

Is Hypothyroidism a Treatment Option in Conditions of Liver Injury and Hepatic Encephalopathy?

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Hyperdynamic circulation observed in portal hypertension is characterized by pronounced vasodilatation, increased systemic and regional blood flows, and augmented cardiac index. Drugs used for the treatment of portal hypertension, such as β -adrenergic blocking agents, have also proved useful in controlling the cardiovascular manifestations of thyrotoxicosis. Moreover, propylthiouracil, a commonly used drug for the treatment of hyperthyroidism, has been used for the management of patients with alcoholic liver disease with favorable response.¹ In a rat model of portal vein ligation, hypothyroidism caused amelioration of the hyperdynamic circulation followed by reduction of the portal pressure.² Therefore, alleviation of the hypermetabolic state by thyroid hormone manipulation might be a treatment option for the hyperdynamic circulation observed in the portal hypertensive state.

Besides the hemodynamic effects, data from recent studies suggest that induced hypothyroidism prevents the development of liver injury in several animal models. An important study by Oren et al³ investigated the effects of experimentally induced hypo- and hyperthyroidism on the development of cirrhosis induced in rats by thioacetamide (TAA). In that study, the authors found that hepatic fibrosis was significantly reduced in hypothyroid rats as compared with euthyroid controls, and was aggravated in TAA-treated hyperthyroid rats.³ Later studies also confirmed that hypothyroidism can minimize lectin concanavalin A-induced acute liver injury⁴ and improve survival in TAA-induced fulminant hepatic failure.⁵

The study by Chang et al⁶ is the first to investigate the effect of chronic thyroid hormone inhibition on hepatic encephalopathy in bile-duct ligated cirrhotic

rats. For more accurate quantification of the degree of hepatic encephalopathy, the authors used automated open field boxes equipped with infrared cells to detect the motor activities of rats. On the basis of consecutive interruption of the infrared monitoring beams, this apparatus could allow them to differentiate non-ambulatory (scratching, gnawing) from ambulatory movements. The additional row of infrared cells above the plane could provide them with more information concerning the movements in the vertical direction. As compared with the control group, this study demonstrated that the amount of total movements were significantly increased in rats with hypothyroidism induced by methimazole.⁶ Probably related to the small sample size, the differences in ambulatory and vertical movements between these 2 groups did not reach statistical significance.

Regarding the impact of hypothyroidism on hepatic damage followed by bile-duct ligation, Chang et al's study showed that plasma levels of ammonia, aspartate aminotransferase and alkaline phosphatase were significantly lower in the methimazole group.⁶ However, the authors did not provide the data to investigate the possible pathogenesis of thyroid hormone manipulation on hepatic damage, and this might affect the scientific value of their article. Another important issue which should be addressed here is that different doses of methimazole might have different effects, and the resulting consequences in cerebral and hepatic tissues might be uneven. All the above points deserve further investigation to justify whether or not and to what degree thyroid hormone inhibition can be used as a treatment option in acute or chronic liver injury and hepatic encephalopathy.

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To date, the mechanisms responsible for the amelioration of liver injury in rats by hypothyroidism remain incompletely understood. However, emerging studies have disclosed that hypothyroidism might protect the liver by inhibiting the generation of free-oxygen radicals, which might cause cell necrosis via oxidation of cellular proteins, DNA, and lipids.^{7,8} Malodialdehyde, derived from lipid peroxidation, was markedly increased in the serum and liver of euthyroid rats treated with TAA, but only slightly increased in hypothyroid rats following TAA administration.⁵ The above findings suggest that, probably by minimizing oxidative injury to hepatocytes, hypothyroidism plays a protective role in rats with fulminant hepatic failure induced by TAA. Similar to TAA-induced fulminant hepatic failure, in a rat model of chronic TAA ingestion,³ liver cirrhosis was completely prevented by hypothyroidism, and experimental evidence suggested that toxic oxygen species produced by lipid peroxidation lead to chronic injury and the development of fibrosis.^{9,10} In contrast, in rats with hyperthyroidism, generalized hypermetabolism and increased hepatocyte oxygen demand lead to an accelerated development of TAA-induced liver cirrhosis and portal hypertension.³ Therefore, it appears that hypometabolism and decreased hepatocyte oxygen demand, associated with hypothyroidism, may be protective for the insulted liver.⁵ This is supported by the fact that the protective role of hypothyroidism in liver injury can also be found in conditions other than toxic liver injury such as immune-mediated hepatitis⁴ or mechanically-induced liver damage such as portal vein and bile-duct ligation.^{2,3}

In addition, several lines of evidence suggest that thyroid status may have immunomodulatory effects: decreased thyroid function is associated with reduced CD41 T lymphocyte activation, increased number and activation of CD81 cells and decreased soluble interleukin (IL)-2 receptors.¹¹ In the study by Bruck et al,⁵ serum levels of tumor necrosis factor (TNF)- α , IL-2, and IL-6 were measured at 2, 6, 24, and 48 hours following TAA administration in hypothyroid and normal rats. The significantly lower serum levels of TNF- α and the other cytokines in the hypothyroid as compared with the euthyroid rats suggest that the suppression of cytokine release might have a role in the prevention of fulminant hepatic failure by hypothyroidism.

In conclusion, this is an interesting study demonstrating that hypothyroidism by chronic methimazole

administration can alleviate the degree of liver injury and hepatic encephalopathy in bile-duct ligated cirrhotic rats. However, the underlying mechanisms responsible for this phenomenon remain incompletely understood, but immunomodulation and minimization of oxidative liver injury are possible mechanisms. Further studies on the pathogenesis are needed to justify whether hypothyroidism can be used as a treatment option during conditions of liver injury and hepatic encephalopathy.

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