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Effect of Thyroid Hormone on the Pathways of Glucose Oxidation in the Intact Rat. (27119)

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An increase in metabolic activity of the phosphogluconate pathway occurs when human erythrocytes are incubated with physiological concentrations of triiodothyronine(1). This raises the possibility that thyroid hormone may stimulate the phosphogluconate pathway *in vivo*. Such a mechanism, if operative *in vivo*, would explain the uncoupling of oxidation from phosphorylation observed in the thyrotoxic animal, since increased metabolism *via* this pathway is accompanied by reduction of triphosphopyridine nucleotide (TPN), the reoxidation of which does not appear to be closely linked with phosphorylation(2). Thus it seems important to evaluate the activity of this pathway of carbohydrate metabolism in the intact animal, both when an excess and a deficit of the thyroid hormone is present.

A widely accepted, although frequently criticized(3,4), method for such an investigation is the measurement of the oxidation of the 1-carbon *vs* the 6-carbon of glucose by the monitoring of expired $C^{14}O_2$ following injection of specifically labeled glucose.

Method. Young (100 g) Wistar littermate female rats were either injected subcutaneously with 250 μg 3,3'5' triiodo-L-thyronine (Sigma Chemical Co.) daily for 7 days, or had the thyroid surgically removed 7-10 days prior to experiment. Oxygen consumption of animals in both experimental groups and in an untreated control group was measured(5) prior to injection of radioactive glucose. Since the average weight of rats in the 3 groups remained essentially similar (differences were not statistically significant) thyroidectomy apparently did not alter food intake and cannot be considered to influence the results.

One and five-tenths microcuries of specifically-labeled radioactive glucose (specific activity: glucose-1-C^{14}, 2.8 μc/mg; glucose-6-C^{14}, 2.0 μc/mg) (Volk Radiochemicals, Chicago) per 100 g rat was injected intravenously by the dorsal tail vein and the expired $C^{14}O_2$ radioactivity was continuously measured by a flow counter with associated graphic recording apparatus.‡ The resulting rate curves were manually integrated and the data are expressed as per cent of injected dose.

Results and discussion. Oxygen consumption, in milliliters O_2 consumed per minute per gram total body weight ($\pm$ SE), is as follows for the 3 groups; hyperthyroid (4 rats), 0.049 $\pm$ 0.005; euthyroid (6 rats), 0.026 $\pm$ 0.001; hypothyroid (6 rats), 0.021 $\pm$ 0.004.

Results from the tracer study, calculated as per cent of injected glucose-C^{14} appearing as $C^{14}O_2$, are presented in Fig. 1. Counting error was less than 5% at all ranges tabulated. In the hyperthyroid animals, rate of oxidation of both the glucose-1-C^{14} and glucose-6-C^{14} is increased (3.4- and 3.7-fold respectively); there being no significant difference between the 2 labeled positions. In the thyroidectomized rats, however, rate of oxi-

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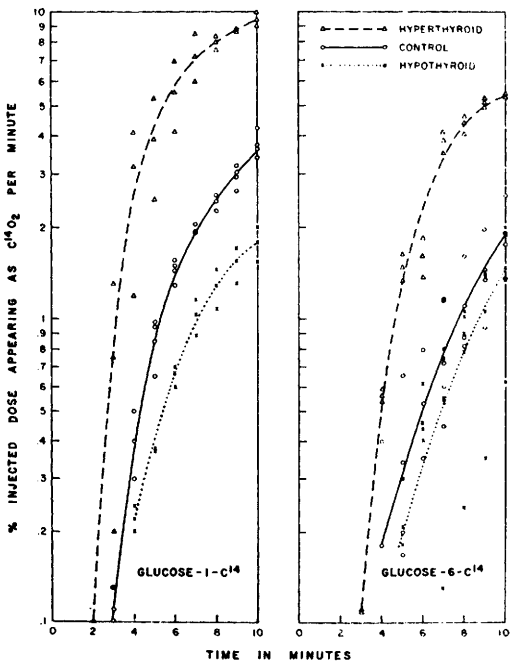

FIG. 1. Cumulative $C^{14}O_2$ following inj. of specifically-labeled glucose-C^{14}. × represents individual determinations.

dation of glucose-1-C^{14} was decreased to a much greater extent than that of glucose-6-C^{14} (0.50 *vs* 0.75-fold respectively).

Similar experiments carried out by Spiro and Ball(6) dealt only with changes in rate of oxidation in the hyperthyroid animals and they concluded that in this subject both phosphogluconate and glycolytic pathways of glucose metabolism were stimulated. Our observations demonstrate that in addition the pathway for oxidation of glucose-1-C^{14} appears to be preferentially depressed.

We therefore suggest that the thyroid hormone(s) in some manner controls the rate of metabolism *via* the phosphogluconate pathway which, in the euthyroid rat, is apparently operating at a maximum rate. It has been demonstrated repeatedly(7,8) that administration of thyroid hormones increases the apparent activity of glucose-6-phosphate and phosphogluconate dehydrogenases. Such effects might explain the data reported here, yet it appears unlikely that this is the whole explanation since our own experiments§ and those of others(7) demonstrate that the thyroid hormones do not increase *in vitro* activity of the purified (isolated) enzymes. However, in the case of erythrocytes, the stimulating effect of the hormones can be demonstrated *in vitro*. Perhaps the effect of the thyroid hormones on the phosphogluconate pathway is a more indirect one.

Summary. These experiments suggest that whereas in the hyperthyroid animal the rate of oxidation of both the C-1 and C-6 carbon of glucose are increased to approximately the same extent, removal of the thyroid hormones leads to a proportionally greater reduction in rate of oxidation of the C-1 carbon. Thus it appears probable that in the euthyroid animal the rate of oxidation of the carbon-1 of glucose (presumably reflecting rate of oxidation *via* the phosphogluconate pathway) is under the influence of the thyroid gland.

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