

# NORADRENALINE

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## VOIES NORADRENERGIQUES

INTERET PHYSIOPATHOLOGIQUE ET PHARMACOLOGIQUE

SYNAPSE NORADRENERGIQUE

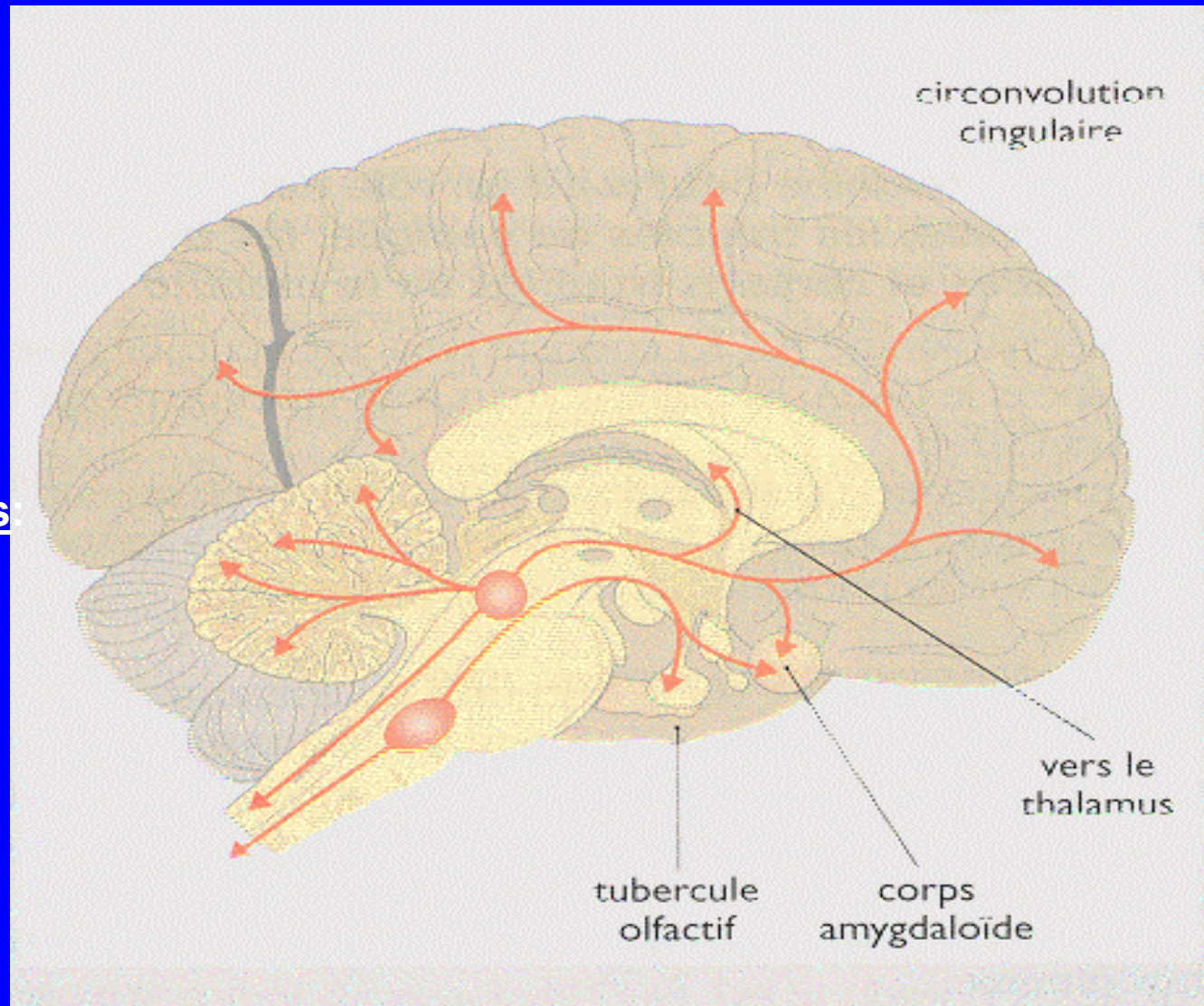
SYNTHESE – DEGRADATION

CAPTURE

INTERACTION LIGAND/RECEPTEUR NORADRENERGIQUE

# VOIES NORADRENERGIQUES

Localisations principales  
locus cerulus  
protubérance annulaire  
mésencéphale



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INTERACTION LIGAND/RECEPTEUR NORADRENERGIQUE

# SEROTONINE / NORADRENALINE AND DEPRESSION

Les concentrations du métabolite principal de la **sérotonine** dans le liquide céphalorachidien de patients dépressifs sont plus faibles que dans la population générale

The role of **norepinephrine (noradrenaline)** depletion in depression has been suggested by the low levels of norepinephrine metabolites in the urine and cerebrospinal fluid of depressed patients

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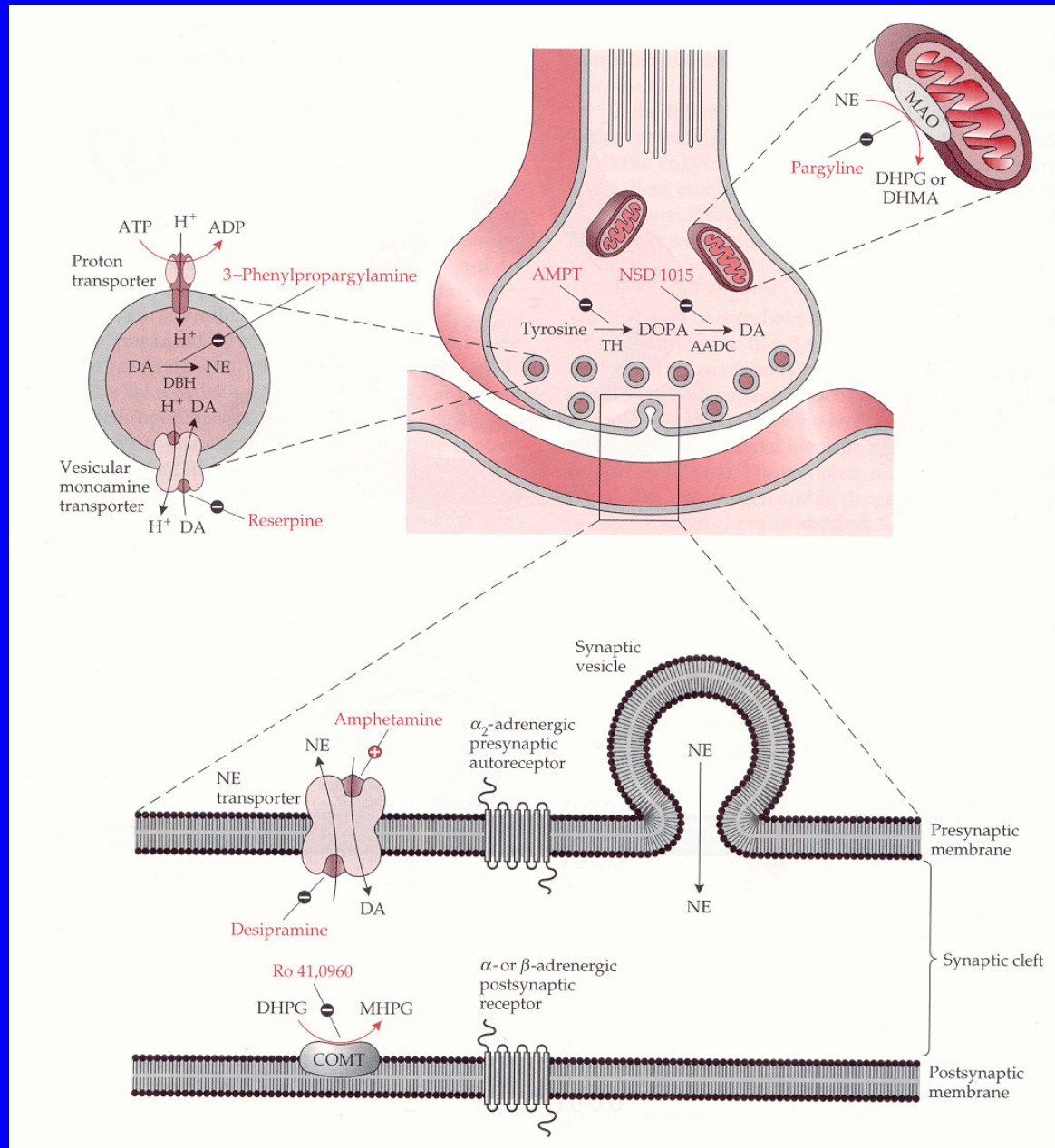
**SYNAPSE NORADRENERGIQUE**

**SYNTHESE - DEGRADATION**

**CAPTURE**

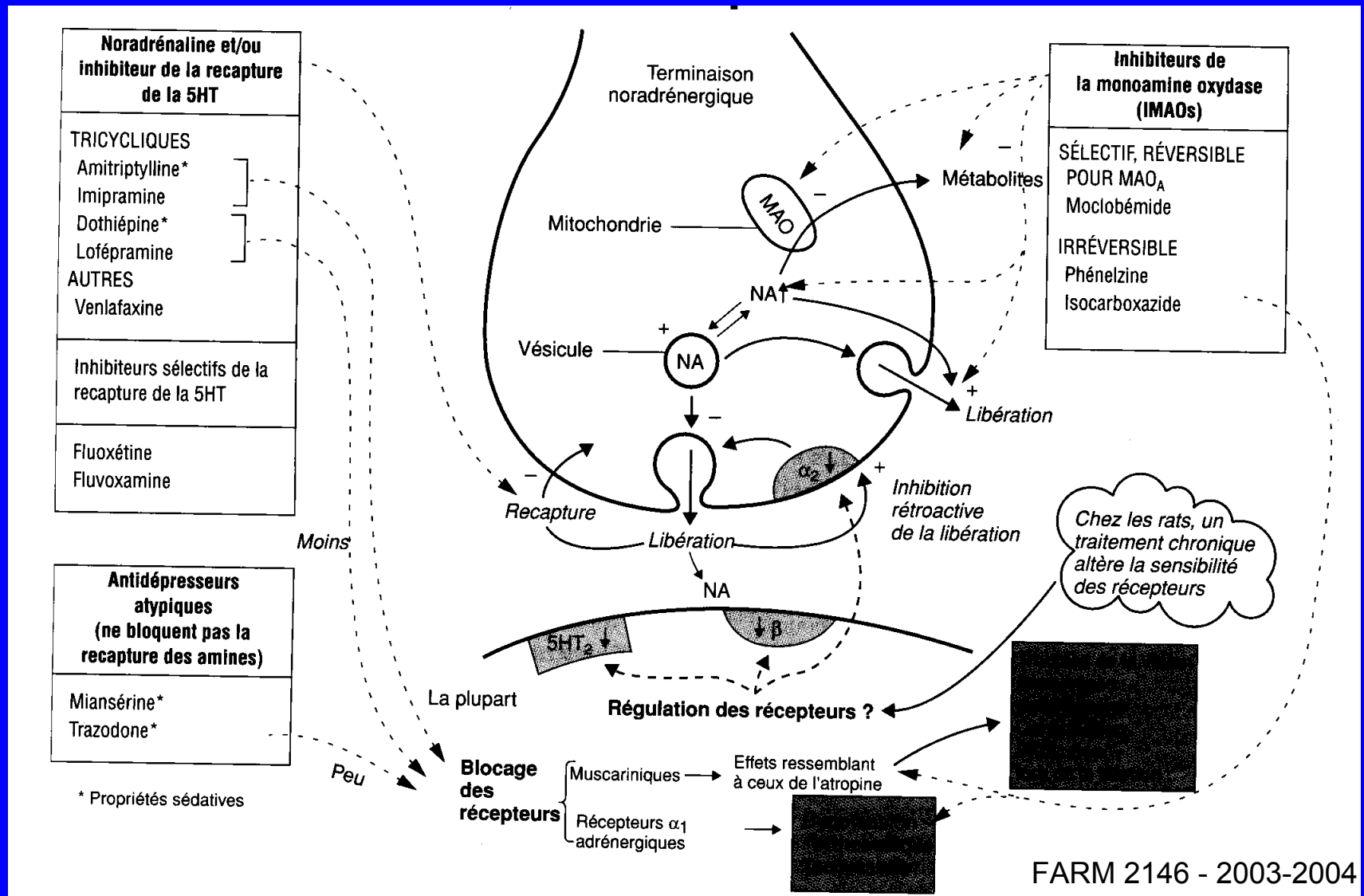
**INTERACTION LIGAND/RECEPTEUR NORADRENERGIQUE**

# SYNAPSE NORADRENERGIQUE





# ACTION AU NIVEAU DE LA SYNAPSE NORADRENERGIQUE





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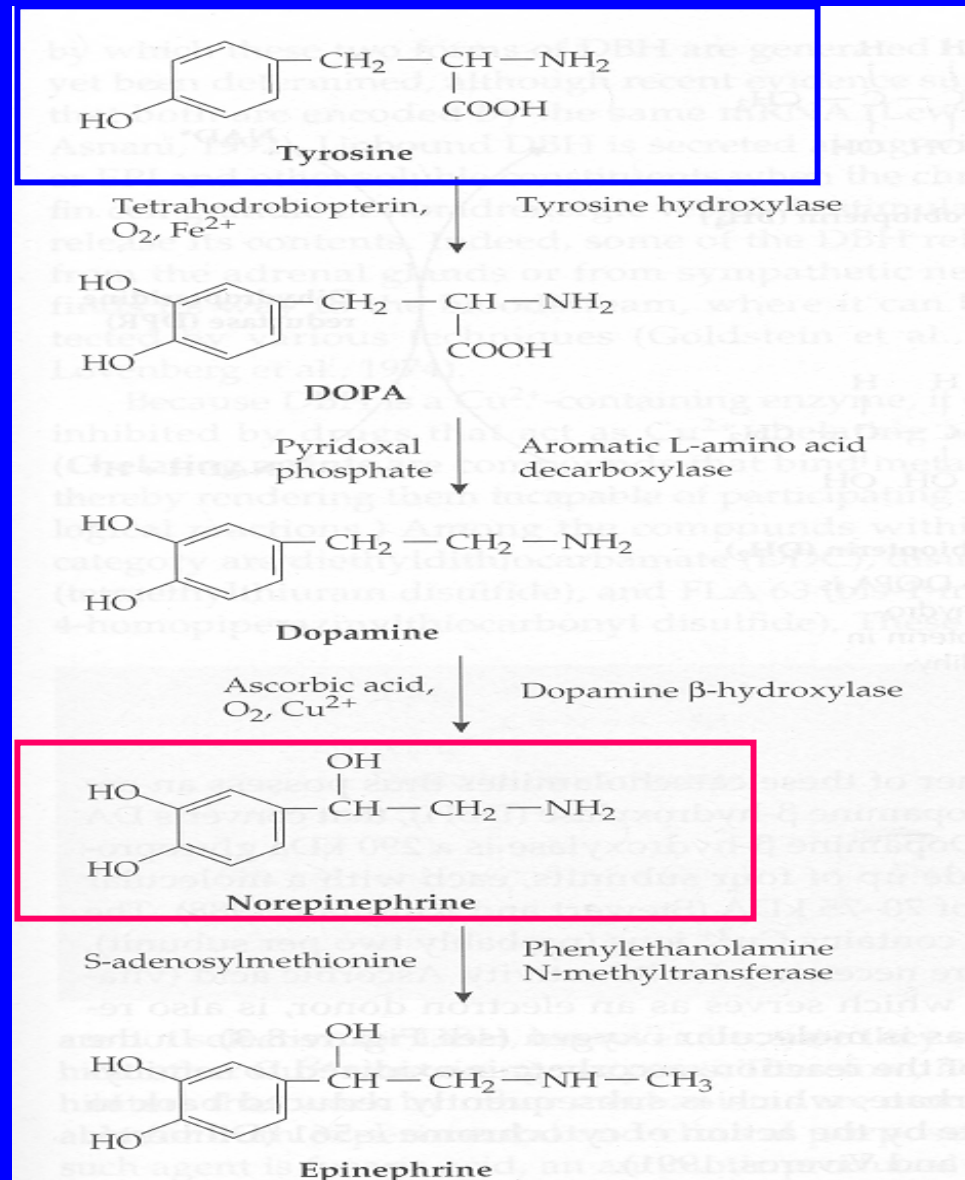
SYNAPSE NORADRENERGIQUE

SYNTHESE - DEGRADATION

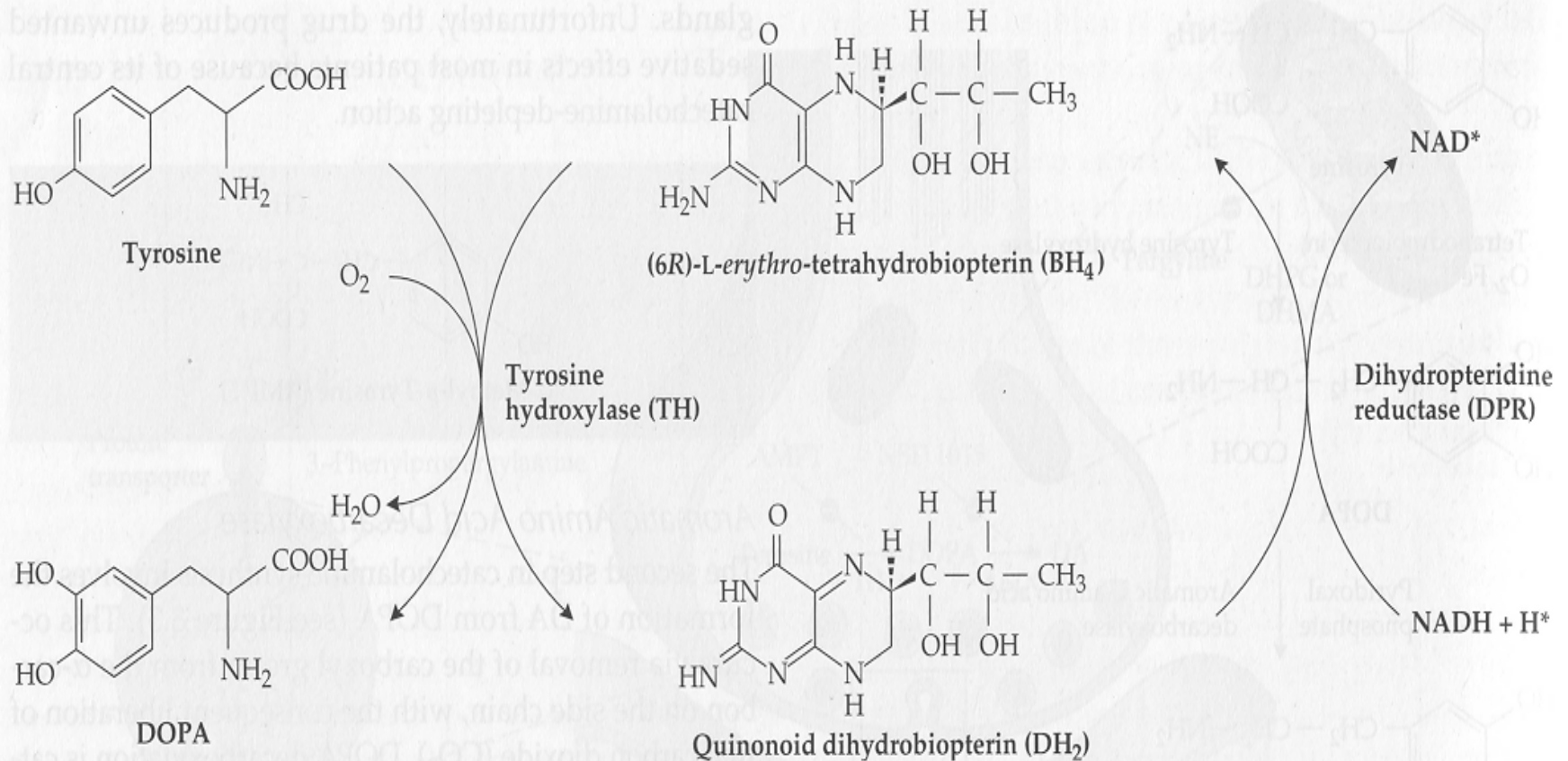
CAPTURE

INTERACTION LIGAND/RECEPTEUR NORADRENERGIQUE

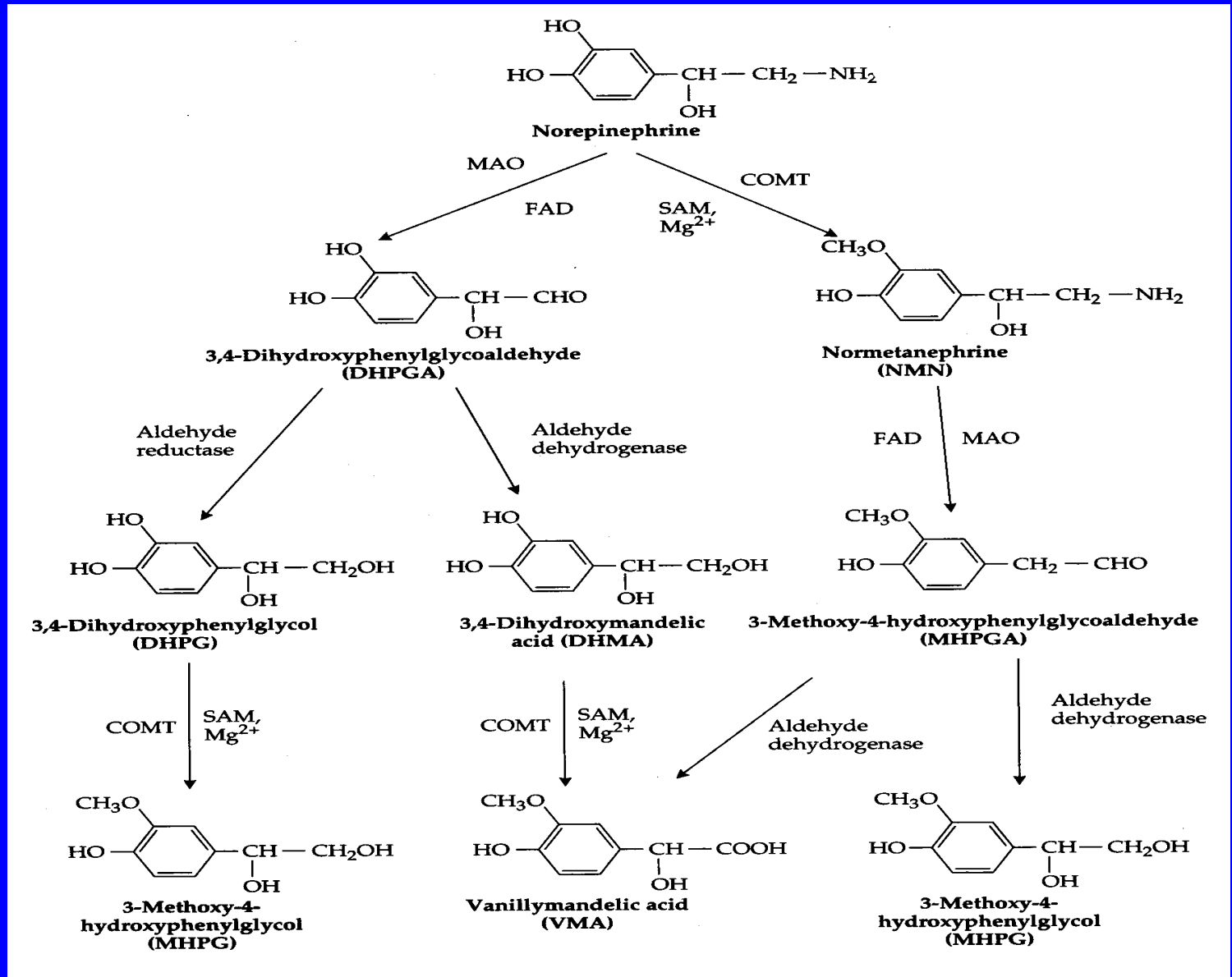
# NORADRENALINE - SYNTHESIS



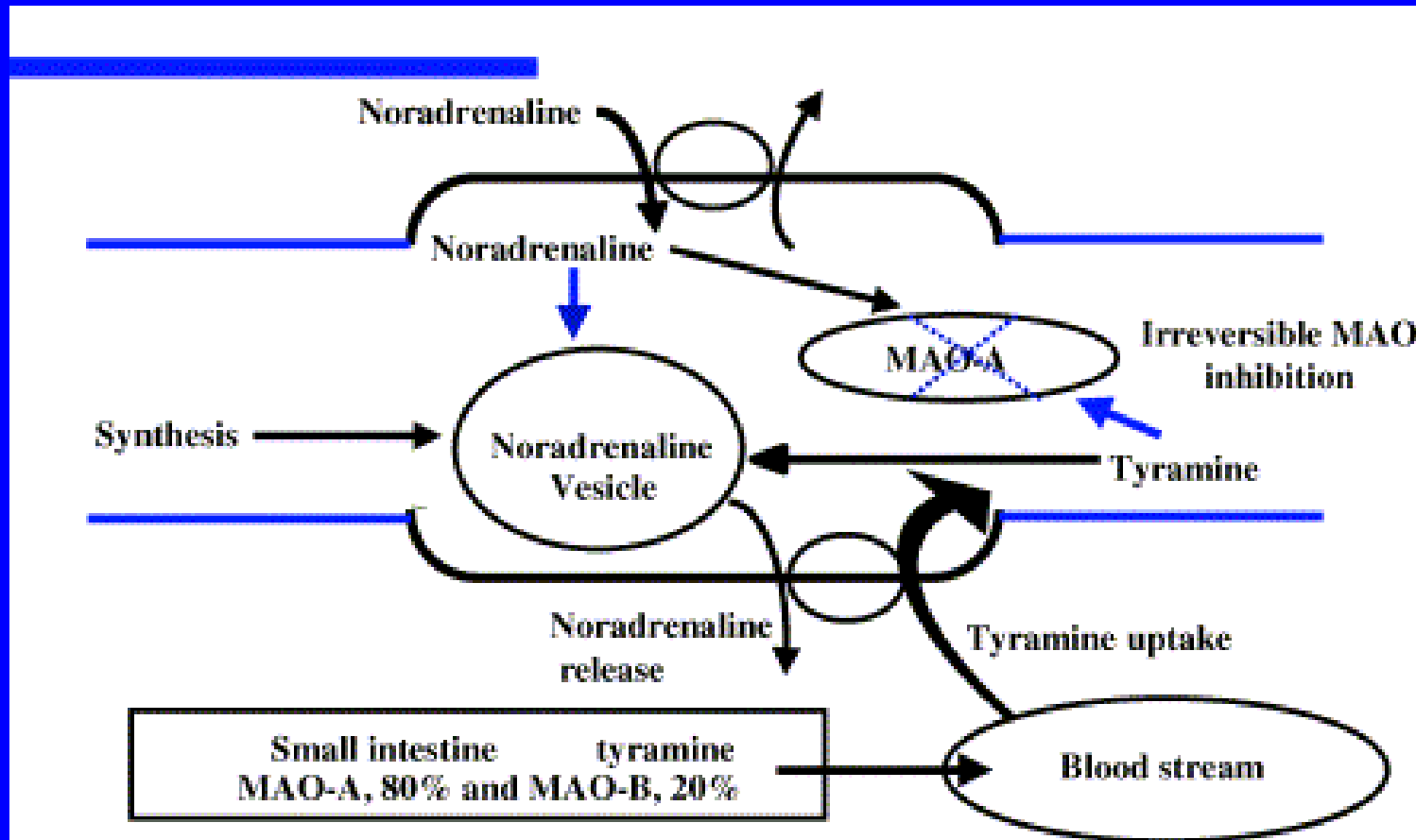
# NORADRENALINE – SYNTHESIS – 1° ETAPE



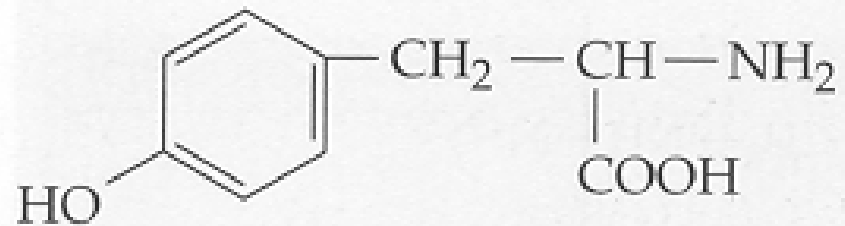
# NORADRENALINE - DEGRADATION



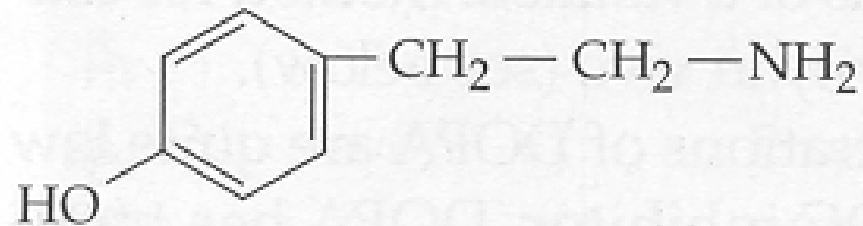
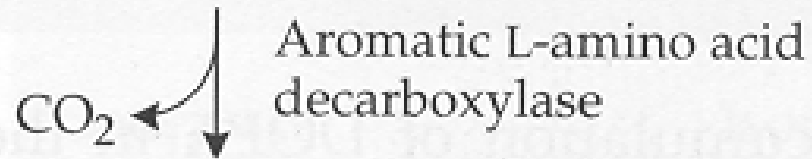
# EFFECT OF MAO-A INHIBITION – CHEESE REACTION



The mechanism of tyramine uptake and induced noradrenaline release from peripheral adrenergic neurons in response to irreversible inhibition of MAO-A in the small intestine, blood vessels and adrenergic neurons

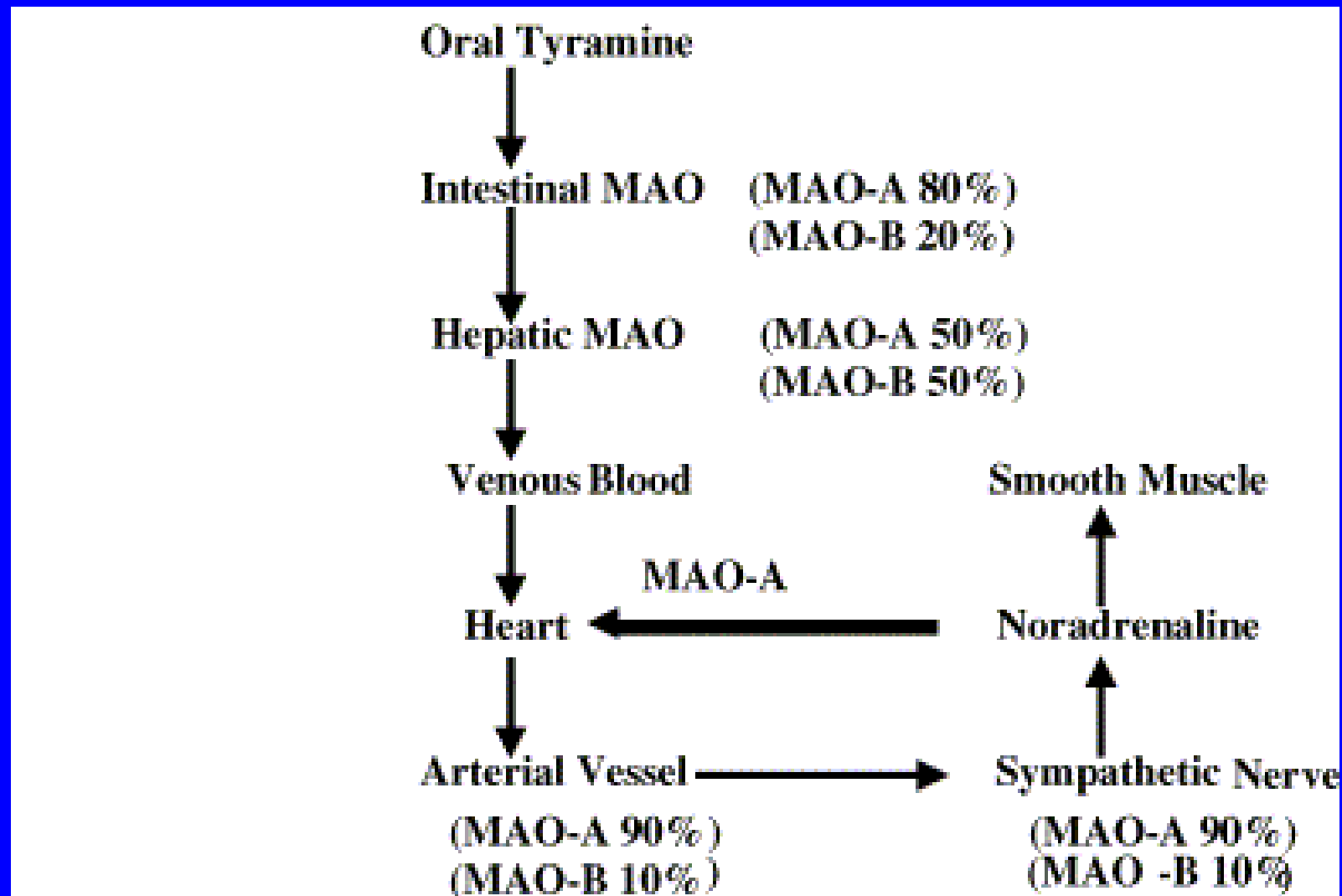


**Tyrosine**



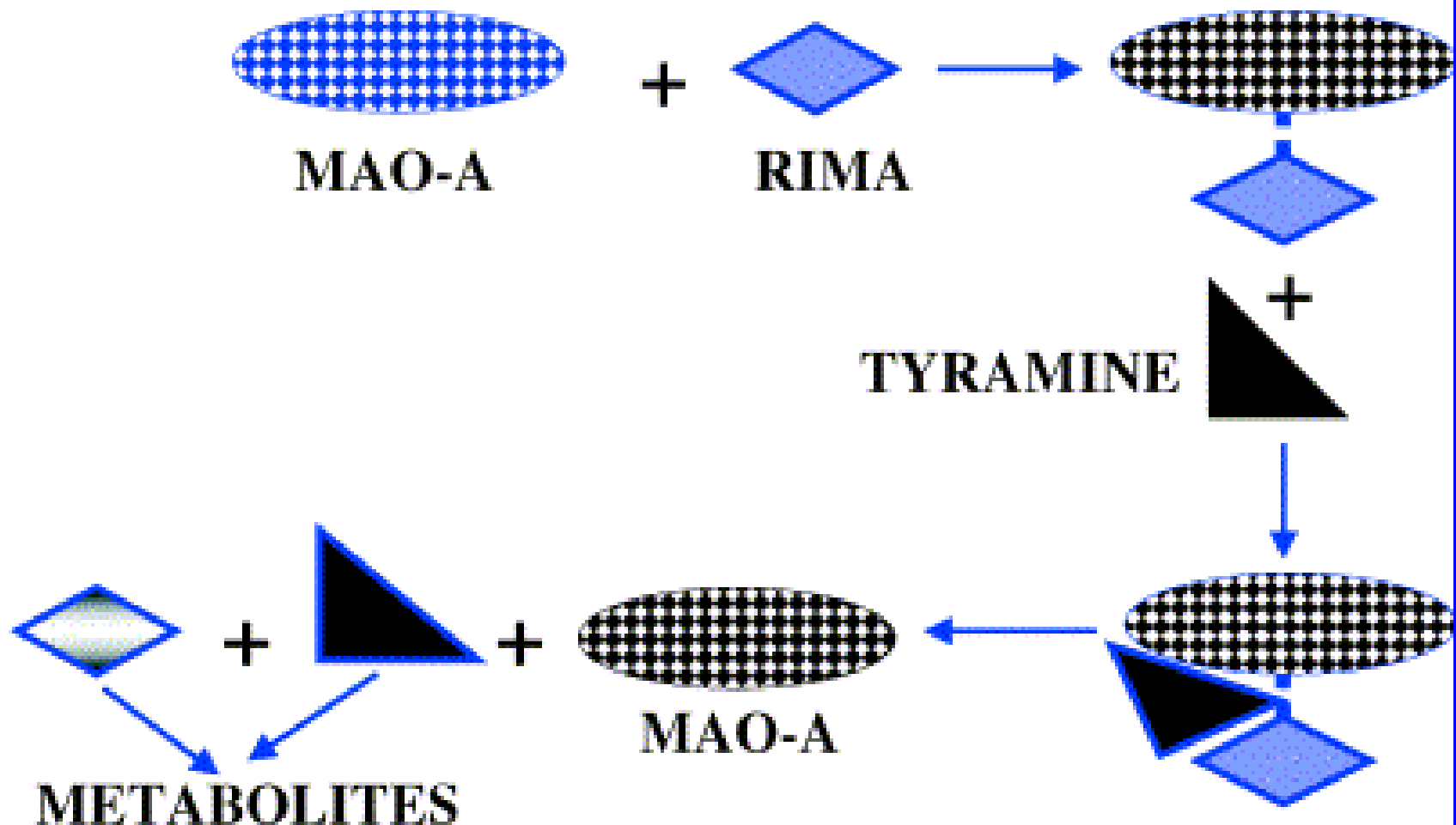
**Tyramine**

# EFFECT OF MAO-A INHIBITION – CHEESE REACTION





# EFFECT OF MAO-A INHIBITION – CHEESE REACTION



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# INHIBITORS OF SEROTONINE / NORADRENALINE REUPTAKE (SNaRI)

Panel 1: SNaRI, NaSSA, and NaRI

Drug	Class	Trade name	Manufacturer	Approved uses
Venlafaxine	SNaRI	Effexor, Effexor XR*	Wyeth-Ayerst	Depression, generalised anxiety disorder
Nefazodone	SNaRI	Serzone, Dutonin, Nefador, Netrel, Rezeril	Eristol-Myers Squibb	Depression
Mirtazapine	NaSSA	Remeron	Organon	Depression
Bupropion	NaRI	Edronax, Vestra, Prolift, Integrex, Norebox	Pharmacia & Upjohn	Depression

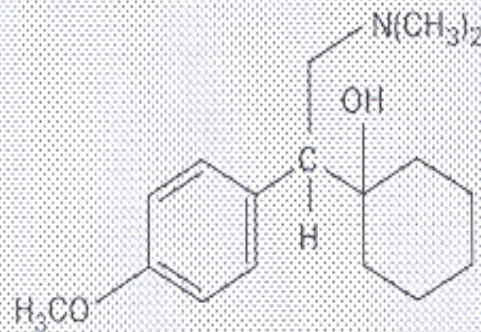
\*Effexor=immediate release, Effexor XR=extended release.

SNaRI=serotonin/noradrenergic reuptake inhibitor, NaSSA=noradrenergic and specific serotonergic antidepressant, NaRI=noradrenergic reuptake inhibitor.

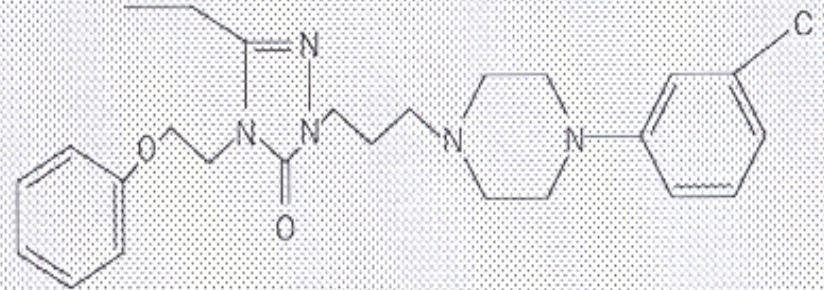


# INHIBITORS OF SEROTONINE / NORADRENALINE REUPTAKE (SNaRI) - Structure

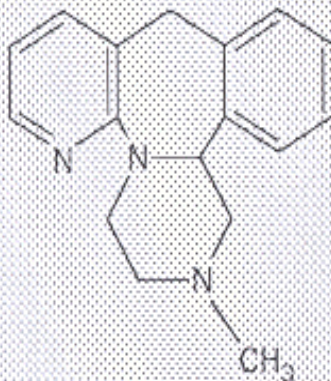
Venlafaxine



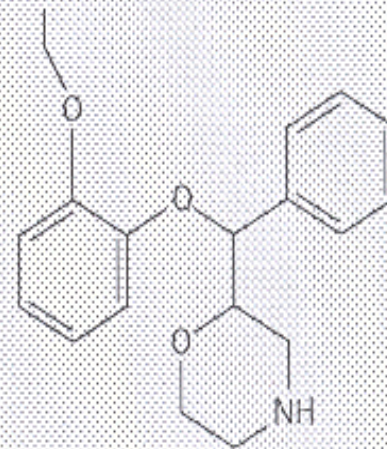
Nefazodone



Mirtazapine



Reboxetine





# INHIBITORS OF SEROTONINE/NORADRENALINE REUPTAKE (SNaRI) - IC50 and receptor binding affinity

Panel 2: in-vitro reuptake inhibitory potencies and receptor-binding affinities of newer antidepressants compared with serotonin reuptake inhibitors

Drug	Potency IC <sub>50</sub> (nmol/L)			Receptor affinity K <sub>i</sub> (nmol/L)			
	5-HT reuptake	NA reuptake	DA reuptake	α <sub>1</sub>	α <sub>2</sub>	H <sub>1</sub>	Mus
Venlafaxine	39	213	2800	>10 000	>10 000	>10 000	>5000
Nefazodone	68	110	470	42	1200	370	>10 000
Mirtazapine	None	>10 000	None	NA	NA	NA	NA
Reboxetine	1070	8	>10 000	>10 000	>10 000	1400	3900
Fluoxetine	25	500	5000	5900	>10 000	1000	1300
Sertraline	7	1400	48	300	5000	>10 000	500
Paroxetine	1	350	5100	>10 000	>10 000	1000	88
Citalopram	3	3900	>10 000	4500	>10 000	470	2900

NA= data not available.

5-HT=5-hydroxytryptamine (serotonin), NA=noradrenaline, DA=dopamine, H<sub>1</sub>=histamine, Mus=muscarinic.

Data from references 2-8.

# INHIBITORS OF SEROTONINE / NORADRENALINE REUPTAKE (SNaRI) - Ki

Inhibition constants ( $K_i$ ) (nM) for blockade of noradrenaline (NA) and serotonin (5-HT) reuptake in vitro<sup>a</sup>

	Noradrenaline	Serotonin	Ratio serotonin/ noradrenaline
Lofepramine	1.9	2400	1263
Maprotiline <sup>b</sup>	12	6100	508
Desipramine	0.6	180	300
Reboxetine <sup>c</sup>	8.0	1070	130
Nortriptyline	2.2	154	70
Doxepin	18	220	12
Amitriptyline	14	84	6.0
Imipramine	14	41	2.9
Dothiepin	28	76	2.7
Mirtazapine <sup>b</sup>	2000	5000	2.5
Venlafaxine	210	39	0.185
Fluoxetine	143	14	0.098
Paroxetine	33	0.73	0.022
Sertraline	220	3.4	0.015
Fluvoxamine <sup>c</sup>	500	4	0.008
Citalopram <sup>c</sup>	4000	1.3	0.0003



# INHIBITORS OF SEROTONINE/NORADRENALINE REUPTAKE (SNaRI) - Pharmacokinetics

Panel 3: Pharmacokinetics of newer antidepressants

Drug	Therapeutic dose range (mg per day)	Bioavailability	Biotransformation pathways	Major metabolites	Half-life	Elimination routes	Protein binding
Venlafaxine IR	75-225 (divided dose)	45%	CYP2D6 and others	o-desmethyl-venlafaxine (DDV) (active)	4 h (parent) 10 h (DDV)	Urine (87%)	27% (parent) 30% (DDV)
Venlafaxine XR	75-225 (single dose)						
Nefazodone	300-600 (divided dose)	20% (variable)	Dealkylation and hydroxylation, CYP3A4, CYP2D6	Hydroxynefazodone (HH-Nef) (active) Triazolidone (TAD) (active) mCPP	2-4 h (parent), 2-4 h (HH-Nef), 18-33 (TAD), 4-8 (mCPP)	Urine (55%) Faeces (30%)	99% (parent)
Mirtazapine	15-45 (single dose)	50%	(direct 5-HT agonist) Demethylation and hydroxylation, CYP2D6, 1A2, 3A4	Demethylmirtazapine (weak activity)	20-40 h (parent)	Urine (85%) Faeces (15%)	85% (parent)
Reboxetine	8-20 (divided dose)	50%	Dealkylation and hydroxylation, CYP3A4	o-desethylreboxetine (inactive)	13 h (parent)	Urine (78%) Faeces	97% (parent) α-1-acid glycoprotein > albumin

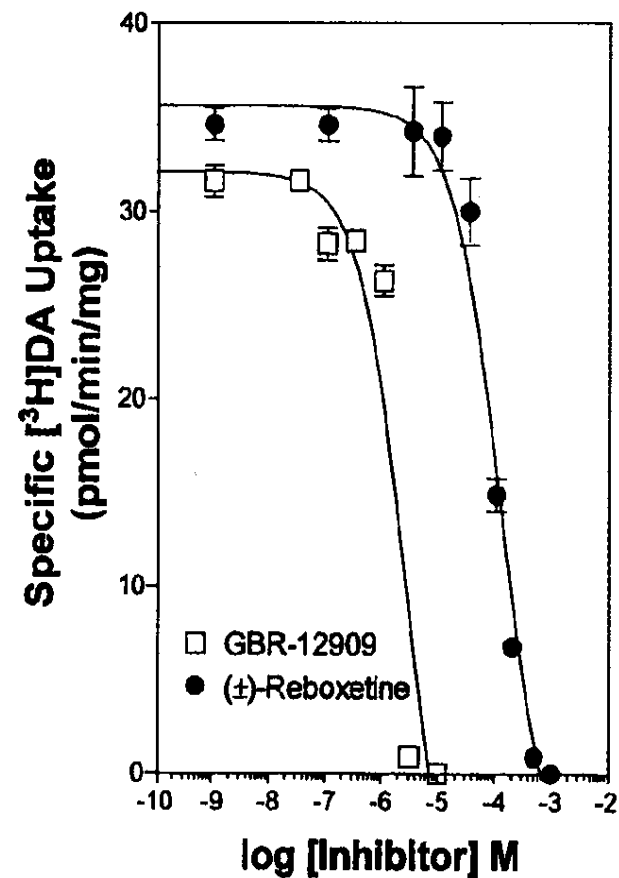
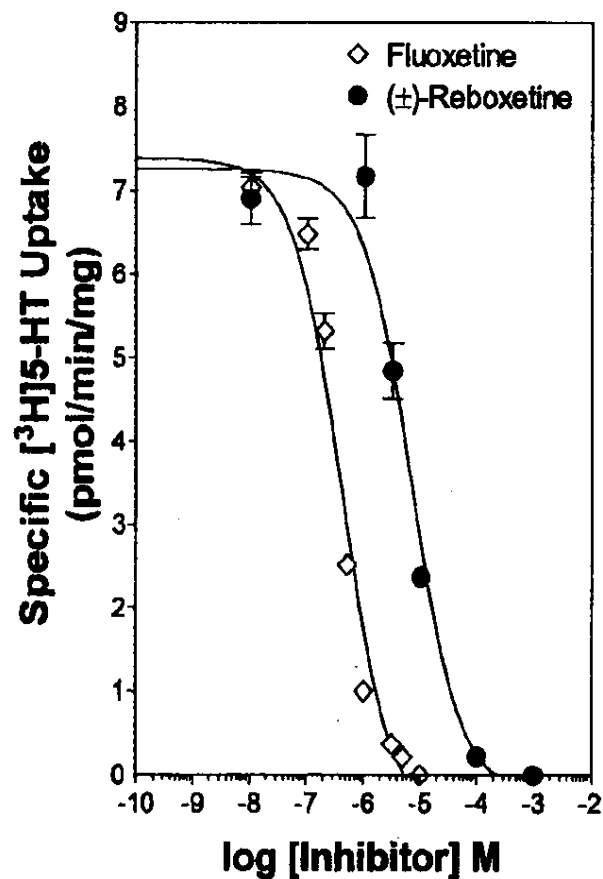
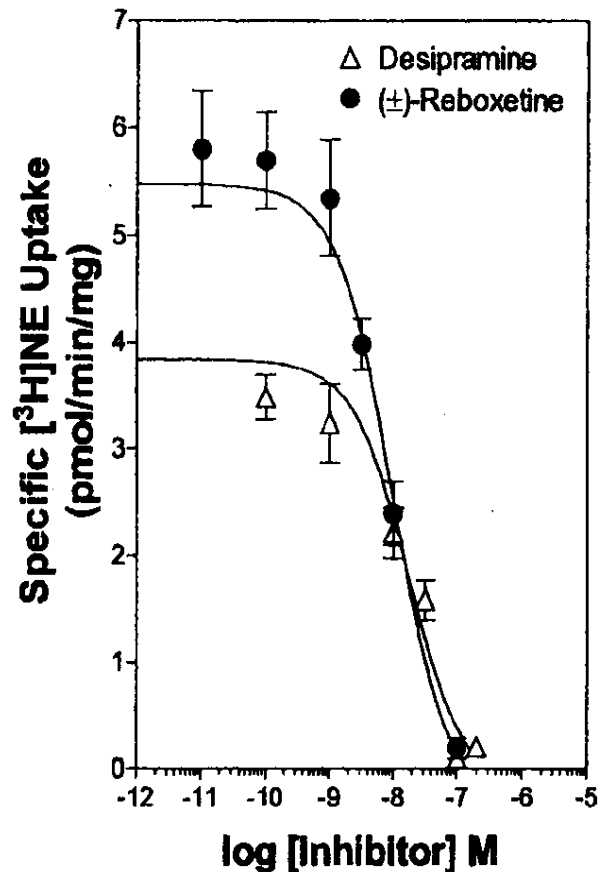


# INHIBITORS OF SEROTONINE / NORADRENALINE REUPTAKE (SNaRI) - Kd

Dissociation constants ( $K_d$ ) (nM) for  $H_1$ -histaminic, M1 muscarinic-cholinergic,  $\alpha_1$ - and  $\alpha_2$ -adrenergic and receptors in vitro<sup>3</sup>

Antidepressant	$H_1$	M <sub>1</sub>	$\alpha_1$	$\alpha_2$
<i>Noradrenergic</i>				
Maprotiline <sup>b</sup>	2.0	200	75	—
Nortriptyline	6.3	37	55	2030
Mirtazapine <sup>d</sup>	9.3	6.2	6.5	6.8 <sup>e</sup>
Desipramine	60	66	100	5500
Lofepramine	360	67	100	2700
Reboxetine <sup>c</sup>	>1000	>1000	>10 000	>10 000
Venlafaxine	>10 000	>10 000	>10 000	>10 000
<i>Reference<sup>f</sup></i>				
Doxepin	0.17	23	23	1270
Amitriptyline	0.95	9.6	24	690
Trazodone	1100	>35 000	42	320

# INHIBITORS OF SEROTONINE / NORADRENALINE REUPTAKE (SNaRI) - Selectivity



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# AGONISTES ET ANTAGONISTES NORADRENERGIQUES

Receptor subtype	Agonists	Antagonists
$\alpha_1$	Phenylephrine, methoxamine	Prazosin, WB-4101, phenoxybenzamine
$\alpha_2$	Clonidine, B-HT 920	Yohimbine, rauwolfscine, idazoxan
General $\beta$	Isoproterenol, albuterol	Propranolol, alprenolol, pindolol
$\beta_1$	Denopamine, xamoterol	Atenolol, bisopropolol
$\beta_2$	Procaterol	ICI-118,551
$\beta_3$	BRL 37344, CL 316,243	