Common mechanisms underlying opioid tolerance and dependence, and neuropathic pain: Role of metabotropic glutamate receptors

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It has been suggested that opioid tolerance and dependence share common mechanisms with neuropathic pain. This short review deals with the role of glutamate and glutamate receptors in opioid tolerance and dependence, and neuropathic pain. Particular attention is given to the role of metabotropic glutamate receptors (mGluRs). First, the different types of glutamate receptors, which include N-methyl-D-aspartate, alpha-amino-3-hydroxyl-5-methylisoxazole-4-propionic acid, kainate and mGluRs, are described. Following this, evidence suggesting that these receptors are involved in opioid tolerance and dependence are summarized. At the end of this section, a model that has been previously proposed to explain mechanisms by which mGluRs may be involved in opioid tolerance and dependence are described. Next is a discussion of the evidence suggesting that glutamate receptors are similarly involved in neuropathic pain, and also in opioid sensitivity associated with neuropathic pain. Again, a hypothetical model used to explain mechanisms by which mGluRs may be involved in neuropathic pain is briefly described. The relevance of the data is discussed in terms of some of the clinical implications of the material presented in the article.

Key Words: Glutamate; Metabotropic glutamate; Metabotropic glutamate receptors; Neuropathy; N-methyl-D-aspartate; Opioid; Opioid dependence; Opioid tolerance; Pain

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Mécanismes communs sous-jacents à la tolérance et à la dépendance aux substances opioïdes, ainsi qu’aux douleurs névropathiques : rôle des récepteurs du glutamate métabotropique

RÉSUMÉ : La tolérance et la dépendance aux substances opioïdes partagent des mécanismes communs aux douleurs névropathiques. Il sera question, dans le présent survol, du rôle du glutamate et des récepteurs du glutamate dans la tolérance et la dépendance aux substances opioïdes, ainsi que dans les douleurs névropathiques. Une attention particulière est accordée au rôle des récepteurs du glutamate métabotropique (mGluR). Tout d’abord, on décrit les différents types de récepteur du glutamate, notamment le N-méthyl-D-aspartate, l’alpha-amino-3-hydroxyl-5-méthyl-isoxazole-4-acide propionique, le kainate et les mGluR. Suite un résumé des données selon lesquelles ces récepteurs sont mis en cause dans la tolérance et la dépendance aux substances opioïdes. À la fin de cette partie, on décrit un modèle déjà proposé pour expliquer comment les mGluR pourraient participer à ce phénomène de tolérance et de dépendance. Ensuite, il y a une discussion sur les éléments qui donnent à penser que les récepteurs du glutamate sont également mis en cause dans les douleurs névropathiques ainsi que dans la sensibilité aux substances opioïdes, associée aux douleurs névropathiques. Encore une fois, on fait une brève description du modèle hypothétique utilisé pour expliquer comment les mGluR contribueraient aux douleurs névropathiques. La pertinence des données est ici discutée en fonction de certaines des incidences cliniques du matériel présenté dans l’article.
Normally, the perception of pain serves as a defense mechanism. When tissue injury occurs, pain causes an organism to initiate a withdrawal response or to avoid use of the injured body part to prevent further injury. However, extreme pain and chronic pain, especially pain that persists after healing is complete, may become counterproductive and debilitating. Thus, the treatment of pain is a major goal of medical care. The most commonly used analgesics are opioids such as morphine. However, the repeated use of opioids may lead to the development of tolerance and dependence. Tolerance is defined as a decreased efficacy of the drug, leading to the requirement for increased doses to achieve the desired analgesic effect. Dependence is a continued need for the drug to maintain a state of physiological equilibrium following repeated administration and leads to an aversive withdrawal syndrome upon removal of the drug. It has been postulated that opioid tolerance and dependence, and one type of chronic pain, neuropathic pain, may share common mechanisms (1). Neuropathic pain syndromes may arise from disease states that progress to nerve injury, such as diabetic neuropathy and postherpetic neuralgia. Neuropathic syndromes may be the result of a traumatic nerve injury, which may be inflicted from a gunshot wound or a car accident. Cancer patients often experience neuropathic pain as a result of either nerve compression by the tumour or cancer treatment-induced nerve damage (radiation damage and chemotherapeutic toxicity). Other neuropathic pain syndromes have a less well defined etiology, and include fibromyalgia and trigeminal neuralgia. Neuropathic pain syndromes are characterized by spontaneous pain, hyperalgesia (increased responsiveness to noxious stimuli) and allodynia (pain-like responsiveness to normally innocuous stimuli) (2-4). The most commonly reported symptoms in patients are cold hyperalgesia, mechanical allodynia and spontaneous pain. Neuropathic pain is particularly difficult to treat and is often unresponsive to opioids (5-7). In this article, the role of glutamate and its receptors, particularly metabotropic glutamate receptors (mGluRs), in opioid tolerance and dependence, and in neuropathic pain and opioid sensitivity associated with neuropathic pain are discussed. Proposed models to explain mechanisms by which mGluRs may be involved in opioid tolerance and dependence, and neuropathic pain are also summarized.

GLUTAMATE RECEPTORS

Glutamate receptors (GluRs) are divided into two broad categories of receptors: ionotropic (iGluRs; they are coupled to ion channels) and mGluRs (they are coupled to guanine nucleotide regulatory [G] proteins).

The most widely studied GluRs are those that are differentially sensitive to N-methyl-D-aspartate (NMDA) receptors. NMDA receptors are composed of four transmembrane domains similar to other ligand-gated channels, an extracellular N-terminus and an intracellular C-terminus (8). NMDA receptors are coupled to an ion channel permeable to calcium, sodium and potassium (9,10), and are gated in a voltage-dependent manner by magnesium (11,12). The NMDA receptor has several binding sites. These include the ligand binding site where glutamate and NMDA act, the phencyclidine (PCP) site inside the ion channel at which noncompetitive antagonists such as MK-801 bind, polyamine binding sites, a distinct site for zinc binding and a redox binding site (13-18). NMDA receptors mediate slow, excitatory postsynaptic potentials, and activation of these receptors leads to the activation of protein kinase C (PKC) and the production of nitric oxide (19).

Receptors differentially sensitive to alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) and kainate are also known as iGluRs, and are coupled to ion channels permeable to sodium, potassium and in some configurations calcium (lacking the GluR2 subunit) (20-22). AMPA and kainate receptors mediate fast excitatory postsynaptic potentials (23-26).

Glutamate also acts at a family of receptors known as mGluRs, which are directly coupled to intracellular second messengers via G proteins. The mGluRs are divided into three groups based on sequence homology, signal transduction mechanisms and receptor pharmacology (27, 28). Group I mGluRs, which include mGluR1 and mGluR5, are positively coupled to phosphatidylinositol (PI) hydrolysis. Activation of these receptors leads to phospholipase C (PLC) catalyzed hydrolysis of phosphoinositol-4,5-bisphosphate (PIP2) into diacylglycerol (DAG) and inositol-1,4,5-trisphosphate (IP3). DAG promotes the translocation and activation of PKC. IP3 stimulates the release of calcium from stores in the endoplasmic reticulum. Calcium also promotes the translocation and activation of PKC. Group II mGluRs, which include mGluR2 and mGluR3, and group III mGluRs (mGluR4,6,7,8) are negatively coupled to the enzyme adenylate cyclase, and activation of these receptors inhibits the production of cyclic adenosine-3’,5’-monophosphate. Activity at group I mGluRs positively modulates NMDA receptor activity via a PKC-mediated mechanism (29-34), while activity at group II and III mGluRs negatively modulates NMDA receptor activity (35).

GLUTAMATE AND OPIOID TOLERANCE AND DEPENDENCE

A role for glutamate in the development of opioid tolerance and dependence has been well established. Glutamate release is enhanced in the spinal cord and locus coeruleus of rats during opioid withdrawal (36,37). Moreover, intracerebroventricular injection of glutamate in morphine-dependent rats has been shown to precipitate withdrawal symptoms (38), and inhibition of glutamate release with lamotrigine attenuated the precipitated withdrawal symptoms (39).

As early as the 1970s, Koyuncuoglu and colleagues (40) postulated that the excitatory amino acids glutamate and aspartate played a role in opioid tolerance and dependence. This group of investigators showed that aspartate antagonized morphine’s effects, and reduced the development of morphine tolerance and dependence (40,41). In later work,
Koyuncuoglu and colleagues (42) showed that NMDA receptor antagonists such as ketamine and dextromorphan attenuated the severity of morphine withdrawal symptoms in rats. The role of NMDA receptors in the development of opioid tolerance and dependence has been verified by many other investigators (43-62) who showed that antagonism of NMDA receptors (with competitive and noncompetitive antagonists) attenuates these phenomena. More recently, it has been shown that administration of antagonists to the glycine site of the NMDA receptor attenuates opioid withdrawal symptoms (63-65). Antisense oligonucleotide knockdown of NMDA receptors has also been shown to reduce precipitated withdrawal symptoms (66). However, it should be noted that some investigators (67-69) have observed that although NMDA antagonists block the development of tolerance to morphine, they fail to affect the development of tolerance to more selective mu-, delta- or kappa-opioid receptor agonists. Contrary to the usual observations, one group (70) even found that cotreatment of rats with the NMDA antagonist MK-801 and morphine exacerbated the precipitated withdrawal symptoms.

The role of AMPA and kainate receptors in opioid tolerance and dependence seems to be more complex and controversial. Some investigators (71,72) have found that treatment with AMPA/kainate antagonists either systemically or directly into the locus coeruleus or central nucleus of the amygdala reduced withdrawal-induced locus coeruleus activation and behavioural symptoms. However, others have shown that while systemic administration of AMPA/kainate antagonists reduced the development of tolerance and acute dependence, there was no effect on the development of chronic dependence (73). Moreover, although systemic administration of a selective AMPA antagonist has been shown to attenuate the development of tolerance to morphine, it failed to affect the development of tolerance to selective delta- or kappa-opioid receptor antagonists (74). In our laboratory, we have shown (59) that intracerebroventricular administration of an AMPA/kainate antagonist failed to reduce the precipitated withdrawal symptoms in morphine-dependent rats.

We have examined the role of mGluRs in opioid dependence and tolerance. We first showed (59) that chronic intracerebroventricular administration of either the nonselective mGluR antagonist L-2-amino-3-phosphonopropionic acid (L-AP3), or the relatively selective group I mGluR antagonist (S)-4-carboxyphenylglycine ([S]-4CPG), concurrently with subcutaneous administration of morphine, significantly attenuated the severity of precipitated withdrawal symptoms. Very recent work from our laboratory showed that antisense oligonucleotide knockdown of spinal mGluR1 attenuated the development of tolerance to morphine (Sharif, et al, unpublished observations). Subsequently, we showed that chronic intracerebroventricular administration of either the nonselective mGluR antagonist alpha-methyl-4-carboxyphenylglycine, the selective group II antagonist 2S,1'R,2'R3'R-2-(2',3'-dicarboxycyclopropyl)glycine, or the selective group III mGluR antagonist alpha-methyl-L-amino-4-phosphonobutanoate (MAP4), concurrently with subcutaneous morphine significantly reduced the severity of the precipitated withdrawal symptoms (75). Similarly, it has been shown that antagonism of group II mGluRs attenuates morphine-induced activation of locus coeruleus neurons (76). In addition, we demonstrated that a single intracerebroventricular injection of the selective group II mGluR agonist 2S,1'R,2'R3'R-2-(2',3'-dicarboxycyclopropyl)glycine, just before the precipitation of withdrawal, significantly reduced the severity of abstinence symptoms (77). Our results were verified by another group of investigators (78) who showed that pretreatment with the group II mGluR agonist LY34570 significantly reduced the severity of abstinence symptoms in rats. Thus, we first established that mGluRs play a significant role in the development of opioid dependence, and this contention has been borne out by further research.

As discussed above, group I mGluRs are positively coupled to PI hydrolysis, and activation of these receptors ultimately leads to the activation of PKC and release of intracellular calcium. Thus, because antagonism of group I mGluRs with (S)-4CPG attenuated morphine withdrawal, it was interesting to examine the role of products of PI hydrolysis in opioid dependence. Toward this end, we showed that chronic inhibition of PKC as well as intracellular calcium release in the brain significantly reduced the severity of precipitated abstinence symptoms (78). Other investigators (79-82) have also shown that inhibition of PKC, as well as other protein kinases, reduces tolerance and dependence associated with repeated opioid administration in rats. Moreover, it has been shown that tolerance is associated with increases in PKC immunoreactivity (83) and activated PKC (80).

Based on our results, and those of others, we developed a hypothetical model to describe some of the mechanisms by which mGluRs may be involved in opioid tolerance and dependence (84,85). The effect of a single, high dose injection of morphine is not entirely clear because some investigators (86) have found that glutamate release is increased in the striatum and nucleus accumbens, whereas others (87) have observed a decrease in the striatum and limbic forebrain. During chronic morphine administration, some investigators (88) observed a decrease in glutamate release; however, an increase in the glutamate to gamma-aminobutyric acid (GABA) ratio is found (87), suggesting that the glutamate concentration may be increased. Increased glutamate activity would overexcite not only NMDA receptors, but also mGluRs. During opioid withdrawal, an increase in glutamate release is generally observed (86,87,89-91). First, we speculate that mGluRs, NMDA receptors and opioid receptors may be colocalized within the same cells. Brain distributions of mGluRs and opioid receptors are similar (92,93), and it has been shown that NMDA receptors and opioid receptors are colocalized (94,95). Increased activity of group I mGluRs would lead to an increase in PI hydrolysis, and thus activation of PKC and release of intracellular calcium from stores in the endoplasmic reticulum. Activated PKC would phosphorylate the G protein on the mu-opioid receptor (96-100),
inducing desensitization and, thus, tolerance. It would also
phosphorylate the NMDA-associated ion channel (101-104),
relieving the magnesium block and resulting in an enhance-
ment of NMDA receptor activity, allowing a greater influx of
calcium. Increased concentrations of intracellular calcu-
mium would promote influx of calcium via voltage-gated calcium
channels (101-103), and further increasing the intracellular
concentration of calcium. Increased concentrations of cal-
ccium may facilitate activation of calcium/calmodulin-
dependent protein kinases, leading to further phosphoryla-
tion and desensitization of mu-opioid receptors (81,105), as
well as leading to the activation of adenylyl cyclase and
increased production of cAMP (103,106). Increased concen-
trations of cAMP may enhance protein kinase A (PKA)-medi-
ted phosphorylation of NMDA receptors (32,107,108), ele-
vate hyperpolarization-activated mixed cation current,
causing depolarization (88,109,110), and increase neuronal
excitation. In regard to groups II and III mGluRs, we hy-
pothesized that there was a heterologous desensitization of
these receptors during chronic morphine treatment that is
prevented by chronic administration of selective antagonists
or overcome by a single injection of a selective agonist just
before the precipitation of withdrawal. In support of this hy-
pothesis, Noble and Cox (111) showed that repeated mor-
phine administration induced heterologous desensitization of
group III mGluRs in the caudate putamen, nucleus accum-
bens, thalamus and periaqueductal grey, as evidenced by a
reduced ability of the group III agonist L-2-amino-4-
phosphobutyric acid to inhibit adenylyl cyclase activity
(Figure 1).

GLUTAMATE AND NEUROPATHIC PAIN
As discussed above, it has been suggested that opioid toler-
ance and dependence, and neuropathic pain may share simi-
lar mechanisms (1). Moreover, as discussed above,
neuropathic pain is often unresponsive to opioid analgesics in
both rats and humans (5-7,112-117 and unpublished data).
Indeed, there is a great deal of evidence indicating that gluta-
mate is involved in neuropathic pain as well as opioid toler-
ance and dependence. It has been shown that glutamate
release is enhanced in the spinal cord of nerve-injured rats
(118).

As in the study of opioid tolerance and dependence, most
investigators have concentrated on the role of NMDA re-
ceptors in neuropathic pain. Many of these studies (119-135)
have shown that NMDA antagonists, given either centrally or
systemically, reduce hyperalgesia and allodynia associated
with various models of nerve injury, as well as autotomy
behaviour. However, it should be noted that this is not a
universal observation. Some investigators have shown that,
whereas administration of NMDA receptor antagonists
reduces heat hyperalgesia, there is no appreciable effect on
mechanical allodynia (136). It has also been shown that the
effectiveness of opioid analgesics is restored in nerve-injured
rats treated with NMDA antagonists (112,113,115-117).

There is evidence suggesting that AMPA/kainate recep-
tors are involved in neuropathic pain. It has been shown that
administration of AMPA/kainate antagonists reduces hy-
peralgesia associated with constriction injury of the sciatic
nerve, streptozotocin-induced diabetic neuropathy and dorsal
rhizotomy in rats (119,137,138), mechanical allodynia in spi-
nial cord-injured rats (139,140) and thermal sensitivity in spinalized rats (141). However, reduced muscle tone and sedation are often associated with the use of these antagonists (139).

Recent data from our laboratory indicate that mGluRs are also involved in both the development and maintenance of neuropathic pain. We showed that intrathecal administration of the relatively selective group I mGluR antagonist (S)-4CPG reduces the development of neuropathic pain (125). However, in addition to its antagonistic activity at group I mGluRs, (S)-4CPG has a secondary action whereby it is an agonist at group II mGluRs (27,142,143). Therefore, the precise mechanism through which (S)-4CPG reduced neuropathic pain was not clear. We further explored the relative contribution of group I mGluRs by examining how pretreatment with antibodies selective to either mGluR1 or mGluR5 affected neuropathic pain. We showed that pretreatment with either anti-mGluR1 or anti-mGluR5 antibody significantly reduced cold hyperalgesia associated with a chronic constriction of the sciatic nerve (144). Therefore, we identified a clear role for group I mGluRs in neuropathic pain.

To characterize further the role of group I mGluRs in neuropathic pain, we used the novel technology of antisense oligonucleotides. We initially showed that intrathecal pretreatment with antisense oligonucleotides targeting either mGluR1 or mGluR5 reduced cold hyperalgesia, mechanical allodynia and heat hyperalgesia associated with nerve injury (145). The effect of knockdown of spinal mGluR1 was more robust than knockdown of spinal mGluR5; therefore, we continued our studies with the antisense targeting mGluR1 and examined the role of this receptor in more detail.

We showed that antisense oligonucleotide knockdown of spinal mGluR1 after neuropathic pain is already established significantly reversed cold hyperalgesia, mechanical allodynia and heat hyperalgesia (146 and unpublished data). These results suggest that mGluR1 is involved in the maintenance as well as the development of neuropathic pain.

As previously discussed, neuropathic rats and humans are relatively unresponsive to opioid analogs. In further experiments, we showed that antisense oligonucleotide knockdown of spinal mGluR1 restored the efficacy of intrathecally injected morphine in nerve-injured rats (147 and unpublished data).

Activation of both NMDA receptors and group I mGluRs leads to the activation of PKC. Furthermore, activity at group I mGluRs positively modulates activity at NMDA receptors via a PKC-mediated mechanism (29-34). We and others (1,78-82) have already shown that PKC is involved in opioid tolerance and dependence, and that PKC plays a pivotal role in neuropathic pain. When PKC is in the activated state, it is translocated to the membrane, and it has been shown that spinal PKC is translocated to the membrane in neuropathic rats (148). Moreover, inhibition of PKC in the spinal cord reduces morphine tolerance as well as decreases neuropathic pain (80,149). By using transgenic animals in research studies, it has been shown that PKC knockout mice do not develop neuropathic pain (150). We verified that there is an increase in activated PKC in neuropathic rats, and we also showed that antisense oligonucleotide knockdown of spinal mGluR1 at the lumbar level results in a reduction of activated PKC in the lumbar spinal cord dorsal horn in neuropathic rats (146,151 and unpublished data).

Because of the effects of nerve injury on PKC activity, and the ability of group I mGluRs to modulate positively NMDA receptor activity via PKC-mediated mechanisms, we hypothesized that neuropathic rats would be hypersensitive to the excitatory effects of intrathecally injected NMDA and that antisense oligonucleotide knockdown of spinal mGluR1 would reverse this hypersensitivity. In experiments designed to test this hypothesis, we showed that nerve-injured rats are indeed hypersensitive to the excitatory effects of NMDA, as evidenced by increased time spent exhibiting nociceptive behaviors (151 and unpublished data). We also showed that antisense oligonucleotide knockdown of spinal mGluR1 reversed this NMDA hypersensitivity in neuropathic rats (151 and unpublished data).

Based on our results and those of others, we devised a hypothetical mechanistic model to explain the role of group I mGluRs in neuropathic pain, similar to our model to explain the role of mGluRs in opioid tolerance and dependence (84). We speculate that group I mGluRs, NMDA receptors and opioid receptors are colocalized within the same cells. Nerve injury stimulates an increased release of glutamate (118), therefore, increasing the activation of NMDA receptors and group I mGluRs. Activation of group I mGluRs (as well as NMDA receptors) ultimately leads to the activation of PKC. Activated PKC phosphorylates opioid receptors (96-100), leading to receptor desensitization and reduced efficacy of opioid agonist analogs. In addition, PKC phosphorylates the NMDA-associated ion channel (101-104), increasing NMDA receptor activity, and leads to increased influx of calcium. The increased intracellular concentrations of calcium produce a positive feedback loop, increasing activity of protein kinases and enhancing the phosphorylation of opioid receptors and the NMDA ion channel. Antisense oligonucleotide knockdown of mGluR1 (and mGluR5) reduces the number of these receptors available for activation, reducing PI hydrolysis and protein kinase activation. Thus, the phosphorylation of opioid receptors and NMDA ion channels is attenuated, reducing desensitization of opioid receptors (with a resultant increase in opioid analgesic efficacy) and reducing activity of NMDA receptors (reducing cellular excitation and pain transmission) (Figure 1).

**DISCUSSION**

The roles of glutamate and glutamate receptors have been summarized – particularly those of mGluRs in opioid tolerance and dependence, and neuropathic pain, including opioid sensitivity associated with neuropathic pain. It has been shown that the inhibition of NMDA, AMPA and kainate receptors and mGluRs with antagonists, antibodies and antisense oligonucleotides attenuates opioid tolerance and dependence, and neuropathic pain, as well as restores opioid...
mGluRs, opioid dependence and neuropathic pain

used clinically, their use is often associated with debilitating side effects such as memory, motor and cognitive impairments, and psychotomimetic effects (152-156). Either more selective NMDA antagonists, or perhaps other glutamate receptors, particularly mGluRs, are needed because they may be the best targets for future drug developments.

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