ACTION OF INSULIN ON ADIPOSE TISSUE OF DIABETICS

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The insulin sensitivity of subcutaneous adipose tissue taken by biopsy from 11 healthy women and from 10 women with normal weight but recently diagnosed as suffering from diabetes mellitus was investigated. Unlike in the healthy subjects, no increase in the intensity of glucose oxidation to CO_2 was produced in the adipose tissue of the diabetics by insulin in a concentration of 50 microunits/ml, and the synthesis of glycogen from glucose was not increased by insulin in concentrations of 50 and 100 microunits/ml. The decrease in the sensitivity of the various pathways of glucose metabolism in adipose tissue to insulin in diabetics points to the possibility of a disturbances of the interaction between insulin and the cell membrane in this disease.

KEY WORDS: *Diabetes mellitus; insulin; adipose tissue; carbohydrate metabolism.*

It is now considered that in the early stages of diabetes the cause of the metabolic disturbances is not an absolute but a relative insufficiency of insulin [1, 2, 16], probably resulting from a decrease in the sensitivity of the tissues, especially muscle and adipose tissue, to its action [4, 5, 12, 22, 23]. A decrease in the sensitivity of adipose tissue to insulin has also been found in animals with spontaneous diabetes [10, 14, 15]. However, if insulin actually has a weaker action on oxidation of glucose to CO_2 on the adipose tissue of mice with spontaneous diabetes than in the tissue of healthy animals, the conversion of acetate into fatty acids under the influence of insulin is not reduced in the diabetic mice [15, 21]. In human diabetics weakening of the action of insulin on glucose assimilation by adipose tissue and leukocytes has been observed [17, 18], but in patients with adiposity, whether accompanied or not by diabetes, stimulation of glucose incorporation into lipids under the influence of insulin was unchanged [6]. Insulin does not stimulate the oxidation of glucose to CO_2 in the adipose tissue of diabetic patients with adiposity, but in adiposity unaccompanied by diabetes the hormone has such an action. The contradictory nature of the results can be explained on the grounds that different effects of insulin have been studied in different patients.

The effect of insulin on oxidation of glucose to CO_2 and on the synthesis of glycogen from glucose was investigated simultaneously during incubation of adipose tissue from the same diabetic patients.

EXPERIMENTAL METHOD

Eleven women not suffering from diabetes (control group) and 10 women (aged 35-45 years) with normal weight and suffering from diabetes mellitus were investigated. The diabetes in all these patients had only recently been diagnosed. They had not previously been treated for diabetes or they had received sulfonamides or insulin only for a short period. The diabetes was decompensated in all the patients at the time of the investigation, and hyperglycemia and glycosuria were found. By biopsy 2-3 g of adipose tissue was obtained from the left inguinal region. It was immediately placed in a test tube with buffer solution or insulin solution and incubated in a water bath for 3 h. Stable glucose (200 mg %), bovine serum albumin (2%), and 0.2 μCi of uniformly labeled ^{14}C-glucose were added to the

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TABLE 1. Effect of Insulin on Oxidation of Glucose to CO_2 in Adipose Tissue of Healthy and Diabetic Subjects (M ± m)

Insulin concentration, microunits/ml	Radioactivity of $^{14}CO_2$, counts/min/mg	
	healthy subjects	diabetics
0	605±78	590±82
50	684±78	627±89
100	767±92	654±87
500	883±111	748±93

TABLE 2. Effect of Insulin on Conversion of Glucose into Glycogen in Adipose Tissue of Healthy and Diabetic Subjects (M ± m)

Insulin concentration, microunits/ml	Radioactivity of $^{14}CO_2$, counts/min/mg	
	healthy subjects	diabetics
0	31,37±2,25	31,13±3,23
50	37,87±2,21	31,52±4,14
100	43,44±2,73	33,75±4,01
500	52,45±3,45	38,70±3,99

solutions. Glucose metabolism was studied in the presence of insulin in concentrations of 50, 100, and 500 microunits/ml. Incorporation of ^{14}C-g into CO_2 [20], absorbed by caustic soda and precipitated by barium peroxide, was determined. The residue of $BaCO_3$ was washed and transferred to a target, where its radioactivity was measured with a 4-P gas-flow counter, allowing for the coefficients of self-absorption. The results were expressed in counts/min/mg dry weight of the precipitate.

Glycogen was extracted from the adipose tissue after the end of incubation [12]. After washing, the alcoholic precipitate was transferred to a target, dried, and its radioactivity measured in the same counter.

EXPERIMENTAL RESULTS AND DISCUSSION

The results given in Table 1 show that insulin, in all concentrations tested, stimulated ($P < 0.05$) the oxidation of glucose to CO_2 in the adipose tissue of the healthy subjects. Insulin in a concentration of 50 microunits/ml did not stimulate the oxidation of glucose ($P > 0.1$) in the tissues of the diabetics. Higher concentrations of insulin increased ($P < 0.05$) the oxidation of glucose in these tissues also; virtually no difference was found, moreover, between the radioactivities of $^{14}CO_2$ of the healthy and diabetic subjects in experiments both without insulin and with insulin in all concentrations tested ($P > 0.05$).

Data on the incorporation of labeled glucose into glycogen are given in Table 2. The radioactivity of glycogen in the adipose tissue of the healthy subjects increased progressively ($P < 0.05$) under the influence of all insulin concentrations studied. Insulin in concentrations of 50 and 100 microunits/ml did not increase the radioactivity of glycogen in the adipose tissue of the diabetics, but in a concentration of 500 microunits/ml it significantly increased it ($P < 0.001$). A statistically significant difference ($P \leq 0.05$) between the radioactivity of glycogen in the adipose tissue of the healthy subjects and diabetics was found in insulin in concentrations of 100 and 500 microunits/ml; the radioactivity of glycogen was lower in the tissue of the diabetics incubated in these concentrations of the hormone than in healthy tissues.

The results described above indicate that the action of insulin both on the oxidation of glucose and on the synthesis of glycogen in adipose tissue is reduced in patients with diabetes mellitus; the first effect is weakened by insulin only in a concentration of 50 microunits/ml, but the second in concentrations of 50 and 100 microunits/ml. It can be concluded that the effect of insulin on glucose oxidation in the adipose tissue of diabetics is weakened by a lesser degree. Considering previous observations [5] that the stimulating

action of insulin on lipid synthesis is weakened in the adipose tissue of diabetics, it can tentatively be suggested that in this disease the sensitivity of the adipose tissue to insulin is reduced as reflected in all indices of the action of insulin on glucose metabolism.

Insulin is known to stimulate synthesis of the key enzymes of glycolysis, it forms complexes with enzymes and, by combining with the sulfhydryl groups of proteins or the lipoproteins of the cell membrane, it causes transformation of its structure with an increase in permeability for glucose [3]. Contact between insulin and the specific receptors of the cell membrane is essential for the manifestation of all these effects [7, 9, 11]. The binding of insulin with the membrane receptors is not only an essential condition, but it is sometimes the only condition for the manifestation of its biological action [8].

Since, as the writer has shown, the action of insulin on all pathways of glucose metabolism is disturbed in the adipose tissue of diabetic patients, it can be postulated that the disturbance of interaction between insulin and the cell arises in the initial stage of this process, i.e., at the stage of binding of insulin with the receptors of the membranes. It has in fact recently been shown that the bond between insulin and receptors of the membranes of fat cells and lymphocytes is disturbed in patients with diabetes [13, 22].

The degree of disturbance of the various pathways of glucose metabolism in the cell in diabetes evidently depends on the degree to which they are controlled by insulin under physiological conditions.

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