The Role of NMDA Receptor Antagonists in Nicotine Tolerance, Sensitization, and Physical Dependence: A Preclinical Review

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Nicotine, the primary psychoactive component of tobacco products, produces diverse neurophysiological, motivational, and behavioral effects through several brain regions and neurochemical pathways. Various neurotransmitter systems have been explored to understand the mechanisms behind nicotine tolerance, dependence, and withdrawal. Recent evidence suggests that glutamate neurotransmission has an important role in this phenomenon. The aim of the present review is to discuss preclinical findings concerning the role of *N*-methyl-*D*-aspartate (NMDA) receptor neurotransmission in mediating the behavioral effects of nicotine, tolerance, sensitization, dependence, and withdrawal. Based on preclinical findings, it is hypothesized that NMDA receptors mediate the common adaptive processes that are involved in the development, maintenance, and expression of nicotine addiction. Modulation of glutamatergic neurotransmission with NMDA receptor antagonists may prove to be useful in alleviating the symptoms of nicotine abstinence and facilitate tobacco-smoking cessation.

Key Words: Nicotine, NMDA receptors, tolerance, sensitization dependence

INTRODUCTION

Tobacco smoking is a powerfully addictive behavior with underlying addiction to nicotine. It is far more common than addiction to cocaine, heroin or alcohol.[1] Nicotine, a natural alkaloid (1-methyl-2-[3-pyridyl] pyrrolidine) present in tobacco leaves, is considered to be the major psychoactive and dependence-producing substance in tobacco products.[2-5] Like other drugs of abuse, chronic consumption of nicotine has been shown to produce both tolerance and dependence in humans.[1] In recent years, the use of tobacco has taken a great toll on youth and society. Over three million smoking related deaths are reported annually worldwide. It has been projected that over the coming 30 - 40 years, tobacco will become the largest single health problem worldwide, causing 8.4 million deaths annually.[2] Therefore, it is very important to develop interventions that can reduce and prevent tobacco use. An understanding of the mechanisms by which tobacco addiction occurs is an essential component of this goal.

Chronic use of nicotine and other drugs of abuse leads to three well-known consequences: tolerance, diminished responsiveness to the same dose of nicotine; *sensitization*, an increase in an effect of a drug with chronic use; and *physical dependence*, a neuroadaptive physiological change resulting from chronic drug exposure, such that the absence of the drug results in an unpleasant withdrawal syndrome.[3,4] Since the identification of nicotine as the primary psychoactive component of tobacco smoke, a great deal of research has been undertaken to unravel the neuropharmacological, anatomical, and behavioural underpinnings of its psychoactive effects. Various neural pathways and transmitter systems have emerged to explain the psychoactive and addictive properties of nicotine. Recent studies suggest those excitatory amino acid systems and, in particular, *N*-methyl-*D*-aspartate (NMDA) receptors, may have an

important role in this phenomenon. This review will focus on recent advances in our understanding of the role of NMDA receptors in the behavioral changes that occur following long term nicotine use, including tolerance, sensitization, and physical dependence.

NMDA RECEPTORS

Glutamate is a primary excitatory neurotransmitter for the majority of CNS receptors and is involved in the regulation of variety of neural functions. These receptors have been divided into two major types: metabotropic and ionotropic, based on their biochemical, pharmacological, and molecular profiles.[5] Metabotropic receptors (mGluRs) are coupled through G-proteins to the intracellular second-messenger system, whereas ionotropic glutamate receptors contain ligand-gated ion channels that mediate rapid changes in sodium, calcium, and potassium permeability. Ionotropic receptors are further divided into three major subtypes: NMDA, α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA), and kainate, as defined by the affinities of these synthetic ligands. Of the ionotropic glutamate receptors, the NMDA subtype has been the most extensively characterized. The NMDA receptor consists of a central ion channel and several modulatory sites to which neurotransmitters and drugs can bind and affect receptor activity.[6] Key sites on the receptor include the competitive site, the glycine site, the noncompetitive site, and the polyamine site. Each of the binding sites (glutamate, glycine, polyamine) has been used as a potential target for the development of both receptor and sub-type selective compounds.

Binding of an excitatory amino acid to the competitive site on the receptor complex opens the ion channel and allows entry of calcium ions into the neuron. When calcium enters the neurons, it can activate a variety of calcium-dependent enzymes and thereby modify neuronal function.[7] Competitive antagonists for the NMDA receptor such as LY274614, AP-7, and CPPP selectively block this glutamate recognition site. Activation of NMDA receptors by competitive site agonists requires coactivation of the glycine site on the complex. In other words, activation of the receptor by glutamate is facilitated by the binding of the co-agonist glycine to an allosteric site on the receptor complex. The noncompetitive or phencyclidine (PCP) binding site is located within the ion channel. Drugs acting at this site such as PCP or MK-801 block ion movement through the channel and prevent the influx of calcium, thereby antagonizing the activation of the NMDA receptor. The final key site is the polyamine site. Drugs acting at the polyamine site noncompetitively affect receptor activity.[8,9] Studies based on molecular cloning have shown that the NMDA subtype of glutamate receptor is a heteromultimeric channel consisting of NR1, NR2, and NR3 subunits in various combinations.[10,11] The channel 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.[12] NMDA receptors with different NR1 and NR2 subunit combinations have different electrophysiological and pharmacological properties.[10] Moreover, the NR1 subunits are formed from a single gene product with eight splice variants, whereas NR2 subunits form four different gene products (NR2A, NR2B, NR2C, and NR2D).[13] NMDA receptors show distinct distribution patterns in the adult rat brain compared with the developing brain, suggesting that there might be different populations of neurons with unique NMDA receptor subunit compositions and distinct pharmacological properties.[14,15]

It is now well established that NMDA receptors are widely involved in neural and behavioural plasticity.[16] NMDA receptors have been implicated in several different forms of drug-induced neural and behavioural plasticity, including the development of tolerance, sensitization, or physical dependence to a variety of psychoactive drugs including amphetamine, cocaine, nicotine, ethanol, benzodiazepines, barbiturates, and cannabinoids.[17-20]

At present, a significant number of NMDA antagonists and modulators are being developed. Several of those agents are already approved for clinical use, or are in the late stages (phase II/III) of clinical trials.[21,22] Moreover, 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. desimi-pramine, memantine, amantadine, and dextro-methorphan).

NMDA RECEPTORS AND DEVELOPMENT OF NICOTINE TOLERANCE

Chronic administration of nicotine results in tolerance and dependence in both humans and rodents.[23,24] In the past, the evaluation of nicotine tolerance and withdrawal has been attempted using various models, including operant schedules of reinforcement,[25,26,27] place preference,[28] auditory startle,[29] and activity,[30] as well as discriminative stimulus effects of nicotine.[31] However, the behavioral effects observed in these models in rodents appear to be complex and varied. The equivocal results obtained in these studies may be due to differences in dosage, sex or age of the test animal, route of drug administration, time of evaluation, animal strain used, or the behavioral test employed in the respective study.[32] Nicotine elicits biphasic inhibitory-stimulatory effects on locomotion in a baseline-dependent fashion.[33] In contrast to certain other behavioral effects of nicotine, tolerance does not appear to develop to the stimulant and reinforcing actions.[34] The locomotor stimulant action is rather weak in drug-naïve animals, and becomes more pronounced with repeated administration as tolerance develops to the initial depressant action of the drug.[34] Further, behavioral tolerance develops rapidly with both acute and chronic administration.[35,36] Morley and Garner have demonstrated that chronic administration increases locomotor activity in the light phase, but not in the dark phase, of the diurnal cycle.[37]

Research to date does suggest an interaction between central nicotinic and dopaminergic systems.[38] Evidence implicating dopamine in behavioral effects of nicotine addiction has come from studies utilizing the neurotoxin 6-hydroxy-dopamine to produce lesions of forebrain dopamine systems.[39] *In vitro* and *in vivo* studies show that nicotine can stimulate the release of dopamine in the ventral tegmental area (VTA), striatum, and nucleus accumbens.[40,41] These effects of nicotine also show some selectivity for the

mesolimbic as compared with the nigrostriatal branch of the dopamine system. It is thought that the activation of the mesolimbic dopamine system induced by nicotine underlies the reinforcing and stimulant effects of this drug.[42] Behavioral studies with procedures such as drug discrimination reveal evidence for similarities between the effects of nicotine and drugs that are known to act as direct or indirect dopamine agonists.[43] An interpretation of the extinction-like effect of dopamine-receptor antagonists in terms of impairment of associative stimulus-reward learning has also been provided.[44] Further, selective dopamine antagonists D1 and D2 can also attenuate some of the behavioral effects of nicotine, including stimulation of locomotor activity,[45] nicotine self-administration,[46,47] and the nicotine discriminative stimulus in rats.[48] Jain et al. studied the effect of selective dopaminergic drugs in nicotine tolerance and suggest that tolerance to nicotine may be mediated through a selective dopamine D2 receptor.[49]

The mechanisms by which tolerance to the effects of nicotine develops are not fully understood. However, biochemical studies have shown that chronic exposure to nicotine increases high affinity binding of nicotinic agonists to brain tissue and induces chronic tolerance to many of the drug's behavioral and physiological effects.[50] The increase in receptor number (upregulation) has been interpreted as a compensation for agonist-induced desensitization of nicotinic acetylcholine receptors (nAChRs), and this prolonged desensitization has been proposed as the mechanism of chronic tolerance to nicotine.[51,52] Other work has shown that nicotine exposure over hours to days upregulates high-affinity nicotine binding to receptors through a posttranslational mechanism thought to increase receptor numbers. Nicotine exposure causes a four to sixfold higher binding to alpha4beta2 receptors that does not correspond to any significant change in the number of surface receptors or a change in the assembly, trafficking, or cell-surface turnover of the receptors. Such upregulation might alter the functional state of the receptors.[53]

As noted above, both *in vivo* and *in vitro* studies show that nicotine can release dopamine, but only a few studies have examined the effects of chronic

treatment on this measure. Maisonneuve et al. demonstrated that single doses of nicotine induce reversible acute tolerance to nicotine- induced release in the nucleus accumbens that peaks after one hour and is lost by three hours after nicotine administration.[54] This time-course explains the failure of some studies to observe tolerance between doses of nicotine repeated over 24 hours.[55,56] Further, the results of the studies carried out by Blackburn et al. and Carboni et al. indicate that chronic exposure to nicotine does not result in complete tolerance to nicotine-induced stimulation of dopamine release in the nucleus accumbens.[57,58] These results are apparently at odds to those of Hildebrand et al., who under similar conditions did not observe a significant increase of dialysate conditions.[59]

Recently, the effects of NMDA receptor antagonists on tolerance have been extensively studied, particularly with opiates.[60] Several studies have also indicated that antagonists acting at various modulatory sites of the NMDA receptor reduce tolerance development to the analgesic effects of opiates.[61] More recently, such inhibitory effects on the development of morphine tolerance have been documented for the clinically used compounds memantine and dextromethorphan.[62,63] NMDA antagonists also affect tolerance to the effects of alcohol.[64] The repeated co-administration of NMDA receptor antagonists MK-801 (dizocilpine) or D-CPPene (SDZ EAA 494; 3-(2-carboxypiperazin-4-yl)-1-propenyl-1-phosphonic acid) with nicotine attenuates the development of tolerance to the locomotor depressant,[65] and aversive effects of nicotine in rats.[66] Tolerance to some of the behavioral effects (learning impairment, ataxia) also develops when NMDA antagonists are administered chronically.[67] 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 in laboratory animals.[68,69] 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 in abstinent patients.

In summary, research studies do indicate the potential role of NMDA receptors in tolerance to different effects of opiates and ethanol. However, data from tolerance studies for nicotine have been limited. Additional studies are needed to understand the role of the NMDA receptor in nicotine tolerance.

NMDA RECEPTORS AND DEVELOPMENT OF NICOTINE SENSITIZATION

An alternative phenomenon in addictive behavior is termed sensitization or reverse tolerance. Sensitization refers to a progressive enhancement of species-specific behavioral responses that occurs with repeated drug administration and typically is seen in behavioral effects such as locomotor activity and stereotypy in animals.[70] Recent evidence suggests that repeated injections of drugs that lead to locomotor sensitization enhances a variety of processes related to drug addiction.[71,72] Locomotor sensitization may represent sensitization of an underlying reward/incentive system.[73,74] 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.[73] 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. Historically, the impetus for studying glutamate's role in addiction came from studies of behavioral sensitization. The long lasting nature of behavioral sensitization may be attributable to persistently enhanced responsiveness of neurons that innervate the nucleus accumbens, such as dopamine neurons from the VTA and glutamate neurons from the prefrontal cortex and basolateral amygdala.[75,76]

The mechanisms of the adaptive response to nicotine are not fully understood. Repeated exposure to nicotine has been shown to cause behavioral sensitization associated with an enhanced reactivity of nucleus accumbens dopamine neurons,[77-79] as well as cross-sensitization to other addictive drugs.[80,81] However, other studies did not find such sensitization effects shortly after repeated nicotine exposure.[82,83] These discordant findings could be attributable to the time dependence of drug-induced changes.

Recent evidence suggests that NMDA-mediated neurotransmission is involved in the development of behavioral sensitization of psychostimulants, opioids, and nicotine.[84,85] As reviewed by Wolf,[86] several investigators have found that co-administration of non-competitive NMDA receptor antagonists such as dizocilpine (MK-801), during repeated injections of these addictive drugs interferes with the development or subsequent expression of locomotor sensitization. In a series of experiments, Shoaib, Stolerman, and colleagues demonstrated that repeated co-administration of 0.3 mg/kg dizocilpine along with 0.4 mg/kg nicotine during several sensitization sessions attenuated sensitization to the locomotor stimulant effect of nicotine.[87,88] This co-administration of dizocilpine also prevented sensitization of nicotine-induced dopamine release in the nucleus accumbens and the sensitized increase in nicotinic receptors in a variety of areas, including the nucleus accumbens,[65] that normally occurs with repeated injections of nicotine. However, pretreatment with dizocilpine alone caused a modest enhancement of the behavioural response to a subsequent acute dose of nicotine. Similarly, co-administration of another competitive NMDA antagonist, D-CPPene (2.0 mg/kg), along with 0.4-mg/kg nicotine, attenuated sensitization to the nicotine-induced dopamine release in the nucleus accumbens. There was no enhanced locomotor response that could be attributed to nicotine pretreatment when D-CPPene was co-administered with nicotine. However, pretreatment with D-CPPene alone enhanced the locomotor response to an acute dose of nicotine. Although Shoaib et al. interpret this effect as indicating that dizocilpine has blocked the development of locomotor sensitization to nicotine,[65,88] more recent evidence indicates that similar effects of co-administration of dizocilpine on the subsequent expression of locomotor sensitization to other drugs may be due to state-dependency.[89-91] In other words, animals repeatedly injected with a combination of dizocilpine/nicotine may become sensitized to the combination (and to nicotine), but subsequently fail to express sensitization to nicotine alone, as nicotine does not sufficiently reproduce the sensitized dizocilpine/nicotine state. To resolve this controversy, Kelsey et al. attempted to

determine if the effects of the glutamate NMDA receptor blocker dizocilpine (MK801) on nicotine locomotor sensitization are due to a blockade of the development of sensitization or to state-dependency.[92] They concluded that co-administration of a low dose of dizocilpine can block the development of locomotor sensitization to repeated injections of nicotine without producing state-dependency, and thus NMDA receptor activation appears to be critical for the development, but not the subsequent expression, of nicotine locomotor sensitization. These findings are in accordance with the studies described earlier.[87] More recently, Shim and coworkers studied the role of nitric oxide synthase inhibitors and NMDA receptor antagonists in nicotine-induced behavioral sensitization in the rat.[93] They found that pretreatment with the NMDA receptor antagonist MK-801 during the nicotine induction phase also blocked hyperactivity to nicotine challenge. These results are consistent with previous data demonstrating that pretreatment with MK-801 blocks the development of sensitization to drugs of abuse including nicotine, cocaine, amphetamine or methamphetamine.[94] Furthermore, these results also demonstrate that nicotine-induced behavioral sensitization requires the activation of NMDA receptors not only for its development, but also for its expression. Since nitric oxide (NO) is known to be formed as a results of the activation of NMDA receptors, followed by Ca^{2+} influx and stimulation of Ca^{2+}/calmodulin-dependent NOS,[95] long-term behavioral changes produced by nicotine can be mediated by the activation of NMDA receptors followed by the formation of NO. Therefore, blockade of NMDA receptors and NO formation can result in the development of nicotine-induced sensitization.

All together, there appears to be general agreement that NMDA receptor antagonists inhibit the development of nicotine sensitization. NMDA receptor antagonists have also been found to inhibit the development of sensitization to the stimulant effects of other drugs of abuse like morphine, amphetamine, and cocaine.[4,18,20,70] This finding indicates that glutamate receptor stimulation is a necessary step in the cascade of cellular changes leading to sensitization. These results are

very intriguing, suggesting that NMDA receptors may be involved in sensitization to a variety of different drugs of abuse. Understanding the mechanisms underlying sensitization is of particular interest to the field of substance abuse, because this process may be involved in the craving that arises from repeated drug exposure.[89]

NMDA RECEPTORS AND DEVELOPMENT OF NICOTINE PHYSICAL DEPENDENCE

Withdrawal from nicotine following chronic use results in abstinence syndrome, which reaches peak intensity within 24 hours.[96,97] This syndrome is characterized by a variety of symptoms including irritability, anxiety, difficulty concentrating, restlessness, impatience, excessive hunger, insomnia, drowsiness, and craving for nicotine. Withdrawal reactions can be elicited either by termination of chronic administration of the drug or by acute challenge with the nicotinic receptor antagonist mecamylamine.[98,99] Evidence suggests rodent models of nicotine abstinence syndrome are potentially useful for research to understand the mechanisms of nicotine dependence and to screen proposed interventions to aid in smoking cessation. The few rat models that have been developed rely upon changes in conditioned behavioral responses or changes in body weight and food consumption to measure withdrawal intensity.[100,101] However, the behavioral response of rodents to nicotine using these models is complex and varied. As mentioned above, acute injections of nicotine can depress locomotor activity,[102] while chronic administration can increase locomotor activity.[103] Behavioural tolerance rapidly occurs with both acute and chronic nicotine administration.[104] This model is based primarily upon the frequency of spontaneous behavioral signs observed in nicotine-dependent rats after termination of nicotine. Abstinence behaviour is characterized by signs such as teeth chatter, chewing, gasps, abdominal writhes, body shakes, tremors, ptosis, and seminal ejaculation.[105] In addition, the administration of mecamylamine to rats that have been chronically treated with nicotine using an osmotic minipump induces various withdrawal signs such as teeth-chattering, chewing, abdominal wriths, gasps,

ptosis, wet shake, and tremors.[106] Moreover, this model is similar to widely used rat models of opiate abstinence syndrome and is analogous to methods used to quantify nicotine abstinence in humans.[107,108] In various preclinical studies, mecamylamine has been used to precipitate an abstinence syndrome in nicotine-dependent rats. Mecamylamine has been shown to act as a non-competitive as well as competitive antagonist to nicotine.[109-111] It has also been reported to potently reverse many actions of nicotine including locomotor effects, tremors,[112,113] analgesia,[114] hypothermia,[115] cardiovascular actions,[116] and effects on operant behaviour.[117] In addition, mecamylamine potently attenuates the discriminative stimulus properties of nicotine in experimental animals and in human smokers.[118,119]

There have been several attempts to clarify the mechanisms involved in nicotine dependence.[120,121] Nicotine withdrawal precipitates a deficit in brain reward function, as measured by elevations in intracranial self-stimulation (ICSS) reward thresholds similar to that observed in rats undergoing withdrawal from other drugs of abuse.[122] Avoidance and alleviation of this deficit in brain reward function has been proposed as a motivational factor contributing to craving, relapse, and continued tobacco consumption in human smokers.[97,122] Despite intense investigation into the mechanisms by which acute nicotine use produces its rewarding defects, the mechanisms mediating the reward deficits associated with nicotine withdrawal remain unclear.

Most drugs of abuse have been shown to stimulate excitatory glutamatergic transmission throughout brain reward circuitries.[123] Increase in glutamatergic transmission has been shown to play an important role in mediating the positive reinforcing actions of addictive drugs.[124] Nicotine is thought to act at several loci within the mesolimbic system in order to increase dopamine release within the nucleus accumbens (NAcc) and thereby produce its rewarding effects.[125,126] Initially, nicotine acts at nAChRs located on dopamine neurons in the VTA, and increases their firing rates.[127] Nicotine also acts at presynaptic α7 nAChRs located upon glutamate efferents that arise within the prefrontal cortex (PFC) to increase glutamate release in the VTA.[128,129] This enhanced

glutamate release then acts at NMDA and non-NMDA receptor sites on postsynaptic dopamine neurons and increases their firing rate. Finally, nicotine also acts at α7 nAChRs located on dopamine cell bodies in the VTA and on presynaptic terminals in the NAcc to increase dopamine release.[130] Accordingly, blockade of glutamatergic transmission reduces nicotine's stimulatory action on mesoaccumbens dopamine transmission and attenuates the rewarding actions of nicotine and other drugs of abuse.[131-133]

More recently, it has been documented that neuroadaptations that occur during prolonged exposure to drugs of abuse, which give rise to the deficits in brain reward function associated with withdrawal, may reside in the same neural elements that mediate the acute rewarding actions of these drugs.[134] In contrast to nicotine's acute stimulatory effects, however, nicotine withdrawal attenuates mesoaccumbens dopamine transmission,[59] an action likely to contribute to the reward and motivational deficits associated with nicotine withdrawal.[97] These findings are further supported by studies carried out by Balfour et al.[27]

In addition to its role in mediating the rewarding effects of drug like nicotine, there is also evidence that glutamate is involved in drug dependence and withdrawal states.[135,136] For instance, co-administration of the NMDA receptor antagonist MK-801 blocks the development and/or expression of opiate,[137] ethanol,[138] and benzodiazepine dependence.[139] Recently, the role of glutamate transmission, particularly the involvement of metabotropic glutamate receptors in nicotine withdrawal, has been investigated. Group II mGluRs are inhibitory receptors located at presynaptic and postsynaptic locations.[140] Stimulation of mGluR2/3 decreases glutamate release throughout the hippocampus, striatum, and cortex.[141-143] Interestingly, behavioral experiments with laboratory experiments have shown that the Group II mGluR selective agonist LY 354740 ameliorates the increase in acoustic startle response observed in rats undergoing nicotine withdrawal.[144] This observation led the authors to suggest that enhanced glutamate release may play a role in mediating the aversive aspects of nicotine withdrawal reflected by an increase in startle reactivity.[144]

It is also noteworthy that acute nicotine treatment increases the release of glutamate in various brain sites including the VTA,[128] NAcc,[77] PFC,[145] and hippocampus,[146] whereas acute LY354740 decreases glutamate release. In fact, because withdrawal effects are most often opposite in direction to acute drug actions,[147] it might be expected that nicotine withdrawal would be associated with deficits in glutamate transmission. It is therefore somewhat surprising that a drug that acts to decrease glutamate release ameliorates nicotine withdrawal, particularly because activation of glutamate receptors plays a role in mediating the rewarding actions of nicotine.[148,149] One possible explanation could be that glutamate release is increased only in certain brain sites and not in others and that LY 354740 selectively decreases glutamate release involved in facilitating enhanced startle reactivity. Another possibility could be that mGluR2/3 may be expressed on presynaptic terminals that release a neurotransmitter other than glutamate that enhances startle reactivity during nicotine withdrawal.[150,151] Therefore, LY 354740 may act at these putative mGluR2/3 hetero receptors to block this release and thereby block the enhanced startle reactivity observed during nicotine withdrawal.

A more recent review by Balfour also concluded that repeated nicotine injections increase extracellular dopamine in both the accumbal medial shell and core and lead to burst firing of dopaminergic neurons evoked by the drug.[152] This conclusion is further supported by the observation that stimulation of NMDA receptors on dopamine neurons in the VTA enhances the proportion of the cells that exhibit burst firing.[153] The increases in dopamine efflux in both the accumbal shell and core evoked by either acute or repeated nicotine injections are suppressed or abolished by the administration of NMDA receptor antagonists prior to the nicotine injection, suggesting a pivotal role of glutamate in nicotine's reinforcing effects.[154] Thus, although the molecular and cellular mechanisms underlying the response are different, nicotine shares with amphetamine and cocaine the ability to elicit a substantial and sustained increase in dopamine overflow into the extracellular space between the fibers of the accumbens. It seems reasonable to conclude that this common response to the drugs may be of fundamental importance

to their ability to cause dependence.

In summary, like opiate withdrawal syndrome, nicotine withdrawal syndrome is a complex phenomenon, characterized by several different signs and symptoms. Glutamate may play a role in mediating nicotine withdrawal. Evidence is lacking to suggest that NMDA receptor antagonists inhibit the development of nicotine withdrawal syndrome as a whole or a subset of signs and symptoms. It will be useful to clarify the impact of NMDA receptor antagonists on these effects, both individually and collectively, in order to better understand the potential role of NMDA receptors in the development of these different signs and symptoms and their relationship to one another.

NMDA receptors and ligands (agonists/antagonists/partial agonists) have been implicated in the phenomenon of tolerance, dependence, and, possibly, the management of nicotine dependence. However, the evidence is still highly equivocal, and various other neurochemical mechanisms such as dopamine, cannabinoids, serotonin, acetylcholine, adrenergics, and GABAergics have also been implicated in these phenomena. These receptors and neurotransmitters alone and in combination with NMDA receptors and ligands could be the target for development of future intervention strategies for nicotine dependence.

CONCLUSION

In conclusion, addiction to nicotine is a complex behavioural phenomenon that produces diverse neurophysiological, motivational, and behavioural effects through several brain regions and neurochemical pathways. In spite of decades of research, the mechanisms underlying nicotine tolerance, physical dependence, and withdrawal are still not well understood and several questions remain. A substantial amount of preclinical research suggests the role of glutamatergic, particularly NMDA receptor, neurotransmission in mediating the behavioural effects of alcohol and other drugs of abuse. In animal models, NMDA receptor antagonists modulate many of the effects of the 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, and reduce tolerance to several effects of the drug and to the environment in which the drug effect was experienced. This research also supports the therapeutic potential of NMDA receptor antagonists in alcohol and substance use disorders. Preclinical research studies examining the effects of NMDA receptor antagonists on tolerance, sensitization, and physical dependence of nicotine, though limited, are encouraging. These observations suggest that NMDA receptors are involved in the neural changes that underlie the development of tolerance, sensitization, and physical dependence to nicotine. Hypotheses linking all of the abused substances and nicotine to a common neural circuit and dopaminergic neurotransmitter system have also been suggested. NMDA receptor neurotransmission may interact with dopaminergic pathways, and both systems may play a role in mediating the CNS effects of a variety of substances of abuse, including nicotine. Moreover, nicotine shares many of the properties of a psychostimulant drug of dependence, and it seems reasonable to conclude that this explains the addictive potential of the drug and its role in the neurobiology of tobacco dependence. Furthermore, animal studies also demonstrate commonalities between nicotine withdrawal and opiate abstinence syndrome.

Results of preclinial research conducted so far suggest the therapeutic potential of NMDA receptor antagonists in alcohol and substance use disorders. The progress in applying results of these preclinical studies to the development of clinical medication has been slow but noteworthy. Preliminary clinical studies treating opioid dependence with drugs like dextromethorphan and memantine in both detoxification and relapse prevention have been encouraging.[155] The clinical data regarding the treatment of cocaine dependence are very limited, although some clinical controlled studies have demonstrated beneficial effects of amantadine on cocaine-craving and symptoms of cocaine withdrawal.[156-158] 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.[159]

Collins et al. studied the effect of memantine on cocaine self-administration and suggested that non-competitive antagonists may potentiate acute effects of cocaine.[160] Their study has several limitations, however, and 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. In addition, NMDA antagonist action of the naturally occurring alkaloid ibogaine has been reported, and it has been found to be effective in the treatment of morphine, heroin, alcohol, nicotine, and stimulant abuse.[161,162]

All together, there are currently a limited number of available medications to treat nicotine dependence and other substance abuse disorders. Despite recent advances in the understanding of the neurobiological basis of these disorders and the development of new psychotherapeutic approaches, a lack of viable pharmacological treatments persists. It seems likely that most of the drug therapies introduced to date as aids to smoking cessation act on some but not all of these mechanisms, and this explains why none have proved as efficacious as therapists or smokers would like. At this stage, it is too early to comment on the potential usefulness of NMDA receptor antagonists for nicotine dependence. Several questions remain regarding nicotine addiction. NMDA receptor antagonists might be useful as pharmacological adjuncts in the treatment of nicotine addiction, but further research is needed.

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