

## REGULATION OF GLUCONEOGENESIS AND PENTOSE PHOSPHATE PATHWAY BY INTRACELLULAR AND EXTERNAL METABOLIC REGULATORS: A REVIEW

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### ABSTRACT

The metabolism of sugars is an important source of energy for cells. Animals, including humans, typically obtain significant amounts of glucose and other sugars from the breakdown of starch and glycogen in their diets. Glucose can also be supplied via breakdown of cellular reserves of glycogen. Significantly, glucose also can be synthesized from noncarbohydrate precursors by a process known as gluconeogenesis. Each of these important pathways, as well as the synthesis of glycogen from glucose. Another pathway of glucose catabolism, the pentose phosphate pathway, is the primary source of NADPH, the reduced coenzyme essential to most reductive biosynthetic processes. For example, NADPH is crucial to the biosynthesis of fatty acids and amino acids. The pentose phosphate pathway also results in the production of ribose-5-phosphate, an essential component of ATP, NAD<sup>+</sup>, FAD, coenzyme A, and particularly DNA and RNA.

## INTRODUCTION

### Gluconeogenesis

The ability to synthesize glucose from common metabolites is very important to most organisms. Human metabolism, for example, consumes about  $160 \pm 20$  grams of glucose per day, about 75% of this in the brain. Body fluids carry only about 20 grams of free glucose, and glycogen stores normally can provide only about 180 to 200 grams of free glucose. Thus, the body carries only a little more than a one-day supply of glucose. If glucose is not obtained in the diet, the body must produce new glucose from noncarbohydrate precursors. The term for this activity is gluconeogenesis. Further, muscles consume large amounts of glucose via glycolysis, producing large amounts of pyruvate. In vigorous exercise, muscle cells become anaerobic and pyruvate is converted to lactate.

Gluconeogenesis salvages this pyruvate and lactate and reconverts it to glucose.

### The Substrates of Gluconeogenesis

In addition to pyruvate and lactate, other non-carbohydrate precursors can be used as substrates for gluconeogenesis in animals. These include most of the amino acids, as well as glycerol and all the TCA cycle intermediates. On the other hand, fatty acids are not substrates for gluconeogenesis in animals, because most fatty acids yield only acetyl-CoA upon degradation and animals cannot carry out net synthesis of sugars from acetyl-CoA. Lysine and leucine are the only amino acids that are not substrates for gluconeogenesis. These amino acids produce only acetyl-CoA upon degradation [1].

Nearly All Gluconeogenesis Occurs in the Liver and Kidneys in Animals Interestingly, the mammalian organs that consume the most glucose, namely, brain and muscle, carry out very little glucose synthesis. The major sites of gluconeogenesis are the liver and kidneys, which account for about 90% and 10% of the body's

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gluconeogenic activity, respectively. Glucose produced by gluconeogenesis in the liver and kidney is released into the blood and is subsequently absorbed by brain, heart, muscle, and red blood cells to meet their metabolic needs. In turn, pyruvate and lactate produced in these tissues are returned to the liver and kidney to be used as gluconeogenic substrates [2].

### **Gluconeogenesis Is Not Merely the Reverse of Glycolysis**

In some ways, gluconeogenesis is the reverse of glycolysis. Glucose is synthesized, not catabolized; ATP is consumed, not produced; and NADH is oxidized to NAD<sup>+</sup>, rather than the other way around. However, gluconeogenesis cannot be *merely* the reversal of glycolysis, for two reasons. First, glycolysis is exergonic, with a  $\Delta G^\circ$  of approximately -74 kJ/mol. If gluconeogenesis were merely the reverse, it would be a strongly endergonic process and could not occur spontaneously. Somehow the energetics of the process must be augmented so that gluconeogenesis can proceed spontaneously. Second, the processes of glycolysis and gluconeogenesis must be regulated in a reciprocal fashion so that when glycolysis is active, gluconeogenesis is inhibited, and when gluconeogenesis is proceeding, glycolysis is turned off. Both of these limitations are overcome by having unique reactions within the routes of glycolysis and gluconeogenesis, rather than a completely shared pathway.

### **Gluconeogenesis—Something Borrowed, Something New**

Gluconeogenesis employs three different reactions, catalyzed by three different enzymes, for the three steps of glycolysis that are highly exergonic (and highly regulated) [3]. In essence, seven of the ten steps of glycolysis are merely reversed in gluconeogenesis. The six reactions between fructose-1,6-bisphosphate and PEP are shared by the two pathways, as is the isomerization of glucose-6-P to fructose-6-P.

The three exergonic regulated reactions—the hexokinase (glucokinase), phosphofructokinase and pyruvate kinase reactions—are replaced by alternative reactions in the gluconeogenic pathway [4]. The conversion of pyruvate to PEP that initiates gluconeogenesis is accomplished by two unique reactions. Pyruvate carboxylase catalyzes the first, converting pyruvate to oxaloacetate. Then, PEP carboxykinase catalyzes the conversion of oxaloacetate to PEP. Conversion of fructose-1,6-bisphosphate to fructose-6-phosphate is catalyzed by a specific phosphatase, fructose-1,6-bisphosphatase. The final step to produce glucose, hydrolysis of glucose-6-phosphate, is mediated by glucose-6-phosphatase [5].

### **The Unique Reactions of Gluconeogenesis 1-Pyruvate Carboxylase-A Biotin-Dependent Enzyme**

Initiation of gluconeogenesis occurs in the pyruvate carboxylase reaction—the conversion of pyruvate to oxaloacetate. The reaction takes place in two discrete steps, involves ATP and bicarbonate as substrates, and utilizes biotin as a coenzyme and acetyl-coenzyme A as an allosteric activator. Pyruvate carboxylase is a tetrameric enzyme. Each monomer possesses a biotin covalently linked to the amino group of a lysine residue at the active site. The first step of the reaction involves nucleophilic attack of bicarbonate oxygen at the P of ATP to form carbonylphosphate, an activated form of CO<sub>2</sub>, and ADP. Reaction of carbonylphosphate with biotin occurs rapidly to form N-carboxybiotin, liberating inorganic phosphate. The third step involves abstraction of a proton from the C-3 of pyruvate, forming a carbanion which can attack the carbon of N-carboxybiotin to form oxaloacetate.

### **Pyruvate Carboxylase is Allosterically Activated by Acyl-CoEnzyme**

Two particularly interesting aspects of the pyruvate carboxylase reaction are (a) allosteric activation of the enzyme by acyl-coenzyme A derivatives and (b) compartmentation of the reaction in the mitochondrial matrix. The carboxylation of biotin requires the presence (at an allosteric site) of acetyl-coenzyme A or other acylated coenzyme A derivatives. The second half of the carboxylase reaction—the attack by pyruvate to form oxaloacetate—is not affected by CoA derivatives.

Activation of pyruvate carboxylase by acetyl-CoA provides an important physiological regulation. Acetyl-CoA is the primary substrate for the TCA cycle, and oxaloacetate (formed by pyruvate carboxylase) is an important intermediate in both the TCA cycle and the gluconeogenesis pathway. If levels of ATP and/or acetyl-CoA (or other acyl-CoAs) are low, pyruvate is directed primarily into the TCA cycle, which eventually promotes the synthesis of ATP. If ATP and acetyl-CoA levels are high, pyruvate is converted to oxaloacetate and consumed in gluconeogenesis. Clearly, high levels of ATP and CoA derivatives are signs that energy is abundant and that metabolites will be converted to glucose (and perhaps even glycogen). If the energy status of the cell is low (in terms of ATP and CoA derivatives), pyruvate is consumed in the TCA cycle. Pyruvate carboxylase activation by acetyl-CoA leads to oxaloacetate formation, replenishing the level of TCA cycle intermediates [6]. Compartmentalized Pyruvate Carboxylase Depends on Metabolite Conversion and Transport

The second interesting feature of pyruvate carboxylase is that it is found only in the *matrix* of the mitochondria. By contrast, the next enzyme in the gluconeogenic pathway, PEP carboxykinase, may be localized in the cytosol or in the mitochondria or both. For example, rabbit liver PEP carboxykinase is predominantly mitochondrial, whereas the rat liver enzyme is strictly cytosolic. In human liver, PEP carboxykinase is found both in the cytosol and in the mitochondria.



Pyruvate is transported into the mitochondrial matrix, where it can be converted to acetyl-CoA (for use in the TCA cycle) and then to citrate (for fatty acid synthesis). Alternatively, it may be converted directly to OAA by pyruvate carboxylase and used in gluconeogenesis. In tissues where PEP carboxykinase is found only in the mitochondria, oxaloacetate is converted to PEP, which is then transported to the cytosol for gluconeogenesis. However, in tissues that must convert some oxaloacetate to PEP in the cytosol, a problem arises. Oxaloacetate cannot be transported directly across the mitochondrial membrane. Instead, it must first be transformed into malate or aspartate for transport across the mitochondrial inner membrane. Cytosolic malate and aspartate must be reconverted to oxaloacetate before continuing along the gluconeogenic route [7]

## 2- PEP Carboxykinase

The second reaction in the gluconeogenic pyruvate-PEP bypass is the conversion of oxaloacetate to PEP. Production of a high-energy metabolite such as PEP requires energy. The energetic requirements are handled in two ways here. First, the CO<sub>2</sub> added to pyruvate in the pyruvate carboxylase step is removed in the PEP carboxykinase reaction. Decarboxylation is a favorable process and helps to drive the formation of the very high-energy enol phosphate in PEP. This decarboxylation drives a reaction that would otherwise be highly endergonic. Second, another high-energy phosphate is consumed by the carboxykinase. Mammals and several other species use GTP in this reaction, rather than ATP. The use of GTP here is equivalent to the consumption of an ATP, due to the activity of the nucleoside diphosphate kinase. The substantial free energy of hydrolysis of GTP is crucial to the synthesis of PEP in this step. Once PEP is formed in this way, the phosphoglycerate mutase, phosphoglycerate kinase, glyceraldehyde-3-P dehydrogenase, aldolase, and triose phosphate isomerase reactions act to eventually form fructose-1,6-bisphosphate [8].

## 3-Fructose-1,6-Bisphosphatase

The hydrolysis of fructose-1,6-bisphosphate to fructose-6-phosphate like all phosphate ester hydrolyses, is a thermodynamically favorable (exergonic) reaction under standard-state conditions. Fructose-1,6-bisphosphatase is an allosterically regulated enzyme. Citrate stimulates bisphosphatase activity, but *fructose-2,6-bisphosphate* is a potent allosteric inhibitor. AMP also inhibits the bisphosphatase; the inhibition by AMP is enhanced by fructose-2,6-bisphosphate.

## 4-Glucose-6-Phosphatase

The final step in the gluconeogenesis pathway is the conversion of glucose-6-phosphate to glucose by the action of glucose-6-phosphatase. This enzyme is present in the membranes of the endoplasmic reticulum of liver and kidney cells, but is absent in muscle and brain. For this

reason, gluconeogenesis is not carried out in muscle and brain. Its membrane association is important to its function because the substrate is hydrolyzed as it passes into the endoplasmic reticulum itself. Vesicles form from the endoplasmic reticulum membrane and diffuse to the plasma membrane and fuse with it, releasing their glucose contents into the bloodstream. The glucose-6-phosphatase reaction involves a phosphorylated enzyme intermediate, which may be a phosphohistidine.

## Regulation of Gluconeogenesis

Nearly all of the reactions of glycolysis and gluconeogenesis take place in the cytosol. If metabolic control were not exerted over these reactions, glycolytic degradation of glucose and gluconeogenic synthesis of glucose could operate simultaneously, with no net benefit to the cell and with considerable consumption of ATP. This is prevented by a sophisticated system of reciprocal control, so that glycolysis is inhibited when gluconeogenesis is active, and vice versa. Reciprocal regulation of these two pathways depends largely on the energy status of the cell. When the energy status of the cell is low, glucose is rapidly degraded to produce needed energy. When the energy status is high, pyruvate and other metabolites are utilized for synthesis (and storage) of glucose [3].

In glycolysis, the three regulated enzymes are those catalyzing the strongly exergonic reactions: hexokinase (glucokinase), phosphofructokinase, and pyruvate kinase. As noted, the gluconeogenic pathway replaces these three reactions with corresponding reactions that are exergonic in the direction of glucose synthesis: glucose-6-phosphatase, fructose-1,6-bisphosphatase, and the pyruvate carboxylase-PEP carboxykinase pair, respectively. These are the three most appropriate sites of regulation in gluconeogenesis [9].

## Gluconeogenesis is regulated by Allosteric and Substrate-Level Control Mechanisms

Control is exerted at all of the predicted sites, but in different ways. Glucose-6-phosphatase is not under allosteric control. However, the  $K_m$  for the substrate, glucose-6-phosphate, is considerably higher than the normal range of substrate concentrations. As a result, glucose-6-phosphatase displays a near-linear dependence of activity on substrate concentrations and is thus said to be under substrate-level control by glucose-6-phosphate. Acetyl-CoA is a potent allosteric effector of glycolysis and gluconeogenesis. It allosterically inhibits pyruvate kinase and activates pyruvate carboxylase. Because it also allosterically inhibits pyruvate dehydrogenase (the enzymatic link between glycolysis and the TCA cycle), the cellular fate of pyruvate is strongly dependent on acetyl-CoA levels. A rise in acetyl-CoA indicates that cellular energy levels are high and that carbon metabolites can be directed to glucose synthesis and storage. When acetyl-CoA levels drop, the activities of pyruvate kinase and



pyruvate dehydrogenase increase and flux through the TCA cycle increases, providing needed energy for the cell. Fructose-1,6-bisphosphatase is another important site of gluconeogenic regulation. This enzyme is inhibited by AMP and activated by citrate. These effects by AMP and citrate are the opposites of those exerted on phosphofructokinase in glycolysis, providing another example of reciprocal regulatory effects. When AMP levels increase, gluconeogenic activity is diminished and glycolysis is stimulated. An increase in citrate concentration signals that TCA cycle activity can be curtailed and that pyruvate should be directed to sugar synthesis instead [9].

### Fructose-2,6-Bisphosphate-Allosteric Regulator of Gluconeogenesis

Fructose-2,6-bisphosphate is a potent stimulator of phosphofructokinase. Cognizant of the reciprocal nature of regulation in glycolysis and gluconeogenesis. Inhibition of enzyme occurs in either the presence or absence of AMP, and the effects of AMP and fructose-2,6-bisphosphate are synergistic. Cellular levels of fructose-2,6-bisphosphate are controlled by phosphofructokinase-2 (PFK-2), an enzyme distinct from the phosphofructokinase of the glycolytic pathway, and by fructose-2,6-bisphosphatase (F-2,6-BPase). Remarkably, these two enzymatic activities are both found in the same protein molecule, which is an example of a bifunctional, or tandem, enzyme. The opposing activities of this bifunctional enzyme are themselves regulated in two ways. First, fructose-6-phosphate, the substrate of phosphofructokinase and the product of fructose-1,6-bisphosphatase, allosterically activates PFK-2 and inhibits F-2,6-BPase. Second, the phosphorylation by cAMP-dependent protein kinase of a single Ser residue on the 49-kD subunit of this dimeric enzyme exerts reciprocal control of the PFK-2 and F-2,6-BPase activities. Phosphorylation then inhibits PFK-2 activity (by increasing the  $K_m$  for fructose-6-phosphate) and stimulates F-2,6-BPase activity.

### Substrate Cycles Provide Metabolic Control Mechanisms

If fructose-1,6-bisphosphatase and phosphofructokinase acted simultaneously, they would constitute a substrate cycle in which fructose-1,6-bisphosphate and fructose-6-phosphate became interconverted with net consumption of ATP:

Because substrate cycles such as this appear to operate with no net benefit to the cell, they were once regarded as metabolic quirks and were referred to as *futile cycles*. More recently, substrate cycles have been recognized as important devices for controlling metabolite concentrations.

The three steps in glycolysis and gluconeogenesis that differ constitute three such substrate cycles, each with its own particular metabolic. As already noted, fructose-1,6-bisphosphatase is subject to allosteric inhibition by

fructose-2,6-bisphosphate, whereas phosphofructokinase is allosterically activated by fructose-2,6-bisP. The combination of these effects should permit *either* phosphofructokinase *or* fructose-1,6-bisphosphatase (but not both) to operate at any one time and should thus prevent futile cycling. For instance, in the fasting state, when food (i.e., glucose) intake is zero, phosphofructokinase (and therefore glycolysis) is inactive due to the low concentration of fructose-2,6-bisphosphate. In the liver, gluconeogenesis operates to provide glucose for the brain. However, in the fed state, up to 30% of fructose-1,6-bisphosphate formed from phosphofructokinase is recycled back to fructose-6-P (and then to glucose). Because the dependence of fructose-1,6-bisphosphatase activity on fructose-1,6-bisphosphate is sigmoidal in the presence of fructose-2,6-bisphosphate, substrate cycling occurs only at relatively high levels of fructose-1,6-bisphosphate. Substrate cycling in this case prevents the accumulation of excessively high levels of fructose-1,6-bisphosphate [8].

### Hormonal control of gluconeogenesis

As with glycolysis, glucagon-dependent protein phosphorylation also regulates enzyme activities in gluconeogenesis. Recall that F-2,6-BP levels are regulated by glucagon, with high glucagon (low blood sugar) favoring conversion of F-2,6-BP back into F6P. In addition, glucagon activates lipases in adipose tissue, promoting release of fatty acids into the bloodstream. These fatty acids are broken down in the mitochondria of liver, resulting in high concentrations of acetyl CoA. Acetyl CoA acts as an allosteric activator of pyruvate carboxylase. Both insulin and glucagon regulate the transcription of bypass enzymes: insulin inhibits transcription of phosphoenolpyruvate carboxykinase, and glucagon activates its transcription [10].

### The Pentose Phosphate Pathway

Cells require a constant supply of NADPH for reductive reactions vital to biosynthetic purposes. Much of this requirement is met by a glucose-based metabolic sequence variously called the pentose phosphate pathway, the hexose mono-phosphate shunt, or the phosphogluconate pathway. In addition to providing NADPH for biosynthetic processes, this pathway produces *ribose-5-phosphate*, which is essential for nucleic acid synthesis. Several metabolites of the pentose phosphate pathway can also be shuttled into glycolysis [11].

The pentose phosphate pathway begins with glucose-6-phosphate, a six-carbon sugar, and produces three-, four-, five-, six-, and seven-carbon sugars. As we will see, two successive oxidations lead to the reduction of NADP<sup>+</sup> to NADPH and the release of CO<sub>2</sub>. Five subsequent nonoxidative steps produce a variety of carbohydrates, some of which may enter the glycolytic pathway. The enzymes of the pentose phosphate pathway are particularly abundant in the cytoplasm of liver and





adipose cells. These enzymes are largely absent in muscle, where glucose-6-phosphate is utilized primarily for energy production via glycolysis and the TCA cycle. These pentose phosphate pathway enzymes are located in the cytosol, which is the site of fatty acid synthesis, a pathway heavily dependent on NADPH for reductive reactions.

The Oxidative Steps of the Pentose Phosphate Pathway

### 1- Glucose-6-Phosphate Dehydrogenase

The pentose phosphate pathway begins with the oxidation of glucose-6-phosphate. The products of the reaction are a cyclic ester (the lactone of phosphogluconic acid) and NADPH. Glucose-6-phosphate dehydrogenase, which catalyzes this reaction, is highly specific for NADP<sup>+</sup>. As the first step of a major pathway, the reaction is irreversible and highly regulated. Glucose-6-phosphate dehydrogenase is strongly inhibited by the product coenzyme, NADPH, and also by fatty acid esters of coenzyme A (which are intermediates of fatty acid biosynthesis). Inhibition due to NADPH depends upon the cytosolic NADP<sup>+</sup>/NADPH ratio, which in the liver is about 0.015. The gluconolactone produced is hydrolytically unstable and readily undergoes a spontaneous ring-opening hydrolysis, although an enzyme, gluconolactonase, accelerates this reaction. The linear product, the sugar acid 6-phospho-D-gluconate, is further oxidized.

### 2- Gluconolactonase

The gluconolactone produced is hydrolytically unstable and readily undergoes a spontaneous ring-opening hydrolysis, although an enzyme, gluconolactonase, accelerates this reaction. The linear product, the sugar acid 6-phospho-D-gluconate, is further oxidized.

### 3- 6-Phosphogluconate Dehydrogenase

The oxidative decarboxylation of 6-phosphogluconate by 6-phosphogluconate dehydrogenase yields D-ribulose-5-phosphate and another equivalent of NADPH. There are two distinct steps in the reaction; the initial NADP<sup>+</sup>-dependent dehydrogenation yields an alpha-keto acid, 3-keto-6-phosphogluconate, which is very susceptible to decarboxylation (the second step). The resulting product, D-ribulose-5-P, is the substrate for the nonoxidative reactions composing the rest of this pathway.

The Nonoxidative Steps of the Pentose Phosphate Pathway

This portion of the pathway begins with an isomerization and an epimerization, and it leads to the formation of either D-ribose-5-phosphate or D-xylulose-5-phosphate. These intermediates can then be converted into glycolytic intermediates or directed to biosynthetic processes.

### 4- Phosphopentose Isomerase

This enzyme interconverts ribulose-5-P and ribose-5-P via an enediol intermediate. The reaction (and mechanism) is quite similar to the phosphoglucoisomerase

reaction of glycolysis, which interconverts glucose-6-P and fructose-6-P. The ribose-5-P produced in this reaction is utilized in the biosynthesis of coenzymes (including NADH, NADPH, FAD, and B<sub>12</sub>), nucleotides, and nucleic acids (DNA and RNA). The net reaction for the first four steps of the pentose phosphate pathway is



### 5- Phosphopentose Epimerase

This reaction converts ribulose-5-P to another ketose, namely, xylulose-5-P. This reaction also proceeds by an enediol intermediate, but involves an inversion at C-3. In the reaction, an acidic proton located to a carbonyl carbon is removed to generate the enediolate, but the proton is added back to the same carbon from the opposite side. Note the distinction in nomenclature here. Interchange of groups on a single carbon is an epimerization, and interchange of groups between carbons is referred to as an isomerization.

The pathway has also produced two molecules of NADPH for each glucose-6-P converted to pentose-5-phosphate. The next three steps rearrange the five-carbon skeletons of the pentoses to produce three-, four-, six-, and seven-carbon units, which can be used for various metabolic purposes. Why should the cell do this? Very often, the cellular need for NADPH is considerably greater than the need for ribose-5-phosphate. The next three steps thus return some of the five-carbon units to glyceraldehyde-3-phosphate and fructose-6-phosphate, which can enter the glycolytic pathway. The advantage of this is that the cell has met its needs for NADPH and ribose-5-phosphate in a single pathway, yet at the same time it can return the excess carbon metabolites to glycolysis.

### 6 and 8- Transketolase

The transketolase enzyme acts at both steps 6 and 8 of the pentose phosphate pathway. In both cases, the enzyme catalyzes the transfer of two-carbon units. In these reactions (and also in step 7, the transaldolase reaction, which transfers three-carbon units), the donor molecule is a ketose and the recipient is an aldose. In step 6, xylulose-5-phosphate transfers a two-carbon unit to ribose-5-phosphate to form glyceraldehyde-3-phosphate and sedoheptulose-7-phosphate

### 7- Transaldolase

The transaldolase functions primarily to make a useful glycolytic substrate from the sedoheptulose-7-phosphate produced by the first transketolase reaction. This reaction is quite similar to the aldolase reaction of glycolysis, involving formation of a Schiff base intermediate between the sedoheptulose-7-phosphate and an active-site lysine residue. Elimination of the erythrose-



4-phosphate product leaves an enamine of dihydroxyacetone, which remains stable at the active site until the other substrate comes into position. Attack of the enamine carbanion at the carbonyl carbon of glyceraldehyde-3-phosphate is followed by hydrolysis of the Schiff base (imine) to yield the product fructose-6-phosphate.

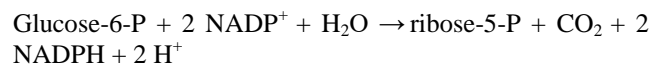
### Utilization of Glucose-6-P Depends on the Cell's Need for ATP, NADPH, and Ribose-5-P

It is clear that glucose-6-phosphate can be used as a substrate either for glycolysis or for the pentose phosphate pathway. The cell makes this choice on the basis of its relative needs for biosynthesis and for energy from metabolism. ATP can be produced in abundance if glucose-6-phosphate is channeled into glycolysis. On the other hand, if NADPH or ribose-5-phosphate is needed, glucose-6-phosphate can be directed to the pentose phosphate pathway. The molecular basis for this regulatory decision depends on the enzymes that metabolize glucose-6-phosphate in glycolysis and the pentose phosphate pathway. In glycolysis, phosphoglucosomerase converts glucose-6-phosphate to fructose-6-phosphate, which is utilized by phosphofructokinase (a highly regulated enzyme) to produce fructose-1,6-bisphosphate. In the pentose phosphate pathway, glucose-6-phosphate dehydrogenase (also highly regulated) produces gluconolactone from glucose-6-phosphate. Thus, the fate of glucose-6-phosphate is determined to a large extent by the relative activities of phosphofructokinase and glucose-6-P dehydrogenase. Recall that PFK is inhibited when the ATP/AMP ratio increases, and that it is inhibited by citrate but activated by fructose-2,6-bisphosphate. Thus, when the energy charge is high, glycolytic flux decreases. Glucose-6-P dehydrogenase, on the other hand, is inhibited by high levels of NADPH and also by the intermediates of fatty acid biosynthesis. Both of these are indicators that biosynthetic demands have been satisfied. If that is the case, glucose-6-phosphate dehydrogenase and the pentose phosphate pathway are inhibited. If NADPH levels drop, the pentose phosphate pathway turns on, and NADPH and ribose-5-phosphate are made for biosynthetic purposes (Mayuko et al., 2010).

Even when the latter choice has been made, however, the cell must still be "cognizant" of the relative needs for ribose-5-phosphate and NADPH (as well as ATP). Depending on these relative needs, the reactions of glycolysis and the pentose phosphate pathway can be combined in novel ways to emphasize the synthesis of needed metabolites. There are four principal possibilities.

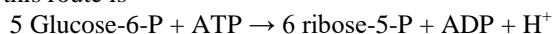
#### 1-Both Ribose-5-P and NADPH are needed by the cell

In this case, the first four reactions of the pentose phosphate pathway predominate. NADPH is produced by the oxidative reactions of the pathway, and ribose-5-P is the principal product of carbon metabolism. As stated earlier, the net reaction for these processes is



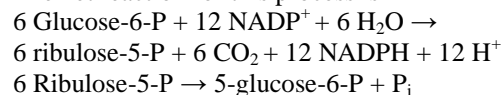
#### 2-More Ribose-5-P than NADPH is needed by the cell

Synthesis of ribose-5-P can be accomplished without production of NADPH if the oxidative steps of the pentose phosphate pathway are bypassed. The key to this route is the extraction of fructose-6-P and glyceraldehyde-3-P, but not glucose-6-P, from glycolysis. The action of transketolase and transaldolase on fructose-6-P and glyceraldehyde-3-P produces three molecules of ribose-5-P from two molecules of fructose-6-P and one of glyceraldehyde-3-P. In this route, as in case 1, no carbon metabolites are returned to glycolysis. The net reaction for this route is



#### 3-More NADPH than Ribose-5-P is needed by the cell

Large amounts of NADPH can be supplied for biosynthesis without concomitant production of ribose-5-P, if ribose-5-P produced in the pentose phosphate pathway is recycled to produce glycolytic intermediates. This alternative involves a complex interplay between the transketolase and transaldolase reactions to convert ribulose-5-P to fructose-6-P and glyceraldehyde-3-P, which can be recycled to glucose-6-P via gluconeogenesis. The net reaction for this process is



#### 4- Both NADPH and ATP are needed by the cell, but Ribose-5-P is not

Under some conditions, both NADPH and ATP must be provided in the cell. This can be accomplished in a series of reactions similar to case 3, if the fructose-6-P and glyceraldehyde-3-P produced in this way proceed through glycolysis to produce ATP and pyruvate, which itself can yield even more ATP by continuing on to the TCA cycle.

The net reaction for this alternative is

$$3 \text{ Glucose-6-P} + 5 \text{ NAD}^+ + 6 \text{ NADP}^+ + 8 \text{ ADP} + 5 \text{ P}_i \rightarrow 5 \text{ pyruvate} + 3 \text{ CO}_2 + 5 \text{ NADH} + 6 \text{ NADPH} + 8 \text{ ATP} + 2 \text{ H}_2\text{O} + 8 \text{ H}^+$$

### Regulation of Glucose Metabolism by External Metabolic Regulators

The liver and skeletal muscle self-regulate carbohydrate metabolism in basically the same way as do other cells. However, these cell types are also required to respond to external signals by altering their carbohydrate metabolism. These two tissues, along with adipose tissue (which is primarily involved in lipid metabolism), act as the major regulators of nutrient levels in circulation during most metabolic conditions.

The regulation has two goals: 1) maintenance of normal circulating glucose levels in the face of changing conditions, and (when necessary) 2) support of physical



activity [13]. These tissues are tightly controlled by external signals: the levels of the pancreatic hormones insulin and glucagon, the adrenal hormones epinephrine and cortisol, and, in the case of skeletal muscle, the neuronal signals that govern muscle contraction. The following description of events simplifies some rather complex processes. In general, glucagon and epinephrine result in phosphorylation of regulatory enzymes, while insulin results in removal of the phosphate; calcium usually increases phosphorylation (one major exception is the mitochondrial enzyme pyruvate dehydrogenase, in which calcium stimulates phosphate removal). Some of the hormones, especially cortisol and insulin, and to a lesser extent glucagon, alter the amounts of the enzymes present in the cell. The phosphorylation and dephosphorylation events occur rapidly, while effects on enzyme concentration are relatively slow processes.

The cells of the liver and muscle must also use the same feedback regulatory metabolites as do “normal cells”;

these effects interact with the hormonal signals to result in the overall metabolic changes that occur within these cells. The two figures below summarize the control of the various pathways by metabolic and hormonal effects in liver and in skeletal muscle.

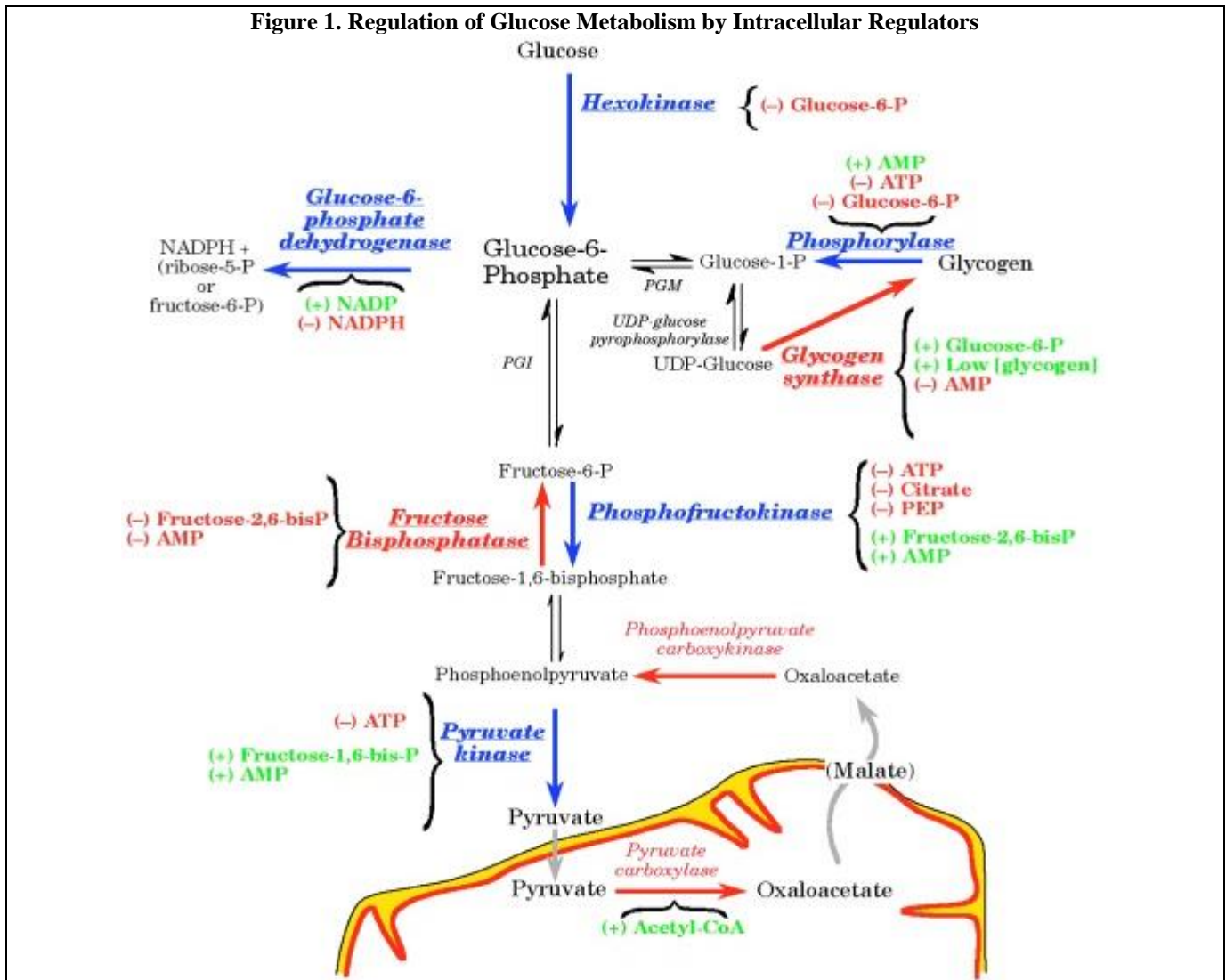
**CONCLUSION**

The present study concluded that, thiamine had a regulatory role in maintaining renal acid base balance. High thiamine diet improved the renal function and response to metabolic acidosis induced by NH<sub>4</sub>Cl in adult male rats.

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**CONFLICT OF INTEREST:**

The authors declare that they have no conflict of interest.



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