Biochemistry

◉ Sheet ○ Slides

Number: 1

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Subject: Fatty Acid Oxidation

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General notes the Doctor mentioned at the beginning of the lecture:

- The reference is the slides but it's suggested to read the summary from the book "Lippincott Ch: 15-18 but we are not going to take all the points in them", and the lecture won't stick to the book order.
- Objectives:
  - ✓ Review the TRIACYLGLYCEROL (TAG) & fatty acids chemistry "today".
  - ✓ Mobilization of TRIACYLGLYCEROL (TAG).
  - ✓ Oxidation of fatty acids.
  - ✓ Ketone bodies.
  - ✓ Biosynthesis of fatty acids and TRIACYLGLYCEROL (TAG).

We are going to start with the oxidation: "chapter 16"

Please refer to slides for better illustration

Mobilization of stored fat & oxidation of fatty acids:

Slide (2):

This is a schematic presentation of TAG structure which contains a glycerol bonded to 3 fatty acids by ester bonds (connects the hydroxyl groups of glycerol with the carboxyl groups of the fatty acids).Ester bond can be hydrolyzed to reform fatty acids and glycerol, most of the fat of the body is stored in the form of TAG in adipose tissue, Tag is very hydrophobic, insoluble in water therefore, it will be stored in the cell without water.

Notice that:

a) The chemical name for this presentation is TAG.
b) Fatty acids "carboxylic acids" when it's bound to something we call it **ACYL**.

Slide (3):

Fatty acids:

- ✓ Long hydrocarbon chain (carbon and hydrogen), which contains many carbons and hydrogen and ends with a Carboxyl group.
- ✓ They are carboxylic acids and they are considered as weak acids, Since:
  pKa "measures the acids' strength" = 4.8 approximately.(weak acid)
- ✓ If PH > PKa, the acid will be in the ionized form "dissociated form".
- ✓ The physiological PH "=7" is above the PKa "=4.5" the fatty acid will be in the ionized form COO^- which increases its solubility but notice that even when it's in the ionized form it's insoluble in water since the presence of the long carbon chain.
- ✓ We don't need to write the structure in this long way, we can put the repeated CH_2 between two brackets which end with (n) "n= repeated times" => "$(CH_2)_n$". Which is the short way to write the structure?

Designating fatty acids:

a) Numbering:

The carboxylic carbon is the carbon number 1 and the next one is 2 and so on …

b) Greek alphabets:

Here, the (α) carbon refers to the first carbon after the carboxylic carbon then (β) followed by (γ) "you don't have to memorize the whole alphabet you just need the first two letters for now". So α is carbon #2.

The last carbon is the omega (ω) carbon * regardless how long the hydrocarbon chain is.

* Omega: is last letter in the Greek alphabet.

E.g. if the hydrocarbon chain of the fatty acids is 16 or 20 carbons long the last carbon is the omega (ω) carbon.

Slide (4):

- ✓ The hydrocarbon chain can be saturated or it may contain one or more double bonds.
- ✓ We need those two methods (the numbers and the Greek alphabet) to designate the location & numbers of double bonds in the fatty acids.
- ✓ We start counting from the carboxylic acid carbon & we found that the first double bond occurs at the carbon number(9) and the second double bond occurs at the carbon number (12)… rather than writing the full structure we can write it as:

$$18{:}2\,\Delta^{9,\,12} \text{ or as } 18{:}(9,12)$$

So , 18: number of carbons, followed by a colon then the locations of the double bonds.

- ✓ The carboxylic acid in the example is a Linoleic Acid.

If we have two double bonds then they must be separated by one CH_2. So, you just add 3 in order to know where the next double bond is.

E.g. you have 3 double bonds and the first one is at carbon number 9 so the second will be at carbon number (9+3=12) and the third will be at carbon number (12+3=15)

- ✓ On the other hand, the location can be determined by the omega (ω). So, we count the omega carbon as the carbon number 1 then we count toward the carboxylic carbon until we reach the first double bond "assume that the first double bond was located at carbon number(9)" then we write it as ω6.*

*Note that we don't determine the other double bonds because we know that the one following the $\omega 6$ will be at carbon number (6+3=9) and so on …

=> We determine only the double bond which is next to the ω carbon.

Some fatty acids of physiological importance:

Slide (5):

Here you can find some of the fatty acid.

The number of carbons in the fatty acid starts from 2 & 4 and up to 24 or 26 and usually the number of carbon atoms is even number, but also odd numbers are existed.

Note: **you don't have to know the numbers of all fatty acid "they are a lot" but these are the most common fatty acid. So try to be familiar with them ☺ "**

- ***Formic acid***: You can't name it as fatty acid "it's just a carboxylic acid" since it doesn't follow the role of fatty acids. "بيزبطش", as well as ***Acetic acid*** and ***Propionic acid***. *"some times they are just added to the formal fatty acids"*

Usually fatty acids start from the 4 carbons chain long (***Butyric acid***) or more (capric acid, 10) (palmitic acid, 16) (palmitoleic acid, 16:1(9)) (stearic acid, 18) ...

The arrows in the slides are for the fatty acids that you have to memories very well (number of carbons & if they are saturated or un saturated) because we are going to talk about them several times.

Usually for the naming we use **IUPAC** (International union of pure and applied chemistry) for naming of any chemical "organic" compound but here in biochemistry we use the common name. So, we don't name butyric acid "common name" as butanoic acid "IUPAC name".

We use the IUPAC name only when writing articles, experiments or papers.

- The common name is derived from the source from where the fatty acid was first obtained "isolated":
    1. Butyric acid >>> butter.
    2. Capric acid >>> Goats' "cupper" milk.
    3. Palmitic acid >>> palm tree.
    4. Oleic acid >>> olive oil.
    5. Linoleic and Linolenic acid >>> linen seed (بزر الكتان).
    6. Arachidonic acid >>> Peanut.

TAG:

Triacylglycerol (TAG) or FAT is the **major energy reserve** and store in the body.

- ✓ Why is it more efficient to store energy in the form of TAG?
- ✓ Why fat not carbohydrate? Even that the metabolism of carbohydrates is much easier and faster?

  The answer:

1. **The fats are more reduced "the oxygen content is low".**

- The oxygen is found more in carbohydrates so they are more oxidized.

- We get energy by oxidation of the fuel molecule in the body => the more reduced "more hydrogen and less oxygen" the more energy can be obtained => it can be oxidized more => producing more energy.

- The amount of energy produced by complete combustion:
    a) 9 kcal per gram of fat.
    b) 4 kcal per gram of carbohydrates.

Note:

Cal: the energy that can raise the temperature of 1 gram of water by one degree.

2. **Lipids by their nature are insoluble in water "Hydrophobic**".

- They don’t combine with water; on the other hand carbohydrates do, since they are hydrophilic.

- You can't find carbohydrates in an aqueous environment without water binding to it; on the other hand fats can be stored without the presence of water.

- Notice that the paper you are holding was made of carbohydrate (cellulose) since the source of it is a tree … if you put it in water, you will notice that it will absorb a big amount.

- The carbohydrates can combine with water:

1 gram carbohydrates: 2 grams H2O … when it's found in an aqueous "hydrated" environment.

- In the cell the carbohydrate is not found as a pure carbohydrate it's combined with water.

- Average adult has 10 Kg of Fat "under his skin" (average adult weight 65-70 Kg).

- How many calories?
  9Kcal >>> 1gram
  So per 10Kg we will find 90,000kcal or 90,000,000cal & this amount of energy
  Is enough to heat $1m^3$ of water from 1^0C to 90^0C.

- **What is the mass of carbohydrates that produces 90,000 kcal ?**
  Since 1 gram of carbohydrate produces 4kcal
  Then 90,000 kcal * 1 gram / 4 kcal = 22,500gram = 22.5 Kg of carbohydrate will produce the same amount. And to store it you need as much as 45 kg of water.
  So, by storing energy in 10kg of fat we save about 55kg of excess weight (carbohydrate + water) => it's a condensed way of storing energy.

- TAGs is a dynamic fuel reserve, we daily consume and re-synthesize fatty acids.

- The major circulating fuel is **glucose** but the major fuel used by tissues is **fatty acids**.

- **Concentrations in fluids:** Fatty acids about 0.5 g and glucose about 20 g, so the fatty acids are constantly being used and re-supplemented (rapid turnover) while glucose is widely available but the tissues prefer fatty acids even though they're found in much lesser amount

- The fatty acids and fats are stored in adipose tissue, the storage is in adipose tissue but the consumption is in other tissue such as the muscles, the liver, the cardiac muscles. So these are the top consumers of energy.

  - The adipocyte contains 90% of fat and 10% are (proteins, H_2O, …).
  - All mammals (Humans + animals) store energy in the form of fat.
  - Plants store energy in the form of carbohydrates and there is no problem with that since the plants can't move from one place to another.
  - The daily requirement of energy "in a typical adult" is around 2000kcal. So, the 10kg of fat "90,000kcal" will be enough for him to survive the next 45 days (1.5 month).

    <u>Slide(9):</u>

- ✓ The preferred fuel is the fatty acids but the glucose is the abundant in the tissues.

  - ✓ We use 60 grams (which is equivalent to 540 kcal) of fatty acids during 12 hours of post-absorptive state while glucose provides 70 grams (280 kcal).

- ✓ Fatty acids are stored as TAG in the adipose tissues.

- ✓ Fatty acids are used as a source of energy in most tissues.

Slide (10):

How does the adipose tissue know that the energy is required? The energy demand increases?

a **hormonal signal** must reach the adipocyte => which induces the hydrolysis of TAG through the hydrolysis of the ester bonds TAG isn't transported as TAGs, it's hydrolyzed by the enzyme ***lipase*** to three fatty acids and a glycerol.

What are the hormones that tell the adipose tissue that energy is required?

1. Glucagon:

It indicates that the level of blood glucose is low therefore; alternative fuel (which is fatty acid) should be made available.

2. Epinephrine and Norepinephrine:

Secreted during stress (fight or flight state), in this case there's an increased demand for energy, so these two hormones stimulate the conversion of TAGs into fatty acids and glycerol.

3. ACTH : this hormone also indicates that energy is required .

What's the mechanism for this?

These hormones bind to receptors(cell-surface receptors) when their concentrations are high , this binding will stimulate the enzyme adenylyl cyclase (same situation in glycogen regulation), adenylyl cyclase will convert ATP into a regulatory molecule which is cAMP .**cAMP** activates **protein kinase** (a kinase is an enzyme that catalyzes the transfer of a phosphate group from ATP to its substrate) , protein kinase phosphorylates many protein including hormone-sensitive lipase ,lipase is activated by this phosphorylation and it catalyzes the conversion of triacyl glycerol into diacyl glycerol and then into monoacyl glycerol then to fatty acid and glycerol.

What's the fate of glycerol?

it’s rapidly transported by the plasma (it’s very soluble in water, an alcohol) to the liver.

1.In the liver, the first step to neutralize glycerol is by phosphorylation, by the enzyme glycerol kinase so glycerol becomes glycerol phosphate.

2.Glycerol phosphate is oxidized (carbon #2 becomes a ketone group) into dihydroxy acetone phosphate (an intermediate of glycolysis and gluconeogenesis), and since we’re talking at a state of fasting or stress, then DHAP is going to be used in gluconeogenesis (because the blood glucose is low).

Notice that this is the only portion of TAGs that can be converted to glucose , fatty acids cannot be converted to glucose, glycerol is a 3- carbon molecule, so out of 50 carbons in TAGs , only 3 are converted to glucose

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B-oxidation of fatty acids:

-Happens at B-carbon (carbon #3)

-Since fatty acids are water-insoluble, they are transported from adipose tissue to other tissues bound to albumin.

They are degraded by beta oxidation (**CH2 becomes C=O (oxidation))** followed by the cleavage of two carbon units.

1.The first step is joining the fatty acid with co-enzyme A, this is the activation step.

2.Beta carbon is converted to c=o followed by the cleavage between carbon 2 and 3.

3.Carbon 2 and 1 will form acetyl CoA and the rest of the molecule will undergo step 2 again and again until the fatty acid is completely degraded to acetyl CoA which will be oxidized in the citric acid cycle.

The End.