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Nicotinic Acetylcholine Receptors in the Ventral Segmental Area are Important Targets for Nicotine and Ethanol Co-dependence

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Abstract

Tobacco and alcohol are the most commonly abused drugs. The nicotine (NIC) in tobacco and the ethanol (EtOH) in alcoholic drinks are responsible for their dependence respectively. The magnitude of tobacco smoking is drastically higher among alcoholics, suggesting a NIC-EtOH co-dependence. However, the mechanisms of NIC-EtOH interaction are not fully known, and the clarification of this action is clinically relevant. The majority of the NIC-EtOH interaction utilizes the ventral tegmental area (VTA) through both dopamine (DA) and non-DA systems. EtOH has been shown to bind directly to some nicotinic acetylcholine receptors (nAChRs) as, of course, does NIC. The non-selective/non-competitive nAChR antagonist mecamylamine (MEC) has been shown to partially block the DA releasing action of EtOH in the nucleus accumbens (NAc), while both the α4β2 nAChR antagonist dihydro-β-erythroidine (DHβE) and the α7 nAChR antagonist methyllycaconitine (MLA) do not. However, the α6-containing nAChRs (α6*-nAChRs) are responsible for both NIC-induced effects on DA release in the NAc and EtOH-induced GABA release in the VTA, suggesting that the α6*-nAChRs likely play a significant role in NIC-EtOH interactions. In this review, we have summarized current studies that reveal how EtOH reward through VTA nAChRs and what nAChR subtypes play roles in mediation of EtOH's effects in mesolimbic circuits. The accumulating lines of evidence suggest that the nAChRs, especially α6*-nAChRs in the VTA are likely important targets for NIC-EtOH interactions and NIC-EtOH co-dependence.

Keywords: Nicotinic acetylcholine receptors; Nicotine; Ethanol; VTA; Dopamine; GABA

Introduction

Tobacco and alcohol are the most commonly abused drugs by humans. Nicotine (NIC) is the major contributor in the continuance of tobacco use [1], while ethanol (EtOH) is the intoxicating agent in alcoholic drinks that can lead to abuse and dependence [2]. Alcohol use has been ascribed both positive and negative effects. While alcohol in low doses has been shown to provide cardiovascular protection [3], binge drinking is associated with higher incidents of cardiovascular disease and associated mortality [4,5]. As with alcohol, tobacco smoking has also been associated with cardiovascular problems. It has also been linked to coronary heart disease [6,7] and strokes [8,9]. Tobacco and alcohol use are leading causes of preventable death in the United States [10]. Smoking tobacco, the leading cause of preventable death, is accountable for approximately 467,000 deaths per year, while alcohol contributes to another 90,000 [10]. The most common type of polydrug use is alcohol and tobacco taken in concert [11,12]. The magnitude of tobacco smoking is extremely high among alcoholics [13] and is drastically higher than the rate in the general population [14,15]. Those who smoke are ten times more likely to be alcoholics than those who do not [16]. Those who are not alcoholics have been more successful than their alcoholic counterparts in quitting smoking, 49% to 7% respectively [16]. Although we know that the co-use of tobacco and alcohol is prevalent, little is known about the mechanisms of action when the two are used collectively. Clarification of these actions would be clinically useful in the treatment for the abuse of both tobacco and alcohol, as many requiring treatment for one also use the other.

Dopamine Dependent Mechanisms in the Mesolimbic System

Projections from the ventral tegmental area (VTA) to the nucleus accumbens (NAc), by way of the medial forebrain bundle, make up a vital component of the mesolimbic pathway [17-20]. The rewarding effects of both NIC and EtOH have been linked to the mesolimbic dopamine (DA) system [21-23], wherein an increase in DA in the NAc is thought to be vital for reward signaling. This system has been connected to the rewarding effects of many abused drugs [22,24-27]. The VTA consists of three major types of neurons: DA, γ-aminobutyric acid (GABA), and glutamate neurons. The most numerous are DA neurons that project to the NAc. The second, GABA neurons, inhibit DA neurons in local circuitry and project to other brain nuclei. Finally, there is a small population of glutamatergic neurons [28] which can innervate both DA and GABA neurons. The NAc is part of the ventral forebrain and is segregated into two regions: the shell and the core. Of the two regions, the shell has been shown to be important for the rewarding effects [29]. The medial VTA seems to consist of the highest number of DA neurons innervating the NAc shell [30].

Dopamine Independent Mechanisms in the Mesolimbic System

Although the mesolimbic DA system's involvement has been known to be critical for most drugs of reward, drugs such as morphine, phencyclidine and NIC also manifest DA independent mechanisms. The necessity of this DA system in the rewarding properties of

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benzodiazepines, barbiturates and caffeine is also questioned [29,31,32]. A rising hypothesis asserts that DA is not requisite for all rewarding effects of opiates, cannabis, cocaine and NIC. The idea that DA in the mesolimbic system is the only way by which reward occurs is perhaps too limiting. Evidence supporting a lack of DA involvement in drug reinforcement has been demonstrated in cocaine self-administration [33], and conditioned place preference [34,35]. Additionally, there has been confirmation that GABA neurons in the mesolimbic pathway are involved in the rewarding properties of opiates [36-38]. It has been reported that $GABA_A$ receptors in the VTA could be a gating mechanism wherein opiate naïve animals utilize a DA independent system, while opiate dependant, and opiate withdrawn, animals utilize a DA dependent system [39]. Following opiate exposure and withdrawal, VTA $GABA_A$ receptors change from acting in an inhibitory manner to an excitatory one. Moreover, high doses of the DA antagonist haloperidol neglected to stop the reinstatement of heroin seeking behavior, giving credence to a notion of a DA independent system, at least in the case of opiates [40,41]. Some assert that DA neurons are not exactly reward neurons, but instead may be pivotal for the initiation and reinstatement of drug use [42]. These conflicting reports on the necessity of DA for the reinstatement of drug use shows that the role of DA is not fully understood. Therefore, DA transmission in the mesolimbic pathway may be important for the motivational effects of abused drugs in dependent animals, while other systems could be exploited when animals are naïve [43,44]. These studies supply verification for the existence of DA independent mechanisms that also contribute to the reinforcing properties of drugs of abuse.

Nicotine and Ethanol Reward Associated with the Ventral Tegmental Area

The effects of both NIC and EtOH involve the VTA [45,46]. The direct excitatory effects of EtOH on neurons in the VTA have been observed [47,48]; both *in vivo* and *in vitro* recordings have shown this effect [49,50]. Rodents will self-administer NIC and EtOH individually into this region [51-55] and synaptic plasticity has been demonstrated in the VTA in response to both substances [56], giving further support to this theory. It is also well known that NIC binds to nAChRs throughout the brain. Rodents with NIC infusions into the VTA demonstrate conditioned place preference. However, similar infusions into areas dorsal or caudal to the VTA do not produce this preference, even if heavily populated by nicotinic receptors [57]. This demonstrates that the medial VTA is essential for the rewarding behaviors of NIC [58]. For the above-mentioned reasons, it is likely that the neural substrates underlying the co-use of NIC and EtOH depend on VTA neuronal activity.

Other midbrain tegmental regions are involved in the reinforcing characteristics of drugs such as opiates and NIC [51,59]. Cholinergic receptors work together with neurons in the NAc, VTA, and pedunculopontine tegmental nucleus (PPTg) to produce the rewarding effects of NIC [20,59,60]. As many drugs of abuse have demonstrated both rewarding and aversive properties [29,61], it has been proposed that the VTA is involved in mediating both of these qualities in actions of NIC [57]. The aversive properties of NIC are reported as being mediated by the mesolimbic DA system, while its rewarding effects are mediated by non-DA neurons projecting from the VTA to the PPTg [57]. Although these two separate effects are thought to be mediated by the same region, two different systems are involved. Blocking the mesolimbic DA pathway with the DA antagonist α-flupenthixol greatly increases the sensitivity to NIC reward in rodents [57]. In fact, a reduction in the amount of DA D1 and D2 receptors is positively correlated with NIC addiction, additionally supporting this finding [62]. Therefore, the VTA mediates the rewarding effects of EtOH and the aversive effects of NIC via DAergic projections to the NAc, while the rewarding properties of NIC are mediated via non-DAergic projections from the VTA to the PPTg [57]. This mediation of both NIC reward and aversion in the VTA could aid in explaining the cross-tolerance observed with NIC and EtOH interactions.

It is currently understood that the mesolimbic system, especially in the VTA, is involved in NIC-EtOH reward. There is, however, a question as to which type or subtype of receptor is most important and on which category of neuron they are found. The origin of long-term potentiation (LTP) induction in NAc DA neurons has been reported to be from presynaptic neurons [63]. GABA neurons play an integral role in the rewarding effects of drugs of abuse [48]. In fact, stimulation of $GABA_A$ receptors is reinforcing [51] and inhibition of GABA neurons in the VTA could lead to increased DA release in the NAc [64]. nAChRs can be found on postsynaptic, preterminal, and presynaptic segments of GABA neurons [65-67], and the reinforcing properties of EtOH is influenced by these receptors. These studies suggest GABA neurons in the VTA serve as an important locus for the modulation of the EtOH effects, possibly by nAChRs.

Nicotine and Ethanol Interactions

Interactions between NIC and EtOH have been demonstrated in an assortment of experiments. Alteration of nAChRs in response to EtOH has been verified [68]. Mouse and rat studies have displayed cross-tolerance between EtOH and NIC [69-72]. Additional testing has elucidated aspects of the interaction between NIC and EtOH on nAChRs. For example, locomotor stimulation in mice by EtOH was partially impeded by the non-selective/non-competitive nAChR antagonist mecamylamine (MEC) [46]. Systemic EtOH induces DA release in the rat NAc and can be blocked by MEC in the VTA but not the NAc [46]. The EtOH ingestion and preference in high EtOH-preferring rats was also decreased by MEC [73,74]. Together, these researches confirm that EtOH's effects are partially facilitated through nAChRs and suggest these receptors as likely candidates for NIC-EtOH interaction.

On the other hand, it is known that the DAergic portion of the mesolimbic pathway is not the only contributor to the reinforcing effects of NIC and EtOH. Many neuron systems and receptor types have been implicated in the interaction involving NIC and EtOH. The serotonin [75], endogenous opioid [76], glutamatergic [77], and cholinergic [60,78] systems have been associated with NIC and EtOH interactions. Cholinergic receptors, especially nAChRs, have been implicated in this association for some time, but they are not the only mediators of the NIC EtOH interaction. Aside from nAChRs, endocannabinoid CB_1 receptors have been implicated in EtOH and NIC seeking [79], NIC-EtOH cross-sensitization [71], and interactive effects of NIC and EtOH involved in passive avoidance learning [80]. Although nAChRs are not the sole agents involved in the NIC-EtOH interaction, they seem to have greater effects on this relationship than CB_1 receptors in both number and impact.

Nicotinic Acetylcholine Receptors and Ethanol

In the VTA, nAChRs are involved in mediating some reinforcing properties of EtOH [81]. nAChRs are ligand-gated ion channels expressed in a variety of compositions with two subtypes, α and β. Nine types of α subunits (α2-α10) are known to be expressed vertebrates, as well as three β subunit types (β2-β4) [82]. The pentameric structure

of each individual nAChR determines the variety of ion that is able to pass through the receptor's channel [82]. For example, the α4β2 receptor mostly permits the passage of sodium through its pore while the α7 receptor has relevantly high Ca^{2+} permeability [82]. The known subunits found in the human brain are thought to be α3-α7 and β2-β4, although not all are presently known [82,83]. Many nicotinic receptors, composed of diverse combinations of subunits, are present in the human brain. The most common nicotinic pentamers consist of heteromeric α4 and β2 subunits or homomeric α7 subunits. The heteromeric pentamers could be joined as $\alpha4_{(2)}\beta2_{(3)}$, $\alpha4_{(3)}\beta2_{(2)}$. Upregulation of some nAChRs in the mouse midbrain has been shown in the presence of NIC and EtOH together [84]. Some have argued that EtOH is simply a co-agonist and requires NIC to elicit a cholinergic response [85]. However, EtOH is not only a co-agonist in the presence of a ligand binding to cholinergic receptors, but also operates directly on some types of nAChRs *in vitro* [83,86] and *in vivo* [87-89]. The sensitivity and effects elicited by EtOH binding to nAChRs are dependent upon subunit composition [90].

Because α4β2 and α7 nAChRs are the most numerous of the subtypes in the human brain [86,91], they have been investigated for their relevance in the NIC and EtOH relationship. Human nAChRs expressed in *Xenopus* oocytes have demonstrated that α4β2 and α2β4 nAChRs have the highest affinity to EtOH, while α4β4, α2β2 and α7 nAChRs also respond to EtOH [90]. All combinations of α2, α4, β2 and β4 subunits enhanced receptor function in response to EtOH, while EtOH inhibited the functional α7 homomeric nAChRs expressed in these *Xenopus* oocytes [92,93]. The results seen in α4β2 and α7 nAChRs have also been confirmed in cultured rat neurons [83,94]. A microdialysis study has shown that DA release because of systemic EtOH involved nAChRs in the VTA [95]. It has also been proposed that α4 containing nAChRs enable modulation of the withdrawal effects of EtOH in mice [78]. Together, these data illustrate the crucial role of nAChRs in the interaction of these two substances.

As previously stated, EtOH acts as an antagonist on α7 nAChRs [93,96,97]. However, the intraperitoneal administration of selective α7 nAChR antagonist methyllycaconitine did not obstruct either the locomotor activity or DA overflow induced by systemic EtOH [81,98]. As α7 nAChRs are located on glutamatergic terminals in the VTA [21] which innervate both GABA and DA neurons [99], the effects of this blockade could cause changes in neuronal firing in the VTA local circuitry as well as projections to the NAc and PPTg. Interestingly, the α4β2 nAChR antagonist, DHβE also failed to block changes in DA levels recorded from the NAc when it is microinfused into the VTA [85]. Since a change of DA levels is normally found in response to EtOH [81,85], this failure is puzzling, as there is evidence of EtOH binding to α4β2 nAChRs in oocytes. Pretreatment with MEC significantly attenuated alcohol drinking in a rat limited access paradigm, but pretreatment with DHβE had no effect [100]. Thus, nAChRs are partially responsible for the reinforcing effects of EtOH, but the roles of both α4β2 and α7 nAChRs in the association between NIC and EtOH are unclear.

The α6 Subunit in Nicotinic Acetylcholine Receptors

Almost two decades ago, the α-conotoxin MII (α-CtxMII), derived from the *Conus magnus* marine snail, was identified and was shown to antagonize α3β2 containing nAChRs [101]. Soon thereafter, it was discovered that β2 knockout mice did not self-administer NIC, nor were they sensitive to NIC induced DA release in the NAc much unlike their wild-type opposites [102]. These data display the necessity of the β2 subunit in the VTA is necessary for the rewarding properties of NIC [103,104]. It is evident that the β2 subunit is critical for NIC reinforcement, but not when paired with the α4 subunit alone because DHβE does not block NIC induced DA effects in the NAc [85]. More recently, α6 knockout mice revealed that α-CtxMII binds to α6 containing nAChRs (α6*-nAChRs). The α6β2 containing pentamer rather than α3β2 pentamer was found to modulate NIC induced changes in DA systems [105]. In addition, the α4 subunit could play a role in NIC reward when paired with the α6 subunit [106-108]. Studies using immunoprecipitation discovered that not only were α6 and β2 subunits expressed in the same receptors, but the β3 subunit was also found in most α6*-nAChR pentamers in mesolimbic and nigrostriatal DA pathways [109,110]. β3 knockout mouse studies confirmed that this subunit plays a role in α-CtxMII binding [109,111-114], and this subunit may be involved in control of ion permeability and receptor location [82]. α-CtxMII administered in the VTA was able to reduce EtOH induced NAc DA release in [115], and locomotor activity [116]. In addition, α6 knockout mice failed to self-administer NIC, while self-administration of the drug was restored with the reintroduction of the α6 subunit [117]. Fast-scan cyclic voltammetry studies have shown that α6β2 subunit containing nAChRs are responsible for the majority of NIC induced affects on DA release in the NAc [118]. In further behavioral studies, α-CtxMII perfusion into the VTA blocked recognition of EtOH associated cues [119] and voluntary EtOH drinking in rodents [115]. Genetic, electrophysiological, and pharmacological techniques have been employed to demonstrate functional α6*-nAChRs situated on GABA terminals innervating DA neurons in the VTA [120]. The combined data robustly propose α6 and β2 containing nAChRs are located on these terminals, however α4 subunits are not [120]. Therefore, the majority of α6*-nAChRs in the mesolimbic pathway are part of either an $\alpha6_{(1)}\alpha4_{(1)}\beta2_{(2)}\beta3_{(1)}$ or an $\alpha6_{(2)}\beta2_{(2)}\beta3_{(1)}$ heteromeric pentamer [104,109,113,121-123] with the later located on VTA GABAergic boutons [120]; both these receptors may have a significant role in the actions of both NIC and EtOH.

Conclusion

The neural network underlying the interaction between NIC and EtOH is complex. Their interaction utilizes the mesolimbic DA system and the majority of its mediation takes place within the VTA. The VTA mediates rewarding effects of EtOH and aversive effects of NIC through the NAc; the rewarding properties of NIC are meditated through the PPTg. The nAChR antagonist MEC has been shown to attenuate EtOH induced DA release in the NAc. However, both α7 (MLA) and α4β2 (DHβE) antagonists could not block this effect. The mixed results involving α7 and α4β2 nAChRs suggest that more research is needed in order to uncover their involvement in the mediation of EtOH reward. However, the α6*-nAChR antagonist α-CtxMII was helpful in the identification of the critical role α6 subunits have in the rewarding effects of both NIC and EtOH. Many types of nAChRs affect NIC-EtOH co-use, however, the $\alpha6_{(2)}\beta2_{(2)}\beta3_{(1)}$ nAChR pentamers in the meslolimbic DA pathway situated on VTA GABA terminals are a likely site for NIC-EtOH interactions. Future research could target α6*-nAChRs in order to combat NIC-EtOH co-dependence.

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