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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.

LA ADMINISTRACIÓN CRÓNICA DE PROPILTIOURACILO REDUCE LA CIRCULACIÓN HIPERDINÁMICA EN RATAS CON HIPERTENSIÓN PORTAL

OBJETIVO: evaluar el efecto del estado hipotiroideo inducido por la administración crónica de propiltiouracilo sobre los parámetros hemodinámicos esplácnicos y sistémicos en ratas con hipertensión portal secundaria a la ligadura de la vena porta.

MÉTODOS: la hipertensión portal fue inducida mediante la ligadura quirúrgica de la vena porta. El índice cardíaco y el flujo sanguíneo portal se determinaron mediante microesferas radioactivas. Las determinaciones se llevaron a cabo tras el tratamiento con propiltiouracilo (1 mg/ml) en el agua durante 5 días.

RESULTADOS: las ratas con hipertensión portal tratadas con propiltiouracilo mostraron una presión portal inferior (12,4 ± 1,9 frente a 16,3 ± 0,7 mmHg; p < 0,05) y un flujo sanguíneo portal superior (11,6 ± 0,7 frente a 3,2 ± 1,3 ml/min/100 g; p < 0,05) a los de los animales no tratados. La vasoconstricción esplácnica en los animales tratados se asoció a una resistencia vascular periférica (2,3 ± 0,4 frente a 1,8 ± 0,3 mmHg/ml/min/100 g; p < 0,05) mayor que la de los animales control.

CONCLUSIÓN: los resultados obtenidos indican que es posible reducir la presión portal mediante la inducción de un estado hipotiroideo a través de la administración crónica de propiltiouracilo.

INTRODUCTION

Portal hipertension 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[1]. The mechanisms underlying these circulatory changes are not well known, but humoral and endothelial-related factors, such as nitric oxide, have been implicated[2-4].

Experimental and clinical evidence has shown similar systemic hemodynamic patterns in chronic liver disease and hyperthyroidism[1,5]. 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[6-8]. 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.

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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 described[9,10]. Briefly, the animals were anesthesized 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 ^{85}Sr, injected into the left ventricle[9,10] 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 testes were used to check the proper mixing of microspheres after injection into the left ventricle, and radioactivity in lungs was assessed to exclude animals with left-to-right heart perforations. In addition, the thyroid gland was dissected and weighed.

Calculations

Cardiac output and arterial blood flows to each organ were calculated as previously described[9,10]. 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 arteriolar 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 $p < 0.05$.

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

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

Data expressed as mean ± SEM. Significant difference from placebo is shown as *$p < 0.05$.

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/100g for portal venous inflow[11]. 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 necrosis[12,13]. Moreover, Oren et al[14] 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-

tion 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 vasodilatory 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[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[1,5]. This led to regard both states as hyperdynamic. It is possible that an increase in cathecolamine levels play a role in the pathogenesis of portal hypertension and hyperthyroidism[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[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[18] who showed that hypothyroidism induced by methimazole caused an amelioration of systemic and splanchnic hyperdinamic 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[15,16] and as a vasoconstrictor in the latter[18]. 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[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.

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