A Possible Mechanism for General Anesthesia

by Scott P. Layne

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The first general anesthesia for human surgery was administered at the Massachusetts General Hospital in Boston in 1846. The patient was put to sleep by breathing diethyl ether from a glass vesicle. and the surgeon quickly dissected a tumor located under the jaw. After completing the operation the surgeon remarked to his audience, "Gentlemen, this is no humbug. "

Since this first successful demonstration of diethyl ether. researchers have discovered well over twenty drugs that induce general anesthesia. These drugs have highly diverse chemical structures and physical properties and, as a whole, lend little insight into their mechanism of action. In order to overcome this perplexity, H. Meyer and E. Overton (about the year 1900) originally proposed that anesthetic potency could be related to lipid volubility. They showed that stronger anesthetic agents were more oil-soluble than weaker ones and used this relationship to argue that anesthetics insert into the lipid bilayer and thereby expand its volume. More recent theories along this line have suggested that the expanded lipid bilayer compresses intrinsic membrane proteins and thereby disturbs normal protein shape and function. These theories have suggested also that the membrane-bound anesthetic molecules "fluidize" the lipid bilayer. This increased fluidity, in turn, alters the permeability of the membrane. While these popular ideas might be applicable to agents that are both volatile and highly lipid-soluble (oil-to-gas partition coefficient $\geq 100:1$), they are not particularly suitable to a large class of *intravenous* general anesthetics that are orders of magnitude less lipid-soluble and are capable of forming hydrogen bonds. For the case of hydrogen-bonding anesthetic agents, the simplest idea is that they act by binding directly to a particularly sensitive protein, which may or may not be located in a lipid membrane, and inhibiting its normal function.

In this discussion we will focus on an important class of intravenous general anesthetics that are only slightly lipid-soluble and are capable of forming hydrogen bonds. These agents are represented primarily by *barbiturates*. From Fig. 1 it is easy to see that a barbiturate contains four H–N–C=O groups in its ring. These H–N–C=O groups are very similar to the peptide groups in proteins that are important to the propagation of solitons (see "Solitons in Biology"). The other drugs shown in Fig. 1 also contain H-N-C=O groups but to a lesser extent than barbiturates. Hydantoins contain three peptide groups, glutethimides and succinimides contain two, and urethanes contain one. These drugs are not used as general anesthetics per se, but they nevertheless have a similar inhibitory effect on the central nervous system. The potency of these six drugs appears to be related directly to the number of H–N–C=O groups in the molecule. This is supported by the fact that N-methylated barbiturates (which contain two H–N-C=O groups) are shorter acting and less potent than nonmethylated barbiturates and that trimethadione (which is devoid of H–N-C=O groups) is inactive until
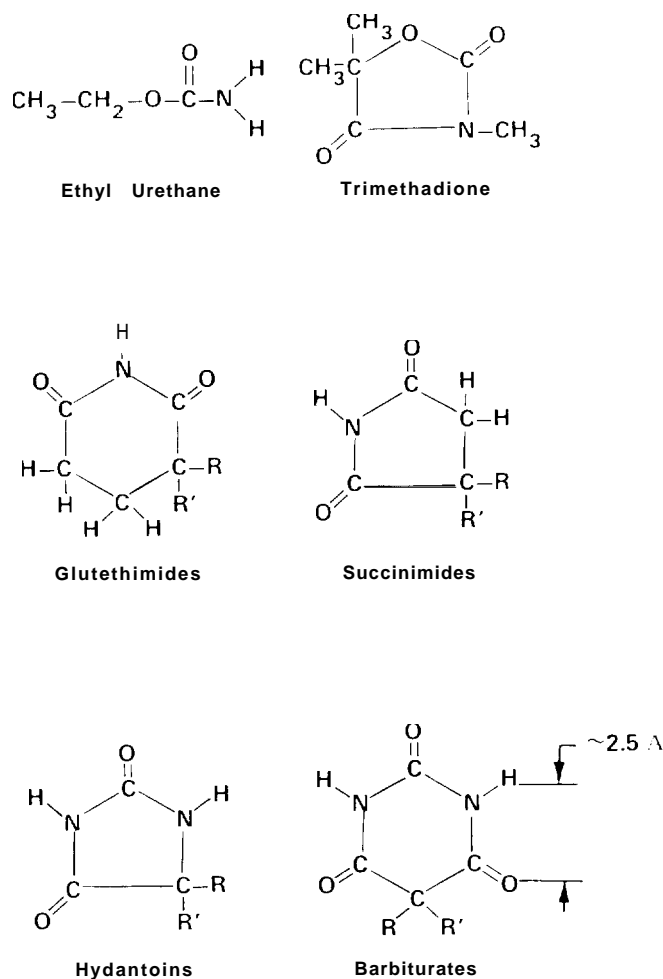

Ethyl Urethane   **Trimethadione**

Glutethimides   **Succinimides**

Hydantoins   **Barbiturates**

Fig. 1. The six drugs shown above, all of which contain H–N–C=O groups, inhibit the central nervous system. Hydantoins, succinimides, and trimethadione are used primarily as antiepileptic agents, whereas glutethimides are used as sedatives. Ethyl urethane is a common veterinary general anesthetic but is not used in humans because its actions are not smooth. The presence of an alkyl or aryl group at R and R' confers increasing lipid solubility, and, generally, increased lipid solubility promotes an increased drug potency.

it is demethylated by hepatic enzymes. After demethylation, trimetha-dione contains two H-N-C=O groups.

C. Sandorfy and coworkers have shown by infrared spectroscopy that barbiturates are capable of dissociating hydrogen bonds in the 1-cyclohexyluracil/9-ethyladenine dimer. This dimer forms hydrogen bonds of the N-H . . . O=C type that is common to proteins. They have also shown that barbiturates form hydrogen bonds with solutions of N,N-dimethylacetamide (NNDA) and N-methylacetamide (NMA). In this instance the N-H groups of barbiturates act as proton donors, and the O=C groups on NNDA and NMA act as proton acceptors. From these data we can infer that barbiturates are capable of forming hydrogen bonds with proteins, and, for the case of *a*-helical proteins, this bonding might take the form shown in Fig. 2. Note that this type of two-point hydrogen bonding along a spine of the a helix has half the chance of taking place if an N–H group in the barbiturate ring is replaced by an N–CH$_3$ group.

How does the binding of an anesthetic molecule to a protein modify normal protein behavior? We shall answer this question using the soliton model as a paradigm for *normal* protein function. The soliton model proposes that u-helical proteins effect the transport of ATP hydrolysis energy through a coupling of vibrational excitations to displacements along the spines of the helix. This coupling leads to a self-focusing of vibrational energy that has remarkably stable qualities (see "What Isa Soliton?"). We suggest that the binding of an anesthetic molecule to a protein interferes with soliton propagation. We suggest further that this type of interference would be most important in two separate regions of a cell where soliton propagation is an attractive candidate: first, in the a-helical proteins of the inner mitochondrial membrane, which appear to participate in ATP synthesis and electron transport, and second, in the membrane proteins of neurons, which are responsible for chemical reception and signal transduction. This proposal is motivated by the fact that barbiturates are capable of binding to these sites and further by the fact that these proteins have significant a-helical character. To see whether this idea makes sense from a theoretical standpoint. we need to calculate the effect of anethestic binding on soliton propagation.

When a barbiturate binds to an a helix, it will form new hydrogen bonds between anesthetic and protein molecules at the expense of the protein's hydrogen bond(s), This kind of anesthetic binding will result in either broken hydrogen bonds within the protein or in weakened hydrogen bonds of increased length; we shall call this increase AR. We assumed for the numerical investigation that the hydrogen bonds within the protein are merely weakened and are not completely broken. We chose for $\triangle R$ a value of 0.8 angstrom, which corresponds roughly to a decrease in hydrogen-bond energy of 55 percent. It is straightforward to calculate the new dipole-dipole interaction energy *J*, if we assume that the two dipoles within the protein remain colinear. The decrease in *J* will be proportional to $(R+\triangle R)^{-3}$. However, it is not
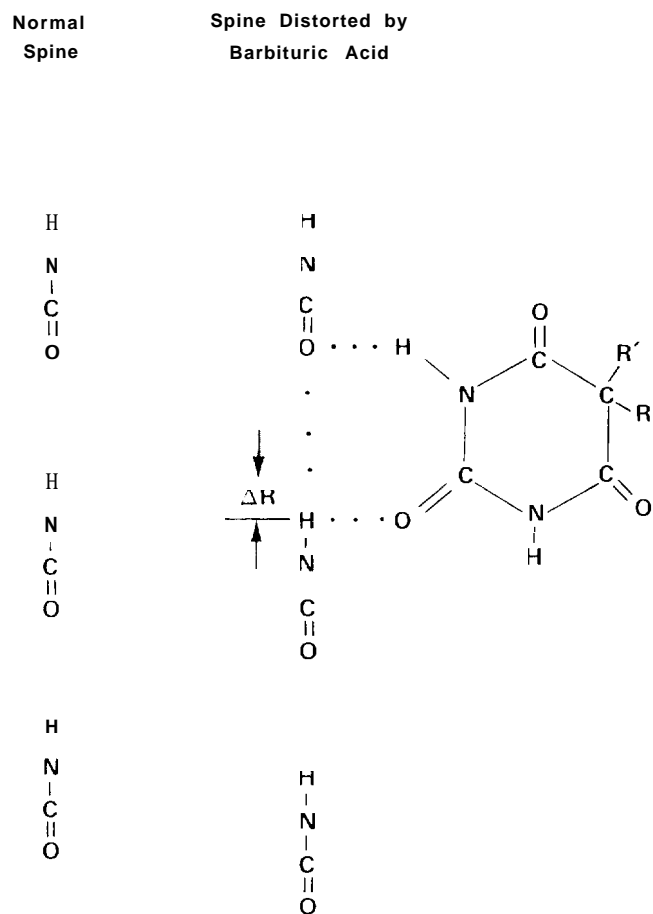

Fig. 2. A possible interaction of a barbiturate, via its H–N-C=O moieties, with one spine of an a-helical protein. The spiral configuratim of the protein is stabilized by its weak hydrogen bonds, and the binding of a barbiturate changes the localized structure within the helix. In this instance, the hydrogen bond is weakened and its bond length increases by the distance △R.
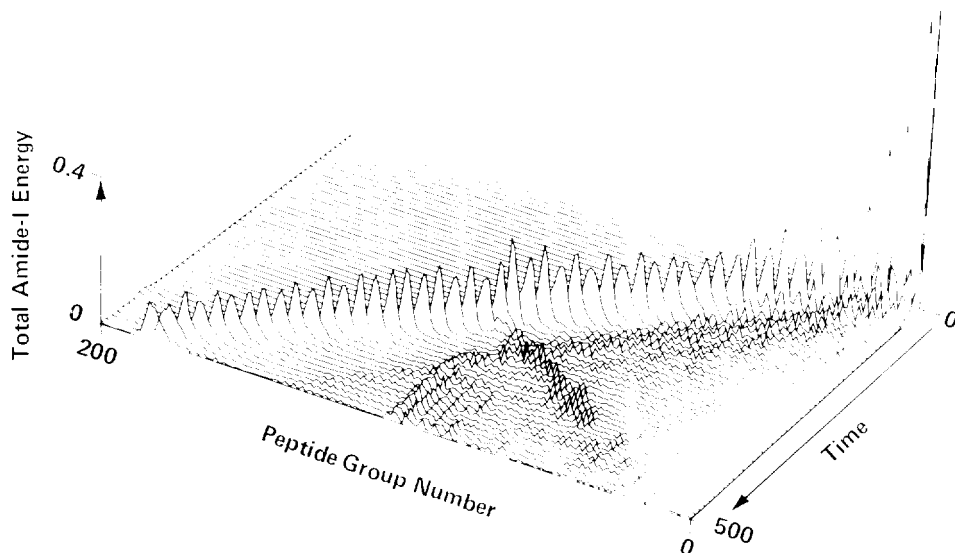
Fig. 3. Numerical calculation simulating the perturbation of a soliton by an anesthetic agent. The perturbation involves changes in the values of **J, K,** *and* X *for peptide groups 100 to 103. The total amide-I energy is plotted as a function of peptide group number and time. Notice that the soliton loses amplitude and widens by the time it reaches the end of the helix.*
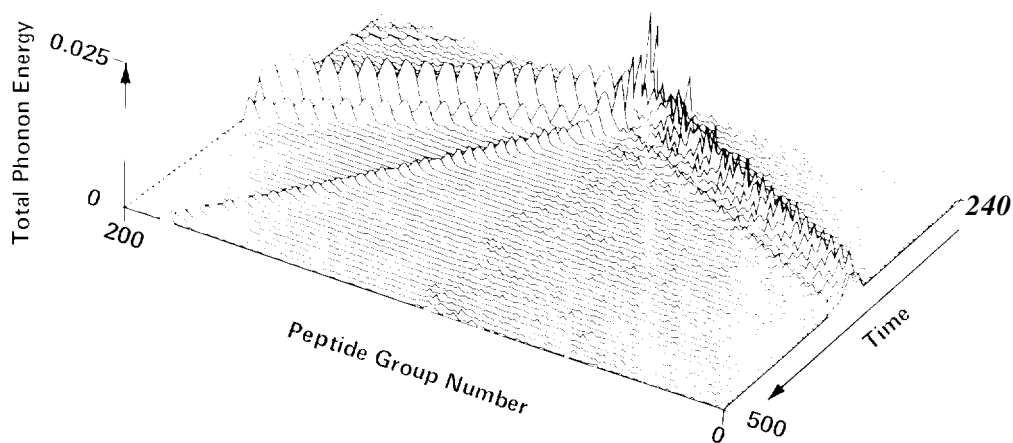

Fig, 4. This figure is the counterpart to Fig. 3. The total phonon energy is plotted as a function of peptide group number and time. In this view time has been restricted to the interval between 240 and 500 computer time units. At time 250 the soliton is just entering the region of perturbation. It radiates energy in the form of phonons as it travels through the altered peptide groups. After emerging from the region of perturbation, the soliton is seen as the low-amplitude wave, which moves at about three-eighths of the sound speed. Note that the phonon energy of the soliton is small compared to its bond energy.

as easy to calculate a new value for the hydrogen-bond spring constant K nor a new value for the coupling constant X in weaker hydrogen bonds. As a crude estimate we assumed that K decreased proportionally to hydrogen-bond energy, and thus our new spring constant has the value of 0.45 K. We also assumed that X is slightly decreased in weaker hydrogen bonds to the lower value that was calculated by V. Kuprievich and Z. Kudritskaya. Hence, at the point of anesthetic binding we chose $X = 0.3 \times 10^{-10}$ newton, which is just below threshold for soliton formation,

The results of this numerical investigation are presented in Figs. 3 and 4. The decreased values of J, K, and X were restricted to peptide group numbers $n = 100$ to 103 on the three spines of the a helix. The perturbation was restricted to this narrow region because an anesthetic molecule is expected to weaken the hydrogen bonds in only a small region of the protein. This procedure also ensured that the soliton was well formed before entering the perturbed region. Figure 3 can be compared directly to Fig. 10 in "Solitons in Biology," It is apparent that after 500 computer time units the soliton, which traveled through the perturbation, is appreciably degraded. Figure 4 reveals that energy is radiated by the soliton in the form of phonons as it travels through the perturbation. These phonons are seen to move at the sound velocity in the a helix, which is approximately eight-thirds the soliton velocity. Up to this point we have neglected the fact that the H–N–C=O groups in the barbiturate are capable of dipole-dipole coupling to the H-N–C=O groups in the helix. Such a coupling should further degrade soliton propagation. since the interaction energy between barbiturate and a helix would be appreciable. The dipole-dipole coupling of the anesthetic molecule to the protein will depend on the number of H-N-C=O groups within it and on its spatial orientation relative to the protein.

As a final consideration of this model we pose the question: How many proteins are inhibited during general anesthesia? Barbiturates exhibit their anesthetic activity at a concentration between 200 and 1000 micromolar. At this concentration they reduce the metabolic activity of the brain by 10 to 15 percent, as measured by oxygen utilization. Taking the average membrane protein to encompass a volume of 20 angstroms x 20 angstroms x 40 angstroms = 1.6×10^4 cubic angstroms implies that about 1 percent of typical membrane proteins are associated with an anesthetic molecule. Such a small figure points out that the brain is very sensitive to alterations at the molecular level. Consciousness appears to require the coordinated effort of almost every protein.

We have presented a simplified theoretical model for anesthetic activity, taking advantage of the fact that the a helix is an important structure in membrane and cytoskeletal proteins. If the Davydov soliton finds experimental support in biology, then such a model may help to explain some of the molecular mechanisms behind general anesthesia. ∎

Further Reading

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