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REVIEW ARTICLE

Glutamate: a role in normal brain function, anaesthesia, analgesia and CNS injury

M. J. HUDSPITH

Glutamate is the major excitatory amino acid (EAA) neurotransmitter in the central nervous system (CNS).[78] EAA neurones and synapses are distributed widely throughout the CNS,[36 231] but they are concentrated particularly in the hippocampus,[91] the outer layers of the cerebral cortex[91] and the substantia gelatinosa of the spinal cord.[194] Within these regions EAA play key roles in physiological processes including learning and memory (and hence awareness under anaesthesia), central pain transduction mechanisms and pathological processes such as excitotoxic neuronal injury which follows CNS trauma or ischaemia. Thus an understanding of the role of EAA in the CNS is relevant to normal higher brain function and to anaesthesia, analgesia and intensive care.

A broad spectrum of pharmacological agents which alter EAA-mediated neurotransmission are already available and many more are under development. These include: (i) drugs that specifically target the release of EAA (e.g. the novel antiepileptic drugs felbamate and lamotrigine), (ii) drugs that modify the interactions of EAA with specific receptors (e.g ketamine) and (iii) volatile and i.v. anaesthetic agents which may have a common mechanism of action that, at least in part, involves EAA-mediated neurotransmission. To understand the potential applications of these agents it is necessary to consider first how EAA act at the level of the synapse and the individual neurone. To do so involves a brief outline of EAA receptor subtypes and how their activation affects the postsynaptic neurone. It may then be possible to explain how EAA and their receptors are involved in cognition, anaesthesia, analgesia and neurointensive care and therefore to provide a framework to assess the possible clinical applications of drugs which modify EAA-mediated neurotransmission.

Excitatory amino acid neurotransmission

A diagrammatic representation of an EAA synapse comprising a presynaptic nerve terminal and a postsynaptic neurone expressing multiple EAA receptor subtypes is shown in figure 1 and described first in terms of presynaptic events and then activation of postsynaptic receptors.

PRESYNAPTIC EVENTS

Glutamate, synthesized by the deamination of glutamine or via the tricarboxylic acid cycle, is released into the synaptic cleft in response to depolarization of the presynaptic nerve terminal. The release of glutamate from presynaptic terminals (and that of other neurotransmitters), is a Ca^{2+}-dependent process regulated by multiple types of Ca^{2+} channel. N-type and P-type Ca^{2+} channels are probably the most important determinants of exocytotic neurotransmitter release from presynaptic nerve terminals throughout the CNS[55] although other channel types (such as Q and R) may also be involved. Importantly, different Ca^{2+} channel types may be involved in the exocytotic release of neurotransmitter from different neurones within the CNS and from different sites in individual neurones.[55] After release of glutamate, binding to specific receptor types described in the following section determines the postsynaptic response.

In common with many other central neurotransmitter systems,[88] the actions of glutamate within the synaptic cleft are terminated by high affinity sodium-dependent uptake. Glutamate transporters are localized in both pre- and postsynaptic neuronal elements together with glial cells.[182] Three, or possibly four, glutamate transporters have been characterized[64 96 164 201] (for a recent review see Malandro and Kilberg[128]), each of which are transmembrane proteins of approximately 60–70 kDa size with K_m values for glutamate in the low micromolar range.

EXCITATORY AMINO ACID RECEPTORS

Two main subgroups of EAA receptors have been identified: *ionotropic* and *metabotropic* receptors.[191 223] Ionotropic glutamate receptors (*i*Glu-receptors) are so named because such receptors are ligand-operated ion channels (LOC) and a change in membrane permeability to specific cations occurs

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M. J. HUDSPITH, PHD, FRCA, University Department of Anaesthesia, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ.

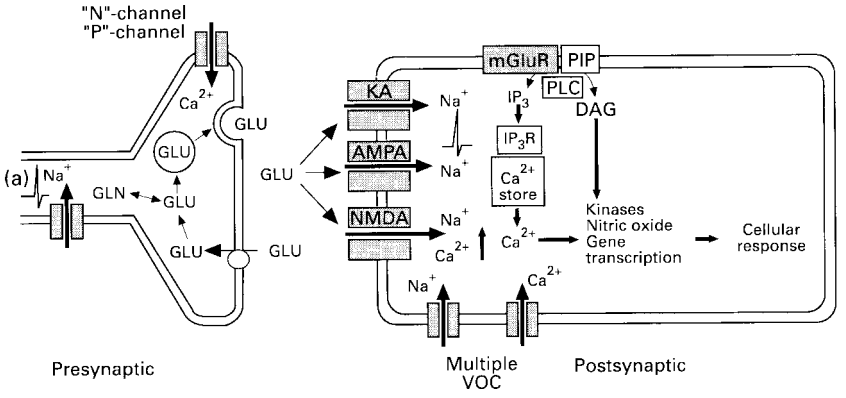

Figure 1 Schematic representation of an excitatory amino acid (EAA) synapse within the CNS. Glutamate is released from the presynaptic nerve terminal in response to depolarization-dependent Ca^{2+} entry through "N-" or "P-" type voltage-operated Ca^{2+} channels. Glutamate within the synaptic cleft can bind to ionotropic and metabotropic glutamate receptors (mGluR) on the postsynaptic neurone: individual neurones may express multiple glutamate receptor subtypes. Receptor activation evokes a cellular response via increases in intracellular Ca^{2+} and activation of protein kinases. GLU = glutamate; NMDA = *N*-methyl-D-aspartate; KA = kainate; GLN = glutamine; AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate; PIP = phosphatidyl-inositol-4,5-bisphosphate; PLC = phospholipase C; IP_3 = inositol-l,4,5-trisphosphate; IP_3R = IP_3 receptor; DAG = diacylglycerol; VOC = voltage-operated ion channel; (a) = depolarization and action potential generation.

within a few milliseconds of agonist binding (see below). The *i*Glu-receptor family can be classified pharmacologically according to activation by specific agonists into three subtypes: *AMPA* receptors (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate), *KA* receptors (kainate) and *NMDA* receptors (*N*-methyl-D-aspartate).

The family of metabotropic glutamate receptors (*m*Glu-receptors; for clarity, *m*GluR in fig. 1) are receptors linked to G-proteins that modulate intracellular second messengers such as inositol phosphates and cyclic nucleotides. Their classification is complicated by the lack of ligands showing selectivity for individual *m*Glu-receptor subtypes. However eight *m*Glu-receptor subtypes have been identified by molecular biological techniques (for reviews see Miller,[139] Nicoletti and colleagues,[150] and Pin and Duvoisin[163]); all are members of the 7-transmembrane receptor superfamily and can be further classified according to sequence homology and signal transduction pathways into three groups (see table 1). Whereas activation of *i*Glu-receptors results in a response (i.e. membrane depolarization) within a few milliseconds of agonist binding, the G-protein coupled *m*Glu-receptors evoke changes in neuronal excitation on a time scale of hundreds of milliseconds to seconds.

In contrast to the 7-transmembrane *m*Glu receptor, ionotropic EAA receptors are composed of multiple subunits. At least 16 genes encoding *i*Glu receptor subunits have been characterized (see table 2: for reviews see Seeburg[193] and Sucher and colleagues[203]), and some of these genes (notably those encoding the NMDAR1[56] and GluR1-GluR4[197] subunits) undergo RNA editing producing multiple splice variants. Accordingly, multiple variants of glutamate receptor subtypes are expressed throughout the CNS and can be identified using molecular biological techniques.[83 206 232] However, for the purpose of this review the pharmacological classification listed above will be used. The roles of the *i*Glu-receptor family in systems of relevance to anaesthesia and analgesia are currently better characterized than those of the *m*Glu-receptor family; much of the following therefore concentrates on *i*Glu-receptor mediated mechanisms of neurotransmission.

Ionotropic receptors

When activated, *i*Glu-receptors undergo a conformational change that results in the opening of their

Table 1 Classification of metabotropic glutamate receptors $m\text{Glu}_1$–$m\text{Glu}_8$ (modified and redrawn from IUPHAR[87] and Nicoletti and colleagues[150]). 4CPG = S-4-carboxyphenylglycine; L-AP4 = L-amino-4-phosphonobutanoate; 2R,4R-APDC = 2R,4R-aminopyrrolidine-2,4-dicarboxylate; cAMP = cyclic 3',5'-adenosine-monophosphate; DCG-IV = (2S,1'R,2'R,3'R))-2-(2',3'-dicarboxycyclopropyl)glycine; DHPG = 3,5,dihydrophenylglycine; MAP4 = methyl-L-AP4; MCCG = 2S,1'S,2'S-2-methyl-2-(2'-carboxycyclopropyl)glycine; MPPG = (RS)-α-methyl-4-phosphonophenylglycine; IP_3 = Inositol 1,4,5 trisphosphate; I_K = Voltage-operated K^+-channel; I_{ca} = Voltage-operated Ca^{2+}-channel

*m*Glu receptor subtypes		Agonists	Antagonists	Transduction pathway (G-protein effector)
Group 1	$m\text{Glu}_1$	DHPG	4CPG	↑IP_3
	$m\text{Glu}_5$			↓I_K
Group 2	$m\text{Glu}_2$	DCG-IV	MCCG	↓cAMP
	$m\text{Glu}_3$	2R,4R-APDC		↓I_{ca}(L,N,P channel)
				↑I_K
Group 3	$m\text{Glu}_4$	L-AP4	MAP4	↓cAMP
	$m\text{Glu}_{6-8}$		MPPG	↓I_{ca} (N,P channel)

Table 2 Classification of ionotropic glutamate receptors (modified and redrawn from IUPHAR[86]). D-AP5 = D-amino-5-phosphonopentanoate; AMPA=D,L-α-amino-3-hydroxy-5-methyl-4-isoxalone propionic acid; CGS19755 = 4-phosphonomethyl-2-piperidine carboxylic acid; KA = kainate; MNQX = 5,7-dinitroquinoline-2,3-dione; NBQX = 6-nitro-7-sulphamobenzyl(*f*)quinoxaline-2,3-dione; NMDA = *N*-methyl-D-aspartate; NS102 = 6-cyano-7-nitro-2,3-quinoxalinedione

*i*Glu receptor subtype	Subunit genes		Agonist	Antagonists	Transduction pathways
AMPA	GluR1 GluR2 GluR3 GluR4		AMPA	NBQX	$\uparrow[Na^+]_i$ ($\uparrow[Ca^{2+}]_i$?)
KA	GluR5 GluR6 GluR7 KA1 KA2		Kainate	NS102	$\uparrow[Na^+]_i$
NMDA	NR1 NR2A NR2B NR2C NR2D	Competitive site Modulatory site	NMDA Glycine	D-AP5 CGS19755 5,7-dichlorokynurenate MNQX	$\uparrow[Ca^{2+}]_i$

respective ligand-operated channel (LOC). The gating properties and ion flux through *i*Glu-receptor LOC may be modified by the binding of other ligands to modulatory binding sites separate from the glutamate binding site. Activation of *i*Glu-receptors causes transmembrane flux of cations resulting in depolarization of the postsynaptic membrane. Subsequent postsynaptic events may be a direct consequence of cation entry and/or opening of voltage-operated ion channels and further cation entry (see fig. 1).

AMPA receptors. AMPA receptor channels consist of homomeric or heteromeric assemblies of GluR1-GluR4 subunits[193] (see table 2); the resultant receptor channel is primarily a Na^+ channel with rapid kinetics of activation and deactivation. Such a kinetic profile renders AMPA receptors ideal for mediation of fast excitatory neurotransmission throughout the CNS, and their generally very low Ca^{2+} permeability ensures that this glutamate-activated excitation does not trigger longer term biochemical processes evoked by an increase in intracellular Ca^{2+} concentrations.

All AMPA receptors show onset, offset and desensitization time courses in the order of a few milliseconds, although current:voltage relationships and cation permeability are specifically determined by subunit composition. For example, the normally cation impermeable AMPA receptor channel may permit Ca^{2+} entry if the GluR2 is absent,[81] although whether AMPA receptor-mediated Ca^{2+} entry has physiological relevance is unclear. A second binding site for 2,3 benzodiazepines attenuates the response of the channel to prolonged agonist stimulation and 2,3 benzodiazepines act as non-competitive AMPA antagonists.[51]

Kainate receptors. The neurotoxin, kainate (KA), binds to a specific high affinity KA receptor (identified in sensory ganglia) and activates a rapidly desensitizing Na^+ channel[82] with similar kinetics to the AMPA receptor. High affinity kainate receptors can be generated *in vitro* from multimeric assemblies of GluR5–7 and KA1 or KA2 subunits[193] (table 2) but again, precise kinetic variables of activation and inactivation are determined by subunit composition. Kainate also binds to the AMPA receptor with a lower affinity resulting in persistent, non-desensitizing activation of the AMPA receptor channel and this effect may overshadow transient high affinity KA receptor responses in central neurones.[193] Currently the distinction between AMPA and kainate receptors is somewhat blurred dependent on classification according to gating or ligand binding, however, activation of either receptor subtype by the endogenous ligand glutamate results in rapid, although transient, depolarization of the postsynaptic membrane.

NMDA receptors. The NMDA receptor channel preferentially permits Ca^{2+} entry[119] and the kinetics of this channel are much slower than those of the two preceding types of *i*Glu-receptor with channel opening persisting for several tens or hundreds of milliseconds. NMDA receptors can be reconstituted *in vitro* as heteromeric combinations of the NR1 subunit and one of four NR2 subunits (NR2A-D)[193 203] (table 2). The NR1 subunit common to all NMDA receptors exists in at least eight splice variants,[232] and this together with the four NR2 subunits provide the potential for a vast array of NMDA receptor subtypes to exist within the CNS. As with each of the ionotropic glutamate receptor classes, subunit composition determines the (complex) gating properties of the channel, however caution has been recommended in comparing the pharmacological properties of recombinant NMDA receptors with those of native neurones[203] and no attempt is made in the following to differentiate between NMDA receptor subtypes.

The gating properties of the NMDA receptor channel are complex and subject to modulation at several different sites (fig. 2). In addition to its binding site for EAA such as NMDA or glutamate, the receptor has a second binding site for glycine which facilitates the actions of glutamate or NMDA.[93] However, in the resting (i.e. non-depolarized) state, the NMDA receptor channel is blocked by Mg^{2+} ions at a site deep within the channel itself[133 152] and binding of NMDA or glutamate to the agonist binding site, even in the presence of glycine, does not result in Ca^{2+} entry through the postsynaptic

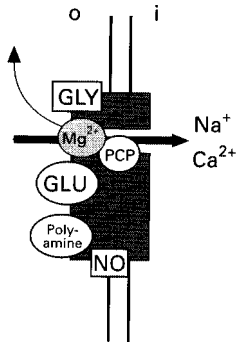

Figure 2 Schematic representation of the NMDA receptor complex. In the non-depolarized neuronal membrane, binding of glutamate and glycine does not result in Ca^{2+} entry while the ion channel remains blocked by Mg^{2+}. Depolarization removes the Mg^{2+} block enabling cation entry. Cation flux is inhibited by agents binding to the phencyclidine site within the ion channel and modulated by agents interacting with the polyamine and redox sites. i = Intracellular; o = extracellular; GLU = glutamate; GLY = glycine; PCP = phencyclidine; NO = redox site.

membrane. Depolarization of the membrane removes the Mg^{2+}-mediated channel blockade and Ca^{2+} flux through the channel can then occur. Calcium entry through the NMDA receptor channel can also be modulated by micromolar concentrations of Zn^{2+} ions[132 220] which inhibit channel opening time in a voltage-independent manner.[134] The NMDA receptor channel is subject to further modulation by agents such as dizolcipine (MK-801) that bind to a site (phencyclidine binding site) within the channel itself[92]; binding to this site is enhanced significantly when the channel is activated and such agents (which include the dissociative anaesthetics ketamine and phencyclidine) are known as *open-channel blockers*. Outside the channel are further modulatory sites: these include a polyamine binding site[175] and a redox site[110] where sulphydryl groups of the subunits may interact with nitric oxide (NO) derivatives to modify channel function.

The slow kinetics of dissociation of glutamate from its agonist site (time constants of decay in the order of tens or hundreds of milliseconds), and the necessity of coincident membrane depolarization to permit channel opening enable the NMDA receptor to function as a molecular detection device for near coincident pre- and postsynaptic depolarization. The resultant increase in intracellular Ca^{2+} may trigger sequences of molecular events that lead to longer term changes in neuronal function.

Excitatory amino acids and anaesthesia

General anaesthetic agents have a broad spectrum of actions; they modify both inhibitory and excitatory neurotransmission at presynaptic and postsynaptic loci within the CNS[67 108 166 176]; nevertheless their precise mode of action remains uncertain and undoubtedly they interact with multiple neurotransmitter systems by a variety of mechanisms.[115]

Table 3 Anaesthetic effects on EAA neurotransmission. L-GLU, NMDA, AMPA/KA indicates effect on neurone (either depolarisation or Ca^{2+} entry) in response to specific agonist. ↓ = inhibition, ↔↓ = inhibition at high concentration, ↑ = potentiation, ↔ = no effect. B = whole brain, C = cerebral cortex, H = hippocampus, Th = thalamus, Sp = spinal cord, O = oocytes expressing human brain mRNA

Anaesthetic	EAA release	Ref.	L-GLU	Ref.	NMDA	Ref.	AMPA/KA	Ref.
Isoflurane	↓ C	[138] [190]	↓ C	[168]	↓ C	[24] [168]	↓ C	[24]
	↓ H	[13] [109] [124]			↔↓ C	[131]	↓ H	[169] [218]
	↓ Sp	[187]			↓ H	[169] [229]		
	↔ H	[161]			↓ Sp	[187]		
Enflurane	↓ C	[138] [190]	—		↓ C	[7] [131]	↓ O	[112]
	↑ B	[79]			↓ O	[112]		
Halothane	↓ C	[178] [190]	↓ C	[168] [178]	↓ C	[7] [131] [168]	↓ C	[24]
	↔↑ C	[5]	↔ H	[162]	↔ C	[24]	↓ H	[148] [169]
	↓ H	[124] [162] [179]			↓ H	[148] [169]	↔ H	[162]
	↔ B	[79]			↔ H	[162]		
Methoxyflurane	↓ C	[177]	↓ C	[177] [178]	↓ C	[131]	—	
	↓ H	[179]						
Diethylether	↓ C	[177]	↓ C	[177] [178]	↓ C	[24] [131]	↓ C	[24]
	↓ H	[179]			↓ H	[218]	↔ H	[218]
	↔ B	[79]						
Trichloroethylene	↓ C	[177]	↓ C	[178]	—		—	
Propofol	—		↓ B	[15]	↓ H	[14]	↔ H	[14]
Barbiturate	↓ C	[33] [140]	↓ C	[178]	↓ H	[188]	↓ C	[24]
	↔ C	[190]	↓ H	[188]	↔ H	[218]	↓ H	[188] [218]
	↓ Th	[100]						

Attempts have been made to produce "unitary theories of anaesthesia" and one proposed mechanism, common to general anaesthetic action is that of potentiation of the inhibitory neurotransmitter γ-amino-butyric acid (GABA) at the $GABA_A$ receptor Cl^- channel.[67] However, there is a growing body of evidence that general anaesthetic agents also modify EAA-mediated excitatory neurotransmission in the CNS, and this has important implications with regard to the means by which anaesthetics suppress the responses to, and awareness of, noxious stimuli. The evidence for anaesthetic effects on EAA is reviewed below (data summarized in table 3).

PRESYNAPTIC EFFECTS OF GENERAL ANAESTHETICS

As stated above, the release of EAA neurotransmitters is dependent on Ca^{2+} entry into nerve terminals through N-type, P-type and possibly other voltage-operated channels in the presynaptic membrane.[55] Voltage-operated Ca^{2+} channels are themselves a target of general anaesthetic action and the evidence for their inhibition by volatile and i.v. anaesthetics in a variety of neuronal populations has been reviewed recently.[102] Two studies that specifically examined anaesthetic effects on Ca^{2+} channel subtypes in hippocampal neurones have shown that halothane, enflurane and isoflurane markedly inhibit multiple Ca^{2+} channel types at clinically relevant concentrations.[106 202] It should be noted that Ca^{2+} channel sensitivity to general anaesthetics may vary in different neuronal populations as P-type Ca^{2+} channels were unaffected by isoflurane in cerebellar neurones[76] but may be sensitive to this agent in hippocampal neurones.[202]

Inhibition of Ca^{2+} channel function would be expected to reduce the release of EAA and several early studies suggested that both volatile anaesthetics[177 178 179] and barbiturates[33 100 140] could decrease the depolarization-evoked release of EAA neurotransmitters from central neurones. Recent studies have confirmed this effect with the demonstration that both isoflurane[109 124] and halothane[124 162] at clinically relevant concentrations (0.5–2 MAC) markedly inhibit release of glutamate from hippocampal neurones in a dose-dependent manner. Furthermore, data demonstrating inhibition by halothane, enflurane and isoflurane of glutamate release[138 190] associated with reduced Ca^{2+} entry[138] in cerebral cortical nerve terminals strongly suggest that presynaptic inhibition of glutamate release may be a common property of volatile anaesthetic agents.

The specific sodium-dependent glutamate transporters that limit the synaptic duration of EAA by uptake into both neurones and astroglia have been shown not to be sensitive to clinically relevant concentrations of either volatile or i.v. anaesthetics.[149]

POSTSYNAPTIC EFFECTS OF GENERAL ANAESTHETICS

When postsynaptic effects are considered, it is clear that volatile and i.v. anaesthetic agents have in general, inhibitory effects on the excitatory responses of CNS neurones to exogenously applied EAA agonists (see table 1). Inhibition of each of the *i*Glu-receptor subtypes has been reported by a number of investigators,[14 148 169 188 218 229] however, subtype specific effects on *i*Glu-receptor function have not been consistent. This may reflect the different methodologies used in these studies; most notably this applies to halothane which under different conditions may either inhibit[148 169] or have no effect[162] on hippocampal NMDA receptor and AMPA receptor function.

The data in table 1 demonstrate that general anaesthetic agents apparently share a common property of inhibiting EAA-mediated neurotransmission at several sites within the mammalian CNS. However, the predominant site and nature of the inhibition differs according to the region of the CNS and the anaesthetic agent under investigation. Presynaptically, this may reflect the variations in Ca^{2+} channel populations responsible for neurotransmitter release[55] and their different sensitivities to anaesthetics in different areas of the CNS.[76 202] When postsynaptic effects are considered, the recent report that anaesthetic agents can have subunit selective actions at glutamate receptors[50] indicates that variations in *i*Glu-receptor subunit composition throughout the CNS[83] may determine the response to anaesthetics in different brain regions.

IS INHIBITION OF EAA NEUROTRANSMISSION CAUSAL TO ANAESTHESIA?

If inhibition of EAA-mediated neurotransmission causes the anaesthetic state, then specific pharmacological manipulation of EAA neurotransmission should affect anaesthesia induced by other volatile or i.v. agents. This is clearly seen with glutamate antagonists which markedly reduce the MAC for other anaesthetic agents *in vivo*. This has been demonstrated, for example with the non-competitive NMDA antagonists ketamine,[39] phencyclidine[39 189] and MK-801/dizolcipine[107 189], the competitive NMDA antagonists CGS 19755 and D-CPP-ene[40 107] and agents acting at the polyamine site[41] and also the glycine site[121] of the NMDA receptor. The AMPA receptor competitive antagonist NBQX appears to share similar properties.[120] Furthermore, riluzole (a drug inducing a use-dependent block of presynaptic glutamate fibres[123]) has been reported to reduce the MAC for halothane and potentiate barbiturate anaesthesia *in vivo*.[130]

There is thus convincing evidence that a state of anaesthesia is associated with inhibition of EAA neurotransmission throughout the CNS. Significantly, inhibition of spinal cord EAA neurotransmission[34 186 187] could also contribute to anaesthesia (in the sense of *unresponsiveness to surgical stimuli*) with the demonstration that the MAC for isoflurane in the rat is independent of forebrain integrity[170 171] and that a site of action distal to the brainstem contributes significantly to the anaesthetic effects of isoflurane in the goat.[422]

It must be emphasized that anaesthesia induced in humans with glutamate antagonists such as ketamine or phencyclidine differs from that induced by other anaesthetic agents. It is characterized by

sedation, hypertonus, amnesia and profound analgesia[54] and has been termed dissociative anaesthesia, referring to a supposed "dissociation of the limbic from the thalamo-neocortical systems".[35] When auditory evoked responses (AER) are used to assess depth of anaesthesia, it is apparent that the effects of ketamine differ from those of the majority of general anaesthetics. Using this technique, volatile agents, propofol, etomidate and barbiturates significantly reduce the amplitude and increase the latency of the early cortical part of the AER,[94] whereas ketamine (in common with opioids and benzodiazepines) has little or no effect on the AER.[192] Further differences between ketamine and other i.v. anaesthetics are apparent when effects on cerebral metabolism are considered. Barbiturates globally depress cerebral metabolism[80] while other i.v. agents (such as propofol, Althesin and etomidate) predominantly depress forebrain metabolism and spare hindbrain metabolism.[38 42 43] In contrast, anaesthetic doses of ketamine have little effect on metabolism in most brain regions but cause a marked increase in metabolism in the hippocampus.[37 44] Enhanced hippocampal metabolism has also been shown with volatile anaesthetics[146 157] although this is accompanied by global inhibition of metabolism in other brain regions.[77 157]

If the increased hippocampal metabolism seen with anaesthetic doses of ketamine is mediated via its action at the NMDA receptor, then similar increases observed with volatile agents may indicate a common mechanism of action. Conversely, the markedly different effects seen with barbiturates, propofol, etomidate and Althesin suggest that actions on EAA neurotransmission may be less significant with these i.v. anaesthetics. The effects of different anaesthetics on cerebral metabolism may reflect the balance between anaesthetic actions on EAA neurotransmission and inhibitory neurotransmitter systems, notably the $GABA_A$ receptor (for reviews see Frank and Lieb[67] and Pocock and Richards[166]). This balance could in turn determine the clinical manifestations of the anaesthetic state induced by each individual agent.

EAA and memory: is this how anaesthetics prevent recall?

Sub-anaesthetic or sedative doses of general anaesthetics have powerful inhibitory effects on short term memory,[68 143] and the reduction in the transfer of information from the periphery to the cerebral cortex[3] associated with general anaesthesia prevents the recall of intraoperative events. EAA neurotransmission plays a central role in the pharmacology of learning and memory[90 142]; therefore it is important to consider if this absence of memory for intraoperative events is a consequence of inhibition by general anaesthetics of EAA-mediated processes. In order to do so, it is necessary first to provide an overview of the fundamental mechanisms involved in memory at both synaptic and more global levels, and subsequently to review the available data relating to anaesthetic interactions with these systems.

Current theories propose that at the synaptic level, learning and memory are a consequence of long-term potentiation (LTP) of synapses in specific neuronal pathways within the CNS.[19] First described in the hippocampus by Bliss and Lømo in 1973,[20] LTP is a form of synaptic plasticity causing facilitation of neurotransmission which may last for up to several weeks *in vitro*. LTP has been demonstrated subsequently in other regions of the CNS, including the cerebral cortex[8 17] and spinal cord.[165 172] The mechanisms underlying LTP have been investigated extensively and it is clear that EAA play a key role.

This key role for EAA in memory has been confirmed in animal models of learning using the Morris water maze. This tests the ability of the rat to learn the location of a hidden platform in a tank of opaque water in which it is forced to swim.[142] Intracerebroventricular administration of NMDA antagonists impairs the ability of the rat to learn a new location of the platform, but not to find a location that was learned previously; importantly, this impairment is associated with disruption of hippocampal LTP *in vivo*.[142] These and similar data from a variety of animal models of learning and memory provide good evidence that "*NMDA receptors are involved in the acquisition of new information but not in its subsequent retrieval or expression*.[142] Similarly, in humans, administration of sub-anaesthetic doses of the non-competitive NMDA antagonists ketamine and phencyclidine causes dose-dependent anterograde amnesia but has no effect on established memory.[9 69]

The hippocampus undoubtedly plays an important role in learning and memory,[199] as is evident in humans from the gross impairment of short term memory in patients with hippocampal lesions, but it does not function in isolation: current concepts of memory propose that the hippocampus functions in concert with neuronal networks of the cerebral cortex. Memory "traces" are thought to be retained briefly in the cortical areas that process incoming information, but hippocampal activation (presumably involving LTP as described above) is essential to establish *new* memory. After hippocampal activation, medial temporal lobe structures direct the consolidation of memories in specific neuronal networks of the neocortex[198 199] where again NMDA-mediated LTP may play a critical role.[137] Activation of specific hippocampal and cortical regions during learning and memory has been confirmed *in vivo* in humans using positron emission tomography studies of cerebral blood flow[181 120] and has led to the development of a model of hemispheric asymmetry for memory encoding and retrieval (HERA) involving large distributed cortical neuronal networks.[208]

The data discussed above provide a mechanistic model for a human memory system consisting of several systems and subsystems.[219] Two separate systems, explicit memory and implicit memory, can be identified readily by psychological tests. The former requires deliberate and conscious retrieval of information and can be assessed by recall and recognition tests, while the latter does not require conscious recall but is manifest as improvement in performance in skill learning or task-completion

tests. General anaesthesia by definition inhibits explicit memory of intraoperative events, however, several studies have demonstrated that some forms of implicit memory may still occur during anaesthesia (reviewed in Ghoneim and Block[68]), thereby suggesting that the different systems of memory may be differentially sensitive to anaesthetics. For example, using sub-anaesthetic concentrations of isoflurane it has been shown that implicit memory occurs at concentrations of isoflurane (0.15–0.3 MAC) that impair explicit recall[57]; and when coherent frequency of auditory evoked response is used to assess quantitatively depth of anaesthesia,[143] inhibition of implicit memory requires a greater depth of anaesthesia than does inhibition of explicit recall.

DOES INHIBITION OF EAA-DEPENDENT NEUROTRANSMISSION SUPPRESS LEARNING AND MEMORY UNDER GENERAL ANAESTHESIA?

To answer this question we need to consider the mechanisms of hippocampal LTP, the best understood synaptic model of memory.[19] A schematic representation of the processes involved in hippocampal LTP is shown in figure 3.

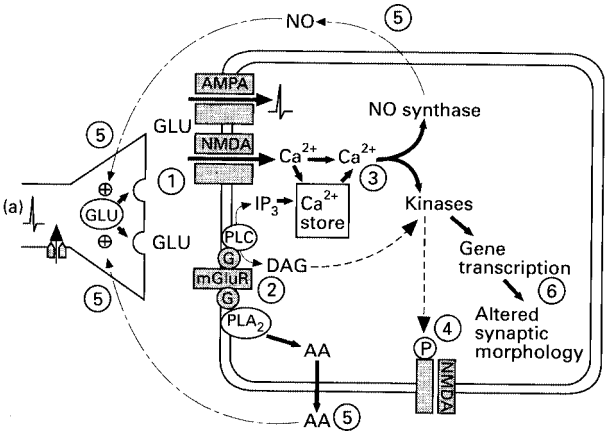

Figure 3 Schematic representation of the mechanisms involved in hippocampal long-term potentiation (LTP). ① Induction of LTP is dependent on EAA release and NMDA receptor activation resulting in enhanced Ca^{2+} entry into the postsynaptic neurone. ② This Ca^{2+} signal may be supplemented by Ca^{2+} release from inositol 1,4,5-trisphosphate (IP_3) gated stores which occurs as a consequence of co-activation of *m*Glu-receptors.[58] ③ The increase in Ca^{2+} concentration in the postsynaptic cell initiates a chain of events at the synapse secondary to the activation of numerous Ca^{2+} dependent enzymes. ④ This results in postsynaptic hyperexcitability as a consequence of phosphorylation and altered expression of membrane proteins, including an increase in EAA receptor number. ⑤ This may be augmented by release of retrograde transmitter(s) (possible candidates include NO and arachidonic acid) causing the presynaptic nerve terminal to enhance its release of EAA. Together pre- and postsynaptic events lead to enhanced transmission at the affected synapses. ⑥ These events are consolidated by changes in gene transcription and altered synaptic morphology, and while *induction* of LTP is prevented by NMDA antagonists, *established* LTP is unaffected by these agents. GLU = Glutamate; NMDA = *N*-methyl-D-aspartate; AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate; mGluR = metabotropic glutamate receptor; PIP = phosphatidyl-inositol-4,5-bisphosphate; NO = nitric oxide; PLC = phospholipase C; IP_3 = inositol-1,4,5-trisphosphate; IP_3R = IP_3 receptor; PLA_2 = phospholipase A_2; G = GTP-binding protein; P = phosphorylation site; DAG = diacylglycerol; (a) = depolarization and action potential generation.

It is clear that volatile and i.v. anaesthetics inhibit EAA neurotransmission (table 1), and most,[13 101 124 125 126 179], but not all,[161] electrophysiological studies have suggested that hippocampal excitatory neurotransmission in particular is inhibited. Anaesthetic inhibition of EAA release and NMDA receptor function therefore has the potential to modify the induction (step 1) of LTP. Furthermore, there is evidence that IP_3-gated Ca^{2+} stores are depleted by volatile anaesthetics[45] suggesting that the second phase of LTP-induction might also be sensitive to volatile anaesthetic inhibition. Is this a means by which anaesthetics suppress learning and memory?

Only two studies have specifically examined the effects of volatile anaesthetics on hippocampal LTP and these have produced conflicting results. MacIver, Tauck and Kendig[126] demonstrated that *in vitro*, both halothane and methoxyflurane at clinically relevant concentrations attenuated excitatory neurotransmission in the hippocampus, but while halothane markedly inhibited induction of LTP, methoxyflurane had no effect. In a separate study in which LTP was induced in the anaesthetized rat *in vivo*, it was reported that hippocampal excitatory neurotransmission and induction of LTP was unaffected by halothane, enflurane or isoflurane at clinically relevant concentrations.[161] The insensitivity of hippocampal neurotransmission to volatile anaesthetics in the latter study does not correlate with the inhibitory effects of volatile anaesthetics reported elsewhere, but it must be noted that control values for hippocampal neurotransmission in this study were measured in animals already anaesthetized with urethane, an agent which may itself affect excitatory neurotransmission in the hippocampus and induction of LTP.[174]

In conclusion, there is clear evidence that inhibition of EAA neurotransmission is a common property of general anaesthetics (although the presynaptic or postsynaptic locus of inhibition may vary with each agent), and direct, or indirect, modification of NMDA receptor function has been putatively proposed as the final common pathway of anaesthetic action.[66] However, although NMDA antagonists both contribute to the anaesthetic state and suppress memory, effects that are clearly associated with inhibition of hippocampal LTP *in vivo*, it remains uncertain if volatile and i.v. anaesthetic agents share this effect on LTP. Further studies are necessary to confirm whether the loss of awareness caused by general anaesthesia is a consequence of inhibition of LTP in the hippocampus or cerebral cortex.

Excitatory amino acids and pain

Peripheral tissue injury creates a continuing noxious input to the spinal cord via Aδ and C-fibres which results in a progressive increase in the response of neurones within the spinal cord dorsal horn to further afferent input. This plasticity of spinal cord processing of nociceptive information plays a critical role in post-injury pain hypersensitivity[225] and chronic pain syndromes[30] and is termed central

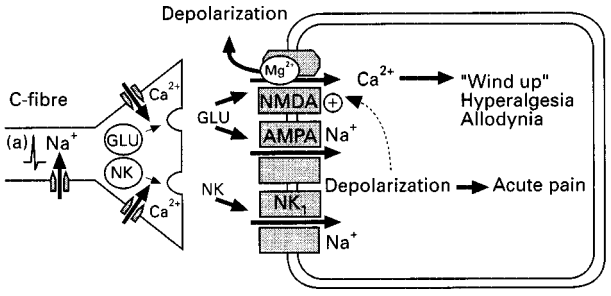

Figure 4 Diagrammatic representation of the pharmacology of spinal pain transduction within the dorsal horn. Acute pain is mediated by glutamate acting at AMPA/KA receptors and neurokinins acting at NK_1 receptors, the consequence of which is brief postsynaptic depolarization of dorsal horn neurones and activation of central pain pathways. More prolonged afferent input via Aδ and C-fibres causes NMDA receptor activation when AMPA receptor- and neurokinin receptor-mediated depolarization of the dorsal horn neurone is of sufficient magnitude and duration to remove the Mg^{2+} block of the NMDA receptor LOC. NMDA receptor activation (with possible contribution from *m*Glu-receptor) leads to central sensitization and resultant hyperalgesia. GLU = Glutamate; NMDA = *N*-methyl-D-aspartate; NK = neurokinin; AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate; (a) = depolarization and action potential generation.

sensitization. The pharmacology of central sensitization and spinal pain transduction has been a subject of many recent reviews[48 52 212 224 227] and it is clear that EAA play a key role (fig. 4). Aδ and C-fibre primary afferent nerve terminals within the substantia gelatinosa of the spinal cord release glutamate (and neurokinins) in response to noxious stimuli. Glutamate binds to both *i*Glu-receptor and *m*Glu-receptor subtypes which may be co-localized on the same postsynaptic cell. The acute response to injury at the synaptic level is mediated by glutamate acting at AMPA receptors and neurokinins acting at NK_1 receptors, the consequence of which is brief depolarization of dorsal horn neurones and activation of central pain pathways. More prolonged afferent input via Aδ and C-fibres causes NMDA receptor activation when AMPA receptor and neurokinin receptor mediated depolarization of the dorsal horn neurone is of sufficient magnitude and duration to remove the Mg^{2+} block of the NMDA receptor channel. NMDA receptor activation (with a possible contribution from *m*Glu-receptor) leads to central sensitization and resultant hyperalgesia. Central sensitization may be consolidated by protein kinase C-mediated phosphorylation of the NMDA receptor which reduces the Mg^{2+} gating characteristics of the channel[26]; indeed, inhibition of protein kinase C has been reported to prevent the development of hyperalgesia in a rat model of central sensitization.[230]

ANAESTHETIC AND ANALGESIC EFFECTS ON SPINAL EAA MECHANISMS

Before reviewing the analgesic or "anti-hyperalgesic" potential of agents that block EAA receptors, it is of interest to examine how established anaesthetic and analgesic agents may interact with EAA neurotransmission in the spinal cord.

Sub-anaesthetic concentrations of some volatile anaesthetic agents may produce intense analgesia. Trichloroethylene and methoxyflurane were used previously for obstetric analgesia and there is good evidence that isoflurane may be similarly effective.[217] Such analgesia may be a consequence of direct effects on acute pain transduction at the level of the spinal cord where electrophysiological studies have shown isoflurane to inhibit nociceptive responses dependent on both NMDA receptor- and non-NMDA receptor-mediated EAA neurotransmission.[34 186 187] There is also some evidence[1 72 153] that modern volatile anaesthetic agents (halothane, enflurane, isoflurane and desflurane) can partially suppress spinal cord sensitization in a rat model in which subcutaneous formalin injection produces a biphasic behavioural response,[221] the second phase of which corresponds to dorsal horn NMDA receptor activation.[75] However, when formalin-induced sensitization in the spinal cord was measured by expression of the immediate early gene *c-fos* (a molecular marker of nociception[144]) halothane anaesthesia was without effect.[205] Therefore, the potential of volatile anaesthetics to influence pain in the postoperative period may be limited. Nitrous oxide has also been reported to inhibit central sensitization in a dose-dependent manner,[72 153] however nitrous oxide induces endorphin release[65] and its effects on central sensitization are partially reversed by naloxone. This does not suggest a direct effect on spinal EAA neurotransmission, but rather the activation of supraspinal opioid receptor mediated mechanisms which influence spinal sensitization.[70 74] Surprisingly, the effect of combined administration of nitrous oxide with either isoflurane[1] or halothane[72 153] was antagonistic and resulted in markedly less inhibition of central sensitization than did the administration of each volatile agent alone. The mechanism and site of this interaction is unclear, and further studies are warranted to assess the clinical significance of this finding.

The spinal analgesic actions of opioid agonists and α_2-receptor agonists, at least in part, involve EAA neurotransmission. The demonstration that inhibition of the release of glutamate from dorsal horn nociceptive neurones is a consequence of both opioid[46 97] and α_2-agonist[95] administration may explain their synergistic analgesic effects in animal models of pain.[141 158 159] Postsynaptically the NMDA receptor ion channel complex may be directly modulated in addition by μ opioid receptor agonists.[184] Furthermore, a complex interrelationship between NMDA receptor and μ-opioid receptor mechanisms may control the development of spinal tolerance and dependence on opioids.[53]

EAA ANTAGONISTS AS ANALGESICS

There is now a considerable literature encompassing the analgesic or antinociceptive effects of agents that inhibit EAA neurotransmission (for reviews see Dickenson,[48] Dray, Urban and Dickenson,[52] Sukiennik and Kream,[204] Urban, Thompson and Dray[212] and Yaksh and Malmbergh[227]). Many studies have focused on the NMDA receptor, where

open-channel blockade,[31 61 228] competitive glutamate antagonism,[31 75] glycine site antagonism[31 49] or polyamine site manipulation[29] modify the response to painful stimuli in animal models of pain. Despite the diversity of pain models that have been used in these and other studies, most data suggest that NMDA receptor antagonism causes significant antinociception against persistent inflammatory or neuropathic models of pain but has little effect on brief nociceptive tests of acute pain. A clear demonstration of this effect is seen with the rat formalin model which may correspond to post-surgical pain; in this model which results in a brief acute pain behavioural response followed after a latent period by a longer inflammatory second phase associated with central sensitization, administration of NMDA receptor antagonists has no effect on the first phase but reduces or abolishes the delayed second phase of this test.[75 228] Similarly, in a study of human experimental pain, ketamine had no effect on a single noxious electrical stimulus, but had a marked analgesic effect on repeated stimuli associated with central sensitization.[6]

Given that the initial response to injury involves activation of AMPA receptors in the substantia gelatinosa, antagonism at this site has the potential to produce analgesia. Two groups have reported that the competitive AMPA antagonist NBQX has antinociceptive effects that differ qualitatively from those of NMDA receptor antagonism,[156 226] but a more recent study[31] failed to demonstrate any antinociceptive effect of AMPA antagonists in a variety of pain models. Irrespective of whether or not AMPA-antagonism can cause analgesia, it should be noted that Dickenson[47] considered that this pharmacological approach might be disadvantageous because it would not target a pathologically activated pain pathway but would inhibit a broad spectrum of afferent and efferent fast excitatory synaptic pathways throughout the CNS. Although NMDA receptor-mediated mechanisms are more specific to pain pathways it is unlikely to be their sole function in the spinal cord, for example spinal NMDA receptor-mediated pathways may also play a key role in the control of locomotion.[2] This could explain the motor dysfunction that has frequently accompanied administration of EAA antagonists and which has important implications regarding the interpretation of their effects in tests of nociception.[31] However, combined administration of competitive and non-competitive NMDA antagonists with agents acting at glycine and polyamine sites can produce highly effective antinociception in the formalin test without behavioural effects or motor dysfunction[32] and suggests that this problem may not be insurmountable.

Excitatory amino acids and neurotoxicity

After traumatic or ischaemic damage to the CNS there is a pathological release of EAA from neurones and glia which plays a central role in mediating more extensive *excitotoxic* neuronal degeneration. In animal models, massive increases in extracellular levels of glutamate follow ischaemic[12] or traumatic insult to the brain[98] or to the spinal cord.[116] Similar increases in glutamate concentrations have been measured in cerebrospinal fluid in humans after head injury[11] and this increase appears to persist for several days after injury. These increased extracellular glutamate concentrations activate an excitotoxic cascade as a consequence of uncontrolled activation of both *i*Glu-receptors and *m*Glu-receptors. The molecular mechanism of this cascade has been reviewed recently[118] and can be summarized as follows (see fig. 5). Ca^{2+} entry through both EAA-operated and voltage-operated Ca^{2+} channels, together with Ca^{2+} release from intracellular stores results in uncontrolled activation of neuronal protein kinases, phospholipases, proteases and nitric oxide synthase. The consequent proteolysis, lipid peroxidation and free radical formation results in degeneration of central neurones. Although EAA-mediated neuronal death can occur within minutes and a proportion of neurones die in the acute phase of injury, a large number of neurones instead suffer delayed death.[118] Much interest has therefore arisen from the potential to ameliorate excitotoxic neuronal damage by modification of EAA release, EAA receptor antagonism or inhibition of subsequent proteolysis and lipid peroxidation.[122]

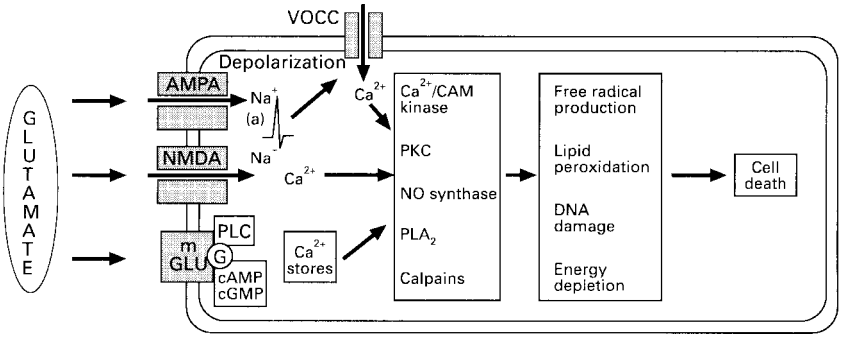

Figure 5 Schematic representation of the central role of glutamate in excitotoxic neuronal injury (modified and redrawn from Lynch and Dawson[118]). GLU = Glutamate; NMDA = *N*-methyl-D-aspartate; AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate; G = G-protein; NO = nitric oxide; PLC = phospholipase C; PLA_2 = phospholipase A_2; VOCC = voltage-operated Ca^{2+} channel; cAMP = adenosine 3'-5'-monophosphate; cGMP = cyclic guanine 3'-5'-monophosphate; (a) = depolarization and action potential generation.

STRATEGIES TO REDUCE EAA RELEASE

Of all the strategies to reduce EAA release, it is essential to first consider the beneficial effects of controlled hypothermia. It is well established that mild to moderate hypothermia results in significant cerebral protection against ischaemic brain injury[214]; this protective effect cannot wholly be explained by a global reduction in cerebral metabolic rate. However, it has recently been reported that mild to moderate hypothermia can markedly reduce the release of glutamate after experimental global cerebral ischaemia.[84] Given that the magnitude of this effect was much greater than the estimated reduction in global cerebral metabolic rate, the authors concluded that a reduction in glutamate release may contribute significantly to the neuroprotective effect of mild to moderate hypothermia.

As discussed previously, volatile anaesthetic agents, notably isoflurane[109] can strongly inhibit the depolarization-evoked release of EAA *in vitro* and it has been argued that this may result in protection from cerebral ischaemia. Recent evidence demonstrates that isoflurane can effectively inhibit the ischaemia-induced release of glutamate to an extent comparable with that of hypothermia[60 147 160] and may also reduce ischaemia-induced NMDA receptor activation *in vitro*,[16] however, in animal models of ischaemic neuronal injury, isoflurane anaesthesia does not appear to reduce injury in comparison with nitrous oxide anaesthesia[215] and its neuroprotective potential *in vivo* remains the subject of debate.

Several novel anticonvulsant agents share a common mechanism of action in that they reduce EAA release from central neurones, probably as a consequence of an inhibitory effect at presynaptic Na^+ channels.[211] This class of agents are neuroprotective in animal models of focal or global cerebral ischaemia: thus riluzole,[167] felbamate,[216] lamotrigine and its congeners[196 222] all reduce infarct size or neuronal loss after ischaemic insult and may improve neurological outcome and survival. They are most effective when administered before ischaemia, but importantly, a window of opportunity appears to exist in the immediate post-ischaemic period when their administration is also protective.

EAA ANTAGONISTS AS NEUROPROTECTIVE AGENTS

Postsynaptic neuronal depolarization, both as a direct consequence of ischaemia and as a result of *i*Glu-receptor activation, removes the Mg^{2+} block of the NMDA receptor thereby allowing uncontrolled Ca^{2+} entry via the NMDA receptor LOC. In consequence NMDA receptor antagonists have attracted much interest as potential cerebral protective agents.[113]

Competitive antagonists at the NMDA receptor such as d-CPP-ene and CGS 19755 are clearly neuroprotective when administered pre-emptively or immediately after injury in models of global and focal ischaemia.[135] However, their efficacy when administered after injury/ischaemia may be limited by the relatively slow penetration into the CNS after parenteral administration, consequently there may therefore be only a narrow window of opportunity for their administration. Open-channel NMDA antagonists such as dizolcipine have the theoretical advantage over competitive EAA antagonists in that antagonism should not be overcome by the pathologically high glutamate concentrations associated with cerebral ischaemia. Dizolcipine clearly provides protection in animal models of cerebral ischaemia[89] and traumatic injury to the brain or spinal cord.[63] Again, cerebral protection is evident whether administered before or after injury, but although agents such as dizolcipine penetrate readily into the CNS after systemic administration, it is unclear if they are more effective when administered after injury than are competitive antagonists. A variety of other open-channel NMDA antagonists have been shown to have experimental neuroprotective properties[113] and, significantly, these include agents which have been used in humans such as the dissociative anaesthetic ketamine[117] and the antitussive agent dextromethorphan.[27 62]

The multiple modulatory sites of the NMDA receptor provide other potential pharmacological targets for cerebral protection. For example, the neuroprotective properties of felbamate may result from glycine site antagonism in addition to its previously described effects on glutamate release.[211 216] Nitroso compounds such as nitroprusside or glyceryl trinitrate which interact with the redox modulatory site and prevent EAA-induced neuronal death *in vitro*,[110 114] are another intriguing class of agents with potential neuroprotective properties.[73] The degree of physiological blockade of the NMDA receptor channel by Mg^{2+} ions may also be an important determinant of neuronal injury, particularly given that tissue Mg^{2+} concentrations have been reported to decline rapidly after both major surgery[185 207] and CNS injury.[111] Magnesium administration has been reported to be protective against CNS ischaemia,[71 195 213] and enhanced blockade of the NMDA receptor channel may at least in part underlie this action.

Clinical implications

The ubiquity of EAA neurones throughout the CNS emphasizes the importance of EAA-mediated neurotransmission in anaesthesia, analgesia and neurological intensive care. Equally, the importance of EAA neurotransmission in cognition, memory, sensation and motor function certainly contributes to the broad spectrum of neuropsychological side effects that have limited the clinical use of dissociative anaesthetic agents such as ketamine. Nevertheless, we already influence this system with the use of volatile (and to a lesser extent i.v.) anaesthetic agents without all of these adverse effects. Furthermore, there is evidence that indicates that it may be the high affinity of established dissociative anaesthetic agents (including ketamine) for the NMDA receptor, and their slow dissociation from the open-channel binding site, that results in their adverse neuropsychological profile.[180] Drugs with

more rapid dissociation kinetics from the open channel, or those interacting with other binding sites on the NMDA receptor, may have a more attractive side effect profile, and these together with their targeting at spinal (as opposed to higher) centres provides the potential for a broader clinical use of these agents. Much interest has centred on the role of EAA neurotransmission in the fields of pain[48 52 212 227] and cerebral protection[89 113 135 180] although less emphasis has been placed on its potential role in anaesthesia.

There is no doubt that inhibition of EAA neurotransmission in the CNS, by antagonism of a variety of receptor sites[39 40 41 120 121 189] and to a lesser extent by inhibition of glutamate release,[130] can promote or induce anaesthesia but the adverse behavioural effects of high doses of many of these agents make it unlikely that they could be widely exploited for clinical anaesthesia, particularly where rapid recovery is required. However, the ability of this group of drugs to reduce the MAC of other anaesthetic agents suggests that they could have a useful role, particularly in high-risk patients. The added advantages of intense analgesia and cerebral protection suggest that inhibition of EAA neurotransmission may contribute to optimally balanced anaesthesia with special relevance to trauma, cardiac and neurosurgery. Furthermore, given the ability of NMDA antagonists to inhibit LTP and induce anterograde amnesia, these agents may prove useful in this high-risk group to reduce the risk of intraoperative awareness.

The importance of the NMDA receptor in the induction and maintenance of central sensitization and the contribution of this process to both acute surgical pain and perhaps more importantly, chronic pain syndromes strongly suggests that agents affecting spinal EAA neurotransmission may be useful analgesic agents in areas where currently available agents are of only limited efficacy. As discussed above, this could involve the systemic administration of such agents as anaesthetic adjuncts, and there is, for example, evidence that systemic peroperative administration of ketamine may reduce postoperative wound hyperalgesia[209] and analgesic requirements[183 209] without psychotomimetic side effects. There is also recent evidence that similar benefit may be achieved with the peroperative administration of magnesium sulphate,[207] an effect that at least in part may be a consequence of NMDA ionophore blockade.

In the chronic pain setting, several reports indicate that ketamine can provide analgesia and relief of hyperaesthesia/allodynia in neuropathic pain resistant to conventional therapy with tricyclic antidepressant, anticonvulsant and membrane stabilizing agents.[10 59 151 200] Similarly, subcutaneous or i.v. infusion of ketamine may be highly efficacious in opioid-resistant cancer pain.[136] Unfortunately, in several cases, dosage has been limited or treatment terminated by psychotomimetic effects, and certainly for outpatient treatment of chronic pain, an agent lacking psychotomimetic effects and suitable for oral administration is ideally required. The antitussive dextromethorphan is the only other agent in clinical use with NMDA antagonist activity[28] and it has a good safety record, but a study of oral administration of this agent failed to show any benefit in a group of patients with neuropathic pain resistant to conventional therapies.[127] However, there is an encouraging recent report of oral administration of ketamine providing pain relief without significant side effects in opioid-resistant neuropathic pain.[23]

In an attempt to limit supraspinally mediated adverse effects, considerable interest has focused on intrathecal or extradural administration of NMDA receptor antagonists, thereby targeting EAA synapses in the substantia gelatinosa of the spinal cord. While experience in human subjects is limited, animal studies convincingly demonstrate the effectiveness of spinally administered NMDA receptor antagonists in a variety of pain models corresponding to both post-surgical and chronic pain states. Although many of the studies of NMDA receptor open-channel blockers such as ketamine and dizolcipine (MK801) have shown significant motor and behavioural effects even after spinal administration, co-administration of low doses of open-channel blockers with agents acting at other regulatory sites on the NMDA receptor may circumvent behavioural and motor problems[32] rendering them more suitable for clinical use. Concern has also been expressed regarding the neurotoxicity of ketamine and dizolcipine.[129 154 155] However, low concentrations of preservative-free ketamine are not neurotoxic[21] and have been used in humans by both intrathecal[18] and extradural[85 99 145 173] routes. Competitive antagonists may have fewer adverse effects and there is evidence that the potent NMDA antagonist CPP is effective in several pain models at doses that do not affect motor function or behaviour.[104] This finding, together with its apparent lack of neurotoxicity[105] or effect on spinal cord blood flow,[103] indicates that CPP may be a prototypical agent for clinical spinal administration in human.

Pathological release of glutamate clearly plays a key role in ischaemic excitotoxic damage to the CNS. It is possible to modify both the release of glutamate and its receptor-mediated effects at multiple sites and a combination of agents acting both pre- and postsynaptically, perhaps in conjunction with mild to moderate hypothermia, may be necessary to minimize neuronal damage. Concern has been expressed over the behavioural and neuropsychological effects of glutamate antagonists—particularly those acting at the NMDA open-channel site—at the dosage required for cerebral protection.[113] However, both memantine (an anti-Parkinsonian drug which blocks the NMDA receptor open-channel site with low affinity and rapid kinetics of dissociation) and felbamate (a glycine site NMDA receptor antagonist and an inhibitor of glutamate release) have been shown to be effective in animal models of CNS ischaemia at concentrations that are tolerated clinically in humans.[25 216] They may therefore be prototypical agents for perioperative use in neurosurgical and perhaps cardiac anaesthesia if rapid recovery is required. The multiple facets of EAA-mediated excitotoxicity provide many intriguing therapeutic

possibilities in this area and in addition to evaluating new agents it may be necessary to reappraise the use of established techniques, including volatile anaesthetics, magnesium administration and the use of nitroso compounds such as glyceryl trinitrate.

The clinical pharmacology of EAA neurotransmission is still in its infancy; few of the agents that specifically influence EAA release or interact with the growing family of glutamate receptors have as yet progressed beyond preliminary clinical studies or isolated case reports. Nevertheless, an understanding of this rapidly expanding field of pharmacology is of paramount importance in order that we may optimize our management of high-risk patients and acute or chronic pain.

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