# Lecture 9 - Fatty Acid Metabolism

Chem 454: Regulatory Mechanisms in Biochemistry
University of Wisconsin-Eau Claire

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## Introduction

Fatty acids play several important roles:

- Building blocks for phopsholipids and glycolipids
- Target proteins to membranes
- High energy source of fuel
- Fatty acid derivatives are used as hormones and intracellular messengers

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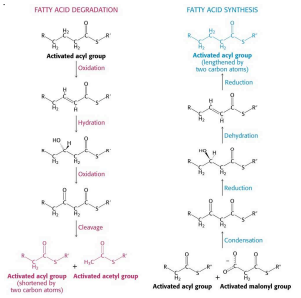
## Introduction

Overview of fatty acid synthesis

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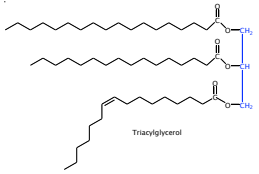
## 1. Triglycerides

Triglycerides are a highly concentrated store of energy

- 9 kcal/g *vs* 4 kcal/g for glycogen
- Glycogen is also highly hydrated, 2 g $H_2O$/g glycogen

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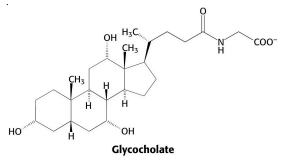
## 1.1 Pancreatic Lipases

- Dietary triacylglycerols must be broken down before being absorbed by the intestines.
- Bile salts, which act as detergents, are used to solublize the triacylglycerols




Glycocholate



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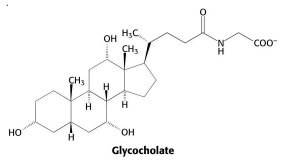


Glycocholate



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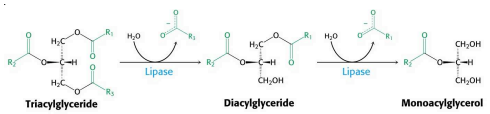
## 1.1 Pancreatic Lipases

Pancreatic lipases hydrolyze the ester bonds of the triacylglycerols while in the micelles.




Triacylglyceride Diacylglyceride Monoacylglycerol



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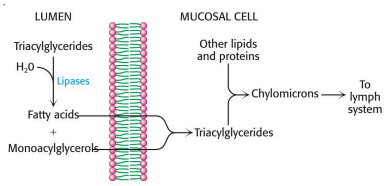
## 1.1 Chylomicrons

In the intestinal mucosal cells, the fatty acids and monoacylglycerides are resynthesized into triacylglycerides and packaged into *chylomicrons*.



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## 2. Utilization of Fatty Acids as Fuel

Three stages of processing

- Triglycerols are degraded to fatty acids and glycerol in the adipose tissue and transported to other tissues.
- Fatty acids are activated and transported into the mitochondria.
- Fatty acids are broken down into two-carbon acetyl-CoA units and fed into the citric acid cycle.



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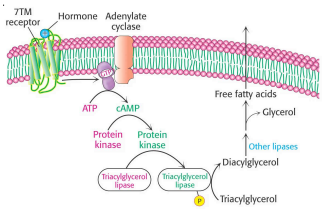
## 2.1 Breakdown of Triacylglycerols

In the adipose tissue, lipases are activated by hormone signaled phosphorylation



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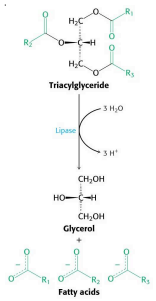
## 2.1 Breakdown of Triacylglycerols

The lipases break the triacylglycerols down to fatty acids and glycerol

- The fatty acids are transportred in the blood by serum albumin



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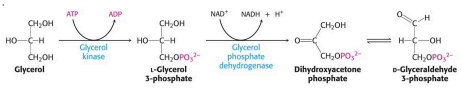
## 2.1 Breakdown of Triacylglycerols

The glycerol is absorbed by the liver and converted to glycolytic intermediates.



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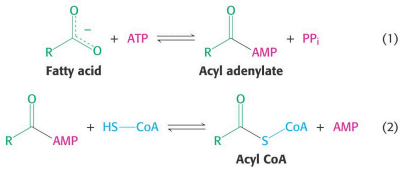
## 2.2 Activation of Fatty Acids

Acyl CoA synthetase reaction occurs in the on the mitochondrial membrane.

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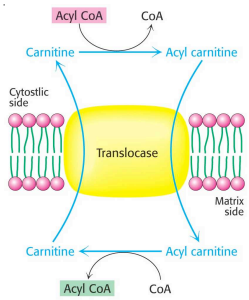
## 2.3 Transport into Mitochonrial Matrix

Carnitine carries long-chain activated fatty acids into the mitochondrial matrix

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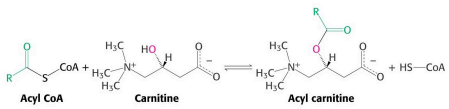


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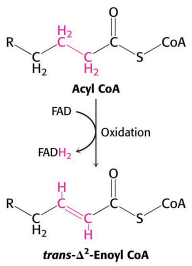
## 2.4 Fatty acid oxidation

Each round in fatty acid degradation involves four reactions

1. oxidation to *trans*-$\Delta^2$-Enoly-CoA

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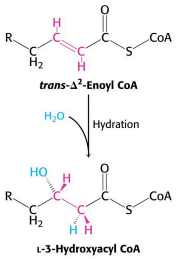
## 2.4 Fatty acid oxidation

Each round in fatty acid degradation involves four reactions

2. Hydration to L-3-Hydroxylacyl CoA



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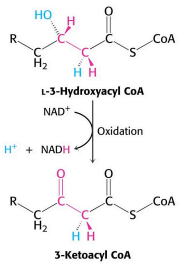
## 2.4 Fatty acid oxidation

Each round in fatty acid degradation involves four reactions

3. Oxidation to 3-Ketoacyl CoA



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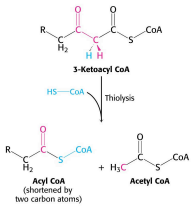
## 2.4 Fatty acid oxidation

Each round in fatty acid degradation involves four reactions

4. Thiolysis to produce Acetyl-CoA



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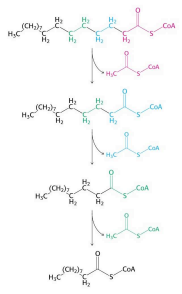
## 2.4 Fatty acid oxidation

Each round in fatty acid degradation involves four reactions

- The process repeats itself





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## 2.4 Fatty acid oxidation

Each round in fatty acid degradation involves four reactions

**TABLE 22.1 Principal reactions in fatty acid oxidation**

| Step | Reaction | Enzyme |
|---|---|---|
| 1 | Fatty acid + CoA + ATP ⟹ acyl CoA + AMP + $PP_i$ | Acyl CoA synthetase [also called fatty acid thiokinase and fatty acid:CoA ligase (AMP)] |
| 2 | Carnitine + acyl CoA ⟹ acyl carnitine + CoA | Carnitine acyltransferase (also called carnitine palmitoyl transferase) |
| 3 | Acyl CoA + E-FAD ⟶ *trans*-$\Delta^2$-enoyl CoA + E-$FADH_2$ | Acyl CoA dehydrogenases (several isozymes having different chain-length specificity) |
| 4 | *trans*-$\Delta^2$-Enoyl CoA + $H_2O$ ⟹ L-3-hydroxyacyl CoA | Enoyl CoA hydratase (also called crotonase or 3-hydroxyacyl CoA hydrolyase) |
| 5 | L-3-Hydroxyacyl CoA + $NAD^+$ ⟹ 3-ketoacyl CoA + NADH + $H^+$ | L-3-Hydroxyacyl CoA dehydrogenase |
| 6 | 3-Ketoacyl CoA + CoA ⟹ acetyl CoA + acyl CoA (shortened by $C_2$) | β-Ketothiolase (also called thiolase) |



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## 2.5 ATP Yield

The complete oxidation of the sixteen carbon palmitoyl-CoA produces 106 ATP's

Palmitoyl–CoA + 7 FAD + 7 $NAD^+$ 7 CoASH + $H_2O$ ⟶

8 Acetyl–CoA + 7 $FADH_2$ + 7 NADH + 7 $H^+$



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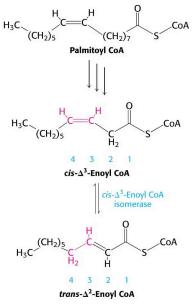
## 3.1 Special Cases

Unsaturated fatty acids (monounsaturated)



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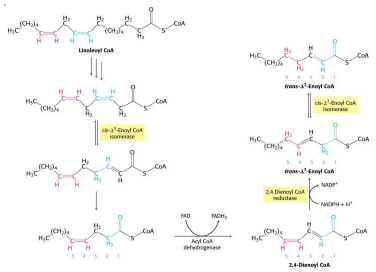
## 3.1 Special Cases

Unsaturated fatty acids (polyunsaturated)



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## 3.2 Odd-Chain (skip)





## 3.3 Propionyl-CoA (skip)





## 3.4 Peroxisomes (skip)





## 3.5 Ketone Bodies

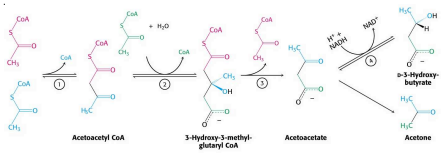
Use of fatty acids in the citric acid cycle requires carbohydrates for the the production of oxaloacetate.

During starvation or diabetes, OAA is used to make glucose

- Fatty acids are then used to make ketone bodies (acetoacetate and D-3-hydroxybutarate)

## 3.5 Ketone Bodies

Ketone bodies, acetoacetate and 3-hydroxybutarate are formed from Acetyl-CoA








## 3.6 Ketone Bodies as a Fuel Source

The liver is the major source of ketone bodies.

- It is transported in the blood to other tissues

Acetoacetate in the tissues

- Acetoacetate is first activated to acetoacetate by transferring the CoASH from succinyl-CoA.
- It is then split into two Acetyl-CoA by a thiolase reaction





## 3.7 Fatty Acids Cannot be Used to Synthesize Glucose

Even though the citric acid cycle intermediate oxaloacetate can be used to synthesize glucose, Acetyl-CoA cannot be used to synthesize oxaloacetate.

- The two carbons that enter the citric acid cycle as Acetyl-CoA leave as $CO_2$.





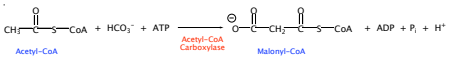
## 4. Fatty Acid Synthesis.

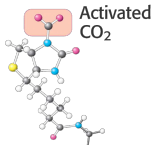
Fatty acid are synthesized and degraded by different pathways.

- Synthesis takes place in the cytosol.
- Intermediates are attached to the acyl carrier protein (ACP).
- In higher organisms, the active sites for the synthesis reactions are all on the same polypeptide.
- The activated donor in the synthesis is malonyl-ACP.
- Fatty acid reduction uses NADPH + $H^+$.
- Elongation stops at $C_{16}$ (palmitic acid)

## 4.1 Formation of Malonyl Coenzyme A

Formation of malonyl-CoA is the committed step in fatty acid synthesis.

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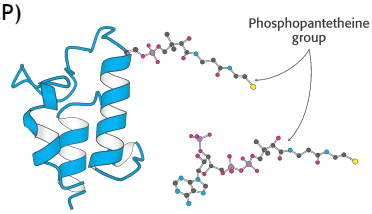
## 4.2 Acyl Carrier Protein

The intermediates in fatty acid synthesis are covalently linked to the acyl carrier protein (ACP)

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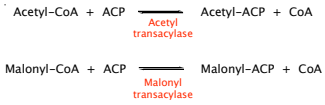
## 4.3 Elongation

In bacteria the enzymes that are involved in elongation are separate proteins; in higher organisms the activities all reside on the same polypeptide.

- To start an elongation cycle, Acetyl-CoA and Malonyl-CoA are each transferred to an acyl carrier protein

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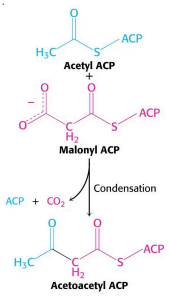
## 4.3 Elongation

Acyl-malonyl ACP condensing enzyme forms Acetoacetyl-ACP.

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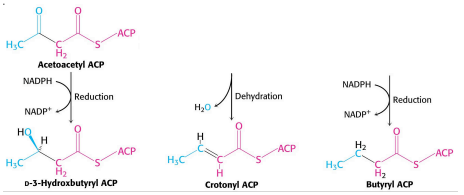
## 4.3 Elongation

The next three reactions are similar to the reverse of fatty acid degradation, except

- The NADPH is used instead of NADH and $FADH_2$
- The D-enantiomer of Hydroxybutarate is formed instead of the L-enantiomer



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## 4.3 Elongation

The elongation cycle is repeated six more times, using malonyl-CoA each time, to produce palmityl-ACP.

A thioesterase then cleaves the palmityl-CoA from the ACP.



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## 4.4 Multifunctional Fatty Acid Synthase

Domain 1
- Substrate entry (AT & MT) and condensation unit (CE)

Domain 2
- Reduction unit (DH, ER & KR)

Domain 3
- Palmitate release unit (TE)



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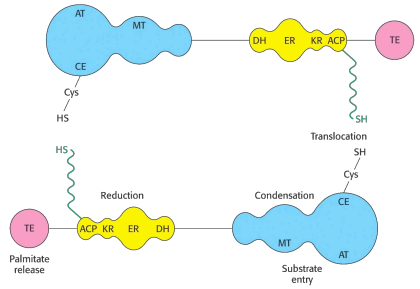
## 4.4 Multifunctional Fatty Acid Synthase



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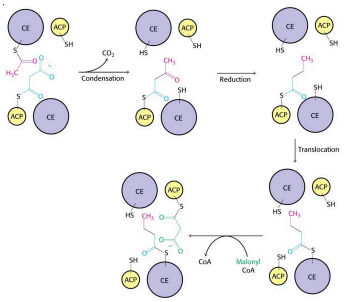
## 4.5 Fatty Acid Synthase Mechanism

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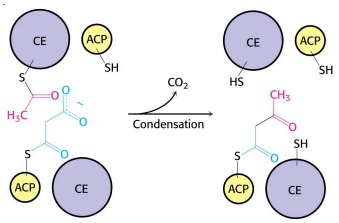
## 4.5 Fatty Acid Synthase Mechanism

Condensation of Acyl-CoA with Malonyl-CoA:

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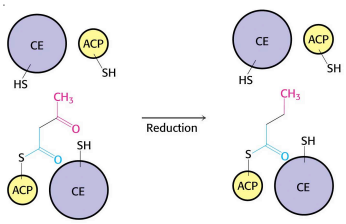
## 4.5 Fatty Acid Synthase Mechanism

Reduction of the acetoacetate unit:

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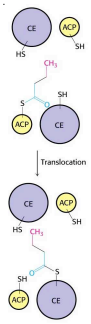
## 4.5 Fatty Acid Synthase Mechanism

Translocation to the condensing enzyme

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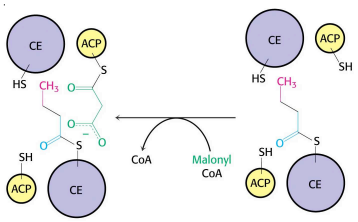
## 4.5 Fatty Acid Synthase Mechanism

Transfer of Malonyl group to the other ACP:

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## 4.6 Stoichiometry of FA synthesis

The stoichiometry of palmitate synthesis:

- Synthesis of palmitate from Malonyl-CoA

$$\text{Acetyl-CoA} + 7\ \text{malonyl-CoA} + 14\ \text{NADPH} + 20\ H^+ \longrightarrow \text{palmitate} + 7\ CO_2 + 14\ NADP^+ + 8\ \text{CoA} + 6\ H_2O$$

- Synthesis of Malonyl-CoA from Acetyl-CoA

$$7\ \text{Acetyl-CoA} + 7\ CO_2 + 7\ \text{ATP} \longrightarrow 7\ \text{Malonyl-CoA} + 7\ \text{ADP} + 7\ P_i + 14\ H^+$$

- Overall synthesis

$$\text{Acetyl-CoA} + 7\ \text{ATP} + 14\ \text{NADPH} + 6\ H^+ \longrightarrow \text{palmitate} + 14\ NADP^+ + 8\ \text{CoA} + 6\ H_2O + 7\ \text{ADP} + 7\ P_i$$

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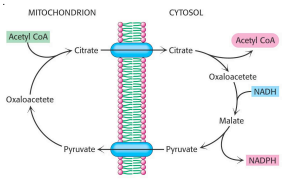
## 4.7 Citrate Shuttle

Acetyl-CoA is synthesized in the mitochondrial matrix, whereas fatty acids are synthesized in the cytosol

- Acetyl-CoA units are shuttled out of the mitochondrial matrix as citrate:




$$\text{Citrate} + \text{ATP} + \text{CoA} + H_2O \xrightarrow[\text{Lyase}]{\text{Citrate}} \text{Acetyl-CoA} + \text{ADP} + P_i + \text{Oxaloacetate}$$

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## 4.8 Sources of NADPH

The malate dehydrogenase and $NADP^+$-linked malate enzyme reactions of the citrate shuttle exchange NADH for NADPH

$$\text{Oxaloacetate} + \text{NADH} + H^+ \xrightarrow[\text{Dehydrogenase}]{\text{Malate}} \text{Malate} + NAD^+$$

$$\text{Malate} + NADP^+ \xrightarrow[\text{Enzyme}]{NADP^+\text{-linked Malate}} \text{Pyruvate} + CO_2\ \text{NADPH}$$

$$\text{Pyruvate} + CO_2 + \text{ATP} + H_2O \xrightarrow[\text{Carboxylase}]{\text{Pyruvate}} \text{Oxaloacetate} + \text{ADP} + P_i + 2\ H^+$$

$$NADP^+ + \text{NADH} + \text{ATP} + H_2O \longrightarrow \text{NADPH} + NAD^+ + \text{ADP} + P_i + H^+$$

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## 4.9 Fatty Acid Synthase Inhibitors (skip)

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## 4.10 Variations on a Theme (skip)

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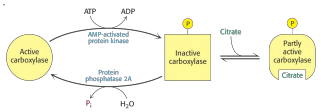
## 5. Regulation of Fatty Acid Synthesis

Regulation of Acetyl carboxylase

- Global
  - + insulin
  - - glucagon
  - - epinephrine
- Local
  - + Citrate
  - - Palmitoyl-CoA
  - - AMP

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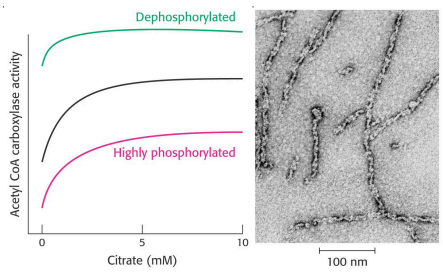
## 5.1 Regulation of Fatty Acid Synthesis







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## 6. Elongation and Unsaturation

Endoplasmic reticulum systmes introduce double bonds into long chain acyl-CoA's

- Reaction combines both NADH and the acyl-CoA's to reduce $O_2$ to $H_2O$.





## 6.1 Elongation and Unsaturation

Elongation and unsaturation convert palmitoyl-CoA to other fatty acids.

- Reactions occur on the cytosolic face of the endoplasmic reticulum.
- Malonyl-CoA is the donor in elongation reactions





## 6.2 Eicosanoid Hormones

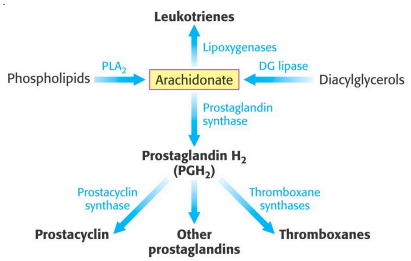
Eicosanoid horomones are synthesized from arachadonic acid (20:4).

- Prostaglandins
  - 20-carbon fatty acid containing 5-carbon ring
  - Prostacyclins
  - Thromboxanes
- Leukotrienes
  - contain three conjugated double bonds

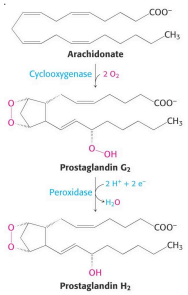




## 6.2 Eicosanoid Hormones



## 6.2 Eicosanoid Hormones



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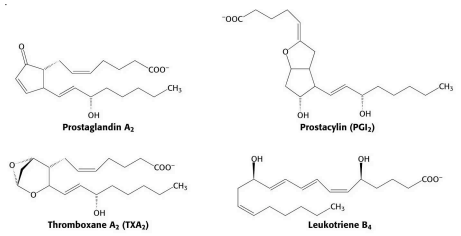
## 6.2 Eicosanoid Hormones



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