Chronic administration of propylthiouracil ameliorates hyperdynamic circulation in portal hypertensive rats

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ABSTRACT
OBJECTIVE: To evaluate the effect of a hypothyroid state, induced by chronic propylthiouracil administration, on splanchnic and systemic hemodynamic parameters in rats with portal hypertension due to portal vein ligation.

METHODS: Portal hypertension was induced by surgical stenosis of the portal vein. Cardiac index and portal blood flow were measured using radioactive microspheres. Measurements were performed after treatment with propylthiouracil (1 mg/ml in drinking water) for 5 days.

RESULTS: Propylthiouracil-treated portal hypertensive rats had a lower portal pressure (12.4 ± 1.9 versus 16.3 ± 0.7 mmHg; p < 0.05) and portal blood flow (11.6 ± 0.7 versus 13.2 ± 1.3 ml/min/100 g; p < 0.05) than non-treated animals. Splanchnic vasoconstriction in treated animals was associated with a higher peripheral vascular resistance (2.3 ± 0.4 versus 1.8 ± 0.3 mmHg/ml/min/100 g; p < 0.05) than controls.

CONCLUSION: These results suggest that portal pressure can be lowered by inducing a hypothyroid state by chronic administration of propylthiouracil.

INTRODUCTION
Portal hypertension in humans and experimental models has been associated with a hyperdynamic state characterized by increased splanchnic blood flow and reduced systemic and splanchnic vascular resistance. The mechanisms underlying these circulatory changes are not well known, but humoral and endothelial-related factors, such as nitric oxide, have been implicated.

Experimental and clinical evidence has shown similar systemic hemodynamic patterns in chronic liver disease and hyperthyroidism. In addition, it has been demonstrated that propranolol is useful at reducing portal pressure in patients with chronic liver disease as well as in the treatment of the cardiovascular manifestations of thyrotoxicosis. The fact that these two clinically different entities share common hemodynamic features and respond to the same treatment has prompted us to hypothesize that a treatment specific for one of them could be useful for ameliorating the hemodynamic abnormalities associated with the other. Based on this, we sought to evaluate the effect of an antithyroid drug on portal hypertension.

In the present study, the effects of chronic administration of propylthiouracil (PTU), an antithyroid drug, on systemic and splanchnic hemodynamic parameters were evaluated in a rat model of portal hypertension.
METHODS

Adult male Sprague-Dawley rats were used. The animals were housed in individual cages and allowed free access to rat chow and water until the time of the study. Treatment of the animals during the experiments was approved by the local committee for animal experimentation.

Induction of portal hypertension

Portal hypertension was induced by partial portal vein ligation. For this purpose, a midline abdominal incision was made under ether anesthesia and the portal vein was exposed and freed from surrounding tissue. A ligature (silk gut 3-0) was made around a 20-gauge blunt-tipped needle lying alongside the portal vein. Subsequent removal of the needle yielded a calibrated stenosis of the portal vein.

Experimental design

Portal hypertensive rats were randomly allocated into 2 groups: group 1 comprised 8 rats that received PTU in drinking water (1 mg/ml) for 5 days, starting at 2 weeks after surgery. Group 2 was composed of 8 animals that received water.

Surgical procedures

The techniques used for hemodynamic measurements have been previously described9,10. Briefly, the animals were anesthetized with ketamine (150 mg/kg, i.m.). The left femoral and right carotid arteries were exposed and cannulated with PE-50 catheters (Portex Ltd., Kent, UK). The right carotid catheter was advanced into the left ventricle during continuous pressure monitoring. Arterial pressure was measured via the femoral artery, while the femoral vein provided a route for drug administration. Portal pressure was measured by inserting a 16 G ‘butterfly’ needle into the portal vein. All pressure measurements were made with pressure transducers at the level of the right atrium. The arterial and venous pressure transducers were calibrated daily.

Microspheres technique

Cardiac index and regional blood flows were measured using 60,000 microspheres (15 μm diameter, New England Nuclear, MA, USA) labelled with 85Sr, injected into the left ventricle9,10 while a reference sample was withdrawn for 75 sec at a rate of 1 ml/min from the femoral artery with a preweighed syringe. Upon completion of the study, the animals were killed, under ketamine anesthesia, by an intravenous injection of saturated potassium chloride. The organs were dissected, cleaned, weighed and counted in a gamma-counter (Tecnuar, Argentina). The kidneys and thyroid gland was dissected and weighed.

Calculations

Cardiac output and arterial blood flows to each organ were calculated as previously described9,10. Portal venous inflow was calculated as the sum of blood supply to stomach, spleen, small and large intestines, pancreas and mesentery. Values of vascular resistance (VR) in different vascular territories were calculated as:

VR = P (mmHg)/Q (ml/min)

where P was the pressure gradient between inflow and outflow in the territory, and Q was the blood flow through it. For peripheral vascular resistance, P was the difference between mean arterial pressure and right arterial pressure (assumed to be 0) and Q was cardiac output. Splanchnic arterial resistance was calculated as mean arterial pressure minus portal pressure, divided by portal venous inflow.

Statistical analysis

Results are expressed as Mean ± SEM. Statistical comparisons were performed using paired and unpaired Student’s t test and Mann-Whitney test. Results were considered significant at p < 0.05.

RESULTS

Baseline data

Control partially portal-vein ligated animals exhibited a hyperdynamic state characterized by a higher cardiac index, a lower mean arterial pressure and systemic vascular resistance, and a higher portal venous inflow than sham-operated rats (table I). Values in normal rats in our laboratory are 34 ± 3 ml/min/100 g for cardiac index, 117 ± 6 mmHg for mean arterial pressure and 6.8 ± 0.4 mmHg/min/100 g for portal venous inflow9,10. Hypothyroidism was manifested by a significant increase in the thyroid gland weight in portal hypertensive rats (55 ± 13 versus vehicle 10 ± 4 mg; p < 0.01).

Effect of PTU on systemic and splanchnic hemodynamics

Cardiac index in PTU-treated rats was significantly lower than in the vehicle group. Accordingly, systemic vascular resistance was significantly higher in the PTU-treated group (table I). PTU administration caused a significant fall in portal pressure (table I), which decreased by 23% (from 16.3 ± 0.7 to 12.4 ± 1.9 mmHg; p < 0.05). This reduction in portal pressure was evident in all portal hypertensive rats and was associated with a reduction in portal venous inflow (from 13.2 ± 1.3 to 11.6 ± 0.7 ml/min/100g; p < 0.05). This effect was mainly due to a significantly higher splanchnic vascular resistance.

DISCUSSION

During the last years, several studies have shown that PTU protects chronically ethanol-treated rats from hypoxia-induced centrilobular necrosis12,13. Moreover, Oren et al14 have recently demonstrated that PTU also prevents experimentally induced cirrhosis in the rat. Collectively, these findings suggest that the development of a hypothyroid state plays a role in the prevention of hepatic damage in experimental models. The mechanism by which PTU has this beneficial effect is unknown. A possible explana-

TABLE I. Effect of placebo or propylthiouracil (PTU) on systemic and splanchnic hemodynamics in portal hypertensive rats

<table>
<thead>
<tr>
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<th>Placebo (n = 8)</th>
<th>PTU (n = 8)</th>
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<tbody>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>98 ± 4</td>
<td>104 ± 4</td>
</tr>
<tr>
<td>Cardiac Index (ml/min/100 g)</td>
<td>52.8 ± 3.6</td>
<td>4.6 ± 4.3*</td>
</tr>
<tr>
<td>Systemic vascular resistance (mmHg/ml/min/100 g)</td>
<td>1.8 ± 0.3</td>
<td>2.3 ± 0.4*</td>
</tr>
<tr>
<td>Portal pressure (mmHg)</td>
<td>16.3 ± 0.7</td>
<td>12.4 ± 1.9*</td>
</tr>
<tr>
<td>Portal venous inflow (ml/min/100 g)</td>
<td>13.2 ± 1.3</td>
<td>11.6 ± 0.7*</td>
</tr>
<tr>
<td>Splanchnic vascular resistance (mmHg/ml/min/100 g)</td>
<td>6.2 ± 0.6</td>
<td>7.9 ± 0.7*</td>
</tr>
</tbody>
</table>

Data expressed as mean ± SEM. Significant difference from placebo is shown as *p < 0.05.
ton to account for both effects is that PTU decreases the hypermetabolic state associated with both situations due to a metabolic and/or hemodynamic effect. In this regard, experimental and clinical evidence has shown that acute PTU administration causes a vasoconstrictor effect, manifested in the splanchnic circulation by a significant increase in portal blood flow in awake unrestrained normal rats and in patients with alcoholic cirrhosis\textsuperscript{15,16}. On the other hand, it is known that two different clinical situations, namely portal hypertension and hyperthyroidism, share many hemodynamic similarities. In fact, a high cardiac output and a low peripheral vascular resistance have been observed in both situations\textsuperscript{1,5}. This led to regard both states as hyperdynamic. It is possible that an increase in catecholamine levels play a role in the pathogenesis of portal hypertension and hyperthyroidism\textsuperscript{1,17}. This fact may explain, at least in part, why administration of propranolol is useful at reducing portal pressure in patients with chronic liver disease as well as in the treatment of the cardiovascular manifestations of thyrotoxicosis\textsuperscript{1,6,8}. The present study evaluated the chronic systemic and splanchnic effects of PTU in rats with portal hypertension due to portal vein ligation. Our results show that inducing a hypothyroid state by chronic PTU administration causes a significant reduction (23\%) in portal pressure in portal vein ligated rats. A significant decrease in portal blood flow was also observed in portal hypertensive rats, suggesting that the mechanism of the PTU-induced decrease in portal pressure is related to a reduction in portal venous inflow. These splanchnic hemodynamic changes may result from systemic vasoconstriction, evidenced by a significant decrease in cardiac output and an increase in peripheral vascular resistance. This is supported, at least in part, by the direct relationship between cardiac output and portal blood flow observed in the present study (R = 0.61; p < 0.05). These results are similar to those by Oren et al\textsuperscript{18} who showed that hypothyroidism induced by methimazole caused an amelioration of systemic and splanchnic hyperdynamic circulation in portal hypertensive rats.

We have observed a discrepancy between the acute and chronic effects of PTU on portal blood flow, acting as a vasodilatory drug in the former case\textsuperscript{15,16} and as a vasoconstrictor in the latter\textsuperscript{8}. Previous studies suggest that vasodilation resulting from acute PTU treatment is independent of the thyroid gland, which is supported by the fact that methimazole, a drug with an antithyroid effect, does not alter portal blood flow in normal rats when administered in acute form\textsuperscript{15,16}. In contrast, chronic administration of both PTU and methimazole, having similar antithyroid effects, results in systemic and splanchnic vasoconstriction in portal hypertensive rats.

Development of a hypothyroid state as result of PTU or methimazole treatment is clearly not the most appropriate approach to the management of portal hypertension. Further studies must be addressed to evaluate whether the action of PTU on the hemodynamic alterations associated with portal hypertension is mediated or not by its antithyroid effect.

REFERENCES