Hemodynamics of the Isolated Perfused Liver of Hypothyroid and Hyperthyroid Rats[1] (34157)

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Experimentally induced hyperthyroidism increases, but hypothyroidism (thyroidectomy) does not affect, the lethality of barbiturates in rats (1). One possible explanation is the effect of thyroid state on metabolism and specifically on hepatic drug metabolizing enzyme systems. Conney and Garren (2) showed both stimulation and inhibition of drug metabolism by thyroxine administration. Another possible effect due to altered thyroid state may be alteration of hepatic hemodynamics so that more or less barbiturate reaches the liver. The purpose of the present work was to determine the effects of experimental hyperthyroidism and hypothyroidism on hepatic hemodynamics in the isolated perfused rat liver.

Methods. Male Simonsen Sprague-Dawley rats weighing 200–300 g were housed in stainless steel cages and allowed food and water *ad libitum*. Drug solutions were prepared so that the desired dosage was injected intraperitoneally in 0.01 ml/g of body weight. L-Triiodothyronine was dissolved in a small volume of 0.75 *N* sodium hydroxide; when made to volume with distilled water the resulting pH of the solution was 9.0.

Thyroid treatments. Rats, 80–100 g, were thyroidectomized under pentobarbital anesthesia. Other groups of rats were sham-operated at the same time and served as euthyroid controls. All operated animals were allowed 30 days for recovery and development of hypothyroidism. Hyperthyroidism was induced in rats by intraperitoneal injection of L-triiodothyronine (California Corporation for Biochemical Research), 0.2 mg/kg, daily for 5 days. Control animals were injected for 5 days with an equal volume of dilute sodium hydroxide solution (pH 9.0). At various times during and after induction of the altered thyroid state, the body weights and rectal temperatures of randomly selected animals were recorded. Basal metabolic rates were determined utilizing a modified Phipps and Bird metabolism apparatus and were measured between 9 a.m. and 3 p.m. to reduce time-of-day variation. Values were expressed as means ± standard errors. At the end of the treatment periods, the animals were sacrificed, livers were isolated and perfused.

Isolated rat liver perfusion. Modified Brauer *et al.* (3) perfusion apparatus, surgical preparation, perfusate and perfusion techniques of Plaa and associates (4) were used. Basal resistance to blood flow in the liver was determined by their protocol: blood flow (ml/min) was recorded at 8, 10, and 12 mm Hg and corrected to ml/g of liver/min. Increased flow in the face of constant pressure reflected a reduction in resistance.

Statistical analyses. Data were analyzed using a group comparison Student's *t* test (5); $p<0.05$ was considered significant.

Histopathology. Livers of other treated and control rats were removed and weighed. Sections of the liver were taken for histopathologic examination, fixed in buffered 10% formalin and stained with hematoxylin and eosin or sudan red. Sections for electron microscopic examination were fixed in gluteraldehyde and osmium tetroxide.

Results. Thyroid state parameters. The mean basal metabolic rate of the triiodothyronine (T_3) group by the fifth day of treat-

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TABLE I. Basal Metabolic Rate[a] of Triiodothyronine (T_3)-Treated, Thyroidectomized, and Control Rats.

Day:[b]	1	2	3	4	5
Control	76.9 ± 3.7	80.2 ± 5.5	101.0 ± 26.2	83.8 ± 8.4	91.5 ± 4.6
T_3	84.1 ± 3.4	112.7 ± 13.5	103.0 ± 11.5	132.9 ± 11.1[c]	168.6 ± 8.8[c]

Day:[b]	0	7–10	30
Sham-operated	79.6 ± 2.0	77.7 ± 7.5	89.2 ± 5.5
Thyroidectomized	79.6 ± 2.0	76.7 ± 3.9	63.2 ± 3.1[c]

[a] Mean ± standard error in Cal/m²/hr.

[b] Day of treatment.

[c] Indicates a significant difference from corresponding control at $p < 0.05$.

ment was 54% greater than control mean (Table I). Mean body temperature of the T_3-treated animals was significantly elevated on the fifth day of treatment to 39.1 ± 0.2° as compared to control, 37.6 ± 0.1°. The control group had a significant mean weight gain of 31 g for a 5-day period; the treated group did not gain weight. The T_3-treatment decreased liver weight by 23% from 4.0 ± 0.1 to 3.6 ± 0.1% of body weight (Table II).

A significant decrease in basal metabolic rate of 29% was observed in thyroidectomized rats at 30 days following thyroidectomy (Table I) and was accompanied by a significant hypothermic response: mean body temperature of sham-operated rats was 36.6 ± 0.1° vs. thyroidectomized group, 35.9 ± 0.1°. Thyroidectomized animals gained significantly less weight over the 30-day period when compared to sham-operated controls (Table II). Both groups had a mean body weight of 97 ± 4 g at the start of the 30-day period. Thyroidectomy decreased liver weight by 40% from 4.1 ± 0.1 to 2.9 ± 0.2% of body weight (Table II).

Perfusion data. Total flow in milliliters per minute was recorded at 8, 10, and 12 mm Hg pressures. Following the experiment the liver was weighed and the flow as expressed as ml/g of liver/min. Mean ± SE blood flow of livers obtained from T_3-treated rats was 6.8 ± 0.6, 8.3 ± 0.6, and 9.5 ± 0.7 ml/g of liver/min vs. euthyroid, 5.1 ± 0.3, 6.3 ± 0.4, and 7.3 ± 0.4 ml/g of liver/min at 8, 10, and 12 mm Hg, respectively (Fig. 1a); a significant increase at each of the three perfusion pressures. However, hypothyroidism also significantly increased blood flow at the perfusion pressures from euthyroid basal levels of 5.0 ± 0.3, 6.2 ± 0.3, and 7.2 ± 0.4 ml/g of liver/min, respectively, to 7.8 ± 0.4, 9.8 ± 0.5, and 11.7 ± 0.7 mg/g of liver/min (Fig. 1b). Hyperthyroidism and hypothyroidism decreased hepatic vascular resistance by 22% and 37% respectively (Table III). These resistance changes correlated with the increased hepatic blood flow. Within a group

TABLE II. Body and Liver Weight of Triiodothyronine (T_3)-Treated, Thyroidectomized, and Control Rats.

	Body wt (g)	Liver wt (g)	(%)[a]
Control[b]	308 ± 5	12.3 ± 0.5	4.0 ± 0.1
T_3[b]	266 ± 10[c]	9.5 ± 0.4[c]	3.6 ± 0.1[c]
Sham-operated[d]	313 ± 7	12.9 ± 0.5	4.1 ± 0.1
Thyroidectomized[d]	268 ± 20[c]	7.7 ± 0.4[c]	2.9 ± 0.2[c]

[a] (%) = (liver wt × 100)/body wt.

[b] After 5 days of treatment; T_3 = triiodothyronine, 0.2 mg/kg, ip; control = vehicle injected.

[c] Significantly different from corresponding control ($p < 0.05$).

[d] Thirty days after thyroidectomy or sham-operation; initial body weights of both groups, 97 ± 4 g.

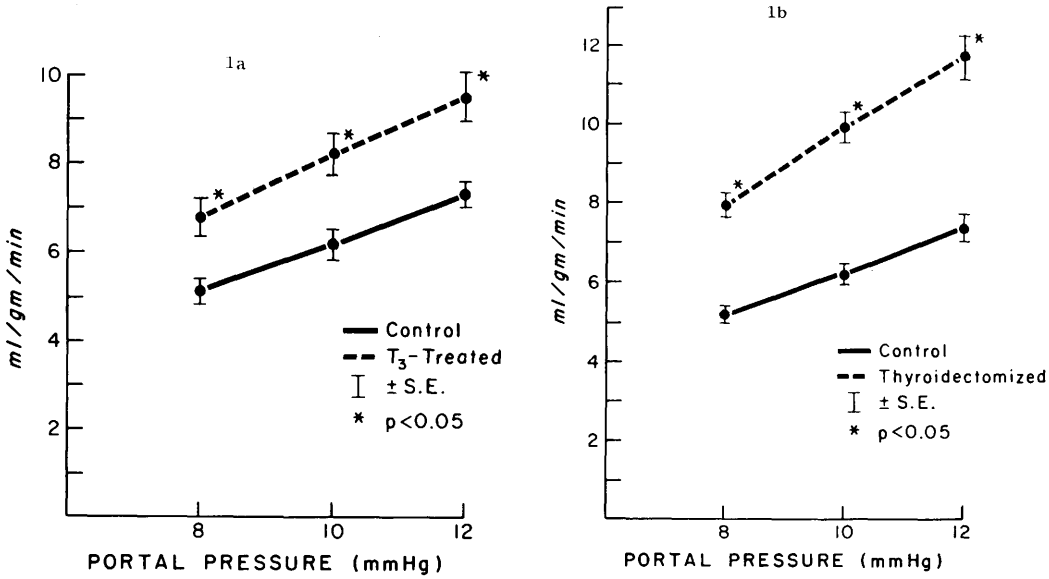

FIG. 1. Pressure–flow relationships in isolated, perfused rat livers. (a) rats treated for 5 days with triiodothyronine, 0.2 mg/kg/day. (b) rats thyroidectomized 30 days previously. Portal pressure (mmHg) on abscissa; portal flow rate (ml/g of liver/min) on ordinate; each point is mean ± SE of data from 8 livers.

resistance remained constant with increasing pressure indicating the integrity of the hepatic vasculature.

Histopathology. Histopathologic examination of livers taken from T_3-treated and thyroidectomized rats revealed no remarkable changes in hepatocytes or liver architecture by light microscopy. In addition, examination of other livers from T_3-treated and thyroidectomized rats by electron microscopy revealed no remarkable changes in the subcellular components of the hepatocytes.

Discussion. Basal metabolic rates and body temperature data present evidence that hypothyroid and hyperthyroid states of the experimental animals were achieved. Both treatments resulted in reduced liver weights which were disproportional to body weight reductions. Histologic examination by light and electron microscopy showed no evidence of cellular or subcellular injury. Thus the induced states did not appear to produce degenerative changes in the liver parenchyma.

The two thyroid states had similar effects

TABLE III. Effect of Triiodothyronine (T_3) Treatment and Thyroidectomy on Hepatic Vascular Resistance.

	Resistance[a]		
Pressure (mm Hg):	8	10	12
Control[b]	1.62 ± 0.10	1.64 ± 0.09	1.69 ± 0.09
T_3[b]	1.26 ± 0.14[c]	1.27 ± 0.12[c]	1.32 ± 0.12[c]
Sham-operated[d]	1.63 ± 0.10	1.65 ± 0.08	1.69 ± 0.09
Thyroidectomized[d]	1.04 ± 0.05[c]	1.04 ± 0.05[c]	1.05 ± 0.05[c]

[a] Resistance = pressure/flow per g of liver.

[b] After 5 days of treatment; T_3 = triiodothyronine, 0.2 mg/kg, ip; control = vehicle injected.

[c] Significantly different from corresponding controls ($p < 0.05$).

[d] Thirty days after thyroidectomy or sham operation; initial body weights of both groups, 80–100 g.

on hepatic hemodynamics at a given pressure, blood flow per gram of liver increased and resistance was reduced. The net blood flow (ml/min) was essentially the same in control, T_3, and thyroidectomized groups which means that the volume of perfusate passing through the smaller test livers was as great as that passing through the larger control livers. These findings were unexpected. Increased cardiac output and higher cellular oxygen demand seen in hyperthyroidism suggested increased hepatic blood flow. Reduced cardiac output seen in hypothyroidism suggested reduced hepatic blood flow. However, increased hepatic blood flow may be the consequence of different mechanisms in hyperthyroid and hypothyroid states although reduced liver mass appeared to be a factor in each state. The data presented do not provide information on the possible different mechanisms. These results were obtained in isolated perfused rat livers which do not allow for possible extrahepatic influences. Confirmation of such results by *in vivo* experiments would be desirable.

These studies were undertaken as a consequence of earlier investigations on the effect of thyroid state on barbiturate toxicity in rats (1): toxicity of barbiturates was increased in hyperthyroid rats and unchanged in hypothyroid rats except for the thiobarbiturate, thiopental. Increased toxicity of barbiturates in hyperthyroid rats may be the consequence of altered metabolism or altered blood flow. A decrease in blood flow could be a possible mechanism of increased toxicity. However, the observed increase in blood flow can account for increased toxicity only if the poorly accepted hypothesis of Catz and Yaffe (6), namely that barbiturates are biotransformed to more toxic products, is operable. The reduction in liver size without apparent degenerative changes can contribute to increased toxicity if the smaller size means there is a significant reduction in the amount of available drug metabolizing enzymes. On the other hand if liver blood flow or mass do contribute to the ability of the liver to biotransform barbiturates, then the lack of effect of these factors on barbiturate toxicity in hypothyroid rats cannot be explained. Therefore, the conclusion is reached that neither reduction in liver mass nor resistance to blood flow are critical factors in the enhanced toxicity of barbiturates in experimental hyperthyroidism or unaltered toxicity in experimental hypothyroidism.

Summary. Livers of Sprague-Dawley (Simonsen) hypothyroid, hyperthyroid and euthyroid rats were isolated and perfused, pressure–flow relationships were measured and vascular resistance was calculated. Both hyperthyroid and hypothyroid rat livers exhibited reduced vascular resistance and increased blood flow per gram of liver despite a reduction in liver mass and apparent absence of pathologic change.

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