Evidence for the Coordinate Control of Glycogen Synthesis, Glucose Utilization, and Glycolysis in *Escherichia coli*

I. QUANTITATIVE COVARIANCE OF THE RATE OF GLUCOSE UTILIZATION AND THE CELLULAR LEVEL OF FRUCTOSE 1,6-DIPHOSPHATE DURING EXPONENTIAL GROWTH AND NUTRIENT LIMITATION*

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DAVID N. DIETZLER, MARY P. LECKIE, PEGGY E. BERGSTEIN, AND MAURA J. SUGHRUE

*From the Departments of Pediatrics and Pharmacology, Washington University School of Medicine, St. Louis, Missouri 63110*

In cultures of *Escherichia coli* W4597(K) and G34 under various nutritional conditions the rates of glucose utilization and cellular levels of fructose-1,6-P₂ are quantitatively related by the Hill equation where the value of the Hill coefficient is approximately equal to 2. This is the first evidence that fructose-P₂, or any metabolite which covaries with fructose-P₂, modulates glucose utilization in *E. coli*. In light of previous observations from our laboratory this new observation and those in the succeeding report provide the first evidence that in *E. coli* glycolysis, glycogen synthesis and glucose utilization are coordinately regulated, thus providing for the coupling of ATP utilization and production under various metabolic circumstances. Alterations in the level of ATP apparently affect the velocity of phosphofructokinase, the rate-limiting enzyme in glycolysis, altering the cellular levels of glucose-6-P or fructose-P₂.

Changes in the levels of these hexose phosphates are quantitatively related to alterations in the rates of glucose utilization and glycogen synthesis in the intact *E. coli* cell.

Previous studies (1-4) in this laboratory using *Escherichia coli* W4597(K) and G34 have provided quantitative evidence that the regulation of glycogen synthesis in *E. coli* proposed by others (5-7) on the basis of in vitro experiments does function in vivo. These two organisms were chosen for our previous studies because glycolan accounts for all of the glucose liberated on acid hydrolysis (8, 9), obviating the use of more complex enzymatic methods (10, 11) for the measurement of glycogen. While correlating the rates of glycogen synthesis in various nutritional states of these organisms with the cellular levels of the effectors of glycogen synthesis, we also noted that the rates of glucose utilization paralleled the cellular level of fructose-1,6-P₂. This last correlation is described here.

In this report we reproduce the observation of Sigal *et al.* (8) that the rate of glucose utilization by *E. coli* G34, an organism "leaky" for threonine, decreases when the exogenous supply of threonine is exhausted in the presence of excess glucose. We also demonstrate for the first time that time the rate of glucose utilization decreases when the exogenous supply of nitrogen (NH₄⁺) is exhausted in cultures of *E. coli* W4597(K) in the presence of excess glucose. In both cases glucose serves as the sole source of carbon and energy. The rates of glucose utilization per cell and cellular levels of fructose-P₂ are significantly higher during rapid exponential growth than during the nondividing stationary phase (NH₄⁺ limitation). The rate and fructose-P₂ level in slow exponential growth (threonine limitation) are between these two cases. Using the computer program of Atkins (12) we demonstrate that the rates of glucose utilization and cellular levels of fructose-P₂ are quantitatively related by the Hill equation where the value of the Hill coefficient is approximately equal to 2. This quantitative correlation is the first evidence that the cellular level of fructose-P₂ may play a role in the regulation of glucose utilization.

This new observation coupled with previous observations from our laboratory provide evidence that *E. coli* glycolysis, glycogen synthesis, and glucose utilization are coordinately regulated. The following report concerning the effects of dinitrophenol on metabolic processes in *E. coli* also provides evidence for the existence of coordinate regulation of these three processes. From the data in the subsequent report an empirical relationship is developed which quantitatively correlates the rate of glucose utilization and the cellular levels of fructose-P₂ and glucose-6-P.

**EXPERIMENTAL PROCEDURE**

**Organisms and Culture Techniques**

*Escherichia coli* G34, which was kindly provided by Dr. Harrison Echols (University of California, Berkeley), and W4597(K) are uridine diphosphate glucose pyrophosphorylase-negative derivatives of *E. coli* K12. *E. coli* G34 has an absolute requirement for leucine and is "leaky"
concentration during periodic intervals is maximum at the initiation of exponential growth (Figs. 1 and 2) as well as during the slower exponential growth (8). The concentration of glucose in cultures of either organism is linearly related to the concentration of protein during rapid exponential growth. The procedure described by Atkins (12) to determine the statistically most probable value of the kinetic constants of the Hill equation for a given set of data was modified for use on a desk-top calculator (Hewlitt-Packard 9810).

RESULTS

The generation times during rapid exponential growth of cultures of Escherichia coli W4597(K) and G34 were approximately 1.6 hours and for G34 in the absence of exogenous threonine were approximately 4.2 hours in the experiments presented here. A typical growth pattern of E. coli G34 in the presence and absence of exogenous threonine is demonstrated in Fig. 1. Typical growth patterns of E. coli W4597(K) under the experimental conditions used here have been described in detail (1, 2).

The concentration of glucose in cultures of either organism is linearly related to the concentration of protein during rapid exponential growth (Figs. 1 and 2) as well as during the slower exponential phase in cultures of E. coli G34 following the depletion of threonine (Fig. 1). The concentration of protein in each of these conditions is proportional to the cell density (1, 3) and thus the slopes of these lines are proportional to the rates for threonine (8). These cells were cultured aerobically at 32°C on a synthetic medium containing d-glucose as carbon source and NH₄Cl as nitrogen source in the amounts specified below; sulfate, phosphate, and minerals were maintained in all cases at the levels reported previously (1). The medium for E. coli G34 was supplemented with L-leucine and L-threonine. In the experiments described in this report the cells were cultured in the following manner.

E. coli W4597(K)-A culture containing 2.0 g of glucose and 0.18 g of NH₄Cl (limiting nutrient) was inoculated into 1 liter of fresh medium containing 2.0 g of glucose and depending on the experiment either 0.18 or 0.26 g of NH₄Cl (limiting nutrient). The newly inoculated culture served for the collection of samples for glucose, glycogen, and metabolite assays. After 0.25 hours of glucose starvation a 100-ml aliquot of this culture was inoculated into 1 liter of fresh medium containing 2.0 g of glucose, 1.0 g of NH₄Cl, 0.04 g of threonine (limiting nutrient), and 0.16 g of leucine/liter initially was grown overnigt and allowed to achieve glucose depletion. An absorbance of 1.0 at 450 nm (1-cm light path) corresponds to 150 mg of protein/liter of culture in strain W4597(K) and 130 mg/liter of culture in strain G34 (1, 3). At the onset of nitrogen starvation cultures of E. coli W4597(K) contained approximately 180 or 250 mg of protein/liter of culture depending on the initial concentration of NH₄Cl and, as has been previously observed (1), this concentration of protein was maintained throughout the period studied. The depletion of exogenous threonine occurred at a cell population equivalent to approximately 120 mg of protein/liter in cultures of E. coli G34 and was followed by a slower rate of exponential growth as previously observed by Sigal et al. (8).

Sample Collection and Metabolite Analyses

At periodic intervals during the 1.5-hour period of exponential growth immediately preceding nutrient depletion and during the first 3.0 hours of the nutrient-limited phase cells were rapidly collected as described by Lowry et al. (13) on a Millipore filter with suction, frozen, and extracted with HClO₄ and the extract was neutralized. ATP, glucose-6-P, and fructose-2-P in these extracts were measured by the fluorometric procedures of Lowry et al. (14, 15). At 0.25-hour intervals over a period of at least 5 hours in exponential growth and 3.0 hours during nutrient limitation, another aliquot was added to 0.1 volume of 100% trichloroacetic acid, the sample was centrifuged, and an aliquot of the supernatant fluid was neutralized with K₂HPO₄. Ammonium nitrogen was analyzed in these samples as reported previously (1); glucose was measured using glucose oxidase (Glucostat Technical Bulletin, Worthington Biochemical Corp.).

Rates of Nutrient Utilization

For both culture glucose and ammonium nitrogen during exponential growth the nutrient concentration is related to protein in the culture by the expression

\[ \frac{N_o - N}{P_o - P} = K_s \]

where \( N_o \) and \( P_o \) are the concentrations of nutrient and protein present in the culture at the initiation of exponential growth, \( N \) and \( P \) are the respective concentrations at any time during exponential growth, and \( K_s \) is a proportionality constant. Differentiating this relationship with respect to time yields

\[ -\frac{dN}{dt} = K_p \frac{dP}{dt} \]

During exponential growth

\[ \frac{dP}{dt} = \frac{\ln 2}{T} P \]

where \( T \) is the generation time, and substitution yields

\[ -\frac{dN}{dt} = \frac{\ln 2}{T} P_s \]

Therefore, the rate of utilization of the nutrient per weight of protein is constant throughout the exponential phase and since protein during this phase is proportional to cell density, this rate is proportional to the rate of utilization per cell. The slope of the regression line for a plot of nutrient concentration versus protein concentration in the culture during the exponential phase is equal to the constant \( K_s \). The value of the growth constant \( \ln 2/T \) can be obtained from the slope of the regression line for a plot of log absorbance versus time during the exponential phase. Multiplication of these two constants yields the constant rate of nutrient utilization per weight of protein in the exponential phase.

During the nitrogen-starved stationary phase the relationship expressing the disappearance of glucose in the culture over time is

\[ \frac{G_s - G}{t - t_s} = C_s \]

where \( G_s \) and \( t_s \) are the glucose concentration and the time after inoculation at the initiation of the stationary phase, \( G \) and \( t \) are the respective values of the glucose concentration and time at any time during the stationary phase, and \( C_s \) is a proportionality constant. Differentiating this relationship with respect to time yields

\[ -\frac{dC_s}{dt} = \frac{C_s}{P_s} \]

which is proportional to the constant rate per cell, during the stationary phase. The slope of the regression line for a plot of glucose in the culture versus time for the stationary phase is equal to the constant \( C \). The value of \( P_s \) can be obtained from the absorbance of the culture at the time nitrogen was exhausted (1). Division of the slope by \( P_s \) yields the constant rate of glucose utilization.

Determination of Kinetic Constants

The procedure described by Atkins (12) to determine the statistically most probable value of the kinetic constants of the Hill equation for a given set of data was modified for use on a desk-top calculator (Hewlitt-Packard 9810).
The rates of glucose utilization in each of the nutrient conditions can be calculated from these data as described under "Experimental Procedures," and in the legend to Fig. 2.

The growth of the organism in these conditions is demonstrated in the inset. The arrows indicate the depletion of the exogenous supply of threonine. The rates of glucose utilization in each of the nutrient conditions can be calculated from these data as described under "Experimental Procedures," and in the legend to Fig. 2.

The concentration of protein in cultures of this organism remains constant throughout this nondividing phase (1) and thus the slope of this line divided by the constant level of cellular protein yields a rate which is proportional to the rate of glucose utilization per cell.

The levels of fructose-6-P, ATP, and glucose-6-P in each of these conditions remained constant (that is, in steady state) throughout the periods studied (Table I). Variations in these levels in a particular experiment were within the limits of error of the analytical procedures. In all of these nutritional conditions the levels of glucose-6-P were essentially identical. The levels of ATP were similar in each of the cultures during nutrient limitation (10.9 to 12.3 μmol/g of protein) and the levels were higher than the levels observed in the fully alimented phase of growth (7.28 to 8.16 μmol/g of protein). It is true that the lower levels of ATP during fully alimented growth were accompanied by higher rates of glucose utilization and that the higher ATP levels during nutrient limitation correspond to lower rates of glucose utilization. But in each of these states the rates of glucose utilization varied at least 45%, while the levels of ATP remained relatively constant. Additionally it should be noted that in each of these states a change in the rate of glucose utilization is not always accompanied by a reciprocal change in ATP.

In contrast to the poor correlation between reciprocal changes in glucose utilization and ATP, a change in the rate of glucose utilization was paralleled in every case by a corresponding change in the level of fructose-P,

In contrast with other conditions initial duplicate studies of the rapid exponential growth phase of E. coli G34 exhibited quite different rates of glucose utilization (10.8 and 8.50 mmol/g of protein/hour) and fructose-P2 (11.4 and 7.80 μmol/g of protein) (Table I). Therefore two more examinations of this growth condition were conducted and in these cases quite similar rates of glucose utilization (9.81 and 9.60) and fructose-P2 levels (9.90 and 9.40) were observed and the values of both these parameters fell between the values observed in the initial experiments. However, in all cases the level of fructose-P2 paralleled the rate of glucose utilization, while there were essentially no differences in the levels of ATP or glucose-6-P.

The 10 values of the constant rates of glucose utilization (v) and the concomitant steady state levels of fructose-P2 (A) were fitted to the Hill equation (16)

\[ v = \frac{VA^n}{(A_{0.5}^n + A^n)} \]

using the digital computer program of Atkins (12). In this procedure the nonlinear regression of Wilkinson (17) is performed for a number of different values of n, the Hill coefficient. For each value of n, the regression yields a value for V (the maximal velocity), A0.5 (the concentration of fructose-P2 at which half-maximal velocity is obtained), and the sum of squares of residuals about the fitted curve. A plot of the sum of squares of residuals against the Hill coefficient yields a curve with a single minimum (12). The value of n at this minimum, along with the value of V and A0.5 determined for this n, provide the statistically most probable fit of a given set of data to the Hill equation. Using this procedure with the rates of glucose utilization and fructose-P2 levels presented here (Table I), the minimum sum of squares of residuals is obtained when n is equal to 2.29 (Fig. 3). At this value of n the values obtained for V and A0.5 are, respectively, 12.91 mmol/protein/hour and 5.86 μmol/g of protein (or, by division by 5 ml of cell water/g of protein (1), 1.16 mM). A plot of the Hill equation according to the linear rearrangement advocated by Hoffstee (18).
TABLE I

Cellular levels of fructose-1,6-P₂, ATP, and glucose-6-P and rates of glucose utilization during exponential growth and nutrient limitation of Escherichia coli W4597(K) and G34

The growth of the organisms, composition of the media, and glucose and metabolite assays are the same as those indicated under "Experimental Procedure." The rates of glucose utilization are expressed as millimoles of glucose utilized per g of protein per hour. Metabolites are expressed as micromoles per g of protein; each value represents the mean of determinations on at least five different extracts and the standard deviation is contained in parentheses. Fully alimented cultures were in the rapid exponential phase of growth. Cultures limited by lack of threonine grew at a slower exponential rate. Cultures starved for NH₄⁺ were in a nondividing stationary phase.

| E. coli Strain | Experimental Condition | Glucose Utilization | Fru-P₂ | ATP | Glc-6-P |
|---------------|------------------------|--------------------|--------|-----|---------|
| W4597(K)      | Fully Alimented        | 11.32              | 15.0 (0.6) | 8.16 (0.08) | 3.60 (0.14) |
| W4597(K)      | Fully Alimented        | 10.91              | 11.6 (0.6) | 7.28 (0.50) | 3.56 (0.36) |
| G34           | Fully Alimented        | 10.82              | 11.4 (0.4) | 7.50 (0.48) | 3.18 (0.24) |
| G34           | Fully Alimented        | 9.81               | 9.89 (0.54) | 8.10 (0.59) | 3.41 (0.21) |
| G34           | Fully Alimented        | 9.60               | 9.41 (0.27) | 7.63 (0.36) | 3.53 (0.27) |
| G34           | Fully Alimented        | 8.50               | 7.80 (0.64) | 7.98 (0.38) | 3.50 (0.20) |
| G34           | Threonine Limited      | 5.83               | 5.52 (0.19) | 11.6 (0.6) | 3.40 (0.09) |
| G34           | Threonine Limited      | 5.70               | 5.37 (0.14) | 12.3 (0.6) | 3.31 (0.13) |
| W4597(K)      | NH₄⁺ Starved           | 4.33               | 4.20 (0.30) | 10.9 (0.5) | 3.76 (0.09) |
| W4597(K)      | NH₄⁺ Starved           | 4.00               | 4.15 (0.34) | 11.5 (0.6) | 3.92 (0.26) |

Fig. 3. The optimum value of the Hill coefficient (n), which is attained at the minimum value of the sum of squares of residuals, obtained by performing the nonlinear regression of Wilkinson (16) on the rates of glucose utilization (v) and fructose-1,6-P₂ levels (A) taken from Table I.

\[ v = V - \frac{A}{A_{0.5}}^n \]

using the optimum Hill coefficient of 2.29 and the values of V and A₀.5 obtained in the computer analysis demonstrates the fit of the in vivo data reported here (Fig. 4).

DISCUSSION

It is clear from the experimental data presented here that a quantitative correlation exists between the rate of glucose utilization and the cellular level of fructose-P₂. The existence of a causal relationship between the two parameters is indicated by the quantitative correlation; however, it does not indicate which is cause and which is effect. The data of this report and those of the succeeding report (19), where the rate of glucose utilization varies over an approximately 3-fold range while the cellular level of fructose-P₂ remains constant, are difficult to interpret in terms of the rate of glucose utilization regulating the cellular level of fructose-P₂. However, in both cases it is possible to interpret the data in terms of an over-all mechanism for the coordinated control of glycogen synthesis, glucose utilization, and glycolysis, part of which involves the level of fructose-P₂ contributing to the regulation of glucose utilization.

The good fit of the rates of glucose utilization and the cellular levels of fructose-P₂ presented here to the Hill equation where the n for fructose-P₂ is approximately equal to 2 indicates that the relationship between these two parameters is...
that of the velocity of an enzyme and a positive allosteric effector of that enzyme. A similar relationship was observed in a prior report between the rates of glycogen synthesis in vivo and the cellular levels of fructose-P. Since in vitro fructose-P₂ is an allosteric activator of ADP-glucose synthetase, the rate-limiting enzyme of bacterial glycogen synthesis, it was possible to interpret that relationship as evidence that fructose-P₂ allosterically modulated ADP-glucose synthetase in the intact cell. However, no enzyme related to the utilization of glucose which is allosterically modulated in vivo by fructose-P₂ has been described. Thus, even though the data presented here are consistent with the cellular level of fructose-P₂ contributing to the regulation of the rate of glucose utilization, at present there is no evidence concerning the molecular site at which this regulation is exerted.

The relationship observed between the rate of glucose utilization and the level of fructose-P₂ may reflect the effect of a metabolite which covaries with fructose-P₂. Of the glycolytic intermediates only dihydroxyacetone-P and glyceraldehyde-3-P have been demonstrated to covary with fructose-P₂ in vivo. Thus any of these three metabolites could be the actual effector. At present it is not possible to precisely determine the levels of the triose phosphates in the cells used in the experiments presented here. For the sake of brevity, in subsequent parts of this discussion we will refer to the effects of fructose-P₂ on glucose utilization, but it should be kept in mind that fructose-P₂, in this context refers as well to dihydroxyacetone-P and glyceraldehyde-3-P. In the terms of the subsequent discussion it makes no difference which is the actual effector.

The usefulness of a mechanism whereby the cellular level of fructose-P₂ contributes to the regulation of glucose utilization is indicated by the following considerations. The increase in ATP which occurred at the onset of nutrient limitation apparently reflects the decreased use of ATP for net protein and nucleic acid synthesis. Since the level of ATP was maintained at a higher steady state level for approximately 3 hours following nutrient depletion, it is apparent that the decreased utilization of ATP was matched by a decreased ATP production. The decreased rates of glucose utilization which were observed following the transitions to nutrient starvations would provide for a decreased ATP production. Apparently these decreases in the rates of glucose utilization were not directly effected by the accompanying increases in ATP since significantly different rates of glucose utilization occurred in the presence of essentially the same level of ATP in the various nutrient depletions. It appears rather that the increased level of ATP, a negative effector of <i>E. coli</i> phosphofructokinase in vitro in certain conditions (23), serves as an indirect control of glucose utilization by decreasing the activity of this enzyme. A decrease in the activity of phosphofructokinase would be expected to result in a decrease in the level of fructose-P₂ as we have observed in each of these cultures following nutrient limitation.

According to the interpretation we have presented for the observed quantitative relationship between the rate of glucose utilization and the cellular level of fructose-P₂, the decrease in fructose-P₂ would effect a decrease in the rate of glucose utilization, thus decreasing the production of ATP and completing the coupling of ATP production and utilization. The interpretation that fructose-P₂ is a positive effector of glucose utilization also provides an important link in presenting a unified mechanism for the Pasteur effect in the intact <i>E. coli</i> cell. The mechanism of the Pasteur effect will be discussed in detail in the succeeding report.

This report provides evidence that fructose-P₂ is an allosteric activator of glucose utilization in vivo and is the first evidence for any allosteric regulation of glucose utilization. Previous reports from this laboratory have provided evidence that fructose-P₂ is an activator of glycogen syntheses (3, 4) and that glucose-6-P is an inhibitor of glucose utilization (19) in vivo. When all of these observations are correlated with the observations of the succeeding report evidence is provided for a mechanism whereby glycolysis, glucose utilization, and glycogen synthesis are coordinately regulated in the intact <i>E. coli</i> cell. This mechanism provides for the coupling of ATP utilization and production in various metabolic circumstances.

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4 Inhibition of <i>E. coli</i> phosphofructokinase by ATP in vitro is observed when the ratio of MgCl₂ to ATP is 1:1 (23); however, none is observed when this ratio is 10:1 (24). In <i>situ</i> slight inhibition is observed with a ratio of 2.5:1 (25).

4 An increase in the level of glucose-6-P would also be expected to accompany a decrease in the activity of phosphofructokinase; however, during nutrient limitation in each of the experiments presented here the level of glucose-6-P was maintained at the level present during the fully anaerobic phase of growth. Evidently the decreased utilization of glucose-6-P via the hexose monophosphate shunt (26) and glycolysis (events which would cause a rise in glucose-6-P) was balanced by the decreased conversion of extracellular glucose to intracellular glucose-6-P and the increased synthesis of glycogen (1) (events which would cause a fall in glucose-6-P).
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D N Dietzler, M P Leckie, P E Bergstein and M J Sughrue

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