Opioid Dependence and NMDA Receptors

Michael J. Glass

Abstract

Opioids can induce dependence and elicit a withdrawal syndrome in users after the cessation of drug action. Opioid withdrawal is characterized by aversive symptoms that can elicit distress-relieving drug-seeking behavior and that thus contribute to the development and persistence of addiction. Animal models have been instrumental in scientists’ evolving understanding of the critical role of limbic brain system N-methyl-d-aspartate (NMDA)-type glutamate receptors in both the opioid withdrawal response and learned aversive behaviors that may have persistent effects on drug-seeking behaviors. In addition, the NMDA receptors’ involvement in opioid reward suggests that manipulating NMDA receptor function may prove beneficial in managing diverse components of opioid addiction.

Key Words: addiction; glutamate; limbic system; morphine; neural plasticity; N-methyl-d-aspartate (NMDA); opioid; reward; withdrawal

Introduction

A clinically relevant analgesic and an abused euphorogenic agent, the prototypic opioid morphine is an alkaloid of the opium poppy, Papaver somniferum. The use of morphine and related opioids can result in a clinical condition classified as substance dependence in diagnostic manuals of mental disorders (APA 1994) but commonly known as addiction. Addiction is conceptualized as a chronic and relapsing brain disease characterized by compulsive drug seeking and consumption, loss of control in limiting intake, physical dependence, and withdrawal after abstinence (for a review of current models of addiction, Koob and Volkow 2010).

The addiction risk with illicit use of opioids may be greater than 20%; it is probably much lower when medically prescribed opioids are appropriately used for pain relief. Recidivism is high; in treatment settings, relapse rates can exceed 60% (for reviews, Fields 2007; O’Brien 2008; Veilleux et al. 2010).

Given the increasing trends in opioid abuse, particularly in the nonmedicinal use of prescription medications, and the attendant risk of serious health problems, such as AIDS, hepatitis C, and a myriad of psychiatric conditions, opioid addiction is a significant public health concern (for a discussion of recent epidemiological trends in opioid use, SAMHSA 2010a,b).

Opioid addiction pharmacotherapy currently includes full (e.g., methadone) or partial (e.g., buprenorphine) mu opioid receptor (µOR1) agonists. In addition, non-opioid-based drugs (e.g., the α2-adrenergic receptor agonists clonidine and lofexidine) have been used as antwithdrawal agents (Stotts et al. 2009). However, the long-term efficacy of these agents is limited by risks of abuse and dependence, unpleasant side effects, and relapse proclivity.

The development of new pharmacological treatments, an important goal of addiction research, will depend significantly on progress in neurobiological research. Because of ethical concerns and experimental complications in the conduct of research with substance-abusing human populations, animal research is essential to progress in basic addiction neurobiology and drug therapy.

The animal literature clearly indicates that no single brain structure mediates opioid dependence. As with the larger phenomenon of addiction, the processes underlying dependence are distributed across a highly complex network of sensory, limbic, and memory systems that regulate homeostasis (for reviews of these pathways, Koob and Volkow 2010). Despite this underlying neural complexity, opioid dependence is frequently associated with glutamate-dependent synaptic plasticity in key brain areas. Therefore, glutamate-mediated neural adaptability is a critical organizing principle that guides much contemporary empirical and theoretical work in addiction neurobiology.

In this context, the ionotropic N-methyl-d-aspartate (NMDA1)-type glutamate receptor has attained particular prominence. It is an established molecular substrate of neural adaptability, learning, and memory (Rebola et al. 2010)—features shared by other plasticity-related proteins (e.g., neuronal pentraxins; see Reti et al. 2011 in this issue) involved in opioid addiction. Close associations between the NMDA and opioid receptor systems have been well established in relation to opioid dependence (Glass 2010). Clinical pharmacological
reports (Bisaga et al. 1997, 2001) and genetic association studies (Levran et al. 2009) highlight the potential importance of NMDA receptors in human opioid addiction. Moreover, a robust animal literature, reviewed below, confirms the critical contribution of NMDA receptors to opioid dependence. However, progress in this field has been less than straightforward, partly because of the intricate neuropsychopharmacology of many NMDA receptor antagonists (see Trujillo et al. 2011 in this issue) as well as the complex developmental genetics of the NMDA receptor (see Barr et al. 2011 in this issue).

This article presents an overview of established findings regarding the NMDA receptor and opioid dependence in the context of the immediate withdrawal response and learned aversive behaviors. For a more comprehensive picture of NMDA receptor involvement in opioid addiction, a brief discussion of what is known about this protein’s role in learned rewarding behaviors is also provided.

**Morphine Dependence: Cellular Adaptations, Behavioral Withdrawal, and Brain Circuitry**

**Cellular Adaptations**

Morphine’s major acute biological effects are mediated by activation of the µOR, a member of the G protein–coupled receptor superfamily that interacts with inhibitory G proteins (Lopez and Salome 2009).

Opioid dependence reflects homeostatic adaptations following drug exposure. The initiation of morphine dependence requires functional µORs (Matthes et al. 1996) and the subsequent modulation of neurotransmitter receptor activity, protein kinases, transcription factors, and the expression of various genes that are critically involved in neural plasticity (for reviews of recent trends, Kreek et al. 2009; Russo et al. 2010). Morphine-dependent adaptations, classically characterized by adenylate cyclase–mediated cyclic adenosine monophosphate (cAMP) production, are expressed at the cellular level by the need to increase drug concentration to achieve a given cellular effect (e.g., tolerance) and a profound rebound hyperexcitability (e.g., cellular withdrawal) when the drug is withheld (for an in-depth review of these topics, Christie 2008).

**Behavioral Withdrawal**

In experimental animals, morphine dependence can be induced by various administration protocols (Adams and Holtzman 1990; Adams and Wooten 1990; Bhargava and Villar 1991; Cerletti et al. 1976). One experimental variable that has a high impact on morphine-mediated neural adaptability is the intermittency of drug exposure (Fischer et al. 2008; Fitzgerald et al. 1996), a finding with important implications for modeling human addiction (for a discussion of efforts to model human addiction, Koob and Kreek 2007).

Withdrawal can be elicited by terminating drug administration (spontaneous withdrawal) or, more commonly, by administering a short-acting opioid receptor antagonist, such as naloxone, in the presence of morphine (precipitated withdrawal). The latter approach enables dose-dependent control of the onset, magnitude, and symptomatology of the withdrawal response (Schulteis et al. 1994).

Opioid withdrawal is marked by diverse symptoms that are typically classified into functional categories: motor responses (Kantak and Miczek 1988; Martin et al. 1963), autonomic function (Brown et al. 1988; Delle et al. 1990; McNally and Carrive 2006), neuroendocrine activity (Zhou et al. 2006), immunological function (Feng et al. 2006), sensory processing (Dunbar and Yaksh 1996), and emotional reactions (Stinus et al. 1990). Table 1 shows some of the most prominent symptoms in each class of withdrawal symptom; of these, drug “craving,” a fixation with drug acquisition and consumption, is a hallmark of withdrawal.

The withdrawal syndrome resembles defensive avoidance or escape reactions normally seen after exposure to threatening and/or noxious stimuli. By provoking drug-seeking behaviors that relieve the distress of withdrawal (i.e., negative reinforcement), dependence may play a particularly important role in the compulsive aspects of addictive processes, characterized by preservative behavior despite adverse consequences (for a review of these concepts, Koob 2009; Hopf et al. 2011 in this issue).

Dependence also has behavioral consequences (e.g., adaptations in reward function, stress responsivity, and persistent learned reactions to drug and drug-withdrawal-associated cues) that outlast acute withdrawal and detoxification. These effects are the product of both drug-induced modulation of

---

**Table 1 Acute opioid withdrawal symptoms in rodent models**

<table>
<thead>
<tr>
<th>Class</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Escape/avoidance</td>
<td>Escape jumping, wet-dog shakes, defensive social behavior</td>
</tr>
<tr>
<td>Autonomic</td>
<td>Hypertension, hyperventilation, diarrhea, lacrimation, catecholamine release</td>
</tr>
<tr>
<td>Neuroendocrine</td>
<td>Adrenocorticotropic hormone release, corticosterone release</td>
</tr>
<tr>
<td>Immunological</td>
<td>Immune system suppression</td>
</tr>
<tr>
<td>Sensory/nociceptive</td>
<td>Hyperalgesia</td>
</tr>
<tr>
<td>Affective/motivational</td>
<td>Dysphoria, anxiety, increased reward thresholds, drug “craving”</td>
</tr>
</tbody>
</table>
brain reward and stress systems (Koob 2009) and the formation of learned associations between the withdrawal state and withdrawal-associated cues. These processes may decrease the rewarding properties of natural (nondrug) rewards, increase the incentive value of opioids, and heighten the salience of learned aversive cues that contribute to stress-alleviating drug-seeking behaviors.

Brain Circuitry

The ventral striatum and associated cortical, amygdala, and hippocampal glutamate systems are instrumental in coordinating sensory information, memory, affect, and behavioral responses critical to homeostasis, which can become dysregulated during opioid dependence (Figure 1).

As noted in a recent review by Koob and Volkow (2010), there has been considerable research interest in the relationships between the compulsive aspects of addictive behaviors and the dysregulation of endogenous opioid, catecholamine (dopamine and norepinephrine), corticotropin-releasing factor, gamma-aminobutyric acid (GABA), and glutamate signaling in the ventral striatum and amygdala. In particular, the nucleus accumbens (NAc), central nucleus of the amygdala (CeA), and forebrain projecting catecholamine areas in the ventral tegmental area (VTA; the mesolimbic dopamine pathway)

Figure 1  Schematic representation of neural pathways involved in opioid withdrawal behaviors (illustrated in a sagittal rodent brain section). Medullary nuclei—that is, nucleus of the solitary tract (NTS) and the ventrolateral medulla (VLM)—mediate cardiovascular, respiratory, and gastrointestinal function (dashed red arrows). Hypothalamic systems (HYP) are involved in neuroendocrine processes (dashed yellow arrow). Midbrain regions—periaqueductal gray (PAG) and ventral tegmental area (VTA)—are involved in coordinating defensive reactions (dashed grey arrows). Ventral forebrain areas—nucleus accumbens (NAc), bed nucleus of the stria terminalis (BNST), and central amygdala (CeA)—are important in conditioned affective processes (dashed black arrows). These regions receive glutamate inputs (solid green arrows) from the cerebral cortex (CTX), hippocampus (HPC), thalamus (THAL), and lateral amygdala (not shown); dopamine from the VTA (dark blue); and noradrenergic inputs from the NTS and VLM (light blue arrow). Ventral forebrain GABAergic pathways to the forebrain, midbrain, and brainstem are illustrated by solid grey arrows.
and caudal medulla (i.e., the ventral noradrenergic bundle) play important roles in long-term changes in affect as well as in learning and memory, which are essential to the development and persistence of opioid dependence (Koob and Volkow 2010).

Neural plasticity involving NMDA receptors in these systems is important in linking stress, emotional learning, and addictive behaviors (Rainnie et al. 2004; Ungless et al. 2003). The mesolimbic system receives substantial glutamate inputs from other neural regions—the cerebral cortex, lateral amygdala, thalamus, and hippocampus—involved in opioid addiction. Most components of this circuitry express both NMDA receptor subunit genes (Sato et al. 1995) and NMDA receptor protein (Petralia et al. 1994) and ligand binding sites (Monaghan and Cotman 1985). These expression patterns overlap with areas of µOR expression (Mansour et al. 1995), and high-resolution ultrastructural analyses show that NMDA receptor and µOR cellular distributions are conducive to direct and indirect neuronal interactions in many of these brain areas (Commons et al. 1999; Glass et al. 2009; Gracy et al. 1997; Milner and Drake 2001).

In addition, NMDA receptor expression, at transcriptional and posttranscriptional levels, is sensitive to opioid exposure in many of these brain areas (Bajo et al. 2006; Turchan et al. 2003). Opioids have also been shown (Nugent et al. 2007) to modulate NMDA receptor–dependent forms of neural adaptability (e.g., long-term potentiation). Interactions between the NMDA receptor and the D₁ dopamine receptor may also be involved in neural signaling processes that are highly relevant for opioid dependence (Lee et al. 2002; Scott and Aperia 2009).

Role of NMDA Receptors in Opioid Withdrawal

During the late 1980s and early 1990s, critical advances in the molecular biology, pharmacology, neurophysiology, and behavioral neuropharmacology of the glutamate receptor system established that neural plasticity and memory processes highly relevant to opioid addiction were mediated by the NMDA receptor in addition to the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor (Figure 2; for reviews, Dingledine et al. 1999; Hollmann et al. 1994; Rebola et al. 2010).

Because cellular activity is required before the NMDA receptor can become functional, this protein has been described as a “coincidence detector,” coincidence being critical for the association of correlated signals from distinct inputs necessary for learning at the synaptic level (Sjöström et al. 2008). Activation of glutamatergic inputs that trigger NMDA receptor activation can thus become linked with concurrent opioid withdrawal–induced signaling events. Because of potential synergies in downstream signaling pathways induced by opioid withdrawal and NMDA receptor activation, these signaling events may be particularly potent and contribute to long-lasting adaptations in neural function.

Several seminal reports in the 1990s provided direct behavioral pharmacological evidence that NMDA receptors were importantly involved in morphine dependence (Higgins et al. 1992; Tanganelli et al. 1991; Trujillo and Akil 1991) as well as in related phenomena such as morphine analgesic tolerance (for a review, Inturrisi 2005). Much subsequent research has supported and extended many of these early findings.

Behavioral Pharmacology

Studies of morphine dependence in rodents have repeatedly shown that systemic administration of NMDA receptor antagonists attenuates withdrawal (Belozertseva et al. 2000; Gonzalez et al. 1997). Furthermore, the literature indicates that blockade of NMDA receptors inhibits many of the diverse symptoms of opioid withdrawal: blood pressure elevation (Buccafusco et al. 1995), diarrhea (Ninan and Kulkarni 2000), immunosuppression (Alonzo and Bayer 2003), hyperalgesia (Dunbar and Yaksh 1996), escape behavior (e.g., jumping; Trujillo and Akil 1991), fear and anxiety (Harris et al. 2008), and social aggression (Sukhotina and Bespalov 2000).

In addition to their broad-spectrum antiwithdrawal effects in chronically treated animals, NMDA receptor antagonists inhibit withdrawal behaviors after a single opioid exposure (Kawasaki et al. 2005; McLemore et al. 1997), indicating that NMDA receptors are involved in the development of opioid plasticity at early stages.

Genetic Manipulation

As a potential alternative to pharmacology, genetic models involving constitutive gene disruption, through knockout or mutation, have been used to study NMDA receptors and opioid dependence. One of the difficulties of using constitutive gene-targeting approaches is that deletion of the Nr1 gene is lethal (Betz et al. 1996), and Nr2b knockout mice have an impaired suckling response that requires hand feeding to prevent neonatal death (Kutsuwada et al. 1996). Alternative genetic models include Nr1-receptor-subunit-deficient mice (Mohn et al. 1999) and Nr2a-subunit knockout mice (Sakimura et al. 1995). Consistent with much of the pharmacological literature, mice with constitutive deletion of the Nr2a subunit gene show a reduction in naloxone-precipitated withdrawal (Inoue et al. 2003). Constitutive deletion of scaffolding proteins involved in anchoring NMDA receptors to the plasma membrane, thereby decreasing their expression at functional cellular locations, also attenuates morphine withdrawal (Liaw et al. 2008).

Neuropharmacology

The neuroanatomical relationship between NMDA receptors and opioid dependence has been the subject of in vivo research using intracranial drug administration methodology and spatial-temporal gene transfer.
Figure 2  The glutamate-sensitive N-methyl-D-aspartate (NMDA) receptor is a tetrameric heteromer (top schematic) composed of the essential NMDA receptor subunits 1 (NR1) and NR2, the latter of which exists as one of four isoforms (NR2A-D). Notable characteristics of the NMDA receptor are its voltage-dependent ion channel blockade by magnesium (Mg$^{2+}$) requiring cellular depolarization, usually involving the activation of non-calcium-permeable α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (dark green) for channel permeability (green bolts). Binding of glutamate and cofactor glycine are necessary for channel activation and subsequent calcium (Ca$^{2+}$) influx. NMDA receptor activation is also associated with the stimulation of potent downstream activators, many of which are modulated by opioid withdrawal, as indicated by naloxone blockade of morphine binding to the µ opioid receptor (µOR; red bolt). NMDA receptor activation can modulate numerous intracellular signaling processes involving (A) protein kinase (PKA, ERK1/2, and CaMKII) activity and phosphorylation events that can affect surface expression of functional proteins such as the non-calcium-permeable AMPA receptors that are critical for plasticity. Kinases such as ERK can also translocate to the cell body where they can influence (B) transcriptional events involving activation of transcription factors (CREB and ELK), immediate early genes (fos, jun, zif268, and arc) and gene expression. These events contribute to (C) long-term adaptations involving synthesis and trafficking of plasticity-related proteins (PRPs, which include neurotrophins, cytoskeletal proteins, adhesion molecules, and AMPA-type glutamate receptors) that can influence long-term synaptic transmission as well as structural plasticity (e.g., changes in cellular morphology and synapse formation and pruning). CaMKII, calcium/calmodulin-dependent protein kinase II; cAMP, cyclic adenosine monophosphate; CREB, cAMP response element binding; ERK, extracellular regulated kinase; PKA, protein kinase A.
A study in the late 1990s showed that conditional knockdown of Nrl by ventricular administration of an antisense oligonucleotide resulted in the attenuation of naloxone-precipitated withdrawal in rats chronically exposed to morphine, suggesting that functional NMDA receptors in the forebrain are necessary for the full expression of opioid withdrawal behaviors (Zhu and Ho 1998).

More recently, the strategy of microinjecting NMDA receptor antagonists into select brain sites has been used to identify critical brain regions. Blockade of NMDA receptors in the NAc (Ji et al. 2004), as well as its major source of dopamine input (the VTA) has been reported to inhibit naloxone-precipitated withdrawal (Wang et al. 2005). Nucleus accumbens expression of NMDA receptors containing the NR2A subunit may be important in opioid withdrawal after chronic opioid administration. Although, as described above, Nrla knockout mice showed an attenuated opioid withdrawal response, a normal opioid dependence phenotype was produced in these animals by NAc electroporation of Nr2a complementary DNA (Inoue et al. 2003).

The critical role of NMDA receptors in the mesoaccumbal dopamine pathway is also indicated by the ability of NMDA receptor antagonists to normalize changes in NAc dopamine release in response to acute naloxone-precipitated withdrawal (Rossetti et al. 1992). In addition, the abstinence-associated increase of NAc ΔFosB, a member of the Fos family of transcription factors that can remain elevated even weeks after the termination of drug exposure (Nestler et al. 2001), is inhibited by blockade of NMDA receptors in the VTA (Wang et al. 2005). Together, these findings suggest that functional NMDA receptors in the mesoaccumbal pathway are critically involved in dopamine signaling and gene expression patterns associated with opioid dependence.

Manipulating NMDA receptor activity in other components of brain motivational systems can produce behavioral effects distinct from those seen in the VTA and NAc. For example, in the central amygdala, a brain area essential for learned emotional behaviors, neither inhibiting local NMDA receptor activation by direct microinjection of NMDA receptor antagonists (Watanabe et al. 2002) nor conditional deletion of the Nrl gene (Glass et al. 2008) affected somatic signs of opioid withdrawal. However, these treatments did affect other aspects of opioid dependence, as discussed below.

Role of NMDA Receptors in Learned Place Aversion and Extinction

Dependence has typically been studied in the context of the immediate withdrawal response. However, because many of the most important features of dependence outlast acute withdrawal and detoxification, research is focusing more and more on learning and memory as well as the extinction of learned behaviors, all of which involve NMDA receptors.

Conditioned Place Aversion

Animals learn to avoid stimuli paired with aversive periods of opioid withdrawal, a phenomenon termed “conditioned aversion” (Jacquet 1973). A common experimental strategy in studies of learned aversions is the conditioned place aversion paradigm (for a review of drug-induced place learning, Cunningham et al. 2006).

Withdrawal-conditioned place aversion is a form of classical or pavlovian context conditioning in which the experience of opioid withdrawal in a neutral environment, such as a chamber fitted with discriminable cues (tactile, visual, or olfactory), can evoke a response similar to the aversive treatment itself. Thus after training, animals spend much less time in the withdrawal-paired environment relative to pretraining conditions. Even very mild bouts of opioid withdrawal can induce aversive learning (Gracy et al. 2001), and place aversion may persist for weeks after training (Stinus et al. 2000).

There is some overlap between brain areas important for the manifestation of somatomotor withdrawal and conditioned place aversion, but there are also divergences. For example, the NAc, among the most sensitive areas for place aversion, is also involved in somatic withdrawal, as described above. The CeA, in contrast, has a less clear involvement in overt withdrawal, although it is highly sensitive to place aversion (Stinus et al. 1990). These findings suggest that the neural systems that mediate various withdrawal-associated behaviors are dissociable (Glass 2010).

As with other opioid dependence–related behaviors, systemic administration of NMDA receptor antagonists can attenuate the conditioned aversive properties of withdrawal (Higgins et al. 1992; Kawasaki et al. 2005). Neuropharmacological (Watanabe et al. 2002) or spatiotemporal gene deletion (Glass et al. 2008) studies have shown that inhibiting NMDA receptor activation in the CeA can attenuate opioid withdrawal place aversion, even though, as mentioned above, these treatments do not affect somatic withdrawal symptoms.

Further studies involving manipulation of NMDA receptor function in specific brain sites are needed to provide a more comprehensive brain map linking this protein to learned and other behaviors related to opioid withdrawal.

Extinction of Conditioned Place Aversion

If the experience of withdrawal-associated cues can contribute to drug-seeking behaviors, then inhibiting learned aversive behaviors might prove to be a useful strategy in addiction treatment. Extinction is an active learning process involving the formation of inhibitory memories capable of suppressing the expression of previously learned associations (for a recent review, Quirk et al. 2010). In the context of classical conditioning, the extinction of opioid withdrawal place aversion is characterized by a reduction in the conditioned response (place avoidance) when the conditioned environment (withdrawal-paired chamber) is no longer associated with the conditioning stimulus (withdrawal).
The extinction of opioid withdrawal aversive learning has been shown to involve NMDA receptors: Myers and Carlezon (2010) reported that the administration of the NMDA receptor partial agonist D-cycloserine can accelerate the extinction of opioid withdrawal place aversion. This finding is consistent with clinical reports that D-cycloserine, when combined with behavioral therapy, can augment the extinction of learned behaviors associated with anxiety disorders (Ganasen et al. 2010).

The efficacy of a glutamate agonist in facilitating extinction may be related to the documented addiction-related dysfunction of forebrain glutamate systems (for a review, Reissner and Kalivas 2010). Two brain regions shown to have depressed NMDA receptor protein levels in response to opioid dependence are the prefrontal cortex and hippocampus (Murray et al. 2007), areas where NMDA receptors play an important role in the extinction of conditioned fear (Gomes et al. 2010; Peters et al. 2010). The ability of D-cycloserine to accelerate extinction may be a result of correcting glutamate dysfunction in cortical and hippocampal circuits, resulting in improved cognitive function and learning flexibility.

Role of NMDA Receptors in Reward Learning

Reward learning and relapse are essential to the larger syndrome of addiction. The following paragraphs briefly review evidence showing that the NMDA receptor is essential for behaviors related to the rewarding properties of opioids.

There is a significant counterpart to the place aversion phenomenon discussed above: place preference. This classically conditioned approach response to rewarding stimuli can be produced by many drugs of abuse (Tzschtentke 2007), and, like place aversion, is dependent on NMDA receptors (Popik et al. 2003; Tzschtentke and Schmidt 1995). Neuropharmacological studies using local microinjection of NMDA receptor antagonists implicate mesolimbic brain areas—the NAc (Huang et al. 2003; Popik and Kolasiewicz 1999), the VTA (Harris et al. 2004), and the CeA (Rezayof et al. 2007)—in morphine place preference. The conditioned place preference paradigm is particularly useful as a relatively straightforward method to study the reinstatement of previously learned responses associated with opioid reward (Aguilar et al. 2009), and is relevant to the resumption of drug-seeking behavior following remission.

Animals are first trained to express a morphine place preference and then the response is extinguished. Subsequent exposure to drug-associated cues, stress, or the drug itself (called drug priming) can reestablish the place preference behavior (for a review, Lu et al. 2003). Studies have used this method to show that NMDA receptor blockade can inhibit the reinstatement of morphine place preference produced by morphine priming (Popik et al. 2006; Ribeiro Do Couto et al. 2005). Functional NMDA receptors in the NAc and dorsal hippocampus may be important in this process; intracranial (NAc or hippocampus) administration of the putative NR2B-expressing NMDA receptor antagonist ifenprodil attenuated morphine-primed, but not forced-swim stress-induced, reinstatement of place preference (Ma et al. 2007).

Conclusion

Animal research has been indispensable in the development of an integrated multilevel framework for understanding the development of opioid addictive behaviors. One of the key insights derived from such research is that the NMDA receptor is instrumental in opioid dependence behaviors, including the opioid withdrawal response, learned contextual aversion, and the extinction of conditioned aversive responses. The NMDA receptor is also involved in other essential components of addictive behaviors, such as the development of learned rewarding behaviors, and in the reinstatement of extinguished responses, which has important implications for addiction relapse. Although the NMDA receptor is involved in multiple components of opioid addiction, its role in specific behaviors (e.g., somatic withdrawal or place aversion) may be differentially mediated by distinct brain substrates.

In addition to the animal research reviewed above, reports demonstrate relationships between the NMDA receptor and opioid addiction in human populations. For example, NMDA receptor antagonists have been shown to attenuate acute opioid withdrawal in humans (Bisaga et al. 2001). Furthermore, there are genetic linkages between certain NMDA receptor subunit gene variants and protection against opioid addiction susceptibility in human addict populations (Levran et al. 2009). Together with the animal literature, these results suggest that the NMDA receptor may be a useful target in addiction pharmacotherapy.

Acknowledgments

This work was supported by grants (DA-024030 and DA-027128) from the National Institutes of Health National Institute on Drug Abuse.2

References


2Editor’s note: NIDA provided partial funding for this issue.


