EFFECT OF HYDROCORTISONE ON THE BLOOD SUGAR AND GLYCOGENESIS IN RATS WITH TUMORS

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In fasting control rats and rats with tumors most exogenous glucose-C^{14} is utilized for glycogen synthesis in the liver only during the first 3 h after administration of hydrocortisone. In fasting rats with Zajdela's hepatoma the threshold of sensitivity of the liver tissue to the induction of glycogen synthesis by hydrocortisone and to the final hyperglycemic effect of this hormone is raised. The substrate induction of glycogenesis in the liver is not disturbed in rats with tumors.

KEY WORDS: glycogen synthesis; liver; hydrocortisone; Zajdela's hepatoma.

Considerable accumulation of glycogen in the liver and persistent glycemia are observed in intact animals for 24 h or more after a single injection of glucocorticoids [3, 12-14]. Meanwhile the liver glycogen is synthesized mainly from the carbon skeleton of amino acids, whereas in the first 3-6 h after administration of the hormone chiefly preexisting glucose and glucose formed from metabolites of carbohydrates and lipids are used for glycogen synthesis [4, 13, 19]. It had thus to be established whether animals with tumors give the same response to the hormone or whether it may differ because of the constant tendency toward hypoglycemia created by the tumor [9, 11, 18], exhausting the glycogen reserves [7, 8, 10, 15] in the liver and altering the sensitivity of organs participating in gluconeogenesis to glucocorticoids.

The object of this investigation was to shed further light on this problem.

EXPERIMENTAL METHOD

Albino rats weighing 150-200 g (healthy animals or animals with Zajdela's hepatoma 4-5 days after intraperitoneal inoculation with 0.5 ml of a suspension of tumor cells from the ascites fluid), deprived of food for 24 h, were given an intraperitoneal injection of 10 mg hydrocortisone acetate (Gedeon Richter, Hungary) and were decapitated 3, 6, and 24 h later. Rats of the control group and rats with tumors but not treated with the hormone were killed at the same time. All the animals, 1 h before decapitation, received an intraperitoneal injection of 25 μCi D-glucose-C^{14} with specific activity 75 mCi/g. Each group contained 7-15 rats.

The glucose concentration in the animals' blood was determined by an enzymic method [2]. Glycogen was extracted from the liver [6], its specific activity was measured, and its content determined by estimating the glucose concentration after hydrolysis of the glycogen by the same enzymic method. The radioactivity of glycogen-C^{14} was measured with a Mark II (Nuclear Chicago) counter.

EXPERIMENTAL RESULTS

The blood glucose concentration in fasting rats with Zajdela's hepatoma was significantly ($P < 0.001$) higher than in the controls. The writers showed previously [1] that glucose was formed in the liver and re-

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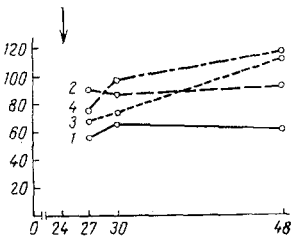

Fig. 1

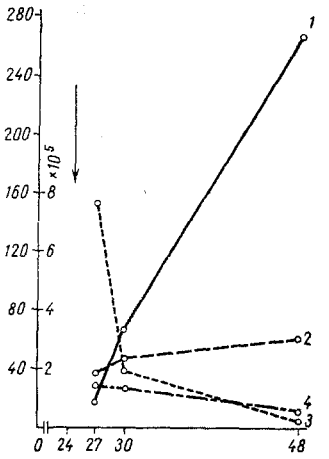

Fig. 2

Fig. 1. Blood sugar in control rats (1, 3) and rats with tumors (2, 4); (3, 4) rats receiving hydrocortisone (time of injection shown by arrow). Ordinate, blood glucose concentration (in mg%); abscissa, duration of fasting (in h).

Fig. 2. Concentration (1, 2) and specific activity (3, 4) of glycogen in the liver of control rats (1, 3) and rats with tumors (2, 4) after administration of hydrocortisone. Ordinate, on the left – glycogen concentration (in μg/g liver), on the right – specific activity of glycogen (in pulses/min/g glycogen); abscissa, period of fasting (in h).

nal cortex of rats with a tumor from tyrosine, leucine, and sodium acetate on a scale several times greater than normally. Administration of hydrocortisone increased the blood glucose concentration in all the animals; this increase was particularly marked after 24 h.

The glycogen concentration in the liver of the rats with tumors after fasting for 30 h was lower (4.5 1 mg/g tissue; $P < 0.02$) than in the controls (7.4 ± 0.3 mg/g tissue). Later, however (fasting for 48 h), this difference between the two series diminished (7.0 ± 1 mg/g in the control, 5.1 ± 0.4 mg/g in the experimental group; $P > 0.05$).

A completely different picture was observed after the administration of hydrocortisone: the liver glycogen content in the fasting animals of both groups increased sharply to reach its highest level after 24 h. However, whereas in the control rats the liver glycogen concentration increased by 39 times under these conditions, in the animals with tumors it increased by only 12.5 times compared with that in animals not receiving the hormone. The response of the liver to the hormone was thus weaker in the rats with tumors.

Throughout the period of fasting the specific activity of glycogen-C^{14} in the liver of rats (control and with the tumor) not treated with the hormone was virtually identical. In other words, glycogen synthesis from glucose-C^{14} was undisturbed in the rats of both groups. However, as was pointed out above, the blood glucose level in the rats with a tumor was always higher than in the control animals. This hyperglycemia was probably maintained as a result of the greatly stimulated gluconeogenesis.

After the injection of hydrocortisone (Fig. 2) the specific activity of glycogen-C^{14} in the liver of the control rats rose sharply only in the first 3 h and after 24 h it was back to normal. These results show, on the one hand, the considerable dilution of glycogen-C^{14} by nonradioactive glycogen newly formed in the liver, and on the other hand, the intensive synthesis of labeled glycogen from exogenous glucose-C^{14} during the first 3 h after injection of the hormone. During the same period the specific activity of glycogen-C^{14} in the liver of the rats with tumors was 4.8 times lower than in the control animals; this difference then disappeared. The difference between the specific activity of glycogen in the control and experimental series can evidently be attributed to the fact that the intensive synthesis of glycogen in the rats with a tumor (giving rise to an increase in its concentration at the end of this period) was observed sooner than in the control animals.

During prolonged starvation of rats with tumors the blood glucose level is thus maintained at a significantly higher level than in the control animals. The final hyperglycemic effect of hydrocortisone was the same in the rats of both groups, although 24 h after injection of the hormone the blood glucose concentration in the animals with tumors was increased by only 21.5% (compared with 82% normally), and the quantity of glycogen accumulating in their liver was several times less. Consequently, in rats with Zajdela's hepatoma the threshold of sensitivity of the liver tissue to the action of hydrocortisone in inducing glycogen synthesis is increased. Substrate induction of glycogenesis in rats with Zajdela's hepatoma was undisturbed – exogenous glucose-C^{14} was evidently utilized earlier in the biosynthesis of the liver glycogen by the fasting rats with tumors than by the control rats.

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