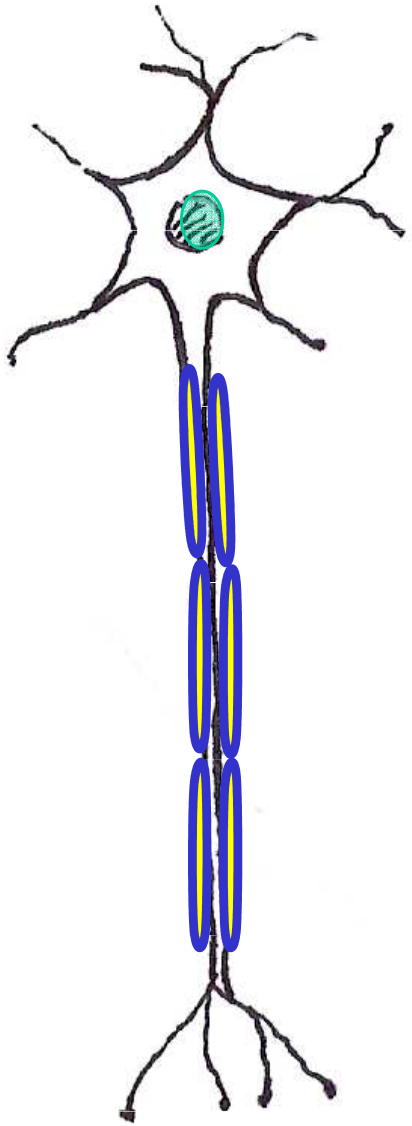
Nerve cells
Neurotransmission across synapses

Biochemistry II
Lecture 7

2009 (J.S.)

Neurons



Dendrites

with receptors of neurotransmitters.

Perikaryon – the metabolic centre of neuron, with intensive proteosynthesis, is highly susceptible to low supply of oxygen.

Axon

– the primary active transport of Na^+ and K^+ ions across axolemma and voltage operated ion channels enables inception and spreading of action potentials.

– **axonal transport** (both anterograde and retrograde) provides shifts of proteins, mitochondria, and synaptic vesicles between perikaryon and synaptic terminals.

Myelin sheaths are wrapped about most axons, segmentation of sheaths by nodes of Ranvier enables the rapid saltatory conduction of nerve impulses.

Axon terminals - synapses

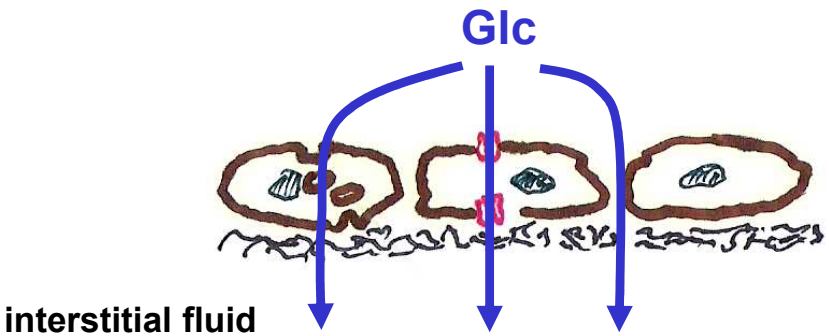
– neurotransmitters are released from synaptic vesicles into the synaptic cleft by exocytosis.

Glucose

is the **main nutrient** for the nervous system. If glucose is lacking (prolonged starvation), utilization of **ketone bodies** can meet up to one half of requirements for energy.

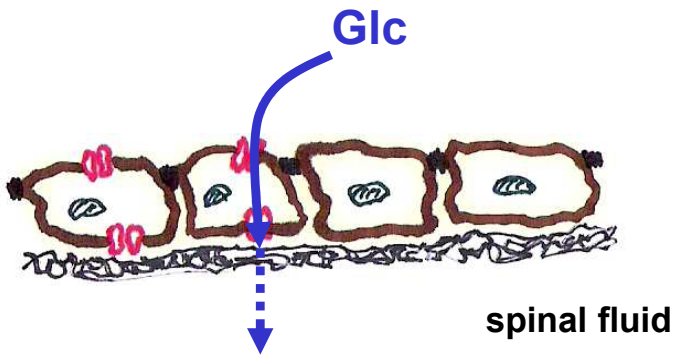
In CNS, the **transport of glucose through capillary walls** is much less efficient, when compared with other tissues. Thus impairments of consciousness are usually the first clinical symptoms of hypoglycaemia.

Walls of blood capillaries in peripheral tissues



– free diffusion through intercellular space
– pinocytosis (transcytosis)
– glucose transporters

- in in the brain

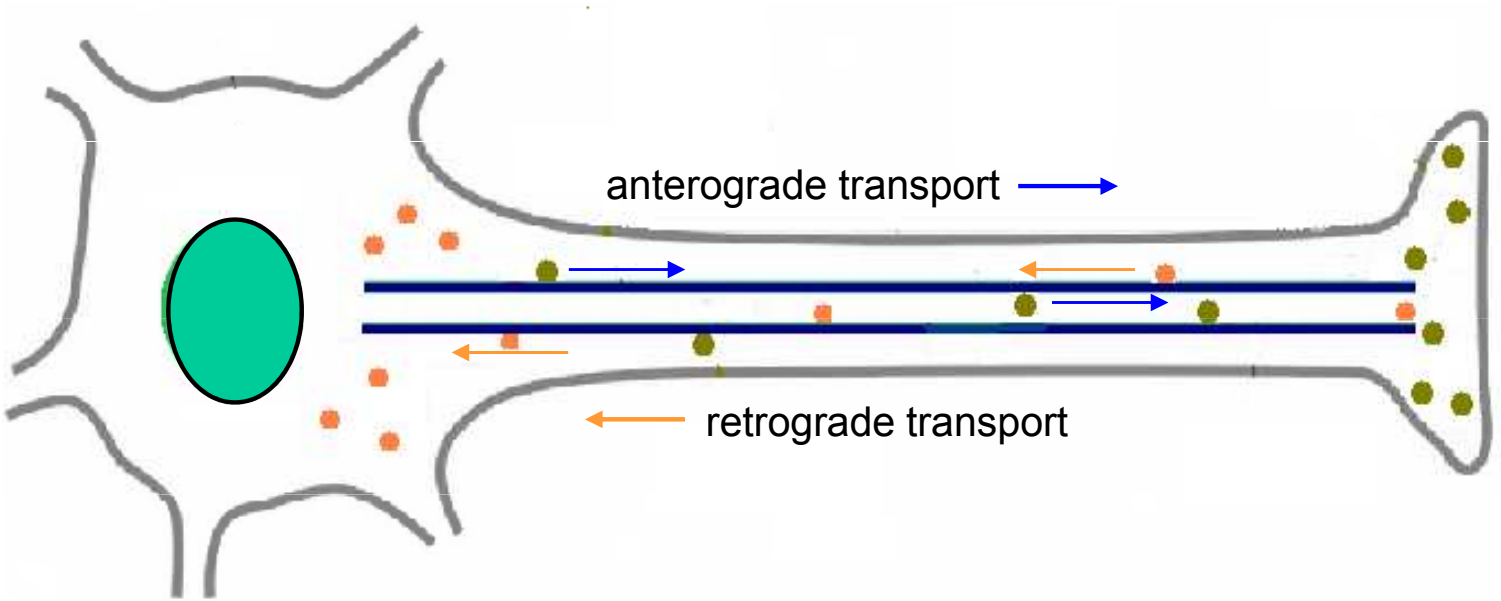


– numerous tight junctions limit free diffusion
– no pinocytosis
– the basement membrane is highly consistent
– transporters GLUT3 have low efficiency

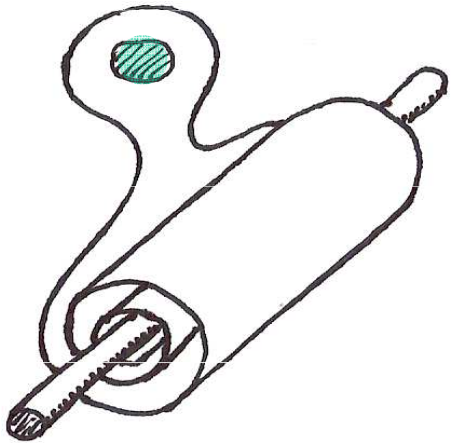
Axonal transport

In the axon, there is a fast axonal transport along microtubules. It works on the principle of a molecular motor, via the motile proteins.

Kinesin drifts proteins, synaptic vesicles, and mitochondria in anterograde transport, **dynein** in retrograde transport.



Myelin

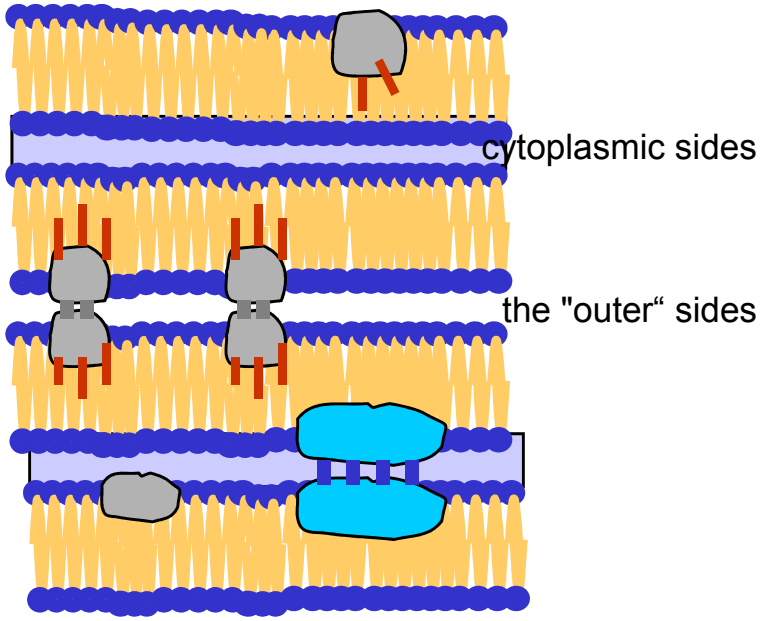


Myelin sheaths are formed by wrapping of protruding parts of glial cells round the axons; oligodendrocytes produce myelin sheaths in CNS, the Schwann cells in the peripheral part of the nervous system. Numerous plasma membranes are tightly packed so that the original intracellular and extracellular spaces cannot be differentiated easily.

Myelin membranes contain about 80 % lipids.

The main proteins are

- proteolipidic protein,
- the basic protein of myelin (encephalitogen),
- high molecular-weight protein called Wolfram's protein.



Nerve impulse

Neurons are irritable cells that react, after an adequate stimulation, by formation of **nerve impulses – action potentials** caused by changes in ion flows across cell membranes. Action potential spread without decreasing along axons to the axon terminals.

The lipidic dilayer is practically impermeable to the unevenly distributed Na^+ and K^+ ions. The **resting membrane potential** –70 mV on the inner side of the plasma membrane.

Sodium and potassium ion channels allow the passive passage across the membrane:

- **leakage (voltage-independent) K^+ channels,**
- **ligand-gated Na^+/K^+ channel,**
- **voltage-operated Na^+ channel,** and
- **voltage-operated K^+ channel.**

The inward flow of Na^+ is the cause of **depolarization** (spike potential), the following outward flow of K^+ **repolarization** and the refractory phase.

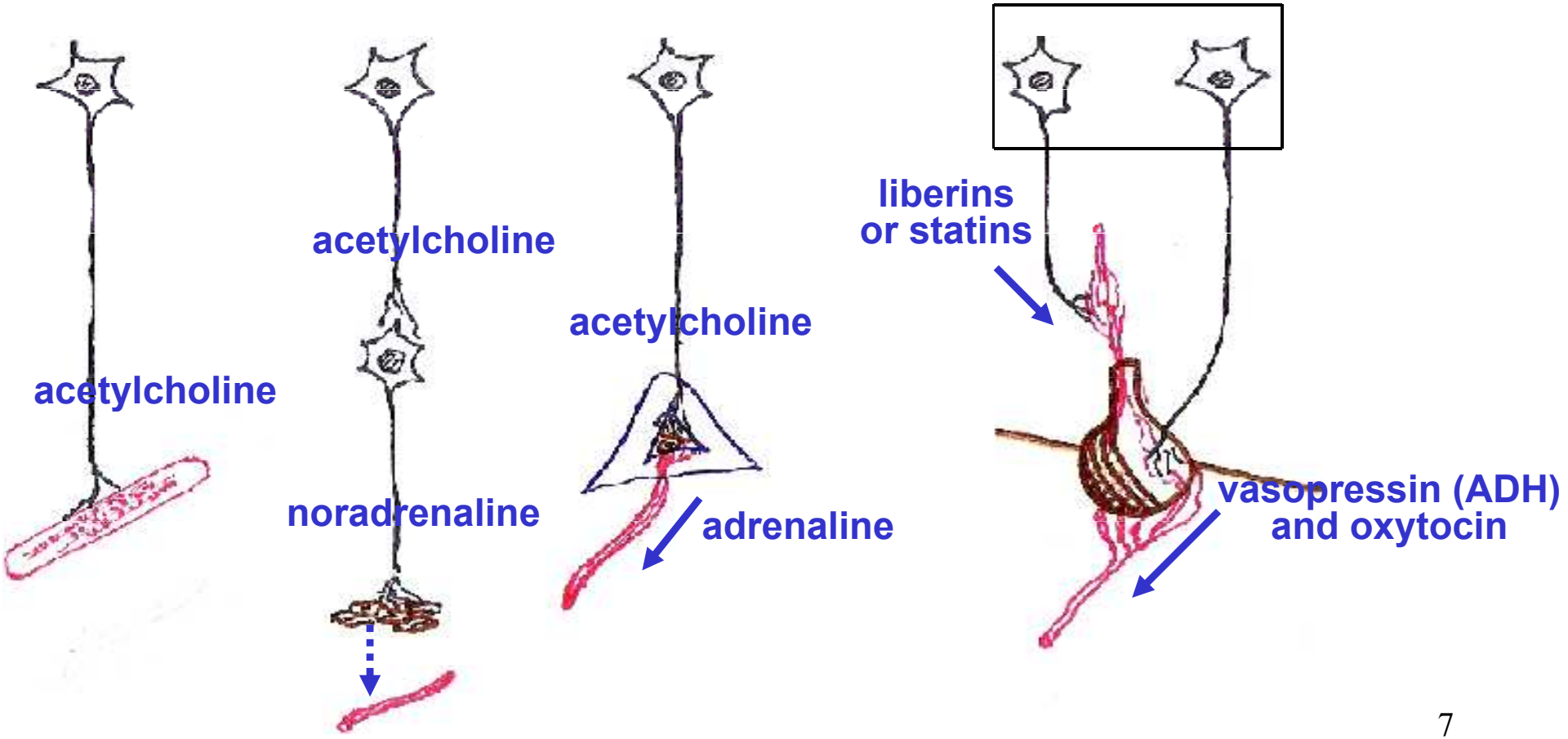
The original uneven distribution of ions is restored by

- **Na^+,K^+–ATPase**.

Neurosecretion

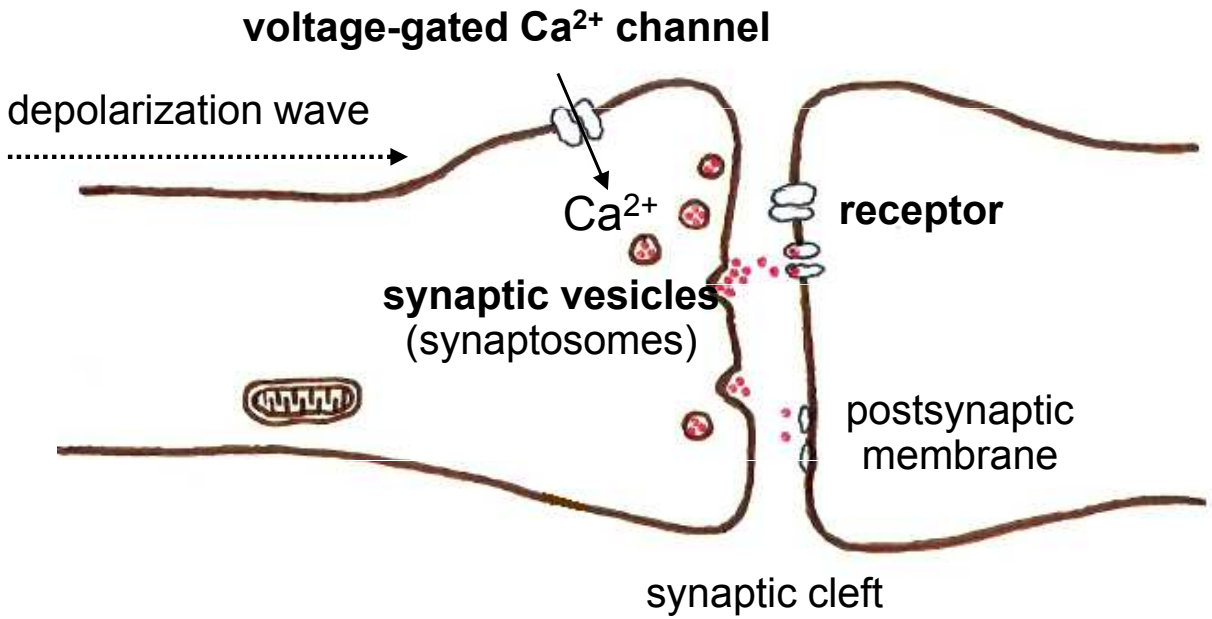
Stimulated neurons release **neurotransmitters** by exocytosis of synaptic vesicles (synaptosomes) into the synaptic clefts.

In the central nervous system, specific neuron types release **neurohormones** or other **neuropeptides**, which may have special regulatory functions (co-transmitters, neuromodulators).



Synaptic transmission

Neurotransmitters act as **chemical signals** between nerve cells or between nerve cells and the target cells.



The response to the neurotransmitter depends on the receptor type:

- **ionotropic receptors** (ion channels) evoke a change in the membrane potential - an electrical signal,
- **metabotropic receptors** are coupled to second messenger pathway, the evoked signal is a chemical one.

Neurotransmitters

A large number (much more than 30) of neurotransmitters have been described. Many of them are derived from simple compounds, such as **amino acids** and **biogenic amines**, but some **peptides** are also known to be important neurotransmitters. The principal transporters:

Central nervous system

inhibitory **GABA** (at least 50 %)
glycine (spinal cord)

excitatory **glutamate** (more than 10 %)
acetylcholine (about10 %)
dopamine
(about 1 %, in the striatum 15 %)
serotonin
histamine
aspartate
noradrenaline (less than 1 %,
but in the hypothalamus 5 %)
adenosine

neuromodulatory **endorphins**, **enkephalins**, endozepines, delta-sleep inducing peptide, and possibly endopsychosins.

Peripheral neurons

– <u>efferent</u>
excitatory **acetylcholine**
noradrenaline

– <u>afferent sensory neurons</u>
excitatory glutamate
(Aβ fibres, tactile stimuli)
peptide substance P
(C and Aδ fibres, nociceptive)

Neurotransmitter receptors

In contradistinction to numerous types of hormone receptors, only two basal types of neurotransmitter receptors occur:

Ionotropic receptors – ligand-gated ion channels (ROC), e.g.

excitatory – **acetylcholine nicotinic** - Na^+/K^+ channel,

– glutamate (CNS, some afferent sensory neurons)
- $Na^+/Ca^{2+}/K^+$ channel,

inhibitory – **$GABA_A$ receptor** (brain) - Cl^- channel

Metabotropic receptors activating G proteins, e.g.

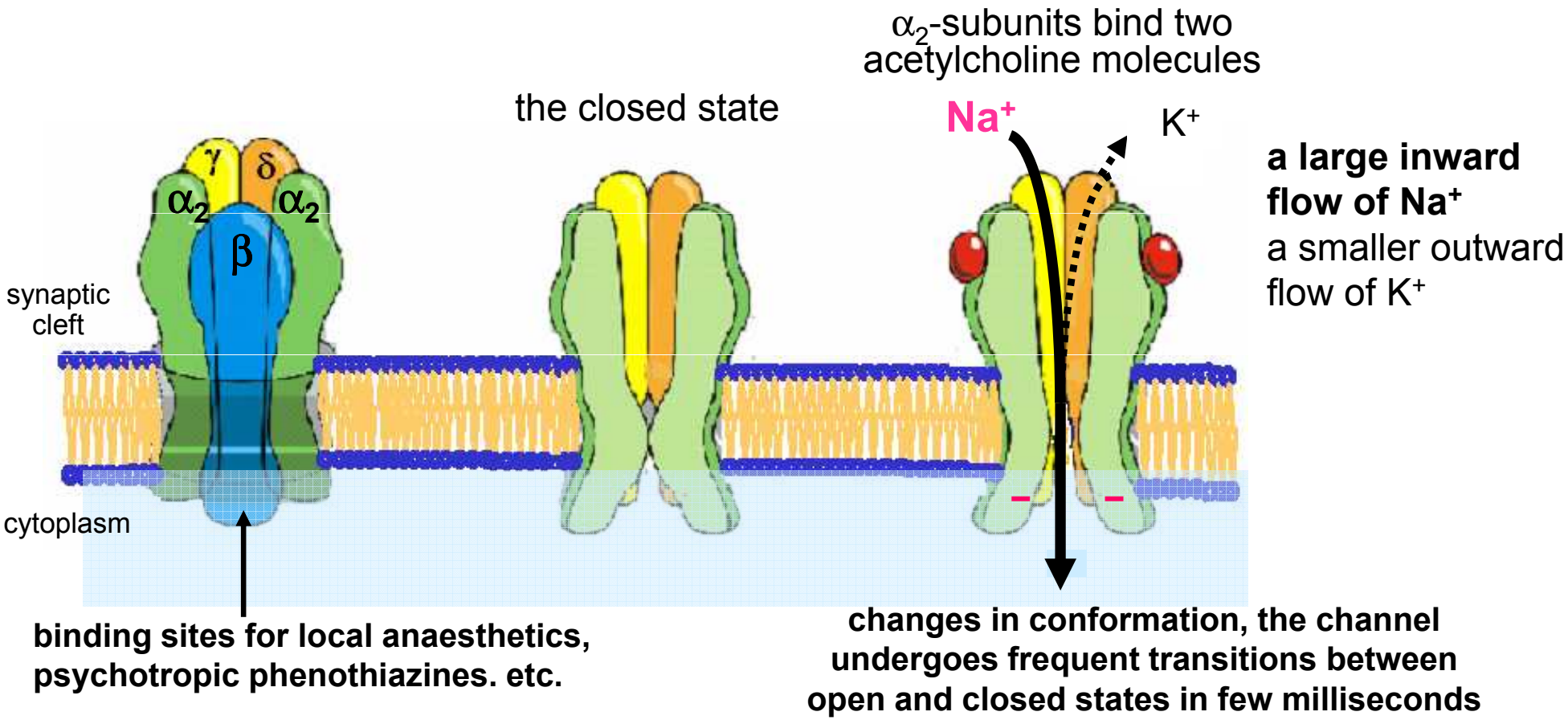
G_s protein – **β-adrenergic**, $GABA_B$ receptor, dopamine D_1,

G_i protein – **α_2-adrenergic**, dopamine D_3,
acetylcholine muscarinic M_2 (opens also K^+ channel),

G_q protein – **acetylcholine muscarinic M_1, α_1-adrenergic.**

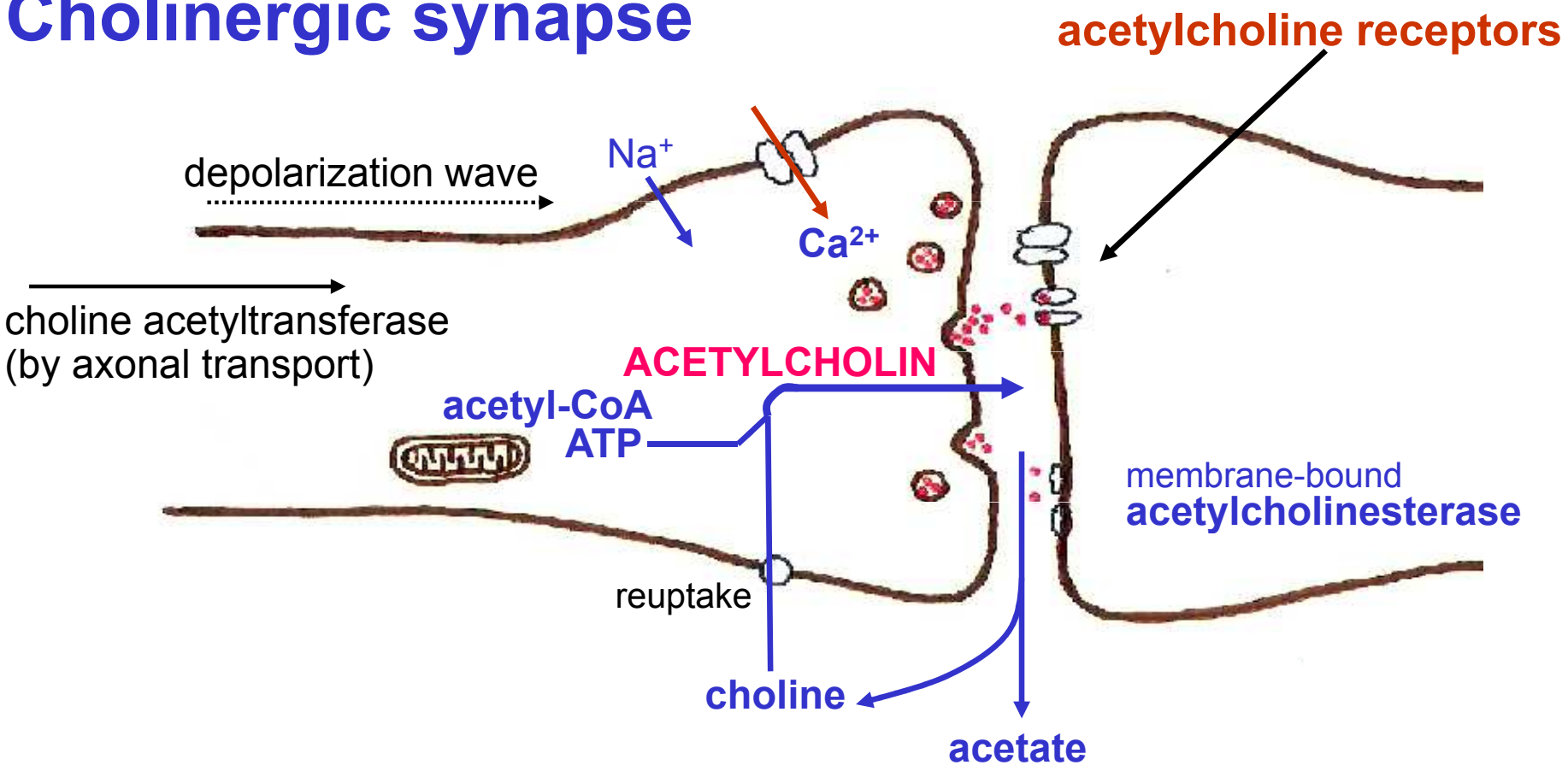
Ligand-gated ion channels (ROC, receptor-operated channels)

Acetylcholine nicotinic receptor – Na^+/K^+ channel, e.g., is the asymmetric pentamer of four kinds of membrane-spanning homologous subunits that is activated by binding of two molecules of acetylcholine.



D-**Tubocurarine** is an antagonist of acetylcholine that prevents channel opening.
Succinylcholine is a myorelaxant that produces muscular end plate depolarization.

Cholinergic synapse



Increase in intracellular [Ca^{2+}] activates Ca^{2+}-calmodulin-dependent protein-kinase that phosphorylates synapsin-1; its interaction with the membrane of synaptic vesicles initiates their fusion with the presynaptic membrane and neurotransmitter exocytosis. The membranes of vesicles are recycled.

At neuromuscular junctions, the arrival of a nerve impulse releases about 300 vesicles (approx. 40 000 acetylcholine molecules in each), which raises the acetylcholine concentration in the cleft more than 10 000 times.

Acetylcholine receptors

exist in two principal types that are named **nicotinic** and **muscarinic** after the two exogenous agonists.

Nicotinic cholinergic receptors

are acetylcholine-operated **Na^+/K^+ channels** (see picture 11);

in the peripheral nervous system, they occur

- in the dendrites of nearly all peripheral efferent neurons (including adrenergic neurons), and
- at neuromuscular junctions ion the cytoplasmic membranes of skeletal muscles.

Muscarinic cholinergic receptors

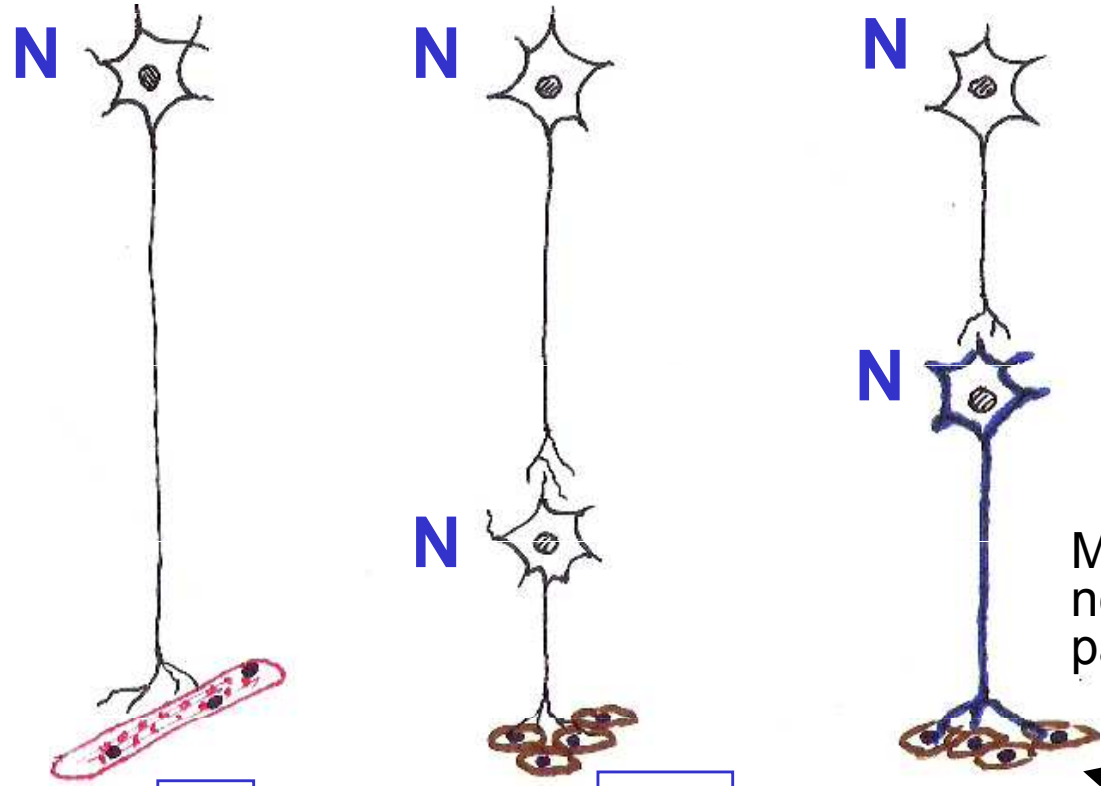
Five **types M_{1-5}** that exhibit different functions are known.

In the peripheral tissues innervated by the parasympathetic system, receptors **M_1** predominate, the other types occur mostly in CNS.

After acetylcholine has bound at **muscarinic receptors M_1**, the complex **activates G_q proteins**; the consequence - activation of the phosphatidylinositol cascade: IP_3 increases the **intracellular Ca^{2+}** concentration, **proteinkinase C** is activated by diacylglycerol.

Atropin is an acetylcholine antagonist at muscarinic receptors.

Acetylcholine (cholinergic) receptors of the peripheral efferent neurons



Most postganglionic neurons of the sympathetic path are **adrenergic**

N

M_1

Adrenergic receptors

motor neurons (neuromuscular junction)

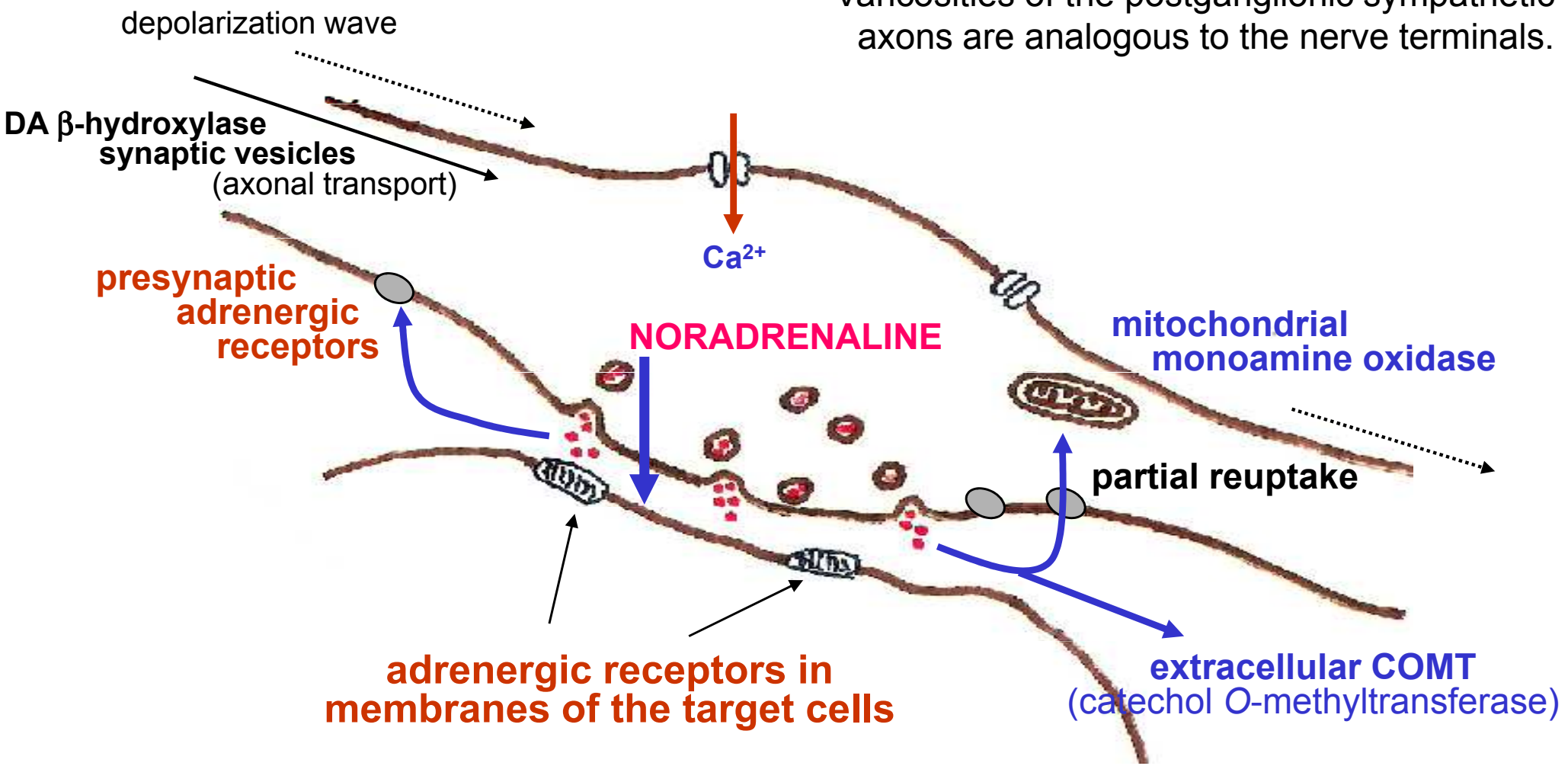
parasympathetic system

sympathetic system

Adrenergic synapse

Neurotransmitter of most postganglionic sympathetic neurons is **noradrenaline**.

Varicosities of the postganglionic sympathetic axons are analogous to the nerve terminals.



Adrenergic receptors

of all types are receptors cooperating with G proteins.

β-Adrenergic receptors

After binding an agonist, all types of β-receptors **activate G_s proteins** so that adenylate cyclase is stimulated, **cAMP** concentration increases, and **proteinkinase A** is activated. Particular types differ namely in their location and affinity to various catecholamines:

- β_1 are present in the membranes of cardiomyocytes,
- β_2 in the smooth muscles and blood vessels of the bronchial stem,
- β_3 in the adipose tissue.

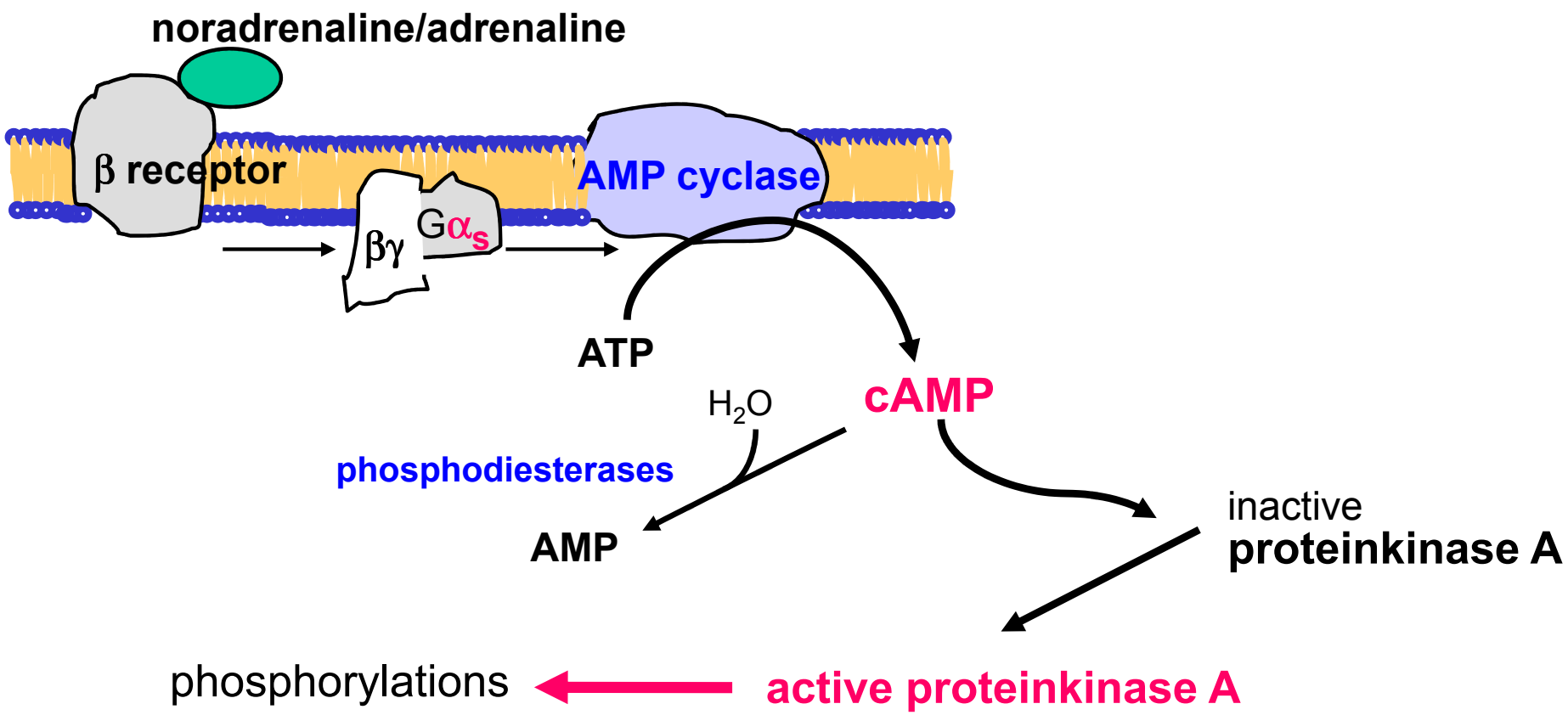
α_2-Adrenergic receptors

The effect is quite opposite to that of β-receptors, binding of catecholamines results in the **interaction with G_i protein**, **decrease in adenylate cyclase activity and in cAMP** concentration.

α_1-Adrenergic receptors

activate G_q proteins and initiate the phosphatidylinositol cascade by **stimulation of phospholipase C** resulting in an increase of intracellular Ca^{2+} concentration and activation of proteinkinase C.

Adrenergic receptors β_1, β_2, and β_3



The **typical effects** of β-stimulation:

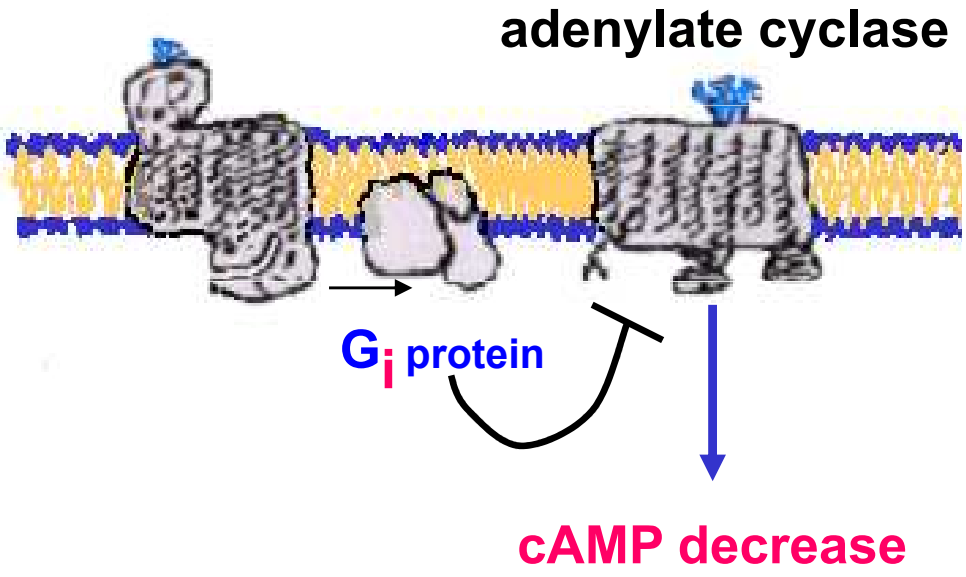
β_1 – tachycardia, inotropic effect in the myocard,

β_2 – bronchodilation, vasodilation in the bronchial tree,,

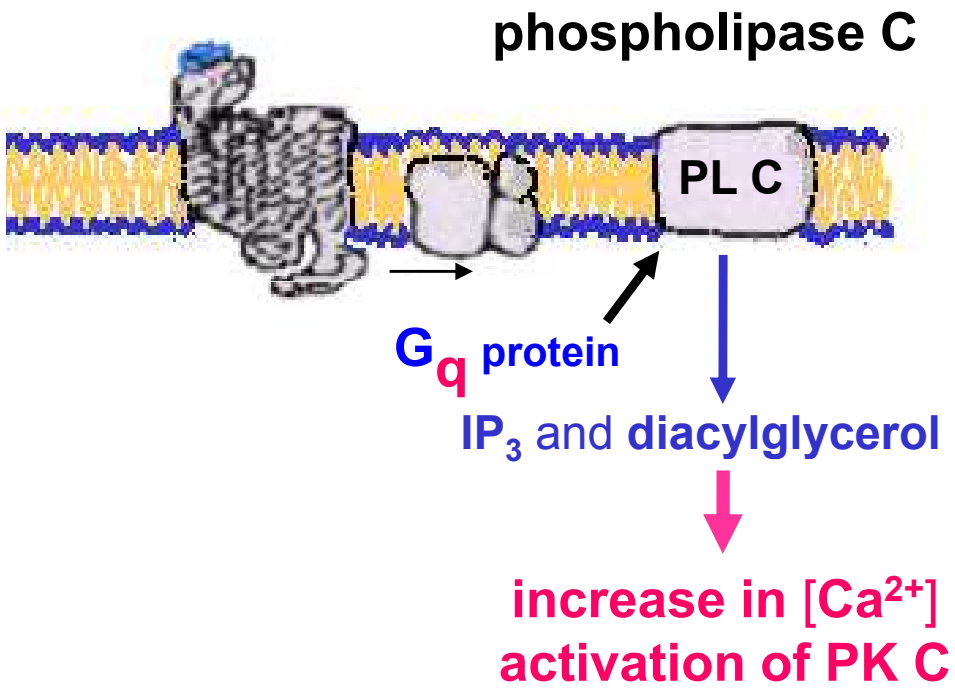
β_3 – mobilization of fat stores, thermogenesis.

Adrenergic receptors α_2 a α_1

Receptors α_2



Receptors α_1



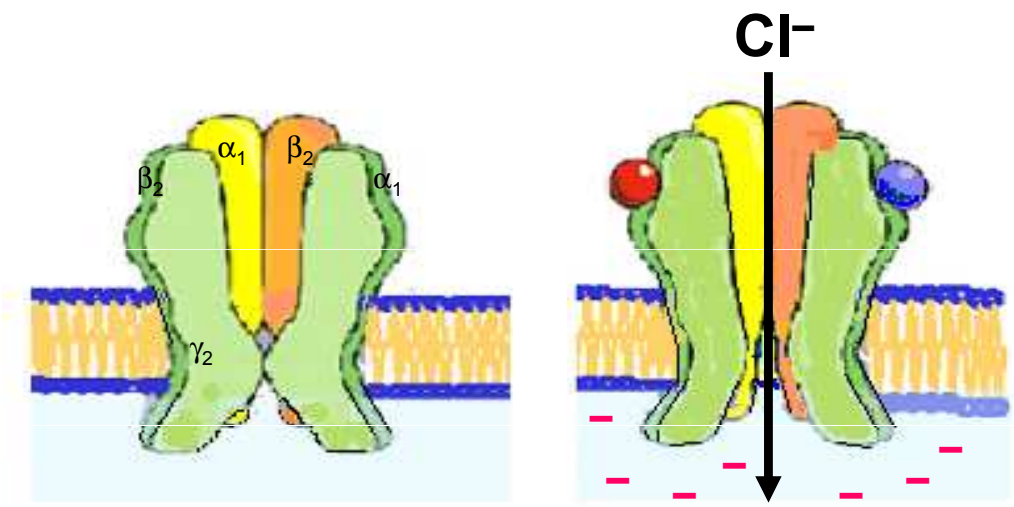
The **typical effects of adrenergic**

α_2-stimulation:
glandular secretion inhibited

α_1-stimulation:
vasoconstriction
bronchoconstriction
motility of GIT inhibited

Inhibitory $GABA_A$ receptor

is a ligand-gated channel (ROC) for **chloride anions**. The interaction with **γ-aminobutyric acid (GABA)** opens the channel. The influx of Cl^- is the cause of **hyperpolarization** of the postsynaptic membrane and thus its depolarization (formation of an action potential) disabled.

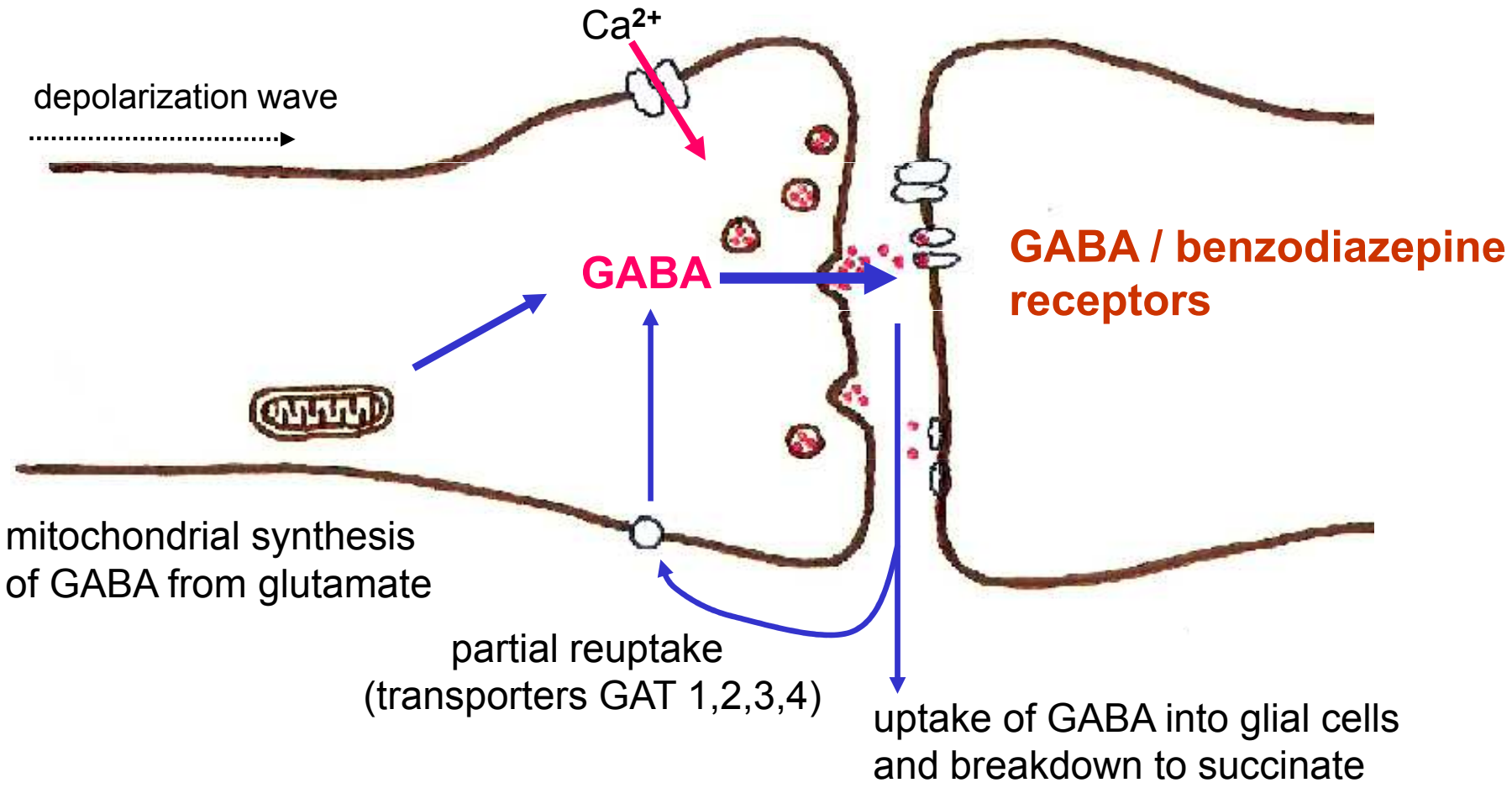


The receptor is a heteropentamer (three subunit types). Besides the **binding site for GABA**, it has at least eleven **allosteric modulatory sites** for compounds that enhance the response to endogenous GABA – reduction of anxiety and muscular relaxation: anaesthetics, ethanol, and many useful drugs, e.g. benzodiazepines (hence the alternative name **GABA/benzodiazepine receptors**), meprobamate, and also barbiturates. Some ligands compete for the diazepam site or act as antagonists (inverse agonists) so that they cause discomfort and anxiety, e.g. endogenous peptides called endozepines.

In the spinal cord and the brain stem, **glycine** has the similar function as GABA in the brain. The inhibitory actions of glycine are potently blocked by the alkaloid **strychnine**, a convulsant poison in man and animals.

Inhibitory synapse

GABA (γ-aminobutyric acid) is the major inhibitory neurotransmitter in CNS. Gabaergic synapses represent about 60 % of all synapses within the brain.



Receptors for the major neurotransmitters

Ion channels (ROC)	**Receptors cooperating with G-proteins**		
	G_s (cAMP increase)	G_i (cAMP decrease)	G_q (IP_3/DG formation)
Na^+/K^+ – **acetylcholine nicotinic**	–	acetylcholine muscarinic $M_{2,4}$	**acetylcholine muscarinic $M_{1,3,5}$**
–	**adrenergic β_1, β_2**, β_3	**adrenergic α_2**	**adrenergic α_1**
$Na^+/Ca^{2+}/K^+$ – glutamate ionophors	–	glutamate mGluR group II and III	glutamate mGluR group I
–	dopamine $D_{1,5}$	dopamin $D_{3,4}$	dopamine D_2
– serotonin 5-HT_3	serotonin 5-$HT_{4,6}$	serotonin 5-HT_1	serotonin 5-HT_2
–	histamine H_2	histamine $H_{3,4}$	histamine H_1
–	–	–	tachykinin NK-1 for substance P
Cl^- – **$GABA_A$** – glycine	$GABA_B$ (metabotropic)	–	–