heart most active & most needing of ATP
demand = supply
↓
by oxidative phosphorylation [aerobic]

NADH
$FADH_2$
↓
mitochondria ETC
extract e^- & H (e^- e^- H^+ H^+) + O_2 = H_2O

30% of myocardial size is mitochondria !

ATP is stored as
PC - phosphocreatine
CK - creatine kinase
↳ more secure
in HIGH DEMAND

main energy source of the heart:
- 60% → FA ★
- 35% → carb / glucose
- 5% → ketone / AA

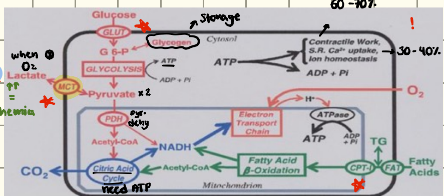
→ = acetyl CoA to krebs cycle
↓
3 NADH / 1 FADH + 1 whole ATP
↓
10 ATP / cycle !!

2.5 NAD
1.5 FAD

FA → glucose
most → acetyl CoA , glycolysis
little → T.G , glycolagen

★! indicators of ischemia
↑ high blood
lactate / NADH

35%   60 - 70%



60%

soure of fatty acids:
H.S lipase [hormone sensetive] CPT 1
↳ free unestrified FA from TG
- ↑ % = ↑ energy for heart
- ⊗ % = ischemia

G6P & NAD^+ → pyruvate & NADH

GAPDH [glyceraldehyde-3-phosphate dehydrogenase]

main regeneration of NAD^+ → oxidative phosphorylation
↳ ⊗ O_2 → GAPDH
↑ by NAD^+ ↓ by NADH

يعني NADH بيعطيني NAD^+ نعشان أرجع مخزون ال NAD لازم أحول ال NADH
بس إذا عندي كثير NADH بصير توقف انتاج ال NADH لأنه خلص كافي فبعمل ⊗ GAPDH
بس إذا في كثير NAD^+ منشان تخلص كل ال NADH عنا موجود NAD^+ فيحفز ال GAPDH ↑↑

"main"   شروط:

★ glucose from blood → myocyte by GLUT-4   insulin dependant ★
& GLUT 1 [accessory]   active
conc. gradient

glycolysis in cytoplasm → 2 pyruvate

Pyruvate
1. ✓O_2 acetyl CoA by pyr. dehyd. [decarboxylation]
2. alanine A.A ↓ liver → pyruvate again by cahil cycle
3. lactate [lact. dehyd.] ⊗ O_2 ↓ NADH → NAD^+ MCT trans.
4. oxaloacetate A.A [carboxylation] 4C

= ⊗ accumulation of NADH ? ⊗
if no more energy needed   glycolysis inhibition
! lactate = fatigue BAD

✓ energy but ⊗ O_2 ??? – heart failure / hypertrophy
anearobic نعتمد عل
= main CARB not FA.

↑↑ carb = ↑↑ insulin = ↑↑ glucose cellular uptake

regulation:
G → G6P → F6P → F 1,6 BP (→ F 2,6 BP)
rate limiting step by PFK-1
! imp !

↳ solution: liver → pyruvate   TCA 3 NADH / 1 FADH / 1 ATP
lactate → pyruvate → acetyl CoA → NAD^+ → NADH (1 NADH)
→ ATP in starvation   1 lactate = 15 ATP !

⊕ ↑ glucose [fructose 2,6 bisphosphate] alt pathway F.1,6 غير
↓ energy [AMP, ADP, Pi] / كمان فيه وجود ال ما غيره   . بيعملها
phosphofructokinase-2   ATP تبعه
⊖ ↑ energy [ATP, citrate, H]

G6P ↑↑↑ = وين نوديه ؟؟
1) glycogen ~30ml/mol
2) PPP pathway ! هامة
NADPH   ribose 5 phosphate → nucleotides
⊗ ROS   xylulose → transcription factor
✓ glutathione regen.
3) polyol pathway   unknown why
G6P → alcohol derivative [sorbitol]
↑ aldose reductase   ↑↑ in ischemic - reprefusion injury
4) F6P
uridine diphosphate - N - acetylglucosamine
intermediate in protein synthesis
! in diabetes

part 2

bio 1

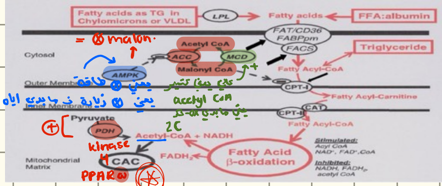
↑↑ FA w/o glucose → lipotoxicity unwanted

= MI [diabetes]

[keto diet]

- accumulation
- ↑↑ O_2 used = free radical = heart failure
- fetal enzyme loss affecting β-oxidation

goal: FA & glucose balance



fatty acid metabolism

1. food TG → chylomicron
2. liver TG → VLDL
3. fatty tissue TG
4. free fatty acid w/ albumin

liver can NOT use TG so we break it into glycerol / 3 FA mol. by HSL hormone-sensitive lipase

into myocardial cell:

1) simple diffusion ONLY short & very short chains
2) translocase / CD36 !!!
3) fatty acid binding protein

MCFA medium, LCFA long

✱ translocase / CD36 : [FAT]

- most regulated
- in cytoplasm, only expressed when needed
  - ↑ expression = ↑ FA into cell علاج ذو حدين
  - ? factors enhancing expression:
    - insulin insensitivity ⊗ GLUT 4 ⊗ glucose, FA main
    - ↑ work load + ↑ energy need [↑ demand]
    - ↓ Glut 4 or can't use glucose

in mitochondrial matrix:

fatty acid β-oxi. [fatty acyl CoA]

1. acetyl-CoA | into TCA cycle = 3 NADH, 1 FADH, 1 ATP
2. NADH | intermediants i can
3. FADH | use to make ATP

note:

↑ energy level = ↑ ATP,

↑ ATP / ↓ AMP ratio	↑↑ acetyl-CoA
↑ NADH / ↓ NAD^+ ratio	→ TCA limited
↑ $FADH_2$ / FAD ratio	→ into FA 2-2-2-2 chain
↑ acetyl-CoA : CoA	2C —carboxylation→ 3C malonyl CoA +2+2+2 = FA
↑ pyruvate / lactate	acetyl-CoA carboxylase ACC ✱ Co-factor needed: B7 / biotin
↑ citrate	! result: ⊗ glycolysis needed

عكسهم يعني العكس تماماً

↓ FK ↓ PDH

⊗ β-oxidation

MCAD ! [by PPAR α/β/δ/γ] (medium chain FA dehydrogenase)

so, STOP catabolism & START anabolism

↑↑ FA dependency = ↑ NADH → ⊗ need of pyruvate conversion
↑ $FADH_2$ = ⊗ glycolysis / inhibition
↑ acetyl CoA / citrate

but, if no FA [60% of energy] → HIGH dependency on pyruvate / lactate
↓
= low energy

O_2 in degradation:

oxidative phosphorylation = free radicals → lipid peroxidation → تخرب الـ cell memb.

Cardiac efficacy / SAFER on heart ?

	FA	glucose / lactate
1 O_2 →	2.8 ATP	3.17 ATP

only ideally, realistic = balance

FA < glucose / lactate — أحسن من جهة استخدام الـ O₂ أكثر
↑ ATP ↓ O_2 — يقلل الـ free radical

but, glucose is actually NOT better + not ↑ ATP per unit

1 FA = 92 ATP w/ 46 O_2
1 glu. = 30 ATP w/ 12 O_2

but to balance → 3x

so, 3x glu = 90 ATP w/ [36 O_2] → SAFER

↑ glu ↓ O_2

- ischemia
- MI
- cell damage

free radical

proof:

in DM, ischemia, AMI → ↓ FA oxi = prevent further damage

↳ heart shift to glucose = ↓ O_2 demand ~ 11-13%

any enzyme +P = inactivation

↳ kinase, p. adder

PPAR [regulation system]

acceptor

PPAR γ co-activator =
- ↑ proliferation of regulatory enzymes — 1. production / storage of TG; 2. β-oxidation / breaking TG; 3. glycolysis

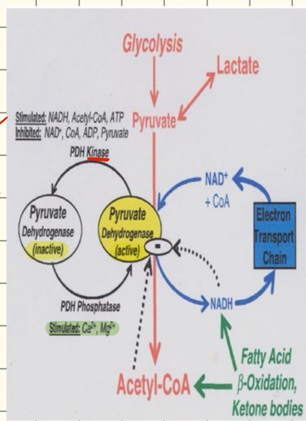
أهميته: مهم جداً !!

- maintain 65/35% balance
- eradicate free radicals [anti-oxidant] SOD, superoxide dismutase / catalase
- regulate apoptosis [IGF-1 / PI3K] Cu/Zn, Cu/Mn (insulin growth factor)
- regulate FA uptake

how to switch on / off PDH pyruvate dehydrogenase

off : + phosphate by PDH kinase
on : − phosphate by phosphatase

↑ energy (−) inactivate



fatty acid vs glucose

fetus: flexible, whatever is available

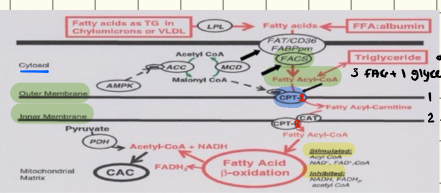
born: ↑ FA dependent why?
- ↑ dietary FA
- ↑ O_2 FA needs more O_2

↳ balance / selection

restriction: infant w/ FA meta. gene mutation
= ⊗ balance, ↑ glucose = cardiotoxicity = cardiomyopathy

adult w/ HF & LV hypertrophy

so, BALANCE is a must



FA not active, need to trap it inside so it doesn't leave → FA → fatty acyl + CoA by fatty-acyl CoA synthase

in cystol: بس جزء بيتحول مش كله

10-30% : $FAC \times 3$ + 1 glycerol = TG storage [diacylglycerol acyltransferase] [PPAR α]

70-90% : β-oxidation BUT β-ox is in mitochondria عشان اوصل لهنا 2 membranes

↳ use shuttle: [carnitine shuttle]

FA-CoA + carnitine → FA-car. [by carnitine palmitoyltransferase] CPT-1 @ outer

b/w outer & inner by CAT, carnitine acyl translocase — بيحط carnitine on fatty acyl

@ inner membrane CPT-2 — بيرجع CoA = fatty-acyl CoA

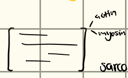
5. Pyruvate dehydrogenase multienzyme complex is a key regulatory enzyme in glucose utilization: it can be inhibited by all of the following except?
a. ATP/ADP → when high energy
b. NADH+H+/NAD
c. Acetyl CoA/CoA
d. Citrate/pyruvate
e. NADPH+H+/NADP — not energy indicator

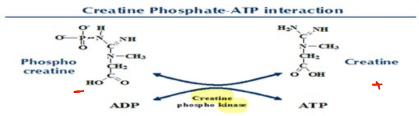
6. PFK-I is catalyzing the conversion of fructose 6-phosphate into fructose 1, 6 biphosphate, all of the following can inhibit this enzyme except? low → high energy
Select one:
a. decrease ADP/ATP ratio XXX
b. increase NADH+H+/NAD ratio
c. decrease Activity of PI3 kinase
d. increase Activity of electron transport chain
e. decrease Activity of PFK-2

2. The following enzyme is **promoted** by peroxisome proliferator-activated receptorY (PPARγ)?
Select one:
a. medium acyl-CoA dehydrogenase XXX MCAD α/β/δ/γ
b. Long-chain acyl-CoA dehydrogenase
c. Pyruvate dehydrogenase kinase → α
d. Diacylglycerol acyltransferase
e. Hexokinase

Bio 2

creatine → in ms. physiologically (actin, myosin)





ATP needed for contraction

so we capture extra ATP energy by putting it into PC

so that we dont lose it — used 75/100, 25 react w/ creatine → ADP

↳ then when contraction [first 10-30s], we fully depend on PC for energy ⊛

↑ enough time to activate glycolysis to make new ATP

isoforms:

- M → muscle
- B → brain

MM — MB — BB
↑ ms. — ↑ cardiac ms. — ↑ brain

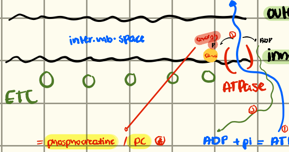
↳ CK-MB ↑↑ in myocardial infarction

CK-mito ~10-40%

① function:

- to capture energy — since ATP $T_{1/2}$ ↓

↳ through PC-CK system



inner @ outer surface of inner membrane

↳ by creatine kinase [ATP/ADP translocase] / [ANT]

REVERSABLE ✱

• level of PK/CK relates to cell health

MI, cardiopathy, HF → LOW PK

healthy heart — 2/3 creatine is phosphorylated

↑ PC / ATP ↓↓

heart failure — most creatine NOT phosphorylated

↓ PC / ATP ↑↑

↳ ↓ PC = ↑ mortality

② ketone bodies

→ when low glucose level

NOT major source of energy

main source: acetyl-CoA [in liver, in mitochondria] !

when TOO much to point where TCA can NOT accept

↓ ketone

↓ peripheral — EXCEPT liver

NADH, ATP — energy source

↓ CO_2

1. when energy needed?
   - excersise
   - brain all time
   - heart all time

brain might uses ketone bodies — in case of multiple day severe starvation

mainly glucose dependant
1) Brain 2) RBC

2. when HIGH formation of acetyl-CoA
   - ⊗ glucose / starvation
   - carb-free diet — shift to FA.
   - can't utilize glucose / ⊗ insulin ↳ by changing hormones [↓ insulin] (build) [↑ glucagon] [↑ stress hormones] (break)
   - ⊗ glycolysis / enzyme lack — = ↑ glucose of blood — = lipolysis

3 FA — TG → HSL → FFA → acetyl. CoA (too much) → TCA / ketone

glycerol → DHAP glycolysis int. → glucose

protein → AA → ATP / glucose

glycogen → glucose

ketoneogenesis

result: ↑ glucose

to maintain NORMAL glucose level if glucose is low

for brain/RBC, but rest of body uses FA...

DM → ↑↑ glucose = hyperglycemia ①

but;

healthy → normal blood glucose

② ketosis / ketonemia ↑ ketone bodies

③ ⊗ ± acidosis — ketone bodies are acidic

D K A — diabetic (↑ glu.), ketonemia, acidosis

only Pathological causes of ketosis — DM, alcoholism, drug, metabolic / enzyme def. (↑G ↓Ws) # von-gierke's diesease

→ physiological
- fasting
- excersize
- starving

④ diuresis / hyperosmolar

♡ H_2O → leaves w/ urine

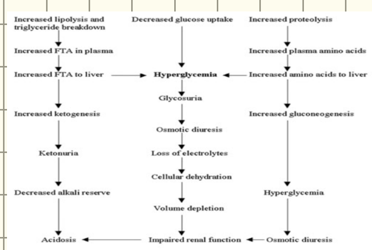
= ↑↑ urine

- dehydration
- electrolyte imbalance (Na, Cl, K, Ph)

attempt acidosis compensation

1) HCO_3^- buffer limited → ↓ in blood [free HCO_3] as result
2) RS compensation / hyperventilation [kussmaul resp.]
3) intracellular cation shift — ✱ potassium depletion

H^+ into cell, K^+/H_2O out cell



ketone continued:- ✱✱✱

note:

since:

activating TCA uses gluconeogenesis intermediates ↓↓ of int.

available for TCA

100 oxaloacetate — 70 TCA / 30 glucose from other sources

so = shift to ketone body production

types of ketone bodies

acetoacetate — acetone — β-hydroxy acetate

decarboxylation — reduction +H

ketone?

acetyl CoA + acetyl CoA = acetoacetyl CoA + acetyl CoA = HMG-CoA (HMG synthase) → ketone body / cholesterol (HMG-CoA reductase)

↓ hydrolyzed — HMG-lyase

¹acetoacetate

−CO_2 ↙ ↘ +H

²acetone — ³β-hydrox.

[produce] succiny-CoA [need]

ketolysis — = succinate !

β-hydrox → acetoacetate (2x acetyl) → acetoacetyl CoA (acetyl CoA / acetyl CoA) → acetyl CoA, acetyl CoA

β-H. dehydrogenase — β. ket. trans. thiophorase

↓ not in liver, thats why liver can't use it — Q.

⊛ regulation:

moderate carbs
- ✓ ATP
- ⊗ need for FA which might caus acetyl-CoA product
- ⊗ ketone bodies

excess carbs
- gly → pyruvate → ↑↑ acetyl CoA too much
- ↳ creat FA as storage

no free carbs
- Main depend on FA
- acetyl CoA ✗ TCA ما بتستوعب كمية الـ
- ↓↓ oxaloacetate وأنا ما بحتاج طاقة
- so, ↑↑ acetyl CoA
- ↓ ketogenesis ✱

15. in the high altitude (⊗ O_2), you stayed for an hour; the following changes will happen in metabolic pathways of your cardiomyocytes except?
Select one:
a. increase Glycolysis (anaerobic) ✓
b. decrease B oxidation of fatty acids (O2 depend.) ✓
c. increase production of phosphocreatine ✗ (⊗ O2 = ⊗ energy)
d. Accumulation of NADH+H and lactic acid
e. decrease Oxidative electron transport chain activity ✓ (ETC ⊗ terminal O2)

⊛ HF: ↓↓ O_2

- ⊗ FA ox.
- ↓ resp. chain rxn
- ↑ glycolysis & glucose ox → anaerobic glycolysis = lactic acid + NADH

ischemia: change structure / enzymes
- loss contractile function
- arrythmia
- cell death

too much = ⊗ glycolysis = cell death

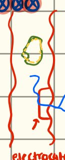
generally: Q.
- ↓ ATP / ADP
- ↑ AMP
- ↑ inorganic Ph
- ↑ lactate
- ↑ NADH
- ↓ PC

Bio 3

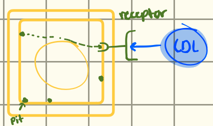
cholesterol:

prokaryotes [bacteria] ⊗⊗⊗

- plant → phytosterol → healthy → competition absorb
- animal (egg) → MOST
- human → denovo → liver most 80%, intestine, skin



intestine
- to lymph
- to liver → lipoprotein VDRL → LDL → peripheral tissue
- carried by chylomicrons
- to make cell membrane



من الآخر إنه الـ natural coles. بيفوت الـintestine و

بيصير emulsification بسبب الـ bile ، بعدين بيروح ع الـ liver من طريق

الـchylomicron الي بيحمله ، ومن بيرسلهم peripheral على شكل VDRL الي جسيم بيصير LDL بعدين

بيصير internalize و بيكسر الـ LDL عشان يعطي الـcholesterol و بيستخدمه عشان تكوين الـ cell wall

in case of free blood cholesterol?

scavengare قمامة to get rid of it → HDL from liver

why is too much cholesterol / too less BAD?

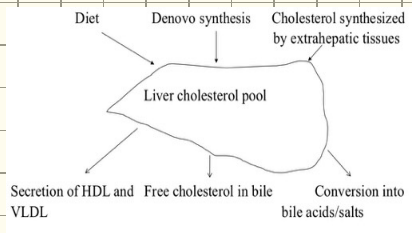
chol w/ bile → blood → GI lost → brough back to liver by

enterohepatic circulation, 50%

بنرجع كم كبير نفقدناه حق ولو بنقدر نصنعه بس

لأنه عملية تصنيع الـ chol بتوخذ طاقة كبيرة جداً!!

↑↑ = high disease / aterio slerosis



why is cholesterol important?

1. cell membrane

pits: methyl β-cyclodextrin MβCD, removes cholesterol from plasma mb. proves all these functions are cholesterol dependant

- ↳ maintain fluidity, to allow permeability / selectivity [⊗ H+ ? Na+]
- ↳ "pits", clathrin, signals عشان يدخل الـLDL وين = endocytosis / nerve conduction
- ↳ antioxidant OH group, neutralize free radical
- ↳ signal transduction / transporter mol.

2. synthesis to certain chemicals

- ↳ bile acid imp. for emulsification / coating
- ↳ vit. D3, A, E, K
- ↳ chol. derivative hormones — sex. H, androgen-H

HORMONE - DEPENDANT
- insulin ↑ → ↑ HMGR ph-ase → ↑ prosphetase
- stress-H. ↓ glucagon, NE → ↑ cAMP → ↓ prosphetase

ketone: similar start up!

acetyl CoA + acetyl CoA = acetoacetyl CoA + acetyl CoA = HMG-CoA (HMG synthase) → ketone body / cholesterol → HMG-CoA reductase !

نقطة الإختلاف ⊛ ↑ cystolic isoform

!!! Regulatory step: (F+G")

HMG-CoA + HMG-CoA reductase needs reducing substance ↑ NADPH

* STATIN دوا بيقلله من الـch. ، صرن بيشتغل

↓

mevalonic acid بس نعرف اسمه

↓

+5C + 2P = PP (page 7)

↓

Farnsyl-PP — Farnesyl intermediant يعني Q.

هو اللي بيعطيني أم الـ int. اللي

↓

[cholesterol pathway intermediates:] بستخدمهم في أشياء ثانية

- prenylated protein
- coenzyme Q / ubiquinon
- dolichol
- heme a

+) gera. PP — أصلا "ل" بيعطيني الـ prenylated proteins

* bisphesphonate كمان دوا

37. In cholesterol synthetic pathway, which of the following coenzymes is serving as a hydrogen donor in the reactions catalyzed by HMG-CoA reductase and squalene epoxidase?
Select one:
a. NAD
b. Pantothenic acid
c. NADPH XXX — reducing substance, proton donor, ⊗ energy relation
d. Lipoic acid
e. FAD

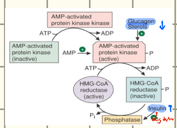
29. Phosphorylated PPI-1 is one of the enzymes that play a critical role in regulating cholesterol synthesis through the direct inhibition of the following enzyme?
Select one:
a. Liver kinase B1
b. Protein phosphatase 2C — PP1 → phosphetase inhibitor
c. Protein kinase A
d. Calcium calmodulin-dependent protein kinase kinase (caMKK)
e. AMP activated kinase

⊛ Cholesterol synthesis ⊛

main precursor: acetyl CoA → all in mito, so need to transport

↳ only diff: mito. → it out to cystol!

ketone: matrix, Cholesterol: cystol



- very energy dependant 150 ATP
  - ATP
  - NADPH [as source of PROTON not for energy]

pyruvate	malate → pyruvate [cycle repeats] (NADP+ → NADPH)
↓ ATP, CO_2	↑ NADH → NAD+
oxaloacetate 4C	oxaloacetate
↓ acetyl CoA 2C	↑ ADP, acetyl CoA
citrate →	citrate
IN matrix	IN cystol

6. Prenylated proteins and Coenzyme Q can be produced in order from the following intermediates of cholesterol synthetic pathway? Select one:
a. Farnesyl pyrophosphate and HMG-CoA
b. Squalene and geranylgeranyl pyrophosphate
c. Dimethylallyl pyrophosphate and 2,3 oxidosqualene
d. Geranylgeranyl pyrophosphate and Farnesyl pyrophosphate
e. Mevalonate 5 phosphate and mevalonate 5 pyrophosphate

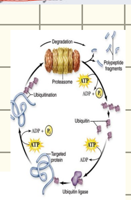
13. Choose the statement that best describes the ubiquitin proteasome degradation pathway?
Select one:
a. Ubiquitin molecules have the sterol sensing domain to start HMG CoA reductase degradation (on enz. itself)
b. Signaling is not involving the targeted enzyme only
c. It requires a sterol sensing domain in SREBP and HMG-CoA reductase
d. Ubiquitin small molecules are ligated to the targeted protein enzymatically XXX
e. Monomeric ubiquitin is enough for signaling the targeted enzyme (poly)

SSD sterol sending domain

if ↑ ch., SSD calls ubiquitines that coat HMGR,

then sends it to a degrading enzyme [proteasome] → breaks unnecessary proteins

⊕ needs ubiquitine ligase to stick.



→ regulation of cholesterol synthesis:

HOW?! 4 ways, 3/4 depending on cholesterol level

normal level 150 - 200 mg/dl

to maintain that, 1- diet 2- de novo

cellular supply regulation: 3x

① HMGR (rate limiting step)

② excess intracellular / serum free cholesterol

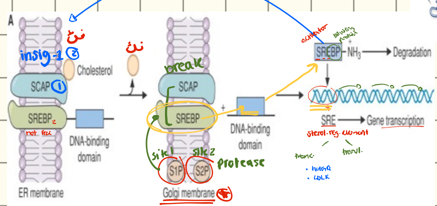
ACAT, acetyl CoA chol. acetyl trans.

↓

trapping by ⊕ acetyl CoA

③ peripherally, LDL receptor / HDL reverse transport — back to liver / to periph. tissue

1) feed back inhibition
   ↳ end product creats -ve feedback
2) rate of enzyme degredation
   ↳ by ubiquitine - proteozome pathway
3) control gene expression [long term]
   ↳ stop / silence OR stim HMGR - gene
4) phosphorylation - dephosphorylation [short term] — NOT ch. dependant



1) ↑ level of free chol. = ↓ level of free SREB — bound = inactive

insig-1 + Scap → maintain it bound

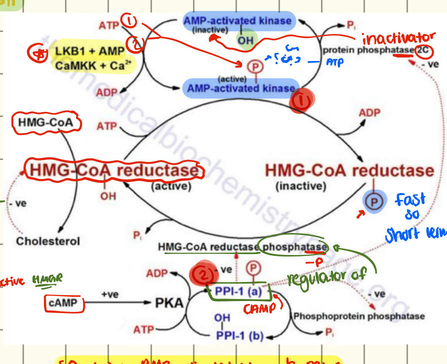
2) ↓ Ch. level → FREE SREBP

@ golgi: S1P/S2P → break SCAP off SREPP = activate Ch. synth. pathway → HMGR, LDLR, other steps

⊕ P = inactivate → kinase

⊖ P = activate

pg. 16



LKB1 + AMP
CaMKK + Ca2+
ATP
ADP
AMP-activated kinase (inactive)
AMP-activated kinase (active)
protein phosphatase 2C
inactivator
HMG-CoA
HMG-CoA reductase (active)
HMG-CoA reductase (inactive)
Cholesterol
HMG-CoA reductase phosphatase
regulator of
PPI-1 (a)
PPI-1 (b)
cAMP
PKA
Phosphoprotein phosphatase
fast so short term

SO, (-) by AMP-activated kinase & PPI-1

+ AMP kinase
- AMP phosphetase 2C
(regulated)

kinase يعني يضيف عليه P.

1) ATP + cofactors — AMP, LKB1, CaMKK, Ca++ !

! Jaundice

- pre-hepatic
- hep.
- post-h. (obs.)

nothing reaches GI & it goes back to blood including ch.

obstructive → ↑↑↑ hypercholesterolemia

hepatic ⊗ synthesis → ↓↓↓ hypocholesterolemia

! PP1 - ph.ase → inh

↓

maintain P = maintain inactive HMGR

source: cAMP

1,2,3 → -ve

! thyroidism

hypothyroidism ↑↑↑

breaking LDL receptor, Ch. accumilates

hyperthyroidism ↓↓↓

hyper-metabolism, breaking everything