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DYNAMICS OF INSULIN SECRETION IN DOGS WITH ALLOXAN DIABETES

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Hypoinsulinemia in the superior pancreatico-duodenal vein and depression of the first phase of insulin secretion by the pancreas, characteristic of alloxan diabetes of different degrees of severity, are not observed in the femoral vein. The results of an investigation of the dynamics of the insulin and glucose concentrations in the superior pancreatico-duodenal vein emphasize the dominant role of the pancreatic factor in the pathogenesis of alloxan diabetes in dogs. Data obtained by the study of these indices in the peripheral femoral vein do not reflect this state of affairs adequately.

KEY WORDS: insulin secretion; alloxan diabetes.

There is no general agreement in the literature on the character of the insulin insufficiency in diabetes mellitus. It has been suggested that the cause of the diabetes is not an absolute but a relative insulin deficiency [1] caused by depression of the "acute" liberation of insulin [9, 10]. The insulin response to glucose in patients with diabetes mellitus has been shown [12] to be weaker, and that the first phase of insulin secretion is depressed particularly sharply in this case. The study of the concentration of immunoreactive insulin (IRI) has also revealed a reduction in the "acute" liberation of insulin after intravenous injection of glucose in patients with diabetes mellitus, which is more marked in the portal vein than in the peripheral vessels [2]. The weakening of the insulin response, it is considered, may be the principal pathogenetic component common to all types of diabetes, including prediabetes [3-7]. Unlike the insulin level in blood from the portal vein, the peripheral insulin level has been shown not to reflect insulin secretion adequately [8].

The object of this investigation was to study the dynamics of insulin secretion in dogs with alloxan diabetes of different degrees of severity.

EXPERIMENTAL METHOD

Alloxan diabetes was induced in 9 dogs weighing 18-25 kg by intravenous injection of alloxan in a dose of 60-65 mg/kg body weight. A glucose tolerance test (GTT) was carried out 16-18 days later on these and 5 control animals. The superior pancreatico-duodenal and femoral veins were catheterized under anesthesia, after which 100 ml physiological saline was injected subcutaneously by the drip method during the next 90 min. The first blood samples were taken from the catheters from fasting dogs, and 40% glucose solution was injected over a period of 10 min into the opposite femoral vein to the one catheterized, in a dose of 1 g/kg body weight. Blood samples were taken immediately after the end of the glucose infusion and at definite times during the

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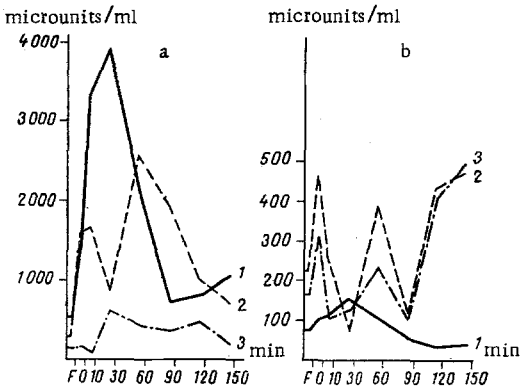

Fig. 1. Dynamics of plasma IRI in blood from superior pancreatico-duodenal (a) and femoral (b) veins of dogs with alloxan diabetes during intravenous GTT: 1) normal; 2) moderately severe diabetes; 3) severe diabetes. Abscissa, here and in Figs. 2 and 3: time (in min); F) fasting state, O) end of administration of glucose; ordinate, IRI concentration (in microunits/ml).

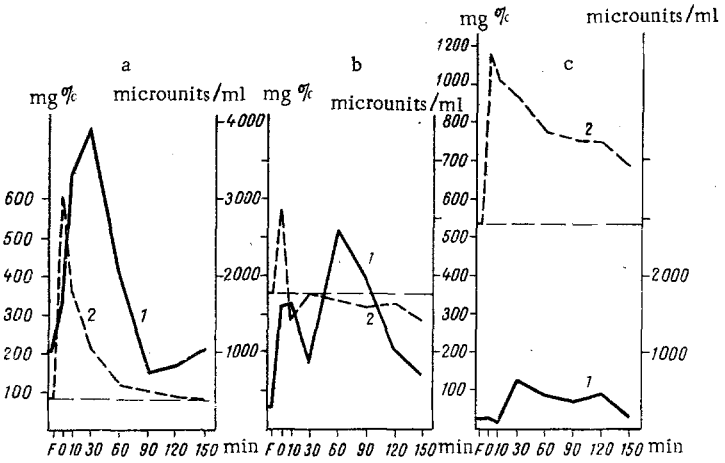

Fig. 2. Ratio between insulin and glucose levels in blood from superior pancreatico-duodenal vein in dogs with alloxan diabetes during GTT: a) normal; b) moderately severe diabetes; c) severe diabetes. 1) Insulin; 2) glucose. Ordinate: left – glucose concentration (in mg %); right – insulin concentration (in microunits/ml).

next 2.5 h. The blood was centrifuged for 1 h at 4°C. The plasma was frozen at −20°C and used to determine IRI with the aid of standard kits (from Cea-Ire-Sorin, France) for use in experimental investigations of dogs [11]. Parallel determinations of the blood sugar concentration were made by the orthotoluidine method.

EXPERIMENTAL RESULTS

The insulin concentration in the blood of the superior pancreatico-duodenal vein was distinctly reduced in the diabetic dogs, both in the fasting state and throughout the period of the GTT (Fig. 1a). The hypoinsulinemia was found to depend on the severity of the diabetes. The greatest deficiency of insulin secretion took place in the first phase of "acute" liberation of insulin. This was confirmed by the total increase in insulin, which was reduced in diabetes, especially during the first hour of the GTT, and in moderately severe diabetes its mean value was 60% and in the severe form of diabetes only 12% of normal. The increase in insulin after 2.5 h

TABLE 1. Combined Increase in Insulin and Glucose Concentrations and Insulinogenic Index in Blood from Superior Pancreatico-Duodenal Vein of Dogs with Alloxan Diabetes during Intravenous GTT (M ± m)

Index	Time of GTT, h	Normal	Moderately severe diabetes	Severe diabetes
Combined increase in insulin concentration, microunits/ml	1	8014±2880	4779±3564 (60)	964±596 (12)
	2,5	9489±6404	7552±1760 (80)	596±319 (17)
Combined increase in glucose concentration, mg %	1	969±456	803±496 (83)	2024±763 (210)
	2,5	978±409	695±412 (71)	2731±1017 (280)
Insulinogenic index	1	9,25±6,0	6,98±5,0 (75)	0,67±0,45 (7)
	2,5	13,0±9,8	10,6±6,5 (81)	0,81±0,52 (6)

Legend. Change in index (in %) compared with normal (100%) shown in parentheses.

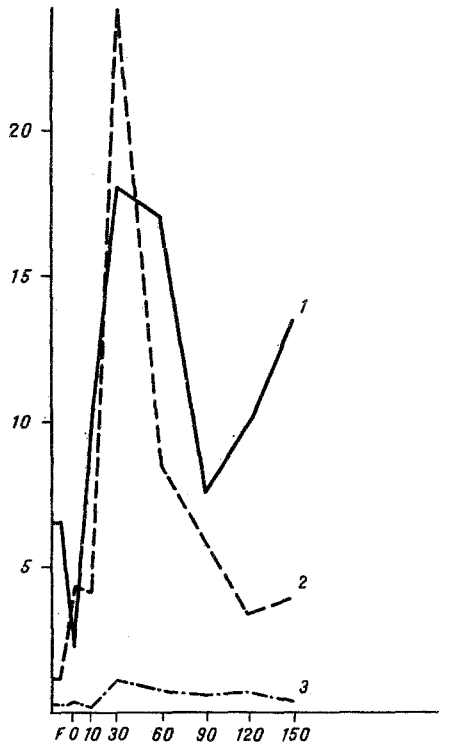

Fig. 3. Ratio of insulin/glucose concentration in blood from superior pancreatico-duodenal vein of dogs with alloxan diabetes during intravenous GTT. Legend of curves as in Fig. 1. Ordinate, ratio of insulin/glucose concentration.

of the GTT was 80% in moderately severe diabetes and 17% in the severe form of diabetes of the control level (Table 1).

Data on the ratio between the glucose and insulin levels in blood from the superior pancreatico-duodenal vein in the course of the intravenous GTT in normal dogs and dogs with various degrees of severity of diabetes are given in Fig. 2. In the control animals (Fig. 2a), intravenous injection of glucose, leading to rapidly developing hyperglycemia, caused an insulin response of the pancreas in which "acute" liberation of insulin – the first phase of its secretion – predominated. The raised blood sugar concentration fell rapidly, and approached the control level after 1 h. In moderately severe alloxan diabetes the fasting blood sugar was raised on average to 355 mg % whereas the insulin concentration in blood from the superior pancreatico-duodenal vein fell sharply

(Fig. 2b). During the GTT the insulin concentration rose by a lesser degree. In this case, as was observed previously, the first phase of insulin secretion was sharply depressed. However, the blood insulin concentration throughout the GTT was evidently sufficient in moderately severe diabetes to maintain the blood sugar above the initial level, while not reaching the control. The combined increase in glucose during the GTT in moderately severe diabetes was reduced after 1 h to 83%, and after 2.5 h to 71% of the corresponding control (Table 1). In moderately severe diabetes, dynamic equilibrium was thus apparently established in the glucose metabolism at a definite level of hyperglycemia. In the severe form of alloxan diabetes (Fig. 2c) (the mean fasting blood sugar was 535 mg %), the insulin concentration in blood from the superior pancreatico-duodenal vein was reduced even more. Intravenous injection of glucose in the severe form of alloxan diabetes caused a very slight insulin response compared with normal and with moderately severe diabetes. The weak insulin response in the severe form of alloxan diabetes was accompanied throughout the GTT by a stable and high hyperglycemia. The very small increase in insulin during the GTT did not cause the glucose concentration to fall to its initial level, as in the control, or below the initial level, as in moderately severe diabetes. The total increase in glucose under these circumstances rose sharply, especially after 1 h of the GTT, when it was 210%, and after 2.5 h, when it was 280% compared with the corresponding controls (Table 1).

Figure 3 reflects the dynamics of the ratio between the insulin concentration and glucose concentration in blood from the superior pancreatico-duodenal vein during the intravenous GTT. In moderately severe diabetes this index increased considerably, whereas in the severe form of diabetes it fell sharply below normal.

The insulinogenic index (the ratio between the combined increase in insulin and the combined increase in glucose) is an important index of the internal secretory function of the pancreas. The insulinogenic index also fell sharply in diabetes of different degrees of severity, and especially in the severe form (Table 1). The greatest decrease in this index during the first hour of the GTT in the severe form of diabetes was evidence of sharp inhibition of the "acute" liberation of insulin in the first phase of its secretion by the pancreas. The insulin concentration in blood from the femoral vein of fasting dogs with moderately severe and severe forms of diabetes was increased (Fig. 1b). In the course of the intravenous GTT the insulin concentration in blood from the femoral vein also exceeded the control level considerably in diabetes. Under these circumstances, and contrary to the results of investigation of blood from the superior pancreatico-duodenal vein, the first peak of the rise in the insulin concentration in blood from the femoral vein during diabetes was higher than normal. Changes in the insulin concentration in blood from the peripheral vessels are determined to a lesser degree by changes in the insulin secretion by the pancreas. The insulin concentration in the blood of the peripheral vessels reflects not only the secretion of insulin by the pancreas, but also evidently other processes taking place at the periphery (the breakdown and utilization of insulin, etc.).

The results obtained during this study of the insulin concentration in the blood of the superior pancreatico-duodenal and femoral veins are evidence of differences between the indices studied in the blood from these vessels during diabetes. Investigation of insulin secretion based on the study of the insulin concentration in the efferent vessel of the pancreas is more valuable.

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