

FATTY ACID OXIDATION

Lectures by Dr S.J. Brookes

If you have any questions relating to these lecture make an appointment for a Wednesday afternoon in the Division of Oral Biology (level 6). Alternatively you can email any problems to Dr. Brookes who will reply to your message as soon as possible (s.j.brookes@leeds.ac.uk).

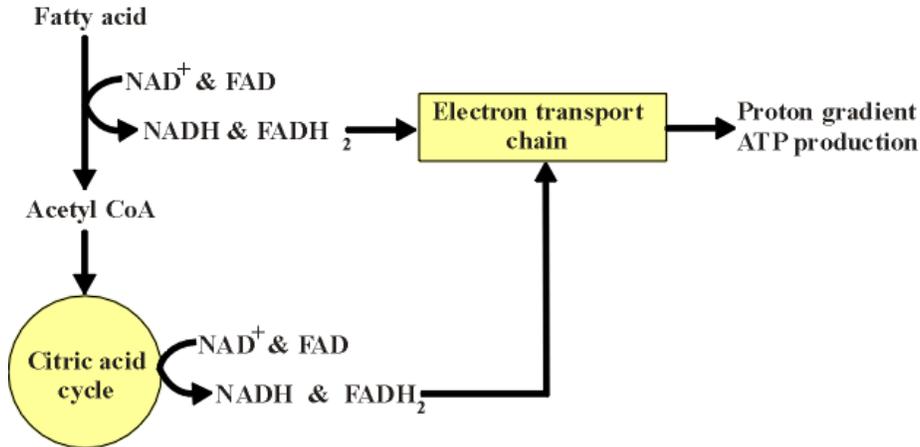
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INTRODUCTION

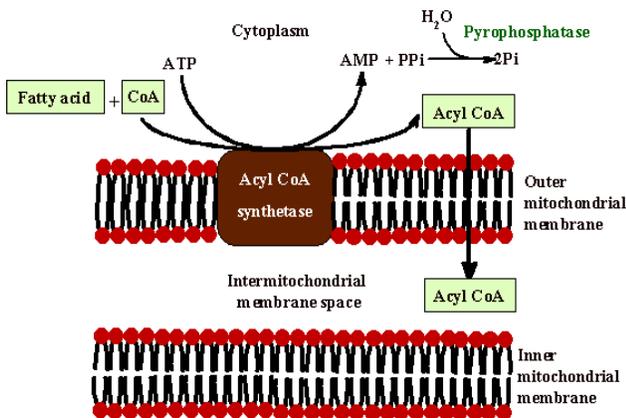
Triacyl glycerols consist of a glycerol backbone to which 2 or 3 fatty acids have been esterified. The fatty acids have to be hydrolysed before they can be oxidised. This is dealt with under [nutrition](#). Fatty acids are highly reduced molecules. They are oxidised by NAD^+ and FAD which pass the reducing potential on to the electron transport chain to power [ATP generation](#). Fatty acid oxidation also generates acetyl CoA which can enter the citric acid cycle for generation of even more NADH and FADH_2



Fatty acid oxidation occurs in the mitochondria so it is easily feeds acetyl CoA into citric acid cycle and $\text{NADH}/\text{FADH}_2$ into the electron transport chain.

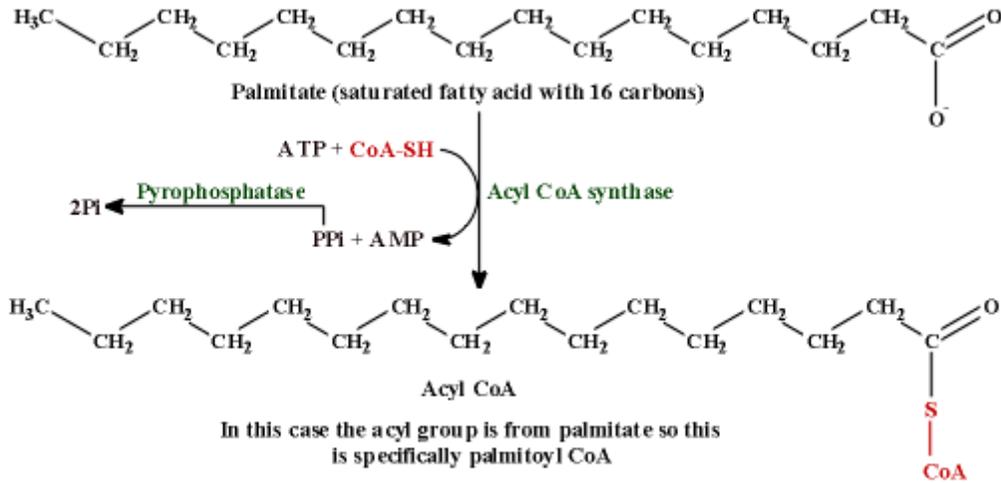
Step 1: Activation on the outer mitochondrial membrane:

Before oxidation, fatty acids are activated by attaching CoA:



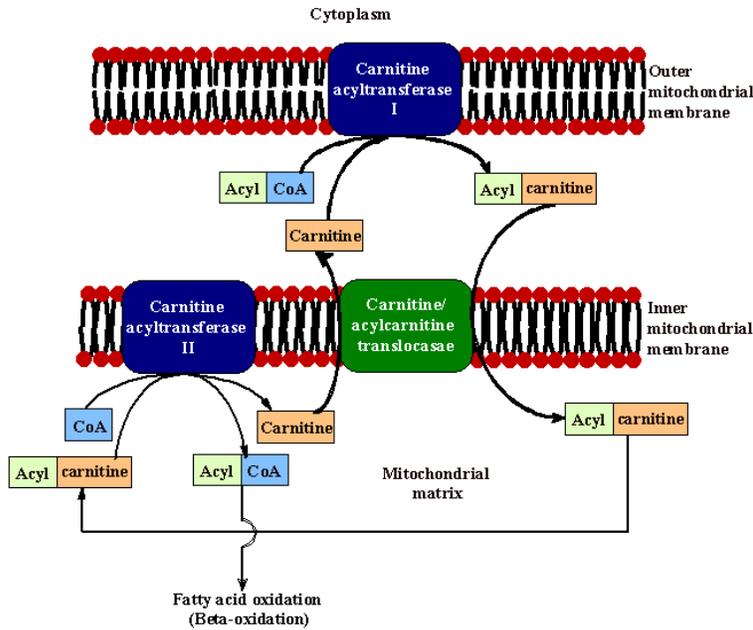
Attachment of CoA occurs on the cytoplasmic face of the outer mitochondrial membrane - catalysed by **acyl CoA synthetase**. ATP is hydrolysed to AMP and pyrophosphatase (PPi). Rapid hydrolysis of PPi to inorganic phosphate (Pi) by **pyrophosphatase** consumes a second "high energy" phosphate bond. Hydrolysis of these two high energy phosphate bonds drives the reaction. The energy change is so large that the reaction is irreversible. In other words, the equivalent of 2ATP are used in this activation step.

It might help you to look at this chemically:



Step 2: Transport of Acyl CoA into mitochondria:

. Activation occurs in the cytosol but oxidation occurs in mitochondria. Inner mitochondrial membrane is impermeable to long chain acyl CoA molecules so a transport system is required



Acyl CoA (where acyl is long chain fatty acid) is converted to acylcarnitine by **carnitine acyltransferase I** on the inner surface of the outer mitochondrial membrane.

Acylcarnitine is transported across the inner mitochondrial membrane by **carnitine-acylcarnitine translocase** in exchange for carnitine.

Once in the matrix, acylcarnitine is converted back acyl CoA by **carnitine acyltransferase II**. The liberated carnitine can be exchanged for another incoming molecule of acylcarnitine.

The acylcarnitine is now inside the matrix and has access to the enzymes catalysing fatty acid oxidation (beta-oxidation).

Step 3: Oxidation of Acyl CoA:

- 8 acetyl CoA enter citric acid cycle and give:
 - 24 NADH = 72 ATP (by oxidative phosphorylation)
 - 8 FADH₂ = 16 ATP (by oxidative phosphorylation)
 - 8 GTP = 8 ATP
- 7 NADH generated by beta oxidation itself = 21 ATP (by oxidative phosphorylation)
- 7 FADH₂ generated by beta oxidation itself = 14 ATP (by oxidative phosphorylation)

Total number of ATP from 1 molecule of palmitate = $72 + 16 + 8 + 21 + 14 = 131$.

But **remember** we used to high energy phosphate bonds (equivalent of 2 ATP) to activate palmitate to palmitoyl CoA. Therefore, the ATP yield is 129.

Beta oxidation of unsaturated fatty acids (fatty acids with double bonds)

Accessory enzymes are required for dealing with fatty acids having double bonds. Basically the *cis* double bonds in unsaturated fatty acids have to be converted to *trans* double bonds to allow beta oxidation to continue.

How do fatty acids compare with glucose as a store of energy?

In terms of ATP per carbon atom oxidised the ATP yield from palmitate = $129/16 = 8$ ATP per carbon.

The total yield of ATP from 1 glucose molecule going through glycolysis and the citric acid cycle is:

- 2ATP generated in glycolysis directly.
- 2 NADH generated in glycolysis = 6 ATP ((by oxidative phosphorylation).
- 2 NADH generated when 2 pyruvate are converted to 2 acetyl CoA = 6 ATP (by oxidative phosphorylation)
- 2 acetyl CoA enter citric acid cycle to generate
 - 6 NADH = 18 ATP (by oxidative phosphorylation)
 - 2 FADH₂ = 4 ATP (by oxidative phosphorylation)
 - 2 GTP = 2ATP

Total number of ATP from 1 molecule of glucose = $2 + 6 + 6 + 18 + 4 + 2 = 38$.

In terms of ATP per carbon atom oxidised the ATP yield from glucose = $38/6 = 6.3$ ATP (remember glucose has 6 carbons).

Fatty acids yield 8 ATP per carbon while glucose yields 6.3 ATP per carbon. This is a reflection of the fact that carbons in fatty acids are more reduced than in glucose. This makes fat a better store of energy than glucose.

Regulation of beta oxidation

Largely by concentration of free fatty acids available.

Malonyl CoA inhibits carnitine transferase which will inhibit entry of acyl CoA into mitochondria. Malonyl CoA is an intermediate of fatty acid synthesis. Fatty acid synthesis and fatty acid breakdown do not occur together.

Ketone bodies

When beta-oxidation outstrips carbohydrate breakdown (e.g. during starvation and uncontrolled diabetes) ketone bodies are produced by liver mitochondria. This is because the large amount of acetyl CoA produced by beta oxidation overloads the citric acid cycle (limited carbohydrate means that citric acid intermediates will be depleted - not enough oxaloacetate to condense with all that acetyl CoA). Instead, acetyl CoA is converted to ketone bodies (acetoacetate, acetone and 3-hydroxybutyrate). These travel from the liver in the blood to the muscle where they are converted back to acetyl CoA and enter the citric acid cycle. In starvation the brain can also use ketone bodies as fuel.

Ketone bodies (from fat breakdown) are an easy way of transporting the energy stored in fat from the liver to the other tissues because they are soluble in the blood (the acetone comes from spontaneous decomposition of acetoacetate in the blood and can be smelt on the breath).

