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AGE DIFFERENCES IN PANCREATIC INSULAR FUNCTION

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Age differences in pancreatic insular function and indices of insulin production during sugar loading tests were studied in experiments on rats. Despite hyperinsulinemia and a higher rate of insulin liberation in old animals the utilization of glucose is worsened, evidence of the development of relative insulin insufficiency. Hyperinsulinemia in old animals is accompanied by a decrease in the total blood insulin activity and an increase in the "coefficient of inactivation" of insulin. The development of relative insulin insufficiency with age may be due to both insular and extrapancreatic factors, leading to a reduction in the biological activity of insulin.

KEY WORDS: insulin; age dynamics; sugar loading.

Homeostasis is maintained during aging by definite changes in the system of neurohumoral regulation [2, 13]. Special attention is attracted to the age evolution of the pancreatic insular apparatus.

Investigations have shown [8, 9, 11] that the endocrine part of the pancreas undergoes definite changes with age; information on age changes in the insulin activity of the blood has also been published [4, 5, 10]. However, data on the age dynamics of the blood insulin level are few in number and contradictory in nature [12, 16, 17].

It was decided to study the response of the insular apparatus to glucose administration and its changes with age.

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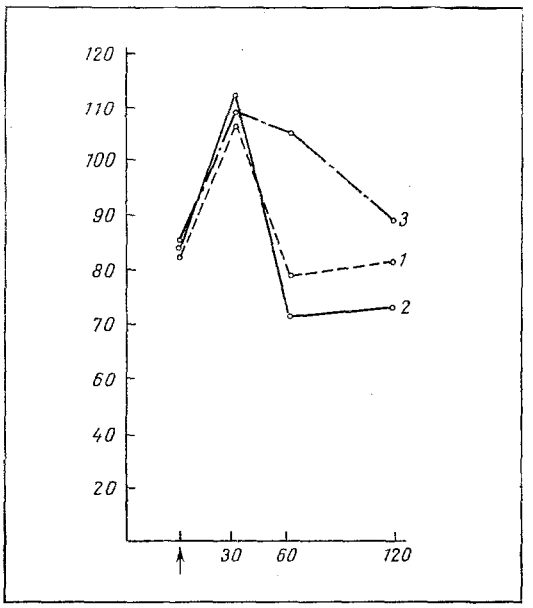

Fig. 1. Changes in blood sugar during glucose loading in rats of different ages. Abscissa, time of blood sampling (in min); ordinate, sugar concentration (in mg%). 1) Young, 2) middle-aged, 3) old rats. Arrow indicates time of injection of glucose.

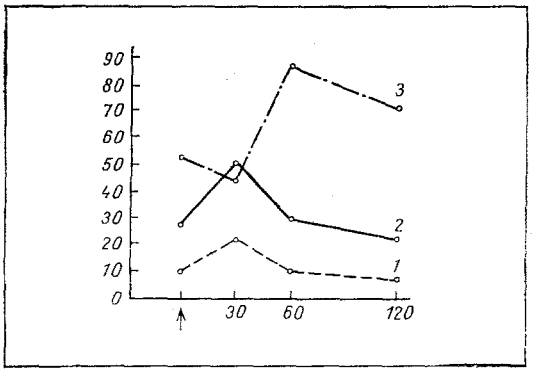

Fig. 2

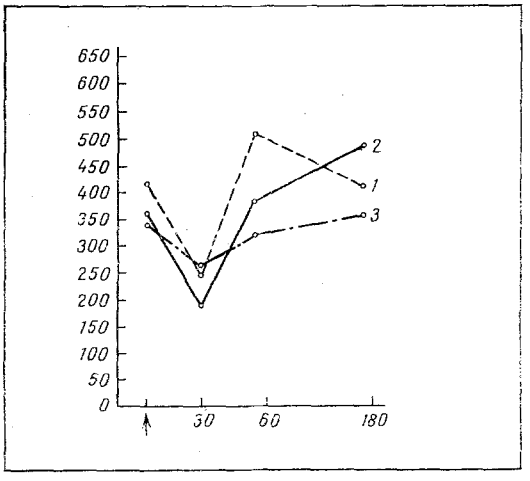

Fig. 3

Fig. 2. Changes in plasma IRI concentration during glucose loading in rats of different ages. Ordinate, IRI concentration (in microunits/ml). Remainder of legend as in Fig. 1.

Fig. 3. Changes in NEFA concentration during glucose loading in rats of different ages. Ordinate, NEFA concentration (in meq/liter). Remainder of legend as in Fig. 1.

EXPERIMENTAL METHOD

Male rats of three age groups were used: 1.5-2 months (young), 10-12 months (middle-aged), and 28-32 months (old). The blood levels of sugar (orthotoluidine method), immunoreactive insulin (IRI) (using Kits produced by the firm of "Cea-Ire-Sorin", France), and nonesterified fatty acids (NEFA) were determined [15]. Total insulin activity also was determined. Sugar loading was carried out by intraperitoneal injection of 40% glucose solution in a dose of 100 mg/100 g body weight. Blood samples were taken before and 30, 60, and 120 min after the injection of glucose. The total rise in the blood sugar and IRI above the initial level, the rate of insulin secretion, and the insulin–glucose index were calculated [7, 14, 18].

TABLE 1. Indices of Insulin Production in Rats of Different Ages (M ± m)

Age of animals	Number of animals	Index of elevation of blood sugar	Index of elevation of IRI (in micro-units/ml)	Rate of liberation of insulin (in micro-units/min)	Insulin–glucose index	Total blood insulin activity (in mg/g/3 h)	Coefficient of insulin inactivation in blood
1.5-2 months (young)	10	15,3±0,7	3,1±0,15	0,37±0,07	0,2±0,05	0,8±0,08	1,35±0,8
10—12 months (middle-aged)	10	6,6±0,95	6,9±0,9	0,8±0,05	1,0±0,08	3,9±0,9	7,2±1,0
P		<0,001	<0,001	<0,001	<0,001	<0,01	<0,001
28—32 months (old)	10	31±1,4	12±0,9	1,4±0,09	0,38±0,05	2,0±0,1	26±3,0
P		<0,001	<0,001	<0,001	>0,05	<0,01	<0,001
P_1		<0,001	<0,001	<0,001	<0,001	<0,05	<0,001

Legend. P by comparison with young animals, P_1 by comparison with middle-aged animals.

EXPERIMENTAL RESULTS AND DISCUSSION

The blood sugar was practically identical in the rats of the different ages. However, sugar loading revealed certain age differences in the blood sugar dynamics (Fig. 1). For instance, although in rats of all age groups the maximal level of the blood sugar was reached after 30 min and the maximal increase in the sugar concentration was 44-52%, 60 min after the injection of glucose the blood sugar level in the young and middle-aged rats had returned to normal whereas in the old rats it still remained high. As a result, the index of increase in blood sugar in the group of old animals was almost five times greater than in the middle-aged group and almost twice as high as in the group of young animals (Table 1). This suggests that in old age the intensity of glucose utilization decreases.

Considerable age differences also were observed in the dynamics of IRI. In the initial state a marked increase in the IRI concentration in the blood plasma was observed with age (Fig. 2). In the young and middle-aged animals the greatest liberation of IRI was observed 30 min after injection of glucose. After 60 min the IRI level had returned to its initial value, but after 120 min it was a little below the initial level. In the old rats, on the other hand, the time of the maximal increase in the IRI level was 60 min; after 120 min it still remained much higher than initially. As a result of this the index of elevation of IRI in the old animals was much greater than in the young and middle-aged groups. In the old rats, the index characterizing the rate of insulin liberation also was higher (Table 1). Meanwhile, although the IRI level in the old rats was much higher than in animals of the young and middle-aged groups, the maximal increase in IRI relative to its initial level was much lower. In young animals, for instance, it was 104%, compared with 79% in the middle-aged and only 64% in the old rats. This points to a reduction in the possible amplitude of the response of the insular apparatus in old rats.

The effect of insulin depends not only on its absolute, but also on its so-called effective concentration in the blood (the "activity" of the insulin). For this reason, the "coefficient of inactivation", or the ratio between the IRI level and the total blood insulin activity, was calculated [3]. This index shows by how many times the blood insulin activity (or the effective concentration of the hormone) is less than its possible concentration. The "coefficient of inactivation" rose steadily during aging of the animals. Moreover, in the old animals the total blood insulin activity, an integral index of the insulin production of the body, also was reduced in the old animals (Table 1).

Age differences also were found in the dynamics of NEFA (Fig. 3). For instance, 30 min after the injection of glucose the NEFA level was much lower in the animals of all age groups, but in the old rats their concentration remained highest.

It can be concluded from these results that with age the utilization of glucose in the body worsens, although the blood sugar level in the old animals was virtually the same as in the young and middle-aged groups of rats. The reason could be a compensatory increase in the IRI level in the blood of the old rats. Such a compensatory mechanism can be supposed to maintain the essential carbohydrate utilization, but at the expense of an ever-increasing quantity of insulin. Despite the hyperinsulinemia, signs of relative insulin insufficiency were observed in the old animals. The hyperinsulinemia in them occurred against the background of a decrease in the total insulin activity of the blood and an increase in the "coefficient of inactivation," indicating a decrease in the biological activity of the hormone. The reasons for this decrease could be changes in the properties of the molecule itself (the "mutant hormone") and also various extrapancreatic factors, notably elevation of the blood NEFA level [1, 6].

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ROLE OF THE SPLANCHNIC NERVES IN REGULATION OF MAXIMAL GLUCOSE TRANSPORT IN THE KIDNEYS

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Glomerular filtration is reduced in the kidney on the side of the stimulated splanchnic nerve but maximal glucose reabsorption is unchanged. After demedullation of the adrenals, splanchnic nerve stimulation increases filtration in the contralateral kidney without changing maximal glucose transport. Adrenergic fibers of the splanchnic nerve have no direct action on maximal glucose transport in the kidneys.

KEY WORDS: splanchnic nerve; maximal glucose transport in the kidneys; demedullation of the adrenals.

Data on nervous regulation of tubular transport of glucose in the kidneys are few in number and contradictory in nature [3, 7].

In the investigation described below the role of the splanchnic nerves in the regulation of maximal glucose transport in the proximal tubules of the dog kidney was studied.

EXPERIMENTAL METHOD

The dogs used had their ureters exteriorized separately. The control group consisted of 11 animals. In the experimental group 15 dogs underwent adrenal demedullation: Six of these animals received adrenalin by intravenous injection in a dose of 0.1 mg/kg daily (except on the day of the operation) [2]. During the period

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