TITLE: THE EFFECT OF VOLATILE ANESTHETICS ON ALBUMIN SYNTHESIS AND SECRETION IN THE GUINEA PIG LIVER SLICES.

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Volatile anesthetics have previously been shown to inhibit the production of hepatic proteins - albumin, transferrin, and fibrinogen - in ex situ perfused rat livers[1]. Since guinea pigs have proven to be a more reliable model of anesthetic associated hepatotoxicity than the rat[2], the effect of anesthetics on albumin synthesis and secretion in this species was assessed. Liver slices, which have proven to be a good model for studying anesthetic hepatotoxicity[3], were used since they allow for a controlled exposure and sensitive evaluation on liver protein biosynthesis.

Precision-cut liver slices (250-300 μM thick) were incubated in sealed roller vials (3 slices/vial) containing supplemented Krebs-Henseleit buffer at 37°C under 95% O_2 atmosphere. Volatile anesthetics were volatilized from a filter paper wick in the vial to produce constant concentrations in the medium. Albumin synthesis and secretion were measured using a immunoprecipitation technique.

While halothane (1→2.1 mM) and enflurane (2.2 mM) inhibited albumin synthesis and secretion, isoflurane (2.2 mM) and sevoflurane (1.3 mM) had no effect. Halothane decreased the synthesis of albumin more than it did its secretion. Halothane was a more potent inhibitor of albumin synthesis than enflurane. Deuterated halothane (1.7 mM), which is resistant to biotransformation, did not inhibit either albumin synthesis or secretion, indicating the importance of halothane metabolism in producing toxic effects. These results are consistent with the in vivo hepatotoxicity studies in the guinea pig[2] and correlate well with the perfused rat liver results[1]. Alterations in albumin synthesis and secretion appears to be an early and sensitive indicator of cytotoxic injury.

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References

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TITLE: EFFECTS OF HALOTHANE REDUCTION ON THE REGIO-SPECIFIC METABOLISM OF R- AND S-WARFARIN IN HEPATIC MICROSOMES

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Introduction A consequence of halothane reduction by cytochrome P-450 (P450) is P450 inactivation, and formation of a spectral complex between halothane and P450 (1). Since P450 exists as multiple forms, this study attempted to determine if halothane selectively inactivates the P-450 forms induced by phenobarbital (PB). This was done by assessing the ability of microsomes from PB treated rats to metabolize the P450 probes, R- and S-warfarin, in the presence and absence of complex after halothane reduction.

Methods Hepatic microsomes (3mg/ml, 4.5ml) from PB treated rats were incubated (37°C) under nitrogen, without or with halothane (16 umoles) for 10 min. After incubation, halothane and its metabolites were removed by evacuating and purging the vials with nitrogen for 30 min. In some microsomes complex was eliminated by photolysis with high intensity light. Subsequent warfarin incubations were carried out under air with R- or S-warfarin (1mM) for 4 min, and warfarin metabolites analyzed (2).

Results Halothane reduction selectively impaired the formation of R-warfarin metabolites (Table). 7-OH warfarin, whose formation is due to PB-C, was impaired to the greatest degree (88%). In addition to dehydrowarfarin, the metabolite least affected was 10-OH (37%) whose formation is due to PB-PCN/E. While 4'-OH was inhibited 58%, photolysis of the complex resulted in an increased ability of these microsomes (+29) to form only 4'-OH, whose formation from R-warfarin alone is due to PB-B. The effects of halothane reduction on the metabolism of S-warfarin showed similar results except complex photolysis did not result in increased 4'OH formation.

Table- Effects of Halothane on R-warfarin Metabolism
nmol/mg/min + S.E.

	Control	(±complex)	(-complex)
Dehydro	0.59±0.01	0.45±0.01(-24)	0.41±0.01 (-9)
4'-OH	0.36±0.01	0.15±0.01 (-58)	0.21±0.01 (+29)
6-OH	0.51±0.01	0.19±0.01 (-63)	0.19±0.003 ns
8-OH	0.25±0.01	0.10±.003 (-60)	0.11±0.01 ns
10-OH	4.40±0.01	2.76±0.05 (-37)	2.46±0.10 (-11)
7-OH	3.24±0.04	0.39±0.03 (-88)	0.33±0.04 ns

Discussion This study presents evidence that halothane selectively inactivates the P450s in PB induced microsomes. That most susceptible to destruction appears to be PB-C, based on the high degree of loss of 7-OH warfarin hydroxylase activity. PB-PCN/E and PB-B, on the other hand, are not extensively inactivated; however the fact that only 4'OH formation from R-warfarin is increased by complex photolysis, indicates that PB-B is the form bound as complex.

References:

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