Dietary Regulation of 6-Phosphogluconate Dehydrogenase Synthesis*

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DANA PROCSAL, LARRY WIBNERRY, AND DAROLD HOLTEN

From the Department of Biochemistry, University of California, Riverside, California 92502

The relative rates of synthesis and degradation for rat liver 6-phosphogluconate dehydrogenase have been determined in animals maintained at several dietary states. Relative rates of synthesis were determined by pulse-labeling the enzyme either in live rats and determining the radioactivity in the purified enzyme or in whole cell suspensions of hepatocytes followed by precipitation of the enzyme with a specific antisera. The relative rate of synthesis of the enzyme in rats fed a high carbohydrate-fat-free diet was approximately 3.7 to 5.6 times greater than that in animals fed a pellet diet or in fasted rats, respectively. In contrast, a half-life of 13 to 19 hours was determined for the degradation of the enzyme in all three nutritional states. We have concluded that nutritional alterations in the levels of this enzyme in rat liver are caused by alterations in the rate of enzyme synthesis. Glucagon has no effect on the rate of synthesis of this enzyme.

In seeking to understand the regulation of enzyme levels in mammalian systems by diet and hormones, we have selected as models rat liver 6-phosphogluconate dehydrogenase (6-phospho-D-glucose:NADP+ oxidoreductase (decarboxylating), EC 1.1.1.44) and glucose-6-P dehydrogenase (6-glucose-6-phosphate:NADP+ oxidoreductase, EC 1.1.1.49), which catalyze the oxidative steps of the pentose phosphate shunt. The levels of these lipogenic enzymes are subnormal in fasted animals, and can be raised to supranormal levels by refeeding a high carbohydrate diet (1-3). Other lipogenic enzymes respond in a similar manner as the pentose phosphate shunt dehydrogenase to nutritional manipulation, suggesting that this group of functionally related enzymes is regulated in a coordinate fashion (4).

In previous studies, a kinetic analysis by the method of Berlin and Schimke (5) was employed to demonstrate that changes in the levels of the pentose phosphate shunt dehydrogenases induced by diet were the result of alterations in the rate of enzyme synthesis (6, 7). Significantly, the rates of 6-phosphogluconate dehydrogenase (6) and glucose-6-P dehydrogenase (7) synthesis were found to be directly proportional to dietary carbohydrate intake. The putative regulating agents inulin (8) and dietary fat (9, 10) were found to alter the levels of carbohydrate consumed, and thus to indirectly affect the rate of enzyme synthesis (6, 7).

The validity of the kinetic method is dependent upon a number of assumptions which have not been verified in the case of 6-phosphogluconate dehydrogenase. Thus, in this investigation, we have measured the relative rates of synthesis and apparent rate of degradation for 6-phosphogluconate dehydrogenase at several dietary states by an independent method involving the isolation of isotopically labeled enzyme. The results of these studies confirm the conclusion that the levels of rat liver 6-phosphogluconate dehydrogenase are controlled by regulating the rate of enzyme synthesis. Glucagon, which can inhibit the dietary induction of the lipogenic enzymes glucose-6-P dehydrogenase (11) and fatty acid synthetase (12), has no effect on the rate of synthesis of 6-phosphogluconate dehydrogenase. This enzyme thus appears to represent an excellent model for the regulation of enzyme synthesis by dietary factors since its synthesis is not complicated by a repression by glucagon.

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MATERIALS AND METHODS

**Materials—Salt mixture P-H, vitamin diet fortification mixture in dextrose, vitamin-free casein, cellulose (Alphacel), and dextrose were obtained from Nutritional Biochemicals; NADP+, NADPH, glucose-6-P, and 6-P-gluconate were purchased from Boehringer Mannheim. Glucagon and the ion exchange resins DEAE- and CM-cellulose were Sigma products. N,N'-Bis(2-hydroxyethyl)glycine was obtained from Calbiochem. The radioactive compound 1-[4,5-3H]leucine (1 Ci/mmol) was obtained from Amersham/Searle. 1-[14C]leucine (0.12 x 106 dpm/ml) and Protosol tissue solubilizer were New England Nuclear products. All other chemicals were reagent grade.

Treatment of Animals—Young male rats of the Sprague-Dawley strain (150 to 250 g) were obtained from a local supplier and housed in individual cages. Induced animals are defined as animals which were fasted for 48 hours and then refed a high carbohydrate-fat-free diet containing 60% glucose, 30% casein, 5% salt mixture, 2% vitamin mixture, and 3% cellulose. The composition of the salt and vitamin mixtures is described by Benevenga et al. (13). Pellet-fed rats were maintained on a Purina rat chow pellet diet. Fasted rats were fed a pellet diet prior to starvation. When food consumption was monitored, rats were pretrained to eat from nonspill metabolism feeders obtained from the Wahman Manufacturing Co.
Glucagon-treated rats were injected subcutaneously with 0.2 mg of glucagon/100-g rat. Glucagon injections were repeated at 6-hour intervals over a 48-hour time period. In experiments where rats were administered radioactively labeled amino acid, 125 μCi of [4,5-3H]leucine intraperitoneally. Glucagon injections were repeated at 6-hour intervals over a 48-hour time period. In experiments where rats were administered radioactively labeled amino acid, 125 μCi of [4,5-3H]leucine intraperitoneally.

Enzyme Activity Determinations—6-Phosphogluconate dehydrogenase (14) and glucose-6-P dehydrogenase (6) activity were measured as described previously by following the rate of production of NADPH as an increase in absorbance at 340 nm with the aid of a Gilford model 875 spectrophotometer. One unit of enzyme is defined as that amount of enzyme required to produce 1 μmol of NADPH/min. All enzyme assays were performed at 30°. Protein was determined by the method of Lowry et al. (15) and specific activity is expressed as units of enzyme activity/mg of protein.

Purification of 6-Phosphogluconate Dehydrogenase—A modification of the purification procedure described by Procasil and Holten (14) was employed to isolate rat liver 6-phosphogluconate dehydrogenase. Crude rat liver supernatant fractions were subjected to ammonium sulfate treatment as described previously (14). The precipitate fraction (at 50% saturation with ammonium sulfate) was dissolved in 25 mM potassium phosphate in 1 mM EDTA (pH 6.9). The column was eluted with equilibrating buffer until the absorbance at 280 nm was less than 0.01, the enzyme was eluted in a batchwise fashion with 30 mM potassium phosphate in 1 mM EDTA, pH 6.9. The column containing the 6-phosphogluconate dehydrogenase activity was pooled, dialyzed against 1 mM EDTA (pH 6.9), and applied to a small CM-cellulose column previously equilibrated with 5 mM potassium phosphate in 1 mM EDTA (pH 7.0). After washing the column with equilibrating buffer until the absorbance at 280 nm was less than 0.10, the enzyme was eluted in a batchwise fashion with 30 mM potassium phosphate in 1 mM EDTA, pH 6.9. After staining with trichloroacetic acid (17). In those cases where only one protein band through the DEAE-cellulose step) was added to 1 ml to bring the total enzyme activity to 4 units. An equivalent amount of anti-6-phosphogluconate dehydrogenase serum was added followed by incubation at 37° for 90 min. The reaction was stopped by the addition of the standard to the mixture in ice for 15 min, centrifuging, and sonicating in cold 0.15 M KCl. A postmicroscopic supernant fraction was prepared by centrifuging at 100,000 × g for 60 min.

Radioactivity incorporated into total soluble protein was determined as described above except that the protein was solubilized by papain digestion and the supernatant was filtered in a suitable nucleic acid solution. Only those preparations showing greater than 80% viability after staining with trypan blue were employed in these studies.

Radioactivity was incorporated into the enzyme by adding 20 μCi of [3H]leucine (specific activity 1 Ci/mmol) of cell suspension. The 19 other amino acids were added to a final concentration of 2 mM. After 1 hour of incubation the cells were washed twice with 90% 0.4 M KCl and then resuspended in a suitable nucleic acid solution. After 15 to 30 min, cells were gently dispersed and the suspension filtered through two layers of nylon mesh. Cells were washed several times with the supernatant of Krebs bicarbonate buffer by low speed centrifugation and then resuspended in a suitable nucleic acid solution. Only those preparations showing greater than 80% viability after staining with trypan blue were employed in these studies.

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of liver tissue. In addition, the homogeneity of purified preparations can be conveniently and reliably determined by the criterion of polyacrylamide disc gel electrophoresis.

The experiments summarized in Table I were designed to obtain an estimation of the rate of 6-phosphogluconate dehydrogenase synthesis by measuring the incorporation of isotope into the enzyme following the injection of radioactively labeled amino acid. Rats maintained at the indicated nutritional state were given a single injection of 125 μCi of [3H]leucine and sacrificed 30 min later. The radioactivity incorporated into that amount of 6-phosphogluconate dehydrogenase, and total soluble protein in 1 g of liver, is listed in Columns A and B, respectively. The results are expressed as the relative rate of synthesis (A/B) which is a measure of the rate of incorporation of isotope into 6-phosphogluconate dehydrogenase relative to that in total soluble protein. This calculation corrects for differences in the size of the amino acid pool and the amount of isotope administered. These data show the rate of 6-phosphogluconate dehydrogenase synthesis in the induced rat to be 3.5 times greater than that of the pellet-fed animal and 5.6 times greater than in a 48-hour fasted rat. These differences in the rate of synthesis are paralleled by a 2.7- or 8.7-fold greater enzyme activity in induced rats than in pellet-fed rats or 48-hour fasted rats, respectively.

These data provide strong evidence that the dietary induction of 6-phosphogluconate dehydrogenase is due to an increase in the rate of enzyme synthesis.

In these experiments only enzymes which were pure by the criteria of disc gel electrophoresis were counted for induced or pellet-fed rats. However, the enzyme isolated from fasted rats always appeared to contain two or three minor contaminating proteins in addition to 6-phosphogluconate dehydrogenase. Unfortunately, the limited amount of radioactivity per mg of purified 6-phosphogluconate dehydrogenase was not sufficient to allow us to subject the enzyme to electrophoresis, slice the gel, and demonstrate a coincidence of radioactivity with enzyme. We therefore employed the method of Berry and Friend (19) to prepare whole cell suspensions of hepatocytes from induced, pellet-fed, and fasted rats. These cells, when incubated with [3H]leucine, showed a much higher incorporation of radioactivity into protein and allowed us to isolate, by immunoprecipitation with a specific antibody against 6-phosphogluconate dehydrogenase, very highly labeled enzyme.

The monospecific nature of this antiserum is demonstrated in Fig. 1. Whole cell suspensions were prepared from livers from induced, pellet-fed, and fasted rats and these were incubated with [3H]leucine as described under "Materials and Methods." The postmicrosomal supernatant fraction from each liver, 1 ml, was allowed to react with 6-phosphogluconate dehydrogenase antiserum and the resulting immunoprecipitate was reduced, alkylated, and subjected to electrophoresis on 10% polyacrylamide gels in the presence of 0.1% sodium dodecyl sulfate and 6 M urea (21). Gels were then scanned at 280 nm in a Gilford linear analyzer prior to being frozen and cut into 1-mm slices which were extracted with Protosol (20) and counted for 3H. The only radioactive peak coincided exactly with the migration observed with 6-phosphogluconate dehydrogenase standards. Furthermore, the amount of radioactivity in 6-phosphogluconate dehydrogenase was considerably reduced in animals which were fed the pellet diet and lower yet in fasted animals. The radioactivity in these peaks has been normalized to a constant amount of radioactivity incorporated into total soluble protein and is therefore proportional to the relative rate of enzyme synthesis. In a second, control immunoprecipitate the 3H-labeled supernatant fraction from an induced liver was treated with 6-phosphogluconate dehydrogenase antiserum and the resulting immunoprecipitate was

### Table I

Relative rates of synthesis for 6-phosphogluconate dehydrogenase determined in live rats

<table>
<thead>
<tr>
<th>Nutritional state</th>
<th>1H Leucine incorporation</th>
<th>Relative rate of synthesis</th>
<th>Enzyme specific activity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6-Phosphogluconate dehydrogenase (A)</td>
<td>Total soluble protein (B)</td>
<td>(A/B x 10^4)</td>
</tr>
<tr>
<td>Induced</td>
<td>1.6 x 10^8</td>
<td>1.8 x 10^4</td>
<td>89</td>
</tr>
<tr>
<td>Pellet-fed</td>
<td>1.0 x 10^9</td>
<td>2.1 x 10^4</td>
<td>90</td>
</tr>
<tr>
<td>Fasted (a)</td>
<td>0.55 x 10^8</td>
<td>2.5 x 10^4</td>
<td>24</td>
</tr>
<tr>
<td>Fasted (b)</td>
<td>0.4 x 10^8</td>
<td>1.6 x 10^4</td>
<td>25</td>
</tr>
</tbody>
</table>

Fig. 1. Specificity of the antiserum raised against rat liver 6-phosphogluconate dehydrogenase (6PGDH). Rats were maintained on a Purina rat chow pellet diet, fasted for 2 days, or fasted for 2 days, and refed a high carbohydrate/fat-free diet for 4 days (induced rats). Whole cell suspensions of hepatocytes were prepared, labeled with [3H]leucine, and immunoprecipitated as described under "Materials and Methods." The immunoprecipitates were then subjected to electrophoresis (after reduction and alkylation) in the presence of 0.1% sodium dodecyl sulfate and 6 M urea. Gels were sliced, extracted with Protosol, and counted. Arrows indicate the positions of goat IgG H and L chains used as internal standards and the 6-phosphogluconate dehydrogenase subunit.
Table II

Relative rates of 6-phosphogluconate dehydrogenase synthesis determined using whole liver cell suspensions

The three nutritional states were produced as in Table I except rats were fasted for 48 hours only. Each number represents a single animal. Whole cell suspensions, immunoprecipitations, and disc gel electrophoreses were done as described under “Materials and Methods” and the legend to Fig. 1. The dpm in 6-phosphogluconate dehydrogenase were calculated by summing the radioactivity under the 6-phosphogluconate dehydrogenase peak and correcting for the 14% efficiency with which radioactivity in the enzyme is recovered from polyacrylamide gels (unpublished observations).

<table>
<thead>
<tr>
<th>Nutritional state</th>
<th>6-Phospho-</th>
<th>Soluble</th>
<th>Relative rate of Specific activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>state</td>
<td>glucose</td>
<td>protein</td>
<td>synthesis</td>
</tr>
<tr>
<td></td>
<td>dehydro-</td>
<td>× 10^{-7}</td>
<td>A/B × 10^{4}</td>
</tr>
<tr>
<td></td>
<td>genase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>dpn</td>
<td>dpn</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasted</td>
<td>4.92</td>
<td>1.06</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>4.48</td>
<td>1.31</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>2.96</td>
<td>0.98</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>7.92</td>
<td>1.41</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Induced</td>
<td>2.52</td>
<td>1.71</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>1.74</td>
<td>1.84</td>
<td>9.5</td>
</tr>
<tr>
<td></td>
<td>1.45</td>
<td>1.76</td>
<td>8.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>11 ± 2</td>
</tr>
<tr>
<td>Pellet-fed</td>
<td>0.99</td>
<td>1.05</td>
<td>9.4</td>
</tr>
<tr>
<td></td>
<td>0.79</td>
<td>1.35</td>
<td>5.9</td>
</tr>
<tr>
<td></td>
<td>1.32</td>
<td>1.91</td>
<td>6.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>7.4 ± 1</td>
</tr>
</tbody>
</table>

*a* Mean ± standard error.

removed. Then an identical amount (4 units) of nonradioactive enzyme was added and precipitated with antiserum as in the first immunoprecipitate. Although the total amount of protein present in the immunoprecipitate was identical in both cases, the second control precipitate showed no radioactivity above background. This demonstrates that all of the radioactive enzyme had been removed in the first immunoprecipitate and the washing procedure removes any nonspecifically absorbed proteins from that immunoprecipitate.

The data in Fig. 1 establishes that the radioactivity precipitated by the antiserum is indeed 6-phosphogluconate dehydrogenase and supports the data in Table I showing that the induction of this enzyme is due to an increase in the rate of enzyme synthesis. These experiments were repeated with additional animals and the data are reported in Table II. Once again the data completely support the contention that dietary alterations in the level of 6-phosphogluconate dehydrogenase in response to nutritional manipulation.

Rudack et al. (22) reported that the induction of rat liver glucose-6-P dehydrogenase which normally occurs when 48-hour fasted rats are refed a high carbohydrate fat-free diet can be inhibited by cyclic AMP or glucagon treatment. Subsequent studies revealed that glucagon inhibited the induction of the enzyme by preventing an increase in the rate of glucose-6-P dehydrogenase synthesis ([11]). These observations led us to investigate the effect of glucagon on the rate of 6-phosphogluconate dehydrogenase synthesis. Rats were fasted for 48 hours and then refed a 60% glucose fat-free diet for 2 days. Glucagon-treated rats received hormone injections every 6 hours while control rats were injected with saline. All of the animals were pulse labeled with 125 μCi of [3H]leucine 30 min before sacrificing and the relative rate of synthesis was determined as described under “Materials and Methods.” The results of the study, as presented in Table III, clearly demonstrate that neither the level of 6-phosphogluconate dehydrogenase nor the rate of synthesis of the enzyme was decreased by glucagon treatment. In marked contrast, the level of glucose-6-P dehydrogenase was lowered by as much as 50% in the same glucagon-treated animals.

**DISCUSSION**

In the experiments reported in Tables I and III and Fig. 2 we have purified 6-phosphogluconate dehydrogenase by column chromatography prior to measuring the radioactivity incorporated into the enzyme. It was therefore critical to establish the purity of these preparations. In our hands the best criteria for

The half-life \( t_{1/2} \) can be calculated from the equation \( t_{1/2} = \frac{0.693}{k_d} \).
relative rate of enzyme synthesis reported in Tables I and II is twice the value expected if there was a 33% decrease in the rate of enzyme degradation upon changing from the pellet-fed to the induced state. Thus, given the difficulties encountered in measuring protein degradation, we do not feel that the rate of 6-phosphogluconate dehydrogenase degradation in the pellet-fed state differs significantly from that in the induced or fasted state.

It has previously been reported from this laboratory that the half-lives for 6-phosphogluconate dehydrogenase in the induced and pellet-fed dietary state were 13.5 hours and 80 hours, respectively (7). These results were obtained by following the time course for a change in enzyme specific activity when animals were switched from one dietary steady state to a new steady state. The validity of the results obtained by this kinetic method is based upon the assumption that, after an initial lag phase, the rates of synthesis and degradation abruptly change to values characteristic of the new steady state.

The half-life of 19 hours for the enzyme in the induced state determined in this investigation is somewhat longer than the previously reported value of 13.5 hours. However, we consider these two values to be in good agreement since the half-life of 19 hours determined by the loss of radioactivity probably overestimates the true half-life due to the re-utilization of labeled leucine. It was not possible for us to correct for this re-utilization; however, Poole (23) has reported that it is possible to minimize the error contributed by re-utilization by selecting an appropriate time period to measure protein degradation. Accordingly, our measurements were made over a 24- to 32-hour time period, and therefore our results probably overestimate the rate of 6-phosphogluconate dehydrogenase degradation by less than 20%. Thus, in this instance, we have been able to confirm results obtained by the kinetic method.

The half-life (80 hours) for the enzyme in pellet-fed animals determined by the kinetic method greatly exceeds the value of 13 hours reported here. In view of this observation, it is clear that caution must be taken when interpreting results determined by the kinetic method, and that further confirmation by an independent method is required.

The lack of any effect of glucagon on the rate of 6-phosphogluconate dehydrogenase synthesis indicated that levels of this enzyme are not regulated by cyclic AMP. Recent studies have shown that the levels of at least two other lipogenic enzymes (glucose-6-P dehydrogenase (11) and fatty acid synthetase (12)) are decreased by cyclic AMP. Thus there appear to be at least two types of mechanism regulating the synthesis of lipogenic enzymes. Glucose-6-P dehydrogenase and fatty acid synthetase may represent enzymes whose synthesis is regulated by both dietary and hormonal factors. 6-Phosphogluconate dehydrogenase may represent an enzyme whose rate of synthesis is regulated by dietary factors without an involvement of cyclic AMP.

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### Table III

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Enzyme level</th>
<th>Relative rate of synthesis</th>
<th>Carbohydrate consumption</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(units/mg protein)</td>
<td>(dpm/g liver)</td>
<td>kcal/100 g rat/day</td>
</tr>
<tr>
<td>Control</td>
<td>0.37</td>
<td>4.8 x 10^5</td>
<td>87</td>
</tr>
<tr>
<td>Glucagon</td>
<td>0.24</td>
<td>3.3 x 10^5</td>
<td>130</td>
</tr>
</tbody>
</table>

Activity when fasted animals are switched to the induced dietary state. It was surprising, therefore, that the enzyme was apparently degraded more rapidly in pellet-fed animals. If the half-life was 13 hours in the pellet-fed rat then one would expect in the induced animal a 33% decrease in the rate of degradation and a correspondingly smaller increase in the rate of enzyme synthesis. However, the 3.6- to 3.8-fold greater relative rate of enzyme synthesis reported in Tables I and II is twice the value expected if there was a 33% decrease in the rate of enzyme degradation upon changing from the pellet-fed to the induced state. Thus, given the difficulties encountered in measuring protein degradation, we do not feel that the rate of 6-phosphogluconate dehydrogenase degradation in the pellet-fed state differs significantly from that in the induced or fasted state.

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