Hepatic Glycolytic Enzyme Activities in the Alloxan-diabetic Rat: Response to Glucose and Fructose Feeding*

WALTER M. FITCH,† R. HILL,‡ AND I. L. CHAIKOFF

From the Department of Physiology, University of California, Berkeley, California

(Received for publication, May 25, 1959)

In an earlier report (1) we compared the responses of hepatic glycolytic enzyme activities of normal rats fed either glucose or fructose for 3 days. The enzymes studied were phosphoglucomutase, glucose 6-phosphatase, phosphoglucose isomerase, and the dehydrogenases of glucose 6-phosphate and gluconate 6-phosphate. When the diets containing free hexoses were substituted for the stock diet, the activities of isomerase and both dehydrogenases were augmented, but the response to fructose feeding exceeded by far that observed with glucose. Only the fructose diet augmented the phosphatase activity, whereas neither diet affected the mutase activity.

The present report concerns the responses to hexose feeding of these hepatic enzymes in the diabetic rat. It is shown that the magnitude of response to either hexose by the diabetic rat does not approach that by the normal rat. Our findings indicate that the liver of the diabetic rat is characterized by a reduced response to the substitution of hexose-containing diets.

EXPERIMENTAL PROCEDURE

Male Long-Evans rats weighing from 175 to 200 g, which had been raised on a commercially prepared stock diet (Table I), were used in this study. Diabetes was induced by a single intravenous injection of 40 mg of recrystallized alloxan monohydrate (Eastman) per kg of body weight. Food and water consumption and the volume of urine excreted by each rat were measured daily. All diabetic rats were subjected to a 7-hour fast about 10 days after the injection of the alloxan, and only those which had a fasting blood sugar in excess of 200 mg per 100 ml were selected for study. The diabetic rats used here ingested about the same for the three diets employed: the Labration stock diet (devoid of free hexoses), the diet containing 60% glucose, and the one containing 60% fructose.

The influence of diabetes upon the activities of isomerase and glucose 6-phosphatase (5, 6) and a reduction in those of mutase (7) and gluconate 6-phosphate dehydrogenase (8) have been observed by other investigators, and it is shown here that the extent of change in activity induced by diabetes in these three enzymes is about the same for the three diets employed: the Labration stock diet (devoid of free hexoses), the diet containing 60% glucose, and the one containing 60% fructose.

The effect of diabetes upon hepatic glycolytic enzyme activities of rats fed three different diets—The relation of the levels of enzyme activity in the diabetic rat to those in normal rats is shown in Table III. A rise in the levels of activity of glucose 6-phosphatase (5, 6) and a reduction in those of mutase (7) and gluconate 6-phosphate dehydrogenase (8) have been observed by other investigators, and it is shown here that the extent of change in activity induced by diabetes in these three enzymes is about the same for the three diets employed: the Labration stock diet (devoid of free hexoses), the diet containing 60% glucose, and the one containing 60% fructose.

Effect of Substitution of 60% Glucose or Fructose Diet for Stock Diet upon Hepatic Glycolytic Enzyme Activities of Diabetic Rat—The responses of enzyme activities of normal and diabetic rats to glucose-containing and fructose-containing diets are shown in Fig. 1. It is clear that the enzymatic responses of the diabetic rat to the substitution of either of the hexose-containing diets were impaired. A significant response to the glucose diet was found in only two enzymes of the diabetic rat, glucose 6-phosphate and gluconate 6-phosphate dehydrogenases. When the fructose diet was substituted, four of the enzymes responded. The increases in the activities of the two dehydrogenases that followed the feeding of the fructose-containing diet were greater than those that followed the feeding of the glucose diet.

DISCUSSION

In a previous communication it was pointed out that, in normal rats, the substitution of a diet containing 60% free hexose for a stock diet devoid of free hexose altered significantly the activi-

* Aided by a grant from the National Science Foundation.
† Present address, Department of Pharmacology, Stanford University, Stanford, California.
‡ Fellow of the American Heart Association.
TABLE I
Composition of diets

<table>
<thead>
<tr>
<th>Constituent</th>
<th>Labration*</th>
<th>Synthetic diet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbohydrate</td>
<td>46.5%</td>
<td>60%</td>
</tr>
<tr>
<td>Protein</td>
<td>24.7%</td>
<td>22%</td>
</tr>
<tr>
<td>Fat</td>
<td>5.2%</td>
<td>0%</td>
</tr>
<tr>
<td>Fiber</td>
<td>4.0%</td>
<td>9.8%</td>
</tr>
</tbody>
</table>

* A nutritionally complete diet obtained from Diablo Laboratories, Berkeley, California.
† The synthetic diet contained either glucose or fructose as the sole carbohydrate. In addition to the constituents listed above, this diet contained 2.0% liver VioBin, 0.2% of a vitamin B mixture (3), and 6.0% of Hawk-Oser salt mixture (4).

TABLE II
Specific activities of glycolytic enzymes of livers of diabetic rats fed three different diets

Averages and their standard errors are given in the table.

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Labration</th>
<th>60% Glucose</th>
<th>60% Fructose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phosphoglucomutase</td>
<td>9</td>
<td>120 ± 12</td>
<td>110 ± 8</td>
</tr>
<tr>
<td>Glucose 6-phosphatase</td>
<td>9</td>
<td>53 ± 5</td>
<td>50 ± 5</td>
</tr>
<tr>
<td>Phosphogluucose isomerase</td>
<td>6</td>
<td>600 ± 12</td>
<td>600 ± 30</td>
</tr>
<tr>
<td>Phosphoglucone dehydrogenase</td>
<td>9</td>
<td>6.7 ± 0.8</td>
<td>12 ± 2.6</td>
</tr>
<tr>
<td>Phosphogluconate dehydrogenase</td>
<td>7</td>
<td>12 ± 0.8</td>
<td>15 ± 0.7</td>
</tr>
</tbody>
</table>

TABLE III
Effect of diabetes on hepatic glycolytic enzyme activities of rats fed three different diets

The result of each determination on the liver of a diabetic rat fed a given diet was expressed as a percentage of the average value found for the livers of normal rats fed the corresponding diets. The averages of these percentages and their standard errors are given below.

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Diet fed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Labration</td>
</tr>
<tr>
<td>Phosphoglucomutase</td>
<td>77 ± 8</td>
</tr>
<tr>
<td>Glucose 6-phosphatase</td>
<td>180 ± 18</td>
</tr>
<tr>
<td>Phosphoglucone isomerase</td>
<td>103 ± 2</td>
</tr>
<tr>
<td>Phosphoglucone dehydrogenase</td>
<td>102 ± 12</td>
</tr>
<tr>
<td>Phosphogluconate dehydrogenase</td>
<td>69 ± 5</td>
</tr>
</tbody>
</table>

Activities of several hepatic enzymes. When the same dietary substitution was made in the diabetic rat, the extent of change in enzyme activity was invariably less than that found in the normal rat. Thus diabetes apparently reduces the ability of the liver to respond to the substitution of a high hexose diet.

As shown in Table III, the percentage change induced in the activity of each enzyme by diabetes was the same regardless of whether the diet contained 60% glucose or fructose. This equality in enzymatic response of the diabetic rat to the two hexose-containing diets suggests that diabetes has an effect which cannot be ascribed solely to a block in glucose utilization.

Felts et al. (9) have shown that the proportion of glucose metabolized in the liver for lipogenesis via the hexose monophosphate oxidative pathway (pentose cycle) is reduced in the diabetic rat. In this connection it is of interest to note that the levels of activity of the two dehydrogenases in the diabetic rat liver are similarly decreased (8). Gluconeogenesis is increased in the diabetic rat, a finding consonant with augmented activity in glucose 6-phosphatase observed by us and others (5, 6). Both the glycogen content and the mutase activity of the liver of the alloxan-diabetic rat are reduced (10). Thus, a change in the activity of an enzyme appears to reflect qualitatively an alteration in the usage of a metabolic pathway in which the given enzyme participates. It should not be inferred, however, that the altered metabolism need be ascribed to the changed levels of enzymatic activity. On the contrary, evidence obtained in this laboratory suggests that alterations in enzyme activity can follow changes in the throughput of a metabolic pathway.

SUMMARY

1. The activities of phosphoglucomutase, glucose 6-phosphatase, phosphoglucone isomerase, and the dehydrogenases of gluconate 6-phosphate and glucose 6-phosphate were measured in the livers of alloxan-diabetic rats that were (a) maintained on a stock diet containing no free hexoses and in which whole
ground wheat was the principal source of carbohydrate and (b) fed for 3 days a synthetic diet in which either 60% glucose or fructose was the only carbohydrate source.

2. The activities of phosphoglucose isomerase and glucose 6-phosphate dehydrogenase exhibited varied responses to diabetes. They were unaffected in the diabetic rats fed the stock diet, and decreased in those fed the 60% glucose or fructose diet.

3. The activities of phosphoglucomutase and gluconate 6-phosphate dehydrogenase were reduced in the diabetic rats regardless of the diet fed.

4. Glucose 6-phosphatase was the only enzyme whose activity was elevated in the liver of the alloxan-diabetic rat, and this elevation was observed with the stock diet as well as with the two hexose-containing diets.

5. The significance of the findings is discussed.

REFERENCES
Hepatic Glycolytic Enzyme Activities in the Alloxan-diabetic Rat: Response to Glucose and Fructose Feeding
Walter M. Fitch, R. Hill and I. L. Chaikoff


Access the most updated version of this article at http://www.jbc.org/content/234/11/2811.citation

Alerts:
- When this article is cited
- When a correction for this article is posted

Click here to choose from all of JBC's e-mail alerts

This article cites 0 references, 0 of which can be accessed free at http://www.jbc.org/content/234/11/2811.citation.full.html#ref-list-1