2nd seminar

Antipsychotics, AntiParkinson agents

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Dopaminergic neurotransmission

- Dopamin metabolism:
  - Phe ➔ Tyr ➔ di-OH-Phe (DOPA) ➔ dopamin (enzymes: Phe-hydroxylase, Tyr-hydroxylase, DOPA-decarboxylase)
  - the released Dopamine may be reuptaken back to the presynaptic nerve ending OR
  - it may be broken down by COMT (Catechol-O-methyl transferase) or MAO (Monoamine oxidases) (primarily MAO-B)

Dopaminergic neurotransmission

Dopamine receptors:

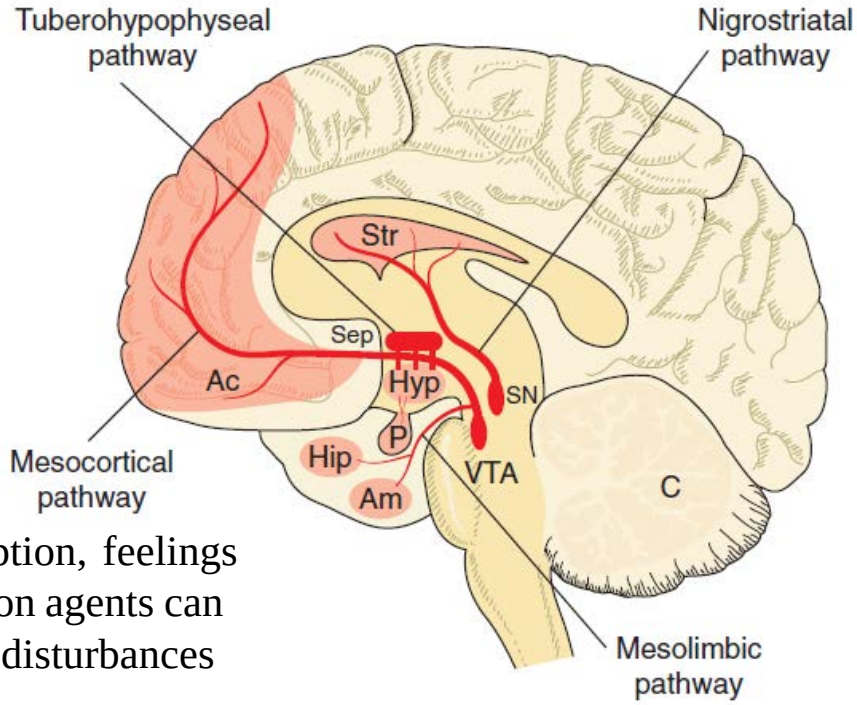
D_1-like, D_2-like

(μM)
- D_1:Gs→AC→cAMP↑ putamen, cortex, nucleus accumbens

(nM)
- D_2 :Gi→cAMP↓, seen above
- D_3 :Gi→cAMP↓ frontal cortex, mesencephalon
- D_4 :Gi→cAMP↓ cortex

(μM)
- D_5 :Gs→AC→cAMP↑, hippocampus, hypothalamus

Dopaminergic pathways



Ac: nucleus accumbens
Am: amygdaloid nucleus
C: cerebellum
Hip: Hippocampus
Hyp: Hypothalamus
P: pituitary gland
Sep: Septum
SN: substantia nigra
Str: Corpus striatum
VTA: ventral tegmental area
(Rang&Dale 7th Ed.)

Dopaminergic systems

- nigrostriatal pathway
  - substantia nigra→corpus striatum
  - coordination of voluntary movement
  - deficiency!→Parkinson's disease
- mesolimbic-mesocortical pathway
  - mesencephalon→limbic system/cortex
  - cognitive functions, self-reward system, perception, feelings
  - overstimulation! ➔ side effects of antiParkinson agents can be cognitive and behavioural neuropsychiatric disturbances
  - Mesolimbic overactivity = positive symptoms
  - Mesocortical dysfunction = negative symptoms
- hypothalamo-hypophyseal (tuberoinfundibular) pathway
  - hypothalamus → hypophysis
  - endocrine functions
  - dopamin = PIF, prolactin secretion↓ ➔ side effects of antipsychotics may be hyperprolactinaemia ➔ galactorrhea (milk leakage) (even in male patients)
- medullary-periventricular pathway
  - around III.-IV. ventricle
  - eating behavior ➔ antipsychotics may provoke obesity
- area postrema
  - chemosensitive trigger zone
  - antpsychotics ➔ antiemetic effects

Schizophrenia

- psychiatric disease
- etiology:
  - dopamine hypothesis
    - hyperfunction of mesolimbic dopaminergic pathway
    - primarily described (development of typical antipsychotics-D2R antagonism)
    - D_2 R blocking drugs reduce psychotic symptoms
    - D_2 R activating drugs (levodopa, bromocriptine) produce psychosis
    - post-mortem study – increased D_2 R density in midbrain (mesencephalon)
    - increased dopamine levels in putamen, nucleus accumbens
  - serotonin hypothesis
    - indole hallucinogenes (LSD), mescalin provoke psychotic symptoms
    - $5HT_{2A}$ R agonism – hallucinations
    - inverse agonists of $5HT_{2A}$ R (AAP-clozapine, queitapine) reduce sch. sympt.
  - glutamate hypothesis
    - hypofunction of NMDA R located on GABAerg neurons provoke schizphr.

Schizophrenia

Symptoms:

- positive symptoms:
  - illusions / delusions (irreal)
  - auditory/visual hallucinations
  - thinking disorders
  - motoric excitement (agitation), agressive behaviour
- negative symptoms:
  - blunted reactions and emotions
  - poverty of speech (alogia)
  - inability to experience pleasure (anhedonia)
  - lack of motivation
  - lack of social relationships
  - nonchalance, indifference (apathia)

Antipsychotics (neuroleptics)

Classification (based on chemical structure)

- phenothiazine derivatives
  - propyl-amines
    - chlorpromazine
    - promethazine
  - piperidine derivatives
    - thioridazine
  - piperazine derivatives
    - perphenazine
- thioxanthene derivatives
  - Thiothixene, methixen, chlorprothixen
  - Flupenthixol, Zuclopenthixol
- butyrophenon derivatives
  - haloperidol
  - droperidol
- benzamide derivatives
  - tiaprid
  - suliprid
- dibenzodiazepines
  - clozapine
  - olanzapine
  - quetiapine
- benzioxazol derivatives
  - risperidon

Classification (based on receptor selectivity and side effect profile):

typical antipsychotics

atypical antipsychotics

Typical Antipsychotics

- D_2 R antagonism
- anti-cholinerg effect (obstipation)
- anti-adrenerg effect (orthostatic hypotension)
- reduction of the positive symptoms of schizophrenia (⇔negatives rise)
- broad side effect profile
  - Extrapyramidal symptoms (dopamine depletion of nigrostriatal pathway)
    - acute
      - achatisia (uncontrolled restlessness)
      - acute dystonic reactions (spastic retrocollis/torticollis)
    - chronic
      - MNS (malignant neuroleptic syndrome: fever, sweating, muscle rigidity, confusion, altered consciousness) - therapy: bromocriptin, danthrolen
      - pseudo Parkinson syndrome (bradykinesia, rigidity, tremor)
      - perioral tremor („rabbit syndrome")
      - tardive dyskinesia (choreo-athetoid movements (video))
  - (cont.)

Tardive dyskinesia, retrocollis 2:52-3:25

Perioral tremor (rabbit-syndrome)

choreo-athetosis

Typical Antipsychotics

- broad side effect profile (cont.)
  - endocrine effects (dopamine depletion of tuberoinfundibular pathway)
    - hyperprolactinaemia, galactorrhea, amenorrhea
    - gynecomastia, impotence
  - antiemetic effects (D_2R blocking in area postrema)
    - Promethazine (Pipolphen)
      is a phenothiazine in structure, but rather an anti-histamine (H_1R-blocker)
      with antiemetic effect and weak anti-psychotic effect
  - cardiac toxicity
    - thioridazine
      - QT prolongation, arrhythmias

Typical (1st gen.) antipsychotics in Hungary

Levomepromazine

Fluphenazine

phenothiazines

Haloperidol

Droperidol

butyrophenons

zuclopenthixol

flupenthixol

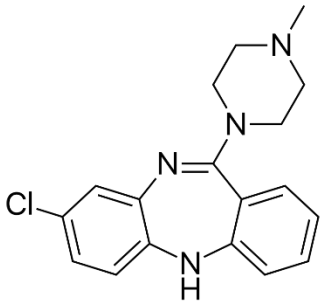
chlorprothixen

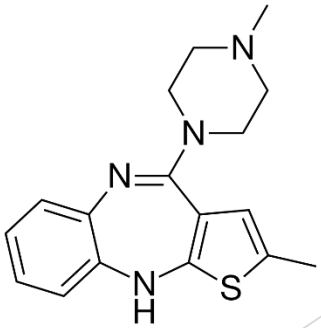
thioxanthenes

Atypical Antipsychotics

- expanded receptor profile (not just D_2R)
- reduction both of the positive and negative symptoms of schizophrenia
- reduced side effect profile

- Dibenzo-diazepine derivatives
  - Clozapine (Leponex®)
    - blocking $D_4R > D_2R = 5HT_{2A}R > D_1R$
    - central adrenerg effect
    - mesolimbic selectivity
    - side effects
      - obesity, insulin resistance
      - agranulocytosis (occurs in about 1% of patients)
      - myocarditis
  - olanzapine (Zyprexa®)
    - $5HT_{2A}R > H1R > D_4R > D2R$
    - mesolimbic selectivity
    - side effects
      - obesity,
      - insulin resistance
  - Similar: quetiapine, clotiapine





Atypical Antipsychotics

- Benzioxazole-derivatives
  - risperidone (Risperdal®)
    - blocking $D_2R > 5HT_{2A}R > H_1R$
    - mesolimbic selectivity
    - side effects
      - Extrapyramidal symptoms
      - hyperprolactinaemia
      - sedation
      - headache
      - malignant neuroleptic syndrome
    - 9-OH-risperidone = Paliperidon (Invega, Xeplion)

  - sertindole (Serdolect®), ziprasidone (Zeldox), lurasidone
    - $D_2R > 5HT_{2A}R > \alpha 1$
    - side effects
      - QT prolongation

Atypical Antipsychotics

- Dichlorphenylpiperazine-derivatives
  - aripiprazole (Abilify®)
    - D_2R partial agonist (!)
      $5HT_{2A}R$ antagonist

- Benzamid-derivatives
  - Sulpiride (Depral®), tiapride (Tiapridal®), amisulpride (Amipride®, Amitrex®)
    - $D_2R = D_3R > D_4R$
    - side effects
      - Extrapyramidal symptoms
      - hyperprolactinaemia

Development of obesity and insulin resistance during Atypical Anti-Psychotic-treatment

weight gain

- blocking H_1R in hypothalamus
- TNF-α hypersecretion
- α_2 adrenergic agonism
- decreased leptin levels, leptin resistance

insulin resistance

- $5HT_{1A}R$ antagonism → decreased response of pancreatic β cells
- M_3R antagonism → decreased response of pancreatic β cells
- inhibitory effect on GLUT transporters in skeletal muscle

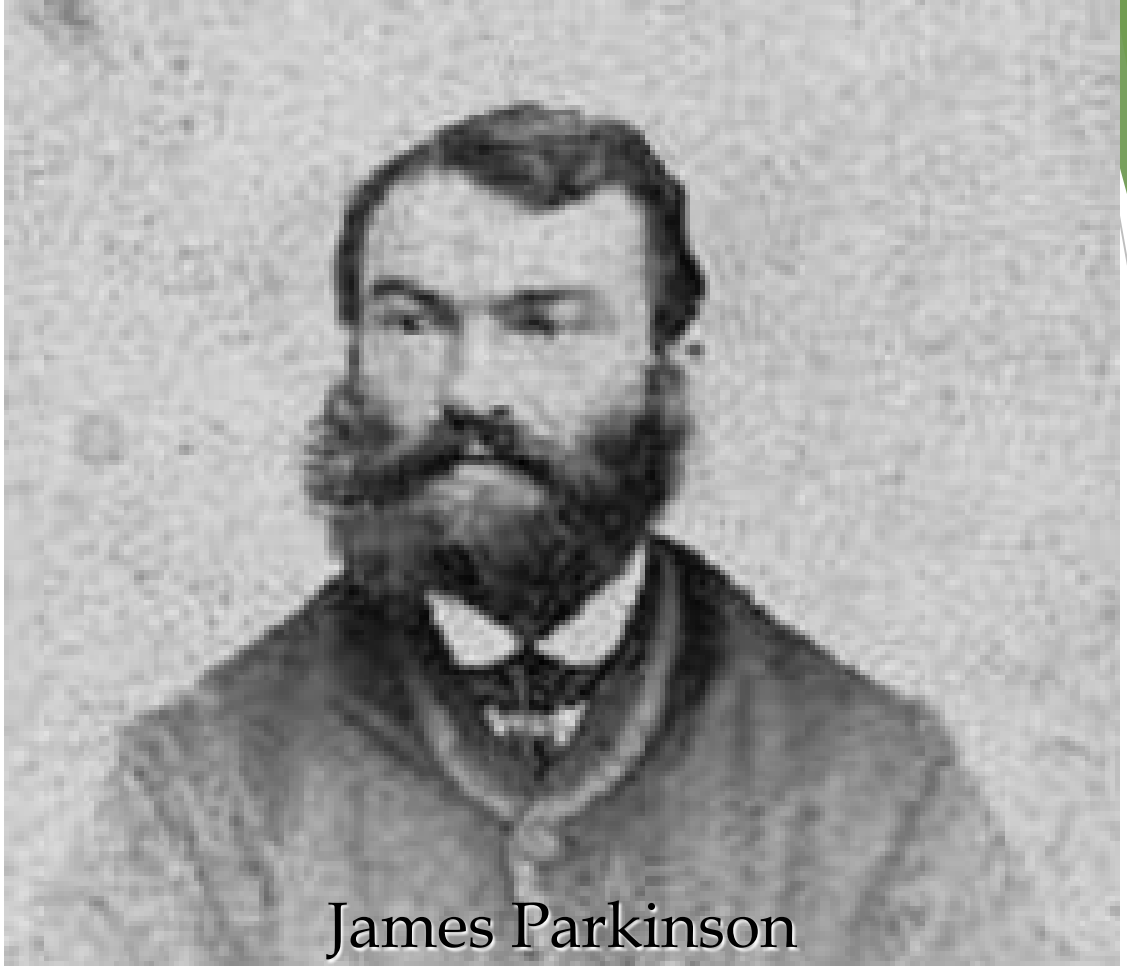
Clinical use

- ***Behavioural emergencies*** *(e.g. violent patients with a* range of psychopathologies including *mania, toxic delirium, schizophrenia and others):*
  - – antipsychotic drugs (e.g. chlorpromazine, haloperidol, olanzepine, risperidone) can rapidly control hyperactive psychotic states

- ***Schizophrenia****:*
  - – most chronic schizophrenic patients are treated with first-generation antipsychotic drugs. Depot injections (decanoate) may be useful ➔ increasing compliance
  - – newer antipsychotic drugs (e.g. amisulpride, olanzapine, risperidone) are used if extrapyramidal symptoms are troublesome or if symptom control is inadequate
  - – clozapine can cause *agranulocytosis but is* especially effective against 'negative' features of schizophrenia.
- **Other indications: nausea/vomiting, hiccups, premedication before surgeries, tic, Tourette sy, Huntington chorea**

Tic (1:13-) (complex 4:15-) (vocal 6:58-) (complex vocal 8:45-)

Antiparkinson drugs



James Parkinson
English physician, geologist, and palaeontologist, was educated for the medical profession, and practised in Hoxton, from about the year 1785. The best known of his works is *Essay on the Shaking Palsy*, which is the first profile of the disease which now bears his name, Parkinson's.

Extrapyramidal movement disorders

<u>akinetic/hypokinetic rigid syndromes</u>

Parkinson's disease,

<u>hyperkinetic rigid syndromes</u>

chorea, tic, athetosis, ballismus

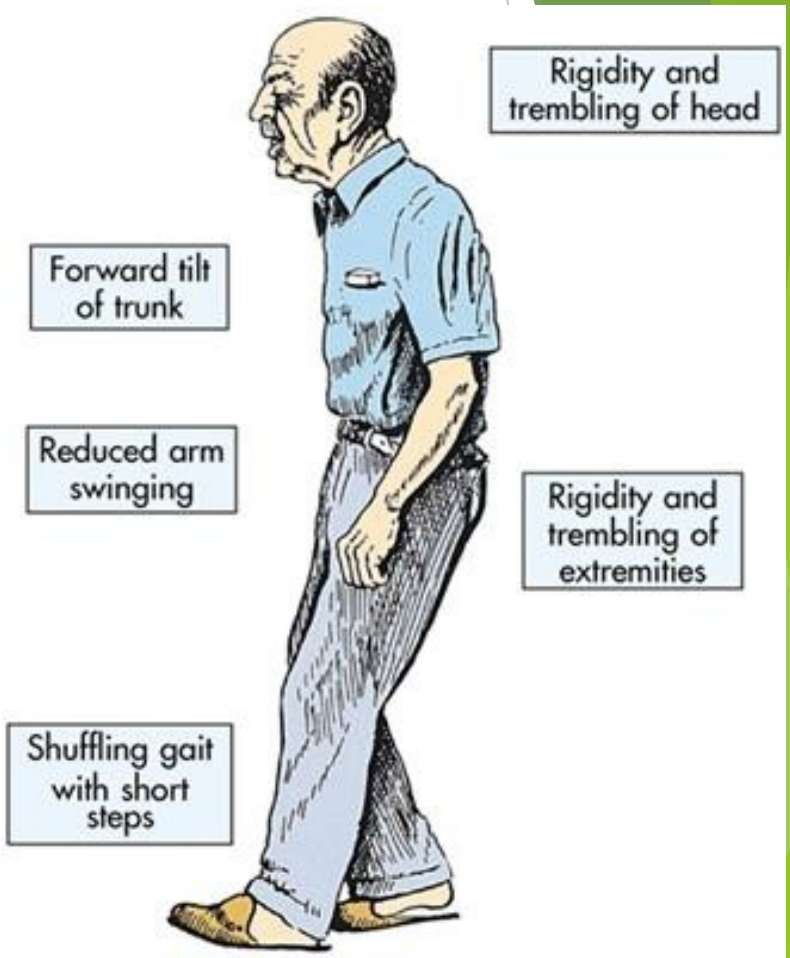
<u>Parkinsonism:</u>

- Etiology:
  - dopamine depletion of nigrostriatal dopaminergic pathway→disbalance of dopamin/ACh
  - uncontrolled function of GABAergic neurons (c.striatum→ substantia nigra, globus pallidus, cortex)
  - background:
    - exogenous:
      - MPTP (neurotoxin) a contamination in a pethidin-analogue →MAO-B→MPP+ (selective destruction of dopaminerg neurons) → new age in therapy, role of MAO inhibitors
      - drugs: dopamin receptor antagonists (antipsychotic drugs-butyrophenone/phenotiazine), reserpine (depletes dopamine stores)
      - injury, viral encephalitis, carbon-monoxyde intoxication
    - endogenous:
      - tumor, metabolic disturbances, stroke, inflammation, circulatory disturbances, oxigen-deficit,
      - mutation of α-synuclein, Leucine-rich repeat kinase 2 (LRRK2) proteins

Parkinson's disease

Symptoms:

- impaired motorium
  - hypo/bradykinesis
    - starting hezitation, freezing
    - writing-spasm (mogigraphia)
  - rigor (stiffness)
  - tremor (trembling)
- impaired cognitive functions
  - cognitive slowing
  - dementia
  - aphasia
- autonomic symptoms
  - hypersalivation
  - obstipation
  - hypotension



Characteristic symptoms of Parkinson’s disease (1:08-1:34), (2:25-3:20)

Parkinson’s disease

Pharmacological ways

1. dopamine substitution:
   - levodopa

2. dopamine R agonism:
   - bromocriptin
   - pergolide
   - pramipexole - ropinirole
   - apomorphine
   - rotigotine

3. MAO/COMT inhibition:
   - selegilin
   - tolcapone/entacapone

4. acetylcholine blocking drugs:
   - benztropine mesylate
   - biperiden

Dopamine substitution

- levodopa (Dopaflex®)
  - metabolic precursor of dopamine
  - Metabolises to active form in CNS by DOPA decarboxylase
  - rapidly absorbed from small intestine
  - half-time:1-3 hours
  - only 3% of administered levodopa enters CNS (first pass metab., peripheral decarboxylase)
  - peripheral DOPA decarboxylase inhibitor
    - carbidopa
    - benserazid
  - adverse effects:
    - vomiting, nausea (area postrema D2R agonism)
    - cardiac arrhytmias (tachycardia, VES), hypotension
    - dyskinesias (choreoathetosis)
    - hallucinations, nightmares, euphoria (therapy:clozapine)
    - fluctuation in response, probably due to fluctuation in drug plasma-levels
      - "end of dose akinesia" / "wearing off" phenomenon = drug's effect decreases by morning ➔ solution: retard formulations
      - "on/off" phenomenon (unrelated to timing of doses) = sudden cessation of drug effect = akinesia, then it comes back; during on-period, mobility is improved, but psychosis may occur
  - clinical use
    - levodopa (100 mg) + carbidopa/benserazid – Sinement®/Madopar®
    - levodopa+carbidopa+COMT inhibitor (entacapone) (see later slide)
    - tolerance in 3-4 years
    - decrease gradually! (abrupt cessation may cause akinetic state)
  - Contraindications
    - psychotic patients
    - patients taking MAO-A inhibitor

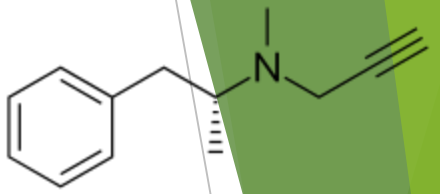
Duodopa intestinal gel
levodopa + carbidopa

Dopamine R agonists

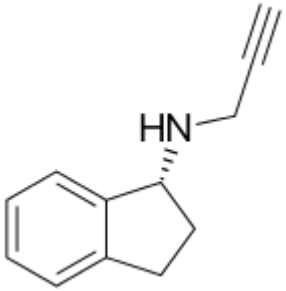
- bromocriptine
  - ergot derivative
  - D_2R agonist
  - adverse effect: nausea, vomiting
  - indication: akinetic crisis, hyperprolactinaemia
  - therapeutic dose: 7,5 - 30 mg
- pergolide
  - ergot derivative
  - D_1R and D_2R
  - more effective, than bromcriptine (for combination therapy/in refractory cases)
  - adverse effect: cardiac valvulopathy, cardiac arrhythmias
- pramipexole, ropinirole
  - D_3R agonism (not ergot derivative)
  - as monotherapy – first line drug in management of early PD
  - alternative route in case of levodopa therapy fluctuation
- apomorphine
  - D_2R agonism
  - For temporary relief of „off phenomenon”, akinetic crisis
  - adverse effect: nausea, dyskinesias, drowsiness
  - dosage: 3-6 mg / max. 10 mg subcutaneous injection
- rotigotine
  - skin patch
  - early treatment of Parkinson’s disease

MAO inhibitors

- selegiline (Deprenyl®, Jumex®)
  - irreversible inhibitor of MAO-B
    (at higher dose: MAO-A as well)
  - adjunctive therapy
    - prolonged effect/reduced dose of levodopa
    - reduce on/off, end of dose phenomenon
  - th. dose: 2x5mg/day
  - adverse effect: insomnia

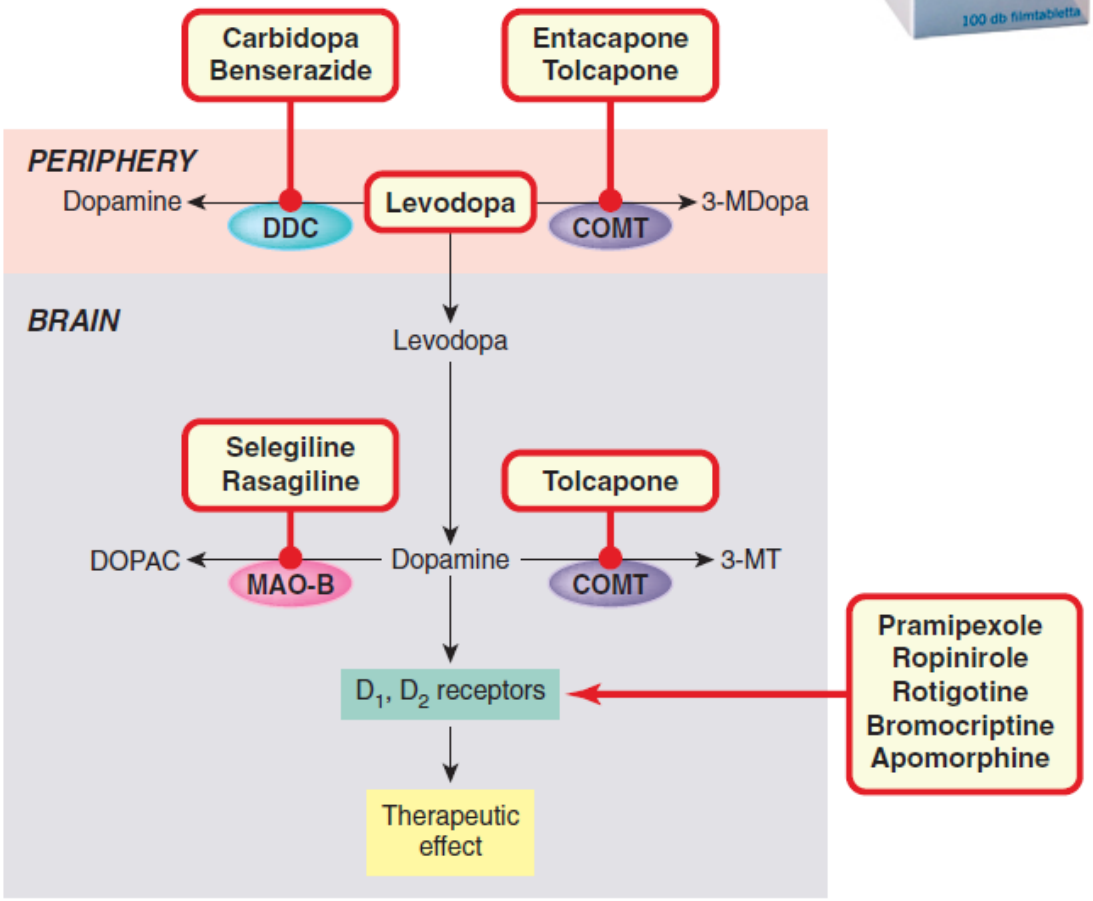


- rasagiline
  - more potent (1mg/day)
  - contraindications: SSRI, tricyclic antidepressants
    → serotonin syndrome



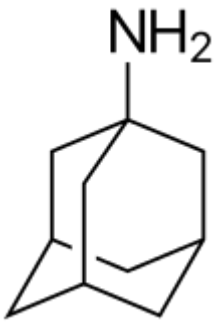
COMT inhibitors

- compensatory activation of COMT (due to inhib. of DOPA decarb.)
  - Level of 3-O-Methyl-Dopa increases, competition with levodopa for transport (in intestinal mucosa and blood brain barrrier)
- tolcapone, entacapone
  - selective COMT inhibitors
  - rapidly absorbed
  - half-life: 2 hours
  - effects:
    - reduces levodopa dose
  - adverse effects:
    - prolong „on” period
    - abdominal pain
    - dyskinesias
    - diarrhea
    - hepatotoxicity (tolcapone)
  - therapeutical dose:
    - entacapone 3x200mg/day
    - tolcapone 5x100 mg/day



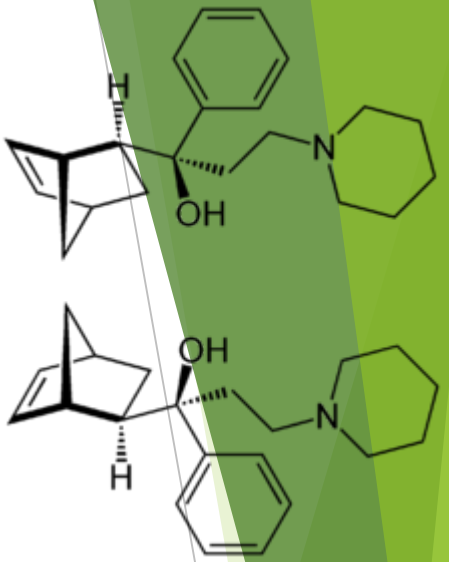
Amantadine (Viregyt® , PK-Merz®)

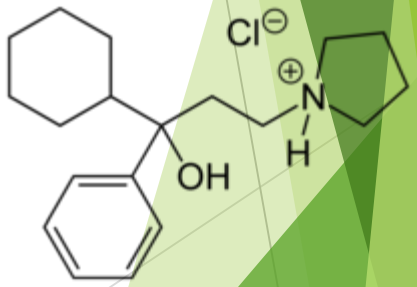
- antiviral agent
- pharmacodynamic effects:
  - facilitating dopamine synthesis, release
  - antagonism on $\alpha_{2A}R \rightarrow$ potentiating dopaminergic function
  - Blocks NMDA (glutamate) R
  - Anticholinergic property
- clinical use:
  - acute application
  - beneficial effects in rigor, tremor, akinesia
  - 2x100mg/day p.o.
- adverse effects:
  - depression, irritability, insomnia, agitation, confusion
  - acute toxic psychosis
- contraindications:
  - seizures
  - heart failure



Ach blocking drugs

- central acting antimuscarinic preparations
  - benztropine mesylate
  - biperiden
  - orphenadrine
  - procyclidine
  - trihexyphenidyl





- Mechanism of action:
  - antimuscarinic effect (blocking M_1R, M_3R)

- adverse effects:
  - tachycardia
  - mydriasis
  - dry mouth/skin
  - obstipation
  - agitation/agression