Biochemistry of Cardiac Muscle-1

Specifity of cardiac metabolism

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

This sentence mean: there must be equilibrium between demand (الحاجة) and energy supply to the heart.

- 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.

- Cardiac depend on fatty acids mainly as the source of energy.

Heart needs

ATP

الي انقفنا إنه يتم تصنيعه عن طريق

Oxidative phosphorylation

it means that I have intermediates:
- NADH
- $FADH_2$

they enter → Mitochondria → to enter ETC

They have energy in the form of electrons

Mitochondria: تمثل 30% من حجم ال Cardiac myocytes

In ETC these electrons enter chains of reactions

خلال التفاعلات الإلكترونات بكونوا أعطوا طاقة كامنة داخل السلسلة.

لـ هاي الطاقة رح أستخدمها بأني أحول

ADP → ATP

(عن طريق عملية phosphorylation)

e^- e^- e^- → O_2 → آخر مستقبل للالكترونات و أعطيه "H" الموجود في NADH, FADH → to form H_2O molecule.

نهاية هاي التفاعلات

Sources of NADH and FADH

- fatty acids 60% ← تستخدم في حالة unesterified state
- glucose 35%
- Ketone bodies, Amino acids 5%

→ Acetyl COA → it will enter → Krebs cycle

- NADH = 2.5 ATP
- FADH = 1.5 ATP

Krebs cycle:
- 1 ATP
- 3 NADH = 7.5 ATP
- 1 FADH = 1.5 ATP

إذاً ال Krebs cycle تنتج 10 ATP

* خلينا نتفق إنه ال Cardiac myocytes تعتمد بشكل كبير على free FA and carbohydrates الموجودة برا في الدم و هي بتكون قادرة على تخزين كمية كتير قليلة من Free fA and carbohydrates in the form of:

FA → triglycerides   glucose → glycogen

* إذاً جزء منهم يتم تحويله إلى ATP للاستهلاكه و الجزء الآخر يتم تخزينه لوقت الحاجة.

glucose in blood

بدخل عن طريق transporter معين

↓

cardiomyocytes → If we are in the state of needing ATP this glucose will undergo glycolysis

الي هو عبارة عن GLUT 4 (Main) + GLUT 1 (accessory)

* There are some conditions that have to exist so the glucose can enter through GLUT 4 transporter:
- Insulin → because that transporter is insulin dependant
- concentration gradient → outside is higher than inside
- The cell must be in active state and O_2 exist

***glycolysis produce:**
1. 2 NADH
2. 2 ATP

glycolysis → end product → pyruvate

Also it produce 2 NADH

pyruvate → then it will be converted into Acetyl CoA through enzyme Pyruvate dehydrogenase

Acetyl CoA enters ETC

في هاي الحالة أنا بكون في عندي O_2 حتى إنه اقدر أكمل السلسلة.

pyruvate → إذا أنا مش بحاجة طاقة هذا ال pyruvate ممكن يتحول إلى alanine بطلع من cardiac myocytes و بروح على liver وبدخل في Chahil cycle ويتحول مرة أخرى إلى pyruvate then glucose

glucose → glycolysis → pyruvate → (lactate dehydrogenase) → lactate

2 NADH → أيضا تراكمهم يؤدي إنه أدخل في lactate pathway عشان أحولهم إلى NAD^+ و تضل عملية glycolysis continuous

(If there is no O_2 this pyruvate will not be converted into Acetyl COA and it will undergo another pathway which is lactate pathway)

lactate → يؤدي إلى حدوث fatigue to the muscle ففي هاي الحالة بوديه على liver وهناك بتدخل Chori cycle وحيث برجعها إلى pyruvate

*pyruvate also may be converted into oxaloacetate

*pyruvate → Acetyl COA (decarboxylation)

*pyruvate → oxaloacetate (Carboxylation)

* ATP that is produced is used in:

1- Contraction
2- Ca^{+2} uptake to the smooth endoplasmic reticulum.

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;

→ Free fatty acids, glucose

acetyl CoA

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

→ And that will produce ATP

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).

→ when ATP is produced (حتى إنه يتم استهلاكها), the phosphate group will be taked and added to the creatine

بالشكل الصحيح وهي تضيع

لـ باستخدام الإنزيم PC-CK وإنتاج مادة PC (energy store)

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

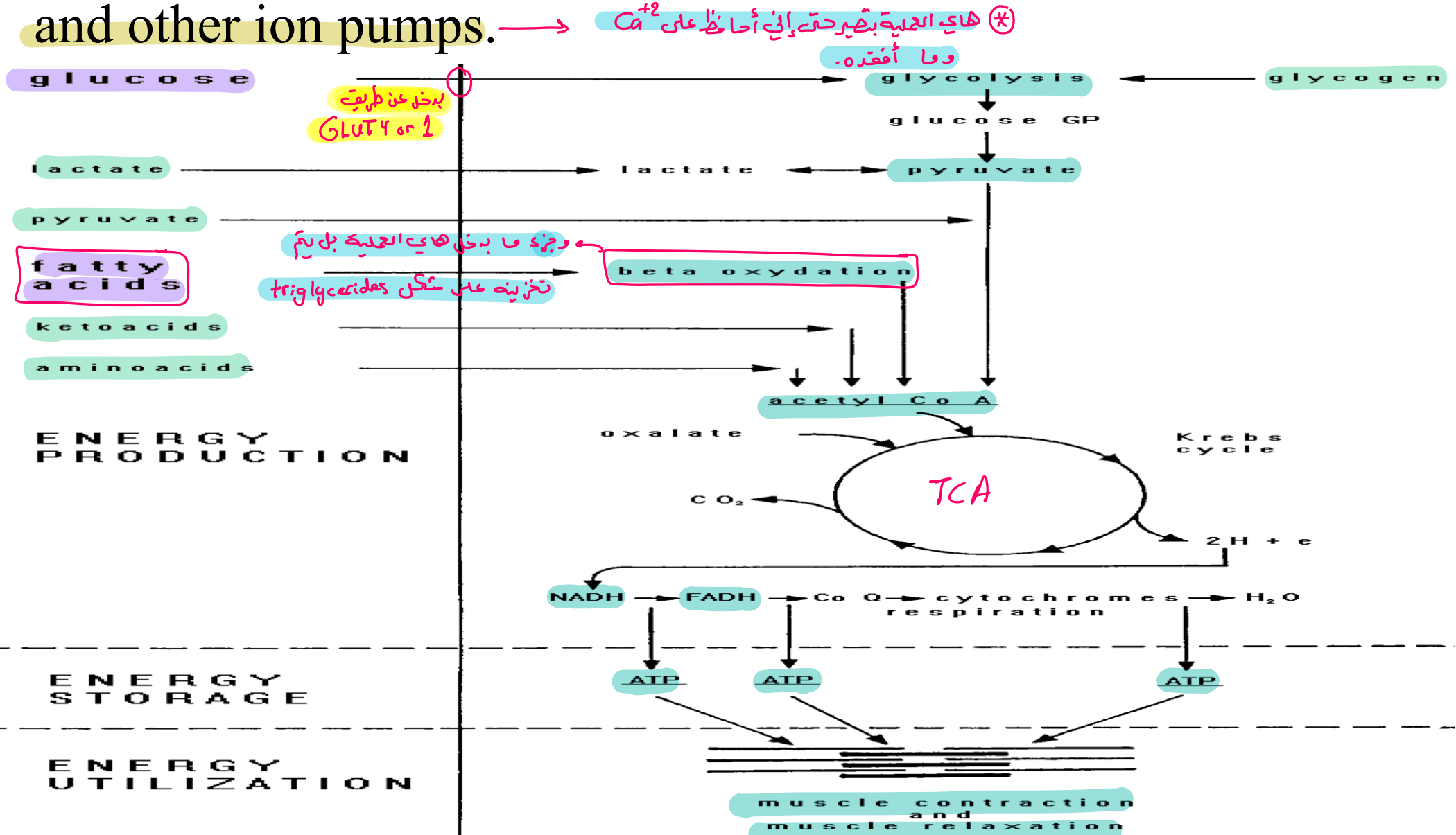
- The metabolic machinery of the heart utilizes oxygen up to 80%-90% of the maximum capacity of ETC ; however, at a resting state, the heart operates at only 15%-25% of its maximum oxidative capacity.
- Cardiomyocytes show an elevated rate of ATP hydrolysis, which is strongly linked to oxidative phosphorylation 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.

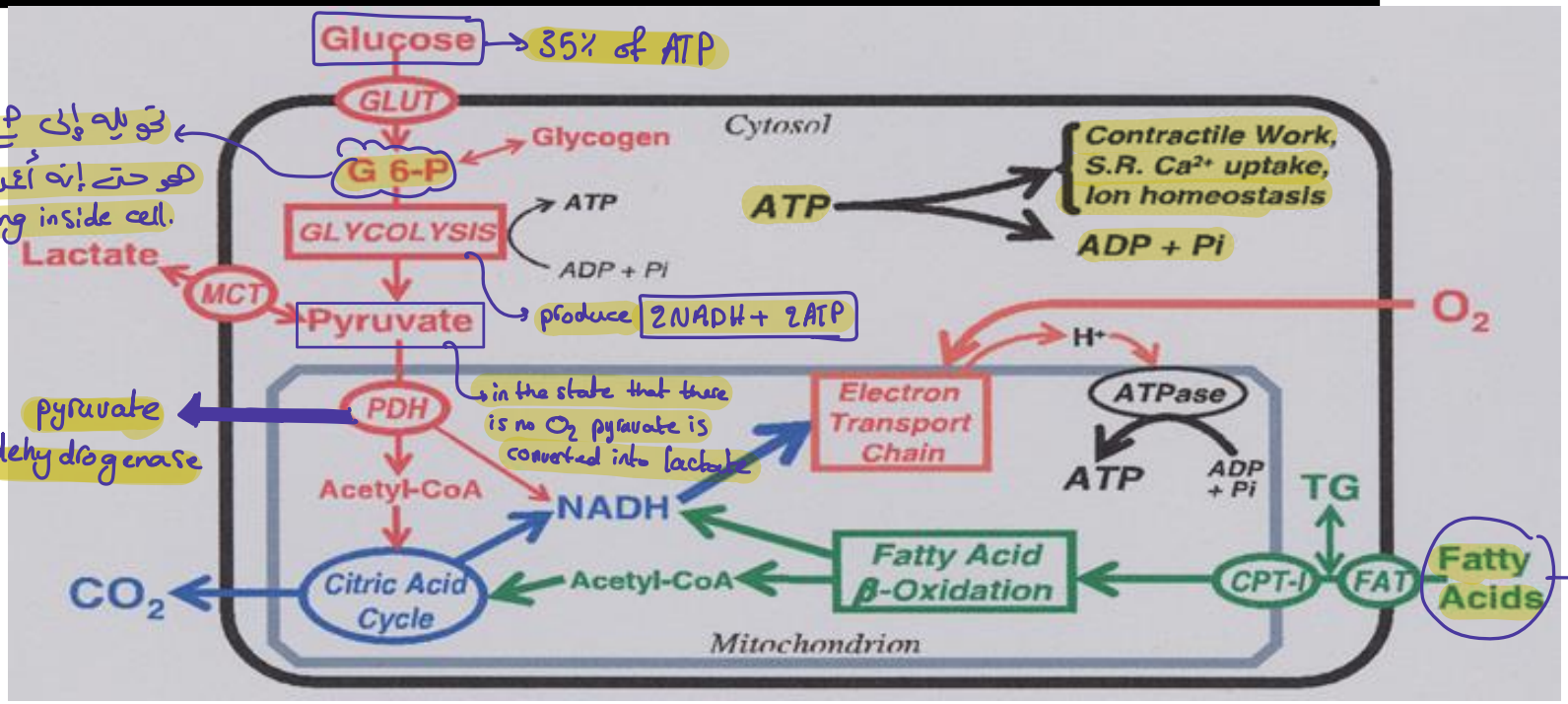
2- 35% from carbohydrates

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.



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). → So in Cardiac muscle glycogen pool is $\frac{1}{5}$ glycogen pool in skeletal muscle.

- Glucose transport into cardiomyocyte is regulated by ① transmembrane glucose gradient and the ② content of glucose transporter in the sarcolema –GLUT-4 which is translocating to the membrane in response to signaling by insulin, ③ 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 CO2 and NAD+.

* The main process for regenerating NAD^+ is oxidative phosphorylation → في حال عدم وجود O_2 يتم اللجوء إلى lactate pathway

- Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) converts glyceraldehyde-3-phosphate to 1,3-diphosphoglycerate → production of NADH.

→ This is the enzyme that produce NADH in glycolysis process.

→ regenerating أنا بعمل لل NAD^+ حتى إنه مايتم تنشيط GAPDH through negative feedback.

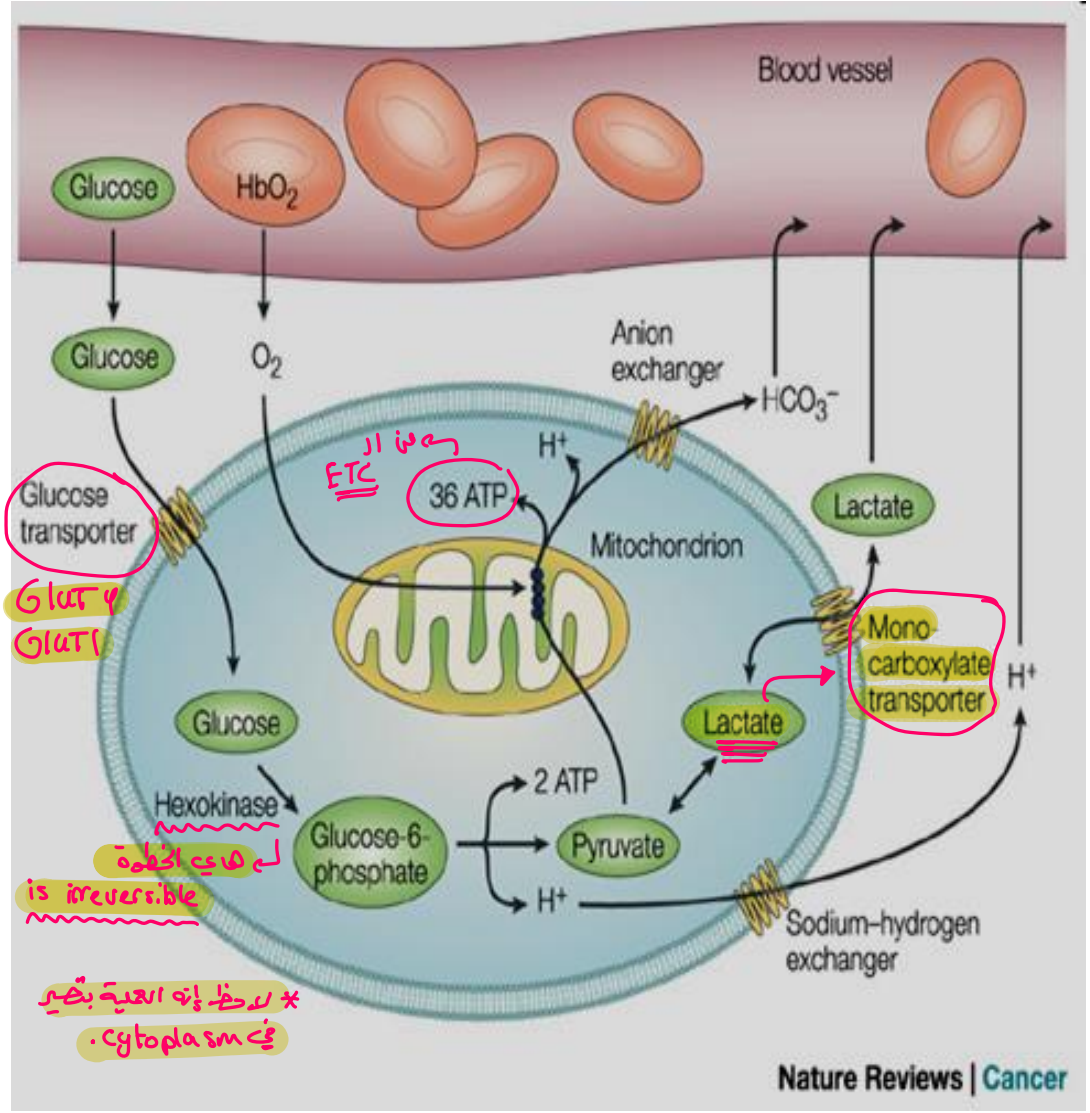
- GAPDH is major regulatory step, it is inhibited by the accumulation of NADH and activated by NAD^+.

→ because there is no O_2 and there will be a shuttle to the lactate pathway.

- Severe ischemia in heart → lactate and NADH accumulation → cessation of oxidative metabolism and lactate production.

اقرأ الصورة في next slide first.

- 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. which is increase in ↑H^+.
- PFK-1 can be also stimulated by fructose 2,6-bisphosphate (formed from fructose 6-phosphate by PFK-2).



- In the mitochondria pyruvate is:

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

or

2- Carboxylated into oxaloacetate by pyruvate carboxylase

or

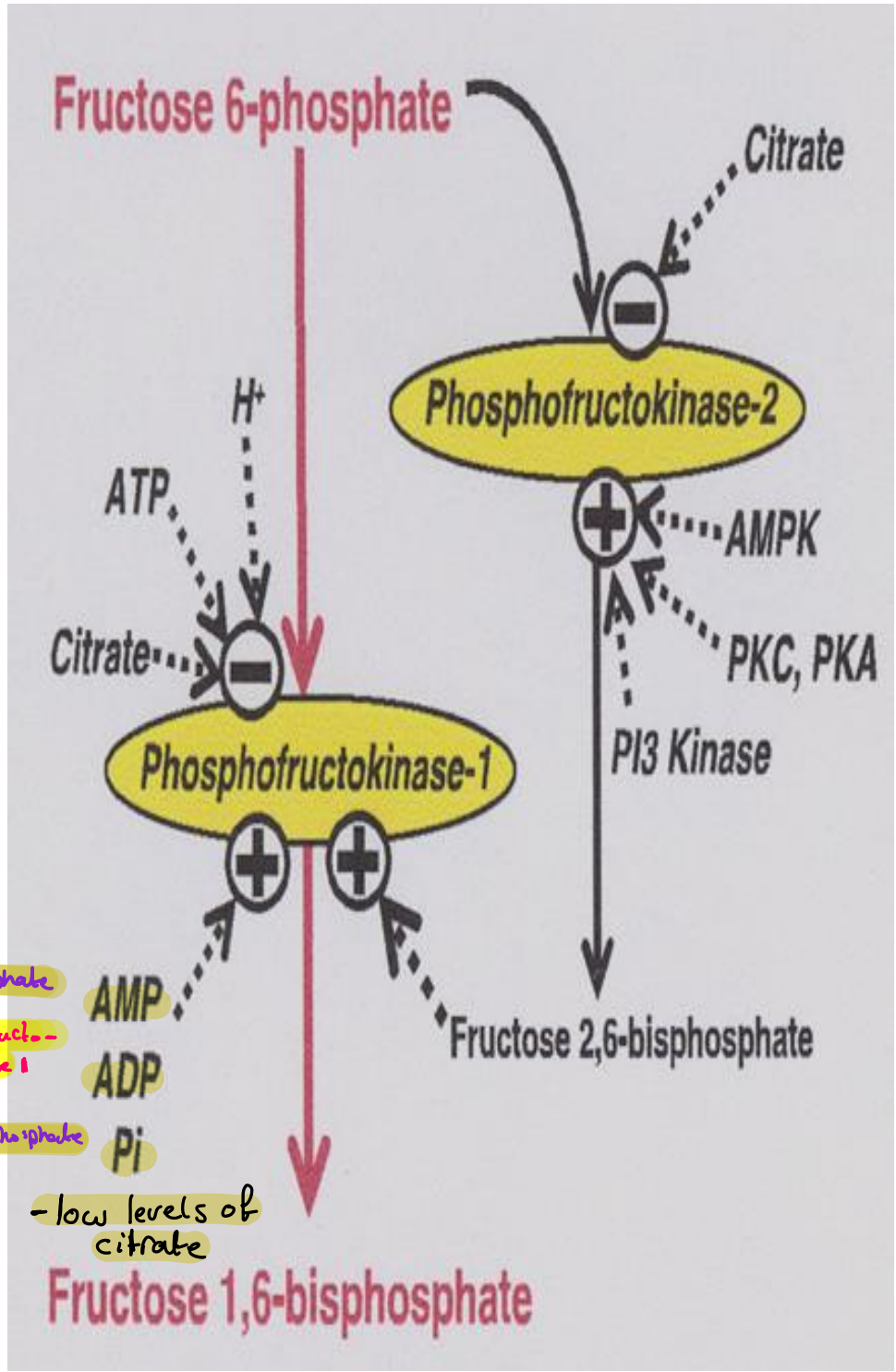
- Reduced in cytosol to lactate by lactate dehydrogenase.

* Glycolysis:

glucose —(glucokinase enzyme)→ glucose-6-phosphate → fructose-6-phosphate

هذي الخطوة هي عبارة عن regulatory process. ← phospho fructo-kinase 1

fructose-1,6-Biphosphate



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

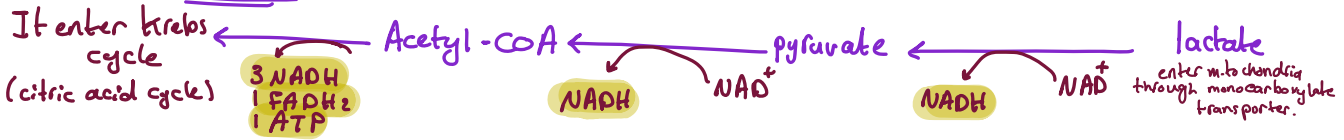
It's located in the mitochondrial matrix.

- PDH – mitochondrial multicomplex, activity is controlled by work, substrate and hormones.

monocarboxylate transporter.

- 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).

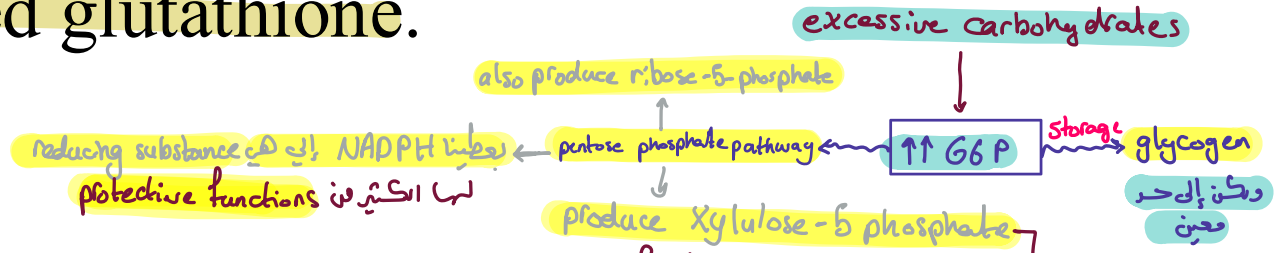
* لـ يكون جسمي لـ طبيعي على يتم استخدام glucose ويصير pyruvate بعطيني 15ATP



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.

- 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.



- 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.

transcriptional factor كعوامل مساعدة

- 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.

This is the enzyme that convert glucose into sorbitol.

- 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

هذا عبارة عن intermediate يدخل في عملية تصنيع proteins.

- 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.

These reasons indicates why our body use FA to produce just 60% of ATP, not more than that.

This lipotoxicity happen due to:

[1] accumulation of FA in cardiomyocytes

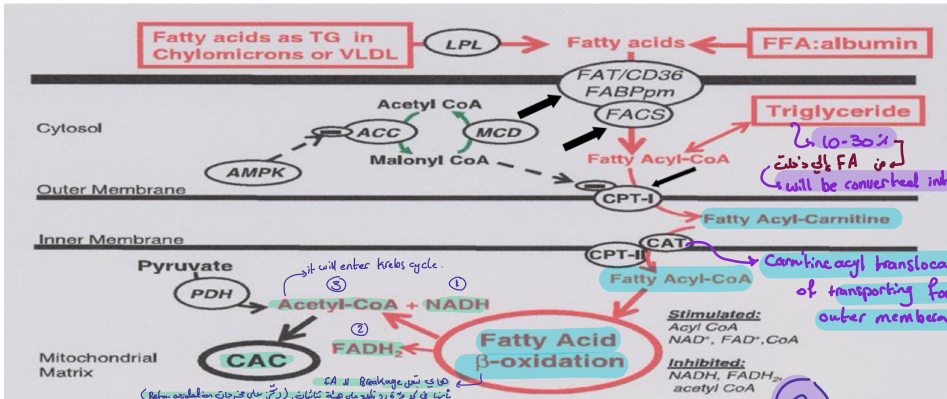
[2] Utilize large amount of O_2 in ATP synthesis from FA in compare with glycolysis.

[3] Oxygen radicals may be produced from ETC → لأنه لما نكون في النهاية H2O عكس يكون في تفاعلات غير مكتملة تؤدي إلى تكوين إحدى ال free radicals

* النّاس إلّي ما رح يقدروا يعتمدوا على glucose وبكونوا معرّضين إلى lipotoxicity:

① مرضى ال DM
لأنه بكون في عندهم insulin resistance
وما بنقدر ندخّل ال carbohydrate إلى الداخل عن طريق GLUT transporters

② الأشخاص إلّي بكونوا معتمدين Specific type of diet that contain ↓glucose



10-30% من FA إلّي دخلت will be converted into triglycerides.

Carnitine acyl translocase is responsible of transporting fatty acyl carnitine from outer membrane to the inner membrane.

it will enter krebs cycle. ③ ①

②

هاي بتعني ال Breakage ل FA بأنها في كل مرة رح تطلع على هيئة ثنائيات. (ركّز على مخرجات Beta-oxidation)

①

* Sources of fatty acids:

1- from diet → that contains triglycerides
هاي تحتوي على FA فلمّا تدخل على الأمعاء بتطلع على صورة Chylomicrons

2- liver contain a storage of triglycerides
بطلعها ال liver على هيئة VLDL

3- Triglycerides produced from fatty tissue in our body.

4- free fatty acids that is conjugated with general transporter as Albumin.

②

* triglycerides is not the one that we use it.

by Hormone sensitive lipase → glycerol, 3 fatty acids

3 fatty acids can enter the cell by 3 ways:

① Simple diffusion
But this way is used by very short or short fatty acids.

② By fatty acid translocase (CD36)
→ the most important because it highly regulated

③ By fatty acid binding protein

خلينا نحكي شوي عن (CD36):

① normally it exists in the cytoplasm and appear on the surface when it's needed.

[2] CD36 expression on the surface increases in many situations as:

[1] insulin insensitivity
لأنه في هاي الحالة ما بقدر أستخدم GLUT4

[2] High work load (I need more energy than usual)

[3] When there is ↓↓ glucose or we can't use glucose.

بس هاي الحالات هي جميعها سلاح ذو حدّين لأنه زيادة وجود ↑FA ممكن أن تؤدي إلى حدوث lipotoxicity ← عشان هيك هاي العملية لازم تكون منظّمة

it's regulated by PPAR

③

PPAR is activated by coactivator

هنا ال coactivator أنواع α, β, gamma.....

when it's activated a proliferation for regulatory enzymes will be done, they may regulate the following metabolic processes:

[1] Production and synthesis of triglycerides

[2] Break down of triglycerides through beta oxidation.

[3] Glycolysis and ATP production from glucose.

[4] Production of antioxidants
لأنه عملية تصنيع الطاقة هي بالنهاية oxygen dependant، هذا الشي ممكن يؤدي إلى تكوين free radicals إلّي ممكن تدمّر خلايا الجسم.

[5] regulate apoptosis and prevent too much apoptosis
لأنه زي ما نحن بنعرف إنه ال Cardiac myocytes ما بتتجددوا.

[6] It also regulates fatty acids uptake by cells.

carnitine acyl tranplocase

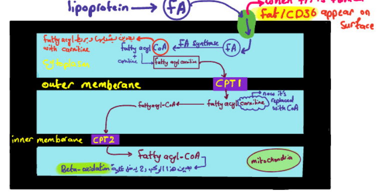
[1] Fatty acids (60%):
القلب يصنّع كمية قليلة من FA ←
طيب من وين بده يجيب FA ؟!!؟

[1] Vascular component
We have 2 types of lipoproteins that can transmit FA from vessels to the heart.

Lipoproteins → Chylomicrons → exist in the intestine
Lipoproteins → VLDL → exist in the liver.

[2] These FA may be attached to the albumins

① وصل lipoprotein إلى القلب
← حتى إني أحصل على FA أحتاج إلى lipoprotein Lipase

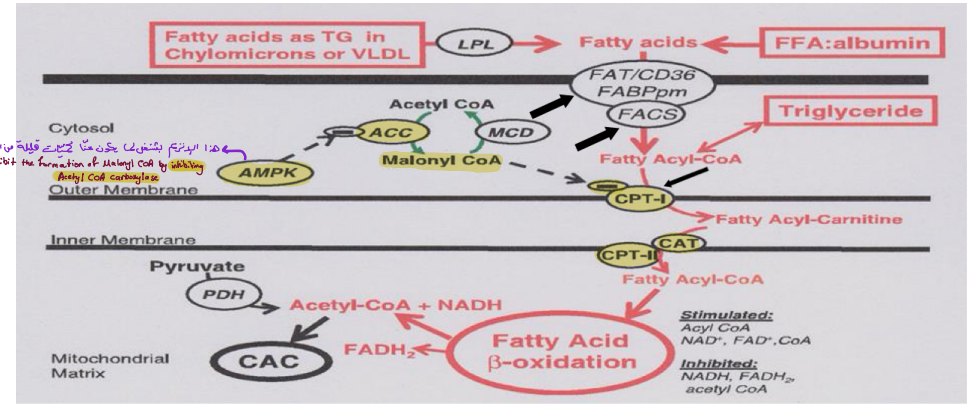


Acetyl-COA يتم الحصول عليه من

* معلومة:
① إذا كان عندي كمية كبيرة من Malonyl CoA موجودة في cytoplasm
→ that means that we have a storage for energy and that will lead to inhibit CPT1 → no fatty acid intake.

② إلّي بنظّم العمليات السابقة هو PPAR (peroxisome proliferator-activated receptor)
وهو مسؤول عن عدّة أمور:

[1] Fatty acid storage
[2] Fatty acid oxidation
[3] glucose metabolism
[4] oxidative stress (anti-oxidant)
[5] prevent apoptosis
[6] ↑↑ expression of Fat.



* Things indicates high level of energy.

① ↑ATP , ↑ ATP، AMP
② ↑NADH , ↑NADH : NAD^+
③ ↑FADH , ↑FADH : FAD^+
④ ↑Acytel-COA , ↑Acetyl CoA : CoA
وجودها كالمها يعني ما في acetyl-CoA معناها ما في طاقة.
⑤ ↑pyruvate
⑥ ↑citrate

⑦ ↑ Malonyl CoA
يتم تكوينه لما يكون عند الشخص كميات كبيرة من Acetyl-CoA عن طريق :

Acetyl-CoA —(Acetyl-CoA carboxylase)→ Malonyl CoA
(إلي أصلها عبارة عن Short chain fatty acid)

وجود أكثر من Malonyl-CoA يؤدي في النهاية إلى تكوين الـ FA الكبير

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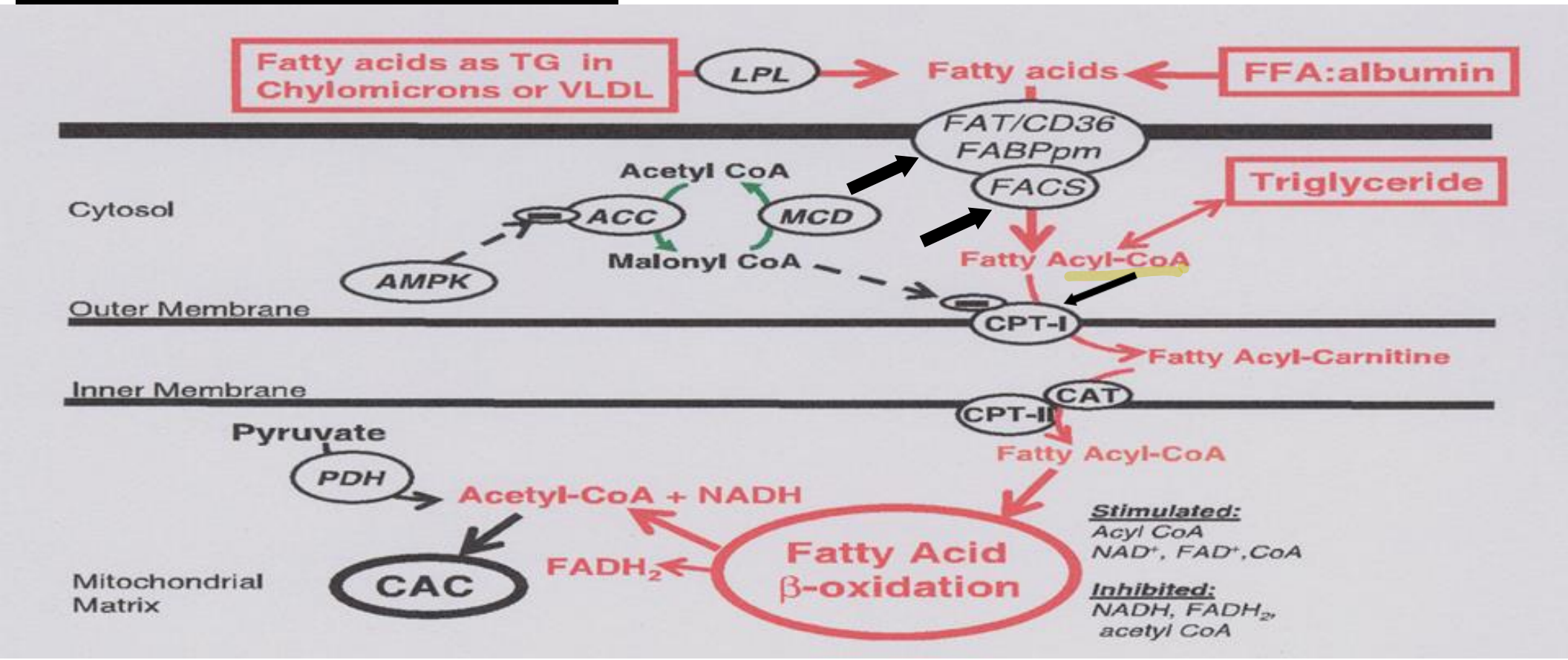
* لو بدنا نقارن ما بين الـ FA و glucose من حيث الـ efficacy :

	FA	Glucose
* كمية الـ ATP الناتجة عن استخدام $1O_2$	2.8 ATP	3.17 ATP — إذا تأكسد glucose في الهواء. النقطة بأنه أعطاني أكثر ATP لنفس كمية الأكسجين O_2
* لو بدنا نستخدم 1 molecule من كل وحدة فيهم	1 FA ⟶ 92 ATP and consume (46) O_2	1 glucose ⟶ 30 ATP consume 12 O_2 atoms. لو نوحّد الأشياء عشان نعرف نقارن : 3 glucose ⟶ 90 ATP ↳ consume 36 O_2 atoms

لـ إذا يتم استهلاك O_2 أقل في هاي الحالة

* في هاي المقارنات واضح إنه الضرر الذي يسببه glucose أقل من الضرر الذي يسببه الـ FA ، ولكن الطريقة التي يستخدمها Heart أكثر هي FA oxidation

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.

CD36

→ that is used for trapping fatty acids.

- 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.

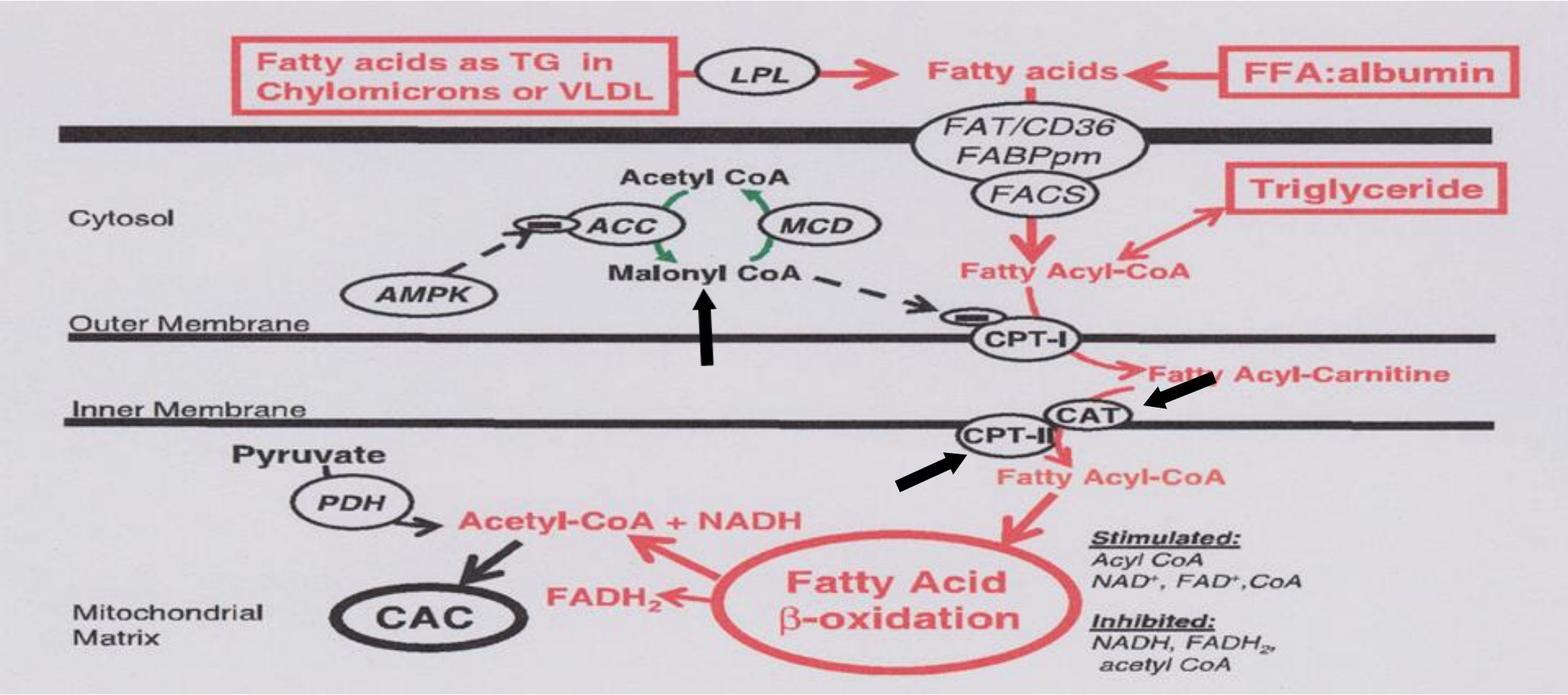
- Excessive expression of FAT/CD36 has been associated with impaired cardiac insulin sensitivity, reduced uptake of glucose, and excessive uptake of FAs, subsequently causing cardiomyocyte lipotoxicity and retention of GLUT4 in their cytoplasm.

↳ and that may also lead to the formation of oxygen free radicals.

- 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 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).

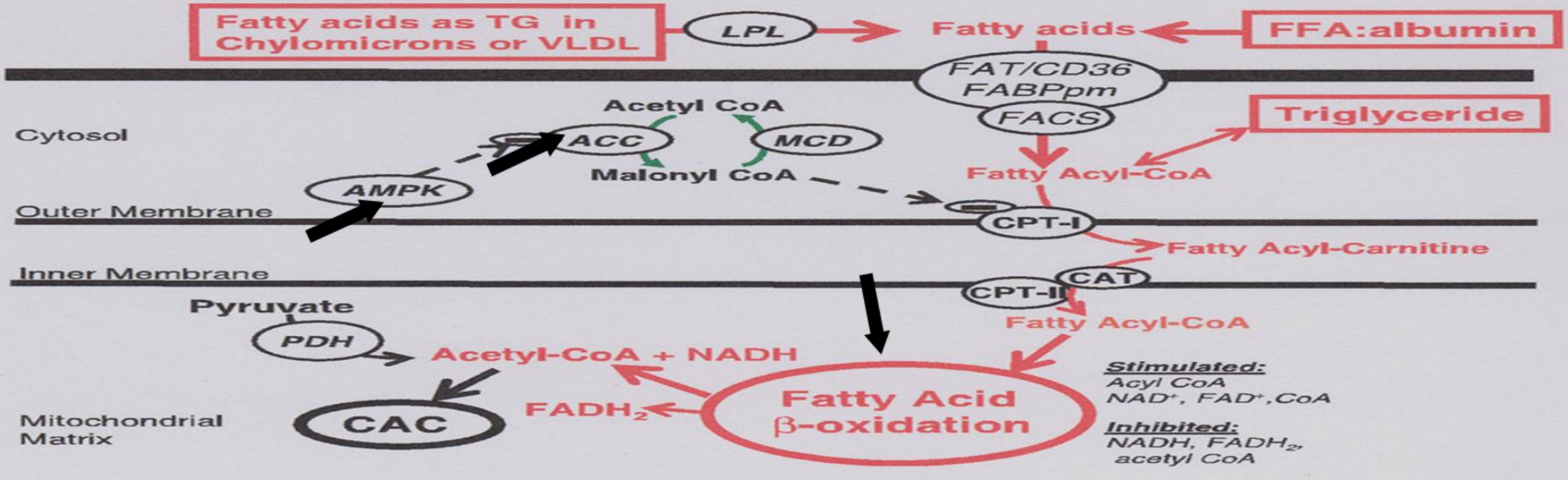
- PPAR and PPARγ also plays an important role in the regulation of oxidative stress in the cardiovascular system, with several isoforms implicated in various transcriptional mechanisms for antioxidant genes. Such as promoting the transcription and activation of Cu/Zn-SOD, Cu/Mn-SOD and catalase in cardiac tissues. Furthermore, PPARα augments IGF-1 transcription, subsequently activating the IGF-1/PI3K pathway, inhibiting apoptosis and protecting cardiomyocytes under ischemic stress.



- Long chain fatty acyl-CoA can be:
  1- Esterified to triacylglycerols (to store it) (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.



- 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.

هذا الإنزيم يحتاج إلى cofactor: Biotin = B7

Malonyl CoA هون بحكيلنا أشياء بتحفّز تصنيع ... واللي هي لما يكون عنّا High energy

← يثبّط عملية تصنيع Malonyl CoA لذلك وجود هذا الإنزيم يدل إنه كمية الطاقة الموجودة قليلة.

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

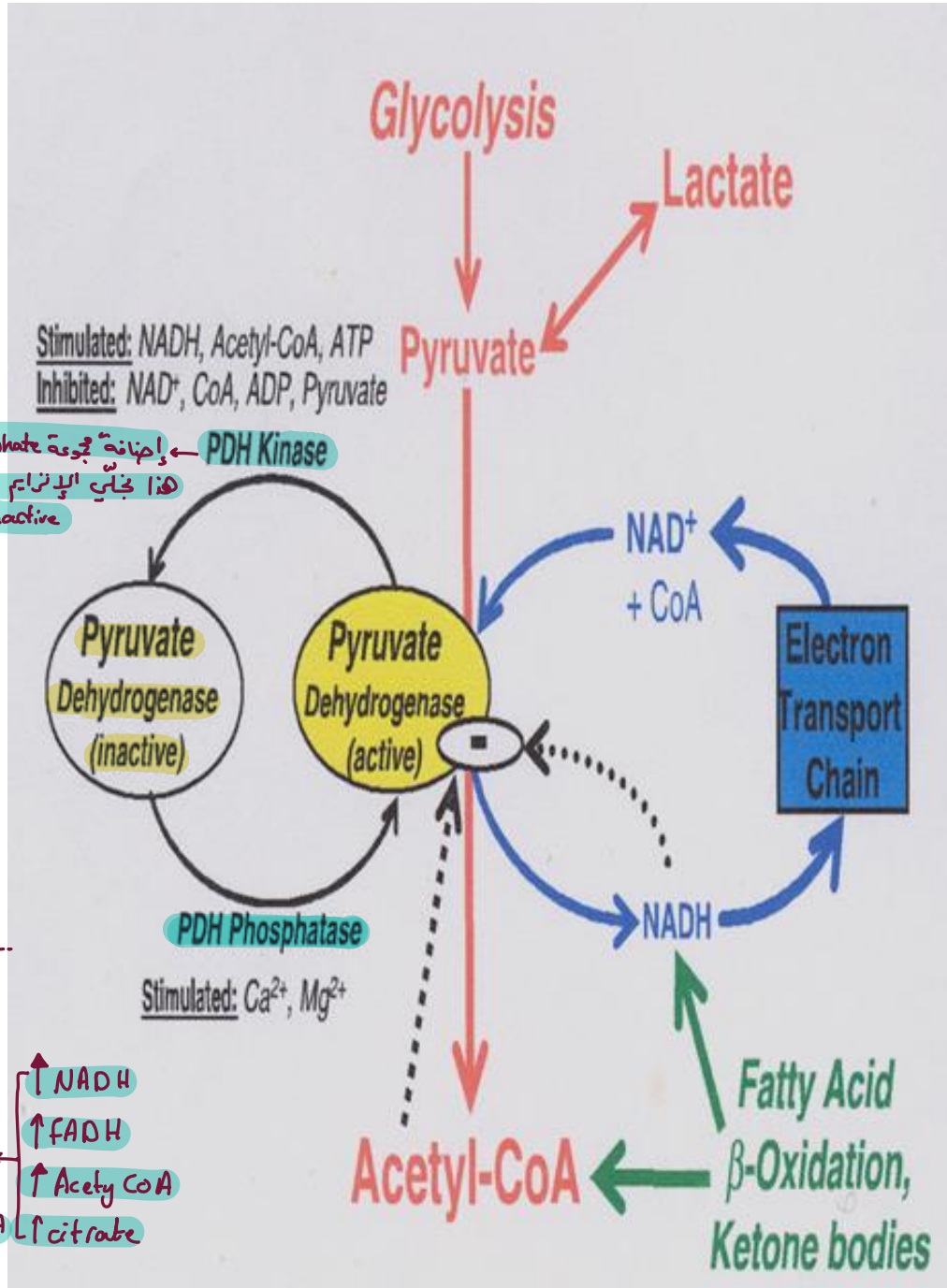
- FAs undergo β-oxidation generating NADH and FADH2. Acetyl-CoA formed in b-oxidation generate more NADH in TCA cycle.

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. → this enzyme that add phosphate group to PDH and that lead to inactivate it.
- Inhibition of FA oxidation increases glucose and lactate uptake and oxidation by:

1- Decreasing citrate levels and activation of PFK → phospho fructo kinase.

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.
- Infants with mutations in genes involved in FAs metabolism have been documented to develop cardiomyopathy when under stress. → because there will be no balance between glucose and FA utilization.
- 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.

↓ O_2 consumption → ↓free radical : أي
↓ damage

- 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

- 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 FAs 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 ceramides.

يعني ↑ تخريب cell membrane وتعمل مشاكل تو.

Acute myocardial Infarction

it's fatty acid.

- 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.