Biochemistry of Cardiac Muscle-1

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Biochemistry of Cardia...

Biochemistry of Cardiac Muscle-1

aerobic = Oxygen + blood ((not O only))

Specifity of cardiac metabolism

-The heart is one of the most active and highly oxidative organ in the body. aerobic oxidation be of huge amount of energy Produced ((30 with glucose)) while fatty acid oxidation ((92))

- 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.

if were oxidized Glucose or Protien 4,1 while Fat is 9,5 Kcal

thats why heart depends on fatty acid and fatty oxidation thats why mitochondria is huge

((largest mitochondria is in the liver))

Cardiac muscle tries to make balance between energy and contraction

under anaerobic condition Glucose will Produce 2 ATP instead of 30

Pyruvat → lactite

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;

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

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).

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

طريقة عمل الطاقات :-

1- أصل ال Primary substrate ⇐ lipid or glucose

2- كسره لعمل ATP ((Oxidative Phosphorylation))

3- خزن ال ATP لـ انتقال ال CK enzyme

If ischemia, anerobic condition ⇒ excesive oxidation of Glucose ⇒ lactic acidosis ⇒ liver ⇒ to be converted to glucose by Corie Cycle thats why heart disease is always associated with liver disease ((liver exhaustion))

accumulation of lactate in heart = HF

Temporary ischemia = Chest Pain

angina = Permanent ischemia

MI = Coronary Plug

PC = Reserve of energy when needed ((fastest way to give energy ((10-30 sec))

last Product that we always seek is acetyl CoA wich is used in TCA cycle

even amino acids with deamination will Provide acetyl CoA

[PK] = 3 [ATP] in all muscles including cardiac muscle

- The metabolic machinery of the heart utilizes oxygen up to during activity 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. Heart depends On aerobic metabolism ((oxidative phosphorylation))
- 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.

Albumin is the carrier and supplier

FAs biosynthesis < FAs Oxidation

- High Oxygen Demand: When the body is in motion, during physical activity, exercise, or in response to increased metabolic demands (e.g., during stress or illness), the heart needs to pump more blood and oxygen to supply energy to the body's cells. This is when the heart operates at or near its maximum oxidative capacity, utilizing 80%-90% of the ETC's capacity. The high demand for energy during these times requires the heart to work harder, and it adapts by increasing its oxygen consumption to meet the energy needs.
- Low Oxygen Demand: In contrast, during periods of rest, when the body's energy requirements are reduced, the heart doesn't need to work as vigorously. At rest, the heart operates at only 15%-25% of its maximum oxidative capacity because the demand for oxygen and energy is much lower. The heart pumps less frequently and with less force, resulting in decreased oxygen utilization. This is an energy-saving mechanism to ensure that oxygen is conserved for times when it is needed most.

  So, the heart's metabolic machinery is adaptable, adjusting its oxygen consumption and energy production to match the body's varying oxygen and energy demands, ranging from low levels at rest to near-maximum capacity during periods of high activity or stress.

30% to 10% من ال Fat الذي بيتكسر بالقلب مصدره الأساسي

هو القلب نفسه بينما معظم ال Fat يأتي برفقة ال Albumin

ليتكسر بالقلب.

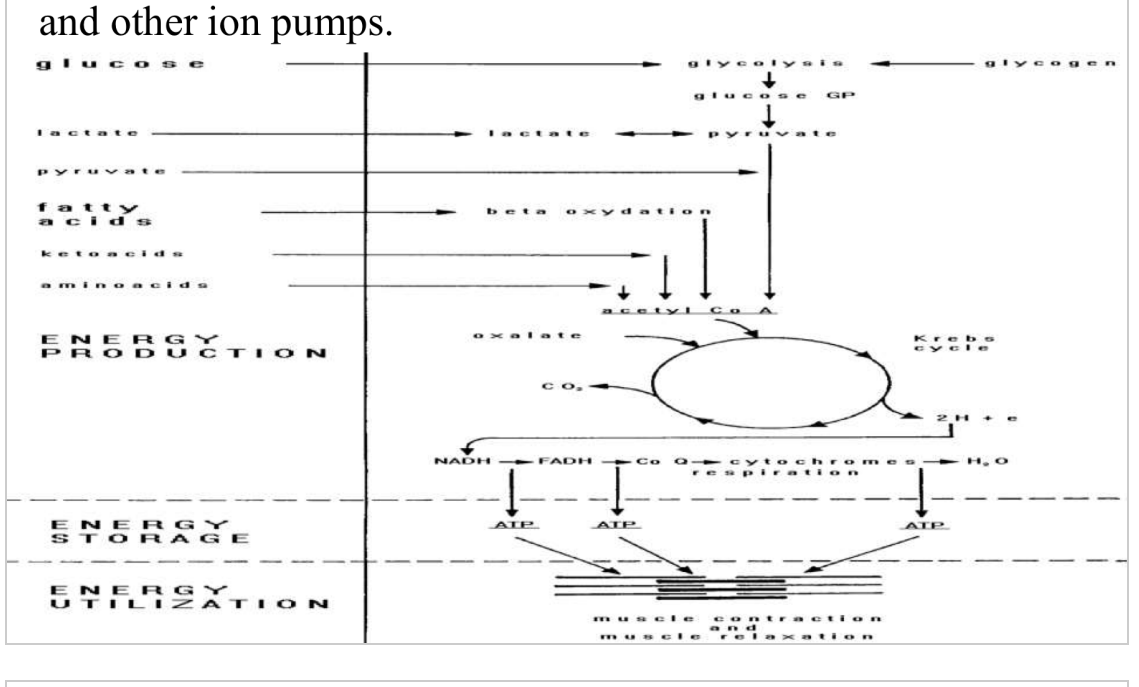
if i want to Know Powerful activity of cardiac muscle then i should estimate the amount of non-estrefied FAs in the circulation

liver failure ⇒ hypoalbuminemia ⇒ ↓ nonestrefied fatty acid ⇒ ↓ Energy

2- 35% from carbohydrates

3- 5% from amino acids an ketone bodies.

- ~ 60-70% of ATP hydrolysis is used for muscle contraction, ~30 - 40% for the sarcoplasmic reticulum (SR) Ca^{2+}-ATPase and other ion pumps.



glucose
glycolysis
glycogen
glucose GP
lactate
lactate
pyruvate
pyruvate
fatty acids
beta oxydation
ketoacids
aminoacids
acetyl Co A
ENERGY PRODUCTION
oxalate
Krebs cycle
CO2
2H + e
NADH
FADH
Co Q
cytochromes
respiration
H2O
ATP
ATP
ATP
ENERGY STORAGE
ENERGY UTILIZATION
muscle contraction and muscle relaxation

30 mmol/g glycogen Pool in Cardiac muscle

150 mmol/g // // // skeletal muscle

Heart depends on transporters wich depends on insulin

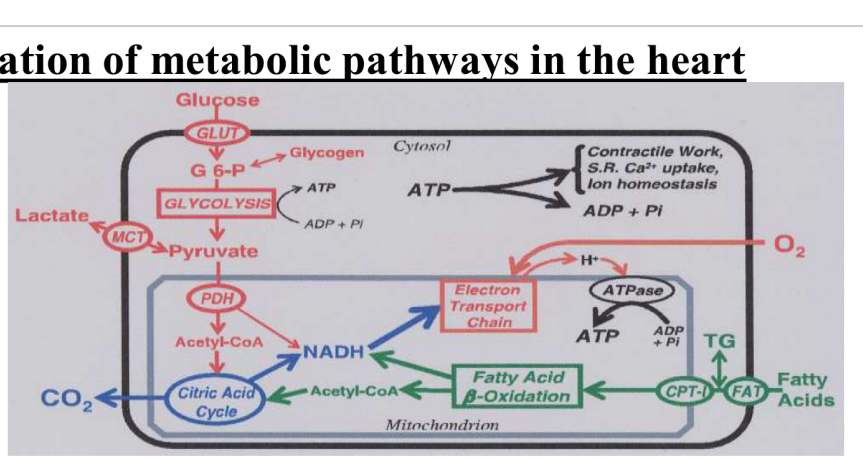
Kwashurkor: Kids food has 0 energy value ⇒ no fat and no protien

leads to: cardiac Protiens degeneration ⇒ Atrophy. ((low Protein content in myocardium))

DM ⇒ no insulin action ⇒ ↓ Cardiomyocytes glucose (inhibition of GLUT4)

leads to ⇒ ↑ fats ⇒ Cardiac lipotoxicity

Regulation of metabolic pathways in the heart



Glucose
GLUT
G 6-P
Glycogen
Cytosol
GLYCOLYSIS
ATP
ADP + Pi
ATP
Contractile Work, S.R. Ca2+ uptake, Ion homeostasis
ADP + Pi
Lactate
MCT
Pyruvate
O2
PDH
Electron Transport Chain
H+
ATPase
Acetyl-CoA
NADH
ATP
ADP + Pi
TG
CO2
Citric Acid Cycle
Acetyl-CoA
Fatty Acid β-Oxidation
CPT-I
FAT
Fatty Acids
Mitochondrion

- CAC is fueled by acetyl-CoA formed by oxidative decarboxylation of pyruvate (glycolysis) (10-40%) + from β-oxidation of FA (60-90%). main source is β oxidation
-The reducing equivalents: NADH and FADH$_2$ (generated by glycolysis, oxidation of lactate, pyruvate and β-oxidation of Fatty Acids Fas) deliver electrons to ETC → ATP (oxidative phosphorylation). ((each acetyl CoA makes 10 ATP)) ⇒ 9 from reducing equivalents ((FADH$_2$ + NADH))

1 substrate level phosphorylation ((GTP))

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). 5 times less

  Cardiac muscle depends on external Glucose and FAs
- 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. Glut 4: insulin-dependent ⇒ ↑insulin → ↑uptake of Glucose

Glut 1: insulin-independent ⇒ Glucose doesn't need insulin. Majority of glucose enters cells from GLUT4

- 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 CO2 and NAD+.

Reaction number 6

- 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.

lactate dehydrogenase depends on Zinc cofactor

lactate → Pyruvate = 2,5 ATP

+

Pyruvate → acetyl CoA = 2,5 ATP

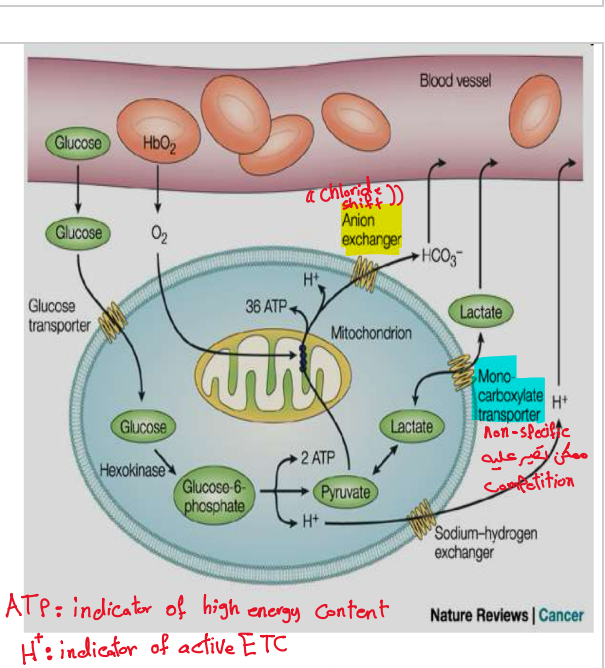
+

acetyl CoA = 10 ATP

∴ lactate Produces = 15 ATP

((half the amount of Glucose))

- PFK-1, the key regulatory enzyme in glycolytic pathway catalyzes the second irreversible step.
- 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).



Blood vessel
Glucose
HbO2
((chloride shift))
Anion exchanger
HCO3-
Glucose
O2
H+
Glucose transporter
36 ATP
Mitochondrion
Lactate
Monocarboxylate transporter
H+
Non-specific
competition
Glucose
Lactate
Hexokinase
Glucose-6-phosphate
2 ATP
Pyruvate
H+
Sodium-hydrogen exchanger
Nature Reviews | Cancer

ATP: indicator of high energy content

H$^+$: indicator of active ETC

Citrate: indicator of active TCA

PFK1 is under affect of energy content intracellularly

H, ~~ATP~~, citrate are Proofs for high activity of CAC wich inhibits PFK 1

- In the mitochondria pyruvate is:

1- Oxiditively decarboxylated into acetyl CoA by pyruvate dehydrogenase (PDH)

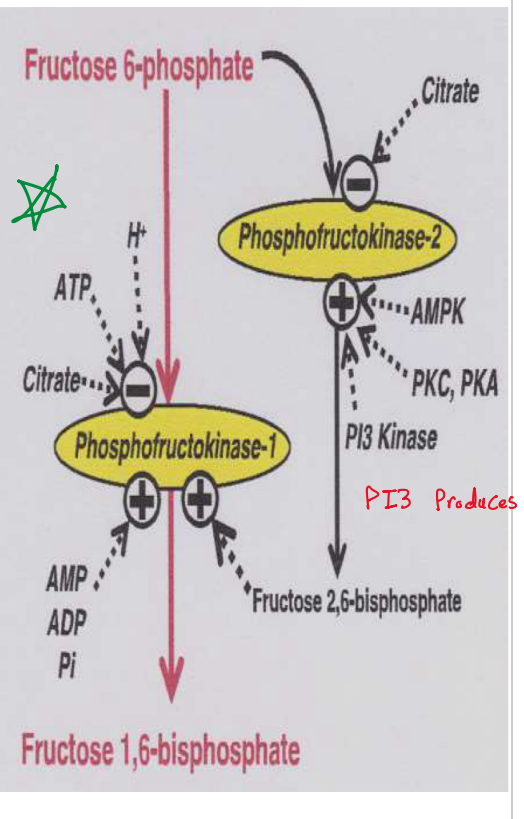
or

2- Carboxylated into oxaloacetate by pyruvate carboxylase

or

- Reduced in cytosol to lactate by lactate dehydrogenase.

Or converted by transaminase to aspartic acid.



Fructose 6-phosphate
Citrate
Phosphofructokinase-2
H+
ATP
AMPK
PKC, PKA
Citrate
PI3 Kinase
Phosphofructokinase-1
AMP
ADP
Pi
Fructose 2,6-bisphosphate
Fructose 1,6-bisphosphate

PI3 Produces IP3 and DAG

- The control of PDH activity is an essential part of overall control of glucose metabolism.
- Pyruvate dehydrogenase 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.

HF = ↓ contractility + ↓ Pumping + ↓ O$_2$ ⇒ anerobic

Glucose dependency > lipid metabolism

عشان هيك بياكل Glucose كثير

- 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.

Selenium is glutathione Coenzyme

if ↑ Glucose dependency in the heart

1- PPP → R5P ((nucliec acid synthesis)) → NADPH → Glutathione Peroxidase activation ((antioxidation))

2- G6P →(Aldose) Sorbitol ((Polyol Pathway)) → diabetic cataracts

3- hexosamine biosynthetic Pathway Glutamine F6P amidotransferase → UDPN acetylglucosamine → O-linked Glycosylation ⇒ Production of glycoProtions

if ↓ insulin sensitivity this would lead to decrease in Udp wich results in dangerous affects on Various organs

- 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. diabetic Cataracts

- 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.

- 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.

Chylomicrons: transportation of exogenous FAs ((from food) in intestine)) ↑TAG content

VLDL: liver ((endogenous)) ↓TAG content

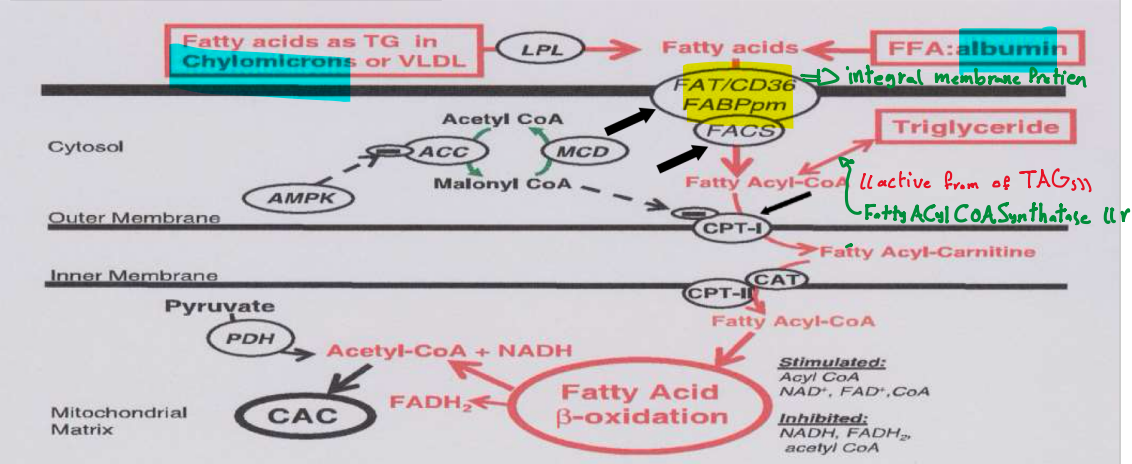
Vascular endothelium secretes LPL wich releases free fatty acids

albumin gives Fat to FABP and CD36

when FAs enters the cell it should be converted to active form ((fatty acyl Coenzyme A)) by its synthetase enzyme for cellular trapping. why synthetase not synthase? synthetase consumes 2 ATP wich makes it regulatory step

the control of fate of FAs is amount of energy ((ATP))

Fatty acids metabolism



Fatty acids as TG in Chylomicrons or VLDL
LPL
Fatty acids
FFA:albumin
FAT/CD36 FABPpm
→ integral membrane Protien
FACS
Triglyceride
Cytosol
Acetyl CoA
ACC
MCD
Malonyl CoA
AMPK
Fatty Acyl-CoA
((active from of TAGs))
Fatty AcylCoASynthatase ((require ATP thus energy is regulating fate of TAGs))
Outer Membrane
CPT-I
Fatty Acyl-Carnitine
Inner Membrane
CAT
CPT-II
Fatty Acyl-CoA
Pyruvate
PDH
Acetyl-CoA + NADH
FADH2
Fatty Acid β-oxidation
CAC
Mitochondrial Matrix
Stimulated: Acyl CoA NAD+, FAD+, CoA
Inhibited: NADH, FADH2, acetyl CoA

- 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.

Controls:

1- FattyAcylCoASynthetase need of energy

2- CD36 migration to cell membrane according to cell demand of energy ((regulates Production and migration

3- amount of energy ((ATP))

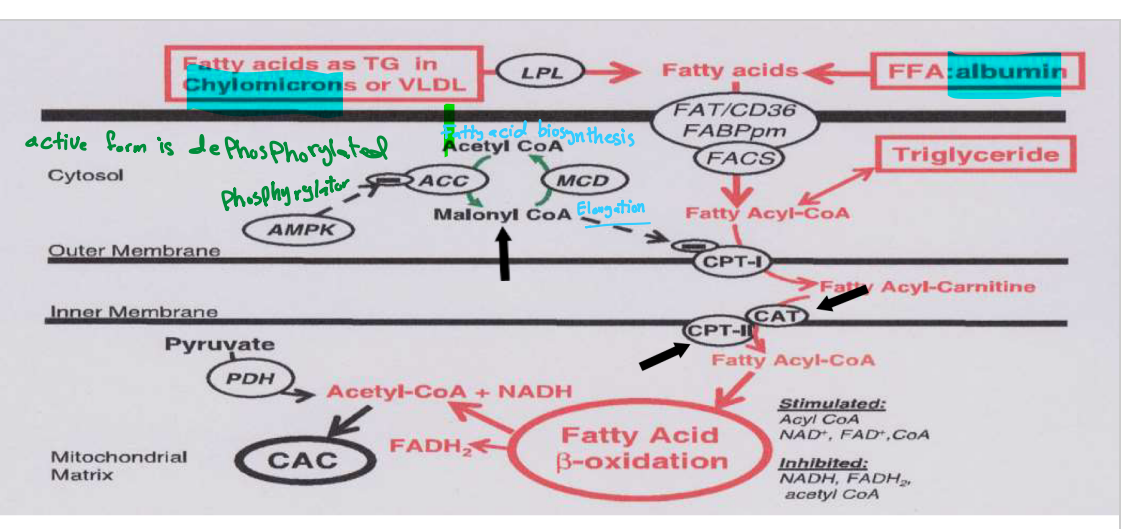
- FAT/CD36 is one of the main translocases, most abundantly expressed in cardiomyocytes, an 80 kDa integral membrane glycoprotein which is stored in intracellular compartments and transported towards the cell membrane in response to increased energy demands. It is also the most important FAs translocase 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. another reason: Problem in GLUT4

- 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. the Cofactor Controls: FA storage - oxidation - glucose metabolism

- 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).

  (regulates FA oxidation indirectly)
- 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 Cytosolic Cu/Zn-SOD, mitochondrial 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.



Fatty acids as TG in Chylomicrons or VLDL
LPL
Fatty acids
FFA:albumin
FAT/CD36 FABPpm
FACS
Triglyceride
active form is dephosphorylated
fatty acid biosynthesis
Acetyl CoA
Cytosol
Phosphylator
ACC
MCD
Elongation
AMPK
Malonyl CoA
Fatty Acyl-CoA
Outer Membrane
CPT-I
Fatty Acyl-Carnitine
Inner Membrane
CAT
CPT-II
Pyruvate
Fatty Acyl-CoA
PDH
Acetyl-CoA + NADH
FADH2
Fatty Acid β-oxidation
CAC
Mitochondrial Matrix
Stimulated: Acyl CoA NAD+, FAD+, CoA
Inhibited: NADH, FADH2, acetyl CoA

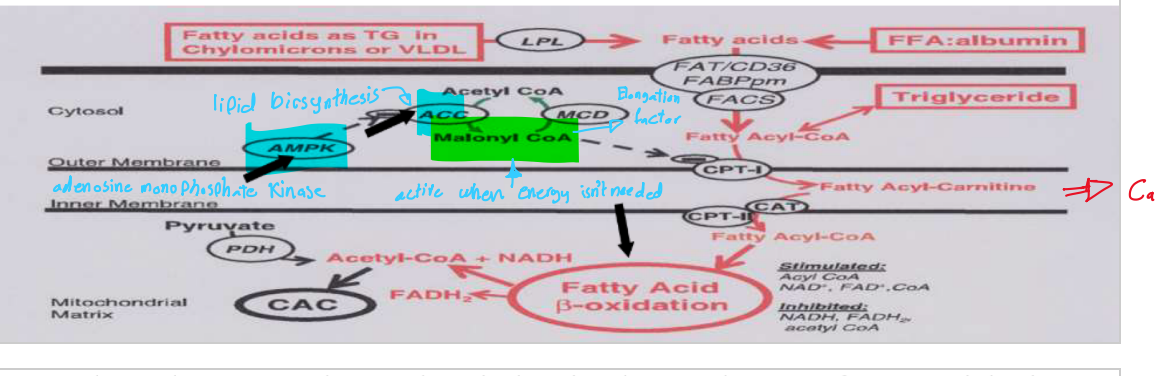
- Long chain fatty acyl-CoA can be:

  1- Esterified to triacylglycerols (glycerolphosphate acyltransferase) →→intracardiac triacylglycerols pool (10-30% of FA)

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

- Carnitine acyltranslocase (CAT) transports long-chain acylcarnitine across the inner membrane in exchange for free carnitine.
- 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).
- Two isoforms of CPT-I:
  - liver CPT-Iα and heart CPT-Iβ
  - CPT-Iβ is 30-fold more sensitive to malonyl -CoA inhibition.



Fatty acids as TG in Chylomicrons or VLDL
LPL
Fatty acids
FFA:albumin
FAT/CD36 FABPpm
Cytosol
lipid biosynthesis
Acetyl CoA
Elongation factor
FACS
Triglyceride
ACC
MCD
AMPK
Malonyl CoA
Fatty Acyl-CoA
Outer Membrane
adenosine monophosphate Kinase
active when energy isn't needed
CPT-I
Fatty Acyl-Carnitine
Inner Membrane
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Pyruvate
Fatty Acyl-CoA
PDH
Acetyl-CoA + NADH
FADH2
Fatty Acid β-oxidation
CAC
Mitochondrial Matrix
Stimulated: Acyl CoA NAD+, FAD+, CoA
Inhibited: NADH, FADH2, acetyl CoA

⇒ Carnitine shuttle

- 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)
  - Rapid rate of turnover in the heart.

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

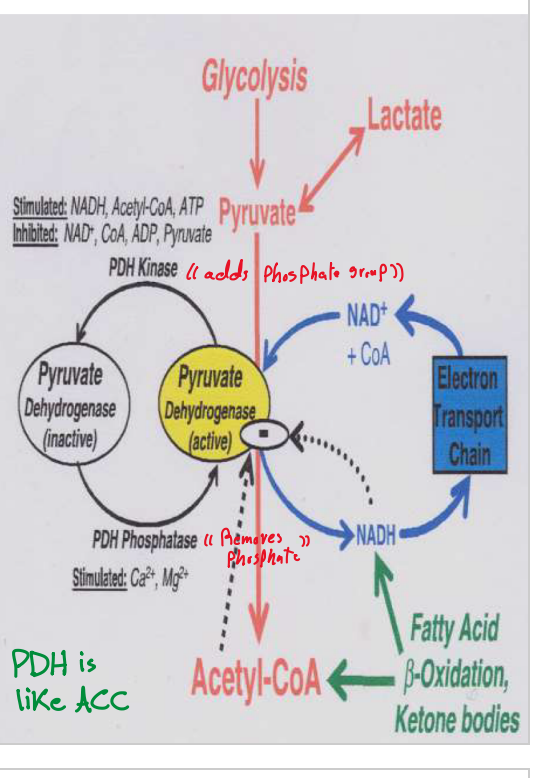
- FAs undergo β-oxidation generating NADH and FADH2. Acetyl-CoA formed in b-oxidation generate more NADH in TCA cycle.

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.
- 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



Glycolysis
Lactate
Stimulated: NADH, Acetyl-CoA, ATP
Inhibited: NAD+, CoA, ADP, Pyruvate
Pyruvate
PDH Kinase ((adds Phosphate group))
NAD+ + CoA
Pyruvate Dehydrogenase (inactive)
Pyruvate Dehydrogenase (active)
Electron Transport Chain
PDH Phosphatase ((Removes Phosphate))
Stimulated: Ca2+, Mg2+
NADH
PDH is like ACC
Acetyl-CoA
Fatty Acid β-Oxidation, Ketone bodies

Cardiomiocyte are flexible, in fetal development β oxidation > adult β oxidation

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. They have sufficient O$_2$ and fat
- Infants with mutations in genes involved in FA metabolism have been documented to develop cardiomyopathy when under stress. develoPes to HF
- 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.

- The ATP synthesis/oxygen consumption rates for glucose and lactic acid are 3.17 and 3.00, respectively; whereas they are 2.80 and 2.86 for palmitate and oleate, respectively

92 needs 23 O$_2$ in β oxidation

90 ATP needs 18 O$_2$ in Glucose metabolism

- 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. ((increased risk for oxidative stress
- 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 ceramides. ⇒ not metabolised in cardiomyocytes

ركز: عدد ال Atoms مو عدد ال molecule يعني مو O$_2$

- 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.