

Metabolism

Bioenergetics:

- It is the study of the energy changes accompanying biochemical reactions.
- Biologic systems are essentially isothermic and use chemical energy to power living processes.

Free energy:

- G is energy that can do work when temperature and pressure are uniform, as in a (living cell.) →

Starting from unicellular organism which is the bacteria, ending with the multi cellular organism which is the human or animals or plants

The free energy change (ΔG)

- It is difference between the free-energy content of the products and the free-energy content of the reactants under standard conditions. It depends on the nature and concentration of initial reactants and the final products.

❖ Principle goal of metabolic reactions → **produce energy**

Importance of studying bioenergetics

↓
Know which type
of reaction I have

Isothermic, exothermic, endothermic

↓
**type of reaction is reversible or irreversible
>>Reversible = isometric (some exceptions)
NOTE → all reactions in biological system are
iso thermic (with standard based conditions →
temp./ h+ / pressure)

Reactants (L. side) → products (R. side)

Exo. → ΔG^-
Endo. → ΔG^+
Iso. → no ΔG

1) Iso thermic :

- Amount of energy in left = right
- NO loss of energy, NO increase
- Equation = zero

2) Endothermic

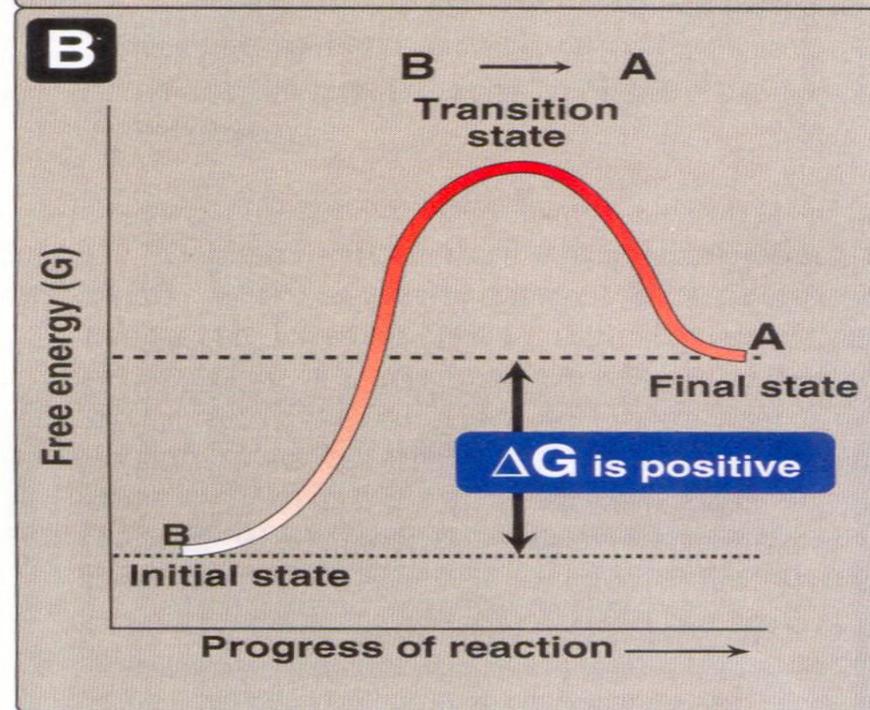
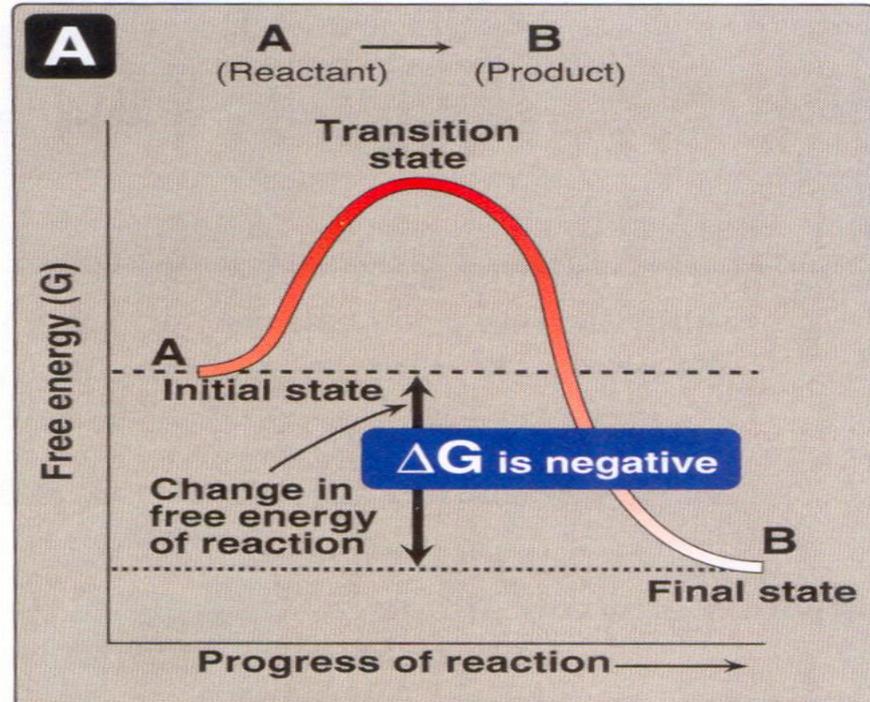
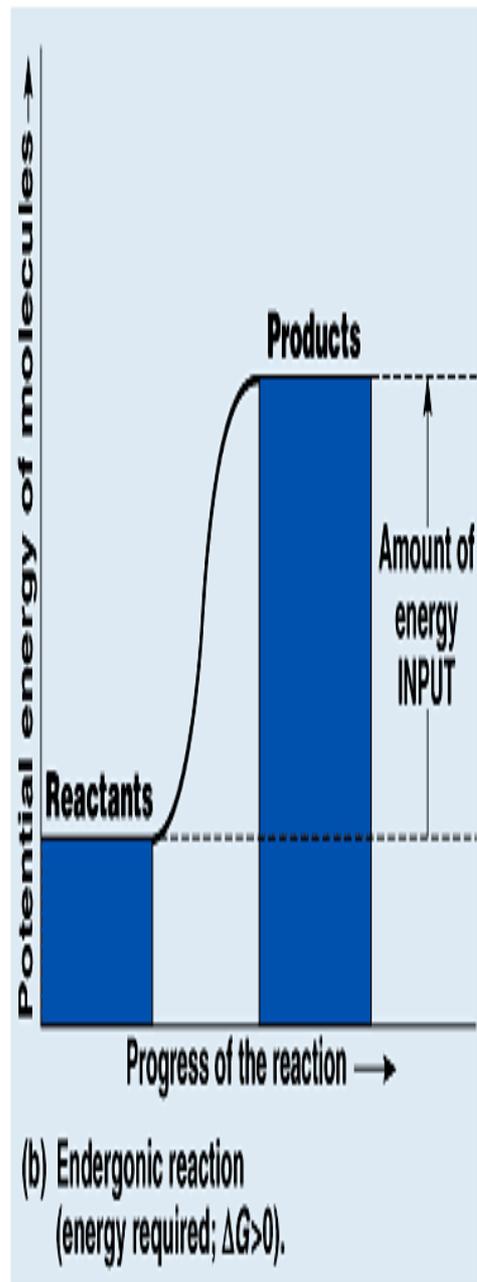
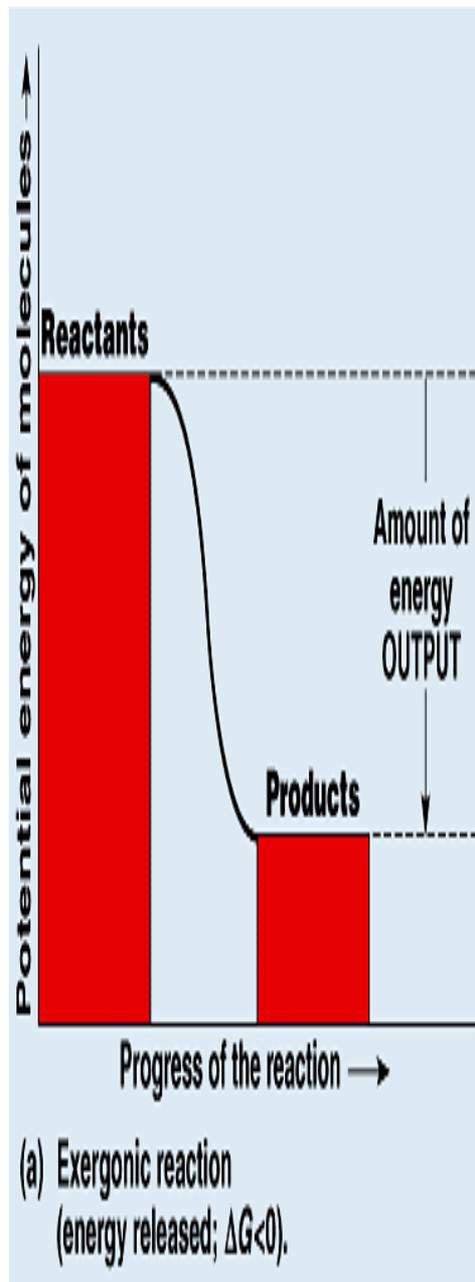
- Right > left
- Absorption of energy
- Endergonic ΔG^+

3) Exothermic

- Left > right
- Exergonic
- Liberation of energy to surrounding environment

** this reaction has the tendency to be completed unlike endo.

→ ΔG^-



Stages of chemical reactions

1- Activation Energy:

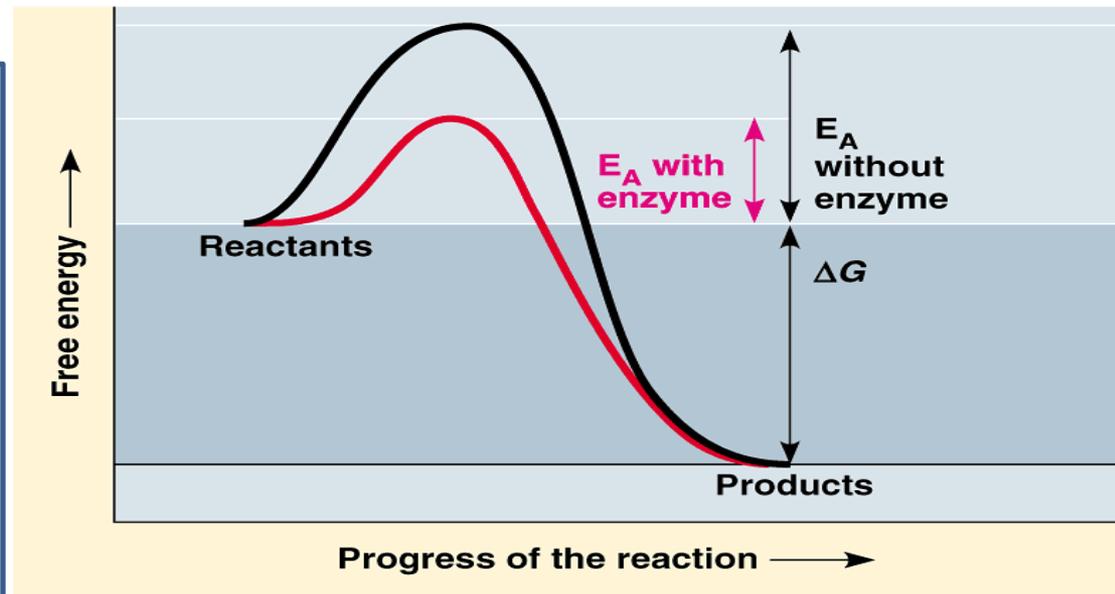
- Amount of energy that reactant molecules must absorb to start a reaction.
- This energy is usually provided in the form of heat absorbed by the reactant molecules from the surroundings.

2- Transition State:

- Unstable condition of reactant molecules that have absorbed sufficient free energy to react.

3- Products

- ❖ **In transition state: there is large amount of energy which is suitable for them to be in the transition state**
- ❖ **The reactant molecule will absorb an amount of energy from the surrounding environment and not to be in this unstable state**
- ❖ **Then substrate converted to product + The enzyme exit as is**



Metabolic pathways can be grouped into two pathways:

Summation of the reactions occur in our cells either be catabolism or anabolism

1- Catabolic reactions: degrade molecules to create smaller molecules and energy (**accompany with oxidation of these building unit, association with liberation energy**)

2- Anabolic reactions: synthesize molecules for cell maintenance, growth and reproduction

- Catabolism is characterized by oxidation reactions and by release of free energy which is transformed to ATP.
- Anabolism is characterized by reduction reactions and by utilization of energy accumulated in ATP molecules. (**reduction reaction**)
- Catabolism and anabolism are tightly linked together by their coordinated energy requirements: catabolic processes release the energy from food and collect it in the ATP; anabolic processes use the free energy stored in ATP to perform work.

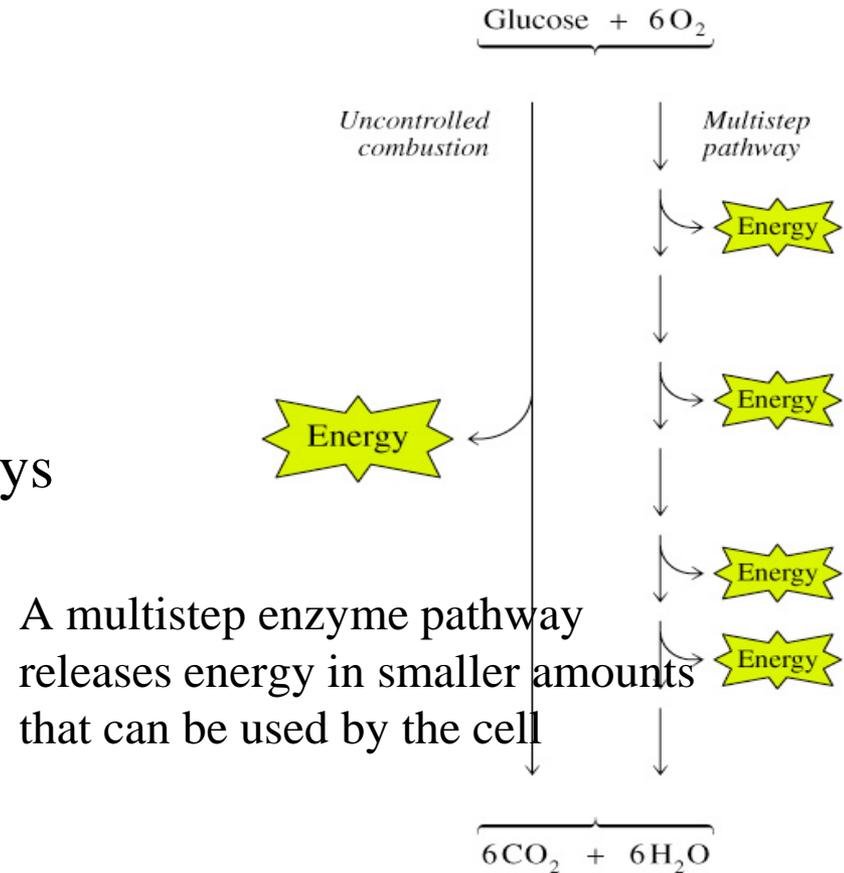
****Single step pathway** (energy produced once) will be huge amount of energy & it can cause harmful effect (dangerous to our cells)

****multiple step pathway:** **1)** glycolysis → (3 reaction called key regulation steps) which do regulation of glycolytic pathway **2)** citric acid cycle → (3 reactions key regulation steps) by it the cell control the cycle. **Which is better?** Multiple step pathway

Metabolism proceeds by discrete steps

- Multiple-step pathways permit control of energy input and output
- Catabolic multi-step pathways provide energy in smaller stepwise amounts
- Each enzyme in a multi-step pathway usually catalyzes only one single step in the pathway
- Control points occur in multistep pathways
- Metabolic pathways are regulated to permit organisms to respond to changing conditions
- Most pathways are irreversible
- Flux: flow of material through a metabolic pathway which depends upon:
 - 1- Supply of substrates
 - 2- Removal of products
 - 3- Pathway enzyme activities

Single-step versus multi-step pathways



Flux mean → continuation at these reactions and to occur this it has to be **1)** continuous supply of substrates (the availability of substrate is stimulating the activity of the enzyme) **2)** removal of products (by end product inhibition or feedback inhibition) **3)** pathway enzyme activates (depending on different factor including hormonal factor)

Levels of metabolism regulation

- 1- Nervous system.
- 2- Endocrine system.
- 3- Interaction between organs. (e.g. brain depend on glucose)
- 4- Cell (membrane) level. Or compartmentation or compartmentalization)

Not all metabolic pathways occur on the same side of the cell

- 5- Molecular level (genetic level regulation by controlling activity of different genes)

Stages of metabolism

Catabolism

Stage I. Breakdown of macromolecules (proteins, carbohydrates and lipids to respective building blocks.

Stage II. Amino acids, fatty acids and glucose are oxidized to common metabolite (acetyl CoA)

Stage III. Acetyl CoA is oxidized in citric acid cycle to CO_2 and water. As result reduced cofactor, NADH_2 and FADH_2 , are formed which give up their electrons. Electrons are transported via the tissue respiration chain and released energy is coupled directly to ATP synthesis.

Slide7:

****stage 1** → by enzymes (lipase...etc)

****stage 2** → oxidation of small molecules to produce common intermediate metabolite

****stage 3** → returning of acetyl Co-A to CAC to produce energy

>>NOTE: conversion reaction because it end to one molecule (acetyl Co-A)

Slide8:

****** the coupling between (ana. & cata.) / **(LIMITED)**

Part of energy produced by cata. Used in ana.

COMPARTMENTATION:

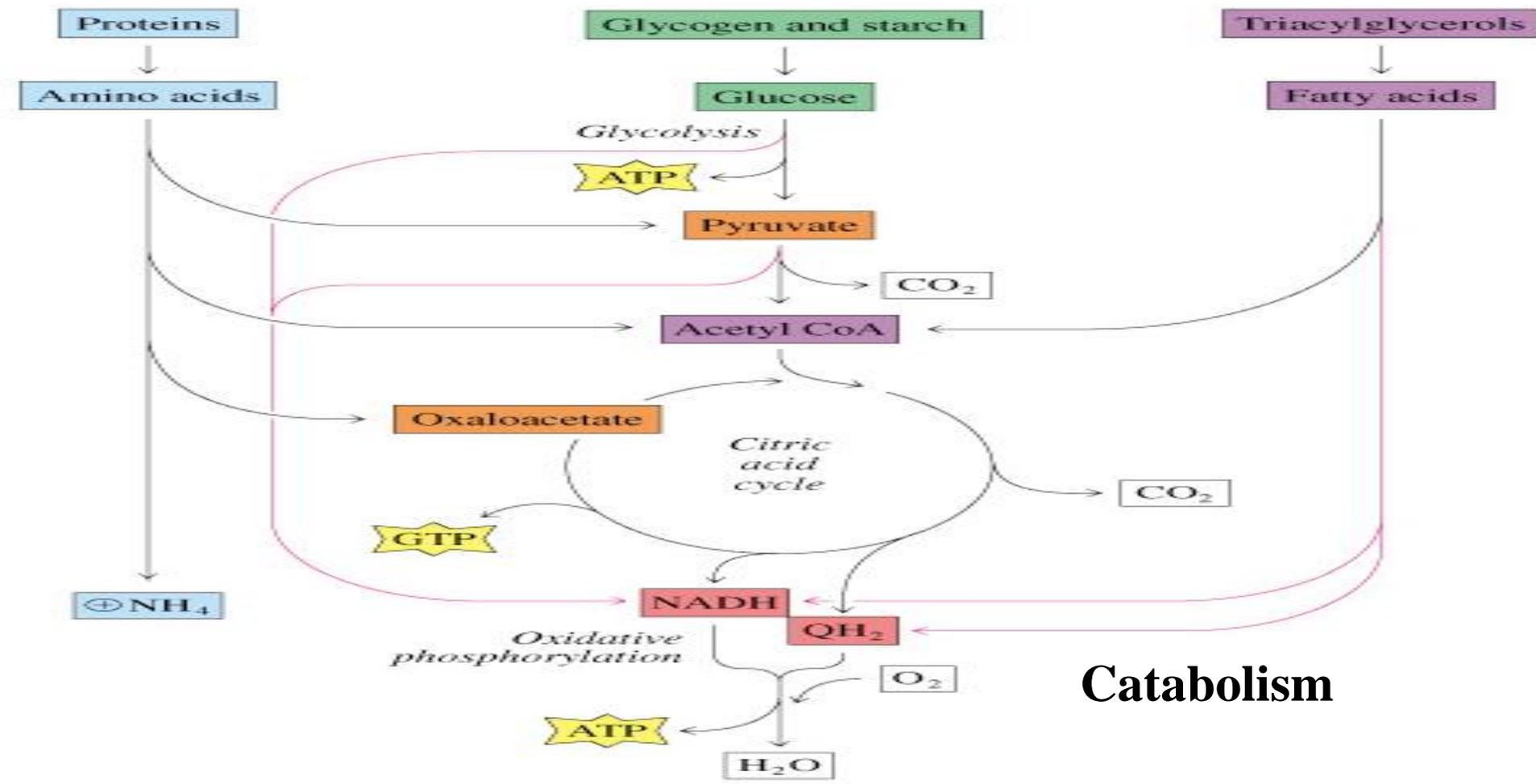
2. Allow cell to carry opposing reactions like:

(fatty acid oxidation & synthesis) → coupling but to limited stage

..Reactions depend on enzymes

Catabolism is characterized by convergence of three major routes toward a final common pathway.

Different proteins, fats and carbohydrates enter the same pathway TCA cycle.



Anabolism can also be divided into stages, however the anabolic pathways are characterized by divergence.

Monosaccharide synthesis begin with CO_2 , oxaloacetate, pyruvate or lactate.

Amino acids are synthesized from acetyl CoA, pyruvate or keto acids of Krebs cycle.

Fatty acids are constructed from acetyl CoA.

On the next stage monosaccharides, amino acids and fatty acids are used for the synthesis of polysaccharides, proteins and fats.

Compartmentation of metabolic processes in cell

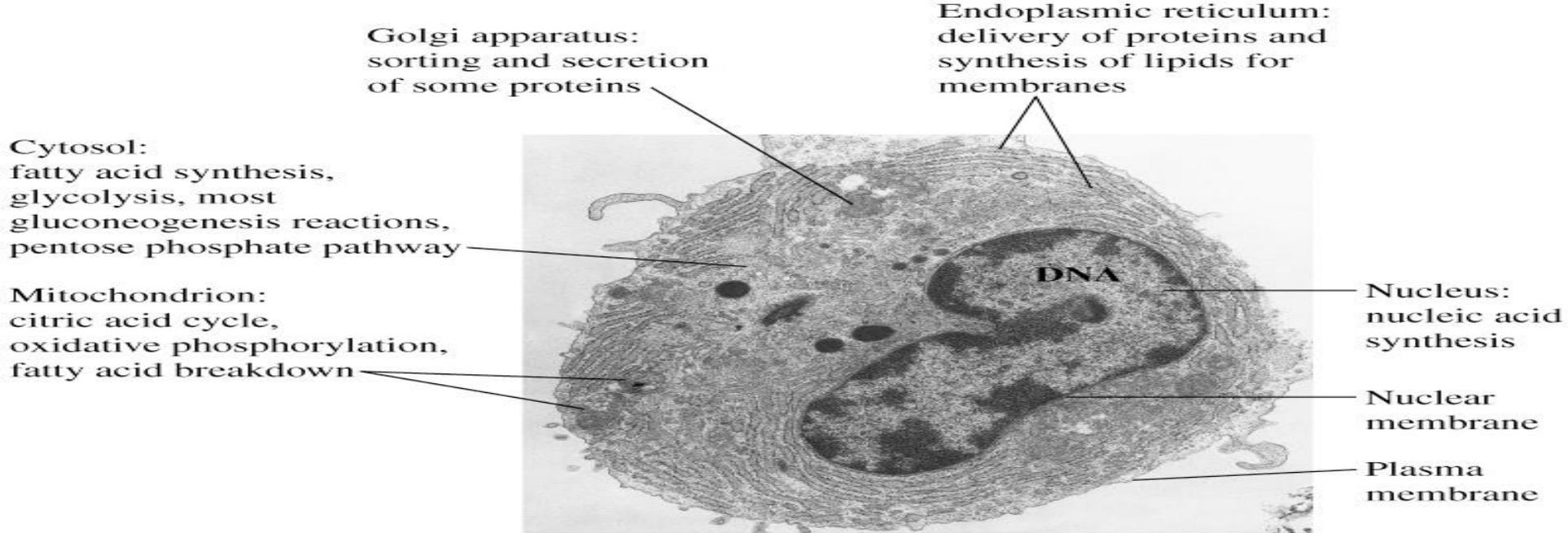
-permits:

- 1- Separate pools of metabolites within a cell
 - 2- Simultaneous operation of opposing metabolic paths
 - 3- High local concentrations of metabolites
- Example: fatty acid synthesis enzymes (cytosol), fatty acid breakdown enzymes (mitochondria)

They are catabolic reaction in the fatty acid oxidation and anabolic reaction in the fatty acid synthesis

Is very important





The chemistry of metabolism

There are about 3000 reactions in human cell.

All these reactions are divided into six categories:

- 1- Oxidation-reduction reactions
- 2- Group transfer reactions
- 3- Hydrolysis reactions
- 4- Nonhydrolytic cleavage reactions
- 5- Isomerization and rearrangement reactions (**rearrange molecule intracellular**)
- 6- Bond formation reactions using energy from ATP (**DNA ligase enzyme which is responsible for linking of bonding of different fragment of the DNA**)

How energy can be produced?

1) Common obligatory intermediate

A+B with energy \rightarrow I \rightarrow B+D

I: represent the common obligatory intermediate

By dehydrogenation (H⁺ carriers) NAD +NADP+FAD \rightarrow ETC in mitochondria \rightarrow translation of H⁺ in oxidation/reduction reactions into energy

2) Alternative way

Substrate level phosphorylation. Why? no ETC

High energy compound \rightarrow low energy compound. Or

High potential \rightarrow high , intermediate compound

e.g. Creatine phosphate +energy \rightarrow ADP \rightarrow creatine + ATP

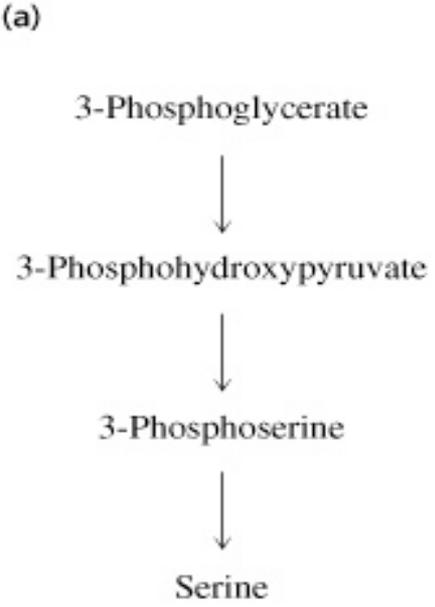
***Phosphoenolpyruvate** because the energy in it is higher than the required energy for formation of high energy bond in ATP can transfer energy with phosphate to ADP for formation of another molecule of ATP when hydrolysis of high energy bond.

Which facilitate the hydrolysis of high energy bond \rightarrow 2 oxygen adjacent to each other and each of them carry -ive charge and will be rebaliture between -ive charge allow breaking down of this high energy bond

Metabolic pathway may be:

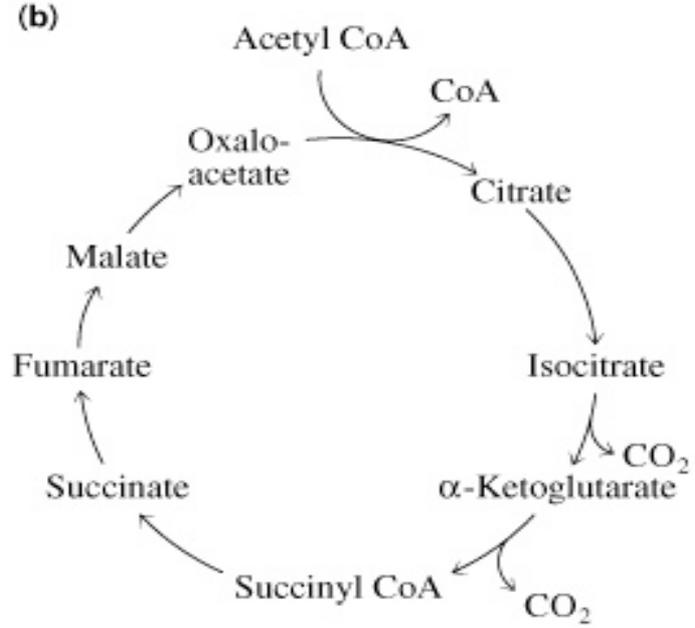
(a) Linear
(Glycolysis)

- *Uronic acid pathway
- *Phosphate pathway

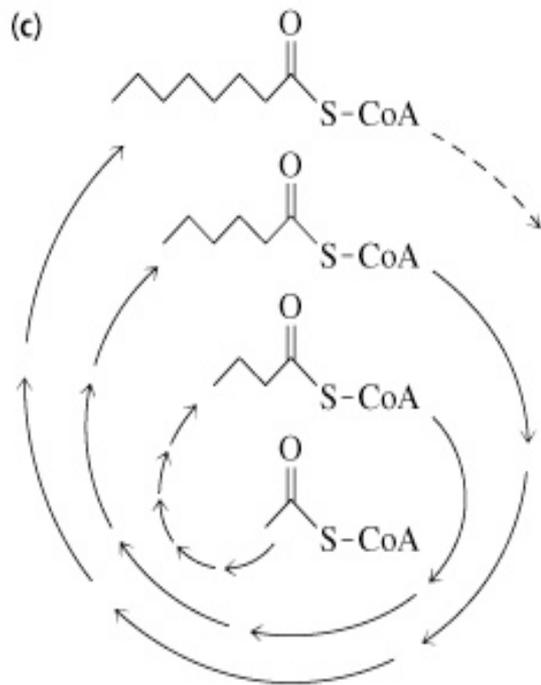


(b) Cyclic
(TCA cycle)

Krebs cycle



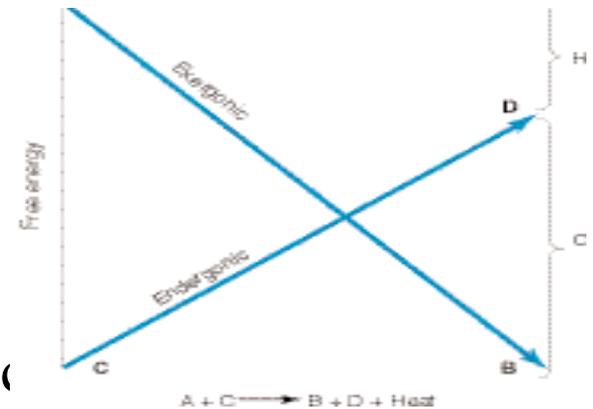
(c) Spiral pathway
(Fatty acid biosynthesis)



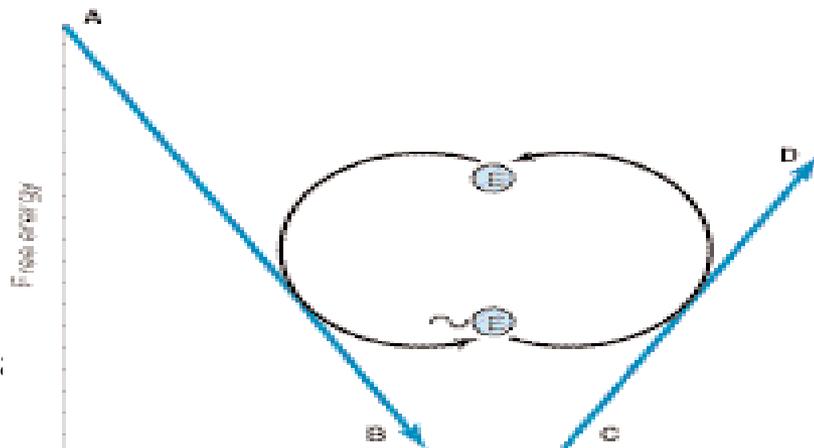
The end product of the first cycle is the reactant of the second cycle and so on. e.g. fatty acid oxidation

- In practice, an endergonic process cannot exist independently but must be a component of a coupled exergonic- endergonic system where the overall net change is exergonic.
- One possible mechanism of coupling could be observed if common obligatory intermediate (I) took part in both reactions.

$$A + C \rightarrow I \rightarrow B + D$$
- Some exergonic and endergonic reactions in biologic systems are coupled in this way.
- Indeed, these relationships supply a basis for the concept of respiratory control, the process that prevents an organism from burning out of oxygen.
- The coupling concept is provided by forming an intermediate carrier through dehydrogenation/hydrogenations reactions



- An alternative method of coupling an exergonic to an endergonic process is to synthesize a compound of high-energy potential in the exergonic reaction and to incorporate this new compound into the endergonic reaction, thus effecting a transference of free energy from the exergonic to the endergonic pathway.
- The biologic advantage of this mechanism is that the compound of high potential energy, ($\sim E$), unlike I in the previous system.

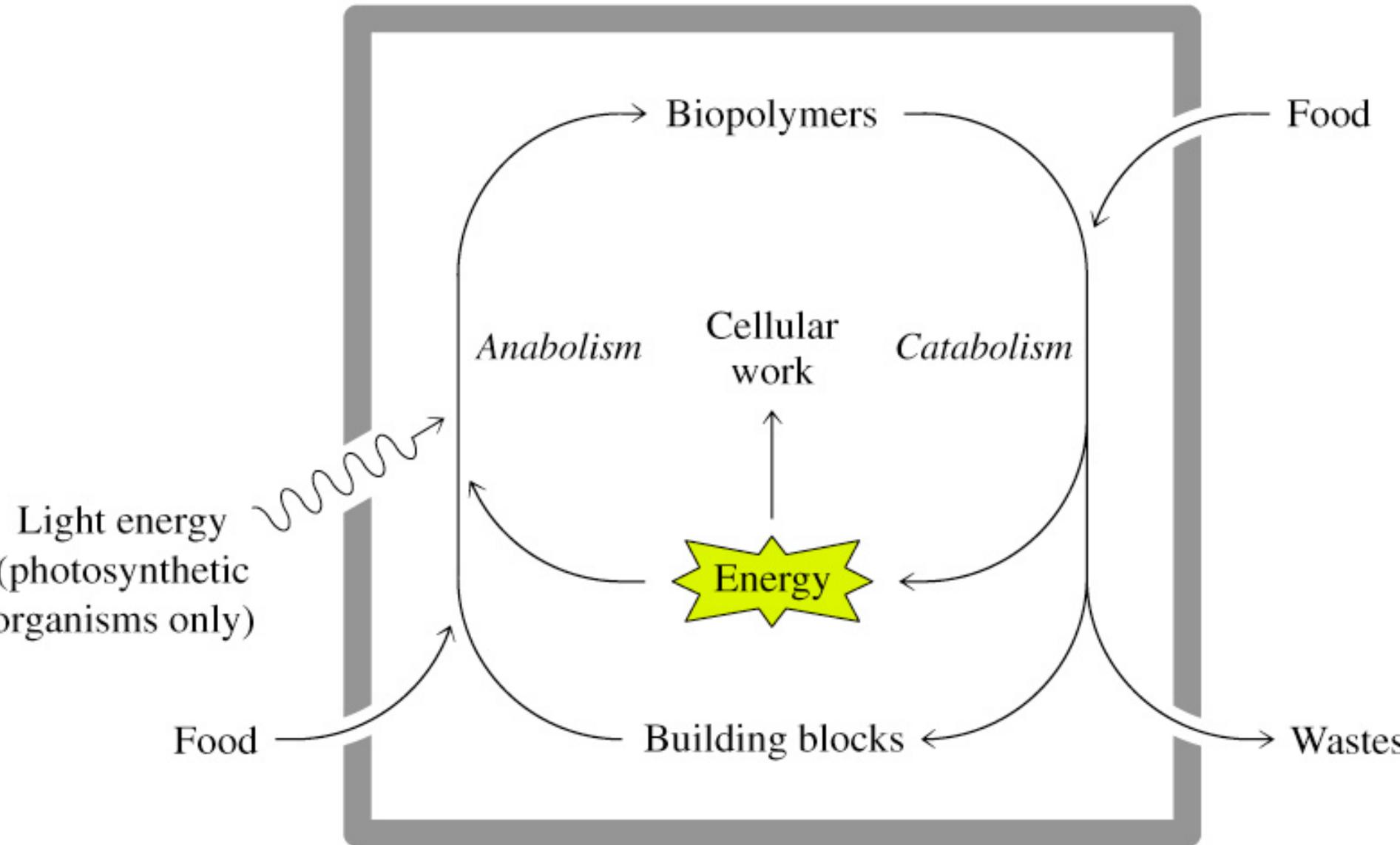


**** energy transfer from one compound to another which called substrate level phosphorylation NO ETC**

- Tr: via a high-energy intermediate compound ($\sim E$)

an endergonic reaction

Anabolism and catabolism are coupled by energy



The Intermediate value for the free energy of hydrolysis of ATP

- The standard free energy of hydrolysis of a number of biochemically important phosphates.
- The tendency of each of the phosphate groups to transfer to a suitable acceptor may be obtained from the $\Delta G_0'$ of hydrolysis at 37 °C.
- The value for the hydrolysis of the terminal phosphate of ATP divides the list of energy compounds into two groups:
- Low-energy phosphates, exemplified by the ester phosphates found in the intermediates of glycolysis, have ΔG_0 values smaller than that of ATP, while in high-energy phosphates the value is higher than that of ATP.
- The components of the high-energy phosphates compounds, including ATP, are usually anhydrides (1-phosphate of 1,3-biphosphoglycerate), enolphosphates (phosphoenolpyruvate), and phosphoguanidines (creatine phosphate, arginine phosphate).
- The intermediate position of ATP allows it to play an important role in energy transfer.

$\Delta G_0 \rightarrow$ determine the tendency of transfer phosphate and energy from one compound to another one

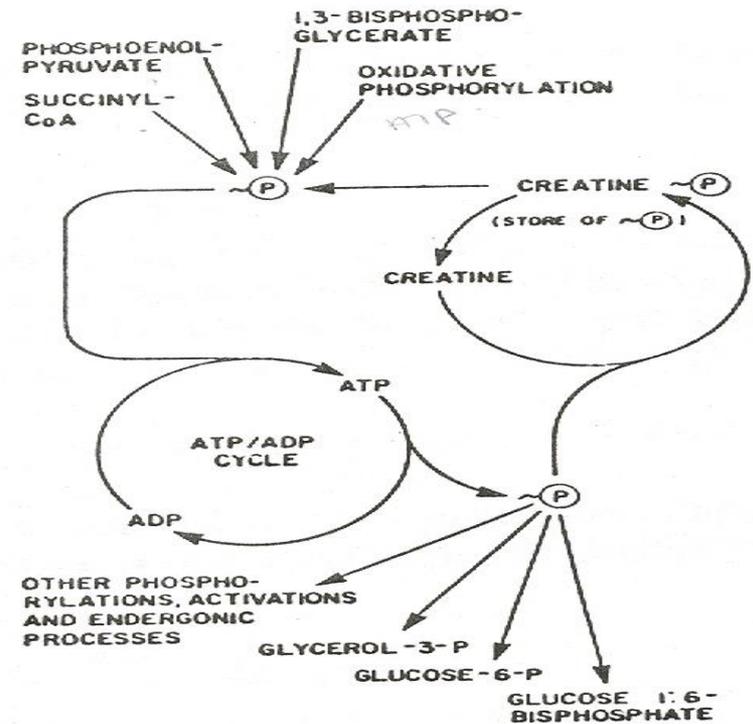
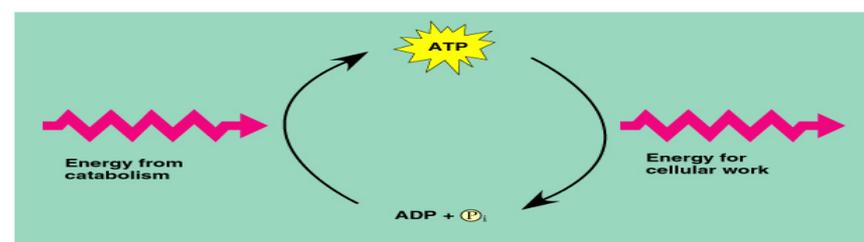
- The high free energy change on hydrolysis of ATP is due to relief of charge repulsion of adjacent negatively charged oxygen atoms.
- Other “high-energy compounds, **but they are not contain phosphate**” are thiol esters as coenzyme A (acetyl-CoA), acyl carrier protein, amino acid esters involved in protein synthesis, S- adenosylmethionine (SAM), UDPGlc (uridine diphosphate glucose), and PRPP (5-phosphoribosyl-1-pyrophosphate). SAM:

****SAM: participate in methyl group transfer**
****PRPP: play role in synthesis of nucleated of RNA and DNA**

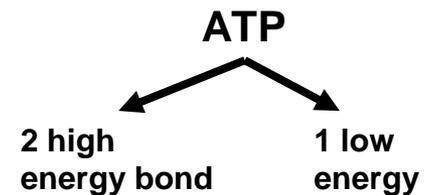
Compound	kJ/mol	kcal/mol
Phosphoenolpyruvate	-61.9	-14.8
Carbamoyl phosphate	-51.4	-12.3
1,3-Bisphosphoglycerate	-49.3	-11.8
Creatine phosphate	-43.1	-10.3
ATP → ADP + Pi	-30.5	-7.3
ADP → AMP + Pi	-27.6	-6.6
Pyrophosphate	-27.6	-6.6
Glucose 1-phosphate	-20.9	-5.0

G0> amount of energy needed for the formation of ATP → formation of ATP
G0< amount of energy needed energy → NO formation

- ATP powers cellular work by coupling exergonic reactions to endergonic reactions
- A cell does three main kinds of work: Mechanical, Transport and Chemical
- To do work, cells manage energy resources by energy coupling, the use of an exergonic process to drive an endergonic one
- ATP is the cell's energy shuttle providing energy for cellular functions



Role of ATP/ADP cycle in transfer of high-energy phosphate.



****ATP splitting down into \rightarrow AMP + pyrophosphate**

Which mean loss of 2 high energy bond

****2ATP splitting down into \rightarrow ADP + phosphate . There is one high energy bond broken down in these molecule**

*** Is the ADP that produce here can be utilize as a source of energy?! NO**

Sources of ATP.

ATP levels are maintained through several processes:

1. Adenylate kinase.

- ATP has two "high-energy" phosphate groups. Splitting off the gamma phosphate group of ATP yields ADP and inorganic phosphate.
- Splitting off both high-energy groups in one step yields AMP and inorganic pyrophosphate (ppi). **(loss of 2 high energy bond)**
- Adenylate kinase, an enzyme found in all tissues, catalyzes a transfer of the energy-rich phosphate bond from one ADP molecule to another, giving ATP and AMP.
- The conversion is very rapid in muscle and liver.

2ADP

ATP + AMP

- (1) ADP: use as phosphate group and energy donor**
- (2) ADP: use as phosphate group and energy acceptor**

- AMP levels are crucial in adjusting the balance between carbohydrate and fatty acid metabolism in varying physiological situations.
- AMP is an active intracellular signal substance.
- AMP is also an activator of glycogen mobilization and, therefore, sugar metabolism.

2. Creatine Phosphokinase / Phosphocreatine. (Fastest source of energy)

- **Used during explosive or maximal intensity of muscular exercise**
- Most of our body tissues contain phosphocreatine at concentrations approximately three times that of ATP.
- Phosphocreatine is a reserve source of high-energy phosphate.
- This reserve can be transferred to ADP, thus forming ATP to replace that used by working muscle.
- While the creatine phosphokinase reaction is the most rapid ATP-yielding reaction we possess, the amount of ATP which is produced is quite small.
- Muscle tissues have about 5 mmol/l ATP and approximately 17-20 mmol/l of creatine phosphate.
- Under extreme work (sprinting, for example) the phosphocreatine reserves are used up in about 30-40 seconds.
- However, "seconds do count" in sport. During those few seconds muscles can and do work with "explosive force".

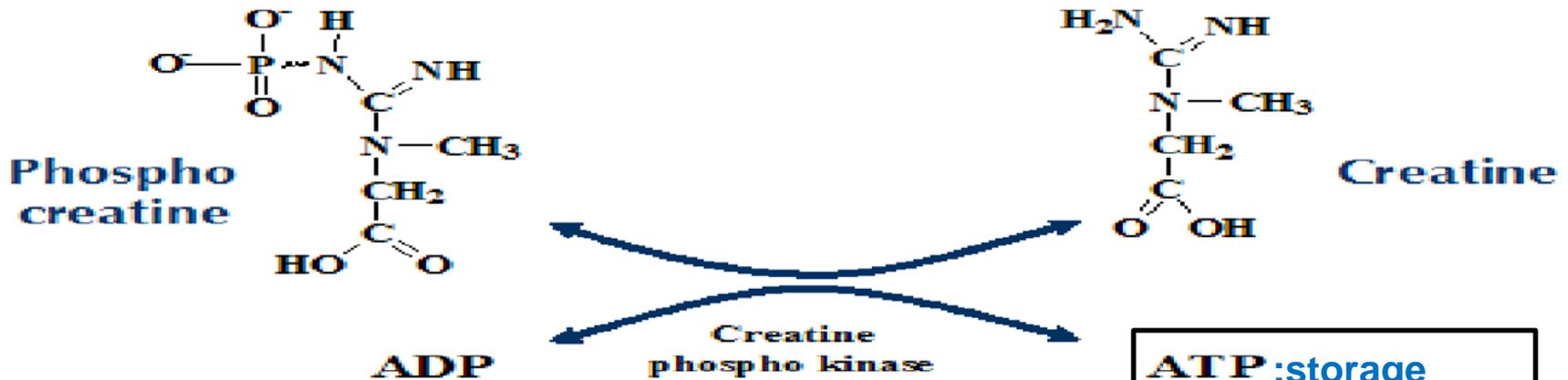
TABLE 1.1

THE ENERGY SYSTEMS AND THEIR APPROXIMATE CONTRIBUTIONS TO VARIOUS DURATIONS OF EXERCISE AT MAXIMAL INTENSITY (1)

ENERGY SYSTEM	DURATION
Phosphocreatine system	0-10 seconds
Phosphocreatine system and glycolytic system (slow)	10-30 seconds
Glycolytic system (fast)	30 seconds-2 minutes
Glycolytic system (fast) and oxidative system	2-3 minutes
Oxidative system Only ETS	< 3 minutes and rest

Starting to utilize of activity of ETS

Creatine Phosphate-ATP interaction



ATP :storage form in the muscle

Glycolytic system (fast) → because the creatine phosphate already complete depletion

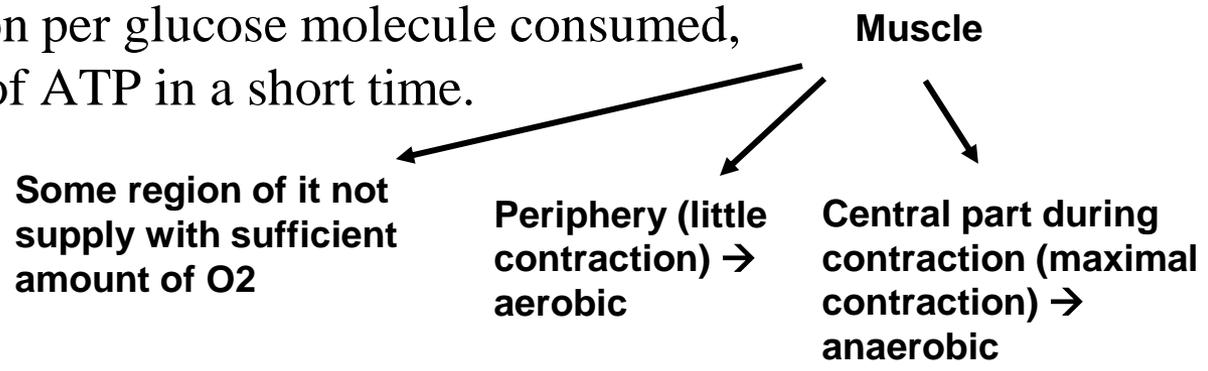
1.3 CHARACTERISTICS OF THE PHOSPHOCREATINE SYSTEM

1. It involves only one chemical step.
2. It is catalyzed by the enzyme creatine kinase (CK).
3. Its chemical reaction is very fast. 5-10s
4. One ATP is generated per phosphocreatine molecule.
5. The reaction lasts for 5 to 10 seconds at maximal intensity.
6. It is anaerobic.
7. Fatigue is associated with the depletion of phosphocreatine.
8. It is the dominant energy system in speed and explosive power events. **Because it the fastest source of energy**

Anaerobic condition cannot be supplied in sufficient amount of oxygen or cannot contain mitochondria as RBC and muscle

3. Anaerobic Metabolism.

- In "second place" in the ATP-synthesis race (after phosphocreatine) comes ATP synthesis coupled to anaerobic metabolism.
- This is the cytosolic formation of ATP driven by oxidation of glucose (or glucosyl groups from glycogen) to pyruvate and lactate.
- ATP formation through cytosolic glycolysis proceeds with a speed equal to about 50% of that we see using creatine phosphate and creatine phosphokinase.
- Rapid, yes, but how much ATP can we make when the oxidation process is limited to formation of pyruvate and lactate from glucose or glycogen?
- Only two ATP molecules result for each glucose molecule that is processed.
- Three ATPs are formed for each glucosyl group that derived from glycogen.
- The anaerobic glycolysis is very rapid. While it is relatively ineffective measured by energy production per glucose molecule consumed, glycolysis does turn out a lot of ATP in a short time.



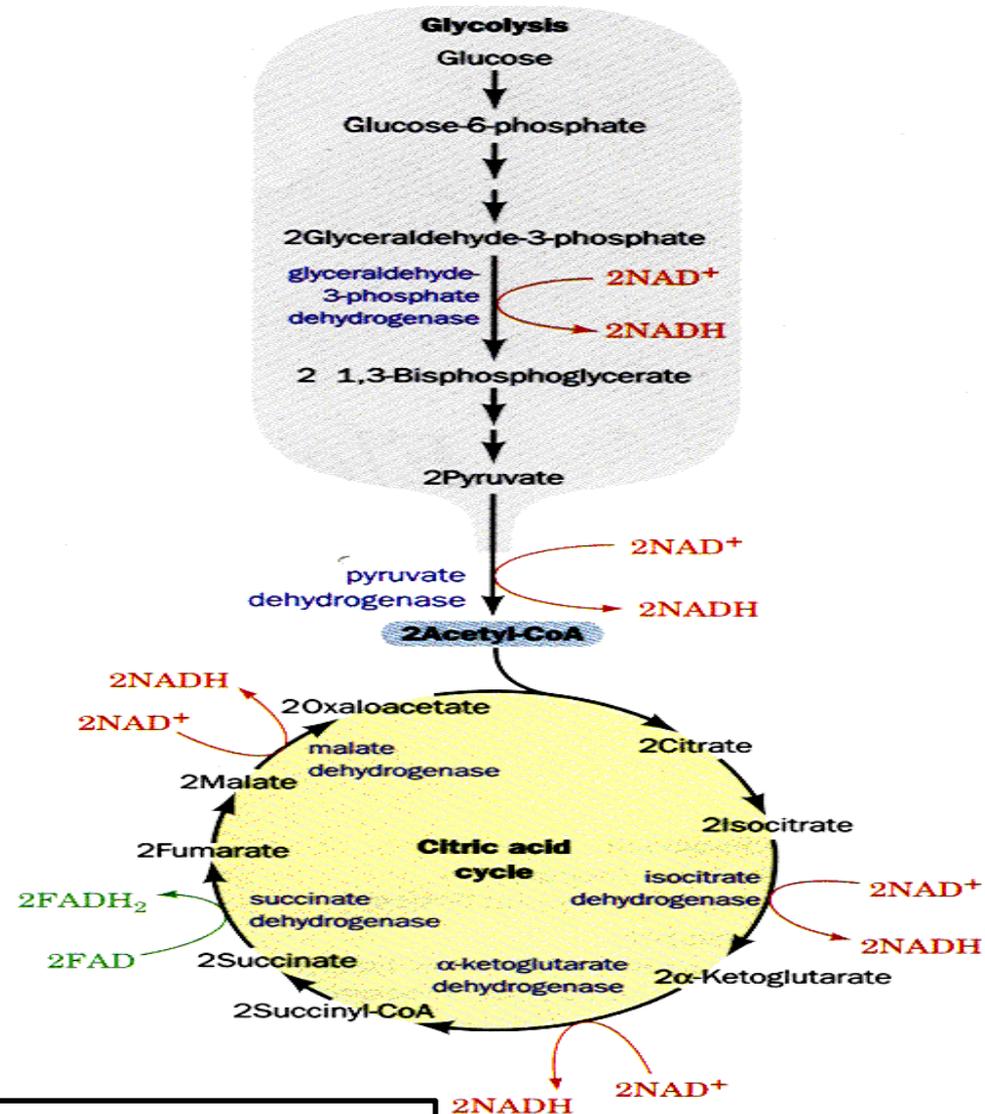
- The big (and painful) disadvantage is that a lot of lactic acid is produced and accumulates in the working muscle. **Leading to fatigue**
- Furthermore, lipids cannot be used as substrates for anaerobic metabolism.
- Only glucose or glycogen work here.
- If we press anaerobic glycolysis to the limits, muscles exhaust their stored glycogen and take up so much glucose from the blood that hypoglycemia and CNS malfunction result. **(because CNS depend on glucose and if there is decrease in glucose)**

there will be sufficient oxygen and mitochondria to produce more energy 4. Aerobic Metabolism. (slower)

- ATP-balancing
- ATP synthesis
- All of our cells, with the important exception of blood cells, contain Mitochondria which use oxygen and form water while oxidizing our "food".
- Mitochondrial substrate is acetyl-CoA.
- All food that can be reduced to 2-carbon fragments can serve as a substrate for mitochondrial ATP production.

The net result pyruvic acid which will be converted inside the mitochondria into acetyl Co-A

- The combustion process is coupled to reduction of oxygen giving water as a product.
- Approximately 30% of the energy released in this process is trapped in the terminal phosphate group in ATP.
- The rest of the energy in acetyl-CoA escapes as heat, keeping us nice and warm!
- We produce around 10 moles of ATP for each mole of acetyl-CoA that is processed.
- While aerobic synthesis of ATP is the most effective way to produce "useable energy", it is a relatively slow process.



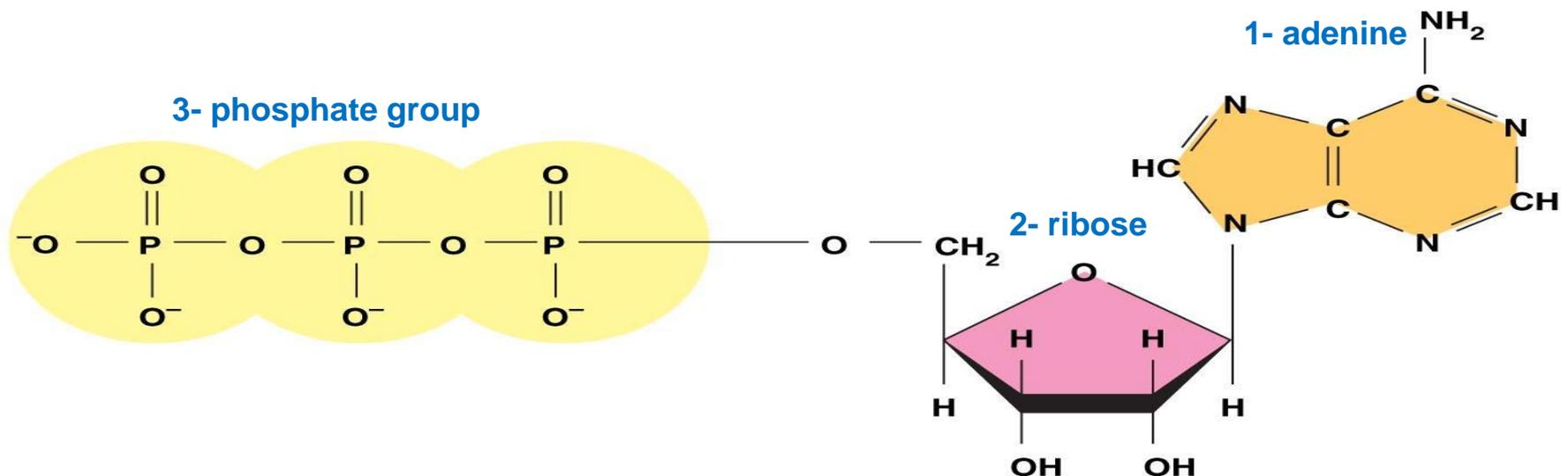
Creatine phosphate > glycolysis (anaerobic condition) > aerobic

ATP (adenosine triphosphate)

- Compounds with high energy bonds release large quantities of free energy on hydrolysis.
- The most important parts of the ATP molecule are its two phosphodiester bonds (high energy bonds).
- Breaking down either of these bonds is accompanied by the release of energy (7.3 Kcal/mol for each bond).

Importance of ATP as a source of energy :

- 1- Synthesis of macromolecules: such as DNA and RNA, protein,etc
- 2- Support the endergonic reaction in metabolic pathways.
- 3- Important for active transport across membranes.
- 4- Important for muscle contraction...etc.
- 5- transmission of impulses along neurons.



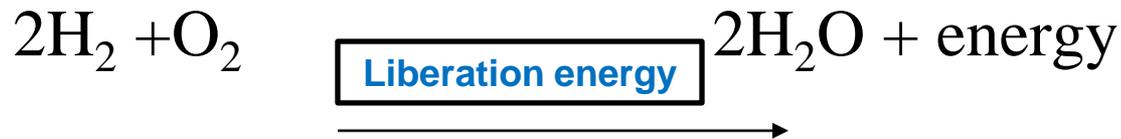
Electron transport chain (ETC)

Found in the inner mitochondrial membrane

**to release the energy from nutrient it depend on redox reaction

Oxidation reduction reactions (Redox reactions)

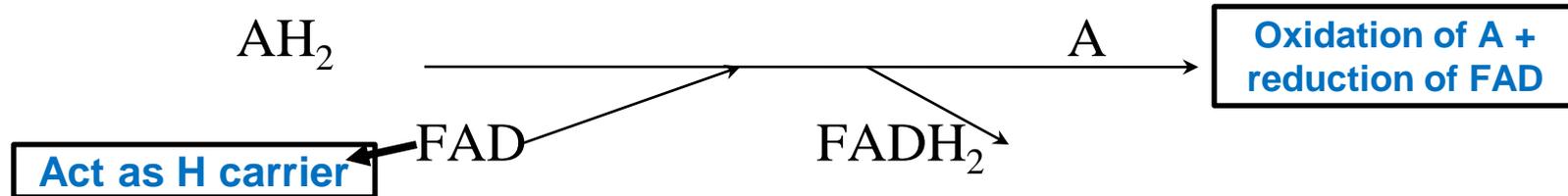
- Commonly the oxidation reactions are accompanied by reduction reactions and they are called redox reaction.
- Redox reactions are accompanied by energy liberation, necessary for the cells.
- In the redox reaction. H_2 is oxidized while, O_2 is reduced, and if occurs it will be accompanied by a massive energy explosion (**produced in multistep not one**).



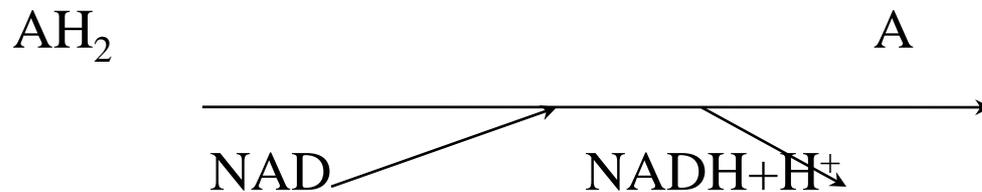
- Instead of massive energy is liberated, hydrogen must be transferred to oxygen in gradual steps. Thus, small fractions of energy are liberated and stored for further use (**and large part of energy will be liberated as heat (50-60%) of the total amount of energy produced**)

Electrons are transferred from one molecule to another in one of four different ways

- They may be transferred directly as electrons as the Fe 2+ / Fe 3+ redox pair.
- Electrons may be transferred as incorporated in hydrogen atoms as in case of FAD



- Electrons may be transferred as hydride ions (H⁻)



- Electron may be transferred as a direct combination of an organic reductant with oxygen



1)a) ETC depend on reduction /oxidation reaction, b) electron should be transferred from the least affinity to the highest affinity (for electron), c) electron will be jumping from C1 (least) → C2 → C3 (highest) with gradual increase in e- affinity (C2)

2) Depend on organization of different components in ETC