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Review

The history of the pharmacology and cloning of ionotropic glutamate receptors and the development of idiosyncratic nomenclature

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ABSTRACT

In this article, the beginnings of glutamate pharmacology are traced from the early doubts about 'non-specific' excitatory effects, through glutamate- and aspartate-preferring receptors, to NMDA, quisqualate/AMPA and kainate subtypes, and finally to the cloning of genes for these receptor subunits. The development of selective antagonists, crucial to the subtype classification, allowed the fundamental importance of glutamate receptors to synaptic activity throughout the CNS to be realised. The ability to be able to express and manipulate cloned receptor subunits is leading to huge advances in our understanding of these receptors. Similarly the tortuous path of the nomenclature is followed from naming with reference to exogenous agonists, through abortive early attempts at generic schemes, and back to the NC-IUPHAR system based on the natural agonist, the defining exogenous agonist and the gene names.

1. The first inklings

The realisation in 1930s–1950s that central synaptic transmission was likely to be chemical rather than electrical evoked questions as to the nature of the chemicals involved (Dale, 1952; McLennan, 1963; Eccles, 1964). Acetylcholine and monoamines were accepted as transmitter substances at peripheral synapses and in some non-mammalian preparations. With a few notable exceptions, however, these substances failed to mimic the rapid synaptic excitation of central neurones when administered microelectrophoretically via multibarrelled microelectrodes directly into the extracellular environment of single neurones in the mammalian central nervous system (McLennan, 1963; Eccles, 1964; Curtis, 1963). This powerful technique (Curtis and Eccles, 1958) had been valuable in confirming the cholinergic nature of transmission at the neuromuscular junction (Nastuk, 1953; Del Castillo and Katz, 1955) and helping establish the role of acetylcholine at the motor axon collateral synapse onto Renshaw cells in the spinal cord (Curtis and Eccles, 1958). The slow onset of and recovery from the changes in excitability induced by acetylcholine and monoamines on most central neurones ruled them out as the transmitters of the fast excitation seen following afferent stimulation.

Several diverse pieces of evidence brought an interest in acidic amino acids as excitants in the mammalian CNS. Firstly, L-glutamate and L-aspartate were found in high concentrations throughout the brain (Berl and Waelsch, 1958). Secondly they induced convulsions (Hayashi, 1952, 1954) and spreading depression (van Harreveld, 1959; Purpura et al., 1959) when applied to the cerebro-cortical surface. Thirdly, they elicited depolarisation of the crayfish muscle (van Harreveld, 1959). Quite independently of these findings, however, Curtis, Phillis and Watkins, working in Eccles group in Canberra, investigated the role of these acidic amino acids, using the technique of microelectrophoresis on the excitability of spinal neurones (Curtis et al., 1959, 1960). The results were outstanding, i.e. fast excitation following extra-, but not intra-, cellular administration. Both depolarisation and an increase in action potential firing were elicited that ostensibly mimicked the action of synaptic events (Fig. 1A and B). However, the authors were not convinced that they had identified the fast excitatory transmitter of the mammalian CNS.

2. Early doubts

Their concerns arose when the detail was examined with respect to the criteria required to establish substances as neurotransmitters (e.g. McLennan, 1963): (i) all neurones were excited in a non-specific manner, even the cholinoceptive Renshaw cells, (ii) there was no apparent enzymatic breakdown to terminate transmitter action, (iii) there was little evidence for the release from nerve terminals of these acidic amino acids, and (iv) the reversal potential for the exogenous amino acids was more hyperpolarised than that for synaptic potential. Additionally, the unnatural D-isomers were as potent as the L-isomers, and glutamic, aspartic and cysteic acids all

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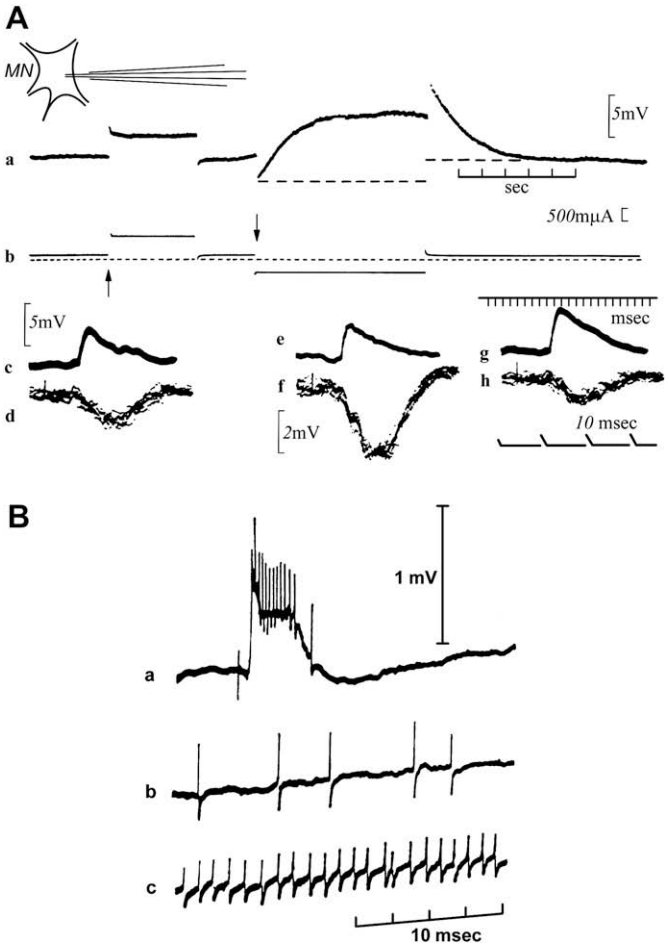

Fig. 1. Aspartate and glutamate excite central neurones. A. Intracellular record (a) showing the action of L-aspartate on the membrane potential of a gastrocnemius spinal motoneurone in vivo. L-aspartate (520 nA) was ejected from an outer barrel of the multibarrel electrode illustrated in the inset; the electrophoretic current (b) is switched and reversed to demonstrate the coupling artefacts (see dashed line on the intracellular record) and the clear depolarising effect of L-aspartate. The lower records show excitatory (c,e,g) and inhibitory (d,f,h) synaptic potentials from the same neurone before (c,d), during (e,f) and after (g,h) ejection of L-aspartate. The reduced epsp and increased epsp were thought to be a result of the change in driving force as a result of the aspartate-induced depolarisation (modified from Curtis et al., 1960). B. Extracellular record of a spinal motoneurone in vivo showing (a) a synaptic response with action potential discharges coincident with the field potential, (b,c) the firing of this neurone in response to the electrophoretic ejection of L-glutamate (20 and 120 nA respectively) (modified from Curtis et al., 1960). Note these are some of the earliest records showing effects of acidic amino acids on single neurones.

had similar potencies as excitants. In addition, their equivalent neutral amino acids, γ-aminobutyric, β-alanine and taurine, were equally active as depressants (Curtis and Watkins, 1960). It was therefore assumed that these naturally occurring amino acids controlled the background excitability in a humoral manner via non-specific receptors on the neuronal membrane. Hence their candidature as transmitters was de-emphasised. Nevertheless over the next few years by investigating these concerns, these authors and their co-workers were at the forefront of re-establishing a transmitter role for L-glutamate.

Briefly some of the early key evidence that answered the first four concerns can be listed:

(i) In addition to the cholinergic excitation of Renshaw cells from recurrent motor axon collaterals, non-cholinergic synaptic excitation of these cells was also demonstrated (Curtis et al., 1961). The discovery that the hotspots for glutamate excitation on crustacean muscle corresponded to sites of synaptic innervation (Takeuchi and Takeuchi, 1963) was also a strong argument against the 'non-specific' claim. Later differential sensitivity of groups of neurones to glutamate ligands also pointed to a more specific type of action (see below).

(ii) Eccles and Jaeger (1957) had earlier considered that diffusion alone could account for removal of transmitter and later Eccles (1964) argued that reversal of the membrane potential during the synaptic event would drive an anionic transmitter, e.g. glutamate, from its receptors. The discovery that active transport processes for acidic amino acids limited the action of extracellular glutamate (Balcar and Johnston, 1972; Lodge et al., 1979; Johnston, 1976) also reduced this concern.

(iii) Similarly evidence for the machinery for glutamate synthesis from glutamine (e.g. Bradford and Ward, 1976; Hamberger et al., 1978; Ward and Bradford, 1979), for uptake (e.g. Logan and Snyder, 1971; Balcar and Johnston, 1972; see Johnston, 1976) and for calcium-dependence of synaptic release (e.g. Roberts, 1974; Davies and Johnston, 1976) followed later.

(iv) By today's standards, the methodology for measuring the reversal potential was relatively crude. Differences in location on neuronal membranes of synaptic events versus exogenous glutamate, the rectification properties of various glutamate receptor-channel complexes and the differential contributions of receptor subtypes to synaptically released and to exogenously administered transmitter could all be contributory to the small reversal potential discrepancy (see e.g. Crunelli et al., 1984). Hence this concern has been dismissed.

3. Hints of diversity

Following on from their initial studies, Watkins synthesised and Curtis and Watkins (1963) tested a large series of acidic amino acids. Among these earliest compounds was *N*-methyl-aspartate, the D-isomer (NMDA) of which has played such a prominent role in defining receptor nomenclature. NMDA proved to be greater than 10 times more potent than L-glutamate itself whereas the L-isomer was similar in potency to L- and D-glutamate. Similarly D-homocysteate was several times more potent than L-homocysteate and glutamate. Such data suggested that there were preferred conformations for activity of these acidic amino acids. This supports the case for specific receptors but the D-isomer pre-eminence seemed at odds with the known stereochemistry of natural compounds. It was not until the stereoselectivity of the transport systems for a number of these amino acids had been considered in relationship to their excitatory properties that this concern began to be understood. Thus in general, the D-isomers were removed from the extracellular environment less avidly and hence their apparent potency in intact preparations was increased (Balcar and Johnston, 1972; Curtis and Johnston, 1974).

Two key pieces of research were important in developing the idea of subtypes of glutamate receptors. Firstly the discovery of antagonists that (i) were selective between the inhibitory amino acids, glycine and GABA, namely strychnine and bicuculline respectively, and (ii) differentiated between synaptic inhibitions convinced researchers of the potential for equivalent acidic amino acid excitatory synapses (see e.g. Curtis and Johnston, 1974). Secondly, the differential distribution of L-glutamate and L-aspartate in the CNS suggested separate roles for these two putative transmitters (Graham et al., 1967; Johnston, 1968; Duggan and Johnston, 1970; see Curtis and Johnston, 1974).

4. Aspartate- and glutamate-preferring receptors

Until the end of 1960s, the relative potencies of glutamate, aspartate and related compounds were thought to be similar

throughout the CNS but indications that this was not true came from early studies of McLennan et al. (1968) on thalamic neurones and Duggan (1974) who showed differential sensitivity to aspartate and glutamate respectively of spinal neurones activated polysynaptically or monosynaptically. Such differences were accentuated when the structurally restrained compounds were tested (McCulloch et al., 1974). These latter authors used NMDA and kainate, a highly potent compound first described by Shinozaki and Konishi (1970), which was to play an important role in nomenclature. By the early 1970s, excitatory amino acids were tentatively divided into 'glutamate-preferring' and 'aspartate-preferring' categories, with kainate and NMDA being regarded as the key exogenous ligands. Another potent excitant due to play a similar nomenclature role, quisqualate, was discovered by Shinozaki and Shibuya (1974) and rapidly assessed on mammalian neurones (Biscoe et al., 1975, 1976).

Early attempts at studying the binding of glutamate and aspartate did not help to reveal clearly different transmitter binding sites, although the sodium-independent and -dependent sites were indicative of transmitter receptors and transporters respectively (see Roberts, 1981); the ^{14}C-glutamate, in use at that time, had too low a specific activity to be very useful in binding studies. The discovery and characterisation of NMDA-insensitive ^{3}H-kainate binding, however, supported conclusions of selectivity from the earlier electrophysiology (Simon et al., 1976; London and Coyle, 1979).

5. NMDA and non-NMDA receptors

The next major breakthrough in characterising excitatory amino acid receptors was the discovery of antagonists related to glutamate, which were weakly selective. These included glutamic acid diethyl ester (GDEE), D-α-aminoadipate (DαAA) and 1-hydroxy-3-aminopyrrolidone-2 (HA-966). In the early studies, GDEE (Haldeman and McLennan, 1972) and DαAA/HA-966 (e.g. Biscoe et al., 1977) showed some selectivity between glutamate and aspartate respectively but greater selectivity between their structural analogues. At this time, the nomenclature was changing from 'aspartate-preferring' receptors to 'NMDA' or 'NMA' receptors and 'glutamate-preferring' receptors were becoming 'non-NMDA' receptors. For example, Davies and Watkins (1979), comparing DαAA and GDEE and some other antagonists on agonist excitation in the cat spinal cord, divided them pharmacologically such that NMDA and L-homocysteate were in a DαAA-sensitive group, L-glutamate, kainate and quisqualate were in a DαAA-resistant group and L-aspartate was intermediate (Fig. 2A and C). Similar observations had been made earlier using HA-966 (Curtis et al., 1973; Davies and Watkins, 1973).

In parallel with these organic antagonists, Evans made the novel and striking observation that the divalent cation, magnesium, also selectively reduced responses to NMDA (Fig. 3A; Evans et al., 1977; Ault et al., 1980). This was later shown to be due to magnesium and other divalent cations limiting channel conductance in a voltage-dependent manner (Nowak et al., 1984; Mayer et al., 1984). All these studies strongly supported the idea of NMDA and non-NMDA receptors for the presumed transmitters, L-aspartate and L-glutamate.

6. NMDA, quisqualate and kainate receptors

In a subsequent blinded experiment comparing the two antagonists, McLennan and Lodge (1979) had a similar result with DαAA but found that, of the above agonists, GDEE selectively reduced responses to L-glutamate, L-cysteate and quisqualate. Excitations induced by kainate, however, remained resistant to both DαAA and GDEE, a result similar to that observed by Hicks et al. (1978). This evidence for three receptor subtypes, namely NMDA, quisqualate and kainate, was confirmed in independent studies by Davies and Watkins (1981) using γ-D-glutamylglycine (DGG) and by Davies and Watkins (1985) using γ-D-glutamylaminomethyl sulfonate (GAMS), both of which reduced kainate more than quisqualate responses. A distinct presynaptic role for kainate receptors had been demonstrated by Biziere and Coyle (1979) and by Köhler et al. (1979) who showed that de-afferentation reduced the neurotoxicity of kainate. Further strong evidence for a separate kainate subtype was provided by Evans who demonstrated the selective depolarising effect of kainate (and glutamate) on dorsal root C fibres (Fig. 8A; Agrawal and Evans, 1986). Because quisqualate, AMPA (see below) and NMDA were essentially inactive on this preparation (Fig. 8A), this receptor on nociceptive afferents was uniquely sensitive to kainate. These observations were subsequently confirmed with more sophisticated technology on dorsal root ganglion neurones (Huettner, 1990; Wong and Mayer, 1993).

This 30-year-old 3-subtype classification, namely NMDA, AMPA and kainate receptors, with all its limitations, has stood the test of time and underpins the modern nomenclature (see below).

7. AMPA not quisqualate

Only the name of the 'quisqualate' receptor has been changed. Povl Krogsgaard-Larsen, a chemist from Denmark, synthesised a series of isoxazoles to be tested in Curtis's group just as the McLennan and Lodge (1979) work was being completed there. Tested under the same conditions, the potent excitatory action of α-amino-3-hydroxy-5-methylisoxazolepropionic acid (AMPA) was antagonised by GDEE and not by DαAA (Fig. 4A; Krogsgaard-Larsen et al., 1980). Therefore, when later quisqualate was found to act at metabotropic glutamate receptors (Sladeczek et al., 1985; Nicoletti et al., 1986), it was sensible to change the 'quisqualate' nomenclature to 'AMPA'. Like all changes in nomenclature, however, it took some time for this change to be universally employed. Interestingly, although more potent agonists have been found for NMDA receptors (e.g. tetrazol-5-yl-glycine; Schoepp et al., 1991) and for kainate receptors (e.g. domoic acid; Biscoe et al., 1975, 1976), the original names have been retained. During 1980s, the concept of the NMDA, AMPA and kainate subclasses of glutamate receptor became well entrenched (Watkins and Evans, 1981; McLennan, 1983; Collingridge and Lester, 1989).

8. NMDA receptors and synaptic events

In parallel with their value in elucidating the receptor pharmacology, these antagonists, including magnesium, facilitated the answer to the fundamental query as to the role of these newly demonstrated receptors in synaptic events in the CNS. Although the earliest experiments were not necessarily convincing, the steadily accumulating data showing reduction of synaptic excitations with DαAA strengthened the case (e.g. Haldeman and McLennan, 1972; Biscoe et al., 1977; Lodge et al., 1978; Davies and Watkins, 1979) for NMDA receptors mediating 'polysynaptic' excitations (Fig. 2B and C). Subsequently, the development of highly selective NMDA antagonists, such as the very important D-2-amino-5-phosphonopentanoate (D-AP5; e.g. Davies and Watkins, 1982; Collingridge et al., 1983; Evans et al., 1982), added considerable confidence to some of the earlier conclusions about receptors subtypes and led to numerous investigations confirming the synaptic role of NMDA receptors throughout the CNS.

During most of the above studies, it was generally considered that L-aspartate was the likely transmitter at NMDA receptors, largely because of its greater sensitivity to NMDA antagonists than L-glutamate. Other compounds considered as potential transmitters at that time included L-homocysteate (see e.g. Do et al.,

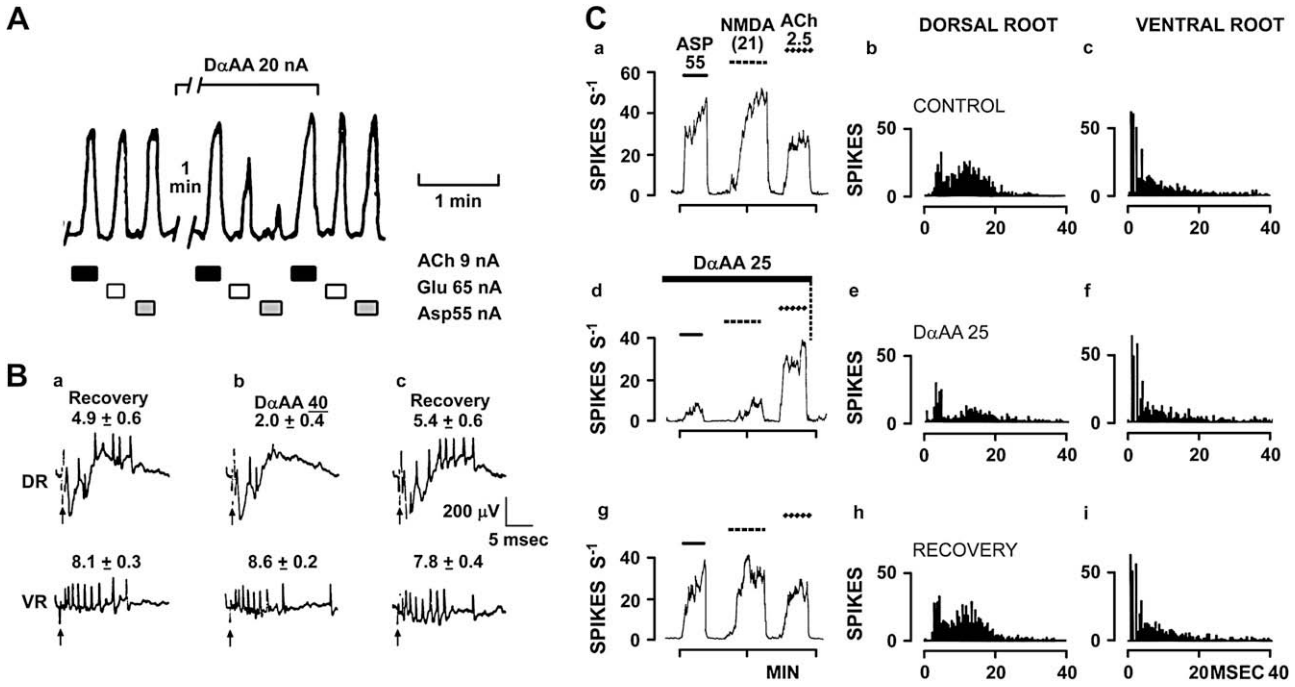

Fig. 2. D-α-aminoadipate selectively reduces responses of Renshaw cells to aspartate, NMDA and synaptic excitation from afferent nerves. A. Ratemeter record showing selective and reversible antagonism of aspartate during ejection of 20 nA DαAA. B. Synaptic responses of the same cell following dorsal (DR) and ventral (VR) root stimulation before (a), during (b) and after (c) ejection of 40 nA DαAA. (A and B modified from Davies and Watkins, 1979). C. Ratemeter records showing selective and reversible antagonism of aspartate and NMDA before (a), during (b) and after (c) ejection of 25 nA DαAA, and histograms of the synaptic responses to dorsal and ventral root stimulation before (b,c), during (e,f) and after (h,i) ejection of 25 nA DαAA (modified from Lodge et al., 1978). Note that these are some of the first published records convincingly showing selective excitatory amino acid antagonism and selective reduction of the afferent synaptic responses. The responses to acetylcholine and to recurrent ventral root stimulation are unaffected.

1986) and quinolinate (Stone and Perkins, 1981). However, the observation that L-glutamate displaced D-AP5 binding 10×, 4× and 100× more potently than L-aspartate, L-homocysteate and quinolinate (Olverman et al., 1984) negated the former argument. Therefore, L-glutamate assumed the status of the neurotransmitter at NMDA receptors in the brain.

D-AP5 also opened the way for new concepts to be discovered. Thus, for example, Collingridge et al. (1983) first identified the role of this receptor in synaptic plasticity within the hippocampus, which was subsequently related to deficits in spatial learning in the water maze tests (Morris, 1989). Now this receptor is established as a major player in many forms of Long Term Potentiation and Long Term Depression throughout the CNS (see Bliss and Collingridge, 1993). Experiments with D-AP5, and its heptanoate homologue, D-AP7, were also crucial to understanding the central role of NMDA receptors in epilepsy (Croucher et al., 1982), ischaemic neurodegeneration (Simon et al., 1984) and pain (see Dickenson, 1990). Such insights into the potential therapeutic role of NMDA antagonists led to huge synthetic activity in both the pharmaceutical industry and academia. By the mid-1990s, a handful of such compounds had been tested in man (see Herrling, 1997).

9. The glycine site of NMDA receptors

NMDA receptor pharmacology took on new and interesting aspects during 1980s. In Ascher's lab, the requirement for glycine (or related amino acid) as a co-agonist with L-glutamate (Johnson and Ascher, 1987). The nanomolar affinity of this strychnine-insensitive glycine binding site together with the micromolar glycine concentration in CSF (Curtis and Johnston, 1974; Kleckner and Dingledine, 1988) suggested that, unless the receptors were protected by a very high affinity transport process, the glycine site would be fully occupied in physiological conditions. This, however, remains a topic of debate even today. Shortly afterwards, pharmacological studies demonstrated this to be the site of action of HA-966 (see above) as an NMDA antagonist (Fletcher and Lodge, 1988; Foster and Kemp, 1989; Drejer et al., 1989; Lodge and Jones, 1990) (see Fig. 6). The NMDA blocking action of kynurenic acid and in particular 7-chlorokynurenate was also shown to be via this glycine site (Kemp et al., 1988; Mayer et al., 1988; Birch et al., 1988; Kessler et al., 1989). This glycine receptor became the target of considerable pharmacological activity (Kemp and Leeson, 1993).

10. Ketamine and phencyclidine

Also in the early 1980s, while studying the central effects of various general anaesthetics, Lodge's group noted that unlike barbiturates and steroid anaesthetics which potentiated GABA mediated inhibitions, the dissociative anaesthetic, ketamine, selectively reduced polysynaptic spinal reflexes (Lodge and Anis, 1984). The mechanism of action of ketamine was shown to be postsynaptic antagonism at the NMDA receptor (Fig. 5A; Anis et al., 1983). This effect was non-competitive in nature (Lodge and Johnston, 1985; Martin and Lodge, 1985) occurring in a use- and voltage-dependent manner indicative of channel blockade (Honey et al., 1985). The related drug, phencyclidine (PCP) was approximately 10× more potent than ketamine as an NMDA antagonist (Fig. 5B; Anis et al., 1983), a finding which paralleled behavioural studies and PCP binding studies. Several pharmaceutical companies, that were searching for 'PCP antagonists' as potential antipsychotics, made their compounds available. As a result, about 20 compounds, arycyclohexylamines, dioxalanes, benz(*f*)isoquinolines, benzomorphans, etc., including stereoisomeric pairs, were examined between 1982 and 1986 (see Lodge and Berry, 1984; Lodge et al., 1988). Their relative NMDA antagonist potencies were found to closely correlate with their relative potencies in PCP binding studies and in behavioural studies of the discriminative cues of these psychotomimetic agents (see Lodge and Berry, 1984;

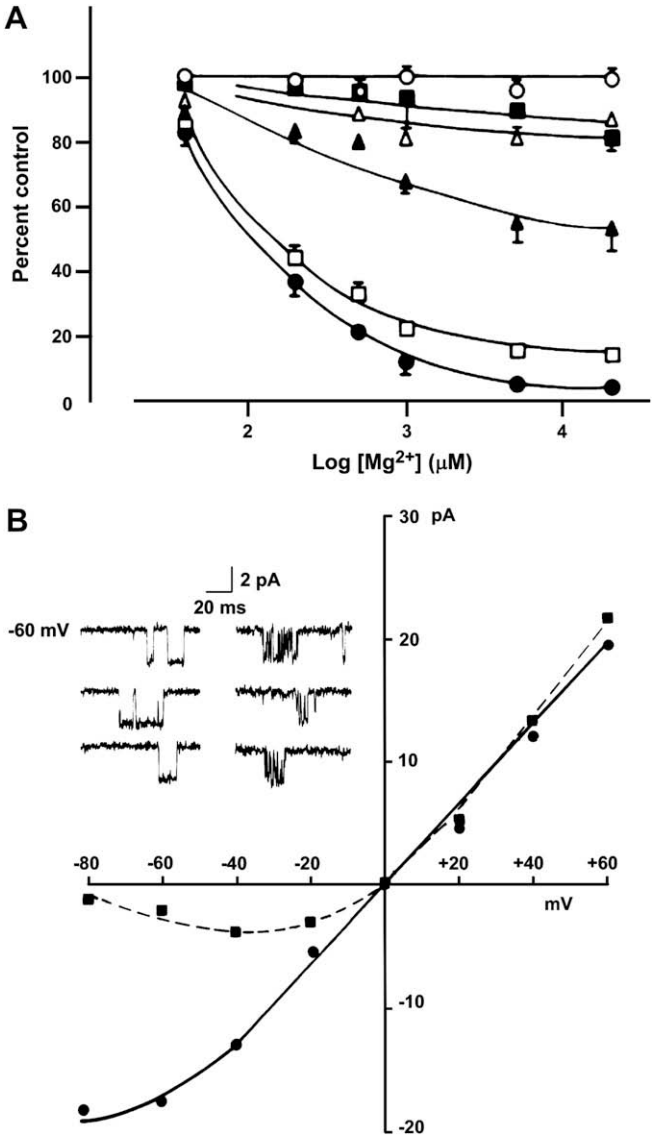

Fig. 3. Magnesium reduces NMDA responses. A. Dose–response curves from an isolated hemisected spinal cord showing the effects of magnesium on depolarising responses of frog ventral roots to the following amino acids from the top downwards: quisqualate, kainate, L-glutamate, L-aspartate, L-homocysteate and NMDA (modified from Ault et al., 1980). B. Current–voltage curve from a cortical neurone in culture showing the non-linearity (negative slope conductance) of the curve introduced by the presence of magnesium (dashed line) compared with that in magnesium-free medium (solid line). Inset shows single channel openings in responses to NMDA in the magnesium-free medium (left hand records) and after addition of magnesium to the medium (right hand records). The flickering nature of the channel current in magnesium is thought to represent the slow movement of magnesium ions through the channel. Note that establishment of this block by normal extracellular levels of magnesium was very central to understanding the mode of action of NMDA receptor channels (modified from Johnson and Ascher, 1988).

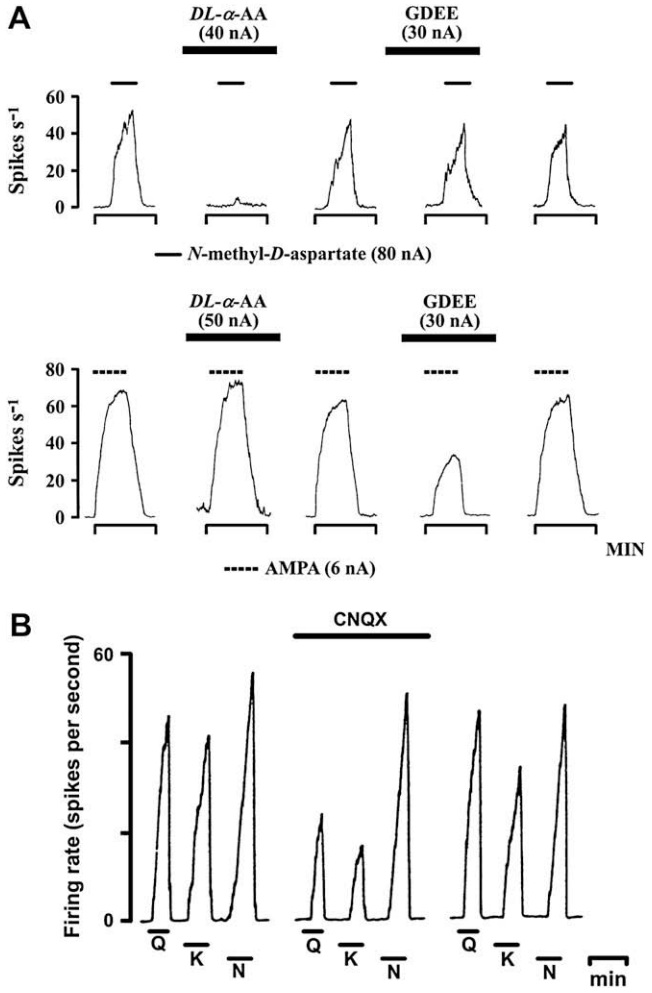

Fig. 4. Non-NMDA receptor pharmacology. A. DLαAA reduces responses to NMDA but not to AMPA whereas GDEE reduces responses to AMPA and not those to NMDA. This degree of selectivity with GDEE was fairly typical, it being unusual to see full block without some reduction of the response to NMDA. Note this is the first published record showing the effects of AMPA on central neurones (modified from Krogsgaard-Larsen et al., 1980). B. CNQX reduces responses to quisqualate and kainate of spinal neurones to much the same extent but with no effect on the responses to NMDA (modified from Honore et al., 1988). Note AMPA became the agonist of choice for receptors of the same name and CNQX and later NBQX became very useful agents for determining synaptic responses mediated by non-NMDA receptors.

Lodge et al., 1988). Because ketamine and PCP induce schizophrenia-like symptoms in man (Domino et al., 1965; see Domino and Luby, 1981), it was suggested that modulating glutamate function might ameliorate psychotic symptoms (see Lodge and Berry, 1984; Lodge et al., 1988), a strategy subsequently followed by many pharmaceutical companies. This discovery underpins the glutamate hypothesis of schizophrenia (Carlsson et al., 2001).

One of the most potent and selective of these use-dependent and voltage-dependent channel blockers is MK-801 (Wong et al., 1986) which has proved a valuable tool for studying NMDA receptor function (Wong and Kemp, 1991). Indeed its various putative therapeutic goals spurred the search for other NMDA antagonists. Although several of these have been progressed towards the clinic, the potential side-effect problems, particularly of a psychoactive nature, have prevented their development. One of these, aptiganel, was tested in a stroke trial (see Herrling, 1997) but failed efficacy measures probably due to dose constraints and poor trial design. Ketamine is still widely used and has strong advocates as an analgesic/anaesthetic agent (see Sinner and Graf, 2008; Campbell-Fleming and Williams, 2008). Beside ketamine, however, the only therapeutically successful NMDA antagonist developed to date is memantine which is also a low affinity, use- and voltage-dependent analogue (Parsons et al., 1999, 2007; Rogawski and Wenk, 2003). Excitingly, new data are emerging that a single treatment with ketamine produces a long lasting anti-depressant effect in treatment-resistant patients (Berman et al., 2000; Zarate et al., 2006).

These compounds, unlike the polar competitive antagonists, have rapid access to the CNS following systemic administration (Fig. 5) and, in the case of ketamine, a short duration of action. This makes them ideal for studying the role of NMDA receptors in physiological and behavioural experiments. Thus, ketamine was

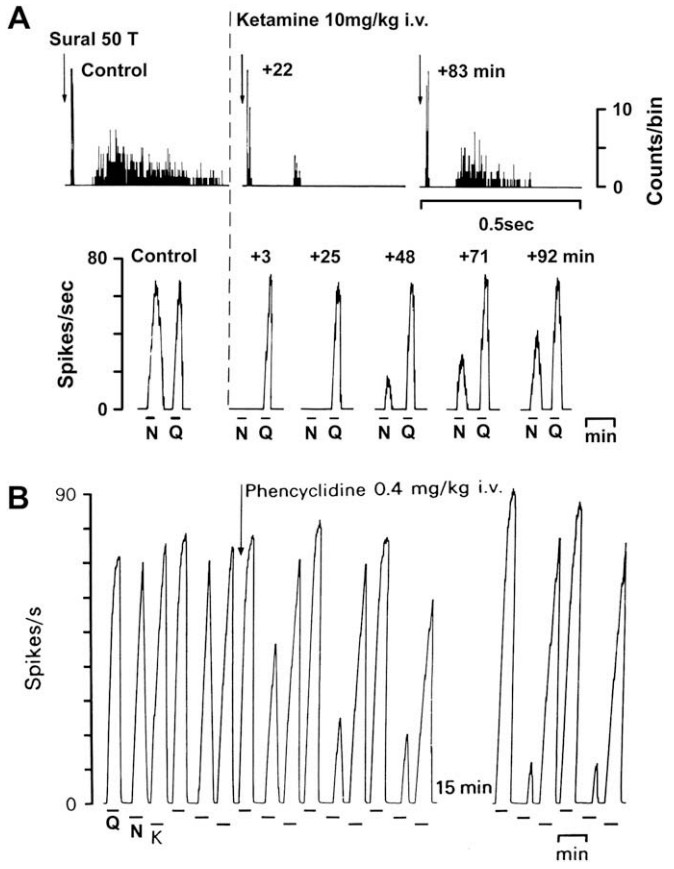

Fig. 5. Ketamine and phencyclidine as NMDA antagonists. A. Ketamine (10 mg/kg i.v.) selectively blocks polysynaptic responses of a spinal neurone with little effect on the earlier monosynaptic response following stimulation of high threshold afferents in the sural nerve. Concomitantly the responses to electrophoretic NMDA are abolished whereas responses to quisqualate are unaffected. Partial recovery is seen over the next 90 min (modified from Lodge et al., 1983). B. Phencyclidine (0.4 mg/kg i.v.) almost blocks responses to NMDA whereas responses to quisqualate and kainate are not reduced. The recovery from phencyclidine usually required more than 1 h of stable recording. Note these are some of the first records showing NMDA antagonism by these dissociative anaesthetics.

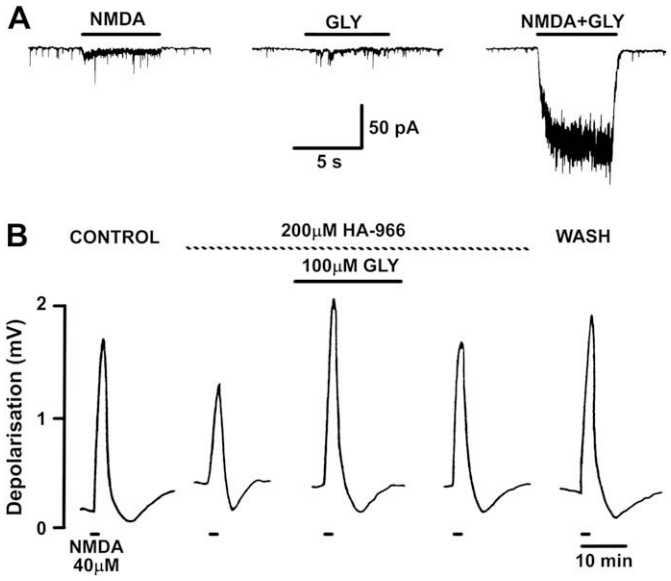

Fig. 6. Glycine as a co-agonist for NMDA receptor activation. A. Whole cell currents from a patch clamp recording from a neurone in culture, showing minimal current induced by NMDA or glycine alone, but a robust response when applied together. Precautions had been taken to minimise glycine content of the perfusing medium. Note this requirement for two agonists was a unique and exciting finding (modified from Johnson and Ascher, 1988). B. NMDA antagonism by HA-966 is reversed by co-administration of glycine. Glycine did not reverse the NMDA antagonism induced by D-AP5 or by ketamine. Note HA-966 was amongst the first selective NMDA antagonists to be discovered (see text) but its structure was atypical of the other competitive antagonists such as DαAA known at the time. Hence it was some 20 years before its mode of action was understood (modified from Fletcher and Lodge, 1988).

used to demonstrate the role of NMDA receptors in spinal cord 'wind-up', a short term potentiation of nociceptive responses often linked to sensitisation in pain pathways (Davies and Lodge, 1987).

Finally, the schizophrenomimetic properties of ketamine and PCP predicted that other NMDA antagonists would have similar behavioural properties. Although this hasn't been tested to the full, two competitive antagonists, D-CPPene and CGS197555 showed psychogenic effects in man (Herrling, 1997).

11. Blind alleys

Despite this clear pharmacological separation of the three receptor subtypes, there have been suggestions that the different receptors could operate the same channel.

Eric Barnard's group extracted separate quisqualate and kainate binding proteins from *Xenopus* brain which could be recombined to produce a unitary receptor for these two agonists (Henley et al., 1989). Later they also found that an NMDA receptor could associate with non-NMDA receptors so that the different ligands could operate the same complex (Henley et al., 1992) and that such complexes occur in *Xenopus* brain (Soloviev et al., 1998). Such a unitary receptor appears unique to *Xenopus* and has not appeared from cloning endeavours in mammals.

A similar conclusion was made from analyses of sub-conductance states of single channel openings in cultured mammalian neurones. Thus it was suggested that, although kainate and quisqualate preferentially activated lower conductance states and NMDA higher conductance states, transitions between the states indicated a common channel for the different receptor subtypes in hippocampal neurones (Jahr and Stevens, 1987) and possibly in cerebellar Purkinje cells (Cull-Candy and Usowicz, 1987). This idea appeared at odds with the observations of the selectivity of the channel blocking NMDA antagonists, such as ketamine, PCP and MK-801 and was quickly dropped.

12. Binding studies

Binding studies in 1980s also made major contributions to our understanding of the receptor subtypes (Foster and Fagg, 1984; Honore and Drejer, 1988; Watkins and Olverman, 1988; Monaghan and Cotman, 1982; Monaghan et al., 1989; Young and Fagg, 1990). High specific activity ^{3}H-glutamate also proved an invaluable tool for describing the localisation of receptors. Thus, using selective ligands to displace glutamate binding and the technique of auto-radiography, Monaghan and Cotman (1982) and Monaghan et al. (1984) showed the differential distribution of the three ionotropic receptor types. Ann Young's group demonstrated the identical localisation of the PCP, NMDA and strychnine-insensitive glycine binding sites in hippocampal and cortical regions of the rat brain (Maragos et al., 1991; McDonald et al., 1990). Similarly, the ^{3}H-glutamate bound to two sites on postsynaptic densities displaced by quisqualate and NMDA respectively, confirming the pharmacology of synaptic excitation as described above (Fagg and Matus, 1984). With the development of ^{3}H-labelled AMPA and kainate radioligands, support for separate receptors of the same name was forthcoming. Thus, for example, the effect of inorganic ions and of

glutamate receptor ligands on the binding of AMPA and kainate were quite different (Honore and Drejer, 1988).

13. AMPA and kainate antagonists

As mentioned above, the relatively poor selectivity of such compounds as GDEE and DGG, limited the investigation of the non-NMDA receptors' subtypes. The discovery therefore of the quinoxalinediones, DNQX and CNQX (Honore et al., 1988; Fletcher et al., 1988) and later of NBQX (2,3-dihydroxy-6-nitro-7-sulfamylbenz(*f*)quinoxaline; Sheardown et al., 1990) was an important breakthrough. NBQX had a 30-fold greater affinity for AMPA binding than for kainate binding and, unlike CNQX and DNQX, was essentially free of activity at the glycine site of the NMDA receptor. On cortical wedges, the selectivity of NBQX was reflected with approximate pA_2 values versus AMPA, kainate and NMDA of 7.1, 5.6 and <4, respectively (Lodge et al., 1991). It was, however, only weakly selective between AMPA and kainate excitations on spinal neurones in vivo (Lodge and Jones, 1990). This reflects both the non-specificity of NBQX and to a greater extent that of kainate, which induces depolarisation via both AMPA and kainate receptors, as suggested from binding studies (e.g. Honore and Drejer, 1988).

In 1989, a 2,3-benzodiazepine, GYKI52466, was reported to block monosynaptic reflexes but not via a GABA potentiating mechanism (Tarnawa et al., 1989). When tested directly on central neurones, GYKI52466 and structural analogues, preferentially reduced responses to AMPA in a non-competitive manner (Ouardouz and Durand, 1991; Lodge et al., 1992, 1996; Donevan and Rogawski, 1993; Bleakman et al., 1996; Paternain et al., 1995; Wilding and Huettner, 1995) (see Fig. 7A). This and related compounds, e.g. GYKI53655 (LY300168) and SYM2206, are valuable tools for separating the roles of AMPA and kainate receptors (Lerma et al., 1997; Bleakman and Lodge, 1998).

Almost in parallel with the demonstration of this negative allosteric modulator of AMPA receptor function was the elucidation of potent compounds that had the reverse effect. Cyclothiazide and related substances were shown to enhance responses to AMPA receptor agonists by reducing desensitisation/deactivation at this receptor (Bertolino et al., 1993; Zorumski et al., 1993; Palmer and Lodge, 1993; Patneau et al., 1993) (see Fig. 7B). Some older nootropic compounds such as aniracetam have a similar action (e.g. Ito et al., 1990; Tang et al., 1991; Staubli et al., 1992). Newer compounds with similar activities were soon discovered and characterised by Cortex Pharmaceuticals and Eli Lilly & Co. (e.g. Lynch et al., 1997; Arai et al., 2000; Murray et al., 2003). Although negative allosteric modulators of kainate receptors had not yet been described, certain plant lectins, and in particular concanavalin A, a blocker of glutamate receptor desensitisation on insect muscles (Mathers and Usherwood, 1978), reduced the desensitisation of kainate receptors on DRG neurones (Huettner, 1990; Pook et al., 1993). Wong and Mayer (1993) used these two blockers of desensitisation to distinguish between AMPA-preferring and kainate-preferring receptors. The sites of action on the AMPA receptor protein for the positive and negative allosteric modulators have been shown to be separate (Mayer and Armstrong, 2004; Balannick et al., 2005; Jin et al., 2005).

14. AMPA and kainate receptors in synaptic events

The quinoxalinediones were used to establish a role for non-NMDA receptors in synaptic transmission. Thus on hippocampal, cortical, amygdala, nigral, thalamic, brainstem and spinal neurones, synaptic responses were significantly reduced by CNQX and DNQX (Fletcher et al., 1988; Blake et al., 1988; Davies and Collingridge, 1989; Salt and Eaton, 1989; Long et al., 1990; Andreasen et al., 1989; Mereu et al., 1991; Rainnie et al., 1991). In all such experiments, it is the early fast component that is sensitive to non-NMDA antagonists, i.e. the reverse of that described with NMDA antagonists (e.g. Lodge et al., 1978; Davies and Watkins, 1979).

The question as to whether the pharmacologically distinct excitations are mediated at the same or different synapses was answered by Dale and Roberts (1985). Using a less selective antagonist, they clearly showed that unitary EPSCs had early non-NMDA and later NMDA receptor-mediated components, showing that release from a single afferent could activate both receptor types. This concept was substantiated in later studies (Forsythe and Westbrook, 1988; Collingridge et al., 1988; Sillar and Roberts, 1988; Andreasen et al., 1988; McBain and Dingledine, 1992; Clark and Collingridge, 1995). One important use of CNQX, and other quinoxalinediones, was to block AMPA and kainate receptor-mediated synaptic transmission and thereby enable the synaptic activation of pure NMDA receptor-mediated synaptic responses (Blake et al., 1988; Davies et al., 1989). This approach has since been exploited extensively, for example to demonstrate the plasticity of NMDA receptor-mediated synaptic transmission (e.g. Bashir et al., 1991).

GYKI52466 and related 2.3-benzodiazepines were used to define the majority of these postsynaptic non-NMDA receptors as AMPA receptors, rather than kainate receptors, on cortical, brainstem, thalamic and spinal neurones (Turner and Salt, 1998; Ouardouz and Durand, 1994; Világi et al., 1998; Rammes et al., 1994). In some experiments cyclothiazide and GYKI52466 had opposing effects confirming the identity of these postsynaptic receptors as the AMPA subtype (e.g. Rammes et al., 1994; Vyklicky et al., 1991).

Blocking AMPA receptors with these 2,3-benzodiazepines also helped to reveal a role for kainate receptors (Paternain et al., 1995). Thus, activation of kainate receptors was found to regulate both excitatory (Chittajallu et al., 1996) and inhibitory (Clarke et al., 1997) synaptic transmission as well as contributing to the synaptic response at mossy fibre synapses in the hippocampus (Vignes and Collingridge, 1997; Castillo et al., 1997). The presynaptic effects are most likely due to changes in calcium entry into terminals (Kamiya and Ozawa, 1998). Kainate receptors mediating synaptic excitation in the mossy fibre pathway to CA3 were also demonstrated by blocking AMPA receptors with 2,3-benzodiazepines (Vignes and Collingridge, 1997; Frerking et al., 1998; Yamamoto et al., 1998). In the same fashion, kainate receptor-mediated synaptic responses have been demonstrated in the basolateral amygdala (Li and Rogawski, 1998) and in spinal nociceptive transmission (Simmons et al., 1998). Other pharmacological evidence supports this spinal role of kainate receptors (Stanfa and Dickenson, 1999; Li et al., 1999).

15. Diversity within the NMDA, AMPA and kainate classes

Two other actions of glutamate-like agonists were found at about the same time: (i) L-AP4 reduced synaptic excitation without antagonism at the three receptor subtypes, and (ii) trans-ACPD induced excitation, an effect not reversed by the known glutamate antagonists. These effects, initially considered as being due to ionotropic receptors, are now known to be mediated by G-protein coupled, metabotropic glutamate receptors (see e.g. Monaghan et al., 1989; Schoepp and Conn, 1993).

Even before the impact of cloning was realised, there were hints of pharmacological differences within the NMDA, AMPA and kainate classes of receptor. For example, diversity of NMDA receptors was well established before its cloning (e.g. Yoneda and Ogita, 1991; Monaghan and Beaton, 1992). Differences in the affinity for agonists and antagonists (Monaghan et al., 1988; Monaghan and Beaton, 1991), in glycine binding (O'Shea et al., 1991), in PCP binding (Ebert et al., 1991), in MK-801 binding and polyamine effects (Reynolds and Palmer, 1991) and in the effects of ifenprodil (Reynolds and

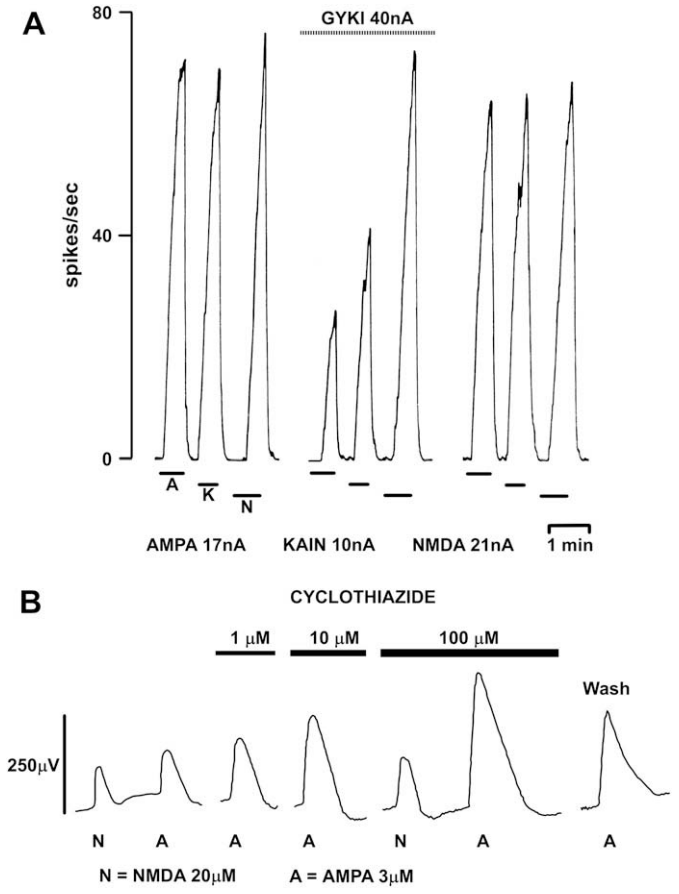

Fig. 7. Allosteric antagonism and potentiation of responses to AMPA. A. GYKI52466 reversibly reduces responses of this spinal neurone to AMPA and kainate but not to NMDA. Note that although kainate responses are reduced, 2,3-bezodiazepines such as GYKI52466 are very selective for AMPA receptors. Kainate activates both AMPA and kainate receptors. Note GYKI52466 was the first truly selective AMPA antagonist described (modified from Lodge et al., 1992). B. Cyclothiazide potentiates responses to AMPA and not those to NMDA on a cortical slice preparation. Cyclothiazide is also inactive on kainate receptors making it also a useful compound for discriminating between AMPA and kainate responses (Woolley and Lodge, unpublished observation).

Miller, 1989; Rao et al., 1989) all pointed to NMDA receptor heterogeneity (see Monaghan and Buller, 1994).

High and low affinity binding sites for AMPA and kainate receptors were described. Although the AMPA sites appeared to be interconvertible, the two kainate binding sites could represent subdivisions of kainate receptors (see Honore and Drejer, 1988; Honore et al., 1989; Young and Fagg, 1990; Monaghan et al., 1989). The two AMPA binding sites are probably explained by desensitised and non-desensitised states of the same AMPA receptors (O'Brien and Fischbach, 1986; Patneau and Mayer, 1991).

Differences in the rectification and calcium permeability properties of AMPA and kainate receptors have been identified (e.g. Iino et al., 1990; Brorson et al., 1992). Similarly variations in sensitivity to Joro spider polyamine toxins led to description of Type I and II AMPA receptors in hippocampal neurones (Iino et al., 1996). Previously, argiotoxin had been shown to reduce responses of rat spinal neurones to AMPA rather than to NMDA (Jones and Lodge, 1991) whereas on cortical neurones, argiotoxin selectively reduced responses to NMDA (Priestley et al., 1989). These results are consistent with diversity within both the AMPA and NMDA receptor populations (Williams, 1993, 1997).

Interestingly, kainate receptor heterogeneity was suspected from early studies of kainate actions on hippocampal CA1 neurones (Kehl et al., 1984); direct depolarisation, presynaptic facilitation of excitatory synapses and inhibition of GABAergic inputs have separate characteristics suggestive of 'a number of distinct receptor types' (McLennan et al., 1984).

16. Cloning of glutamate receptors: the AMPA receptor subunits

The first cloning depended on the observation that brain mRNA injected into *Xenopus* oocytes by Miledi et al. induced responses to glutamate and kainate (Gunderson et al., 1984). Several years later, in Heinemann's group this experiment was replicated and the most effective sample of brain mRNA was used to produce a cDNA library which in turn was used to produce 44,000 pools of mRNA. Only one of these pools produced a reasonable glutamate-induced current when injected back into the oocytes. The active pool had then to be continually subdivided until the cDNA coding for the glutamate receptor was found. The sense, but not the anti-sense, mRNA transcribed from this clone resulted in glutamate-activated currents which were considerably larger when kainate was used as the agonist. The DNA was sequenced and the amino acid structure deduced (Hollmann et al., 1989) and named GluR-K1 on the basis of its sensitivity to kainate. In the next 2 years, the same basic protein was reported by six other groups and, interestingly with respect to nomenclature, given 5 other names! Nakanishi et al. (1990) retained GluR-K1, Keinanen et al. (1990) named it GluR-A, Sakimura et al. (1990) named the mouse version α1, whereas Puckett et al. (1991), Potier et al. (1992) and Sun et al. (1992) named the human version GluH1, KR4 and HBGR1 respectively. The initial implication was that these were kainate receptors. It quickly became apparent using binding studies that this was an AMPA receptor protein, showing, as with the native AMPA receptors, non-desensitising responses to kainate (see e.g. Sommer et al., 1990) and the name GluR1 and GluR-A became the commonly used names thereafter (Hollmann and Heinemann, 1994; Nakanishi and Masu, 1994; Sprengel and Seeburg, 1993).

Following on from the original report from Heinemann's group (Hollmann et al., 1989), cloning by sequence homology revealed further AMPA receptor family members in the next few years. Thus Boulter et al. (1990), Keinanen et al. (1990), Nakanishi et al. (1990), and Sakimura et al. (1990) described a second subunit as GluR2, GluR-B, GluR-K2 or α2 respectively, a third one as GluR3 or GluR-C and a fourth one as GluR4 or GluR-D. These all had about 70% sequence homology with each other and a similar pharmacology. They were initially thought of as AMPA/kainate receptors.

17. Cloning of glutamate receptors: the kainate receptor subunits

Homology screening also led to the discovery of a subunit with 40% homology to GluR1–4, which was named GluR5 (Bettler et al., 1990). The lower homology suggested the possibility of a different subtype, but the weak responses of GluR5 to agonists did not allow it to be classified pharmacologically (Bettler et al., 1990). However, a subsequent study by Sommer et al. (1992) reported the desensitisation to kainate of this subunit (GluR5) akin to that seen in sensory neurones (Huettner, 1990). This defined GluR5 as a member of the kainate family; also called EAA3 in man (Korczak et al., 1995). In between times, Egebjerg et al. (1991) had described GluR6, another subunit with similar kainate-preferring properties, its equivalents in the mouse and in the human were named respectively β2 by Morita et al. (1992) and humEAA4 by Hoo et al. (1994). A third member of this series was cloned as GluR7 by Bettler et al. (1992) and GluR7 by Lomeli et al. (1992). This group of 3 subunits has about 70% homology between them and about 40% homology with the AMPA receptors, GluR1-4. They bind kainate

with high affinity and form functional channels activated by glutamate and kainate which are enhanced in the presence of concanavalin A (Hollmann and Heinemann, 1994; Nakanishi and Masu, 1994; Sprengel and Seeburg, 1993).

A subunit with even higher kainate affinity, KA1, was cloned by Werner et al. (1991); this was followed by the cloning of a second one variously named KA2 in the rat (Herb et al., 1992) and γ in the mouse (Sakimura et al., 1992). The equivalents in man were named as humEAA1 and humEAA2 (Kamboj et al., 1992, 1994). They share about 70% homology with each other but only about 40% with GluR1–4 and GluR5–7. These subunits did not form functional channels when expressed alone or with each other but did combine with the GluR5–6 group to produce functional channels with modified properties (Herb et al., 1992; Hollmann and Heinemann, 1994).

18. Cloning of glutamate receptors: the NMDA receptor subunits

The NMDA subunits were cloned roughly in parallel with the kainate receptors. The first one was named NMDAR1 or NR1 in the rat (Moriyoshi et al., 1991) and also in the human (Karp et al., 1993), but called ζ (zeta) in the mouse (Yamazaki et al., 1992b). A second series, the NR2 subunits, followed shortly. Monyer et al. (1992) and Monyer and Seeburg (1993) cloned the rat NR2A–D. Meguro et al. (1992) cloned the mouse ε1, Kutsuwada et al. (1992) the mouse ε1–ε3 and Ikeda et al. (1992) the mouse ε4. The full family was also completed by Ishii et al. (1993) who named them NMDAR2A–NMDAR2D. It quickly became apparent that the NR1 subunit bound glycine and not glutamate whereas the NR2 subunits bind glutamate, which accounts for the co-agonist property of native NMDA receptors. It is therefore somewhat surprising, knowing this, that Moriyoshi et al. (1991) were able to show glutamate-activated currents after expression of NR1 alone. These responses were considerably enhanced by inclusion of one or more of the NR2 subunits, which by themselves had no detectable function. The NR2 subunits have a 40% homology with each other and a 25% homology with NR1 but low homology with the AMPA and kainate receptor subtypes. The NR2 subunits convey differences in pharmacology, e.g. the NR2B subunit combinations underlie the sensitivity to ifenprodil and related compounds. Latterly a third type of NMDA subunit was cloned, this NR3 subtype (initially called NMDAR-L; Sucher et al., 1995 or chi-1/χ-1; Ciabarra et al., 1995) also binds glycine rather than glutamate and co-expression with other NMDA subunits caused an inhibition of the currents evoked by NMDA and glutamate. No such inhibition was observed when the NR3 was expressed with GluR1 or GluR6. A second member of the glycine-sensitive NR3 group, namely NR3B, was cloned later (Matsuda et al., 2002).

19. Cloning of other glutamate binding proteins

In addition to the above subunits, several proteins have been cloned that bind glutamate and have some homology with the above receptor subunits. These include two rat delta units, δ1 (Yamazaki et al., 1992a) expressed throughout the developing brain, and δ2 expressed mainly in the cerebellum (Lomeli et al., 1993; Araki et al., 1993). Although apparently not forming functional channels with any of the known subunits, the δ2 subunit is crucial for synaptic plasticity in the cerebellum. Earlier, kainate binding proteins from the chick (Gregor et al., 1989) and from the frog (Wenthold et al., 1990) and from rat brain (Hampson et al., 1987) were identified but their functions have remained elusive. Other glutamate binding proteins thought at the time to be subunits of the NMDA complex were isolated and some were cloned but not prove to be functionally active (Kumar et al., 1991). Although the role of these proteins is very sketchy, it should be remembered that the situation with KA1 and KA2 was similar until their partners, e.g. GluK5 and GluK6, were elucidated.

20. Molecular diversity and pharmacological development

The results of the above and subsequent molecular biological studies have opened our eyes to the potential diversity of ionotropic glutamate receptors. Assuming that there are homomeric and heteromeric combinations within each of these three groups resulting in tetrameric receptors, the potential for combinations is enormous. Totally beyond the scope of this review, there are also numerous possibilities for post-transcriptional and post-translational variations, each adding nuances to receptor functions. Thus, the number of splice variants is large, RNA editing is a feature of many of these subunits (Sommer et al., 1991). Such diversity will have to be dealt with eventually by the NC-IUPHAR Nomenclature Committee. As an example, for NR1 alone there are 3 sites for splice variants resulting in 8 potential combinations. There are at least 5 ways of naming such splice variants!! (see Zukin and Bennett, 1995), and pedantically this is a glycine, rather than glutamate, receptor subunit! In the first extracellular loop of the GluR1–4, there is the possibility of alternative exons resulting from splice variants which affect rates of desensitisation, and hence are named 'flip' and 'flop' and to complicate matters further there is an RNA editing site immediately preceding this region which also contributes to the receptor kinetics (Lomeli et al., 1994) – again the opportunities for naming are complex!

Characterisation of the recombinant receptors has greatly aided our understanding of the glutamate pharmacology. For example, within the above 'flip/flop' domain is a single amino acid that determines sensitivity to cyclothiazide. The Q/R editing site within the ionophores of the AMPA and kainate receptors determines their calcium permeability and their sensitivity to polyamines, including the wasp and spider toxins, and hence rectification properties – the edited and unedited forms will need denoting in the nomenclature. Similarly, an equivalently located asparagine residue controls the calcium permeability and magnesium block of NMDA receptor channels. Ifenprodil and related compounds act selectively at NMDA receptors containing NR2B subunits.

Screening of compounds on the cloned receptors has also led to novel pharmacology. An interesting example is that certain isoxazoles and decahydroisoquinolines, originally thought to be selective agonists and antagonist respectively for AMPA receptors (Schoepp et al., 1995; Bleakman and Lodge, 1998), also showed activity at the kainate subunits expressed on DRG neurones. This ultimately led to the elucidation of both agonists, ATPA and iodowillardiine, and antagonists, LY382884 and ACET, which are highly selective for the GluR5 receptor subunit (Fig. 8B; see Bleakman and Lodge, 1998; Jane et al., 2009; Dargan et al., 2009).

21. Early nomenclature proposals

While the diversity of native receptors was being elucidated, suggestions were made for a nomenclature more generic in nature, akin to the D1 and D2 names for dopamine receptors. For example, Nadler et al. used the terms GLU A, GLU B and GLU C to describe glutamate binding sites differentially sensitive to a variety of inorganic ions and of receptor ligands (Werling et al., 1983; Nadler et al., 1985). These terms, however, did not easily map to the traditional glutamate receptor subdivisions. In 1983 based on electrophysiological and biochemical measures, Lynch et al. proposed the terms: G1 for a synaptic receptor activated by homocysteate but not NMDA and G2 for an extrasynaptic receptor that desensitises to L-glutamate, in addition to an NMDA and a kainate receptor (Fagni et al., 1983: Baudry et al., 1983); this

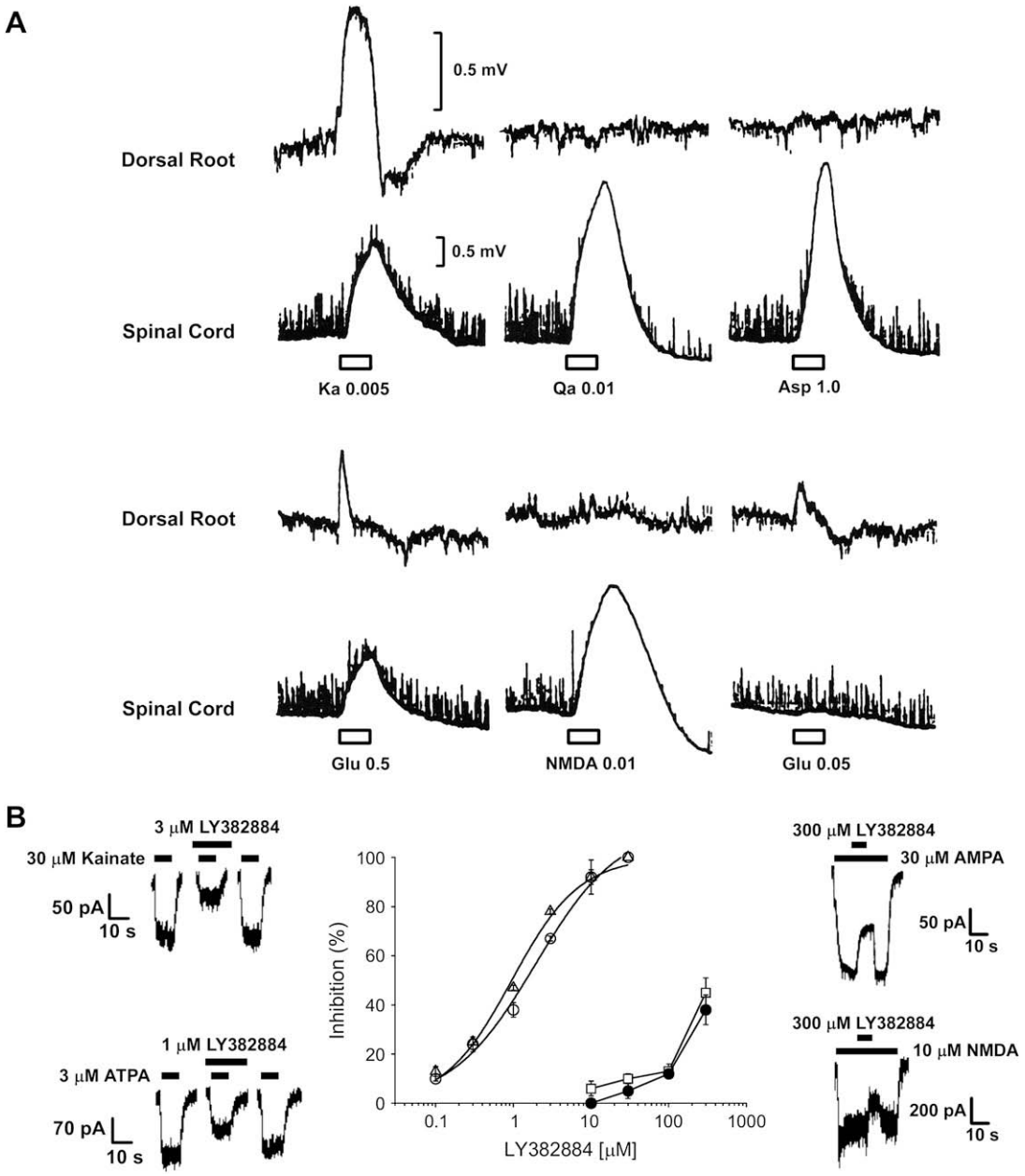

Fig. 8. Kainate receptors. A. In vitro spinal cord preparation using grease seal technique to show concurrent depolarising effect of a series of excitatory amino acids on the dorsal root versus spinal cord. Dorsal root C fibres respond uniquely to kainate and glutamate. They show no depolarisation to quisqualate, AMPA or to NMDA. Note this was the first convincing demonstration of a response mediated by kainate receptors (modified from Agrawal and Evans, 1986). B. LY382884 3 μM selective reduces whole cell currents activated by kainate and ATPA (left hand records) on dorsal root ganglion neurones but requires 300 μM to reduce whole cell currents activated by AMPA and NMDA on hippocampal neurones. The full dose–response curves for these effects of LY382884 are shown in the center panel. Note LY382884 was the first truly selective kainate receptor antagonist described (modified from Bortolotto et al., 1999).

nomenclature was occasionally used (e.g. Pin et al., 1989). Foster and Fagg in 1984 first suggested A_{1-3} but this clashed with the nomenclature for the adenosine receptors, and so the same authors subsequently proposed AA_{1-3} to represent the 'NMDA, quisqualate and kainate' receptors respectively (Fagg et al., 1986). AA was derived from Acidic Amino acid. They argued logically that because of the cross-interaction between the ligands and receptors and particularly the non-specificity of quisqualate, terms based solely on exogenous agonists were not appropriate. They used the generic AA because the nature of the natural transmitter was still hotly debated and they didn't accept a proposal using 'E1–3' (E for excitatory) because other receptors were not named by function. Despite a concerted effort over several years (e.g. Foster and Fagg, 1988) and some wider use (e.g. Récasens et al., 1987; Beal et al., 1989), the majority of the field remained conservative, however, and in the pre-cloning era stayed with the NMDA, AMPA and kainate receptor nomenclature.

22. Towards a new consensus nomenclature

However, with the advent of cloning and multiplicity of receptor subunits and the idiosyncratic naming by the workers involved (see above), there was a demand for some uniformity. Under the auspices of the IUPHAR Nomenclature Committee in 2001, Lodge and Dingledine proposed a new nomenclature based on the guidelines from IUPHAR (capital letters for the transmitter and

subscripts for the subtypes), and a commonly expressed desire to retain the identity with respect to (i) the differentiating agonists and (ii) the terms commonly in use at the time. Thus the NMDA and AMPA receptor subunits were proposed to be GLU_{N1}, $GLU_{N2A–D}$ and $GLU_{N3A–B}$ and $GLU_{A1–4}$; the decision for the kainate subtypes was more fraught but $GLU_{K5–7}$ and $GLU_{K1–2}$ were proposed for GluR5–7 and KA1–2, the hope being that $GLU_{K3–4}$ might emerge from the ongoing cloning efforts. Note the 'R' for receptor is dropped because these are subunits rather than the functional multimeric receptors.

Despite general agreement from a large number of participants (Lodge and Dingledine, 2001), this nomenclature had limited use. So the variation in subunit names presently in use remains diverse and confusing especially to the non-expert! The new proposal, developed by Graham Collingridge and his NC-IUPHAR subcommittee, deals with a number of issues that were wrong with the 2001 attempt (Collingridge et al., 2009). Namely the technical difficulty of switching into and out of subscript mode has been avoided. Thus for example, GLU_{N1} and GLU_{A4} have become GluN1 and GluA4 respectively. The nomenclature of kainate subunits has been aligned, as was previously the case for the NMDA and AMPA subunits, with the GENBANK entries. Thus GluR5–7 ($GLU_{K5–7}$) become GluK1–3, and KA1–2 ($GLU_{K1–2}$) become GluK4–5; the respective genes are GRIK1–3 and GRIK4–5. This more logical scheme should also be easier to use and hopefully will be readily adopted.

23. Conclusion

From humble developments and heroic experiments describing the role of glutamate as a neurotransmitter and the pharmacological subdivisions of receptor subtypes, the cloning and expression of 16 genes coding for glutamate receptor subunits was realised. The characterisation of these recombinant receptors from the NMDA, AMPA and kainate families has added enormously to our understanding of native receptors. The use of site-directed mutagenesis, receptor hybridisation techniques, molecular modelling of binding sites, X-ray crystal structure, high throughput screens, patch clamp electrophysiology, transgenic animals, etc. has and will continue to direct research for more selective compounds and to help determine the physiological and pathological roles of these ligand-gated ion channels.

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