# INDICES OF CARBOHYDRATE METABOLISM IN THE MYOCARDIUM IN EXPERIMENTAL THYROTOXICOSIS

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Experimental thyrotoxicosis is accompanied by an increase in the concentrations of pyruvate and lactate in the arterial blood and an increase in their utilization by the heart.

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If thyroid hormones are present in the body in excess, they considerably reduce the energy-producing efficiency of tissue respiration. One of the more important ways in which these disturbances can be compensated is by a more rapid convertion of the products of intermediate metabolism, along pathways associated with the liberation of biologically usable energy [16]. This naturally leads to increased utilization of oxygen by the tissues [1].

Giving regard to differences in the energy-producing efficiency of oxidation of different substrates, it was decided to investigate the character of the substrates oxidized in thyrotoxicosis. Results of an investigation of the carbohydrate metabolism of the myocardium in experimental thyrotoxicosis are described in this paper.

## EXPERIMENTAL METHOD

Experiments were carried out on male cats (21 controls and 26 experimental animals) weighing 2800-4500 g. Thyrotoxicosis was produced by feeding the animals with thyroid extract for 25-30 days in doses designed to ensure the rapid development of the pathological state. When the acute experiment began, the animals receiving thyroid had lost 30-40% of their body weight, the serum concentration of protein-bound iodine had increased from $4.09 \pm 0.4$ to $22.35 \pm 2.92$ $\mu g\%$, and the mean heart rate had increased from $132.9 \pm 3.3$ to $200.9 \pm 10.7$ beats/min. Under anesthesia (urethane, 0.6 g/kg, and chloralose, 40-60 mg/kg, intravenously) and artificial respiration the chest was opened by Kaverina's method [4] and a polyethylene catheter introduced through the right auricle into the coronary sinus. The volume velocity of the coronary blood flow was recorded by means of a combined pump and flow meter designed by Kisin and Tsaturov [6]. The absorption of oxygen by 100 g myocardium per minute (A) was determined simultaneously by means of the O-36 oxyhemograph modified by Kisin [5].

After stabilization of the blood pressure, respiration, and velocity of the coronary blood flow, blood was taken simultaneously from the sinus venosus and coronary artery into cooled test tubes. The heart was then quickly removed from the chest and weighed samples of myocardium taken for determination of glycogen [20]. The heart, freed from its vessels, was washed in cold physiological saline, dried, and weighed. The glucose concentration in the blood samples was determined by a colorimetric method [19], and pyruvate and lactate were determined spectrophotometrically after the addition of NAD and NAD $\cdot H_2$ [15, 17]. The absorption of substrate by 100 g myocardium per minute (B) was determined from the arteriovenous difference (AVD) in substrate concentration and the coronary blood flow.

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The contribution of substrate to the oxygen consumption of the myocardium (C) was calculated from the formula:

$$C = \frac{B \times \text{oxygen equivalent} \times 100}{A}$$

The oxygen equivalent for glucose and lactate is 0.75, and for pyruvate 0.64 [13].

## EXPERIMENTAL RESULTS

In agreement with published data [12] it was found that with an excess of thyroid hormones in the body the oxygen absorption by the myocardium rose sharply (from 7.1 ± 0.2 to 15 ± 1.7 ml/ min/100 g), and this was due entirely to an increase in the coronary blood flow (from 5.17 ± 0.06 to 11.85 ± 0.52 ml/min) and not to increased absorption of oxygen from the arterial blood.

The glucose concentration in the arterial blood of the control cats varied from 144 to 275 mg% (mean 207.1 ± 9.8 mg%). In the experimental animals the mean value was 267.7 ± 10.6 mg% ($P < 0.001$). Cats are known to have a high basal blood sugar [3]. Furthermore the operation, causing excitation of the sympathico-adrenal system [14], could also raise the blood sugar. The hyperglycemic effect of thyroid hormones thus demonstrated has frequently been described in the literature.

The AVD for glucose in the coronary blood remained practically the same in the control and experimental animals. Glucose assimilation by the myocardium was 3.3 ± 0.7 in the control and 5.92 ± 1 mg/100 g body weight/min in the experiment ($P < 0.01$). In four cases in control animals and 10 in experimental animals, the glucose concentration was higher in blood from the sinus venosus than in arterial blood. These results conflict with the view that the myocardium cannot liberate glucose into the blood because it does not contain glucose-6-phosphatase [9]. Several workers [7, 11, 18], in experiments on dogs, have frequently observed negative extraction of glucose by the myocardium.

In the present experiments thyrotoxicosis was accompanied by a marked increase in the pyruvate concentration in the arterial blood (from 0.76 ± 0.03 to 1.15 ± 0.08 mg%; $P < 0.001$). As in the case of glucose, no difference was found in the AVR for pyruvate (control 0.26 ± 0.03, experiment 0.27 ± 0.04 mg%). However, since the coronary blood flow in thyrotoxicosis was sharply increased, the absorption of pyruvate by the myocardium was increased in the experimental animals to 0.274 ± 0.05 mg/100 g/min (control 0.128 ± 0.01 mg/100 g/min; $P < 0.01$).

The lactate concentration in the arterial blood was almost four times higher (43.7 ± 3.51 mg%) in the animals with thyrotoxicosis than in the controls (12.2 ± 1.4 mg%). In contrast to the figures given above, the AVD of this substrate also was increased in thyrotoxicosis (from 2.36 ± 0.6 to 6.8 ± 1.3 mg%; $P < 0.02$). In four cases in the experimental animals, the lactate concentration in blood from the sinus venosus was higher than in the arterial blood. So far as the absorption of lactate by the myocardium is concerned, in the control animals it was 1.13 ± 0.3 and in the experimental animals 5.85 mg/100 g/min ($P < 0.002$).

The glycogen concentration in the myocardium of animals with thyrotoxicosis was lowered compared with the control (0.044 ± 0.08 and 0.294 ± 0.04 mg%, respectively; $P < 0.001$), in agreement with data in the literature [2].

The contribution of pyruvate to the oxygen consumption of the control and experimental animals was 1.06 and 0.9%, respectively, and that of lactate was 12.7 and 41.5%, respectively.

The results described indicate profound changes in the carbohydrate metabolism of the myocardium in animals with experimental thyrotoxicosis. Under the influence of an excess of thyroid hormones, marked structural and functional changes are known to take place in the mitochondria, and these may be responsible for the increased liberation of a glycolysis-mobilizing factor into the hyaloplasm [8]. It can be assumed that in cases when processes of glycolysis are activated in thyrotoxicosis to correspond to the activity of the tricarboxylic acid cycle, oxidation of pyruvate takes place intensively and it is not converted into lactate. Moreover, under those conditions the distinguishing feature of the myocardium reveals itself clearly: its ability to utilize lactate present in blood reaching the heart. When a deficiency of the Krebs cycle exists, lactate is cleared from the myocardium into the blood stream. It has been shown in Severin's laboratory [10] that in the presence of an excess of thyroid hormones, heart homogenates oxidize lactate intensively. This process takes place on the surface of the mitochondria and is unconnected with ATP synthesis. Despite difficulties in comparing results obtained in vitro and in vivo, an attempt was made to attribute part

of the increased heat production observed in thyrotoxicosis to increased oxidation of lactate on the surface of the mitochondria.

Calculation of the contribution of individual intermediate compounds of carbohydrate metabolism to the oxygen consumption of the myocardium shows that in thyrotoxicosis the heart consumes about the same amount of oxygen in oxidation of carbohydrates as normally. In the analysis of this problem, the relative nature of these calculations must be remembered. Since the energy-producing efficiency of intermediate compounds of carbohydrate metabolism is comparatively low, the possibility is not ruled out that the observed increase in utilization of these intermediate compounds by the heart in thyrotoxicosis reflects increased consumption not only for oxidation, but also for biosynthesis.

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