ketone starch lipid protein amine carbohydrates isomers

Biochemistry

◉ Sheet ○ Slides

Subject :	fatty acid oxidation
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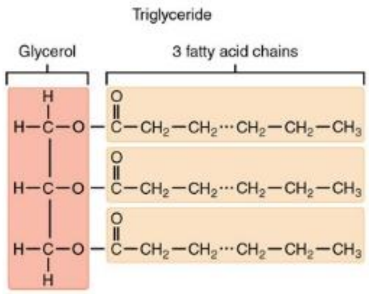
In this sheet we will talk about mobilization of stored fat and an overview of fatty acid oxidation.

Fat is stored in the adipose tissue in the form of Triacylglycerol (TAG) which is the chemical form of fat and oil (fat and oil differ in their melting point, fat is solid at room temperature whereas oil is liquid). TAG is composed from a glycerol molecule attached to three fatty acids.



- Glycerol is a three carbon molecule with three hydroxyl groups (poly alcohol), each hydroxyl group is attached to a fatty acid molecule forming an ester bond.

-A fatty acid consist of a hydrophobic hydrocarbon chain that ends with a carboxyl group.

Fatty acids are poorly soluble in water and they are weak acids with a pka ≈ 4.8 therefore fatty acids at physiological PH will be in their ionized form (deprotonated) –coo¯ hence their name will end with the suffix –ate (e.g. linolenic acid >> linolenate).

Usually fatty acids with an even number of carbon atoms are predominant but there are some odd numbered fatty acids but to less extent.

-There are two ways in numbering carbon atoms in the FA:

1) By counting from carboxyl carbon as carbon number one to the end of the hydrocarbon chain.

2) By naming the second carbon adjacent to the carboxyl carbon as α and the next one as β until the last carbon atom which is designated as ω (omega carbon) regardless how long the hydrocarbon chain is. ω carbon is always the last carbon atom in the terminal methyl group of the chain.

-Fatty acid can be saturated or unsaturated with one or more double bonds, double bonds are always separated by two single bonds that means we always have a methylene group separating the two double bonds $–Ch_{2.}$

-Knowing positions of the double bonds

1) By counting from the carboxyl carbon
for example: CH3-CH2 -CH2 -CH2 -CH2 -CH=CH-CH2 -CH=CH-(CH2)7 –COO

$18{:}2^{9,\,12.}$ 9 indicates that the location of the first double bond is on carbon 9, and carbon number 12 is where the second double bond is.

2) We can also specify the double bond location relative to the ω end of the chain, for example:

CH3-CH2 -CH2 -CH2 -CH2 -CH=CH-CH2 -CH=CH-(CH2)7 -COO

This is a ω6 fatty acid, the last double bond is on the sixth carbon atom from the direction of the ω carbon. (Note: no need to add the location of the next double bond)

-Here are the common fatty acids we need to memorize with the location of their double bonds:

COMMON NAME	STRUCTURE
Butyric acid	4:0
Capric acid	10:0
Palmitic acid	16:0
Palmitoleic acid	$16{:}1^{9}$
Stearic acid	18:0
Oleic acid	$18{:}1^{9}$
Linoleic acid	$18{:}2^{9,12}$
Linolenic acid	$18{:}3^{9,12,15}$
Arachidonic acid	$20{:}4^{5,8,11,14}$

ðNotice we are using common names, which refer to the source from where we isolated these fatty acids:
butyric acid >> in butter
Capric acid >>goats (capper) milk
Palmitic acid >>palm tree
Stearic acid >> wax
Oleic acid >> olive oil
Linoleic acid and linolenic acid >>derived from linen C (plant)
Arachidonic >> plants

Note: to make it easier to memorize the location of multiple double bonds you can add three after the location of the first one e.g. linoleic acid 18:2 its first double bond is on carbon 9 the second will be on 12 (9+ 3) .

-Triacylglycerol or fat is the major energy reserve in the body; the idea of synthesizing TAG is to store the excess energy in order to be used when needed.
Why do we store energy in the form of fat not carbohydrates?

1) Fat is more reduced than carbohydrate (fat contains less oxygen), thus fat can be oxidized therefor more energy will be produced. The amount of energy yield from composition of one gram of fat is 9 kcal whereas burning one gram of carbohydrate gives 4 kcal. So it is more efficient to store fat because we store more energy in less mass.

2) The second reason is because fat is hydrophobic; fat and oil can't be mixed with water so we can store fat in cells separately without being mixed with water. But carbohydrates are highly soluble in water, for example: if we put starch or glycogen in a water environment they would absorb water. So that each gram of carbohydrate will store two grams of water with it.

- Please see the following example:

Average adult has 10 kg of fat. How many calories are 10 kg of fat?

It's equal to 90000 kcal, if we assumed that the daily intake of calories is 2000 kcal, this amount of energy is enough to supply our body for 45 days (90000/2000).

Now, what is the mass of carbohydrate that produces 90,000 kcal?

1gram >>4 kcal

X >> 90,000 kcal   X = 90,000/4 = 22500 gram of carbohydrates

How much water will be stored with the 22500 gram of carbohydrate?

1 gram of carbs >> 2 gram of water

2250 grams >> X   X = 2 *22500 = 45000 gram of water

What is the total amount that would be stored?

Carbohydrate mass + water mass = 22500 + 45000 = 67500 gram = 67.5 kg

- 67.5 kg of carbohydrate is a huge amount to be stored in our body in comparison to 10 kg of fat that yield the same amount of energy. That's why we store energy in the form of fat not carbohydrate.

- Fat storage happens in both animals and humans. But plants store energy in the form of carbohydrate for the need of getting larger in size.

- Fat is the major energy reserve in our body but that doesn't mean it's static and we only burn it when we are fasting. Fatty acids are preferred because, they are the major fuel used by tissues during fasting and in between meals and during rest for muscles. While glucose is the major fuel in extracellular fluid, hence the circulating fuel is mainly glucose.

Fuel type	Amount in fluids (gram)	Amount used/ 12 hours fasting gram
Fatty acids	0.4	60 grams (540kcal)
glucose	20	70 grams (280 kcal)

According to the following table:

The amount of fatty acids in the extracellular fluid is about 0.4 gram (this amount is constant at any time). Whereas the amount used in span of 12 hours fasting is 60 gram (540 kcal) which means there is continuous turnover of fatty acids (used and displaced) by tissues. On the other hand, at any time we have 20 gram/liter of glucose in the extracellular fluid, we use 70 gram of glucose (280 kcal) after fasting for 12 hours. This means that fatty acids are the major fuel used by tissues (skeletal muscle , cardiac muscle , liver) in between meals , but glucose is the major fuel in the extracellular fluid because it is ready available for fast energy production.

In order to produce energy from fat we need to mobilize fat from its stores (adipocytes). Fat mobilization occur by hormonal signal that reach the adipocyte then fat is transformed in the form of fatty acid by binding to albumin in order to reach the tissues.

We have hormonal signal >> hydrolysis of TAG >> 3FA + glycerol

This reaction happens in the adipocyte by the action of lipase enzyme, lipase is a Hormone sensitive lipase (activated by hormonal signals).

The hormones that activate lipase are:

1) Glucagon > because when blood glucose level is low , glucagon will be means we should secreted , which depend on another fuel to maintain the concentration of glucose , that's why fat degradation is switched on.

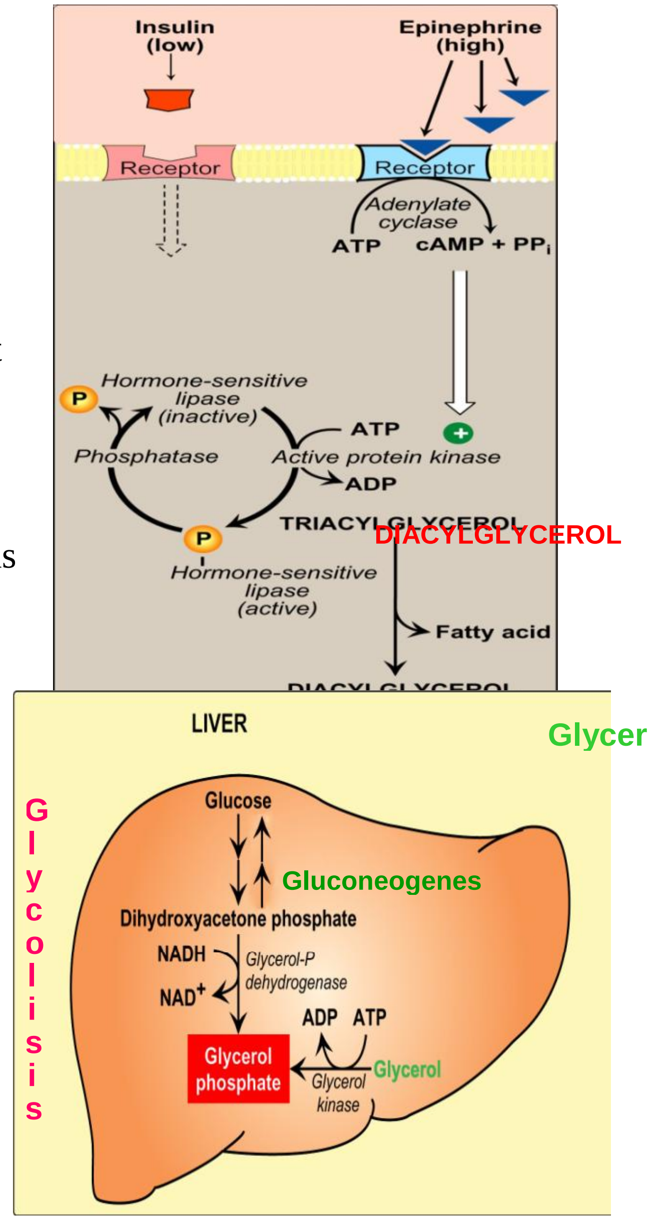
2) Epinephrine > indicates stress state; which means more demand for energy, stress state can be seen when someone is escaping his muscles will need energy, also infections cause stress state.

3) Norepinephrine > also indicates stress state.

4) ACTH >it's the hormone that stimulate the adrenal gland to secret steroid.

For your information: ACTH is adrenocorticotropic hormone.

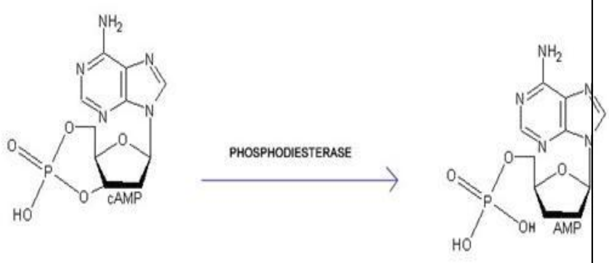
-Have a look at the figure:



It shows how mobilization of TAG occur in adipocytes. Here insulin concentration is low which means it won't bind to its receptors while epinephrine concentration is high so it will bind to its receptor. Binding of Epinephrine will activate G protein then the activated alpha subunit will activate Adenylate Cyclase which will transfer ATP to cAMP + PPi. Then cAMP acts as a second messenger by binding to the two regulatory subunits of protein kinase causing the release of its two catalytic subunits (active protein kinase). then active protein kinase will phosphorylate hormone sensitive lipase (inactive) to its phosphorylated form (active hormone sensitive lipase).then 3 fatty acids and glycerol are released per one TAG.

-TAG > Diacylglycerol > monoacylglycerol > 3 fatty acids + glycerol (all reactions are done by active lipase).

« Notice that this mechanism is similar to glucose degradation in the liver, where phosphorylase kinase is activated by response to glucagon or epinephrine binding to their receptors. Here is a helpful rule the doctor mentioned about regulation:



When blood glucose level is low this means I will need glycogen degradation therefore phosphorylation will lead to activation for all enzymes (inactive dephosphorylated ð active phosphorylated form), and the second thing is I need to use other fuel resources to decrease the use of glucose hence make it more available, that's why we turn on mobilization of fat so we can use it as an energy source. In both pathways phosphorylation leads to activation of the enzymes.

On the other hand, when we have elevated level of blood glucose (+insulin); dephosphorylation will lead to activation of enzymes, like glycogen synthase A is activated by dephosphorylation. And lipase is in activated by the action of phosphatase removing the phosphate group from its active form therefore increase dependence on glucose.

«Regulation should be easily turned on and off:

-High insulin will lead to activation of phosphatase which will dephosphorylate lipase (switching off mobilization of fat) .
-cAMP will be inactivated by hydrolysis, this reaction is catalyzed by Phosodiesterase which hydrolyze the ester bond that is formed on carbon number three of the ribose sugar therefore inactivating cAMP action.
cAMP>>5'AMP.

To sum up:

All phosphates added by kinase are removed by the action of -phosphatase.

If the enzyme release (produce intact) glucose then it is activated by -phosphorylation.

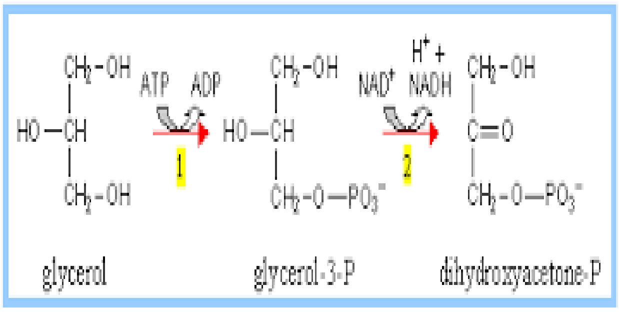
-If the enzyme decreases glucose level then it is inactivated by phosphorylation.

* the doctor also mentioned that : phosphodiesterase is inhibited by caffeine .

Now what will happen for the released glycerol and fatty acids?

Glycerol will move to the liver where it will be phosphorylated to glycerol phosphate by the action of glycerol kinase. Then glycerol phosphate will be oxidized by Glycerol phosphate dehydrogenase to Dihydroxyacetone phosphate, this reaction needs the coenzyme NAD+.

-Glycerol phosphate dehydrogenase will produce NADH by oxidation of glycerol phosphate at the hydroxyl group of carbon number 2.



-Dihydroxyacetone phosphate is a triose (ketose) sugar and an intermediate in glycolysis and gluconeogenesis. Therefore under these condition glucagon stimulation and low levels of blood glucose we would expect that the dihydroxyacetone phosphate sugar will go to the gluconeogenesis pathway because we need glucose. Thus the liver will provide glucose from glycerol and energy from fatty acids.

Notice that glycerol percentage in TAG is very small ≈ 6%. And fatty acids have the largest portion ≈ 94% that can't be converted to glucose instead oxidized to provide energy.

Over view of βoxidation of fatty acid:

-It is named βoxidation because oxidation happens to carbon number three (from the direction of carboxyl carbon) the methylene group of beta carbon will be oxidized to a keto group (carbon atom double bonded to Oxygen). Oxidation is done by loss of hydrogen atoms and binding to oxygen.

Then oxidation is followed by cleavage of the first two carbon atoms by:

Addition of CoA to the carboxyl carbon then βoxidation, then cleavage of the bond between carbon number 2 (αcarbon) and carbon number 3 (βcarbon) by addition of CoA. the resulting compounds are : acetyl- CoA (2 carbons) + acyl- CoA (2 carbon units less than the first Acyl-CoA produced) . Acyl-CoA will continue in the cycle, βoxidized then cleaved producing more Acetyl-CoA.