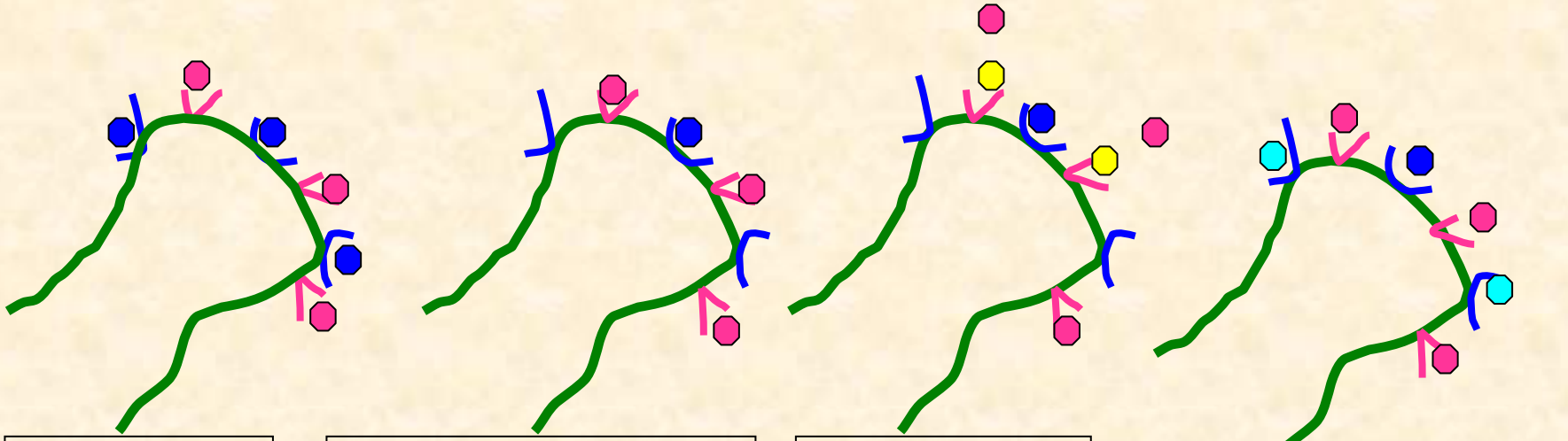
DRUGS IN PARKINSONISM

Clinical signs

- **tremor**
- **muscle rigidity**
- **bradykinesis (postural reflex disorders, slow down initiation of movements)**

ANTIPARKINSONIC AGENTS



normální | **parkinsonismus** | **treatment** | **treatment**

- DA
- Ach

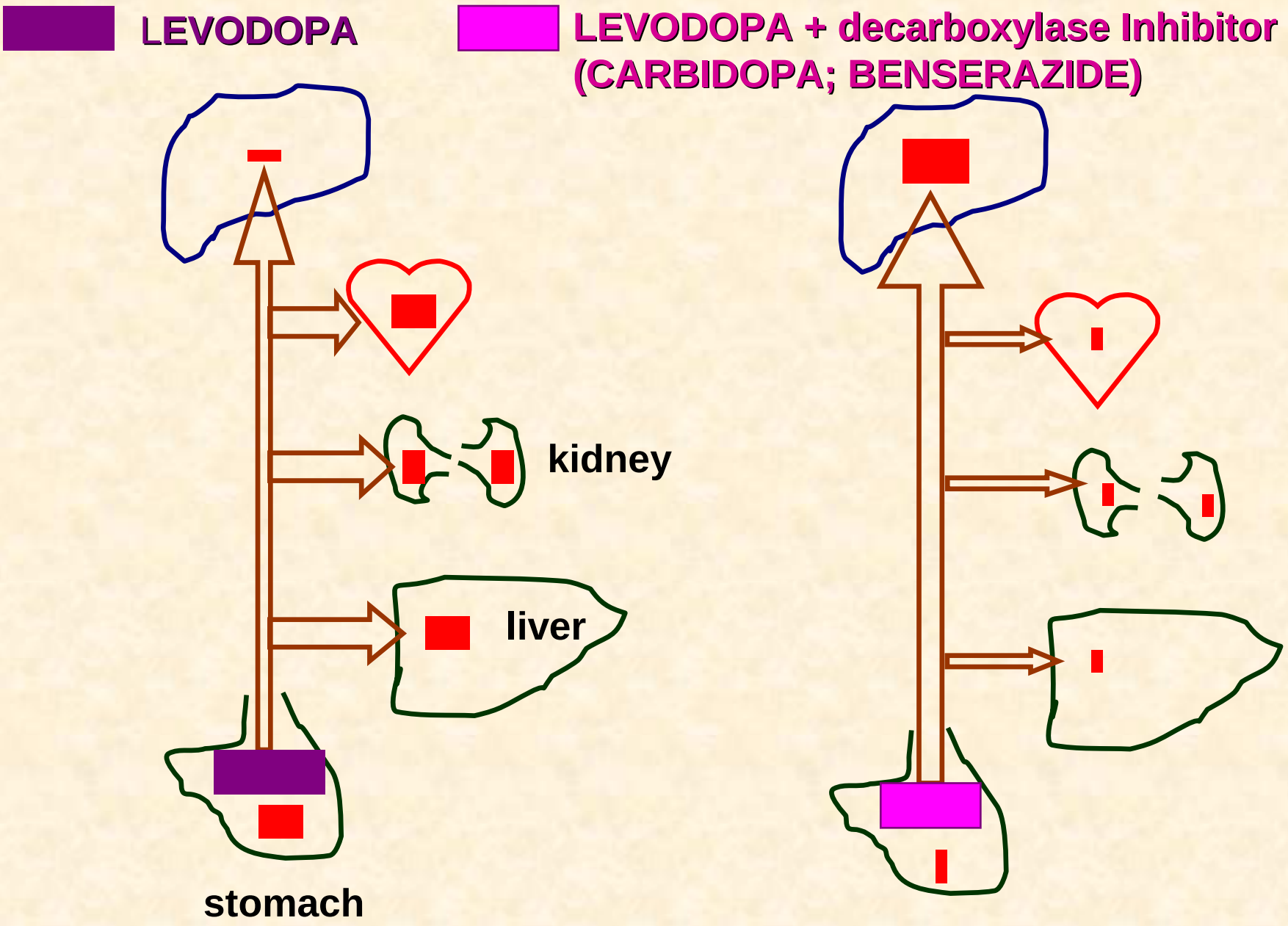
anticholinergic drug

dopaminergic drug

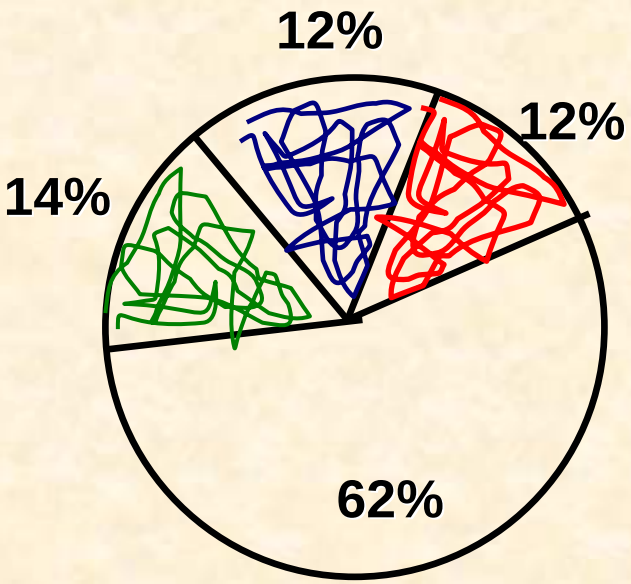
Pharmacotherapy in Parkinson's disease

- **central anticholinergics (benztropine, etoprazine, procyclidin, trihexyfenidyl, orfenadrin);**
  H_1 antihistaminergics

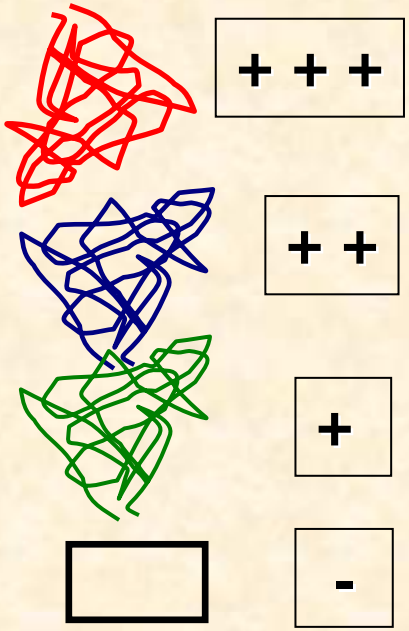
- **dopaminergics *(dopamine does not pass blood-brain barrier):***
  - **levodopa**
  - **amantadine**
  - **bromocriptine, lisuride, pergolide, pramipexol ($D_{2/3}$ r. agonist)**
  - **ropinirol (relatively selective D_2-receptor agonist)**
  - **MAO_B inhibitor (selegilin, reversible - caroxazone)**
  - **COMT inhibitors (tolcapone, entakapone)**
  - **adenosine A_{2A} receptor antagonist (theophyline)**


LEVODOPA
LEVODOPA + decarboxylase Inhibitor
(CARBIDOPA; BENSERAZIDE)
kidney
liver
stomach

L-DOPA 4.8 g/day



L-DOPA 0.8 g/day + benserazide 0.2 g/day



AMANTADINE

- increases DA release
- slows down DA re-uptake
- NMDA glutamatergic receptor antagonist
- anticholinergic effect

Adverse effects:

- hallucinations
- fuzziness
- night-mares
- sleeplesness
- sleepiness
- dysarthria

BROMOCRIPTINE

- D_2 receptors stimulation in striatum
- prolactine synthesis and release inhibited
  (for treatment of galactorhea)
- decreases growth hormone secretion in acromegaly

ADVERSE EFFECTS:

- smeary vision, diplopia
- dyskinesia
- dizziness
- constipation
- mental disorders

CENTRAL ANTICHOLINERGICS

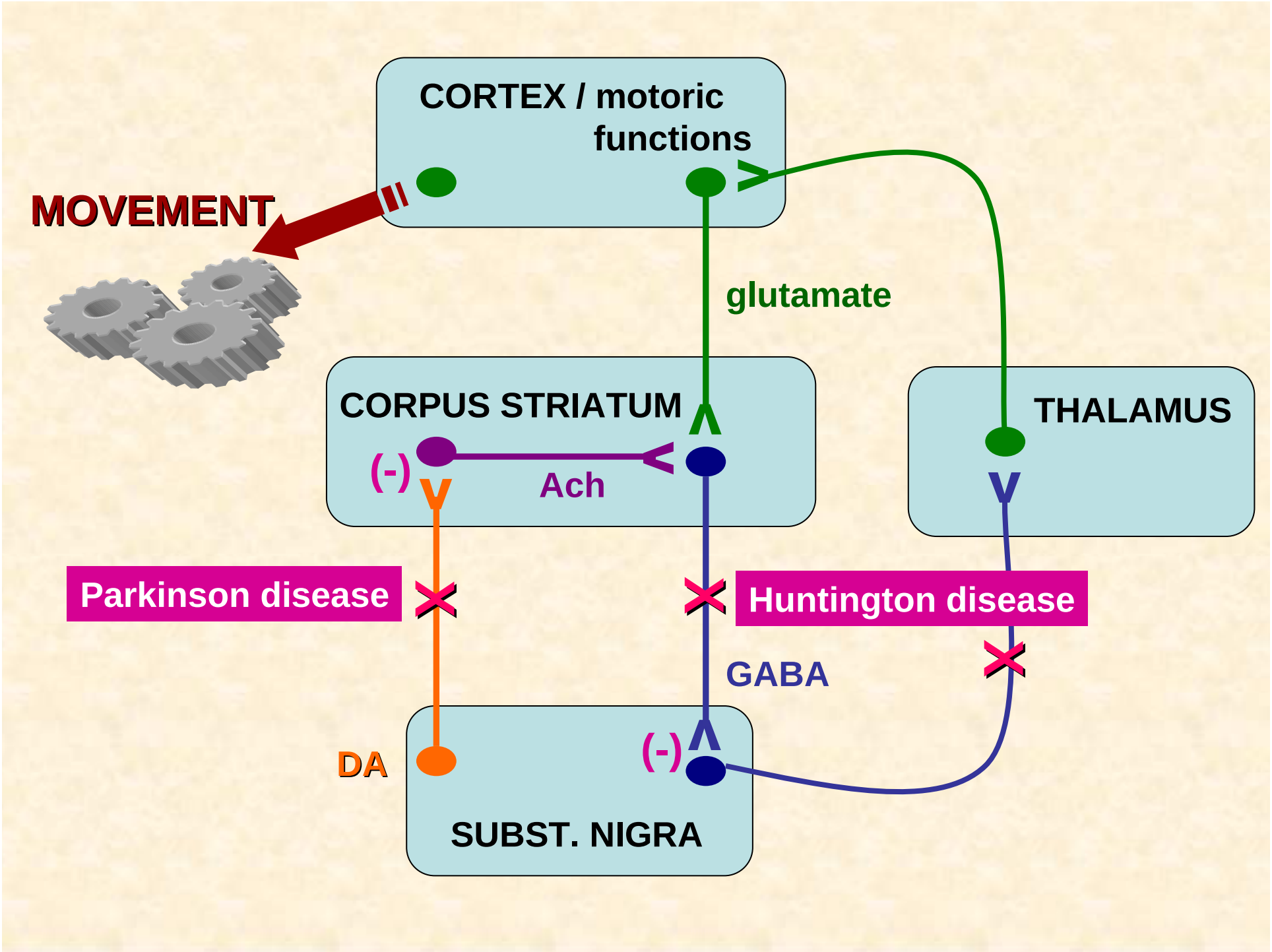
Adverse effects:

- peripheral: dry mouth, smeary vision,
  tachycardia, constipation, urine retention,
  mydriasis, vomiting

- central: sleepiness, nervosity, memory disorders

Therapy of muscle rigidity

GABAergics - benzodiazepines
- baclofen !!


CORTEX / motoric functions
MOVEMENT
glutamate
CORPUS STRIATUM
THALAMUS
(-)
Ach
Parkinson disease
Huntington disease
GABA
DA
(-)
SUBST. NIGRA

Pharmacotherapy of Huntington's disease

HUNTINGTON DIS. = geneticaly based hyperkinetic disorder with progressive dementia

huntingtine = protein autosomally coded by dominant gene

↓

through interaction with other cell proteins involved in excitotoxicity, apoptosis

- clasical antidopaminergic antipsychotics (neuroleptics)
- reserpine, meserpine, tetrabenazine (depletion of DA)
- central myorelaxant agents (e.g. baclofen)
- drugs decreasing excitotoxicity

COGNITIVES

DEMENTIA

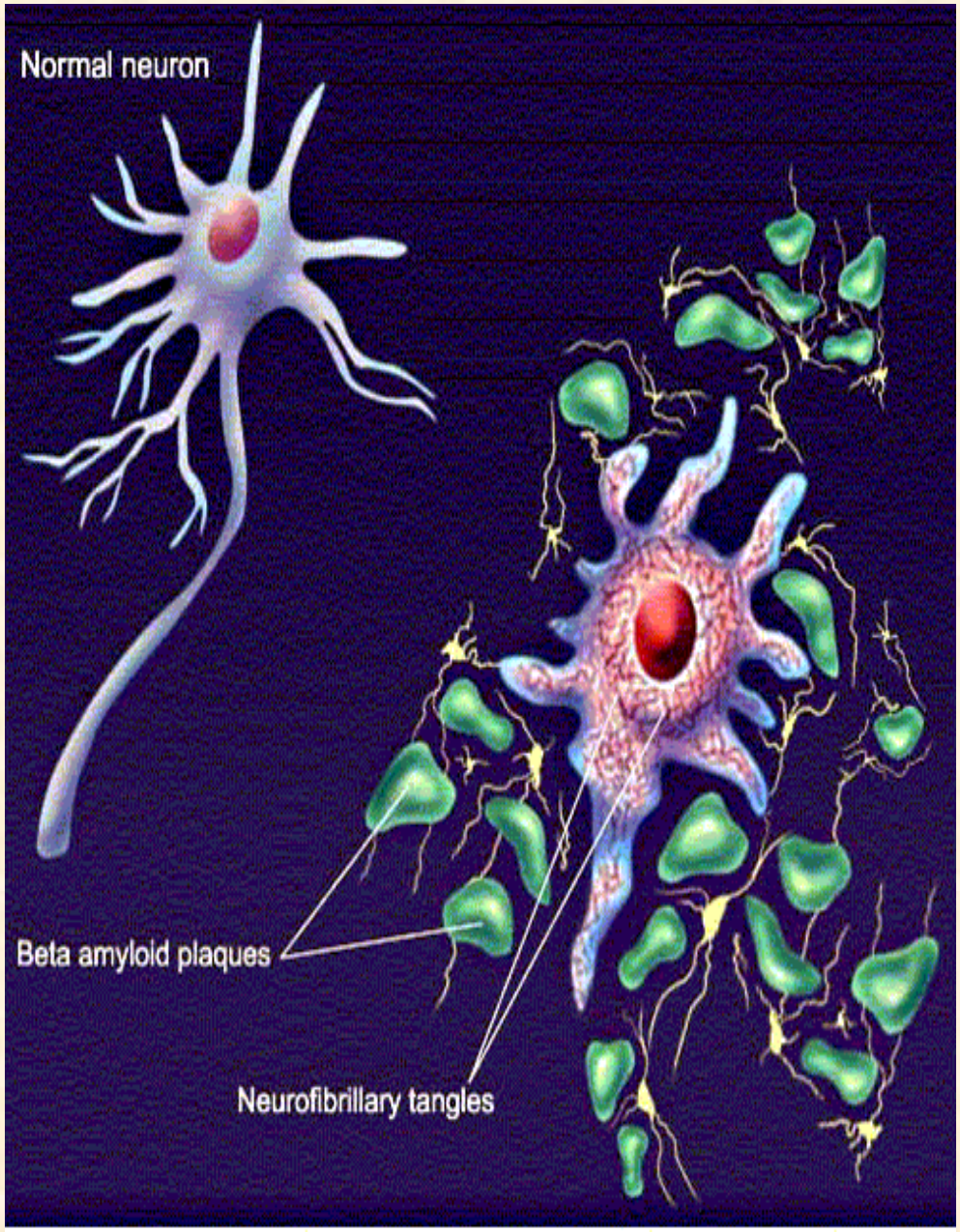
1. **Alzheimer type (50%)** — **presenile (until 65)**
   senile (after 65)

2. **vascular type *(in past : arteriosclerotic)***

3. **mixed type (ad 1. + ad 2. – 10-20%)**

4. **various – alcoholic**
   intoxicant
   postraumatic } **10-20% better treatable**
   rain tumours
   encephalitis (e.g. in AIDS)
   metabolic (B_{12} carency, hepatocerebral sy.)
   hypothyreosis
   Parkinson's disease
   Huntington's disease

Alzheimer's disease



beta-amyloid gene mutation (fragment of neuron membrane protein precursor)
extracellular plaques

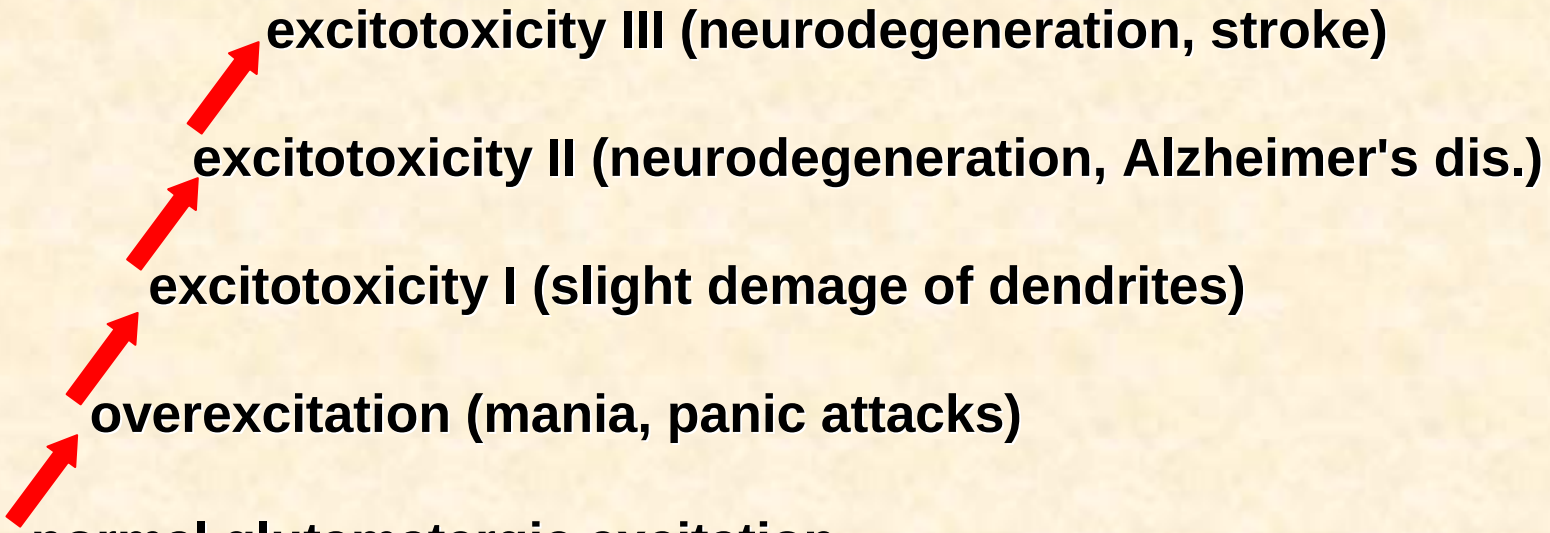
neurofibrillary tangles of abnormally phosphorylated **tau-protein**

+

deficit of Ach-ergic activity

+

excitotoxicity



EXCITOTOXICITY

→ excessive Ca^{2+} channel opening

↓

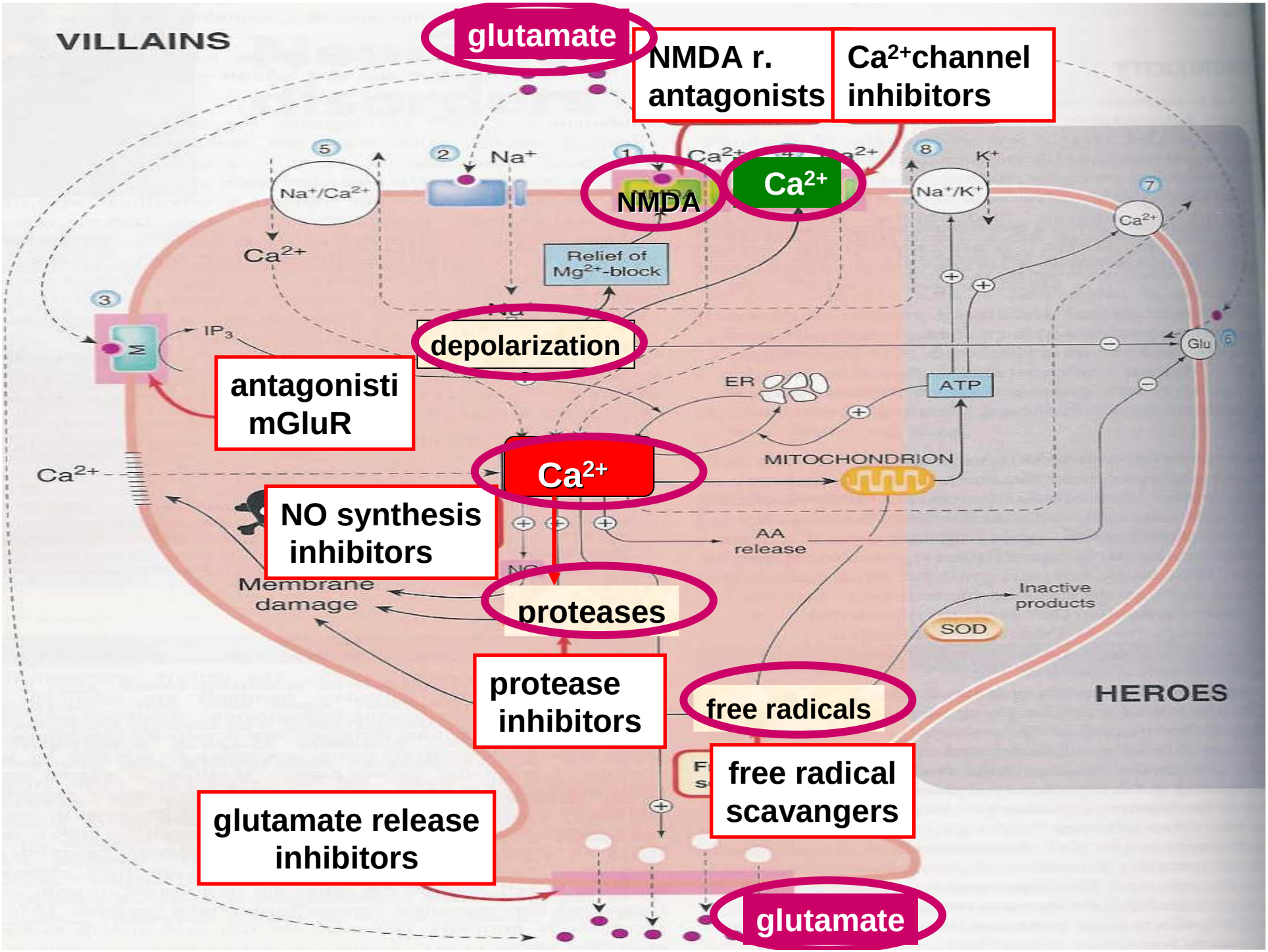
→ Ca^{2+} → activation of proteases, free radical production, lipid peroxidation

↓

→ damage of further compounds and cell components

↓

→ gradually resulting in cell death


VILLAINS
glutamate
NMDA r. antagonists
Ca2+channel inhibitors
Na+/Ca2+
Na+
NMDA
Ca2+
Na+/K+
K+
Ca2+
Relief of Mg2+-block
depolarization
IP3
antagonisti mGluR
ER
ATP
Glu
MITOCHONDRION
Ca2+
NO synthesis inhibitors
AA release
Membrane damage
proteases
Inactive products
SOD
protease inhibitors
free radicals
HEROES
free radical scavangers
glutamate release inhibitors
glutamate

PHARMACOTHERAPY

in past:

- cerebral vasodilators

- cell metabolic enhacers

(hydergine – mixture of ergot alcaloids changing *"second messenger system" - cAMP*)

- vitamins, hormones, chelation

(B_6, B_{12}, estrogen, desferrioxamine – to remove Aluminium)

currently:

- **cholinergic enhancers (donepezil, rivastigmin)**
- **nootropics**
- **scavangers of free radicals (vit. E, selegilin, Ginkgo biloba ..)**
- **calcium channel blockers**
- **NMDA r. antagonists (memantine)**

PHARMACOTHERAPY

in the future:

- **better cholinergics**

- **blokade of amyloid construction on DNA level**

- **growth factors/ implantation of healthy neuronal tissue**

CHOLINERGICS

acetylcholinesterase inhibitors

donepezil (! 1x per day , 5-10 mg !)

reversible, but noncompetitive
(butyrylcholinesterase is not inhibited)
? release of growth factors?
? inhibition of amyloid deposition ?

unset of effects primarily after 6 week

Adverse effects:

- **nausea, vomiting, diarhea, hyperacidity, weight lost**
- **sleeplessness, extraordinary dreams, sleepiness**
- **convulsions**
- **depression**

rivastigmine

cholinesterase+pseudocholinesterase reversible inhibition
? release of growth factors, inhibition of amyloid deposit ?

galantamine

cholinesterase inhibitor
+
allosteric modulator of nicotinic receptors

NMDA glutamatergic receptor INHIBITOR

memantine

memory is not improved,
slowing down progression of neurodegenerative changes

possible co-administration with cholinesterase inhibitors

NOOTROPICS

(NEURODYNAMICS)

Greek - noos = mind
tropein = towards

1972 - NOOTROPIL, UCB / piracetam

MAIN EFFECT
improvement of the CNS mechanisms associated with cognitive functions

MECHANISMS OF ACTION
- **improvement of the metabolism in the nervous cell (the utilization of glucose and oxygen)**
- **improvement of blood microcirculation in the brain**
- **other pharmacological activities as e.g. glutamatergic effects, cholinergic effects . . .**

USE OF NOOTROPICS

- unconsiousness of different etiology
- brain injury
- mental retardation, dyslexia
- brain function disorders in the elderly
- Alzheimer's disease
- organic psychosyndrome
- amnesia
- vertigo
- aphasia
- after the electro-convulsive treatment
- delirium tremens
- Parkinson's disease

piracetam – cyclic derivate of GABA

pyritinol (pyrithioxine) – vitamine B_6 derivate

meclophenoxate (centrophenoxine) – part of the molecule is a synthetic auxin, which is similar to the growth factor of plants - auxin

BRAIN VASODILATORS

papaverine (500-600 mg/day)
dihydroergotoxine
clomethiazol
naphtydrophuryl
cinnarizine . . .