ANESTHETICS ALTER THE SOLUBILITY OF NONPOLAR COMPOUNDS IN WATER*

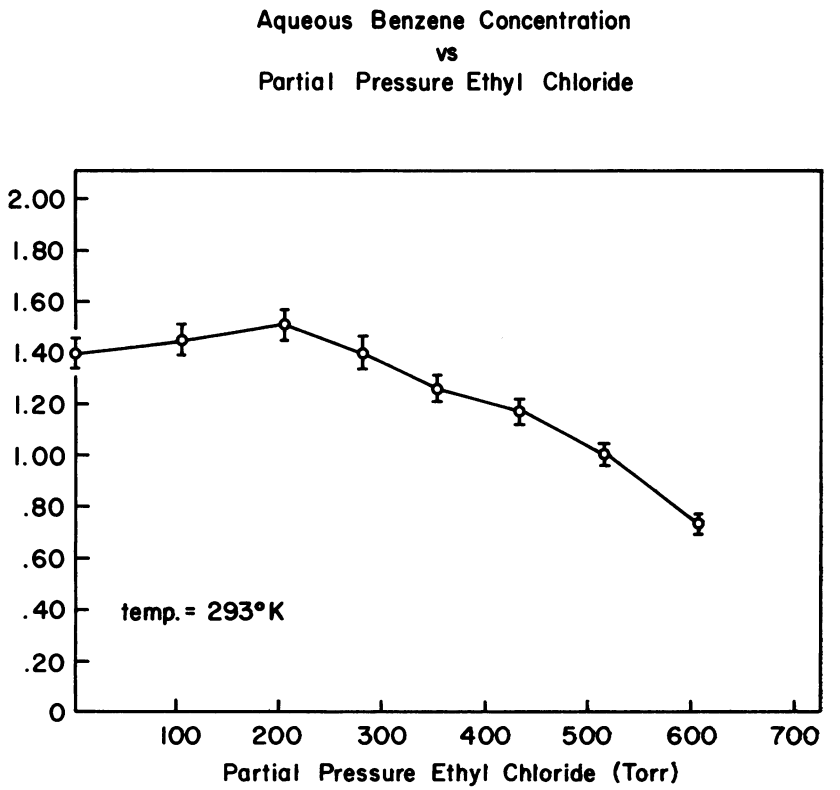
CHARLES BUFFINGTON, M.D., AND HERMAN TURNDORF, M.D.

Department of Anesthesiology
New York University Medical Center
New York, N.Y.

GENERAL anesthetics produce narcosis by altering cellular function in the central nervous system.[1] Although the underlying mechanisms still are not well understood, attention is focusing on the possibility that reversible changes in the macromolecules of cell membranes are a primary cause.[2] Since the function of macromolecules depends primarily on their conformation, particular interest is being focused on anesthetic changes in parameters determining macromolecular conformation. Conformation is determined by the sum of thermodynamic free energies resulting from the interaction of macromolecular subunits with one another and with the surrounding aqueous solution of ions and molecules.[3] The low aqueous solubility of nonpolar subunits is of major energetic significance in determining conformation.[4] It is reasonable to assume that alterations in the aqueous solubility of nonpolar units of membrane macromolecules may alter the function of membranes by affecting conformation energetics. This study was designed to determine the effect of anesthetics on the solubility of a nonpolar compound in water.

Benzene was chosen as a model because it is relatively simple, it resembles several amino acids, and it has well-defined ultraviolet absorption bands. Benzene was equilibrated with triple distilled, degassed water in a thermostated reaction vessel of a vacuum manifold. A Carey 17 spectrophotometer equipped with a 1 mm. quartz flow cell was used to determine the amount of benzene dissolved in the aqueous phase. Air, nitrous oxide, cyclopropane, or ethyl chloride was then added to a measured total system pressure of 650 to 735 torr and allowed to equilibrate. The concentration of dissolved benzene then was redetermined.

*Presented before the Section on Anesthesiology and Resuscitation of the New York Academy of Medicine May 7, 1975.



The addition of ethyl chloride to a closed system containing benzene and water produces a nonlinear alteration in the aqueous solubility of benzene.

The addition of air to the system in place of an anesthetic did not change the solubility of benzene in water; this rules out total pressure as a variable. The addition of nitrous oxide, cyclopropane, or ethyl chloride decreased the concentration of benzene by 7%, 13%, and 48%, respectively (see accompanying table). Graded increments of ethyl chloride produced a nonlinear decrease in the concentration of benzene (see accompanying figure). Shifts in wavelengths in the ultraviolet spectrum of benzene were not seen with any anesthetic, suggesting that no change occurred in the immediate environment of water-solvated benzene molecules. Such shifts commonly occur when close association between benzene and molecules other than water alters the field surrounding benzene and influences the energy levels available to the electrons in the benzene molecule. The π^* transitions re-

IN A CLOSED SYSTEM THE CONCENTRATION OF BENZENE IN WATER DECREASES WHEN NITROUS OXIDE, CYCLOPROPANE, OR ETHYL CHLORIDE IS ADDED

Agents	*Total systemic pressure (torr)*	*Aqueous benzene concentration (moles/l. × 10^2)*	*Decrease (%)*
Benzene and water	93 ± 2	2.20 ± 0.05	0
Benzene, water, and air	735 ± 2	2.20 ± 0.05	0
Benzene, water, and nitrous oxide	708 ± 2	2.04 ± 0.05	7
Benzene, water, and cyclopropane	648 ± 2	1.92 ± 0.05	13
Benzene, water, and ethyl chloride	690 ± 2	1.13 ± 0.05	48

sponsible for several sharp bands in the ultraviolet spectrum of benzene are especially sensitive to such solvent effects.

Nitrous oxide, cyclopropane, and ethyl chloride can be added to the list of substances presently known to increase hydrophobicity, since each of these significantly lowers the solubility of benzene in aqueous solution. These results, previously unreported, suggest that anesthetics may perturb the conformation of macromolecules by increasing the degree of hydrophobicity of constituent nonpolar groups. Further experimental work will provide thermodynamic data to clarify the underlying question of whether anesthetics predominantly affect the tendency of nonpolar molecules to leave the hydrophobic phase or their tendency to be accepted into the aqueous phase. Other experiments will measure the effects of anesthetic agents on the conformational stability of aqueous solutions of macromolecules. The causes of the noted alterations in the solubility of nonpolar groups will then be coupled with their effects on macromolecular conformation to provide a clearer picture of still another way in which anesthetic agents affect biological systems.

Summary

Three gaseous anesthetics have been shown to decrease the solubility of benzene in water. Similar effects on the aqueous solubility of nonpolar components of membrane macromolecules would alter the energetics determining macromolecular conformation and consequently affect the function of macromolecules responsible for properties of membranes.

REFERENCES

1. Jenkins, L.: *General Anesthesia and the Central Nervous System.* Baltimore, Williams and Wilkins, 1969, p. 167.
2. Ueda, I. and Kamaya, H.: Kinetic and thermodynamic aspects of the mechanism of general anesthesia in a model system of firefly luminescence *in vitro. Anesthesiology 38*:425, 1973.
3. Lumry, R. and Biltonen, R.: Thermodynamic and Kinetic Aspects of Protein Conformation in Relation to Physiological Function. In: *Structure and Stability of Biological Macromolecules,* Timasheff, S. and Fasman, G., editors. New York, Dekker, 1969, chap. 2.
4. Kauzmann, W.: Some factors in the interpretation of protein denaturation. *Advances Protein Chem. 14*:1, 1959.