23

carbohydratesisomersketone starchlipidproteinamine

Biochemistry

Doctor 2017 | Medicine | JU

Sheet Slides

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Concepts covered in this sheet:

- *Oxidation of FA with odd # of carbon atoms.*
- *Oxidation of very long fatty acids.*
- *Oxidation of FA at alpha carbon.*
- *Ketone bodies.*

Please, always refer to the pictures attached to understand faster and better.

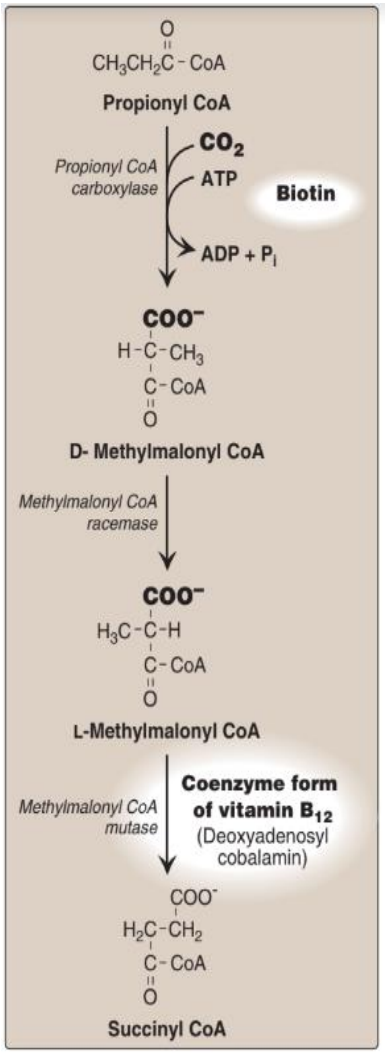
β-Oxidation of Fatty Acids with odd # of carbons

10% of the animal fats is odd numbered

- The β-oxidation of a saturated fatty acid with an **odd number** of carbon atoms *(e.g. 15 carbons)* proceeds by the **same** reaction steps as that of fatty acids with an **even number** *(as discussed in the prev. sheet)* for 6 cycles, until the **final three carbons** are reached forming **propionyl CoA**. This compound, propionyl CoA, is metabolized by a **three**-step pathway:

1- First, **propionyl CoA** is **carboxylated,** forming **D-methylmalonyl CoA**.

> ***Note:*** *The enzyme **propionyl CoA carboxylase** has an absolute requirement for the coenzyme **biotin**, as do most other carboxylases.*
>
> ***Recall:*** *__Carboxylation__ reactions are always **endergonic** (need energy; ATP) while **Decarboxylation** reactions where CO2 is released, are always **exergonic** (release energy).*



2- Next, the **D-isomer** is converted to the **L-form** by the enzyme, **methylmalonyl CoA racemase**.

3- Finally, the carbons of **L-methylmalonyl CoA** are rearranged by **methylmalonyl CoA mutase**, forming **succinyl CoA**, which can enter the **TCA** cycle.

> ***Note:*** *The enzyme, **methylmalonyl CoA mutase**, requires a coenzyme form of **vitamin B12** for its action. In patients with vitamin B12 **deficiency**, both **propionate** and **methylmalonate** are **excreted** in the urine causing **Methylmelanouria**.*
>
> *Only **2** reactions in human body require **Vit B12**, the other one will be discussed later in our course.*

- This is the **only** way, **fatty acid** which can be converted to **glucose**. Where **propionyl CoA** is converted to **oxaloacetate** at the end of TCA cycle and the **oxaloacetate** will be converted to **glucose** by **gluconeogenesis** pathway.

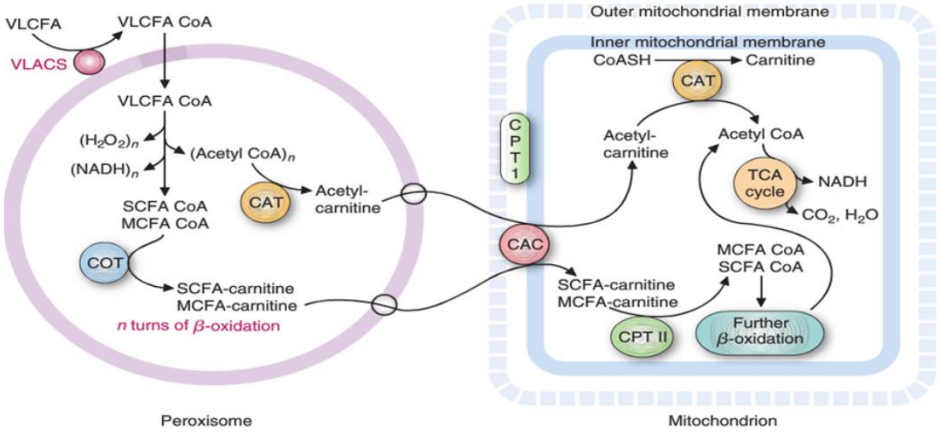
- In the past, the **status** of **vitamin B12** is known by:

  a- Indirect measurement *(used in the past):* done by measuring the amount of **methylmalonyl CoA** in the **urine**. So, if the concentration of methylmalonyl CoA is **high** in the urine, this means that the patient has **vitamin B12 deficiency**.

  b- Direct measurement *(used nowadays):* done by taking a **blood sample** and measuring the level of **vitamin B12** in the plasma in laboratories.

Oxidation of very long Fatty Acids in peroxisomes

- Very long fatty acids (VLCFA), or those **22+** carbons long *(found mostly in the brain)*, undergo β-oxidation in **peroxisomes**. The reaction continues until the FA becomes **medium** or **short** chain, so that it can be **transported** *(linked to carnitine)* into the **mitochondria** for **further** oxidation.



- **VLCFA**: Very long chained fatty acid.

- **MCFA**: Medium chained fatty acid

- **SCFA**: Short chained fatty acid

- Recall, the **first initial step** in the **oxidation** in the **mitochondria** *(where an oxidation reaction occur producing $FADH_2$)* is catalyzed by a **dehydrogenase**. In the **peroxisome**, the first step is catalyzed by a **FAD-containing acyl CoA oxidase**.

> ***Note:*** ***Oxidase*** → *Transfers the electrons to **oxygen** (substrate) producing **H_2O** or **H_2O_2**.*
>
> ***Dehydrogenases*** → *Transfer the electrons to dinucleotides (**NAD** or **FAD** or **NADP**).*

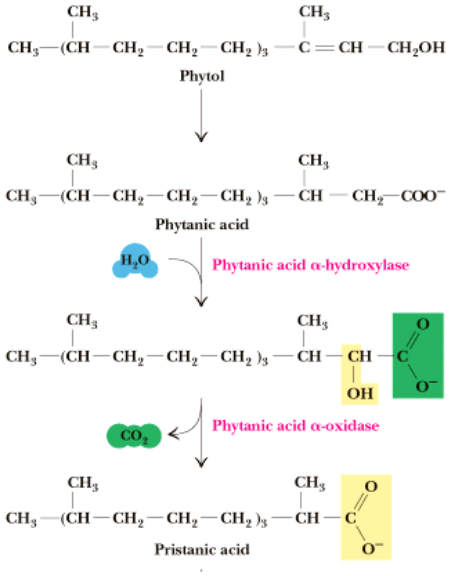
- The **$FADH_2$** produced from the first step is then oxidized by **oxygen**. The oxygen is reduced to **H_2O_2** which is further reduced to **H_2O** by **catalase**.

> ***Note:*** *The produced **$FADH_2$** is **not** used in the **ETC**, because the reaction is **not** in the **mitochondria**.*

α-Oxidation of fatty acids

- **β-Branched**-chain fatty acids *(e.g. 20 carbon fatty acid, phytanic acid)*, cannot be used as a **substrates** for **acyl CoA dehydrogenase** because of the methyl group on their **β-carbon**.

  Therefore, the FA undergoes **α-Oxidation:**



1- An **oxidative hydroxylase** *(phytanoyl CoA α-hydroxylase)*, hydroxylate the fatty acid at the **α-carbon**.

2- Then, an **oxidative-decarboxylation** reaction occur:

   a- The **hydroxyl** group on the α carbon is **oxidized** to a **carboxyl group**.

   b- **Decarboxylation** of the carboxyl group occurs, releasing **CO2**.

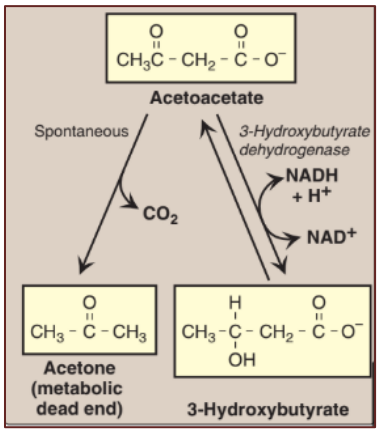
3- The fatty acid now has a free **β-carbon** and can undergo **β-oxidation** normally *(the branch is now on the **α-carbon** instead of being on the **β-carbon**).*

- **Green leaves** of plants *(which contain chlorophyll)* is the main **source** of these fatty acid. When consumed, they can be **metabolized** by this type of oxidation.

- Some people may have **deficiencies** in the **oxidative hydroxylase enzyme** *(Refsum disease).* This results in the **accumulation** of **phytanic acid** in the plasma and tissues, leading to the **destruction** of cells in tissues *(mainly the nervous tissue)* causing **neurological** disorders. The treatment involves dietary **restriction** *(of chlorophyll containing food)* to **stop** disease progression.

Ketone Bodies: An alternative fuel for cells

- The compounds categorized as Ketone Bodies are:



1- **Acetoacetate**, which is a **derivative** of butyric acid.

2- **3-hydroxybutyrate**, which is a product of **reducing acetoacetate** by **NADH**.

3- **Acetone**, which is formed when **acetoacetate** is **spontaneously decarboxylated** releasing CO_2.

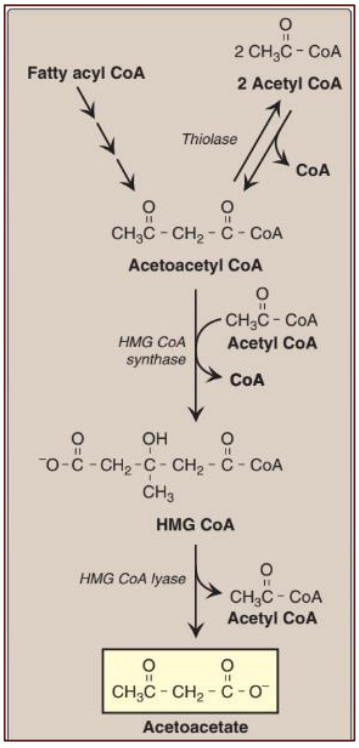
Spontaneously here means that the rxn doesn't require an enzyme

- **The Liver's mitochondria** has the capacity to convert **acetyl CoA** (precursor) derived from fatty acid oxidation into **ketone bodies**, producing them at **high** rates during **fasting** or **uncontrolled diabetes type 1** *(each case will be discussed below).*

- Ketone bodies are synthesized in the liver through the following pathway:

1- The first step, is the **formation of Acetoacetyl CoA** through the condensation of **2 acetyl CoA** catalyzed by the enzyme **Thiolase**, releasing a **CoA** molecule.

> ***Note:*** *This reaction is the **reversal** to the **last** reaction in **β-oxidation** (same enzyme), where **Acetoacetyl CoA** is cleaved into **2 acetyl CoA**. Therefore, **high** amounts of **acetyl CoA** whether it's coming from β oxidation or from any other sources **induce** this **condensation***



2- **Mitochondrial HMG CoA synthase**, combines a 3rd molecule of **Acetyl CoA** with **Acetoacetyl CoA** to produce **HMG CoA,** releasing a second **CoA**.

> ***Note:*** ***HMG CoA synthase** is the **rate-limiting step** in the synthesis of ketone bodies, and is present in **significant** quantities **only** in the **liver**.*

3- **Cleavage of Acetyl CoA** from **HMG CoA** to form **Acetoacetate** by the enzyme **HMG CoA lyase.**

→ **The Net synthesis of this reaction is** *(reactants and intermediates are not counted):*

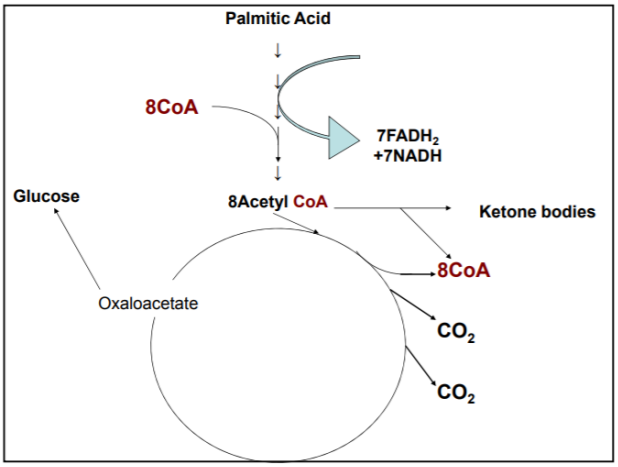
2 Acetyl CoA → Acetoacetate + 2 CoA

- **Purpose of the previous pathway** *(relate to the net reaction):*
  - **a-** Removal of **acetyl CoA**
  - **b-** Regenerating **CoA**.
  - **c-** Production of **acetoacetate**.

Ketone bodies production role in the Liver:

- β-oxidation of **palmitic acid (**16-carbon fatty acid), yields:
  - **a-** 7 **NADH and 7 $FADH_2$**: They get reoxidized in the ETC to **produce energy**.
  - **b-** **8 acetyl CoA**: They enter TCA cycle, combine with oxaloacetate **producing citrate** and **free CoA.**

    → **Oxaloacetate** is required continuously in order to **regenerate CoA.**



- However, **during fasting** concentration of blood **glucose** is **low**. So, **gluconeogenesis** occurs by consuming **oxaloacetate** to form **glucose**. The level of **oxaloacetate** is highly **decreased**, therefore, the TCA cycle will **stop**.

  ➔ The **Acetyl CoA** that is produced by **β oxidation** will **trapped** in cells *(there is no sufficient oxaloacetate),* thus **preventing** the **regeneration** of **CoA** from the acetyl CoA to keep the β-oxidation going on.

  ➔ Our body responds to this trouble by **producing ketone bodies** where **acetyl CoA** is **consumed** generating **free CoA** that is essential for β oxidation to keep going, producing energy.

> ***Note:*** ***Acetoacetate*** *is considered a* ***waste product*** *in the* ***liver****, since the purpose of the liver producing ketone bodies is the* ***consumption*** *of* ***acetyl CoA*** *to* ***regenerate CoA,*** *which is significant during* ***fasting*** *to provide* ***energy*** *to the peripheral tissues.*

Uncontrolled (untreated) Diabetes

- When the rate of **formation** of ketone bodies is **greater** than the rate of their **use**, their levels begin to **rise** in the **blood** (ketonemia) and, eventually, in the **urine** (ketonuria). This is seen most often in cases of uncontrolled **Type 1 diabetes.**
- In the case of diabetes, **insulin** level is **low** while the **glucagon** level is **high**.

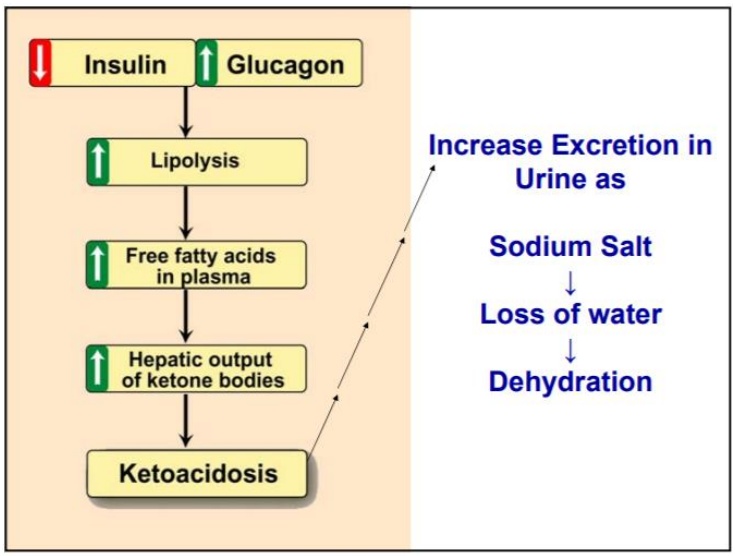
  ➔ Therefore, even if the glucose concentration is **high** in the blood, low insulin will **induce gluconeogenesis**.

  ➔ **Lipolysis** is **activated** and continuously **increasing** the free fatty acids in the plasma.

  ➔ These fatty acids will convert into **ketone bodies**, **increasing** their **concentrations** in the blood.

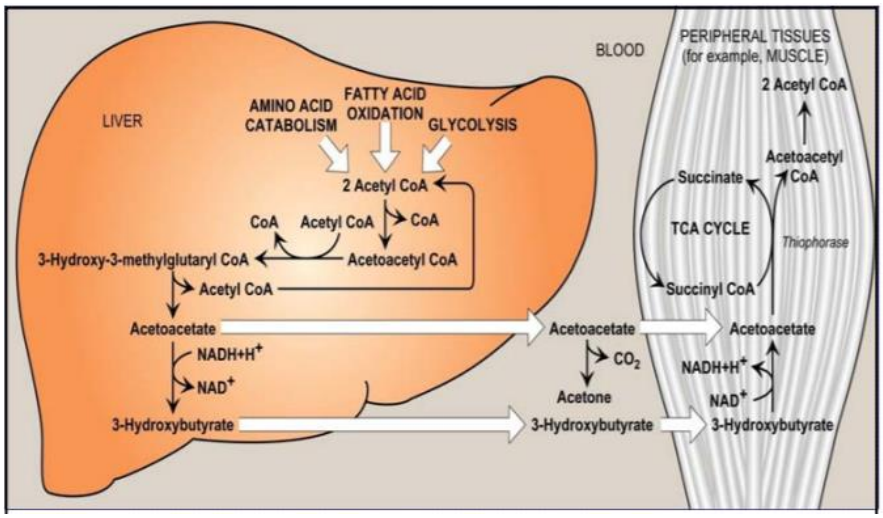
  ➔ Thus, the **pH** of the blood will **drop** causing a state called **diabetic ketoacidosis** (DKA).

- The diabetic ketoacidosis (DKA) is a very common case in uncontrolled diabetes. **excretion** of **glucose** and **ketone bodies** in the **urine** as **sodium salts**, results in **dehydration** of the body, which may lead eventually to a **coma** or **death** if not managed.



Use of ketone bodies for the peripheral tissue

Skeletal Muscle, Cardiac Muscle and the brain, but excluding cells lacking mitochondria (e.g. red blood cells), efficiently **oxidize acetoacetate** and **3-hydroxybutyrate** to provide **energy** during starvation.



1- **3-Hydroxybutyrate** is oxidized to **acetoacetate** by 3-hydroxy butyrate **dehydrogenase**, producing NADH.

2- The CoA transferase **Thiophorase**, transfers CoA from **succinyl CoA** to **Acetoacetate** forming **acetoacetyl CoA** and **succinate** which is used in the **TCA cycle**, providing **energy**.

Note 1: *This reaction is **reversible**, but the product, **acetoacetyl CoA**, is **actively** removed by its conversion to **two acetyl CoA** (lowering its conc.). Thus, **favoring** forming **acetoacetyl CoA.***

Note 2: *The **liver**, **lacks** the **Thiophorase** enzyme. That is why it does not use **ketone bodies** as a source of **energy**.*

In summary:

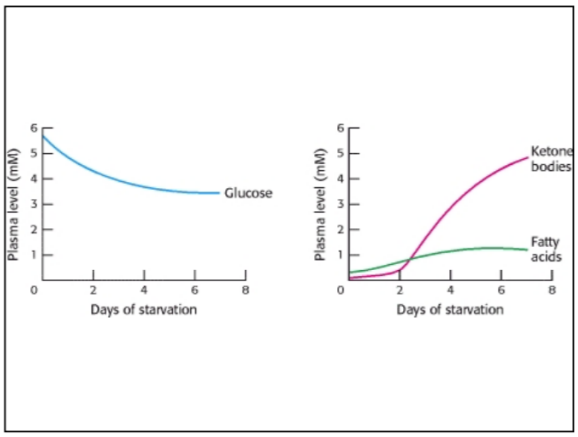
Liver → *While **fasting**, **gluconeogenesis** occurs, **highly** consuming **oxaloacetate**. Thus, acetyl CoA is accumulated. Ketone bodies are produced to **consume** the **acetyl CoA**, **regenerating** free CoA used for **beta oxidation** to provide **energy** for tissues. (main purpose is regenerating CoA)*

Peripheral Tissue → ***Thiophorase**, forms **succinate** from **acetoacetate** which is used in the TCA cycle to provide the **energy needed**. (main purpose is producing Acetyl CoA)*

Ketone Bodies role in preserving protein during starvation

- Before fasting, glucose concentration is about 5.5 mmol/L, and after 2- 3 days, blood glucose is still high at about 4mmol/L. Glucose level is maintained by **gluconeogenesis**.

- **Triacylglycerols** can be used to produce **glucose**. Glycerol *(which is an insignificant part of TGs)* is converted to **DHAP**; an intermediate in gluconeogenesis.



- **Proteins** are cleaved into **AAs** and used to **nourish** the **intermediates** of **gluconeogenesis**. However, proteins aren't stored to be used as a source of energy, they have their own **vital functions** in our bodies. Thus, the body needs to depend **less** on proteins as a source of energy.

> ***Note:*** *The concentration of **nitrogen** in the **urine**, indicates how much **proteins** are **degraded**.*

→ During **fasting**, the insulin/glucagon ratio **decreases** and catecholamines are secreted **activating** the **degradation** of TGs by lipases in white adipose tissues releasing **free fatty acids** and converting them to **ketone bodies** by the liver.

Ketones bodies level **increases** in the blood, so the brain starts to use it as a source of energy, that means that the brain starts **depending** on **fatty acids** as source of energy instead of **proteins**. Therefore, proteins are **preserved** to do their functions.

The numbers in the figure are not for memorization just understand the concept

- After 40 days of continuous fasting, the brain has **decreased** its consumption of **glucose**.

- The brain and the muscles adapt and start depending on **ketone bodies** as a source of energy. Thus, preserving **proteins** to do their functions.

Reduction of Glu utilization → Proteins are preserved

Fuel metabolism in starvation

	Amount formed or consumed in 24 hours (grams)	
Fuel exchanges and consumption	**3rd day**	**40th day**
Fuel use by the brain		
Glucose	100	40
Ketone bodies	50	100
All other use of glucose	50	40
Fuel mobilization		
Adipose-tissue lipolysis	180	180
Muscle-protein degradation	75	20
Fuel output of the liver		
Glucose	150	80
Ketone bodies	150	150

The sheet got written through hard times, so pardon me for any inconveniences. Good Luck ♥