works, how can we understand anesthesia?

Against this backdrop, in this issue of ANESTHESIOLOGY, we encounter a paper on the actions of an inhalation anesthetic on single, transmitter-activated ion channels.[5] Isoflurane is shown to produce a dose-dependent "flickering" of the nicotinic ACh-activated ion channel, causing that pore to fluctuate rapidly between open and closed states under conditions in which a

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drug-free channel would otherwise remain open. The authors analyze their findings in terms of alternative models for drug-induced closure, and conclude that, rather than directly "plugging" the channel, in the mode of classic open-channel block, the anesthetic induces closure through an allosteric mechanism. The findings are discussed with regard to both cerebral effects of anesthesia and peripheral neuromuscular blockade.

Three important aspects attend this publication. The first is methodology, in which the paper uses and describes the "patch-clamp" technique and related analysis for study of single ion channels. The description is elaborate and somewhat pedagogical, however, for the laudable reason of introducing an important new method to a readership largely unfamiliar with the techniques. Actions of anesthetics are being investigated in many laboratories by means of the patch-clamp;[6] therefore, anesthesiologists should be cognizant of these studies and the consequence of the results.

The second important aspect is the institutional source. This paper comes not from a department of physiology or pharmacology, but from a department of anesthesiology. Increasingly, basic neuroscience is being conducted in the context of a clinical department. The outcome should be reciprocally beneficial, with researchers (many of them anesthesiologists) informing clinicians from the perspective of basic science and learning from clinicians about the breadth, as well as the finer details, of clinical phenomena. I believe that this model presages a major component of medical research in the 1990s.

The third aspect comprises relevance. What, you may ask, is the relation between flickering blockade caused by isoflurane of nicotinic acetylcholine receptors (nAChR), in cloned or cultured muscle cells, and the clinical anesthetic state? The answer is two-fold; the immediate relevance is questionable, but the general consequence is extensive. Anesthetic agents exert major effects on membranes and thereby modify the function of ion channels, *inter alia*. We know that both ACh- and GABA-activated ion channels are altered by inhalation anesthetics, barbiturates, and steroids, while other membrane-intrinsic proteins are probably also affected.[7–10] An emerging theme suggests that similar features occur among different ion channels, including the primary sequence of the amino acids that compose the protein and the pattern of "gating" as channels undergo sequences of conformational transitions.[11] Therefore, a detailed description of the kinetic modifications rendered by an anesthetic on one particular channel may be generalizable to others. By implication, the underlying physico-chemical mechanisms may also have common origins. Since we now know more about the structure, biochemistry, molecular pharmacology, and function of the nAChR-associated channel than about any other ion channel, so does it rate primary consideration as a model for anesthetic schema.

General anesthesia remains a behavioral enigma. How do we safely put people to sleep, subject them to surgical trauma, and then restore them to consciousness and well-being? The question may well not be answered in the next decade, but it certainly will be asked in better terms. And what is science if not a thoughtful approach to more enlightened inquiry? Inquiry regarding anesthesia should occur at many levels, behavioral, neurophysiological, biochemical, and pharmacological, at the cellular domain and with an appreciation for the diverse anesthetic actions on subcellular structures, including ion channels. Along the way, we will become more informed and, thus, improve the practice and intellectual content of anesthesia.

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