

Alcohol and nicotinic acetylcholine receptors

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ABSTRACT

Background: The frequent co-abuse of alcohol and tobacco may suggest that they share some common neurological mechanisms. For example, nicotine acts on Nicotinic acetylcholine receptors (nAChRs) in the brain to release dopamine to sustain addiction. Might nAChRs be entwined with alcohol?

Objectives: This review summarizes recent studies on the relationship between alcohol and nAChRs, including the role of nAChRs in molecular biological studies, genetic studies and pharmacological studies on alcohol, which indicate that nAChRs have been potently modulated by alcohol.

Methods: We performed a cross-referenced literature search on biological, genetic and pharmacological studies of alcohol and nAChRs.

Results: Molecular biological and genetic studies indicated that nAChR (genes) may be important in mediating alcohol intake, but we still lack substantial evidence about how it works. Pharmacological studies proved the correlation between nAChRs and alcohol intake, and the association between nicotine and alcohol at the nAChRs. The positive findings of varenicline (a partial agonist at the $\alpha_4\beta_2$ nAChR, smoking-cessation pharmaceutical) treatment for alcoholism, provides a new insight for treating co-abuse of these two substances.

Conclusions: Molecular biological, genetic and pharmacological studies of alcohol at the nAChR level, provide a new sight for preventing and treating the co-abuse of alcohol and nicotine. Given the important role of nAChRs in nicotine dependence, the interaction between alcohol and nAChRs would provide a new insight in finding effective pharmacological treatments, in decreasing or stopping alcohol consumption and cigarette smoking concurrently.

Keywords: Alcohol, Nicotinic acetylcholine receptors, Molecular biological studies, Genetic studies, Pharmacological studies

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1. INTRODUCTION

Alcohol and tobacco are the most commonly used addictive drugs in the world. A large body of evidence from epidemiological studies, indicate that cigarette smoking and alcohol intake are positively correlated.^{1–3} Compared to non-smokers, smokers have approximately a ten-fold risk of developing alcoholism.⁴ On the other hand, nicotine dependence appears more severe in smokers with a history of alcohol dependence.⁵ The concomitant use of tobacco and alcohol multiplies the risk of cancers.⁶ Furthermore, adolescents with co-occurrence of alcohol and cigarette use exhibit increased risk of personal and social problems.⁷ Additionally, behavioral genetic studies suggest that co-abuse of alcohol and tobacco might be due in part to genetic factors common to the etiology of both substances.^{8,9}

Although there are many possible reasons for the co-abuse of nicotine and alcohol, one possible mechanism is that both nicotine and alcohol act at the level of the neurotransmitter receptor system, the neuronal nicotinic acetylcholine receptors (nAChRs).¹⁰ Alcohol acts on many receptor systems, whereas nicotine acts specific directly on nAChRs.^{11–14} Nicotine activates nAChRs in the mesocorticolimbic dopaminergic system that projects from the ventral tegmental area to the nucleus accumbens and the prefrontal cortex.^{15,16} Nine nAChR alpha subtypes (alpha2–alpha10) and three nAChR beta subtypes (beta2–beta4) have been identified.^{17–20} These differ in functional significance, distribution and sensitivity to nicotine. In the mammalian brain, the abundant subunits of nAChRs are $\alpha 4\beta 2$ and $\alpha 7$.^{21,22} The molecular composition of the nAChRs located on dopaminergic neurons may have a role in modulating dopaminergic neuronal activity.²¹ Nicotine regulates dopamine release by stimulating nAChRs on dopamine cell bodies within the substantia nigra and ventral tegmental area (SN/VTA), and on presynaptic nAChRs located on striatal terminals. This indicates the formation of different nAChR subtypes on cell bodies and terminals of the nigrostriatal and mesolimbic pathways.²³

A large body of evidence from animal and human studies has demonstrated that nAChRs mediate the effects of nicotine.^{24–30} Interestingly, several studies indicate that nAChRs also mediate some of the effects of alcohol.^{31–33} and nAChR mediated signaling is critical in regulating nicotine-induced ethanol drinking behaviors.³⁴ They serve as sensors for ethanol in lung fibroblasts.³⁵ However, only few studies investigated the role of these receptors in modulating alcohol's effects on the brain. The limited literature suggests that the effects of nAChR partial agonists and antagonists shows promise for the management of alcohol dependence and other alcohol use disorders. Due to the limitations in efficacy with current medications for the treatment of alcohol abuse and dependence, to clarify the link between alcohol and nAChRs may provide alternative pharmacotherapies for co-abusers of alcohol and nicotine.

In this short review, we present a comprehensive discussion of the association between alcohol and nAChRs, focusing on the role of nAChRs in molecular biological studies, genetic studies and pharmacological studies of alcohol.

2. ALCOHOL AND NICOTINIC ACETYLCHOLINE RECEPTORS (NACHRS)

Alcohol is known to modulate the activity of a variety of neurotransmitters, such as gamma amino butyric acid (GABA), N-methyl-D-aspartate (NMDA) and glutamate, in the central nervous system.³⁶ Animal studies indicate that alcohol also acts on different nAChR subtypes.³⁷ Previous studies imply a strong link between alcohol and nAChRs at a molecular or genetic level.^{1,38}

2.1 Molecular biological studies

Neuronal nAChRs are known to be an important target of various chemicals, including nicotine and alcohol.^{37,39} The most abundant nAChRs in the central nervous system are the heteromeric alpha4beta2 and homomeric alpha 7 nAChRs, which make up more than 90% of brain nAChRs. These two subtypes are widely and abundantly expressed in the brain.^{21,22} Effective molecular biological tools contribute to the study of the complex alcohol actions on nAChRs. Recently, nAChRs have become a specific focus of study because they are not only potently modulated by nicotine and alcohol, but are also ubiquitously distributed in the brain and central nervous system.¹⁰ We know that nAChRs modulate the release of various neurotransmitters, including GABA and dopamine, play pivotal roles in the behavioral effects of alcohol, and that certain subtypes of nAChRs are highly sensitive to the modulating action of alcohol. For example, Borghese et al. found that most of the mutations in the alpha2 subunit, in either the 261 or the 283 position, induced changes in acetylcholine (ACh) sensitivity

and increased the action of alcohol, but none was able to decrease ethanol potentiation;⁴⁰ Other studies showed that the alpha₄beta₂ neuronal nAChRs are sensitive to ethanol modulation, being potentiated over a wide range of ACh concentrations.^{38,41} They found that the ethanol acts on the alpha₄beta₂ nAChRs at the whole-cell level. Moreover, it has been demonstrated that ethanol may increase agonist affinity for nAChRs,⁴² and low concentrations of ethanol produced an increase in desensitization of nAChRs responses.⁴³

It is well established that ethanol modulates the functional activity of alpha₄beta₂ nAChRs when measured *in vitro*.⁴⁴ Animal studies found that alpha₄beta₂-containing nAChRs may play important roles in modulating the effects of ethanol on the acoustic startle response,⁴⁵ as well as ethanol withdrawal.⁴⁶ Furthermore, a human study found a low dose of alcohol also alters the acoustic startle response.⁴⁷ These studies provide strong support for the notion that nAChRs contribute to the ethanol behaviors, (drinking and locomotor activation), and ethanol withdrawal syndrome.

Zuo et al. studied the dual action of n-butanol on neuronal nicotinic alpha₄beta₂ acetylcholine receptors⁴⁸ and the dual action of n-alcohols on neuronal nAChRs.⁴¹ The dual action of n-butanol on neuronal nicotinic alpha₄beta₂ acetylcholine receptors, indicated that butanol activated receptors as a partial agonist,⁴⁸ and the dual action of n-alcohols on neuronal AChRs suggested that potentiating and inhibitory actions are exerted through two different binding sites. They found that normal alcohols, (n-alcohols), exert a dual action on both alpha₄beta₂ and alpha₃beta₂ AChRs, with short-chain alcohols potentiating and long-chain alcohols inhibiting acetylcholine (ACh)-induced currents with a differential chain length dependency.^{41,49} The short-chain alcohols enhance the whole-cell currents by increasing open probability.⁵⁰ The dual action suggested that the potentiation by short-chain alcohols⁵⁰ and the inhibition by long-chain alcohols⁴¹ could be mediated by different mechanisms.

It is also suggested that ethanol modulates the functional activity of alpha₇ neuronal nicotinic cholinergic receptors (nAChR). Yu et al. found that acutely applied ethanol inhibits the function of nicotinic acetylcholine alpha₇ receptors, expressed in *Xenopus* oocytes, by a non-competitive mechanism that involves the amino-terminal domain of the receptor.⁵¹ Later, Oz et al. found that ethanol has additive inhibitory effects on the function of neuronal alpha₇-nACh receptors, expressed in *Xenopus* oocytes, through distinct regions of the receptor.⁵² Furthermore, ethanol-induced neurotoxicity is enhanced in cultures derived from alpha₇ nAChR null mutant mice, which may indicate that inhibition of alpha₇ nAChR by ethanol provides partial protection against the alcohol neurotoxicity.

Many studies have assessed the effects of ethanol on receptors with different subunit compositions, Cardoso et al. found that the alpha₂beta₄ and alpha₄beta₂ combinations were the most sensitive receptors, and the alpha₃ subunit plus either the beta₂ or beta₄ subunits were the most insensitive receptors to potentiation by ethanol, in *xenopus* oocytes. This may indicate that the sensitivity to ethanol of nAChRs depends on the subunit composition of the receptors expressed.⁴⁴ Different combinations of rats' nAChRs subunits expressed in *Xenopus* oocytes are sensitive to acute exposure to ethanol under some experimental conditions. Covernton and Connolly examined the action of alcohol on the agonist responses of several neuronal nAChR subtypes functionally expressed in *Xenopus* oocytes, and found that all the subunit combinations of nAChRs can be modulated by high concentrations of ethanol in a rapidly reversible manner.⁵³ Zou et al. found that the human alpha₄beta₂ AChRs stably expressed in human embryonic kidney 293 cells, are potently modulated by alcohols,⁴¹ and ethanol increases the open probability of channels by stabilizing the alpha₄beta₂ AChRs in an open state.⁵⁰ The alpha₃beta₂ AChRs are insensitive to ethanol because ethanol is at the transition point from potentiation to inhibition among n-alcohols with different carbon-chain lengths. The differential action on the alpha₄beta₂ and alpha₃beta₂ AChRs may explain the differential action of ethanol on the central nervous system.⁴⁹

However, some studies found that alcohol modulation of neuronal AChRs is alpha subunit dependent. nAChRs containing the alpha₄ subunit modulate alcohol reward⁵⁴ and the alpha₅ nAChR subunit is important for the sedative effects of ethanol.⁵⁵ Recently, Dawson et al. suggest that beta₂* nAChRs have a measurable role in mediating specific behavioral effects induced by acute ethanol exposure without affecting drinking behavior directly, in mice.⁵⁶

Several studies indicated that ethanol has multiple actions on channels desensitization or resensitization. The n-alcohols appear to act on both sites (sites of excitatory and inhibitory function) and their ability to enhance (short-chain), inhibit (long-chain), or produce no effect (intermediate-chain) depends upon their relative action at these two sites.⁵⁷ Liu et al. found that short-chain n-alcohols may increase burst frequency, by increasing the channel opening rate.⁵⁸ There are several

studies which found that ethanol has different effects on the nAChRs in different situations, which indicate that both the inhibiting^{44,51,53} and potentiating⁵³ effects of ethanol have been illustrated, showing the complexity of ethanol actions on nAChRs. These findings provide indications for the direct actions of ethanol on certain nAChR subtypes. Interestingly, Wu et al. found that ethanol stabilizes the open channel state of the Torpedo nAChR.⁵⁹ Furthermore, at the single-channel level, ethanol increases channel open time and decreases channel conductance in muscle nAChRs.^{60–62} Although desensitization is known to be an important aspect of the actions on these nAChRs, future studies should clarify how alcohol might alter it, to provide new insights into which actions of alcohol might involve nAChR activity.

In a single-channel study, two levels of single-channel conductance state currents were observed in the alpha4beta2 AChRs that were stably expressed in HEK293 cells. Maximum Ach induced currents, even when evoked by high concentrations of Ach, were augmented by ethanol, in alpha4beta2 AChRs in rat cortical neurons and in human alpha4beta2 AChRs stably expressed in HEK cells.^{38,41} The changes in single-channel analyses of ethanol modulation of neuronal nicotinic acetylcholine indicate that ethanol stabilizes the alpha4beta2 receptor-channel in the opening state. This explains how the maximum acetylcholine-induced whole-cell currents are further potentiated by ethanol.⁵⁰ The results of single-channel, patch-clamp experiments, that unveiled the detailed mechanisms of the inhibitory action of octanol on alpha4beta2 AChRs, found that the potentiating action of short-chain alcohols and the inhibitory action of long-chain alcohols on neuronal nicotinic AChR, are mediated through different mechanisms.⁶³ It is worthwhile pointing out that ethanol concentration deserves special attention when assessing its ability to modulate specific receptor subtype function.⁶⁴ Generally, a concentration of more than 100 mM is needed to observe any effects, as compared to the more physiological relevant concentrations, around 20 mM, required for the alteration of GABA-A or NMDA receptor function. The effective concentration of alcohols, including ethanol, need to be included when discussing their ability to modulate specific receptor subtype function, as this will show the relative potency.

2.2 Genetic studies

It is well known that Co-use and disorders of alcohol and nicotine in human beings are frequent, especially among the youngest.⁶⁵ Evidence from genetic studies suggests that these two disorders have shared genetic vulnerability.^{66–69} To assess whether the nAChR genes have been involved in alcohol dependence, researchers have conducted many studies to examine the role of these receptor genes in modulating alcohol's actions.³⁷

2.2.1 Animal genetic studies

Butt et al. found that alcohol enhancement of nicotinic receptor function is influenced by a polymorphism (A529T) in the coding region of the mouse alpha4 gene (Chrna4).⁷⁰ The A529T polymorphism is linked with variability in a variety of nicotine related and alcohol related phenotypes.^{45,70–73} Studies with mice lacking the beta2 subunit have shown that those actions of alcohol are mediated by alpha4beta2 nAChRs. Thus, Owens et al. suggest that nAChR subunit (alpha4beta2) genes should be evaluated as potential contributors to both alcoholism and tobacco abuse.⁴⁵ A recent study found partial agonists of the alpha3beta4 nAChRs reduce ethanol consumption and seeking in rats, which implicates that CHRNA3 and CHRN4 genes are involved in ethanol-mediated behaviors.⁷⁴ Researchers have also done work on the alpha7 nAChR gene, they utilized primary neuronal cultures of cerebral cortex from alpha7 nAChR null mutant mice, to examine the role of alpha7 nAChR in modulating the neurotoxic properties of subchronic, “binge” ethanol and beta-amyloid. They found that knockout of the alpha7 nAChR gene selectively enhanced ethanol-, but not beta-amyloid-induced neurotoxicity.⁷⁵ Deletion of the alpha7 nicotinic receptor subunit gene results in increased sensitivity to several, but not all, behavioral effects produced by ethanol.⁷⁶

2.2.2 Human genetic studies

Behavioral genetics studies strongly suggest that problem use of both alcohol and tobacco may be partly due to genetic factors, common to the etiology of the use of both substances.⁷⁷ One current study of adolescent twins, biological siblings, and adoptive (biologically unrelated) siblings, drawn from community-based samples, demonstrated a genetic correlation of about 0.60, between tobacco and alcohol problem use.⁷⁸ Various lines of evidence suggesting that nAChRs may be involved in

smoking behavior.⁷⁹ and human genetic studies also found that the nAChRs are involved in ethanol-related behaviors.^{8,9,80}

Chronic ethanol exposure reduces the number of nAChRs in both, SH-SY5Y cells (the human neuroblastoma SH-SY5Y cell line expresses nAChR alpha3, alpha5, alpha7, beta2, and beta4 subunits) and M10 cells (the M10 fibroblast cell line is a stably transfected cell line expressing the alpha4beta2 nAChR subtype). Changes in the levels of nAChR protein and mRNA may be involved in the development of dependence, tolerance, and addiction to chronic ethanol and nicotine exposure.³⁹ Evidence for an association between nAChR genes and alcohol consumption has been detected. For example, a 1068 young adults sample study, found that the neuronal nicotinic receptor beta2 subunit gene (CHRNA2) associated with subjective responses to alcohol and nicotine, this study provided the first evidence for association between the CHRNA2 gene with nicotine and alcohol subjective responses;⁸ to test whether polymorphism of the AChR alpha4 subunit gene (CHRNA4) modulates enhancement of nicotinic receptor function by ethanol, Kim et al. found that the polymorphisms in CHRNA4 is associated with alcoholism;⁸⁰ a large sample study presented evidence that age of initiation of alcohol and tobacco use is associated with the CHRNA5/A3/B4 locus polymorphisms in two separate samples: a selected sample of young adults, and a population-representative adult sample;⁹ Landgren et al. disclosed a haplotype association between the CHRNA6 gene and heavy alcohol use;⁸¹ a nAChR subunit knockout mice study suggests that alpha7 nAChR genes modulate ethanol consumption,⁸² while another knock-out mice study implicates that activation of alpha4 nAChRs is necessary and sufficient for varenicline reduction of alcohol consumption,⁸³

It is clear that nAChRs are involved in the dopamine activating and reinforcing properties of ethanol.⁸⁴ nAChRs in the ventral tegmental area mediate dopamine activating and the conditioned reinforcing properties of ethanol-associated cues in the rat.³¹ Genetic Studies also found that nAChR genes are involved in alcohol (for instance, CHRNA4 associated with alcoholism and CHRNA2 associated with subjective responses to alcohol). A line of studies implicate that common genetic factors may contribute to the concurrent use of these two substances, and that nAChR genes may be involved in both cigarette smoking and alcohol intake.⁶⁷ Therefore, pharmacological manipulations of selective nAChRs may work as effective treatment strategies to prevent cigarette smoking and alcohol drinking, limit relapse and weaken the reinforcing effects.

2.3 Pharmacological studies

It is estimated that more than 80% of individuals, with a diagnosis of alcohol dependence, also smoke heavily.^{4,85} This suggests that individuals who use alcohol are significantly more likely to smoke than those who do not. This may indicate that alcohol and nicotine share some important mechanisms (including pharmacological mechanisms). We know that alcohol and nicotine have effects in the central nervous system, and nicotine acts specifically on nAChRs.^{15,16} A line of pharmacological studies, indicate that alcohol can act on different nAChR subtypes.^{31-33,86} Both animal and human studies, examined the role of nAChRs subtypes in decreasing voluntary alcohol consumption or modulate alcohol drinking behavior.⁸⁷ Despite the fact that the co-use of alcohol and tobacco has been a major public health challenge, there is no Food and Drugs Administration (FDA) approved medication to treat comorbid use of these substances.

2.3.1 Animal pharmacological studies

Alcohol and nicotine have many psychopharmacological effects in common, which may partly explain why co-use of these two drugs often is observed in individuals. It is well known that both nicotine and ethanol act on nAChRs that underlie diverse neuronal processes,^{37,88} such as those involved in reward/reinforcement⁸⁹ and learning/memory.^{25,90-92} Thus, the nAChRs antagonists may influence pharmacological action of alcohol consumption. The most frequent studied pharmaceuticals are Mecamylamine and Varenicline.

Mecamylamine is a noncompetitive *nicotinic antagonist* that is well absorbed from the *gastrointestinal tract* and crosses the *blood-brain barrier*, and in rodents it can antagonize nicotine-induced accumbal dopamine release.⁹³ Mecamylamine has been used as a *ganglionic blocker* in treating *hypertension*. Nicotine-induced behavioral activation is reduced by administration of this compound.⁹⁴ This effect is thought to be due to its action of blocking *alpha3beta4* nicotinic receptors in the brain. Thus, it is a sometimes used as an anti-addictive drug to help people stop smoking tobacco.

A series of animal studies have shown that ethanol-induced accumbal dopamine release and ethanol consumption may be antagonized by mecamylamine.^{84,95–100} Several pharmacological experiments have illustrated a role of nAChRs in modulating behavioral and neurochemical effects of alcohol. The nonselective central nAChR antagonist mecamylamine, blocked the conditioned reinforcing properties of ethanol⁹⁶ and the ethanol-associated cues,³¹ and reduced the ethanol consumption.^{101–104} When it perfused in the Ventral Tegmental Area (VTA), but not in the Nucleus Accumbens (nAc) area, mecamylamine (50 microM) completely antagonized the accumbal dopamine overflow with systemic ethanol (2.5 g/kg, i.p.).⁹⁷ However, Ericson et al. found that perfusion of mecamylamine occurred only in the anterior VTA, but not in the posterior VTA, this completely blocked the elevation of accumbal dopamine levels observed after ethanol perfusion in nAc.¹⁰⁵ This may indicate that ethanol produces its mesolimbic dopamine activating and reinforcing effects via activation of VTA nAChRs. Furthermore, the mesolimbic dopamine activating effects of ethanol may be due to an indirect, rather than direct, activation of VTA.¹⁰¹ These results provide evidence that antagonists of central AChRs may be useful in the treatment of alcoholism.^{95,97}

There is a large body of literature to show that mecamylamine decreased voluntary ethanol consumption and preference^{95,96,98,99,106–108} and withdrawal symptoms¹⁰⁹ in (especially “high-preferring”) rats. Moreover, local perfusion of mecamylamine in the VTA prevents systemic ethanol-induced dopamine release in the nAc.⁹⁷ It abolishes ethanol intake, as well as the associated accumbal dopamine release in ethanol high-preferring rats,⁹⁸ and ethanol elevated accumbal dopamine levels via indirect activation of ventral tegmental nAChRs.¹⁰¹ These studies indicate that AChRs in the VTA are involved in the positive reinforcing effects of ethanol. Thus, mecamylamine, or other antagonists, specifically aimed at ventral tegmental AChRs may represent a new pharmacological treatment principle against alcohol abuse.

In mice, mecamylamine reduces ethanol-induced locomotor stimulation, an activity commonly correlated with dopaminergic functioning.^{110,111} Blomqvist et al. found that mecamylamine partly counteracted the locomotor activity stimulatory effect of ethanol, in doses having no locomotor activity reducing effects. The dihydroxyphenylacetic acid (DOPAC)/dopamine (DA) quotient increase in mouse brain after ethanol was partly antagonized by mecamylamine, which suggest that part of the locomotor activity and dopamine turnover-increasing effect of ethanol is mediated via activation of central nAChRs.¹¹² Furthermore, mecamylamine, but not the peripherally acting quaternary nAChR-antagonist hexamethonium, antagonized ethanol-induced accumbal dopamine release in the nAc of rats and mice, which further indicated that alcohol was involved in central, rather than peripheral, nAChRs.^{95,111} Administration of mecamylamine (0.5–2.0 mg/kg, i.p.), dose dependently attenuated expression of sensitization to locomotor stimulant effect of ethanol and mecamylamine did not affect locomotor activity.¹¹⁰ However, results from one study suggested the stimulatory effects of ethanol, on locomotor activity and dopamine release, do not involve the alpha4beta2 or alpha7 subunit compositions of the nAChR, and that the effects of mecamylamine are mediated through a site not directly associated with the alpha4beta2 or alpha7 subunit, but associated with the alpha3beta2 or alpha6.¹¹¹ Finding the distinct subunit composition of the nAChR involved in the behavioral and neurochemical effects of ethanol may contribute to the future development of highly selective compounds as a pharmacological complement in the treatment of alcoholism.

More recently, varenicline, an alpha4beta2 nicotinic receptor partial agonist and alpha7 nicotinic receptor full agonist, prescribed for smoking cessation, has been shown to decrease ethanol seeking, ethanol consumption^{32,107} and ameliorate ethanol-induced deficits in learning.^{32,91} Steensland et al. reported that acute administration of varenicline reduced nicotine reward, selectively reduced ethanol seeking, using an operant self-administration drinking paradigm, and also decreased voluntary ethanol in animals chronically exposed to ethanol for 2 months before varenicline treatment. Furthermore, chronic varenicline administration decreased ethanol consumption. The selectivity of varenicline in decreasing ethanol consumption may suggest that varenicline is an effective drug for the treatment of alcohol dependence in human beings.³² Sotomayor-Zarate et al. further proved that both varenicline and cytosine (nAChR partial agonists) reduce alcohol consumption in an alcoholic rat model, with varenicline producing a greater and longer-lasting reduction than cytosine. Long-term use (more than 8–10 days), of both varenicline and cytosine induced tolerance to their effects on ethanol consumption.¹¹³ Gulick and Gould found that varenicline dose-dependently ameliorated ethanol-induced conditioning deficits for all three doses of (1.0, 1.5, 2.0 g/kg i.p.) ethanol, when administered before training but not when administered 24 h later, before testing. In addition, varenicline did not

alter blood alcohol concentration, which indicated that varenicline may be useful for treating ethanol-associated disruptions in cognitive processes.⁹¹ The finding of varenicline's effects on ethanol-induced learning deficits may increase understanding of the effects of ethanol on learning and find new treatments for alcoholism. Bito-Onon et al. examined the effects of co-administered nicotine and ethanol on the activity of nAChRs in rats. They found that nicotine (0.2 mg/kg and 0.8 mg/kg, s.c.) increases operant 20% ethanol self-administration, varenicline (2 mg/kg, s.c.) decreases operant ethanol self-administration, and nicotine-induced increases in ethanol self-administration, which further suggests that nAChRs play an important role in increasing ethanol self-administration, and that varenicline may be an effective treatment for both alcohol and nicotine.¹⁰⁷

2.3.2 Human pharmacological studies

The high co-abuse of alcohol and nicotine may partly result from the common psychopharmacological effects of these two substances. The substantial interaction between alcohol and nAChRs raises the possibility of pharmacotherapies that could treat alcohol and nicotine dependence concurrently, by blocking nAChRs. This may contribute to a decrease alcohol consumption and smoking for co-users of these substances. In this section, we will address the most frequently studied pharmaceuticals, mecamylamine and varenicline.

In humans, mecamylamine has been originally utilized as a therapeutic agent to treat hypertension.¹¹⁴ It has been shown to be useful when co-administered with transdermal nicotine for smoking cessation.^{115,116} Recently, studies used mecamylamine to study the role of nAChRs in the effects of nicotine, as well as alcohol, in human beings.¹¹⁴ Studies suggested that the nonselective nAChR antagonist mecamylamine reduces the reinforcing actions of alcohol in humans.^{33,86} For example, mecamylamine (15 mg) decreased blood alcohol levels (BALs) after a small fixed dose of alcohol (0.2 g/kg). Even when the lower BALs were taken into account, mecamylamine reduced ratings of stimulation after alcohol intake. However, mecamylamine did not significantly reduce choice for alcohol versus money.³³ Blomqvist et al. proved that mecamylamine reduced BALs and the subjective stimulant effects of alcohol, which indicated that mecamylamine seems to modify, both the pharmacokinetic profile of alcohol and the rewarding effects of alcohol, in healthy volunteers.¹¹⁷ Furthermore, the effects of attenuating the stimulant and euphoric effects of alcohol and reducing the self-reported desire to consume additional alcohol beverages were most pronounced in men, even though women exhibited greater physiologic reactions to mecamylamine.⁸⁶ In these studies, mecamylamine attenuated the stimulant or euphoric subjective effects of alcohol and decreased the self-reported desire to consume more alcohol, which may suggest that the drug would also decrease consumption of alcohol.

It is not known whether chronic mecamylamine administration would be well tolerated in alcohol-dependence individuals or not, and this is a critical determinant of its potential value as a pharmacological treatment of alcohol abuse and alcohol dependence. Although the human studies support a role for nicotinic neurotransmission in the reinforcing effects of alcohol, it is unclear whether mecamylamine alone will be useful in alcoholism treatment. A nicotinic antagonist that is selective for receptors in the VTA, and have minimal effects on peripheral nicotinic receptors, could be a better candidate for the treatment of alcohol dependence.

At present several human researches provide a good starting point to suggest that varenicline might be investigated as a potential treatment for alcohol use disorders.¹¹⁸⁻¹²¹ McKee et al. found that varenicline reduced the number of drinks consumed, and increased the possibility of abstaining from any drinking during the self-administration period. It also attenuated alcohol craving, as well as subjectively reinforcing alcohol effects;¹²⁰ interestingly, Kuehn et al. found that varenicline strongly attenuated cue induced relapse to alcohol seeking, but not nicotine seeking;¹²² recently, Childs et al. found that varenicline attenuated alcohol-induced negative subjective responses and alcohol-induced eye-tracking impairments;¹¹⁸ furthermore, varenicline decreases alcohol consumption in heavy-drinking smokers.¹²¹ Meszaros et al. assessed the safety and effectiveness of varenicline for treatment of concurrent nicotine and alcohol dependence in schizophrenia, with an 8-week, double-blind, randomized, placebo-controlled trial. With a small sample size, safety concerns (limiting recruitment), and poor tolerability (gastrointestinal adverse effects), this study suggests that concurrent alcohol and nicotine dependence in schizophrenia may present special obstacles to successful treatment with varenicline.¹²³ Larger sample, with long-term clinical trial, should be undertaken before pursuing this compound as a potential dual treatment for both alcohol and tobacco use disorders. As well this, it

side effects cannot be neglected,^{124,125} such as nausea, depression and suicide ideation. The side effects should be carefully assessed and might decrease its long-term effects, although adverse events associated with varenicline were minimal in those pilot studies.^{119,120}

3. SUMMARY AND CONCLUSIONS

More research needs to be done to learn about how alcohol acts at the level of nAChRs. For example, researchers still do not know that alcohol acts directly or indirectly at these nAChRs; whether mecamylamine has long-term effects on the treatment of alcohol dependence and how the drug acts at these nAChRs; genetics studies indicated that nAChR genes may be important in mediating alcohol, but we still lack substantial evidence about how the nAChR genes mediate alcohol, and which of the nAChR genes play an important role in mediating alcohol. However, there is exciting data proving the correlation between nAChRs and alcohol, the correlation between nicotine and alcohol at the level of nAChRs, as well as the contribution of such interactions to the co-abuse of alcohol and nicotine. In an animal study,³² we found that varenicline, an $\alpha_4\beta_2$ nicotinic receptor partial agonist and α_7 nicotinic receptor full agonist for effective smoking cessation, has been shown to decrease ethanol seeking and consumption. A line of clinical study has shown the effects of varenicline in smoking cessation. The ongoing human study of varenicline in the treatment of alcoholism may also prove to be effective in the treatment of drinking problems in humans, which may be a new target for treating the comorbidity of these two substances.

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