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Review

# NMDA receptors as targets for drug action in neuropathic pain

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**Abstract**

Hyperalgesia and allodynia following peripheral tissue or nerve injury are not only due to an increase in the sensitivity of primary afferent nociceptors at the site of injury but also depend on NMDA receptor-mediated central changes in synaptic excitability. Functional inhibition of NMDA receptors can be achieved through actions at different recognition sites such as the primary transmitter site (competitive), strychnine-insensitive glycine site ($glycine_B$), polyamine site (NR2B selective) and phencyclidine site located inside the cationic channel. Unfortunately, most agents which completely block NMDA receptors cause numerous side effects such as memory impairment, psychotomimetic effects, ataxia and motor incoordination. There is now, however, considerable evidence that moderate affinity channel blockers, $glycine_B$ and NR2B selective antagonists show a much better profile in animal models than high affinity channel blockers and competitive NMDA receptor antagonists. These "therapeutically" safe NMDA receptor antagonists are also able to slow or prevent the development of opioid tolerance, indicating the utility of their combination with opioids in the treatment of chronic pain. The antinociceptive effects of NMDA receptor antagonists and opioids could be predicted to be synergistic and the presence of an NMDA receptor antagonist should block both the development of chronic pain states and inhibit the development of tolerance to the analgesic effects of morphine. Peripheral NMDA receptors offer a very attractive target for NMDA receptor antagonists that do not cross the blood brain barrier in inflammatory and visceral pain. Such agents might be predicted to be devoid of CNS side effects at doses producing powerful antinociception at peripheral NMDA receptors. © 2001 Elsevier Science B.V. All rights reserved.

*Keywords:* NMDA receptor; Pain, chronic; Opioid tolerance

## 1. Glutamate in chronic pain

Despite intensive research on the neurobiological mechanisms of chronic pain, this therapeutic area remains one of the least satisfactorily covered by current drugs. Malfunctioning of glutamatergic neurotransmission has been implicated in a wide variety of neurological diseases such as acute stroke and trauma, chronic neurodegenerative diseases, epilepsy, schizophrenia and depression (see Parsons et al., 1998). Of particular relevance for this review is the involvement of glutamate in diseases reflecting long-term plastic changes in the central nervous system (CNS) such as chronic pain, opioid tolerance, dependence and addiction (Bennett, 2000).

Glutamate activates two major classes of receptors: ionotropic and metabotropic. Ionotropic receptors are classified into three major subclasses: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), kainate and *N*-methyl-D-aspartate (NMDA). There is considerable preclinical evidence that hyperalgesia and allodynia following peripheral tissue or nerve injury is not only due to an increase in the sensitivity of primary afferent nociceptors at the site of injury but also depends on NMDA receptor-mediated central changes in synaptic excitability (Dickenson, 1990; Dickenson et al., 1997; Ren, 1994; Sandkuhler and Liu, 1998).

## 2. NMDA receptor antagonists

Functional inhibition of NMDA receptors can be achieved through actions at different recognition sites such as the primary transmitter site (competitive), strychnine-insensitive glycine site ($glycine_B$), polyamine site (NR2B selective) and phencyclidine site located inside the cationic channel (see Parsons et al., 1998). NMDA channel blockers act in an uncompetitive "use-dependent" manner, meaning that they only block the channel in the open state.

Unfortunately, antagonists which completely block NMDA receptors cause numerous side effects such as memory impairment, psychotomimetic effects, ataxia and

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motor incoordination, as they also impair normal synaptic transmission—a two-edged sword. The challenge has therefore been to develop NMDA receptor antagonists that prevent the *pathological* activation of NMDA receptors but allow their *physiological* activation.

### 2.1. Uncompetitive antagonists

It has been suggested that uncompetitive NMDA receptor antagonists with rapid unblocking kinetics but somewhat less pronounced voltage-dependency than $Mg^{2+}$ should be able to antagonise the pathological effects of the sustained, but relatively small increases in extracellular glutamate concentration, but, like $Mg^{2+}$, leave the channel as a result of strong depolarisation following physiological activation (e.g. Parsons et al., 1999). Thus, uncompetitive NMDA receptor antagonists with moderate, rather than high affinity may be desirable. Memantine, amantadine, ketamine and dextromethorphan are clinically used agents which belong to this category (Hewitt, 2000; Schmid et al., 1999; Gordon et al., 1999). Others such as remacemide, (*S*)-alpha-phenyl-2-pyridineethanamine dihydrochloride (ARL 15896AR), bis-3flour-phenyl-propanamine (NPS-1506) and possibly the cannabinoid Dexanibinol (HU-211) are at different stages of clinical development (see Fig. 1 and Parsons et al., 1998).

Although the hypothesis underlying the ability of low affinity open channel blockers to differentiate between phasic physiological and tonic pathological activation of NMDA receptors during ischaemia has gained relatively wide acceptance (Chen et al., 1992; Rogawski, 1993; Kornhuber and Weller, 1997; Mealing et al., 1997; Parsons et al., 1999), it is still unclear how such compounds could differentiate between normal and abnormal synaptic activation of NMDA receptors. One possible explanation is that the forms of synaptic activity in the two states are different. Long-term potentiation is a biophysical model for the patterns of NMDA receptor-dependent synaptic activity underlying memory formation (Collingridge and Bliss, 1995; Herron et al., 1986) and is normally induced by delivering a high frequency tetanic stimulus (typically 100 Hz for 1 s). Under such conditions, drugs such as memantine can leave the open NMDA receptor channel during the stimulus burst. Indeed very high concentrations of memantine are required to block the induction of long-term potentiation both in vivo and in vitro (Barnes et al., 1996; Frankiewicz et al., 1996). Wind-up is a biophysical model for the patterns of synaptic activity underlying the induction of chronic pain states (Dickenson, 1990; Dickenson et al., 1997; Ren, 1994) and is normally induced by repetitive stimulation at much lower frequencies but for longer periods (typically 0.5 Hz for 5–10 s). Most NMDA receptor antagonists block this form of synaptic activity, including therapeutically relevant doses of moderate affinity uncompetitive antagonists. It should be noted, however, that the relevance of wind-up for the induction of chronic pain states has recently been questioned because wind-up, central sensitisation and hyperalgesia are not the same phenomena, even though they share some common properties (Herrero et al., 2000). Long-term depression is also an NMDA receptor-dependent biophysical model of synaptic plasticity that is induced by lower frequency stimulation over longer periods of time (Bear and Malenka, 1994; Malenka, 1994; Baudry, 1996) and requires less pro-

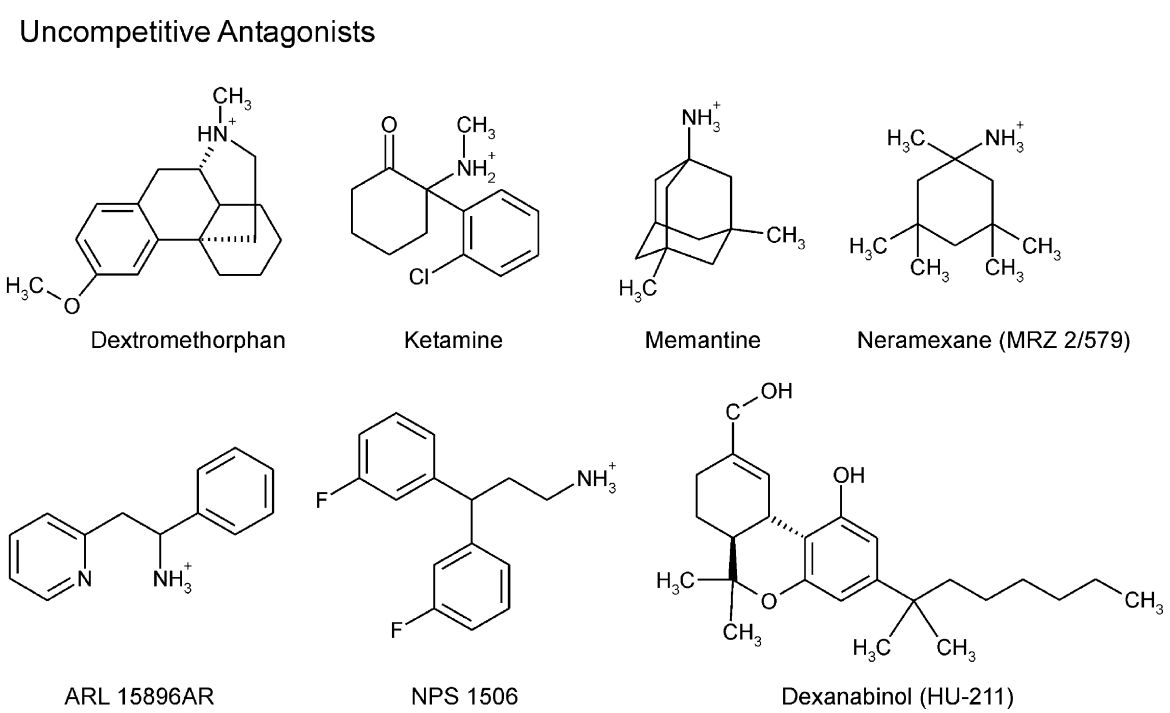


Fig. 1. Uncompetitive antagonists.

nounced increases in intracellular $Ca^{2+}$ than long-term potentiation (Artola and Singer, 1993; Hansel et al., 1996). It seems likely that during the induction of wind-up or long-term depression for each successive NMDA-receptor mediated EPSP, the duration is too short and the degree of depolarisation too low to allow sufficient relief of blockade by low affinity open channel blockers. In other words, such compounds can block moderate NMDA receptor activation underlying, e.g. chronic pain states (modelled by wind-up) or the development of drug tolerance (possibly modelled by long-term depression) but do not block stronger NMDA receptor activation underlying memory formation (modelled by long-term potentiation).

Whatever the biophysical mechanism underlying this difference, therapeutically relevant doses of memantine selectively block formalin-induced tonic nociceptive responses in rats (Eisenberg et al., 1993) and produce a prophylactic antinociceptive effect against carrageenan-induced hyperalgesia (Neugebauer et al., 1993; Eisenberg et al., 1994) at doses devoid of side effects. Memantine also blocks and reverses thermal hyperalgesia and mechanical allodynia in rat models of painful mononeuropathy without obvious effects on motor reflexes following systemic (Carlton and Hargett, 1995; Eisenberg et al., 1995) and local spinal administration (Chaplan et al., 1997). Interestingly, in a recent study, memantine produced powerful inhibition of wind-up after selective ligation of the L5/L6 spinal nerves with little effect in sham controls in contrast to dizocilpine ((+) 5-methyl-10,11-dihydro-5*H*-dibenzo[a,d] cyclohepten 5,10 imine, (+)MK 801), which non-selectively blocked responses (Suzuki et al., 2001). Clinical trials with memantine in post herpetic neuralgia and diabetic neuropathic pain syndrome are presently underway. Ketamine is also effective in various animal models of hyperalgesia and allodynia and, like memantine, has been reported to have antinociceptive effects in some of these models at doses devoid of obvious side effects (Mao et al., 1993; Qian et al., 1996; Ren et al., 1992). Others, however, have reported that the effects of ketamine are only seen at doses producing ataxia (Chaplan et al., 1997; Laird et al., 1995; Yaksh, 1989). This may be related to its somewhat higher potency and associated slower unblocking kinetics.

### 2.2. Glycine site antagonists

Another promising target for NMDA receptor antagonism is the glycine$_B$ modulatory site (for review see Danysz and Parsons, 1998). Full antagonists of this site may offer a promising therapeutic profile due to their ability to increase NMDA receptor glycine-dependent desensitization. Prolonged repetitive activation of NMDA receptors would be effectively reduced at concentrations having little effect on more transient activation as the time course for full desensitization is quite long (tau several hundred milliseconds). This property may also allow such compounds to differentiate between various forms of NMDA receptor-mediated synaptic plasticity, e.g. block long-term depression and wind-up at concentrations having less effect on long-term potentiation. This idea is supported by recent data indicating that systemically active glycine$_B$ antagonists have good therapeutic indices following systemic administration in models of hyperalgesia (Vaccarino et al., 1993; Millan and Seguin, 1994; Laird et al., 1996; Quartaroli et al., 1999) as anxiolytics, possible anti-psychotomimetics, neuroprotective agents in models of focal ischaemia and trauma, and anti-epileptics (see Danysz and Parsons, 1998). In contrast to high affinity uncompetitive antagonists, glycine$_B$ antagonists do not have psychotomimetic effects (Löscher et al., 1994; Karcz-Kubicha et al., 1999) and have even been reported to possess antipsychotic activity (Bristow et al., 1995, 1996). They have no negative effects on learning at doses effectively blocking NMDA receptor in vivo (see Danysz and Parsons, 1998). Finally, unlike high affinity uncompetitive antagonists such as (+)-MK-801 and phencyclidine

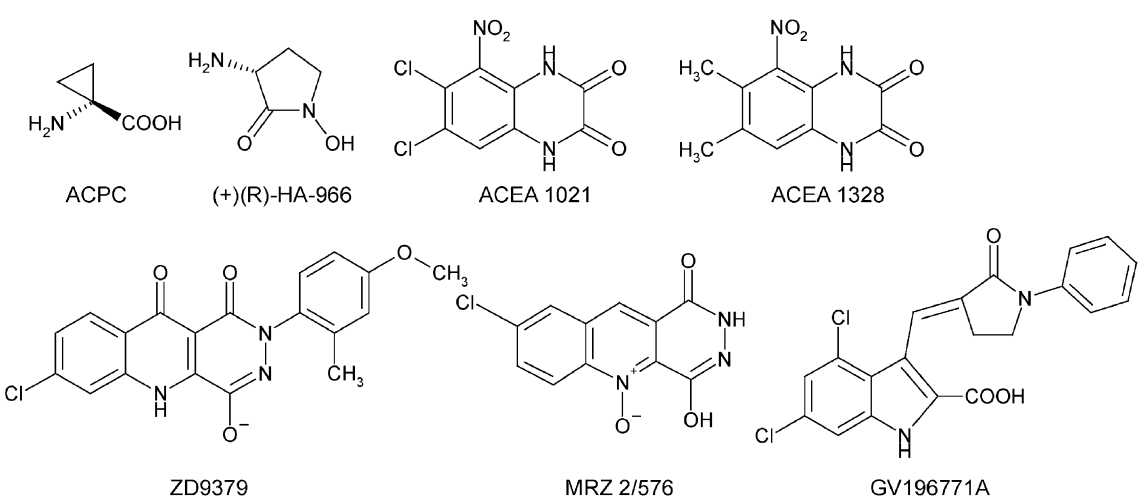


Fig. 2. Glycine site antagonists.

(PCP), even very high doses do not cause any neurodegenerative changes in the cingulate/retrosplenial cortex of rats (Chen et al., 1993; Hargreaves et al., 1993; Berger et al., 1994).

The glaxo compound GV 196771A is presently in phase I clinical trials for pain (see Fig. 2). This glycine$_B$ antagonists was effective in blocking the development of hyperalgesia following chronic sciatic nerve ligation in rats when given orally at 3 mg/kg twice daily for 10 days. GV 196771A also dose-dependently reversed established hyperalgesia for up to 8 h. The therapeutic profile was promising in as much as the second phase of formalin-induced hyperalgesia was antagonized with an $ID_{50}$ of 0.6 mg/kg p.o. whereas 10 mg/kg had no effect on the first phase (Quartaroli et al., 1999). Other systemically active glycine$_B$ antagonists presently under development and with therapeutic potential in the treatment of pain include 5-nitro-6,7-dichloro-1,4-dihydro-2,3-quinoxalinedione (ACEA-1021, Licostinel, Lutfy et al., 1995, 1996), 7-Chloro-4-hydroxy-2-(4′-methoxyphenyl)-6′-methyl-1, 2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione (ZD9379, Tatlisumak et al., 1998) and 8-chloro-4-hydroxy-1-oxo-1,2-dihydropyridazinol[4,5-]quinoline-5-oxide choline (MRZ 2/576, Parsons et al., 1997).

### *2.3. NR2B selective antagonists*

Subtype selective agents may also offer a promising approach to minimize side effects as agents would not produce maximal inhibition of responses of neurones expressing heterogeneous receptors. Thus, cortical and hippocampal neurones express both NR2A and NR2B receptors in approximately similar proportions, but very little NR2C or NR2D. NR2B selective agents therefore block NMDA receptor mediated responses of such neurones to a maximal level of around 30–50% of control. The NR2B selective agent (1*S*,2*S*)-1-(4-hydroxy-phenyl)-2-(4-hydroxy-4-phenylpiperidino)-1-propanol (CP-101,606, see Fig. 3) has indeed been reported to be effective in suppressing hyperalgesia in animal models of chronic pain (carrageenan, 4-Phorbol-12-myristate-13-acetate (PMA), capsaicin and allodynia in neuropathic rats) at doses devoid of negative side effects in motor co-ordination or behaviour (Taniguchi et al., 1997; Boyce et al., 1999). A good separation was also reported for (*R*-(*R**,*S**)-(4-hydroxyphenyl)-methyl-4-(phenylmethyl)-1-piperidinepropanol ((±)-Ro 25-6981, Boyce et al., 1999) indicating that NR2B selective antagonists may also have clinical utility for the treatment of neuropathic and other pain conditions in man with a reduced side-effect profile. Unfortunately, several NR2B selective agents seem to block human ether-a-go-go-related gene (HERG)-mediated K(+) currents and may thereby produce severe side effects by increasing the cardiac Q/T interval.

## 3. Wind-up

More recent studies have addressed the issue whether it is possible to reproduce clinically the well characterized inhibition of wind-up seen with NMDA receptor antagonists in animal models. Dextromethorphan and ketamine, but not morphine significantly reduced both the area of secondary hyperalgesia and temporally summated 'wind-up-like pain' to repeated von Frey filament stimulation in healthy human volunteers with experimental first degree burn injury (Ilkjaer et al., 1997; Mikkelsen et al., 1999). Ketamine was also effective in reducing secondary hyperalgesia and allodynia induced by capsaicin in a double-blind, placebo-controlled, human experimental study (Andersen et al., 1996). Similar effects on "wind-up-like" pain were previously reported with i.v. ketamine and oral dextromethorphan in healthy volunteers, rating the intensity of summated second pain in response to repeated painful electric shocks and heat pulses (Price et al., 1994; Arendtnielsen et al., 1995).

## 4. Opioid tolerance

It is believed that phenomena such as sensitisation, tolerance and drug-dependence might also involve synaptic plasticity. In fact, numerous studies indicate that NMDA receptor antagonists block sensitisation to amphetamine and cocaine as well as tolerance and dependence to ethanol and opioids in animal models (Trujillo, 2000; Trujillo and Akil, 1991, 1995; Pasternak and Inturrisi, 1995; Mao, 1999). Recent studies indicate that the uncompetitive NMDA receptor antagonists dextromethorphan, memantine and MRZ 2/579 (1,3,3,5,5-pentamethylcyclohexylamine, neramexane) are not only able to prevent the development

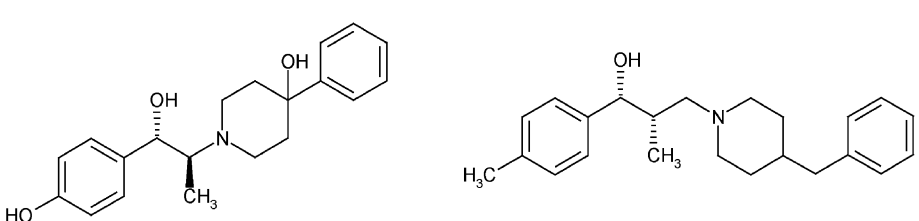


Fig. 3. NR2B selective anatagonists.

of morphine tolerance, but also reverse established tolerance even in the continuing presence of this opioid and prevent the expression of withdrawal symptoms in rats (Popik and Skolnick, 1996; Popik and Danysz, 1997; Popik and Kozela, 1999; Houghton et al., 2001). Moreover, acquisition of i.v. morphine self-administration in drug- and experimentally naive mice was inhibited by pretreatment with MRZ 2/579 (Semenova et al., 1999). Likewise, systemically active glycine$_B$ antagonists attenuate both physical dependence to morphine and the development of tolerance to the antinociceptive effects of opioids following repeated administration. Thus, 5-nitro-6,7-dimethyl-1,4-dihydro-2,3-quinoxalinedione (ACEA-1328) and ACEA-1021 completely blocked tolerance to morphine-induced antinociception in the tail flick test in mice, without affecting the basal nociceptive response or potentiating morphine-induced antinociceptive effects (Lutfy et al., 1995, 1996; Pasternak and Inturrisi, 1995). In contrast, the ability of MRZ 2/576 to attenuate morphine tolerance was associated with an increased morphine peak analgesia and duration in the tail-flick test (Popik et al., 1998; Belozertseva et al., 2000a,b). Administration of either (+)-(3*R*)-3-Amino-1-hydroxypyrrolidin-2-one ((+)-HA-966) or morphine alone was devoid of effects on the mechanical hyper responsiveness to von Frey hair stimulation in a model of chronic constriction injury whereas combined administration of (+)-HA-966 (2.5 mg/kg s.c.) and morphine (0.25, 0.5 and 1 mg/kg i.v.) dose-dependently increased the mechanical response thresholds (Christensen, 1999). This effect was naloxone-sensitive and was not accompanied by motor deficits (ibid.). When given alone 1-aminocyclopropane-carboxylic acid (ACPC, 50 and 150 mg/kg) had no analgesic actions in the tailflick assay and did not change morphine's potency in naive mice (Kolesnikov et al., 1994). However, chronic administration of this "functional" NMDA receptor antagonist both prevented and reversed morphine tolerance (ibid.). Also supportive for the role of NMDA receptors in opioid dependence is the finding that the opioid methadone (used in the therapy of addiction) also blocks NMDA receptors (Ebert et al., 1995) and that both the D- and L-isomer inhibit [$^3$H](+)-MK-801 binding to spinal cord membranes at therapeutically relevant concentrations: $K_d$s of 2.6 and 2.8 μM (Gorman et al., 1997). However, a recent paper concluded that NMDA antagonism does not contribute to the mechanism of D-methadone antinociception in vivo as both the antinociceptive and antagonism of responses to micro-iontophoretic NMDA were reversed by the opioid receptor antagonist naloxone (Chizh et al., 2000).

On a similar line, there are some indications that NMDA receptor activation may have a critical role in the mechanisms underlying the reduced effectiveness of opioids in chronic neuropathic pain states. For example, the antinociceptive effects of morphine are reduced in nerve-injured rats in the absence of daily exposure to morphine and this effect can be prevented by treatment with (+)-MK-801 (Mao et al., 1995). This may be due to the fact that NMDA receptor activation attenuates opioid receptor G protein coupling via activation of protein kinase C (Cai et al., 1997; Fan et al., 1998) and that opioid receptor activation increases NMDA receptor function via phosphorylation (Swope et al., 1999).

Taken together with the above mentioned effects of some NMDA receptor antagonists in models of chronic pain, these data indicate the utility of the combined use of therapeutically safe NMDA receptor antagonists with opioids in the treatment of chronic pain (Eide et al., 1995; Elliott et al., 1995; Bennett, 2000). The antinociceptive effects of NMDA receptor antagonists and opioids could be predicted to be synergistic and the presence of an NMDA receptor antagonist should block both the development of chronic pain states and inhibit the development of tolerance to the analgesic effects of morphine. Indeed, this approach has recently been pursued by Algos with morphidex (a combination of morphine and dextromethorphan), which is in phase III clinical trials for the treatment of chronic pain (see Parsons et al., 1998).

## 5. Peripheral NMDA receptors

Recent data indicate that peripheral NMDA receptors are also involved in inflammatory somatic and visceral pain. Peripheral glutamate receptors are associated with unmyelinated axons (Carlton et al., 1995) and the number of somatic sensory axons containing ionotropic glutamate receptors increases during peripheral sensitization due to inflammation (Carlton and Coggeshall, 1999; Coggeshall and Carlton, 1999). Subcutaneous administration of formalin into the plantar surface of rat hindpaws causes an increase in glutamate and aspartate concentrations in this tissue (Omote et al., 1998). Local injection of glutamatergic agonists to glabrous skin evokes pain-related behaviours in rats (Carlton et al., 1995; Jackson et al., 1995; Zhou et al., 1996) and peripherally administered glutamate receptor antagonists can prevent this effect as well as formalin or inflammation-induced hyperalgesia (Jackson et al., 1995; Davidson et al., 1997; Carlton et al., 1998; Davidson and Carlton, 1998). Similar effects have also been seen in experiments using local administration to the knee joint cavity in rats (Lawand et al., 1997). Local injection of ketamine into the skin on one calf of 10 healthy volunteers reduced primary and secondary hyperalgesia following a local experimental first degree burn injury, supporting the role of peripheral NMDA receptors in mediating secondary hyperalgesia in humans (Warncke et al., 1997)

Immunohistochemical studies indicate that NR1 subunits are expressed on the cell bodies and peripheral terminals of primary afferent nerves innervating the colon. Moreover, colorectal distension activation of single afferents in decentralised pelvic nerves was inhibited by me-

mantine, indicating that peripheral NMDA receptors are important in normal visceral pain transmission, and may provide a novel mechanism for development of peripheral sensitization and visceral hyperalgesia (McRoberts et al., 2001). Increases in blood pressure evoked by graded distension of the normal ureter was potently blocked by the glycine$_B$ antagonist MRZ 2/576, suggesting that NMDA receptors are involved in the processing of acute nociceptive inputs from viscera (Olivar and Laird, 1999). Moreover, the effective dose ($ID_{50}$ = 0.2 mg/kg) was at least 10-fold lower than that known to antagonize NMDA receptors in the CNS (Parsons et al., 1997), indicating that peripheral NMDA receptors may also be involved in this effect.

## 6. Conclusions

(1) NMDA receptor antagonists which completely block NMDA receptors cause numerous side effects such as memory impairment, psychotomimetic effects, ataxia and motor incoordination, and they also impair normal synaptic transmission—a two-edged sword.

(2) The challenge has therefore been to develop NMDA receptor antagonists that prevent the pathological activation of NMDA receptors but allow their physiological activation.

(3) There is now considerable evidence that moderate affinity channel blockers, glycine$_B$ and NR2B selective antagonists show a much better profile in animal models of chronic pain than high affinity channel blockers and competitive NMDA receptor antagonists.

(4) These therapeutically safe NMDA receptor antagonists are also able to slow or prevent the development of opioid tolerance, indicating the utility of their combination with opioids in the treatment of chronic pain. The antinociceptive effects of NMDA receptor antagonists and opioids could be predicted to be synergistic and the presence of an NMDA receptor antagonist should block both the development of chronic pain states and inhibit the development of tolerance to the analgesic effects of morphine.

(5) The involvement of peripheral NMDA receptors in inflammatory and visceral nociception offers a very attractive target for NMDA receptor antagonists that do not cross the blood brain barrier. Such agents might be predicted to be devoid of CNS side effects at doses producing powerful antinociception at peripheral NMDA receptors.

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