النادي الطبي MC

Done By :
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لا تنسونا من دعائكم بالتوفيق

(لا يوجد امتحانه ميد أو فاينال نخلوا منه هذا الجدول)

Glycogen storage diseases

Inborn errors of glycogen metabolism

Classified into different types according to the deficient enzyme

Type	Disease Name	Defective enzyme	Glycogen levels	Glycogen structure	Principal tissue affected	Characteristic feature
I	Von Gierke's disease	Glucose-6-phosphatase (G6pase)	High	Normal	Liver, kidney	I: Fasting hypoglycaemia (not responding to adrenaline), hepatomegaly
II	Pompe's disease	α-1,4 Glucosidase	Very high	Normal	All organs	II: early death before 2 years
III	Cori's Forbes' disease	Debranching enzyme	High	Short outer branches	Liver, Heart, Muscle	III: mild fasting hypoglycaemia
IV	Andersen's disease	Branching enzyme	Normal	Long outer branches	Liver, Spleen, Muscle	IV: hepatosplenomegaly, mild hypoglycaemia, results in synthesis of straight chain glycogen only
V	McArdle's disease	Muscle Phosphorylase	High	Normal	Muscle	V: exercise intolerance, painful muscle cramps during exercise
VI	Hers' disease	Liver Phosphorylase	High	Normal	Liver	
VII	Tarui's disease	Phosphofructokinase	High	Normal	Muscle	
VIII	Hepatic phosphorylase kinase deficiency	Phosphorylase kinase	High	Normal	Liver	

Most common

(بس العضلات تتأثر)

(تشنجات)

- Glucose is phosphorylated to G-6-P by **glucokinase** (liver) or hexokinase (muscle)

(سؤال بالإمتحان)

Q in final

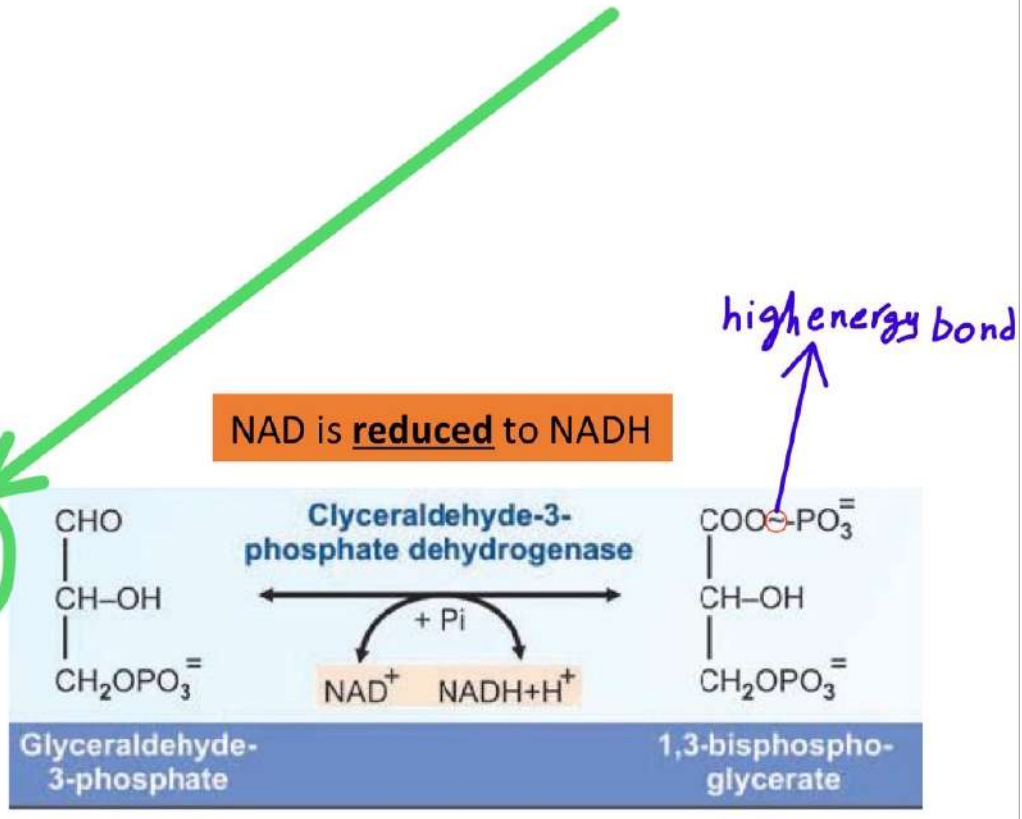
وين بصير كل الـ (metabolic bathway) ؟ بالـ (Cytoplasm)

* أكتر الأشياء اللي جاي بالإمتحان عنه (integration, regulation) أو اشياء رح يقول هدول ابصمهم زي اسمك اللي صحة صعلنة ال (pyruvate) وال (Acetyl CoA)

Step 6: oxidation of glyceraldehyde 3-P to 1,3 bisphosphoglycerate

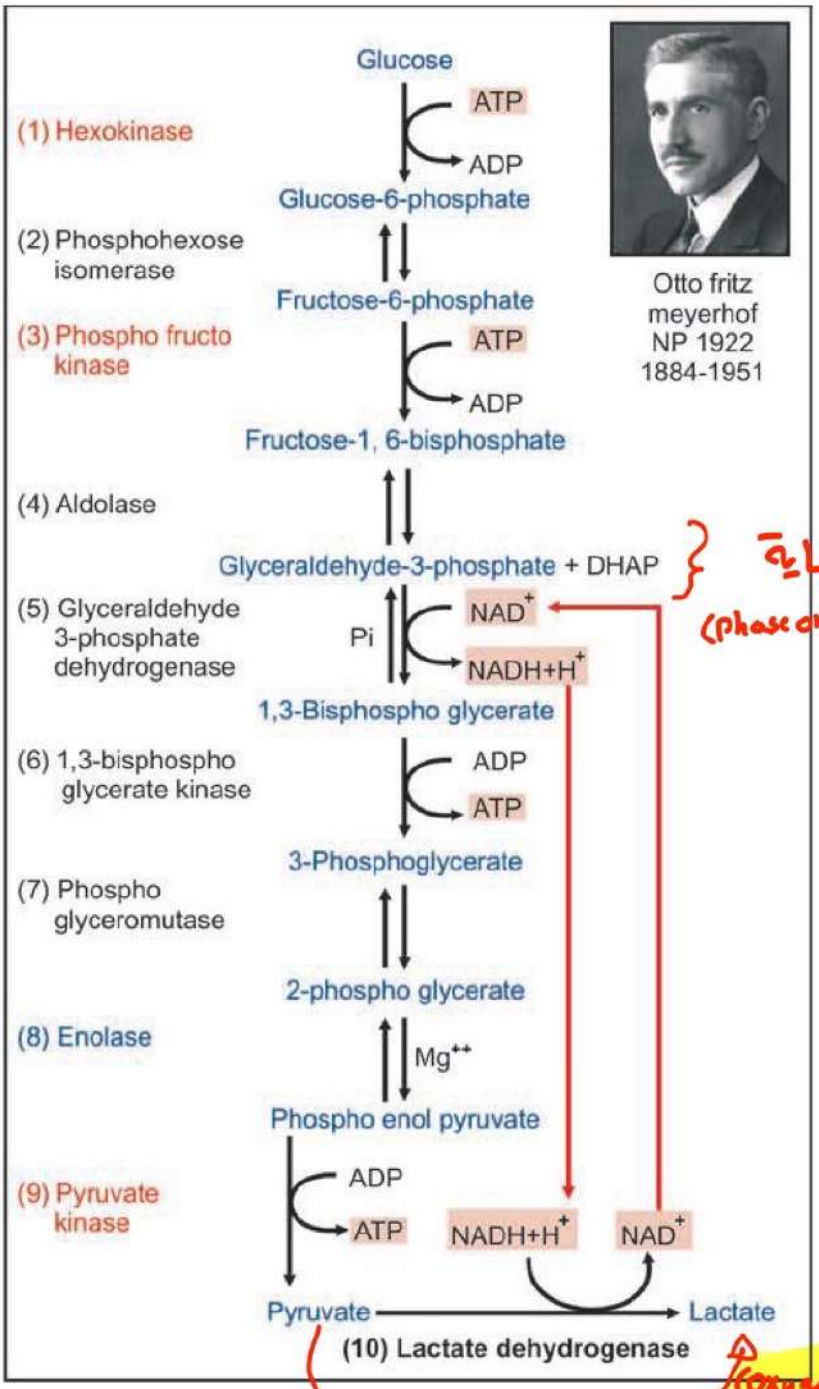
- **Enzyme:** Glyceraldehyde 3-P dehydrogenase
- Reversible
- 2 main events take place:
  - 1) glyceraldehyde-3-phosphate is oxidized by the coenzyme nicotinamide adenine dinucleotide (NAD)
  - 2) the molecule is phosphorylated by the addition of a free phosphate group
- Produces high energy compound:
  - The oxidation of the aldehyde is an exergonic reaction that drives the synthesis of the high energy compound, 1,3 bisphosphoglycerate with high phosphoryl group transfer potential
- Enzyme is a thiol enzyme that has a cysteine residue at the active site
  - Inhibited by iodoacetate → امتحان
- As cells contain only limited amounts of NAD+, glycolysis would come to a stop if NADH formed in this step is not continuously reoxidised

لما تذكر أنه احنا محتاجين نرجع نكون (NAD+) عشان الخطوة السابقة



Step 7: Phosphoryl transfer from 1,3 biphosphoglycerate to ADP to form ATP

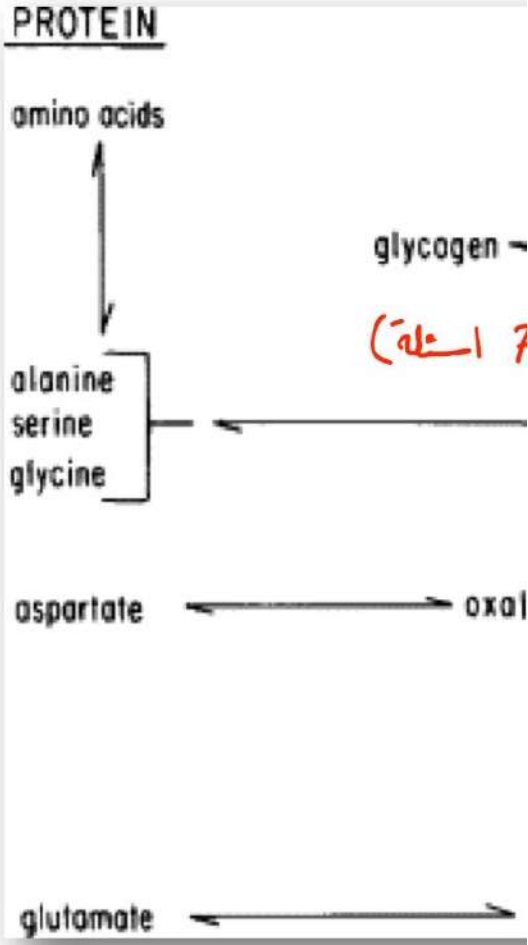
Phosphoenol pyruvate (PEP)



Otto fritz meyerhof NP 1922 1884-1951

نهاية (phase one) ال

Embden-Meyerhof-Parnas



(oxygen) إذا ماعندك سؤال بالإمتحان

Significance of glycolysis

Glycolysis under aerobic conditions

- Means presence of **mitochondria and O2**

تفاعل محوري يحي بالإ متحانه

- Pyruvate will enter mitochondria and undergo oxidative decarboxylation to **acetyl coA**

Pathway	Step	Enzyme	Source	Method of ATP formation	No of ATPs gained per glucose (new calculation)		No of ATPs as per old calculation
Glycolysis	1	Hexokinase	-		Minus	1	Minus 1
Do	3	Phospho-fructokinase	-		Minus	1	Minus 1
Do	5	Glyceralde-hyde-3-P DH	NADH	Respiratory chain	2.5 x 2 =	5	3 x 2 = 6
Do	6	1,3-BPG kinase	ATP	Substrate level	1 x 2 =	2	1 x 2 = 2
Do	9	Pyruvate kinase	ATP	Substrate level	1 x 2 =	2	1 x 2 = 2
Pyruvate to Acetyl CoA	-	Pyruvate dehydrogenase	NADH	Respiratory chain	2.5 x 2 =	5	3 x 2 = 6

امتحانه

1.5 x 2 for FADH2 if glycerol phosphate shuttle

Oxidative decarboxylation of pyruvic acid

- It occurs in the **mitochondria**
- It is **irreversible** → (لأنه (Acetyl CoA) اللي جاي منه الدهون ما يمكن تصنيع الكربوهيدرات منه)

- It needs:

1-Pyruvate dehydrogenase complex + 2 other enzymes

2-5 coenzymes: TPP (thiamine pyrophosphate)*, lipoic acid, FAD, NAD^+, CoASH (TLFNC), and + Mg2+ as cofactor

كله حفظ وجاي بالامتحان

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1-Pyruvate dehydrogenase complex + 2 other enzymes

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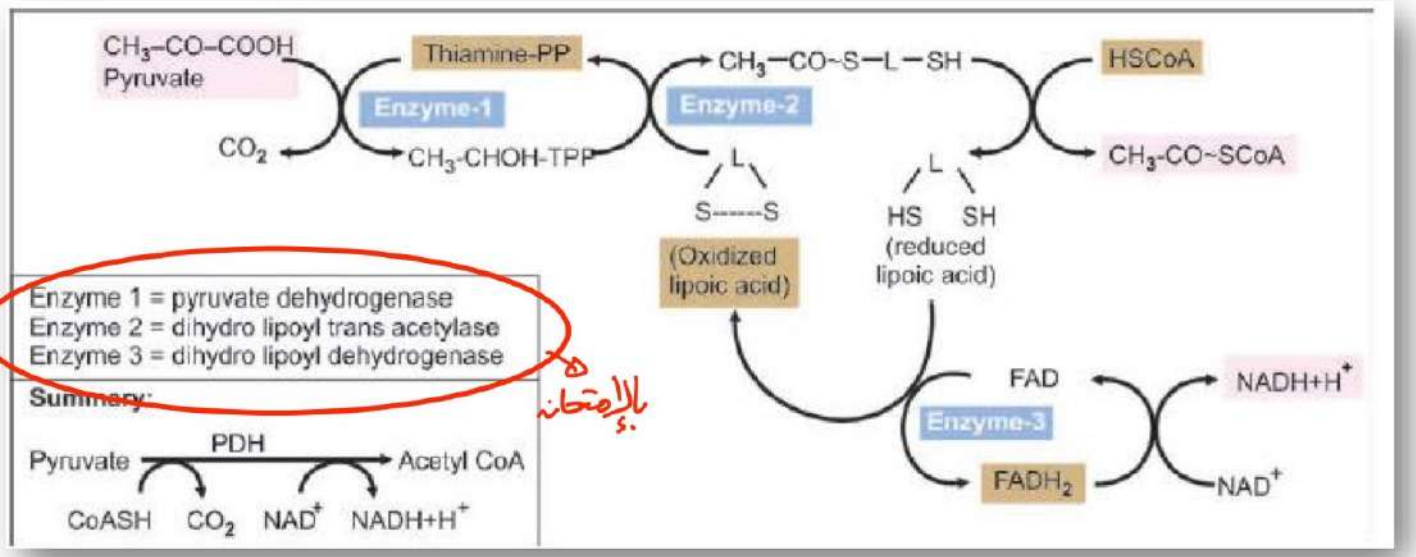
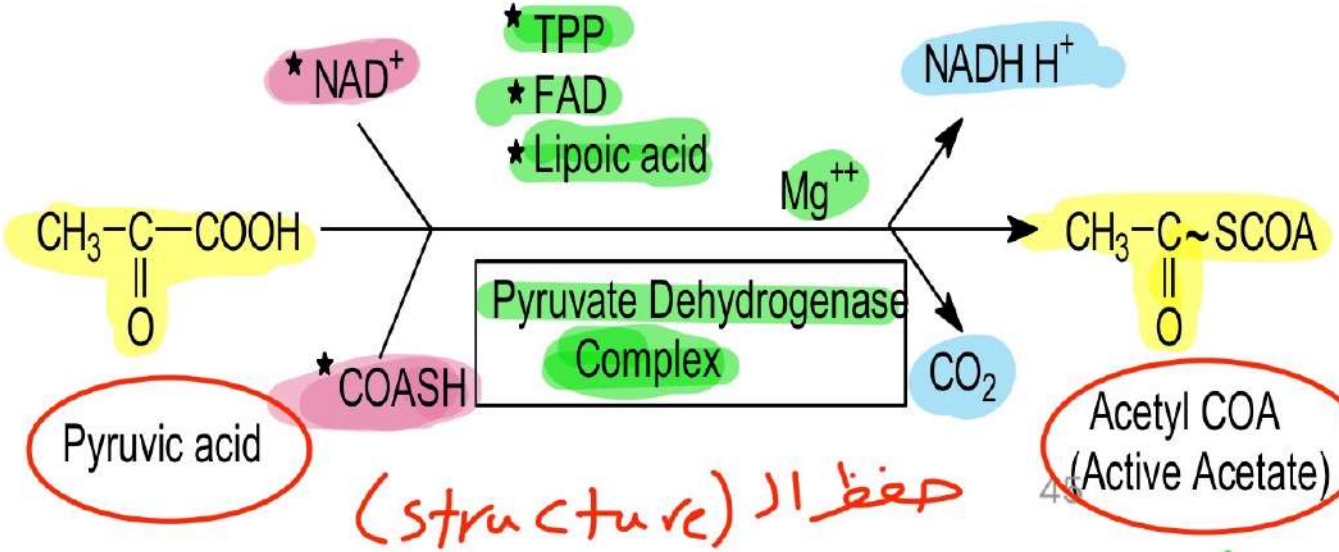
كله حفظ وجاي بالإمتحان

* عشان هيك اللي عنده (Alcohol Abuse) بكون عنده (thiamine deficiency) كتير فبصير عنده مشكله في الـ (Pyrovate dehydrogenase) فبزيد الـ (Pyrovate) فيتحول إلى (lactate) يتراكم وبصير lactic acidosis

هذا الحكي مهم وممكن يكون عليه سؤال كيس بالإمتحان

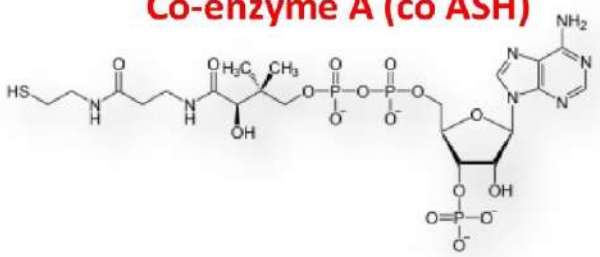


بالامتحان



(structure) حفظ ال

Co-enzyme A (co ASH)



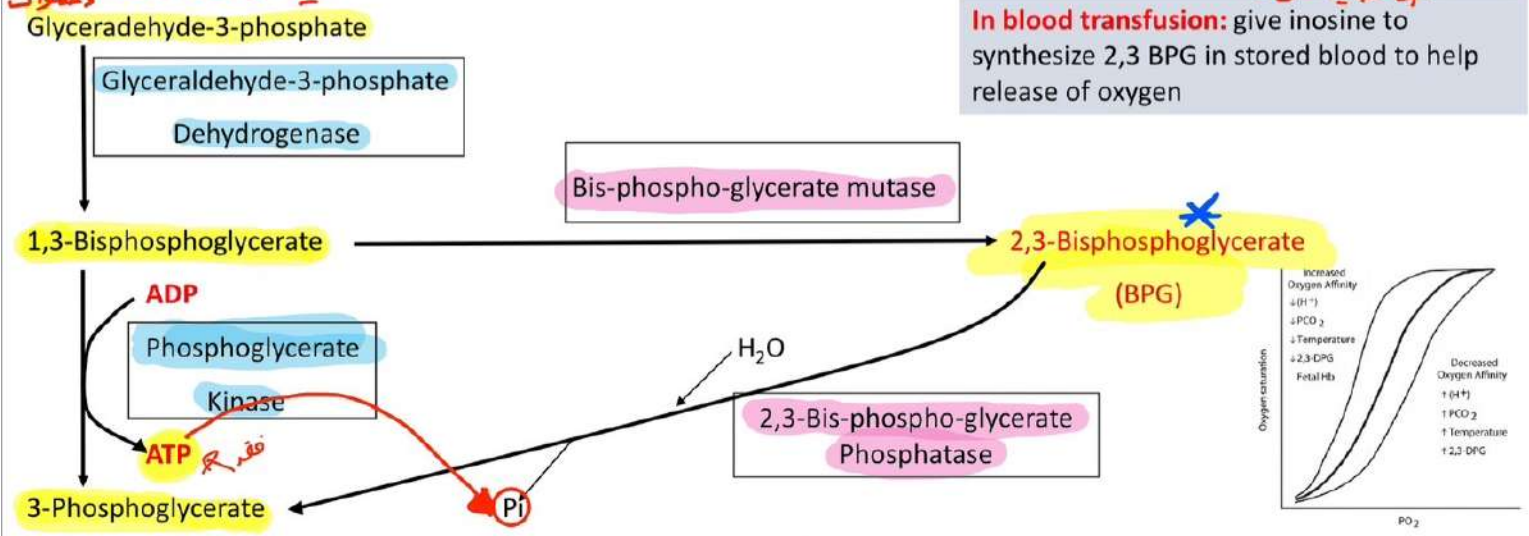
Glycolysis In Erythrocytes (Rapaport Lubering cycle) (داخلة بالإمتحان)

The reaction catalyzed by phospho-glycerate kinase is sometimes replaced by an alternative two-step reaction that avoids ATP formation and produces 2,3-bisphospho-glycerate (diphospho-glycerate or DPG) as shown below. **2, 3-BPG binds haemoglobin and reduces its affinity for oxygen** and thus makes oxygen more readily available for tissues.

في طريقتين للتحويل: خطوتين وخطوات

خاصية مهمة

In blood transfusion: give inosine to synthesize 2,3 BPG in stored blood to help release of oxygen



Every DPG mole produced decreases ATP production in erythrocytes by 1 mole as the phosphor-glycerate kinase step is omitted.

48

* بقلل الـ (Affinity) تاعت الهيموغلوبين لـ (Oxygen).

- للناس اللي ساكنين في مناطق عالية مثل (جبال) (mexico city) على ارتفاع (3000 m) الـ (Affinity) تاعتهم (2,3 Bisphosphoglycerate) اللي بنقل الـ (Oxygen) واحطيتهم عشان يقدر يتكيف بشكل أسهل فبزيد عندهم (Oxygen) بشكل أسهل لـ (tissues) باتجاه معين فعندما أنت بتصير تطلع الـ (hemoglubin saturated curve)

بس بالمقابل أنت قاعد بتخسر (ATP)

Final Exam

الشرح الذي في الأعلى مهم وسيأتي عليه سؤال في الإمتحان النهائي

Gluconeogenesis: Definition

- Metabolic process by which glucose in synthesised from non-carbohydrate precursors:
  - Lactate (تذكر أنه (Lactate) يصنع بال (muscle) وبما يروح على ال (liver) يتحول إلى (glucose))
  - Glucogenic amino acids (major source of glucose after glycogen is depleted) — المصدر الأساسي لل (gluconeogenesis)
  - Glycerol (part of TAG) — يتم استنفادها
  - Odd chain fatty acids (rare); Propionyl coA (minor source)

سؤال كمي إلي متحانه

الجواب بكونه واحد منه AA

leucine

lysine

عدا :

لا يمكنه تكوين ال (glucose) من الدهون إلا في استثنائين :

Glycerol –

Odd chain F. A. –

ال (odd chain) مستحيل يصنع (glucose)

* كمية ال (odd) بالجسم قليلة جدًا

Important facts about gluconeogenesis

سؤال في الإمتحان

- **Sites of occurrence:** partially in mitochondria and partially in cytosol of liver (85-90%) & kidney cortex (أكثر شي في الـ liver)

✕سؤال ممكن ييجي بالإمتحان بعتمد فهمه على محاضرة 12/11/10

اذا بدأت من (lactate) وبعد هيك صنعت (Glucose) وبعد هيك حرقته بال(krebs cycle)

بدنا نفكر منه(4) منطلقات :

الأول أنني بدي أحول منه (Lactate) إلى (Pyrovate) والتي ستنتج (NADH) وكما أعلم أنني أحتاج (2) عشانه صدول (3C) والجلوكوز (6C) ، إذا أنا سأنتج (2 NADH) يعني (5ATP).

الثاني أنه بدي أحول من(Pyrovate) إلى (Glucose) عنه طريقة ال (Gluconeogenesis) والتي ستستلك منه (Pyrovate) وستستهلك (6ATP) وتستهلك 2NADH

الثالث أنه أنا عشانه ادخله بـ (krebs cycle) بدي (Acetyl CoA) وأنا عارف أنه بال (Glycolysis) منه (Glucose) إلى (Pyrovate) بنتج عندي (2NADH)+(2ATP) يعني (7ATP) ، ولما أحول منه (Pyrovate) إلى (Acetyl CoA) ينتج عندنا (5ATP)

الرابع وهو (krebs cycle) لكل (1Acetyl coA) ينتج عندنا (10ATP) ← X2 ← 20 ATP

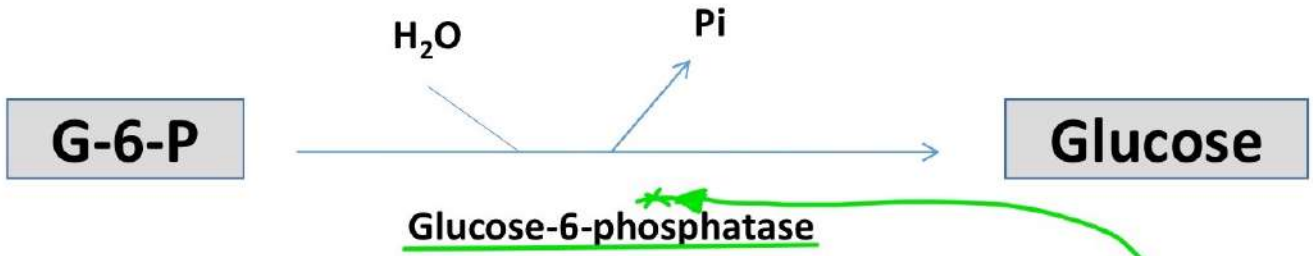
الحصلة : استهلكنا 11ATP ، وأنتجنا (5+20+5+7)

37 - 11 = 26

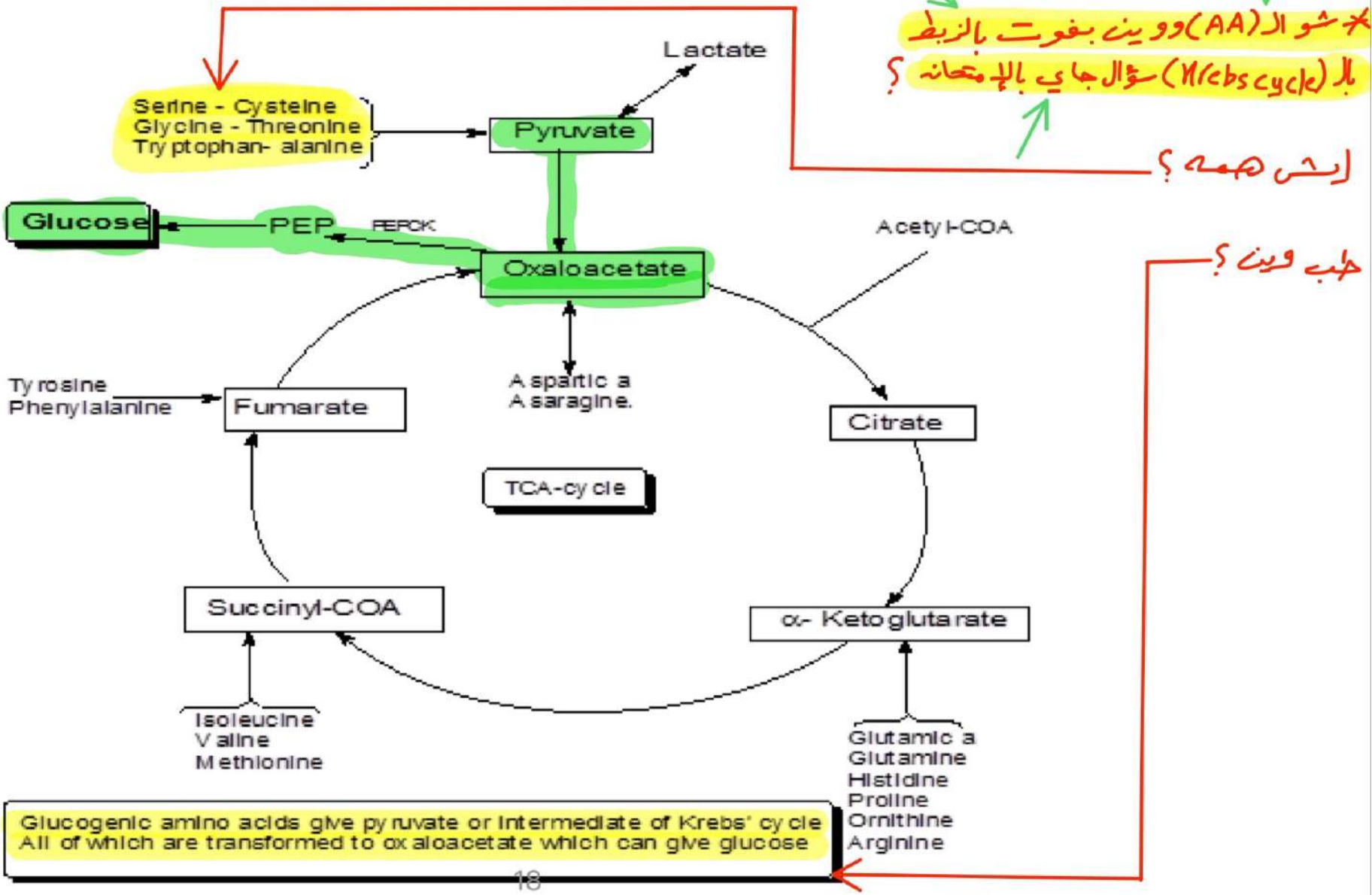
(C) **Reversal of the Hexokinase Reaction:**

- G-6-phosphatase is present in the liver & (kidney, & intestines) lesser extent
  - Liver provides >85% of glucose produced in body
    - This proportion ↓ in prolonged starvation → kidney production ↑
  - Totally absent in brain, muscles and adipose tissues

- In skeletal muscles gluconeogenesis ends in G-6-P which cannot leave the cell , but G-6-P can form glycogen



* سؤال في الإمتحان أين يقع هذا الأنزيم بالخلية ؟ في ال


Lactate
Serine - Cysteine
Glycine - Threonine
Tryptophan- alanine
Pyruvate
Glucose
PEP
PEPCK
Oxaloacetate
Acetyl-COA
Tyrosine
Phenylalanine
Fumarate
Aspartic a
Asaragine.
Citrate
TCA-cycle
Succinyl-COA
α- Ketoglutarate
Isoleucine
Valine
Methionine
Glutamic a
Glutamine
Histidine
Proline
Ornithine
Arginine
Glucogenic amino acids give pyruvate or intermediate of Krebs' cycle
All of which are transformed to oxaloacetate which can give glucose

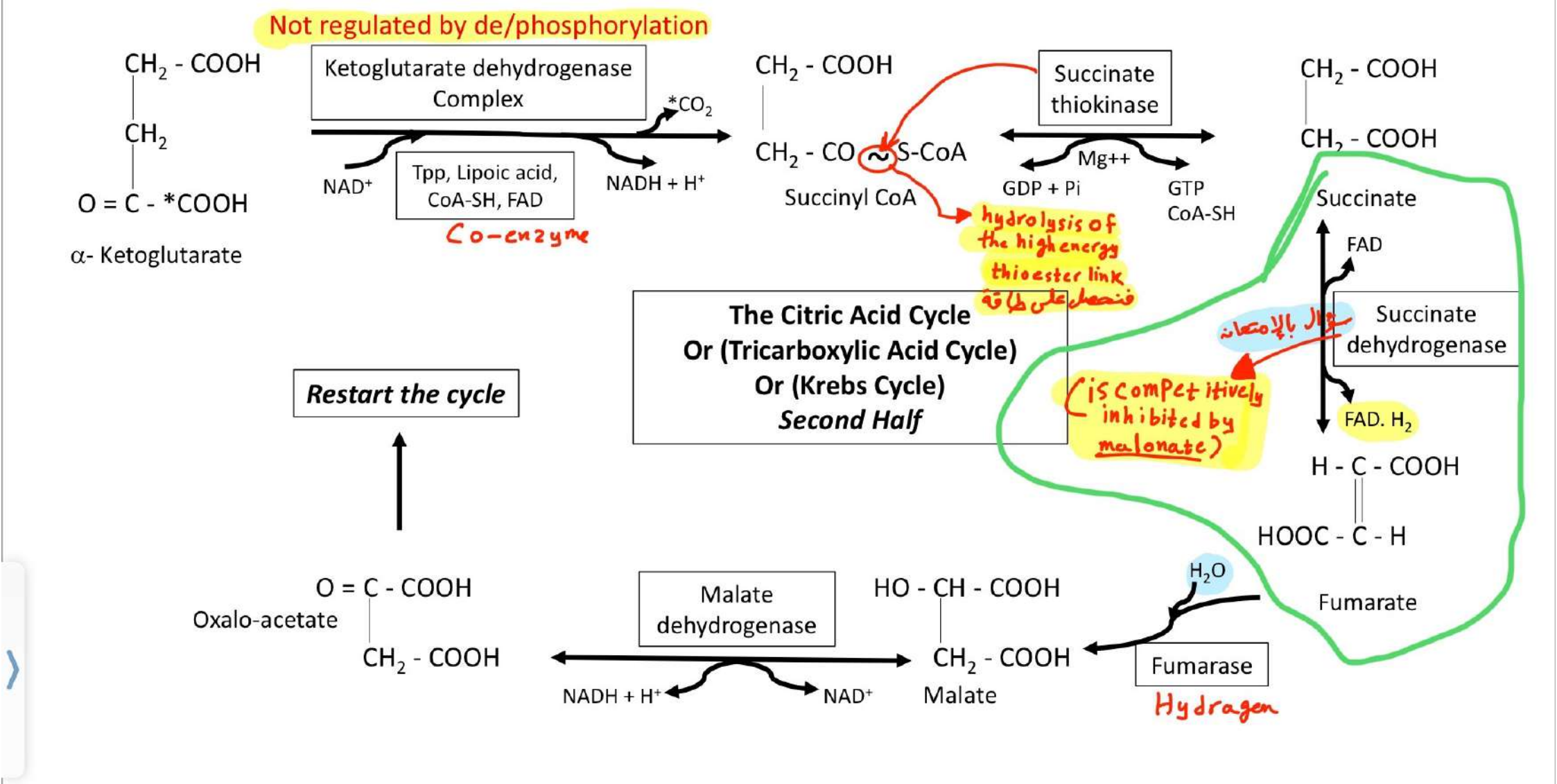
سؤال دائما بيجي بالإمتحان

- **Even chain FAs cannot be converted to glucose as the pyruvate dehydrogenase reaction is strictly irreversible**

Carbohydrate↑ → Glycolysis↑ → Pyrovate↑

- High energy status of cells (excess CHO) → ↑ acetyl coA → ↑ in oxaloacetate (via stimulation of pyruvate carboxylase) → to form citrate → enables FA synthesis

(بيجي بالعادة بالإمتحان وبكثرة)


Not regulated by de/phosphorylation
CH2 - COOH
CH2
O = C - *COOH
α- Ketoglutarate
Ketoglutarate dehydrogenase Complex
*CO2
NAD+
Tpp, Lipoic acid, CoA-SH, FAD
NADH + H+
Co-enzyme
CH2 - COOH
CH2 - CO ~ S-CoA
Succinyl CoA
Succinate thiokinase
Mg++
GDP + Pi
GTP
CoA-SH
hydrolysis of the high energy thioester link فتنحل على طاقة
CH2 - COOH
CH2 - COOH
Succinate
FAD
Succinate dehydrogenase
FAD. H2
H - C - COOH
HOOC - C - H
Fumarate
يثبط بالإضافة
(is competitively inhibited by malonate)
The Citric Acid Cycle
Or (Tricarboxylic Acid Cycle)
Or (Krebs Cycle)
Second Half
Restart the cycle
O = C - COOH
Oxalo-acetate
CH2 - COOH
Malate dehydrogenase
NADH + H+
NAD+
HO - CH - COOH
CH2 - COOH
Malate
H2O
Fumarase
Hydragen

Important facts of Krebs cycle

- على عكس Contrary to glycolysis, Krebs cycle can only happen under aerobic conditions

- Enzymes of TCA are found in the mitochondrial matrix, in close proximity to the enzymes of the respiratory chain

- Different isocitrate dehydrogenases are seen (isoenzymes)
  - NAD+ specific in mitochondria
  - NADP+ specific in cytoplasm

سؤال بالإمتحان

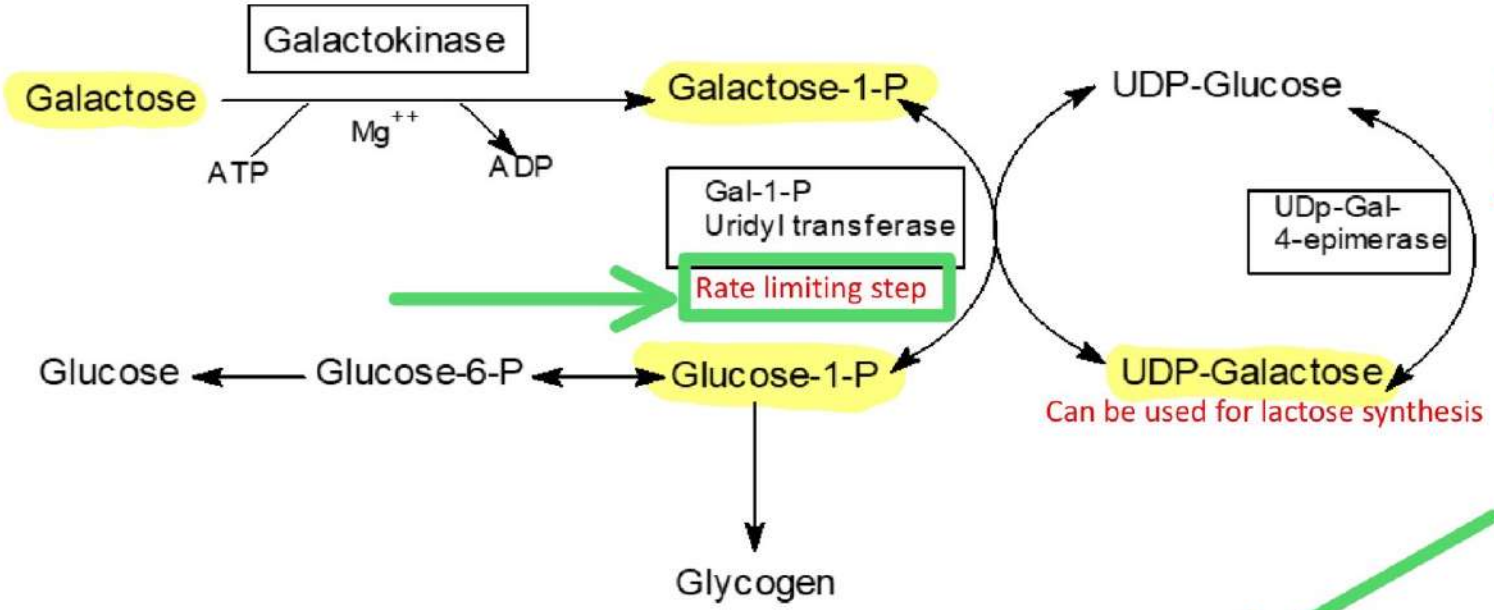
- **Alpha ketoglutarate dehydrogenase is irreversible step** (the only always irreversible)
  - Citrate synthase is irreversible but body can reverse it via ATP-citrate lyase
  - IDH step of the citric acid cycle is often (**but not always**) an irreversible reaction due to its large negative change in free energy

(isocitrate dehydrogenases) I D H

Comparison of HMP pathway and glycolysis

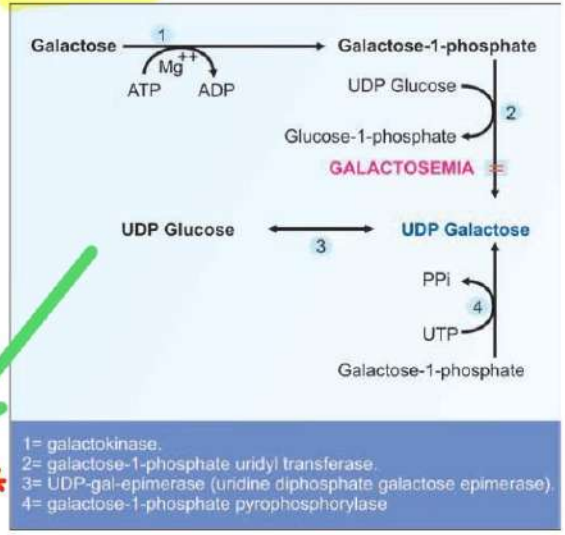
	HMP	Glycolysis
Complexity	Multi-cyclic process	Simple, linear
Oxidation	Early in the pathway	Later in the pathway
CO2	Produced (glucose molecule enter in) لكل	Not produced يصير بال(Krebs cycle)
ATP	Not generated	Generated (6-8 ATP)
Riboses	Are generated	Not generated
Dehydrogenase	NADP-specific	NAD-specific

Steps to convert galactose to glucose



Can be used for lactose synthesis

- Reaction is reversible
- If dietary supply of galactose is deficient, glucose can still be epimerized to galactose



If we need to produce lactose in mammary tissues:

UDP glactose + glucose → lactose (enzyme is lactase synthase)

مهم

* الأم المرضعة مش بالضرورة توضنكتير (Galactose) لأنها بتقدر تحول منه (Glucose → Galactose)

Galactosemia: (تراكمر الـ (Galactose في الدم)

- Congenital disease caused by deficiency of:
  - **Galactokinase (mild disease)**
  - **Galactose-1-P uridyl transferase** or **UDP-Gal epimerase (sereve disease)** (most common and sever)

- The deficiency of **galactose-1-P uridyl transferase is more common**

سؤال بالإمتحان

POLYOL PATHWAY OF GLUCOSE

Sorbitol is very poorly absorbed from intestine. It involves the reduction of glucose by aldose reductase to sorbitol, which can then be oxidized to fructose. This would amount to the inter-conversion of glucose to fructose (Fig. 10.8).

Glucose when converted to sorbitol, cannot diffuse out of the cell easily and gets trapped there. Sorbitol is normally present in lens of eyes. But in **diabetes mellitus**, when glucose level is high, the sorbitol concentration also increases in the lens. This leads to osmotic damage of the tissue and development of **cataract**. Galactitol also causes cataract (see under galactose metabolism).

Fructose is present in semen in large quantities. It is produced by the polyol pathway. The polyol pathway is active in brain and fructose is seen in CSF. This pathway is inactive in liver.

الجلوكوز يتحول إلى فركتوز عن طريق (Polyol Pathway)

(POLYOL PATHWAY)

PPP: Pentose Phosphate Pathway

Key facts about FA synthesis

- FA synthesis takes place in cytosol and uses NADP as co-enzyme for redox reactions
- **Citrate shuttle** is responsible for moving acetyl coA from mitochondria to the cytosol
- NADPH is an important co-enzyme for de novo FA synthesis; sources:
  - Main source of NADPH is PPP (both FA synthesis and PPP occur in cytosol; no permeability barrier)
  - Malic Enzyme: The reaction helps to transfer cytoplasmic oxaloacetate to the mitochondria

$$\text{Malate} + NADP^+ \rightarrow \text{Pyruvate} + CO_2 + NADPH + H^+$$

- Cytosolic isocitrate dehydrogenase: is NADP dependent (سؤال في الإمتحان) ← (لو كانت (Mitochondrial) بكون (NAD^+ dependent))
- The building block for FA synthesis is malonyl coA (3C)
- FA synthesis in each reaction cycle adds 2 carbons that are derived from malonyl coA following decarboxylation
  - Acetyl (2C) coA is used as a primer for C15 and 16 in palmitate → even number FA
  - If propionyl (3C) coA is used as a primer → odd n FA is formed
  - Short chain FA is formed if chain is released before reaching 16 carbons as in mammary glands

لو وصلت (16C) بتطلع (short)؟

في كل تفاعل منه تفاعلات صناعة الـ FA نضيف (2C) منه (malonyl coA) الذي يحتوي بالأساس على (3C) عن طريق (decarboxilation)

—Arachidonic is n't essential, you can synthesise it, But if we take linoleic acid, it will be essential if we haven't linoleic acid

Triacylglycerol (TAG) in the subcutaneous tissue

- **TAG:** FAs + glycerol

- Liver and adipose tissue are major sites of TAG synthesis
  - In adipose tissue → for storage of energy and (insulation) عزل جسمك
  - In liver → secreted as VLDL & transported to peripheral tissues

- Synthesis of TAG needs activation of glycerol & FAs
  - Active form of glycerol is glycerol 3-P (يتصر ناتجه من خلال طريقتين)
    - **In liver & adipose tissue:** glycerol is produced from glucose via DHAP (from glycolysis)
      - This is active in presence of insulin
    - **In liver only:** glycerokinase phosphorylates glycerol directly
  - Active form of FA is fatty acyl coA (via thiokinase enzyme by reaction btwn acetyl coA & FA)

سؤال سؤالين في الإمتحانه

- Synthesis of TAG (reaction btwn activated FAs and activated glycerol)

- **Fate of TAG:**
  - In liver → exported as VLDL (bound to cholesterol, phospholipids and protein)
  - In adipose tissue → provision of energy when needed

β-oxidation of fatty acids

- **Site:**

All cells containing mitochondria (it isn't happens in the RBCs)

- Remember sites of: Glycolysis in cytosol / gluconeogenesis (mitochondria) بس في منه بال (جزء كبير في الـ cytosol)

FA Synthesis in cytosol / Krebscycle and β-oxidation in mitochondria / Oxidatave Phosphorelation Mitochondria

- **Steps:**

سؤال في الإمتحان: احسب عدد الـ (ATP) الناتج من تكسير (TAG) المكون من (3palmitate and Glycerol) عن طريق الـ (β-oxidation) على النظام الجديد

على افتراض أن الـ (Glycerol) سينتج (DHAP) في الـ (Gluconeogenesis) ؟

1) تكسير الـ (TAG) إلى (1 Glycerol / 3 palmitate) واللتو لا تحتاج إلى طاقة ولا تنتجها

2) الـ (Glycerol) سيدخل في (Gluconeogenesis) فيستهلك (1 ATP) ليتوقف عند (DHAP)

3) كل (palmitate) الـ (Activation) يستهلك (2 ATP) و هو رح يدخل في (7 cycles) وينتج (8 Acetyl CoA) و (7 NADH) و (7 $FADH_2$)

(7 $FADH_2$ = 10.5 ATP / 7 NADH = 17.5 ATP)

الـ (8 Acetyl CoA) سيدخلوا في (Krebs cycle) لينتج كل واحد منهم (10 ATP) = 8 X (10 ATP) = (80 ATP)

∴ الـ (palmitate) الواحد = 108 - 2 = 106 و لانا نتعامل مع (3 palmitate) نضرب الحاصل بـ (3) = 318

- لا ننسى الـ (-2 ATP) من الـ (Glycerol)

الحصلة :-

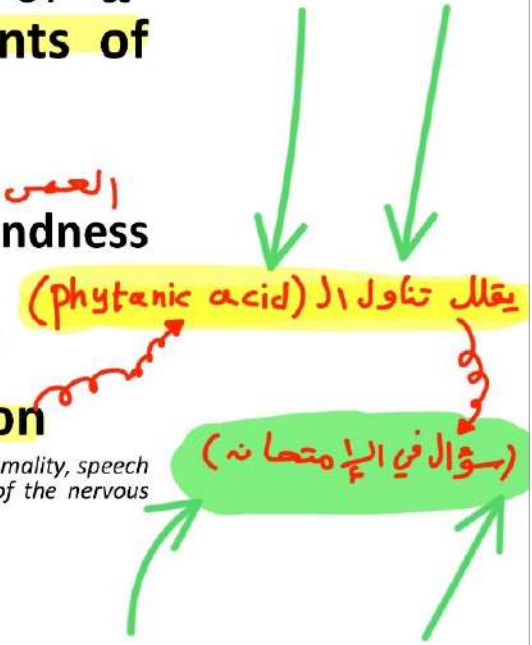
318 - 1 = 317

*Refsum's disease:

- Rare autosomal recessive disorder
- Defect in alpha oxidation
- Due to congenital deficiency of enzyme system of **α-oxidation leading to accumulation of large amounts of phytanic acid in the brain, liver and blood**

Symptoms

– **Polyneuropathy, cerebellar ataxia, deafness** الصمم **and blindness** العمى **occur at young age**



Treatment: dietary restriction to halt disease progression لوقف

- ***Ataxia*** *is a neurological sign consisting of lack of voluntary coordination of muscle movements that can include gait abnormality, speech changes, and abnormalities in eye movements. Ataxia is a clinical manifestation indicating dysfunction of the parts of the nervous system that coordinate movement, such as the cerebellum.*

(جاي عليهم حالات بالإمتحان)

Introduction- ketone bodies (مهمه ٣ حغلات)

- Acetoacetate, β-hydroxyl butyrate & acetone are collectively called ketone bodies
- **Ketogenesis**: formation of ketone bodies (occurs in liver)
- **Ketolysis**: utilization of ketone bodies as fuel (occurs in extrahepatic tissues)
- Under normal conditions, production of ketone bodies is at relatively low rate

(FA) أنت مش محتاج الهم لأنه بالعادة عندك جلوكوز ولو مافي جلوكوز المفروض يكون عندك

- Increased ketone bodies is known as **ketosis** while high blood level is known as **ketonemia**

HMG coA synthase is rate limiting step in synthesis of ketone bodies and is present in significant quantities only in liver

3. Electron transfer through Complex II is not accompanied by proton pumping across the inner membrane, although the QH2 will be used by Complex III to drive proton transfer.

demands.

- **The most important determining factor of oxidative phosphorylation is:**
  - ADP level

* AST and ALT are induced (يزيدوا) by glucocorticoids which favors gluconeogenesis

سؤال موجود بشرح هذه النقطة رح يدخل بالإمتحانه

آخر هدف فيها هو الوصول إلى (glucose) وكيف بدي أعمل؟ عن طريق تكسير الـ (AA) والـ (AST/ALT) باعدوا في الـ (catabolism) فبالتالي متى يكون عندي (glucocorticoids) ويزيدوا بعفنوا (gluconeogenesis) وصار التعفين يتطلب (catabolism of AA) لإستخدام (AST, ALT) كـ (intermediate) عشان نصنع (glucose) فأنا بدي أحفز الـ (catabolism) بتعفن هاي الـ (Enzymes)

* معلومة عامة: الكبدة عندها مهمات بالمحاضرة: زيادة نسبة الـ (Ammonia) في الجسم له تأثير سلبي على الـ (Brain/CNS)
وبتعمل مرض اسمه (encephalopathy) معنى المرض (Brain damage)

* العبء لـ (ATP) 1.5 وليس 4 . طيب ليش ما بنحتاج (ATP) كتير وشو العبء وليش 1.5 بدل 4 ؟

لأ بس بتنتجلي (fumarate) اللي بتحول إلى (malate) في (citric acid cycle) والـ (citric acid cycle) أصلا بتنتجلي (ATP) فلما يتحول (malate)

إلى (oxaloacitate) هذا الشيء بعطيني (NADH) فإذا انتجت وحدة تعادل (2.5 ATP) ـــ (4 - 2.5 = 1.5) ∴ العبء تاع (urea cycle) هو 1.5 وليس 4

هذا السؤال داخل بالإمتحانه حسب كلام الدكتورة

(7) in mitochondria

Step 7: Generation of Heme

- The last step in the formation of heme is the attachment of **ferrous iron** to the protoporphyrin.
  - The enzyme is **ferrochelatase (heme synthase)** which is also located in **mitochondria.**
- Iron atom is coordinately linked with **5 nitrogen atoms** (4 nitrogen of pyrrole rings of proto-porphyrin and 1st nitrogen atom of a histidine residue of globin).
- The remaining valency of iron atom is satisfied with water or oxygen atom.
- When the **ferrous iron (Fe^{++}) in heme gets oxidized to ferric (Fe^{+++}) form, hematin** is formed, which loses the property of carrying the oxygen.
  - Heme is red in color, but hematin is dark brown.

بشكل مناسب

سؤال بالإ متحانة: أنه هنه وين بتتصب (N5) وكيف

(oxigenated) لما يكونه أحمر

فيكونه لونه أغمق (بني)

(Hematin) وبصير

-D Heme with ferric

Regulation of Heme Synthesis

rate limiting step

(negative feedback) وتعني (ALA) بتقول لـ (Heme) * لو زاد عندي

- **ALA synthase** is key rate limiting enzyme.
  - Heme, lead poisoning and steroids **inhibit** its activity.
  - Excess heme in BM is converted to hematin by oxidation of Fe2+ to Fe3+. → وصدنه كمانه بحكي لـ (ALA) بكفي
    - ALA synthase is also **allosterically** inhibited by hematin.

امتحانه

نقص التروية (ALA synthase) أو (Heme) فبصير في حاجة ورا زيادة (RBC) بدنه

- **ALA synthase** is **activated** by hypoxia due to increase in erythropoietin. → هرمونه

- **ALA synthase** is also **activated** by availability of intracellular iron.

TABLE 21.2: Features of important types of po

Type	Enzyme defect
Acute intermittent porphyria (AIP) the most common	PBG-deaminase (UPG-I synthase) (enzyme 2)
Congenital erythropoietic porphyria	UPG-cosynthase (enzyme 3b)
Porphyria cutanea tarda (skin) the second most common	UPG-decarboxylase (enz 4)
Hereditary coproporphyria	CPG-III-oxidase (enzyme 5) بسبب نقص
Hereditary protoporphyria	Heme synthase or Ferrochelatase (enzyme 7)

PBG = Porphobilinogen; CP = Coproporphyrin; ALA = delt

Cholesterol

عاد حاجي الجملة (3-4 مرات)

It is the main steroid in humans (present in **all** cells especially nervous system & plasma)

- It is a precursor form **all** other steroids

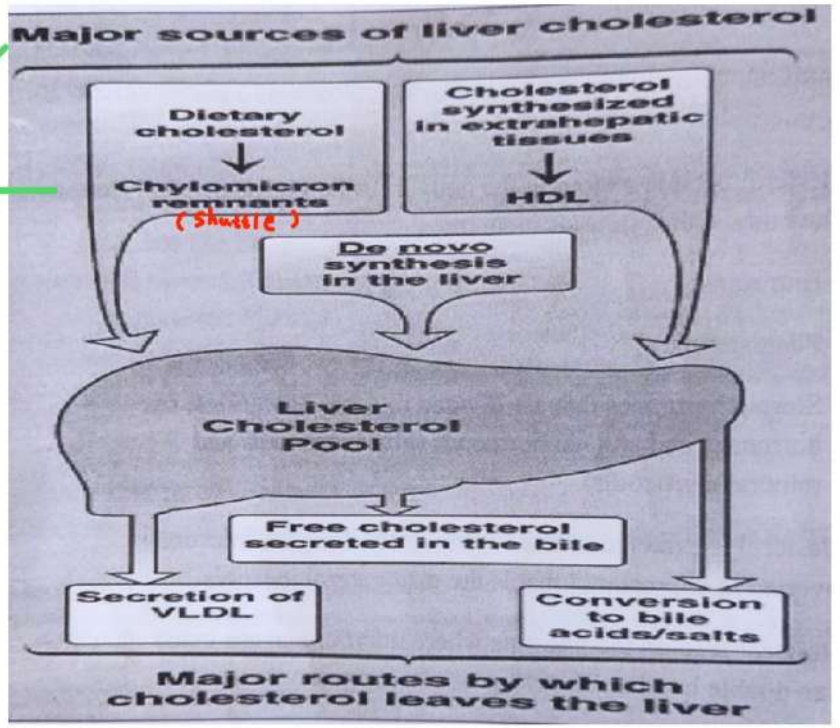
Important facts about cholesterol metabolism

- Liver plays a central role in regulation of body's cholesterol
  - Liver & intestines main site of synthesis
  - Enzymes involved in synthesis are in cytosol & ER
  - Liver is principle organ that removes cholesterol from blood
- Cholesterol is **not** a dietary essential
- **All carbons are provided by acetyl coA** + NADPH
- Balance depends on input and output
- Any imbalance leads to gradual deposition of cholesterol in tissues especially lining of vessels → **coronary artery disease**

سؤال في الإمتحان

(تصنيع ال(cholesterol يتم في ال(cytoplasm) وايضا في ال(Mitochondria))

(يمكن تصنيعه داخل الجسم)



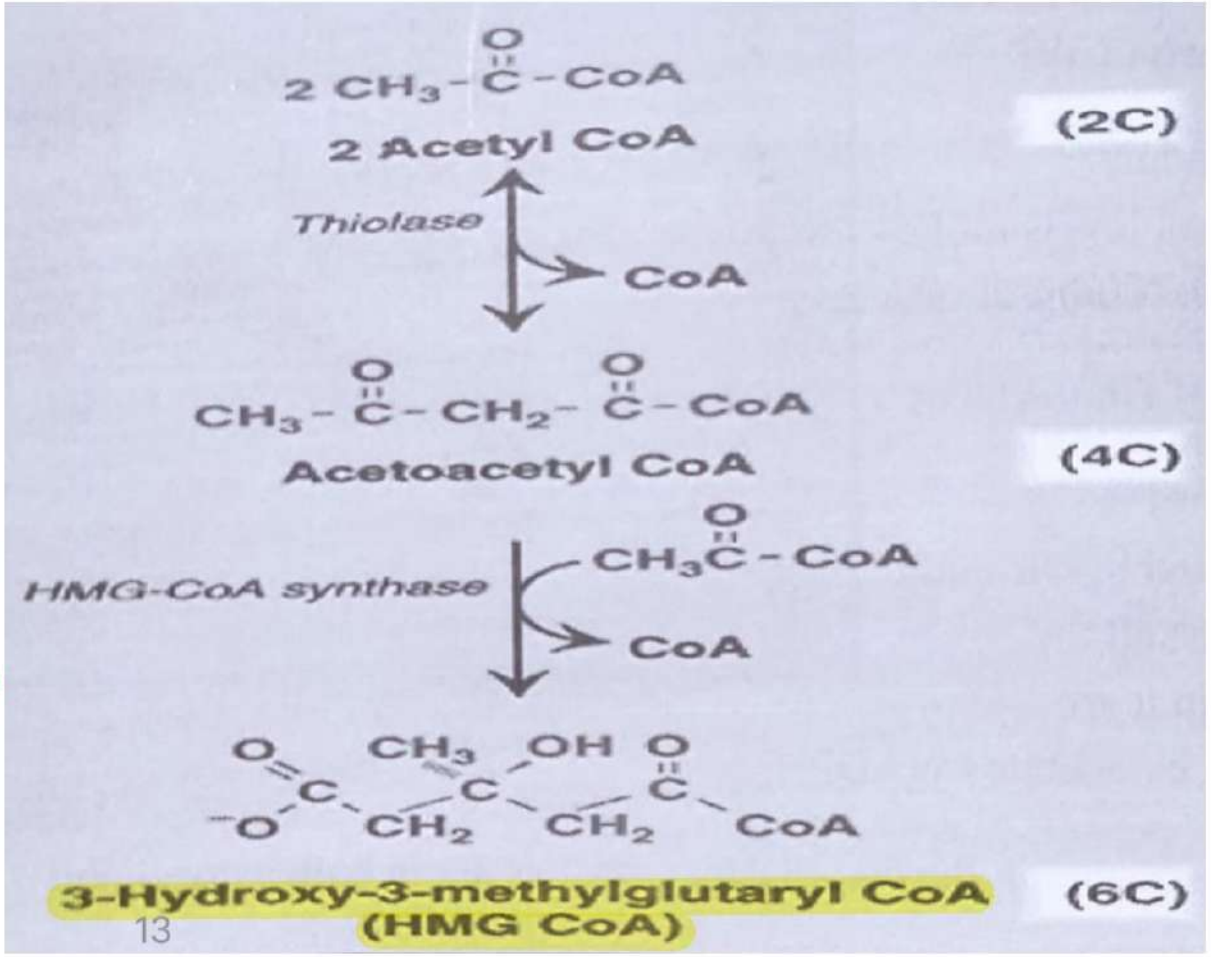
3acetyl coA (2C)

Synthesis of HMG coA from acetyl coA

Isoenzymes of HMG co synthase

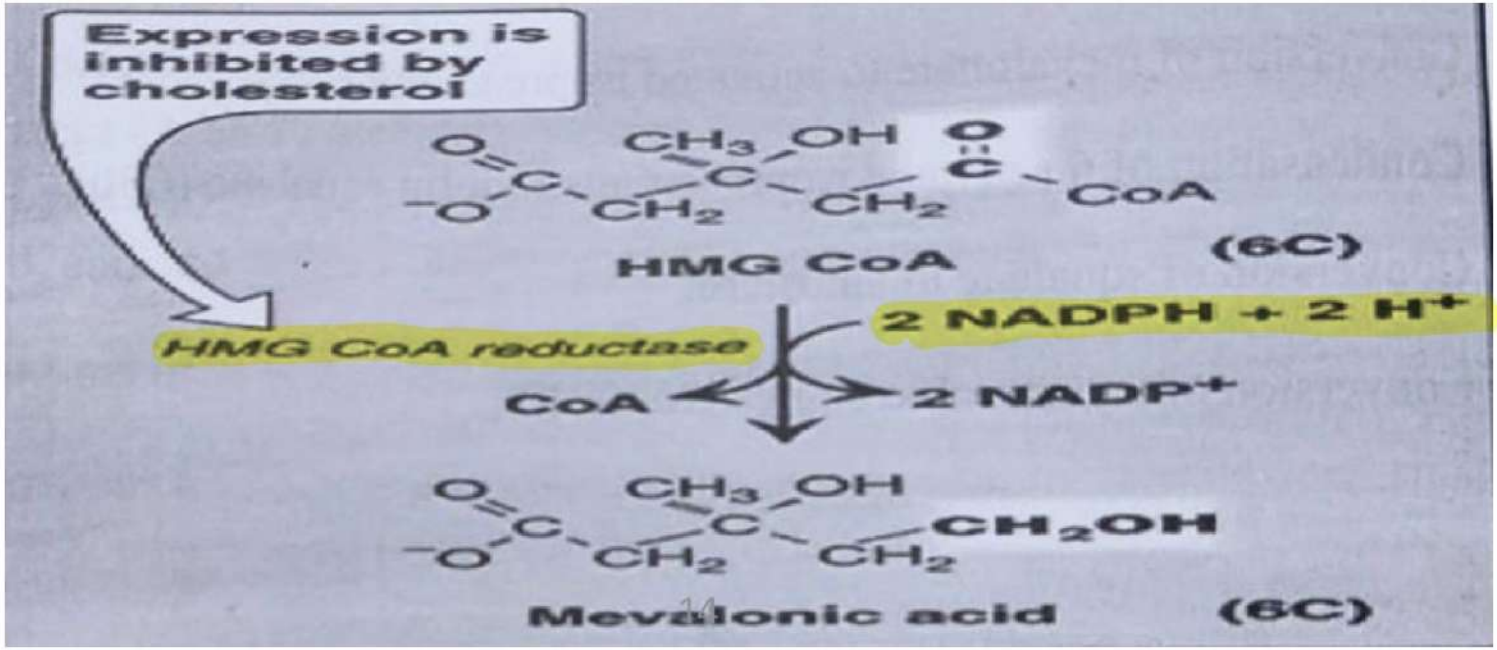
- Cytosolic enzyme → cholesterol synthesis
- Mitochondrial enzyme → ketone body synthesis

سؤال في الامتحان



Synthesis of mevalonic acid (mevalonate)

- Enzyme: **HMG coA reductase (rate limiting & key regulated step in cholesterol synthesis)** (كرر المعلومة مرتين)
  - **Reaction is irreversible**



Eicosanoids

- Derived from eicosa (20 carbons) polyenoic FAs (arachidonic acid 20:4)
- The dietary precursor is the essential FA linoleic acid (18:2)
- Produced by most mammalian cells
- Have physiological and pharmacological actions
- Hormone-like molecules:
  - Autocrine
  - Paracrine
- Subscript number in an eicosanoid denotes n of double bond (e.g. PGE2)

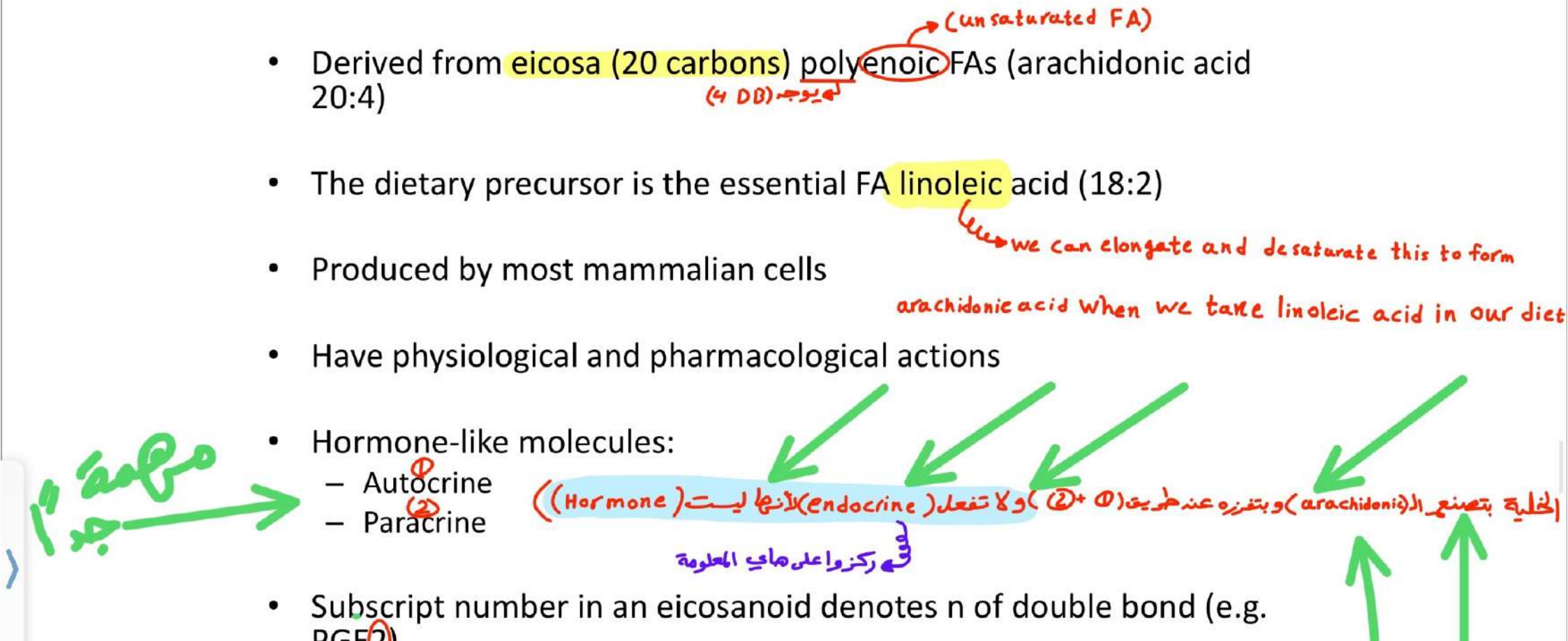


TABLE 8.2: Adaptations during starvation

Fed state	*Skeletal muscle*	*Cardiac muscle*
Preferred fuel at rest	Fatty acids	FFA, ketone bodies, lactate
Exercise	Glycogen to lactate	Fatty acids
Starvation Adaptations	Protein breakdown; release of amino acids; FFA, ketone bodies and branched chain amino acids utilized	Fatty acids, branched chain amino acids and ketone bodies utilized

TABLE 8.3: Major fuels in different organs

	Brain	*Skeletal muscle*	*Cardiac muscle*	*Adipose tissue*
After a meal	Glucose	Glucose, Fatty acids	Glucose, pyruvate	Fatty acids; glucose
Fasting (short-term)	Glucose	Fatty acids	Fatty acids	Fatty acids
Fasting (long-term)	Glucose; ketone bodies	Ketone bodies; Branched chain aa	Ketone bodies	Fatty acids; ketone bodies
Exercise		Glycogen	Fatty acids	

Major fuels in differe

Enzyme	Fed	Fasting	Starvation	Activator	Inhibitor
Glucokinase	Increase	Decrease	Decrease	Insulin, Glucose	F-6-P
Phosphofructokinase1	Increase	Decrease	Decrease	F-2,6-bisP, AMP	ATP, Citrate
Fructose 1,6 bisphosphatase	Decrease	Increase	Increase	ATP, Citrate	F-2,6-bisP, AMP
Pyruvate carboxylase	Decrease	Increase	Increase	AcetylCoA	
PEPCK	Decrease	Increase	Increase	Glucocorticoids	Insulin
Glycogen phosphorylase	Decrease	Increase		Glucagon, AMP	Insulin
Glycogen synthase	Increase	Decrease	Decrease	Insulin, G-6-P	Glucagon
Carnitine acyl transferase		Increase	Increase	Glucagon	Malonyl CoA
Acetyl CoA carboxylase	Increase	Decrease	Decrease	Insulin, Citrate	Fatty acylCoA
Hormone sensitive lipase	Decrease	Increase	Increase	Glucagon	Insulin

Conversion Of Carbohydrates To Proteins

(intermediates of Krebs cycle and Pyrovate عن طريق ال (carbohydrates) يجوا منه ال)

Carbohydrate

- Occurs mainly in liver
- Most of non-essential amino acids → products of glycolysis
  - 3-phosphoglycerate → sreine
  - Pyruvate → alanine
  - Oxaloacetate → aspartate
  - a-ketoglutarate → glutamate
  - Serine ⇔ glycine & cysteine

Conversion Of Fats To Carbohydrates

بشكل أساسي مش ممكن السبب أنه (Pyrovat-DH is completely irreversible)

طيب كيف بصير؟ بصير عنه طريقة (minor) عن طريق

- Normal conditions → minor

جاي من TAG

- Glycerol → DHAP → glucose (gluconeogenesis)

- Last 3 C of odd chain FA (rare in nature) → propionyl-CoA → succinyl-CoA → TCA → Oxaloacetate → glucose

سؤال بالإمتحان: على الـ (Reactions of Pyrovatedehydrogenase/Pyrovate Carboxilase)

- رح تنسأل عنهم بكثرة/ - في أسئلة متعلقة بالـ(irreversebility)