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Recent Advances in Nicotinic Receptor Signaling in Alcohol Abuse and Alcoholism

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Abstract

Alcohol is the most commonly abused legal substance and alcoholism is a serious public health problem. It is a leading cause of preventable death in the world. The cellular and molecular mechanisms of alcohol reward and addiction are still not well understood. Emerging evidence indicates that unlike other drugs of abuse, such as nicotine, cocaine, or opioids, alcohol targets numerous channel proteins, receptor molecules, and signaling pathways in the brain. Previously, research has identified brain nicotinic acetylcholine receptors (nAChRs), a heterogeneous family of pentameric ligand-gated cation channels expressed in the mammalian brain, as critical molecular targets for alcohol abuse and dependence. Genetic variations encoding nAChR subunits have been shown to increase the vulnerability to develop alcohol dependence. Here, we review recent insights into the rewarding effects of alcohol, as they pertain to different nAChR subtypes, associated signaling molecules, and pathways that contribute to the molecular mechanisms of alcoholism and/or comorbid brain disorders. Understanding these cellular changes and molecular underpinnings may be useful for the advancement of brain nicotinic–cholinergic mechanisms, and will lead to a better translational and therapeutic outcome for alcoholism and/or comorbid conditions.

1. INTRODUCTION

Alcohol is the most commonly abused legal substance by humans. Alcoholism is a complex and chronic relapsing disorder that represents a serious global public health problem.[1] Alcoholism related deaths are estimated to account for 4% of all deaths worldwide and this number will be higher in the coming decades.[2] The prevalence of fetal alcohol syndrome, caused by mother's alcohol abuse and dependence, is also a significant problem in the United States and other industrialized nations.[3] The estimated healthcare and economic cost from alcohol abuse and alcoholism in the United States, is significantly higher than many other diseases, including cancer.[4] Thus, there is a need for better understanding of this complex brain disorder, for better therapeutic approaches to reduce alcohol abuse and relapse. Like nicotine addiction, emerging evidence suggests that neuronal nicotinic acetylcholine receptors (nAChRs), in the mesocorticolimbic-dopamine system, mediate the

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rewarding effects of alcohol and the development of alcohol dependence.[5–9] Therefore, nAChRs are potential molecular targets for alcohol abuse and alcoholism. The primary focus of this review is to provide new insights into the rewarding effects of alcohol, as they pertain to different nAChR subtypes and other cholinergic factors that contribute to the molecular mechanisms of alcoholism. Understanding these cellular changes and molecular underpinnings, will lead to a better translational and therapeutic outcome of alcoholism. Considering the diversity of nAChRs in the brain, this chapter will discuss the role of different nAChR subunits, involving alcohol abuse and alcoholism obtained from genetic, preclinical, and clinical studies. In addition, the role of nAChRs in alcohol, nicotine coabuse, and other comorbid brain disorders will be discussed. The molecular targets and neurobiological mechanisms within the nAChRs system may offer a better understanding and effective therapeutic alternative to combat this complex relapsing brain disorder.

2. MESOLIMBIC-DOPAMINE SYSTEM AND nAChRs

Genetic, preclinical, and clinical studies have identified the brain nAChRs and membrane bound ion channels in the mesolimbic-dopamine system, as being involved in alcohol dependence.[10–18] The nAChRs are pentameric ligand-gated cation channels with a diverse composition, which is widely expressed throughout the central nervous system (CNS).[19–22] The nAChR-mediated signaling plays a critical role in many drug addiction processes, including the development of alcoholism.[23–27] Twelve neuronal nAChR subunits, which are classified as either alpha subunits (β2–β10) or beta subunits (β2–β4), have been identified.[19,28–31] These subunits assemble to form diverse functional nAChRs, which can be further subdivided into two major groups of brain nAChR subtypes.[23,24,27] For example, heteromeric receptors are assembled from both alpha (β2–β6) and beta subunits. The functional properties of such heteromeric receptors, depend on both the specific β and β subunits within the receptor complex and the β:β ratio of the subunits.[28–31] Previous research indicates that the most abundant nAChRs in the CNS are β4β2★, receptors containing both β4 and β2 subunits, and sometimes additional subunits (denoted by the asterisk). These receptors account for >90% of the high affinity nicotine binding sites in the brain.[30] The β4 and β2 subunits are colocalized in many parts of the brain, including thalamic nuclei, cortex, and ventral striatum.[19,30]

On the other hand, homomeric receptors, such as, β7 nAChR subtypes, are predominantly located in the hippocampal regions and cortical or subcortical regions, including the ventral striatum.[31] In addition, neuronal nAChRs containing β6 subunits are expressed in dopamine-rich areas (e. g., the mesocorticolimbic reward neurocircuit). Thus, β6★ receptors may be a new/novel drug target to treat many forms of drug addiction, including alcohol dependence.[25] A number of *invitro* or *invivo* studies have confirmed that alcohol activates the mesolimbic-dopamine system and elevates the synaptic release of dopamine in the ventral striatum, which partially mediates the rewarding effects of alcohol and other drugs of abuse.[32–35] Therefore, mesocorticolimbic nAChRs are considered to be a molecular switch, activated by addictive behaviors.[9,15,36–38] Neuronal nAChRs are widely expressed at the synapse, cell body, and axons in the CNS.[21] Presynaptic nAChRs are involved in regulating the release of ACh, monoamines, and amino acids.[39–43] In particular, dopamine release is

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regulated by β4β2★, β3β2★, and β6★ nAChRs (★ indicates a possible involvement of other receptor subunits) in nigrostriatal/mesocorticolimbic terminals.[44–47]

3. KNOCKOUT AND TRANSGENIC MODELS AND nAChRs

Recent reports with nAChR subtype knockout (KO) mice have provided important information about both brain nAChR function and the mediation of addiction-related behavior.[23,48,49] For example, early research showed that mice lacking the β2 subunit do not display too many nicotine-associated responses, including nicotine-induced DA release in the dorsal and ventral striatum, as well as nicotine-elicited increases in the firing rate of associated DA neurons.[50,51] The lack of nicotine effect on the mesolimbic DA systems in β2 subtype nAChR KO mice is consistent with the absence of nicotine self-administration by these animals.[51] The β4 subunit requires a β2 subunit for assembly in a majority of heteromeric nAChRs in the brain. These and other studies using genetically modified mice suggest that β4/β2★ nAChRs are critical for nicotine-related reward behaviors.[52,53] Despite the distribution of the β7 subunit in the brain, in particular its presence in the mesocorticolimbic system, studies in β7 KO mice are not definitive about a role for the β7 subunit in nicotine reward and conditioning.[48] However, β7★ nAChRs are important for long-term potentiation, neuroplasticity associated with learning, and memory in the mesolimbic reward pathway.[48] KO mouse studies targeting the β6 subunit indicate that β6 partners with β2 nAChRs and may play an important role in nicotine addiction related behavior.[54] Like nicotine addiction, genetic studies have revealed that nAChRs are involved in ethanol self-administration, and reward behavior as well.[11] For example, a number of genetic studies have been conducted to identify the role of nAChR subtypes in ethanol-drinking behavior. Acute ethanol drinking behavior is reduced in β4 KO mice, compared to wild type (WT), indicating a role for the nAChR β4★subunit in ethanol abuse.[11,26] Similarly, ethanol-related behavior and ethanol-induced midbrain dopaminergic function get decreased in β4 KO mice.[55] On the other hand, β2 KO mice behave similar to WT type mice in ethanol drinking behaviors.[56] In addition, β6 KO and β3 KO mice also display ethanol drinking behavior that is similar to WT mice in a two-bottle ethanol drinking paradigm.[56] Moreover, β7 KO and WT mice consume similar amounts of ethanol, although there was a potential gender effect regarding β7 nAChRs effects on ethanol consumption.[56] Again, β5 KO mice do not differ in acute ethanol consumption, compared to WT mice.[57] Like nicotine-related behavior (as mentioned earlier), studies with transgenic over expression of the β5, β3, and β4 receptor subunit genes indicate these subunits have a complex role in the modulation of ethanol-related behaviors.[58] Together, these data indicate that nAChRs containing β5, β6, β2, or β3 subunits may not be critical in ethanol drinking behaviors. Overall, the evidence suggests that β4 receptors in the midbrain may be essential for ethanol-related behavior. These studies represent genetic mechanisms in ethanol dependence, involving brain nAChRs and associated neurobiological mechanisms.

It is widely recognized that brain nAChR subtypes are important mediators of the rewarding effects of ethanol and drugs of abuse.[55,59–66] For example, systemic or local administration of nAChR ligands reduce ethanol drinking in a number of animal models.[32,60,61,65] Furthermore, nAChRs in the ventral tegmental area (VTA) regulate ethanol consumption and associated mesolimbic neurochemical effects (e.g., dopamine release in the nucleus

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accumbens (Acb)), as shown in various preclinical studies.[60,62] However, some of these ligands produce mixed effects in alcohol/ethanol drinking behavior in humans,[59,63] indicating mixed efficacy for treating ethanol dependence through nAChRs in the mesolimbic-dopamine system. Similarly, specific nAChR ligands may be resistant to pharmacologically efficacious reductions in ethanol drinking behavior, thus suggesting a role for other nAChR targets, such as β6β2★.[33,36] Additional studies with the β7 nAChR ligand were found to be ineffective in reducing ethanol-taking behavior of animal models.[56] In other works, a partial β4β2★ nAChR agonist was shown to reduce alcohol drinking in both animal models and humans.[16,26,56,65,67–75] Given the mixed results with pharmacological efficacy on ethanol drinking behavior, the role of specific nAChR subtypes needs further investigation. Additional studies with cytisine, a partial agonist at β4β2★ and lobeline, which is a nonselective antagonist, were found to reduce ethanol-taking behavior in a number of preclinical models.[17,66,73–77] Interestingly, these nAChR ligands also altered alcohol-induced increases in mesolimbic tissue DA levels in mice,[77] supporting the important role of mesolimbic nAChRs in alcohol dependence. Confirming this, the nAChR ligands were found to reduce ethanol-taking behavior in a genetic animal model for alcohol abuse and dependence[78] or inbred mice,[74] indicating nAChRs are potential molecular targets for individuals with a genetic predisposition to develop alcohol dependence.

Thus, evidence suggests that selective desensitization of nAChRs with partial agonistic activity[79,80] reduces ethanol-taking behavior in rats selectively bred for an alcohol preference.[80,81] In addition with the involvement of nAChRs in ethanol-taking behavior, some of these ligands[26,75,81,82] also decrease the alcohol deprivation effect, which is an animal model of relapse behavior.[78,83–87] Emerging preclinical studies suggest that nicotine exposure reinstates alcohol seeking behaviors in rodents following extinction of alcohol reinforcement.[88,89] Therefore, examination of cholinergic mechanisms associated with relapse is also important for new drug development to treat ethanol abuse and dependence.[5,90] Overall, the existing animal and human studies suggest that ethanol-induced activation of the mesolimbic DA system involves brain diverse nAChRs stimulation, including β4β2★, β6β2★, as well as β3β4★ subtypes.[91] Thus, central nAChRs continue to be critical targets for the reinforcing and DA-activating effects of ethanol and underscore the need to conduct more subunit-specific nAChR research regarding ethanol abuse and dependence.

4. ALCOHOL, NICOTINE COABUSE, AND nAChRs

Due to the prevalence of ethanol and nicotine couse,[92] and the extremely high rates of smoking in individuals diagnosed with alcohol dependence,[93,94,95] investigators have been working to develop models of coabuse in animals. However, till date very few such models have been validated. In one such model, within-session intravenous nicotine and oral ethanol drinking was demonstrated in Wistar rats.[96] More recently, ethanol-preferring (P) rats show oral operant intake of combined ethanol and nicotine solutions, that results in blood ethanol concentrations of approximately 100 mg% and blood nicotine levels of approximately 25 ng/mL. These levels are similar to levels obtained in human binge drinking and smoking.[97] Additionally, in adolescent C57BL/6 mice, exposure to cigarette smoke for 6 h/day for 16 days increased intake of 10% ethanol three to five fold in a scheduled access paradigm.[98]

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Also, chronic nicotine exposure in C3H mice during adolescence enhances ethanol withdrawal effects in adulthood.[99]

In a study using rats selectively bred for high versus low locomotor activity induced by a novel field, it was found that adolescent exposure to nicotine facilitated an ethanol-induced conditioned place preference in early adulthood.[100] Regarding β4β2★ receptors, a recent study revealed that chronic ethanol exposure/intake, including *in utero* exposure, by rhesus monkeys significantly decreased β4β2★ levels in the frontal and insular cortex.[101] In a study involving *in utero* exposure of rats, it was found that gestational exposure to ethanol and nicotine significantly increased nicotine self-administration during adolescence, and this effect seemed to be due to glutamatergic modulation of the mesolimbic-dopamine system.[102] These data suggest a possible interaction between stages of development and cigarette smoke/nicotine exposure to increase ethanol and/or nicotine intake through different mechanisms that may extend into adulthood.

Animals selected for ethanol preference also show an increased sensitivity to the reinforcing effects of various drugs, including nicotine.[97] For instance, the P rat shows elevated sensitivity to the self-administration of intravenous nicotine, compared to the nonpreferring (NP) rat.[103] Consistent with this finding, P-rats are more sensitive than Wistar rats to the self-administration of nicotine directly into the posterior ventral tegmental area (pVTA) using the intracranial self-administration technique,[104] and ethanol and nicotine are co-self-administered into the pVTA at low concentrations that do not support self-administration individually.[105] However, in a recent study employing DBA/2J mice, nicotine was found to enhance the locomotor stimulating, but not the conditioned rewarding effects of ethanol, suggesting that in this model, combined stimulant effects of nicotine and ethanol do not predict enhanced reward.[106,107]

Overall, current data suggest that ethanol and nicotine coabuse is rooted in the basic biological underpinnings of both drugs, supposedly by targeting β4β2★ nAChR subtype in the mesolimbic-dopamine system. The drugs may function synergistically on some measures and each drug affects the other in terms of abuse liability. Emerging findings would suggest that the selection of ethanol-preference may increase the potential intake of nicotine coabuse, and adolescent coabuse may be lead to elevated levels of coabuse in adulthood. Additional studies are clearly needed to provide a better understanding of the mechanisms that are involved in ethanol and nicotine coabuse.

5. GENETIC POLYMORPHISMS, ALCOHOL DEPENDENCE AND nAChRs

Emerging evidence indicates that cholinergic genes may play a significant role in ethanol-dependent behavior.[108] For example, significant associations between CHRNA6 polymorphisms (rs1072003, rs2304297, and rs892413) as well as CHRNB3 polymorphism (rs13280604) and excessive ethanol-drinking behavior have been reported.[109] In a recent study, using Hispanic and non-Hispanic white subjects from the Social and Emotional Contexts of Adolescent Smoking Patterns, revealed multiple polymorphisms of CHRNA4 were associated with a significantly elevated risk for adolescent binge drinking.[110] These authors reported that polymorphisms for other nAChR genes were not associated with this

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risk, which may be related to the ethnicity of the sample. Additional studies from the Nicotine Addiction Genetics consortium in Finland, reported a significant association between the CHRNB4 polymorphism rs11636753 and regular ethanol drinking with comorbidity for depression, which may have been sex dependent.[111] Regarding addiction in general, although polysubstance abuse may be a factor, the CHRNA5 risk polymorphism (rs16969968) is not only associated with nicotine dependence,[112] but also associated with other drugs of abuse, such as cocaine.[113] Similarly, other CHRNA5 polymorphisms (rs615470 and rs684513) have significant associations with ethanol and cocaine dependence, respectively.[113] Given an early onset of ethanol, drug use and abuse increases the probability of developing dependence later in life, it is important to examine whether these effects are under genetic control. One studyexamining polymorphisms within the CHRNA5-A3-B4 gene cluster found a significant association with the age of initiating the use of multiple abused substances.[114] Similarly, recent findings from the San Diego Sibling Pair study indicate that, variants for CHRNA5 within this cluster are significantly associated with subjective level of response (i.e., intoxication) to ethanol.[115] Interestingly, a recent study indicated missense variants in CHRNA3 may confer resistance to cocaine dependence in African Americans.[116] However, it was also reported that a missense variant in CHRNB3 called rs149775276, was significantly associated with ethanol and cocaine dependence in European Americans.[116] Combined findings indicate that multiple polymorphisms associated with nAChR genes and addictions, have been identified. Moreover, these associations predict dependence on a number of abused substances and/or associated behaviors, across national, ethnic, and psychiatric groups. Taken together, these studies suggest that nAChRs could be important targets for the development of therapeutics targeting multiple addictions, including alcoholism.

6. ALCOHOL DEPENDENCE, COMORBID PSYCHIATRIC CONDITION AND nAChRs

Recent evidence indicates that nAChRs are involved in drug addiction and comorbid psychiatric disorders, such as anxiety or depression.[117] Just as in nicotine addiction,[118] it has been proposed that there is a relationship between ethanol dependence and depression.[119,120] For example, patients with depression have higher rates of ethanol-related problems, than the general population.[121,122] Ethanol abstinence-related depression increases the chance of relapse because people may use ethanol for self-medication.[123] A number of studies have determined how genetic predisposition to high ethanol intake affects depression-like behavior, and how genetic predisposition to depression-like behavior affects ethanol intake in rats, but the results are not well established,[124] probably due to the challenges of defining criteria for valid animal models of these disorders. Previous studies suggest that chronic ethanol consumption in mice increases depression-like behavior during abstinence from ethanol.[125,126] Therefore, alcoholism and depression supposedly share common molecular targets and associated neurobiological mechanisms. For example, abstinence from ethanol increases ACh release in the Acb,[127] and microdialysis studies indicate that ethanol abstinence induces rapid and sustained increases in extracellular ACh levels in the hippocampus.[128] A reduction in serotonergic neurotransmission has also been implicated in subpopulations of alcoholic patients.[129,130] And, the efficacy of selective

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serotonin reuptake inhibitors (SSRIs) provides strong support for the role of serotonin in depression, although SSRI treatment efficacy is highly variable for maintaining long-term abstinence from ethanol.[131] Alcoholism,[132] nicotine addiction,[133] and depression[134,135] are disorders mediated by neuroplasticity including transcriptional control, especially with brain-derived neurotrophic factor (BDNF) and activity-regulated cytoskeleton-associated protein (Arc)[136] pathways. Regarding this, prolonged exposure to and abstinence from ethanol causes long-lasting neuroadaptations, which may underlie the development of depression-like behavior.[126] Moreover, chronic ethanol consumption reduces the expression of BDNF in the rat hippocampus, which is an effect seen in depression-like behavior in animal models.[137] Given the common neurobiological mechanisms in ethanol dependence and comorbid depression, it is possible that β_2★-nAChRs modulation and associated molecular mechanisms will be critical in reducing depression, in the presence of ethanol abuse and dependence. Therefore, the contribution of specific nAChR subtypes, and their molecular signaling in comorbid conditions, needs considerable additional investigation.

7. ALCOHOL, TRANSCRIPTION FACTORS, AND nAChRs

Evidence indicates that nAChRs modulate acute ethanol-induced increased expression of Fos family in the immediate early genes, such as c-Fos in midbrain dopaminergic neurons.[17,26] In addition, both partial agonists and antagonists targeting nAChRs, reduce acute ethanol-induced c-Fos expression in the VTA and Acb.[17,26] Similarly deltaFosB, which is a truncated splice variant of FosB gene, activity is associated with chronic ethanol exposure and neuroplasticity in the mesolimbic reward neurocircuit.[138,139,140,141] Also, recent research suggests that nAChRs modulate deltaFosB upregulation in both ventral and dorsal striatum.[76] For example, partial agonists at nAChRs reduce chronic ethanol drinking behavior and its associated striatal deltaFosB upregulation.[76] Overall, these studies support the possible role of nAChRs in modulating long-lasting behavioral and molecular neuroadaptations that may be related to alcoholism. However, the role of nAChRs on other important transcription factors, such as cAMP-responsive element binding (CREB) expression requires further investigation.[142,143]

8. CONCLUSIONS

In this review, evidence has been presented for the fact that AChRs in the mesolimbic-dopamine system are important molecular targets for ethanol abuse and alcoholism. It is evident from *in vitro* and *in vivo* studies that nAChRs are critically involved with synaptic activity of mesolimbic dopa-mine as well as associated cellular and molecular mechanisms, which underlie the addictive properties produced by ethanol. Given the variety of nAChR subtypes, localization and functions of these nAChRs are potential mediators of the complex neurobiological effects of ethanol. While the nAChR subtypes share a common structure, their pharmacological properties on drug addiction, including models of alcoholism, may depend on nAChR subunit composition. We believe that multiple nAChR subtypes could be targets for neurobiological effects of ethanol and their contribution to alcoholism. Therefore, understanding subtype-selective mechanisms will be critical for future translational research. Thus, brain nAChRs represent a potential molecular target for treating ethanol abuse and dependence. The fact that ethanol and nicotine addiction often cooccur in humans, is widely

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recognized in this literature. Recent evidence indicates a genetic corelation between these two addictive disorders. Preclinical and clinical studies suggest that both nicotine and ethanol can, either directly or indirectly, activate the mesolimbic-dopamine system, which putatively mediates the rewarding effects and ethanol-induced addictive behavior, associated with nAChRs. Emerging data also indicate that neuronal nAChRs are involved in addiction and comorbid psychiatric disorders, such as anxiety or depression. Finally, it is important to note that nAChRs modulate important transcription factors, such as c-Fos or deltaFosB, in the mesolimbic-dopamine system that may be associated with chronic effects of ethanol. However, the role of nAChRs on CREB or BDNF expression associated with alcoholism remains to be determined. Overall, the evidence supporting a role for nAChRs in the neurobiological effects of ethanol is significant from a translational perspective, as are the implications of nAChRs in addictive behaviors, and a variety of comorbid psychiatric and cognitive conditions. Additional research and a refined understanding of the specific contribution of nAChR subtypes, and associated neurobiological mechanisms involving alcoholism and comorbid neuropsychiatric conditions, may identify new molecular targets and signaling pathways for the development of better treatment and prevention strategies.

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