Lipogenesis and Carbohydrate Utilization

Effects of Glucose Concentration and Insulin in Rat Liver and Adipose Tissue

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We have recently reported that stock-fed normal rat adipose tissues are considerably more active in converting uniformly labeled C^{14} glucose into fatty acids in vitro than are the livers of the same animals.[1] The rates of glucose oxidation based on equal fresh weights are of comparable magnitude in both tissues. Alloxan diabetes abolished lipogenesis and depressed the carbohydrate oxidation in each case. Insulin restored both capacities to normal values and above depending on the length of administration.

The glucose concentration used in these experiments was 400 mg. per 100 cc., an arbitrary value which clearly does not match the physiological concentrations encountered in the normal and the insulin-treated animals. In an attempt to evaluate the relative participation of these tissues in carbohydrate utilization more precisely, we have investigated the effects of varying glucose levels on their lipogenic and oxidative activities.

EXPERIMENTAL PROCEDURES

The experiments were designed to use pooled tissues for each of the glucose concentrations tested. One hundred mg. of the adipose tissue, or liver, respectively, from six rats were used per flask. The medium contained uniformly labeled glucose in concentrations shown in figures 1, 2 and 3. The same incubation and analytical methods were used as in the earlier investigation.[1] Male Wistar rats weighing about 400 gms. were used. The insulin treated rats received 36 units of protamine zinc insulin over a period of 3 days so that a sustained hormonal effect was maintained during its administration. The rats gained weight rapidly during this time. The last injection was given 2 to 3 hours before the experiment, and blood sugar levels at sacrifice averaged about 50 mg. per 100 cc. The alloxan diabetic rats of that group in which hepatic oxidation was investigated, showed average blood glucose levels of 602 mg. per 100 cc., an average glucosuria of 11 gm. per day and a weight loss of 33 per cent from the time of the alloxan administration. The other group from which adipose tissue was taken showed corresponding values of 421 mg. per 100 cc., 9 gm., and 7 per cent.

EXPERIMENTAL OBSERVATIONS

Lipogenesis and Glucose Oxidation. Lipogenesis in normal liver was not detectable until a concentration of 400 mg. per 100 cc. of glucose was used. Adipose tissue, under identical circumstances, actively incorporated glucose C^{14} into its fatty acids at 50 mg. per 100 cc. and increased in this activity slightly at higher levels. Insulin treatment enabled the liver to commence lipogenesis at 50 mg. per 100 cc. and respond to higher glucose concentrations with marked increases in lipogenic capacity. Adipose tissues from such animals also had an activity elevated above normal, which exceeded that in the liver

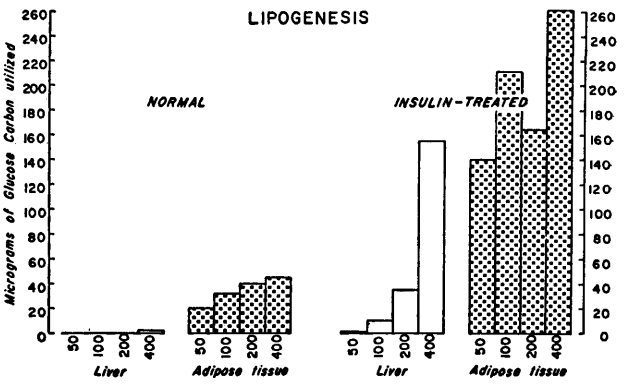

FIG. 1. Formation of fatty acids and carbon dioxide from radio glucose (50-1,600 mg. per 100 cc.). Values in micromoles per gm. of tissue per 3 hours.

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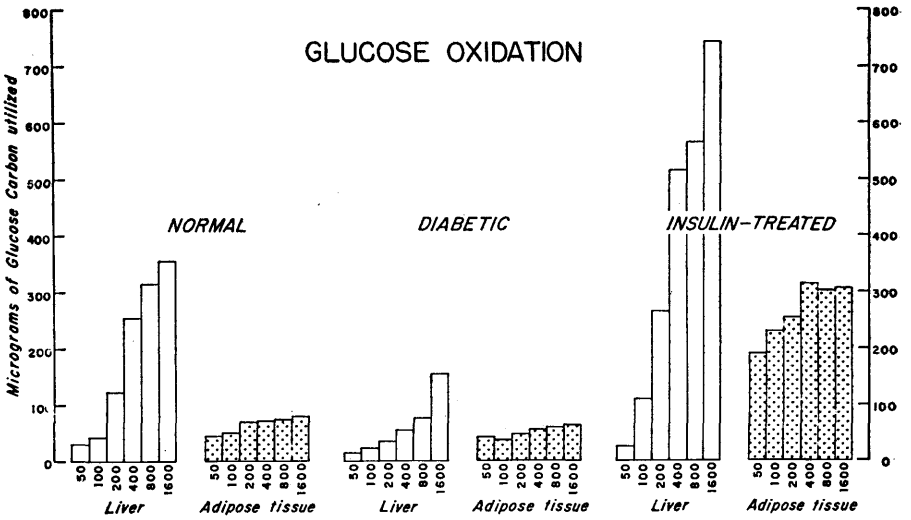

FIG. 2. See figure 1.

at all substrate levels except the highest studied. Lipogenesis in adipose tissue of the normal and hormonally stimulated animals did not respond to glucose concentrations as dramatically as did the process in the liver (figure 1). Preliminary experiments have indicated that both tissues from diabetic animals exhibit no detectable lipogenic activity at glucose levels up to 1,600 mg. per 100 cc.

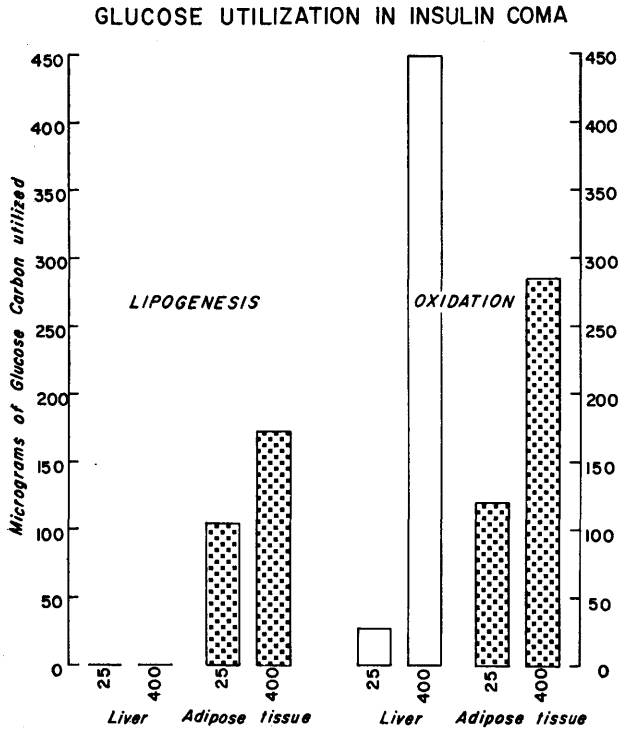

FIG. 3. Formation of fatty acids and carbon dioxide from radio glucose (25 and 400 mg. per 100 cc.). See figure 1.

Glucose oxidation (figure 2) was far more dependent on the exogenous concentration in normal liver than in adipose tissue. The latter appears to be functioning almost at a saturated substrate level at 50 mg. per 100 cc. Hepatic tissues from alloxan diabetic rats exhibited depressed oxidative rates which paralleled the normal values at corresponding sugar levels. Diabetic adipose tissue oxidation rates were not significantly different from normal, indicating a greater resistance of this tissue's oxidative function towards insulin deficiency. It should be pointed out, however, that these animals were not *maximally* diabetic. Unpublished investigations using the classical method of determining the glucose balance indicate that such diabetic rats are still able to utilize about half the amount of glucose utilized by normal animals.[2] In rats manifesting a more severe diabetes adipose tissue oxidation is also depressed.[1]

Insulin administered in moderate doses over a three day period enhanced oxidation in both tissues without distorting their characteristic response to the glucose concentrations. It is also of interest to note that adipose tissue carbohydrate oxidation as well as lipogenesis is greater than that in the liver at those glucose levels which correspond to the glycemic condition of the animal (figures 1 and 2).

Effects of Hypoglycemia. More acute hypoglycemia, averaging 25 mg. per 100 cc., was developed in rats given 40 units of protamine zinc insulin over a two- to four-hour period during which time food was withheld. When insulin reactions (unconsciousness or convulsions) were evident, the animals were sacrificed and their livers and adipose tissues incubated as before, using two glucose concentrations, 400 mg. per 100 cc. and 25 mg. per

100 cc.[3] The latter corresponded to the average blood sugar levels of these animals. Lipogenesis was absent in liver in both carbohydrate levels. Adipose tissue was clearly active in fat synthesis under these conditions and indeed was significantly more active than when taken from normal animals. Increasing the glucose level led to an enhanced oxidative response of the hepatic tissues, but the activity at the 25 mg. per 100 cc. glucose level (prevailing in vivo) was less than that in adipose tissue. The oxidative activity in adipose tissue at this level exceeded that found in the normal animals at 100 mg. per 100 cc., while, in the liver, no appreciable change from normal was seen.

DISCUSSION

Renold and co-workers have recently studied the biochemical sequence of events after insulin administration.[3] Their experiments suggested that insulin exerted immediate metabolic effects on the periphery only, while its effects on hepatic metabolism were more gradual, representing "either a different type of hormonal action or a metabolic adaption to the new demands created by the peripheral changes." Our data confirm the greater immediate extrahepatic action of insulin and suggest that adipose tissue as one element of the metabolic periphery may play an important part in the biochemical effects induced by the hormone. Furthermore, since adipose tissue suffers comparatively little diminution in its ability to utilize carbohydrates at falling blood sugar levels, it is tempting to think of it as a major site of metabolism during severe hypoglycemia. Earlier investigations have already indicated that adipose tissue may be of considerable importance in carbohydrate metabolism.[4, 5]

Our previous reports[1, 6] on the quantitative superiority of adipose tissue over liver as a site of fat formation in vitro have been amplified by these studies. They indicate even more strongly that the liver, under various conditions, may play only a supplementary role in lipogenesis. Adipose tissue, an organ of significant proportions in terms of total body weight, appears capable of major activities in the carbohydrate metabolism of the organism.

SUMMARY

Lipogenesis in isolated normal liver tissue of the rat was not detectable until a concentration of 400 mg. per 100 cc. of glucose was used. In contrast adipose tissue actively incorporated glucose C^{14} into its fatty acids at 50 mg. per 100 cc. Insulin administration led to lipogenesis by the liver at a glucose concentration of 50 mg. per 100 cc. and also stimulated lipogenesis at higher glucose levels both in liver and in adipose tissue. In general insulin did not enhance lipogenesis as much in adipose tissue as it did in liver. Diabetic tissues had no detectable lipogenic activity.

Glucose oxidation by adipose tissue appeared near maximum at glucose levels of 50 mg. per 100 cc. whereas in liver the oxidative removal of glucose increased with rising concentrations. Comparing glucose oxidation at prevailing blood levels of 100 mg. per 100 cc. for normals and 400 mg. per 100 cc. for alloxan diabetic rats, there was no significant difference between the two groups in either liver or adipose tissue. Insulin administration enhanced the oxidation of glucose in both tissues without distorting their characteristic responses to carbohydrate concentration.

In tissues from hypoglycemic rats, lipogenesis was absent in liver at glucose concentrations of 25 to 400 mg. per 100 cc. In contrast adipose tissue was clearly active in fat synthesis under these conditions and significantly more so than when taken from normal animals.

The data confirm the greater immediate extrahepatic action of insulin and suggest that adipose tissue may be an important site of the action of insulin.

SUMMARIO IN INTERLINGUA

Lipogenese e Utilisation de Hydratos de Carbon: Effectos de Concentration de Glucosa e Insulina in Histos Hepatic e Adipose de Rattos

Lipogenese in isolate normal histos hepatic de rattos non esseva detegibile usque un concentration de glucosa de 400 mg per 100 cm cubic esseva usate. In contrasto con isto, histos adipose incorporava glucosa a C^{14} activemente in su acidos grasse a un concentration de 50 mg per 100 cm cubic. Le administration de insulina resultava in lipogenese per le hepate a un concentration de glucosa de 50 mg per 100 cm cubic e etiam stimulava lipogenese a plus alte nivellos de glucosa in histos tanto hepatic como etiam adipose. In general, insulina non promoveva lipogenese tanto in histos adipose como illo lo faceva in histos hepatic. Histos diabetic non habeva un detegibile activitate lipogenic.

Le oxydation de glucosa per histos adipose pareva attinger su maximo in le vicinitate de nivellos de 50 mg per 100 cm cubic, durante que in histos hepatic le oxydation de glucosa accresceva con accrescente concentrationes. Le comparation del oxydation de glucosa in le presentia prevalente de nivellos sanguinee de 100 mg per 100 cm cubic in le caso de rattos normal e de 400 mg per 100 cm cubic in le caso de rattos con diabete alloxanogene monstrava nulle differentia significative inter

le duo gruppos in histos hepatic o in histos adipose. Le administration de insulina promoveva le oxydation de glucosa in ambe histos sin alterar lor responsas characteristic al concentration de hydrato de carbon.

In histos ab rattos hypoglycemic, lipogenese esseva absente in histos hepatic a concentrationes de glucosa ab 25 a 400 mg per 100 cm cubic. In contrasto con isto, histos adipose esseva clarmente active in le synthese de grassia sub le mentionate conditiones. Le grado de iste activitate esseva significativemente plus alte quando le histos adipose esseva prendite ab rattos normal.

Le datos citate confirma le plus grande immediate action extrahepatic de insulina; illos indica que histos adipose es possibilemente un importante sito del action de insulina.

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The Facets of Age

The problem of our senior citizens is becoming more important as the years go by. With each passing year the average life span grows longer, resulting in an ever-increasing population of aging or, perhaps we should say, aged persons.

Since 1940 the people sixty-five years and over have increased by nearly 50 per cent in the United States and now total 13,500,000. Between 1940 and 1950 the entire population of New York State increased 10 per cent, while our sixty-five and over group increased 39.3 per cent. One can not overestimate, therefore, the need for an active program aimed at alleviation of the many facets of the problems involved in the aging process. Such an attack must include not only a physiologic survey of the situation, but also and even more important the psychologic, social, and economic factors involved require attention and consideration.

Let us consider first of all, the thoughts and feelings of the aging:

In the involutional phase of the life cycle the ordinarily adequate adjustment between the instinctive force for self-preservation and race preservation breaks down, and a new physiologic adjustment and psychologic attitude are required. At this time of life the instinctive drive for race preservation abates, and the self-preservation drive reasserts itself more consciously. This results in an over-awareness of self and a lack of concern for others which at times occasions a most serious problem of adjustment. A change in philosophy is required. If this fails, the person becomes apprehensive and depressed.

He quite often distorts reality and exaggerates his limitations, so that a picture of neuroticism appears. External stimuli lose their zest, and anticipations which formerly gave rise to pleasure cause only a cynical attitude to develop which pervades his whole outlook on life.

Diminution of sensory acuity, especially of hearing and sight, so frequently found, interfere with social acceptability and ability to maintain effective comunication with the environment so that the individual tends to isolate himself. Someone has quite aptly applied the term, "social disarticulation," to this particular problem. Such partial isolation leads to misinterpretations and suspicions which, if allowed to go uncorrected, become distorted and result in increasing anxieties, fear, and discouragement. There are, of course, many other physical changes incident to the aging process, but time precludes the possibility of discussing all of them. Suffice it to say that physical changes constitute a real threat to older persons, but the important thing is the manner in which these changes are accepted.

H. A. Steckel, M.D., from an article
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