BCH 3000
(Prinsip Biokimia)
Semester 2 - 2012-2013
(Lipid Metabolism)

Biosintesis lipid: sistem mitokondria dan ekstra-mitokondria. Edaran dan enzim yang terlibat. Sintesis asid lemak tepu dan tak tepu. Sintesis kolesterol. Pengawalan sintesis
Lipid digestion

- Sources
- Degradation, absorption and transport of lipid
- Importance of bile salts
- Lipoprotein complex, biosynthesis, functions and uptake
- Control/regulation
A large and diverse group of naturally occurring organic compounds that are related by their solubility in nonpolar organic solvents (e.g. ether, chloroform, acetone & benzene) and general insolubility in water.

- are all esters of moderate to long chain fatty acids = TRIACYLGLYCEROL = TRIGLYCERIDES
- Acid or base-catalyzed hydrolysis yields the component fatty acid + the alcohol component of the lipid- ie. glycerol
IN MAMMALS

- 5 - 25% or more of body weight are fat
- TG contains a lot of saturated fatty acids
- Present in adipose tissue in fat globules

Figure 9-2. Scanning electron micrograph of adipocytes. Each adipocyte contains a fat globule that occupies nearly the entire cell. [Fred E. Hossler/Visuals Unlimited.]
PLANT FATS

• TG contains a lot of **unsaturated fatty acids** → liquid form (oil)

• Olive oil, coconut oil, palm oil – liquid at room temperature
Triacylglycerides are (TG) composed of a glycerol backbone to which 3 fatty acids are esterified.

Basic composition of a triacylglyceride. The glycerol backbone is in blue.
Basic Structure of Triacylglycerides

- Aliphatic monocarboxylic acids derived from or contained in esterified form in an animal or vegetable fat, oil or wax
- Can be saturated and unsaturated, depending on double bonds.
- Also, they also differ in length
- Their main use is for the long term energy storage
<table>
<thead>
<tr>
<th>Formula</th>
<th>Common Name</th>
<th>Chain Length</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₃(CH₂)₁₀CO₂H</td>
<td>lauric acid (12C)</td>
<td>12C</td>
</tr>
<tr>
<td>CH₃(CH₂)₁₂CO₂H</td>
<td>myristic acid (14C)</td>
<td>14C</td>
</tr>
<tr>
<td>CH₃(CH₂)₁₄CO₂H</td>
<td>palmitic acid (16C)</td>
<td>16C</td>
</tr>
<tr>
<td>CH₃(CH₂)₁₆CO₂H</td>
<td>stearic acid (18C)</td>
<td>18C</td>
</tr>
<tr>
<td>CH₃(CH₂)₁₈CO₂H</td>
<td>arachidic acid (20C)</td>
<td>20C</td>
</tr>
</tbody>
</table>
# UNSATURATED FATTY ACIDS

<table>
<thead>
<tr>
<th>Formula</th>
<th>Common Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{CH}_3(\text{CH}_2)_5\text{CH}=\text{CH}(\text{CH}_2)_7\text{CO}_2\text{H} ) ((16:1^{\Delta 9}))</td>
<td>palmitoleic acid</td>
</tr>
<tr>
<td>( \text{CH}_3(\text{CH}_2)_7\text{CH}=\text{CH}(\text{CH}_2)_7\text{CO}_2\text{H} ) ((18:1^{\Delta 9}))</td>
<td>oleic acid</td>
</tr>
<tr>
<td>( \text{CH}_3(\text{CH}_2)_4\text{CH}=\text{CHCH}_2\text{CH}=\text{CH}(\text{CH}_2)_7\text{CO}_2\text{H} )</td>
<td>linoleic acid ((18:2^{\Delta 9,12}))</td>
</tr>
<tr>
<td>( \text{CH}_3\text{CH}_2\text{CH}=\text{CHCH}_2\text{CH}=\text{CHCH}_2\text{CH}=\text{CH}(\text{CH}_2)_7\text{CO}_2\text{H} ) ((18:3^{\Delta 9,12,15}))</td>
<td>linolenic acid</td>
</tr>
<tr>
<td>( \text{CH}_3(\text{CH}_2)_4(\text{CH}=\text{CHCH}_2)_4(\text{CH}_2)_2\text{CO}_2\text{H} )</td>
<td>arachidonic acid ((20:4^{\Delta 5,8,11,14}))</td>
</tr>
</tbody>
</table>
Lipid Function and Metabolism Summary

Lipids Stored as Adipose Tissue
- Insulation
- Support vital organs
- Generate heat

Lipid Ingestion
- Digestion and Absorption
  - Stored as energy reserve
- Lipids in Blood as Lipoproteins
  - Synthesized from carbohydrates and proteins
  - Oxidize for energy
  - Convert to brain and nerve tissue
  - Excreted in feces
Comparison of Energy sources

**Glycogen**
- Typically store a one day supply
- Less energy per gram than for fat
- About 70% by weight is water

**Fat**
- Usually store a one month supply
- May store much more
- More energy per gram – no water
- Released after glycogen is gone
3 primary sources of triacylglycerols (TG)

1. Dietary triacylglycerols (TG)
2. TG synthesised in the liver
3. TG stored in fat cells

Fat From Diet

- lipid intake ~ 60-150 g per day
- more than 90% is TG
- the rest - phospholipid, cholesterol and free fatty acids)
Fatty acids must be delivered to cells where \( \beta \)-oxidation occurs

- Liver
- Heart
- Skeletal muscles
Digestion of Lipids

- Dietary fats do not dissolve in water
- \[ \therefore \text{ they are not easily broken down by fat-digesting enzymes (lipase)} \]
- \[ \therefore \text{ fats tend to take longer to digest than carbohydrates or proteins} \]
Fat Breakdown In The Small Intestine

- Fat molecules must be broken down into smaller more manageable molecules – How?
- digestive enzyme lipase, which enters the duodenum from the pancreas
- Lipase $\rightarrow$ fatty acid molecules and glycerol molecules
- However, fat is insoluble in water $\rightarrow$ pancreatic lipase enzymes cannot attack them, since lipase is a water soluble enzyme and can only attack the surface of the fat molecules
- How overcome???
To overcome this problem the digestive system uses a substance called **bile**

- produced in the **liver** but stored in the **gallbladder**
- Enters the duodenum via the **bile duct**
- Bile **emulsifies** fats - meaning, it disperses them into small droplets which then become suspended in the watery contents of the digestive tract.
- Emulsification allows lipase to gain easier access to the fat molecules and thus accelerates their breakdown and digestion.
Overview of lipid digestion
Hydrolysis of triacylglycerols

- A protein *colipase* is required to aid binding of the pancreatic lipase at the lipid-water interface.
- Monoacylglycerols, fatty acids, and cholesterol are absorbed by intestinal epithelial cells. Within intestinal epithelial cells, triacylglycerols are resynthesized from fatty acids and monoacylglycerols.
After hydrolysis

- Fatty acids & monoacylglycerols pass through the wall of the small intestine
- They are then reassembled into triacylglycerols (i.e. bentuk semula)
- A protein is added and chylomicrons are produced
- Chylomicrons are then passed via the lymph system to the blood
Absorption of lipids in intestines

- Triacylglycerols are digested into monoacylglycerols, fatty acids, and glycerol.
- These compounds are absorbed by the intestinal mucosa cells and resynthesized into triacylglycerols.
- The resynthesized triacylglycerols, along with phosphoglycerols, cholesterol, and proteins, form chylomicrons.
- Chylomicrons are transported through the lymph to the liver via the blood.
- Free fatty acids are transported in the blood bound to albumin, a serum protein secreted by the liver.

- Most other lipids are transported in the blood as part of complex particles called lipoproteins.
Lipoproteins

- differ in their content of proteins and lipids
- They are classified based on their density:
  a. chylomicron (largest; lowest in density due to high lipid/protein ratio; highest in triacylglycerols as % of weight)
  b. VLDL (very low density lipoprotein; 2nd highest in triacylglycerols as % of weight)
  c. IDL (intermediate density lipoprotein)
  d. LDL (low density lipoprotein, highest in cholesteryl esters as % of weight)
  e. HDL (high density lipoprotein, highest in density due to high protein/lipid ratio)
Structure of chylomicron
Fate of dietary phospholipids

- Similar to that of triacylglycerols
- Hydrolysed by pancreatic phospholipase secreted into the intestine
- Major phospholipase is phospholipase $A_2$ – catalyse the hydrolysis of the ester bond at C-2 of a glycerophospholipid $\rightarrow$ lypoosphoglycercide and a fatty acid
- Lysophosphoglycercides are absorbed by the intestine and reesterified to glycerophospholipids in intestinal cells
Cleavage site

Enzymic action of phospholipase A_2

Phospholipase A_2

Fatty acids + Lysophospholipids

Eicosanoids

PAF
Fate of dietary cholesterol

- Most dietary cholesterol are unesterified.
- Dietary cholesterol that are esterified are hydrolysed in the lumen by the action of esterase.
- Free cholesterol = insoluble in water – solubilized by bile salts for absorption.
What happens to the fatty acids??
Triacylglycerols

General view of what happens to the fatty acids
Fatty acids must be delivered to cells where β-oxidation occurs

- Liver
- Heart
- Skeletal muscles
β-Oxidation of fatty acids

- **Cyclic series of reactions**
- **Occur within the mitochondria**
- **End result = two carbon units being hydrolysed from the fatty acid chain with each cycle = acetyl CoA**
- **With each oxidation cycle, a molecule of NAD is reduced to NADH and one FAD is reduced to FADH →→→ electron transport chain → ATP synthesis.**
- **The acetyl CoA are oxidised to CO₂ in the citric acid cycle →→→ further ATP synthesis.**
Triacylglycerols

General view of what happens to the fatty acids
The first phase = Activation step = conversion of the fatty acids into fatty acyl-CoA

Requires energy - occurs in the cytosol
Activation step

- Fatty acyl CoA then enters mitochondria
- But, Inner mitochondrial membrane is \textit{impermeable} to long chain acyl CoA molecules so a transport system is required
- i.e via carnitine
Fatty acids are cut through β-oxidation of fatty acyl-CoA – 4 reactions

1. Formation of trans-α,β double bond through dehydrogenation – by acyl-CoA dehydrogenase

2. Hydration of double bond – enoyl-CoA hydratase → 3-L-hydroxyacyl-CoA

3. Dehydrogenation by 3-L-hydroxyacyl-CoA dehydrogenase to form β-ketoacyl-CoA

4. Cleavage of Cα-Cβ with CoA by β-ketoacyl-CoA thiolase (thiolysis) → acetyl-CoA + new acyl-CoA with minus 2 carbon atoms
**β-Oxidation**

- Oxidation
- Hydration
- Thiolysis

1. acyl SCoA
2. acyl SCoA dehydrogenase
3. trans enoyl SCoA
4. enol SCoA hydratase
5. L-3-hydroxyacyl SCoA dehydrogenase
6. 3-ketoacyl SCoA thiolase
7. N-2 acyl SCoA
8. acetyl SCoA

- Oxidation
- Hydration
- Thiolysis
After activation, fatty acid CoA esters enter the mitochondria for further processing.

- Fatty acids are recycled through the same five step process.
- Two carbons are removed each time.
- An acetyl CoA is produced with each pass.
- Acetyl CoA then goes on to the citric acid cycle for energy production.
Fatty acid

\[ \text{NAD}^+ \text{ & FAD} \quad \text{NADH} \text{ & FADH}_2 \]

Acetyl CoA

\[ \text{NAD}^+ \text{ & FAD} \quad \text{NADH} \text{ & FADH}_2 \]

Citric acid cycle

Electron transport chain

Proton gradient

ATP production
Why called $\beta$-Oxidation?

In this process, the $\beta$ carbon on the fatty acid is oxidized via a ketone intermediate to the level of a thioester.

$\beta$ carbon

$\alpha$ carbon

$\beta$ carbon

$\alpha$ carbon
How many ATPs produced? - e.g. Stearic acid

- Acetyl CoA further oxidised by **Citric acid Cycle**
- **FADH$_2$** and **NADH** converted to ATP via **electron transport system** & **oxidative phosphorylation**
Energy from fatty acids – stearic acid

<table>
<thead>
<tr>
<th>Step</th>
<th>ATP/Unit</th>
<th>Total ATP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activation step</td>
<td>-2</td>
<td></td>
</tr>
<tr>
<td>9 acetyl CoA</td>
<td>12</td>
<td>90</td>
</tr>
<tr>
<td>8 FADH$_2$</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>8 (NADH + H$^+$)</td>
<td>3</td>
<td>20</td>
</tr>
<tr>
<td><strong>Total ATP</strong></td>
<td></td>
<td><strong>120</strong></td>
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Degradation of palmitic acid

1) \( \text{CH}_3\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CO}\text{-CoA} \)
2) \( \text{CH}_3\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CO}\text{-CoA} + \text{CH}_3\text{-CO}\text{-CoA} \)
3) \( \text{CH}_3\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CO}\text{-CoA} + \text{CH}_3\text{-CO}\text{-CoA} \)
4) \( \text{CH}_3\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CO}\text{-CoA} + \text{CH}_3\text{-CO}\text{-CoA} \)
5) \( \text{CH}_3\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CO}\text{-CoA} + \text{CH}_3\text{-CO}\text{-CoA} \)
6) \( \text{CH}_3\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CO}\text{-CoA} + \text{CH}_3\text{-CO}\text{-CoA} \)
7) \( \text{CH}_3\text{-CH}_2\text{-CH}_2\text{-CO}\text{-CoA} + \text{CH}_3\text{-CO}\text{-CoA} \)

After the 7th round you are left with an 8th acetyl CoA (\( \text{CH}_2\text{-CO}\text{-CoA} \)).

Palmitoyl CoA + 7FAD + 7NAD + 7CoA + 7H\(_2\)O \(\rightarrow\) 8Acetyl CoA + 7FADH\(_2\) + 7NADH + 7H\(^+\)
Most acetyl Co-A are routed to TCA cycle.

During starvation OAA from TCA cycle is required to form glucose during gluconeogenesis.

Excess Acetyl CoA from fatty acid oxidation is routed to form ketone bodies i.e. acetoacetate, acetone and β-hydroxybutyrate.

Ketone bodies are formed in the liver, transported easily (water soluble) and metabolized in other organs.

Reconverted to acetyl CoA in mitochondria.
Figure 16.13
Biosynthesis of β-hydroxybutyrate, acetoacetate, and acetone.

3-Hydroxy-3-methylglutaryl CoA (HMG CoA)

β-Hydroxybutyrate
Food (diet) is not the only source of fat

All organisms can synthesise fatty acids for long term energy storage & membrane structure

In humans, excess acetyl-CoA is converted to fatty acid esters

Synthesis of fatty acids is similar to degradation but the location is different.
Fatty acid synthesis occurs primarily in the cytoplasm of these tissues:

a. liver
b. adipose (fat) - adipocytes
c. central nervous system
d. lactating mammary gland
Differences between fatty acid oxidation and synthesis

a. Oxidation in mitochondria & peroxisomes; synthesis in cytosol

b. Active intermediates (thioesters) in oxidation = CoA derivatives. In synthesis, intermediates are thioesters to acyl carrier protein (ACP)

c. Oxidation carried by separate enzymes while synthesis carried out by multifunctional protein of two identical polypeptide chains
d. Oxidation and synthesis proceed in **two-carbon steps**

e. Oxidation results in a **2-carbon product**; synthesis requires a **3-carbon substrate** (malonyl-CoA) which transfers a 2-carbon unit to the growing chain; CO$_2$ released

f. Reducing power for oxidation depends on **NAD$^+$** and **ubiquinone**; synthesis depends on **NADPH**
Fatty acid synthesis is the process of combining eight two-carbon fragments (acetyl groups from acetyl CoA) to form a 16-carbon saturated fatty acid, palmitate.

Palmitate can then be modified to give rise to the other fatty acids. These modifications may include:

1. chain elongation to give longer fatty acids, such as the 18-carbon stearate.

2. desaturation, giving unsaturated fatty acids
Fatty acid synthesis in eukaryotes – 3 stages

i. Mitochondrial acetyl-CoA transported into cytosol

ii. Carboxylation of acetyl-CoA $\Rightarrow$ malonyl-CoA = substrate for elongation that extend the fatty acyl chain

iii. Assembly of fatty acid chain – by fatty acid synthase

8 acetyl CoA + 7 ATP + 14 (NADPH + H$^+$) $\Rightarrow$ palmitate (16:0)$^+$
8CoA + 7(ADP+P$_i$) + 14 NADP$^+$ + 6H$_2$O
**BIOSYNTHESIS OF FATTY ACIDS**

- **Synthesis** – in **cytosol** – requires acetyl-CoA

- **Where does acetyl-CoA come from?**
  - Glycolytic breakdown of glucose
  - Also from breakdown of amino acids
  - β-oxidation of fatty acids

```
glycolysis

\[
glucose \rightarrow 2 \text{pyruvate} \rightarrow 2 \text{acetyl CoA}
\]

dehydrogenase

Glucose is the major source of acetyl CoA for fatty acid synthesis.
```
Acetyl coenzyme A, showing its constituents
i. In majority of instances the saturated straight-chain C16, **palmitic acid** is first synthesised

ii. All other fatty acids are made by **modification** of palmitic acid.

iii. **Acetyl-CoA** is the direct source of all carbon atoms for this synthesis

iv. In mammalian systems, the sequence of reactions is carried out by **fatty acid synthase**
i. Fatty acids are synthesized in a repetitive process (spiral pathway) in which 2-carbon units are added to the growing end of a hydrocarbon chain.

ii. begins with the creation Acetoacetyl ACP (4 C) –How?? - by the condensation of two carbons from acetyl CoA (acetyl ACP in eukaryotes) and another two carbon compound from the 3-carbon compound in malonyl ACP ➔ 3-ketoacyl compound (= Acetoacetyl ACP (4 C))

iii. 3-ketoacyl compound is repetitively elongated by additional 2-carbon acetyl units, with reduction and dehydration steps in each cycle.
● The most common product of fatty acid synthesis in plants and animals = **palmitate** (16:0)

● But also cells contain
  ○ Longer-chain fatty acids (e.g. stearate)
  ○ Unsaturated fatty acids (e.g. oleate)

● ∴ palmitate produced by the fatty acid synthase is modified – 3 processes – **elongation, desaturation & hydroxylation**

● **Synthesis of these requires many enzymes in the endoplasmic reticulum & mitochondria**
The overall reaction:

\[
2 \text{NADPH} + 2 \text{H}^+ + \text{HO}_2\text{C}-\text{CH}_2-\text{C} \sim \text{S-CoA} + \text{R-C} \sim \text{S-CoA} \rightarrow \text{malonyl CoA} + \text{long chain fatty acyl CoA}
\]

\[
\text{R-CH}_2-\text{CH}_2-\text{C} \sim \text{S-CoA} + 2 \text{NADP}^+ + \text{CO}_2 + \text{H}_2\text{O} + \text{CoASH}
\]

Fatty acyl-CoA lengthened by 2 carbons
The overall reaction:

\[ \text{NADH} + \text{NADPH} + 2 \text{H}^+ + \text{CH}_3-\text{C} \sim \text{S-CoA} + \text{R-} \text{C} \sim \text{S-CoA} \rightarrow \text{acetyl CoA} + \text{long chain fatty acyl CoA} \]

\[ \text{R-CH}_2-\text{CH}_2-\text{C} \sim \text{S-CoA} + \text{NADP}^+ + \text{NAD}^+ + \text{H}_2\text{O} + \text{CoASH} \]

Fatty acyl-CoA lengthened by 2 carbons
Ketone bodies

- Under normal conditions - healthy individuals – $\beta$-oxidation produces acetyl-CoA $\rightarrow$ citric acid cycle
- Normal conditions = proper balance of carbohydrate and fatty acid degradation – carbohydrate provide at least half of the energy
- Under
  - Fasting
  - Starvation
  - Untreated diabetes mellitus
  - Low carbohydrate diet

Excess acetyl-CoA because of excessive breakdown of fatty acids
Ketone bodies

- The common factor in all conditions = lack of carbohydrate or impaired utilization of CHO (glucose)
- Without the availability of carbohydrate, fatty acids become the fuel molecule of choice for heart, skeletal muscle and liver
- Brain – cannot utilize fatty acids – require high & continuous supply of glucose – gluconeogenesis
- Excessive fatty acid catabolism leads to
  1. Excessive acetyl-CoA
  2. Low levels of oxaloacetate
General view of fatty acid metabolism
Ketone bodies

- Produced from excess acetyl-CoA
- Produced via ketogenesis – in mitochondria
  
  1. Acetoacetate
  2. D-β-hydroxybutyrate
  3. Acetone
Ketogenesis
Cholesterol is the starting point for the synthesis of many other biomolecules

- **Bile salts** – polar steroid derivatives
- **Vitamin D3** – cholecalcioferol
- **Steroid hormones**
  - Progesterone
  - Glucocorticoids
  - Mineralcorticoids
  - Androgens
  - Estrogens
Cholesterol metabolism

- Cholesterol
  - Bile salts
  - Progesterone
    - Glucocorticoids
    - Mineralocorticoids
  - Vitamin D
    - Androgens
    - Estrogens
Cholesterol is a precursor for other important steroid molecules: the bile salts, steroid hormones, and vitamin D.

### Bile Salts

- highly effective *detergents* because they contain both polar and nonpolar regions.
- synthesized in the *liver*, stored and concentrated in the *gall bladder*, and then released into the *small intestine*.
- Bile salts, the major constituent of bile, *solubilize* *dietary lipids*
Cholesterol is the precursor of the five major classes of **steroid hormones**:

1. Progestagens
2. Glucocorticoids
3. Mineralocorticoids
4. Androgens and
5. Estrogens

These hormones are **powerful signal molecules** that regulate a host of organismal functions.
Steroid Hormones.

- are small and **hydrophobic**
- **derived from cholesterol**, including estrogen, progesterone, testosterone, and cortisol.
- Since they are small and hydrophobic, they can diffuse through the cell membrane.
- These hormones bind steroid **hormone receptors** after they have diffused into the cell through the plasma membrane.
1. Binding of steroid hormone to receptor
2. Translocation of steroid-receptor complex to nucleus
3. Binding of complex to DNA regulatory site
4. Transcription
5. Translation

Source: "Module 6," <http://www.thepepproject.net/>
Steroid Hormones.

- The hormone bound receptors enter the nucleus and bind to target regions in genes that regulate transcription, turning the genes on or off.
- Steroid hormone signals are changes in gene transcription and protein expression caused by the steroid hormone receptors.
1. **Progestagen – e.g. Pogesterone**

- prepares the lining of the uterus for implantation of an ovum
- also essential for the maintenance of pregnancy.
2. **Androgens** – e.g. testosterone
   - male secondary sex characteristics,

3. **Estrogens** – e.g. estradiol
   - are required for the development of *female secondary sex characteristics*.
   - along with progesterone, also participate in the *ovarian cycle*
4. **Glucocorticoids – e.g. cortisol**

- promote **gluconeogenesis** and the formation of glycogen
- enhance the **degradation of fat and protein**, and inhibit the inflammatory response.
- They enable animals to **respond to stress** —indeed, the absence of glucocorticoids can be fatal.

![Cortisol molecular structure](image)
5. **Mineralocorticoids (primarily aldosterone)**

- act on the **distal tubules** of the kidney to increase the reabsorption of $\text{Na}^+$ and the excretion of $\text{K}^+$ and $\text{H}^+$, which leads to an **increase in blood volume and blood pressure**

![Aldosterone molecule](attachment:image.png)
The major **sites** of synthesis of these classes of hormones

- Progestagens - corpus luteum;
- estrogens - ovaries
- androgens – testes and
- glucocorticoids and mineralocorticoids - adrenal cortex
Cholesterol

Cortisol
Glucocorticoid

Progesterone
Sex steroids

Androstenedione