5.2: Lipolysis, β-oxidation, and ketogenesis

The processes of lipolysis, \( \beta \)-oxidation, and ketogenesis work in concert within the cell but should be considered distinct pathways.

Lipolysis

Lipolysis is the release of fatty acids from adipose tissue where they are stored as triacylglycerols (TAGs). This process is mediated by increasing levels of glucagon and epinephrine, which bind G-protein coupled receptors on the adipose tissue and activate lipolysis. This cell-signaling cascade phosphorylates and activates hormone-sensitive lipase, the regulatory enzyme for lipolysis. Once phosphorylated (through hormone-mediated increase in cAMP) this enzyme will hydrolyze TAGs to three long-chain fatty acids (LCFAs) and glycerol. The LCFAs are released into the bloodstream and will circulate bound to albumin (fatty acids are hydrophobic and require a protein carrier). LCFAs will be taken up and oxidized by peripheral tissues and the liver under fasted conditions. The glycerol will also be released and used as a substrate for hepatic gluconeogenesis (section 5.1) (figure 5.6).
β-oxidation (oxidation of free fatty acids)

Fatty acid oxidation is a high energy yielding process. It can support the cellular energy needs during fasting and under conditions when excess energy is needed (exercise). After uptake from circulation, the LCFAs must be transferred into the mitochondria where β-oxidation occurs. Initially, the LCFAs are activated to acyl-CoA derivatives in the cytosol by acyl-CoA synthetase. The fatty acyl-CoA can then be transferred across the mitochondrial membranes using a series of transport proteins: carnitine palmitoyltransferase 1 and 2 (CPT1 and CPT2) (figure 5.9).
short- and medium-chain fatty acids can move into the mitochondria without the steps that result in the generation of CoA will inhibit CPT1 therefore ensuring that \( \beta \)-oxidation is not occurring at the same time as fatty acid synthesis.

\( \beta \)-oxidation is regulated primarily at the level of transport of LCFAs across the mitochondrial membrane. Malonyl-CoA will inhibit CPT1 therefore ensuring that \( \beta \)-oxidation is not occurring at the same time as fatty acid synthesis.

Regulation of \( \beta \)-oxidation

\( \beta \)-oxidation is an iterative process that involves a series of enzymes that preferentially oxidize different length fatty acids (long, medium, and short). The full \( \beta \)-oxidation spiral consists of four steps that result in the generation of acetyl-CoA, NADH, and FADH\(_2\) for each cycle (figure 5.9). The NADH and FADH\(_2\) generated will be oxidized in the ETC to produce ATP. The acetyl-CoA can be oxidized in the TCA cycle, but more likely it will be used in ketogenesis. Oxidation of odd chain fatty acids will result in the generation of propionyl-CoA as the final carbon unit, which can also be oxidized in the TCA cycle. The acetyl-CoA from \( \beta \)-oxidation also plays a key role in the allosteric activation of pyruvate carboxylase, which is necessary for gluconeogenesis to occur (section 5.1).

Figure 5.9: Overview of LCFA transport into the mitochondria and \( \beta \)-oxidation.

CPT1 sits on the outer mitochondrial membrane and transfers the fatty acyl-CoA to carnitine. Fatty acyl carnitine is transferred into the mitochondrial matrix through CPT2, and the carnitine is released and recycled. Only long-chain fatty acyl-CoAs require carnitine as a carrier; short- and medium-chain fatty acids can move into the mitochondria without the assistance of these transporters. Once in the matrix, the fatty acyl-CoA is now ready to undergo \( \beta \)-oxidation (figure 5.9).

\( \beta \)-oxidation is an iterative process that involves a series of enzymes that preferentially oxidize different length fatty acids (long, medium, and short). The full \( \beta \)-oxidation spiral consists of four steps that result in the generation of acetyl-CoA, NADH, and FADH\(_2\) for each cycle (figure 5.9). The NADH and FADH\(_2\) generated will be oxidized in the ETC to produce ATP. The acetyl-CoA can be oxidized in the TCA cycle, but more likely it will be used in ketogenesis. Oxidation of odd chain fatty acids will result in the generation of propionyl-CoA as the final carbon unit, which can also be oxidized in the TCA cycle. The acetyl-CoA from \( \beta \)-oxidation also plays a key role in the allosteric activation of pyruvate carboxylase, which is necessary for gluconeogenesis to occur (section 5.1).
Additionally, the rate of ATP production (ATP/ADP ratio) will also regulate the rate of NADH and FADH$_2$ produced through β-oxidation (figure 5.10).

**Ketogenesis**

As mentioned above, the acetyl-CoA produced by β-oxidation is primarily used for ketogenesis — the synthesis of ketone bodies. Substrates for ketogenesis can also come from the oxidation of ketogenic amino acids. In the fasted state, the process of β-oxidation generates a significant amount of acetyl-CoA, and although some of this substrate can be oxidized in the TCA cycle, we need to consider the other metabolic processes occurring. First, the significant amount of NADH generated through β-oxidation reduces flux through the TCA cycle by decreasing the activity of both α-ketoglutarate dehydrogenase and isocitrate dehydrogenase. Second, the process of gluconeogenesis is occurring, and intermediates of the TCA cycle, specifically malate, are actively being moved out of the mitochondria. The combination of these two processes reduces the TCA cycle activity allowing for an accumulation of acetyl-CoA. As acetyl-CoA levels elevate in the mitochondria, this will drive the thiolase reaction to generate acetoacetyl-CoA from two acetyl-CoA molecules (figure 5.11).

This compound is the substrate for HMG-CoA synthase, which generates 3-hydroxy-3-methyl glutaryl-CoA (HMG-CoA).
HMG-CoA is then accepted by HMG-CoA lyase where an acetyl-CoA group is removed to generate acetoacetate. Acetoacetate can either undergo spontaneous decarboxylation to acetone, which can be exhaled, or it can be reduced to \(\text{\(\beta\)}\)-hydroxybutyrate using NADH. Acetoacetate and \(\text{\(\beta\)}\)-hydroxybutyrate are the two primary ketone bodies in circulation, and the ratio of the two is dependent on levels of NADH (figure 5.11). These two ketone bodies can be used as fuel in most tissues with the exception of the liver, which lacks thiophorase, the enzyme needed to metabolize these substrates. Ketone oxidation is not a primary fuel source, as fatty acid oxidation is preferred, but it can supply energy to some peripheral tissues. The brain can also oxidize ketones but only under extreme situations, such as starvation states.

### Summary of pathway regulation

Table 5.2: Summary of pathway regulation.

<table>
<thead>
<tr>
<th>Metabolic pathway</th>
<th>Major regulatory enzyme</th>
<th>Allosteric effectors</th>
<th>Hormonal effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipolysis</td>
<td>Hormone-sensitive lipase</td>
<td>None</td>
<td>Epi (\uparrow)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Insulin (\downarrow)</td>
</tr>
<tr>
<td>(\text{(\beta)})-oxidation</td>
<td>Carnitine palmitoyltransferase (CPT1)</td>
<td>Malonyl-CoA (-)</td>
<td>None</td>
</tr>
</tbody>
</table>

### References and resources

**Text**


**Figures**

Grey, Kindred, Figure 5.8 Process of lipolysis. 2021. [https://archive.org/details/5.6_20210924 CC BY 4.0](https://archive.org/details/5.6_20210924 CC BY 4.0). Added red
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