Introductory lecture and student registration

Glutamate Receptors and Synaptic Plasticity

Aims and Scope

To understand the basic functioning of glutamatergic synapses in the brain, with a special emphasis on the properties of glutamate receptors

To understand the primary mechanisms of synaptic plasticity, especially long-term potentiation (LTP) and long-term depression (LTD)

Glutamate Receptors and Synaptic Plasticity

The main goal of this course is to provide more specialised background information that is necessary for graduate students to pursue various cellular and molecular neuroscience projects in the Department of Brain and Cognitive Sciences (BCS). This course will run in parallel with, but will build upon, the core course that will introduce the fundamental principles of the nervous system.

The course will start with a description of the glutamate receptor subtypes and how glutamate synapses operate in the brain. This will pave the way for a detailed discussion of the mechanisms of synaptic plasticity, in particular long-term potentiation (LTP) and long-term depression (LTD) in various brain regions. The relevance of synaptic plasticity for learning & memory will be described. In addition, how synaptic plasticity is being studied in the context of experimental models of neurological and psychiatric disorders will also be discussed.

Glutamate Receptors and Synaptic Plasticity

Most seminars will last 2-3 hours and will typically be divided into two blocks of teaching of approximately 1 hour each, with a coffee break in between. There will be two types of "seminars". Each topic will start with didactic teaching to introduce the subject. Students will then have time to prepare for their presentations. Student presentations will involve presenting a recent research publication (journal club style). Towards the end of the course students will be divided into teams to write a grant application.

This course will enable the students to engage in self-directed learning. It will involve research, team work and verbal presentations.

Reading materials:

General reading: Neuroscience: Exploring the Brain (3rd Edition, by Mark Bear, Barry Connors, and Michael Paradiso)
(Each seminar will have specific additional reading material)

Grading criteria:
Attendance (10%)
In-class attitude & class participation (15%)
Journal club presentations (25%)
Project (50%)
total (100%)

Glutamate Receptors and Synaptic Plasticity

Week 1 (Sep 7):		
Lecture 1:	Introduction to the Course	Graham Collingridge
Lecture 2:	History of iGluRs.	Graham Collingridge
Week 2 (Sep 14):		
Lecture 3	AMPA & NMDA receptors.	Graham Collingridge
Lecture 4	Kainate receptors	
Week 3 (Sep 21):	Thanksgiving	
No Class		
Week 4 (Sep 28):	Preparation time:	
Week 5 (Oct 5):	Journal Club on iGluRs.	

Glutamate Receptors and Synaptic Plasticity

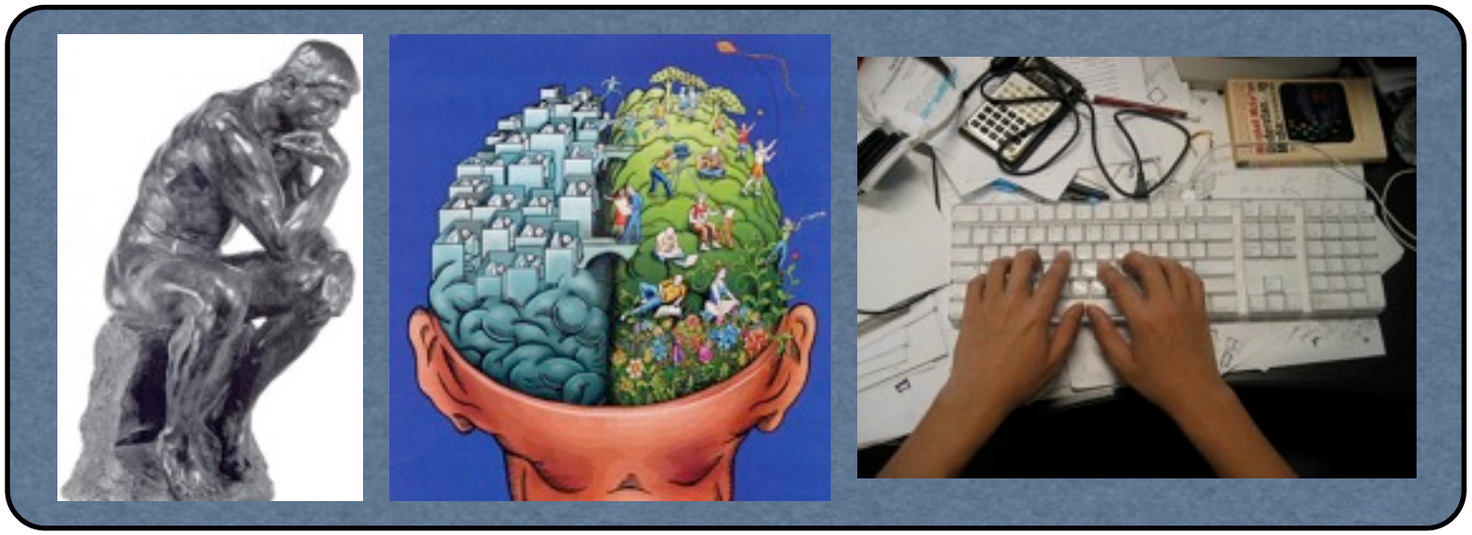
Week 6 (Oct 8):	Journal Club on iGluRs	
Week 7 (Oct 19):		
Lecture 5:	LTP in the hippocampus 1	Tim Bliss
Lecture 6;	LTP in the hippocampus 11	Graham Collingridge
Week 8 (Oct 26):		
	The LTP debate	
Week 9 (Nov 2):		
Lecture 7:	LTD in the hippocampus 1	Graham Collingridge
Lecture 8:	LTD in the hippocampus 2	Graham Collingridge
Week 10 (Nov 9):	Journal Club on LTD	

Glutamate Receptors and Synaptic Plasticity

Week 11 (Nov 16) Journal Club on LTD

Week 12 (Nov 23) Select and discuss research proposal

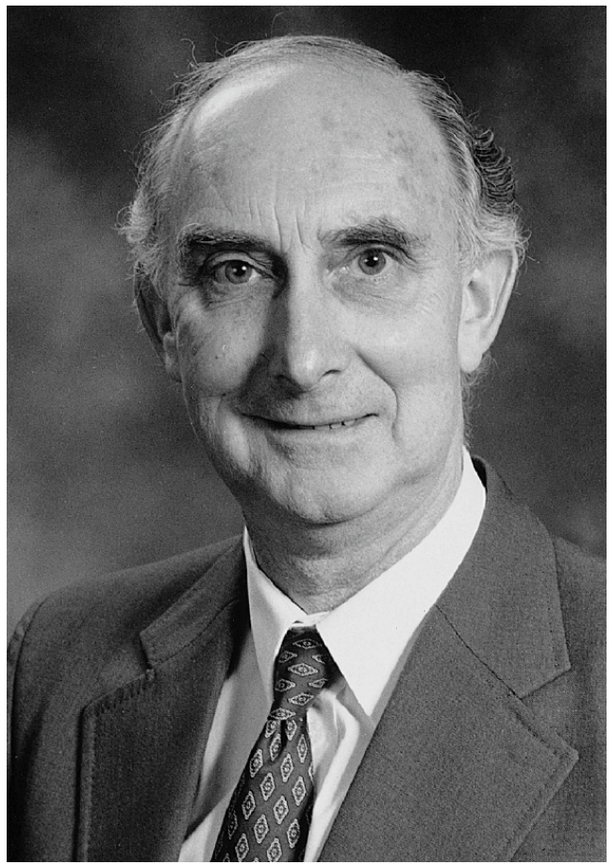
Week 13 (Nov 30) Prepare research proposal
Project



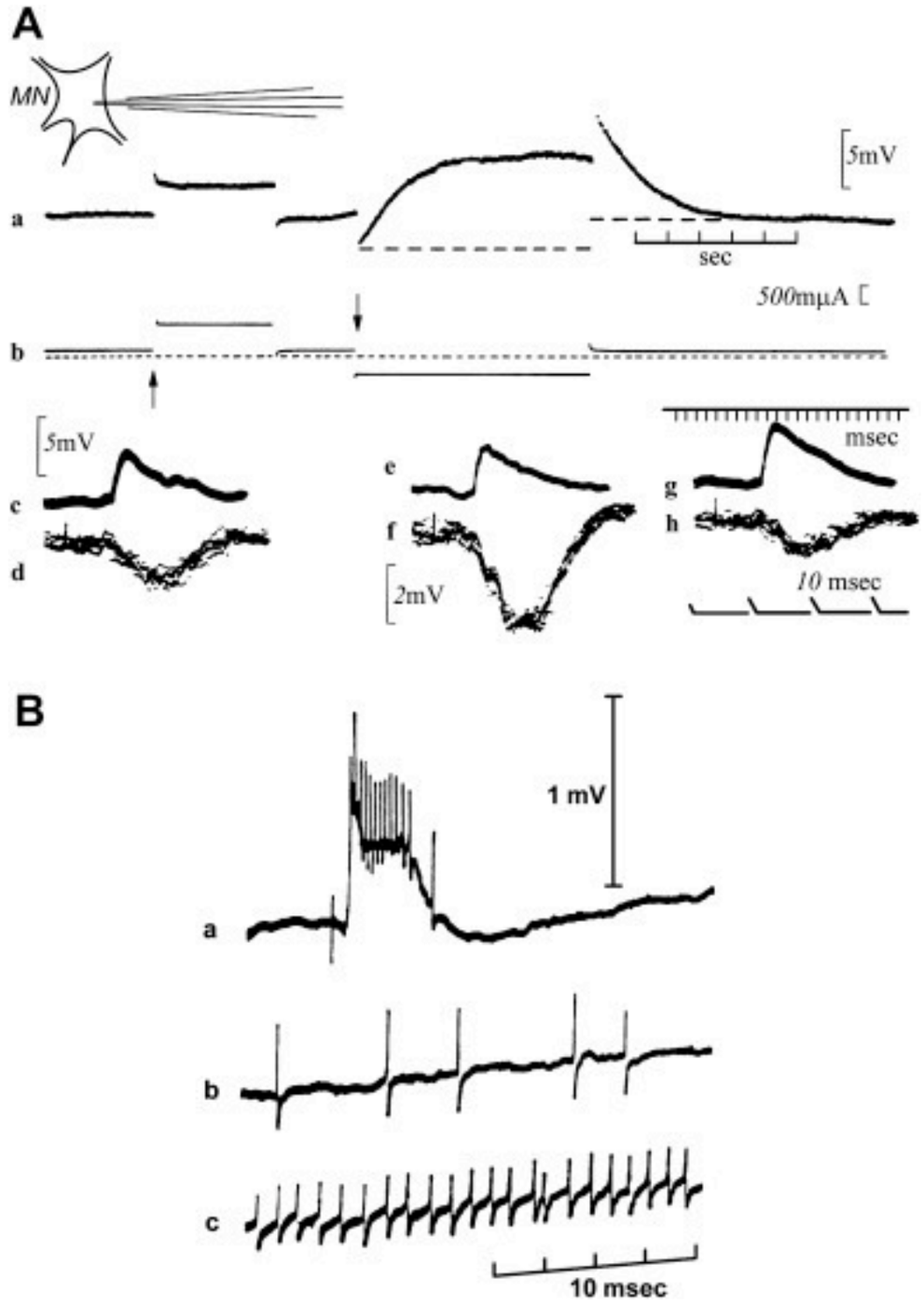
Week 14 (Dec 7)
Project presentations

Week 15 (Dec 14)
Feedback on research presentations, course marks and feedback.

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)

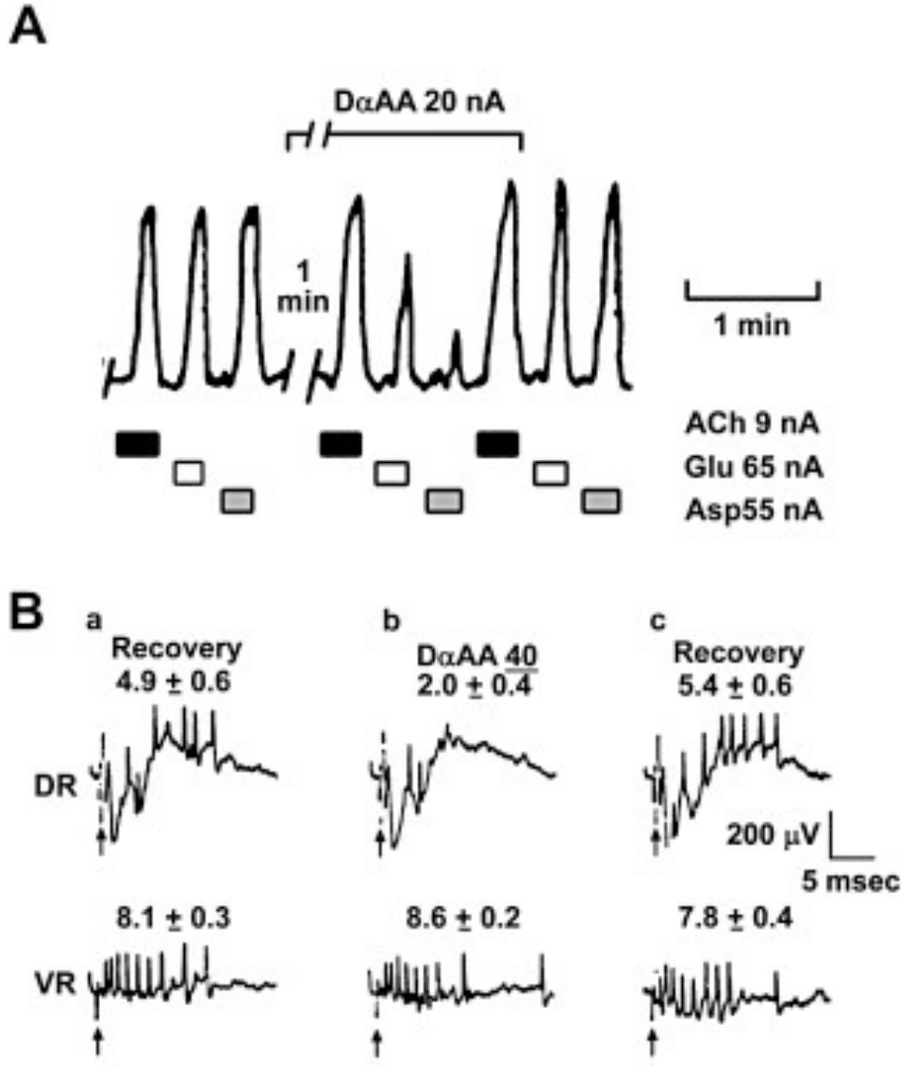
Ketamine & phencyclidine (PCP)

glycine-site antagonists

NMDA RECEPTORS

NMDARs mediate synaptic transmission

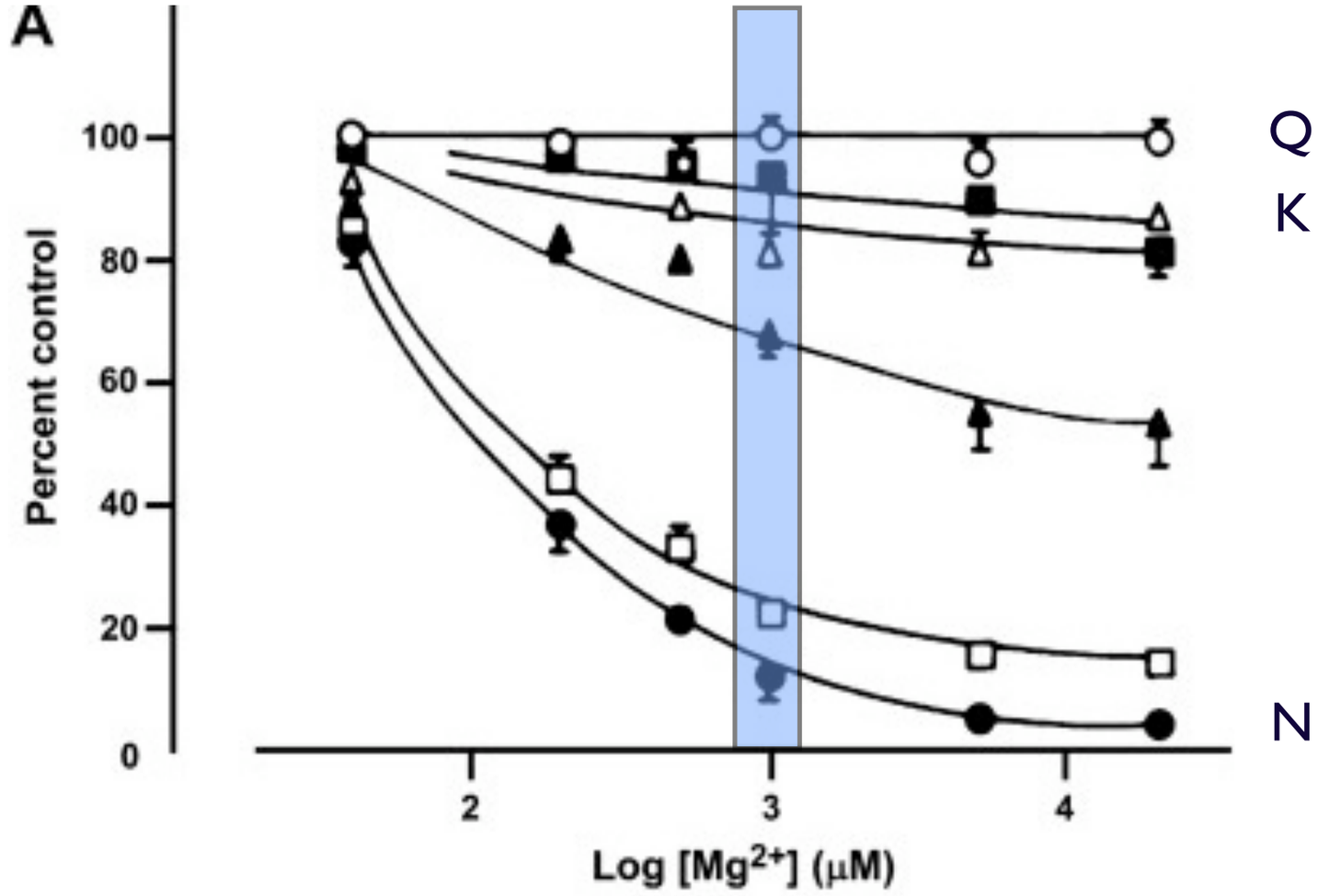
(first direct evidence that L-glutamate is an excitatory neurotransmitter)



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

NMDA RECEPTORS

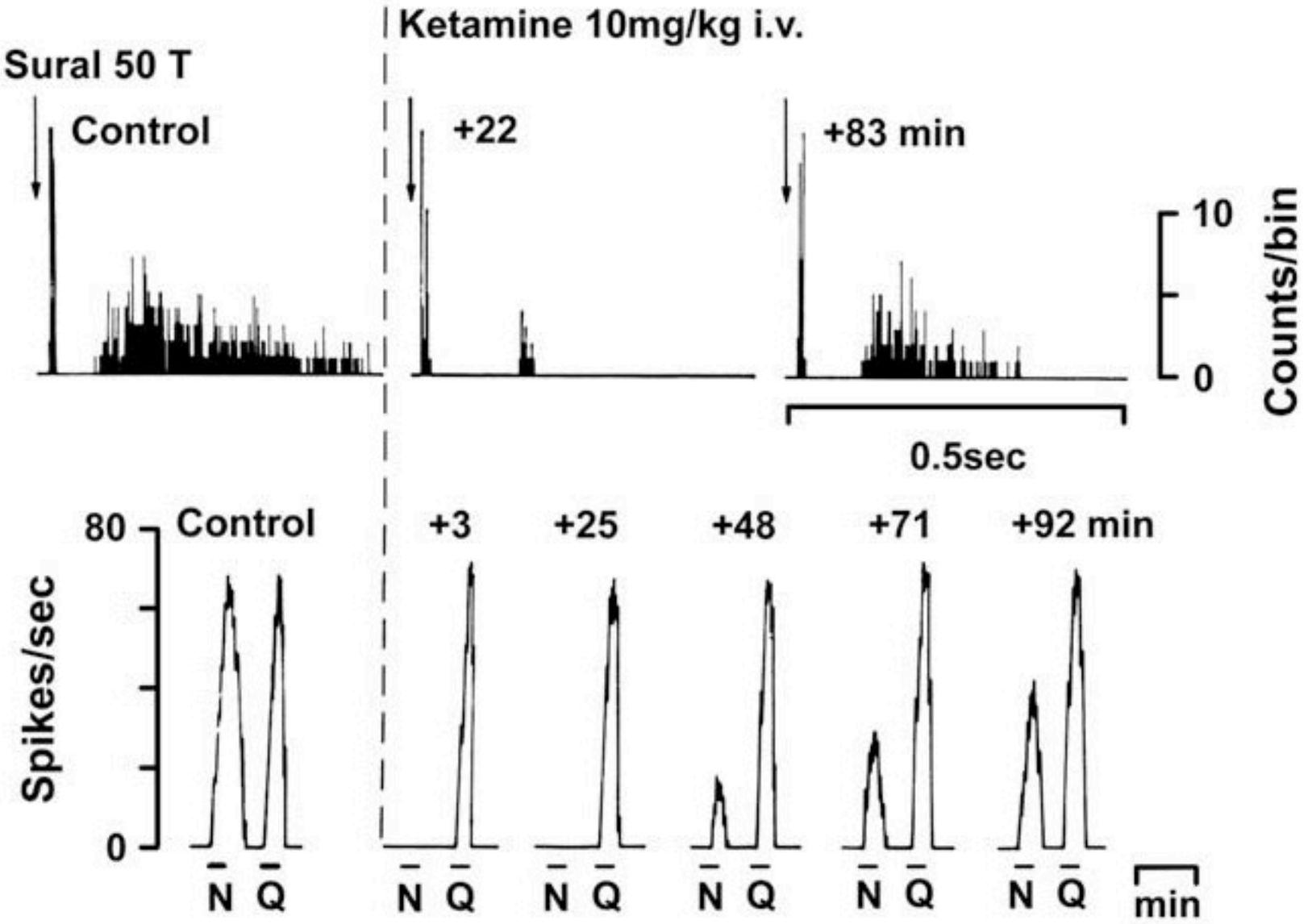
Mg^{2+} is a potent, selective NMDA antagonist



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

NMDA RECEPTORS

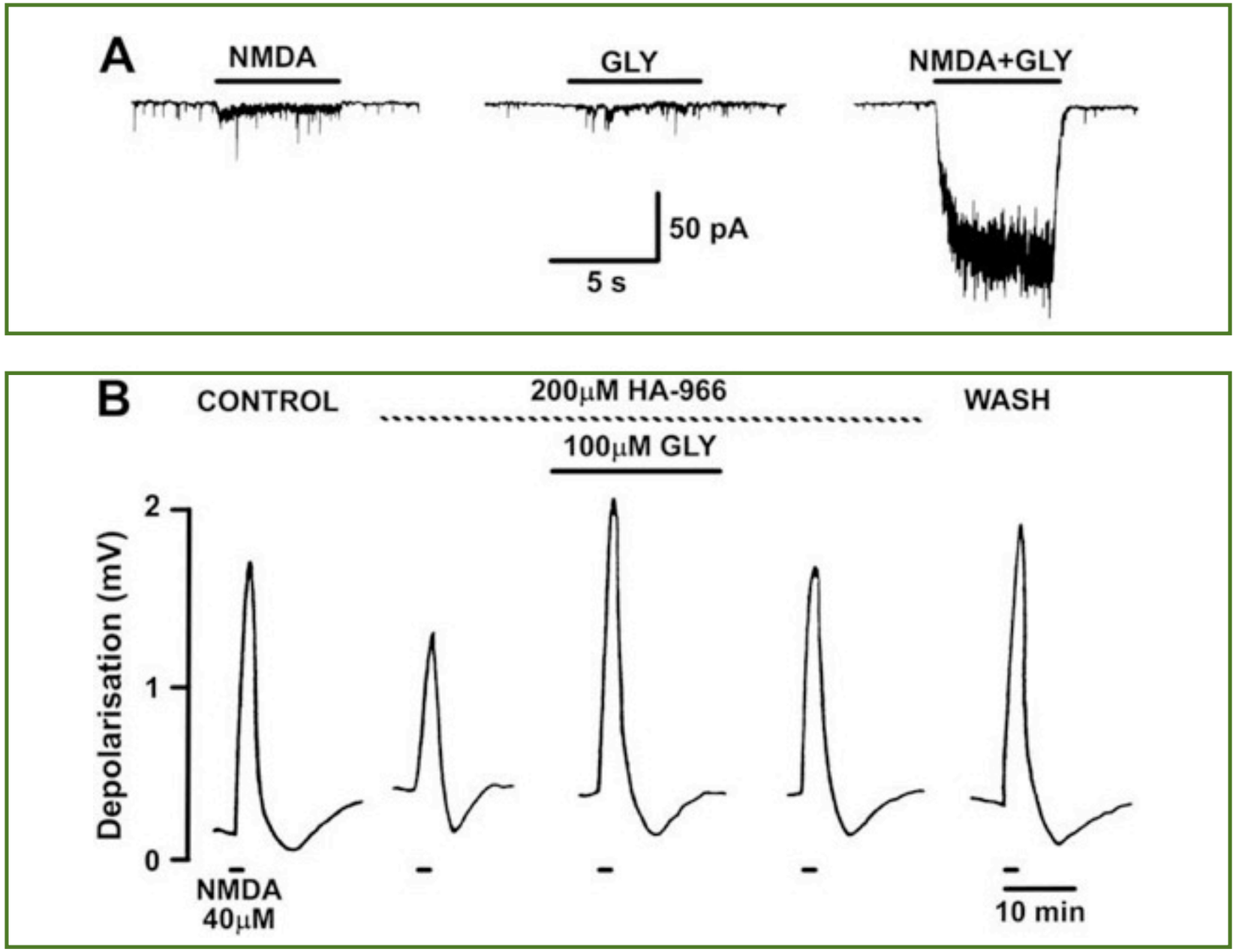
Dissociative anaesthetics (ketamine, phencyclidine etc) are selective NMDAR antagonists



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

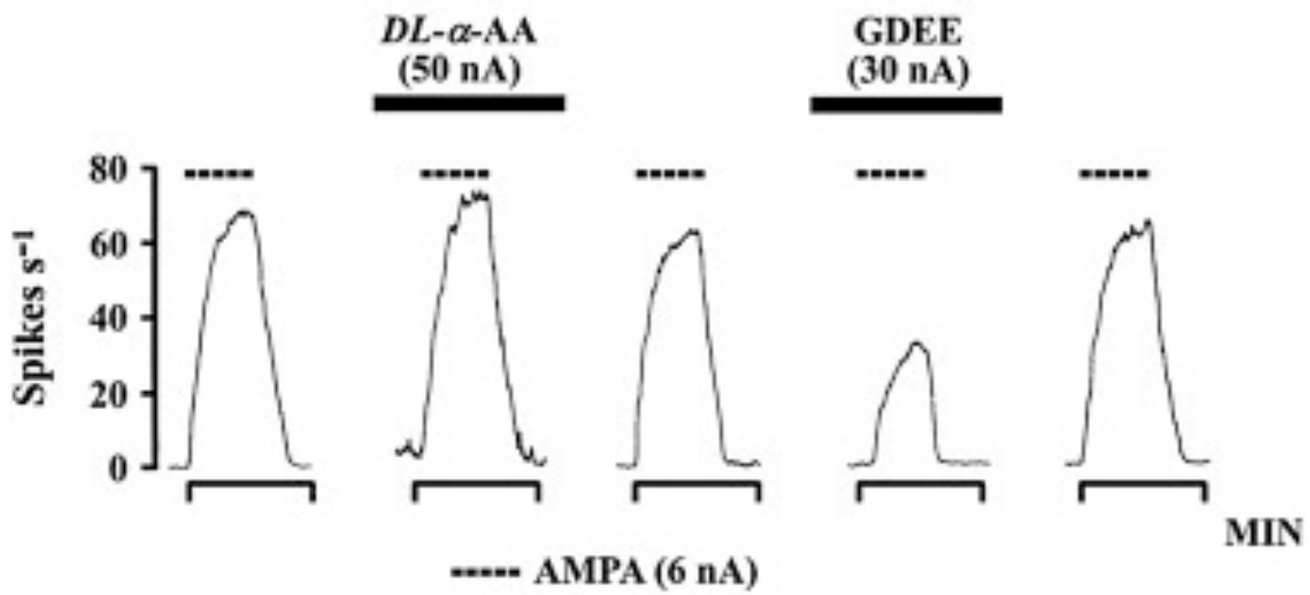
AMPA RECEPTORS

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

Quisqualate receptor renamed the AMPA receptor

AMPA RECEPTORS

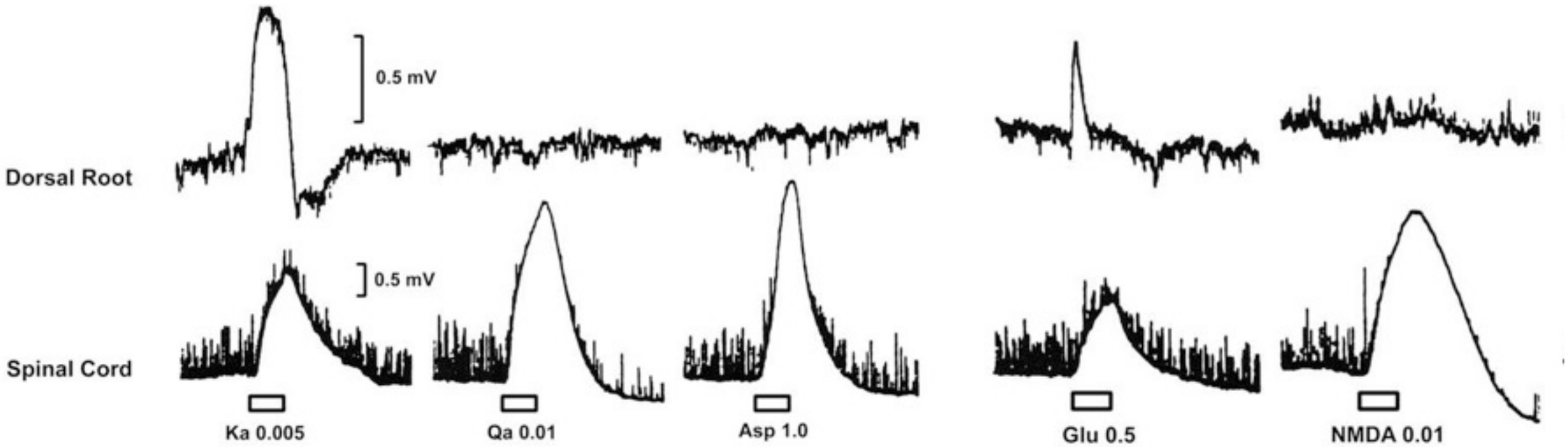
AMPA excites central neurons



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)

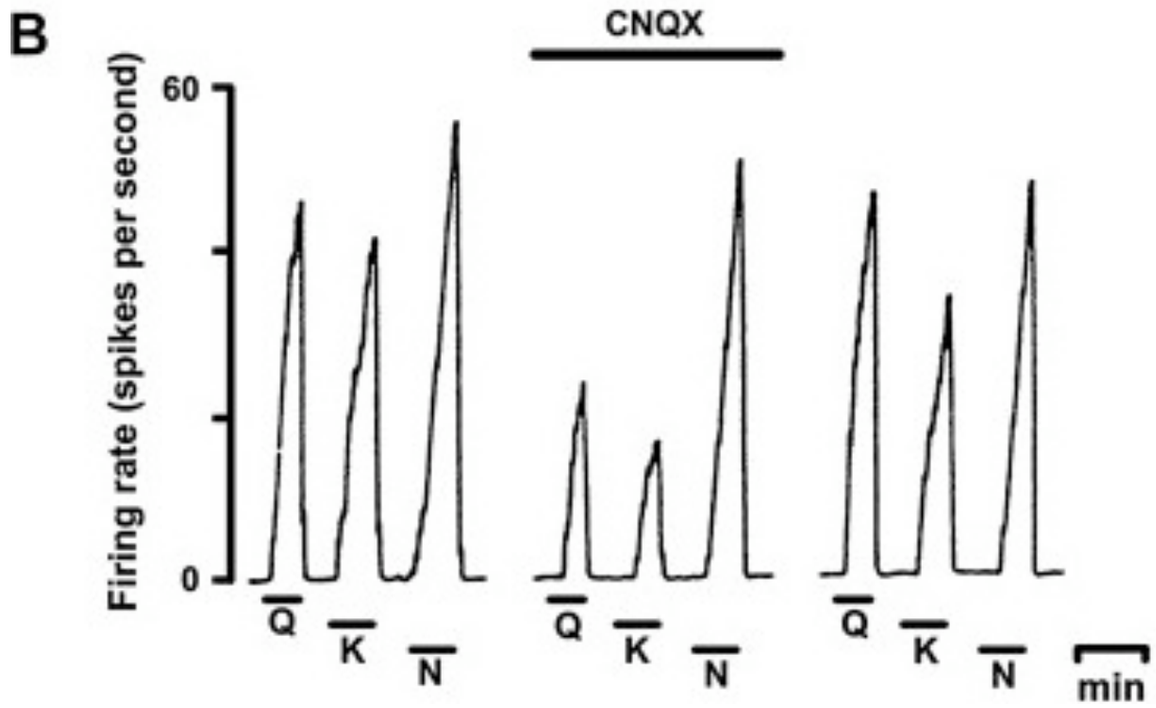
Ability to completely block AMPAR transmission but spare NMDAR transmission

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

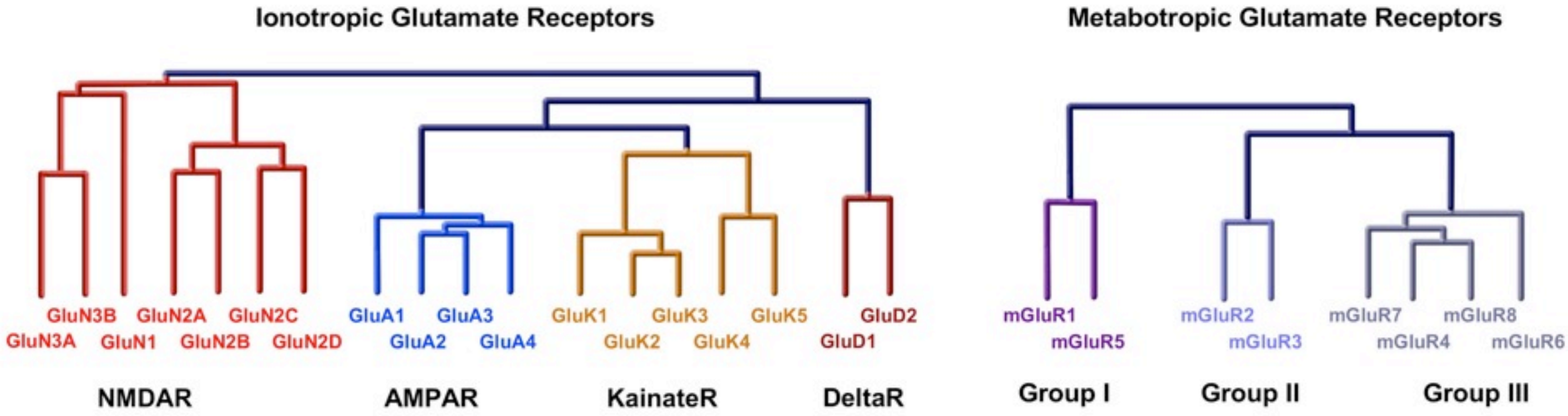
G-protein coupled receptors

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

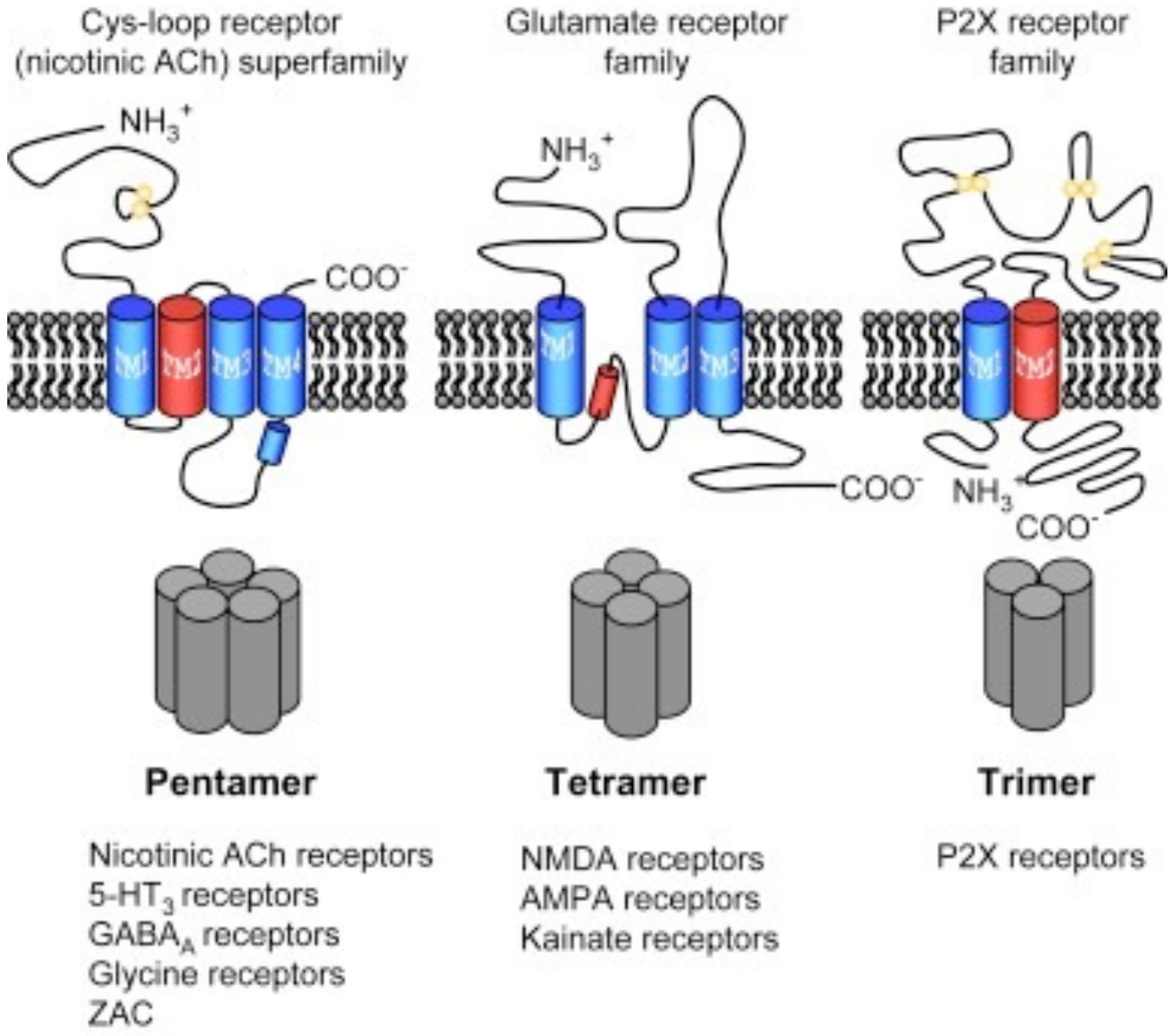
http://www.genenames.org/

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

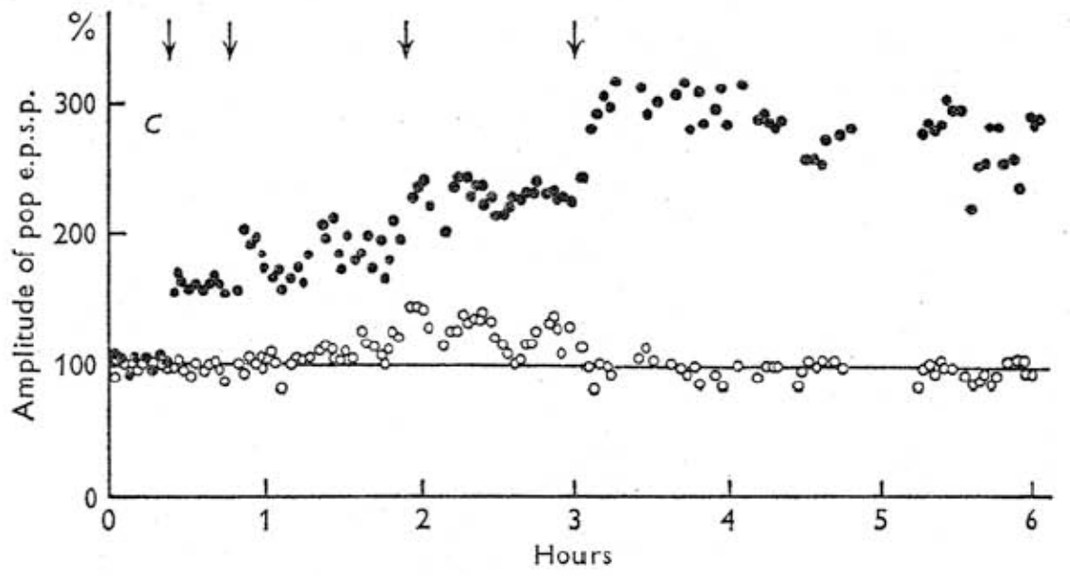
J. Physiol. (1973), **232**, *pp.* 331–356
With 12 *text-figures*
Printed in Great Britain

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

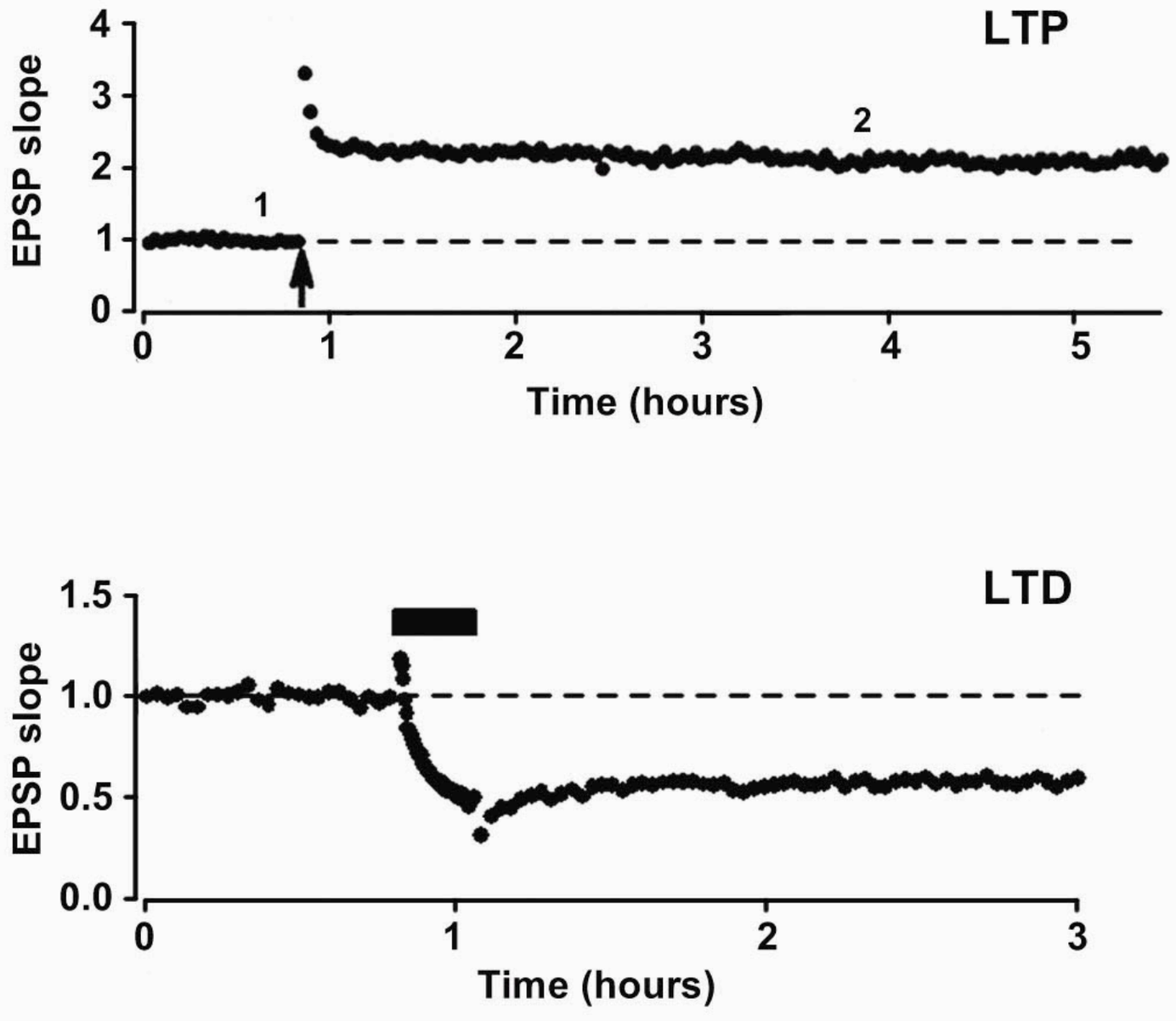
By T. V. P. BLISS and T. LØMO

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

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

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