INTERMOLECULAR INTERACTIONS AND ANESTHESIA

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RECENT THEORIES of the mechanism of anesthesia concentrate on the perturbation exerted by anesthetics on the membrane of the nerve cell (for reviews, see references 1-4). Since there exists a good relationship between the lipid solubilities of anesthetics and their anesthetic potencies, it is usually assumed that they act through hydrophobic interactions in the lipid layers of the membrane. This leads to the “hydrophobic site theory,” which, in turn, is the basis of the “unitary hypothesis” implying that the mechanisms of action of all inhalational anesthetics are essentially the same. Hydrophobic site theories are usually given preference over the earlier suggestions by Pauling and Miller to the effect that the site of action is in the aqueous phases of the central nervous system. According to recent theories by Eyring et al. and by Changeux et al., anesthetics induce conformational changes in the lipids and/or proteins that constitute the nerve cell membrane, thereby changing its permeability to ions. It follows that since the right conformation of these macromolecules is stabilized by intermolecular interactions and since inhalational anesthetics are known to exert their influence on the nervous system without undergoing chemical reactions [although they might be metabolized afterwards (see ref. 11)], any attempt to explain the mechanism of anesthesia at the molecular level must involve a study of the changes in the pattern of these associations.

A remarkable fact about anesthetics is the complete lack of a common chemical type among them. The following molecules, for example, exert anesthetic action: Xe, N2O, C2H4, C3H6, C6F6, SF6, CCl3F, CCl3, (C2H5)2O, CF3-CHCl2, CF3-CHClBr, and many others. This, in itself, shows that the common denominator, if it exists, should be looked for not at the chemical but at the subchemical level, i.e., that of intermolecular interactions. Then we can divide anesthetic molecules into the following categories:

a) Nonpolar and not highly polarizable molecules associating mainly through dispersion forces (such as Xe or C3F8). In an aqueous medium they would behave hydrophobically. In the cell membrane, they would interact with the hydrophobic parts of the membrane macromolecules.

b) Nonpolar or weakly polar but highly polarizable molecules. These are expected to interact with both the polar and hydrophobic parts of lipids and/or proteins. The energy of association would come from both dispersion and dipole-induced dipole or ion-induced dipole forces. (SF6 and cyclopropane are possible examples.)

c) Molecules whose association might have, in addition, partial charge transfer character. Fluorocarbons containing higher halogens are possible examples.

d) Molecules that, in addition, can form hydrogen bonds as proton acceptors, such as ether.

e) Molecules that can form hydrogen bonds as proton donors, such as chloroform, halothane, methoxyflurane. These molecules are also able to enter interactions of the b) or c) type.

f) Molecules that are able to form hydrogen bonds both as proton donors and as proton acceptors. Methoxyflurane, which contains an ether linkage as well as a mobile hydrogen, is an example.

All are able to interact with hydrophobic sites, and this is likely to constitute the common ground for all types of inhalational anesthetics. The possibility for additional (b to f) interactions is expected to characterize the more potent anesthetics.

In view of the complexity of the intermolecular interactions that must occur in the membrane and the relatively narrow range of energies they involve, overall relationships such as the one between anesthetic potency and lipid solubility or volume changes in the membrane might be compatible with a variety of different modes of action at the molecular level.

It has been observed in our laboratory that fluorocarbon anesthetics containing higher halogens (types c and e) hinder the formation of (“break”) hydrogen bonds. This effect was systematically studied by infrared spectroscopy in model systems containing hydrogen bonds of the N—H—N, O—H—O, N—H—O=C and S—H—S types and was found to be quite general. Furthermore, a parallelism was found between this hydrogen bond-breaking property and anesthetic potency. So we have suggested that for
this type of anesthetic the mechanism of anesthesia might involve the perturbation of hydrogen bonds.\textsuperscript{14,15}

The latter might be those that exist between lipids and proteins and the surrounding water molecules or hydrogen bonds within the macromolecules forming the membrane. If this is so, there should exist competing mechanisms of association that under the given circumstances are energetically more favorable than the hydrogen bonds that are dissociated or perturbed. The competing associations into which the anesthetic might enter could be of any of the types a to f.

One possible way to perturb hydrogen bonds is by formation of another hydrogen bond. It is significant in this respect that some of the most potent anesthetics, such as chloroform, halothane, methoxyflurane, and enfurane, contain a mobile hydrogen atom, enabling the anesthetic to form hydrogen bonds as a proton donor (type e). Therefore, through a new series of measurements,\textsuperscript{17} we studied the associations between these anesthetics and systems containing hydrogen bonds of the N—H—N, O—H—O and N—H—O=C types. In each case, we found evidence for the formation of hydrogen bonds of the C—H—X (X = N or O) type and the simultaneous breaking of hydrogen bonds that existed in the system. However, this hydrogen bond-breaking property was found\textsuperscript{18–19} with several halo- and fluorocarbons that do not contain hydrogen at all, and from this and a more detailed look at our spectra, we can conclude that these anesthetics can act through more than one mechanism (hydrogen bond formation as proton donors, and interactions of types b or c) whose relative importances vary from one anesthetic to the other. This is, perhaps, why they are so potent.

We have also studied the breaking by anesthetics or denaturing agents (halothane, chloroform, tetramethyldiurea) of hydrogen bonds involving water, with similar results.\textsuperscript{16} These hydrogen bonds were of the water—ether or water—water type. (To our knowledge, tetramethyldiurea is not an anesthetic. It is our belief, however, that since both anesthesia and denaturation must imply the perturbation of hydrogen bonds and the change of conformation of biological macromolecules, the difference is probably in the extent and reversibility or irreversibility of the perturbation only.)

We are only at the beginning of our studies of anesthetics that are not of the fluorocarbon type (ethylene, cyclopropane, \textsubscript{2}N_{2}O, etc.). However, we should like to draw attention to the theoretical work of Leroy and co-workers,\textsuperscript{19} who have shown that, due to their polarizability, relatively high dipole moments are produced in the associations of such molecules. This might be the way in which they perturb the nerve cell membrane.

These observations might help us to approach the mechanism of anesthesia at the molecular level. They do not contradict existing theories based on lipid solubility, volume changes, and fluidization of the membrane or conformational changes. (Cf. references 1 to 4.) In particular, the Meyer-Overton rule is and will always remain one of the basic facts about anesthesia. The question is whether it leads necessarily to the assumption that, at the molecular level, all inhalational anesthetics must act in the same way and through hydrophobic interactions only. (Denson,\textsuperscript{20} in a recent review, says: "The Meyer-Overton theory seems to suggest the site of accumulation of anesthetics but not their mechanism of action.") To make it more precise, the question is not whether hydrophobic interactions are important: they certainly are; but whether they are the only ones that are important. In this sense, the suggestion we made in 1974\textsuperscript{14,15} constituted a challenge to the unitary hypothesis based on hydrophobic interactions only. In subsequent years a strong line of papers appeared reporting a thorough new look at the Meyer-Overton rule. Hensch and co-workers\textsuperscript{21} examined the partition coefficients of a number of gaseous anesthetics in the octanol—water system and came to the conclusion that "relative anesthetic potency depends on hydrophobicity of the anesthetic and on a polar factor." Di Paolo, Kier and Hall\textsuperscript{22} arrived at similar conclusions through a theoretical analysis of the relationship between anesthetic potency and the partition coefficients. They also emphasized the importance of the polar term. The latter has been further confirmed in the recent nuclear magnetic resonance study by Kochler \textit{et al.}\textsuperscript{23} of the solvent effects on halothane in a number of solvents. In particular, all these researchers recognized the importance of the "polar hydrogen" in anesthetics of our types e and f. As stated above, it has been shown recently\textsuperscript{17} that these actually form hydrogen bonds.

It is, perhaps, interesting that while these new developments have not produced any evidence for the formation of clathrate hydrates or "icebergs," the requirement that a part of the interactions causing anesthesia affect the hydrophilic parts of the membrane is a point in common with Pauling’s and Miller’s theories.

It is the writer’s opinion that while hydrophobic interactions undoubtedly play an important role in the mechanism of anesthesia, polar interactions, including hydrogen bonding and the perturbation of molecular associations, cannot be disregarded. Further theories of anesthesia will have to take this into account.

References


2. Miller KW, Smith EB: Intermolecular forces and the phar-
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