Hormonal regulation of lipid metabolism

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Regulation in general

- A) Short term (response time of minutes or less):
  - substrate availability
  - allosteric interactions
  - covalent modifications (phosphorylation/dephosphorylation)

- B) Long-term (response time of hours or days):
  - changes in the rate of protein (enzyme) synthesis or breakdown

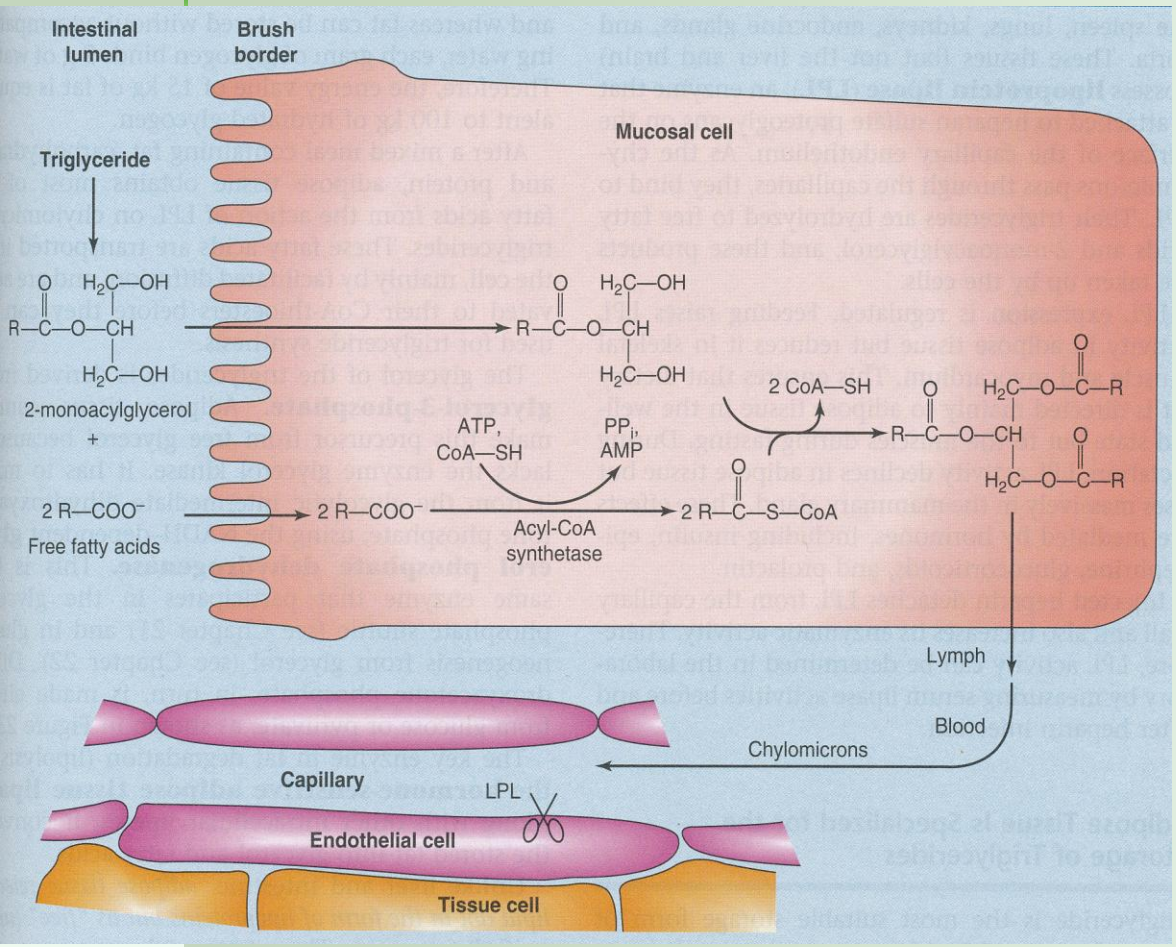
Regulation of lipid metabolism

- Involves all the aforementioned mechanisms
- Regulation – in response to the differing energy needs and dietary states of an organism
- Pancreatic α cells respond to the low blood Glc concentration of the fasting and energy-demanding states by secreting glucagon; the β cells respond to the high blood Glc conc. of the fed and resting states by secreting insulin
- Targets: enzymes of FA synthesis and oxidation

Lipid metabolism

- Main processes:
  - 1) digestion, absorption, and transport of dietary fat
  - 2) generation of metabolic energy from fat:
    - a) lipolysis, b) β-oxidation
  - 3) storage of excess fat in adipose tissue

1) Absorption and transport



- The main products of fat digestion are free **FA** and **2-monoacylglycerols** (produced by the action of pancreatic lipase)
- After absorption, FA is activated to **acyl-coenzyme A** (in the ER) which then reacts with 2-monoacylglycerol to form **triacylglycerol**
- In the ER, TGs are assembled into **chylomicrons** that are collected by the lymph and carried to the blood stream

- TGs in chylomicrons are utilized by adipose tissue, heart, skeletal muscle, lactating mammary gland and, to a lesser extent, by the spleen, lungs, kidneys…

- These tissues (but not the liver and brain!) express **lipoprotein lipase** (LPL), attached to the surface of the capillary endothelium, that hydrolyzes TGs to FA and 2-monoacylglycerols; the products are taken up by the cells

Regulation at the level of LPL

- In the *adipose tissue*, the amount of LPL is **increased** by **feeding/ insulin** and **decreased** by **starvation**

x

- In contrast, the amount of LPL in *heart* is **decreased** by **insulin** and **increased** by **starvation**

dietary fat is directed mainly to the adipose tissue (for storage) in the well-fed state but to the muscles during fasting (for oxidation)

2a) FA release from adipose tissue

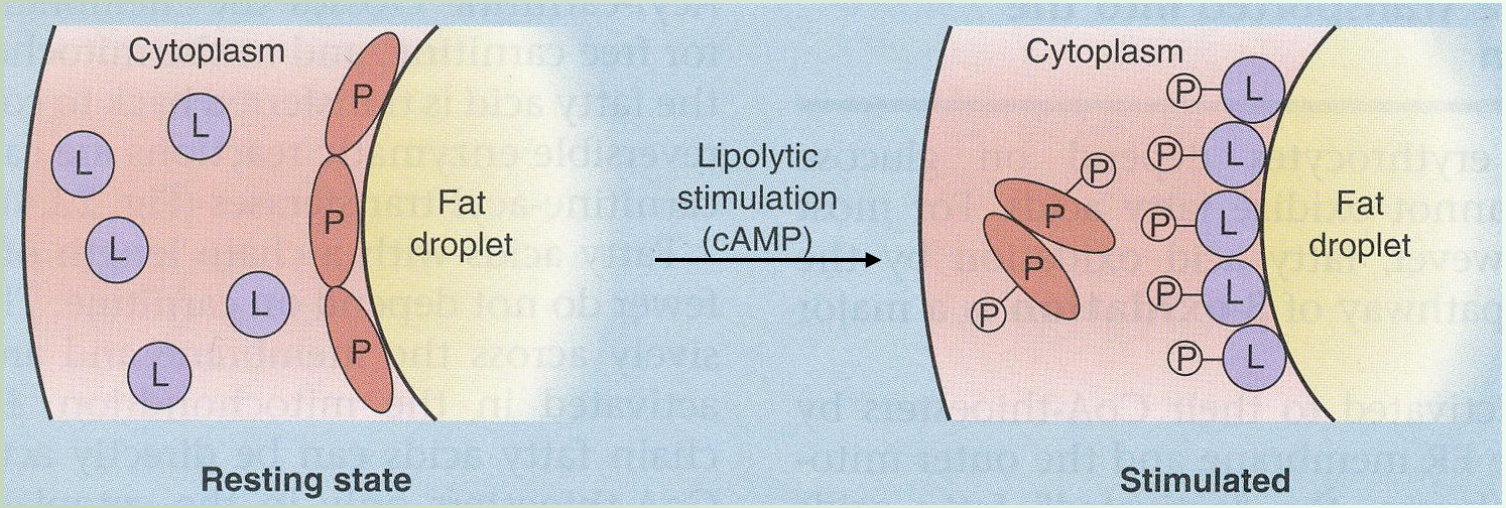
- Hormone-sensitive lipase converts the fat stored in adipose tissue into glycerol and FAs that are transported to distant sites bound to serum albumin (x liver and intestine release lipids in the form of lipoproteins)

- The hydrolysis rate controls the concentration of FAs in the blood and thus regulates FA oxidation

Regulation at the level of hormone-sensitive lipase

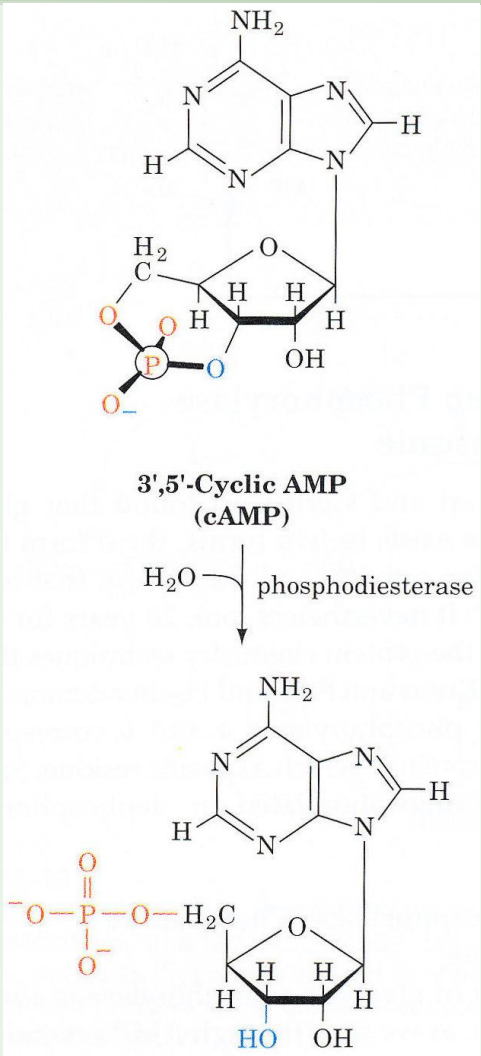
- A) Norepinephrine, epinephrine, and glucagon released during physical exercise, stress, or fasting stimulate lipolysis through the β-receptors, cAMP, PKA, and HSL $\Rightarrow \uparrow$ blood FA levels
  - $\Rightarrow$ stimulation of β-oxidation in other tissues (liver, muscle)
  - $\Rightarrow$ stimulation of production of ketone bodies in the liver

Mechanism



- In the resting state, the hormone-sensitive lipase is cytoplasmic and the surface of the fat droplet is covered by the protein perilipin.
- The cAMP-stimulated protein kinase A phosphorylates both perilipin and lipase $\Rightarrow$ perilipin detaches from the fat droplet x lipase binds.

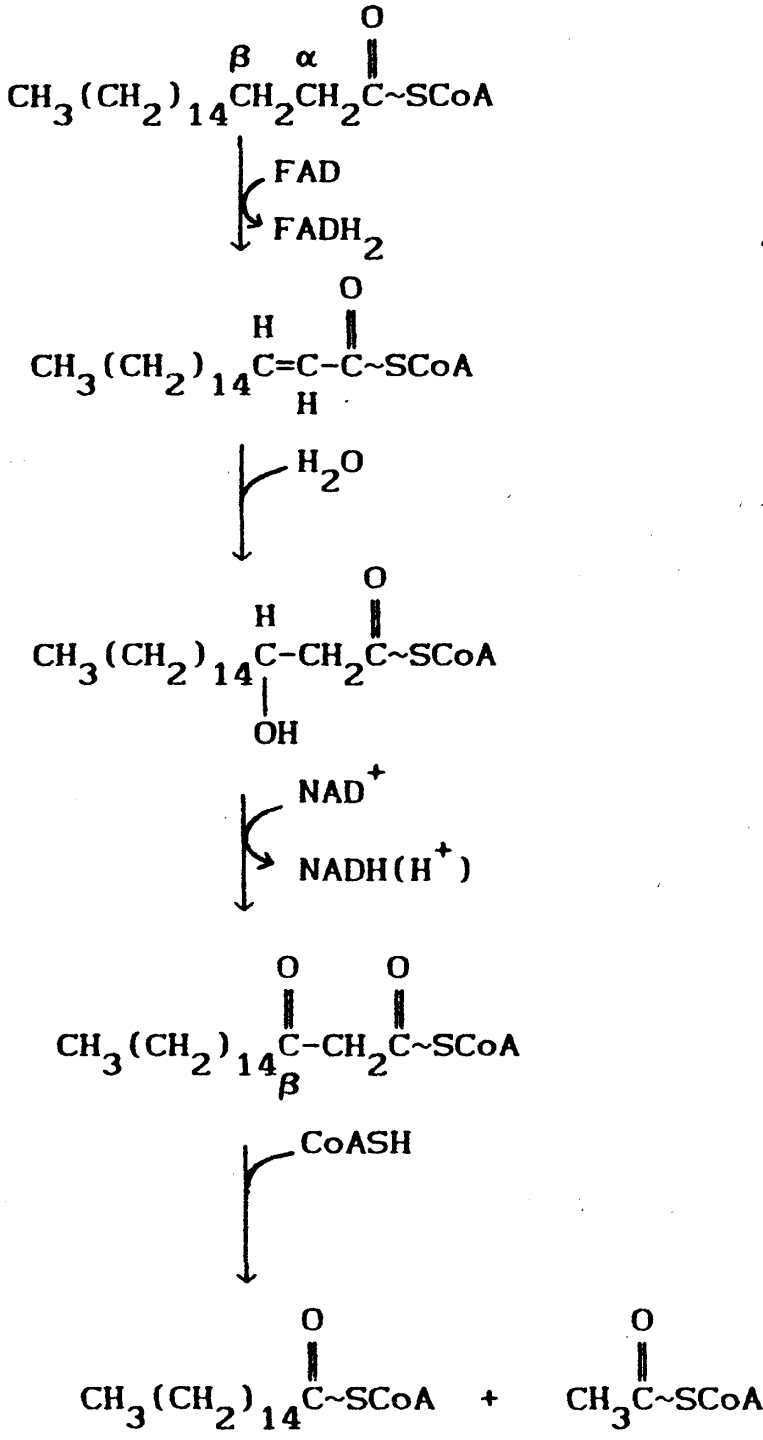
- B) Insulin is released after Glc and AA intake and signals the abundance of dietary nutrients that are eligible for storage
  - Insulin inhibits HSL through phosphodiesterase degrading cAMP
- Thus, the glucagon:insulin ratio is of prime importance in regulation of lipid metabolism



- C) Glucocorticoids, growth hormone, and the thyroid hormones facilitate lipolysis by inducing the synthesis of lipolytic proteins:
  - glucocorticoids induce the synthesis of the hormone-sensitive lipase

2b) β-oxidation

- FAs are activated to acyl-CoA by enzymes on the ER membrane and transported into the mitochondrion by carnitine
- β-oxidation produces:
  - acetyl-CoA, NADH, $FADH_2$

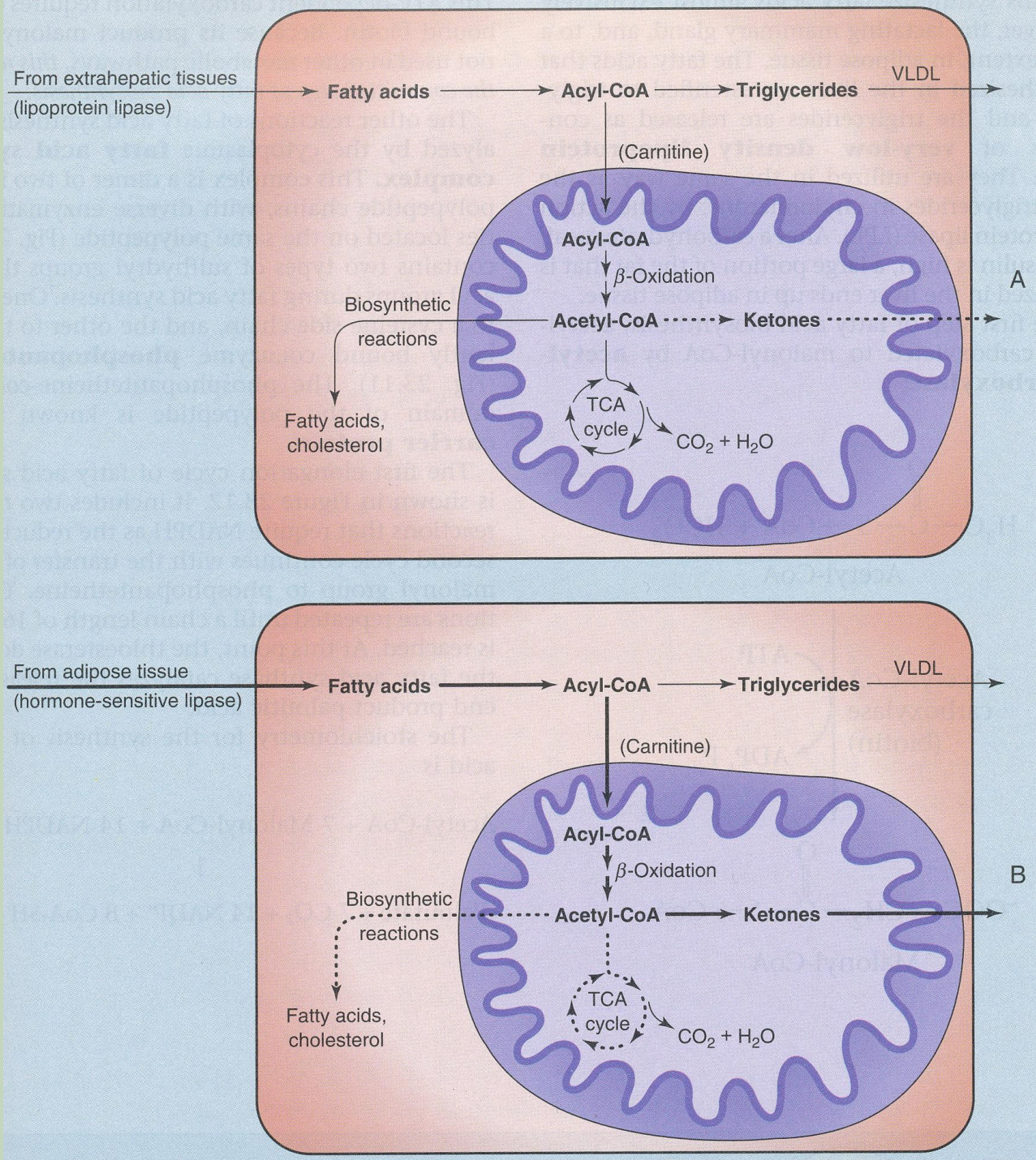


Regulation of FA oxidation

- A) Use of FAs by the tissues is proportional to the plasma FFA level; therefore, FA oxidation is regulated at the level of HSL
  - *During fasting*, the hormonal stimulation of adipose tissue lipolysis (HSL) provides a large amount of FA
  - FA are rather oxidized (than esterified) in the liver because of an increased activity of CPT1 (see below)
  - acetyl-CoA formed by β-oxidation is not used for biosynthesis *during fasting*, its oxidation by the TCA cycle is minimal, and it is used preferentially for the synthesis of ketone bodies

after a carbohydrate-rich meal

during fasting



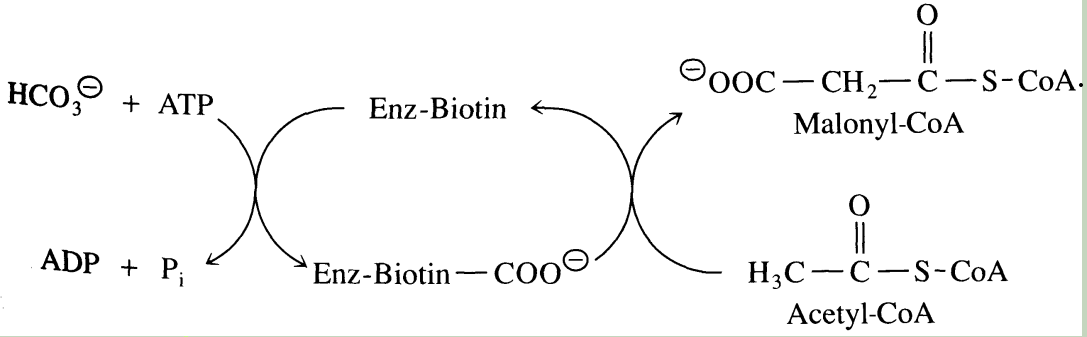
- **B) Carnitine-palmitoyl transferase I** (CPT1) is inhibited by **malonyl-CoA** that is formed in the FA biosynthesis by acetyl-CoA carboxylase ⇒ β-oxidation is inhibited when FA synthesis is active

  - Thus, in the fed state, nearly all FAs entering the liver are esterified to acylglycerols and transported out of the liver in the form of VLDL

  - When FA level increases with the onset of starvation, ACC is inhibited by **acyl-CoA** and malonyl-CoA decreases ⇒ stimulation of β-oxidation

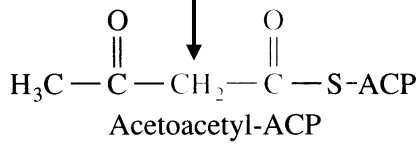
3) FA biosynthesis

- On a high-carbohydrate diet when excess energy is stored in the form of fat
- In the liver, lactating mammary gland, and, to a lesser extent, in the adipose tissue
- FA synthesized in the liver are esterified to TGs which are released in the form of VLDL
- VLDL are utilized by the action of LPL (mainly in the adipose tissue)



malonyl-ACP + acetyl-ACP

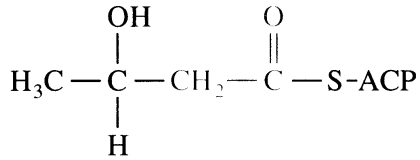
– CO_2



Acetoacetyl-ACP

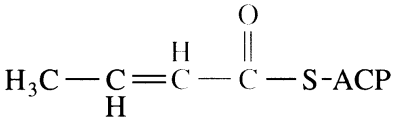
$NADPH + H^{\oplus}$

$NADP^{\oplus}$



D-β-Hydroxybutyryl-ACP

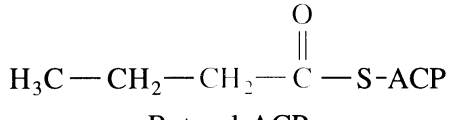
H_2O



trans-Butenoyl-ACP

$NADPH + H^{\oplus}$

$NADP^{\oplus}$



Butyryl-ACP

condensation with another malonyl

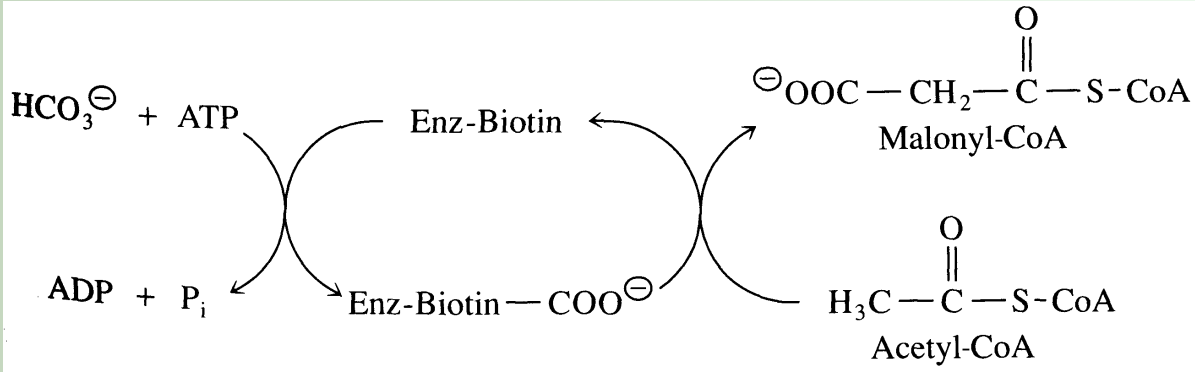
reduction

dehydration

reduction

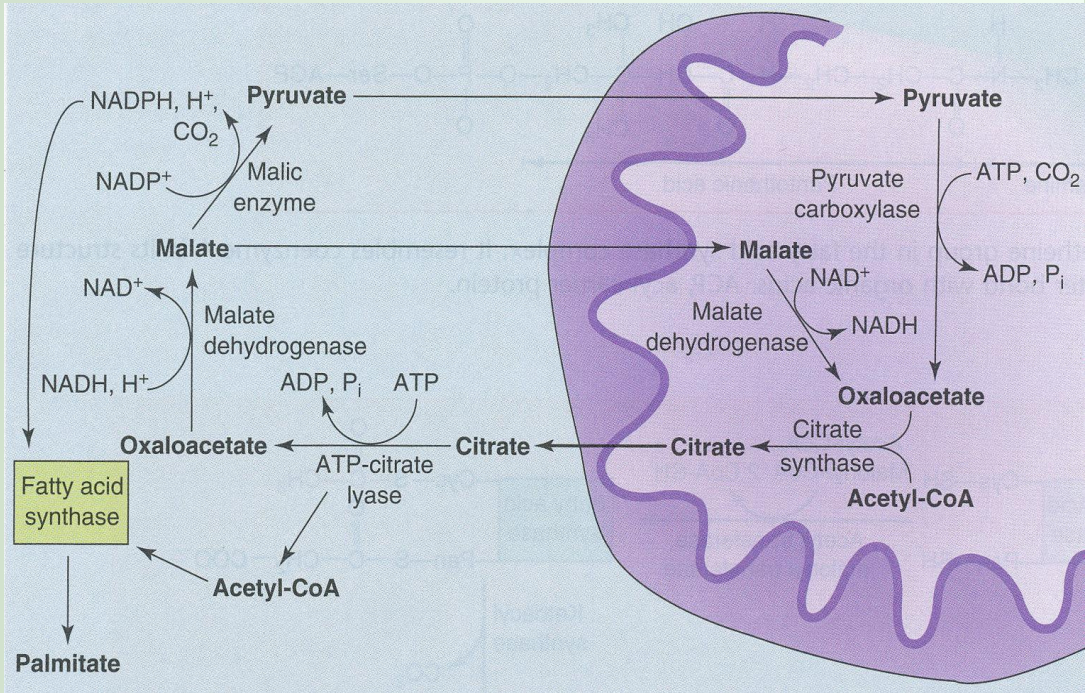
Regulation of FA synthesis

- Mainly at the level of **acetyl-CoA carboxylase** (ACC):



- 1) Acetyl-CoA carboxylase is allosterically activated by citrate and inhibited by CoA-thioesters of long-chain FAs such as palmitoyl-CoA (well-fed liver has a higher citrate level and lower acyl-CoA level than does the fasting liver)

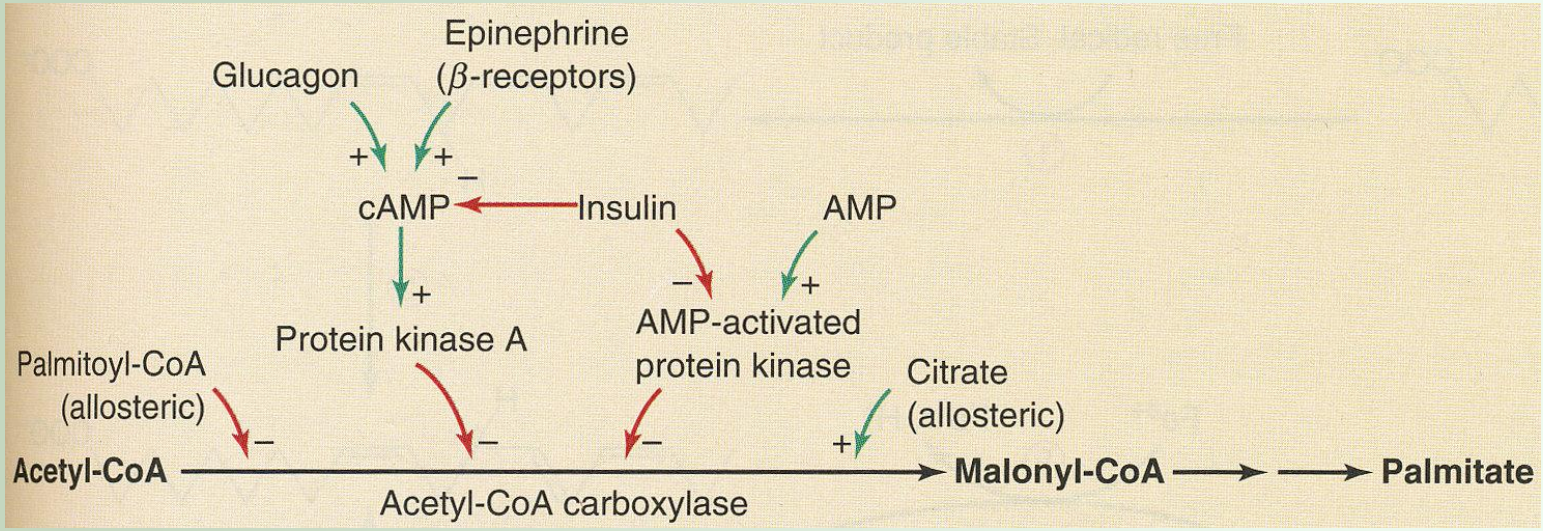
acetyl-CoA must be converted to citrate to get from the mitochondrion into cytoplasm



- 2) acetyl-CoA carboxylase is stimulated by insulin and inhibited by glucagon and epinephrine
  - glucagon and epinephrine mediate activation of the cAMP-dependent protein kinase A, which inactivates ACC
  - insulin antagonizes this cascade by inducing phosphodiesterase that degrades cAMP
  - insulin stimulates the synthesis of ACC and fatty acid synthase, starvation inhibits it (long-term regulation)
- Thus, cAMP-dependent phosphorylation simultaneously inhibits FA synthesis and stimulates FA oxidation (by activation of HSL)

- 3) acetyl-CoA carboxylase is inhibited by phosphorylation by the AMP-activated protein kinase (AMPK)
  - AMPK is activated when the cellular energy charge is dangerously low (high AMP/ATP ratio) and helps the cell to survive the energy shortage by switching-off non-essential biosynthetic pathways such as FA synthesis
  - In the liver, AMPK is inhibited by insulin

Regulation of ACC – overview



Long-term regulation

- Starvation and/or regular exercise, by decreasing the glucose concentration in the blood, change the body‘s hormone balance
- This results in long-term increases in the levels of FA oxidation enzymes (heart LPL) accompanied by long-term decreases in those of lipid biosynthesis (ACC, fatty acid synthase)

insulin (-)

glucagon, epinephrine (+)

insulin (+)

insulin (-) → AMP-dependent phosphorylation

low insulin:glucagon ratio

⇓

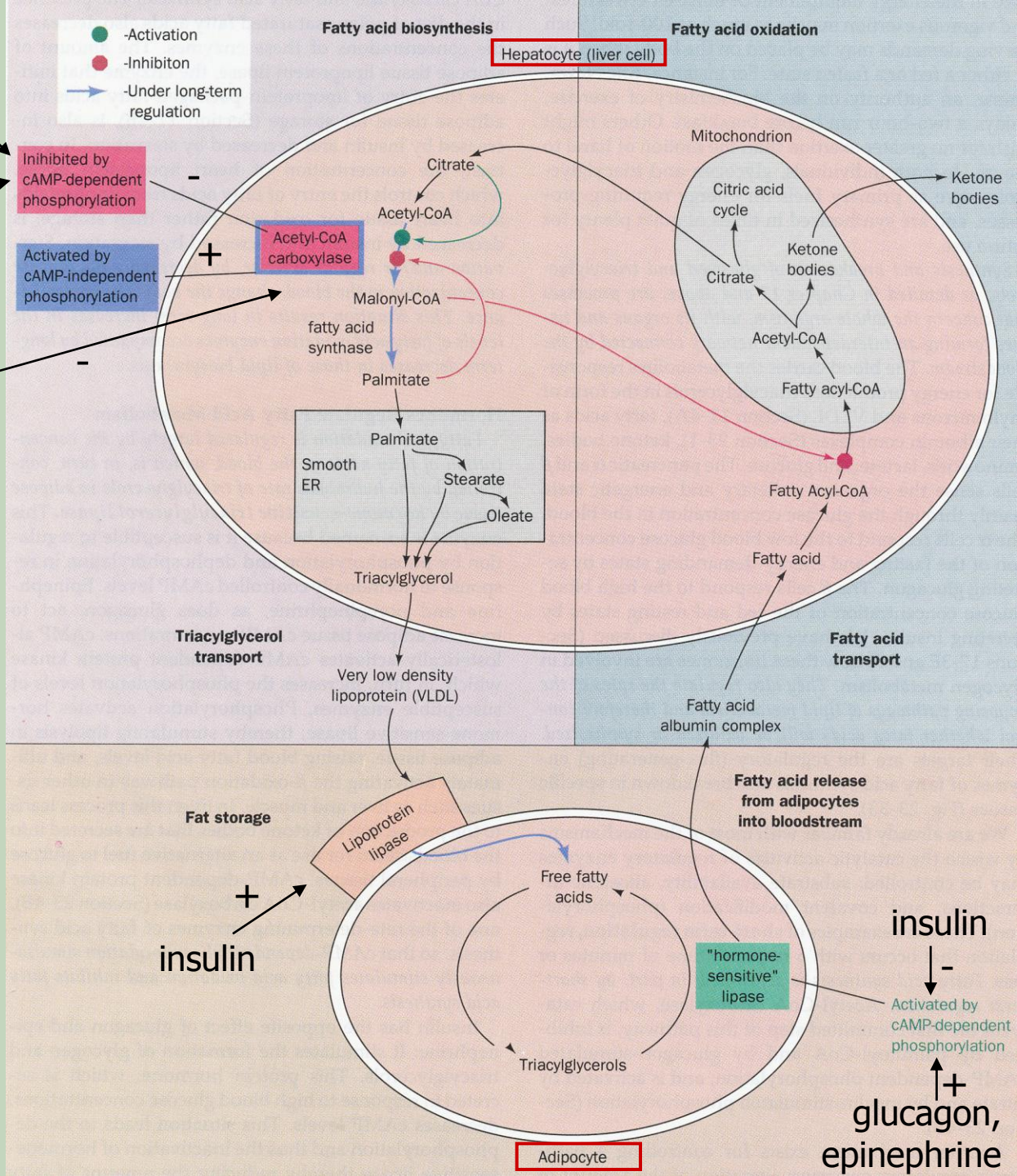
FA oxidation

X

high insulin:glucagon ratio

⇓

FA synthesis



Summary: effects of various hormones

Activity	Insulin	Glucagon
acetyl-CoA carboxylase	+	-
hormon-sensitive lipase	-	+
Synthesis	**Insulin**	**Glucagon**
acetyl-CoA carboxylase	+	-
FA synthase	+	-

Adipose tissue as an endocrine organ

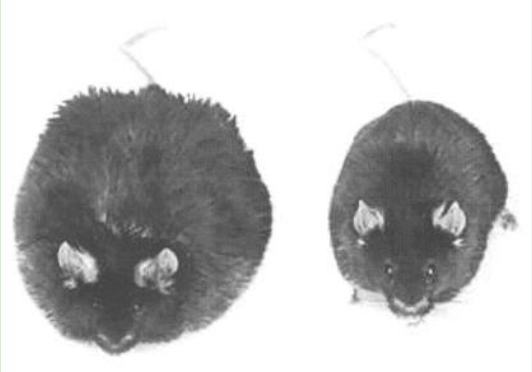
- Adipose tissue itself secretes various factors that regulate glucose and lipid metabolism
- Two of the best-characterized are:
  - leptin
  - adiponectin

Leptin

- Protein, released from adipocytes as their TG levels increase
- Binds to the receptors in the hypothalamus, which leads to the release of neuropeptides that signal a **cessation of eating** (anorexigenic factors)
- In the muscle and liver, it stimulates **FA oxidation** – at least in part through AMPK

Leptin

ob/ob mouse possesses mutations in the gene encoding for leptin ($\Rightarrow$ absence of functional protein) and is massively obese



- Giving leptin to leptin-deficient patients results in a weight loss, but administering leptin to obese patients does not have the same effect
- In fact, leptin concentration is increased in obese patients, but leptin sensitivity is impaired (probably due to the development of leptin resistance in many obese patients)

Adiponectin

- Protein; unlike leptin, adiponectin secretion is reduced as the adipocyte gets larger (e.g. in obese patients)
- Adiponectin binding to receptors leads to activation of AMPK and PPARα
- Effects (via AMPK and PPARα):
  - ↑ FA oxidation by the liver and muscle
  - ↑ uptake and utilization of glucose by the muscle
  - ↓ hepatic glucose production
- In obesity, less adiponectin is released and therefore, it is more difficult for FA and Glc to be used by the tissues