Glucose Is Essential for Proliferation and the Glycolytic Enzyme Induction That Provokes a Transition to Glycolytic Energy Production*

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Erich F. Greiner, Michael Guppy, and Karl Brand

From the Institute of Biochemistry, Medical Faculty, University of Erlangen-Nuremberg, D-91054 Erlangen, Federal Republic of Germany, and the Biochemistry Department, University of Western Australia, Nedlands, Australia

A transition from aerobic to anaerobic metabolism occurs as mitogen-activated thymocytes undergo proliferation. Glucose utilization and lactate formation increases 18- and 38-fold, respectively, during proliferation. The absolute amount of \(^14\)C in lactate formation increases during proliferation. The absolute amount of \(^14\)CO\(_2\) production by pyruvate dehydrogenase remains constant, while \(^14\)CO\(_2\) production by the tricarboxylic acid cycle is reduced during transition from a resting to a proliferating state.

Addition of 2,4-dinitrophenol, an agent uncoupling oxidative phosphorylation and phenacetinemethosulfate, an electron acceptor, provide evidence that the reduction of glucose oxidation in proliferating thymocytes is caused neither by limitation of the tricarboxylic acid cycle itself nor by an insufficient supply of ADP. Our data suggest that enhanced cytosolic regeneration of NAD\(^+\) by induction of the glycolytic enzymes during proliferation effectively competes with NADH transport and its subsequent oxidation in the mitochondria.

Mitogen-stimulated rat thymocytes cultured in a conventional medium containing glucose induce their glycolytic enzymes 8-10-fold in the S phase of the cell cycle and divide within a culture period of 72 h. Replacement of glucose by glutamine, glutamine and ribose, or glutamine and uridine prevents glycolytic enzyme induction and thymocyte proliferation. The effect of glucose on glycolytic enzyme induction cannot be mimicked by 3-O-methylglucose or 2-deoxyglucose.

In conclusion, glucose is required for proliferation and the glycolytic enzyme induction that mediates the transition from oxidative to glycolytic energy production during the G\(_1\)/S transition of rat thymocytes.

Proliferating cells and tumor cells maintain a high glycolytic rate even under aerobic conditions. Observations on aerobic glycolysis in tumor cells prompted Warburg to postulate an altered respiratory function causing an increased glycolytic capacity and high rate of lactate formation from glucose in the presence of oxygen (Warburg et al., 1924; Warburg, 1956). Crabtree described the inhibition of oxygen consumption by the addition of glucose (Crabtree, 1929) resulting in enhanced aerobic glycolysis in tumor tissues. Data from former reports suggest that there are many aspects to the presumably multifactorial origin of aerobic glycolysis (for reviews, see Baggetto (1992) and Argiles and Lopez-Soriano (1990)). Altered control of glycolysis was discussed as a consequence of induction of isoenzymes with special features, in particular hexokinase (Arora and Pedersen, 1988), 6-phosphofructo-1-kinase (Dunaway and Kasten, 1985; Eigenbrodt et al., 1988), 6-phosphofructo-2-kinase (Hue and Rider, 1967; Crepin et al., 1989), and pyruvate kinase (Eigenbrodt and Glossmann, 1980; Noguchi et al., 1984). Alterations in the activity of Na\(^+\)-K\(^+\)-ATPase were documented, thus increasing the ADP availability and consequently the flow through pyruvate kinase (Racker, 1976). Furthermore, the increased cytosolic cyclic AMP, which is required to oxidize NADH cytosolically by lactate dehydrogenase (La Noue et al., 1977), so that qualitative and quantitative changes in enzyme activity and hexose transport account, at least in part, for aerobic glycolysis (Weinhouse, 1976; Weber, 1977; Eigenbrodt und Glossmann, 1980; Eigenbrodt et al., 1985; Brand et al., 1988; Board et al., 1990), but the interaction of the pathways of oxidative glucose metabolism and aerobic glycolysis in proliferating cells remains to be elucidated.

Rat thymocytes provide a useful tool to study the changes in energy metabolism occurring as cells undergo a transition from the resting to the proliferating state (Brand, 1985; Brand et al., 1988). Glucose and glutamine are the two major exogenous fuels for rat mesenteric lymphocytes (Ardawi and Newsholme, 1983) and rat thymocytes (Brand, 1985). Resting rat thymocytes degrade glucose at least partially aerobically to CO\(_2\), whereas proliferating cells metabolize glucose almost completely to lactate (Brand, 1985) indicating a profound Crabtree effect (Guppy et al., 1983). Increased rates of glycolysis in cultured proliferating human lymphocytes (Wang et al., 1976; Tollefsbol and Cohen, 1985) and rat thymocytes (Brand, 1985) have been reported to peak in concert with DNA synthesis. Enhanced glucose utilization in mitogen-activated lymphocytes has been shown to be accompanied by increased glycolytic enzyme activities (Ardawi and Newsholme, 1982; Tollefsbol and Cohen, 1985; Brand, 1985; Brand et al., 1988). In contrast to human lymphocytes (Marjanovic et al., 1990), no alteration in the isoenzyme pattern of glycolytic enzymes could be observed in rat thymocytes.

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† To whom correspondence should be addressed: Inst. für Biochemie, Medizinische Fakultät, Universität Erlangen-Nürnberg, Fahrstraße 17, D-91054 Erlangen, Federal Republic of Germany. Tel.: 49-9131-854620; Fax: 49-9131-854605.

1 The enzymes used are as follows: hexokinase, ATP:α-hexose-6-phosphotransferase (EC 1.4.1.3.); lactate dehydrogenase, +lactate:NAD\(^+\) oxidoreductase (EC 1.1.1.27); 6-phosphofructo-1-kinase, ATP:fructose-6-phosphate-1-phosphotransferase (EC 2.7.1.11); pyruvate kinase, ATP:pyruvate 2-O-phosphotransferase (EC 2.7.1.40).

E. F. Greiner and K. Brand, unpublished data.
Glucose-dependent Glycolytic Enzyme Induction and Its Effects on Glucose Metabolism

EXPERIMENTAL PROCEDURES

Materials—Female outbred Wistar rats (6-9 weeks old) were used for all experiments. [U-14C]glucose, [3,4-14C]glucose, and [U-14C]glutamine were obtained from Amersham Buchler (Braunschweig, Germany (FRG)). Concanavalin A (ConA),3 2-mercaptoethanol, EDTA, and Heps buffer were purchased from Serva (Heidelberg, FRG); RPMI 1640 medium without glucose, fetal calf serum, and antibiotics from Life Technologies, Inc. (Karlsruhe, FRG); RPMI 1640 medium from Biochrom (Berlin, FRG); 2-phenylethylamine from Fluka (Neu-Ulm, FRG); Rothiscint from Roth (Karlsruhe, FRG); and 2,4-dinitrophenol, and phenylmethanesulfonate from Sigma (Deisenhofen, FRG). Enzymes, coenzymes, and substrates used in metabolite and enzyme assays, and interleukin 2 (recombinant) were obtained from Boehringer (Mannheim, FRG). Proleukin was a product of Eurocetus (Frankfurt, FRG), Percoll was purchased from Pharmacia (Freiburg, FRG). Monoclonal antibody R 73 raised against the T-cell receptor of rat was developed by Hünig et al. (1989) and kindly provided by Dr. F. Eichmann (Erlangen, FRG).

Cell Preparation and Cell Culture—Thymocytes were prepared from the thymus gland of 6 to 9-week-old female outbred Wistar rats by teasing out the thymus through a nylon mesh into sterile phosphate-buffered saline containing 136.0 mM NaCl, 4.7 mM KCl, 1.3 mM CaCl2, 1.3 mM KH2PO4, 0.8 mM MgSO4·7H2O at pH 7.4 as described by Culvenor and Weidemann (1976). Large thymocytes, able to proliferate, were separated from non-dividing small thymocytes by Percoll density gradient centrifugation according to Salisburg et al. (1979). Large thymocytes (10-15% of total thymocytes) were stimulated either by concanavalin A (10 μg/ml) or by mitogenic monoclonal anti-T-cell receptor antibody cross-linked to anti-thymocytes) were stimulated either by concanavalin A (10 pg/ml) or by interleukin 2 (10 units/ml). ConA and interleukin 2. Incubations, 14CO2 collection, scintillation counting, and calculations were done as described by Brand (1986). Glucose was measured by the coupled hexokinase/glucose-6-phosphate dehydrogenase method described by Bergmeyer et al. (1974), lactate by the method of Gamewen and Bergmeyer (1974), and pyruvate by the method of Lammert and Neubert (1984). The contribution of the pentose phosphate pathway to glucose metabolism was calculated according to Katz et al. (1966), whereas the rates of the pyruvate dehydrogenase reaction and the tricarboxylic acid cycle were estimated by the release of 14CO2 from [3,4-14C]glucose and from [6-14C]glucose.

RESULTS AND DISCUSSION

Alterations of Glucose Metabolism during Transition from the Resting to the Proliferating State—Resting thymocytes utilize 42.6 ± 1.23 μmol of glucose/1010 cells/h, whereas proliferating cells consume 740 ± 5 μmol of glucose/1010 cells/h (Table I). Lactate production increases 38-fold as the thymocytes undergo the transition from the resting to the proliferating state. However, approximately 36 μmol of CO2 were produced from [U-14C]glucose in both cell cycle stages. Hence, even in the presence of oxygen, proliferating rat thymocytes metabolize 90% of the glucose utilized to lactate and oxidize less than 1% of the glucose to CO2, whereas resting thymocytes degrade 15% of the glucose oxidatively to CO2 (Table I).

To investigate the mechanism underlying the transition from partly aerobic to almost completely anaerobic glucose metabolism during cell cycle progression, experiments were conducted to delineate metabolic pathways by using different labeled 14C-glucose in proliferating cells compared to resting cells.

14CO2 production from [1-14C]glucose increases from 5.1 ± 0.51 to 11.6 ± 1.01 μmol/1010 cells/h during proliferation, whereas 14CO2 production from [3,4-14C]glucose remains constant (~21 μmol/1010 cells/h). However, 14CO2 production from [6-14C]glucose decreases by more than 50%, from 1.98 ± 0.19...
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The ratio of [3,4-14C]glucose produced by proliferating cells is 18 times less than that of resting cells. From these results one might assume that the capacity of pyruvate dehydrogenase is limiting, thus causing increased anaerobic glycolysis. However, comparison of the rates of glucose oxidation by the tricarboxylic acid cycle to the flux rates via pyruvate dehydrogenase reveals that only 9.3% of pyruvate dehydrogenase is completely degraded in the tricarboxylic acid cycle to CO₂ by proliferating cells, and only 19% by resting cells (Table II). This calculation is based on the assumption that all pyruvate except for pyruvate converted to lactate by lactate dehydrogenase is exclusively decarboxylated by pyruvate dehydrogenase to form acetyl-CoA. However, Curi et al. (1988) reported that the rate of conversion of [3-14C]pyruvate into 14CO₂ by 5 to 10-fold as compared to 1.5-fold in resting and more than 3-fold in proliferating cells, respectively, as judged from 14CO₂ release from [6-14C]glucose increases from 3.12 (5.10 - 1.98) μmol/10⁶ cells/hour in proliferating rat thymocytes to 10.7 (11.6 - 0.93) μmol/10⁶ cells/h as the thymocytes undergo transition from the resting to the proliferating state. The oxidative branch of the PPS cycle yields sufficient amounts of NADPH required for reductive biosyntheses and of precursors for nucleic acid synthesis by the de novo and salvage pathways. These have been determined to amount to 6.58 μmol/10⁶ cells/hour in proliferating rat thymocytes (Schobitz et al., 1991). Furthermore, the relative PPS activity can be enhanced to 16% or 13%, respectively, in both cell-cycle stages by adding phenazinemethosulfate (PPS), whereas the addition of 2,4-di-nitrophenol (2,4-DNP) nearly abolishes PPS activity (Table III). PPS, as an electron acceptor, was used to oxidize the reduced cosubstrates NADH and NADPH, thus preventing limitation of glucose oxidation by a potential deficiency of NADPH and NAD⁺. 2,4-DNP was used to uncouple oxidative phosphorylation, so that oxidative glucose metabolism becomes independent of the ADP supply.

<table>
<thead>
<tr>
<th>Addition</th>
<th>R = 6-[14C]glucose to 14CO₂</th>
<th>3,4-[14C]glucose to 14CO₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>0.19</td>
<td>0.093</td>
</tr>
<tr>
<td>2,4-DNP (0.100 mm)</td>
<td>0.34</td>
<td>0.18</td>
</tr>
<tr>
<td>PMS (0.050 mm/0.100 mm)</td>
<td>0.12</td>
<td>0.67</td>
</tr>
</tbody>
</table>

In summary, aerobic glycolysis is neither due to ADP limitation, nor to limitation by the pyruvate dehydrogenase reaction and the citric acid cycle, but may be due to a limitation of NAD⁺ and FAD supply for glucose oxidation.
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Oxygen consumption rates measured in the presence of glutamine alone compared to those observed in the presence of glucose and glutamine reveal that proliferating thymocytes do up-regulate oxidative metabolism under particular conditions but do not exhaust their capacity for oxidative metabolism whenever glucose is present (Guppy et al., 1993). Hence, no deficiency in mitochondrial oxidation per se can be postulated.

Proliferating cells seem to be able to oxidize increased amounts of NADH and FADH$_2$ generated by the oxidation of fatty acids and/or amino acids, but they cannot take advantage of this oxidative capacity for glucose metabolism. Perhaps NADH and FADH$_2$ generated by fatty and/or amino acid oxidation limit glucose oxidation by competing with the reduced cosubstrates produced by pyruvate dehydrogenase, the citric acid cycle, the glycerol-phosphate shuttle, or the malate-aspartate shuttle for oxidative phosphorylation. In addition, acetyl-CoA formed by fatty and/or amino acid oxidation could compete with the acetyl-CoA generated by pyruvate dehydrogenase as a substrate for the citric acid cycle, thus reducing glucose oxidation.

For the mitochondrial oxidation of the cytosolic-generated NADH, the electrons of this coenzyme have to be imported into the mitochondria either by the glycerol-phosphate shuttle or by the malate-aspartate shuttle. During tumor-bearing states these shuttles seem to be somehow impaired (LaNoue et al., 1977). The data obtained in thymocytes point to a competition between mitochondrial NADH oxidation and the utilization of NADH by lactate dehydrogenase for regeneration of (cytosolic) glycolytic NAD$^+$. Because of the marked induction of glycolytic enzymes in the S phase cells, it appears that the lactate dehydrogenase reaction outcompetes the hydrogen shuttles resulting in a decreased rate of entry of reducing equivalents into the mitochondria and their subsequent mitochondrial oxidation. This scenario is feasible despite the fact that lactate dehydrogenase is an equilibrium enzyme. Lactate dehydrogenase would not change its mass action ratio, but since there is a more than 10-fold induction of the enzyme, and since the enzyme is in equilibrium with the enzyme-substrate complex (ES), there is more ES and thus more flux to lactate. So, despite an unchanged mass action ratio of lactate dehydrogenase, less pyruvate would go through pyruvate dehydrogenase. Consequently, lactate dehydrogenase diverts pyruvate away from entering the mitochondria. Data from new experimental approaches shown in Table I support this concept. Addition of phenacinemethosulfate, serving as a lactate dehydrogenase inhibitor, prevents lactate formation by oxidizing cytosolic-generated NADH, and subsequently boosting mitochondrial $^{14}$CO$_2$ production from $[^6,^{13}$C]glucose and reducing glucose consumption (Table I).

Glucose Requirement for Glycolytic Enzyme Induction and Proliferation—Thymocytes cultured in a glucose free medium containing 10 mM glutamine do not induce the glycolytic enzymes hexokinase, 6-phosphofructo-1-kinase, pyruvate kinase, and lactate dehydrogenase (Fig. 1). Moreover, these cells do not proliferate (Fig. 2), whereas thymocytes grown in a conventional medium containing 12 mM glucose and 2 mM glutamine induce glycolytic enzymes 8–10-fold in the S phase of the cell cycle and 2-fold in the G$_0$ of culture (Figs. 1 and 2). Thus, glycolytic enzyme induction and proliferation strictly depend on the presence of exogenous glucose.

Glutamine, not sugar, has been proposed as the major energy source for cultured HeLa cells (Reiter et al., 1979) and other vertebrate cells (Wice et al., 1981). T-lymphocytes (Ardaoui and Newsholme, 1985) and thymocytes (Brand et al., 1984; Brand, 1985) utilize glutamine and respond to mitogens by increased glutamine metabolism when they are grown in the presence of glucose. However, thymocytes cannot be grown in the absence of glucose (<10 $\mu$M) on glutamine alone (Fig. 2). Since fructose-1,6-bisphosphatase activity could not be detected in resting nor in proliferating thymocytes, glutamine cannot serve as a gluconeogenic amino acid and consequently not as a precursor for the pentose phosphates required for nucleic acid synthesis. This is probably the case for all circulating cells, but the experiments have yet to be done.

However, thymocytes cultured in a medium containing 10 mM ribose and 2 mM glutamine do not proliferate either (data not shown). Presumably, ribose cannot be phosphorylated efficiently to ribose-5-phosphate because of a low or absent activity of ribokinase like in HeLa or hepatoma cells (Wice and Kennell, 1982; Wice et al., 1981). Consequently ribose cannot serve as a precursor for nucleic acid synthesis in thymocytes, thus preventing proliferation.

Cultured HeLa cells could be grown in the complete absence of glucose (<10 $\mu$M) when the medium was supplemented with specific nucleosides at <1 mM (Wice et al., 1981; Wice and Kennell, 1982). However, rat thymocytes cultured in a sugar-free medium supplemented with dialyzed fetal calf serum neither grow on uridine nor induce glycolytic enzymes by addition of uridine (Table IV). Thymocytes grown in a RPMI 1640 containing 10 mM uridine and 2 mM glutamine and non-dialyzed fetal calf serum induce glycolytic enzyme activities 3–5-fold, and $[^3H]$thymidine incorporation increases 17-fold as these cells undergo proliferation. The glycolytic enzyme induction, the increase in $[^3H]$thymidine incorporation and the marginal proliferation could be hindered by the process of dialyzing the fetal calf serum against phosphate-buffered saline. However, thymocytes grown in medium supplemented with dialyzed serum and glucose proliferate and induce their glycolytic enzymes (Table IV) in a quantitative similar manner to cells cultured in medium supplemented with non-dialyzed serum. Therefore our data provide new direct evidence that glucose is essential for thymocyte proliferation and cannot be replaced by uridine in contrast to HeLa cells, hepatoma cells, or fibroblasts (Wice and Kennell, 1982).

In conclusion, induction of the key glycolytic enzymes and the subsequent cell proliferation strictly depends on glucose. One might postulate that exogenous glucose triggers the proliferation by induction of glycolytic enzymes or vice versa. A mechanism for this could revolve around the Crabtree effect (the inhibition of oxygen consumption by the addition of glucose), which must by necessity result in aerobic glycolysis (the production of lactate despite the presence of mitochondria and oxygen). Aerobic glycolysis demands a high capacity of the glycolytic pathway, which can be met by increased glycolytic enzyme activities. The induction of the glycolytic enzymes therefore depends on glucose. 3-O-Methyglucose, which is not phosphorylated and further metabolized, does not mimic the effect of glucose on glycolytic enzyme induction (Fig. 3). Thymocytes cultured in RPMI 1640 containing 10 mM 3-O-methylglucose and less than 0.5 mM residual glucose do not proliferate, whereas cells cultured in medium containing 10 mM of the 2-deoxy analogue of glucose die within the culture period. No induction of glycolytic enzymes can be observed under this condition. 2-Deoxyglucose is phosphorylated but not further metabolized. 2-Deoxyglucose 6-phosphate accumulates and inhibits hexokinase competitively. Blocking of glycolysis at the level of hexokinase might contribute to cell death, as well as the lack of precursors for nucleic acid synthesis and of NADPH required for reductive biosyntheses.

Recent reports indicate a crucial role of glucose in regulating gene expression. German (1993) demonstrates that intermedi-
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Hexokinase

Pyruvate Kinase

Lactate Dehydrogenase

**FIG. 1.** Glycolytic enzyme activities of rat thymocytes cultured in the presence or absence of glucose. Enzyme activities were determined in extracts prepared from thymocytes at 24-h intervals during a 72-h culturing period in nine separate experiments. Thymocytes were cultured in RPMI 1640 medium containing either 0 mM glucose/10 mM glutamine (solid bars) or 10 mM glucose/2 mM glutamine (hatched bars). For details see "Experimental Procedures." Enzyme activities are given in mmol/10^6 cells/h ± S.E., where n ≥ 7.

Rat thymocytes stimulated by concanavalin A and interleukin 2 increase their cellular pyruvate kinase activity, pyruvate kinase protein, and pyruvate kinase mRNA levels 8-12-fold in the S phase of the cell cycle (Netzker et al., 1992). Thymocytes express exclusively pyruvate kinase PK M2, and no change in the isoenzyme pattern could be observed as the cells undergo proliferation (Netzker et al., 1992). Similar results could be obtained for hexokinase, 6-phosphofructo-1-kinase, aldolase, and the bifunctional enzyme 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase (Netzker et al., 1994).

Our data reveal for the first time that glucose is permissive for induction of the key glycolytic enzymes during cell cycle progression and growth. The induction of these enzymes in the presence of glucose suggests a role for glucose in regulating cellular metabolism and proliferation.

**FIG. 2.** Analysis of the cell number of concanavalin A and interleukin 2-stimulated rat thymocytes cultured in the presence or absence of glucose. Number of cells/70 ml of culture medium containing either 0 mM glucose/10 mM glutamine (solid bars) or 10 mM glucose/2 mM glutamine (hatched bars) were determined at 24-h intervals during a 72-h culturing period in more than seven separate experiments. For details see "Experimental Procedures."
TABLE IV
Effect of uridine on glycolytic enzyme induction and proliferation of rat thymocytes

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Glycolytic enzyme activities</th>
<th>[3H]Thymidine uptake</th>
<th>Doubling of cell number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Culture time (h)</td>
<td>Enzyme Amount</td>
<td>(dpm/h) (×10⁷ cells)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>HK 0.582</td>
<td>550</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PFK 0.549</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PK 6.15</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>LDH 11.1</td>
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<td></td>
</tr>
<tr>
<td>48</td>
<td>HK 4.96</td>
<td>75,096</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PFK 4.46</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PK 69.2</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>LDH 91.0</td>
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</tr>
<tr>
<td>48</td>
<td>HK 3.19</td>
<td>9534</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PFK 1.77</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>PK 37.7</td>
<td></td>
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<td></td>
<td>LDH 45.6</td>
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<tr>
<td>48</td>
<td>HK 4.65</td>
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<tr>
<td></td>
<td>PFK 3.59</td>
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<tr>
<td></td>
<td>PK 43.9</td>
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<td>LDH 83.5</td>
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<td>48</td>
<td>HK ND</td>
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<tr>
<td></td>
<td>PFK ND</td>
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</tr>
<tr>
<td></td>
<td>PK 3.38</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>LDH 7.38</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

![Graph](image-url)

**Fig. 3. Effects of 3-O-methylglucose on glycolytic enzyme induction.** Enzyme activities were determined in extracts prepared from resting thymocytes (○) and thymocytes cultured for 48 h in RPMI 1640 medium containing either less than 0.5 mM glucose (□), 10 mM glucose (■), or 10 mM 3-O-methylglucose and less than 0.5 mM glucose (△). Enzyme activities are given in mmol/h/10⁶ cells/h, and each data point represents the mean of two independent experiments. HK, hexokinase; PFK, 6-phosphofructo-1-kinase; PK, pyruvate kinase; LDH, lactate dehydrogenase. For details see "Experimental Procedures."

progression of rat thymocytes. The effect of glucose was not mimicked by the unmetabolizable 3-O-methyl analogue of glucose. Which intermediates of glucose metabolism serve as signal molecules in thymocytes is as yet unknown. Both fructose 1,6-bisphosphate and fructose 2,6-bisphosphate might be candidates, since their concentrations increase markedly in distinct cell cycle phases.⁶

Currently, the model system of resting and proliferating rat thymocytes is being used to investigate whether stabilization of the mRNA or stimulation of gene transcription causes the induction of the key glycolytic enzymes. If the expression of pyruvate kinase and other glycolytic enzymes is transcriptionally controlled by glucose, common regulatory cis-acting elements and/or trans-acting factors will be able to be determined eventually.

In summary, these data represent a transition from oxidative to glycolytic energy metabolism occurring as thymocytes undergo proliferation and provide for the first time direct evidence that it is not an altered respiratory function that limits oxidative metabolism, but increased glycolytic enzyme activities that drive lactate formation despite the presence of oxygen. Our data reveal that glucose induces a shift from oxidative to glycolytic energy production during the G₁/S transition of rat thymocytes by inducing the glycolytic enzymes. Since tumor cells present similar characteristics of glucose metabolism regardless of what causes tumor formation, studying the regulation of glucose metabolism in controlled proliferating thymocytes can provide new important information on cancer metabolism and potentially new approaches to tumor therapy.

REFERENCES