Biochemistry of human organs and tissues II

EVROPSKÁ UNIE
Evropské strukturální a investiční fondy
Operační program Výzkum, vývoj a vzdělávání

MINISTERSTVO ŠKOLSTVÍ, MLÁDEŽE A TĚLOVÝCHOVY

Liver

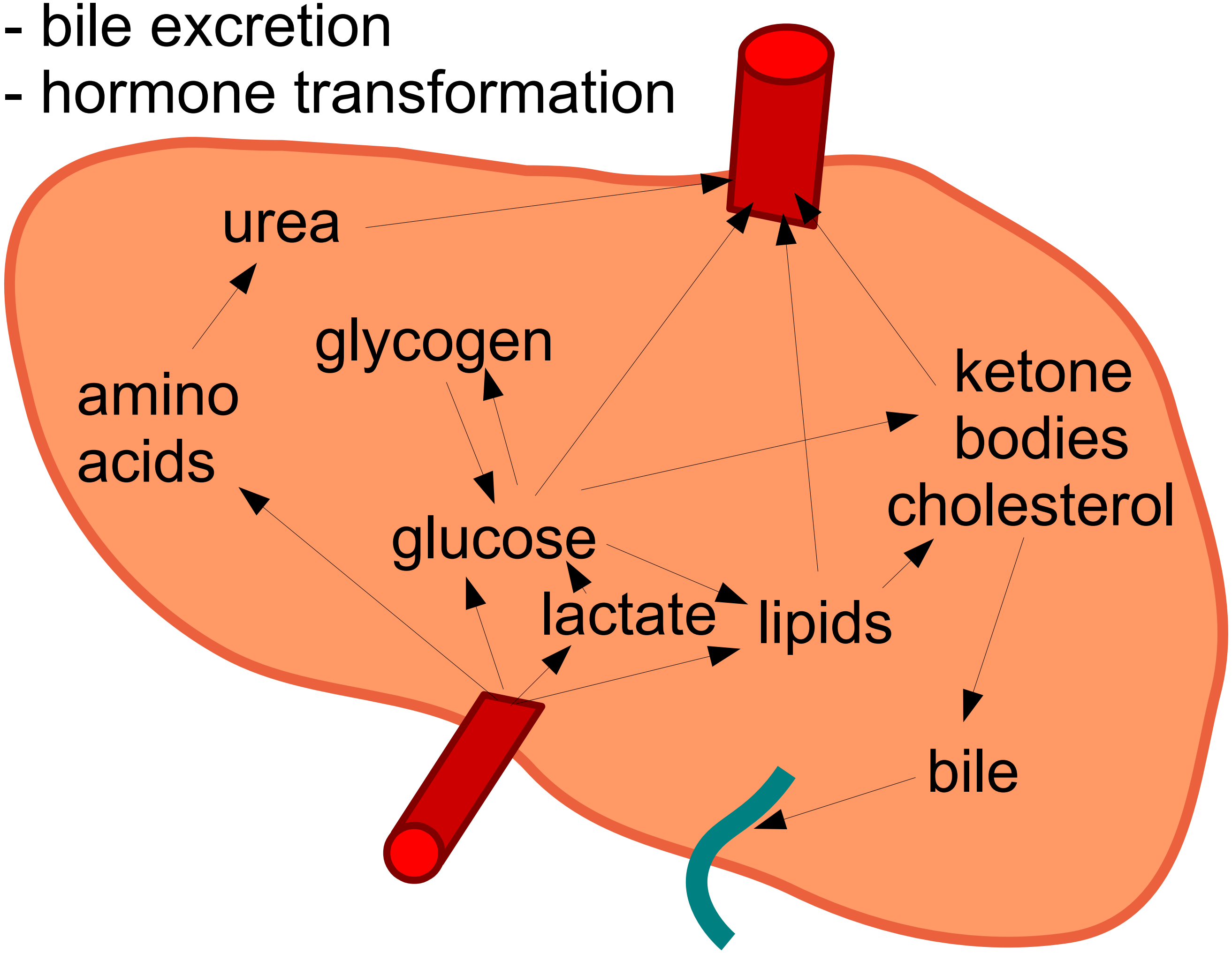
Liver plays many roles in human metabolism. It participates in the metabolism of fatty acids and cholesterol and in the control of lipoproteins (see previous lecture). It also participates in gluconeogenesis of glucose from lactate. Muscles under intensive work with lack of oxygen produce lactate from glucose. Lactate is transported by blood to liver where it is converted back to glucose. Glucose can go back to muscles. Combination of glucose-to-lactate metabolism in muscles and lactate-to-glucose metabolism in liver is known as Cori cycle. Liver stores glycogen. Liver also produces ketone bodies. Condensation of AcCoA produces acetoacetat, 3-hydroxybutyrate and acetone. These compounds are known as ketone bodies. They can be used by other tissues as a source of energy. High production of ketone bodies is typical for starving, low-carbohydrate high-fat diet, alcohol intoxication or improperly treated type 1 diabetes. Liver also metabolizes amino acids.

Cytochrome P450 (CYP, named for its visible light absorption at 450 nm in the complex with CO) is a complex of multiple liver enzyme with a broad substrate and reaction specificity. In nature they metabolize natural secondary metabolites from plants and other food. In medicine it plays an important role in metabolism of drugs. In general it oxidases non-polar exogenous molecules to more polar, and thus more soluble, products. More soluble products can be excreted more easily. There are many isoenzymes of CYP. For a new drug it is important to determine which CYP isoenzyme metabolize it because this influences its half live in body, genetic differences in drug function or interactions between drugs. Some drugs (as well as some natural products) are known to inhibit some CYPs, which may prolong the effect of other drugs.

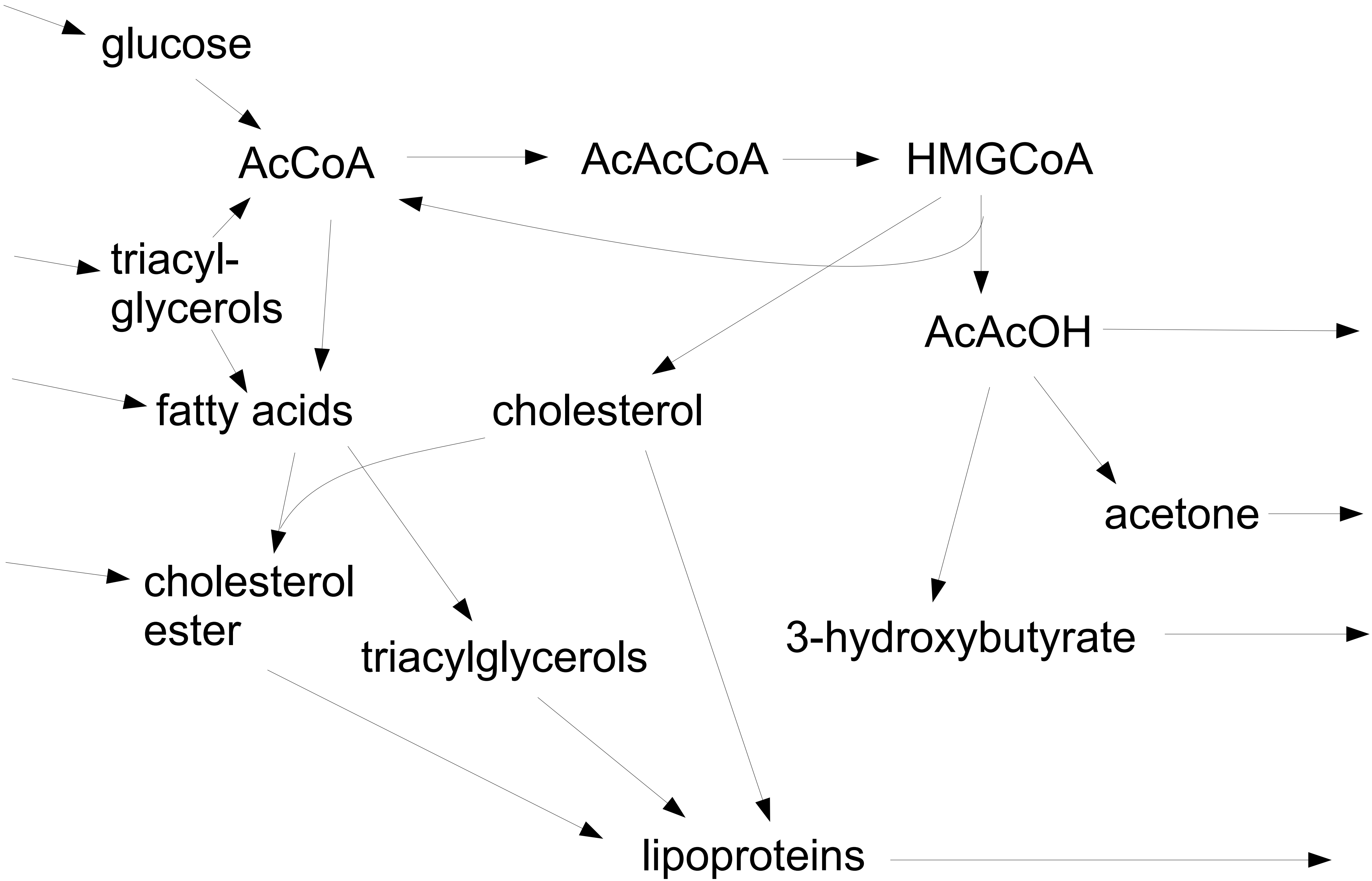
Liver metabolizes ethanol by alcohol dehydrogenase and other enzymes. High ethanol consumption causes production of ketone bodies, acidosis and high lipid production. It can also cause that ethanol becomes oxidized by an alternative microsomal ethanol oxidizing system.

Liver

Function:
- input of nutrients from small intestine
- metabolism of saccharides, lipids, amino acids etc.
- storage (glycogen, B12, iron)
- detoxification
- bile excretion
- hormone transformation



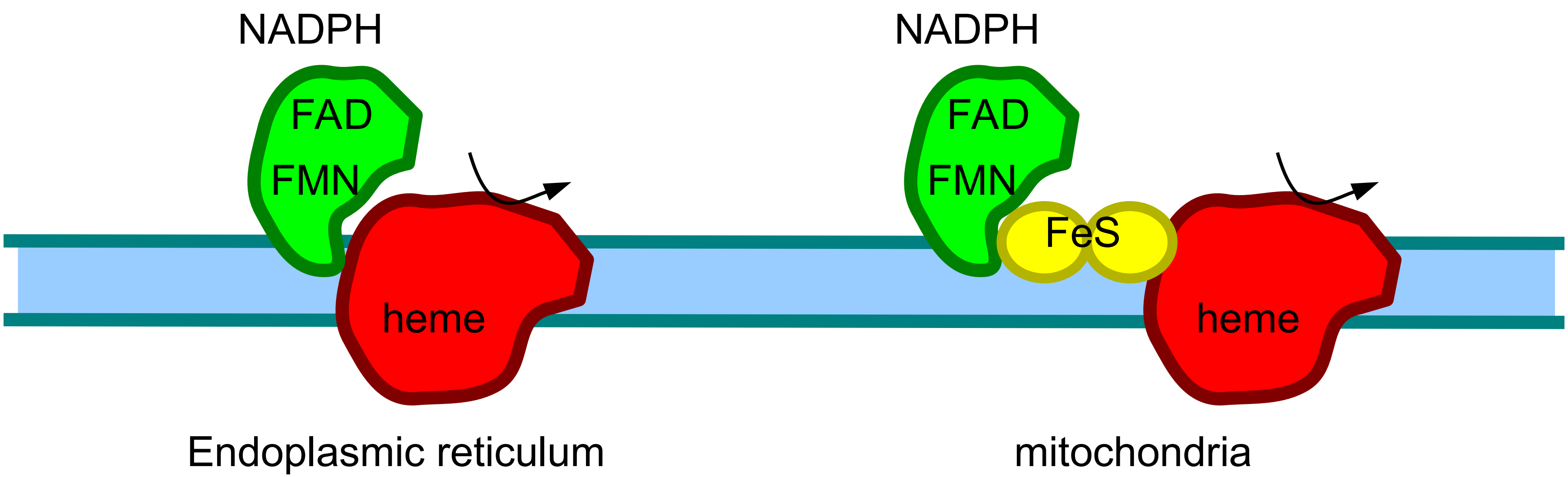
Liver


glucose
AcCoA
AcAcCoA
HMGCoA
triacyl-
glycerols
AcAcOH
fatty acids
cholesterol
acetone
cholesterol
ester
3-hydroxybutyrate
triacylglycerols
lipoproteins

Liver

Cytochrome P450

$$R\text{-}H + O_2 + NADPH + H^+ \rightarrow R\text{-}O\text{-}H + H_2O + NADP^+$$



hydroxylation, epoxidation, dealkylation, oxidation of N, S, P etc.
~60 isoforms
CYP 3A4, 2C19, 1A2, 2A6, 2B6 are major drug metabolizes
sterol metabolism

Liver

ethanol metabolism

ethanol $\xrightarrow{\text{NADH}}$ acetaldehyde $\xrightarrow{\text{NADH}}$ acetate $\xrightarrow{\text{–ATP}}$ AcCoA

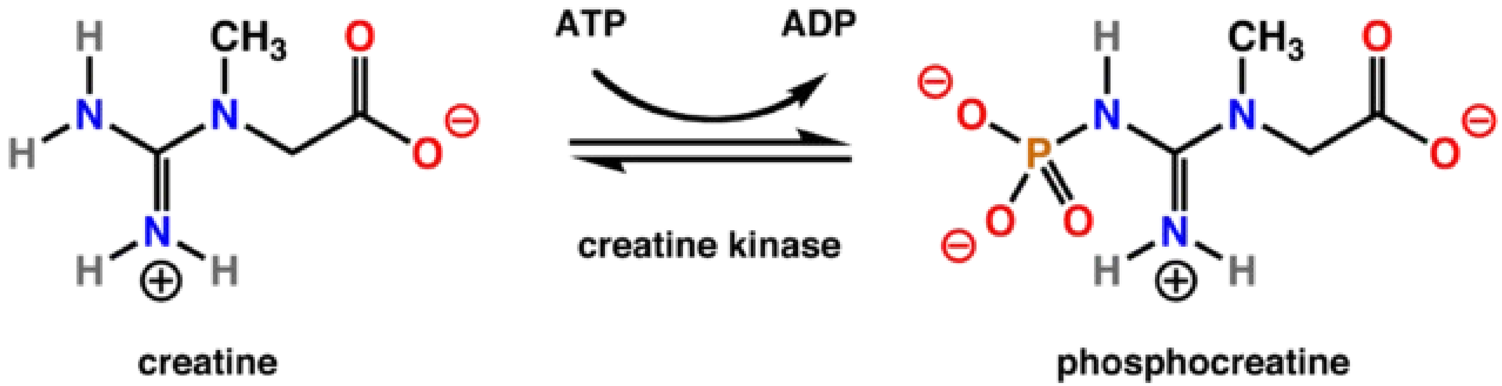
high energy input
high NADH/NAD$^+$ ratio
suppression of citric acid cycle
lactate synthesis, acidosis
lactate in blood reduces clearance of uric acid
high production of ketone bodies
high lipid production
degradation of ethanol by microsomal alcohol oxidase
(one of CYP isoenzyme)
acetaldehyde toxicity (reaction with free amines)

Muscles

Skeletal muscles convert energy stored in ATP to the mechanical work. It receives the signal from neuron in the form of acetylcholine neurotransmitter. This activates ligand-gated ion channel (nicotinic receptor) which releases flow of Na^{+} into the cell. This releases Ca^{2+} from sarcoplasmic reticulum (special endoplasmic reticulum for Ca^{2+} storage) into cytoplasm. This activate actin-myosin system. Actin is rather static filamental protein. On the other hand, myosin is a molecular motor that can “walk” on actin. It is activated by Ca^{2+}. While hydrolysing ATP it can make one step on actin filament.

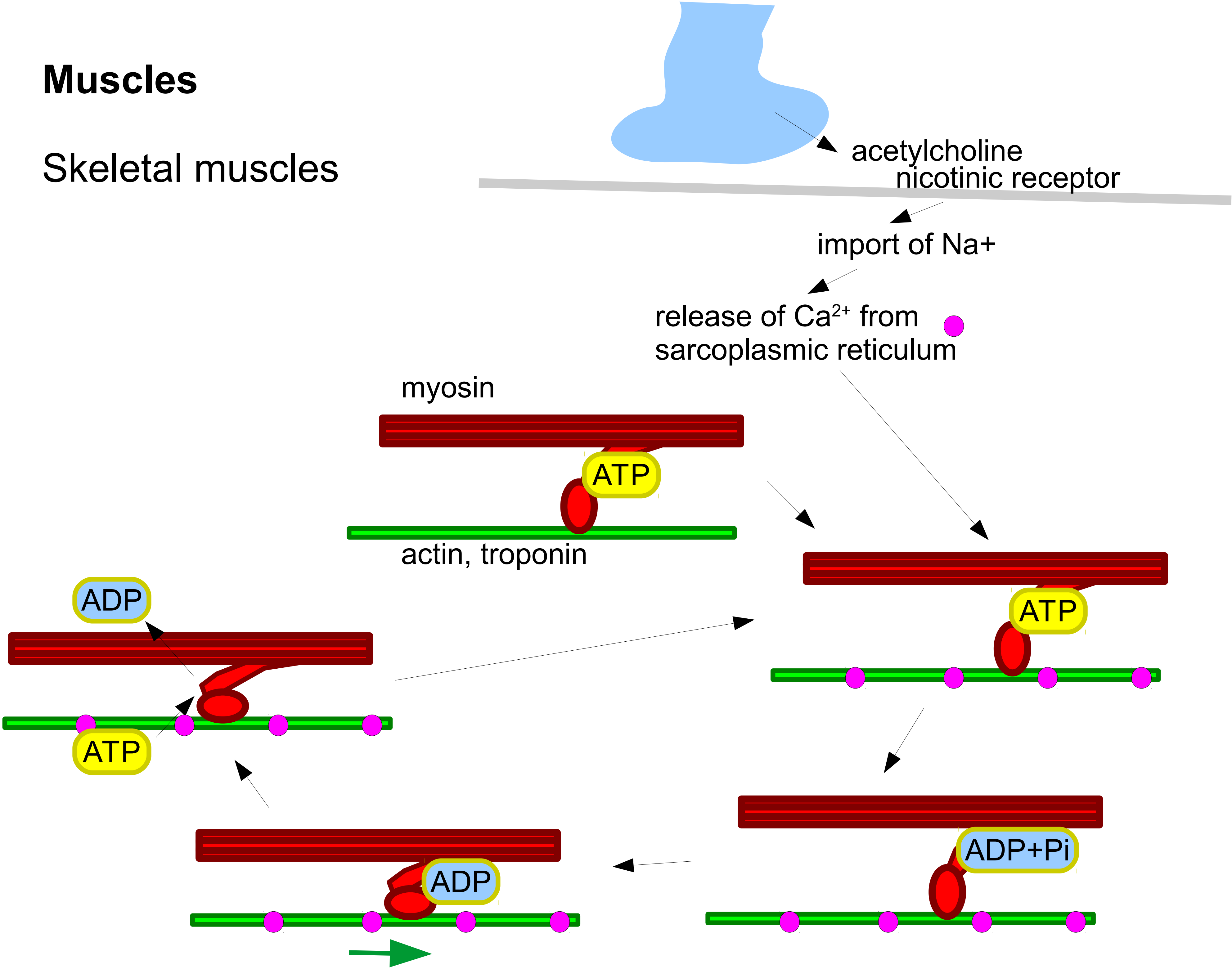
creatine

Muscles need lot of energy and often do not have enough oxygen for this. To solve this they can produce lactate. Beside this they may store energy by reversible formation of phosphocreatin.



Muscles

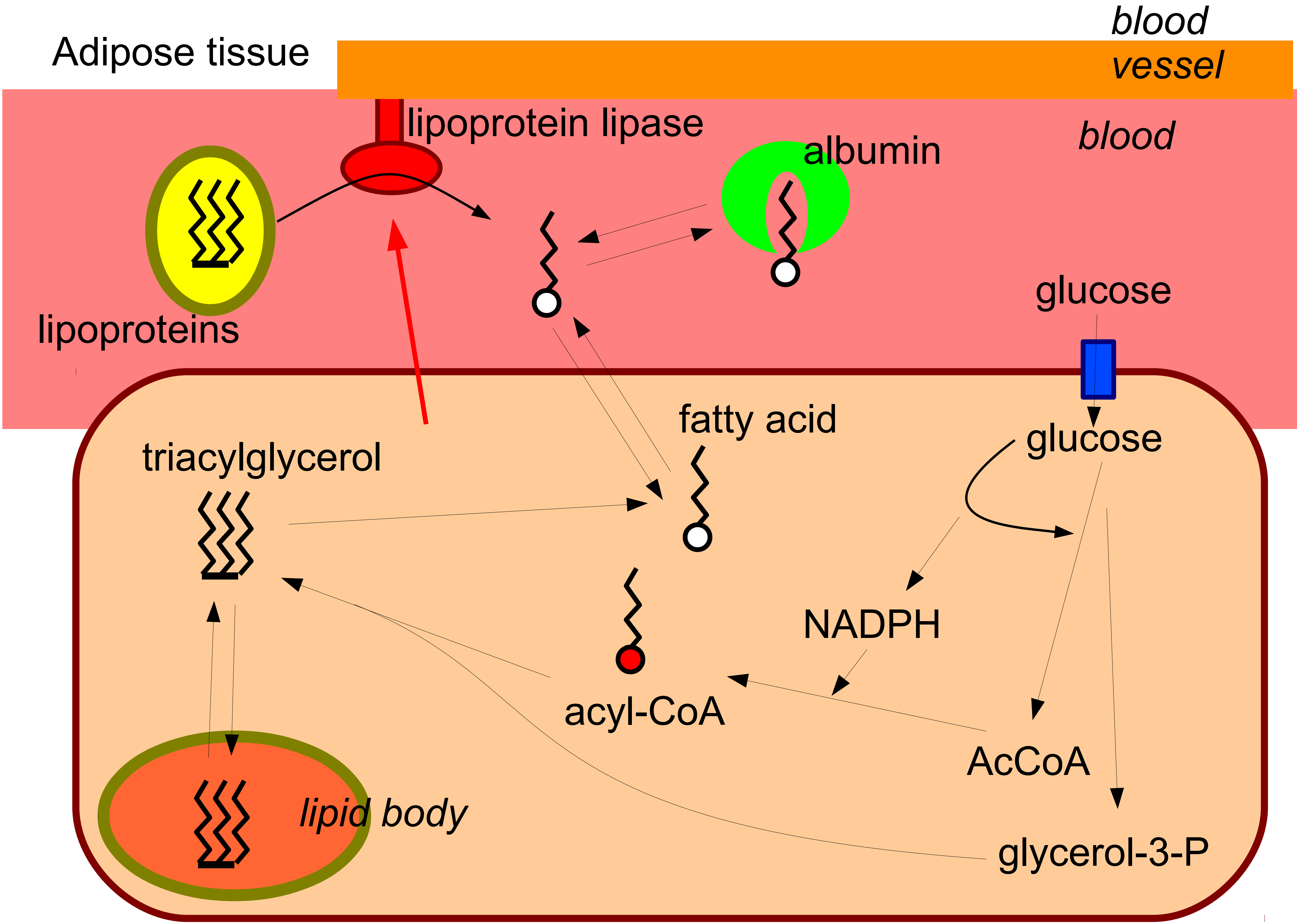
Skeletal muscles

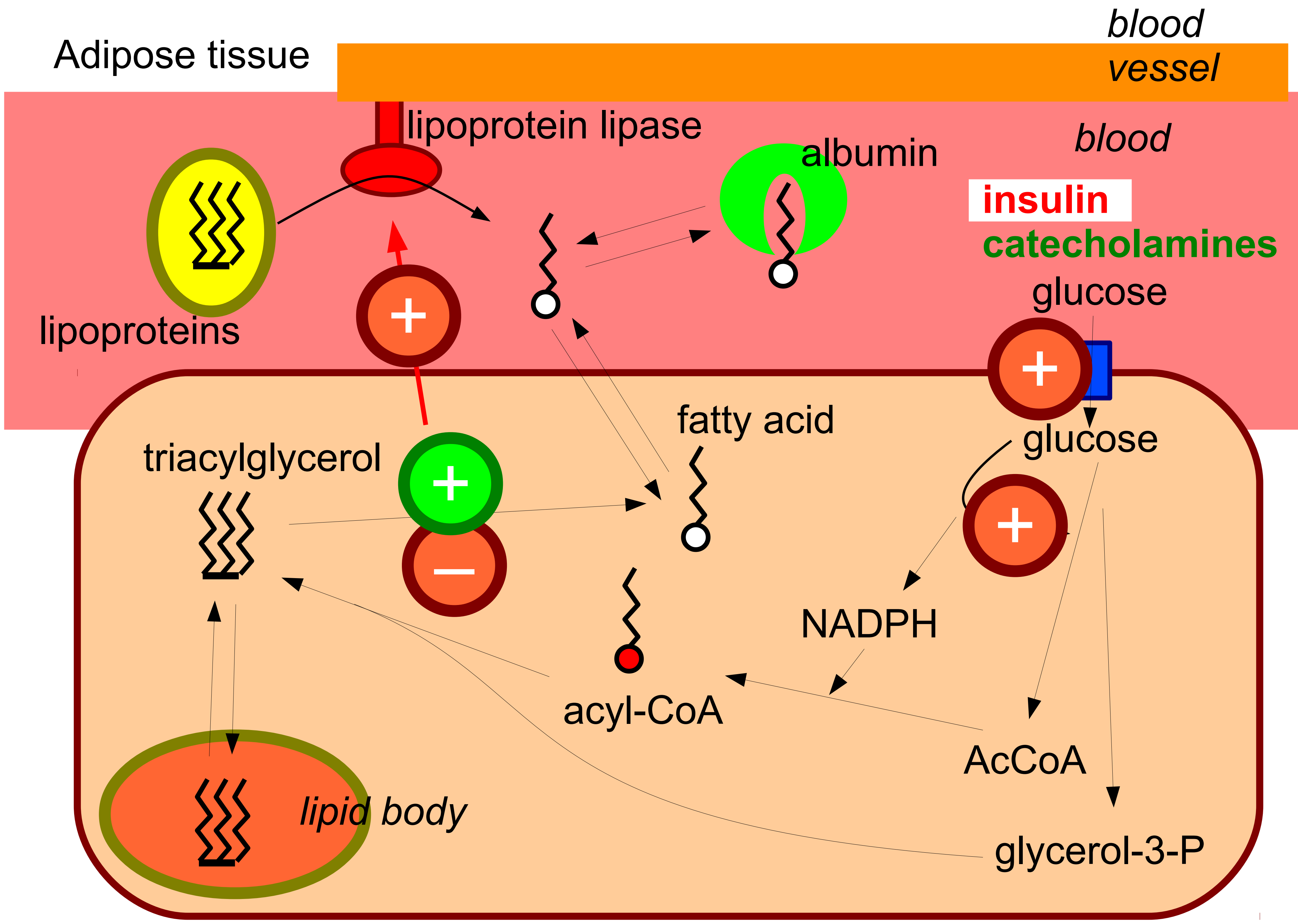


Adipose tissue

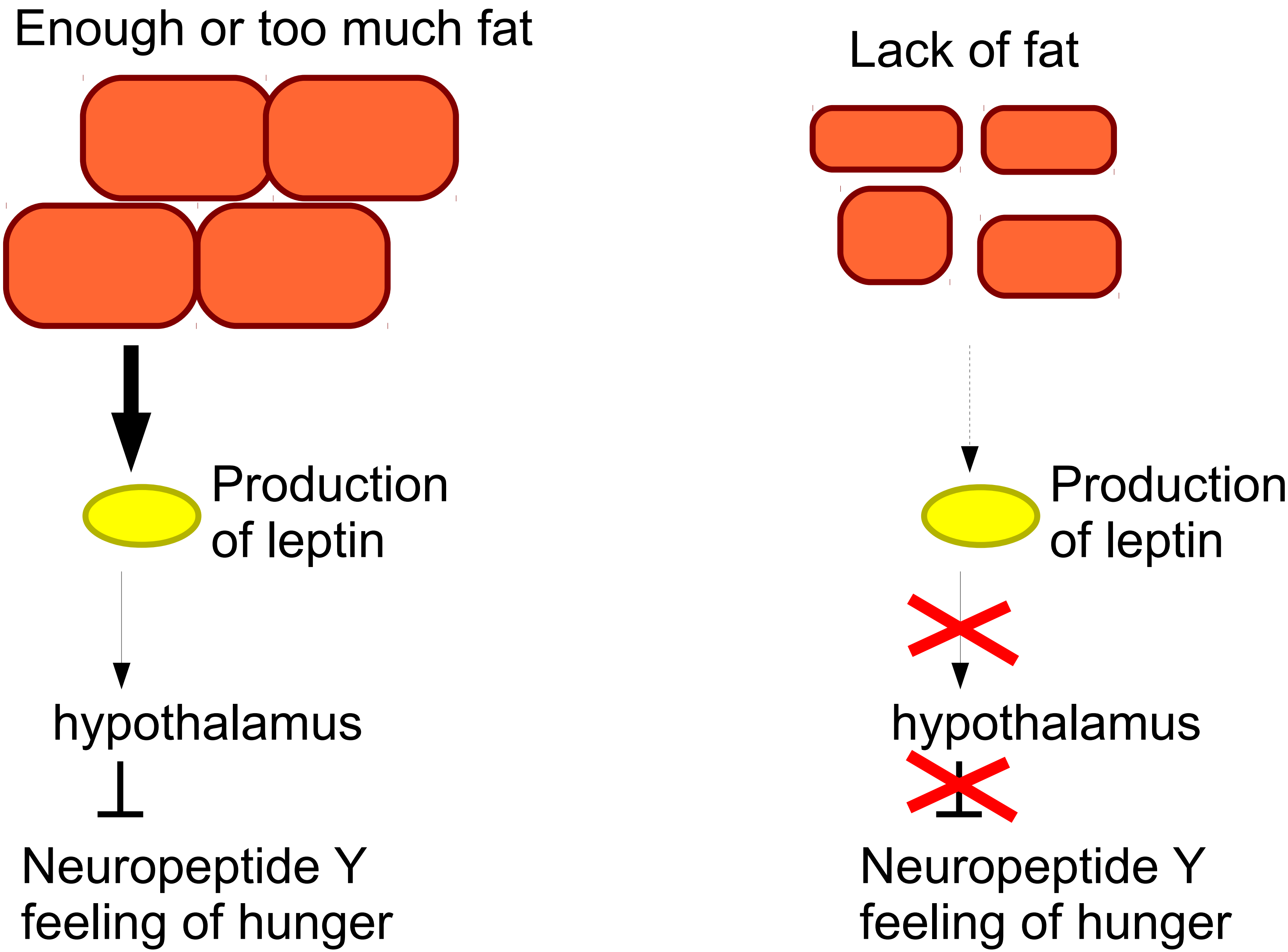
Adipose tissues store lipids. It takes glucose from blood and convert it to AcCoA. It also produces NADPH by pentose phosphate pathway. Next it uses these two components to produce fatty acids and triacylglycerols. These are stored in lipid droplets stabilized by phospholipid monolayer and interface proteins. These triacylglycerols can be utilized by a lipase and fatty acids can be released to blood. Free fatty acids are produced in blood by lipoprotein lipase and they are immediately ingested by muscle or other cells and utilized as a source of energy. Free fatty acids can also circulate in blood bound to albumin. Insulin promotes intake and metabolism of glucose by adipose cells. It also enhances production of lipoprotein lipase. Catecholamines support cellular hydrolysis of triacylglycerols.

Adipose tissue plays also a hormonal role. For example it produces the hormone called leptin with hunger-inhibiting function. In healthy individuals there is a reasonable amount of fat in the adipose tissue. Its reduction by starving reduces amount of produced leptin, which in turn supports hunger. On the other hand, high amount of adipose produces high amount of leptin and inhibits hunger. This balances the amount of adipose tissue. This is also the reason why fast loss of fat may cause reduction of leptin, which triggers hunger. In contrast, ghrelin hormone produced by stomach causes hunger. Some stomach surgery used to treat obesity may reduce production of ghrelin and thus inhibit hunger.


Adipose tissue
blood
vessel
lipoprotein lipase
albumin
blood
lipoproteins
glucose
fatty acid
glucose
triacylglycerol
NADPH
acyl-CoA
AcCoA
lipid body
glycerol-3-P


Adipose tissue
blood vessel
lipoprotein lipase
albumin
blood
insulin
catecholamines
glucose
lipoproteins
fatty acid
glucose
triacylglycerol
NADPH
acyl-CoA
AcCoA
lipid body
glycerol-3-P

Adipose


Enough or too much fat
Production
of leptin
hypothalamus
Neuropeptide Y
feeling of hunger
Lack of fat
Production
of leptin
hypothalamus
Neuropeptide Y
feeling of hunger

Adipose

Insulin resistance:

obesity, high concentration of free fatty acids in blood

$\downarrow$

switch from glucose metabolism to fatty acid metabolism in many tissues

$\downarrow$

lack of absorption of glucose

$\downarrow$

high glucose concentration in blood, type II diabetes

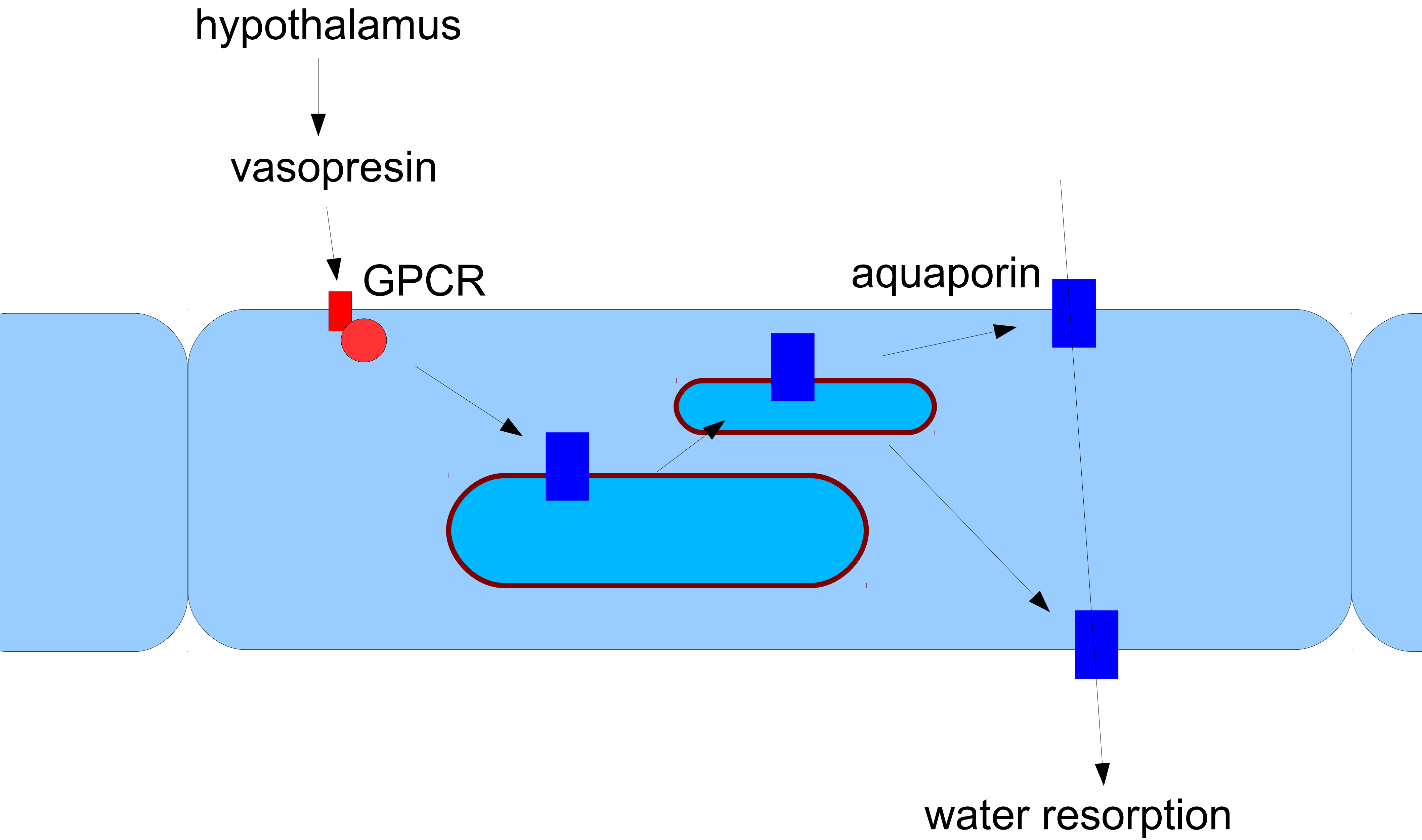
Kidney

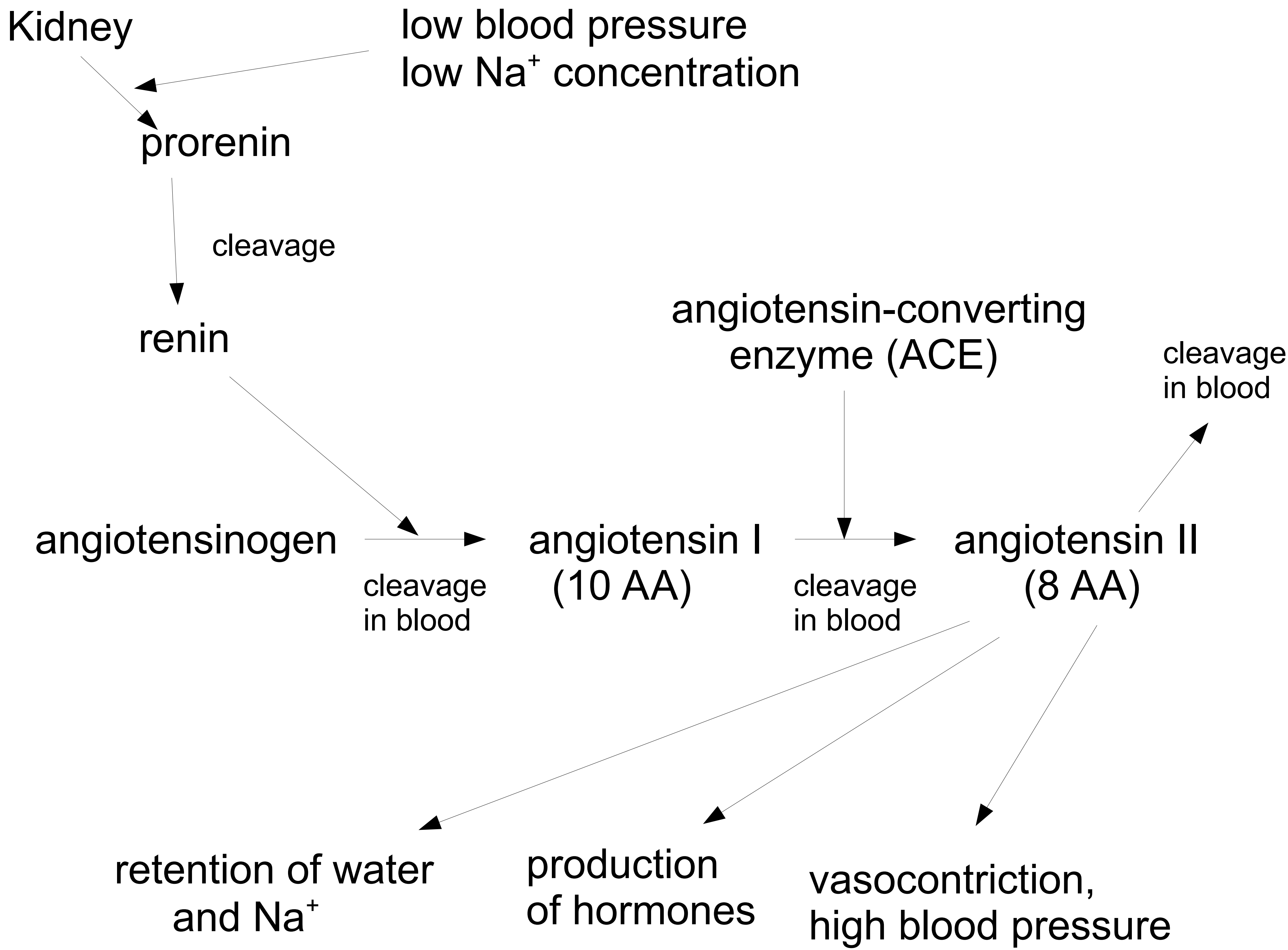
Kidney filters blood. It separates blood elements and large proteins and retains them in blood. Water, small molecules and ions can pass. Next, useful small molecules are resorbed by special mechanisms. Kidney play important role in acidobasic and osmotic homeostasis and blood pressure control.

Peptidic hormone vasopressin binds to its receptor (GPCR). The signal causes higher production of protein aquaporin and its insertion to the membrane. Aquaporin transports water molecules (but not ions) through the membrane. Because of different concentrations of ions on different sides of membranes (osmotic pressure) water is resorbed.

Kidney is also related to renin-angiotensin system. Protein angiotensinogen is produced by liver. In blood it is cleaved by protease renin to peptide angiotensin I. Renin is produced by kidney. Angiotensin I can be further hydrolysed by angiotensin converting enzyme (ACE) to angiotensin II. Angiotensin II supports vasoconstriction and increases blood pressure. It also influences kidney and renin production. ACE is very important target of drugs used to treat hypertension.

Kidney


hypothalamus
vasopresin
GPCR
aquaporin
water resorption



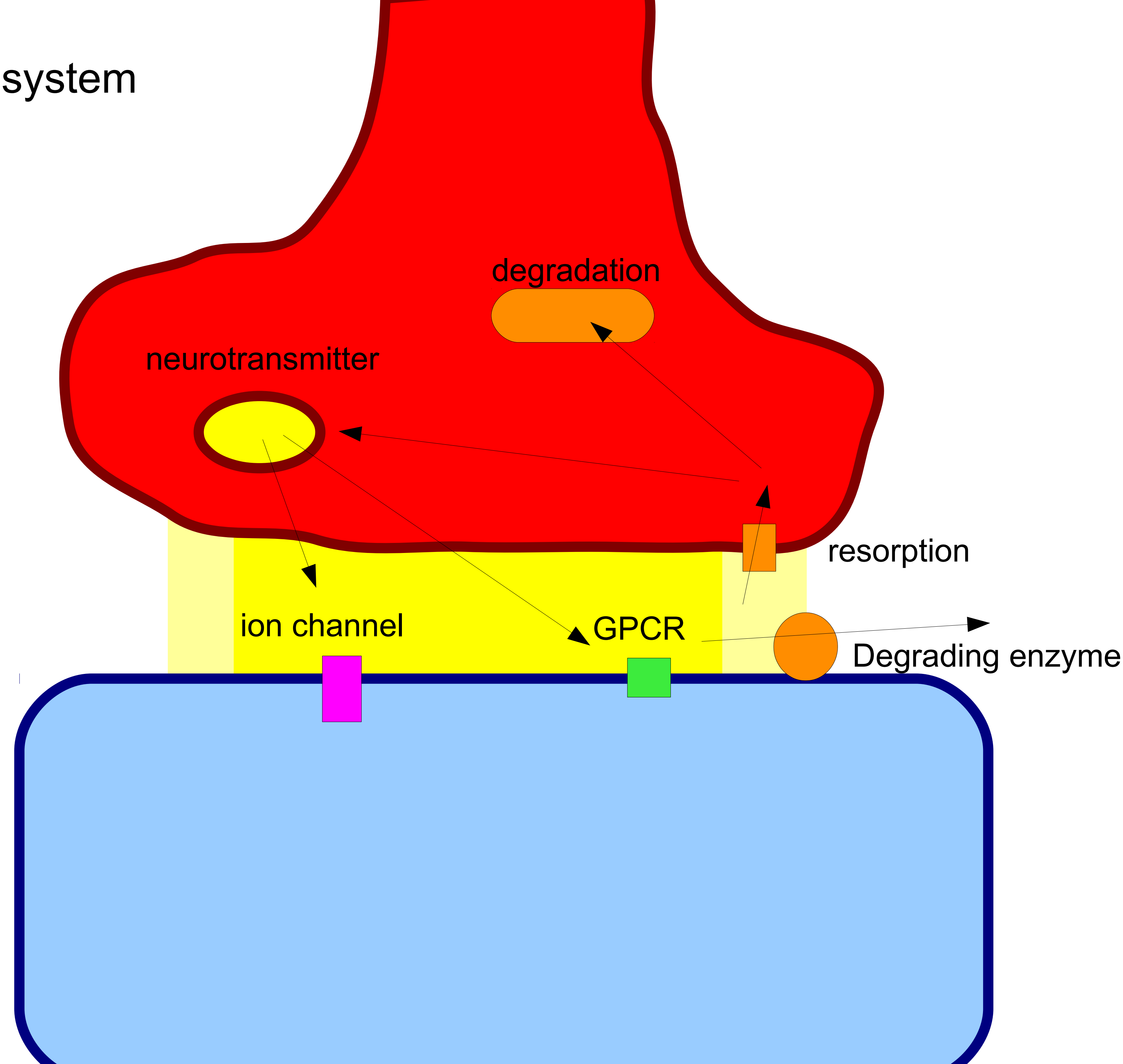
Kidney
low blood pressure
low Na+ concentration
prorenin
cleavage
renin
angiotensin-converting
enzyme (ACE)
cleavage
in blood
angiotensinogen
cleavage
in blood
angiotensin I
(10 AA)
cleavage
in blood
angiotensin II
(8 AA)
retention of water
and Na+
production
of hormones
vasocontriction,
high blood pressure

Nervous system

A signal is transduced within a neuron in form of electric signal as explained in the lecture dedicated to receptors. Transduction of a signal from one neuron to another neuron or to other target cell is facilitated by neurotransmitters. In general, the neurotransmitter is stored in the neuron in vesicles. Activation by electric signal causes that these vesicle fuse with the membrane and release its content into the space between cells (synaptic cleft). On the target cell it bind to receptors (GPCRs or ion channels) and activates other mechanisms. It is necessary to terminate this signalling. Otherwise once activated cell would be active for a long time. Termination of the signal can be done by degradation of the neurotransmitter, by its resorption or by combination of both processes. Acetylcholine esterase acts directly in the synaptic cleft by hydrolysing acetylcholine. Monoamine oxidase and catechol-*O*-methyltransferase metabolize neurotransmitters (catecholamines) inside the neuronal cell.

Many chemical compounds interfere these processes. For example neurotoxic gasses inhibit acetylcholine esterase and thus prolong neuronal signalling by acetylecholine. Cocaine prolong the effect of dopamine by inhibiting its reuptake. Amphetamines activate some GPCRs, inhibit reuptake of catecholamines and may also inhibit metabolism of catecholamines. Some other drug of abuse, such as opiates or LSD, act directly on GPCRs.

Nervous system



Nervous system

Neurotransmitters

Neurotransmitter	Effect	Receptor	Nerv. syst.	Termination
acetylcholine	+/–	M,I	CNS and PNS	AChEsterase
glutamate	+/–	M,I	CNS	resorption
glycine	–	I	CNS	resorption
GABA	–	I	CNS	resorption, metab.
dopamine	+/–	M	CNS and PNS	resorption, metab.
noradrenalin	+/–	M	CNS and PNS	resorption, metab.
adrenalin	+/–	M	CNS and PNS	resorption, metab.
serotonin	+/–	M,I	CNS	resorption, metab.
histamine	+/–	M	CNS	resorption, metab.
endorphins	–	M	CNS	cleavage
enkephalins	–	M	CNS	cleavage
dynorphins	–	M	CNS	cleavage
adenosine, ATP	+/–	M	CNS	resorption

+ activating / – inhibiton
CNS central / PNS periferal nervous
I ionotropic (Na^+, K^+, Cl^-) / M metabolotropic (cAMP, Ca^{2+})

Nervous system

Neurotransmitters

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glycine	–	I	CNS	resorption
GABA	–	I	CNS	resorption, metab.
dopamine	+/–	M	CNS and PNS	resorption, metab.
noradrenalin	+/–	M	CNS and PNS	resorption, metab.
	+/–	M	CNS and PNS	b.
	+/–	M,I	CNS	b.
histamine	+/–	M	CNS	ab.
endorphins	–	M	CNS	
enkephalins	–	M	CNS	cleavage
dynorphins	–	M	CNS	cleavage
a	—	M	CNS	resorption

\+ n

C iferal nervous

I ionotropic (Na^+, K^+, Cl^-) / M metabolotropic (cAMP, Ca^{2+})

Paralytic gasses antialzheimer drugs

Amphetamins, antidepressants

Amphetamins, kokain

Amphetamins

antidepressants

opiates

coffein

Nervous system

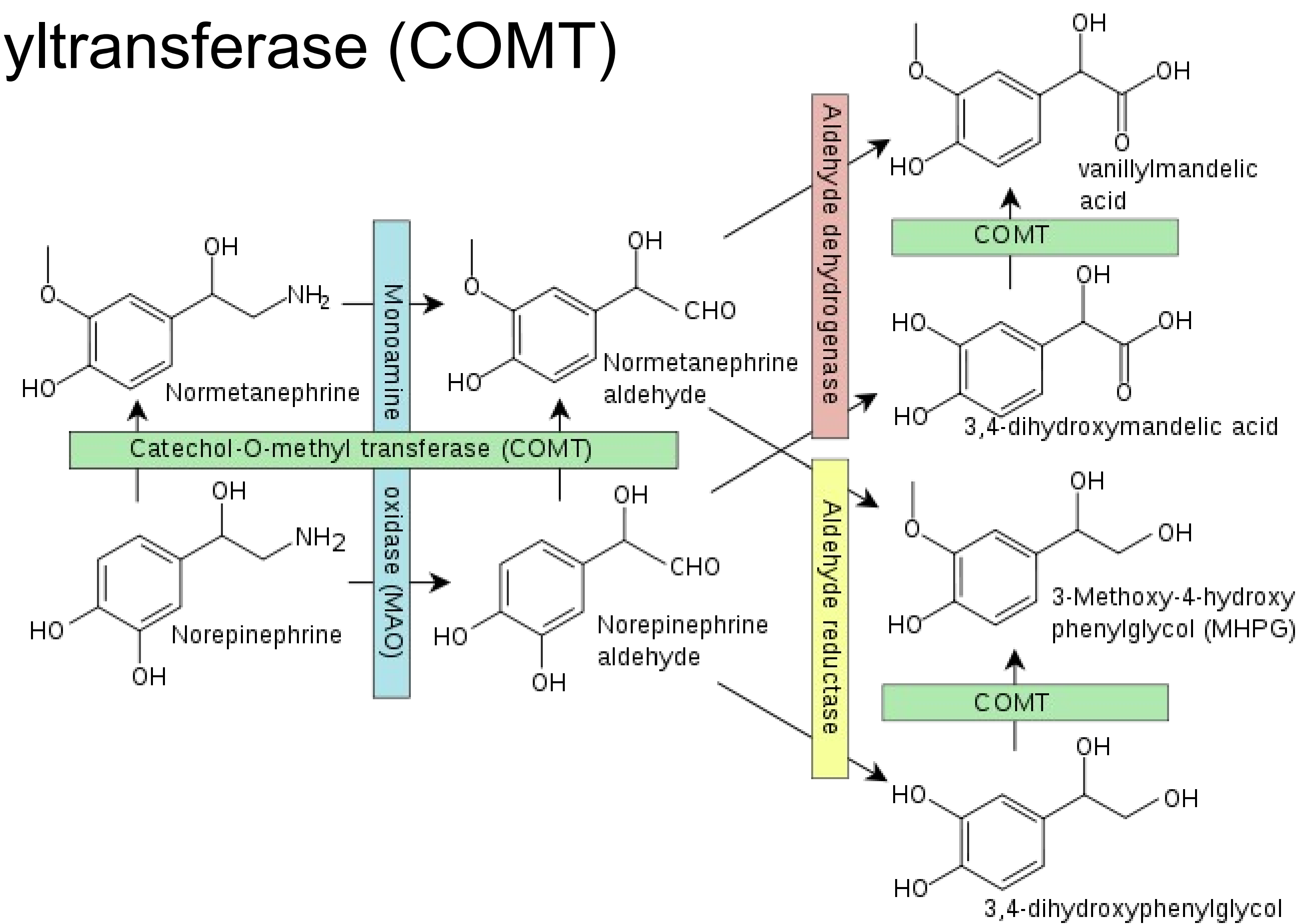
Neurotransmitter degraders

Acetylcholine esterase

acetylcholine + H_2O → acetate + choline

monoamine oxidase

catechol-*O*-methyltransferase (COMT)



Hormones

Hormones have been discovered as compounds present in blood with some effect on physiology of some organs. From the chemical point of view they are diverse. Protein and peptide hormones usually influence target tissues by binding to membrane receptors, mostly GPCRs (glucagon, angiotensin, oxytocin, vasopressin and many others) or less commonly receptor protein kinases (insulin). Steroid hormones use completely different mechanism. These compounds are so hydrophobic that they can spontaneously pass through the membrane and reach nucleus. Here they bind to special receptors and directly regulate transcription.

Chemistry:

- proteins, peptides, steroids, amino acid derivatives, others

Role:

- metabolism, growth, differentiation, homoeostasis, digestion etc.

Distance of action:

- endocrine, paracrine, autocrine

Hormones

Chemistry:
- proteins, peptides, steroids, amino acid derivatives

Role:
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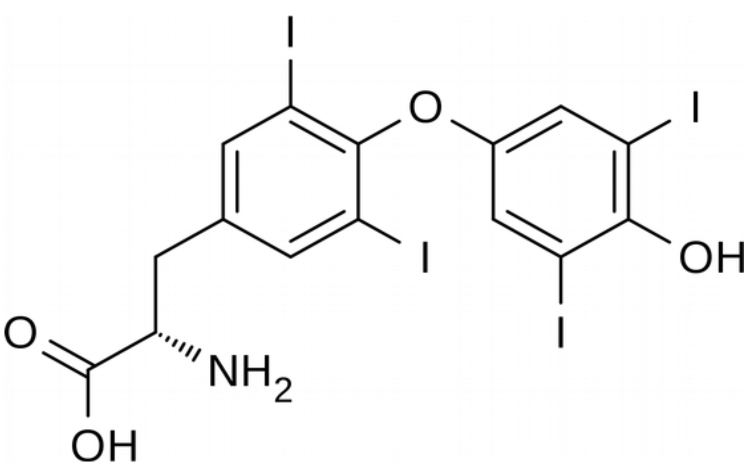
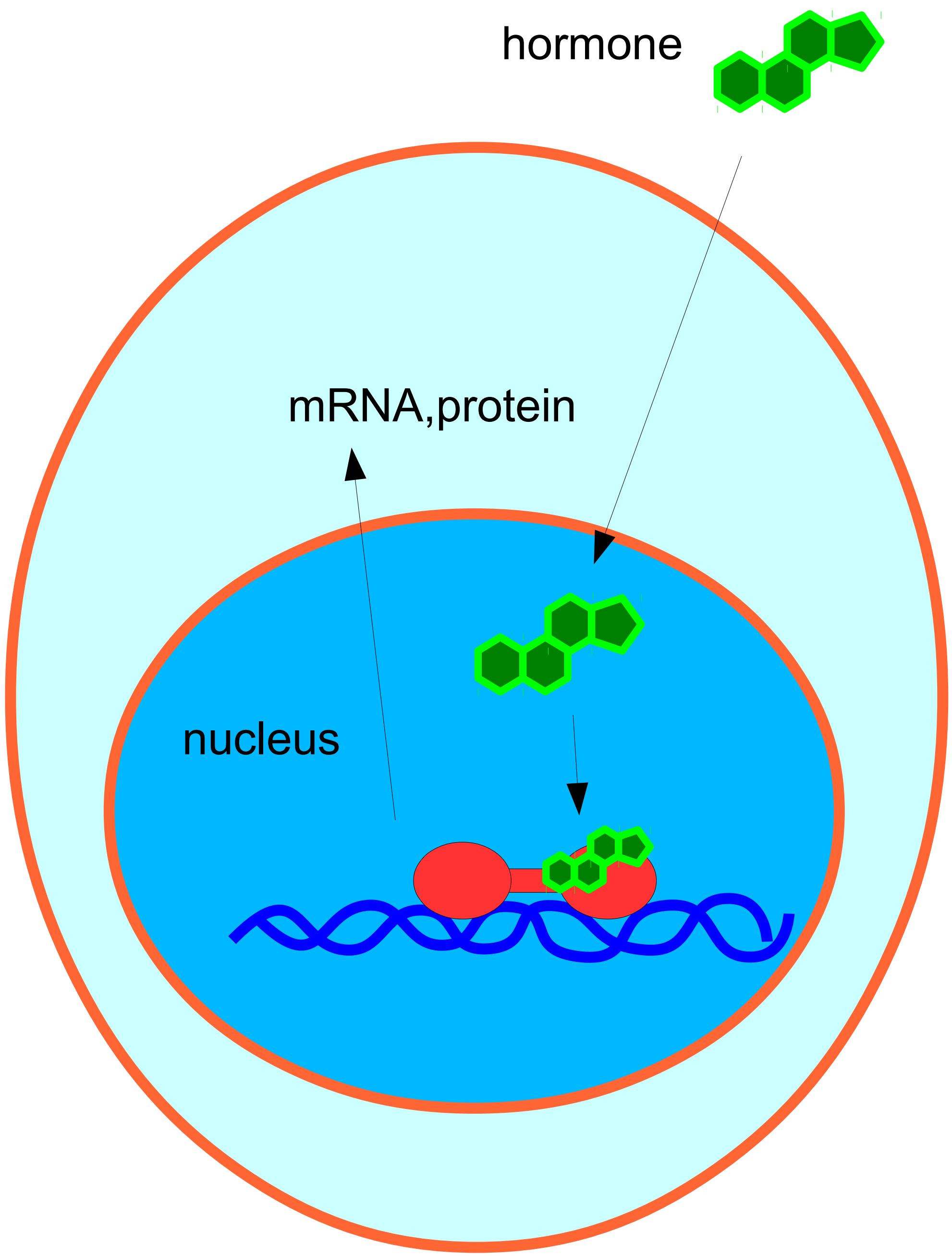
Hormones

Steroid hormones and
thydoid hormones:





Hormones

Steroid hormones examples:

Corticosteroids – produced by adrenal cortex

- cortisol – lipolysis, proteolysis, gluconeogenesis, immunosuppressive
- aldosterone – function of kidney, reabsorption of Na^+

Sexual steroids:

♂ Androgens – testosterone

♀ Estrogens – estradiol

♀ Gestagens – progesterone

Hormones

Peptide hormones examples:

Insulin – 30+21 amino acids – glucose sorption, glycogen metabolism
Glucagon – 29 amino acids – glycogen metabolism
Angiotensin II – 8 amino acids – blood pressure
Vasopressin – 9 amino acids – blood pressure, water resorption in kidney
Oxytocin – 9 amino acids – uterine contraction, milk ejection, …
growth hormone, adrenocorticotropic hormone, …

Other hormones:

Thyroxine – tyrosine derivative, contains iodine – thermogenesis, basal metabolism, embryonic development