Fatty Acid and Glucose Oxidation

Structure of Fatty Acids

Fatty acid oxidation can only be done in cells that have mitochondria.

- It consumes a lot of co – factors like NAD, FAD and CoA
- Is reciprocally related to glucose oxidation. As such, when one pathway of oxidation is active, the other is more suppressed.

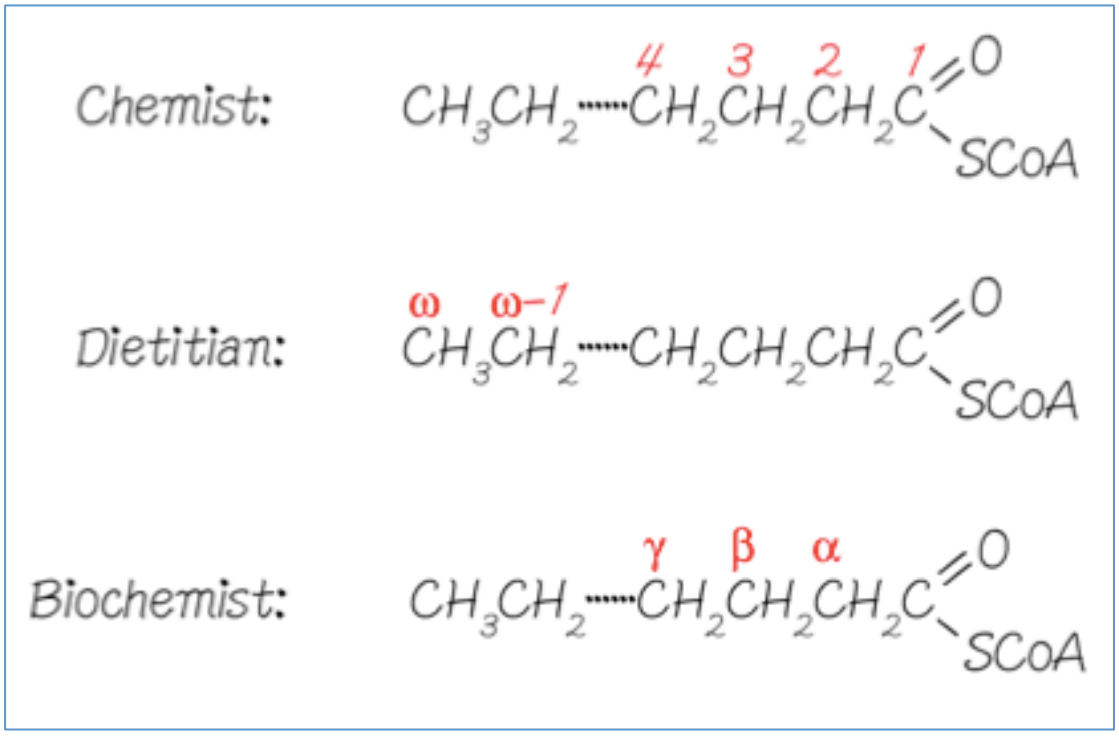

Figure 1 Different nomenclatures of fatty acids (Denyer, 2016)

Transport of Fatty Acid into the Cell

Before fatty acid can be oxidized (by NAD and FAD) into Acetyl CoA, it needs a way of transport from fat stores to the cell and the mitochondria within that.

Fatty Acid Transport in the Blood: Albumin

In the blood, fatty acid binds to a protein called ***albumin***.

- As fatty acid has a hydrophobic end and a hydrophilic end, it very similar in structure to detergent, and not suited to be in the blood stream by itself
- Hence, albumin is needed to transport fatty acid in the blood stream. Albumin has multiple binding sites for fatty acid

Fatty Acid Transport into the Cell: Fatty Acid Binding Protein

Once near the cell, fatty acids dissociate from albumin, and cross the cell membrane by following the concentration gradient. *There is now evidence to suggest there is active transport during exercise when FA uptake needs increasing.* Once in the cytoplasm of the cell, the fatty acid binds to a ***Fatty Acid Binding Protein (FABP)***. At this point, the fatty acid can still (theoretically) dissociated from FABP, then return to the blood stream by attaching to albumin.

Trapping of Fatty Acid in the Cell

Once inside the cell, ***Coenzyme A (CoA)*** dissociates fatty acids from FABP, resulting in a Fatty Acyl – CoA unit. At this point, the fatty acid has been 'locked in' to the cytoplasm, and is going to be metabolized or stored as fat.

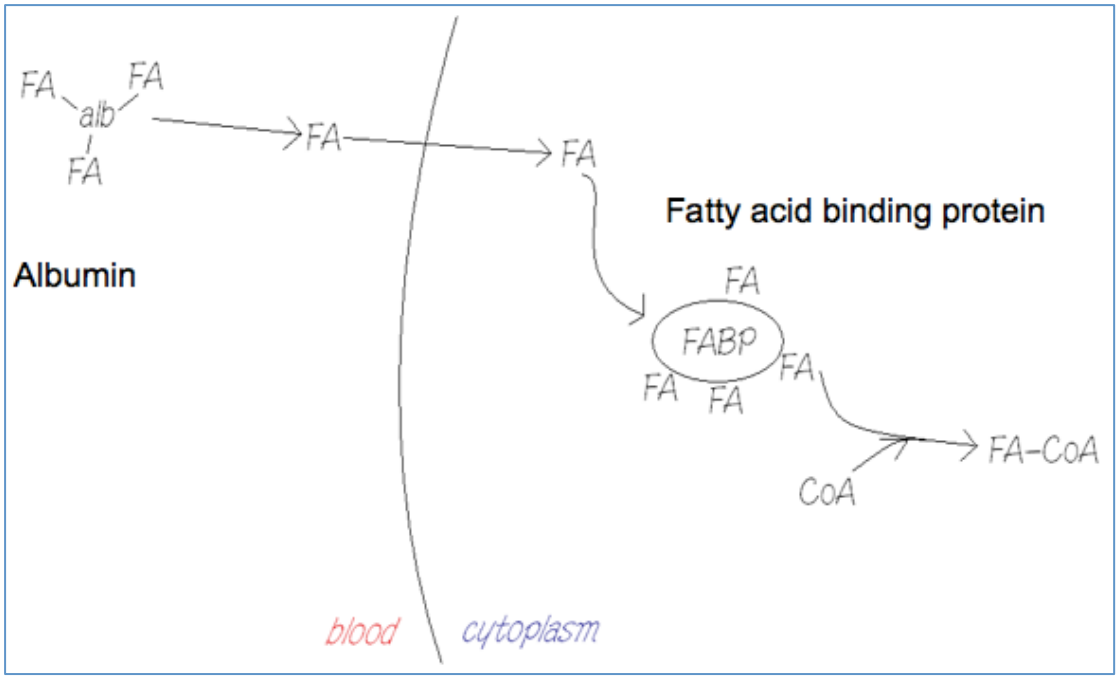

Figure 2 Transport and 'trapping' of Fatty Acid in the cell (Denyer, 2016)

For CoA to bind to FA, it requires an input of energy. This is done through the cleaving of two phosphates off ATP. *Hence, even though oxidation of fatty acids generates ATP, it requires an input of ATP first.*

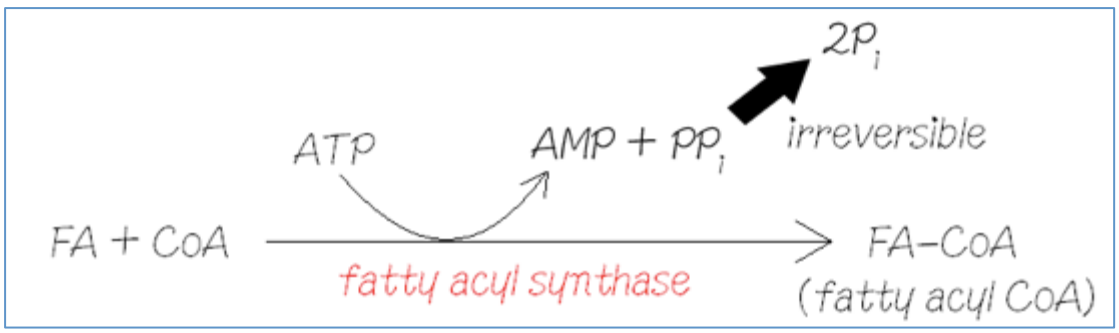

Figure 3 Energy for FA to bind to CoA provided by ATP (Denyer, 2016)

Transport of Fatty Acids into the Mitochondria

Whilst the attachment of CoA to Fatty Acids ensures that it stays in the cytoplasm rather than leaving the cell, it also means that FA – CoA can't enter the mitochondrial matrix.

Hence, a protein called ***carnitine*** pulls the Fatty Acid off Fatty Acyl CoA, resulting in Fatty Acyl Carnitine. This can move through the membrane wall, via an enzymatic carrier called ***CAT – 1***. (Carnitine Acyltransfersase 1)
Once inside the matrix, ***CAT – II*** helps carnitine dissociates from Fatty Acid and is free to return to the cytoplasm. The fatty acid then re-associates with CoA units from inside the matrix.

CAT – 1 is regulated by Malonyl CoA, which is produced when glucose oxidation increases. Hence, the reciprocal relationship between glucose and fatty acid oxidation can be seen here.

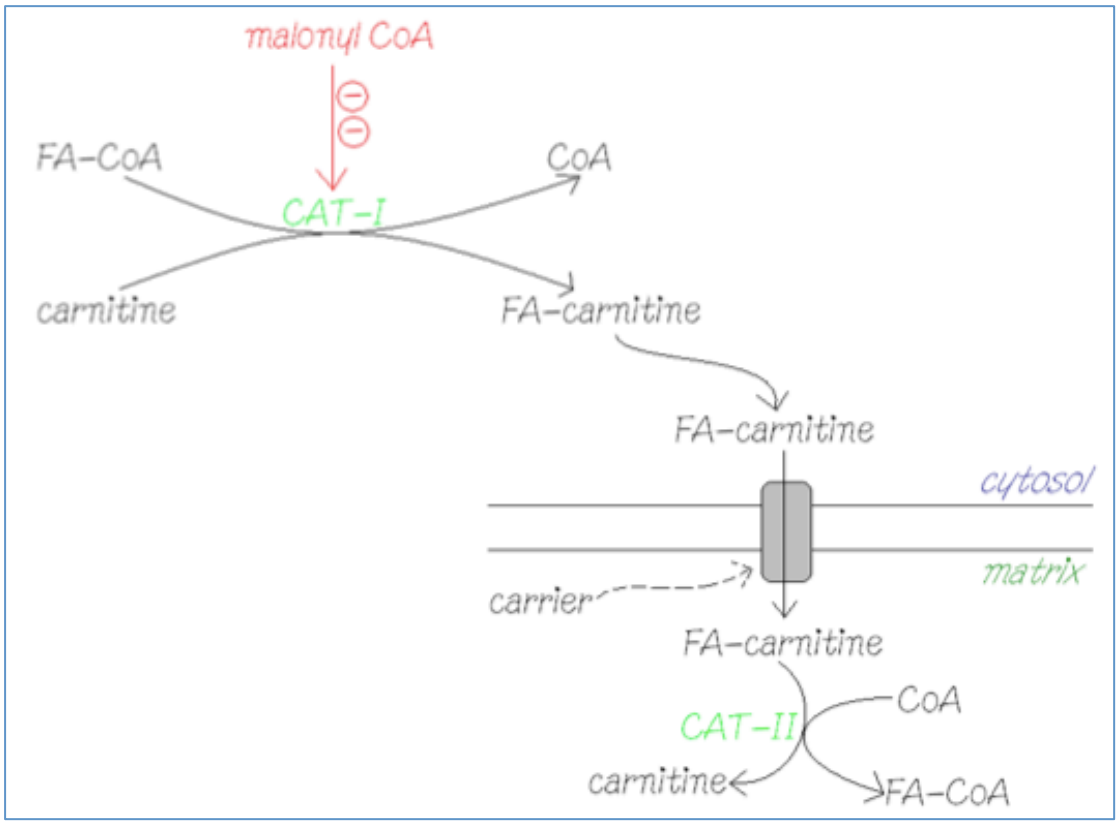

Figure 4 FA - CoA requires Carnitine to move into the matrix (Denyer, 2016)

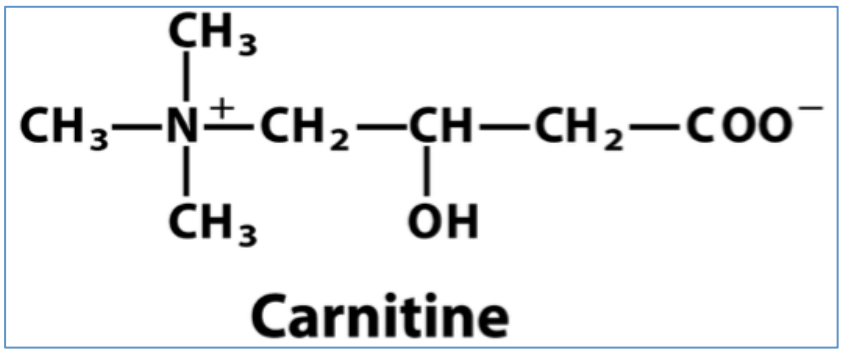

Figure 5 The structure of Carnitine (Denyer, 2016)

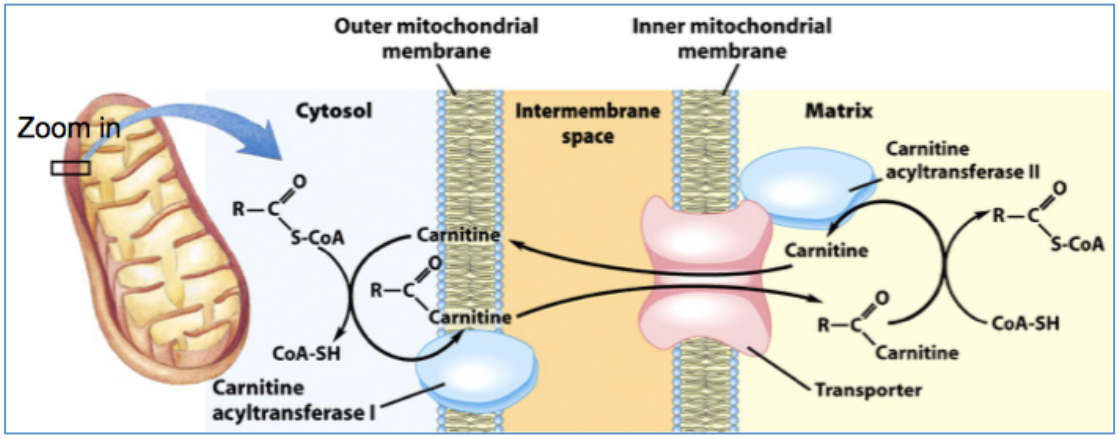

Figure 6 Another visualization of carnitine and CAT - 1 (Nelson et al, 2013. p. 672)

Oxidation of Fatty Acids in the Mitochondria

As detailed briefly in the overview of fuel oxidation, fatty acid is 'ripped apart' by NAD and FAD, resulting in Acetyl CoA.

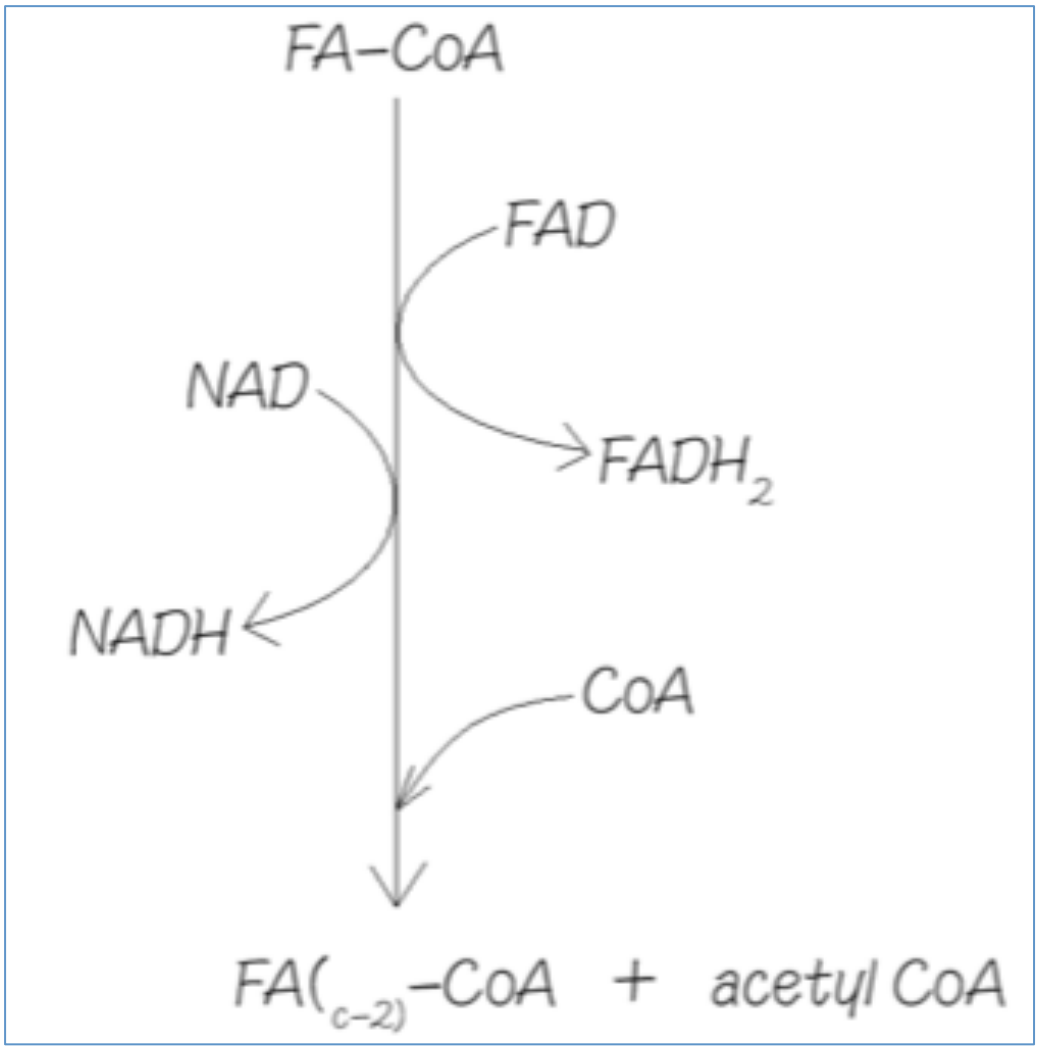

Figure 7 Oxidisation of Fatty Acid (Denyer, 2016)

1. FAD oxidation

FAD comes in and 'steals' two hydrogens of the alpha and beta carbons of the fatty acid, resulting in a double bond between the alpha and beta carbons:

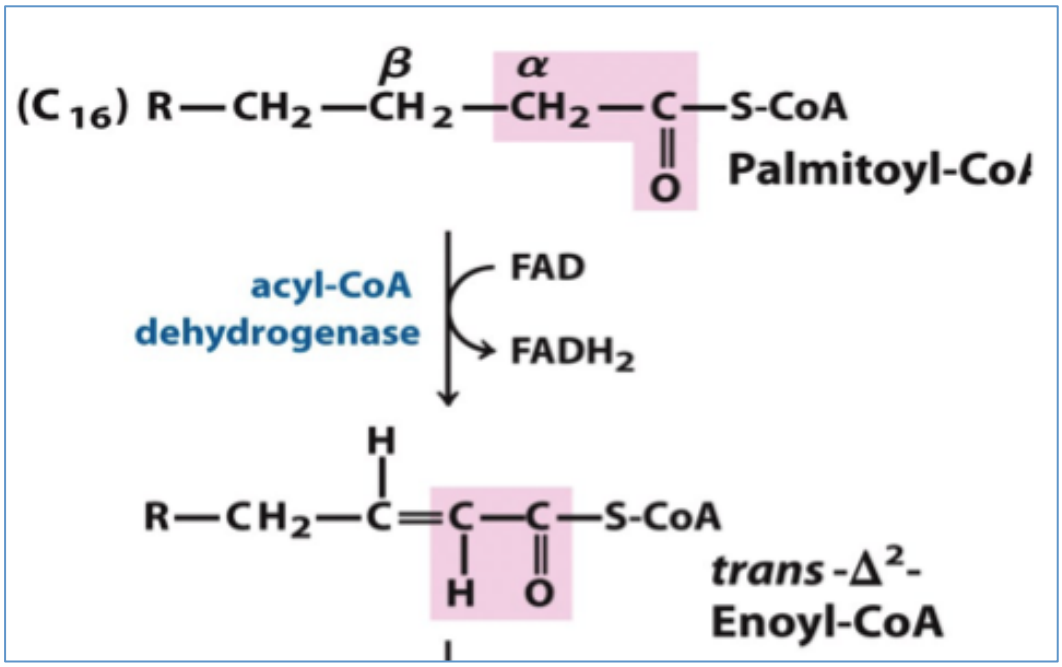

Figure 8 FAD Oxidation of Fatty Acid (Nelson et al, 2013. p. 673)

2. Hydration of Fatty Acid

Water comes in and creates a hydroxyl group on the beta carbon, as well as a hydrogen to the alpha carbon, thus breaking the double bond into a single again:

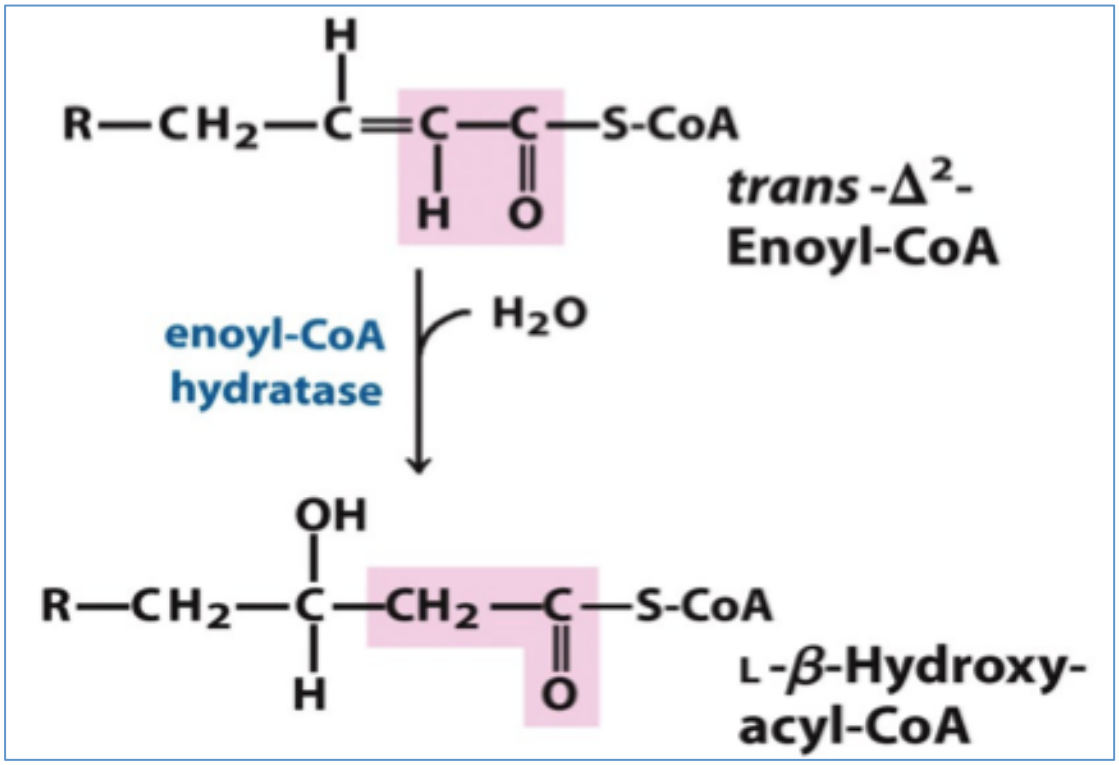

Figure 9 Hydration of Fatty Acid (Nelson et al, 2013. p.673)

3. NAD oxidation

NAD oxidation 'steals off' two hydrogens from the beta carbon, resulting in a double bonded C = O forming.

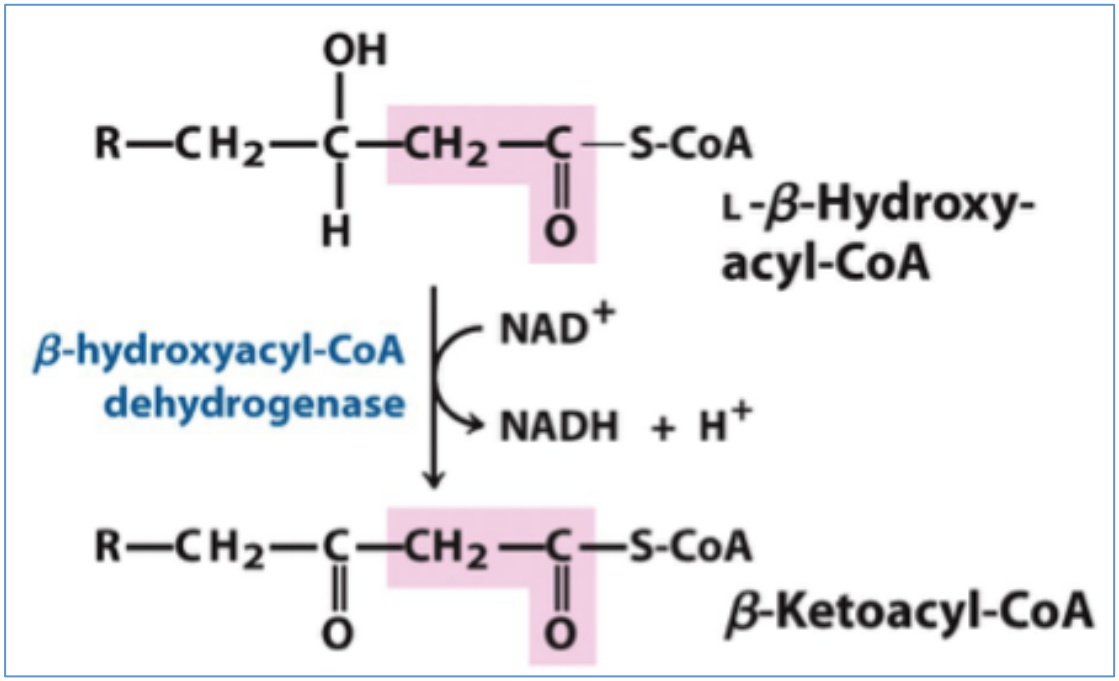

Figure 10 NAD oxidation of Fatty Acid (Nelson et al, 2013. p. 673)

4. CoA group cleaves off acetate

CoA then cleaves off the acetate (highlighted in red), resulting in ***Acetyl CoA*** and a fatty acid chain that is now two carbons shorter.

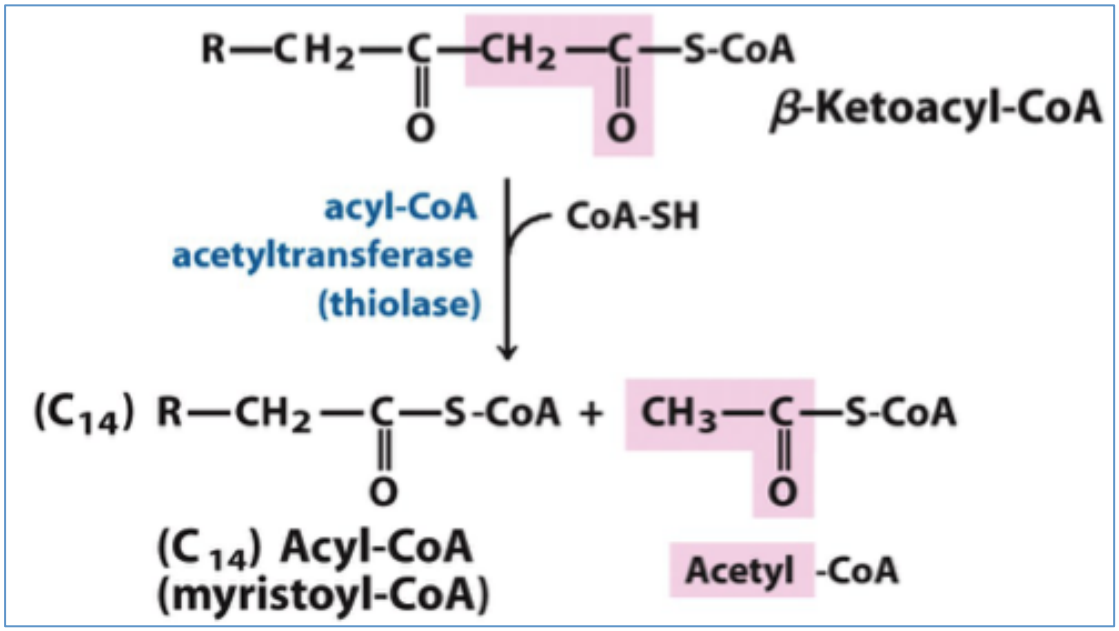

Figure 11 CoA group cleaves off acetate to become Acetyl CoA (Nelson et al, 2013. p. 673)

This single process would require one NAD, FAD and CoA unit, simply to 'steal' two carbons. A 16-chain fatty acid would thus need 7 NAD, FAD and 8 CoA units.

(Remember the last two carbon units don't need to be ripped off, but still need to be made into Acetyl CoA)

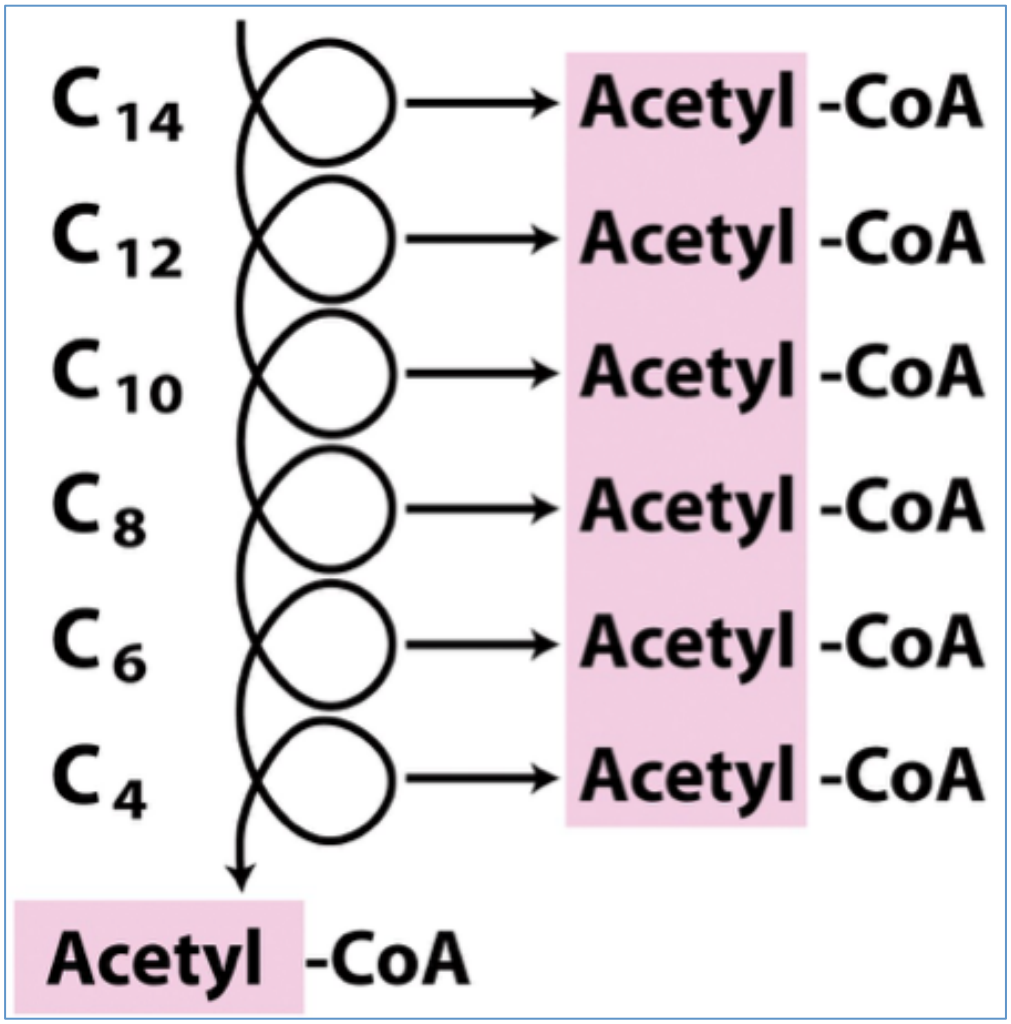

Figure 12 Eventually, ß oxidation results in this (Nelson et al, 2008. Figure 17 - 8b)

The acetyl CoA then enters the Krebs/TCA/Citric Acid Cycle.

Regulation of Fatty Acid Oxidation

Cofactor Availability

NAD, FAD and CoA are all needed for oxidation. To continually regenerate the availability of these cofactors:

- NADH and $FADH_2$ can be recycled once they unload their electrons to the electron transport chain, and are free to return to oxidation
- CoA can be recycled once Acetyl CoA enters the Krebs/TCA/Citric Acid Cycle, and unloads its Acetyl unit.

Rate Limiting Enzymes

The rate-limiting enzyme is the slowest enzyme in the overall metabolic pathway, which determines the ultimate speed at which the process can occur. Also called a *Flux Generating Step*, it can be likened to the gates at a train station.

If only one gate is open, the rate of travellers exiting the station will be just as slow, regardless of how efficient the walking path outside may be. Hence, the rate of customer output from the station is determined by the gate.

Linking back to enzyme kinetics, the Vmax of a rate-limiting enzyme will not change if the already high [substrate] increases from S1 to S2, as it has been saturated with substrate. *Similarly, the rate of customers leaving the station with only one gate will not change if there are 100 or 200 customers.* Generally, rate-limiting enzymes are already at Vmax.

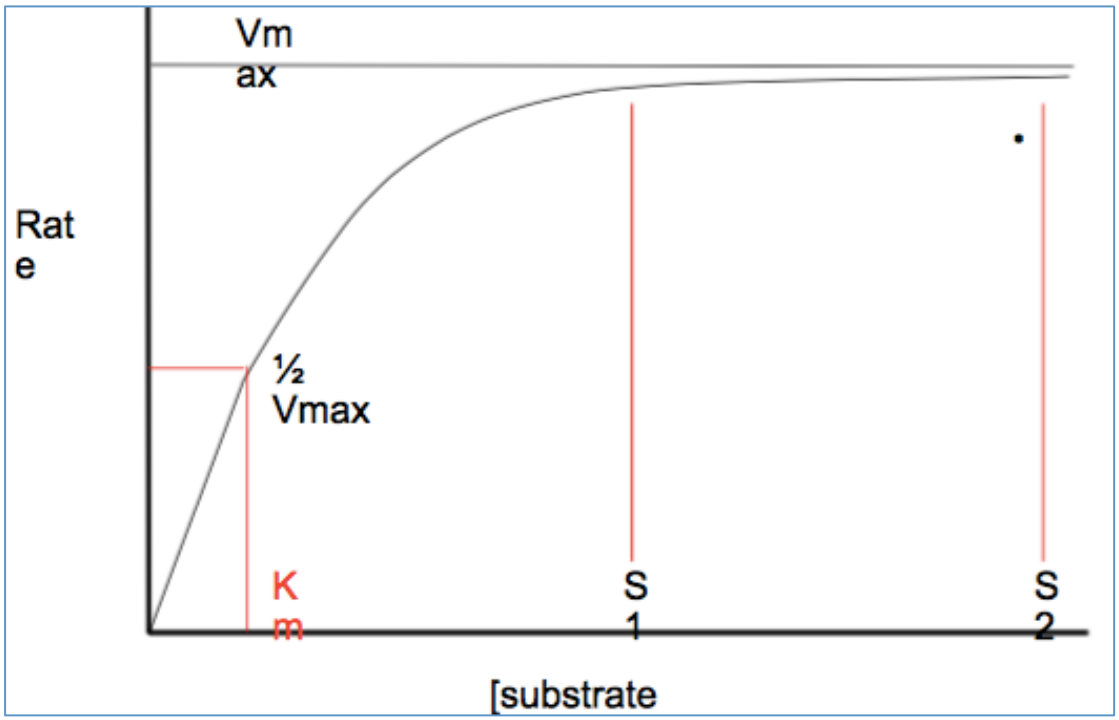

Figure 13 A recap on enzyme kinetics (Denyer, 2016)

Rate limiting enzymes are thus:

- **Slow**
- **Irreversible**
- **Saturated with substrate**

There are ways to regulate these enzymes, and thus the rate of oxidation:

1. ***Switching Enzymes on or off (Covalent Modification)***
   By manipulating the enzyme (by phosphorylation, for example), their activity can be suppressed or activated.
   In the train analogy, this would be equivalent to opening or closing extra gates.

2. ***Allosteric Changes to Enzymes***
   Small molecules binding to the enzyme cause an allosteric shape change, which can increase or decrease the rate at which the enzyme acts.
   In the train analogy, this would be equivalent to changing the gate so that it can process the tickets faster or slower.

3. ***Making and destroying Enzymes***
   Enzymes can be completely destroyed or created to match their demand. *In the train analogy, this would be equivalent to creating new gates during peak hour and dismantling them afterwards*.

The speed of these Rate Limiting Enzymes thus dictates the rate of fatty acid oxidation. *It should be important to note that it is almost impossible for enzymes to reverse the process that it catalyzes.*

In ß – oxidation of fatty acids, the rate-limiting step is not completely known. It is believed that it can change depending on the circumstance. For example:

- In females with low iron, the RLS is *CAT-I*, where carnitine pulls the CoA unit off Fatty Acid.
- In people who are unfit, the RLS can be a limit in ß oxidation enzymes
- In people with low body fat, the RLS can be a limit in fatty acid availability