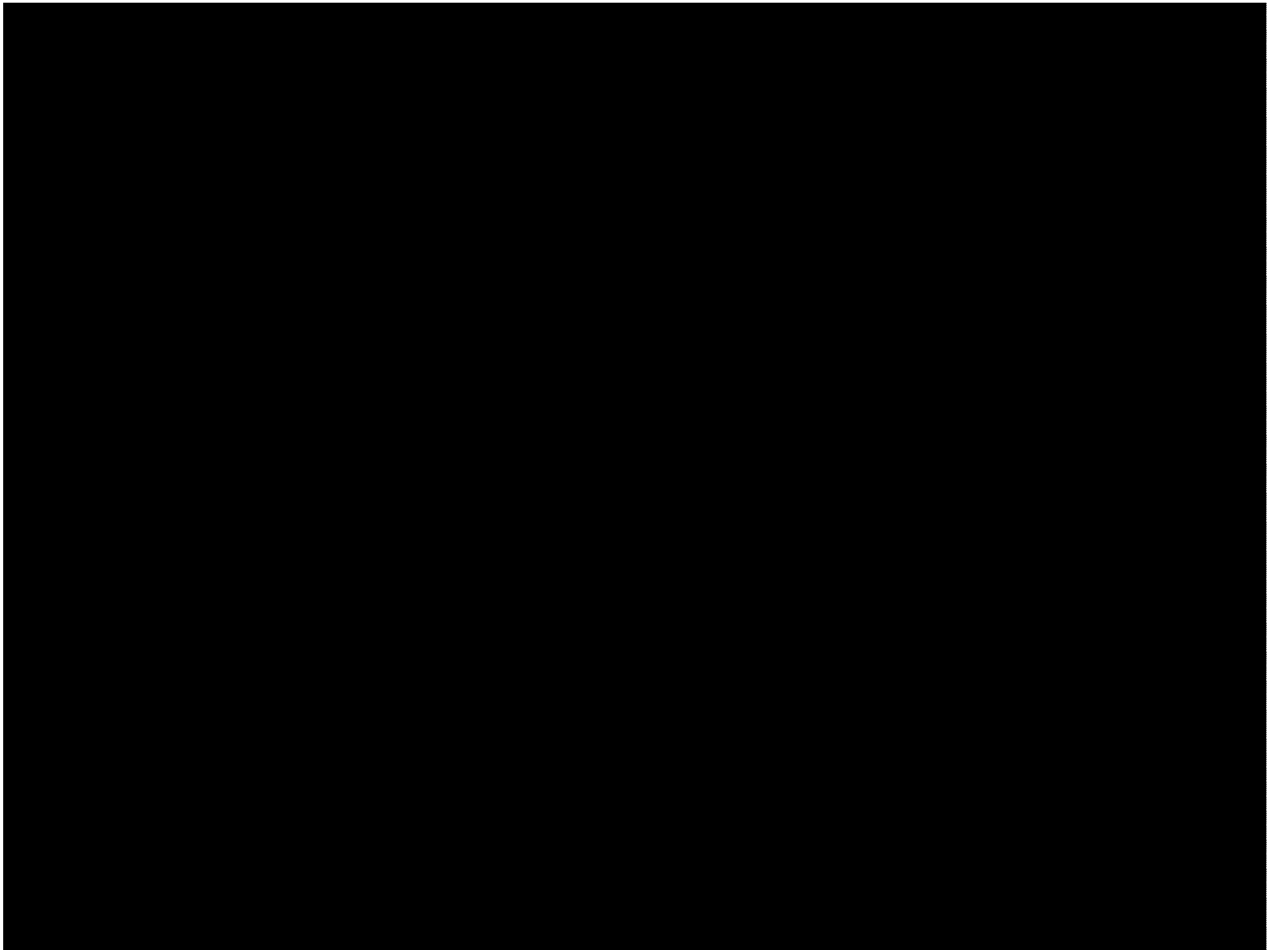
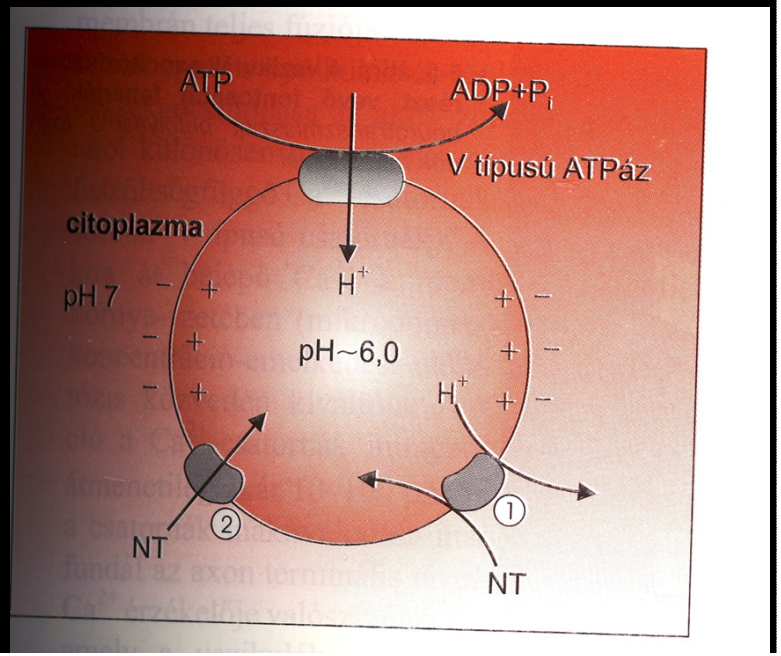
# Biochemistry of central nervous system (CNS)

# Blood-brain barrier (BBB)

- Endothelial cells, feet of astrocytes
- Small concentration changes do not affect the composition of cerebrospinal fluid
- Macromolecules do not cross the BBB
- Amino acids have special transporters
- Glucose diffuses freely




ATP
ADP+P$_i$
V típusú ATPáz
citoplazma
pH 7
H$^+$
pH~6,0
H$^+$
NT
②
①
NT

# General characteristics

- Cns IS BUILT UP FROM $2x10^{10}$ neurons and 3 times more glial cells
- The weigh of the human brain is about 2% of the total body weight, but glucose utilization reaches 66%
- The $O_2$ consumption is about 25% of the total
- The main energy source for the brain is ATP generated by oxidative phosphorylation
- creatine phosphate is able to store energy
- The CNS is protected from general metabolites of the blood plasma by the blood-brain-barrier
- Nervous tissue is rich in phospholipids, sphingolipids, which play an important role in cell membrane functions and myelin formation
- water content: Myelin 40%, white matter 70%, grey matter 80%

# Carbohydrate metabolism

- The usual main energy source is glucose which is metabolized to pyruvate and lactate via glycolysis (90%)
- Hexokinase activity is about 20x as high as other tissues
- The drop of glu concentration in CSF to 10-20% of the normal may cause come
- B vitamins are important in the function of pyruvate dehydrogenase complex (vitamin $B_1$, $B_2$, $B_3$, $B_5$)
- lack of vitamin $B_1$ causes Wernike-Korsakoff syndrome

- TCA cycle is fully used
  minimal amount lactate leave the brain
- Anoxia = lack of oxygen supply
- low blood glucose level
- Risk the function of the brain

# Carbohydrate metabolism

- Glucose is not only an energy source, but is also used for the synthesis of gangliosides, cerebrosides and various glycoprotein of the CNS
- Glycogen content is less than 0.1%
- In chronic hypoglycemia ketone bodies can be used as energy source
- GLUT transporters of the brain are insulin independent
- 3-5% of glucose is used in HMP shunt to produce NADPH for fatty acid and cholesterol synthesis and to produce ribose

# ATP

- For maintaining the activity of ATP driven **ion pumps**
- For the fast turnover of **RNA**, **proteins** and **transmitter substances**
- For assembly of **cytoskeletal system**
- For **motor proteins** involved in axonal and vesicle transport processes
- To maintain the high activity of different **kinases**

# Amino acid and protein metabolism

- There is an unequal distribution of amino acids between the CNS and the blood plasma
- CNS contains in general 4 times more amino acids and about 400 times more glutamate and aspartate than other tissues
- The high glutamate level is essential for the synthesis of both the main excitatory(glutamate) and inhibitory (GABA) amino acids of the brain
- Another important role is to remove ammonia

# Lipid metabolism

- Fatty acids for cell membranes and myelin are synthesized within the CNS since they slowly pass the blood-brain-barrier
- thus the rate of their synthesis is high at early stages of the life
- CNS is rich in very long chain (C22-C24 atoms) fatty aids
- Due to a slow turnover, fatty acid synthesis decreases with age
- This is also true for cholesterol (about 25% of total chol. content of the body is found in the CNS)

# Nucleic acid and nucleotides

- **Moto neurons** and large **pyramidal cells** contain the highest **RNA** concentration of the body
- De novo synthesis of **pyrimidine** bases from $CO_2$ and glutamine as amino group donor does not take place due to the **absence of carbamoyl-phosphate synthetase**
- Enzymes of **purine** synthesis are present but synthesis is slow
- The lack of **hypoxanthine-guanine-phosphoribosyl transferase** may cause severe neurological disturbances (**Lesh-Nyhan syndrome**)

# Neurotransmitters

A. Classic neurotransmitters: small molecules, synthetized in axon terminals, stored in vesicles
   1. acetylcholine
   2. biogen amines
      - Catecholamines: dopamine, norepinephrine, epinephrine
      - Serotonin
      - Histamine
   3. Amino acids
      - excitatory: Glutamate, aspartate
      - inhibitory: GABA, glycine
   4. Purinerg transmitters
      - ATP
      - adenosine

B. Gas neurotransmitters
   - NO, (CO, $H_2S$)

C. peptides
   - Vasopressin, Cholecystokinin, VIP, substance P

# Glutamate

- Glutamate is the main excitatory neurotransmitter of the cerebral cortex
- Do not cross the blood-brain-barrier, it is synthesized within the axon terminals
- synthesis:
  - Transamination of α-ketoglutarate
  - Deamination of glutamine
  - Glutamate dehydrogenase

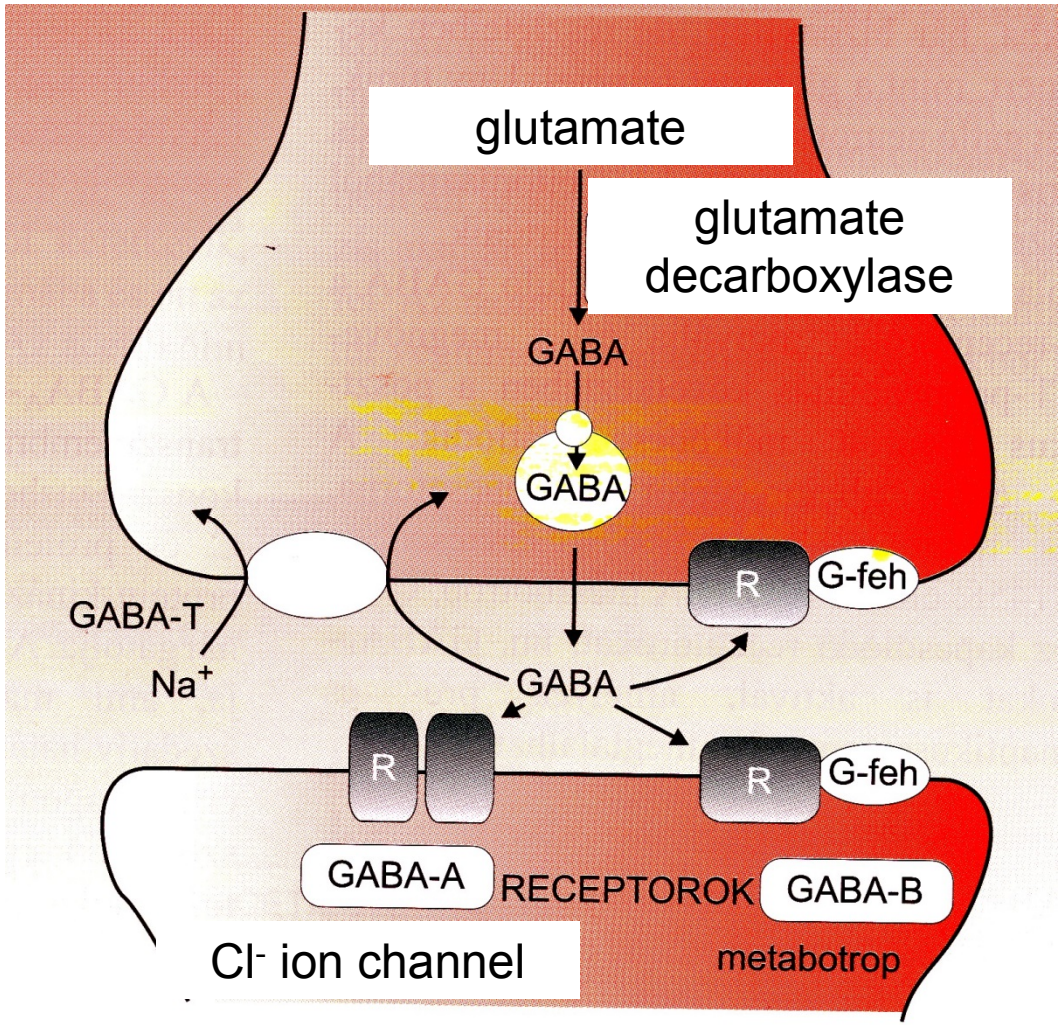
# Glutamate receptors

- 1.IONOTROPIC receptors
  - Ion channels
  - NMDA: N-methyl-D-aspartate
  - AMPA: α-amino-3-OH-5-metil-4-izoxazol-propionsav
    - They open sodium channels and cause depolarization resulting in an excitatory postsynaptic potential
  - kainic

- 2.METABOTROPIC receptors
  - G protein-coupled receptors
  - Pre and postsynaptic receptors
  - presynaptic receptors can inhibit or activate
- Inactivating
  - presynaptic reuptake

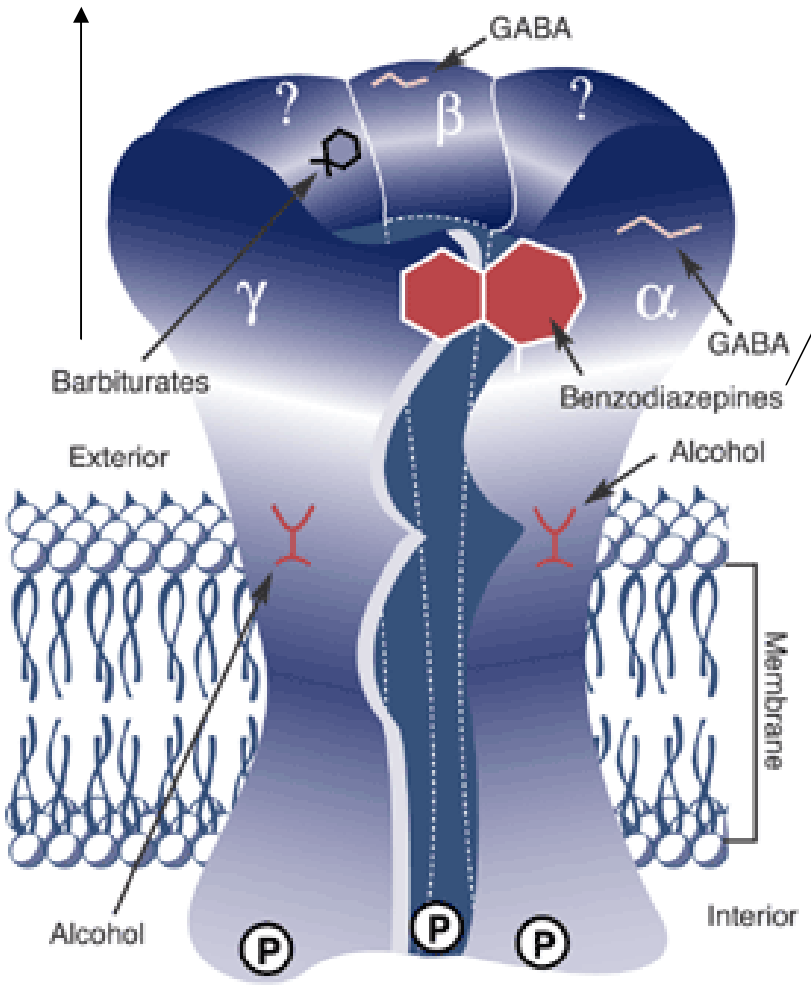
# GABA

- This is the major inhibitory transmitter of the cerebral cortex
- It is formed by the glutamate decarboxylase enzyme from glutamate



# GABA receptors

long open period

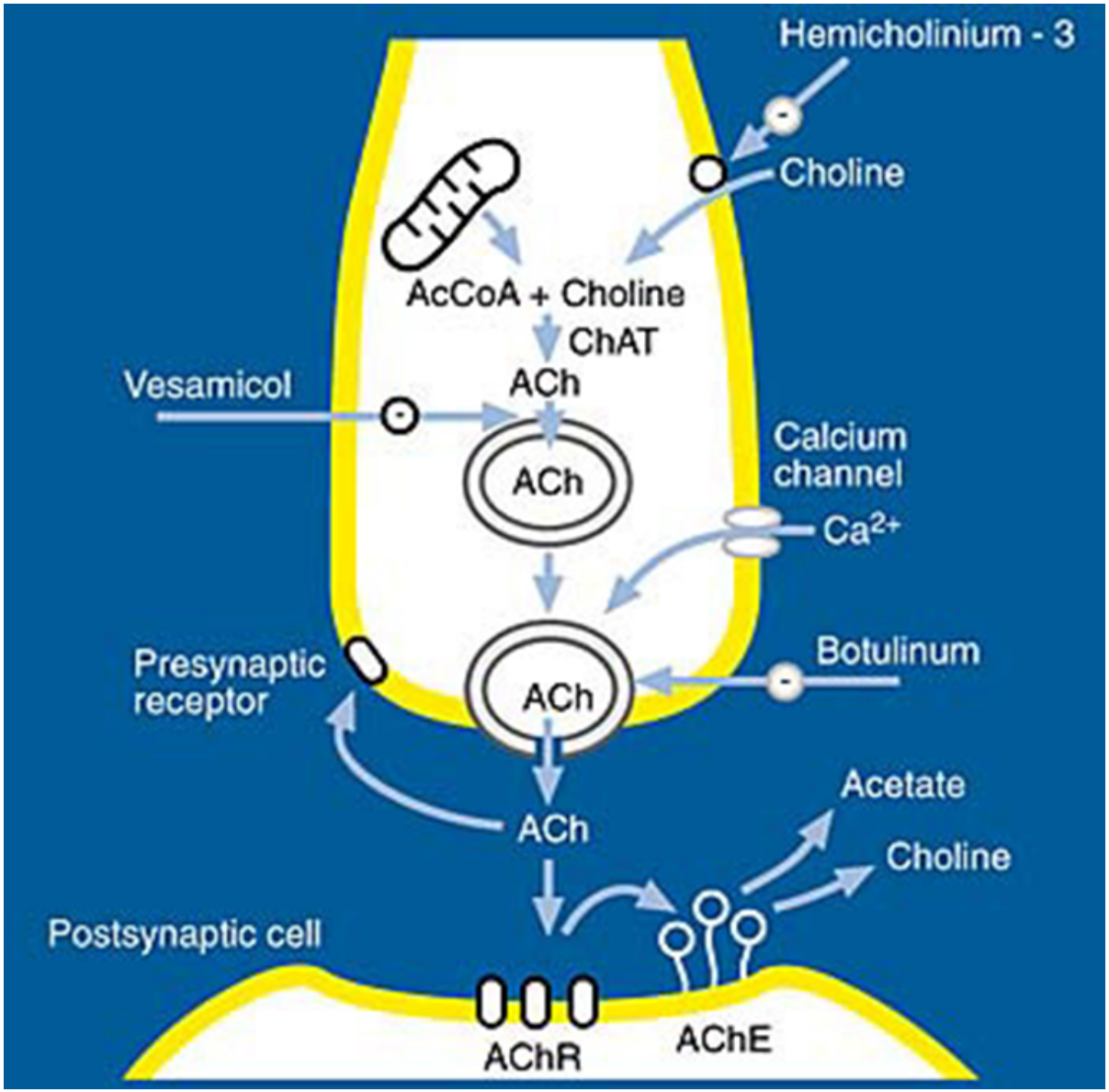



increase the possibility of opening

- **GABA A receptor**
- Cl- channel
- Several allosteric sites
- intracell. phosphorylation sites
- alcohol stimulate it (sedative effect)

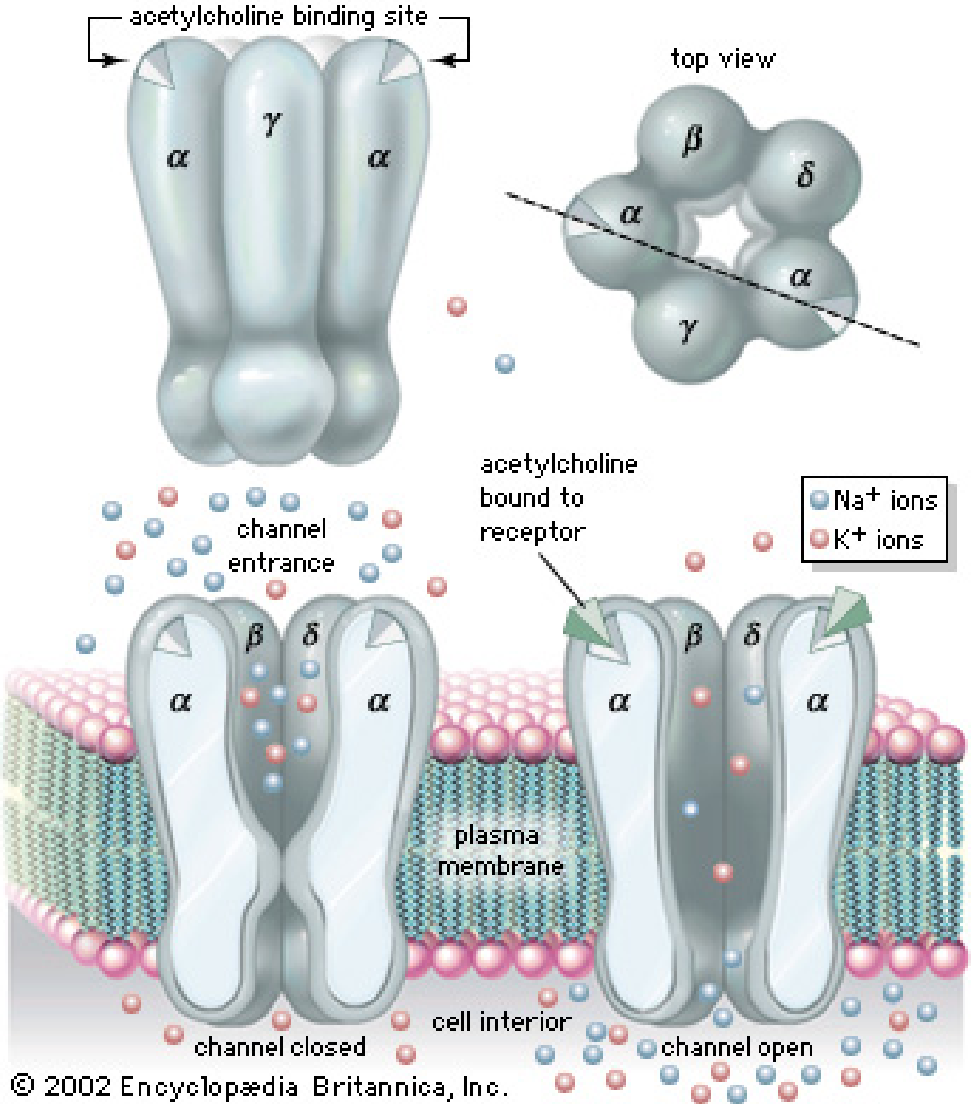
**GABA B receptor**
- **metabotropic, G protein coupled**

# ACETYLCHOLINE




- Serine => ethanolamine => choline
- Nicotinic Ach receptors: ion channel
- Muscarinic Ach receptors: G protein coupled receptors, 7 transmembrane domain
- ACh-estherase inactivates it

# nicotinic acetylcholine receptors




- nicotine activates it
- ionotrop receptors
- Nicotinic receptors are made up of five receptor subunits
- Opening of the channel allows positively charged ions, in particular, **sodium** and calcium, K, to enter the cell.
- can be blocked by curare
- Found in the neuromuscular junction

- CNS (2 types)
- positively charged ions
- depolarization

# Muscarinic acetylcholine receptor

- **Muscarinic receptors** are those membrane-bound acetylcholine receptors that are more sensitive to muscarine than to nicotine
- belong to a class of metabotropic receptors which use G proteins as their signaling mechanism.
- the signaling molecule (the ligand) binds to a receptor which has seven transmembrane regions, in this case the ligand is Ach.
- This receptor is bound to intracellular proteins, known as G proteins, which begin the information cascade within the cell.

*Amanita muscaria* from which muscarine was isolated

## Muscarinic Acetylcholine Receptors

| | M1 | M2 | M3 | M4 | M5 |
|---|---|---|---|---|---|
| Distribution | Cortex, hippocampus | Heart | Exocrine glands, GI tract | Neostriatum | Substantia nigra |
| G protein | Gαq | G αi | G αq | G αi | G αq |
| Intracellular response | Phospholipase C | Adenylyl cyclase inhibition | Phospholipase C | Adenylyl cyclase inhibition | Phospholipase C |

Receptor blockers: atropin, scopolamine

# Release of acetylcholine

- Inhibition (sympathetic effects)
- Botulinum toxin A (Clostridium species)
- It is sold commercially under the brand names **Botox** for this purpose.
- Botulinum toxin A :
  - it is used in minute doses both to treat painful muscle spasms, and as a cosmetic treatment
- Botulism: Double vision, drooping of both eyelids, loss of facial expression, swallowing problems, difficulty with talking, reduced movement of the muscles of respiration, dilated pupils, dry mouth and throat, constipation
- There are two primary Botulinum Antitoxins available for treatment of botulism

- Stimulation (parasympathetic effects)
- α-latrotoxin (widow spiders of the genus Latrodectus) (black widow, Latrodectus mactans); (redback spider, Latrodectus hasseltii);
- Piloerection, raised blood pressure, generalized muscle pain, abdominal cramps, extreme sweating, .
- Antivenin

# Cholinergic receptor inhibitors

- **Nicotinic receptor**
- ❑ Tubocurarine (non-depolarizing neuromuscular-blocking drug)
- climbing vine (Chondrodendron tomentosum)
- skeletal muscle relaxation
- ❑ Succinylcholine
- depolarizing neuromuscular blocker (does not allow the muscle cell to repolarize)
- First small, local, involuntary muscle contraction
- paralytic effect

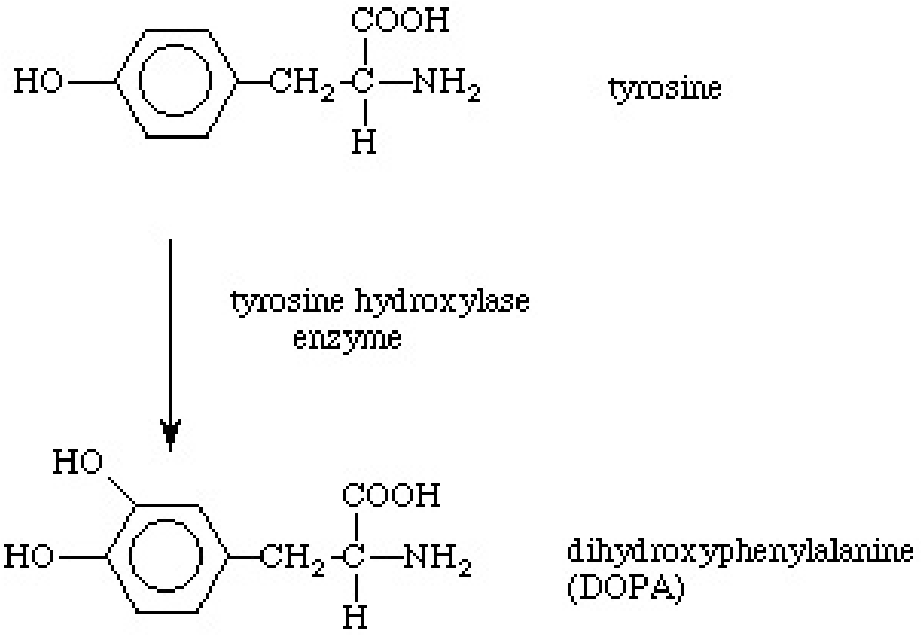
- **Muscarinic receptor**
- Muscarine, atropine, scopolamine
- Heart: increased heart rate, contractility
- Dilatation of pupil
- Decrease of gastrointestinal functions (secretion, peristaltic)

# Inhibitors of cholinesterase

- Reversible
- Physostigmine, neostigmine
- Intestinal atonia
- Diagnosis and therapy of myasthenia gravis
- Physostigmine is the antidote of atropin
- glaucoma, Alzheimer's disease
- parasympathomimetic alkaloids

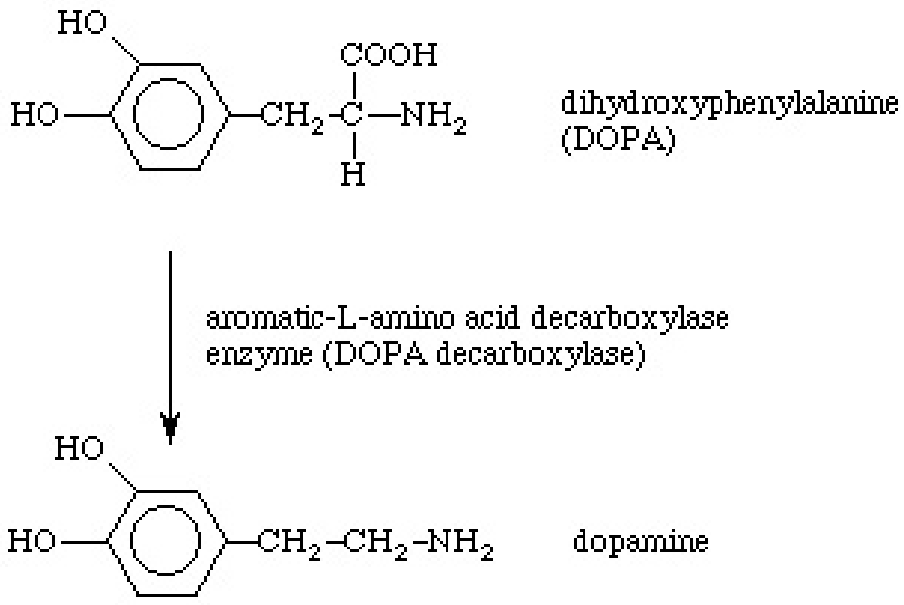
- Irreversible
- Alkylphosphates: DFP, malathione (insecticides)
- tabun, sarin (chemical weapons)
- runny nose, constriction of the pupils, difficulty breathing, nausea, victim vomits, defecates and urinates, coma, death
- Ecothiopate (glaucoma treatment), cyclophosphamide (cytotoxic-cytostatic drug)

# Catecholamines (dopamine, NA, A)




- The amino acid tyrosine is the starting material. It is taken up into catecholaminergic nerves by an active transport system
- inside the nerve, an additional hydroxyl group is added to the aromatic ring
- Tyrosine hydroxylation is the **rate limiting** step in the synthesis of catecholamines and is subject to feedback inhibition by the end products.

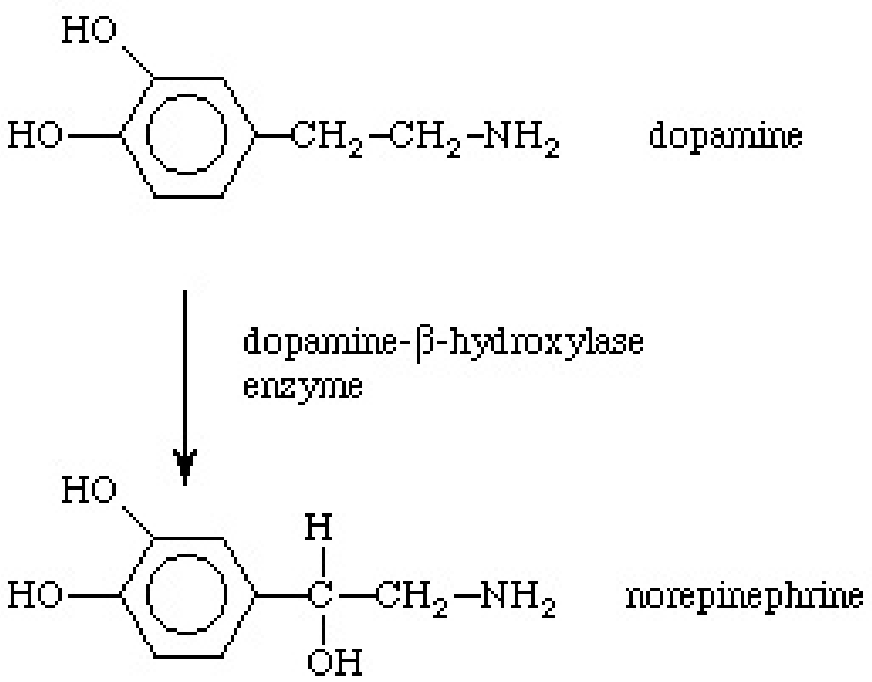
# Catecholamines (dopamine, NA, A)




- **DOPA decarboxylation**

- DOPA is used in the treatment of Parkinson's disease

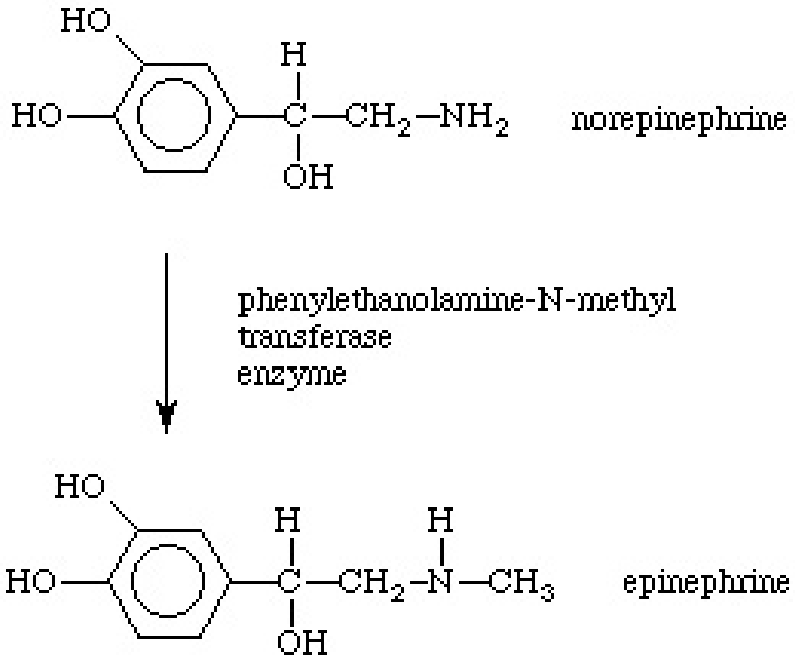
# Catecholamines (dopamine, NA, A)




- **Dopamine hydroxylation**

•DOPAMINE in catecholaminergic nerves is taken up into synaptic vesicles and is converted to norepinephrine (NE) by the addition of a hydroxyl group on the carbon second (beta) from the amino group

# Catecholamines (dopamine, NA, A)




**N-methylation**

# adrenergic receptors

- are a class of G protein-coupled receptors that are targets of the catecholamines
- There are several types of adrenergic receptors, but there are two main groups: α-Adrenergic and β-Adrenergic.
- receptors bind norepinephrine and epinephrine

# Roles in Circulation

- epinephrine reacts with both α- and β-adrenoreceptors, causing vasoconstriction and vasodilation, respectively.
- Although α receptors are less sensitive to epinephrine, when activated, they override the vasodilation mediated by β-adrenoreceptors.
- The result is that high levels of circulating epinephrine cause vasoconstriction.
- At lower levels of circulating epinephrine, β-adrenoreceptor stimulation dominates, producing an overall vasodilation.

# Inactivation of catecholamines

- Occurs by the action of 2 enzymes:

1. Monoamino-Oxidase (MAO)

   - MAO-A is present in extraneuronal tissues

   - MAO-B is a characteristic enzyme of the outer mitochondrial membrane of neurons

2. Catechol-O-methyl transferase (COMT)

# COMT

- It is present in glial cells and several extraneuronal tissues
- It methylates phenolic OH groups on catecholamines

---

- From epinephrine and norepinephrine


# Dopamine receptors

- are a class of metabotropic G protein-coupled receptors that are prominent in the vertebrate central nervous system (CNS).
- The neurotransmitter dopamine is the primary endogenous ligand for dopamine receptors.
- There are five subtypes of dopamine receptors, D1, D2, D3, D4, and D5.

# Patobiochemistry

- Defects of dopamine synthesis in substantia nigra results in Parkinsonism
- Therapy: L-DOPA
- Increased dopamine synthesis results in schizophrenia

# Serotonin

- Tryptophan → 5-hydroxytryptophan → serotonin (5-hydroxytryptamine)
- tryptophan hydroxylase, amino acid decarboxylase
- Receptors 5-$HT_1$, 5-$HT_{2,}$ 5-$HT_3$, 5-$HT_4$, 5-$HT_5$, 5-$HT_6$, 5-$HT_7$
- 5-HT receptors, are a group of G protein-coupled receptors
- Except 5-$HT_3$, it is a ligand gated ion channel
- central and peripheral nervous systems

# Serotonin

- Psychedelic drugs
  - Psilocybin (psilocybin mushrooms), mescaline (San Pedro cactus), LSD are agonists, primarily at $5HT_{2A/2C}$ receptors
- Antidepressants
  - Selective serotonin re-uptake inhibitors
    - Citalopram, Fluoxetine
  - Monoamine oxidase inhibitors
    - Benmoxin, …
- Antiemetics
  - 5-HT3 antagonists
    - ondansetron, granisetron, tropisetron

# Histamine

- Histidine → histamine
- histidine decarboxylase
- histamine receptors are a class of G protein-coupled receptors

➢ $H_1$ receptor
  - smooth muscles, glands, vascular endothelial cells, central nervous system
  - Allergic reactions, activity of CNS
  - Loratadine, Desloratadine
  - Hydroxyzine (ATARAX)

➢ $H_2$ receptor
  - mast cells, **enterochromaffin-like cells**, and neurons
  - gastric acid secretion
  - Ranitidine, …

➢ $H_3$, $H_4$ receptors