PASSION ACADEMIC TEAM

YU - MEDICINE

Cardiovascular System

Sheet# 1 - BIOCHEMISTRY

Lec. Date : 21 / 03 2020 CE .

Lec. Title : Biochemistry & Metabolism Of Cardiac Muscle .

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If you come by any mistake , please kindly report it to shaghafbatch@gmail.com

Biochemistry and metabolism of cardiac muscle

CVS – Biochemistry (1)
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Sources of ATP

- Stored in muscle cell (limited)
- Synthesized from macronutrients

Common Processes for ATP production:

Anaerobic System

a. ATP–CP system (phosphogen system)

b. Anaerobic glycolysis (lactic acid system)

Aerobic System

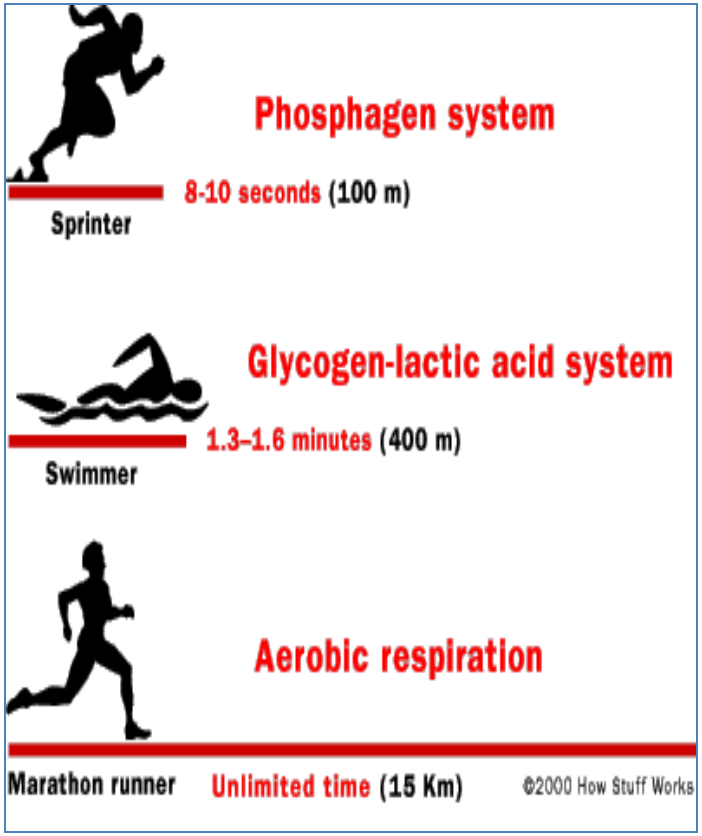
a. Aerobic glycolysis

b. Fatty acid oxidation

c. TCA Cycle

"The production of ATP is never achieved by the exclusive use of one energy system, but rather by the coordinated response of all energy systems contributing to different degrees".

Which pathway your clients use for the primary production of ATP depends on how quickly they need it and how much of it they need.



(record)

***There are different sources of ATP in human system:**

1- stored in muscle cell (limited) : ATP amount here is limited and low

2- synthesized from macronutrients like proteins, fatty acids, glucagon….

***In general there are common processes for ATP production " classified depend on requirement of O2 "**

1- anaerobic system (doesn't need O2)

e.g. A. ATP-CP system (phosphagen system)

b. Anaerobic glycolysis (lactic acid system)

note : anaerobic system produce low amount of energy

2- aerobic system (need O2)

- A. Aerobic glycolysis
- b. Fatty acid oxidation
- c. TCA Cycle

(record about this figure)

- Human system will use pathway of ATP production depend on action or how quickly you need ATP and how much you need.

e.g. 1) we use phosphagen system when we need immediate source of ATP like when you are running suddenly for (8-10)S approximately less than 10m phosphagen system will be ready to provide you immediate ATP .

2) If we need more intense type of energy like when you are swimming for (1.3-1.6) for 400m your body will turn on glycogen-lactic acid system

Cont..

3) If you are marathon runner you are running for along time about 15 Km so, you will need huge amount of energy, so your body will turn on aerobic system to produce huge amount of ATP.

نفس الحكي وكِذا

- Since our muscles don't store much ATP, we must constantly resynthesize it. Depends on how quickly they need it and how much of it they need. Lifting heavy weights, for instance, requires energy much more quickly than jogging on the treadmill, necessitating the reliance on different energy systems. However, the production of ATP is never achieved by the exclusive use of one energy system, but rather by the coordinated response of all energy systems contributing to different degrees.

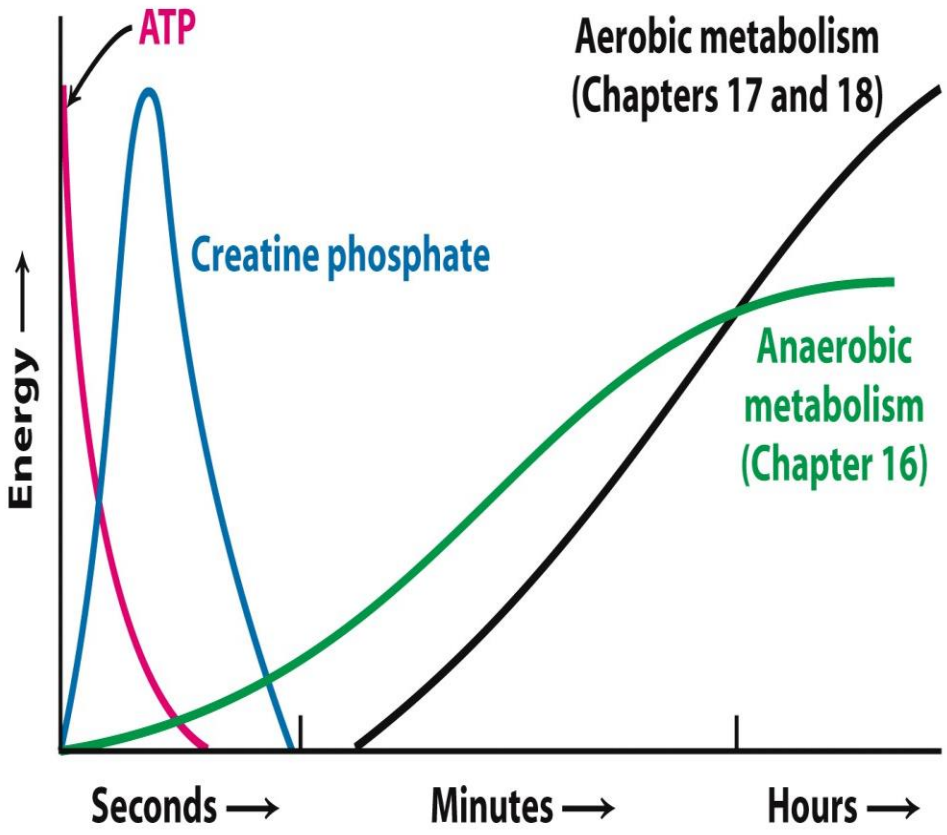


Figure 15.7
Biochemistry, Seventh Edition

Sources of ATP

- The primary sources of energy are lactate and glucose for fetal heart, **fatty acids** comprise 60% to 80% of the energy source in adult heart to run the contractile machinery and ion pumps to maintain rhythmic beating and integrity of the myocardium.

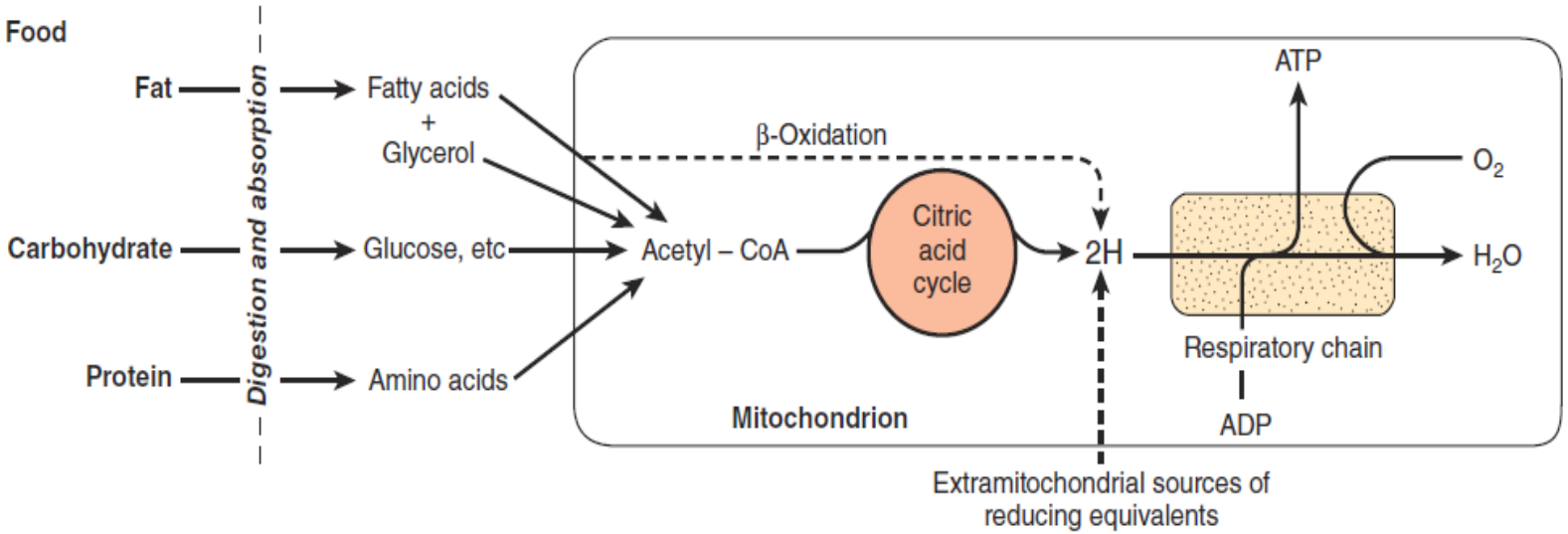


FIGURE 13–2 **Role of the respiratory chain of mitochondria in the conversion of food energy to ATP.** Oxidation of the major foodstuffs leads to the generation of reducing equivalents (2H) that are collected by the respiratory chain for oxidation and coupled generation of ATP.

(record ‘’ about previous slide and figure 13-2’’)

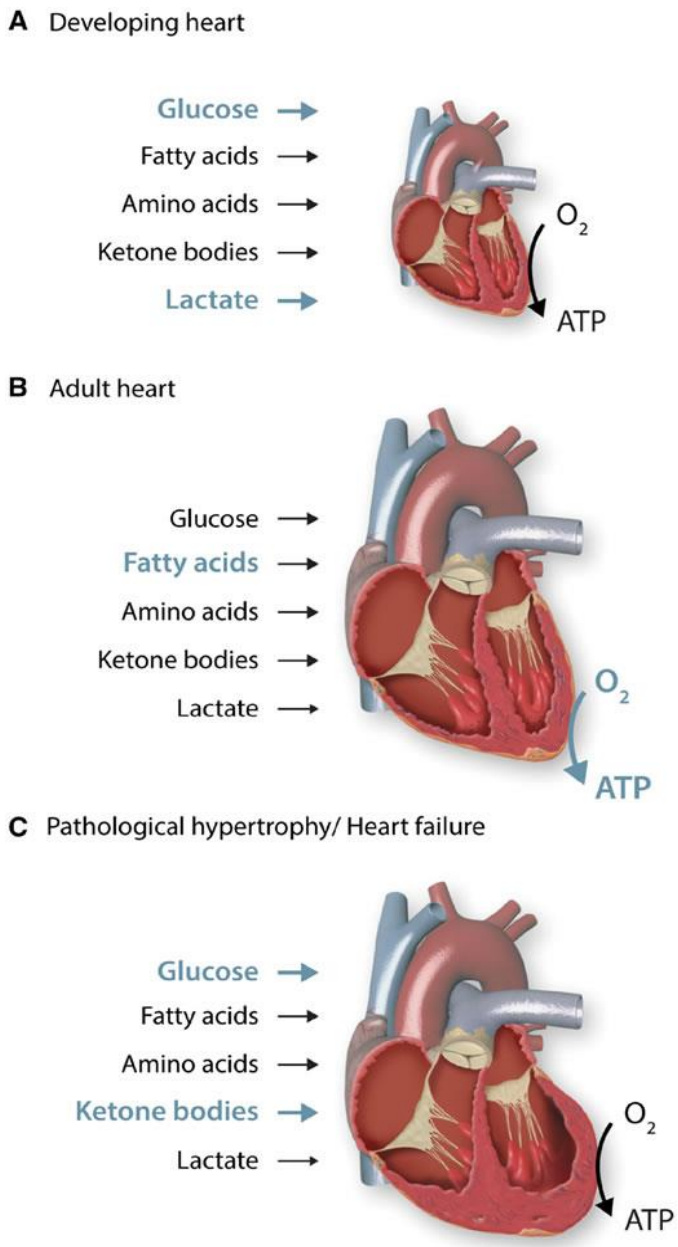
- Sources of ATP are different according to the stage of human life for example in fetal heart the primary sources of energy are lactate and glucose whereas in adult heart depend mainly in fatty acid to run the contractile machinery and ion pumps to maintain rhythmic beating and integrity of the myocardium.
- About figure :

Food have different type of macromolecules like fat , proteins carbohydrate , all of these macromolecules will be digested and absorbed and break down to their primary units , and these unites in certain mechanism will convert to acetyl CoA which will enter to citric acid cycle and this cycle will produce hydrogen carrier which will go to ETC to produce ATP from ADP and we will have h2o as byproduct .

* In some cases like beta oxidation directly produce hydrogen carrier that will go to cellular respiration so, this machinery doesn't undergo to citric acid cycle it is independent machinery.

Heart and ATP Facts

- Heart consumes more energy than any other organ.
- Heart cycles ~ 6 kg of ATP each day, which is about 20-30 times its own weight.
- Mitochondrial respiration produces > 90% of energy.
- Mitochondria occupy ~30% of cardiomyocyte space.
- > 95% of ATP formation comes from oxidative phosphorylation in mitochondria.
- **Under basal aerobic conditions, <u>60%</u> of energy comes from <u>FFA</u> and <u>triglycerides</u>, <u>35%</u> from <u>carbohydrates</u>, <u>5%</u> from <u>amino acids</u> an <u>ketone bodies</u>.**
- Energy supplied to the myocardium is used for mechanical activity such as *contraction* (65%) and *relaxation* (15%) and for *electrical activity* (5%), the rest is spend on other cellular function (20%).

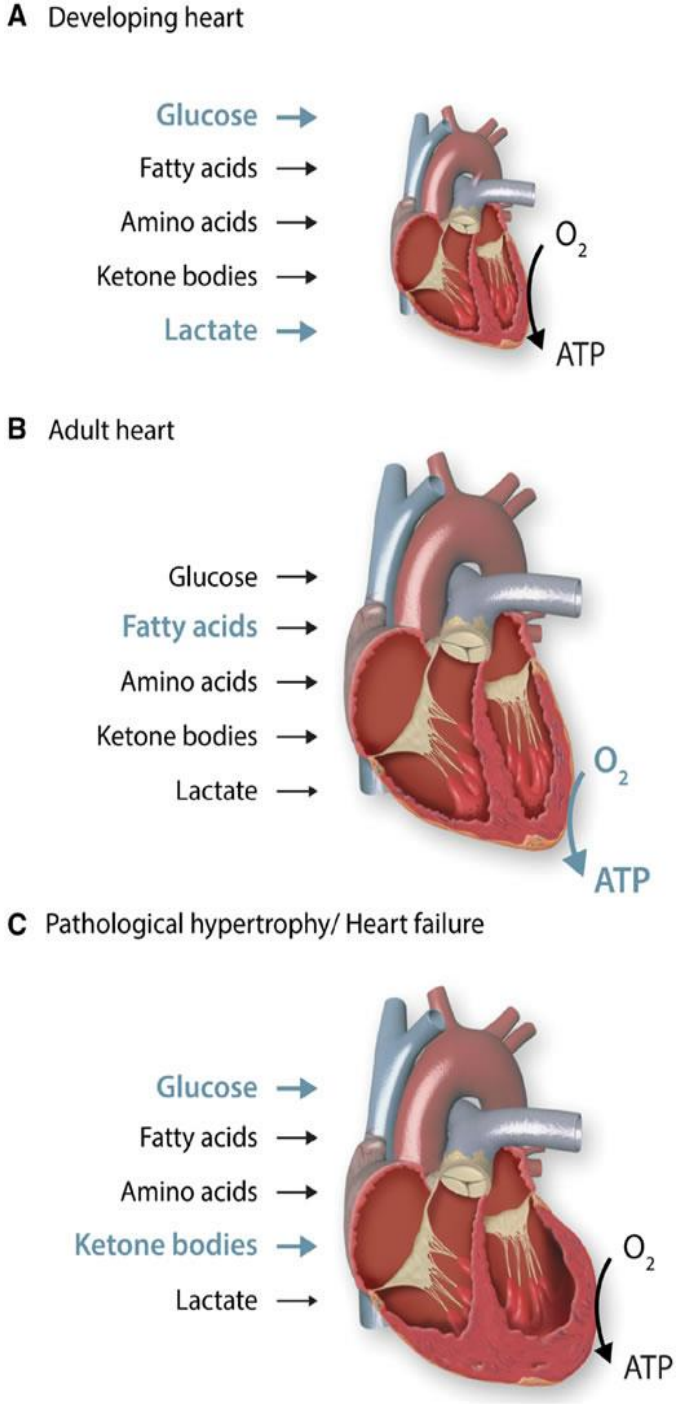


(record)

There are many facts about ATP in heart , they are special and unique:

- Heart consumes more energy than any other organ.
- Heart cycles ~ 6 kg of ATP each day, which is about 20-30 times its own weight.
- Mitochondrial respiration produces > 90% of energy.(produce most of ATP)
- Mitochondria occupy ~30% of cardiomyocyte space.
- > 95% of ATP formation comes from oxidative phosphorylation in mitochondria.
- **Under basal aerobic conditions, 60% of energy comes from FFA and triglycerides, 35% from carbohydrates, 5% from amino acids an ketone bodies.**

- Cont …
- As we talked previously there are different sources of ATP depend on development stage and condition of heart like in fetal stage (glucose and lactate) , in adult (fatty acid) and in pathological hypertrophy / heart failure the primary sources of energy are glucose and ketone bodies



SEVERAL mechanisms replenish store of ATP in muscles

(1) Glycolysis, using blood glucose or muscle glycogen

(2) Oxidative phosphorylation

(3) Creatine phosphate

(4) from two molecules of ADP in a reaction catalyzed by adenylyl kinase (Figure 49–16).

ATP Sources

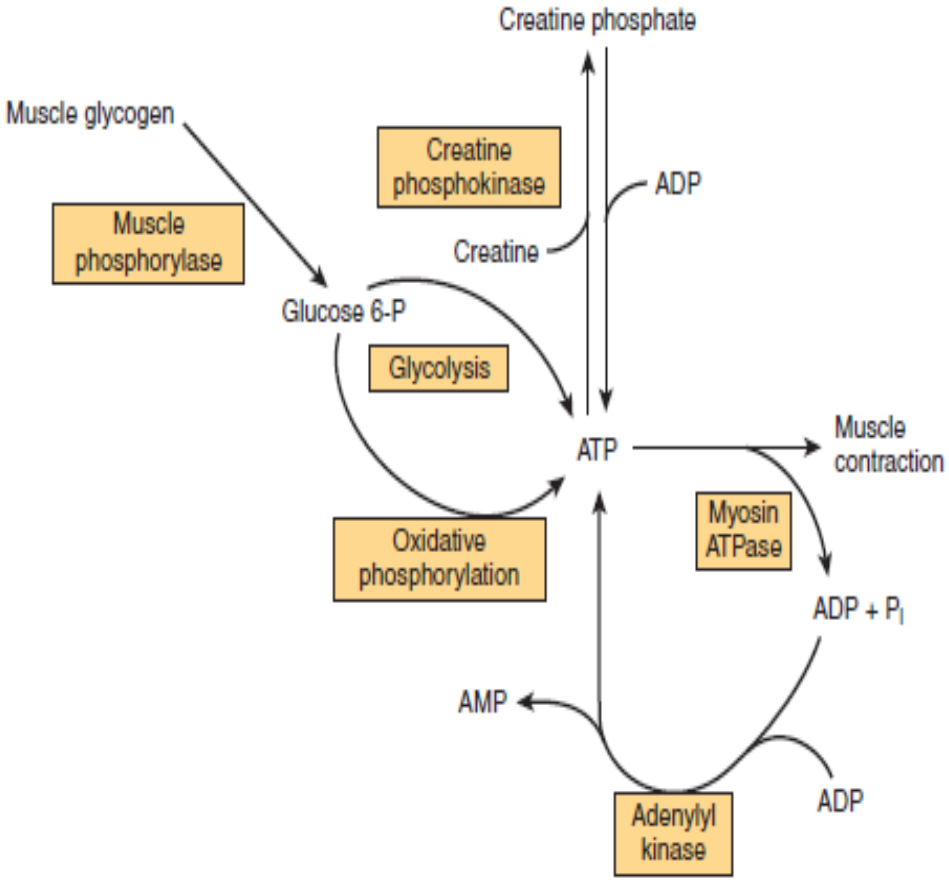


FIGURE 49–16 The multiple sources of ATP in muscle.

ATP–CP system (phosphogen system)

1. A high energy phosphoric ester that serves as a reservoir of phosphate-bond energy.
2. This system is used for durations of up to 10 seconds. The ATP–CP system neither uses oxygen nor produces lactic acid if oxygen is unavailable and is thus said to be alactic anaerobic. This is the primary system behind very short, powerful movements like a golf swing, a 100 m sprint or powerlifting.
3. Two type of phosphogen system

   A. Phosphocreatine in vertebrates (skeletal muscle, heart, spermatozoa, and brain)

   B. Phosphoarginine in invertebrates (muscle).

(record)

- **ATP–CP system (phosphogen system) :** is ATP production system , body use it when body need immediate ATP production and it is A high
  energy phosphoric ester that serves as a reservoir of phosphate-bond energy.
- There are two types of phosphogen pathway depending on amino acid which is present :

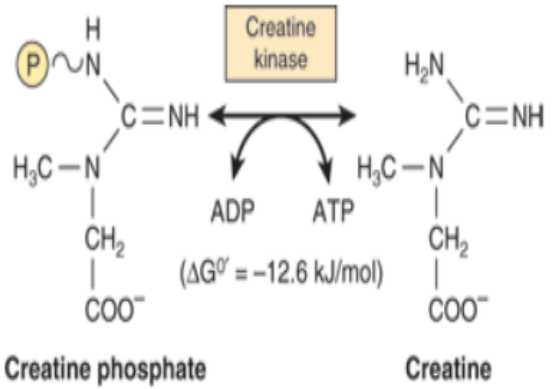
A. Phosphocreatine in vertebrates (skeletal muscle, heart, spermatozoa, and brain)

B. Phosphoarginine in invertebrates (muscle).

ATP–CP system (phosphogen system)

1. The human body need too much ATP, but too much ATP will prevent the TCA cycle and glycolysis.
2. Preventing TCA cycle and glycolysis from turning off (keeps them on).
3. Keep ATP production maximal.
4. Extra phosphate is stored in creatine.
5. Heavily exercise we don't need these process to turn off.

Figure 11–7.



Source: Murray RK, Bender DA, Botham KM, Kennelly PJ, Rodwell VW, Weil PA: *Harper's Illustrated Biochemistry, 28th Edition:* http://www.accessmedicine.com

Transfer of high-energy phosphate between ATP and creatine.

$$\text{Creatine phosphate} + H_2O \rightarrow \text{Creatine} + Pi \qquad \Delta G^{o\prime} = -43.3 \frac{kj}{mol}$$

$$ADP + P_i \rightarrow ATP + H_2O \qquad \Delta G^{o\prime} = 30.5 \frac{kj}{mol}$$

$$\text{Creatine phosphate} + ADP \rightarrow \text{Creatine} + ATP \qquad \Delta G^{o\prime} = -12.8 \frac{kj}{mol}$$

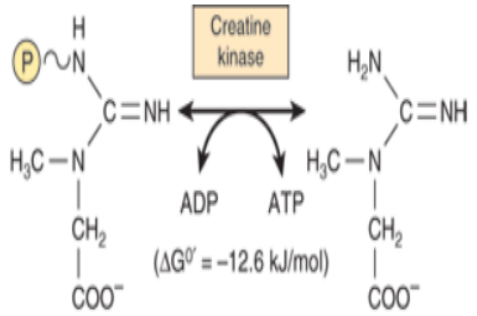
(RECORD)

*Creatine phosphate stored in muscles , creatine kinase removes Phosphate group from CP and transfer it to ADP to form ATP.

Note : from one molecule of creatine phosphate we can produce about 12.6 KJ/mol.

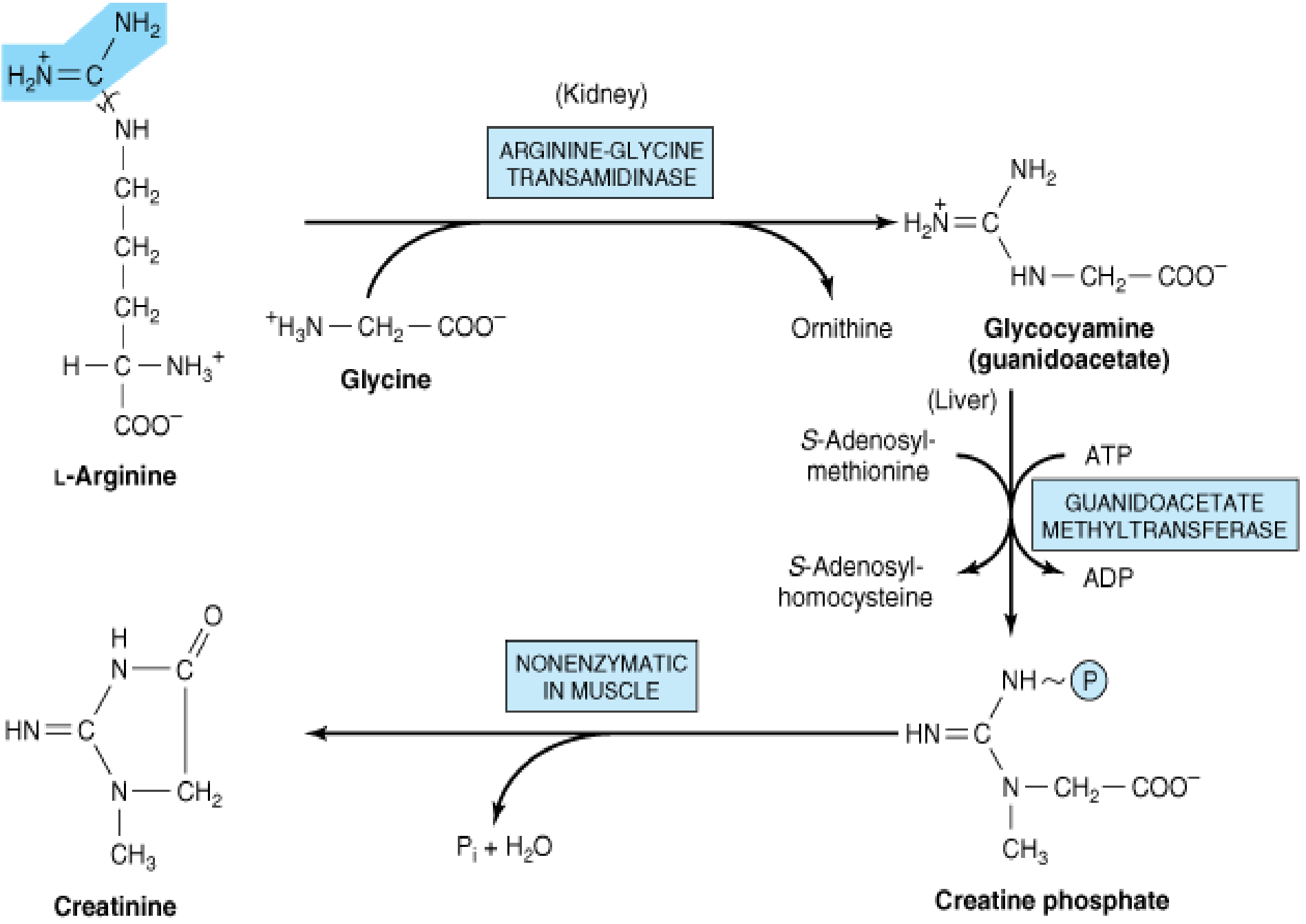
*there is what we called feedback or negative feedback that means your body when it has too much of ATP or free ATP that will inhibit classified pathway (TCA, glycolysis) from produce ATP, so body will depend in non classical pathway like phosphogen that will keep ATP production maximal .

Figure 11–7.



Transfer of high-energy phosphate between ATP and creatine.

Creatine phosphate	-43.1	-10.3
ATP → AMP + PP_i	-32.2	-7.7
ATP → ADP + P_i	-30.5	-7.3


(Kidney)
ARGININE-GLYCINE TRANSAMIDINASE
Glycine
Ornithine
Glycocyamine (guanidoacetate)
L-Arginine
(Liver)
S-Adenosyl-methionine
ATP
GUANIDOACETATE METHYLTRANSFERASE
S-Adenosyl-homocysteine
ADP
NONENZYMATIC IN MUSCLE
Creatinine
Creatine phosphate
Pi + H2O

(record ‘’ about figure ‘’)

- Creatinine can be synthesized produce from 2 main amino acids : L- Arginine , Glycine , in kidney there is starting synthesize of creatinine from them and then Arginine Glycine TRANSAMIDINASE enzyme will produce intermediate molecule then will produce creatine phosphate(CP) , CP will convert to creatinine by non enzymatic reaction in muscle .

* CP: system involve in storage and transmission of phosphate bond energy m and we said creatinine is synthesized in liver and can produce in pancreas also and it stores in muscles and brain.

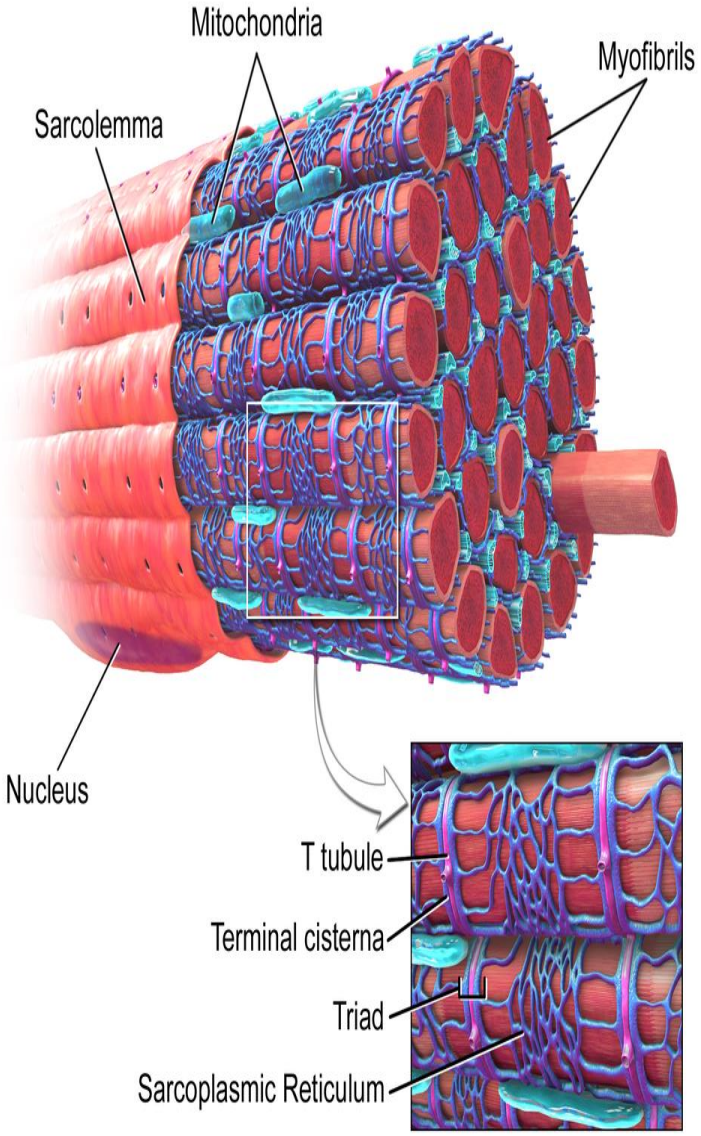
Creatine Phosphate Shuttle
"It is fast transport process"

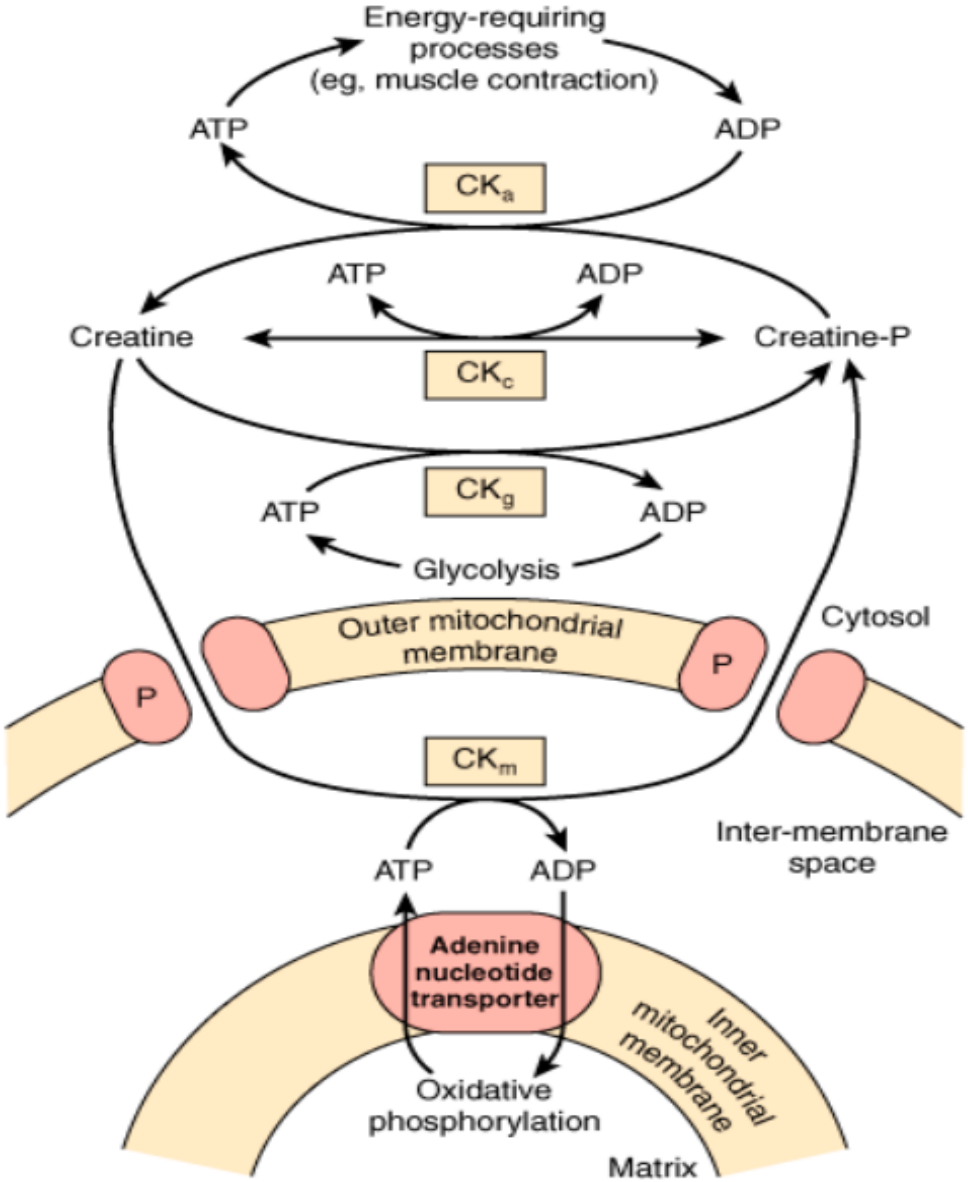
The **creatine phosphate shuttle** is an intracellular energy shuttle which facilitates transport of high energy phosphate from muscle cell mitochondria to myofibrils.

In mitochondria, ATP levels are very high as a result of glycolysis, TCA cycle and oxidative phosphorylation processes, whereas creatine phosphate levels are low.

This makes conversion of creatine to P-creatine a highly favored reaction. As a result the P- creatine become a very-high-energy compound, and then diffuses from mitochondria to myofibrils.

In myofibrils, during exercise (contraction) ADP levels are very high, which favors resynthesis of ATP. Thus phosphocreatine breakdown to creatine giving its inorganic phosphate for ATP formation.





The creatine phosphate shuttle of heart and skeletal muscle. The shuttle allows rapid transport of high-energy phosphate from the mitochondrial matrix into the cytosol. (CK_a , creatine kinase concerned with large requirements for ATP, eg, muscular contraction; CK_c , creatine kinase for maintaining equilibrium between creatine and creatine phosphate and ATP/ADP; CK_g , creatine kinase coupling glycolysis to creatine phosphate synthesis; CK_m , mitochondrial creatine kinase mediating creatine phosphate production from ATP formed in oxidative phosphorylation; P, pore protein in outer mitochondrial membrane.)

(record ‘’ about figure”)

*Creatine phosphate shuttle it is rapid transport process of high energy phosphate from mitochondrial matrix into the cytosol.

*In beginning oxidative phosphorylation occurs in mitochondria and then ADENASE NUCLEOTIDE TRANSPORTER will transfer ATP from matrix to inner then P will join with creatine and CP system.

*CK_m will carry high energy phosphate from inner to cystol where part of it “P” will join with Creatine and form another shuttle system which called Cka which will degradate CP and give us P and store high energy P and use ATP in different body process like muscle contraction.

In some vertebrates, arginine phosphate plays a similar role as **creatine phosphate shuttle.**

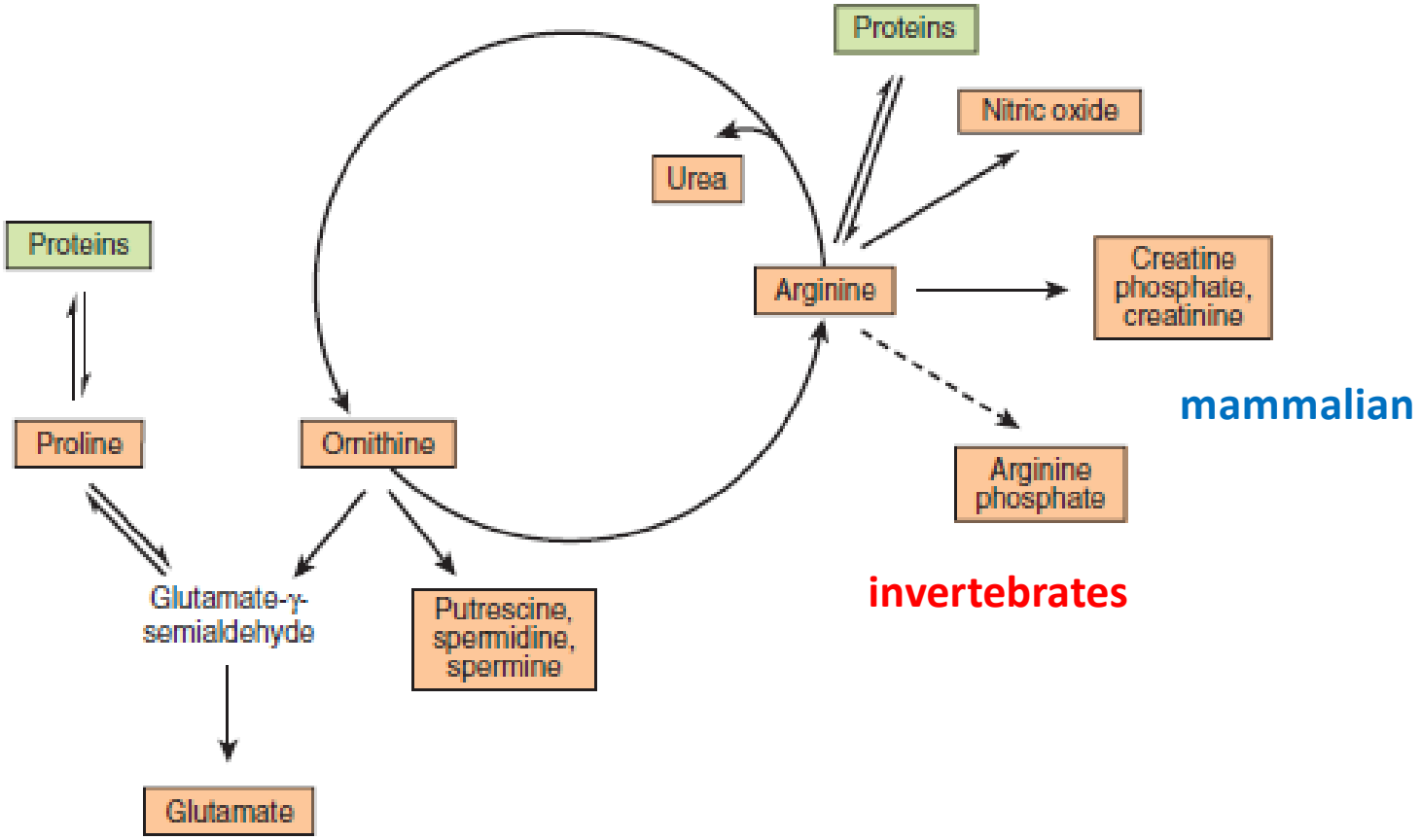


FIGURE 30–1 Arginine, ornithine, and proline metabolism. Reactions with solid arrows all occur in mammalian tissues. Putrescine and spermine synthesis occurs in both mammals and bacteria. Arginine phosphate of invertebrate muscle functions as a phosphagen analogous to creatine phosphate of mammalian muscle.

(record) “ arginine shuttle “

*Arginine can convert to many molecules for example use to build proteins , can convert to NO by NO synthase enzyme and to CP and creatinine .

In invertebrate will convert to arginine shuttle system “ arginine phosphate” which is alternative to creatine phosphate shuttle system .

* Also it can give omithine which is a major amino acid that used in spermidine fot produce energy.

Lactate Metabolism

- Under anaerobic condition (ischemia) pyruvate is converted to lactic acid – **nonoxidative glycolysis.**

- Lactate is released in the blood stream through specific transporter.

During starvation, lactate can be recycled to pyruvate.

- NAD^+ is reduced to NADH.
- Pyruvate is then burned aerobically in the TCA.

(RECORD)

*lactate Metabolism:

* It is very famous pathway and it doesn’t need O2 “ anaerobic , non oxidative glycolysis, it involves conversion of pyruvate to lactate acid , Lactate is released in the blood stream through specific transporter.

- It can occur under ischemia condition and starvation .

*note : lactate acid can cause acidosis , so in starvation person can have acidosis so we doesn’t depend on lactate metabolism for long time.

Carbohydrate Metabolism Occurs mainly in mitochondria

Glycolytic substrate is derived from exogenous glucose and glycogen stores.

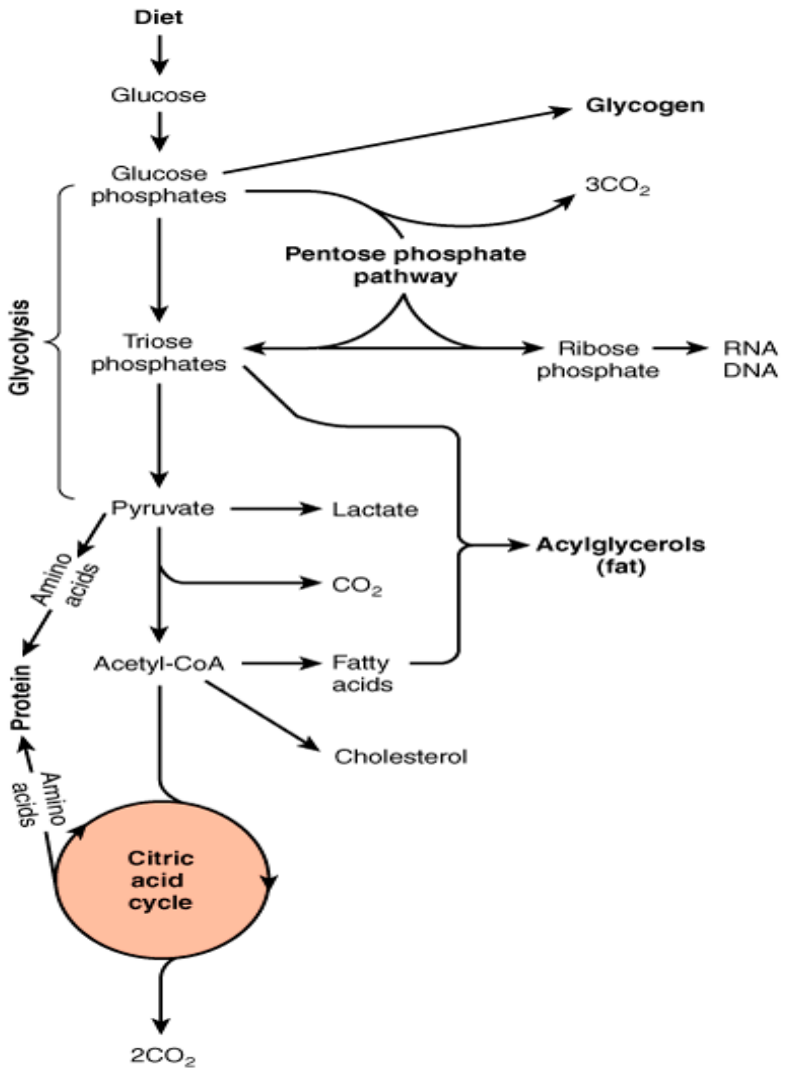
- Glycogen pool in the heart is relatively small (~30 μmol/g wet wt compared with ~150 μmol/g wet wt in skeletal muscles).

- Glucose transport into cardiomyocyte is regulated by transmembrane glucose gradient and the content of glucose transporter in the sarcolema – GLUT-4 (lesser extent GLUT-1).

Carbohydrate Metabolism

- In the mitochondria pyruvate is:
  - dexarboxylated and oxidized into **acetyl CoA** by *pyruvate dehydrogenase (PDH)" major enzyme that produce energy"*
  - or carboxylated into **oxalacetate** by *pyruvate carboxylase.*
  - or reducted to lactate.
- **The control of PDH activity is an essential part of overall control of glucose metabolism**."» مهم
- PDH – mitochondrial multicomplex, activity is controlled by work, substrate and hormones.

Carbohydrate Metabolism



By glycolysis process will give G6P and then Triose phosphate then pyruvate then Acetyl CoA which will enter citric acid cycle to produce ATPs

FIGURE 14–2 **Overview of carbohydrate metabolism showing the major pathways and end products.** Gluconeogenesis is not shown.

Source of long-chain fatty acids:

A. dietary lipid

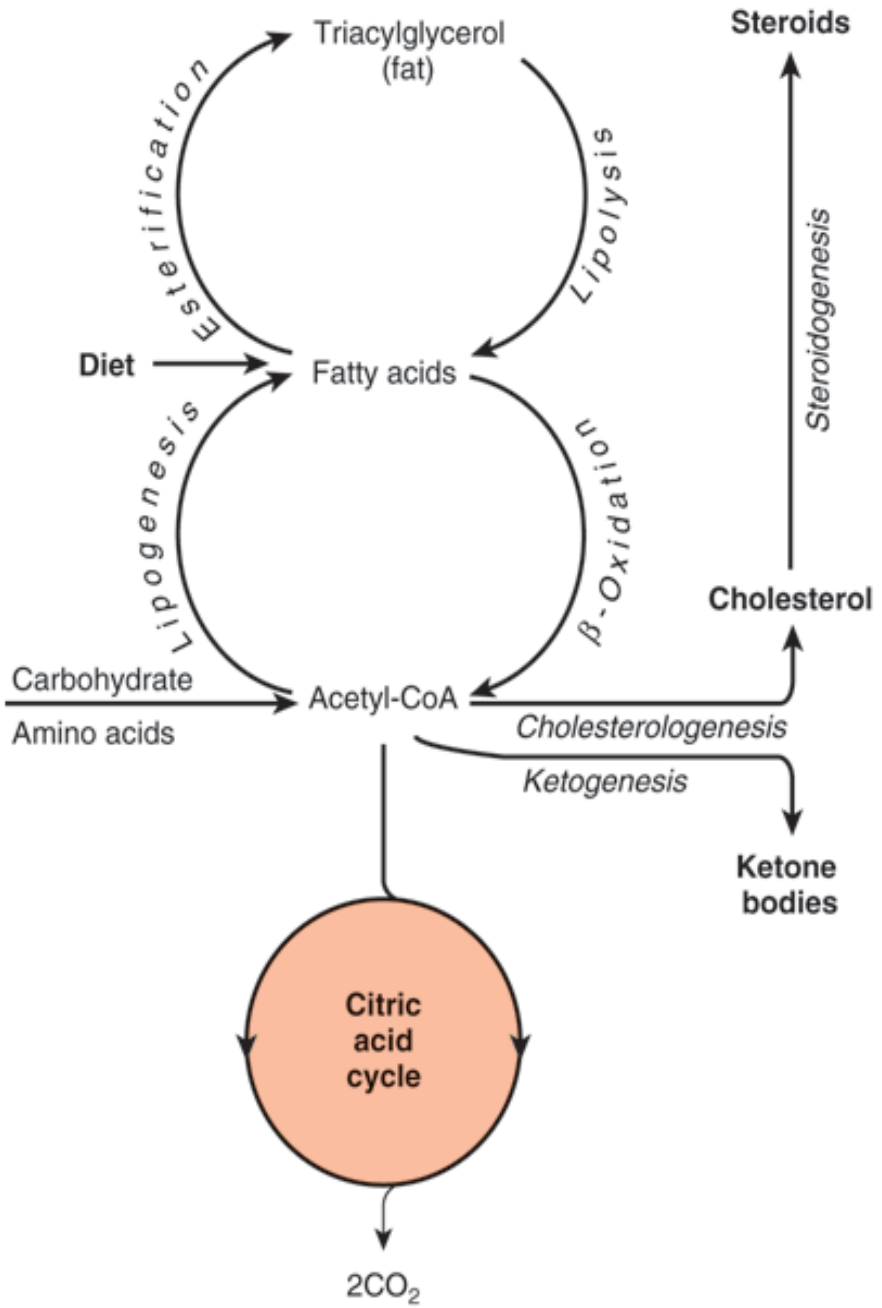
B. *de novo* synthesis from acetyl-CoA derived from carbohydrate or amino acids.

Fatty acids may be:

A. oxidized to acetyl-CoA (β-oxidation) or esterified with glycerol, forming triacylglycerol (fat) as the body's main fuel reserve.

Acetyl-CoA formed by β-oxidation may undergo three fates:

1. Oxidized to CO_2 + H_2O *via* the citric acid cycle.
2. Precursor for synthesis of cholesterol and other steroids.
3. In the liver, it is used to form ketone bodies (acetoacetate and 3-hydroxybutyrate) that are important fuels in prolonged fasting.



(RECORD)

- We will talk about degradation of fatty acid mainly long fatty acid chain , in general we know that diet contain FA these FA (fatty acid) have two fates mainly :

1) Undergo beta oxidation which form acetyl CoA which will go to citric acid cycle to produce energy " there are other fates of acetyl CoA we will talk about it .
2) Estrifigation which will form triacylgcerol " 3fatty acids + glycerol "

CONT…

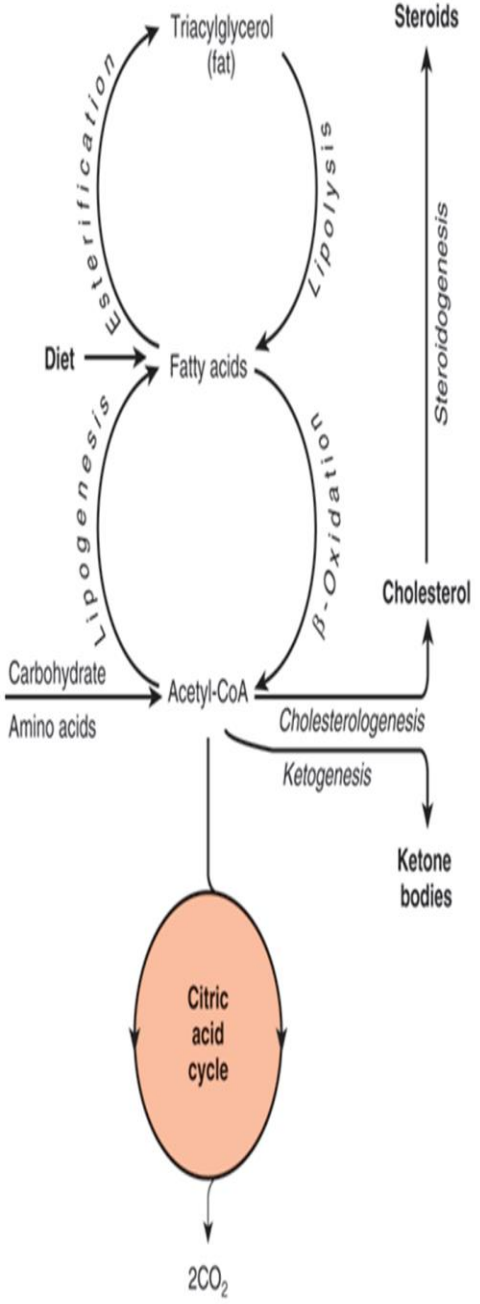
Acetyl-CoA formed by β-oxidation may undergo three fates:

1) Oxidized to CO_2 + H_2O *via* the citric acid cycle to produce energy .
2) Precursor for synthesis of cholesterol and other steroids which will give different hormones.
3) In the liver, it is used to form ketone bodies (acetoacetate and 3-hydroxybutyrate) by ketogenesis that are important fuels in prolonged fasting.

*note :

There is common intermediate between degradation of FA ,A.A and carbohydrate to produce energy which is Acetyl CoA which will go to citric acid cycle to produce energy

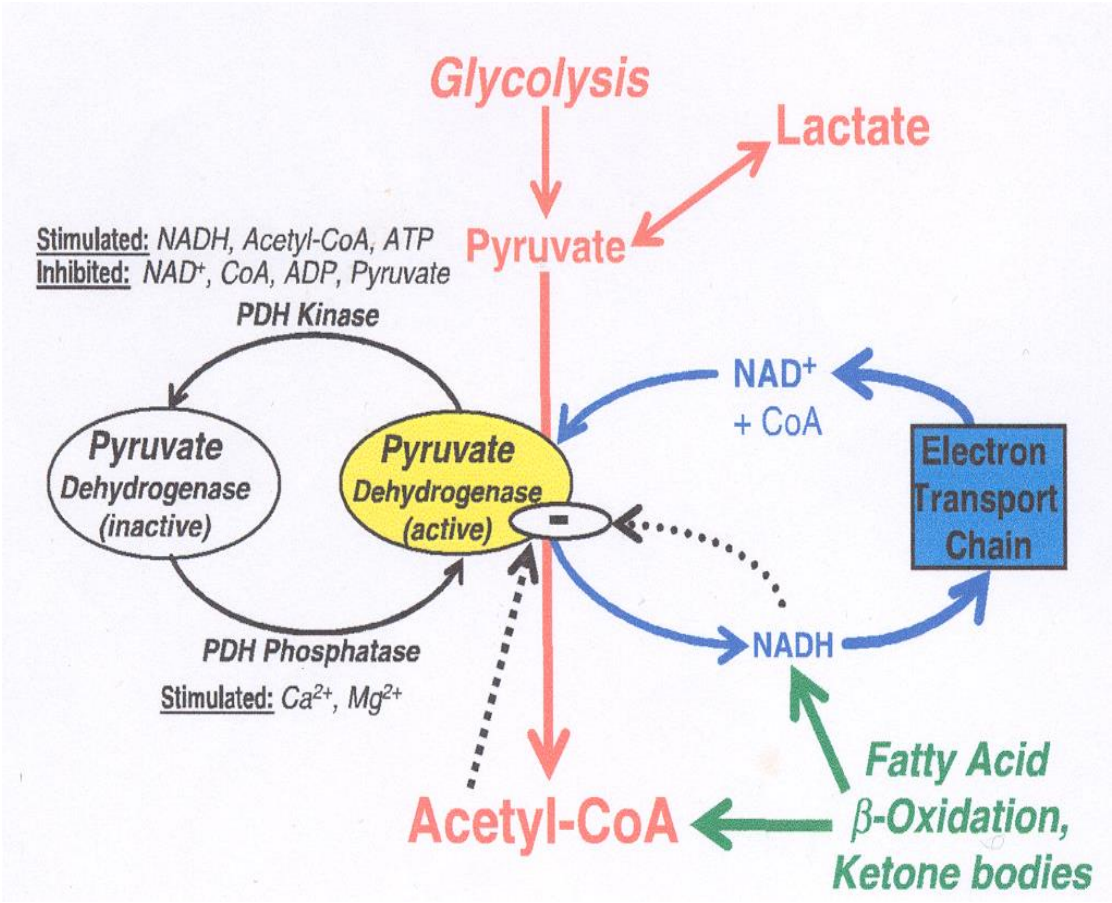
مية مرة حكيناها بعرف

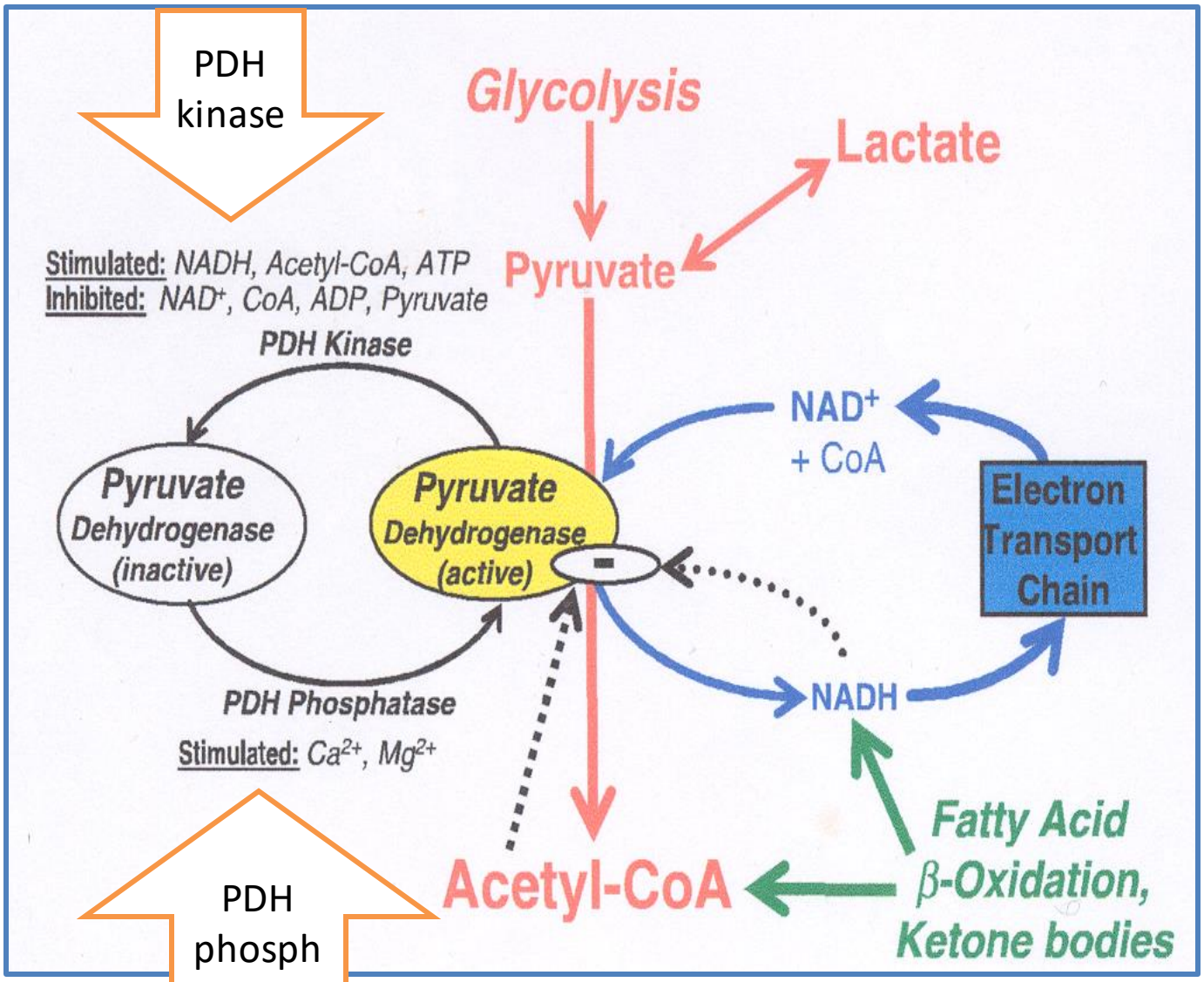


Interregulation of fatty acid and carbohydrate oxidation

مهم كثير « ركزوا على متى بصيرله
Inhibition or stimulation
لكل انزيم

- The 1º physiological regulator of flux through PDH and the rate of glucose oxidation in the heart is fatty acid oxidation.
- **PDH activity is inhibited by high rate of FA oxidation** *via* an increase in mitochondrial acetyl-CoA/free CoA and NADH/NAD^+ which activates PDH kinase.



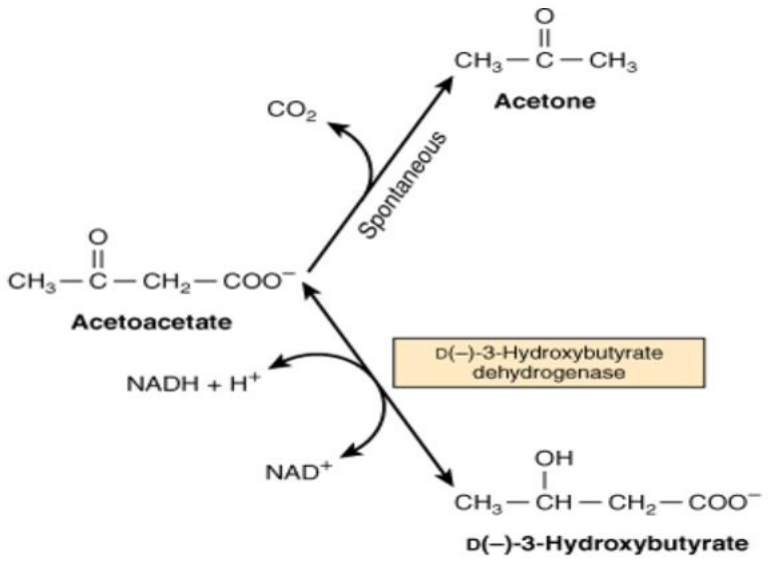


So , pyruvate also is regulated by glycolysis

Ketone Body Metabolism

- During **starvation** or poorly controlled **diabetes** the heart extracts and oxidizes **ketone bodies** (β-hydroxybutyrate and acetoacetate).
- Low insulin and high fatty acids then↑ ketone bodies.
- ***Ketone bodies become a major substrate for myocardium***.
- *Ketone bodies inhibit **PDH** (inhibition of glucose oxidation) and fatty acid β-oxidation.*

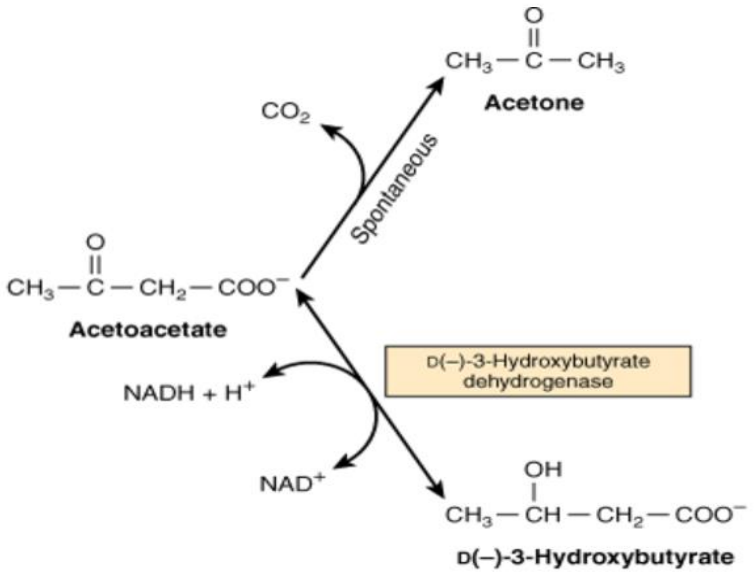
KETOGENESIS OCCURS WHEN THERE IS A HIGH RATE OF FATTY ACID OXIDATION IN THE LIVER



- Ketone bodies are very important specially for person with poor control diabetic or for who suffer from starvation case .
- In general body will have low insulin and high fatty acid which will produce ketone bodies
- ***Ketone bodies become a major substrate for myocardium***.
- Body become dependent on FA to produce energy not glucose , that will make Ketone bodies

* فالأشخاص الي بكونوا ديابيتيك وكذا حيصيروا نحيفين لانه جسمهم حيستهلك الدهون مش الغلوكوز فبكون في حرق دهون مستمر بأجسامهم ونتيجة هذا الحرق رح ينتج الكيتونز

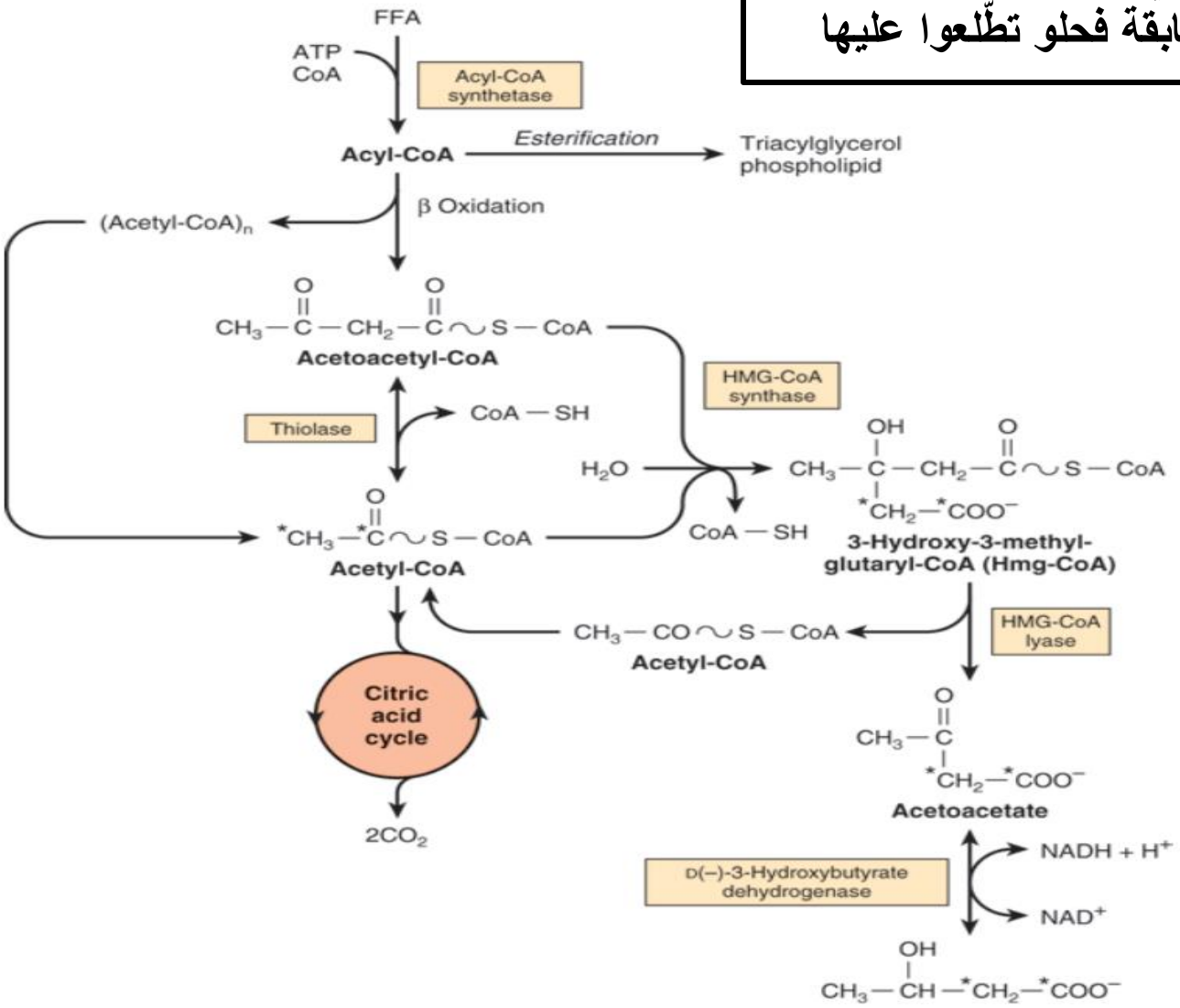
Acetoacetate can give acetone or 3-hy.. Which are Keton bodies

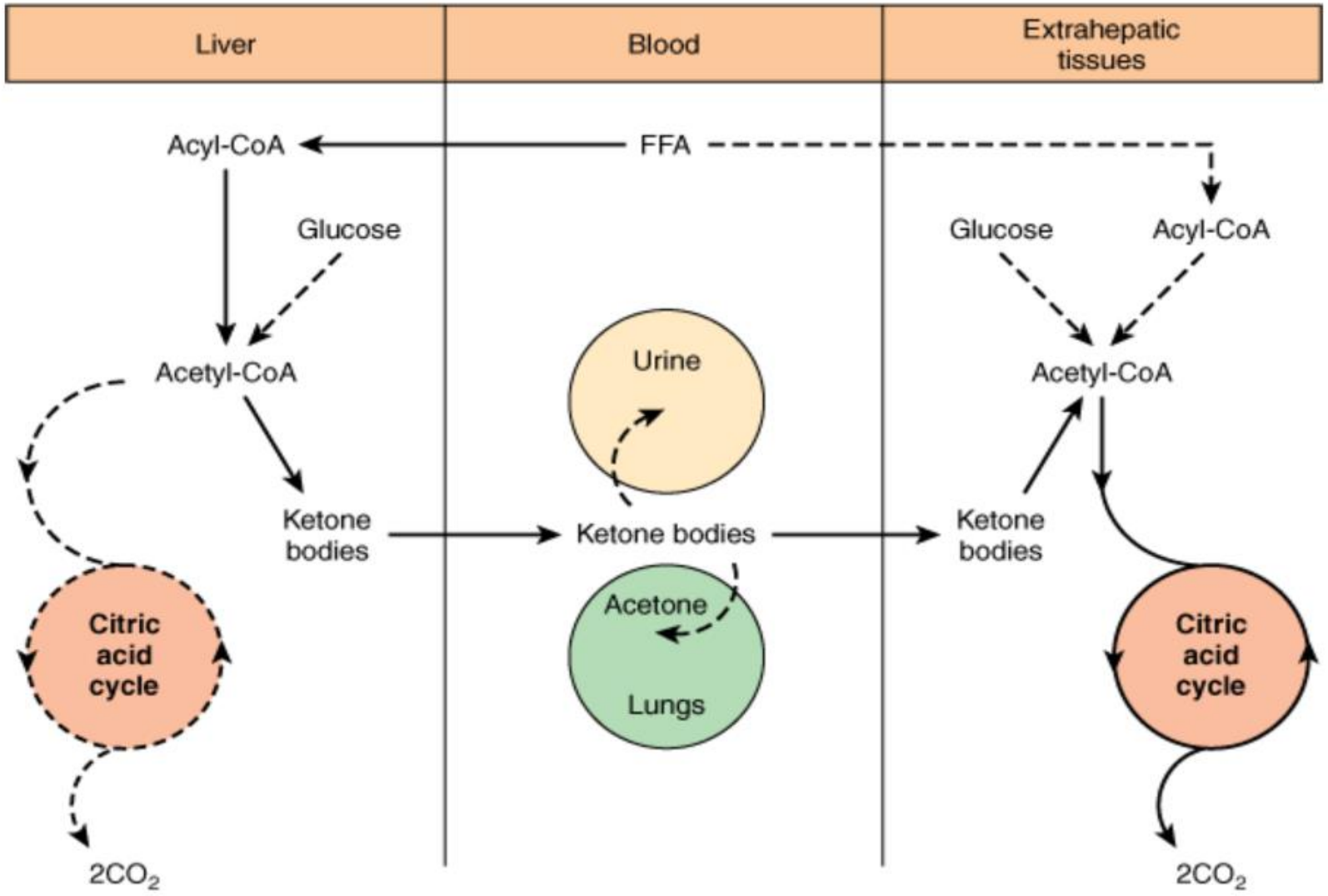


(cont..)

* Ketone bodies are acidic chemical enzyme , for example in diabetic person this can cause diabetic keto acidosis so blood will be acidic environment and smell will be fruity like acetone smell.

ما حكى عنها اشي اعتقد انها تلخيص لكل التفاعلات السابقة فحلو تطّلعوا عليها





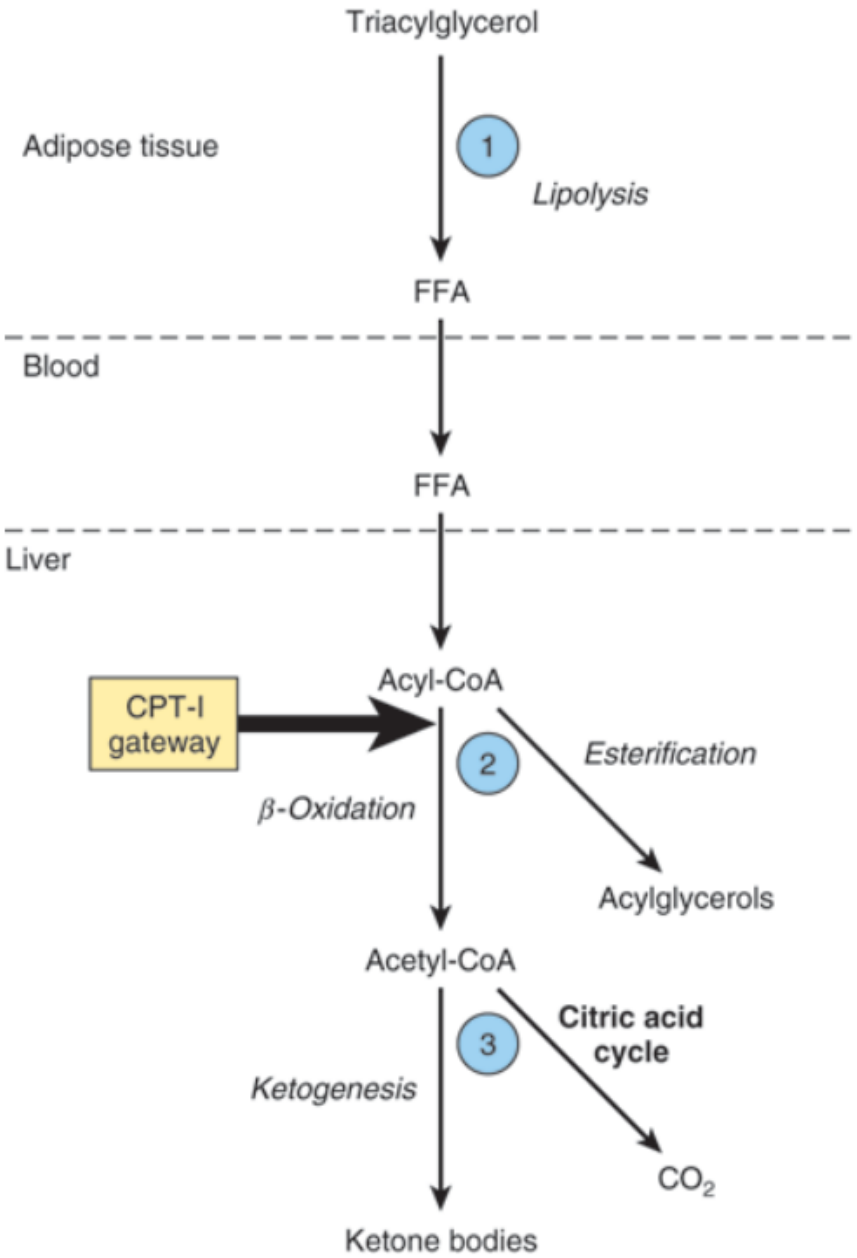
Source: Murray RK, Bender DA, Botham KM, Kennelly PJ, Rodwell VW, Weil PA: *Harper's Illustrated Biochemistry, 28th Edition:* http://www.accessmedicine.com

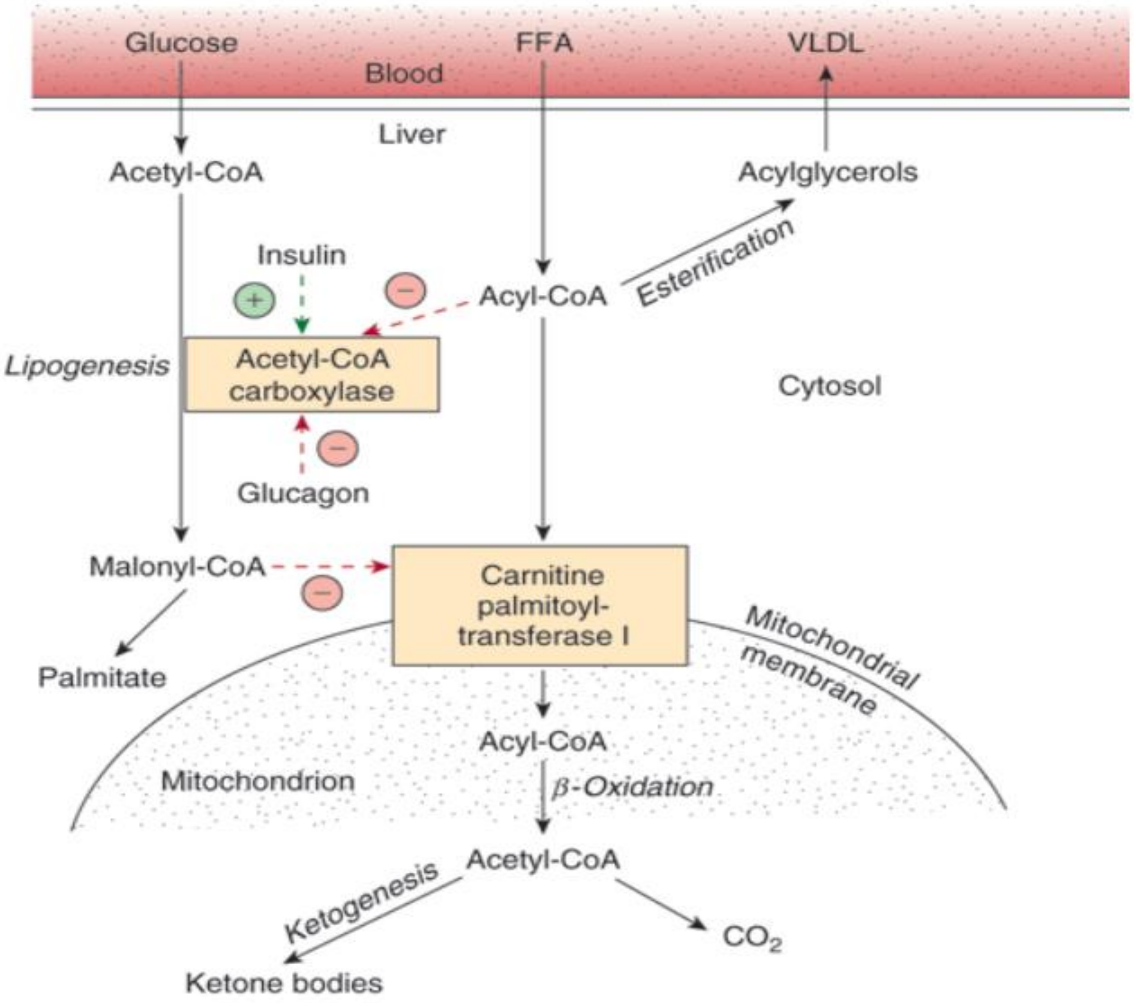
Formation, utilization, and excretion of ketone bodies. (The main pathway is indicated by the solid arrows.)

- (RECORD “ about figure “)

*FFA in blood will transfer to liver and give Acyl-CoA which will convert Acetyl CoA and produce ketone bodies which will go to circulation and increase acidity of it , acetone can go to lung and make fruity breath , then ketone bodies will be excreted by kidney through urine and some of ketone bodies will produce Acetyl CoA in extrahepatic tissue which will enter citric acid cycle to produce energy.

KETOGENESIS IS REGULATED AT THREE CRUCIAL STEPS




Glucose
Blood
FFA
VLDL
Liver
Acetyl-CoA
Acylglycerols
Insulin
Acyl-CoA
Esterification
Lipogenesis
Acetyl-CoA carboxylase
Cytosol
Glucagon
Malonyl-CoA
Carnitine palmitoyl-transferase I
Mitochondrial membrane
Palmitate
Acyl-CoA
Mitochondrion
β-Oxidation
Acetyl-CoA
Ketogenesis
CO2
Ketone bodies

Some Aspects of Myocardial Biochemistry of Heart Failure

- Heart failure reduces the capacity to transduce the energy from food stuff into ATP.

- In the advanced stage of HF ⇨
  - Down regulation in FA oxidation;
  - Increased glycolysis and glucose oxidation;
  - Reduced respiratory chain activity.

Cardiac Muscle and Ischemia

- Coronary artery occlusion → ischemia → significant change in cell structure, chemistry and function:
  - Loss of contractile function
  - Arrhythmias
  - Cell death

- The decrease of the ATP / ADP, the accumulation of AMP, inorganic phosphate, metabolic products are removed (lactate).

- The rapid decline in creatine phosphate - creatine kinase reaction is only short-term mechanism to compensate for reduced ATP production in mitochondria.

Cardiac Muscle and Ischemia

- **Mild ischemia:**
- Reduces the concentration of ATP and creatine phosphate, increases the level of inorganic phosphate → activation of glycolysis (glucose needed from the bloodstream into the heart cells) → increase in the concentration of pyruvate → conversion by LDH to lactate.

- **Prolonged ischemia :**
- The accumulation of substrates (lactate, NADH and H^+) → inhibition of glycolysis at the level of *phosphofructokinase* and *glyceraldehyde-3-dehydrogenase*.

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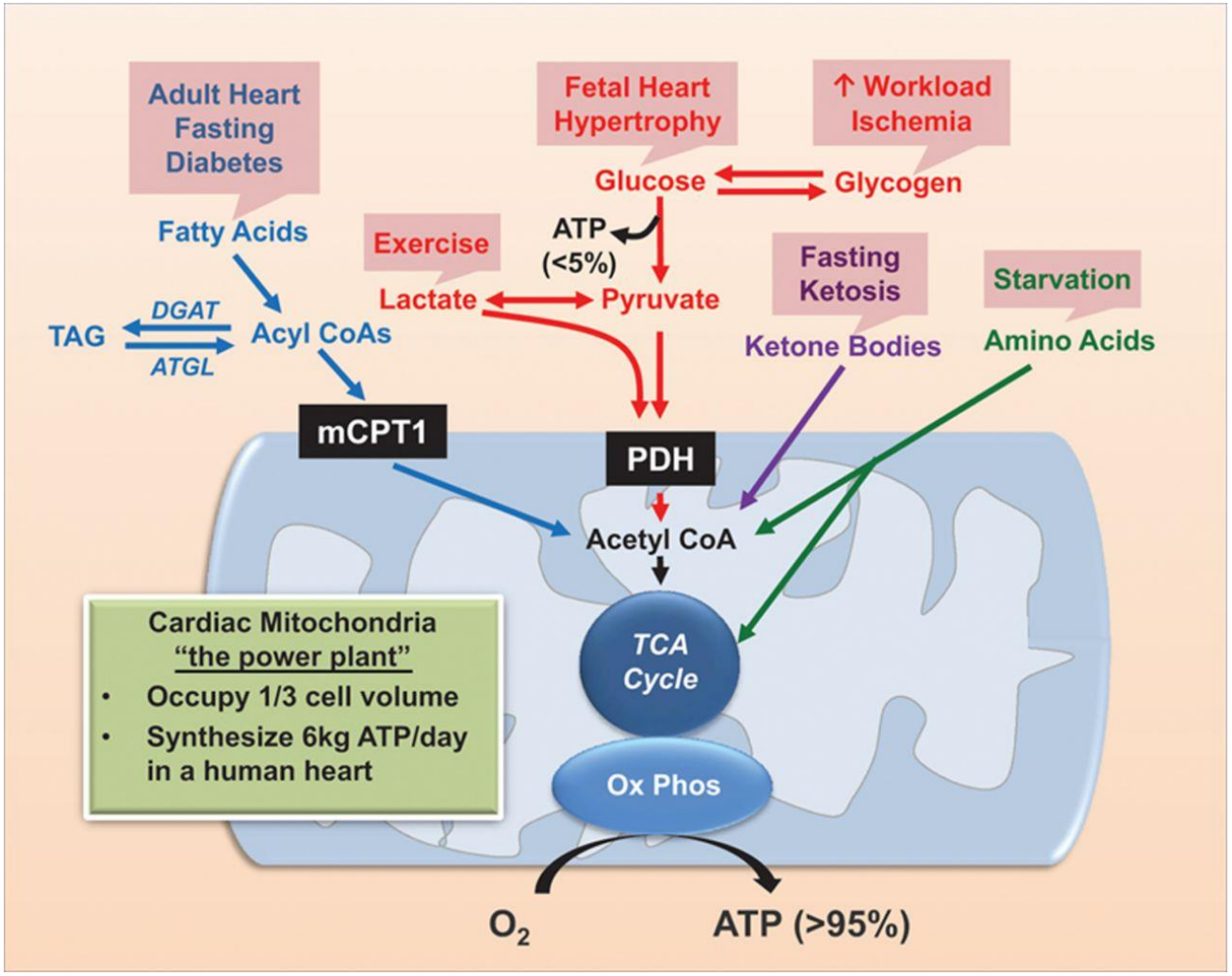
Overview of the metabolic network.



Stephen C. Kolwicz, Jr et al. Circ Res. 2013;113:603-616

- This is overview of the metabolic pathways in different casas
- **In adult heart, Fasting and diabetes there are depending on FA which will convert to Acyl Coa then we have transporter (mCPT1) which transfer acyl CoA to mitochondria to convert it to acetyl CoA which will use TCA to produce energy .**
- **If there is workload and ischemia there will be degradation of glycogen to glucose and then convert it to pyruvate and by PDH will give acetyl CoA which will use TCA to produce energy .**
- **If there are fetal heart / hypertrophy will depend on glucose only which will convert to pyruvate and by PDH will give acetyl CoA which will use TCA to produce energy .**
- **If there is heavy exercise there is depending on anaerobic pathway (lactate pathway) which will convert by PDH to acetyl CoA which will use TCA to produce energy**
- **In starvation : depending on amino acid …**
- **In fasting , ketosis : depending on ketone bodies and then same step .**

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- Harpers Illustrated Biochemistry
- lippincott's Illustrated Reviews: Biochemistry