Introduction to Psychopharmacology

Neurotransmitter Systems

Pharmacology of dopamine in the CNS

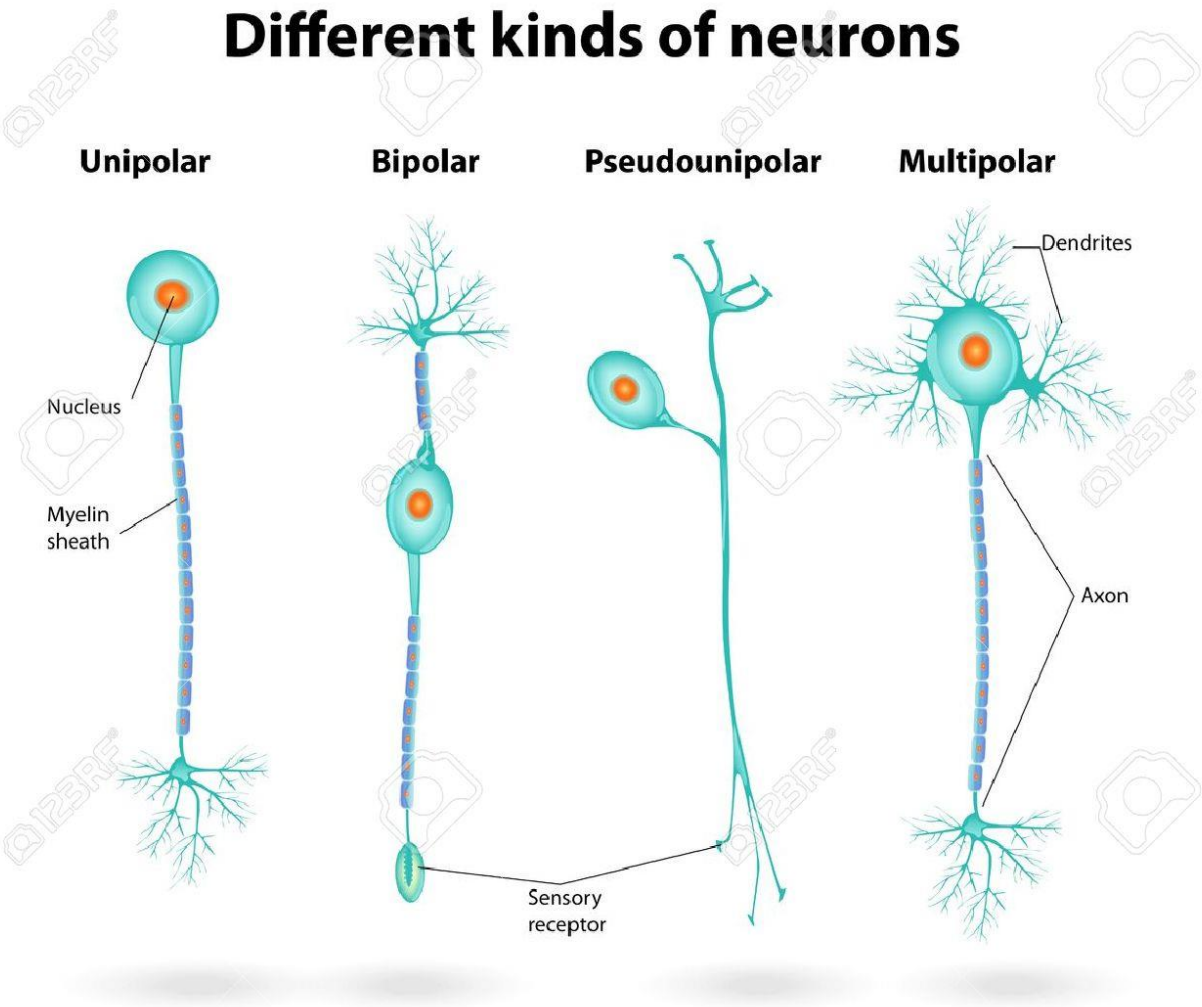
Antipsychotics

Antiparkinsonics

Prokinetics

Jan Juřica

Neuron


Different kinds of neurons
Unipolar
Bipolar
Pseudounipolar
Multipolar
Nucleus
Myelin sheath
Sensory receptor
Dendrites
Axon

Types of neuronal synapses

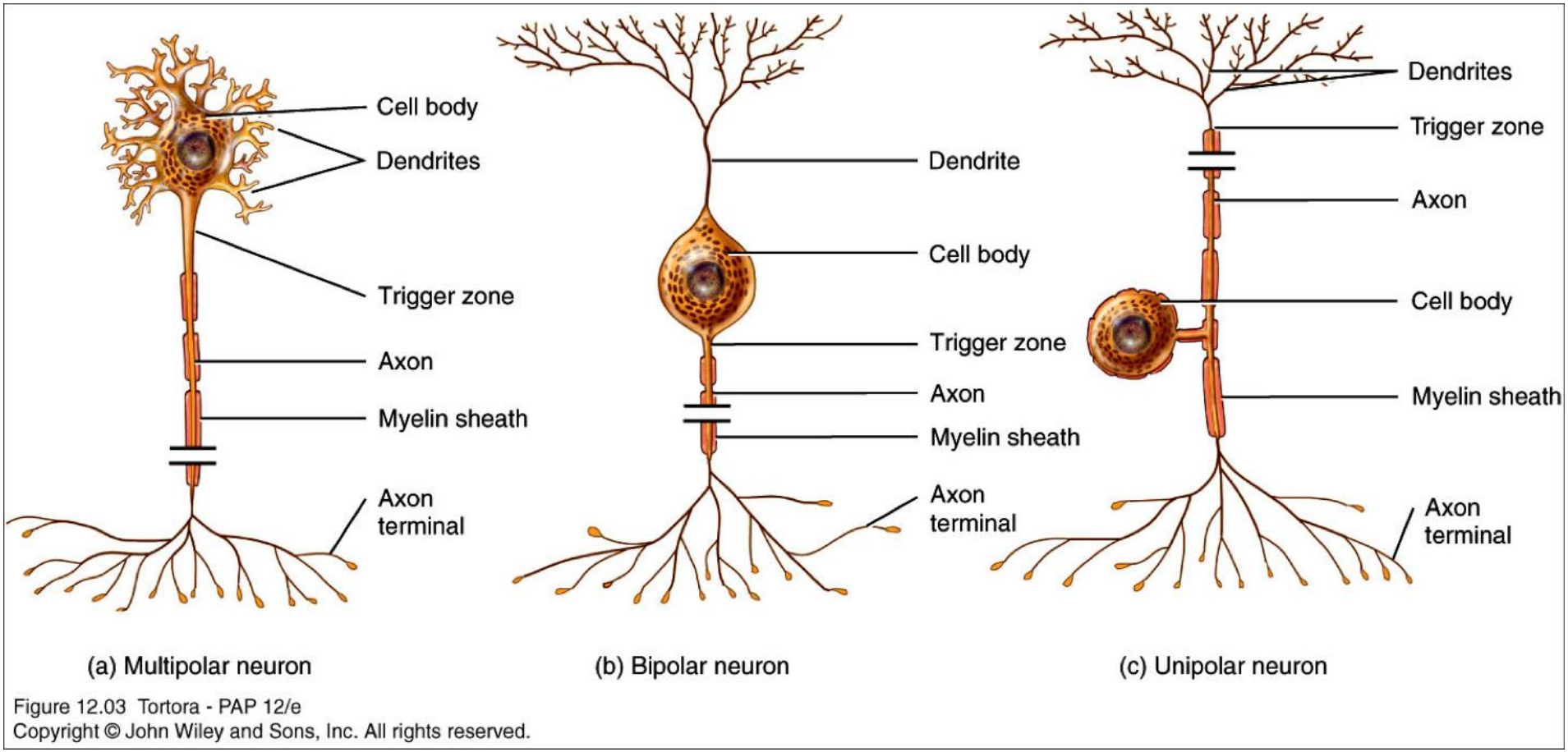
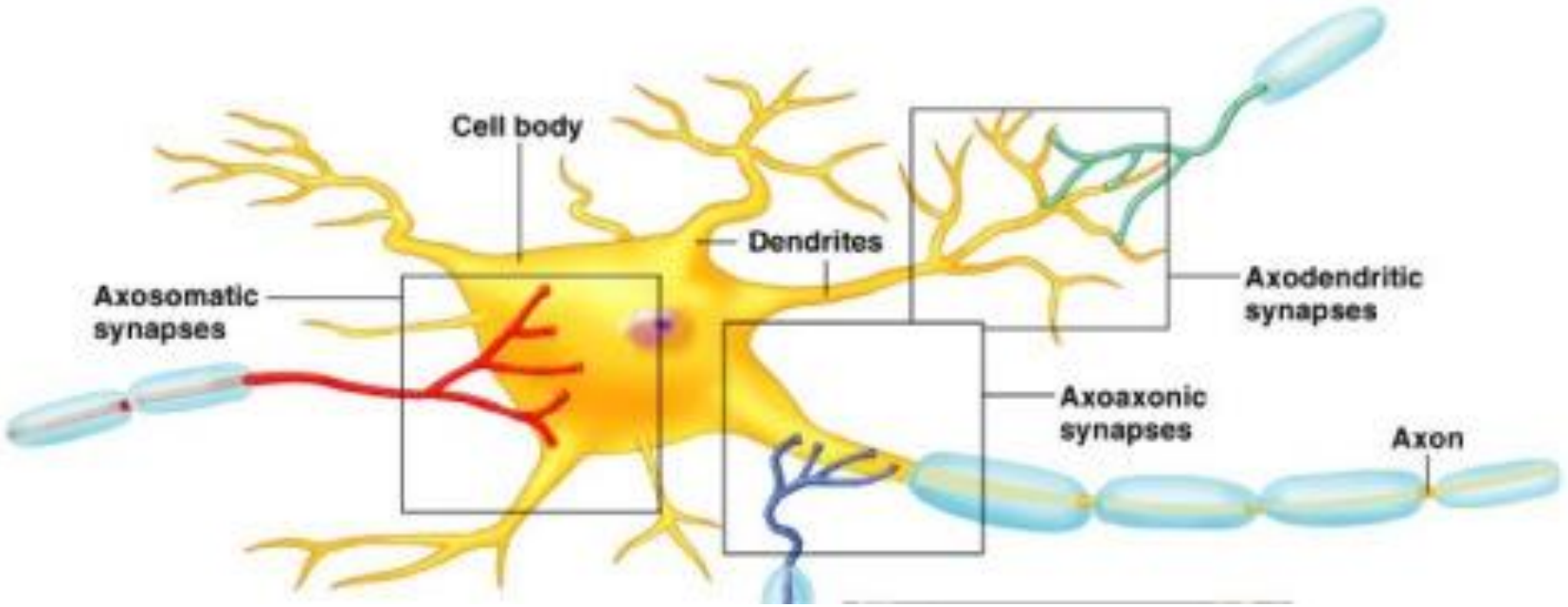


Figure 12.03 Tortora - PAP 12/e

Types of synapses



Types of mediators within CNS

	Example	Molecular target	Main function
Classical NT	NA, DA, 5-HT, Glu, GABA	Ion channel, G-PCR	fast and slow neurotransmission, neuromodulation
Neuropeptides	substance P, neuropeptid Y, endorphins, enkephalins, CRH…	G-PCR	neuromodulation
Lipidic mediators	PG, AEA, 2-AG (endocannabinoids)	G-PCR	neuromodulation
NO		guanylyl- cyclase	neuromodulation
Neurotrofins, cytokines	NGF, BDNF, IL-1	rcp coupled with kinase	neuronal growth, sprouting, survival and plasticity
Steroids	androgens, estrogens, neurosteroids	nuclear and membrane receptors	functional plasticity

Neurotransmitters

- Synthesized presynaptically
- Released after stimulation with action potential
- Postsynaptic membrane receptors
- Synapse stimulation triggers the AP
- Blocking interrupts synaptic signaling

Classification of neurotransmitters

Classical" - small molecules

a) amines- monoamines

catecholamines (dopamine, noradrenaline)

indolamines (serotonin, melatonin)

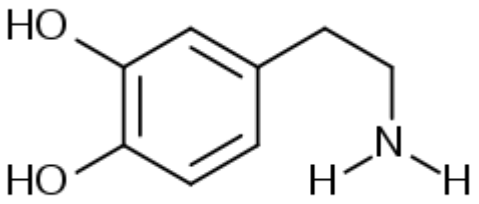
quaternary amines

acetylcholine

b) Amino acids (glutamate, glycine, GABA)

Peptides - "neurohormones" - these are not true neurotransmitters - are carried by blood (vasopressin, somatostatin, neurotensin)

Dopamine



↑ anxiety, aggression anxiety, aggression

↓ attenuation, depression, apathy

Synthesis - TYR (tetrahydrobiopterin, folate)

Storage - in ATP / loose vesicles

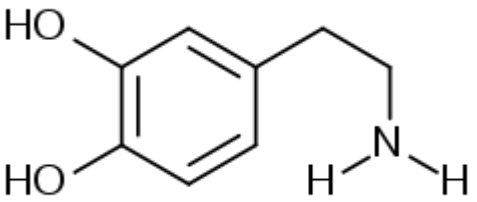
Release - depolarization (tonic GABA inhibition)

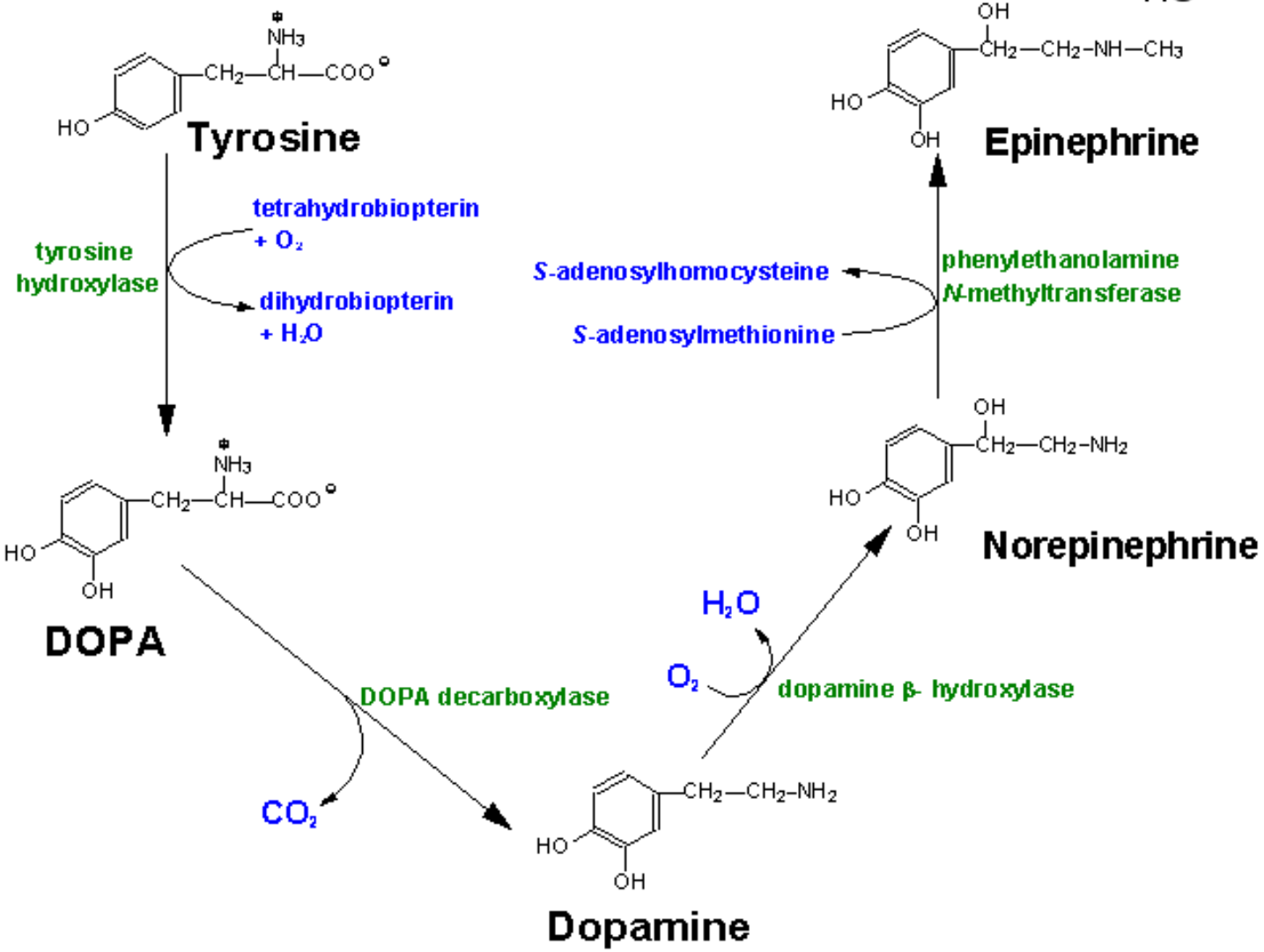
Effect on rcp. - D_1-D_5

Degradation - reuptake !, MAOA + MAOB

Pharmacology - agonists, antagonists

Dopamine


HO
HO
N
H
H


Tyrosine
tyrosine hydroxylase
tetrahydrobiopterin + O2
dihydrobiopterin + H2O
DOPA
DOPA decarboxylase
CO2
Dopamine
H2O
O2
dopamine β- hydroxylase
Norepinephrine
S-adenosylhomocysteine
S-adenosylmethionine
phenylethanolamine N-methyltransferase
Epinephrine

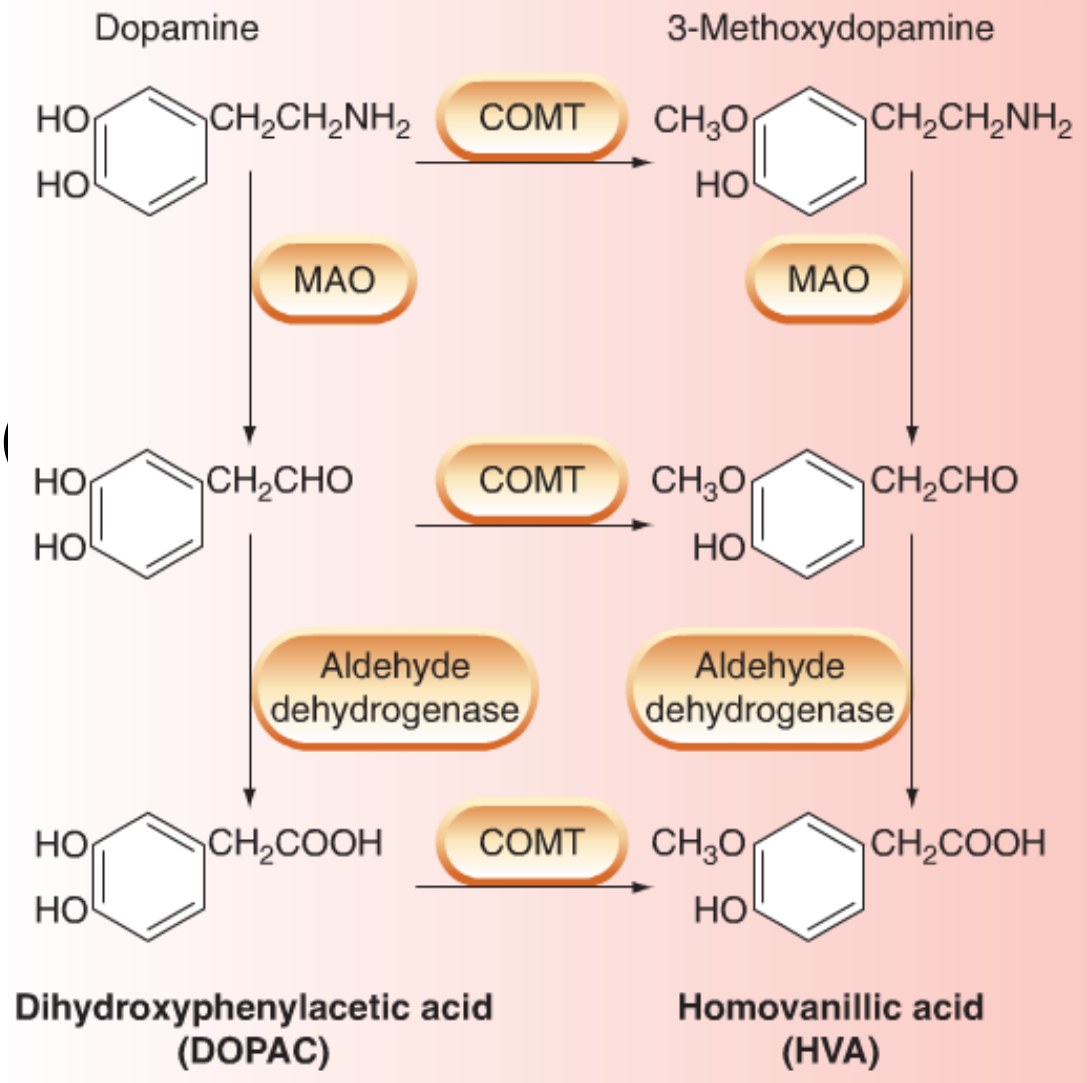
Dopamine

- 1957 Kathleen Montagu († 1966)

↑agresivity
↓apathy

- „reward, arousal“

- Parkinson disease, psychoses (
- depression, anxiety (GAD)



Dopamine

Controls within CNS:

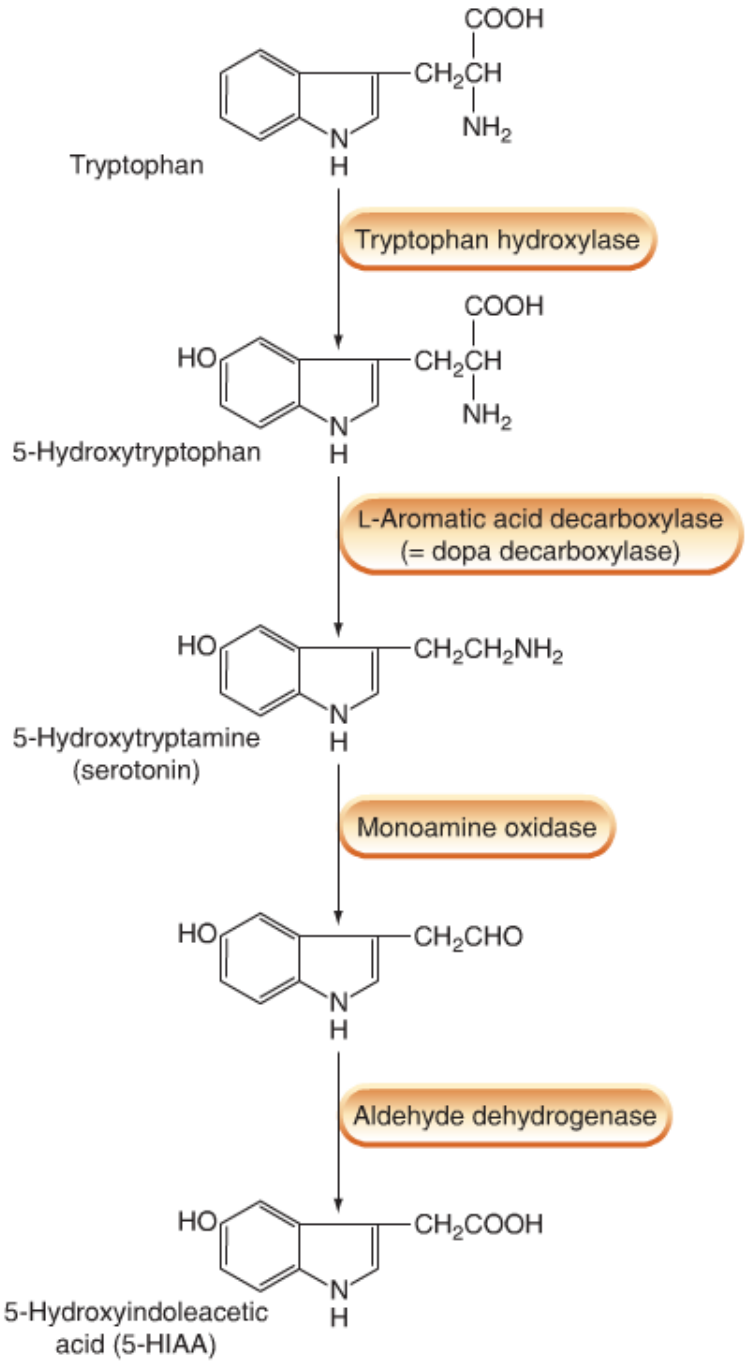
motoric function (nigrostriatal)
behavior, psychological integration, reward – addiction
(mesolimbic, mesocortical)
Endocrine (tuberoinfundibular)

Peripheral controls: GIT motility, blood pressure, vomiting (medulla + peripheral rcp)

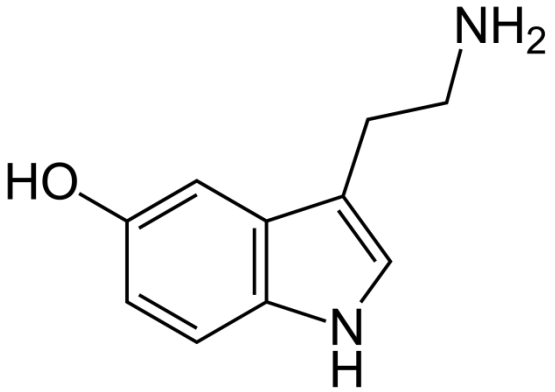
Serotonin – 5HT

Vittorio Erspamer (1909-1999)

1935-“Enteramin“
(enterochromafinnic cells.)
1947 „Sero-tonin“ (serum)



Serotonin – 5HT



↑ anxiety, aggression

↓ shock, depression

Synthesis form TRP (tetrahydrobiopterin, folate)

Storage - in ATP / loose vesicles

Relaxation – depolarization

Effect on rcp. - 5HT1-5HT7

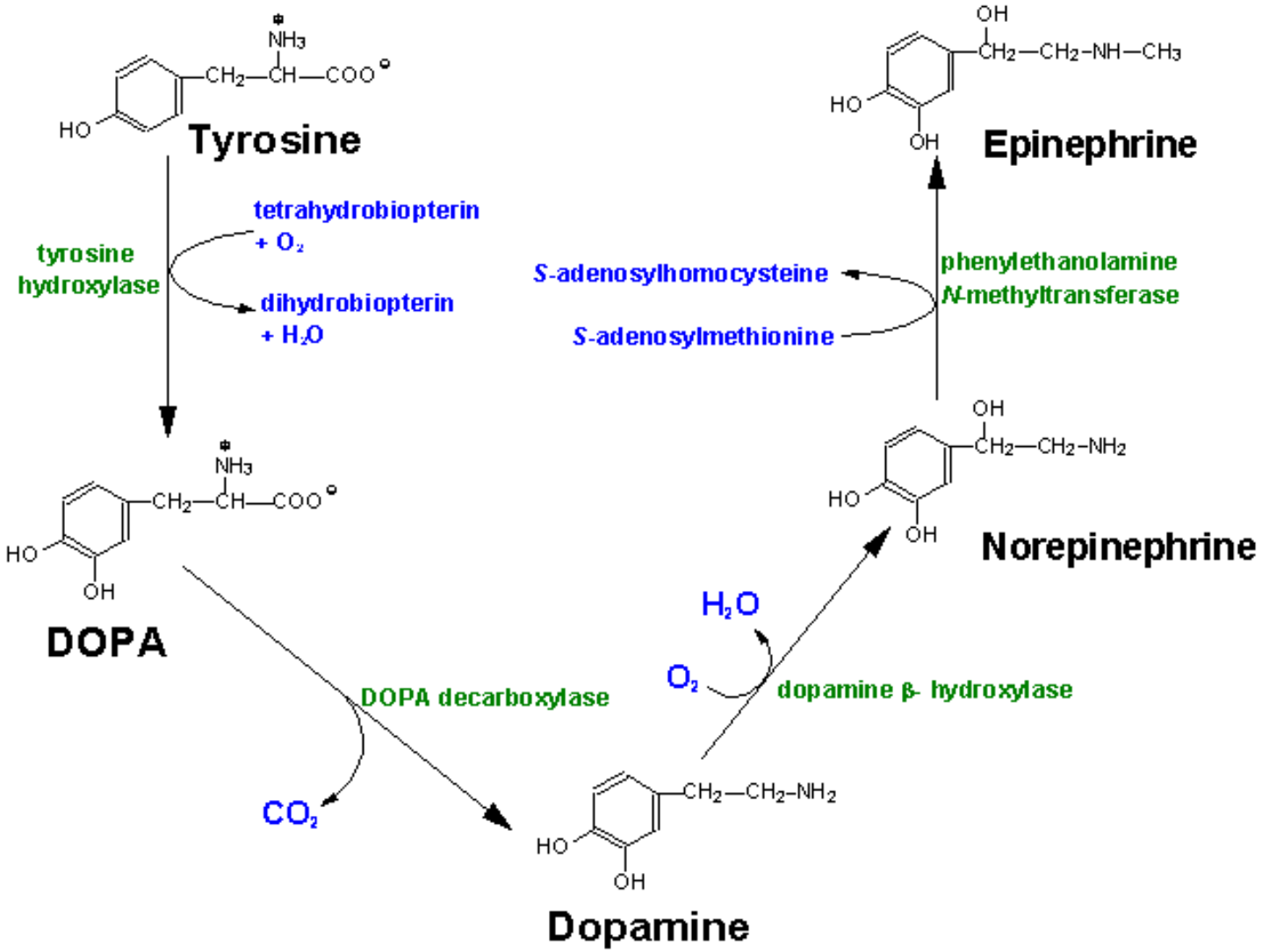
Degradation - reuptake !, MAOA

Pharmacology - agonists, antagonists

Serotonin – 5HT

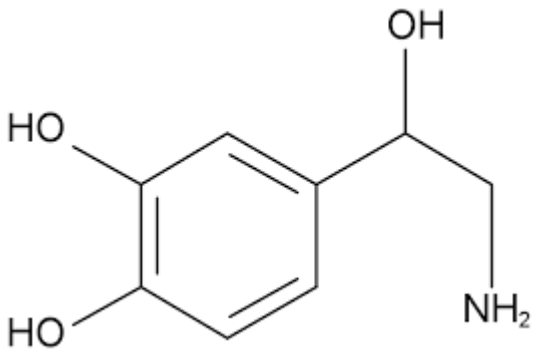
Receptor	Location	Main function	Signalling system	Significant drugs: *Agonists*	Significant drugs: *Antagonists*
5-HT_{1A}	CNS	Neuronal inhibition Behavioural effects: sleep, feeding, thermoregulation, anxiety	G protein (G_i/G_o) ↓ cAMP (may also modulate Ca^{2+} channels)	8-OH-DPAT, triptans, clozapine, buspirone (PA), cabergoline	Methiothepin, yohimbine, ketanserin, pizotifen, spiperone
5-HT_{1B}	CNS, vascular smooth muscle, many other sites	Presynaptic inhibition Behavioural effects Pulmonary vasoconstriction	G protein (G_i/G_o) ↓ cAMP (may also modulate Ca^{2+} channels)	8-OH-DPAT, triptans, clozapine, cabergoline, dihydroergotamine	Methiothepin, yohimbine, ketanserin, spiperone
5-HT_{1D}	CNS, blood vessels	Cerebral vasoconstriction Behavioural effects: locomotion	G protein (G_i/G_o) ↓ cAMP (may also modulate Ca^{2+} channels)	8-OH-DPAT, triptans, clozapine, cabergoline, dihydro-ergotamine/ ergotamine	Methiothepin, yohimbine, ketanserin, methysergide, spiperone
5-HT_{1E}	CNS	–	G protein (G_i/G_o) ↓ cAMP (may also modulate Ca^{2+} channels)	8-OH-DPAT, triptans; clozapine, dihydroergotamine	Methiothepin, yohimbine, methysergide
5-HT_{1F}	CNS, uterus, heart, GI tract	–	G protein (G_i/G_o) ↓ cAMP (may also modulate Ca^{2+} channels)	8-OH-DPAT, triptans; clozapine dihydro-ergotamine/ergotamine, lamistidan	Methiothepin, yohimbine, methysergide
5-HT_{2A}	CNS, PNS, smooth muscle, platelets	Neuronal excitation Behavioural effects Smooth muscle contraction (gut, bronchi, etc.) Platelet aggregation Vasoconstriction/vasodilatation	G protein (G_q/G_{11}) ↑ IP_3, Ca^{2+}	LSD, cabergoline, methysergide (PA), 8-OH-DPAT, ergotamine (PA)	Ketanserin, clozapine, methiothepin, methysergide
5-HT_{2B}	Gastric fundus	Contraction	G protein (G_q/G_{11}) ↑ IP_3, Ca^{2+}	LSD, cabergoline, methysergide (PA), 8-OH-DPAT, ergotamine (PA)	Ketanserin, clozapine, methiothepin, yohimbine
5-HT_{2C}	CNS, lymphocytes	–	G protein (G_q/G_{11}) ↑ IP_3, Ca^{2+}	LSD, cabergoline, methysergide (PA), 8-OH-DPAT, ergotamine (PA)	Ketanserin, clozapine, methiothepin, methysergide
5-HT_3	PNS, CNS	Neuronal excitation (autonomic, nociceptive neurons) Emesis Behavioural effects: anxiety	Ligand-gated cation channel	2-Me-5-HT, chloromethyl biguanide	Dolesatron, granisetron, ondansetron, palonosetron, tropisetron
5-HT_4	PNS (GI tract), CNS	Neuronal excitation GI motility	G protein (G_s) ↑ cAMP	Metoclopramide, tegaserod, cisapride	Tropisteron
5-HT_{5A}	CNS	Modulation of exploratory behaviour (rodents)?	G protein (G_s) ↑ cAMP	Triptans, 8-OH-DPAT	Methiothepin, clozapine, methysergide, yohimbine, ketanserin
5-HT_6	CNS, leukocytes	Learning and memory?	G protein (G_s) ↑ cAMP	LSD, ergotamine	Methiothepin, clozapine, spiperone, methysergide dihydro-ergotamine
5-HT_7	CNS, GI tract, blood vessels	Thermoregulation? Circadian rhythm?	G protein (G_s) ↑ cAMP	Buspirone, cisapride, 8-OH-DPAT, LSD,	Methiothepin, clozapine, methysergide, buspirone dihydro-ergotamine, ketanserin, yohimbine

Noradrenaline



Noradrenaline

regulator of activity of other projection systems,



NA pathways modulate the excitatory function of glutamate, as well as the inhibitory function of GABA. „arousal“, vigility, alertness, regulation of BP

Afective disorders (depression)

α_1 - postsynaptic neurons, mediates the excitatory effect of NA (α1A, α1B, α1C)

α_2-usually presynaptic, inhibitory effects. - presynaptic inhibition of NA release (α2A, α2B, α2C)

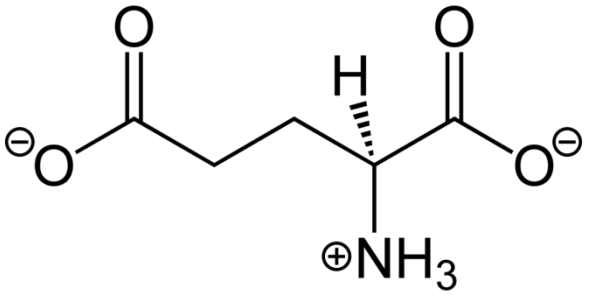
β_1-neuronal excitatory receptor, cortex, striatum, hippocampus

β_2-glial cells, cerebellum, integration of the nervous and immune system;

β_3 - probably not in the CNS

Glutamate

- main excitatory neurotransmitter in CNS, 50% CNS synapses
- ubiquitous, discrete centers and their projections can not be defined
- synaptic plasticity, memory retention, and the learning process

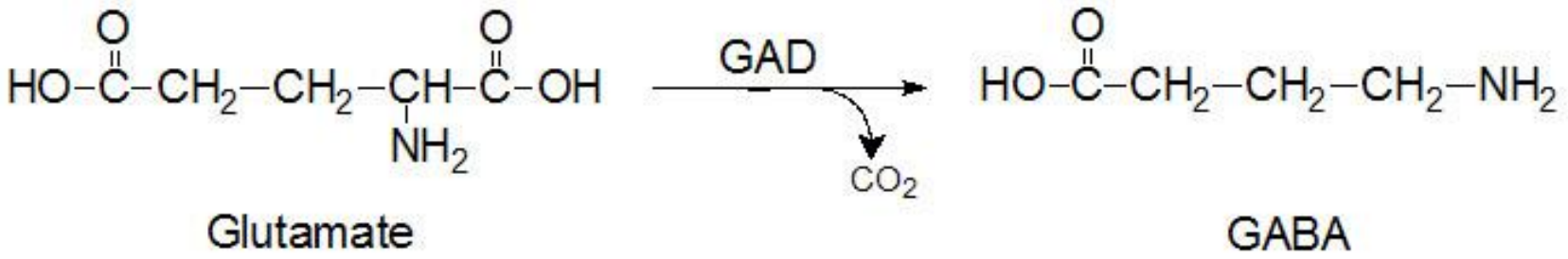


Glutamate

- **main excitatory neurotransmitter in CNS, 50% CNS synapses**
- **ubiquitous**, discrete centers and their projections can not be defined
- synaptic plasticity, memory retention, and the learning process

- Rcp: ionotropic: AMPA, NMDA, kainate
  metabotropic : mGluR1-8

GABA



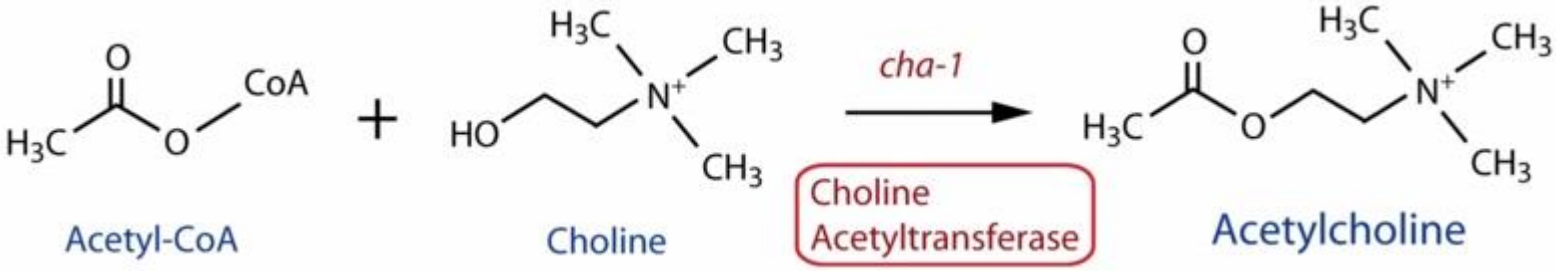
- the most important inhibitory NT (spinal cord, brain stem: Gly)
- 20% of the neurons in the CNS are GABA-ergic, 30% of the synapses - NT GABA
- Synthesis - GLU, storage – vesicles
- Degradation - reuptake, transamination
- Transporters GAT1 and GAT3 (tiagabin-iGAT)
- GABA transaminase (inhibition: vigabatrin)
- Effect on rcp. - $GABA_A$, $GABA_B$, $GABA_C$ ($GABA_A$-rho)
- Pharmacology - allosteric modulation, i. GAT, transamination

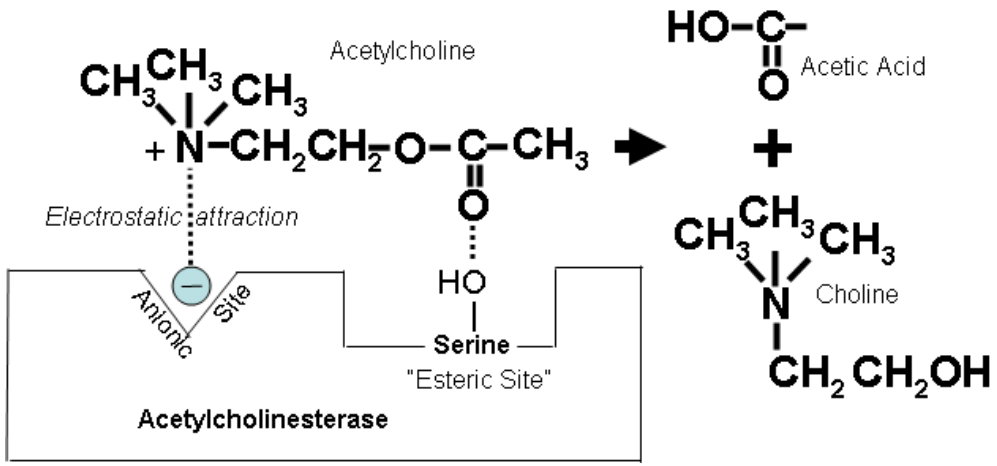
Glycine

- **ionotropic rcp.** coupled with **Cl channel** (membrane hyperpolarization).
- in the gray matter of the spinal cord
- main neurotransmitter of inhibitory interneurons

- allosteric **modulator of NMDA rcp**.
- excitability in terms of facilitating the activity of the glutamatergic system.

Acetylcholine





Arousal, learning and memory (cognitive fctions), reward, motoric functions

M1-M4 receptors

Dementia, Parkinson's disease, modulation of pain transduction

Endocannabinoids

Anandamide, 2-arachidonoylglycerol, Noladin ether
Virodhamine, N-arachidonoyl dopamine..+ endocannabinoid-like compounds

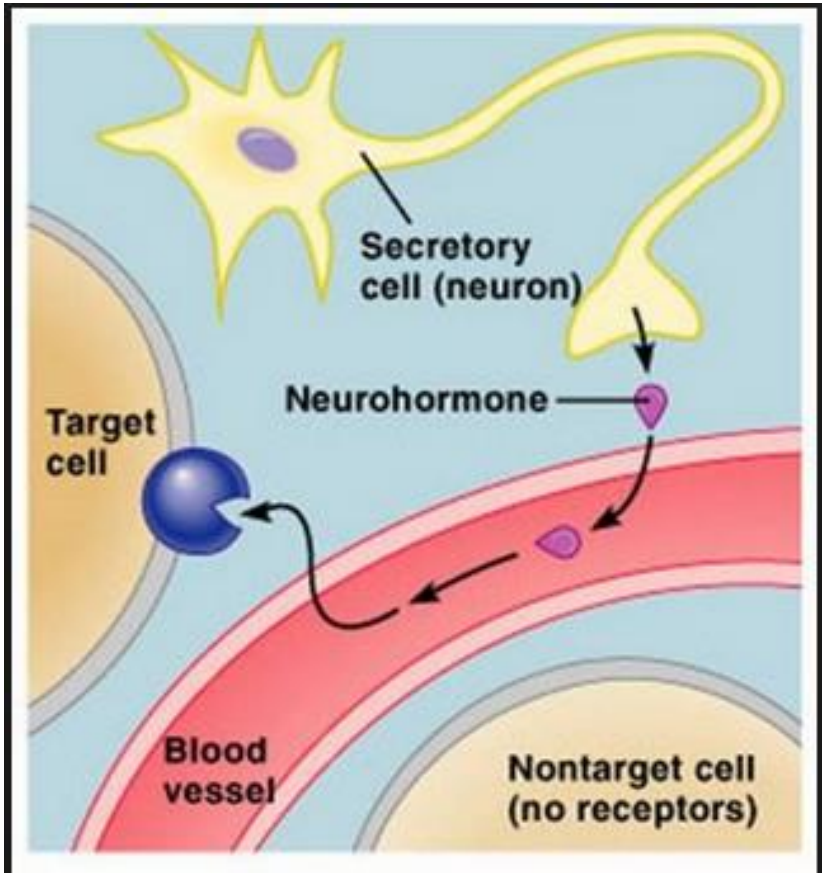
- **CB_1 receptors**
  in high density in the CNS,
- **CB_2 receptors**
  especially on PNS neurons, hematopoietic and immunocompetent cells.

  - antinociception and immune response modulation

CVS – AMI, obesity, dislipidemia
CNS – MS, addiction, psychoses, parkinsonism
Immune system
Pain
Respir. System- Asthma bronchiale
Eye - Glaucoma, ARMD

Neurohormons/neuropeptides

- Neuron-secreted
- Diffuse into the bloodstream
- Blood transport
- Effect on the target cell
- oxytocine, vasopressine, FSH, CRH, ACTH



Ways of modulating neurotransmission

Influence on

- synthesis of NT
- storage NT
- release of NT
- NT on postsynaptic rcp

autoreceptors
heteroreceptors

- presynaptic modulation
  - inhibition
  - disinhibition
- up-regulation
- down-regulation

Possibilities of therapeutic-driven influence on receptor systems

+

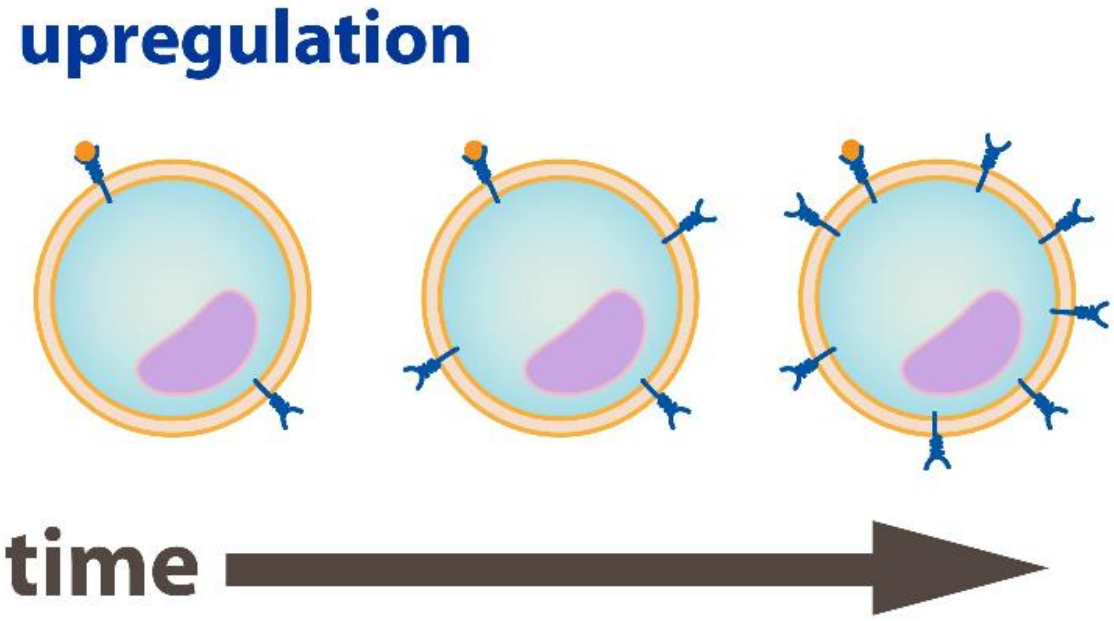
- stimulation of release (amphetamines, cocaine)
- inhibition of reuptake (SSRI, NDRI, SNRI)
- inhibition of degradation (i-MAO)
- stimulation of synthesis (precursors – TYR, TRP)
- agonism on rcp. (SARI-5HT1A)

-

- blockade of release
- suppression of synthesis (fake substrate -methyldopa)
- Storage inhibition (reserpin)
- partial agonism / antagonism at rcp. (SARI, NASSA, fluoxetine - 5HT2C,

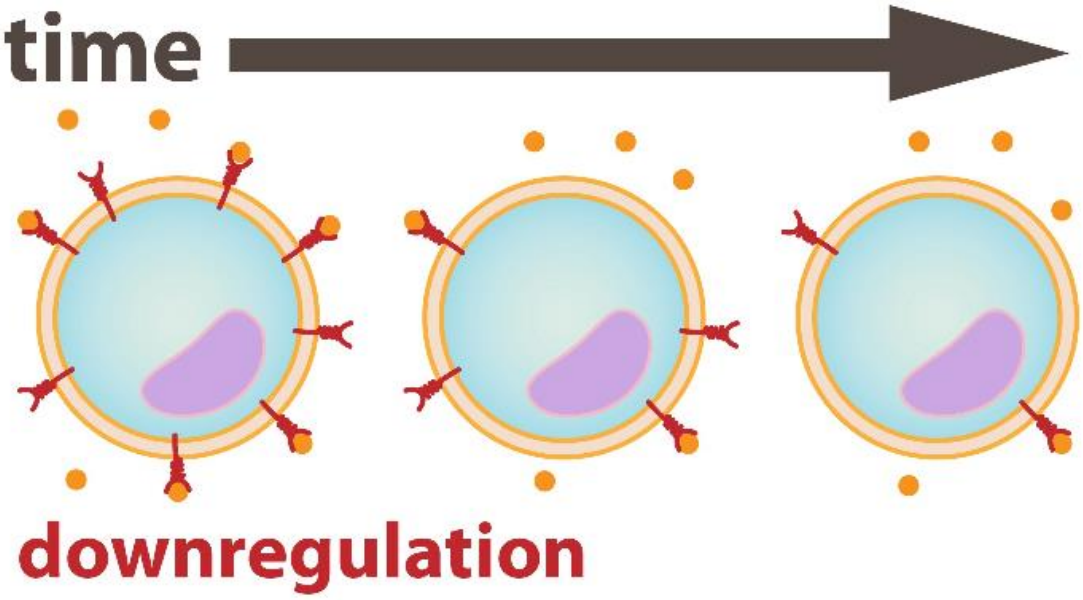
Up-regulation

- Long-term reduction of NT - cells synthesize more Rcp and expose them to their membrane → increase receptor density.



Down-regulation

- Long-term increased supply of NT
  - internalize receptors (decrease in number)
  - inactivate intracellular cascade (loss of function)



Intracellular signaling of the membrane receptor

Signal from activated membrane rcp. → intracellular signaling pathways.

This may further:

Amplify signal - successively switching to multiple signaling molecules, several hormone / NT molecules can cause significant change of function, signal amplification

Diverge the signal to several target locations, 1 activated receptor may affect several functions of the target cell

Converge signals - 2 insufficiently strong signals can cause a change in the concentration of a signal molecule sufficient to produce a specific effect

Signal transduction

"**First messengers**" - monoamines - binding to pre / postsynaptic receptors signal propagation through postsynaptic structures into the cell nucleus

Intra-cellular processes:

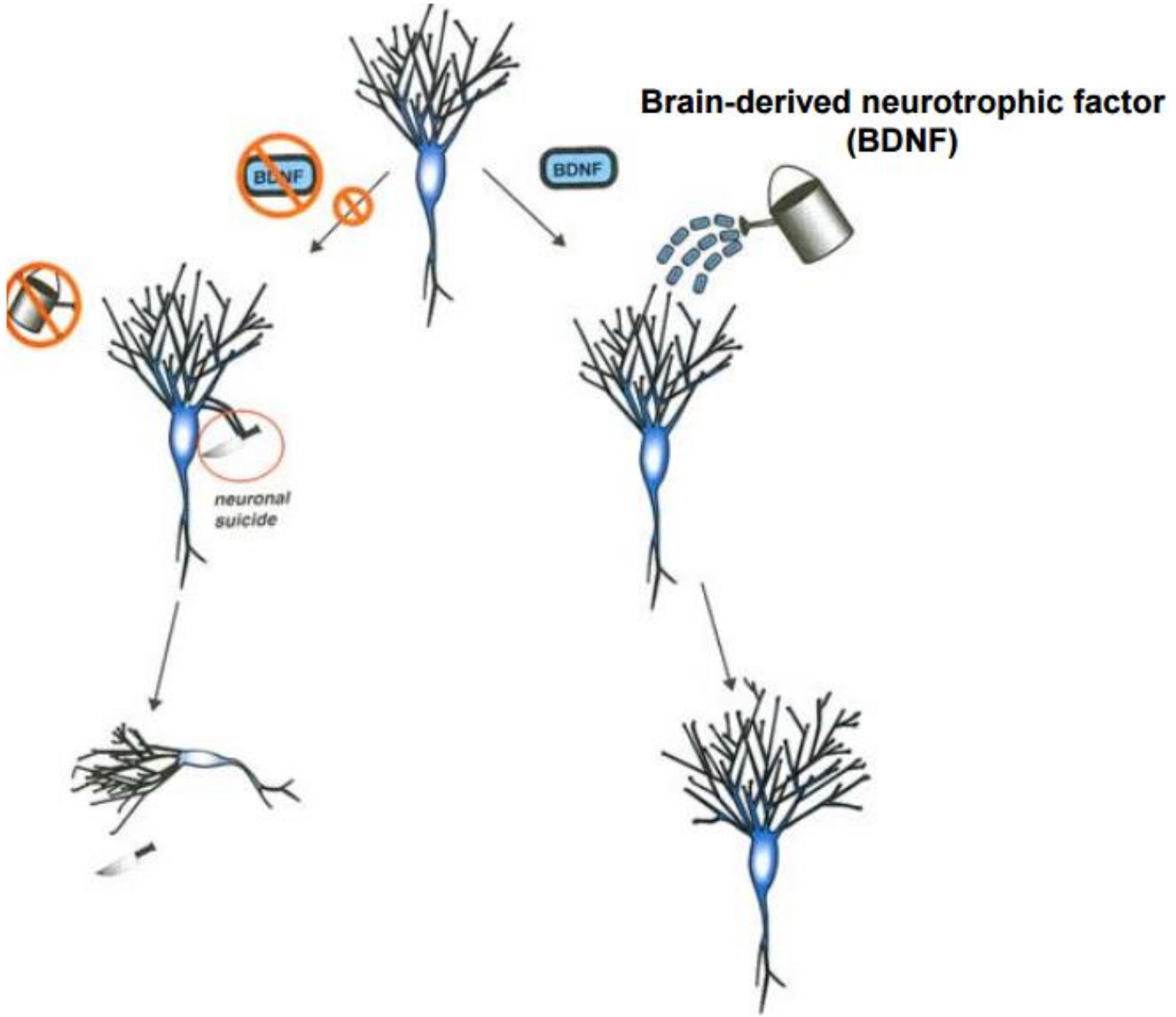
"**Second messengers**" - cAMP, IP3

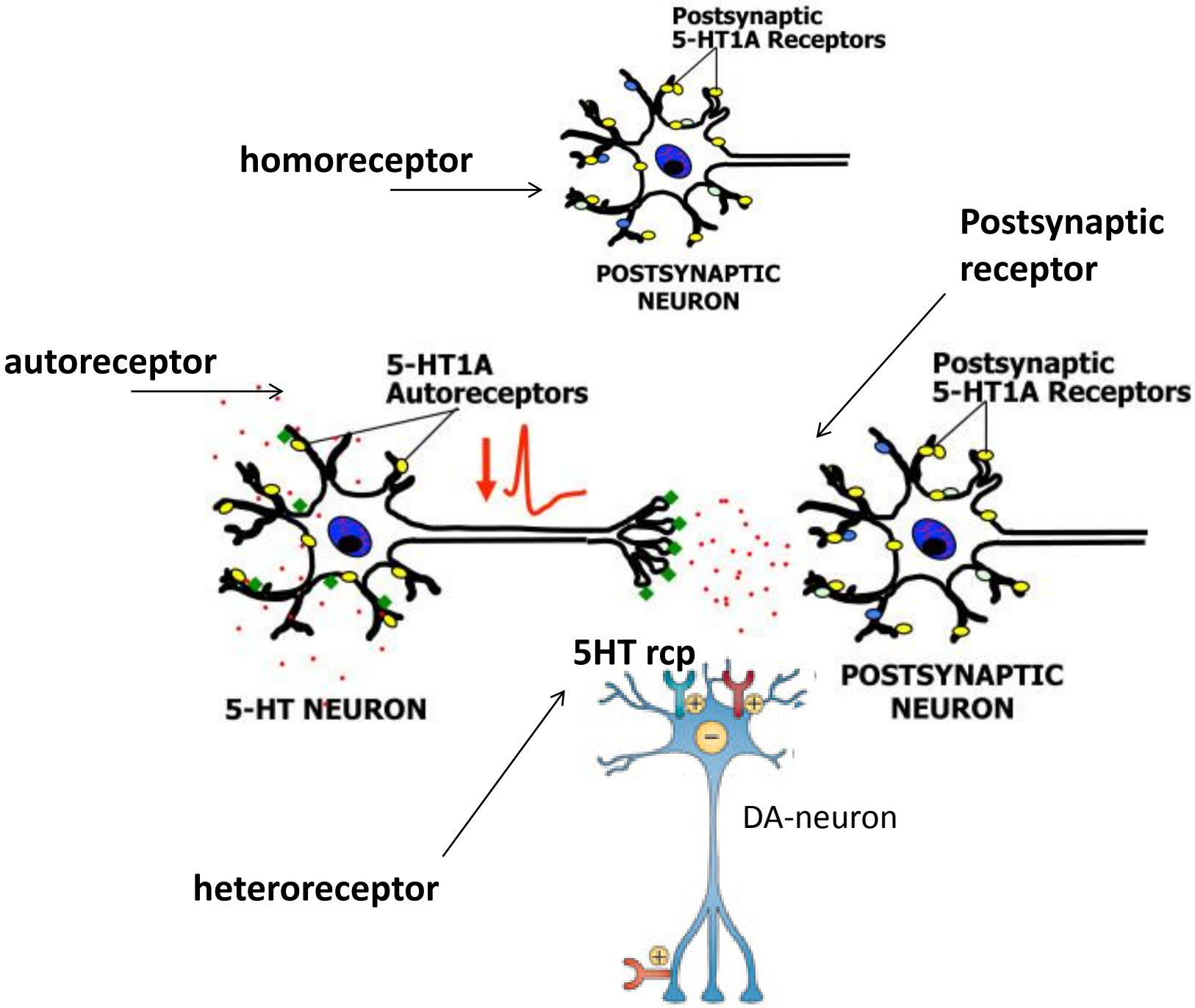
"**Third messengers**" - early genes, modification of gene expression of cellular proteins – **c**yclic AMP **r**esponse-**e**lement **b**inding protein –

CREB protein - regulation of gene transcription - influencing expression of genes for brain-derived neurotrophic factor

BDNF - neuronal development and differentiation (neurogenesis)

BDNF


Brain-derived neurotrophic factor
(BDNF)
BDNF
BDNF
neuronal
suicide


Postsynaptic
5-HT1A Receptors
homoreceptor
POSTSYNAPTIC
NEURON
Postsynaptic
receptor
autoreceptor
5-HT1A
Autoreceptors
Postsynaptic
5-HT1A Receptors
5-HT NEURON
5HT rcp
POSTSYNAPTIC
NEURON
DA-neuron
heteroreceptor

Lehmann classification of psychotropic substances

Affectivity	**↑ antidepressants, anxiolytics**
	↓ dysforics/antimanics
Vigility	**↑ psychostimulants/nootropics**
	↓ hypnotics/sedatives
Psychic integrity/intergration	**↑ neuroleptics**
	↓ halucinogens/psychodysleptics/delirogens
memory and cognitive functions	**↑ kognitive enhancers/** nootropics
	↓ anticholinergics, dementogens, neurotoxins, amnestics

ATC Classification

N: NERVOUS SYSTEM
N01: ANESTHETICS
N02: ANALGESICS
N03: ANTIEPILEPTICS
N04: ANTI-PARKINSON DRUGS
N05: PSYCHOLEPTICS
N05A: ANTIPSYCHOTICS
N05B: ANXIOLYTICS
N05C: HYPNOTICS AND SEDATIVES
N06: PSYCHOANALEPTICS
N06A: ANTIDEPRESSANTS
N06B: PSYCHOSTIMULANTS, AGENTS USED FOR ADHD AND NOOTROPICS
N06C: PSYCHOLEPTICS AND PSYCHOANALEPTICS IN COMBINATION
N06D: ANTI-DEMENTIA DRUGS
N07: OTHER NERVOUS SYSTEM DRUGS

Classification of psychotropic drugs

- a new classification of psychotropic drugs is created based on the main mechanisms of effects

(neuroscience based nomenclature - NbN) - ECNP (European College of Neuropsychopharmacology)

- Phone app !

https://www.ecnp.eu/~/media/Files/ecnp/Projects%20and%20initiatives/Nomenclature/140214%20Nomenclature%20list.pdf

Antipsychotics

Drugs used predominantly in the therapy of psychoses but also other indications:

pharmacoresistant depression
psychotic depression
anxiety
Huntington's disease
Tourette's syndrome
anesthesia / neuroleptanalgesia
sleep disorders
nausea, vomitus

Schizofrenia

- belong among psychoses with predominance of emotional disturbances, thinking, behavior, and personality disorder
- the most striking symptoms are delusions and hallucinations
- onset/Dg usually around 20th year of age
- genetic predisposition - gender incidence - polygenic inheritance
- affects about 1% of the population Dg. ICD 10: F20XX

Symptoms of schizofrenia

"**Positive" symptoms** - hallucinations, delusions, disintegration of thinking, speaking, catatonia, agitation, paranoia

"Negative" - absent, blunted or incongruous emotional responses, apathy, social withdrawal, anhedonia, lethargy, sexual dysfunction, impaired attention

Substances capable of causing psychosis

- levodopa (DA)
- CNS stimulants (NA, DA, 5HT)
  - cocain
  - amphetamins
  - khat, kathinon, methkathinon, mezkalin
- halucinogens
- cannabis
- apomorphine (D_2)
- bupropion (NDRI)
- phencyclidin, ketamine (NMDA antag.)

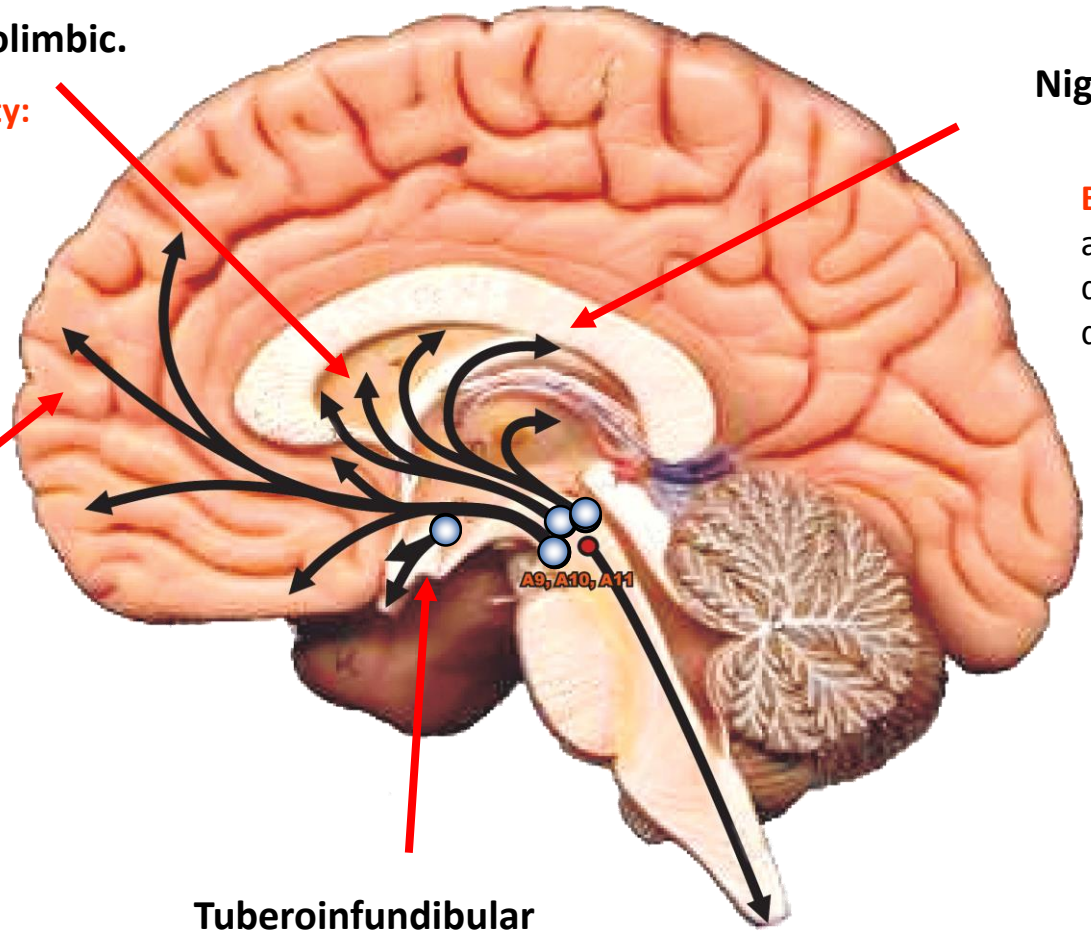
Biological correlates

1. *Genetic factors*
2. *Neurodevelopmental abnormalities*
3. *Environmental influences (stressors)*

Structural and functional changes

1. *Enlarged brain ventricles*
2. *Atrophy in some areas of the cortex*
3. *Reduced volume of basal ganglia*

Dopaminergic pathways in the human brain



Mesolimbic.

Hyperactivity: positive symptoms

Nigrostriatal

Blockade: EPS, akathisia, dyskinesis, dystonia…

Mesocortical

Hypoactivity: negative and cognitive symptoms

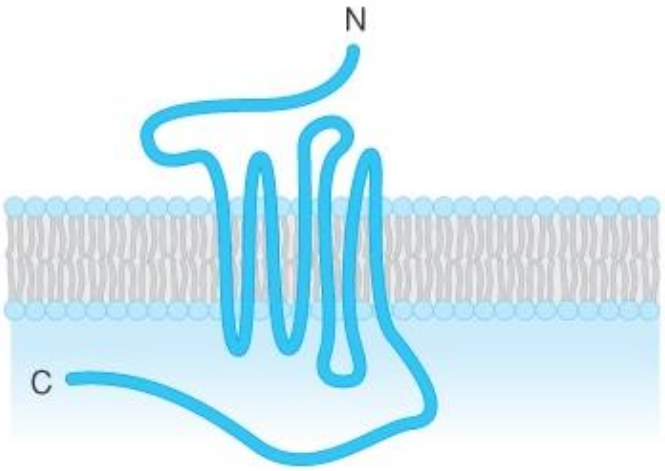
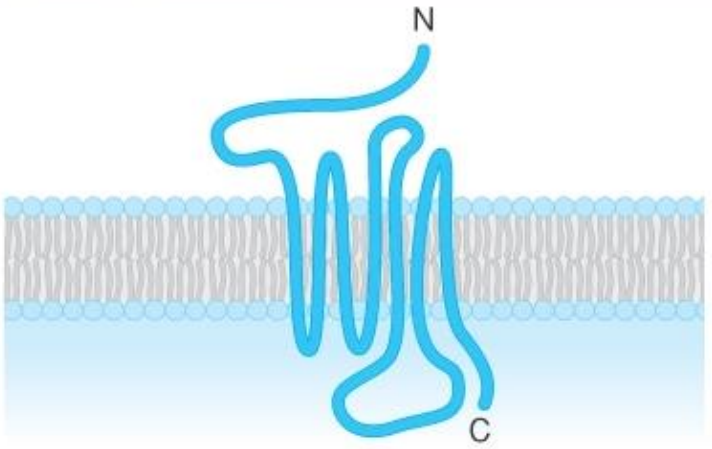
Tuberoinfundibular

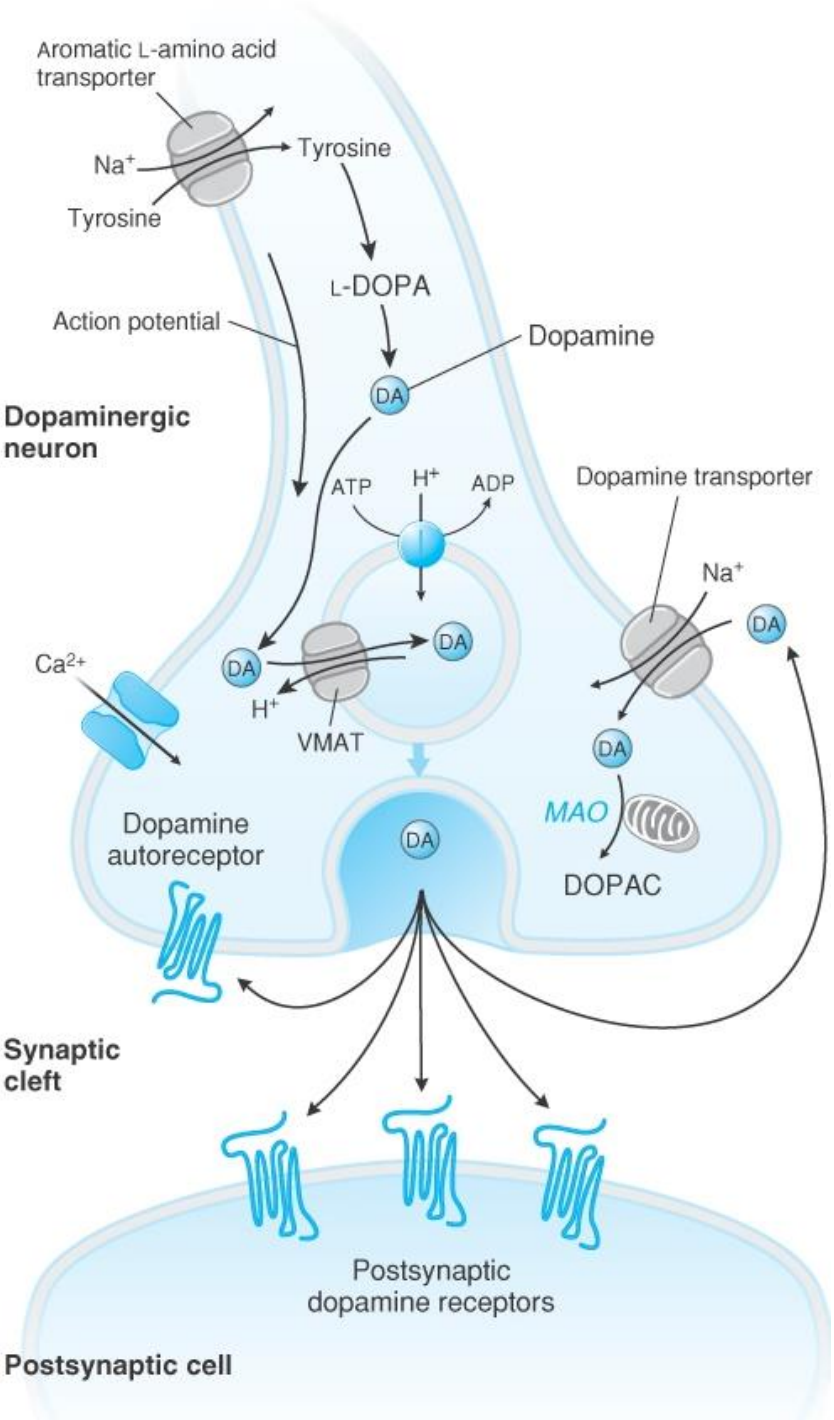
Block: hyperprolaktinaemia

DA-ergic pathways

Nigrostriatal pathway → DA supressess activity of Ach → **inhibition of NS pathway → EPS**

Tuberoinfundibular pathway → **inhibition of TI** → hyperprolactinaemia

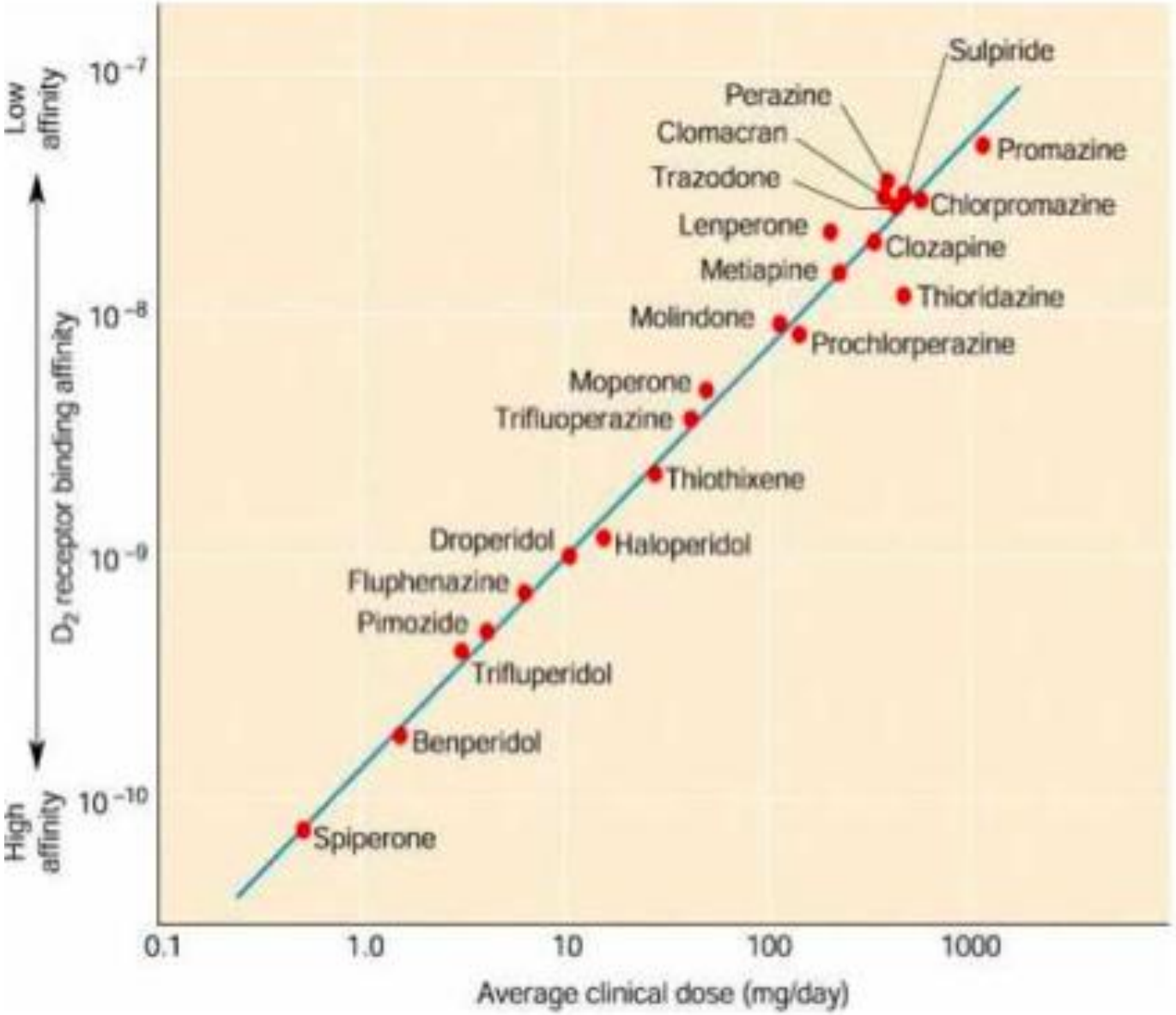
	D1 Receptor Family		D2 Receptor Family		
Schematic structure					
Second messenger systems	⬆ cAMP (via G_s) ⬆ PIP_2 hydrolysis Ca^{2+} mobilization (via IP_3) PKC activation (via DAG)		⬇ cAMP (via G_i) ⬆ K^+ currents ⬇ Voltage-gated Ca^{2+} currents		
Distribution in CNS	**D1** Striatum Neocortex	**D5** Hippocampus Hypothalamus	**D2** Striatum Substantia nigra Pituitary gland	**D3** Olfactory tubercle Nucleus accumbens Hypothalamus	**D4** Frontal cortex Medulla Midbrain


Aromatic L-amino acid transporter
Na+
Tyrosine
Tyrosine
L-DOPA
Action potential
Dopamine
DA
Dopaminergic neuron
ATP
H+
ADP
Dopamine transporter
Na+
DA
Ca2+
DA
DA
H+
VMAT
DA
MAO
Dopamine autoreceptor
DA
DOPAC
Synaptic cleft
Postsynaptic dopamine receptors
Postsynaptic cell

Dopamine hypothesis of schizophrenia

- Antipsychotics reduce DA-activity on synapses
- Drugs increasing DA in the limbic system trigger psychosis
- Drugs that reduce DA-activity in the limbic system (DA antagonists on postsynaptic D receptors) reduce psychotic symptomatology
- Affinity of older "classical" APs to D2 rcp. correlates with their clinical effect

Dopamine hypothesis of schizophrenia



Dopamine hypothesis of schizophrenia

- post-mortem increased DA density in pat. with schizophrenia.
- changes in HVA levels in plasma, urine, cerebrospinal fluid.

Neuromodulators of schizophrenia

- **Dopaminergic system**

  Hyperactivity in the milsolimbic pathway - positive symptoms

  Hypoactivity in the prefrontal cortex - negative symptoms

- **Glutamatergic system**

  Exciting aminoacid - probably a dopamine release modulator. In patients with schizophrenia, the amount of NMDA receptors is reduced.

- **Serotonergic system**

  Associated with glutamate and dopamine

  Increase in the number of serotonin receptors in the prefrontal cortex

- GABA system

  An increased number of receptors, lower levels of enzymes necessary for GABA synthesis, dopamine

Classification of antipsychotics

1st. Generation

Classical (basic, sedative):

doses up to hundreds of milligrams

Incisive:

doses in mg to tens of milligrams

2nd. Generation

less: EPS, tardive dyskinesias, prolactinemias, malignant neuroleptic. syndrome)

MARTA (Multi-Acting Receptor Targeted Agents)

SDA (Serotonin-Dopamine Antagonist)

D2 / D3 antagonists

DSSS (Dopamine-Serotonin System Stabilizers)

3rd. Generation ?

Agonists of DA autoreceptors, partial agonists, glutamatergic, beta blockers, peptides?

Classical (Typical) antipsychotics

- affects positive, less negative symptoms, can aggravate cognition. dysfunction
- Mechanism of action: reduction of dopaminergic neurotransmission (blockade of postsynaptic D_2 receptors

AE Extrapyramidal syndrome

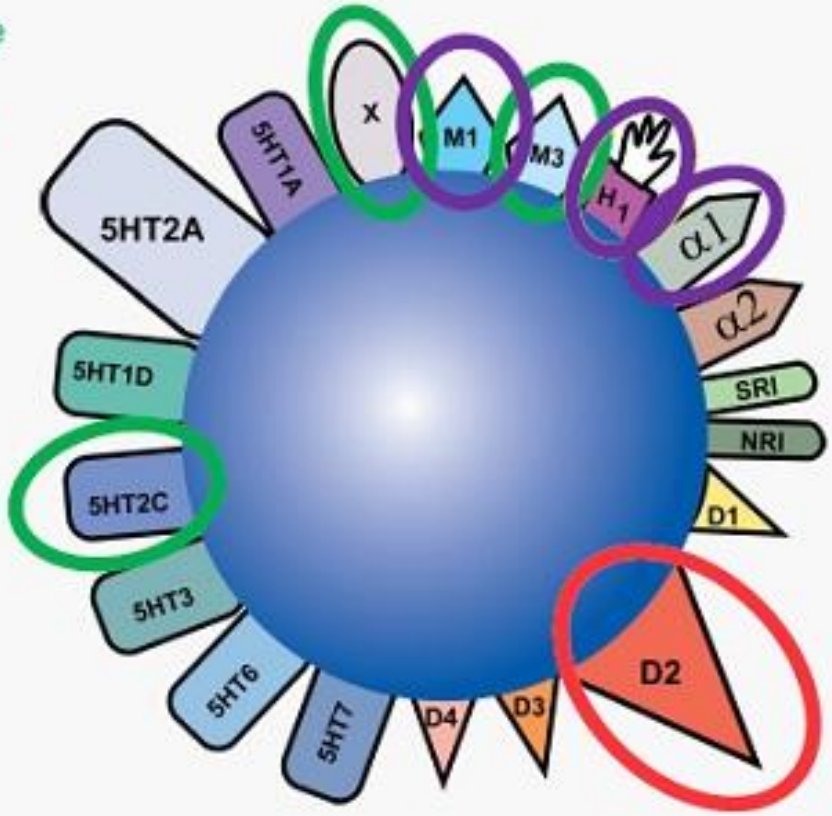
Early (parkinsonoid, acute dyskinesia, akathisia)

Late (tardive dyskinesia and dystonia, tardive akathisia)

Neuroleptic malignant syndrome, hyperprolactinemia, anticholinergic, antihistamine, adrenolytic and others

Antipsychotic binding profile

Cardiometabolic side effects, including weight gain, insulin resistance, and increased fasting triglycerides



Sedation

Increased Prolactin

Tardive Dyskinesia

EPS

Classical (Typical) antipsychotics -basal

Chlorpromazine D_2 antag. , one of the first APs, effective on posit. symptoms; doses up to 800 mg/day

AE: EPS (tardive dyskinesia), ↑ weight, prolactin

Overdose: EPS, respir. depression, coma (with alcohol)

Thioridazine

D_2 antag. , considered in ther. failure of 1st line treatment

AE: sedation, EPS, ↑ weight, ↑ QTc

mtb: CYP2D6

overdose: confusion, respir. depression, hypotension, seizures, coma generally: risk >benefit

Classical (Typical) antipsychotics -basal

Levomepromazine –D_2 antag. + another antag. (NA, 5HT, H, Ach)
more pronounced sedation, less EPS, adjuvant with analgesics

antiemetic, antihistaminic, anti-adrenergic and anticholinergic effects

AE: Orthostatic collapse, QTc prolongation, torsades

Classical (Typical) antipsychotics - incisive

Flupentixol - D2 antag, not so sedative, more EPS

AE: EPS - initiation of therapy, TD, insomnia, tachycardia, ↑ weight, dyslipidemia, rarely NMS

i.m.- noncompliance

Haloperidol - D_2 antag. , since the 1960s, highly potent, better than phenothiazines, long $T_{1/2,}$ less sedation, influencing BP

better tolerability (blood count, liver injury)

Comparison of basal and incisive AP

Basal AP

- Low potency
  (high doses – hundreds of milligrams)
- Sedation to hypnosis
- D_2 receptor blockade
- slower PK
- Frequent anticholinergic and antihistaminic adverse effects
- ↓ EPS

Incisive AP

- High potency (lower doses)
- Little sedation
- Block D_2 receptor
- faster PK
- Causes ↑ EPS

Atypical antipsychotics

- higher efficacy, better tolerability
- affect positive and negative symptoms, cognition
- D_2 receptor occupancy <80%, binding to multiple neurotransmitter systems
- affect not only transport of dopamine but also other neuromediators (serotonin)
- wide span between antipsychotic effects and EPS
- selective extrastriatal (mesolimbic) blockade of dopamine D_1, D_2 receptors
- risperidone, ziprasidone, olanzapine, quetiapine ...

Atypical antipsychotics

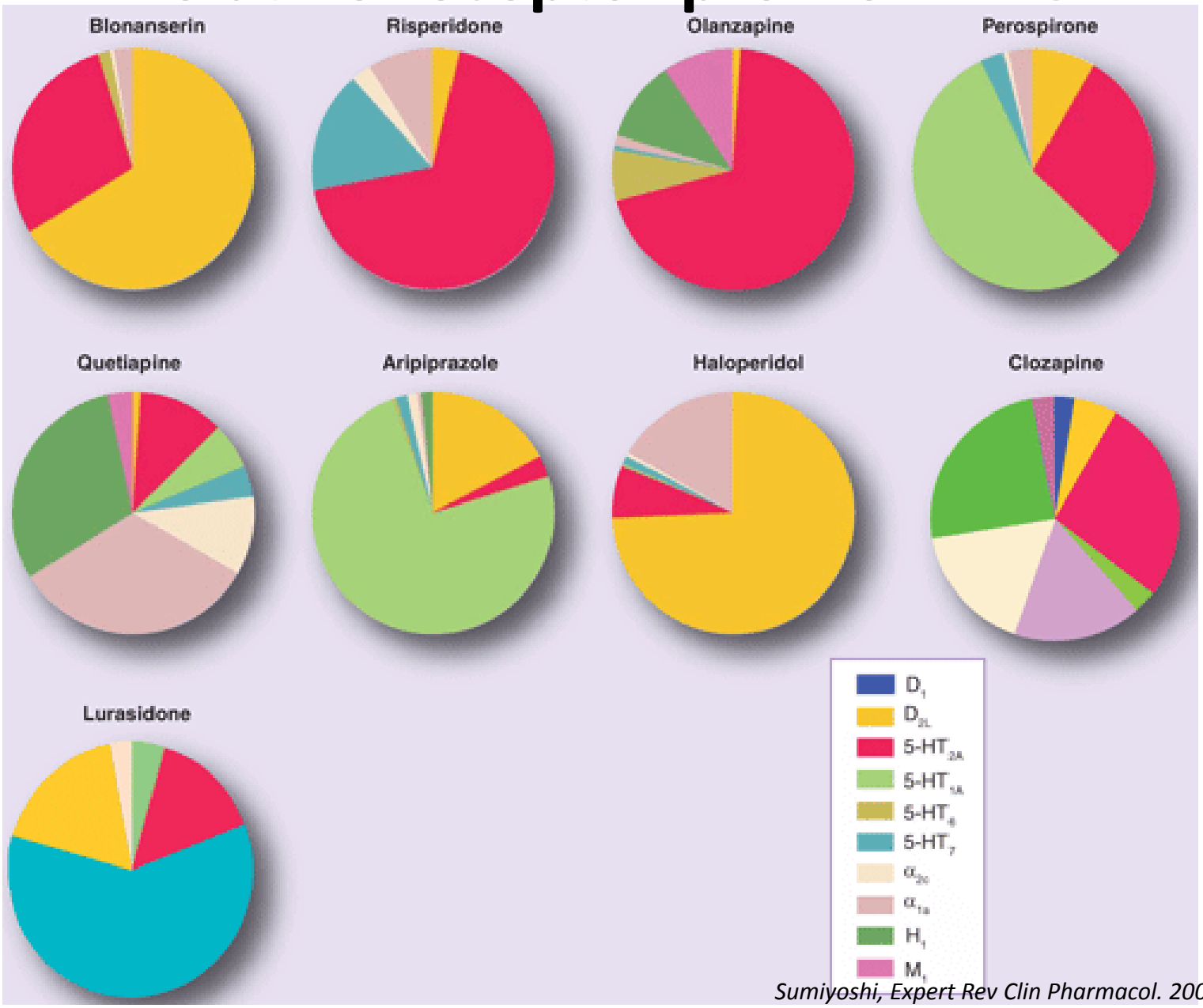
- **selective D_2/D_3 receptor** antagonists sulpiride, amisulpride
- **selective serotonin and dopamine receptor antagonists (SDAs)**

  risperidone, ziprasidone, iloperidone, sertindole
- **multi-receptor antagonists (MARTA:** D, 5-HT, α, H1, M)

  clozapine, olanzapine, quetiapine and zotepine
- **DSSS** (D2) **stabilizer**

  aripiprazole

Relative receptor profile AP2G



Sumiyoshi, Expert Rev Clin Pharmacol. 2008;1:791-802 .

Atypical antipsychotics - MARTA

olanzapine antag. D_2, antag. $5HT_{2A}$ (↑ disinhibition DA)

$5HT_{2C}$ - improving cognitive symptoms

better efficiency

Available depot injectable DDF

No/low risk of agranulocytosis

AE: sedation, weight gain, tachycardia, rarely TD

Atypical antipsychotics - MARTA

clozapine

antag. D_2 , antag. $5HT_{2A}$ (↑ release DA)

$5HT_{1A}$, $5HT_{2C}$, (cognitive, affective symptoms)

minimal impact on the nigrostriatal system

Effect on alpha, 5HT2 rcp

Useful in: Pharmacoresistant psychoses - responds about 1/3

risk of suicidium, aggressive patients, EPS

AE: sedation, weight gain,

agranulocytosis - genetic test

Atypical antipsychotics - SDA

risperidone

antag. D_2 , antag. 5HT2A (↑ release DA) , α1, 5HT7 (antidepresive action)

p.o. i.m. depot inj.

Active metabolite 9-OH risperidon = Paliperidon

I: schizophrenia, mania, bipolar disorder, behavioral disorders in children, ADHD, resistant OCD

AE: weight gain, dyslipidemia, hyperprolactinemia

Atypical antipsychotics - DSSS

aripiprazole – partial agonist D_2 + 5HT1A, antag. 5HT2A

(localy increases DA –improves cognitive fctions, affectivity)

blocks 5HT2C, 5HT7 –antidepresive action

¨ lacks sedation, weight gain

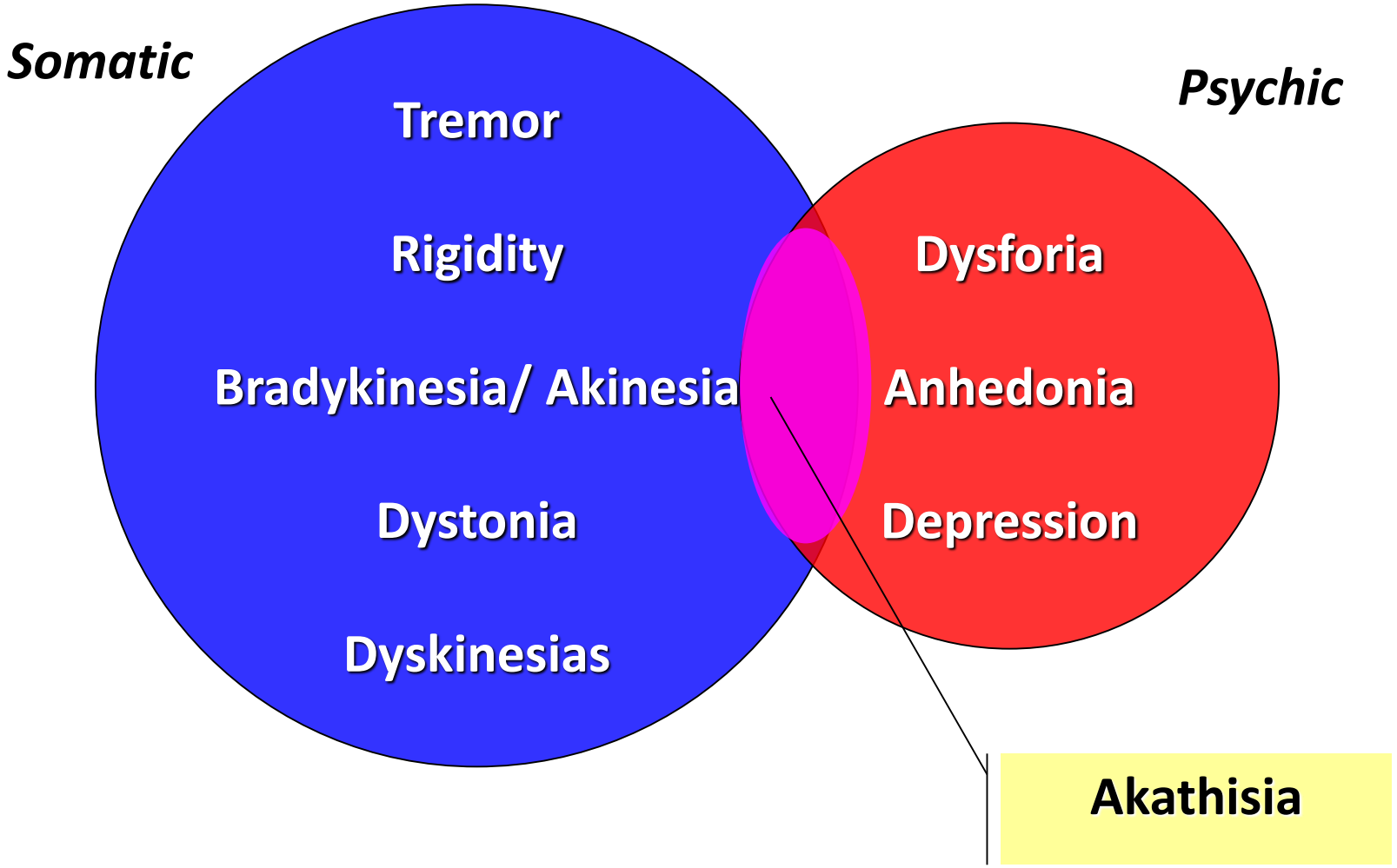
p.o. + depot inj.

Other Indications: augmentation of antidepressants,

Pharmacokinetics

- Most of APs are rapidly, but incompletely absorbed
- significant 1st pass effect
- F = 25-65%
- Most lipophilic
- Most are significantly bound to proteins (92-98 %).
- Large Vd (> 7 L / Kg).
- Slow elimination

"Traditional" drug side effects of typical APs



Adverse effects

Blockade of D_2 receptors in NS pathway

EPS - early (acute)
- late (tardive)

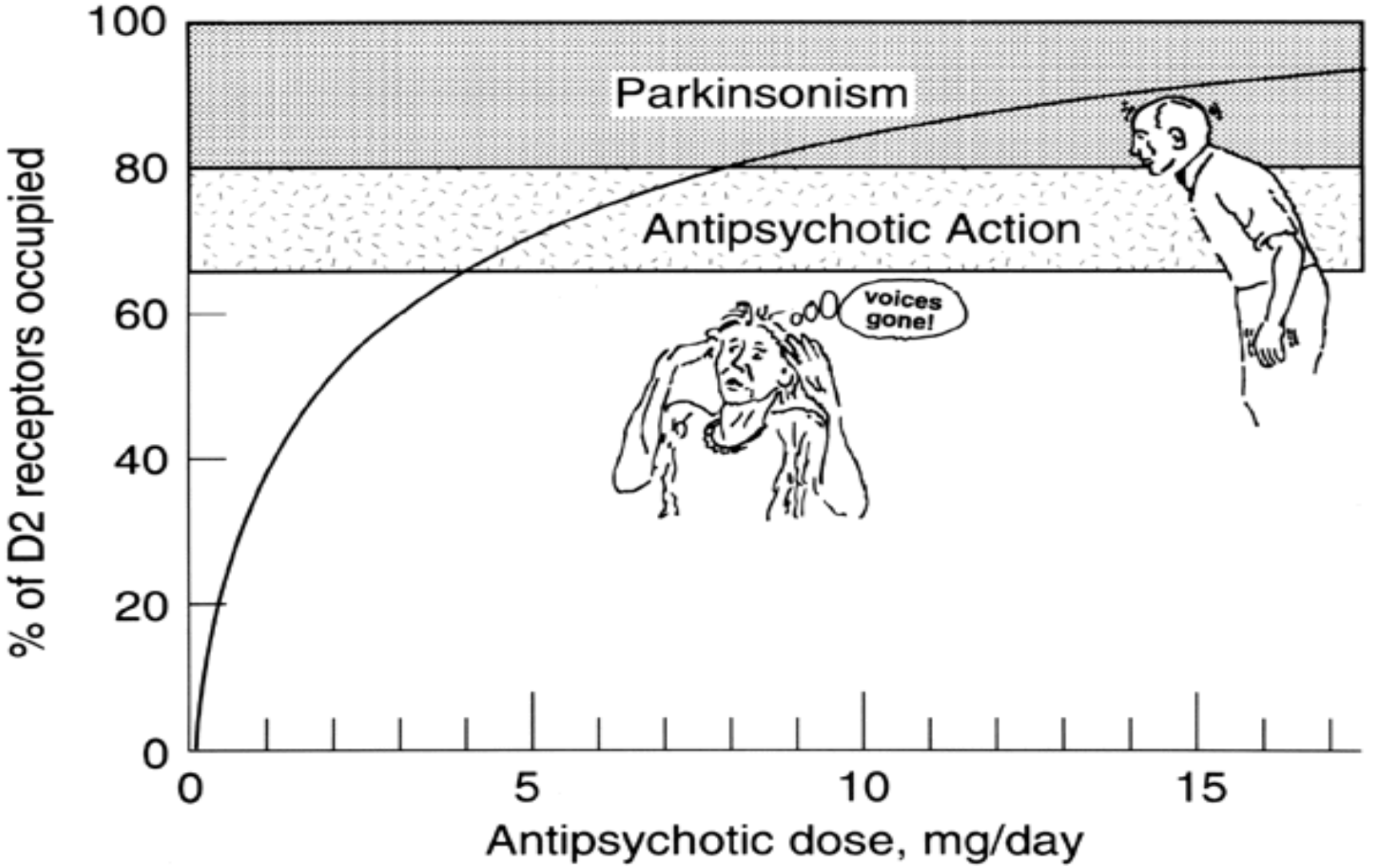
Severity does not correlate with dose !

Acute dystonia

- involuntary contraction of individual muscles or muscle groups of prolonged duration, causing abnormal movements or positioning of different body parts.
- occurs in up to 25-33% of all patients treated with typical AP

https://www.youtube.com/watch?v=2krwEbm5hBo

https://www.youtube.com/watch?v=9WH3HPTChkQ


100
80
60
40
20
0
% of D2 receptors occupied
Parkinsonism
Antipsychotic Action
voices gone!
0
5
10
15
Antipsychotic dose, mg/day

Adverse effects

Blockade of D_2 receptors in nigrostriatal pathway

EPS

Akathisia

- intense mental discomfort, compulsive movement restlessness

https://www.youtube.com/watch?v=W_iiy8ISvdY

Adverse effects

Blockade of D_2 receptors in nigrostriatal pathway

EPS

Parkinson's syndrome (PS)

combination of bradykinesia (movement retardation)

Akinesia (inability to start movement)

hypokinesia (reduction of motion range)

Stiffness/rigidity (increased muscle tone)

shaking

Typical APs : about 30-50**%.**

https://www.youtube.com/watch?v=6HKMusvSfeI

Neuroleptic malignant syndrome

- rare, severe AE
- may be lethal

- may occur at any time during treatment
- no association with
  - age
  - duration of treatment
  - dose
  - specific drug

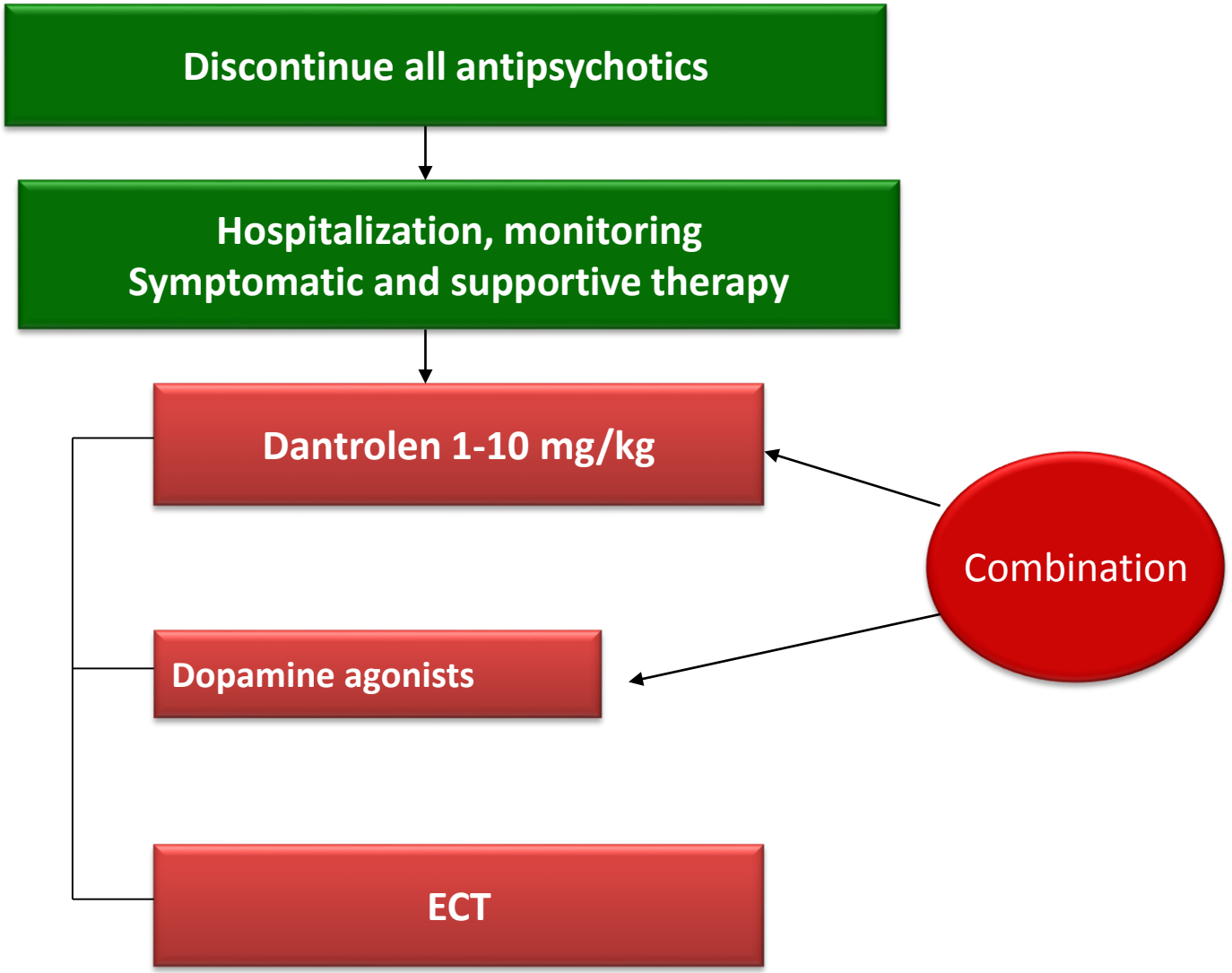
Neuroleptic malignant syndrome

1. AP treatment in the previous 7 days (in depot inj. In previous 2-4 weeks)
2. Hypertermia > 38 st. C
3. Muscle rigidity
4. 5symptoms of:
   - Changes in mental state
   - Tachycardia
   - Hypertension or hypotension
   - Tachypnoea or hypoxia
   - Sweating or salivation
   - Tremor
   - Incontinence
   - Increased creatine phosphokinase or myoglobinuria
   - Leukocytosis
   - Metabolic acidosis

Excluding other neuropsychiatric or somatic disease

Seifertová, 2008

Treatment of NMS



Seifertová, 2008

Adverse effects

block ACh rcp.

dry mouth
blurred vision
urine retention
constipation

clozapine
chlorpromazine
tioridazine

Adverse effects

Blockade α-adrenergic rcp.

Orthostatic hypotension

chlorpromazine
tioridazine

Blockade of H_1 – rcp

sedation, weight gain

risperidone
haloperidol

Adverse effects

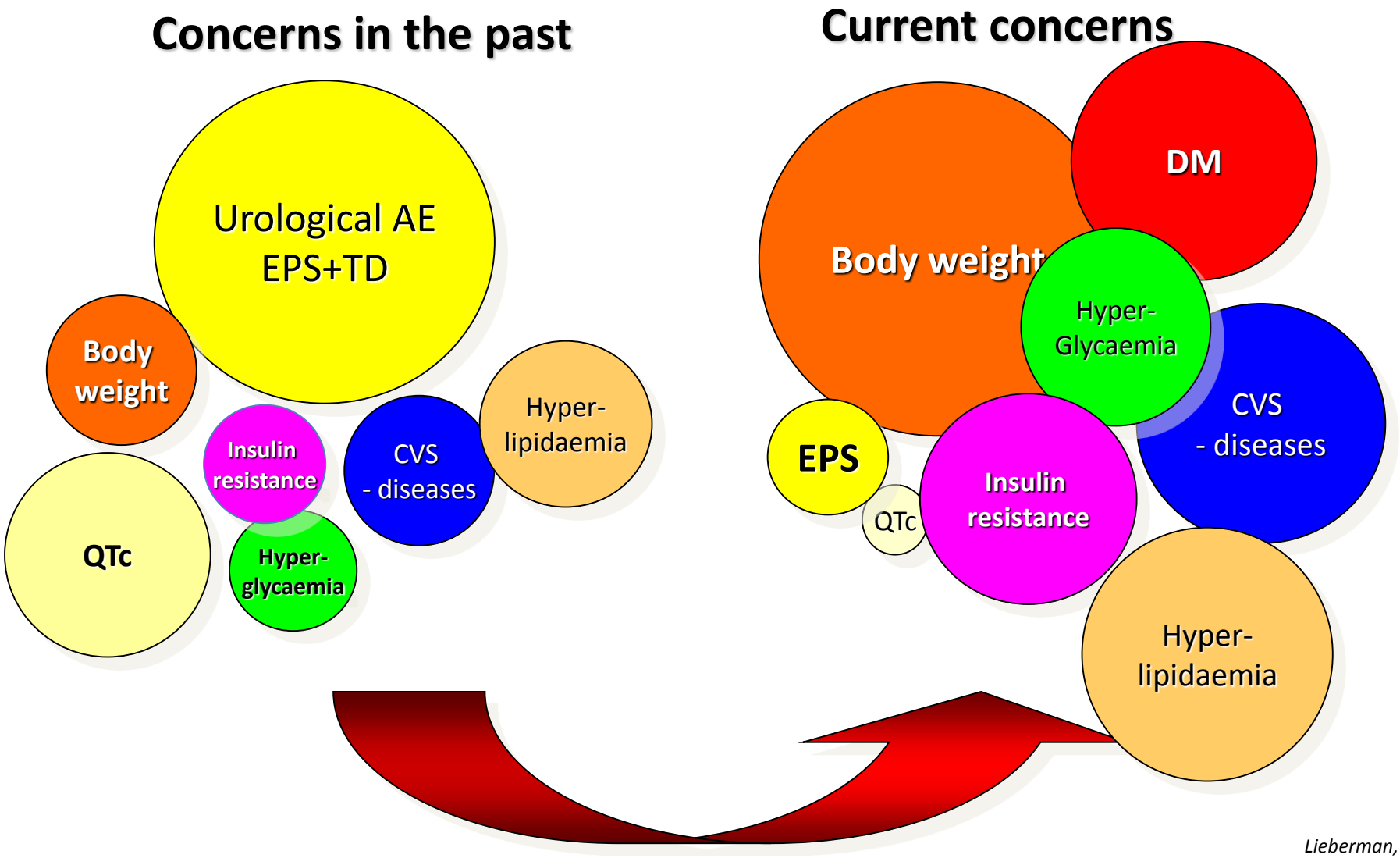
Blockade of D rcp. on basal ganglia

- Catalepsy (muscular rigidity and fixity of posture regardless, decreased sensitivity to pain)

Blockade of D2 rcp. In lactotrophic cells of hypophysis increase in prolactin, galactorhoea

risperidone

Side effects earlier and now



Lieberman, 2006

Best choice

Worst choice

SEDATION	WEIGHT GAIN	EPS
Aripiprazole	Aripiprazole	Clozapine
Iloperidone	Lurasidone	Iloperidone
Lurasidone	Ziprasidone	Quetiapine
Paliperidone	Asenapine	Aripiprazole
Risperidone	Iloperidone	Asenapine
Ziprasidone	Paliperidone	Lurasidone
Asenapine	Risperidone	Olanzapine
Olanzapine	Quetiapine	Ziprasidone
Clozapine	Clozapine	Paliperidone
Quetiapine	Olanzapine	Risperidone

Causes of relapse

- Insufficient efficacy of antipsychotics
- Non-compliance
- Abuse of addictive substances
- Psychosocial Stressors

Hoeschl 2009, *Weiden et al., 1995*

Restriction of non-adherence / therapeutic failure

- AP with better tolerance and better efficiency
- Depot forms
  - Injection (once every 14 -21 days)
  - Implants
- ITAREPS - https://www.itareps.com/cs/?c=cz
  - Information Technology Aided Relaps Prevention in Schizophrenia

Neurodegenerative disorders

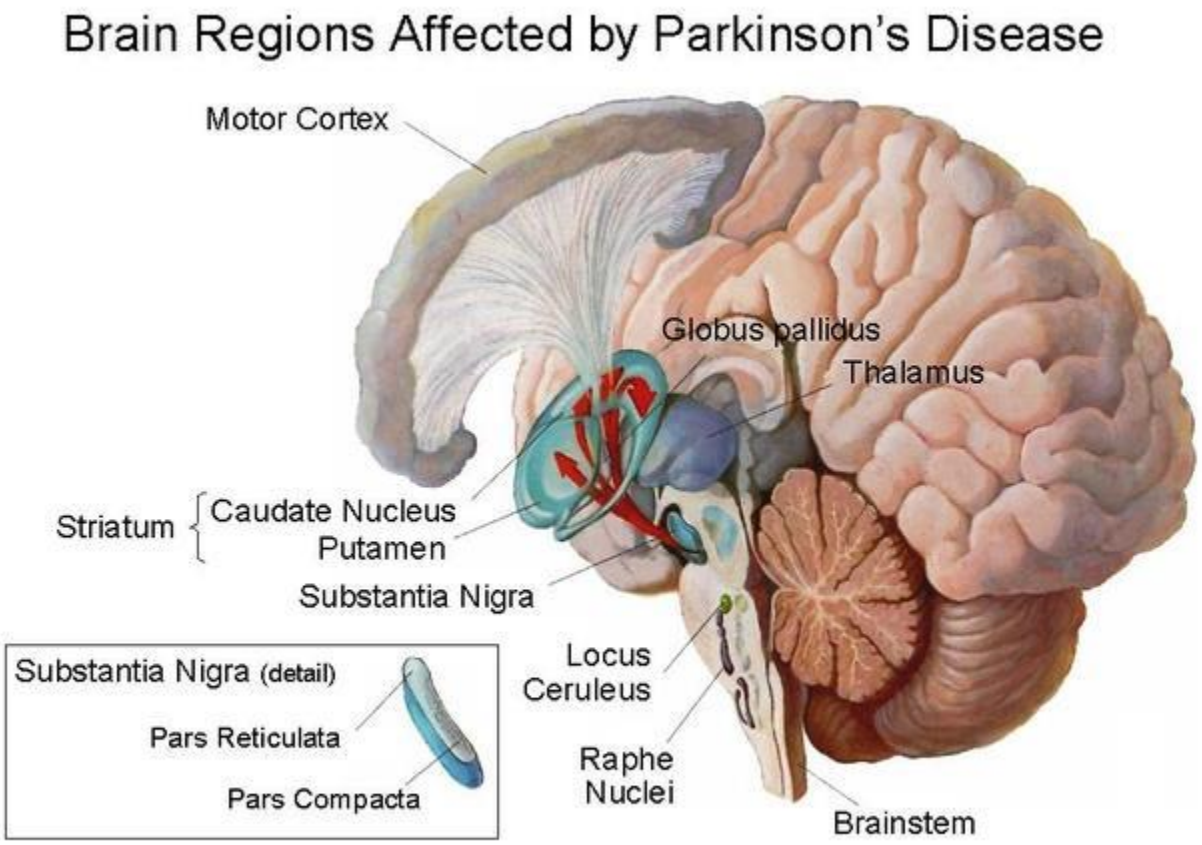
Parkinson's disease

Alzheimer's disease

Huntington's disease

Parkinson's disease (PD)

- Degeneration of dopaminergic (DA) neurons in substantia nigra (basal ganglia)



Parkinson's disease

Motor symptoms

- Resting tremor

https://www.youtube.com/watch?v=7uhT2ipQpKs

- Muscle rigidity

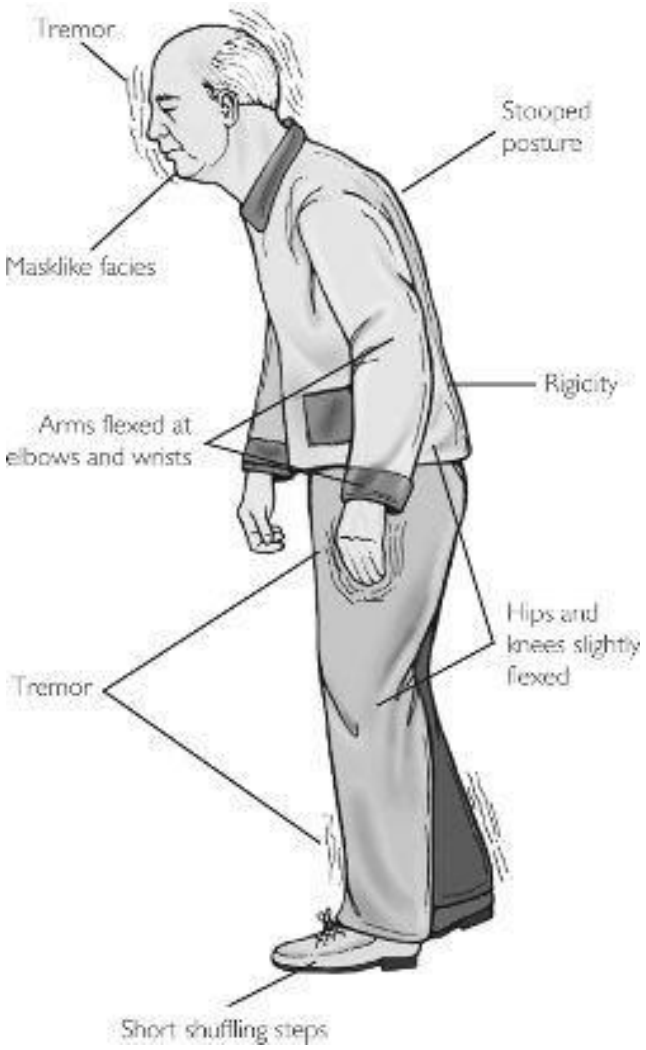
https://www.youtube.com/watch?v=kDOi0m5N7Lw

- Bradykinesia, akinesia

https://www.youtube.com/watch?v=5ZzIk-jC7RA

- Gait problems

https://www.youtube.com/watch?v=j86omOwx0Hk



Non-motor symptoms

- „mask“ face
- Speech and writing problems
- Anosmia
- Vegetative imbalance (e.g. constipation)
- Blood pressure changes
- High sebum production, especially in face
- Psychiatric comorbidities (depression, dementia)
- …

Parkinsonian syndrome (secondary)

- Symptoms resemble PD but have different etiology
  - Viral encephalitis
  - Iatrogenic – by DA blockade (typical antipsychotics, antihistaminics of 1st gen., antiemetics, etc.)

Therapy of PD

- Symptomatic pharmacotherapy
  A. Dopaminergic drugs
     1) DA precursor
     2) Inhibitors of DA degradation enzymes
     3) DA agonists
  B. Anticholinergic drugs

- Rehabilitation

A. Dopaminergic drugs

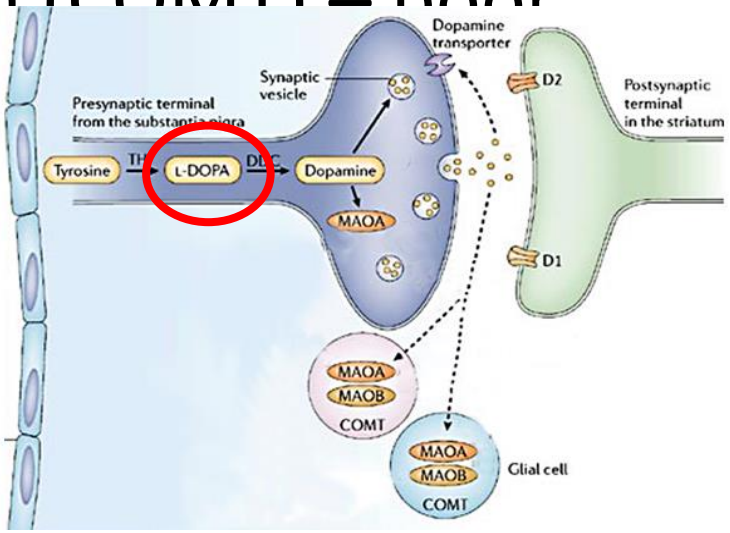
1) DA precursor
   - Levodopa (L-dopa)

2) Indirect dopaminergic drugs
   - MAO inhibitors
   - DA re-uptake inhibitors

3) Direct DA agonists

1) DA precursor: levodopa (L-dopa)

- First choice since 1969
- L-dopa crosses BBB (unlike DA) and DA decarboxylase converts it to DA
- Only around 1-3 % gets to CNS due to peripheral decarboxylation (COMT) – poor bioavailability (9 %)



antagonists of L-dopa peripheral breakdown

- **carbidopa**
- **benserazide**
  - Peripheral inhibitors of DOPA-decarboxylase (do not cross BBB)
  - In fixed combinations with L-dopa 4:1 (L-dopa : inhibitor)

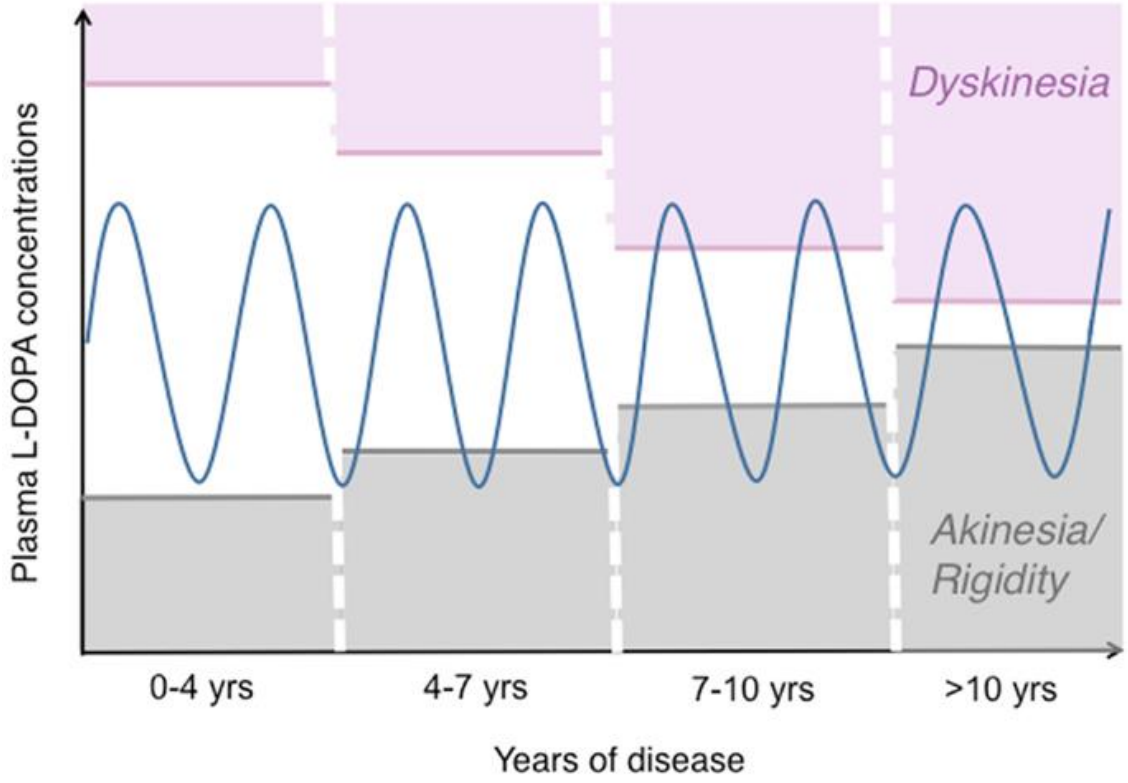
- **tolcapone, entacapone**
  - COMT inhibitors (entacapone acts on periphery only)
  - Fixed combinations: L-dopa + carbidopa + entacapone

Adverse effects of L-dopa and its combinations

- Dyskinesia, on-off syndrome

https://www.youtube.com/watch?v=AaOWRYqMQc0

https://www.youtube.com/watch?v=qvENE02Kiwo (animal model)



Adverse effects of L-dopa and its combinations

- **on-off syndrome**
- chorea, dystonia, extrapyramidal and motor disorders
- hallucinations, fuzziness, vertigo, night mares, sleepiness, fatigue, insomnia, depression, euphoria, dementia, abnormal dreams
- palpitations, arrhythmias, orthostatic hypotension
- anorexia, nausea, vomiting, dry mouth, bitter taste in mouth
- Levodopa + dopaminergic drugs: impulsivity disorders, compulsive behavior, gambling, hypersexuality, compulsive overeating, shopping
- **punding – repetitive compulsive behavior**

New drug dosage forms of L-dopa

- To reduce the on-off phenomenon

- Intestinal gel L-dopa/carbidopa (orphan status)
  - Nasogastric administration or by endoscopic gastrostomy (pump)
  - Quick absorption, stable levels
  - Allows better symptom control

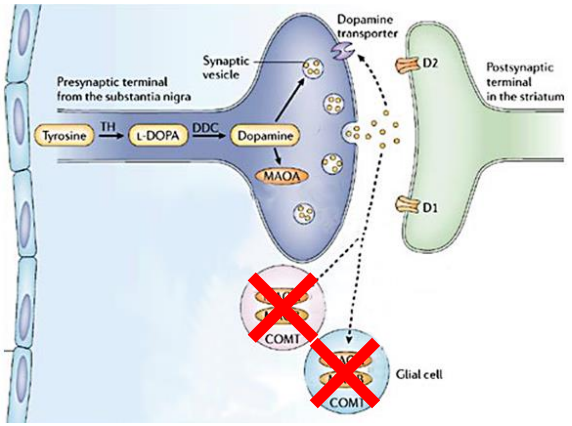
2) Indirect dopaminergic drugs

- MAO-B inhibitors
  - Reversible
  - Irreversible
- DA re-uptake inhibitor (amantadine)
- New: safinamide (inhibits MAO-B and re-uptake)

MAO-B inhibitors

Irreversible inhibitors

- **selegiline**
- **rasagiline** (neuroprotective?)
  - Prevent MPTP damage



Reversible inhibitors

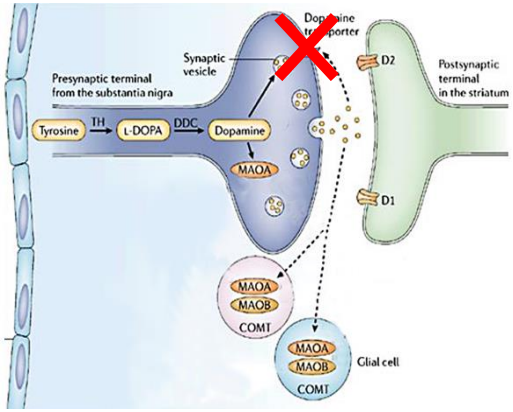
- **caroxazone** – antidepressant (RIMA)
  - discontinued, 5x more selective to MAO-B
- **safinamide** (new)

IMAO-B adverse events

- vertigo, headache, sleep disturbances, mood changes, nausea, dry mouth, bradycardia, supraventricular tachycardia
- In combination with levodopa may increase its AE (dyskinesia)
- non-selective drugs at higher doses also inhibit MAO-A, leading to hypertension crisis (tyramine reaction)

DA re-uptake inhibitor

- **amantadine**
  - Inhibits DA re-uptake, increases DA release
  - Antiviral drug (flu), NMDA antagonist, used for L-dopa induced dyskinesia
  - Antiparkinsonian effects wear off after approx. 6 months
  - AE: similar as in other drugs, mild

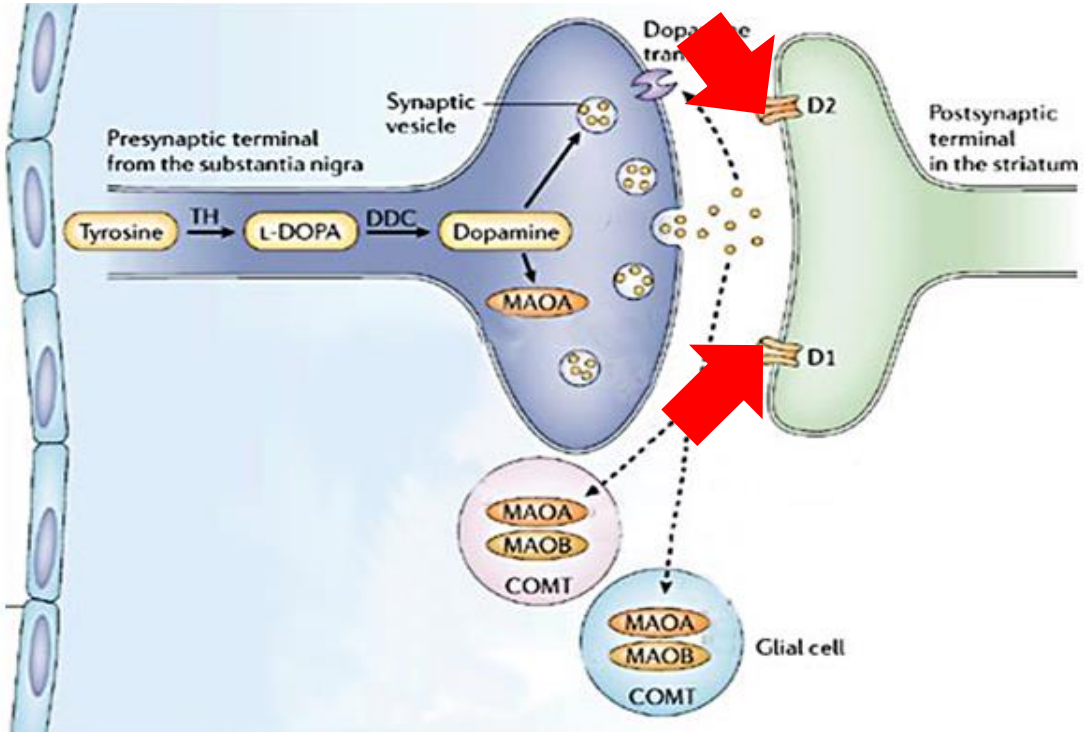


safinamide

- highly selective reversible MAO-B inhibitor + inhibits DA reuptake → DA agonistic effect
- blocks calcium channels type N → GLU antagonism (lowers GLU release)
- reduces L-dopa induced dyskinesia
- monotherapy or L-dopa combination

3) Direct DA agonists

- Ergot alkaloid derivatives:
  - **bromokriptine** (also to suppress lactation)
  - **cabergoline, lisuride, pergolide**



3) Direct DA agonists

- Non-ergot drugs:
  - **pramipexole** – agonist of D2, D3 a D4, oral
  - **ropinirole** – mostly D2 agonists, oral
  - **rotigotine** – agonist of D3, D2 a D1, transdermal

  - **apomorphine** – D1 and D2 agonist, injection, mostly used as a quick relieve in patients with variable response to DA drugs

- Initial therapy, postponing L-dopa treatment
- Add-on to L-dopa treatment (reduction of L-dopa doses)

B. Anticholinergic drugs

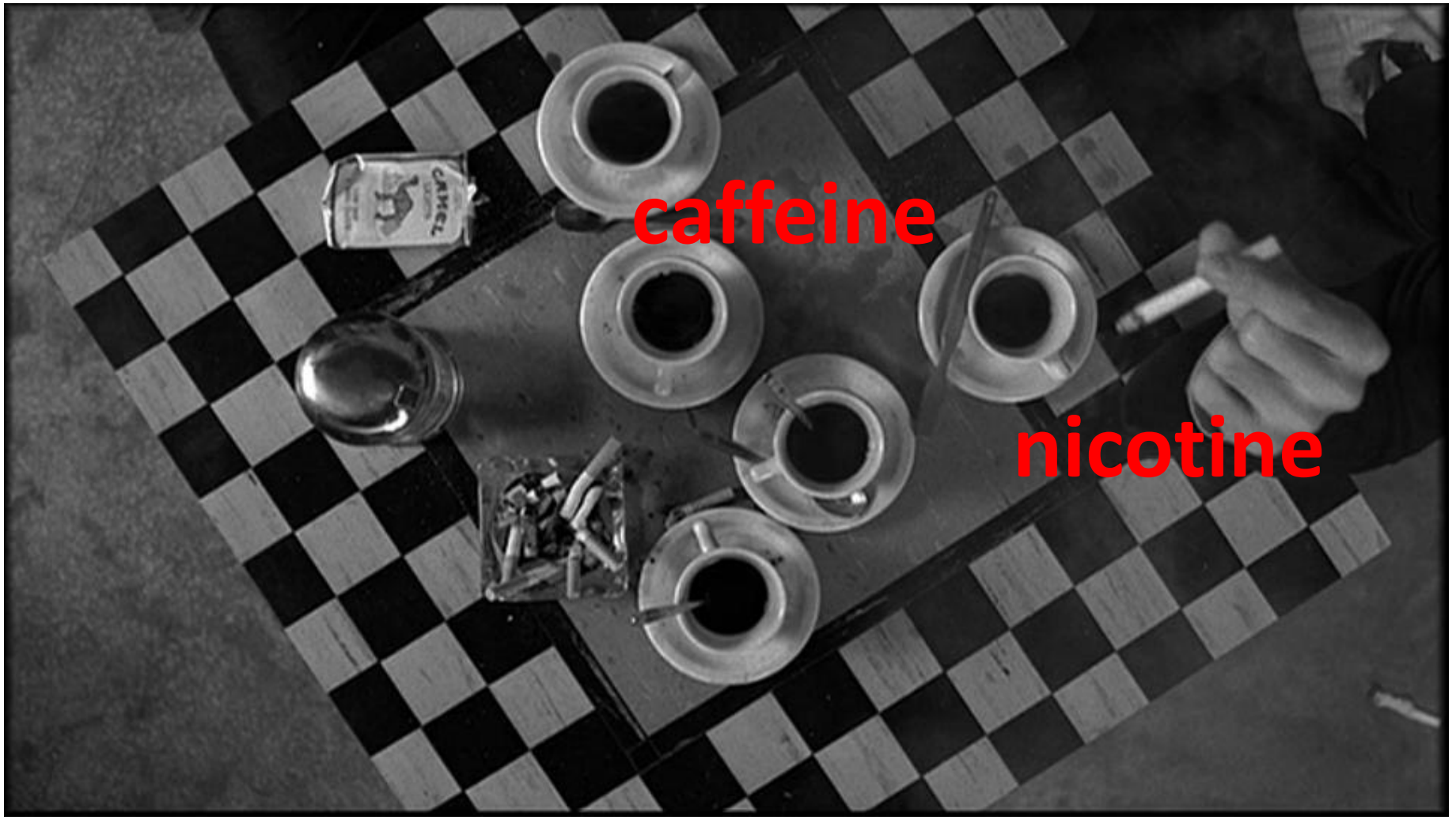
- Against relative prevalence of cholinergic system in striatum and normalization of increased gland secretion, tremor and partially also rigidity and bradykinesia
- Drugs with good CNS penetration
  - **biperiden** – mostly M1 antagonist
  - **orphenadrin** - M, H1, NMDA antagonist (central myorelaxant, combined with diclofenac)

- AE: typical for PSL, pro-dementive effect!
- In case patient does not respond, we can try a different drug.

B. Anticholinergic drugs

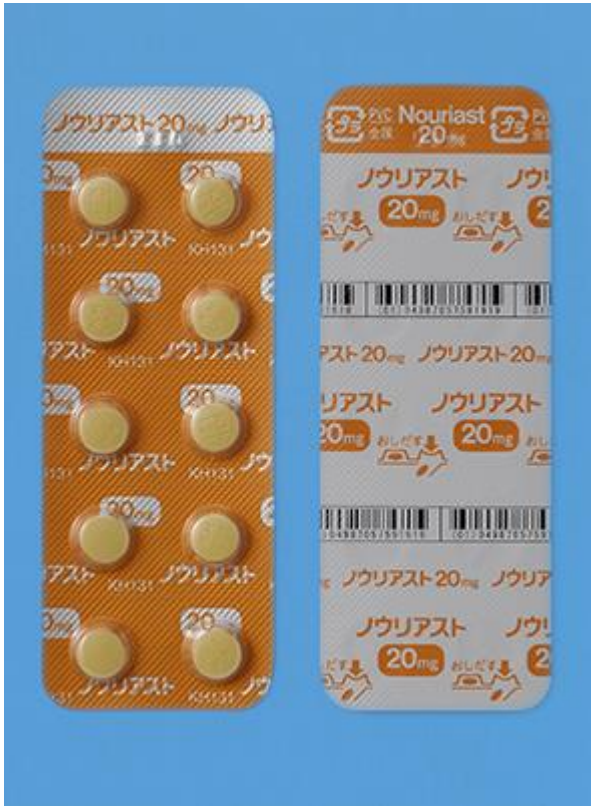
- Other drugs with central cholinergic effects:
  - H1 antihistaminics – 1st generation
  - tricyclic antidepressants

„PD, coffee and cigarettes“



Caffeine and PD

- Regular intake of caffeine is associated with lower tendency to PD development
- **Caffeine** is adenosine A2A receptor antagonist
- First drug with this mechanism:
  - **istradefylline**, registered in Japan, FDA rejected the application in the 2008 for lack of data



Nicotine and PD

- Smokers have approximately 60% lower probability to develop PD than non-smokers
- **Nicotine** effects:
  - Neuroprotective for DA neurons
  - Reducing L-dopa induced dyskinesia
  - Improving cognitive faculties
- Unclear issues
  - Clinical relevance
  - Route of administration

Prokinetics

D2 receptor antagonists:

– **metoclopramide**

– **itopride**

– **domperidone**

- (alizapride, cisapride)

– **sulpiride**

- acts centrally on the CTZ and also has a peripheral action on the GIT itself

– increasing the motility of the oesophagus, stomach and intestine

- metoclopramide crosses BBB (unwanted effects including disorders of movement, fatigue, motor restlessness, prolactin release

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Multimediální skripta 3LF UK (http://fblt.cz/skripta/)

Lectures: prof. Šulcová, Mohr, Höschl, Votava, J. Rudá