C13. PPARs and the Regulation of Metabolism

We have spent little time discussing the detailed anabolic and catabolic pathways of metabolism. That is the topic of another biochemistry course. However, it should be clear that the one pathway should be activated and the other inhibited, depending on the energy state of the individual. In the well fed state (high levels of carbohydrates and lipids), glycogen, triacylglycerides, and fatty acids synthesis should be activated, while glycogen breakdown (glycogenolysis), mobilization of triglycerides reserves (breakdown of TAGs to form free fatty acids), and fatty acid oxidation should be minimized. In the fasting state, the opposite pathways should be activated. The regulatory control of these opposing processes is complicated, but PPARs have been shown to have a major role. PPARs (peroxisome proliferator-activated receptors) are nuclear receptors that are ligand-gated transcription factors. These proteins were initially discovered to be the binding target of small synthetic drugs called peroxisome proliferators. Later the relevant physiological ligands were found to include long chain polyunsaturated fatty acids, oxidized fatty acids, and eicosanoid derivatives of arachidonic acid (20:4Δ5,8,11,14). PPAR, in the presence of ligand binds a second protein, the retinoid X receptor (RXR) which binds 9-cis-retinoic acid). The heterodimer binds to peroxisome proliferator response element in the promoter region of genes involved in lipid transport and metabolism, and activates their transcription. Given these facts, common chronic diseases with lipid abnormalities (cardiovascular disease, diabetes, obesity) would be expected to be affected by PPARs. There are three types of PPARs: α, β, and γ. Only the major two types, α and γ, will be discussed.

<table>
<thead>
<tr>
<th>PPAR Type</th>
<th>location</th>
<th>ligand activator</th>
<th>effects</th>
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<tbody>
<tr>
<td>α</td>
<td>brown adipose tissue, liver (some in kidney, heart, and skeletal muscle)</td>
<td>long chain unsaturated fatty acid like linolenic acid, oxidized fatty acid, eicosanoids (8S-HETE, LT B4)</td>
<td>fatty acid catabolism - FA transport, FA oxidation in peroxisomes and mitochondria,</td>
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<tr>
<td>γ</td>
<td>adipose cells, some in colon</td>
<td>15-deoxy-D-prostaglandin J2</td>
<td>storage of fatty acids - lipoprotein lipase,</td>
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Fatty acids are oxidized when food is scarce, but are stored as triacylglycerides when they are abundant. PPARs \( \alpha \) and \( \gamma \) have differential effects in the fed and fasting states:

**Organ**

**Fed:** Synthesize FA, triacylglycerides. CHO and fat in circulation. Increased PPAR

**Fasting:** Oxidize FA, break down triacylglycerides. Increased PPAR

**Liver**

(PPAR-\( \alpha \))

Glc taken up by liver where it can be stored as glycogen. If glycogen reserves are high, Glc is funneled through glycolysis to pyruvate then to acetyl-CoA. Acetyl CoA then is used in the synthesis of fatty acid, which are esterified to glycerol to form TAGs. These leave liver as VLDL (very low density lipoprotein). Sterol response element binding protein (SREBP) levels increase, leading to increase in transcription of genes involved in above processes.

**Adipocyte**

(PPAR-\( \gamma \))

SREBP and PPAR-\( \gamma \) levels increases (from insulin signaling). Also SREBP activates PPAR-gene transcription. Lead to uptake of Glc and FA into fat cells (through stimulation of breakdown of blood TAGs, to fatty acids which can be imported into fat cells. Glc through glycolysis to glyceraldehyde 3P which with FAs are converted to TAGs. Increased TAGs lead to leptin release by adipocytes. (This hormone leads to decreasing storage of TAGs. (AG)

Drugs that bind to and either mimic (agonist) PPAR -\( \alpha \)-\( \gamma \)y effects are useful therapeutically in conditions characterized by lipid abnormalities (diabetes, cardiovascular disease). Drugs that bind to and activate PPAR-\( \gamma \) (Rezulin, Avandia) can lower blood glucose levels and are used to treat type II diabetes. Drugs that activate PPAR-\( \alpha \) (fibrites like gemfibrozil) can lower serum triglycerides (by stimulating liver fatty acid oxidation). Both drugs ultimately lower serum lipids.

PPARs also have an effect on plasma lipoprotein (LDL, HDL) levels. Both also might have a role in inflammation, which can promote cardiovascular disease. Fibrates, which interact with PPAR-\( \alpha \), appear to inhibit the inflammatory response mediated by the immune system by decreasing the release of protein "hormones" or cytokines, from stimulated immune cells.

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**EXTERNAI**

- Pathways for PPAR-mediated activation of gene transcription.

https://bio.libretexts.org/Bookshelves/Biochemistry/Book%3A_Biochemistry_Online_(Jakubowski)/08%3A_OXIDATION%2F%2F
• Pathway for PPAR-α-mediated activation of gene transcription

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