

# Catecolaminas

# Aspectos gerais

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- Rins
- Sistema Nervoso Autônomo
- Sistema Nervoso Central

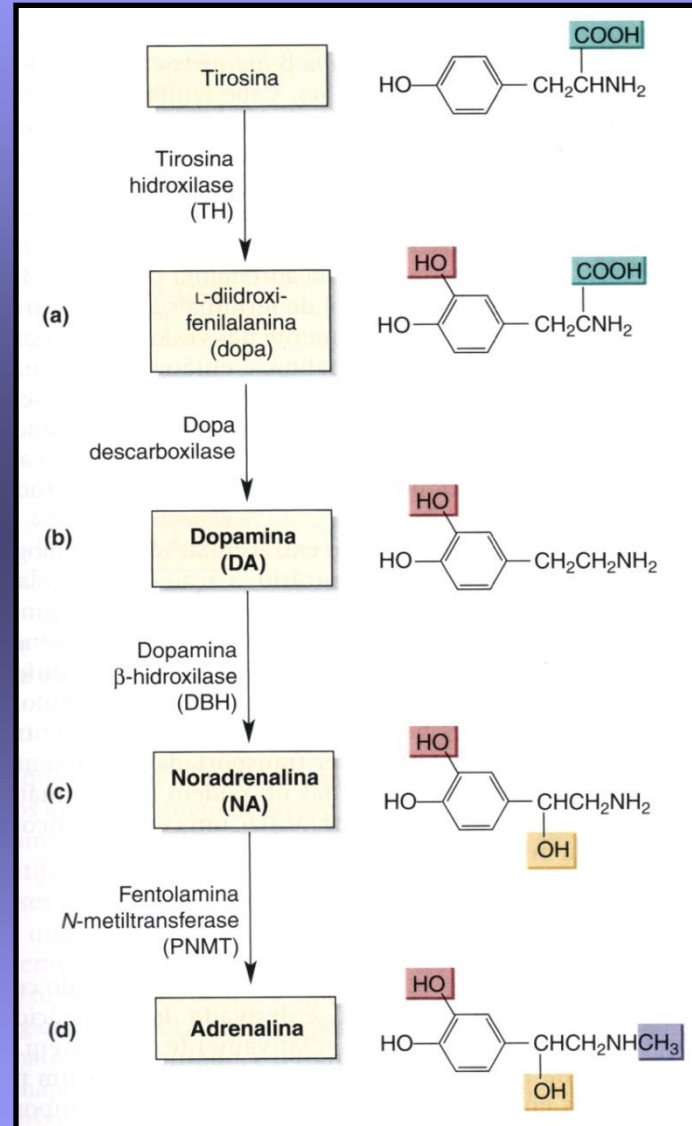
# Catecolaminas

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- ✓ Dopamina
- ✓ Noradrenalina
- ✓ Adrenalina

# Via de Síntese

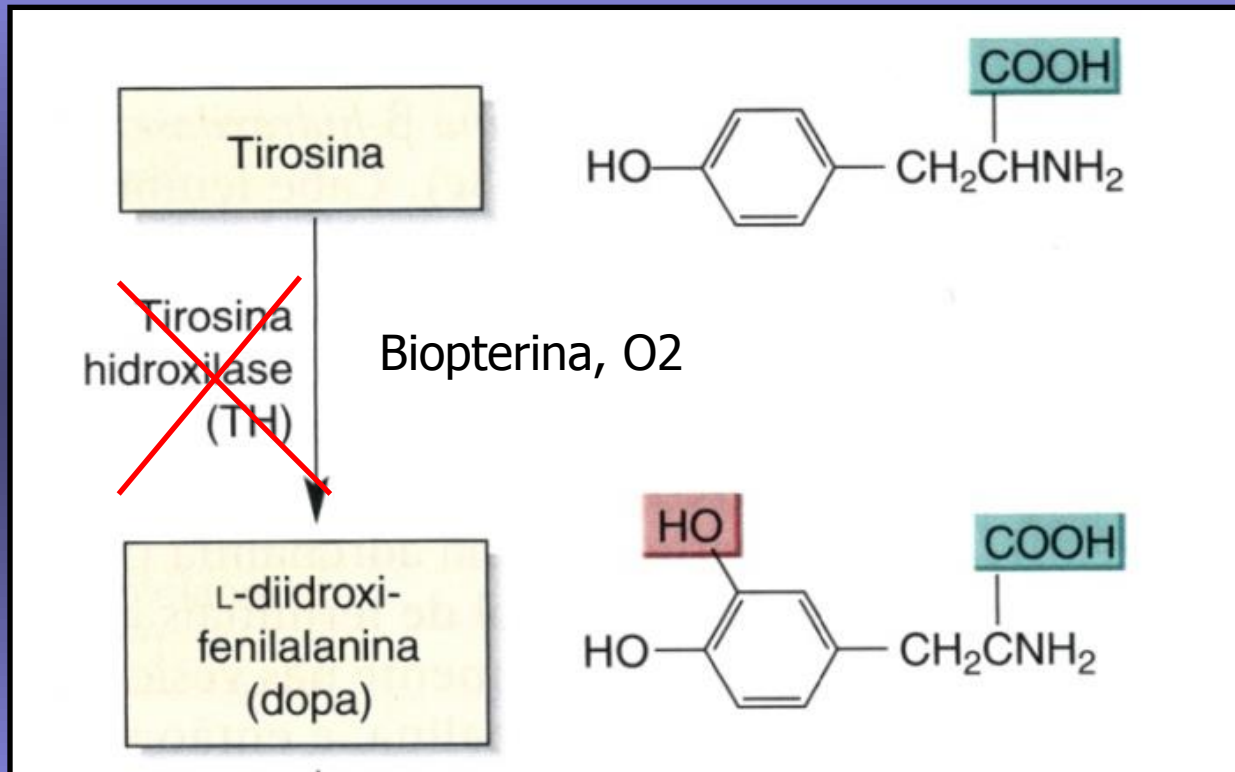
## Catecolaminas



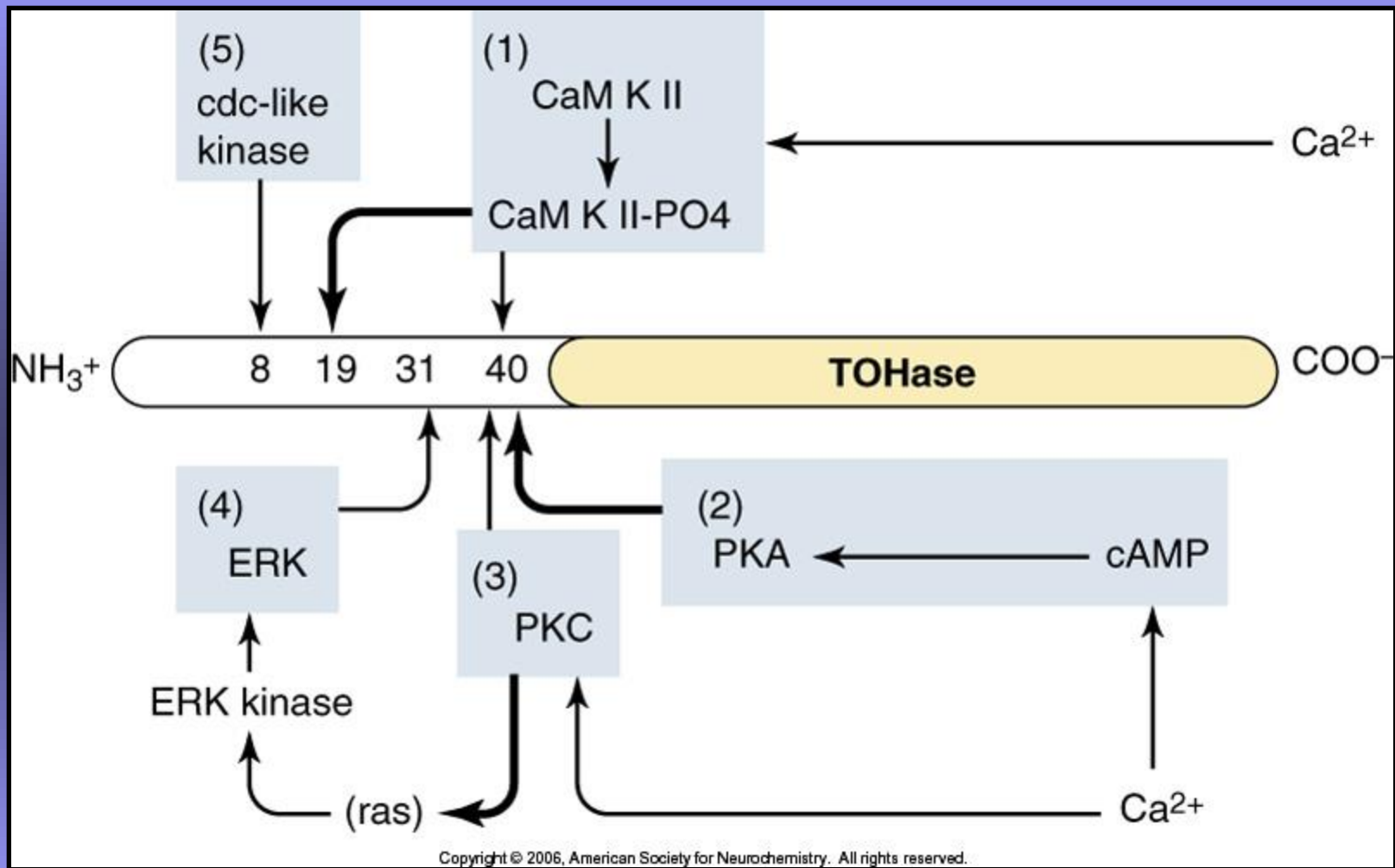
# Via de Síntese

## Tirosina Hidroxilase

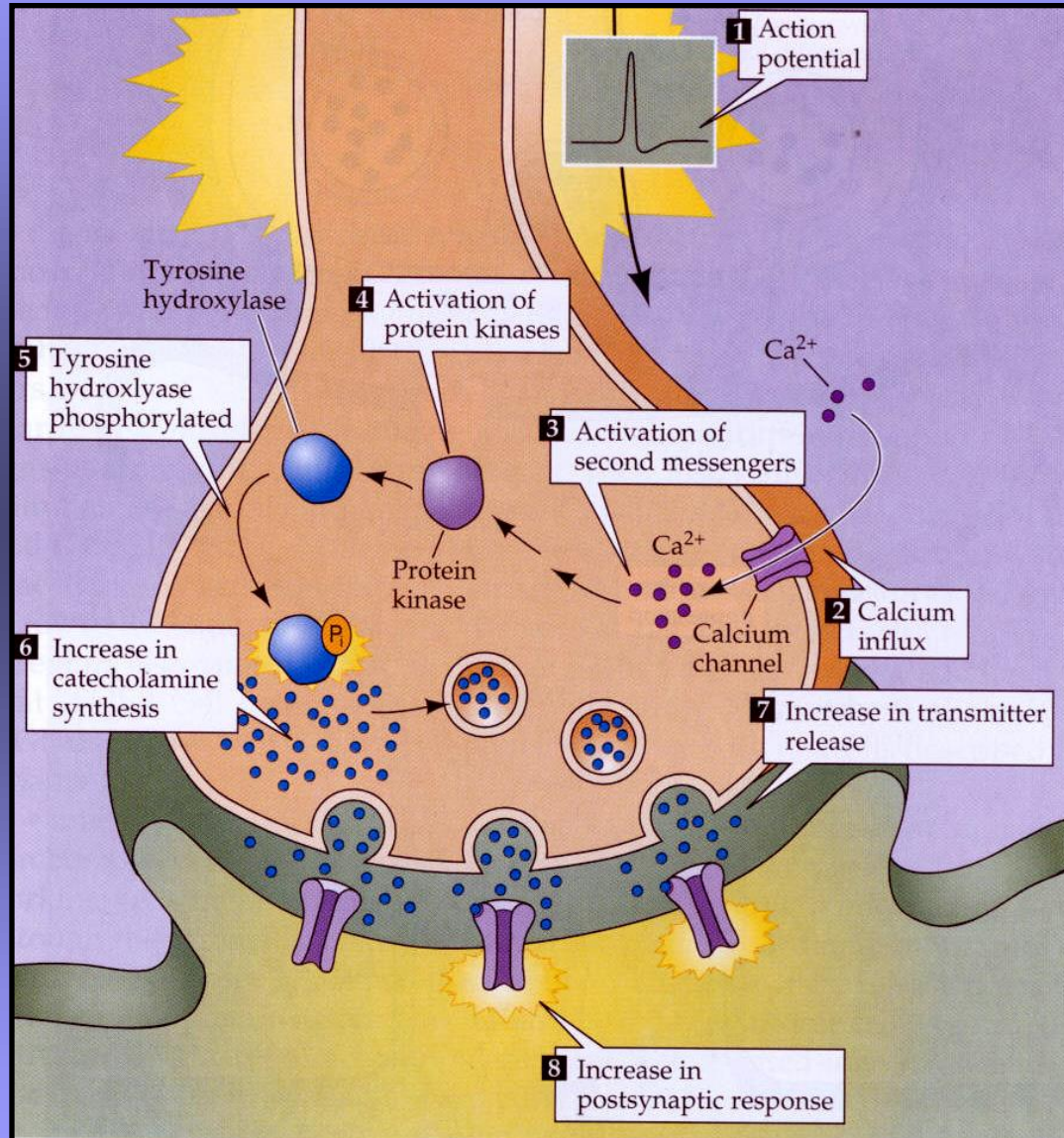
AMPT



# Tirosina Hidroxilase

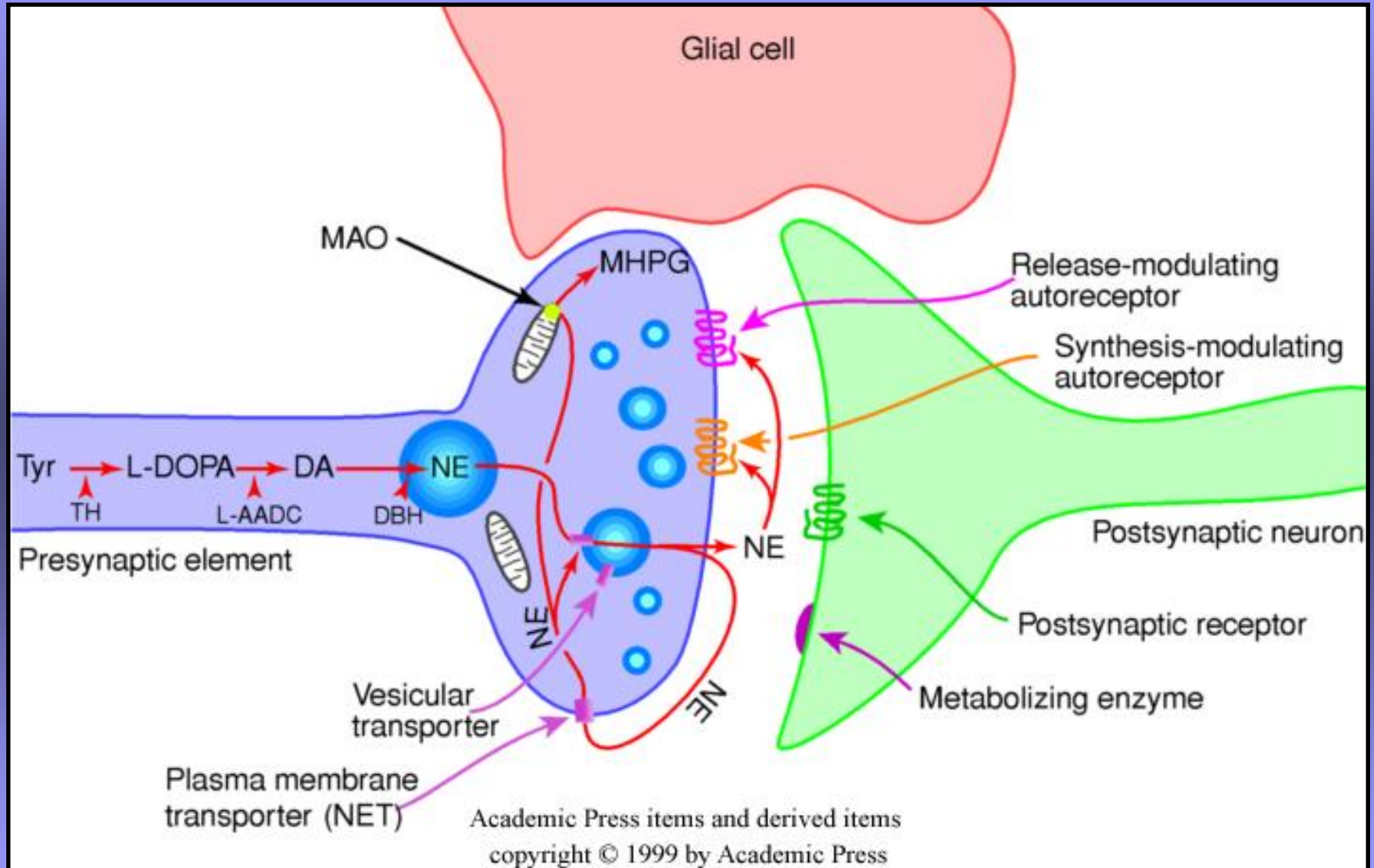


# Tirosina Hidroxilase



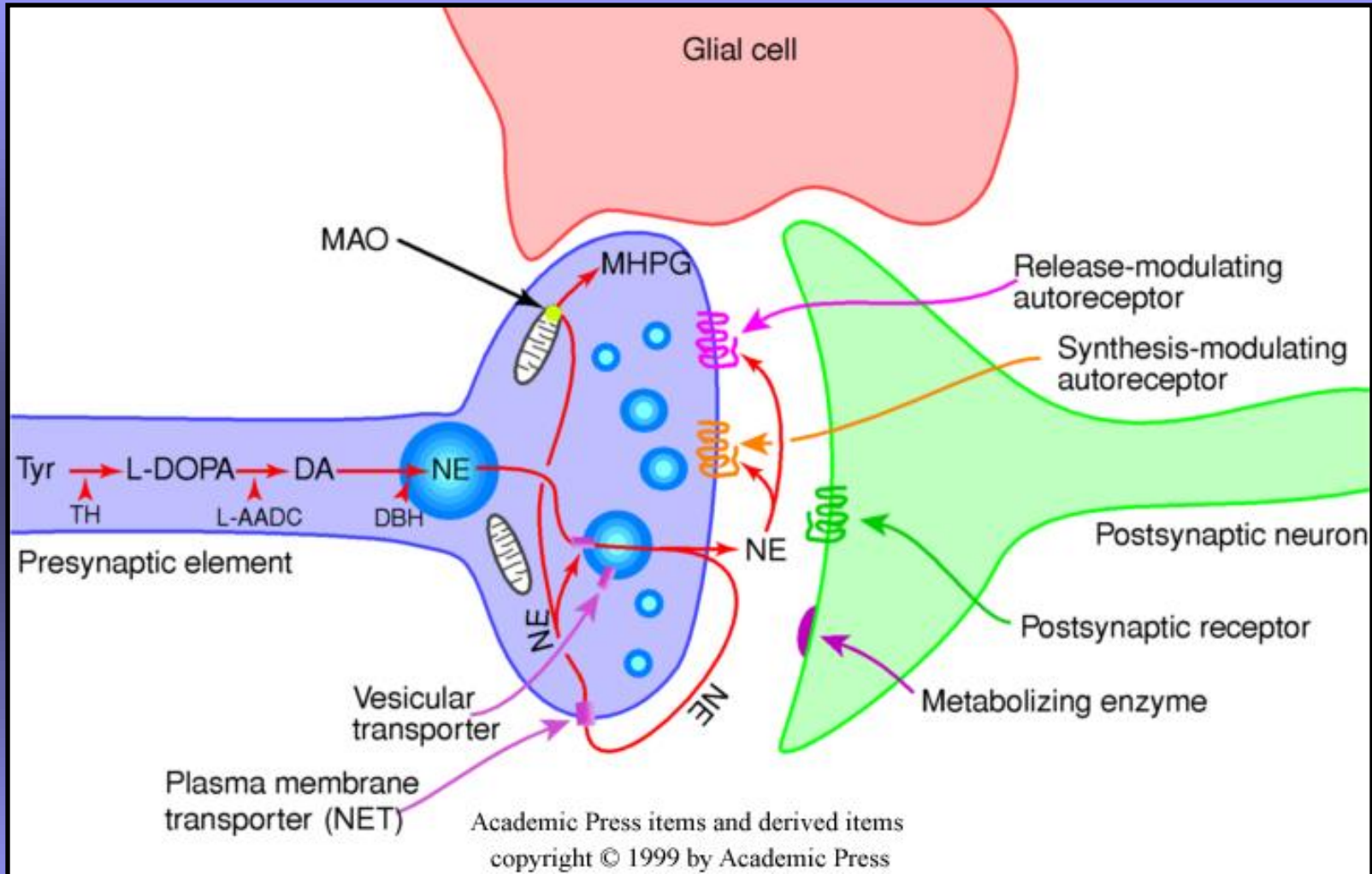


# Via de Síntese



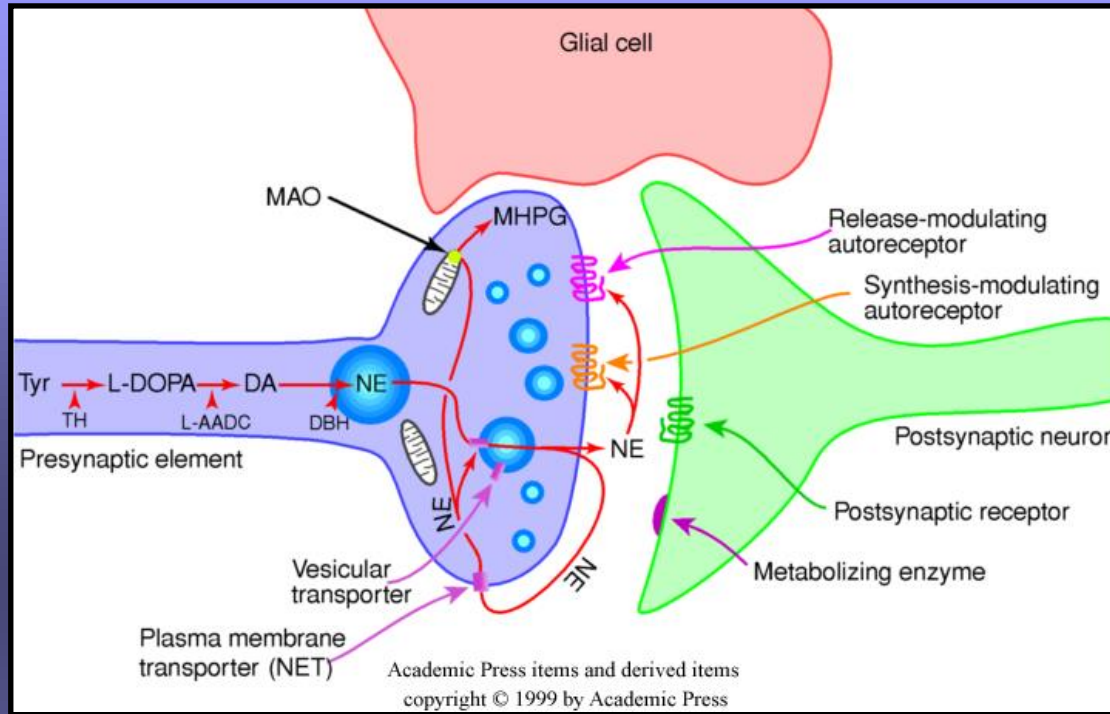


# Transportadores vesiculares de aminas (VMAT2)

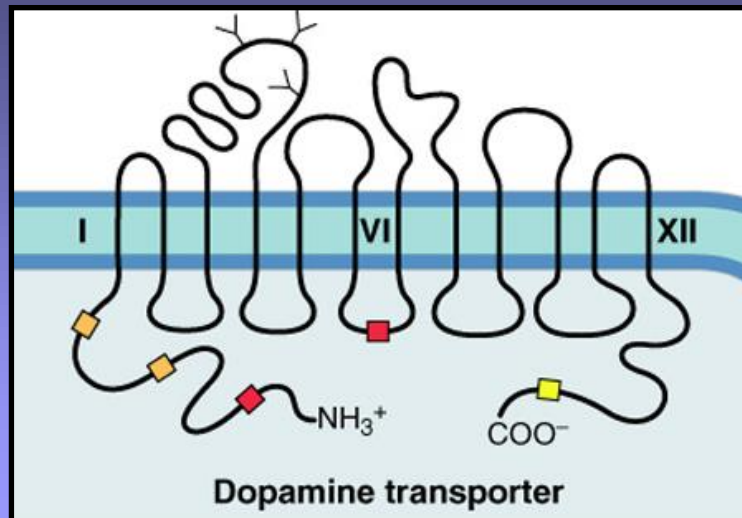


Reserpina

# Transportadores de aminas (NET e DAT)



Ouabaína  
Veratridina



# Sistema catecolaminérgico

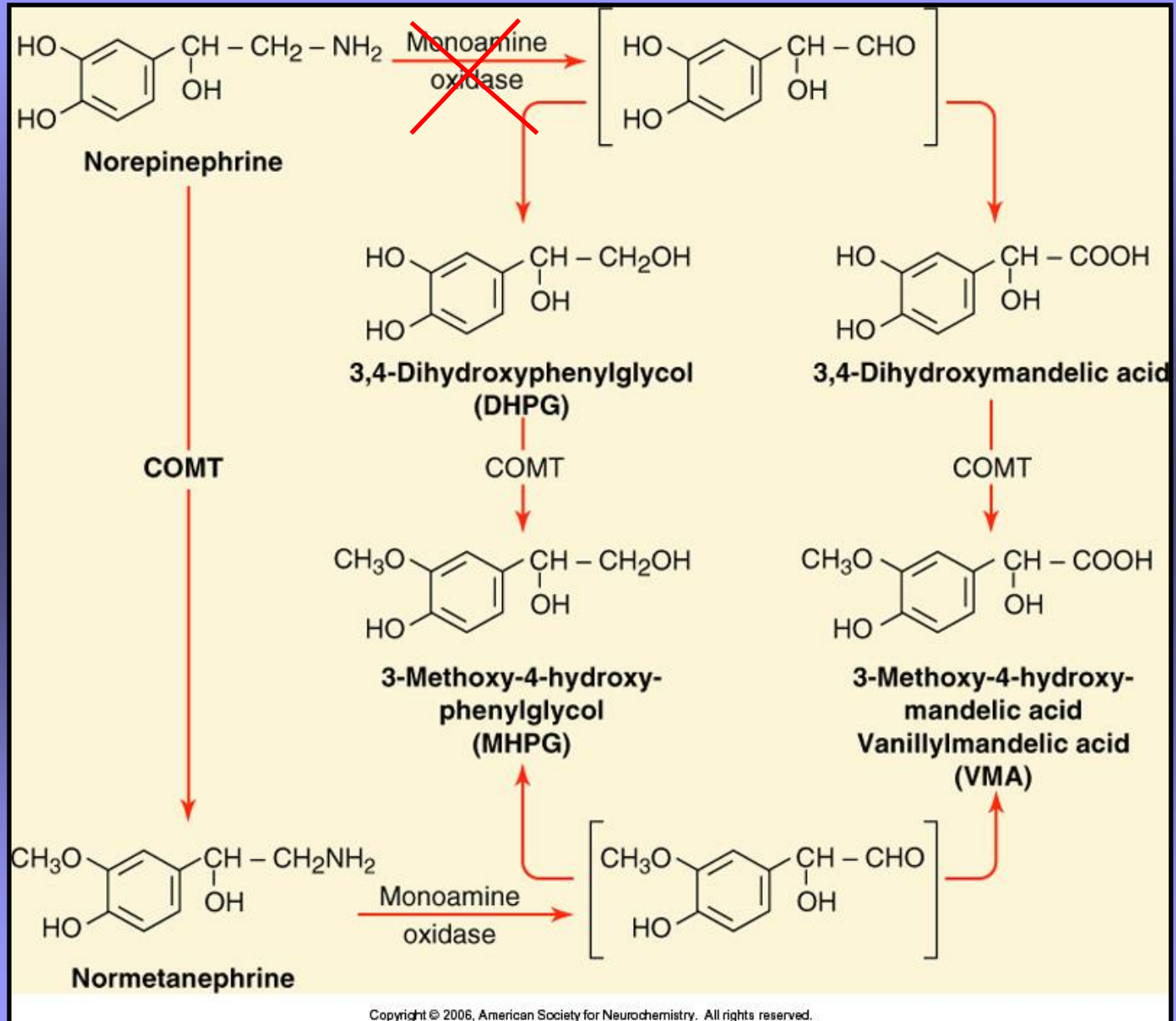
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**TABLE 12-2** Properties of amine transporters

	<b>NET</b>	<b>DAT</b>	<b>VMAT-2</b>
Mechanism	NaCl- dependent	NaCl-dependent	H <sup>+</sup> -dependent
Transmembrane segments	12	12	12
Amino acids	617	620	742
Chromosome	16	5	10
Blockers	Nisoxetine, desipramine	GBR12909, RTI- 121	Reserpine, tetrabenazine

# Via de Degradação

Clorgilina  
Deprenil



# Sistema catecolaminérgico

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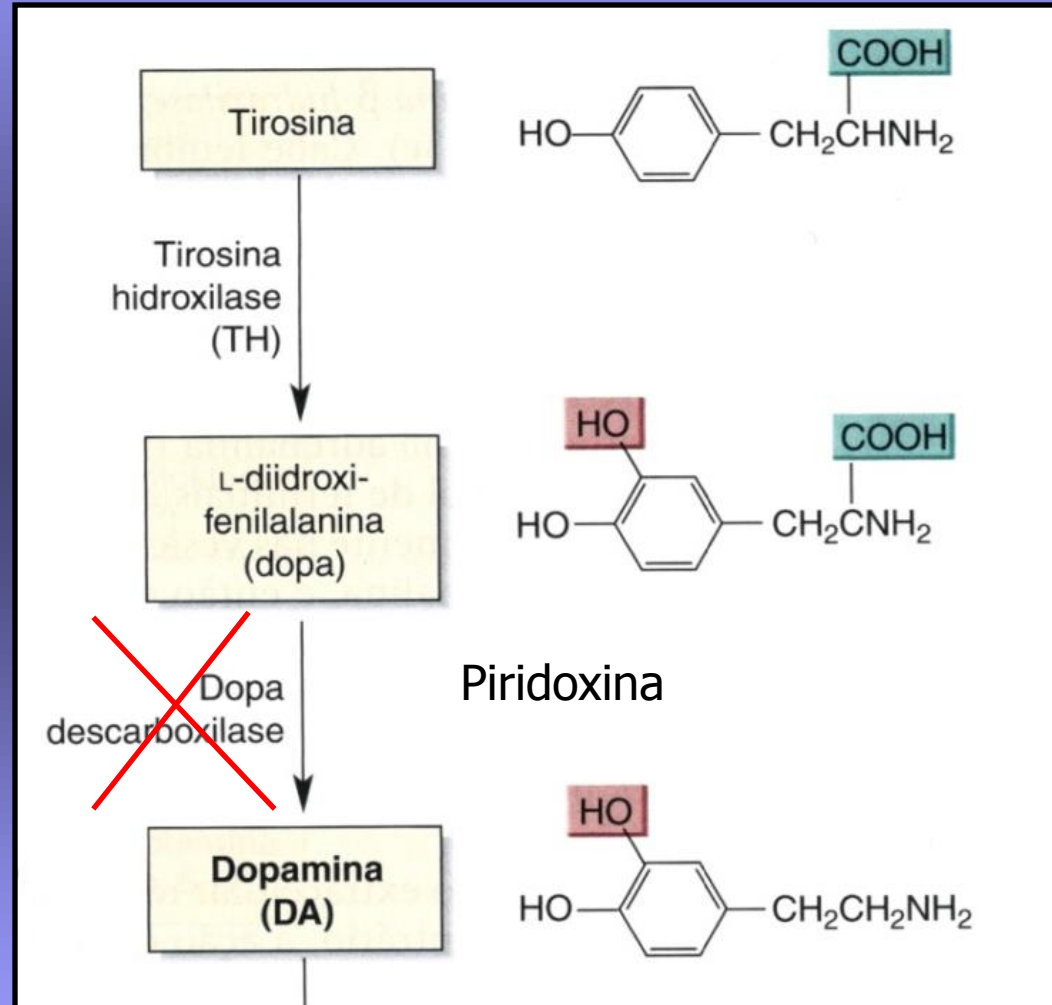
**TABLE 12-1** Studies with knockout mice

Tyrosine hydroxylase	Not viable
Dopamine beta hydroxylase	Hypersensitive to amphetamine
MAO-A	Aggressive behavior
COMT	Complex alterations in anxiety and aggression
VMAT2	Not viable
DAT	Growth retardation and hyperactivity
NET	Enhanced opiate-mediated analgesia and responses to psychostimulants

# Dopamina

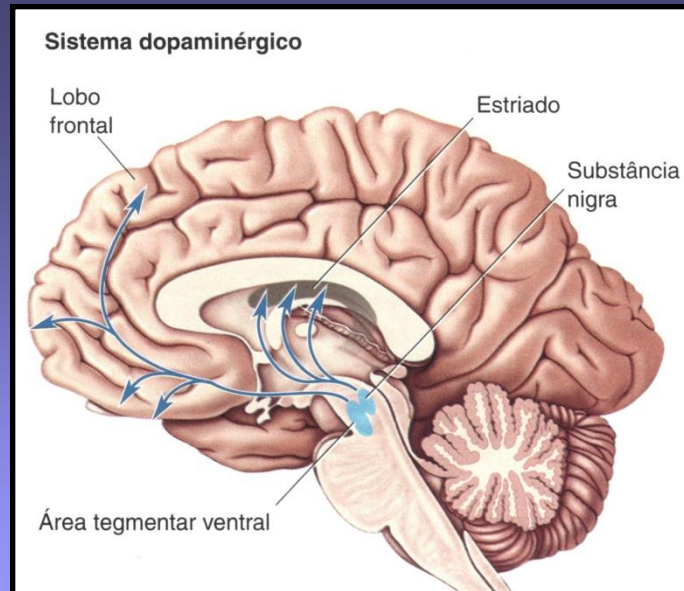
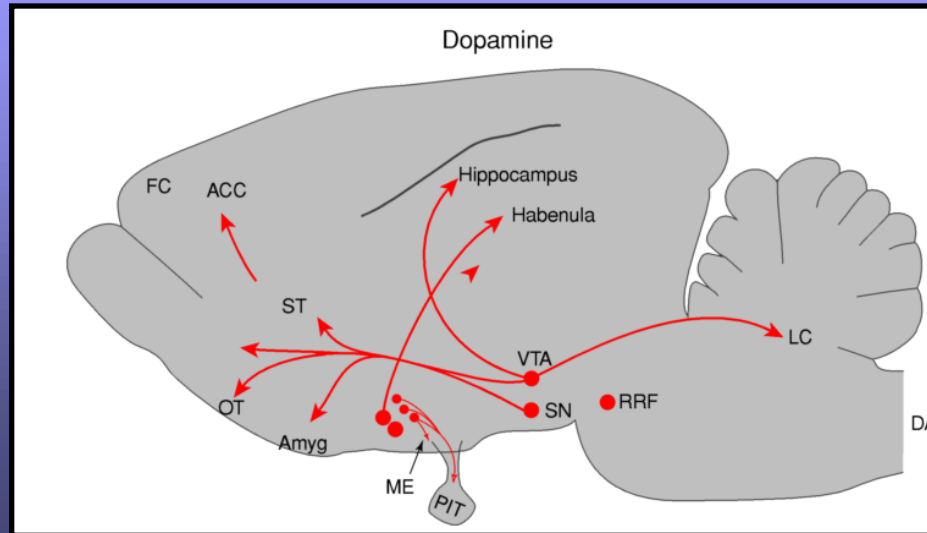
## Dopamina descarboxilase

$\alpha$ -metildopa





# Distribuição





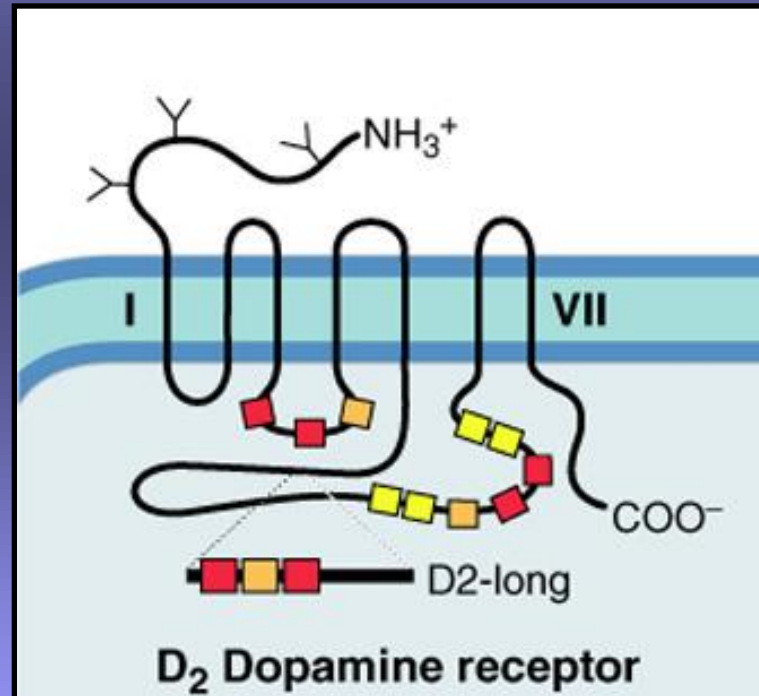
# Receptores de dopamina

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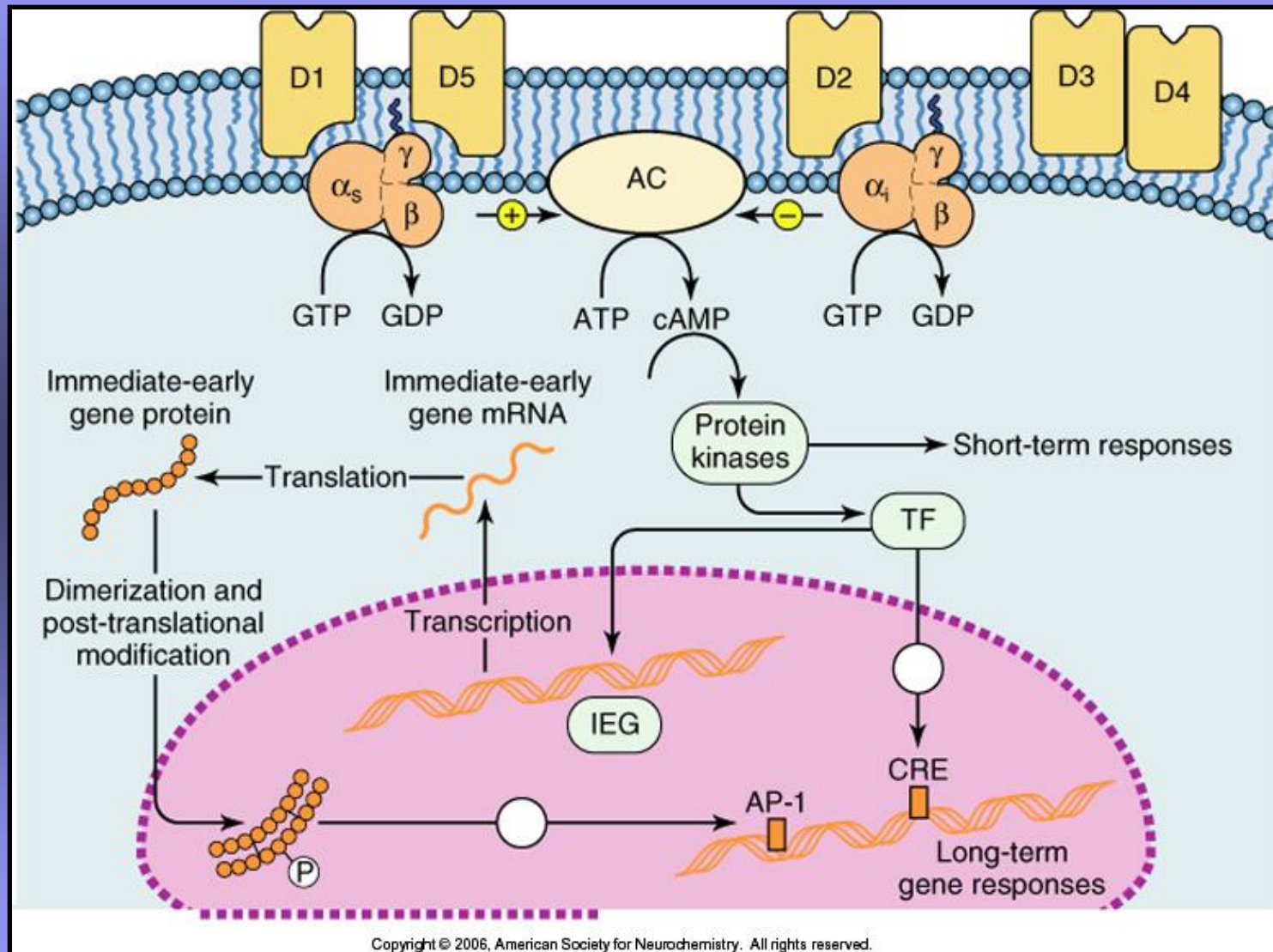
D<sub>1</sub>- like (D<sub>1</sub> e D<sub>5</sub>) - G<sub>s</sub>

5 subtipos

D<sub>2</sub>- like (D<sub>2</sub>, D<sub>3</sub> e D<sub>4</sub>) - G<sub>i</sub>



# Receptores de dopamina



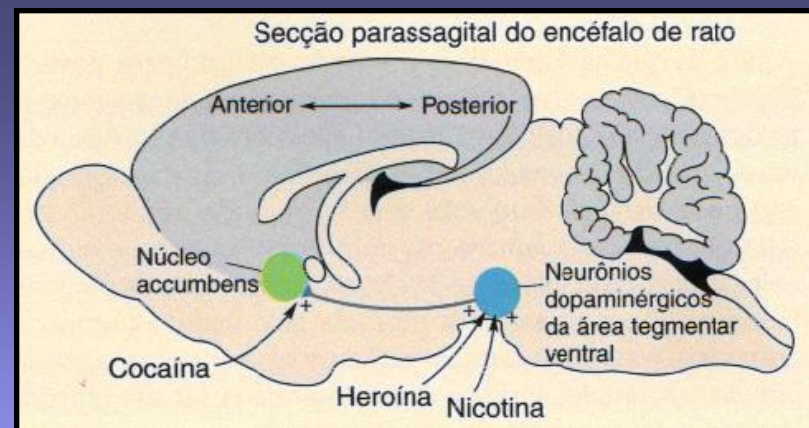
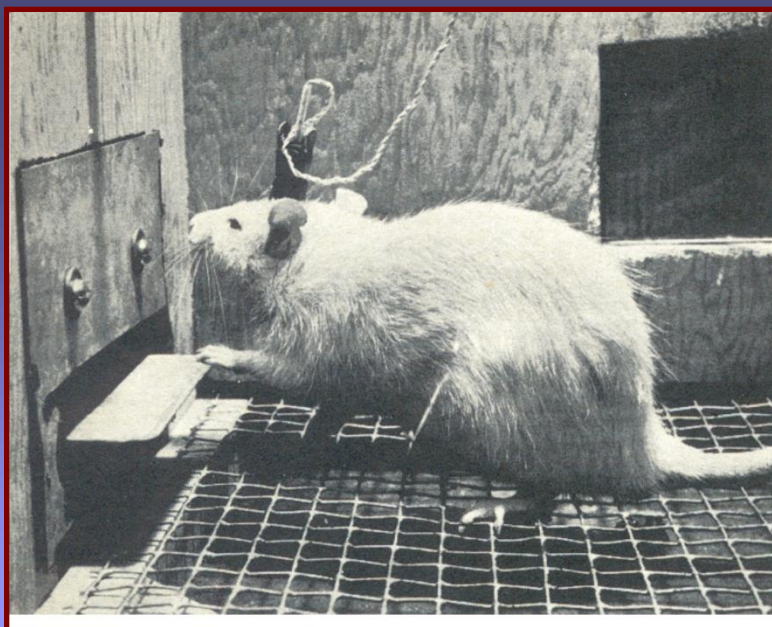
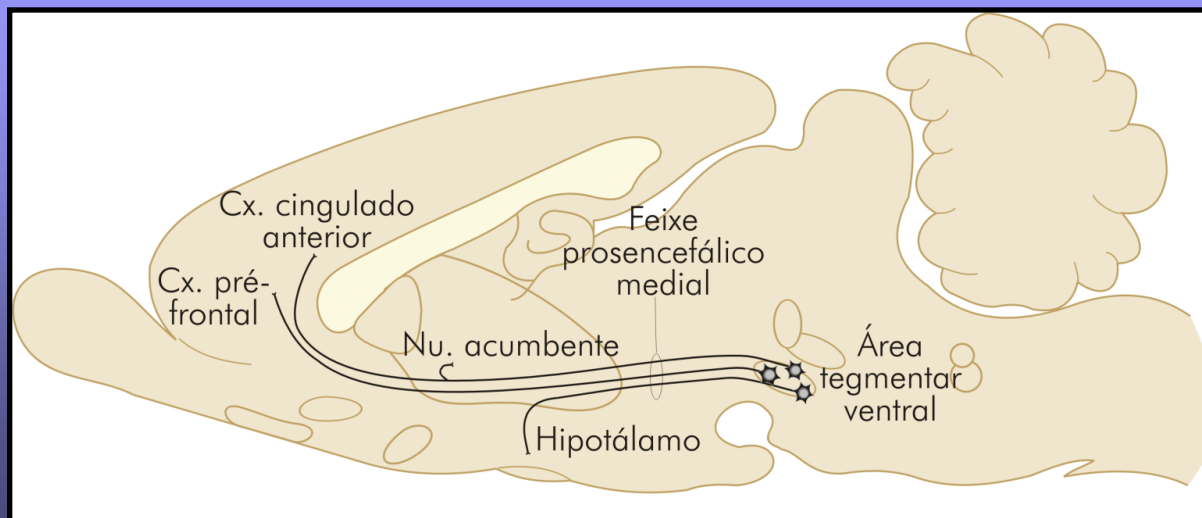
# Receptores de dopamina

**TABLE 12-3** Properties of human dopamine receptor subtypes

	<i>D<sub>1</sub>-like</i>			<i>D<sub>2</sub>-like</i>	
	<b>D<sub>1</sub></b>	<b>D<sub>5</sub></b>		<b>D<sub>2</sub></b>	<b>D<sub>3</sub></b>
Amino acids	446	477	415/444	400	387
Chromosome	5	4	11	3	11
Effector pathways	↑cAMP	↑cAMP	↓cAMP ↑K <sup>+</sup> channel ↓Ca <sup>2+</sup> channel	↓cAMP ↑K <sup>+</sup> channel ↓Ca <sup>2+</sup> channel	↓cAMP ↑K <sup>+</sup> channel ↓Ca <sup>2+</sup> channel
Distribution	Caudate/putamen, nucleus accumbens, olfactory tubercle, cerebral cortex	Hippocampus, hypothalamus, cerebral cortex	Caudate/putamen, nucleus accumbens, midbrain	Olfactory tubercle, hypothalamus,	Frontal cortex, medulla, midbrain, nucleus accumbens

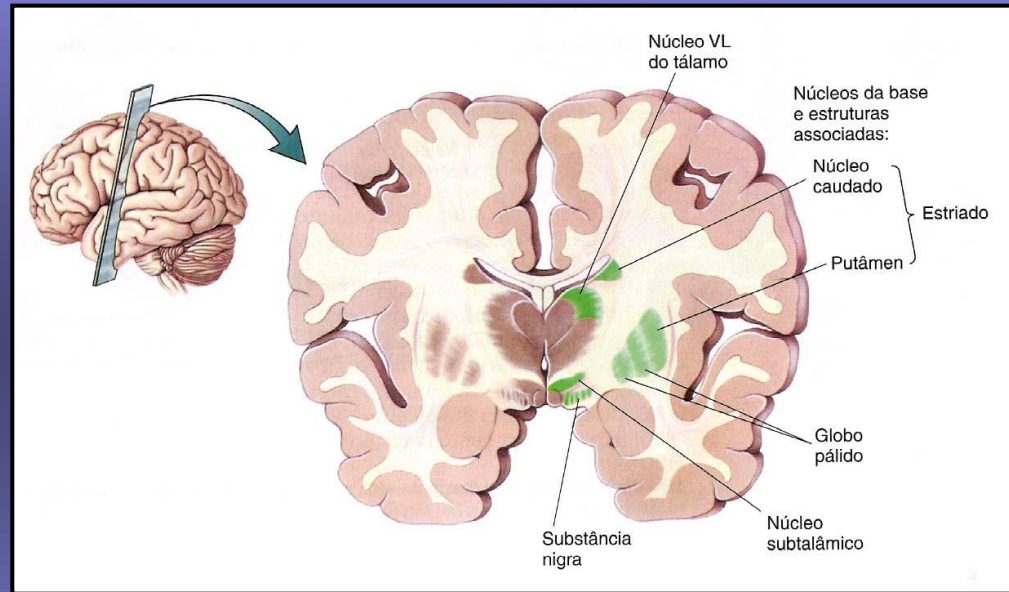
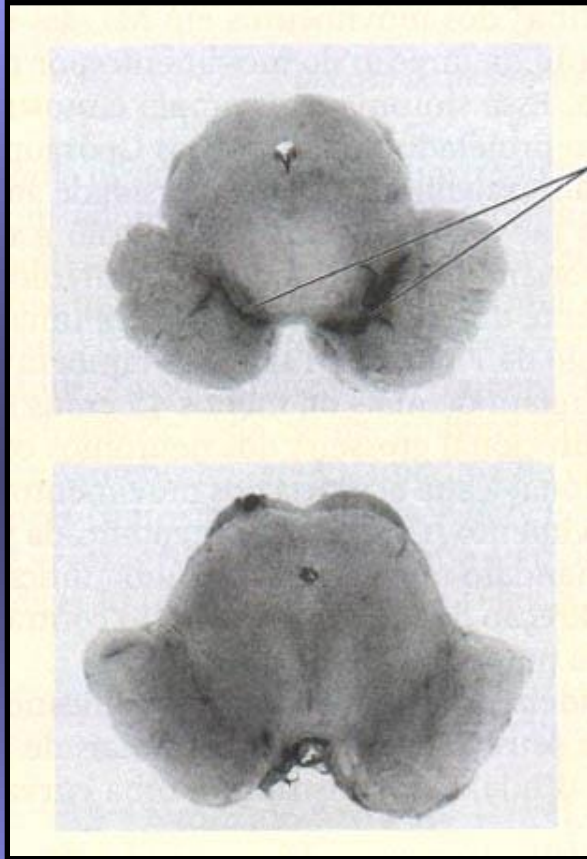
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# Dopamina e o Sistema córtico-mesolímbico

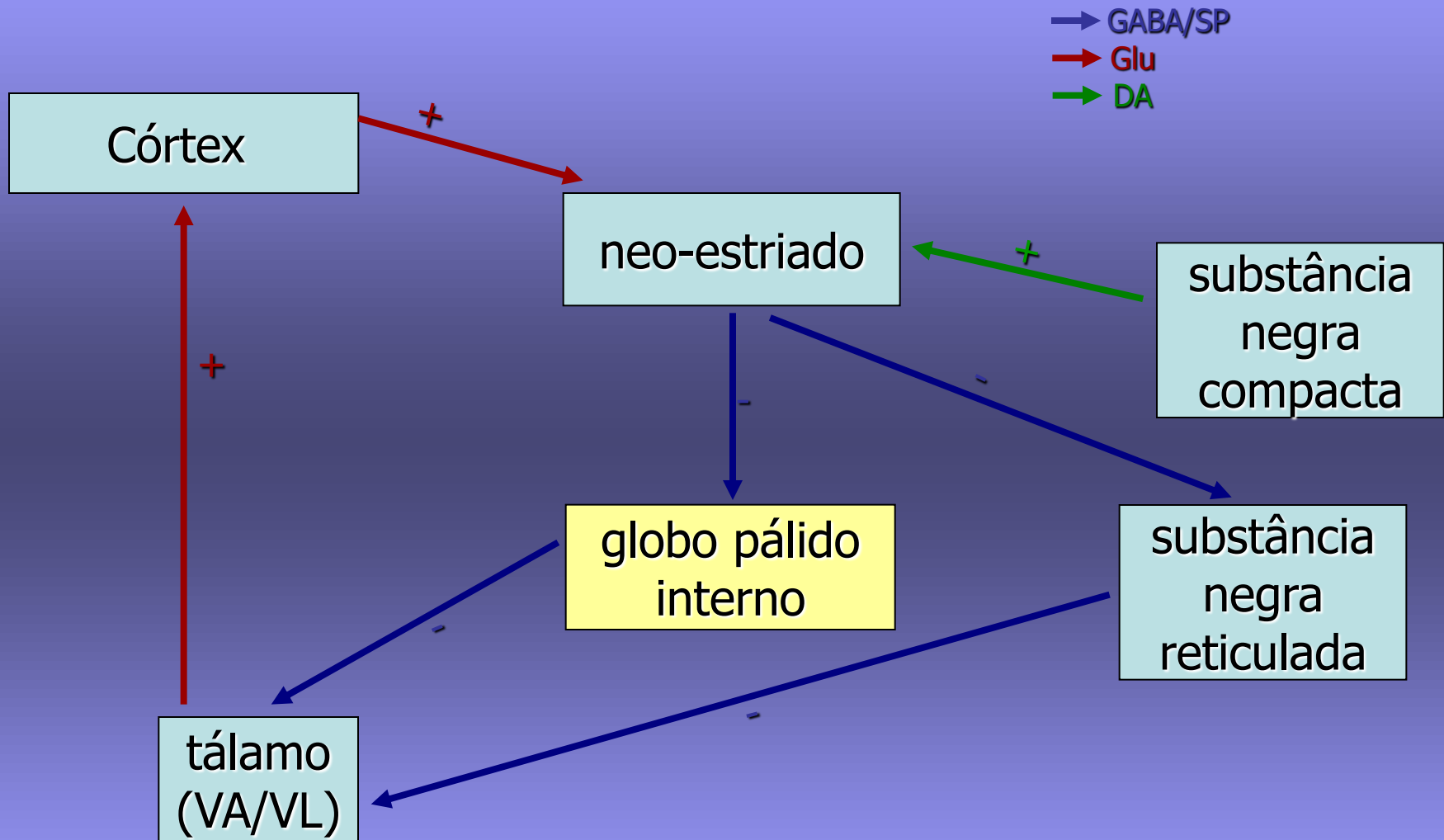




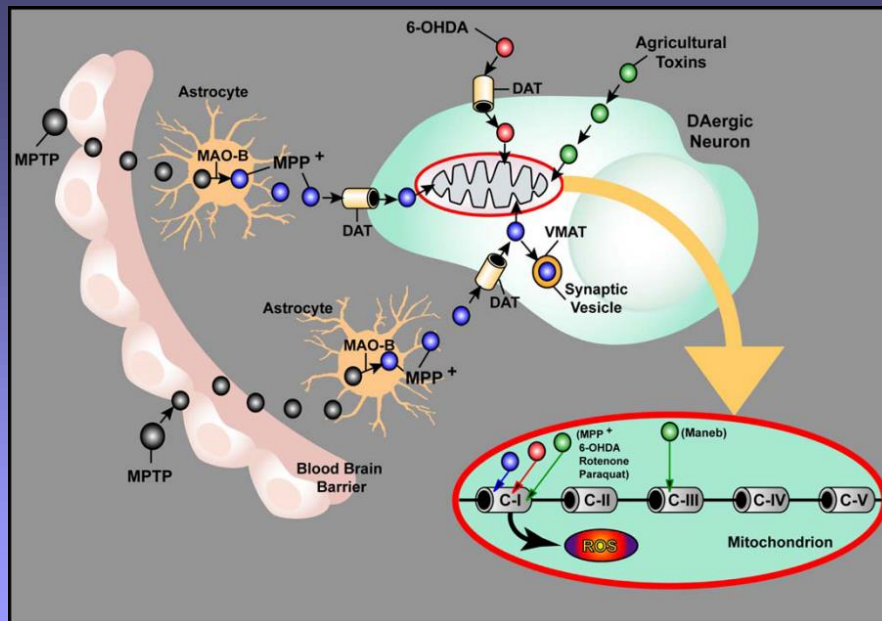
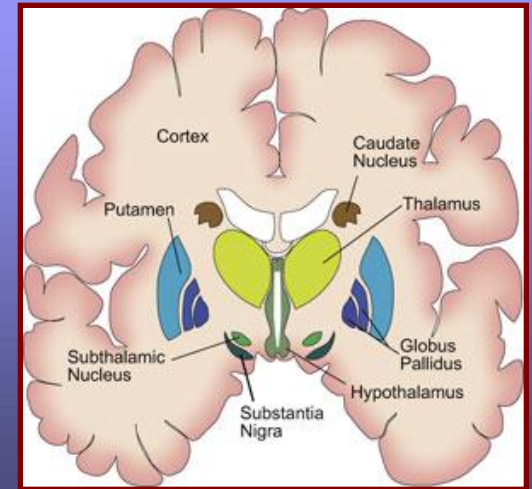
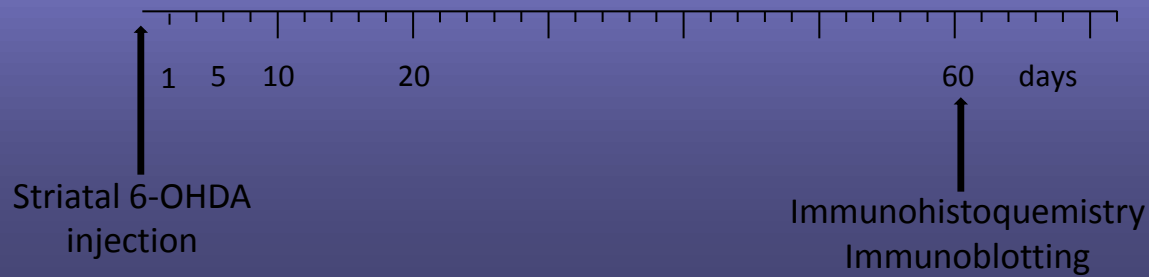
# Dopamina e a doença de Parkinson



# Dopamina e a doença de Parkinson



# Dopamina e a doença de Parkinson

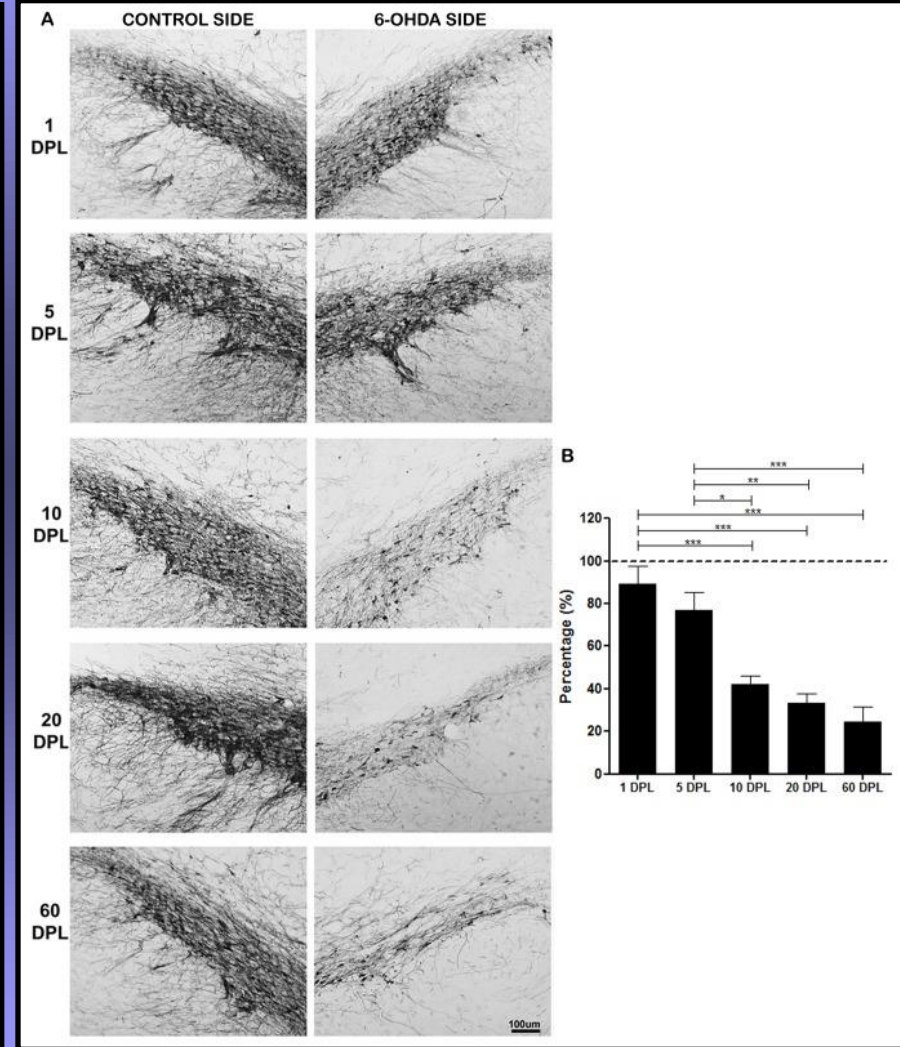
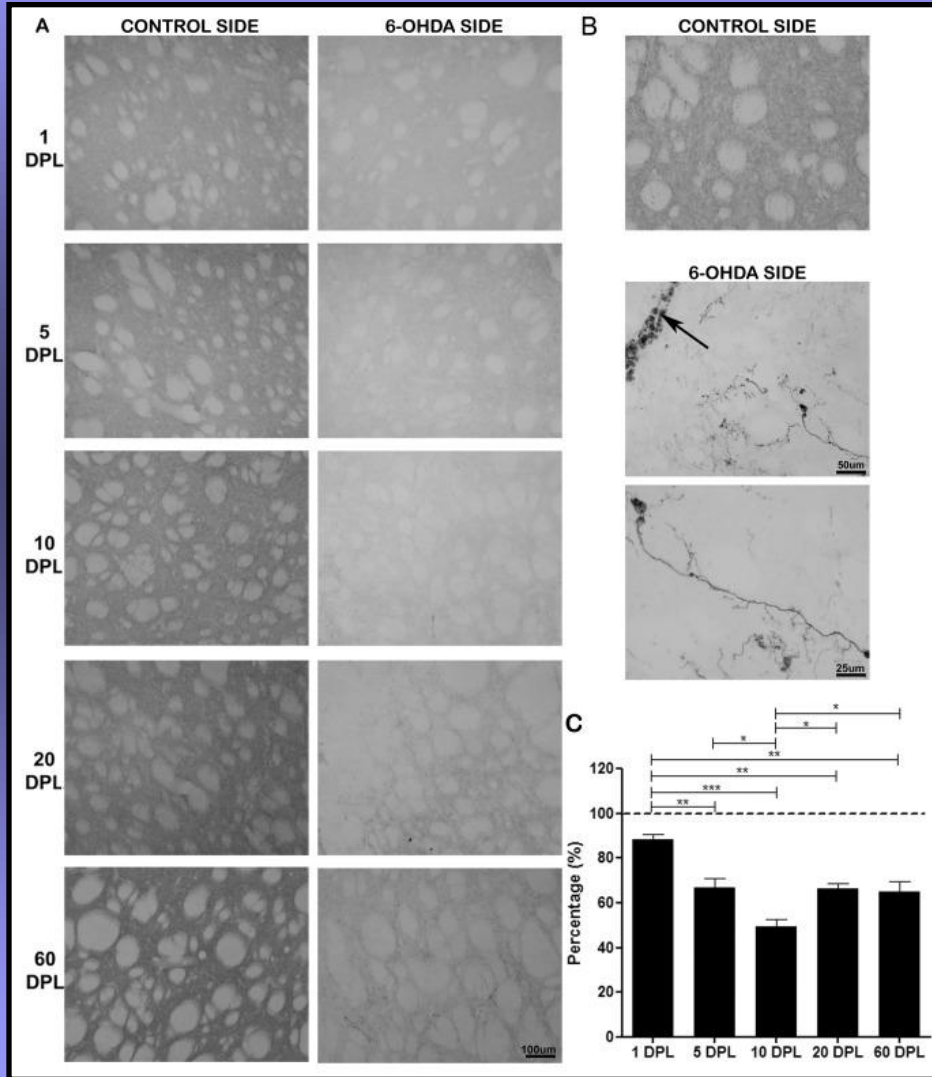


Shober, 2004; Torrão et al., 2012



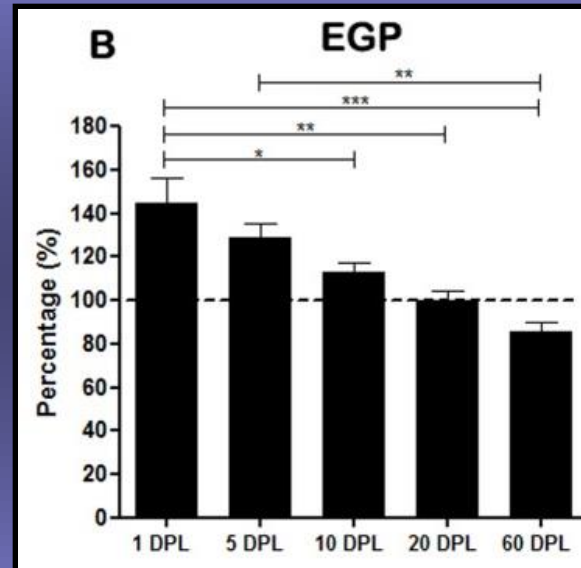
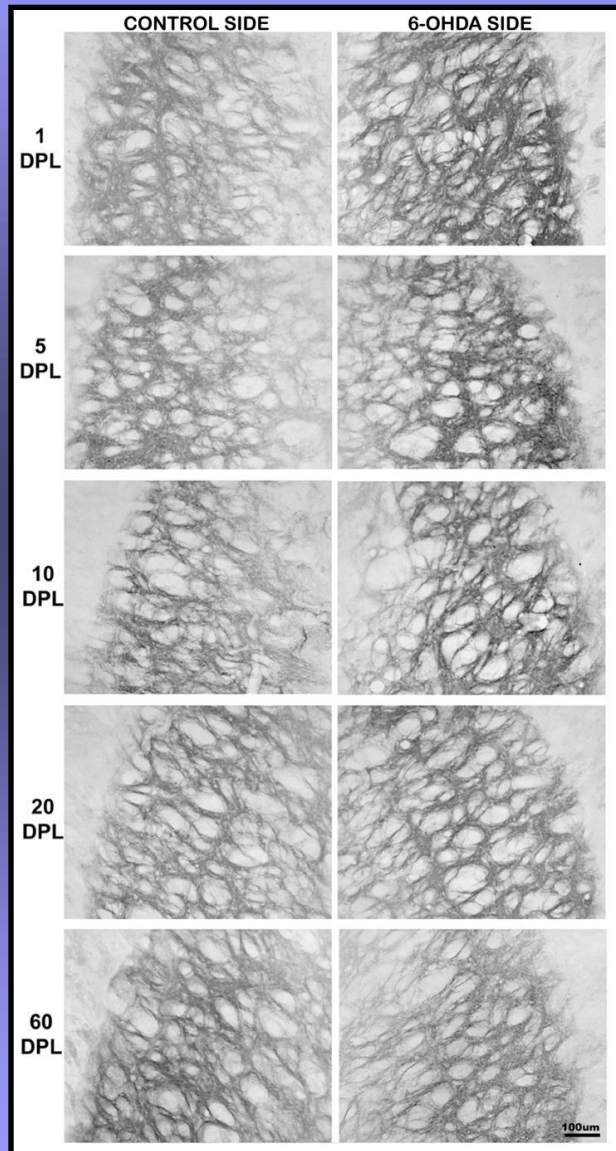
# Dopamina e a doença de Parkinson

6-OHDA PRODUCED A GRADUAL REDUCTION OF TH IN STRIATUM AND SNpc



# Dopamina e a doença de Parkinson

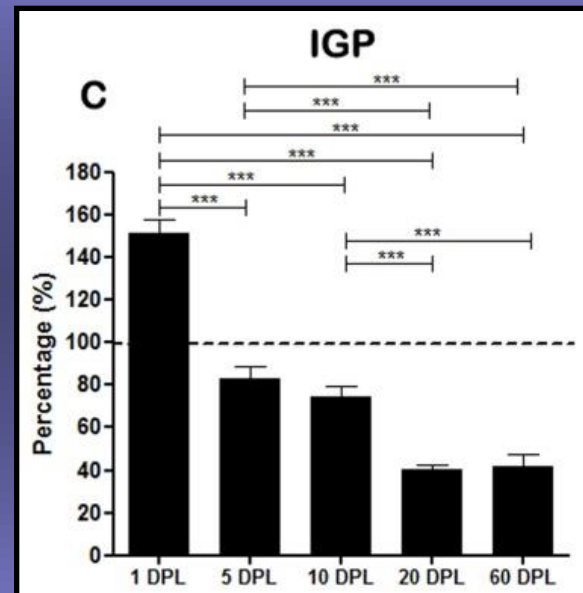
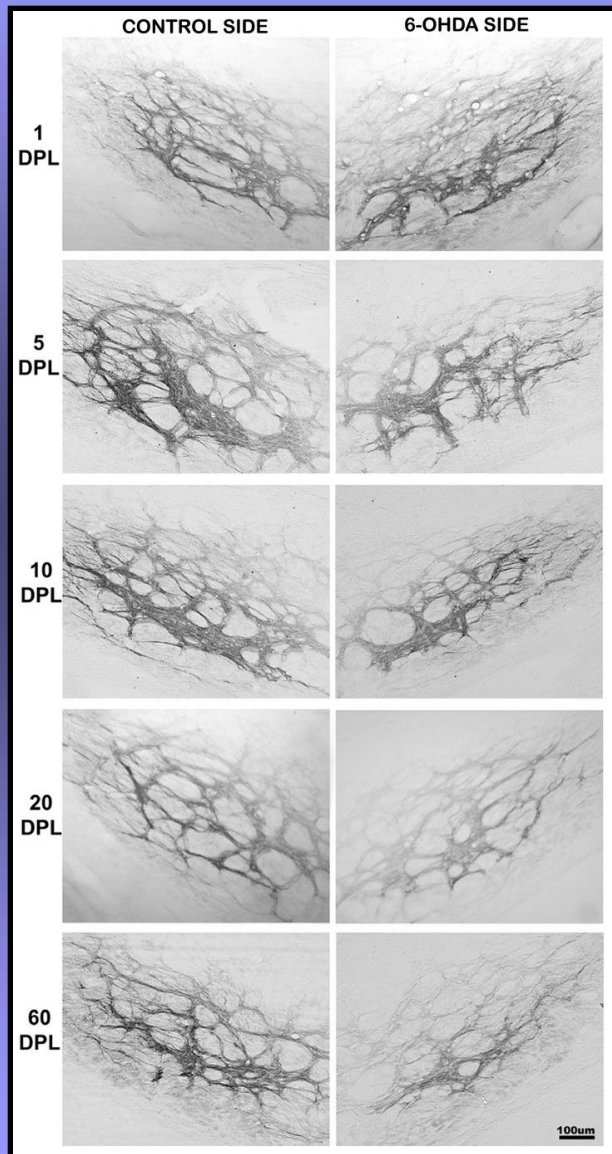
## 6-OHDA PRODUCED BIPHASIC CHANGES OF CB1 IN GLOBUS PALLIDUS



Chaves-Kirsten *et al.*, 2013

# Dopamina e a doença de Parkinson

## 6-OHDA PRODUCED BIPHASIC CHANGES OF CB1 IN GLOBUS PALLIDUS

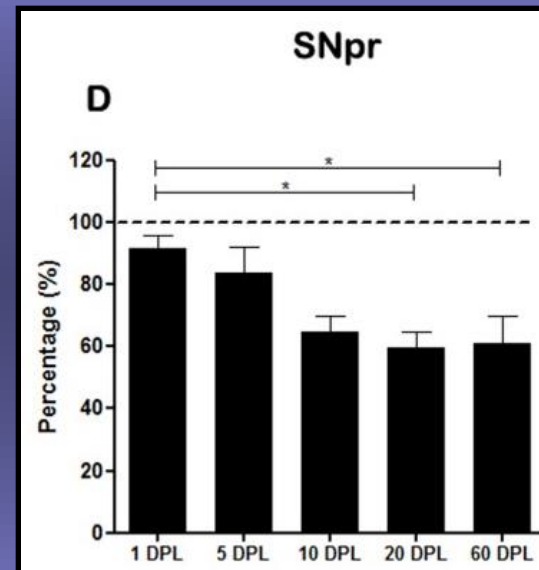
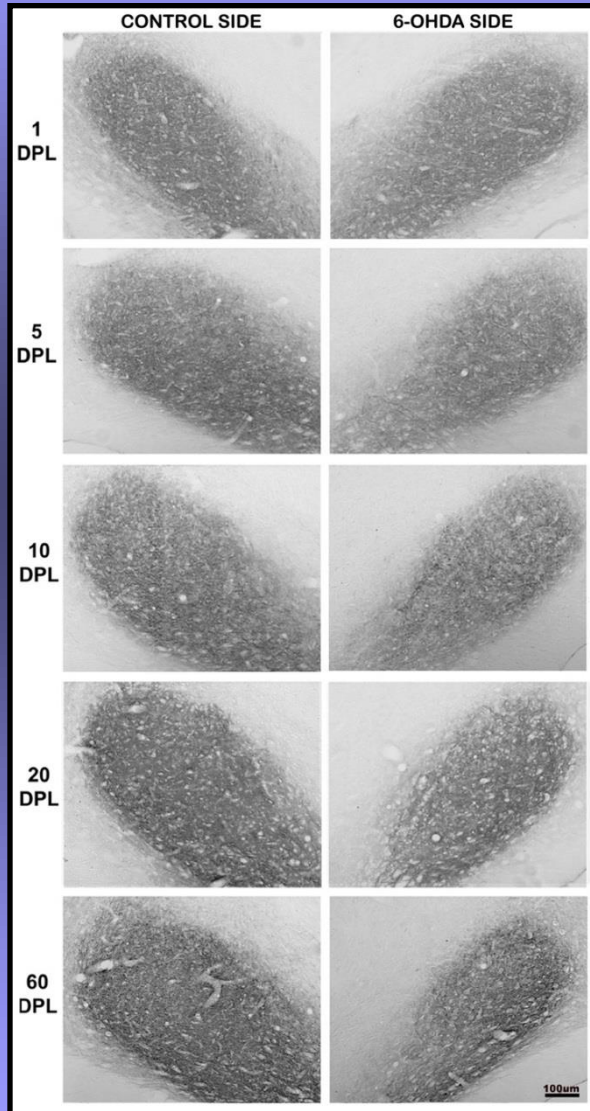


Chaves-Kirsten *et al.*, 2013



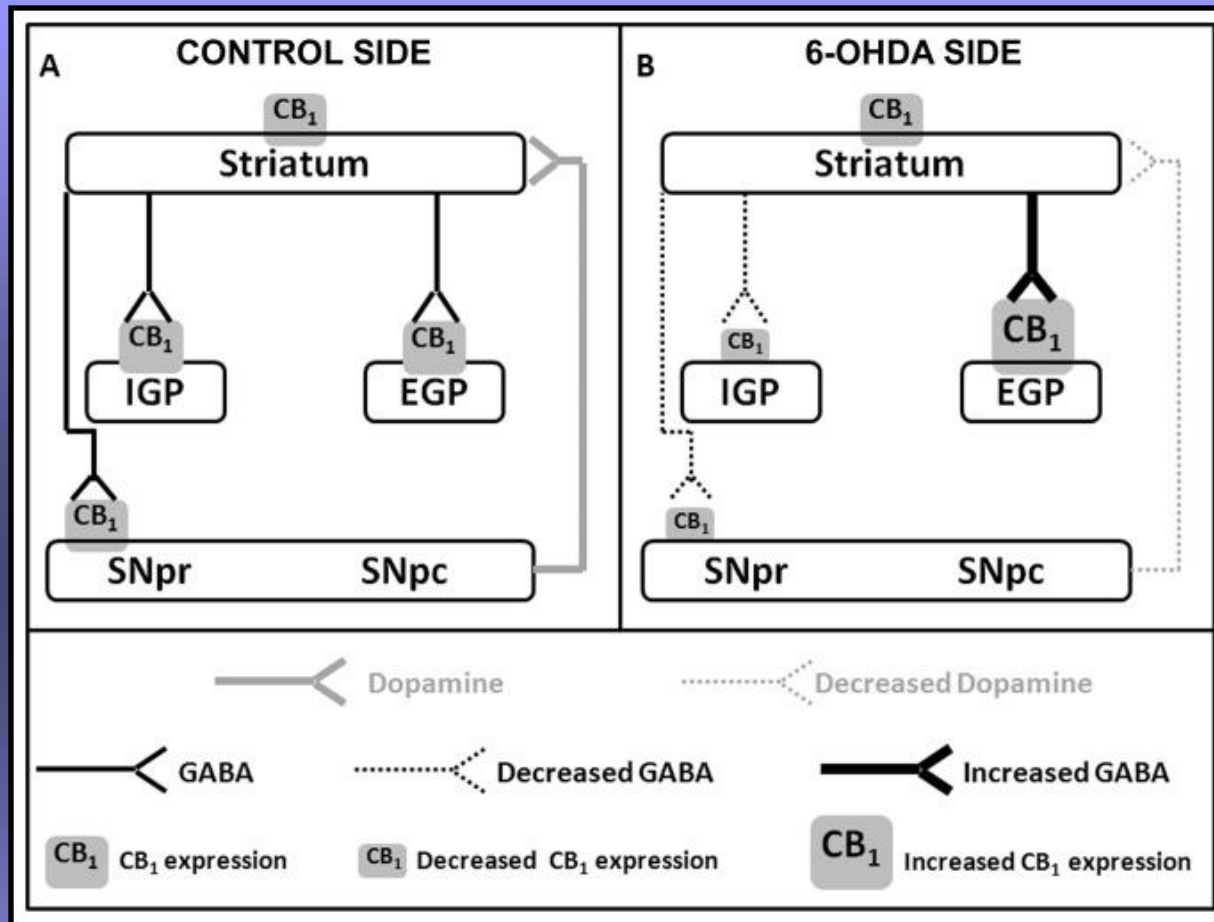
# Dopamina e a doença de Parkinson

6-OHDA PRODUCED A GRADUAL REDUCTION OF CB1 IN SN<sub>pc</sub>



Chaves-Kirsten *et al.*, 2013

# Dopamina e a doença de Parkinson



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PLOS ONE

## Temporal Changes of CB1 Cannabinoid Receptor in the Basal Ganglia as a Possible Structure-Specific Plasticity Process in 6-OHDA Lesioned Rats

Gabriela P. Chaves-Kirsten<sup>1\*</sup>, Caio H. Y. Mazucanti<sup>2</sup>, Caroline C. Real<sup>3</sup>, Bruna M. Souza<sup>1</sup>, Luiz R. G. Britto<sup>3</sup>, Andréa S. Torráo<sup>1</sup>

# Dopamina e Esquizofrenia

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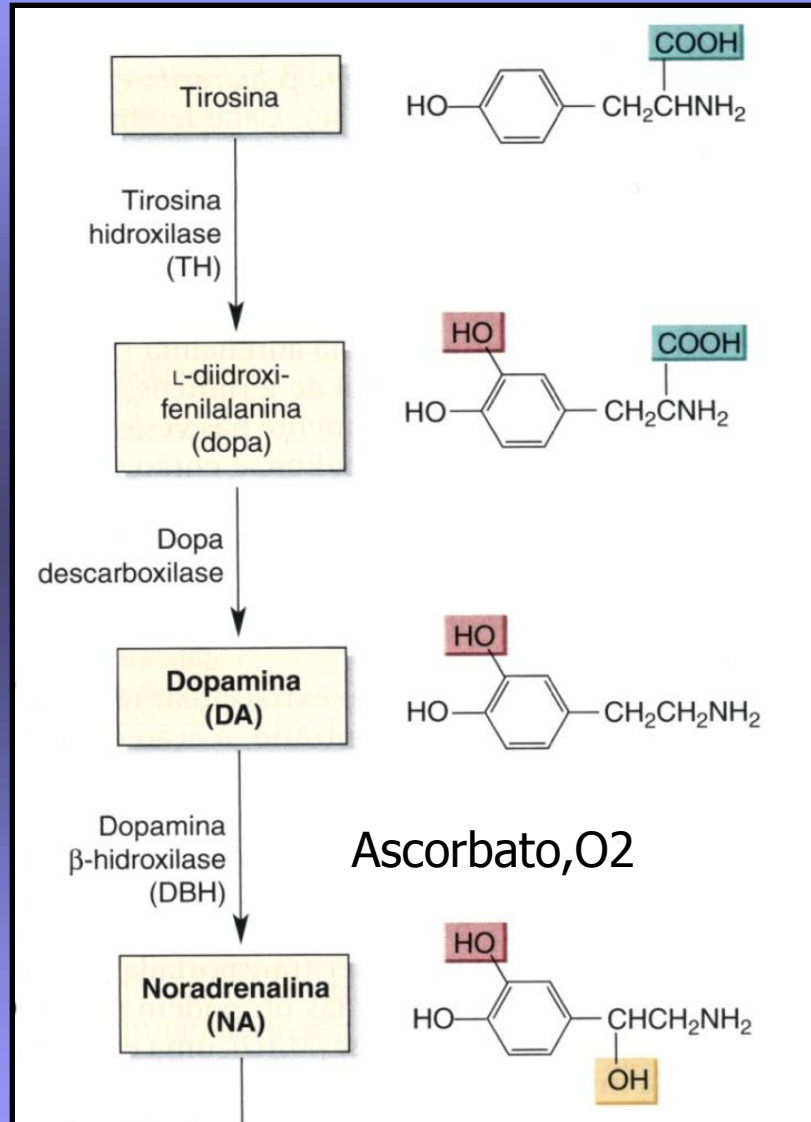
Hipótese dopaminérgica:

anfetamina ↑ DA

clorpromazina (antipsicótico)

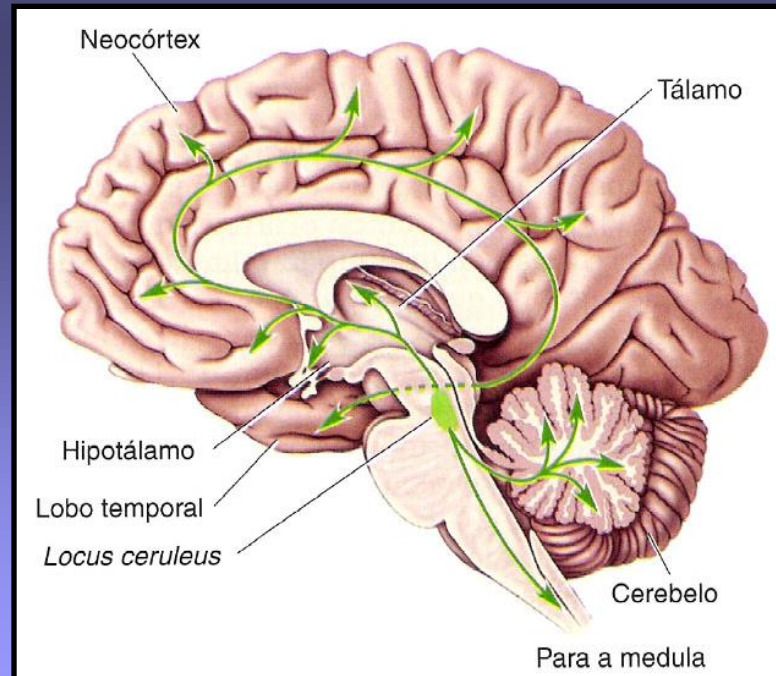
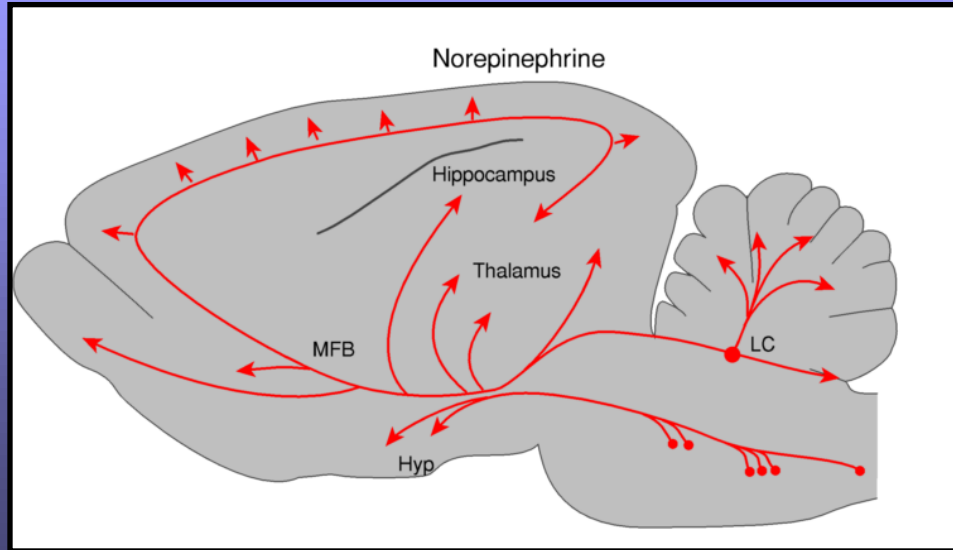
# Via de Síntese

## Dopamina $\beta$ -hidroxilase



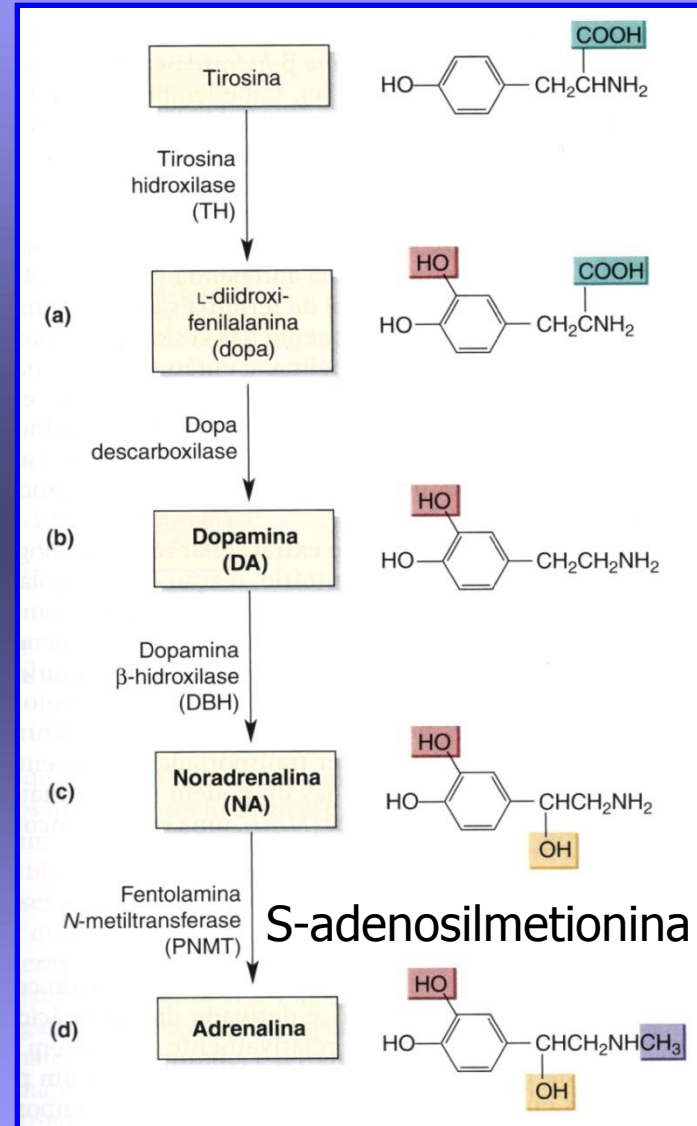


# Distribuição



# Via de Síntese

## Feniletanolamina N-metiltransferase



# Receptores de noradrenalina

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9 subtipos

$\alpha_1$  -  $G_{q/11}$  (músculo liso)

$\alpha_2$  -  $G_i$  (↓ secreção pancreática)

$\beta$  -  $G_s$  (coração e brônquios)

# Receptores de noradrenalina

**TABLE 12-4** Properties of human  $\alpha_1$ -adrenergic receptor subtypes

	$\alpha_{1A}$	$\alpha_{1B}$	$\alpha_{1D}$
Amino acids	430–476	515	560
Chromosome	8	5	20
Effector pathways	$\uparrow$ Ca <sup>2+</sup> , protein kinase C	$\uparrow$ Ca <sup>2+</sup> , protein kinase C	$\uparrow$ Ca <sup>2+</sup> , protein kinase C
Distribution	Heart, liver, cerebellum, cerebral cortex, blood vessels	Spleen, kidney, fetal brain, blood vessels	Aorta, cerebral cortex

Modified with permission from references [35, 57].

# Receptores de noradrenalina

**TABLE 12-5** Properties of human  $\alpha_2$ -adrenergic receptor subtypes

	$\alpha_{2A}$	$\alpha_{2B}$	$\alpha_{2C}$
Amino acids	450	450	461
Chromosome	10	2	4
Effector pathways	$\downarrow$ cAMP	$\downarrow$ cAMP	$\downarrow$ cAMP
Distribution	Pancreas, small intestine, locus ceruleus, hippocampus	Liver, thalamus	Heart, lung, aorta, hippocampus, olfactory bulb

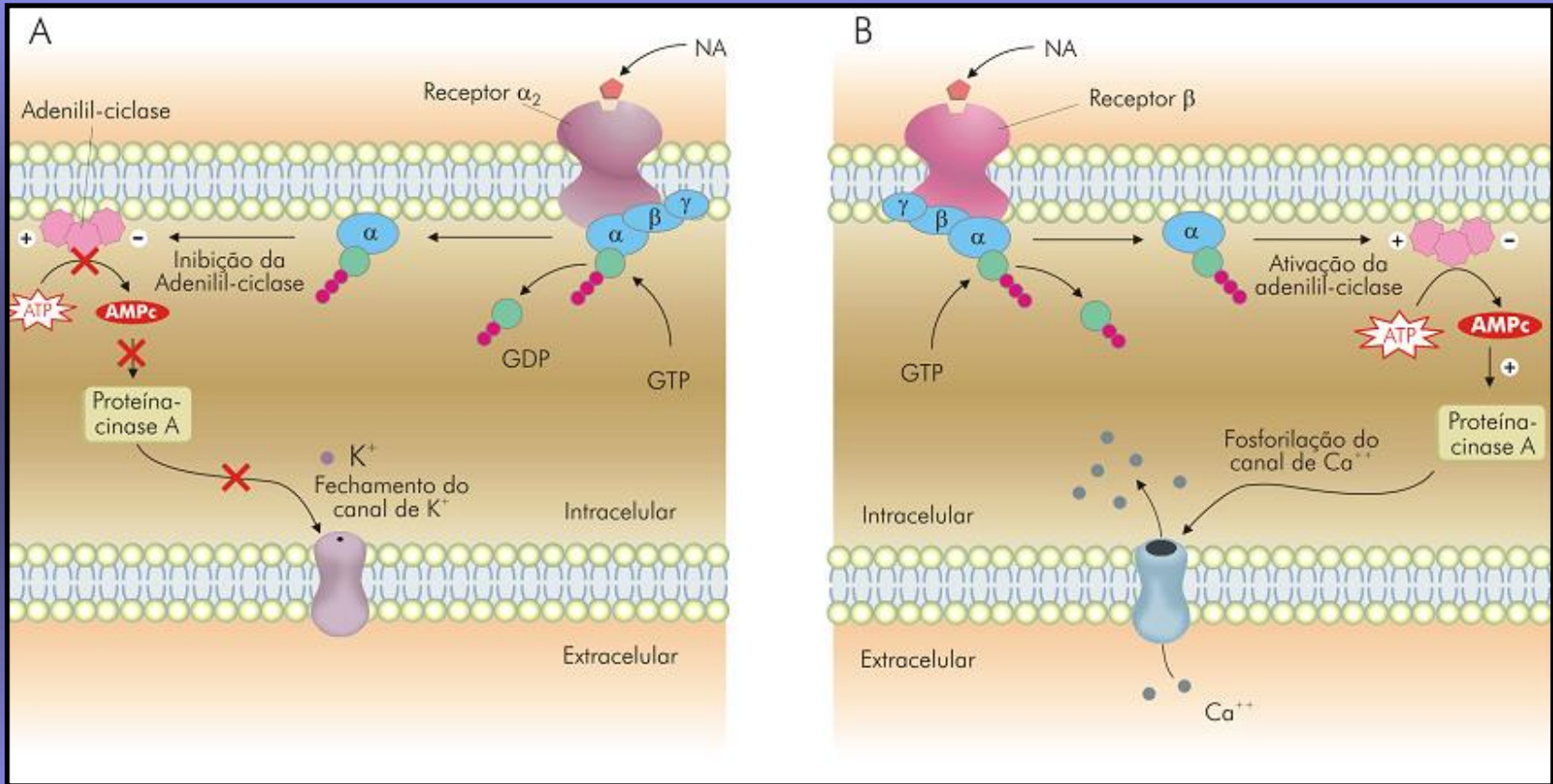
Modified from [57] with permission.

# Receptores de noradrenalina

**TABLE 12-6** Properties of human  $\beta$ -adrenergic receptor subtypes

	$\beta_1$	$\beta_2$	$\beta_3$
Amino acids	477	413	402/408
Chromosome	10	5	8
Effector pathways	$\uparrow$ cAMP	$\uparrow$ cAMP	$\uparrow$ cAMP
Distribution	Heart, kidney, cerebral cortex, hypothalamus	Lung, liver, cerebellum, hippocampus, cerebral cortex, smooth muscle, olfactory bulb	Fat, brain (?)

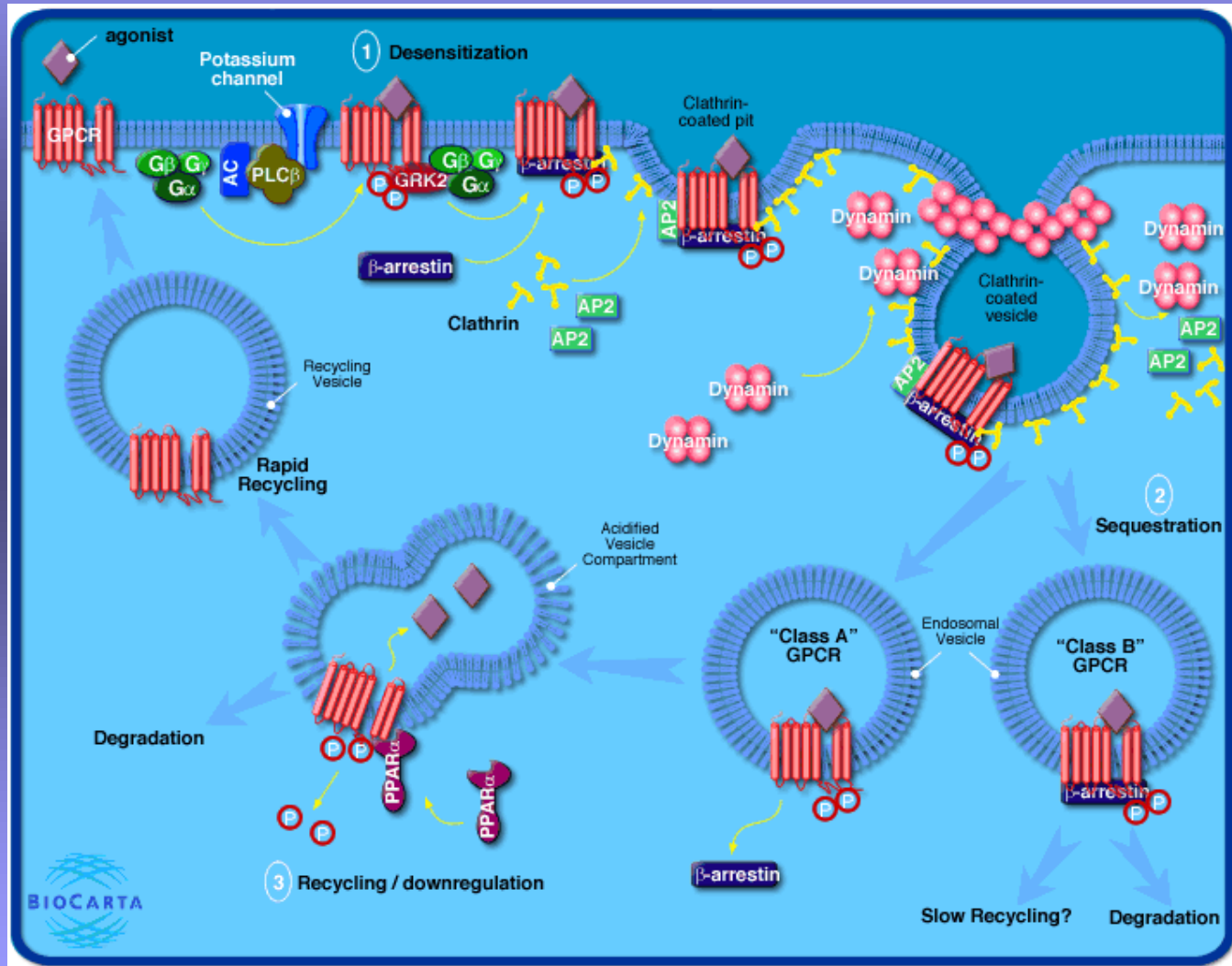
# Receptores de noradrenalina





# Receptores catecolaminérgicos

Dessensibilização – exposição crônica a agonistas ( $\beta 2$ )



# Receptores catecolaminérgicos

**TABLE 12-7** Characteristics of catecholamine receptor knockout mice

<b>Knockout</b>	<b>Phenotype</b>
$\alpha_{1A}$ -adrenergic receptor	Decreased blood pressure
$\alpha_{1B}$ -adrenergic receptor	Decreased blood pressure, decreased response to CNS stimulants
$\alpha_{1D}$ -adrenergic receptor	Decreased blood pressure
$\alpha_{2A}$ -adrenergic receptor	Increased sympathetic activity, tachycardia, loss of hypotensive response to $\alpha_2$ agonists
$\alpha_{2B}$ -adrenergic receptor	Decreased vasoconstrictor response to $\alpha_2$ agonists
$\alpha_{2C}$ -adrenergic receptor	No overt phenotype
$\beta_1$ -adrenergic receptor	Most die prenatally, survivors have impaired cardiac response
$\beta_2$ -adrenergic receptor	Changes in vascular tone and energy metabolism during stress
$\beta_3$ -adrenergic receptor	Altered leptin and insulin concentrations after agonist treatment
D <sub>1</sub> -dopamine receptor	Reduced agonist responses, hyperlocomotion
D <sub>2</sub> -dopamine receptor	Parkinsonian-like motor impairment
D <sub>3</sub> -dopamine receptor	Hyperactivity
D <sub>4</sub> -dopamine receptor	Reduced locomotion, hypersensitivity to ethanol and stimulants
D <sub>5</sub> -dopamine receptor	Reduced agonist induced locomotion, startle, and prepulse inhibition

# Receptores catecolaminérgicos

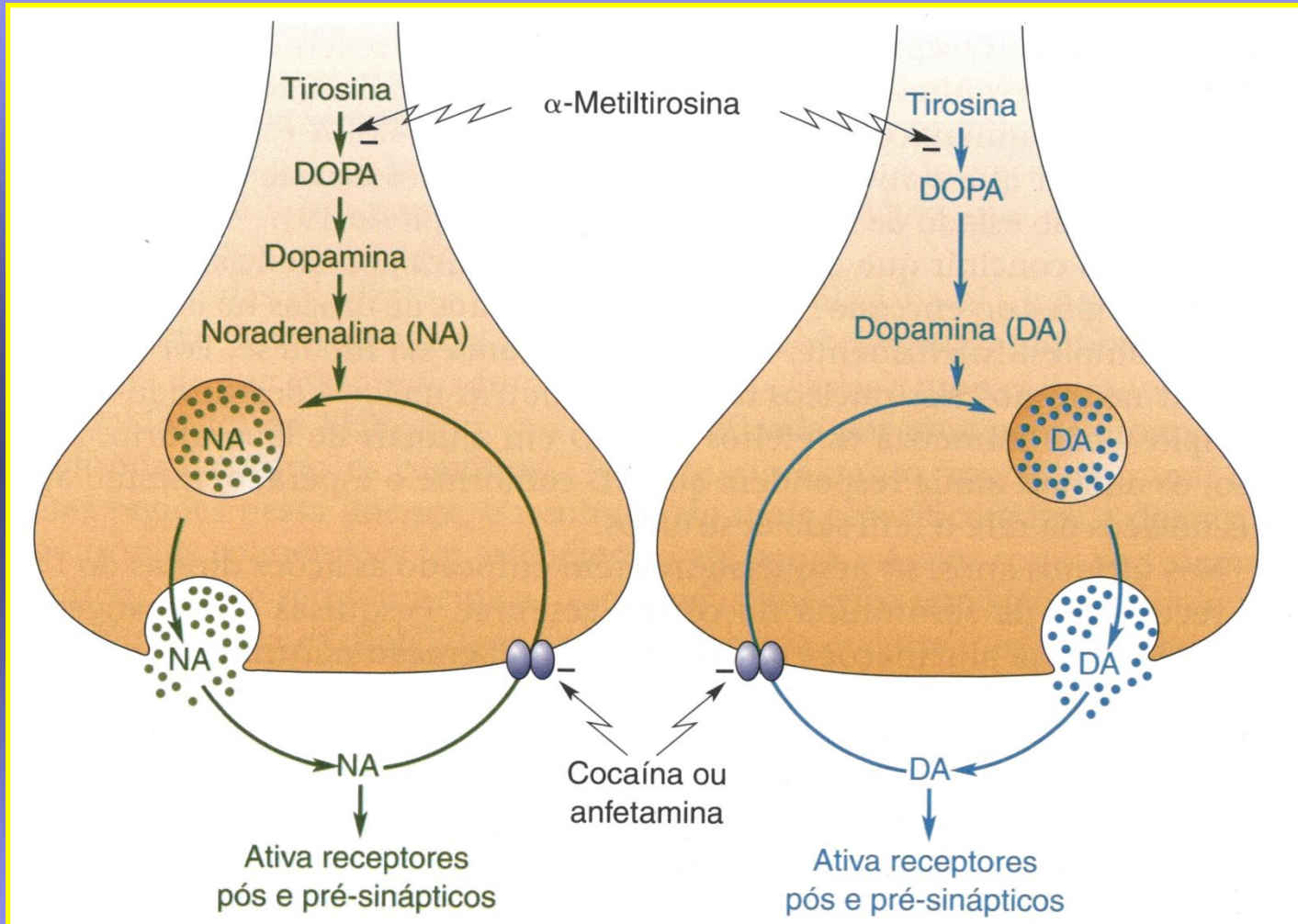
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Sensibilização – exposição crônica a antagonista (↑ receptores)

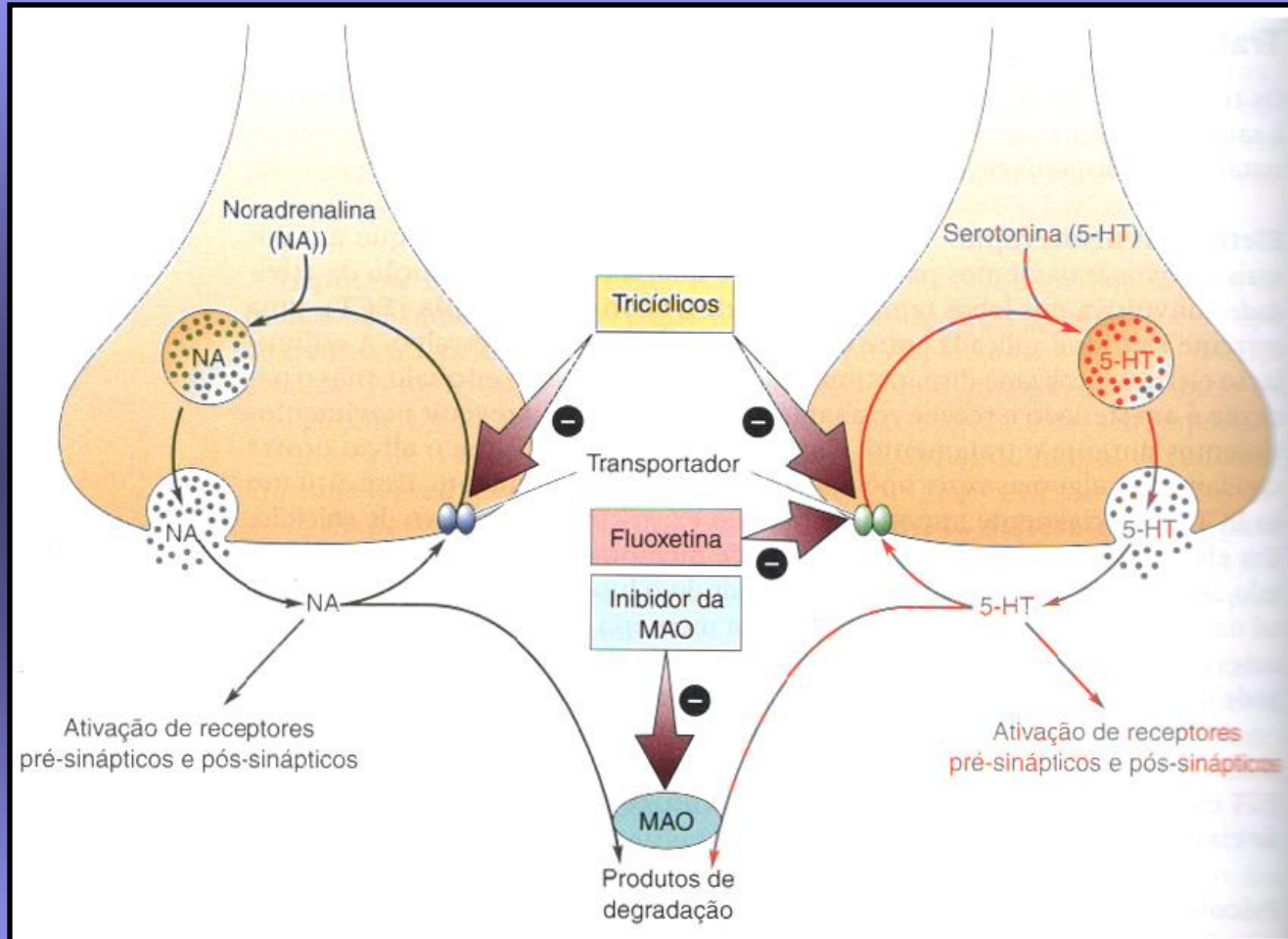
Supersensibilidade efetora – neurotoxinas (6-OHDA)

Subsensibilidade – antidepressivos ou inibidores da MAO

# Catecolaminas e ação de drogas

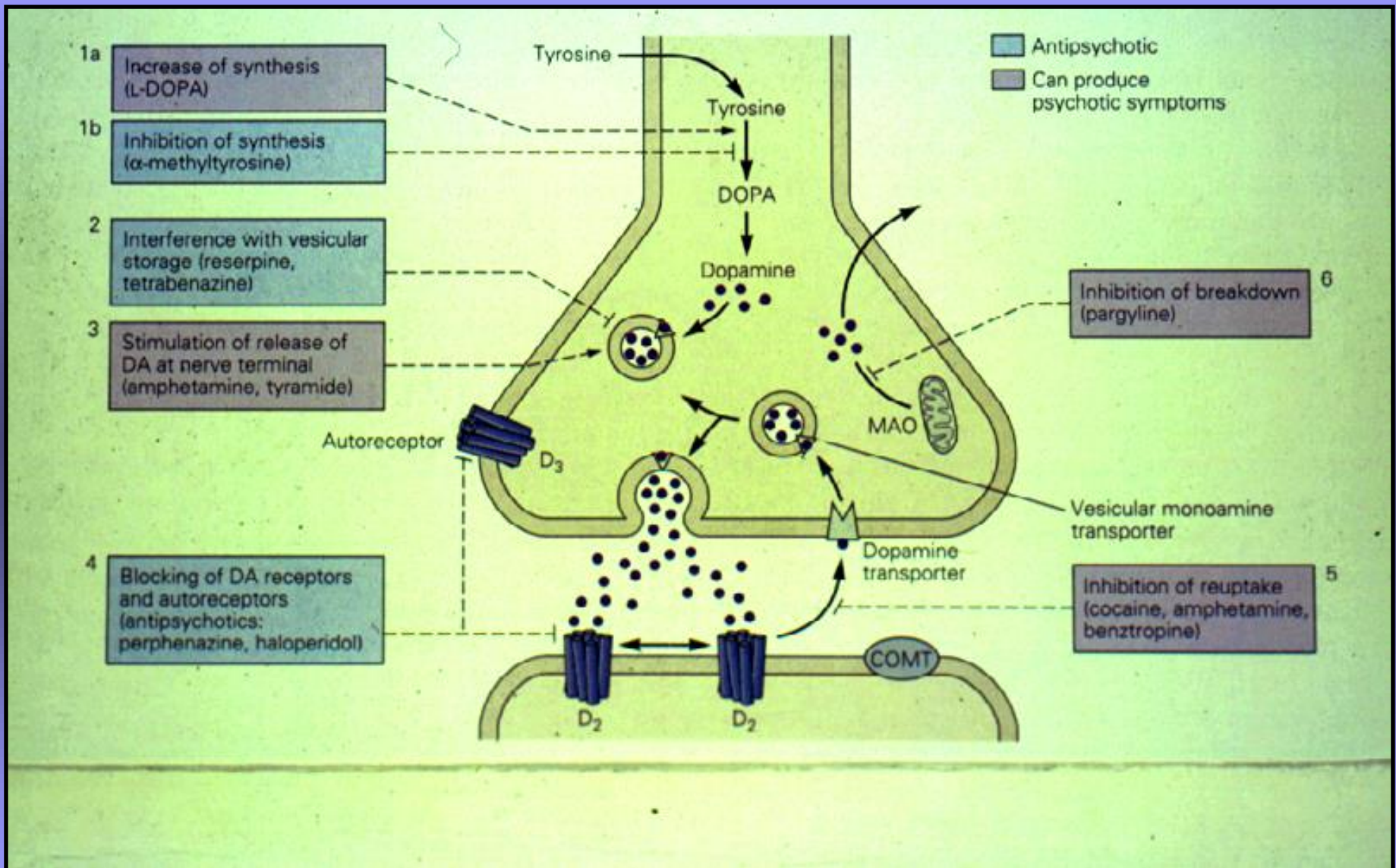


# Catecolaminas e transtornos do humor





# Catecolaminas e ação de drogas





# Adrenergic Transmission

these are indirectly acting sympathomimetic amines. they compete for uptake 1 and vesicular uptake, thus displacing NA at two points. Amphetamine also reduces vesicular packaging of amines by reducing the pH gradient.

Although a sympathetic *en passant* synapse is shown, the synthesis and reuptake mechanisms shown apply equally well to CNS adrenergic and dopaminergic neurones.

ephedrine also has direct effect by activating  $\beta_2$  receptors. used to relieve bronchospasm as a nasal decongestant

- amphetamine
- tyramine
- ephedrine
- ecstasy

doesn't cross the BBB, therefore often used as adjunct in L-DOPA treatment of Parkinson's, as it reduces the peripheral effects.

this enzyme is rate-limiting, and is feedback-inhibited; phosphorylation reduces this effect (PKC, PKA and  $Ca^{2+}$ -Calmodulin dependent PK); chronic electrical stimulation upregulates its transcription

forms false neurotransmitter ( $\alpha$ -methylnoradrenaline) - less effective at  $\alpha_1$ , but more effective at  $\alpha_2$ , hence gives greater feedback inhibition too

works peripherally and centrally to block catecholamine accumulation of vesicles, thus depletes stores; once used in psychiatry and hypertension, but caused depression

taken up by uptake 1; competes for uptake into vesicles, displacing NA into cytoplasm where it will leak out, thus gives initial sympathetic hyperactivity. when given chronically in low doses, will cause NA depletion, and at high concentrations can inhibit vesicular fusion. once used as antihypertensive

up to 50% of NA taken up by uptake 1 is recycled this way

## DEAMINATED METABOLITES

