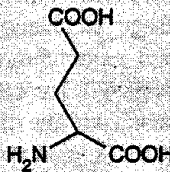
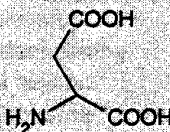


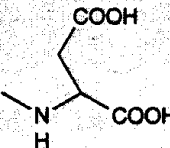
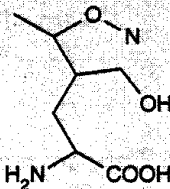
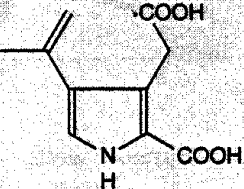
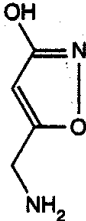
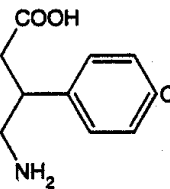
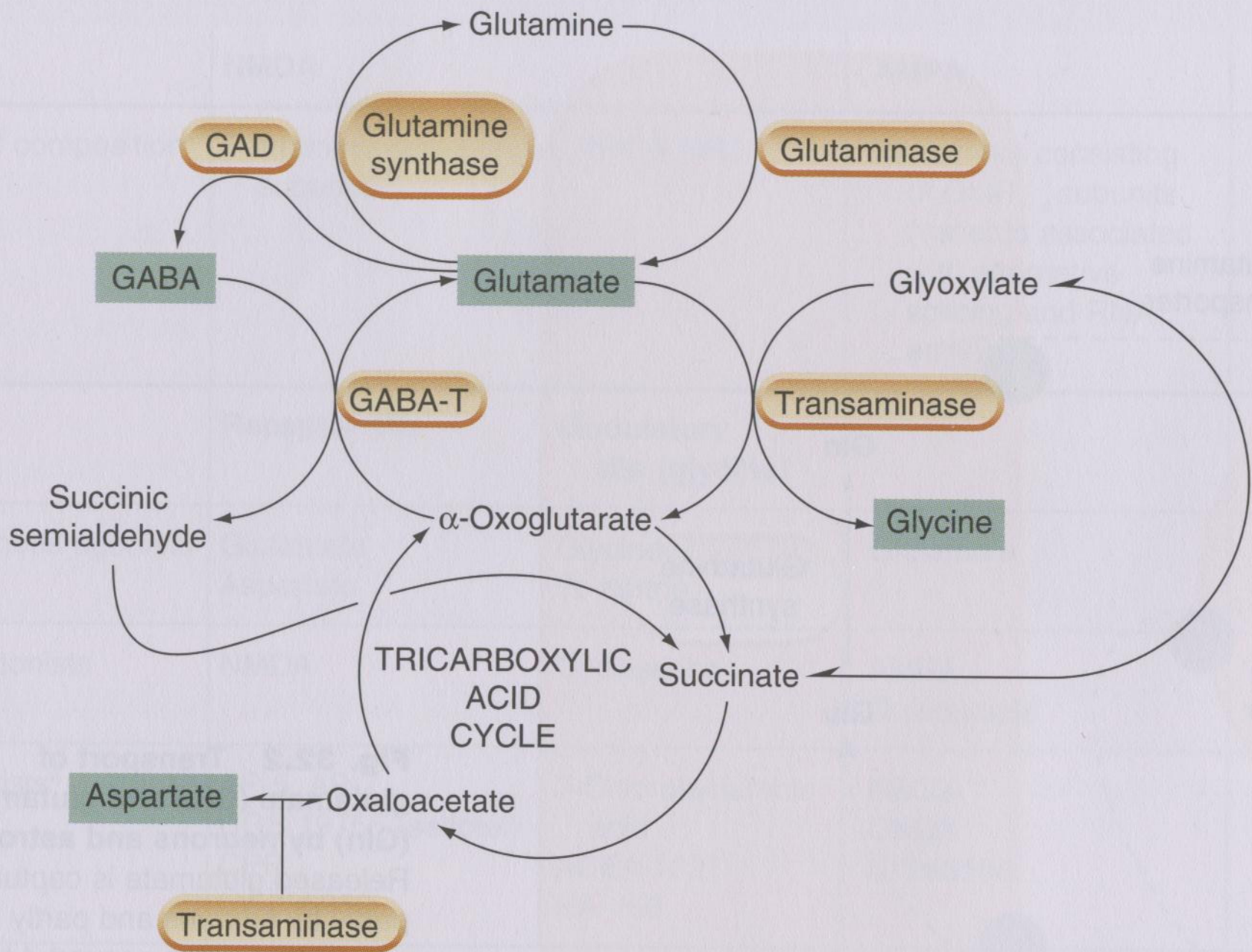
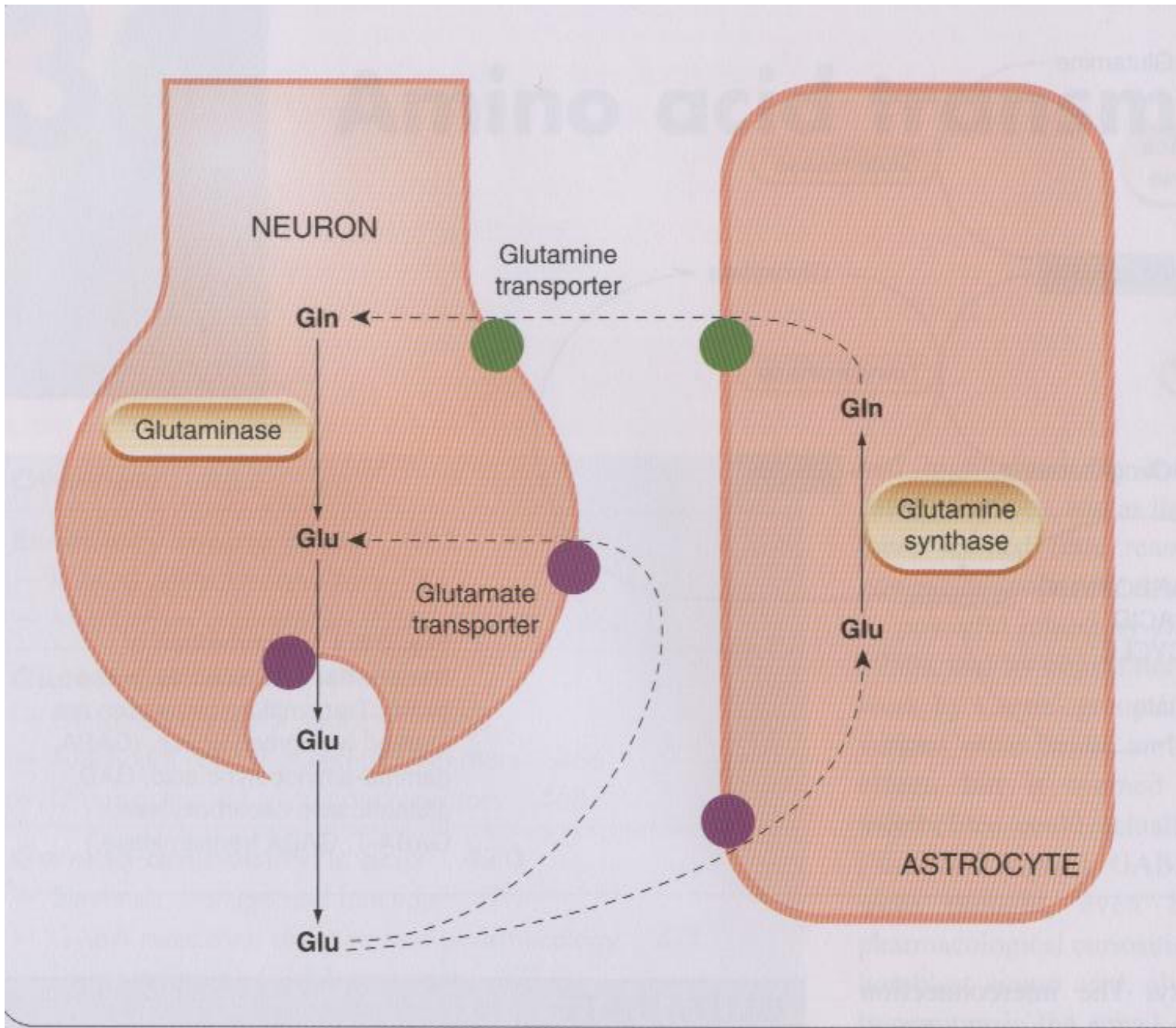


# Aminoácidos-neurotransmissores

|                     | EXCITATORY  | INHIBITORY  |
|---------------------|---|---|
| TRANSMITTERS        | <br>Glutamate <br>Aspartate  | <br>GABA <br>Glycine      |
| SYNTHETIC ANALOGUES | <br>NMDA <br>AMPA <br>Kainate | <br>Muscimol <br>Baclofen |

**Fig. 29.2** Structures of agonists acting on glutamate, GABA and glycine receptors. The receptor specificity of these compounds is shown in Tables 29.1 and 29.2.

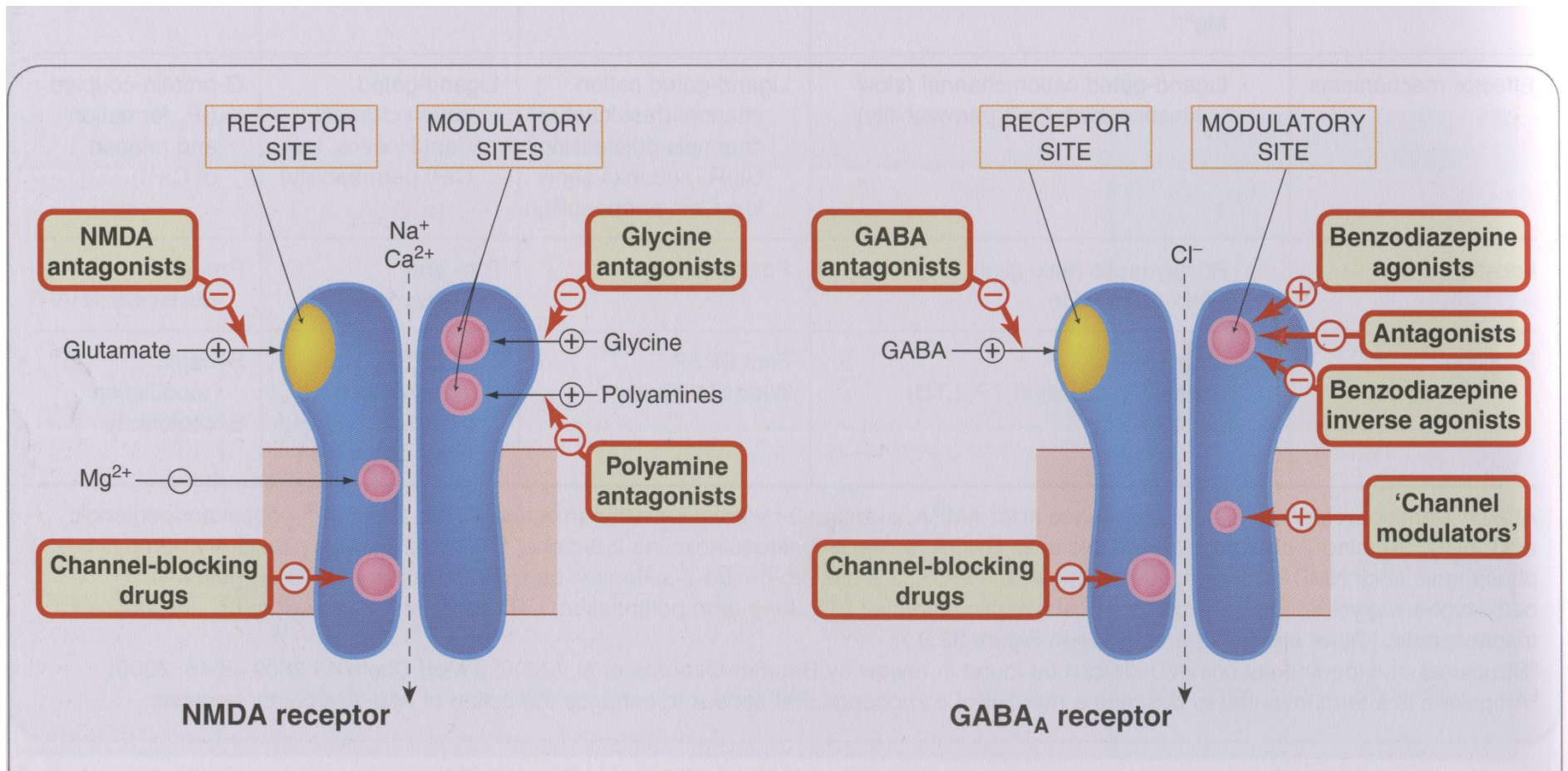




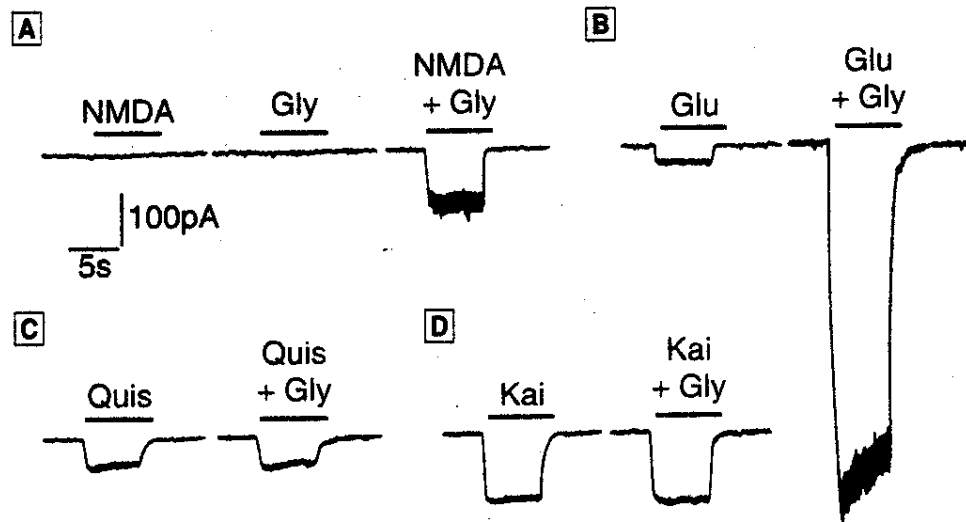


|                          | <b>NMDA</b>   |   | <b>AMPA</b>  | <b>Kainate</b>   | <b>Metabotropic</b>  |
|--------------------------|---|---|--|--|--|
| Subunit composition      | Pentamers consisting of NR1 & NR2 subunits  |   | Pentamers consisting of GluR <sub>1-4</sub> subunits (variants associated with alternative splicing and RNA editing)               | Pentamers consisting of GluR <sub>5-7</sub> subunits, plus KA 1-2              | Monomeric GPCRs  |
|                          | <b>Receptor site</b>  | <b>Modulatory site (glycine)</b>              |  |  |  |
| Endogenous agonists      | Glutamate<br>Aspartate  | Glycine,<br>D-serine                          | Glutamate  | Glutamate  | Glutamate  |
| Other agonists           | NMDA  | Cycloserine                                   | AMPA<br>Quisqualate  | Kainate<br>Domoate   | D-AP4,<br>ACPD   |
| Antagonists <sup>a</sup> | AP-5, AP-7<br>CGS 19755 (selfotel)<br>CPP<br>LY 235959  | 7-Chlorokynurenic acid<br>ACEA 1021<br>HA-466 | NBQX<br>CNQX<br>LY293558   | NBQX<br>LY 377770  | MCPG   |
| Other modulators         | Polyamines (e.g. spermine, spermidine)<br>Mg <sup>2+</sup> , Zn <sup>2+</sup>                             |   | Cyclothiazide,<br>Aniracetam,<br>Ampakines <sup>b</sup>  | –  | –  |
| Channel blockers         | Dizocilpine (MK801)<br>Phencyclidine<br>Ketamine<br>Dextromethorphan<br>Mg <sup>2+</sup> <b>Memantina</b> |   | –  | –  | Not applicable   |
| Effector mechanisms      | Ligand-gated cation channel (slow kinetics, high Ca <sup>2+</sup> permeability)                           |   | Ligand-gated cation channel (fast kinetics; channels possessing GluR <sub>2</sub> subunits show low Ca <sup>2+</sup> permeability) | Ligand-gated cation channel (fast kinetics, low Ca <sup>2+</sup> permeability) | G-protein-coupled (IP <sub>3</sub> formation and release of Ca <sup>2+</sup> ) |
| Location                 | Postsynaptic (also glial)<br>Wide distribution  |   | Postsynaptic   | Pre- and postsynaptic  | Pre- and postsynaptic  |
| Function                 | Slow EPSP<br>Synaptic plasticity (LTP, LTD)<br>Excitotoxicity   |   | Fast EPSP<br>Wide distribution   | Fast EPSP<br>?presynaptic inhibition<br>Limited distribution                   | Synaptic modulation<br>Excitotoxicity  |





# Potenciação da resposta ao glutamato pela glicina

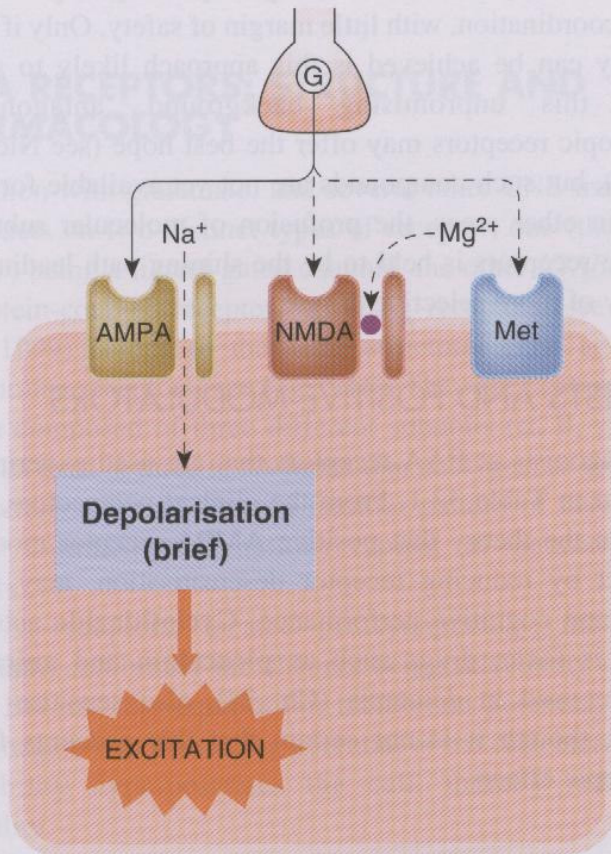


**Fig. 29.3 Facilitation of NMDA by glycine.** Recordings from mouse brain neurons in culture (whole patch-clamp technique). Downward deflections represent inward current through EAA-activated ion channels. **A** NMDA (10  $\mu\text{mol/l}$ ) or glycine (1  $\mu\text{mol/l}$ ) applied separately had little or no effect, but together produced a response. **B** The response to glutamate (10  $\mu\text{mol/l}$ , Glu) was strongly potentiated by glycine (1  $\mu\text{mol/l}$ , Gly). **C** and **D** Responses of AMPA and kainate receptors to quisqualate (Quis) and kainate (Kai) were unaffected by glycine. (From: Johnson J W, Ascher P 1987 Nature 325: 529–531)



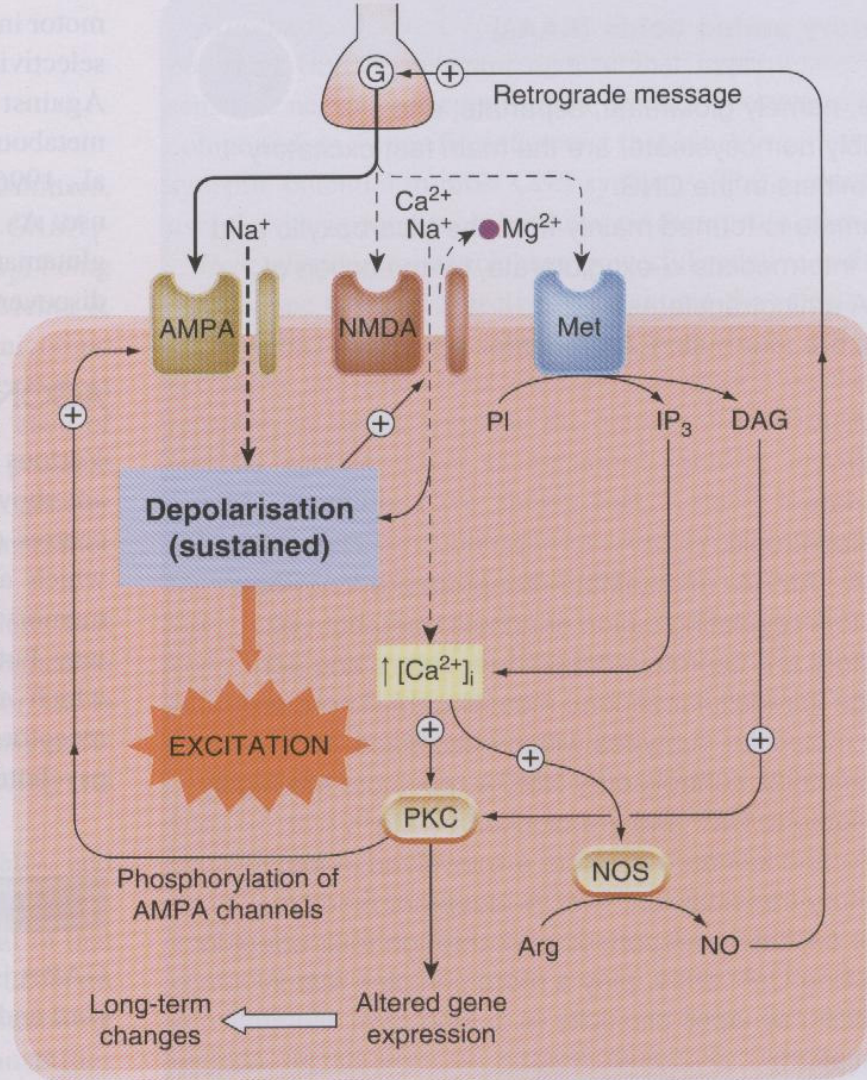
**A Normal transmission**

- AMPA receptors only activated



**B After conditioning train**

- AMPA, NMDA, metabotropic receptors activated
- Increased  $[\text{Ca}^{2+}]_i$
- Activation of PKC and NOS



## **Receptores NMDA**

Plasticidade sináptica e LTP (“long-term potentiation)

Excitotoxicidade



## Glutamato

Fármacos actualmente disponíveis para terapêutica médica

Tratamento da epilepsia:

Lamotrigina (inib. Lib. Glut.)

Felbamato (antag. NMDA)

Topiramato (antag. AMPA/Kainato)

Tratamento da Doença de Alzheimer:

Memantina (antag. NMDA)

## Glutamato e toxicodependência

### Fenciclidina (“pó de anjo”)

- Inicialmente utilizada como anestésico
- “Viagens más” ocasionalmente
- Episódios psicóticos recorrentes