# Fatty Acid Synthesis and Degradation

Introduction

- **Triacylglycerols** are **highly concentrated energy stores** for two reasons:
    - They are **very reduced**, and their oxidation therefore releases more energy than that of carbohydrates.
    - They are **anhydrous** and do not need to be **coordinated to water** when stored (unlike, for example, glycogen). This **saves space**.
- They can be used as "long distance fuel", especially in the heart (the "dustbin" of the body in terms of substrate metabolism).
- In **mammals**, the major site of **triacylglycerol accumulation** is the **cytoplasm** of **adipose cells**. Droplets of **triacylglycerol coalesce** to form a **large globule**, which may occupy most of the cell volume. They are also present in **muscles** and in the **liver**.
- Intestinal enzymes called **lipases**, secreted by the **pancreas** digest triacylglycerols into **fatty acids** and **monoacylglycerol**. These **non-water-soluble** molecules are made available to lipases by the formation of **micelles** thanks to **bile salts**.
- These are then **re-assembled** and assembled into **chylomicrons**, which travel in the **lymph system** to places were lipid is needed.
- **Fatty acids** can then be **oxidised** in the **mitochondria** in a process called **β-oxidation**. This converts fatty acids to **Acetyl CoA** which can be use din the **citric acid cycle**.
- Note, however, that **energy** from **fatty axis oxidation** is more O_2 **intensive** than that from glucose. Thus, **foetal heart metabolism** relies on **glucose** until soon after birth when it switches to **fatty acids**, because originally, oxygen is **sparse**.

Fatty Acid Degradation

- Once **triacylglycerols** are split into **glycerol** and **fatty acids**, the **glycerol** leaves towards the **liver**, where it is converted into a **glycolytic intermediate**.

- **Fatty acid degradation** occurs in the **mitochondria**. Before they enter the matrix, though, they must be **activated** through the formation of a **thiosester linkage** to **CoA**. This takes place on the **outer mitochondrial membrane** and is catalysed by **acyl CoA synthetase** (or **fatty acid thiokinase**):
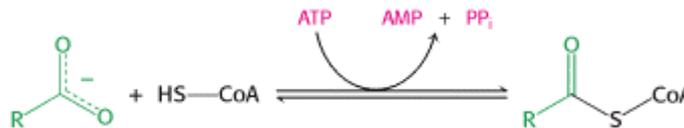


  This reaction occurs in **two steps**:

  1) The fatty acid reacts with **ATP** – the **carboxyl group** of the acid becomes bonded to the **phosphate group** of **AMP**. The other two groups are released as **pyrophosphate** (PP_i).

  2) The **sulfhydryl group** of **CoA** *attacks* this species (which is **tightly bound** to the enzyme) to form **Acyl CoA** and **AMP**.

  The **equilibrium constant** for this reaction is **close to 1** (one high-energy molecule is broken down, one is created). The overall reaction is **driven forward** by the **rapid oxidation** of **pyrophosphate** by a **pyrophosphatase**.

  Note that this reaction requires the **equivalent** of **2 ATP**, because **AMP** and not **ADP** is produced.

- This **long-chain activated fatty acid** then needs to be transported **into the mitochondrion**. This cannot occur by diffusion, and so a **special transport mechanism** is used:

  1) The **acyl group** is transferred from **Acyl CoA** to the **hydroxyl group** of **carnitine** (a **zawitterionic alcohol**, found in **red meat**) by **carnitine acyltransferase I**, which is **bound** to the **outer mitochondrial membrane**.

2) **Acyl carnitine** is then **shuttled** across the **inner mitochondrial membrane** by a **translocase** [**carnitine** in exchange of **acyl carnitine**].

3) The **acyl group** is transferred **back to CoA** by **carnitine acyltransferase II**.

- **β-oxidation** now occurs (so called because oxidation takes place at the β carbon). Each **round** of **β-oxidation** produces **Acetyl CoA**, **NADH** and **FADH₂** by **shortening** the **activated fatty acid** by **one unit**. The reactions are as follows:
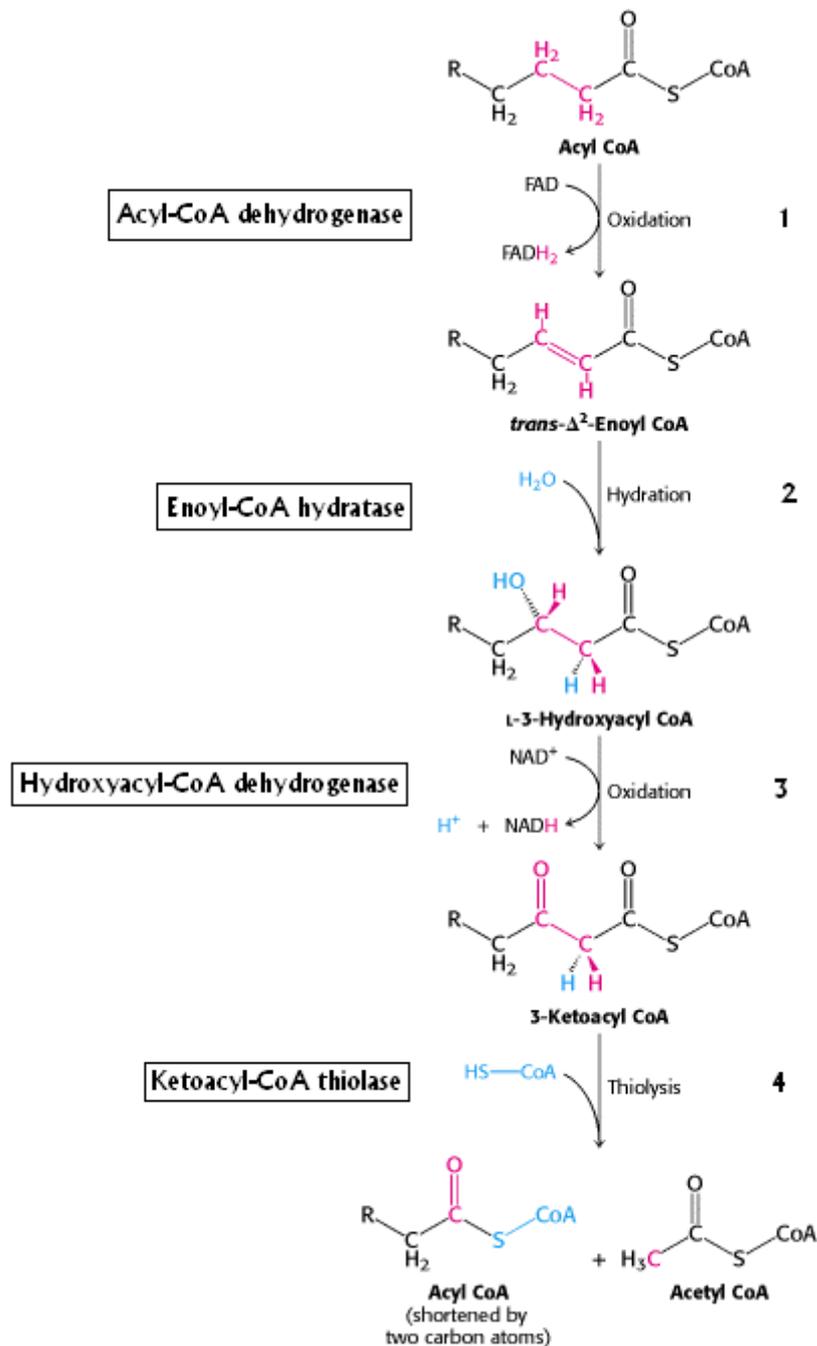
A few notes:

1) **FAD** rather than **NAD$^+$** is the **electron acceptor** because the ΔG for the reaction is **insufficient** to drive the reduction of NAD$^+$.

   Electrons from the **FADH$_2$ prosthetic group** of the enzyme are transferred to a second **flavoprotein** called **electron-transferring flavoprotein** (**ETF**). In turn, ETF **donates** electrons to **ETF:ubiquinone redeuctase** (an iron-sulphur protein). **Q** is thereby reduced to **QH$_2$**, which enters the **respiratory chain**. Consequently, **1.5 molecules** of ATP are generated per **FADH$_2$**.

   Different **versions** of this enzyme act on different **lengths** of **activated fatty acids**.

2) This **hydration** is **stereospecific**. When the **trans** double bond is **hydrated**, only the **L** isomer results.

3) This enzyme is also **stereospecific**.

4) We have now succeeded in **oxidising** the **methylene** group at C-3 to a **keto group**. All that needs to happen now is **cleavage**.

Note also that this reaction is **very similar** to the **regeneration** of **oxaloacetate** from **succinate** in the **citric acid cycle**.

- This releases a **huge** amount of energy. From **palmitate**, up to **106 ATP** can be released.

- Note that the situation is not so simple in **unsaturated acids** and in **odd-chain fatty acids**:

  o *Unsaturated fatty acids* – when the reaction reaches a **double bond** in between carbons **3 and 4**, a double bond can't be created in between carbons **2** and **3**. This is solved by an enzyme that simply **shifts** the double bond! (See diagram).

  Odd numbered double bonds (eg: one bewteen carbon **4 and 5**) first have to be treated with a **reductase** and *then* with the **isomerase**.
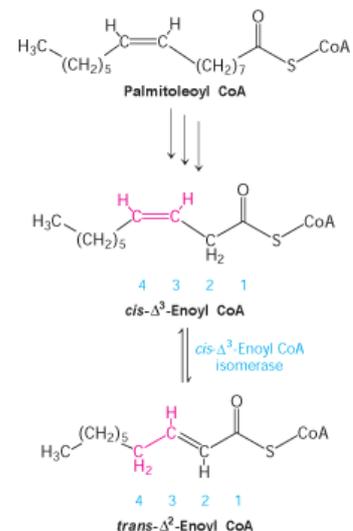
o ***Odd-chain fatty acids*** – these proceed as normal, but the **final step** leads to a molecule of **propionyl CoA** as well as **acetyl CoA**. This is then converted to **Succinyl CoA** (requiring ATP), an unusual process which requires **vitamin B$_{12}$**.

- The **oxidation of fatty acids** can also occur in **peroxisomes**, where it **halts** at **octanoyl CoA** (this probably serves to shorten long chain acids to make them better substrates for β-oxidation). The only difference is that the **high energy electrons** are used to make **H$_2$O$_2$**, which is then broken down by **catalase** into **H$_2$O** and **½O$_2$**.

Ketone bodies

The **Acetyl CoA** formed can enter the **citric acid cycle** *only* if it can combine with **oxaloacetate**. The availability of oxaloacetate, however, depends on an **adequate supply of carbohydrate** [since oxaloacetate is usually form from pyruvate]. If **carbohydrate** is **unavailable** or **improperly utilised**, or if **oxaloacetate** is used to form **glucose** by **gluconeogenesis** (eg: during **starvation** or **diabetes**), then **Acetyl CoA** is converted into **ketone bodies** (**3-hydroxybutyrate** [reduced acetoacetate] and **acetoacetate**, which spontaneously decarboxylates to **acetone**) [**2 Acetyl CoA** per **ketone body**].

The **primary site of production** of **ketone bodies** is the **liver**. Thence, they can **diffuse out** to **other organs**. These are **normal fuels for respiration**, and some organs prefer them to glucose (eg: the heart). **Acetoacetate** can be used as **fuel** for **respiration** as shown on the right. (The **liver** is able to **export aceotacetate** because it lacks **CoA transferase**). The **brain**, however, needs **glucose to function**, though during **starvation**, it can adapt to use 75% ketone bodies.

Acetoacetate
— Succinyl CoA
CoA transferase
→ Succinate
Acetoacetyl CoA
— CoA
Thiolase
2 Acetyl CoA
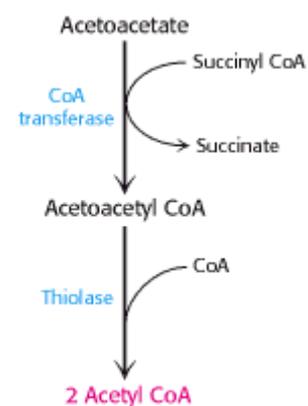
Ketone bodies are basically a **water-soluble**, **transportable** form of **acetyl units**. They also play a **control mechanism** – **high levels** of **acetoacetate** in the blood lead to a **decrease** in the rate of **lipolysis** in **adipose tissue**.

Note that what happens during **diabetes** is that the **absence of insulin** means that **glucose** is **not taken up by the liver**, which is therefore not able to synthesise **oxaloacetate**. Furthermore, **adipose cells continue to release fatty acids in the bloodstream**. The liver therefore produces **large amounts of ketone bodies** which are moderately strong **acids**. Severe **acidosis** results.

Animals cannot convert fatty acids in glucose

We noted before that **Acetyl CoA** could not be converted to **pyruvate** or **oxaloacetate** in animals (because the **pyruvate** $\rightarrow$ **acetyl CoA** reaction is **irreversible**). When **Acetyl CoA** enters the cycle, two carbons go in and two go out – **oxaloacetate** is not formed **de novo**. In contrast, plants have enzymes allowing the conversion of **Acetyl CoA** into **oxaloacetate**.