Influence of Thyroid Function on Experimental Liver Injuries

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Experiments were performed with female rats to observe the correlations between thyroid function and liver damages. A method was elaborated based on the test of the total dye eliminating capacity of the rat liver. There were no essential changes in the elimination of BSP in animals with healthy liver in either hyperthyrosis or hypothyrosis. Subacute carbontetrachloride intoxication produced a slight change while chronic intoxication resulted in a severe change in the liver functions at carbontetrachloride dosages which in themselves hardly had any toxic effect. This was proven both by increased blood BSP levels and by histological findings. The total dye eliminating capacity of the liver was not impaired when carbontetrachloride treatment was performed in thyroidectomized rats. Hypothyroidism was found to have protective effect on the experimental liver lesion.

Thyroid hyperfunction is often combined with hepatic injuries, the most severe clinical manifestation of these being coma Basedowicum. The histological pictures of such hepatic failures were described in detail by Weller in 1933. The differences in the laboratory findings were also analyzed by several authors. Concerning the postoperative complications of Basedow disease, Foss et al. and Szeleczy pointed out the importance of liver injury.

The relation of increased thyroxine production and impaired liver function was explained by emptied liver glycogen store, by impairment of oxidative phosphorylation, and by activity changes of mitochondrial enzyme systems. It is known furthermore that hyperthyroidism, as well as thyroxine treatment, increases the susceptibility to different hepatotoxic agents. According to Zbinden, hyperthyroidism may be considered to increase in general the toxicity of various drugs.

In some of our previous investigations performed on thyroidectomized rats we have found that the experimental liver was not damaged. This was proven by survival data, histological findings and also by maintained hormone inactivating capacity of the liver.

On the basis of these findings it seemed to be of interest to examine the effect of changes in thyroid function on the healthy and intoxicated liver, and whether depres-
sion or hypersecretion of the hormones influences the hepatic failure.

To assess the hepatic functions we have devised a method based on the theory of Lang, for determining the 'total dye eliminating capacity' of the liver. This method is apt to differentiate the storing and excreting abilities, both independent processes, of the liver.

**MATERIALS AND METHODS**

*Method for examining hepatic functions in animals*

According to Eberhard and Grafe, the absorption and the excretion of the bromsulphophthalein (BSP) are separate processes. These may well be differentiated by the method of Lang. The decreased blood concentration of BSP refers to the storing capacity of the liver. A subsequent intravenous injection of the sodium salt of dehydrocholic acid (DHCNa) causes the backflow of the BSP (bound to the hepatic cells) to the blood. In such a way the dye-excreting capacity of the liver may be determined. There is a certain competition between BSP and DHCNa, and DHCNa has a greater affinity for cytoplasmic proteins. We adopted this principle in the following way.

Rats received intraperitoneally 100 mg/kg BSP in a 0.45% sodium salt solution. Thirty minutes later, 100 mg/kg DHCNa were injected intravenously. Exactly two minutes later the animals were bled. The BSP concentration of the serum was measured according to Varga et al. and expressed in mg/100 ml of serum.

The BSP level determined by our method, taking the time of blood sampling into consideration, would represent both the storing and excreting functions of the liver.

*Experimental procedures*

Our experiments were performed on 55 female rats. The BSP concentration of the sera of thyroxine-treated and of thyroidectomized rats were compared with normal controls. We examined the effect of chronic and subacute carbontetrachloride (CCl₄) intoxication. Changes following thyroidectomy in chronic liver lesion and the consequences of thyroxine

![Body weight (g)](image)

Fig. 1. The body weights of the animals 10 days before treatment, 1 day before treatment, 10th (the last day) of the thyroxine treatment. Each column represents the mean value with the standard deviation of the values obtained from 12 rats.
Fig. 2. The body temperatures of the animals treated with thyroxine for 10 days at a dose of 100 µg/kg/day (subcutaneous injection). The arrow indicates the first day of the treatment. --- treated animals; ----- untreated animals. The values were obtained from 12 animals of each group.

Results

BSP elimination in animals with healthy liver showed no essential changes either under the influence of thyroxine treatment or following thyroidectomy. The subacute CCl₄ intoxication increased the BSP level of the blood but only to a small extent. Chronic liver injury increased the concentration of BSP in the serum. Rats receiving both thyroxine and CCl₄ showed significantly increased BSP values as compared with those treated with the same dose of CCl₄ alone (p<0.01).

Changes produced by the CCl₄ treatment following thyroidectomy were not substantial when the values were compared with those of thyroidectomized animals. These results are summarised in Fig. 3.
The investigation of the hepatic functions led us to conclude that thyroxine treatment enhance the damaging effect of subacute CCl₄ intoxication on the liver. To confirm this we examined histological sections from the livers of five rats each of the two groups. Subacute CCl₄ treatment produced a slight histological damage. There were centrilobular hepatic cells showing variable degrees of degeneration, some necrotic and balloon cells. There was no increase of the connective tissue. The administration of thyroxine and CCl₄ produced severe changes in the livers of all the animals thus treated. The picture of a fresh CCl₄ lesion was visible in the sections, with the characteristic degeneration of different grades and infiltration of leucocytes and macrophages.

**DISCUSSION**

Our experiments indicated that functional changes of the thyroid did not influence the total dye eliminatory capacity of the healthy liver. Hyperthyrosis following thyroxine treatment was proven by the rise of body temperature and decrease in body weight of the rats. In spite of this, no signs of direct liver intoxication could be observed for the BSP levels. Pathological values were obtained only when thyroxine treatment was combined with liver injuries, for instance, by the
administration of a dose of CCl₄ which, by itself, did not seem to impair the liver functions so far as judged by the BSP elimination, although it appeared to bring about a slight injury which could be noticed in the histological sections.

Thyroxine treatment, as well as hyperthyrosis, increased the hepatotoxicity of CCl₄. It is of interest that thyroxine potentiates the hepatotoxicity of CCl₄ and that the combined treatment with thyroxine and CCl₄ exerts an even more severe effect than chronic CCl₄ treatment alone. This was revealed by the increased BSP values and by the histological findings showing the characteristics of a fresh CCl₄ damage.

Hypothyrosis brought about the increased body weight, low body temperature and changes in the quality of the animals’ hair. In hypothyrosis the BSP levels were not essentially changed even when thyroidectomized rats were further treated with CCl₄. We may conclude that the protecting effect of hypothyrosis on liver function against CCl₄—which was observed by us previously in other parameters as well—could be proven with this special and sensitive liver function test, too.

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