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Review

Opiate physical dependence and *N*-methyl-D-aspartate receptors

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Abstract

The present review focused the involvement of *N*-methyl-D-aspartate (NMDA) receptors in morphine physical dependence. The increased levels of extracellular glutamate, NMDA receptor ζ subunit (NR1) mRNA, NMDA receptor ε1 subunit (NR2A) protein, phosphorylated Ca^{2+}/calmodulin kinase II (p-CaMKII) protein, c-fos mRNA, c-Fos protein, are observed in the specific brain areas of mice and/or rats showing signs of naloxone-precipitated withdrawal. In preclinical and clinical studies, a variety of NMDA receptor antagonists and pretreatment with an antisense oligonucleotide of the NR1 have been reported to inhibit the development, expression and/or maintenance of opiate physical dependence. In contrast to data obtained in adult animals, NMDA receptor antagonists are neither effective in blocking the development of opiate dependence nor the expression of opiate withdrawal in neonatal rats. In the NMDA receptor-deficient mice, the NR2A knockout mice show the marked loss of typical withdrawal abstinence behaviors precipitated by naloxone. The rescue of NR2A protein by electroporation into the nucleus accumbens of NR2A knockout mice reverses the loss of abstinence behaviors. The activation of CaMKII and increased expression of c-Fos protein in the brain of animals with naloxone-precipitated withdrawal syndrome are prevented by NMDA receptor antagonists, whereas the increased levels of extracellular glutamate are not prevented by them. These findings indicate that glutamatergic neurotransmission at the NMDA receptor site contributes to the development, expression and maintenance of opiate dependence, and suggest that NMDA receptor antagonists may be a useful adjunct in the treatment of opiate dependence.

Keywords: Opiate; Physical dependence; *N*-methyl-D-aspartate (NMDA) receptor; Signal cascade; Ontogeny

Contents

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1. Introduction

Abstinence from the chronic administration of opiates like morphine results in a characteristic morbidity including anxiety, nausea, insomnia, hot and cold flashes, muscle aches, perspiration and diarrhea. Such symptoms may pose clinical problems in the management of patients with pain that require prolonged treatment with opiates (Bisaga et al., 2001). It is of clinical importance to determine the mechanisms underlying physical dependence and to develop medications that can prevent the development of dependence or to reverse existing dependence. In humans, physical dependence can be assessed by observing the emergence of a withdrawal syndrome following discontinuation of chronic opiate administration or the administration of a competitive opiate antagonist such as naloxone (Bisaga et al., 2001; Wikler et al., 1953). Treatment with opiate antagonists can be used to probe the degree of underlying dependence (Wang et al., 1974), and can serve as a model to evaluate novel medications to treat the withdrawal syndrome from opiates (e.g., Bisaga et al., 2001; Rosen et al., 1996a). The neurophysiology underlying opiate withdrawal symptoms is not completely understood. Several neurotransmitter systems, including the dopaminergic (Harris and Aston-Jones, 1994; Pothos et al., 1991), cholinergic (Bristow et al., 1997; Buccafusco, 1991, 1992; Rada et al., 1991; Tjon Tien Ril et al., 1993), noradrenergic (see, for review, Maldonado, 1997; Van Bockstaele et al., 2001), and glutamatergic (see, for review, Rasmussen, 1995; Siggins et al., 2003; Trujillo, 2000; Zhu and Barr, 2001a; Zhu et al., 1998), have been shown to play an important role in opiate withdrawal.

Glutamate is the major excitatory neurotransmitter in the central nervous systems, and glutamate receptors have been divided into *N*-methyl-D-aspartate (NMDA) and non-NMDA receptors based on their pharmacological and physiological properties. The NMDA receptors have a well-established role in neuronal plasticity (e.g., LTP) (Ozawa et al., 1998) and are also involved in opiate-related neural plasticity. In fact, there are several evidences to indicate that the NMDA receptors play a key role in opiate tolerance, dependence and withdrawal (Herman et al., 1995; Inturrisi, 1997; Mao, 1999; Mayer et al., 1999; Trujillo, 1999; Zhu and Barr, 2001b). Specifically, the opiate systems interact with NMDA receptors such that activation of the μ-opiate receptor results in Ca^{2+} influx through the NMDA receptor ion-channel complex. The subsequent activation of various Ca^{2+}-dependent second messenger system cascades, such as the activation of Ca^{2+}/calmodulin-dependent kinase (Fan et al., 1999; Hamdy et al., 2004; Liang et al., 2004; Lou et al., 1999; Lu et al., 2000) and extracellular signal-regulated protein kinase (Ren et al., 2004; Schulz and Hollt, 1998), plays a central role in these phenomena. In this review, we focused the glutamatergic systems and summarized recent evidence from several investigators demonstrating that NMDA receptors are involved in opiate physical dependence.

2. NMDA receptor antagonists

2.1. Pharmacological events

There are several evidences on the ability of NMDA receptor antagonists to inhibit the *development*, *expression* and *maintenance* of opiate physical dependence. All non-competitive NMDA receptor antagonists such as ketamine, dextromethorphan, (+)-5-methyl-10,11-dihydro-5H-dibenzo[*a*,*d*]cyclohepten-5,10-imine (MK-801; dizocilpine) and memantine attenuate the expression of withdrawal syndrome (including jumping, teeth-chattering, diarrhea, ptosis, etc.) in morphine-dependent mice (Cappendijk et al., 1993; Tanganelli et al., 1991), rats (Koyuncuoglu et al., 1990, 1992; Rasmussen et al., 1991; Tokuyama et al., 1996) and guinea pigs (Tanganelli et al., 1991) when administered immediately before naloxone-precipitated morphine withdrawal. Dizocilpine also attenuates the withdrawal from butorphanol (Tokuyama et al., 1996). (+)-6-Phosphonomethyl-decahydroisoquinoline-3-carboxylic acid (LY-274614) (Rasmussen et al., 1991) and DL-(*E*)-2-amino-4-methyl-5-phosphono-pentanoate carboxy-ethyl-ester (CGP39551) (Gonzalez et al., 1997), competitive NMDA receptor antagonists, also block naloxone-precipitated morphine withdrawal in morphine-dependent rats and mice, respectively. Further, 5,7-dichloro-kynurenic acid (5,7-DCKA), a glycine site antagonist on NMDA receptors, has been reported to inhibit escape jumping behavior precipitated by naloxone in morphine-dependent mice (Cappendijk et al., 1993).

Furthermore, the treatment with NMDA receptor antagonists has been shown to prevent the development of opiate dependence. All NMDA receptor antagonists prevent naloxone-precipitated withdrawal syndrome when co-administered morphine during the development of physical dependence (e.g., Bespalov et al., 1999; Higgins et al., 1992; Rasmussen et al., 1991; Trujillo, 2000; Trujillo and Akil, 1991). In our recent study (Hamdy et al., 2004), co-administration of dizocilpine and morphine prevented the development of morphine physical dependence, evidenced by a significant reduction of withdrawal syndrome consistent with several previous findings. It is unlikely that the effect of dizocilpine is due to acute interaction between dizocilpine and morphine or naloxone on the day of withdrawal, since acute injection of dizocilpine before morphine or naloxone does not modify withdrawal behavioral manifestations in chronic morphine-treated mice. These findings suggest that chronic co-administration of dizocilpine and morphine attenuates the development of morphine dependence without affecting the acute effects of morphine (Hamdy et al., 2004).

As described above, several studies have found that NMDA receptor antagonists inhibit the expression and development of opiate physical dependence. Trujillo and Akil (1993, 1995) have demonstrated that doses required to inhibit the expression of physical dependence are typically greater than those required to inhibit the development of

such phenomenon (Trujillo, 1995, 2000). Further, Gonzalez et al. (1997), who examined the dose responses of dizocilpine, ketamine and CGP 39551 on the development and expression of morphine dependence, have found that doses of dizocilpine necessary to inhibit the expression of withdrawal are considerably greater than those necessary to prevent the development of physical dependence. Because doses of NMDA receptor antagonists required to inhibit the expression of opiate physical dependence are often high enough to produce significant locomotor effects, it is suggested that this may be due to non-specific behavioral competition (Bläsig et al., 1973), rather than a specific inhibition of the neuronal mechanisms underlying withdrawal (Trujillo, 1995, 2000; Trujillo and Akil, 1993, 1995). On the other hand, some studies have shown inhibition of the expression of certain aspects of withdrawal at relatively low doses of NMDA receptor antagonists (Higgins et al., 1992; Popik and Danysz, 1997; Popik and Skolnick, 1996; Popik et al., 1998). These results suggest that NMDA receptors have a role in the development of opiate physical dependence, as well as in certain aspects of the expression of physical dependence.

Once established, physical dependence persists even though opiate agonists are no longer present. Popik and Skolnick (1996) have firstly reported the ability of memantine to block the maintenance of morphine physical dependence. The morphine physical dependence was present 3 days after cessation of morphine administration. Repeated treatment with memantine during a 3-day morphine-free period abolished naloxone-precipitated jumping. In contrast, when administered concurrently with morphine after dependence had already been well established, memantine failed to affect the maintenance of morphine dependence. Based on these findings, NMDA receptor antagonists appear to inhibit the maintenance of opiate dependence, an action distinct from their acute inhibitory effects on the expression of physical dependence. This line of evidence suggests that the development and persistence of neuroadaptations that underlie opiate dependence may rely on NMDA-receptor-mediated neurotransmission. We cannot adequately explain the ability of NMDA receptor antagonists to affect the maintenance of opiate dependence, although NMDA receptor antagonists, like memantine, may be beneficial in the treatment of the maintenance, as well as expression/development, of opiate dependence.

2.2. Signal cascade

The mechanisms underlying the inhibitory effects of NMDA receptor antagonists on the opiate physical dependence are not clear. Chronic opiate treatment causes adaptive increases in Ca^{2+} accumulation and an increase in the expression of CaMKII protein (Lou et al., 1999). The increase in Ca^{2+} activates CaMKII (Sheng et al., 1991). CaMKII has an important role in the phosphorylation of cyclic AMP response element binding protein (CREB), and the phosphorylation of CREB produces an increase in its activity, which leads to an increase in c-fos mRNA expression (Sheng et al., 1991). Gene expression is thought to play an important role in many forms of neuronal plasticity. The severity of morphine dependence is related to the extent of morphine use, and withdrawal symptoms persist long after elimination (Eddy et al., 1965; Jaffe, 1990). Such long-lasting behavioral modifications hint of plastic changes within the nervous system, some of which may be partially mediated by the regulation of gene expression (Graybiel et al., 1990; Nestler et al., 1993). Expression of c-fos mRNA (Beckmann et al., 1995; Rasmussen, 1995; Ren et al., 2004) and c-Fos protein (Hamdy et al., 2000; Stornetta et al., 1993) is increased in several brain regions of morphine-withdrawal animals. The glutamatergic systems have been reported to be able to modulate the expression of c-fos mRNA as morphine-withdrawal signs (Rasmussen, 1995.). We have recently reported that the Ca^{2+}/calmodulin-dependent signal pathway is involved in the dizocilpine-mediated attenuation of withdrawal syndrome and c-Fos protein expression (Hamdy et al., 2004). We have found an increase in the levels of phosphorylated CaMKII and c-Fos protein in the cingulate cortex. The activation of CaMKII and increased expression of c-Fos protein after naloxone-precipitated withdrawal in the cingulate cortex are inhibited by repeated co-administration of dizocilpine and morphine. Activation of NMDA receptors leads to the opening of receptor-gated ion channels, which allows Ca^{2+} to enter the neuron, where it participates in numerous processes, including the activation of protein kinases (Wroblewski and Danysz, 1989). Dizocilpine is a non-competitive receptor antagonist that acts by blocking the ion channel (Wong et al., 1986). According to these findings, we have speculated that the chronic co-administration of dizocilpine and morphine inhibits morphine-induced Ca^{2+} participation in neurons. This inhibits the activation of CaMKII responsible for the phosphorylation of CREB. These findings support that chronic co-administration of dizocilpine and morphine, at least in part, through inhibition of CaMKII in the cingulate cortex, can attenuate the development of morphine dependence and c-Fos protein expression induced by naloxone-challenge (Fig. 1). However, further study should be carried out to clarify other molecular mechanisms (such as cyclic AMP and/or extracellular signal-regulated protein kinase signaling cascades) through the NMDA receptors.

2.3. Others

Neurochemical studies using in vivo microdialysis method have shown an elevated extracellular glutamate levels within the locus coeruleus during naloxone-precipitated morphine- (Aghajanian et al., 1994; Tokuyama et al., 1996; Zhang et al., 1994) and butorphanol-withdrawal syndrome (Feng et al., 1995). Direct neurochemical evidences have shown that intracerebroventricular

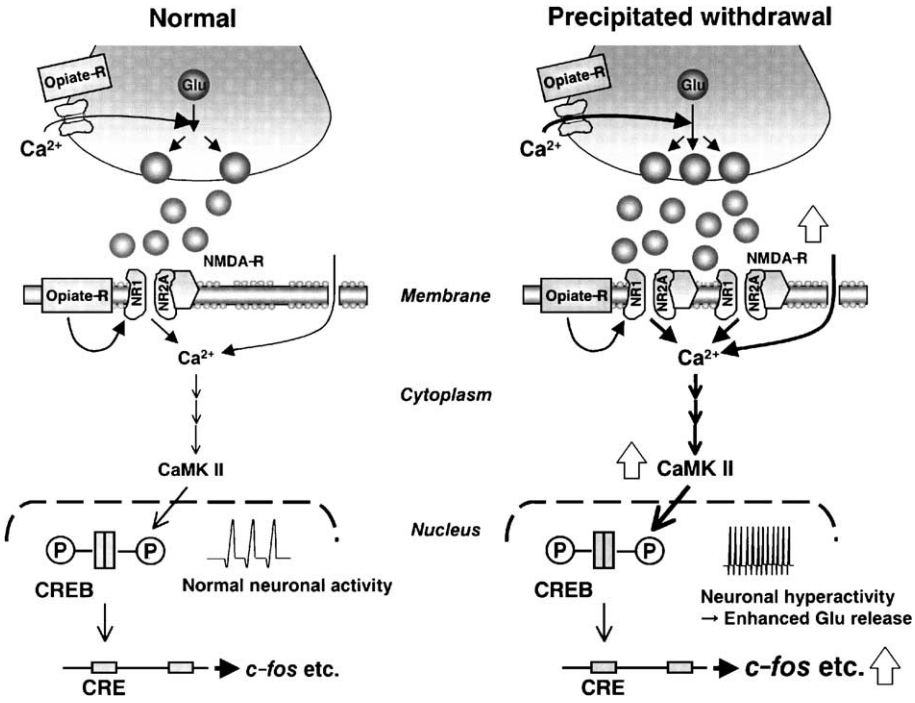

Fig. 1. Dynamic roles of NMDA receptors in opiate withdrawal. Chronic opiate exposure could lead to the activation of NMDA receptors. Ca^{2+} influx through the NMDA receptor ion-channel is the major trigger responsible for subsequent biochemical cascades that follow exposure to opiates. Glu: glutamate; Opiate-R: opiate receptors; NMDA-R: *N*-methyl-D-aspartate receptors; NR1: NMDA receptor ζ subunit; NR2A: NMDA receptor ε1 subunit; CaMKII: Ca^{2+}/calmodulin kinase II; CREB: cyclic AMP response element binding protein; CRE: CREB binding protein; ⇧ increase/facilitation.

(Tokuyama et al., 1996) or locus coeruleus (Tokuyama et al., 1998) injection of glutamate induces withdrawal syndrome in morphine- or butorphanol-dependent animals, suggesting the importance of glutamate in the locus coeruleus for the expression of withdrawal syndrome from opiates. Although dizocilpine prevents the withdrawal syndrome, it fails to block the elevation of glutamate in the locus coeruleus (Tokuyama et al., 2001). These results suggest the expression of opiate withdrawal induced by an expeditious release of glutamate might be mainly mediated by the postsynaptic NMDA receptors in the locus coeruleus region of opiate-dependent animals (Tokuyama et al., 2001).

3. NMDA receptor subunits

Recent studies have revealed the molecular and functional diversity of the NMDA receptor subunits, which are classified into the NMDA receptor ζ subunit (NR1) and ε subunit (NR2) families according to amino acid sequence homology (Kutsuwada et al., 1992; Meguro et al., 1992; Monyer et al., 1992). In situ hybridization and immunocytochemical studies have shown that the NR1 subunit is ubiquitously expressed in the brain (see, for review, Dunah et al., 1999; McBain and Mayer, 1994), whereas NR2 subunits show a more specific spatial expression. In adult rats, thus, NR2A and NR2B subunits are preferentially located in the forebrain, whereas NR2C is mostly expressed in the cerebellum, and NR2D in the brain stem and spinal cord. The vast majority of accumbens medium spiny neurons express NR2A and NR2B subunits, with a clear predominance for the latter (Chen and Reiner, 1996; Landwehrmeyer et al., 1995; Standaert et al., 1996).

It has been demonstrated that the NR1 subunit of the NMDA receptor is involved in the development of morphine dependence. Zhu et al. (1999) have reported that using in situ hybridization techniques, the expression of the NR1 subunit mRNA is increased in the locus coeruleus and the hypothalamic paraventricular nucleus, but not in the frontal cortex, caudate-putamen, nucleus accumbens, amygdale, CA1, CA2 and the dentate gyrus of the hippocampus, following 3 days of intracerebroventricular morphine infusion, whereas the expression of NR2A and NR2B subunit mRNAs does not change after morphine treatment in any brain regions. They have also found that the pretreatment with an antisense oligonucleotide corresponding to nucleotides 4–21 of the NMDA receptor NR1 subunit attenuates the morphine-withdrawal syndrome including escape behaviors, rearing, stretching, teeth chattering, vocalization and penis licking (Zhu and Ho, 1998).

On the other hand, knockout animals studied by using a gene-targeting recombination technique are a powerful tool with which to investigate the causal relationship between molecular and phenotypical aspects of disease. In research on drug addiction, studies with genetically modified animals have established a role for certain proteins that mediate the acute and/or chronic effects of addictive drugs

in the central nervous systems. We have reported that NR2A knockout mice exhibit a malfunction of NMDA receptors, as evidenced by alterations of [^{3}H]MK-801 binding as well as $^{45}Ca^{2+}$ uptake though the NMDA receptors (Miyamoto et al., 2001). Other investigators have also demonstrated in electrophysiological analyses that NR2A knockout mice exhibit a reduction in NMDA receptor channel current and LTP after a standard tetanic stimulation in the hippocampal CA1, but the saturation level of hippocampal LTP does not change after a stronger tetanic stimulation (Kiyama et al., 1998; Sakimura et al., 1995). Therefore, NR2A knockout mutant mice have been suggested to be useful for investigating the role of NMDA receptors, especially the function of the NR2A subunit, in morphine physical dependence. We have investigated the physical dependence to morphine of NR2A knockout mice with genetically reduced NMDA receptor function. Both wild-type and NR2A knockout mice repeatedly treated with morphine show withdrawal symptoms (jumping and forepaw tremor) after treatment with naloxone (Miyamoto et al., 2004). In NR2A knockout mice, however, the signs of naloxone-precipitated morphine-withdrawal symptoms are significantly less obvious than those in wild-type mice. Our findings in NR2A knockout mice are consistent with the pharmacological results, suggesting that adaptive changes through NMDA receptors, especially the NR2A subunit-containing receptors, play an important role in the development of morphine physical dependence (Miyamoto et al., 2004). As described above, NR2A knockout mice show marked loss of typical withdrawal abstinence behaviors, and in the wild-type mice significant enhancement of NR2A protein expression is only observed in the nucleus accumbens after development of dependence by chronic morphine treatment (Inoue et al., 2003). Furthermore, the rescue of NR2A protein by electroporation into the nucleus accumbens of NR2A knockout mice significantly reverses the loss of abstinence behaviors, such as wet-dog shake, paw tremors, and backward locomotion, whereas withdrawal jumping behavior was only partial. These findings suggest that NR2A has locus-specific roles in the development of morphine physical dependence (Inoue et al., 2003).

4. Ontogeny of NMDA receptors

Infants have been known to suffer adverse effects due to maternal opiate use. Zhu and Barr (2001a) have suggested first that it is difficult to separate factors that are due to opiate use and those that are due to the abuse of other drugs, poor prenatal care, poor nutrition or other complications experienced by the mothers of these children. Animal studies have shown that young rat pups and fetal rats show opiate dependence when the dams are exposed to opiates during their pregnancy or the pups, which are directly treated with opiates (Barr and Wang, 1992; Barr et al., 1998; Jones and Barr, 1995, 2000; Thornton and Smith, 1997; Thornton et al., 1997; Windh et al., 1995).

Recently, several NMDA receptor-related compounds have been investigated in young rats. In contrast to results from the adult rats, NMDA receptor antagonists are neither effective in blocking the development (Bell and Beglan, 1995a,b; Zhu and Barr, 2001a) nor the expression of opiate withdrawal (Zhu and Barr, 2000, 2001a) in neonatal rats. However, opiate dependence can be induced in young rats, and nitric oxide synthase inhibitors (Zhu and Barr, 2000), but not NMDA receptor antagonists, are effective in inhibiting this process. It has been suggested that in the young, opiate actions rely on the same second messenger systems as in the adult, although the factors that activate these systems are different. Recently, interesting findings have been reported that dizocilpine is ineffective in blocking both the development of morphine dependence and the expression of morphine withdrawal in the 7-day aged rat, but is partially effective in the 14-day aged rat and fully effective in the 21-day aged rat (Zhu and Barr, 2001b). There is a transition age, around the second postnatal week when dizocilpine becomes effective in morphine withdrawal (Zhu and Barr, 2001b). Thus, from a developmental perspective, during early life, receptors other than NMDA receptors might link to the same second messenger system as in adult life and, at a later time, either confer this role to NMDA receptors or recede to an auxiliary role (Zhu and Barr, 2001a,b).

5. Clinical application of NMDA receptor antagonists

Considering the potential clinical application of preclinical findings, it will be of value to further explore specific behaviors related to pain and addiction, including analgesia, physical dependence and reward to determine the therapeutic potential for drugs acting on the NMDA receptor ion-channel complex (Trujillo, 2000). It should be focused on finding drugs or drug combinations that will be therapeutically beneficial without the psychotomimetic adverse effects of the high affinity non-competitive NMDA receptor antagonists. Clinical research is already underway to determine the potential role for NMDA receptor antagonists [e.g., 3-(2-carboxypiperazin-4-yl)propyl-1-phosphonic acid (CPP), ketamine, dextromethorphan], alone or in combination with opiates, in the treatment of pain (Bisaga et al., 1997, 2001; Isbell and Fraser, 1953; Koyuncuoglu, 1991; Koyuncuoglu and Saydam, 1990; Rosen et al., 1996b). A measurable withdrawal syndrome can be precipitated in humans even after the administration of a single dose of morphine (Bickel et al., 1988), and dextromethorphan and memantine appeared to reduce signs and symptoms of opiate dependence (Bisaga et al., 1997, 2001; Koyuncuoglu, 1991; Koyuncuoglu and Saydam, 1990), although other investigators have failed to find the effect of dextromethorphan (Isbell and Fraser, 1953; Rosen et al., 1996b). Thus, clinical studies have been inconclusive, this discrep-

ancy might be due to the difference in the methodologies used (Bisaga et al., 2001).

Bisaga et al. (2001) have demonstrated that memantine may be useful in clinical practice because of its extended effect on physical dependence and lack of inter-individual variability in the metabolism of this medication as compared to dextromethorphan. Memantine may be clinically useful in detoxification from opiate when used alone, with adjunct non-opiate medication(s), or in combination with decreasing doses of an opioid agonist (e.g., methadone) (Bisaga et al., 2000, 2001).

6. Conclusion

It is clear that NMDA receptors are fundamental mediators of the expression, development and maintenance of opiate-induced physical dependence in adults. However, different mechanisms such as different glutamate receptor types linked to signal cascades during ontogeny (Zhu and Barr, 2001a) might exist in the young. Thus, in the young very different therapeutic approaches might be necessary for the treatment of the clinically adverse effects of opiates from those used in the adult. It is expected that our understanding of the role of glutamate-mediated neurotransmission in opiate physical dependence will benefit from two lines of research: (1) the analysis of molecular mechanisms by cellular and molecular approaches, and (2) the use of various glutamate receptor subunit knockout animals in developmental studies on opiate actions.

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