

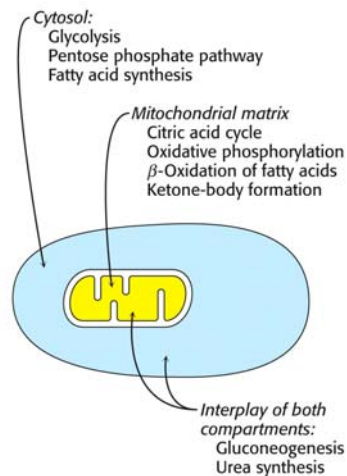
Integration of Metabolism

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I. Central Themes of Metabolism

1. ATP is the universal energy carrier.
2. ATP is generated by the oxidation of metabolic fuels
 - Glucose
 - Fatty Acids
 - Amino Acids
3. NADPH is the redox agent for reductive biosynthesis.
4. Biomolecules are constructed from a small set of building blocks.
5. Biosynthetic and Degradation pathways are distinct.

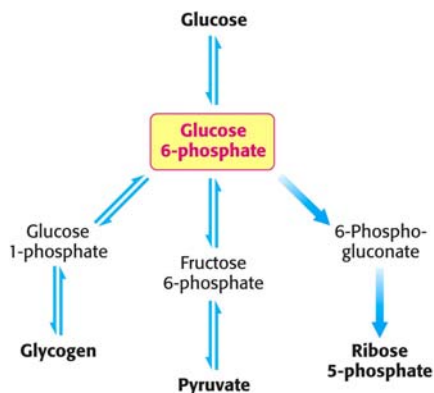
II. Major Metabolic Pathways



1. Glycolysis
2. Gluconeogenesis
3. Glycogen Metabolism
4. Fatty Acid Metabolism
5. Citric Acid Cycle
6. Oxidative Phosphorylation
7. Amino Acid Metabolism

Only the liver can carry out all of the reaction the major pathways.

The key junction points are Glucose-6-phosphate, Pyruvate and Acetyl CoA,

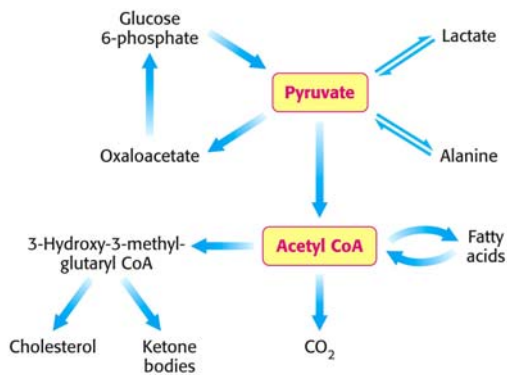


When glucose is transported into the cell it is rapidly phosphorylated to glucose-6-phosphate. Glucose-6-phosphate may be catabolized into pyruvate, stored as glycogen or converted into ribose 5-phosphate by the pentose phosphate pathway.

Glucose 6-phosphate can be generated from glycogen stores or by gluconeogenesis.

Pyruvate is another key junction point. Pyruvate is generated from glucose 6-phosphate by glycolysis. Pyruvate is converted into lactate under anaerobic

conditions to regenerate NAD^+ . This buys time for active tissues. The lactate produced must be subsequently oxidized back into pyruvate. Pyruvate is also transaminated to form alanine. Several amino acids are degraded into pyruvate. Pyruvate may be carboxylated to form oxaloacetate in the matrix of the mitochondria. This is the first step of gluconeogenesis. This reaction also replenishes the intermediates of the citric acid cycle. The fourth fate of pyruvate is the reduction of pyruvate into acetyl CoA by the pyruvate dehydrogenase complex. This is an irreversible step committing the pyruvate for oxidation.



The third junction point is acetyl CoA. Acetyl CoA is the activate 2-carbon unit produced by the oxidative decarboxylation of pyruvate or by the β -oxidation of fatty acids. Acetyl CoA is also produced by the degradation of ketogenic amino acids. Acetyl CoA may be completely oxidized into CO_2 via the citric acid cycle, converted into HMG-CoA which in turn may be converted into ketone bodies or cholesterol. Acetyl CoA may be exported into the cytosol and converted into fatty acids.

III. Organ Specialization

1. Brain

Glucose is the primary fuel for the brain. Only under prolonged starvation does the brain use ketone bodies as fuel. The brain has no capacity to store fuels and needs a continuous supply of glucose. The brain consumes a lot of energy to maintain the electrostatic potentials required for nerve impulse transmission. The average brain consumes 120 g of glucose a day. 70% of the energy is used to maintain the Na^+ , K^+ membrane potentials. The brain also synthesizes neurotransmitters and receptors.

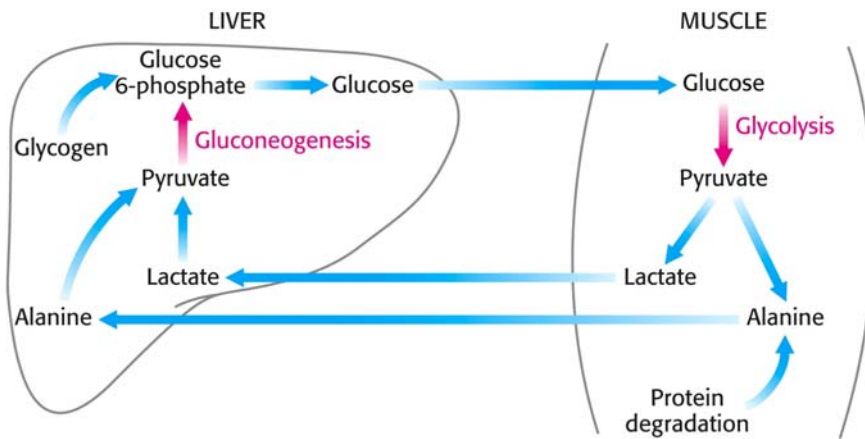
Glucose is transported into the brain by the GLUT3 glucose transporter. This transporter has a K_m for glucose of 1.6 mM. The blood glucose concentration is maintained around 5 mM. So the transporter is saturated under normal conditions. Thus the brain has a steady continuous supply of glucose. The steady concentration of glucose in the brain tissue is around 1 mM.

If the blood glucose concentration drops below 2.2 mM which is around the K_m of the GLUT3 transporter, the brain is in trouble. If the blood glucose concentration remains below 2.2 mM, the brain becomes dysfunctional leading to coma and brain death. Fatty acids cannot fuel the brain because they cannot traverse the brain blood barrier. Under prolonged starvation ketone bodies can replace glucose as a fuel for the brain.

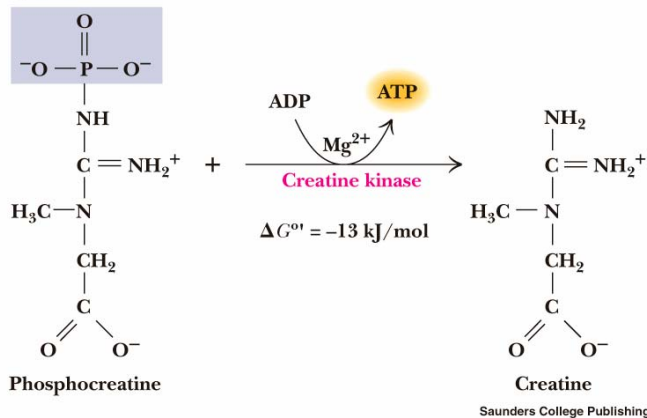
2. Muscle

The muscles can use glucose, fatty acids and ketone bodies for fuel. Unlike the brain the muscles have stores of glycogen. This glycogen is readily converted into glucose when needed for bursts of activity. ATP can be generated faster by glycolysis than by oxidative phosphorylation. As a result, the rate of glycolysis far exceeds the maximum rate of the citric acid cycle. When this happens pyruvate is converted into lactate to regenerate NAD^+ needed for glycolysis. The accumulation of lactic acid decreases the pH and reduces the muscle efficiency. The lactate is released by the muscle tissue into the blood where it is absorbed by the liver and by gluconeogenesis reconverted back into glucose. This interchange is called the Cori cycle. This shifts the metabolic burden for the reduction of lactate from the

active muscle tissue to the liver. The muscles account for 50% of the total oxygen consumption in the resting state, but during vigorous exercise the muscles account for 90% of the oxygen consumption. After a period of intense muscular activity, heavy breathing occurs for some time. Much of the oxygen is used for oxidative phosphorylation to restore ATP and phosphocreatine levels. The liver requires ATP to convert lactate back into glucose.



Garrett & Grisham: Biochemistry, 2/e
Figure 28.10

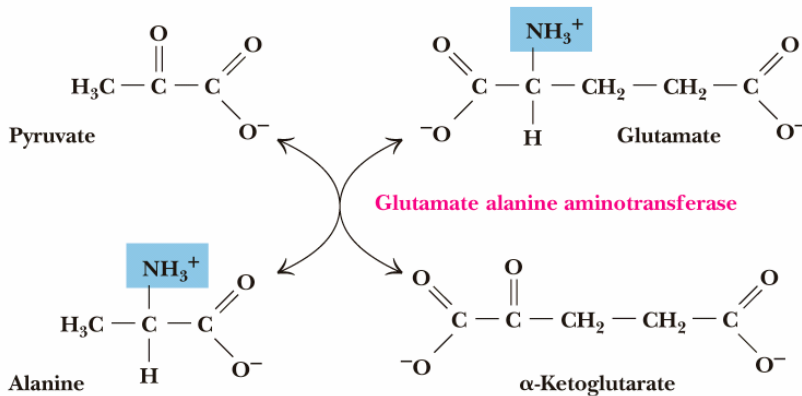


Skeletal muscle contains 10-30 mM phosphocreatine. Phosphocreatine is used to rapidly regenerate ATP from ADP using phosphocreatine kinase. During vigorous muscular work all the phosphocreatine is converted into creatine. During recovery phase creatine is rephosphorylated to phosphocreatine.

Muscle fatigue is not the result of the depletion of phosphocreatine and glycogen reserves. Nor is muscle fatigue caused by the accumulation of lactate. Muscle fatigue is caused by the decrease in pH caused by the 2 protons produced from converting glucose into 2 lactate molecules. The pH of muscle cells may fall to 6.4 during intense

muscular activity. Phosphofructokinase activity is diminished as the pH decreases, which slows the flux of metabolites through glycolysis, slowing down the production of ATP, producing fatigue.

During fasting or during excessive activity, muscle tissue is degraded into amino acids and the carbon skeletons are used for fuel. Muscle tissues lack the enzymes to convert ammonia into urea. Instead, Alanine transaminase transfers the amino group to pyruvate to form alanine. Under these conditions the muscle tissue produces large amount of alanine by the transamination of pyruvate. Alanine is released by the muscle tissue into the blood stream where is absorbed by the liver, deaminated to reform pyruvate which is then converted into glucose by gluconeogenesis. The amino group of alanine is converted into urea by the urea cycle.



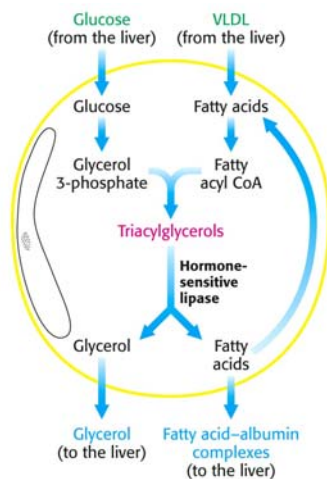
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In the resting state, the major source of fuel for the muscles is fatty acids. 85% of the resting muscle tissue's needs are met by fatty acid catabolism.

3. Heart Muscle

The heart muscle always functions aerobically and has virtually no glycogen reserves. Fatty acids are the fuel of choice for heart muscle; ketone bodies may also be the fuel for heart tissue. The heart will use ketone bodies over glucose as a source of fuel. Lactate can also serve as a fuel for the heart.

4. Adipose Tissue



The function of the adipose tissue is to store triacylglycerols and release fatty acids as needed. The liver is the major site of fatty acid synthesis. These fatty acids are esterified with glycerol to form triacylglycerols and packaged for transport as very low density lipoproteins. The adipose tissue absorbs the free fatty acids carried by the very low density lipoproteins by hydrolyzing the triacylglycerols with extracellular lipoprotein lipases. The lipases are activated by insulin. After the fatty acids have been transported into the adipose cell, the triacylglycerols are reassembled and stored. Adipose tissue needs a steady supply of glucose to generate glycerol 3-phosphate needed for triacylglycerol synthesis.

When the blood glucose concentration is low, glucagon activates a lipase which hydrolyzes the triacylglycerol stores in the adipose tissue. The free fatty acids and glycerol are released into the blood stream. Serum albumin carries the fatty acids to the tissues and the glycerol is absorbed by the liver and used for gluconeogenesis.

5. The Kidney

The major role of the kidney is to produce urine which is a vehicle for excreting water soluble waste products. During starvation the kidney becomes an important site of gluconeogenesis and may produce up to half of the blood's glucose.

6.) The Liver

The liver is the center of metabolism. The liver maintains the blood glucose level and regulates the concentration of metabolites in the blood. The liver stores a day supply of glucose as glycogen. The liver synthesizes fatty acids, cholesterol and bile salts. When the blood glucose concentration is high, fatty acids are synthesized by the liver, converted into triacylglycerols and packaged as very low density lipoproteins which are secreted into blood. During the fasting state the liver produces ketone bodies which fuel the heart and muscles preserving glucose for the brain. The liver has many enzymatic differences compared to other tissues.

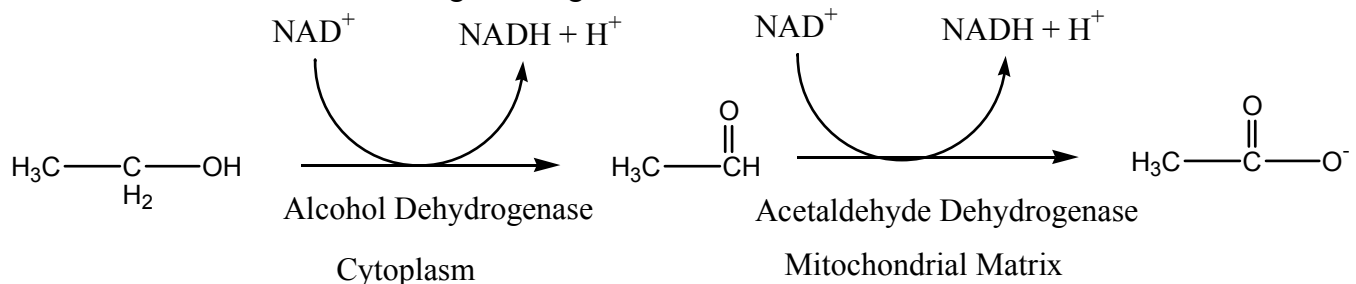
- The liver has glucokinase instead of hexokinase. Glucokinase has a K_m for glucose of 5 mM. Which means at the typical blood glucose concentration, Glucokinase operates at half its maximal velocity. Glucokinase activity increases rapidly as the blood glucose concentration goes up.
- Only the liver and kidneys contain Glucose 6-phosphatase, because only these tissues maintain the blood glucose level.
- The liver does not contain CoA transferase which is required to use ketone bodies as fuel. Thus the liver produces the ketone bodies but can not utilize them so they are exported out into the blood stream.

Only the liver and kidneys contain CPSI and the urea cycle enzymes.

The majority of amino acids are catabolized in the liver. The reason is that the only the liver (and kidneys) can converted the ammonia produced by the catabolism of amino acids into urea.

IV. Alcohol Metabolism

The liver is also the where ethanol metabolism occurs. Excessive ethanol consumption causes a number of health problems most notably liver damage. Ethanol cannot be excreted. It must be metabolized. The liver contains alcohol dehydrogenase and aldehyde dehydrogenase which oxidize ethanol into acetate. This oxidation consumes 2 NAD^+ generating 2 $NADH$.



The excess $NADH$ slows down the rate of gluconeogenesis as NAD^+ becomes limiting for converting lactate back into pyruvate. The excess $NADH$ slows down glycolysis as NAD^+ becomes limiting for converting glyceraldehydes 3-phosphate into 1,3-bisphosphoglycerate. The β -oxidation of fatty acids also slows down as NAD^+ becomes limiting. This results in higher triacylglycerol levels in the liver. For Alcoholics the triacylglycerols accumulate as fatty deposits in the liver. Because the liver is unable to convert lactate into glucose, the blood lactate concentration goes up which causes acidosis producing all of those unpleasant hang over side effects.

The acetate is converted into Acetyl-CoA in the matrix of the mitochondria. The citric acid cycle is shut down because the matrix concentration of NADH is high shutting of isocitrate dehydrogenase and α -ketoglutarate dehydrogenase. The acetyl-CoA is thus diverted into ketone bodies, which are released into the blood exacerbating the acidosis condition.

Liver damage from excessive alcohol consumption occurs in three stages.

1. Development of fatty liver deposits.
2. Alcohol hepatitis- groups of liver cells begin to die producing inflammation.
3. Cirrhosis of the liver-Fibrous structures and scar tissue are produced around the dead liver cells which blocks many of the liver's necessary functions such as converting ammonia into urea. The blood ammonia concentration rises producing neurological effects which lead to coma and death.

V. Hormonal Regulation of Fuel Metabolism

The liver maintains a constant blood glucose concentration of 5 mM. In order to maintain this level, the hormone actions of insulin, glucagon and epinephrine regulated metabolism in the body tissues. Insulin is the hormone that signals the blood glucose concentration is high. The actions induce by insulin result in the uptake of glucose by the cells. Excess glucose is converted into glycogen or triacylglycerols. Glucagon signals that the blood glucose concentration is low. The tissues respond by mobilizing stored energy via glycogenolysis, mobilization of fatty acids and gluconeogenesis. Epinephrine is released into the blood to prepare the tissues for a fight or flight response.

1.) Epinephrine

When an animal is confronted with a stressful situation (such as a final exam), the brain triggers the release of epinephrine and norepinephrine from the adrenal medulla. Both of these hormones increase the heart rate and increase the blood pressure. This increases the amount of oxygen flowing to the tissues. Epinephrine binds to receptors that are found primarily in the muscle, adipose and liver tissues. In the liver, epinephrine activates gluconeogenesis and glycogen phosphorylase and simultaneously inactivates glycogen synthase by the cAMP phosphorylation cascade. The liver's glycogen stores are mobilized increasing the blood glucose concentration. Epinephrine promotes glycolysis in the muscle tissue by raising the concentration of fructose-2,6-bisphosphate which is an allosteric activator of PFK. Epinephrine mobilizes fatty acids from the adipose tissue.

2.) Glucagon

Glucagon is the hormone that signals low blood glucose levels. Glucagon stimulates glycogenolysis and gluconeogenesis in the liver and inhibits glycogen synthesis and glycolysis. Glucagon also binds to receptors in the adipose tissue activating the lipase which mobilizes fatty acids and glycerol. All of the effects of glucagon are mediated by the cAMP phosphorylation cascade.

3.) Insulin

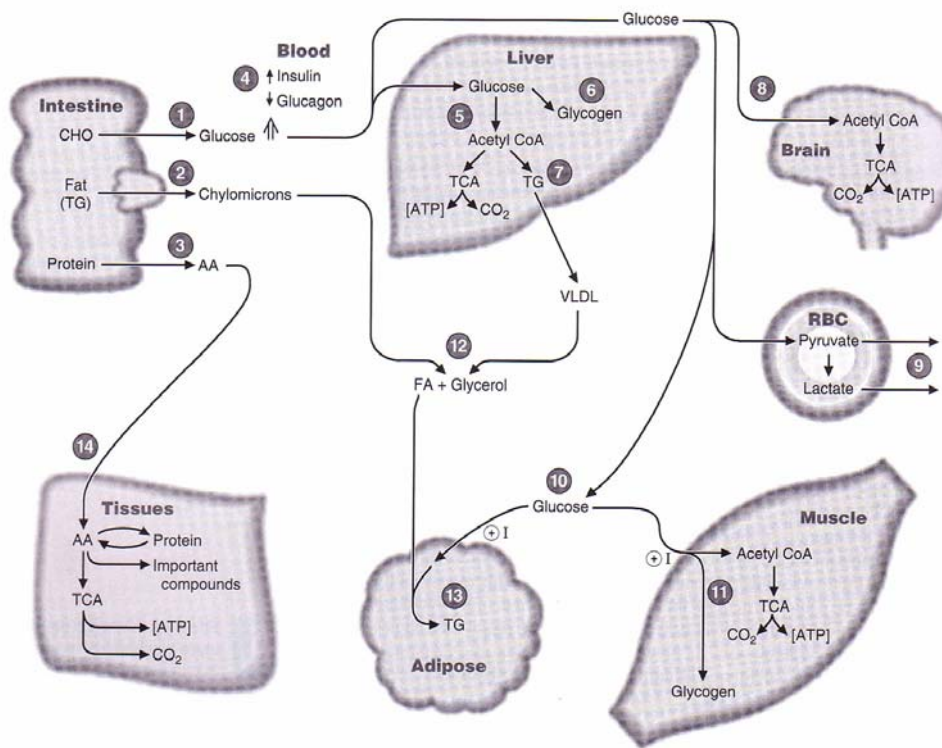
Insulin signals high blood glucose levels. Insulin increases the rate of glucose uptake by the tissues. Insulin activates glycogen synthase and simultaneously inactivates glycogen phosphorylase. Thus promoting the storage of excess glucose in the form of glycogen. Insulin also binds to receptors of adipose tissues and promotes fatty acid biosynthesis and the synthesis of triacylglycerols. Insulin also activates the absorption of fatty acids from the VLDL, further promoting triacylglycerol synthesis.

4.) Cortisol

Cortisol is a steroid hormone that signals long term stress. The stress could be anxiety, fear, pain, infections, chronic low blood glucose levels. Cortisol is produced by the adrenal cortex. Cortisol acts on muscle, liver and adipose tissue. Cortisol is a slow acting hormone that alters metabolism by changing the expression of the genes of metabolic enzymes. All steroid hormones pass through the cell's plasma membrane and the nuclear envelope and bind to nuclear receptors that regulate the expression of specific genes. In the adipose tissue, cortisol stimulates the release of fatty acids from triacylglycerol stores. Cortisol stimulates the breakdown of muscle proteins and increases the rate of the export of amino acids to the liver to be used in gluconeogenesis. Cortisol promotes gluconeogenesis by increasing the cellular concentration of pyruvate carboxylase in the liver tissue.

VI. Metabolic States

1.) Fed State



Dietary Carbohydrates.

After a typical American high carbohydrate meal, the pancreas is stimulated by the high concentration of glucose to release insulin into the blood stream simultaneously shutting down the release glucagon. The blood stream passes from the intestines to the hepatic portal vein. The liver is the first tissue the blood passes through after absorbing nutrients from the intestine. Insulin activates the liver to transport a good portion of the dietary glucose into the liver cells. Insulin activates glycolysis, so some of the glucose is used to generate ATP. The remainder of the glucose is converted into glycogen or triacylglycerols.

When the liver glycogen reaches its maximum, all of the excess glucose is diverted towards triacylglycerols. The liver synthesizes both the fatty acids and the glycerol from glucose.

Triacylglycerides are not normally stored in the liver. They are packaged with lipoproteins, phospholipids and cholesterol to form VLDL's which are released into the blood stream. Some of the fatty acids of the VLDL are taken up by the tissues, but most end up being stored in the adipose tissue.

The remainder of the glucose travels to the peripheral tissues. Insulin activates the uptake of glucose by the muscle tissue and the adipose tissue. Insulin also stimulates the adipose tissue to absorb the fatty acids carried by the VLDL's. The adipose tissue needs glucose to generate glycerol to produce triacylglycerols.

Dietary Lipids

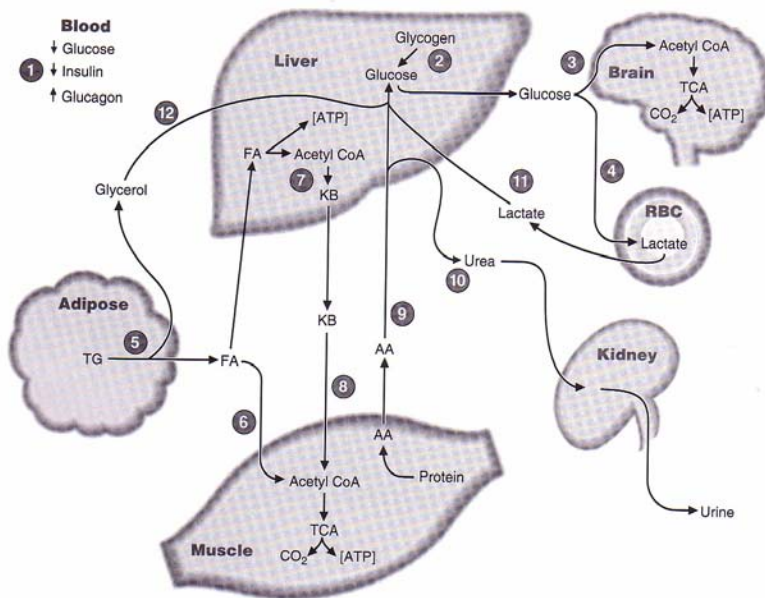
The intestinal mucosa cells absorb cholesterol, fatty acids and monoacylglycerols from the small intestine. They then reassemble the triacylglycerols and package them with cholesterol, phospholipids and lipoproteins to form chylomicrons. The chylomicrons are released into the blood stream, where tissues absorb the fatty acids. The fatty acids carried in the triacylglycerols in the chylomicrons are absorbed by the adipose tissue, reconverted into triacylglycerols and stored. The remnants of chylomicrons are absorbed by the liver cells.

Dietary Amino Acids

The intestinal mucosa cells absorb amino acids and release them into the blood stream where they are absorbed by the tissues that need them. They may be used for protein biosynthesis, converted into hemes and other cofactors or degraded and used for energy.

2.) Fasting State

Within one hour of a meal the blood glucose level begins to fall. The insulin concentration also begins to fall and the glucagon concentration begins to rise. These changes in hormone concentrations trigger the release of metabolic fuels from the body stores.

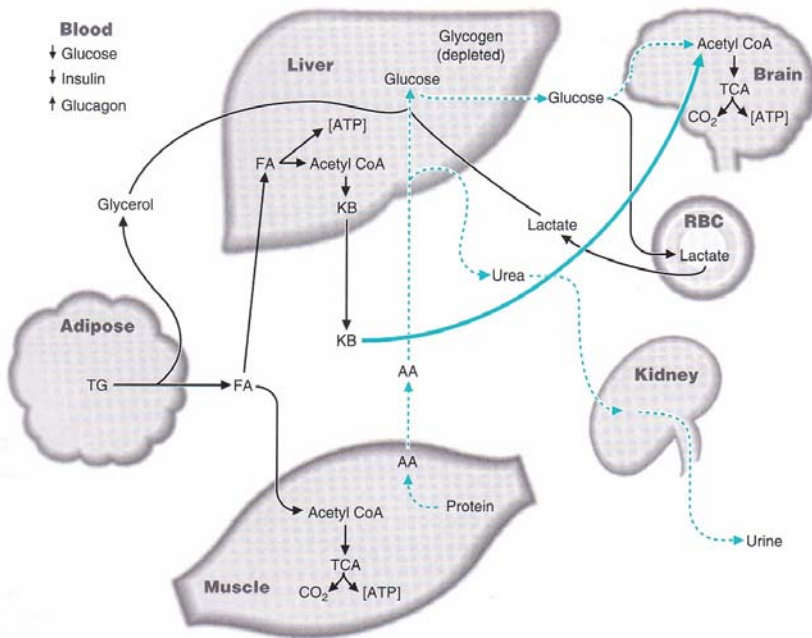


Glucagon stimulates glycogenolysis, the break down of liver glycogen to maintain the blood glucose concentration. Glucagon also stimulates gluconeogenesis, synthesizing glucose from lactate, alanine, and glycerol. As fasting progresses, gluconeogenesis becomes more important to maintain the blood glucose concentration. After 30 hours of fasting, the liver glycogen stores are depleted, and gluconeogenesis is generating all of the blood glucose. Only the glycerol moiety of triacylglycerols can be used as source of glucose. Glucagon also stimulates the break down of proteins and the catabolism of amino acids. This generates ammonia which the liver converts into urea to be excreted.

During fasting the triacylglycerols stored in the adipose tissue become the major energy source. The glycerol component is used for gluconeogenesis and the fatty acids released are oxidized by tissues such as muscle and heart tissue. The liver absorbs these fatty acids and converts them into ketone bodies which are released in the blood. These ketone bodies can fuel the muscles and heart saving glucose for the brain.

Starvation State

Prolong fasting produces the starvation state. Metabolic changes have to occur because the rate of protein catabolism would rapidly consume all of the body's protein. After 4-5 days of fasting, the body enters the starvation state. The muscles quit relying on ketone bodies for fuel and rely solely on fatty acids stored in the adipose tissue for fuel. The result is a higher concentration of ketone bodies in the blood stream. The brain begins to utilize these ketone bodies as a source of fuel. Glucose is still required to fuel the red blood cells, but now the liver needs to produce only a fraction of glucose as it did in the fasting state. The decrease in gluconeogenesis spares the muscle tissue. The decreased rate of amino acid catabolism reduces the rate of urea production.



The adipose tissue plays an important role during starvation. How long you will survive starvation depends on how much fat you have stored. During starvation fatty acids are fueling every tissue of the body except the red blood cells. When the starving person runs out of stored triacylglycerols, Proteins become the only source of fuel. Soon the proteins of the individual have become so depleted that the heart, kidneys and other tissues stop functioning.

VII. Metabolic Fuels and Athletic Performance.

The metabolic fuels used by a sprinter and a marathon runner differ. The protein in muscle cells that converts the chemical energy stored in ATP into movement is myosin. The amount of ATP in the muscle tissue is limited. Creatine phosphate is stored in the muscle tissue to quickly regenerate ATP from ADP. The creatine phosphate stores are also limited. The ATP and creatine phosphate stores can power the muscles for intense muscular work for 5 to 6 seconds. Thus the maximum speed in a sprint can only be maintained for 5 to 6 seconds. The winner of a 100 yard dash is the one who slows down the least.

The velocity of the running is also dependent on the rate of ATP production from other fuels. A 100 meter sprint is powered by ATP, Phosphocreatine and anaerobic glycolysis of muscle glycogen. Generating ATP via glycolysis is faster than oxidative phosphorylation but slower than the regeneration of ATP by phosphocreatine. Lets look at how the concentrations change in the muscle cell during the sprint. Before the sprint the concentration of ATP in the muscle tissue is 5.2 mM, The concentration of phosphocreatine is 9.2 mM, the concentration of lactate is 1.6 mM and the pH is 7.42. After a 10 second sprint, the concentration of ATP is 3.7 mM, Phosphocreatine = 2.6 mM, Lactate= 8.4 mM and the pH = 7.20. The lower pH significantly reduces the activity of PFK which controls the flux through the glycolytic pathway. This pace in short cannot be maintained for more than 10 seconds.

Longer runs require a higher energy yield by the complete oxidation of glucose into CO₂. Oxidative phosphorylation is 100 times slower than glycolysis. The longer the run, the greater the demand for oxidative phosphorylation. The bulk of the energy for a 1000 meter run comes from oxidative phosphorylation. Because oxidative phosphorylation is slower than glycolysis the running pace must be slower.

Running a marathon requires the mobilization of several metabolic fuels and requires the cooperation of the liver, muscle and adipose tissue to mobilize the energy so that it can be tapped for the long run. Trained marathon runners have increased glycogen stores and consume equal amounts of fatty acids and glycogen during the run. In order to do this, the blood sugar level must be low to produce a high glucagon/insulin ratio. This high ratio mobilizes fatty acids from adipose tissue. These fatty acids are absorbed by the muscles, and oxidized completely into CO₂. Enough glycogen is spared this way, to sprint towards the finish line.

