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REVIEW

The nicotinic acetylcholine receptor partial agonist varenicline and the treatment of drug dependence: A review

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Abstract

Drug dependence is a chronic brain disease characterized by recurrent episodes of relapse, even when the person is motivated to quit. Relapse is a major problem and new pharmacotherapies are needed to prevent relapse episodes. The nicotinic acetylcholine receptor (nAChR) plays an important role in nicotine dependence, alcohol consumption and cue-induced cocaine craving. Stimulation of the nAChR has been found to alter and modulate cell firing in brain areas important for the maintenance of drug dependence. Varenicline, an $\alpha 4\beta 2$ nAChR partial agonist and an $\alpha 7$ nAChR full agonist registered for the treatment of nicotine dependence, significantly reduces nicotine craving and prevents relapse. In addition, varenicline reduces alcohol consumption in rats. Based on a review of the available literature, we hypothesize a potential role for varenicline in the prevention of relapse in patients recovering from drug dependence other than nicotine dependence.

1. Introduction

Drug dependence is a prevalent disorder that creates a variety of social, financial and medical problems. Because drug dependence is a chronic relapse disease, there is a critical need for effective pharmacotherapies to help patients in their efforts to overcome the disease. Once abstinent, recovering addicts experience craving episodes triggered by environmental cues, stress, or the use of even a small amount of the drug itself (Shaham et al., 2003). Craving episodes are often followed by renewed drug-seeking and relapse, making it difficult for recovering addicts to remain abstinent. Relapse largely contributes to health costs and social problems for the dependent individual as well as for the problems of society as a whole.

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Thus far, several pharmacotherapies were tested to evaluate treatment effects in different types of dependence. Although some of the medications were effective, none of them showed large effect sizes leaving ample space for improvement. For example, proven effective and registered medications are available for the treatment of alcohol dependence, but effect sizes are moderate at best with numbers needed to treat (NNT) ranging between 7 and 15 depending on the medication and the outcome measure (e.g. Rosner et al., 2008). A similar situation exists for opioid dependence with several moderately effective medications registered for the treatment of heroin dependence (Gowing et al., 2009; Lobmaier et al., 2008; Mattick et al., 2009; O'Connor et al., 1997; van den Brink and Haasen, 2006). In cocaine-dependent patients, a broad range of pharmacological compounds were tested to reduce craving and relapse, but no large scale trials were conducted and none of the compounds has been registered so far (Kampman, 2008; Karila et al., 2008; van den Brink and van Ree, 2003). Recently, the opioid receptor antagonist naltrexone was found to be helpful in treating amphetamine dependence, but replication studies are needed for a final conclusion (Hill and Sofuoglu, 2007; Jayaram-Lindstrom et al., 2008; Rose and Grant, 2008). For cannabis dependence, no large scale clinical trials are available thus far (Benyamina et al., 2008; Clapper et al., 2009; Nordstrom and Levin, 2007). The antidepressant bupropion and nicotine replacement therapies are effective and registered for the treatment of nicotine dependence, but effect sizes are small and relapse is frequent (Cahill et al., 2008; Stead et al., 2008; Hughes et al., 2007). Recently, cytisine (a partial agonist of nicotinic acetylcholine receptors (nAChRs)) and the newer, related compound varenicline were introduced, showing substantial reductions in nicotine craving and smoking (Cahill et al., 2008).

Developing effective treatments for patients with a substance-use disorder remains a challenge and it is necessary to continue the search for new pharmacotherapies that help recovering addicts overcome craving and relapse. Here, we suggest a role for nAChR partial agonists, such as varenicline, in preventing relapse to drugs of abuse. This review aims to assemble theoretical and experimental support for a potential role of drugs targeting nicotinic receptors in the treatment of drug dependence, with a special focus on varenicline.

2. The process of drug dependence and the brain

2.1. Phases in development of drug dependence, involved brain structures and neurotransmitters

Risk factors can drive and predict initial drug use. These include environmental factors such as parental drug use, peer-group relationships, and family, school and/or employment problems. Additionally, genetics play a role in the onset (Uhl et al., 2008), but do not per se lead to drug dependence; it merely increases the risk of developing dependence in the presence of environmental risk factors (Crabbe, 2002; Nestler, 2000).

Drugs of abuse act in the brain as rewards, producing activity in the central nervous system via neurotransmitters. Important brain structures in acute reward mechanisms include the ventral tegmental area (VTA) and nucleus accumbens (NcA), part of the ventral striatum, with dopamine (DA) as the main neurotransmitter (Koob and Bloom, 1988; Koob and Volkow, 2009; Volkow et al., 1999). Rewarding effects also occur when drug use is expected, and are driven by DA in the thalamus, basal ganglia, occipital cortex, and cerebellum (Schultz et al., 2000; Volkow et al., 2003).

When transitioning to frequent drug use, drug induced changes occur in the brain: drugs become less rewarding and increasing amounts of the drug are needed to obtain the desired effect; this is known as tolerance (Wonnacott et al., 2005). Moreover, the hippocampus and amygdala play key roles in associating previous, positive drug experiences with memory (Hyman et al., 2006). Brain areas such as the NcA core, basolateral amygdala, thalamus, and orbitofrontal cortex (OFC) (neurotransmitters DA, dynorphin and glutamate) link drug use experiences with environments and other drug-associated cues; a process termed conditioning (Belin and Everitt, 2008). Cues that predict use acquire increased motivational significance, and facilitate drug use (Berke and Hyman, 2000; Volkow et al., 2006). Furthermore, increased salience is associated with altered drug reward value, modulated by the OFC and the neurotransmitter DA (Volkow et al., 2007b).

While changes develop due to frequent use, drug use evolves from being recreational to becoming habitual. During the process of habit formation, dorsal striatal subdivisions (the putamen and caudate nucleus) become involved through DAergic input (Barnes et al., 2005; Yin and Knowlton, 2006). As seen in animal models of drug dependence, drug consumption becomes compulsive (Roberts et al., 2007; Vanderschuren and Everitt, 2004). In the light of automated actions, the dorsal striatum and DA play an important role (Di Chiara, 1998; Everitt and Robbins, 2005; Hyman and Malenka, 2001; Robbins and Everitt, 2002; Volkow et al., 2007a).

Unfortunately, some individuals get to a stage where they cannot stop the compulsive use of drugs and become dependent. Even in abstinent persons, drug-related cues are able to produce craving (Hyman, 2005; Koob et al., 2004), activate drug seeking and reinstate consumption (Hyman and Malenka, 2001; Robinson and Berridge, 2003). Moreover, reactions to cues can occur unconsciously (Childress et al., 2008; Graybiel, 1998), making it difficult for abstinent addicts to recognize, anticipate, or prevent relapse. Furthermore, withdrawal symptoms play an important role in relapse during detoxification. The locus coeruleus, frontal cortices, NcA and VTA, and neurotransmitters norepinephrine, glutamate, DA and gamma amino butyric acid (GABA) are most importantly involved in these processes (Riahi et al., 2009; Koob and Volkow, 2009).

Also important in drug dependence, are the processes of decision making, conflict monitoring, and motor inhibition. The brain areas involved in making choices and monitoring conflicts include the anterior cingulate cortex (ACC) and the dorsolateral prefrontal cortex (DLPFC) respectively (Bechara et al., 2000; Carter and van Veen, 2007). These brain areas are not sufficiently active in drug-dependent individuals. Motor inhibition is also decreased in dependent individuals, and subsequent motivational pressure easily leads to increased drug intake (Arnsten, 2006). Disruptions in conflict monitoring and decision making (both PFC) may partially

explain why drug-dependent individuals keep taking drugs despite the knowledge of serious negative consequences (Bechara et al., 2000).

In summary, drug dependence is a complex process where the brain adapts to the continued presence of drugs. Adaptations in the brain lead to behavior that is characterized by the search for and consumption of more drugs, regardless of negative consequences. When drug-dependent individuals stop using the drug and become abstinent, drug-related cues and stress can recurrently lead to craving and relapse.

Many drugs of abuse, ranging from nicotine to cocaine, share common functions at the neurochemical, molecular, and anatomical levels. Similar and enduring neuroadaptations occur that far outlast the initial acute effects of the drug. Such adaptations are believed to underlie compulsive drug-seeking behavior and the tendency to relapse (Kelley, 2002).

2.2. Role of dopamine in the process of drug dependence

Endogenous DA increases in the VTA, NcA, OFC and thalamus are associated with reward after administration of stimulant substances of abuse such as nicotine, cocaine and methamphetamine (Volkow et al., 1999; for review see Koob and Volkow, 2009). These drugs stimulate endogenous DA release more intensely than natural rewards, causing drugs to become more salient than natural rewards. The brain DA reward system includes the VTA and NcA, wherein associations are formed between drug-related stimuli and behavior, i.e., drug-seeking consumption (Schultz, 2006, 2007). These conditioned stimuli or cues enhance extracellular DA firing to initiate craving (Schultz, 2006). In drug-dependent subjects, cue-elicit craving is correlated with DA release (Volkow et al., 2006; Zijlstra et al., 2008). Subsequently, craving is hypothesized to be due to neuroadaptations of the mesolimbic DA system (Franken et al., 2005; Koob et al., 2004; Robinson and Berridge, 1993). Furthermore, the DA system is implicated in attentional bias towards drug-related stimuli (Franken et al., 2004) and is associated with the development and storage of memory (Volkow et al., 2007a).

Neurochemical events are likely to contribute to long-lasting alterations induced by addictive drugs. Many drugs of abuse increase release of DA in brain reward areas such as the NcA and PFC. However, chronic drug use leads to hypodopaminergic function (Nader et al., 2006; Volkow et al., 2008), which may be explained by adaptations at the level of postsynaptic DA receptors. After repeated drug use, receptors show down-regulation with a long-term reduction of DA receptor binding (Nikolaus et al., 2007; Volkow et al., 1993). DA receptors remain down-regulated after abstinence (Volkow et al., 1993), although some rate of recovery was noted in non-human primates (Nader et al., 2006). Based on these and other findings, Blum et al. (2008) proposed that upregulation of the DA receptors in the NcA by activating rather than blocking DA receptors could result in an effective treatment for substance-use disorders.

In summary, the DA system modulates the aspects of learning, reward and motivation (Hyman, 2005; Wise, 1998) and chronic drug use leads to a decrease in postsynaptic DA receptor availability. Therefore, increasing DA receptor availability is a potential treatment strategy for drug dependence (Blum et al., 2008; Nader et al., 2006).

3. The role of nicotinic acetylcholine receptors in drug dependence

The brain contains different neurotransmitter systems, such as a DAergic, serotonergic, GABAergic and glutamatergic system. In addition, an extensive network of connections is modulated by acetylcholine (ACh): the cholinergic system. The receptors of the cholinergic system are divided into muscarinic acetylcholine receptors (mAChRs) and nicotinic acetylcholine receptors (nAChRs). Because varenicline has a strong affinity to the nAChRs and not to the mAChRs, we focus on the nicotinic receptor subtype to assess the potential role of varenicline in the treatment of drug dependence.

Nicotinic AChRs are ionotropic; they form ion-channels in the plasma membrane of the cell that can be opened by ACh and nicotine (Itier and Bertrand, 2001). Nicotinic AChRs include 5 subunits, formed by combinations of α-subunits ($\alpha2-\alpha10$) and β-subunits ($\beta2-\beta4$). Combinations result in receptors with different neuronal distribution and affinity regarding ligand binding (Changeux et al., 1998). The $\alpha4\beta2$ nAChR consists of two $\alpha4$- and three $\beta2$-subunits combined to a neuronal nicotinic receptor with high affinity for nicotine, which is widely distributed and represented in the rat brain (Flores et al., 1992; Wada et al., 1989) and stably expressed in the human brain (Gopalakrishnan et al., 1996).The subgroup of $\alpha7$ nAChRs is widely present in the human central nervous system. They are found in the cortex, hippocampus, VTA, and striatum, where they are expressed both pre- and post-synaptically on cholinergic neurons as well as on glutamate- and GABA neurons (Jones and Wonnacott, 2004; McGehee and Role, 1996).

Nicotinic AChRs seem to be centrally involved in the neuroadaptations induced by exogenous nicotine, amphetamine and cocaine. For example, repeated nicotine exposure results in an increase in functional nAChRs and, more specifically, sensitization of the mesolimbic DA response to nicotine (Balfour, 2004). In addition, Schoffelmeer et al. (2002) showed that endogenous release of DA following amphetamine and cocaine administration and subsequent nAChR activation is a precondition for increased DA release in the NcA and behavioral sensitization. Thus, nAChR activation may be crucial for the development of dependence to many drugs of abuse (Schoffelmeer et al., 2002).

3.1. Nicotine and the dopaminergic system

One third of the $\alpha4\beta2$ nAChRs are located on DAergic cell bodies in the mesostriatal DA system (Clarke and Pert, 1985; Zhou et al., 2003). Subsequently, nicotine enhances DA release through presynaptic nAChRs in striatal synapses and is thus characteristic for reward-related signaling (Dani and De Biasi, 2001; Di Chiara, 2000; Pidoplichko et al., 1997; Rapier et al., 1988; Rice and Cragg, 2004). When pretreated with a nAChR blocker, no increase in DA release was observed after nicotine administration (Giorguieff-Chesselet et al., 1979; Imperato et al., 1986). Moreover, knockout mice lacking the nAChR $\beta2$-subunit show no increased DA levels in

dorsal and ventral striatum and fail to maintain nicotine self-administration as compared to wild-type siblings (Marubio et al., 2003; Picciotto et al., 1998). Additionally, the presence of α4-containing-nAChRs is sufficient for nicotine-induced reward, tolerance and sensitization (Tapper et al., 2004). In summary, stimulation of the nAChRs results in increases in extracellular DA, an effect that seems to be dependent on the presence of α4β2 nAChRs, and is blocked by nAChR blockers such as mecamylamine.

3.2. Role of nicotinic acetylcholine receptors in drug dependence

A direct and indirect role for nAChRs in drug dependence have been observed. For example, nAChRs are found in the hippocampus, where they directly facilitate the flow of excitatory information through the process of synaptic strengthening or Long-Term Potentiation (LTP) (Cooke and Bliss, 2006; Gray et al., 1996; Jones et al., 1999; Mansvelder and McGehee, 2000). LTP is a process contributing to the maintenance of drug dependence and relapse through cellular mechanisms important in learning and memory (Changeux et al., 1998; Jones et al., 1999). In addition, nAChRs are present in the frontal cortex, where they are directly implicated in attention, memory, and associative learning (Levin and Simon, 1998; Pepeu and Giovannini, 2004).

Indirectly, nAChR activation influences neurotransmitter systems, such as the choline, glutamate, norepinephrine, DA, serotonin, GABA, and endocannabinoid systems, and these changes in turn affect cognitive functioning with a role in drug dependence (Dani, 2001). For example, the endocannabinoid system is implicated in reward association; glutamate projections in the VTA are related with the development of incentive sensitization for drug use and play a crucial role in cue-reactivity and relapse; the neurotransmitter serotonin and the serotonin-1A receptor are important in cue-induced locomotor behavior; and the GABAergic system modulates the efficiency of the reinforcing effects of a drug (Arnold, 2005; Kalivas, 2004; Muller et al., 2003; Roberts, 2005). Finally, part of the DA signal is modulated by cholinergic input, and DA release associated with reward in drug dependence processes could thus be influenced by modulating the nAChR (Keath et al., 2007; Pidoplichko et al., 1997; Wonnacott et al., 2000). As mentioned previously, an increase in extracellular DA in the NcA due to nAChR activation appears to be associated with the rewarding and addictive properties not only of nicotine, but also of other psychostimulant drugs of abuse, such as cocaine and amphetamine (Kelley, 2002; Schoffelmeer et al., 2002). Furthermore, we cannot exclude that different neurotransmitter systems activated through the nAChRs, could themselves activate the DA system. This could be executed through intermediate inhibitory GABAergic and excitatory glutamatergic synapses (Kalivas, 1993; McGehee et al., 1995; Pidoplichko et al., 1997; Role and Berg, 1996; Wonnacott et al., 1990, 2000) and would lead to a further regulation of the activity of DA cells in the VTA and downstream on the reward system (Di Chiara, 2000). Through nAChR activation, nicotine enhances the actions of glutamate and DA, thus providing a potential mechanism of action for the addictive properties of the drug.

Different studies provide evidence that modulating nAChRs could play a more general role in drug dependence and is not limited to just nicotine dependence. Exposure of whole cells to ethanol for only 3 h resulted in long-lasting changes in nAChR expression levels that remained elevated for nearly a week following withdrawal (Dohrman and Reiter, 2003). Also, polymorphisms in the β2 subunit gene of the nAChR were found to be associated with subjective responses to alcohol (Ehringer et al., 2007). Parish et al. (2005) looked at the density and distribution of DA terminal arbors, using α4 subunit knockout mice. Cocaine, amphetamine, haloperidol or nicotine was administered for 8 weeks in order to assess the role of the α4 nAChR in regulating the arbor size of DAergic neurons. The results showed normal functioning of DA D_2 receptor signaling in α4 knockout mice, but reduced reuptake of DA and an altered profile of the DA transporter (DAT). This study provides additional evidence for a role of nAChRs in altering DA response, specifically by regulating terminal arbor size of DA neurons (Parish et al., 2005). Additionally, in opiate dependence, nAChRs in the VTA seem to be important for modulating morphine-state-dependent learning (Rezayof et al., 2008).

In summary, nAChRs seem to contribute to the development of drug dependence both directly and indirectly. Nicotinic AChRs contribute to hippocampal LTP important for learning and memory, processes that are crucial for the development of drug dependence. Indirectly, nAChRs activate the terminal fields of the DA reward system in the brain that contribute to persistence of drug dependence.

3.3. Full nicotinic acetylcholine receptor antagonists, agonists, and partial agonists

Full agonists, such as nicotine replacement therapy (NRT), aim to replace the activation induced by nicotine at the nAChRs, therefore reducing withdrawal symptoms during nicotine abstinence (Carrozzi et al., 2008). NRT is proven effective in smoking cessation (Silagy et al., 2004), although it does not produce complete abstinence because the smoker is still physically dependent on the effects of nicotine. Antagonists, such as mecamylamine, fully block the nAChRs and indirectly reduce DA release (Lancaster and Stead, 2000). Therefore, a full antagonist may deactivate the reward circuit and reduce craving. However, antagonists are prone to induce withdrawal symptoms (Carrozzi et al., 2008), although this was not found in smokers (Eissenberg et al., 1996; Rose et al., 1989).

Modulating nAChRs can be achieved using nAChR agonists, antagonists or partial agonists. A nAChR agonist will mimic the effects of nicotine by activating the receptor, whereas a full antagonist blocks the signal to the cell. Antagonists compete with agonists for occupancy of the receptors, in order to block activation by nicotine or another agonist. Partial agonists display the properties of both agonists and antagonists. They occupy the receptor but only partially activate it compared to a full agonist. As a consequence, the action of a partial agonist is dependent on the current receptor occupancy (Childress and O'Brien, 2000). In the situation of full receptor agonist occupancy, the presence of a partial agonist will result in antagonistic pharmacodynamic effects, whereas in the situation of low agonist occupancy, the presence of a partial agonist will result in a (mild) agonistic pharmacodynamic effect. For

example, in a storage phosphor imaging study in drug-naïve rats, 2 week daily injections of varenicline (2 mg/kg body weight) increased DA $D_{2/3}$ receptor availability one day post-treatment with about 14% in the dorsal striatum and with about 15% in the NcA compared to rats receiving daily saline injections (Crunelle et al., 2009). In cigarette smokers, a partial agonist would mostly work as an antagonist after smoking but as an agonist during abstinence or withdrawal. To sum up, the rewarding effects of smoking would decrease substantially but not disappear completely (Coe et al., 2005; Rollema et al., 2007a), whereas during drug abstinence, withdrawal symptoms and craving episodes would occur less frequently due to the release of a low amount of DA.

4. Partial nicotinic acetylcholine receptor agonists in smoking cessation studies

Varenicline is an $\alpha4\beta2$ nAChR partial agonist and an $\alpha7$ nAChR full agonist, which is currently registered for smoking cessation in adults. As indicated by the most recent Cochrane review (Cahill et al., 2008), treatment with cytisine and its derivative varenicline results in decreased craving, decreased withdrawal symptoms, less pleasure when smoking and an increased chance for long-term abstinence. The results of a clinical trial showed that treatment with 2 mg/day varenicline for 12 consecutive weeks produced an abstinence rate 3 times higher than placebo 12 months after treatment. Cytisine, also a partial agonist of the $\alpha4\beta2$ nAChR and the parent compound of varenicline, showed a 1.5 times higher abstinence rate compared to placebo. Also in rat studies, both varenicline and cytisine antagonized nicotine's stimulant effects (Lesage et al., 2009), although the effects were less pronounced for cytisine than for varenicline, probably due to the greater affinity of varenicline to the $\alpha4\beta2$ receptor (Coe et al., 2005). Additionally, varenicline has a longer half-life and better brain permeability than cytisine (Rollema et al., 2007b). On the other hand, cytisine is less expensive than varenicline (Etter, 2006; Etter et al., 2008). The newer compound varenicline with its high selectivity and potency was produced as an upgrade for cytisine (Foulds, 2006). More nicotinic partial agonists were tested for their potential aid in nicotine dependence, such as dianicline (SSR591813) and lobeline (Cohen et al., 2003; Stead and Hughes, 2000). Whereas dianicline was effective (Cohen et al., 2003), lobeline sublingual tablets showed no significant positive effect (Stead and Hughes, 2000).

Due to its improved outcome in smoking cessation compared to other nicotinic partial agonists, we further focus on varenicline. In a clinical trial, treatment with varenicline 2 mg/day was significantly more effective than bupropion 300 mg/day treatment (overall OR 1.66) in reducing craving and withdrawal symptoms. Moreover, smoking satisfaction was significantly reduced for those who continued smoking during varenicline treatment (Gonzales et al., 2006). Furthermore, 12 week treatment with varenicline was more effective than 10 week NRT (Aubin et al., 2008). That is, varenicline significantly reduced craving, withdrawal symptoms and smoking satisfaction, and significantly more participants remained abstinent after 12 months (26% vs. 20%; OR 1.40) than without treatment. Here as well, participants who continued smoking reported decreased smoking satisfaction compared to the NRT group, which could reflect the relative antagonistic effect of varenicline at the $\alpha4\beta2$ nAChRs (Coe et al., 2005).

Abuse liability of varenicline was evaluated in smokers and non-smokers (McColl et al., 2008). Abuse liability for the highest dose of varenicline (3 mg) was similar to the abuse liability of the placebo condition. In general, partial agonists have a lower abuse potential compared to full agonists due to their inability to attain maximal agonist response (McColl et al., 2008). This would make partial agonists such as varenicline suitable for the treatment of drug dependence.

A full antagonist may also be effective in smoking cessation. However, a full antagonist (such as mecamylamine) may induce more withdrawal symptoms than a partial agonist. Surprisingly, mecamylamine did not precipitate withdrawal symptoms in smokers (Eissenberg et al., 1996) and decreased the subjective rewarding effects of smoking and decreased the desire to smoke (Rose et al., 1989). However, evidence suggests that mecamylamine in combination with NRT is more effective than NRT alone, mecamylamine alone, or placebo in smoking cessation (Lancaster and Stead, 2000). This could be due to a functional effect of the agonist NRT (reduction of the withdrawal effects) in combination with the effect of the antagonist mecamylamine (attenuation of the reinforcing effects of nicotine) (Rollema et al., 2007b; Rose and Levin, 1992; Rose et al., 1994). Subsequently, the development of a nicotine partial agonist such as varenicline, which is a functional combination of an agonist and an antagonist, is hypothesized to be optimal in the treatment of nicotine dependence (Rollema et al., 2007b).

However, the partial agonist varenicline may induce severe side-effects, including suicidal attempts, depression, psychosis, or paranoia (Kasliwal et al., 2009; Kintz et al., 2009; Kutscher et al., 2009; Lyon, 2008). Whether these side-effects are due to varenicline itself, withdrawal from nicotine, or comorbid psychiatric disorders, is undetermined (Kasliwal et al., 2009). However, the use of varenicline in addicted subjects needs to be monitored extensively in future clinical trials for alcohol and cocaine dependences, as the side-effects following the use of varenicline in dependent populations is still unknown. When using varenicline in combination with alcohol during a human study, however, only minimal adverse events (mood and nausea) were observed (McKee et al., 2009).

5. Varenicline and alcohol dependence

Smoking is strongly correlated with alcohol dependence (DiFranza and Guerrera, 1990; Funk et al., 2006). Consequently, a series of studies were performed on the role of nAChRs on alcohol abuse and alcohol dependence.

From studies performed in animals and humans, we know that ethanol-induced activation of the mesocorticolimbic DA system involves central nAChR stimulation (Blomqvist et al., 1993, 1997, 2002, 1996; Chi and de Wit, 2003; Ericson et al., 1998). In fact, the rewarding effects of ethanol are dependent on the activation of the nAChRs, which in turn activate the brain mesolimbic DA system (Soderpalm et al., 2000); and blocking of the nAChRs in the VTA abolishes the alcohol-induced increase in DA release in an indirect way (Ericson et al., 2003; Tizabi et al., 2002). Moreover,

mecamylamine blocks ethanol-induced DA release in the rat NcA through nAChRs mainly from the VTA, and results in reduced ethanol consumption in rats (Blomqvist et al., 1993, 1997; Ericson et al., 1998).

In human studies, mecamylamine decreases the stimulant-like effects of alcohol in social drinkers (Blomqvist et al., 2002). In order to overcome some of the methodological limitations of the former study (no control group, only one dose of mecamylamine), Chi and de Wit (2003) replicated and extended the study using a double-blind design including 14 males and 13 females with either mecamylamine (7.5 mg or 15 mg) or placebo, followed by alcohol consumption (0.8 g/kg body weight) or placebo. They found reduced self-reported subjective euphoria after alcohol intake and a reduced desire to consume more alcohol in the mecamylamine condition. However, Young et al. (2005) found no reduction in choice for alcohol in the mecamylamine versus the placebo condition, raising questions with regard to the efficacy of full nAChR blockade in the treatment of alcohol dependence (Young et al., 2005).

In rats, varenicline inhibited ethanol consumption and ethanol seeking while having no effect on sucrose seeking or water consumption, and produced no effect on inactive lever pressing of the self-administration chamber (Steensland et al., 2007). Thus, varenicline had no effect on locomotor behavior, which suggests that varenicline may have a potential role in the selective reduction of alcohol consumption in humans. In a microdialysis study in rats, acute administration of an intermediate dose of varenicline (1.5 mg/kg body weight) increased extracellular DA levels in the NcA with 55% of basal levels, while 5-day pretreatment with varenicline significantly attenuated increased NcA DA following combined nicotine and alcohol administration as compared to vehicle-treated rats (Ericson et al., 2009). Recently, a human study in heavy-drinking smokers showed that varenicline reduced the number of drinks compared to placebo, and 7 days pretreatment with varenicline decreased alcohol consumption during a 2-h self-administration session (McKee et al., 2009). Unfortunately, this is the only human study available on the effect of varenicline on human alcohol consumption.

6. Approaches for nicotinic acetylcholine receptor modulation in other drug dependences

Until now, no studies were performed to investigate the effect of varenicline in drug dependence other than nicotine and alcohol dependence. Only lobeline was studied in dependence other than nicotine, suggesting that this partial nAChR agonist could be effective in the treatment of stimulant abuse and dependence, e.g. cocaine and methamphetamine (Harrod et al., 2001; Miller et al., 2001; Polston et al., 2006).

The effect of mecamylamine on cocaine self-administration was studied in rats. After being trained on a self-administration paradigm for cocaine, either saline or mecamylamine (1, 2, or 4 mg/kg sc) was administered. Mecamylamine significantly reduced cocaine self-administration in rats, without decreasing general behavioral locomotion or food intake (Levin et al., 2000). Also, in mice, blocking nAChRs with mecamylamine up to 3 mg/kg body weight produced dose-dependent suppression of both cocaine- and nicotine self-administration (Blokhina et al., 2005). Moreover, daily intravenous mecamylamine (70 μg/infusion delivered concurrently with each cocaine injection) was able to block escalation from moderate to excessive cocaine use in rats (Hansen and Mark, 2007). In addition, inactivation of nAChRs (by using β2 knockout mice) significantly attenuated place preference as a measure for the rewarding effects of a drug, and provided evidence that activation of nAChRs potentiates cocaine reinforcement (Zachariou et al., 2001).

Administration of nicotine antagonists directly into the VTA or NcA alters cocaine-elicited increases in DA response in opposite ways depending on the type of nAChR targeted. For example, perfusion of methyllycaconitine (an α7 nAChR antagonist) increased, mecamylamine decreased (a relatively selective α3β4 nAChR antagonist), and dihydro-β-erythroidine (an antagonist of heteromeric nAChR subtypes) did not alter cocaine-elicited increase of DA perfused levels (Zanetti et al., 2007), thus providing evidence that several pathways and nAChR subunits may be involved in cocaine-elicited DA release. Also cocaine sensitization is shown to be influenced by α7 and β2 subunits of the nAChR: inhibition of these receptor subtypes is necessary to prevent development of sensitization to cocaine-elicit increases in DA release in the ventral striatum of mice (Zanetti et al., 2006).

On the other hand, no effect of nAChR blockage by mecamylamine was found on cocaine-or methamphetamine induced locomotor behavior in mice known to be extremely sensitive to locomotor effects of psychostimulants (Kamens and Phillips, 2008). It is possible that the dosages of mecamylamine (although up to 6 mg/kg body weight) were not high enough to induce their blocking effects in these mice. Interestingly, the dosage seemed to block ethanol-induced locomotor behavior, although ethanol locomotor behavior might not be as persistent as cocaine-induced locomotor behavior. Another explanation might be that different pathways are involved in ethanol and cocaine sensitizations.

In a double-blind clinical study, 20 patients with a history of crack cocaine smoking (all cigarette smokers) were given 22 mg nicotine or placebo patches, and subsequently exposed to crack cocaine-related environmental cues. Patients were assessed on craving, anxiety, skin conductance and temperature. Nicotine administration was significantly enhanced following crack cocaine-cue exposure in the absence of tobacco-smoking related cues, suggesting that nicotine exposure by itself enhances cocaine craving (Reid et al., 1998). Subsequently, Reid et al. (1999) tested mecamylamine for its effects on cue-induced cocaine craving in 23 cocaine-dependent subjects in a double-blind, randomized, counterbalanced design. Mecamylamine reduced craving for cocaine induced by cocaine-cue exposure by approximately 50% during the active testing day, suggesting a potential role for nAChR modulation in craving and relapse prevention for abused drugs such as cocaine. Also desire to use cocaine was significantly reduced by mecamylamine (Reid et al., 1999). The work by Reid et al. (1998, 1999) is important in showing that it is possible to modulate conditioned cocaine craving using a nicotinergic drug.

Nicotinic AChR modulation also shows promising results for amphetamine dependence (Miller and Segert, 2005; Hiranita et al., 2004). Pre-treating rats with mecamylamine attenuated the hyperactivity and sensitization produced by

repeated ephedrine 10 mg/kg injections, indicating the mediating role of nAChRs in amphetamine dependence (Miller and Segert, 2005). Contradictory effects were found on methamphetamine-seeking behavior in rats where nicotine administration unexpectedly attenuated methamphetamine-seeking behavior, and mecamylamine attenuated this effect, suggesting that nAChR-activating compounds could be used for relapse prevention (Hiranita et al., 2004).

Unfortunately, thus far, no animal or human studies were performed to assess the effect of varenicline on drug craving or drug consumption.

7. Discussion

In this review, we have focused on the interconnection between DA and the central cholinergic system in areas critically important for the development and persistence of addictive behaviors: locomotor activation, craving, and drug seeking. Nicotinic AChRs influence a variety of cognitive processes important in drug dependence and are able to modulate non-cholinergic neurotransmitter systems indirectly. Most importantly, nAChRs are necessary for DA release in the VTA and striatum, which are important areas responsible for reward in drug dependence. Partial agonists are unique because they adapt to the current (basal) neurotransmitter concentration in the system, and nAChR partial agonists could therefore be considered extremely beneficial for treating substance-use disorders by modulating the availability of DA receptors. Varenicline, a nAChR partial agonist, is a highly effective treatment of nicotine dependence. Varenicline significantly reduces craving in nicotine dependence, probably by stabilizing DA release in the brain. Similar results were found in animal models of alcohol dependence, suggesting a broader role for varenicline in the treatment of drug dependence.

Partial nAChR agonists are more effective in smoking cessation than full nAChR antagonists. One explanation could be that full antagonists cause more withdrawal symptoms, which could significantly increase the risk for relapse. Unexpectedly, this was not the case for mecamylamine. However, the combination of antagonist (mecamylamine) and agonist (NRT) treatment seemed to be more effective in decreasing nicotine craving than a full agonist or a full antagonist alone (Lancaster and Stead, 2000). This gives reason to believe that a compound that combines agonist and antagonist functions would be the most effective strategy in the treatment of drug dependence. We, therefore, believe that varenicline is a good candidate to effectively reduce cue-reactivity and craving through partial blockage of DA release in brain areas responsible for the rewarding effects of drugs, while still releasing enough DA to prevent anhedonia due to low DA release until the brain adapts again. Continued use of varenicline may induce upregulation of DA D_2 receptors (Crunelle et al., 2009), which would lead to reduced drug-seeking behavior, and a reduction in relapse episodes on the longer term.

Drug addicted individuals are well-known for their low retention rates and their limited adherence regarding medication intake. Fortunately, varenicline treatment for nicotine dependence (2 mg/day) during only 12 weeks has shown to remain effective for a minimum of 40 weeks post-treatment (Cahill et al., 2008). Therefore, varenicline seems to be a realistic candidate in preventing relapse episodes in detoxified drug addicts. Moreover, varenicline is not very likely to be abused (McColl et al., 2008), yet another reason for the use of a partial agonist.

However, VTA DA neurons express different types on nAChRs (Yang et al., 2009) and varenicline also has affinity for other receptor subunits, including the alpha7, the alpha3beta4, the alpha3beta2 and the alpha6 containing subunit (Mihalak et al., 2006). Different nAChR subunits may be involved in the reward mechanisms of different drugs, and, in this regard, a study by Larsson et al. (2002) contradicts the involvement of alpha4beta2 receptors in alcohol-mediated behavior in a mice study. Therefore, varenicline might also decrease alcohol consumption, for example, through interaction with other subunits than alpha4beta2. Future work might give more understanding on this negative finding on alpha4beta2 receptor modulation for alcohol consumption.

Thus far, no human studies were performed on the working mechanism or on the efficacy of varenicline in drug dependence other than nicotine and alcohol dependence. Some studies have focused on full nAChR antagonists and their role in cocaine dependence but no studies thus far have studied the effect of a partial agonist. Future clinical studies, however, plan to assess the potential effectiveness of varenicline in alcohol dependent individuals (Löf and Söderpalm; Plebani; www.clinicaltrials.gov), cocaine-dependent individuals (Plebani; www.clinicaltrials.gov), and the safety of varenicline in amphetamine-dependent volunteers (London; www.clinicaltrials.gov). Our group plans further research on the role of varenicline for reducing craving in cocaine detoxified patients using imaging techniques.

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Conflict of interest

All authors declare that they have no conflicts of interest.

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