HYPERGLYCEMIA AND GLUCONEOGENESIS IN THE LIVER OF MICE WITH TUMORS

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Gluconeogenesis, when sharply stimulated by exhaustion of the liver glycogen reserves, is one of the factors maintaining the normal blood sugar level in mice with tumors. Hyperglycemia induced by glucose leads to an increase in the liver glycogen content and a decrease in the intensity of gluconeogenesis in control mice and also in mice with tumors. Only in the latter, however, does glycogen synthesis from noncarbohydrate compounds rise again steadily after the injections of glucose are discontinued.

KEY WORDS: gluconeogenesis; hyperglycemia; glucose; tumor Ca-755.

As a result of gluconeogenesis, lactate and glycerol are reutilized in the body and the carbohydrate skeleton of certain amino acids, whether absorbed from the alimentary tract or mobilized as a result of the breakdown of tissue proteins, is converted into glucose [7]. In an animal with a constant tendency toward hypoglycemia because of the action of a tumor as a glucose trap [2, 4, 6, 12], in most cases compensatory stimulation of gluconeogenesis is observed, so that the normal blood sugar level is maintained even under these unfavorable conditions [1, 10].

Severe hypoglycemia, progressing with the growth of the living mass of the tumor, arises in animals with transplanted tumors, for their body is unable to intensify gluconeogenesis sufficiently to provide for the loss of glucose assimilated energetically by the neoplasm [12].

These arguments are supported by data in the literature on the maintenance of the normal blood sugar in rats with tumors, for the activity of the enzymes of gluconeogenesis in their liver is increased [9]. So far as patients with cancer are concerned, there is only scanty evidence, indirect at that, of correlation between hypoglycemia and the inability of the body to stimulate gluconeogenesis [8, 11].

In this paper the writers present new data on gluconeogenesis in mice with tumors and on the effect of exogenous glucose on the blood sugar level, the liver glycogen concentration, and the intensity of gluconeogenesis.

EXPERIMENTAL METHOD

Experiments were carried out on male (CBA $\times$C57BL)F_1 weighing 20-22 g, divided into four groups: healthy mice and mice with tumors, and healthy mice and mice with tumors receiving daily intraperitoneal injections of 40% glucose solution in a dose of 10 mg/g body weight. The control mice and half of the mice with tumors (immediately after transplantation) received glucose daily for 10 days, and the other half of the mice received glucose twice a day for 5 days, in the morning and evening, starting 15 days after transplantation of the tumor. The first generation hybrids were inoculated subcutaneously with a Ca-755 tumor, syngeneic for mice of one of the parental lines (C57BL).

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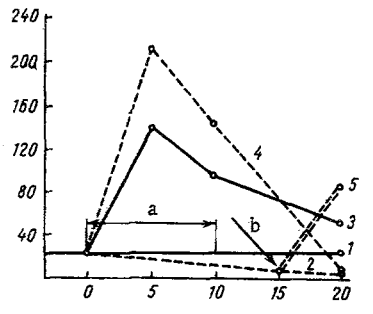

Fig. 1

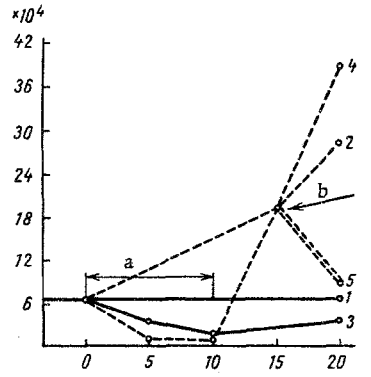

Fig. 2

Fig. 1. Glycogen metabolism in the liver of control mice (1, 3) and mice with tumors (2, 4, 5); 3, 4) daily injection of glucose for 10 days (a), 5) for 5 days, twice a day; beginning of glucose injections indicated by arrow (b). Abscissa, time (in days); ordinate, glycogen concentration (in mg/g liver).

Fig. 2. Intensity of synthesis of glycogen-C^{14} from tyrosine-U-C^{14} in liver of control mice and mice with tumors. Legend as in Fig. 1. Abscissa, time (in days); ordinate, specific activity of newly formed glycogen (in pulses/min/g glycogen).

On the day of the experiment, immediately after the injection of glucose, the mice were deprived of food, but 4 h later they were given an intraperitoneal injection of 10 Ci uniformly labeled tyrosine-C^{14} (Radiochemical Centre, Amersham, England) with a specific activity of 507 mCi/mmole.

The mice were decapitated 1 h after injection of the label (during this period part of the labeled tyrosine was converted into glucose-C^{14} which, in turn, was incorporated into glycogen), the liver was extracted, and the glycogen isolated from it by the method of Good et al. [5]. The glycogen was then dissolved in hot water and one-fifth of the total volume was applied to filters to count the radioactivity in a liquid gas-flow counter (Nuclear Chicago, Mark II). The rest of the glycogen was hydrolyzed in 2 N sulfuric acid and the glucose of the glycogen determined in the digest by an enzymic method [3] with some modification. The glycogen content was expressed in mg/g liver and its specific activity in pulses/min/g glycogen. The blood glucose was determined by the same enzymic method.

EXPERIMENTAL RESULTS

Transplantation of the tumor into mice did not affect the blood sugar level; normally it was 101 ± 5 mg% and 20 h after transplantation it was 98 ± 13 mg%.

Preliminary experiments showed that a single intraperitoneal injection of glucose in a dose of 10 mg/kg increased the blood glucose concentration in healthy mice after 1 h to 848 mg % and the hyperglycemia continued for 3 h. In the next experiments all procedures on the mice took place 5 h after the injection of glucose; by this time the blood glucose in the healthy mice was back to its initial level.

As a result of administration of glucose for 5 days the hyperglycemia in the healthy mice reached 141 ± 9 mg%, whereas in mice with tumors it was lower: 120 ± 5 mg %.

After administration of glucose to the mice for 10 days the hyperglycemia was the same in both groups (133 ± 8 mg% in the control, 130 ± 5 mg% in the experiment). However, the blood sugar of the healthy mice still remained at its former level even 10 days after the end of the glucose injections, whereas in the mice with tumors it had fallen to 71 ± 7 mg %. Administration of glucose to mice with established tumors did not change the blood glucose concentration (103 ± 10 mg%).

Throughout the period of observation the blood sugar remained normal in the mice with a Ca-755 tumor; hyperglycemia appeared only if the glucose was injected immediately after transplantation of the tumor.

It will be clear from Fig. 1 that by the 20th day after transplantation of the tumor the liver glycogen

content in the normally fed mice with tumors was reduced to less than one-tenth of its normal level – to 1.87 mg/g liver.

After daily administration of glucose the liver glycogen content in the mice increased sharply. In the healthy mice after 5 days it was increased by 6.3 times, compared with 13.2 times in the mice with tumors after the same period; 10 days after the injection of glucose the increase was 4.3 and 14 times, respectively. These observations correlate with the changes described above in the blood glucose concentration and it can be concluded from them that the synthesis of glycogen was more intensive in the liver of the mice with the Ca-755 tumor.

After the end of the glucose injections the liver glycogen content of the healthy mice decreased gradually, but after 10 days it was still above normal. If the administration of glucose to the mice with tumors was discontinued, their liver glycogen content fell catastrophically quickly to the level characteristic of mice with tumors not receiving glucose. These results are evidence of the increased mobilization of glycogen from the liver of animals with tumors, probably to compensate for the constant tendency toward hypoglycemia [12]. The glycogen content in the liver of the mice with tumors could be increased even if glucose administration began during the period of rapid growth of the tumor (Fig. 1).

Development of tumors in mice thus exhausts the glycogen reserves in the liver not through inhibition of its synthesis but through its intensified breakdown.

The synthesis of glycogen-C^{14} making use of the carbohydrate skeleton of the glucogenic amino acid tyrosine-C^{14} increased sharply in the mice with tumors (Fig. 2). By the 20th day after inoculation of the tumor the intensity of synthesis was 4.2 times greater than normally. Consequently, a chronic glycogen deficiency in the liver of animals with tumors stimulates endogenous carbohydrate formation sharply.

Intraperitoneal injection of glucose lowered the intensity of gluconeogenesis in the liver both of the healthy mice and of mice with tumors, but in the former the rate of formation of glycogen-C^{14} from tyrosine-C^{14} remained low even after the end of the glucose injections, whereas in the animals with tumors under the same conditions gluconeogenesis again was sharply intensified. Excessive stimulation of gluconeogenesis in the mice with tumors, after the end of glucose injections, correlated closely (Fig. 1) with the decrease in the liver glycogen and in the blood glucose concentration. Consequently, the rate of mobilization of glycogen from the liver was sharply increased in the mice with the Ca-755 tumor, as a result of which its synthesis from noncarbohydrate compounds was stimulated sharply. Probably the demand of the tumor for the newly formed glucose rose considerably again immediately after administration of the additional quantity of carbohydrates to the mice had ended.

Increased formation of glucose from labeled tyrosine could be considerably reduced in intensity in the mice with the Ca-755 tumor if the glucose was injected not only immediately after transplantation of the tumor but also during its growth (Fig. 2).

After transplantation of a tumor into (CBA $\times$ C57BL)F_1 mice the synthesis of glycogen from noncarbohydrate compounds in the liver is sharply intensified; this is one of the factors enabling the normal blood sugar to be maintained. Excessive administration of exogenous glucose lowers the intensity of gluconeogenesis both in healthy mice and in animals with tumors, but the after-effect of glucose disappears much sooner in the animals with tumors than in healthy mice.

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