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Mechanisms of General Anesthesia

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Although general anesthetics are often said to be nonspecific agents, it is likely that they act at a much more restricted set of target sites than commonly believed. The traditional view has been that the primary targets are lipid portions of nerve membranes, but recent evidence shows that the effects on lipid bilayers of clinically relevant levels of anesthetics are very small. Effects on most proteins are also small, but there are notable examples of proteins that are extremely sensitive to anesthetics and mimic the pharmacological profile of anesthetic target sites in animals. Such target sites are amphiphilic in nature, having both hydrophobic and polar components. The polar components appear to behave as good hydrogen-bond acceptors but poor hydrogen-bond donors. Although the targets can accept molecules with a wide variety of shapes and chemical groupings, they are unaffected by molecules exceeding a certain size. Overall, the data can be explained by supposing that the primary target sites underlying general anesthesia are amphiphilic pockets of circumscribed dimensions on particularly sensitive proteins in the central nervous system.

Introduction

Although there has been active research into the mechanisms underlying general anesthesia for well over a century, there is no generally accepted or entirely satisfactory definition of general anesthesia itself. A definition such as "reversible, drug-induced loss of consciousness" is fine until one ask the questions "What is consciousness?" and "How am I going to measure it?" However, if one takes a pragmatic approach and uses an end point that can be precisely and reliably determined (such as purposeful response to a surgical incision or loss of righting reflex), then a surprisingly simple picture emerges. Not only are the potencies for a given anesthetic agent acting on a variety of different animals in very good agreement (*1*), but the potencies for an extraordinarily wide range of different anesthetics can be accurately predicted on the basis of very simple physicochemical properties (*2,3*).

This simple picture is often and easily obscured by either a more complex definition of general anesthesia or attention to the many disparate effects that different agents can have on factors unrelated to consciousness. For example, if one uses changes in the complex electroencephalogram (EEG) pattern as a way of defining the anesthetic state (*4*), then it is hardly surprising that a complex picture emerges. Indeed, the use of the EEG pattern as a criterion has led to the suggestion (*4*) that enflurane causes a totally different anesthetic state than that caused by halothane. Quite a different conclusion would have been reached, however, if cerebral oxygen consumption had been chosen, since this parameter is affected in a very similar way by these two agents (*5*). Attention to unrelated side effects can cause similar confusion. For example, different agents can have very different effects on respiration and on the cardiovascular system; some agents cause excitation while others do not; and some are effective analgesics at low concentrations while others actually reduce the threshold to pain.

One of the major impediments to understanding general anesthesia lies in distinguishing between what are essentially side effects (albeit of considerable clinical importance) and the principal feature that all anesthetic agents have in common: their ability to render an animal unconscious and thus insensitive to pain. The reason that this differentiation is a particular problem in the field of general anesthesia is that most general anesthetics are remarkably impotent, acting at much higher concentrations than most other drugs so that diverse side effects are inevitable. Despite these problems, however, major progress has been made towards understanding the mechanisms underlying general anesthesia, and certain clear principles have emerged. In this short review we will attempt to summarize these ideas with particular regard to the largest class of general anesthetics—simple molecules that are chemically inert and relatively apolar.

Nature of Primary Target Sites in General Anesthesia

General Considerations

The ultimate effector sites that cause general anesthesia may be quite different from the primary target

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sites where anesthetic molecules actually bind. For example, it is generally supposed that changes in the properties of neuronal ion channels cause general anesthesia, but this could result from the anesthetic molecules interacting with any of the following primary sites: *a*) the channel proteins themselves, *b*) proteins that regulate channel activities (e.g., by phosphorylating them), or *c*) the surrounding lipid bilayer. It is information that bears on the molecular nature of the unknown primary sites that we shall consider.

The one property of these anesthetic target sites that is most widely quoted is that they are apolar or hydrophobic. But this emphasis can be misleading since it is only part of the story. Consider, for example, the two closely related anesthetics *n*-butane and *n*-butanol (Table 1). It can be seen that the gas-phase potencies of butane and butanol are in the ratio 1:2000. In other words, replacing a hydrogen atom on butane with a hydroxyl (OH) group increases the gas-phase potency by over three orders of magnitude. This is a surprising result. Since alkanes are clearly more hydrophobic than alcohols, we might expect them to be more potent as general anesthetics. However, this is because we are used to expressing potencies in terms of aqueous concentrations (Table 1). What this simple comparison tells us is that the primary target sites in general anesthesia are not only apolar but also polar. A comparison of the corresponding *n*-hexadecane/gas partition coefficients in Table 1 shows that the potency ratio would be only 1:6 if the site was as apolar as a hydrocarbon solvent. We have previously (*8*) arrived at this same conclusion in a more rigorous fashion by trying to correlate a wide range of general anesthetic potencies with partition coefficients between various organic solvents and water. The data correlated well only if the solvent contained both polar and apolar characteristics. For example, *n*-octanol gave excellent correlations while *n*-hexadecane gave very poor correlations. How can one account for this result? There are two extreme possibilities: there are some sites that are apolar and others that are polar, or all the sites are both polar and apolar, i.e., they are amphiphilic. As the sites are presently unknown, it is not possible to choose between these possibilities. However, support for the latter option comes from studies (*11,12*) with the pure soluble firefly luciferase enzyme (see ensuing material), in which the anesthetic binding site appears to be a single amphiphilic pocket containing both polar and apolar regions.

Table 1. Gaseous and aqueous concentrations for general anesthesia together with hexadecane/gas partition coefficients for three closely related anesthetics.

	P_{50}, atm[a]	ED_{50}, mM[b]	K (hd/gas)[c]
Butane (CH_3–CH_2–CH_2–CH_3)	0.20	0.17	42
Ether (CH_3–CH_2–O–CH_2–CH_3)	0.019	9.3	120
Butanol (CH_3–CH_2–CH_2–CH_2–OH)	0.00010	12	240

[a] P_{50} is the partial pressure of a given agent required to anesthetize 50% of a population of animals. P_{50} values for *n*-butane and diethyl ether are for man (*6*). An *n*-butanol value was derived from an ED_{50} concentration for tadpoles (*6*) using the list of activity coefficients provided by Hine and Mookerjee (*7*).

[b] ED_{50} is the aqueous concentration of a given agent required to anesthetize 50% of a population of animals. The *n*-butanol value is for tadpoles (*6*). The butane and ether values were derived from P_{50} values for man using Bunsen solubility coefficients. (*6*).

[c] K(hd/gas) is the hexadecane/gas partition coefficient (expressed as ratios of molar concentrations at 25°C). Values were calculated using the data in Franks and Lieb (*8*), Abraham (*9*), Aveyard and Mitchell (*10*), and Firestone et al. (*6*).

Having established the polar/apolar nature of the primary target sites, it is possible to define the polar characteristics more precisely. Let us refer again to Table 1 but this time compare both gas-phase and aqueous general anesthetic concentrations for all three closely related general anesthetics: *n*-butane, diethyl ether, and *n*-butanol. First, it can be seen that, compared to adding an ether oxygen (O) atom to butane, replacing a hydrogen atom with a hydroxyl group (OH) makes a general anesthetic almost 200 times more potent from the gas phase. Now an ether oxygen can only accept H-bonds, whereas a hydroxyl group can both accept and donate H-bonds. By elimination, it must be the H-bond donating ability of butanol that makes it so very much more potent than ether from the gas phase. It thus follows that the polar regions on the primary target sites must be good H-bond acceptors. On the other hand, consider the fact that from the aqueous phase ether and butanol are almost equally potent, yet about two orders of magnitude less potent than butane. This suggests that the H-bond donating ability of the primary target site polar regions is poor compared with water, while their H-bond accepting ability must be comparable to that of water. Overall, then, the polar regions of the primary target sites appear to be excellent H-bond acceptors but poor H-bond donors.

A characteristic property of general anesthetic agents that sets them apart from other pharmacological agents is that they come in many different shapes and sizes with no requirement for specific chemical groupings. For example, both the simple rare gas xenon (which is a single atom) and the complex halogenated agent halothane ($CF_3CHClBr$) are excellent general anesthetics. On the other hand, there is a size limitation, which is illustrated by the so-called cutoff effect: as one ascends an homologous series of anesthetics, aqueous-phase potencies steadily increase until, rather abruptly, they disappear completely (*12–15*). For example, dodecanol is the most potent *n*-alcohol, whereas tetradecanol is completely impotent as a general anesthetic. These considerations, in turn, imply that the primary target sites in general anesthesia can interact with a wide variety of molecular sizes, shapes, and chemical groups but are unaffected by molecules that exceed a critical size.

In summary, the primary target sites in general anesthesia have the following general properties: *a*) they are both polar and apolar; *b*) their polar regions are excellent H-bond acceptors but poor H-bond donors; *c*) they can bind anesthetic molecules having a wide variety of sizes, shapes, and chemical groupings; and *d*) they are unaffected by molecules that exceed a certain size.

In the next section we will consider the growing evi-

dence that points to the specific molecular nature of general anesthetic target sites.

Are the Primary Target Sites Proteins or Lipids?

Since the finding by Meyer (*16*) and Overton (*17*) at the turn of the century that general anesthetic potencies correlate reasonably well with solubilities in the fatlike solvent olive oil, the traditional view has been that the primary target sites are fatlike lipid regions in the brain. This viewpoint, however, has not been unanimous; over the years several workers have proposed that the target sites are proteins rather than lipids. Only recently (see following material) has evidence accumulated that strongly favors protein sites of action. A notion even further removed from the mainstream has been that of Pauling (*18*) and Miller (*19*) who independently put forward the idea that the target sites were water. Anesthetics were proposed to stabilize icelike clathrates that, in turn, impeded neuronal function. This theory has now been largely abandoned by workers in the field because of the poor correlation between the general anesthetic potencies and the clathrate-forming abilities of various agents (*1*).

The modern interpretation of the classical work of Meyer (*16*) and Overton (*17*) has been that general anesthetics dissolve in lipid-bilayer regions of nerve cell membranes and so alter the properties of lipids (e.g., fluidity, thickness, surface tension, lateral surface pressure) surrounding crucial membrane proteins (usually assumed to be ion channels) that protein function is compromised (*2,3,14,20–22*). The attraction of these lipid theories has been that, in most cases, it has been possible to experimentally demonstrate that anesthetics can indeed produce the advertised effects; it was largely for this reason that lipid theories reached a height of popularity some 10 years ago. Since then, however, it has slowly become clear that there are serious quantitative difficulties with the lipid theories and with many of the experiments that supported them. In fact, most of these experiments had been performed using high, indeed toxic, anesthetic concentrations, perhaps for the simple reason that effects at general anesthetic ED_{50} concentrations are usually extremely small (*3*). Workers had generally assumed that significant (albeit small) effects at clinical levels could be inferred from the large and often very significant effects observed at high anesthetic levels. More recent experiments using electron spin resonance (*23*), X-ray and neutron diffraction (*8*), deuterium nuclear magnetic resonance (*24*), and Raman scattering (*25*) have shown that clinical anesthetic levels cause barely detectable changes in lipid bilayer structure and fluidity.

However, it is clear that the introduction of even one molecule of anesthetic into a lipid bilayer must produce some effect. The problem is the significance this effect has in a physiological sense. In order to understand this problem, we have compared the effects of small changes in temperature with the effects of clinical levels of general anesthetics on lipid bilayers, using our own and other data. We found that in almost all cases changes in bilayer properties produced by surgical ED_{50} levels of general anesthetics could be mimicked by changes in temperature of less than 1°C (*3*). For comparison, normal human diurnal variations in body temperature exceed 1°C, while strenuous exercise can cause a rise of 2 to 3°C. Furthermore, body temperatures of cold-blooded animals can be changed by 10°C or more without inducing general anesthesia. An example of such a comparison of the effects of temperature and anesthetic concentration on the fluidity of lipid bilayers is given in Figure 1, using the data of Harris and Groh (*26*). By using a judicious mixture of lipids and a very sensitive technique (fluorescence polarization of a lipid probe), they were able to measure small but statistically significant changes in lipid fluidity at surgical ED_{50} concentrations of the volatile agents enflurane, chloroform, and ether. However, in comparison with the changes produced by small changes in temperature, it is clear from Figure 1 that the anesthetic-induced changes were very small indeed, even up to three times surgical ED_{50} concentrations.

While the effects of anesthetics and changes in temperature are, of course, not strictly equivalent, the fact that less than a 1°C change in temperature can mimic almost any perturbation in bilayer properties caused by

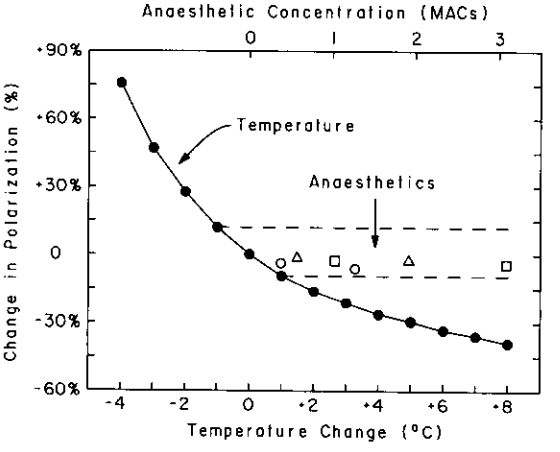

FIGURE 1. The effects of surgical concentrations of enflurane (△), chloroform (○), and diethyl ether (□) on lipid bilayers can be mimicked by a small change in temperature (●). In this example, lipid fluidity was monitored by measuring the fluorescence polarization of a probe molecule (diphenyl hexatriene). The change in polarization for a lipid bilayer particularly sensitive to anesthetics was measured as a function of changing temperature (from 30°C) and as a function of anesthetic concentration (at 30°C). It can be seen that the changes in fluidity caused by three anesthetics at up to three times their human general anesthetic concentrations (MAC, minimum alveolar concentration) fall well within those produced by a ± 1°C change in temperature (horizontal dashed lines). The original polarization data (kindly provided by R. A. Harris, University of Colorado, Denver), for ganglioside-containing bilayers of dimyristoyl lecithin, are plotted in Harris and Groh (*26*). From Franks and Lieb (*27*) with permission.

an ED_{50} concentration of general anesthetics emphasizes how very small these perturbations are. Why are these anesthetic-induced changes in lipid bilayer properties so small? The reason becomes apparent when one considers (*27,28*) the concentration of halothane in a plasma membrane. At the surgical P_{50} partial pressure, there is only about 1 molecule of anesthetic for every 80 molecules of lipid. Since the lipids in plasma membranes at physiological temperatures are almost always already in a fluid state, it is not surprising that the addition of one small anesthetic molecule to 80 large lipid molecules produces only a minuscule effect. While it is certainly not possible to absolutely rule out a role for lipid bilayers in producing general anesthesia (for example, lipids at a protein/lipid interface just might be especially sensitive), the quantitative arguments previously mentioned suggest rather strongly that the case for such a role is presently very weak indeed.

About 5 years ago, support for the alternative idea that proteins were directly affected was persuasive, but by no means overwhelming (*3*). Most proteins, like lipids, are insensitive to surgical ED_{50} concentrations of general anesthetics. This is perhaps to be expected, because if many proteins were sensitive none of us would survive an operation! However, there were reports in the literature that one class of proteins, the light-emitting luciferase enzymes, might be sensitive. We chose to work with the luciferase enzyme from the North American firefly *Photinus pyralis* (*11*). In order to be certain that any effects of anesthetics were on the enzyme itself and not on either lipid or another protein, we purified the enzyme from firefly lanterns to a purity of 99%. We then measured the activity of the enzyme at different concentrations of its normal substrate (a hydrophobic heterocylic molecule called firefly luciferin) and a wide range of general anesthetics. We found that anesthetic inhibition was strictly competitive with luciferin. This finding suggested that anesthetics bound to the hydrophobic pocket that normally binds luciferin, and thus occluded it, making luciferin binding impossible. This would explain why anesthetic molecules of different sizes and shapes could all inhibit the enzyme. Using the popular lock-and-key analogy for enzyme catalysis, one might say that anesthetics simply jam the lock so that the key (luciferin) cannot fit into the lock (the hydrophobic substrate-binding pocket on the luciferase enzyme).

What came as much more of a surprise was that the ED_{50} concentrations of a wide range of general anesthetics for inhibiting the enzyme were almost exactly the same as the ED_{50} concentrations for producing general anesthesia (*11*). This is shown in Figure 2, where the diagonal line is the line of identity between ED_{50} concentrations for inhibiting luciferase activity (on the ordinate) and for producing general anesthesia (on the abscissa). This striking result shows clearly that the famous correlation of Meyer (*16*) and Overton (*17*) (between anesthetic potency and fat solubility) can be explained in terms of anesthetics binding to a protein molecule.

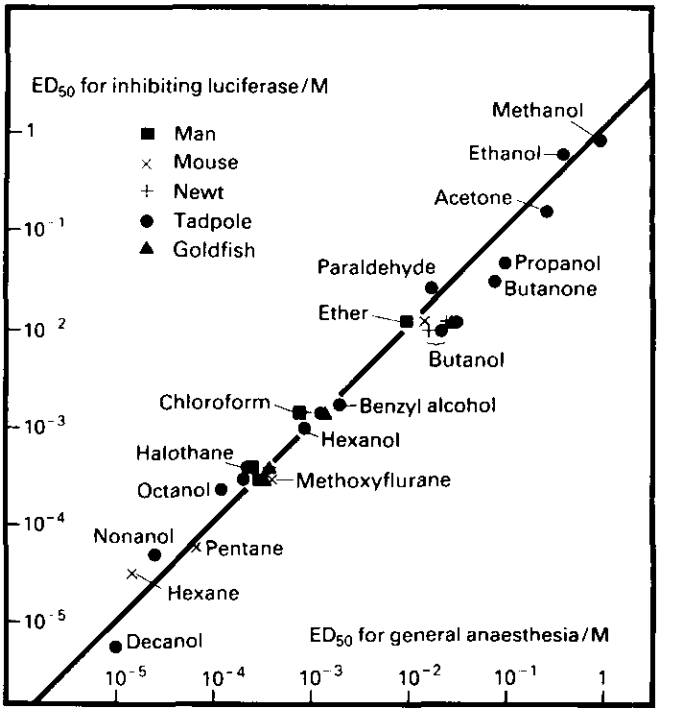

FIGURE 2. Comparison of general anesthetic concentrations needed to anesthetize whole animals and to inhibit firefly luciferase activity by 50%, for a diverse range of simple anesthetics over a 100,000-fold range of aqueous potencies. The data (*11*) are plotted as potencies, defined as reciprocals of aqueous ED_{50} molar concentrations. From Franks and Lieb (*29*) with permission.

Evidence that the anesthetic molecules were binding to a circumscribed region on the protein (rather than, say, to an extended subunit interface) came from the observation that the binding site would accept only a single large anesthetic molecule but more than one small anesthetic molecule. From these data it could be inferred that the anesthetic binding site must have a volume of roughly 400 $Å^3$. Moreover, by comparing the binding of alcohols and alkanes, it was clear that the pocket contained both polar and apolar parts, a feature apparently shared by general anesthetic binding sites in animals (see previous section). Such an amphiphilic binding pocket could also naturally account for the cut-off effect observed with animal anesthetic potencies (*12*). If a long-chain anesthetic molecule has a volume that is comparable to the binding pocket and can bind within it, then adding methylene groups will not greatly increase the binding energy because these additional groups must remain largely in water. The aqueous solubility, however, continues to decrease so that a point is inevitably reached when the agent is insufficiently soluble to act as an effective inhibitor. Such a cutoff is, in fact, observed with the firefly luciferase enzyme (Fig. 3) and provides, in our view, a plausible molecular interpretation of the cut-off effect in animal potencies. More recently we have shown (*32*) that the earlier suggestion (*15*) that the cutoff was due to a limited solubility of long-chain molecules in lipid bilayers was incorrect and

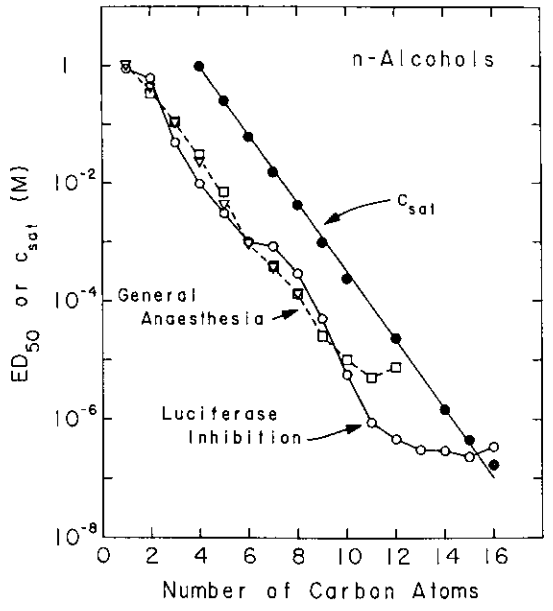

FIGURE 3. The cutoff effect for the homologous series of *n*-alcohols. The ED_{50} values (*12*) are the concentrations of anesthetics required to inhibit firefly luciferase activity (*12*) by 50% (○) or to anesthetize whole animals. Data for tadpoles (□) and (▽) from Brink and Posternak (*30*). The c_{sat} values (●) are the aqueous solubilities of the alcohols (*31*). The fact that the cutoff for general anesthesia occurs slightly before that for luciferase inhibition can be interpreted as showing that the target sites involved in general anesthesia are, on the average, somewhat smaller than the anesthetic-binding pocket on the luciferase enzyme.

that long-chain alcohols, at least, continue to partition into lipid bilayers long after their biological activity has ceased.

In summary, there are good reasons for questioning the traditional view that general anesthetics act by perturbing lipid bilayers, and there is ample evidence to suggest that protein molecules are the most plausible primary target sites. Amphiphilic pockets on proteins can account for the potencies of a diverse range of simple agents as well as the surprising lack of potency of long-chain compounds (i.e., the cutoff effect). Since the majority of protein molecules that have been investigated were found to be relatively insensitive to anesthetics, it appears that anesthetic sensitivity among proteins will prove to be the exception rather than the rule. Identifying these crucial sensitive protein molecules amongst the tens of thousands of other proteins in the central nervous system is the next but, by far, the most difficult step along the road to understanding the mechanisms underlying general anesthesia. Some recent progress in this area is discussed in the following section.

Are General Anesthetics Specific or Nonspecific?

It is often stated that general anesthetics are nonspecific or that they act in a nonspecific manner. Such statements can cause confusion and are interpreted quite differently by different people. What is certainly true is that anesthetics, unlike most drugs, do not require specific chemical groups; in this sense there would appear to be little or no specificity (except in the general sense of being sufficiently apolar to pass easily across the blood-brain barrier). However, this diversity has also been taken to imply that anesthetics act nonspecifically, and it is here that confusion arises. "Nonspecificity" is sometimes taken to mean that anesthetics act in an unconventional way (e.g., by increasing the thickness of membranes) or that they act at such a large variety of different target sites that they cannot be thought of as having a specific mode of action. As discussed previously, it is our opinion that neither of these views is correct. We believe that not only do general anesthetics act in a conventional manner (i.e., by binding to pockets on proteins) but that a rather limited number of target sites are likely to be involved.

Recent work (*33*) from our laboratory on the effects of volatile general anesthetics on molluscan central neurons supports the idea that general anesthetics probably act at a relatively restricted number of target sites. We used the great pond snail *Lymnaea stagnalis* to study the effects of anesthetics on identified neurons in the hope that any differential effects we observed between neurons could be pursued to the molecular level. We found that in a cluster of apparently identical spontaneously-active neurons, a single cell displayed an unusual sensitivity to volatile general anesthetics. This is illustrated in Figure 4 (top), which shows that the normal firing activity of the sensitive cell (about 1 action potential/sec) is completely but reversibly inhibited in the presence of surgical levels of halothane. These halothane levels hyperpolarize the membrane potential to well below the level needed to initiate firing activity. We showed that this hyperpolarization was caused by a novel anesthetic-activated outward potassium current that was present in the sensitive cell but was absent in the surrounding anesthetic-insensitive cells. The lack of effect on a neighboring insensitive cell is shown in Figure 4 (bottom).

The anesthetic-activated potassium current rapidly saturates with increasing levels of halothane (Fig. 5), with a half-maximal response at only 0.0063 atm, which is close to the general anesthetic P_{50} for *Lymnaea* [0.0083 atm (*34*)] and the minimum alveolar concentration for man [0.0075 atm (*35*)]. This saturation is consistent with a binding site on a protein molecule. As discussed above, it is likely that the anesthetics are exerting their effects by binding directly to protein molecules, but whether these are the channel proteins *per se* or other proteins that regulate the channels remains to be seen. It also, of course, remains to be determined whether similar anesthetic-activated currents are present in the brains of higher animals and, if so, what role they play in the induction and maintenance of general anesthesia. What is clear, however, is that general anesthetics, despite their extraordinary diversity, may exert their primary effects at a relatively small and

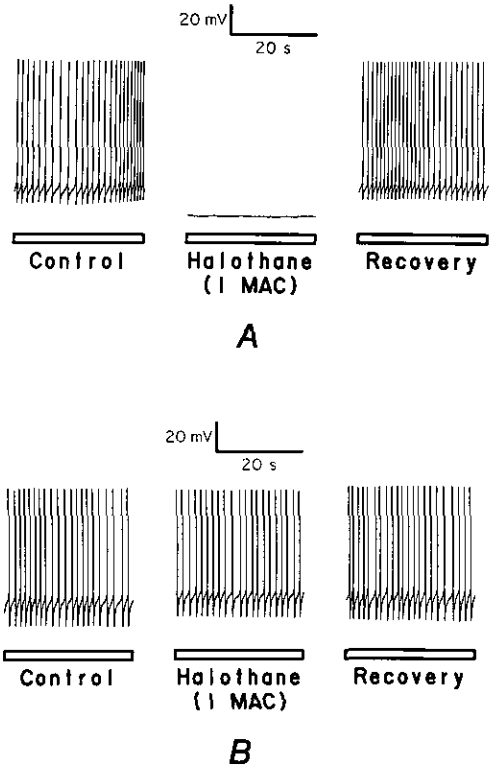

FIGURE 4. Selectivity of general anesthetic action at the neuronal level. Reversible inhibition of the spontaneous firing activity of a central neuron in *Lymnaea stagnalis* by halothane at a concentration of 1 MAC (*A*). Lack of effect of 1 MAC halothane on a neighboring but otherwise apparently identical neuron (*B*). This selectivity is due to an anesthetic-activated potassium current $I_{K(An)}$ which is present in the sensitive but not in the insensitive cell [see text and Franks and Lieb (*33*) for further details].

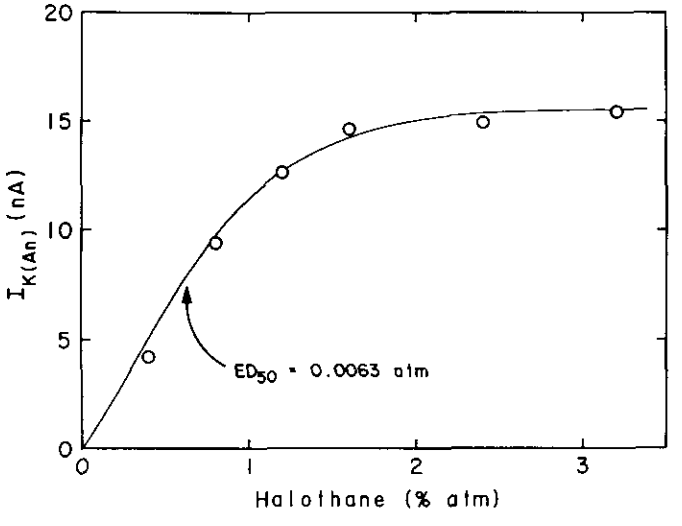

FIGURE 5. The halothane dose-response curve for the anesthetic-activated current, $I_{K(An)}$. The current was measured 15 sec after a jump from a holding potential of -80 mV to a membrane potential of 0 mV. The half-maximal effect occurs at 0.0063 atm halothane [see text and Franks and Lieb (*33*) for further details]. From Franks and Lieb (*33*) with permission.

distinct set of target sites. This raises the hope of developing new general anesthetic agents that are much more selective and safer than those currently in use.

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