SYSTÈME GLUTAMATERGIQUE ET EPILEPSIE

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Acides aminés excitateurs

Le glutamate

localisation, biosynthèse et métabolisme
stockage
recapture
synapse glutamatergique

Les récepteurs canaux du glutamate

structure, localisation et rôle
les récepteurs NMDA et leurs ligands

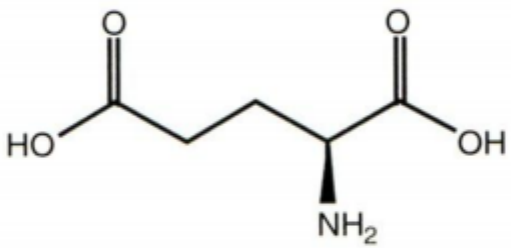
Les RCPGs du glutamate

diversité
intérêt potentiel des ligands

Effets physiologiques du glutamate

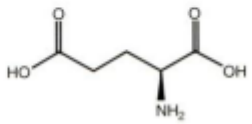
potentialisation à long terme
développement et plasticité synaptique
rôle nocif, excito-toxicité

Le glutamate

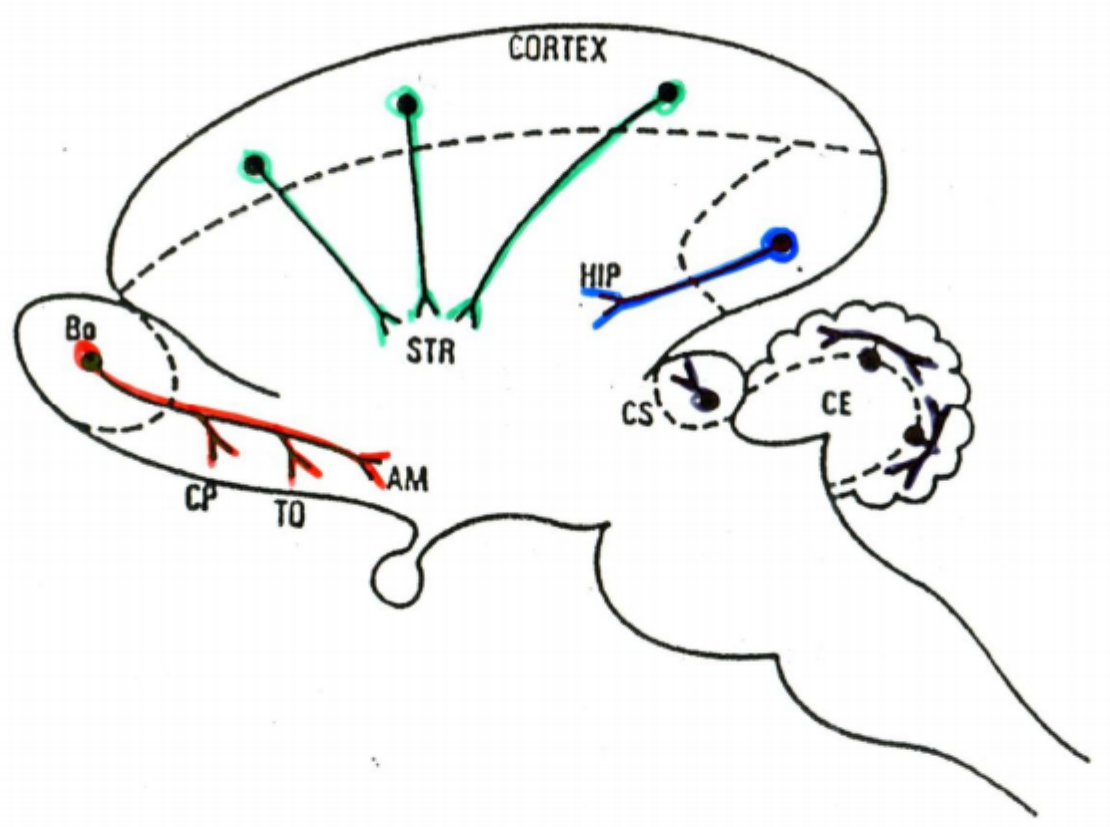


médiateur de ~ 50% des neurones centraux

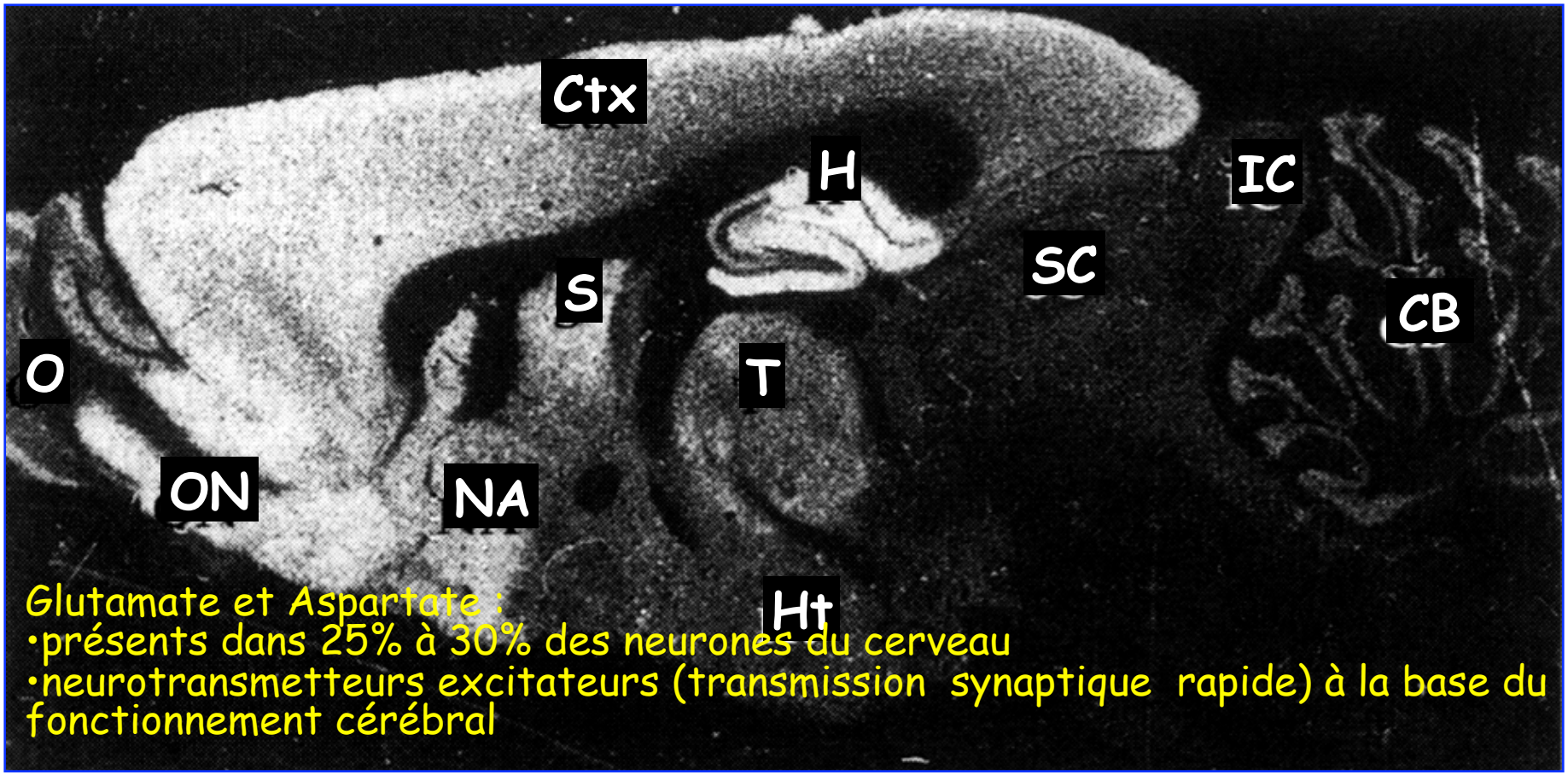
Le glutamate



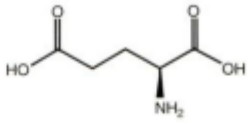
Voies glutamatergiques



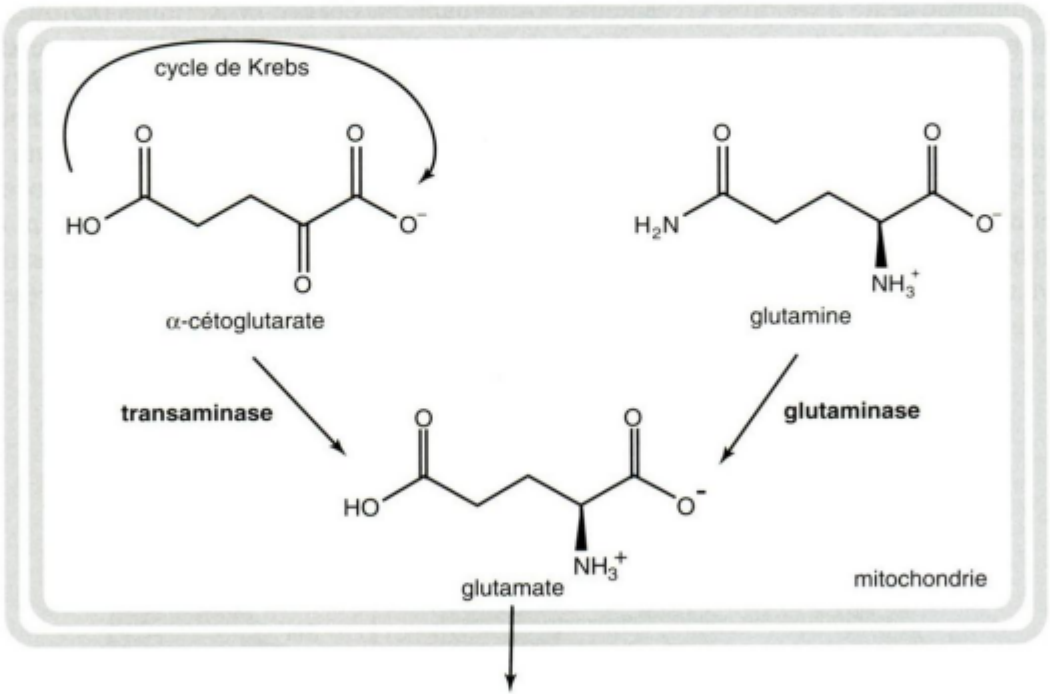
Voies glutamatergiques



Le glutamate



Biosynthèse

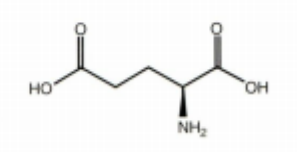


Métabolisme

GABA

Glutamine

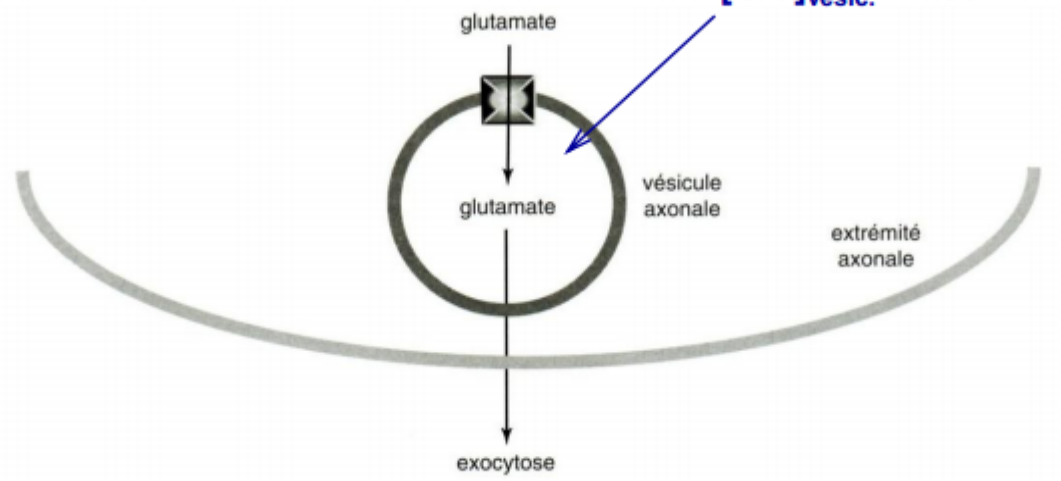
Le glutamate



Stockage et exocytose

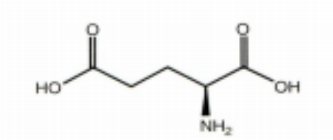
$[Glu]_{intracell.}$ ~ 10 mM

$[Glu]_{vésic.}$ ~ 100 mM

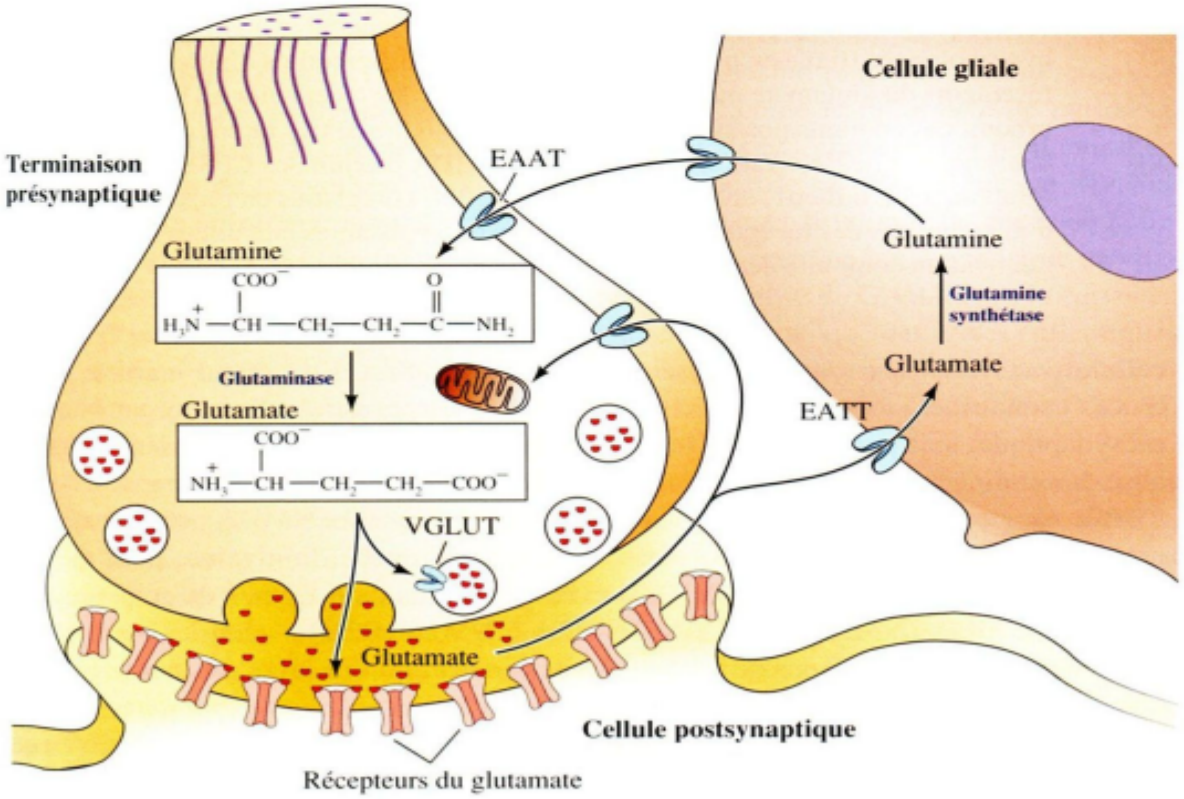


$[Glu]_{extracell.}$ ~ 1 µM

Le glutamate



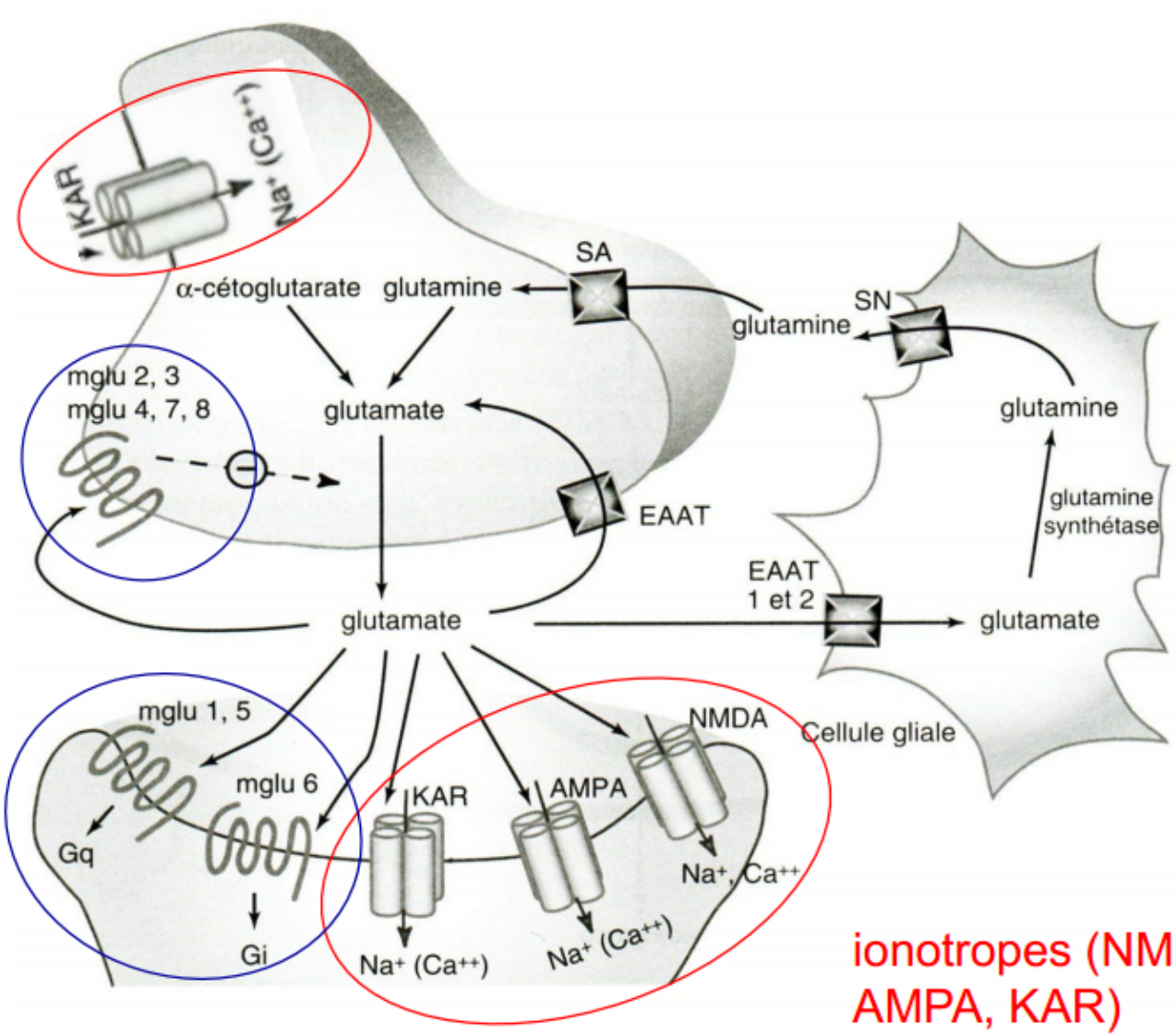
Synapse glutamatergique



Les récepteurs du glutamate

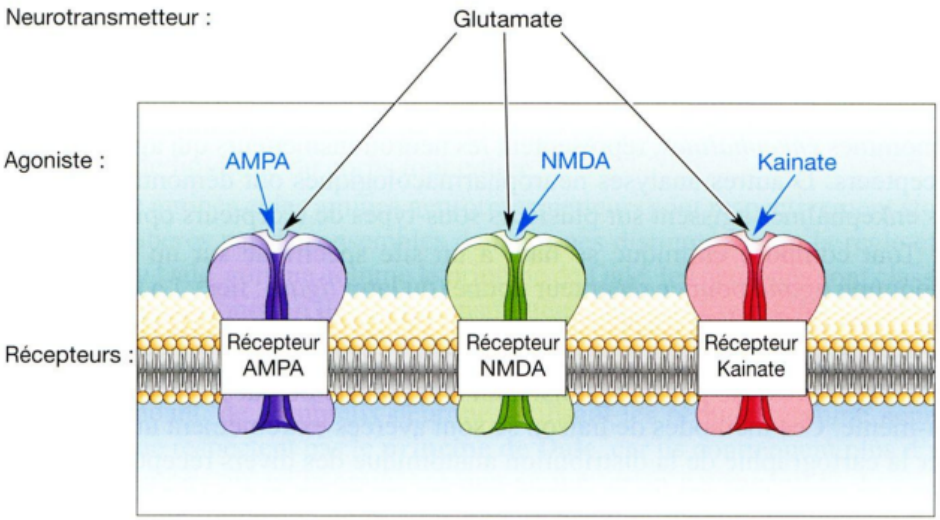
ionotrope (KAR)

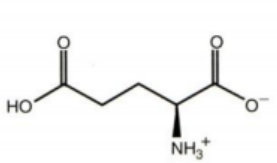
métabotropiques (mGlu1-8)



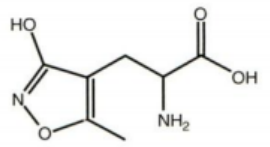
ionotropes (NMDA, AMPA, KAR)

Les récepteurs canaux du glutamate

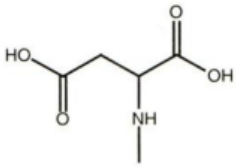




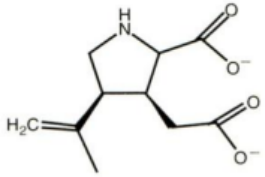
glutamate



AMPA



NMDA



kaïnate

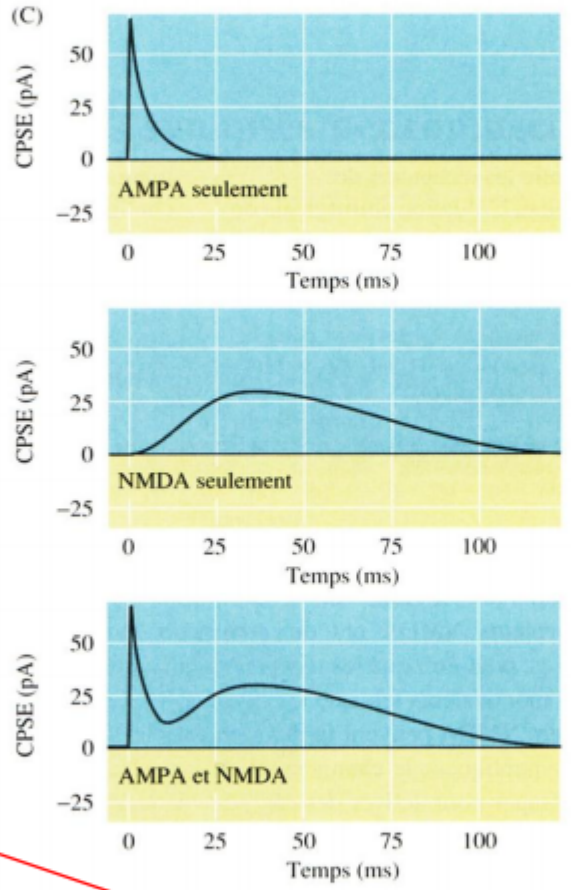
- NMDA, 6-sous-unités clonées : NR1, NR2A, NR2B, NR2C, NR2D, NR3A ;
- AMPA, 4 sous-unités clonées : GluR1, GluR2, GluR3, GluR4 ;
- KAR, 5 sous-unités clonées : GluR5, GluR6, GluR7, KA1, KA2.

Les récepteurs canaux du glutamate

Localisation et rôle

Les récepteurs NMDA et AMPA

- post-synaptiques
- somato-dendritiques
- colocalisés

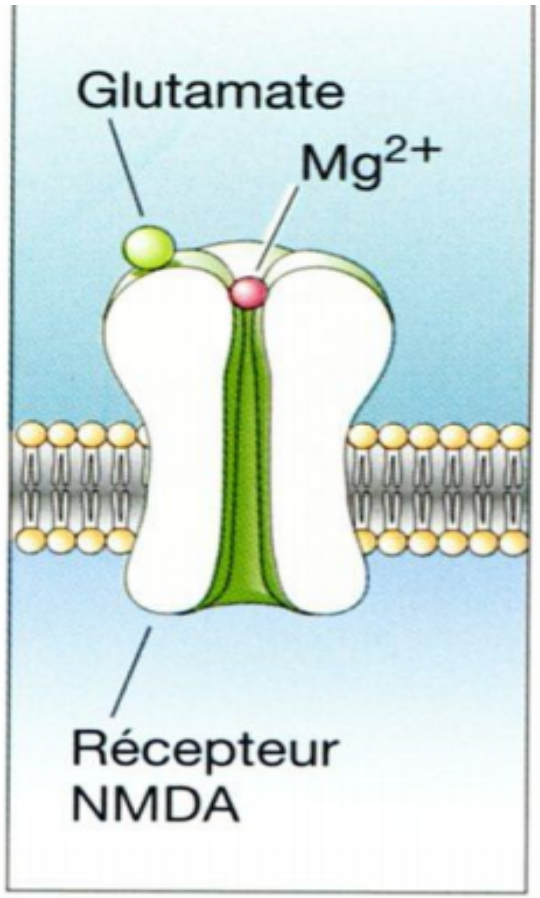


dépolarisation membranaire

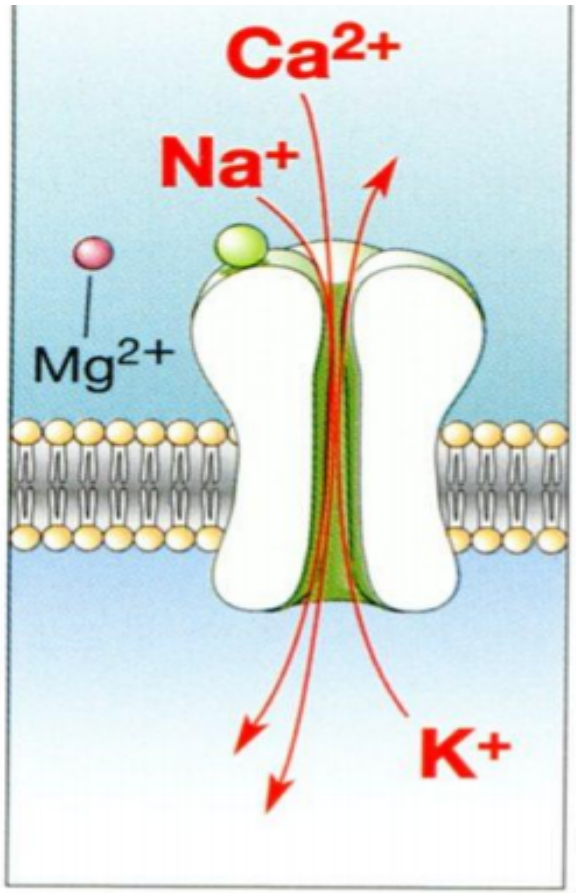
exocytose de neuromédiateurs

potentialisation à long terme

apoptose



(a) Glutamate



(b) Glutamate
et dépolarisation

Ligands (I)

Les agonistes

- NMDA
- glutamate, aspartate
- glycine (co-agoniste)

Les modulateurs allostériques endogènes

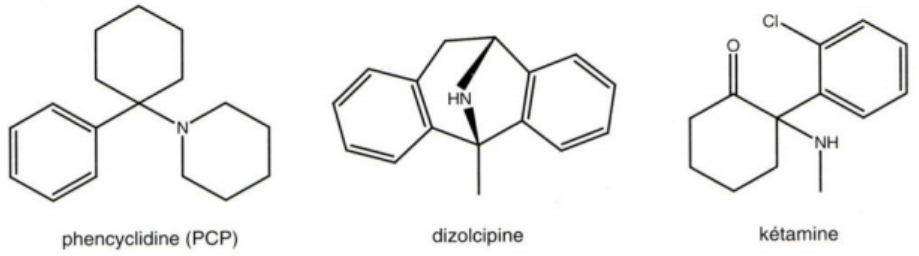
- Mg^{2+} 
- Zn^{2+}, H^{+} 
- polyamines 
- neurostéroïdes 
- ***phosphorylation*** 

Les récepteurs NMDA du glutamate

Ligands (II)

Les modulateurs allostériques à effet anesthésique

- phencyclidine (PCP)
- dizolcipine
- kétamine



phencyclidine (PCP) dizolcipine kétamine

- protoxyde d'azote (N_2O)

Les récepteurs NMDA du glutamate

Ligands (III)

Autres modulateurs allostériques d'intérêt thérapeutique

- Amantadine (Mantadix®)	*Parkinson*
- Mémantine (Ebixa®)	*Alzheimer*
- dextrométhorphane	*anti-tussif*
- ifenprodil (Validex)	vasodilateur périphérique

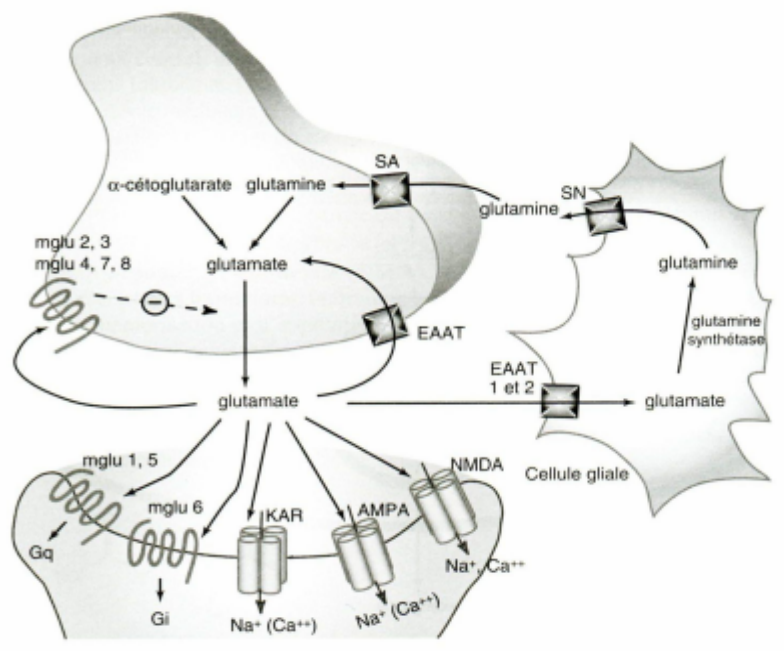
Les RCPGs du glutamate

Les récepteurs présynaptiques

mglu 1 et 5 (groupe I)
Gq

mglu 2 et 3 (groupe II)
Gi

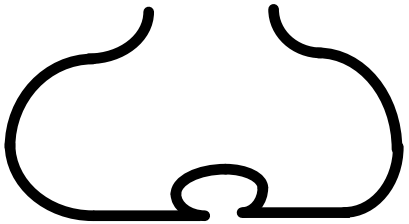
mglu 4, 6, 7 et 8 (groupe III)
Gi

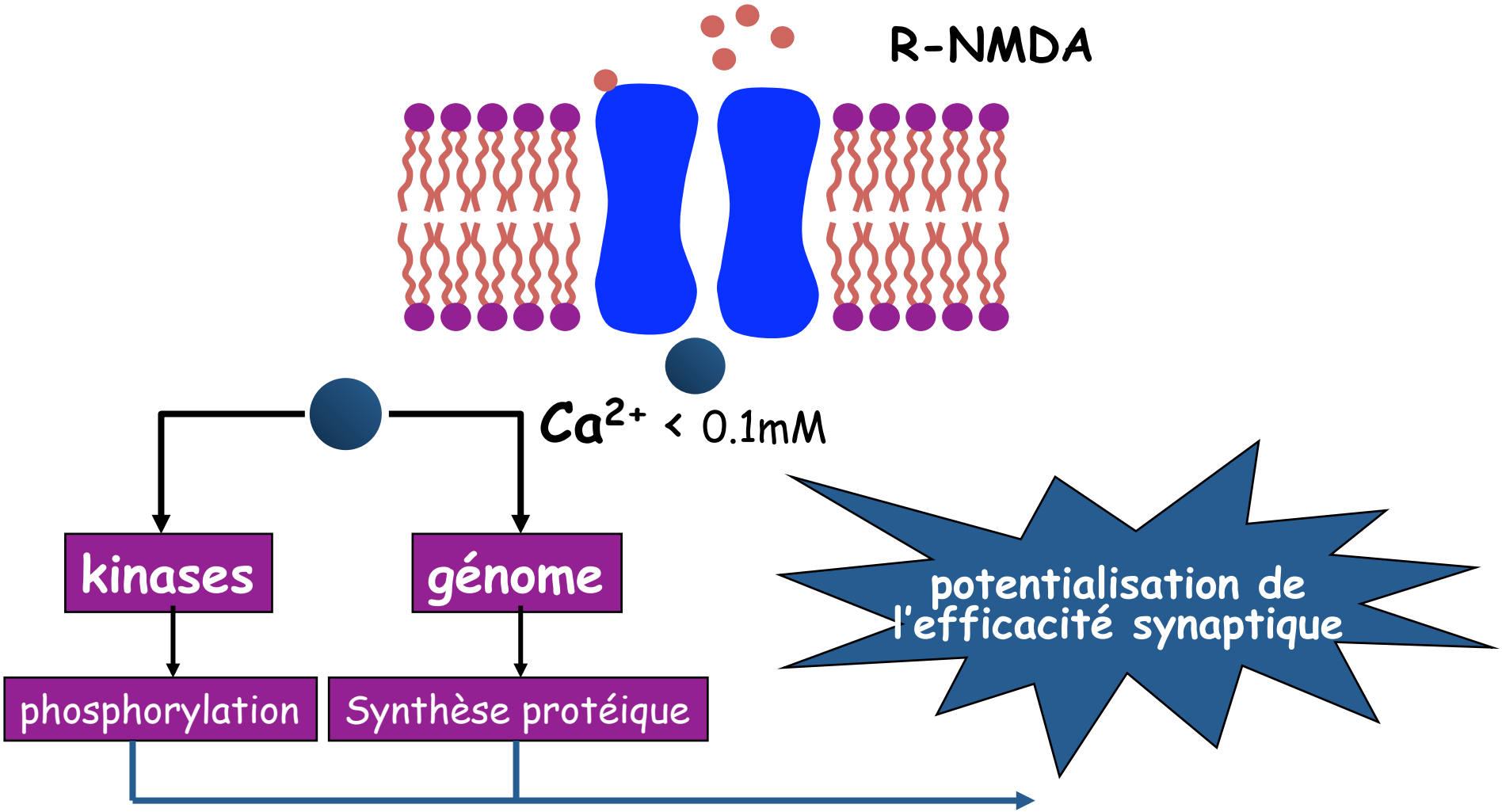


fonctions

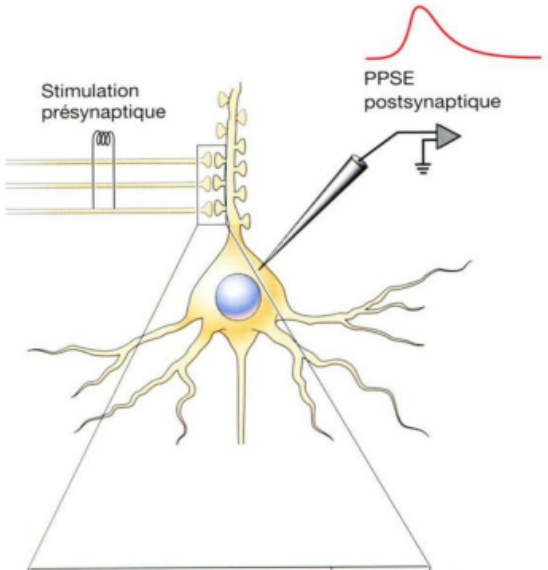
Effets physiologiques du glutamate

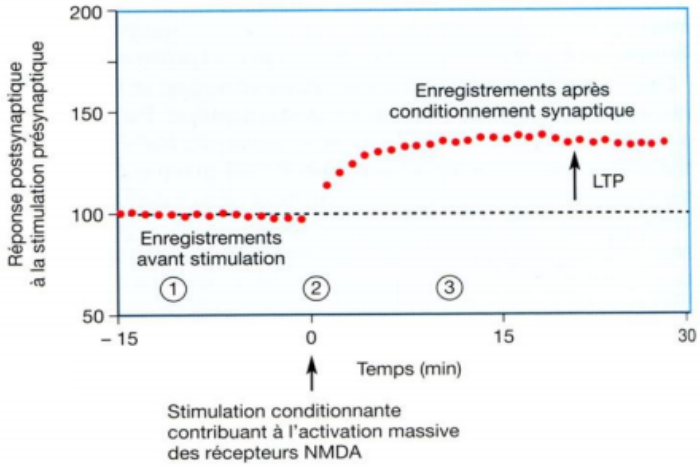
Rôle dans le développement et plasticité synaptique

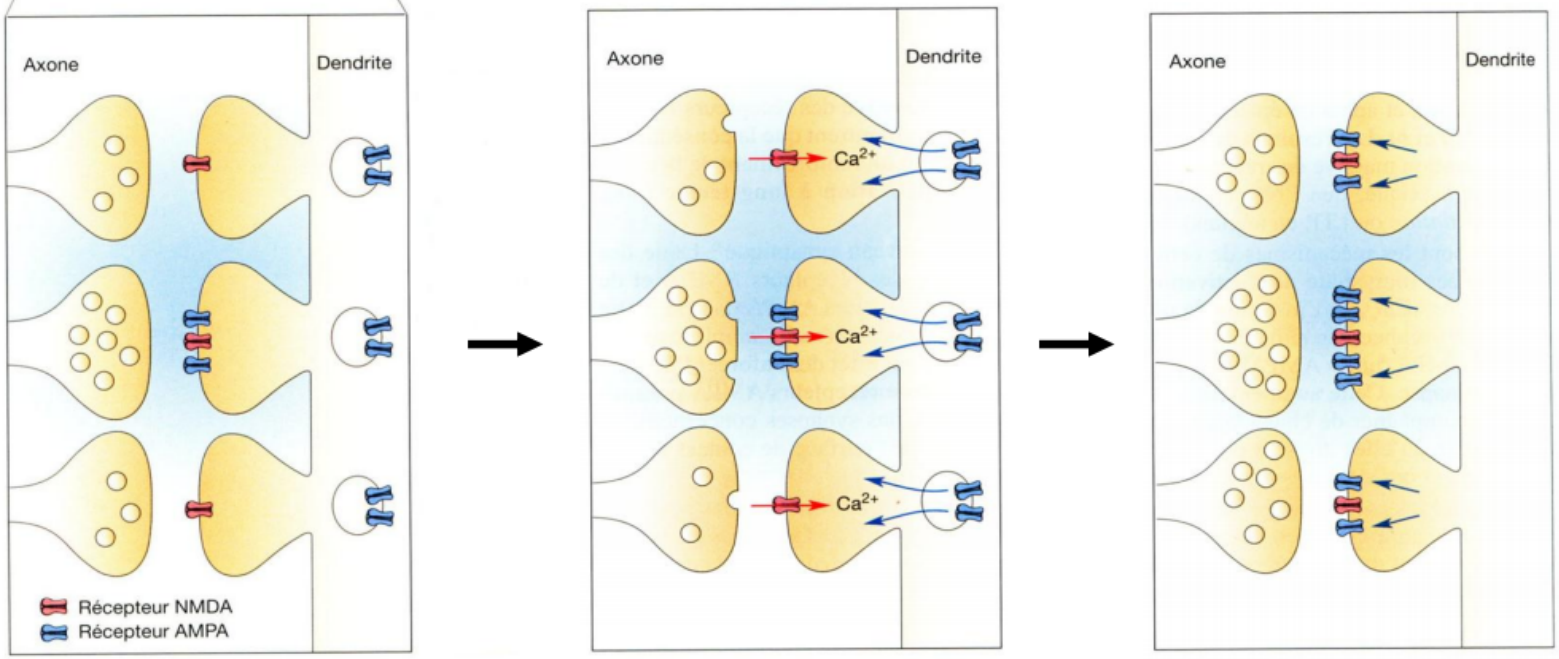
Glutamate,  R-NMDA et PLT



Potentialisation à long terme

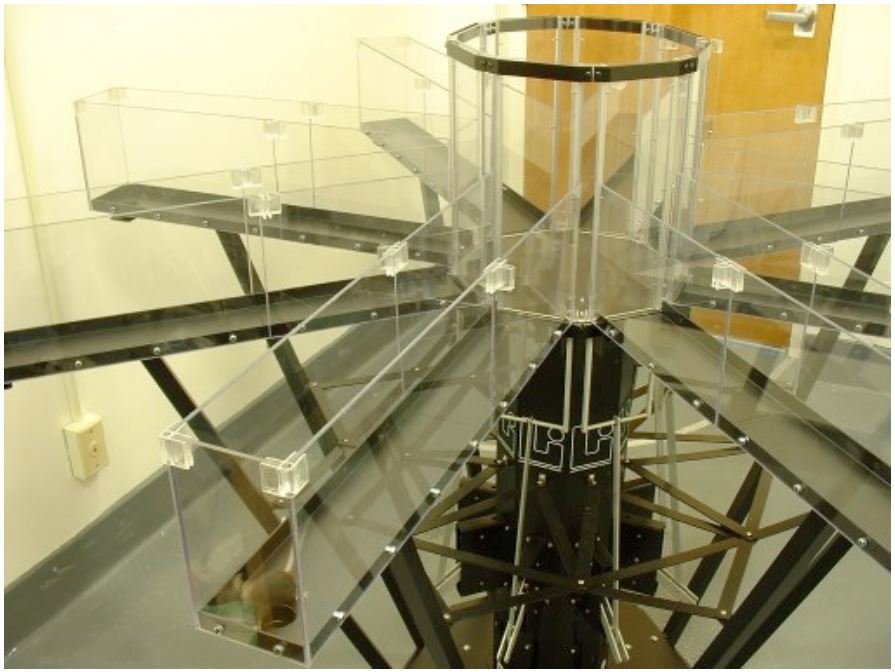


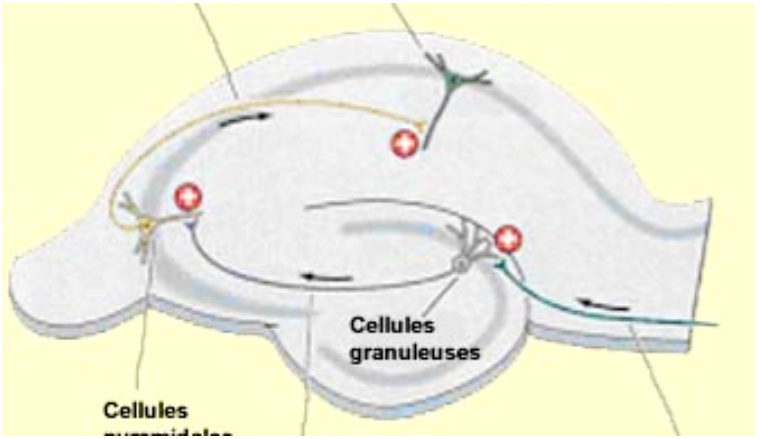




1 - Avant induction de LTP **2 - Pendant induction de LTP** **3 - Après induction de LTP**

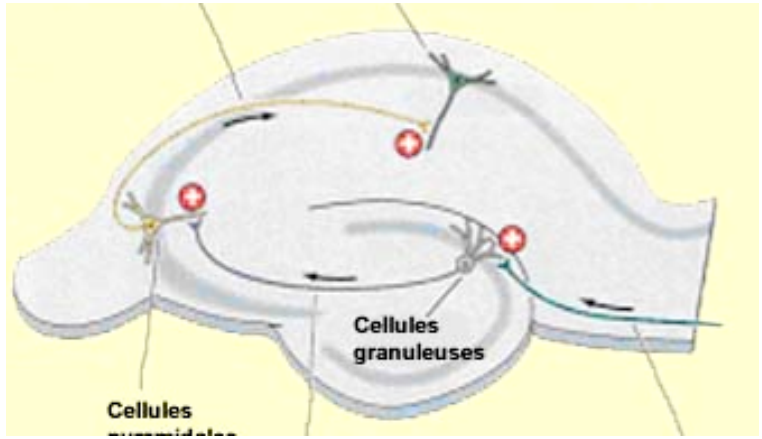
Tests de mémoire spatiale chez les Rongeurs (mémoire consciente)



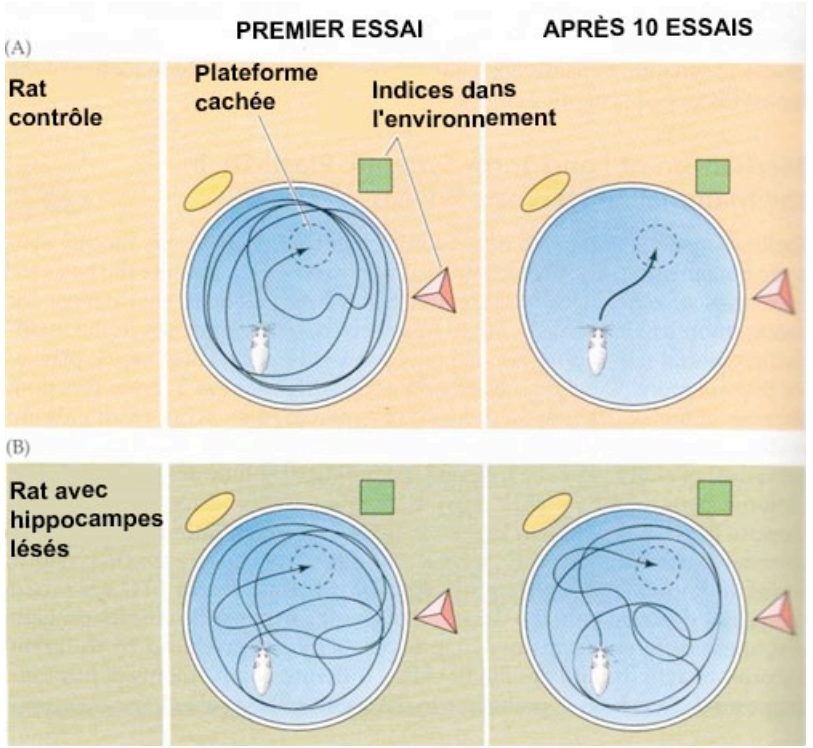


Labyrinthes radial…

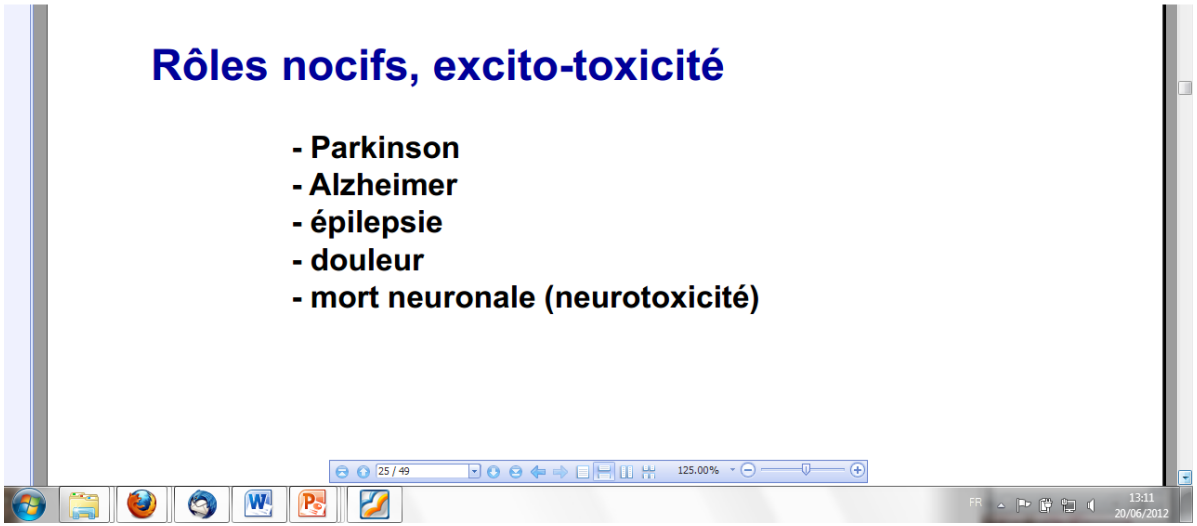
Tests de mémoire spatiale chez les Rongeurs (mémoire consciente)



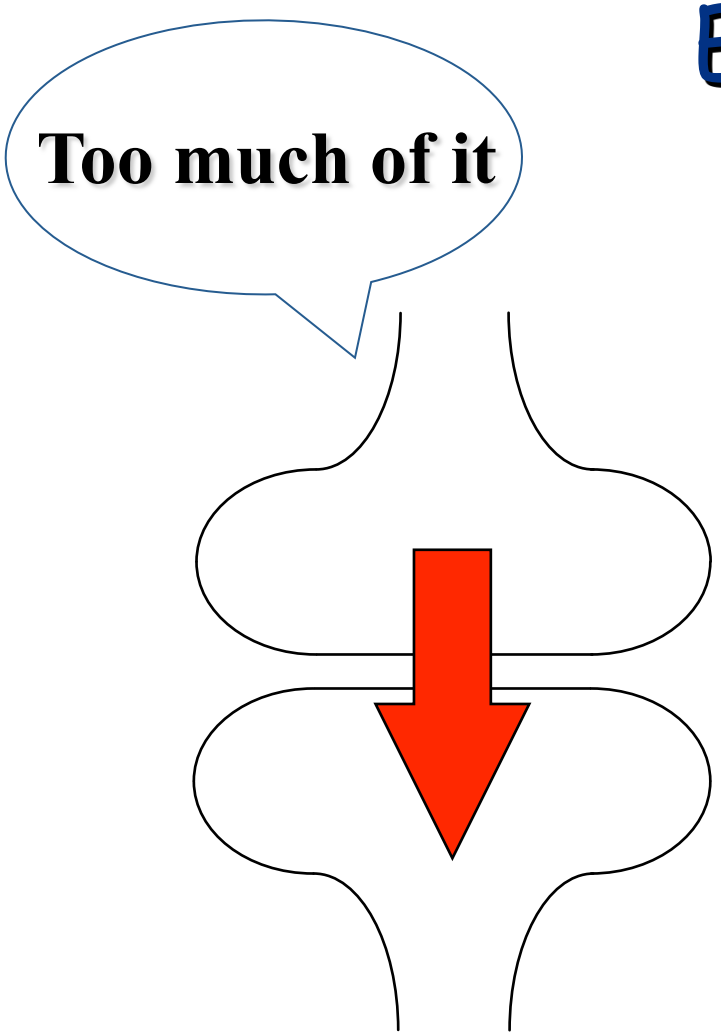
Labyrinthe aquatique…



fonctions

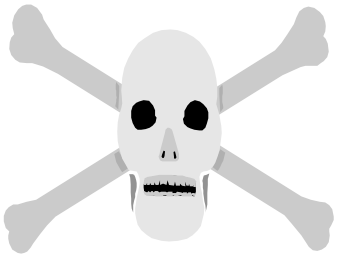

Rôles nocifs, excito-toxicité
- Parkinson
- Alzheimer
- épilepsie
- douleur
- mort neuronale (neurotoxicité)
25 / 49
125.00%
FR
13:11
20/06/2012

Excitotoxicité

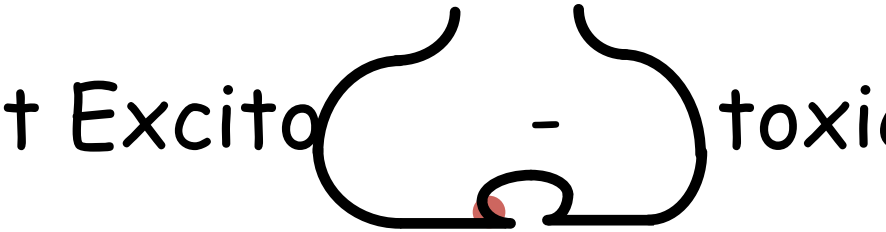


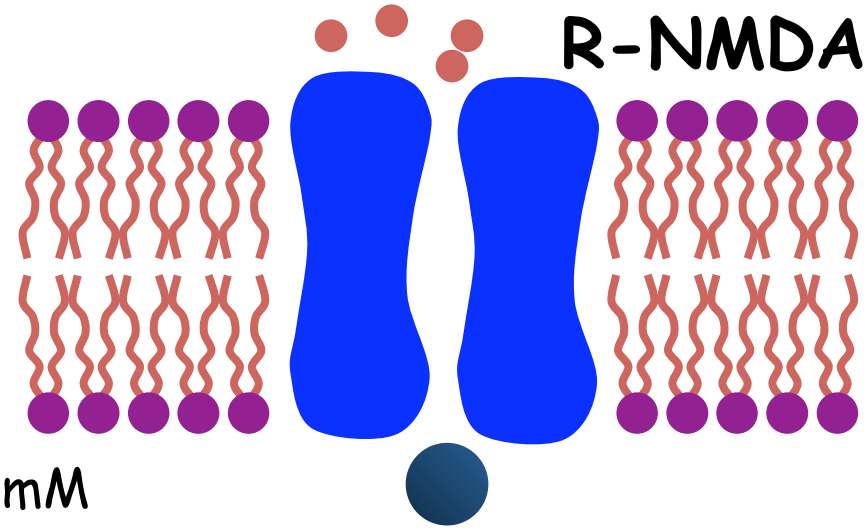
Glutamate-mediated synaptic transmission

Excessive excitation

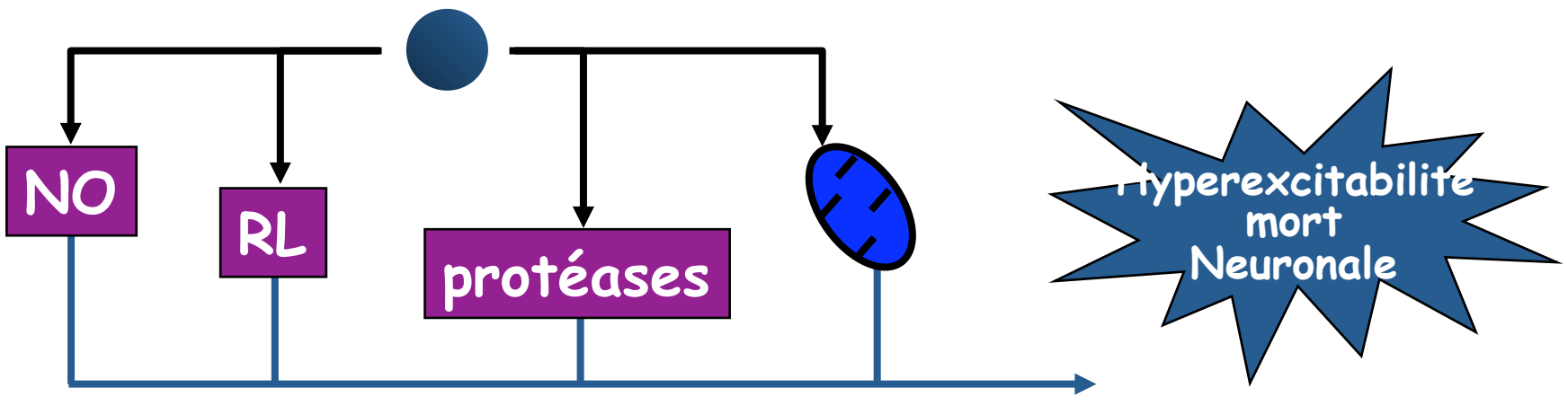


R-NMDA et Excito - toxicité



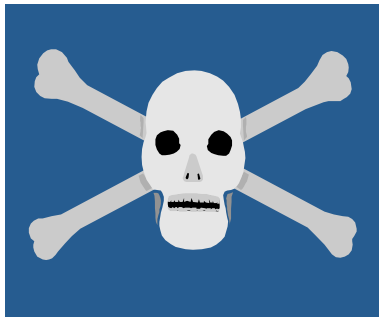


Ca^{2+} > 0.1mM



Intracellular Ca^{2+}-overload

$[Ca^{2+}]_i$ ↗

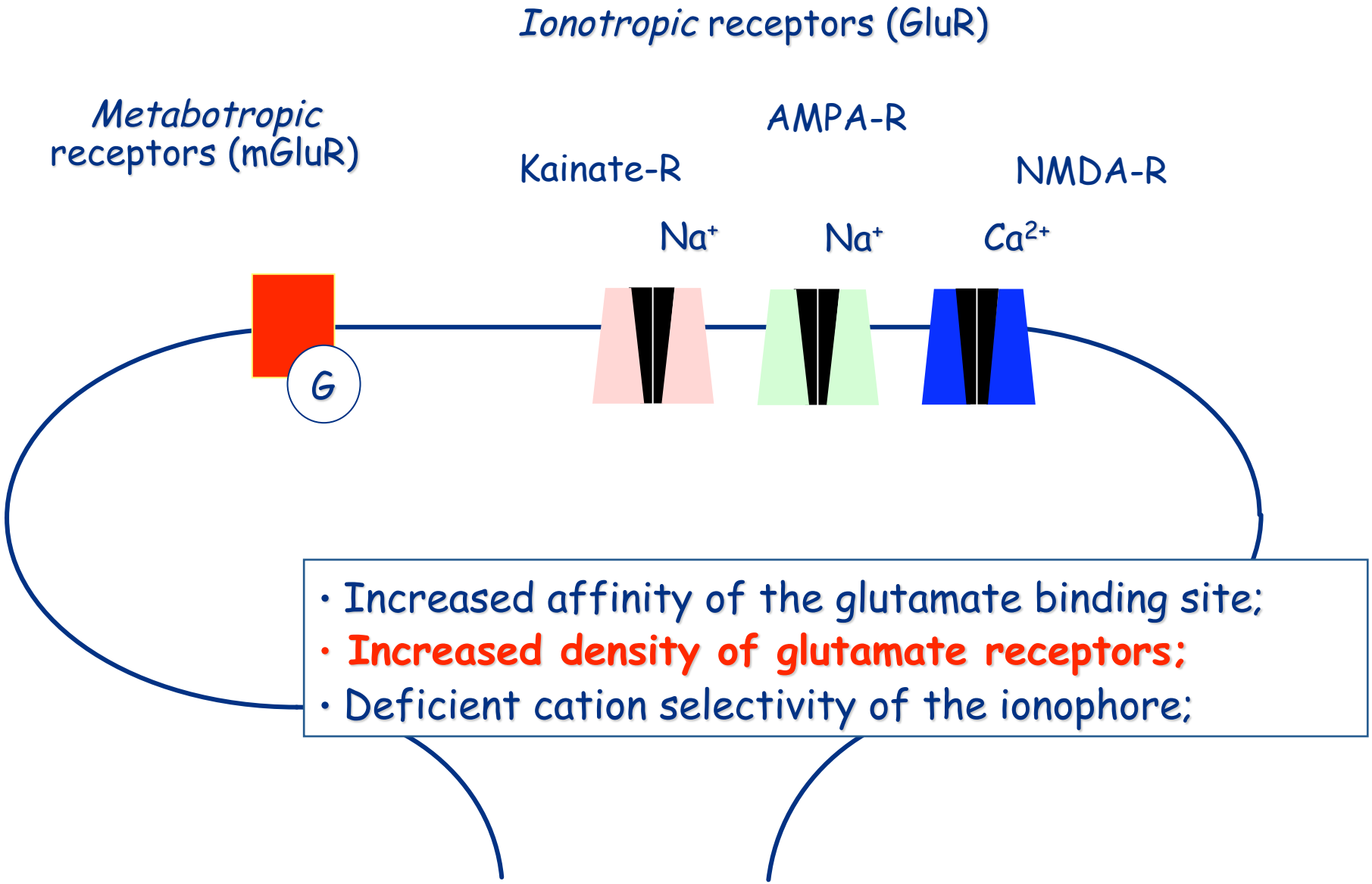


Ca^{2+}-activated

- Proteases (*cytoskeleton breakdown*)
- Phospholipases (*release of arachidonic acid*)
- NO synthases
- Endonucleases (*DNA breakdown*)

Free radical production

Postsynaptic abnormalities leading to excessive excitation



- Increased affinity of the glutamate binding site;
- **Increased density of glutamate receptors;**
- Deficient cation selectivity of the ionophore;

Excitotoxicité endogène et exogène

1970-1984 | **1984** | Post-1984

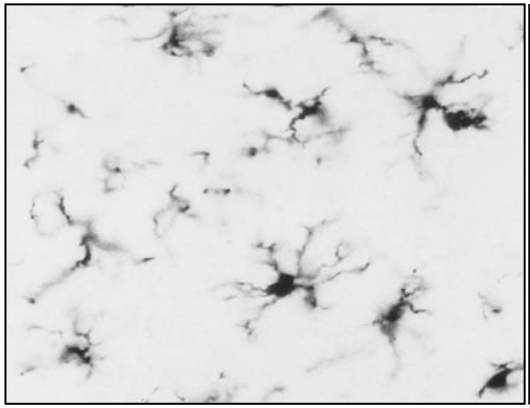
Olney J.
Schwarcz R.
...

Agonists of glutamate-ionotropic receptors :

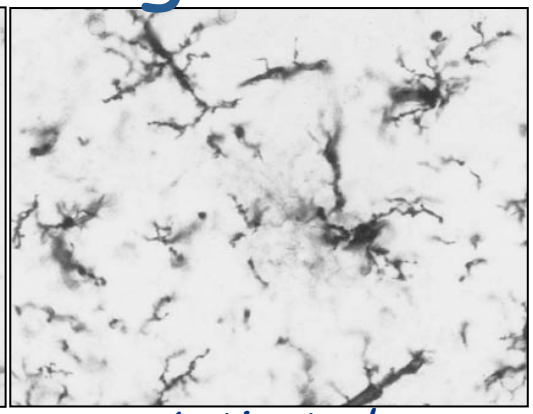
Kainic acid
Quinolinic acid
NMDA
Glutamate **(exogenous)**

Neuronal death

Excitotoxicité endogène

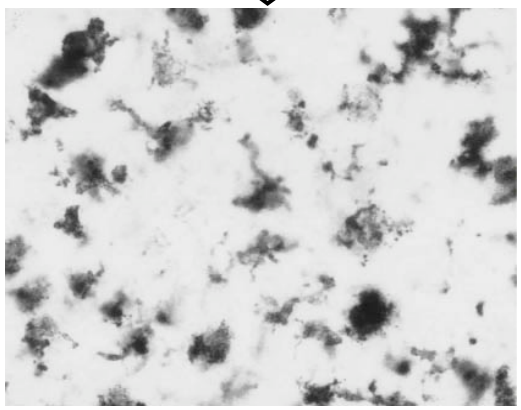


Resting microglia in normal brain



Activated microglia in diseased brain

Invading circulating monocytes



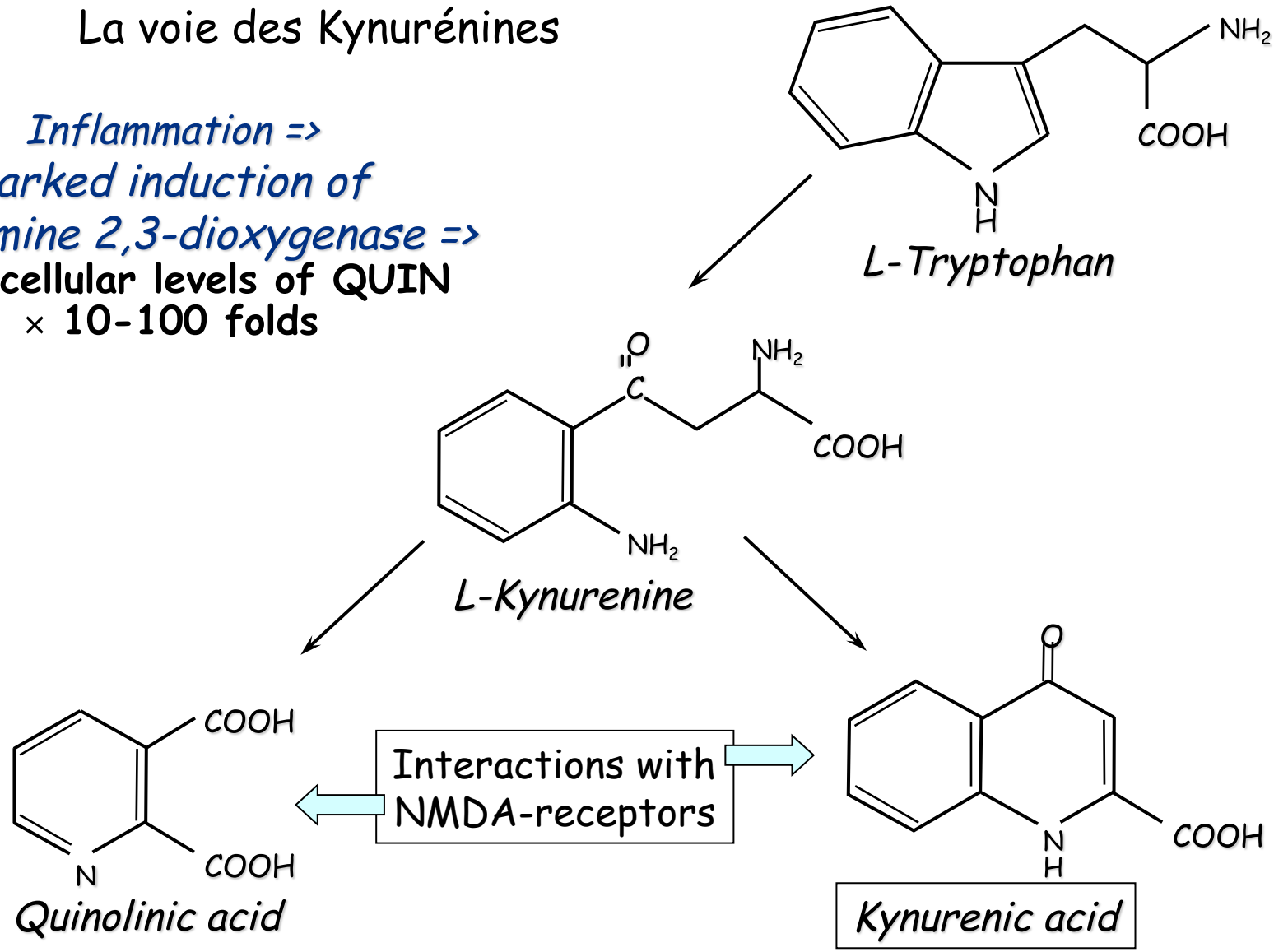
Phagocytic macrophages

Marked induction of indolamine 2,3-dioxygenase

Excitotoxicité endogène

La voie des Kynurénines

Inflammation =>
marked induction of
indolamine 2,3-dioxygenase =>
Extracellular levels of QUIN
× 10-100 folds



Intérêt [potentiel] des ligands des récepteurs du glutamate

Récepteurs ionotropes

Agonistes	activateurs mnésiques
Antagonistes	neuroprotecteurs, anticonvulsivant, traitement douleur chronique

Récepteurs métabotropiques

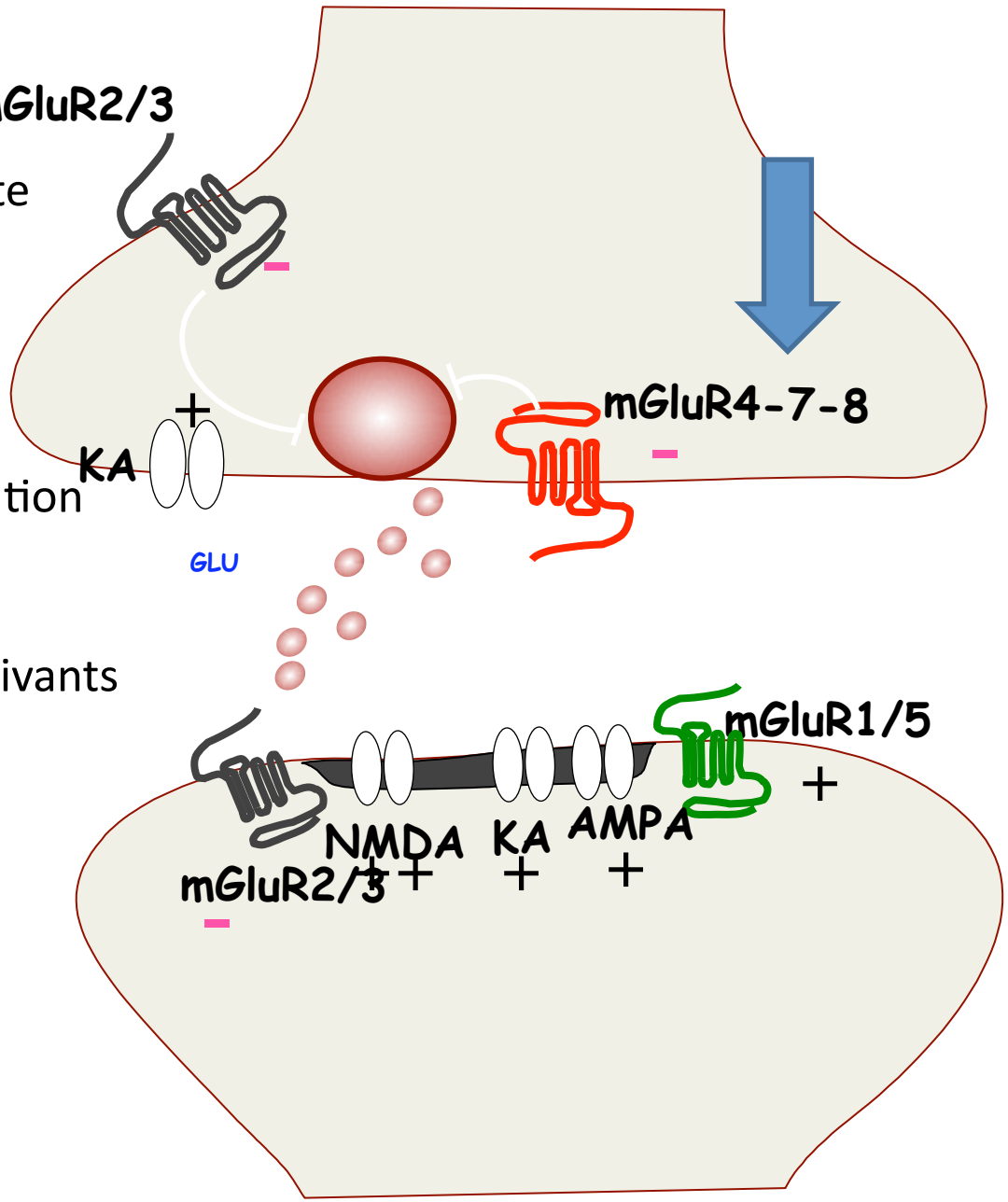
Agonistes	traitement de neurodégénérescence
Antagonistes (mglu5)	diminution de la dépendance aux drogues traitement douleur

Modulation de la transmission glutamatergique

Pendant les crises

augmentation libération de glutamate

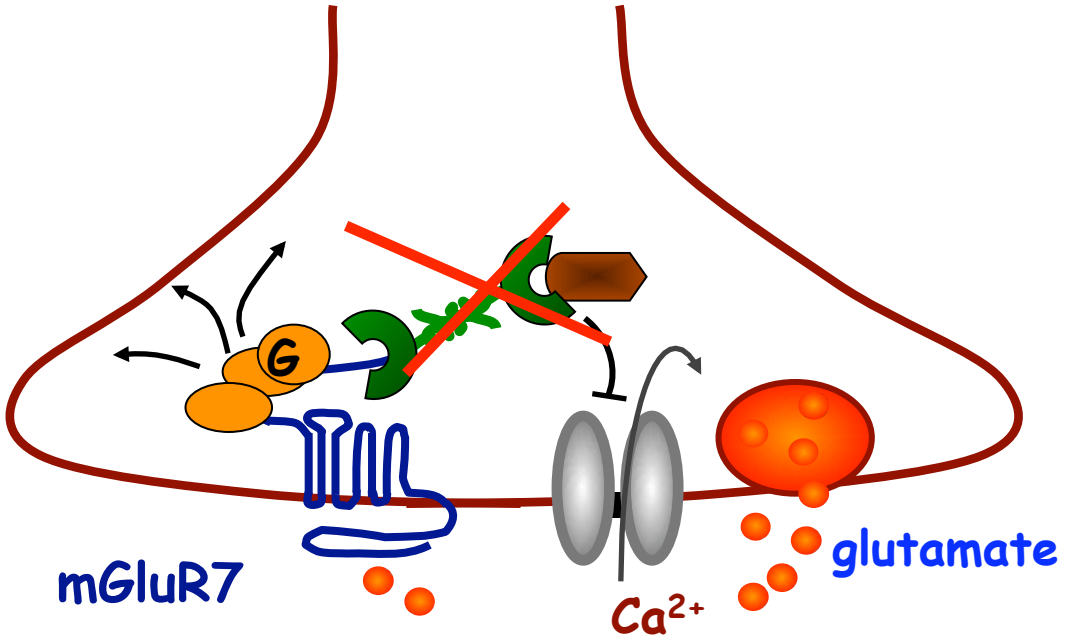
- Suractivation des recepteurs

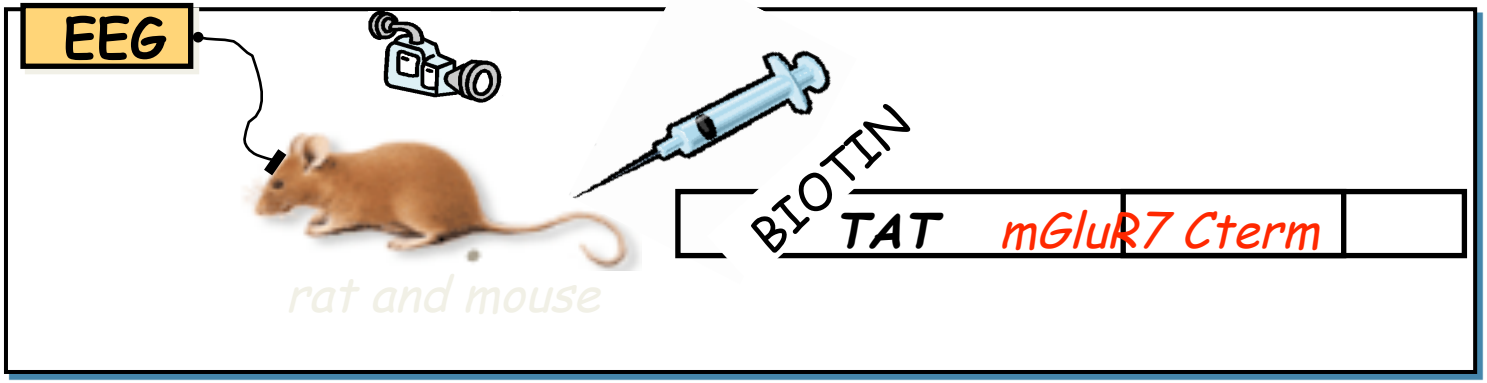


- mGluR4, mGluR7: modulent libération présynaptique de glutamate
- agonistes : anticonvulsivants
- souris KO: + sensibles aux convulsivants

- mGluR1 et mGluR5: augmentent [Ca2+]I => excitation
- agonistes : pro-convulsivants
- antagonistes : anticonvulsivants

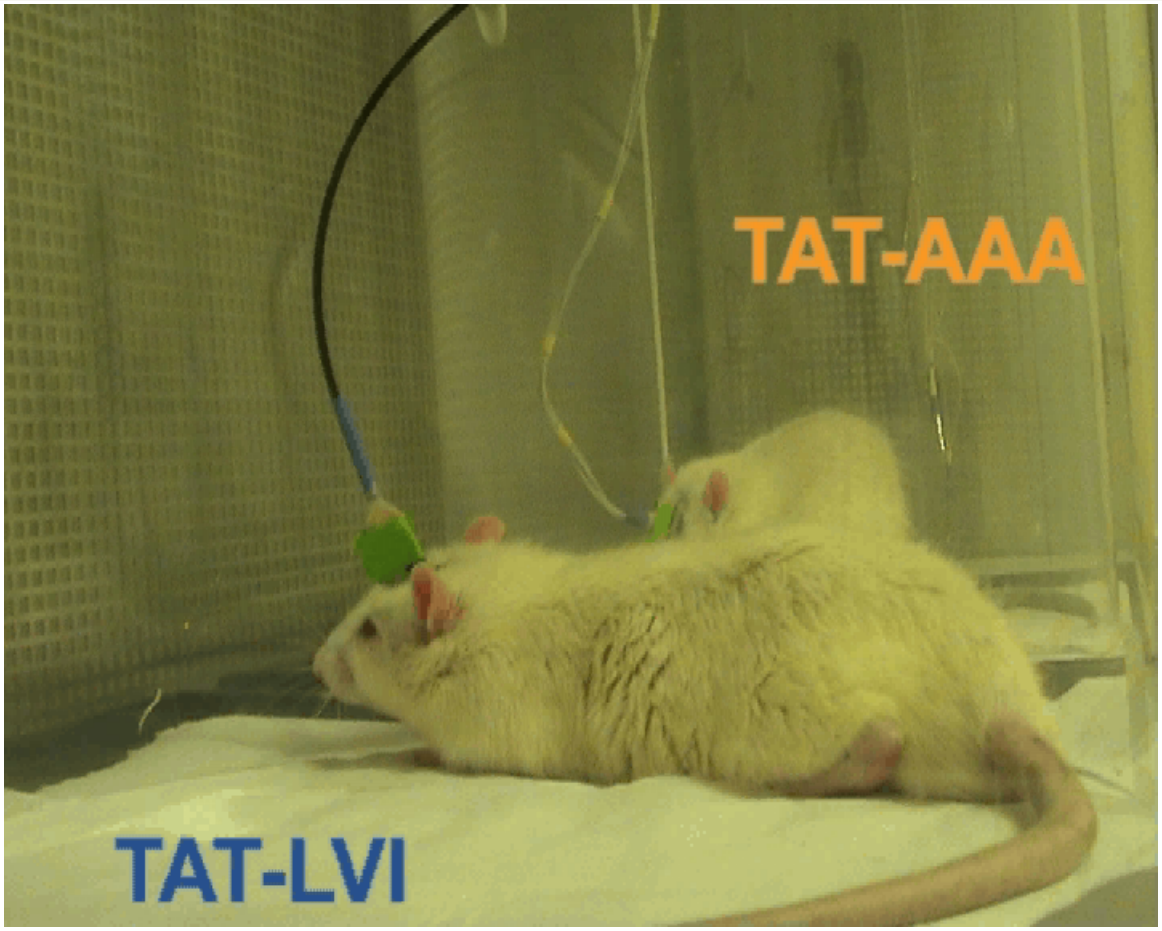
A peptidic antagonist of mGluR7 signalling



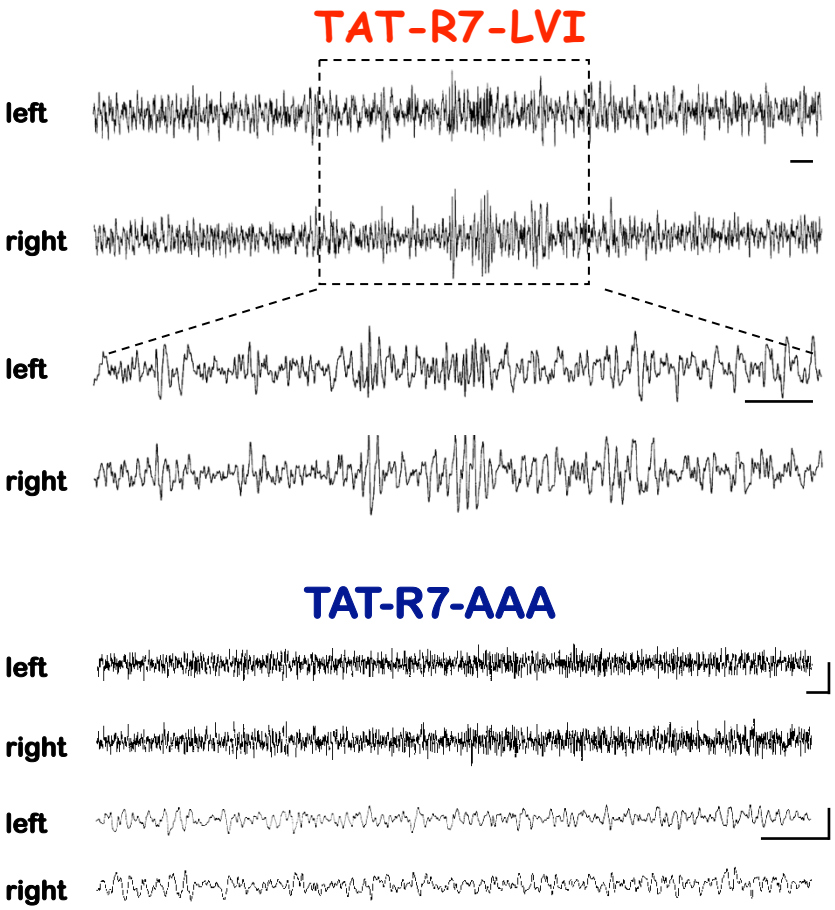


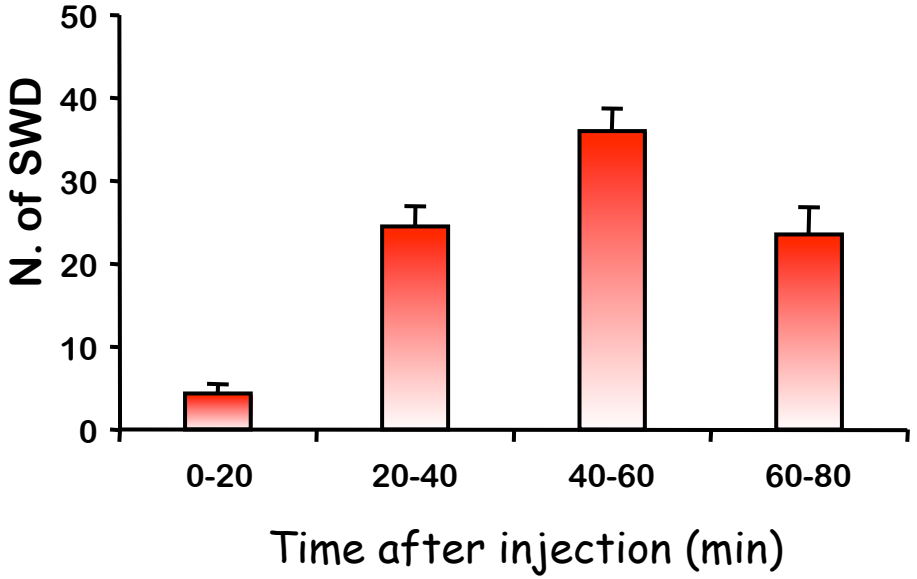
Behaviour

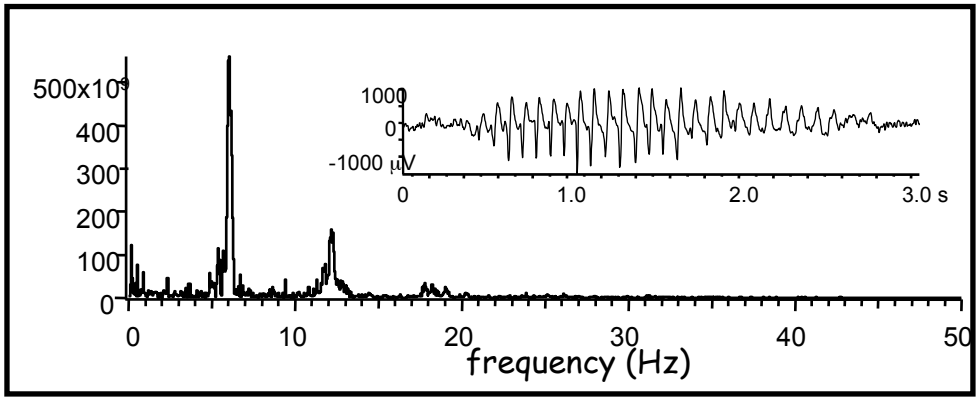
Arrest of exploratory activity
Facial myoclonus / chewing
Vibrissae movements



Cortical EEG recordings

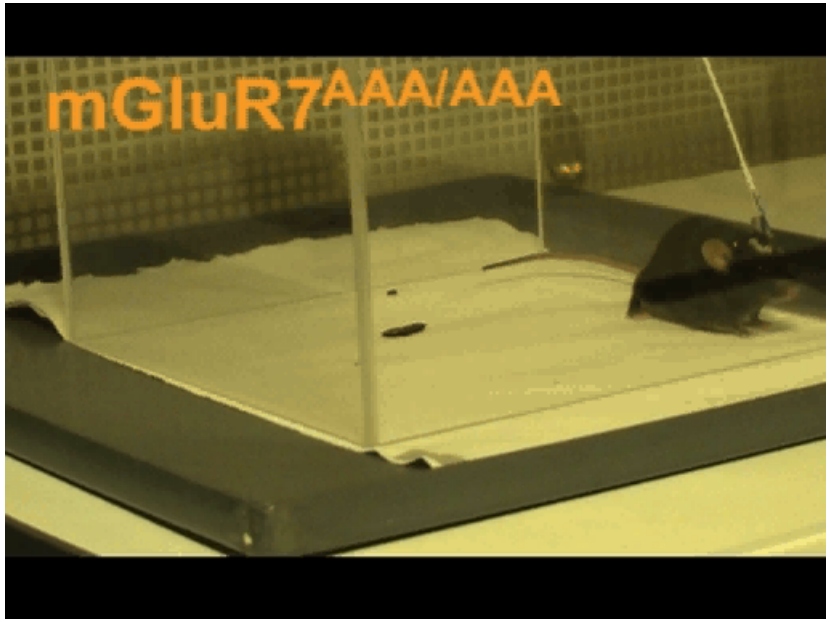


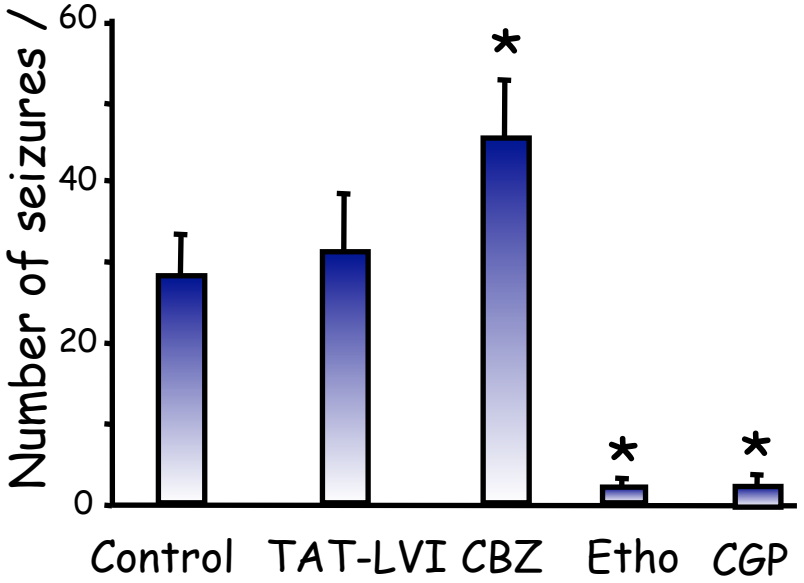


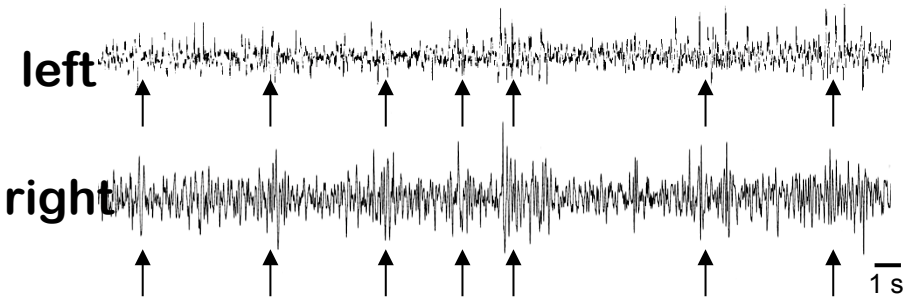


The effect is specific to mGluR7-PDZ interactions

mGluR7$^{AAA/AAA}$ KI mouse







Bertaso et al. Nature Neuroscience 2008