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carbohydratesisomersketone starchlipidproteinamine

Biochemistry

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Sheet Slides

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β-Oxidation of Fatty Acids

The oxidation of fatty acids occurs in 3 steps:

Step 1: Activation of the Fatty acid

$$FA + HS\text{-}CoA + ATP \leftrightarrow FA\text{-}CoA + AMP + PPi$$

- The fatty acid is **activated** by binding to **CoA**. The **high** energy bond that connects the fatty acid to CoA (FA-CoA) is a **thioester** bond.

  The **hydrolysis** of the **thioester** bond yields **7.5 Kcal/mol** which is similar to the energy produced after the hydrolysis of **ATP 7.3 kcal/mol.**

  To produce this high energy bond, energy in the form of **ATP** is required. ATP is **cleaved** giving **pyrophosphate** (PPi) and **AMP**.

$$ATP \rightarrow AMP + PPi$$

- The **high** energy bond in the ATP is **cleaved forming** another **high** energy bond (thioester). Therefore, the **net** energy difference is *almost* **0.** This means that the reaction is at equilibrium where the products and the reactants are **equally** favored.

  Naturally, we need the **formation** of **products** to be **favored** which can only be achieved by **decreasing** the products **concentration**.

  Therefore, the inorganic pyrophosphate (PPi), is **continuously** broken down into **two** phosphate ions by the inorganic **pyrophosphatase** enzyme. The action of this enzyme means that very **little** PPi remains in the cell, making the **synthesis** of the fatty acyl-CoA **favored**.

$$PPi + H_2O \rightarrow 2\ Pi$$

- Now, to convert AMP into ADP, the following reaction is considered:

$$AMP + ATP \leftrightarrow ADP + ADP$$

  By adding the 2 reactions:

$$FA + HS\text{-}CoA + ATP \rightarrow FA\text{-}CoA + \cancel{AMP} + PPi$$

$$\cancel{AMP} + ATP \leftrightarrow ADP + ADP$$

$$FA + HS\text{-}CoA + 2\ ATP \rightarrow FA\text{-}CoA + 2\ ADP + PPi$$

Rule: ATP conversion to AMP + 2 Pi is **equivalent** to hydrolysis of 2 ATP to 2 ADP.

Enzyme used in the first step: **Thiokinase** *(Acyl CoA Synthetase; using 2 ATP)*

> ***Note**: **Synthetase** → Enzyme **requires** ATP, **Synthase** → Enzyme **doesn't** require ATP.*

Location of this reaction: At the **outer mitochondrial membrane**, then the **activated** fatty acyl it is transferred into the **mitochondrial matrix** where the **β-oxidation** occurs.

> ***Note**: **All fatty acyl CoA** can diffuse through the **outer** membrane. Then, **short** and **medium** fatty acyl diffuse normally through the **inner** membrane into the **matrix**. However, the **inner** membrane is **impermeable** to **long-chain** acyl groups.*

Last Product: **Fatty Acyl CoA** is produced from the first step (FA-CoA).

Step 2: Transport of long chain Acyl CoA across inner mitochondrial membrane.

The **inner mitochondrial membrane** is **impermeable** to **long** chained Acyl CoA. A **carrier** system is needed to transport them into the mitochondrial matrix, which is the **Carnitine Shuttle**.

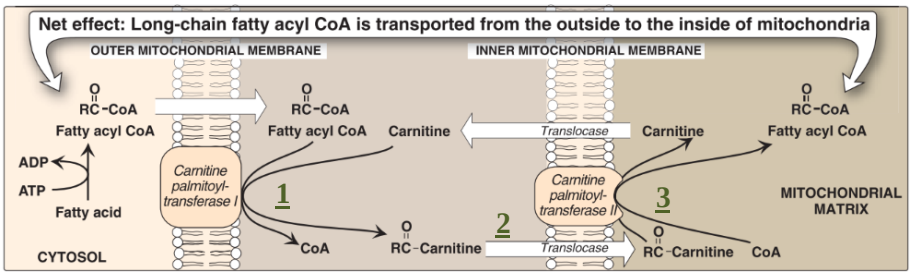
The Carnitine Shuttle consists of:

a- **Carrier molecule:** Carnitine

b- **Two enzymes**: Carnitine palmitoyl transferase 1 *(CPT-1)* and Carnitine palmitoyl transferase 2 *(CPT-2)*.

c- **Membrane transport protein**: Translocase.

Steps of Long chain acyl CoA translocation through the Carnitine Shuttle system:



1- **CPT-1** transfers the **acyl group** from **CoA** to **carnitine** forming **acylcarnitine**, regenerating free **CoA** in the **intermembranous** space.

2- The **translocase**, it transports the **acylcarnitine** into the mitochondrial **matrix** in exchange for **free** carnitine.

3- **CPT-2** transfers the **acyl group** from **carnitine** to another **CoA** in the mitochondrial **matrix**, regenerating a **free** carnitine.

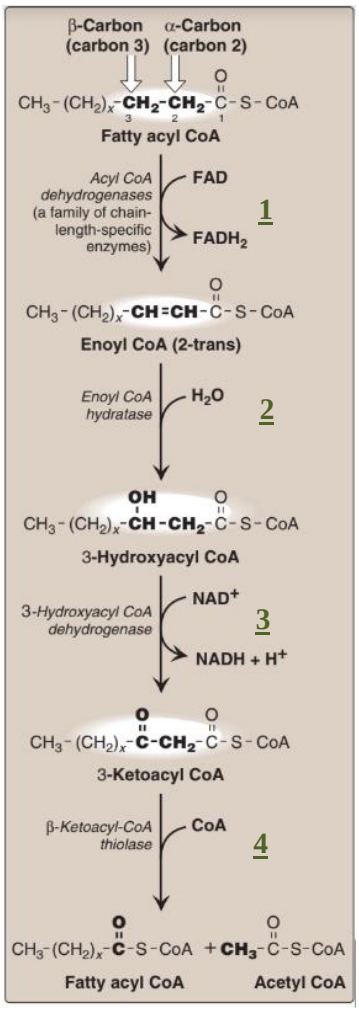
***Note 1**: CPT-1 is found in the **outer mitochondrial membrane**, while **the CPT-2** is found in the **inner mitochondrial membrane**.*

***Note 2**: The **Carnitine Shuttle** is **inhibited** during **fatty acid synthesis**.*

***Remember**: This shuttle is For **Long chain fatty acids**, it is not required for **medium** and **short** chain fatty acids since they simply **diffuse** through the **inner** mitochondrial membrane.*

The **fatty Acyl CoA** is in the mitochondrial **matrix** now, further **beta oxidation** of the activated fatty acid will lead to production of **acetyl CoA**, a main intermediate in the TCA cycle.

Step 3: β- Oxidation of fatty acids reactions



Reactions -**shorting** the fatty acid chain by **2 carbons** in **each cycle**- are **repeated**, until we end up with **only** acetyl groups, which is the **purpose** of this beta oxidation. Each cycle consists of 4 **reactions:**

1- An **oxidation** reaction that produces **FADH2**, catalyzed by **Acyl CoA dehydrogenase**.

2- A **hydration** step catalyzed by **enoyl CoA hydratase.**

3- A second **oxidation** reaction that produces **NADH**, catalyzed by a **3-hydroxyacyl CoA dehydrogenase**.

4- Finally, a **thiolytic cleavage** that releases a molecule of **acetyl CoA**, catalyzed by **thiolase**.

***Note:** The last step involving the **cleavage** of ketoacyl CoA, is catalyzed by **thiolase** which cleaves the bond by **adding CoA**, which produces an **activated** fatty acyl. However, if a **hydrolase enzyme** is used cleaving the bond by adding **water**, this would result in an **inactivated** fatty acyl that needs to be **activated again** to be **oxidized**.*

Calculating Energy Yield from FA Oxidation

This is only for FA with even # of carbon atoms

Important rules to calculate any Energy Yield from saturated FA Oxidation:

- **Activation** of the Fatty acid **consumes 2 ATP.**
- **Each cycle** of reactions releases: **2 carbon atoms**, **1 NADH and 1 $FADH_2$**

→ Number of **cycles** needed to **degrade** the fatty acid to Acetyl CoA's = $(\frac{\#\ of\ Carbons}{2}) - 1$

→ Number of **NADH** and **$FADH_2$** is **equal** to the number of **cycles.**

- In each cycle, **1 acetyl CoA** is produced except for the **last cycle** where the number of carbons **equals 4**, thus this cycle will yield **2 CoA**.

→ Number of **acetyl CoA** = $(\frac{\#\ of\ Carbons}{2})$

> ***Recall:*** *1 FADH2 = **2 ATP,** 1 NADH= **3 ATP,** 1 Acetyl CoA= **12 ATP.***

Example: **Calculate** the **energy yield** from the **oxidation** of a **16-Carbon** fatty acid (palmitate).

- Number of **Cycles** to **degrade** the FA = $\frac{16}{2} - 1 = 7$
- Number of **acetyl CoA** molecules= $\frac{16}{2} = 8$ → 96 ATP
- **FADH2**= 7 → 14 ATP
  NADH= 7 → 21 ATP
- Activation of the fatty acid **consumed** 2 ATP
  → Net **129 ATP** is yielded per mol of palmitate.

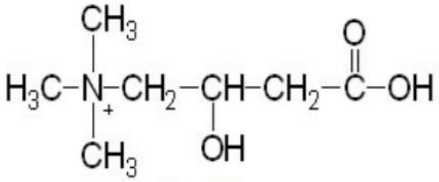
> ***Note:*** ***Palmitic acid*** *produces **129 ATP** when oxidized, while glucose produces only **38 ATP.** That is why it is **more efficient** to store energy in the form of **Fats** rather than **carbohydrates**.*

Carnitine

Sources:

1- Carnitine can be obtained from the **diet**, where it is found primarily in **meat** products.

2- Carnitine can also be **synthesized** from the amino acids **lysine** and **methionine** by an enzymatic pathway found in the **liver** and the kidneys.



Functions:

1- **Export** of **branched** chain acyl groups from **mitochondria**.

2- **Excretion** of acyl groups that **cannot** be metabolized in the body.

3- In the **Carnitine Shuffle** system, where it **transports fatty acyls**.

Carnitine Deficiencies:

a- **Secondary Deficiencies (acquired after birth):**

1- In patients with liver disease causing **decreased synthesis** of carnitine.

2- In individuals suffering from **malnutrition** or those on strictly vegetarian diets.

3- In those with an **increased requirement** for carnitine as a result of, for example, pregnancy, severe infections, burns, or trauma.

4- In those who undergo **hemodialysis**, which removes carnitine from the blood.

We can evade this deficiency by administering **medium and short Fatty acid chains** which **don't** require Carnitine.

b- **Primary (Congenital) Deficiencies (acquired since birth):**

1- Impaired enzymes that **synthesize carnitine**.

2- Impaired **reuptake** by cells from the plasma by cardiac and skeletal muscle and the kidneys.

3- Impaired renal tubular **reabsorption** of carnitine causing it to be execrated.

These details weren't mentioned by the doctor, he mentioned them fast and briefly…

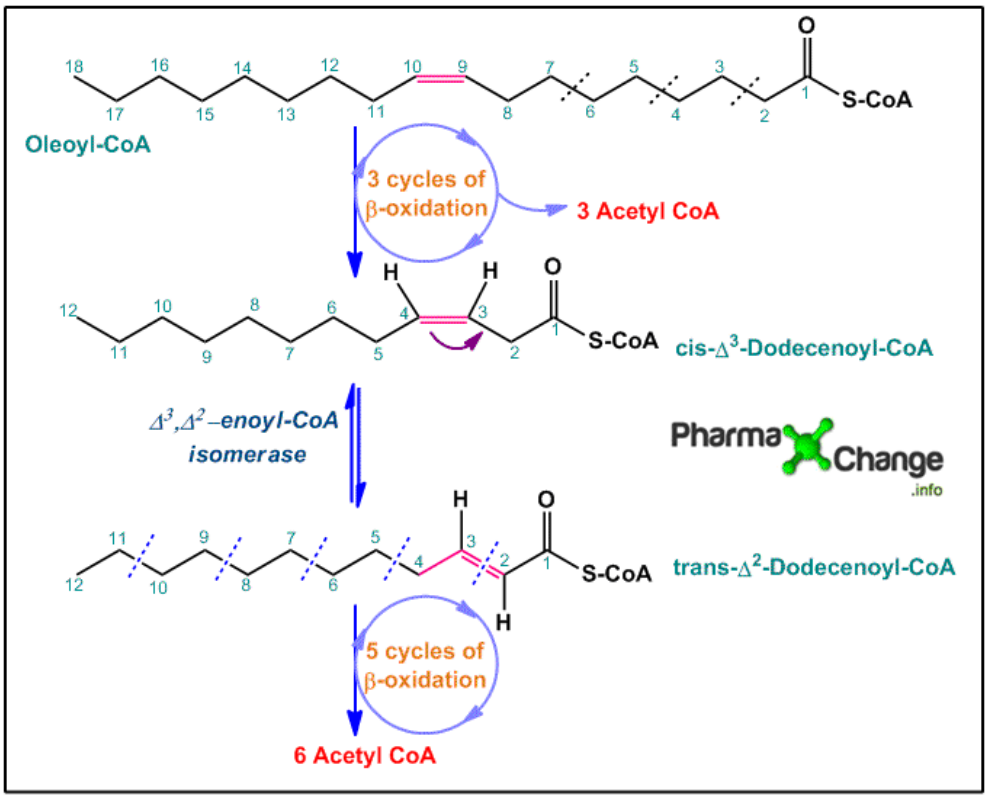
CPT-1 deficiency *affects the* ***liver****, where an inability to use Long Chain FA for* ***fuel*** *greatly impairs the tissue's ability to* ***synthesize*** *glucose during a* ***fast****. This can lead to severe* ***hypoglycemia****,* ***coma****, and* ***death****.*

CPT-2 deficiency *occurs primarily in* ***cardiac*** *and* ***skeletal*** *muscle, where symptoms of carnitine deficiency range from* ***cardiomyopathy*** *to* ***muscle weakness****.*

Oxidation of Unsaturated FA

1- Oleic Acid (18 Carbons)

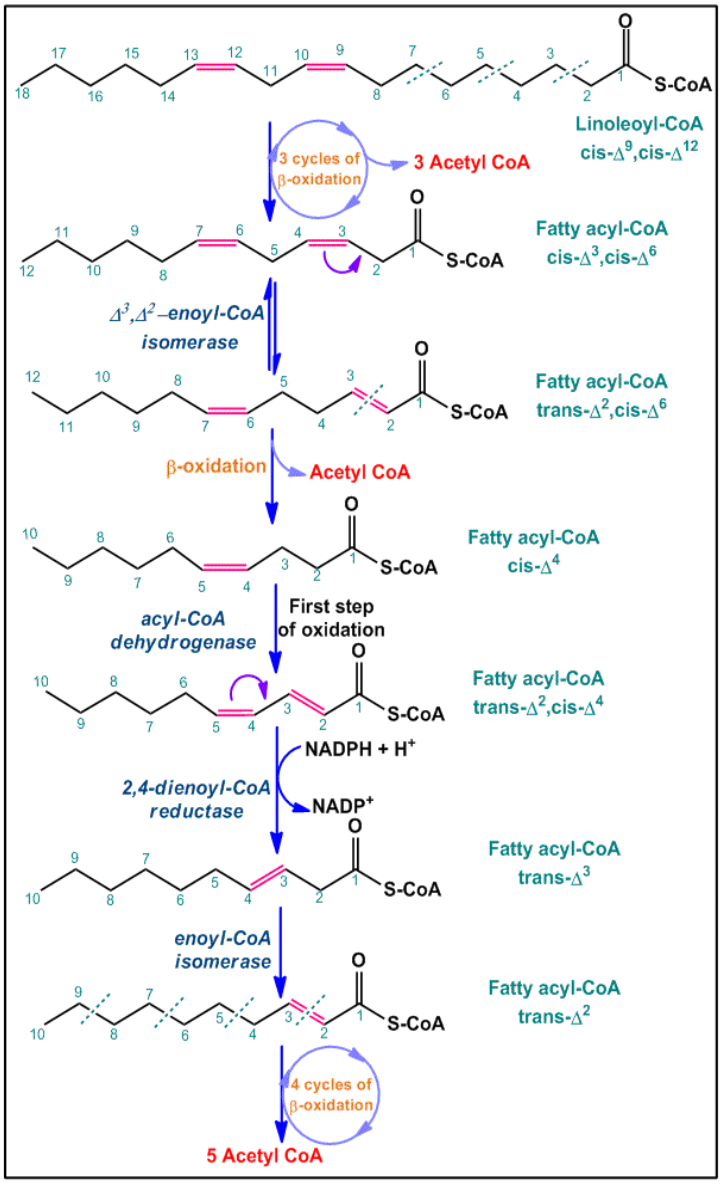
- Oleic acid has a double bond at **carbon #9**, this means that the in the first **8** carbons **no** double bonds are present, so we can produce **3 acetyl Co-A** molecules in the **same** way described previously until we end up with the remaining part of the Oleic acid, that is **12 carbons** with a double bond at **carbon #3.**
- Therefore, an **isomerase** is required, which converts the **3-cis** derivative obtained after 3 rounds of β-oxidation to the **2-trans** derivative, which is required as a **substrate** by the **enoyl CoA hydratase** *(rxn #2 of FA oxidation).*
- Afterwards, the reaction proceeds in the **same** way as the oxidation of **saturated** fatty acids that was discussed previously.



2- Linoleic Acid (18 Carbons)

- This fatty acid has **2** double bonds, one at **carbon #9** and the other at **carbon #12**. Just like oleic acid, the first **three cycles** can go on normally, then we get a 12-carbon fatty acid with double bonds at **carbon #3 and #6.**
- Through an **isomerase** the double bond at carbon #3 is **moved** to carbon #2, a 4th cycle can proceed now. The remaining fatty acid is a 10-carbon unit with a single double bond at **carbon #4**.
- A **dehydrogenase** forms **another** double bond at **carbon #2,** now we have **conjugated** double bonds. Then, a **reductase removes** one double bond and moves the other to **carbon #3**. Now an **isomerase** can move the double bond to carbon #2, then the oxidation proceeds normally.

Conclusion: ***Oleic acid*** *requires only an* ***isomerase****, while* ***linoleic acid*** *requires a* ***reductase****,* ***dehydrogenase*** *and an* ***isomerase****.*



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