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Effects of Propylthiouracil and Methimazole on Splanchnic Hemodynamics in Awake and Unrestrained Rats

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The treatment of alcoholic liver disease with propylthiouracil is based on its effect of suppressing the ethanol-induced increase in hepatic oxygen consumption. It has been postulated that liver necrosis ensues when the increase in oxygen demand by the liver exceeds oxygen delivery to this organ. Data are now presented which show that propylthiouracil also increases portal blood flow in awake, unrestrained rats.

Liver blood flow was determined using the labeled microsphere technique in rats at various intervals (0.25, 0.5, 1.0, 3.0, 6.0 and 24 hr) after oral propylthiouracil (50 mg per kg). Administration of propylthiouracil (dose range: 6.25 to 100.0 mg per kg) produced a dose-dependent increase in portal blood flow when given either orally or intraarterially. Maximal flows were obtained with 50 mg per kg (controls = 37.8 ± 1.5, oral propylthiouracil = 50.7 ± 2.2 ml·kg^{-1}·min^{-1}). This increase in portal blood flow was accompanied by a decrease in preportal vascular resistance (controls = 2.61 ± 0.16; propylthiouracil, 50 mg per kg = 1.79 ± 0.09 mmHg per ml·kg^{-1}·min^{-1}). These effects were correlated with the plasma concentrations of propylthiouracil ($r = 0.67$, $n = 68$, $p \leq 0.001$). The effect of oral propylthiouracil (50 mg per kg) on portal blood flow started at 0.5 hr and lasted for 6 hr after administration, whereas total liver blood flow was increased for 3 hr. Oral propylthiouracil (50 mg per kg) for 5 days resulted in a 53% increase in thyroid weight, an 85% reduction in ^{125}I thyroid uptake and a 74% decrease in serum thyroxine concentration. This treatment, however, did not modify portal blood flow, nor the response to acute propylthiouracil. Oral administration of equipotent doses of another antithyroid drug, methimazole (10 and 20 mg per kg), had no effect on portal blood flow. Because of the rapid increase in portal blood flow following a single oral or parenteral dose of propylthiouracil and the lack of effect of methimazole, it is concluded that this response of propylthiouracil is independent of its effect on the thyroid gland and of intestinal absorption. The increase in portal blood flow can contribute to the protective effect of propylthiouracil against alcohol-induced liver necrosis by increasing oxygen delivery to the liver.

The antithyroid drug propylthiouracil (PTU) has been shown experimentally to be effective in protecting the liver against alcohol-induced, and amino acid-induced, hypoxic liver cell damage (1–3). In a long-term clinical trial, PTU has also been demonstrated to reduce mortality in patients with alcoholic liver disease by over 50% (4).

It has been postulated that ethanol-induced hepatocellular necrosis is the result of hypoxic damage and that it occurs when two factors interact, namely: (a) the increase in oxygen requirement of the liver that follows alcohol intake, and (b) an inadequate oxygen availability to meet this increase in oxygen requirement (5). Thus, two mechanisms could be effective in preventing alcohol-induced liver necrosis: (a) a reduction in oxygen consumption by the liver, or (b) an increase in liver blood flow, which would deliver more oxygen to the liver, or a combination of the two mechanisms.

PTU has been used both experimentally and clinically because it reduces the increase in oxygen consumption induced by acute or chronic ethanol intake (1, 6). However, the possibility of PTU also having a direct effect on liver blood flow has not been explored. In the present study, we investigated the effects of PTU and of methimazole, another antithyroid drug, on splanchnic hemodynamics.

MATERIALS AND METHODS

Male Sprague-Dawley rats (Charles River Breeding Laboratories, St. Constant, Quebec, Canada), weighing 220 to 330 gm, were housed in a temperature- and humidity-controlled environment and fed a laboratory chow diet. Prior to the experiments, the rats were fasted overnight with water *ad libitum*. This protocol was approved by the University of Toronto Animal Care Committee. The rats were treated humanely throughout these studies.

Hemodynamic Studies. Blood flow and cardiac output were measured by the microsphere method in awake and unrestrained rats, as reported in 1986 by McKaigney et al. (7). Briefly, under ketamine anesthesia (85 mg per kg), the left femoral artery was cannulated with polyethylene tubing, and the cannula was then advanced to 1 cm above the aortic

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bifurcation. The right carotid artery was then cannulated, and a catheter was advanced into the left ventricle while monitoring pressure. The cannulae were capped with rubber injection ports and tunneled subcutaneously to the midback, where they were brought out onto the skin surface. The operation lasted about 25 min. The rats were allowed to wake up and recover unrestrained for 4 to 5 hr. All blood flow studies were performed while the animals were awake and unrestrained. During the experiments, body temperatures, as measured with rectal probes, were maintained at 37.5°C with heating lamps.

Liver Blood Flow Experiments. Microspheres (16.5 ± 0.1-μm diameter) labeled with either ^{46}Sc or ^{57}Co (New England Nuclear, Boston, MA) were used for blood flow determinations. The microspheres were mixed and diluted as described by Stanek et al. (8) and were counted prior to injection. The microspheres were injected into the left ventricle over a period of 20 sec using an infusion pump. A reference blood sample of 1.5 ml was taken from the femoral artery using a withdrawal pump, starting from 10 sec before the infusion of microspheres and continuing for 90 sec. Ficoll (13.4%, 0.6 ml) was given as has been described by Stanek et al. (8) for volume replacement to prevent a fall in blood pressure due to blood withdrawal. The rats were then killed, and the heart, lungs, liver, kidneys, spleen, stomach, pancreas, omentum, small intestine and large intestine were removed for counting.

Calculations. Cardiac output (CO) in units of ml per min per kg was determined from the formula:

$$CO = \frac{\text{Net counts injected} \times \text{Reference sample withdrawal rate}}{\text{Net counts in reference sample} \times \text{Body weight}}$$

Organ blood flow (OBF) in units of ml per min per kg was calculated from the formula:

$$OBF = \frac{\text{Net counts in organ}}{\text{Net counts injected}} \times CO$$

All flow rates were calculated with respect to body weight and expressed as ml per kg per min. Early studies showed no difference in the conclusions derived when this expression was used as opposed to blood flows expressed per gm of organ weight (7).

Portal blood flow was determined indirectly from the sum of blood flow to the spleen, stomach, pancreas, omentum and small and large intestines. Hepatic arterial flow was calculated from the counts in the liver. Total liver blood flow was considered to be the sum of the portal blood flow and hepatic arterial blood flow. Preportal vascular resistance was calculated as mean arterial pressure minus average portal vein pressures (mmHg), divided by portal blood flow and expressed as mmHg per ml per kg per min.

In separate experiments in anesthetized rats, portal vein pressure was determined 1 hr after the administration of either water (n = 6), or PTU (50 mg per kg; n = 6) by gavage. Portal vein pressures were: control = 7.4 ± 0.2 mmHg and PTU = 8.0 ± 0.4 mmHg. (The range of these pressures was from 7.0 to 10.0 mmHg.) This avoided the use of anesthesia or portal vein catheterization to obtain portal vein pressures, since both techniques could interfere with the splanchnic hemodynamic responses (7, 9, 10). The portal vein pressures obtained in this study with PTU are similar to those previously reported by us (11).

Administration of PTU, Methimazole and Ethanol. PTU, 6-*n*-propyl-2-thiouracil (Sigma Chemical Co., St. Louis, MO), was administered by gavage in water (1 ml per 100 gm body weight) at doses ranging from 6.25 to 100 mg per kg. PTU was dissolved in water by adjusting to pH 9.5 with NaOH. Control animals received an equivalent volume of water at pH 9.5. Drug solutions were freshly prepared on each experimental day. When given parenterally, PTU was dissolved in saline (pH 9.5), and controls received an equivalent volume of saline adjusted to the same pH.

Methimazole (Sigma Chemical Co.) was administered by gavage at doses of 10 or 20 mg per kg in water (1 ml per 100 gm). Controls received the same volume of water by gavage.

Ethanol (2 gm per kg) was given by gavage in a 20% (w/v) solution in a volume of 1 ml per 100 gm. Controls received the same volume of water by gavage.

Measurements of Uptake of Iodine by the Thyroid Gland and Serum Thyroxine (T_4). Rats were given 5 to 10 μCi of ^{125}I (Amersham International, Oakville, Ontario, Canada), injected into the left femoral artery. Four hours after receiving the tracer, the animals were killed and the thyroid gland was rapidly removed, dissected free of connective tissue and weighed. Radioactivity in the gland was counted in a gamma counter (Nuclear Chicago, Model 1185, Chicago, IL). Iodine uptake was expressed as a percentage of the total ^{125}I administered.

The hormone thyroxine T_4 was measured in serum by radioimmunoassay (12).

Determination of PTU in Plasma. Plasma samples were obtained immediately following blood flow determinations and were stored at −20°C. PTU concentrations were determined by high-performance liquid chromatography as previously described (13). The method has been modified as follows: mobile phase; acetonitrile 15%, sodium phosphate 0.01 *M*, pH 4.5; 85%; flow rate: 4 ml per min; retention time = 2.1 min.

Experiments Designed to Show the Effect of PTU on Liver Blood Flow. The purpose of these experiments was to determine the dose relationship of oral PTU on liver blood flow. Rats were given PTU at doses ranging from 6.25 to 100.0 mg per kg in water (1 ml per 100 gm) administered by gavage. Organ blood flows were determined after 1 hr.

In order to determine the duration of the effect of PTU in liver blood flow, rats were given PTU (50 mg per kg) by gavage, and organ blood flows were determined in six groups of animals at 0.25, 0.5, 1, 3, 6 and 24 hr after administration of PTU. The dose of 50 mg per kg was selected for these and other experiments because it has been previously shown to protect against alcohol-induced hypoxic liver damage (1, 2). Controls (dose = 0) were given an equivalent volume of water and blood flows were determined at the same intervals. Since there were no differences between the control groups, these data were combined.

The effect of parenteral PTU on liver blood flow was analyzed in experiments performed to determine whether the route of administration influenced the response of liver blood flow to PTU. Rats were infused intraarterially with PTU (25 or 50 mg per kg) in a volume of saline (1 ml per 100 g) over 30 min. Organ blood flow was determined 30 min after the end of the infusion. Control rats were infused with an equal volume of saline.

Experiments were undertaken to determine the effect of mild hypothyroidism in the portal blood flow response to PTU. Rats were given PTU (50 mg per kg) by gavage, daily for 5 days. Controls received an equal volume of water daily by gavage. On Day 6 rats were divided into two groups. One was given another dose of PTU (50 mg per kg) by gavage; the other received an equal volume of water, and organ blood flow was determined 1 hr later. Another group of rats received PTU (50 mg per kg, n = 6), or water (n = 6) by gavage, for 5 days. On Day 6, the uptake of ^{125}I by the thyroid, thyroid gland weight and serum levels of thyroxine were determined.

Experiments were performed to test the possibility that 5 days of administration modified the hemodynamic response to ethanol. Rats were treated with PTU (50 mg per kg) as above,

and on Day 6 they were given ethanol (2 gm per kg) by gavage. Controls received an equal volume of water (1 ml per 100 gm). Organ blood flow was determined after 1 hr.

Experiments Designed to Show the Effect of Methimazole on Liver Blood Flow. In order to determine whether another antithyroid drug also had effects on liver blood flow, rats were given methimazole (10 or 20 mg per kg) by gavage. This range of doses is equivalent in antithyroid potency to the dose of PTU used in the present study (14). Methimazole, like PTU, protects against hypoxic liver damage (2). Blood flows were determined 1 hr after methimazole administration. Controls received an equivalent volume of water (1 ml per 100 gm) 1 hr before blood flow determinations.

Data Analysis. Data are presented as means ± S.E. Significance was considered to be $p < 0.05$. All data were subjected to analysis of variance, with intergroup differences being determined by the least-significant difference method.

RESULTS

Effects of Oral PTU on Liver Blood Flow. PTU administration resulted in a dose-dependent increase in portal blood flow and in a decrease in preportal vascular resistance which were not accompanied by changes in hepatic artery blood flow (Fig. 1, Table 1). The increase in portal blood flow was due primarily to increases in intestinal blood flow. Acute oral PTU had no effect on cardiac output, coronary or renal blood flows. The increases in portal blood flow were positively correlated with the plasma levels of PTU at the different doses employed ($r = 0.67$; $p < 0.001$; Fig. 2).

The effect of PTU on portal blood flow was also observed when PTU was infused intraarterially (controls = 41.0 ± 2.1 $ml \cdot kg^{-1} \cdot min^{-1}$; PTU (50 mg per kg) = 52.1 ± 3.0 $ml \cdot kg^{-1} \cdot min^{-1}$). As seen by the data in Table 2, this effect was mainly the result of an increase in intestinal blood flow, whereas blood flow to other organs was not affected.

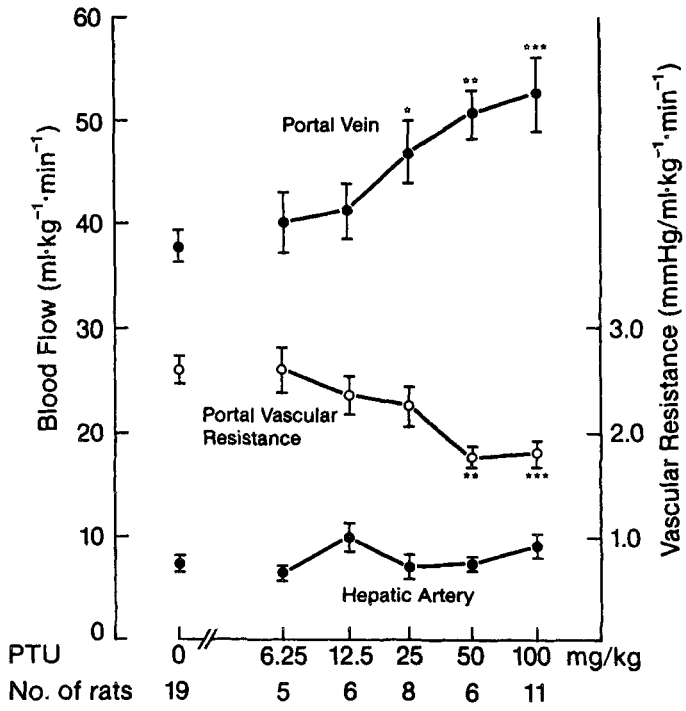

FIG. 1. Effect of increasing doses of PTU on portal vein flow, preportal vascular resistance and hepatic artery blood flows. PTU was administered by gavage in water. Control rats (dose = 0) received an identical volume of water. *Bars* = S.D. * = $p < 0.05$; ** = $p < 0.01$; *** = $p < 0.001$.

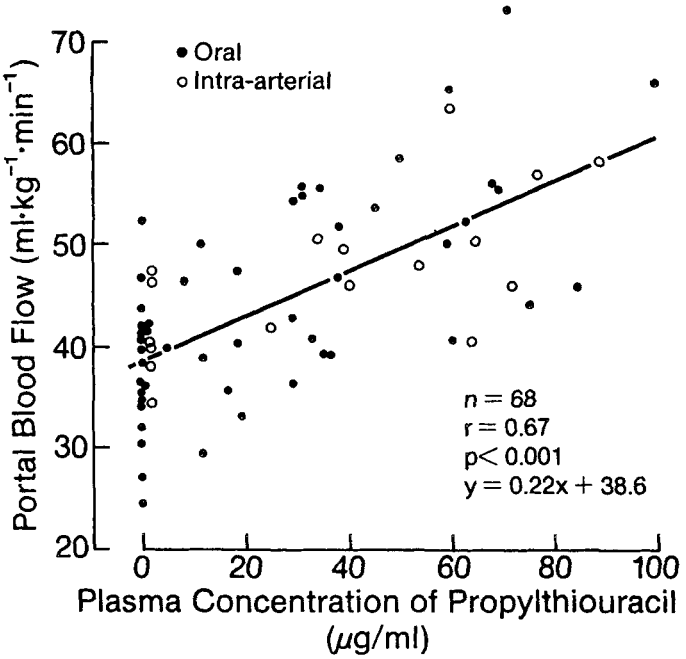

FIG. 2. Correlation between plasma concentration of PTU and portal blood flow. PTU was administered either orally at doses ranging from 6.25 to 100.0 mg per kg in water, or intraarterially in the two doses, 25 or 50 mg per kg, in 1 ml per 100 gm saline over 30 min. Controls either received water by gavage or were infused with an equal volume of saline.

TABLE 1. Effect of oral PTU on cardiac output and splanchnic blood flow

PTU[a] (mg/kg)	n[b]	Cardiac output ($ml \cdot kg^{-1} \cdot min^{-1}$)	Blood flow ($ml \cdot kg^{-1} \cdot min^{-1}$)					Plasma PTU concentration (μg/ml)
			Total liver	Spleen	Stomach	Small intestine	Large intestine	
0	19	219 ± 10	45.1 ± 1.7	3.2 ± 0.3	2.9 ± 0.2	21.5 ± 1.2	10.2 ± 0.4	0
6.25	5	242 ± 20	46.5 ± 3.1	3.9 ± 0.6	3.1 ± 0.6	22.0 ± 1.4	10.9 ± 0.9	7.8 ± 1.4
12.5	6	239 ± 15	51.2 ± 4.1	3.1 ± 0.5	3.0 ± 0.5	23.6 ± 1.4	11.5 ± 0.9	18.3 ± 0.5
25	8	241 ± 14	54.0 ± 3.2[c]	3.3 ± 0.3	3.7 ± 0.3	27.3 ± 2.4[c]	12.6 ± 0.9[c]	32.5 ± 0.9
50	6	246 ± 12	58.2 ± 2.2[d]	3.2 ± 0.3	3.3 ± 0.3	31.3 ± 1.6[d]	13.1 ± 0.7[d]	43.2 ± 4.4
100	11	252 ± 15	62.0 ± 3.8[d]	3.6 ± 0.6	3.2 ± 0.3	30.9 ± 2.2[d]	15.1 ± 0.8[d]	81.1 ± 7.2

[a] Propylthiouracil was given orally by gavage.
[b] n = number of rats.
[c] $p < 0.05$ compared to control (dose = 0).
[d] $p < 0.01$ compared to control (dose = 0).

TABLE 2. Effect of intraarterial PTU on cardiac output and splanchnic blood flow

PTU[a] (mg/kg)	n[b]	Cardiac output (ml·kg^{-1}·min^{-1})	Blood flow (ml·kg^{-1}·min^{-1})						PPVR[c]	Plasma PTU concentration (μg/ml)
			Hepatic artery	Portal vein	Spleen	Stomach	Small intestine	Large intestine		
0	6	210 ± 10	8.5 ± 1.6	41.0 ± 2.1	3.1 ± 0.7	3.3 ± 0.3	24.2 ± 1.6	10.4 ± 0.6	2.29 ± 0.20	0
25	4	217 ± 7	7.4 ± 1.7	47.0 ± 1.9	3.0 ± 0.6	3.2 ± 0.4	28.0 ± 0.7	12.8 ± 0.5	1.88 ± 0.08	34.6 ± 3.5
50	7	250 ± 15	8.4 ± 1.3	52.1 ± 3.0[d]	3.8 ± 0.6	4.2 ± 0.5	30.9 ± 1.4[d]	13.2 ± 1.1[e]	1.81 ± 0.08[e]	68.7 ± 4.5

[a] Propylthiouracil was infused intraarterially over 30 min.
[b] n = number of rats.
[c] PPVR = preportal vascular resistance.
[d] $p < 0.01$ compared to control (dose = 0).
[e] $p < 0.05$ compared to control (dose = 0).

TABLE 3. Duration of oral PTU effect on splanchnic blood flow

Time after PTU[a] (hr)	n[b]	Blood flow (ml·kg^{-1}·min^{-1})			PPVR[c]	Plasma PTU concentration (μg/ml)
		Portal vein	Hepatic artery	Total liver		
Controls	41	41.5 ± 1.1	7.8 ± 0.5	49.4 ± 1.0	2.22 ± 0.07	0
0.25	8	44.8 ± 2.4	7.3 ± 0.8	52.2 ± 2.9	1.98 ± 0.07	35.2 ± 3.0
0.5	9	51.8 ± 4.2[d]	5.0 ± 0.9[e]	56.8 ± 3.9[e]	1.68 ± 0.12[d]	40.9 ± 5.0
1	6	50.7 ± 2.2[e]	7.6 ± 0.4	58.2 ± 2.2[e]	1.75 ± 0.09[d]	43.2 ± 4.4
3	8	52.7 ± 3.8[d]	4.2 ± 0.8[d]	56.9 ± 3.9[e]	1.74 ± 0.12[d]	43.9 ± 3.4
6	8	49.6 ± 2.5[e]	4.1 ± 0.9[d]	53.7 ± 2.4	1.81 ± 0.09[d]	37.4 ± 2.7
24	5	38.1 ± 2.8	8.5 ± 0.8	46.6 ± 2.6	2.31 ± 0.12	9.0 ± 1.1

[a] Propylthiouracil (50 mg/kg) was given orally by gavage.
[b] n = number of rats.
[c] PPVR = preportal vascular resistance.
[d] $p < 0.01$ compared to controls.
[e] $p < 0.05$ compared to controls.

Time Course of Portal Blood Flow Response to PTU. Following an oral dose of PTU (50 mg per kg), there was a significant increase in total liver blood flow ($p < 0.05$) at 0.5, 1.0 and 3 hr. At 6 hr, although portal blood flow was still significantly increased, total liver blood flow had returned to normal levels primarily due to a decrease in hepatic artery blood flow (Table 3). Preportal vascular resistance was reduced in parallel with the changes in portal blood flow. Twenty-four hours after oral PTU, the plasma concentrations of the drug were 9.0 ± 1.1 μg per ml, and blood flows had returned to control values (Table 3).

Effect of 5 Days of PTU Treatment on the Acute Response to PTU and to Ethanol. The administration of PTU (50 mg per kg) daily for 5 days resulted in a 53% increase in thyroid weight (controls = 21.7 ± 1.6 mg; 5-day PTU = 33.2 ± 3.0 mg; $p < 0.01$) and in an 85% reduction of ^{125}I uptake (controls = 5.4 ± 0.5%; 5-day PTU = 0.8 ± 0.2%; $p < 0.001$). PTU reduced the serum thyroxine levels by 74% (controls = 71.2 ± 2.9; 5-day PTU = 18.2 ± 3.2 n*M* per liter; $p < 0.001$). This degree of hypothyroidism did not alter the response to an acute dose of PTU (50 mg per kg), which resulted in a 43% increase in portal blood flow blood flow (controls = 34.8 ± 3.3; 5-day PTU, plus water = 35.3 ± 2.5; 5-day PTU, plus an acute dose of PTU = 50.0 ± 2.9 ml·kg^{-1}·min^{-1}; $p < 0.01$).

The response to oral ethanol (2 gm per kg) was unchanged following 5 days of PTU treatment. An increase in portal blood flow of 61% was observed following ethanol (controls = 34.8 ± 3.3; 5-day PTU, plus ethanol, 2 gm per kg, = 56.2 ± 3.5 ml·kg^{-1}·min^{-1}, $p < 0.01$; acute ethanol, 2 gm per kg, without PTU = 58.4 ± 4.5 ml·kg^{-1}·min^{-1}; $p < 0.01$).

Effect of Methimazole on Liver Blood Flow. The administration of methimazole at 10 and 20 mg per kg, doses equivalent in antithyroid effect to PTU at 50 to 100 mg per kg (12), had no effect on liver blood flow (control = 42.5 ± 3.4; methimazole (10 mg per kg) = 40.7 ± 2.0; methimazole (20 mg per kg) = 43.5 ± 4.2 ml·kg^{-1}·min^{-1}; Table 4).

DISCUSSION

The most important finding in the present study is that the acute administration of PTU increases portal blood flow in awake and unrestrained rats from 41.0 ± 2.1 ml·kg^{-1}·min^{-1} to 52.1 ± 3.0 ml·kg^{-1}·min^{-1}. This previously unreported effect of PTU was found to be independent of its thyroid actions, was demonstrated to be dose dependent and was observed following both oral and intraarterial administration of the drug. The increase in portal blood flow induced by PTU was not accompanied by changes in portal pressure.

Methimazole, a drug that, like PTU, suppresses thyroxine synthesis (14), had no effect on portal blood flow at doses which have equivalent antithyroid potencies.

Our data, at this time, do not allow us to speculate on the mechanism of the increase in blood flow caused by PTU. The response to PTU does not appear to be mediated by a direct local effect in the intestine while being

TABLE 4. Effect of oral methimazole on cardiac output and splanchnic blood flow

Methimazole[a] (mg/kg)	n[b]	Cardiac output (ml·kg^{-1}·min^{-1})	Blood flow (ml·kg^{-1}·min^{-1})						
			Hepatic artery	Portal vein	Spleen	Stomach	Small intestine	Large intestine	PPVR[c]
0	8	256 ± 19	6.4 ± 0.9	42.5 ± 3.4	2.1 ± 0.3	3.8 ± 0.4	24.3 ± 2.0	12.4 ± 1.0	2.27 ± 0.18
10	6	223 ± 8	6.8 ± 1.0	40.7 ± 2.0	2.8 ± 0.2	3.4 ± 0.4	22.8 ± 0.9	11.8 ± 1.0	2.35 ± 0.14
20	7	218 ± 10	8.7 ± 0.7	43.5 ± 4.2	2.6 ± 0.2	3.6 ± 0.7	25.6 ± 3.0	11.7 ± 0.6	2.04 ± 0.17

[a] Methimazole was given orally by gavage.
[b] n = number of rats.
[c] PPVR = preportal vascular resistance.

absorbed, since a similar response of portal blood flow was obtained when PTU was administered intraarterially. The effect of PTU on portal blood flow was observed 30 min after administration and lasted for at least 3 hr. At 6 hr, although the increase in portal blood flow was still present, total liver blood flow had returned to normal.

There is a finding in this study that might be of relevance for patients receiving PTU in the treatment of alcoholic liver disease. The induction of mild hypothyroidism by giving a high dose of PTU for 5 days did not modify the increase in portal blood flow that follows acute PTU or ethanol administration.

Although the main purpose of this study was to determine the effects of PTU on liver hemodynamics in the normal rat, we think that some speculation as to the possible clinical relevance of the findings is in order. According to the hypoxic theory, liver necrosis occurs when the ethanol-induced increase in liver oxygen consumption is not met by an adequate oxygen delivery to the liver (5). Therefore, theoretically, alcohol-induced liver necrosis could be prevented by: (a) inhibiting the increase in oxygen consumption, (b) increasing oxygen delivery or (c) a combination of these two mechanisms.

An interesting feature of the increase in liver oxygen consumption, induced by both acute and chronic administration of ethanol, is the fact that thyroid hormone function appears to be *permissive* for such an effect to occur. Thyroidectomy or the administration of PTU markedly suppresses or abolishes both acute and chronically induced hypermetabolic states (1, 6, 15). This observation led to the idea that PTU should also prevent alcohol-induced liver damage. Indeed, this was the case in experiments in which PTU protected rats against this type of liver damage (1, 2). Furthermore, recently PTU has been shown to reduce mortality in patients with alcoholic liver disease (4). The importance of the suppression of the hypermetabolic state in the mechanism of the protective effect of PTU is emphasized by the fact that methimazole, a drug that has the antithyroid action of PTU but that, as shown in the present study, does not affect portal blood flow, has a similar protective effect against alcohol-induced liver damage (2).

In this study, we show that, in addition to the main effect of PTU described above, PTU also increases portal blood flow and therefore probably oxygen delivery to the liver. This action of PTU could potentiate the effectiveness of the drug in normalizing the oxygen supply/demand balance in the liver and thus could also play a contributory role in preventing alcohol-induced liver damage in certain circumstances. This possibility is supported by the demonstration that an increase in portal blood flow can completely compensate for the increase in liver oxygen consumption that accompanies ethanol intake (16–18).

One situation in which an increase in portal blood flow might be of special importance is the period following alcohol withdrawal. During alcohol withdrawal the increase in oxygen demand by the liver persists for several days or weeks (19–22). In this situation, alcohol is not present to be metabolized and, therefore, the increase in the liver oxygen demand is not met by a simultaneous increase in liver blood flow (19, 20). These observations agree with our previous findings that the increase in portal blood flow observed following alcohol intake is adenosine mediated and that it lasts only as long as alcohol is being metabolized into acetate (7, 11, 23, 24). Furthermore, under these conditions of withdrawal, which can occur on a daily basis in many alcoholics, hepatic blood flow has also been found to be reduced (20, 21). This critical situation of liver hypoxia that exists during withdrawal could be the explanation of the observation that this period is sometimes accompanied by a clinical deterioration of liver disease (25–28).

It should be emphasized that the importance of the PTU-induced increase in portal blood flow in the prevention of alcohol-induced liver damage will only be elucidated when methodologies exist which allow for the determination of the oxygen supply/demand state of the liver in the absence of possible distorting factors such as anesthesia, catheterization and surgical interventions (9, 10).

In summary, we now report that PTU increases portal blood flow in awake and unrestrained rats through an effect that is independent of its thyroid actions. A drug such as PTU, acting both by decreasing liver oxygen demand and potentially increasing oxygen delivery through an increase in portal blood flow, might be especially useful in preventing alcohol-induced liver damage.

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