Biochemical Pharmacology, Vol. 56, pp. 553–559, 1998.

ISSN 0006-2952/98/$19.00 + 0.00
PII S0006-2952(98)00088-4

COMMENTARY

Opioid Analgesics as Noncompetitive *N*-Methyl-D-aspartate (NMDA) Antagonists

Bjarke Ebert,‡ Christian Thorkildsen,* Steen Andersen,† Lona L. Christrup* and Hans Hjeds**

*PharmaBiotec Research Center, Departments of Pharmacology, Medicinal Chemistry, and Pharmacy, The Royal Danish School of Pharmacy, DK-2100 Copenhagen; and †Pain Clinic, Department of Anesthesiology, Amtssygehuset Roskilde, Roskilde, Denmark

ABSTRACT. Much evidence points to the involvement of *N*-methyl-D-aspartate (NMDA) receptors in the development and maintainance of neuropathic pain. In neuropathic pain, there is generally involved a presumed opioid-insensitive component, which apparently can be blocked by NMDA receptor antagonists. However, in order to obtain complete analgesia, a combination of an NMDA receptor antagonist and an opioid receptor agonist is needed. Recent *in vitro* data have demonstrated that methadone, ketobemidone, and dextropropoxyphene, in addition to being opioid receptor agonists, also are weak noncompetitive NMDA receptor antagonists. Clinical anecdotes suggest that the NMDA receptor antagonism of these opioids may play a significant role in the pharmacological action of these compounds; however, no clinical studies have been conducted to support this issue. In the present commentary, we discuss evidence for the NMDA receptor antagonism of these compounds and its relevance for clinical pain treatment; an overview of structure–activity relationships for the relevant opioids as noncompetitive NMDA receptor antagonists also is given. It is concluded that although the finding that some opioids are weak noncompetitive NMDA receptor antagonists *in vitro* has created much attention among clinicians, no clinical studies have been conducted to evaluate the applicability of these compounds in the treatment of neuropathic pain conditions. BIOCHEM PHARMACOL **56**;5:553–559, 1998. © 1998 Elsevier Science Inc.

KEY WORDS. NMDA; pain; ketobemidone; methadone; A29; dextropropoxyphene; fentanyl

Strong opioids have been available for the last 2300 years. From the point of identification of morphine as one of the active ingredients in the opium poppy (*Papaver somniferum*), much focus has been directed towards the development of morphine-like substances devoid of the side-effects of morphine. Initially, more potent compounds were developed and subsequently, in the light of the identification of different opioid receptor subtypes, compounds with preference for one subtype over the others were synthesized and characterized. Based on *in vitro* test systems, these compounds were further developed into new drugs, which, despite the subtype selectivity, possessed most of the side-effects characteristic of morphine-like compounds. From an outside perspective, it may look as if most of the development of more potent and/or subtype-selective compounds has led primarily to drugs with significantly improved pharmacokinetic properties, but with little or no improvement in their pharmacodynamic profile. Hence, despite the development of compounds with up to 1000 times higher affinity for the μ opioid receptor subtype than morphine and a significantly increased μ receptor subtype selectivity, compared with morphine, most of these compounds still have the same side-effects and show a similar therapeutic window.

One explanation for this lack of pharmacodynamic improvement may be that, although the compounds are much more potent than morphine, they still exert their effect through interaction with the μ opioid receptor, the fundamental responsible receptor for both the positive and the negative effects of the opioids. This hypothesis is supported by the development of μ receptor knockout mice, where morphine is devoid of analgesic effects [1]. However, opioid analgesics with preference for κ or ∂ receptors still exert their analgesic action in the μ receptor knockout mice, underlying the importance of these receptor subtypes in the action of analgesics [1].

Another explanation may be that the *in vitro* determined subtype selectivity is an artificial constant resembling the *in vivo* situation only slightly. Most of the opioid analgesics that are accessible on the market possess an *in vitro* preference for the μ receptor, compared to the ∂ or κ receptors. However, the plasma concentrations obtained *in vivo* are, in most cases, of such a magnitude that some degree of activation of the other receptor subtypes should be expected, leading to a complex pharmacological re-

‡ Corresponding author: Bjarke Ebert, Ph.D., PharmaBiotec Research Center, Department of Pharmacology, The Royal Danish School of Pharmacy, 2-Universitetsparken, DK-2100 Copenhagen, Denmark. Tel. 45-3-537-0850, Ext. 380; FAX 45-3-537-4457; E-mail: bjarke@medchem.dfh.dk.

sponse. Strong evidence against this hypothesis are results where brain concentrations of morphine, for example, have been determined. These results confirm that brain concentrations are within the range where receptors, based on *in vitro* binding profiles, are activated [2, 3]. Furthermore, the pharmacological action of the opioid analgesics seems to be strongly dependent on the animal model used, and in which area the response is measured. An example of this is found in the results by Hill *et al.* [4] where the effect of a systemic dose of morphine was determined at the spinal cord level and at the thalamic level. A three times higher dose of morphine was needed to block nociceptive responses at the spinal cord level than at the thalamic level. An explanation for this observation may well be that a small reduction in response at the single synapse may add up during the transduction of the signal from the periphery to the brain, ultimately leading to a blockade of the response at the brain level, despite the very low concentration of morphine in the brain. Only a little work has been reported in this research area; consequently, a deeper understanding of the relationship between opioid concentrations, receptor occupancy at the different levels of the nociceptive pathways, and the analgesic action of opioids still remains elusive.

Selective opioid receptor agonists acting preferentially at the μ subtype of the opioid receptor complex are used as highly potent and effective analgesics in the clinic under severe pain conditions [5]. The molecular basis of opioid receptor-mediated analgesia is thought to be a combined presynaptic and postsynaptic hyperpolarization, resulting in a reduced release of an endogenous mediator(s), e.g. glutamate, and a reduced sensitivity to released mediators, respectively [6–8]. However, under certain conditions, the effectiveness of opioids is nil or much less than expected. Neuropathic pain occurring after amputation and/or after severe nerve injury has been shown to respond poorly to opioids [9]. The background of the reduced opioid responsiveness has been debated for years [5]. Some authors [10] have reported that it is possible to achieve sufficient pain relief with opioids in patients suffering from neuropathic pain, although an increased dose is needed, whereas others [11] find that even a high dose of opioids gives insufficient pain relief. The common denominator of neuropathic pain seems to involve an over-activation of the glutamate receptor subtype, termed the NMDA* receptor [12, 13]. Based on this hypothesis, several potent and selective noncompetitive NMDA antagonists have been investigated in animal models of neuropathic pain [5, 14–16]. Noncompetitive NMDA antagonists like MK-801 [17] are potent inhibitors of neuropathic pain in all animal models tested [18]; however, only a few have been exposed to clinical trials. The reasons for this are, first that severe psychotomimetic side-effects are observed in humans when high doses of the dissociative anaesthetics PCP and ketamine are applied, and, second, the finding that MK-801 in rats induces reversible cerebral vacualization after relatively short periods of treatment [19]. Quite interestingly, weaker noncompetitive NMDA receptor antagonists, like memantine, or more potent noncompetitive NMDA antagonists [20] do not seem to produce the severe side-effects observed of ketamine when administered intravenously. This suggests that either peak concentrations of potent noncompetitive NMDA antagonists are especially problematic or that the biotransformation of these compounds into weaker NMDA receptor ligands may prevent the severe side-effects [21, 22]. Thus far, no clinical data have confirmed the hypothesis that low-affinity NMDA receptor antagonists have significantly fewer side-effects than potent NMDA receptor antagonists, when given in equipotent doses; however, much attention has been drawn towards the development of low-affinity, noncompetitive NMDA receptor antagonists in order to avoid the severe side-effects observed from high-affinity MK-801-like compounds. Ketamine, which possesses a submicromolar affinity for the [^{3}H]MK-801-labelled binding site at the NMDA receptor complex [23], is, in subanaesthetic doses, an effective analgesic in neuropathic pain conditions [24], and recent data have suggested that the strong analgesic effect of ketamine, following oral administration, may be ascribed to the high affinity for the NMDA receptor of the main metabolite, norketamine [25].

Dextromethorphan, an antitussive with an affinity for the NMDA receptor similar to that of ketamine [26], has been tested as an analgesic in humans with only little effect [27], although tolerance to the analgesic morphine is reduced [28, 29]. Similar, nonconclusive data with the weak noncompetitive NMDA receptor antagonist memantine have been obtained in humans. Therefore, it is debatable whether low-affinity, noncompetitive NMDA receptor antagonists are able to reduce neuropathic pain in the clinical situation, whereas the potent noncompetitive NMDA receptor antagonist ketamine has been shown to work under both *in vitro* and *in vivo* conditions.

However, neuropathic pain is not only a question of NMDA receptor activation or poor opioid responsiveness. Much evidence points to neuropathic pain as a complex continuum of pains ranging from complete responsiveness to morphine to unresponsiveness to morphine. To provide adequate treatment of neuropathic pain, it is therefore most likely that a combination of opioid and noncompetitive NMDA receptor antagonists is of particular value. Even though several *in vitro* experiments seem to confirm the above-stated hypothesis [30, 31] or ultimatively any combination of hyperpolarizing drugs and noncompetitive NMDA receptor antagonists, the suggestion has yet to be confirmed in clinical trials.

To evaluate the concept of "poly receptor targeting" or "dirty drug pharmacology," it is necessary to conduct clinical trials either with mixtures of different pharmacological agents or with compounds that possess affinity for several different receptor populations. Whereas several

* *Abbreviations:* A29, (*RS*)-3-dimethylamino-1,1-diphenylbut-1-ene; MK-801, (*RS*)-5-methyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene-5,10-imine; NMDA, *N*-methyl-D-aspartate; and PCP, phencyclidine.

studies are now on the way to evaluating the significance of combining morphine and ketamine, for example, not many studies have been conducted with "dirty" pharmacological compounds. The reason for this may be the lack of understanding of the consequences of modulating several receptor systems at the same time or the unavailability of obvious test compounds.

KETOBEMIDONE

Ketobemidone has been used in Europe for the last 50 years [32]. Based on clinical experience and clinical anecdotes, our group has tried to rationalize the clinical practice in order to select compounds suitable for the evaluation of a combination of opioid receptor agonism and noncompetitive NMDA receptor antagonism. The first compound tested was the potent opioid receptor agonist ketobemidone. Clinical anecdotes described patients with opioid-resistant pain that obtained almost complete analgesia by switching to ketobemidone. By using [^{3}H]MK-801 binding and a functional assay, the rat cortical wedge preparation [33, 34], where a number of excitatory amino acid receptor ligands have been tested extensively, we were able to demonstrate that ketobemidone is indeed a weak noncompetitive NMDA receptor antagonist with an approximately 30-fold lower affinity for the NMDA receptor than ketamine (Fig. 1) [35]. It is questionable whether this very weak affinity for the NMDA receptor seen in comparison with a low nanomolar affinity for the μ opioid receptor [36] is more than an interesting finding. However, animal studies clearly demonstrated that in a wind-up model, an animal model equivalent to neuropathic pain, the NMDA receptor antagonist component of ketobemidone clearly was present and contributed to the pharmacological effect of ketobemidone, which was significantly different from that of morphine [37]. Furthermore, the effects of ketobemidone on neurophysiological parameters sensitive to morphine were similar to those of morphine, demonstrating that in systems primarily modulated by μ opioid receptors, the pharmacological profile of ketobemidone resembles that of a pure μ opioid receptor agonist [37]. Despite these very promising findings, it still remains to be demonstrated that the NMDA receptor antagonist activity of ketobemidone contributes to the clinical efficacy of this compound in humans.

Three other important aspects with respect to ketobemidone and other weak NMDA receptor antagonists still need to be addressed, despite the fact that some of these compounds have been available for more than 50 years.

Do any of the metabolites of ketobemidone exert actions at the NMDA receptor? In pharmacokinetic studies, it has been demonstrated that following oral administration, ketobemidone undergoes extensively first-pass metabolism to norketobemidone [38]. In preliminary studies, we have shown norketobemidone to be five times more potent than ketobemidone at NMDA receptors, suggesting that this metabolite may have clinical significance. However, little is known about the pharmakokinetics and pharmacodynamics of norketobemidone, so despite its presence in plasma, it is still questionable whether norketobemidone or any of the other metabolites plays a clinically significant role.

Are the concentrations obtained in different compartments of the body of such a magnitude that a reasonable level of NMDA receptor blockade may be expected? Based on the *in vitro* determined binding affinities and the *in vivo* optimal clinical concentrations of most of these compounds, only a marginal reduction in the NMDA response in the presence of the compounds may be expected. However, as in the case with opioids, it may well be that the neuronal network(s) responsible for the processing of pain from the periphery to the central nervous system only needs a very small inhibition at some of the "relay stations" in order to obtain a full blockade of the signal to the brain. Therefore, more research into the understanding of the relationship between the NMDA receptor blockade at different "relay stations" and the output of a neuronal circuit is needed.

Does the *in vivo* analgesic activity of the characterized weak noncompetitive NMDA receptor antagonists correlate with the activity determined *in vitro*? Much attention has been directed towards the development of NMDA receptor antagonists as novel drugs for the treatment of neuropathic pain, and the clinical activity of ketamine points towards the validity of this approach. However, ketamine, like most of the other compounds possessing an amino group and an aromatic group (Fig. 1), interacts with a number of neurotransmitter systems [39]. Therefore, if ketobemidone turns out to be an effective analgesic drug for the treatment of neuropathic pain, it may well be that either the sum of different receptor actions is the key point for the clinical effect or that none of the determined affinities of ketobemidone is responsible for this analgesic action and that a thus far unidentified receptor subtype may play an important role. This situation seems to have been the case with respect to the tricyclic antidepressants of the imipramine and amitriptyline type. Amitriptyline is a noradrenaline/serotonin uptake inhibitor [40] and a noncompetitive NMDA receptor antagonist [41]. Clinical studies have shown that amitriptyline is active against neuropathic pain [42]. Based on these findings it was initially hypothesized that the effect at noradrenaline/serotonin uptake systems was responsible for the analgesic action [43]. However, with the development of selective noradrenergic and serotonin uptake inhibitors, devoid of NMDA receptor affinities, the neuropathic analgesic effects vanished. Amitriptyline is at present thought to exert its analgesic action via the NMDA receptor [43]; however, this has not been proven clinically.

At present, ketobemidone is available exclusively in Scandinavia, either alone or in combination with the cholinergic antagonist A29 [44]. The combination of A29 and ketobemidone has long been questioned in light of the finding that cholinergic antagonists, in general, do not exert analgesic actions. However, after the introduction of

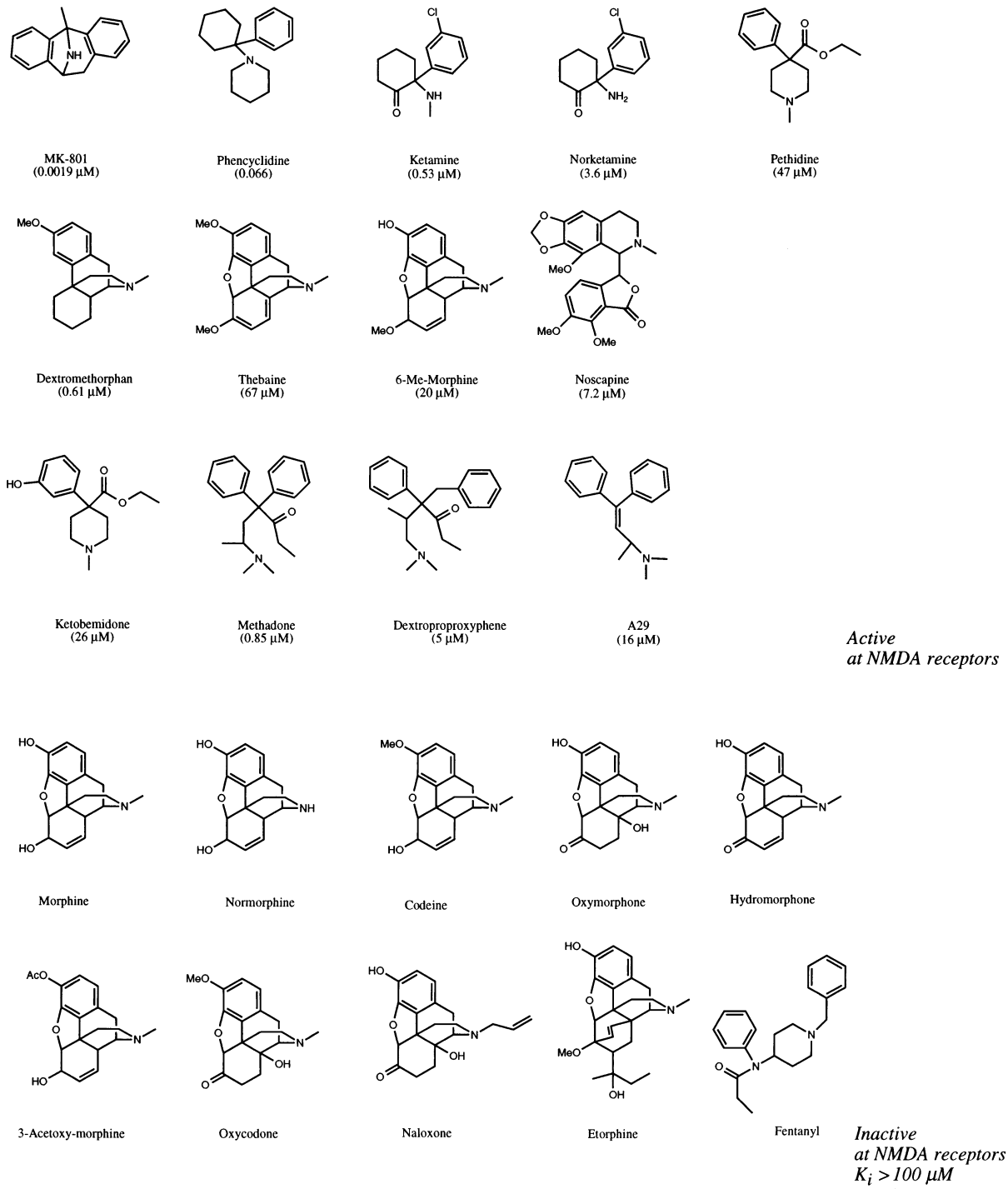

FIG. 1. Structures of a series of opioids and their K_i values determined by evaluating their affinity in [^{3}H]MK-801 binding assays as previously described [26].

pure ketobemidone, reports of the need to increase the dose of pure ketobemidone, as compared with the mixture, indicated that A29 under certain circumstances may have an analgesic action. We recently disclosed that A29, in addition to being a cholinergic antagonist, is also a non-competitive NMDA receptor antagonist, equipotent with ketobemidone [45], which may explain, in part, some of the clinical experience with the comparison of ketobemidone plus or minus A29. However, as in the case of ketobemidone, little is known about the pharmacokinetics of A29, so it is too premature to use A29 as a "novel" noncompetitive NMDA receptor antagonist. Furthermore, A29 is extensively metabolized in the liver to nor-A29 [38], which our preliminary studies suggest also is a noncompetitive NMDA receptor antagonist. Knowledge concerning the pharmacodynamic properties of ketobemidone and A29 is, therefore,

sparse, and it still remains to be demonstrated that ketobemidone, alone or in combination with A29, exerts clinical relevant NMDA receptor antagonism *in vivo*. However, such clinical studies are now underway.

METHADONE

Methadone, which is a synthetic μ opioid receptor agonist with an affinity for the μ receptor comparable to that of morphine [46], is used mainly for the treatment of drug addicts and, to a much lesser extent, as an analgesic. The reason for this is mainly that methadone has a highly variable biological bioavailability and a long and variable biological half-life, making it an optimal treatment for patients suffering from more complicated pain. When comparing the chemical structure of methadone with that of A29 (Fig. 1), the similarity is striking, and the characterization of methadone in binding assays and functional assays showed the compound to be a potent noncompetitive NMDA receptor antagonist with an affinity for the MK-801 binding site of approximately 1 μM, equal to that of ketamine [35]. *In vitro* studies of the enantiomers have shown both enantiomers to possess noncompetitive NMDA receptor antagonist affinity [47]. Again, it still remains to be demonstrated that the NMDA antagonist activity of methadone contributes to its clinical efficacy. However, as studies with opioid dependency have shown that the withdrawal symptoms are much less pronounced when opioid agonists are combined with noncompetitive NMDA receptor antagonists [29, 48], it can be speculated that the use of methadone in the treatment of drug addicts may depend, to some degree, on the noncompetitive NMDA receptor antagonism. As in the case of ketobemidone, when given orally, methadone is metabolized extensively to normethadone, which spontaneously cyclizes to 2-ethylidine-1,5-dimethyl-3,3-diphenylpyrrolidine [49]. The pharmacological profile of this metabolite has yet to be described.

DEXTROPROPOXYPHENE

Dextropropoxyphene is a weak opioid receptor agonist, which during the last 40 years has been used for the treatment of pain. The potency of dextropropoxyphene is much lower than that of morphine and codeine, reflecting a low affinity for the μ opioid receptor. Structurally, dextropropoxyphene is very similar to methadone (Fig. 1), suggesting that dextropropoxyphene may act as a noncompetitive NMDA receptor agonist. *In vitro* studies subsequently have shown that dextropropoxyphene is a noncompetitive NMDA receptor antagonist with an affinity of 5 μM, which is approximately five times weaker than that of methadone [50]. It still remains to be demonstrated in clinical studies that the NMDA receptor antagonism of dextropropoxyphene plays an important role for clinical efficacy.

STRUCTURE–ACTIVITY RELATIONSHIPS FOR MORPHINE-LIKE OPIOIDS

To further determine which structural characteristics are essential for the interaction of opioids with the NMDA receptor, we characterized a series of commercially available opioids with respect to their affinity for the [^{3}H]MK-801-labelled NMDA receptor complex and in the rat cortical wedge preparation. As illustrated in Fig. 1, where the compounds are grouped according to the affinity determined in [^{3}H]MK-801 binding, the presence of any polar group in or close to the 6 position of the ring system seems to prevent NMDA receptor affinity, whereas protection of the 6-hydroxy group (as in thebaine and 6-Me-morphine) or the absence of polar groups (dextromethorphan) facilitates the binding to the MK-801 binding site. Noscapine, an antitussive that is a weak opioid receptor agonist, too, is a weak noncompetitive NMDA receptor antagonist, reflecting that the key structural determinants for MK-801 affinity are an amino group and an aromatic group. This structure–activity relationship is very similar to the relationship seen for MK-801-like ligands, where introduction of hydrophilic substituents into the MK-801 structure reduces binding affinity significantly [51, 52]. As shown in Fig. 1, when tested in [^{3}H]MK-801 binding, the affinity of the active compounds is in the mid-micromolar range, underlining that the compounds are weak antagonists at the NMDA receptor. An earlier study by Choi and Viseskul [53] showed that most opioids, including fentanyl, are able to protect cultured neurones against NMDA-mediated neurotoxicity in a naloxone-independent manner. As fentanyl does not inhibit [^{3}H]MK-801 binding as well as NMDA responses in the rat cortical wedge preparation (Fig. 1), these findings may reflect that different mechanisms may take place during prolonged NMDA exposure in the cultured neurones and the relatively short exposure to NMDA in the rat cortical wedge preparation.

CONCLUSION

Although the finding that some opioids are weak noncompetitive NMDA receptor antagonists *in vitro* has created much attention among clinicians, no clinical studies have evaluated the applicability of these compounds in the treatment of neuropathic pain conditions. The present knowledge about the action of these compounds with respect to NMDA receptors *in vivo* is so sparse that much basic research is still needed.

This work was supported by the Lundbeck Foundation. We wish to thank Dr. R. G. Hill, MSD Neuroscience Research Centre, Terlings Park, U.K., for very constructive suggestions.

References

1. Matthes HWD, Maldonado R, Simonin F, Valverde O, Slowe S, Kitchen I, Befort K, Dierich A, Le Meur M, Dollé P, Tzavara E, Hanoune J, Roques BP and Kieffer BL, Loss of

morphine-induced analgesia, reward effect and withdrawal symptoms in mice lacking the μ-opioid-receptor gene. *Nature* **383:** 819–823, 1996.
2. Matos FF, Rollema H, Taiwo YO, Levine JD and Basbaum AI, Relationship between analgesia and extracellular morphine in brain and spinal cord in awake rats. *Brain Res* **693:** 187–195, 1995.
3. D'Honneur G, Gilton A, Sandouk P, Scherrmann JM and Duvaldestin P, Plasma and cerebrospinal fluid concentrations of morphine and morphine glucoronides after oral morphine. The influence of renal failure. *Anesthiology* **81:** 87–93, 1994.
4. Hill RG, Salt TE and Pepper CM, A comparison of the effectiveness of intravenous morphine at attenuating the nociceptive responses of medullary dorsal horn and thalamic neurones. *Life Sci* **31:** 2331–2334, 1982.
5. Dickenson AH, Neurophysiology of opioid poorly responsive pain. *Cancer Surv* **21:** 5–16, 1994.
6. Duggan AW and North RA, Electrophysiology of opiates. *Pharmacol Rev* **35:** 219–281, 1984.
7. McFadzean J, The ionic mechanisms underlying opioid actions. *Neuropeptides* **11:** 173–180, 1988.
8. North RA, Drug receptors and the inhibition of nerve cells. *Br J Pharmacol* **98:** 13–28, 1989.
9. Arner S and Meyerson BA, Lack of analgesic effect of opiates on neuropathic and idiopathic forms of pain. *Pain* **33:** 11–23, 1988.
10. Portenoy RK, Foley KM and Inturrisi CE, The nature of opioid responsiveness and its implications for neuropathic pain: New hypotheses derived from studies of opioid infusions. *Pain* **43:** 273–286, 1990.
11. Jadad AR, Carroll D, Glynn CJ, Moore RA and McQuay HJ, Morphine responsiveness of chronic pain: Double-blind randomised crossover study with patient-controlled analgesia. *Lancet* **339:** 1367–1371, 1992.
12. Haley JE, Sullivan AF and Dickenson AH, Evidence for spinal *N*-methyl-D-aspartate receptor involvement in prolonged chemical nociception in the rat. *Brain Res* **518:** 218–226, 1990.
13. Dickenson AH and Sullivan AF, Evidence for a role of the NMDA receptor in the frequency dependent potentiation of deep rat dorsal horn nociceptive neurones following C fibre stimulation. *Neuropharmacology* **26:** 1235–1238, 1987.
14. Coderre TJ and Van Empel I, The utility of excitatory amino acid antagonists as analgesic agents. II. Assessment of antinociceptive activity of combinations of competitive and noncompetitive NMDA antagonists with agents acting at allosteric glycine and polyamine receptor sites. *Pain* **59:** 353–360, 1994.
15. Coderre TJ and Van Empel I, The utility of excitatory amino acid antagonists as analgesic agents. I. Comparison of antinociceptive activity of various classes of EAA antagonists in mechanical, thermal and chemical nociceptive tests. *Pain* **59:** 345–352, 1994.
16. Coderre TJ, Katz J, Vaccarino AL and Meezack R, Contribution of central neuroplasticity to pathological pain: Review of clinical and experimental evidence. *Pain* **52:** 259–285, 1993.
17. Wong EHF, Kemp JA, Priestly T, Knight AR, Woodruff GN and Iversen LL, The anticonvulsant MK-801 is a potent *N*-methyl-D-aspartate antagonist. *Proc Natl Acad Sci USA* **83:** 7104–7108, 1986.
18. Mao J, Price DD, Mayer DJ, Lu J and Hayes RL, Intrathecal MK-801 and local nerve anesthesia synergistically reduce nociceptive behaviours in rats with experimental peripheral mononeuropathy. *Brain Res* **576:** 254–262, 1992.
19. Olney JW, Labruyere J and Price MT, Pathological changes induced in cerebrocortical neurons by phencyclidine and related drugs. *Science* **244:** 1360–1362, 1989.
20. Tortella FC, Pellicano M and Bowery NG, Dextromethorphan and neuromodulation: Old drug coughs up new activities. *Trends Pharmacol Sci* **10:** 501–507, 1989.
21. Kharasch ED and Labroo R, Metabolism of ketamine stereoisomers by human liver microsomes. *Anesthesiology* **77:** 1201–1207, 1992.
22. Grant IS, Nimmo WS and Clements JA, Pharmacokinetics and analgesic effects of i.m. and oral ketamine. *Br J Anaesth* **53:** 805–810, 1981.
23. Martin D and Lodge D, Ketamine acts as a noncompetitive *N*-methyl-D-aspartate antagonist on frog spinal cord *in vitro*. *Neuropharmacology* **10:** 999–1003, 1985.
24. Reich DL and Silvay G, Ketamine: An update on the first twenty-five years of clinical experience. *Can J Anaesth* **36:** 186–197, 1989.
25. Ebert B, Mikkelsen S, Thorkildsen C and Borgbjerg FM, Norketamine, the main metabolite of ketamine, is a noncompetitive NMDA receptor antagonist in the rat cortex and spinal cord. *Eur J Pharmacol* **333:** 99–104, 1997.
26. Ebert B, Wong EHF and Krogsgaard-Larsen P, Identification of a novel NMDA receptor in rat cerebellum. *Eur J Pharmacol Mol Pharmacol* **208:** 49–52, 1991.
27. McQuay HJ, Carroll D, Jadad AR, Glynn CJ, Jack T, Moore RA and Wiffeh PJ, Dextromethorphan for the treatment of neuropathic pain: A double-blind randomised controlled crossover trial with integral n-of-1 design. *Pain* **59:** 127–133, 1994.
28. Price DD, Mao J, Frenk H and Mayer DJ, The *N*-methyl-D-aspartate receptor antagonist dextromethorphan selectively reduces temporal summation of second pain in man. *Pain* **59:** 165–174, 1994.
29. Elliot K, Hynansky A and Inturrisi CE, Dextromethorphan attenuates and reverses analgesic tolerance to morphine. *Pain* **59:** 361–368, 1994.
30. Ren K, Wind-up and the NMDA receptor: From animal studies to humans. *Pain* **59:** 157–158, 1994.
31. Chapman V and Dickenson AH, The combination of NMDA antagonism and morphine produces profound antinociception in the rat dorsal horn. *Brain Res* **573:** 321–323, 1992.
32. Petersen PV, Studies on a new spasmolytic compound 1,1-diphenyl-3-demethylaminobutene-1 (A29) and a potent analgesic, ketobemidone (A21). *Acta Pharmacol Toxicol* **7:** 51–64, 1951.
33. Harrison NL and Simmonds MA, Quantitative studies on some antagonists of *N*-methyl-D-aspartate in slices of rat cerebral cortex. *Br J Pharmacol* **84:** 381–391, 1985.
34. Wheatley PL, A simple method for recording excitatory amino acid evoked depolarizations of rat cortex *in vitro*. *Br J Pharmacol* **87:** 159P, 1986.
35. Ebert B, Andersen S and Krogsgaard-Larsen P, Ketobemidone, methadone and pethidine are noncompetitive NMDA antagonists in the rat cortex and spinal cord. *Neurosci Lett* **187:** 165–168, 1995.
36. Christensen CB, The opioid receptor binding profile of ketobemidone and morphine. *Pharmacol Toxicol* **73:** 344–345, 1993.
37. Andersen S, Dickenson AH, Kohn M, Reeve A, Rahman W and Ebert B, The opioid ketobemidone has a NMDA blocking effect. *Pain* **67:** 369–374, 1996.
38. Anderson P, Arnér S, Bondesson U, Boréus LO and Hartvig P, Single-dose kinetics and bioavailability of ketobemidone. *Acta Anaesthesiol Scand Suppl* **74:** 59–62, 1982.
39. Husveith O, Maurset A and Øye I, Interaction of chiral forms of ketamine with opioid, phencyclidine, σ and muscarinic receptors. *Pharmacol Toxicol* **77:** 355–359, 1995.
40. Hall H and Ogren SO, Effects of antidepressant drugs on different receptors in the brain. *Eur J Pharmacol* **70:** 393–407, 1981.
41. Reynolds IJ and Miller RJ, Tricyclic antidepressants block

N-methyl-D-aspartate receptors: Similarities to the action of zinc. *Br J Pharmacol* **95:** 95–102, 1988.
42. Eisenach JC and Gebhart GF, Intrathecal amitriptyline acts as an *N*-methyl-D-aspartate receptor antagonist in the presence of inflammatory hyperalgesia in rats. *Anesthesiology* **83:** 1046–1054, 1995.
43. Onghena P and Van Houdenhove B, Antidepressant-induced analgesia in chronic non-maligant pain: A meta-analysis of 39 placebo-controlled studies. *Pain* **49:** 205–219, 1992.
44. Larsen JJ and Christensen AV, The antinociceptive effect of ketobemidone in comparison with Ketogin®. *Acta Pharmacol Toxicol* **52:** 100–104, 1983.
45. Ebert B, Thorkildsen C and Andersen S, Ketobemidone plus (*RS*)-3-dimethylamino-1,1-diphenylbut-1-ene (A29) is more potent at NMDA receptors than ketobemidone alone; evidence for A29 as a noncompetitive NMDA receptor antagonist. *Pharmacol Toxicol* **82:** 157–160, 1998.
46. Kristensen K, Christensen CB and Christrup LL, The mu_1, mu_2, delta, kappa opioid receptor binding profiles of methadone stereoisomers and morphine. *Life Sci* **56:** PL45–PL50, 1994.
47. Gorman AL, Elliott KJ and Inturrisi CE, The *d*- and *l*-isomers of methadone bind to the noncompetitive site on the *N*-methyl-D-aspartate (NMDA) receptor in rat forebrain and spinal cord. *Neurosci Lett* **223:** 5–8, 1997.
48. Bilsky EJ, Inturrisi CE, Sadée W, Hruby VJ and Porreca F, Competitive and noncompetitive NMDA antagonists block the development of antinociceptive tolerance to morphine, but not to selective mu or delta opioid agonists in mice. *Pain* **68:** 229–237, 1996.
49. Beckett AH, Taylor JF, Casy AF and Hassan MM, The biotransformation of methadone in man: Synthesis and identification of a major metabolite. *Pharm Pharmacol* **20:** 754–762, 1968.
50. Ebert B, Andersen S, Hjeds H and Dickenson AH, Dextropropoxyphene acts as a noncompetitive NMDA antagonist. *Pain Symptom Management* **15:** 269–274, 1998.
51. Lyle TA, Magill CA, Britcher SF, Denny GH, Thompson WJ, Murphy JS, Knight AR, Kemp JA, Marshall GR, Middlemiss DN, Wong EHF and Anderson PS, Structure and activity of hydrogenated derivatives (+)-5-methyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine (MK-801). *J Med Chem* **33:** 1047–1052, 1990.
52. Thompson WJ, Anderson PS, Britcher SF, Lyle TA, Thies JE, Magill CA, Varga SL, Schwering JE, Lyle PA, Christy ME, Evans BE, Colton MD, Holloway MK, Springer JP, Hirshfield JM, Ball RG, Amato JS, Larsen RD, Wong EHF, Kemp JA, Tricklebank MD, Singh L, Oles R, Priestly T, Marshall GR, Knight AR, Middlemiss DN, Woodruff GN and Iversen LL, Synthesis and pharmacological evaluation of a series of dibenzo[*a*,*d*]cycloalkenimines as *N*-methyl-D-aspartate antagonists. *J Med Chem* **33:** 789–808, 1990.
53. Choi DW and Viseskul V, Opioids and non-opioid enantiomers selectively attenuate *N*-methyl-D-aspartate neurotoxicity in cortical neurones. *Eur J Pharmacol* **155:** 27–35, 1988.