Metabolic Regulation

(BIOC 315)

Dr. Othman Baothman

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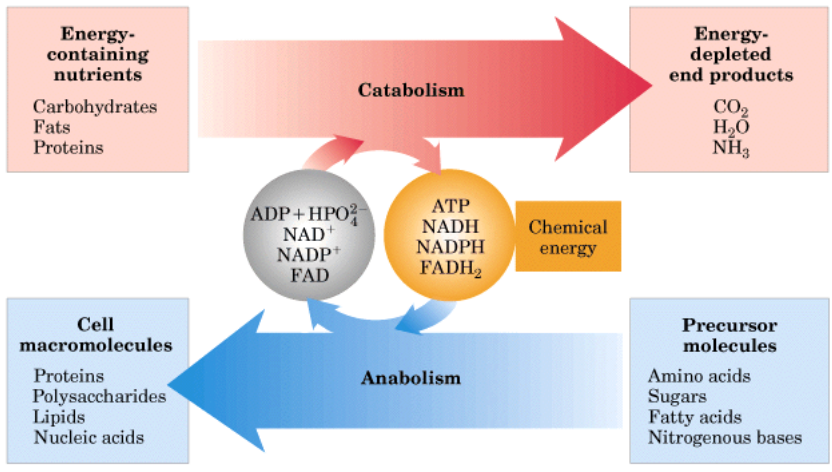
Fuel Storage

The major fuel depots in animals are:

- fat stored in adipose tissue
- glycogen in liver and muscle
- protein mainly in skeletal muscle

In general, the order of preference for use of the different fuels is:

glycogen > fat > protein



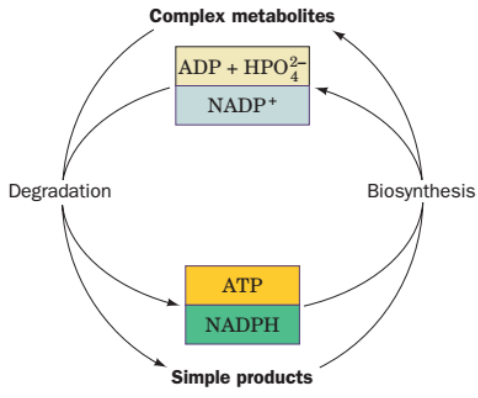
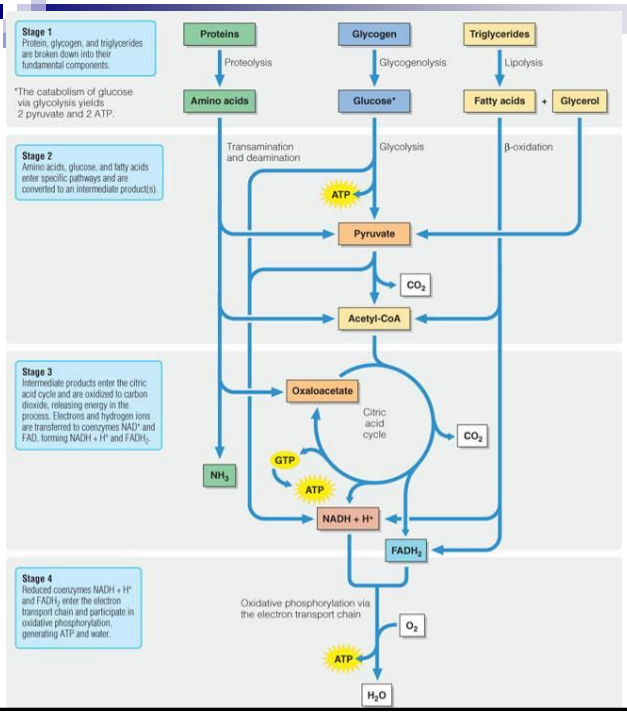


Figure 16-2 **ATP and NADPH are the sources of free energy for biosynthetic reactions.** They are generated through the degradation of complex metabolites.



Catabolism: The Breakdown of Macro-nutrients for Energy Stages 1-4

Regulated enzymes

- Because enzymes guide and regulate the metabolism of a cell, they tend to be carefully controlled.
- There are factors that can effect or control the activity of the enzyme.
- One of the most important of those factors is **Allosteric regulation**

Importance

- Helps to use the substrate economically
- Regulate the metabolic pathways and their interrelations

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ALLOSTERIC REGULATION

What is allosteric enzymes?

Allostearic "occupying another space"

Allosteric site was first proposed by Jacques Monod

Substances which bind to allostearic site can modify their activity – Allosteric effector

Allosteric effectors

Substances that bind to allosteric site and modifies the activity of the protein

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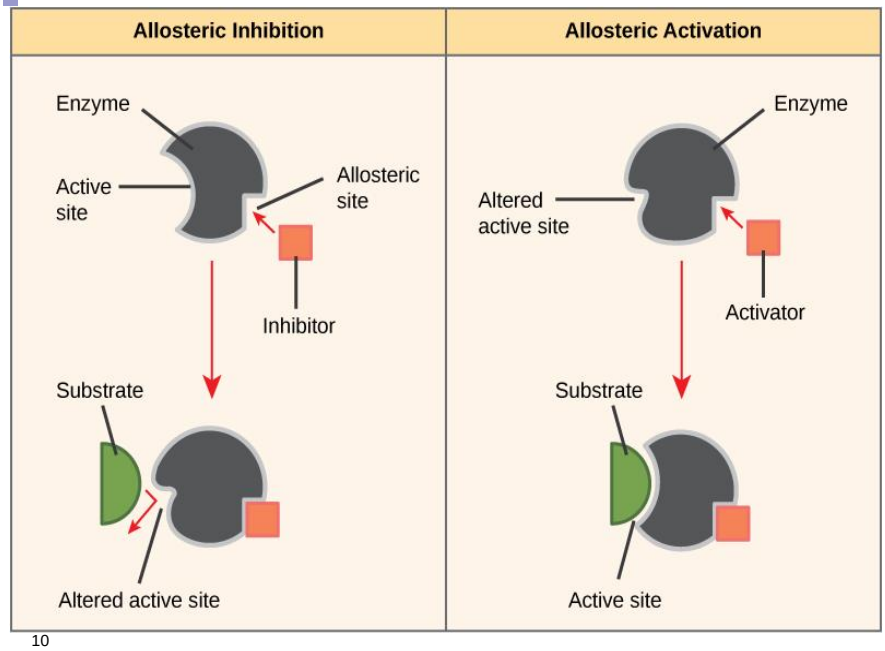

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Binding of an allosteric effector induces conformational change in the enzyme

Allosteric activator and inhibitor exhibit positive and negative cooperativities with the substrate

Allosteric activator :-
on binding to the allosteric site promote binding of substrate to the active site or the catalytic action
Allosteric inhibitor:- has opposite action

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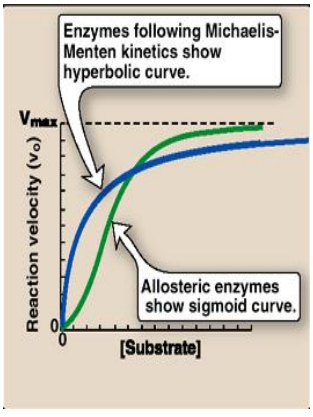

1. Maximal velocity (Vmax) : The rate of an enzyme-catalyzed reaction increases with substrate concentration until (Vmax) is reached (see Figure).
2. Hyperbolic shape of the enzyme: Most enzymes show Michaelis-Menten kinetics (similar in shape to that of the oxygen-dissociation curve of myoglobin).
•Allosteric enzymes frequently show a sigmoidal curve that is similar in shape to the oxygen dissociation curve of hemoglobin.

Glycolysis: General Functions

- Provide ATP energy
- Generate intermediates for other pathways
  - Hexose monophosphate pathway
  - Glycogen synthesis
  - Pyruvate dehydrogenase
    - Fatty acid synthesis
    - Krebs' Cycle
  - Glycerol-phosphate (TG synthesis)

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Glycolysis: Specific tissue functions

- RBC's
  - Rely exclusively for energy تعتمد حصرا على الطاقة
- Skeletal muscle
  - Source of energy during exercise, particularly high intensity exercise
- Adipose tissue
  - Source of glycerol-P for TG synthesis
  - Source of acetyl-CoA for FA synthesis
- Liver
  - Source of acetyl-CoA for FA synthesis
  - Source of glycerol-P for TG synthesis

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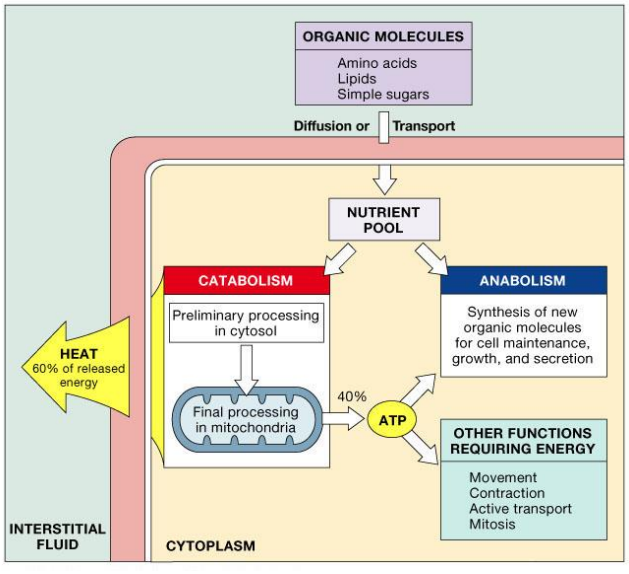
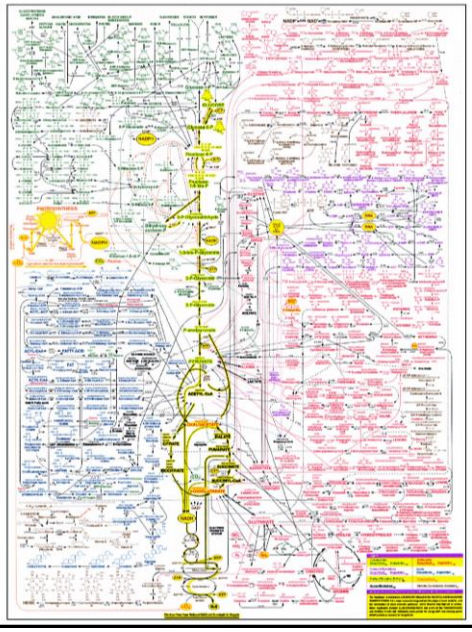
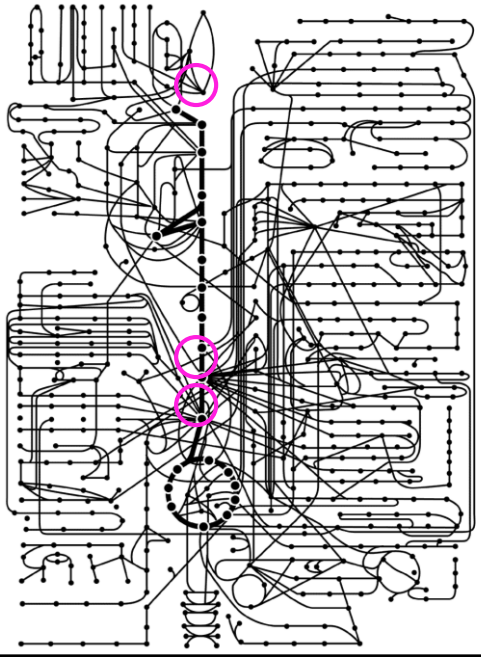
Cellular Metabolism



Integration of Metabolism





Key Junctions

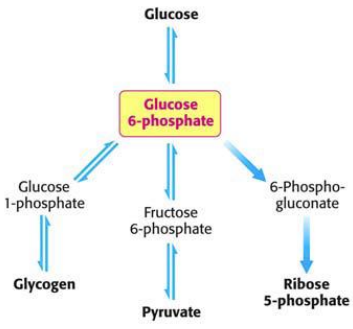
Glucose-6-phosphate

Pyruvate

Acetyl CoA

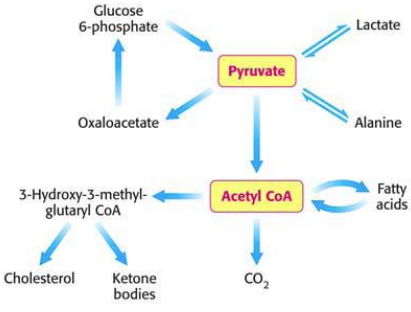
The key junction point

- 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.



The key junction point

- Pyruvate is another key junction point.
- Pyruvate is generated from glucose 6-phosphate by glycolysis. Pyruvate is converted into lactate under anaerobic conditions. This buys time for active tissues. The lactate produced must be subsequently oxidized back into pyruvate.
- Pyruvate is also transaminated to from 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.
- 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 key junction point

- 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.

1. Glycolysis and glycogen metabolism

- Glycolysis and glycogen metabolism work depend on the energy demand:
  - Under high energy demand the fuel glycolysis needed
  - Under low energy demand supplying precursors for glycogen synthesis

Metabolic regulation of glycolysis

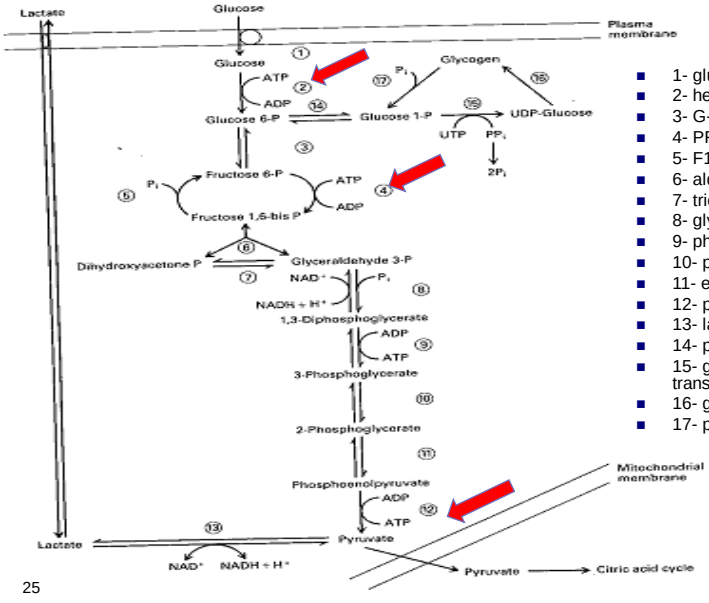
- There are three regulatory enzymes of glycolysis:

(a) Phosphofructokinase (PFK)

(b) Hexokinase

(c) Pyruvate kinase

Glycolysis and glycogen metabolism



- 1- glucose transport
- 2- hexokinase
- 3- G-6 isomerase
- 4- PFK
- 5- F1,6-bis P
- 6- aldolase
- 7- triose P isomerase
- 8- glyc 3-P dehydrog
- 9- phosphoglycerate kinase
- 10- phosphoglyceromutase
- 11- enolase
- 12- pyruv kinase
- 13- lact dehdro
- 14- phosphoglucomutase
- 15- gluco 1-Puridyl transferase
- 16- glycogen synthetase
- 17- phophorylase

(a) Phosphofructokinase (PFK)

- PFK is rate-limiting and committed step of glycolysis:
- It catalyses the reaction:

Fructose 6-phosphate +ATP → fructose 1,6-bisphospahte +ADP

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Regulation of PFK by ATP

- The end-product of glycolysis is ATP which act as feedback inhibitor as well as a substrate (allosteric effect).
- PFK has catalytic site and has a second binding site for ATP as regulatory function leading to inhibition of enzyme.
- ATP concentration in resting muscle 5mmol/l, in this concentration ATP is inhibited (see next figure)

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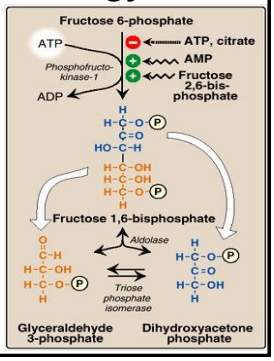
Regulation of PFK by AMP

- Conversely, PFK-1 is activated allosterically by high concentrations of AMP, which signal that the cell's energy stores are depleted



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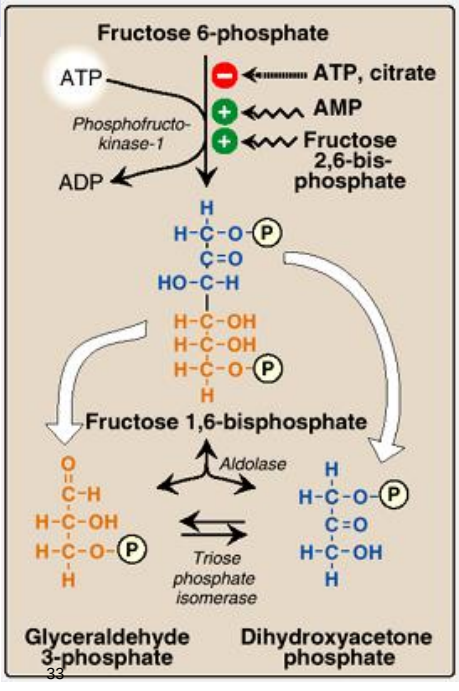

- Energy investment phase: Conversion of fructose 6-phosphate to triose phosphates.

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Regulation of PFK by citrate

- High levels of **citrate**, an intermediate in the TCA cycle, also inhibit PFK-1.

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b. Hexokinase (HK)

- This enzyme catalyse the phosphorylation of glucose
- HK is inhibited by the reaction product, glucose 6-phosphate (G6P).
- In muscle, G6P is substrate for two reactions: (see next figure)

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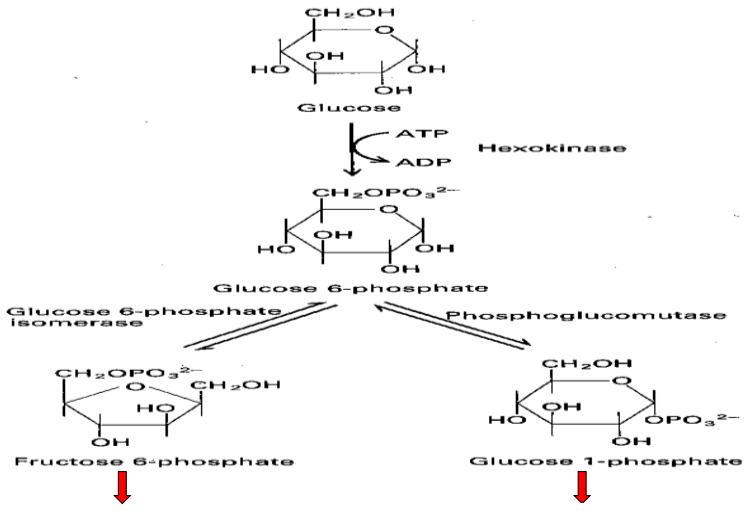
HK pathway



Glycolysis

Glycogen metabolism

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The control of HK is important in keeping the supply of glycogen synthesis

- Glycogen synthesis is working when glycolysis is low.
- Inhibition of PFK will lead to increase of F6P, lead increase G6P.
- In the well-fed state, glycogen synthase (GS) is allosterically activated by glucose 6-phosphate when it is present in high concentrations

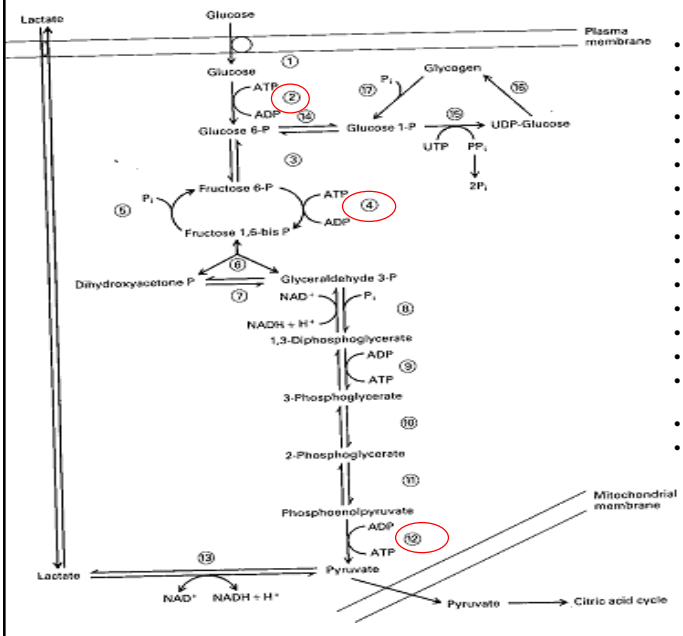
G6P → **GS** **Glycogen synthesis**

F6P

F 1,6 BPase **PFK**

F1,6 BP

Glycolysis



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- 11- enolase
- 12- pyr kinase
- 13- lact dehdro
- 14- phosphoglucomutase
- 15- gluco 1-Puridyl transferase
- 16- glycogen synthetase
- 17- phophorylase

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c. Regulation of pyruvate Kinase

- Signs of abundant energy supply allosterically inhibit all pyruvate kinase isoforms

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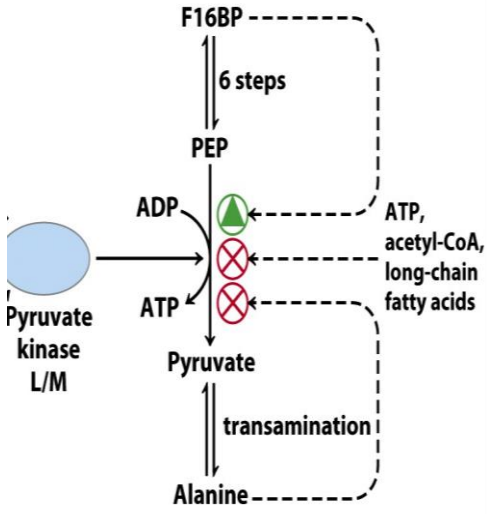
Regulation of pyruvate kinase



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How glucose can be transported across cell membranes?

Glucose and galactose cannot diffuse directly into cells, but enters by one of two transport mechanisms

1- **Glucose transporters (GLUT)**

- It is family isoforms GLUT-1 to GLUT-14.
- **allowing the movement of glucose across cell membranes from a high glucose concentration to a lower one**.

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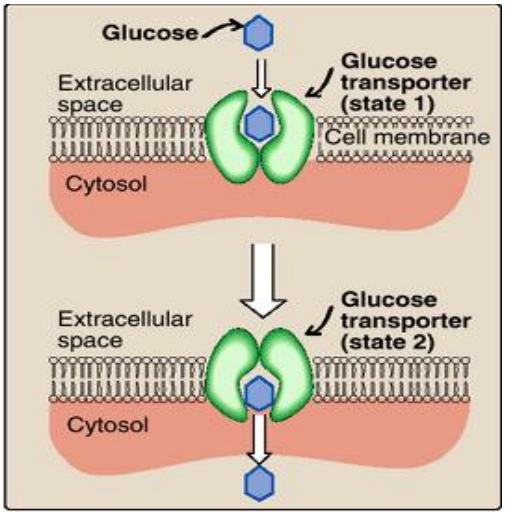
The facilitated transport of glucose through a cell membrane.



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2. The **sodium-glucose cotransporter (SGLT)**

- It is also family SGLT-1 needs to be able to its function is to move glucose **from a low to high concentration**

For example, intestinal lumen.

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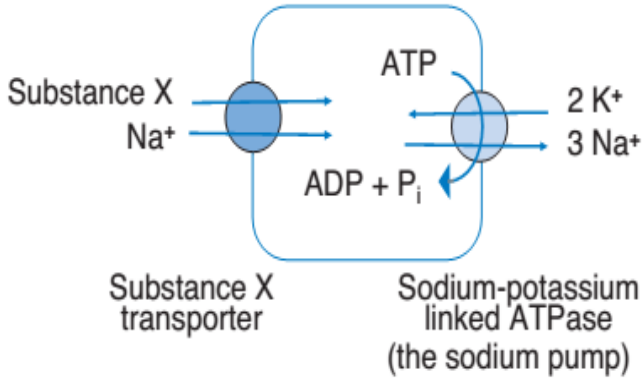

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	Tissue Location	Functions
Facilitative bidirectional transporters		
GLUT 1	Brain, kidney, colon, placenta, erythrocyte	Uptake of glucose
GLUT 2	Liver, pancreatic B cell, small intestine, kidney	Rapid uptake and release of glucose
GLUT 3	Brain, kidney, placenta	Uptake of glucose
GLUT 4	Heart and skeletal muscle, adipose tissue	Insulin-stimulated uptake of glucose
GLUT 5	Small intestine	Absorption of glucose
Sodium-dependent unidirectional transporter		
SGLT 1	Small intestine and kidney	Active uptake of glucose from lumen of intestine and reabsorption of glucose in proximal tubule of kidney against a concentration gradient

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Metabolic regulation of fuels during feed and fast state

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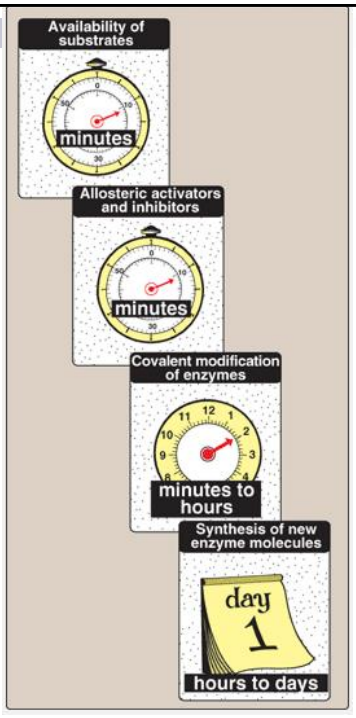
Overview of the Absorptive State

- The absorptive state is the two- to four-hour period after ingestion of a normal meal.
- increases in plasma glucose, amino acids, and triacylglycerols.
- Pancreas cells responds to the increased levels of glucose and amino acids with an increased secretion of insulin and a drop in the release of glucagon.
- The elevated insulin to glucagon ratio and the ready availability of circulating substrates make the absorptive state into an anabolic period characterized by increased synthesis of TAG and glycogen to replenish fuel stores, and enhanced synthesis of protein.
- All tissues use glucose as a fuel, and the metabolic response of the body is dominated by alterations in the metabolism of liver, adipose tissue, muscle, and brain.
- In this chapter, an “organ map” is introduced that traces the movement of metabolites between tissues. The goal is to create an expanded and clinically useful vision of whole-body metabolism.

- The time required for reversible allosteric control, regulation by phosphorylation, and transcriptional control is typically in milliseconds, seconds, and hours, respectively.



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Brain

- In resting adults, the brain uses 20% of the oxygen consumed, although it is only ~2% of body mass.

- it has no fuel reserves.

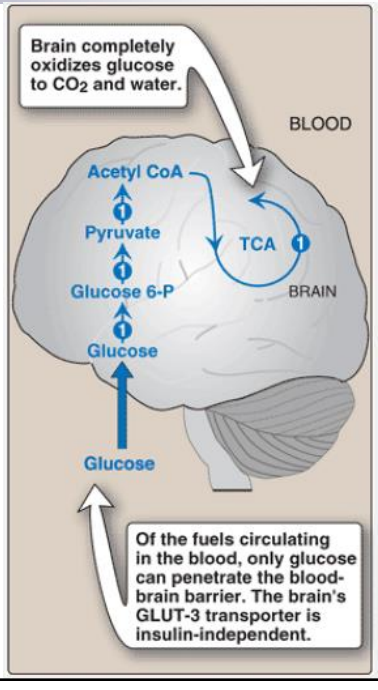
- the brain uses the glucose to make ATP which it needs to power the Na^+,K^+-ATPase to maintain the membrane potential necessary for transmission of nerve impulses.

- glucose is the normal fuel but ketone bodies (e.g. β-hydroxybutyrate) can partially substitute for glucose during starvation. The β-hydroxybutyrate is converted to acetyl-CoA for energy production via the citric acid cycle.

Brain in well-fed state

- **A. Carbohydrate Metabolism:**
  In the well-fed state, the brain uses glucose exclusively as a fuel, completely oxidizing about 140 g/day glucose to carbon dioxide and water. The brain contains no stores of glycogen, and is therefore completely dependent on the availability of blood glucose. If the blood glucose levels fall below approximately 30 mg /dl (normal blood glucose is 70-90 mg/dl) cerebral function is impaired.

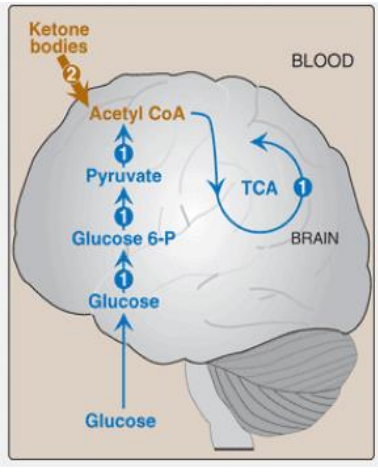
Carbohydrate metabolism in brain in the absorptive state.



- **<u>B. Fat Metabolism:</u>**
  The brain has no significant stores of triacylglycerols. Blood fatty acids do not efficiently cross the blood-brain barrier. Thus, the oxidation of fatty acids is of little importance to the brain.

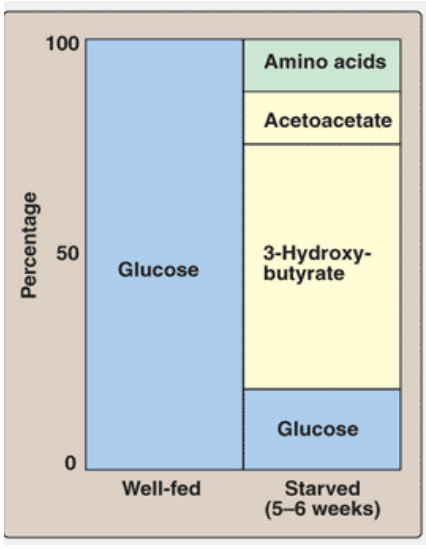
Brain in fasting

- During the first days of fasting, the brain continues to use only glucose as a fuel.
- In prolonged fasting (greater than 2-3 weeks) , plasma ketone bodies reach markedly high levels and are used in addition to glucose as a fuel by the brain.
- This decreases the need for protein catabolism for gluconeogenesis.



Fuel sources used by the brain to meet energy needs.

In prolonged fasting (greater than two to three weeks), plasma ketone bodies reach significantly elevated levels, and replace glucose as the primary fuel for the brain



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Muscle

- in resting adults, skeletal muscle uses 30% of the oxygen consumed, although during intense exercise it may use 90%.

- ATP is needed for muscle contraction and relaxation.

- Resting muscle uses **fatty acids (**its major fuel source**)**, glucose, and ketone bodies for fuel and makes ATP via oxidative phosphorylation.

- Muscle fatigue (inability to maintain power output) begins about 20 seconds after maximum exertion

- Resting muscle contains about 2% glycogen and an amount of phosphocreatine capable of providing enough ATP to power about 4 seconds of exertion.

Heart muscle differs from skeletal muscle in three important ways:

- The heart is continuously active, wherease skeletal muscle contracts intermittent on demand
- the heart has a completely aerobic metabolism
- The heart contains negligible energy stores such as glycogen or lipid .
- Thus, any interruption of the vascular supply results in rapid death of myocardial cells .
- Heart muscle uses glucose, free fatty acid and ketone bodies as fuels.

Resting skeletal muscle in the well-fed state

- **A. Carbohydrate Metabolism:**
  1. Increased glucose transport: due to increase insulin (glucose transporter 4). Glucose is phosphorylated to glucose 6-phosphate and metabolized to produce the energy needs of the muscle. This contrasts with the postabsorptive state in which ketone bodies and fatty acids are the major fuels of resting muscle.
  2. Increased glycogen synthesis:
  The increased insulin to glucagon ratio and the availability of glucose 6-phosphate stimulate glycogenesis, especially if glycogen stores have been depleted as a result of exercise.

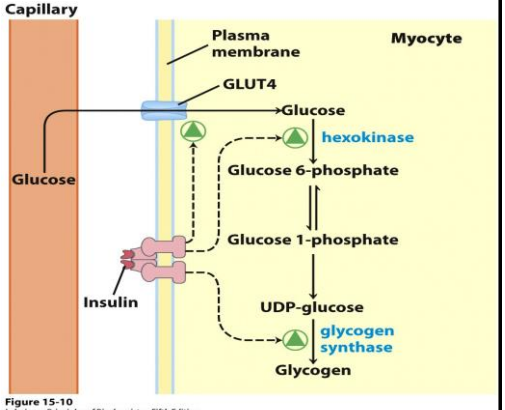

Figure 15-10
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Resting skeletal muscle in the well-fed state

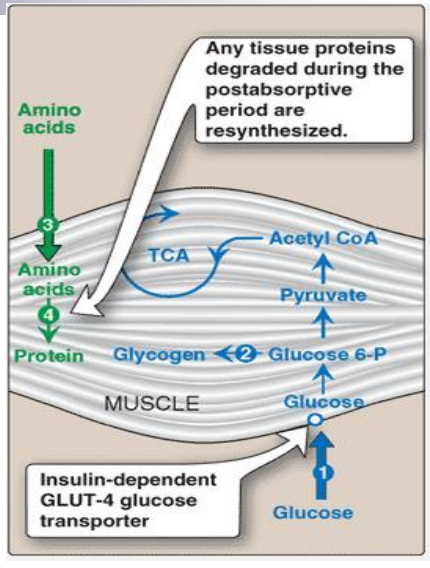
- **B. Fat Metabolism**
  Fatty acids are of secondary importance as a fuel for muscle in the well-fed state in which glucose is the primary source of energy.

- **C. Amino Acid Metabolism:**

1. Increased protein synthesis:
An increase in amino acid uptake and protein synthesis occurs in the absorptive period after ingestion of a meal containing protein (stimulated by insulin).

2. Increased uptake of branched-chain amino acids:
Muscle is the principal site for degradation of branched-chain amino acids. Leucine, isoleucine, and valine are taken up by muscle, where they are used for protein synthesis and as sources of energy.

Muscle in well-fed state

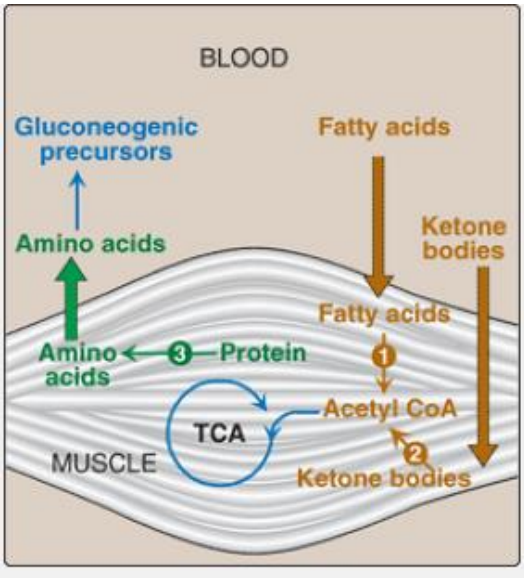


Resting Skeletal Muscle in Fasting

- Resting muscle uses fatty acids as its major fuel source. Exercising muscle initially uses its glycogen stores as a source of energy. During intense exercise, glucose -6-phosphate derived from glycogen is converted to lactate by anaerobic glycolysis. As these glycogen reserves are depleted, free fatty acids provided by the mobilization of triacylglycerol from adipose tissue become the major sources.
- **Carbohydrate Metabolism:**
  Glucose transport and subsequent glucose metabolism are depressed because of low blood insulin.
- **Fat Metabolism:**
  During the first 2 weeks of fasting, muscle uses fatty acids from adipose tissue and ketone bodies from the liver as fuels. After about 3 weeks of fasting, muscle decreases its utilization of ketone bodies and oxidize only fatty acids. This leads to a further increase in the already elevated levels of blood ketone bodies.
- **Protein Metabolism:**
  During the first few days of starvation there is rapid breakdown of muscle protein, giving amino acids that are used by the liver for gluconeogenesis. Alanine and glutamine are quantitatively the most important glucogenic amino acids released from muscle. After several weeks of fasting, the rate of muscle proteolysis decreases due to a decline in the need for glucose as a fuel for brain

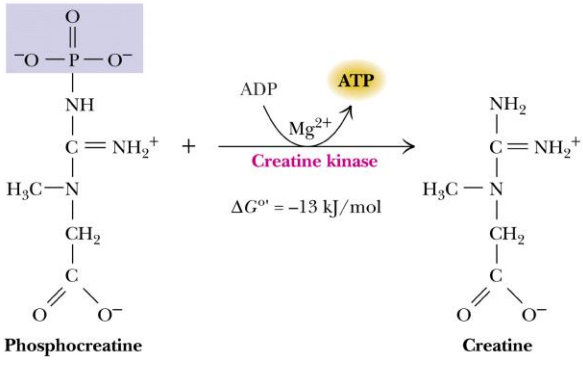
Muscle in fasting

fat and protein metabolism in skeletal muscle during starvation.



Phosphocreatine serves as a reservoir of ATP-synthesizing potential.

- during intense muscular activity existing ATP supplies are exhausted in about 2 seconds. Phosphocreatine regenerates ATP levels for a few extra seconds.



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Liver

- The liver is the metabolic hub of the body. It makes the fuel that supplies the brain, muscles, and other organs.
- The liver plays a central role in the regulation of **carbohydrate, lipid, and amino acid** metabolism.
- The liver removes about two-thirds of the **glucose** absorbed by the intestine and converts it to glucose-6-phosphate.

  glycolysis | glycogen | ribose-5-phosphate

- The liver also makes glucose by gluconeogenesis and glycogen breakdown and releases it into the blood.

X

- The liver also plays a central role in **lipid metabolism**.
- In the **well fed state** dietary fatty acids are converted to triacylglycerols (fat) and secreted into the blood as **VLDL**.
- In the **fasted state** the liver converts fatty acids into ketone bodies.

- The liver also plays a central role in **amino acid metabolism.**
- The liver removes most of the **amino acids** absorbed by the intestine. The priority use is protein synthesis.
- Excess amino acids are **deaminated** and converted into common metabolic intermediates.

- the liver secretes about 30 g of urea/day.

- the α-ketoacids are used as fuels or for gluconeogenesis.

- α-ketoacids are the major fuel for the liver itself.

A. Carbohydrate metabolism during fed state

ايض الكربوهيدرات في الكبد في حالة الشبع

- Glucose is absorbed from the intestine into the portal vein where its concentration may reach almost 10 mM after meal.
- في حالة الشبع، يتم امتصاص الجلوكوز من الأمعاء الى داخل الوريد البابي طريق ناقل بروتيني متخصص، يسمى GLUT-2 يقوم بنقل الجلوكوز عبر الغشاء الخلوي من او إلى داخل الخلية. وهذا الناقل هو أحد ١٤ نوعا من النواقل المتنوعة تختلف حسب نوع النسيج الموجود فيه هذا الناقل (انظر جدول ١).
- Rather, hepatic metabolism of glucose is increased by This increased use of glucose is not a result of stimulated glucose transport into the hepatocyte, because **this process is normally rapid** and GLUT-2 is not influenced by insulin.
- the following mechanisms:

Mechanisms of increased glucose in fed state

1. **Increased phosphorylation of glucose:**

High level of glucose in the heptocytes allow *glucokinase* (GK) (or hexokinase 4) to phosphorylate glucose to G6P (see fig 2 (1)). This contrasts with the post-absorptive state in which hepatic glucose levels are lower and *glucokinase* is largely inactive because of its low affinity (high K_m) for glucose.

زيادة فسفرة الجلوكوز:

ارتفاع مستوى الجلوكوز في خلايا الكبد يسمح لأنزيم غلوكوكيناز (GK) (أو هيكسوكيناز ٤) أن يفسفر الجلوكوز إلى G6P، وهذا بعكس حالة ما بعد الأكل بساعات حيث أن مستويات الجلوكوز في الكبد تنخفض ويقل بشكل كبير نشاطية أنزيم غلوكوكيناز بسبب تفضيله منخفض للجلوكوز.

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Major metabolic pathways in liver in the absorptive state (حالة الشبع)

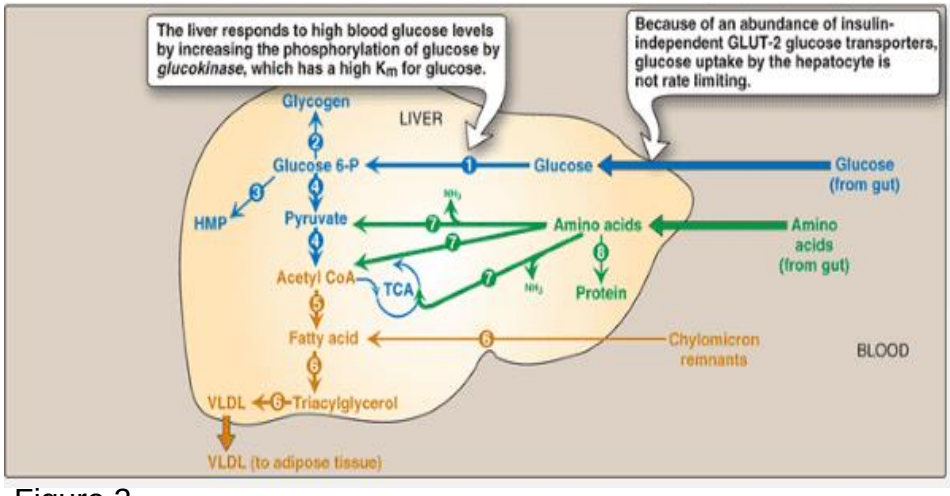

Figure 2

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In fed state

2. Increased glycogen synthesis:

G6P $\xrightarrow{\text{glycogen synthase}}$ glycogen

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In fed state

زيادة نشاط المسار الأيضي لسكر هيكسوز أحادي الفوسفات

3. Increased activity of the hexose monophosphate pathway (HMP) (see Figure 2, ③).

زيادة المسار الأيضي لتحلل الجلوكوز

4. Increased glycolysis (See Fig 2, 4)

انخفاض المسار الأيضي لتصنيع السكر

5. Decreased gluconeogenesis

- Pyruvate carboxylase inactive
- The high level of insulin in the absorptive period also favors inactivation of other enzymes unique to gluconeogenesis, such as fructose 1,6-bisphosphatase

80

B. Fat metabolism in the liver during fed state

- **Increased fatty acid synthesis**
  - Liver is the primary tissue for de novo synthesis of fatty acids (see Figure 2, ⑤).
  - Fatty acid synthesis is favored by the availability of substrates (acetyl CoA and NADPH derived from the metabolism of glucose).

- **Increased TAG synthesis**

TAG synthesis from:

- **acetyl CoA**
- **TAG component of chylomicron** remnants removed from the blood by hepatocytes. (see Figure 2, 6).

84

Major metabolic pathways in liver in the absorptive state (حالة الشبع)

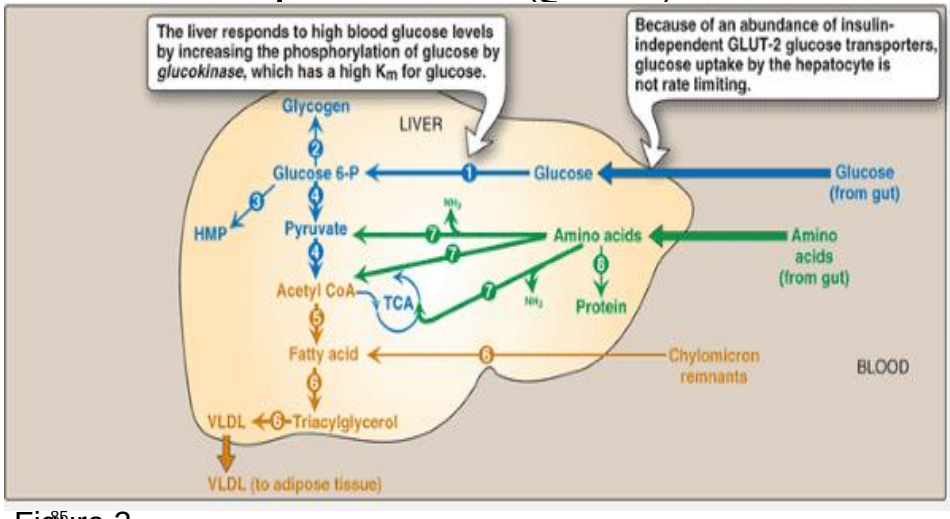

Figure 2

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C. Protein metabolism in the liver during fed state

- **Deaminated** and converted to **T**CA cycle intermediates (for energy or used in fatty acid synthesis).
- **Increased protein synthesis**

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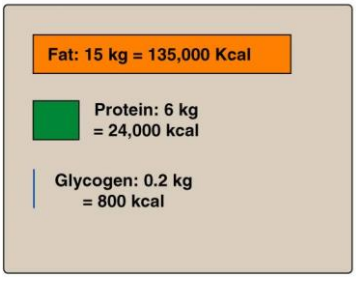
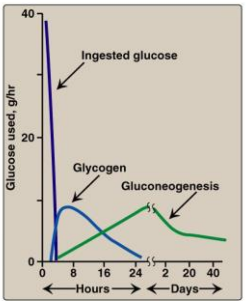
Liver in Fasting

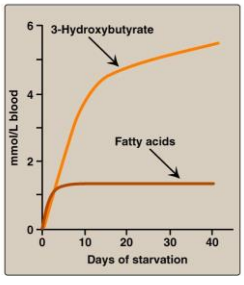
- **Carbohydrate Metabolism.**
  The liver first uses glycogen degradation, then gluconeogenesis to maintain blood glucose levels.
  1-Increased glyconeolysis: several hours after a meal, blood glucose levels decrease stimulating the secretion of glucagon and inhibiting insulin secretion. . The increased glucagon to insulin ratio stimulates glyconeolysis. Liver glycogen is nearly depleted after 10 – 18 hours of fasting. Thus hepatic glyconeolysis is a transient response to early fasting. Adult's liver contains 100 g of glycogen in the well -fed state.
  2-Increaased Gluconeogensis: gluconeogensis begins 4 –6 hours after the last meal and becomes fully active as liver glycogen stores are depleted. Gluconeogenesis plays an essential role in maintaining blood glucose during both overnight and prolonged fasting. The main sources for gluconeogenesis are amino acids, glycerol and lactate.

Energy Reserves During Fasting



Only 30% of body protein is available for energy production

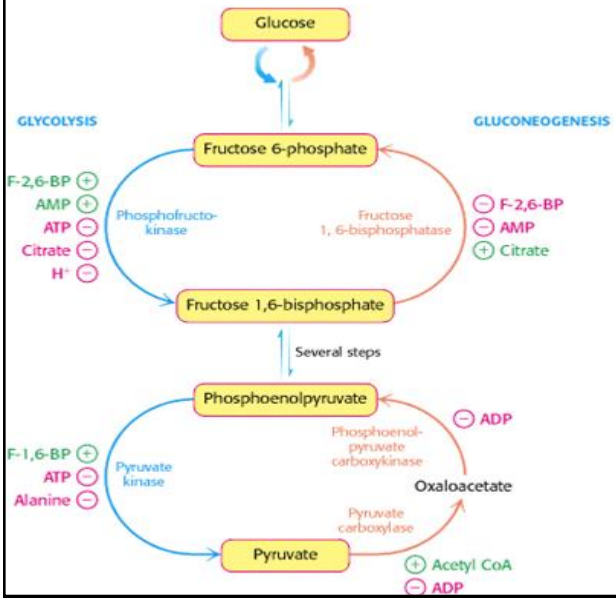




B. Increased gluconeogenesis

- The carbon skeletons for gluconeogenesis are derived primarily from:
- **Gluconeogenic amino acids**
- **Lactate in muscle**
- **Glycerol in adipose**
- Gluconeogenesis plays an essential role in maintaining blood glucose during both overnight and prolonged fasting.

Reciprocal Regulation of Gluconeogenesis and Glycolysis in the Liver



- Glycolysis and Gluconeogenesis are reciprocally regulated .
- When glycolysis is on Gluconeogenesis is turned off especially in the fed state, whereas under conditions of starvation, gluconeogenesis is fully on and glycolysis is turned off.
- Both the cycles are never active at the same pace at the same time.

Liver in Fasting

Glycogen degradation (blue color) as part of the overall metabolic response of the liver.

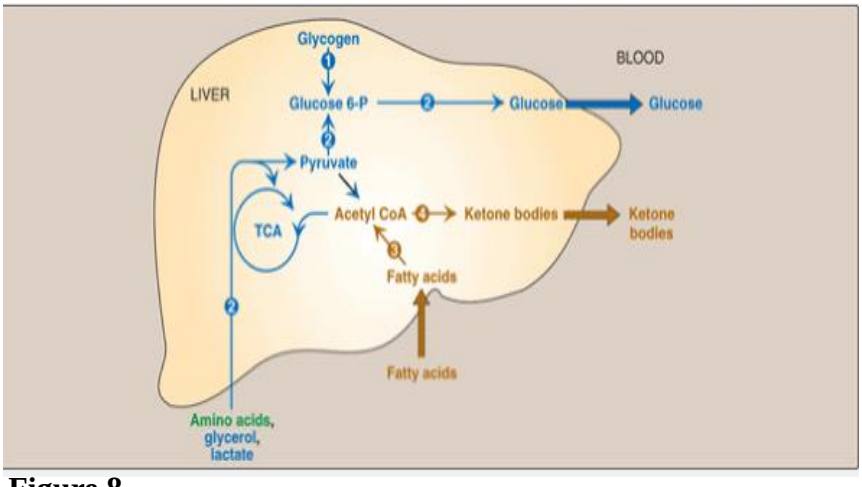


Figure 8

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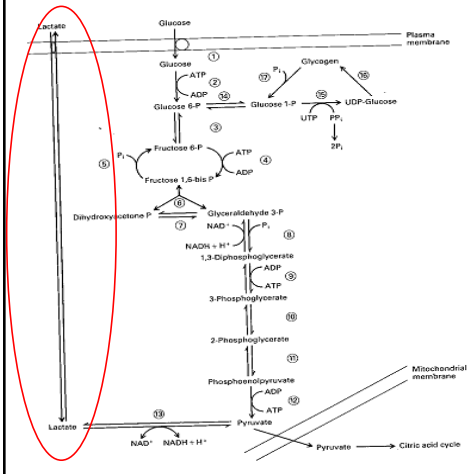
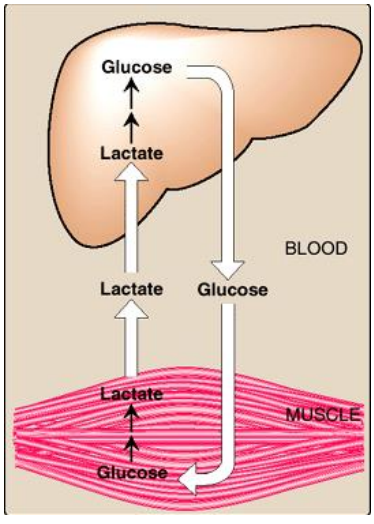
Cori cycle





شكل رقم ١٢

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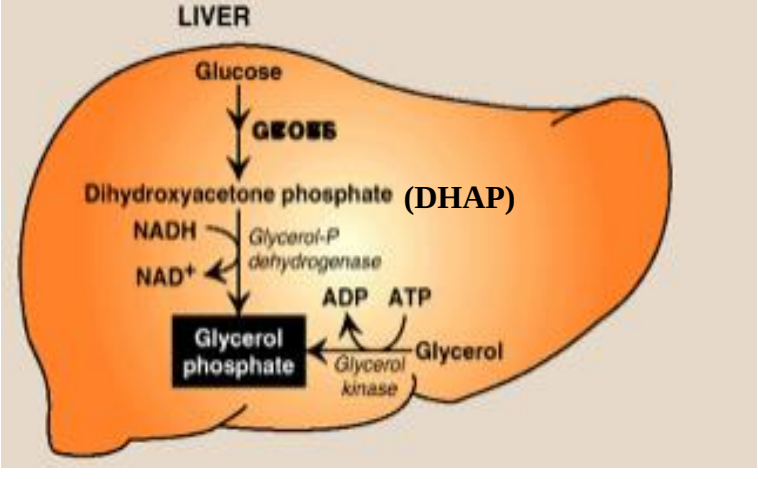
Pathways for production of glycerol phosphate in liver



شكل رقم ١٣

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- **Amino acids**: can be degraded except leucine, to form compounds that can be converted to glucose through gluconeogenesis. During starvation, the protein are broken down to provide the amino acids that function as precursors for gluconeogenesis. Some amino acids in the liver are deaminated and the ammonia is excreted in the form of urea.

الأهمية الفسيولوجية للأحماض الأمينية بالنسبة لمسار استحداث السكر gluconeogenesis
يمكن للأحماض الأمينية أن يتحلل بإستثناء الليوسين والأيزوليوسين ، لتكون مركبات يمكن أن تتحول إلى جلوكوز. أثناء المجاعة، تتكسر البروتينات الى أحماض أمينية حيث تعمل كسلائف لاستحداث السكر. بعض الأحماض الأمينية في الكبد يمكن أن يحدث لها نزع للأمين وتفرز الأمونيا في البول في صورة اليوريا.

سؤال: لماذا الليوسين والأيزوليوسين أثناء المجاعة لا يمكنهما أن يتحولا-مثل باقي الأحماض الأمينية - الى مركبات يمكن أن تتحول إلى جلوكوز؟.

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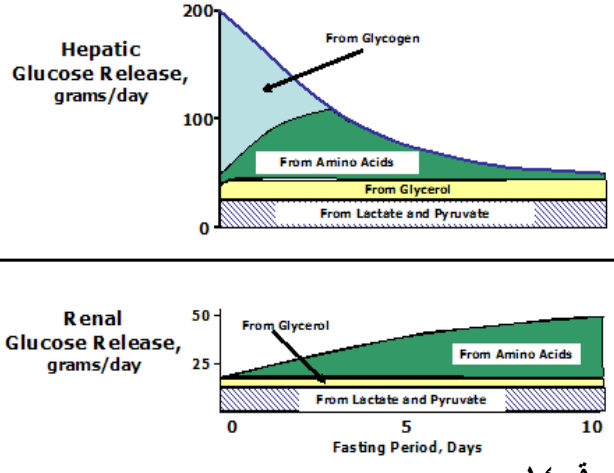
Production of glucose in starvation



شكل رقم ١٤

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Fat metabolism in liver during fasting

1. **Increased fatty acid oxidation**

The oxidation of fatty acids derived from adipose tissue is the major source of energy in hepatic tissue in the postabsorptive state (see Figure, ….. ③).

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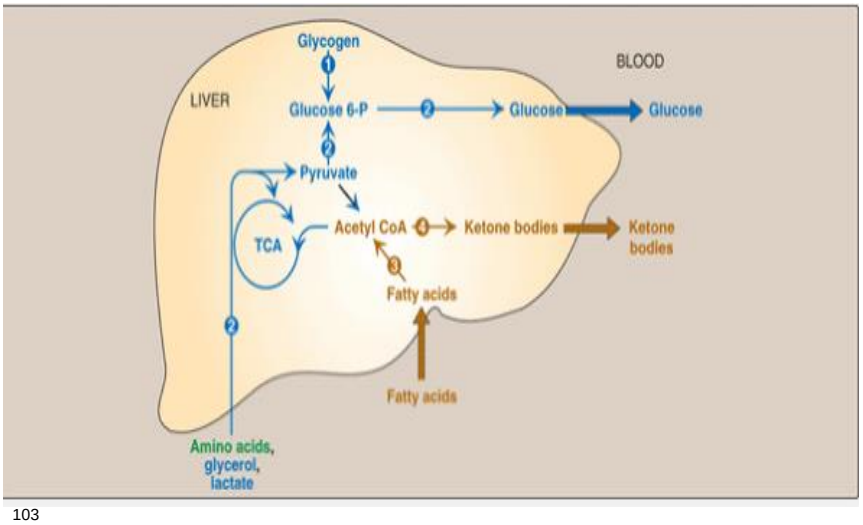
During fasting

The oxidation of fatty acids (brown color) coming from adipose tissue is the major source of energy in liver



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Fat metabolism in liver during fasting

2. Increased synthesis of ketone bodies

- used as fuels by peripheral tissues.
- liver cannot use ketone bodies as a fuel.
- Ketogenesis is favoured when the concentration of acetyl CoA, produced from fatty acid metabolism, exceeds the oxidative capacity of the TCA cycle.
- The availability of circulating ketone bodies is important in fasting because they can be used for fuel by most tissues, including brain tissue.
- Ketogenesis as part of the overall hepatic response to fasting is shown in Figure ١٦.
-

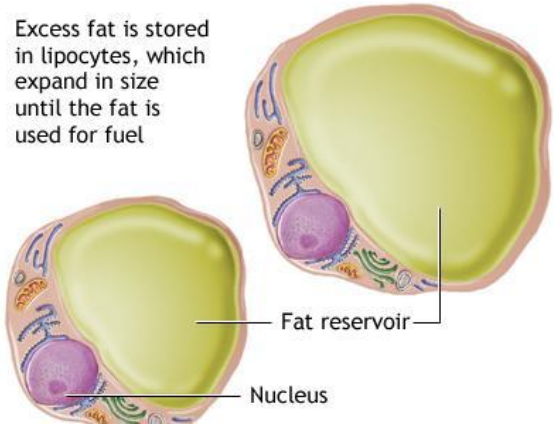
- الأحماض الكيتونية تستخدم كوقود بواسطة الأنسجة الطرفية.
- الكبد لا يمكن استخدام الأجسام الكيتونية كوقود.
- ويفضل مسار توليد الكيتون عندما يكون تركيز الاسيتيل كو ايه (acetyl CoA)، التي تنتج من التمثيل الغذائي الأحماض الدهنية، متجاوزة وزائدة القدرة التأكسدية لدورة كربس.
- وجود الكيتونات في الدورة الدموية مهم في حالة الصيام لأنها يمكن أن تستخدم كوقود من قبل معظم الأنسجة، بما في ذلك أنسجة المخ.
- وعموماً فإن عملية توليد الكيتون تعتبرجزء من استجابة الكبد للصيام كما هو موضح في الشكل ١٦.

Adipose Tissue

Introduction

- Mammals have two types of adipose tissue: **White fat**: the storage and release of lipid as fuel reserve.
- **Brown fat**: used to generate heat. Contain many more mitochondria than white fat, and this is what gives it its colours.
- **There is a third type of adipose tissue, Biege fat is 'brown-like' adipocytes?**
- Stored lipid is oxidised in the tissue itself and the mitochondria can be uncoupled so that the oxidation generates heat.
- Brown fat is important in the newborn and in hibernating mammals.
- In white fat is stored as one droplet that typically almost fills the cell (see figure..). In function, the similarity is that both types of cell store triacylglycerol and may release fatty acids.
- The difference is that brown fat cells have a much higher oxidative capacity and may oxidize a large proportion of the fatty acids released from storage.
- In a 70 kg man, adipose tissue weighs approximately 14 kg, or about half as much as the total muscle mass. In obese individuals adipose tissue can constitute up to 70% of body weight.

Colorized transmission electron micrograph of adipocytes.



Adipose Tissue

- consists mainly of cells called adipocytes that do not replicate.

-Adipocytes have a high rate of metabolic activity - triacylglycerol molecules turn over every few days.

- normally, free fatty acids are obtained from the liver for fat synthesis.

- because adipocytes lack glycerol kinase they cannot recycle the glycerol from fat breakdown but must obtain glycerol-3-phosphate by reducing the DHAP (Dihydroxyacetone Phosphate) produced by glycolysis.

- adipocytes also need glucose to feed the pentose phosphate pathway for NADPH production.

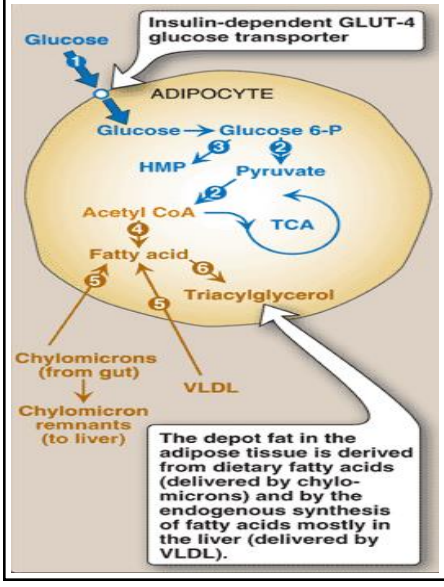
-Insulin is required for glucose uptake.

Adipose tissue in the well-fed state

- Adipose tissue is second only to the liver in its ability to distribute fuel molecules. In a 70 kg man adipose tissue weighs about 14 kg or about half as much as the total muscle mass. In obese individuals adipose tissue can constitute up to 70% of body weight.
- **A. Carbohydrate Metabolism**
  1. Increased glucose transport: stimulated by insulin (glucose transport)
  2. Increased glycolysis: to provide glycerol phosphate for triacylglycerol synthesis
  3. Increased activity in the HMP: To supply NADPH (essential for fat synthesis).

- **B. Fat Metabolism**
  1. Increased synthesis of fatty acids:
  De novo synthesis of fatty acids from acetyl CoA in adipose tissue is nearly undetectable in humans, except when refeeding a previously fasted individual. Most of the fatty acids added to the lipid stores of adipocytes is provided by dietary fat (in the form of chylomicrons), and a lesser amount is supplied by VLDL from the liver
  2. Increased triacylglycerol synthesis:
  Fatty acid + glycerol → triacylglycerol (TG)
  Adipocytes lack glycerol kinase, so that glycerol 3-phosphate used in triacylglycerol synthesis must come from the metabolism of glucose. Thus, in the well-fed state, elevated levels of glucose and insulin favor storage of TG
  3. Decreased triacylglycerol degradation:
  Insulin inhibits the **hormone-sensitive lipase** (dephosphorylated form) and thus inhibits triacylglycerol degradation is in the well-fed state.

Carbohydrates and fat metabolism in adipose tissue in fed state



Adipose Tissue in Fasting

- **Carbohydrate Metabolism:**
  Glucose transport into the adipocyte and its metabolism are depressed due to low levels of blood insulin .This leads to a decrease in fatty acid and triacyl-glycerol synthesis.

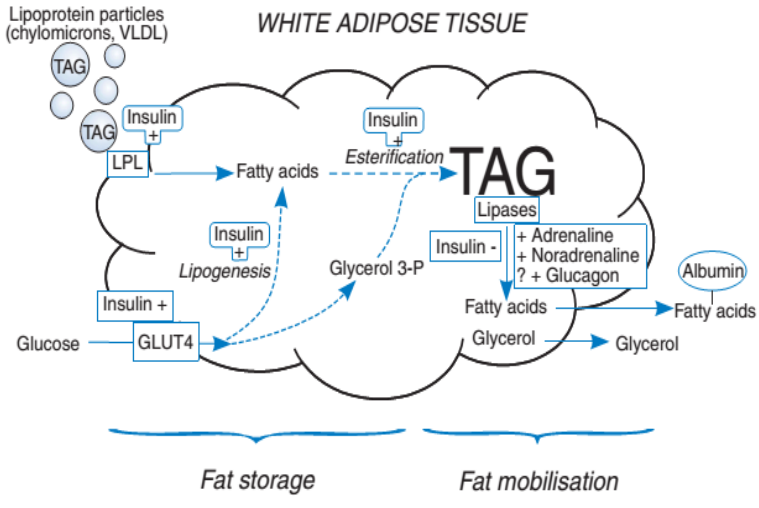
- **Fat Metabolism:**

  1-Increased degradation of triaclyglycerols: The activation of hormone – sensitive lipase and subsequent hydrolysis of stored triacylglycerol are stimulated by high levels of epinephrine.

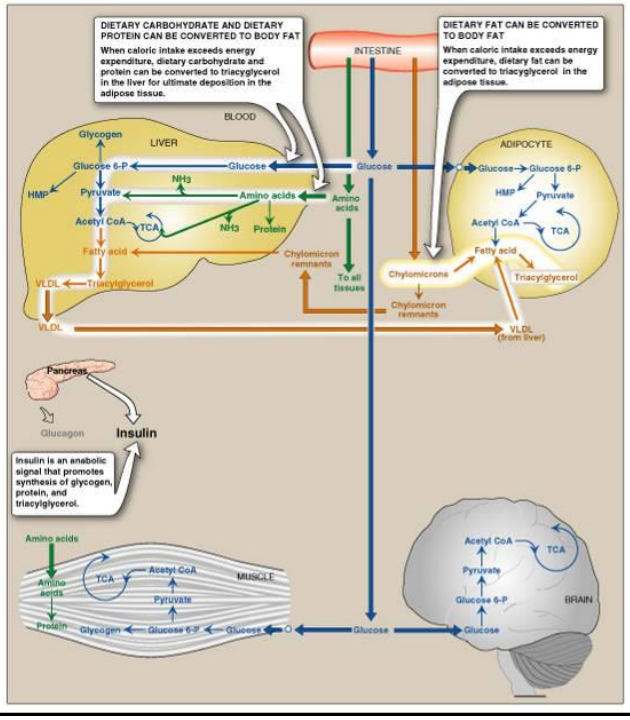
  2-Increased release of fatty acids: Fatty acids resulting from the hydrolysis of stored triacylglycerol are released into the blood. Bound to albumin, they are transported to other tissues for use as fuel. Part of the fatty acids is oxidized in the adipose tissue to produce energy. The glycerol produced from triacylglycerol degradation is used by the liver for gluconeogenesis.

  3-Decreased uptake of fatty acid: In fasting, lipoprotein lipase activity of adipose tissue is low. Thus, circulating triacylglycerol of lipoproteins is not available for triacylglycerol synthesis in adipose tissue

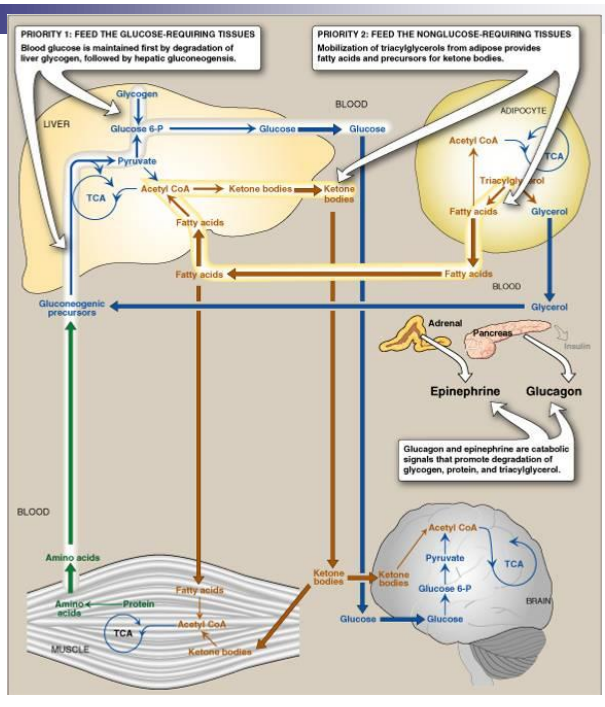
Regulation metabolism of adipose tissue in fed state and during fasting



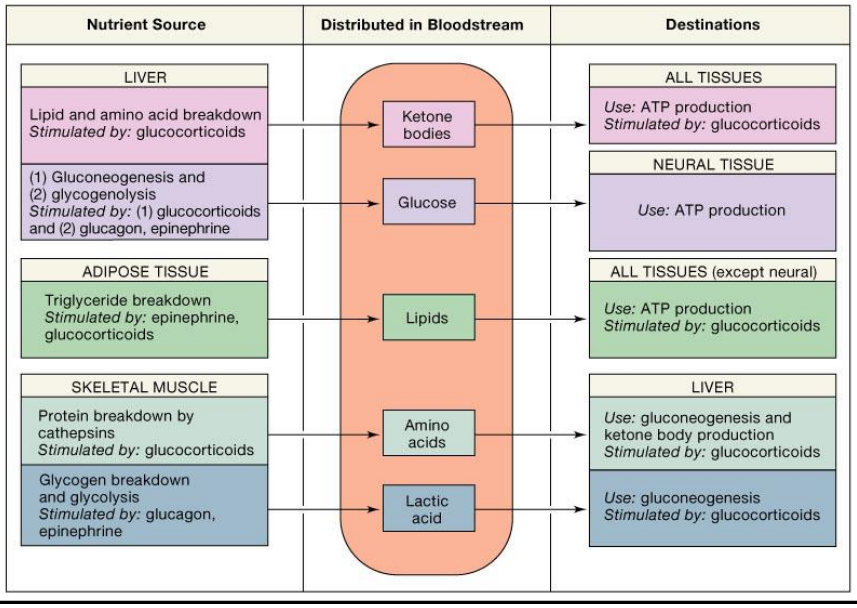
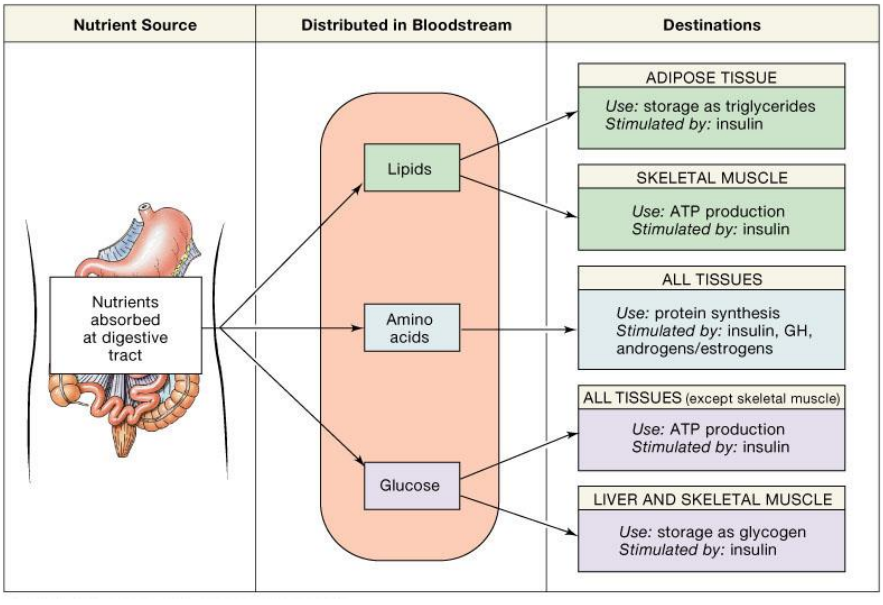
Intertissue relationships in the absorptive state



Intertissue relationships during starvation



The Postabsorptive State



The Absorptive State