CHANGES IN NITROGEN METABOLISM IN THE LIVER DEPENDING ON SEVERITY OF THYROTOXICOSIS IN RABBITS

S. G. Gasanov and A. S. Arslanov

UDC 616.441-008.61-092.9-07:616.36-008.939.6-074

At the height of development of the disease (14th-18th day) in rabbits with experimental thyrotoxicosis proteolysis in the liver is intensified (the nonprotein nitrogen/protein nitrogen ratio is increased), and the content of nitrogen-containing products of protein breakdown rises. The urea-forming function of the liver is undisturbed and the content of urea in the organ is increased.

Later (28th-35th day) the coefficient of proteolysis in the liver rises. The content of nitrogen-containing products of protein breakdown and of urea in the organ increases still further, and the urea-forming function of the liver is depressed.

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Liver damage in thyrotoxicosis is associated with the entry of an excess of thyroid hormones into the liver, where carbohydrate oxidation is stimulated, the glycogen content is reduced, and protein breakdown is intensified. According to V. N. Galakhova [4], thyroxin not only stimulates carbohydrate oxidation but also inhibits glycogen synthesis in the liver.

As a result of exhaustion of the glycogen reserves and the increased oxygen utilization of the liver cells, the sensitivity of the liver to various hepatotropic poisons is increased. As the disease develops further, fatty infiltration occurs, followed by severe degeneration, leading to disturbances of liver function [1, 10].

A number of workers [6, 8] consider that the decreases in liver glycogen is one of the factors contributing to the disturbances of function and stimulation of protein breakdown in the liver. Some investigators have noted a disturbance of the proteinogenic function of the liver (where albumin is mainly synthesized) during this period, resulting in changes in the serum albumin-globulin ratio [7, 9]. Although these disturbances of protein metabolism in thyrotoxicosis have been more fully studied and are firmly established, some of the intermediate processes of protein metabolism (deamination of amino acids and urea synthesis) have received little study. The results obtained are conflicting, because the state of the nitrogen metabolism in the liver has been judged from the blood nitrogen indices without making allowance for the degree of liver damage and the severity of the disease.

In the present investigation some indices of nitrogen metabolism in the liver have been compared with the severity of the course of thyrotoxicosis.

EXPERIMENTAL METHOD

Experimental thyrotoxicosis was produced in male rabbits weighing 2.5-3.5 kg by oral administration of the tablets containing dry thyroid in increasing doses (from 0.4 to 1.2 g thyroid daily). Group 1 included the animals after 14-18 days, when their body weight had fallen by 15-25% below its initial level. This state was conventionally described as moderately severe thyrotoxicosis. Group 2 included rabbits after 28-35 days, when their body weight had fallen by more than 25%. This state was described as a severe form of thyrotoxicosis.

Department of Pathophysiology, Institute of Experimental Endocrinology and Hormone Chemistry, Academy of Medical Sciences of the USSR, Moscow (Presented by Active Member of the Academy of Medical Sciences of the USSR N. A. Fedorov). Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 65, No. 3, pp. 63-65, March, 1968. Original article submitted March 25, 1966.

TABLE 1. Changes in Body Weight and in Some Indices of Nitrogen Metabolism in the Liver of Rabbits Depending on Severity of Thyrotoxicosis (M±m)

Experimental conditions	No. of rabbits	Wt. of rabbits (in kg)		Coefficient of proteolysis (in %)	Nonprotein nitrogen (in g%)	Principal components of nonprotein nitrogen		
		initial	final			urea nitrogen (in mg%)	amino-acid nitrogen (in mg %)	residual nitrogen (in g%)
Control group	11	2,9	3,1	11,5±0,7	0,24±0,015	45,9±4,4	62,3±4,1	0,19±0,015
Thyrotoxicosis (14th-18th day)	11	3,2	2,6	15,4±0,6 $P>0,01$	0,36±0,02 $P>0,001$	65,2±5,0 $P>0,02$	72,5±4,7 $P<0,1$	0,29±0,02 $P>0,01$
Thyrotoxicosis (28th-35th day)	8	3,0	2,1	15,9±0,5 $P>0,001$	0,39±0,02 $P>0,001$	46,7±4,8 —	86,9±6,6 $P<0,01$	0,34±0,02 $P>0,001$

To assess the state of metabolism in the liver of the experimental rabbits the following indices were used: the coefficient of proteolysis calculated from the ratio nonprotein nitrogen/protein nitrogen in the liver, the coefficient of urea synthesis calculated from the ratio between urea nitrogen and nonprotein nitrogen in the liver. The total and nonprotein nitrogen were determined by the Kjeldahl method, urea nitrogen by the phenol-hypochlorite reaction [5], and changes in the total amino acid content in liver tissue by the method of Pope and Stevens [14].

EXPERIMENTAL RESULTS

As Table 1 shows, during development of thyrotoxicosis in rabbits marked changes take place in their metabolic processes, accompanied by a decrease in weight of the experimental animals and disturbance of nitrogen metabolism in the liver. During the development of thyrotoxicosis in the experimental rabbits the nonprotein nitrogen content increased and the coefficient of proteolysis in the liver rose from 11.5 to 15.9%, indicating stimulation of catabolic processes in the liver.

In the animals of group 2, with severe thyrotoxicosis, inhibition of urea formation in the liver and a more marked accumulation of amino acids and other nitrogen-containing products of protein breakdown in the liver tissue were observed.

The results of these experiments shed some light on the contradictions regarding individual components of nitrogen metabolism in thyrotoxicosis. They show, for instance, that the increased elimination of nitrogen with the urine is due mainly to increased excretion of urea at the beginning and at the height of thyrotoxicosis and to a relative decrease in its excretion when the nitrogen balance is negative and during the subsequent development of the disease, when liver function, especially urea synthesis, is restricted [2, 3, 12].

It may thus be concluded from the results described above that the urea-forming function of the liver depends on the degree of liver damage by thyroid hormones. In severe cases of thyrotoxicosis, in the "thyrotoxic liver," activity of the enzyme systems responsible for urea synthesis is evidently disturbed.

So far as changes in the content of amino-acid nitrogen are concerned, they completely reflect changes in the blood level of amino-acid nitrogen described in a previous paper. These results also agree with clinical observations indicating that the blood amino-acid concentration is dependent on the severity of thyrotoxicosis [11].

Attention is drawn to the fact that the process of deamination of aminoacids in the liver evidently lags behind the intensified protein breakdown, causing an increase in the content of amino-acid nitrogen in the liver tissue. Furthermore, a definite relationship exists between the increase in amino nitrogen in the liver and the severity of thyrotoxicosis in rabbits, determined by the more severe liver damage by thyroid hormones. As many workers have pointed out [2, 3], the deamination of amino acids is inhibited in this period. This is presumably connected with inhibition of oxidative deamination of amino acids because of the disturbance of the circulation in the liver. Failure of the blood flow to keep pace with the oxygen demand in the liver in

thyrotoxicosis begins to manifest itself significantly, depending on the degree of liver damage by thyroid hormones [13].

The decrease in the blood urea and in its elimination in the urine, associated with increased elimination of nitrogen of amino acids and other nitrogen-containing products are bad prognostic signs indicating severe liver damage in thyrotoxicosis.

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