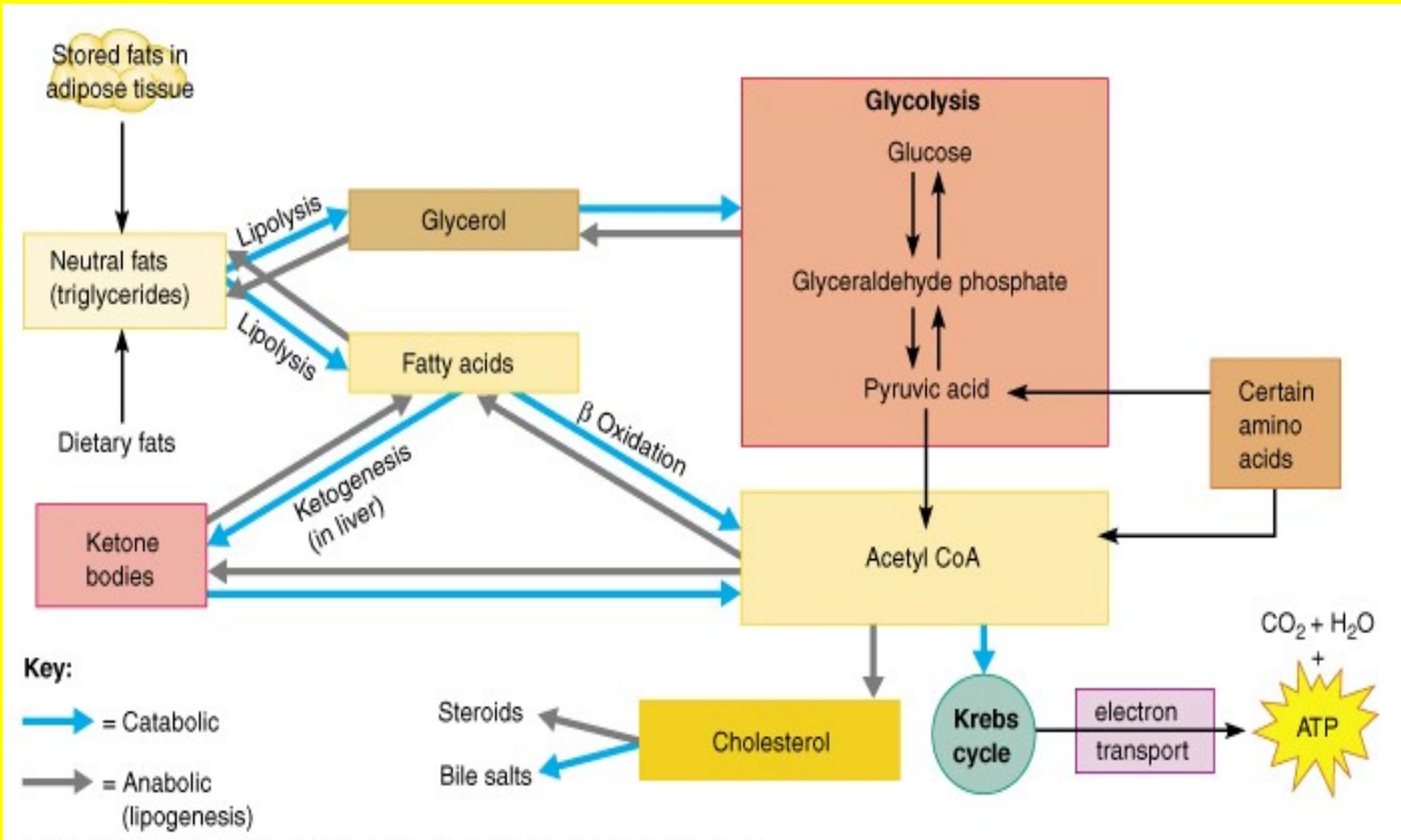


LIPID METABOLISM



- Most Animal Cells Derive Their Energy from Fatty Acids Between Meals

Most energy after meal is derived from sugars (food);

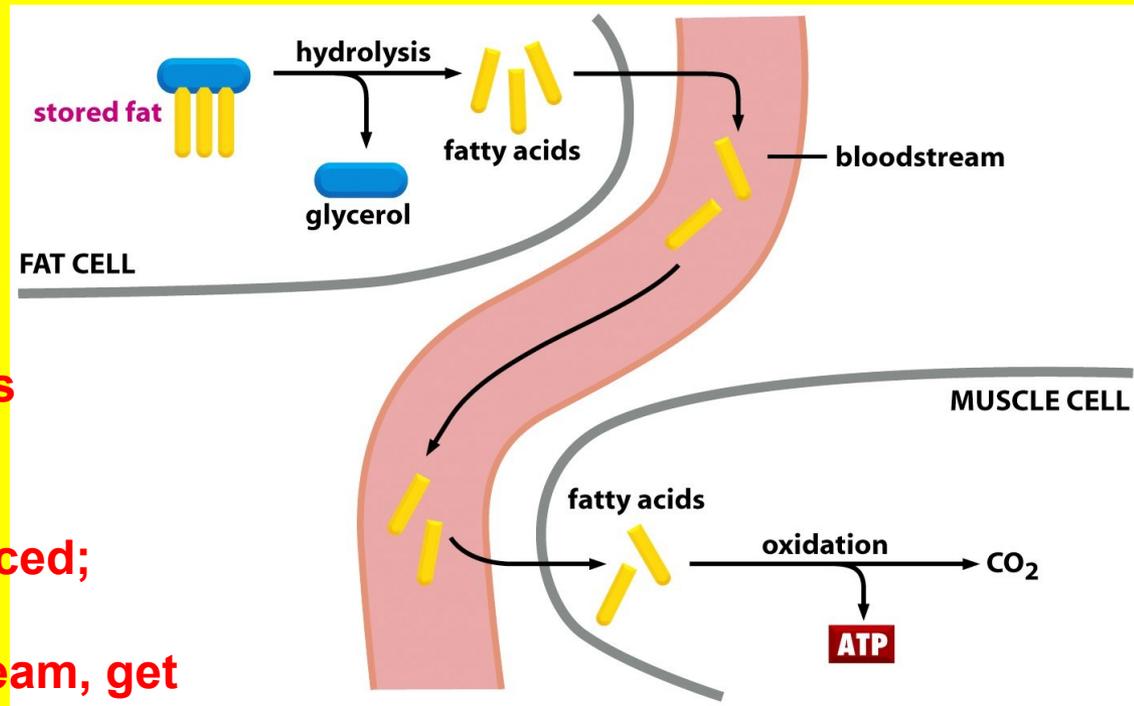
Excess sugar – to replenish glycogen or make fats

By morning no sugars left:

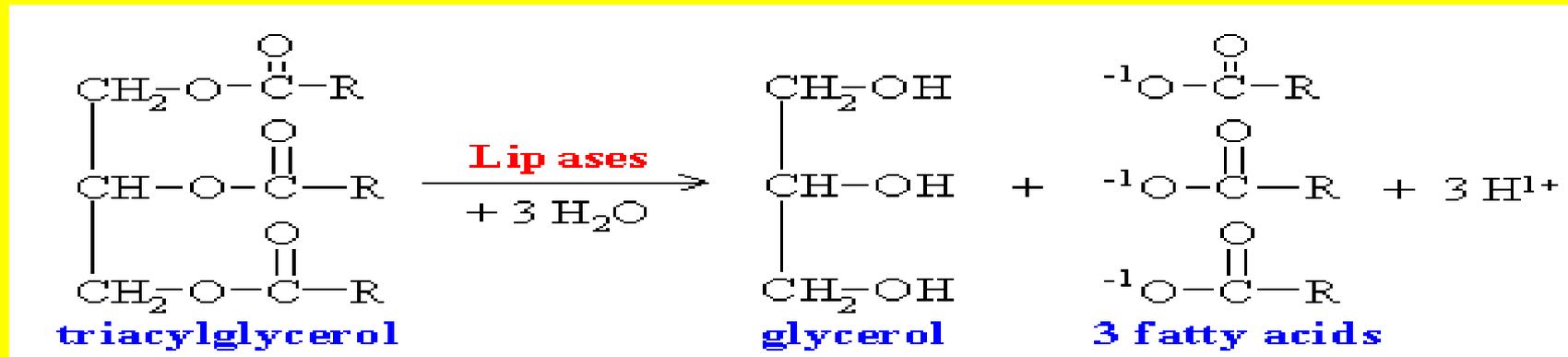
- triggers the breakdown of fats for energy production;

-fatty acids and glycerol produced;

-fatty acids go to the blood stream, get oxidized and ATP is produced



- The majority of fatty acids are stored as triacylglycerols in fat cells (~16% of body weight is triacylglycerols).
- A variety of different hormones (including epinephrine, norepinephrine, glucagon, adrenalcorticotrophic hormone) bind to membrane receptors of fat cells.
- The hormones initiate cAMP-mediated stimulation of a specific kinases.
- The kinases phosphorylates lipases activating them for the breakdown of lipids.



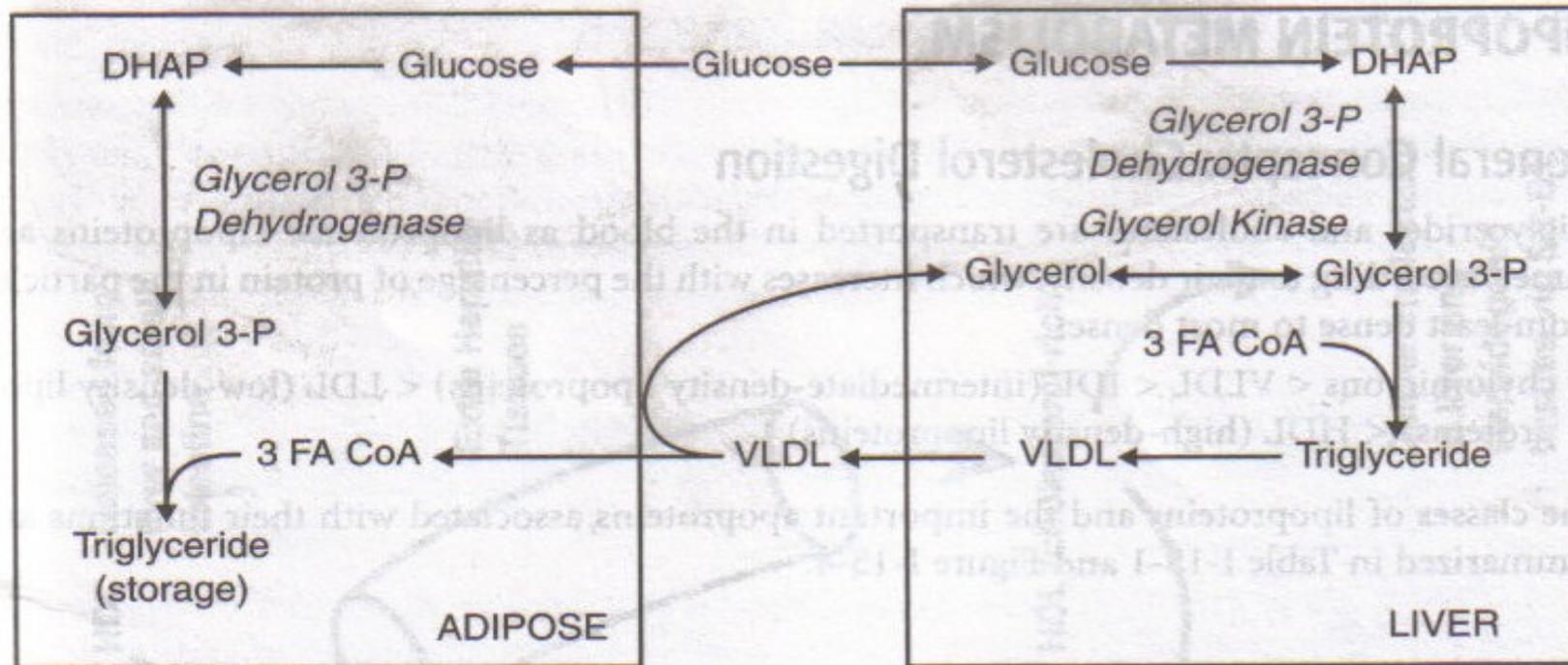
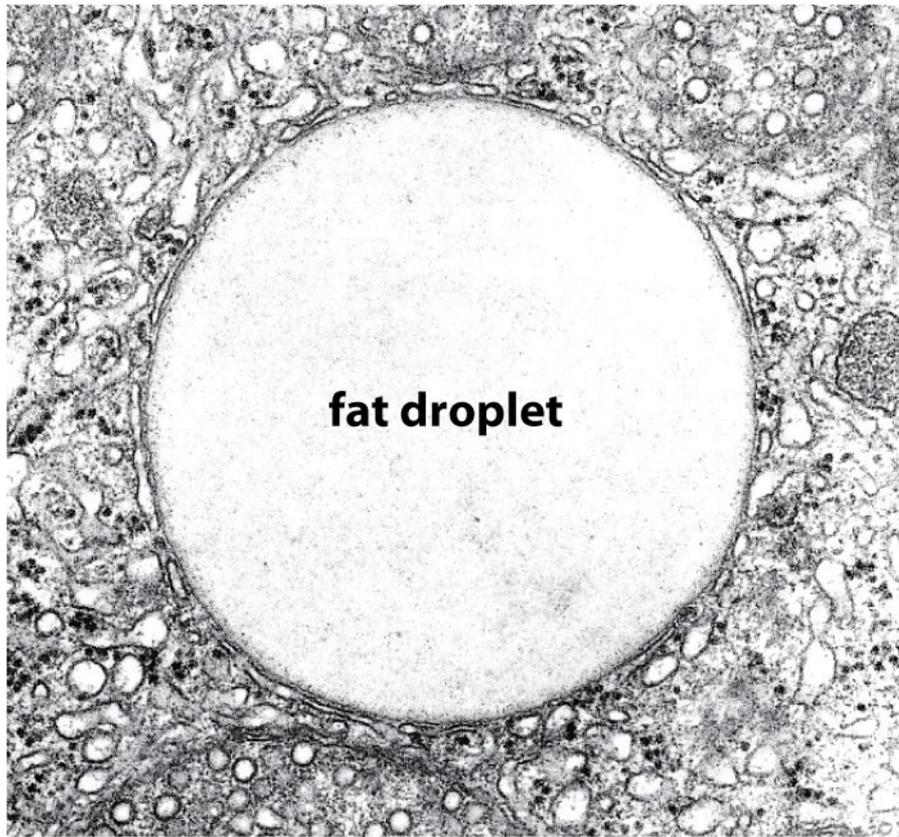


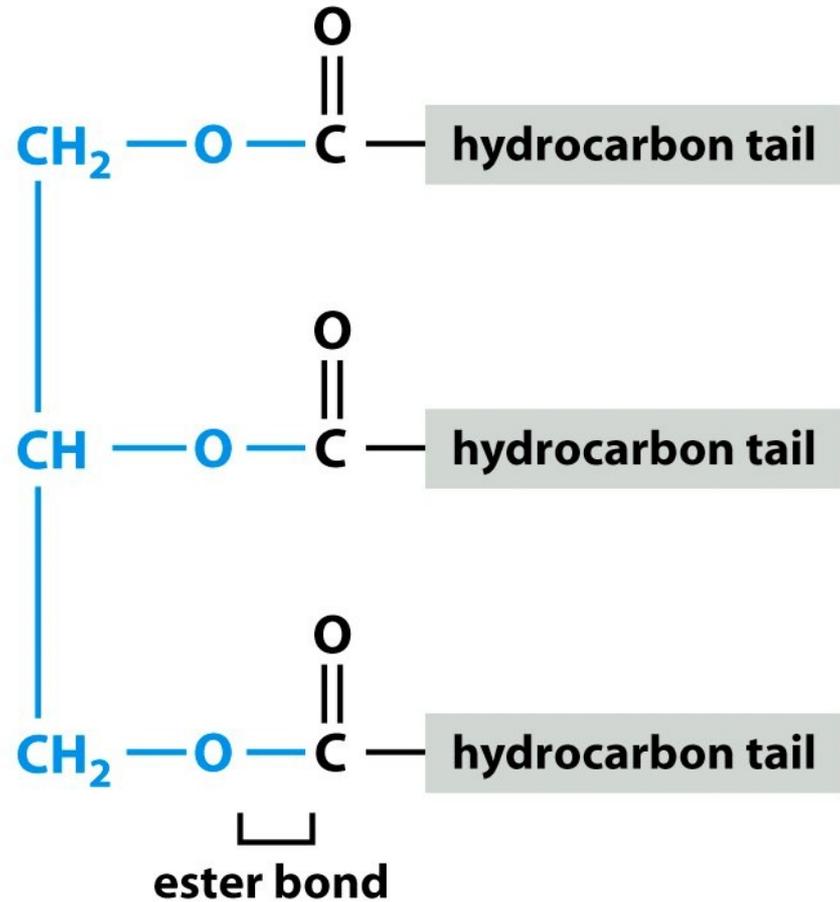
Figure I-15-2. Glycerol 3-P Dehydrogenase and Glycerol Kinase in Triglyceride Synthesis and Storage

- **Now when we want to release fatty acids from triacylglycerols for our use**
- The initial event in the mobilization and utilization of stored fat as an energy source is the release of free fatty acids and glycerol **by hydrolysis of triacylglycerols by lipases**, an event referred to as lipolysis or **the breakdown of fats** .
- **Two metabolic pathways are components of lipolysis. These are.....**
- **A) Release of fatty acids from triacylglycerols, and**
- **B) Beta oxidation (discussed elsewhere)**

Release of fatty acids from triacylglycerols to form glycerol (used in glycolysis) **and fatty acids** (used in generating acetyl CoA)

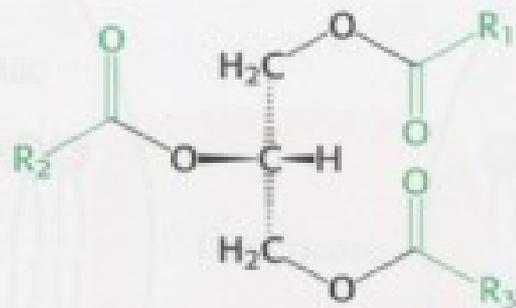


1 μm

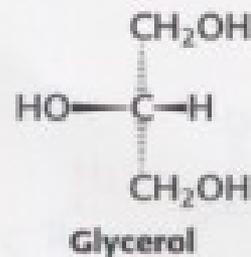
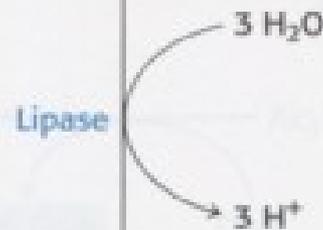


- The process of releasing fatty acids from triacylglycerols is initiated by a **hormone-sensitive triacylglycerol lipase**, that removes a fatty acid from either carbon 1 or carbon 3 of the triacylglycerol.
- This hormone-sensitive lipase is a **controlled enzyme (it is a cyclic AMP-regulated lipase)**.

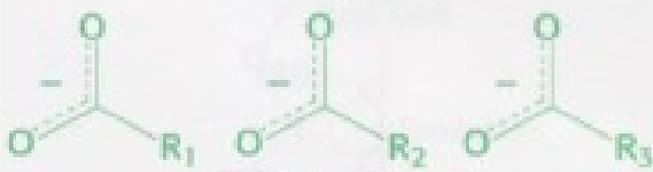
- This discussion shows how both the hormones **epinephrine** or **glucagon** can fine tune the activity or stimulate the activity of the **hormone-sensitive triacylglycerol lipase**, that removes a fatty acid from either carbon 1 or carbon 3 of the triacylglycerol.
- **After the hormone-sensitive triacylglycerol lipase has begun the process, additional lipases specific for monoacylglycerol or diacylglycerol remove the remaining fatty acids.**



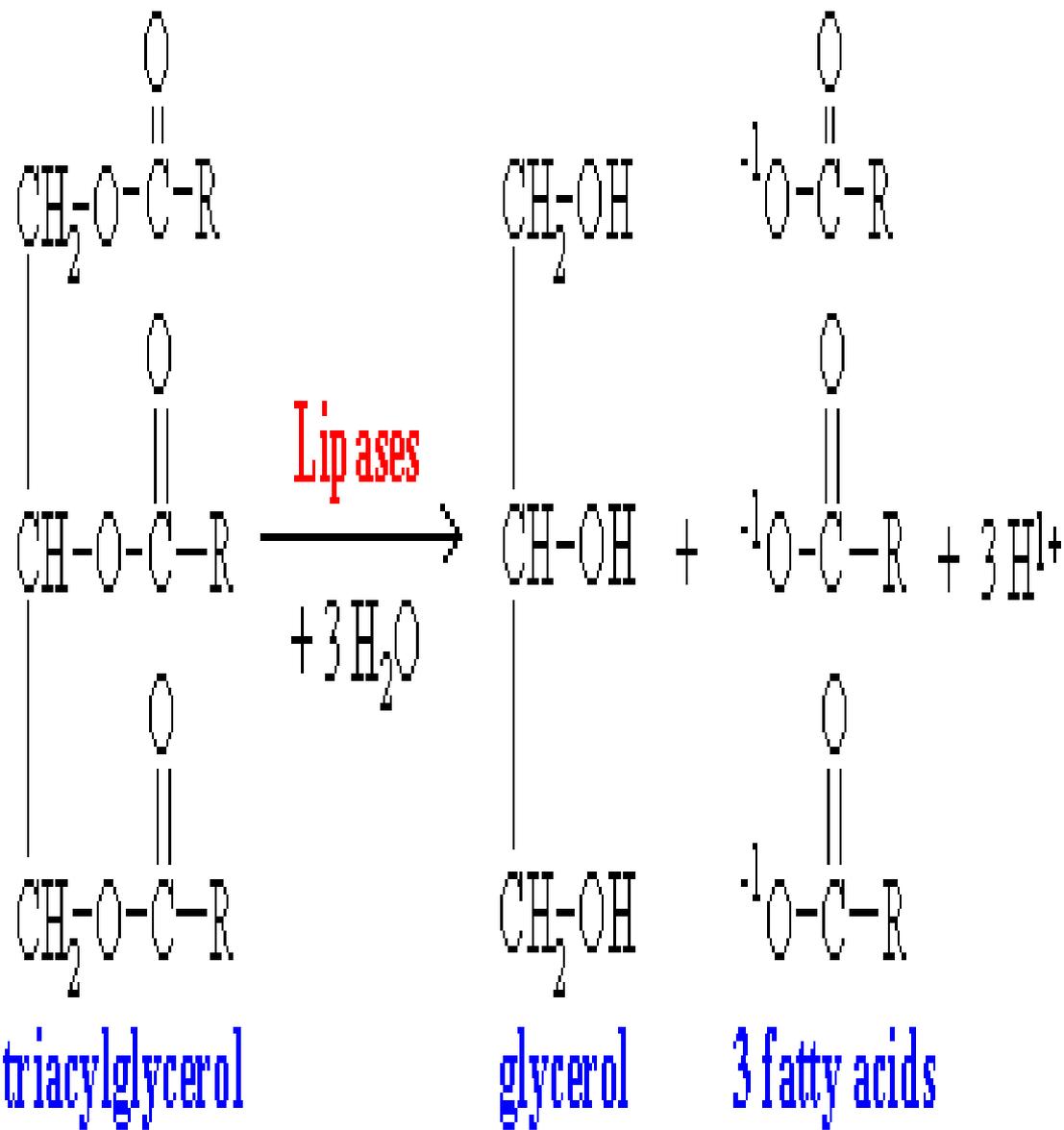
Triacylglyceride

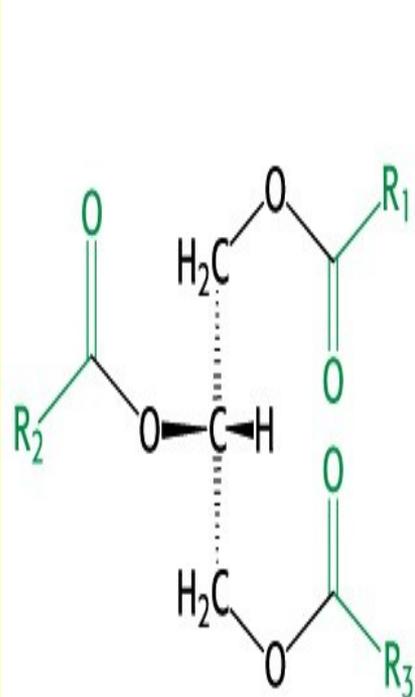


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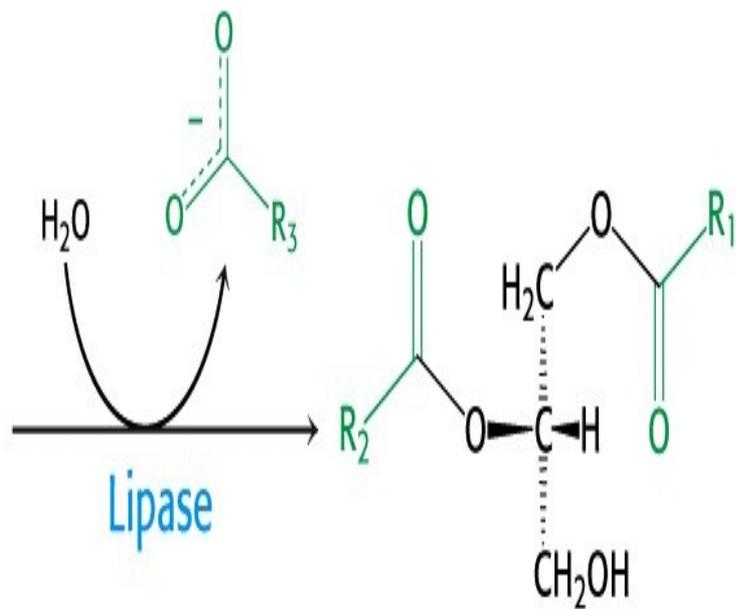


Fatty acids

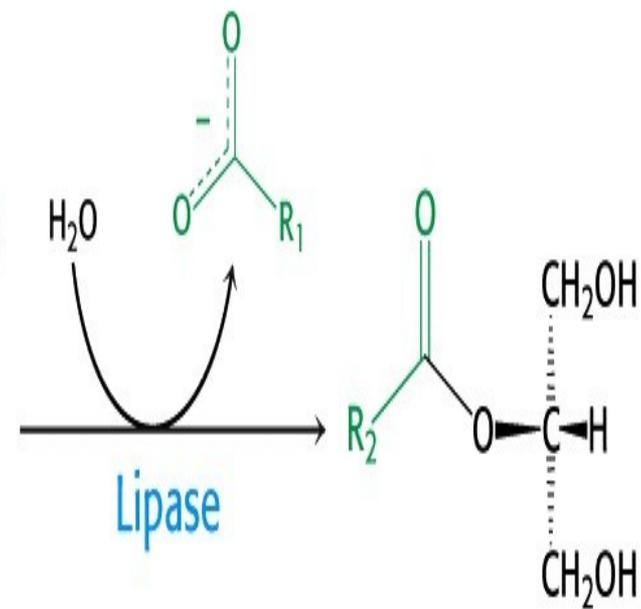




Triacylglyceride



Diacylglyceride



Monoacylglycerol

- **Activation of hormone-sensitive lipase:**
Hormone-sensitive lipase is activated when phosphorylated by a 3',5'-cyclic AMP—dependent protein kinase.
- 3',5'-Cyclic AMP is produced in the fat cell when one of several hormones (primarily epinephrine) binds to receptors on the cell membrane and activates adenylate cyclase.

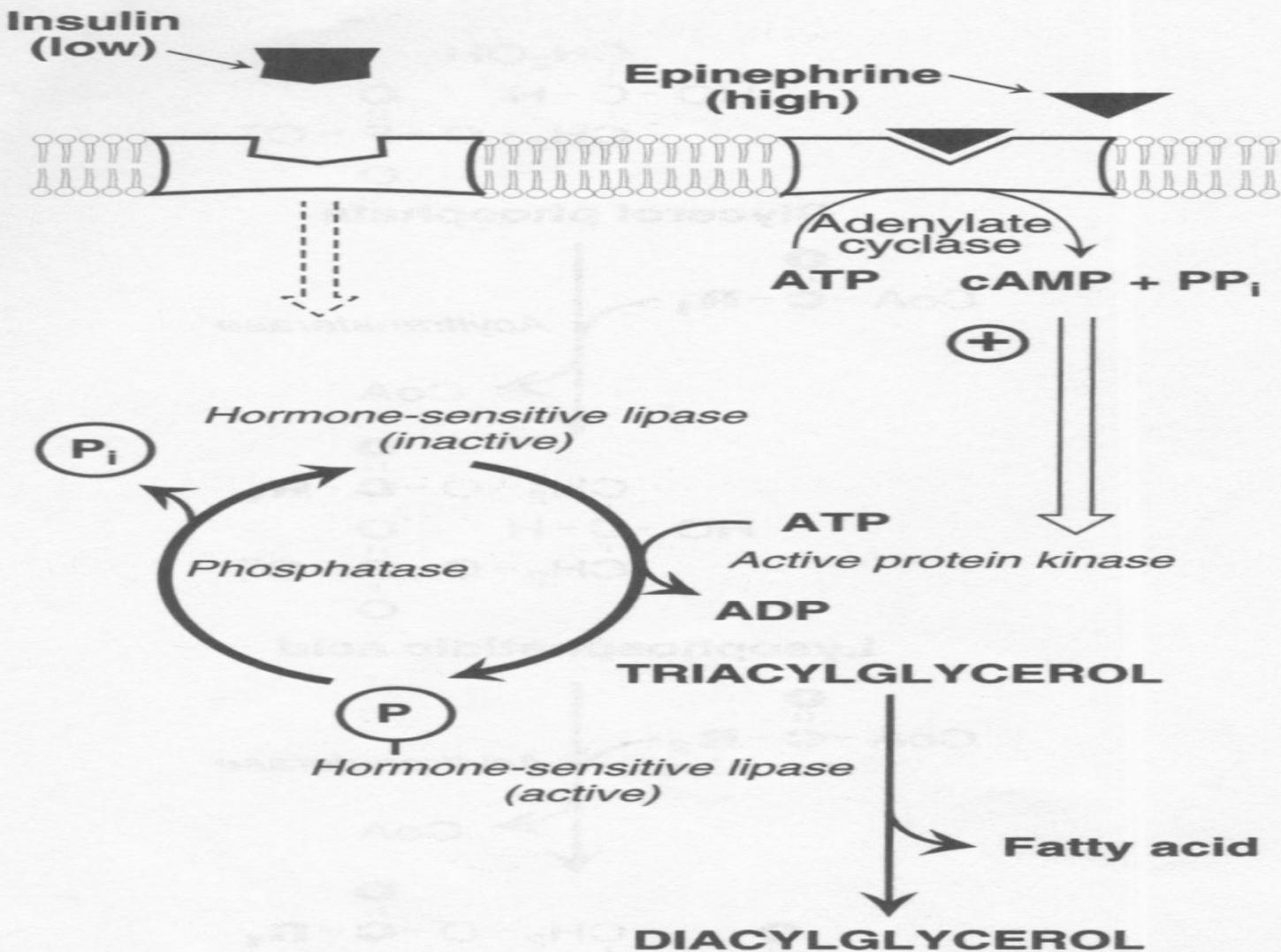
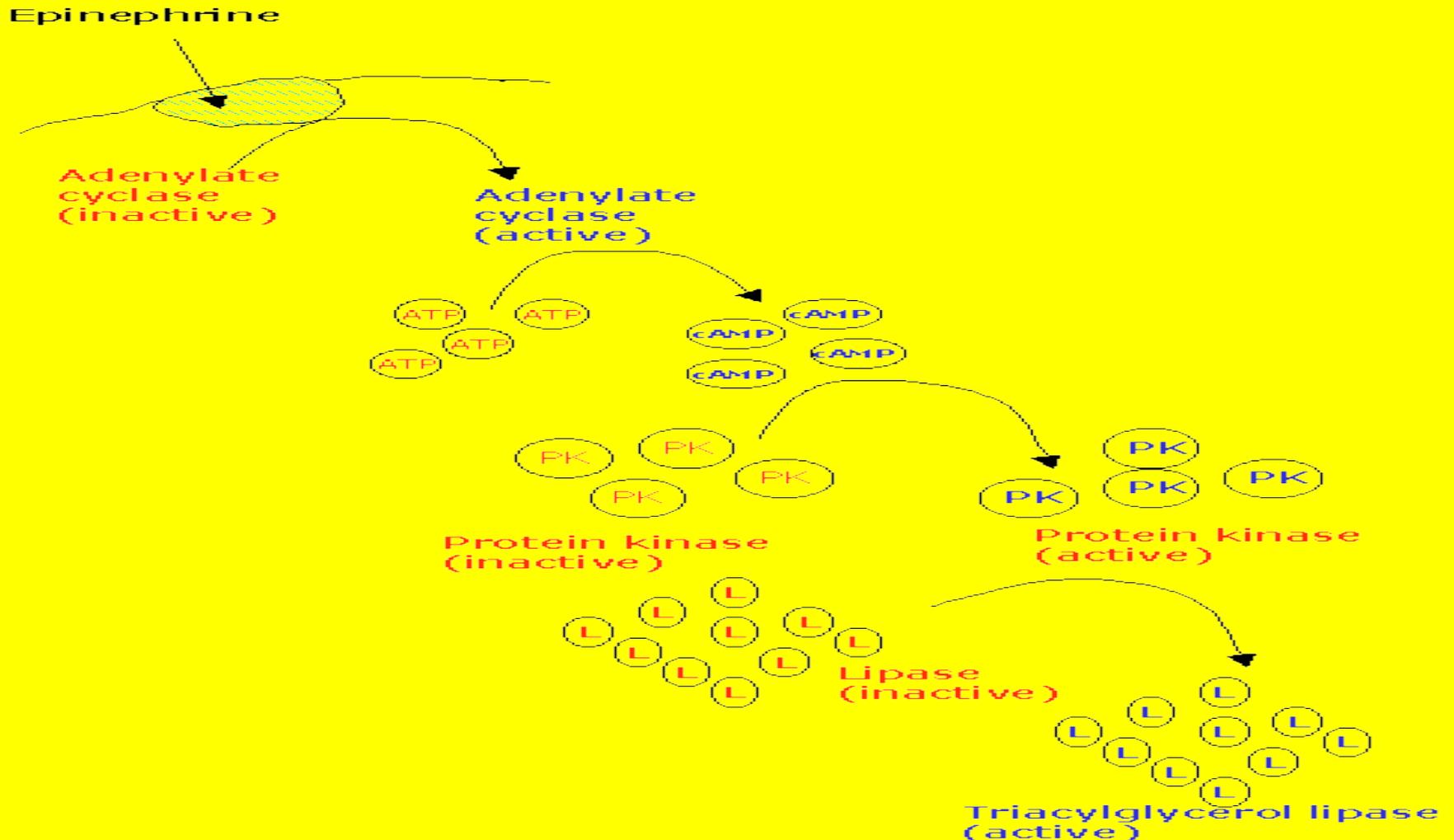


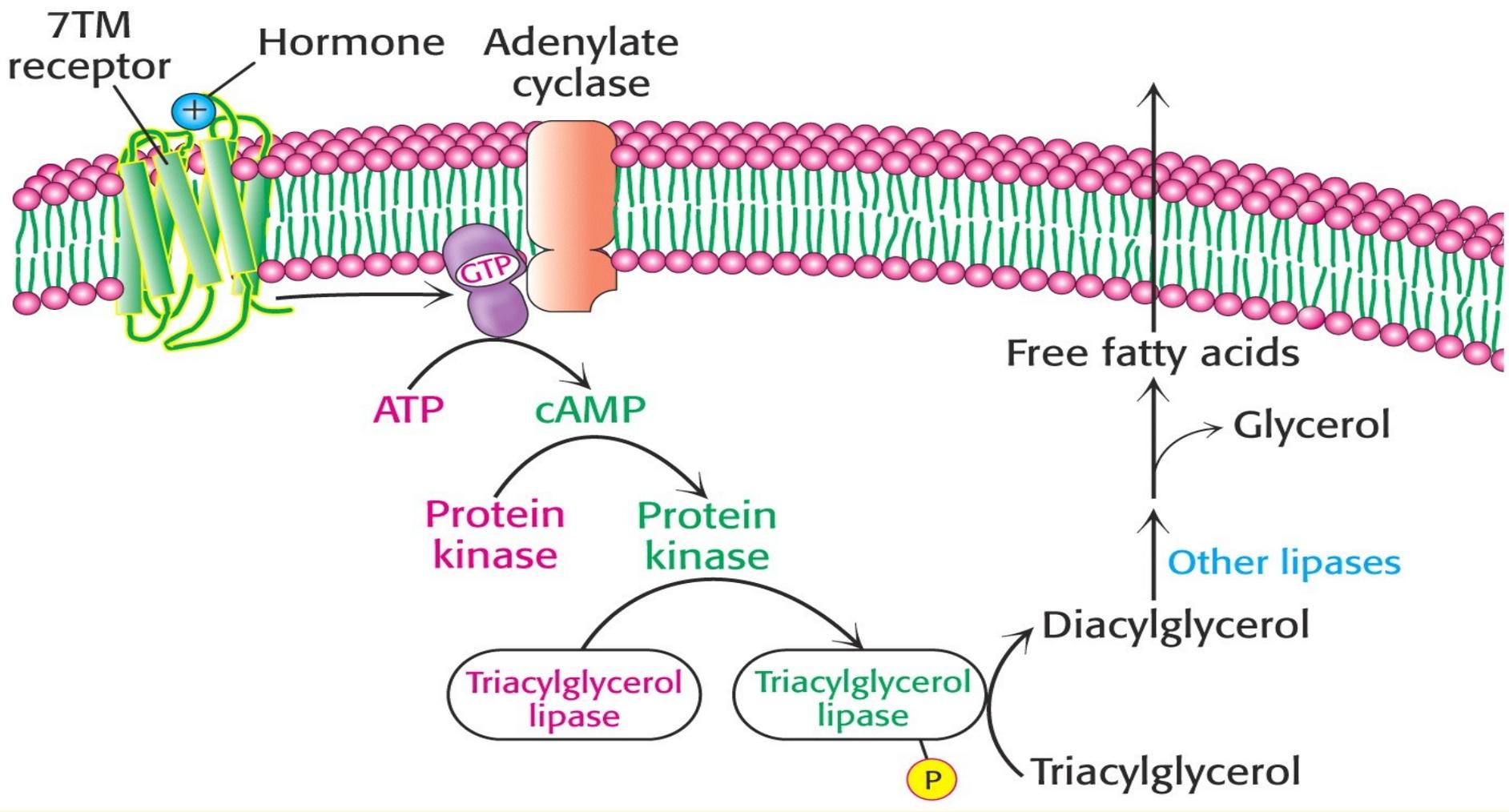
Figure 17.15
 Hormonal regulation of triacylglycerol degradation in the adipocyte.

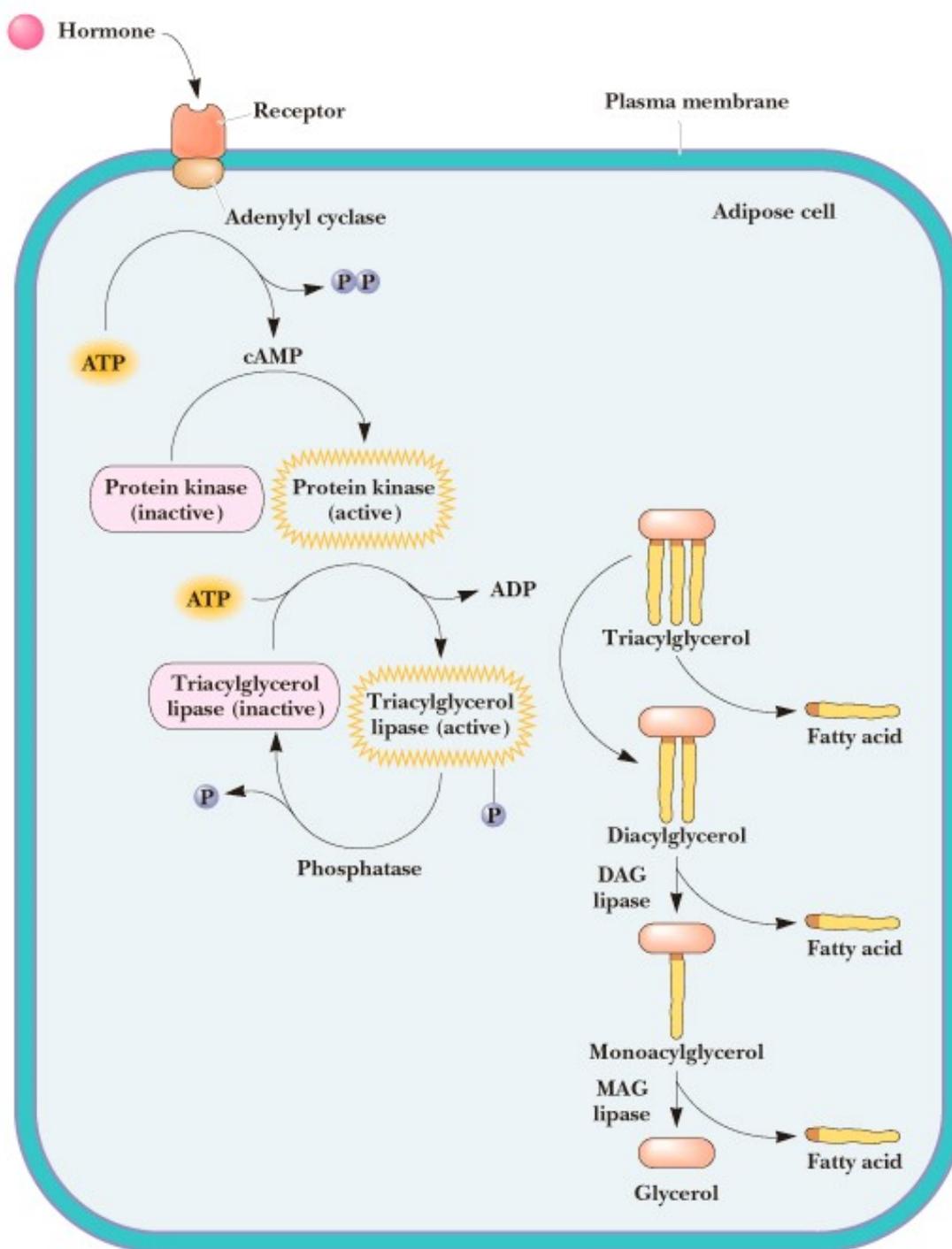
- **Think DOMINO EFFECT HERE!**

As with glycogen breakdown, the hormone activation of triacylglycerol lipase occurs through a cyclic AMP cascade. This provides the cell with the ability to control lipase activation and amplify the signal of the hormone.



Mobilization of triacylglycerols. Triacylglycerols in adipose tissue are converted into free fatty acids and glycerol for release into the bloodstream in response to hormonal signals. A hormone-sensitive lipase initiates the process.





Hormone-dependent degradation of triacylglycerols to release fatty acids in adipose tissue

- **This explains how COVALENT MODIFICATION controls** the effects of insulin on lipogenesis and lipolysis and how it **controls** the effects of glucagon on lipogenesis and lipolysis.
- **NOTE** that although three lipases are involved in the hydrolysis of a triacylglyceride **ONLY triacylglycerol lipase is activated by epinephrine or glucagon.**

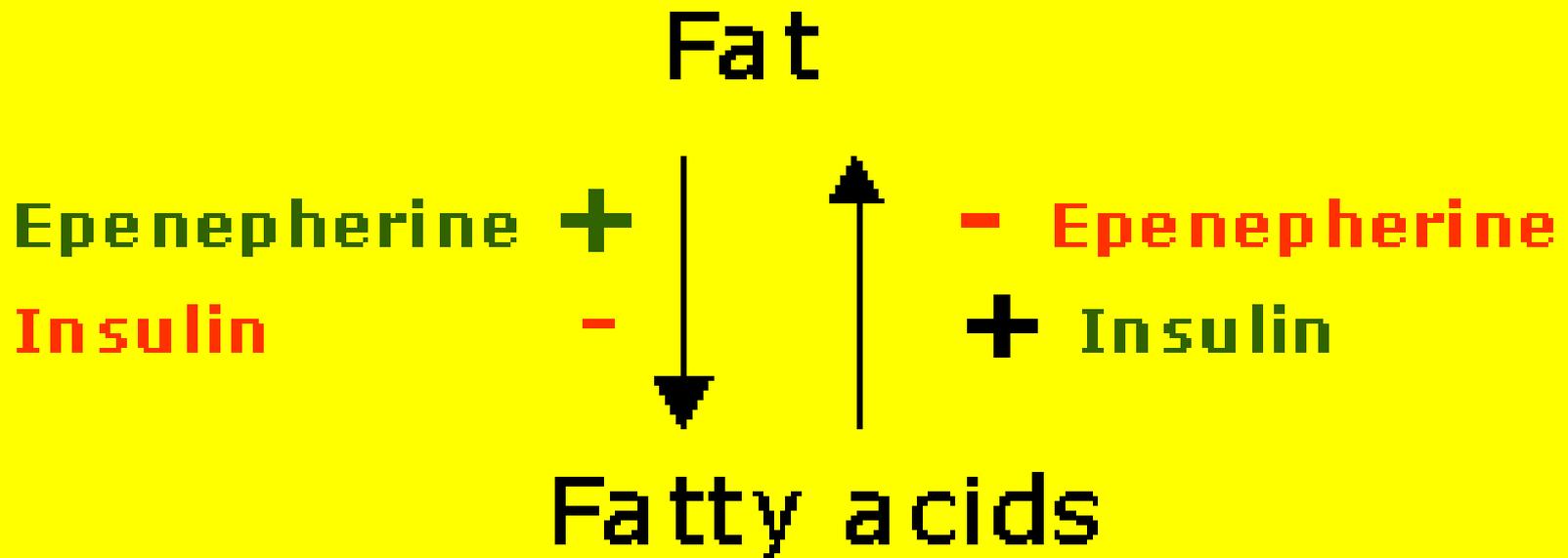
- **How is this Hormone-sensitive**
Triacylglycerol lipase regulated again?
- **By covalent modification** initiated when **secondary messengers** in the form of a **variety of different hormones (including epinephrine, norepinephrine, glucagon, adrenalcorticotrophic hormone)** bind to **membrane receptors of fat cells.**
- **1. These hormones initiate cAMP-mediated stimulation of specific kinases.**
- **2. The kinases in turn phosphorylates lipases activating them for the breakdown of lipids.**

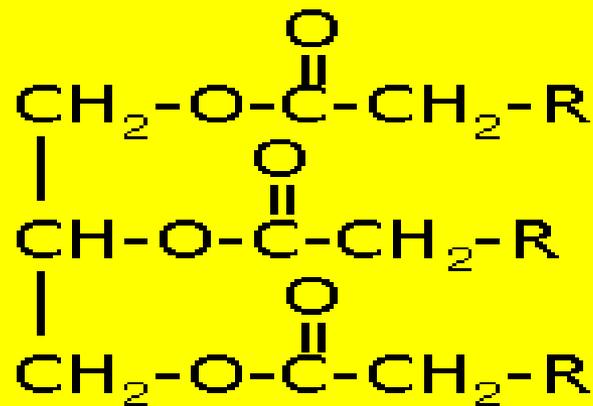
- **What is the effect of insulin on lipolysis?**
- **Insulin inhibits lipolysis.**
- **What is the effect of epinephrine and glucagon on lipolysis?**
- **Epinephrine, norepinephrine, glucagon, and adrenocorticotrophic hormone all induce lipolysis**
- **In adipose cells, these hormones trigger receptors that activate adenylate cyclase .**
- **The increased level of cyclic AMP then stimulates protein kinase A, which activates the lipases by phosphorylating them**

- **NOTE THAT ONCE YOU MAKE FAT THAT INSULIN IS NOT INTERESTED IN YOU BREAKING IT DOWN AGAIN !**
- NOTE ALSO THAT INSULIN IS NOT THE ONLY HORMONE PLAYER IN METABOLISM

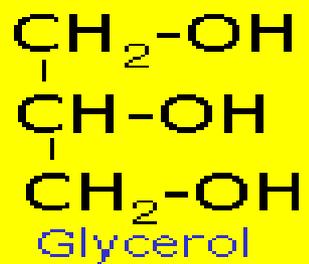
Hormonal control of lipolysis

The breakdown of triglycerides by lipases is under hormonal control. **The main enzymes involved are epinephrine and glucagon and insulin. Epinephrine and glucagon activate the breakdown of lipolysis while insulin inhibits fat breakdown.**





Triglyceride



Glyceraldehyde 3 P

Acetyl CoA

Gluconeogenesis

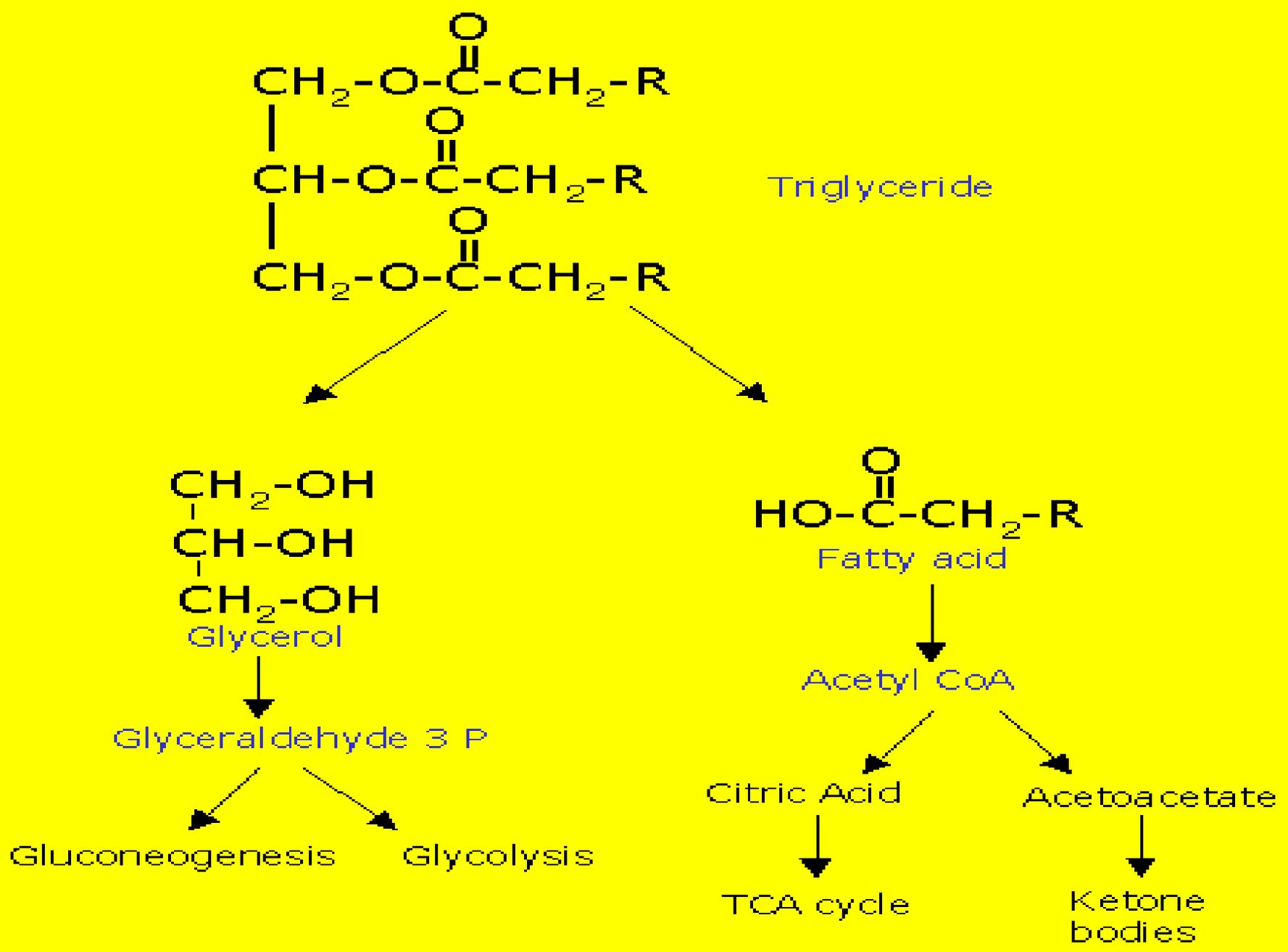
Glycolysis

Citric Acid

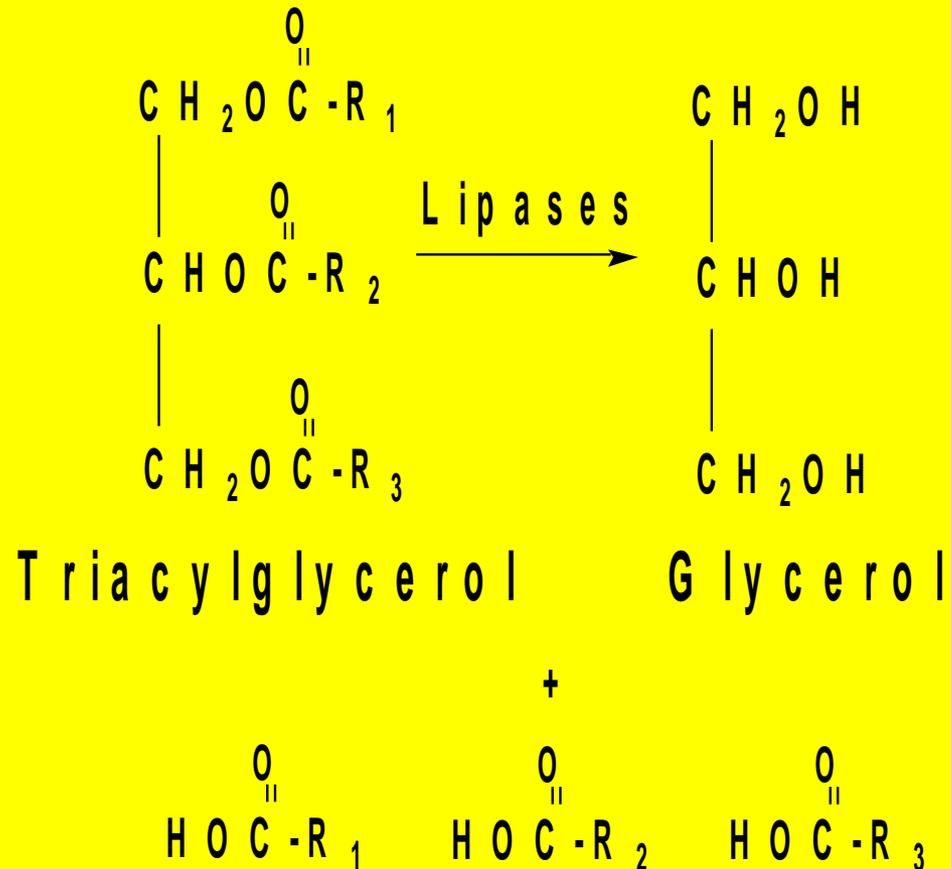
Acetoacetate

TCA cycle

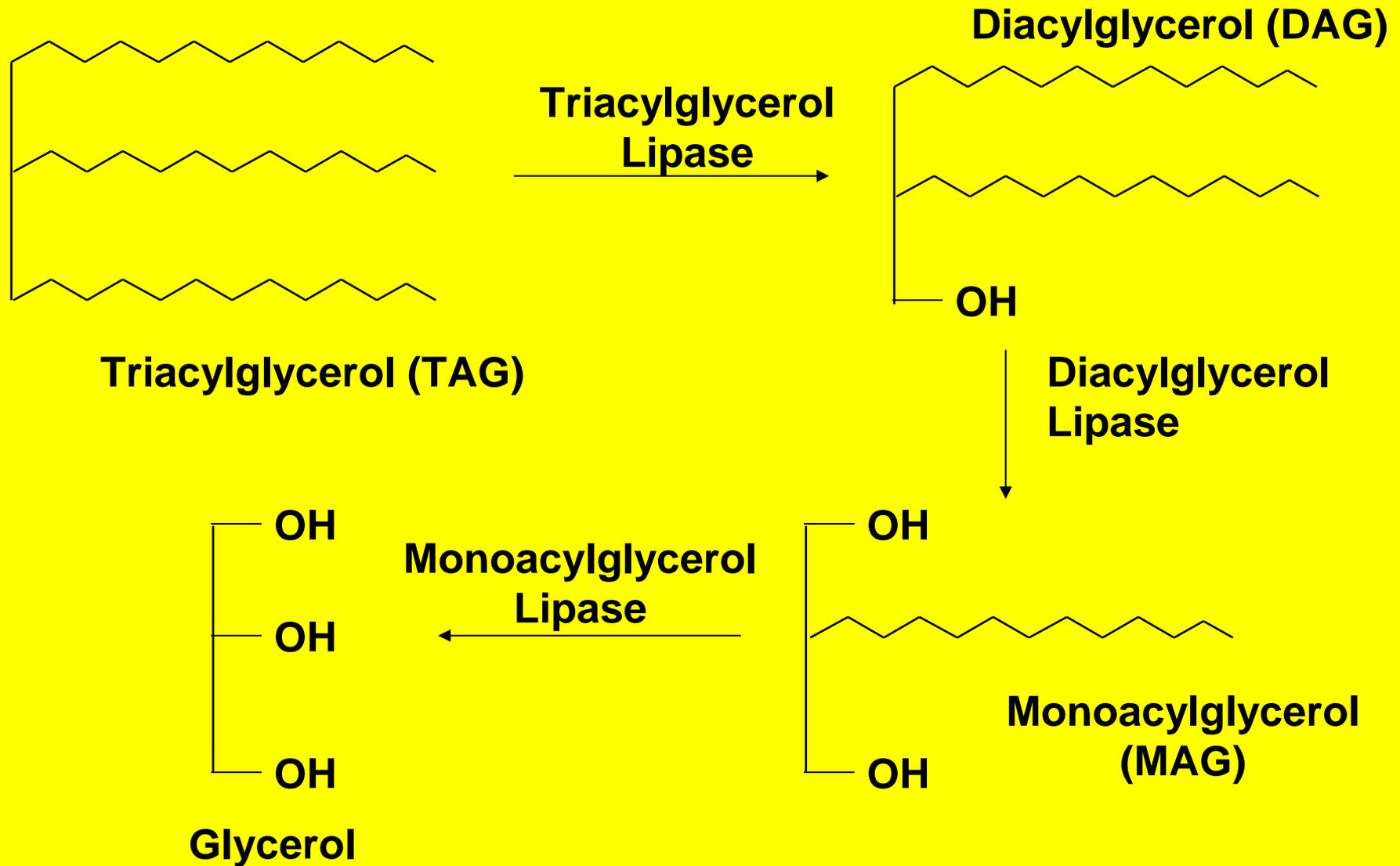
Ketone bodies



Release of Fatty Acids from Triacylglycerols- REVIEW



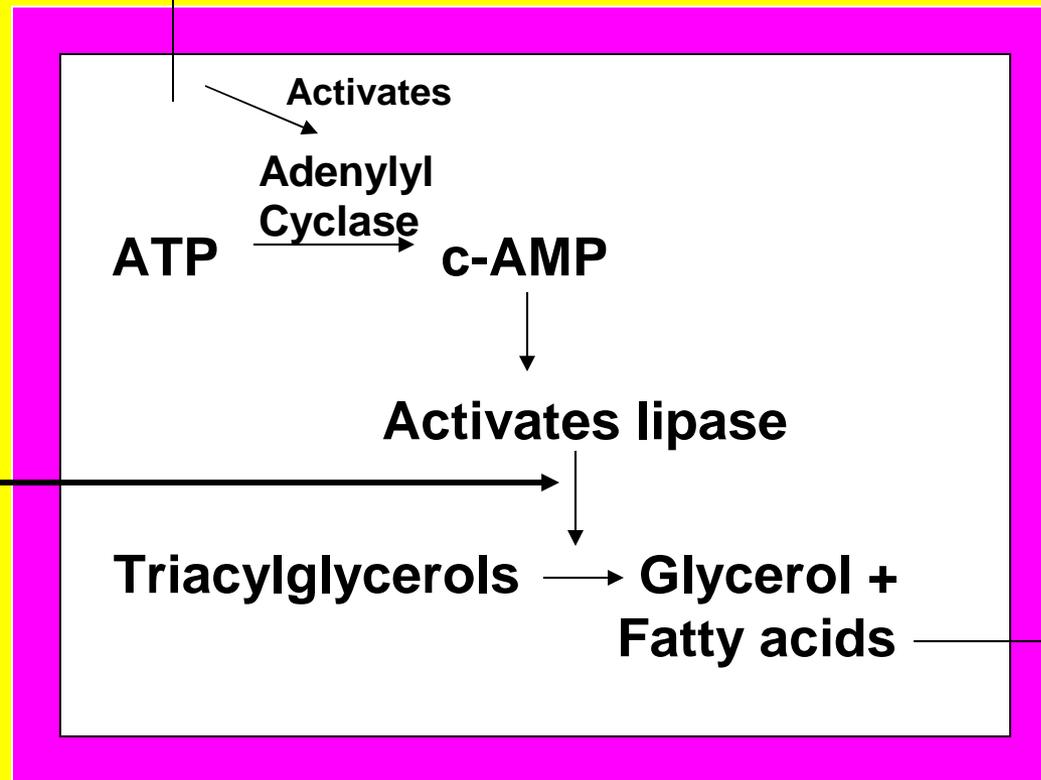
Acylglycerol Lipases



Lipolysis

Hormone
(Adrenalin, Glucagon, ACTH)

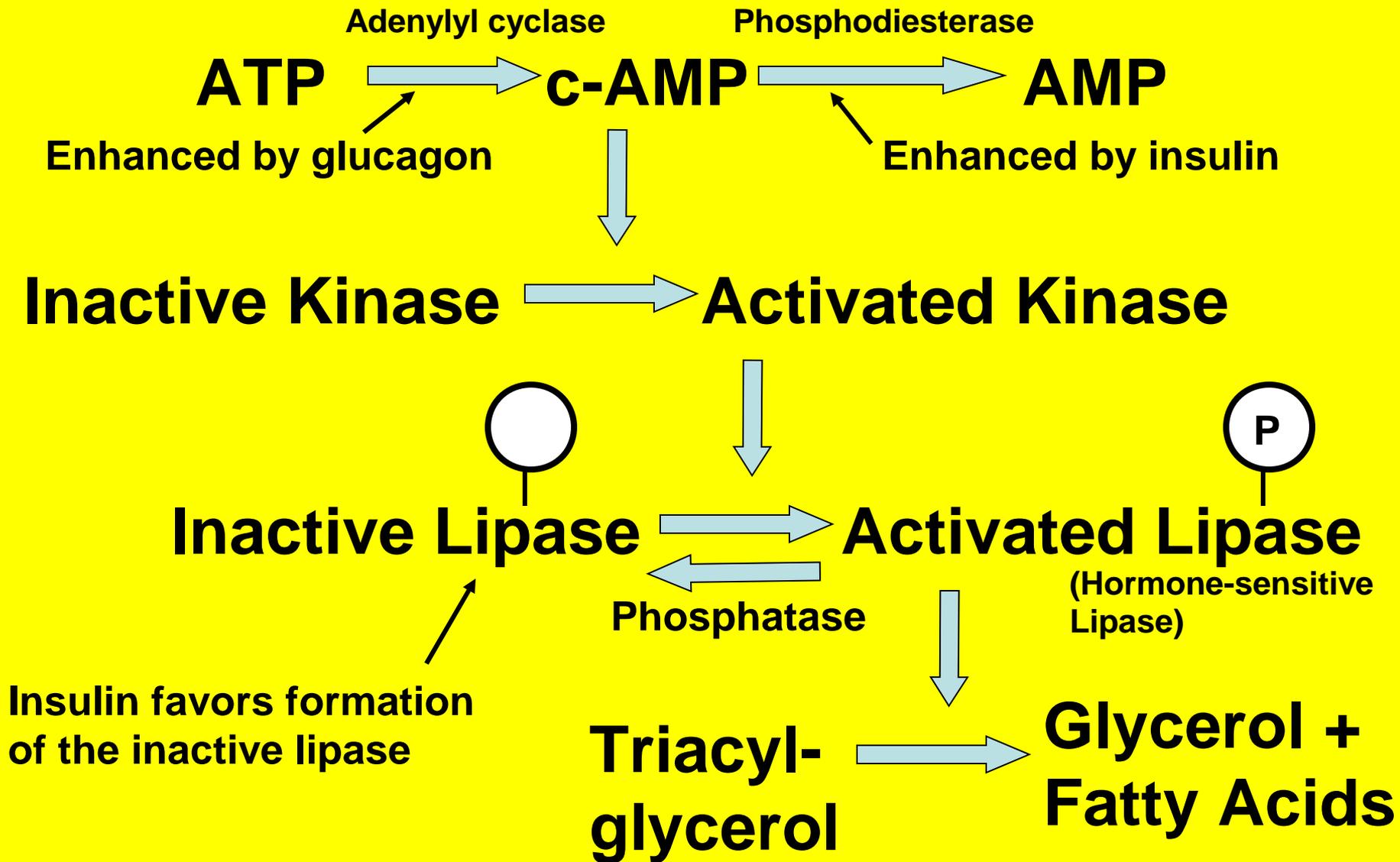
Receptor (7TM)



Insulin
blocks this
step

Blood

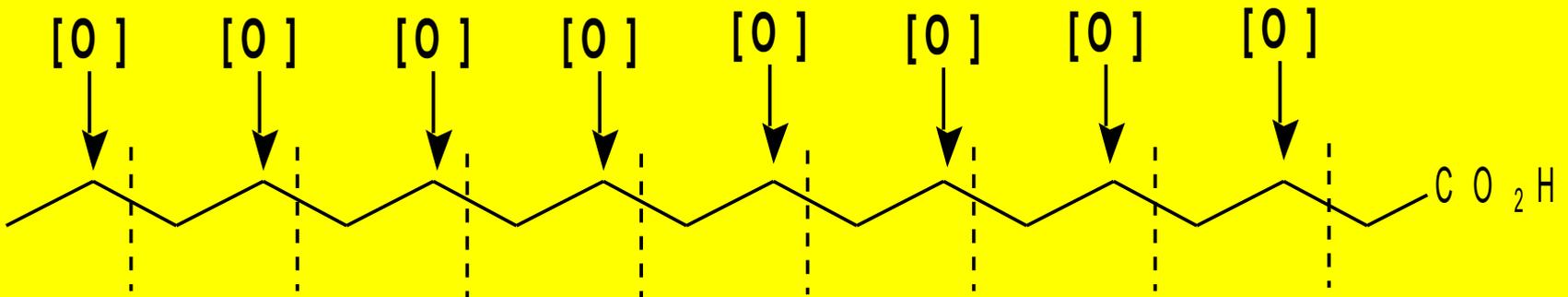
Adipose Cell



- Having described the hydrolytic breakdown of triacylglycerol to form free fatty acids and, glycerol; it is necessary to describe the
- **fate of the free fatty acids**,... and the fate of the glycerol.
- **The fate of the free fatty acids** will be discussed in three sections under beta oxidation, fatty acid synthesis or lipogenesis and ketone body metabolism.
- But we will mention a few things at this point.

- **The free (unesterified) fatty acid molecules released in the hydrolysis of tryglycerides may move through the cell membrane of the adipocyte and immediately bind to albumin in the plasma, which carries them to the heart, skeletal muscle and liver, where they diffuse into the cells and are metabolized and oxidized to produce acetyl CoA, NADH and FADH₂ by beta oxidation if there is need for energy production.**

- **Beta oxidation** is the major pathway for catabolism of fatty acids. It occurs in the mitochondria.
- In beta oxidation the fatty acids are cleaved so that two-carbon fragments are successively removed from the carboxyl end of the fatty acyl CoA, **to produce acetyl CoA units.**



- **However, erythrocytes, the adrenal medulla, the brain and other nervous tissue cannot use plasma free fatty acids for fuel, regardless of the blood levels of fatty acid.**
- **Erythrocytes lack mitochondria, and fatty acids do not cross the blood-brain barrier efficiently.**
- **Since neither erythrocytes nor brain can use fatty acids, they continue to rely on glucose during normal periods of fasting.**
- **The free fatty acids derived from the hydrolysis of triacylglycerol may also directly enter adjacent muscle cells or adipocytes.**
- **Alternatively, the free fatty acids may be transported in the blood in association with serum albumin until they are taken up by cells.**

- **Short-chain fatty acids (2-4 carbons) and medium-chain fatty acids (6-12 carbons) diffuse freely into mitochondria to be oxidized.....BUT**
- **Long-chain fatty acids (14—20 carbons) are transported into the mitochondrion by the carnitine shuttle (described later) to be oxidized.**
- **Very long-chain fatty acids (>20 carbons) enter peroxisomes via an unknown mechanism for oxidation.**

Processing of Lipid Reserves: Overview

- 1. Lipid Mobilization:**
In adipose tissue TAGs hydrolyzed to fatty acids plus glycerol
- 2. Transport of Fatty Acids in Blood To Tissues**
- 3. Activation of Fatty Acids as CoA Ester**
- 4. Transport into Mitochondria**
- 5. Metabolism to Acetyl CoA via beta oxidation**

- **Summary of the fate of free fatty acids:**
- **Free fatty acids may enter adjacent muscle cells or adipocytes and be stored.**
- **Adipocytes may re-esterify the free fatty acids to form triacylglycerol for storage until free fatty acids are required by the body for any purpose**
- **Free fatty acids** may be transported by serum albumin to tissues where cells oxidize them for energy **via β -Oxidation.....and the acetylCoA** is then taken into the Krebs cycle and converted into carbon dioxide, reduced NAD and FAD and ATP.

- **Free fatty acids may also enter**
- **Biosynthesis of neutral fats (i.e synthesis of triglycerides)**
- **Biosynthesis of phosphoglycerides**
- **Biosynthesis of sphingolipids**
- **Biosynthesis of cholesterol esters**

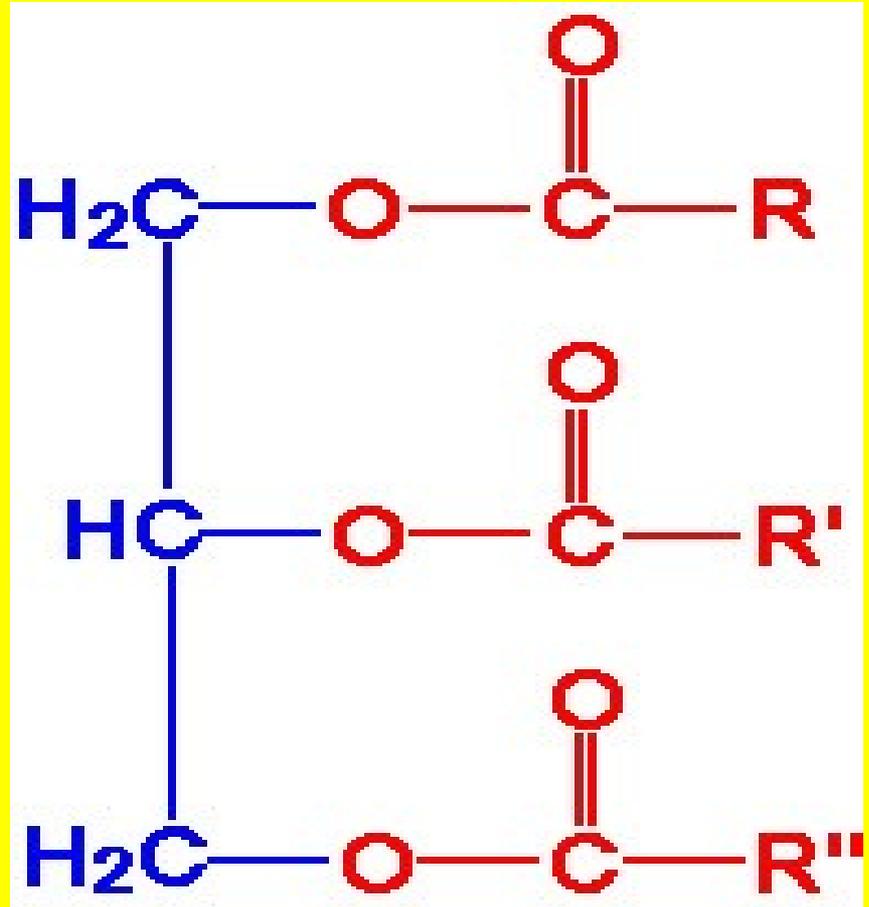
- **We will now discuss what are the possible fates of the glycerol released in the hydrolysis of tryglycerides**

LIST OF ROLES PLAYED BY GLYCEROL IN METABOLISM

- Glycerol is involved in
- **1- glycolysis**
- **2- gluconeogenesis**
- **3- the synthesis of triglycerides**
- **4-amino acid biosynthesis (glycine, serine and cysteine)**
- **5- the glycerophosphate shuttle**
- **6- in the biosynthesis of membrane phospholipids**

Glycerol

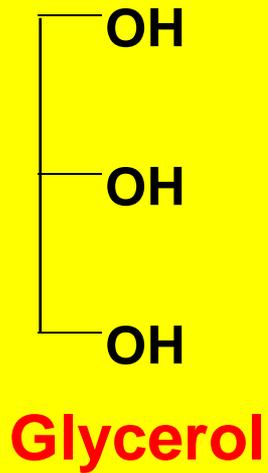
- (CH₂OH·CHOH·CH₂OH), in its pure form, is a sweet-tasting, clear, colorless, odorless, viscous liquid.
- It is completely soluble in water and alcohols, slightly soluble in many common solvents like ether and dioxane and is insoluble in hydrocarbons.
- At low temperatures, glycerol sometimes forms crystals which tend to melt at 17.9° C. Liquid glycerol boils at 290° C under normal atmospheric pressure.
- Its specific gravity is 1.26 and its molecular weight is 92.09.



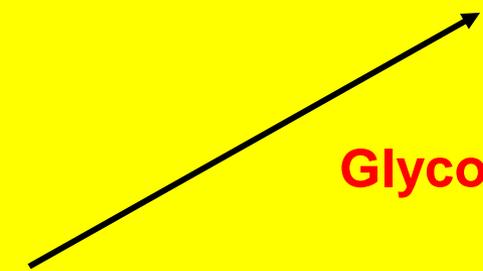
- The glycerol produced in the hydrolysis of tryglycerides is metabolized primarily by the liver and funneled into glycolysis
- The glycerol is first converted into **glyceraldehyde 3 phosphate (PGAL) or dihydroxyacetone phosphate (DHAP) in glycolysis.**
- Just as glucose 6 phosphate is the hub for glucose metabolism, **glyceraldehyde 3 phosphate (PGAL) or dihydroxyacetone phosphate are the hub for glycerol metabolism.**

Fate of Glycerol

In Liver:



**Dihydroxyacetone
Phosphate**



Glycolysis

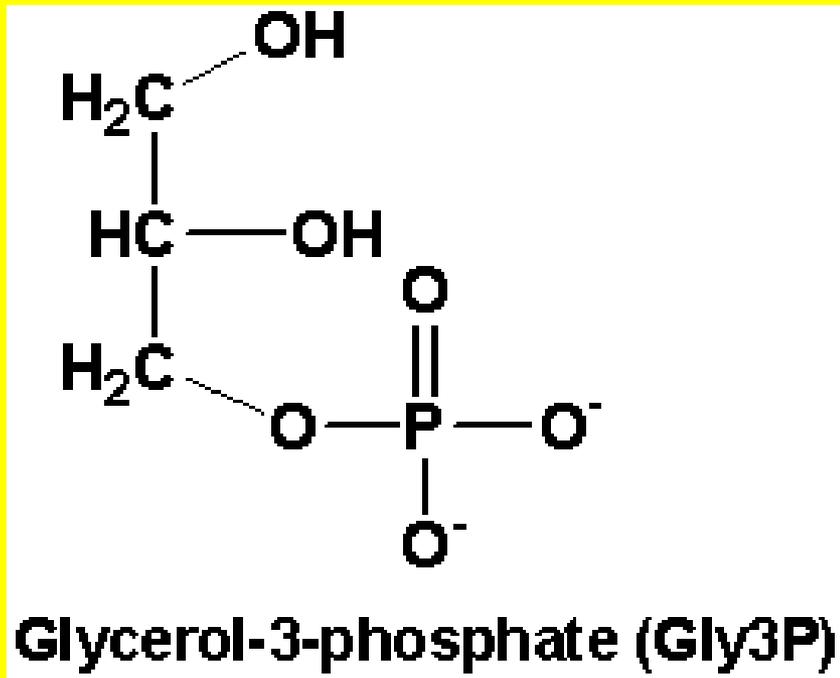
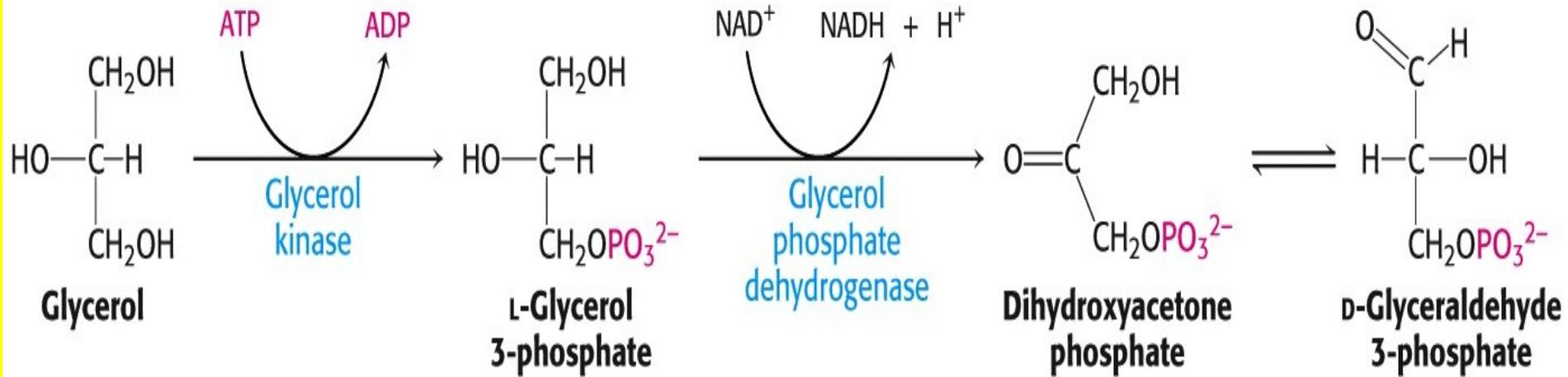
Pyruvate

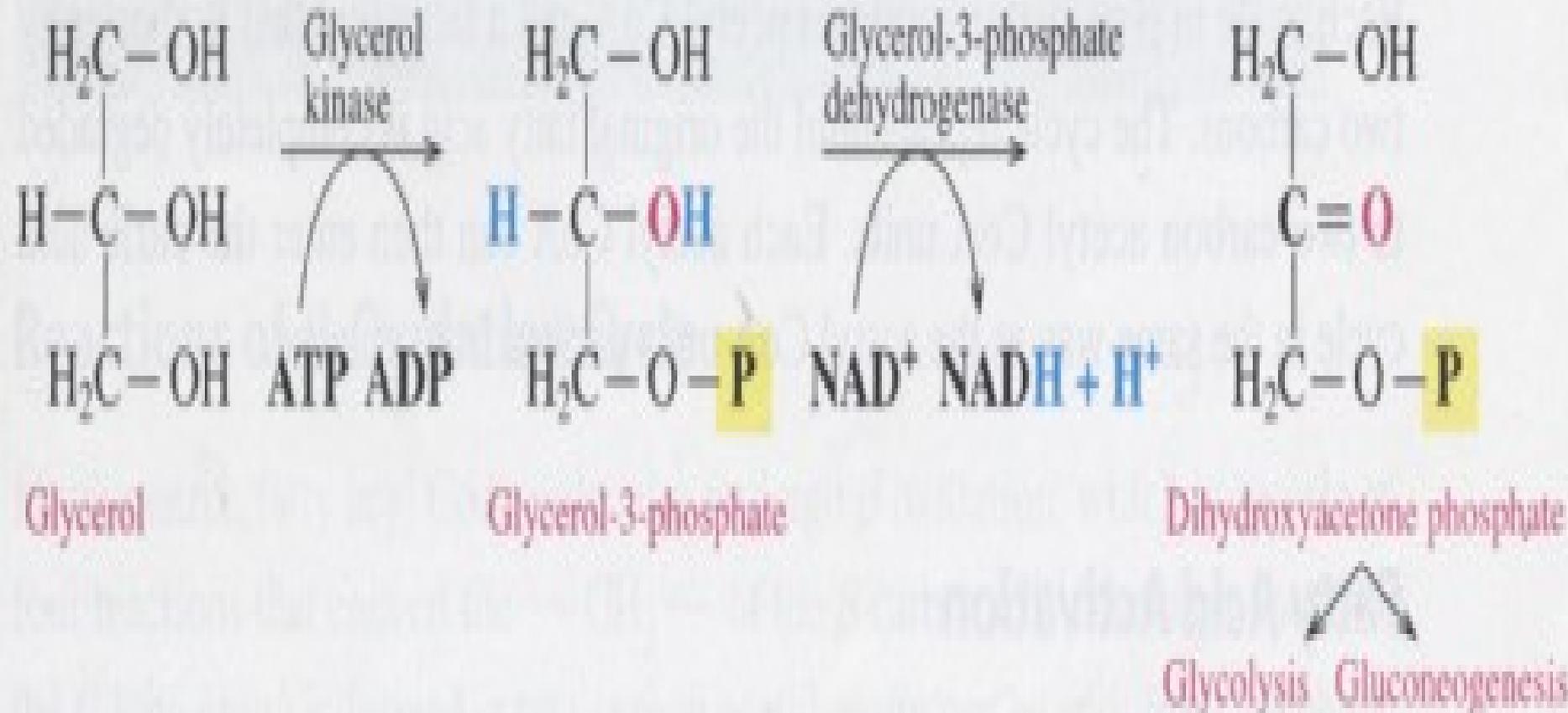


Gluconeogenesis

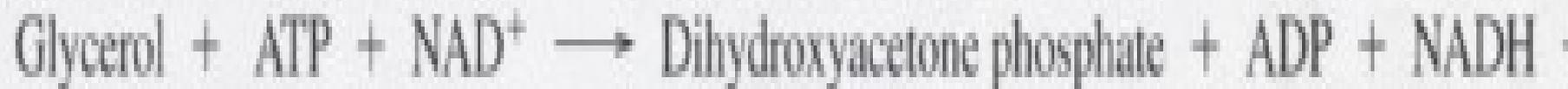
Glucose

- Glycerol that is released from triacylglycerol is used almost exclusively by the liver **to produce glycerol 3-phosphate, which can enter glycolysis or gluconeogenesis by oxidation to dihydroxyacetone phosphate**





The overall reaction for the metabolism of glycerol is written as follows:



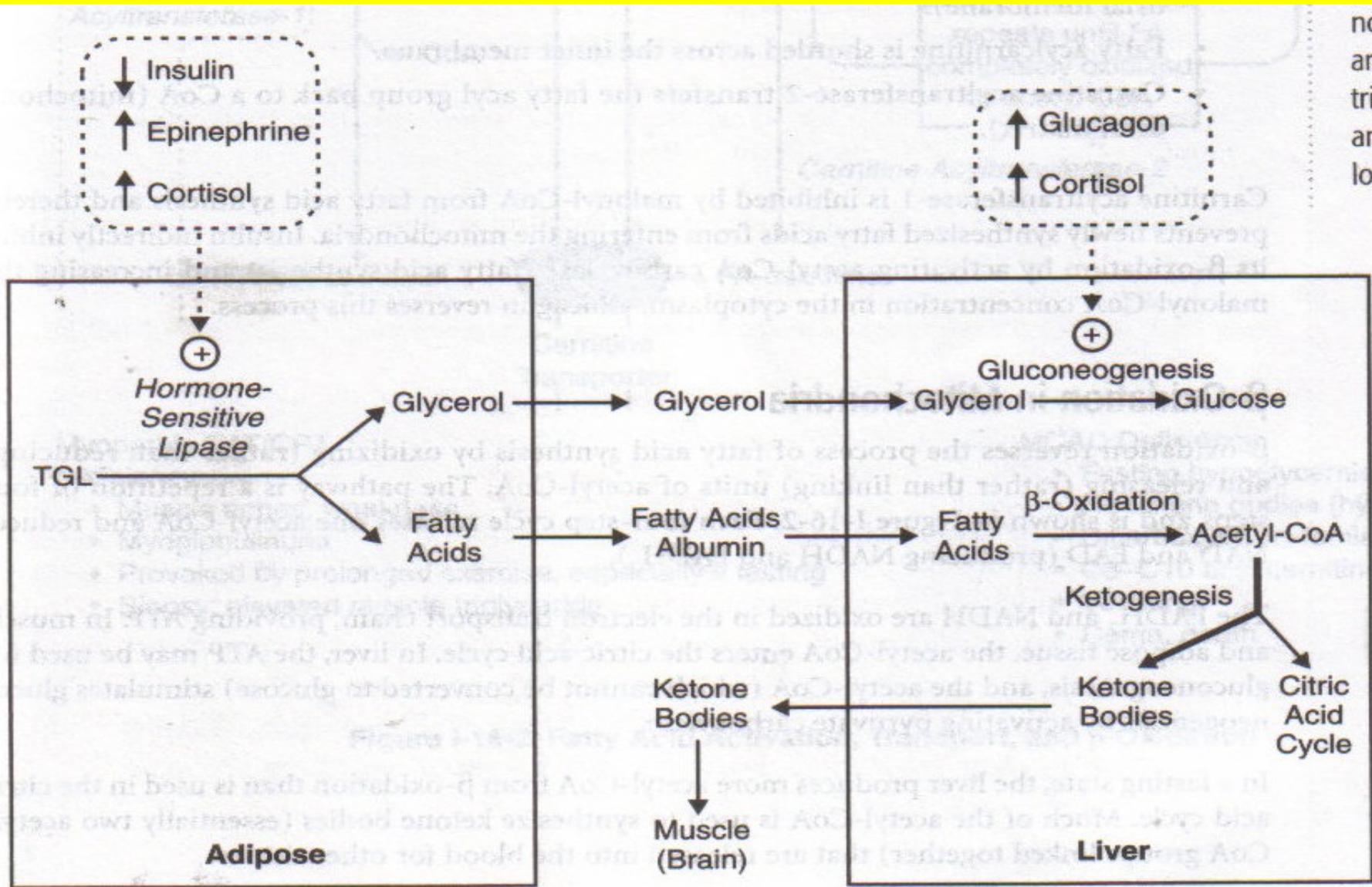
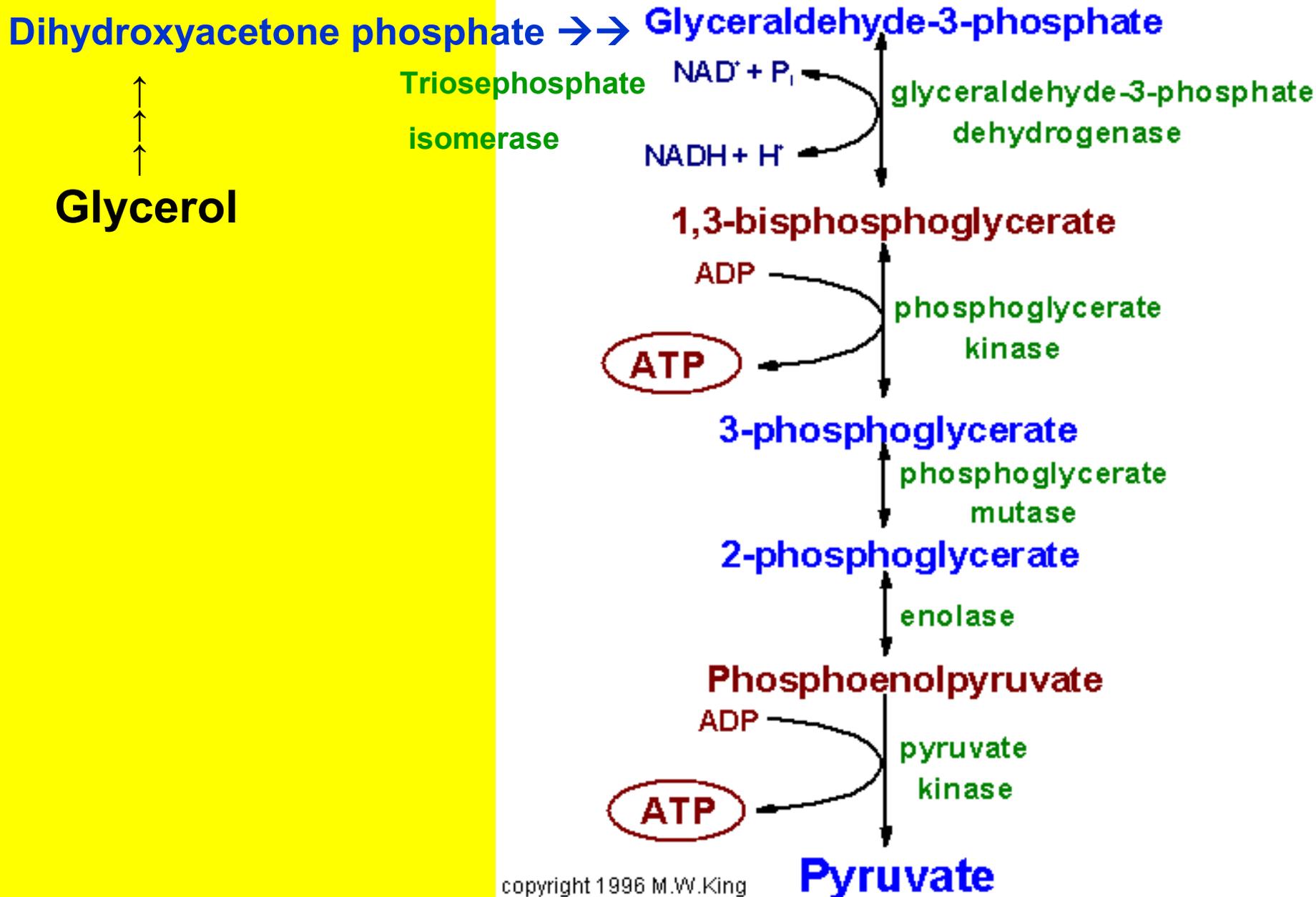


Figure I-16-1. Lipolysis of Triglyceride in Response to Hypoglycemia and Stress

- **GLYCEROL IN GLYCOLYSIS**
- **Glycerol enters the glycolytic (and gluconeogenesis) pathway via the conversion of glycerol-3-phosphate to dihydroxyacetone phosphate (DHAP) catalyzed by glycerol-3-phosphate dehydrogenase as described above.**
- **DHAP then enters the glycolytic pathway if the liver cell needs energy by being isomerised to glyceraldehyde 3 phosphate.**

Glycolytic Pathway



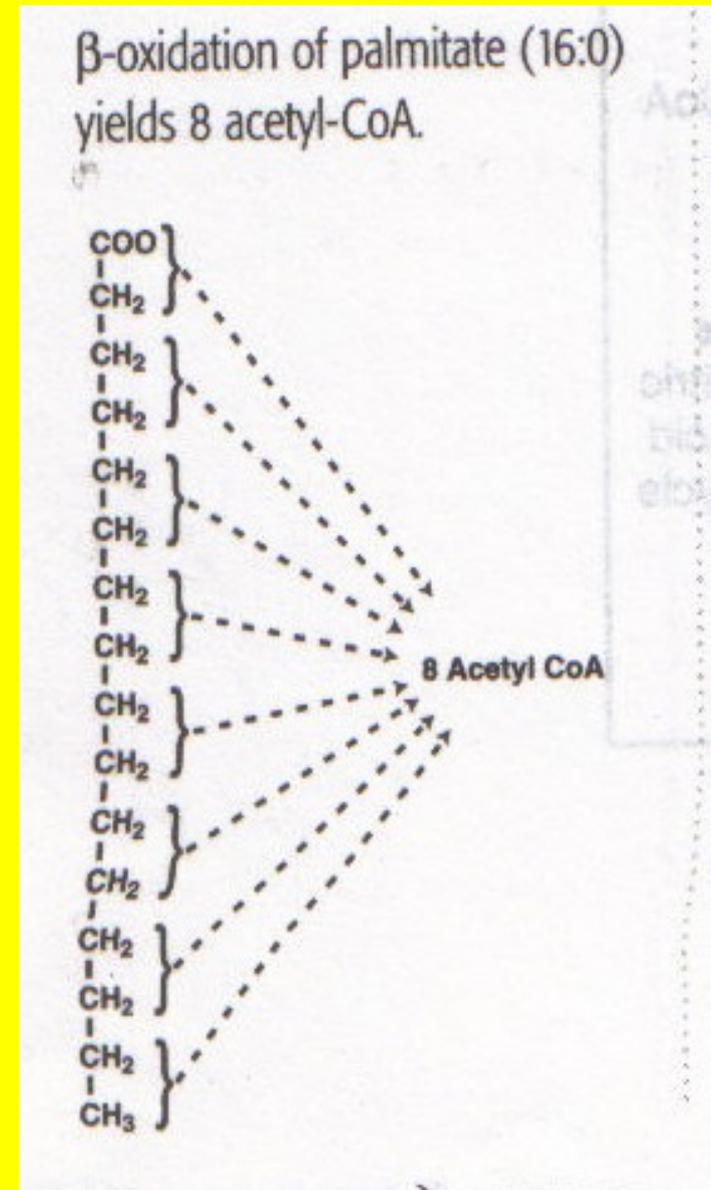
- NOTE THAT GLYCEROL LIBERATED FROM TRI GLYCERIDE BREAKDOWN ENTERS GLYCOLYSIS AND PRODUCES PYRUVATE
- **GLYCEROL IS BASICALLY A SUGAR!**
- Next the pyruvate will be converted to ACETYL COA!
- **REMEMBER ACETYL COA**

- You can see then that the glycerol liberated from fat digestion can be used to make ACETLY COA UNITS when fats are used in excess.
- Next we will see that the FATTY ACIDS liberated from fat digestion can be used to make ACETLY COA UNITS.
- This happens routinely

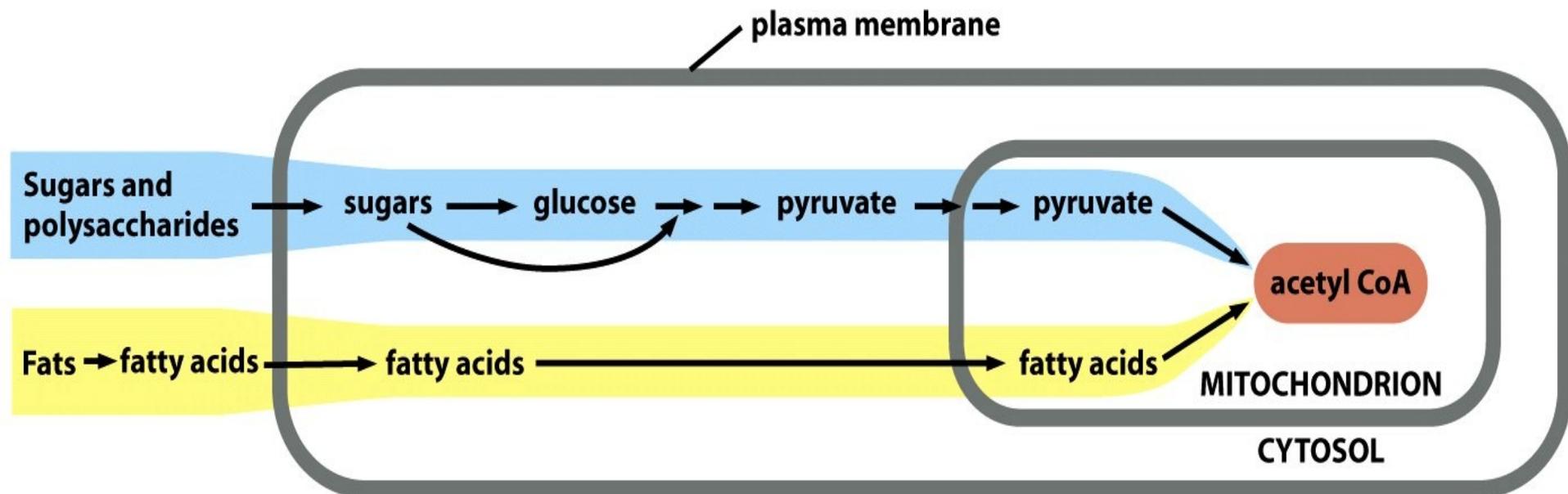
- **Free fatty acids move out of adipocytes through the cell membrane and binds to albumin of plasma and are transported to the tissues where they are oxidized.**
- **These free fatty acids are carried by the blood to the heart, skeletal muscle and liver, where they are metabolized and oxidized to produce acetyl CoA, NADH and FADH₂ in beta oxidation .**

β -OXIDATION OF FATTY ACIDS

- is the **oxidative breakdown of fatty acids to acetyl-CoA in the mitochondrion with the release of reduced cofactors**
- is the major pathway for the catabolism of saturated fatty acids in which **two carbon fragments are successively removed from the –COOH end of a fatty acids as acetyl CoA units.**
- (The 2-C units are released as acetyl- CoA, not free acetate.)
- is also called Knoop's spiral
- **is thus basically the cleavage of fatty acids to acetate in tissues**
- **it occurs in the mitochondrion**



- **Beta oxidation is a catabolic metabolic pathway by which fatty acids in the form of activated acyl-CoA molecules, are broken down in the mitochondria and/or in peroxisomes two carbon units at a time to yield acetyl CoA.**
- **The two carbon units then become acetyl groups that are converted into acetyl CoA.**
- These acetyl CoA units are then used in the Krebs Cycle to each make one ATP , 3 NADH⁺ + H⁺ and 1 FADH₂.
- **If a fatty acid has 18 carbon units, then 9 acetyl COA units would be made.**



- **So if you eat lots of fat whether saturated or unsaturated YOU WILL MAKE LOTS OF ACETYLCOA!**
- **In the next slide we see one of the things that happens when you have excess acetylCoA units... YOU MAKE KETONE BODIES.**

Acetyl CoA

+

Acetyl CoA

CoA

Acetoacetyl CoA

Acetoacetate

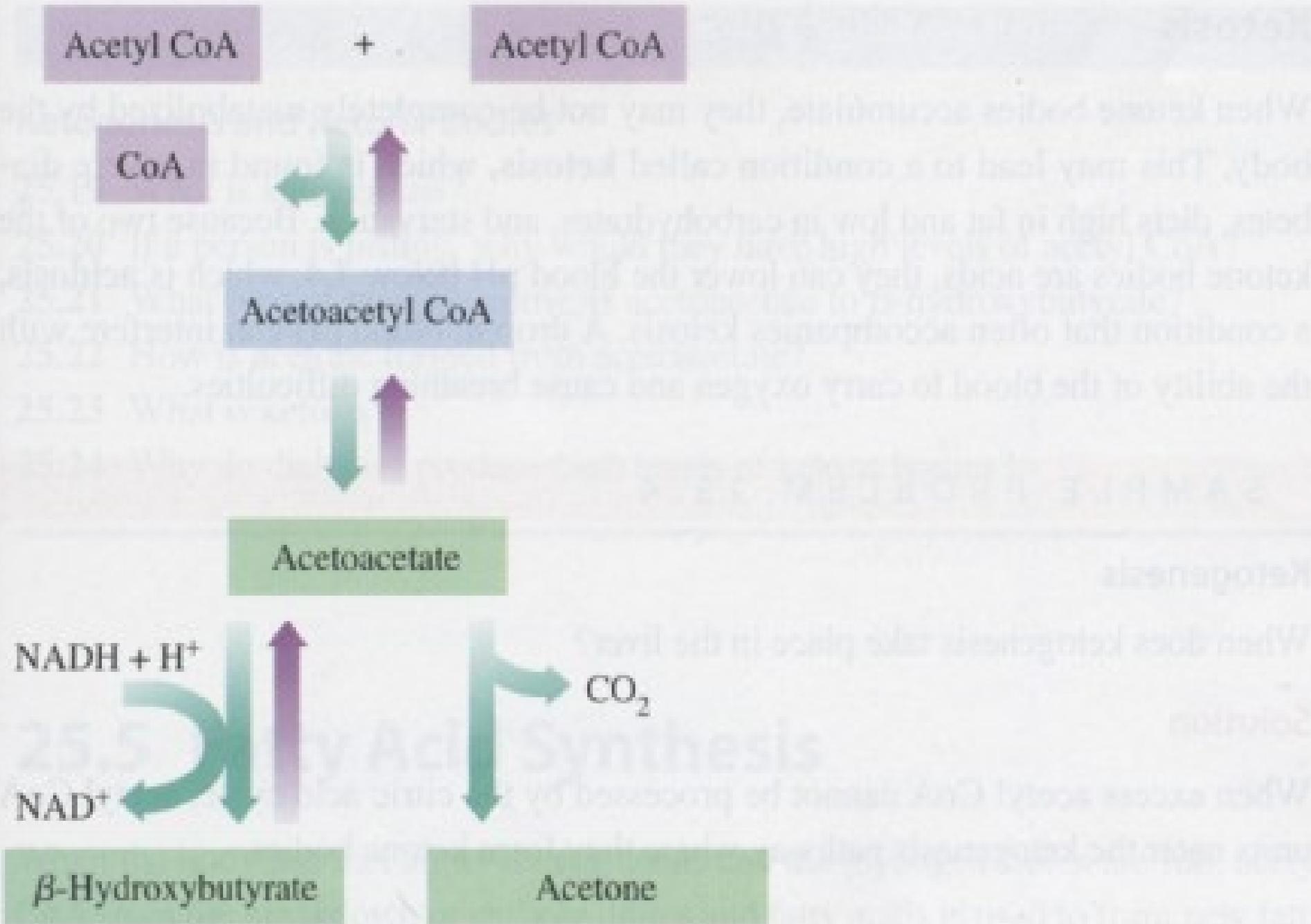
NADH + H⁺

NAD⁺

β -Hydroxybutyrate

CO₂

Acetone



- **WHERE ARE THEY ARE MADE?**

- The major site of production of acetoacetate and 3-hydroxybutyrate **is the liver.**
- Ketone bodies are produced in the liver when the amount of acetylCoA exceeds the oxidative capacity of the liver.....**when there is excess acetylCoA in the blood.**

- Ketone bodies are produced in the liver when the amount of acetylCoA exceeds the oxidative capacity of the liver.....**when there is excess acetylCoA in the blood.**
- **Normally, when fat and carbohydrate degradation are appropriately balanced, the acetyl CoA formed in fatty acid oxidation enters the citric acid cycle.**

- **But during high rates of fatty acid oxidation (as occurs in states such as diabetes, fasting and starvation), when carbohydrates are not available to meet energy needs, or are properly utilized, the body breaks down body fat by a process called beta oxidation of fats.**
- **Under these conditions, when fatty acid degradation predominates, and occurs more rapidly than glycolysis, large and excessive amounts of acetyl-CoA are generated from fatty acids, but little oxaloacetate is generated from pyruvate.**

- But during **high rates of fatty acid oxidation**when fatty acid degradation predominates, and occurs more rapidly than glycolysis, **large and excessive amounts of acetyl-CoA are generated from fatty acids, by beta oxidation of fats, but little oxaloacetate is generated from pyruvate.**

-

- **The large amounts of acetyl-CoA generated exceeds the capacity of the TCA cycle to function, since entry of acetyl CoA into the TCA depends on the availability of oxaloacetate for the condensation reaction that forms citrate to start the TCA.**
- **But the supply of oxaloacetate is too low to allow all of the acetyl CoA that is made in the increased fat and protein breakdown that accompanies these states to enter the citric acid cycle.**
- **So this pathway becomes very limited in its function.**

- In such circumstances when oxaloacetate levels are too low, oxaloacetate is diverted from entering the citric acid cycle to gluconeogenesis to form glucose and is thus unavailable for condensation with acetyl CoA.
- The excess acetyl CoA from the beta-oxidation pathway or protein degradation is diverted to form the ketone bodies acetone, acetoacetate and β -hydroxybutyrate.

- **Ketone bodies are thus produced in the course of breakdown of fatty acids, in states when fatty acid breakdown predominates**, because at some point beta oxidation reaches the point where the fatty acid is degraded to the 4-carbon **acetoacetyl CoA**.
- **Acetoacetyl CoA can either:**
 - 1- break down further to acetyl CoA,
 - 2- be used for synthesis of cholesterol and its many derivatives, or .
 - 3- be converted to the ketones (acetoacetate (C4), hydroxybutyrate (C4), and acetone (C3), in the process of ketogenesis.

- **When there are elevated levels of ketone bodies in the blood, the blood pH becomes acidic, and can lead to death due to ketosis or ketoacidosis, which can often be detected by the odor of acetone on the breath.**
- **Because two of the ketone bodies are acids, they can lower the blood pH below 7.4, which is acidosis, a condition that often accompanies ketosis.**
- **A drop in blood pH can interfere with the ability of the blood to carry oxygen and cause breathing difficulties.**

- **When there are elevated levels of ketone bodies in the blood, the blood pH becomes acidic, and can lead to death due to ketosis or ketoacidosis , which can often be detected by the odor of acetone on the breath.**
- **Because two of the ketone bodies are acids, they can lower the blood pH below 7.4, which is acidosis, a condition that often accompanies ketosis.**
- **A drop in blood pH can interfere with the ability of the blood to carry oxygen and cause breathing difficulties.**

- **NOTE** that the first two reactions in cholesterol biosynthesis are shared by the pathway that produces ketone bodies.
- Liver parenchymal cells contain two isoenzyme forms of HMG CoA synthase: the one in the cytosol is involved in cholesterol synthesis, while the other has a mitochondrial location and functions in the synthesis of ketone bodies.

Two Fates of HMG-CoA

