Sedative-hypnotics
Antiepileptics
Treatment of neurodegenerative disorders

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Sedative-hypnotics

Anxiolytic effect

reduction of anxiety without influencing motor or mental functions (not easy to distinguish from sedation)

Sedative effect

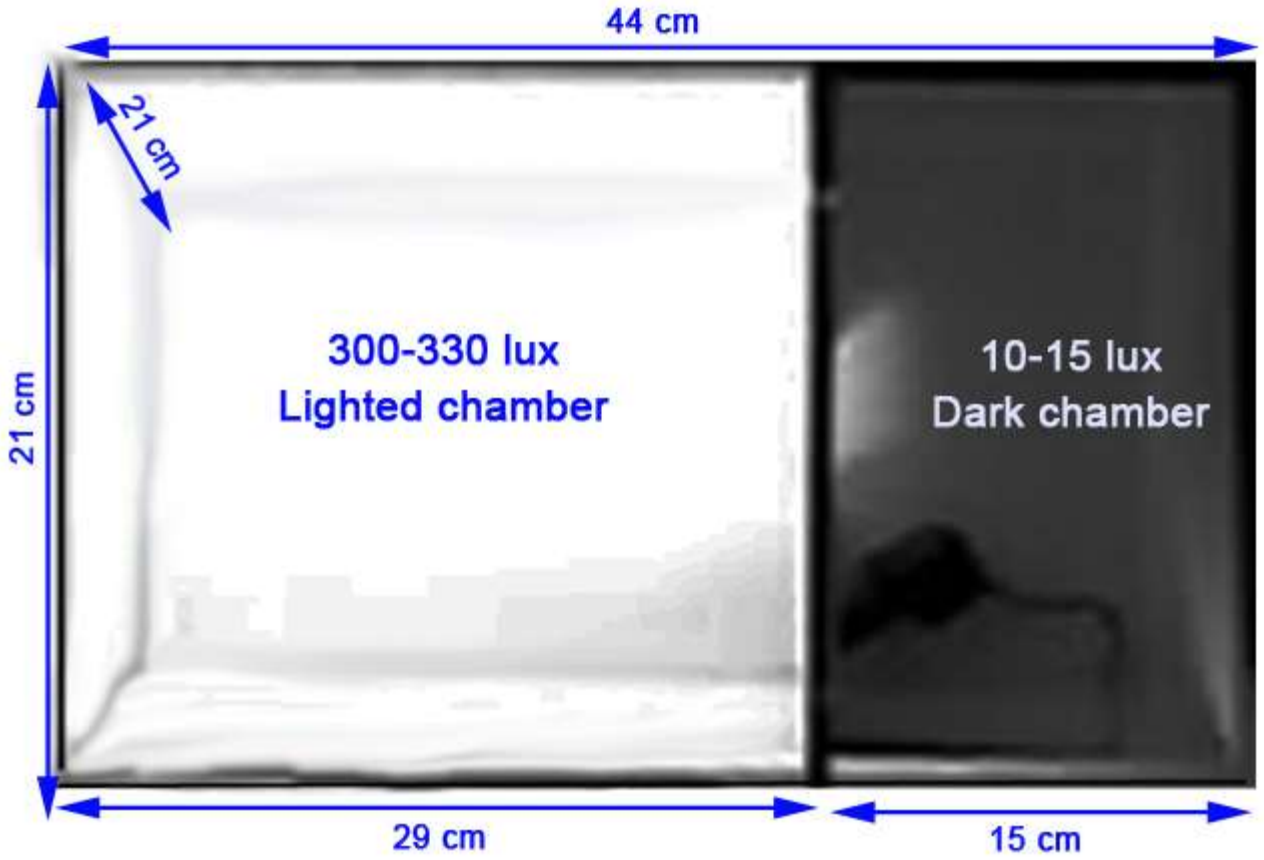
suppression of responsiveness to a constant level of stimulation; decrease of motor and mental functions

Hypnotic effect

producing drowsiness, promoting the onset and maintenance of a state of sleep that as far as possible resembles the natural sleep state

"elevated plus maze"

Light/dark box test



Anxiety disorders

- **Panic disorder** (dyspnea, palpitation, tremor, sweating, nausea - gastrointestinal discomfort, depersonalizations, feeling of hot/cold, substernal pain, fear of death, general fear)

Anxiety disorders

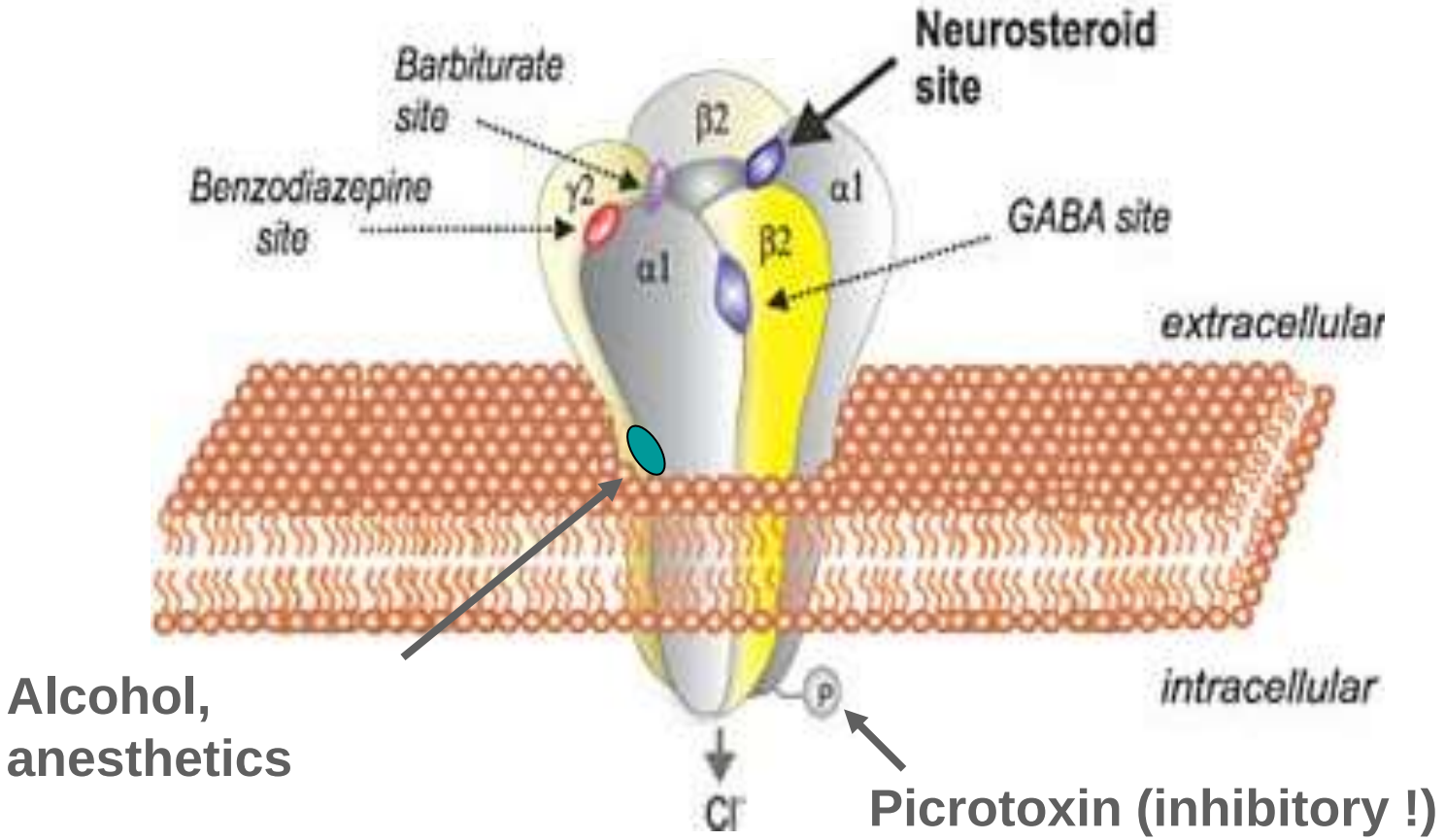
- **Obsessive-compulsive disorder (OCD)**
- **Posttraumatic stress disorder (PTSD)**
- **Generalized anxiety disorder (GAD)**
- **Premenstrual dysphoric disorder (PMDD)**

Mode of action of sedato-hypnotics

- GABA-erg model

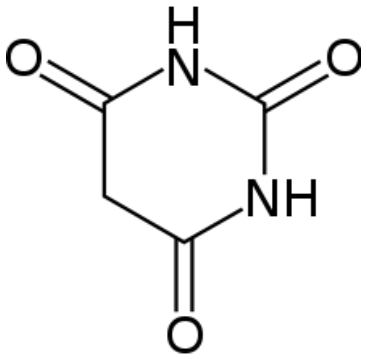
Mode of action of anxiolytics

- GABA-erg model
- 5-HT-erg model
- NA-erg model



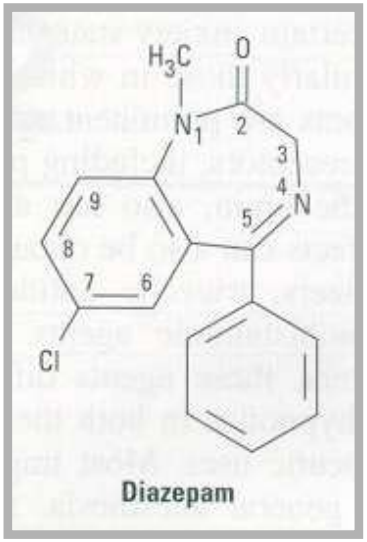
Benzodiazepines and barbiturates are positive allosteric modulators.

Structure of barbiturates

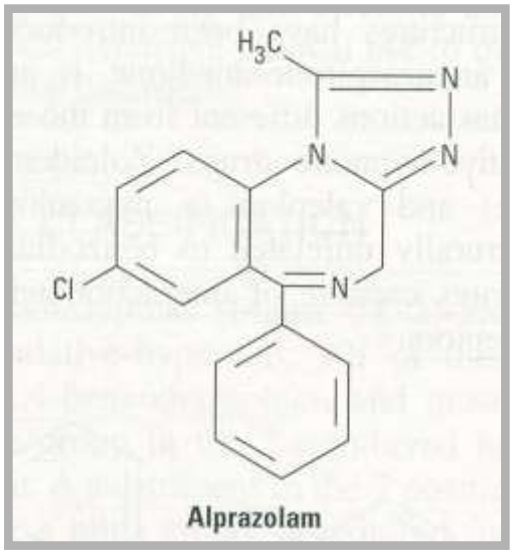


Barbituric acid

Structure of benzodiazepines



Diazepam



Alprazolam

Stimulation of BZ binding site

↓

increases the frequency of opening of Cl^- channel

Stimulation of barbiturate binding site

↓

prolongs the opening of Cl^- channel

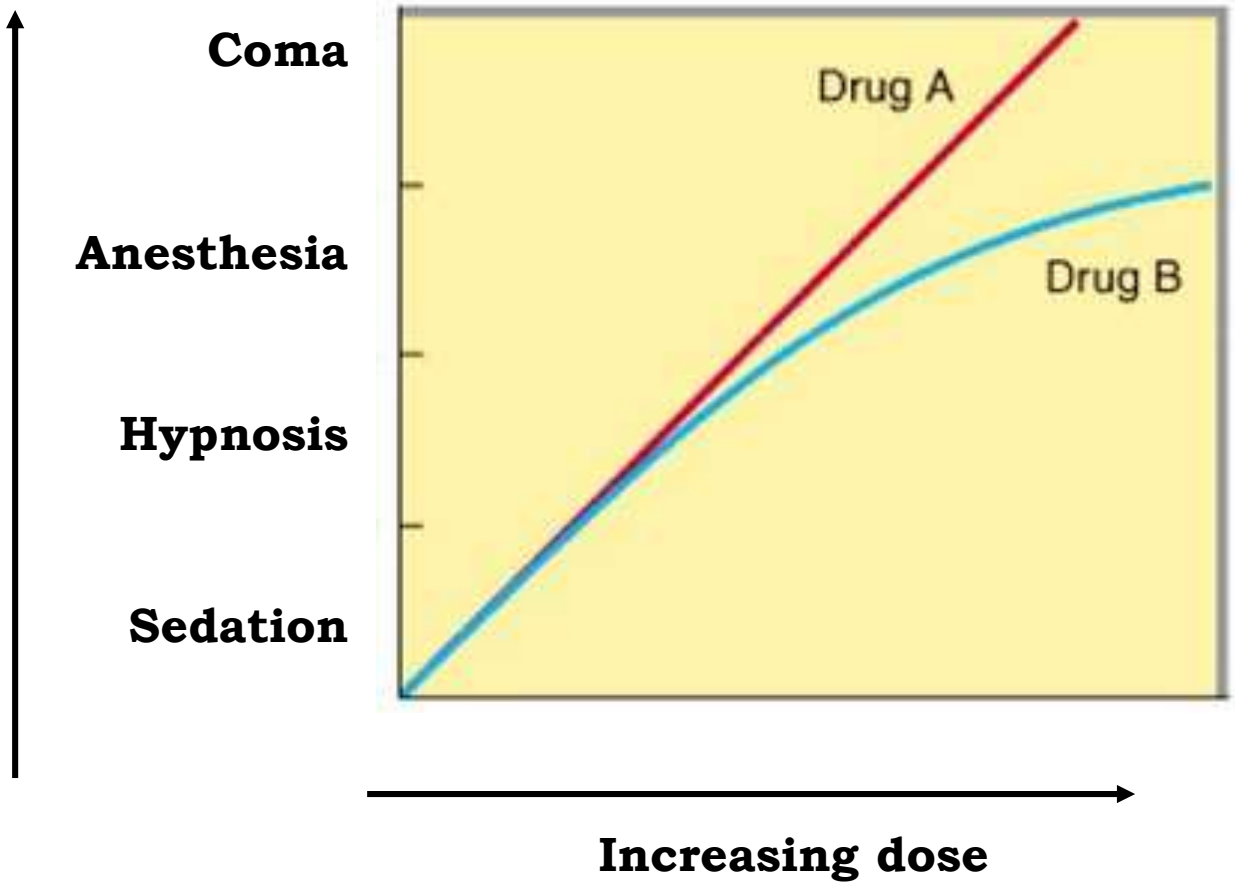
BZs function only in the presence of GABA

Barbiturates (in high dose) show GABA-like effect (direct opening of Cl^- channel)

Barbiturates also inhibit the AMPA (glutamate) receptor

Theoretical dose-response curve for sedative-hypnotics

(like barbiturates)



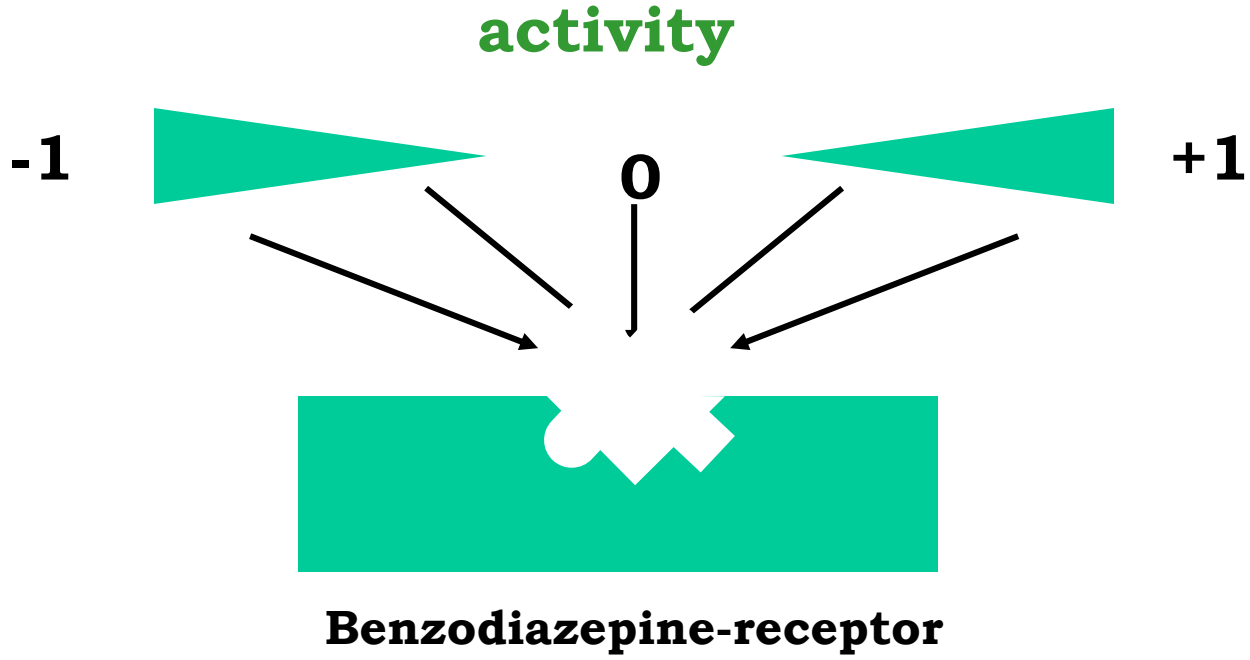
(like BZ)

Sedative-hypnotics anxyolytics

- **Benzodiazepines**
- **Non benzodiazepine hypnotics**
- **Non GABA-erg anxiolytics**
- **Barbiturates**
- **others**

  Piperidine-dions, alcohols and aldehydes

β-carbolines	flumazenil	BZs
full inverse agonist	competetive antagonist	full agonist



Effects and Clinical Indication of BZs I.

- **sedation**

  responses given to outer stimuli decrease

  decrease of the spontaneous activity!

  e.g. **chlordiazepoxide, diazepam**

- **relief of anxiety (treatment of panic disorder)**

  relief of the punishment-induced behavioral inhibition

  e.g. **alprazolam, diazepam**

VOGEL CONFLICT TEST

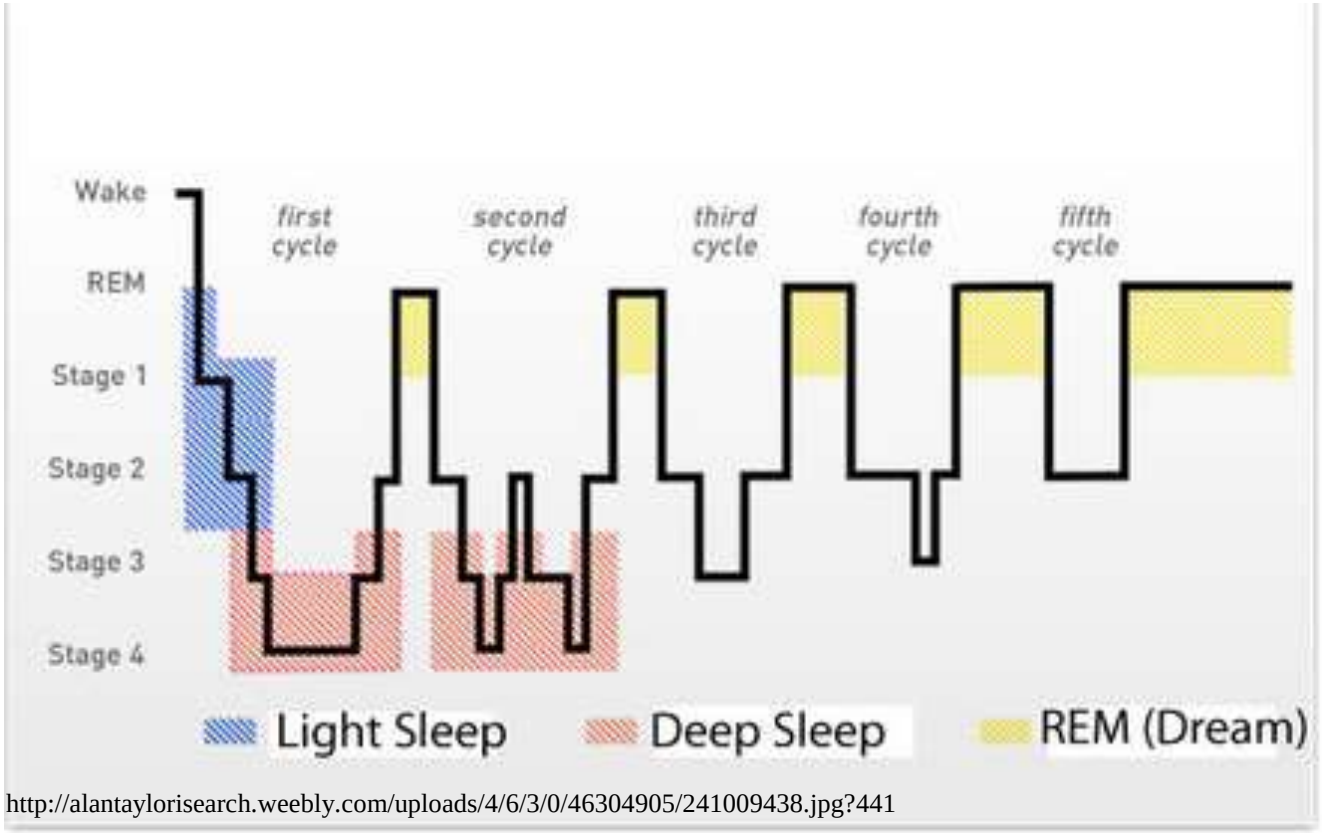
Suppressing behavior through punishment

- 48 hours of water deprivation the animals are punished with a mild electrical shock every 20 licks when finally given water
- Parameter measured - number of licks
- Anxiolytics (benzodiazepines, some antidepressants) promote accepting the punishment

Effects and Clinical Indication of BZs II.

- **anterograde amnesia** (advantageous in anesthesia)

Sleep cycles



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1 hours 8

REM - Rapid Eye Movement

during the final phase of sleep the brain becomes more active

Effects and Clinical Indication of BZs II.

- **hypnotic (nREM2 ↑, REM↓, nREM3,4↓)**
  e.g. **midazolam, triazolam**

- **anticonvulsant/antiepileptic**
  e.g. **diazepam, lorazepam** (in convulsion)
  clonazepam, nitrazepam (for prophylaxis)

- **premedication before general anesthesia**
  diazepam

- **iv. anesthetic** (induction or part of TIVA)
  midazolam, lorazepam, diazepam

- **muscle relaxation** (action in the spinal cord)
  diazepam

Most frequent central adverse effects of BZs I

- **daytime sedation, „hangover" effect**
  (with long-acting drugs)
- **daytime anxiety**
  (with short-acting drugs)
- **anterograde amnesia**
- **irritability, tension**
- **muscle hypotonia**
- **rebound phenomenon**
  (sleeplessness, dysphoria, etc.)

Most frequent central adverse effects of BZs II

- **confusion** (in elder patients)
- **interaction with ethanol**

- **psychological dependence**
  (marked with short-acting drugs)
- **tolerance**
  (especially to antiepileptic action)

Other adverse effects of BZs

- **depression of cardiovascular system**
  (mainly in case of heart failure)

- **depression of respiratory system**
  (mainly in case of chronic pulmonary disorders)

These adverse effects may develop during intravenous administration

Barbiturates

Long-lasting duration ***(6-10 hrs)***

phenobarbital

Medium-lasting duration **(4-6 hrs)**

e.g. **amobarbital**

Short-lasting duration **(2-3 hrs)**

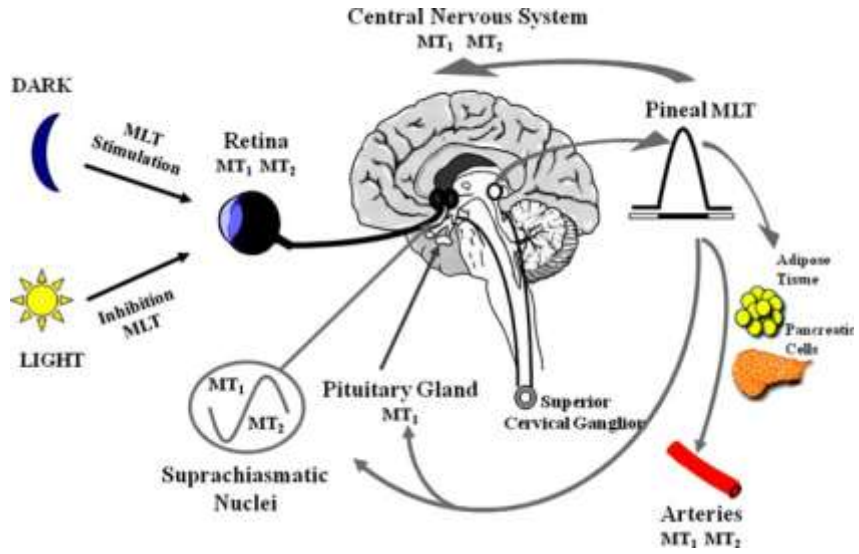
e.g. **cyclobarbital**

Ultra-short duration *(i.v. anesthetics)*

thiopental, methohexital

Melatonin

Melatonin is
produced in the pineal gland
involved in control of circadian rhytm



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Secretion of melatonin decreases in line with the age

Melatonin – short half-life (40 min); retard oral preparation

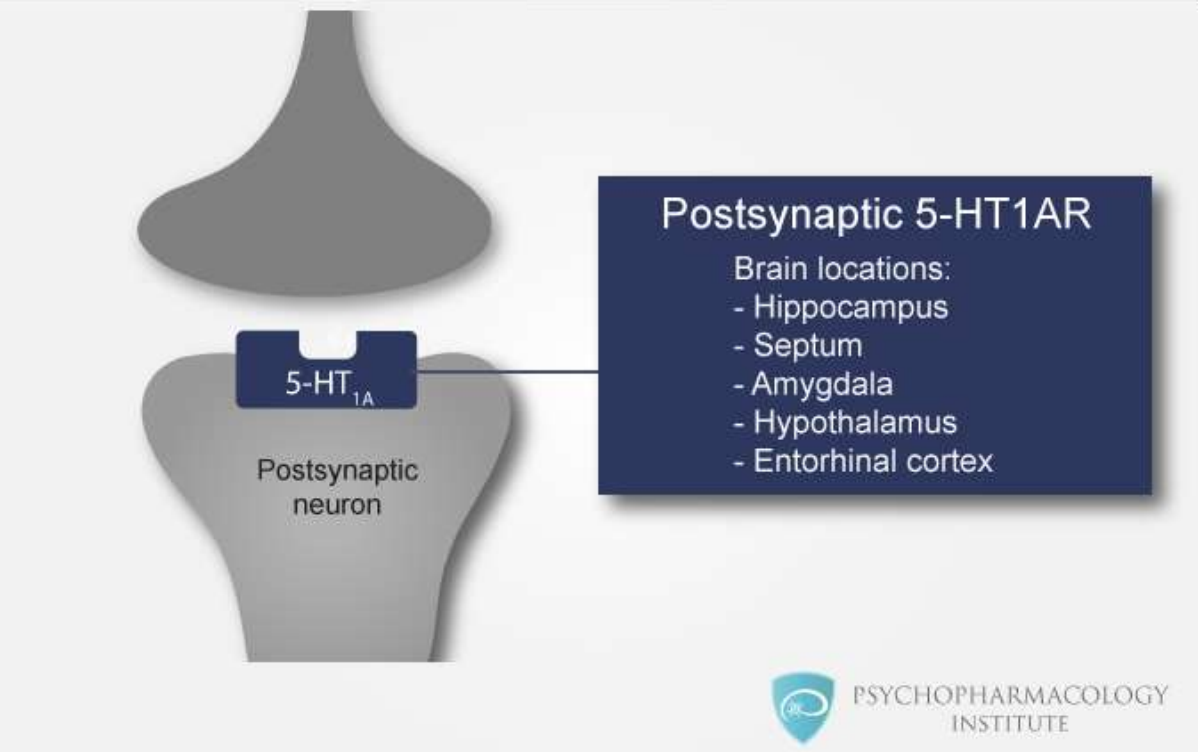
Ramelteon – melatonin receptor agonist

Indication over 55 years, jet-leg

no effect on sleep architecture, no rebound insomnia

Anxiolytics
(5-HT-erg MODELL)

- **5-HT$_{1A}$ partial agonists**
  buspiron



Anxiolytics
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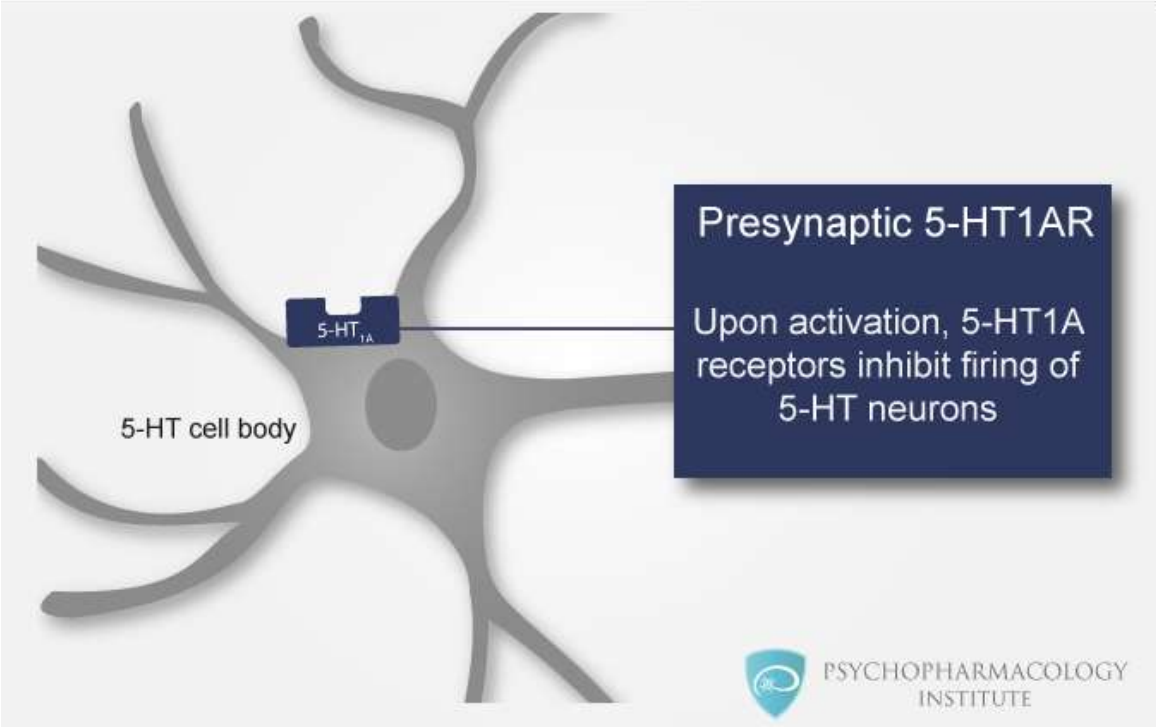
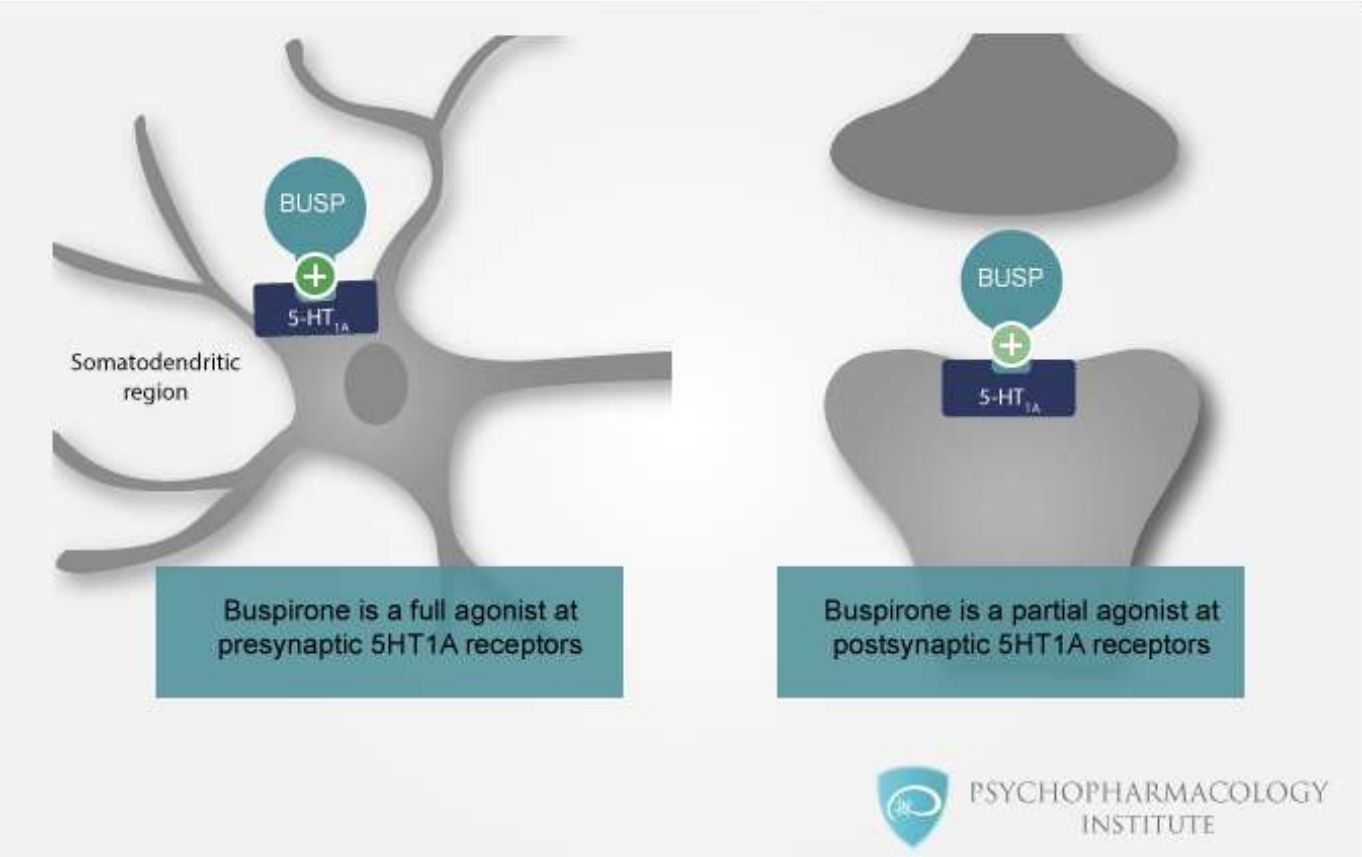




Mechanism of action is not clear

It decreases 5-HT levels in specific brain areas while increasing DA and NA levels
It is a weak DA receptor antagonist, mainly presynaptically

Anxiolytics
(5-HT-erg MODELL)

- **5-HT_{1A} partial agonist**
  buspirone
  (GAD)

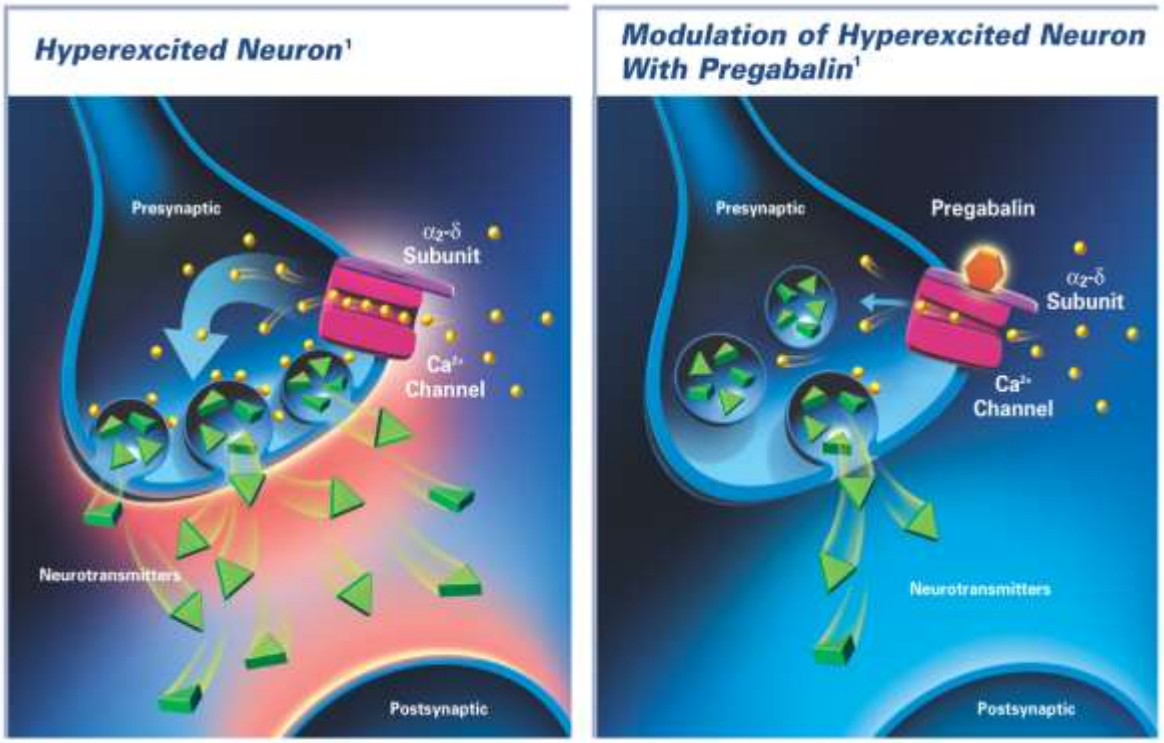
- **SSRI (5-HT reuptake inhibitors)**
  fluvoxamine, fluoxetine, etc.
  (panic disorder)

- **5-HT_2 antagonists**
  mianserin

Anxiolytics
(Glutamate-erg MODELL)

pregabalin – in GAD

It inhibits the N-type presynaptic Ca channel – modulates the function of hyperexcited neurons



ANTIEPILEPTICS

(Drugs used for treatment of epilepsy and epileptiform seizures)

- **Seizure**: abnormal synchronization and excessive excitation of a population of cortical neurons

- **Epilepsy**: a tendency toward recurrent seizures unprovoked by acute systemic or neurologic insults

epileptic seizure, is a period of symptoms due to abnormally excessive or synchronous neuronal activity in the brain.

Classification of seizure types

- **Partial seizures**

  Simple partial seizure (4%)

  Complex partial seizure (16%)

  Partial seizure secondarily generalized (36%)

- **Generalized seizures**

  Grand mal (generalized tonic-clonic - 33%)

  Petit mal (absence - 1%)

  Myoclonic seizures (1%)

  Atonic seizures (less than 1%)

Characteristics of antiepileptic treatment

Seizures generally vanish spontaneously

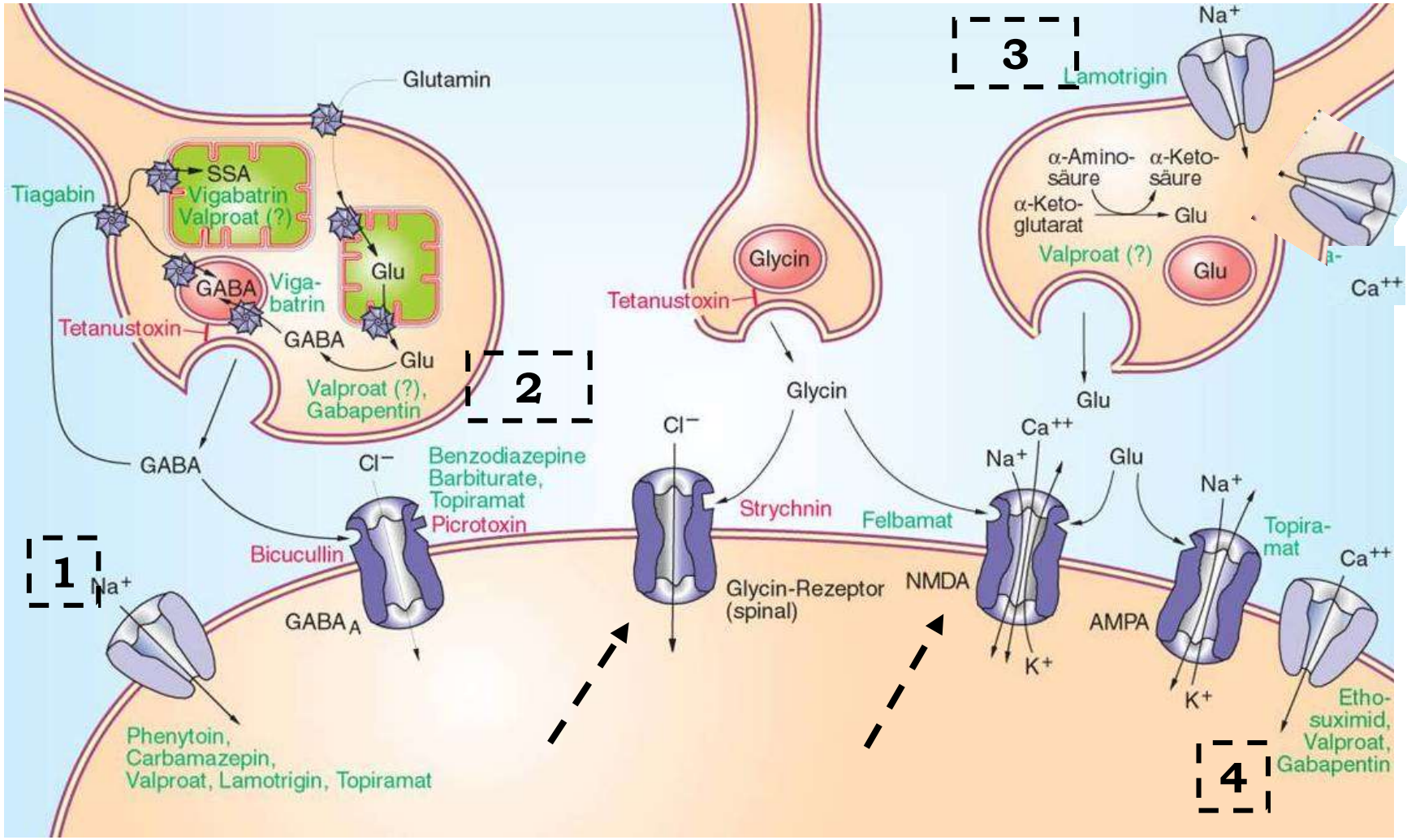
Chronic treatment – aim is to prevent the seizures

Acute treatment - treatment of acute seizures or critical care of epileptic state (seizure lasting more than five minutes or two or more seizures within a five-minute period **without the person returning to normal** between them

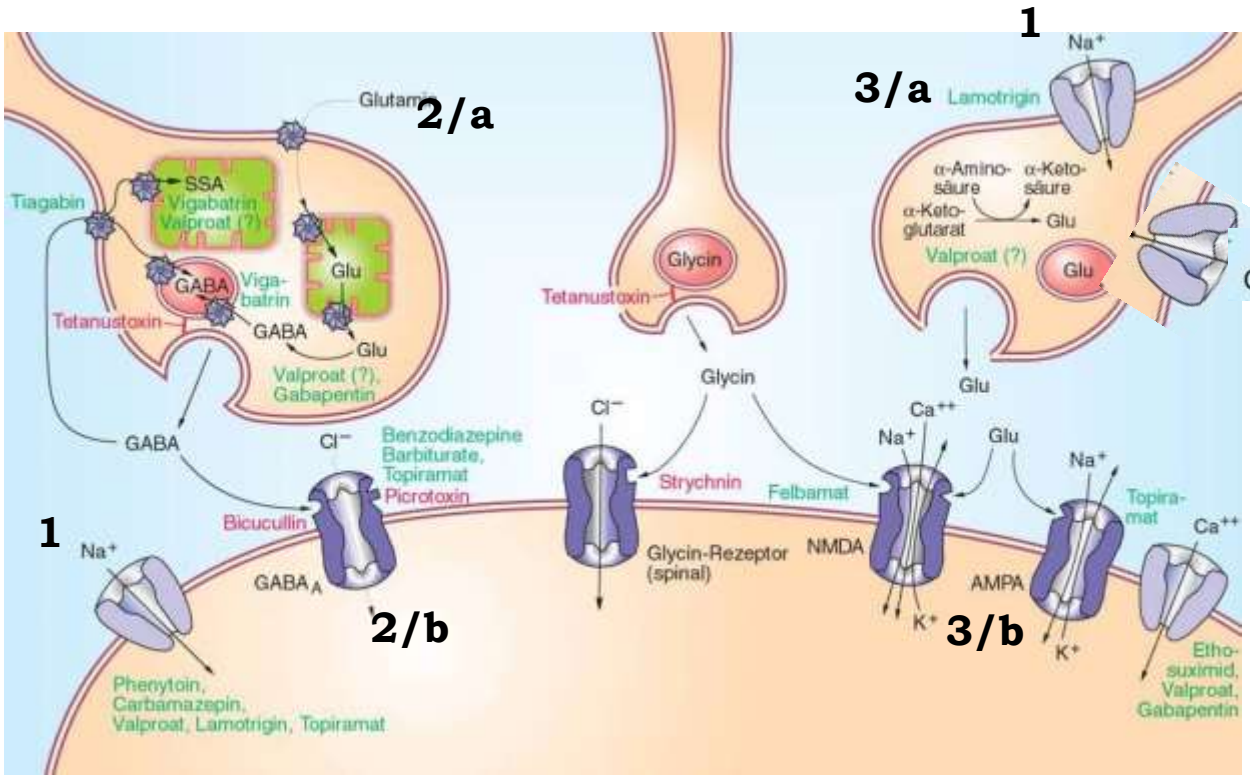
Special problems during the chronic treatment:

- withdrawn of the therapy may provoke seizures
- long-term, frequently life-long treatment
- treatment in pregnancy

Mechanism involved in convulsion



Classification of antiepileptics according to the mechanism of action



1 – agents inhibiting of the voltage-dependent Na+ channels (use dependence)

2 – agents acting on the GABA system

3 – agents acting on the glutamate system

Classification of antiepileptics according to the clinical usage

Agents used only for treatment of partial seizures and generalized tonic-clonic seizures

(not in absence)

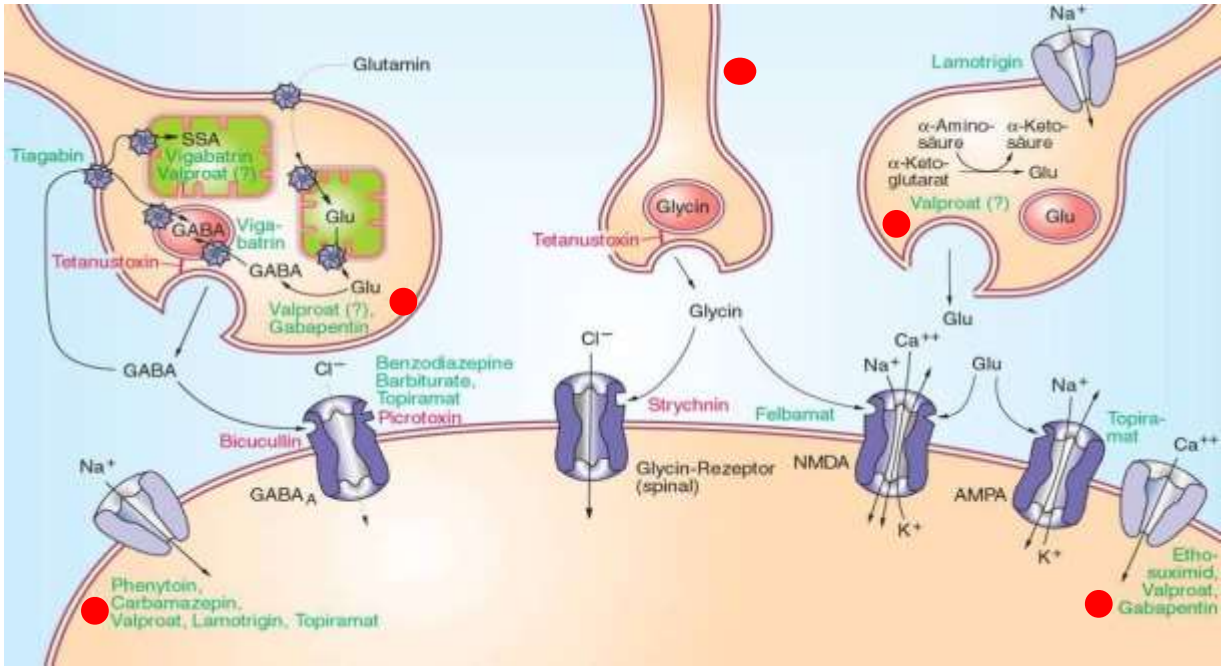
Agents used in absence

„Broad spectrum antiepileptics" - used for more types of epilepsy

Broad spectrum antiepileptics I

Valproate

Mechanism of action:



- inhibition of the voltage-dependent Na+ channels
- inhibition of the T-type Ca++ channels
- enhancement of GABA transmission (inhibition of GABA transaminase, stimulation of GABA synthesis?)
- decrease of glutamate transmission?

Valproate

usage: in all types of epilepsy

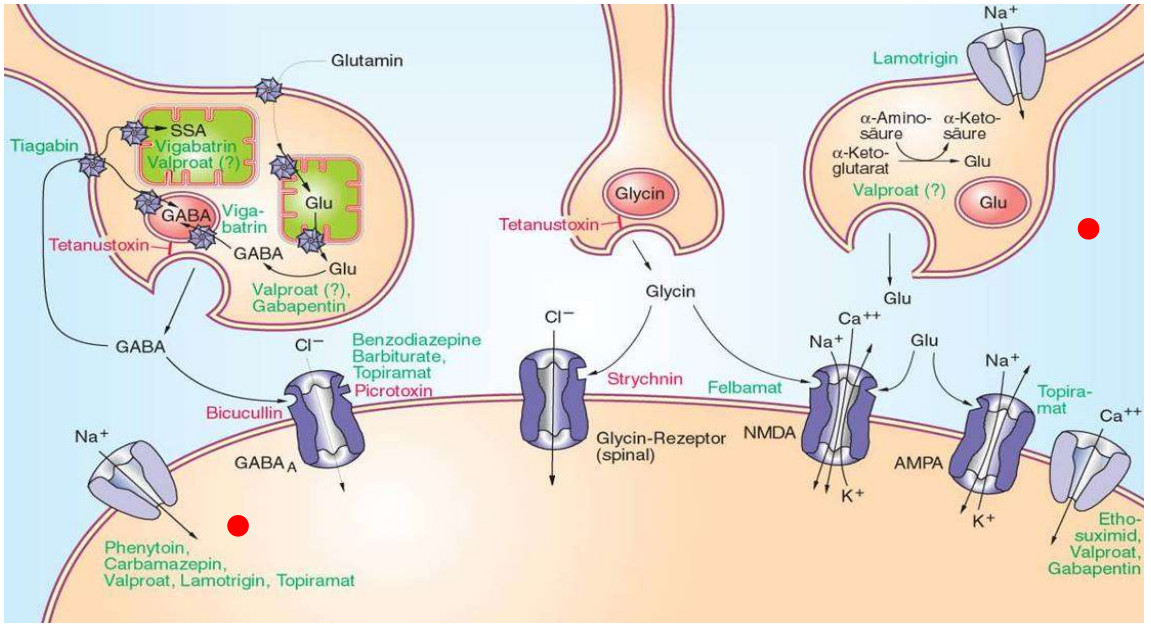
bipolar affective disorder
(treatment and prophylaxis of manic episodes)
migraine prophylaxis

adverse effects: **Teratogenic !!**
hematological abnormalities
neurological symptoms
hepatotoxicity
weight gain (sometimes weight loss)

tabl., retard tabl., inj.

Broad spectrum antiepileptics II

Lamotrigine

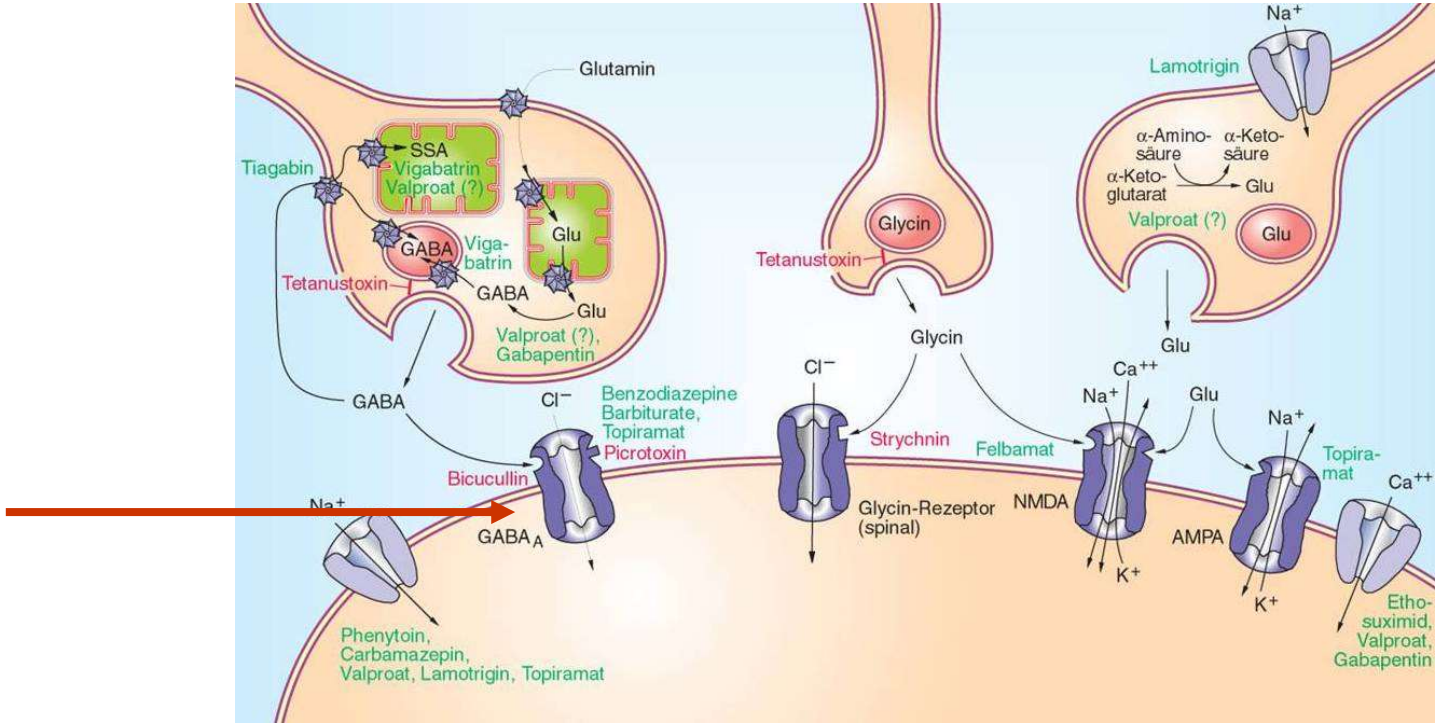


Mechanism of action:

- inhibition of the voltage-dependent Na^+ channel
- reduction of glutamate release via inhibition of presynaptic Na^+ channel
- inhibition of the T-type Ca^{++} channel ?

Broad spectrum antiepileptics III

Benzodiazepines



Mechanism of action:

activation of the BZ binding site on the GABA-A receptor

Broad spectrum antiepileptics III

Benzodiazepines

Usage

Clonazepam

- **first line drug in absence**
- **adjacent is other types of epilepsy**
- **other indications: panic disease, anxiety disorder**

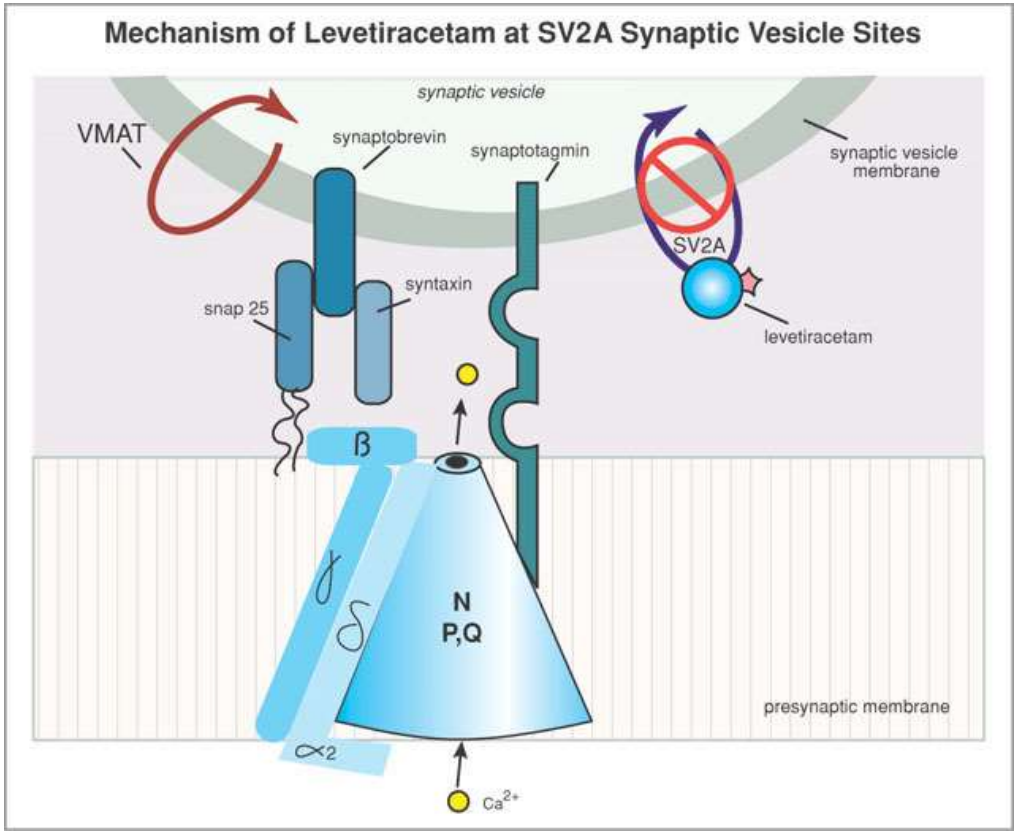
In epileptic state clonazepam, diazepam i.v.

disadvantages: sedation and tolerance

Broad spectrum antiepileptics III

Levetiracetam

binds to the synaptic vesicular protein 2A, which plays role in the fusion of the vesicula and membrane and in the neurotranszmitter exocytosis



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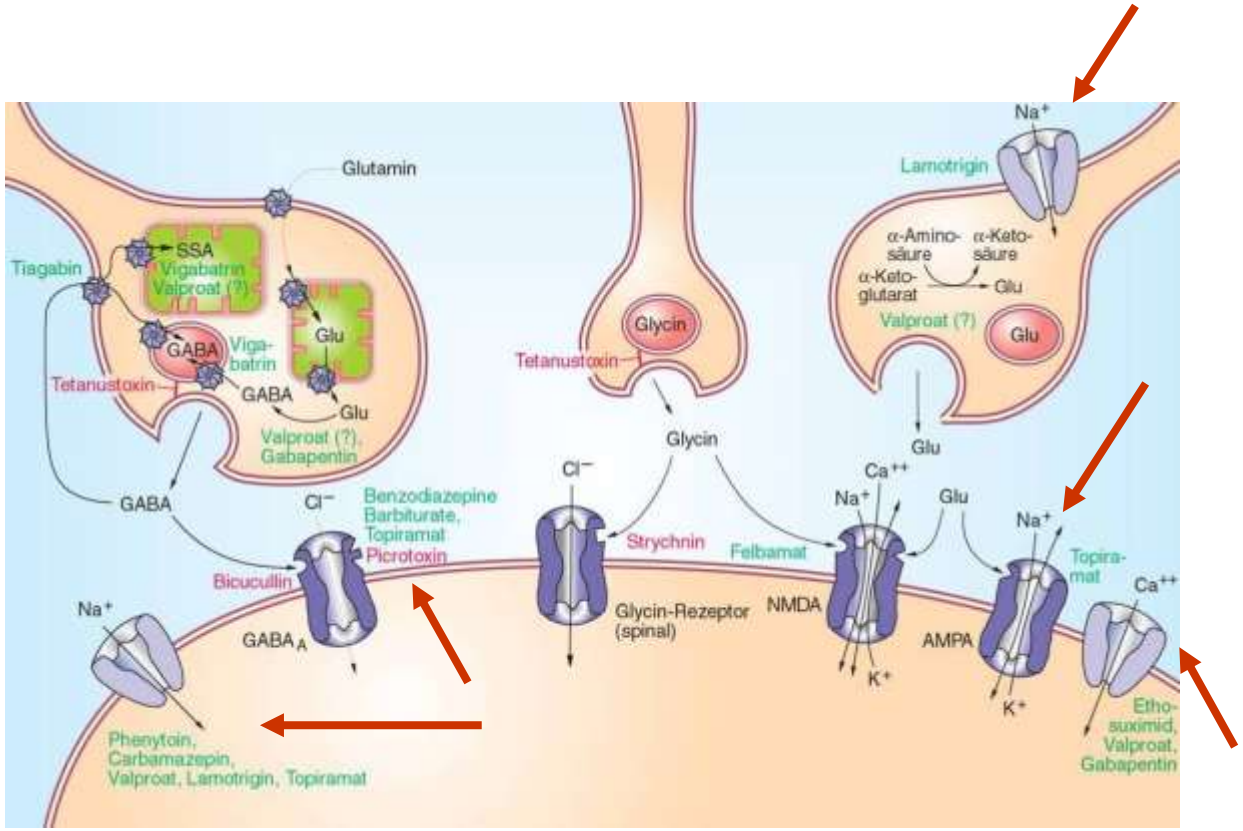
Indication: monotherapy in new patients in partial epilepsy, otherwise adjacent therapy

Broad spectrum antiepileptics IV

Topiramate



mechanism of action:

inhibition of the voltage dependent Na^+ channel

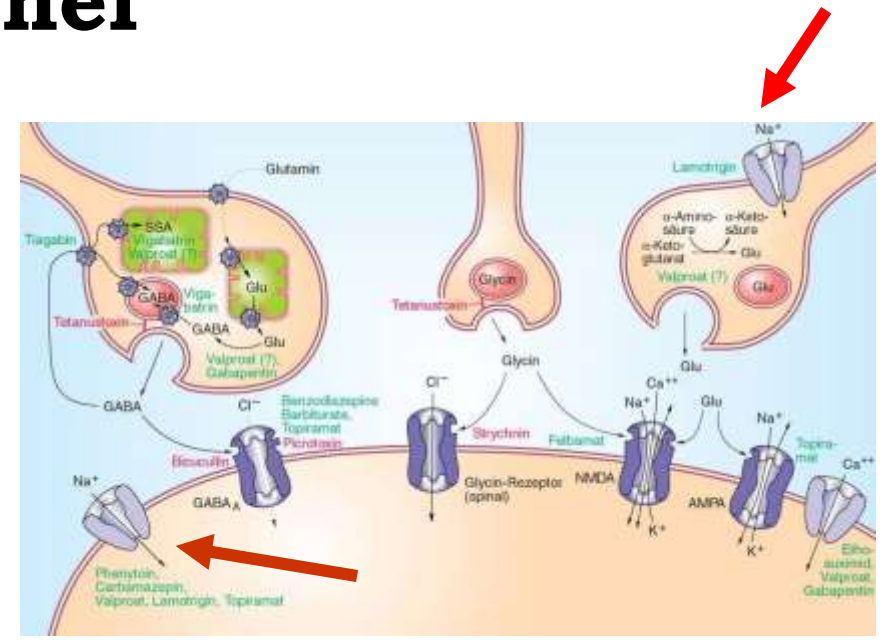
enhancement of the effect of GABA

inhibition of AMPA receptor

inhibition of the T-type Ca^{++} channel ?

Agents acting on partial and generalized tonic-clonic seizures I.

Drugs acting on the Na^+ channel



Na^+ channel inhibitors

usage: **partial epilepsy**
generalized tonic-clonic epilepsy

adverse effects: **neurological symptoms,**
enzyme induction

Carbamazepine

Other indications: trigeminal neuralgia, neuropathy,
bipolar affective disorder,
ethanol withdrawal syndrome,
central diabetes insipidus

Phenytoin

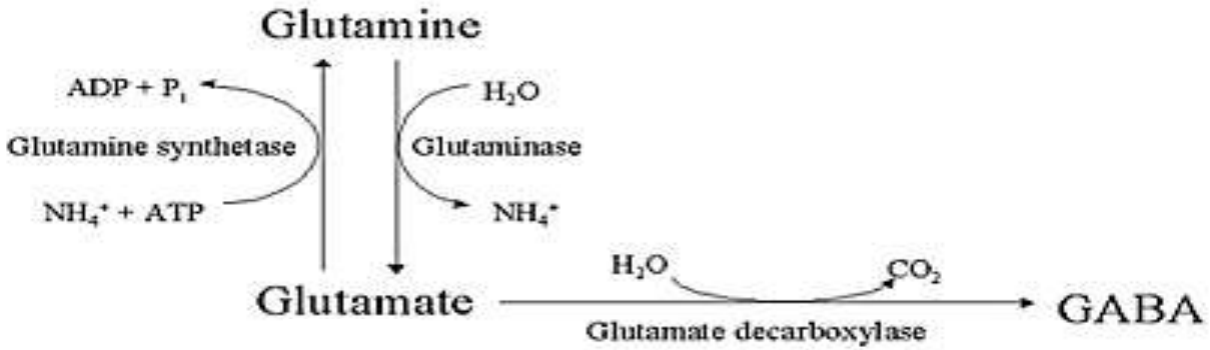
alternative possibility

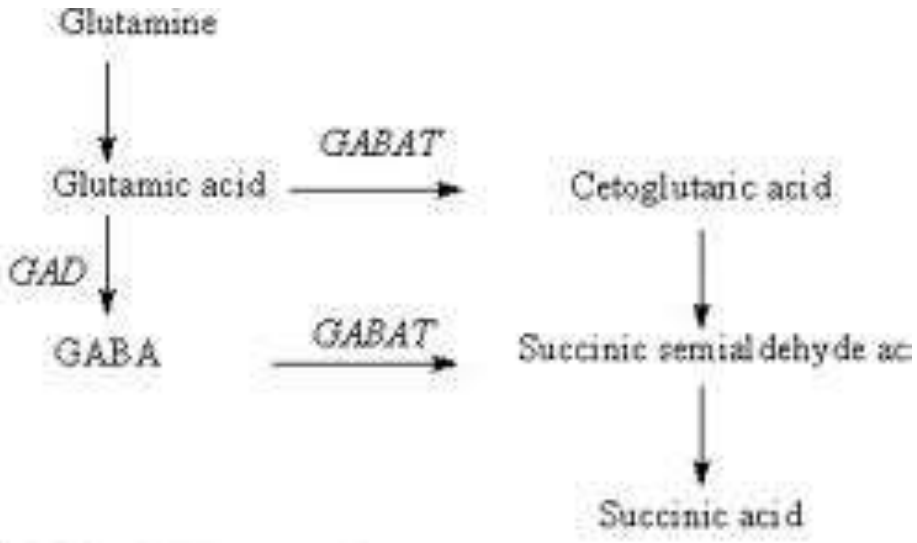
Special adverse effects: gingiva hyperplasia
teratogenic !!!

Agents acting on partial and generalized tonic-clonic seizures II.

Drugs acting on the GABA system

GABA synthesis, GABA, GLU metabolism





GAD – glutamát decarboxiláz
GAT – GABA transzamináz

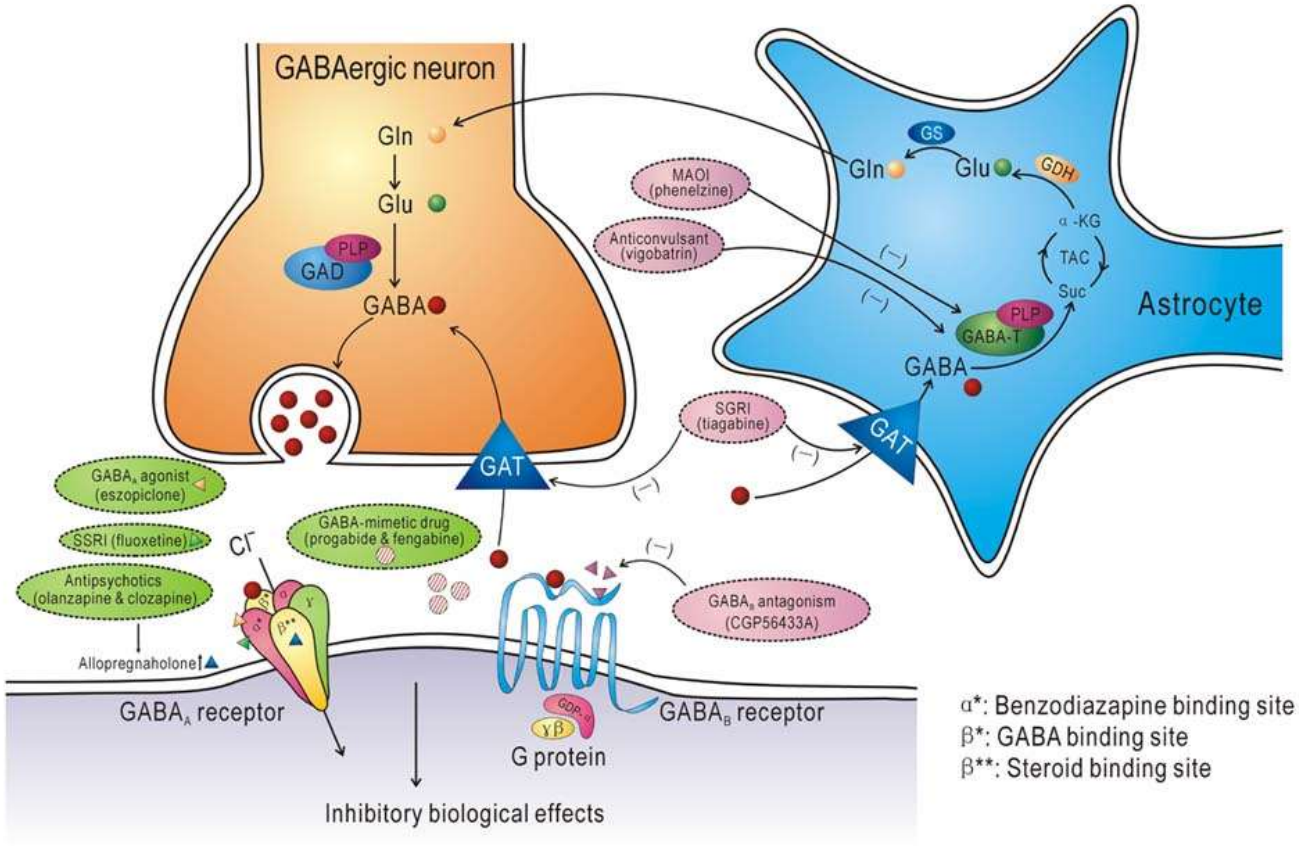
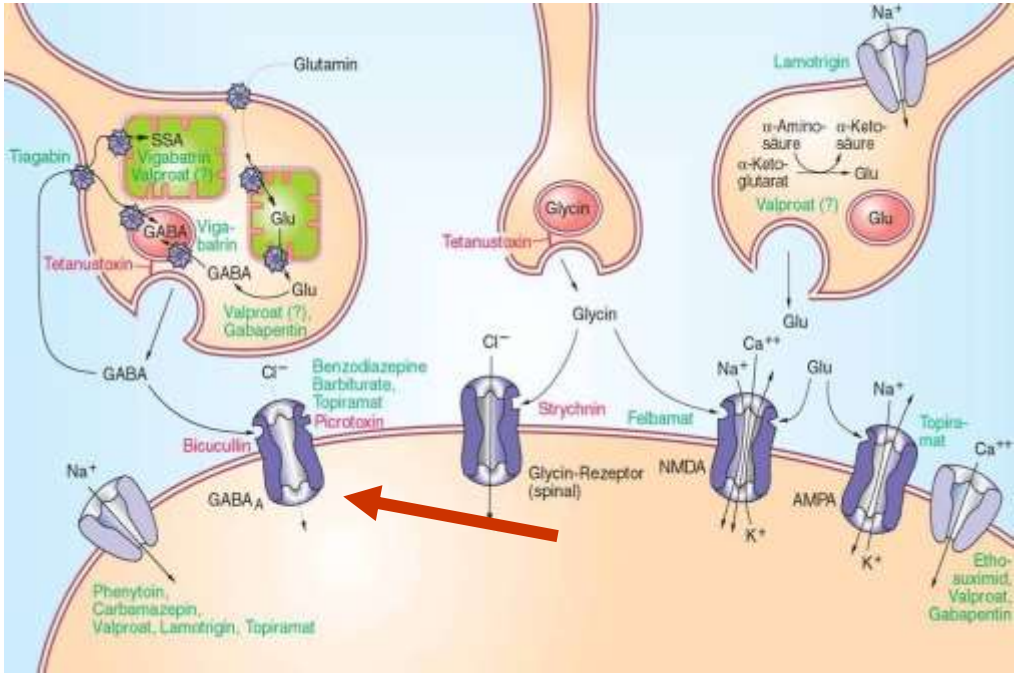


Figure 1: The glutamate/glutamine/GABA cycle and potential antidepressant targets in GABAergic system

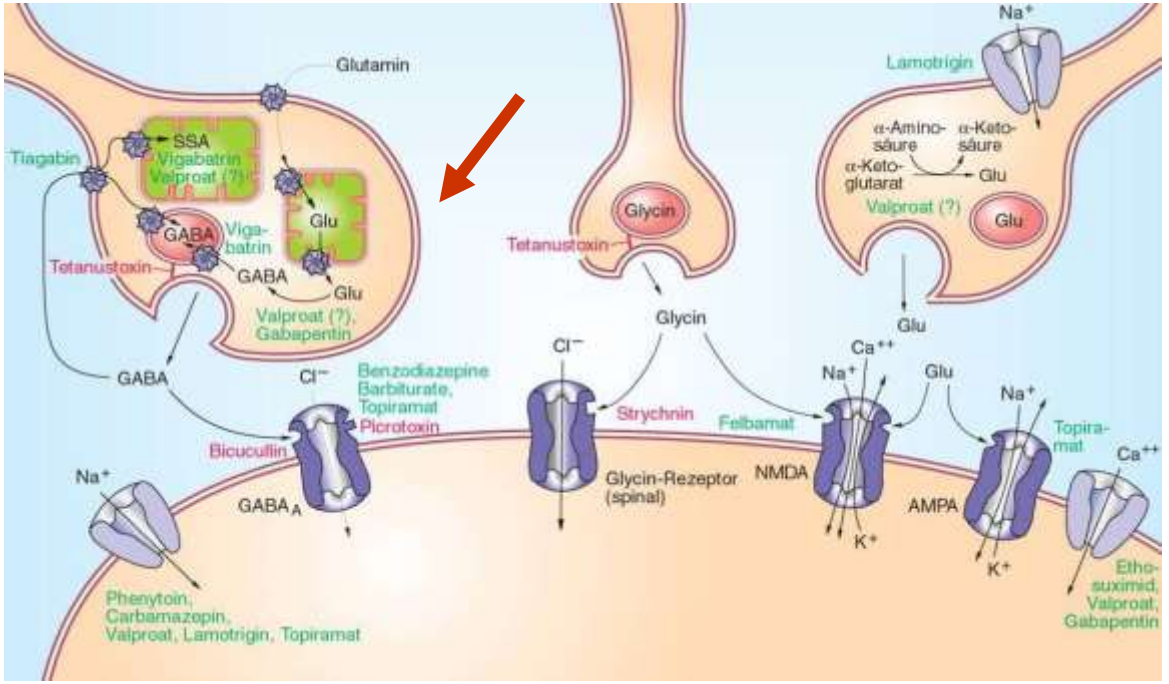
Drugs acting on the GABA system I

Phenobarbital



second-line drug because of sedation, strong enzyme induction and dependence

Drugs acting on the GABA system II



Vigabatrin

Selective and irreversible GABA-transaminase inhibitor

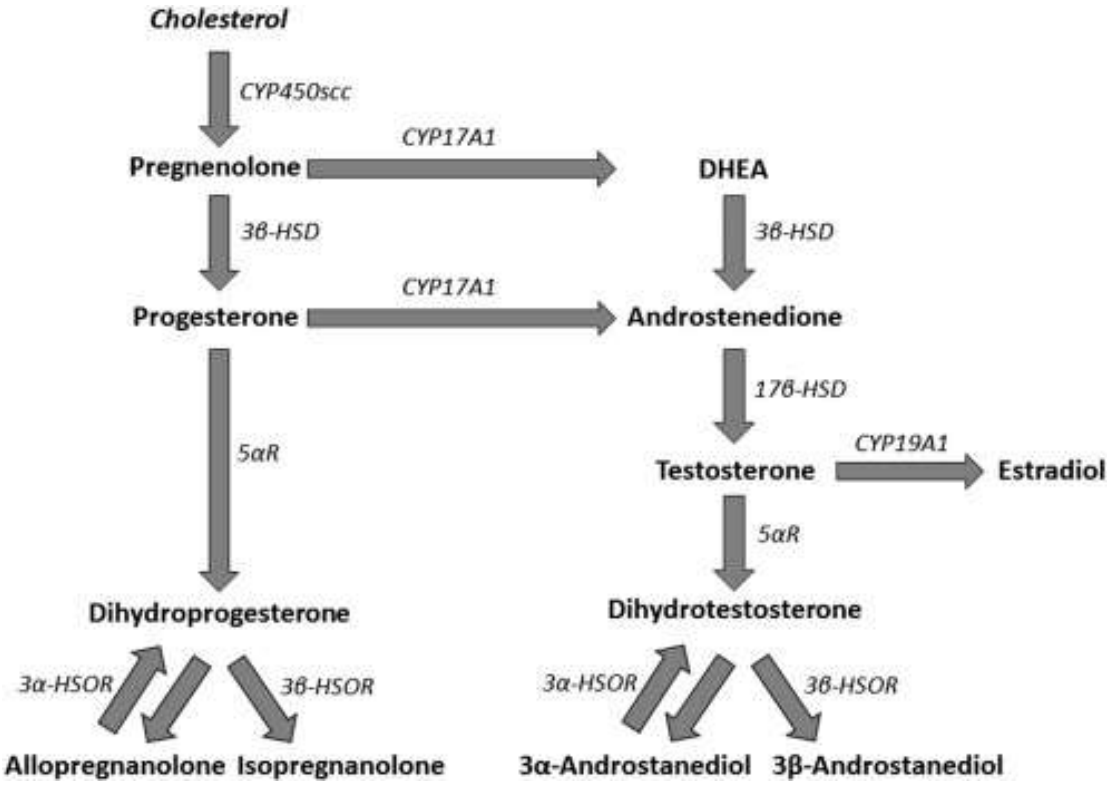
Tiagabin

inhibitor of GABA uptake

Drugs acting on the GABA system III

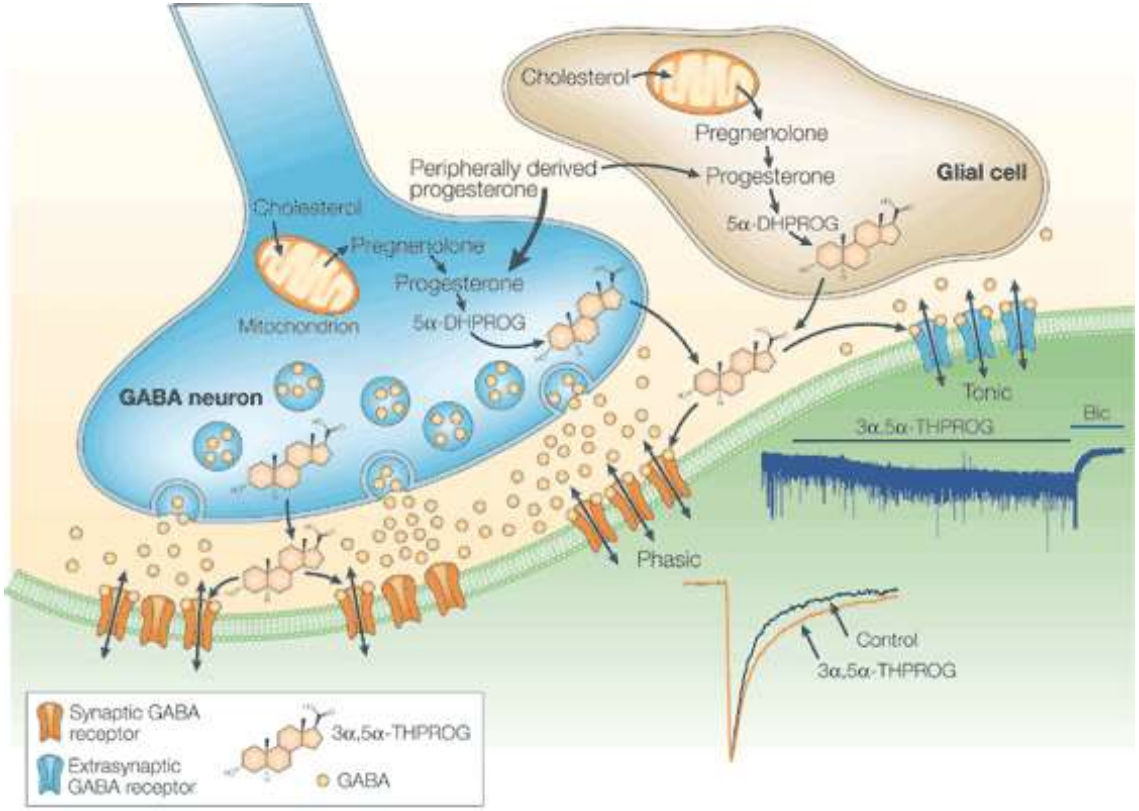
Neurosteroids

endogenous steroids synthetized in the brain



Drugs acting on the GABA system III

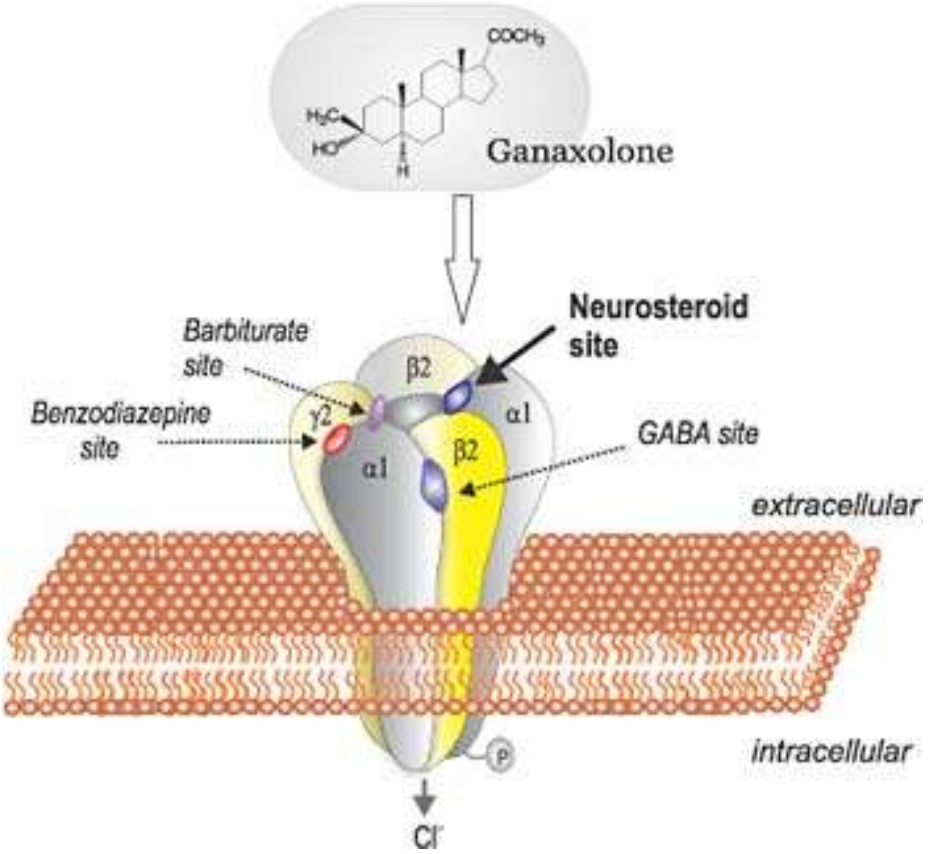
Neurosteroids



They are produced both in the neurons and the glial cells

Drugs acting on the GABA system III

neurosteroids



- **Ganaxolone**

  orphan drug for treatment of the special cdkl5, a rare genetic disorder associated with seizures

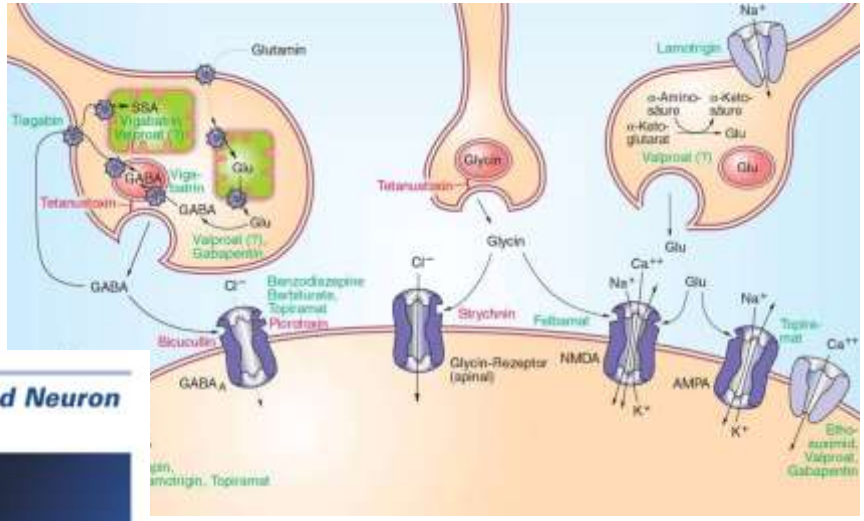
Agents acting on partial and generalized tonic-clonic seizures III.

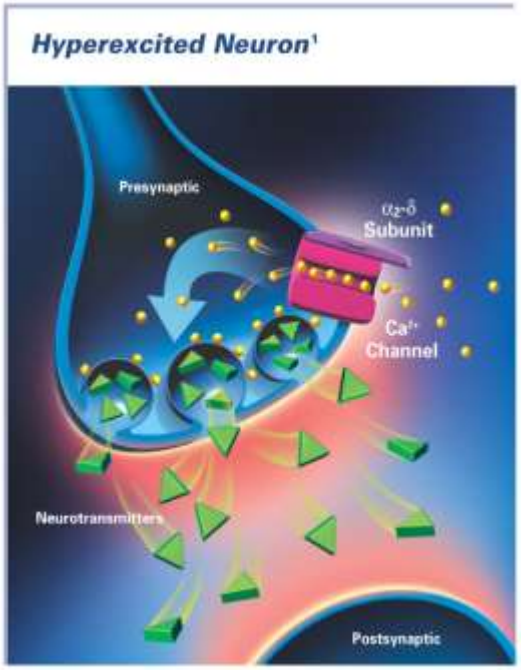
Drugs acting on the glutamate system

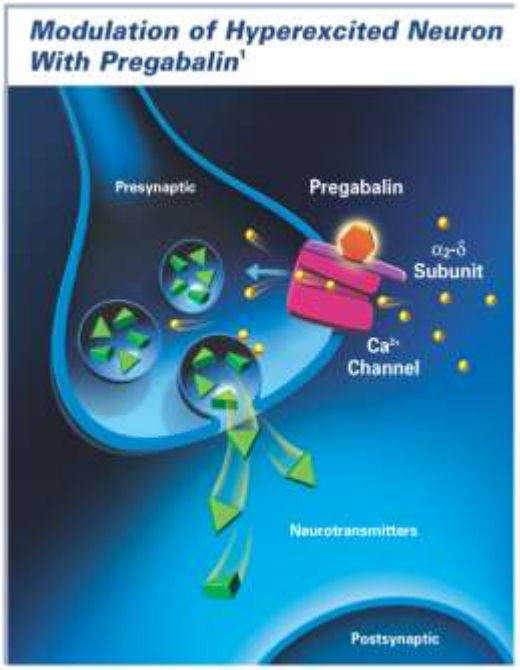
Drugs acting on the glutamate system I

- **Gabapentin and Pregabalin**

Mechanism of action:
affect the hyperexcited neurons, inhibit the N type Ca^{++} channel



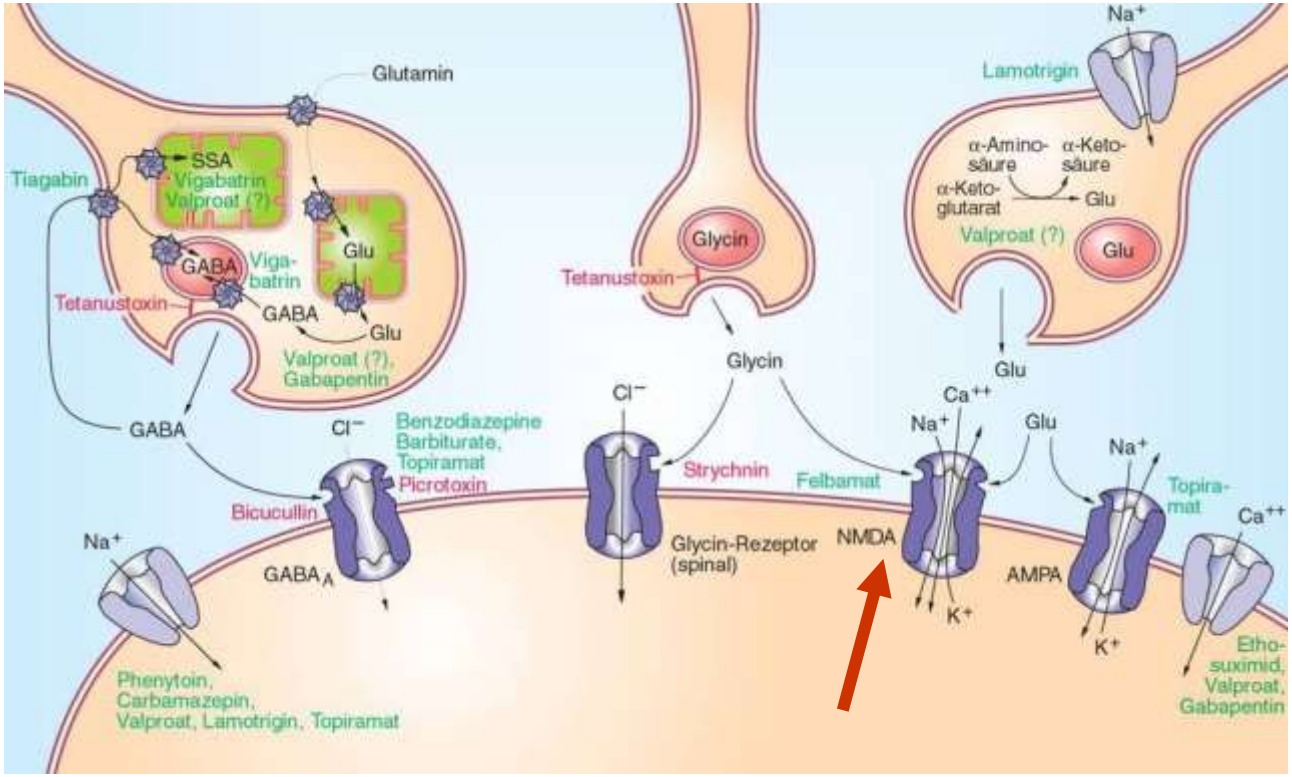




Other indications: neuropathic pain, GAD (pregabalin)

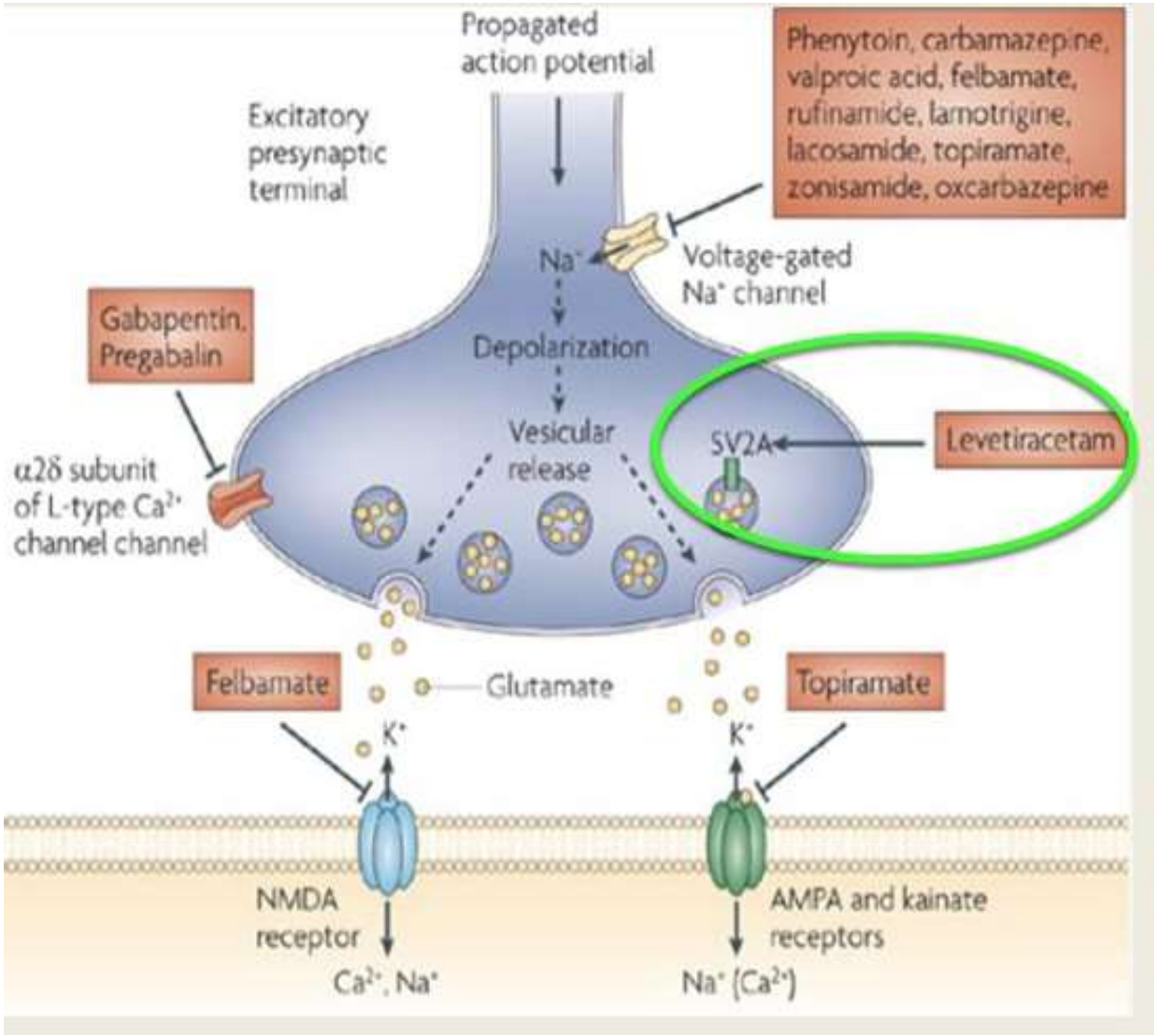
Drugs acting on the glutamate system II

Felbamate



risk of potentially fatal aplastic anemia and liver failure limits its usage for refractory cases

Drugs acting on the glutamate system III



New drugs

New drugs, which are used generally as adjacent therapy or used with special indication.
Their advantages might be lower toxicity and lower possibilities of drug interaction

Rufinamide, lancosamide - Na^+ channel blockers

Retigabine – opener of the voltage dependent K^+ channels

Cannabidiol - phytocannabinoid – not psychoactive
mechanism of action is not clear, presumably it does not bind to the CB1 receptors

Used in special syndromes (epileptic encephalopathies like Dravet syndrome and Lennox-Gastaut syndrome)

Treatment of petit mal

Broad spectrum antiepileptics

Ethosuximide

- **alternative**
- **inhibits the T-type Ca^{++} channels in the thalamus**

Treatment of epileptic state

- **Diazepam, clonazepam or lorazepam iv., midazolam im., nasal spray, diazepam rectally**
- **Phenytoin iv., Phosphenytoin iv., im.**
- **Valproate iv.**
- **Levetiracetam iv,**
- **Phenobarbital iv.**
- **(in resistant cases general anesthesia, propofol, thiopental, perhaps muscle relaxant)**

In pregnancy – $MgSO_4$ iv

Neurodegenerative disorders

Parkinsonism/Huntington chorea

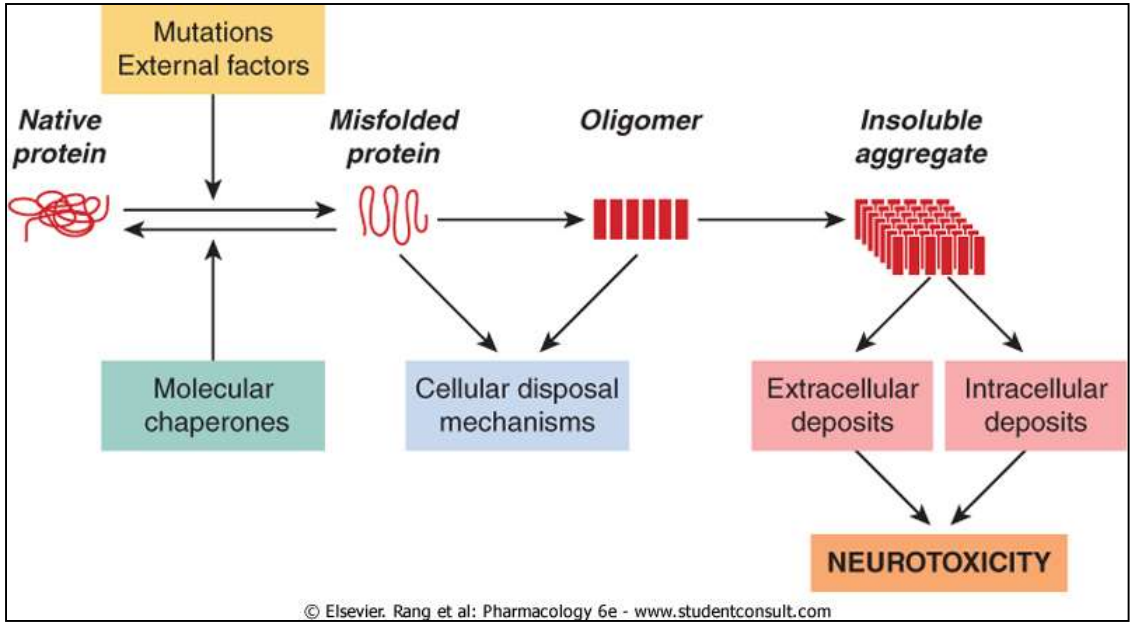
Alzheimer's disease

Stroke, ischemic dementia

Common characteristics

➢ protein aggregation

- defending mechanisms are damaged (chaperon and ubiquitin-proteosome system)
- Enhanced formation of abnormal proteins (protein miss folding, post translational modifications)
- Changes provoked by protein-aggregates are irreversible



Common characteristics

The same type of aggregates may appear in various disorders – not easy to differentiate the disorders

Alzheimer-disease - **β-amyloid plaques / tau neurofibrillary tangles**

Parkinson-disease - **α-synuclein / ubiquitin Lewy bodies**

Prion-disease - **prion protein**

Amyotrophic lateral sclerosis - **ubiquitin / SOD mutants**

Common characteristics

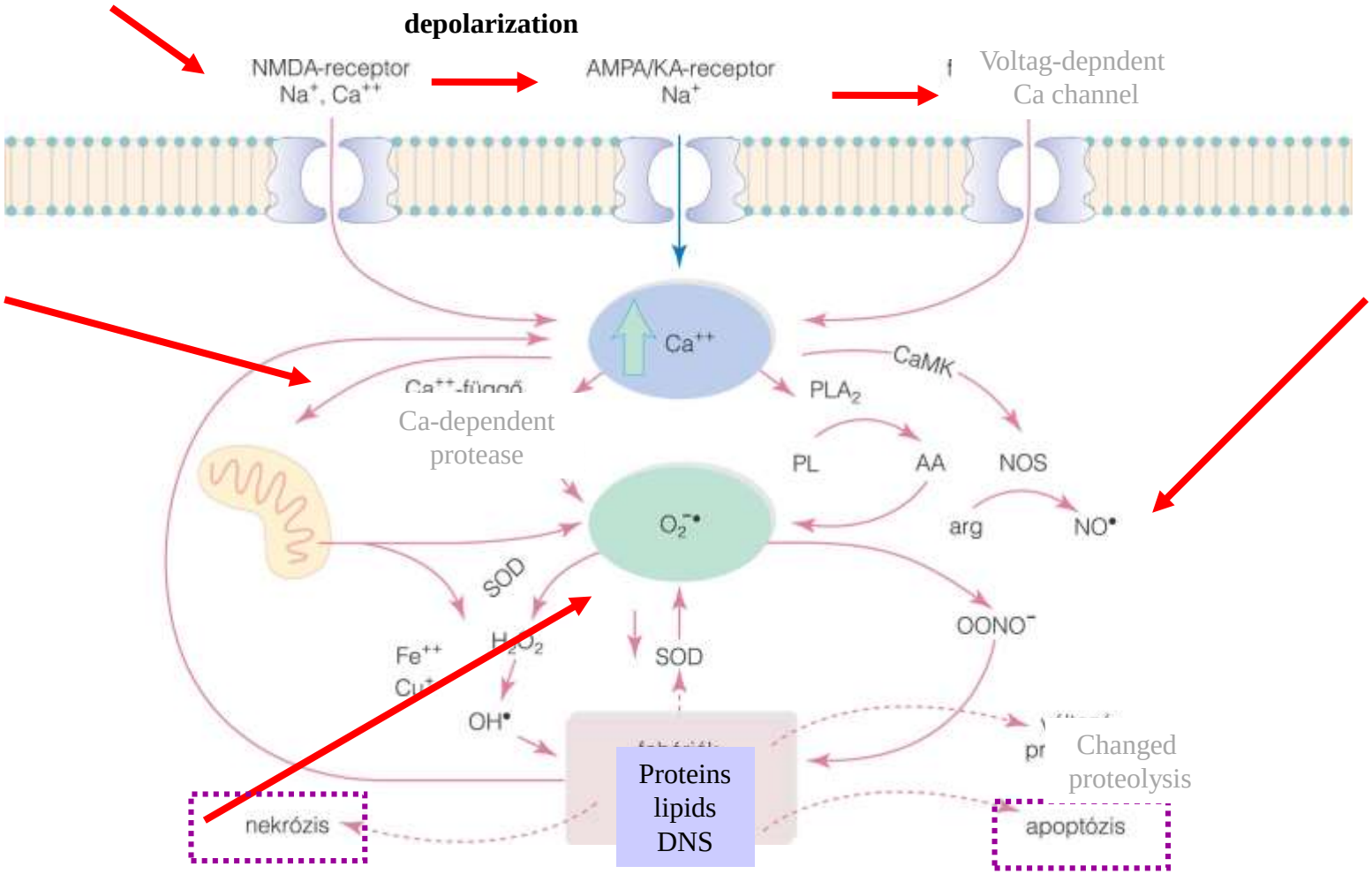
- **mitochondrial function abnormalities**

- mitochondrial membrane depolarization
- Production of free-radicals
- Damage of ATP productions
- Release of proapoptotic factors

- **exocytotoxicity**

continuous
glutamate release

EXOCITOTOXICITY



The cells are swollen, the membrane is destroyed, inflammation

Shrinkage of cells, they are swallowed by the macrophages

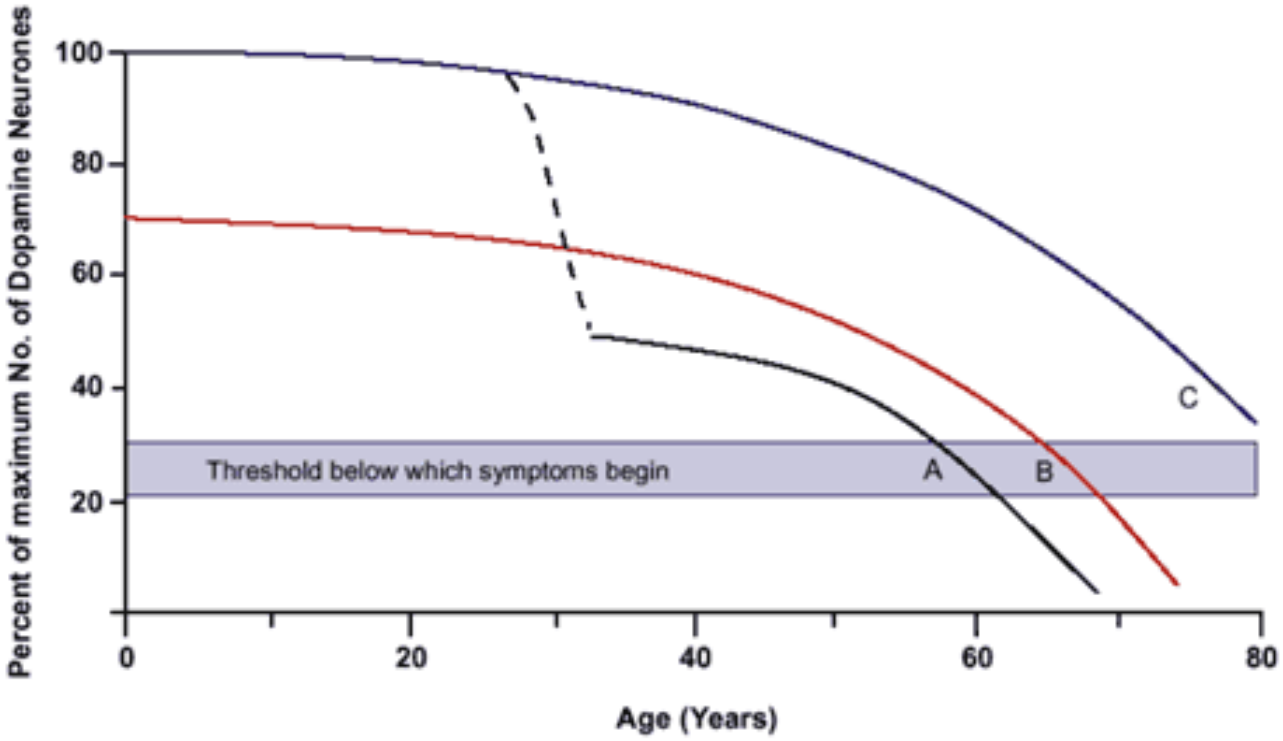
Parkinsonism

James Parkinson published in 1817 six cases about patients having symptoms of paralysis agitans

Pathogenesis - progressive degeneration of the basal ganglions
- decrease in DA level. If the reduction is by 70% the symptoms appear
(also decrease in NA, 5-HT level)

Characteristic symptoms
postural instability
tremor at rest
rigidity
salivation
impairment of voluntary activity (hypokinesia, bradykinesia, akinesia)
dementia

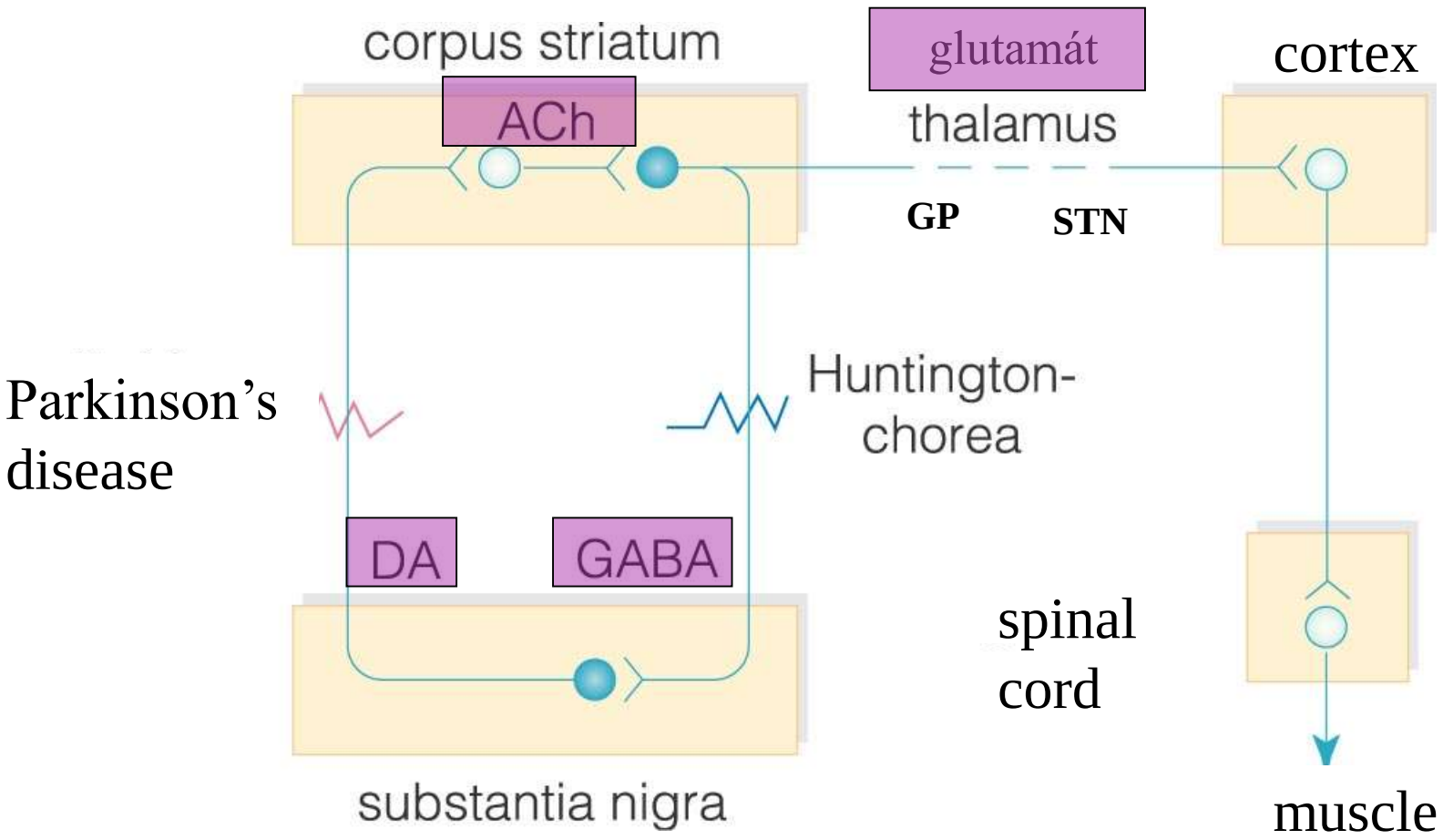
Pathological background of Parkinsonism



Curve A represents a sudden loss of dopamine neurons due to an acute event. **Curve B** represents a reduced complement of dopamine neurons and gradual loss over time, slowly leading to the development of symptoms. As ***curve C*** indicates, most people do not reach the threshold for Parkinson's disease and there is no clear evidence that there is a reduced number of dopamine neurons with aging.

https://www.google.hu/search?hl=hu&site=imghp&tbm=isch&source=hp&biw=1280&bih=899&q=DA+and+aging&oq=DA+and+aging&gs_l=img.12

Simplificated Pathological background of Parkinsonism and Huntington chores



GP – globus pallidus

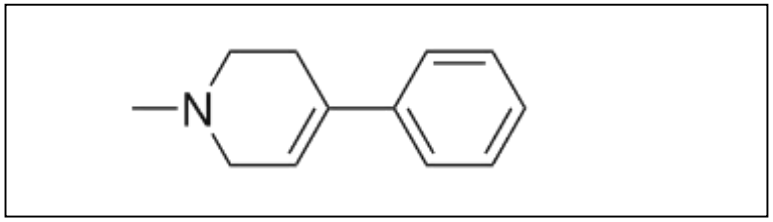
STN – nucleus subthalamicus

Types of Parkinsonism

Idiopathic Parkinsonism

Drug-induced (APs) parkinsonian syndrome (reversible)

MPTP-induced parkinsonian syndrome (irreversible)



1-methyl-4-phenyl-tetrahydropyridine

Therapy of Parkinsonism

Drugs enhancing the dopaminergic tone

Anticholinergic drugs

Drugs enhancing the dopaminergic tone

levodopa

DA receptor agonists

amantadine

inhibitors of the DA metabolism

Levodopa

Levodopa

„replacement" therapy
the „main" drug

Kinetics: good absorption

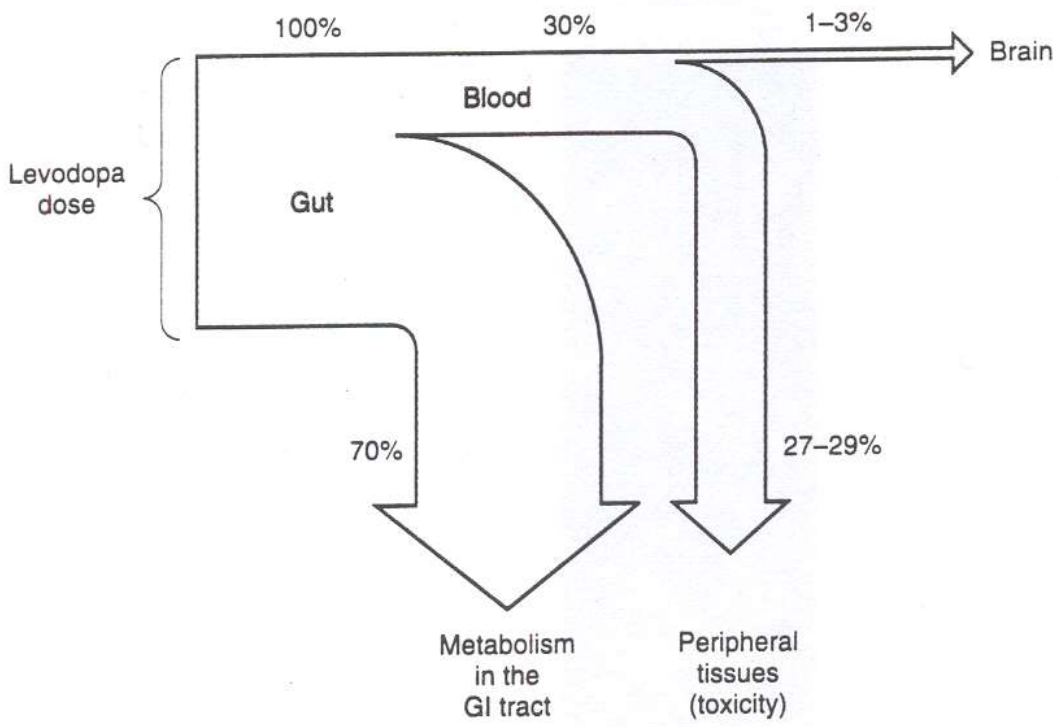
plasma peak	**1-2 hr**
plasma half-life	**1-3 hr**
elimination (via urine)	**6-8 hr**

Retard preparation

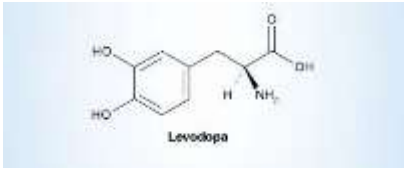
Amino acids inhibit the GI absorption and the penetration trough BBB (competition for the active transport)

Levodopa

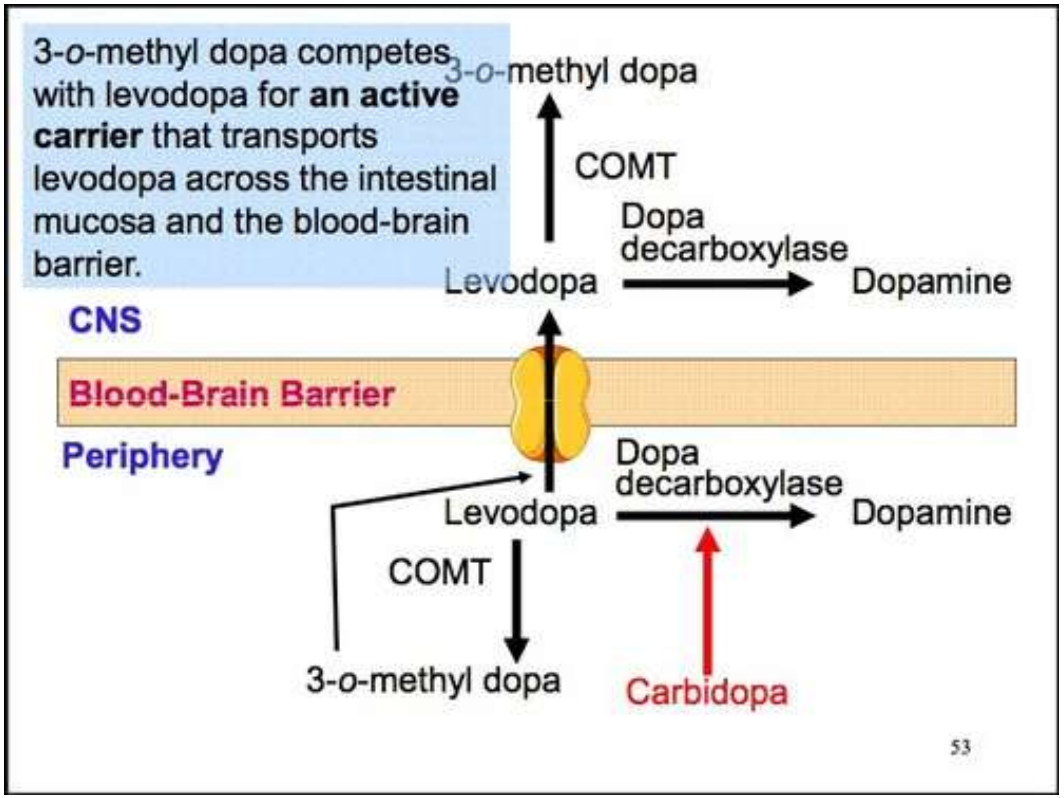
Only 1-3 % enters the brain



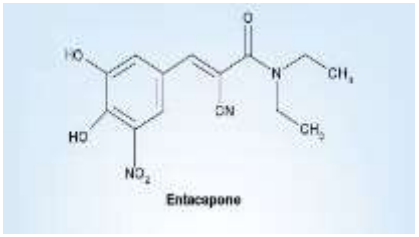
Levodopa (cont.)



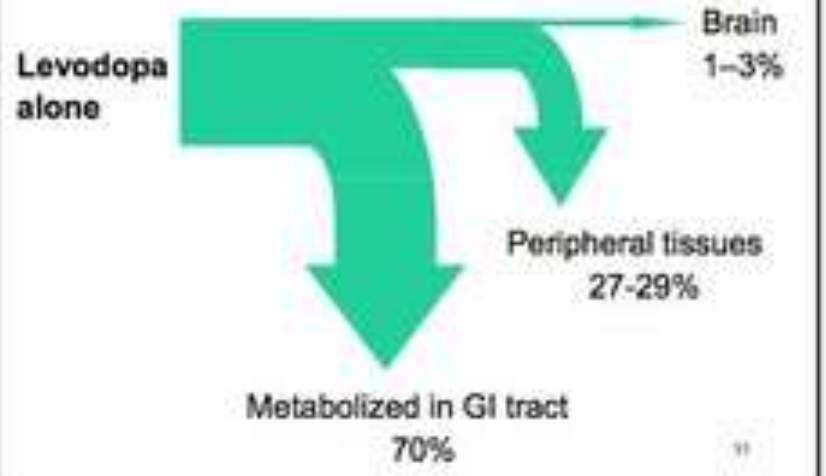
Efficacy can be enhanced by:
peripheral decarboxylase inhibitors
benzerazide, carbidopa



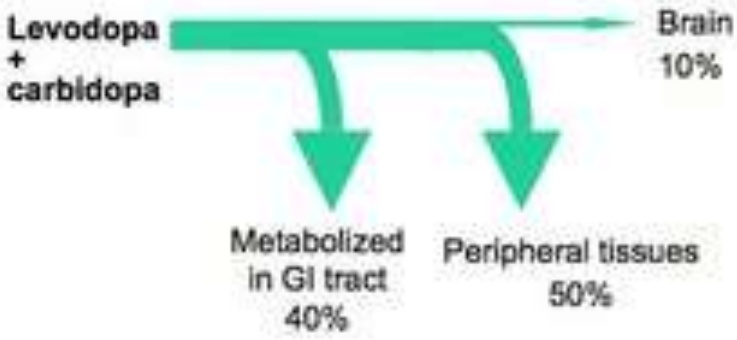
Efficacy can be enhanced by : COMT inhibitors
entacapon

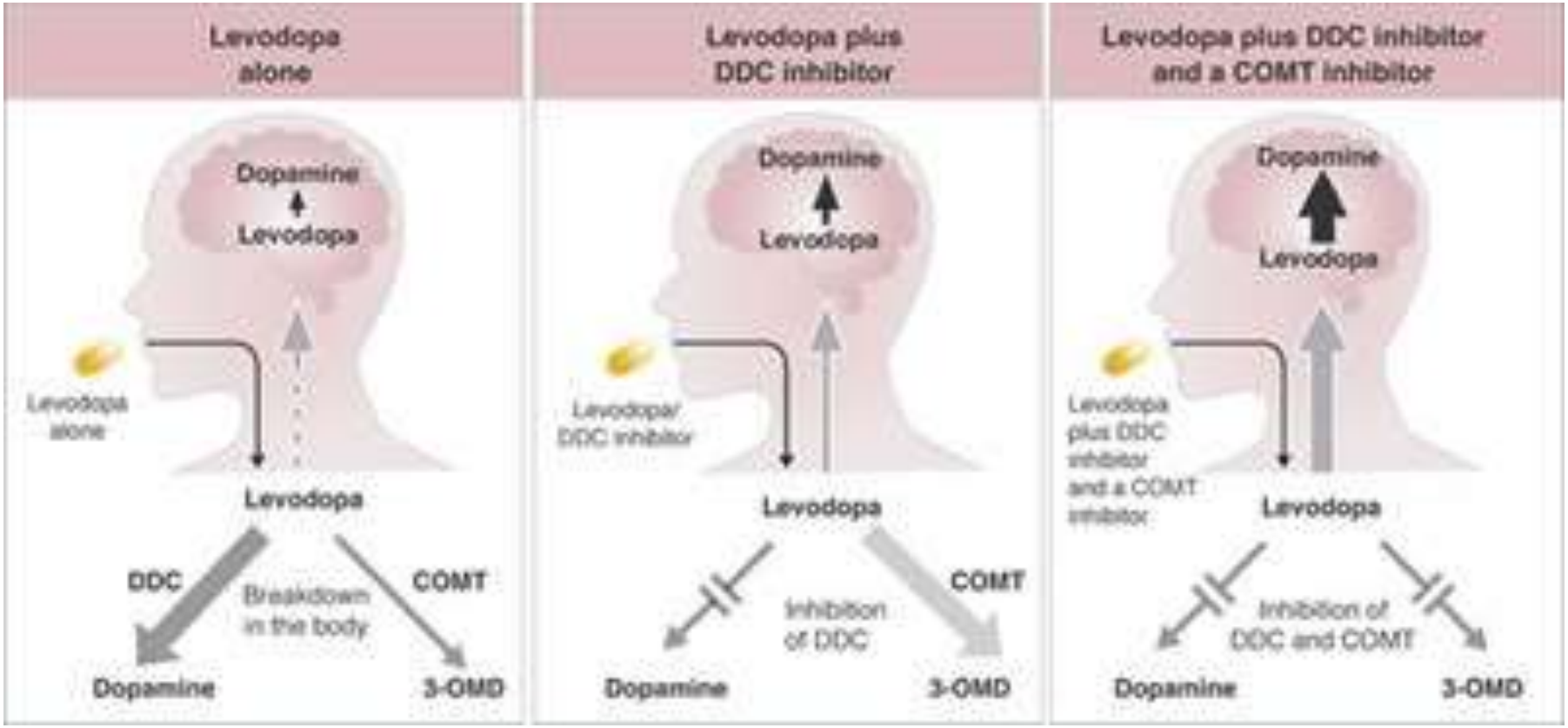


PERIPHERAL METABOLISM OF LEVODOPA



PERIPHERAL METABOLISM OF LEVODOPA




Levodopa alone
Dopamine
Levodopa
Levodopa alone
Levodopa
DDC
Breakdown in the body
COMT
Dopamine
3-OMD
Levodopa plus DDC inhibitor
Dopamine
Levodopa
Levodopa/ DDC inhibitor
Levodopa
Inhibition of DDC
COMT
Dopamine
3-OMD
Levodopa plus DDC inhibitor and a COMT inhibitor
Dopamine
Levodopa
Levodopa plus DDC inhibitor and a COMT inhibitor
Levodopa
Inhibition of DDC and COMT
Dopamine
3-OMD

Levodopa (cont)

Peripheral adverse effects:

Gastrointestinal	nausea, vomiting
Cardiovascular	arrhytmia, orthostatic hypotony

Central adverse effects:

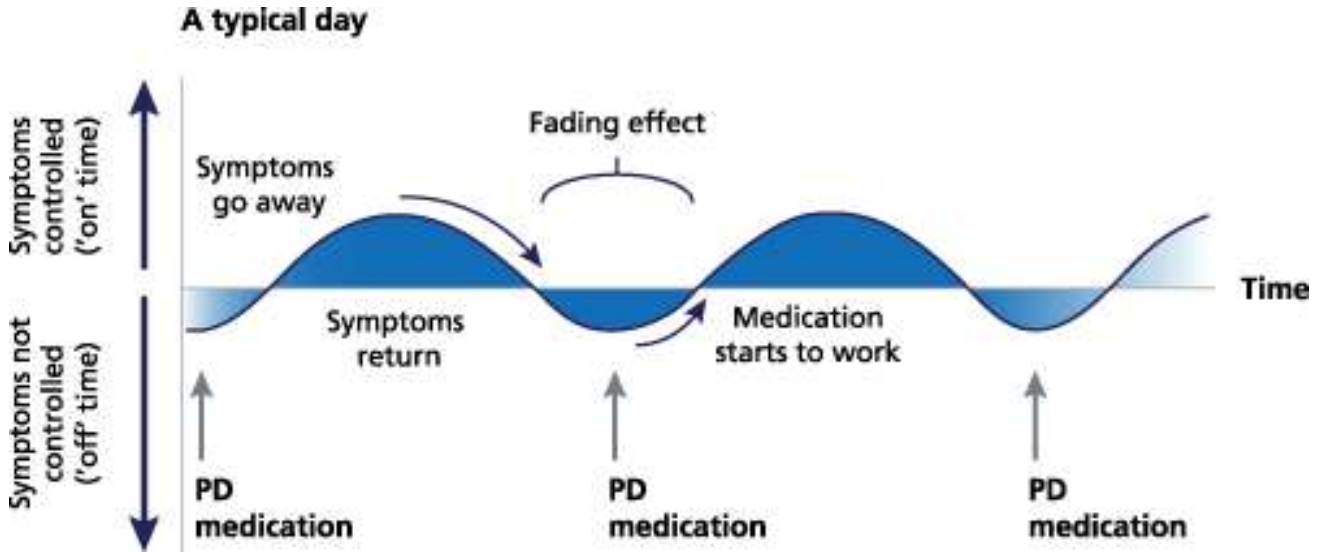
dyskinesia (chorea, tic)

behavioral effects (depression, psychosis, agitation, anxiety, nightmares, etc.)

Levodopa (cont)

During the long-term therapy:

- „end-of-dose" akinesia (shortening of the duration)
- „on-off" symptom (fluctuation of dyskinesia/akinesia)



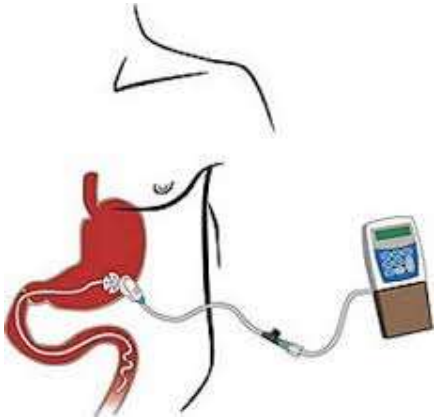
„drug-holiday" (1-2 weeks) may help ??

Contraindications of Levodopa

- psychosis
- MAO inhibitors
- malignant melanoma (dopamine is precursor of melanin)

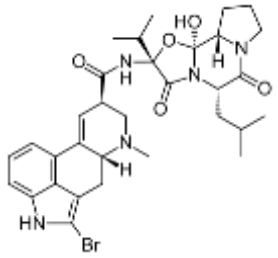
Sudden withdrawn – neuroleptic syndrome

Administration **tablets**
intestinal gel



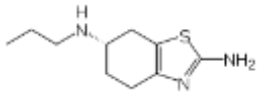
DA receptor agonists

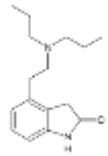
Ergoline derivatives

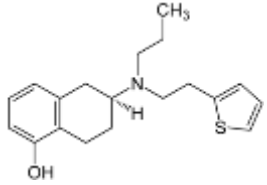


bromocriptine, cabergoline

Non ergoline derivatives

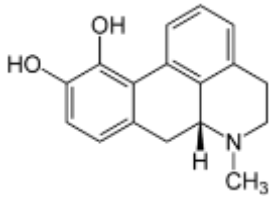




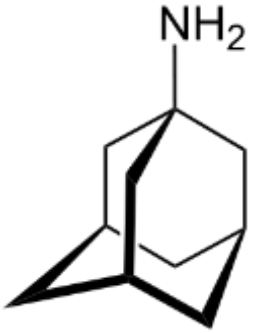


pramipexole, ropirinole (oral) **rotigotine** (patch)

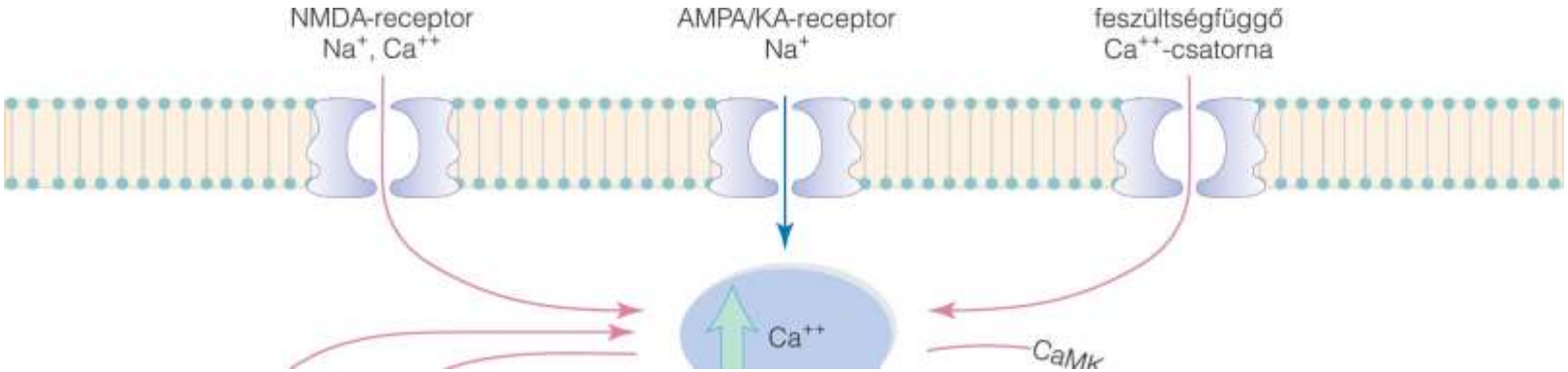
apomorphine



Amantadin



Mechanism of action: DA release ↑
DA reuptake ↓
NMDA antagonist
NMDA-mediated Ach release ↓



Inhibitors of DA metabolism

MAO-B inhibitors (irreversible)

selegiline **tabl., patch**

Mechanism of action

- inhibition of MAO-B (selective, irreversible)
- inhibition of DA reuptake
- enhancement of scavenger function (superoxide dismutase and catalase activity) - neuroprotective effect

Therapeutic indication

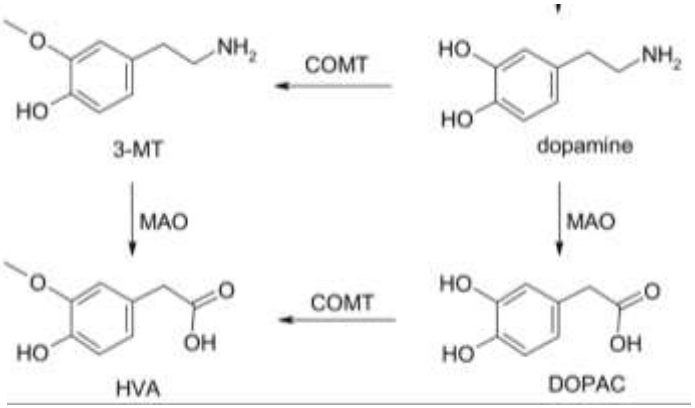
Parkinsonism, Alzheimer's disease, depression

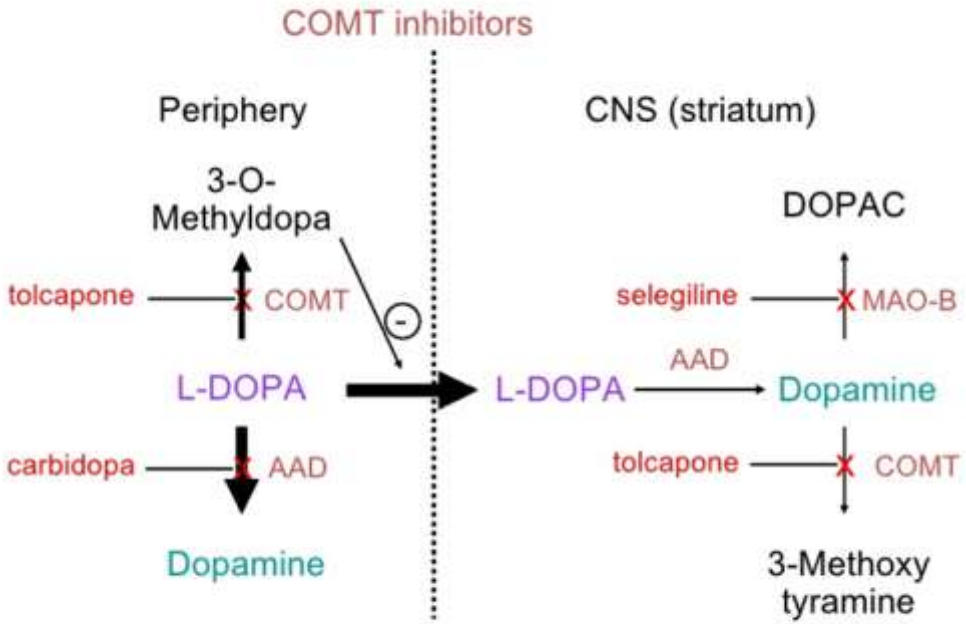
rasagiline **Parkinsonism**

Inhibitors of DA metabolism

COMT inhibitors **entacapone**

MAO-B inhibitors





entacapone does not enter the brain

Centrally acting cholinolytics

procyclidine, orphenadrine, etc.

Therapeutical indication

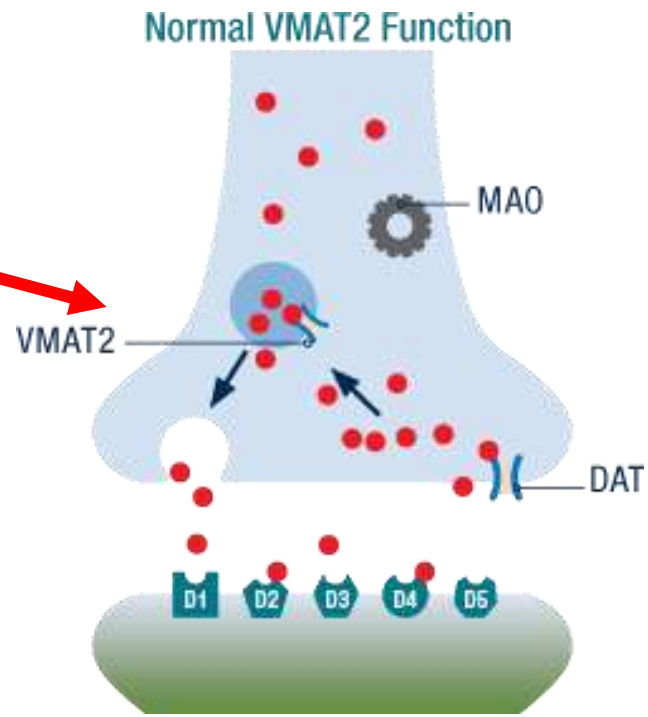
- Parkinsonism (mainly rigor and tremor)
- Antipsychotics-induced EPS (dystony, akathisia)

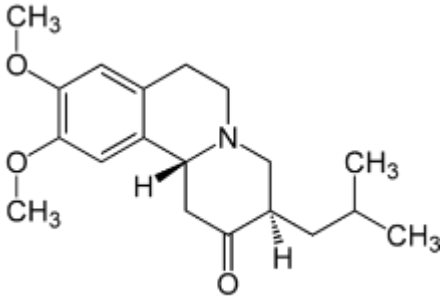
Adverse effects – consequences of parasympatholytic effect, hallucination, delirium

Therapy of Huntington disease

Drugs decreasing the dopaminergic tone

tetrabenazine





Adverse effects – somnolence, anxiety, depression

Contraindication – concomitant treatment with MAO inhibitors, depression, pheochromocytoma, prolactin dependent tumors, nursing

Parkinsonism

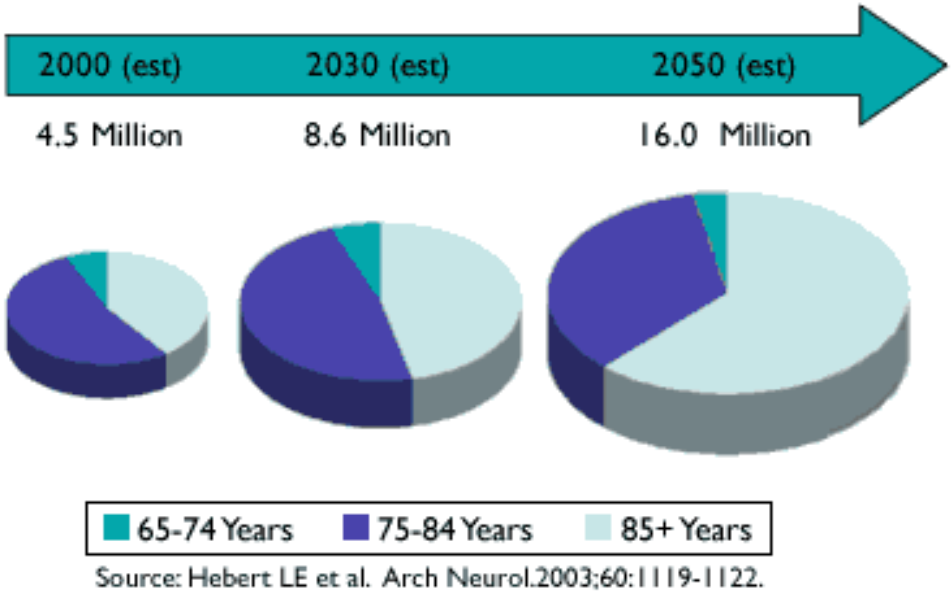
Alzheimer's disease

Stroke, ischemic dementia

Alzheimer's dementia

Alois Alzheimer 1907

Age depending dementia

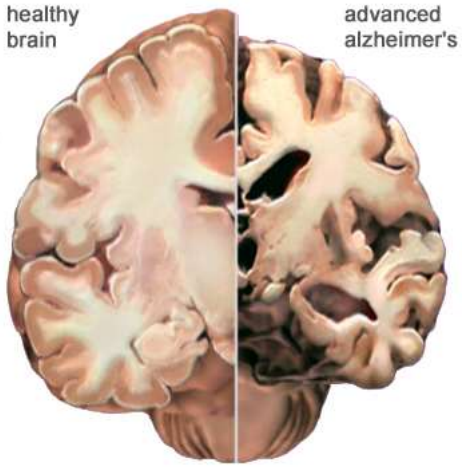


Source: Hebert LE et al. Arch Neurol.2003;60:1119-1122.

US data

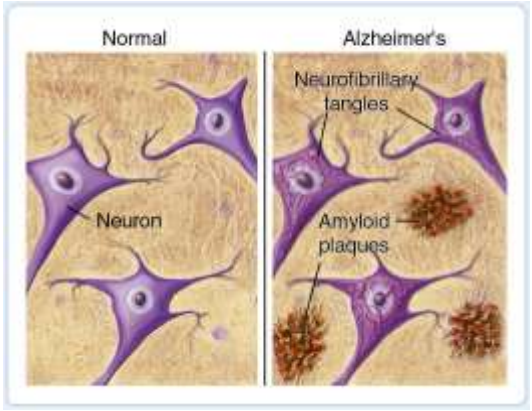
Alzheimer's dementia

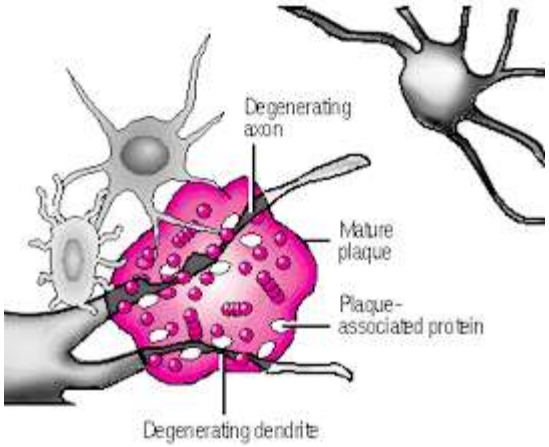
Destruction of the neurons, mainly in the hippocampus and the basal forebrain



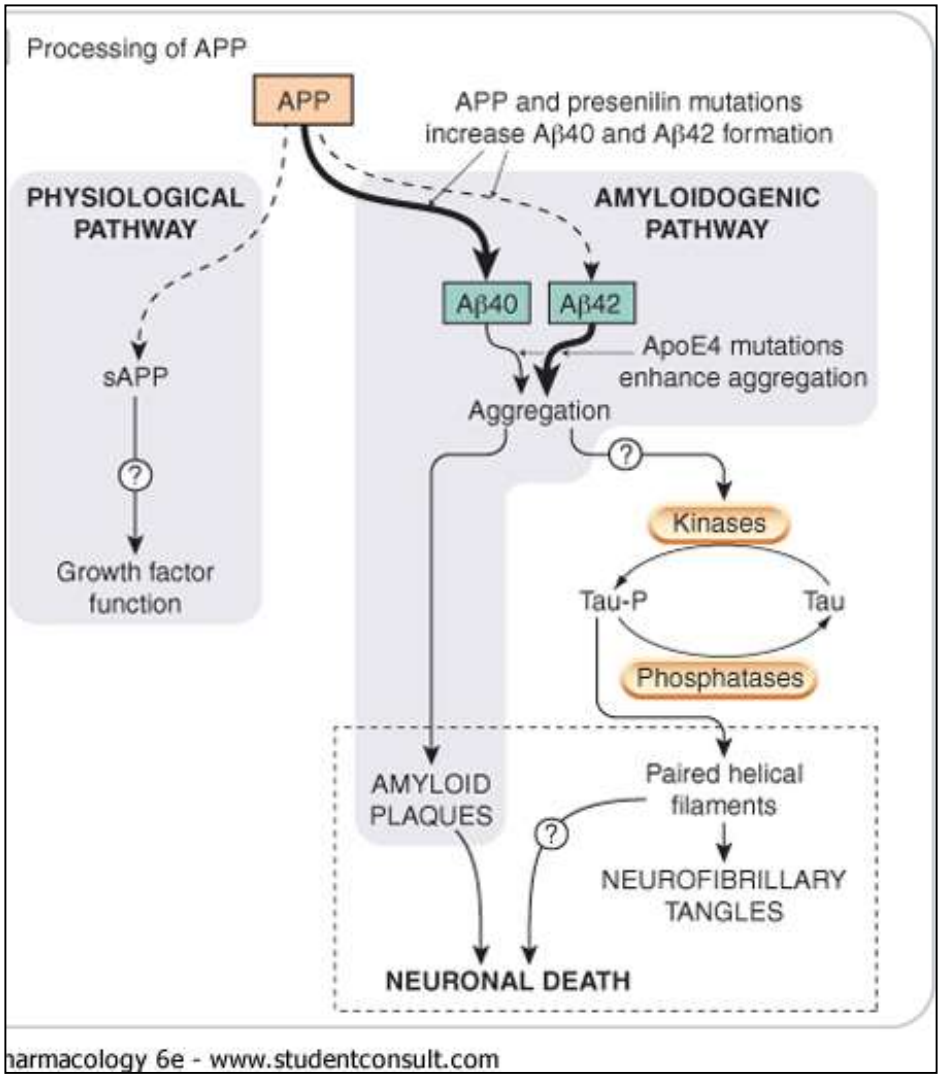
The β-amyloids are formed from precursor proteins by the aid of secretases

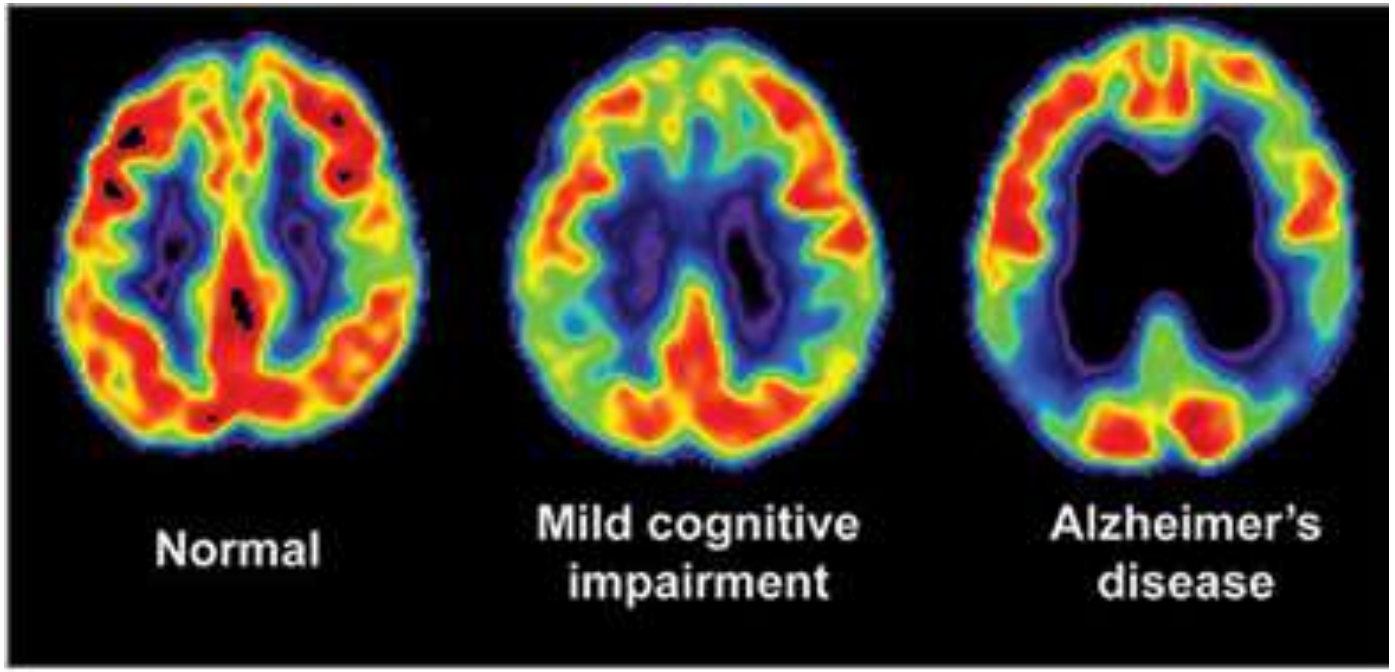
The role of γ-secretase in the formation of $A_\beta 42$ is proved





Presenilins are a family of transmembrane proteins which constitute the catalytic subunits of the γ-secretase intramembrane protease complex





FDG-PET images show reduced glucose metabolism in temporal and parietal regions in Alzheimer's disease and mild cognitive impairment.

Courtesy of Drs. Suzanne Baker, William Jagust, and Susan Landau

Therapy of Alzheimer's dementia

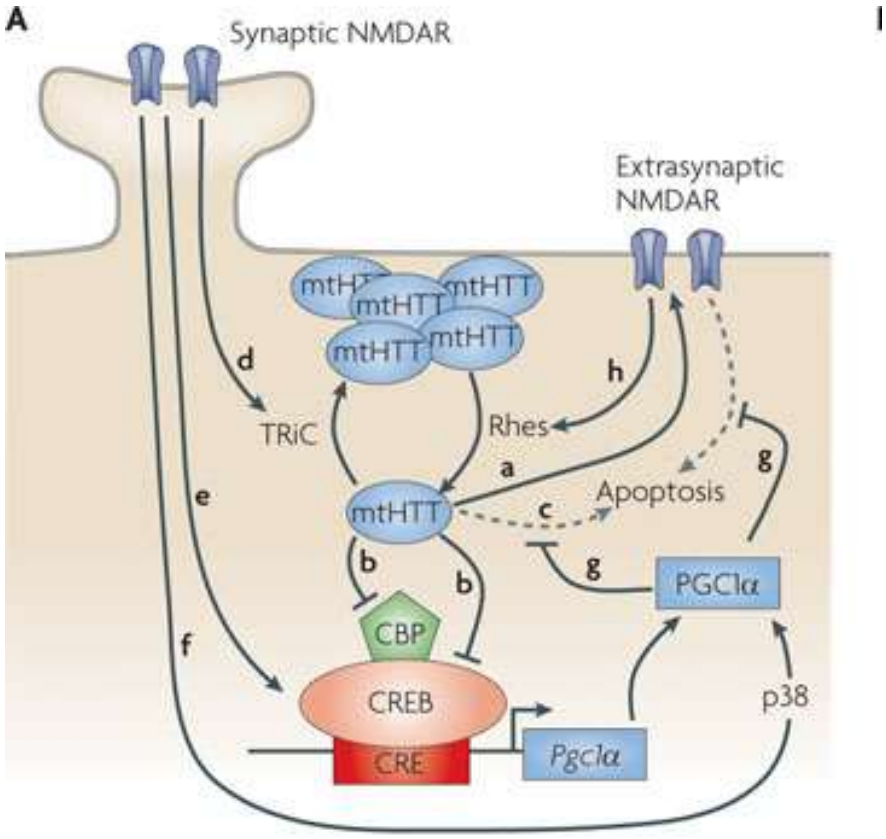
- **Centrally acting cholinesterase inhibitors**

  rivastigmine, donepezil

- **NMDA antagonists**

  memantine

Blocks the extrasynaptic NMDA receptors



Therapy of Alzheimer's dementia

Antioxidants

Selegiline, Gingko biloba

Gingko biloba in very demented patients enhances the risk of stroke

Parkinsonism

Alzheimer's disease

Stroke, ischemic dementia

Therapeutical possibilities for dementias (senile, sclerotic, post stroke, etc.)

NMDA antagonists,
Ca^{++} antagonists,
scavengers,
Ca^{++} activated protease inhibitors,
NO synthesis inhibitors,
cytokines, etc.

- **nootropics**
- **vasodilators**
- **antioxidants**
- **Ca^{++} antagonists**

❖ nootropic agents

A group of drugs aimed to promote the efficiency of the essential brain integrative activity, facilitate learning and memory in patients having symptoms of dementia

piracetam, vinpocetine, Gingko biloba

Mechanism of action of piracetam

haemorheological effects
decrease of thrombocyte aggregation
decrease of adhesion of erythrocytes
decrease of capillary spasm

- **antioxidants**

  Vitamin C, vitamin E, flavonoids

- **Ca antagonists**

  Nimodipine

- **New possibilities**

  Monoclonal antibodies

  solanezumab, aducanumab and gantenerumab