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Bio chemistry

Doctor 2017 | Medicine | JU

Sheet Slides

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DOCTOR

Faisal

last time we started talking about regulation of fatty acid synthesis and degradation

*regulation of fatty acid synthesis by:

1- regulation of acetyl CoA carboxylase -> activated by citrate/inhibited by the product of the pathway-> long chain fatty acyl CoA (feedback inhibition).

2- adding phosphate group to acetyl CoA carboxylase to convert it to inactive form/remove it make the enzyme active.

*general rule:
phosphorylation that occur for enzymes (glycogen phosphorylase/glycogen synthase/pyruvate dehydrogenase/acetyl CoA carboxylase…) minimize the catabolism of glucose and make glucose more available (it occur when glucagon conc. is high).

if glucose conc. is low->synthesis of fatty acid stops and oxidation of fatty acids should be active to produce energy.

3- regulating the amount of enzymes (used in some metabolic pathway) : if the reaction is required-> the enzyme that catalyse this reaction will be synthesized.

The enzyme always undergo turnover (synthesis and degradation of enzyme), so we can regulate the amount of enzyme by changing the rate of synthesis or degradation (the enzyme of fatty acid synthesis are regulated by the rate of their synthesis).

*During fasting->fatty acid synthesis is inactive->↓ synthesis of the enzymes.

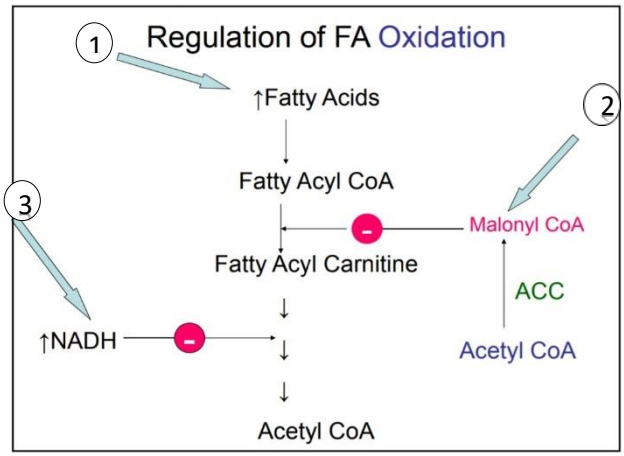
*if there is excess amount of carbohydrate->more active fatty acid synthesis->↑ synthesis of enzymes (fatty acid synthase/malate dehydrogenase and other enzymes).

*the mechanism is by increase or decrease the mRNA of the enzyme.

*regulation of fatty acid oxidation by:

1-the Supply of Fatty Acids: by Hormonal Control (glucagon+epinephrine)-> activation of hormone sensitive lipase increases the release of fatty acids from adipose tissue.

2- Entry into Mitochondria via carnitine shuttle (where oxidation occurs).



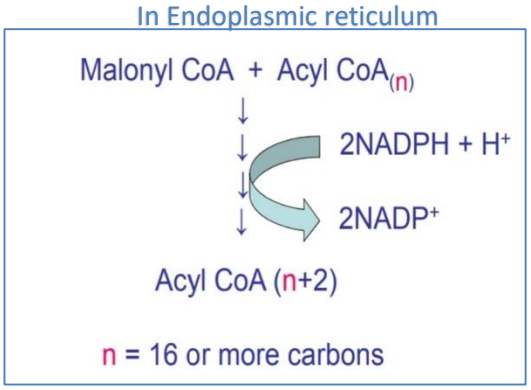
malonyl CoA inhibit the entry of fatty acids to mitochondria because the presence of it indicates that the synthesis of fatty acid is active, so fatty acid degradation should be inhibited.

3- Availability of NADH:↑ NADH->high amount of energy-> inhibit oxidation and start synthesis.

Q: base on the diagram, if you want to design a drug that increase the rate of fatty acid oxidation (based on enzyme inhibition)?

Ans: ACC. Inhibition lead to decrease the level of malonyl CoA (1st step of synthesis) and increase of fatty acid oxidation. This drug will be useful to treat obesity.

*Fatty acid elongation

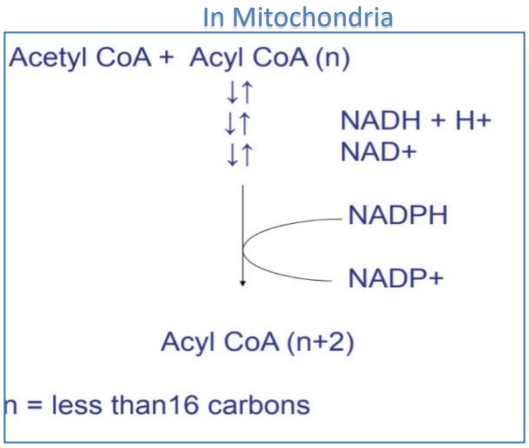


Fatty acid synthase will make fatty acid that have 16 carbon. What about fatty acids that have **more than 16 carbon**?

-The elongation of this fatty acids occur in endoplasmic reticulum (because the reaction involve nonpolar substances).

-Similar sequence of reaction to fatty acid synthase but different place and catalyzed by different enzymes found in endoplasmic reticulum.

-elongation of dietary short and medium fatty acids can occur in the mitochondria.



-the 1st 3 rxn in this pathway is the same last 3 rxn of the **β oxidation** (occurring in the revers direction).The last rxn uses NADPH instead of using FADH2 during elongation.

Introduction of Double Bonds (Synthesis of Monounsaturated FA)

*human can produce **monounsaturated fatty acids** (FA with 1 double bond like oleic and Palmitoleic acids) on the 9th carbon.

And because they can be produce on human, they can be considered non-essential.

• In endoplasmic reticulum.

• No double bond can be introduced beyond carbon 9 in human, therefore these fatty acids are essential fatty acids and we should take them from diet (ex: linoleic, linolenic).

How does it happen? Simply by adding –OH group followed by dehydration (not by removal of 2Hs ☺).

-this rxn is catalyzed by Δ9 Desaturase; Cytochrome b5. E.g: stearic acid is converted to -oleic acid by tow steps outlined below:

-Also, palmitic acid is converted to palmitoleic acid by the same mechanism.

-why the reaction need NADPH? Because we need one oxygen atom to be added to the fatty acid, so the second should be reduced by NADPH.

***Formation and Modification of Polyunsaturated FA** could happens by: Elongation and by Desaturation.

double bonds can be introduced on carbon no.4/5/6 by:Δ4 Desaturase/Δ5 Desaturase/ Δ6 Desaturase.

-the new double bond that we can produce should be 3carbons away from the existing one (CH2 exist between two sequential double bond)

*one example of this mechanism that occur in our body is convert Linoleic acid to Arachidonic acid by:

linoleic acid (18:2Δ9,12) —Δ6 Desaturase→ (18:3Δ6,9,12) —elongase→ (20:3Δ8,11,14) —Δ5 Desaturase→ Arachidonic acid (20:4Δ5,8,11,14)

On the 1st step, double bond is added to the carbon no.6 of the fatty acid (3 carbons before the old double bond) by Δ6 Desaturase.

On the 2nd step, 2 carbon atom is added by the enzyme elongase at carboxyl end.

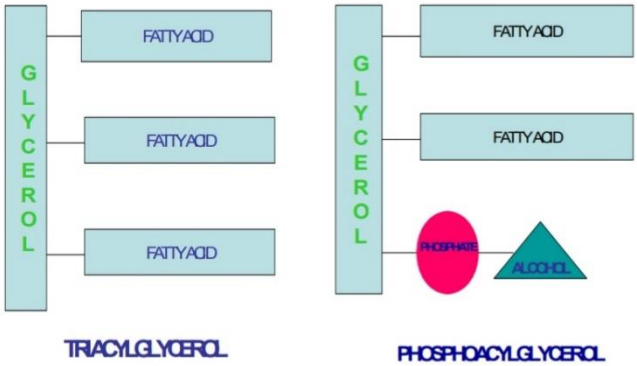
On the 3rd step, another double bond is produced by Δ5 Desaturase. The product of these reaction is Archidonic acid.

*from this reaction, we can conclude that arachidonic acid could be essential or nonessential acording to linoleic acid amount that you ingest (but linoleic acid is always essential).

-note: omega type of the fatty acid does not effected by these reaction since the addition of double bond and carbons occur near carboxyl group(on the example abouve, ω type of all FA is ω6 fatty acids).

*Biosynthesis of Triacylglycerol & Phosphoacylglycerol

TAG Vs phosphoglycerol:



The structure of these two molecules have common part (glecerol+ two FA). So,the pathway of synthesis for them share common steps.

*phosphatidic acid is a common intermediate in their synthesis. It is formed from glycero 2fatty acid+phosphate(phosphoric acid).

The requirment of this biosynthesis is:

- Glycerol Phosphate
- Acyl~CoA (Active form of FA) -produced by acyl CoA synthetase(require 2 ATP).

- Why Active form?
Look at this reaction:

$$TAG + H_2O \longrightarrow DAG + FA \quad \Delta G\ -ve$$
$$DAG + FA \longrightarrow TAG + H_2O \quad \Delta G\ +ve$$

$$DAG + Acyl\sim CoA \longrightarrow TAG + CoA \quad \Delta G\ -ve$$

In the 1st rxn -> ΔG is –ve because it is hydrolysis reaction (hydrolysis reaction is always exergonic).

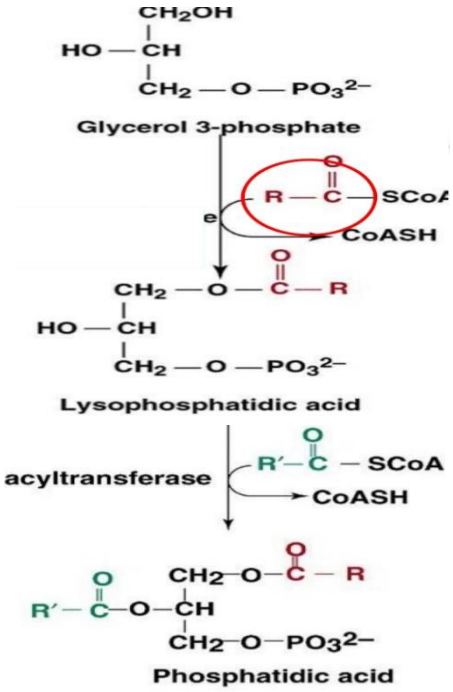
-assume that there is ana enzyme that catalase this rxn in the other direction(enzyme that add FA to DAG) -> ΔG for this rxn will be +ve.

-how can we get this reaction to proceed? By adding FA coming from acyl CoA, so DAG can accept acyl group to produce TAG. In this case -> ΔG is –ve (why?) because the cleavge of high energy thioester bond provide the reaction with energy.

***steps of synthesis phosphatidic acid:**

1- glycerol 3-phosphate accept acyl group from acyl CoA to produce lisophospatedic acid (acyl group is added to the 1st carbon). This rxn is catalized by acyltransferase.

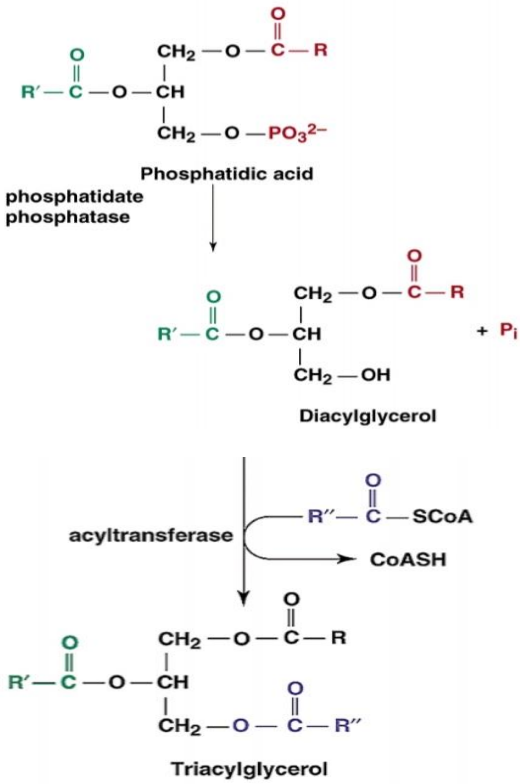
2- lisophospatedic acid can accept one more fatty acid from acyl CoA to give phosphatedic acid. Acyltransferase is also the ensime of this reaction.



***To make TAG from phosphatedic acid, tow step will occur:**

1-hydrolysis of phosphatedic acid, which is catalyzed by phosphotidate phosphatase to remove phosphate group and produce DAG.

2-DAG can accept one more acyl group (also by acyltransferase) to produce TAG.

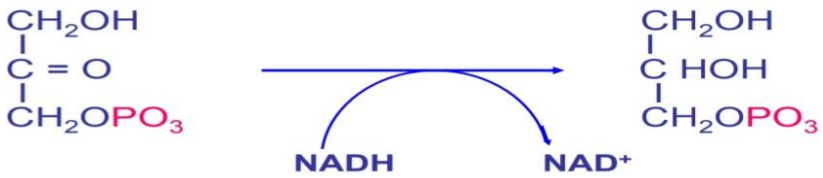


*production of glycerol phosphate:

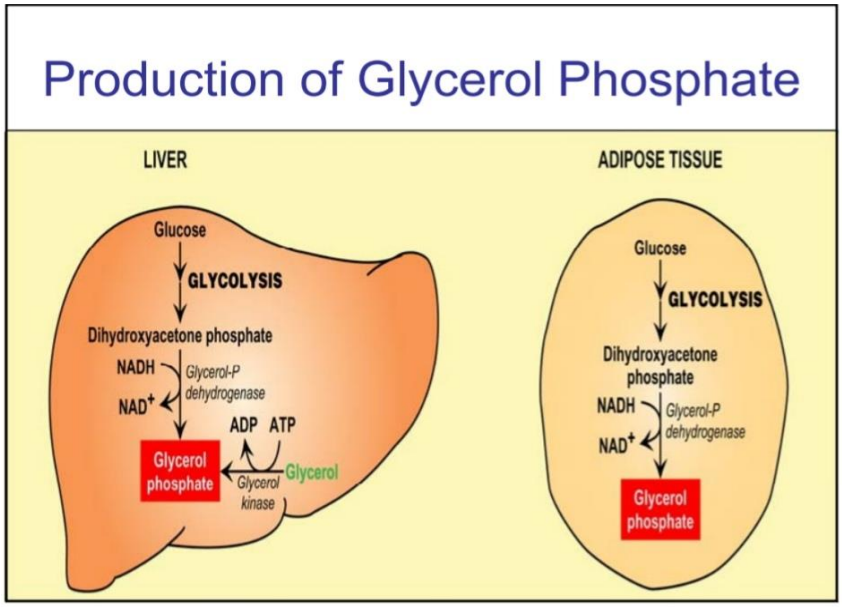
glycerol + ATP $\xrightarrow{\text{Glycerol kinase}}$ glycerol 3-phosphate +ADP (this rxn does not occur in adipose tissue because the lack of the enzyme glycerol kinase)

*the main organs in which fatty acid synthesis is occur are:
1- adipose tissue
2- liver

-glycerol phosphate can be obtained in the adipose tissue through this reaction:



Dihydroxyacetone phosphate is reduced to glycerol 3-phosphate by glycerol phosphate dehydrogenase (by oxidizing NADH to NAD+). This reaction occur in both adipose tissue and liver.



Adipose tissue:

-TAG is form about 85-90% of the volume of adipocyte.

-when energy is needed-> hormone sensitive lipase will hydrolyse TAG TO 3 fatty acids and glycerol. Fatty acids will be transported to the plasma and used as source of energy to other tissue.

-the synthesis need glycerol phosphate and acyl CoA.

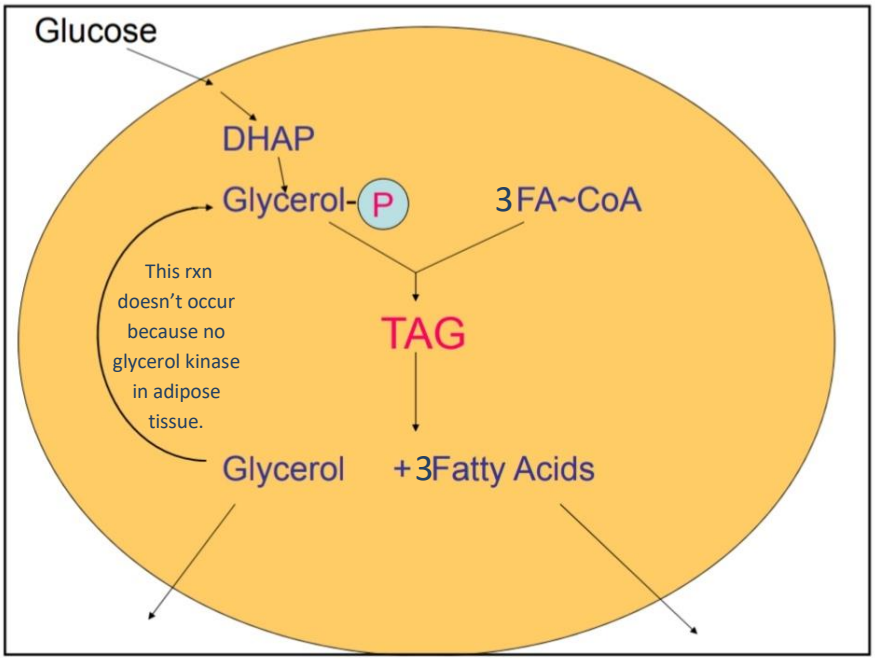
*IF GLYCEROL KINASE IS PRESENT in adipose tissue, glycerol that is produced by hydrolysis will be rephosphorylated and give glycerol phosphate. In this case, synthesis and degradation occur at the same time. This represent just loss of energy (7 ATP will be lost-> 2 for each FA (3*2)and one for glycerol) which is not suitable.

-how this is prevented? By the lack of glycerol kinase, so the cycle will not occur and glycerol is very will be exported. And if there is DHAP (from glycolysis of glucose), there will be synthesis of glycerol phosphate.

How glucose enter the adipose tissue in well fed state?

In this case insulin level is high→ glucose will enter to the adipose tissue (by GLUT4/insulin dependent)→ glycolysis → DHAP→ glycerol phosphate, with acyl CoA in the tissue→ synthesis will take place.

-when insulin level is low (during hypoglycemia), hydrolysis of TAG, glucose won't enter and synthesis won't occur.



At the end of lecture, the doctor talked briefly about phospholipids. It forms of phosphatidic acid which bound with alcohol (serine, ethanolamine, choline -ine indicate amine group- +inositol and glycerol) by ester bond. And the name of phospholipids become phosphatidyl+ the name of alcohol (e.g:phosphatidyl serine). On the next sheet, you will find the structure of them (THE DOCTOR SAID THAT WE SHOULD MEMORISE THEM).

GOOD LUCK GOOD LUCK GOOD LUCK ☺