Pharmacology of the central dopaminergic systems

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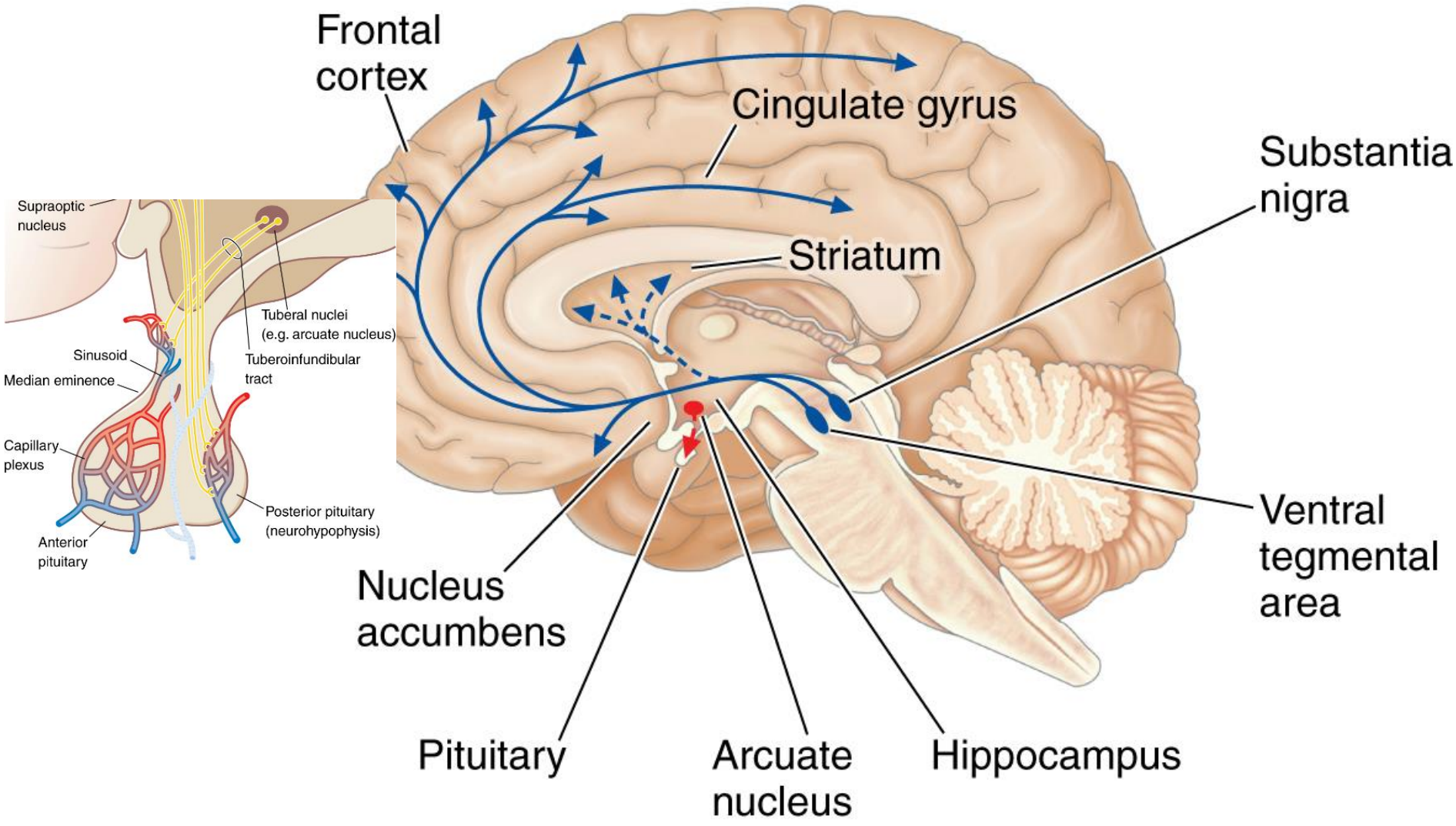
Dopamine (DA)

- 1910 – synthesis of DA
- 1930 – precursor of NA, A
- beginning of the 1950s – DA is a transmitter
- end of 1950s – DA in the CNS
- beginning of the 1960s – DA level decreases in the CNS in Parkinson's disease

- It is rather a neuromodulator than a classic excitatory or inhibitory neurotransmitter

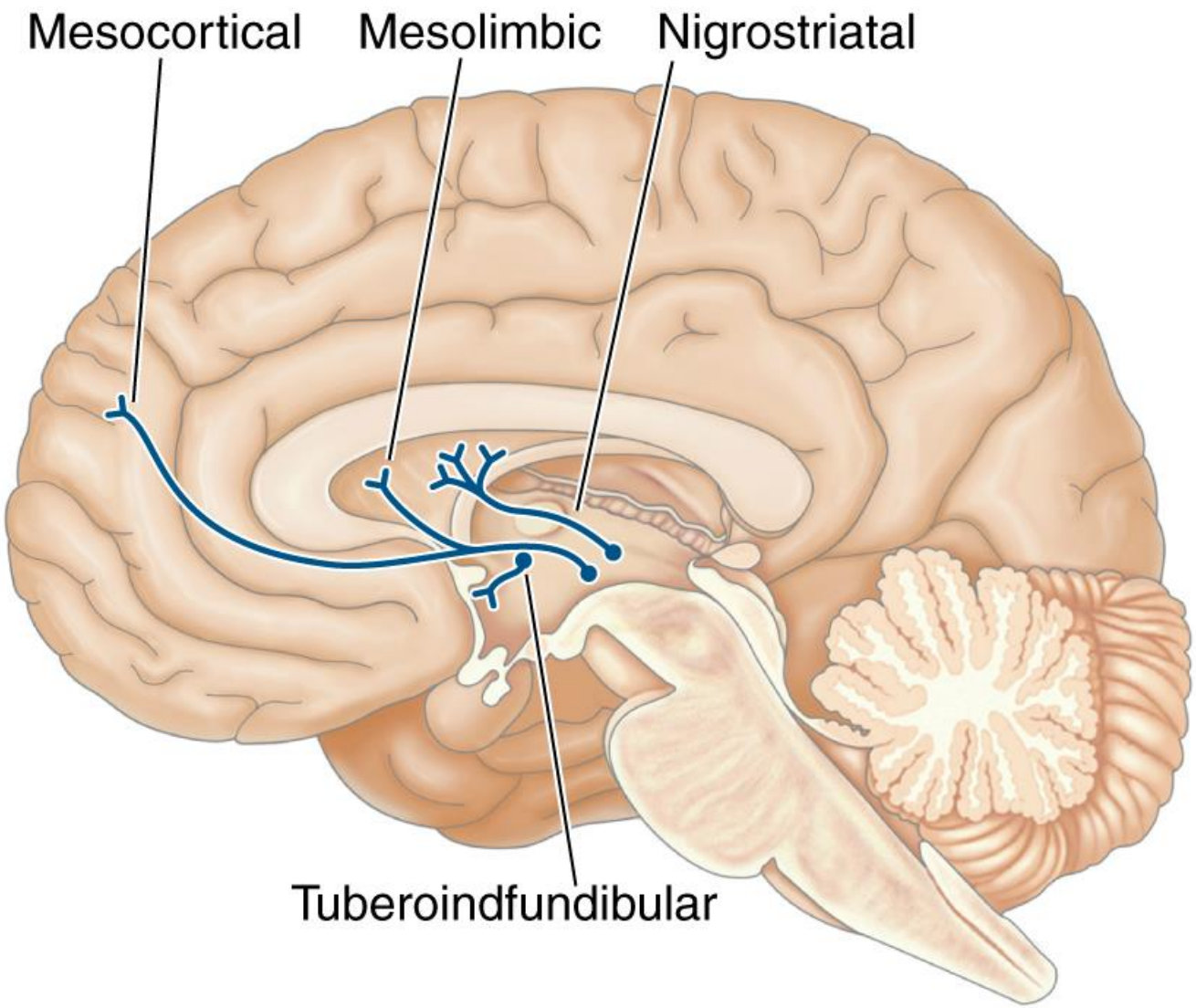
- DA, Tyr, DOPAC oxidation $\rightarrow$ melanin (dark colour of subst. nigra)
- DA-, DOPA-kinons (oxidated products) – bounded to α-synuclein (Lewy bodies)

Major dopaminergic (DAergic) pathways in the brain



Goodman & Gilman's, 12th Ed.

Major DAergic pathways in the brain - simplified



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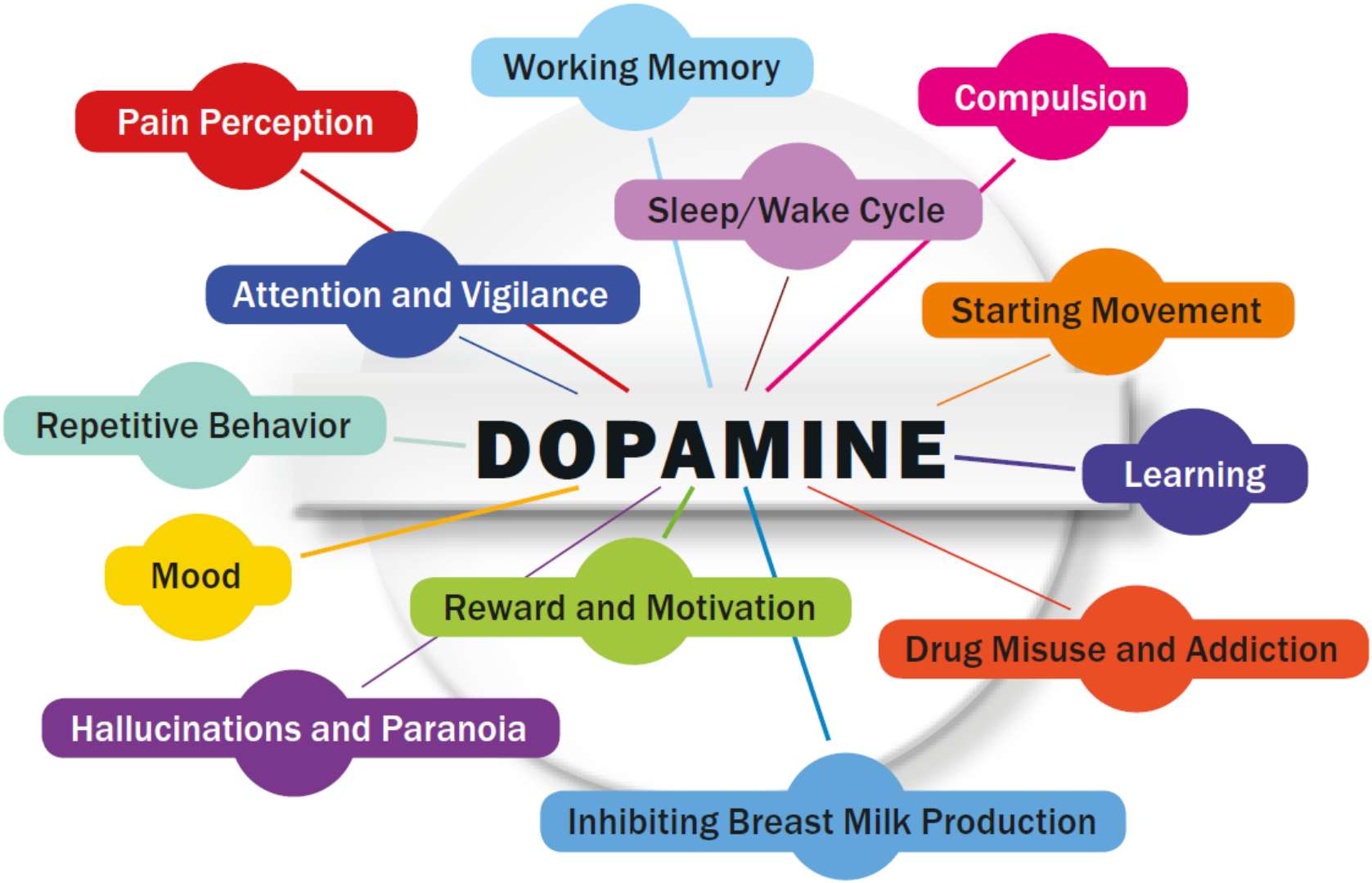
4 main pathways of DAergic neurons in the CNS

Pathway	Associated w/	Dysfunction
1. Mesolimbic	Reward Learned behaviors	Scizophrenia Psychosis Addiction
2. Mesocortical	Motivation Emotion Impulse control Cognitive functions	Scizophrenia Psychosis ADHD
3. Nigrostriatal	Movement regulation	Parkinson Movement side effects
4. Tuberoinfundibular	Regulation of prolactin secretion	Hyperprolactinemia

DA is linked to many facets of experience

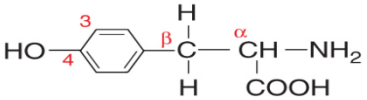


Sci Am Mind, Jan/Feb 2017

Synthesis of DA, NA and A

Phenylalanine (in food) → TYROSINE

phenylalanine hydroxylase (liver)



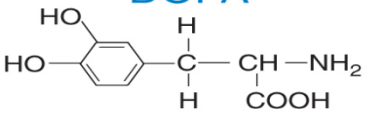
tyrosine-3-monooxygenase (tyrosine hydroxylase)

tetrahydrobiopterin

⊖ Metyrosine

α-methyl-DOPA →

DOPA

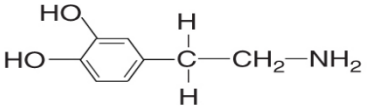


aromatic L-amino acid decarboxylase

pyridoxal phosphate

⊖ Periferal DOPA decarboxylase inhibitors

DOPAMINE

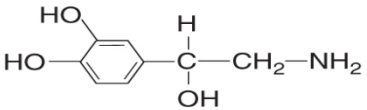


dopamine β-hydroxylase

ascorbate

α-methyl-NA ←

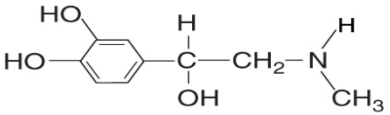
NOREPINEPHRINE



phenylethanolamine-N-methyltransferase

S-adenosylmethionine

EPINEPHRINE



Role of DA in the ANS:

- in the cardiovascular system

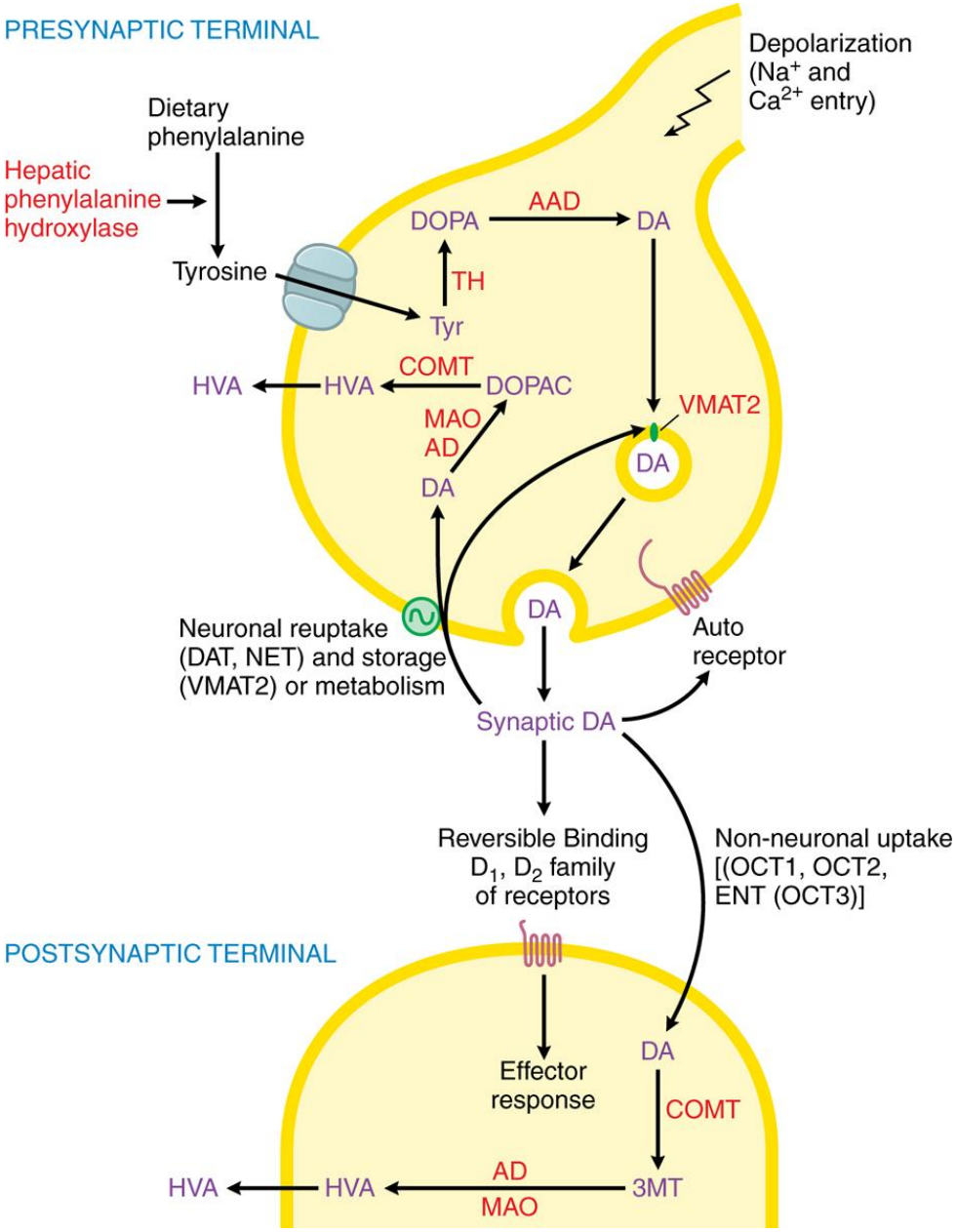
  DA-R → β-R → α-R

- In the kidney

  natriuresis

Goodman & Gilman's, 12th Ed.

Synthesis and inactivation of dopamine



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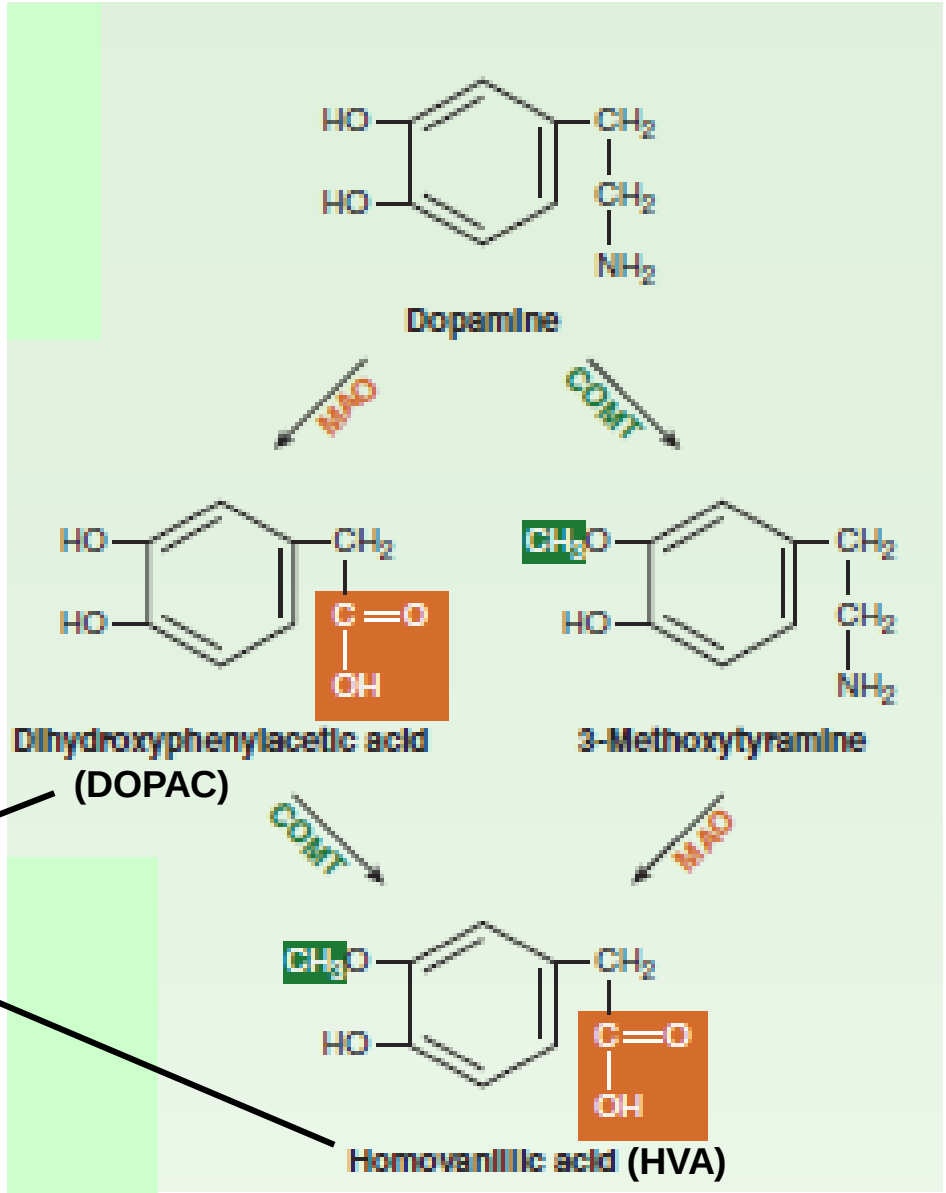
Metabolism of DA by catechol-O-methyltraferase (COMT) & monoamine oxidase (MAO)



Urine

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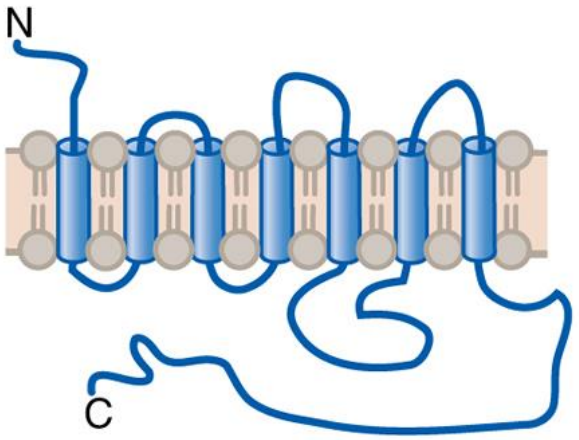
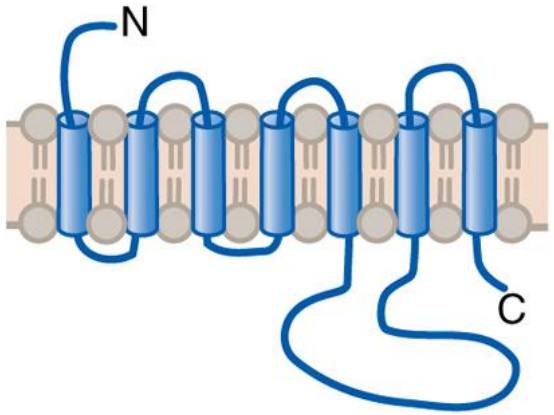
Distribution and characterization of DA receptors in the CNS

D1 receptor family



↑ cyclic AMP

D2 receptor family



↓ cyclic AMP
↑ K^+ currents
↓ voltage-gated Ca^{2+} currents

D_1	D_5
• SNpr	• hypothalamus
• frontal cortex	• striatum
• nucleus Acc	• NAc
• hypothalamus	

$D_{2L/S}$	D_3	D_4
• striatum	• n. accumbens	• PFC
• SNpc	• SNpc	• hypothalamus
• pituitary	• VTA	• amygdala
• PFC	Limbic region	• hippocampus

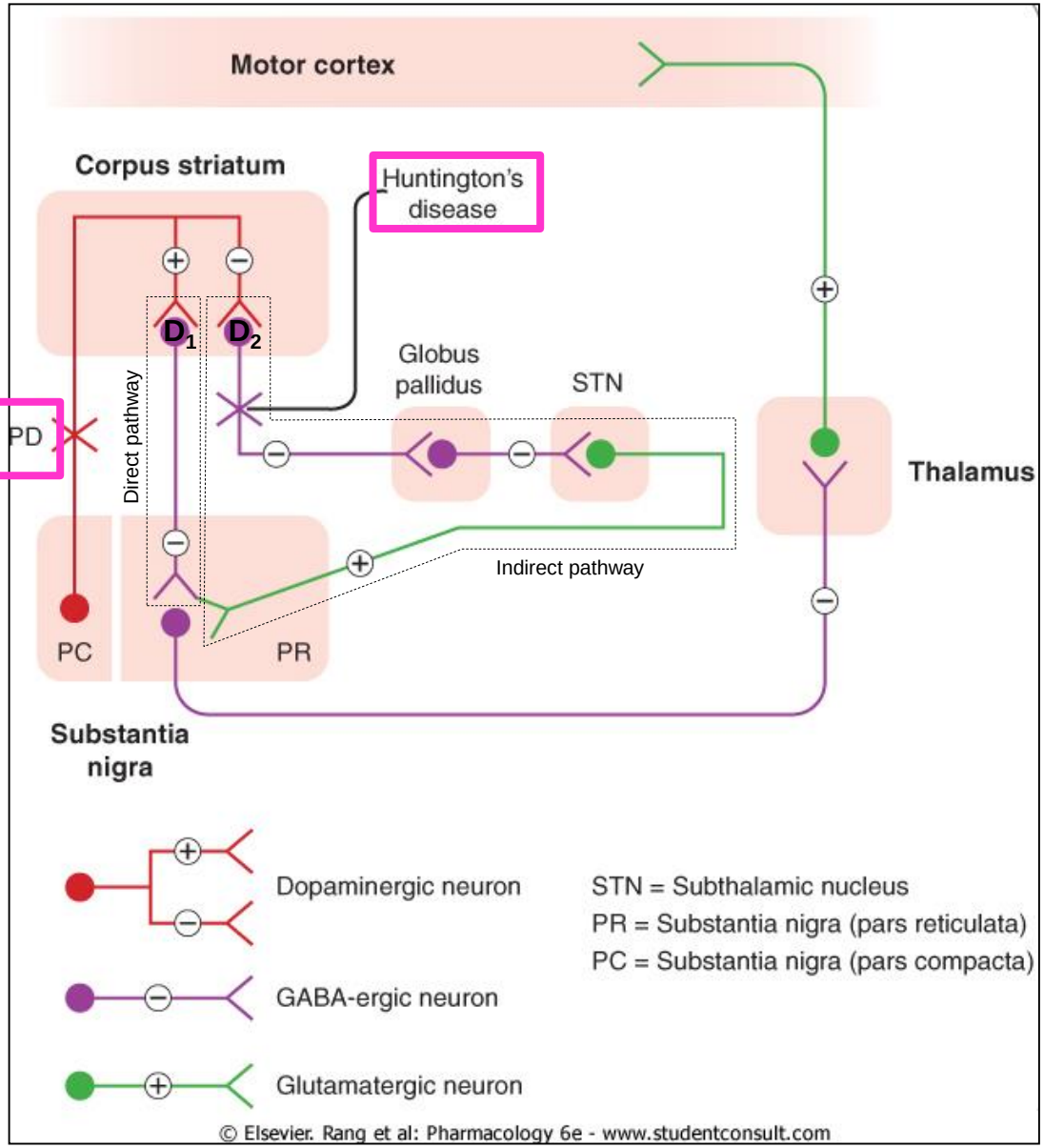
Goodman & Gilman's, 12th Ed.

CNS use of DA receptor agonists

Primary limitations: lack of subtype selectivity

- Parkinson's disease – e.g. ropinirole, rotigotine
- Hyperprolaktinemia – bromocriptine, cabergoline
- Restless leg syndrome (mild DAergic hypofunction) – ropinirole
- ADHD – selective D_4 agonist A-412977 (experimental; no abuse potential; cognitive improvement well below doses of hyperlocomotion)

Simplified diagram of the organisation of the extrapyramidal motor system and the defects that occur in Parkinson's & Huntington's disease



Activation of the direct pathway

⇩

Cortex activation ↑

Activation of the indirect pathway

⇩

Cortex activation ↓

D_1 stim. in the striatum

⇩

Cortex activation ↑

D_2 stim. in the striatum

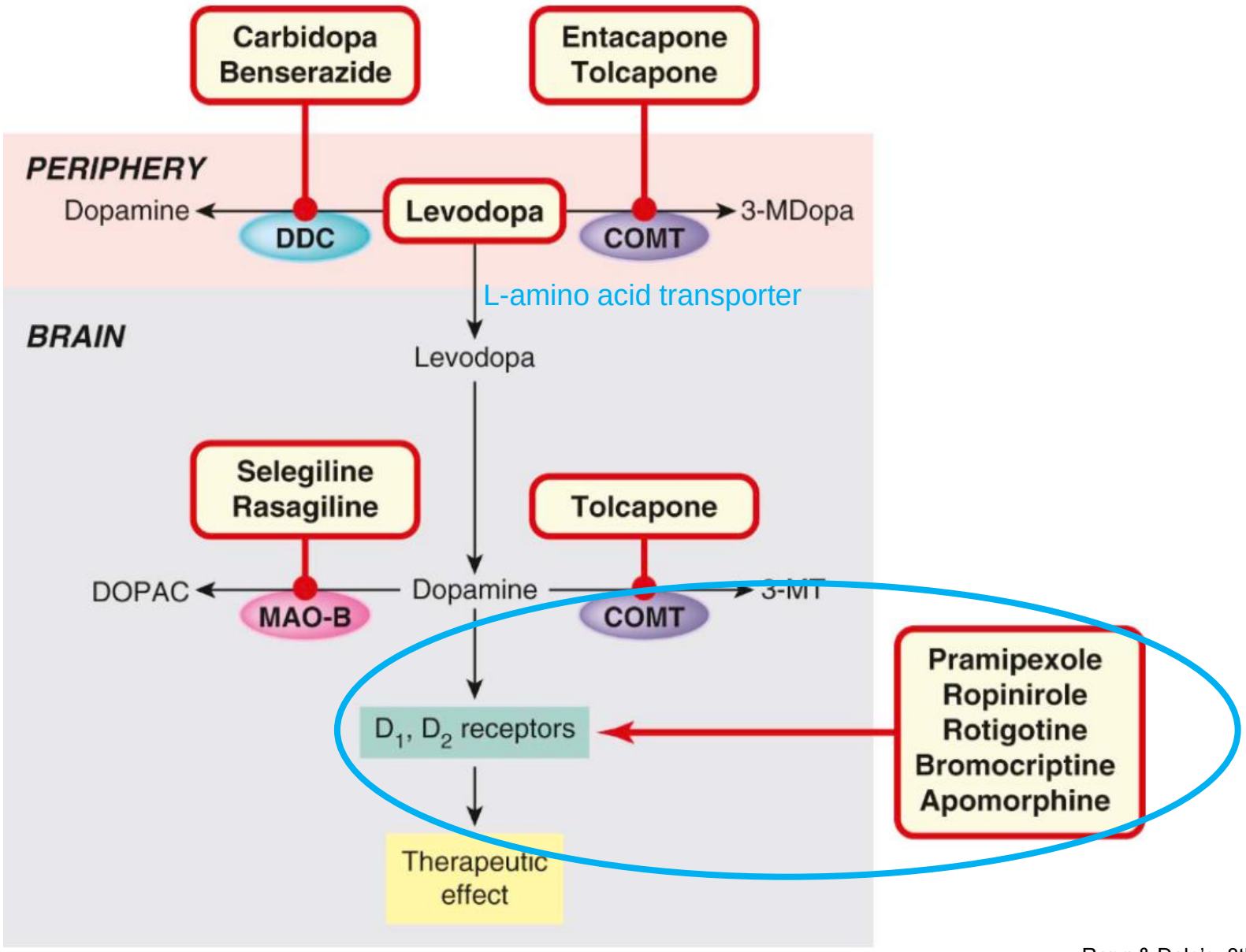
⇩

Cortex activation ↑

PD: excitation of the motor cortex ↓

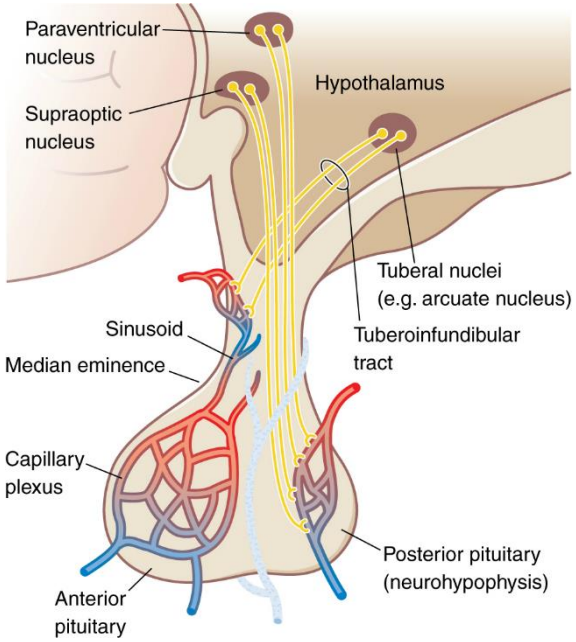
HD: excitation of the motor cortex ↑

Drugs used to treat Parkinson's disease

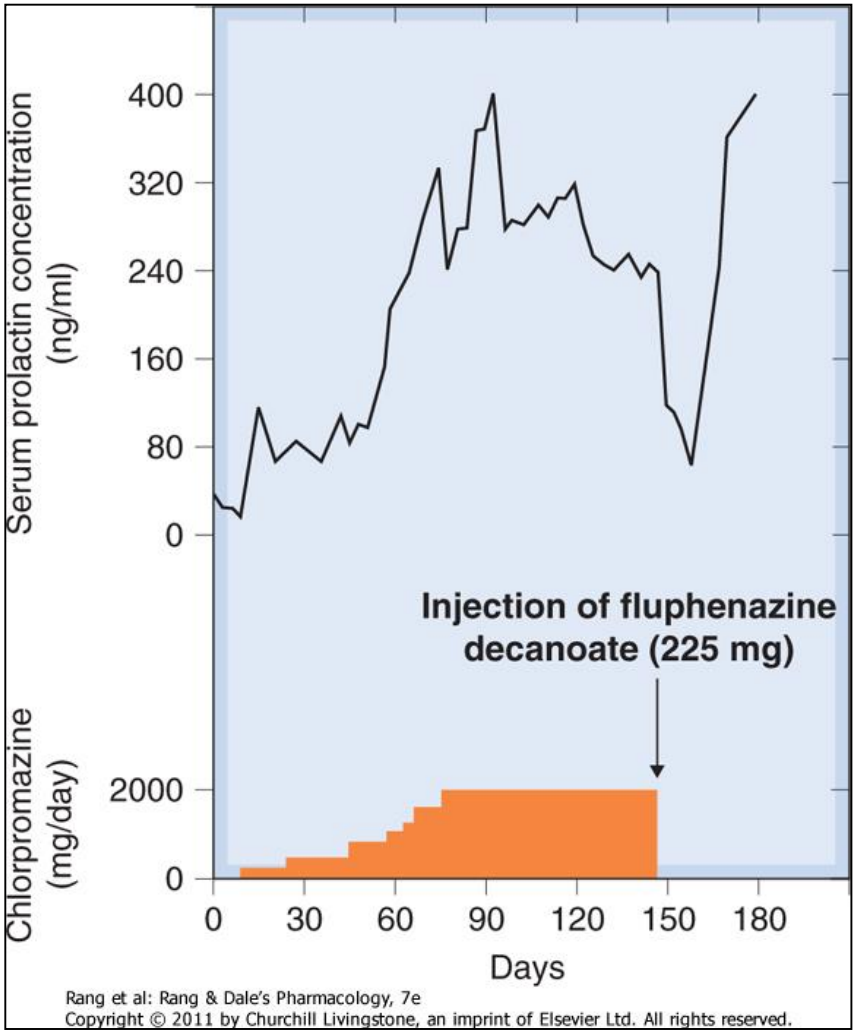


Rang & Dale's, 8th Ed.

Antipsychotics → prolactin secretion ↑
DA-R agonists → prolactin secretion ↓



DA → PRL ↓



When daily dosage with **chlorpromazine** was **replaced** with a **depot** injection of **fluphenazine**, the **plasma prolactin initally dropped, because of the delay in absorption, and then returned to a high level**

Rang & Dale's, 8th Ed.

DA agonist (drug) → addiction (disease), e.g., gambling
→ enhanced appetite

DA – „the pleasure molecule”
or rather prediction of delight

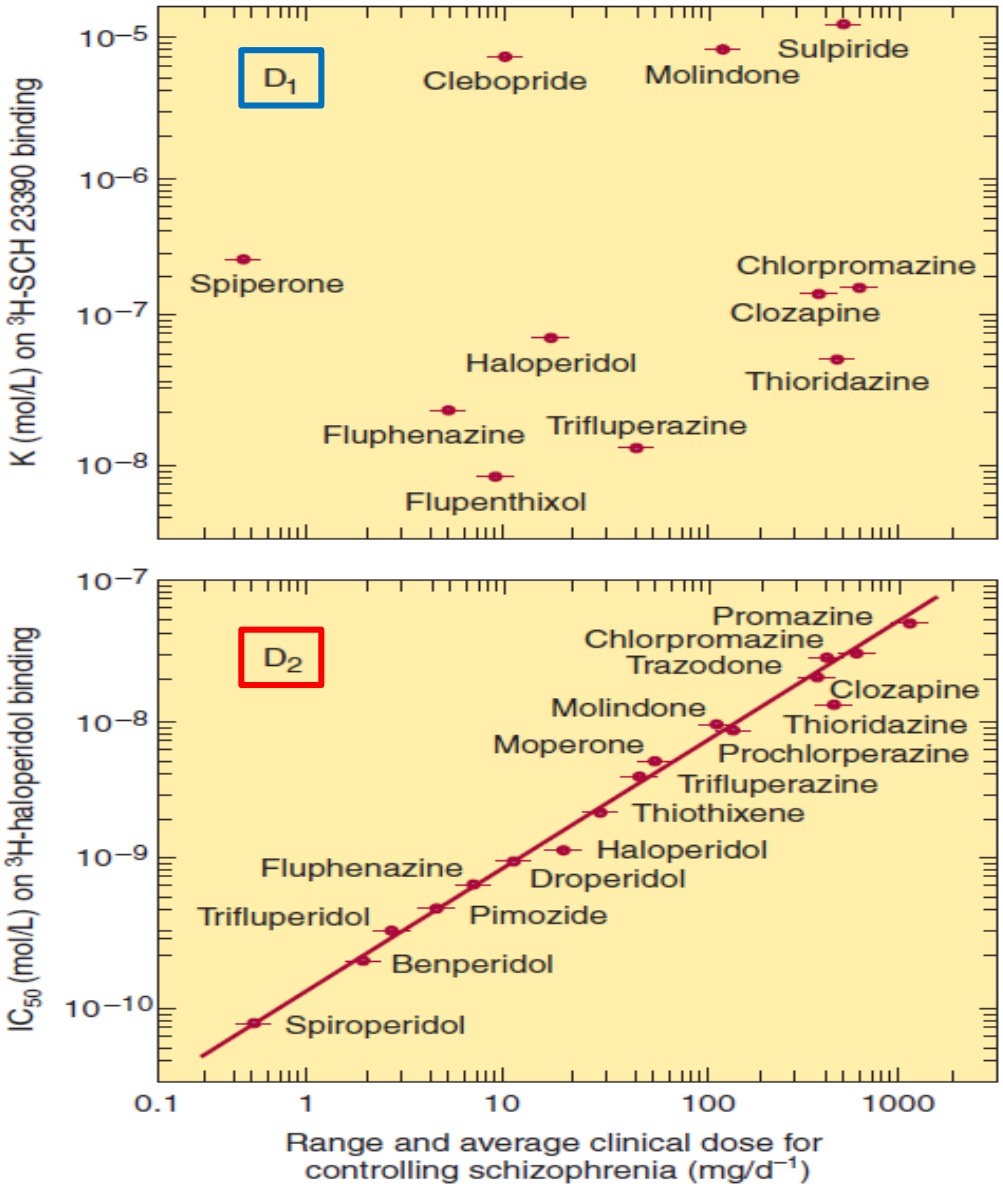
Sign of delight – lip licking

CNS use of DA receptor antagonists

Primary limitation: lack of subtype selectivity

- Schizophrenia, psychosis – 1st & 2nd gen. antipsychotics (e.g. chlorpromazine & clozapine)
- Vomiting – antiemetics (metoclopramide; 1st gen. antipsychotics)
- Huntington disease - antipsychotics (severity of choreoathetotic movements ↓, but may increase muscle rigidity)
- Tics in Tourette's syndrome – risperidone, aripiprazole
- Drug addiction – D_3 selective antagonist (experimental)

Therapeutic potency of antipsychotic drugs ~ binding affinity for to D_1 & D_2



Chlorpromazine: $\alpha_1 = 5\text{-}HT_{2A} > D_2 > D_1$
Haloperidol: $D_2 > \alpha_1 > D_4 > 5\text{-}HT_{2A} > D_1 > H_1$
Clozapine: $D_4 = \alpha_1 > 5\text{-}HT_{2A} > D_2 = D_1$
Olanzapine: $5\text{-}HT_{2A} > H_1 > D_4 > D_2 > \alpha_1 > D_1$
Aripiprazole: $D_2 = 5\text{-}HT_{2A} > D_4 > \alpha_1 = H_1 >> D_1$
Quetiapine: $H_1 > \alpha_1 > M_{1,3} > D_2 > 5\text{-}HT_{2A}$

BG Katzung, 12th Ed.

Main receptorial affinities of antipsychotics

Table 16–2

Potencies of Antipsychotic Agents at Neurotransmitter Receptors[a]

	DOPAMINE	SEROTONIN			$5HT_{2A}/D_2$	DOPAMINE		MUSCARINIC	ADRENERGIC		HISTAMINE
	D_2	$5\text{-}HT_{1A}$	$5\text{-}HT_{2A}$	$5\text{-}HT_{2C}$	RATIO	D_1	D_4	M_1	α_{1A}	α_{2A}	H_1
Typical Agents											
Haloperidol	1.2	2100	57	4500	47	120	5.5	>10,000	12	1130	1700
Fluphenazine	0.8	1000	3.2	990	3.9	17	29	1100	6.5	310	14
Thiothixene	0.7	410	50	1360	72	51	410	>10,000	12	80	8
Perphenazine	0.8	420	5.6	130	7.4	37	40	1500	10	810	8.0
Loxapine	11	2550	4.4	13	0.4	54	8.1	120	42	150	4.9
Molindone	20	3800	>5000	10,000	>250	>10,000	>2000	>10,000	2600	1100	2130
Thioridazine	8.0	140	28	53	3.5	94	6.4	13	3.2	130	16
Chlorpromazine	3.6	2120	3.6	16	1	76	12	32	0.3	250	3.1
Atypical Agents											
Asenapine[b]	1.4	2.7	0.1	0.03	0.05	1.4	1.1	>10,000	1.2	1.2	1.0
Ziprasidone	6.8	12	0.6	13	0.1	30	39	>10,000	18	160	63
Sertindole[b]	2.7	280	0.4	0.90	0.2	12	13	>5000	1.8	640	130
Zotepine[b]	8.0	470	2.7	3.2	0.3	71	39	330	6.0	210	3.2
Risperidone	3.2	420	0.2	50	0.05	240	7.3	>10,000	5.0	16	20
Paliperidone	4.2	20	0.7	48	0.2	41	54	>10,000	2.5	4.7	19
Iloperidone	6.3	90	5.6	43	0.9	130	25	4900	0.3	160	12
Aripiprazole	1.6	6.0	8.7	22	5.0	1200	510	6800	26	74	28
Sulpiride[b]	6.4	>10,000	>10,000	>10,000	>1000	>10,000	54	>10,000	>10000	>5000	>10,000
Olanzapine	31	2300	3.7	10	0.1	70	18	2.5	110	310	2.2
Quetiapine	380	390	640	1840	2.0	990	2020	37	22	2900	6.9
Clozapine	160	120	5.4	9.4	0.03	270	24	6.2	1.6	90	1.1

[a]Data are averaged K_i values (nM) from published sources determined by competition with radioligands for binding to the indicated cloned human receptors. Data derived from receptor binding to human or rat brain tissue is used when cloned human receptor data is lacking.

[b]Not available in the U.S.

Source: NIMH Psychoactive Drug Screening Program (PDSP) K_i Database: http://pdsp.med.unc.edu/pdsp.php (Accessed June 30, 2009).

Goodman & Gilman's, 12th Ed.

A possible subclassification of 2nd generation antipsychotics based on receptor binding

- **Mixed D_2 / 5-$HT_{2A/C}$ antagonists (inverse agonists), (+ 5-HT_{1A} partial agonists & 5-$HT_{6/7}$ antagonists):**

  - tricyclic ones (dibenzepines) – clozapine, olanzapine, quetiapine

  - other heterocyclic ones – risperidone, paliperidone, ziprasidone, sertindole

- **D_2/ D_3 antagonists:**

  - (sulpiride), amisulpride, tiapride

- **D_2 partial agonist / 5-HT_2 antagonist:**

  - aripiprazole

- **D_3 > D_2 partial agonist:**

  - cariprazine

Neurological side effects of antipsychotics

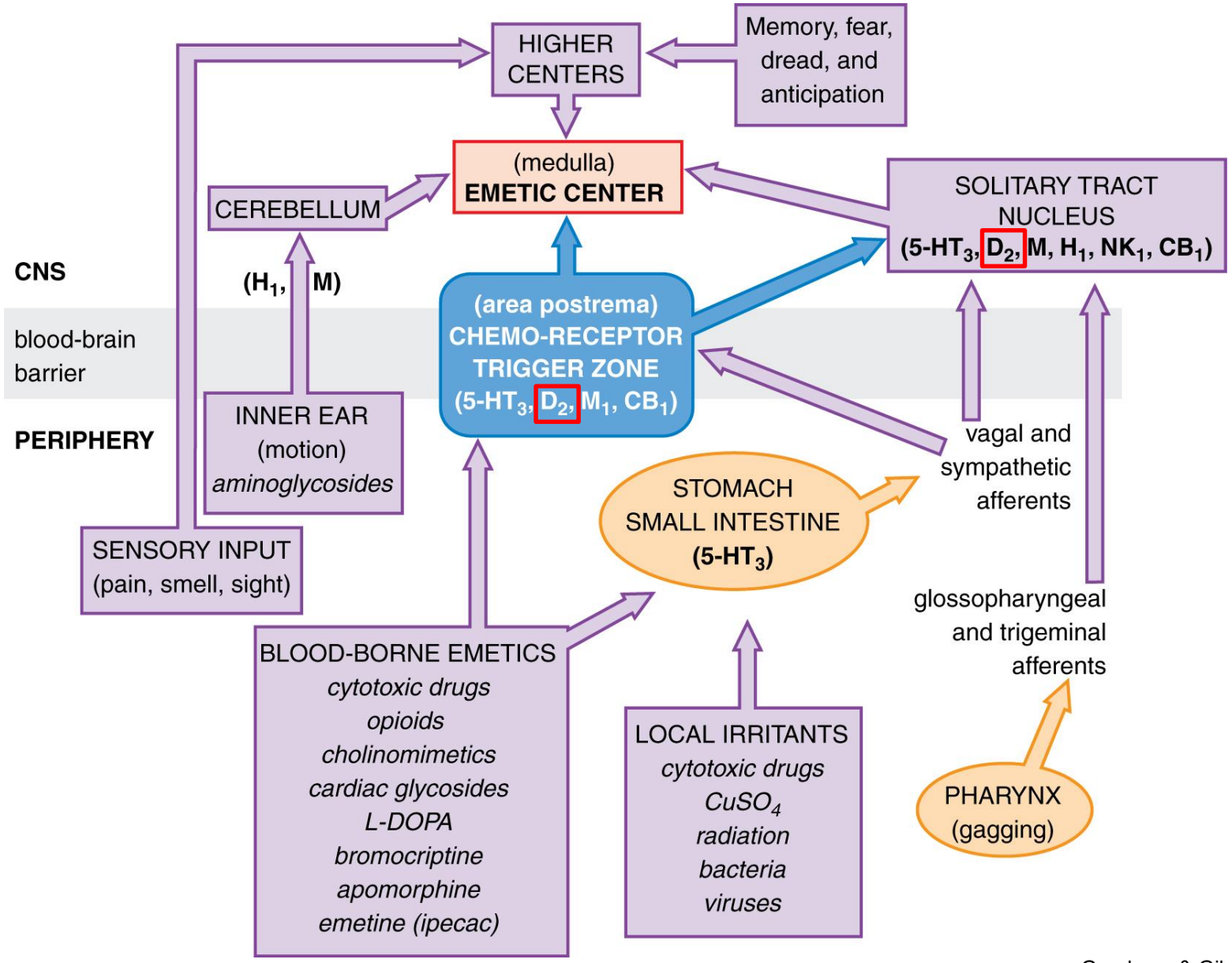
Table 16–4

Neurological Side Effects of Antipsychotic Drugs

REACTION	FEATURES	TIME OF ONSET AND RISK INFO	PROPOSED MECHANISM	TREATMENT
Acute dystonia	Spasm of muscles of tongue, face, neck, back	Time: 1-5 days. Young, antipsychotic naïve patients at highest risk	Acute DA antagonism	Anti-parkinsonian agents are diagnostic and curative[a]
Akathisia	Subjective and objective restlessness; *not* anxiety or "agitation"	Time: 5-60 days	Unknown	Reduce dose or change drug; clonazepam, propranolol more effective than anti-parkinsonian agents[b]
Parkinsonism	Bradykinesia, rigidity, variable tremor, mask facies, shuffling gait	Time: 5-30 days. Elderly at greatest risk	DA antagonism	Dose reduction; change medication; anti-parkinsonian agents[c]
Neuroleptic malignant syndrome	Extreme rigidity, fever, unstable BP, myoglobinemia; can be fatal	Time: weeks–months. Can persist for days after stopping antipsychotic	DA antagonism	Stop antipsychotic immediately; supportive care; dantrolene and bromocriptine[d]
Perioral tremor ("rabbit syndrome")	Perioral tremor (may be a late variant of parkinsonism)	Time: months or years of treatment	Unknown	Anti-parkinsonian agents often help[c]
Tardive dyskinesia	Orofacial dyskinesia; rarely widespread choreoathetosis or dystonia	Time: months, years of treatment. Elderly at 5-fold greater risk. Risk ∝ potency of D_2 blockade	Postsynaptic DA receptor supersensitivity, up-regulation	Prevention crucial; treatment unsatisfactory. May be reversible with early recognition and drug discontinuation

Goodman & Gilman's, 12th Ed.

Mechanism of vomiting & targets of antiemetics



Goodman & Gilman's, 12th Ed.

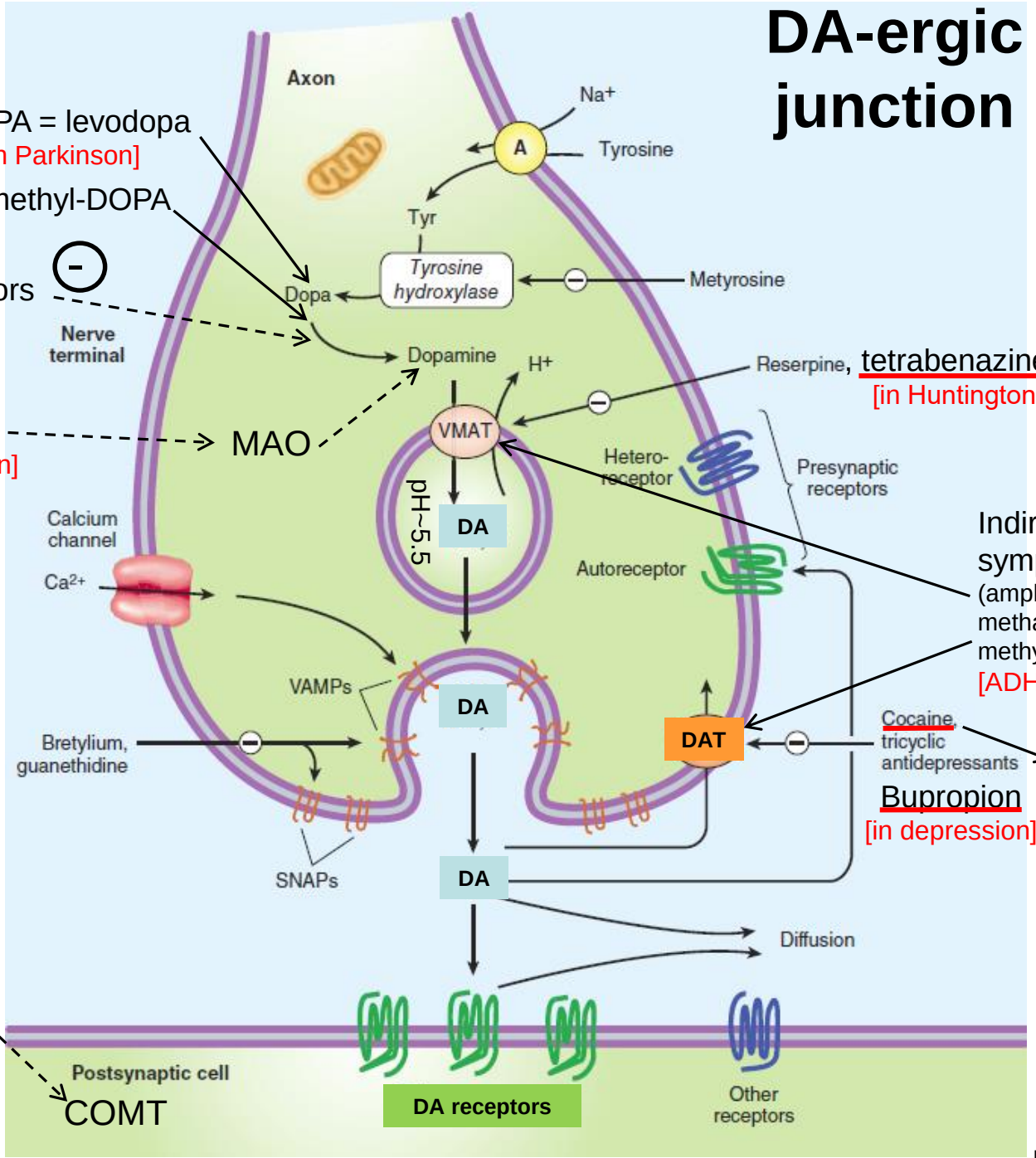
<u>Non-receptorial</u>,

***pre- & postsynaptic* modulation of**

DAergic neurotransmission

Therapeutic uses:
- **Parkinson's disease**
- **Huntington's disease**
- **ADHD**
- **Narcolepsy**
- **Depression**

DA-ergic junction



l-DOPA = levodopa
[in Parkinson]

α-methyl-DOPA

Periferal DOPA decarboxylase inhibitors
[in Parkinson]

MAO-A/BIs
[antidepressant/ in Parkinson]

MAO

Reserpine, tetrabenazine (reversible)
[in Huntington's disease]

Indirectly acting sympathomimetics
(amphetamine, methamphetamine, methylphenidate)
[ADHD, Narcolepsy]

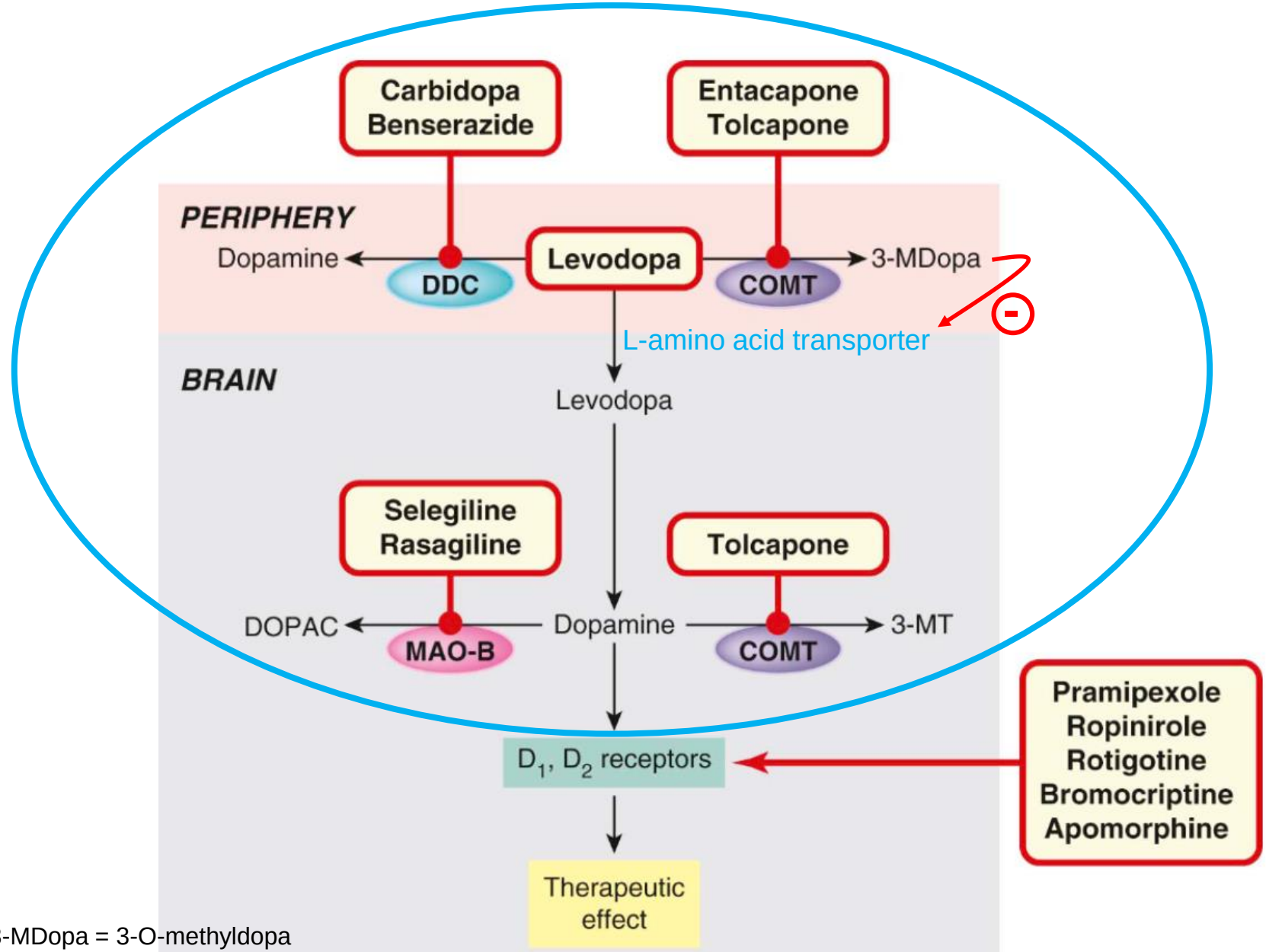
(Locomotor) activity ↑

COMTIs
[in Parkinson]

COMT

BG Katzung, 12th Ed.

Drugs used to treat Parkinson's disease



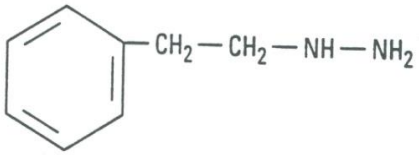
3-MDopa = 3-O-methyldopa
3-MT = 3-Methoxytyramine

Rang & Dale's, 8th Ed.

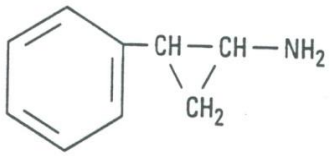
There are two types of MAO

	Substrate	*Inhibitor*
MAO-A	5-HT, NA	clorgyline moclobemide (RIMA)
MAO-B	fenilethylamine DA	selegiline
MAO-A / MAO-B	Tiramine DA	iproniazid, phenelzine, isocarboxazid

MAOIs



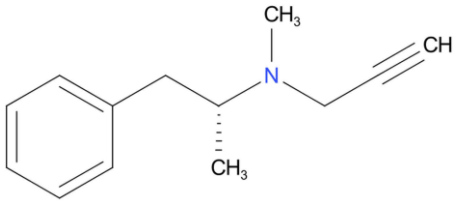
Phenelzine



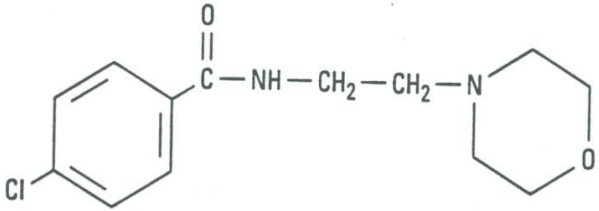
Tranylcypromine

Irreversibele,
Non-selective

Selegiline

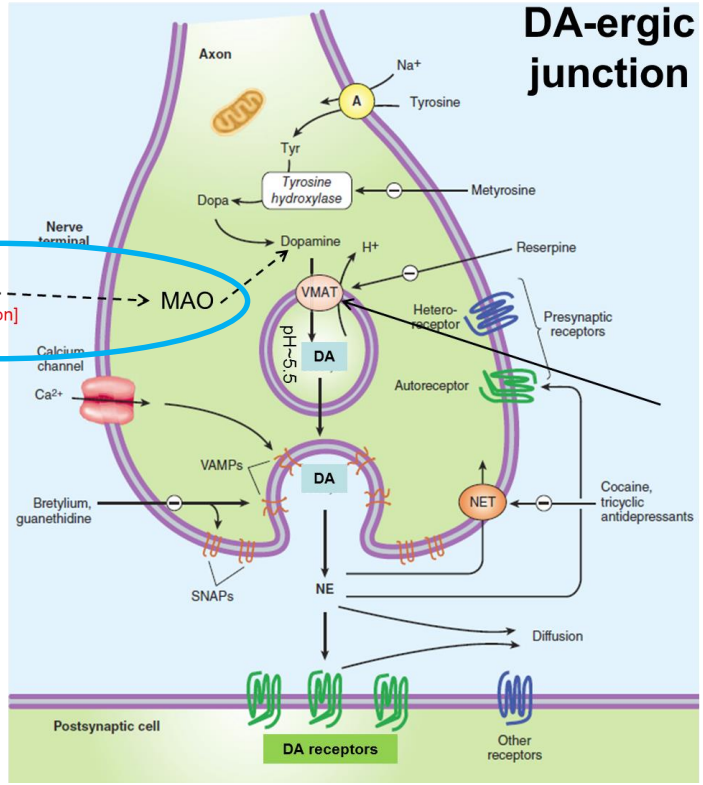


Irreversible,
MAO-B selective



Moclobemide

Reversible,
MAO-A selective (**RIMA**)



Thanks for your attention