

Anesthetics, Membranes, and Metabolism

THE EFFECTS of general anesthetics on the brain and the behavioral responses to their inhalation have been their *raison d'être* for the last 123 years. Clinical safety of anesthetics has, however, more often been dictated by responses of non-neuronal tissues, especially the heart. Although our knowledge of the effects of anesthetics on the heart is far from complete, the last decade has seen major advances in this complex field as increasingly sophisticated research techniques have been applied by competent investigators to the what-how-and-why of effects on the heart. It is now evident that the response of the heart to anesthetics is the result of interaction of a variety of simultaneously operative factors, some direct, some indirect. The indirect factors include reflex changes in activity of the autonomic nervous system, a response of major importance, but not so important that the direct effects should be ignored.

Direct effects have been studied from several points of view. One of these emphasizes changes in mechanical properties of the heart, with special emphasis on myocardial contractility. Another has dealt primarily with alteration in electrical activity within the myocardium, particularly with regard to the effect of anesthetics on transmembrane potentials. A third approach emphasizes the metabolic response of the heart to anesthetics. All three approaches are necessary, and all three have considerable potential value. Probably the responses observed in these areas of investigation are interdependent, though at present it is impossible to say exactly how, for example, changes in the inotropic state of the myocardium are related to membrane stabilization or to metabolic changes.

Many examples of encouraging advances made in the area of metabolic responses of the heart to anesthetics have appeared in recent years and, indeed, recently in this Journal; the latest is the work reported in the present issue by Paradise and Ko. These investigators have simply but ingeniously demonstrated that halothane interferes with glucose metabolism in the myocardium. Furthermore, they have shown that this effect is not the result of in-

hibition of the later stages of glycolysis, oxidative reactions in the tricarboxylic acid cycle, or oxidative phosphorylation. Instead, halothane interferes with glucose metabolism prior to completion of the initial steps of glycolysis. The data do not permit determination of whether halothane impairs glucose uptake (with normal metabolism once it enters the cell), or whether halothane impairs glucose utilization by interference with its early metabolism (with rate of entry into the cell unaffected). It is tempting to accept the former, that is, that halothane decreases rate of entry of glucose into the cell. A new and increasing body of evidence indicates that halothane and other inhalation anesthetics have significant effects on the permeability of membranes to metabolic substrates. This has been observed in the cell membranes, as evidenced by inhibition by anesthetics of the passage of monosaccharides across cell membranes in insulin-independent systems. The phenomenon has also been observed in other types of membranes. The permeability of mitochondrial membranes to metabolites of the tricarboxylic acid cycle has been shown to be decreased by clinical concentrations of inhalation anesthetics. Many of the effects of anesthetics on energy metabolism and oxygen consumption may be the result of this action. Even permeability of membranes investing cytoplasmic microsomes may be affected by anesthetics. The ability of microsomal enzymes to metabolize foreign compounds such as narcotics and hypnotics is often inhibited by inhalation anesthetics, perhaps the result of decreased permeability of microsomal membranes caused by the anesthetics.

The effects of volatile anesthetics on permeability of membranes to un-ionized substrates which pass through by non-energy-consuming mechanisms is a new and fascinating field. Changes in membrane permeability to un-ionized compounds probably occur independently of anesthetic-induced changes in active membrane-transport systems which require expenditure of chemical energy in the form of ATP, including transport mechanisms such as the sodium pump. In addition, changes in

substrate permeability probably take place independently of anesthetic-induced electrical stabilization of membranes. Changes in substrate permeability may not contribute to development of the anesthetic state when defined in terms of electrical stability of transmembrane potential, nor is it likely that they represent the sole explanation for all of the metabolic changes associated with anesthesia. Nevertheless, the concept that anesthetics affect the rate at which substrates pass through biological membranes adds a new perspective

to our understanding of how anesthetics alter the ability of cells to handle metabolites and, therefore, to function normally. This means, of course, that metabolic alterations do not cause the narcotic state, nor *vice versa*, but that the two occur simultaneously and independently.

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RECOVERY ROOM

It was a blipping sound to which he woke,
each breath an act of courage,
searing flame tongues at the top of it.
"It's all over" someone said,
and he knew this was hell.
Voices were in and out of focus—
whirlpooling vortices of color—
and always the green peaks and valleys on the screen,
whose blips were not the rhythm of his pain.

Minutes were days.
Sleep did not bring him to his once familiar self,
but left him drifting in a weed-choked pond,
where nightmare creatures lurked
to catch his limping soul—
which willed, in challenge,
that this now hell shall be a passing through
and not the end.

—*Susanne Lamdin, M.D.*