Title : HALOTHANE-INDUCED HEPATIC NECROSIS IN HYPERTHYROID RATS

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Introduction. The metabolism of halothane to reactive toxic intermediates that covalently bind to liver macromolecules may be related to halothane hepatotoxicity. Current models for the production of halothane hepatic necrosis consist of either pretreating rats with phenobarbital followed by exposure to halothane at low oxygen concentrations (7-14%) or pretreatment of rats with a single dose of polychlorobiphenyl and exposure to halothane at 99% oxygen. We have developed a new model which uses the naturally occurring hormone triiodothyronine (T_3) to sensitise the rat to halothane induced hepatic centrilobular necrosis under normal oxygen tensions.

Methods. Groups of 4-6 male Sprague-Dawley rats (75-125 gms) were treated with T_3 (1-10 mg/kg orally for 6 days or 1 mg/kg SC for 5 days). On the 6th or 7th day the rats were anesthetised with 1% halothane for 2 hours under normal oxygen tensions (21%), hypoxia (14%) and hyperoxia (99%). In addition, groups of rats received phenobarbital (75 mg/kg/day ip 3 days) or phenobarbital and T_3 and then were anesthetised with 1% halothane at 14%, 21% and 99% oxygen for 2 hours. Immediately following or 24 hours after halothane exposure the rats were sacrificed. SGPT, cytochrome P450 and glutathione were measured; and histopathological grading of liver damage based on a scale of 0-4+ was performed.

Results. Centrilobular necrosis occurred in all the livers from rats treated with T_3 and 1% halothane at all of the oxygen tensions studied. No histological abnormalities were present in livers from rats given T_3 or halothane alone. Increasing oxygen tensions reduced the lesion, there being a significant improvement in the severity of the lesion at 99% oxygen compared with 21% oxygen ($p < 0.05$). Pretreatment with phenobarbital alone resulted in hepatic necrosis only if hypoxia was also present in keeping with the previous models, and there was no significant worsening of the T_3 produced lesion when phenobarbital was added at any of the oxygen tensions studied. However, the lesion produced by T_3 and 14% oxygen was significantly worse than the lesion produced by phenobarbital and 14% oxygen ($p < 0.05$). SGPT levels were significantly elevated in the T_3 treated rats immediately after halothane anesthesia ($p < 0.02$) as shown in the table below.

T_3 Dose (mg/kg/ per day)	SGPT U/l ± SEM Pre Hal	Post Hal	24 hrs Post Hal
10	42.5±4.3	776.0±266.7	41.0±5.9
5	51.0±2.5	356.3±156.8	56.2±9.5
1	51.7±6.7	326.6±138.8	41.0±5.9
Control	35.5±5.5	30.0± 2.7	36.3±3.9

There was a significant depression of glutathione (GSH) 24 hours after T_3 administration ($p < 0.001$) but no further fall with continued T_3 pretreatment or with the administration of halothane. The results of the cytochrome P450 estimations are shown below.

	Cytochrome-P450 nmoles/mg microsomal protein T_3	Control
No Anes.	0.41(±0.01)	0.97(±0.04)***
Post halothane	0.27(±0.04)*	0.95(±0.06)***
No Anes.	0.40(±0.03)	0.89(±0.04)**
24 Hrs Post halothane	0.40(±0.04)	0.92(±0.06)**

* $p < 0.05$, ** $p < 0.005$, *** $p < 0.001$.

Conclusions. (1) T_3 sensitises the rat to halothane induced hepatic necrosis at normal oxygen tensions and hyperoxia does not prevent the lesion; (2) T_3 lowers GSH but exposure to halothane does not cause a further fall in GSH regardless of oxygen tension; (3) T_3 lowers cytochrome-P450 and halothane causes a further fall; (4) the mechanism of the hepatic toxicity of halothane in this model remains to be determined. Recently thyroidectomy has been undertaken in hyperthyroid patients prepared solely with propranolol. The thyroid hormone levels in these patients remain elevated though their symptomatology is improved by beta-blockade. These patients, who are also enzyme induced, may be at special risk if halothane is used as an anesthetic agent.