

INTERMEDIARY METABOLISM

Interrelationships of Metabolic Pathways

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CONTENTS

[Metabolic fuels](#)

[Cell Metabolism](#)

[Metabolic pathways](#)

[Regulation of Metabolic Pathways](#)

[Flow of key metabolic substrates](#)

[Pathway interactions](#)

[Metabolism of specialized tissues and organ interrelationship](#)

[Regulation of gluconeogenesis and glycolysis](#)

[Regulation of the Tricarboxylic acid cycle](#)

[Regulation of glycogen synthesis and breakdown](#)

[Regulation of Carbohydrate Biosynthesis](#)

Key words

Metabolic fuel; Regulation in metabolism; Allosteric and hormonal regulation; Interrelationships in metabolic pathways

Introduction

The various metabolic pathways by which carbohydrates, fat and proteins are processed as metabolic fuels for energy supply or as precursors in the biosynthesis of compounds required by the cell for maintenance or growth are interrelated and well coordinated. This interrelation of metabolism could be considered at the following levels:

- A. The flow of key metabolites between different metabolic pathways at the cellular level.
- B. The interdependence of different organs and tissues in maintaining an appropriate metabolic state for the body as a whole.

Metabolic fuels

Definition

1. Metabolic fuels are substances that are used by the body as sources of carbon or oxidized to release free energy, which is used to support anabolic processes and other cellular functions.
2. The molecules utilized as major metabolic fuels are carbohydrates, fats as fatty acids, ketone bodies and proteins as amino acids.

Caloric values of metabolic fuels

1. If an organic substance is reacted with molecular oxygen in a bomb calorimeter and all of the carbon is converted to carbon dioxide (CO_2), the heat evolved is a measure of the potential free energy available in this substance.
2. The caloric value of metabolic fuels is expressed in terms of kilocalories (Kcal) per gram. The caloric values of the major metabolic fuels are listed in Table 1.

Metabolic Fuel	Caloric Values (Kcal/g)
Carbohydrates (glucose, glycogen etc.)	4
Proteins/Amino acids (average)	4
Ketone bodies (hydroxybutyrate, acetoacetate)	4
Fats/Fatty acids	9

Table 1: Caloric Values of the Major Metabolic Fuels
(adapted from Srivastava, L.M., 2004)

Storage of metabolic fuels

1. Circulating glucose in the blood is a major metabolic fuel, and a number of mechanisms are used to maintain adequate blood glucose levels.
2. Carbohydrate is stored primarily as glycogen in the liver and skeletal muscle and in very small amount in most other tissues.
3. Only those cells that contain glucose 6-phosphatase (i.e. liver, kidney and small intestine) can use glycogen to synthesize glucose and regulate blood glucose levels.

4. Triacylglycerols form a potential source of glucose, since the glycerol moiety derived from the hydrolysis of triglycerols can be converted to glucose in tissues where gluconeogenesis take place. Triacylglycerols are also a source of fatty acids.
5. The catabolism of glucogenic amino acids can provide glucose (100g of protein yield 60g of glucose). Thus, the body protein may also be considered a source of fuel.

Utilization of Metabolic Fuels

Feeding-Fasting phenomenon

1. Humans are intermittent feeders. Although in affluent societies the time periods between intakes of food may be rather short during waking hours, most individuals undergo at least a 6 to 8 hour fast overnight. Any consideration of metabolism and the use of metabolic fuels has to take into account this feeding –fasting phenomenon.
2. During feeding and shortly thereafter, the metabolic fuels used by tissues may be derived directly from the ingested, digested and absorbed food molecules. During a fast, metabolic fuels used by tissues are derived from mobilized stores of fuel molecules.
3. The feeding – fasting phenomenon and status of fasting can be defined as follows:
 - a. The fed (postprandial) state occurs just after a meal, and blood/plasma substrate levels are still elevated above fasting levels.
 - b. The fasting (postabsorptive) state occurs several hours after eating.
 - c. Starvation occurs after 2 or 3 days without food.

Cell Metabolism is an Economical Tightly Regulated Process

Cell metabolism operates at maximum economy. The overall rate of energy yielding catabolism is controlled by the needs of the cell for energy in the form of ATP and NADPH. Thus cells conserve just enough nutrients to meet the energy utilization at any given time. Similarly the rate of biosynthesis of building block molecules and of cell macromolecules is also adjusted to immediate needs.

Many animals and plants can store energy-supplying and carbon-supplying nutrients, such as fat and carbohydrates, but they generally cannot store protein, nucleic acids, or simple building block molecules, which are made only when needed and in amounts required. Catabolic pathways are very sensitive and responsive to changes in energy needs, the regulatory mechanisms of central metabolic pathways, particularly those providing energy as ATP. They are capable of responding to metabolic needs quickly and with great sensitivity.

Metabolic pathways are regulated at three levels

Three different types of mechanisms bring about the regulation of metabolic pathways. The first and most immediately responsive form of regulation is through the action of allosteric enzymes, which are capable of changing their catalytic activity in response to stimulatory or inhibitory effectors molecules.

Allosteric enzymes are usually located at or near the beginning of a multienzyme sequence and catalyze its rate-limiting step which is usually an essentially irreversible reaction.

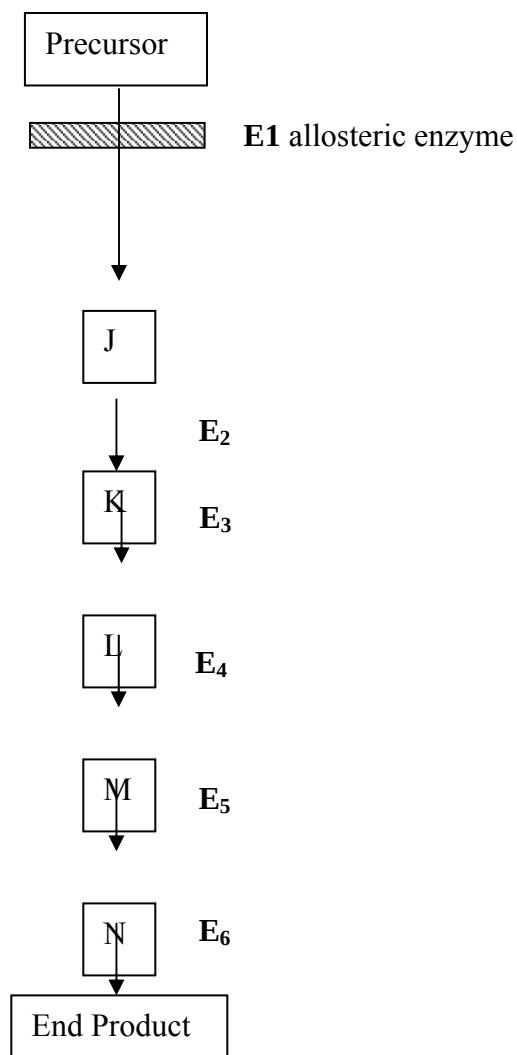


Figure 1: Regulation of catabolic pathways by feedback or end product inhibition by an allosteric enzyme (*adapted from Srivastava, L.M., 2004*)

In catabolic pathways, which lead to the generation of ATP from ADP, the end product ATP often functions as an allosteric inhibitor of an early step in catabolism. In anabolic pathways, the biosynthetic end product, such as an amino acid often functions as an allosteric inhibitor of an early step.

Some allosteric enzymes are stimulated by specific positive modulators. For example, an allosteric enzyme regulating a catabolic sequence may be stimulated by the positive modulators ADP or AMP and inhibited by the negative modulator ATP.

An allosteric enzyme in a given pathway may also be specifically responsive to intermediates or products of other metabolic pathways. In this way the rate of different enzyme systems can be coordinated with each other.

Hormonal Control

Metabolic control is exerted at a second level in higher organisms by hormonal regulation. Hormones are chemical messengers secreted by different endocrine glands and carried by blood to other tissues or organs, where they may stimulate or inhibit some specific metabolic activity. For e.g. the hormone adrenalin, secreted by the medulla of the adrenal gland, is carried by the blood to the liver, where it stimulates the breakdown of glycogen to glucose, thus increasing the blood sugar level. Adrenalin also stimulates the breakdown of glycogen in skeletal muscles to yield lactate and energy as ATP. Adrenalin produces these effects by binding to specific adrenalin receptor sites on the cell surface in liver and muscle. Binding of adrenalin is a signal that is communicated to the interior of the cell, ultimately causing the covalent conversion of a less active to a more active form of glycogen phosphorylase, the first enzyme in a sequence that leads to the formation of glucose and subsequent products from glycogen. The third level at which metabolic regulation is exerted is through control of the concentration of a given enzyme in the cell. The concentration of an enzyme at any given time is the result of a balance between the rate of its synthesis and the rate of its degradation.

Enzyme Induction

The rate of synthesis of certain enzymes is greatly increased (accelerated) under certain conditions so that the actual concentration of the enzyme in the cell is increased substantially e.g. on a high carbohydrate low protein diet the enzymes of the liver that degrade amino acids to acetyl-CoA are present in very low concentrations. Since there is little need for these enzymes as long as the animals are maintained on a low protein diet, they are not made in large amounts. On a protein rich diet however, within a day, its “liver” will show substantially increased concentration of amino acid degrading enzymes.

Thus the liver cell can turn the biosynthesis of specific enzymes on or off, depending on the nature of the incoming nutrients. This is called enzyme induction.

Regulation of Metabolic Pathways

Major metabolic pathways and the flow of metabolites could be regulated by activation, inhibition, covalent modification and allosteric control of enzymes operative in the pathways. These are mentioned in Table 2.

Pathway	Mode of Regulation	Key Enzyme	Substrate that: Stimulate / inhibit
Citric acid cycle	Respiratory control		
Fatty acid oxidation	Respiratory control		
Fatty acid synthesis	Allosteric control	Acetyl CoA carboxylase	Citrate /Palmitoyl CoA
Gluconeogenesis	Allosteric control	F1, 6 BP	Citrate/ F2, 6BP, AMP
Glycogenesis	Reaction cascade	Glycogen synthase	
Glycogenolysis	Reaction cascade	Glycogen phosphorylase	
Glycolysis	Allosteric control	phosphofructokinase	F2, 6BP, AMP/ Citrate ATP
Pentose phosphate	Substrate	Glucose 6-phosphate	NADP+
Pathway (HMP pathway)		availability	dehydrogenase

Table 2: Regulation of metabolic pathways by inhibition/activation/substrate availability

AMP= adenosine monophosphate; ATP= adenosine triphosphate; CoA=coenzyme A; F1, 6BP=fructose 1,6-biphosphate; F2, 6BP=fructose 2,6-biposphate; NADP⁺=oxidized nicotinamide-adenine dinucleotide phosphate. (adapted from Srivastava, L.M., 2004)

Allosteric control of metabolic pathways

The activity of a key enzyme that catalyses the rate limiting committed step in the pathway is modulated by the levels of metabolites that act as activators or inhibitors. Major pathways regulated in this manner are glycolysis, gluconeogenesis, glycogen metabolism and fatty acid synthesis.

A. Glycolysis

Phosphofructokinase action is one of the major site of regulation.

Activators

- a. Fructose 2,6-biposphate (F2, 6BP)
- b. Adenosine monophosphate (AMP)
- c. Adenosine triphosphate (ATP)

Inhibitors

- a. Citrate
- b. Adenosine triphosphate (ATP)

B. Gluconeogenesis

Fructose 1,6-biposphatase (F1, 6BPase) is the site of regulation.

Activators

- a. Citrate
- b. ATP

Inhibitors

- a. F2, 6BP
- b. AMP

C. Fatty acid synthesis

Acetyl coenzyme A (CoA) carboxylase is the site of regulation.

The **activator** is citrate

The **inhibitor** is palmitoyl CoA.

Respiratory Control

Under respiratory control, the flux through a pathway matches the need of the cell for ATP. Pathways regulated in this manner are:

- a. Citric acid cycle.
- b. Fatty acid synthesis.
- c. Electron transport chain and oxidative phosphorylation.

Covalent Modification

Hormone-triggered reaction cascades, which results in the covalent modifications of a key enzyme of a pathway, are used to regulate the following pathways.

- a. Glycogenesis: Glycogen synthase is the target enzyme of this cascade.
- b. Glycogenolysis: Glycogen phosphorylase is the target enzyme of this cascade.

Substrate Availability

It is the primary factor that determines the flux of metabolites through the following pathways.

- a. Pentose phosphate pathway (Hexose monophosphate pathway).
- b. Urea cycle.

Hormonal Regulation of Metabolic Pathways

Various hormones directly and/or indirectly regulate the flow of metabolites through certain pathways (Table 3).

Pathway	Effect of Insulin	Effect of Glucagon/Epinephrine
Cholesterol synthesis	Stimulates	-----
Fatty acid oxidation	Inhibits	-----
Fatty acid synthesis	Stimulates	-----
Gluconeogenesis	Inhibits	Stimulates
Glycogenesis	Stimulates	Inhibits
Glycogenolysis	Inhibits	Stimulates
Glycolysis	Stimulates	Inhibits
Lipogenesis	Stimulates	Inhibits
Lipolysis	Inhibits	Stimulates
Pentose Phosphate Pathway	Stimulates	-----
Protein synthesis	Stimulates	-----
Proteolysis (Protein degradation)	Inhibits	-----

Table 3: Regulation of Major Metabolic Pathways by hormones
(adapted from Srivastava, L.M., 2004)

Regulation of Major Metabolic Pathways by Hormones

1. Insulin signals the fed state and the availability of glucose in the blood through the following actions.
 - a. Insulin stimulates the synthesis of glycogen, fats and proteins.
 - b. Insulin inhibits the degradation of glycogen, fats and proteins.
2. Glucagon and epinephrine signal the fasting state, in which the level of glucose in the blood is low, through the following actions.
 - a. Glucagon and epinephrine inhibits the synthesis of glycogen, fat and proteins.
 - b. Glucagon and epinephrine stimulates the degradation of glycogen, fat and proteins.

Flow of key metabolic substrates between different pathways

Certain metabolites may be used as intermediates in different processes. The control of the direction of flux of these intermediates is a significant factor in the integration of metabolism at the cellular level. Fig 1, 2 and 3 depict the interrelationship of metabolism and denote the control point for regulating metabolic flow in these pathways.

1. Glucose 6-phosphate may be converted to:
 - (i) Glucose in gluconeogenic tissues.

- (ii) Glucose 1-phosphate which is used in glycogen synthesis.
 - (iii) Pyruvate through glycolysis.
 - (iv) Ribose 5-phosphate, a substrate for nucleic acid synthesis, via the pentose phosphate pathway.
2. Pyruvate may be converted to:
- a. Oxaloacetate and metabolized via the TCA cycle.
 - b. Acetyl CoA by pyruvate dehydrogenase.
 - c. Alanine via transamination.
 - d. Lactate in muscle tissue.

Pathway interactions: major oxidative pathways may also act as routes linking other pathways

The citric acid cycle links carbohydrate and fat metabolism and is involved in the metabolism of amino acids. It provides an important control point for regulating metabolite flow in these pathways.

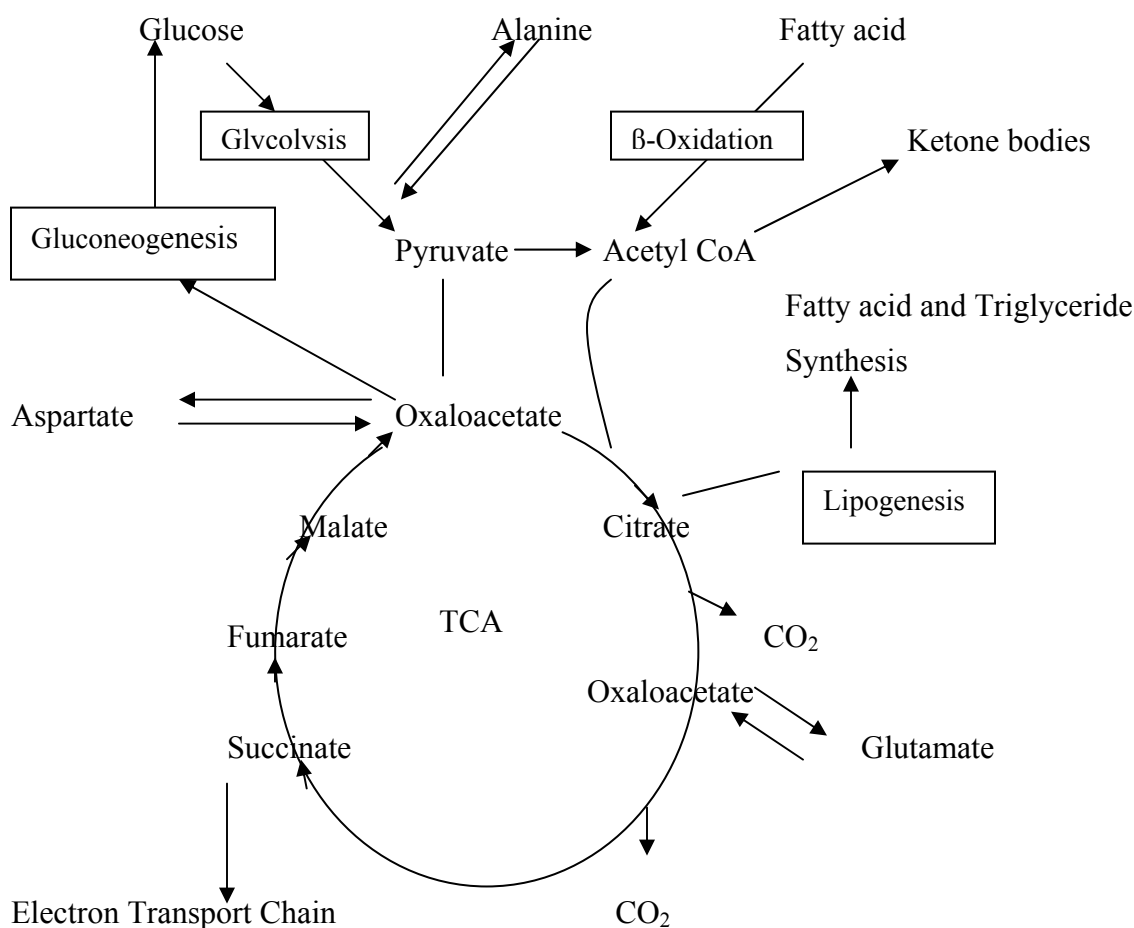


Figure 2. Pathway interactions: Major oxidative pathways may also act as routes linking other pathways. The citric acid cycle links carbohydrate and fat metabolism and is involved in the metabolism of amino acids. It provides an important control point for regulating metabolite flow in these pathways. (adapted from Srivastava, L.M., 2004)

The enzyme of the glycolytic pathway link up the metabolism of glucose and other carbohydrates with fat and amino acid metabolism.

Substrates in boxes are important in interactions of the glycolytic pathway with other pathways.

3. Acetyl Co A may undergo the following actions
 - a. It may be oxidized to CO_2 via the citric acid cycle.
 - b. Acetyl CoA may be used in fatty acid synthesis.
 - c. It may be converted to 3-hydroxy-3-methylglutaryl CoA (HMG CoA), which is a precursor of:
 - i. Cholesterol
 - ii. Ketone bodies
 - d. Converted to cholesterol which can synthesize steroids.

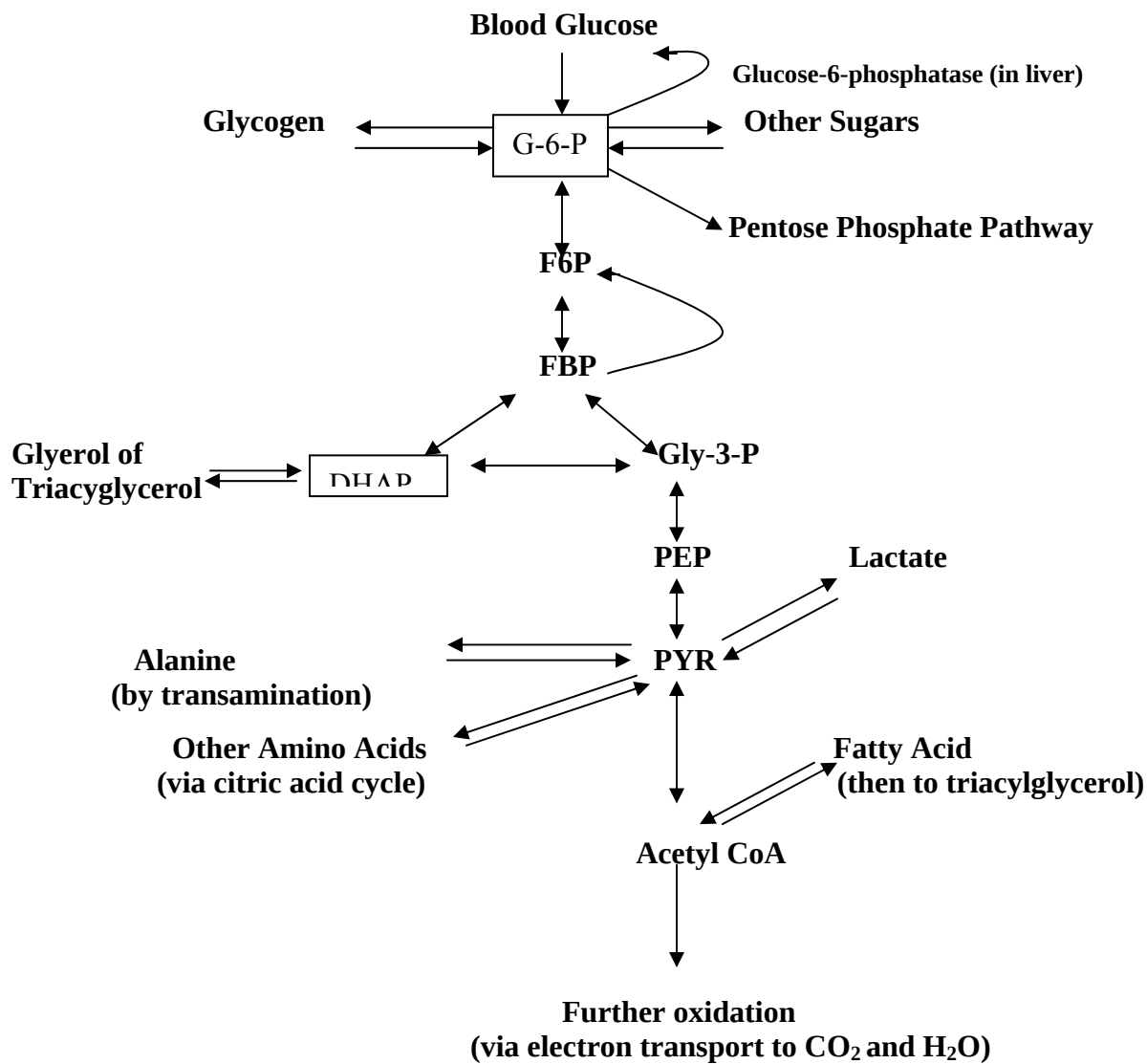


Figure 3. The enzyme of the glycolytic pathways link up the metabolism of glucose and other carbohydrates with fat and amino acid metabolism. Substrates in boxes are important in interaction of the glycolytic pathway with other pathways. (adapted from Srivastava, L.M., 2004)

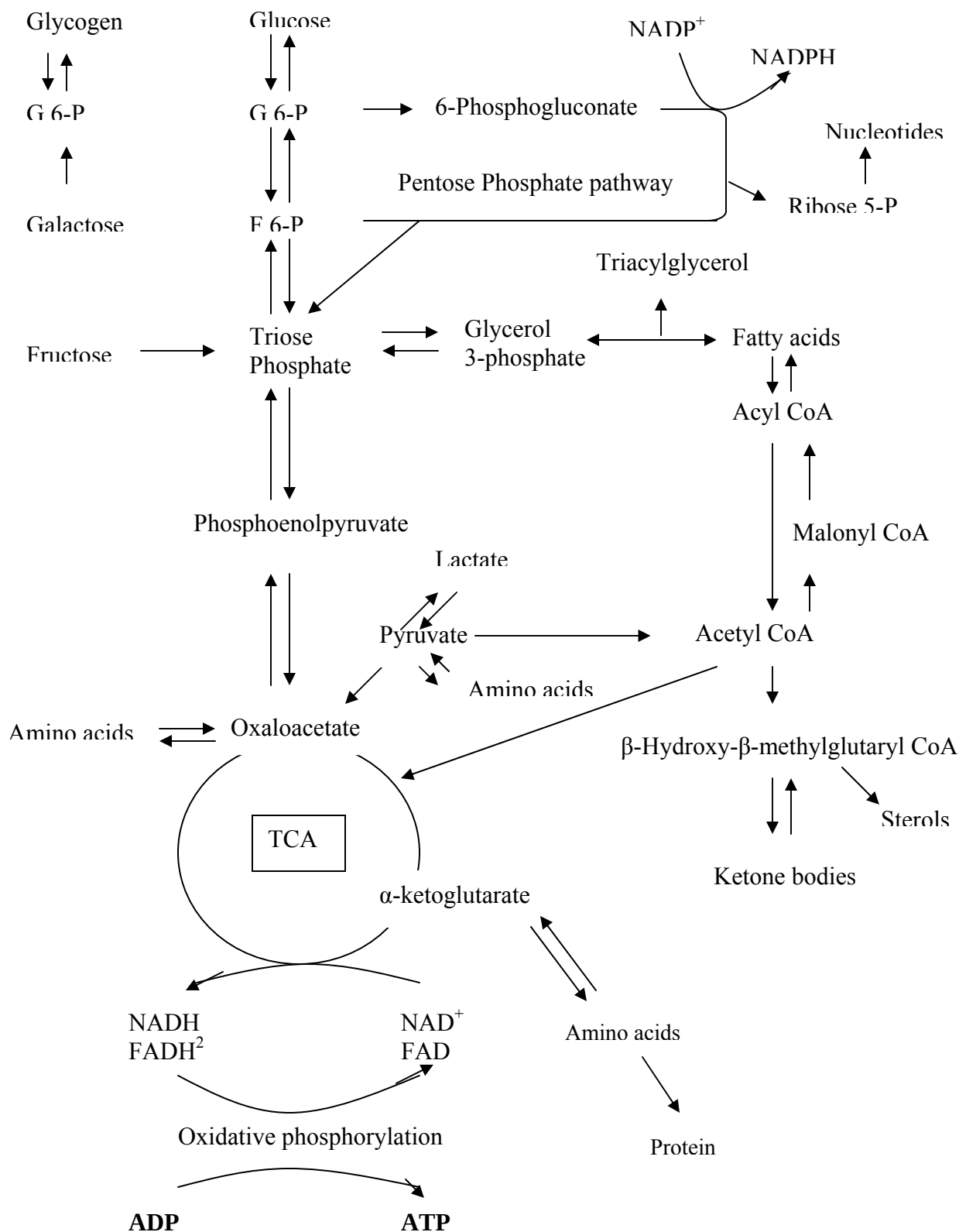


Figure 4: Interrelationship of metabolism at the cellular level

Metabolism of specialized tissues and organ interrelationship

All the metabolic pathways are not present in all cells and tissues, and their distribution varies among the major tissues. The types of fuels that are metabolized and stored also vary depending on the tissue (Figure 5). Moreover, the metabolic profile of the major tissues vary depending on the metabolic state of the body (Table 4). An understanding of Interrelationship of metabolic pathways and organ interrelationship would be helpful in developing a rational approach for the treatment of diseases whenever one encounters abnormalities in the metabolism of such constituents.

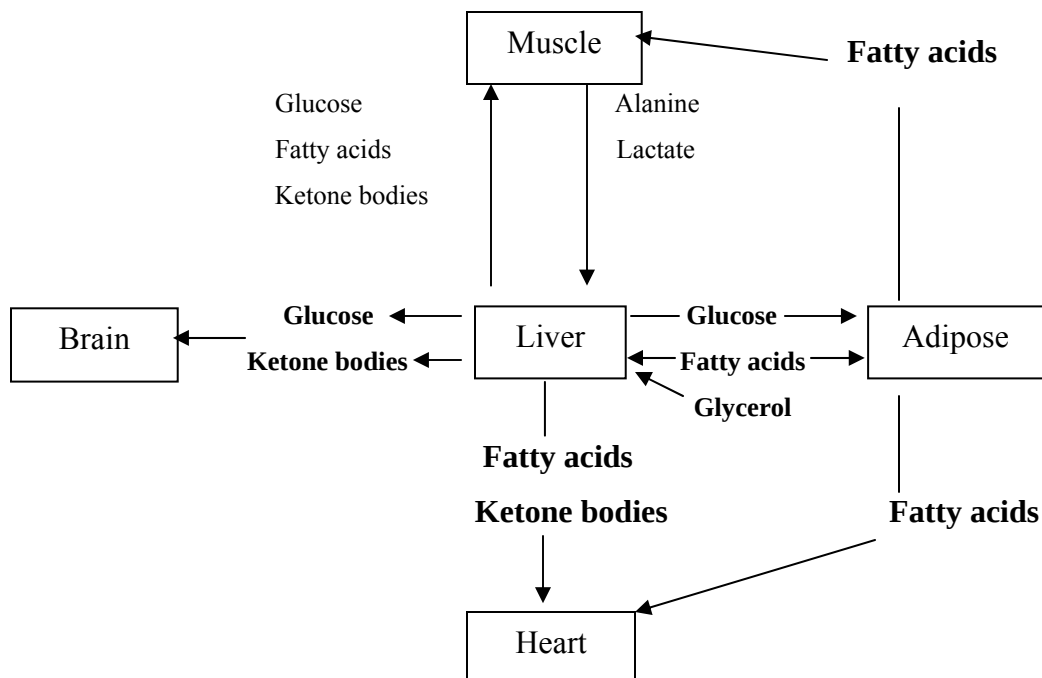


Figure 5. Inter-relationship of metabolism among major organs/tissues of the body
(adapted from Srivastava, L.M., 2004)

Liver

Function

The liver plays a central role in metabolism in regulating the blood levels of glucose and other metabolic fuels. Most low molecular weight metabolites that appear in the blood after digestion are first carried to the liver from the intestine through the portal vein.

Major role of the liver include the following:

- The liver is responsible for the maintenance of blood glucose levels.
 - During the fed state, the liver takes up excess glucose and stores it as glycogen or converts it to fatty acids.
 - During the fasting state, the glycogenolysis and gluconeogenesis by the liver are the major sources of glucose for the rest of the body.
- The liver serves as the major site of fatty acid synthesis.
- The liver synthesizes ketone bodies during starvation.
- The liver synthesizes plasma lipoproteins.

Tissue	Metabolic State	Imported Fuel	Exported Fuel	Stored Fuel
Liver	Fed	Glucose	Fatty acids	Glycogen
	Fasting	Fatty acids	Glucose	-----
	Starvation	Amino acids	Ketone bodies	-----
Muscle	Fed	Glucose	Lactate	Glycogen
	Fasting	Fatty acids		
	Starvation	Fatty acids	Amino acids	
Adipose	Fed	Fatty acids	-----	
	Fasting	-----	Fatty acids, glycerol	-----
	Starvation	-----	Fatty acids, glycerol	-----
Heart	Fed	Fatty acids	-----	-----
	Fasting	Fatty acids	-----	-----
	Starvation	Ketone bodies	-----	-----
Brain	Fed	Glucose	-----	-----
	Fasting	Glucose	-----	-----
	Starvation	Ketone bodies	-----	-----

Table 4: Metabolic Profiles of Major Tissues
(adapted from Srivastava, L.M., 2004)

Skeletal muscle is the major consumer of metabolic fuel and oxygen, owing to its great mass compared with other tissues. Its major role include the following:

- Skeletal muscle maintains large stores of glycogen, which provide a source of glucose for energy during exertion.
- In resting muscle, the preferred fuel is fatty acids.
- The protein contained in muscle may be mobilized as a fuel source, if no other fuel is available.
- Pyruvate, the product of glycolysis, in the skeletal muscle may be converted to either lactate or alanine and exported to the liver, where it is used to regenerate glucose via gluconeogenesis (Cori's cycle) (Figure 6).

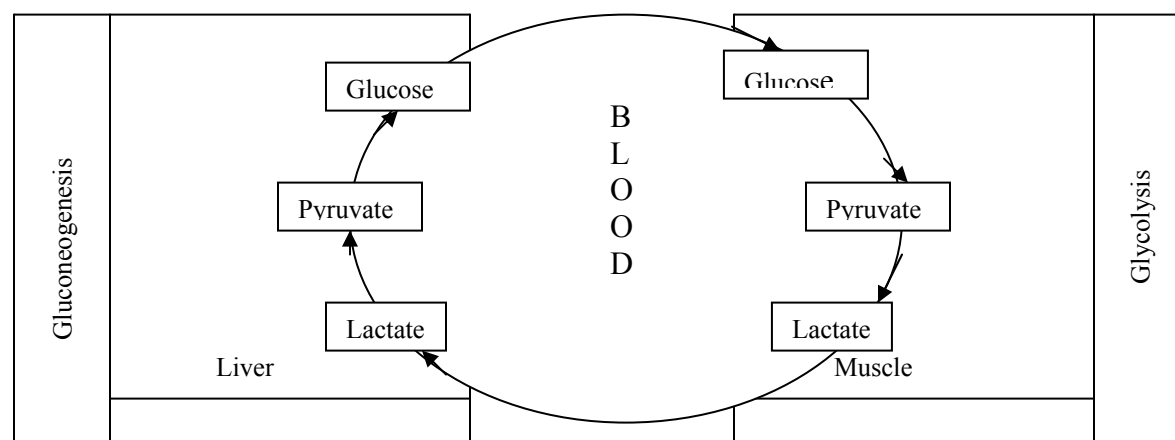


Figure 6. Cori's Cycle (adapted from Srivastava, L.M., 2004)

Heart muscle differs from skeletal muscle in the following manner:

- a) The workload of heart muscle is much less variable than that of skeletal muscle.
- b) Heart muscle is a completely aerobic tissue, whereas skeletal muscle has a limited capacity to function anaerobically.
- c) Heart muscle contains essentially no fuel reserves and must be continuously supplied with fuel from the blood.

Adipose tissue : The primary function of the adipose tissue is the storage of metabolic fuel in the form of triacylglycerols. Its major role include the following:

- a) During the fed state, the adipose tissue synthesizes triacylglycerols from glucose and fatty acids, which are synthesized in the liver and exported as very low-density lipoproteins.
- b) During the fasting state, triacylglycerols are converted to glycerol and fatty acids, which are exported to the liver and other tissues.

Brain tissue normally uses glucose as an exclusive fuel, except during starvation, when it can adapt to use ketone bodies as an energy source. The brain contains essentially no fuel reserves and must be continuously supplied with fuel the blood.

Regulation of gluconeogenesis and glycolysis

Allosteric regulation of opposing pathways from pyruvate to glucose and from glucose to pyruvate is described below. Figure 7 summarizes the control points in the pathways between pyruvate and glucose in animal tissues. The first reaction in the uphill pathway from pyruvate to glucose is catalyzed by a regulatory enzyme, pyruvate carboxylase, which exerts primary control. This reaction is promoted by the allosteric modulator acetyl CoA. As a consequence whenever excess mitochondrial acetyl-CoA builds up beyond the immediate needs of the cell for fuel, glucose synthesis is promoted.

The secondary control point of this pathway is the reaction catalyzed by hexose diphosphatase which is stimulated by the glucose precursors, citrate and 3PG and inhibited by AMP, fructose-1, 6-diphosphate. Thus the pathway from pyruvate to glucose is regulated both by the level of respiratory fuels such as acetyl-CoA and citrate and by the energy charge of the ATP system.

In contrast, the down hill pathway from glucose to pyruvate, is primarily regulated by the allosteric enzyme PFK, which is stimulated by AMP and ADP, fructose-1, 6-diphosphate but inhibited by ATP, citrate and NADH. A secondary point of regulation of glycolysis is provided by hexokinase, which is inhibited by glucose-6-phosphate and possibly acetyl CoA, and PEP. Another regulator of glycolysis is pyruvate kinase which is inhibited by ATP, NADH and alanine but stimulated by fructose-1,6-diphosphate and glucose-6- phosphate

To summarize whenever the cell has an ample level of ATP and whenever respiratory fuels such as acetyl CoA, citrate or NADH are readily available, glycolysis is inhibited and glucogenogeneis promoted, on the contrary when the energy charge is low or respiratory fuels are not available, glycolysis is accelerated and gluconeogeneis is inhibited.

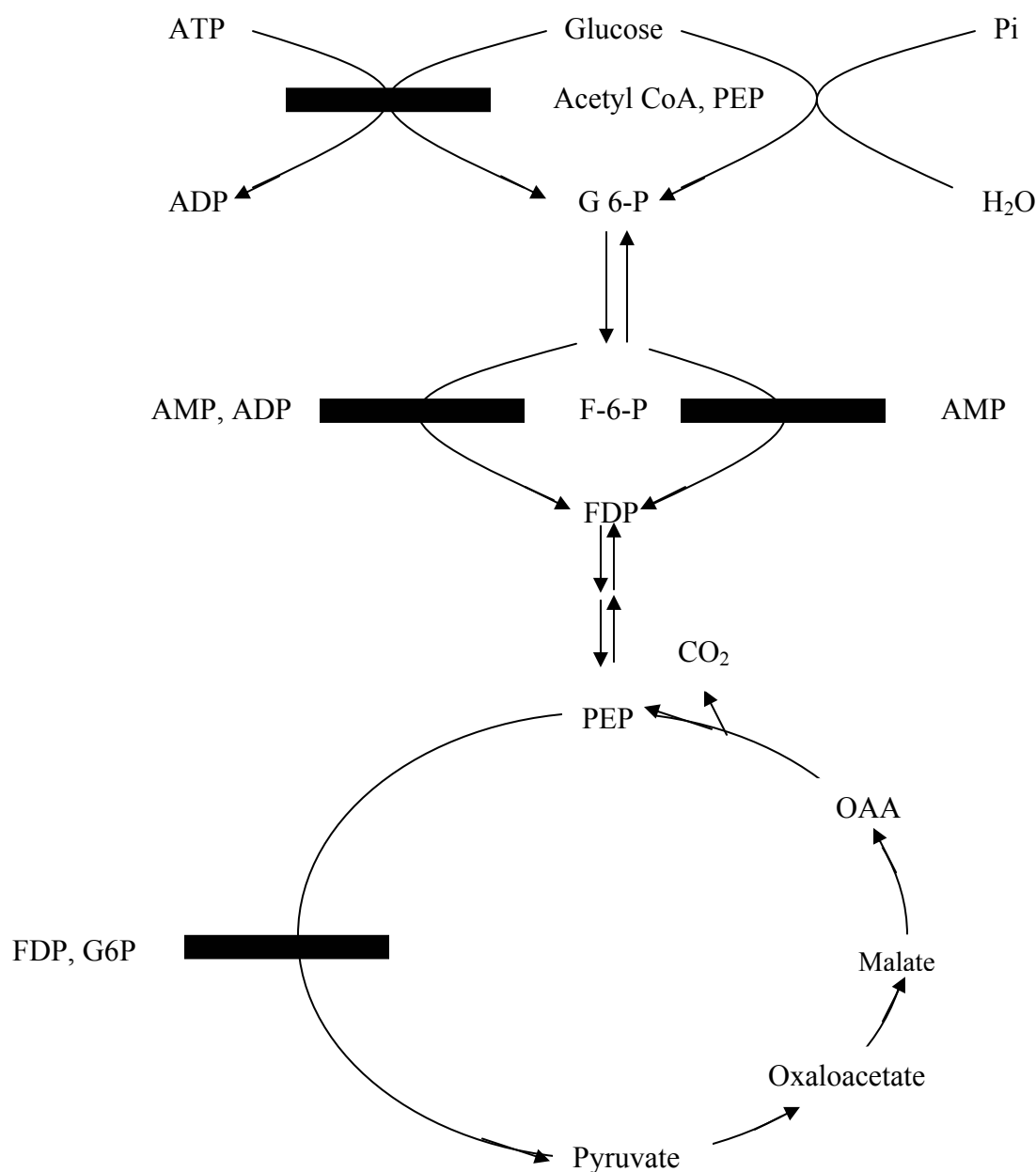


Figure 7: Regulation of Gluconeogenesis and Glycolysis
(adapted from Srivastava, L.M., 2004)

Superimposed on the allosteric regulation of the reactions of glycolysis and gluconeogenesis is the regulation of biosynthesis of certain key enzymes involved in these pathways. Administration of excess glucose, fructose or glycerol to fasted rats, depends the PEPCK activity of the liver (catalyzes the conversion of OAA → PEP). This effect is due to suppression of the biosynthesis of this enzyme, presumably because it is not needed when the liver is supplied with ample supplies of glucose. On the other hand feeding excess glycogenic amino acids enhances the biosynthesis of PEPCK, required for the conversion of these amino acids into glucose.

Regulation of the Tricarboxylic acid cycle

The activity of the pyruvate dehydrogenase complex which furnishes a major portion of the acetyl – CoA input into the cycle, is diminished by the:

1. ATP-dependent phosphorylation of the dehydrogenase component and is activated by the dephosphorylation of the phosphoenzyme.
2. The condensation of acetyl-CoA with oxalacetate to yield citrate (Citrate synthase) is the primary control point of the TCA cycle in most tissues.
3. There are other reactions in the cycle that are under allosteric regulation; at least in some tissues the first of these is the NAD-linked isocitrate dehydrogenase reaction, which requires ADP as a positive or stimulatory allosteric modulator. In some tissues e.g. insect flight muscle Ca^{++} also functions as a positive modulator of this reaction.
4. The other reaction that appears to be under regulation is succinate dehydrogenation which is promoted by high concentration of succinate, phosphate, ATP and reduced ubiquinone, and is potently inhibited by oxaloacetate. Although this reaction is not usually the rate setting step in the cycle, it competes with the NAD linked reactions in donating electrons to the electron transport chain, and thus may affect the integration of the dehydrogenation reaction of the cycle.
5. The TCA cycle also is regulated by the concentration of its intermediates. Because some of the reactions also function in biosynthesis, a complex network of controls regulates the rate of the TCA cycle.

Regulation of glycogen synthesis and breakdown

Glycogen phosphorylase

Glycogen phosphorylase was the first enzyme shown to be allosterically regulated and the first to be shown to be controlled by reversible phosphorylation. It is also one of only a few allosteric enzymes for which the detailed 3-D structures of the active and inactive forms are known from X-ray crystallographic studies.

In skeletal muscle, glycogen phosphorylase occurs in two forms: a catalytically active form, phosphorylase a and a usually inactive form phosphorylase b, latter predominate in resting muscle. The rate of glycogen breakdown in muscle depends in part on the ratios of phosphorylase a (active) to phosphorylase b (less active) which is adjusted by the action of hormones such as epinephrine.

Phosphorylase a consists of two identical subunits in each of which the serine residue at position-14 is phosphorylated. Phosphorylase b is structurally identical except that the serine residues are not phosphorylated. Phosphorylase a is converted into the less active form phosphorylase b by dephosphorylation catalyzed by phosphorylase a phosphatase. Phosphorylase b is converted back into phosphorylase a by the enzyme phosphorylase b kinase which catalyzes phosphate transfer from ATP.

Covalent and allosteric regulation of glycogen phosphorylase in muscle

Hormones ultimately regulate the interconversion of phosphorylase a phosphatase and phosphorylase b kinase. Epinephrine is released into the blood by the adrenal gland leading to the production of ATP, which participates in the conversion phosphorylase b to phosphorylase a. phosphorylase release glucose-1-phosphate from glycogen, which is metabolized in the glycolytic pathway. Superimposed on the hormonal control is faster, allosteric regulation of glycogen phosphorylase b by ATP and AMP. Phosphorylase b is activated by AMP which increases in concentration in muscle during ATP breakdown, in muscle contractions, this stimulation can be prevented by high concentration of ATP which blocks the AMP binding site. Phosphorylase a, which is not stimulated by AMP is sometime referred to as AMP independent form and phosphorylase b as the AMP dependent form (Figure 8).

A third control is at the level of Ca^{+2} which is an allosteric activator of phosphorylase b kinase. A transient role of Ca^{+2} in muscle contraction accelerates conversion of phosphorylase b to phosphorylase a.

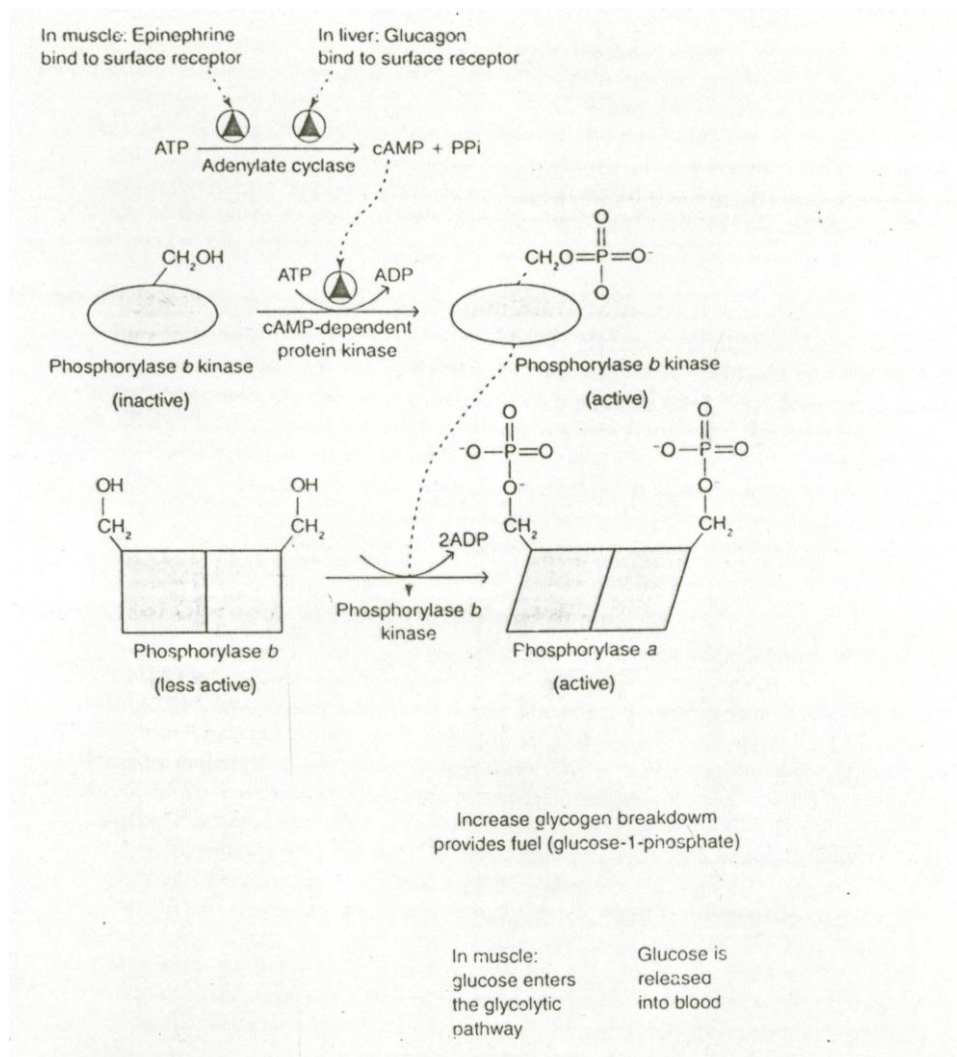


Figure 8: Covalent and allosteric regulation of glycogen phosphorylase in muscle and liver

Liver glycogen phosphorylase

The glycogen phosphorylase of liver is similar to that of muscle. It too is a dimer of identical subunits and it undergoes phosphorylation and dephosphorylation on Ser⁺¹⁴ interconverting the b and a forms. Its regulatory properties are slightly different from those of the muscle enzyme. Liver glycogen serves as a reservoir that releases glucose into blood when glucose levels fall below normal levels (4 to 5 mM). G-1-p is formed which is converted by glucose-6-phosphatase, an enzyme present in liver and very low in muscle to glucose which leaves the liver cell to go into the blood and carried to tissues to be used as fuels. When glucagon binds to its receptor in the plasma membrane, a cascade of events similar to that in muscle results in the conversion of phosphorylase b to phosphorylase a increasing the rate of glycogen breakdown and thereby increasing the rate of glucose increase in the blood. It is also subjected to allosteric regulation, and the allosteric regulator is glucose not AMP. When the level of glucose in the blood rises glucose enters the hepatocyte and binds to the regulatory site of the phosphorylase a causing a conformational change that exposes the phosphorylated Ser⁺¹⁴ residues to dephosphorylation by phosphorylase a phosphatase. In this way glycogen phosphorylase a acts as the glucose sensor of liver slowing down the breakdown of glycogen whenever the level of blood glucose is high which also phosphorylates and thus inactivates glycogen synthase directly.

The regulation of glycogen synthesis and utilization is locked into the regulatory mechanisms of glycolysis and of the TAC cycle.

An excess of glucose reflected as a high concentration of g6p or an ample supply of other fuels reflected as a high energy charge tends to turn on glycogen synthase and turn off glycogen phosphorylase resulting in the storage of glucose as glycogen in the liver and muscle.

Conversely when fuels are required because the energy charge is low as in muscular work or when the blood glucose is low, glycogen phosphorylase is stimulated and glycogen synthase inhibited thus causing liver glycogen to be broken down to yield blood glucose and muscle glycogen to yield glucose 6-phosphate as fuel for glycolysis.

Glycogen synthase like glycogen phosphorylase is subject to regulation through both allosteric and covalent modification. Glycogen synthase occurs in two forms. The phosphorylated form is inactive by itself. This form is however stimulated by the presence of the allosteric modulator g-6-p and is therefore called the D-or dependent form. The phosphate group in the D-form of the enzyme is acted upon by a phosphoprotein phosphatase to yield the dephosphorylated or active form of the glycogen synthase, which does not require g6p and is thus called the I or the independent form. The dephosphorylation of glycogen synthesis itself is inhibited by glycogen, a negative allosteric modulator.

The glycogen phosphorylase of animal tissues exists in two form a and b, phosphorylase a is the more active form and phosphorylase b the less active form.

The I-form of glycogen synthase can be inactivated by protein kinase an enzyme that can phosphorylate several different proteins at the expense of ATP. Protein kinase in turn is allosterically activated by cAMP formed as a result of the binding of certain hormones, such as epinephrine and glucagon to specific receptor sites on cell membranes.

Although the interconversion of glycogen synthase between active and inactive forms by the addition or loss of phosphate groups resembles that of glycogen phosphorylase the net effect of the glycogen synthase regulatory cycle is opposite to that of glycogen phosphorylase. Phosphorylase a, the phosphorylated form of the enzyme is fully active whereas the dephosphorylated form phosphorylase b is inactive unless AMP, which is a positive allosteric modulator is present. Phosphorylase a is dephosphorylated by phosphorylase phosphatase and the resulting Ph-b is rephosphorylated to the active form by phosphorylase kinase. This enzyme also exists in active and inactive or phosphorylated or dephosphorylated forms.

The inactive form is activated through the action of protein kinase, which also phosphorylates (and thus inactivates) glycogen synthase directly. The regulation of glycogen synthesis and utilization is locked into the regulatory mechanisms of glycolysis and of the TCA cycle.

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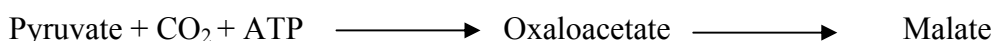
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Superimposed on these controls over glycogen synthase and glycogen phosphorylase which reflect the level of glucose 6-phosphate and the energy charge, is another set of controls involving regulation by hormones particularly epinephrine, glucagon and insulin whose effects are mediated by c AMP or c GMP and other factors.

Regulation of Carbohydrate Biosynthesis

The central common pathway in the biosynthesis of most carbohydrates from non-carbohydrate precursors is the route from pyruvate to glucose 6-phosphate. Most of the reversible reactions of glycolysis are utilized in the biosynthetic direction. However, two irreversible reactions of glycolysis are replaced by bypass reaction that is energetically favourable for synthesis.

In the first the pyruvate is converted into PEP by the mitochondrial sequence



followed by the cytoplasmic sequence



The second bypass is the hydrolysis of FDP to F6p by hexosediphosphatase

Glucose 6-phosphate formed in this central pathway from pyruvate may be dephosphorylated to form free glucose by glucose 6-phosphatase.

The rate of gluconeogenesis is primarily regulated by the first reaction of the sequence (pyruvate carboxylase) and secondarily is hexose diphosphatase. Glycolysis and gluconeogenesis are

independently regulated. They may occur simultaneously and thus may give rise to futile cycle in which ATP energy is lost.

Lactate and the intermediates of the TCA cycle can undergo net conversion into glucose as can the glycogenic amino acids. On the other hand neither acetyl - CoA nor CO₂ can undergo net conversion into glucose in animal tissues. However in plants and microorganisms acetyl CoA is converted into glucose by operation of the glyoxalate cycle.

Nucleoside diphosphate sugars, particularly uridine diphosphate derivatives are precursors of other monosaccharides such as D-galactose, of disaccharides such as sucrose and lactose and of various polysaccharides.

Formation of glycogen by glycogen synthase requires UDPG as the glucose donor. Glycogen synthase occurs in phosphorylated or D form which is relatively inactive but is stimulated somewhat by g6p and a dephosphorylated or I form which is maximally active and is independent of g6p as modulator. The phosphate group of the D-glycogen synthase is removed by a phosphoprotein phosphatase. The I form can be rephosphorylated by protein kinase, whose inactive form is converted into the active enzyme by cyclic adenylate (C AMP)

Glycogen synthase and glycogen phosphorylase activity are independently controlled in muscles and the liver.

Nucleoside diphosphate sugars are also glycosyl donors in the biosynthesis of extracellular structural polysaccharides such as cellulose and xylases and the oligosaccharide side chains of glycoproteins in animals' tissue and the peptidoglycan of cell walls of bacteria.

Major oxidative pathways act as routes linking other pathways. The citric acid cycle links carbohydrate and fat metabolism and is also involved in the metabolism of amino acids. It provides an important control point for regulating metabolite flow in these pathways (Figures 1-3). The regulation of glycogen synthesis and utilization is locked into the regulatory mechanisms of glycolysis and of the TCA cycle.

Suggested Readings

1. Srivastava, L.M. Interrelationship between the metabolism of Carbohydrate, Fats and Proteins. **In** Concepts of Biochemistry for medical students. CBS Publisher, 2004. pp. 307-21.
2. Biochemistry Part I-IV, Volume 1: Molecular aspects of cell biology. Part V, Volume 2. Garret, Reginald H. and Grisham, Charles M. Saunders Publishing and Harcourt Brace Publisher.
3. Harpers biochemistry. Prentice Hall International.