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The pharmacological manipulation of glutamate receptors and neuroprotection

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Abstract

The overactivation of glutamate receptors is a major cause of Ca^{2+} overload in cells, potentially leading to cell damage and death. There is an abundance of agents and mechanisms by which glutamate receptor activation can be prevented or modulated in order to control these effects. They include the well-established, competitive and non-competitive antagonists at the *N*-methyl-D-aspartate (NMDA) receptors and modulators of desensitisation of the α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptors. More recently, it has emerged that some compounds can act selectively at different subunits of glutamate receptors, allowing a differential blockade of subtypes. It is also becoming clear that a number of endogenous compounds, including purines, can modify glutamate receptor sensitivity. The kynurenine pathway is an alternative but distinct pathway to the generation of glutamate receptor ligands. The products of tryptophan metabolism via the kynurenine pathway include both quinolinic acid, a selective agonist at NMDA receptors, and kynurenic acid, an antagonist at several glutamate receptor subtypes. The levels of these metabolites change as a result of the activation of inflammatory processes and immune-competent cells, and may have a significant impact on Ca^{2+} fluxes and neuronal damage. Drugs which target some of these various sites and processes, or which change the balance between the excitotoxin quinolinic acid and the neuroprotective kynurenic acid, could also have potential as neuroprotective drugs.

Keywords: Kynurenine; Quinolinic acid; Kynurenic acid; Glutamate; Neuroprotection; Neurodegeneration

1. Introduction

It is now widely accepted that the neuronal damage which occurs as a result of a stroke is largely attributable, not to the immediate hypoxia or ischaemia itself, but to the massive release of glutamate from neurons and glia (Obrenovitch and Urenjak, 1997). Glutamate then activates at least three types of ionotropic receptors, sensitive, respectively, to *N*-methyl-D-aspartate (NMDA), kainate and α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) (Harris, 1995). These can all increase the intracellular levels of Ca^{2+} (Ascher and Nowak, 1988; Konig et al., 2001) and lead ultimately to the generation of nitric oxide, reactive oxygen species and thus to cell death (Ogura et al., 1988) (Fig. 1).

2. NMDA receptors

2.1. Antagonists

Excellent surveys of the molecular structure of the glutamate receptors and a number of their modulatory sites have been published by Blackstone and Huganir (1995) and Yamakura and Shimoji (1999). Among the most well-established ligands at NMDA receptors are simple structural derivatives of glutamate, such as 2-amino-5-phosphono-pentanoic acid (Perkins et al., 1981; Davies et al., 1981). These compounds are selective antagonists at the NMDA receptor, competing directly at the glutamate or NMDA binding site, but their lipophobicity prevents their being of value as central nervous system (CNS) neuroprotectants after systemic administration. Related compounds with greater facility to cross the blood–brain barrier include selfotel, a competitive NMDA receptor antagonist which was tested in clinical trials for stroke but which has failed to produce a significant degree of protection (Morris et al., 1999) and D-3-(carboxypiperizin-

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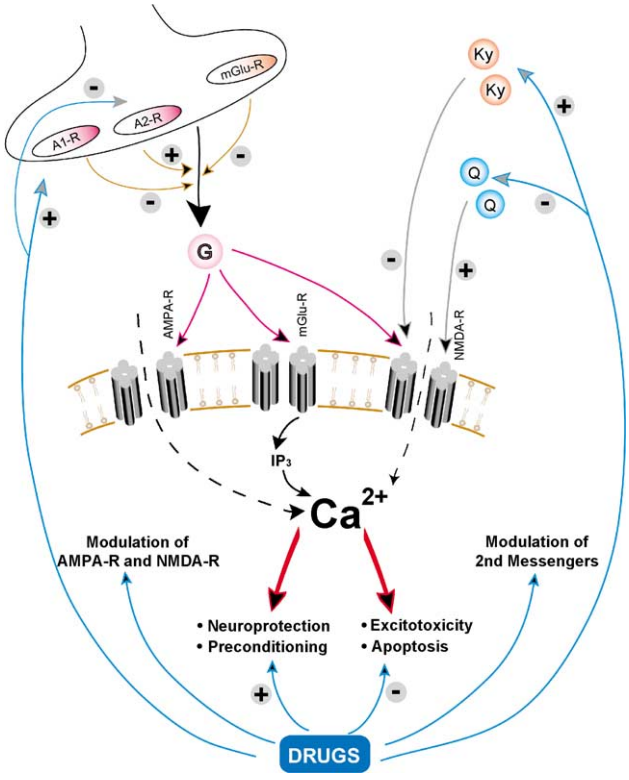

Fig. 1. A diagrammatic summary of some of the mechanisms by which modulation of amino acid receptors can be used to alter intraneuronal Ca^{2+} levels. The various receptor types and associated mechanisms are discussed more fully in the text. At the neuronal surface, there are glutamate (G) ionotropic receptors sensitive to AMPA or NMDA which alter the flux of calcium ions via membrane channels, in addition to the metabotropic family (mGlu receptors), whose influence is exerted primarily via intracellular transduction systems such as the production of IP3. The generation by glial cells of quinolinic acid (Q) as an endogenous agonist at NMDA receptors, and kynurenic acid (Ky) as an antagonist, can modulate the activity of NMDA receptors. The activation of both ionotropic and metabotropic receptors can be modified by a number of drugs, and the release of glutamate from synaptic terminals can also be modified by agents acting at metabotropic glutamate receptors or adenosine receptors. Adenosine A_1 receptors inhibit glutamate release, while adenosine A_2 receptors facilitate release.

4-yl)-propenyl-1-phosphonic acid (CPP-ene). The non-competitive antagonists are best represented by dizocilpine (MK-801), an agent first described as an anticonvulsant compound with an obscure mechanism, but which was subsequently shown to block the ion channel associated with the NMDA receptor. The same mechanism appears to be shared by the anaesthetic agent ketamine.

2.2. Modulators

A variety of allosteric modulatory sites on the NMDA receptor–channel complex allow considerable potential for pharmacological manipulation. The possibilities have increased substantially with the realisation that the different receptor subunits can confer significant differences in pharmacological properties on receptors in different regions of the CNS or even located at different sites on the somatodendritic surface of neurones. The range of subunits, their pharmacology and potential relevance to disease have been reviewed by Cull-Candy et al. (2001).

2.2.1. Polyamines

NMDA receptor activation can be enhanced by activation of a polyamine site (Reynolds, 1995), at which spermine or spermidine are possible endogenous ligands. This site is blocked by ifenprodil (Carter et al., 1989), which consequently reduces overall receptor activation and is neuroprotective. More recently it has been realised that ifenprodil is also able to act specifically on the NR2B subunit of the NMDA receptor, and has been used as a valuable experimental tool to probe the physiological functions of receptors with different subunit composition (Williams, 1993). Presumably this same action could contribute significantly to its neuroprotective activity. A zinc binding site is also associated with the NMDA receptor, with the metal ion being shown to have a preference for the NR2A subunit (Paoletti et al., 1997).

2.2.2. The redox site

In common with several other ligand-gated ion channel receptors, the NMDA variety is susceptible to modulation by agents with oxidising and reducing activity. Among the agents capable of such modulation are those, such as dithiothreitol and 5,5′-dithiobis-2-nitrobenzoic acid, which do not readily cross cell membranes, making it likely that the target site on the receptor is directed towards the extracellular milieu. The target site, which has become known as the redox site, is able to switch the receptor between a less active (oxidised) state and a more efficacious (reduced) state. The redox site is almost certainly of physiological importance, and probably of pathological importance, since a variety of endogenous substances, whose concentrations can be substantially altered experimentally and clinically, are able to act and interact at this site. Among the most prominent of these are free radicals, including the rective oxygen species such as superoxide and hydroxyl radicals which suppress NMDA receptor activation (Aizenman et al., 1990). Nitric oxide, which also inhibits NMDA receptor function may act at least partly at the redox site (Lei et al., 1992), although there is evidence to suggest that there may be several different redox sites and that nitric oxide and other free radicals act largely at different ones (Fagni et al., 1995).

The influence of the redox site or sites is exerted not only on NMDA function examined electrophysiologically, but also in terms of the increase in intracellular Ca^{2+}. Examined most carefully in neuronal cultures, dithiothreitol increases channel conductance and elevations of intracellular Ca^{2+} in parallel, and in a concentration-dependent manner. As a result, the consequences of redox modulation are reflected in the effects of various agents on neurotoxicity. Many forms of cellular damage are accompanied by the generation of free radical species, which will modify NMDA receptor function. The potential link between redox modulation and receptor

activity has been supported by reports that reducing agents can enhance the production of neuronal damage and that this effect can be prevented by oxidising agents such as 5,5′-dithiobis-2-nitrobenzoic acid (Levy et al., 1990).

2.2.3. The glycine site

Johnson and Ascher (1987) were the first to describe an essential co-activator role for glycine, acting at an allosteric site on the NMDA receptor. This site became amenable to pharmacological manipulation with the discovery that kynurenic acid was an antagonist at the NMDA receptor (Perkins and Stone, 1982; Stone, 1993) and the finding that it had an especially high affinity at the glycine site of the NMDA receptor (Birch et al., 1988; Stone, 1993). There then followed 20 years of development of kynurenic acid derivatives as selective NMDA receptor blockers for use in the treatment of strokes and degenerative disorders. Several hundred of these compounds were produced, some entering clinical trials, but with less success in humans than had been shown in animal models (Stone, 2000).

The value of kynurenic acid as a starting point for drug development has been that it is able to antagonise actions mediated by both the NMDA and the non-NMDA groups of glutamate receptors (Perkins and Stone, 1982) although most interest has centred around its more potent activity at the strychnine-resistant glycine site on the NMDA receptor. The rationale behind this interest in receptor selectivity is that under most physiological conditions, the ion channels associated with the NMDA receptor are blocked by Mg^{2+} ions and it is only after initial depolarisation (by, for example, AMPA or kainate receptors) that the voltage-dependent Mg^{2+} block is relieved sufficiently to permit activation of the NMDA channels. These conditions will occur especially under the pathological circumstances of hypoxia, ischaemia, epilepsy and traumatic brain injury, which are associated with elevated levels of extracellular glutamate. Antagonists acting at the NMDA receptors should interfere less with normal fast glutamatergic transmission, which is important in the control of many autonomic functions including cardiovascular and respiratory mechanisms, as well as movement control by the basal ganglia and cognitive functions, than antagonists at kainate and AMPA receptors.

However, kynurenic acid is a compound with a complex pharmacology. It is able to antagonise non-NMDA as well as NMDA receptor activation in rodents (Perkins and Stone, 1982) and primates (Stone, 1993) and may even distinguish subpopulations of kainate receptors (Stone, 1990). There is also evidence from two independent sources that the potency of kynurenic acid in suppressing NMDA receptor-dependent spontaneous neuronal discharges in the hippocampus does not correlate with its activity as an antagonist of NMDA (Stone, 1988; Brady and Swann, 1988). This observation would suggest an additional, novel site of action of kynurenic acid, which will be discussed further below.

The various components of the kynurenine pathway are present primarily in the glial cell population in the CNS, especially astrocytes (Kohler et al., 1988), as well as in immune-competent cells such as microglia, peripheral mast cells and blood macrophages which travel in and out of the CNS across the blood–brain barrier. All these cells can generate up to 1000 times the basal levels of kynurenines when activated by immunogenic stimuli such as bacterial lipopolysaccharide or interferon-γ (Heyes et al., 1996; Espey et al., 1997; see Stone, 2001). As a result of activating the pathway, there is an increased generation of excitotoxic compounds such as quinolinic acid, an endogenous agonist at NMDA receptors (Stone and Perkins, 1981; see Stone, 2001) and 3-hydroxykynurenine. The latter substance does not have any direct activity at glutamate receptors but does produce damage primarily via the formation of free radicals (Eastman and Guilarte, 1990). The potential importance of this glial origin of excitotoxins raises the possibility that at least a proportion of the delayed damage which develops after brain injury induced by kainic acid or ischaemia may be attributable to the secondary activation of glia and macrophages which then generate toxic amounts of quinolinic acid (Behan and Stone, 2000). Quinolinic acid in turn can produce damage not only by activating NMDA receptors, but also by enhancing the formation of reactive oxygen species (Behan et al., 1999).

2.2.3.1. Modulators of the kynurenine pathway. An alternative strategy to the direct blockade of glutamate receptors is to modify activity in the kynurenine pathway, changing the balance between the generation of quinolinic acid and kynurenic acid. Inhibition of the enzymes kynurenine hydroxylase and kynureninase results in a decrease in the levels of endogenous quinolinic acid and an increase of kynurenic acid. Nicotinylalanine was the first inhibitor of these enzymes (Connick et al., 1992; Russi et al., 1992) and was shown to increase the brain content of kynurenic acid (see Harris et al., 1998). A number of compounds related to nicotinylalanine derivatives have been studied since, including *meta*-nitrobenzoylalanine (Pellicciari et al., 1994) which preferentially inhibits kynurenine-3-hydroxylase and *ortho*-methoxybenzoylalanine which preferentially inhibits kynureninase (Natalini et al., 1995).

Another systemic kynurenine-3-hydroxylase inhibitor is 3,4-dichlorobenzoyl-alanine (FCE28833A) (Speciale et al., 1996), an agent which increases the levels of kynurenine and kynurenic acid in rat brain. In hippocampal dialysates, peak increases of 10- and 80-fold the resting levels, respectively, were obtained after a single systemic injection. The evidence obtained to date indicates that 3,4-dichlorobenzoyl-alanine is more effective than *meta*-nitrobenzoylalanine in its ability to divert tryptophan metabolism towards the neuroprotective kynurenic acid. In some experiments, the levels of kynurenic acid remained increased above control levels for 22 h (Speciale et al., 1996).

2.2.3.2. Therapeutic trials of kynurenic acid analogues Several of these compounds have been developed for the

treatment of CNS disorders in which an abnormality of glutamate receptor function has been implicated, such as traumatic head injury, strokes, schizophrenia and epilepsy. Some of the compounds show good penetration of the blood–brain barrier, leading to discussions of their possible value in the prevention or slowing of neurodegenerative disorders (Warner et al., 1995). While clear evidence is still lacking, for many such disorders, that an excessive activation of glutamate receptors is involved in cell damage, there are strong pointers to the involvement of glutamate site ligands in some forms of degeneration. An outstanding example is the massive elevation of quinolinic acid which has been reported in patients suffering from dementia associated with infection by the human immunodeficiency virus (HIV) (Lipton, 1998). The cellular inflammatory response, both inside and outside the central nervous system, which occurs during this infection, results in a large increase in the level of quinolinic acid in the brain (Heyes et al., 1990). This could well contribute to progressive development of neuronal dysfunction either by overstimulating the target NMDA receptors, or by desensitising them and leading to their down-regulation (Lipton, 1998; see Stone, 2001).

An important advantage of the glycine site antagonists over some of the non-competitive compounds which have been examined in neuroprotective models, is that they do not exhibit the serious neurotoxic and psychological side effects of the channel blockers such as dizocilpine and similar problems encountered with the competitive NMDA receptor blockers such as selfotel (Lees, 1997). The adverse effects induced by these drugs include neuronal vacuolisation and disturbing psychotomimetic effects, which may present a serious source of consternation for patients experiencing only a mild form of ischaemic damage. Of the glycine site antagonists, kynurenic acid derivatives and analogues possess a ring structure which makes them acceptably lipophilic, allowing them to penetrate the blood–brain barrier much more readily than many compounds.

2.3. NMDA receptors and preconditioning

Neuronal preconditioning, a phenomenon in which repeated sublethal insults to neurons results in their resistance to more severe insults, has been found in diverse phenomena such as spreading depression, hypoxia/ischemia, epileptic seizure, exposure to toxins and cytokines, and inhibition of oxidative phosphorylation (Bruer et al., 1997). The extent of neuroprotection is influenced by the intensity of the sublethal insult and the latency between that and the final more severe insult (Chen and Simon, 1997). The mechanisms of preconditioning have been shown to involve both short-term processes that include NMDA receptor activation, Ca^{2+} influx and second messenger changes (Bond et al., 1999; Perez-Pizon et al., 1999; Grabb and Choi, 1999), and long-term processes that include changes in gene expression and protein synthesis (Sakurai et al., 1998; Currie et al., 2000). Yano et al. (2001) have shown that preconditioning in gerbil CA1 cells involved activation of protein kinase B; the activation was initiated by Ca^{2+} influx via NMDA receptors (Yano et al., 2001). Ischemia has been shown to cause increased tyrosine phosphorylation of the NR2 subunit. Ischemic preconditioning abolished the phosphorylation and decreased the NR2A and NR2B subunits in the neocortex (Shamloo and Wieloch, 1999). Preconditioning by transient exposure of cultured cortical neurons to NMDA antagonists induced protection to apoptotic and non-apoptotic cell death from a variety of insults including NMDA, AMPA, oxygen–glucose deprivation, β-amyloid, staurosporine, and etoposide. The preconditioning did not block some of the physiological functions of NMDA receptors such as Ca^{2+} influx, but blocked the protein kinase C inactivation that accompanies Ca^{2+}-mediated neuronal toxicity (Tremblay et al., 2000). The authors proposed that the latter effect might be responsible for the neuroprotection.

3. AMPA receptors

In terms of Ca^{2+} regulation, increasing interest is being shown in the receptors sensitive to DL-α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), which can also increase the intracellular levels of Ca^{2+}. AMPA receptor antagonists have been found to be effective in preventing neuronal cell death in several different models of brain ischemia (Sheardown et al., 1990; Judge et al., 1991), Parkinsonism (Klockgether et al., 1991), and seizures (Ohmori et al., 1994).

AMPA receptors are made from a ring of four subunits (Rosenmund et al., 1998). Each subunit, GluR1, GluR2, GluR3 and GluR4, consists of three transmembrane domains (TM1, TM3 and TM4) with an associated intramembrane inverted U-shaped amino acid chain (MD2) between the TM1 and TM3 transmembrane units; the MD2 unit has been proposed to line the ionic channel (Hollmann et al., 1994; Bennett and Dingledine, 1995). Two variants (‘flip’ and ‘flop’) of each subunit are generated by alternative RNA splicing at a small portion (115 bp) preceding the TM4 unit (Sommer et al., 1990). In embryonic brains, the flip form is expressed predominantly while the flop form increases perinatally and dominates in the adult (Pellegrini-Giampietro et al., 1992a).

3.1. AMPA receptors and Ca^{2+}

The functional properties of AMPA receptors in the CNS are influenced to a large extent by the GluR2 subunit which has two RNA editing sites, glutamine (Q)-to-arginine (R) editing at position 586 and arginine (R)-to-glycine (G) editing at position 743 (Jonas et al., 1994; Geiger et al., 1995). RNA editing at the Q/R site is specific to GluR2 whereas R/G editing is specific to GluR2, 3 and 4. Native

AMPA receptors in postnatal animals are mainly of the Q/R edited type, where the presence of the charged arginine instead of the neutral amino acid glutamine tends to prevent Ca^{2+} influx. Hence, native heteromeric AMPA receptors that lack the edited GluR2 subunit have permeability to Ca^{2+} as well as Na^{+} and K^{+}; receptors that have GluR2 subunits are permeable to Na_{+} and K_{+} but not to Ca^{2+} (Sommer et al., 1991; Hollmann et al., 1991; Gu et al., 1996). The Ca^{2+}-permeable AMPA receptors exhibit higher channel conductance. They also show inward rectification due to a channel block at depolarized membrane potentials by the intracellular polyamines spermine and spermidine (Washburn and Dingledine, 1996; Bowie et al., 1998). Although the Ca^{2+} permeability is unrelated to the function of the polyamines, Panchenko et al. (1999) have proposed that the Q/R site contributes to the barrier that regulates movement of polyamines from their binding site. Additionally, the Ca^{2+}-permeable AMPA receptors are blocked by Joro spider toxin, argiotoxin, philanthotoxin, and 1-naphthyl acetyl spermine (extracellularly) at negative membrane potentials (Iino et al., 1996). Ca^{2+}-permeable AMPA receptors have been found in cerebellar glial cells, neocortical, hippocampal, basal ganglia and spinal dorsal horn neurons, some of which are γ-amino-butyrate (GABA)-releasing interneurons (Burnashev et al., 1992; Itazawa et al., 1997; Gotz et al., 1997).

3.2. Desensitisation

Ca^{2+} movements are clearly dependent on receptor sensitivity, and loss of neuronal responses to AMPA receptor agonists may result from desensitisation, internalisation or destruction of the receptors. Stern-bach et al. (1998) have reported that desensitisation of AMPA receptors is regulated by a site on the agonist binding site S1 and is blocked by a leucine-to-tyrosine mutation in the binding domains of GluR1 or GluR3 (Stern-Bach et al., 1998). AMPA receptors composed of the flop variants of GluR3 and GluR4 desensitise faster than those formed with the flip variants (Mosbacher et al., 1994). Partin et al. (1996) have suggested that the flip/flop domain could be influencing desensitisation by modifying the pore via TM4, possibly through re-alignment of the TM1–TM4 contacts (Partin et al., 1996). Desensitisation is also influenced by the R/G site: AMPA receptors consisting of GluR2, -3 and -4 subunits that are edited at the R/G sites exhibit faster recovery rates from desensitisation (Lomeli et al., 1994) than the unedited types. Other possibilities are that desensitisation of AMPA receptors involves multiple events including receptor phosphorylation and depletion of intracellular Ca^{2+} stores (Cowen and Beart, 1998), or that long-term desensitisation of AMPA receptors involves the actions of protein kinases G and C and a protein phosphatase inhibition (Ito and Karachot, 1992).

Removal of desensitisation (i.e., positive modulation of AMPA receptors) can be achieved with the pyrrolidinones aniracetam, piracetam and related compounds. Other positive modulators are the benzothiadiazines cyclothiazide, diazoxide and 7-chloro-3methyl-3-4-dihydro-2*H*-1,2,4 benzothiadiazine (IDRA21) (Desai et al., 1995; Kapus et al., 2000). Novel positive AMPA receptor modulators include the benzoylpiperidine, 1-(quinoxalin-6-ylcarbonyl)-piperidine (CX516), and biarylpropylsulfonamides (Gates et al., 2001; Miu et al., 2001; Nagarajan et al., 2001). Cyclothiazide and aniracetam are more effective at the flip than at the flop splice variants (Partin et al., 1994), whereas 4-[2-(phenylsulfonylamino)ethylthio]-2,6-difluoro-phenoxyacetamide (PEPA) slows desensitisation more effectively at the flop splice variants (Sekiguchi et al., 1997). There is recent evidence that extracellular Ca^{2+} can allosterically inhibit AMPA receptor desensitisation irrespective of the subunit composition and splice variant (Buldakova et al., 2000). Evans Blue, which antagonizes AMPA receptors in some neurons, blocks desensitisation in others (Weiser et al., 1996; Schurmann et al., 1997).

3.2.1. Desensitisation and neuroprotection

Ca^{2+} influx via Ca^{2+}-permeable AMPA receptor did not induce neurotoxicity in cells transfected with Ca^{2+}-permeable AMPA receptors until the receptor desensitisation was removed (Raymond et al., 1996). AMPA receptor desensitisation has been found to serve as a protective mechanism against neuronal overactivity and excitotoxicity in a number of systems (May and Robison, 1993; Ballerini et al., 1995; Glazner et al., 2000). A burst of depolarization (but not single firing) of hippocampal postsynaptic neurons causes inactivation of NMDA receptor excitatory currents, mediated via Ca^{2+} influx. This is consistent with our observations that long-term potentiation in CA1 neurons reduced the sensitivity of hippocampal slices to exogenously applied NMDA and AMPA, and also to hypoxia (Youssef et al., 2000, 2001). The loss of response to AMPA appeared to involve desensitisation of the receptors.

3.3. AMPA receptors, Ca^{2+} and plasticity

Several studies have shown that Ca^{2+} influx through the NMDA receptor channel (e.g., during long-term potentiation) activates calcium-calmodulin-kinase II which then phosphorylates and increases AMPA receptor current (McGlade-McCulloh et al., 1993; Tan et al., 1994; Derkach et al., 1999; Carvalho et al., 2000). Perkinton et al. (1999) have provided an additional mechanism whereby AMPA receptor activation can lead to neuroplasticity. They reported that, in primary cultures of striatal neurons, Ca^{2+} influx through Ca^{2+}-permeable AMPA receptors activated phosphorylation of cyclic AMP response element-binding protein (CREB) via stimulation of the mitogen activated protein kinase (MAPK) (Perkinton et al., 1999). Although the authors had indicated that this effect of AMPA did not involve activation of NMDA receptors or voltage-gated Ca^{2+} channels, Rajadhyaksha et al. (1999) have reported

that, in a similar system, the effect of AMPA receptors on CREB activation was through stimulation of Ca^{2+} influx indirectly via NMDA receptor-mediated activation of L-type Ca^{2+} channels (Rajadhyaksha et al., 1999). The finding that activation of CREB in the suprachiasmatic nucleus of the hamster involved coordinated action of both NMDA and AMPA receptors supports this latter view (Schurov et al., 1999). Additionally, phosphorylation of AMPA receptors by second messengers influences their expression at the plasma membrane, a process that involves interaction between AMPA receptor subunits and postsynaptic domain proteins (Carvalho et al., 1999). In cerebellar stellate cells, repetitive activation of Ca^{2+}-permeable AMPA receptors led to a rapid reduction in Ca^{2+} influx due to removal of GluR2-containing AMPA receptors from the synapses and insertion of GluR2-containing receptors (Liu and Cull-Candy, 2000).

3.4. Neuronal damage via AMPA receptors

There are several claimed instances of cell death caused by AMPA receptor-mediated Ca^{2+} influx. The neuronal death that follows deafferentation of neurones in sensory pathways involves Ca^{2+} influx via AMPA receptors which then leads to phosphorylation of CREB by calmodulin-kinase II and protein kinase A (Zirpel et al., 2000). Also, mutant mice with increased AMPA receptor Ca^{2+}-permeability showed deficits in dendritic architecture and increased neurological disorders including epilepsy (Feldmeyer et al., 1999).

However, the role of Ca^{2+} in neuronal damage is complicated by its role in desensitisation of AMPA receptors and the phenomenon of preconditioning (see below), and Connor et al. (1999) have questioned the role of Ca^{2+} in neuronal death. These workers noted that there was no evidence of ongoing intracellular Ca^{2+} overload 1–3 days after a brief ischemia. More recently, Ambrosio et al. (2000) found no correlation between the degree of cyclothiazide-influenced toxicity and the associated Ca^{2+} influx (Ambrosio et al., 2000).

Since Ca^{2+} flux is largely determined by the GluR2 subunit, changes in subunit gene expression following ischemia are of interest. Frank et al. (1995) reported a roughly equal loss of GluR1, -2 and -3 subunits after ischaemia, whereas Pellegrini-Giampietro et al. (1992) observed a preferential loss of GluR2. Although this latter observation was interpreted as a mechanism in the pathological process, it could also be seen as an intrinsic protective mechanism whereby the increased Ca^{2+} influx via AMPA receptor activation activated neuroprotective processes (see below). The authors later proposed that ischemia-induced downregulation of GluR2 subunits increases Ca^{2+} influx via AMPA receptors and makes neurons more vulnerable (Pellegrini-Giampietro et al., 1997). However, Alsbo et al. (2001) have not observed such a downregulation of GluR2 expression 24 h after ischemia (Alsbo et al., 2001).

3.5. AMPA receptors and Ca^{2+}-binding proteins

Neurons that demonstrate the presence of Ca^{2+}-binding proteins tend to be more resistant to damage from epileptiform discharges or excitatory amino acids (Sloviter, 1989; Heizmann and Braun, 1992). Some authors have attributed the neuroprotection to the Ca^{2+} buffering by the intracellular proteins. However, in the rat forebrain, there is a correlation between the presence of the Ca^{2+}-binding proteins parvalbulmin and calbindin-D28, and the absence of GluR2 expression in the neurons. As expected, such neurons showed high Ca^{2+} permeability (Kondo et al., 2000). Hence, the resistance of such neurons to vulnerability could also be attributed to the increased Ca^{2+} permeability. Type 2 interneurons in the hippocampus are deficient in GluR2 subunits (and hence have increased Ca^{2+} permeability) and are highly resistant to ischemic damage (Bochet et al., 1994).

3.6. AMPA receptors and preconditioning

Several other studies have indicated the involvement of AMPA receptors in preconditioning. In rat hippocampal cell cultures, oxygen–glucose deprivation mediated preconditioning was associated with increased levels of GluR4 flop subunits, and a relative decrease in GluR2 subunits; the preconditioned AMPA receptors exhibited increased AMPA or kainate-induced Ca^{2+} influx which was sensitive to Joro spider toxin. The preconditioned neurons also exhibited increased vulnerability to kainate toxicity but decreased vulnerability to oxygen–glucose deprivation (Ying et al., 1997). In contrast, Alsbo et al. (2001) have reported that in animals that were subjected to ischemic preconditioning there was upregulation of GluR2 and GluR2 flop levels, suggesting that the tolerance could be related to enhanced AMPA receptor desensitisation (Alsbo et al., 2001).

4. Metabotropic glutamate receptors (mGluR)

In addition to its actions on the ionotropic receptors, glutamate also acts on a variety of metabotropic receptors (see Anwyl, 1995; Conn et al., 1995 for reviews), These are coupled to adenylate cyclase or phospholipase C, and in general produce changes of cellular function and membrane conductance on a slower time scale than the ionotropic receptors. Both the mGluR1 and mGluR5 agonist 3,5-dihydroxyphenylglycine (DHPG) and the selective mGluR5 agonist 2-chloro-5-hydroxyphenylglycine (CHPG) are able to potentiate depolarisations induced by NMDA (Attucci et al., 2001; Skeberdis et al., 2001). This action was not correlated with changes of inositol phospholipid metabolism, suggesting that the latter pathway is not responsible for mediating the electrophysiological interaction. On the other hand, buffering intracellular Ca^{2+} prevented the potentiation.

The mGluRs can exist on both postsynaptic and presynaptic sites (Pin and Duvoisin, 1995), with groups II and III appearing to be localised primarily to the presynaptic terminals, and group I receptors at postsynaptic sites (Shigemoto et al., 1997). The presynaptic sites are primarily concerned with the regulation of glutamate release, and the mGluR5 receptors can increase glutamate release. Although glutamate is normally assumed to be the endogenous ligand at these sites, recent evidence has indicated a potent action of some of the endogenous sulphur-containing amino acids such as L-cysteic acid and L-cysteine sulphinic acid (Croucher et al., 2001). Cyclothiazide proved able to prevent the desensitisation of the mGluR5 receptor and to increase the ability of L-cysteic acid to facilitate glutamate release.

Several of the mGluR series have been shown to modify Ca^{2+} levels either at postsynaptic or presynaptic sites. The mGluR1 receptors, for example, increase Ca^{2+} within presynaptic terminals leading to an enhancement of glutamate release (Schwartz and Alford, 2000). Indeed, direct recordings from presynaptic terminals in the lamprey have revealed opposing influences of several mGluR ligands in which transmitter release is decreased as a result of the activation of K^+ conductances, but can be facilitated by an increase in the levels of presynaptic Ca^{2+} (Cochilla and Alford, 1998). Presumably the net physiological effect will be a complex balance depending on the concentration of endogenous glutamate, the relative densities and locations of the several mGluRs, and their differential sensitivity.

Preconditioning may involve changes in activities of mGluRs and the excitatory amino acid transporters, reversal of which appears to generate the increased extracellular glutamate levels associated with ischemia. In CA1 cells of gerbils, ischaemic tolerance was associated with a reduction in mGluR1b and mGluR5 receptors that are considered to be mediate neurotoxicity (Sommer et al., 2000).

4.1. Metabotropic glutamate receptors and neuroprotection

As a result of these various effects of metabotropic receptors, there is now clear agreement that they are able to modulate neuronal cell death. The consensus seems to be that activation of Group I receptors (mGluR1 and mGluR5 receptors) promotes neuronal damage and, correspondingly, antagonists protect (Pellegrini-Giampietro et al., 1999; Bruno et al., 1999). Using ligands selective for individual receptors, both mGluR1 and mGluR 5 antagonists seem to be protective. Although the reduction of damage has been studied primarily against NMDA-induced toxicity or ischaemia, protection by the antagonists is also seen against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) on dopaminergic neurones (Aguirre et al., 2001) and against traumatic brain injury (Lyeth et al., 2001).

Agonists at the Group II receptors (mGluR2 and mGluR3 receptors) protect against NMDA-induced cell damage (Battaglia et al., 1998; Bond et al., 2000; Colwell and Levine, 1999) possibly by a process which requires the synthesis of new protein and the generation of transforming growth factor-β (TGF-β) (Bruno et al., 1998). Again, NMDA has been the primary cause of insult examined by most workers, but group II receptor activation has recently been shown to protect against damage caused by traumatic brain injury (Zwienenburg et al., 2001).

Less attention has been devoted to Group III receptors (mGluR4, mGluR6, mGluR7, mGluR8), but again agonists do appear to be neuroprotective (Gasparini et al., 1999; Pizzi et al., 2000). Interestingly, group III agonists are not protective in mGluR4 (−/−) knockout mice, suggesting that it is this receptor which is primarily responsible for the protection (Bruno et al., 2000). However, the story must be more complex than this, since selective agonists at the mGluR7 receptor are able to protect against NMDA toxicity in cerebellar granule cells (Lafon-Cazal et al., 1999).

5. Receptor interactions

Rosenmund et al. (1995) reported that intracellular Ca^{2+} inactivates NMDA receptors in cultured hippocampal neurons, and that Ca^{2+} influx through NMDA receptors provides negative feedback on NMDA receptor activity (Rosenmund et al., 1995). Inactivation of NMDA receptors can also be induced by AMPA receptor activation. AMPA and NMDA receptors are co-localised at synapses in different parts of the central nervous system (Bekkers and Stevens, 1989). Ca^{2+} influx through a subpopulation of AMPA receptors in rat dorsal horn cultured neurons or hippocampal cells can induce desensitisation of the adjacent NMDA receptors (Medina et al., 1994; Kyrozis et al., 1995). These observations are consistent with that from our in vivo experiments in which activation of NMDA or AMPA receptors in the rat neocortex prevented actions of topically applied NMDA (Addae and Stone, 1986; Addae et al., 2000), although in an intact in-vivo neuronal network the involvement of inhibitory interneurons cannot be ruled out.

6. Purines

Purine nucleosides such as adenosine are known to modulate Ca^{2+} activity within cells. That modulation is exhibited most clearly at presynaptic sites, where adenosine A_1 receptors depress the release of a variety of neurotransmitters and adenosine A_{2A} receptors increase the release of at least some transmitters (Chen and Lambert, 1997; Goncalves et al., 1991; Goncalves and Ribeiro, 1996) although the manner of the Ca^{2+} modulation remains unclear. While there is evidence for a direct effect of adenosine on Ca^{2+} fluxes into synaptic terminals, there are also indications that adenosine might alter the availability of intraterminal Ca^{2+} to the secretory/release process. These effects on Ca^{2+} activity will often oppose the responses to agents such as glutamate which raise intra-

cellular levels. In addition, however, a number of interactions have been identified between purines and glutamate, which may reflect direct interactions at the receptor level.

One of the first to be identified was reflected in the proposal that the activation of NMDA receptors could suppress the presynaptic inhibitory effects of adenosine in the hippocampus (Bartrup and Stone, 1988, 1990). This phenomenon has been strongly supported by more detailed recent data using a paired-pulse paradigm (Nikbakht and Stone, 2001). The converse ability of adenosine receptor activation to suppress sensitivity to NMDA has been demonstrated by De Mendonca et al. (1995) and Norenberg et al. (1997). Activation of NMDA receptors in the hippocampus was reduced by agonists acting at adenosine A_1 receptors, which were shown to inhibit NMDA-induced currents measured during patch-clamp experiments (De Mendonca et al., 1995). On striatal neurones, it is the activation of adenosine A_{2A} receptors which were reported to suppress NMDA-induced currents (Norenberg et al., 1997). These results are potentially of great significance to any discussion of the role of NMDA receptors in brain damage: although adenosine concentrations in the extracellular fluid are normally in the low micromolar range or less, they can increase dramatically to several hundred micromolar as a result of hypoxia, hypoglycaemia or ischaemia. Under these conditions, the endogenous adenosine will then be sufficient to reduce glutamate-induced currents mediated via the NMDA receptor, and thus exert a degree of neuroprotection, although the precise details of this change will depend very much on the degree of ischaemia and the individual dynamics of the adenosine system. An elevation of extracellular adenosine into the range between 1 and 10 μM will begin to activate the potentially protective adenosine A_1 receptor population (von Lubitz et al., 1988, 1989; MacGregor and Stone, 1993; MacGregor et al., 1993). If the levels of adenosine rise further to 20 μM or above, the activation of adenosine A_{2A} receptors may begin to predominate. Since these receptors tend to increase the release of glutamate and several other transmitters, these high adenosine levels could result in an exacerbation of neuronal damage. The balance between adenosine A_{2A} receptor-mediated direct inhibition of NMDA receptor function and their stimulation of glutamate release will then assume substantial significance. Indeed, there is a burgeoning interest in the demonstration that antagonists at adenosine A_{2A} receptors are neuroprotective in animal models of ischaemia (Sheardown and Knutsen, 1996; Monopoli et al., 1998; Ongini et al., 1997) and excitotoxicity (Jones et al., 1998a,b; Stone et al., 2001), findings which may well be explicable on the basis that these compounds are preventing the potentially injurious enhancement of glutamate release.

7. Conclusions

Overall, it is clear that the glutamate receptor population—major determinants of intraneuronal Ca^{2+} levels and thus of neuronal viability—are amenable to manipulation at a large variety of sites. The differential permeability of AMPA receptor subunit combinations to Ca^{2+}, the regulation of desensitisation and the existence of receptor interactions enables the receptors to function with a greater degree of flexibility. Amino acid-mediated Ca^{2+} influx to cells provides a pathway not only for pathological processes but also for physiological (including neuroprotective) ones. There continues to be a massive effort to generate compounds able to act at these sites and have value as neuroprotective drugs. However, the lack of success to date with substances acting directly as antagonists at glutamate receptors may result in a shift of emphasis towards compounds which act indirectly to affect glutamate receptor release or function, such as the kynurenines and purines.

References

Addae, J.I., Stone, T.W., 1986. Effects of topically applied excitatory amino acids on evoked potentials and single cell activity in rat cerebral cortex. Eur. J. Pharmacol. 121, 337–343.

Addae, J.I., Evans, S.M., Ali, N., Stone, T.W., 2000. NMDA-induced changes in a cortical network in vivo are prevented by AMPA. Brain Res. 869, 211–215.

Aguirre, J.A., Andbjer, B., Gonzalez-Baron, S., Hansson, A., Stromberg, I., Agnati, L.F., Fuxe, K., 2001. Group I mGluR antagonist AIDA protects nigral DA cells from MPTP-induced injury. NeuroReport 12, 2615–2617.

Aizenman, E., Hartnett, K.A., Reynolds, I.J., 1990. Oxygen-free radicals regulate NMDA receptor function via a redox modulatory site. Neuron 5, 841–846.

Alsbo, C.W., Wrang, M.L., Moller, F., Diemer, N.H., 2001. Is the AMPA receptor subunit GluR2 mRNA an early indicator of cell fate after ischemia? A quantitative single cell RT-PCR study. Brain Res. 894, 101–108.

Ambrosio, A.F., Silva, A.P., Malva, J.O., Mesquita, J.F., Carvalho, A.P., Carvalho, C.M., 2000. Role of desensitization of AMPA receptors on the neuronal viability and on the $[Ca^{2+}]$i changes in cultured rat hippocampal neurons. Eur. J. Neurosci. 12, 2021–2031.

Anwyl, R., 1995. Metabotropic glutamate receptors. In: Stone, T.W. (Ed.), CNS Neurotransmitters and Modulators: Glutamate. CRC Press, Boca Raton, pp. 143–158.

Ascher, P., Nowak, L., 1988. The role of divalent cations in the NMDA responses of mouse central neurones in culture. J. Physiol. (London) 399, 247–266.

Attucci, S., Carla, V., Mannaioni, G., Moroni, F., 2001. Activation of type 5 metabotropic glutamate receptors enhances NMDA responses in mice cortical wedges. Br. J. Pharmacol. 132, 799–806.

Ballerini, L., Bracci, E., Nistri, A., 1995. Desensitization of AMPA receptors limits the amplitude of EPSPs and the excitability of motoneurons of the rat isolated spinal cord. Eur. J. Neurosci. 7, 1229–1234.

Bartrup, J.T., Stone, T.W., 1988. Interactions of adenosine and magnesium on rat hippocampal slices. Brain Res. 463, 374–379.

Bartrup, J.T., Stone, T.W., 1990. Activation of NMDA receptor-coupled channels suppresses the inhibitory action of adenosine on hippocampal slices. Brain Res. 530, 330–334.

Battaglia, G., Bruno, V., Ngomba, R.T., Di Grezia, R., Copani, A., Nicoletti, F., 1998. Selective activation of group-II metabotropic glutamate receptors is protective against excitotoxic neuronal death. Eur. J. Pharmacol. 356, 271–274.

Behan, W.M.H., Stone, T.W., 2000. Role of kynurenine in the neurotoxic actions of kainic acid. Br. J. Pharmacol. 129, 1764–1770.

Behan, W.M.H., McDonald, M., Darlington, L.G., Stone, T.W., 1999. Oxidative stress as a mechanism for quinolinic acid-induced hippocampal damage: protection by melatonin and deprenyl. Br. J. Pharmacol. 128, 1754–1760.

Bekkers, J.M., Stevens, C.F., 1989. NMDA and non-NMDA receptors are co-localized at individual excitatory synapses in cultured rat hippocampus. Nature 341, 230–233.

Bennett, J.A., Dingledine, R., 1995. Topology profile for a glutamate receptor: three transmembrane domains and a channel-lining reentrant membrane loop. Neuron 14, 373–384.

Birch, P.J., Grossman, C.J., Hayes, A.G., 1988. Kynurenic acid antagonises responses to NMDA via an action at the strychnine-insensitive glycine receptor. Eur. J. Pharmacol. 154, 85–87.

Blackstone, C.D., Huganir, R.L., 1995. Molecular structure of glutamate receptor channels. In: Stone, T.W. (Ed.), CNS Neurotransmitters and Modulators: Glutamate. CRC Press, Boca Raton, pp. 53–68.

Bochet, P., Audinat, E., Lambolez, B., Crepel, F., Rossier, J., Iino, M., Tsuzuki, K., Ozawa, S., 1994. Subunit composition at the single-cell level explains functional properties of a glutamate-gated channel. Neuron 12, 383–388.

Bond, A., Lodge, D., Hicks, C.A., Ward, M.A., O'Neill, M.J., 1999. NMDA receptor antagonism, but not AMPA receptor antagonism attenuates induced ischaemic tolerance in the gerbil hippocampus. Eur. J. Pharmacol. 380, 91–99.

Bond, A., Jones, N.M., Hicks, C.A., Whiffin, G.M., Ward, M.A., O'Neill, M.F., Kingston, A.E., Monn, J.A., Ornstein, P.L., Schoepp, D.D., Lodge, D., O'Neill, M.J., 2000. Neuroprotective effects of LY379268, a selective mGlu2/3 receptor agonist: investigations into possible mechanism of action in vivo. J. Pharmacol. Exp. Ther. 294, 800–809.

Bowie, D., Lange, G.D., Mayer, M.L., 1998. Activity-dependent modulation of glutamate receptors by polyamines. J. Neurosci. 18, 8175–8185.

Brady, R.J., Swann, J.W., 1988. Suppression of ictal-like activity by kynurenic acid does not correlate with its efficacy as an NMDA receptor antagonist. Epilepsy Res. 2, 232–238.

Bruer, U., Weih, M.K., Isaev, N.K., Meisel, A., Ruscher, K., Bergk, A., Trendelenburg, G., Wiegand, F., Victorov, I.V., Dirnagl, U., 1997. Induction of tolerance in rat cortical neurons: hypoxic preconditioning. FEBS Lett. 414, 117–121.

Bruno, V., Battaglia, G., Casabona, G., Copani, A., Caciagli, F., Nicoletti, F., 1998. Neuroprotection by glial metabotropic glutamate receptors is mediated by transforming growth factor-beta. J. Neurosci. 18, 9594–9600.

Bruno, V., Battaglia, G., Kingston, A., O'Neill, M.J., Catania, M.V., Di Grezia, R., Nicoletti, F., 1999. Neuroprotective activity of the potent and selective mGlu1a metabotropic glutamate receptor antagonist, (+)-2-methyl-4 carboxyphenylglycine (LY367385): comparison with LY357366, a broader spectrum antagonist with equal affinity for mGlu1a and mGlu5 receptors. Neuropharmacology 38, 199–207.

Bruno, V., Battaglia, G., Ksiazek, I., van der Putten, H., Catania, M.V., Giuffrida, R., Lukic, S., Leonhardt, T., Inderbitzin, W., Gasparini, F., Kuhn, R., Hampson, D.R., Nicoletti, F., Flor, P.J., 2000. Selective activation of mGlu4 metabotropic glutamate receptors is protective against excitotoxic neuronal death. J. Neurosci. 20, 6413–6420.

Buldakova, S.L., Bolshakov, K.V., Tikhonov, D.B., Magazanik, L.G., 2000. Ca^{2+}-dependent desensitization of AMPA receptors. NeuroReport 11, 2937–2941.

Burnashev, N., Khodorova, A., Jonas, P., Helm, P.J., Wisden, W., Monyer, H., Seeburg, P.H., Sakmann, B., 1992. Ca^{2+}-permeable AMPA-kainate receptors in fusiform cerebellar glial cells. Science 256, 1566–1570.

Carter, C., Rivy, J.-P., Scatton, B., 1989. Ifenprodil and SL82.0715 are antagonists at the polyamine site of the NMDA receptor. Eur. J. Pharmacol. 164, 611–612.

Carvalho, A.L., Kameyama, K., Huganir, R.L., 1999. Characterization of phosphorylation sites on the glutamate receptor 4 subunit of the AMPA receptors. J. Neurosci. 19, 4748–4754.

Carvalho, A.L., Duarte, C.B., Carvalho, A.P., 2000. Regulation of AMPA receptors by phosphorylation. Neurochem. Res. 25, 1245–1255.

Chen, H.M., Lambert, N.A., 1997. Inhibition of dendritic calcium influx by activation of G-protein-coupled receptors in the hippocampus. J. Neurophysiol. 78, 3484–3488.

Chen, J., Simon, R., 1997. Ischemic tolerance in the brain. Neurology 48, 306–311.

Cochilla, A.J., Alford, S., 1998. Metabotropic glutamate receptor-mediated control of neurotransmitter release. Neuron 20, 1007–1016.

Colwell, C.S., Levine, M.S., 1999. Metabotropic glutamate receptor modulation of excitotoxicity in the neostriatum: role of calcium channels. Brain Res. 833, 234–241.

Conn, P.J., Chung, D.S., Winder, D.G., Gereau IV, R.W., Boss, V. 1995. In: Stone, T.W. (Ed.), CNS Neurotransmitters and Modulators: Glutamate. CRC Press, Boca Raton, pp. 181–200.

Connick, J.H., Heywood, G.C., Sills, G.J., Thompson, G.G., Brodie, M.J., Stone, T.W., 1992. Nicotinylalanine increases cerebral kynurenic acid content and has anticonvulsant activity. Gen. Pharmacol. 23, 235–239.

Connor, J.A., Razani-Boroujerdi, S., Greenwood, A.C., Cormier, R.J., Petrozzino, J.J., Lin, R.C., 1999. Reduced voltage-dependent Ca^{2+} signaling in CA1 neurons after brief ischemia in gerbils. J. Neurophysiol. 81, 299–306.

Cowen, M.S., Beart, P.M., 1998. Cyclothiazide and AMPA receptor desensitization: analyses from studies of AMPA-induced release of [^{3}H]-noradrenaline from hippocampal slices. Br. J. Pharmacol. 123, 473–480.

Croucher, M.J., Thomas, L.S., Ahmadi, H., Lawrence, V., Harris, J.R., 2001. Endogenous sulphur-containing amino acids: potent agonists at presynaptic metabotropic glutamate autoreceptors in the rat central nervous system. Br. J. Pharmacol. 133, 815–824.

Cull-Candy, S., Brickley, S., Farrant, M., 2001. NMDA receptor subunits: diversity, development and disease. Curr. Opin. Neurobiol. 11, 327–335.

Currie, R.W., Ellison, J.A., White, R.F., Feuerstein, G.Z., Wang, X., Barone, F.C., 2000. Benign focal ischemic preconditioning induces neuronal Hsp70 and prolonged astrogliosis with expression of Hsp27. Brain Res. 863, 169–181.

Davies, J., Francis, A.A., Jones, A.W., Watkins, J.C., 1981. 2-Amino-5-phosphonovalerate (2APV), a potent and selective antagonist of amino acid-induced and synaptic excitation. Neurosci. Lett. 21, 77–81.

De Mendonca, A., Sebastiao, A.M., Ribeiro, J.A., 1995. Inhibition of NMDA receptor-mediated currents in isolated rat hippocampal neurones by adenosine A1 receptor activation. NeuroReport 6, 1097–1100.

Derkach, V., Barria, A., Soderling, T.R., 1999. Ca^{2+}/calmodulin-kinase II enhances channel conductance of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionate type glutamate receptors. Proc. Natl. Acad. Sci. U. S. A. 96, 3269–3274.

Desai, M.A., Valli, M.J., Monn, J.A., Schoepp, D.D., 1995. 1-BCP, a memory-enhancing agent, selectively potentiates AMPA-induced [^{3}H]norepinephrine release in rat hippocampal slices. Neuropharmacology 34, 141–147.

Eastman, C.L., Guilarte, T.R., 1990. The role of hydrogen peroxide in the in vitro cytotoxicity of 3-hydroxykynurenine. Neurochem. Res. 15, 1101–1107.

Espey, M.G., Chernyshev, O.N. , Reinhard Jr., J.F., Namboodiri, M.A.A., Colton, C.A. 1997. Activated human microglia produce the excitotoxin quinolinic acid. NeuroReport 8, 431–434.

Fagni, L., Olivier, M., Lafon-Cazal, M., Bockaert, J., 1995. Involvement of divalent ions in the nitric oxide-induced blockade of *N*-methyl-D-aspartate receptors in cerebellar granule cells. Mol. Pharmacol. 47, 1239–1247.

Feldmeyer, D., Kask, K., Brusa, R., Kornau, H.C., Kolhekar, R., Rozov, A., Burnashev, N., Jensen, V., Hvalby, O., Sprengel, R., Seeburg, P.H., 1999. Neurological dysfunctions in mice expressing different levels of the Q/R site-unedited AMPAR subunit GluR-B. Nat. Neurosci. 2, 57–64.

Frank, L., Diemer, N.H., Kaiser, F., Sheardown, M., Rasmussen, J.S., Kristensen, P., 1995. Unchanged balance between levels of mRNA encoding AMPA glutamate receptor subtypes following global cerebral ischemia in the rat. Acta Neurol. Scand. 92, 337–343.

Gasparini, F., Bruno, V., Battaglia, G., Lukic, S., Leonhardt, T., Inderbitzin, W., Laurie, D., Sommer, B., Varney, M.A., Hess, S.D., Johnson, E.C., Kuhn, R., Urwyler, S., Sauer, D., Portet, C., Schmutz, M., Nicoletti, F., Flor, P.J., 1999. (*R*,*S*)-4-phosphonophenylglycine, a potent and selective group III metabotropic glutamate receptor agonist, is anticonvulsive and neuroprotective in vivo. J. Pharmacol. Exp. Ther. 289, 1678–1687.

Gates, M., Ogden, A., Bleakman, D., 2001. Pharmacological effects of AMPA receptor potentiators LY392098 and LY404187 on rat neuronal AMPA receptors in vitro. Neuropharmacology 40, 984–991.

Geiger, J.R., Melcher, T., Koh, D.S., Sakmann, B., Seeburg, P.H., Jonas, P., Monyer, H., 1995. Relative abundance of subunit mRNAs determines gating and Ca^{2+} permeability of AMPA receptors in principal neurons and interneurons in rat CNS. Neuron 15, 193–204.

Glazner, G.W., Chan, S.L., Lu, C., Mattson, M.P., 2000. Caspase-mediated degradation of AMPA receptor subunits: a mechanism for preventing excitotoxic necrosis and ensuring apoptosis. J. Neurosci. 20, 3641–3649.

Goncalves, M.L., Ribeiro, J.A., 1996. Adenosine A2 receptor activation facilitates Ca-45($^{2+}$) uptake by rat brain synaptosomes. Eur. J. Pharmacol. 310, 257–261.

Goncalves, M.L., Pinto, F., Ribeiro, J.A., 1991. Effect of adenosine on Ca-45($^{2+}$) uptake by electrically stimulated rat brain synaptosomes. J. Neurochem. 56, 1769–1773.

Gotz, T., Kraushaar, U., Geiger, J., Lubke, J., Berger, T., Jonas, P., 1997. Functional properties of AMPA and NMDA receptors expressed in identified types of basal ganglia neurons. J. Neurosci. 17, 204–215.

Grabb, M.C., Choi, D.W., 1999. Ischemic tolerance in murine cortical cell culture: critical role for NMDA receptors. J. Neurosci. 19, 1657–1662.

Gu, J.G., Albuquerque, C., Lee, C.J., MacDermott, A.B., 1996. Synaptic strengthening through activation of Ca^{2+}-permeable AMPA receptors. Nature 381, 793–796.

Harris, E.W., 1995. Subtypes of glutamate receptors: pharmacological classification. In: Stone, T.W. (Ed.), CNS Neurotransmitters and Modulators: Glutamate. CRC Press, Boca Raton, pp. 95–126.

Harris, C.A., Miranda, A.F., Tanguay, J.J., Boegman, R.J., Beninger, R.J., Jhamandas, K., 1998. Modulation of striatal quinolinate neurotoxicity by elevation of endogenous brain kynurenic acid. Br. J. Pharmacol. 124, 391–399.

Heizmann, C.W., Braun, K., 1992. Changes in Ca($^{2+}$)-binding proteins in human neurodegenerative disorders. Trends Neurosci. 15, 259–264.

Heyes, M.P., Mefford, I.N., Quearry, B.J., Dedhia, M., Lackner, A., 1990. Increased ratio of quinolinic acid to kynurenic acid in cerebrospinal fluid of D retrovirus-infected Rhesus macaques: relationship to clinical and viral status. Ann. Neurol. 27, 666–675.

Heyes, M.P., Achim, C.L., Wiley, C.A., Major, E.O., Saito, K., Markey, S.P., 1996. Human microglia convert L-tryptophan into the neurotoxin quinolinic acid. Biochem. J. 320, 595–597.

Hollmann, M., Hartley, M., Heinemann, S., 1991. Ca^{2+} permeability of KA-AMPA-gated glutamate receptor channels depends on subunit composition. Science 252, 851–853.

Hollmann, M., Maron, C., Heinemann, S., 1994. *N*-Glycosylation site tagging suggests a three transmembrane domain topology for the glutamate receptor GluR1. Neuron 13, 1331–1343.

Iino, M., Koike, M., Isa, T., Ozawa, S., 1996. Voltage-dependent blockage of Ca($^{2+}$)-permeable AMPA receptors by Joro spider toxin in cultured rat hippocampal neurones. J. Physiol. (London) 496, 431–437.

Itazawa, S.I., Isa, T., Ozawa, S., 1997. Inwardly rectifying and Ca^{2+}-permeable AMPA-type glutamate receptor channels in rat neocortical neurons. J. Neurophysiol. 78, 2592–2601.

Ito, M., Karachot, L., 1992. Protein kinases and phosphatase inhibitors mediating long-term desensitization of glutamate receptors in cerebellar Purkinje cells. Neurosci. Res. 14, 27–38.

Johnson, J.W., Ascher, P., 1987. Glycine potentiates the NMDA response in cultured mouse brain neurones. Nature 325, 529–531.

Jonas, P., Racca, C., Sakmann, B., Seeburg, P.H., Monyer, H., 1994. Differences in Ca^{2+} permeability of AMPA-type glutamate receptor channels in neocortical neurons caused by differential GluR-B subunit expression. Neuron 12, 1281–1289.

Jones, P.A., Smith, R.A., Stone, T.W., 1998a. Protection against hippocampal kainate excitotoxicity by intracerebral administration of an adenosine A2A receptor antagonist. Brain Res. 800, 328–335.

Jones, P.A., Smith, R.A., Stone, T.W., 1998b. Protection against kainate-induced excitotoxicity by adenosine A2A receptor agonists and antagonists. Neuroscience 85, 229–237.

Judge, M.E., Sheardown, M.J., Jacobsen, P., Honore, T., 1991. Protection against post-ischemic behavioral pathology by the alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) antagonist 2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo(*f*)quinoxaline (NBQX) in the gerbil. Neurosci. Lett. 133, 291–294.

Kapus, G., Bodi, I., Pataki, A., Gueritaud, J., Szekely, J.I., Tarnawa, I., 2000. Differential modulation of the GYKI 53784-induced inhibition of AMPA currents by various AMPA-positive modulators in cerebellar Purkinje cells. Eur. J. Pharmacol. 397, 43–47.

Klockgether, T., Turski, L., Honore, T., Zhang, Z.M., Gash, D.M., Kurlan, R., Greenamyre, J.T., 1991. The AMPA receptor antagonist NBQX has antiparkinsonian effects in monoamine-depleted rats and MPTP-treated monkeys. Ann. Neurol. 30, 717–723.

Kohler, C., Eriksson, L.G., Flood, P.R., Hardie, J.A., Okuno, E., Schwarcz, R., 1988. Quinolinic acid metabolism in the rat brain: immunohistochemical identification of 3-hydroxyanthranilic acid oxygenase and quinolinic acid phosphoribosyltransferase in the hippocampal region. J. Neurosci. 8, 975–987.

Kondo, M., Okabe, S., Sumino, R., Okado, H., 2000. A high GluR1: GluR2 expression ratio is correlated with expression of Ca^{2+}-binding proteins in rat forebrain neurons. Eur. J. Neurosci. 12, 2812–2822.

Konig, N., Poluch, S., Estabel, J., Durand, M., Crian, M.J., Exbrayat, J.M., 2001. Synaptic and non-synaptic AMPA receptors permeable to calcium. Japan. J. Pharmacol. 86, 1–17.

Kyrozis, A., Goldstein, P.A., Heath, M.J., MacDermott, A.B., 1995. Ca^{2+} entry through a subpopulation of AMPA receptors desensitized neighbouring NMDA receptors in rat dorsal horn neurons. J. Physiol. (London) 485, 373–381.

Lafon-Cazal, M., Fagni, L., Guiraud, M.J., Mary, S., Lerner-Natoli, M., Pin, J.P., Shigemoto, R., Bockaert, J., 1999. mGluR7-like metabotropic glutamate receptors inhibit NMDA-mediated excitotoxicity in cultured mouse cerebellar granule neurons. Eur. J. Neurosci. 11, 663–672.

Lees, K.R., 1997. Cerestat and other NMDA antagonists in ischemic stroke. Neurology 49, S66–S69.

Lei, S.Z., Pan, Z.H., Aggarwal, S.K., Chen, H.S., Hartman, J., Sucher, N.J., Lipton, S.A., 1992. Effect of nitric oxide production on the redox modulatory site of the NMDA receptor–channel complex. Neuron 8, 1087–1099.

Levy, D.I., Sucher, N.J., Lipton, S.A., 1990. Redox modulation of NMDA receptor-mediated toxicity in mammalian central neurons. Neurosci. Lett. 110, 291–296.

Lipton, S.A., 1998. Neuronal injury associated with HIV-1: approaches to treatment. Annu. Rev. Pharmacol. Toxicol. 38, 159–177.

Liu, S.Q., Cull-Candy, S.G., 2000. Synaptic activity at Ca^{2+}-permeable AMPA receptors induces a switch in receptor subtype. Nature 405, 454–458.

Lomeli, H., Mosbacher, J., Melcher, T., Hoger, T., Geiger, J.R., Kuner, T., Monyer, H., Higuchi, M., Bach, A., Seeburg, P.H., 1994. Control of kinetic properties of AMPA receptor channels by nuclear RNA editing. Science 266, 1709–1713.

Lyeth, B.G., Gong, Q.Z., Shields, S., Muizelaar, J.P., Berman, R.F., 2001. Group I metabotropic glutamate antagonist reduces acute neuronal degeneration and behavioral deficits after traumatic brain injury in rats. Exp. Neurol. 169, 191–199.

MacGregor, D.G., Stone, T.W., 1993. Inhibition by the adenosine analogue, ($R-$)-N_6 phenylisopropyladenosine, of kainic acid neurotoxicity in rat hippocampus after systemic administration. Br. J. Pharmacol. 109, 316–321.

MacGregor, D.G., Miller, W.J., Stone, T.W., 1993. Mediation of the neuro-

protective action of *R*-phenylisopropyladenosine through a centrally located adenosine A1 receptor. Br. J. Pharmacol. 110, 470–476.

May, P.C., Robison, P.M., 1993. Cyclothiazide treatment unmasks AMPA excitotoxicity in rat primary hippocampal cultures. J. Neurochem. 60, 1171–1174.

McGlade-McCulloh, E., Yamamoto, H., Tan, S.E., Brickey, D.A., Soderling, T.R., 1993. Phosphorylation and regulation of glutamate receptors by Ca^{2+}/calmodulin dependent protein kinase II. Nature 362, 640–642.

Medina, I., Filippova, N., Barbin, G., Ben Ari, Y., Bregestovski, P., 1994. Kainate-induced inactivation of NMDA currents via an elevation of intracellular Ca^{2+} in hippocampal neurons. J. Neurophysiol. 72, 456–465.

Miu, P., Jarvie, K.R., Radhakrishnan, V., Gates, M.R., Ogden, A., Ornstein, P.L., Zarrinmayeh, H., Ho, K., Peters, D., Grabell, J., Gupta, A., Zimmerman, D.M., Bleakman, D., 2001. Novel AMPA receptor potentiators LY392098 and LY404187: effects on recombinant human AMPA receptors in vitro. Neuropharmacology 40, 976–983.

Monopoli, A., Lozza, G., Forlani, A., Mattavelli, A., Ongini, E., 1998. Blockade of adenosine A_{2A} receptors by SCH 58261 results in neuroprotective effects in cerebral ischaemia in rats. NeuroReport 9, 3955–3959.

Morris, G.F., Bullock, R., Marshall, S.B., Marmarou, A., Maas, A., Marshall, L.F., 1999. Failure of the competitive *N*-methyl-D-aspartate antagonist Selfotel (CGS 19755) in the treatment of severe head injury: results of two phase III clinical trials. J. Neurosurg. 91, 737–743.

Mosbacher, J., Schoepfer, R., Monyer, H., Burnashev, N., Seeburg, P.H., Ruppersberg, J.P., 1994. A molecular determinant for submillisecond desensitization in glutamate receptors. Science 266, 1059–1062.

Nagarajan, N., Quast, C., Boxall, A.R., Shahid, M., Rosenmund, C., 2001. Mechanism and impact of allosteric AMPA receptor modulation by the ampakine CX546. Neuropharmacology 41, 650–663.

Natalini, B., Mattoli, L., Pellicciari, R., Carpenedo, R., Chiarugi, A., Moroni, F., 1995. Synthesis and activity of enantiopure (*S*) (*m*-nitrobenzoyl) alanine, potent kynurenine-3-hydroxylase inhibitor. Biorg. Med. Chem. Lett. 5, 1451–1454.

Nikbakht, M.-R., Stone, T.W., 2001. Suppression of presynaptic responses to adenosine by activation of NMDA receptors. Eur. J. Pharmacol. 427, 13–25.

Norenberg, W., Wirkner, K., Illes, P., 1997. Effect of adenosine and some of its structural analogues on the conductance of NMDA receptor channels in a subset of rat neostriatal neurones. Br. J. Pharmacol. 122, 71–80.

Obrenovitch, T.P., Urenjak, J., 1997. Altered glutamatergic transmission in neurological disorders: from high extracellular glutamate to excessive synaptic efficacy. Prog. Neurobiol. 51, 39–87.

Ogura, A., Miyamoto, M., Kudo, Y., 1988. Neuronal death in vitro: parallelism between survivability of hippocampal neurons and sustained elevation of cytosolic Ca^{2+} after exposure to glutamate receptor agonist. Exp. Brain Res. 73, 447–458.

Ohmori, J., Sakamoto, S., Kubota, H., Shimizu-Sasamata, M., Okada, M., Kawasaki, S., Hidaka, K., Togami, J., Furuya, T., Murase, K., 1994. 6-(1*H*-Imidazol-1-yl)-7-nitro-2,3(1*H*,4*H*)-quinoxalinedione hydrochloride (YM90K) and related compounds: structure–activity relationships for the AMPA-type non-NMDA receptor. J. Med. Chem. 37, 467–475.

Ongini, E., Adami, M., Ferri, C., Bertorelli, R., 1997. Adenosine A_{2A} receptors and neuroprotection. Ann. N. Y. Acad. Sci. 825, 30–48.

Panchenko, V.A., Glasser, C.R., Partin, K.M., Mayer, M.L., 1999. Amino acid substitutions in the pore of rat glutamate receptors at sites influencing block by polyamines. J. Physiol. (London) 520, 337–357.

Paoletti, P., Ascher, P., Neyton, J., 1997. High affinity zinc inhibition of NMDA NR1–NR2A receptors. J. Neurosci. 17, 5711–5725.

Partin, K.M., Patneau, D.K., Mayer, M.L., 1994. Cyclothiazide differentially modulates desensitization of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor splice variants. Mol. Pharmacol. 46, 129–138.

Partin, K.M., Fleck, M.W., Mayer, M.L., 1996. AMPA receptor flip/flop mutants affecting deactivation, desensitization, and modulation by cyclothiazide, aniracetam, and thiocyanate. J. Neurosci. 16, 6634–6647.

Pellegrini-Giampietro, D.E., Zukin, R.S., Bennett, M.V., Cho, S., Pulsinelli, W.A., 1992. Switch in glutamate receptor subunit gene expression in CA1 subfield of hippocampus following global ischemia in rats. Proc. Natl. Acad. Sci. U. S. A. 89, 10499–10503.

Pellegrini-Giampietro, D.E., Gorter, J.A., Bennett, M.V., Zukin, R.S., 1997. The GluR2 (GluR-B) hypothesis: Ca($^{2+}$)-permeable AMPA receptors in neurological disorders. Trends Neurosci. 20, 464–470.

Pellegrini-Giampietro, D.E., Peruginelli, F., Meli, E., Cozzi, A., Albani-Torregrossa, S., Pellicciari, R., Moroni, F., 1999. Protection with metabotropic glutamate 1 receptor antagonists in models of ischemic neuronal death: time-course and mechanisms. Neuropharmacology 38, 1607–1619.

Pellicciari, R., Natalini, B., Costantino, G., Mahmoud, M.R., Mattoli, L., Sadeghpour, B.M., 1994. Modulation of the kynurenine pathway in search for new neuroprotective agents. Synthesis and preliminary evaluation of (*m*-nitrobenzoyl) alanine, a potent inhibitor of kynurenine-3-hydroxylase. J. Med. Chem. 37, 647–655.

Perez-Pinzon, M.A., Born, J.G., Centeno, J.M., 1999. Ca^{2+} and increase excitability promote tolerance against anoxia in hippocampal slices. Brain Res. 833, 20–26.

Perkins, M.N., Stone, T.W., 1982. An iontophoretic investigation of the actions of convulsant kynurenines and their interaction with the endogenous excitant quinolinic acid. Brain Res. 247, 184–187.

Perkins, M.N., Stone, T.W., Collins, J.F., Curry, K., 1981. Phosphonate analogues of carboxylic acids as amino acid antagonists on rat cortical neurons. Neurosci. Lett. 23, 333–336.

Perkinton, M.S., Sihra, T.S., Williams, R.J., 1999. Ca($^{2+}$)-permeable AMPA receptors induce phosphorylation of cAMP response element-binding protein through a phosphatidylinositol 3-kinase-dependent stimulation of the mitogen-activated protein kinase signaling cascade in neurons. J. Neurosci. 19, 5861–5874.

Pin, J.P., Duvoisin, R., 1995. The metabotropic glutamate receptors: structure and function. Neuropharmacology 34, 1–26.

Pizzi, M., Benarese, M., Boroni, F., Goffi, F., Valerio, A., Spano, P.F., 2000. Neuroprotection by metabotropic glutamate receptor agonists on kainate-induced degeneration of motor neurons in spinal cord slices from adult rat. Neuropharmacology 39, 903–910.

Rajadhyaksha, A., Barczak, A., Macias, W., Leveque, J.C., Lewis, S.E., Konradi, C., 1999. L-Type Ca($^{2+}$) channels are essential for glutamate-mediated CREB phosphorylation and c-*fos* gene expression in striatal neurons. J. Neurosci. 19, 6348–6359.

Raymond, L.A., Moshaver, A., Tingley, W.G., Huganir, R.L., 1996. Glutamate receptor ion channel properties predict vulnerability to cytotoxicity in a transfected nonneuronal cell line. Mol. Cell. Neurosci. 7, 102–115.

Reynolds, I.J., 1995. Modulation of glutamate receptor function by polyamines. In: Stone, T.W. (Ed.), CNS Neurotransmitters and Modulators: Glutamate. CRC Press, Boca Raton, pp. 305–322.

Rosenmund, C., Feltz, A., Westbrook, G.L., 1995. Ca^{2+}-dependent inactivation of synaptic NMDA receptors in hippocampal neurons. J. Neurophysiol. 73, 427–430.

Rosenmund, C., Stern-Bach, Y., Stevens, C.F., 1998. The tetrameric structure of a glutamate receptor channel. Science 280, 1596–1599.

Russi, P., Alesiani, M., Lombardi, G., Davolio, P., Pellicciari, R., Moroni, F, 1992. Nicotinylalanine increases the formation of kynurenic acid in the brain and antagonizes convulsions. J. Neurochem. 59, 2076–2080.

Sakurai, M., Hayashi, T., Abe, K., Aoki, M., Sadahiro, M., Tabayashi, K., 1998. Enhancement of heat shock protein expression after transient ischemia in the preconditioned spinal cord of rabbits. J. Vasc. Surg. 27, 720–725.

Schurmann, B., Wu, X., Dietzel, I.D., Lessmann, V., 1997. Differential modulation of AMPA receptor mediated currents by Evans Blue in postnatal rat hippocampal neurones. Br. J. Pharmacol. 121, 237–247.

Schurov, I.L., McNulty, S., Best, J.D., Sloper, P.J., Hastings, M.H., 1999. Glutamatergic induction of CREB phosphorylation and Fos expression

in primary cultures of the suprachiasmatic hypothalamus in vitro is mediated by co-ordinate activity of NMDA and non-NMDA receptors. J. Neuroendocrinol. 11, 43–51.

Schwartz, N.E., Alford, S., 2000. Physiological activation of presynaptic metabotropic glutamate receptors increases intracellular calcium and glutamate release. J. Neurophysiol. 84, 415–427.

Sekiguchi, M., Fleck, M.W., Mayer, M.L., Takeo, J., Chiba, Y., Yamashita, S., Wada, K., 1997. A novel allosteric potentiator of AMPA receptors: 4-2-(phenylsulfonylamino)ethylthio-2,6-difluoro-phenoxyacetamide. J. Neurosci. 17, 5760–5771.

Shamloo, M., Wieloch, T., 1999. Changes in protein tyrosine phosphorylation in the rat brain after cerebral ischemia in a model of ischemic tolerance. J. Cereb. Blood Flow Metab. 19, 173–183.

Sheardown, M.J., Knutsen, L.J.S., 1996. Unexpected neuroprotection observed with the adenosine A_{2A} receptor agonist CGS21680. Drug Dev. Res. 39, 108–114.

Sheardown, M.J., Nielsen, E.O., Hansen, A.J., Jacobsen, P., Honore, T., 1990. 2,3-Dihydroxy-6-nitro-7-sulfamoyl-benzo(*F*)quinoxaline: a neuroprotectant for cerebral ischemia. Science 247, 571–574.

Shigemoto, R., Kinoshita, A., Wada, E., Nomura, S., Ohishi, H., Takada, M., Flor, P.J., Neki, A., Abe, T., Nakanishi, S., Mizuno, N., 1997. Differential localisation of metabotropic glutamate receptor subtypes in the rat hippocampus. J. Neurosci. 17, 7503–7522.

Skeberdis, V.A., Lan, J.-Y., Opitz, T., Zheng, X., Bennett, M.V.L., Zukin, R.S., 2001. mGluR1-mediated potentiation of NMDA receptors involves a rise in intracellular calcium and activation of protein kinase C. Neuropharmacology 40, 856–865.

Sloviter, R.S., 1989. Ca^{2+}-binding protein (calbindin-D28k) and parvalbumin immunocytochemistry: localization in the rat hippocampus with specific reference to the selective vulnerability of hippocampal neurons to seizure activity. J. Comp. Neurol. 280, 183–196.

Sommer, B., Keinanen, K., Verdoorn, T.A., Wisden, W., Burnashev, N., Herb, A., Kohler, M., Takagi, T., Sakmann, B., Seeburg, P.H., 1990. Flip and flop: a cell-specific functional switch in glutamate-operated channels of the CNS. Science 249, 1580–1585.

Sommer, B., Kohler, M., Sprengel, R., Seeburg, P.H., 1991. RNA editing in brain controls a determinant of ion flow in glutamate-gated channels. Cell 67, 11–19.

Sommer, C., Roth, S.U., Kuhn, R., Kiessling, M., 2000. Metabotropic glutamate receptor subtypes are differentially expressed after transient cerebral ischemia without, during and after tolerance induction in the gerbil hippocampus. Brain Res. 872, 172–180.

Speciale, C., Wu, H.Q., Cini, M., Marconi, M., Varasi, M., Schwarcz, R., 1996. (*R*,*S*)-3,4-dichlorobenzoylalanine (FCE 28833A) causes a large and persistent increase in brain kynurenic acid levels in rats. Eur. J. Pharmacol. 315, 263–267.

Stern-Bach, Y., Russo, S., Neuman, M., Rosenmund, C., 1998. A point mutation in the glutamate binding site blocks desensitization of AMPA receptors. Neuron 21, 907–918.

Stone, T.W., 1988. Comparison of kynurenic acid and 2-APV suppression of epileptiform activity in rat hippocampal slices. Neurosci. Lett. 84, 234–238.

Stone, T.W., 1990. Sensitivity of hippocampal neurones to kainic acid, and antagonism by kynurenate. Br. J. Pharmacol. 101, 847–852.

Stone, T.W., 1993. Neuropharmacology of quinolinic and kynurenic acids. Pharmacol. Rev. 45, 309–379.

Stone, T.W., 2000. Development and therapeutic potential of kynurenic acid and kynurenine derivatives for neuroprotection. Trends Pharmacol. Sci. 21, 149–154.

Stone, T.W., 2001. Kynurenines in the CNS: from obscurity to therapeutic importance. Progr. Neurobiol. 64, 185–218.

Stone, T.W., Perkins, M.N., 1981. Quinolinic acid: a potent endogenous excitant at amino acid receptors in CNS. Eur. J. Pharmacol. 72, 411–412.

Stone, T.W., Jones, P.A., Smith, R.A., 2001. Neuroprotection by A2A receptor antagonists. Drug Dev. Res. 52, 323–330.

Tan, S.E., Wenthold, R.J., Soderling, T.R., 1994. Phosphorylation of AMPA-type glutamate receptors by Ca^{2+}/calmodulin-dependent protein kinase II and protein kinase C in cultured hippocampal neurons. J. Neurosci. 14, 1123–1129.

Tremblay, R., Chakravarthy, B., Hewitt, K., Tauskela, J., Morley, P., Atkinson, T., Durkin, J.P., 2000. Transient NMDA receptor inactivation provides long-term protection to cultured cortical neurons from a variety of death signals. J. Neurosci. 20, 7183–7192.

von Lubitz, D.J.K.E., Dambrosia, J.M., Kempski, O., Redmond, D.J., 1988. Cyclohexyl adenosine protects against neuronal death following ischaemia in the CA1 region of gerbil hippocampus. Stroke 19, 1133–1139.

von Lubitz, D.K.E.J., Dambrosia, J.M., Redmond, D.J., 1989. Protective effect of cyclohexyladenosine in treatment of cerebral ischaemia in gerbils. Neuroscience 30, 451–462.

Warner, D.S., Martin, H., Ludwig, P., McAllister, A., Keana, J.F.W., Weber, E., 1995. In vivo models of cerebral ischaemia: effects of parenterally administered NMDA receptor glycine site antagonists. J. Cereb. Blood Flow Metab. 15, 188–196.

Washburn, M.S., Dingledine, R., 1996. Block of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors by polyamines and polyamine toxins. J. Pharmacol. Exp. Ther. 278, 669–678.

Weiser, T., Herrmann, A., Wienrich, M., 1996. Interactions of the dye Evans Blue and GYKI 52466, a 2,3-benzodiazepine, with (*S*)-alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors in cultured rat cortical neurons: electrophysiological evidence for at least two different binding sites for non-competitive antagonists. Neurosci. Lett. 216, 29–32.

Williams, K., 1993. Ifenprodil discriminates subtypes of the NMDA receptor. Selectivity and mechanisms at recombinant heteromeric receptors. Mol. Pharmacol. 44, 851–859.

Yamakura, T., Shimoji, K., 1999. Subunit- and site-specific pharmacology of the NMDA receptor channel. Prog. Neurobiol. 59, 279–298.

Yano, S., Morioka, M., Fukunaga, K., Kawano, T., Hara, T., Kai, Y., Hamada, J., Miyamoto, E., Ushio, Y., 2001. Activation of Akt/protein kinase B contributes to induction of ischemic tolerance in the CA1 subfield of gerbil hippocampus. J. Cereb. Blood Flow Metab. 21, 351–360.

Ying, H.S., Weishaupt, J.H., Grabb, M., Canzoniero, L.M., Sensi, S.L., Sheline, C.T., Monyer, H., Choi, D.W., 1997. Sublethal oxygen–glucose deprivation alters hippocampal neuronal AMPA receptor expression and vulnerability to kainate-induced death. J. Neurosci. 17, 9536–9544.

Youssef, F., Stone, T.W., Addae, J.I., 2000. Interactions of glutamate receptor agonists with long-term potentiation in the rat hippocampal slice. Eur. J. Pharmacol. 398, 349–359.

Youssef, F., Addae, J.I., McRae, A., Stone, T.W., 2001. Long-term potentiation protects rat hippocampal slices from the effects of acute hypoxia. Brain Res. 907, 144–150.

Zirpel, L., Janowiak, M.A., Veltri, C.A., Parks, T.N., 2000. AMPA receptor-mediated, Ca^{2+}-dependent CREB phosphorylation in a subpopulation of auditory neurons surviving activity deprivation. J. Neurosci. 20, 6267–6275.

Zwienenberg, M., Gong, Q.Z., Berman, R.F., Muizelaar, J.P., Lyeth, B.G, 2001. The effect of groups II and III metabotropic glutamate receptor activation on neuronal injury in a rodent model of traumatic brain injury. Neurosurgery 48, 1119–1126.