The induction of *N*-methyl-D-aspartate receptor-dependent long-term potentiation[†]

Graham L. Collingridge

MRC Centre for Synaptic Plasticity, Department of Anatomy, School of Medical Sciences, University Walk, Bristol BS8 1TD, UK

The role of *N*-methyl-D-aspartate (NMDA) receptors in the induction of long-term potentiation (LTP) was established during the 1980s. In this article I present a personal reflection upon the role that my colleagues and I played in the discovery of the mechanism of induction of NMDA receptor-dependent LTP.

Keywords: long-term potentiation; *N*-methyl-D-aspartate; hippocampus; synaptic plasticity; magnesium; glutamate

1. 1980–1982: POTENTIAL EXCITEMENT

I hope my NMDA receptors were working well in the 1980s as I try to recall the events leading up to the establishment of the mechanism of induction of LTP. My story begins in 1980 as I start my first postdoctoral position in the laboratory of Hugh McLennan, in Vancouver. Hugh was interested in L-glutamate as a neurotransmitter in the brain and was one of the pioneers in the identification of multiple classes of glutamate receptor. His PhD student, Stephen Kehl, was studying the actions of L-glutamate on CA1 neurons in the hippocampal slice preparation, when I arrived looking for a project. At that time also, a visitor to Hugh's laboratory, David West, was working on LTP in this slice preparation. When I first saw LTP demonstrated by David, I was hooked and decided to spend the next two years working on this fascinating process. I was already well aware of the existence of multiple types of glutamate receptor, having spent a PhD in London studying with another major player in the glutamate field—John Davies. I asked myself the question whether different subtypes of glutamate receptor may be involved in the mediation of synaptic transmission and the induction of LTP; and this, with Hugh's approval, is what I set out to investigate.

There was no *a priori* reason to suspect one type of glutamate receptor over another with respect to a specific role in synaptic plasticity. I therefore decided to investigate the subtypes in a random order. The first agonist I found in the freezer was kainate. In my first experiment I found that a brief focal application of kainate induced a pronounced, long-lasting facilitation of the population spike recorded from the CA1 cell body region (Collingridge & McLennan 1981). Although this effect superficially resembled LTP it was immediately evident that kainate was not inducing LTP since the potentiation was associated with a sustained

depression of the dendritically recorded fEPSP. Furthermore, there was no occlusion between kainate and tetanus-induced facilitation. Indeed, subsequent experiments also revealed a depression of synaptic inhibition that accounted for the increased excitability (Kehl *et al.* 1984). (I was to return to these effects many years later when improved pharmacological tools enabled the identification of presynaptic kainate receptors regulating both L-glutamate (Chittajallu *et al.* 1996) and GABA release (Clarke *et al.* 1997) in the CA1 region of the hippocampus.) However, as far as LTP was concerned there was no obvious role for kainate receptors at Schaffer collateral/commissural–CA1 synapses. (Ironically, the situation proved to be very different at another synapse in the hippocampus where LTP is independent of the activation of NMDA receptors, the mossy fibre–CA3 synapse (see Bortolotto *et al.* 2003).)

The next agonist I tested was what I thought was *N*-methyl-DL-aspartate, which had little effect in the CA1 region of the hippocampus. I felt unhappy with this result since my previous experiments in the substantia nigra had shown that NMDA was an extremely potent excitant of these neurons (Collingridge & Davies 1979). Although this could obviously be due to a regional difference in sensitivity, I was sufficiently concerned to want to test *bona fide* NMDA, which at the time was not commercially available. On a visit to Bristol I raised my concern with Jeff Watkins who let me have samples, not only of NMDA but also two of his latest glutamate antagonists, (D,L)-2-amino-5-phosphonopentanoate (AP5; note that Jeff originally called his antagonist 2-amino-5-phosphonovalerate according to the earlier chemical nomenclature and the compound is often hence abbreviated as APV—we have switched to Jeff's preferred name of AP5) and DGG. On my return to Vancouver in the spring of 1981 I applied NMDA by iontophoresis to CA1 dendrites and observed dramatic effects. First was a depression of synaptic transmission, which we attributed to depolarization of CA1 neurons, but this was followed by a potentiation of the fEPSP (Collingridge *et al.* 1983a). In my heart I knew at that point that NMDA receptors were a trigger for the induction of LTP. The obvious experiment was to test

[†]Dedicated to Jeff C. Watkins for his discovery of the NMDA receptor.

One contribution of 30 to a Theme Issue 'Long-term potentiation: enhancing neuroscience for 30 years'.

Jeff's specific NMDA receptor antagonist, AP5. This had no effect on basal synaptic transmission or pre-established LTP but blocked the induction of LTP in a reversible manner (Collingridge *et al.* 1983*a*). My head now agreed with my heart. In these same experiments I tested DGG, which is a weak antagonist of AMPA and kainate receptors, and this depressed synaptic transmission. Thus the original hypothesis, that different classes of glutamate receptor mediate synaptic transmission and the induction of LTP, turned out to be correct. The NMDA receptor was identified as the trigger for the induction of LTP and some type of non-NMDA glutamate receptor as the mediator of synaptic transmission. (Beautiful autoradiographic images, produced by Dan Monaghan and Carl Cotman, of AMPA and NMDA receptors showed very high concentrations of both types of receptor in the dendritic layers of area CA1 (Monaghan *et al.* 1983) suggesting that AMPA receptors are the mediators of the synaptic response. Indeed the development of more selective pharmacological tools has confirmed that it is the AMPA receptor, rather than the kainate receptor, which serves this role.)

The amount of AP5 that was available in these first two sets of experiments was so little that we applied the antagonist by iontophoresis, directly into the synaptic region of the slice. However, by the time of my next visit to Bristol, Jeff had synthesized more batches of AP5 and its resolved isomers. We therefore applied these via the perfusate and found that the activity resided in the D isomer and that a concentration of 50 μ M was required to fully block the induction of LTP. We also tested the effects of D-AP5 on synaptic responses at a further five excitatory pathways in the hippocampus and found no effect on basal synaptic transmission in any of these (Collingridge *et al.* 1983*b*). It seemed plausible that the concept that NMDA receptors mediate the induction of LTP but not basal synaptic transmission was a general principle. However, before I could test this directly my two-year postdoctorate was over and my application for a Canadian MRC scholarship to continue this work in Vancouver had been turned down. Next port of call—Sydney—and a change of scene to GABA. During this six-month sojourn with Peter Gage I developed an interest in synaptic channel kinetics (Collingridge *et al.* 1984), a subject that I was to return to when Tim Benke suggested using non-stationary fluctuation analysis to investigate the expression mechanism of NMDA receptor-dependent LTP (Benke *et al.* 1998)—but that is another story.

2. 1984–1985: GATHERING EXCITATION

I returned to Bristol, for a faculty position, and was joined in 1984 by two graduate students, Elizabeth Coan and Robin Lester, and a postdoctoral student, Caroline Herron. Although the role of NMDA receptors as a trigger for the induction of LTP was established, and other groups had started to work in this area, the mechanism of their involvement was not known. We therefore set out to try to establish this process. Our first experiment was to omit Mg^{2+} from the perfusate. Evans, Francis and Watkins had already shown that Mg^{2+} was a potent non-competitive NMDA receptor antagonist (Evans *et al.* 1977) and so it seemed reasonable to assume that this ion was

somehow involved in the induction process. (Indeed, Stephen Kehl and I had briefly explored the effects of Mg^{2+} -free medium on synaptic transmission in the hippocampus but we saw such an extreme increase in excitability that we assumed that the slice had turned epileptic beyond salvation.) In Bristol, we again noted a dramatic increase in synaptic transmission and the appearance of evoked epileptiform activity. However, significantly most of the increase in excitability was reversed by application of D-AP5 (Coan & Collingridge 1985; see also Herron *et al.* 1985*a*). This told us that NMDA receptors could be activated during basal synaptic transmission but that the presence of Mg^{2+} in the perfusate, in concentrations present in the extracellular fluid, was preventing their activation. What we did not know was what was special about high-frequency stimulation, used to induce LTP.

The paper by Ascher and colleagues was an instant revelation. Nowak *et al.* (1984) showed that the Mg^{2+} block of NMDA receptors was a direct interaction with the ion channel and that this channel block was strongly voltage-dependent, decreasing with depolarization. Thus based on the knowledge that (i) NMDA receptors are the trigger for LTP induction (Collingridge *et al.* 1983*a*), (ii) Mg^{2+} prevents the synaptic activation of NMDA receptors during basal synaptic transmission (Coan & Collingridge 1985), and (iii) the Mg^{2+} block of NMDA receptors is strongly voltage-dependent (Mayer *et al.* 1984; Nowak *et al.* 1984), the first part of the scheme for the induction of LTP fell into place (Collingridge 1985; figure 1; see also Wigsström & Gustafsson 1985). The idea that AMPA receptors provide the depolarization to enable the unblocking of the NMDA receptors during high-frequency synaptic transmission quickly gained widespread acceptance and the scheme has since appeared in many guises. More generally, the concept that NMDA receptors are a coincidence detector of conjoint pre- and postsynaptic activity was established by these experiments.

I recall the conversation Caroline Herron and I had in the Highbury Vaults, a watering hole well known to most visitors to Bristol University's Medical School. We wondered why NMDA receptors were not appreciably activated at resting membrane potentials, since the Mg^{2+} block was not complete at -70 mV but intensified as neurons were hyperpolarized. It seemed to us that GABA inhibition provided the reason. The experiment was simple and involved the application of a GABA_A receptor antagonist, which as we expected enabled a single stimulus to elicit an NMDA receptor-mediated response in the presence of Mg^{2+} (Herron *et al.* 1985*b*). There was, fortunately, only a short-lived resistance to our proposal that the hyperpolarizing influence of GABA_A receptor-mediated inhibition was more important than the conductance shunt in limiting the synaptic activation of NMDA receptors (which contradicted the textbook view of the role of inhibition at the time). The ability of GABAergic inhibition to limit the synaptic activation of NMDA receptors also explained the earlier finding that GABA antagonists could greatly facilitate the induction of LTP. A logical prediction from these experiments was that artificial depolarization of the neuron should enable the synaptic activation of NMDA receptors despite the presence of synaptic inhibition. We found that this was indeed the case (see below). We were acutely aware that such depolarization would probably enable sin-

gle shock stimulation to induce LTP and were careful to avoid this complicating factor, which could hinder our analysis of synaptic responses. Others took the view that such a pairing of depolarization and low-frequency synaptic activation provided insights into the 'Hebbian' functioning of these synapses and produced elegant studies demonstrating this (e.g. Kelso *et al.* 1986; Wigström *et al.* 1986).

3. 1986–1988: KINETICS AND COMPETITION

At the time that we started working on the induction mechanisms of LTP the prevailing view was that NMDA receptors mediated a slow component of synaptic transmission because they provided excitation via polysynaptic circuits; an idea formed from studies in the spinal cord. In all our schemes we assumed to the contrary that the synaptic activation of NMDA receptors was monosynaptic. The motivation for this was a combination of Occam's razor and the elegant studies of Dale & Roberts (1985) who showed that NMDA receptors mediated a slow monosynaptic EPSP in *Xenopus* motor neurons. Robin Lester, Caroline Herron and I tested this idea directly by blocking GABA_A receptor-mediated inhibition, depolarizing CA1 neurons to remove the Mg²⁺ block and thereby increase the size of the NMDA receptor-mediated component further, voltage-clamping the neuron and applying D-AP5 to block this synaptic component. What was left was a fast, AMPA receptor-mediated EPSC. Subtraction of this synaptic current from the total EPSC revealed, for the first time, a slow rising and decaying NMDA receptor-mediated EPSC (Collingridge *et al.* 1987, 1988a). Note that the converse experiment of blocking the AMPA receptor component was not possible at the time as available antagonists were not sufficiently potent.

The kinetics of the NMDA receptor-mediated EPSC spoke volumes. The slow rise explained why there was essentially no synaptic activation during low-frequency stimulation; by the time that the conductance is significantly activated, coactivated GABAergic inhibition hyperpolarizes the neuron into a region of substantial Mg²⁺ block. The slow decay, however, enables effective temporal summation at times when the neuron is not hyperpolarized, in particular, by synaptically released GABA. At about the same time an NMDA receptor-mediated EPSC with slow kinetics was also reported in cultured hippocampal neurons by Forsythe & Westbrook (1988). These authors did not discuss the slow rise of the NMDA receptor-mediated current as they attributed this at the time to a voltage-clamp artefact. We knew the slow rise was not an artefact; the simple experiment showing that blockade of GABA_A inhibition enabled single shock activation of NMDA receptors told us that the regulation had physiological significance. We assumed, but were not in a position to test, that the slow rise and decay of the NMDA receptor-mediated EPSC was an intrinsic property of NMDA receptors. Robin Lester, after leaving my laboratory for a postdoctoral position in the laboratory of Craig Jahr, performed the definitive experiment, which elegantly described the kinetic basis of the slow NMDA receptor-mediated EPSC (Lester *et al.* 1990). I was happy to see our ideas given a sound biophysical basis.

The view that high-frequency stimulation enabled the synaptic activation of NMDA receptors was demonstrated

by determining the sensitivity of low- and high-frequency stimulation to AP5. As would be predicted, from the above properties of NMDA receptors, the NMDA receptor-mediated component was visible in the presence of Mg²⁺ and intact synaptic inhibition during high-frequency stimulation (Herron *et al.* 1986). This frequency-dependent synaptic component had the appropriate slow time-course and voltage dependence, and was clearly visible when evoked from resting membrane potentials (Collingridge *et al.* 1988b). What was readily apparent, however, was that it was not the algebraic sum of the equivalent number of appropriately spaced low-frequency synaptic responses—the level of depolarization was far too great during high-frequency stimulation given the dominance of synaptic inhibition during low-frequency stimulation.

At around this time, we heard rumours that Tage Honoré had discovered a family of potent and selective AMPA receptor antagonists and was talking about these for the first time at the European Winter Conference on Brain Research (Tignes, France). We therefore booked a ski holiday in Tignes and gate-crashed the session. The quinoxalinedione antagonists were fantastically effective, and Tage kindly let us have a sample of the most selective compound CNQX. This enabled Jo Blake in my laboratory to demonstrate the slow kinetics and monosynaptic nature of the NMDA receptor-mediated synaptic response directly (Blake *et al.* 1988); any lingering doubts of remaining sceptics were fully and finally dispelled.

4. 1989–1991: LOSING ONE'S INHIBITION

New people joined the laboratory; notably a postdoctoral student, Stephen Davies, and a PhD student, Ceri Davies. Our minds once again turned to synaptic inhibition. It was already known at the time that GABAergic synaptic inhibition was transiently inhibited during periods of repetitive stimulation and the mechanism of this effect was being investigated with respect to epileptiform activity. We wondered if the activity-dependent depression of synaptic inhibition had a physiological function—namely to temporarily suppress the synaptic activation of GABA_A receptor-mediated synaptic inhibition just sufficiently for the appropriate synaptic activation of NMDA receptors (as required to induce LTP). Until that time, synaptic inhibition in the hippocampus had been difficult to study directly, because of the concomitant activation of glutamatergic synapses that both affected synaptic inhibition via polysynaptic activation and produced overlapping synaptic potentials. We needed to be able to study synaptic inhibition without these complications resulting from synaptic excitation. The discovery of CNQX provided us with this opportunity. We blocked both AMPA and NMDA receptor-mediated synaptic transmission, using CNQX and D-AP5, and directly stimulated GABAergic inhibition using an appropriately positioned stimulating electrode (Davies & Collingridge 1989). This led to the characterization of monosynaptic GABAergic inhibition.

To study acute plasticity of the GABAergic system we initially investigated paired-pulse depression of IPSCs. In these studies (Davies *et al.* 1990) we found a pronounced depression of the second IPSC with a maximally effective interval of between 100 and 200 ms (5–10 Hz). Importantly, there was no depression of a second pulse delivered 10 ms

Figure 1. A scheme for the induction of NMDA receptor-dependent LTP. (Redrawn from Collingridge (1985).)

after the first, showing that these inhibitory synapses could follow high frequencies (at least 100 Hz) and, therefore, that the depression was due to some active process. The depression induced by a single stimulus had a powerful influence because, at its peak, it could depress inhibition, typically, by 75% and the effect lasted for a few seconds. In addition, it depressed both GABA_A and GABA_B receptor-mediated synaptic inhibition to the same extent. This profile suggested to us that a receptor-mediated presynaptic inhibition was operating. At the time there was no evidence for functional autoreceptors in the central nervous system but the principle was well established in the peripheral nervous system. Also the pharmacological inhibition of neurotransmitter release by various neurotransmitter agonists was well known; indeed, in this context it had been recently shown that activation of GABA_B receptors, using baclofen, resulted in a depression of synaptic inhibition in the hippocampus (Harrison *et al.* 1988). This all pointed to the existence of GABA_B autoreceptors that provided a powerful regulation of the synaptic release of GABA in the hippocampus. Consistent with this hypothesis, paired-pulse inhibition of IPSCs was largely blocked by the best available GABA_B antagonist, 2-hydroxy-saclofen (Davies *et al.* 1990).

The next step was to determine whether this autoreceptor mechanism is responsible for the activity-dependent depression of synaptic inhibition that enables the induction of LTP. For this we required a more potent and selective GABA_B antagonist. As luck would have it, I happened to be sitting next to Mario Pozza, a scientist from Ciba-Geigy, at a conference dinner and mentioned this to him. His company had a long-standing interest in GABA_B receptors and Mario immediately informed me about their latest GABA_B antagonist, CGP35348. Together we set out to test the theory. We reasoned that a 'priming' protocol described by Diamond *et al.* (1988), whereby a single stimulus is delivered *ca.* 200 ms before a short burst (typically four stimuli at 100 Hz), had temporal characteristics that pointed to a role of GABA_B autoreceptors. Con-

sistent with the hypothesis, CGP35348 prevented the depression of GABA_A receptor-mediated inhibition during the high-frequency burst and fully blocked the induction of priming-induced LTP (Davies *et al.* 1991). As would be predicted from an understanding of the mechanism, GABA_B antagonists do not invariably block the induction of LTP—for example, in the presence of a GABA_A receptor antagonist or during longer high-frequency trains (see Davies & Collingridge (1993, 1996) for a detailed explanation). The role of GABA_B autoreceptors is critically dependent upon the induction parameters employed. They are important when patterns of activation that mimic natural firing activity are used. In this context it is probably no coincidence that the optimal frequency for the GABA_B autoreceptor-mediated depression of synaptic inhibition corresponds to the theta frequency. Therefore, while in many studies (such as those designed to study the expression mechanisms of LTP) GABA_A receptor-mediated inhibition is blocked pharmacologically (with, for example, picrotoxin), from a physiological perspective GABA_B receptors have a crucial role in the induction process—one that has yet to be rigorously explored in the context of learning and memory. From this point onwards we have emphasized the role of activity-dependent changes in synaptic inhibition in the induction of NMDA receptor-dependent LTP (e.g. Collingridge & Singer 1990; figure 2).

5. AFTERTHOUGHTS: SIGNIFICANCE OF NMDA RECEPTOR-DEPENDENT LTP

The mechanism of induction of NMDA receptor-dependent LTP seems to have captured the imagination of many neuroscientists. There are probably several reasons for this. Not least, the *Hebbian* properties of synapses can now be given a molecular basis; namely that synaptically released L-glutamate signals presynaptic activity and postsynaptic depolarization indicates the level

Figure 2. A refinement of the scheme for the induction of NMDA receptor-dependent LTP, incorporating activity-dependent changes in synaptic inhibition. (Redrawn from Collingridge & Singer (1990).)

of postsynaptic activity—with the NMDA receptor acting as the coincidence detector. The requirement for L-glutamate to activate the NMDA receptor can explain *input specificity* as depolarization alone will not activate the NMDA receptor; the precision of specificity will be determined by the extent that L-glutamate can ‘spill-over’ onto neighbouring synapses in sufficient amounts. *Cooperativity* and *associativity* can be explained on the basis that a single input, or small number of inputs, will not be able to provide enough depolarization to sufficiently relieve the Mg^{2+} block of NMDA receptors. However, the coordinated activation of sets of fibres (cooperativity) or the arrival of appropriately timed activity from other pathways (associativity) will provide, or enable, the sufficient depolarization. The coordinated activity is required for the depolarization but not to provide sufficient L-glutamate; the activity of a single synapse provides enough L-glutamate to induce LTP at that synapse—this is clearly demonstrated in a single fibre, pairing experiment where the recording electrode can provide the necessary depolarization to negate the cooperativity requirement of LTP.

The NMDA receptor is clearly important for normal physiological function. Equally clear is how potentially dangerous it can be. If activated inappropriately it may lead to aberrant synaptic plasticity, and such mechanisms may occur during epilepsy—as modelled by kindling. In greater excess, it may lead to death of neurons via the excitotoxic flood of Ca^{2+} into neurons (e.g. Meldrum & Garthwaite 1990). It is widely assumed that this occurs during stroke and trauma, when excessive amounts of L-glutamate act on depolarized neurons. More speculatively, similar mechanisms have been considered to contribute to neurodegenerative disorders. Conversely, it has been considered that hypoactivity of NMDA receptors may contribute to psychiatric and cognitive dysfunction. The finding that phencyclidine is a potent NMDA receptor antagonist (Anis *et al.* 1983) has, given the prominent use of PCP as a model for schizophrenia, led people to wonder whether aberrant NMDA receptor-dependent LTP is at

the heart of this disease. Similarly, the idea of boosting NMDA receptor function underpins certain strategies for developing cognitive enhancing drugs. Indeed, the scientific rationale behind ‘AMPAkines’ is that by facilitating the activity of AMPA receptors this will enhance the synaptic activation of NMDA receptors and hence LTP, as outlined in figure 1.

Paradoxically, NMDA receptor antagonists may actually prove beneficial in cognitive disorders, such as Alzheimer’s disease. Indeed, the weak NMDA receptor channel blocking agent memantine is used in the clinic for this purpose. Again there is a scientific rationale for this effect. Inappropriate activation of the NMDA receptors, as first modelled by bathing slices in Mg^{2+} -free medium (Coan *et al.* 1989), results in a loss of LTP that can be restored by applying an appropriate dose of an NMDA receptor antagonist (i.e. that is sufficient to dampen down the inappropriate activation but not the coordinated activation of NMDA receptors). This model was used to provide the scientific rationale for the beneficial effects of memantine (Parsons *et al.* 1999).

6. CONCLUDING REMARKS

That, in summary, is how I remember the events of the 1980s. In each case the experiments were carried out to test predictions arising from the hypothesis (rather than the hypothesis being retrospectively created to fit the data). Fortunately, the hypothesis was correct (in the sense that it has gained widespread acceptance). My recollections along the way have been helped by writing the occasional review which, in addition to those listed above, include Collingridge (1987) and Collingridge & Bliss (1987) (which to my amazement was the most cited *Trends in Neurosciences* article in their historical survey of 1995), Collingridge (1992) and Bliss & Collingridge (1993) (which to my even greater amazement was the most cited article in neuroscience during the decade of the brain) and Collingridge & Bliss (1995). The level of citations says a lot about

the importance the world's scientific community places on the phenomenal phenomenon of LTP!

I especially thank all my friends who contributed to the work reviewed here—without them none of this would have happened. I also thank the MRC and The Wellcome Trust for their financial support.

REFERENCES

- Anis, N. A., Berry, S. C., Burton, N. R. & Lodge, D. 1983 The dissociative anaesthetics, ketamine and phencyclidine, selectively reduce excitation of central mammalian neurons by N-methyl-aspartate. *Br. J. Pharmacol.* **79**, 565–575.
- Benke, T. A., Lüthi, A., Isaac, J. T. R. & Collingridge, G. L. 1998 Modulation of AMPA receptor unitary conductance by synaptic activity. *Nature* **393**, 793–797.
- Blake, J. F., Brown, M. W. & Collingridge, G. L. 1988 CNQX blocks acidic amino acid induced depolarizations and synaptic components mediated by non-NMDA receptors in rat hippocampal slices. *Neurosci. Lett.* **89**, 182–186.
- Bliss, T. V. P. & Collingridge, G. L. 1993 A synaptic model of memory: long-term potentiation in the hippocampus. *Nature* **361**, 31–39.
- Bortolotto, Z. A., Lauri, S., Isaac, J. T. R. & Collingridge, G. L. 2003 Kainate receptors and the induction of mossy fibre long-term potentiation. *Phil. Trans. R. Soc. Lond. B* **358**, 657–666. (DOI 10.1098/rstb.2002.1216.)
- Chittajallu, R., Vignes, M., Dev, K. K., Barnes, J. M., Collingridge, G. L. & Henley, J. M. 1996 Regulation of glutamate release by presynaptic kainate receptors in the hippocampus. *Nature* **379**, 78–81.
- Clarke, V. R. J. (and 14 others) 1997 A hippocampal GluR5 kainate receptor regulating inhibitory synaptic transmission. *Nature* **389**, 599–603.
- Coan, E. J. & Collingridge, G. L. 1985 Magnesium ions block an N-methyl-D-aspartate receptor-mediated component of synaptic transmission in rat hippocampus. *Neurosci. Lett.* **53**, 21–26.
- Coan, E. J., Irving, A. J. & Collingridge, G. L. 1989 Low-frequency activation of the NMDA receptor system can prevent the induction of LTP. *Neurosci. Lett.* **105**, 205–210.
- Collingridge, G. L. 1985 Long term potentiation in the hippocampus: mechanisms of initiation and modulation by neurotransmitters. *Trends Pharmacol. Sci.* **6**, 407–411.
- Collingridge, G. L. 1987 The role of NMDA receptors in learning and memory. *Nature* **6149**, 604–605.
- Collingridge, G. L. 1992 The mechanism of induction of NMDA receptor-dependent long-term potentiation in the hippocampus. *Exp. Physiol.* **77**, 771–797.
- Collingridge, G. L. & Bliss, T. V. P. 1987 NMDA receptors—their role in long-term potentiation. *Trends Neurosci.* **7**, 288–293.
- Collingridge, G. L. & Bliss, T. V. P. 1995 Memories of NMDA receptors and LTP. *Trends Neurosci.* **18**, 54–56.
- Collingridge, G. L. & Davies, J. 1979 An evaluation of D- α -aminoadipate and D-(and DL)- α -aminosuberate as selective antagonists of excitatory amino acids in the substantia nigra and mesencephalic reticular formation of the rat. *Neuropharmacology* **18**, 193–199.
- Collingridge, G. L. & McLennan, H. 1981 The effect of kainic acid on excitatory synaptic activity in the rat hippocampal slice preparation. *Neurosci. Lett.* **27**, 31–36.
- Collingridge, G. L. & Singer, W. 1990 Excitatory amino acid receptors and synaptic plasticity. *Trends Pharmacol. Sci.* **11**, 290–296.
- Collingridge, G. L., Kehl, S. J. & McLennan, H. 1983a The action of an N-methylaspartate antagonist on synaptic processes in the rat hippocampus. *J. Physiol. (Lond.)* **338**, 27P.
- Collingridge, G. L., Kehl, S. J. & McLennan, H. 1983b Excitatory amino acids in synaptic transmission in the Schaffer collateral-commissural pathway of the rat hippocampus. *J. Physiol.* **334**, 33–46.
- Collingridge, G. L., Gage, P. W. & Robertson, B. 1984 Inhibitory post-synaptic currents in rat hippocampal CA1 neurones. *J. Physiol.* **356**, 551–564.
- Collingridge, G. L., Herron, C. E. & Lester, R. A. J. 1987 NMDA receptor involvement in synaptic potentials evoked by low-frequency stimulation in rat hippocampus *in vitro*. *J. Physiol. (Lond.)* **394**, 151P.
- Collingridge, G. L., Herron, C. E. & Lester, R. A. J. 1988a Frequency-dependent N-methyl-D-aspartate receptor-mediated synaptic transmission in rat hippocampus. *J. Physiol. (Lond.)* **399**, 301–312.
- Collingridge, G. L., Herron, C. E. & Lester, R. A. J. 1988b Synaptic activation of N-methyl-D-aspartate receptors in the Schaffer collateral-commissural pathway of rat hippocampus. *J. Physiol. (Lond.)* **399**, 283–300.
- Dale, N. & Roberts, A. 1985 Dual-component amino acid-mediated synaptic potentials: excitatory drive for swimming in *Xenopus* embryos. *J. Physiol. (Lond.)* **363**, 35–59.
- Davies, C. H. & Collingridge, G. L. 1993 The physiological regulation of synaptic inhibition by GABA_B autoreceptors in rat hippocampus. *J. Physiol. (Lond.)* **472**, 245–265.
- Davies, C. H. & Collingridge, G. L. 1996 Regulation of EPSPs by the synaptic activation of GABA_B autoreceptors in rat hippocampus. *J. Physiol. (Lond.)* **496**, 451–470.
- Davies, S. N. & Collingridge, G. L. 1989 Role of excitatory amino acid receptors in synaptic transmission in area CA1 of rat hippocampus. *Proc. R. Soc. Lond. B* **236**, 373–384.
- Davies, C. H., Davies, S. N. & Collingridge, G. L. 1990 Paired-pulse depression of monosynaptic GABA-mediated inhibitory postsynaptic responses in rat hippocampus. *J. Physiol.* **424**, 513–531.
- Davies, C. H., Starkey, S. J., Pozza, M. F. & Collingridge, G. L. 1991 GABA_B autoreceptors regulate the induction of LTP. *Nature* **349**, 609–611.
- Diamond, D. M., Dunwiddie, T. V. & Rose, G. M. J. 1988 Characteristics of hippocampal primed burst potentiation *in vitro* and in the awake rat. *J. Neurosci.* **8**, 4079–4088.
- Evans, R. H., Francis, A. A. & Watkins, J. C. 1977 Selective antagonism by Mg²⁺ of amino acid-induced depolarizations of spinal neurons. *Experientia* **33**, 489–491.
- Forsythe, I. A. & Westbrook, G. L. 1988 Slow excitatory post-synaptic currents mediated by N-methyl-D-aspartate receptors on cultured mouse central neurones. *J. Physiol. (Lond.)* **396**, 515–533.
- Harrison, N. L., Lange, G. D. & Barker, J. L. 1988 (–)-Baclofen activates presynaptic GABA_B receptors on GABAergic inhibitory neurons from embryonic rat hippocampus. *Neurosci. Lett.* **85**, 105–109.
- Herron, C. E., Lester, R. A. J., Coan, E. J. & Collingridge, G. L. 1985a Intracellular demonstration of an N-methyl-D-aspartate receptor mediated component of synaptic transmission in the rat hippocampus. *Neurosci. Lett.* **60**, 19–23.
- Herron, C. E., Williamson, R. & Collingridge, G. L. 1985b A selective N-methyl-D-aspartate antagonist depresses epileptiform activity in rat hippocampal slices. *Neurosci. Lett.* **61**, 255–260.
- Herron, C. E., Lester, R. A. J., Coan, E. J. & Collingridge, G. L. 1986 Frequency-dependent involvement of NMDA receptors in the hippocampus: a novel synaptic mechanism. *Nature* **322**, 265–268.
- Kehl, S. J., McLennan, H. & Collingridge, G. L. 1984 Effects of folic and kainic acids on synaptic responses of hippocampal neurones. *Neuroscience* **11**, 111–124.

- Kelso, S. R., Ganong, A. H. & Brown, T. H. 1986 Hebbian synapses in hippocampus. *Proc. Natl Acad. Sci. USA* **83**, 5326–5330.
- Lester, R. A. J., Clements, J. D., Westbrook, G. L. & Jahr, C. E. 1990 Channel kinetics determine the time course of NMDA receptor-mediated synaptic currents. *Nature* **346**, 565–567.
- Mayer, M. L., Westbrook, G. L. & Guthrie, P. B. 1984 Voltage-dependent block by Mg^{2+} of NMDA responses in spinal cord neurones. *Nature* **309**, 261–263.
- Meldrum, B. & Garthwaite, J. 1990 Excitatory amino-acid neurotoxicity and neurodegenerative disease. *Trends Pharmacol. Sci.* **11**, 379–387.
- Monaghan, D. T., Holets, V. R., Toy, D. W. & Cotman, C. W. 1983 Anatomical distribution of four pharmacologically distinct 3H -L-glutamate binding sites. *Nature* **306**, 176–179.
- Nowak, L., Bregestovski, P., Ascher, P., Herbert, A. & Prochiantz, A. 1984 Magnesium gates glutamate-activated channels in mouse central neurones. *Nature* **307**, 462–465.
- Parsons, C. G., Danysz, W. & Quack, G. 1999 Memantine is a clinically well tolerated N-methyl-D-aspartate (NMDA) receptor antagonist—a review of preclinical data. *Neuropharmacology* **38**, 735–767.
- Wigström, H. & Gustafsson, B. 1985 On long lasting potentiation in the hippocampus: a proposed mechanism for its dependence on coincident pre- and postsynaptic activity. *Acta Physiol. Scand.* **123**, 519–522.
- Wigström, H., Gustafsson, B., Huang, Y. Y. & Abraham, W. C. 1986 Hippocampal long-term potentiation is induced by pairing single afferent volleys with intracellularly injected depolarizing current pulses. *Acta Physiol. Scand.* **126**, 317–319.

GLOSSARY

- AMPA: α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
- AP5: (D,L)-2-amino-5-phosphonopentanoate
- DGG: γ -D-glutamylglycine
- EPSC: excitatory postsynaptic current
- EPSP: excitatory presynaptic potential
- fEPSP: field excitatory presynaptic potential
- IPSC: inhibitory postsynaptic current
- LTP: long-term potentiation
- NMDA: N-methyl-D-aspartate