# **Metabolism**

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# Content

# Metabolism

The biochemical reactions that happen inside the body.

Metabolism divided into to process

1- Catabolim

2- Anabolism

## Catabolism

The biochemical processes of metabolism by which large molecules are breakdown to small molecules or oxidizing to producing energy.

## Anabolism

The biochemical processes of metabolism by which molecules are synthesized or built up.

## Note

Catabolism and anabolism are separated process, catabolism process occur to produce energy, but anabolism need energy.

## INTRODUCTION

The carbohydrates are source of energy for animal nutrition. The

monosaccharides and oligosaccharides are efficiently metabolized by simple stomach animals. On the other hand, ruminants contain microbes, which secrete enzymes capable of degrading cellulose. Glycogen is a polysaccharide found in animal and fungal cells. Glycogen is a storage form of carbohydrate and is readily utilized when there is deficiency of energy.

## Digestion

The dietary carbohydrates that are most important nutritionally are polysaccharides and disaccharides, since free monosaccharides are not commonly present in the diet in significant quantities. There is, however, some free glucose and fructose in honey, in certain fruits, and in the carbohydrates that are added to processed foods. The cellular use of carbohydrates depends on their absorption from the Gastrointestinal (GI) tract into the blood stream, a process normally restricted to monosaccharides. Therefore, poly saccharides and disaccharides must be hydrolyzed to their constituent monosaccharide units. The hydrolytic enzymes involved are collectively called glycosidases, or, alternatively, carbohydrases.

## 1 Disaccharides

Virtually no digestion of disaccharides or small oligo saccharides occurs in the mouth or stomach. In the human it takes place entirely in the upper small intestine. Unlike amylase, disaccharidase activity is associated with the mucosal cells of the microvilli or brush border rather than with the intestinal lumen. Among the types of enzyme activities located in the mucosal cells are lactase, invertase (sucrase), and isomaltase. The latter is not a disaccharidase but instead hydrolyses branched dextrins, as mentioned in an earlier section. Lactase catalyses the cleavage of lactose to equimolar amounts of galactose and glucose, and sucrase hydrolyses sucrose to yield glucose and one fructose residue; sucrase also hydrolyses maltose and maltotriose to free glucose.

## 2 Polysaccharides

The glycosidase, a-amylase, assumes a particularly important role in polysaccharide digestion because of its specific hydrolytic action on the α-1,4 bonds of the starches. Resistant to the action of this enzyme, therefore, are the β-1,4 bonds of cellulose and the α -1,6 linkages that form branch points in the starch amylopectin. The a-amylase hydrolyses the unbranched amylose rapidly into units of the disaccharide maltose and into the trisaccharide malltotriose, the latter subsequently undergoing slower hydrolysis to maltose and glucose. The enzyme's hydrolytic action on amylopectin produces, in addition to glucose, maltose, and maltotriose, a mixture of branched oligo saccharides, or dextrins, the smallest of which are tetrasaccharides and pentasaccharides. Together with the complementary activity of another glycosidase, α-dextrinase, which hydrolyses the α-1, 6 bonds at the branches, the dextrins are consequently hydrolysed to free glucose.

# Metabolism of carbohydrates

| | |
|---|---|
| Glycolysis | تحليل الجلوكوز - |
| Krebs Cycle | دورة كربس - |
| Glycogenesis | بناء الجلايكوجين - |
| Gluconeogenesis | إستحداث الجلايكوجين - |
| Glycogenolysis | تحليل الجلايكوجين - |

## Glycolysis

Glycolysis is, by definition, the pathway by which glucose is converted into two units of lactic acid, a triose. The pathway can function anaerobically, and in situations in which oxygen debt is in effect, as in times of strenuous exercise, lactate accumulates in the muscle cells, causing the aches and

pains associated with overexertion. The importance of glycolysis in energy metabolism is that it provides the initial sequence of reactions necessary for glucose to be oxidized completely to $CO_2$ and $H_2O$ via the citric acid cycle. In cells that lack mitochondria, such as the erythrocyte, the pathway of glycolysis is the sole provider of ATP by substrate level phosphorylation of ADP. The glycolytic enzymes function within the cytoplasmic matrix of the cell, while the enzymes catalyzing the citric acid (Krebs) cycle reactions are located within the mitochondrion (pp. 8, 9). Further metabolism of the products of glycolysis in the Krebs cycle allows complete oxidation of glucose to $CO_2$ and $H_2O$, with maximal energy production. Some of the energy liberated is salvaged as ATP, while the remainder maintains body temperature. Many cell types are involved in glycolysis, but most of the energy derived from carbohydrates originates in liver, muscle, and adipose tissue. The pathway of glycolysis, showing the entry of dietary fructose and galactose, the following are comments on selected reactions:

1 .The hexokinase/glucokinase reaction consumes 1mol ATP/mol

glucose. Hexokinase (not glucokinase) is negatively regulated by

the product of the reaction, glucose 6-phosphate.

2 .Glucose phosphate isomerase catalyses this inter-conversion of

isomers.

3 .The phosphofructokinase reaction, an important regulatory site, is modulated negatively by ATP and citrate and positively by AMP.

Another ATP is consumed in the reaction.

3 .The aldolase reaction results in the splitting of a hexose bisphosphate into two triose phosphates.

4 .The isomers glyceraldehyde 3-phosphate and dihydroxyacetone phosphate (DHAP) are interconverted by the enzyme triosephosphate isomerase. In an isolated system the equilibrium favors DHAP formation. However, in the cellular environment it is shifted completely toward the production of glyceraldehyde 3- phosphate, since this metabolite is being continuously removed from the equilibrium by the subsequent reaction catalysed by glyceraldehyde 3-phosphate dehydrogenase.

5 .In this reaction, glyceraldehyde 3-phosphate is oxidised to a carboxylic acid, while inorganic phossphate is incorporated as a high-energy anhydride bond. The enzyme is glyceraldehyde 3-phosphate dehydrogenase, which uses NAD as its hydrogen accepting substrate. Under aerobic conditions, the NADH formed is deoxidized to NAD by $O_2$ via the electron transport chain in the mitochondria. The reason the $O_2$ is not necessary to sustain this reaction under anaerobic conditions is that the NAD consumed is restored by a subsequent reaction

6 .This reaction, catalyzed by phosphoglycerate kinase, exemplifies

a substrate level phosphorylation of ADP. Do a little extensive

reading, for a more detailed review of this mechanism by which

ATP can be formed from ADP by the transfer of a phosphate

from a high-energy donor molecule.

7 .Phosphoglyceromutase catalysis the transfer of the phosphate

group from the carbon-3 to carbon-2 of the glyceric acid.

8 .Dehydration of 2-phosphoglycerate by the enzyme enolase

introduces a double bond that imparts high energy to the

phosphate bond.

9 .The product of reaction (9), phosphoenolpyruvate (PEP), donates its phosphate group to ADP in a reaction catalysed by pyruvate kinase. This is the second site of substrate level phosphorylation of ADP in the glycolytic pathway.

10 .The lactate dehydrogenase reaction transfers two hydrogen from NADH and H+ to pyruvate, reducing it to lactate. NAD is formed in the reaction and can replace the NAD consumed in reaction (6) under anaerobic conditions. It must be emphasized that this reaction is most active in situations of oxygen debt, as in prolonged muscular activity. Under normal, aerobic conditions, pyruvate enters the mitochondrion for complete oxidation. A third important option available to pyruvate is its conversion to the amino acid alanine through trans-amination with the amino group donor glutamate. This, together with the fact that pyruvate is also the product of the catabolism of various amino acids, makes it an important link between protein and carbohydrate metabolism.

11 .These two reactions provide the means by which dietary fructose enters the glycolytic pathway. Fructose is an important factor in the average American diet, since nearly half of the carbohydrate consumed is sucrose, and high fructose corn sugar is becoming more popular as a food sweetener. Reaction 12 functions in extrahepatic tissues and involves the direct phosphorylation by hexokinase to form fructose 6-phosphate. This is a relatively unimportant reaction. It is slow and occurs only in the presence of high levels of the ketose. Reaction 13 is the major means by which fructose is converted to glycolysis metabolites.

The phosphorylation occurs at carbon-l and is catalysed by

fructokinase, an enzyme found only in hepatocytes. The fructose Iphosphate is subsequently split by aldolase, designated aldolase B to distinguish it from the enzyme acting on fructose 1,6-bisphosphate, forming DHAP and glyceraldehyde. The latter can then be phosphorylated by glyceraldehyde kinase (or triokinase) at the expense of a second ATP to produce glyceraldehyde 3-phosphate. Fructose is therefore converted to glycolytic intermediates and as such can follow the pathway to pyruvate formation and Krebs cycle oxidation. Alternatively, they can be used in the liver to produce free glucose by a reversal of the first part of the pathway through the action of gluconeogenic enzymes.

Glucose formation from fructose would be particularly important

if fructose provides the major source of carbohydrate in the diet.

Since the phosphorylation of fructose is essentially the responsibility of the liver, the ingestion of large amounts of the ketose can cause a depletion of hepaatocyte ATP, leading to reduction in the rate of various biosynthetic processes such as protein synthesis.
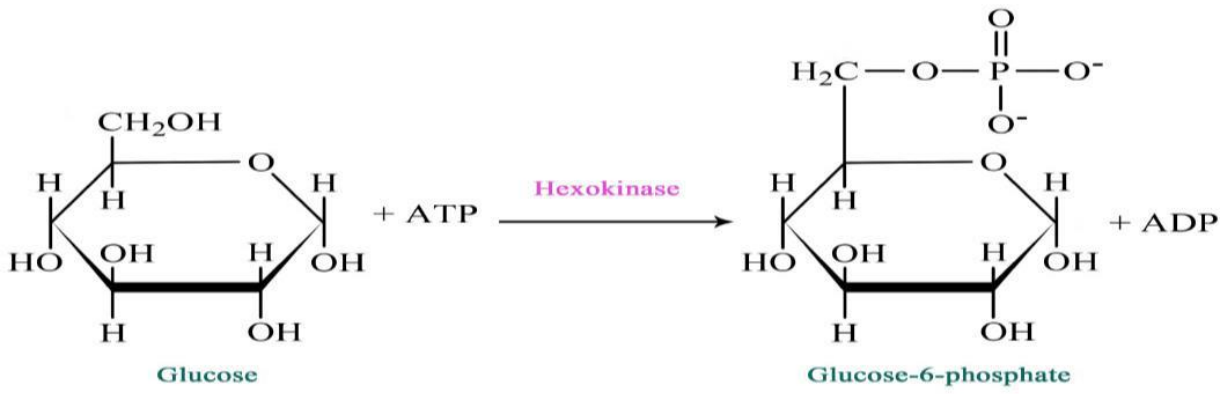
12 Like glucose and fructose, galactose is first phosphorylated. The transfer of the phosphate from ATP is catalysed by galactokinase and the resulting phosphate ester is at carbon-I of the sugar. The major dietary source of galactose is lactose, from which the monosaccharide is hydrolytically released by lactase.
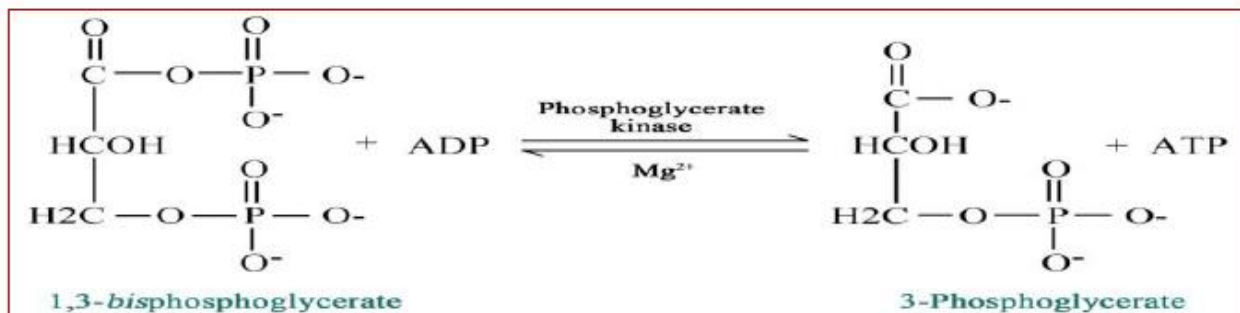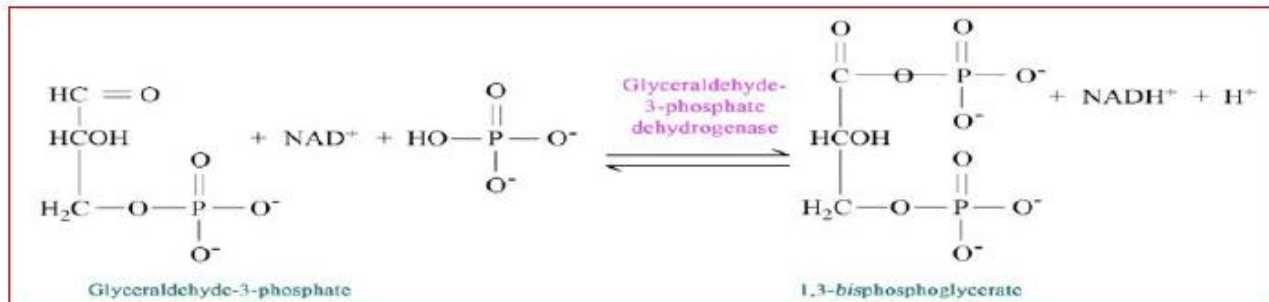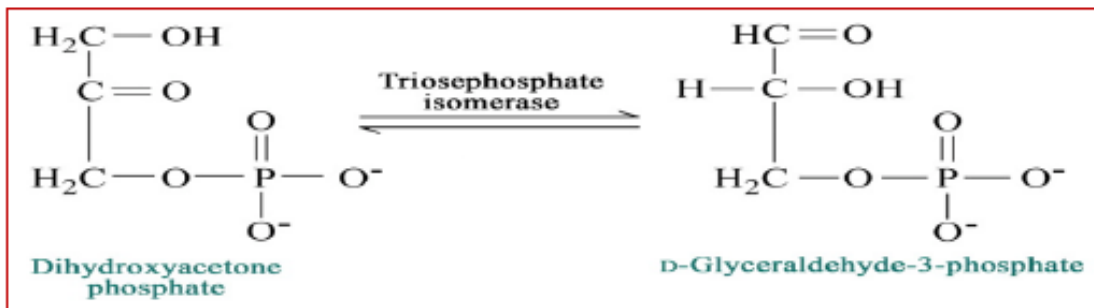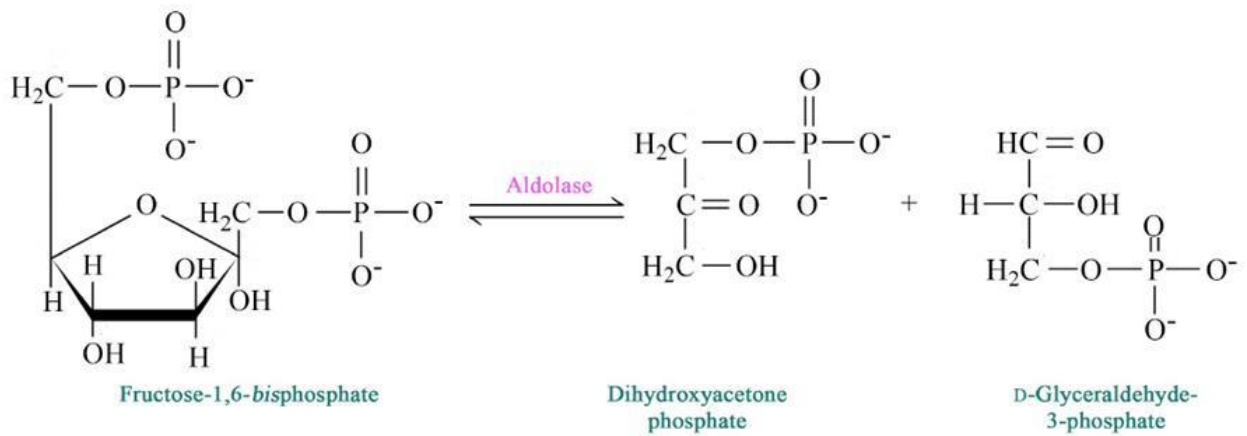
13 .Galactose 1-phosphate can be converted to glucose I phosphate by the enzyme galactose 1-phosphate uridyl transferase. The reaction involves the transfer of a uridyl phosphate residue from UDP glucose to the galactose I-phosphate, yielding glucose 1-phosphate and UDP galactose. As glucose 1-phosphate, galactose can be incorporated into glyycogen through reactions discussed previously. It can enter the
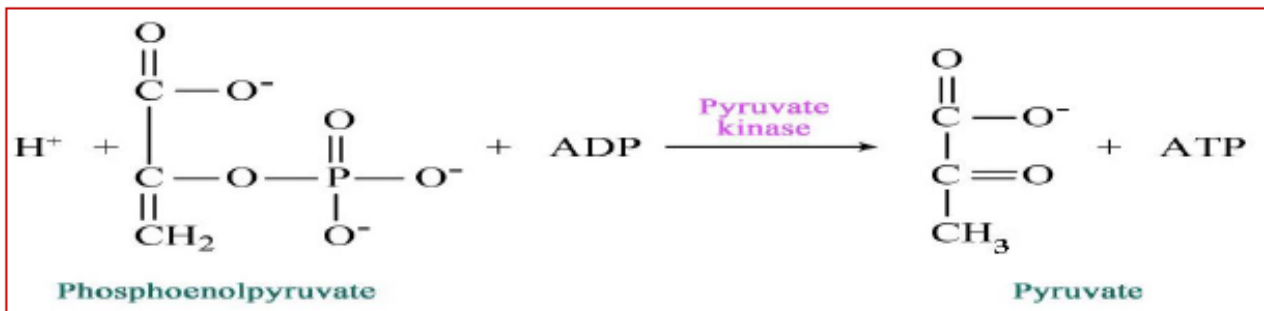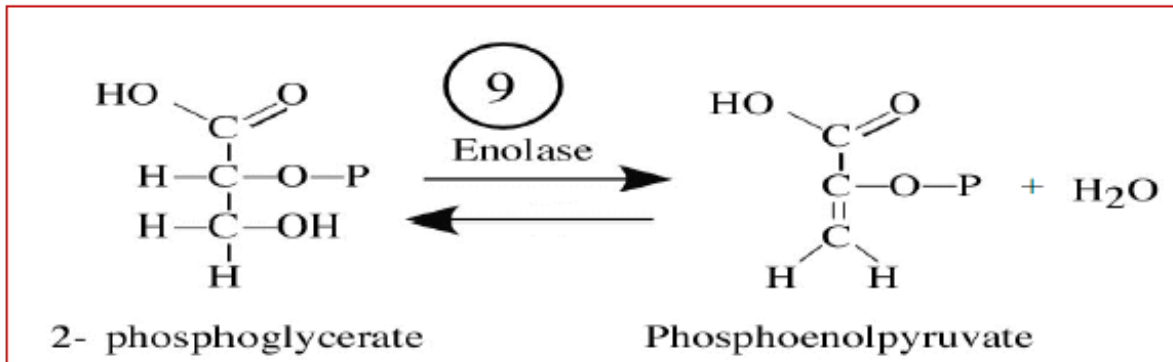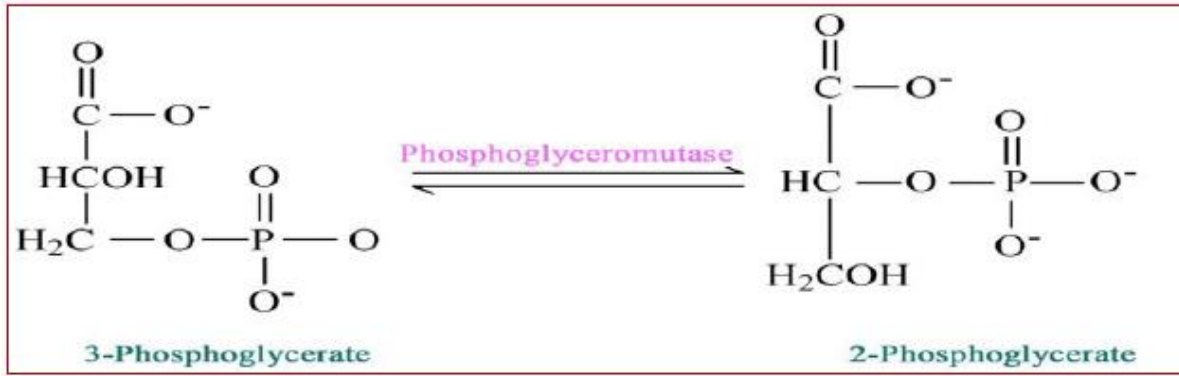
glycolytic pathway following isomerisation to glucose 6-phosphate and be hydrolysed to free glucose in liver cells.

14 .This indicates the entry of glucose 6-phosphate into another pathway called the hexose monophosphate shunt (pentose phosphate pathway), which will be considered next.

$$\text{Glucose} + 2\ Pi + 2\ ADP \longrightarrow 2\ \text{Pyruvate} + 2\ ATP$$

Glucose + ATP → [Hexokinase] → Glucose-6-phosphate + ADP

Glucose-6-phosphate ⇌ [Glucosephosphate isomerase] ⇌ Fructose-6-phosphate

Fructose-6-phosphate + ATP → [Phosphofructokinase, $Mg^{2+}$] → Fructose-1,6-bisphosphate + ADP

Fructose-1,6-bisphosphate → Dihydroxyacetone phosphate + D-Glyceraldehyde-3-phosphate (Aldolase)



Dihydroxyacetone phosphate ⇌ D-Glyceraldehyde-3-phosphate (Triosephosphate isomerase)



Glyceraldehyde-3-phosphate + NAD⁺ + HO—P—O⁻ ⇌ 1,3-bisphosphoglycerate + NADH⁺ + H⁺ (Glyceraldehyde-3-phosphate dehydrogenase)



1,3-bisphosphoglycerate + ADP ⇌ 3-Phosphoglycerate + ATP (Phosphoglycerate kinase, Mg²⁺)

3-Phosphoglycerate      Phosphoglyceromutase      2-Phosphoglycerate



2- phosphoglycerate     Enolase (9)     Phosphoenolpyruvate + $H_2O$



Phosphoenolpyruvate     Pyruvate kinase     Pyruvate

<u>محصلة الطاقة الناتجة من تحلل جزيء من الجلوكوز إلى جزيئيين من البيروفيت</u>

• إستهلاك 1 ATP في الخطوة رقم 1 .

• إستهلاك 1 ATP في الخطوة رقم 3 .

• إنتاج جزيئيين من ال (NADH) باعتبار أن الجلوكوز إنشطر إلى جزيئيين في الخطوة رقم 6 . كل جزيء من ال NADH عند أكسدته يعطي 3 ATP .

• إنتاج 2 ATP في الخطوة رقم 7 باعتبار أن الجلوكوز إنشطر إلى جزيئيين من الجليسر ألدهيد 3 -فوسفات وكل جزء يعطي 1 ATP .

• إنتاج 2 ATP في الخطوة رقم 10 باعتبار وجود جزيئين من 3 -فوسفو إنول بيروفيت ليعطي كلا منهما 1 ATP .

14

وبالتالي يكون الناتج: 1-1+2+2+6 = 8 ATP
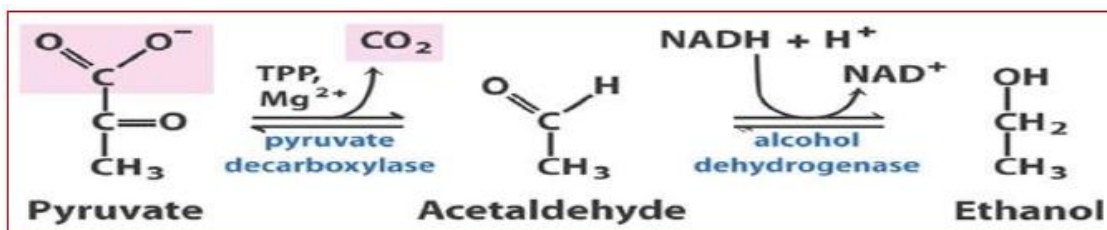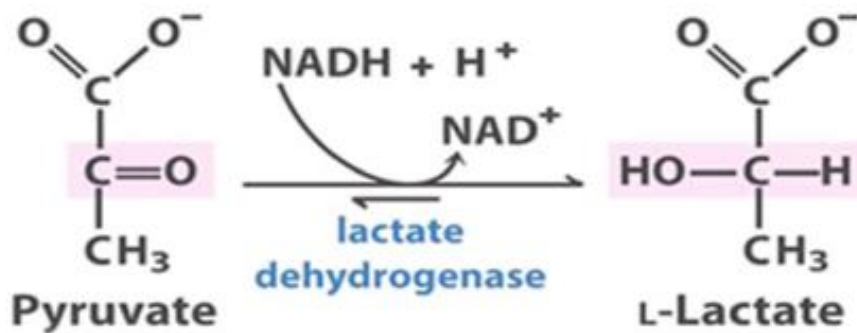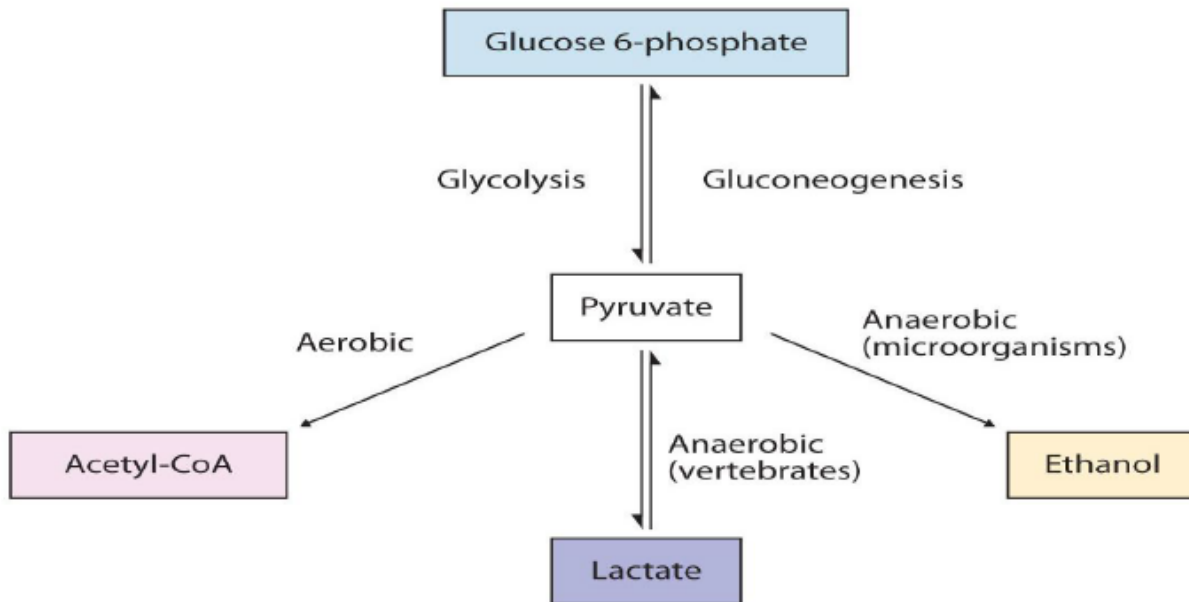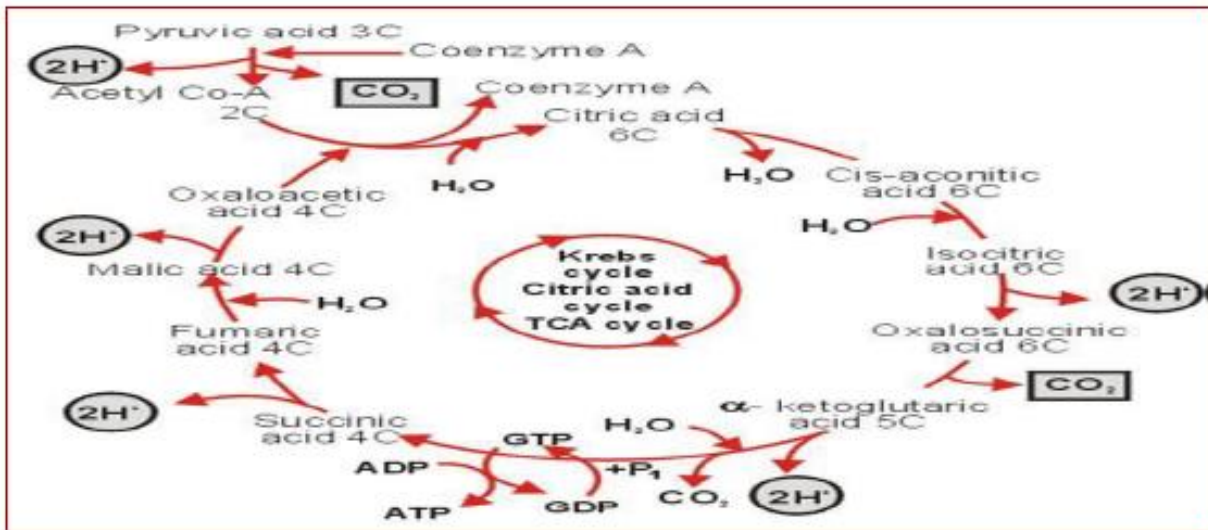
## Krebs Cycle

Alternatively designated the tricarboxylic acid cycle or the citric acid cycle, this sequence of reactions represents the forefront of energy metabolism in the body. It can be thought of as the common and final catabolic pathway because products of carbohydrate, fat, and amino acids feed into the cycle where they can be totally oxidised to $CO_2$ and $H_2O$, with the accompanying generation of large amounts of ATP. Not all entrant substances are totally oxidised. Some Krebs cycle intermediates are used to form glucose by the process of gluconeogenesis, which will be discussed in the next section, and some can be converted to certain amino acids by transamination. However, the importance of the cycle as the nucleus of energy production is evidenced by the estimation that over 90 per cent of energy released from food occurs here.

The high energy output of the Krebs cycle is attributed to mitochondrial electron transport, with oxidative phosphorylation providing the means for ATP formation. The oxidation reactions occurring in the cycle are actually dehydrogenations in which an enzyme catalyses the removal of two

hydrogens to an acceptor co-substrate such as NAD or FAD. Since the enzymes of the cycle and the enzymes and electron carriers of electron transport are both compartmentalised within the mitochondria,

the reduced cosubstrates, NADH and FADH2 are readily reoxidised by $O_2$ via the electron transport chain. In addition to its production of the reduced co-substrates NADH and FADH2, which furnish the energy through their oxidation via electron transport, the Krebs cycle produces most of the carbon dioxide through decarboxylation reactions. Viewing this in its proper perspective with regard to glucose metabolism, it must be recalled that two pyruvates are produced from one glucose during cytoplasmic glycolysis. These pyruvates are in turn transferred into the mitochondria, where decarboxylation leads to the formation of two acetyl CoA units and two molecules of $CO_2$. The two carbons represented by the acetyl CoA are additionally lost as $CO_2$ through Krebs cycle decarboxylations. Most of the $CO_2$ produced is exhaled through the lungs, although some is used in certain synthetic reactions called carboxylation. The Krebs cycle is shown in figure below. It is usually visualized as beginning with the condensation of acetyl CoA with oxaloacetate to form citrate. The acetyl CoA is formed from numerous sources, including the breakdown of fatty acids, glucose (through pyruvate), and certain amino acids. Its formation from pyruvate will be considered now, since this compound links cytoplasmic glycolysis to the mitochondrial Krebs cycle activity. The reaction shown below is generally referred to as the pyruvate dehydrogenase reaction. However, the reaction is a complex one requiring a multienzyme system and various cofactors. The enzymes

and cofactors are contained within an isolable unit called the pyruvate dehydrogenase complex. The cofactors include coenzyme A (CoA )thiamine diphosphate (TDP), $Mg+2$, NAD, FAD, and lipoic acid. Four

vitamins are therefore necessary for the activity of the complex pantothenic acid (a component of CoA), thiamine, niacin, and riboflavin.

The role of these vitamins and others as precursors of coenzymes will be discussed in another unit. The enzymes include pyruvate decarboxylase, dihydroolipoyl dehydrogenase, and dihydrolipoyl transacetylase. The net effect of the complex results in decarboxylation and dehydrogenation of pyruvate with NAD serving as the terminal hydrogen acceptor. This reaction therefore yields energy, since the reoxidation by electron transport of the NADH produces three mol of ATP by oxidative phosphorylation. The reaction is regulated negatively by ATP and by NADH. The condensation of acetyl CoA with oxaloacetate initiates the Krebs cycle reactions. The following are comments on reactions:

1 .The formation of citrate from oxaloacetate and acetyl CoA is catalysed by citrate synthetase. The reaction is regulated negatively by ATP. The isomerisation of citrate to isocitrate involves cis aconitate as an intermediate. The isomerisation, catalysed by aconitase, involves dehydration followed by sterically reversed hydration, resulting in the repositioning of the-OH group onto an adjacent carbon. The first of four

dehydrogenation reactions within the cycle, the isocitratede hydrogenase reaction supplies energy through the respiratory chain reoxidation of the NADH. Note that the first loss of $CO_2$ in the cycle occurs at this site. It arises from the spontaneous decarboxylation of an intermediate compound, oxalosuccinate. The reaction is positively modulated by ADP and negatively modulated by ATP and NADH.

2 .The decarboxylation/dehydrogenation of aglutarate is mechanistically identical to the pyruvate dehydrogenase complex reaction in its multi-enzyme/cofactor requirement. In the reaction, referred to as the α

ketoglutarate dehydrogenase reaction, NAD serves as hydrogen acceptor, and a second carbon is lost as $CO_2$ The pyruvate dehydrogenase, isocitrate dehydrogenase, and aglutarate dehydrogenase reactions account for the loss of the three-carbon equivalent of pyruvate as $CO_2$.

3 .Energy is conserved in the thioester bond of succcinyl CoA. The hydrolysis of that bond by succinyl thiokinase releases enough energy to drive the phosphorylation of guanosine diphosphate (GDP) by inorganic phosphate. The resulting GTP is a high energy phosphate anhydride compound like ATP; as such, GTP can serve as phosphate donor in certain phosphorylation reactions. One such reaction occurs in the gluconeogenesis pathway.

4 .The succinate dehydrogenase reaction uses FAD instead of NAD as hydrogen acceptor. The FADH2 is reoxidised by electron transport to $O_2$, but only two ATPs are formed by oxidative phosphorylation instead of three.

5 .Fumarase incorporates the elements of $H_2O$ across the double bond of fumarate to form malate.

6 .The conversion of malate to oxaloacetate completes the cycle. NAD acts as a hydrogen acceptor in this dehydrogenation reaction catalysed by malate dehydrogenase. It is the fourth site of reduced co substrate formation and therefore of energy release in the cycle.

In summary the complete oxidation of glucose to $CO_2$ and $H_2O$ can be shown by the equation:

$$C_6H_{12}O_6 + 6O_2 \rightarrow 6\ CO_2 + 6\ H_2O + energy.$$

This is achieved by the combined reaction sequences of the glycolytic and Krebs cycle pathways. The amount of released energy conserved as ATP under aerobic conditions is as follows:

The glycolytic sequence, glucose $\rightarrow$ 2 pyruvates, produces two ATPs by substrate level phosphoryllation and either four or six by oxidative phosphoorylation, depending on the shuttle system for NADH-reducing equivalents. Generally, six will be formed due to the overall greater activity of the malate shuttle system. The intra mitochondrial pyruvate dehydrogenase reaction yields two mol of NADH, one for each pyruvate oxidised and therefore six additional ATPs by oxidative phosphorylation.

The oxidation of 1 mol of acetyl CoA in the Krebs cycle yields a total of 12 ATPs. The sites of formation, indicated by reaction number, follow.

3 - 3 .ATP

4 -3 .ATP

5 -1 .ATP (as GTP)

6 -2 .ATP

8-3 .ATP

**Total 12 ATP**

Since 2 mol acetyl CoA derived from one glucose, however, the actual total is 24 ATPs. The total number of ATPs realized for the complete oxidation of 1 mol of glucose is therefore 38, equivalent to 262.8 kcal. It will be recalled that this figure represents only about 40% of the total energy released by mitochondrial electron transport. The remaining 60 per cent, or approximately 394 kcal, is released
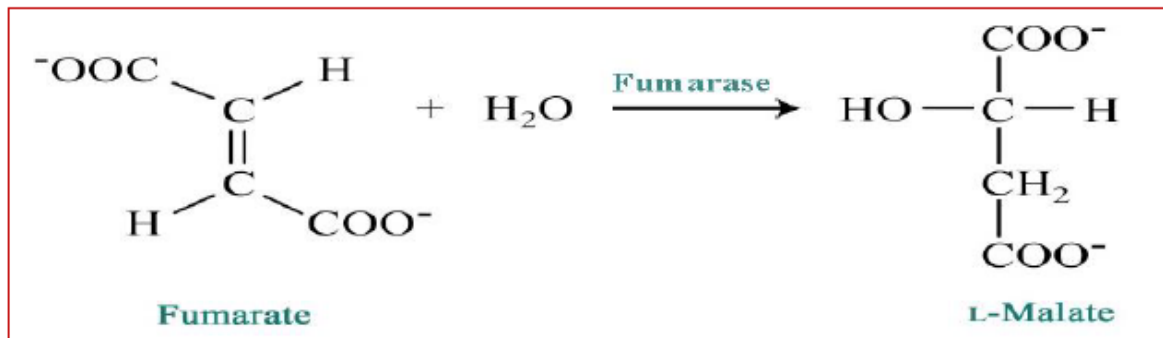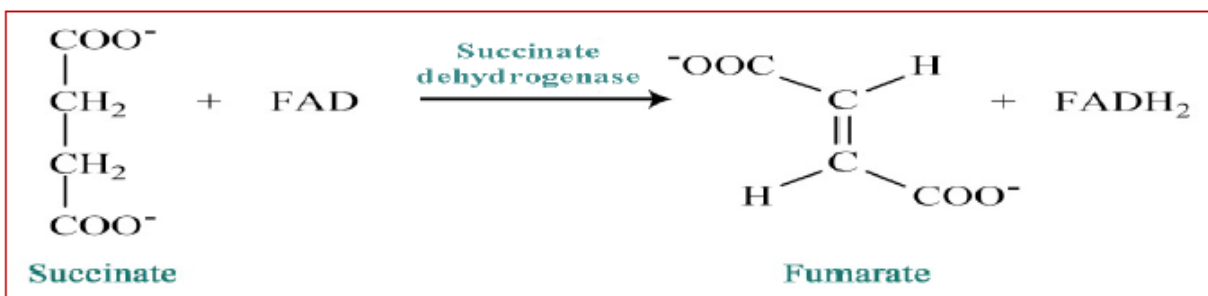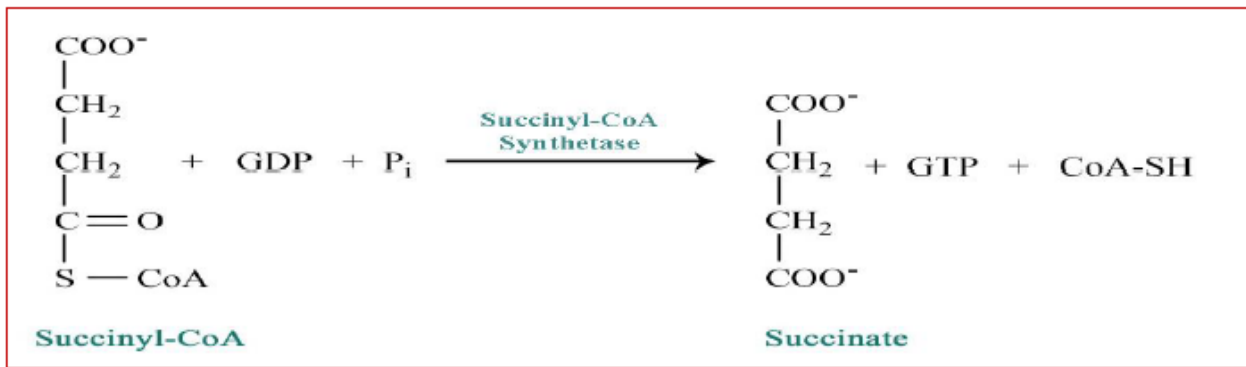
as heat to maintain body temperature has already been mentioned that acetyl CoA is produced by fatty acid oxidation and amino acid catabolism as well as from the glycolytically

derived pyruvate. This clearly leads to an imbalance between the amount of acetyl CoA and oxaloacetate, which condense one to one stoichiometrically in the citrate synthetase reaction. It is therefore important that oxaloacetate and/or Krebs cycle intermediates, which can form oxaloacetate, be replenished in the cycle. Such a mechanism does indeed exist. Oxaloacetate, fumarate, succinyl CoA, and a rate can all be formed from certain amino acids, but the single most important mechanism for ensuring an ample supply of oxaloacetate is the reaction

by which it is formed directly from pyruvate. This reaction, shown below, is catalysed by pyruvate carboxxylase. The "uphill" incorporation of $CO_2$ is accomplished at the expense of ATP, and the reaction requires the participation of biotin. The diversion of pyruvate into oxaloacetate is called an anaplerotic (filling up) process because of its role in restoring oxaloacetate to the cycle. It is of interest that pyruvate carboxylase is regulated positively by acetyl CoA, thereby accelerating oxaloacetate formation in answer to increasing levels of acetyl CoA.
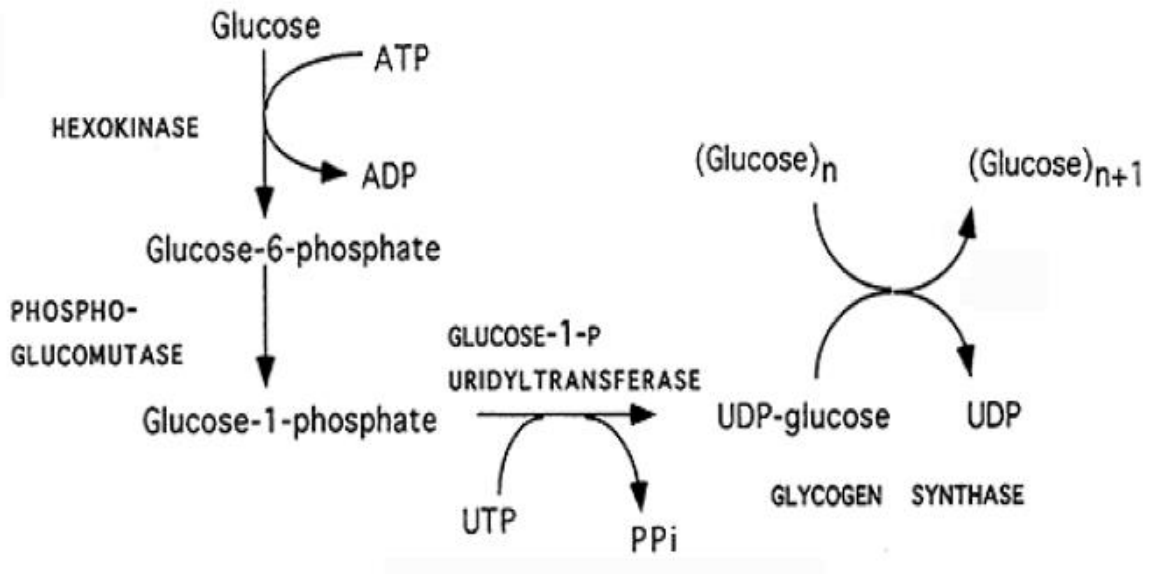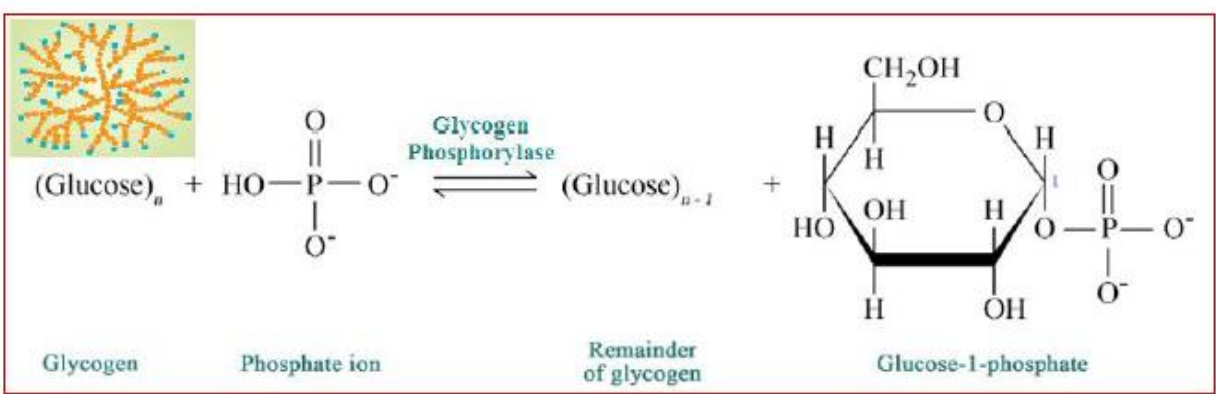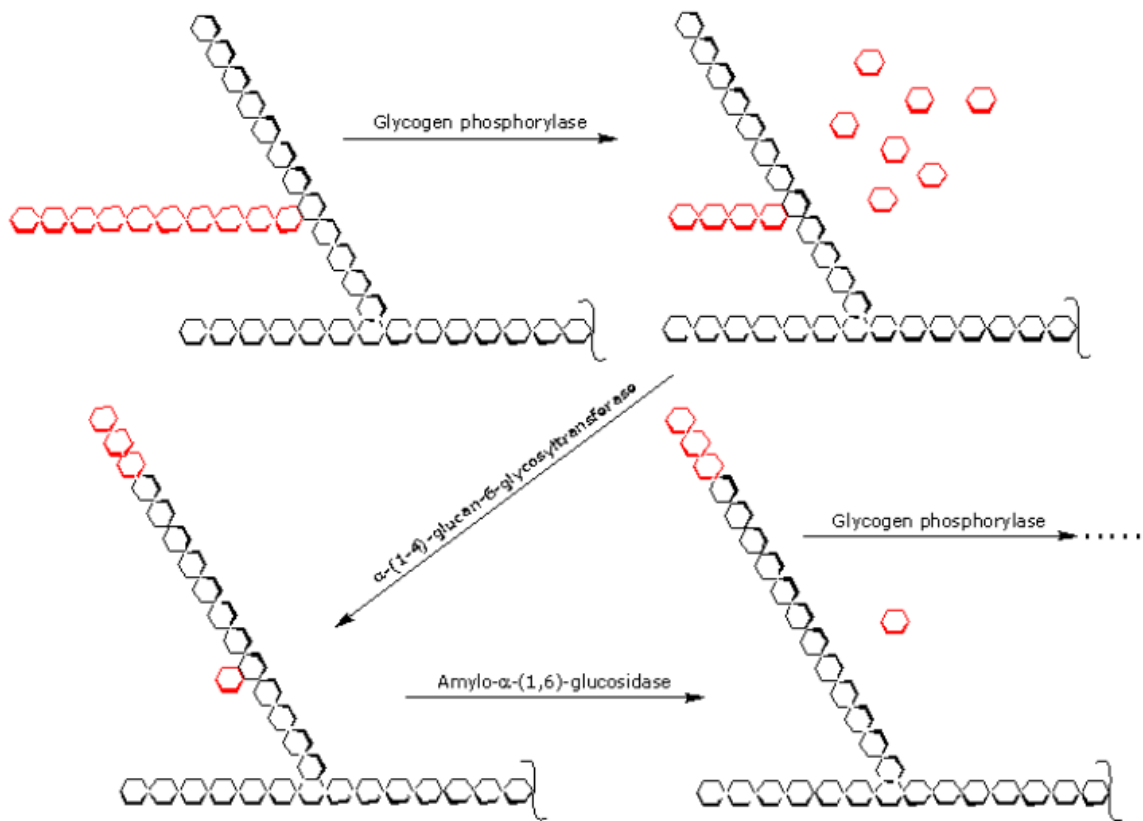


خطوات دورة كربس

Oxaloacetate + Acetyl-CoA + $H_2O$ → (Citrate Synthase) → Citrate + CoA-SH



Citrate → (Aconitase) → Isocitrate



Isocitrate + $NAD^+$ → (Isocitrate dehydrogenase) → Oxalosuccinate → (+ $CO_2$) → $\alpha$-Ketoglutarate
($NADH + H^+$)



$\alpha$-Ketoglutarate + $NAD^+$ + CoA—SH ⇌ (αKGDH, $Mg^{2+}$, TPP) Succinyl-CoA + $NADH + H^+ + CO_2$

Succinyl-CoA + GDP + P$_i$ $\xrightarrow{\text{Succinyl-CoA Synthetase}}$ Succinate + GTP + CoA-SH

Succinate + FAD $\xrightarrow{\text{Succinate dehydrogenase}}$ Fumarate + FADH$_2$

Fumarate + H$_2$O $\xrightarrow{\text{Fumarase}}$ L-Malate

L-Malate + NAD$^+$ $\xrightarrow{\text{Malate Dehydrogenase}}$ Oxaloacetate + NADH + H$^+$

# بناء الجلايكوجين ( **Glycogenesis**)



إستحداث الجلايكوجين ( Gluconeogenesis)

Glycogen phosphorylase

α-(1→4)-glucan-6-glycosyltransferase

Amylo-α-(1,6)-glucosidase

Glycogen phosphorylase

# Proteins Metabolism

# Protein Digestion

Protein breakdown begins in the **stomach**.

<u>No</u> protein hydrolyzing enzymes are found in saliva.

# Hemoglobin Molecule
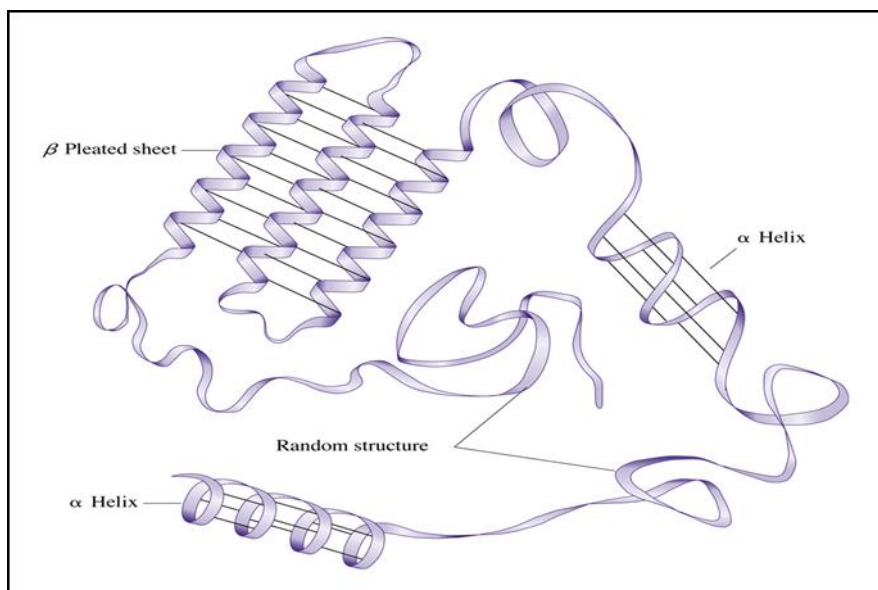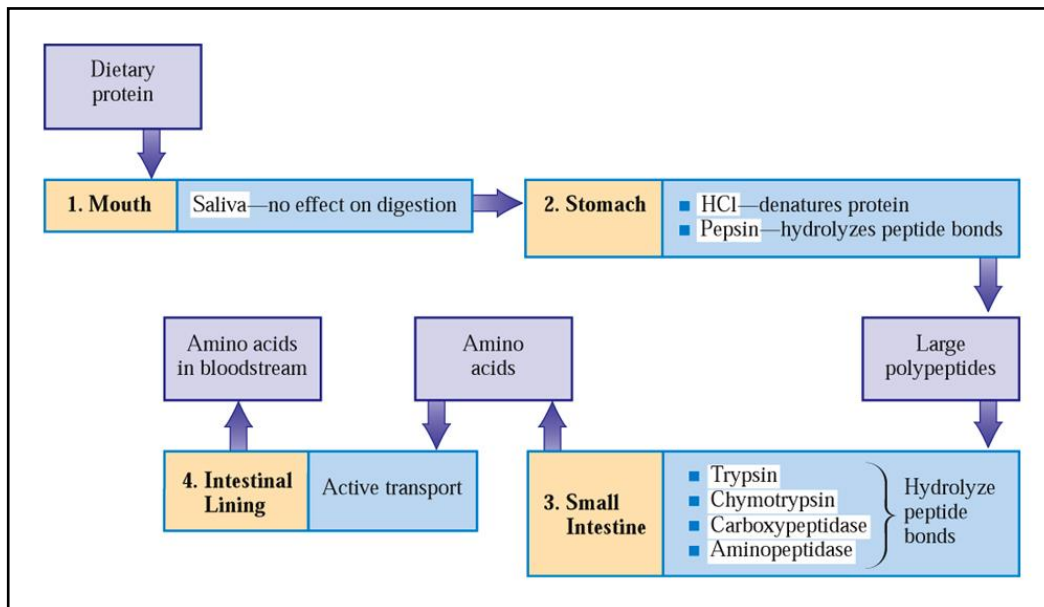




Amino-terminal residue $\longrightarrow$ Carboxyl-terminal residue
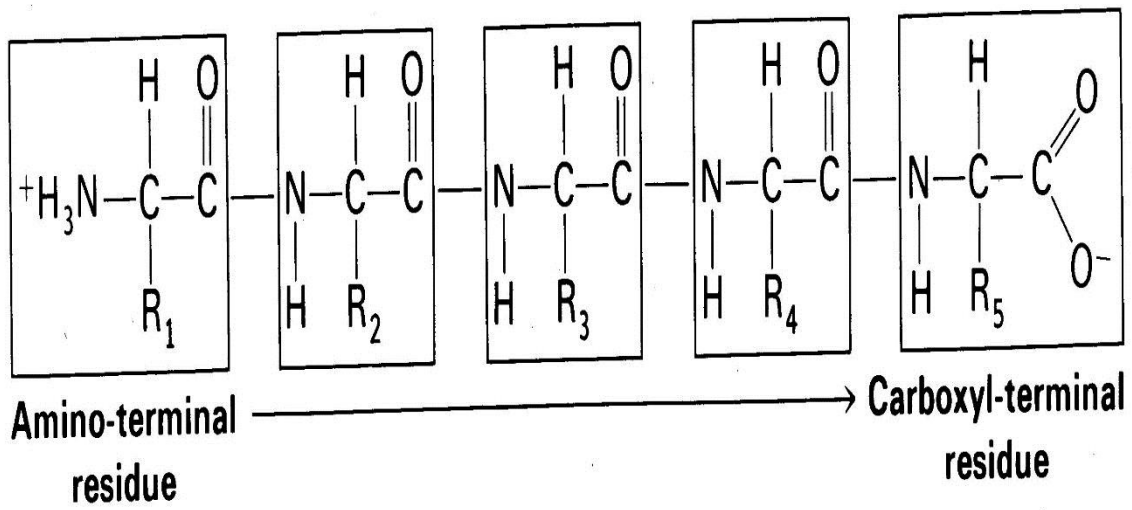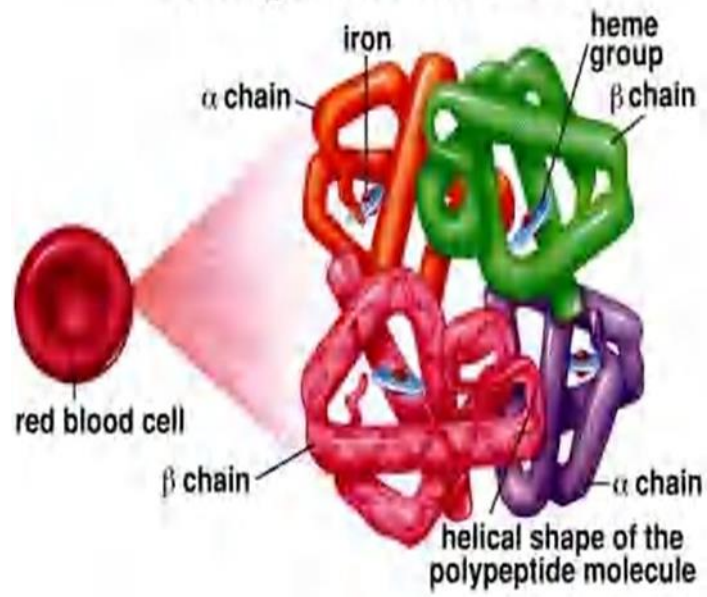
**Hydrolysis** (10% of peptide bonds) & **denaturization** by pepsin enzyme & HCl acid produce **short chain polypeptides** in the stomach.

**Trypsin, chymotrypsin, & carboxypeptidase** from Pancreatic juices, and **Aminopeptidase** from cells in the small intestine Brush Zone create "free" **amino acids**.

Free amino acids are absorbed thru intestinal wall via active transport. Enter bloodstream and are brought to cells.

The total supply of free amino acids available is called: the **Amino Acid Pool**.

3 sources of "free" amino acids:

1. Dietary protein breakdown
2. Biosynthesis of amino acids in the Liver
3. Protein turnover (I prefer apple turnovers)

**Protein turnover** is the breakdown & re-synthesis of body protein:

Old tissues

Damage

Recycling enzymes & hormones
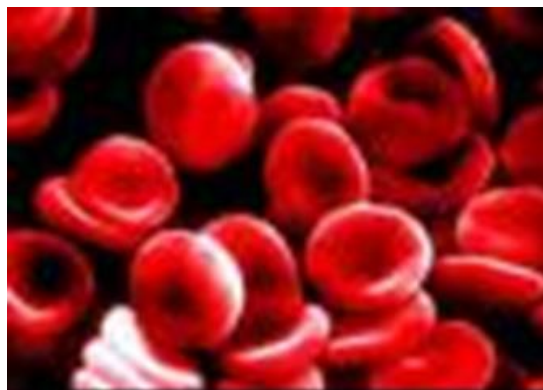
Summary of protein digestion in  the human body. Possible fates for amino acid degradation products.
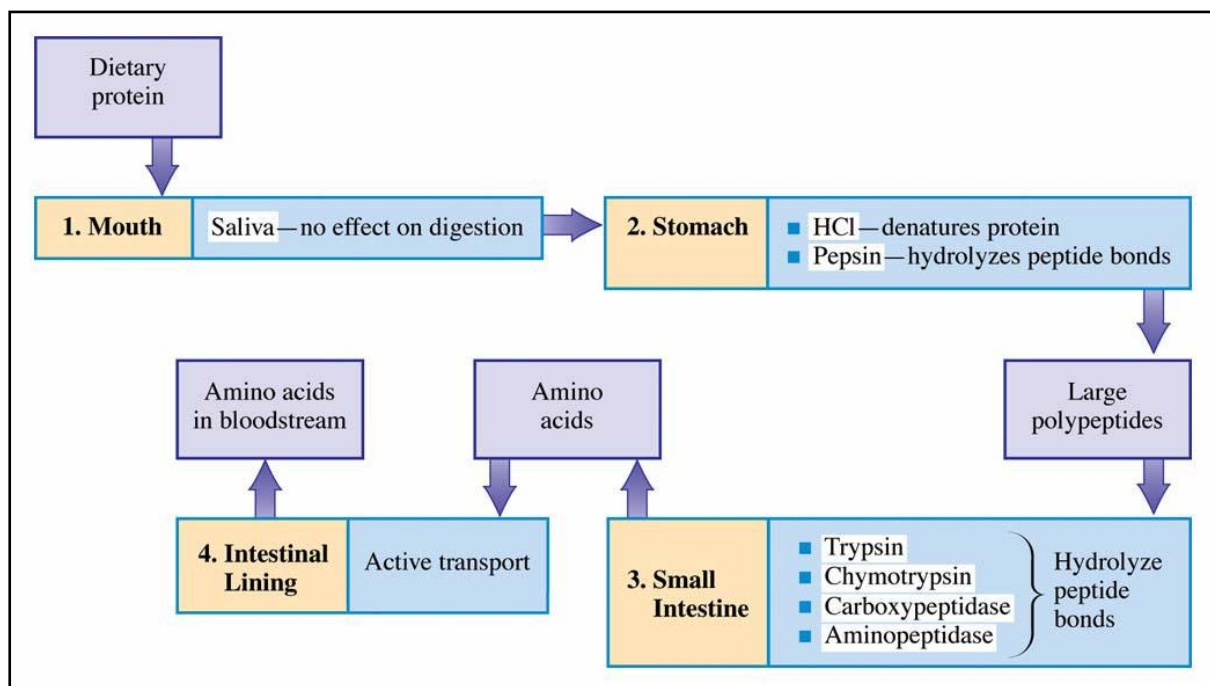
**Transamination and Oxidative Deamination:**

Two steps in degrading amino acids

1) remove a-amino group

2) breakdown & process carbon skeleton

Release of an **amino group** is also two steps:

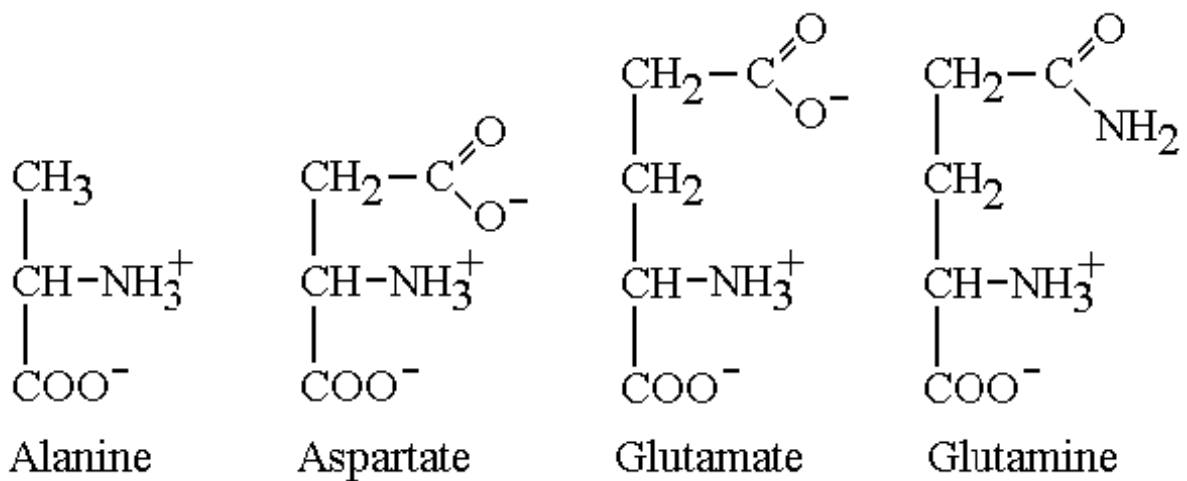     1) **Transamination**

     2) **Oxidative deamination**

**Central role of glutamate:**

Amino acids:

**Glutamate**, **aspartate**, **alanine** & **glutamine**

present in higher concentrations in mammalian cells. Have metabolic

functions as well as roles in proteins.

**Glutamate** is the most important, metabolically

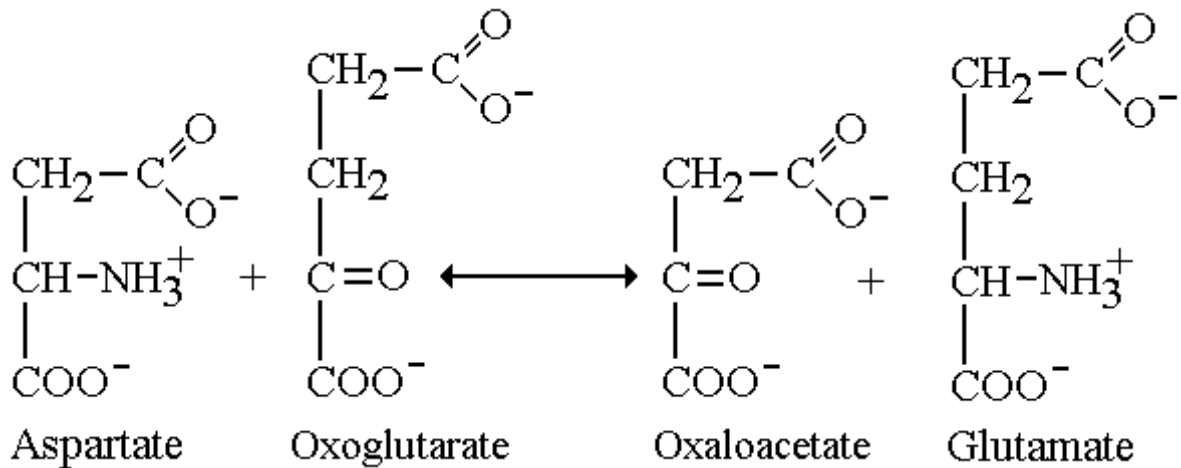Alanine     Aspartate     Glutamate     Glutamine

Some **transaminases** are used for diagnosing disorders:

enzyme **alanine aminotransferase**. Escapes in large amounts from dead or dying liver tissue. Measured in blood samples for diagnostic purposes.



Alanine     Oxoglutarate     Pyruvate     Glutamate
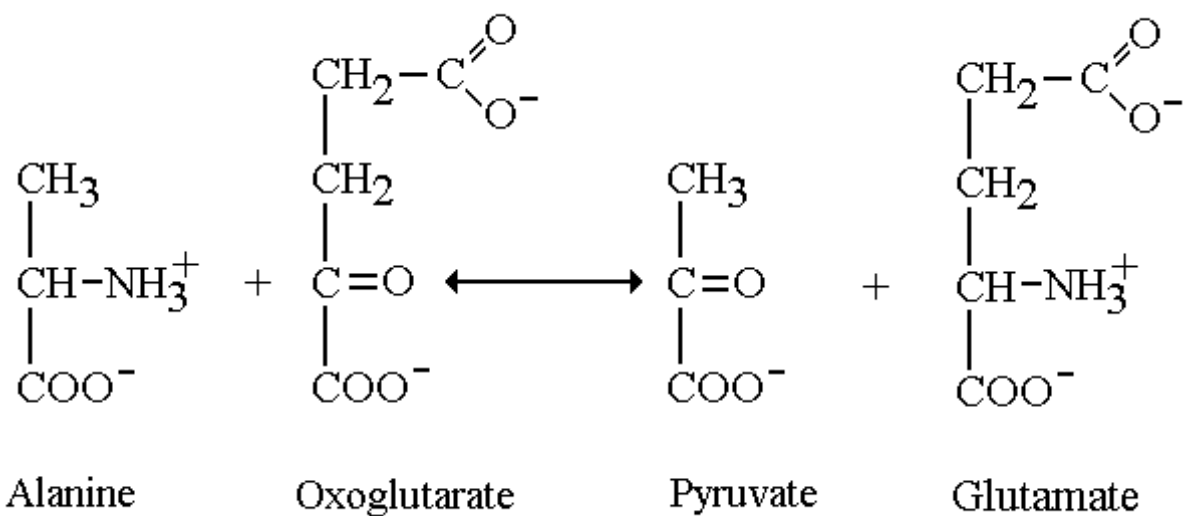
Transaminase enzyme **aspartate aminotransferase** very active enzyme inside heart cells. Also escapes in large amounts from dead or dying heart tissues & enters bloodstream. Measured in blood for diagnosing myocardial infarction.

$$CH_2-C\!\!\diagup^{O}_{\diagdown O^-} \qquad CH_2-C\!\!\diagup^{O}_{\diagdown O^-}$$

Aspartate + Oxoglutarate ⟷ Oxaloacetate + Glutamate

## Trans-deamination (sum it up)

Most **transaminases** share a common substrate and product (oxoglutarate and glutamate) with the enzyme **glutamate dehydrogenase**.
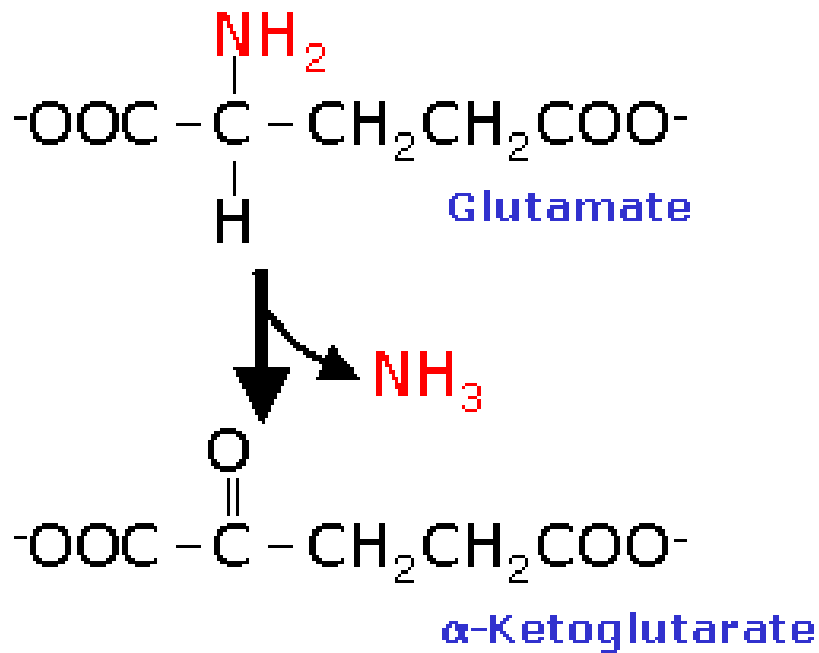
This permits a *combined* N excretion pathway for individual amino acids: "trans-deamination."
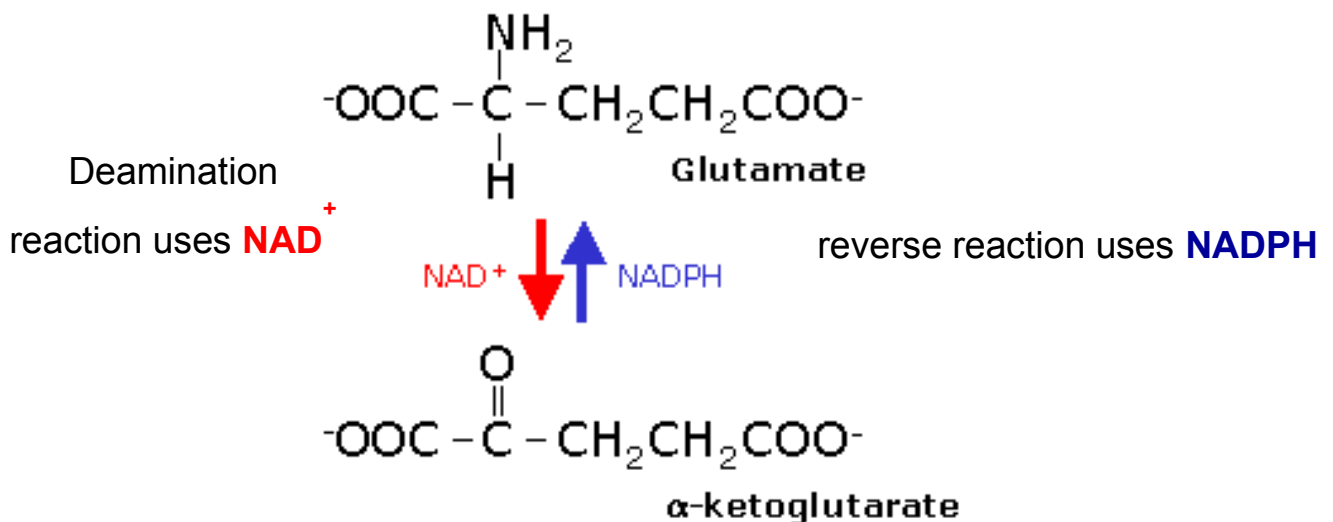
**Glutamate** has a central role in the overall control of nitrogen metabolism.

keto acid ← → glutamate — $H_2O$ — NAD(P)

**trans aminase**      **glutamate dehydrogenase**

amino acid — → oxoglutarate ← — $NH_3$ → NAD(P)H
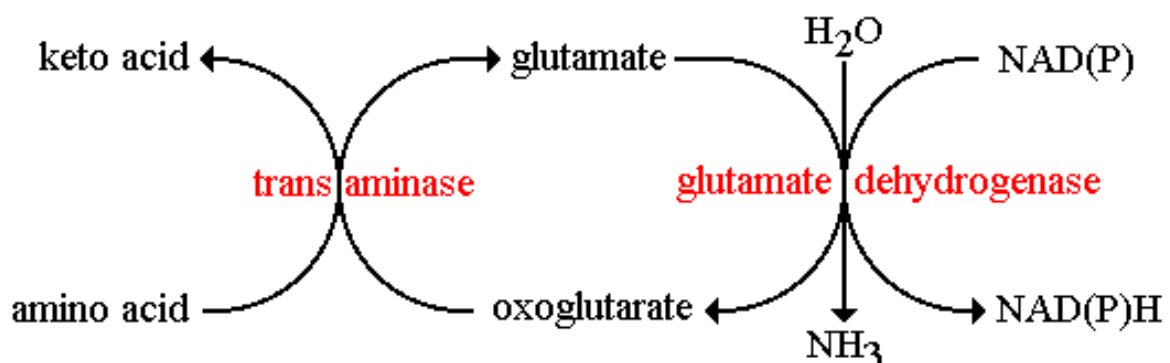
## Oxidative Deamination

The **glutamate** produced from the transamination step is then deaminated by **oxidative deamination** using the enzyme **glutamate dehydrogenase**

32

$$\underset{\text{Glutamate}}{\overset{\displaystyle NH_2}{^-OOC-\overset{|}{\underset{|}{C}}-CH_2CH_2COO^-}}$$

$$\downarrow \searrow NH_3$$

$$\underset{\alpha\text{-Ketoglutarate}}{^-OOC-\overset{\displaystyle O}{\overset{\|}{C}}-CH_2CH_2COO^-}$$

Recycles back to a ketodiacid & releases ammonia

**Glutamate dehydrogenase [GluDH]**  will reversibly convert

**glutamate** to **a-ketoglutarate**  and **a-ketoglutarate** to **glutamate**.

$$\underset{\text{Glutamate}}{\overset{\displaystyle NH_2}{^-OOC-\overset{|}{\underset{|}{C}}-CH_2CH_2COO^-}}$$

Deamination

reaction uses **NAD$^+$**            $NAD^+ \downarrow \uparrow NADPH$            reverse reaction uses **NADPH**

$$\underset{\alpha\text{-ketoglutarate}}{^-OOC-\overset{\displaystyle O}{\overset{\|}{C}}-CH_2CH_2COO^-}$$

Uses *both* **NAD$^+$** and **NADPH** – how to regulate it?

# Urea cycle:

Ammonium salts ($NH_4^+$) are toxic compounds.

**Oxidative deamination** converting glutamate to a-ketoglutarate is an easily shifted equilibrium reaction.

**Ammonium ions** building up favors the synthesis of excessive amounts of glutamate, decreasing the Krebs cycle intermediate

**a-ketoglutarate**.

This in turn decreases **ATP production**, and that affects the nervous system.
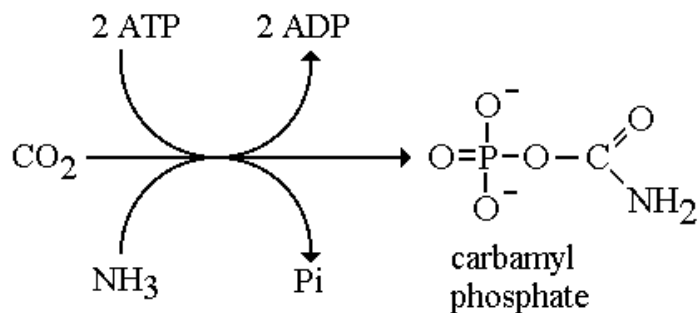
The answer is Urea:

$$H_2N-\overset{\overset{\textstyle O}{\|}}{C}-NH_2$$
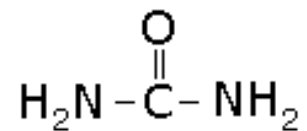
The **inputs** to the urea cycle are $NH_3$, $CO_2$ and aspartic acid and ATP.
The **outputs** are urea, ADP and fumaric acid.
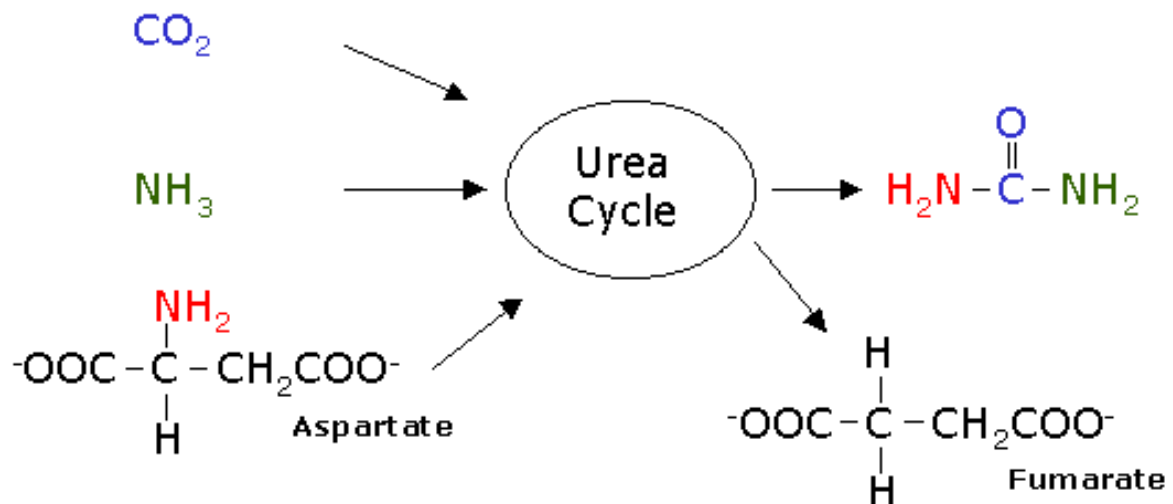


The carbonyl group of urea is derived from **$CO_2$** , **Ammonia** contributes one of the amine groups on urea

The **four-step** <u>urea cycle</u> in which **carbamoyl phosphate** is converted to **urea**.
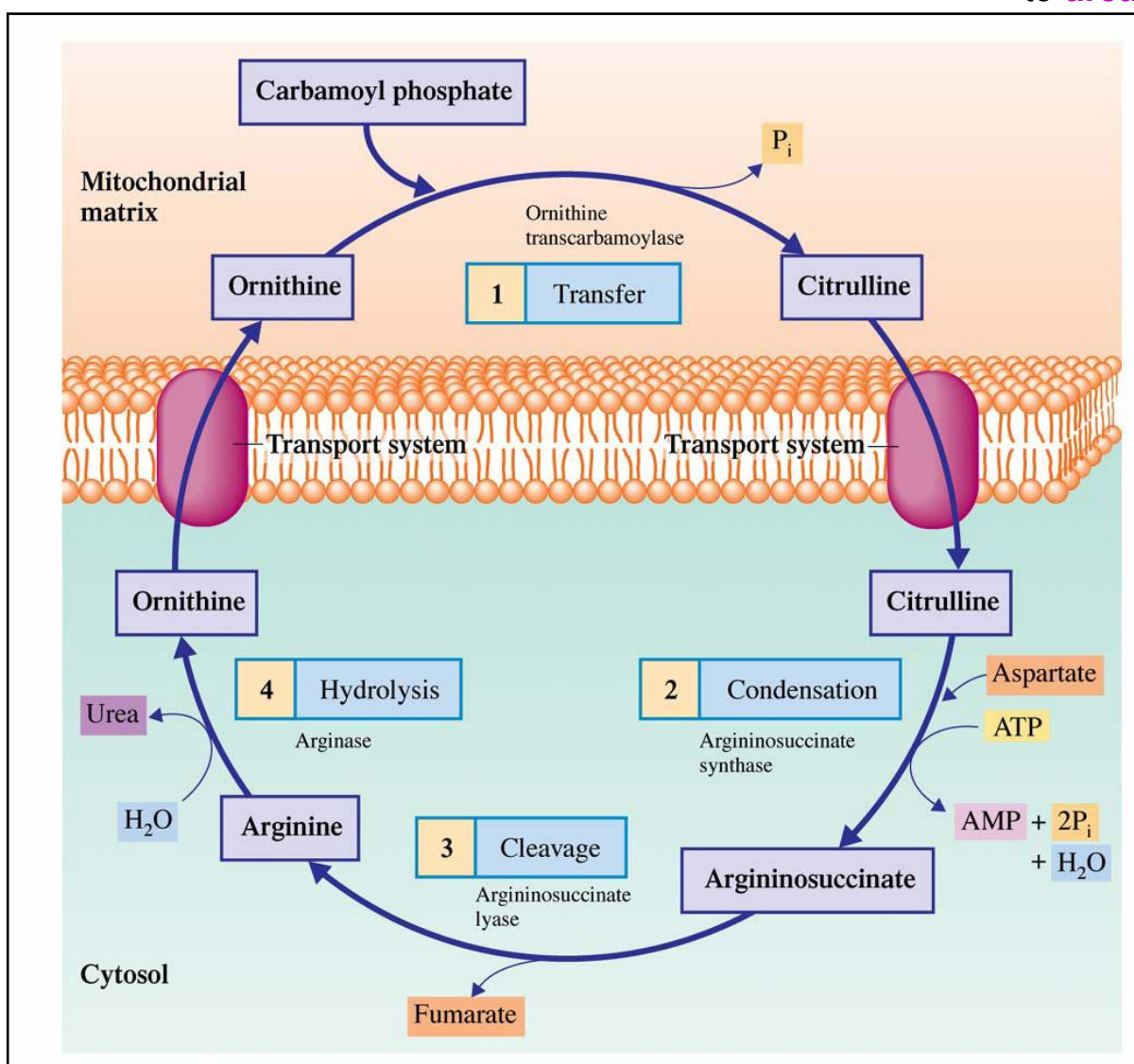


The nitrogen content of the various compounds that participate in the urea cycle
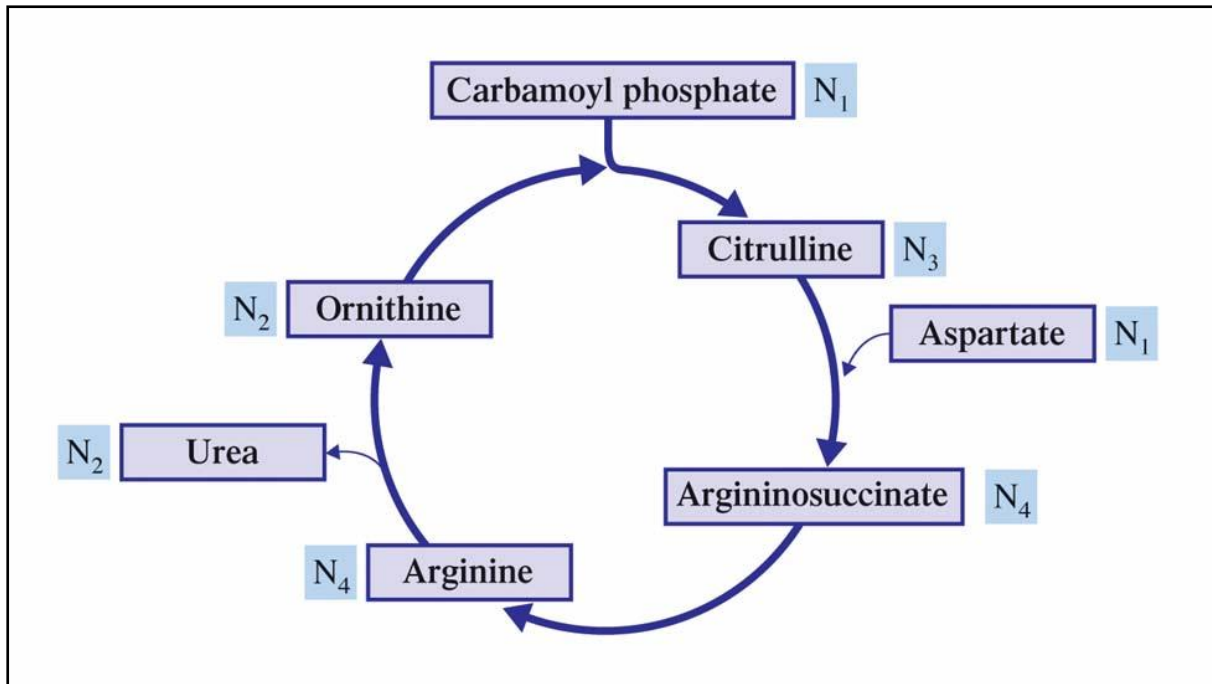
**Fumarate** from the urea cycle enters the Krebs cycle. **Aspartate** produced from **oxaloacetate** of the Krebs cycle enters the urea cycle.
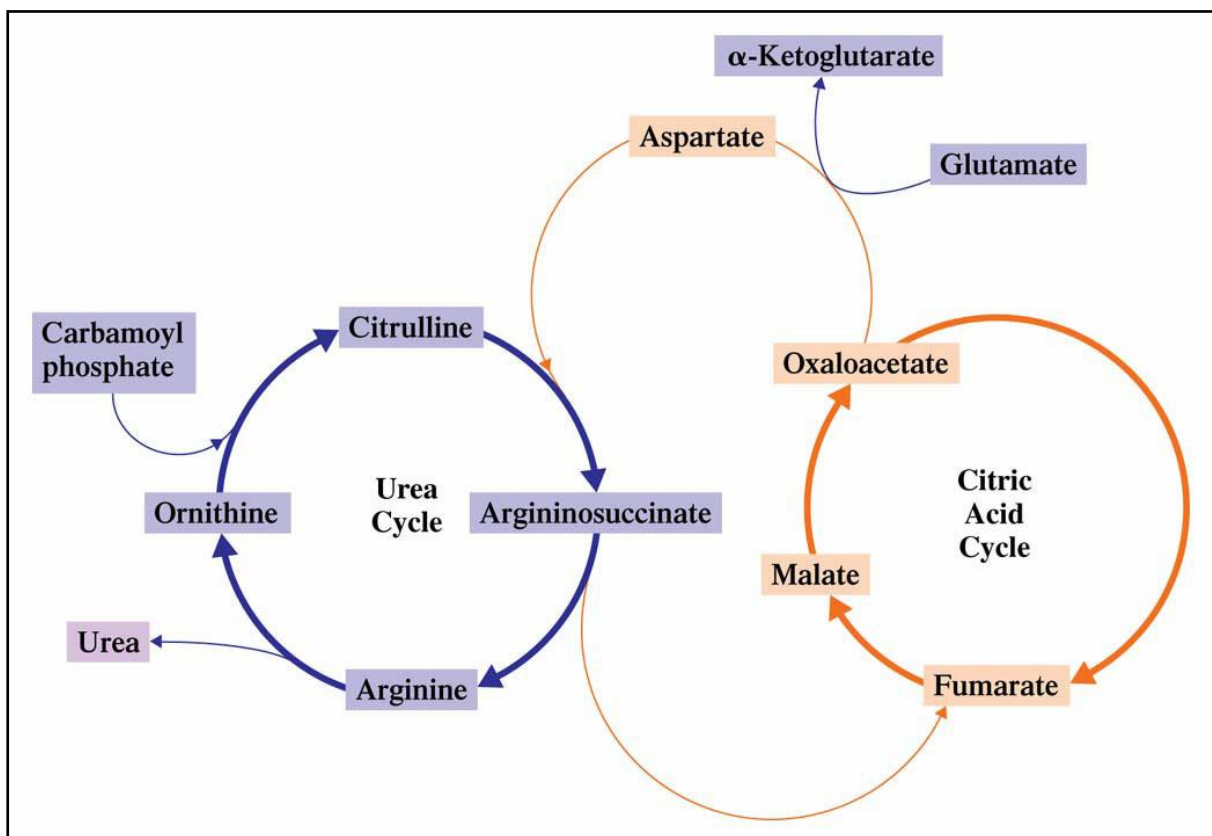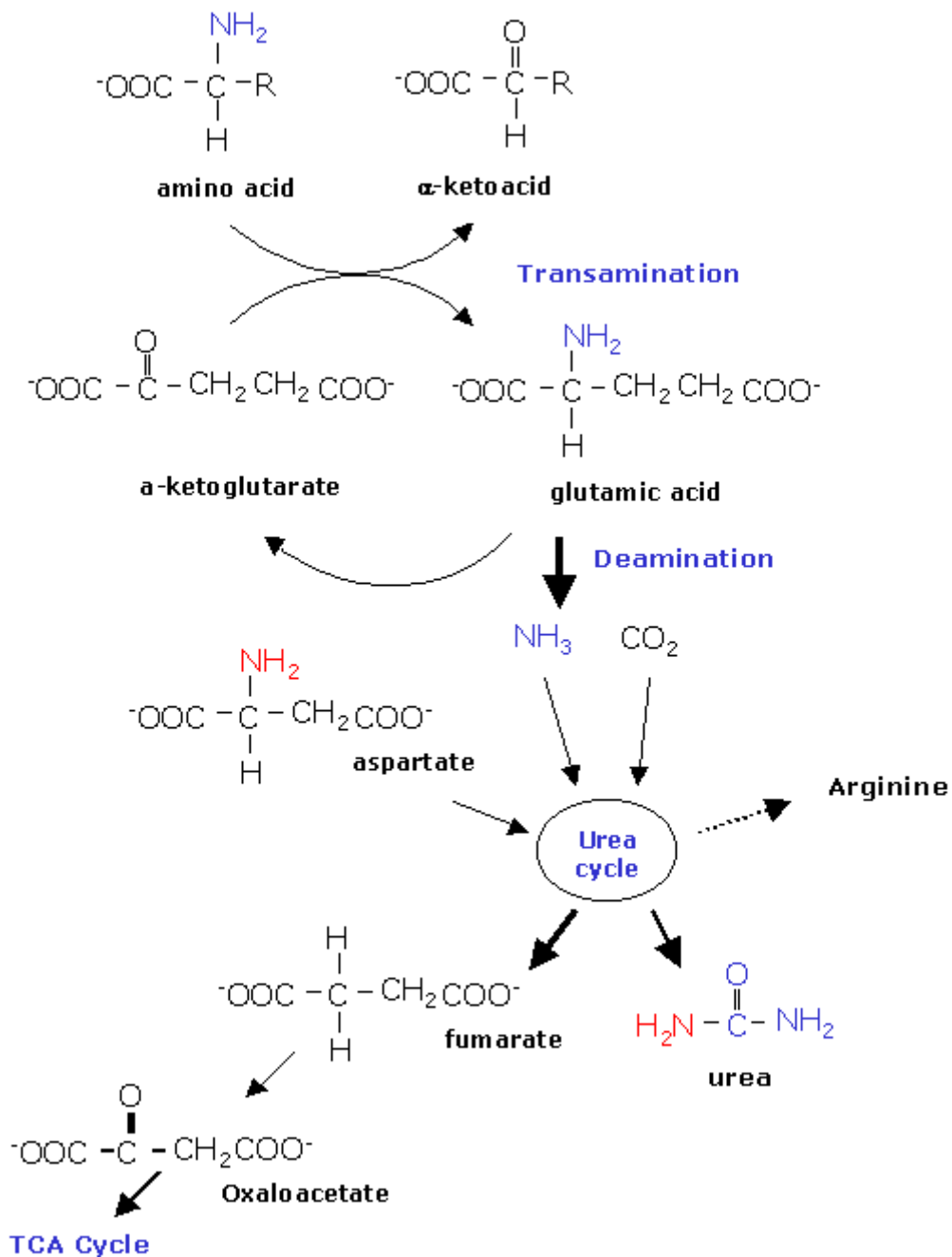


Oxaloacetate has 4 potential fates: transamination; conversion to glucose; formation of citrate; conversion to pyruvate
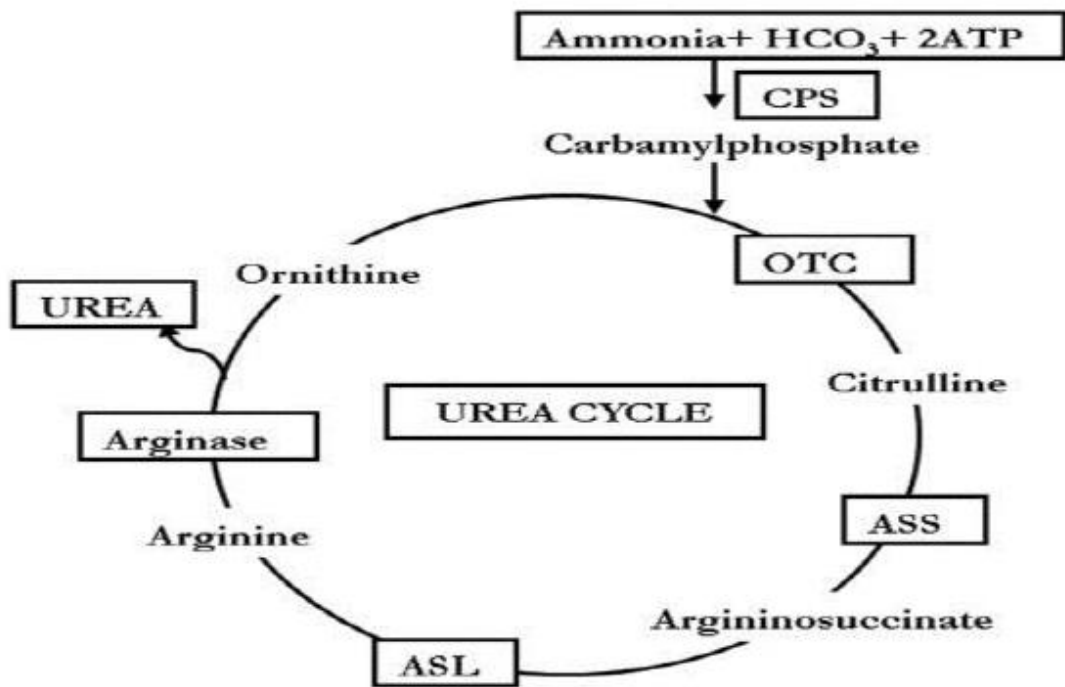
Summary:
**Transamination** takes off amine groups from amino acids and forms
**glutamate**
(ionized glutamic acid)

Amine groups form **ammonia** when removed in **deamination**
This combines with **$CO_2$** & **Aspartate**.

Forms **urea**, **Arginine**,
& **Fumarate**

Reptiles & birds excrete **uric acid** – very *insoluble* purine compound – forms supersaturated solutions. Concentrated urine, supersaturated with uric acid, goes from cloaca into hindgut – uric acid crystalizes & water is reabsorbed.
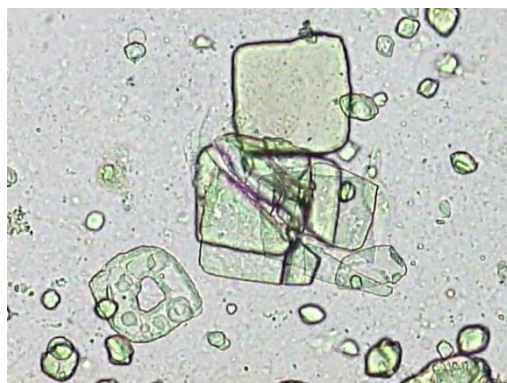


In humans uric acid deposits crystals & causes gout

Gout
Bone erosions
Urate crystals in a tophus
Synovium
© MedicineNet, Inc.
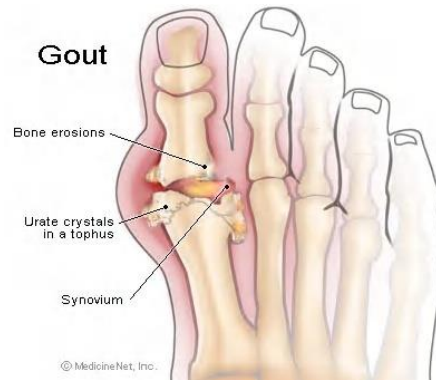
Processing Amino Acid Carbon Skeletons

Transamination or Oxidative deamination both produce a-keto acids

Degradation of these carbon skeletons may take several different pathways:

Amino acid C skeletons that degrade to form a Krebs cycle intermediate can then be used to make glucose via **gluconeogenesis**.

These are called **Glucogenic Amino Acids**.

Amino acid C skeletons that degrade to form **acetyl CoA** or **Acetoacetyl CoA** can form fatty acids or ketone bodies.

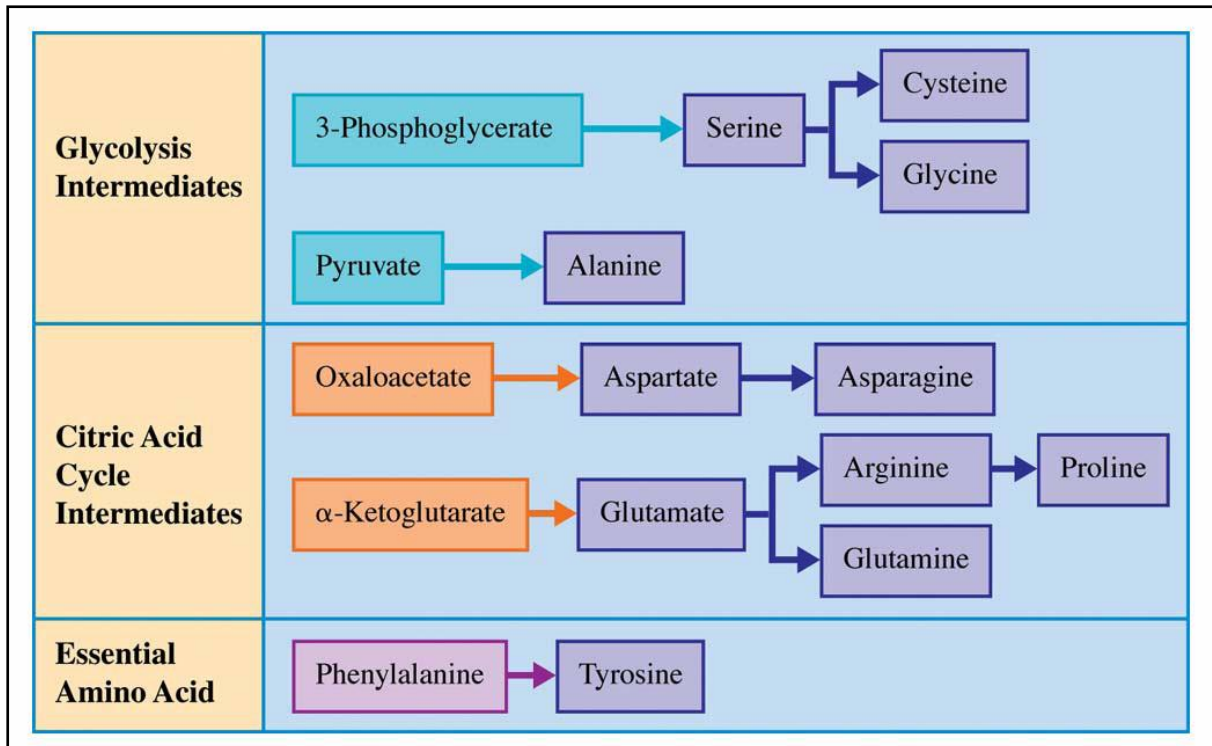These are called **Ketogenic Amino Acids**.

## Amino Acid Biosynthesis

Essential amino acids can be made by plants & bacteria in 7 to 10 steps.

We obtain these amino acids by eating plants.11 Non-essential amino acids synthesized in 1 to 3 steps. Use glycolysis intermediates:

**3-phosphoglycerate** & pyruvate Krebs cycle intermediates:

**Oxaloacetate** & **a-ketoglutarate**.

Starting materials for biosynthesis of 11 **nonessential** amino acids: 1 step, 2 steps, or 3 steps

| Glycolysis Intermediates | 3-Phosphoglycerate → Serine → Cysteine, Glycine; Pyruvate → Alanine |
| --- | --- |
| Citric Acid Cycle Intermediates | Oxaloacetate → Aspartate → Asparagine; α-Ketoglutarate → Glutamate → Arginine → Proline, Glutamine |
| Essential Amino Acid | Phenylalanine → Tyrosine |

Alanine, aspartate, & glutamate use transamination

**Phenylketonuria (PKU)**:

Defective phenylalanine hydroxylase – **phenylalanine** accumulates in body. Phenylalanine is transaminated to **phenylpyruvate**.

Accumulation of phenylpyruvate leads to severe mental retardation in infants. Persons suffering from phenylketonuria should not consume foods containing high levels of phenylalanine, such as aspartame.

# Hemoglobin catabolism

Red blood cells contain oxygen carrying pigments of a conjugated protein: Protein part is *Globin* Non-protein prosthetic group is *Heme*. **Heme** contains four pyrrole (**tetrapyrrole**) groups held together by an **iron** atom. Old red blood cells degraded in the spleen. Globin is hydrolyzed into amino acids. Iron atom stored in a protein (*ferritin*) **Tetrapyrrole** degraded to **bile pigments**.

Review: can you…
- Describe the steps in Protein digestion & absorption
- Explain how Amino Acids are utilized in the body
- Explain **Transamination** and **Oxidative De-amination**
- Describe **The Urea Cycle** – purpose and steps
- Describe how a.a. Carbon Skeletons are processed
- Define and explain Amino Acid Biosynthesis.
- Describe the chemical composition of urine.

# Lipid Metabolism

Fatty acids (F.A.s) are taken up by cells.

They may serve as:

- precursors in synthesis of other compounds
- fuels for energy production
- substrates for ketone body synthesis.

Ketone bodies may be exported to other tissues: used for **energy production**. Some cells **synthesize fatty acids** for storage or export.

## Energy

Fats are an important source of calories. Typically 30-40% of calories in American diet are from **fat**. Fat is the major form of **energy storage**.

Typical body fuel *reserves* are:

**fat:**            **100,000 kcal.**

**protein:**        **25,000 kcal**.

**carbohydrate:**       **650 kcal.**

Provides 60% of energy needs for body at restTAG reserves would enable someone to survive starvation for ~30 days.

## Digestion and Absorption of Lipids

- 98% of ingested lipids are triacylglycerols (TAGs)
- Digestion in the <u>Mouth:</u> enzymes are **aqueous**-little effect on lipids
- Digestion in the <u>Stomach:</u>causes a large *physical* change-

  Churned into droplets:

  **"Chyme"**

# TRIACYLGLYCEROL

$$20:1\Delta 11 \text{ (eicosenoic acid)}$$

$$(sn-1)\quad H_2-C-O$$

$$9$$

$$18:1\Delta 9 \text{ (oleic acid)}$$

$$(sn-2)\quad H-C-O$$

$$13$$

$$22:1\Delta 13 \text{ (erucic acid)}$$

$$(sn-3)\quad H_2-C-O$$

Liver

Bile

Gallbladder

Bile

GASTRIN

Stomach

Acid chyme

CCK

CCK

ENTEROGASTRONE

Pancreatic juices

Pancreas

Duodenum

SECRETIN

+ Stimulation

− Inhibition
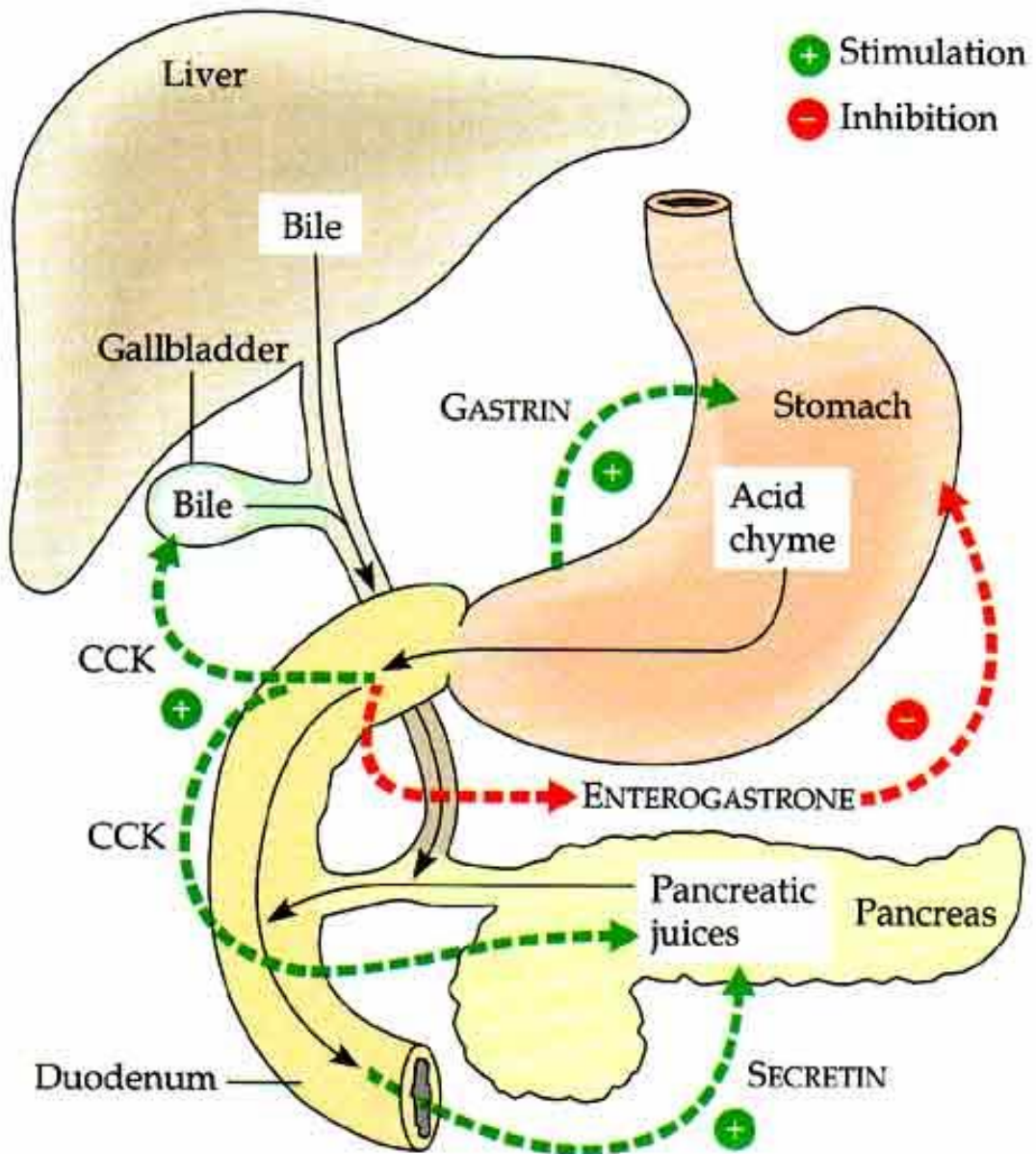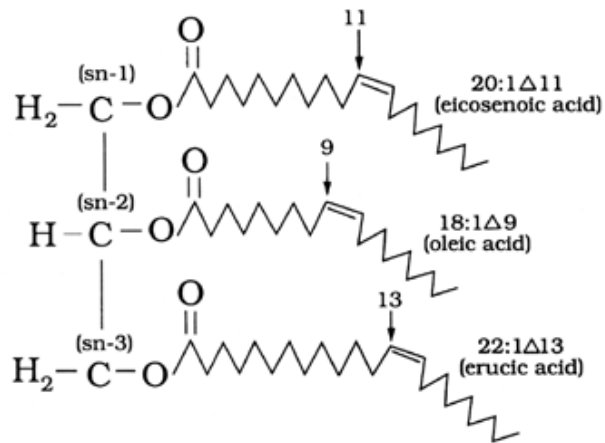
**Gastric Lipase**: Begins actual lipid digestion.~10% of TAGs are hydrolyzed in the **stomach**.Chyme stimulates **cholecystokinin** (CCK) to release **bile** from gallbladder.Bile is an emulsifier
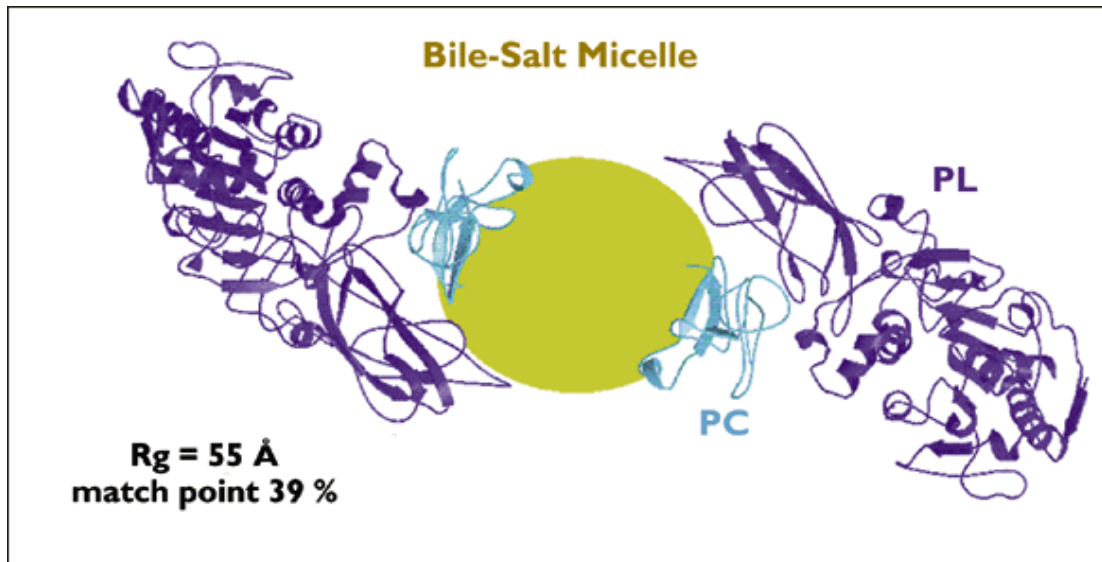


Pancreatic lipase (PL) hydrolyzes insoluble triglyceride by binding to the **bile-salt micelles**TAGs are *partially* hydrolyzed: 2 of the 3 F.A.s have ester linkages hydrolyzed and are released.

**Monoacylglycerol** remains = glycerol and 1 fatty acid
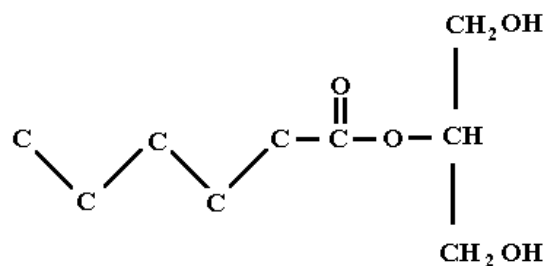


Oil droplets will form spherical **micelle** shapes.Bile salts aid this process clumping fatty acids and monacylglycerols.

hydrophilic, polar head group

hydrophobic, non-polar hydrocarbon chain



Hydrocarbon end orients away from water

Ionic end is soluble in water

Palmitic acid

Oil

Water

(b)

Water

Oil droplet

(c)
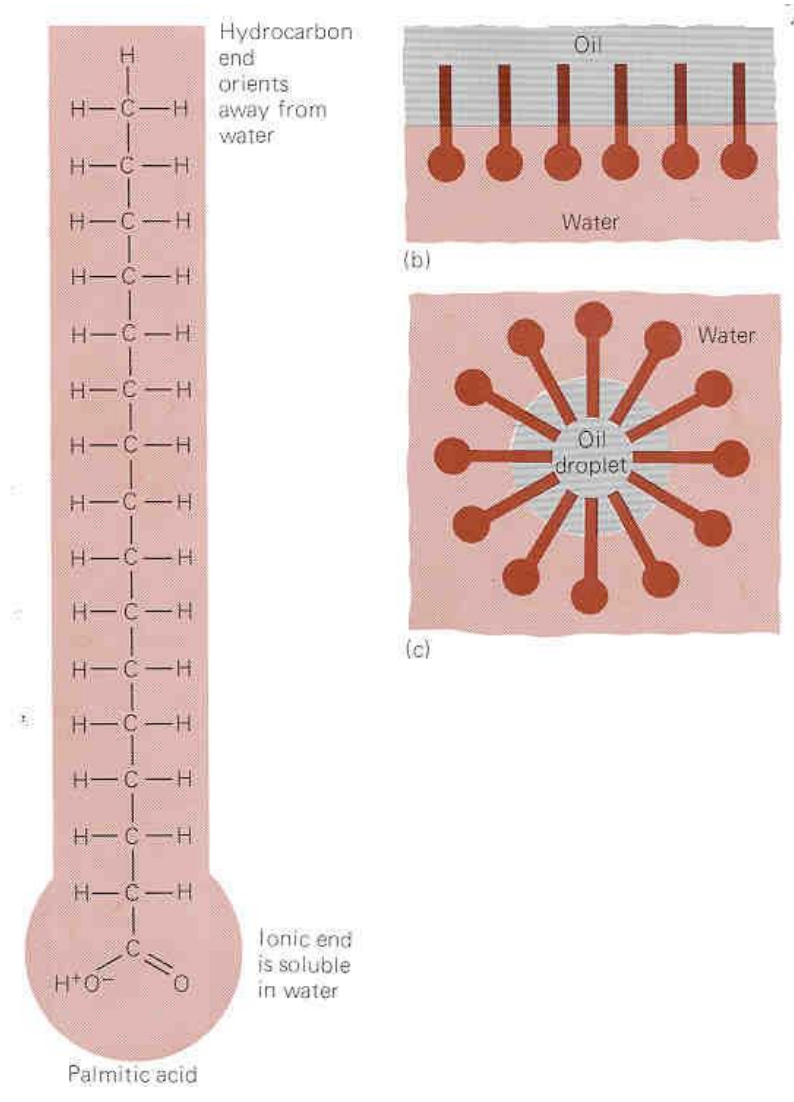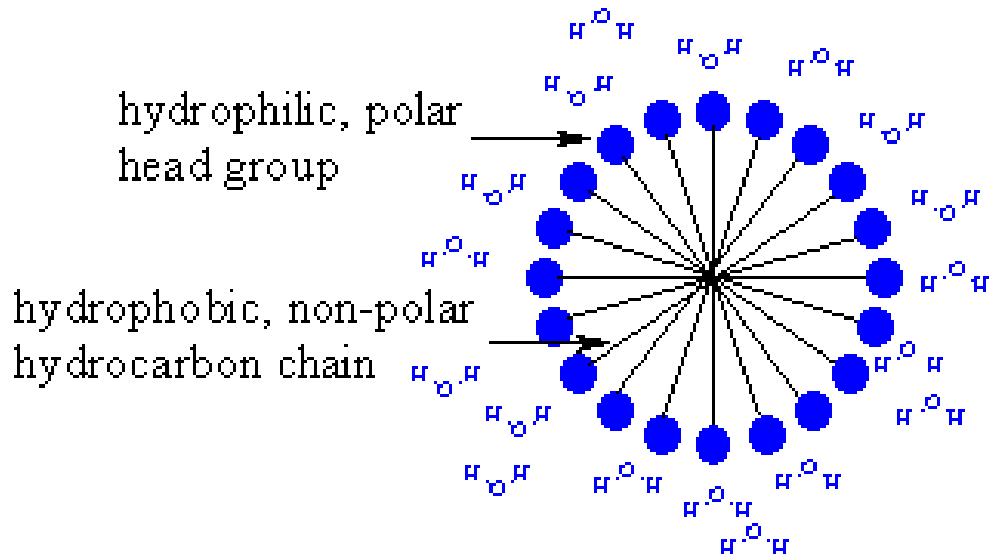
Fatty acid micelle: **hydrophobic** fatty acids & monoacylglycerols
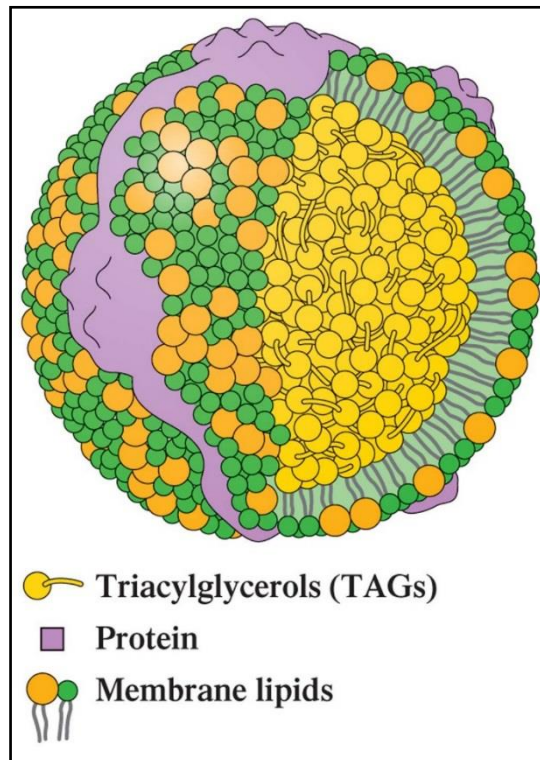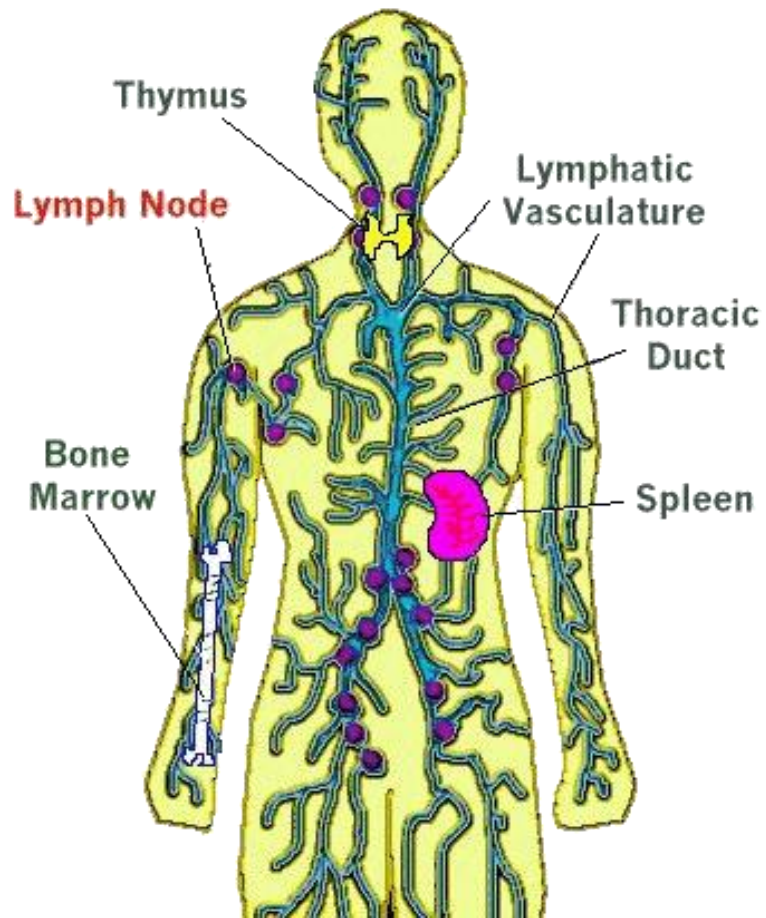
are in the interior. Bile salts on exterior.

Micelles are small enough to penetrate membrane of intestinal cells.
Free fatty acids & monoacylglycerols are reformed into

**triacylglycerols**.
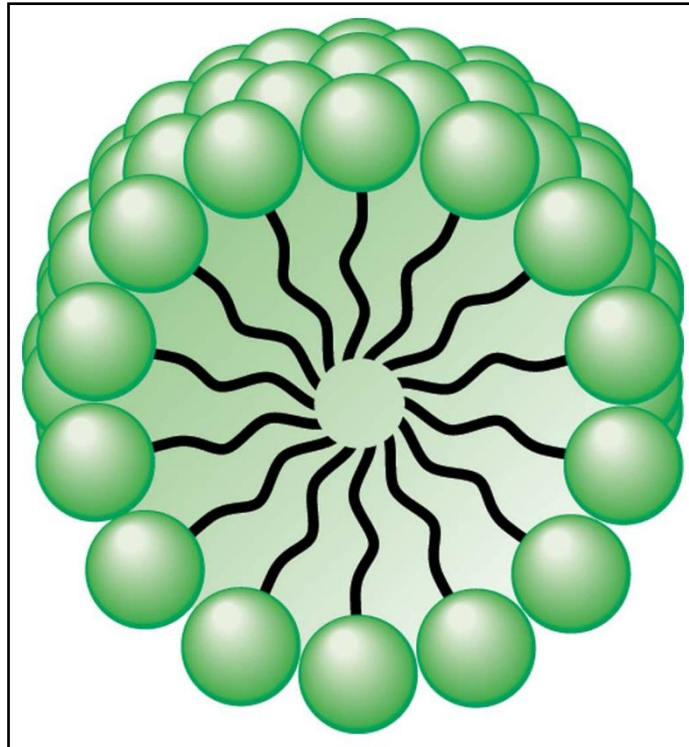


TAGs are combined with membrane & water soluble proteins to form a
**chylomicron**, a lipoprotein.

**Chylomicrons** carry TAGs from intestinal cells into bloodstream
via the **lymph system**.

Thymus

Lymph Node

Lymphatic Vasculature

Thoracic Duct

Bone Marrow

Spleen



🔵 Triacylglycerols (TAGs)

🟪 Protein

🟠🟢 Membrane lipids

Triacylglycerols reach bloodstream & are hydrolyzed down to **glycerol** and **fatty acids**.These are absorbed by cells and processed further for energy by forming **acetyl CoA**. Or Stored as lipids in fat cells (adipose tissue.
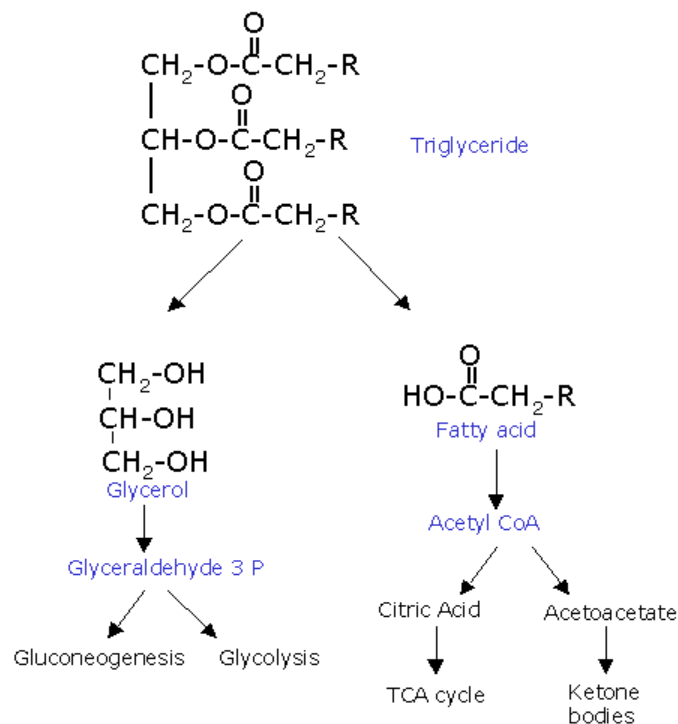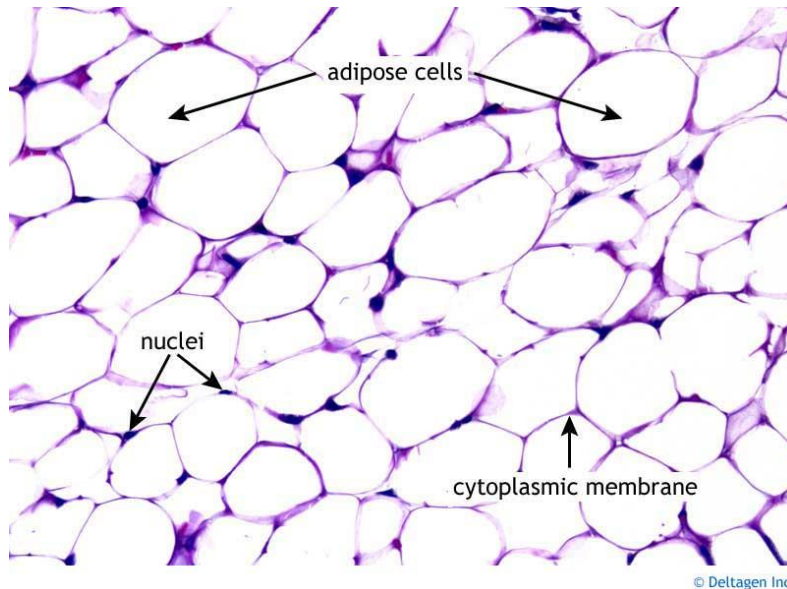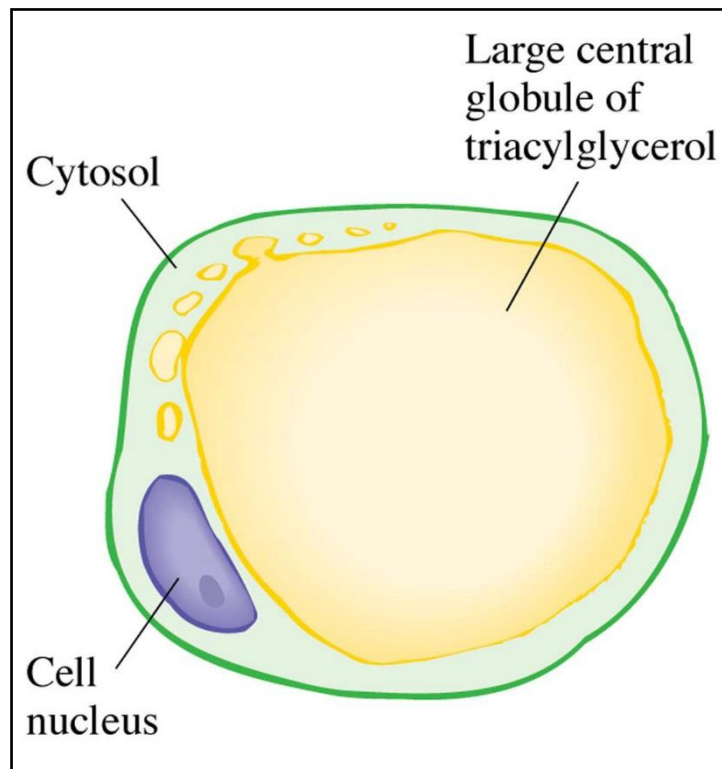




Summary of events that must occur before triacyglycerols (TAGs) can reach the bloodstream through the digestive process.
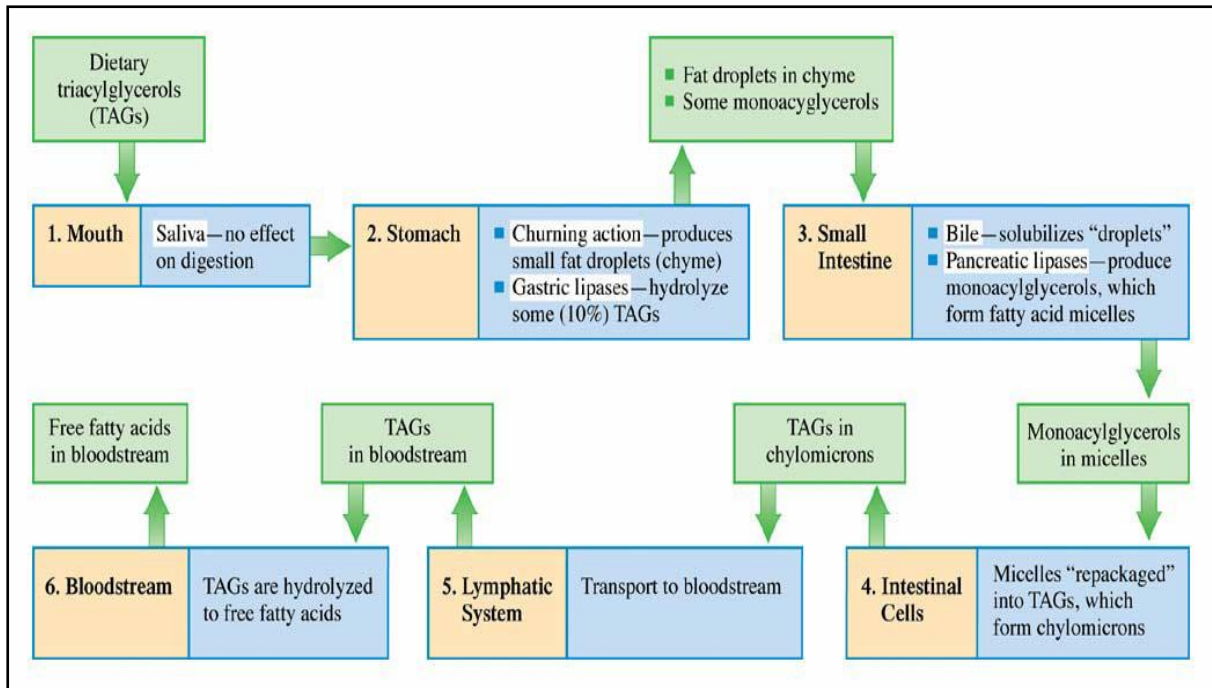
## Triglyceride Storage & Mobilization

**Storage of triacylglycerol** is in **adipocytes** Fatty acids stored primarily as triacylglycerol.Triacylglycerol is **hydrolyzed** to release **fatty acids** when needed.

## Hormonal control of lipolysis

The breakdown of triglycerides by lipases is under hormonal control.

## Hormones involved are:

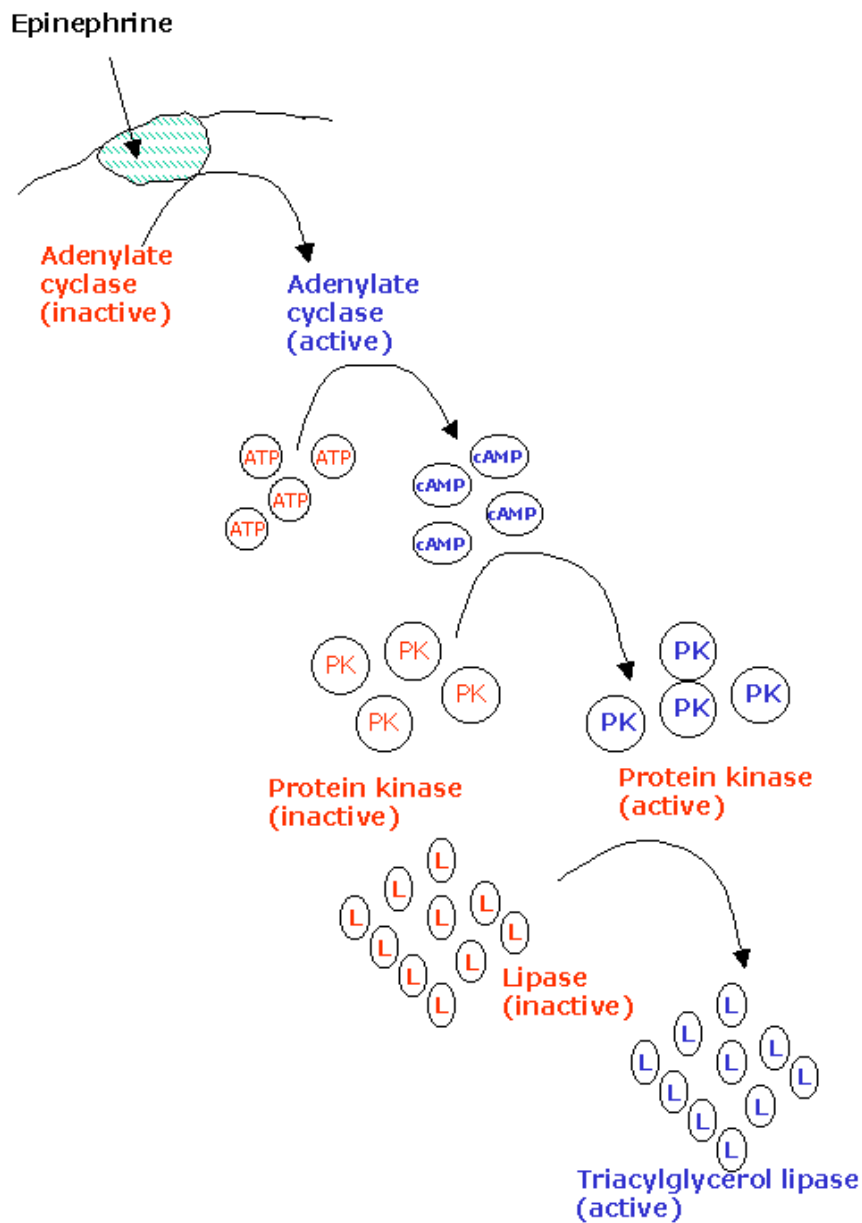Epinephrine, glucagon, and insulin.

**Epinephrine & glucagon**:

promote breakdown of fat (lipolysis)

**Insulin**:

inhibits lipolysis.

## Triacylglycerol Mobilization:

Hydrolyzing lipid reserves in adipose tissue for **energy**.Triggered by hormones~10% TAGs replaced in adipose tissue daily as they get used up for energy.

Hydrolysis of stored triacylglycerols in adipose tissue is triggered by hormones that stimulate cAMP production within adipose cells.
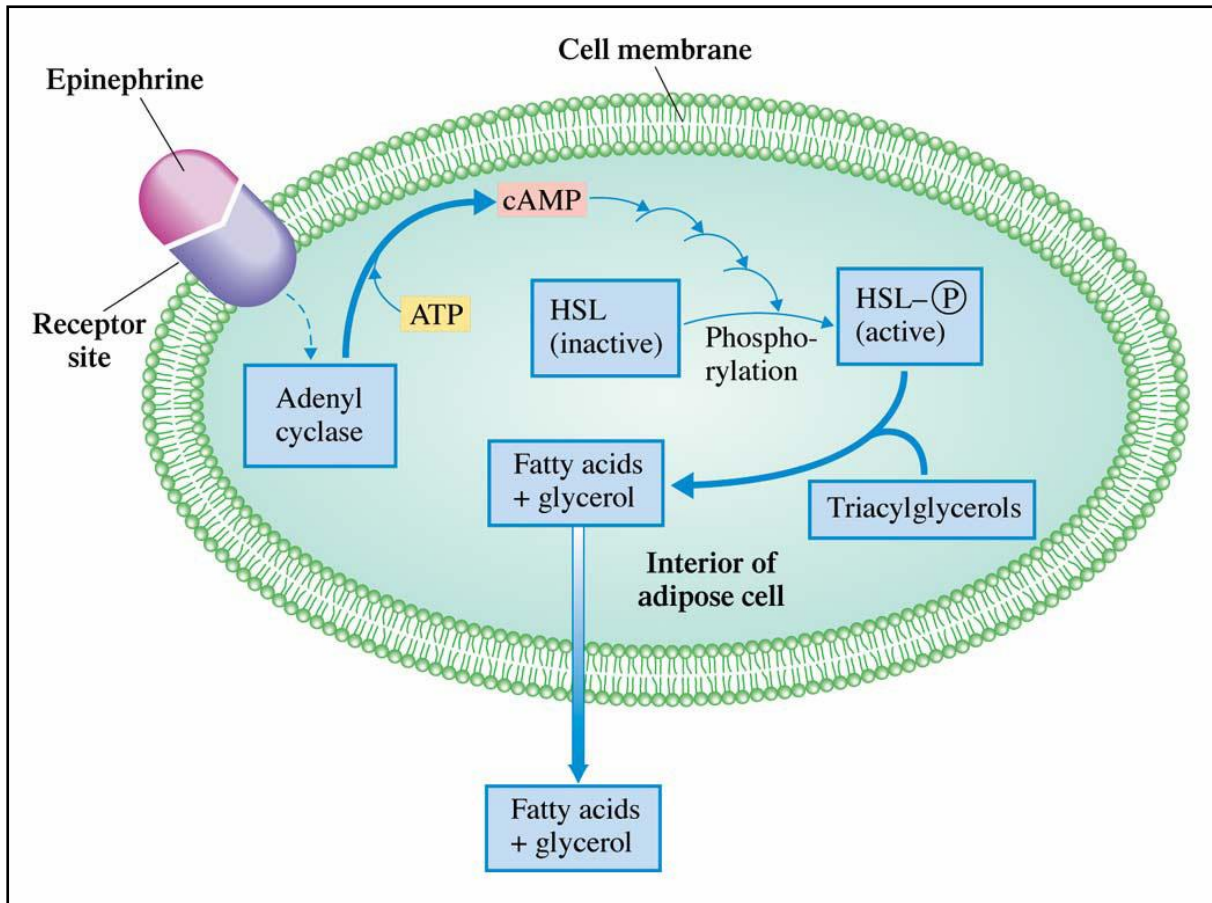
Third time is a charm! TAGs hydrolyzed a $3^{rd}$ time to form fatty acids.

**Tri**acylglycerol lipase **Di**acyclglycerol lipase **Mono**acylglycerol lipase

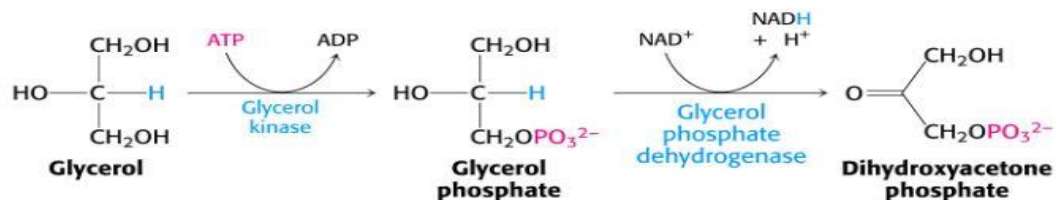Only triacylglycerol lipase is activated by epinephrine.
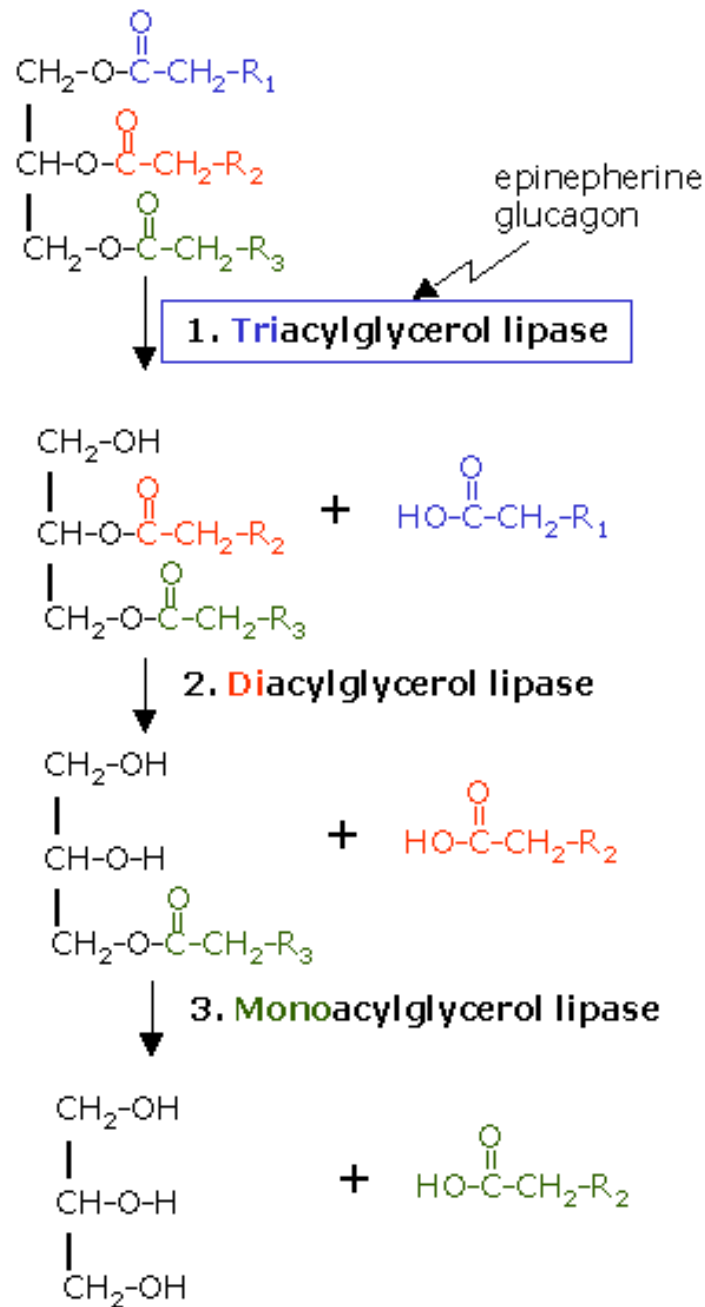
One glycerol formed for each TAG hydrolyzed. Enter bloodstream & go to liver or kidneys for processing. Converted in 2 steps to

**Dihydroxyacetone phosphate**

glycerol
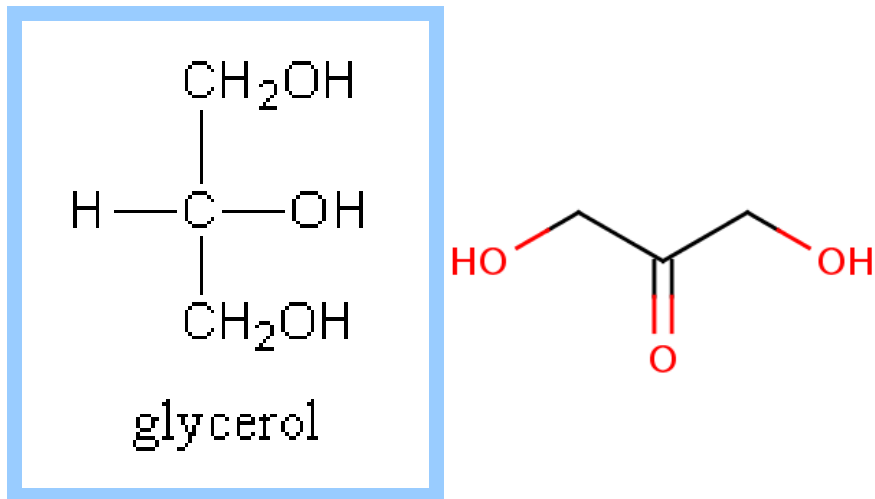
Where will the phosphate be attached?

Uses up one ATP. Reduces one $NAD^+$ to NADH



Primary hydroxyl group is phosphorylated
**Dihydroxyacetone phosphate**
is an intermediate for both

**Glycolysis**:
converted to Pyruvate, then to Acetyl CoA, & eventually to $CO_2$,

releasing its energy.

**Gluconeogenesis**:

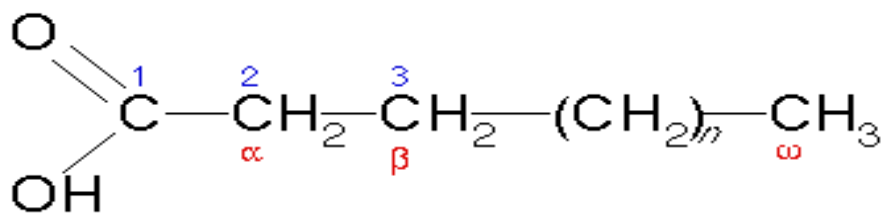creates Glucose from **non-carbohydrate** source

Lipid metabolism & carbohydrate metabolism

are connected.

Fatty acids can also be broken down for energy. What kind of reaction is needed?

**Oxidation**!

Quick review first on fatty acid numbers & letters:



Fatty acid numbering system

## Review Important fatty acids:

| Name | # Carbons: (saturation) |
|---|---|
| Palmitate | 16:0 |
| Stearate | 18:0 |
| Palmitoleate | 16:1 - cis at C9 |
| Oleate | 18:1 - cis at C9 |
| Linoleate | 18:2 - cis at C9 and C12 |
| Linolenate | 18:3 - cis at C9, C12 & C15 |

# Lipid Metabolism

Lipid nomenclature

•Oxidation of Fatty acids

•β-oxidation

•Ketone Bodies

## Lipid nomenclature

Fatty acids

•triacylglycerols: know structure

•phospholipids

•waxes

•sphingolipids

•Glycosphingolipids

•Isoprenoids

•Steriods

•Nomenclature

•saturated: palmitate, stearate, no double bonds

•unsaturated: palmitoleate, Oleate: double bond at cis9 position

•polyunsaturated

•Melting points: saturated vsunsaturated

## Oxidation of Fatty acids

•Know equation for palmitate: $C_{16}H_{32}O + O_2 ---> CO_2 + H_2O$

•Comparison of glucose with palmitatefor ATP production and energy yield

•Mobilization of Triacylglycerols from adipose tissue

–hormonal control: glucagon, epinephrine

–lipases

–transport by lipoproteins

–fate of glycerol

•transport into cytoplasm of cell


# Digestion of lipid in diet

•Triacylglycerolsfrom diet
•broken down in small intestine
•lipases
•bile salts
•transport to adipose tissue



**Triacylglyceride** → **Diacylglyceride** → **Monoacylglycerol**
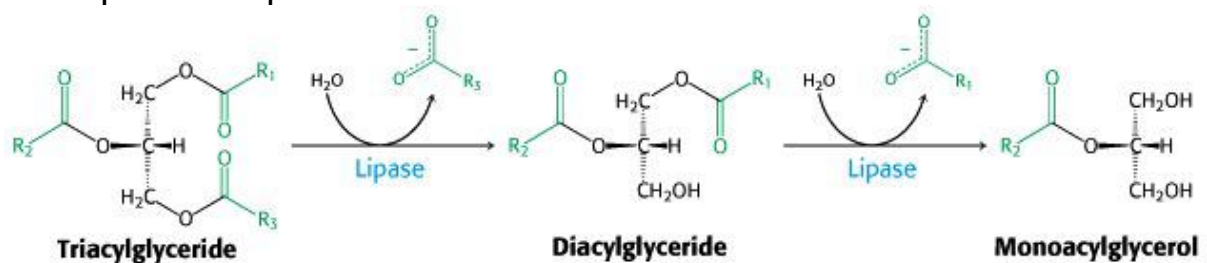
## Mobilization of Triacylglycerols

–hormonal control of lipolysis: glucagon, epinephrine
–lipases
–transport by lipoproteins
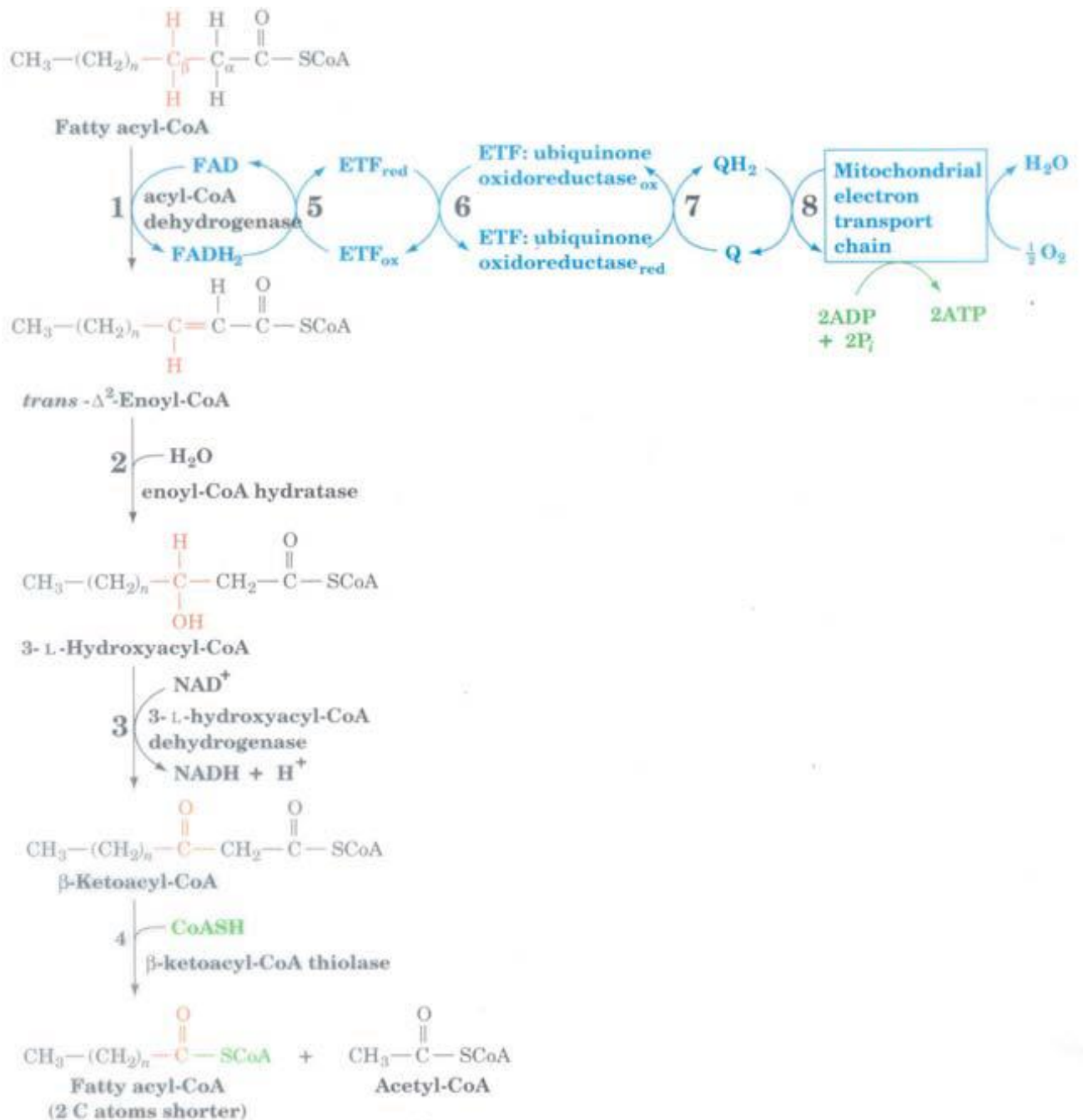–transport into cytoplasm of cell
–Insulin inhibits lipolysis

## Breakdown of triacylglycerides
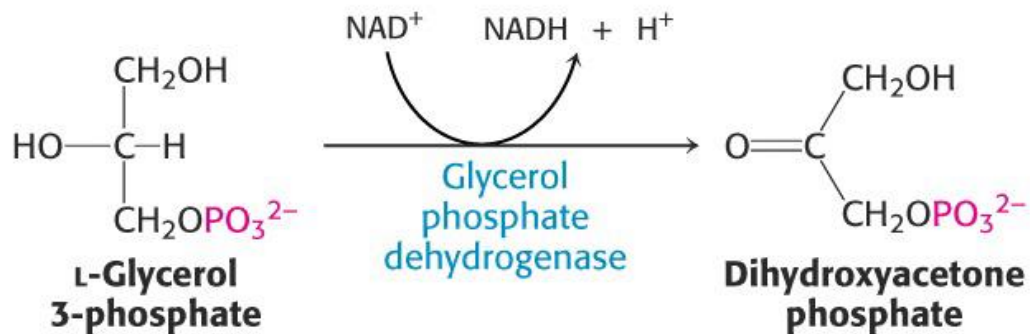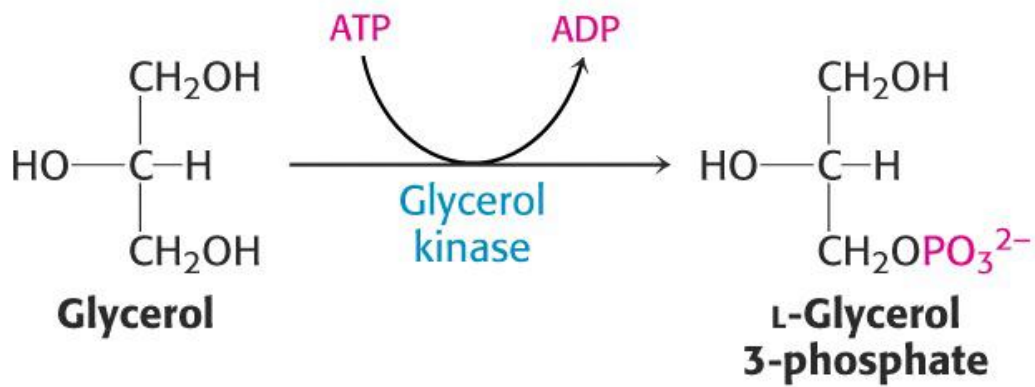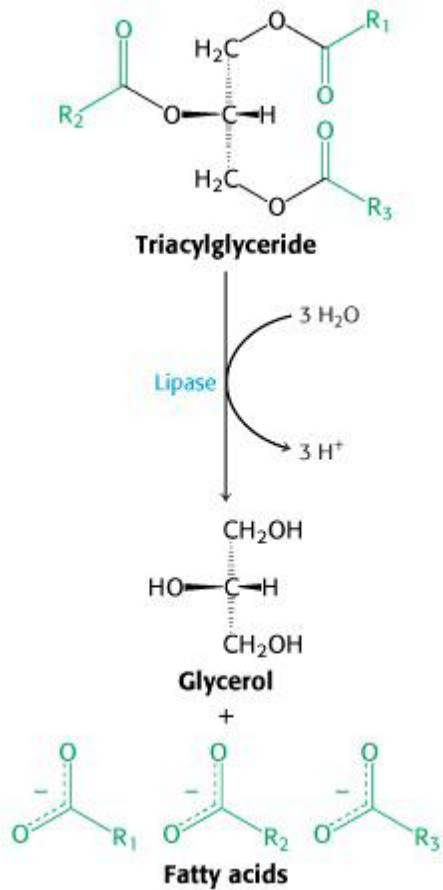
**fate of glycerol**

## β-oxidation
- occurs in mitochondria
- uses FAD and NAD
- produces acetyl CoA

$$CH_3-(CH_2)_n-\underset{H}{\overset{H}{C_\beta}}-\underset{H}{\overset{H}{C_\alpha}}-\overset{O}{\overset{||}{C}}-SCoA$$

**Fatty acyl-CoA**

**1** acyl-CoA dehydrogenase : FAD → FADH$_2$

**5** ETF$_{red}$ / ETF$_{ox}$

**6** ETF: ubiquinone oxidoreductase$_{ox}$ / ETF: ubiquinone oxidoreductase$_{red}$

**7** QH$_2$ / Q

**8** Mitochondrial electron transport chain : H$_2$O, $\frac{1}{2}$O$_2$, 2ADP + 2P$_i$ → 2ATP

$$CH_3-(CH_2)_n-\underset{H}{C}=C-\overset{O}{\overset{||}{C}}-SCoA$$

*trans* -$\Delta^2$-Enoyl-CoA

**2** — H$_2$O
enoyl-CoA hydratase

$$CH_3-(CH_2)_n-\underset{OH}{\overset{H}{C}}-CH_2-\overset{O}{\overset{||}{C}}-SCoA$$

3- L -Hydroxyacyl-CoA

**3** NAD$^+$
3- L -hydroxyacyl-CoA dehydrogenase
NADH + H$^+$

$$CH_3-(CH_2)_n-\overset{O}{\overset{||}{C}}-CH_2-\overset{O}{\overset{||}{C}}-SCoA$$

β-Ketoacyl-CoA

**4** — CoASH
β-ketoacyl-CoA thiolase

$$CH_3-(CH_2)_n-\overset{O}{\overset{||}{C}}-SCoA \quad + \quad CH_3-\overset{O}{\overset{||}{C}}-SCoA$$

**Fatty acyl-CoA** (2 C atoms shorter)     **Acetyl-CoA**

## acylCoA synthetase

•two step reaction
•ATP + FA ---> AMP-FA
•AMP-FA + CoASH------> FA-CoA + AMP
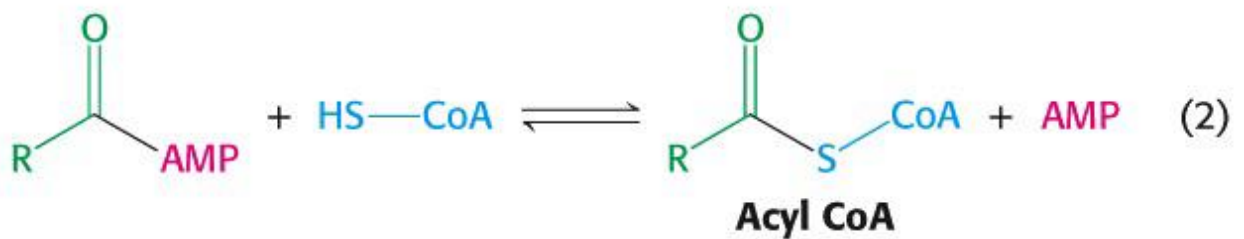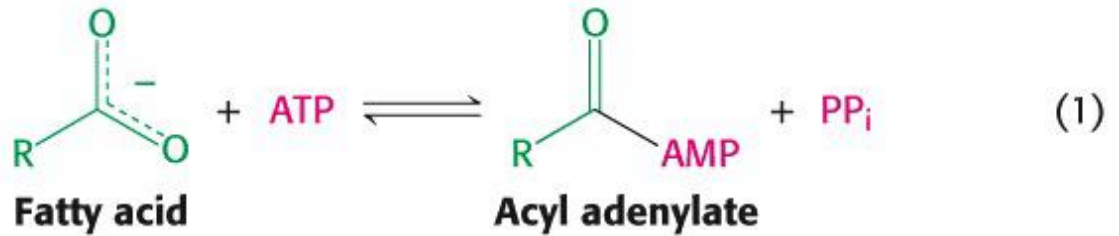


## β-oxidation

AcylCoA dehydrogenase
•enoyl-CoA hydratase
•L-hydroxyacyldehydrogenase
•ketoacyl-CoA thiolase
•Repeat steps
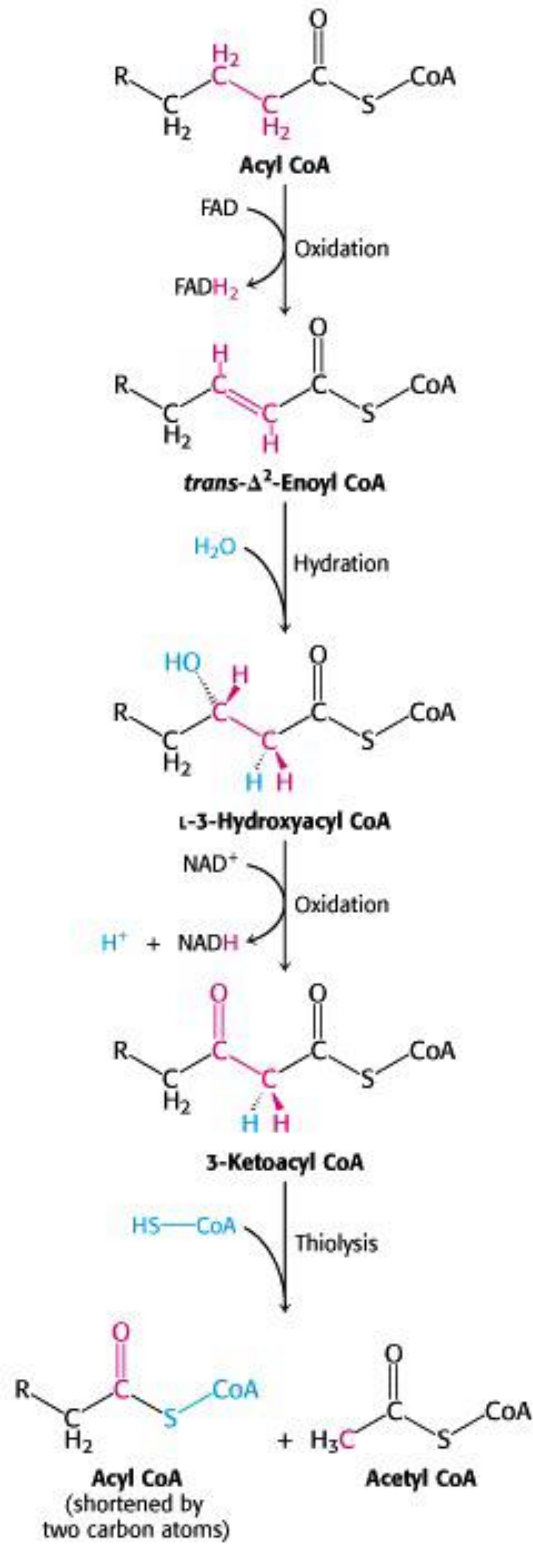
**Summary of Reactions**

**TABLE 22.1 Principal reactions in fatty acid oxidation**

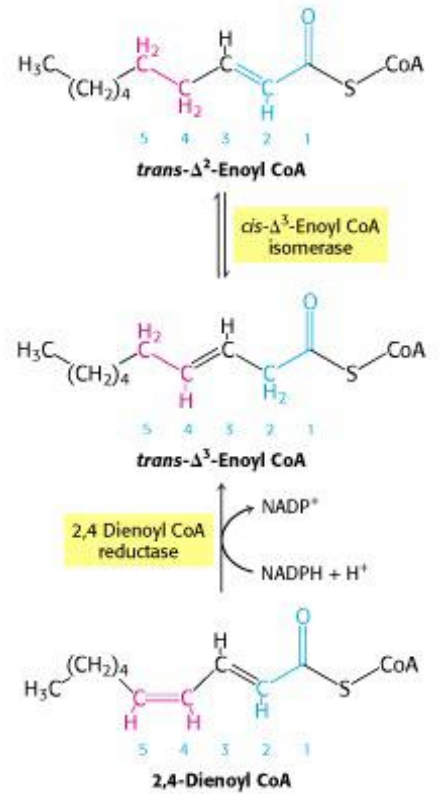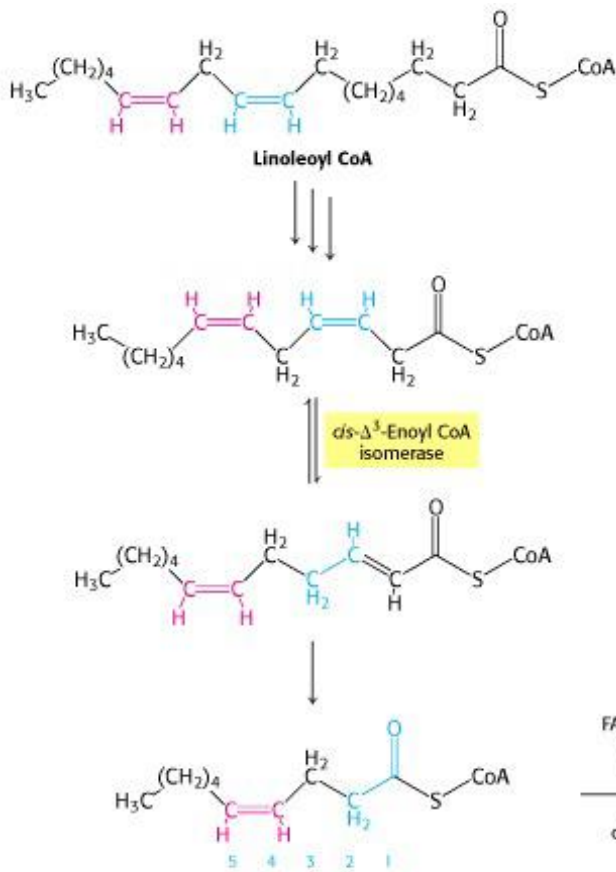| Step | Reaction | Enzyme |
|---|---|---|
| 1 | Fatty acid + CoA + ATP $\rightleftharpoons$ acyl CoA + AMP + PP$_i$ | Acyl CoA synthetase [also called fatty acid thiokinase and fatty acid:CoA ligase (AMP)] |
| 2 | Carnitine + acyl CoA $\rightleftharpoons$ acyl carnitine + CoA | Carnitine acyltransferase (also called carnitine palmitoyl transferase) |
| 3 | Acyl CoA + E-FAD $\longrightarrow$ trans-$\Delta^2$-enoyl CoA + E-FADH$_2$ | Acyl CoA dehydrogenases (several isozymes having different chain-length specificity) |
| 4 | trans-$\Delta^2$-Enoyl CoA + H$_2$O $\rightleftharpoons$ L-3-hydroxyacyl CoA | Enoyl CoA hydratase (also called crotonase or 3-hydroxyacyl CoA hydrolyase) |
| 5 | L-3-Hydroxyacyl CoA + NAD$^+$ $\rightleftharpoons$ 3-ketoacyl CoA + NADH + H$^+$ | L-3-Hydroxyacyl CoA dehydrogenase |
| 6 | 3-Ketoacyl CoA + CoA $\rightleftharpoons$ acetyl CoA + acyl CoA (shortened by C$_2$) | β-Ketothiolase (also called thiolase) |

## Energy production

• NADH and FADH from B-oxidation

• TCA cycle from acetyl CoA
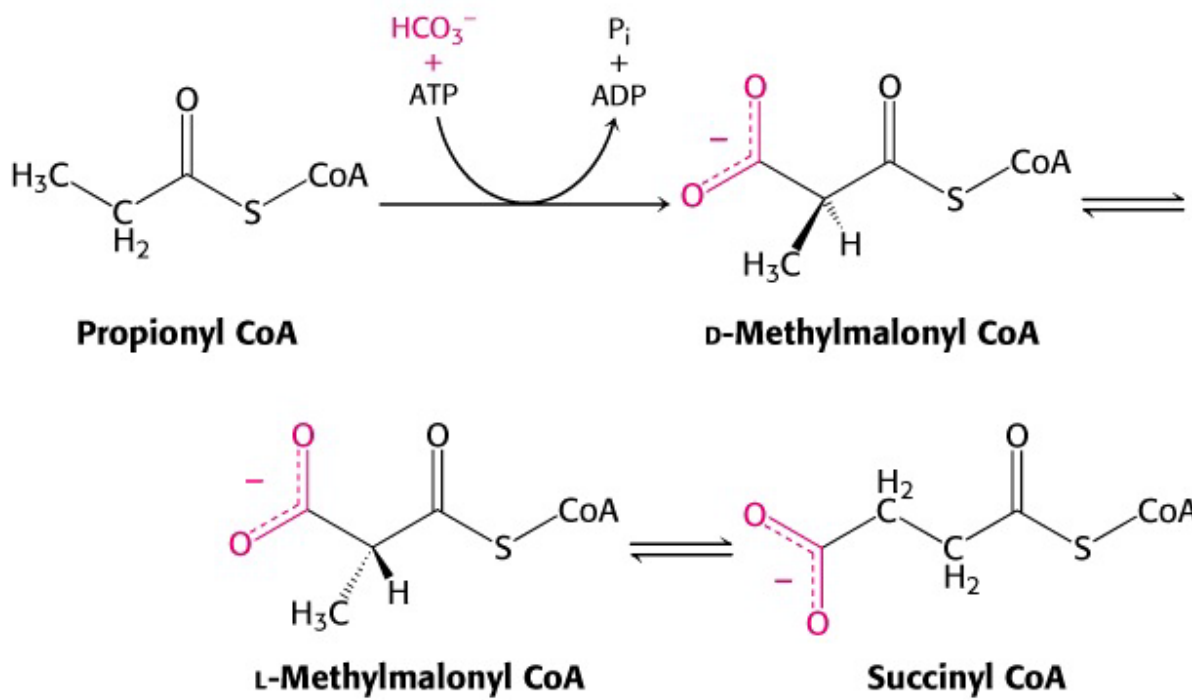
• Total net yield is minus 2 ATP from activation

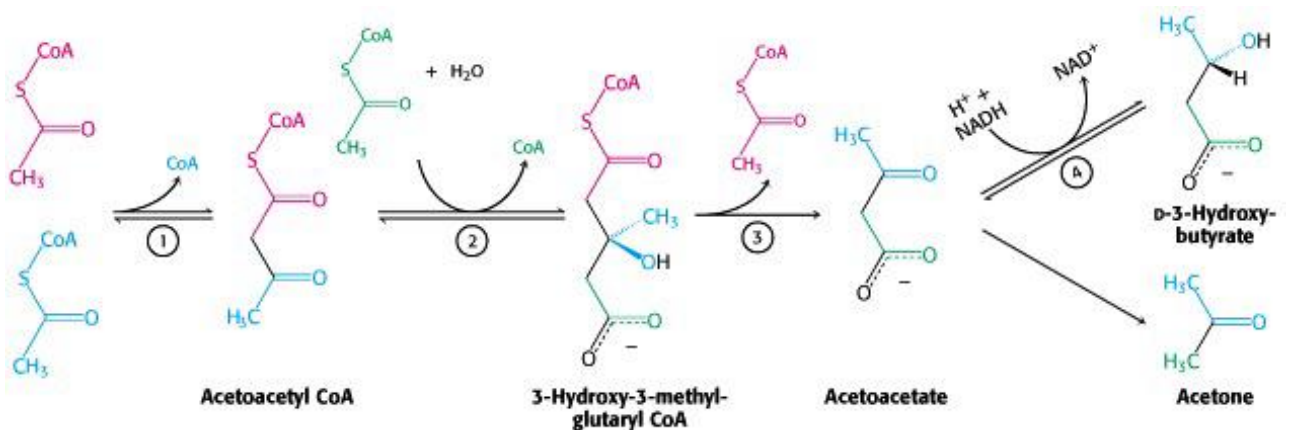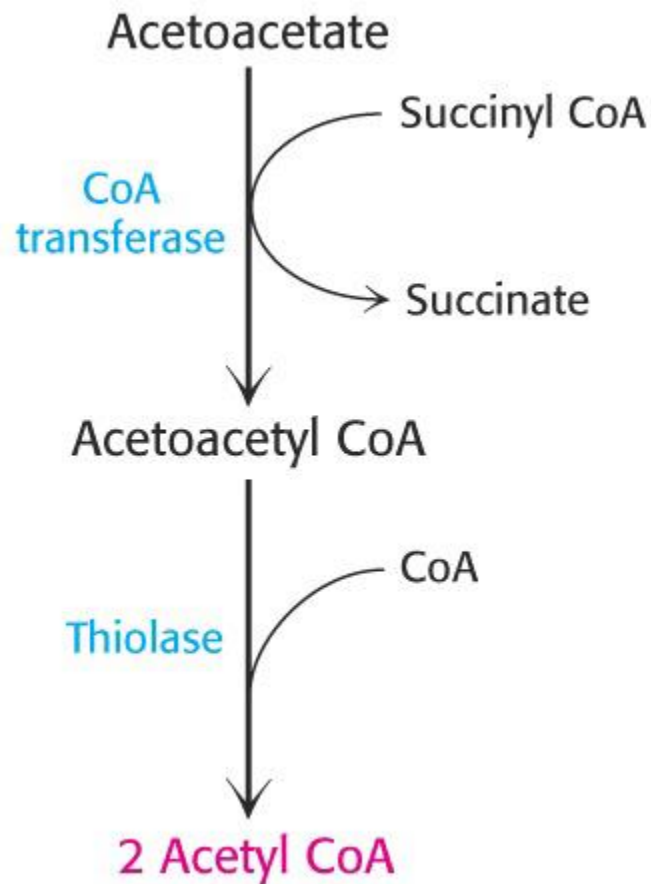## Oxidation of Unsaturated Fatty acids

Palmitoyl CoA

cis-$\Delta^3$-Enoyl CoA

cis-$\Delta^3$-Enoyl CoA isomerase

trans-$\Delta^2$-Enoyl CoA
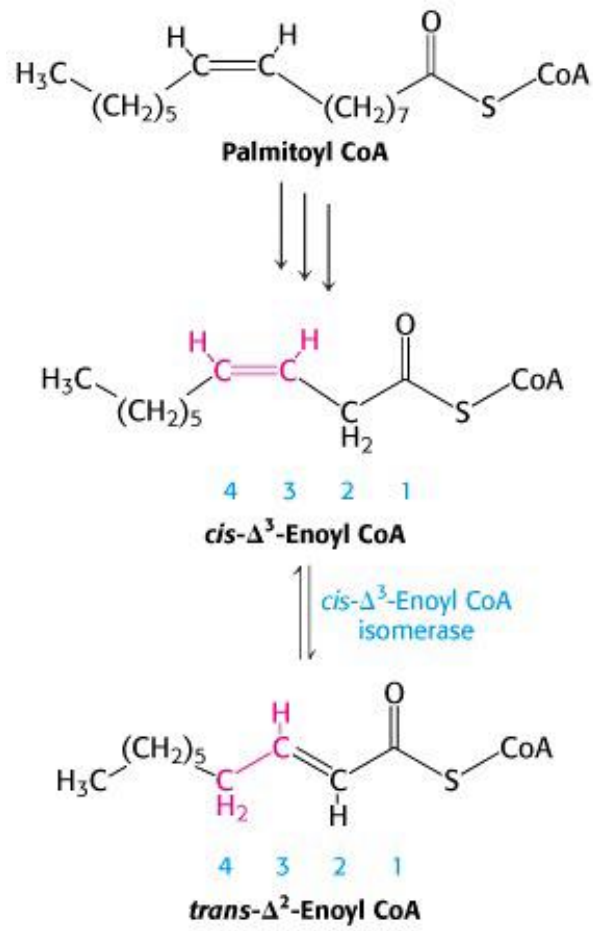
**Unsaturated Fatty acids**

Oxidation of odd chain fatty acids

**Propionyl CoA** → **D-Methylmalonyl CoA**

**L-Methylmalonyl CoA** ⇌ **Succinyl CoA**

- form propionylCoA
- produce succinylCoA

## Ketone Bodies



**Acetoacetyl CoA**     **3-Hydroxy-3-methyl-glutaryl CoA**     **Acetoacetate**     **D-3-Hydroxy-butyrate**     **Acetone**

Acetoacetate
→ (CoA transferase; Succinyl CoA → Succinate) → Acetoacetyl CoA
→ (Thiolase; CoA) → 2 Acetyl CoA

- Acetoacetate

- Acetone

- B-hyroxybutyrate

- HMG CoA synthase

**Referances**

Available online
**1-BIOCHEMISTRY IN PERSPECTIVE**

2-METABOLISM OF CARBOHYDRATES, LIPIDS,

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