

GABA = ACIDE γ -AMINO BUTYRIQUE

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STRUCTURE

VOIES GABAERGIQUES

INTERET PHYSIOPATHOLOGIQUE ET PHARMACOLOGIQUE

SYNAPSE GABAERGIQUES

SYNTHESE

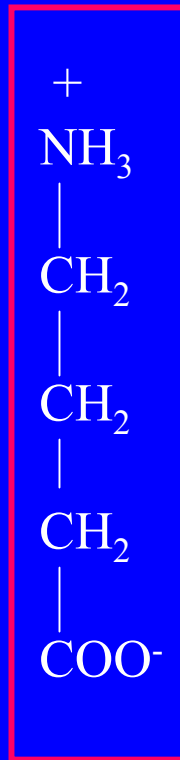
CAPTURE

DEGRADATION

INTERACTION LIGAND/RECEPTEUR GABAERGIQUE

INTERACTION ENTRE RECEPTEURS

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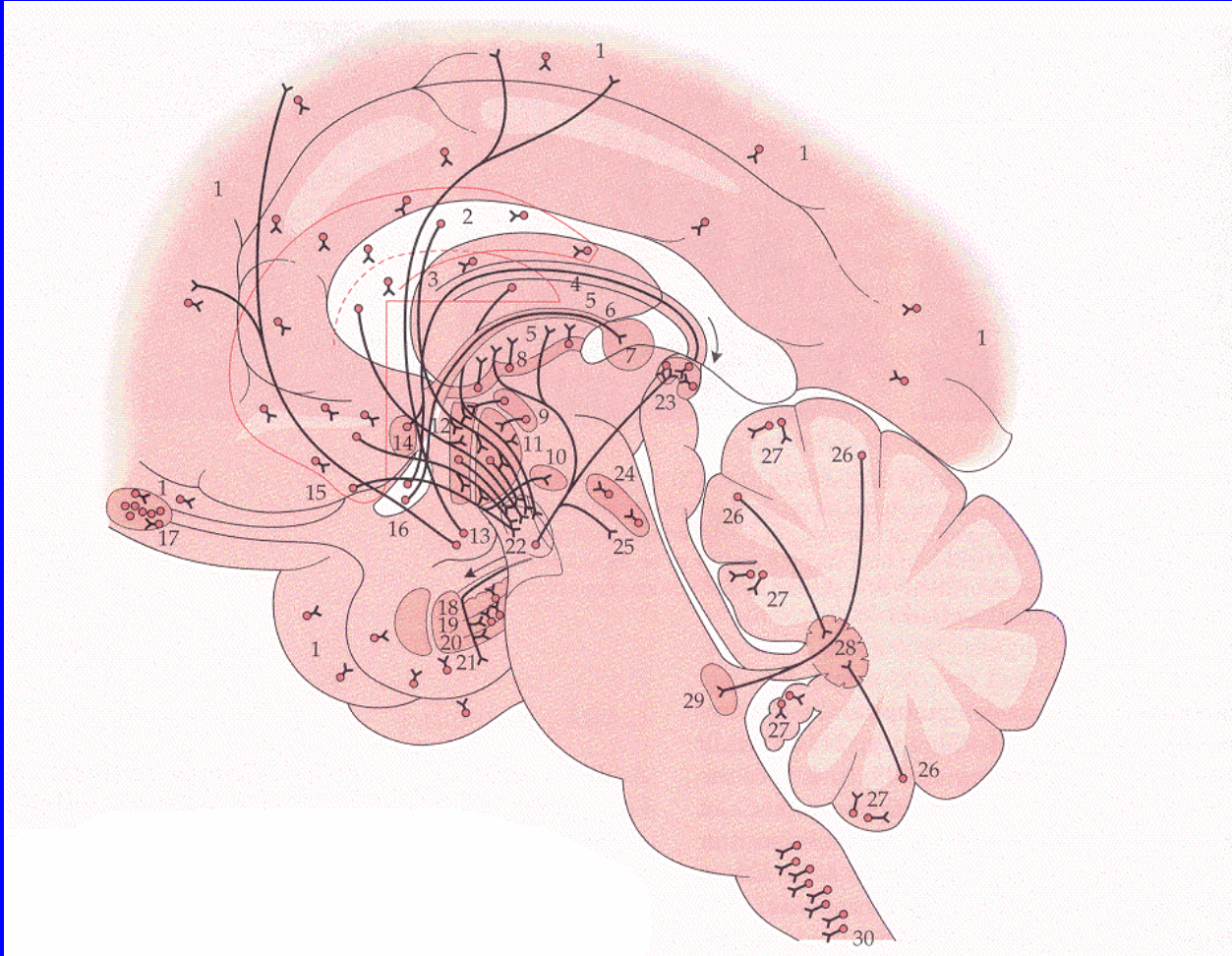
SYNTHESE - DEGRADATION

CAPTURE

INTERACTION LIGAND/RECEPTEUR GABAERGIQUE

INTERACTION ENTRE RECEPTEURS

SYSTEME GABAERGIQUE



- cortex cerebral
- hippocampe
- substance noire
- cervelet
- striatum
- globus pallidus
- bulbes olfactifs

Principles of Neuropharmacology
Feldman, Meyer, Quenzer ed.
Sinauer Associates Inc 1997 pp 424

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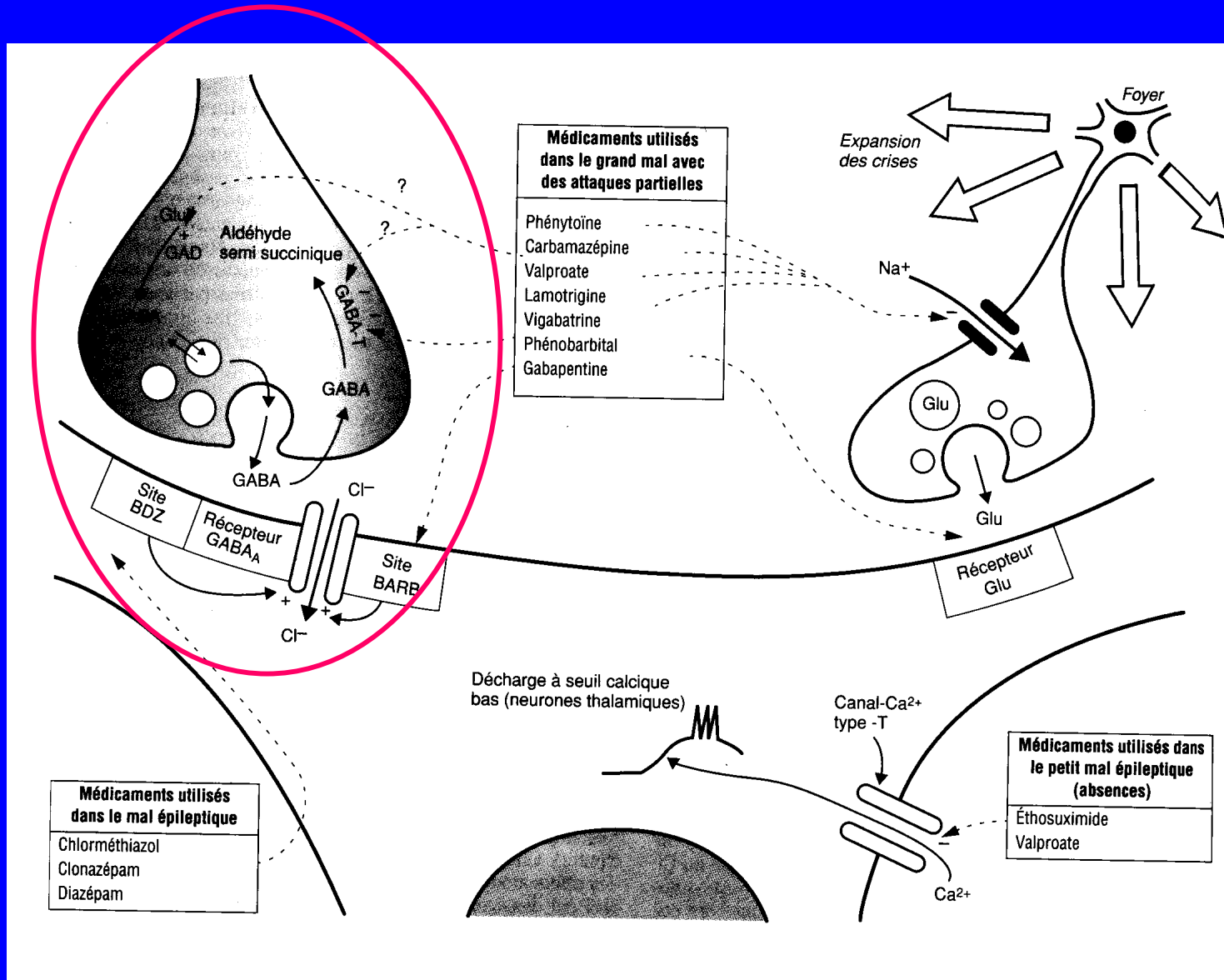
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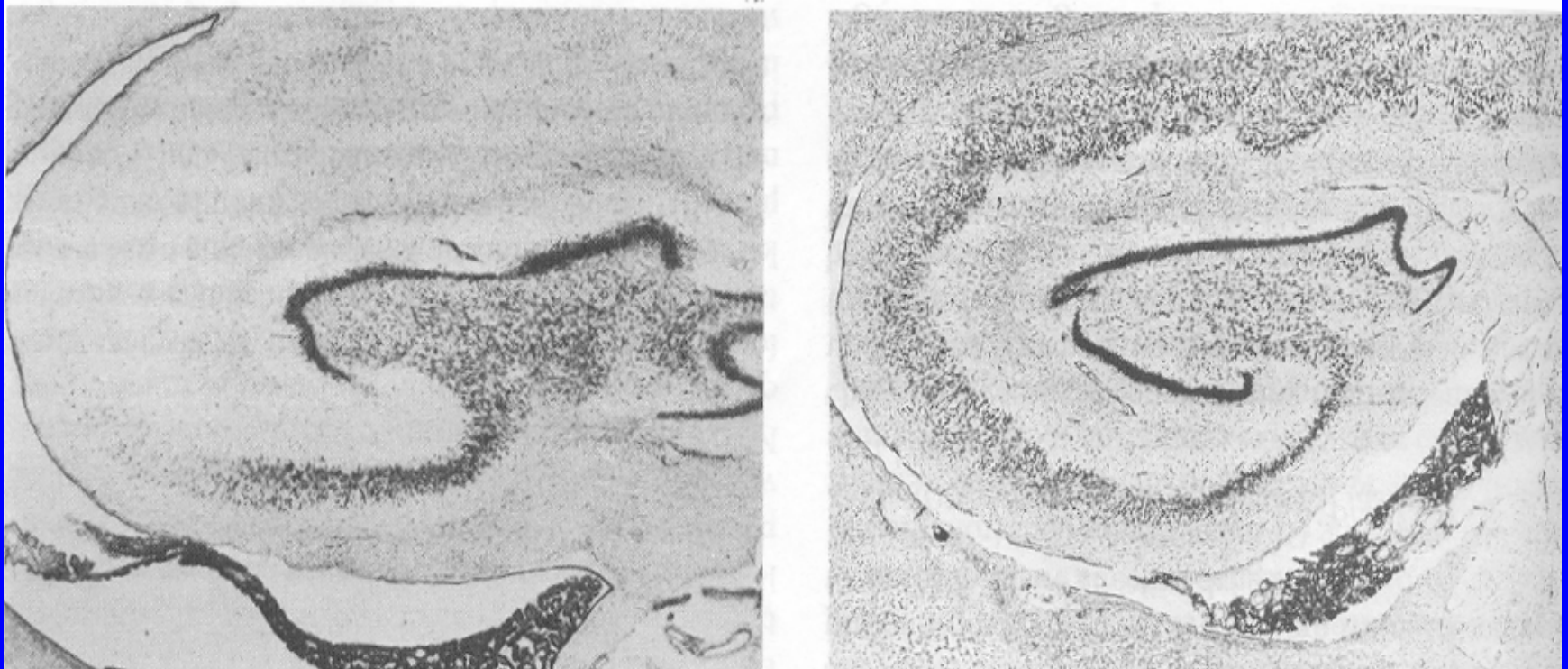
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INTERACTION ENTRE RECEPTEURS

GABA AND EPILEPSIE



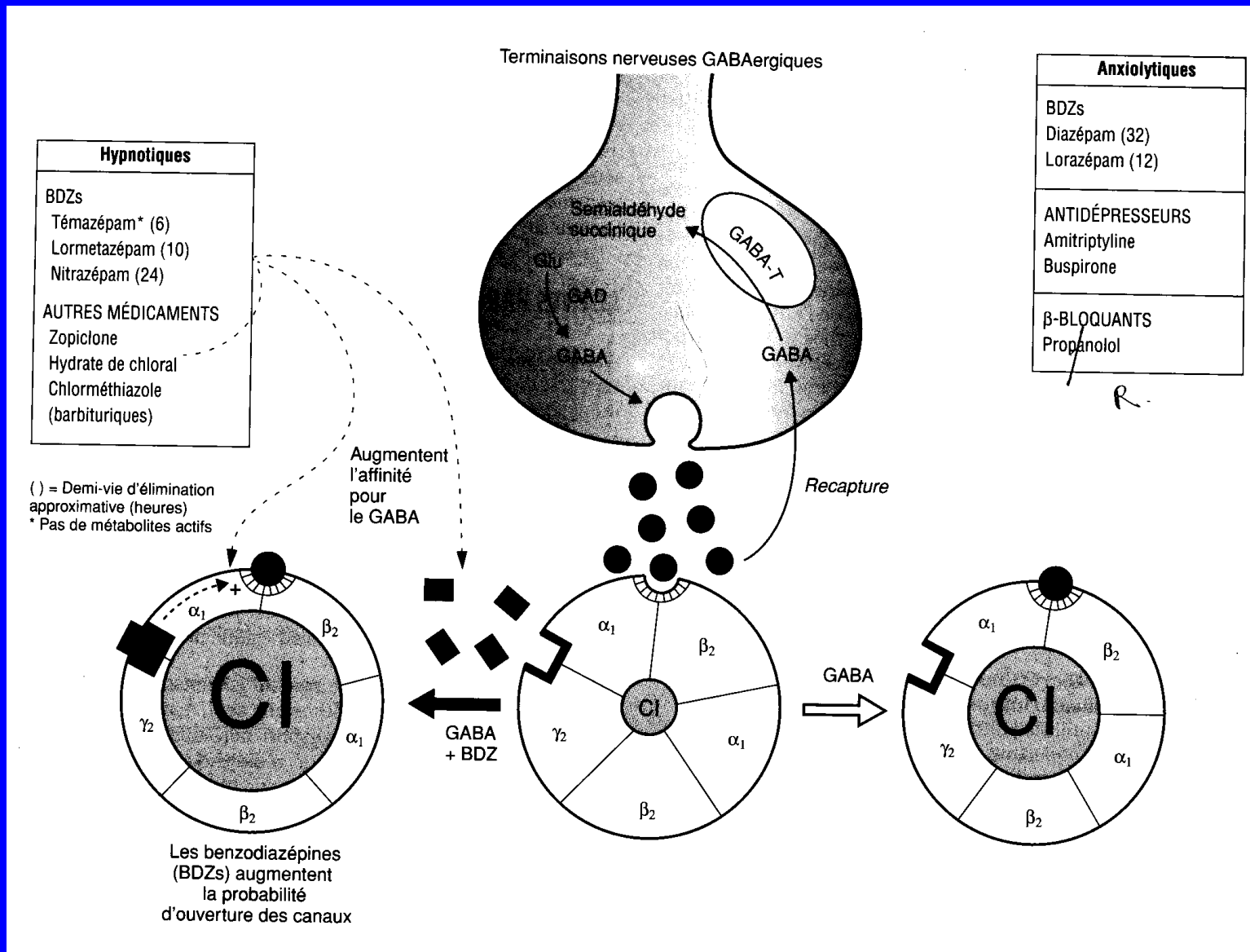
EPILEPSIE ET PERTE NEURONALE



Principles of Neuropharmacology
Feldman, Meyer, Quenzer Ed.
Sinauer Associates Inc. 1997 - pp 409

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GABA AND ANXIETE



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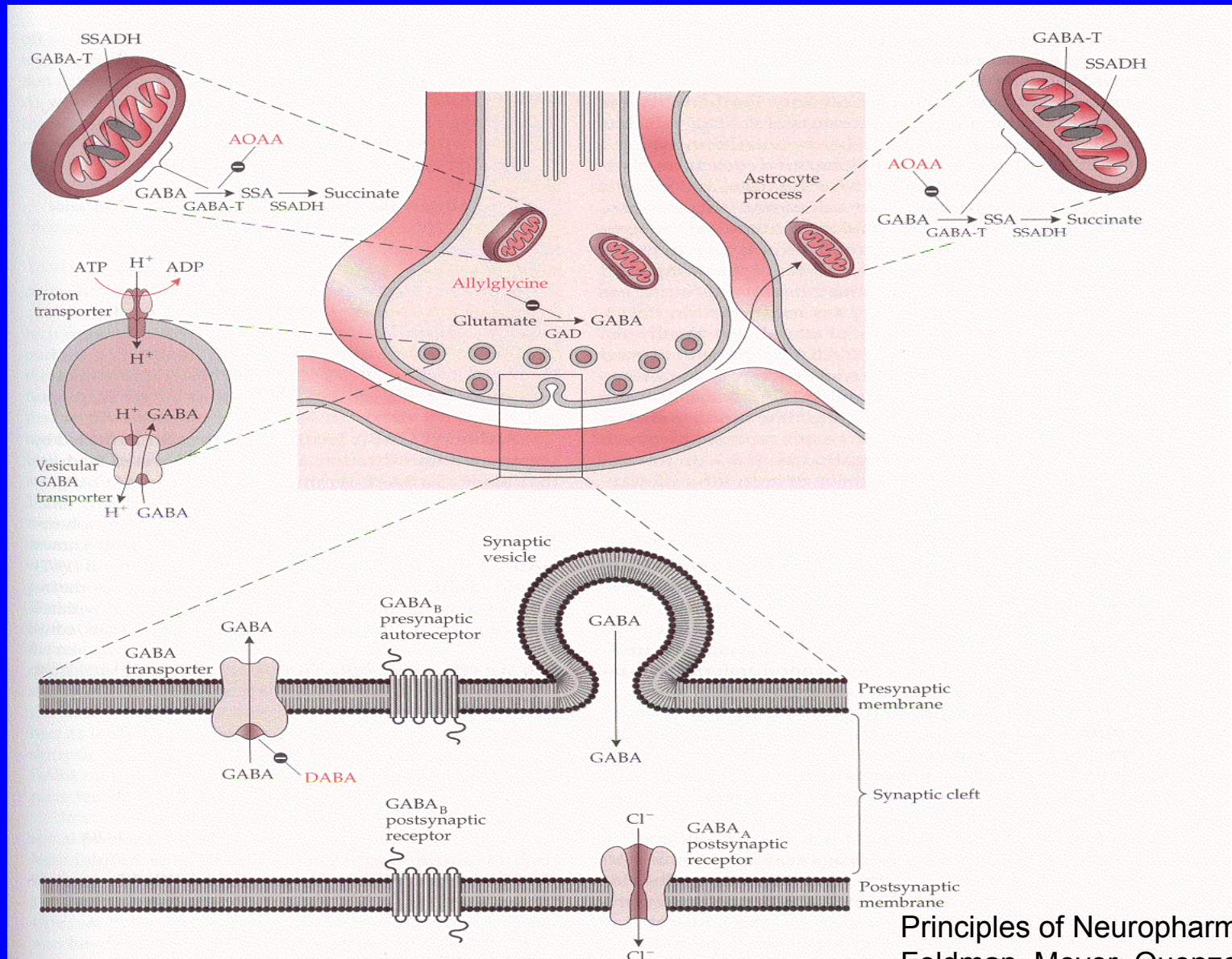
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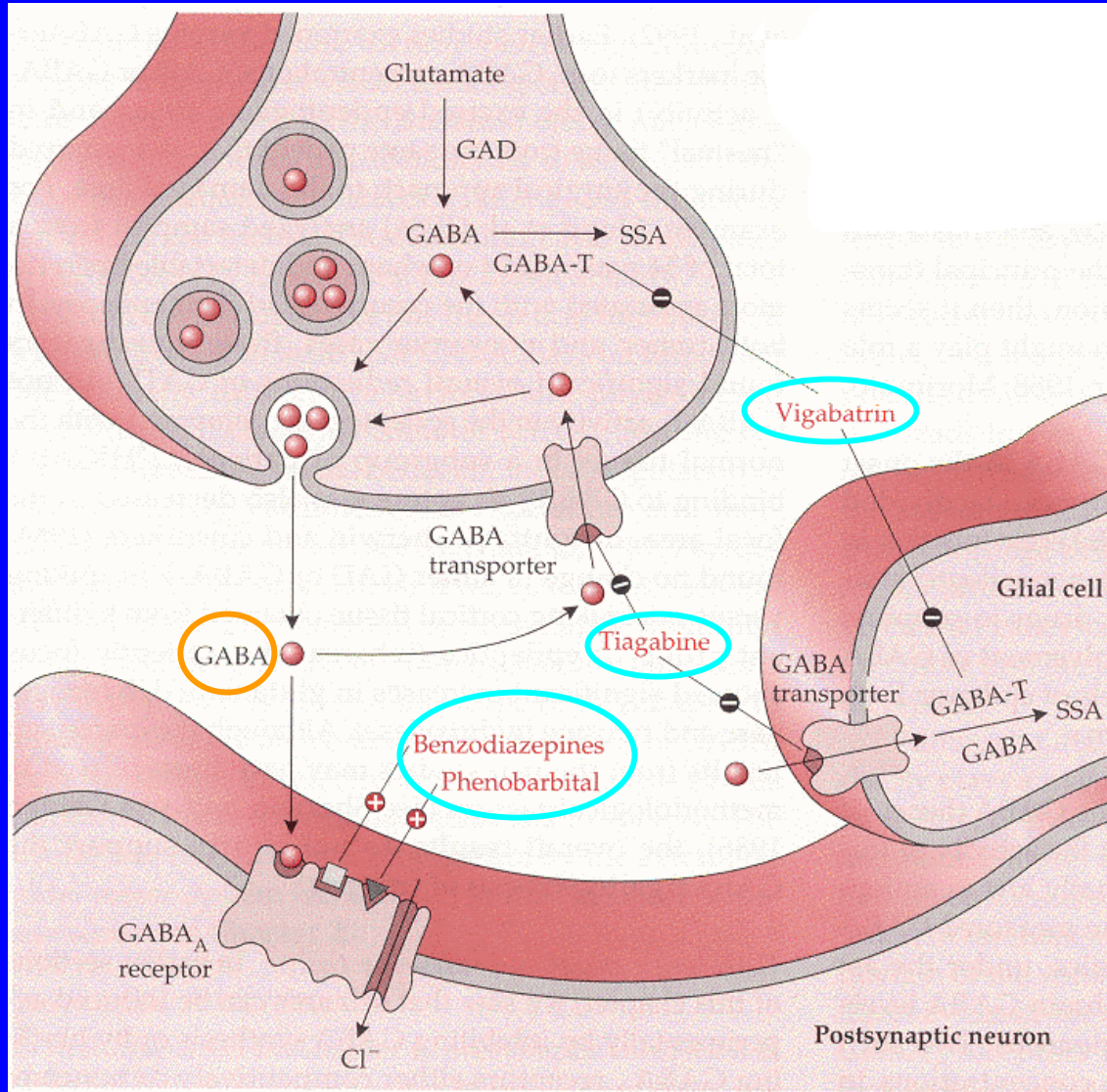
INTERACTION ENTRE RECEPTEURS

SYNAPSE GABAERGIQUE



Principles of Neuropharmacology
Feldman, Meyer, Quenzer ed.
Sinauer Associates Inc 1997 pp 424

MEDICAMENTS AGISSANT SUR LA TRANSMISSION GABAERGIQUE



Principles of Neuropharmacology
Feldman, Meyer, Quenzer ed.
Sinauer Associates Inc 1997 pp 438

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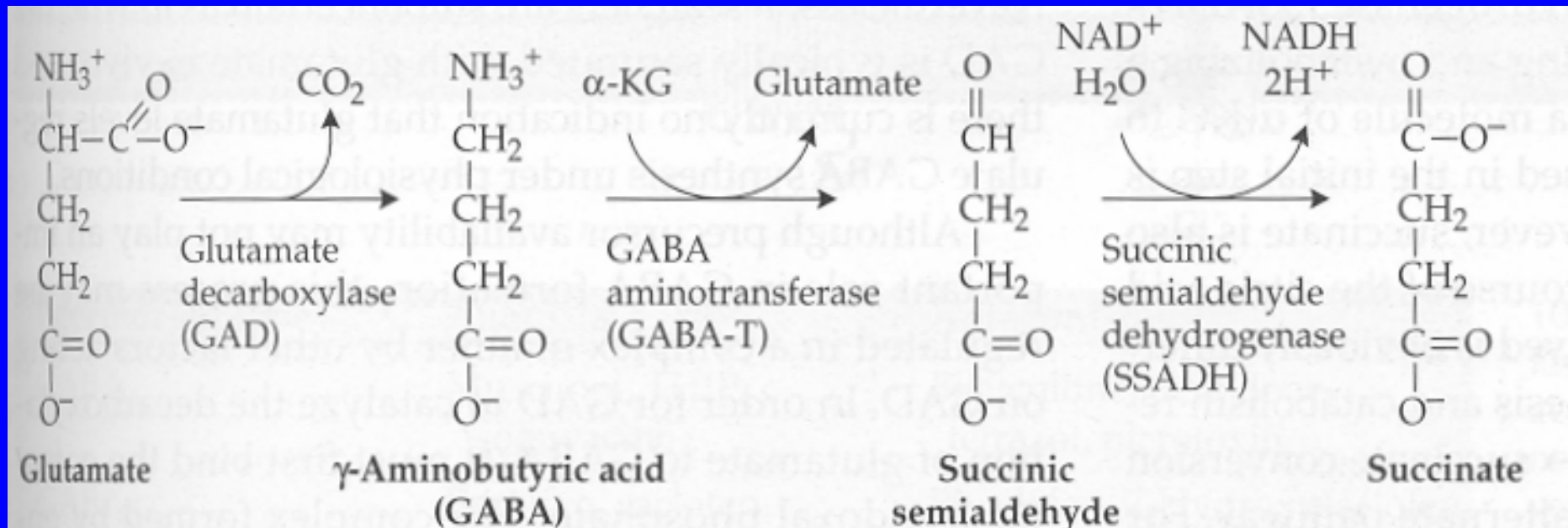
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GABA - DEGRADATION



GABA - SYNTHÈSE

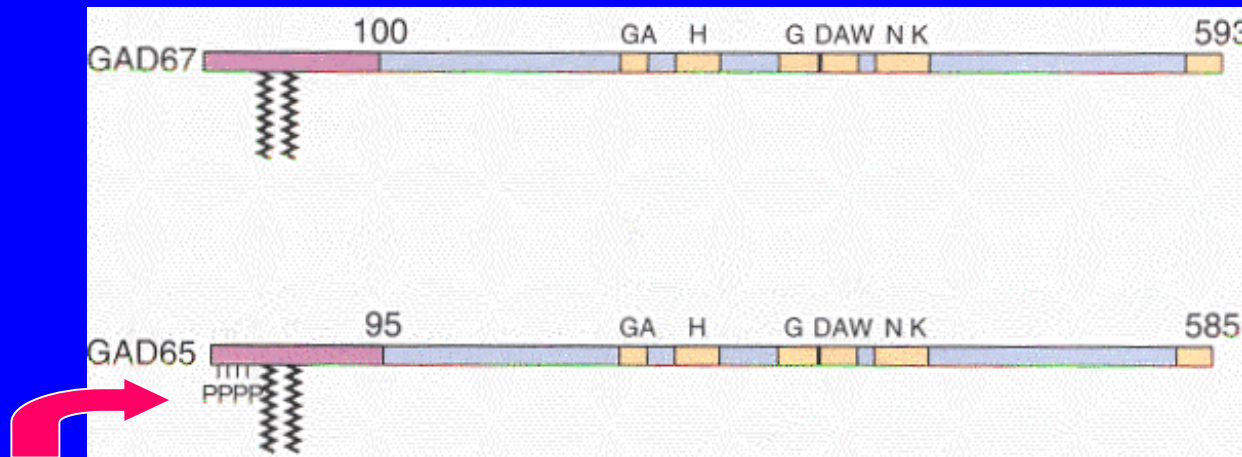
Glutamate decarboxylase = GAD

- enzyme clef ~ synthèse
- présente dans la fraction cytosolique des terminaisons axonales
- cofacteur : pyridoxal phosphate
- existence d'isoformes
 - GAD 67 ~ somato dendritique
 - ~ more widely distributed in cells
 - ~ preferential synthesis of cytoplasmic GABA
 - GAD 65 ~ axonale
 - ~ targeted to membranes and nerve endings
 - ~ preferential synthesis of GABA for vesicular release
- pool of inactive enzyme (apoenzyme)
 - non lié au cofacteur
 - ⇒ synthèse accrue possible en cas de besoin

GABA - SYNTHESIS - GLUTAMATE DECARBOXYLASE

N-terminus

C-terminus



Serine phosphorylated which play a role in membrane association

GAD = glutamate decarboxylase

Catalytic domains: yellow

MEDICAMENTS AGISSANT COMME INHIBITEURS DE LA GLUTAMATE DECARBOXYLASE

Allylglycine

Acide 2-oxo-4 pentenoïque

Acide chelidonique

Acide 3-mercaptopropionique

2-méthyl 3,4 didehydroglutamate

GABA - DEGRADATION

GABA aminotransferase et semi-succinique aldéhyde déshydrogénase

- GABA Aminotransférase: enzyme clef dégradation
- cofacteur : phosphate de pyridoxal
- K_m GABA : 1.1 mM
- GABA
 - acide succinique semi-aldéhyde GABA Aminotransférase
 - succinate semi-succinique aldéhyde déshydrogénase
- mitochondrie

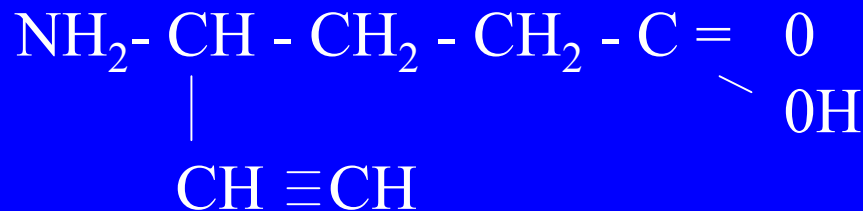
GABA shunt

α -cetoglutarate (biosynthèse; cytosol) → succinate
(dégradation; mitochondrie) (bypasses the citric acid cycle)

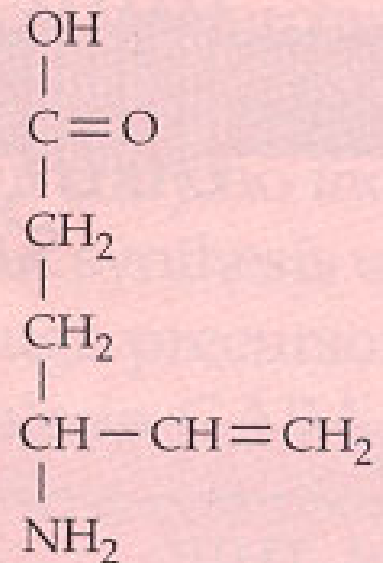
MEDICAMENTS AGISSANT COMME INHIBITEURS DE LA GABA AMINOTRANSFERASE

Isoniazide

γ -Acetylenique GABA



Vinyl-GABA (Vigabatrine)
Inhibiteur suicide



Vigabatrin

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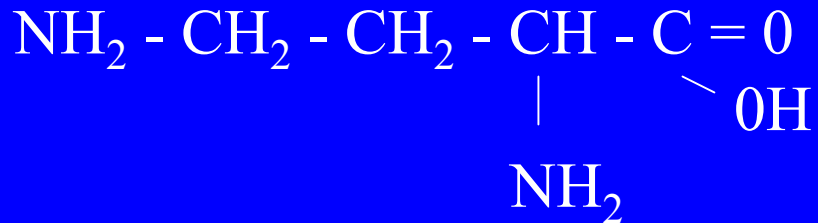
CAPTURE

INTERACTION LIGAND/RECEPTEUR GABAERGIQUE

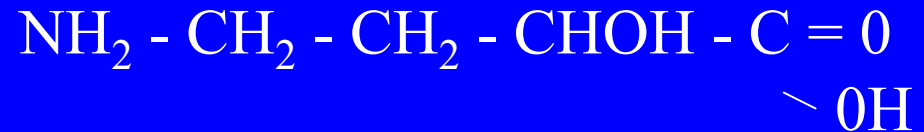
INTERACTION ENTRE RECEPTEURS

MEDICAMENTS AGISSANT COMME INHIBITEURS DE CAPTURE

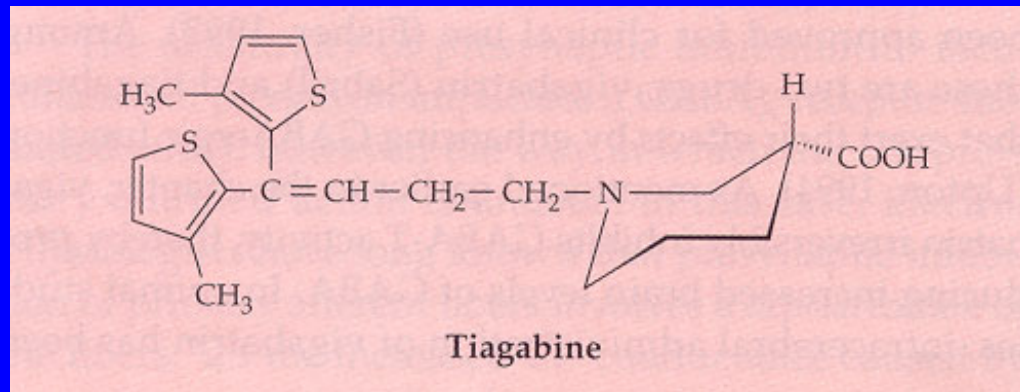
2,4 diaminobutyric acid



2-OH GABA



Tiagabine



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INTERACTION LIGAND/RECEPTEUR GABAERGIQUE

GABA_A

GABA_B

GABA_C

INTERACTION ENTRE RECEPTEURS

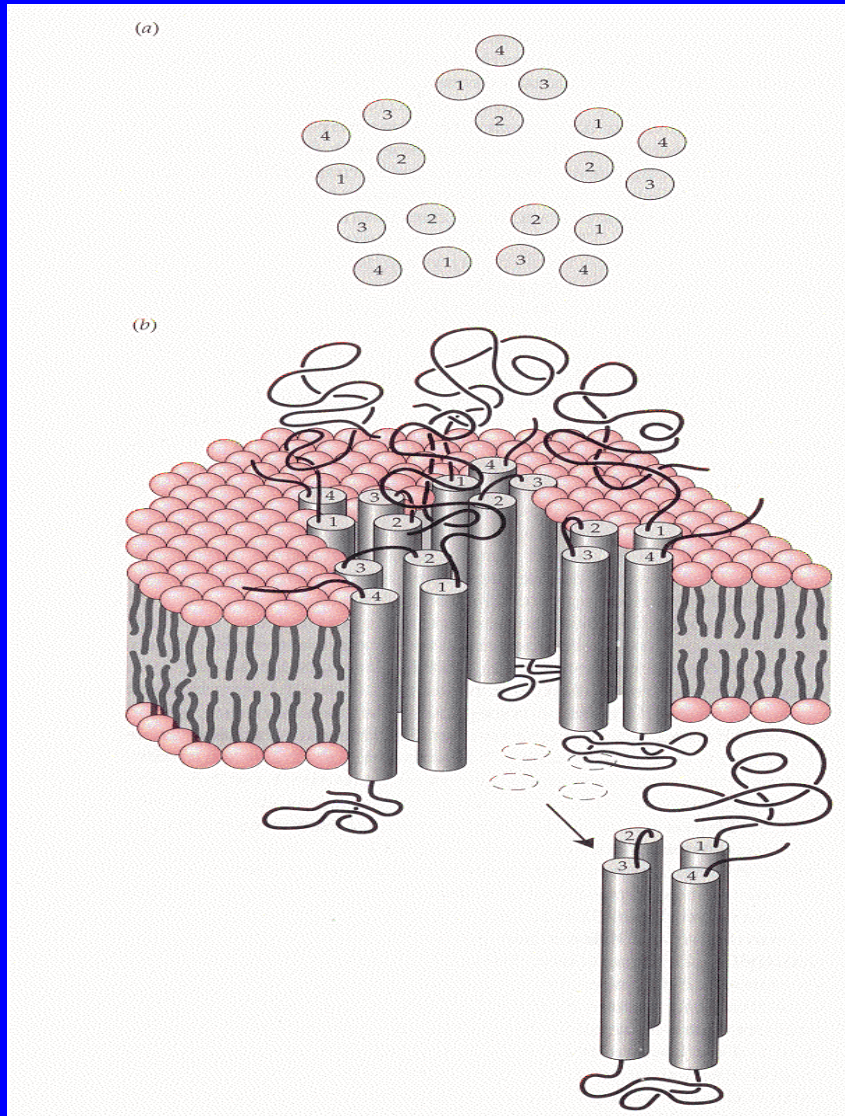
GABA RECEPTORS IN SNC

Table 1. Comparative properties of GABA receptors in the CNS

Characteristic	GABA _A	GABA _B	GABA _C
Receptor mechanism	Ionotropic (Cl ⁻ channel)	Metabotropic (G protein-coupled)	Ionotropic (Cl ⁻ channel)
Protein subunits	$\alpha_{1-6}, \beta_{1-3}, \gamma_{1-3}, \delta$	Not known	ρ_1, ρ_2
Single channel currents	≈ 30 pS	—	≈ 8 pS
Mean channel open time	≈ 25 ms	—	≈ 150 ms
Pharmacology			
GABA	≈ 10 μ M (EC ₅₀)	≈ 10 μ M (EC ₅₀)	≈ 1 μ M (EC ₅₀)
Muscimol	Potent agonist	Inactive	Partial agonist
THIP, P4S	Potent agonists	Inactive	Competitive antagonists
TACA	Potent agonist	Inactive	Potent agonist
CACA	Inactive?	Inactive	Partial agonist
3-APMPA, 3-APPA	Inactive	Potent agonists	Potent competitive antagonists
3-APA	Inactive	Partial agonist	Potent competitive antagonist
Baclofen	Inactive	Agonist	Inactive
Saclofen, phaclofen	Inactive	Competitive antagonists	Inactive
Bicuculline	Competitive antagonist	Inactive	Inactive
Picrotoxin	Noncompetitive antagonist	Inactive	Noncompetitive antagonist

3-APA, 3-aminopropylphosphonic acid; 3-APMPA, [3-aminopropyl(methyl)phosphinic acid; 3-APPA, 3-aminopropylphosphinic acid; CACA, *cis*-4-aminocrotonic acid; P4S, (piperidine-4-sulphonic acid; TACA, *trans*-4-aminocrotonic acid; THIP, 4,5,6,7-tetrahydroisoxazole[4,5-*c*]pyridin-3-ol.

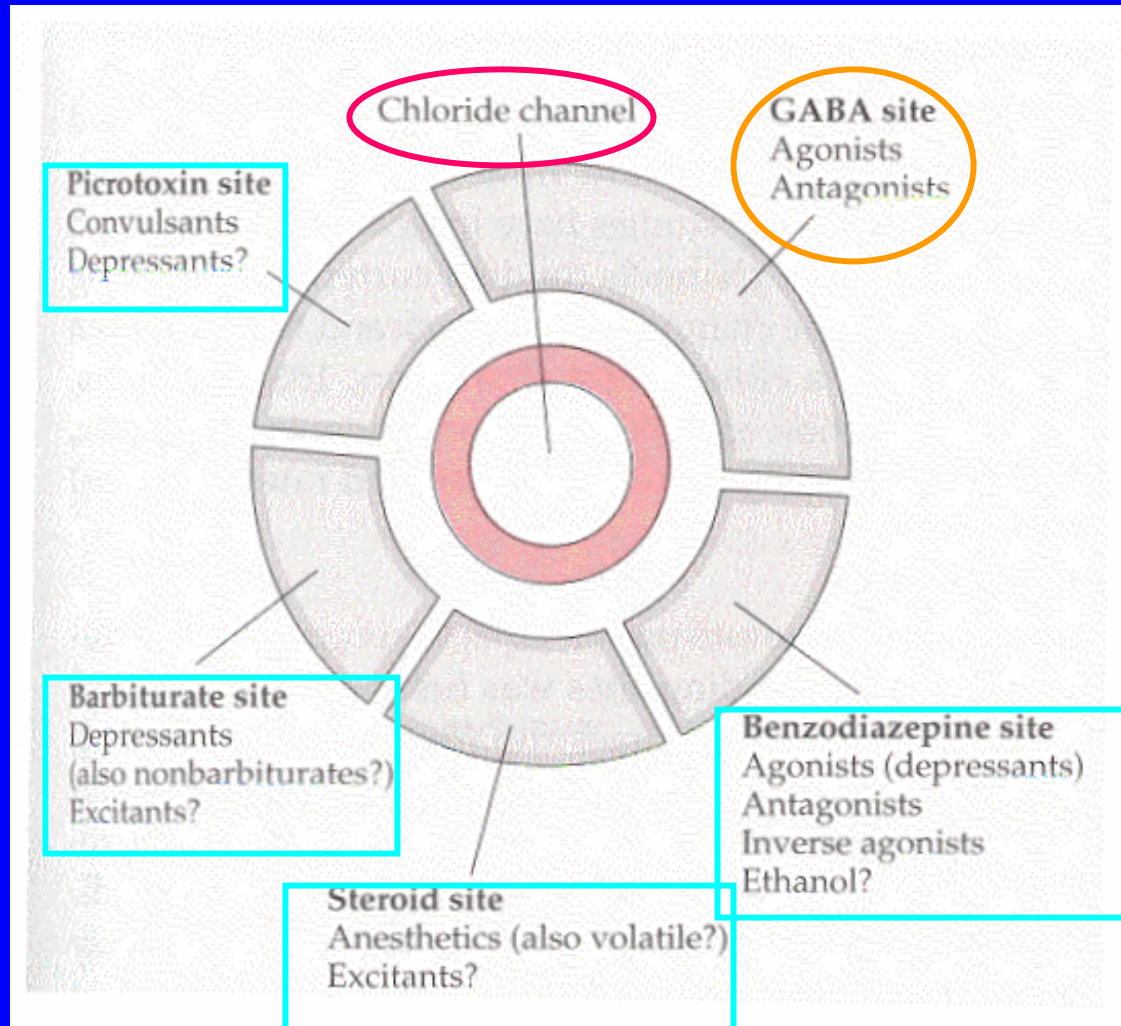
RECEPTEUR GABA_A



5 sous-unités comprenant
chacune 4 segments
transmembranaires

Principles of Neuropharmacology
Feldman, Meyer, Quenzer ed.
Sinauer Associates Inc 1997 pp 424

RECEPTEUR GABA_A



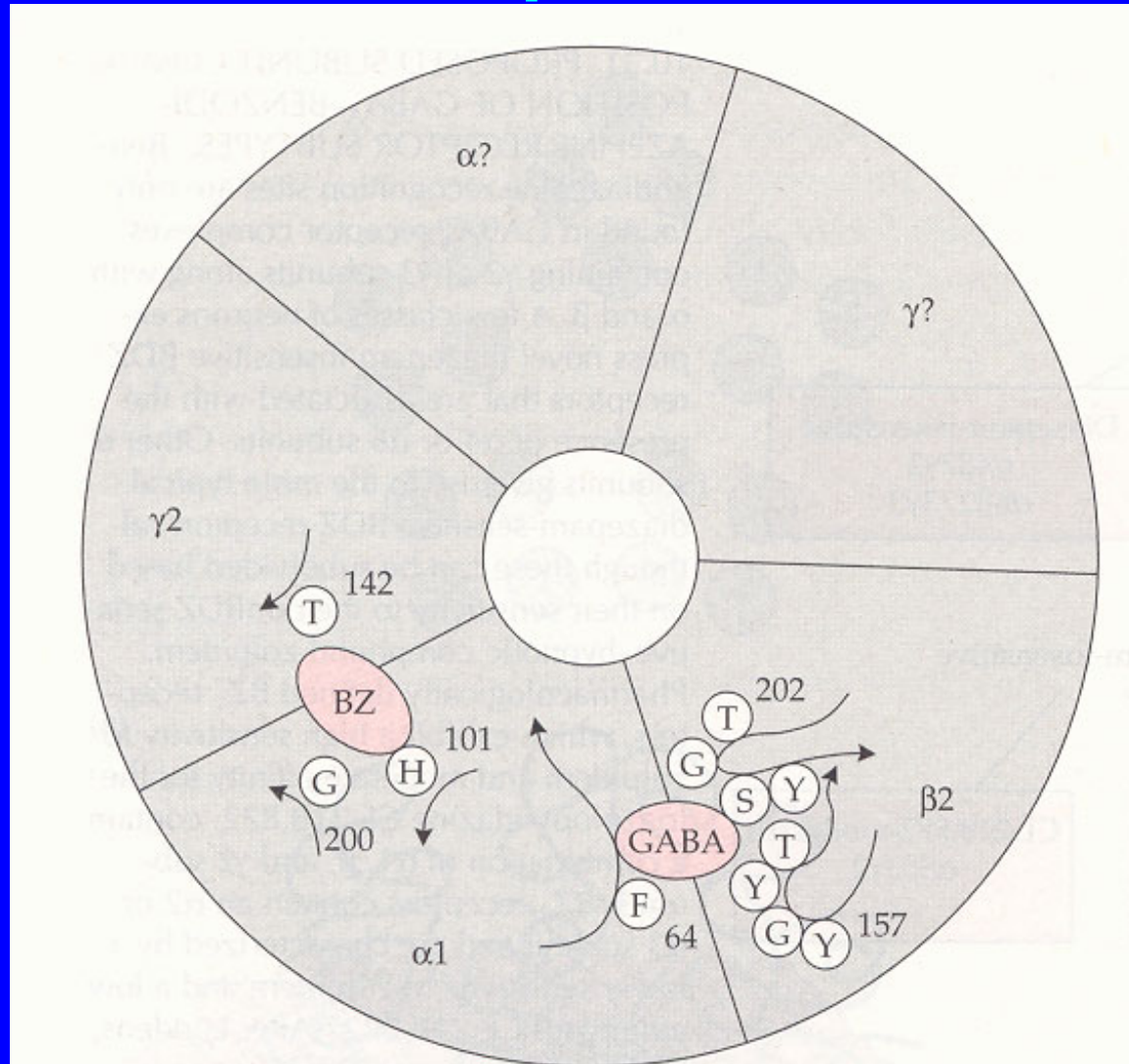
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↗ conductance Cl⁻
→ hyperpolarisation cellule postsynaptique

Principles of Neuropharmacology
Feldman, Meyer, Quenzer ed.
Sinauer Associates Inc 1997 pp 425

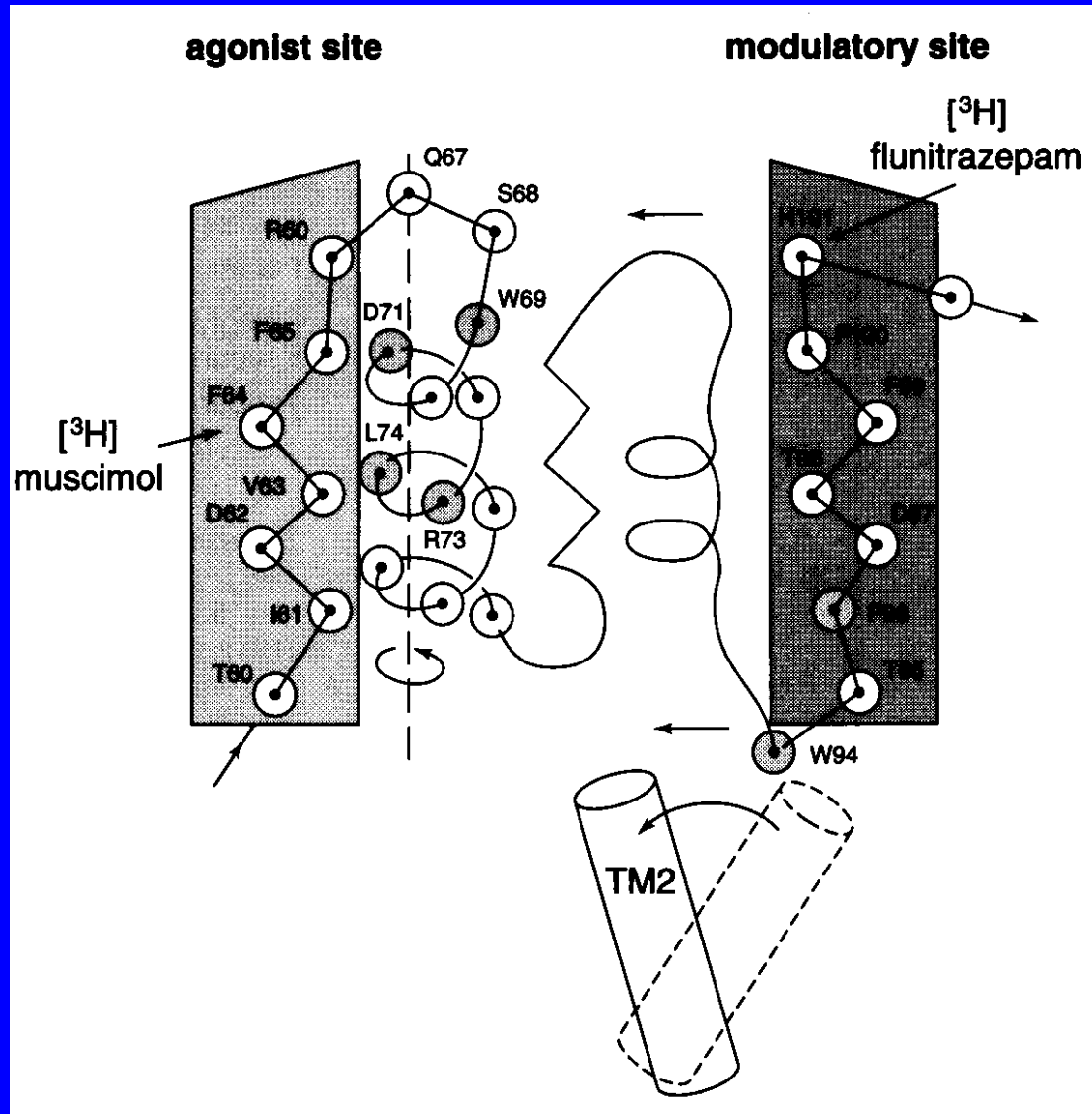
RECEPTEUR GABA_A

Amino acids implicated in the binding of Benzodiazepine and GABA

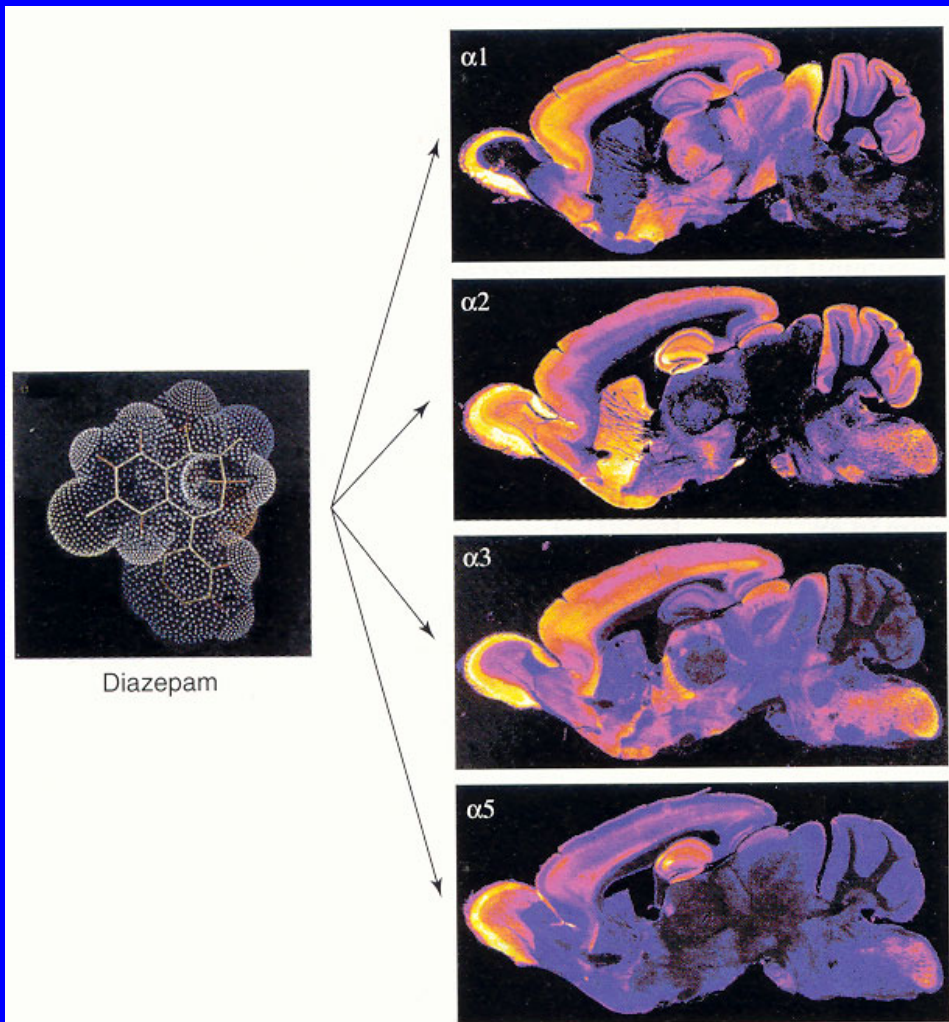


Smith and Olsen *TiPS* (1995) 16:162-168

GABA_A RECEPTOR AND BINDING SITE OF BENZODIAZEPINE



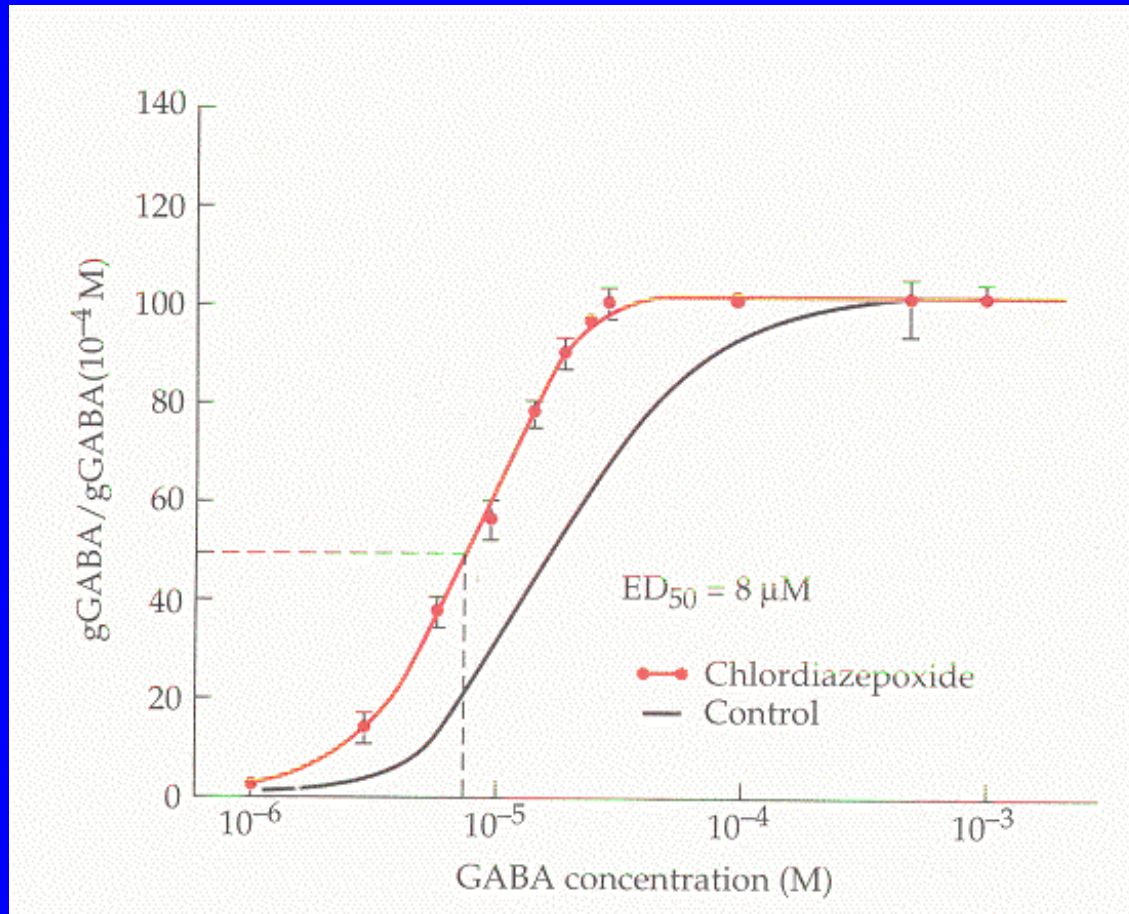
IMMUNOHISTOCHEMICAL DISTRIBUTION OF DIAZEPAM-SENSITIVE GABA_A RECEPTOR SUBTYPES



Level of expression
white>yellow>red>purple

Rudolph et al, *TIPS* (2001) 22: 188-194

BENZODIAZEPINE-INDUCED SHIFT IN THE GABA DOSE-RESPONSE CURVE



Principles of Neuropharmacology
Feldman, Meyer, Quenzer ed.
Sinauer Associates Inc 1997 pp 426

La fixation des benzodiazépines sur un site allostérique du récepteur augmente la puissance du GABA (déplacement de la courbe vers la gauche), mais pas son efficacité maximale

BENZODIAZEPINE PHARMACOLOGY OF GABA_A RECEPTOR SUBTYPES

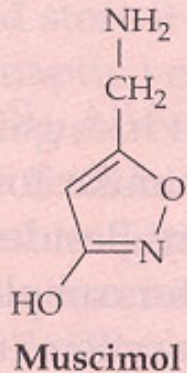
Pharmacological effect ^a	Receptor involved
Anxiolysis	α 2-containing
Sedation	α 1-containing
Anticonvulsion	α 1-containing and those not containing α 1
Anterograde amnesia	α 1-containing

Rudolph et al, *TIPS* (2001) 22: 188-194

RECEPTEUR GABA_A

Muscimol

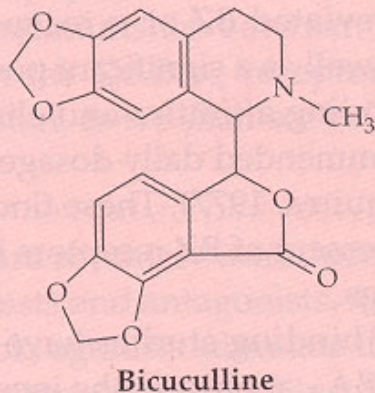
produit de dégradation de l'acide
iboténique ~ *Amonita muscaria*



Agoniste

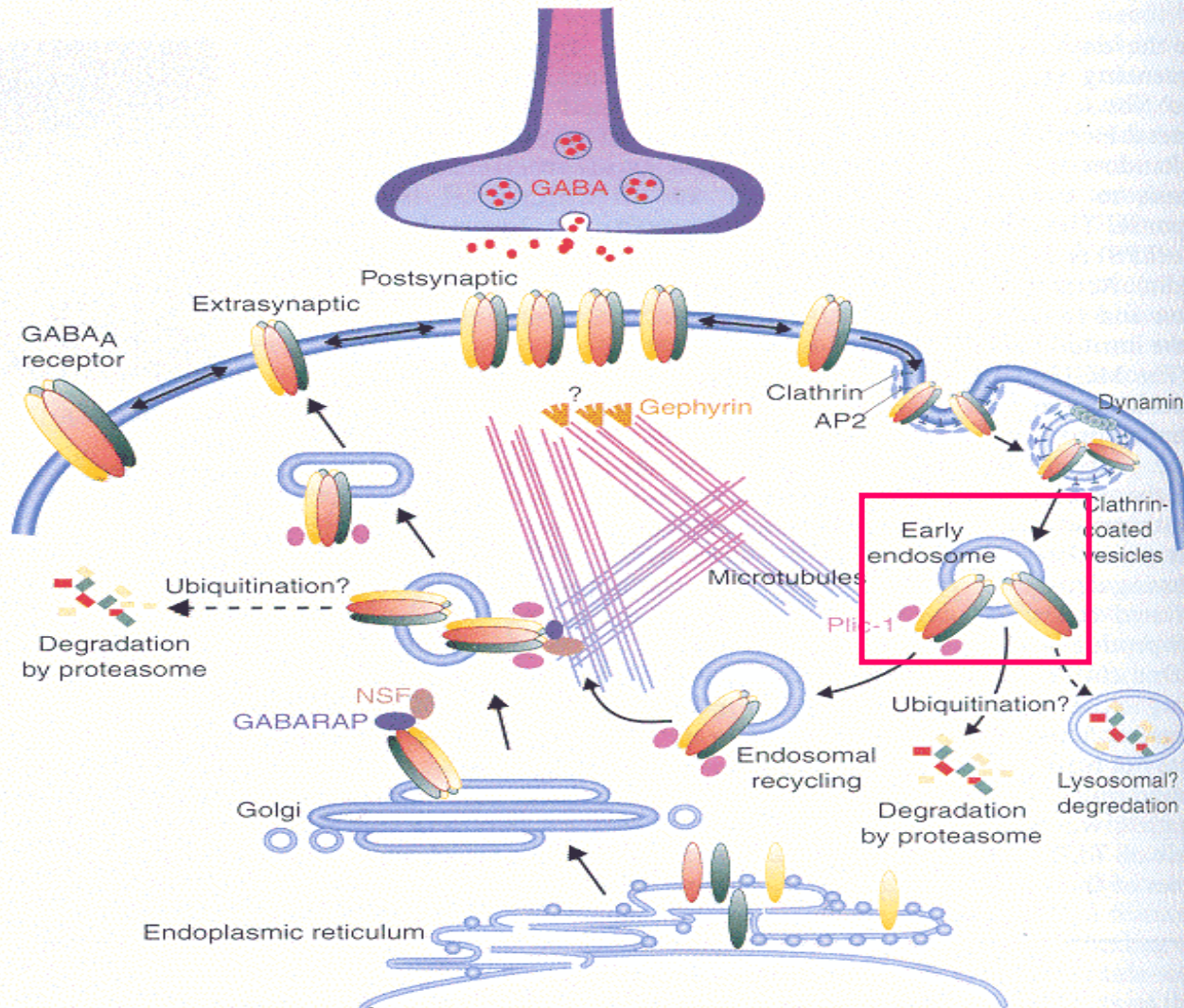
Bicuculline

alcaloïde dérivé de *Dicentra cucullaria*



Antagoniste compétitif

TRAFFICKING AND MEMBRANE TARGETING OF GABA_A RECEPTORS



TRAFFICKING AND MEMBRANE TARGETING OF GABA_A RECEPTORS

Ubiquitin act as a sorting signal in early endosomes

→ conjugation with ubiquitin = means to terminate signalling by rapid downregulation of receptors at the plasma membrane

Plic proteins interfere with the degradation of ubiquitin-substrates → $\nearrow T_{1/2}$

$T_{1/2}$ of GABA receptors \nearrow by binding of the receptor to Plic

⇒ Modulation of the surface expression of GABA receptors

⇒ Rapid adaptation of neural excitability

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GABA_A

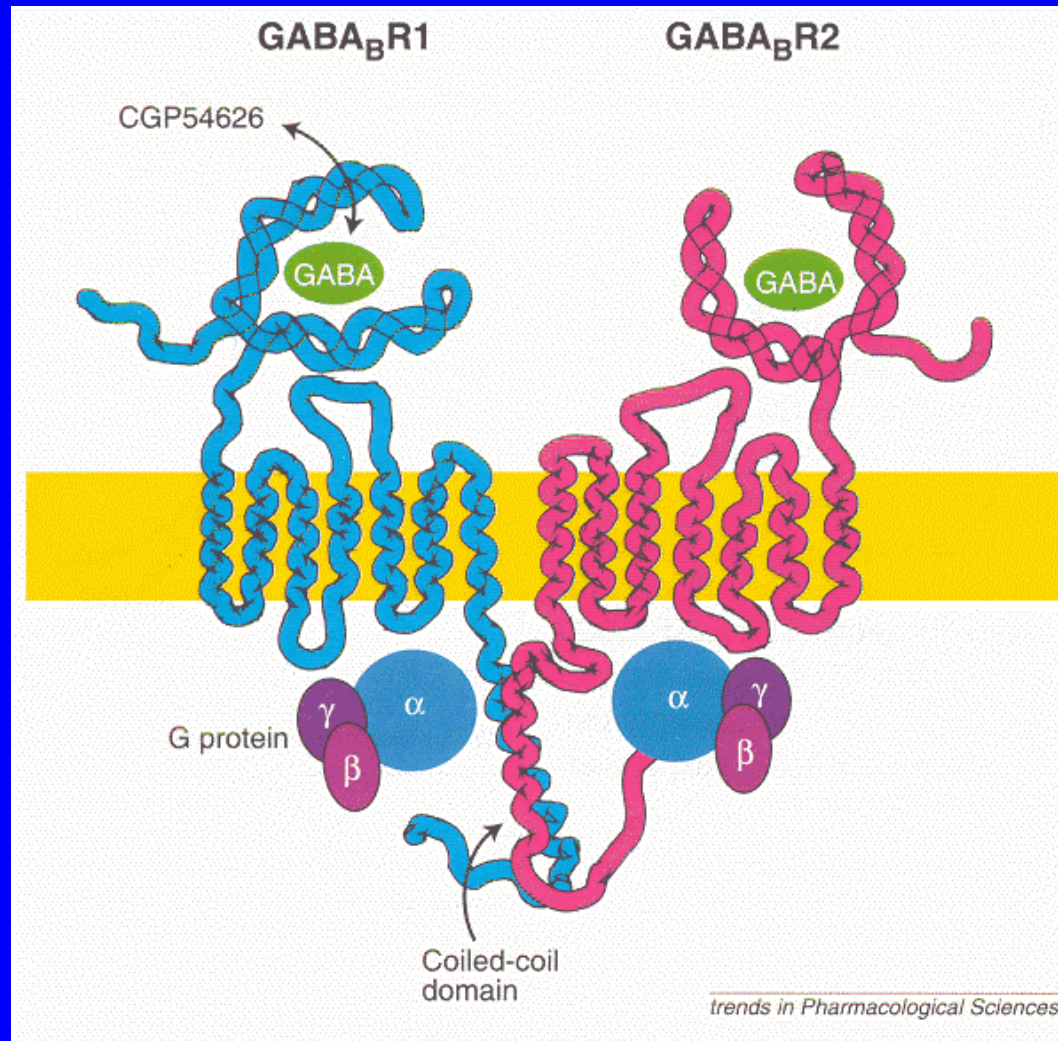
GABA_B

GABA_C

INTERACTION ENTRE RECEPTEURS

GABA_B HETERODIMERS

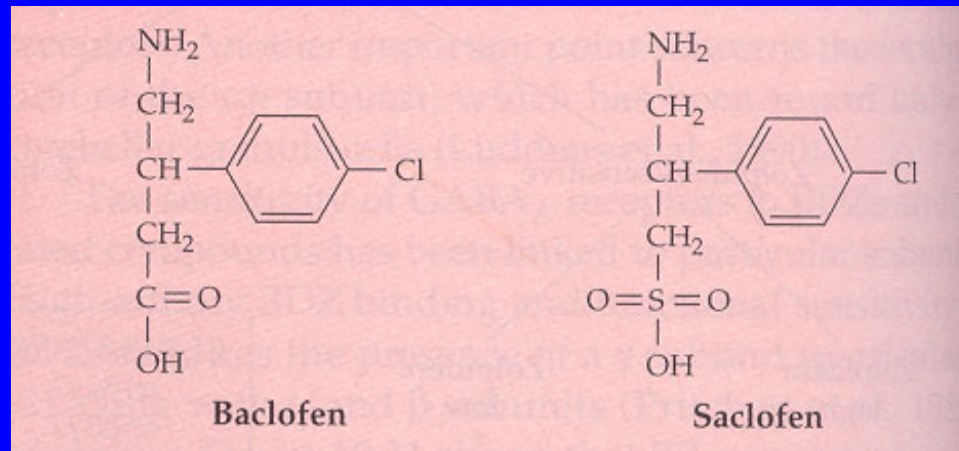
Récepteurs métabotropiques



RECEPTEURS GABA_B

Mécanismes effecteurs

1. Inhibition de l'adenylate cyclase
2. Stimulation de la phospholipase A₂
3. Augmentation de la conductance K⁺
4. Inhibition conductance voltage dependant Ca²⁺



Agonist

Antagonist

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GABA_B

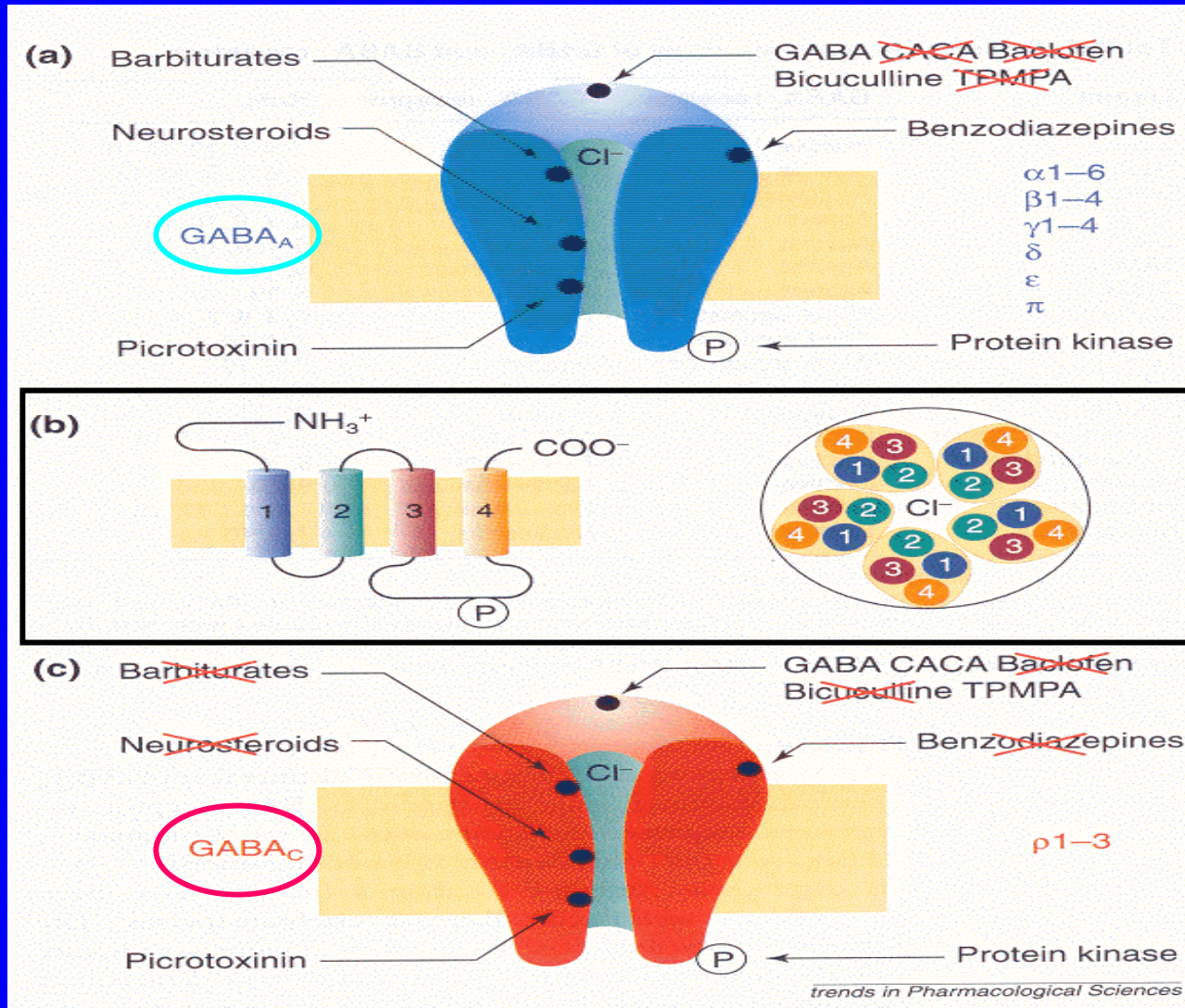
GABA_C

INTERACTION ENTRE RECEPTEURS

RECEPTEUR GABA_c

- activé par :
 - cis-4-aminocrotonic acid
 - GABA
 - Muscinol
- + sensible que GABA_A ou GABA_B
- pas de modulation - benzodiazépines
 - barbituriques
 - neurostéroïdes

COMPARISON BETWEEN GABA_A and GABA_C RECEPTORS



FUNCTIONAL COMPARISON OF GABA_A AND GABA_C RECEPTORS

Property	GABA _C receptor	GABA _A receptor
GABA EC ₅₀	1–4 μ M	5–100 μ M
Hill slope	3–5	2
Activation/inactivation	Slow	Fast
Desensitization	Weak	Strong
Conductance	7 pS	27–30 pS
Open time	150–200 ms	25–30 ms
Selectivity	Anions (Cl ⁻)	Anions (Cl ⁻)
Pore size	5.1 Å	5.6 Å

COMPARISON OF GABA_A AND GABA_C RECEPTORS

Ligand	GABA _C receptor	GABA _A receptor
Bicuculline	Inactive	Antagonist
Baclofen	Inactive	Inactive
Picrotoxinin	Antagonist ^a	Antagonist
TACA	Agonist	Agonist
CACA	Agonist	Inactive
TAMP	Agonist	Weak agonist
CAMP	Agonist	Inactive
Muscimol	Partial agonist	Agonist
Isoguvacine	Weak antagonist	Agonist
THIP	Weak antagonist	Agonist
I4AA	Antagonist	Agonist
TPMPA	Antagonist	Inactive
1,4-Benzodiazepines	Inactive	Modulators ^b
Triazolopyridazines	Inactive	Modulators ^b
Imidazopyridines	Inactive	Modulators ^b
Barbiturates	Inactive	Modulators
Neurosteroids	Inactive	Modulators

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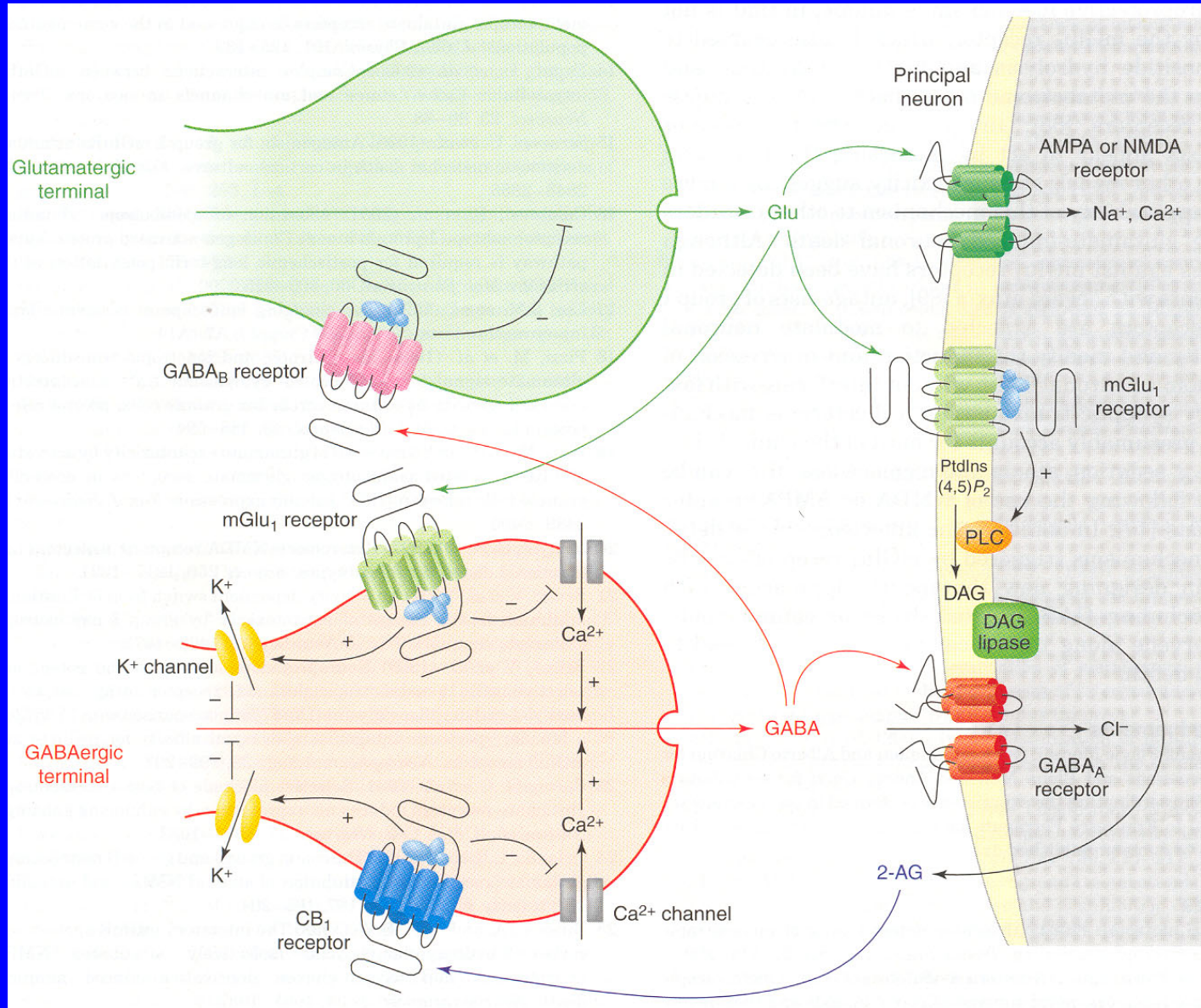
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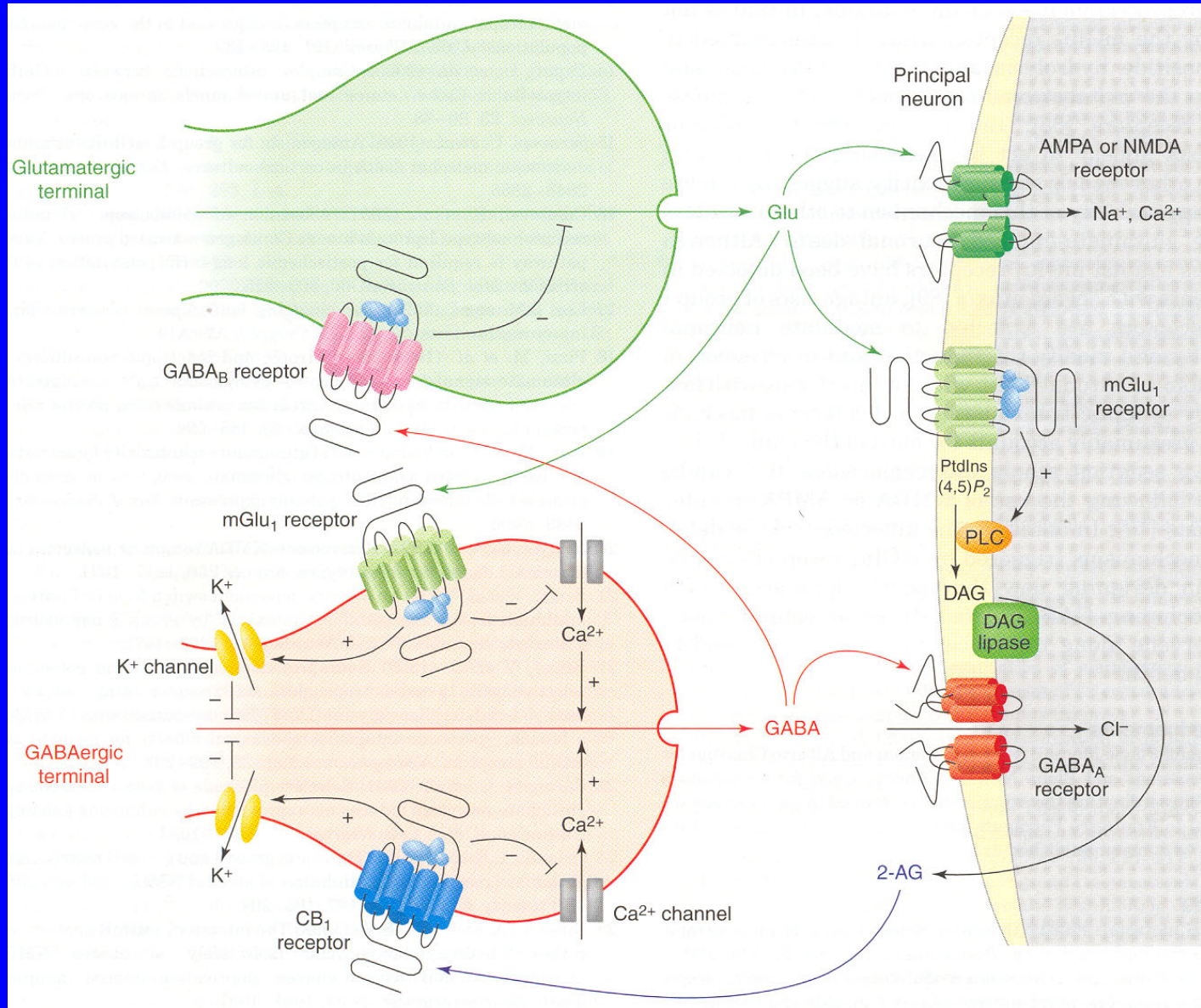
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INTERACTION ENTRE RECEPTEURS

GLUTAMATE –GABA INTERACTIONS



GLUTAMATE –GABA INTERACTIONS



POSSIBLE EXPLANATION FOR THE NEUROPROTECTIVE EFFECTS OF METABOTROPIC GLUTAMATE 1 RECEPTOR ANTAGONISTS

(1) Excessive activation of postsynaptic AMPA and NMDA receptors by glutamate produces a sustained depolarizing influx of Na^+ and Ca^{2+} , which eventually leads to neurodegeneration

(2) Activation of postsynaptic GABA_A receptors produces an influx of Cl^- , hyperpolarization and neuroprotection

(3) GABA can also interact with presynaptic GABA_B receptors that negatively control the release of glutamate, thus leading to reduced excitation of postsynaptic neurons

(4) The release of GABA is negatively-controlled by mGlu1 receptors and cannabinoid CB_1 receptors, via suppression of Ca^{2+} currents through N-type channels or activation of K^+ channels

Antagonists of mGlu1 receptors can lead to increased release of GABA and therefore to neuroprotective hyperpolarization

- Direct blockade of presynaptic mGlu1 receptor on GABAergic terminals
- Indirect inhibition of CB_1 receptors located on GABAergic terminals prompted by mGlu1 receptors located postsynaptically

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