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Novel approaches to targeting glutamate receptors for the treatment of chronic pain: Review article

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Summary. Glutamatergic mechanisms are implicated in acute and chronic pain, and there is a great diversity of glutamate receptors that can be used as targets for novel analgesics. Some approaches, e.g. NMDA receptor antagonism, have been validated clinically, however, the central side-effects have remained the main problem with most compounds. Recently, some novel approaches have been explored as new compounds targeting some modulatory sites at the NMDA receptor (glycine$_B$ and NR2B-subtype selective antagonists), as well as kainate and metabotropic glutamate receptors, have been discovered. Many of these compounds have demonstrated efficacy in animal models of chronic pain, and some of them appear to have a reduced side-effect liability compared to clinically tested NMDA antagonists. These recent advances are reviewed in the present work.

Keywords: NMDA receptors – AMPA receptors – Kainate receptors – Metabotropic glutamate receptors – Inflammatory pain – Neuropathic pain

Introduction

Glutamate interaction with glutamate receptors (GluRs) is fundamental to excitatory transmission in the CNS, and therefore, plays important roles in both normal and pathophysiological nociception. Despite this ubiquitous involvement, acute and chronic pain states often differentially engage different types of GluRs, as the sources, time course and quantities of released glutamate, as well as of its co-transmitters, are different. Being the major neurotransmitter of nociceptive primary afferents, glutamate is released from their central terminals in the spinal cord upon noxious stimulation, activating primarily α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors on second order neurones. Prolonged activation of nociceptors, e.g., resulting from tissue damage, inflammation or nerve injury, evokes a continuous release of glutamate, which, in combination with co-released neuropeptides like substance P, can cause a longer-lasting membrane depolarisation, relieve the voltage-dependent magnesium block of N-methyl-D-aspartic acid (NMDA) receptors and allow their activation by glutamate. This mechanism appears to play a key role in pain chronification. In addition to ionotropic glutamate receptors, some postsynaptically localised metabotropic GluRs (mGluR1, mGluR5) also mediate excitatory synaptic transmission in the spinal cord. In addition to postsynaptic receptors, presynaptic GluRs localised on central terminals of primary afferents also play an important role in segmental nociceptive transmission. These include kainate (particularly GluR5), NMDA and some metabotropic GluR. Acting as autoreceptors, these GluR are presumed to be involved in mechanisms of positive or negative feedback and control neurotransmitter release from primary afferents. Their importance may increase under conditions of increased glutamate release in the spinal cord, i.e., in chronic pain. Furthermore, peripherally localised ionotropic and metabotropic GluRs can be activated by glutamate released from peripheral tissues under conditions of cell injury and inflammation.

Thus, there is a variety of GluRs that can be used as targets for pharmacological intervention for the treatment of pain. Some strategies, such as the development of NMDA antagonists, have been pursued for a relatively long time; here, there have recently been some advances with novel classes of compounds

targeting some modulatory sites (e.g., glycine$_B$ antagonists, ifenprodil-like subtype-selective antagonists). Other GluRs have only recently received attention as pain targets, as potent and selective tool compounds have become available. These include kainate and some metabotropic GluRs, the importance of which in acute and chronic nociception and their potential as targets for the treatment of pain are still being investigated. These recent breakthroughs are summarised in the present review.

NMDA receptor antagonists

The fundamental role of NMDA receptors in neuronal plasticity underlies their involvement in the development and maintenance of nociceptive hypersensitivity. The NMDA receptor, therefore, has long been considered an important target for the treatment of chronic pain. Both animal and human studies confirm the efficacy of NMDA antagonists in chronic pain states, including inflammatory and neuropathic pain (Eide, 2000; Fisher et al., 2000; Sang, 2000), whereas their role in acute nociception appears to be limited (Chizh et al., 1997). Furthermore, there are reports on their antinociceptive action in visceral pain (Olivar and Laird, 1999; McRoberts et al., 2001). However, the use of clinically available NMDA antagonists for the treatment of pain remains very limited due to unacceptable side-effects like psychotomimesis, ataxia, sedation, etc. These side-effects appear to be related to the mechanism of action, as they are seen (both in man and in animal studies) with chemically diverse structures belonging to different classes of NMDA antagonist, such as channel blockers and competitive antagonists. With channel blockers, the apparent neurotoxicity is lower with low-affinity compounds (e.g., memantine) compared to high-affinity antagonists such as MK-801 (Parsons et al., 1999); however, positive results from animal pain models (Eisenberg et al., 1993; 1994; 1995) have not so far been confirmed in chronic pain patients (Eisenberg et al., 1998; Nikolajsen et al., 2000).

One of the most promising current strategies to dissociate the analgesia and side-effects is the development of subtype-selective NMDA antagonists. Ifenprodil and several structurally related compounds (eliprodil, CP-101,606, Ro25-6189, CI-1041 and some others) are highly selective for NMDA receptors containing NR2B subunits (see Chenard and Menniti, 1999; Chizh et al., 2001a, for review). Many of these compounds have been tested in a variety of animal models of pain and found to be active in chronic (both inflammatory and neuropathic pain) and, at least with some compounds, acute pain situations (Bernardi et al., 1996; Taniguchi et al., 1997; Boyce et al., 1999; Carter et al., 2000; Fillhard et al., 2000; Chizh et al., 2001a,b). These studies have established that NR2B-selective antagonists, especially the novel ones that have a lower cross-reactivity to other receptors and ion channels, are better tolerated than other classes of NMDA antagonists. The reasons for this lower side-effect profile of NR2B-selective NMDA antagonists remain unclear. NR2B subunits have a restricted CNS localisation pattern, and are present in structures specifically involved in nociceptive transmission, e.g. on fine primary afferents and in the superficial dorsal horn (Boyce et al., 1999; Ma and Hargreaves, 2000). On the other hand, the density of NR2B subunits is particularly high in the forebrain (Monyer et al., 1994), and some functional data suggest that the spinal cord is not the primary site of antinociceptive action of NR2B-selective antagonists (Momiyama, 2000; Chizh et al., 2001b). Other potential explanations for the improved tolerability of NR2B-selective antagonists are related to their mode of action. Thus, the use-dependency of the NMDA antagonism by ifenprodil-like compounds (Kew et al., 1996) implies a stronger inhibition of the transmission involving greater receptor activation, e.g. under chronic pain conditions, vs. normal physiological transmission with little involvement of NMDA receptors. Furthermore, modulation of the NMDA receptor function by some endogenous substances, such as protons, polyamines and histamine, is also selective for the NR2B subtype (reviewed in Dingledine et al., 1999). Peripheral nociceptive fibres express NR2B subunits (Ma and Hargreaves, 2000), and ifenprodil-like compounds are known to potentiate the proton-induced inhibition and antagonise the polyamine potentiation of NR2B-containing receptors (Mott et al., 1998; Kew and Kemp, 1998). These mechanisms may be important under conditions of tissue injury or inflammation that involve NMDA receptor-mediated peripheral sensitisation, and result in the improved efficacy of NR2B-selective antagonists under these conditions (Chizh et al., 2001a).

Of other classes of NMDA antagonist, antagonists at the glycine$_B$ site of the NMDA receptor also appear to have a lower risk of side-effects. For example, they are devoid of the hallucinogenic and neurotoxic effects whilst being analgesic in animal models of chronic

pain, the most prominent side-effect being motor impairment (Danysz and Parsons, 1998). Although many glycine$_B$ antagonists have been abandoned because of pharmacokinetic problems, primarily lack of brain permeability, some compounds show antinociceptive activity in animal pain models in vivo (Laird et al., 1996; McClean et al., 1998; Chizh et al., 2000a). Interestingly, in some pain models antinociception has been observed after systemic administration of glycine$_B$ antagonists both with and without central access (Chizh et al., 2000a). This leads to one potentially important approach to avoiding central side-effects of NMDA antagonists, that is targeting the peripheral NMDA receptors. NMDA receptors localised on primary afferents (as well as some other subtypes of GluRs, see below) could be activated by peripherally released glutamate, and have been suggested to contribute to peripheral hyperexcitability (Carlton, 2001). The functionality of peripheral NMDA receptors (and other GluRs) on nociceptive afferents in vivo has been demonstrated in experiments with local peripheral injections of glutamate and its agonists, which were found to cause hyperalgesia or allodynia (Carlton et al., 1995; Zhou et al., 1996; Lawand et al., 1997). The importance of peripherally released glutamate in various types of chronic pain states still remains to be elucidated. Of potential sources of glutamate in the periphery, peripheral endings of primary afferents are discussed most frequently; this apparently results from antidromic activation of sensory fibres (Lawand et al., 2000; deGroot et al., 2000; Carlton, 2001). These mechanisms and the involvement of peripheral NMDA receptors have been demonstrated in models of pain induced by inflammation, tissue and nerve injury (Davidson et al., 1997; Lawand et al., 1997; Chizh et al., 2000a), and, recently, in acute visceral nociception (McRoberts et al., 2001). Furthermore, some data from human studies also suggest that peripheral NMDA receptors may be involved in peripheral sensitisation in patients with neuropathic pain (Leung et al., 2001).

Kainate receptors ligands

Of kainate GluRs, the GluR5 subtype (either homomeric or heteromeric assemblies) appears to be the most interesting target for analgesics. GluR5 subunits are highly expressed in trigeminal and dorsal root ganglia (DRG), particularly in small diameter neurones (Partin et al., 1993; Sato et al., 1993; Sahara et al., 1997). They are localised on fine primary afferents, and their activation leads to afferent depolarisation (Agrawal and Evans, 1986; Ault and Hildebrand, 1993), suggesting their possible roles in peripheral sensitisation under conditions of peripheral glutamate release (see above). Furthermore, the distribution pattern of kainate receptors in superficial laminae of the spinal cord (Bonnot et al., 1996; Yung, 1998) also implies their presynaptic localisation on central terminals of nociceptive primary afferents and their autoreceptor role controlling central release of glutamate in the spinal cord. It is still under investigation whether activation of presynaptic kainate receptors facilitates or inhibits spinal nociceptive transmission (see below).

In addition to a presynaptic role of kainate receptors, a postsynaptic kainate receptor-mediated component of excitatory glutamatergic transmission onto second order neurones has been described (Li et al., 1999). This involvement of postsynaptic kainate receptors appears to require activation of nociceptive afferents by high intensity stimulation. The exact stoichiometry and subunit composition of native kainate receptors still remains to be elucidated. It appears from electrophysiological data that the properties of kainate receptors on DRG or trigeminal ganglion neurones (such as agonist sensitivity and desensitisation kinetics) most closely match those of homomeric or heteromeric GluR5 assemblies (Partin et al., 1993; Swanson et al., 1996; Sahara et al., 1997; Bleakman and Lodge, 1998; Chittajallu et al., 1999). In the dorsal horn of the spinal cord, some neurones are responsive to GluR5-selective agonists such as ATPA and (S)-5-iodowillardiine, however, a large proportion of them are not, implying that the subtypes of kainate receptors on these neurones are different from those on sensory neurones (Kerchner et al., 2001).

Several selective GluR5 ligands have recently been developed and tested on nociceptive responses in the spinal cord and in behavioural pain models. In spinal cord or DRG-dorsal horn neurone co-culture preparations in vitro, nociceptive fibre-evoked excitatory postsynaptic potentials or currents of spinal motoneurones or dorsal horn neurones, respectively, can be inhibited by kainate and the GluR5-selective agonist ATPA (Procter et al., 1998; Kerchner et al., 2001; Mascias et al., 2001). Although the effects of kainate receptor agonists are prone to desensitisation (Jones et al., 1997; Wilding and Huettner, 2001), the antinociception seen with GluR5 agonists in vitro appears to re-

sult from receptor activation rather than desensitisation, as it was fully antagonised by a selective GluR5 antagonist LY382884, which did not alter nociceptive responses on its own (Procter et al., 1998). Although systemic ATPA did not have any antinociceptive effect in acute pain models in adult animals in vivo, it was antinociceptive and antihyperalgesic in young rats and in adult rats after spinal administration (Mascias et al., 2001). On the other hand, the GluR5 antagonist LY382884, as well as the desensitising GluR5/GluR6 agonist SYM2081, have been found to be antinociceptive in some models of chronic pain (Simmons et al., 1998; Sutton et al., 1999; Ta et al., 2000). Although the reasons for these discrepancies remain unclear, it is conceivable that the roles of kainate receptors in controlling peripheral excitability and central release of glutamate may be different in acute and chronic pain states. Thus, peripheral release of glutamate under conditions of inflammation, tissue or nerve injury (see above) may lead to peripheral sensitisation via kainate receptor activation; antagonism or desensitisation of these receptors would cause antinociception. These peripheral pathophysiological mechanisms are unlikely to play any important role in acute situations, in which centrally acting agonists could be expected to reduce glutamate release from primary afferents; the reported lack of antinociception (Procter et al., 1998, but cf. Sutton et al., 1999; Li et al., 1999) could be due to a limited central access of the tested compounds. The antinociceptive potential of kainate receptor agonists and antagonists is in need of further investigation.

AMPA receptor antagonists

AMPA receptors are ubiquitously involved in fast synaptic transmission in the CNS, therefore, one can expect that their antagonists would have a broad spectrum of CNS side-effects at or near the antinociceptive dose-range. Indeed, a non-selective inhibition of nociceptive and non-nociceptive spinal transmission has been seen in electrophysiological studies (Cumberbatch et al., 1994), and in both behavioural animal and human models, where it proved difficult to separate the analgesic effect of such compounds from sedation and ataxia (Hunter and Singh, 1994; Sang et al., 1998; Nishiyama et al., 1999). Nevertheless, AMPA antagonists are devoid of neurotoxic effects typical for NMDA antagonists (Danysz et al., 1995), and it still remains to be explored whether there are modulatory approaches that would offer a better therapeutic window. From this perspective, a recent finding that antinociceptive doses of gabapentin, a compound that is used successfully for the treatment of neuropathic pain, selectively inhibit AMPA responses of spinal dorsal horn neurones (Chizh et al., 2000b), warrants further investigations.

Metabotropic glutamate receptors

Group I metabotropic GluRs (mGluR1 and mGluR5) are present peripherally on nociceptive primary afferents (Bhave et al., 2001) as well as in the dorsal horn of the spinal cord, thalamus and some other CNS structures involved in nociceptive transmission (Bordi and Ugolini, 1999). This distribution pattern suggests that these receptors may play a role in peripheral sensitisation and be involved in nociceptive transmission onto second and third order neurones in the spinal cord and thalamus. Indeed, consistent with the localisation of mGluR1 and mGluR5 on unmyelinated sensory fibres, intraplantar injections of either glutamate or selective group I mGluR agonists evoked firing of spinal dorsal horn neurones or thermal hyperalgesia, which were antagonised by selective mGluR1 or mGluR5 antagonists (Bhave et al., 2001; Walker et al., 2001b). Furthermore, intraplantar injections of mGluR1 or mGluR5 antagonists have been shown to attenuate formalin-induced pain behaviour and hyperalgesia after spinal nerve injury or peripheral inflammation (Dogrul et al., 2000; Bhave et al., 2001; Walker et al., 2001b).

In the spinal cord, there seem to be at least two mechanisms by which group I mGluRs may be involved in the development and maintenance of pro-nociceptive hypersensitivity. Firstly, presynaptic group I mGluRs on primary afferent terminals in the spinal cord may control neurotransmitter release onto second order neurones (Bordi and Ugonlini, 1999; Lefebvre et al., 2000). Secondly, postsynaptic group I mGluRs may enhance spinal cord neurone responsiveness to ionotropic glutamate receptor agonist, as group I selective agonists have been shown to facilitate responses of spinal cord neurones to NMDA and AMPA (Jones and Headley, 1995; Ugolini et al., 1997). Consistent with this excitatory role of group I mGluRs, spinal administrations of their selective agonists have been found to reduce thermal and mechanical nociceptive thresholds and to facilitate nociceptive responses (Fisher and Coderre, 1998;

Neugebauer et al., 1999; Dolan and Nolan, 2000). On the other hand, selective antagonists of these receptors show antinociceptive efficacy at the spinal level. In isolated spinal cord preparations, mGluR1 and mGluR5 selective antagonists have been shown to attenuate nociceptive reflex responses and their wind-up (Bordi and Ugolini, 2000; Chen et al., 2000). Spinal applications of mGluR1 antagonists inhibit nociceptive responses of primate spinothalamic tract neurones and their sensitisation (Neugebauer et al., 1999).

In addition to the peripheral and spinal mechanisms, group I mGluRs are implicated in thalamic processing of nociceptive information. Thalamic neurones involved in nociceptive transmission have functional group I mGluR as revealed in electrophysiological studies with iontophoretic application of agonists (Salt et al., 1999; Salt and Binns, 2000). Selective mGluR1 and mGluR5 antagonists have been shown to inhibit responses of thalamic neurones to noxious peripheral stimuli after systemic or iontophoretic application, indicating the involvement of these subtypes in synaptic nociceptive transmission in the thalamus (Salt and Turner, 1998; Salt and Binns, 2000; Binns and Salt, 2001, but cf. Bordi and Ugolini, 2000).

Behavioural studies indicate that group I mGluR antagonism can lead to antinociception, anti-hyperalgesia or anti-allodynia in models of chronic pain. Specific antibodies against mGluR1 or mGluR5 or mGluR1 receptor knock-down in the spinal cord using antisense constructs have been found to increase the latency of acute nociceptive responses and attenuate allodynia in a rat model of neuropathic pain (Young et al., 1998; Fundytus et al., 1998; 2001). Intrathecal and systemic injections of mGluR5 antagonists have shown antiallodynic and antihyperalgesic efficacy in models of neuropathic and inflammatory pain (Dogrul et al., 2000; Walker et al., 2001a), and one mGluR1 antagonist has demonstrated antinociceptive activity in a model of visceral pain (Chen et al., 2000).

Inhibitory metabotropic GluRs (group II and III) also represent potential targets for new analgesics. Some group II and group III mGluRs are present in the superficial dorsal horn, thalamus and cortical areas involved in pain processing, and some subtypes have been shown to be specifically up-regulated in pain-relevant areas under chronic pain conditions, reflecting a possible adaptive role of these inhibitory receptors (Boxall et al., 1998; Azkue et al., 2001; Neto et al., 2001). Although studies with selective tools for group II and III mGluRs in pain are only beginning to appear, the emerging pharmacological evidence also suggests that selective agonists of these receptors have a potential for the treatment of pain (Dolan and Nolan, 2000; Thomas et al., 2001).

Conclusions

The principal role of glutamatergic transmission in acute and chronic pain implies a high analgesic efficacy of compounds modulating this transmission. This has been seen with many ligands acting at such well-investigated glutamate targets as NMDA and AMPA receptors, and with more novel compounds acting at less explored kainate and metabotropic glutamate receptors. However, the major problem of the previous generations of glutamate antagonists has been central side-effects. Although the reports on the side-effect profile of new classes of glutamate modulators have so far been optimistic, the very fact of the ubiquitous role of glutamatergic mechanisms in CNS functions warrants a very thorough approach to their safety investigations.

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