

SEROTONINE

SEROTONINE

STRUCTURE

VOIES SEROTONINERGIQUES

INTERET PHYSIOPATHOLOGIQUE ET PHARMACOLOGIQUE

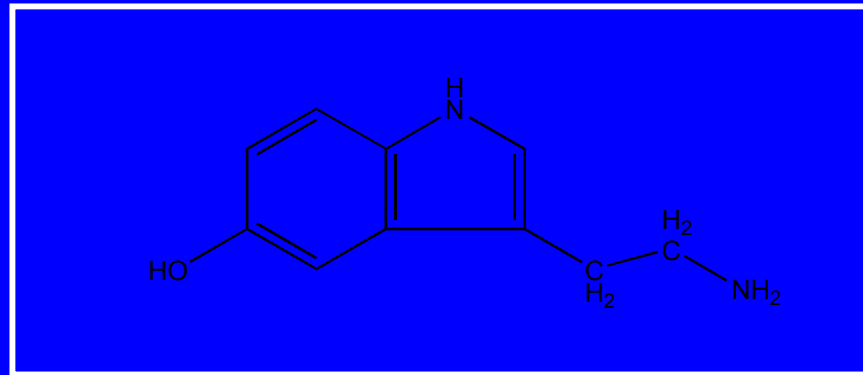
SYNAPSE SEROTONINERGIQUE

SYNTHESE - DEGRADATION

LIBERATION ET STOCKAGE VESICULAIRE

INTERACTION LIGAND/RECEPTEUR SEROTONINERGIQUE

SEROTONINE - 5-hydroxytryptamine (5-HT)



- 
- Effecteur ~ muscles lisses
 - Augmente l'agrégation plaquettaire
 - Neurotransmetteur SNC

{ cellules chromaffines du SNC
plaquettes
SNC

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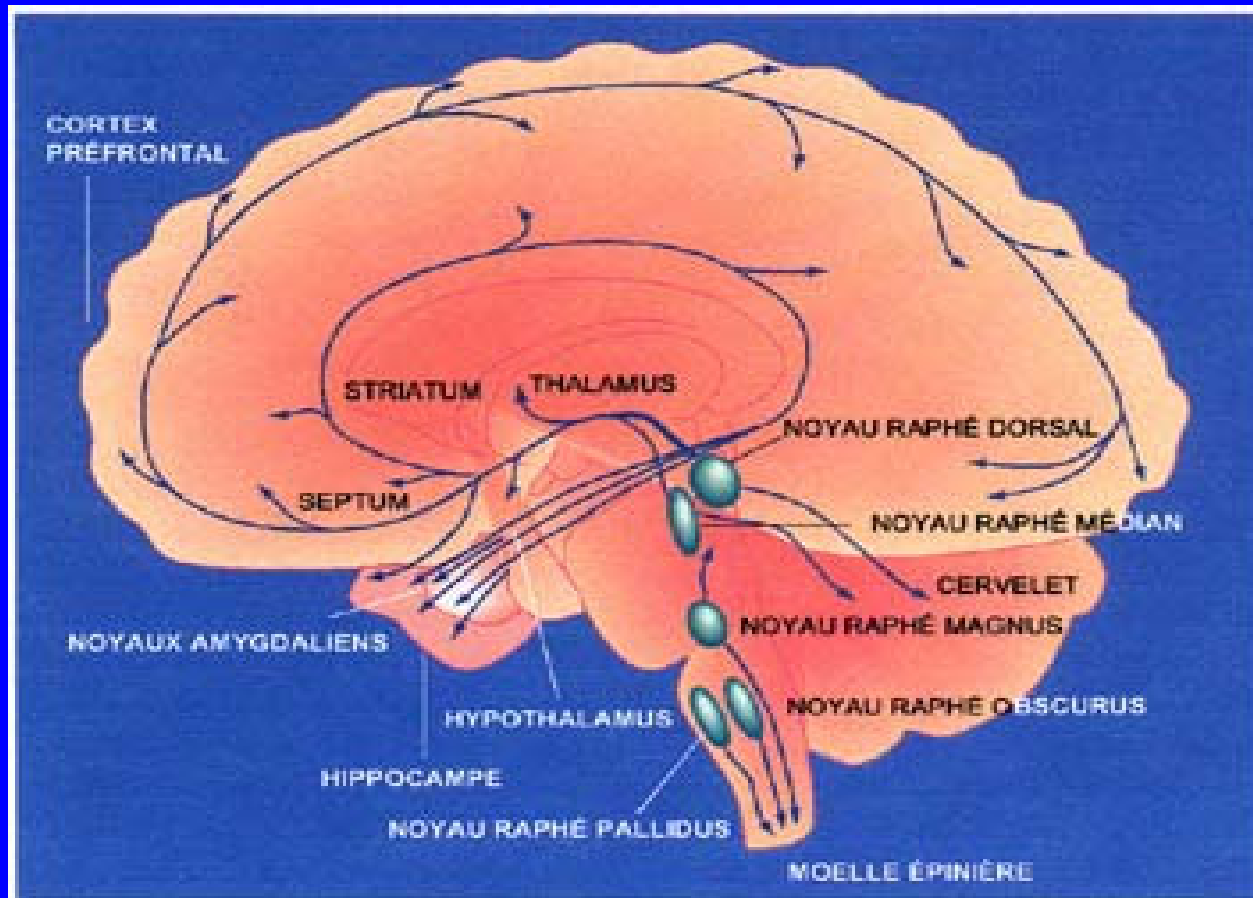
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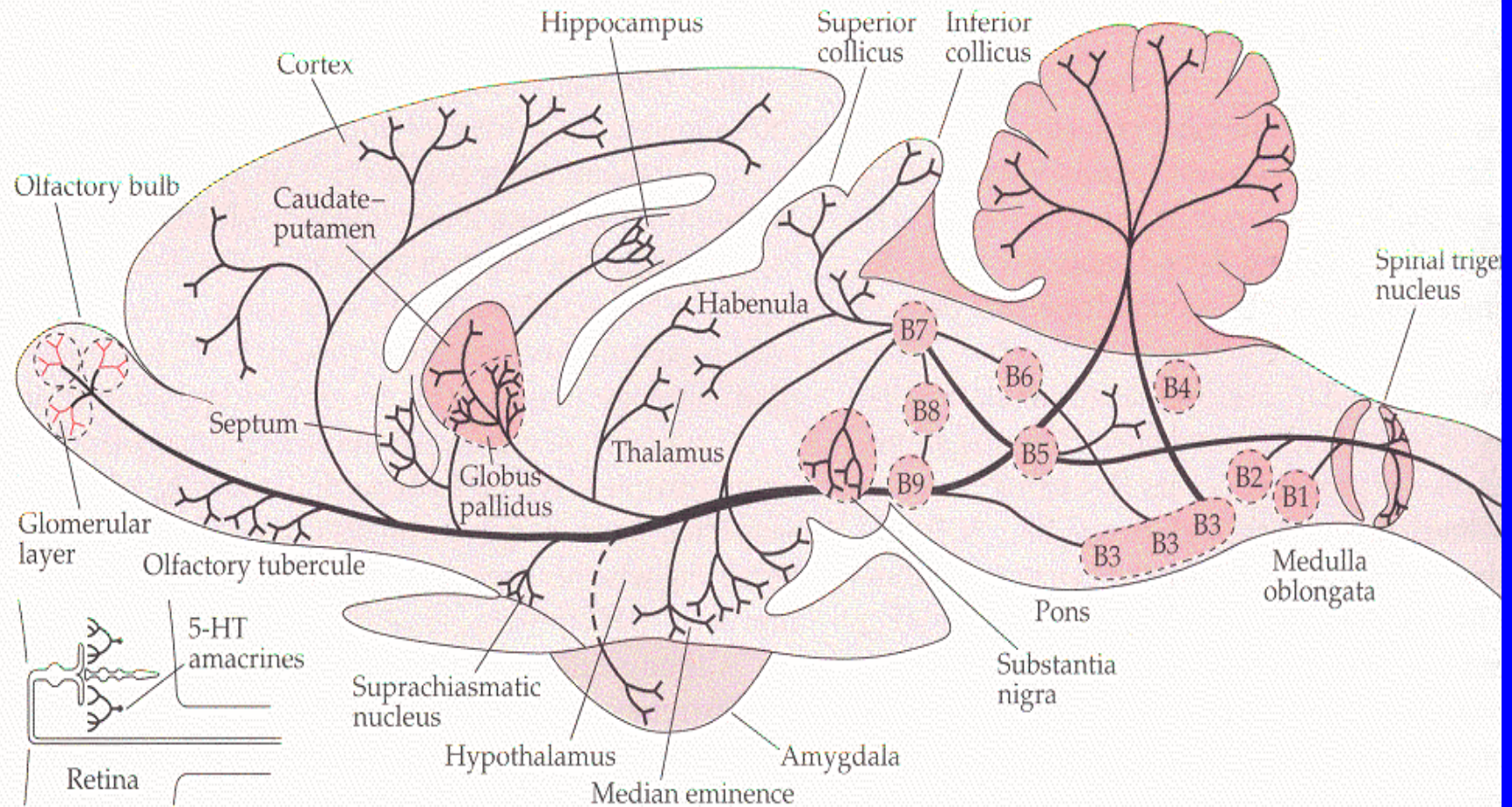
SEROTONINE ~ LOCALISATION ~ SNC



Noyaux du raphé dorsal et médian

Les neurones provenant du raphé se projettent vers le ganglion basal et les diverses parties du système limbique, avec une large distribution dans l'ensemble du cortex cérébral.

SEROTONINE ~ LOCALISATION ~ SNC



Principles of neuropsychopharmacology; Feldman, Meyer, Quenzer Ed; Sinauer associates, Inc 1997; pp 362

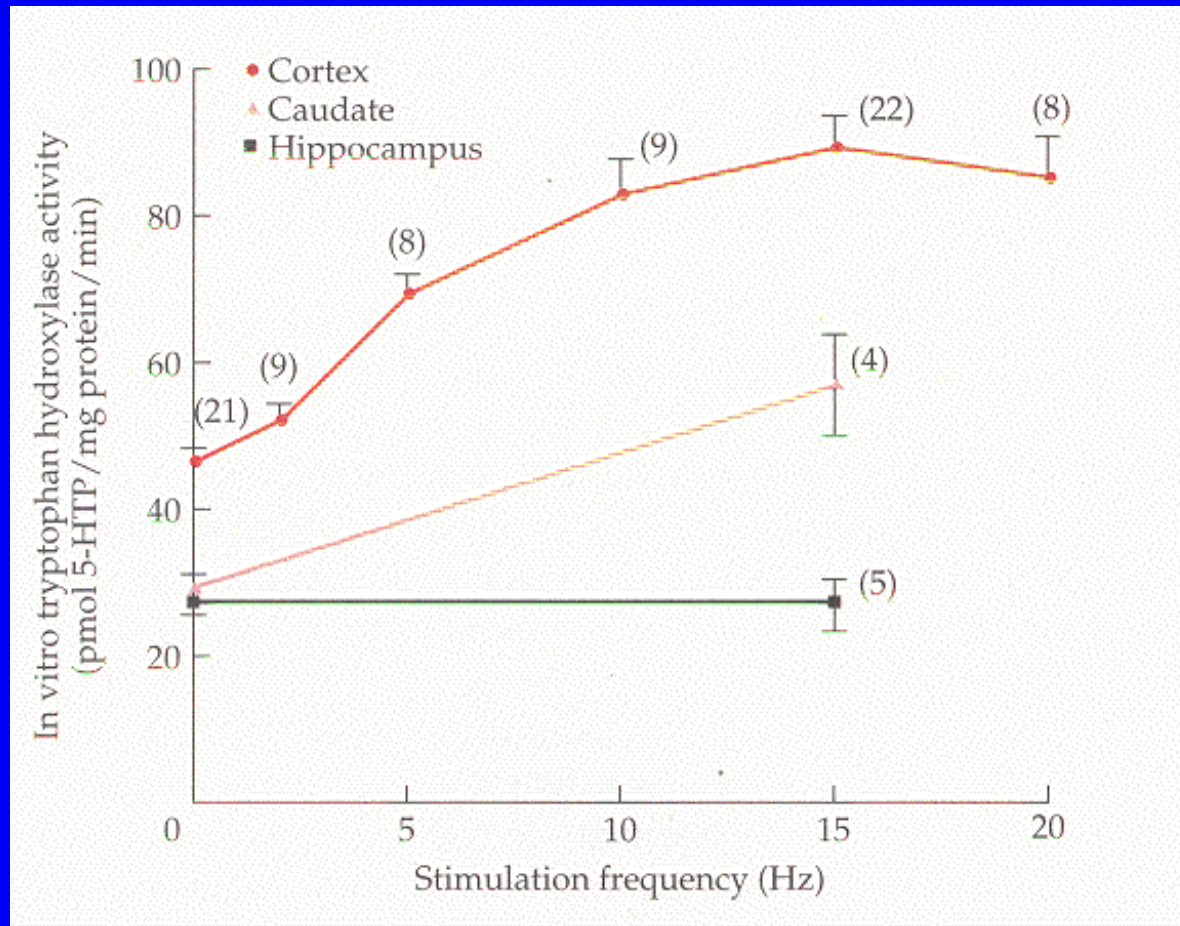
SEROTONINE ~ LOCALISATION ~ SNC

Table 9.1 Relationship between Anatomical Structures and Dahlström and Fuxe's System for Designating Serotonergic Cell Groups^a

5-HT cell group	Anatomical structure(s)
B1	Raphe pallidus nucleus Caudal ventrolateral medulla
B2	Raphe obscurus nucleus
B3	Raphe magnus nucleus Rostral ventrolateral medulla Lateral paragigantocellular reticular nucleus
B4	Raphe obscurus nucleus, dorsolateral part
B5	Median raphe nucleus, caudal part
B6	Dorsal raphe nucleus, caudal part
B7	Dorsal raphe nucleus principal, rostral part
B8	Median raphe nucleus, rostral main part Caudal linear nucleus
B9	Nucleus pontis oralis Nucleus pontis oralis Supralemniscal region

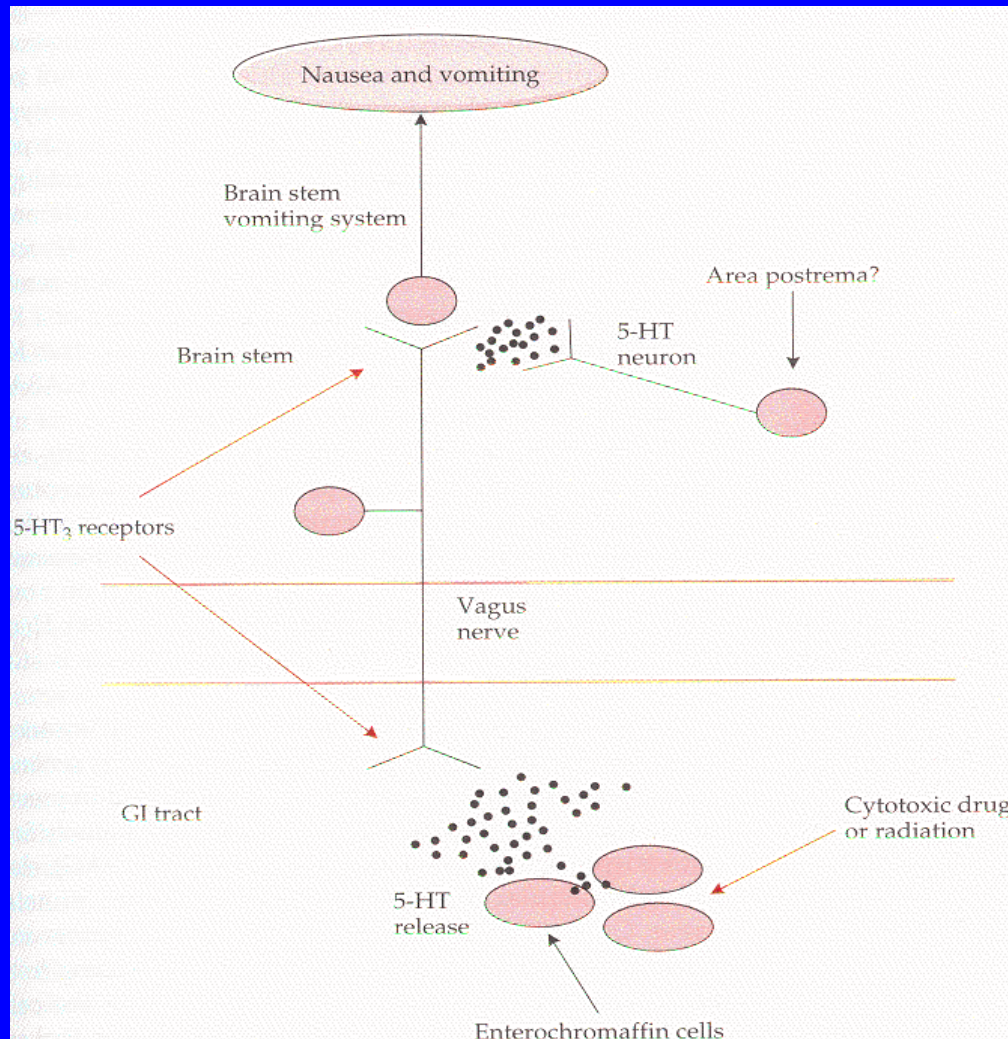
^aThese designations are based on Törk (1990). Other sources may define serotonergic cell groups somewhat differently; for example, the term nucleus raphe pontis has often been used to designate the anatomical structure associated with the B4 or B5 cell group.

SEROTONINE ~ LOCALISATION ~ SNC



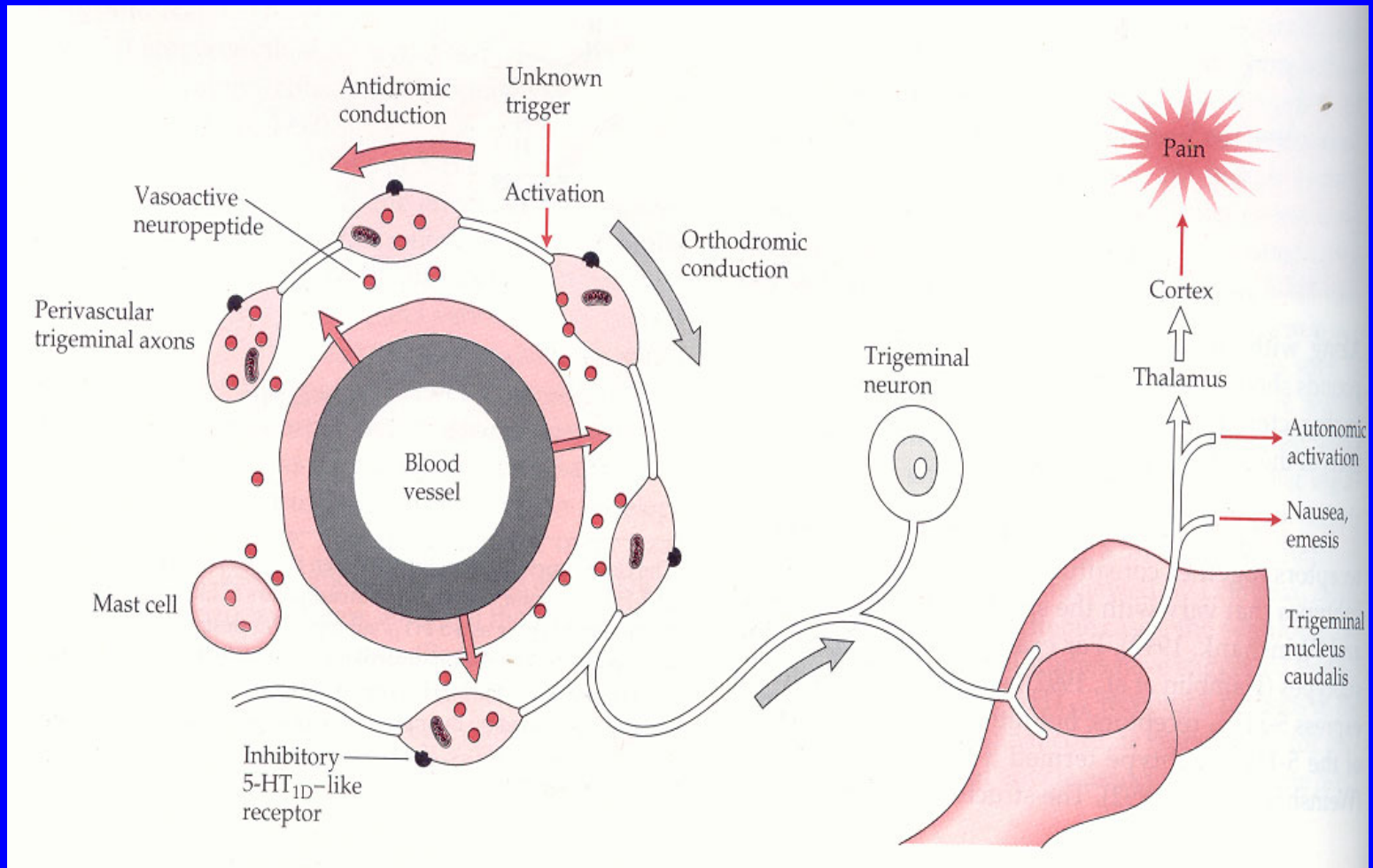
Neuronal activation resulted in a significant increase in enzyme activity in the cerebral cortex and caudate nucleus, both of which receive projections from the dorsal raphe

SEROTONINE - SN CENTRAL - SN PERIPHERIQUE



Principles of neuropsychopharmacology; Feldman, Meyer, Quenzer Ed; Sinauer associates, Inc 1997; pp 377

SEROTONINE - SN CENTRAL - SN PERIPHERIQUE



Principles of neuropsychopharmacology; Feldman, Meyer, Quenzer Ed; Sinauer associates, Inc 1997; pp 360

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INTERACTION LIGAND/RECEPTEUR SEROTONINERGIQUE

ROLES OF SEROTONINE ~ SNC

Sérotonine



Sommeil
Migraine
Comportement alimentaire
Dépression
Comportement sexuel
Agressivité

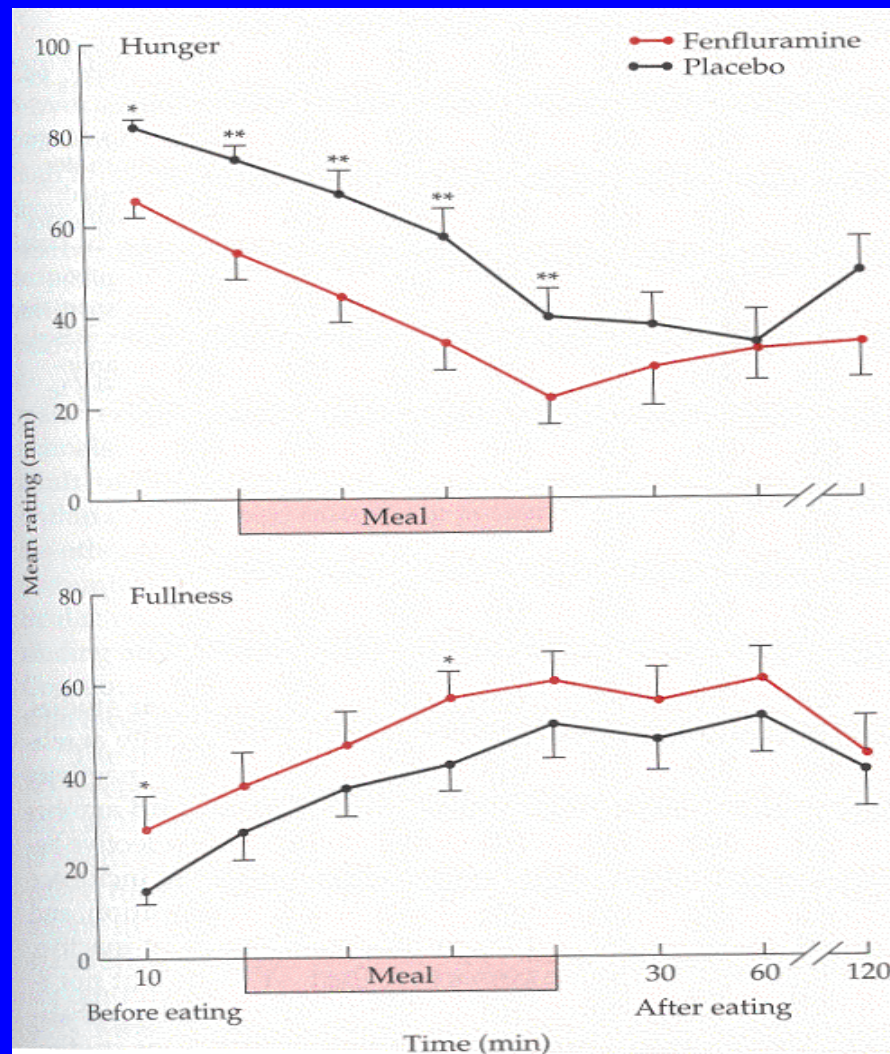
SEROTONINE AND DEPRESSION

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

Table 1. Effects of long-term administration of antidepressant treatments of the 5-HT system assessed using electrophysiological techniques

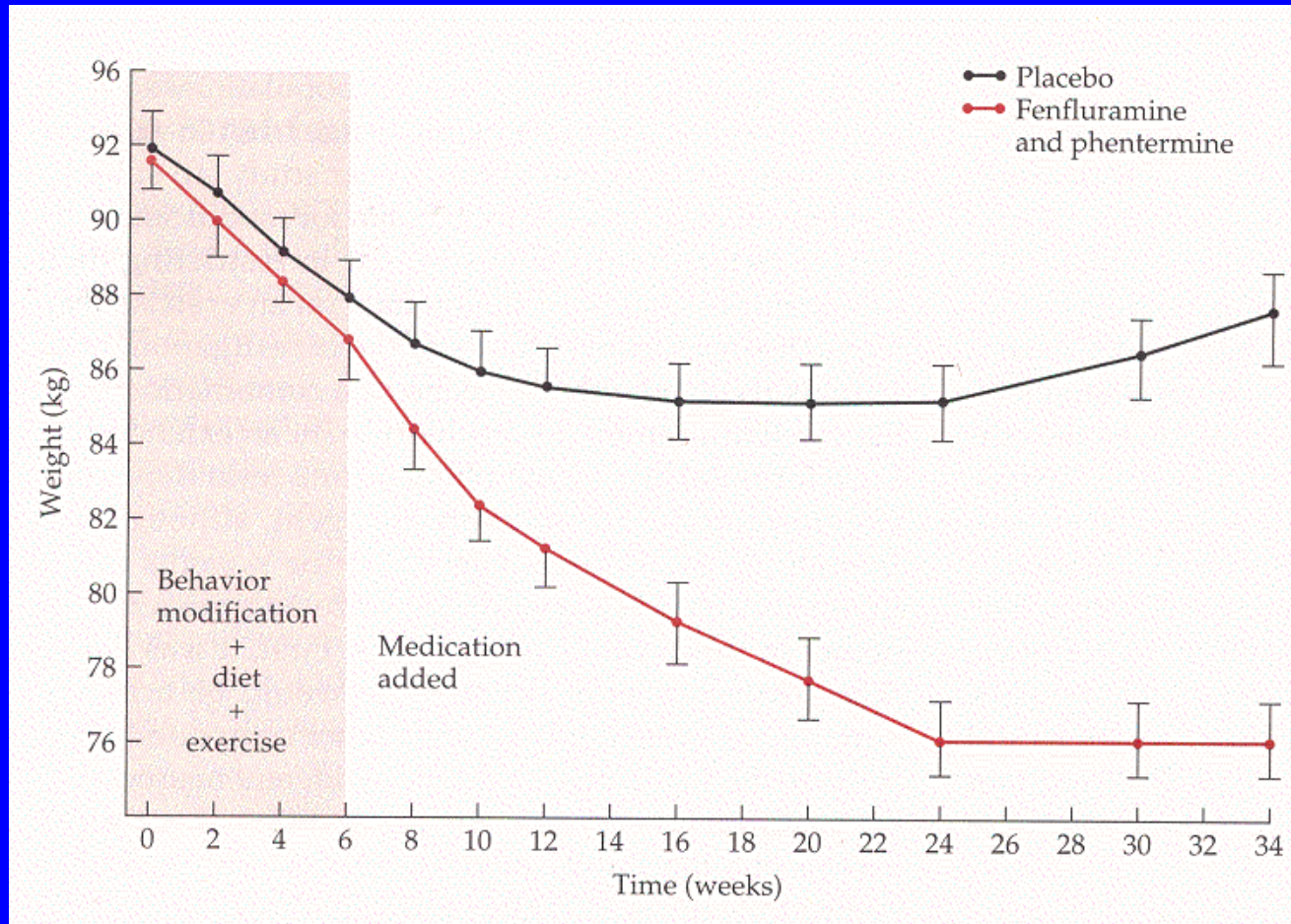
Antidepressant treatment ^a	Responsiveness of somatodendritic 5-HT _{1A} autoreceptors ^b	Function of terminal 5-HT autoreceptors ^c	Function of terminal α_2 -adrenoceptors ^d	Responsiveness of postsynaptic 5-HT receptors ^e	Net 5-HT neurotransmission ^a
Selective 5-HT reuptake inhibitors	↓	↓	n.c.	n.c.	↑
Monoamine oxidase inhibitors	↓	n.c.	↓	n.c. or ↓	↑
5-HT _{1A} receptor agonists	↓	n.c.	n.d.	n.c.	↑ ^f
Tricyclic antidepressants	n.c.	n.c.	n.d.	↑	↑
Electroconvulsive shocks	n.c.	n.c.	n.c.	↑	↑

EFFECT OF FENFLURAMINE ON FEEDING BEHAVIOR



Fenfluramine
augmente la
libération de
sérotonine

EFFECT OF FENFLURAMINE ON FEEDING BEHAVIOR



Principles of neuropsychopharmacology;
Feldman, Meyer, Quenzer
Ed; Sinauer associates, Inc 1997; pp 382

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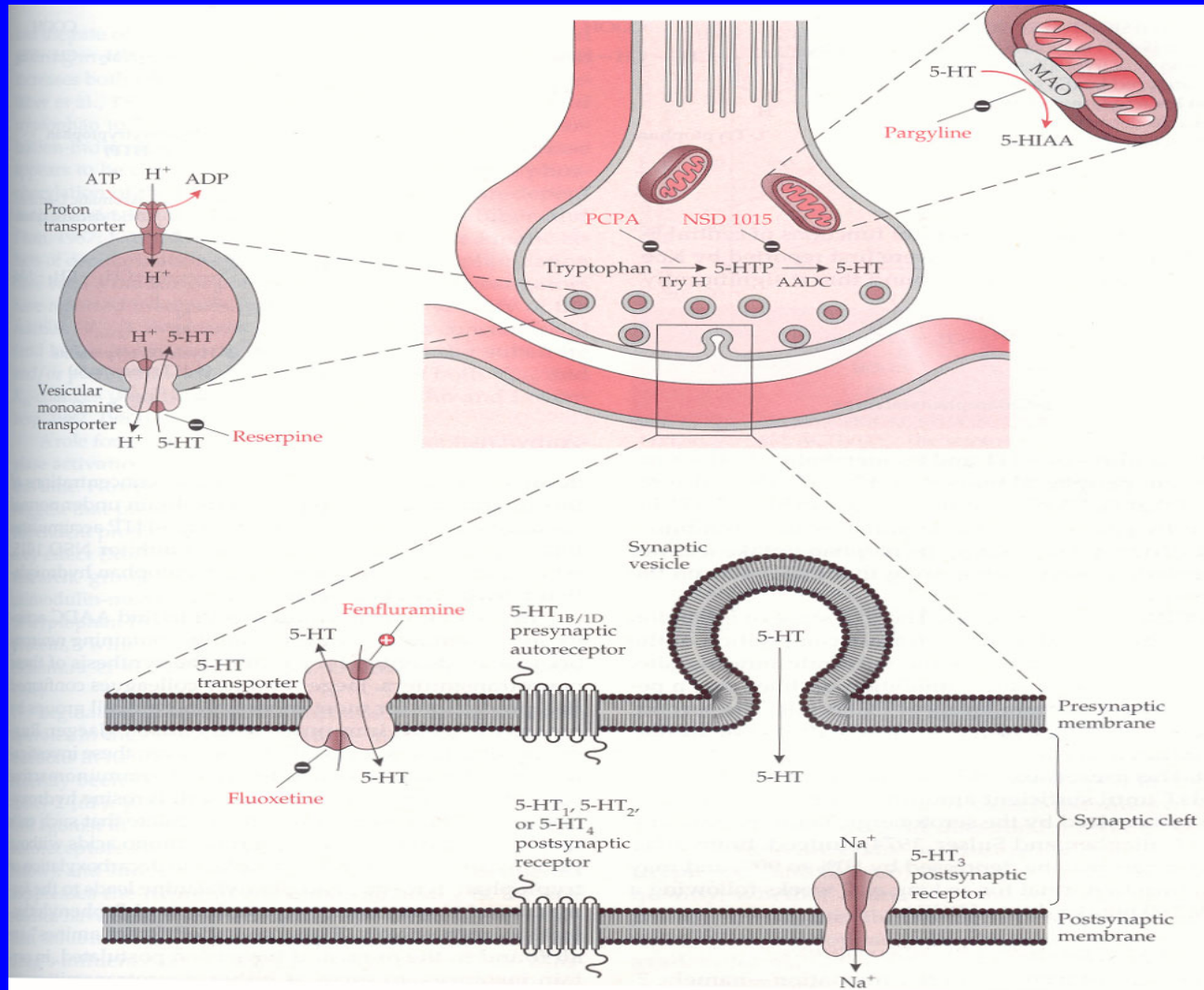
SYNAPSE SEROTONINERGIQUE

SYNTHESE - DEGRADATION

LIBERATION ET STOCKAGE VESICULAIRE

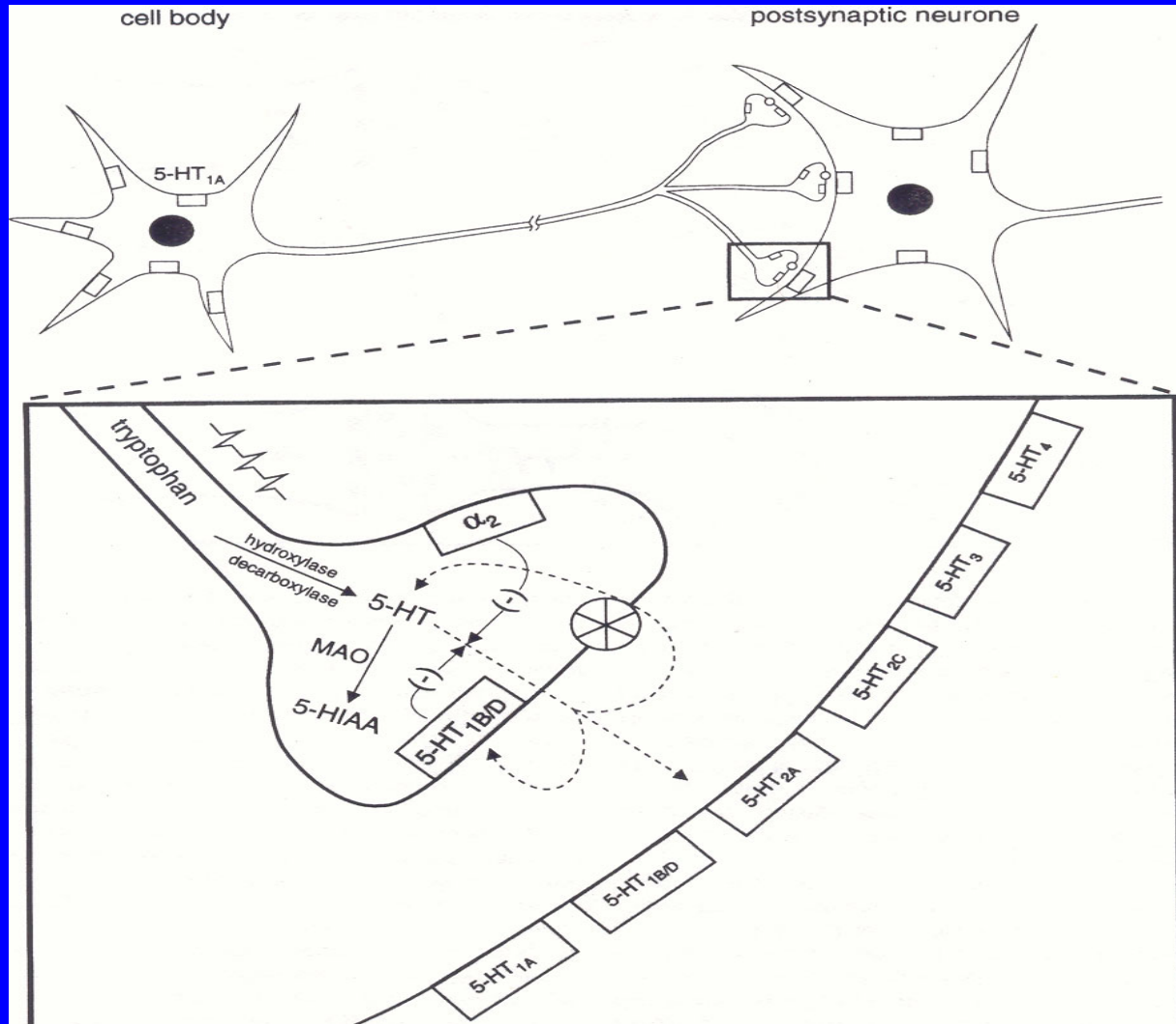
INTERACTION LIGAND/RECEPTEUR SEROTONINERGIQUE

SYNAPSE SEROTONINERGIQUE



From Principles of neuropsychopharmacology; Feldman, Meyer, Quenzer Ed. Sinauer associates, Inc 1997; pp 359

SYNAPSE SEROTONINERGIQUE



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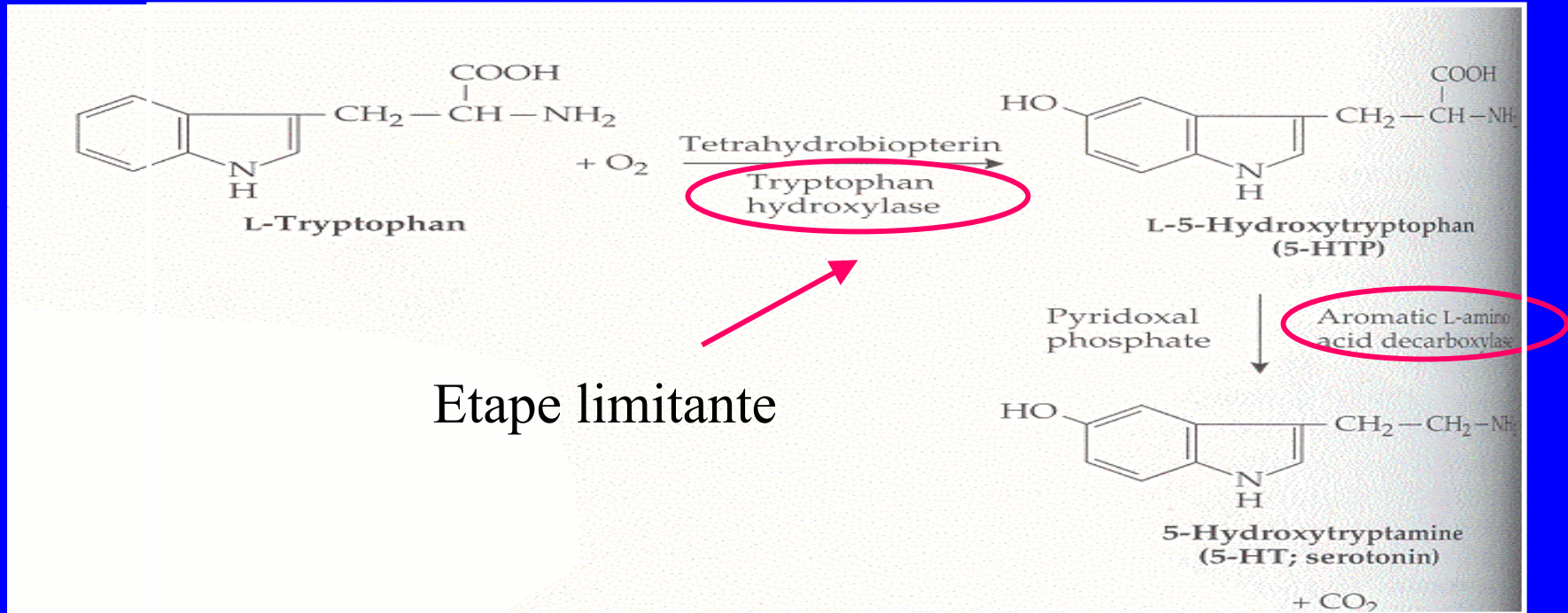
SYNAPSE SEROTONINERGIQUE

SYNTHESE - DEGRADATION

LIBERATION ET STOCKAGE VESICULAIRE

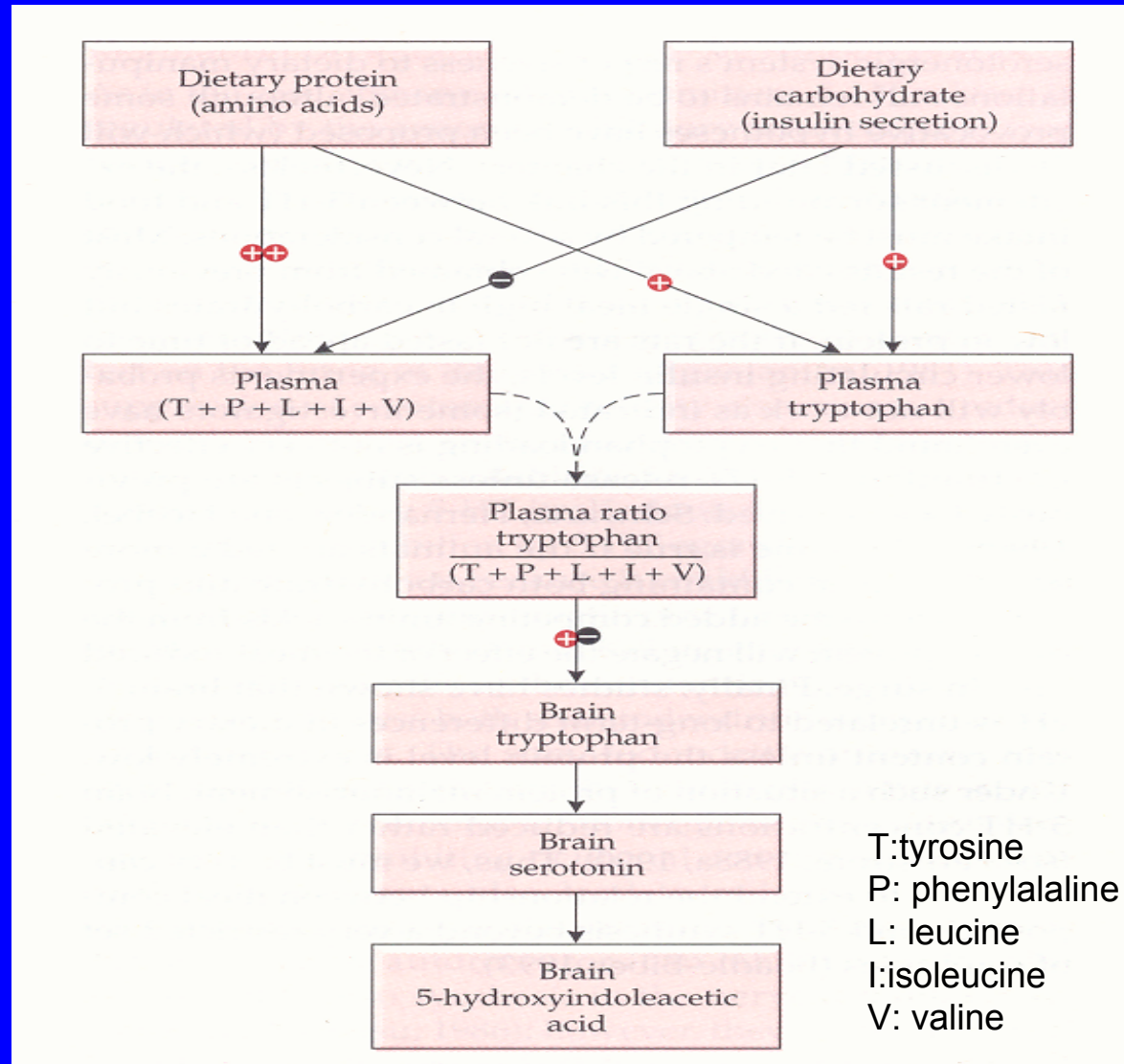
INTERACTION LIGAND/RECEPTEUR SEROTONINERGIQUE

SEROTONINE - SYNTHÈSE



- Le tryptophane est capté de façon active dans le cerveau grâce à un transporteur
- La quantité de tryptophane dans le cerveau est régulée par :
 - sa concentration plasmatique
 - la concentration des acides aminés en compétition avec le tryptophane vis-à-vis du transporteur commun

SYNTHESE DE SEROTONINE ET ALIMENTATION

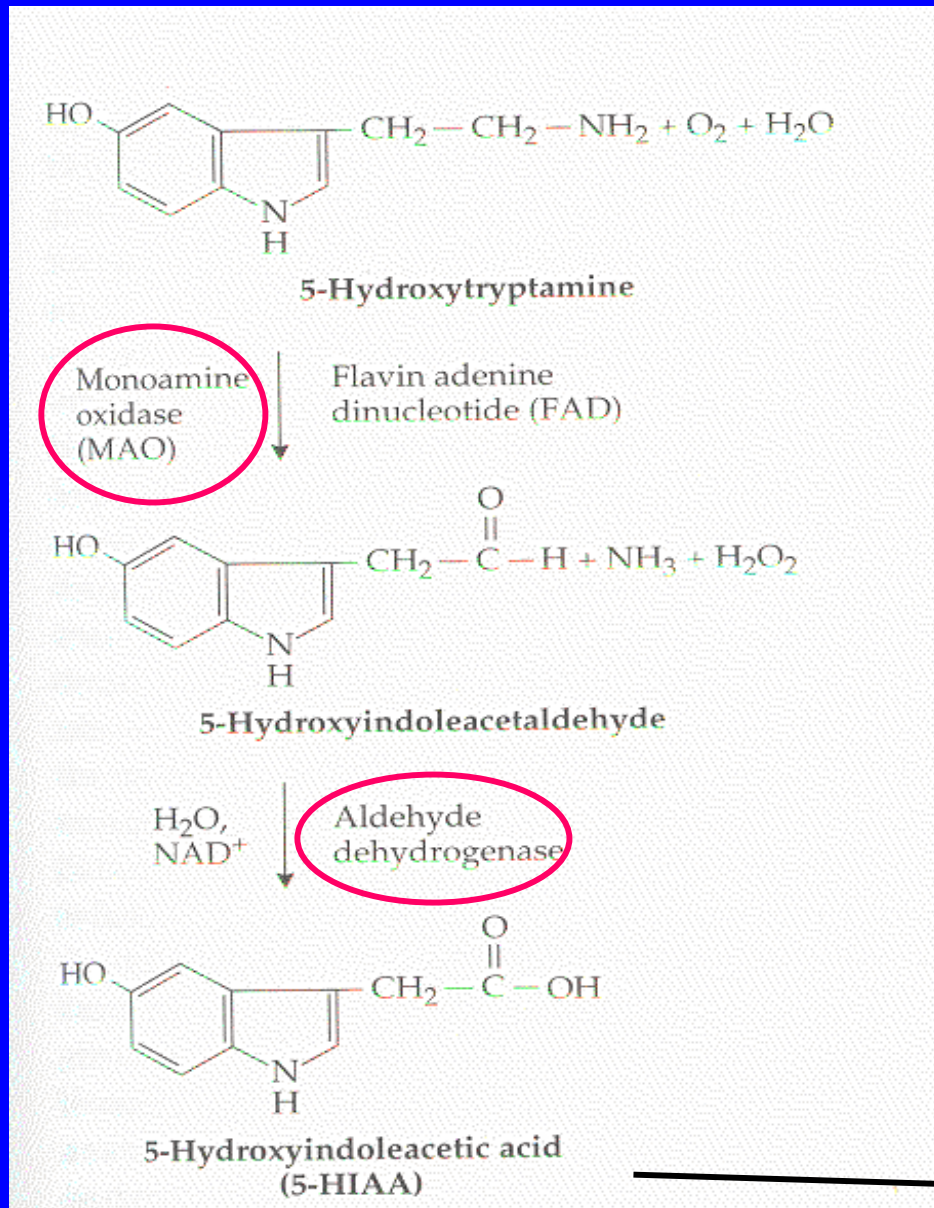


Principles of neuropsychopharmacology
Feldman, Meyer, Quenzer
Ed Sinauer associates, Inc 1997 pp 351

SEROTONINE - POSSIBLE MODULATION ~ SYNTHÈSE

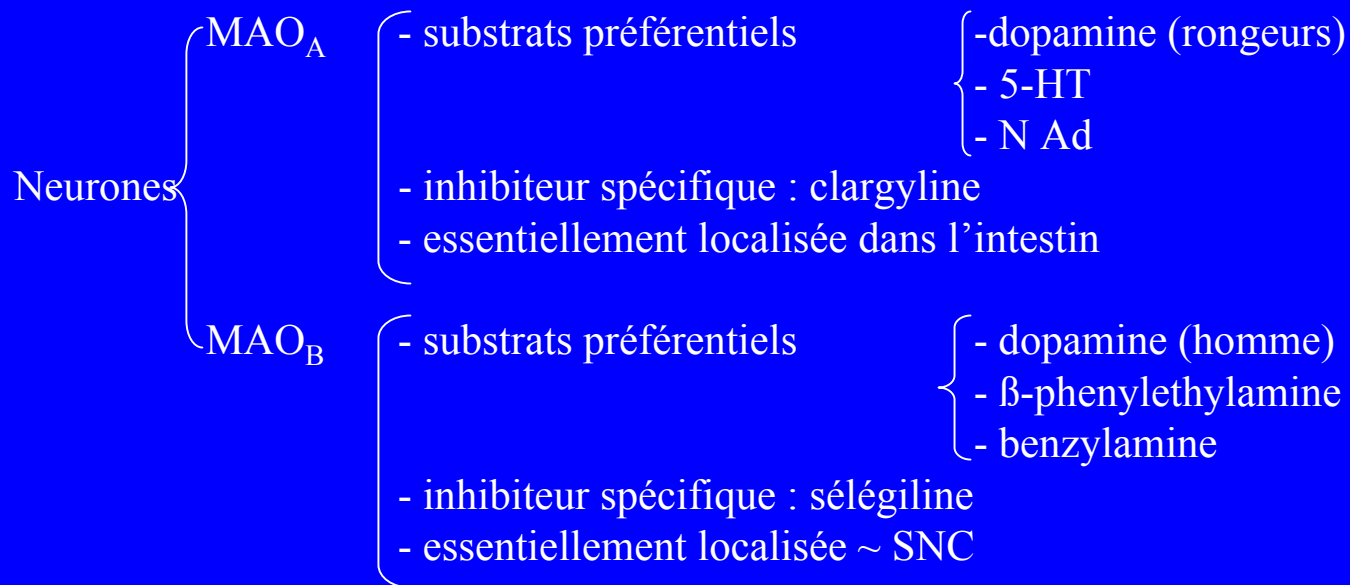
	Activation sérotoninergique	Inhibition sérotoninergique
synthèse	<ul style="list-style-type: none">• ↑ synthèse par apport de précurseur :<ul style="list-style-type: none">- L-Trp- 5-HTP- oxitriptan (Lévotonine®)	<ul style="list-style-type: none">• inhibiteur enzymatique de la <i>TPH</i> :<ul style="list-style-type: none">- non sélectif: p-chlorophénylalanine- sélectif : 6-fluoro-DL-Trp

SEROTONINE - DEGRADATION



Molécule excrétée ↗↗
~ carcinome malin

SEROTONINE - DEGRADATION



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DEGRADATION

INTERACTION LIGAND/RECEPTEUR SEROTONINERGIQUE

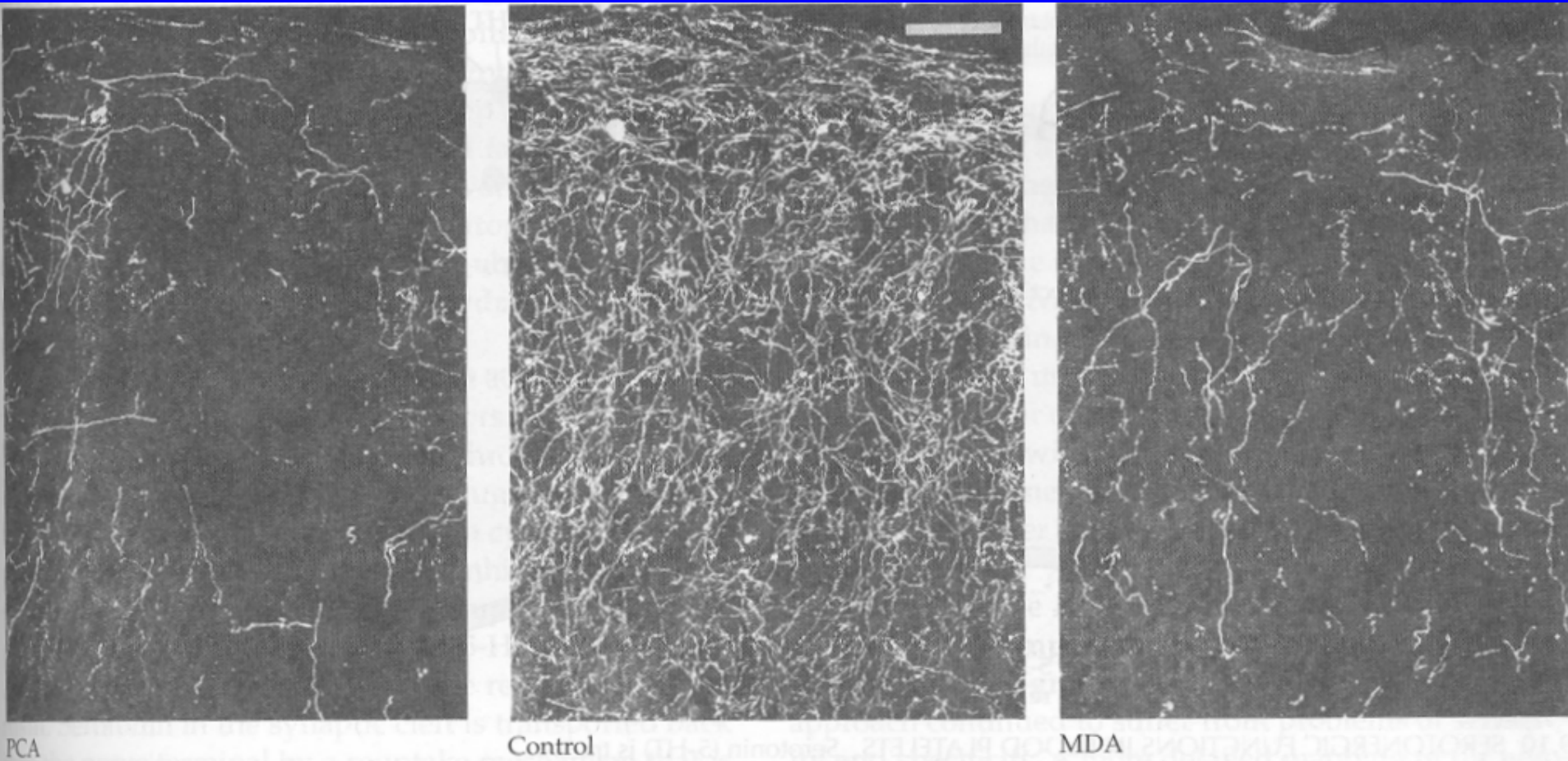
INTERACTION ENTRE SNC / SNP

SEROTONINE - POSSIBLE MODULATION

~ LIBERATION / STOCKAGE

libération stockage	<ul style="list-style-type: none">• ↑ libération : anorexigène (retiré du marché en 1997) fenfluramine (Pondéral®), dexfenfluramine (Isoméride®)	<ul style="list-style-type: none">• ↓ des stocks vésiculaire : réserpine, tétrabénazine
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EFFECT OF AMPHETAMINE DERIVATIVES ON SEROTONINERGIC FIBERS



PCA: para-chloroamphétamine

MDA : 3,4 methylenedioxyamphetamine (“ectasy”)

Augmentation de la libération de 5-HT

SEROTONINE - INHIBITION DE RECAPTURE

Inhibiteurs de recapture sélectifs

Fluoxépine
Fluvoxamine
Paroxétine
Citalopram
Sertraline

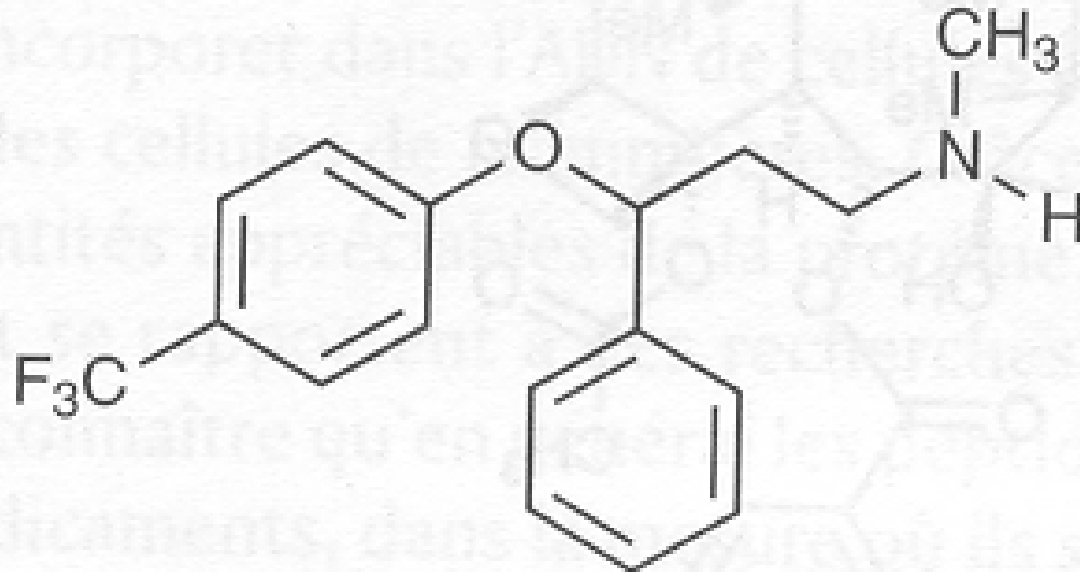
Inhibiteurs de capture non sélectifs

5-HT et DA: cocaïne

5-HT et NA:

- Tricycliques de type imipramine: imipramine, clomipramine, désipramine, amitryptiline
- Autres: milnacipran, venlafaxine

EXEMPLE D'INHIBITEUR SELECTIF DE LA RECAPTURE DE SEROTONINE



Fluoxépine

Le Prozac.

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SYNAPSE SEROTONINERGIQUE

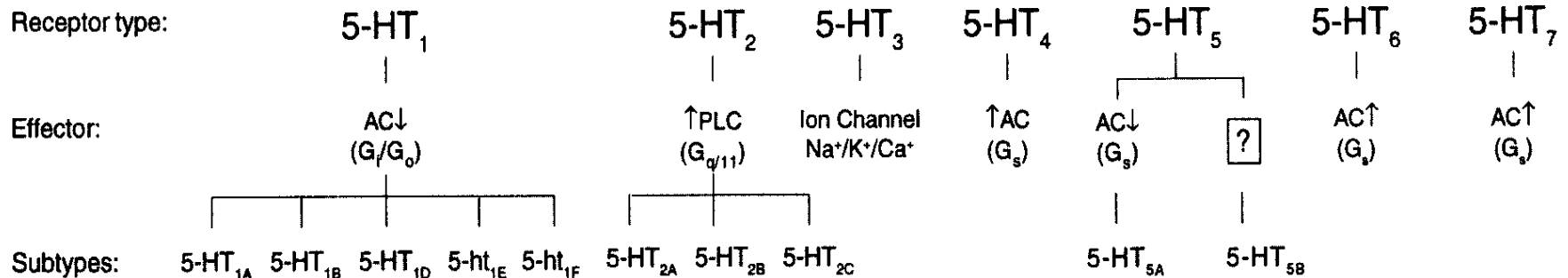
SYNTHESE - DEGRADATION

LIBERATION ET STOCKAGE VESICULAIRE

INTERACTION LIGAND/RECEPTEUR SEROTONINERGIQUE

SEROTONINE AND RECEPTORS

Current classification of Serotonin Receptors



5-HT receptors are at present divided into 7 classes, based upon their pharmacological profiles, cDNA-deduced primary sequences and signal transduction mechanisms. With the exception of the 5-HT₃ receptor, which forms a ligand-gated ion channel, all 5-HT receptors belong to the superfamily of G-protein coupled receptors containing a predicted seven-transmembrane domain structure.

SEROTONINE AND RECEPTORS

	Synapse		Sensibilité	Transduction	Action	Localisation
	pré	post				
1 A	+	±	nM	Gi / AC ouverture K+	-	- raphé - système limbique
1 B/D	+	±	nM	Gi / AC ouverture K+	-	- substance noire - globus pallidus
2		+	μ M	Gq / PLC fermeture K+	+	- 2A : cortex frontal - 2B : périphérie / muscle lisse (vx, bronche et TD)
3		+	μ M	Récepteur canal (ouverture Na+)	+	- bulbe (CTZ) - amygdale
4		+	μ M	Gs / AC	+	- substance noire - hippocampe
5		+	μ M	?	?	- habenula - hippocampe
6		+		Gs / AC	+	- système limbique
7		+		Gs / AC	+	- hypothalamus - système limbique

SEROTONINE AND 5HT1 RECEPTORS

Table 9.2 Pharmacology of 5-HT₁ Receptors

Receptor subtype	Pharmacological properties			
	Agonists	Antagonists	Radioligands	Effector pathways
5-HT _{1A}	8-OH-DPAT, ipsapirone	SDZ 216-525, WAY-100135	[³ H]8-OH-DPAT	↓ cAMP, ↑ K ⁺ channel
5-HT _{1B}	CP-93,129		[¹²⁵ I]GTI, [³ H]CP-96,501	↓ cAMP
5-HT _{1D}	Sumatriptan, 5-(Nonyloxy)tryptamine		[¹²⁵ I]GTI	↓ cAMP
5-HT _{1E}				↓ cAMP
5-HT _{1F}				↓ cAMP

Source: After Humphrey, Hartig, and Hoyer, 1993.

SEROTONINE AND 5HT-1 RECEPTORS

Table 1. Properties of cloned human 5-HT₁ receptors

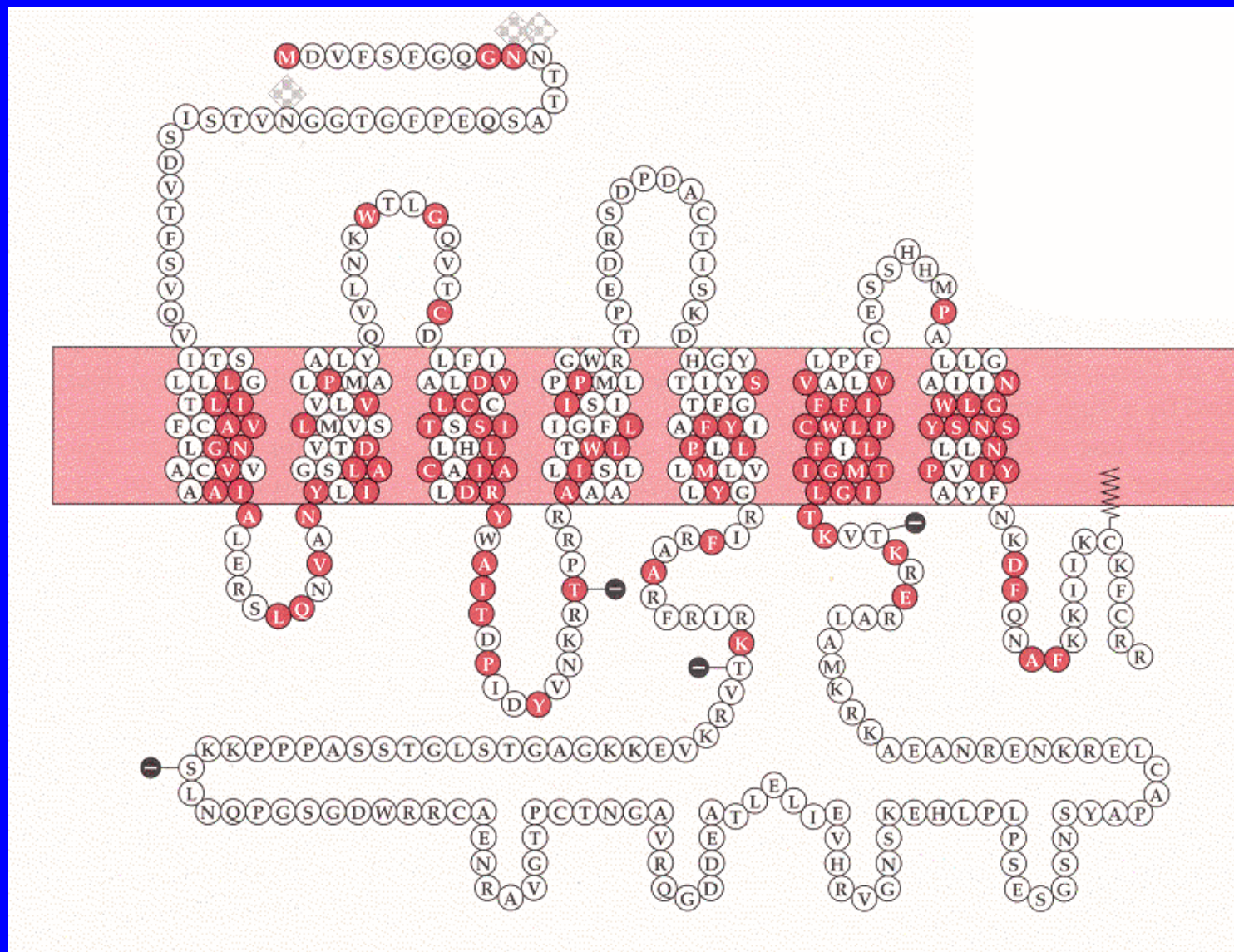
Cloned human 5-HT ₁ receptors					
	1A	1B	1D	1E	1F
Signaling					
Coupling			G _i /G _o		
Signal			↓cAMP, ↑gK and ↓gCa (↑PI)		
Pharmacology					
Agonist	DPAT	Sumatriptan	Sumatriptan	5-HT	5-HT
pEC ₅₀	8.2	6.0	7.0	8.2	6.9
Antagonist	WAY100635	Cyanopindolol	Methiothepin	–	–
pK _i	7.9	8.2	7.7		
Agonist pK _i					
5-HT	8.3	7.4	7.3	8.2	6.9
5-CT	9.5	8.0	7.9	5.1	5.5
Molecular					
Molecular size (aa)	421	390	377	365	367
Chromosome	5.q12	6.q13	1.p35–36	6.q14–15	3.p13–14
mRNA distribution (brain)	Raphe, hippocampus, septum and cortex	Striatum, hippocampus, cerebellum and vascular	Striatum	?	Hippocampus

*Various signaling, pharmacological, molecular and expression properties of the five cloned human 5-HT₁ receptors are summarized based on information found in previous review articles^{2,3}.

^bArrows indicate positive or negative regulation.

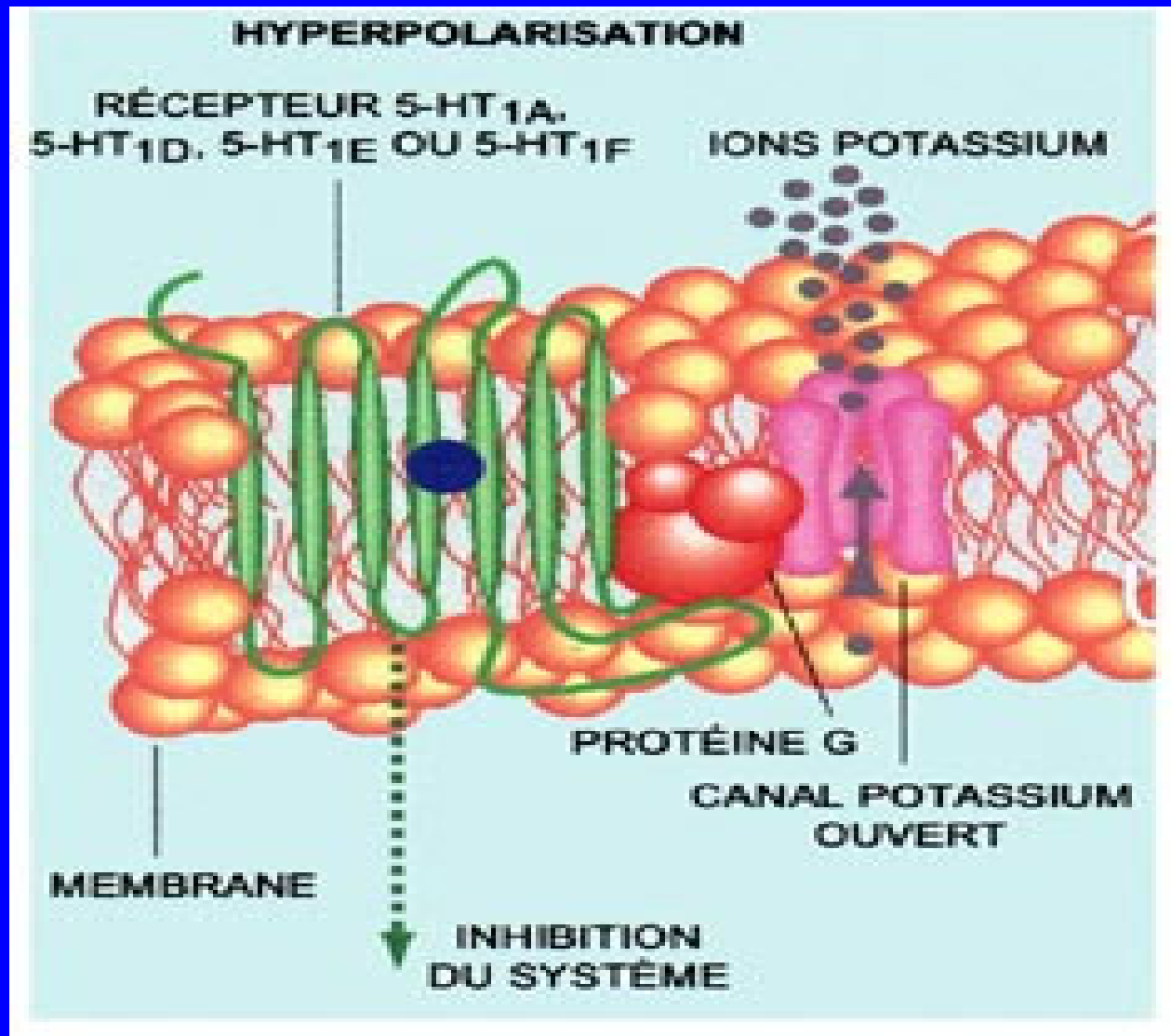
^cAbbreviations: gCa, Ca²⁺ conductance; 5-CT, 5-carboxytryptamine; DPAT, 8-hydroxy-2-(di-n-propylamine)tetralin; gK, K⁺ conductance; PI, phosphatidyl inositol turnover.

STRUCTURE OF 5-HT₁ RAT RECEPTOR

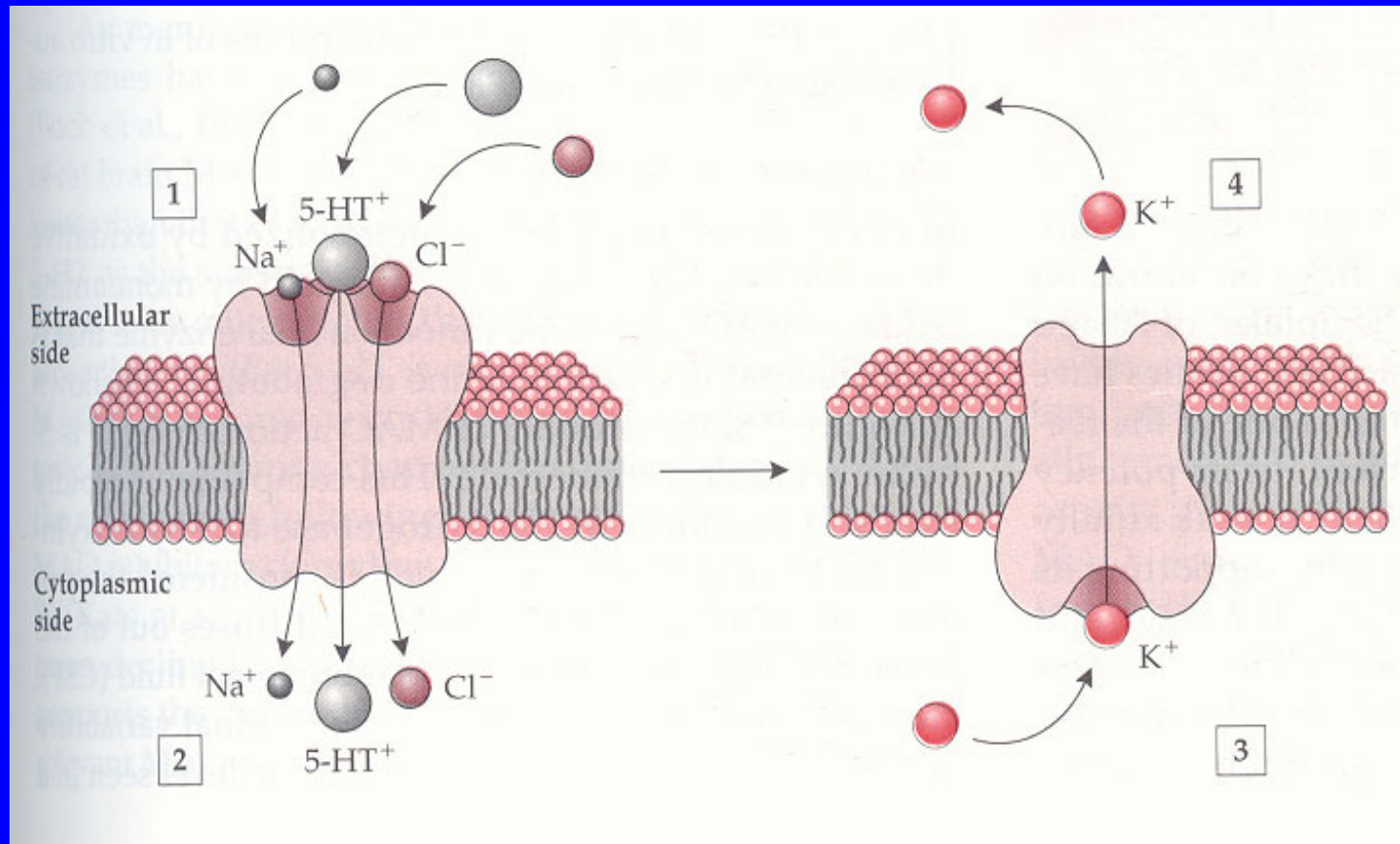


Principles of neuropsychopharmacology; Feldman, Meyer, Quenzer Ed; Sinauer associates, Inc 1997; pp 370

SEROTONINE - 5HT₁ RECEPTORS

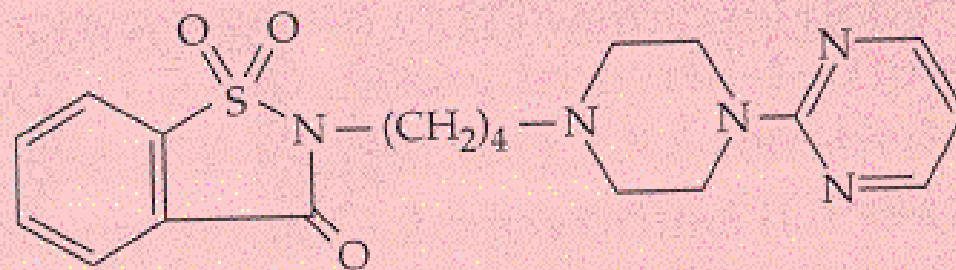


SEROTONINE - TRANSPORT ACROSS THE MEMBRANE

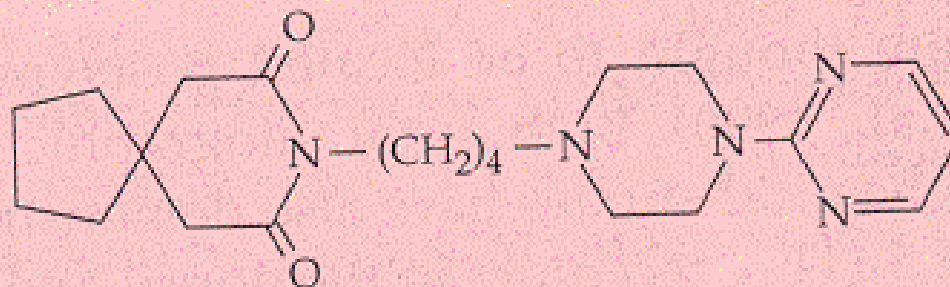


Principles of neuropsychopharmacology; Feldman, Meyer, Quenzer Ed; Sinauer associates, Inc 1997; pp 355

AGONISTS OF 5-HT₁ RECEPTORS

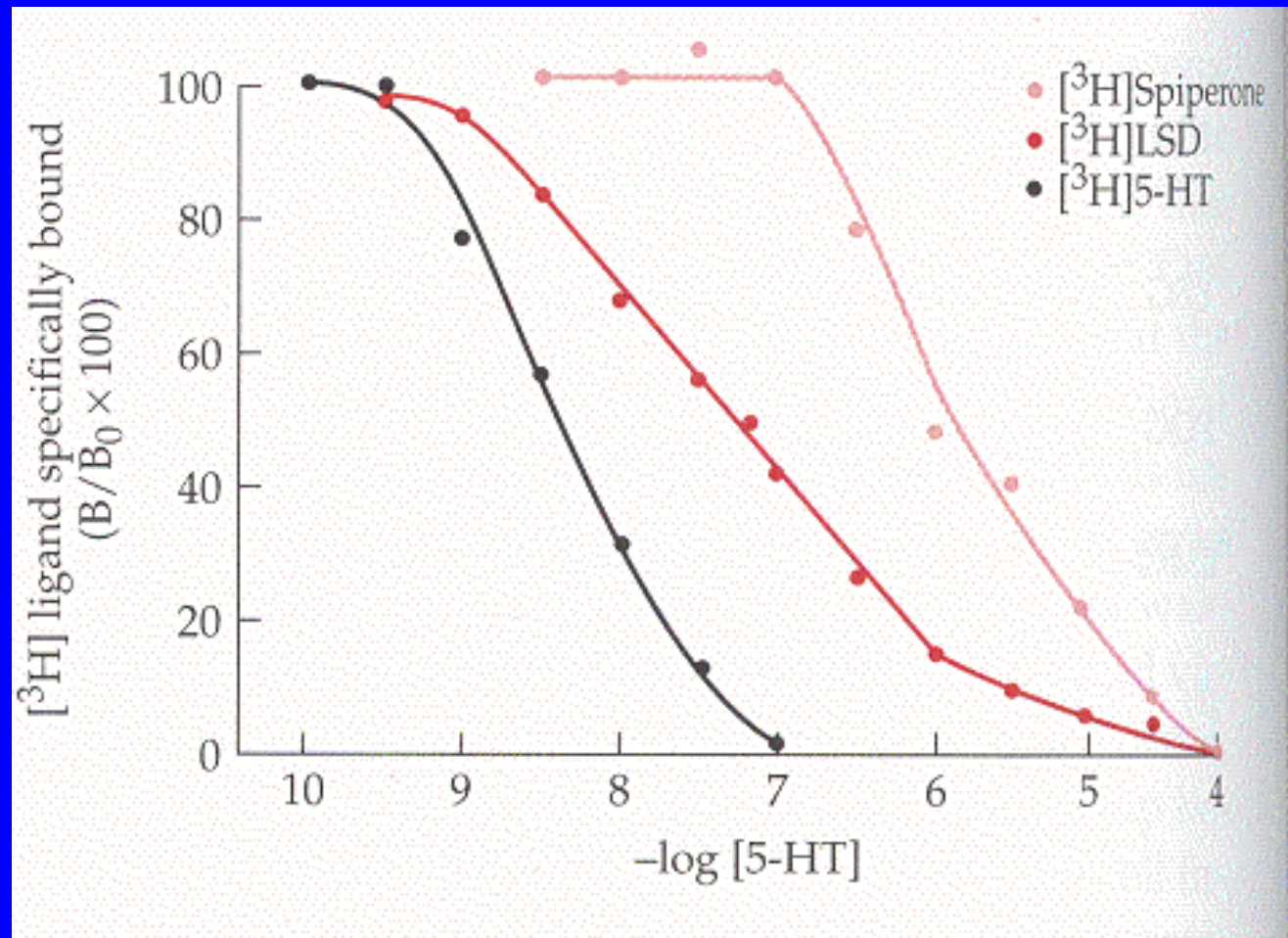


Ipsapirone

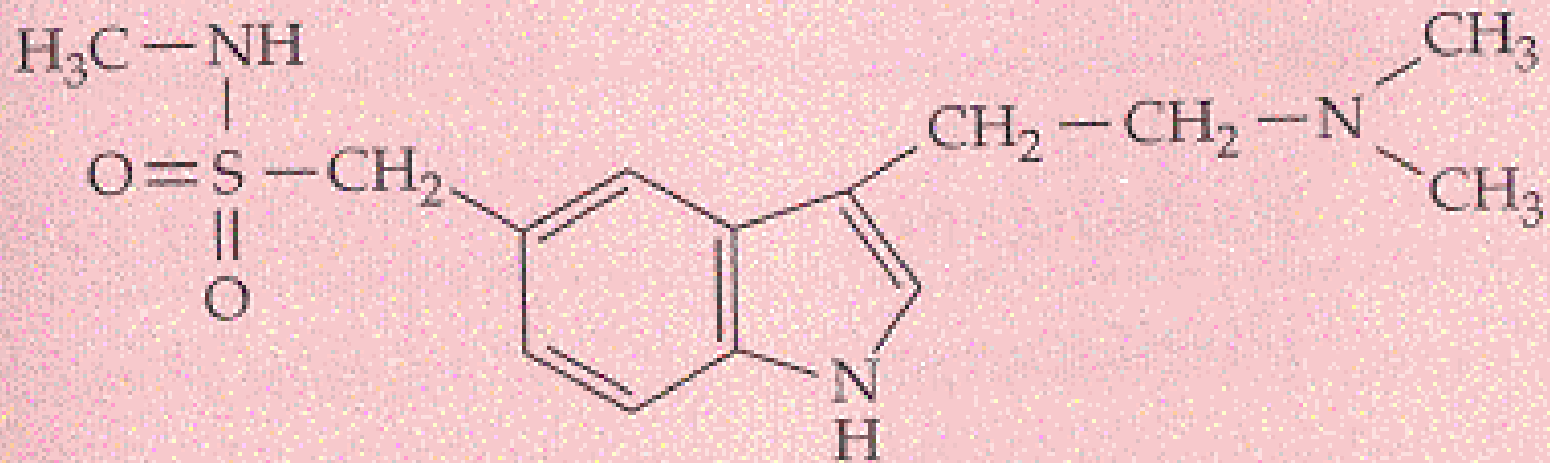


Buspirone

INHIBITION OF BINDING TO RAT FRONTAL CORTEX SEROTONINERGIC RECEPTORS LABELLED BY 5-HT

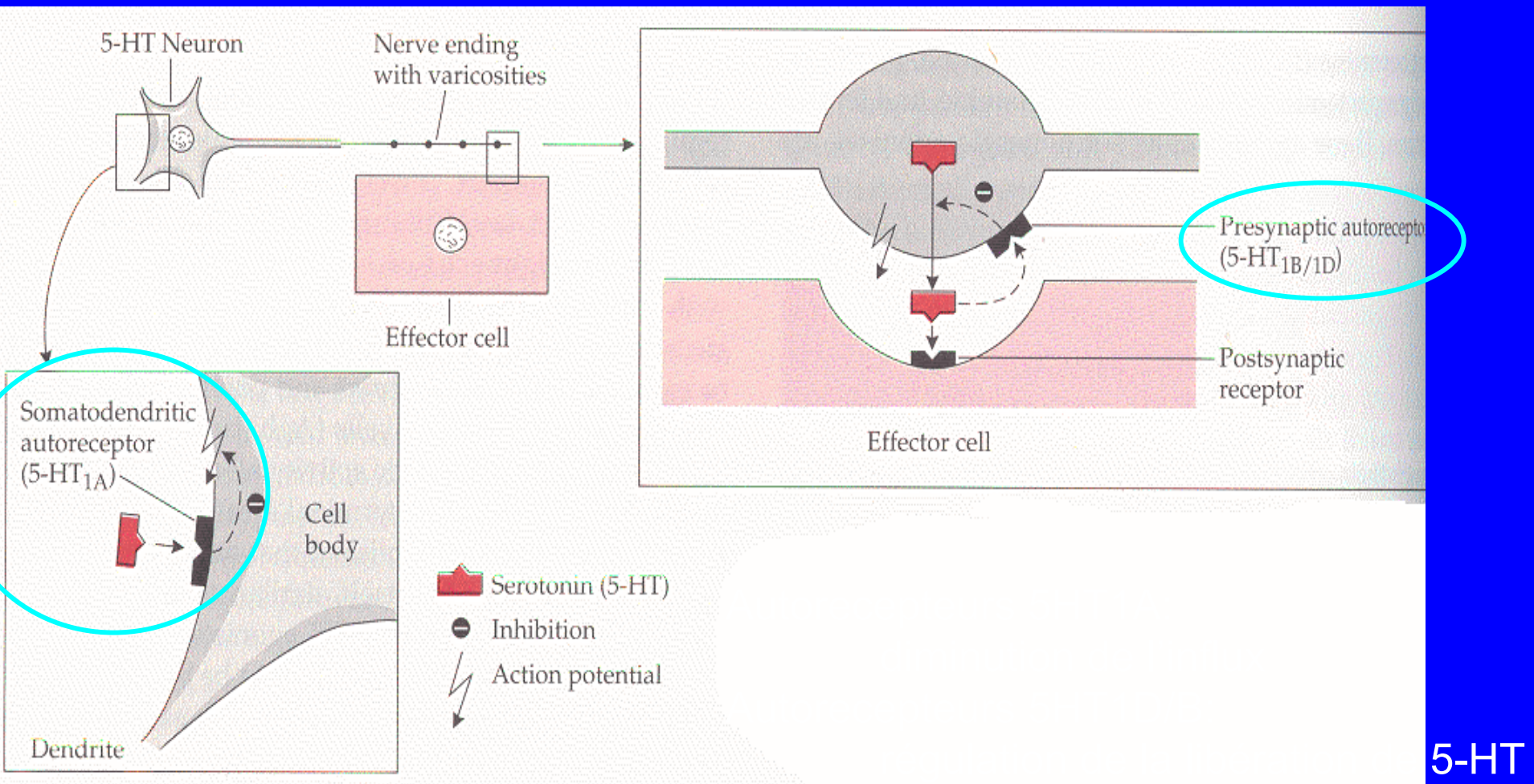


AGONIST OF 5HT1D RECEPTORS



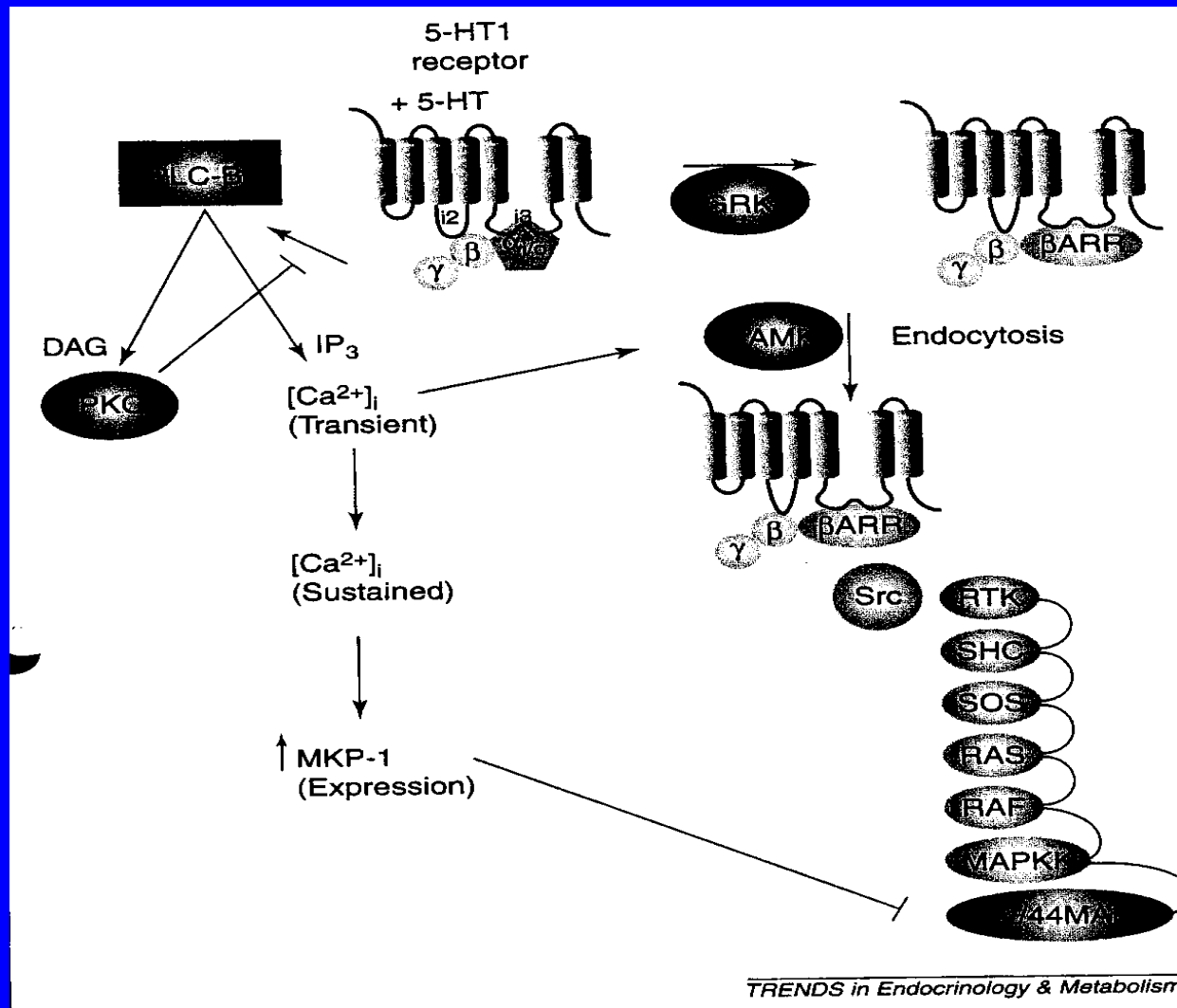
Sumatriptan

SEROTONINE AND AUTORECEPTORS 5HT1



5-HT

5HT-1 RECEPTORS AND TRANSDUCTION



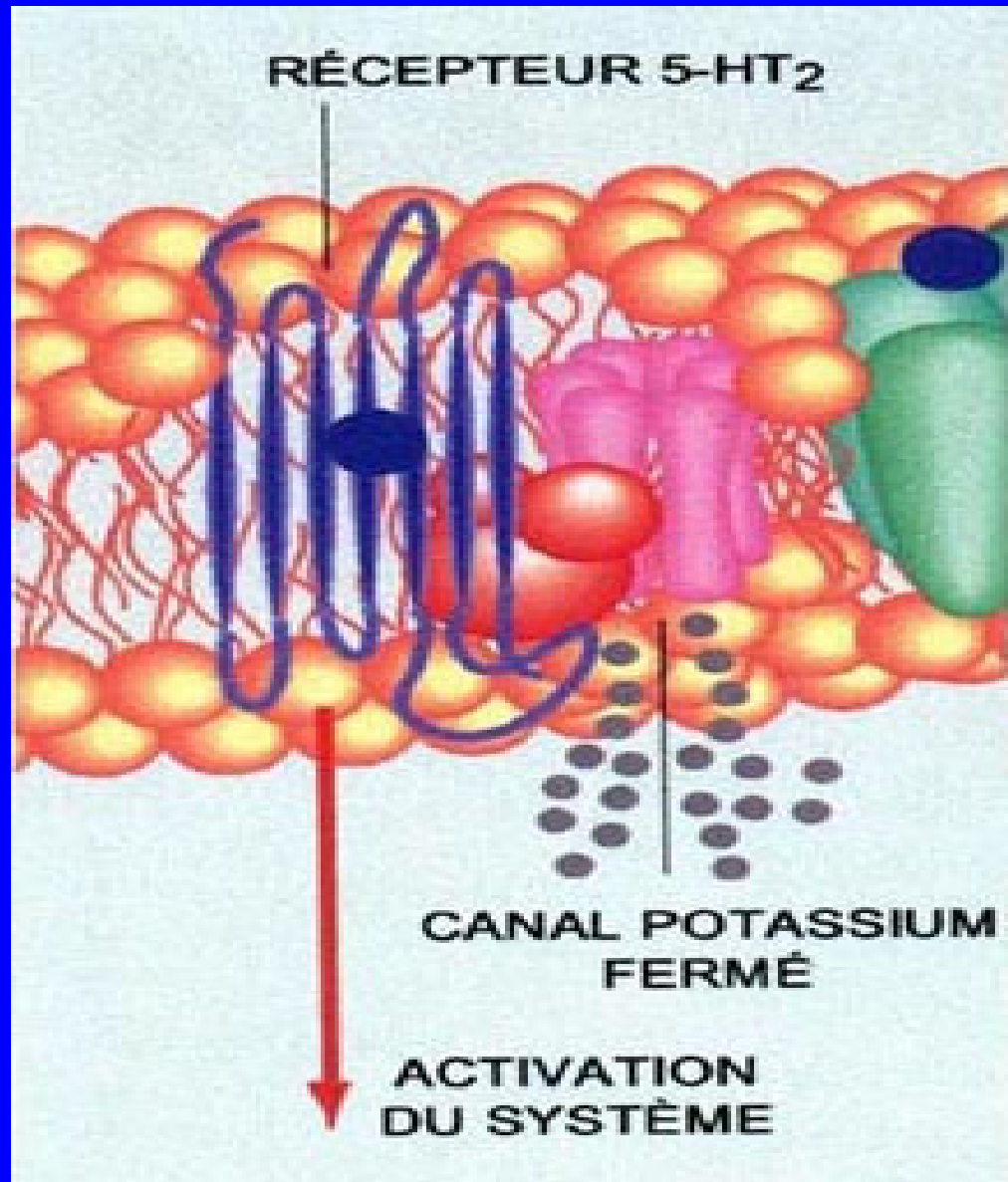
SEROTONINE AND 5HT2/3/4 RECEPTORS

Table 9.3 Pharmacology of 5-HT₂, 5-HT₃, and 5-HT₄ Receptors

Receptor subtype	Agonists	Antagonists	Radioligands	Effector pathway
5-HT _{2A}	α -Methyl-5-HT,	Ketanserin, ritanserin, LY-53857	[³ H]Ketanserin	↑ IP ₃ /DAG
5-HT _{2B}	α -Methyl-5-HT, <i>m</i> -CPP, ^a MK212	SB 200646A, LY-53857		↑ IP ₃ /DAG
5-HT _{2C}	α -Methyl-5-HT <i>m</i> -CPP, ^a MK212	SB 200646A, mesulergine, LY-53857	[³ H]Mesulergine	↑ IP ₃ /DAG
5-HT ₃	2-Methyl-5-HT, <i>m</i> -chlorophenyl- biguanide	Tropisetron, ondansetron, granisetron	[³ H]GR65630, [³ H]zacopride	Cation channel
5-HT ₄	5-Methoxytryptamine, SB 205149, BIMU8	GR113808, RS 23597-190	[³ H]GR113808	↑ cAMP

^a*m*-CPP is a partial agonist at 5-HT_{2B} and 5-HT_{2C} receptors.

SEROTONINE - 5HT₂ RECEPTORS



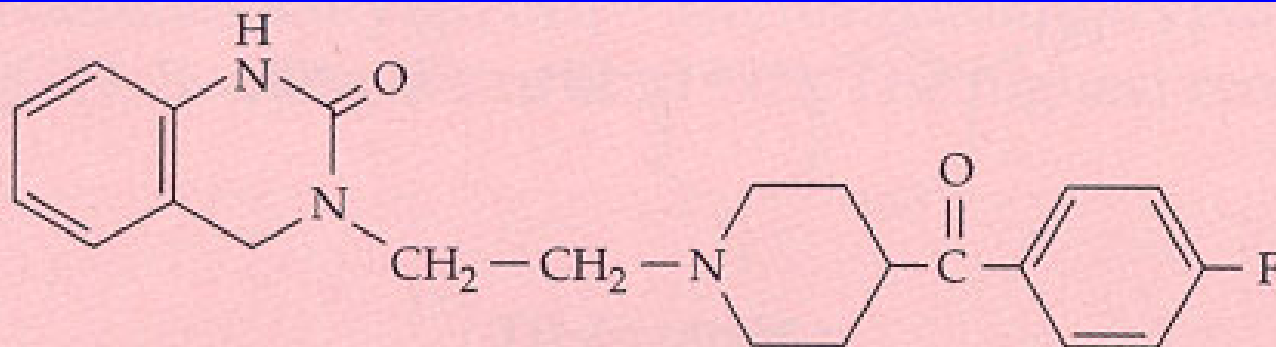
AGONISTS AND ANTAGONISTS OF 5-HT₂ RECEPTORS

5-HT₂ subtype selective ligands

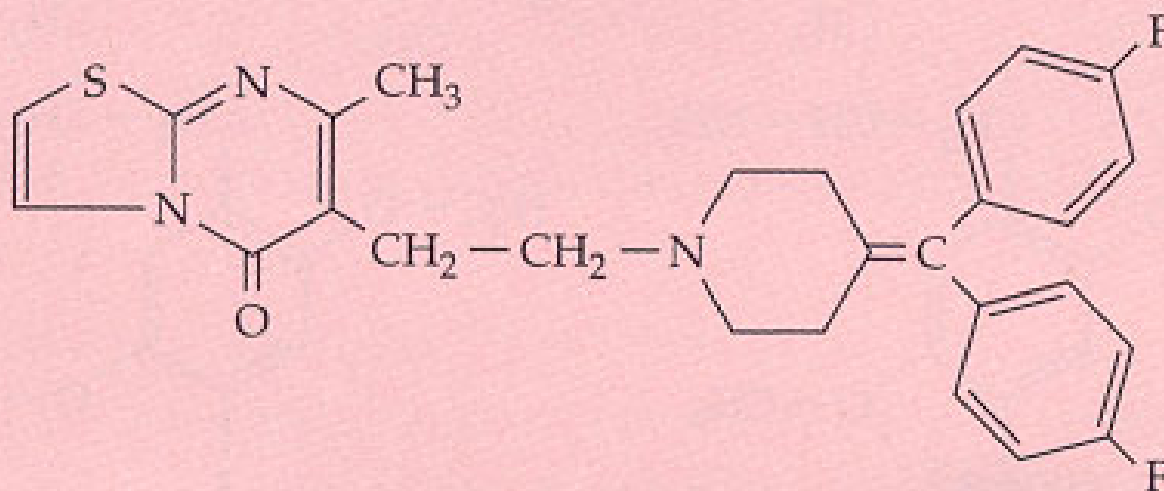
Subtype:	5-HT _{2A}	5-HT _{2B}	5-HT _{2C}
Agonists:	α -Me-5-HT †	α -Me-5-HT † BW 723C86	α -Me-5-HT † MK 212 † mCPP †
Antagonists:	Ketanserin † Spiperone † MDL 11,939 † MDL 100,907	Rauwolscine † SB 206553 SB 204741 LY 266097	SB 206553 RS 102221 SB 221284

† denotes compounds available from Tocris

ANTAGONISTS OF 5-HT₂ RECEPTORS

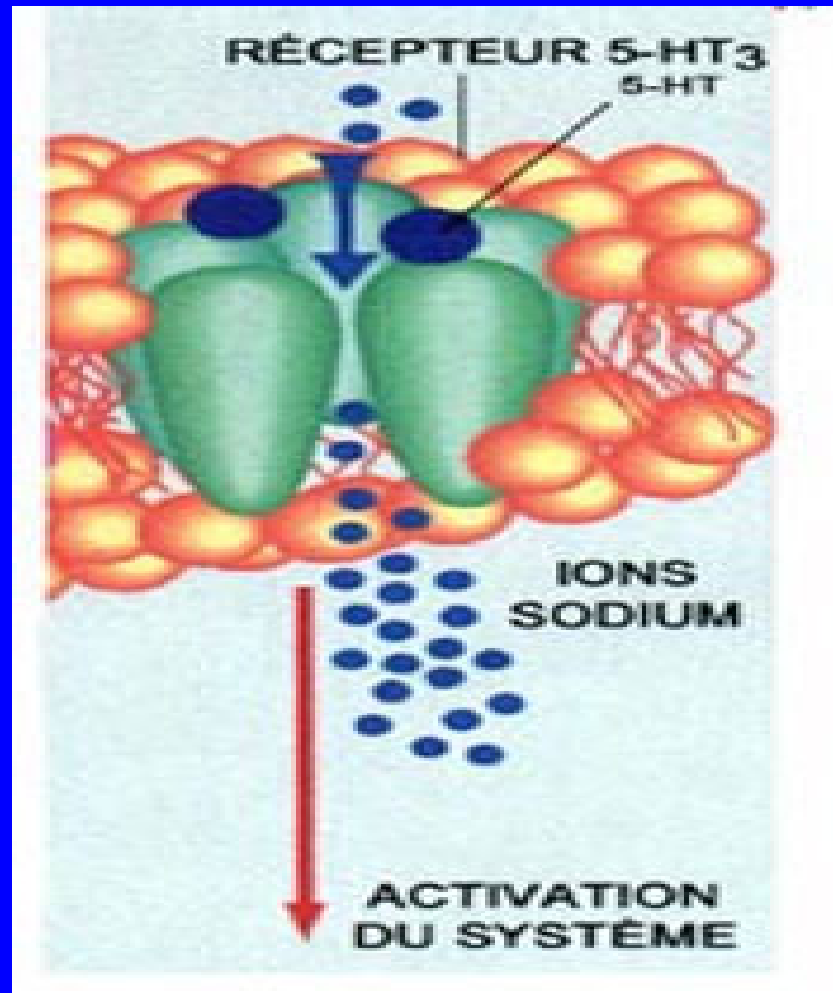


Ketanserin



Ritanserin

5 HT3 RECEPTOR-LIGAND GATED ION CHANNEL



5HT₃ RECEPTOR - LOCALIZATION

The highest densities are found in the

- area postrema
- nucleus tractus solitarius
- substantia gelatinosa
- trigeminal nucleus
- dorsal vagal complex

5HT₃ RECEPTOR EFFECT SNC

* administration of 5HT₃ receptor ligands

- pain
- sensitisation of nociceptive neurons
nausea / vomiting
(underline the emetic side effects of concern
chemotherapy and radiotherapy)

* central 5HT₃ receptor antagonists

- anxiolytic action
- cognitive enhancing effects

AGONISTS AND ANTAGONISTS OF 5-HT₃ RECEPTORS

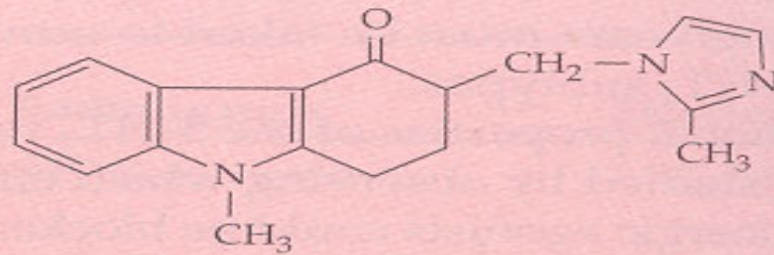
Ligands selective for 5-HT₃ receptors

Agonists: m-Chlorophenylbiguanide †
 RS 56812 †
 2-Methyl-5-hydroxytryptamine †
 Phenylbiguanide †

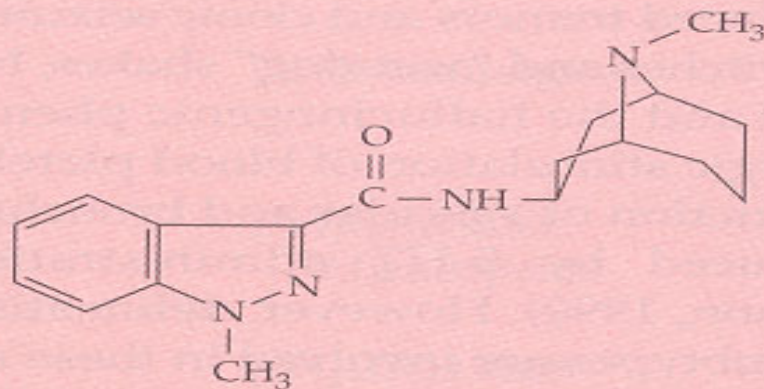
Antagonists: MDL 72222 †
 Y-25130 †
 Granisetron
 Ondansetron
 Tropisetron
 BRL 46470A
 GR 65630

† denotes compounds available from Tocris

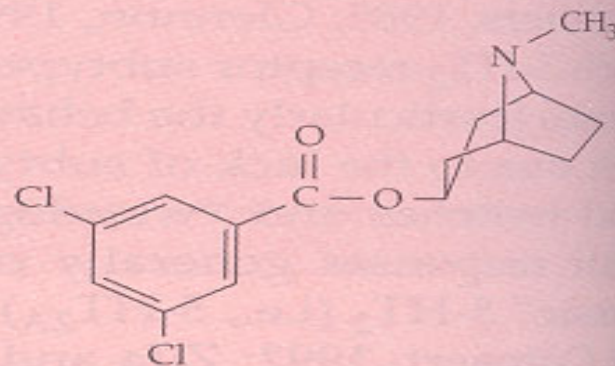
ANTAGONISTS OF 5-HT₃ RECEPTORS



Ondansetron

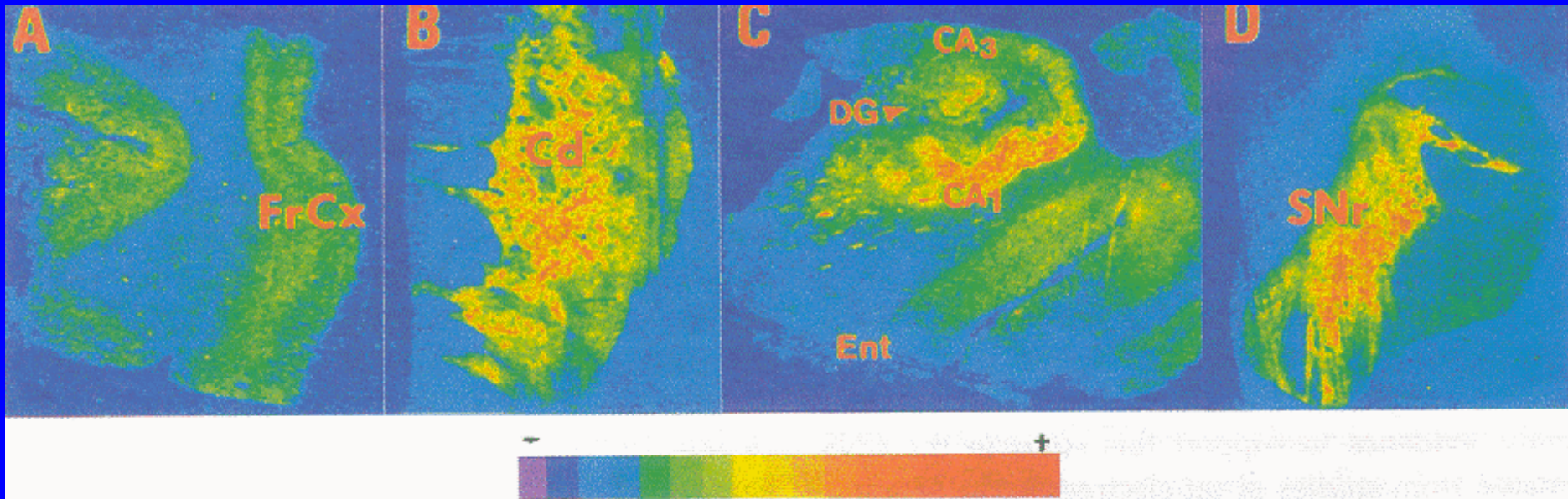


Granisetron



MDL 72222

SEROTONIN AND DISTRIBUTION OF 5-HT₄ RECEPTORS IN HUMAN BRAIN



a: frontal cortex; b: caudate putamen; c: hippocampus; d: substantia nigra

Xenopus laevis

Mouse

Rat

Guinea-pig

Human

1M **LI** **QVQPSHLTDTNLSLHSAKPSDDHQNLLPS** . . . **EFMTERPLNTEQDLT** . **ALNHTKPD** **CGKRL** **LL**
 1MMDVNSSGRPDLYGHLRS **LIL** **PEVGRRL** **QDLSPDGGAAH** **SVVSSWMPHLLSGFPEVTASPA** **TWDAPPDNVSGCGEQIN** .
 1MMDVNSSGRPDLYGHLRS **LIL** **PEVGRGL** **QDLSPDGGAAH** **FPVVSWMMPHLLSGFLEVTASPA** **TWDAPPDNVSGCGEQIN** .
 1MM **GVN** **SSGRPDLYGHL** **HS** **ILLP** . . **GRGLPDWSPDGGAD** **PGVSTWTFRLLSGVPEVAASPS** **SWDGTW** **DNVSGCGEQIN** .
 1MMDVNSSGRPDLYGHLRS **FL** **LPEVGRGL** **PD** **LSPDGGAD** **DPVAGSWA** **PHLLS** . . . **EVTASPA** **TWDAPPDN** **ASGCGEQIN** .

TM1

TM2

Xenopus laevis

Mouse

Rat

Guinea-pig

Human

65 **YG** **DTEK** **IVIG** **VVLS** **II** **ITLFTIAGNALV** **II** **ISVC** **IVKKLRQPSNYL** **VVSLA** **AA** **ADLSVAVAVMPFV** **IT** **ITDL** **VGG** **EW** **IFG** **KV** **F**
 79 **YGR** **VEKVVIGS** **IL** **TLITLL** **TIAGNCLVVISVCFVK** **NV** **RQPSNYL** **LIVSLALADLSVAVAVMPFV** **SV** **TD** **LIGG** **KW** **IFG** **HFF**
 79 **YGR** **VEKVVIGS** **IL** **TLITLL** **TIAGNCLVVISVCFVK** **KLRQPSNYL** **LIVSLALADLSVAVAVMPFV** **SV** **TD** **LIGG** **KW** **IFG** **HFF**
 77 **YGR** **AEKVVIGS** **IL** **TLITLL** **TIAGNCLVVISVCFVK** **KLRQPSNYL** **LIVSLALADLSVAVAV** **IP** **PFV** **SV** **TD** **LIGG** **KW** **IFG** **HFF**
 76 **YGR** **VEKVVIGS** **IL** **TLITLL** **TIAGNCLVVISVCFVK** **KLRQPSNYL** **LIVSLALADLSVAVAVMPFV** **SV** **TD** **LIGG** **KW** **IFG** **HFF**

TM3

TM4

Xenopus laevis

Mouse

Rat

Guinea-pig

Human

144 **CNVFIAMDVMCCTASIMTLCVIS** **V** **D** **RYLGITRPLTY** **P** **ARQNGK** **L** **MAKM** **VFI** **VWLLSASITL** **P** **P** **LF** **GWA** **K** **NVN** **V** **E** **R** **V** **CL** **I**
 158 **CNVFIAMDVMCCTASIMTLCVISIDRYLGITRPLTY** **P** **V** **RQNGKCM** **AKMILSVW** **PL** **SASITL** **P** **P** **LF** **GWAQNVNDDK** **V** **CL** **I**
 158 **CNVFIAMDVMCCTASIMTLCVISIDRYLGITRPLTY** **P** **V** **RQNGKCM** **AKMILSVWLLSASITL** **P** **P** **LF** **GWAQNVNDDK** **V** **CL** **I**
 157 **CNVFIAMDVMCCTASIMTLCVISIDRYLGITRPLTY** **P** **V** **RQNGKCM** **PKMILSVWLLSASITL** **P** **P** **LF** **GWAQNVNDDK** **V** **CL** **I**
 156 **CNVFIAMDVMCCTASIMTLCVISIDRYLGITRPLTY** **P** **V** **RQNGKCM** **AKMILSVWLLSASITL** **P** **P** **LF** **GWAQNVNDDK** **V** **CL** **I**

TM5

Xenopus laevis

Mouse

Rat

Guinea-pig

Human

Pig

223 **SQDFGYT** **V** **YSTAVAFYIP** **M** **T** **VML** **V** **MY** **QRI** **F** **VAAK** **I** **SAE** **KHKF** **V** **NIP** **RL** **YE** **Q** **E** **G** **I** **Y** **C** **L** **E** **D** **K** **L** **P** **P** **K** **N** **S** **K** **K** **K** **A** **V** **E** **E** **F** **A** **S** **L**
 237 **SQDFGYTI** **YSTAVAFYIP** **M** **S** **V** **M** **L** **F** **M** **Y** **Q** **I** **Y** **K** **A** **A** **R** **K** **S** **A** **A** **K** **H** **K** **F** **S** **G** **F** **P** **R** **V** **Q** . **P** **E** **S** **V** **I** **S** **L** **N** **G** **V** **K** **L** **Q** **K** **E** **V** **E** **E** **C** **A** **N** **L**
 237 **SQDFGYTI** **YSTAVAFYIP** **M** **S** **V** **M** **L** **F** **M** **Y** **Q** **I** **Y** **K** **A** **A** **R** **K** **S** **A** **A** **K** **H** **K** **F** **P** **G** **F** **P** **R** **V** **Q** . **P** **E** **S** **V** **I** **S** **L** **N** **G** **V** **K** **L** **Q** **K** **E** **V** **E** **E** **C** **A** **N** **L**
 235 **SQDFGYTI** **YSTAVAFYIP** **M** **S** **V** **M** **L** **F** **M** **Y** **R** **I** **Y** **K** **A** **A** **R** **K** **S** **A** **A** **K** **H** **K** **F** **P** **G** **F** **P** **R** **V** **Q** . **P** **E** **S** **I** **I** **S** **L** **N** **G** **M** **V** **K** **L** **Q** **K** **E** **V** **E** **E** **C** **A** **N** **L**
 234 **SQDFGYTI** **YSTAVAFYIP** **M** **S** **V** **M** **L** **F** **M** **Y** **Q** **I** **Y** **K** **A** **A** **R** **K** **S** **A** **A** **K** **H** **K** **F** **P** **G** **F** **P** **R** **V** **E** . **P** **D** **S** **V** **I** **A** **L** **N** **G** **I** **V** **K** **L** **Q** **K** **E** **V** **E** **E** **C** **A** **N** **L**
 1 **Y** **S** **T** **A** **V** **A** **F** **Y** **I** **P** **M** **S** **V** **M** **L** **F** **M** **Y** **Q** **I** **Y** **K** **A** **A** **R** **K** **S** **A** **A** **K** **H** **K** **F** **P** **G** **F** **P** **R** **E** **E** **P** **D** **S** **V** **I** **S** **L** **N** **G** **M** **V** **K** **L** **Q** **K** **E** **V** **E** **E** **C** **A** **N** **L**

TM6

TM7

Xenopus laevis

Mouse

Rat

Guinea-pig

Human

Pig

302 **S** **K** **L** **I** **R** **Q** **D** **R** **K** **N** **I** **S** **I** **F** **K** **R** **E** **Q** **K** **A** **R** **T** **L** **G** **I** **I** **V** **G** **A** **F** **T** **F** **C** **W** **L** **P** **F** **F** **L** **L** **S** **T** **A** **R** **P** **F** **I** **C** **G** **I** **M** **C** **S** **C** **M** **P** **L** **R** **L** **E** **R** **T** **L** **L** **W** **L** **G** **Y** **T** **N** **S** **L** **I** **N** **P** **L** **I** **Y**
 309 **S** **R** **L** **L** **K** **H** **E** **R** **K** **N** **I** **S** **I** **F** **K** **R** **E** **Q** **K** **A** **A** **T** **T** **L** **G** **I** **I** **V** **G** **A** **F** **T** **V** **C** **W** **L** **P** **F** **F** **L** **L** **S** **T** **A** **R** **P** **F** **I** **C** **G** **T** **S** **C** **S** **C** **I** **P** **L** **W** **E** **R** **T** **C** **L** **W** **L** **G** **Y** **A** **N** **S** **L** **I** **N** **P** **F** **I** **Y**
 309 **S** **R** **L** **L** **K** **H** **E** **R** **K** **N** **I** **S** **I** **F** **K** **R** **E** **Q** **K** **A** **A** **T** **T** **L** **G** **I** **I** **V** **G** **A** **F** **T** **V** **C** **W** **L** **P** **F** **F** **L** **L** **S** **T** **A** **R** **P** **F** **I** **C** **G** **T** **S** **C** **S** **C** **I** **P** **L** **W** **E** **R** **T** **C** **L** **W** **L** **G** **Y** **A** **N** **S** **L** **I** **N** **P** **F** **I** **Y**
 307 **S** **R** **L** **L** **K** **H** **E** **R** **K** **N** **I** **S** **I** **F** **K** **R** **E** **Q** **K** **A** **A** **T** **T** **L** **G** **I** **I** **V** **G** **A** **F** **T** **V** **C** **W** **L** **P** **F** **F** **L** **L** **S** **T** **A** **R** **P** **F** **I** **C** **G** **T** **A** **C** **S** **C** **I** **P** **L** **W** **E** **R** **T** **C** **L** **W** **L** **G** **Y** **A** **N** **S** **L** **I** **N** **P** **F** **I** **Y**
 306 **S** **R** **L** **L** **K** **H** **E** **R** **K** **N** **I** **S** **I** **F** **K** **R** **E** **Q** **K** **A** **A** **T** **T** **L** **G** **I** **I** **V** **G** **A** **F** **T** **V** **C** **W** **L** **P** **F** **F** **L** **L** **S** **T** **A** **R** **P** **F** **I** **C** **G** **T** **S** **C** **S** **C** **I** **P** **L** **W** **E** **R** **T** **F** **L** **W** **L** **G** **Y** **A** **N** **S** **L** **I** **N** **P** **F** **I** **Y**
 66 **S** **R** **L** **L** **K** **H** **E** **R** **K** **N** **I** **S** **I** **F** **K** **R** **E** **Q** **K** **A** **A** **T** **T** **L** **G** **I** **I** **V** **G** **A** **F** **T** **V** **C** **W** **L** **P** **F** **F** **L** **L** **S** **T** **A** **R** **P** **F** **I** **C** **G** **T** **S** **C** **S** **C** **I** **P** **L** **W** **E** **R** **T** **F** **L** **W** **L** **G** **Y** **A** **N** **S** **L** **I** **N** **P** **F** **I** **Y**

Xenopus laevis

Mouse

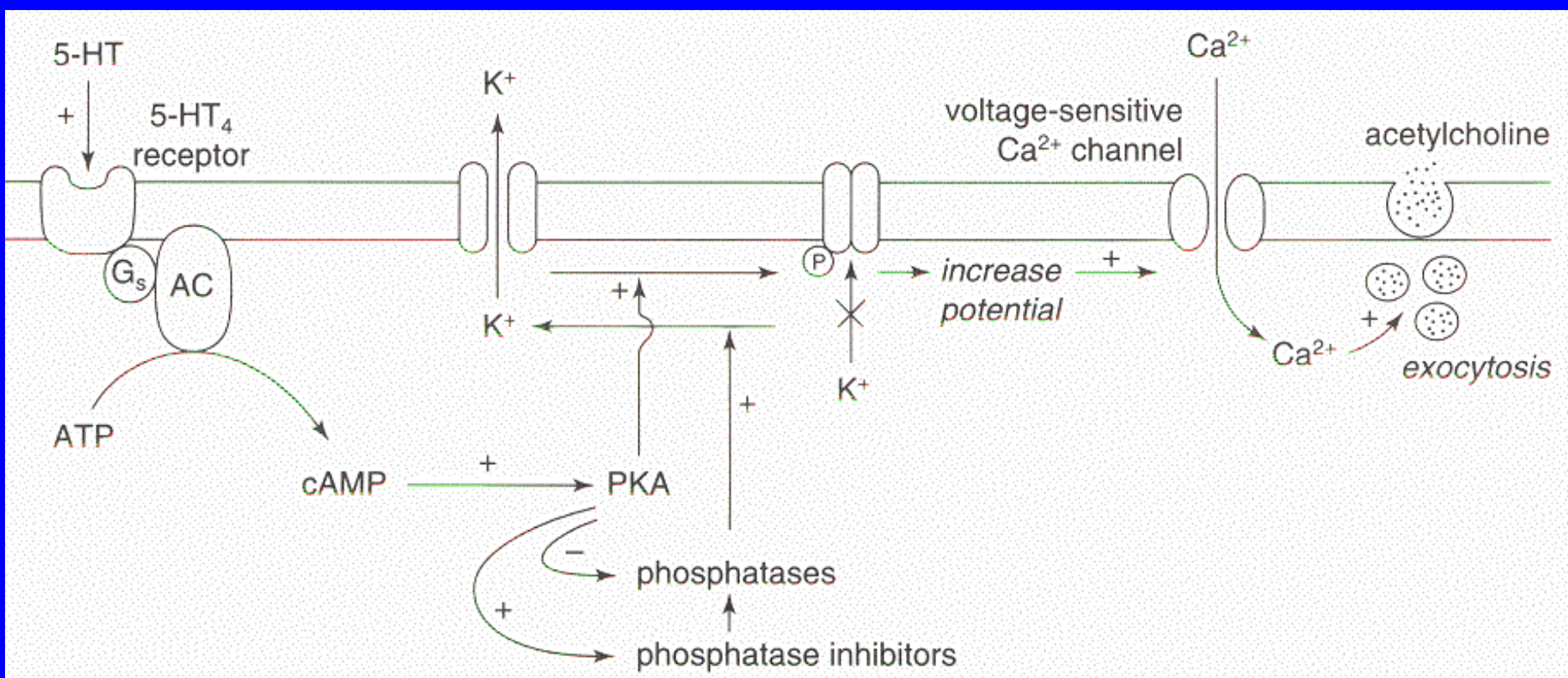
Rat

Guinea-pig

Human

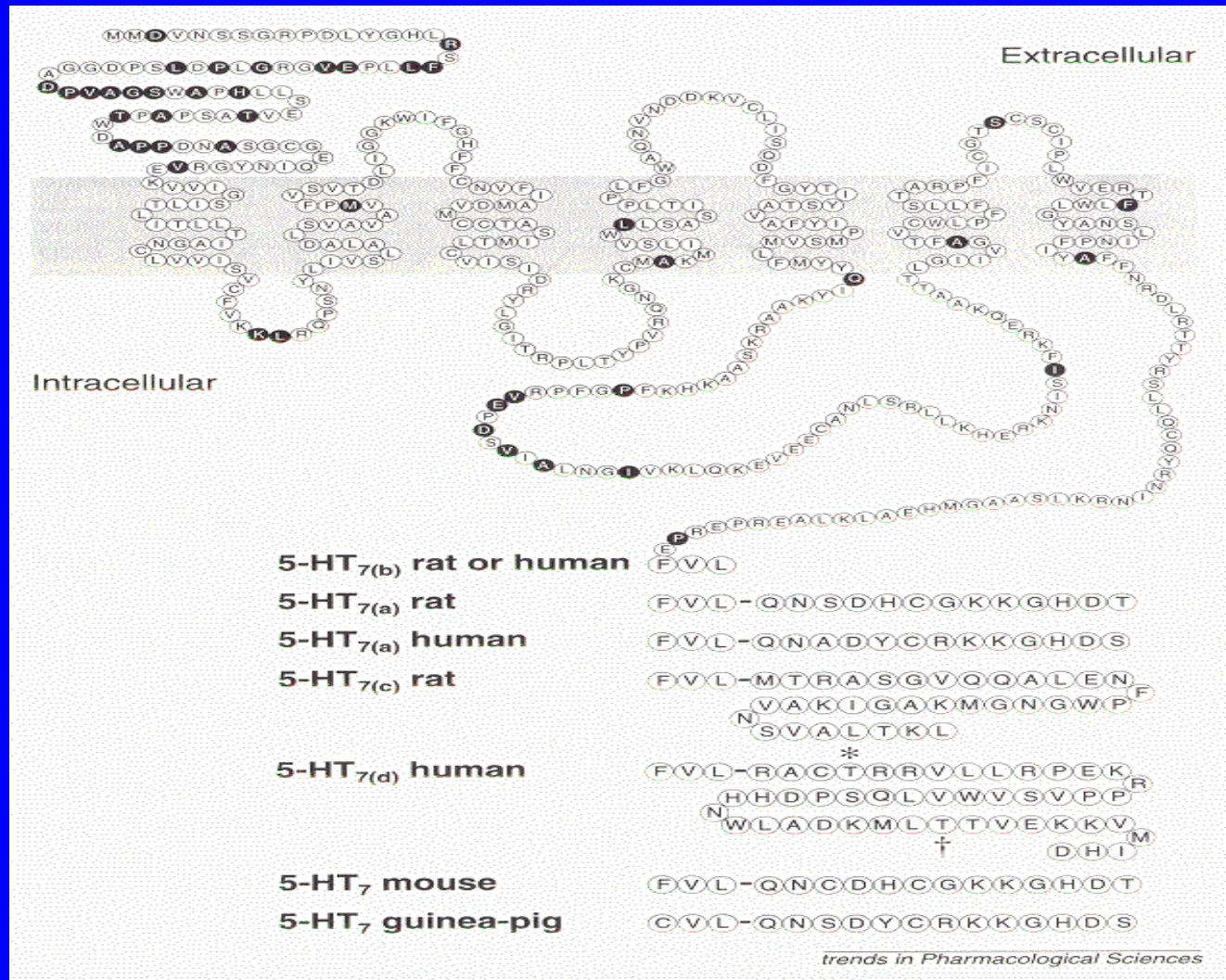
381 **A** **F** **F** **N** **R** **D** **L** **R** **T** **T** **Y** **S** **L** **L** **Q** **C** **Q** **Y** **R** **N** **I** **N** **R** **K** **L** **S** **A** **A** **G** **M** **H** **E** **A** **L** **K** **L** **A** **E** **R** **P** **E** **R** **S** **E** **F** **V** **L** **Q** **N** **S** **D** **H** **C** **G** **K** **K** **G** **H** **D** **T** 425
 388 **A** **F** **F** **N** **R** **D** **L** **R** **T** **T** **Y** **S** **L** **L** **Q** **C** **Q** **Y** **R** **N** **I** **N** **R** **K** **L** **S** **A** **A** **G** **M** **H** **E** **A** **L** **K** **L** **A** **E** **R** **P** **E** **R** **S** **E** **F** **V** **L** **Q** **N** **S** **D** **H** **C** **G** **K** **K** **G** **H** **D** **T** 448
 388 **A** **F** **F** **N** **R** **D** **L** **R** **T** **T** **Y** **S** **L** **L** **Q** **C** **Q** **Y** **R** **N** **I** **N** **R** **K** **L** **S** **A** **A** **G** **M** **H** **E** **A** **L** **K** **L** **A** **E** **R** **P** **E** **R** **S** **E** **F** **V** **L** **Q** **N** **S** **D** **H** **C** **G** **K** **K** **G** **H** **D** **T** 448
 386 **A** **F** **F** **N** **R** **D** **L** **R** **T** **T** **Y** **S** **L** **L** **Q** **C** **Q** **Y** **R** **N** **I** **N** **R** **K** **L** **S** **A** **A** **G** **M** **H** **E** **A** **L** **K** **L** **A** **E** **R** **P** **E** **R** **P** **E** **C** **V** **L** **Q** **N** **S** **D** **Y** **C** **R** **K** **K** **G** **H** **D** **S** 446
 385 **A** **F** **F** **N** **R** **D** **L** **R** **T** **T** **Y** **S** **L** **L** **Q** **C** **Q** **Y** **R** **N** **I** **N** **R** **K** **L** **S** **A** **A** **G** **M** **H** **E** **A** **L** **K** **L** **A** **E** **R** **P** **E** **R** **P** **E** **F** **V** **L** **Q** **N** **A** **D** **Y** **C** **R** **K** **K** **G** **H** **D** **S** 445

SEROTONINE AND RECEPTOR 5-HT₄ AND K⁺ AND Ca²⁺ CHANNELS

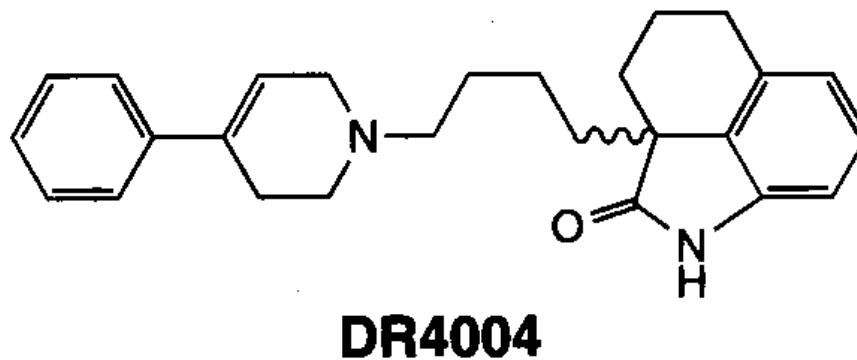
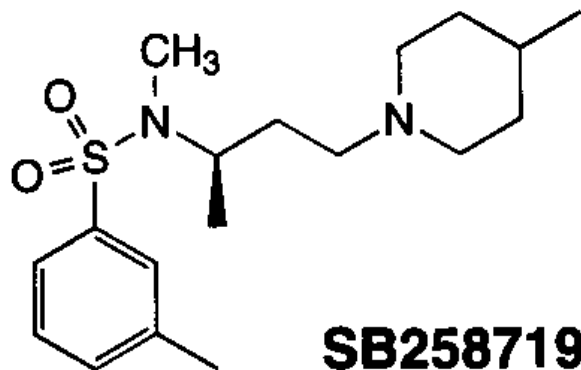


Eglen et al *TIPS* 16: 391-395 (1995)

SEROTONINE AND 5HT7 RECEPTORS



LIGANDS OF 5HT7 RECEPTORS



From Vanhoenacker et al, *TiPS* (2000), 21: 70-77

BINDING OF 5HT7 LIGANDS TO 5HT1 ET 5HT2 RECEPTORS

Receptor	Affinity (pK _i)		Receptor	Affinity (pK _i)	
	SB258719 ^a	DR4004 ^b		SB258719 ^a	DR4004 ^b
5-HT _{1A}	<5.1	6.77	5-HT _{2C}	<4.8	ND
5-HT _{1B}	<5.3	ND	5-HT ₄	<5.0	<6
5-HT _{1D}	5.5	ND	5-HT ₆	<4.8	6.28
5-HT _{1E}	<4.8	ND	5-HT ₇	7.5	8.67
5-HT _{1F}	<5.2	ND	α _{1B} -adrenoceptor	<4.8	ND
5-HT _{2A}	<4.8	c	Dopamine D2	5.4	6.98
5-HT _{2B}	<5.3	ND	Dopamine D3	5.4	ND

^aData from Ref. 15. ^bData from Ref. 17. ^cA pK_i value of 7.01 was reported using rat cerebral cortex and [³H]ketanserin. Abbreviation: ND, not determined.