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Review

In search of a new pharmacological treatment for drug and alcohol addiction: *N*-methyl-D-aspartate (NMDA) antagonists

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Abstract

The most challenging aspect of treating alcohol and drug addiction is the relapsing course of these disorders. Although substitution therapies for nicotine and opioid dependence have proven to be relatively effective, there is a need for new pharmacotherapies designed to decrease the frequency and severity of relapse. The aim of this paper is to provide an overview of the potential utility of *N*-methyl-D-aspartate (NMDA) receptor antagonists as treatments for substance abuse as shown in preclinical models and preliminary clinical trials. It is hypothesized that NMDA receptors mediate the common adaptive processes that are involved the development, maintenance, and expression of drug and alcohol addiction. Modulation of glutamatergic neurotransmission with NMDA receptor antagonists offers a novel treatment approach. It is proposed that NMDA antagonists may have multiple functions in treating addictions, including an attenuation of withdrawal effects, normalization of the affective changes following initiation of abstinence which arise from neurochemical changes resulting from chronic addiction, and an attenuation of conditioned responses arising from drug-related stimuli.

Keywords: NMDA receptor antagonists; Opiates; Psychostimulants; Alcohol; Pharmacotherapy

1. Introduction

Alcohol, opioids, psychostimulants, sedatives and marijuana have different chemical structures and sites of action in the brain. Nonetheless, the pathological pattern of drug and alcohol intake has many similar behavioral features regardless of the addictive substance. It is thought that each of the addictive substances exerts its action via similar neural pathways and neurotransmitter systems (Di Chiara et al., 1998). These common substrates may play a role in the pathophysiology of addictive disorders and may also be potential targets for pharmacological treatments. The present review is intended to demonstrate that the addictive effects of drugs and alcohol may be mediated via shared pathways and that glutamatergic neurotransmission and *N*-methyl-D-aspartate (NMDA) receptors are a critical components of this pathway. Agents that are NMDA receptor antagonists may interfere with the development, maintenance and expression of the pathophysiological processes common to all drugs of abuse and may have potential therapeutic implications.

2. Currently available pharmacological treatment strategies

Current treatment approaches aim at alleviating symptoms of acute abstinence and minimizing the risk of relapse. Detoxification is commonly accomplished using pharmacologically equivalent agonists that produce cross-tolerance and have more favorable pharmacokinetics, followed by a gradual decrease in the dose of the treatment agent. Methadone has been used to facilitate detoxification from opioids (Kleber, 1999). Withdrawal from benzodiazepines, alcohol and other sedative-hypnotics is traditionally managed with long-acting barbiturates or benzodiazepines (Smith and Wesson, 1994). Nicotine replacement therapy has been found to be

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effective in reducing withdrawal symptoms associated with cigarette smoking cessation (Schneider et al., 1984). However, despite adequate treatment of the abstinence syndromes, the relapse rates of the addictive disorders remains very high (Mattick and Hall, 1996). At the present time, detoxification is seen primarily as an opportunity to relieve acute distress associated with abstinence symptoms and to engage patients in psychosocial treatment.

The observation of high relapse rates following detoxification has underscored the need for replacement pharmacotherapies intended for long-term treatment. The most successful example of such therapy is methadone maintenance for opioid dependent individuals (Dole and Nyswander, 1965). Nicotine replacement therapy is another agonist-based treatment that has been found to be effective in aiding cigarette smoking cessation (Silagy et al., 1994). Unfortunately, the relapse rate following discontinuation of methadone and possibly other replacement therapies continues to be high (Ball and Ross, 1991) and most patients require active treatment for long periods of time. Another theoretically promising approach to the treatment of opioid addiction involves maintenance therapy with the opioid antagonist naltrexone. Its ability to block the subjective effects of heroin may lead to a decrease in heroin use through a process of behavioral extinction. However, in clinical practice, naltrexone has very limited acceptability by patients addicted to heroin (Greenstein et al., 1984).

The treatment strategies described so far are aimed at the processes of physiological dependence. However, the observation that detoxification is not effective as a treatment for addictive disorders and that the rate of relapse following the discontinuation of maintenance treatment remains high suggests that such an approach to treatment may not be sufficient in the treatment of addictive diseases. This may imply that, at the neurobiological level, physiological dependence may only partially contribute to the pathophysiology of compulsive drug seeking and drug taking behavior. Another common feature of the therapies discussed so far is that they target specific neurotransmitter systems (e.g. opioid, GABA-ergic or nicotinic receptor systems) that are involved in actions of a particular abused drug rather than the common substrates underlying all addictive processes.

There are a few exceptions to this receptor-targeted strategy. Clonidine, an α_2-adrenergic agonist, decreases the opioid abstinence syndrome (Gold et al., 1978). However, clonidine principally alleviates the physical (i.e. autonomic) but not the psychological (i.e. dysphoria) consequences of opioid withdrawal, does not shorten the length of time for withdrawal, and has significant side effects of hypotension and sedation (Jasinski et al., 1985). Another example is the use of naltrexone and acamprosate as adjuncts in the rehabilitative treatment of alcoholism (Garbutt et al., 1999). In several well designed, placebo-controlled, randomized clinical trials, patients treated with naltrexone, an opioid antagonist, had lower rates of alcohol relapse, number of drinking days and alcohol craving. Acamprosate, has been recently reported in controlled clinical trials to prolong abstinence periods and reduce the amount of alcohol consumed during relapses. The particular mechanism by which naltrexone and acamprosate exert their behavioral effect is unknown.

3. Glutamate as a major excitatory neurotransmitter in the CNS

The last decade has witnessed the growth of information related to actions of glutamate as a neurotransmitter in the mammalian CNS (Lipton and Rosenberg, 1994). Glutamate is a primary excitatory neurotransmitter in a majority of CNS receptors. Nearly all neurons are depolarized by glutamate through the activation of glutamate receptors. These receptors may be divided into two major types: metabotropic and ionotropic. Metabotropic receptors are coupled through G proteins to the intracellular second messenger system. Ionotropic receptors are ligand-gated ion channels that mediate rapid changes in sodium, calcium, and potassium permeability. Subtypes of ionotropic receptors include *N*-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainate acid (KA) receptors, defined by the affinities of these synthetic ligands. The best characterized ionotropic receptor is the NMDA receptor (see Fig. 1). The NMDA subtype of glutamate receptor is a heteromultimeric channel consisting of NR1, NR2, and NR3 subunits in various combinations. It contains discrete recognition sites for glutamate, glycine, divalent cations, polyamines and a site within the channel. NMDA antagonists are structurally diverse, and act on these multiple, allosterically coupled recognition sites (for review see Dingledine et al., 1999). In this review, agents binding to four distinct binding sites at the NMDA receptor complex are discussed. These include: (1) competitive NMDA antagonists: 2-amino-5-phosphovalerate (AP-5), (+/−)2-amino-7-phosphonoheptanoic acid (APH), 2-amino-5-phosphonovaleric acid (APV), 2*R*,4*R*,5*S*-(2-amino-4,5-(1,2-cyclohexyl)-7-phosphonoheptanoic acid) (NPC 17742), (±)-6-phosphonomethyl-decahydroisoquinoline-3-carboxylic acid (LY274614), DL-(E)-2-amino-4-methyl-5-phosphono-3-pentanoic acid (CGP 37849), selfotel (CGS 19755), D-CPP-ene (SDZEAA494); (2) antagonists or partial agonists at the strychnine insensitive glycine binding site: 5,7 dichlorokynurenic acid (5,7-di-Cl-KYN), 7-chloro-4-hydroxy-3(3-phenoxy)phenyl-2(H) chinoline (L-701,324),

1-aminocyclopropan-ecarboxylic acid (ACPC), D-cycloserine, (+/−)-1-1 hydroxy-3-aminopyrrolidone-2 (HA-966); (3) uncompetitive, i.e. open-channel NMDA antagonists: dizocilpine, (MK-801), cerestat (CNS 1102), memantine, dextromethorphan, ibogaine, amantadine, ketamine, phencyclidine (PCP); and (4) polyamine antagonists (eliprodil, ifenprodil), and the partial agonist (acamprosate). Several agents may modulate transmission at the NMDA receptor complex indirectly by inhibiting presynaptic glutamate release (e.g. lamotrigine, riluzole). A significant number of NMDA antagonists and modulators are being developed at the present time. Several of those agents are already approved for clinical use, or are in the late stages (phase II/III) of clinical development (see Herrling, 1997; Danysz and Parsons, 1998). Additionally some of the medications that have been in clinical use for many years have recently been discovered to have some NMDA antagonist properties (e.g. desipramine, memantine, amantadine, and dextromethorphan).

4. Use of NMDA antagonists in animal models of dependence and addiction

Extrapolating from the results of animal laboratory experiments to actual drug-taking behavior in addicted individuals poses enormous difficulties. Nonetheless, this strategy remains a major way of investigating putative anti-addictive therapies in controlled settings.

4.1. Drug self-administration

Several studies have documented that NMDA antagonists inhibit the reinforcing effects of cocaine in animals. MK-801 has been demonstrated to inhibit cocaine self-administration (Schenk et al., 1993b) as well reverse its facilitation after chronic exposure to amphetamine (Schenk et al., 1993a). APV increased responding for cocaine (interpreted as reduction in the reinforcing effects of cocaine) when administered into the nucleus accumbens (NAC) in rats trained to lever press for intravenous cocaine (Pulvirenti et al., 1992). More recently, Pulvirenti et al. (1997) have shown that dextromethorphan significantly reduced intravenous cocaine self-administration in rats administering the drug in a simple continuous reinforcement schedule and also reduced the reinforcing effects of cocaine as measured by responding for cocaine under a progressive-ratio schedule. In rats trained to self-administer intravenous cocaine under a fixed-ratio schedule, intracerebroventricular pretreatment with MK-801 or (+)-HA966, selectively decreased response rates for cocaine without modifying behavior maintained by food or producing an effect on general motor activity (Shoaib et al., 1995; Pierce et al., 1997). In addition, ibogaine has been effective in reducing cocaine self-administration (Cappendijk and Dzoljic, 1993). In contrast to the above, another study showed that under a progressive-ratio schedule of reinforcement, MK-801 increased the break point for cocaine self-administration (Ranaldi et al., 1996), suggesting that NMDA antagonists may also increase the reinforcing effects of self-administered cocaine under some conditions.

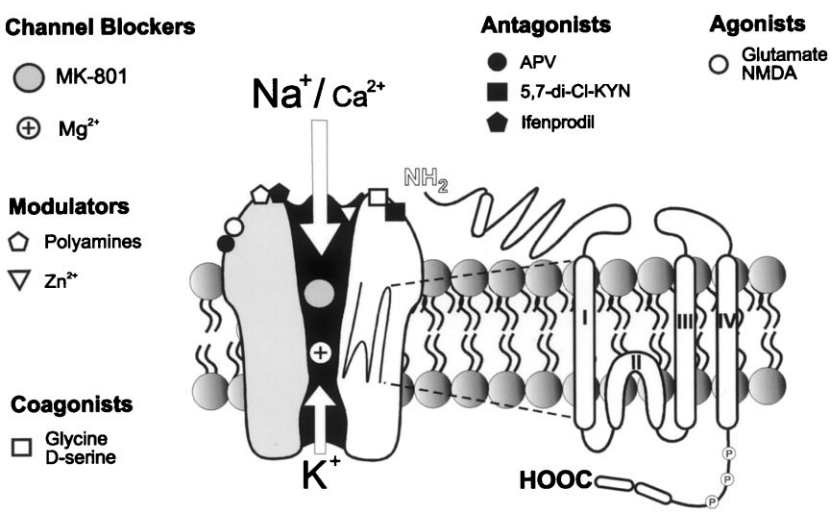

Fig. 1. Diagram representing NMDA receptor ion channel with its various regulatory sites. The receptor is activated by agonists such as glutamate or NMDA. APV is a competitive antagonist, 5,7-di-Cl-KYN binds to a strychnine insensitive glycine site, ifenprodil is a polyamine site antagonist. The open NMDA channel is blocked by Mg^{2+} and by uncompetitive antagonists such as MK-801. Glycine and D-serine act as coagonists. Additionally, polyamines and Zn^{2+} ions modulate the NMDA receptor. There are phosphorylation sites (P) that modulate responses of the receptor to agonists and may play a role in synaptic plasticity. Each subunit is believed to have four regions (I, II, III, and IV) within the cell membrane

Surprisingly, there is little information on the effects of glutamate receptor antagonists on morphine self-administration. Bespalov and Zvartau (1996a) reported that the non-selective glutamate receptor antagonist, kynurenic acid, inhibits acquisition of morphine self-administration in rats. In addition, there is some preliminary information that low- (memantine) but not high- (dizocilpine) affinity NMDA receptor channel antagonists suppress initiation of morphine i.v. self-administration in drug and experimentally naive mice (Semenova et al., 1999). In another study, heroin self-administration remained unaltered after APV was given directly into nucleus accumbens (NAc) (Pulvirenti et al., 1992).

Findings with alcohol self-administration vary depending on the procedures used. AP-5 attenuated the development of ethanol drinking by rats (Lin and Hubbard, 1995). In rats trained to lever-press for ethanol, injections of AP-5 and APH directly into NAC attenuated responding for alcohol without affecting water self-administration (Rassnick et al., 1992). In other studies that found a decrease in operant responding for alcohol, the effects of NMDA antagonists were nonspecific (Shelton and Balster, 1997; Piasecki et al., 1998). However, most of above studies investigated effects of acute pretreatment with NMDA antagonists. Results of studies that used a chronic drinking model, followed by alcohol deprivation, are consistently positive. In rats drinking alcohol solution for several months, a period of alcohol deprivation produced robust increases in alcohol intake (Spanagel and Zieglgansberger, 1997). This effect is interpreted as an increase in alcohol craving. In this model, memantine significantly reduced the alcohol deprivation effect (Holter et al., 1996). During the alcohol deprivation procedure, animals are first exposed to chronic alcohol and test compounds are then given continuously, before and after re-exposure to alcohol. Such a model appears to have substantial relevance to the questions of medication development.

High-affinity uncompetitive NMDA antagonists can themselves function as reinforcers; they are self-administered by animals under some experimental conditions (see Nicholson et al., 1998 and references therein) and PCP or ketamine are abused by humans. In contrast, low-affinity uncompetitive antagonists e.g. memantine or dextromethorphan, appear to have much lower abuse potential. There have been no clinical reports of memantine abuse and only isolated cases of dextromethorphan abuse (Bem and Peck, 1992). Memantine did not produce a conditioned place preference in rats (Popik and Danysz, 1997) but it served as a weak reinforcer in an intravenous self-administration study involving monkeys trained to lever press for infusions of PCP (Nicholson et al., 1998). The doses of memantine that served as reinforcers in monkeys are much higher than doses that are necessary to specifically interact with the binding site of the NMDA receptor, and thus much higher than needed to exert the neuroprotective, and perhaps the anti-addictive effects, in humans (Kornhuber and Weller, 1997).

4.2. Conditioned place preference and conditioned locomotor activation

The conditioned place preference (CPP) paradigm is widely used to assess the rewarding properties of drugs (Mucha and Iversen, 1984). This paradigm represents an indirect measure of drug reinforcement (as opposed to drug self-administration), where trained animals approach previously neutral stimuli or environments (Schulteis et al., 1997). In addition to CPP, the psychomotor activation induced by drugs of abuse can also be conditioned in classical paradigms. After repeated pairing of a psychostimulant or morphine with a particular environment, animals will display hyperactivity when placed in such environment in the absence of the drug.

Inhibitory effects on morphine, cocaine, and metamphetamine-induced CPP have been demonstrated for CGP 37849 and MK-801 (Tzschentke and Schmidt, 1995; Del Pozo et al., 1996). MK-801 not only blocks the development of morphine-induced CPP but also blocks the expression of a conditioned response that has been previously acquired (Bespalov, 1996; Tzschentke and Schmidt, 1997). It should be noted, however, that MK-801 was found not to influence amphetamine-induced conditioned place preference in another study (Hoffman, 1994). Inhibitory effects on morphine reward were also reported for the nonspecific glutamate antagonist, kynurenic acid (Bespalov et al., 1994). Popik and Danysz (1997) and Popik et al. (1998) found recently that memantine, as well as several glycine/NMDA receptor antagonists including L-701342, were able to block specifically both the acquisition of morphine-induced CPP, and the expression of this phenomenon. The competitive NMDA antagonist, NPC 17742 was shown to reduce the expression of morphine-induced conditioned place preference after microinjection into the NAc and ventral tegmental areas (Popik and Kolasiewicz, 1999).

Systemic administration of MK-801 with amphetamine during the amphetamine pre-exposure phase blocked the development of conditioned hyperactivity (Stewart and Druhan, 1993). The expression of this conditioned response was completely prevented by pretreatment with a competitive NMDA receptor antagonist CPP administered directly into the NAc (Bespalov and Zvartau, 1996b). MK-801 blocked the development of cocaine-induced conditioned locomotion (Damianopoulos and Carey, 1995), but did not modify the expression of this phenomenon (Cervo and Samanin, 1996).

4.3. Intracranial self-stimulation

Little is known about the effects of NMDA antagonists in the intracranial self-stimulation model. In one study, kynurenic acid was found to attenuate morphine-induced facilitation of responding, causing a decrease in response rate and an increase in threshold current intensity (Bespalov et al., 1994). In contrast, it has been found that MK-801 potentiated the facilitative effects of morphine (Carlezon and Wise, 1993) and cocaine (Ranaldi et al., 1997) on responding for brain stimulation. These apparently conflicting findings may be related to the fact that kynurenic acid alone produced depression of lever-pressing in self-stimulating animals (Herberg and Rose, 1989) while MK-801 induced a prolonged facilitation of self-stimulation responding in a manner similar to cocaine and amphetamine (Corbett, 1989; Herberg and Rose, 1989).

4.4. Drug tolerance

Tolerance to several actions of drugs of abuse accompanies repeated administration. Corresponding neuroadaptive changes that take place during the development of tolerance may also underlie other manifestations of chronic drug use, including physical dependence. The effects of NMDA antagonists on tolerance have been extensively studied, particularly with opiates (for reviews see Elliott et al., 1995; Herman et al., 1995). Several studies have indicated that antagonists acting at various modulatory sites at the NMDA receptor reduce tolerance development to the analgesic effects of opiates (see Herman and O'Brien, 1997 for review). Recently, such inhibitory effects on the development of morphine tolerance have been documented with memantine given at doses producing serum levels comparable with therapeutic serum levels after medication in humans (Popik and Kozela, 1999). The development of tolerance to diazepam was prevented by concurrent treatment of mice with the D-CPP-ene (Steppuhn and Turski, 1993). NMDA antagonists also affect tolerance to the effects of alcohol. For example, Karcz-Kubicha and Liljequist (1995) recently demonstrated that both uncompetitive as well as competitive NMDA antagonists inhibit tolerance to the hypnotic effects of alcohol. Ketamine and MK-801, at doses that had negligible effects by themselves, prevented the development of acute and chronic tolerance to the motor impairing, hypothermic, and cognitive effects of ethanol (Khanna et al., 1991; Wu et al., 1993; Rafi-Tari et al., 1996). The repeated co-administration of MK-801 or D-CPP-ene with nicotine attenuated the development of tolerance to the locomotor depressant (Shoaib et al., 1994) and aversive (Shoaib and Stolerman, 1996) effects of nicotine in rats. As might be predicted, agents that enhance the function of the NMDA receptor facilitate tolerance to certain actions of drugs of abuse, e.g. tolerance to the ataxic effects of alcohol was facilitated by D-cycloserine (Khanna et al., 1995). Interestingly, NMDA antagonists blocked tolerance induced by repeated ethanol injections only when the development of tolerance was dependent on environmental cues but not when tolerance was environment-independent (Szabo et al., 1994). This suggests that the effect of NMDA antagonists on ethanol tolerance may reflect the more general role of this receptor in processes involving learning and memory (but see opposite findings with opiate tolerance; Tiseo and Inturrisi, 1993).

Although the inhibitory effects of NMDA antagonists on the development of tolerance to several effects of various drugs of abuse are consistent across the literature, one study seems to be of particular importance for the present considerations. Tiseo and Inturrisi (1993) demonstrated that morphine-tolerant animals infused with LY274614 for 7 days, regained their analgesic sensitivity to morphine. This means that in order to achieve the same pharmacological effect, previously tolerant rats would need a lower dose of morphine following a course of treatment with an NMDA antagonist. If applicable to other (e.g. rewarding, euphoriant, dependence-inducing) actions of opioids, these data may indicate that NMDA receptor antagonists treatment may have a potential to interfere with other neuroadaptive changes in the brain that contribute to the maintenance of addictive behavior (see Popik and Skolnick, 1996).

Tolerance to some of the behavioral effects (learning impairment, ataxia) also develops when NMDA antagonists are administered chronically (Hesselink et al., 1999). There are no published reports on whether cross-tolerance exists between opioids or psychostimulants and NMDA antagonists. Preliminary data suggest that cross-tolerance to selected effects exists between NMDA antagonists and alcohol. Such cross-tolerance has been documented in laboratory animals (Fidecka and Langwinski, 1989; Danysz et al., 1992), but it is unknown whether cross-tolerance develops to the subjective and reinforcing effects of alcohol and NMDA antagonists in humans and whether it may be an advantage from the perspective of medication development. Cross-tolerance blockade, as in the case of agonist substitution therapy, can be very effective in decreasing drug use and in preventing relapse following initial exposure (lapse) in abstinent patients. However, the ability of NMDA antagonists to exert cross-tolerance blockade does not seem to be likely for drugs other than alcohol.

4.5. Sensitization

Sensitization refers to an increased magnitude of drug effect with repeated administration and typically is seen in behavioral effects such as locomotor activity and stereotypy (Kalivas et al., 1992). Some of the phenomena manifested in humans with alcohol and drug dependence (e.g. craving, impact of environmental stimuli) seem to be intensified with progressive drug use and therefore are believed to be a result of sensitization (Robinson and Berridge, 1993). These processes may contribute to the maintenance of a pathological behavior and play a role in relapse to drug use after a period of abstinence.

NMDA-mediated neurotransmission is involved in the development of behavioral sensitization of psychostimulants, opioids, and nicotine. It has been shown that the locomotor stimulatory and stereotypy-inducing effects of these drugs can be attenuated by both competitive as well as uncompetitive NMDA antagonists (Wolf and Jeziorski, 1993; Jeziorski et al., 1994; Livezey et al., 1995; Shoaib et al., 1997) (see Wolf, 1998 for a review of the data with psychostimulants). In contrast, in animals previously sensitized to morphine, acute pretreatment with MK-801 did not alter the sensitized locomotor response (Jeziorski et al., 1994). However, MK-801 can, by itself, induce behavioral sensitization (Wolf and Khansa, 1991), and repeated co-administration of MK-801 with cocaine or amphetamine can also enhance locomotor sensitization (Carey et al., 1995; Segal et al., 1995). Pre-exposure to amphetamine, cocaine, morphine and alcohol accelerates the rate of acquisition of drug self-administration or enhancement of drug CPP (Lett, 1989; Piazza et al., 1989). In this paradigm, MK-801 blocked the ability of amphetamine to sensitize subsequent acquisition of cocaine in experienced self-administering rats (Schenk et al., 1993a). If MK-801 had a similar effect in drug dependent patients seeking treatment, it might prevent escalation of drug-use (relapse) in abstinent patients following initial use (lapse).

4.6. Physical dependence

Chronic treatment with many drugs of abuse (particularly opioids, alcohol and benzodiazepines) produces physical dependence. The withdrawal syndrome that emerges upon discontinuation of the drug or administration of an antagonist reveals an existing dependence. Perhaps the first observation concerning the inhibitory effects of NMDA antagonists on drug dependence was a report of a decrease in spontaneous convulsions seen during the barbital abstinence syndrome in rats pretreated with APH (McCaslin and Morgan, 1987). Similar protective effects are also seen after administration of other competitive antagonists, such as CGP 39551 and CGP 37849, in mice (Rabbani et al., 1994). The decrease in spontaneous withdrawal symptoms (wet dog shakes and audiogenic seizures), was seen when rats and mice treated with ethanol for a week were administered ketamine during the withdrawal (Fidecka and Langwinski, 1989). It was later shown that ethanol withdrawal seizures could be attenuated by MK-801 (Morrisett et al., 1990) and CGP 39551 (Liljequist, 1991). This protective effect of glutamate antagonists on seizures induced by discontinuation from chronic alcohol exposure has recently been established for glycine (L-701 324) and polyamine (eliprodil) NMDA receptor antagonists (Kotlinska and Liljequist, 1996). Mice withdrawn from chronic treatment with diazepam show a time- related evolution of muscle rigidity, and seizures after treatment discontinuation. Treatment of mice with D-CPP-ene during this phase prevented the expression of withdrawal symptoms (Steppuhn and Turski, 1993).

Several studies have demonstrated that NMDA receptor antagonists reduce the physical aspects of the expression of morphine dependence as measured by naloxone-precipitated withdrawal (Bristow et al., 1997; Popik and Danysz, 1997; Popik et al., 1998, see also Herman and O'Brien, 1997 for review of earlier studies). The motivational impact of morphine withdrawal (as studied in the conditioned place aversion model) was reduced following treatment with MK-801 (Higgins et al., 1992) and memantine (Popik and Danysz, 1997). In addition, NMDA receptor antagonists inhibit the development of morphine dependence (Trujillo and Akil, 1991), as well as its maintenance, a condition in which one can precipitate the withdrawal syndrome for some time after the administration of an opioid agonist has been discontinued (Popik and Skolnick, 1996; Popik et al., 1998).

4.7. Nitric oxide synthase inhibitors

Several of the effects that have been previously described for NMDA receptor antagonists in animal models of drug dependence and addiction have also been shown for nitric oxide synthase (NOS) inhibitors. These effects may not be surprising since NO is thought to be among the intracellular messengers important in NMDA receptor activation. Most of the literature concerns the effects of NOS inhibitors on opioid tolerance and withdrawal (see Herman et al., 1995; Vaupel et al., 1997, and references therein). In addition NOS inhibitors modulate psychostimulant-induced behavioral sensitization (Haracz et al. 1997; Itzhak, 1997; Kim and Park, 1995; Pudiak and Bozarth, 1993), reduce place preference for ethanol and morphine (Biala and Langwinski, 1996), and reduce cocaine self-administration (Pulvirenti et al., 1996). However, they do not affect brain stimulation reward (Bozarth et al., 1994).

4.8. Acamprosate

Acamprosate (calcium acetyl homotaurine) is a relatively new compound that modulates NMDA receptor function in a complex manner. Depending on the model, it acts as a functional antagonist (Zeise et al., 1993) or agonist (Madamba et al., 1996) of the NMDA receptor, with some inhibitory activity at the presynaptic $GABA_B$ receptor system (Berton et al., 1998). According to recent findings, acamprosate binds to the polyamine site and modulates the NMDA receptor as a partial agonist (i.e. acamprosate activates the NMDA receptor when it is in a relatively inactive state and inhibits the receptor when it is hyperexcited; al Qatari et al., 1998; Naassila et al., 1998). In animal models of dependence acamprosate had effects similar to NMDA antagonists. It selectively reduced ethanol consumption without affecting responding for water in rats (Heyser et al., 1998) and it reduced deprivation-produced enhancement of alcohol self-administration (Spanagel et al., 1996a). Acamprosate did not have any consistent effect on either the intake of heroin during the maintenance phase or the reinstatement of self-administration induced by priming doses of heroin or a footshock stressor (Spanagel et al., 1998). Acamprosate has been found to reduce some of the physical signs of spontaneous withdrawal in alcohol-dependent rats (Spanagel et al., 1996b) and it reduced the aversive properties of naloxone-precipitated morphine withdrawal assessed in the place aversion paradigm (Kratzer and Schmidt, 1998).

5. Clinical studies of NMDA antagonists in addictions

5.1. Dextromethorphan

Dextromethorphan (DXM) is an effective and widely used antitussive drug. It is a dextrorotatory opioid derivative that does not act at opioid receptors but is an uncompetitive NMDA antagonist (Netzer et al., 1993) with a well-established and favorable safety profile that permits its use in the general population as an over-the-counter medication (Bem and Peck, 1992). Three separate trials reported by Koyuncuoglu and coworkers showed DXM to be successful when used alone, or in combination with chlorpromazine or tizanidine (a presynaptic glutamate release inhibitor), in the treatment of opiate abstinence (Koyuncuoglu and Saydam, 1990; Koyuncuoglu, 1991, 1995). In the first of these studies, DXM was compared in a double-blind trial to chlorpromazine in 48 male heroin addicts (Koyuncuoglu and Saydam, 1990). In addition, all patients received diazepam. The observer-rated scores of the abstinence syndrome, as well as of craving, were significantly lower in the group that received DXM. Most of the patients from the chlorpromazine group left the study in the first 24 h and no one remained in the trial on the last (eighth) day, as opposed to 63% of the subjects from the DXM group who completed the trial. Interpretation of the results from this study is confounded by co-administration of the benzodiazepine that, by itself, is effective in reducing symptoms of opiate withdrawal. The results of our recent open-label pilot study provide support for the efficacy, safety and feasibility of DXM in detoxification from opiates (Bisaga et al., 1997). We studied six consecutive patients diagnosed with opioid dependence who had undergone several previous inpatient detoxifications. All subjects received 375 mg of DXM daily. Two of the patients requested a change to methadone during the second day of the trial because of physical discomfort. All patients who completed the study demonstrated a rapid and complete attenuation of withdrawal signs, symptoms, and craving by the fourth day of treatment. The improvement, particularly the alleviation of craving, was most prominent during the first 2 days. Patients who successfully completed the trial reported a positive effect of the treatment on relief from craving. Indeed, it was reported as more favorable than previous detoxification experiences with methadone. DXM was tolerated with minimal side effects. However, two laboratory studies of DXM revealed different effects. Isbel and Fraser (1953) found no significant effect of DXM on the morphine abstinence syndrome, or when DXM was substituted for morphine in opiate-dependent individuals. Rosen et al. (1996) examined the effects of DXM on naloxone-precipitated opiate withdrawal in subjects stabilized on methadone. In this study there was considerable inter-individual variability in response to DXM but no net attenuation was found. The individual variability in response to dextromethorphan, the small number of subjects in the study, a relatively low dose of DXM, and/or the short-lived, intensive withdrawal syndrome precipitated by naloxone might account for the differences between studies.

5.2. Amantadine and memantine

Amantadine and memantine are relatively low affinity uncompetitive NMDA receptor antagonists (Kornhuber et al., 1994). Both medications have been administered clinically for the management of Parkinson's disease, dementia, and spasticity. Amantadine and memantine have side-effect profiles that only rarely include psychiatric side effects (Kornhuber and Weller, 1997). In controlled clinical studies, amantadine appeared to reduce symptoms of cocaine withdrawal (Tennant and Sagherian, 1987; Thompson, 1992), cocaine craving and cocaine usage (Ziedonis and Kosten, 1991; Alterman et al., 1992; Shoptaw et al., 1998). However, there are many studies that had negative

findings (Weddington et al., 1991; Kolar et al., 1992; Kosten et al., 1992; Carroll et al., 1995; Handelsman et al., 1995; Kampman et al., 1996). It is important to emphasize that amantadine has significant actions at nicotinic and sigma receptors as well as enhancement of noradrenergic transmission at the doses necessary to block NMDA receptors (Danysz et al., 1997).

Memantine has been studied in a laboratory model of cocaine self-administration (Collins et al., 1998). Eight cocaine smokers were maintained for 8–11 days on memantine (20 mg daily) and placebo, using a double-blind crossover design. Under these conditions, memantine significantly increased subjective effects of cocaine, including ratings of 'high', 'potency', 'quality', and street value. Ratings of 'I want cocaine' were not significantly different under memantine versus placebo, but they were consistently higher during memantine maintenance across all doses. In spite of the increase in many of the subjective effects of cocaine, memantine did not alter the number of times participants chose cocaine over the monetary alternative. These results confirm some of the preclinical data showing that uncompetitive antagonists may potentiate acute effects of cocaine (see Wolf, 1998). Nonetheless, in the human laboratory paradigm memantine did not affect the reinforcing effects of cocaine. This observation is in contrast to the majority of animal data suggesting that NMDA antagonists reduce the reinforcing and other effects of cocaine that may contribute to the maintenance of cocaine dependence. The relevance of findings from the study by Collins et al., to medication development is unclear. This study had several limitations (e.g. low dose of memantine, short duration of the treatment, population tested in laboratory has no motivation for the treatment, and the predictive validity of laboratory model is unknown as there are no effective medication for the treatment of cocaine dependence). Only further laboratory studies and a clinical trial may help to determine whether memantine will have an advantage over amantadine for the treatment of cocaine dependence.

5.3. Ibogaine

Several anecdotal reports suggest that the naturally occurring alkaloid ibogaine, given in a single dose, decreases drug dependence in laboratory animals and humans (for review see Popik et al., 1995b). The recently described NMDA-antagonistic action of ibogaine (Popik et al., 1995a) might explain ibogaine's claimed effectiveness in the treatment of morphine, heroin, alcohol, nicotine, and stimulant abuse (Sershen et al., 1997). Uncontrolled clinical data strongly suggest that treatment with ibogaine is effective in heroin and cocaine dependence (Sheppard, 1994). Phase I safety trials were undertaken (Mash et al., 1998); however, no controlled clinical trials of ibogaine in the treatment of drug addiction have been carried out. Recently, the results of open-label treatment using ibogaine for drug detoxification have been reported (Kovera et al., 1998). Single doses of ibogaine given to treatment-seeking subjects dependent on opioids and cocaine resulted in minimal or no withdrawal symptoms and decreased drug craving.

5.4. Acamprosate

Acamprosate has been used as an adjunct to conventional outpatient treatment of alcoholism in controlled clinical trials. In the majority of studies, patients who were followed for up to 2 years and who were receiving acamprosate following detoxification showed significantly higher continuous abstinence as compared with patients receiving placebo (Garbutt et al., 1999).

5.5. Cycloserine, lamotrigine

D-cycloserine is a broad-spectrum antibiotic that has been used for the treatment of tuberculosis for over 30 years. It is a partial agonist at the strychnine insensitive glycine-binding site of the NMDA receptor (Watson et al., 1990). At higher doses (over 250 mg/day) cycloserine acts as an NMDA competitive antagonist and therefore the therapeutic window may be limited (see Cascella et al., 1994). Lamotrigine is one of the newer medications approved as an adjunctive treatment for patients with seizure disorders. Its effects may be mediated through actions at voltage-dependent sodium channels, resulting in inhibited release of glutamate and aspartate. Lamotrigine is generally well tolerated (Messenheimer et al., 1998).

Rosen and Kosten (1998) studied the effects of pretreatment with single doses of D-cycloserine (375 and 750 mg/70 kg) on the severity of naloxone-precipitated opiate withdrawal in opiate-dependent subjects. In this paradigm, cycloserine did not affect the severity of withdrawal symptomatology. Using a similar study design, the effect of pretreatment with lamotrigine (250 or 500 mg) has also been tested (Rosen et al., 1998). Lamotrigine attenuated some physiological withdrawal signs in some subjects but no significant effect on most of the withdrawal measures was found

6. Conclusions and a hypothesis concerning the mechanism of action

As outlined initially, the purpose of this review is to present the available data demonstrating that NMDA receptor antagonists have the potential to be developed as medications for clinical syndromes associated with addiction to alcohol and other drugs. In animal models,

NMDA antagonists modulate many of the effects of chronic administration of psychostimulants, opioids, benzodiazepines and alcohol. NMDA antagonists alleviate physical as well as motivational aspects of the withdrawal syndrome, attenuate ongoing drug dependence, reduce tolerance to several effects of these drugs, and inhibit the rewarding aspects of the drug and the environment in which the drug effect was experienced. This ubiquitous involvement of glutamate in many aspects of addiction and to many substances is indeed remarkable. One of the possible explanations of these findings is based on the clinical observation that various drugs of abuse and alcohol share many common behavioral features and have similar impacts on the organism (e.g. tolerance, dependence). These similarities could reflect involvement of closely related or shared neural pathways and adaptive changes in brain neurons and networks that are caused by the repeated exposure to drugs of abuse. Some of the cellular adaptations are similar following chronic exposure to various addicting substances and adaptive changes in glutamatergic transmission may mediate long-term drug effects (Nestler and Aghajanian, 1997). The extensive involvement of glutamatergic neurotransmission in modulation of the processes of neural plasticity (Danysz et al., 1995) could explain its ubiquitous role in learning processes underlying addictive states.

In our opinion, this large body of preclinical data and preliminary clinical findings suggests that NMDA antagonists might be useful as pharmacological adjuncts in the treatment of addictions. They may offer a novel, more rational, therapeutic approach to the treatment of addictive disorders, in particular the prevention of relapse. In this final part of the review we would like to suggest how the findings from preclinical research may relate to the potential benefits of NMDA antagonists in humans, and offer possible mechanism for the putative therapeutic benefits of these compounds in humans.

In order to speculate about the mechanism that may underlie the therapeutic potential of NMDA antagonists in addiction we first consider the two main phases of the pharmacological management of these disorders. The first phase is centered on detoxification and treatment of the acute abstinence syndrome. Unfortunately, even after successful detoxification, many affective and motivational disturbances may persist for several months (Handelsman et al., 1992). The second phase of treatment that aims at the alleviation of these disturbances is most often necessary to prevent relapse of the disease. The potential benefit of NMDA antagonists will be related to these two phases of treatment.

6.1. Detoxification—the acute phase

Extensive animal literature and preliminary clinical observations suggest that NMDA receptor antagonists are excellent candidates to treat withdrawal syndromes from opioids, alcohol, and sedatives. NMDA antagonists may attenuate not only the physical but also affective and motivational components of abstinence states as well as craving. The inhibitory effects of NMDA antagonists on the maintenance of morphine dependence in animals with physiological dependence (Popik and Skolnick, 1996; Popik et al., 1998) may complement their effects on the expression of an abstinence syndrome (Popik and Danysz, 1997). Most likely, the capacity of NMDA antagonists to reverse the neuroadaptive changes that lead to physiological dependence underlie its effects on withdrawal symptoms. Detoxification with NMDA antagonists may have several advantages over current therapies. Currently, detoxification is achieved by the gradual reduction of the agonist concentration in the organism thereby minimizing, but also extending, the withdrawal symptoms. This agonist approach, however, may result in the emergence of subtle withdrawal symptoms after the medication is discontinued. In addition, patients frequently report significant craving during gradual detoxification. NMDA antagonists may have an advantage over traditional methods if they prove to be effective in reversing physiological dependence and therefore reducing protracted withdrawal symptoms and craving as shown in preliminary clinical observations (Bisaga et al., 1997).

6.2. Normalization of chronic neurochemical deficits and conditioned responses—the continuation phase

Adequate pharmacotherapy following successful detoxification has most relevance for long-term outcome and the course of the disease. The ideal therapeutic agent used for this purpose would have a twofold effect. First, it would normalize the neurochemical changes that take place during chronic exposure to alcohol and other drugs. Second, it would have a modulatory effect on the pathological reactivity to drug-related environmental stimuli acquired during the course of addiction.

Neuroadaptations in the receptor systems that develop during chronic exposure to alcohol and other drugs of abuse have been a subject of extensive in vitro and in vivo studies (Nestler and Aghajanian, 1997). Chronic exposure to alcohol, cocaine, and morphine results in several biochemical adaptations in the glutamatergic receptor system in the limbic system which may underlie prominent changes in the structural and functional properties of this neural pathway related to drug and alcohol dependence (Ortiz et al., 1995;

Fitzgerald et al., 1996). Excitatory amino acids are involved in mediation of many of neurochemical changes and behavioral effects resulting from chronic exposure to drugs of abuse, some of which can be prevented or reversed using glutamatergic antagonists. Discussion of the potential mechanisms, neural circuits, and neurotransmitter systems involved in mediating the effects of glutamatergic agents in particular behavioral models is beyond the scope of this review (see Inturrisi, 1997).

Dysphoria, anhedonia, and anxiety are seen commonly in drug and alcohol addiction. In many patients these disturbances develop secondary to the addictive disorder and may be a result of abnormalities induced by repeated drug or alcohol abuse (Markou et al., 1998). In preclinical and early clinical studies, NMDA antagonists appear to have antianxiety and antidepressant effects and are currently being developed as medications for the treatment of these conditions (Danysz and Parsons, 1998). This beneficial effect may support the use of NMDA antagonists in the continuation phase of addiction treatment. NMDA antagonists may also have mild positive subjective and reinforcing effects that may promote compliance with treatment. Improving medication compliance is one of the major challenges in the development of medication for drug and alcohol dependence.

In addition to affective disturbances, several other factors are known to increase the risk of relapse following detoxification from alcohol and other drugs. This includes highly stressful situations, association with drug abusing peers and initial consumption of small amounts of alcohol and other drugs (Brewer et al., 1998). In addition, it has been well documented that individuals recovering from addiction remain highly susceptible to the environmental stimuli associated with previous exposure to drugs (O'Brien et al., 1977; Childress et al., 1986). This abnormal reactivity of the neural networks that were altered by repetitive pairing with drug-induced effects, a form of learning, is thought to underlie the vulnerability to relapse for a long time after the termination of drug use (O'Brien et al., 1998). The main objective of the ideal pharmacological treatment for addictions would be the protective effect against the conditioned and other factors that are known to increase risk of relapse.

The glutamatergic receptor system is central to processes of learning and memory, and therefore may be involved in associative processes occurring between the drug-related effects (reward, abstinence syndrome) and the environment where these internal effects were experienced (conditioning). Glutamatergic pathways that were altered during such conditioning might be involved in mediating this pathological reactivity. Therefore, inhibition of glutamatergic neurotransmission may attenuate the conditioned-drug effects. Animal models of drug-induced conditioned effects permit us to study brain mechanisms involved in mediation of conditioned stimuli. The expression of morphine-induced conditioned place preference may be regarded as a situation where drug treated animals seek or avoid the environment where the positive effects of drug exposure or negative effects of drug withdrawal were previously experienced. These behavioral responses can persist for up to several weeks. Treatment with NMDA antagonists can attenuate the behavioral expression of conditioned aversive or appetitive responses (Bespalov, 1996; Popik and Danysz, 1997; Tzschentke and Schmidt, 1997; Popik et al., 1998). NMDA antagonists may also attenuate the effect of the conditioned environmental stimuli that potentiate the reinforcing aspects of a drug in a given environment. For example, activation of the rewarding effect of brain stimulation by conditioned environmental stimuli is blocked by MK-801 in the rat (Bespalov and Zvartau, 1997). Lesions of the amygdala, which has dense glutamatergic projections to the limbic system, prevents cue-induced reinstatement of cocaine self-administration (Meil and See, 1997). Expression of several other drug-induced conditioned effects are also attenuated by NMDA antagonists (Damianopoulos and Carey, 1995; Bespalov and Zvartau, 1996b). Thus, the ability of NMDA antagonists to block effects of conditioned reinforcers would greatly increase their therapeutic role during recovery. This blockade would interfere with the ability of the conditioned stimuli associated with the abused drug to have incentive value, evoke craving, and, ultimately, relapse. It has been proposed that acamprosate may exert such effects (Littleton, 1995), and the initial reports of patients that were effectively treated with acamprosate support this hypothesis (Wilde and Wagstaff, 1997).

In summary, based on preclinical studies it appears that NMDA antagonists may be clinically useful in the treatment of drug and alcohol addiction. Therapeutic trials with these medication are needed to determine whether the optimism that arises from the preclinical studies is justified for clinical practice.

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