

GLUTAMATE

STRUCTURE

VOIES GLUTAMINERGIQUES

INTERET PHYSIOPATHOLOGIQUE ET PHARMACOLOGIQUE

SYNAPSE GLUTAMINERGIQUE

SYNTHESE

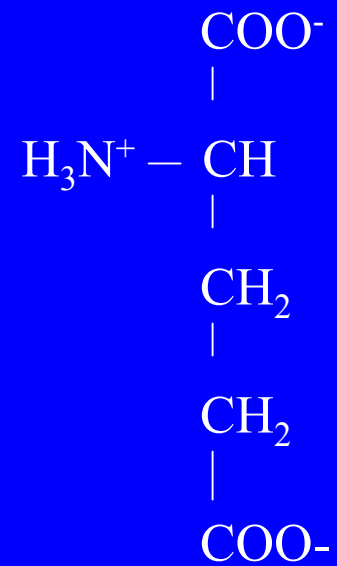
CAPTURE

DEGRADATION

INTERACTION LIGAND/RECEPTEUR GLUTAMINERGIQUE

INTERACTION ENTRE RECEPTEURS

GLUTAMATE



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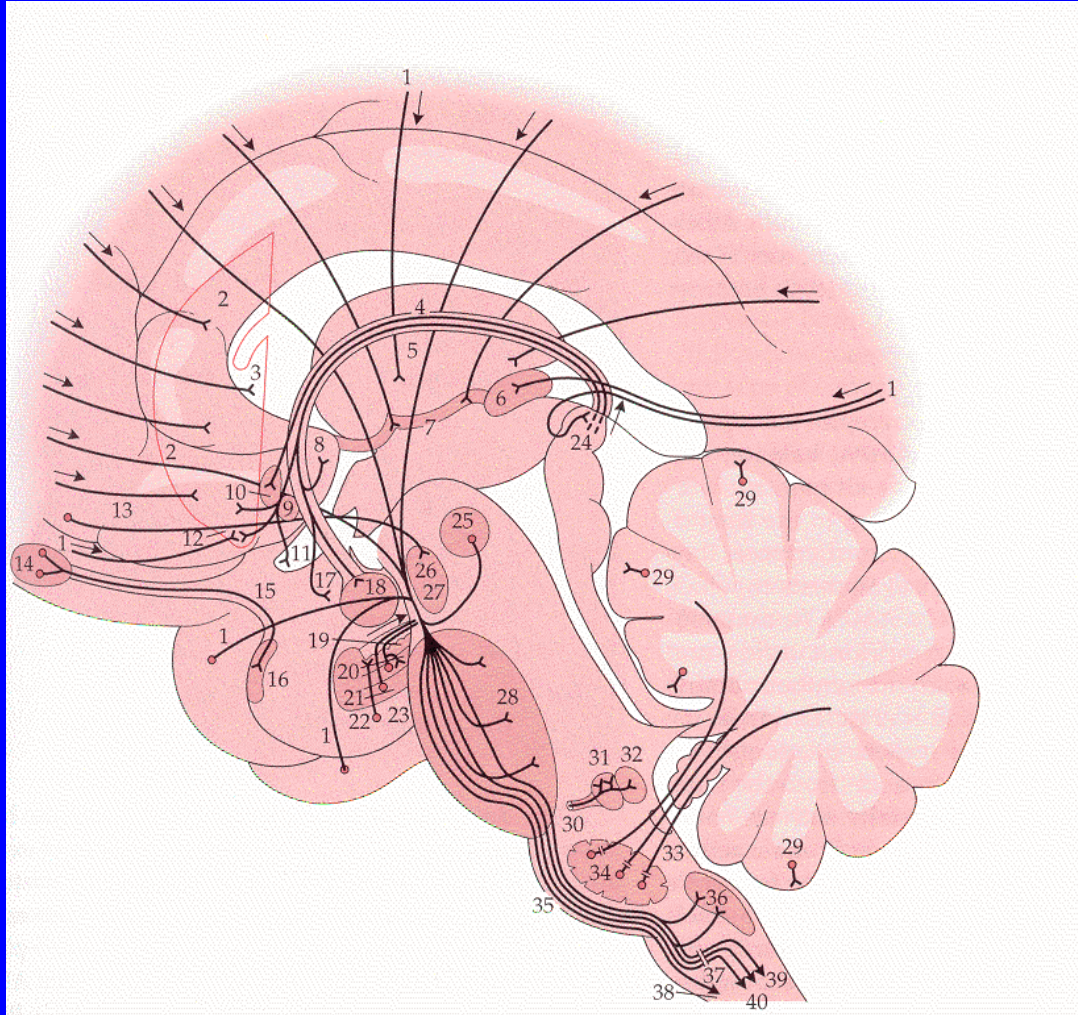
SYNTHESE

DEGRADATION

INTERACTION LIGAND/RECEPTEUR GLUTAMINERGIQUE

INTERACTION ENTRE RECEPTEURS

GLUTAMINERGIC INNERVATIONS



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

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.

Le glutamate est le principal neurotransmetteur

- des cellules thalamocorticales
- des cellules pyramidales
- des cellules corticostriées
- de l'hippocampe

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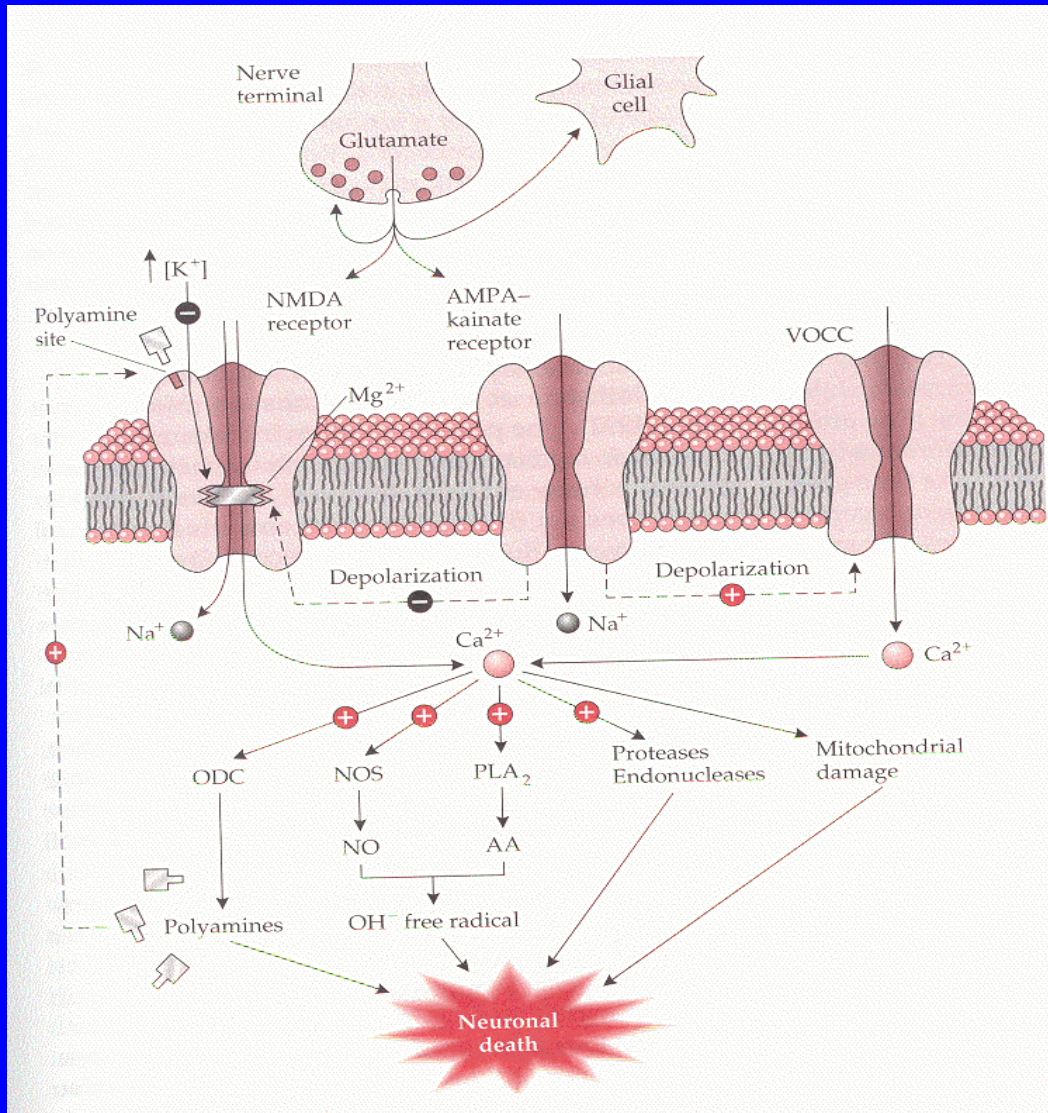
SYNTHESE

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INTERACTION ENTRE RECEPTEURS

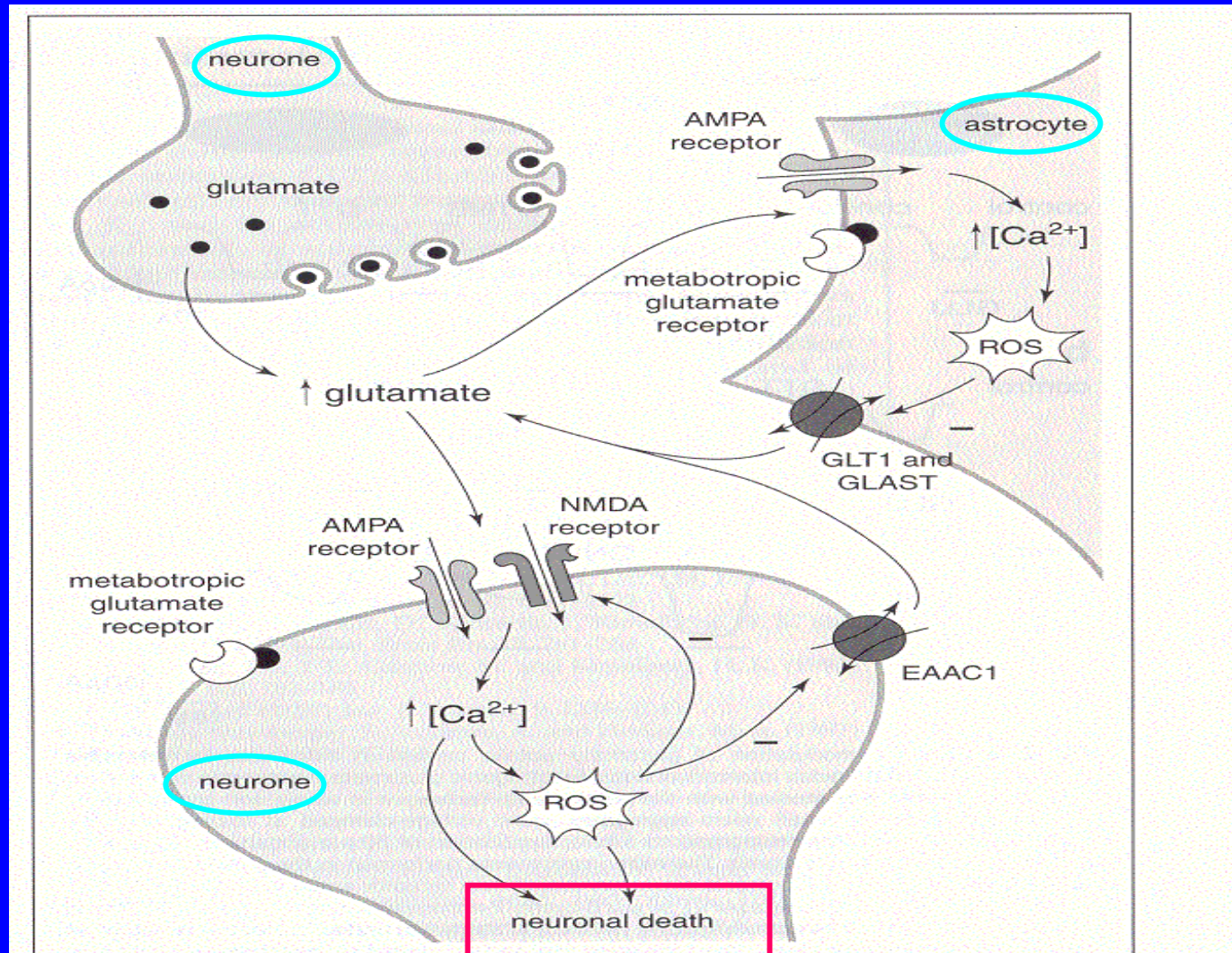
GLUTAMATE AND NEURONAL DEATH



Ischemia ~ increase release and decrease reuptake of glutamate

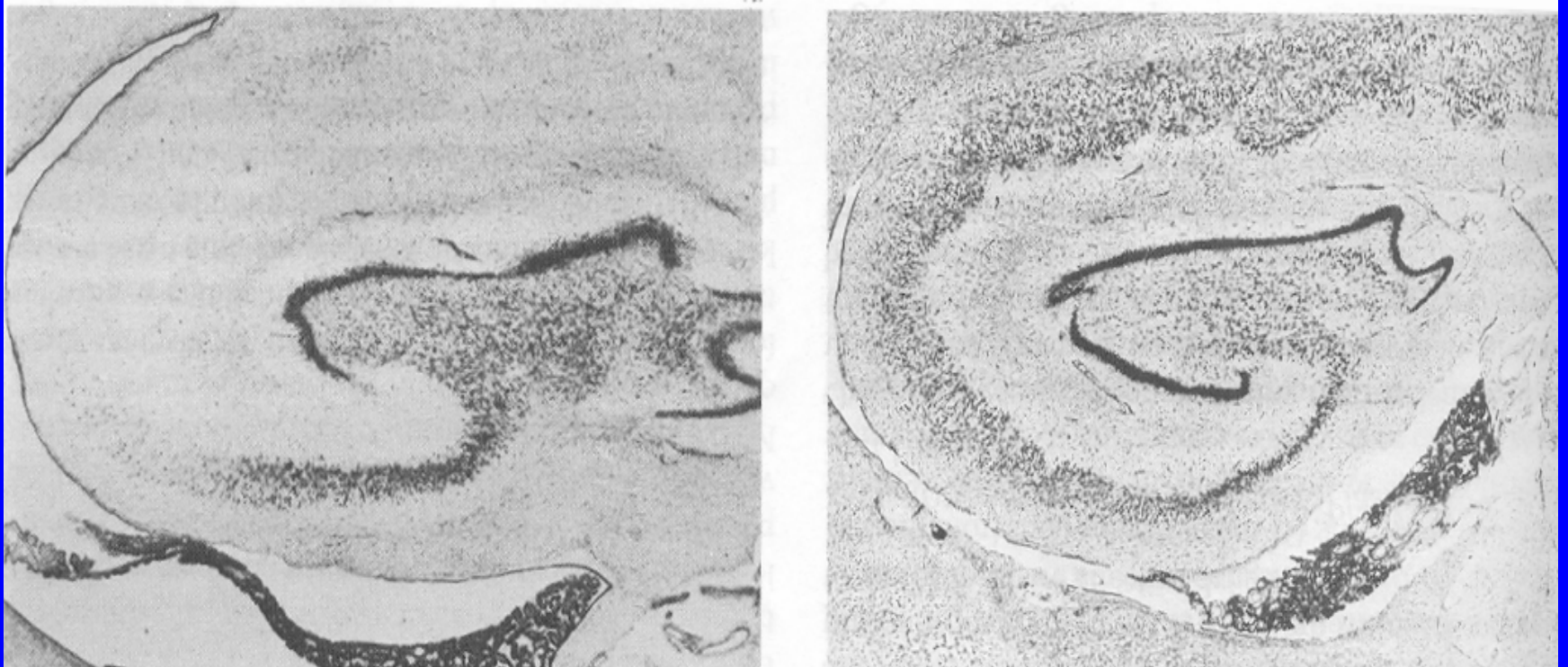
Principles of Neuropharmacology
Feldman, Meyer, Quenzer Ed.
Sinauer Associates Inc. 1997 - pp 415

GLUTAMATE AND NEURONAL DEATH



From Trotti et al *TIPS* (1998) 19: 328-334

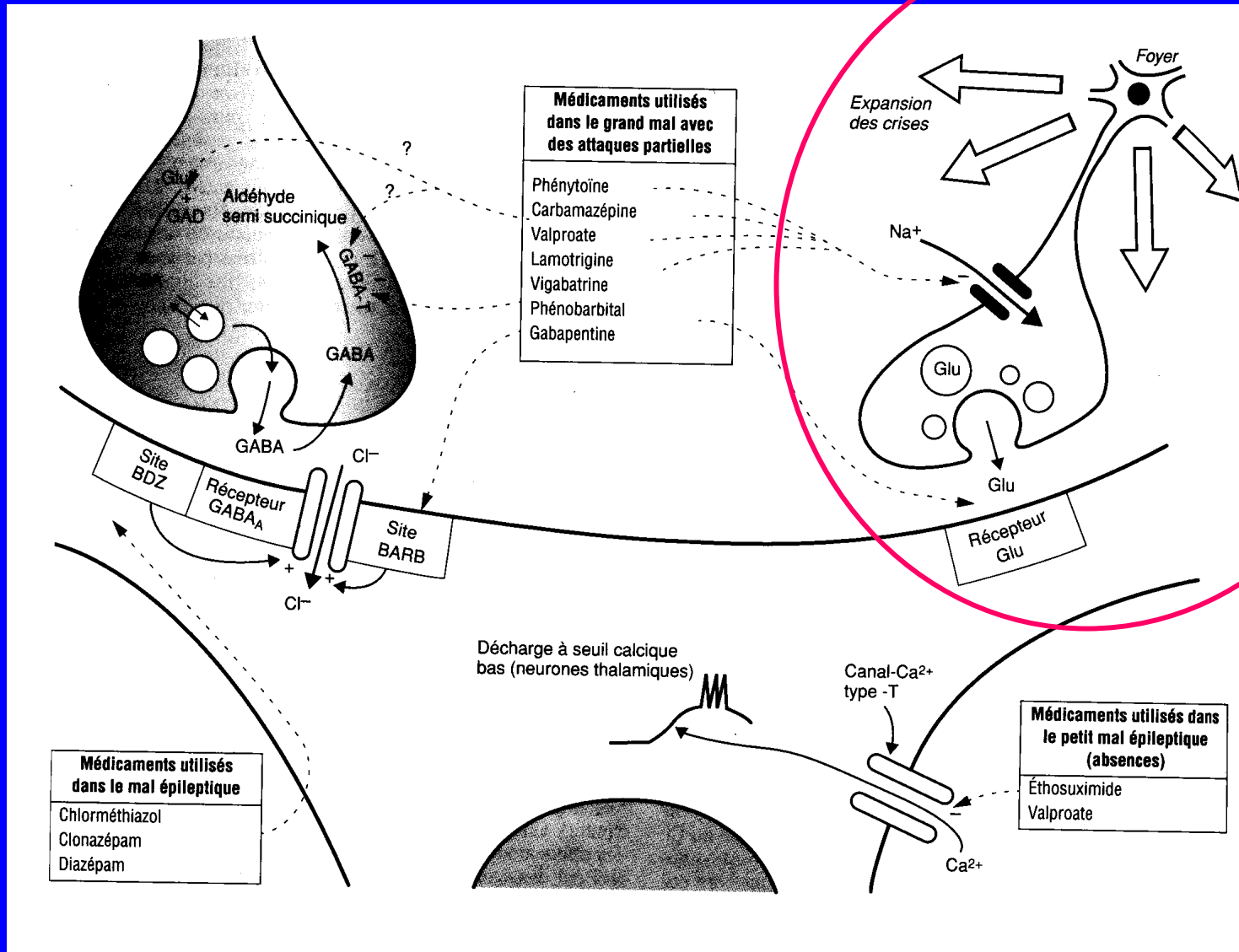
EPILEPSIE ET PERTE NEURONALE



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

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GLUTAMATE AND EPILEPSIE



RECEPTEURS NMDA AND AMPA

Sous-type	Agonistes	Antagonistes	Activité pharmacologique
AMPA	AMPA Acide kainique Acide quinqualique	CNQX NBQX	Dépolarisation rapide des synapses glutaminergiques
NMDA	NMDA	Phenycyclidine ifenprodil	<ul style="list-style-type: none"> - Induction ~ plasticité synaptique - Développement sensibilité aux crises épileptiques et à leur survenue → Antagonistes NMDA = anticonvulsivants - Si activation excessive des récepteurs NMDA ⇒ mort cellulaire (~ ischémie, hypoglycémie cérébrale) → Antagonistes NMDA = neuroprotecteurs

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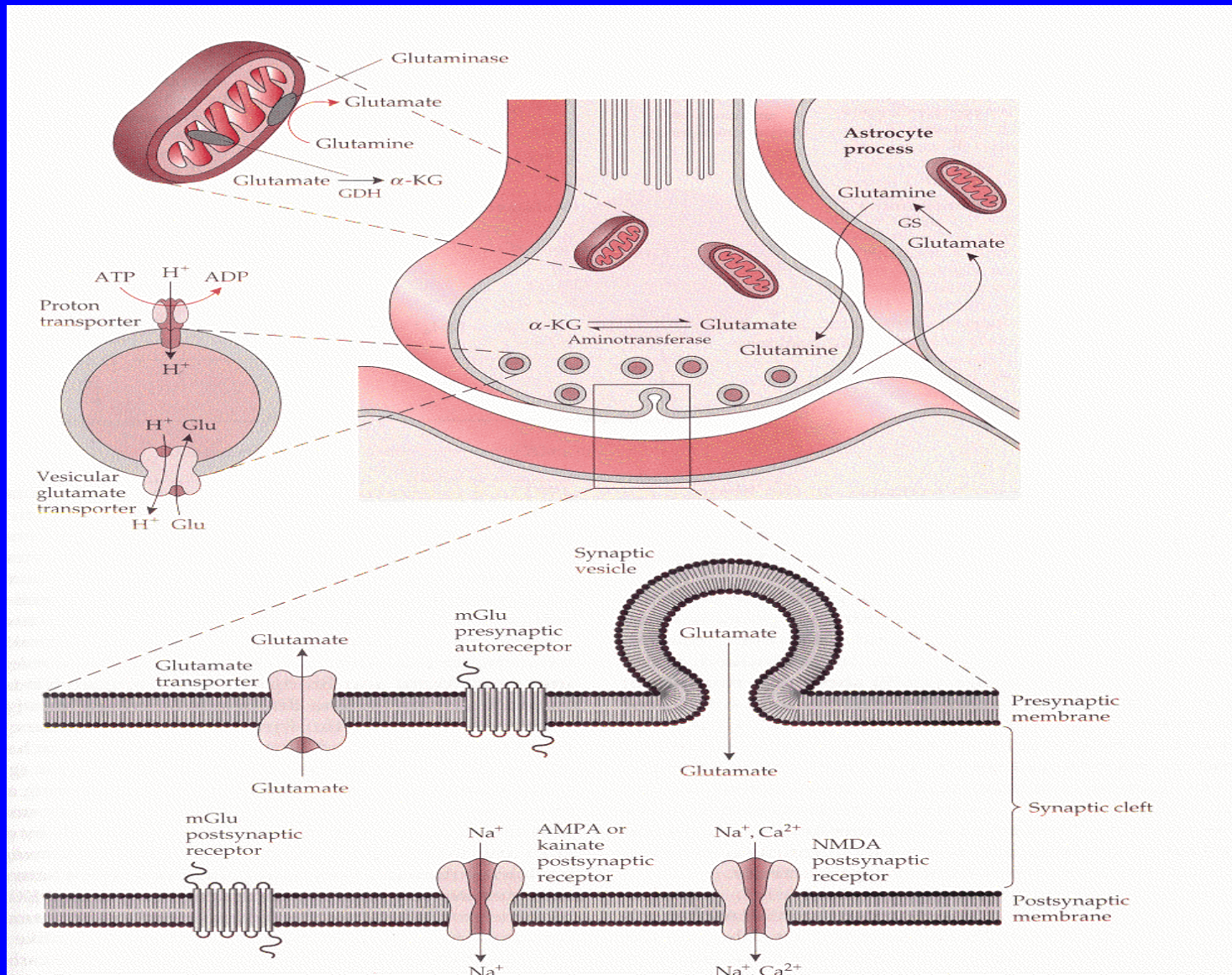
SYNTHESE

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INTERACTION LIGAND/RECEPTEUR GLUTAMINERGIQUE

INTERACTION ENTRE RECEPTEURS

GLUTAMATE - SYNAPSE



GLUTAMATE

STRUCTURE

VOIES DOPAMINERGIQUES

INTERET PHYSIOPATHOLOGIQUE ET PHARMACOLOGIQUE

SYNAPSE DOPAMINERGIQUE

SYNTHESE

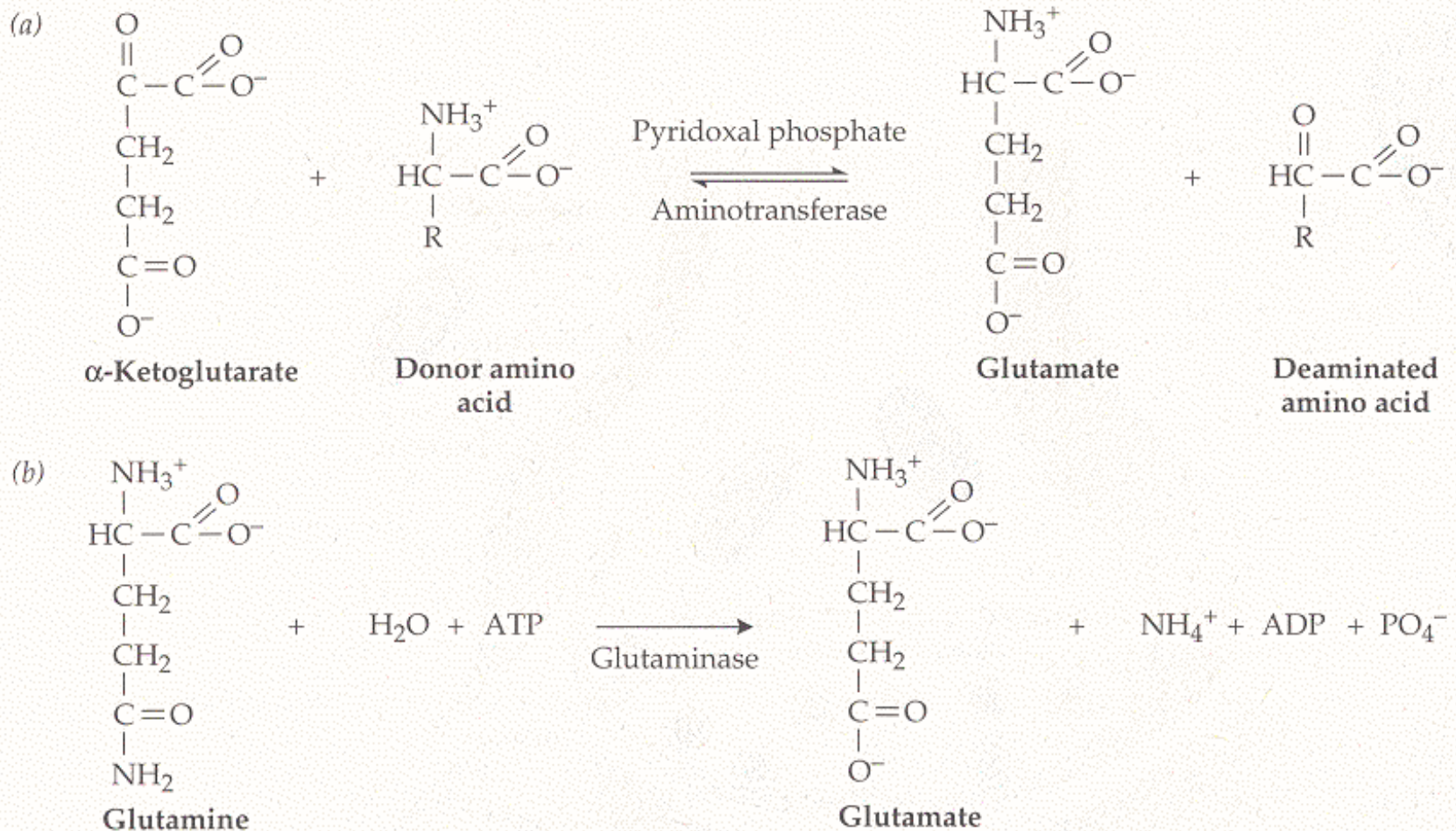
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INTERACTION LIGAND/RECEPTEUR DOPAMINERGIQUE

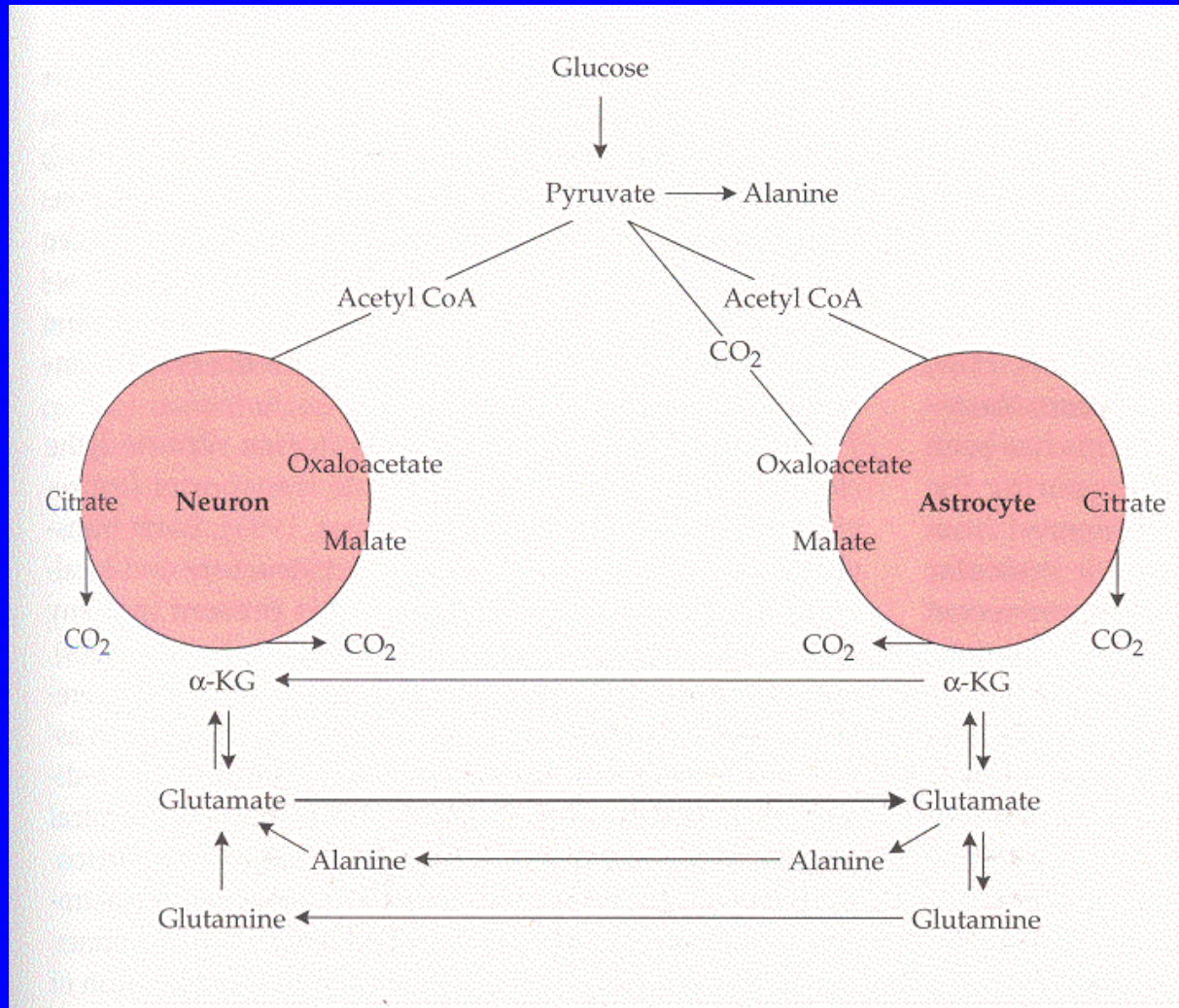
INTERACTION ENTRE RECEPTEURS

GLUTAMATE - SYNTHESIS

2 MAJOR PATHWAYS



GLUTAMATE - SYNTHESIS AND STORAGE IN NEURONS AND ASTROCYTES



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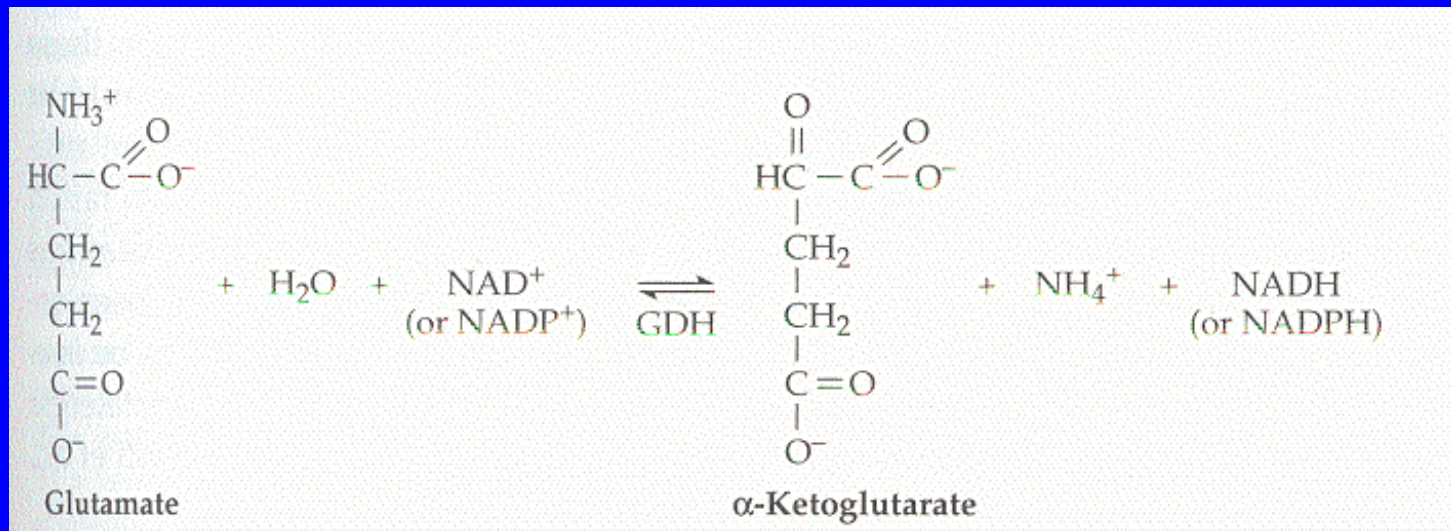
SYNTHESE

DEGRADATION

INTERACTION LIGAND/RECEPTEUR GLUTAMINERGIQUE

INTERACTION ENTRE RECEPTEURS

GLUTAMATE - DEGRADATION



Oxidative deamination by GDH: glutamate deshydrogenase

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INTERACTION LIGAND/RECEPTEUR GLUTAMINERGIQUE

Récepteurs de type canal (NMDA, AMPA, kainate)

Récepteurs métabotropiques mGlu

INTERACTION ENTRE RECEPTEURS

RECEPTEURS AU GLUTAMATE

Table 10.1 Structural and Functional Properties of Excitatory Amino Acid Receptors

Receptor subtype	Properties			
	Superfamily	Genes	Cation selectivity	Second messengers
AMPA	Ligand-gated channel	<i>GluR1–GluR4</i>	Na ⁺ , K ⁺	
Kainate	Ligand-gated channel	<i>GluR5–GluR7, KA1, KA2</i>	Na ⁺ , K ⁺	
NMDA	Ligand-gated channel	<i>NR1, NR2A–NR2D</i>	Na ⁺ , K ⁺ , Ca ²⁺	
Metabotropic	G protein-coupled receptor	<i>mGluR1–mGluR7</i>		IP ₃ , DAG, cAMP

Analogues synthétiques

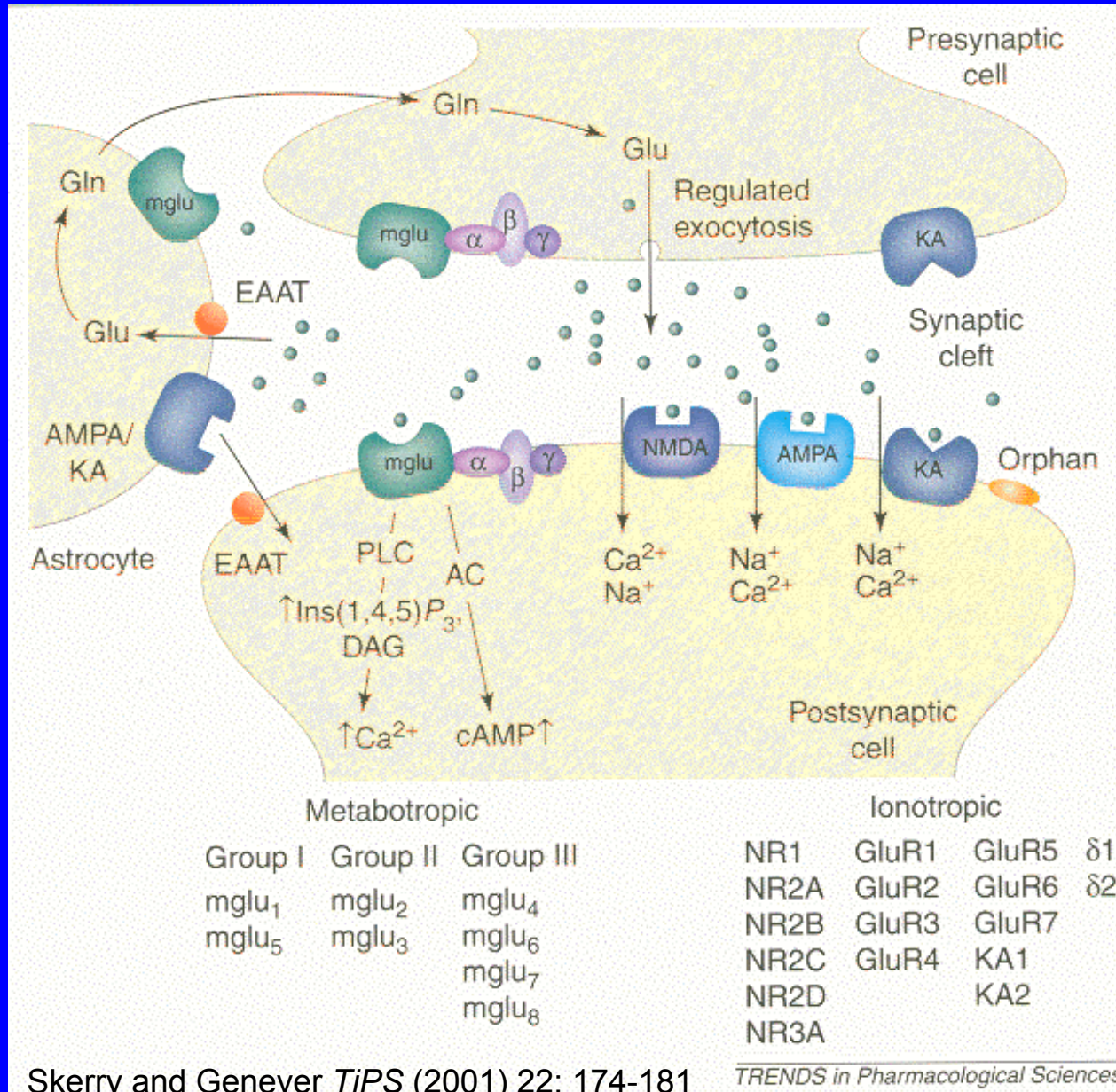
NMDA: N-méthyl-D-aspartate

AMPA: acide α -amino-3-hydroxy-5-methyl-4-isoxazole propionique

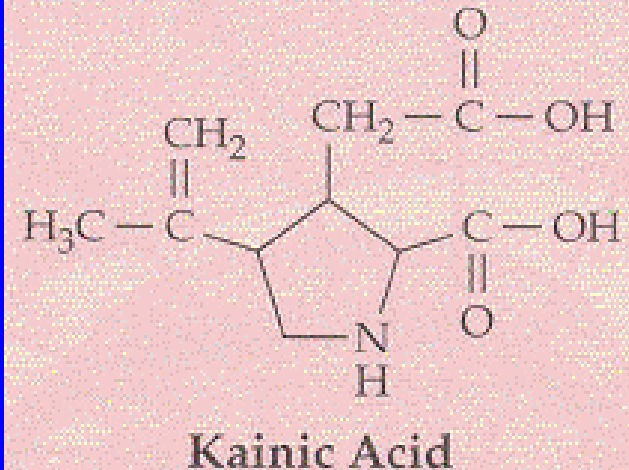
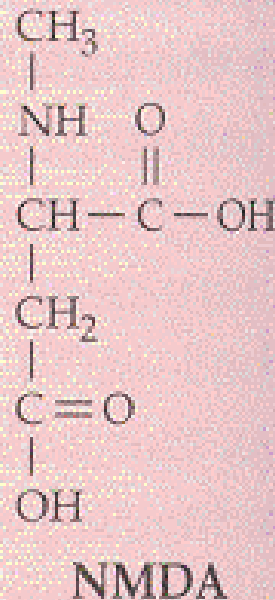
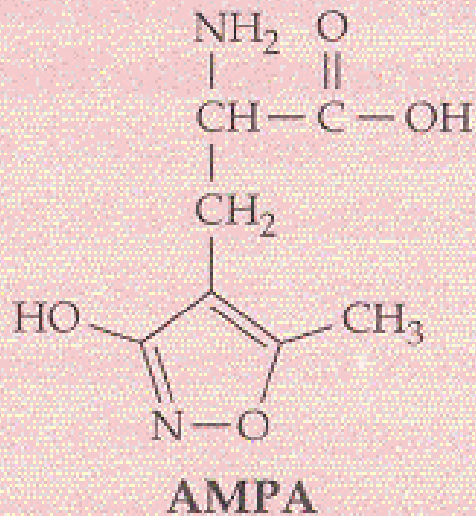
Natural compound isolated from seaweed *Digena simplex*

Kainic acid

GLUTAMATE ET TRANSDUCTION DU SIGNAL



STRUCTURE OF AMPA, NMDA, KAINATE



NMDA: N-méthyl-D-aspartate

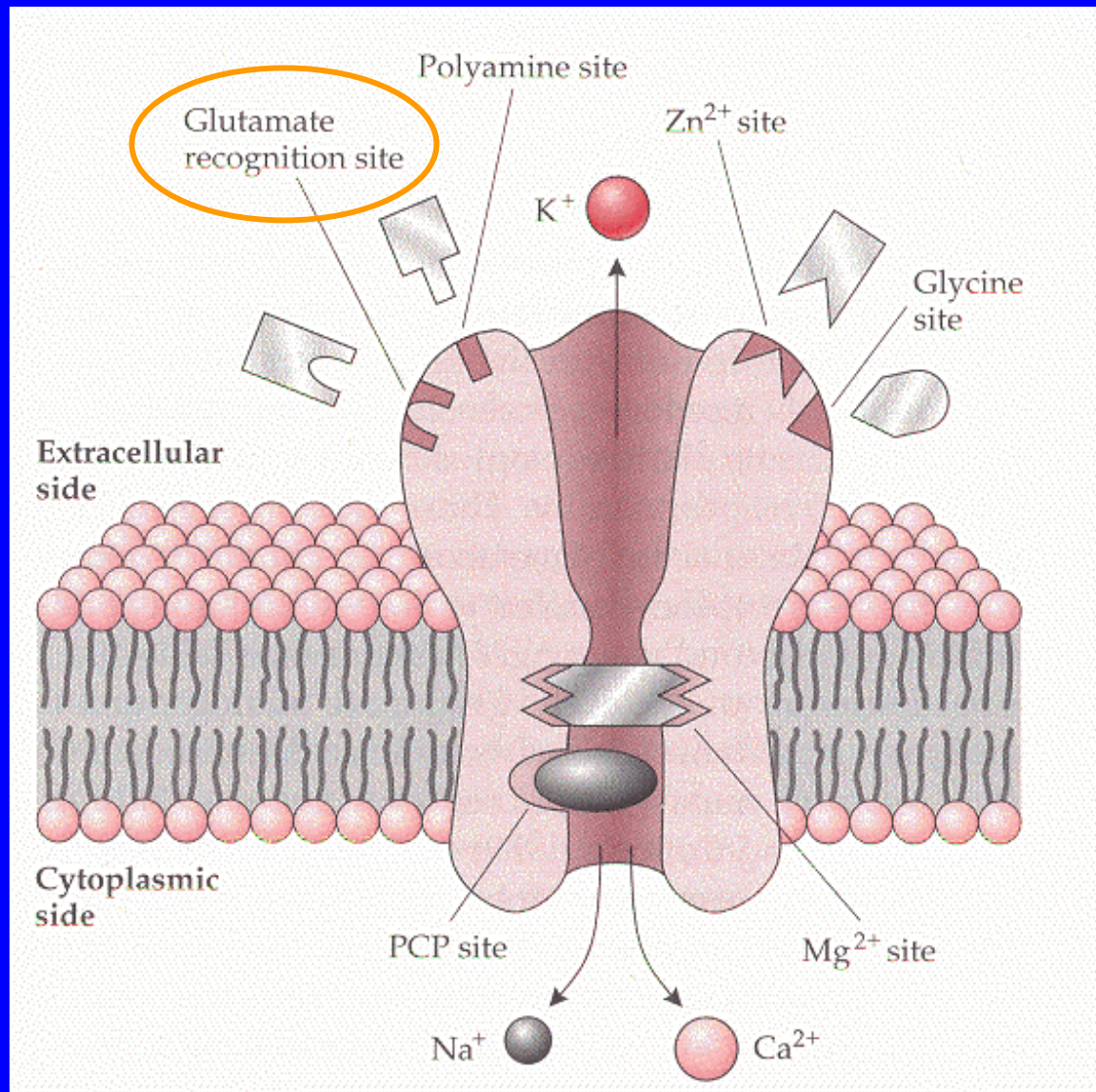
AMPA: acide α -amino-3-hydroxy-5-méthyl-4-isoxazole propionique

RECEPTEURS AU GLUTAMATE

AGONISTES ET ANTAGONISTES

Receptor	Agonists	Antagonists
AMPA/Kainate	AMPA, kainic acid, quisqualic acid, domoic acid	CNQX, NBQX
NMDA	NMDA	CPP, D-AP5 (D-APV), D-AP7
Metabotropic	Quisqualic acid, <i>trans</i> -ACPD, L-AP4	α -Methyl-4-carboxyphenyl glycine

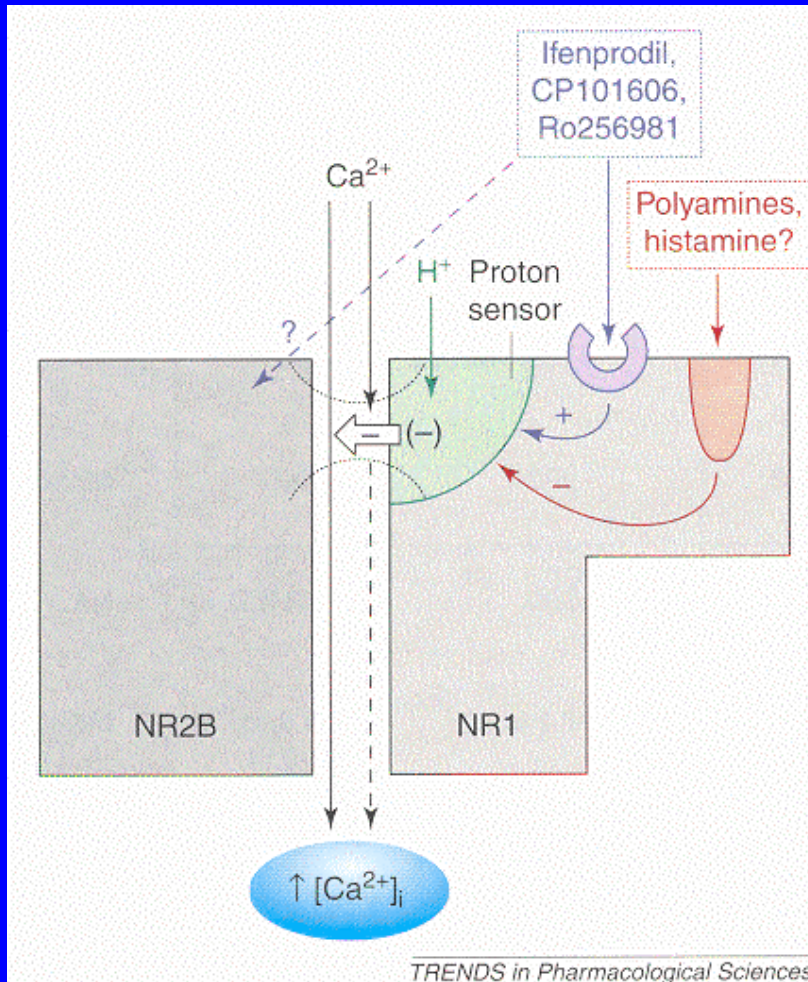
RECEPTEURS NMDA AU GLUTAMATE



Phencyclidine = PCP

RECEPTEURS NMDA

Interactions between endogenous modulators and ifenprodil-like selective antagonists of NR2B-containing NMDA receptors



A protonated H⁺-sensor stabilizes the NR1-NR2B heterodimer in low-conductance state

Polyamines (spermine, spermidine) shield the H⁺-sensor from protons thus attenuating the inhibition by proton and potentialising the influx of Ca²⁺

Ifenprodil enhances the sensitivity to protons

From Chizh et al. *TIPS* 22: 636-642 (2001)

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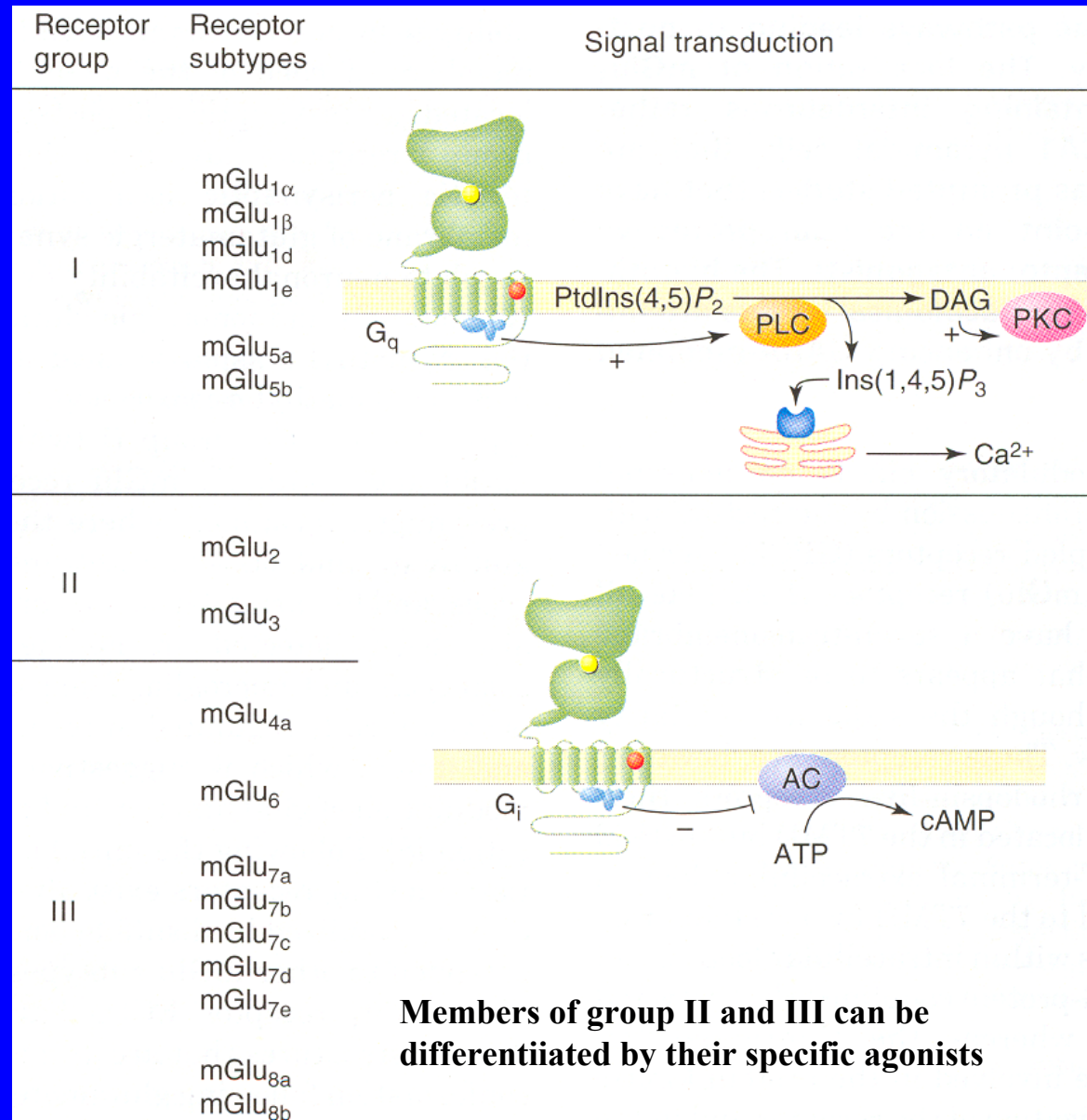
RECEPTEURS METABOTROPIQUES AU GLUTAMATE

GROUP I

Activation de la phospholipase C
(Proteine Gq)

GROUPS II and III

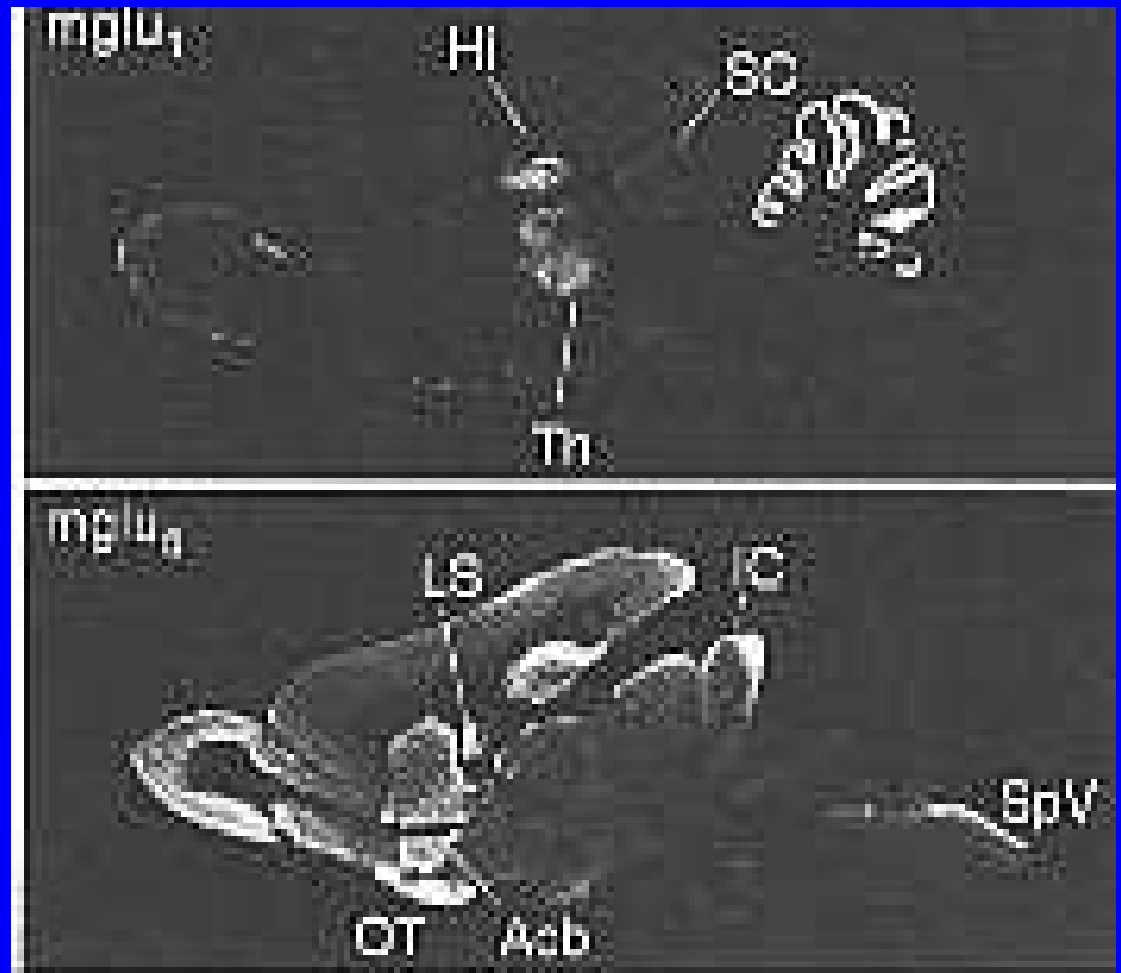
Inhibition of adenylate cyclase
(Proteine Gi)



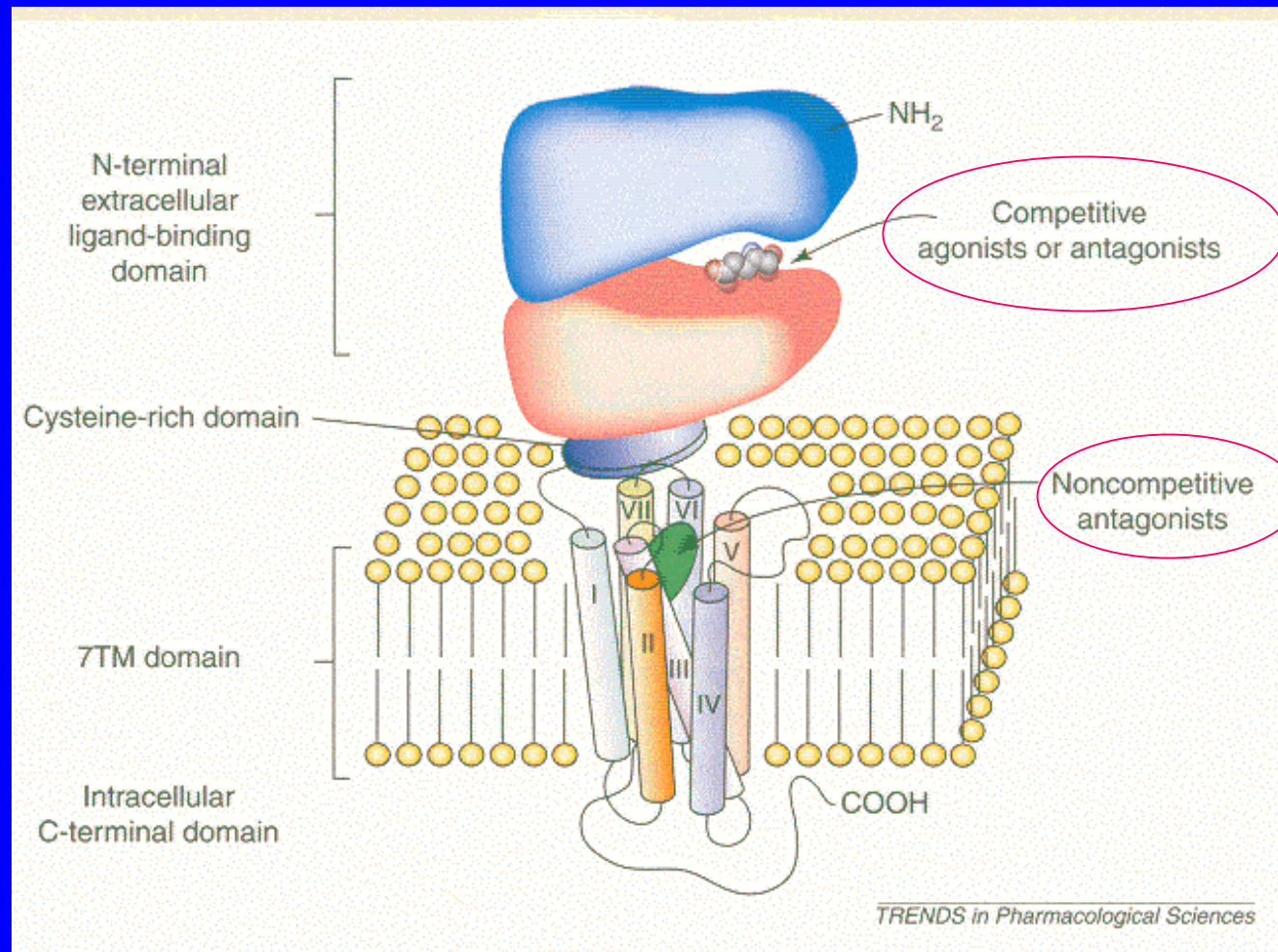
Members of group II and III can be
differentiated by their specific agonists

RECEPTEURS METABOTROPIQUES AU GLUTAMATE - LOCALISATION

Acb: nucleus accumbens
Hi: hippocampus
IC: inferior colliculus
LS: lateral septal nucleus
OT: olfactory tubercle
SC: superior colliculus
SpV: spinal trigeminal nuclei
Th: thalamus



RECEPTEURS METABOTROPIQUES AU GLUTAMATE mGlu5 - STRUCTURE OF THE MONOMERIC FORM

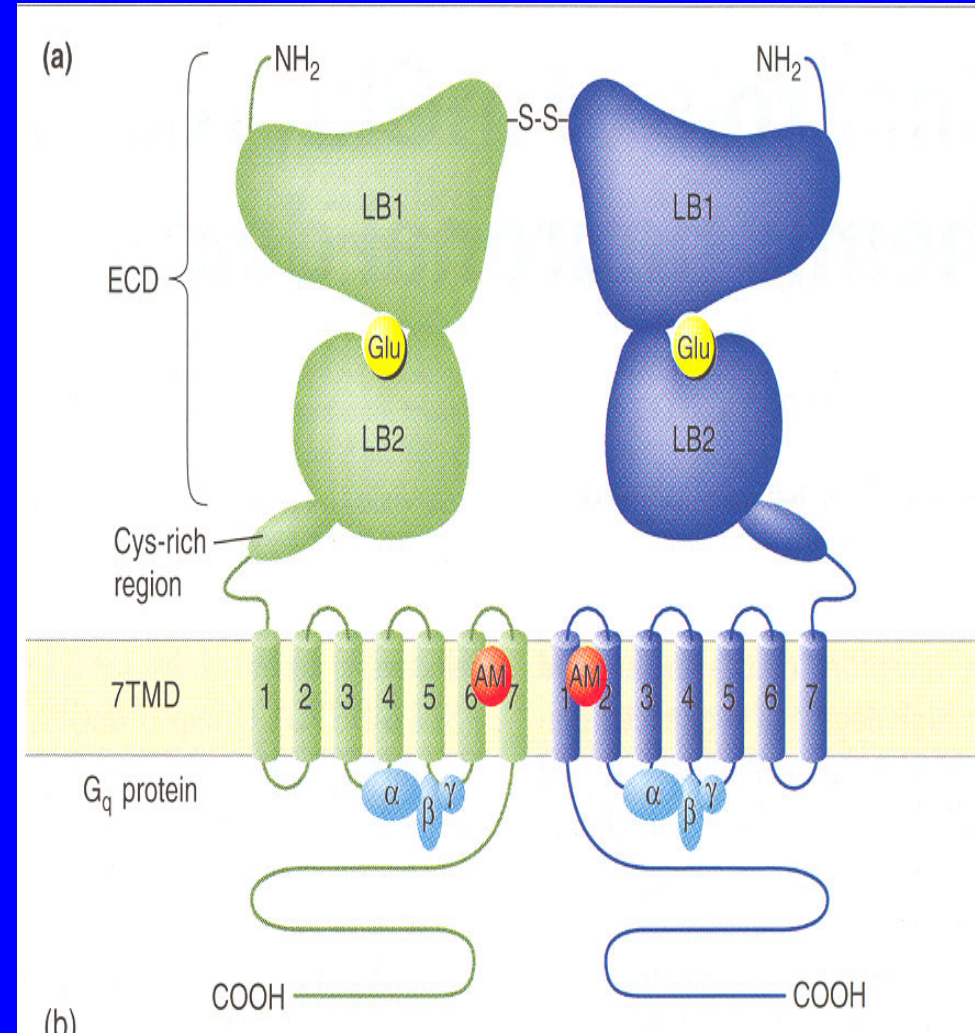


RECEPTEURS METABOTROPIQUES AU GLUTAMATE

Agonist binding site is located in the large N-terminal extracellular domain which is connected to the seven-transmembrane G-protein-coupled receptor by a cysteine rich linker

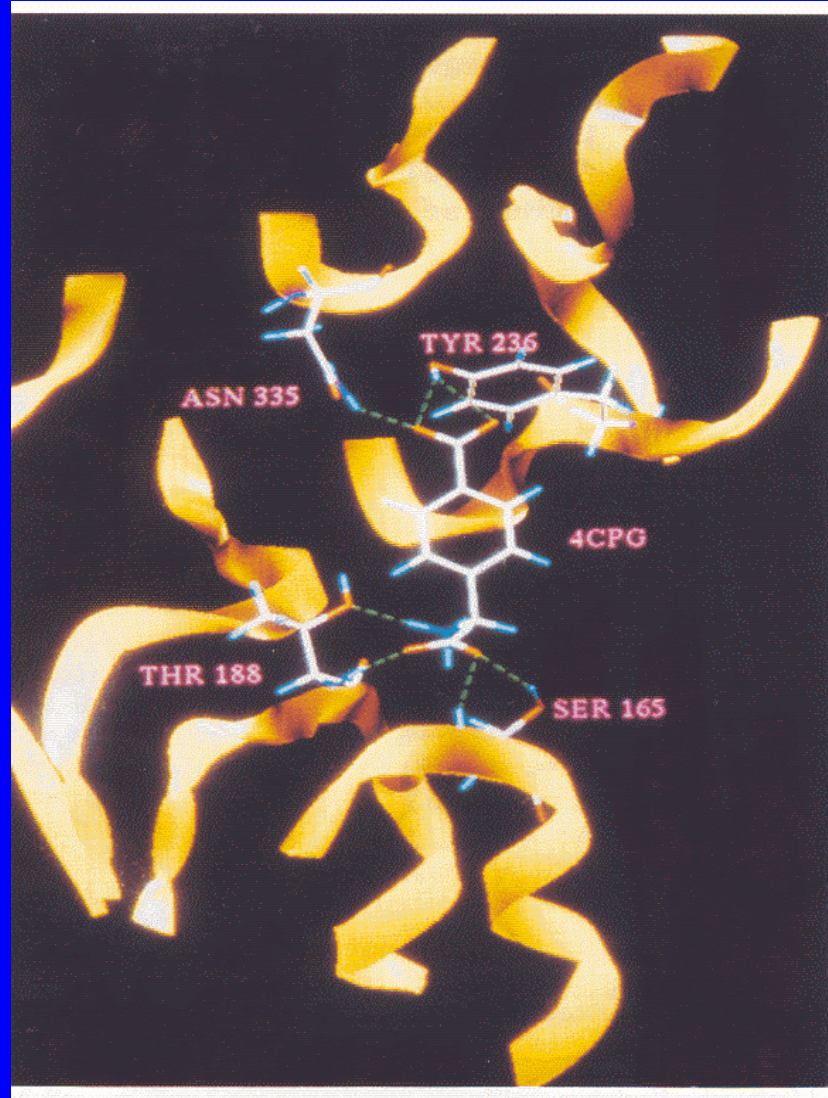
Residues within intracellular loops 2 and 3 appear to be crucial for G-protein coupling selectivity and activation

C-terminal tail contains residues that are involved in the protein kinase C-induced desensitization of the receptor and in the interaction with intracellular proteins



ECB: Extracellular domain
LB: ligand binding lobes
AM: allosteric modulators

mGLU AND RECEPTOR ANTAGONIST 4-CARBOXYPHENYLGLYCINE



Toms et al, *TIPS* (1996) 17: 429-435

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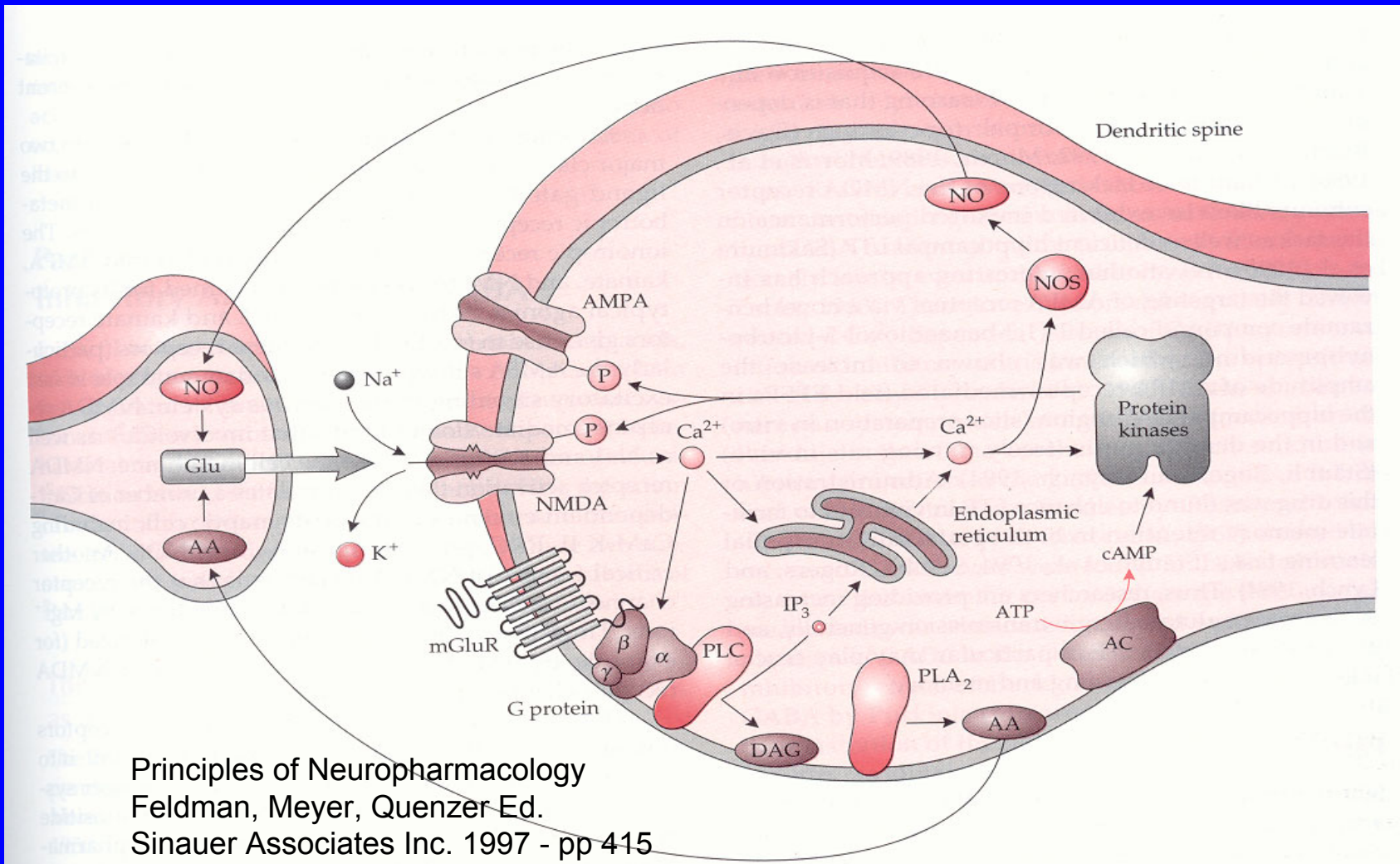
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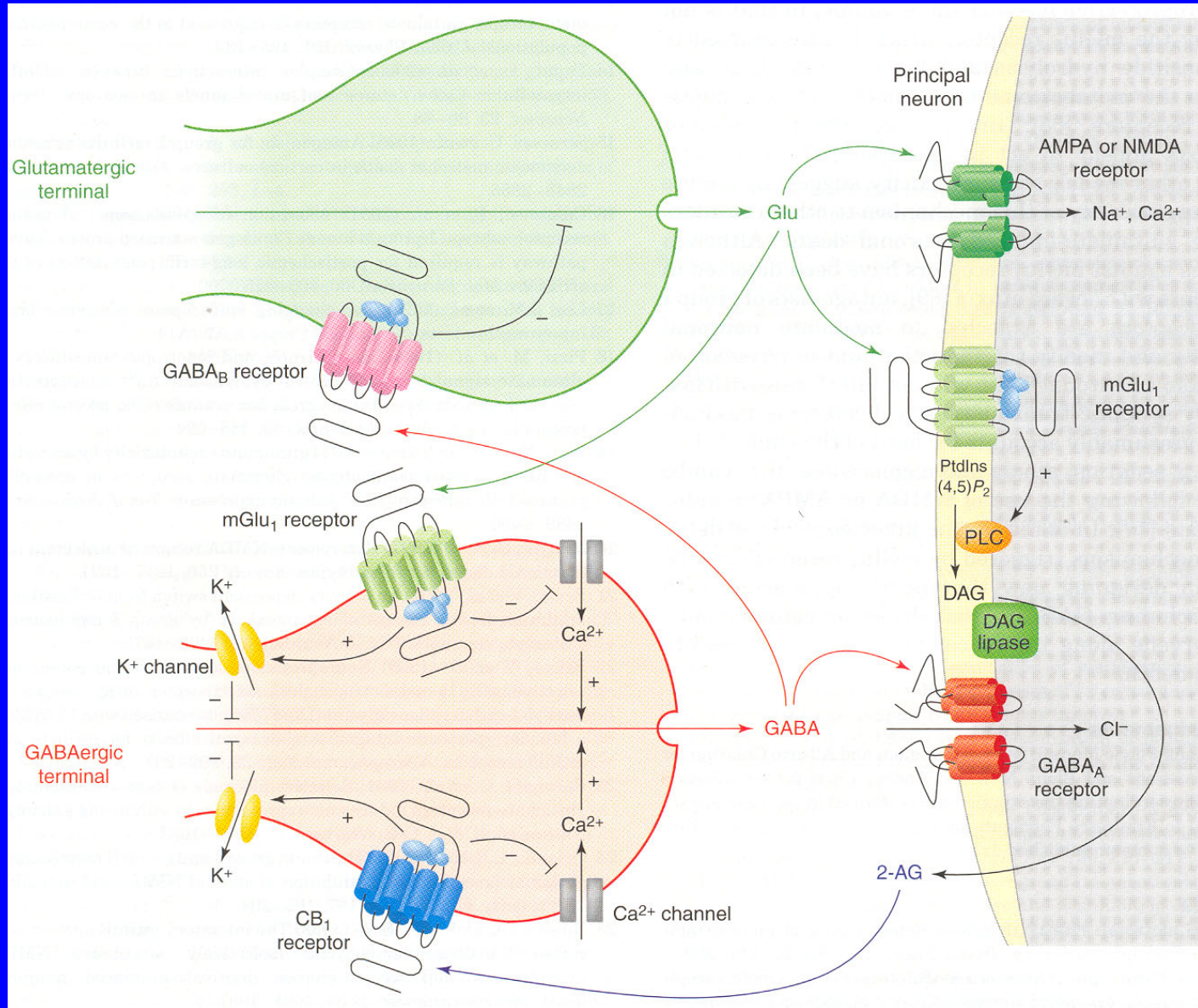
INTERACTION LIGAND/RECEPTEUR GLUTAMINERGIQUE

INTERACTION ENTRE RECEPTEURS

MAINTENANCE OF NMDA RECEPTOR ACTIVATION AND INTERCONNECTIONS BETWEEN METABOTROPIC AND NMDA RECEPTORS



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

