Title: LACK OF GENDER EFFECT OF TRIIODOTHYRONINE ENHANCEMENT OF HALOTHANE INDUCED HEPATOTOXICITY

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Introduction Previous studies (1,2) indicate that there is a gender difference for halothane (H) hepatotoxicity in hyperthyroid rats. Smith et al (1) administered triiodothyronine (T_3) 3 mg/kg daily for six days intraperitoneally (ip) to male and female rats. Subsequent exposure to H showed a 78% incidence of hepatic centrilobular necrosis in males and only 5% incidence in females. Uetrecht et al (2) pretreated male and female rats with T_3 ip, 5 mg/kg daily for five days and observed no histological evidence of H-induced liver necrosis in females compared to a 68.8% incidence in males. In a preliminary experiment, we observed an 85% incidence of H-induced liver injury in female rats pretreated with T_3, 5 mg/kg daily for six days. We used the same strain and weight of rats from the same vendor as did Smith et al and Uetrecht et al. We exposed rats in similar chambers to the same length and concentration of H. Exposure to H was done at the same interval following pretreatment and the livers were removed for examination after same interval following exposure. We concluded that none of the above factors contributed to the observed difference. We also concluded that the difference may have been due to either the dose or duration of the pretreatment schedules which were different. Accordingly, we present our data comparing previously reported T_3 dose schedules and our current schedule to determine the incidence of H-induced liver injury in male and female rats.

Methods Male and female Sprague-Dawley rats (100-125 g) were given T_3 or an equal volume of the vehicle for T_3 ip. The rats were divided into three groups: Group I received T_3, 3 mg/kg or the vehicle daily for six days, Group II 5 mg/kg or the vehicle daily for five days, and Group III 5 mg/kg or the vehicle daily for six days. The number of male and female rats used in each group is shown in the table. Twenty-four hours after the last injection of T_3 or the vehicle rats were anesthetized with H 1% in air for 2 hours. The anesthetic chamber, the administration of H and the monitoring of the concentration of H and oxygen in the chamber were the same as described in previous reports (1,2). Four hours after H exposure, the livers were removed and prepared for examination. Histological grading was performed by a pathologist who was unaware of the treatment. Data were analyzed using Chi square analysis with Yates correction.

Results The livers from Group I male rats had a 75% incidence of H-induced liver necrosis whereas the livers from females had an incidence of 16.5% ($p<0.001$) (Table). In Group II, the incidence of hepatic necrosis was 70% in males and 20% in females ($p<0.02$). However, in Group III the incidence of liver injury was similar in both males and female rats 91.6 and 80% respectively ($p>0.1$). The incidence of necrosis in livers obtained from females in Group III was significantly greater ($p<0.001$) than the incidence in the livers obtained from females in Groups I and II. The severity of the liver lesion in males appears to exceed that in females in all groups. No liver lesions were observed in rats pretreated with the vehicle only and then exposed to H.

Effect of Dose and Duration of T_3 Pretreatment on the Severity and Incidence of Halothane-Induced Hepatic Necrosis in Male and Female Rats

	Dose and Duration of T_3 Pretreatment					
	Group I 3 mg/kg x 6 days		Group II 5 mg/kg x 5 days		Group III 5 mg/kg x 6 days	
Gradet	Male	Female	Male	Female	Male	Female
	(12)§	(30)	(10)	(30)	(12)	(20)
0	3	25	3	24	1	4
1/2+	0	0	0	2	1	1
1+	1	3	2	3	4	10
2+	6	2	4	1	3	4
3+	2	0	1	0	3	1
4+	0	0	0	0	0	0
Incidence %	75*	16.6**	70*	20**	91.6*	80**

† Histopathological grade based on the level of necrotic cells extruding away from a central vein; 0 = no lesion; 1/2+ = first cell level; 1+ = 2-3 cell levels; 2+ = 3-6 cell levels; 3+ = extending from one central vein to another; 4+ = centrilobular necrosis throughout the section.

§ Number in parenthesis indicates total number given T_3; an equal number received vehicle.

* $p<0.001$ males vs females Group I; $p<0.02$ males vs females Group II; no significant difference between males and females Group III.

** $p<0.001$ Group III females vs Group I females, Group III females vs Group II females.

Discussion The published data (1,2) and our observation in hyperthyroid female and male rats suggests that the threshold dose of T_3 to enhance H induced liver injury is greater in the female than in the male rat. Female rats required a cumulative T_3 pretreatment dose of 30 mg/kg (5 mg/kg daily for six days) before the incidence of necrosis was comparable to that observed in male rats. This study suggests that there is a dose-dependent gender effect of T_3 in sensitizing rats to H-hepatotoxicity.

References 1. Smith AC, Berman ML, James RC, Harbison RD: Characterization of hyperthyroidism enhancement of halothane-induced hepatotoxicity. Biochem Pharmacol 32:3531-3539, 1983. 2. Uetrecht J, Wood AJJ, Phythyon JM, Wood M: Contrasting effects on halothane hepatotoxicity in the phenobarbital and triiodothyronine model: mechanistic implications. Anesthesiology 59:196-201, 1983.

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