Halothane and Drug Metabolism

The duration and intensity of action of many drugs depend largely on the speed at which they are metabolized. The speed of metabolism, in turn, is determined by the enzymatic activity, and this is controlled by a number of so-called endogenous factors. These include genetic control (which determines the amount of an enzyme), hormonal control, nutritional status, age, and sex, to name but a few.

In addition to the endogenous factors, exogenous factors or factors foreign to the biological system influence enzymatic activity. Exogenous factors are chiefly chemical and include such things as drugs, insecticides, agricultural chemicals, carcinogens, and certain air pollutants. These xenobiotics alter enzymatic activity in one of two ways. First, they can override the genetic machinery and thereby cause an increase in synthesis of enzymes; this is called enzyme induction, and the list of xenobiotics known to do this now numbers several hundred. In order to produce this change the inducing agent must be administered chronically, but the effect persists for days after the removal of the inducing agent. Halothane and methoxyflurane have been shown to produce enzyme induction in this manner.1,2

Second, xenobiotics can alter enzymatic activity by interacting with the enzyme or enzyme system itself. This may have no effect, or can result in either inhibition of the enzyme system or stimulation of activity. In contrast to enzyme induction, the effect persists only so long as the xenobiotic is present. As is usually the case with drugs, especially with the volatile anesthetics, they act as broad-spectrum enzyme inhibitors. The literature abounds with information concerning the inhibition of enzyme systems by anesthetics, particularly those enzymes located in the various cell membranes containing the drug-oxidizing system. This is a lipid-rich environment, and most of the enzymes present depend on this lipid for their activity. Thus, the volatile anesthetics, being lipophilic, would tend to accumulate in this region and interfere with enzymatic activity.

The article by Brown ("The Diphasic Action of Halothane on the Oxidative Metabolism of Drugs by the Liver: An in vitro Study in the Rat") in this issue of the journal describes a relatively rare effect of a drug—acute stimulation of an enzyme system by halothane. Our present limited knowledge of the mechanisms of drug metabolism and drug interaction permits only a limited discussion of this effect. Therefore, only two points will be stressed. The first is the apparent specificity of this stimulation by the stimulating agent. Brown's data indicate that halothane stimulates a certain type of drug oxidation, namely, aniline hydroxylation. Previous studies have shown that the ability to produce this effect is limited to only a few materials, such as halothane, methoxyflurane, and acetone.3,4 This information is important because it indicates that the stimulation is not just an effect of a lipophilic solvent on a membrane or on an enzyme system in a membrane. Other solvents with equal lipophilicity have been tried, but without the same results.

Brown discusses the fact that there are at least two sites on a cytochrome or on two cytochromes known to function in drug metabolism, the so-called type I and type II sites.

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As he points out, it is reasonable to expect that halothane stimulates the reaction at the type II site by interfering with the type I reaction, thus diverting the flow of electrons to the type II site. This is a good possibility but probably not the entire answer, for two reasons. First, the high specificity on the part of the stimulating agents: one would expect that any chemical that reacts with the type I site would do this. Second—and a stronger point—if the type I site were destroyed, then type II reactions would be stimulated. This does not happen. Therefore, in view of our limited knowledge of the enzyme systems responsible for drug metabolism, the only conclusion that can be reached is that halothane, as well as methoxyflurane and acetone, stimulates certain drug oxidations in a reasonably specific manner.

What is the importance of this to the clinician? Again, unfortunately, little can be said. However, the phenomenon should be kept in mind by the clinician administering drugs to the anesthetized patient, since the patient may not respond to those drugs in the same manner as he would in the unanesthetized state.

Despite the uncertainties of the mechanism and the scope of this stimulation, the work of Brown is an important step, furthering our understanding of the extent of the biochemical reactivity of the volatile anesthetics.

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References

Fluoride and Methoxyflurane Nephropathy

In the past five years several reports indicating that methoxyflurane is capable of producing renal damage have appeared. The validity of these reports has been questioned, however, and acceptance of methoxyflurane as a nephrotoxin has not been widespread. Since the early studies were retrospective, they suffered from deficiencies in experimental design. A recent report by Mazze et al. has overcome a good many of such deficiencies. In a well-controlled prospective clinical trial, these authors found that six of 12 patients anesthetized with methoxyflurane developed high-output renal insufficiency after operation. None of the control patients, anesthetized with halothane, showed signs of renal damage. The nature of the renal lesion was uncovered when polyuria was not reversed by infusions of vasopressin. Since patients were receiving potassium supplementation, potassium-depletion nephritis was ruled out, leading the authors to conclude that methoxyflurane or one of its metabolites acted directly on the kidney to inactivate the renal concentrating mechanism.

A second report from Mazze’s laboratory appears in this issue of Anesthesiology. In this study, the authors have demonstrated metabolic biotransformation of methoxyflurane in man to two major metabolic products, fluoride and oxalic acid. Patients with clinical signs of high-output renal failure had significantly higher plasma levels of fluoride and oxalic acid, suggestive of enhanced metabolism of methoxyflurane. These patients also