lec 1

_Acid-stable lipases: lingual lipase and gastric lipase >>

are Significant in infants and patients with pancreatic lipase deficiency or pancreatic insufficiency (e.g., cystic fibrosis).

_Two mechanisms of emulsification in the duodenum: It occure because of the aques environment in stomach while the FAs hydrophobic

1) Peristalsis: mechanical mixing leading to smaller droplets

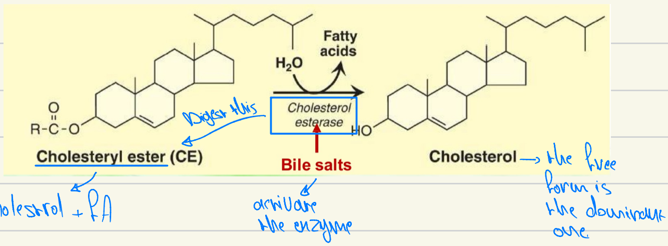
2) Conjugated bile salts (for it digested by pancreatic enzymes)

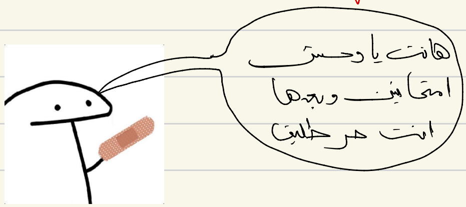
_The majority of digestion occurs in the intestine by pancreatic lipase. → هنا الحكي بصير لمبس عدة. بروتين اسمه Co-lipase

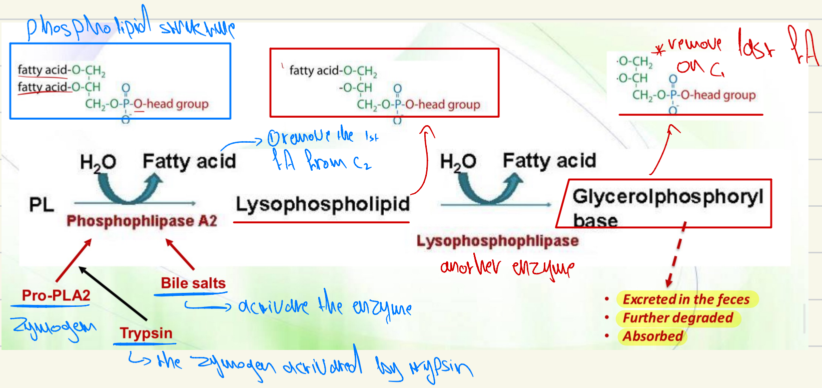
طبعًا كل واحد co-lipase بيربط بواحد lipase عشان هيك ratio بتكون 1:1 . ووظيفته انه يسمح لل pancreatic lipase انه يهضم ال lipid الـ

متغطى بـ bile salt. لانه وجود phosphate بيحول دون ذلك. اعرفوا انه هاد co-lipase بيفرز ع شكل zymogen من البنكرياس.

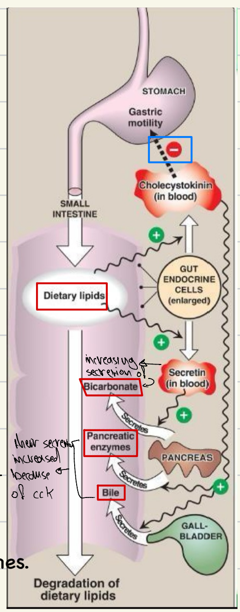
وبصير active by trypsin.







phospholipid structure
fatty acid-O-CH2
fatty acid-O-CH
CH2-O-P-O-head group
-O-CH
remove last FA on C1
PL
H_2O
Fatty acid
Phosphophlipase A2
Lysophospholipid
remove the 1st FA from C2
Lysophosphphlipase
another enzyme
Glycerolphosphoryl base
Pro-PLA2
zymogen
Bile salts
activate the enzyme
Trypsin
the zymogen activated by trypsin
Excreted in the feces
Further degraded
Absorbed



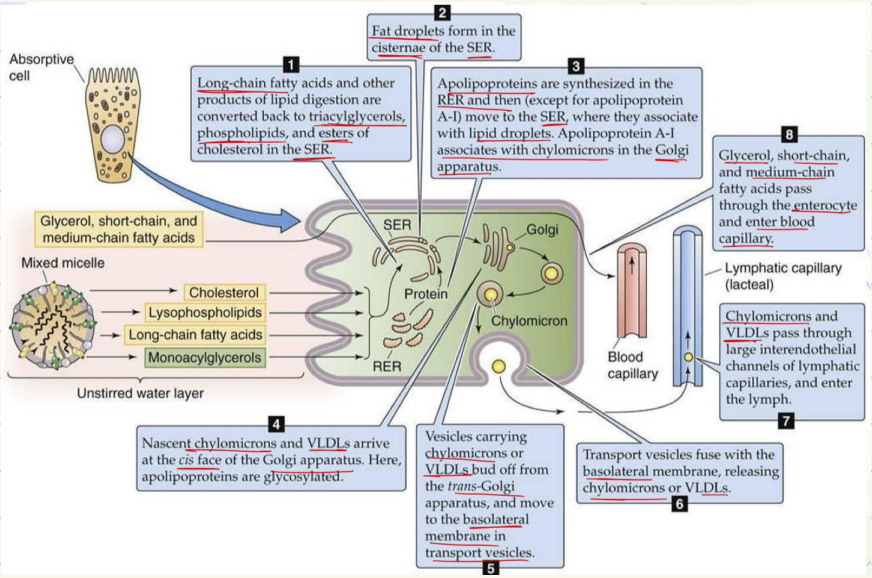
STOMACH
Gastric motility
Cholecystokinin (in blood)
SMALL INTESTINE
GUT ENDOCRINE CELLS (enlarged)
Dietary lipids
Secretin (in blood)
Bicarbonate
increasing secretion of
Pancreatic enzymes
their secretion increased because of cck
PANCREAS
Secretes
Bile
GALL-BLADDER
Degradation of dietary lipids

when food reach the stomach it will secrete two hormons

_both of (secretin and cholecystokinin) → ↓ gastric Motality

bicarbonate-rich solution to neutralize the pH and make it optimal for the digestive pancreatic enzymes.

شوفوا الكلام ع الرسمة



- People with high cholesterol level are given statin, which decreases the blood cholesterol level by inhibits synthesis of it.
- The uptake of fatty acids across the enterocyte brush- border membrane occurs by passive diffusion and by protein-mediated mechanisms.

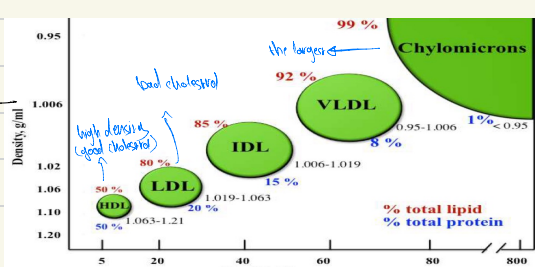
- Principal causes of steatorrhea:
  1. Short bowel disease
  2. Liver or biliary tract disease
  3. Pancreatic exocrine insufficiency
  4. Cystic fibrosis

- Celiac disease is an autoimmune response to gliadin Gluten is a protein composed of 2 poly peptide chains, glutenin and gliadin. Gliadin is rich in proline and glutamine, making it resistant to digestion, resulting in inflammatory response(this inflammatory response damages the enterocytes). Scientists found that patients with celiac disease have antibodies against enzyme known as transglutaminase. Celiac disease is an autoimmune disease. And Tissue biopsy: absence of villous surface epithelial cells resulting in decreased nutrient absorption.

#end with lec 1.

#lec 2

- Those lipoprotein are transporter (composed of protein and lipid mainly phospholipids) and the density of them increase when the protein component increase. (high protein : lipid ratio)

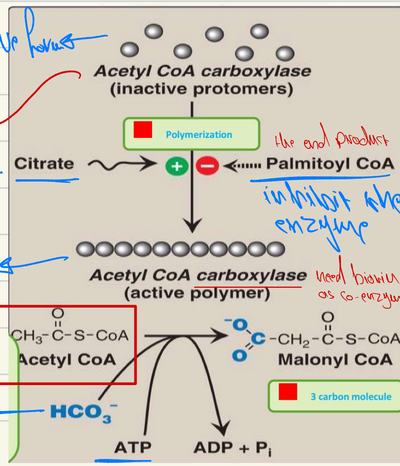


EXAM question, the first intermediate in glycolysis that glycerol is converted to is DHAP

*FA synthesis ⇒

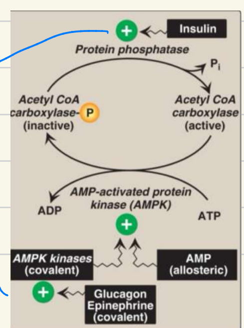
When ATP (or NADH) increases:
↓
ATP inhibits isocitrate dehydrogenase → So isocitrate doesn't convert to α-ketoglutarate and return back to citrate.
↓
Citrate is transported into the cytosol
↓
Citrate is cleaved into oxaloacetate and acetyl CoA by ATP citrate lyase → this acetyl CoA that we need in FA synthesis

Synthesis of malonyl-CoA >> The reaction is a rate-limiting reaction.



inactive form
هاد اللي بيعمل polymerization للـ active form بيصير عشان
activate the enzyme (Citrate)
inhibit the enzyme (Palmitoyl CoA, the end product)
active form
need biotin (B7) as co-enzyme
هاد اللي بيجي من Citrate
بتروح منها CO2 وبتنضاف على acetyl CoA
الـ HCO3 بعد كذا

Regulation of ACC



في حال كان insulin عالي بيصير well fed يعني activation for phosphatase عشان يشيل الفوسفات عن ACC ويصير active.

لما ترتفع نسبة glucagon, epinephrin، بعمل activation لـ cAMP و PKA ويروح يفسفر الـ ACC ويصير inactive

(short term regulation)

_Regulation of ACC synthesis >> long-term regulation

1) ACC synthesis is regulated by transcription factors:

-The carbohydrate response element-binding protein (ChREBP) :

- ChREBP is inactivated by phosphorylation by PKA and AMPK preventing its nuclear localization. (high glucagon level)

- It is dephosphorylated by excess glucose.

2) The sterol regulatory element-binding protein-1c (SREBP-1c)

-SREBP-1 is activated by Insulin. → which indicate good amount of glucose

*Fatty acid synthase, glucokinase, ATP citrate lyase and liver pyruvate kinase are similarly regulated.

_Metformin (trade name : Glucophage) is given to pre-diabetic individuals which are susceptible of having diabetes

_Metformin lowers plasma TAG through Activation of AMPK, resulting in inhibition of ACC activity (by phosphorylation) and inhibition of ACC and fatty acid synthase expression (by decreasing ChREBP and SREBP-1c).

يقلل هذا الدواء نسبة glucose في الدم عن طريق انه بزيد glucose uptake by muscle

_Fatty acid synthase (FAS) → https://youtu.be/46NOG7u5KW0?si=bg-l_Py7SrmzT-_P تم شرح بهذا الفيديو، بنصحكم تحضروه

End with lec 2

lec 3

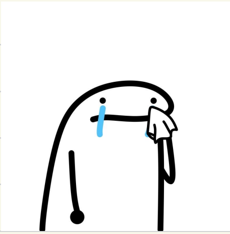
* تكملة لمواضيع 2.

_Sources of molecules

1) Acetyl CoA from Pyruvate

2) NADH (for oxaloacetate to malate) from Glycolysis

3) NADPH from Pentose phosphate pathway and Malate to pyruvate



لملم دموعك ليس
ينفعك البكاء ولا العويل

_Further elongation

1) Location: smooth endoplasmic reticulum

Different enzymes are needed.

Two-carbon donor: Malonyl CoA

Source of electrons: NADPH

No ACP or multifunctional enzyme is needed.

Note: the brain has additional enzymes allowing it to produce the very-long-chain fatty acids ([VLCFA] over 22 carbons)

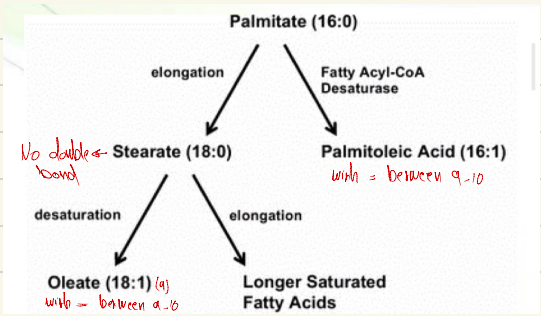
2) Location: mitochondria

Two-carbon donor: Acetyl CoA

Source of electrons: NADPH and NADH

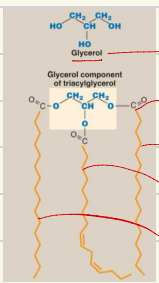
Substrates: fatty acids shorter than 16

- Chain desaturation
- Enzymes: fatty acyl CoA desaturases
- Substrates: long-chain fatty acids
- Location: smooth endoplasmic reticulum
- Acceptor of electrons: oxygen (O2), cytochrome b5, and its flavin adenine dinucleotide (FAD)-linked reductase
- Donor of electrons: NADH
- The first double bond is inserted between carbons 9 and 10, producing oleic acid, 18:1(9), and small amounts of palmitoleic acid, 16:1(9).



Humans have carbon 9, 6, 5, and 4 desaturases but cannot introduce double bonds from carbon 10 to the ω end of the chain. Therefore, the polyunsaturated ω-6 linoleic acid and ω-3 linolenic acid are essential.

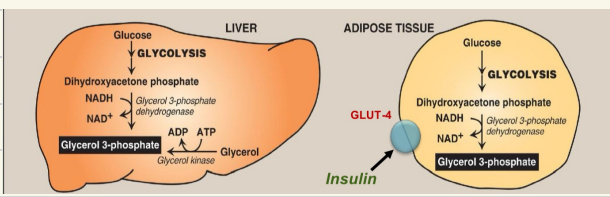
Triacylglycerol structure



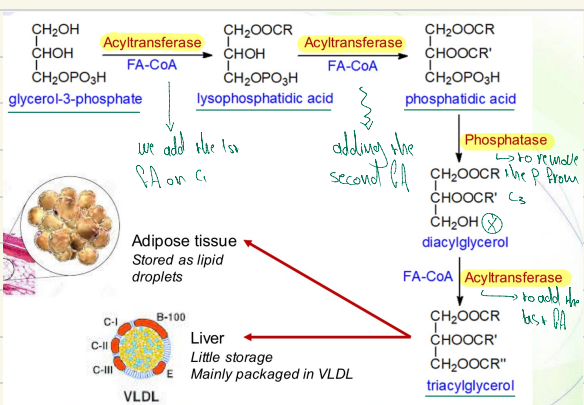
which synthesized from Glycerol 3 P
the bond is ester bond
the first FA usually saturated
the second FA = polyunsaturated
the third FA can be both

Glycerol 3 p synthesis

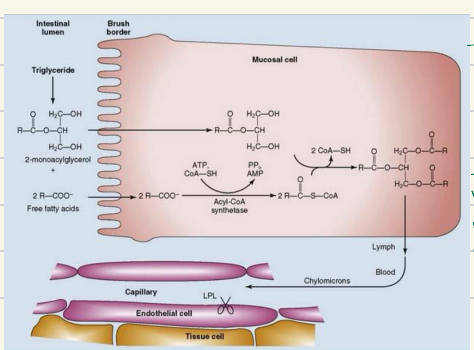
by two mechanisms :-
1) DHAP converted to Glycerol 3 P.
2) Glycerol will be phosphorylated.
the liver has both and adipose just the 1st



Synthesis of triacylglycerol

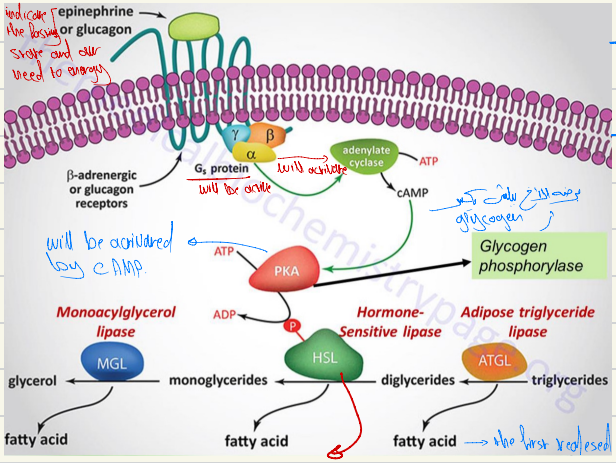


In addition to these two pathways (as in the liver), TAG is synthesized via
the MAG pathway in the intestinal mucosal cells.



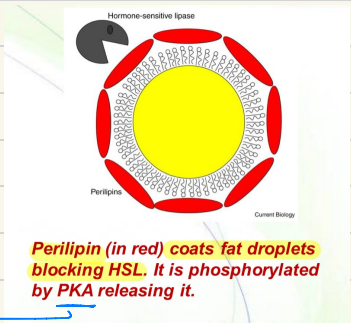
TAG are resynthesized in the intestine after eating it
Then it carried by chylomicron through lymphatic and circulatory

Hormonal regulation (TAG degradation)



HSL is under regulation of protein kinase A (PKA) which is activated by cAMP and its level increases when there is epinephrine or glucagon.

triglycerides become diglycerides by an enzyme called ATGL (adipose triglyceride lipase) and releasing 1 fatty acid >> diglycerides become monoglycerides by an enzyme called HSL and releasing 1 fatty acid >> monoglycerides become glycerol by an enzyme called MGL (monoacylglycerol lipase) and releasing the last fatty acid



Perilipin (in red) coats fat droplets blocking HSL. It is phosphorylated by PKA releasing it.

it will be phosphorylated by PKA and be active in order to degrade the TAG.

will phosphorylate this perilipin to release it.

Glyceroneogenesis

Notes:

- **Purpose: regulating the levels of FAs in blood.**
- **Glycerol leaves the adipocytes into the liver.**
- **Failure in regulating glyceroneogenesis may lead to Type 2 diabetes.**

Fatty acid β-oxidation

this takes place in the mitochondria (mitochondrial matrix), fatty acid synthesis takes place in the cytosol (there is a separation of these two opposite pathways)

https://youtu.be/jfQPB6tjfOo?si=ngEB-f-oQ0OGe21- Part one

https://youtu.be/mvPGq8tdT_Q?si=SDIlmDgvstq8zer3 Part two

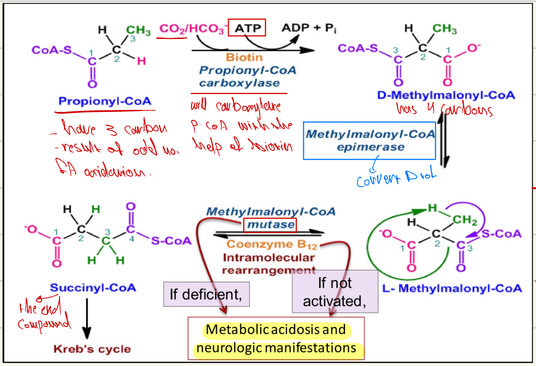
End with lec 3

#lec 4.

MCAD deficiency

- An autosomal-recessive disorder
- Most common inborn error of β-oxidation (1:14,000 births worldwide)
- Higher incidence among Caucasians of Northern European descent
- Decreased ability to oxidize MCFAs (lack of energy)
- Severe hypoglycemia and hypoketonemia
- Treatment: avoidance of fasting

Oxidation of odd-numbered FAs



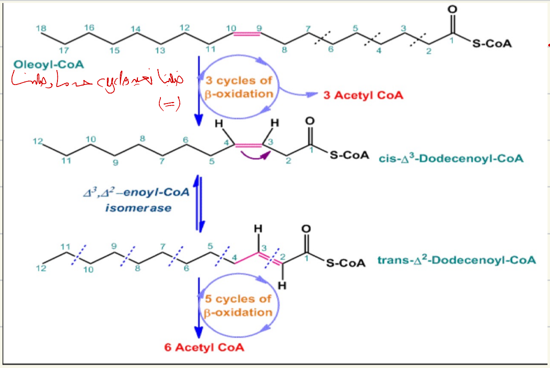
Propionyl-CoA
CO_2/HCO_3^-
ATP
ADP + P_i
Biotin
Propionyl-CoA carboxylase
D-Methylmalonyl-CoA
Methylmalonyl-CoA epimerase
L- Methylmalonyl-CoA
Methylmalonyl-CoA mutase
Coenzyme B_{12}
Intramolecular rearrangement
Succinyl-CoA
Kreb's cycle
If deficient,
If not activated,
Metabolic acidosis and neurologic manifestations
- have 3 carbon
- result of odd no. FA oxidation.
will carboxylate P. CoA with the help of biotin
has 4 carbons
convert D → L
the end compound

* when we have odd number of FA we end with compound has 3 carbons which is called propionyl CoA.

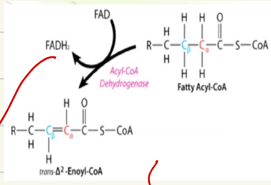
- Because Krebs cycle is not started from the beginning, it makes less energy, therefore there is aloss of electrons.

- People with B12 deficiency may have neurological manifestations and metabolic acidosis because of the accumulation of L-methylmalonyl-CoA.

Monounsaturated fatty acid β-oxidation



هون المشكلة بالأيزومريز لما توصل (=)، الها ح يصير نفس الخطوات بس احنا skip لأول خطوة في β-oxidation اللي كانت (oxidation) وأول خطوة (=) وظيفتها تضيف (=) والآن حطالها اياها داير

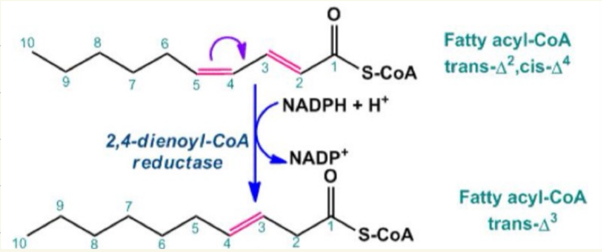


* هيها الخطوة الأولى دي

هنا حط بالك انه خسرنا electrons لانه ما في $FADH_2$ اكون يعني خسر loss of energy

لما بالك قلت ال ATP لاني ناقص هاي $FADH_2$

Polyunsaturated fatty acid β-oxidation

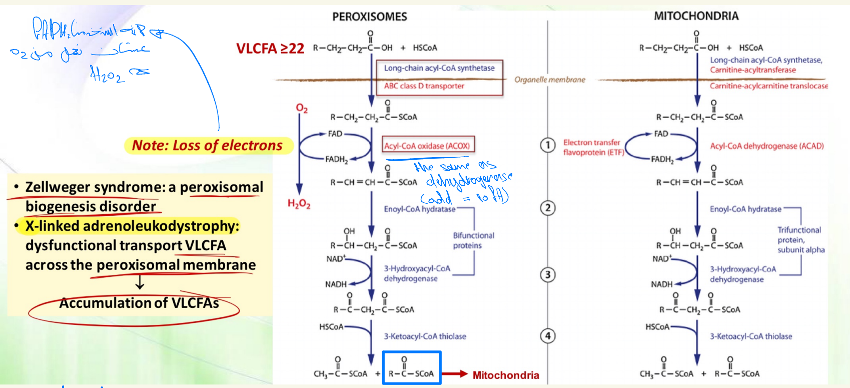


سوف هون اقتبنا الرابط عشان يجي من between (1=) و كون (2=) وبدون (=) بتطلع معصورة زي ما طالع فوق ونعمل skip لل 8 خطوة

- in polyunsaturated FA there is loss of electrons twice, first is in the reduction using the reductase, and the second is by skipping the step.

Peroxisomal β-oxidation

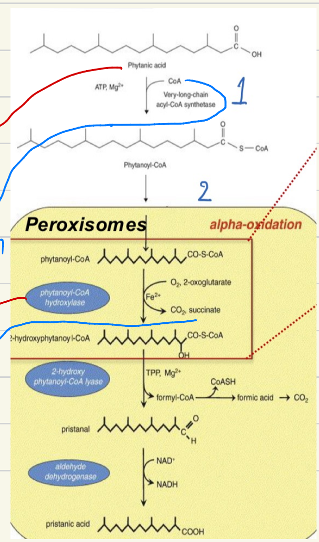
→ occur in peroxisom.


PEROXISOMES
MITOCHONDRIA
VLCFA ≥22
Long-chain acyl-CoA synthetase
ABC class D transporter
Organelle membrane
Long-chain acyl-CoA synthetase, Carnitine-acyltransferase
Carnitine-acylcarnitine translocase
Acyl-CoA oxidase (ACOX)
Electron transfer flavoprotein (ETF)
Acyl-CoA dehydrogenase (ACAD)
Enoyl-CoA hydratase
Bifunctional proteins
3-Hydroxyacyl-CoA dehydrogenase
Trifunctional protein, subunit alpha
3-Ketoacyl-CoA thiolase
Mitochondria
Note: Loss of electrons
Zellweger syndrome: a peroxisomal biogenesis disorder
X-linked adrenoleukodystrophy: dysfunctional transport VLCFA across the peroxisomal membrane
Accumulation of VLCFAs
the same as dehydrogenase (add = to FA)

الهدف انه نقصّر طول VLCFA عشان اقدر ادخلها ل β-oxidation in mitochondria.

العلاقات بس same الاهم في خسارة ح في peroxisome

بس لما طوله صار مناسب انتقل mitochondria


Phytanic acid
ATP, Mg2+
CoA
Very-long-chain acyl-CoA synthetase
Phytanoyl-CoA
Peroxisomes
alpha-oxidation
phytanoyl-CoA
phytanoyl-CoA hydroxylase
O2, 2-oxoglutarate
CO2, succinate
2-hydroxyphytanoyl-CoA
2-hydroxy phytanoyl-CoA lyase
TPP, Mg2+
CoASH
formyl-CoA
formic acid → CO2
pristanal
aldehyde dehydrogenase
NAD+
NADH
pristanic acid

Peroxisomal α-oxidation

is basically the metabolism of chlorophyll

phytanic acid is an intermediate of chlorophyll metabolism.

It will be activated by CoA, then transported to the

here this enzyme will hydroxylate (add OH) the ph.CoA

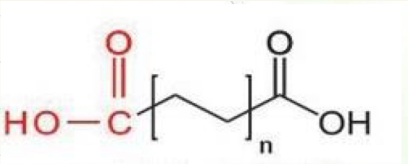
CO_2, succinate will be released.

When fully degraded, it generates 4 byproducts
formyl-CoA, propionyl-CoA, acetyl-CoA, 2-methyl-propionyl-CoA.

Refsum disease is an autosomal-recessive disorder caused by a deficiency of peroxisomal PhyH.

ω-Oxidation (oxidation for last carbon) by conversion the methyl group to carboxyl or adding the carboxylic to methyl.

وبعدين خطوات عادية مثل B-oxidation بس تبلش من omega

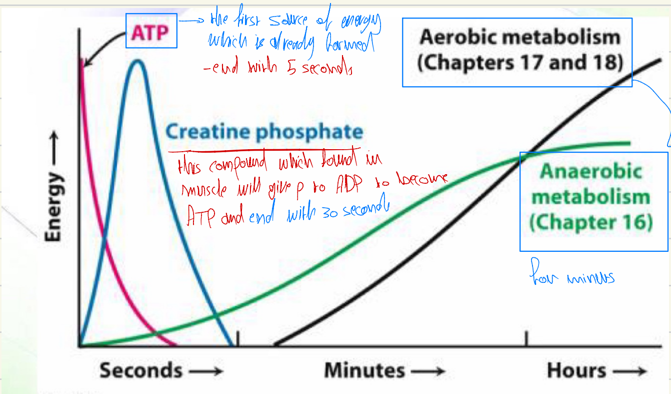


ω-Oxidation is a minor pathway of the SER, It generates dicarboxylic acids.
It is upregulated in certain conditions such as MCAD deficiency.

dicarboxylic acid

TAGs are the body's major fuel storage reserve.
The complete oxidation of fatty acids to CO_2 and H_2O generates 9 kcal/g offat (as compared to 4 kcal/g protein or carbohydrate)

Exercise and sources of energy

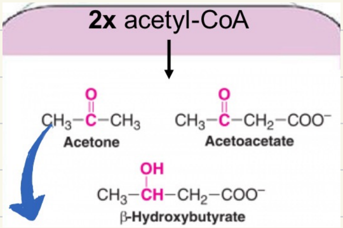


لما الشخص يبلش يركض جسمه ما بيرجع ح يستمر بالركض أو التمارين

4th source : Aerobic metabolism (needs oxygen) to produce more ATP and the Aerobic metabolism is
important for runners to run long distance for long time without exhausting and this is why runners
exercise more and more to have more oxygen to make Aerobic metabolism to produce more ATP to run
long distance for long time .

- for short distance the body use ATP and creatine.p

ketone bodies



→ 2 acetyl CoA (condensation together in liver) then transport to blood stream to other organs (brain, heart) not RBCs and liver, in prolonged starvation.

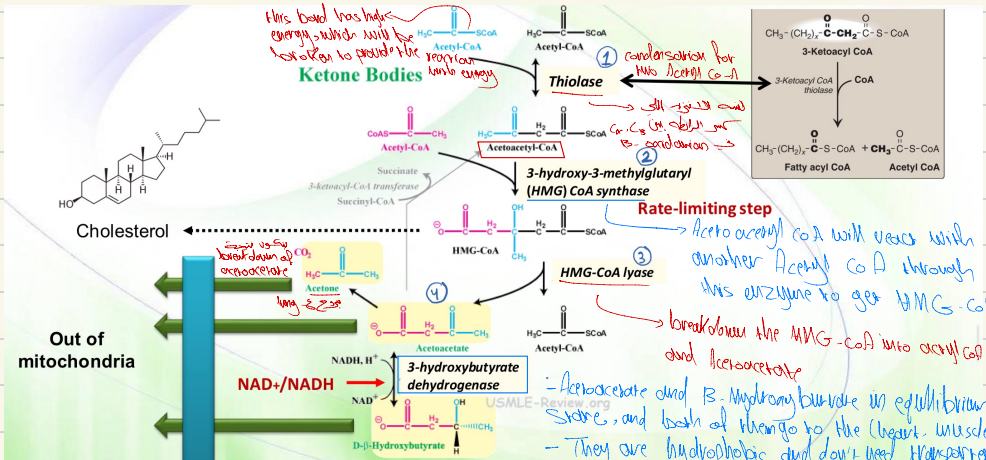
ketone bodies is responsible in generating
- **At wake-up time: 3-4% of energy**
- **Prolonged fasting: 30-40% of energy**

The longer the starvation period the greater the dependence on ketone bodies

Advantages:
Soluble (no carrier is needed)
Fast
Spare glucose

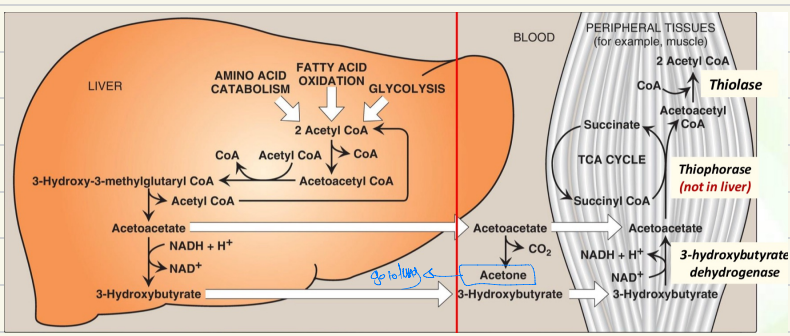
aceton have fruity smell in diabetic people. (volatile)

The reactions (in the mitochondrion.)



ketone bodies are quick sources of energy

Use of ketone bodies



- Hydroxybutyrate will be oxidized to Acetoacetate which will converted to Acetoacetyl CoA by thiophorase and cleaved into two acyl CoA by thiolase
- acyl CoA enter krebs cycle.

There are 2 types of cells that can NOT utilize ketone bodies:
1.RBCs, they don't have mitochondria.
2. liver, because liver cells don't have thiophorase enzyme, so they stick in the point where they have just acetoacetate and hydroxybutyrate.(exam question!!!!)

Under glucose-poor condition,

When cellular glucose is low, **oxaloacetate is diverted into gluconeogenesis**. In addition,
1. Excess FA breakdown produces large amounts of acetyl CoA.
2. Acetyl CoA inhibits pyruvate dehydrogenase.
3. Pyruvate is diverted toward oxaloacetate by pyruvate carboxylase.
4. Oxaloacetate is converted to malate,
5. and then back to oxaloacetate in the cytosol
6. Gluconeogenesis is activated and **oxaloacetate is depleted**.
7. **Acetyl CoA is diverted into ketogenesis**

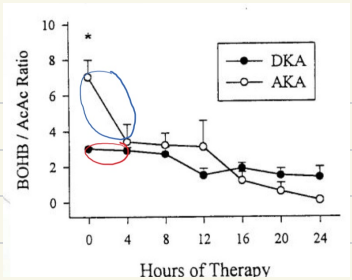
Diabetic ketoacidosis

important numbers

Normally,
Levels of ketone bodies: <3 mg/dl
NAD+:NADH is 10:1
3HB:AcAc is ~1:1
Under uncontrolled diabetes,
Levels of ketone bodies: 90 mg/dl and urinary excretion of ketone bodies may be 5,000 mg/24 hours.
The end-results:
Acidemia (ketoacidosis), Dehydration and Fruity odor of breath

Alcoholic ketoacidosis

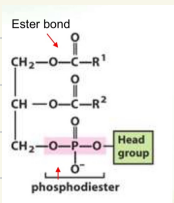
There is also,
Acidemia (ketoacidosis) But, 3HB:Ac is ~3:1
The ratio gets back to 1:1 after a few hours Gluconeogenesis is suppressed.
Pyruvate is converted to lactate leading to hypovolemia, heart failure, and sepsis.



End with lec 4.

#lec 5

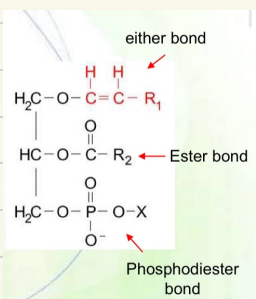
Classification of Glycerophospholipids



the parent

Phosphatidic acid	—	—H
Phosphatidylethanolamine	Ethanolamine	$-CH_2-CH_2-\overset{+}{N}H_3$
Phosphatidylcholine (lecithin)	Choline	$-CH_2-CH_2-\overset{+}{N}(CH_3)_3$
Phosphatidylserine	Serine	$-CH_2-\underset{COO^-}{CH}-\overset{+}{N}H_3$
Phosphatidylglycerol	Glycerol	$-CH_2-\underset{OH}{CH}-CH_2-OH$
Phosphatidylinositol 4,5-bisphosphate	*myo*-Inositol 4,5-bisphosphate	
Cardiolipin	Phosphatidyl-glycerol	

Plasmalogens



Sources of choline and ethanolamine

Choline and ethanolamine are obtained from diet, synthesized, or re-cycled from the turnover of pre existing phospholipids
Diet is still essential since demand > supply

Synthesis

Location: smooth ER
Except for ether lipids
Activation by CDP is necessary.

1)the backbone (the Diacylglycerol)
CDP-Diacylglycerol + glycerol >> phosphatidylglycerol + CMP
CDP-Diacylglycerol + inositol >> phosphatidylinositol + CMP
2)the head group
CDP-choline + Diacylglycerol >> phosphatidylcholine + CMP
CDP-ethanolamine + Diacylglycerol >> phosphatidylethanolamine + CMP

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