LIPOLYTIC ACTIVITY OF ADIPOSE TISSUE IN EXPERIMENTAL ALLOXAN DIABETES

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There are many reports in the literature of an increased concentration of nonesterified higher free fatty acids (NEFA) in the blood of patients with diabetes mellitus [3, 5, 10]. V. I. Uspenskii, working in this laboratory, has observed a similar phenomenon in rats with alloxan diabetes. An increased blood concentration of NEFA is generally accepted [7, 8, 13] to be the result of increased lipolytic activity of adipose tissue. Wertheimer [13], and Wenkeova and Pav [12] described an increase in this activity in the epididymal fat pad of rats with alloxan diabetes.

The increased lipolytic activity of the adipose tissue in patients with diabetes mellitus may result from the fact that in this disease the utilization of glucose by adipose tissue is disturbed, thus interfering with the resynthesis of triglycerides, for our previous investigations [1] showed that in normal conditions the presence of glucose in the incubation medium depresses the liberation of NEFA into the medium. Meanwhile, in insulin deficiency, the synthesis of higher fatty acids from metabolic products of glucose is disturbed, so that the fat depots are depleted. Observations in this laboratory have shown that when adipose tissue is depleted, its lipolytic activity is depressed [2]. Hence, in diabetes, the conditions favor at the same time an increase and a decrease in the output of fatty acids from adipose tissue.

The object of this investigation was to study the changes in the lipolytic activity of adipose tissue at various stages of development of diabetes, and to determine whether, in fact, the presence of glucose in the incubation medium of adipose tissue inhibits lipolysis as it does in normal animals. An attempt was also made to discover whether the degree of hyperglycemia in diabetes is related to the intensity of the lipolytic activity of the adipose tissue.

EXPERIMENTAL METHOD

Experiments were carried out on male alibino rats weighing 120-200 g deprived of food for 18 h. Diabetes was produced by giving the animals one or two subcutaneous injections of a 2.5% solution of alloxan in phosphate-citrate buffer (pH 4.2), the dose of alloxan being 15 mg/100 g body weight. The animals were sacrificed on the 7th-20th day (first series of experiments), the 30th-54th day (2nd series) and the 72nd-90th day (3rd series) after the development of diabetes.

The lipolytic activity of the epididymal fat pad was determined by in vitro experiments using the method described in our previous paper [1]. The activity was expressed as the difference between the NEFA concentrations in meq/ml/g tissue before and after incubation. The NEFA was determined by Dole's method [7]. In the experiments to study the effect of glucose on lipolysis, glucose was added in sufficient quantity to make its concentration in the incubation medium up to 50 and 300 mg%. The blood sugar was determined by Sakhibov's modification of the anthrone method [4].

EXPERIMENTAL RESULTS

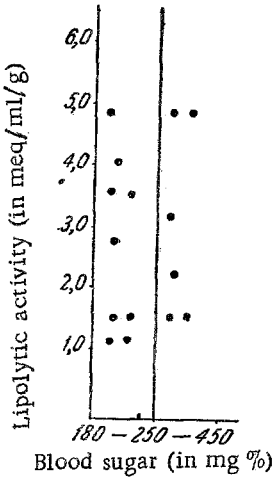
It is clear from the results given in Table 1 that in diabetes lasting 7-20 days the lipolytic activity of the adipose tissue fell by 48% of its normal value. When the diabetes lasted 30-54 or 72-90 days, the lipolytic activity was normal.

TABLE 1. Lipolytic Activity of the Epididymal Fat Pad of Rats with Alloxan Diabetes (mean data, M ± m)

Experimental conditions	Number of rats	Blood sugar (in mg %)	Lipolytic activity (in meq/ml/g)
Normal	11	82—110	4,85±0,59
First series	16	280±21	2,5±0,45 (—48%) $P<0,01$
Second "	8	281±32	4,1±0,48 (—15%) $P>0,05$
Third "	4	242±39	5,3 (+9,4%)
Diabetes lasting 7-18 days, 2-6 days after cessation of glycosuria	12	94—114	2,8±0,45 $P<0,02$

TABLE 2. Lipolytic Activity of Epididymal Fat Pad of Normal Rats and Rats with Alloxan Diabetes after Addition of Glucose to Incubation Medium (mean data, M ± m)

Experimental conditions	Number of rats	Blood sugar (in mg %)	Lipolytic activity (in meq/ml/g) after addition of 50 mg % glucose	Lipolytic activity (in meq/ml/g) after addition of 300 mg % glucose
Normal	11	82—110	1,58±0,52	0,26±0,37
First series	12	280±21	1,8±0,51 (+13%) $P>0,5$	1,2±0,49 $P>0,1$
Second " »	8	281±32	3,2±0,53 (+102%) $P<0,001$	2,5±0,6 $P<0,01$
Third " »	3	242±39	3,6±1,14 (+127%) $P<0,001$	3,3±0,75 $P<0,001$
Diabetes lasting 7-18 days, 2-6 days after cessation of glycosuria	12	94—114	1,06±0,39 $P>0,25$	1,1±0,39 $P>0,1$



Lipolytic activity of epididymal fat pad and hyperglycemia in rats with experimental alloxan diabetes.

It is clear from the figure that no regular relationship was present between the severity of the diabetes (the degree of hyperglycemia) and the intensity of lipolysis.

The absence of an increase, and in some cases an actual depression, of lipolysis in the early stages of development of diabetes may be attributable to the fact that the synthesis of lipids from carbohydrates was inhibited because of the insulin deficiency, resulting in a considerable depletion of the adipose tissue. As mentioned above, during depletion of adipose tissue its lipolytic activity is considerably depressed. The decreased lipolysis in the adipose tissue in the early stages of development of diabetes may also have been the result of the toxic action of alloxan. This is suggested by the fact that the lipolytic activity of the adipose tissue remained low at this period in the animals for several days after cessation of the glycosuria and normalization of the blood sugar (i.e., after restoration of islet-cell function) (see Table 1).

The addition of glucose to the medium used for incubation of adipose tissue from normal animals depresses its lipolytic activity [1, 9, 11]. This is because α-glycerophosphate is formed during glucose metabolism, and this compound is essential for the synthesis of triglycerides. Synthesis of triglycerides is thus more marked than their breakdown.

The addition of glucose to the medium used for incubation of adipose tissue from animals with alloxan diabetes lasting for 30-54 and 72-90 days depressed lipolysis to a lesser degree than in normal animals (Table 2). Similar results were obtained by Buckle and co-workers [6] after addition of 100 mg % of glucose to the medium.

The inhibition of the lipolytic activity of the adipose tissue by glucose in the animals with diabetes was less marked in our investigations, with glucose concentrations of both 50 mg % and 300 mg %. This was presumably because of interference with access of glucose to the adipose tissue and with its metabolism in diabetes. This interference led to a decrease in the synthesis of α-glycerophosphate, essential for synthesis of triglycerides in adipose tissue. With the decrease in the synthesis of triglycerides, the output of NEFA into the medium was increased. Consequently, when adipose tissue from diabetic animals was incubated in vitro in conditions closely similar to those found in vivo (with glucose present), its lipolytic activity rose above the level observed in the same conditions in tissue from normal animals. This increase in the lipolytic activity of the adipose tissue was directly related to the concentration of glucose in the medium and to the duration of the diabetes.

In the early stages of development of diabetes (7-20 days), and 2-6 days after the cessation of glycosuria (see Table 2), the less marked inhibition of the lipolytic activity of the adipose tissue was by no means so regular as in the experiments in which the duration of the diabetes was longer. In some animals this inhibition was weaker than in normal animals, while in others it was identical. On the average, the difference between the degrees of inhibition of lipolysis by glucose in these two groups was indistinguishable from normal. As pointed out above, in the early period of alloxan diabetes the alloxan apparently has a toxic action on the adipose tissue in some animals.

SUMMARY

Experiments were staged in vitro. In alloxan diabetes lipolysis of adipose tissue in the incubation medium without glucose is either unchanged or reduced.

In the presence of glucose in the incubation medium the output of free nonesterified fatty acids (NEFA) from the adipose tissue increases by comparison with the adipose tissue of normal animals placed in the same experimental conditions; this is the result of a lessened inhibition by glucose of lipolytic activity in the adipose tissue of diabetic animals. In other words, in connection with disturbed glucose metabolism in the adipose tissue during diabetes there is a derangement of triglyceride synthesis and a relative prevalence of lipolysis. This may be one of the causes of increased blood NEFA content in diabetes mellitus.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.
