No.1

Doctor 2020 - wateen - medicine - MU

biochemistry sheet

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Biochemistry of Cardiac Muscle – 1

Specifity of cardiac metabolism

The heart is one of the most active and highly oxidative Organ in the body.

Myocardial cells are the most highly oxidative cells (based on oxidative phosphorylation for producing energy)

- **Myocardial function depends on a fine equilibrium between The work the heart has to perform to meet the requirements of The body which conjugates a series of electrophysiological, Biochemical and mechanic events, resulting in the pumping Of blood to all bodily tissues and the energy to be synthesized And transferred as ATP molecules to sustain excitation-Contraction coupling.**

- **To support high rates of cardiac power, metabolism is designed To generate large amount of ATP by oxidative phosphorylation To meet energetic demand for generating the needed Mechanical force, and for maintaining cellular homeostasis**

-the difference between aerobic and anaerobic is the amount of energy produced, 1 glucose: Aerobic >38 ATP, anaerobic > 2 ATP (by substrate level phosphorylation) thats why the cardiac muscle can't work under anaerobic conditions and the first mission for the heart is bumbing the oxigynated blood to the boody and this bumbing in need for continuous contraction in the cardiac muscle which be in nned for huge amount of energy

- under aerobic conditions the ATP production will increase and also allowing the cardiac muscle not only depending on glucose oxidation as the main source of energy but also depend on fatty acid oxidation

The energetic metabolism of the cardiomyocyte consists of three key components:

1- **Capture and utilization of primary substrates, with the incorporation of their metabolites into TCA cycle;**

-Uptaking the nutrients from the circulation and by nutrients we mean the substances that the myocardial cells use to produce energy

-The first main source is fatty acids
In 2nd place is glucose, 3rd is amino acids and ketone bodies

-60% of energy is coming from beta oxidation of the fatty acids under 2 conditions (1- in mitochondria 2- presence of o2

2- **Oxidative phosphorylation, which occurs in ETC within the internal mitochondrial membrane; and**

-Oxidation of these nutrients to give the common intermediate in all metabolic pathways which is acetyl CoA

-All the food (carbohydrates, amino acids, proteins) are all end up giving acetyl CoA

3- **The phosphocreatine (PC)-creatine kinase (CK) energy transference system, a network for phosphate transference from ATP to creatine (an "energy-storing" molecule), through mitochondrial CK and yielding PC (an important source of energy under high-demand conditions).**

-storage of energy, in the form of phosphocreatine by the enzyme phosphocreatine kinase

- **N.B. Mitochondria occupies ~30% of cardiomyocyte space**

- **The metabolic machinery of the heart utilizes oxygen up to 80%-90% of the maximum capacity of ETC ; however, at a Resting state, the heart operates at only 15%-25% of its Maximum oxidative capacity.**

- **Cardiomyocytes show an elevated rate of ATP hydrolysis, Which is strongly linked to oxidative phosphorylation because Under non-ischemic conditions, over 95% of these cells' ATP is Produced in this process.**

- **Under basal aerobic conditions:**

1- **60% of energy comes from FAs, but their synthesizing Capacity for these molecules is relatively low. As a result, These cells depend fundamentally on the influx of FAs from The vascular compartment, and thus, the rate of FAs Consumption by cardiac muscle is principally determined by The concentration of non-esterified FAs in plasma**

2 sources of fatty acids:

1- Uptake of FA from the circulation (70-90% immediately starts beta oxidation) or

2- hydrolysis of TAG (triacylglycerol) from the INSIDE of the cardiomyocyte (TAG pool) by the enzyme hormone sensitive lipase to produce FA that will be metabolized by beta oxidation to form energy

- **(10-30%) will be stored in form of triacylglycerol, it get used when shortage (decrease) of concentration of non-esterified fatty acids in plasma , so the cardiac muscle depend on the activity of hormone sensitive lipase to hydrolyze TGA pool and give the fatty acids to be metabolized by beta oxidation**

Lipid profile: cholesterol, LDL, HDL, …… And non-esterified FAs, should be in sufficient amount to be used by the cardiomyocytes, if not sufficient indicates that the cardiomyocytes are depending more on glucose which is not enough for cardiac muscle (1 gram of glucose gives 1/3 of energy required for the heart)

- non-esterified FAs are an indicator of the activity of the heart .

2- 35% from carbohydrates

2nd main source of energy is from carbohydrates (glucose)

2 sources of glucose:

1- uptake of glucose form the plasma through GLUT 4, which is insulin dependent (that's why DM patients are at increased risk of HF, because of lack or resist of insulin this will cause no eternalization of GLUT 4 on the cell surface which made inside cardio cells >> decrease in glucose intake this will push the cardiomyocytes to depend more on fatty acids which will increase the uptaking that will lead to lipotoxicity which will cause heart failure) .
-GLUT 1 helps GLUT 4 in glucose uptaking

Not all glucose uptaken is utilized but some are stored as glycogen

2- glycogen pool, but is VERY LIMITED, 1/5 of the glycogen stored in skeletal muscle cells, 30 mmol / g wet weight of the cardiac muscle Vs. 150 mmol/g wet weight of skeletal muscle

Ketone bodies: aceto acetic acid, beta hydroxy buteric acid and acetone

naturally produced in small amounts

Used as source of energy (aceto acetic acid and beta hydroxy buteric acid, but not acetone because it is volatile will be exhaled, as in the breath of DM patients > which is manifestation of diabetic keto acidosis or called diabetic coma indicating poorly controlled blood sugar level usually very high)

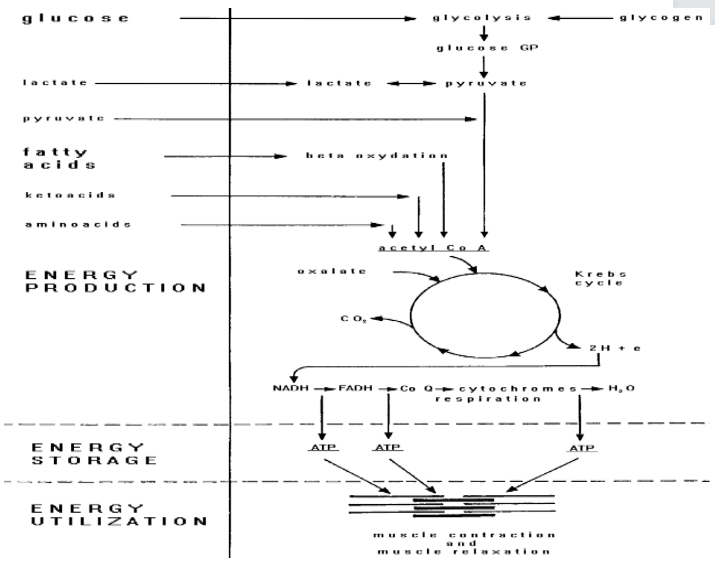
2- 5% from amino acids an ketone bodies.

-Ketone bodies: aceto acetic acid, beta hydroxy buteric acid and acetone naturally produced in small amounts

-building unit of the ketone bodies is active acetate which it's main source is beta oxidation of fatty acids

-So the people who has more lipolysis and more beta oxidation there will be more production of acetyl CoA which will cause hypercholesterolemia in DM patients (acetyl CoA is building unit for cholesterol).

-Used as source of energy (aceto acetic acid and beta hydroxy buteric acid, but not acetone because it is volatile will be exhaled, as in the breath of DM patients > which is manifestation of diabetic keto acidosis or called diabetic coma indicating poorly controlled blood sugar level usually very high)



~ 60-70% of ATP hydrolysis is used for muscle contraction,

~30 – 40% for the sarcoplasmic reticulum (SR) Ca2+-ATPaseand other ion pumps.

DM patients are at risk of 2 types of coma:

1- hypoglycemic: cold sweats

2- hyperglycemic: acetone smell in the breath, no cold sweats why? Because they have polyuria due to osmotic diuresis (urine volume > 1.5 L/day) this water is from the plasma and from the cells > dehydration > no sweat

But the problem with ketones that the building block is acetyl CoA (active acetate, is the product of beta oxidation of FAs)

Patients with increased lipolysis (as DM patients) > beta oxidation > more and more acetyl CoA which is the building block of ketones and cholesterol > hypercholesterolemia

So in DM patients we measure cholesterol and LDL/HDL ratio (if > 3.1 increased risk of atherosclerosis and heart disease)

Transamination of amino acids give the molecules that are used in citric acid cycle

Acetyl CoA (90% from beta oxidation and 10% from glycolysis)

pyruvate to acetyl CoA through oxidative decarboxylation in the mitochondrial matrix (next slide)

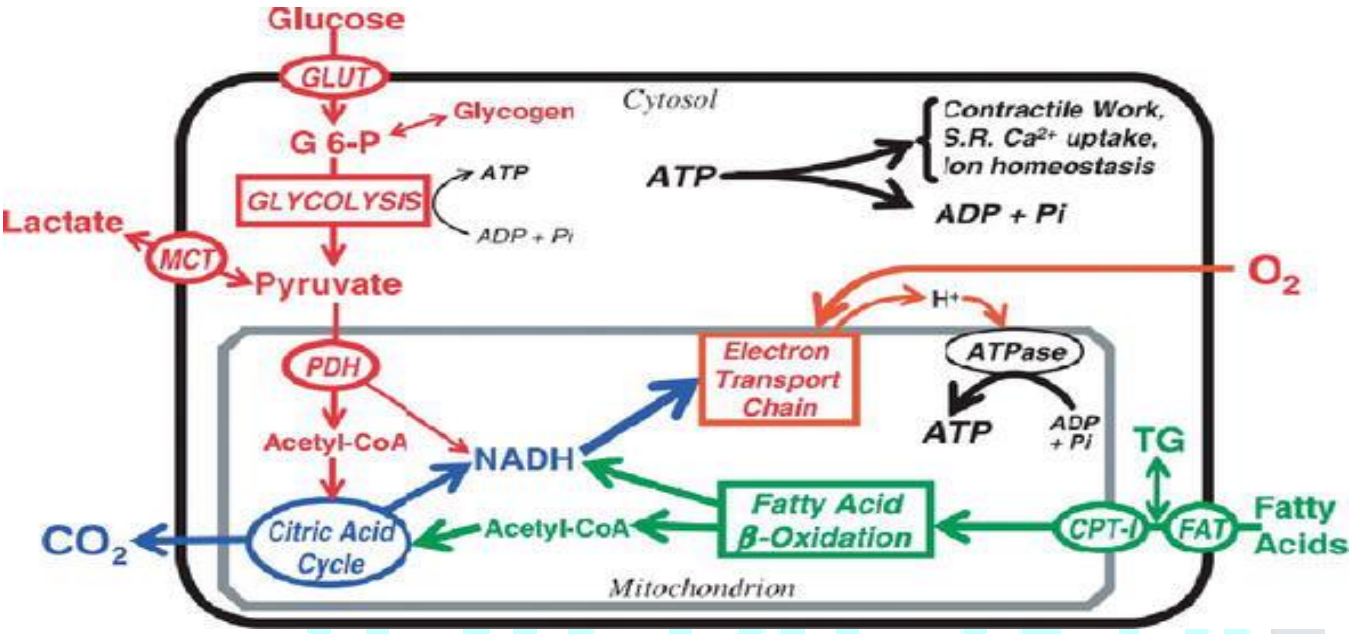
1 acetyl CoA entering the citric acid cycle gives 3 NADH, 1 FADH2, 2CO2, 1ATP (by substrate level phosphorylation) >>> 10 ATP

Assuming that 1 NADH gives 2.5 ATP, 1 FADH2 gives 1.5 ATP

Regulation of metabolic pathways in the heart

- **CAC is fueled by acetyl-CoA formed by oxidative decarboxylation of pyruvate (glycolysis) (10-40%) + from β- oxidation of FA (60-90%).**

- **The reducing equivalents: NADH and $FADH_2$ (generated by glycolysis, oxidation of lactate, pyruvate and β-oxidation of Fas) deliver electrons to ETC → ATP (oxidative phosphorylation).**



Carbohydrate metabolism

Glycolytic substrate is derived from exogenous glucose and glycogen stores.

- **Glycogen pool in the heart is relatively small (~30 mmol/g Wet wt compared with ~150 mmol/g wet wt in skeletal Muscles).**

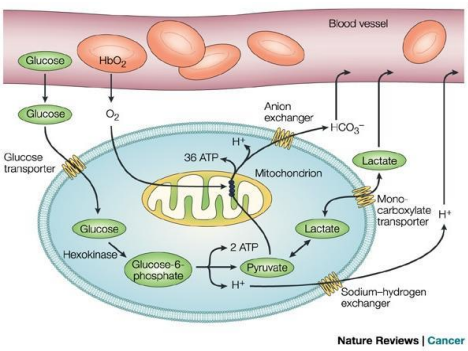
- **Glucose transport into cardiomyocyte is regulated by Transmembrane glucose gradient and the content of glucose Transporter in the sarcolema –GLUT-4 which is translocating to The membrane in response to signaling by insulin, increased Work demand, or ischemia, with GLUT1 playing an Accessory role .**

- Glycolytic pathway converts glucose 6-phosphate and NAD^+ to pyruvate and NADH, generating 2 ATP molecules for each glucose molecule. Under anaerobic condition, pyruvate is converted to lactic acid (non-oxidative

glycolysis). Under aerobic condition, pyruvate and NADH are shuttled to the mitochondrial matrix to generate CO_2 and NAD+.

- **Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) converts glyceraldehyde-3-phosphate to 1,3- diphosphoglycerate → production of NADH.**
- **GAPDH is major regulatory step, it is inhibited by the accumulation of NADH and activated by NAD^+.**
- **Severe ischemia in heart → lactate and NADH accumulation → cessation of oxidative metabolism and lactate production**
- **Regulatory enzymes in glycolysis (hexokinase, phosphofructokinase, and pyruvate kinase) as well as Glyceraldehyde-3-phosphate dehydrogenase (although it is a reversible reaction)**
- **In anaerobic conditions (ischemia) pyruvate is reduced to lactate by lactate dehydrogenase enzyme with oxidizing NADH to NAD+ (increased lactic acid levels)**
- **Lactate > liver to form glucose (gluconeogenesis), called cori cycle**
- **One of lines in treatment of MI is O2**
- **If there is Accumulation of lactic acid in cardiac muscle will cause fatigue > arrhythmias and HF**
- **So we need to get MI suspect patients to ICU to get oxygen immediately**
- **PFK-1, the key regulatory Enzyme in glycolytic pathway Catalyzes the second irreversible step.**

We have a collection of exchangers , so if CO2 is formed it will be dissolved in water by carbonicanhydrase enzyme and it will give us bicarbonate and hydrogen ions , bicarbonate which will go outside and Hydrogen ions will go out side through Na ,h+ exchange the h+ will join the bicarbonate out side to form carbonic acid which will dissociate into water and CO2



- **PFK-1 utilized ATP → fructose 1,6-bisphosphate, Is activated by ADP, AMP and Pi and inhibited by ATP And fall in pH .**
-
- **PFK-1 can be also Stimulated by fructose 2,6- Bisphosphate (formed from Fructose 6-phosphate by PFK-2).**
- **Mono carboxylate transporter functions to get lactate out the cardiomyocyte and not entering from plasma to the cell when lactic acid level in the muscle is high**
  But if there is shortage in glucose and FA the transporter will allow the entry of lactate back in the cell to produce energy > 15 ATP

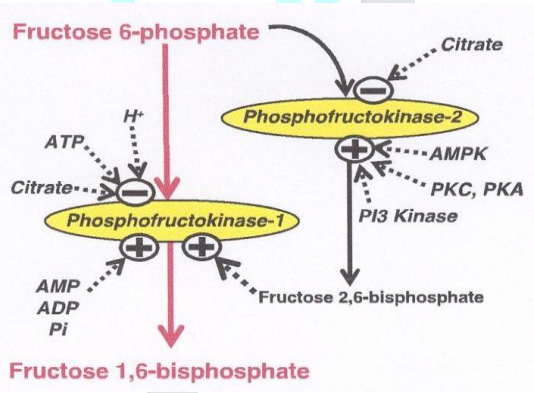
- **In the mitochondria pyruvate is:**

1- **Oxidatively decarboxylated Into acetyl CoA by pyruvate Dehydrogenase (PDH)**

Phosphofructokinase-1 is controlled by the ATP and citrate concentration, If high ATP and citrate it will inhibit it and vice versa

Fructose 2,6-bisphosphate is an activator of Phosphofructokinase-1which is also inhibit by high citrate levels

4 kinase activate Phosphofructokinase-2 which are : AMPK , PKC , PKA , PI3 Kinase



Or

2- **Carboxylated into oxaloacetate By pyruvate carboxylase**

Or

Reduced in cytosol to lactate by Lactate dehydrogenase

oxaloacetate fate

Either > Kreps cycle (in the mitochondria) > for energy production

Or oxaloacetate can undergo a transamination reaction (oxaloacetate + glutamate>>>>> aspartate + alpha ketoglutarate) by the enzyme aspartate amino transferase > aspartic acid for protein synthesis

Pyruvate can turn into lactate by lactatedehydrogenase enzyme either go to the liver or to myocardial cells if need for energy by Mono carboxylate transporter

pyruvate transamination reaction (pyruvate + glutamate >>> alanine) by the enzyme alanine amino transferase

- **The control of PDH activity is an essential part of overall control of glucose metabolism.**
- **PDH – mitochondrial multicomplex, activity is controlled by work, substrate and hormones.**
- **Lactate is released in the blood stream through specific transporter, which has critical role in maintaining the intracellular pH (removes also the protons produced by glycolysis).**

Lactate metabolism

- During starvation, lactate can be recycled to pyruvate.
NAD+ is reduced to NADH [2.5 ATP - lactate oxidation to pyruvate].

- Pyruvate is then burned aerobically in the CAC, liberating (12.5) ATP per cycle

-PDH regulation, activation by low energy forms, inhibition by any high energy form

-Total 15 ATP (lactate to pyruvate produce 1 NADH, transition step 1 NADH, and 3 NADH from CAC = 5*3= 15 ATP

- **Although only 2% the heart's ATP is produced in glycolysis, but It becomes very important under anaerobic or ischemic status.**
- **Indeed, in heart failure and hypertrophy, there is a metabolic Switch towards favoring carbohydrate over FAs metabolism in the Heart.**
- **Glycolytic intermediates can participate in several additional Pathways that do not lend to ATP generation.**
- **These pathways are of biological significance in the heart Despite the small fluxes.**

- **Glucose 6-phosphate produced by the hexokinase reaction Enters PPP, yielding NADPH during the oxidative phase and 5- Carbon sugars in the non-oxidative phase.**

- **The supply of NADPH from the PPP is important for Antioxidant defense as NADPH is required for maintaining the Level of reduced glutathione**
- **PPP previously named hexose monophosphate shunt**

- **End products of the non-oxidative phase of the PPP are also of significance as ribose 5-phosphate becomes a substrate for nucleotide or nucleic acid synthesis while xylulose 5-phosphate has been suggested as a transcriptional signaling molecule.**

- **An alternative fate of G6P is the production of sorbitol, via the enzyme aldose reductase , in the polyol pathway.**

- **The role of polyol pathway in normal cardiac metabolism is unknown but increased flux has been noted in diabetic patients and has been associated with abnormal glucose metabolism and cardiac dysfunction. Also, increased aldose reductase flux has been implicated in the myocardial response to ischemia- reperfusion injury**

-Sorbitol: alcohol (of glucose and mannose)
-Aldose reductase is present in cardiomyocytes but its function and importance is unknown
But they discovered that sorbitol present in higher amounts in patients with heart disease indicating abnormal glucose metabolism (glycolysis and CAC)
-And also high in ischemia-reperfusion injury (after formation of collateral vessels)

- **The glycolytic intermediate fructose 6-phosphate can diverge into the hexosamine biosynthetic pathway, yielding uridine diphosphate -N-acetylglucosamine , via the enzyme glutamine fructose 6-phosphate amidotransferase**

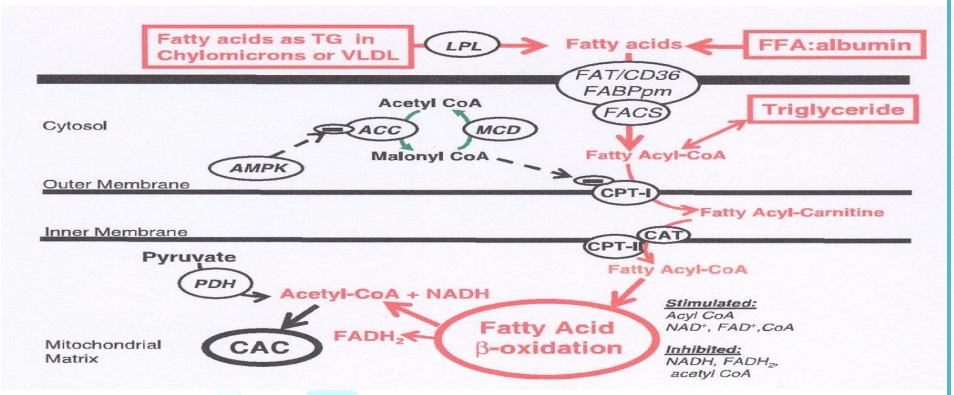
- **Uridine diphosphate –N -acetylglucosamine is participating in O-linked glycosylation reactions of proteins, it is observed in diabetes and**

proposed to be responsible for alteration of insulin sensitivity and fatty acids oxidation

- **Uridine diphosphate –N -acetylglucosamine high levels in patients with insulin insensitivity**

Fatty acids metabolism

- FAs enter the cardiomyocyte by:



Passive diffusion
Protein-mediated transport across sarcolema – fatty acid translocase (FAT) or plasma membrane fatty acid binding protein (FABP).

- Fatty acyl-CoA synthase (FACS) activates nonesterified F.A. by esterification to fatty acyl-CoA

LPL: lipoprotein lipase enzyme

Albumin: nonspecific carrier of FAs

FAs has 2 sources from outside (chylomicrons or VLDL) by LPL enzyme which get carried on albumin as a nonspecific carrier to be uptaken by the cardiomyocyte

on the outer surface of cardiomyocytes there are two types of proteins 1- called FAT (fatty acid translocase) and CD36 with it 2- fatty acid binding protein reaptake FAs or by passive diffusion

After entry it should be activated to prevent it from leaving the cell by Fatty acetyl-CoA synthase

- FAT/CD36 is one of the main translocases, most abundantly Expressed in cardiomyocytes, an 80 kDa integral membrane Glycoprotein which is stored in intracellular compartments and Transported towards the cell membrane in response to increased Energy demands. It is also the most important FAs

translocase In the heart and has a key role in the entry of long-chain FAs Into cardiomyocytes.

- **Excessive expression of FAT/CD36 has been associated with Impaired cardiac insulin sensitivity, reduced uptake of glucose, And excessive uptake of FAs, subsequently causing Cardiomyocyte lipotoxicity and retention of GLUT4 in their Cytoplasm.**

- **In addition to plasma concentration of FAs, an important long-Term regulator of β-oxidation of Fas is the modulation by Peroxisome proliferator-activated receptor (PPAR).**

- **Numerous coactivator proteins, such as PPAR-γ co-activator 1-α can powerfully induce the transcription of PPAR target Genes**

- **FAT/CD36 most abundantly expressed in cardiomyocytes, more than any other tissue, why? More uptake of fatty acids in the heart cells Highly regulated**

- **The targeted genes are including those involved in FAs storage (such as diacylglycerol acyltransferase, promoted by PPARα), FA oxidation (such as medium-chain acyl-CoA dehydrogenase, Promoted by PPARα/ β/δ/γ), and glucose metabolism (such as Pyruvate dehydrogenase kinase 4, promoted by PPARα).**

- **PPAR and PPARγ also plays an important role in the Regulation of oxidative stress in the cardiovascular system, with Several isoforms implicated in various transcriptional Mechanisms for antioxidant genes. Such as promoting the Transcription and activation of Cu/Zn-SOD, Cu/Mn-SOD and Catalase in cardiac tissues. Furthermore, PPARα augments IGF-1 Transcription, subsequently activating the IGF-1/PI3K pathway, Inhibiting apoptosis and protecting cardiomyocytes under Ischemic stress**

Cu/Mn-SOD in mitochondria
Cu/Zn-SOD in cytoplasm

-Why there is 2 types of SOD in the myocardial cells ?
To prevent free radicals or oxidative stress like super oxide which is the first free radical produced due to highly oxidative character of the cardiomyocyte and also protect cardiomyocyte from other problems like by enhancing the rate of expressing of the gene encoding for inulin like growth factor 1 and therefore activating ib3 kinase enzyme the combination of these protects cardiomyocytes from apoptosis especially in the cases of ischemic stress
-Why MI are dangerous? because once the heart doesn't receive o2 it will start fibrosis
Inferior MI is the most dangerous type of MI because it is the least of them in blood supply and the infraction takes a wide space of the inferior space

- **SOD: superoxide dismutase**
- **PI3K: phosphatidylinositol 4-kinase**
- **IGF: insulin like growth factor**

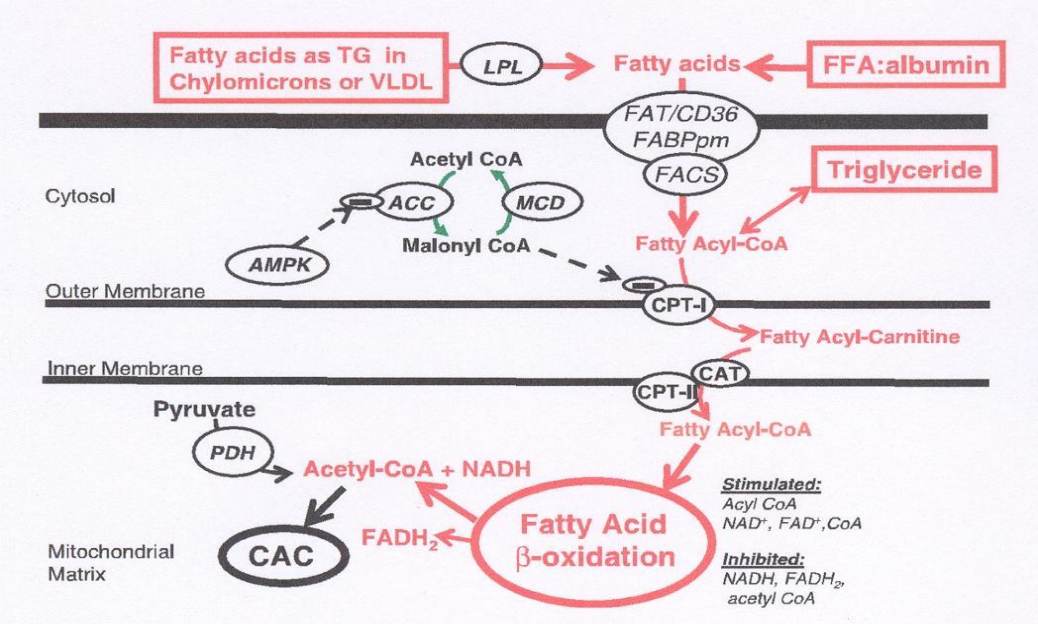
- Long chain fatty acyl-CoA can be:
1- Esterified to triacylglycerols (glycerolphosphate acyltransferase) →→ intracardiac triacylglycerols pool (10-30% of FA)

The fatty acids have 2 sources
Out sides: chylomicrons and VLDL
Inside: triglyceride

****we need to be carful when we describe 2 medications to a patient if they are both have albumin carrier because if the concentration of one of them higher than the other then it will bind with all the albumin binding sight which will result in defective of the medication , this called drug interaction**

2-Or converted to long chain fatty acylcarnitine by carnitine palmitoyltransferase -I (CPT-I) between inner and outer mitochondria membranes

-First condition of the beta oxidation reaction is the entry of the fatty acyl-CoA to the mitochondria



-Mitochondria doesn't allow long chain to enter so it needs a carrier called carnitine and has 3 enzymes :1)CPT-1 ,2) CPT-11, 3)CAT
-CPT-1 : found on the outer surface of the mitochondria membrane to receive fatty acyl-CoA and take the fatty acyl from the CoA and bind it with carnitine to from fatty acyl-carnitine so its able to enter the mitochondria

- **Carnitine acyltranslocase (CAT) transports long-chain Acylcarnitine across the inner membrane in exchange for free Carnitine.**
- **-CAT: take out carnitine from the outer and carry it to the inner membrane and the moment CAT deliver fatty acyl-carnitine to CPT-11 so the carnitine detached out to start a new cycle and CPT-11 binds fatty acyl with CoA**
- **-all fatty acid oxidation found in the mitochondria except for the activation of the fatty acids**
- **Carnitine palmitoyltransferase II (CPT-II) regenerates long Chain acyl-CoA to free fatty acyl-CoA CPT-I can be strongly inhibited by malonyl CoA (on the Cytosolic side of the enzyme).**

  Malonyl CoA is one of the controlling FAs oxidation enzymes, it's a physiological regulator of FAs oxidation which inhibits for the most important enzyme in FAs oxidation which CPT-1 ,

- its also elongating factor in the FAs biosynthesis , the process of FAs synthesis called De novo , the malonyl CoA is the one adding 2 carbons each time in the synthesis process

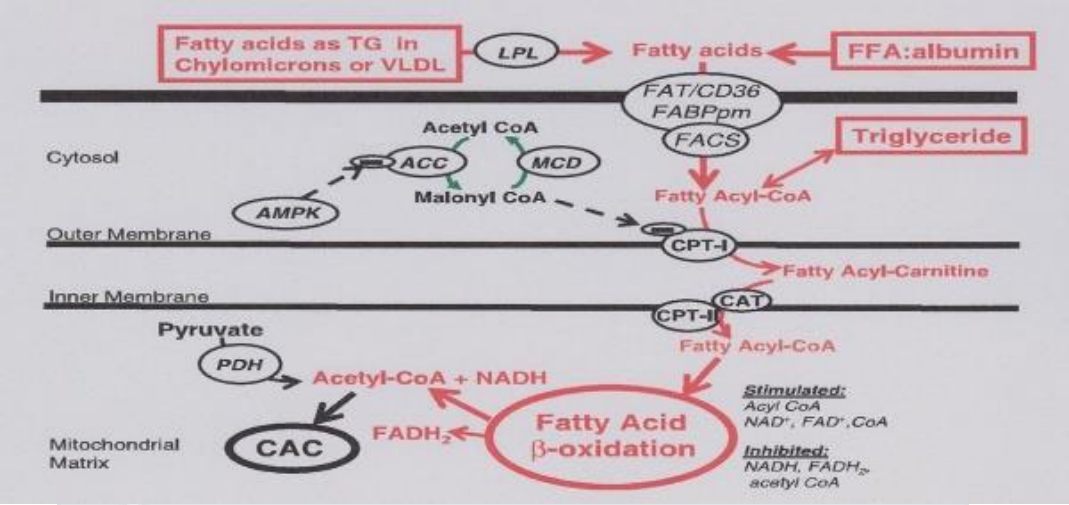
عشان هيك Malonyl CoA بشتغل في عملية (تصنيع ال FAs) عكس عملية ال FAs oxidation

ويوقف عمل ال CPT-1 و لا يمكن للعمليتين انهم يحدثوا مع بعض (FAs oxidation and synthesis)

*** Two isoforms of CPT-I:**

- liver CPT-Iα and heart CPT-Iβ

- CPT-Iβ is 30-fold more sensitive to malonyl -CoA Inhibition



- **Malonyl -CoA – key physiological regulator of FA oxidation In heart (in malonyl -CoA →↑ FAs uptake and oxidation).**
- **Formed from the carboxylation of acetyl-CoA (acetyl-CoA carboxylase – ACC) from extramitochondrial acetyl-CoA (derived from citrate via ATP-citrate lyase reaction)**
- **The carboxylation of acetyl-CoA to form malonyl-CoA requires 4 things**
  1- B7 or vitamin H :as the carrier of CO2
  2- CO2 :in the form of bicarbonate
  3- ATP: for the fixating of carbon dioxide in acetyl-CoA
  4- Manganese : as a cofactor

-the acetyl-CoA coming from the citrate from the citric acid which meets ATP -citrate lyase enzyme to form oxaloacetate and acetyl-CoA and then acetyl-CoA turns into malonyl-CoA by carboxylase enzyme

- **Rapid rate of turnover in the heart.**

- **ACC activity is inhibited by phosphorylation of AMPK (AMP-activated protein kinase) → acceleration of FA Oxidation.**

ACC is one of the enzymes controlled by phosphate group , which its active form is the dephosphorylated form of this enzyme and the not active form is the phosphorylated one.

So if the cardiac muscles is not in need for FAs they inhibit their synthesis by phosphorylation of ACC

- **FAs undergo β-oxidation generating NADH and FADH2.**
  Acetyl-CoA formed in b-oxidation generate more NADH in TCA cycle.

Interregulation of fatty acid and carbohydrate oxidation

- **The primary 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.**
  The 2nd enzyme in carbohydrates oxidation that should be controlled is pyruvate dehydrogenase multi enzymes complex that turn the pyruvate into acetyl CoA , this reaction produce energy and lead to more energy producing and its inhibited by the increased amounts of NADH , ATP and acetyl -CoA these factors don't inhibit the enzyme work directly but work through 2 enzymes 1- pyruvate dehydrogenase kinase 2- pyruvate dehydrogenase phosphatase
  So if the factor works on the activation of pyruvate dehydrogenase kinase it will inhibit pyruvate dehydrogenase multi enzyme complex and if the factors inhibit the pyruvate dehydrogenase kinase it will activate the pyruvate dehydrogenase multi enzyme complex except for pyruvate dehydrogenase phosphatase because its under the influence of Ca and Mg and this enzyme will remove the phosphate group from pyruvate dehydrogenase in its unactive form to get back to its active form

- **Inhibition of FA oxidation Increases glucose and lactate Uptake and oxidation by:**

1- **Decreasing citrate levels And activation of PFK**
2- **Lowering acetyl CoA And/or NADH levels in the Mitochondria**

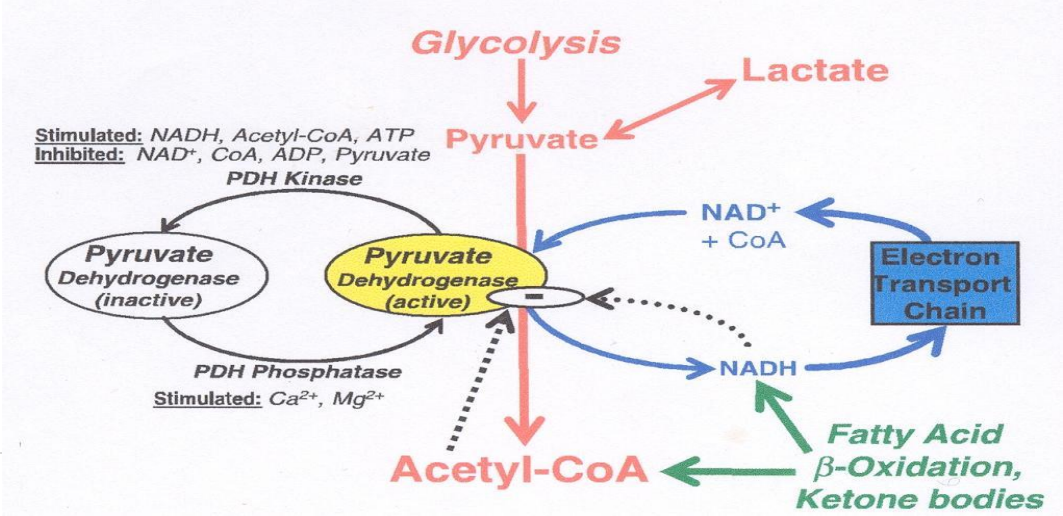
Fatty acids vs. glucose as energetic substrates

- **The selection of energetic substrates in cardiomyocytes is a fundamental step for the constant generation of ATP which depends on the dynamic metabolic requirements in each body at a given time.**

- **This flexibility is present during fetal development; however, after birth, FAs become the preferential substrates, due to the increased availability of oxygen and dietary fats.** ركز ع الفقرة هاي

Because it has FAs and O2 comes through placenta and the haemoglobin in fetus has alpha2 and gamma2 and that means more affinity for O2 than adult that has alpha 2 and beta 2 in their haemoglobin
So the fetus inside uterus has O2 and FAs so if there is and genetic defect responsible for FAs metabolism (uptaking , oxidation, transferring) this will affect the energy production because the fatus 90% of energy is produced from FAs (the mother protect him from lipotoxicity)
But if the O2 levels decreased the energy will decrease too because one of the genes is defected it will lead cardio myopathy ,heart failure and left ventricular hypertrophy

- **Infants with mutations in genes involved in FA metabolism have been documented to develop cardiomyopathy when under stress.**



- **Likewise, in heart failure and left ventricular hypertrophy (when the oxidative capacity of mitochondria in cardiomyocytes is diminished), there is a shift towards a predominance for glucose metabolism**

- **Several reports have shown that cardiac efficiency, in Terms of oxygen consumption, is greater when oxidizing Glucose and lactate rather than FAs.**

- **The increase in oxygen consumption during utilization of FAs is accompanied with no changes in mechanical capacity of the left ventricle, which suggests a greater functional capacity for This chamber when utilizing glucose.**

- **This may be due to the higher level of oxidative stress caused by the oxidation of FA in comparison with carbohydrates, due to the increased oxygen consumption rate in the former.**

FAs metabolism means more beta oxidation interaction which means more NADH which means more incidence of free radical formation which means more oxidative stress happening

- **The ATP synthesis/oxygen consumption rates for glucose and Lactic acid are 3.17 and 3.00, respectively; whereas**

- **When comparing palmitate with glucose, the complete Oxidation of 1 molecule of palmitate yields 92 ATP molecules And requires 46 oxygen atoms, while 1 molecule of glucose Generates 30 ATP molecules and uses 12 oxygen atoms.**

- **Thus, despite FAs clearly yielding greater amount of ATP, this Occurs at the expense of larger oxygen requirements.**

- **Furthermore, β-oxidation of FA generates more lipid Peroxidation due to ↑ delivery of NADH and FADH2 to ETC and Production of superoxide anion.**

- **In addition, elevated free FAs are harmful in the ischemic Myocardium, augmenting cell damage in the first hours of AMI.**

- **Various systemic conditions such as obesity cause elevated Serum free FAs which can potentiate β-oxidation, and thus Increase lipid traffic in cardiomyocytes, prompting lipotoxicity.**

- **This process can lead to contractile dysfunction, insulin Resistance and apoptosis in association with accumulation of ceramidesthey are 2.80 and 2.86 for palmitate and oleate, respectively**

- **Partial inhibition of free FAs oxidation in the myocardium can Prevent or diminish tissue damage and dysfunction under Conditions of ischemia or reperfusion, diabetic cardiomyopathy, And AMI.**

- **This occurs because the heart shifts towards glucose as the main Source for ATP synthesis, which reduces the oxygen demand by 11%-13% and therefore improves cardiac efficiency and protects Mitochondrial function.**

أعِنّا يا ربِّ على وقتنا الضيّق،
ولا تكِلنا إلى أنفسنا الهلوعة،
وكثِّر لنا ثمارَ جُهدنا القليل،
واجعل عاقبتنا خيرًا في الأمور كلِّها