A Theoretical Study of Hepatic Glycogen Metabolism*

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SUMMARY

Hepatic glycogen metabolism is investigated with the aid of a mathematical model under the assumptions of steady state conditions for glucose 6-phosphate, glucose 1-phosphate, and uridine diphosphate glucose, and constant concentrations of adenosine triphosphate, uridine triphosphate, inorganic phosphate, and pyrophosphate. The model, which includes a constant rate of gluconeogenesis, contains 32 input parameters, and is based on enzymatic reaction mechanisms and kinetic data in vitro pertaining to six reactions which interconvert blood glucose and liver glycogen. Calculations in the model have been programmed for the IBM-1620 digital computer.

The predicted rates of net glucose production and net glycogen synthesis and the steady state concentrations of glucose-6-P and UDP-glucose compare favorably with experimental observations. The glucose-1-P concentration is shown to be near the equilibrium concentration in the phosphoglucomutase reaction. The predicted glucose threshold for net glycogen synthesis is 90 mg/100 ml, and the predicted glucose threshold for net glucose production is 149 mg/100 ml.

The results indicate that the hepatic glycogen system is well stabilized in that a 100-fold change in the glucose concentration, from 5 to 500 mg/100 ml, produces about a 2-fold change in the steady state concentrations of the components and in most enzymatic rates. If the inorganic phosphate concentration is taken as a decreasing function of the glucose concentration, the steady state intermediates are further stabilized but more net glucose production and glycogen synthesis result.

It is shown that the rate of gluconeogenesis accounts for the separate hepatic thresholds for net glucose production and net glycogen synthesis and for the latter threshold occurring within the normal glucose concentration range.

The results imply that mass action effects are more important than the dependence of glycogen synthetase on glucose-6-P in determining the steady state concentration of UDP-glucose.

In the model, phosphoglucomutase and UDP-glucose pyrophosphorylase are near equilibrium, and the amount of either enzyme is not critical. The amount of glucokinase, glucose 6-phosphatase, glycogen synthetase, or phosphofructokinase is critical even though these enzymes may not be "rate-limiting" on the basis of maximal velocity data.

The necessity of considering UDP-glucose pyrophosphorylase as a reversible reaction is established on the basis of maximal velocity data and from the point of view of glycogen synthetase being an effective control point in the system.

It is shown that the dependence of glycogen synthetase on glucose-6-P severely limits enzymatic activity but that it allows the enzymatic rate to vary more extensively with changes in the glucose-6-P and UDP-glucose concentrations.

The results suggest that the assumption that the reactions occur in a homogeneous phase without compartments is not a good one, and the possibility of two pools of glucose-6-P and glucose-1-P is suggested.

A simulation of fasting or diabetes produces results consistent with experimental observation. A simulation of the early effects of glucocorticoid administration raises the question of increased glucose production under conditions of a nonincreasing glucose-6-P concentration.

The liver plays an important role in the regulation of the glucose concentration in the blood; it stores glucose as glycogen and it produces glucose anew by gluconeogenesis (1, 2).

The present study considers these hepatic functions in the context of a mathematical model of hepatic glycogen metabolism based on the kinetics of the reactions which interconvert blood glucose and liver glycogen. The study illustrates the value of using kinetic data in vitro in predicting physiological characteristics of the system in vivo. Several factors which influence the system are examined, the assumption that the reactions occur in a homogeneous phase without compartments is evaluated, and certain abnormal metabolic states are successfully simulated.

There have recently appeared related studies and models of the glycolytic pathway which are based on kinetic data (3, 4).

METHOD

Assumptions and Description of Model—The reactions considered in the model are depicted in Fig. 1.† Since the liver cell mem-

† In figures, tables, and equations the following nonstandard abbreviations appear: G, glucose; P, inorganic phosphate; PP,
brane is freely permeable to glucose (5, 6), this membrane is neglected in the model and the blood and liver glucose concentrations are assumed equal.

A constant production of glucose-6-P by gluconeogenesis is signified in Fig. 1 as GNEO. Although GNEO is used to simulate gluconeogenesis, the term reflects the net effect of the glycolytic and oxidative pathways which utilize glucose-6-P and the gluconeogenic pathway which produces glucose-6-P. The constant rate of GNEO is taken as 1 × 10⁻⁴ M per min, which corresponds approximately to the value obtained for the total incorporation of labeled pyruvate into glucose and glycogen in liver slices (7).

The branching and debranching of glycogen are ignored in the model. This assumption is compatible with the observations of Stetten and Stetten (8) that the ratio of unbranched to branched residues is at least 12 and that active glycogen turnover occurs at the periphery of the molecule. Other reactions involving UDP-glucose in transformations to UDP-galactose and UDP-glucuronic acid are excluded for simplicity and because they are not directly concerned with glycogen storage.

The rates of the enzymatic reactions are specified in terms of kinetic data in vitro obtained from the literature, and interpreted in terms of the individual reaction mechanisms using the Briggs-Haldane kinetic theory (9). The enzymatic rate equations were derived directly from the reaction mechanisms by making the steady state assumption for the enzyme substrate complexes (10, 11); some of the derivations were checked by the King-Altman technique (12). The enzymatic mechanisms and rate equations appear in Table I.

The rate equation for glucokinase is a modified Briggs-Haldane equation where ⁴ is the maximum velocity, and the kinetic constant of one substrate was determined in the presence of a high concentration of the other substrate. The empirical equation is consistent with the data of Salas et al. (13), the poorly understood inhibition by ADP being omitted. In the normal well fed animal, glucokinase accounts for at least 80% of hepatic phospho-

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Table I

**Enzymatic mechanisms and rate equations**

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Reaction Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glucokinase</strong></td>
<td>ATP + G + $E_1$ → G-6-P + ADP + $E_1$</td>
</tr>
<tr>
<td><strong>Glucose 6-phosphatase</strong></td>
<td>G-6-P + $E_2$ → G + P + $E_2$</td>
</tr>
<tr>
<td><strong>Phosphoglucomutase</strong></td>
<td>G-6-P + $E_3$ → G-1,6-di-P + $E_3$</td>
</tr>
<tr>
<td><strong>UDP-glucose pyrophosphorylase</strong></td>
<td>UTP + G-1-P + $E_4$ → UTP + G-1-P + $E_4$</td>
</tr>
<tr>
<td><strong>Glycogen synthetase</strong></td>
<td>G-6-P + $E_5$ → G-1-P + UDPG + P + $E_5$</td>
</tr>
<tr>
<td><strong>Phosphorylase</strong></td>
<td>AMP + $E_6$ → G-1-P + P</td>
</tr>
</tbody>
</table>

**Notes:**
- A symbol represents a compound in the chemical equations (reaction mechanisms), and that same symbol represents the concentration of that compound in the mathematical equations (rate equations).
- The 32 input constants used in the model appear in Table II; the values were obtained directly from the literature with the following exceptions. The constant concentrations of UTP and PPi were chosen to simplify the calculations. The reported UTP and PPi concentrations coupled with an observed UDP-glucose concentration of $3 \times 10^{-4}$ M (44) and a physiological enzymatic activity; although there is a precedent for these control mechanisms in muscle, they have not been reported in liver.
TABLE II

Kinetic data and constant concentrations used in model

If a value used in the model differs significantly from those in available experimental reports, the latter appear in brackets; these deviations are discussed in the text. Except where noted, the values pertain to liver. The units of the velocity constants and GNEO are moles per liter per min; those for the kinetic constants and the constant concentrations are moles per liter.

<table>
<thead>
<tr>
<th>Kinetic data</th>
<th>Value used</th>
<th>Remarks</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_1$</td>
<td>$2.00 \times 10^{-4}$</td>
<td></td>
<td>(13, 14, 30–32)</td>
</tr>
<tr>
<td>$K_2$</td>
<td>$2.27 \times 10^{-2}$</td>
<td></td>
<td>(33)</td>
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<tr>
<td>$K_{ATP}$</td>
<td>$3.00 \times 10^{-4}$</td>
<td></td>
<td>(33)</td>
</tr>
<tr>
<td>$V_2$</td>
<td>$1.60 \times 10^{-2}$</td>
<td></td>
<td>(34, 35)</td>
</tr>
<tr>
<td>$K_{G-6-P}$</td>
<td>$2.00 \times 10^{-2}$</td>
<td></td>
<td>(17, 35, 36)</td>
</tr>
<tr>
<td>$V_{31}$</td>
<td>$1.04 \times 10^{-2}$</td>
<td></td>
<td>(37)</td>
</tr>
<tr>
<td>$V_{32}$</td>
<td>$3.77 \times 10^{-2}$</td>
<td></td>
<td>Calculated from $K_{eq}$</td>
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<tr>
<td>$K_{G-1-P}$</td>
<td>$8.65 \times 10^{-4}$</td>
<td>Muscle enzyme</td>
<td>(20)</td>
</tr>
<tr>
<td>$K_{G-L-P}$</td>
<td>$2.46 \times 10^{-3}$</td>
<td>Muscle enzyme</td>
<td>(20)</td>
</tr>
<tr>
<td>$V_{41}$</td>
<td>$1.06 \times 10^{-2}$</td>
<td></td>
<td>(37)</td>
</tr>
<tr>
<td>$V_{42}$</td>
<td>$5.90 \times 10^{-2}$</td>
<td></td>
<td>Brain enzyme</td>
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<tr>
<td>$K_{TP}$</td>
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<tr>
<td>$K_{TP}$</td>
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<td>Muscle enzyme</td>
</tr>
<tr>
<td>$V_5$</td>
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<td></td>
<td>Brain enzyme</td>
</tr>
<tr>
<td>$K_{S1}$</td>
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<td></td>
<td>(41)</td>
</tr>
<tr>
<td>$K_{S2}$</td>
<td>$4.50 \times 10^{-4}$</td>
<td></td>
<td>(26)</td>
</tr>
<tr>
<td>$K_{S4}$</td>
<td>$6 \times 10^{-4}$</td>
<td></td>
<td>(26)</td>
</tr>
<tr>
<td>$K_{S4}$</td>
<td>$1.25 \times 10^{-3}$</td>
<td></td>
<td>[5.00 $\times 10^{-3}$]</td>
</tr>
<tr>
<td>$V_{51}$</td>
<td>$3.12 \times 10^{-2}$</td>
<td></td>
<td>Calculated from $K_{eq}$</td>
</tr>
<tr>
<td>$V_{52}$</td>
<td>$1.00 \times 10^{-3}$</td>
<td></td>
<td>Muscle phosphorylase b</td>
</tr>
<tr>
<td>$K_{S4}$</td>
<td>$8.00 \times 10^{-4}$</td>
<td></td>
<td>Muscle phosphorylase b</td>
</tr>
<tr>
<td>$K_{AMP}$</td>
<td>$3.00 \times 10^{-4}$</td>
<td></td>
<td>Muscle phosphorylase b</td>
</tr>
<tr>
<td>$K_{G-L-P}$</td>
<td>$2.50 \times 10^{-4}$</td>
<td></td>
<td>Muscle phosphorylase b</td>
</tr>
<tr>
<td>$GNEO$</td>
<td>$1.00 \times 10^{-4}$</td>
<td></td>
<td>(7)</td>
</tr>
</tbody>
</table>

Constant concentrations

| ATP          | $2.00 \times 10^{-2}$ |          | (42, 43) |
| UTP          | $1.80 \times 10^{-2}$ |          | (42) |
| PP1          | $1.60 \times 10^{-5}$ |          | (5.00 $\times 10^{-5}$) | (42) |
| P1           | $3.00 \times 10^{-3}$ |          | (42) |
| AMP          | $2.60 \times 10^{-4}$ |          | (42) |

This value was taken from maximal rates of hepatic phosphorylation which include both glucokinase and hexokinase activity. Thus hexokinase has been incorporated in the model as glucokinase.

A value of $9 \times 10^{-5}$ M was recently reported for the liver enzyme (22).

The observed kinetic constant for glucose-6-P in the glycogen synthetase reaction of $6 \times 10^{-4}$ M was obtained at a UDP-glucose concentration about 10 times its kinetic constant. The rate equation for glycogen synthetase (Table I) predicts that the observed constant is actually $(K_{S1}K_{S4})/UDP-glucose$ (assuming $K_{S4}$ is infinite and $K_{S4}$ is zero, i.e. no catalysis without glucose-6-P).

Hence, $K_{S4}$, the dissociation constant of glucose-6-P, is calculated to be $6 \times 10^{-4}$ M. Smaller values, however, have been reported for the muscle enzyme (21).

$K_{S4} = k_3/k_4$ (see Table I).

The other deviations from experimental data involve the dissociation constant for glucose-6-P in the glycogen synthetase reaction ($K_{S4}$) and the maximum velocities of phosphorylase ($V_{41}$ and $V_{42}$). In order to have adequate synthetase activity while still assuming strong dependence on low concentrations of glucose-6-P (44), a small dissociation constant for glucose-6-P was chosen. The mechanism of the reaction (Table I) indicates that precise determination of this constant is difficult (Table II). Models with properties nearly identical with those of the present model...
and which use a larger dissociation constant were also constructed as part of this study. These models either operate at high, nonphysiological concentrations of glucose-6-P and UDP-glucose, or assume more total synthetase activity or partial dependence of the reaction on glucose-6-P.

The alteration in the maximum velocities of phosphorylase is necessary to ensure a physiological balance with glycogen synthetase; the reported maximum velocities of the two enzymes (Table II) are similar but the low glucose-6-P concentration severely limits synthetase activity. The necessary change in the phosphorylase velocities emphasizes the inadequacy of the phosphorylase reaction scheme which, for example, does not include the interconversion of active and inactive forms (46). The activity of this enzyme is nearly constant in the model. Although altering the maximum velocities is probably the simplest way of limiting the activity, changing any of the kinetic constants or constant concentrations in the rate equation would be equally effective. In the model the phosphorylase equation assumes a more important role in the study with a varying phosphate concentration (see "Results").

If changes in $K_{a1}$, $V_{a1}$, and $V_{a2}$ are not made, glycogen breakdown greatly exceeds glycogen synthesis, and the predicted glucose concentration at which the rates are equal exceeds 500 mg/100 ml, a value with no physiological meaning. The steady state concentrations of the intermediates are also several times the observed values.

Mathematical Model —The following system of differential equations expressing the rates of change of the concentrations of the components (Fig. 1) in terms of the enzymatic rate equations (Table I) constitutes the mathematical model of the system detailed in the previous paragraphs (the $v_i$ appear in Table I):

$$\begin{align*}
\frac{d(G)}{dt} &= v_1 - v_1 \\
\frac{d(G-6-P)}{dt} &= v_2 - v_2 + GNEO \\
\frac{d(G-1-P)}{dt} &= v_3 - v_3 + v_4 \\
\frac{d(UDPG)}{dt} &= v_5 - v_5 \\
\frac{d(Glyc)}{dt} &= v_6 - v_6
\end{align*}$$

If the steady state assumption is made for glucose-6-P, glucose-1-P, and UDP-glucose, this system reduces to

$$\frac{d(G)}{dt} = -\frac{d(Glyc)}{dt} + GNEO \tag{6}$$

This deduction from the mathematical model confirms the fact that under steady state conditions, net hepatic glucose production is the sum of net glycogen breakdown and gluconeogenesis. Inspection of the mathematical model also allows the further deduction that with constant concentrations of ATP, UTP, $P_i$, $PP_i$, and $5'AMP$, a specified glucose concentration determines the net rates of glycogen synthesis and glucose production, the steady state concentrations of the three intermediates, and the rates of the six enzymatic reactions. This algebraic calculation sequence (see "Appendix") which produces the steady state solution to Equations 1 to 5 has been programmed for the IBM-1620 digital computer in order to save time in repeating the process under a multitude of varying conditions. To shorten the calculations the glucose-6-P concentration is specified and the glucose concentration is calculated along with the steady state concentrations of glucose-1-P and UDP-glucose. The selection of a large constant UTP concentration and a small constant $PP_i$ concentration (see above) simplifies the calculations and avoids a cubic equation. Further simplification is obtained by assuming that the steady state assumption is made for glucose-6-P and UDP-glucose. The selection of a large constant UTP concentration and a small constant $PP_i$ concentration (see above) simplifies the calculations and avoids a cubic equation. Further simplification is obtained by assuming that the net rate of glycogen synthesis is small relative to the maximum velocities in the phosphoglucomutase reaction ($10^4$ versus $10^2 \text{ m per min}$). These simplifications introduce about a 12% error in the glucose-1-P concentration which occurs at high glucose concentrations.

RESULTS

The predicted net rates of glucose production and glycogen synthesis and the predicted steady state concentrations of glucose-6-P, glucose-1-P, and UDP-glucose are shown in Fig. 2. The predicted blood glucose threshold for net glycogen synthesis is about 90 mg/100 ml, and the predicted threshold for net glucose uptake is 149 mg/100 ml. The difference in the thresholds is accounted for by the constant rate of gluconeogenesis; at a particular threshold the appropriate derivative in Equation 6 is zero, and the derivatives for glucose and glycogen are not zero simultaneously unless GNEO equals zero. The model predicts that the steady state concentrations of glucose-6-P, glucose-1-P, and UDP-glucose increase with the glucose concentration.

The predicted rates of the enzymatic reactions are shown in Fig. 3. Under steady state conditions the rate of glucose 6-phosphatase ($v_2$) is the absolute rate of glucose production, and the rates of UDP-glucose pyrophosphorylase ($v_5$) and glycogen synthetase ($v_6$) are equal. Since the glucose-6-P concentration in the model rises as the glucose concentration increases (Fig. 2), the rate of glucose 6-phosphatase also increases with the glucose concentration.

The predicted enzymatic rates and steady state concentrations at glucose concentrations of 5 and 500 mg/100 ml are shown in Table III. Over the 100-fold change in blood glucose concentration, the concentrations of the intermediates are stabilized and change only about 2-fold. Glucokinase activity increases about 50-fold because of its large kinetic constant for glucose. Glycogen synthetase activity reflects increases in both the concentrations of glucose-6-P and UDP-glucose.

If the rate of glucose 6-phosphatase is plotted against glucose-6-P, phosphoglucomutase against glucose-6-P, UDP-glucose pyrophosphorylase against glucose-1-P, glycogen synthetase against glucose-6-P or UDP-glucose, and phosphorylase against glucose-6-P, linear curves result. Thus, with the exception of glucokinase, which is a nonlinear function of its substrate (Fig. 3), the model predicts that the other enzymatic rates are linear functions of their substrates, activators, or inhibitors over the glucose concentration range of 0 to 500 mg/100 ml.

In Table IV the predicted characteristics of the glycogen system are compared with observed characteristics. The thresholds for glucose production and glycogen synthesis depend on many factors, in particular, on the rate of gluconeogenesis. The limited rates of net glucose production and net glycogen synthesis are predicted by the model and are discussed later in terms of the homogeneous phase assumption. The predicted concentrations of glucose-6-P and UDP-glucose compare favorably with the observed concentrations; reliable estimations of glucose-1-P are not available.
FIG. 2. The normal glycogen system. The curve marked glycogen synthesis is the net rate of change of glycogen \((d(Glyc)/dt)\), and the curve marked glucose uptake is the negative rate of change of the glucose concentration \((-d(G)/dt)\) in molar per min \(\times 10^4\). The steady state concentrations of glucose-6-P, glucose-1-P, and UDP-glucose are shown in units of \(10^5\), \(10^6\), and \(10^4\) M, respectively.

Contribution of Individual Reactions—In the model gluconeogenesis enhances both glycogen synthesis and glucose production. The model predicts that gluconeogenesis accounts for \(\frac{1}{2}\) of the net glucose production at 5 mg/100 ml and \(\frac{1}{4}\) of net glycogen synthesis at 500 mg/100 ml. In considering the various sources of glucose-6-P in the model, gluconeogenesis provided \(\frac{1}{2}\) of the glucose-6-P at a glucose concentration of 5 mg/100 ml, \(\frac{1}{2}\) at 112 mg/100 ml, and \(\frac{1}{2}\) at 500 mg/100 ml.

If gluconeogenesis is deleted from the model, the predicted threshold for both glucose production and glycogen synthesis is about 130 mg/100 ml, which is above the normal blood glucose concentration. If gluconeogenesis is increased 3-fold, the threshold for glycogen synthesis falls from 90 to 35 mg/100 ml and the rate of synthesis increases about 50%; the threshold for glucose production rises from 149 to 210 mg/100 ml, and the rate of production increases about 25%. There is also a 15 to 20% increase in the steady state concentrations of the intermediates. Conversely, net utilization of glucose-6-P by the oxidative and glycolytic pathways (simulated by a negative GNEO of \(1 \times 10^{-4}\) M per min) results in the opposite changes: the thresholds for glycogen synthesis and glucose production become 165 and 100 mg/100 ml, respectively, and the rates of these processes and the steady state concentrations of the intermediates are diminished. Thus the model elaborates the important role played by gluconeogenesis in determining the separate thresholds for hepatic glycogen synthesis and glucose production.

The model predicts that the glycogen system is very sensitive to changes in the glucokinase reaction. If the amount of enzyme
Fig. 3. Individual enzymatic velocities. $v_1$, glucokinase; $v_2$, glucose 6-phosphatase; $v_3$, phosphoglucomutase; $v_4$, glycogen synthetase (or UDP-glucose pyrophosphorylase); and $v_6$, phosphorylase. The difference between the upper two curves is $d(G)/dt$; and the difference between the lower two curves, $d(Glyc)/dt$. Under steady state conditions $v_4 = v_5$ and $v_3 = d(Glyc)/dt$.

is decreased by 20% (simulated by a 20% decrease in $V_3$) the thresholds for glycogen synthesis and glucose production rise to 125 and 205 mg/100 ml, respectively, and glucose production and glycogen breakdown are enhanced. If the kinetic constant for glucose is increased by 20% (to 429 mg/100 ml), the two thresholds become 107 and 180 mg/100 ml, respectively. Thus the system is slightly more sensitive to the amount of enzyme than to the kinetic constant for glucose. Since the selected ATP concentration is nearly 10 times larger than its kinetic constant, decreasing this concentration by 25% produces minimal changes at glucose concentrations below 250 mg/100 ml, and increasing ATP has almost no effect on the system.

If the amount of glucose 6-phosphatase is increased by 50% (simulated by increasing $V_2$), glucose is produced at rates 1.5 to 2 times normal at all glucose concentrations below about 300 mg/100 ml. Even though phosphorylase is the “rate-limiting” enzyme in the pathway of glucose production (on the basis of the maximal velocity data in Table II), the model predicts that an increase in glucose 6-phosphatase activity greatly enhances glucose production.

The model predicts that the phosphoglucomutase reaction is never far from equilibrium with the equilibrium ratio of glucose-6-P to glucose-1-P of 12.7 occurring at 90 mg/100 ml; at 5 mg/100 ml the predicted ratio is 12.3, and at 500 mg/100 ml, 13.8. Only factors which alter the equilibrium constant (Table I), hence catalysis, in one direction more than in the other, affect the glycogen system; for example, decreasing by half the amount of enzyme has negligible effect on the system.
TABLE III

<table>
<thead>
<tr>
<th></th>
<th>Column A</th>
<th>Column B</th>
<th>Ratio (B:A)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose-6-P</td>
<td>$4.30 \times 10^{-4}$</td>
<td>$9.10 \times 10^{-4}$</td>
<td>2.1</td>
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<tr>
<td>Glucose-1-P</td>
<td>$3.60 \times 10^{-4}$</td>
<td>$6.51 \times 10^{-4}$</td>
<td>1.8</td>
</tr>
<tr>
<td>UDP-glucose</td>
<td>$3.59 \times 10^{-4}$</td>
<td>$6.08 \times 10^{-4}$</td>
<td>1.7</td>
</tr>
<tr>
<td>Glucokinase ($v_1$)</td>
<td>$1.97 \times 10^{-5}$</td>
<td>$1.01 \times 10^{-3}$</td>
<td>51</td>
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<tr>
<td>Glucose 6-phosphatase ($v_2$)</td>
<td>$3.37 \times 10^{-4}$</td>
<td>$6.96 \times 10^{-4}$</td>
<td>2.1</td>
</tr>
<tr>
<td>UDP-glucose pyrophosphorylase ($v_4$) or glycogen synthetase ($v_6$)</td>
<td>$4.24 \times 10^{-4}$</td>
<td>$1.0 \times 10^{-3}$</td>
<td>2.4</td>
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<tr>
<td>Phosphorylase ($v_6$)</td>
<td>$6.41 \times 10^{-4}$</td>
<td>$5.93 \times 10^{-4}$</td>
<td>0.92</td>
</tr>
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</table>

* Column A, glucose concentration, 5 mg/100 ml; Column B, glucose concentration, 500 mg/100 ml. Ratio of B:A, 100.

TABLE IV

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Predicted</th>
<th>Observed</th>
<th>Reference</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood glucose threshold for net glycogen synthesis</td>
<td>90 mg/100 ml</td>
<td>115-150 mg/100 ml</td>
<td>(5, 47, 48)</td>
<td>Studies in vivo in rats and dogs</td>
</tr>
<tr>
<td>Blood glucose threshold for net glucose production</td>
<td>149 mg/100 ml</td>
<td>1000 mg/100 ml</td>
<td></td>
<td>Fasted, anesthetized rats</td>
</tr>
<tr>
<td>Net rate of glycogen synthesis at 400 mg/100 ml</td>
<td>$3.6 \times 10^{-4}$ M/min</td>
<td>$3.4 \times 10^{-4}$ M/min</td>
<td>(49)</td>
<td>Liver slices: media rich in K⁺</td>
</tr>
<tr>
<td>Net rate of glycogen synthesis at 1000 mg/100 ml</td>
<td>$6.5 \times 10^{-4}$ M/min</td>
<td>$10 \times 10^{-4}$ M/min</td>
<td>(50)</td>
<td>Liver slices: media rich in K⁺</td>
</tr>
<tr>
<td>Net rate of glycogen synthesis at 500 mg/100 ml</td>
<td>$4.0 \times 10^{-4}$ M/min</td>
<td>$0.5-3 \times 10^{-4}$ M/min</td>
<td>(51)</td>
<td></td>
</tr>
<tr>
<td>Net glucose production at 80 mg/100 ml</td>
<td>$1.3 \times 10^{-4}$ M/min</td>
<td>$3 \times 10^{-4}$ M/min</td>
<td>(52)</td>
<td>Canine study in vivo (liver assumed to be 2.5% of body weight)</td>
</tr>
<tr>
<td>Net glucose production at 0 mg/100 ml</td>
<td>$3 \times 10^{-4}$ M/min</td>
<td>$9-18 \times 10^{-4}$ M/min</td>
<td>(53)</td>
<td>Liver slice: Pi concentration 10 times the concentration in the model</td>
</tr>
<tr>
<td>Absolute rate of glucose production (glucose-6-phosphatase) at 107 mg/100 ml</td>
<td>$4.8 \times 10^{-4}$ M/min</td>
<td>$5.6 \times 10^{-4}$ M/min</td>
<td>(54)</td>
<td>Canine study in vivo (liver assumed to be 2.5% of body weight)</td>
</tr>
<tr>
<td>Steady state concentration of glucose-6-P (80 mg/100 ml)</td>
<td>$5.6 \times 10^{-5}$ M</td>
<td>$5.5 \times 10^{-5}$ M</td>
<td>(44)</td>
<td>Rat liver</td>
</tr>
<tr>
<td>Steady state concentration of glucose-1-P (80 mg/100 ml)</td>
<td>$4.4 \times 10^{-4}$ M</td>
<td>$5.5 \times 10^{-4}$ M</td>
<td>(44)</td>
<td>Rat liver</td>
</tr>
<tr>
<td>Steady state concentration of UDP-glucose (80 mg/100 ml)</td>
<td>$4.0 \times 10^{-4}$ M</td>
<td>$3.0 \times 10^{-4}$ M</td>
<td>(44)</td>
<td></td>
</tr>
</tbody>
</table>

UDP-glucose pyrophosphorylase, like phosphoglucomutase, is never far from equilibrium; the minimum ratio of reactants and products is 0.7 and the equilibrium constant in the model is unity. Only factors which affect the equilibrium constant (Table I) affect the glycogen system; the system is relatively insensitive to changes in the amount of enzyme, and changing the constant concentrations of UTP and PP⁻ together has no effect.

Both the glucose-6-P and UDP-glucose concentrations increase with the glucose concentration (Fig. 2); hence, the UDP-glucose concentration is an increasing function of the glucose-6-P concentration. (A plot of UDP-glucose against glucose-6-P reveals an increasing function at all glucose-6-P concentrations corresponding to glucose concentrations of at least 5000 mg/100 ml.) On the basis of the law of mass action, UDP-glucose should reflect increases in its precursor, glucose-6-P; however, glycogen synthetase, which utilizes UDP-glucose, is totally dependent in this model on glucose-6-P, and an increase in this latter compound could produce a fall in UDP-glucose. The model predicts that the former mechanism predominates.

Glycogen synthetase responds more to changes in UDP-glucose than to changes in glucose-6-P. For example, if the equilibrium constant of phosphoglucomutase is arbitrarily taken to favor glucose-1-P formation, glucose-6-P falls but UDP-glucose rises, and there is a net stimulation of glycogen synthesis.

The model predicts two consequences of the dependence of glycogen synthetase on glucose-6-P. Since both glucose-6-P and UDP-glucose increase with the glucose concentration, the synthetase rate rises more than if the enzyme were independent of glucose-6-P (Table III). Secondly, because of the low intracellular concentration of glucose-6-P, dependence on glucose-6-P severely limits synthetase activity.
If the synthetase enzyme is taken as partially independent of glucose-6-P by including catalysis without glucose-6-P (a finite \(K_{34}\) and \(K_{44}\) greater than zero in Table I), there results a very significant increase in glycogen synthesis. Changes in the catalytic ability of the independent species \((k_2/k_3)\), which are akin to changes in the amount of enzyme, are of greater consequence than changes in the kinetic constant \((K_{34})\).

The rate of phosphorylase in the model is maintained nearly constant with a constant phosphate concentration of \(3 \times 10^{-3} \text{ M}\). If the phosphate concentration is varied from \(5 \times 10^{-4} \text{ M}\) at a glucose concentration of 5 mg/100 ml to \(1 \times 10^{-4} \text{ M}\) at a glucose concentration of 500 mg/100 ml (with the normal value occurring at 149 mg/100 ml), the glycogen system becomes a more responsive one (Fig. 4). There is more net glucose production and glycogen synthesis, yet the steady state concentrations of the intermediates show less variation than normal. Under these conditions the rate of phosphorylase varies nearly 3-fold over the glucose concentration range of 5 to 500 mg/100 ml, and the reaction assumes a more dynamic role in the glycogen system.

Simulations of Abnormal Conditions in Vivo—The model is used to simulate abnormal conditions in vivo by incorporating the various enzymatic changes which occur in these conditions. The results reflect the extent of the changes which are, in some cases, arbitrary.

In the fasting and diabetic animal, glucokinase activity falls about 50\%, glucose 6-phosphatase activity increases 50\%, and gluconeogenesis increases (1). The conditions are simulated by imposing a 50\% decrease in the maximum velocity of glucokinase, a 50\% increase in the maximum velocity for glucose 6-phosphatase, a 3-fold increase in the constant rate of gluconeogensi
Fig. 5. Fasting or diabetes. To simulate these abnormalities the maximum velocity of glucokinase is decreased 50%, that for glucose 6-phosphatase increased 50%, and GNEO increased 3-fold. The effect of hexokinase, which becomes more significant with decreased glucokinase activity, has not been included. Fig. 2 (broken lines) is presented for comparison.

(GNEO). The model (Fig. 5) predicts that glycogen is synthesized only at glucose concentrations greater than 285 mg/100 ml. At a glucose concentration of 500 mg/100 ml the rate of glycogen synthesis is one-eighth of normal. The liver produces glucose at all glucose concentrations below 1300 mg/100 ml. At a glucose concentration of 100 mg/100 ml the rate of glucose production is 4 times normal. The intermediates are decreased about 15% at low glucose concentrations and about 30% at high glucose concentrations. These results compare favorably with experimental observation, since the blood glucose threshold for hepatic glucose production in diabetic dogs reported by Madison et al. (2) is about 900 mg/100 ml, and lower concentrations of glucose-6-P and UDP-glucose are also found in fasting and diabetes (44, 55).

When glucocorticoids are administered to adrenalectomized animals the observations within 4 hours include an increased blood glucose concentration, increased glycogen synthesis, increased gluconeogenesis (measured as increased pyruvate incorporation into glucose), and an increase in total glycogen synthetase activity (7, 44, 56). (Glucose 6-phosphatase is not increased at 4 hours (7).) In the fasted, adrenalectomized animal glucocorticoids produce lowered glucose-6-P and UDP-glucose concentrations; in the fed, adrenalectomized animal these intermediates remain unaltered or show slight elevation at 6 hours (44). Glucocorticoid administration is simulated by a 4-fold increase in gluconeogenesis and a 50% increase in the maximum velocity of glycogen synthetase.

If these two changes are superimposed on the normal system
Hepatic Glycogen Metabolism

Fig. 6. Glucocorticoid administration to a fed animal. The maximum velocity for glycogen synthetase is increased 50% and GNEO is increased 4-fold. Fig. 2 (broken lines) is presented for comparison.

(fed animal) (Fig. 6), the model predicts glycogen synthesis at all glucose concentrations and at rates 2 to 3 times normal. Glucose production, however, is essentially unchanged, and there is almost no change in the concentrations of the intermediates except at high glucose concentrations. If the two changes are superimposed on the fasting condition where gluconeogenesis is already 3 times normal, the model predicts glycogen synthesis at glucose concentrations above 55 mg/100 ml and at rates 4 to 5 times the fasting rate. There is a slight decrease in glucose production and a 10% fall in the intermediates. If glucocorticoid administration were simulated by a larger than 4-fold increase in gluconeogenesis (or a smaller increase in glycogen synthetase), glucose production would be enhanced and the concentrations of the intermediates would increase.

DISCUSSION

The model of hepatic glycogen metabolism used in this study predicts characteristics which are difficult to determine experimentally. At glucose concentrations of 0 to 500 mg/100 ml, values are predicted for absolute and net rates of glucose production and glycogen synthesis and the steady state concentrations of glucose-6-P, glucose-1-P, and UDP-glucose. The glucose-1-P concentration, which is at the lower limit of experimental detection, is shown to be near the equilibrium concentration in the phosphoglucomutase reaction. The predicted characteristics compare favorably with observed characteristics (Table IV), and it is therefore concluded that with the present system kinetic data in vitro are useful in predicting many physiological characteristics of a system of biochemical reactions in vivo.
Several reasonable hypotheses about the system are put forth. The results suggest that mass action effects are more important than the dependence of glycogen synthetase on glucose-6-P in determining the steady state concentration of UDP-glucose. They also suggest that the glycogen system is well stabilized, with a 100-fold change in the glucose concentration producing about a 2-fold change in the other components. The P1 concentration, which affects phosphorylase activity, further stabilizes the intermediates and produces more glucose production and glycogen synthesis. Morgan and Parmeggiani (57) have emphasized the role of P1 in controlling glycogenolysis in heart muscle.

The model points out the important role of gluconeogenesis in determining the separate hepatic thresholds for glucose production and glycogen synthesis. Without gluconeogenesis the threshold for glycogen synthesis would be above the normal blood glucose concentration range, and continual glycogen breakdown would be occurring at normal glucose concentrations. Inordinately high or sustained postprandial glucose concentrations would be required to supply the necessary store of glycogen.

The model emphasizes the distinction between enzymes which are reversible in their physiological setting (phosphoglucomutase and UDP-glucose pyrophosphorylase) as opposed to physiologically irreversible enzymes (the four other). With a reversible enzyme only factors which affect the equilibrium constant, hence catalysis in one direction more than the other, affect the glycogen system. The system is relatively insensitive to changes in the amount of these enzymes. On the other hand, the system is very sensitive to changes in the amount of enzyme in irreversible reactions because net glucose production depends on a balance between glucokinase and glucose-6-phosphatase, and net glycogen synthesis, on a balance between glycogen synthetase and phosphorylase. Even though phosphorylase is the "rate-limiting" enzyme in the pathway of glucose production on the basis of maximum velocity data (Table II), changing the amount of glucose-6-phosphatase definitely affects the glycogen system.

In this connection it is interesting to observe that the hormones which act on the glycogen system and which might affect catalysis of a reaction symmetrically act at the four irreversible steps and not on the two reversible reactions.

Even though UDP-glucose pyrophosphorylase always catalyzes the net formation of UDP-glucose in the model, the reverse reaction must be included. Of the six enzymes of the glycogen system, the pyrophosphorylase has the largest maximal velocity (59). Histochemical studies reveal a perinuclear distribution of a special compartment for glucose-6-P and glucose-1-P. Glucose 6-phosphatase is a microsomal enzyme (58) which catalyzes the net formation of glucose from glucose-6-P in the presence of glucose-1-P and glycogen results in net UTP utilization. (The cyclic interconversion of glucose-1-P and glycogen results in net UTP utilization.)

The inconsistency between the predicted and observed behavior of glucose-6-phosphatase, the limited glucose production predicted by the model, and the net utilization of ATP and UTP could be avoided by assuming a special compartment for glucose-6-phosphatase and phosphoglucomutase and two pools of glucose-6-P and glucose-1-P. Glucose-6-phosphatase is a microsomal enzyme (59). Histochemical studies reveal a perinuclear distribution for the enzyme in liver (60) and in the β-cell of the pancreas. The limitation of glucose-6-phosphatase to glucose-6-P would limit the amount of glucose released into the circulation. If the kinetic constant for glucose were orders of magnitude below the physiological glucose concentration, with hexokinase, the phosphorylation rate would be independent of the glucose concentration (possible inhibition by glucose-6-P being neglected). The larger the kinetic constant for glucose, the more sensitive the phosphorylation reaction to the glucose concentration.

The kinetic data in Table II are of two types: maximum velocity constants which reflect the total amount of enzyme and kinetic constants for the substrates (and activators). Generally speaking, changes in the maximum velocity produce greater changes in the kinetic rates than do changes in the kinetic constants, because the substrates or activator concentrations often attenuate the changes in the kinetic constants. However, where the substrate concentration is much smaller than the kinetic constant, as with glucose-6-phosphatase, the kinetic constant behaves as the inverse of the maximum velocity constant.

One purpose of the study was to evaluate the assumption that the reactions occur in a homogeneous phase without compartments. For many reasons it appears that this is not a good assumption. First, the model predicts that the glucose-6-P concentration rises as the glucose concentration rises (Fig. 2), which is consistent with experimental observation (44, 55). A consequence of the homogeneous phase assumption in the model is that glucose and glucose-6-phosphatase must be present at the glycogen concentration. Morgan and Parmeggiani (57) have emphasized the role of P1 in controlling glycogenolysis in heart muscle.

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pancreas (61). The additional compartment would completely separate the glycogen synthetic and degradative pathways. Since gluconeogenesis stimulates both glycogen synthesis and glucose production, the glucose-6-P produced by this route should probably be included in both pools. The possibility of two hepatic glucose-6-P pools has been suggested by Segal and Lopez (62), among others.

An alternative but less likely hypothesis to explain the behavior of glucose 6-phosphatase would be the existence of an inhibitor of the enzyme. The inhibitor would have to be potent to overcome the increase in the enzymatic rate produced by the increase in glucose-6-P, and it would also have to increase with the glucose concentration. The inhibition by glucose itself is not adequate (18) nor does insulin affect the enzyme directly (63). Inorganic phosphate inhibits the enzyme slightly (17) but it is unlikely that the phosphate concentration increases with the glucose concentration. Furthermore, in comparison with glucokinase (and hexokinase), glucose 6-phosphatase activity is low owing to the low intracellular glucose-6-P concentration; inhibition of the enzyme would further lower this activity and would probably destroy the balance between hepatic phosphorylation and dephosphorylation and would result in a nonphysiological threshold for glucose production. Even with inhibition of glucose 6-phosphatase, net ATP utilization would still result.

The simulation of fasting and diabetes produces results which are consistent with the semiquantitative level with experimental observations. The simulation of the early effects of glucocorticoids shows no increase in hepatic glucose production. An increase in gluconeogenesis larger than the arbitrary 4-fold one imposed, or a smaller increase in glycogen synthetase, would result in increased net glucose production and elevated concentrations of the intermediates. If the liver contributes to the early hyperglycemia following glucocorticoid administration (64), it is difficult to reconcile the increased hepatic glucose output with the observations that glucose 6-phosphatase activity is low except at 4 hours (7) and that the glucose-6-P concentration is not increased (44). The question of two glucose-6-P pools again arises.

As is true with all theoretical formulations, the present model, which is based on experimental mechanisms and data and which predicts many physiological properties, cannot be considered the unique model of glycogen metabolism. The model assumes steady state conditions for glucose-6-P, glucose-1-P, and UDP-glucose. Other models can be constructed which assume lesser dependence of glycogen synthetase on glucose-6-P or which provide broader variation in phosphorylase activity, or where gluconeogenesis and the concentrations of ATP, UTP, and P1 are varied with the glucose concentration. Nor does this model include hormonal activity that varies with the glucose concentration such as may occur with insulin, epinephrine, and glucagon. Several features of the model in this study have been dictated by the availability of experimental data. Furthermore, errors in the input parameters affect the model to different degrees depending on the sensitivity of the system to a particular parameter. For example, in the glucokinase reaction a 20% change in the maximum velocity or in the kinetic constant of glucose produces significant changes in the system, whereas a 2-fold change in the kinetic constant for ATP or in the constant ATP concentration is of little consequence. These considerations taken together imply that the predictions of the present study, while suggesting quantitative trends and patterns, do not necessarily reflect the absolute amount or degree of change of the system in vivo.

Acknowledgments—The author is particularly grateful to Dr. Anthony F. Bartholomay for his continual interest, guidance, and encouragement in all phases of this work and in the preparation of the manuscript. He thanks Dr. Joseph B. Alpers for many helpful suggestions and fruitful discussions of the biochemistry and Miss Yuling Li for assistance in programming and operating the computer.

APPENDIX

Steady State Calculation Sequence—The following calculation sequence uses a glucose-6-P concentration and equations (A-1 to A-5) to calculate net rates of change of glucose and glycogen, the concentrations of glucose, glucose-1-P, and UDP-glucose, and the six enzymatic rates.\(^8\)

\[
\frac{d(G)}{dt} = v_1(G) + GNEO - v_2(G-6-P) \quad (A-1)
\]

\[
\frac{d(G-6-P)}{dt} = v_1(G) - v_2(G-6-P) - v_3(G-6-P, G-1-P) + GNEO = 0 \quad (A-2)
\]

\[
\frac{d(G-1-P)}{dt} = v_3(G-6-P, G-1-P) - v_4(G-1-P, UDPG) - v_5(G-6-P, G-1-P) = 0 \quad (A-3)
\]

\[
\frac{d(UDPG)}{dt} = v_4(G-1-P, UDPG) - v_5(UDPG, G-6-P) = 0 \quad (A-4)
\]

\[
\frac{d(Glyc)}{dt} = v_6(UDPG, G-6-P) = 0 \quad (A-5)
\]

With UDP-glucose in the steady state, \(v_6 = v_5\) and UDP-glucose may be expressed in terms of glucose-6-P and glucose-1-P and substituted into the expression for \(v_5\), yielding

\[
v_5 = v_6(G-6-P, G-1-P) \quad (A-6)
\]

With this substitution Equation A-5 becomes

\[
\frac{d(Glyc)}{dt} = \frac{d(Glyc)}{dt}(G-6-P, G-1-P) \quad (A-7)
\]

With glucose-1-P and UDP-glucose in the steady state, \(Glyc/ dt = v_6(G-6-P, G-1-P)\), or

\[
G-1-P = G-1-P(d(Glyc)/dt, G-6-P) \quad (A-8)
\]

Substituting A-8 into A-7 yields

\[
\frac{d(Glyc)}{dt} = \frac{d(Glyc)}{dt}(G-6-P) \quad (A-9)
\]

and the net rate of glycogen synthesis may be found at a given glucose-6-P concentration. Glucose-1-P is found from Equation A-8, and \(v_5\) is calculated from \(v_5\) and \(d(Glyc)/dt\) in Equation A-5. UDP-glucose is found from the \(v_5\) term in Equation A-4.

Having calculated \(d(G)/dt\) from

\[
\frac{d(G)}{dt} = -\frac{d(Glyc)}{dt} + GNEO \quad (A-10)
\]

\(v_1\) is found from Equation A-1, which is then used to obtain the glucose concentration. It is, of course, possible to start with the glucose concentration, but the calculations are more cumbersome.

Calculation of Kinetic Constants for Phosphorylase—Rate Equation A-11 is derived from the enzymatic mechanism in

\* The compounds that participate in each reaction are indicated in parentheses. \(V_i(x, y)\) denotes \(V_i\) is a function of \(x\) and \(y\).
\[ v = \frac{(V_1 \cdot K_{G-1-P}\cdot P) - (V_2 \cdot K_{G-1-P})}{(K_p \cdot G-1-P) + (K_{G-1-P}\cdot P) + (K_p \cdot K_{G-1-P})} \left( \frac{G-6-P}{K_{G+P}} + 1 \right) + 1 \]

(A-11)

where \( K_p = K_p \left( K_{AMP}/AMP + 1 \right) \). The latter expression implies that the observed kinetic constant for \( P_1 \) decreases with the activator, 5'-AMP, but that a plot of \( K_{AMP} \) against 1/AMP has slope \( K_p \cdot K_{AMP} \) and intercept \( K_p \) and \( K_{AMP} \) (Table II) are known from measurements of \( K_{AMP} \) at different glucose-1-P concentrations.

In the absence of glucose-6-P and one substrate, for example, glucose-1-P, Equation A-11 reduces to

\[ v = \frac{V_1 \cdot P}{P + K_p} \]

(A-12)

where \( K_{AMP} = \frac{1}{P} \cdot K_p \cdot K_{AMP} \).

This latter expression implies that the observed kinetic constant for 5'-AMP decreases with the substrate, glucose-1-P, but that a plot of \( K_{AMP} \) against 1/AMP has slope \( K_p \cdot K_{AMP} \) and intercept \( K_p \) and \( K_{AMP} \) (Table II) may be found from the data of Helrich and Cori (28). Equation A-12 may be rearranged to

\[ v = \frac{V_1 \cdot AMP}{AMP \left( \frac{P + K_p}{P} \right) + K_{AMP}} \]

(A-13)

where

\[ K_{AMP} = \left( \frac{1}{P} \right) \cdot K_p \cdot K_{AMP} \]

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