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Mechanism of Liver Necrosis in Hyperthyroid Rats

To the Editor:—I read with great interest the recent article by Berman *et al.*[1] on the hepatotoxicity of halothane, enflurane, and isoflurane in rats pretreated with triiodothyronine (T3). These authors felt that their data suggest a mechanism of liver damage different from that previously proposed of toxic intermediate production via a reductive pathway.[2] On the contrary, their data are consistent with this theory.

Previous studies by Israel and co-workers[3] have demonstrated the presence of a hypermetabolic state in the liver of rats pretreated with T3. Their work suggests that diminished amounts of oxygen would reach the areas of the terminal hepatic vein (central vein), resulting in a relative hypoxia in this zone III of the liver.

As a result, a relative shift to a reductive pathway of biotransformation would be expected, increasing the production of reactive intermediates and the hepatotoxicity of volatile anaesthetic agents. In light of this, Berman's data would support the relationship between reductive metabolism and hepatic toxicity.

It would be of interest to see if a free radical scavanger such as N-acetylcysteine or cystamine could play a protective role in this setting, further supporting the hypoxia–reductive metabolism link to the hepatotoxicity of halothane.

Also, the authors did not state whether the histologic findings in the enflurane- and isoflurane-treated rats were significantly different compared with the phenobarbital and air control.

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2. Ross WT Jr, Daggy BP, Cardell RR Jr: Hepatic necrosis caused by halothane and hypoxia in phenobarbital treated rats. ANESTHESIOLOGY 51:327–333, 1979
3. Israel Y, Videla L, Bernstein J: Liver hypermetabolic state after chronic ethanol consumption: Hormonal interrelations and pathogenic implications. Fed Proc 34:2052–2059, 1975

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In reply:—Dr. Carmichael suggests that the mechanism of liver necrosis induced by isoflurane, enflurane, and halothane in hyperthyroid rats[1] is consistent with the production of toxic intermediates via a reductive pathway. We do not agree for the following reasons: 1) Liver cytochrome P-450 is decreased in triiodothyronine (T_3) pretreated rats (reference 5 in our article[1]), an effect opposite to that of phenobarbital. Therefore, the metabolism of volatile anesthetics would be inhibited, and for halothane this appears to be confirmed by the observation of Smith* who observed that, in T_3 pretreated rats compared with euthyroid rats anesthetized with halothane in 21% oxygen, the tissue levels of the reductive metabolites of halothane, chlorotrifluoroethane, and chlorodifluroethylene are reduced markedly. Furthermore, plasma levels of inorganic fluoride, another reductive metabolite of halothane, are not elevated in hyperthyroid rats anesthetized with halothane in 21% oxygen but are elevated markedly in phenobarbital pretreated rats anesthetized with halothane under hypoxic conditions.[2] 2) Isoflurane and enflurane undergo limited oxidative metabolism but are not metabolized in the presence of low oxygen tensions (reference 13 in our article[1]). 3) Under aerobic or anerobic incubation conditions, no *in vitro* covalent binding of ^{14}C from halothane could be detected in liver microsomal proteins prepared from hyperthyroid rats* and the amount of ^{14}C from halothane covalently bound to hepatic microsomal lipids prepared from hyperthyroid rats was significantly less than the amount bound to microsomal lipids prepared from euthyroid and phenobarbital pretreated rats.* Because euthyroid rats did not have hepatotoxicity develop *in vivo, in vitro* covalent binding to microsomal lipids does not correlate with halothane-induced liver damage. Thus the available data indicate that the mechanism of hepatotoxicity induced by the volatile anesthetics in hyperthyroid rats may not be via a reductive pathway.

* Smith AC: Halothane hepatoxicity in hyperthyroid rats. Ph.D. Thesis Vanderbilt University, 1982.