- The history of GABA and Glutamate as neurotransmitters

- There are three criteria for a chemical to be classified as a neurotransmitter:

- It must be synthesized and stored in presynaptic terminals (Synthesis and storage of the chemical can be demonstrated with immunocytochemistry and in situ hybridization).

- It must be released from terminals upon stimulation (release of the chemical upon stimulation can be shown with a chemical assay).

- It must have specific receptors on the postsynaptic cells (The presence of the receptors can be demonstrated with neuropharmacological methods or autoradiography

The discovery of GABA as a neurotransmitter

GABA discovered in large quantities in the brain (Awapara et al, 1950, Roberts and Frankel, 1950 and Udenfriend, 1950). Thought to have metabolic function.

The crayfish stretch receptor is discovered (Alexandrowicz, 1951)

Kuffler and Florey decide that this is a good preparation to apply brain extracts to to try and discover neurotransmitters.

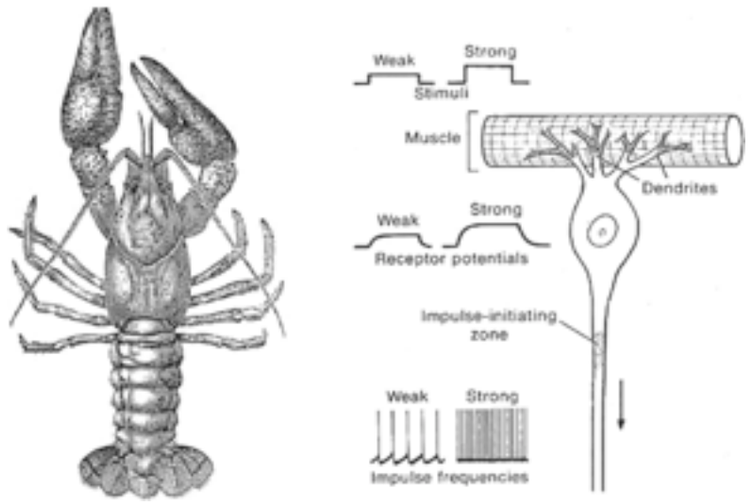
Discovered Factor I (I for inhibition) (Florey, 1954).

All known constituents of mammalian brain applied to the crayfish stretch receptor, and Factor I shown to be GABA.

Ernst Florey
(Salzburg 1927 – Konstanz 1997)

K. A. C. Elliott
(1903–1985)

Crayfish stretch receptor



The discovery of GABA as a neurotransmitter

Subsequently both GABA and synaptic inhibition were found to result in a selective increase in Cl- conductance.

High content of GABA in inhibitory axons shown (Kravitz et al., 1963)

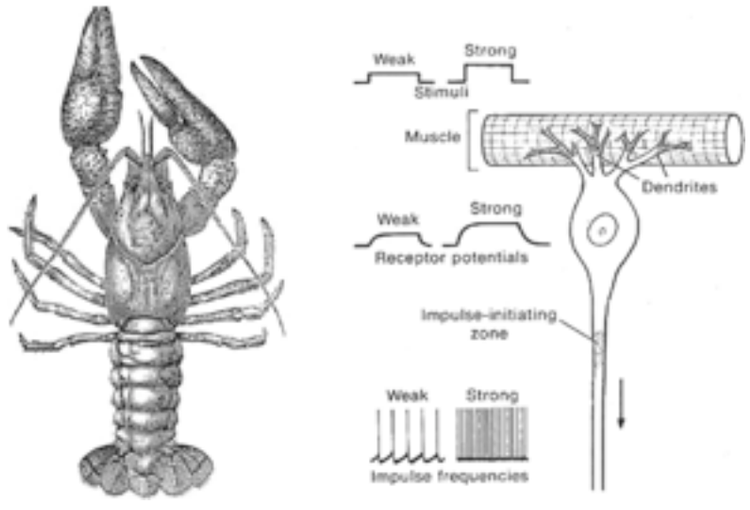
GABA shown to be selectively released (Otzuka et al., 1966)

Case is clear for GABA in crustaceans!

Ernst Florey
(Salzburg 1927 – Konstanz 1997)

K. A. C. Elliott
(1903–1985)

Crayfish stretch receptor



The discovery of GABA as a neurotransmitter

But...

Florey decided that GABA was not Factor I (Florey and McLennan., 1959 Florey and Chapman., 1961).

GABAs anticonvulsant action was considered to be an indirect effect (Hayashi et al., 1959 - with 125 collaborators)

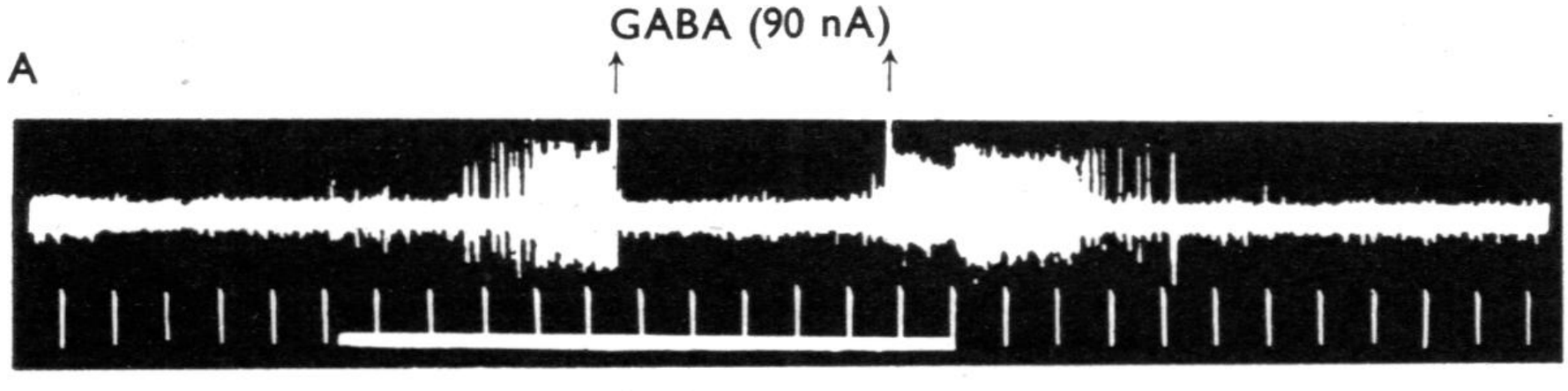
Tests of GABA on spinal neurons by microiontophoresis demonstrated strong inhibition of neuronal firing (Curtis et al., 1959), but because this was insensitive to strychnine and did not cause hyperpolarisation... was thought to be incompatible with a physiological role.

By the 1960s GABA was not considered a synaptic transmitter in the vertibrae CNS

Thought to be a potential modulator of excitability

The discovery of GABA as a neurotransmitter

But then...



Knrjevic and Phillis 1963

Iontophoretic application of GABA on cerebral neurons

The discovery of GABA as a neurotransmitter

GABA content of synaptoneurosomes sufficient to cause inhibition of cell (Krnjevic and Whittaker, 1965)

GABA released in the neocortex and the cerebellum (Jasper and Koyama 1969, Obata and Takeda 1969)

Inhibition could be blocked by picrotoxin and bicuculine (Galindo 1969, Curtis et al., 1970)

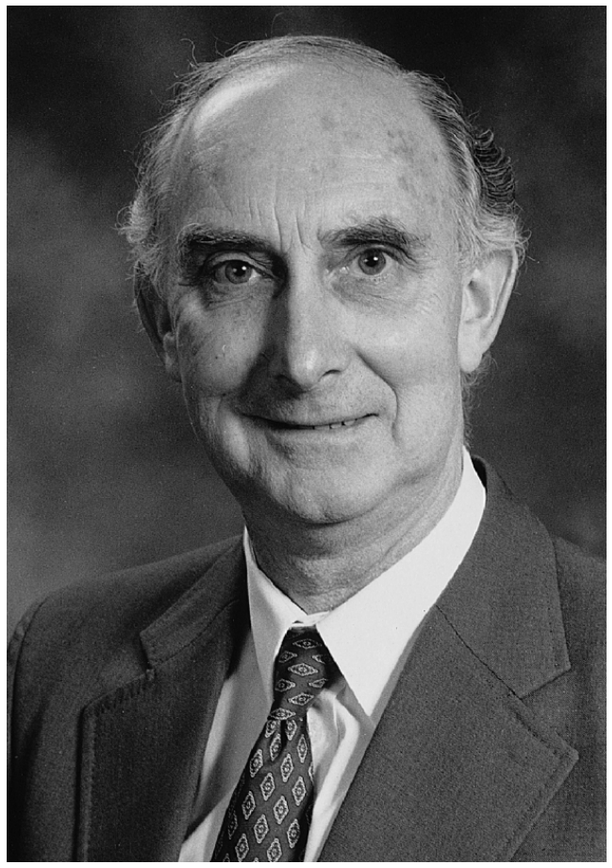
The discovery of Glutamate as a neurotransmitter

L-glutamate and L-aspartate found in high concentrations in the brain (Berl and Walsh, 1958)

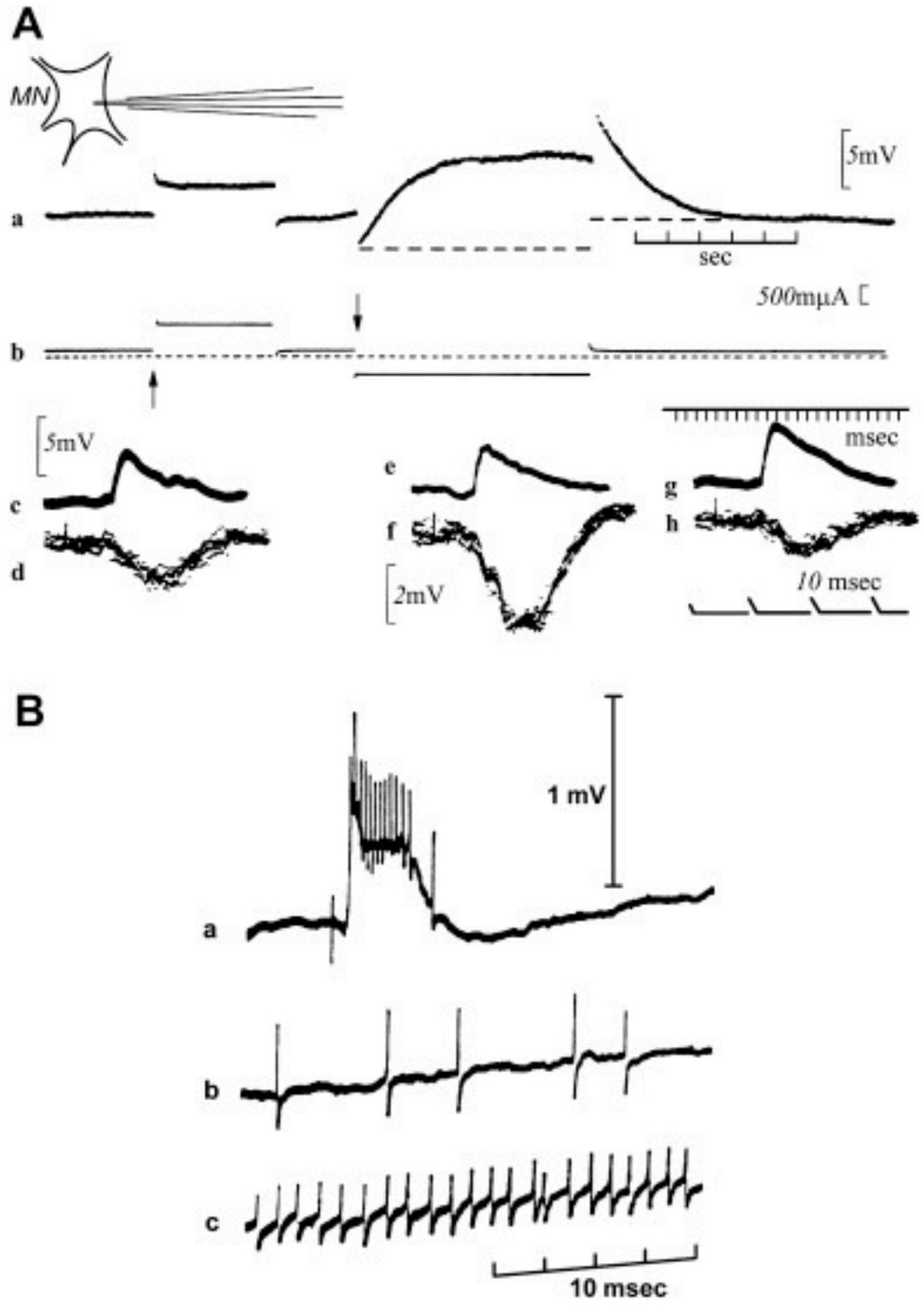
They produce convulsions when applied to cerebro-cortical surface (Hayashi, 1952, 1954)

Cause depolarisation of the crayfish stretch receptor (van Harreveld, 1959)

Glutamate excites central neurons



Jeff Watkins



Curtis et al, 1960 J. Physiol. 150, 656-682

IONOTROPIC GLUTAMATE RECEPTORS

Early studies identified two classes of glutamate receptor termed glutamate preferring and aspartate preferring

1962 - NMDA (N-methyl-D-aspartate) synthesised by Jeff Watkins

Discovery of quisqualate (a natural product) was followed by the naming of the two receptors: NMDA and quisqualate (or non-NMDA) receptors

Discovery of selective NMDA receptor antagonists soon followed:

D-α-aminoadipate (DαAA)

Mg^{2+} ions

2-amino-5-phosphonovalerate / D-2-amino-5-phosphonopentanoate (2APV or D-AP5)
(Davies et al, 1981 *Neurosci Lett*, 21, 77-81)

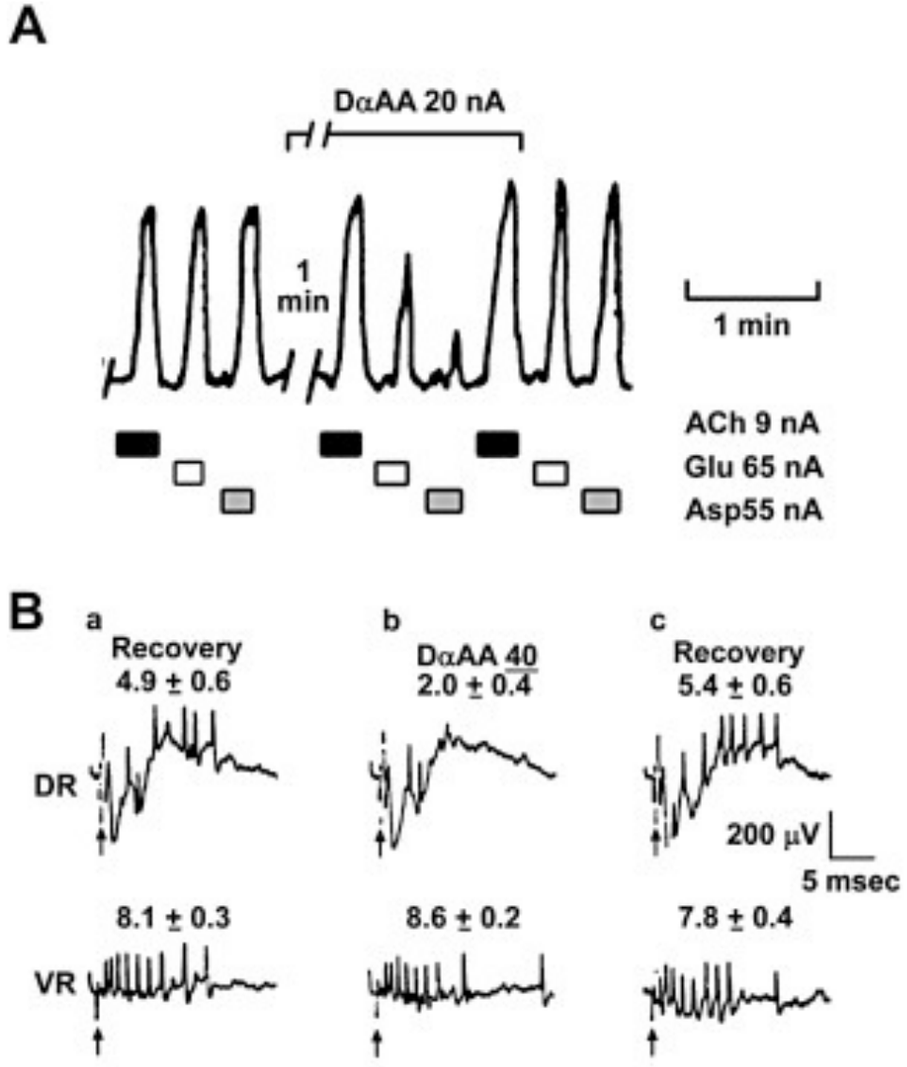
Ketamine & phencyclidine (PCP)

glycine-site antagonists

NMDA RECEPTORS

NMDARs mediate synaptic transmission

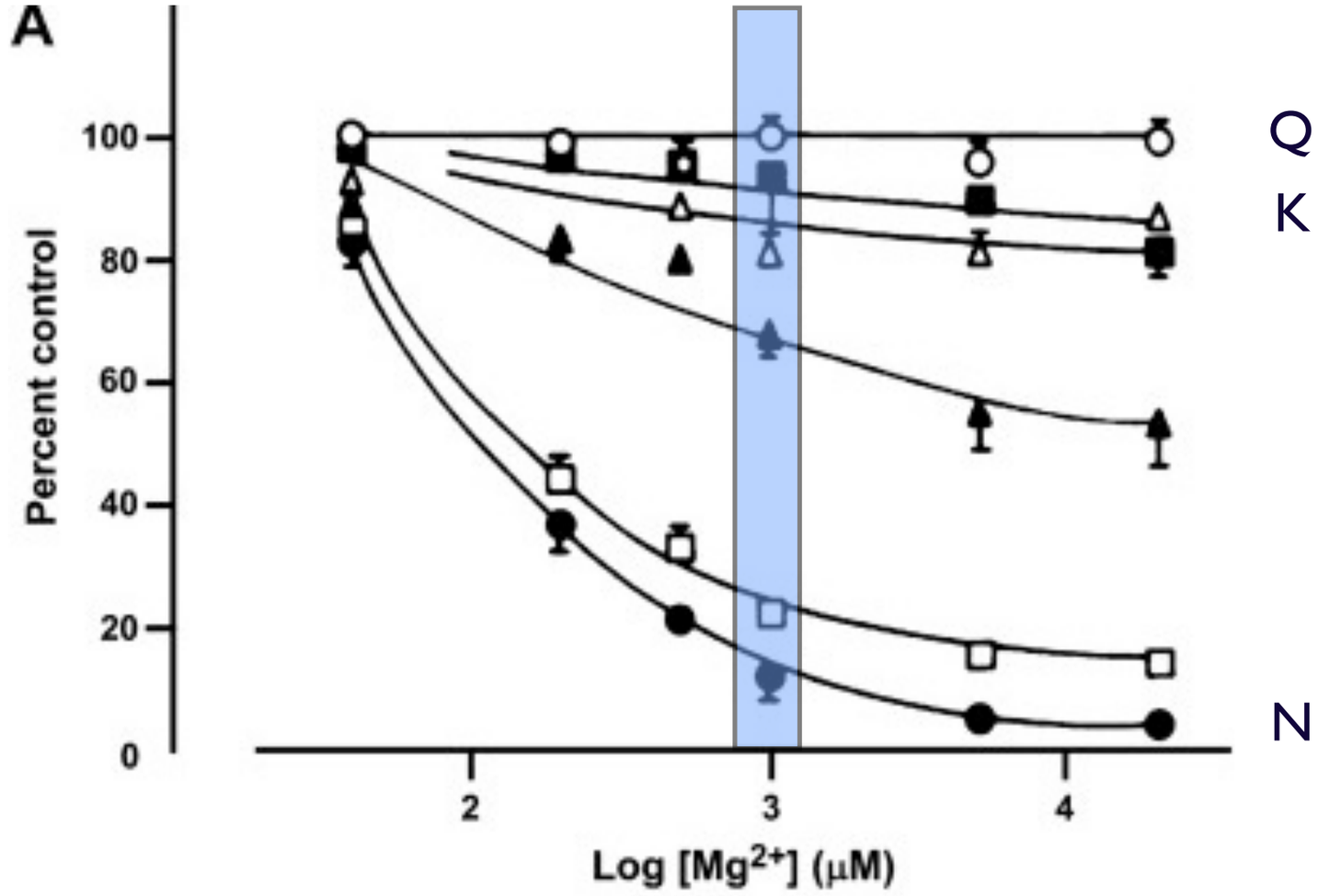
(first direct evidence that L-glutamate is an excitatory neurotransmitter)



Davies & Watkins, (1979) *J. Physiol.* 297, 621-636

NMDA RECEPTORS

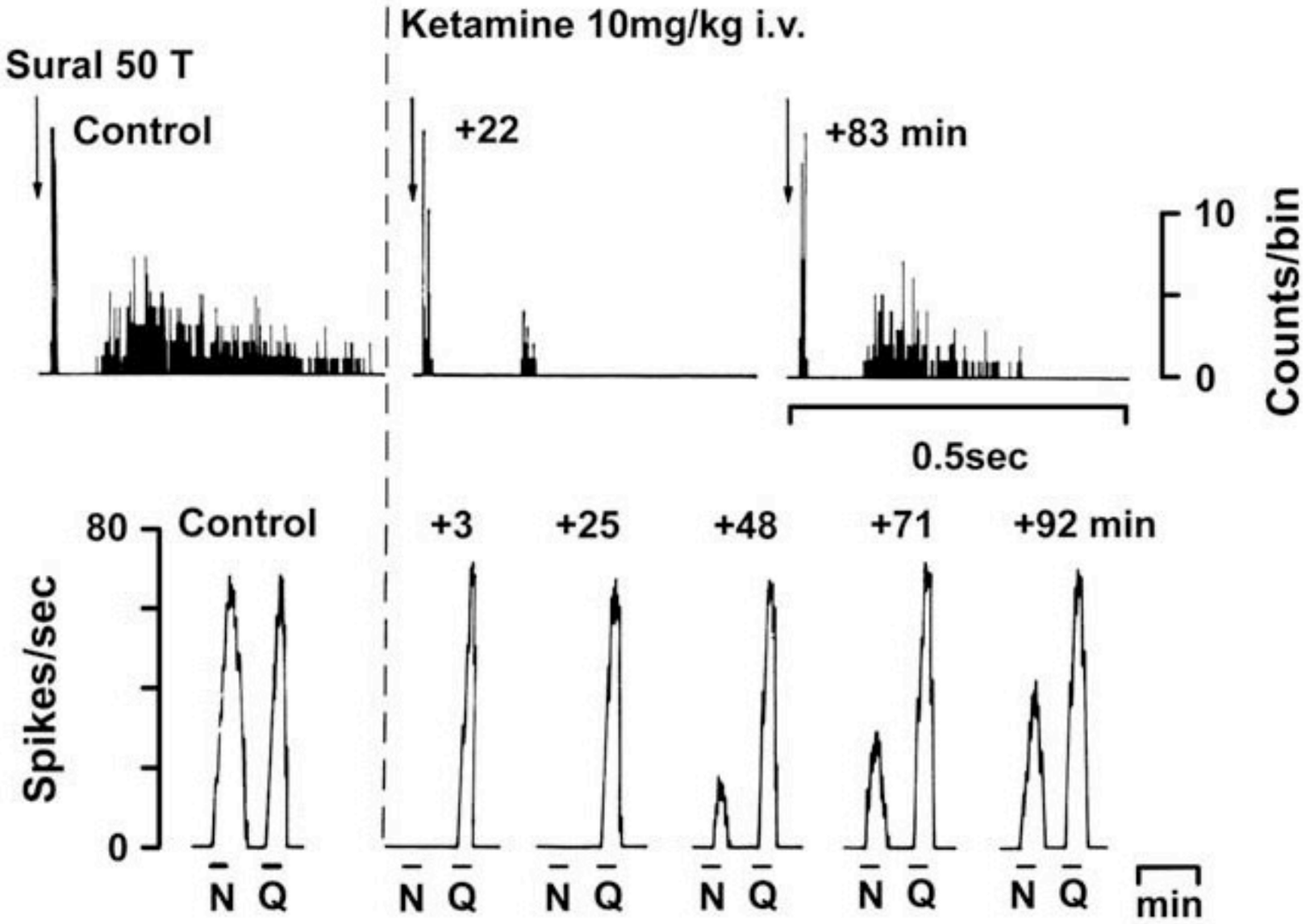
Mg^{2+} is a potent, selective NMDA antagonist



Ault et al, (1980) *J. Physiol.* 307, 413-428

NMDA RECEPTORS

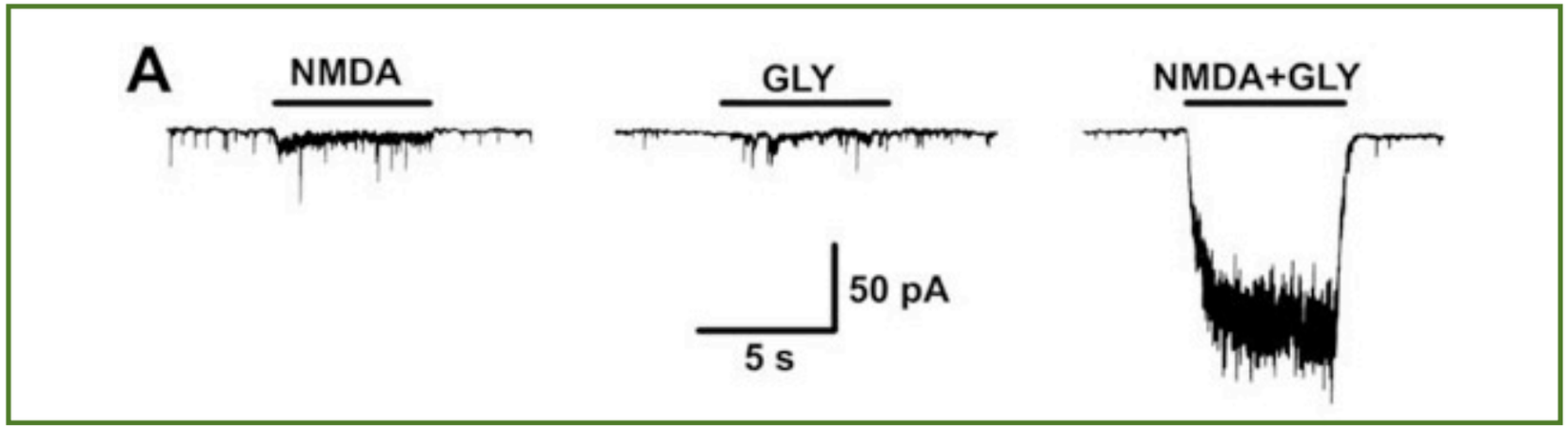
Dissociative anaesthetics (ketamine, phencyclidine etc) are selective NMDAR antagonists

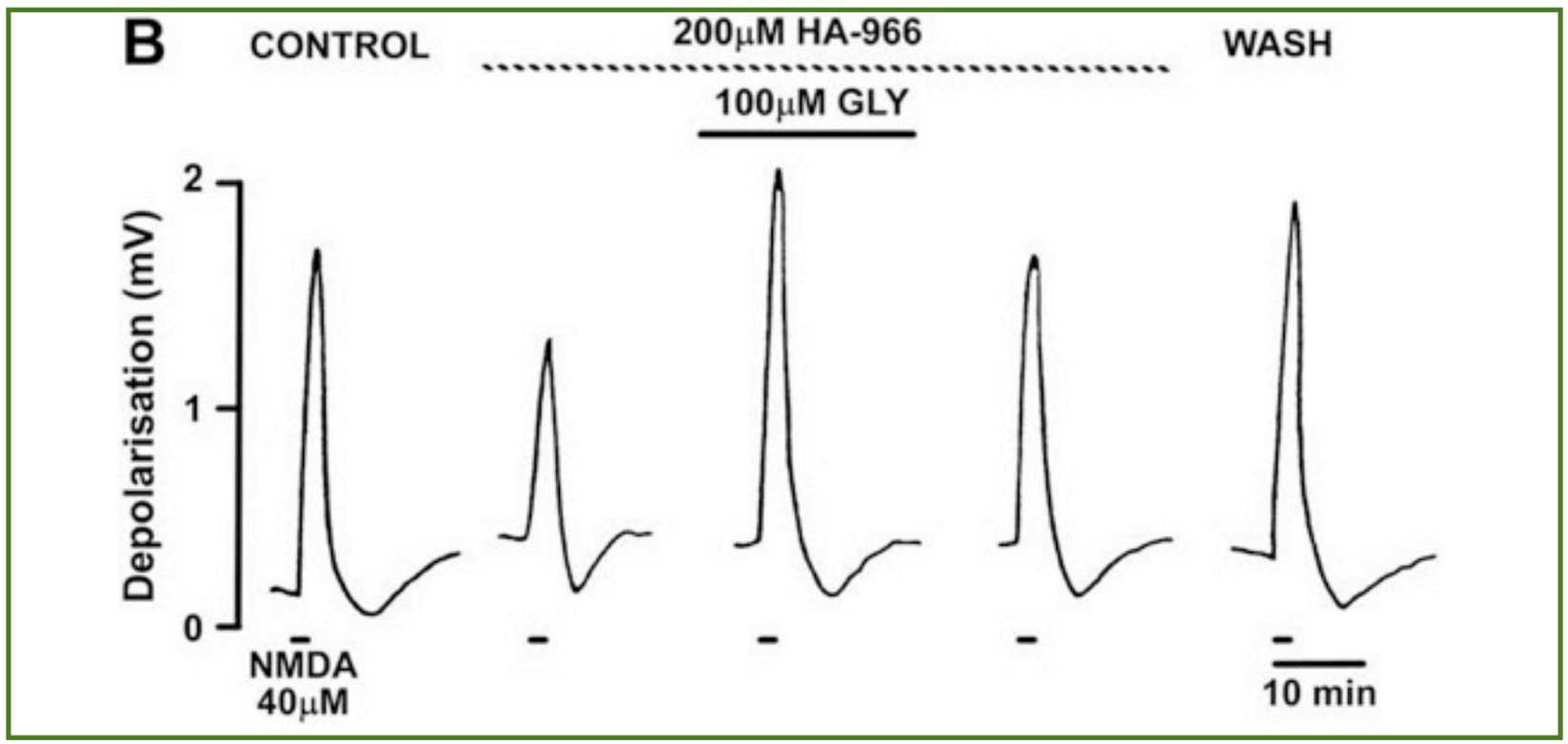


Anis et al, (1983) *Br J Pharmacol.* 79, 565-575

NMDA RECEPTORS

Discovery of the glycine co-agonist site and glycine site antagonists





Johnson & Ascher, (1987) *Nature.* 325, 529-531

Fletcher & Lodge (1988) Eur J Pharmacol 151, 161-162

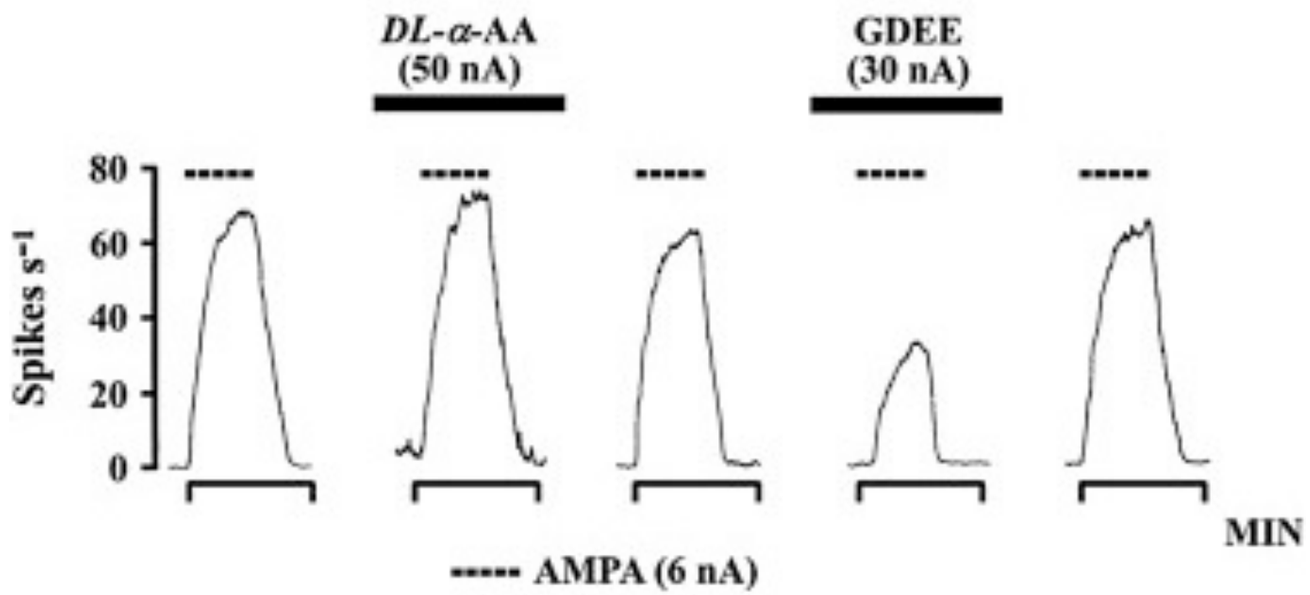
AMPA RECEPTORS

AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) was synthesised.

Quisqualate receptor renamed the AMPA receptor

AMPA RECEPTORS

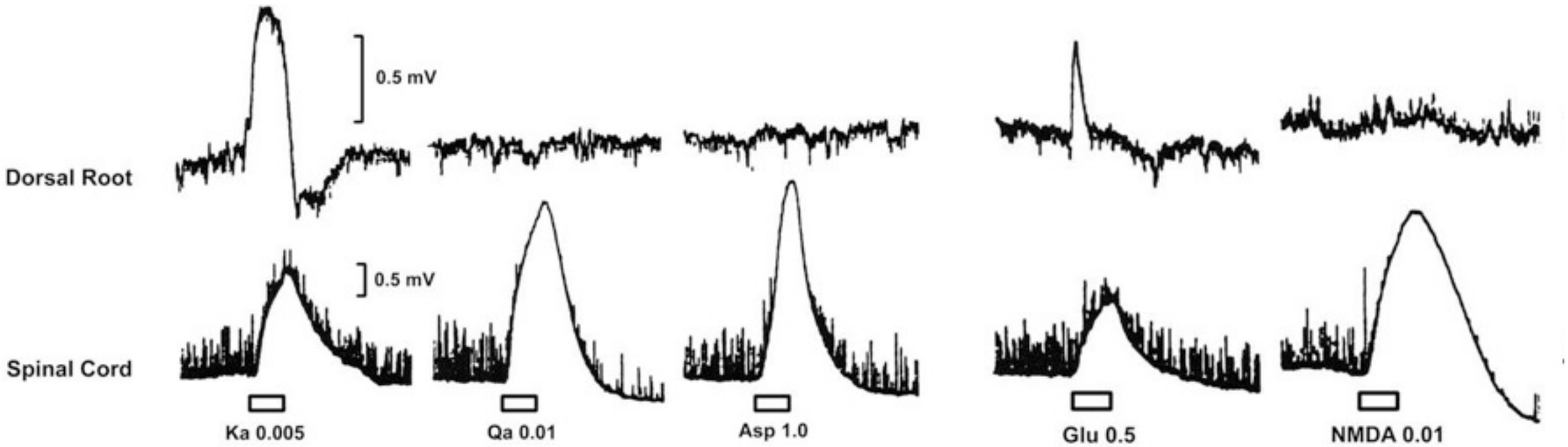
AMPA excites central neurons



Krogsgaard-Larsen et al, (1980) *Nature*. 284, 64-66

KA RECEPTORS

Direct evidence for kainate receptors: KA specifically depolarises dorsal routes.



Agrawal & Evans, (1986) *Br J Pharmacol.* 87, 345-355

AMPA RECEPTORS

First AMPAR antagonists developed

(e.g., GDEE, glutamate diethyl ester; DGG; γ-D-glutamylglycine)

Evidence that AMPARs mediate synaptic transmission

Discovery of quinoxalinediones (DNQX, CNQX, NBQX)

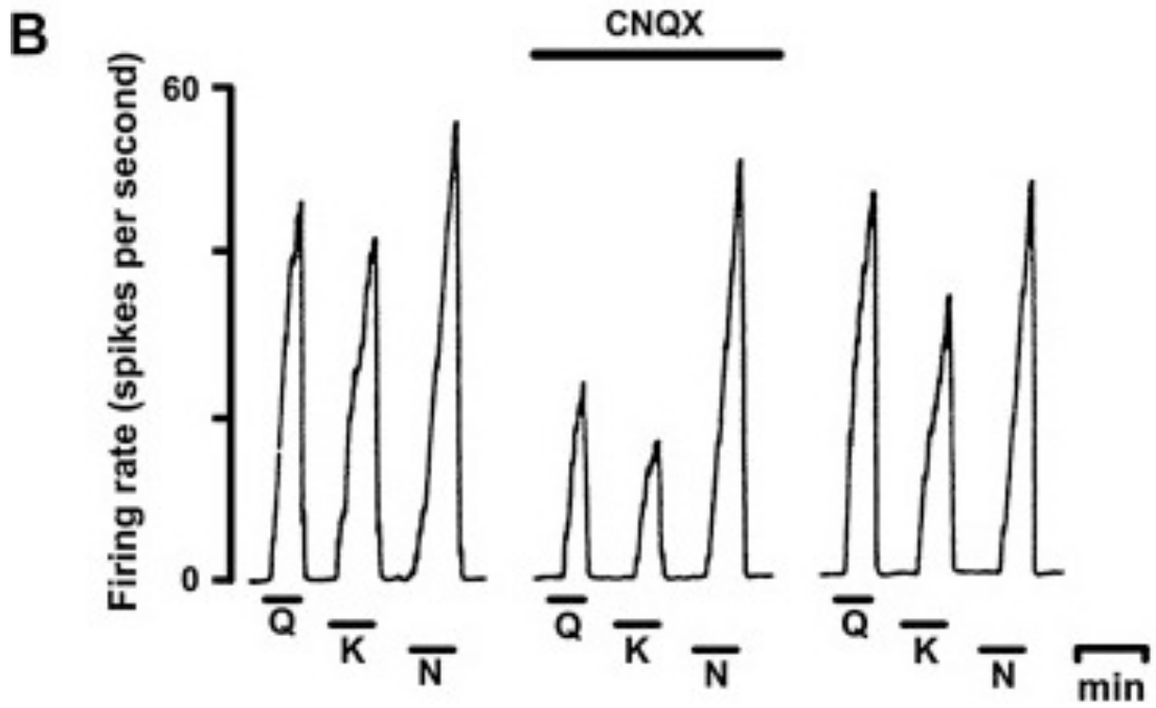
Ability to completely block AMPAR transmission but spare NMDAR transmission

Discovery of GYKI compounds (GYKI52466, GYKI53655)

Able to block AMPAR but spare kainate receptor transmission

AMPA RECEPTORS

Quinoxalinediones selectively antagonise AMPARs and KARs



Honore et al, (1988) *Science*. 241, 701-703

DNQX (6,7-dinitroquinoxaline-2,3-dione)

CNQX (6,cyano-7-nitroquinoxaline-2,3-dione)

NBQX (2,3-dihydroxy-6-nitro-7-sulphamoyl-benzo[f]qinoxaline-2,3-dione)

IONOTROPIC GLUTAMATE RECEPTORS

Receptors of major neurotransmitter in brain

Three main classes - AMPA, NMDA, kainate (KA)

Composed of four subunits

Subunit composition affects properties

METABOTROPIC GLUTAMATE RECEPTORS

Receptors of major neurotransmitter in brain

Eight subtypes, divided into three groups - I, II and III

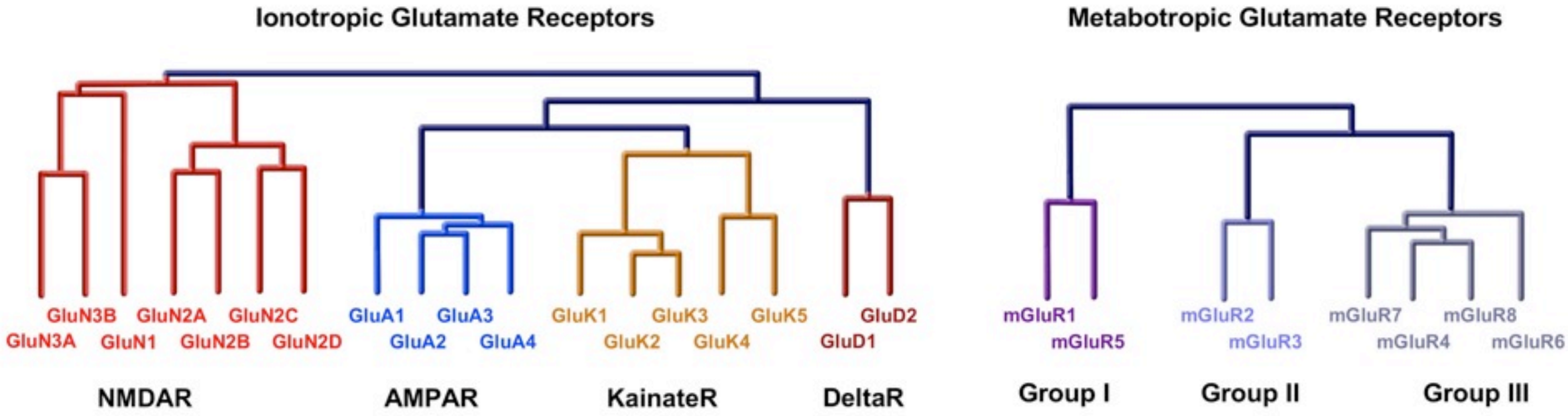
G-protein coupled receptors

Can be inhibitory as well as excitatory

IONOTROPIC GLUTAMATE RECEPTORS

Subunits share sequence homology - IUPHAR nomenclature

http://www.iuphar-db.org/nomenclature.html



IUPHAR nomenclature and previous nomenclature

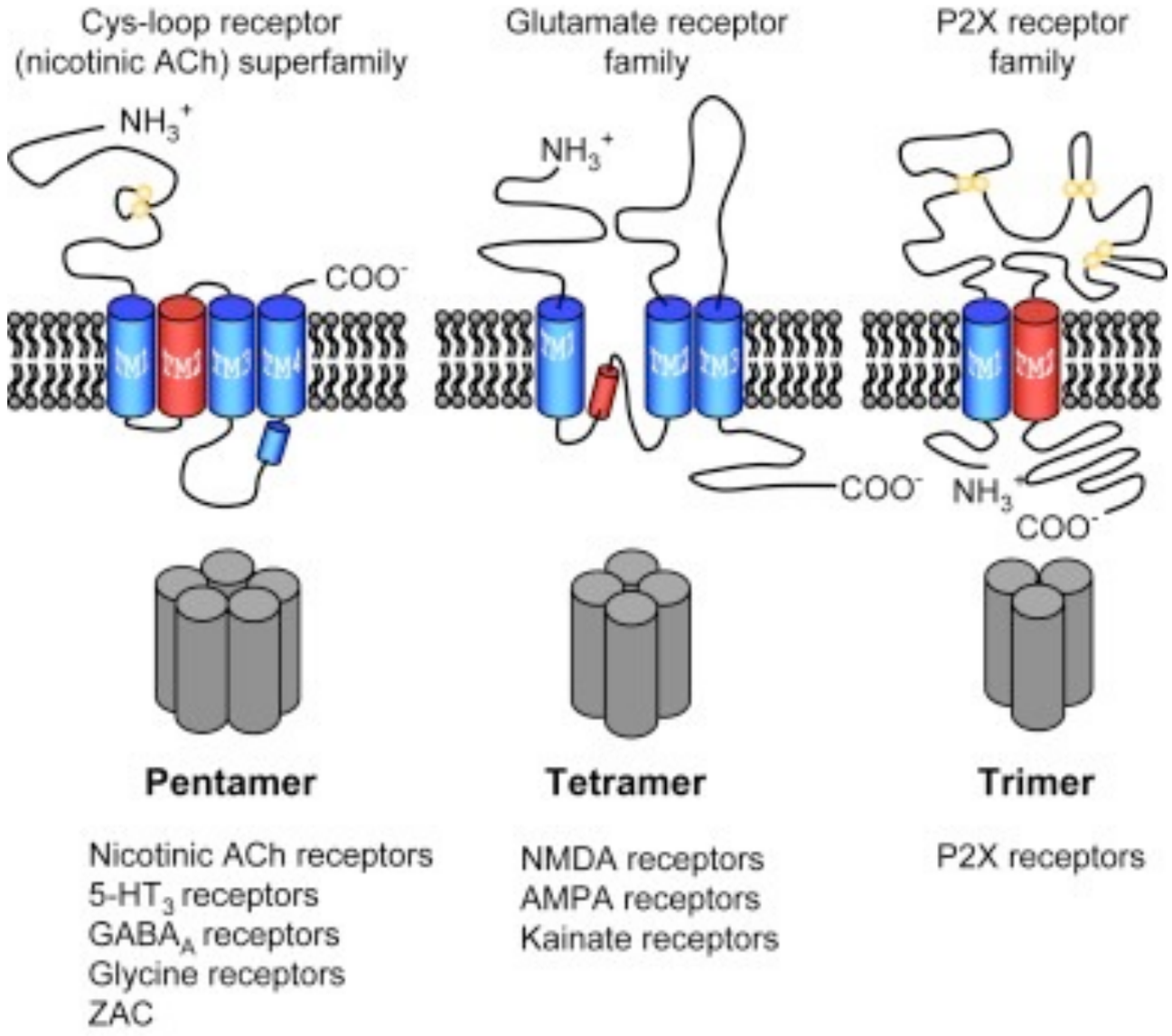
http://www.genenames.org/

Subunit	Gene	Old subunit names
GluA1	*GRIA1*	GLU_{A1}, GluR1, GluRA, GluR-A, GluR-K1, HBGR1
GluA2	*GRIA2*	GLU_{A2}, GluR2, GluRB, GluR-B, GluR-K2, HBGR2
GluA3	*GRIA3*	GLU_{A3}, GluR3, GluRC, GluR-C, GluR-K3
GluA4	*GRIA4*	GLU_{A4}, GluR4, GluRD, GluR-D
GluK1	*GRIK1*	GLU_{K5}, GluR5, GluR-5, EAA3
GluK2	*GRIK2*	GLU_{K6}, GluR6, GluR-6, EAA4
GluK3	*GRIK3*	GLU_{K7}, GluR7, GluR-7, EAA5
GluK4	*GRIK4*	GLU_{K1}, KA1, KA-1, EAA1
GluK5	*GRIK5*	GLU_{K2}, KA2, KA-2, EAA2
GluN1	*GRIN1*	GLU_{N1}, NMDA-R1, NR1, GluRξ1
GluN2A	*GRIN2A*	GLU_{N2A}, NMDA-R2A, NR2A, GluR1
GluN2B	*GRIN2B*	GLU_{N2B}, NMDA-R2B, NR2B, hNR3, GluR2
GluN2C	*GRIN2C*	GLU_{N2C}, NMDA-R2C, NR2C, GluR3
GluN2D	*GRIN2D*	GLU_{N2D}, NMDA-R2D, NR2D, GluR4
GluN3A	*GRIN3A*	GLU_{N3A}, NMDA-R3A, NMDAR-L, chi-1
GluN3B	*GRIN2B*	GLU_{N3B}, NMDA-R3B
GluD1	*GRID1*	GluRδ1
GluD2	*GRID2*	GluRδ2

Iu = *RI*

Collingridge et al, (2009) *Neuropharmacology*, 56, 2-5.

Schematic of the three structural categories of ligand-gated ion channel subunit.



All glutamate receptor subunits have the membrane topology of an extracellular N-terminus, three transmembrane domains (formed by M1, M3 and M4), a channel lining re-entrant ‘p-loop’ (M2) located between M1 and M3 that enters and exits the membrane at its cytoplasmic surface, and an intracellular C-terminus

Collingridge et al, (2009) *Neuropharmacology*, 56, 2-5.

Long term potentiation: the synaptic basis of memory

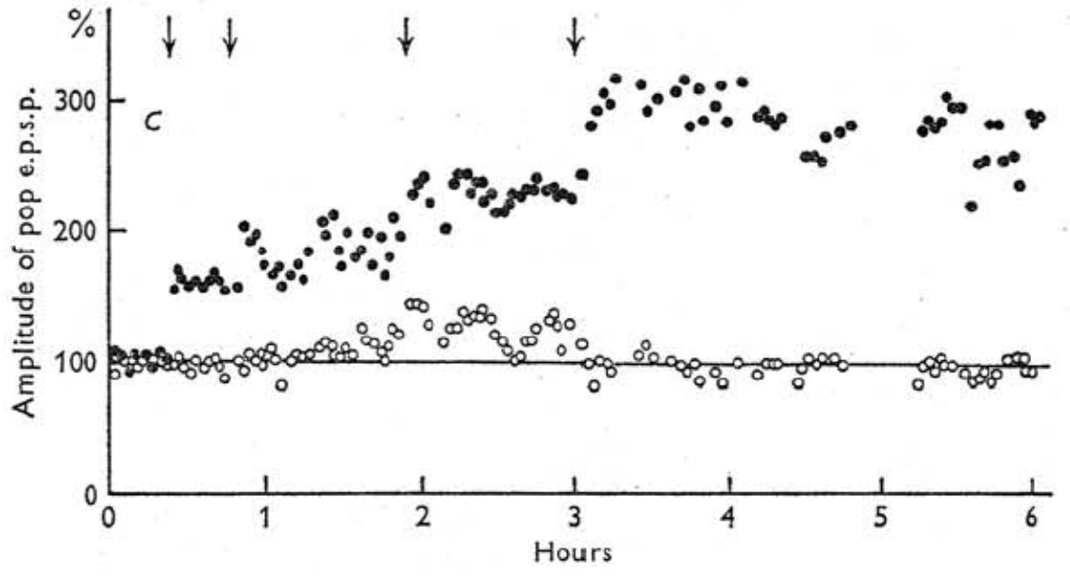
J. Physiol. (1973), **232**, *pp.* 331–356
With 12 text-figures
Printed in Great Britain

LONG-LASTING POTENTIATION OF SYNAPTIC TRANSMISSION IN THE DENTATE AREA OF THE ANAESTHETIZED RABBIT FOLLOWING STIMULATION OF THE PERFORANT PATH

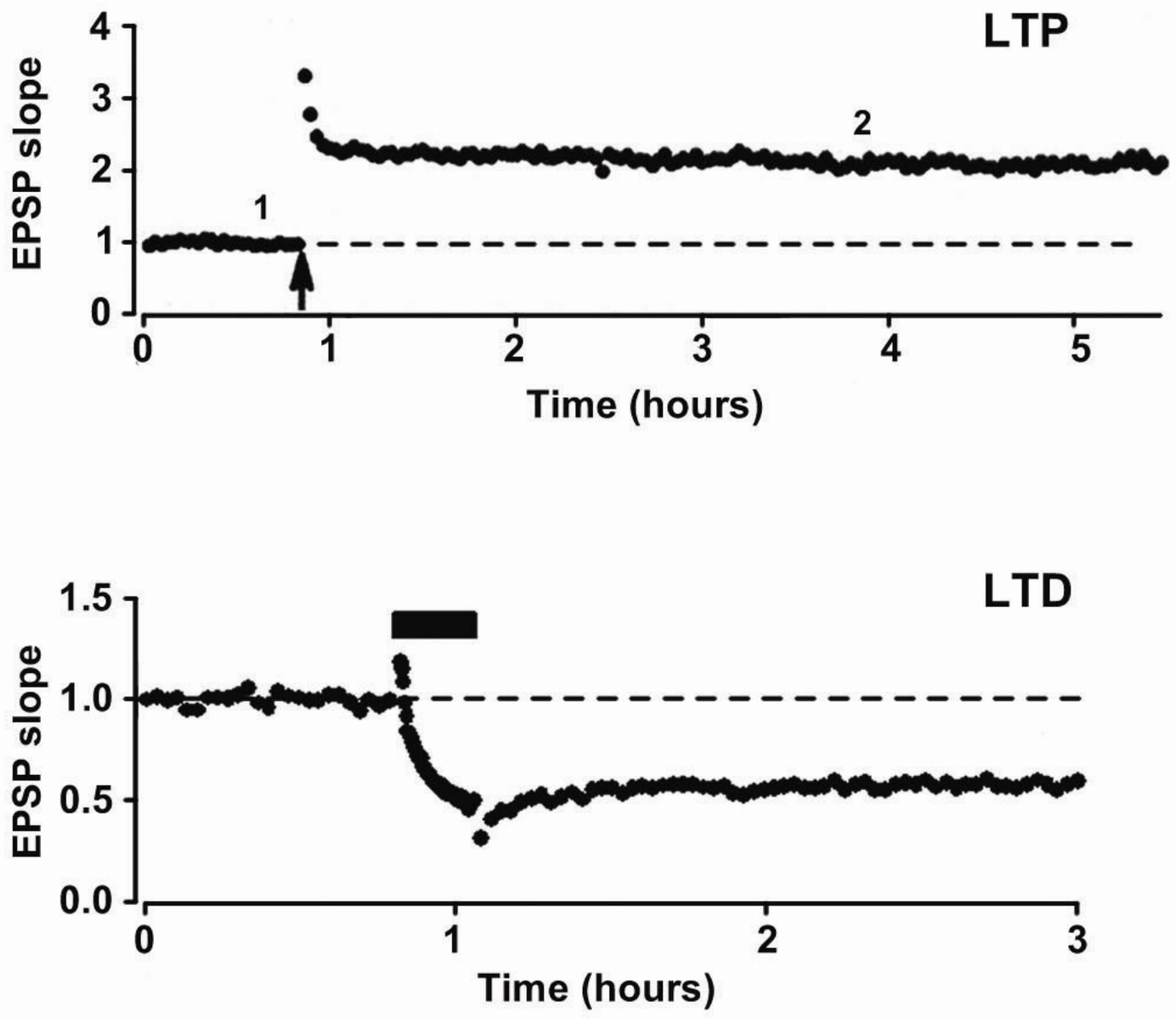
By T. V. P. BLISS and T. LØMO

From the National Institute for Medical Research, Mill Hill, London NW7 1AA and the Institute of Neurophysiology, University of Oslo, Norway

(*Received 12 February 1973*)



Bi-directional synaptic plasticity: LTP and LTD



READING

GABA

Bowery and Smart, (2006) *British Journal of Pharmacology* 147, S109-S119.

Krnjevic (2004) *Biochemical Pharmacology,* 68, 1549-1555.

Glutamate

Collingridge et al, (2009) *Neuropharmacology*, 56, 2-5.

Lodge (2009) *Neuropharmacology,* 56, 6-21.