TRANSMISSION GABAERGIQUE

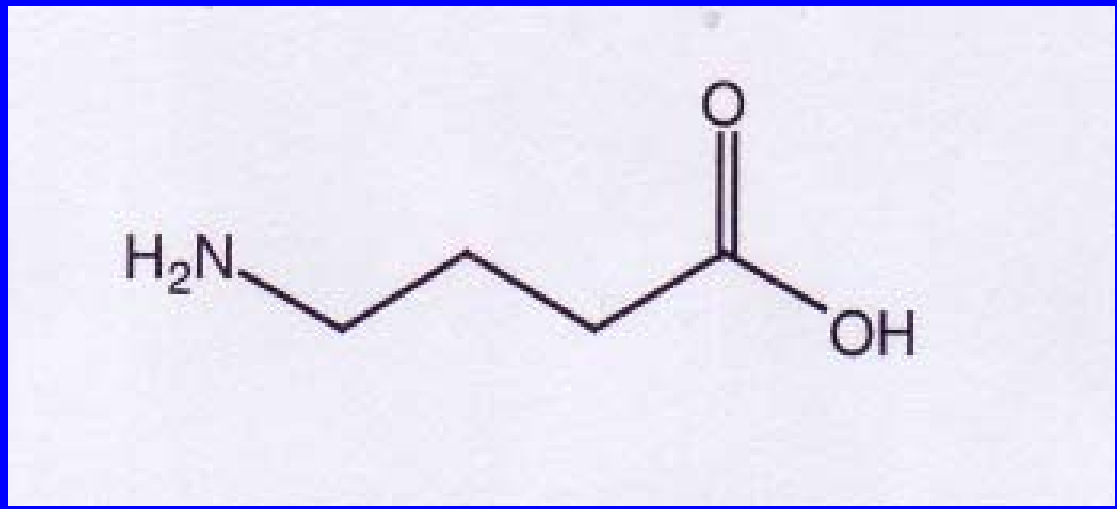
GABA = ACIDE γ-AMINO BUTYRIQUE

STRUCTURE

VOIES GABAERGIQUES
INTERET PHYSIOPATHOLOGIQUE ET PHARMACOLOGIQUE
SYNAPSE GABAERGIQUES
SYNTHESE
CAPTURE
DEGRADATION
INTERACTION LIGAND/RECEPTEUR GABAERGIQUE
INTERACTION ENTRE RECEPTEURS

GABA = ACIDE γ-AMINO BUTYRIQUE

Principal neurotransmetteur inhibiteur



Le GABA serait impliqué dans au moins 30% des synapses du cerveau

GABA = ACIDE γ-AMINO BUTYRIQUE

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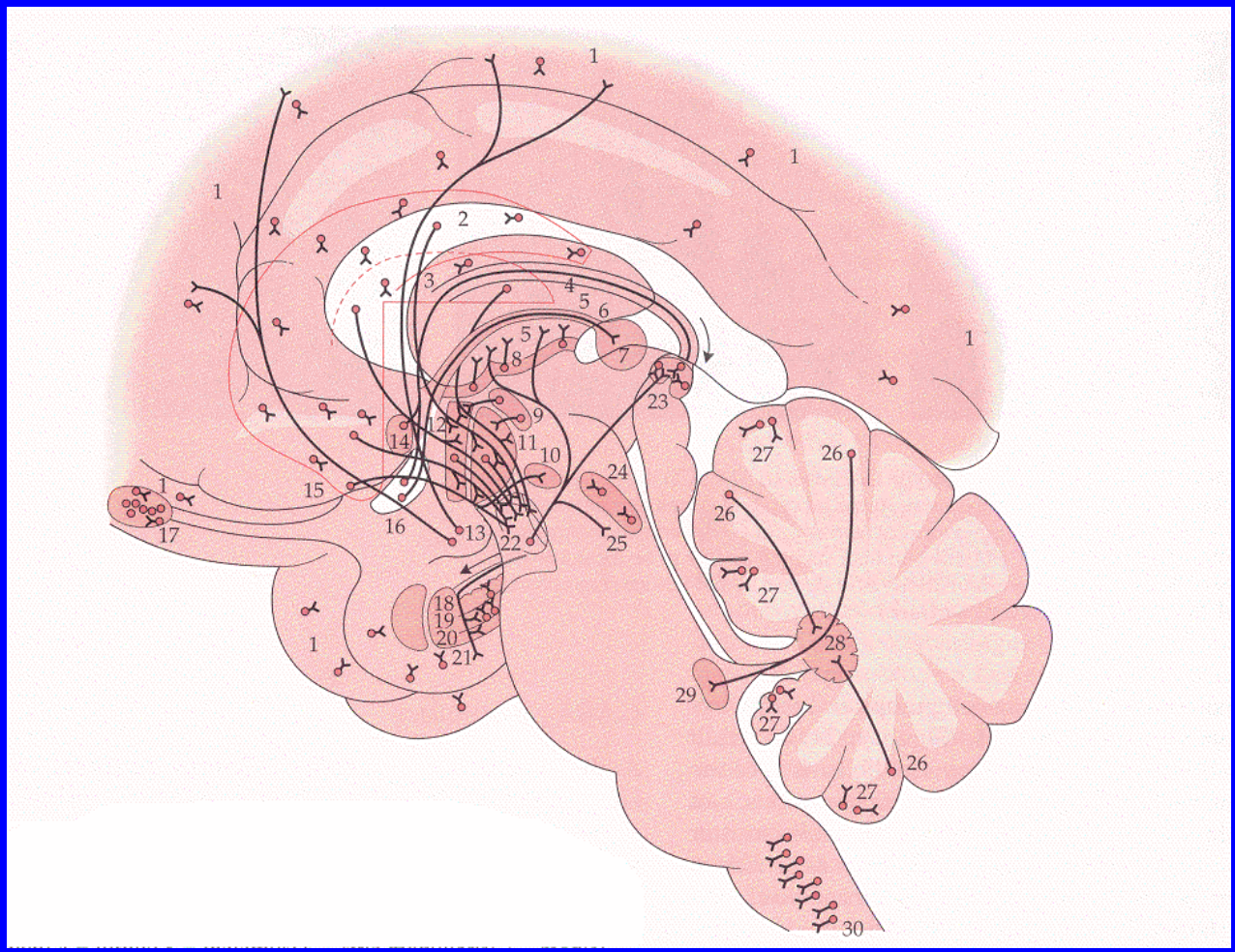
SYSTEME GABAERGIQUE



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

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

GABA = ACIDE γ-AMINO BUTYRIQUE

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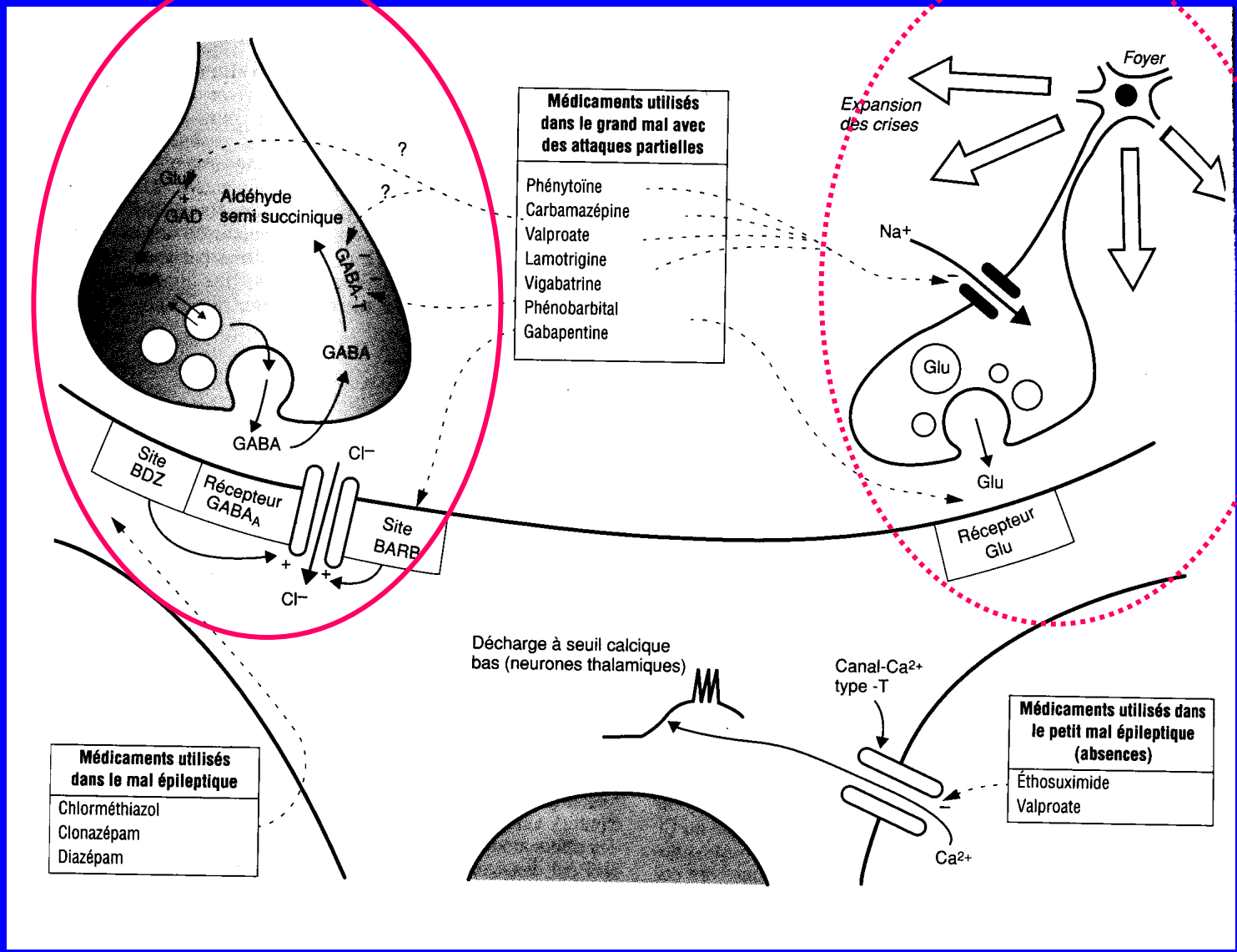
EQUILIBRE GLUTAMATE/GABA ET EPILEPSIE



Neal, Pharmacologie médicale (1999) pp 56

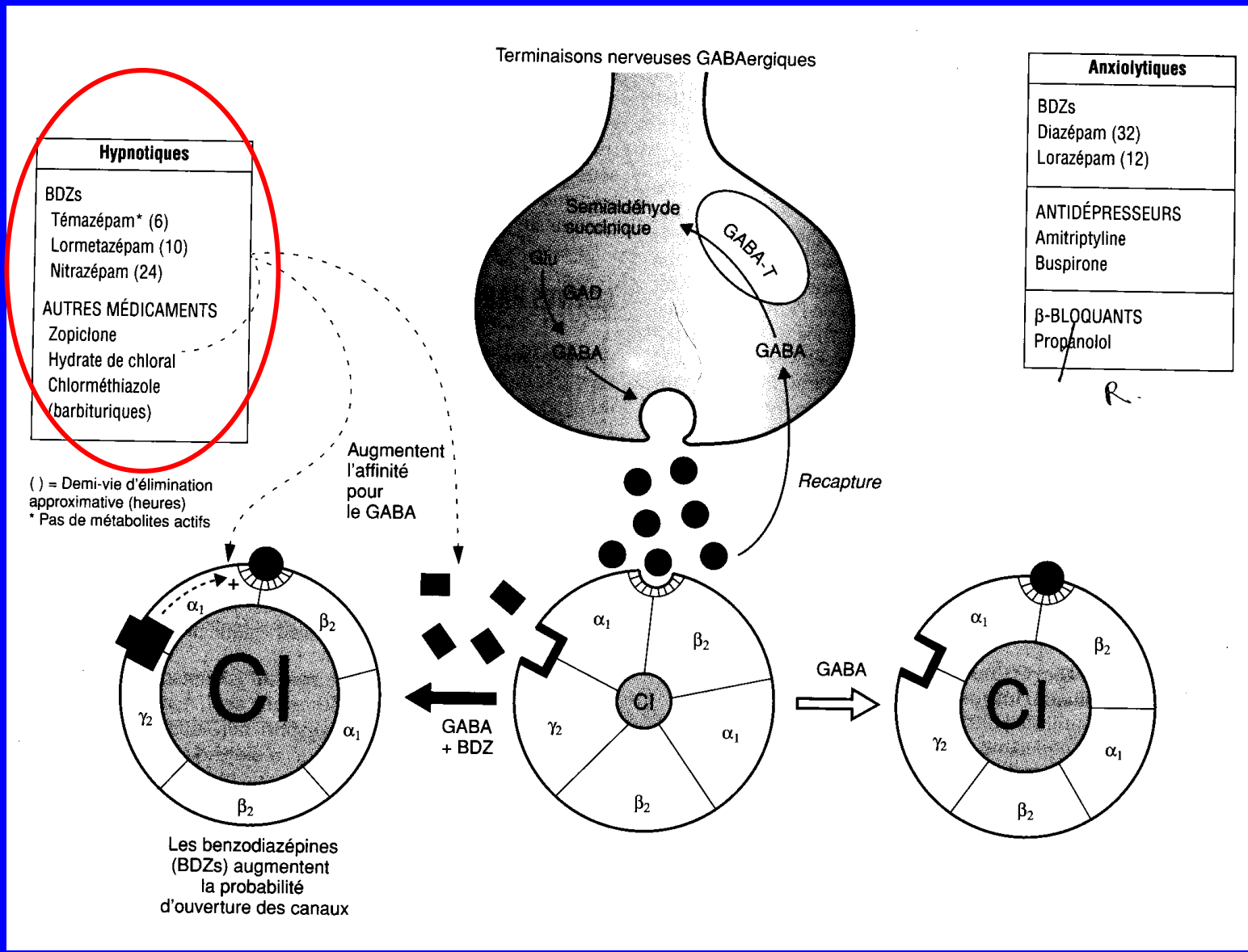
EQUILIBRE GLUTAMATE/GABA DANS L'ISCHEMIE CEREBRALE

Lors d'un épisode aigu d'ischémie cérébrale, l'activité glutamatergique augmente, ce qui peut conduire à la mort neuronale.

Parallèlement l'activité gabaergique diminue.

Intérêt de stimuler l'activité gabaergique pour privilégier un effet neuroprotecteur

GABA AND ANXIETE



Neal, Pharmacologie médicale (1999) pp 54

GABA = ACIDE γ-AMINO BUTYRIQUE

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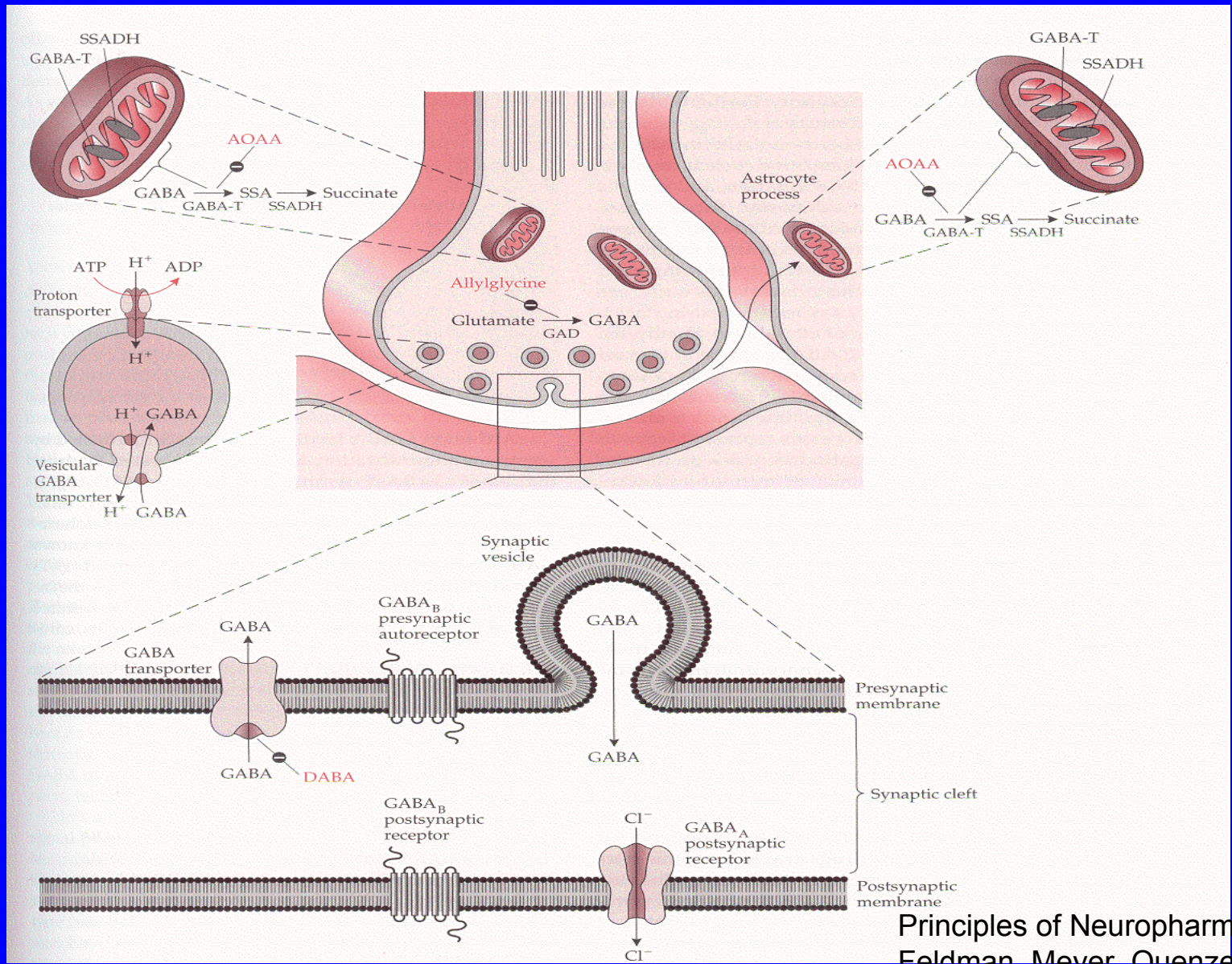
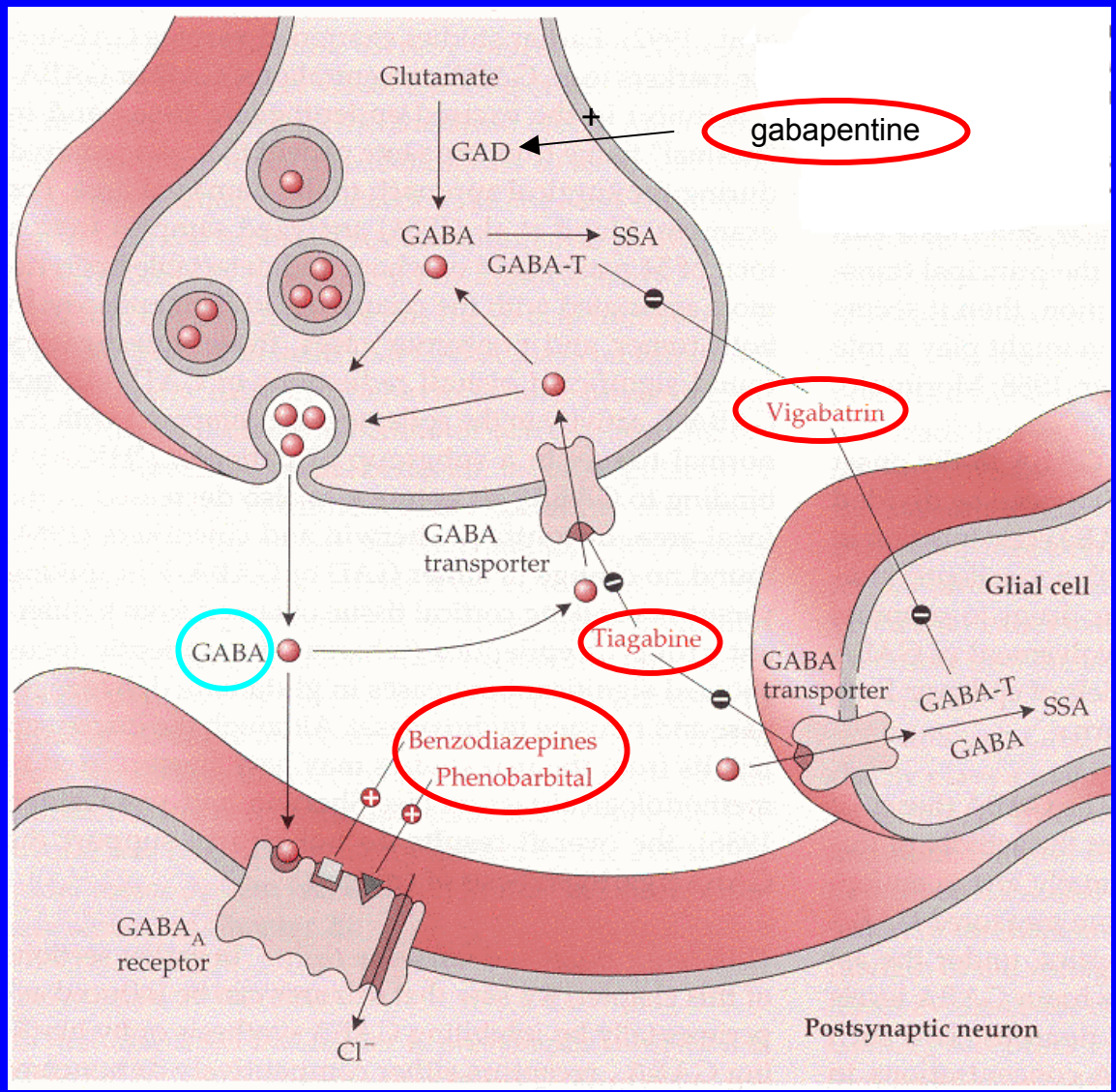
SYNAPSE GABAERGIQUE



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

GABA = ACIDE γ-AMINO BUTYRIQUE

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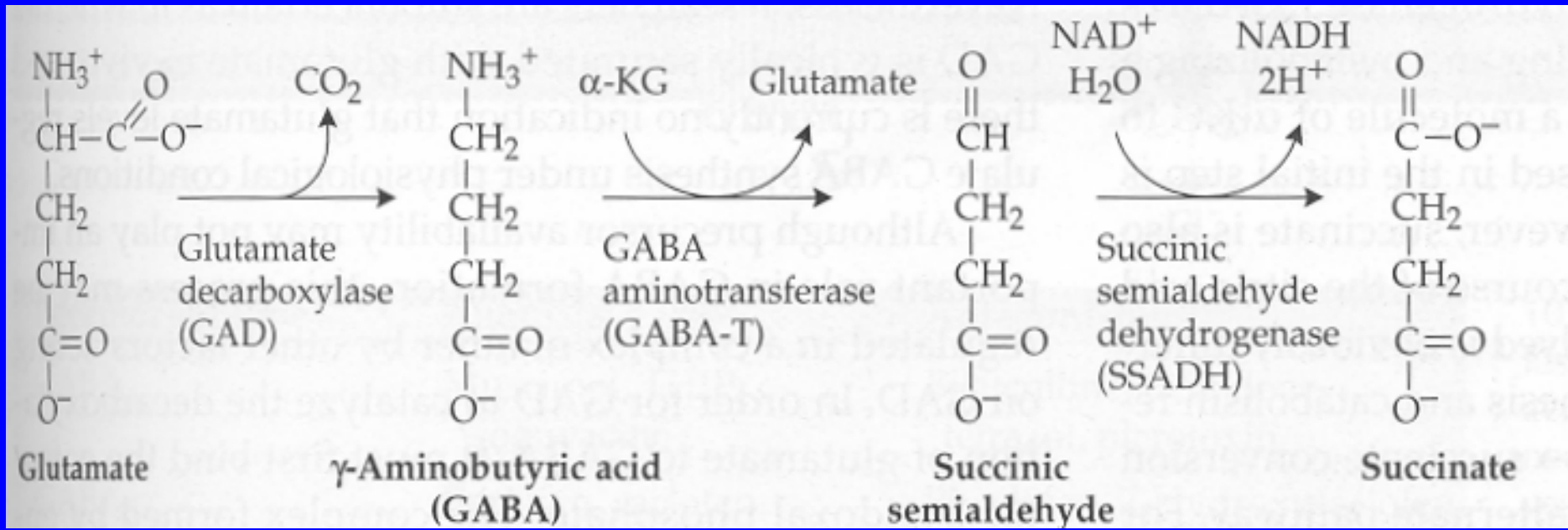
GABA – SYNTHESE/DEGRADATION



Biosynthèse (GAD; cytosol)

Dégradation (GABA-T; mitochondrie)

→ **Importance en terme de régulation**

GABA - SYNTHESE

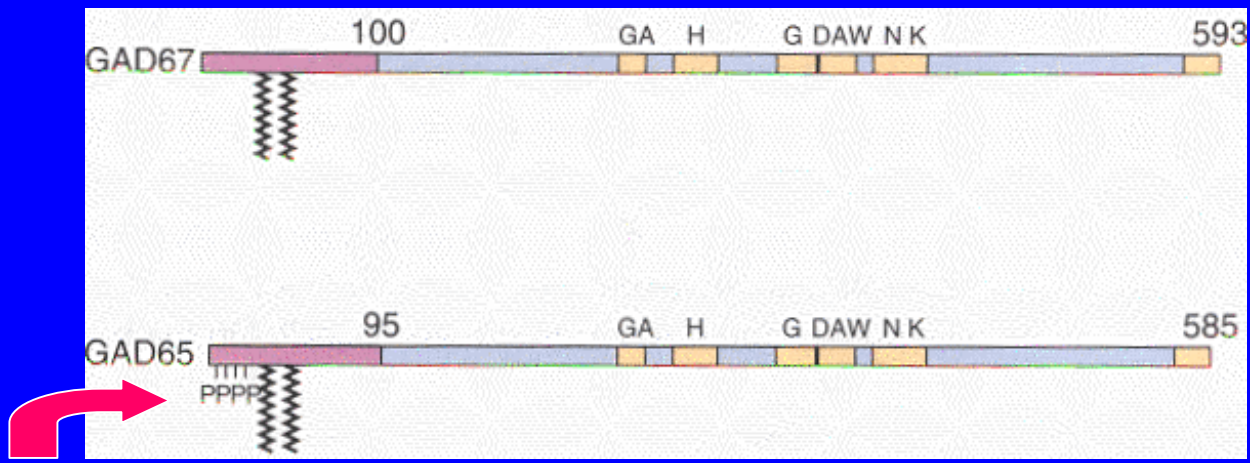
Glutamate decarboxylase = GAD

- 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 - SYNTHESE - GLUTAMATE DECARBOXYLASE

N-terminus

C-terminus



Serine phosphorylated which play a role in membrane association

GAD = glutamate decarboxylase

Catalytic domains: yellow

Soghomonian and Martin, *TiPS* (1998) : 19: 500-505

MEDICAMENTS AGISSANT AU NIVEAU DE LA GLUTAMATE DECARBOXYLASE

INHIBITEURS

Allylglycine

Acide 2-oxo-4 pentenoique

Acide chelidonique

Acide 3-mercaptopropionique

2-methyl 3,4 didehydroglutamate

ACTIVATEURS

Gabapentine

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

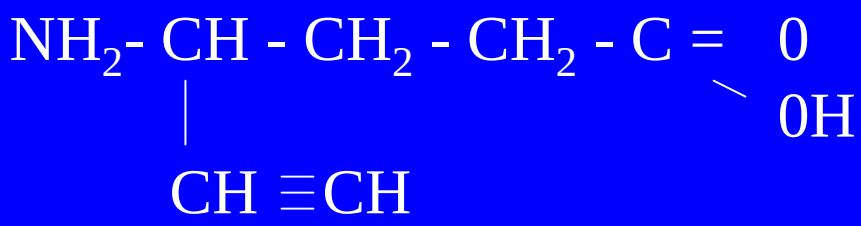
GABA shunt

α-cetoglutarate →succinate **(qui peut rentrer dans le cycle de Krebs)**

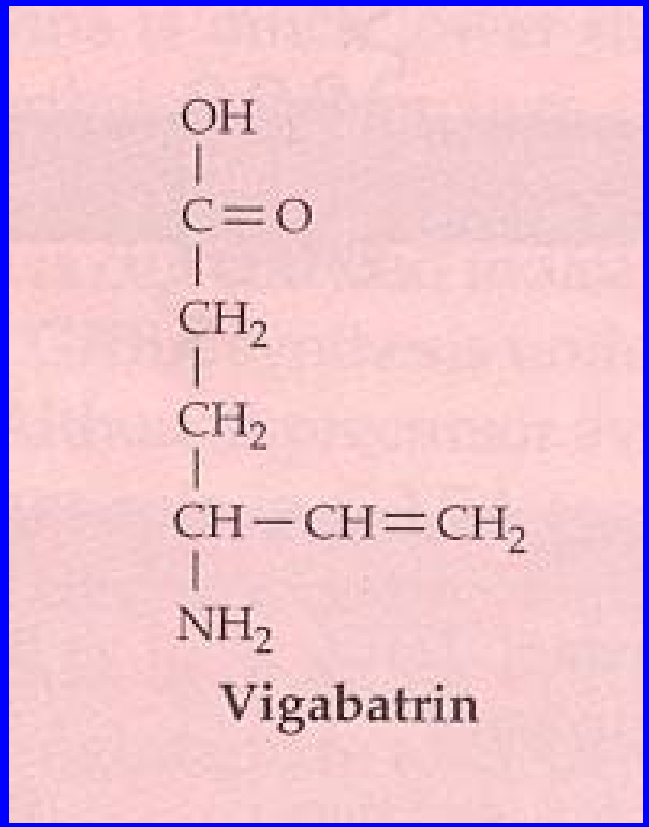
MEDICAMENTS AGISSANT COMME INHIBITEURS DE LA GABA AMINOTRANSFERASE

Isoniazide

γ-Acetylenique GABA



Vinyl-GABA (Vigabatrine)
Inhibiteur suicide



GABA = ACIDE γ-AMINO BUTYRIQUE

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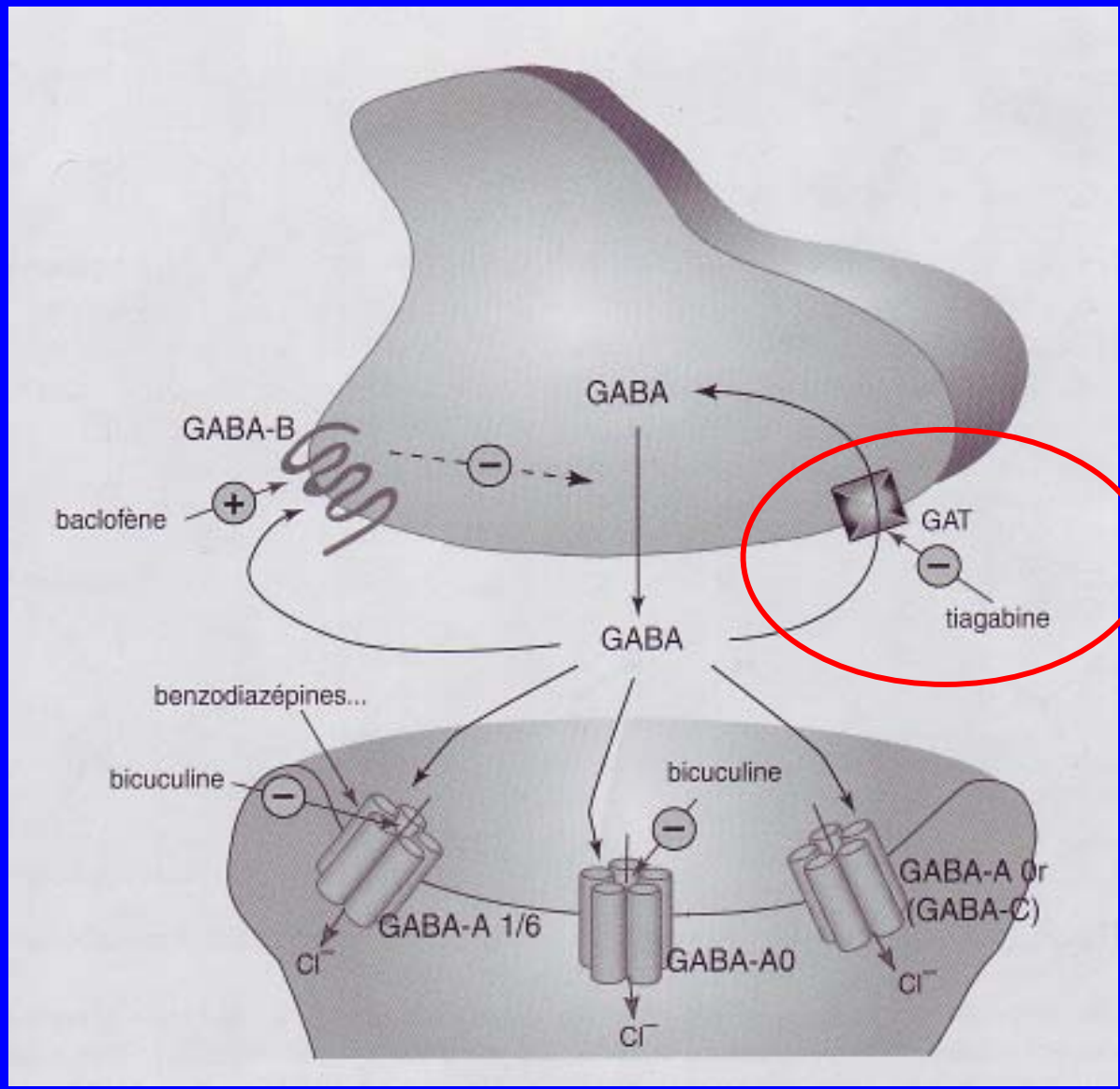
GABA - RECAPTURE



From Pharmacologie, Landry et Gies, Ed Dunod (2003); Pg 421

MEDICAMENTS AGISSANT COMME INHIBITEURS DE CAPTURE

Quatre types de transporteurs au GABA ont été identifiés

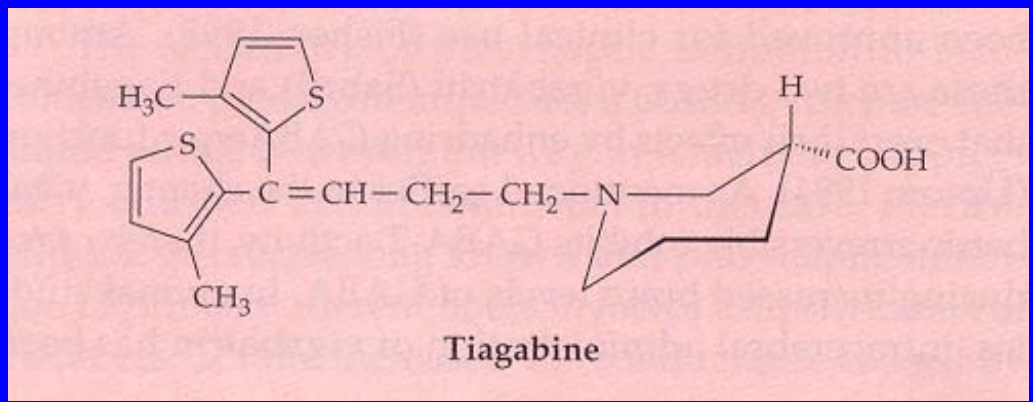
- **GAT1 et GAT4: exprimés principalement au niveau neuronal**
- **GAT 2 et GAT3: transporteurs principalement exprimés par les cellules gliales mais aussi par les cellules rénales et hépatiques**

Rôle de l'hétérogénéité cellulaire???

MEDICAMENTS AGISSANT COMME INHIBITEURS DE CAPTURE

2,4 diaminobutyric acid	**2-OH GABA**
$NH_2 - CH_2 - CH_2 - CH(NH_2) - C(=O)OH$	$NH_2 - CH_2 - CH_2 - CHOH - C(=O)OH$

Tiagabine



Tiagabine

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INTERACTION LIGAND/RECEPTEUR GABAERGIQUE
- $GABA_A$
- $GABA_B$
- $GABA_C$

INTERACTION ENTRE RECEPTEURS

GABA RECEPTORS IN SNC

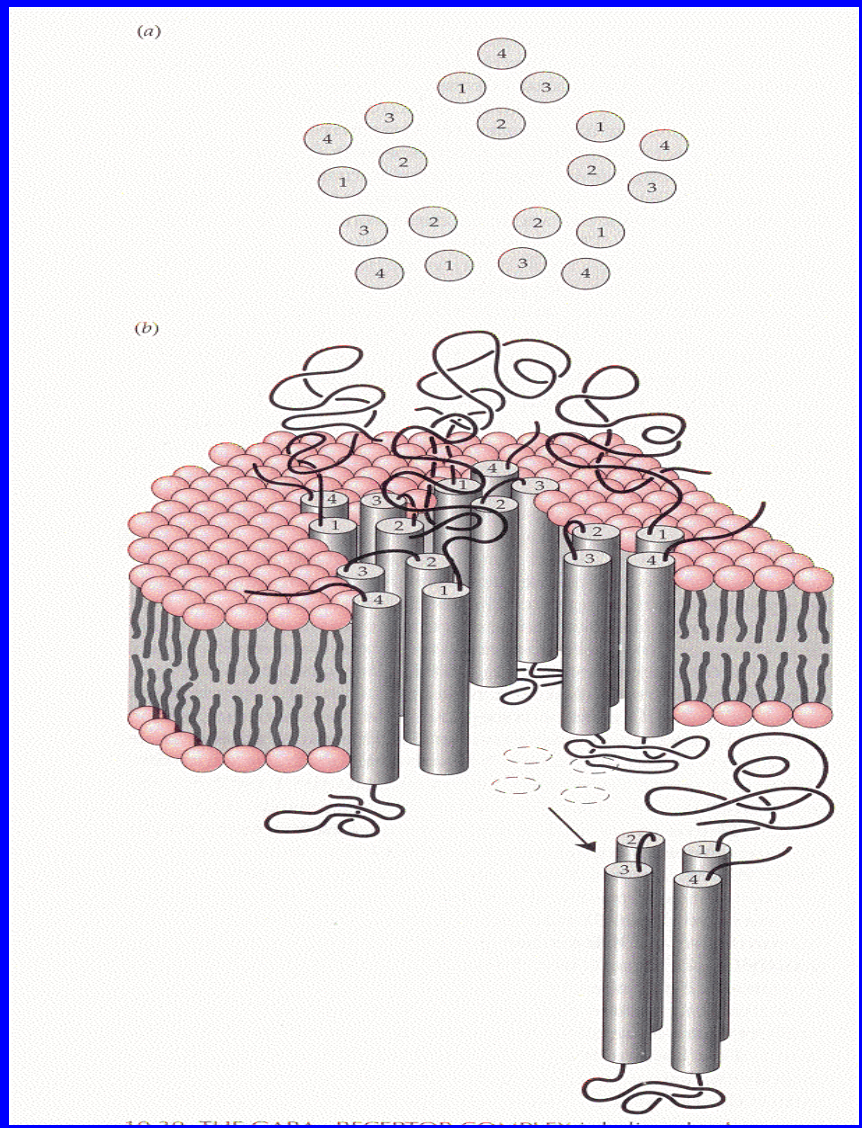
Table 1. Comparative properties of GABA receptors in the CNS

Characteristic	$GABA_A$	$GABA_B$	$GABA_C$
Receptor mechanism	Ionotropic (Cl^- channel)	Metabotropic (G protein-coupled)	Ionotropic (Cl^- channel)
Protein subunits	α_{1-6}, β_{1-3}, γ_{1-3}, δ	Not known	ρ_1, ρ_2
Single channel currents	≈30 pS	–	≈8 pS
Mean channel open time	≈25 ms	–	≈150 ms
Pharmacology			
GABA	≈10 μM (EC_{50})	≈10 μM (EC_{50})	≈1 μM (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.

Johnston, *TiPS* (1996) 17: 319-323

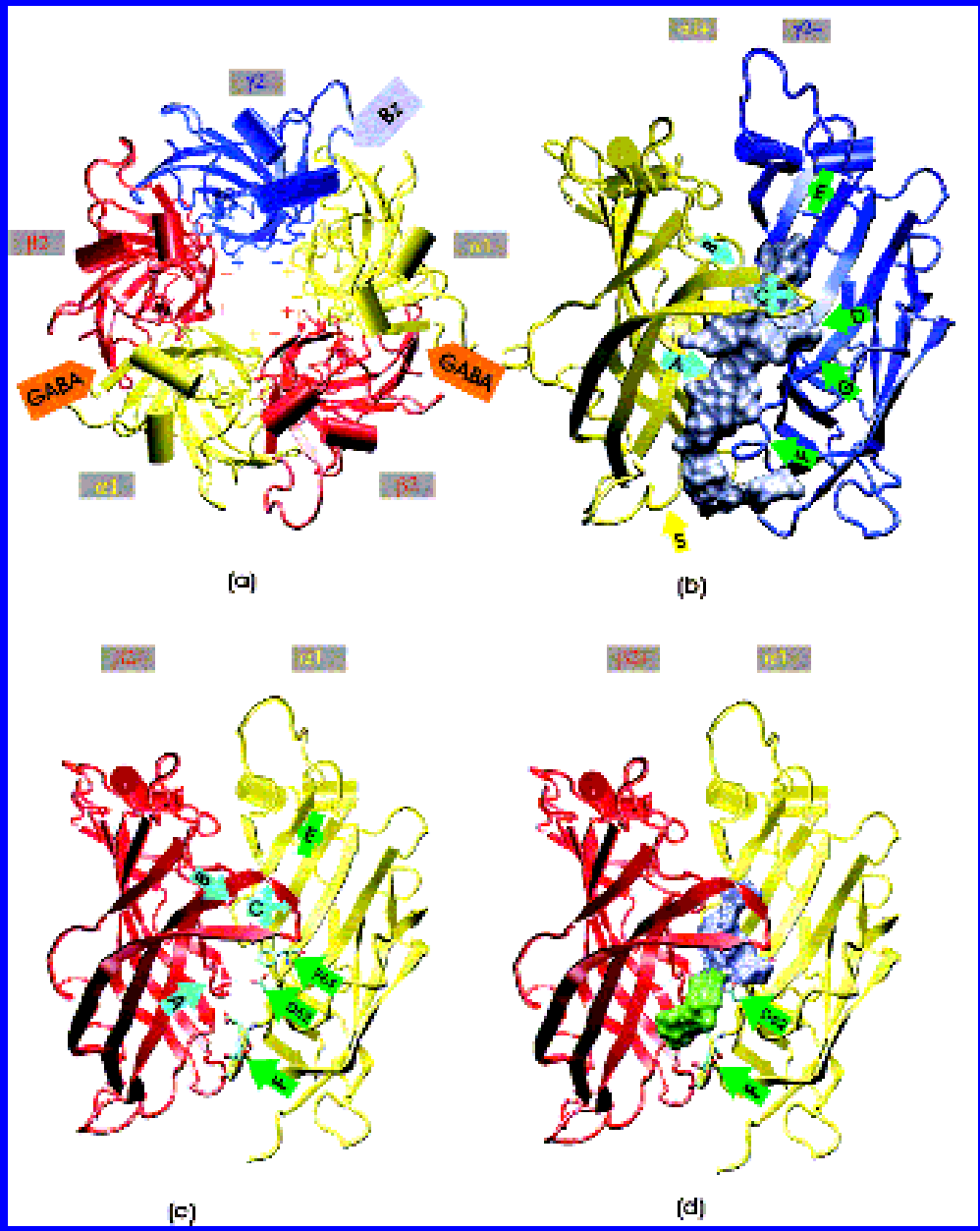
RECEPTEUR $GABA_A$



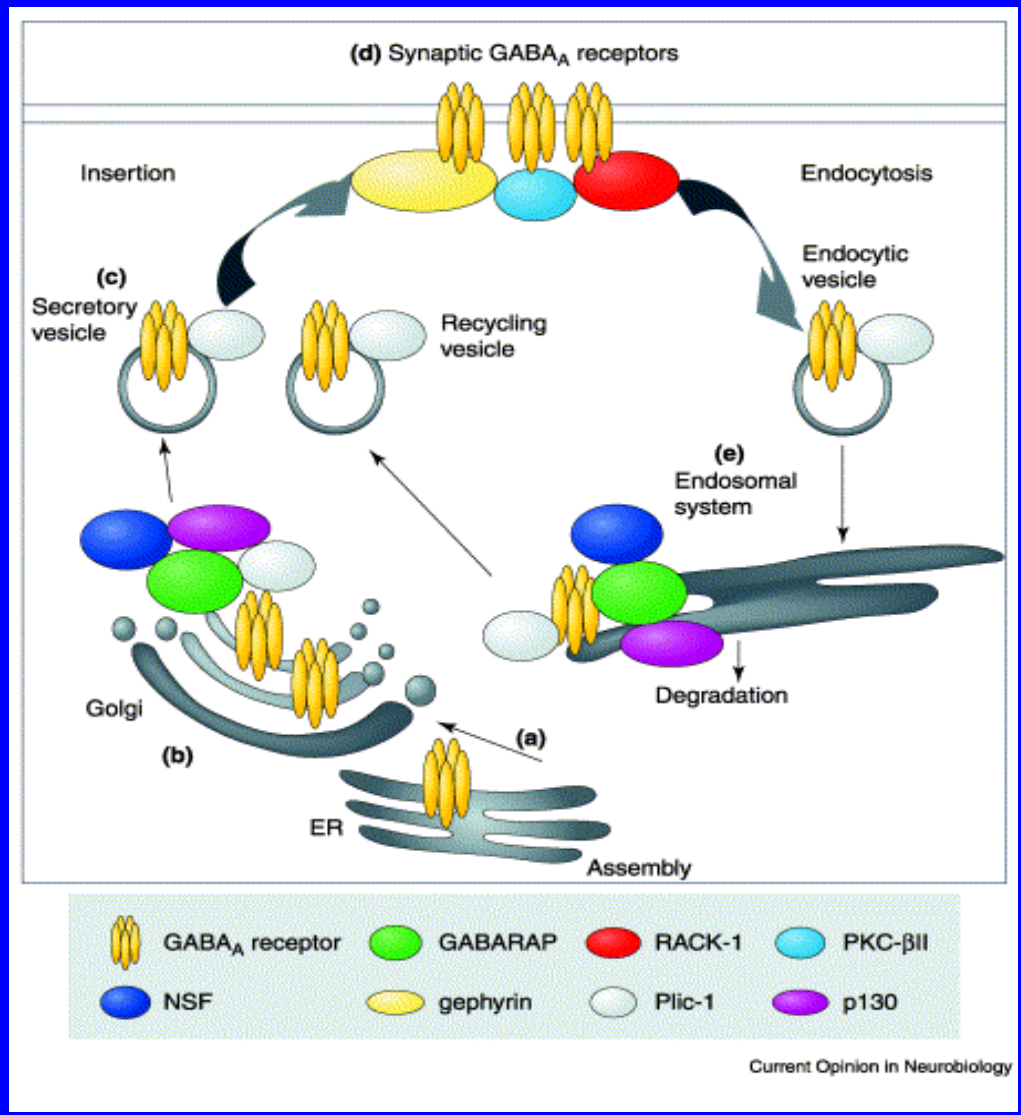
5 sous-unités comprenant chacune 4 segments transmembranaires

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

RECEPTEUR $GABA_A$

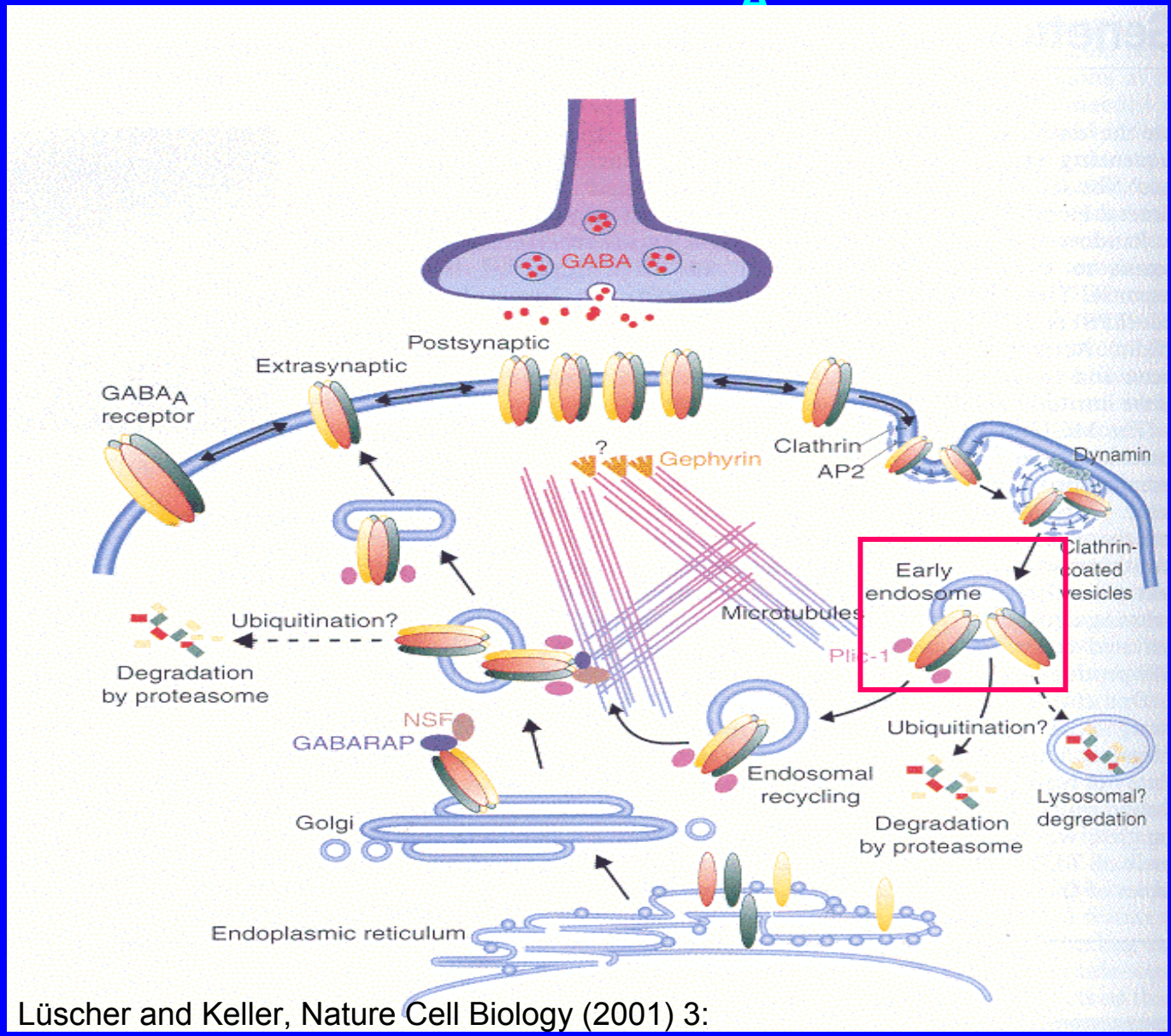


TRAFFICKING AND MEMBRANE TARGETING OF $GABA_A$ RECEPTORS



Kittler and Moss, (2003), Cur. Opin. Neurobiol, 13: 341-347

TRAFFICKING AND MEMBRANE TARGETING OF $GABA_A$ RECEPTORS



Lüscher and Keller, Nature Cell Biology (2001) 3:

TRAFFICKING AND MEMBRANE TARGETING OF $GABA_A$ RECEPTORS

Ubiquitin act as a sorting signal in early endosomes

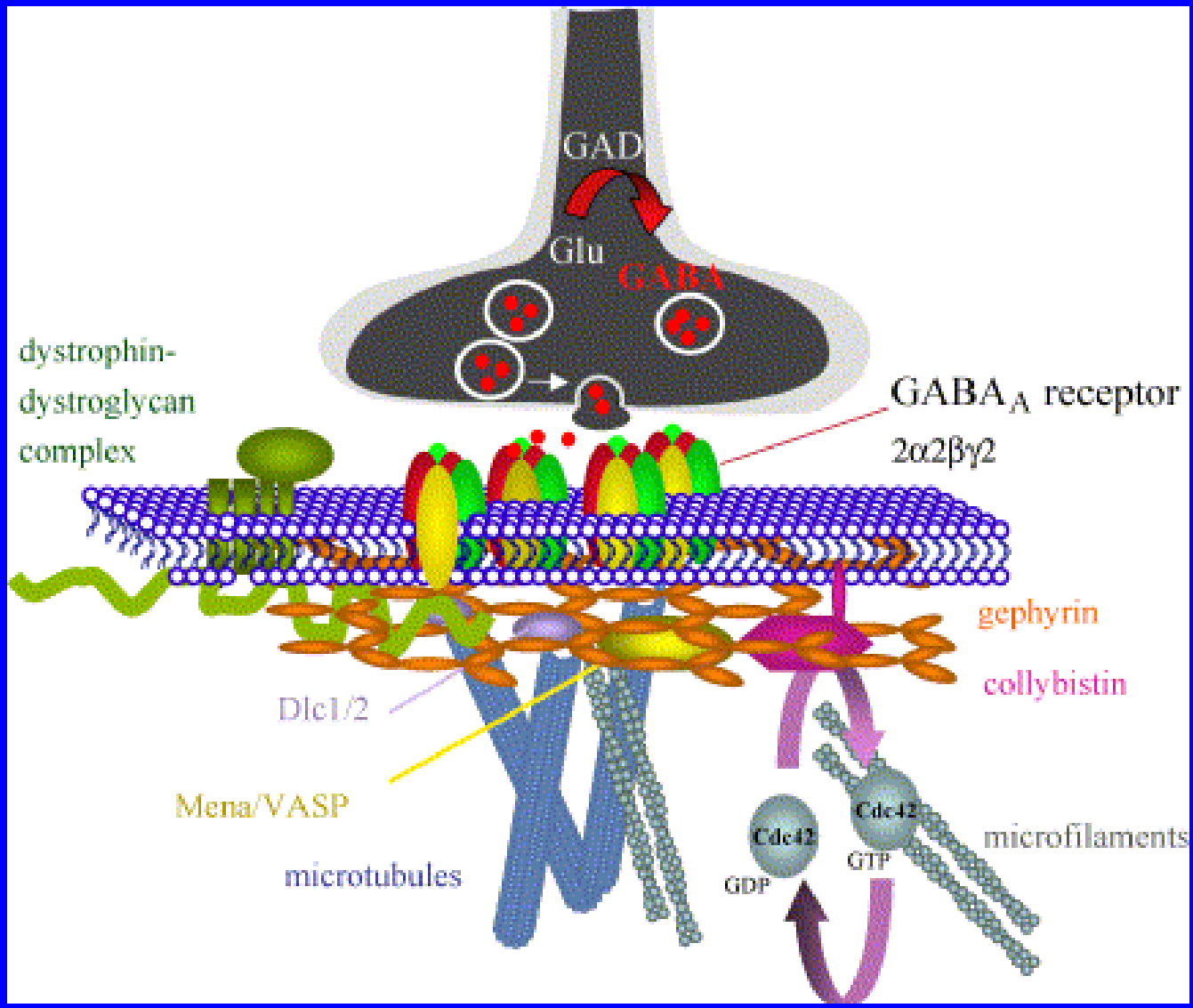
→conjugation with ubiquitin = means to terminate signalling by rapid downregulation of receptors at the plasma membrane

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

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

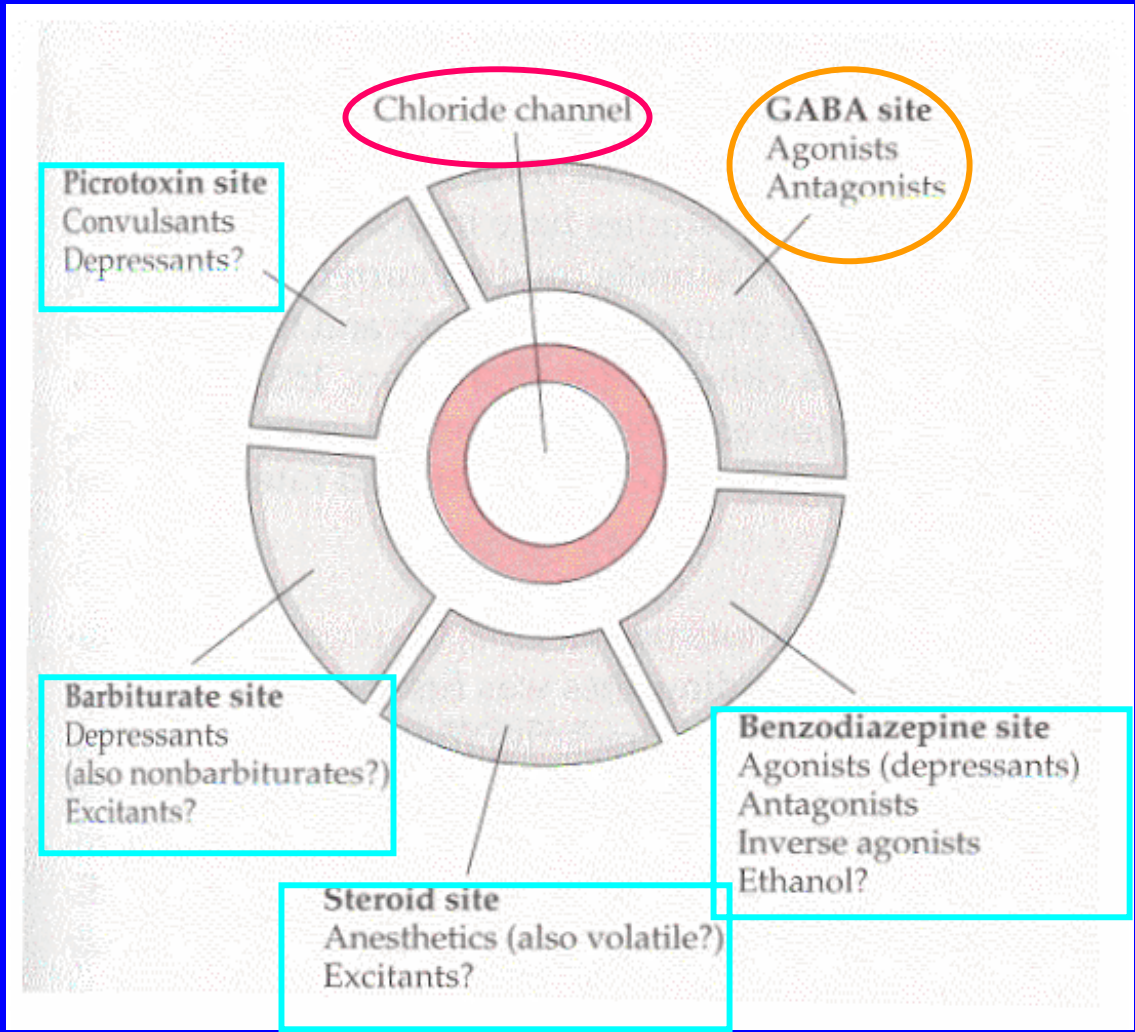
⇨Modulation of the surface expression of GABA receptors
⇨Rapid adaptation of neural excitability

GABA A RECEPTEUR ET PROTEINES ASSOCIEES



Lüscher and Keller, (2004), Pharmacology and Therapeutics, 102: 195-221

RECEPTEUR $GABA_A$

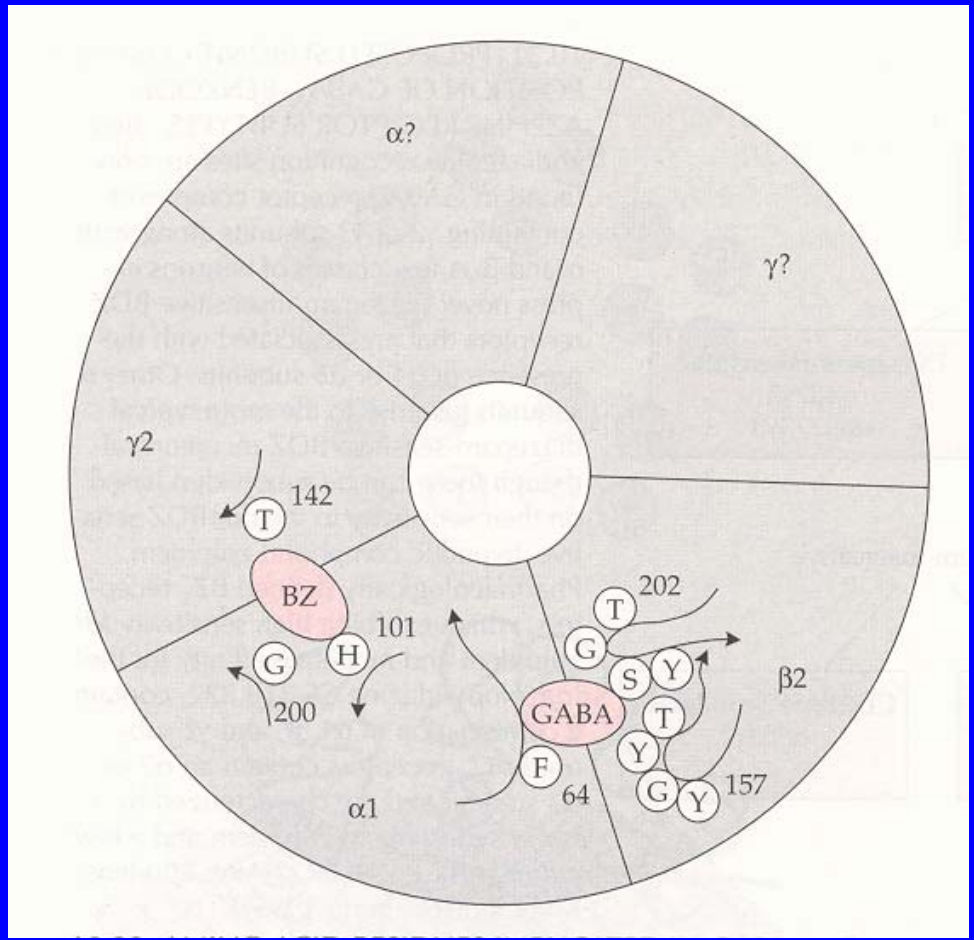


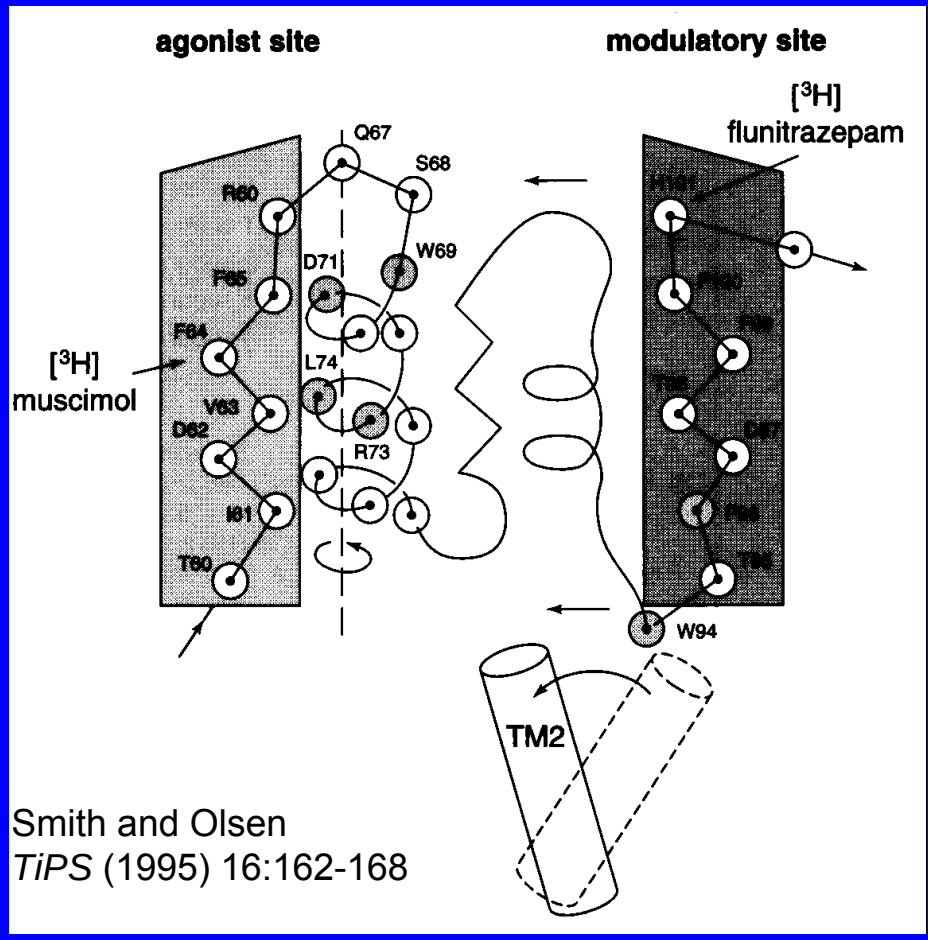
FARM 2146
2004-2005

↗conductance Cl^-
Hyperpolarisation cellule postsynaptique
Diminution du potentiel d'action

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

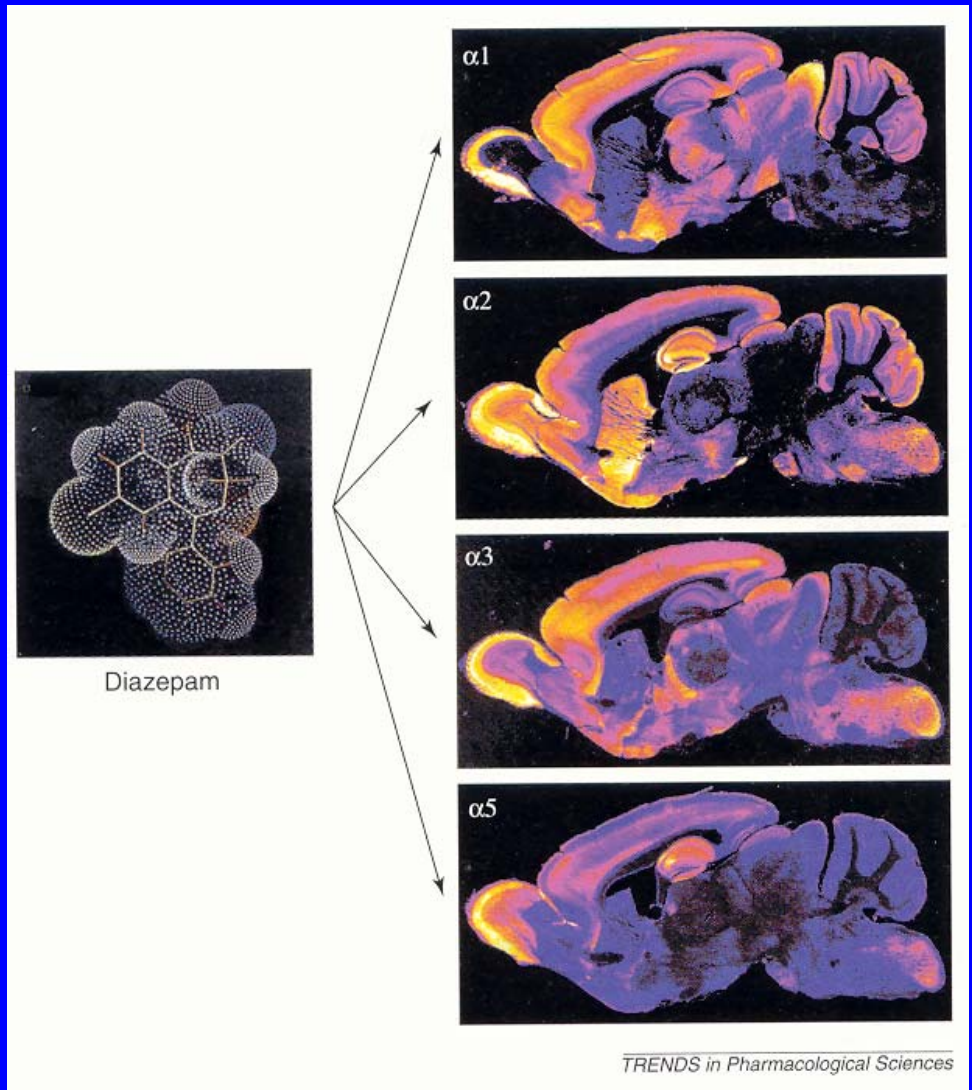
RECEPTEUR $GABA_A$
LIAISON DES BENZODIAZEPINES





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

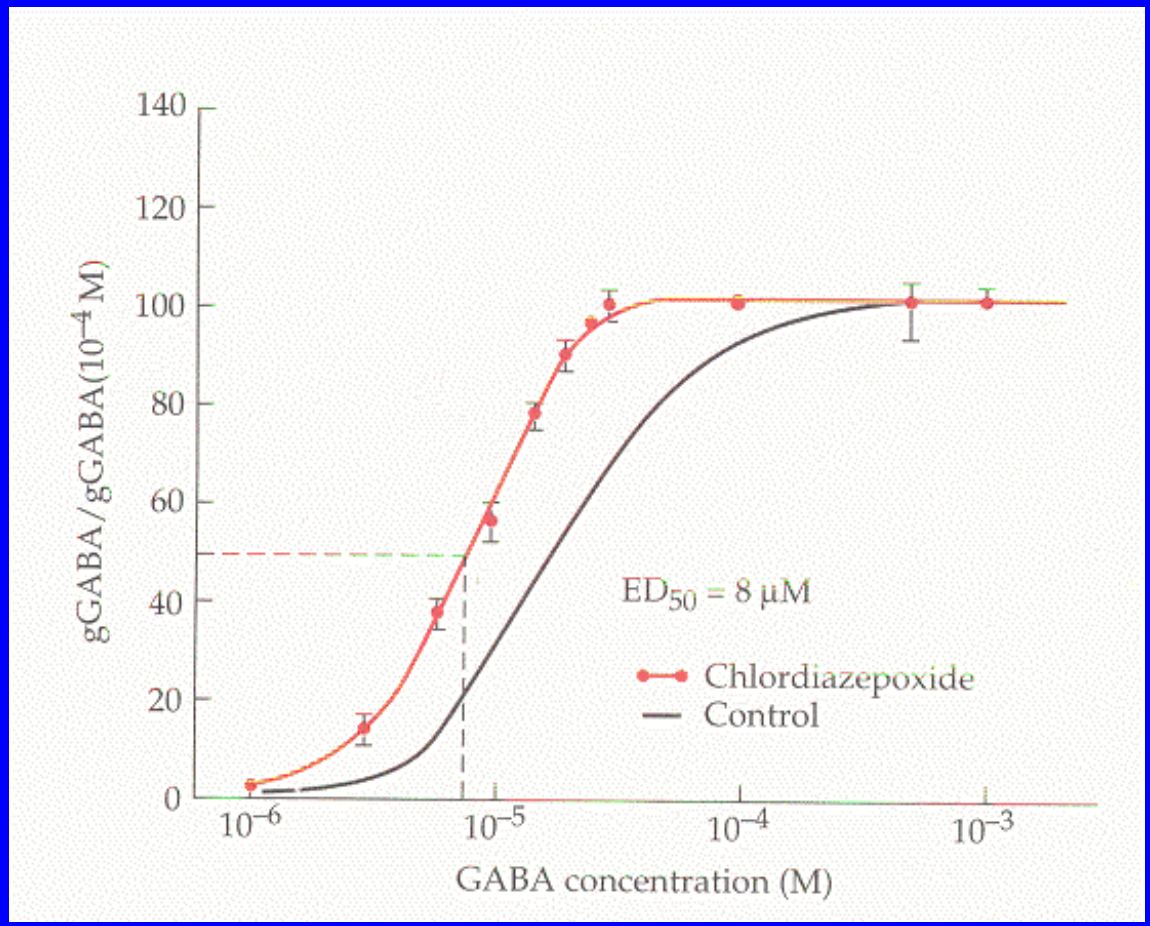
IMMUNOHISTOCHEMICAL DISTRIBUTION OF DIAZEPAM-SENSITIVE $GABA_A$ RECEPTOR SUBTYPES



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

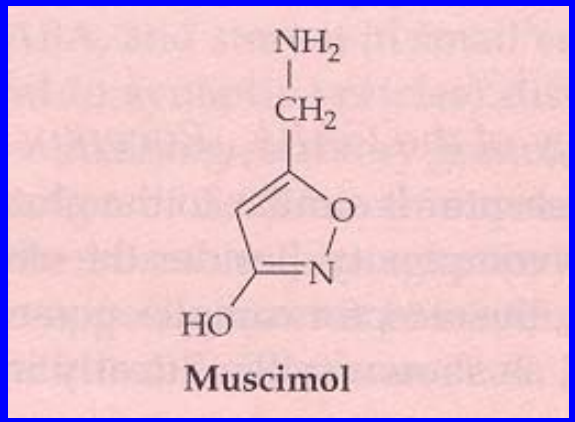
BENZODIAZEPINE PHARMACOLOGY OF $GABA_A$ RECEPTOR SUBTYPES

Pharmacological effect[a]	Receptor involved
Anxiolysis	α2-containing
Sedation	α1-containing
Anticonvulsion	α1-containing and those not containing α1
Anterograde amnesia	α1-containing

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

RECEPTEUR $GABA_A$

Muscinol



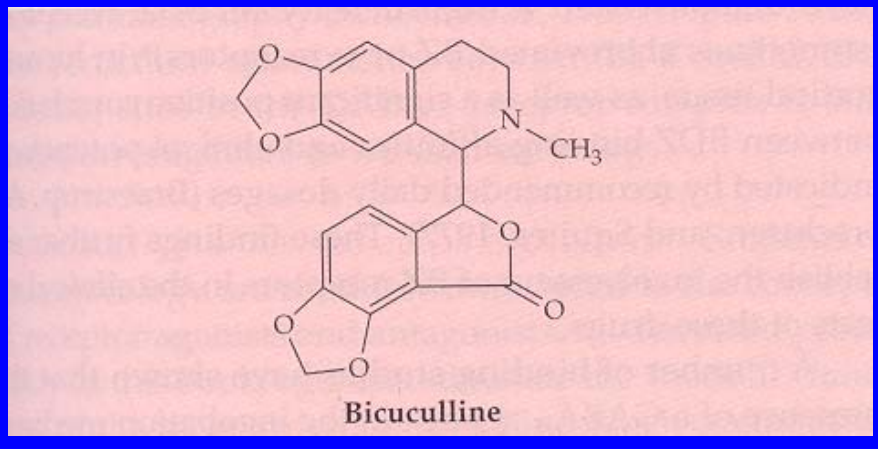
Muscimol

produit de dégradation de l'acide iboténique ~ Amonita muscaria

Agoniste

Bicuculline

alcaloide dérivé de Dicentra cucullaria



Bicuculline

Antagoniste compétitif

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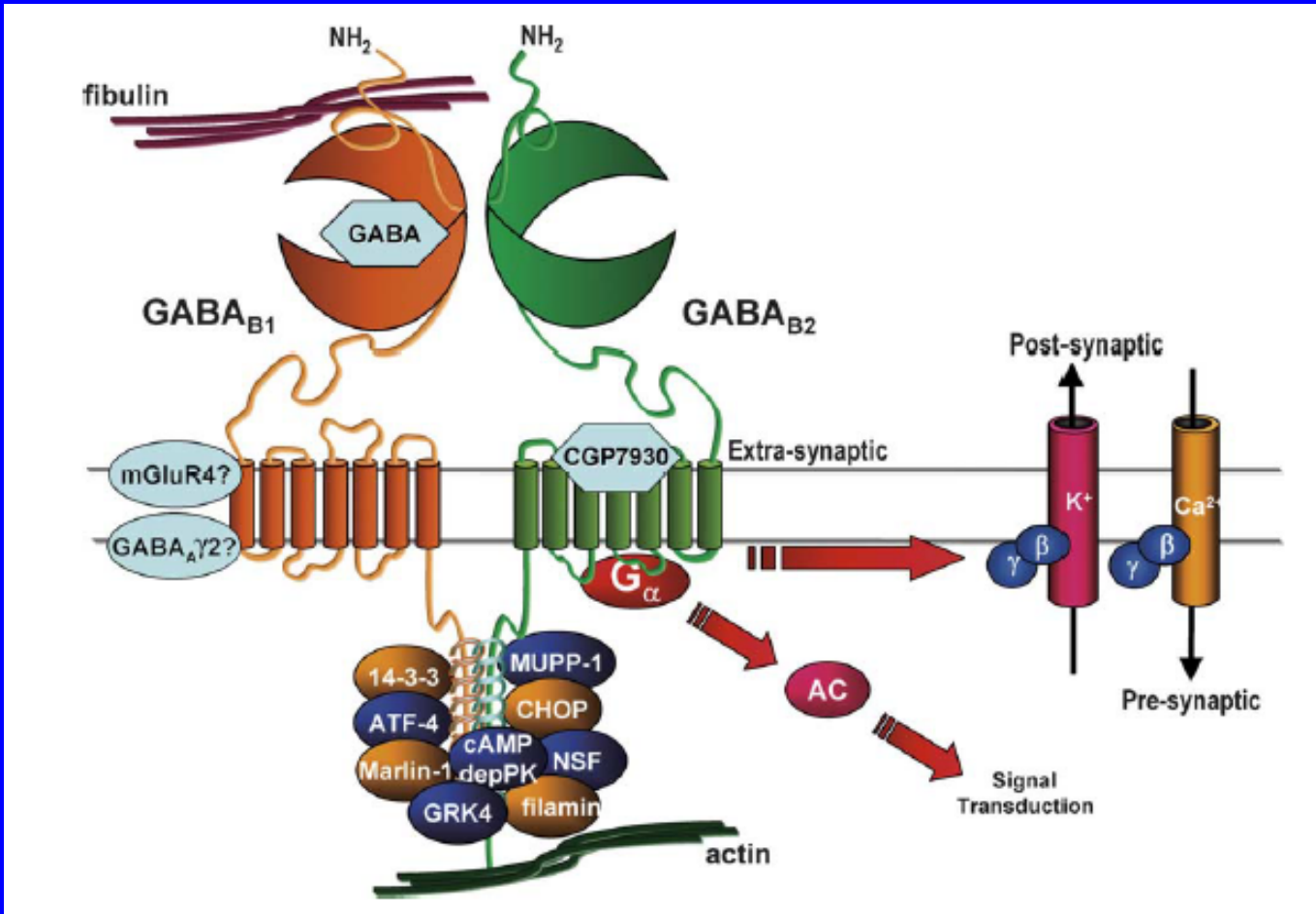
INTERACTION ENTRE RECEPTEURS

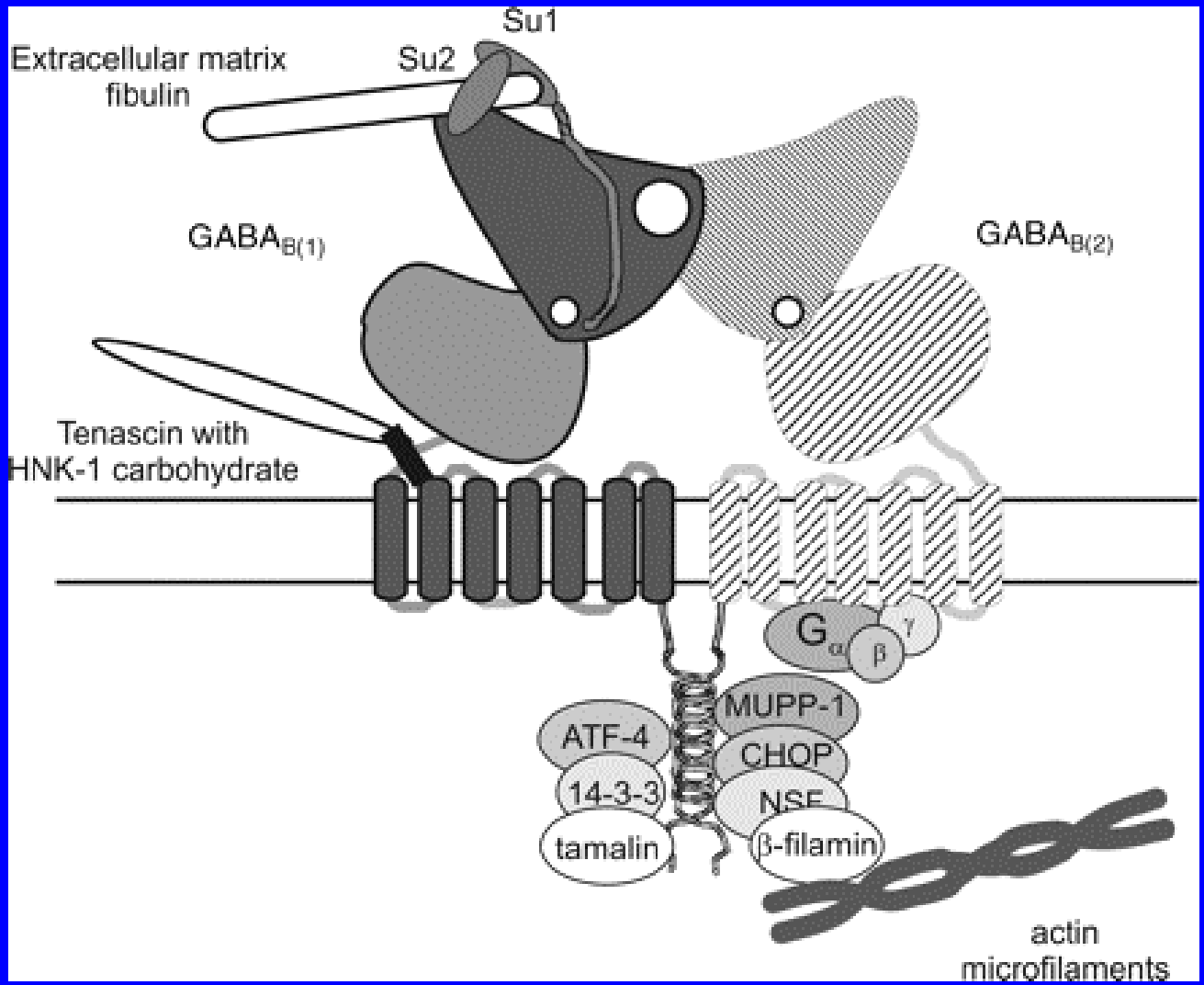
$GABA_B$ HETERODIMERS

Récepteurs métabotropiques



Couve et al (2004) Biochem. Pharmacol. 68: 1527-1536

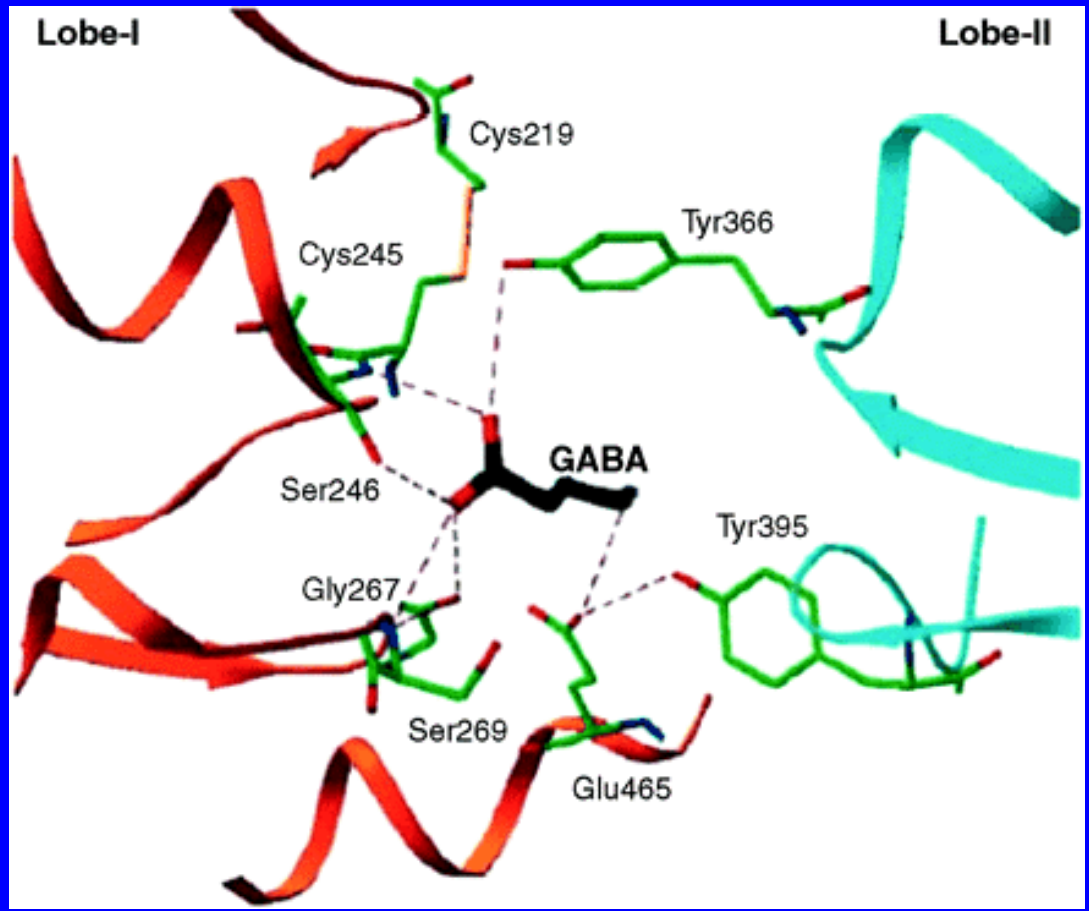
GABA B RECEPTOR INTERACTING PROTEINS



Bettler et al, (2004), Physiol Rev. 84: 835-867

GABA BINDING SITE IN GABA B RECEPTEUR

GABA docked into the ligand-binding site of GABA (B)

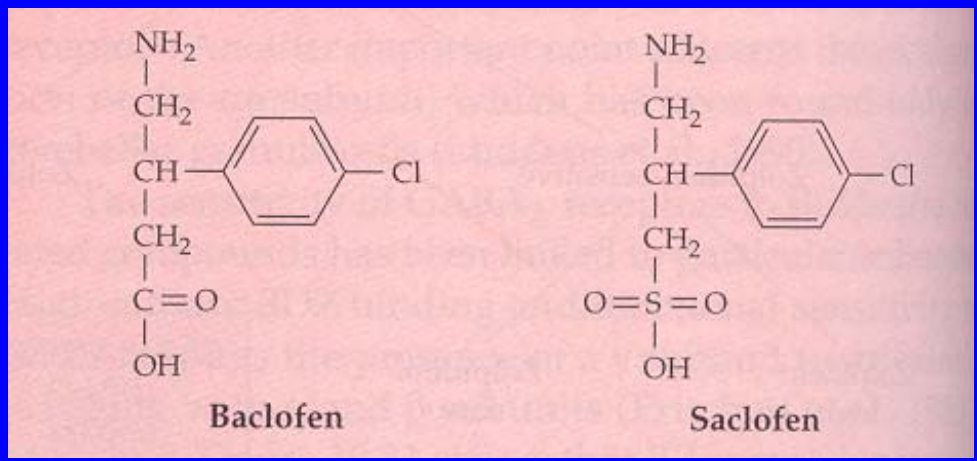


Bettler et al, (2004), Physiol Rev. 84: 835-867

RECEPTEURS $GABA_B$

Mécanismes effecteurs

1. Inhibition de l'adenylate cyclase
2. Stimulation de la phospholipase A_2
3. Augmentation de la conductance K^+
4. Inhibition conductance voltage dependant Ca^{2+}



Agonist

Antagonist

RECEPTEURS SEROTONINERGIQUES ~ Gs

GABA B présynaptique	GABA B-postsynaptique
Gi (α)	Gi
Inactivation Adenylyl cyclase	Inactivation Adenyly cyclase
↘ cAMP	↘ cAMP
Inactivation PKA	Inactivation PKA
↘ phosphorylation des canaux calciques	↗ conductance potassique
↘ influx calcique	hyperpolarisation
↘ exocytose	↘ potentiel d'action

AGONISTES DES RECEPTEURS GABA B: DE l'ANESTHESIE AUX DROGUES

GHB ou γ-hydroxy-butyrate

- **Largement utilisé en anesthésiologie mais retiré du marché en 1990**

- **Vente illicite sous de nombreux noms: *Ecstasy liquide, Renutrient, Liquide X, Scoop, Soap, Salty water…***

- **Drogue du viol en raison de l'état de confusion, d'inconscience et d'amnésie qu'il induit.**

GABA = ACIDE γ-AMINO BUTYRIQUE

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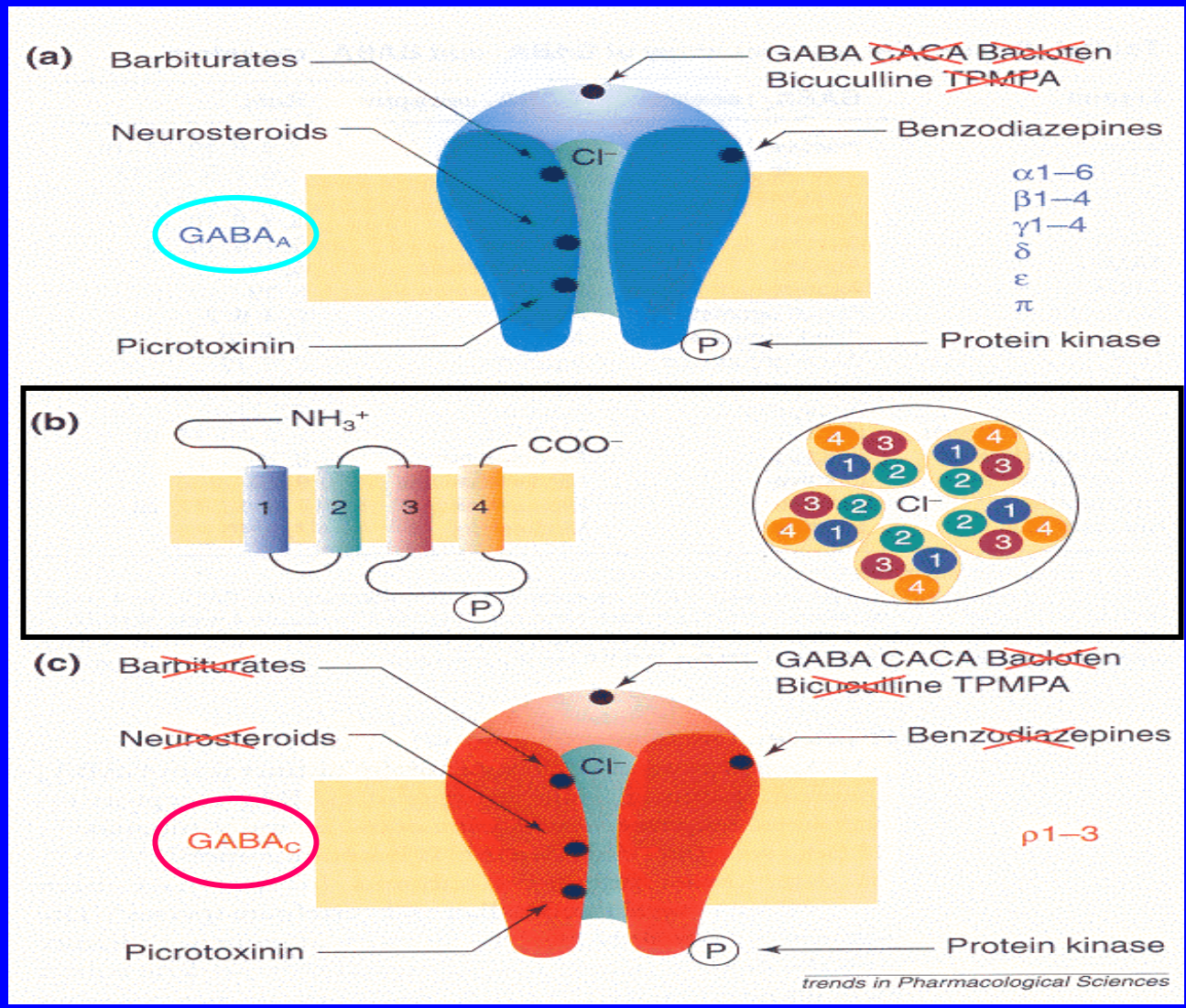
- $GABA_A$
- $GABA_B$
- $GABA_C$

INTERACTION ENTRE RECEPTEURS

RECEPTEUR GABAc

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

COMPARISON BETWEEN $GABA_A$ and $GABA_C$ RECEPTORS



Bormann *TiPS* (2000) 21: 16-19

FUNCTIONAL COMPARISON OF $GABA_A$ AND $GABA_C$ RECEPTORS

Property	$GABA_C$ receptor	$GABA_A$ receptor
GABA EC_{50}	1–4 μM	5–100 μM
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

Bormann *TiPS* (2000) 21: 16-19

COMPARISON OF $GABA_A$ AND $GABA_C$ RECEPTORS

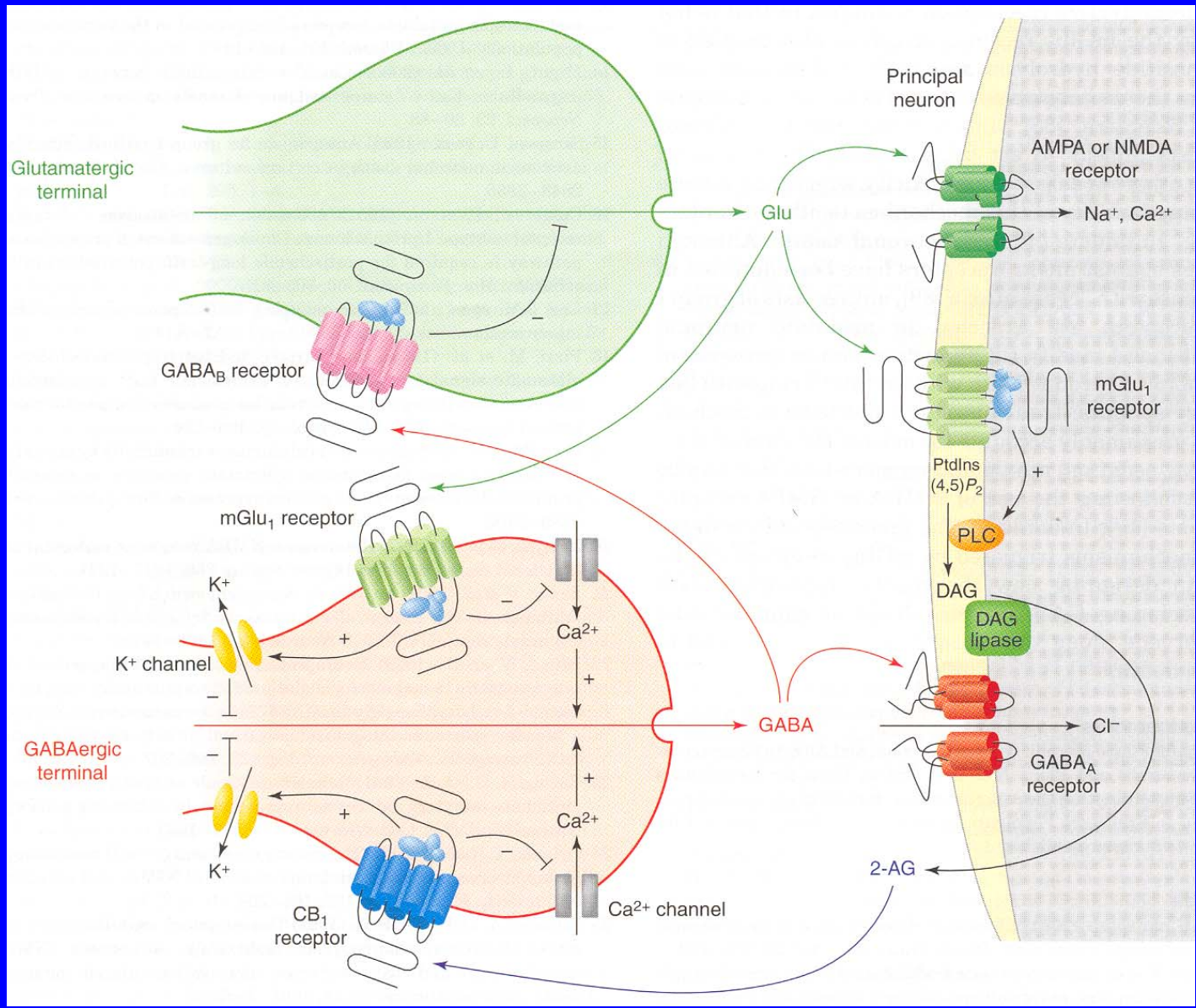
Ligand	$GABA_C$ receptor	$GABA_A$ receptor
Bicuculline	Inactive	Antagonist
Baclofen	Inactive	Inactive
Picrotoxinin	Antagonist[a]	Antagonist
TACA	Agonist	Agonist
CACA	Agonist	Inactive
TAMP	Agonist	Weak agonist
CAMP	Agonist	Inactive
Muscimol	Partial agonist	Agonist
Isoguvacine	Weak antagonist	Agonist
THIP	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

GABA = ACIDE γ-AMINO BUTYRIQUE

STRUCTURE
VOIES GABAERGIQUES
INTERET PHYSIOPATHOLOGIQUE ET PHARMACOLOGIQUE
SYNAPSE GABAERGIQUES ET CIBLES PHARMACOLOGIQUES
SYNTHESE
DEGRADATION
CAPTURE
INTERACTION LIGAND/RECEPTEUR GABAERGIQUE

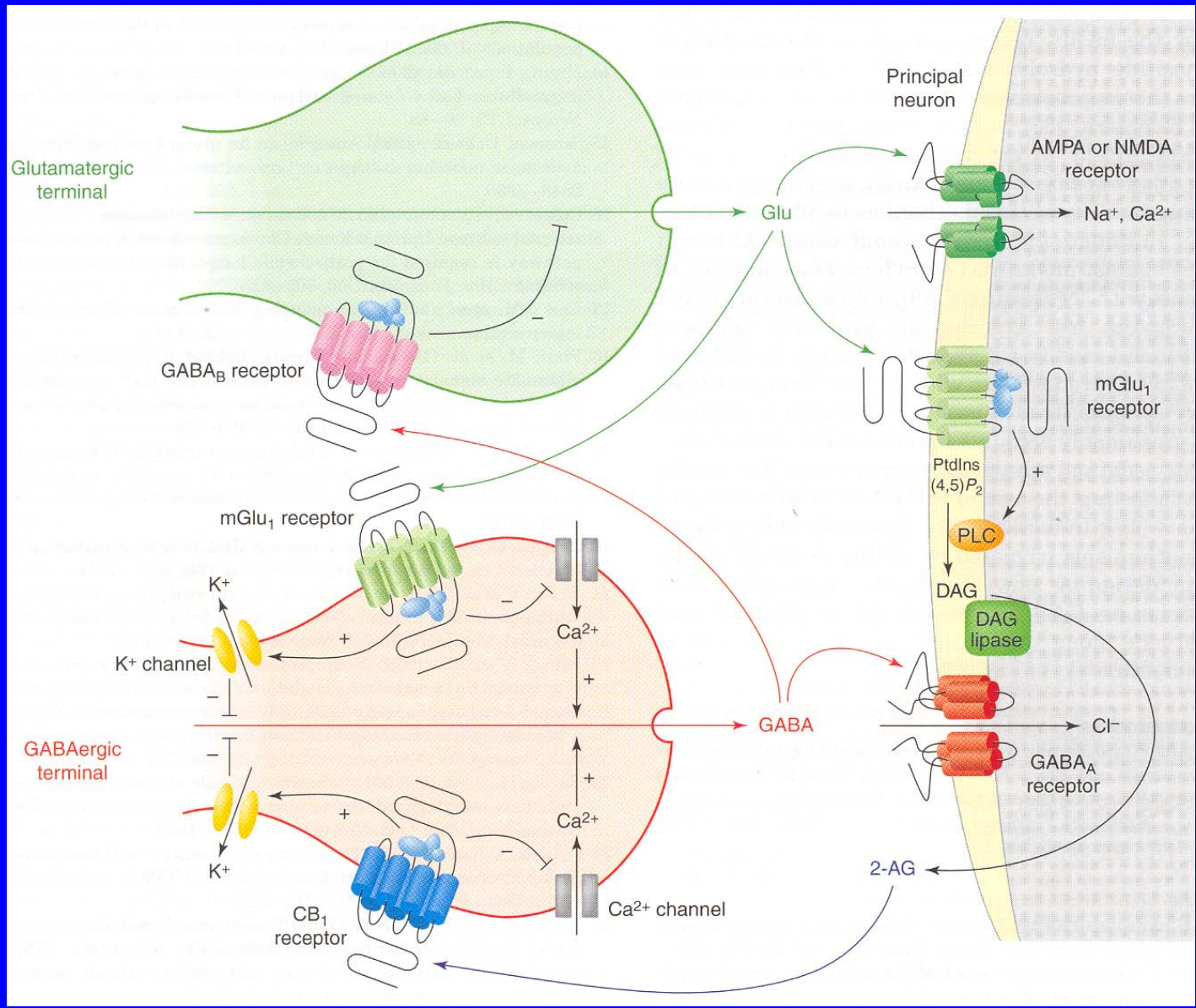
INTERACTION ENTRE RECEPTEURS

GLUTAMATE –GABA INTERACTIONS



Pelligrini-Giampietro et al, *TiPS* (2003) 24 461-470

GLUTAMATE –GABA INTERACTIONS



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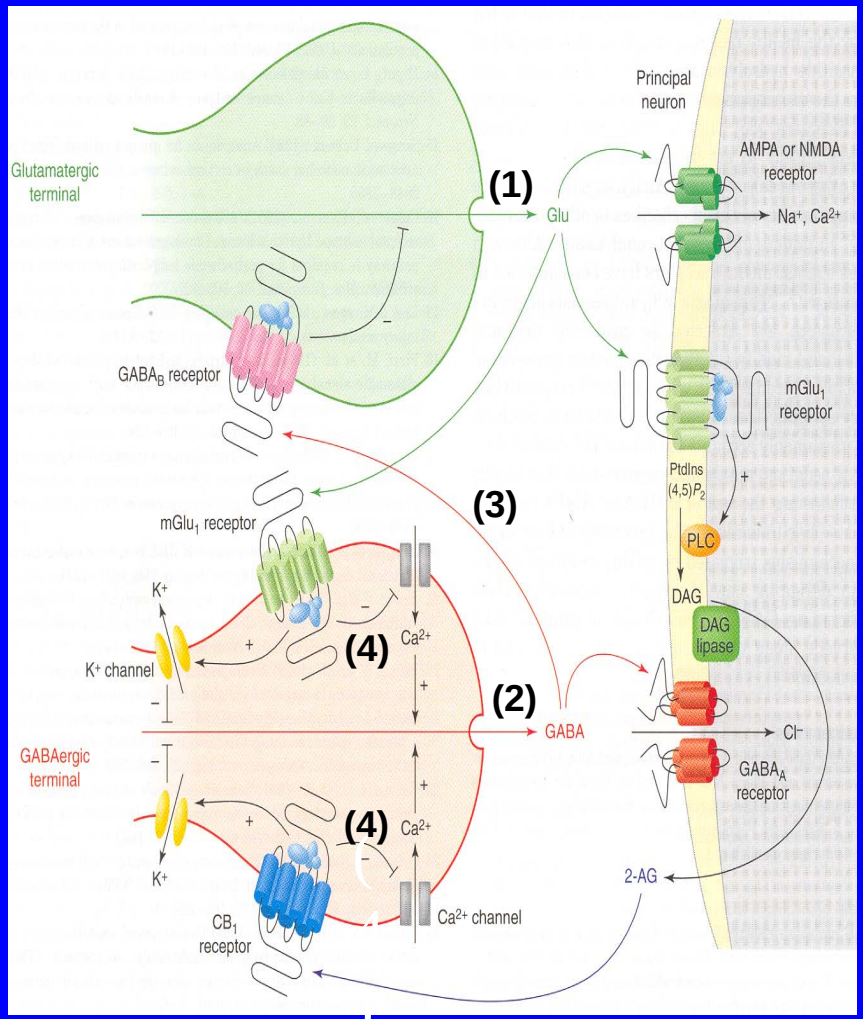
POSSIBLE EXPLANATION FOR THE NEUROPROTECTIVE EFFECTS OF METABOTROPIC GLUTAMATE 1 RECEPTOR ANTAGONISTS



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(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 postsynaptique $GABA_A$ 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 CB1 receptors, via suppression of Ca^{2+} currents through N-type channels or activation of K^+ channels

<u>Antagonists of mGlu1 receptors can lead to increased release of GABA and therefore to neuroprotective hyperpolarization</u>

- **Direct blockade of presynaptic mGLU1 receptor on GABAergic terminals**
- **Indirect inhibition of CB1 receptors located on GABAergic terminals promoted by mGlu1 receptors located postsynapically**