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The role of nicotinic acetylcholine receptors in alcohol-related behaviors

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Abstract

Alcohol use disorder (AUD) causes an alarming economic and health burden in the United States. Unfortunately, this disease does not exist in isolation; AUD is highly comorbid with nicotine use. Results from both human and animal models demonstrate a genetic correlation between alcohol and nicotine behaviors. These data support the idea of shared genetic and neural mechanisms underlying these behaviors. Nicotine acts directly at nicotinic acetylcholine receptors (nAChR) to have its pharmacological effect. Interestingly, alcohol also acts both directly and indirectly at these receptors. Research utilizing genetically engineered rodents and pharmacological manipulations suggest a role for nAChR in several ethanol behaviors. The current manuscript collates this literature and discusses findings that implicate specific nAChR subunits in ethanol phenotypes. These data suggest future directions for targeting nAChR as novel therapeutics for AUD.

Keywords

Alcohol; Ethanol; Nicotinic acetylcholine receptors

1.1 Introduction

Alcohol misuse causes approximately 88,000 deaths each year, making it the third cause of preventable death in the United States (Sacks et al., 2015). Alcohol use disorder (AUD) is the clinical term for the misuse of alcohol. AUD is described as the inability to stop or control alcohol use despite significant adverse social, occupational, or health consequences (American Psychiatric Association, 2013). The 2017 National Survey on Drug Use and Health reported that an estimated 14.5 million adults were diagnosed with AUD in the United States (Substance Abuse and Mental Health Services Administration, 2018). Thus, AUD is a significant public health issue that has prompted the investigation into the neurobiological underpinnings of this disease as a means to develop targeted therapeutics.

Interestingly, a large portion of individuals diagnosed with AUD also use nicotine. In fact, as many as 80% of individuals who are addicted to alcohol also smoke cigarettes (Li et al., 2007). Data from both human studies and animal models have provided evidence of genetic

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correlations among alcohol and nicotine traits (Bergstrom et al., 2003; Madden et al., 2000; Swan et al., 1997; True et al., 1999). These data suggest that common genes, and thus neural mechanisms, underlie the response to these drugs. One common site of action for nicotine and alcohol is the nicotinic acetylcholine receptor (nAChR) system. Nicotine exerts its effects on the brain by directly interacting with nAChRs, and alcohol also interacts with these receptors through both direct and indirect mechanisms (Davis and De Fiebre, 2006). The effects of alcohol on nAChRs are complex and dependent on the subunit composition, dose tested, and length of the alcohol chain. For example, low dose ethanol acts as a positive allosteric modulator at $\alpha 6$ -containing nAChRs, but not $\alpha 3\beta 4$, $\alpha 4\beta 2$, or $\alpha 7$ receptors (Gao et al., 2019). In general short chain alcohols potentiate acetylcholine receptors currents, but as the carbon-chain length increases it inhibits current. For ethanol, the same concentration potentiates $\alpha 4\beta 2$ receptors, but inhibits $\alpha 3\beta 2$ functioning (Zuo et al., 2002, 2001). These data support the role of nAChRs in ethanol behaviors highlighting the importance of subunit composition, which is the focus of this review.

nAChRs are pentameric ligand-gated ion channels that are involved in various biological processes. In normal conditions, the endogenous ligand acetylcholine binds to nAChRs to induce a conformational change that allows cations to flow into the cell. nAChRs exists as heteromeric channels comprised of α ($\alpha 2$ – $\alpha 6$) and β ($\beta 2$ – $\beta 4$) subunits or as homomeric channels, containing a single α ($\alpha 7$, 9, or 10) subunit (Dani and Bertrand, 2006). The subunit composition of each channel determines the specificity for which ions flow through the receptor. For instance, the homomeric $\alpha 7$ receptor readily allows Ca^{2+} to flow into the channel once opened, while the heteromeric $\alpha 4\beta 2$ nAChR allows both Na^{2+} and Ca^{2+} to enter the cell (Davis and De Fiebre, 2006). The nAChR subunit composition also determines ligand specificity. For example, $\alpha 4\beta 2$ nAChRs have the highest affinity for nicotine binding (Albuquerque et al., 2009). Taken together, the subunit composition of nicotinic receptors is important for their functionality.

nAChRs are expressed in many brain regions including the interpeduncular nucleus (Grady et al., 2009), medial habenula (Hsu et al., 2013), substantia nigra (Azam et al., 2002; Gotti et al., 2006b), striatum (Gotti et al., 2006a), locus coeruleus (Gotti et al., 2006a), and ventral tegmental area (VTA) (Azam et al., 2002; Gotti et al., 2006a). These regions are involved in the mesocorticolimbic and habenula-interpeduncular pathways, which are important for modulating drug reward and withdrawal. Key projections in the mesocorticolimbic pathway originate from the VTA, where dopaminergic neurons project to several forebrain regions, including the nucleus accumbens (NAc) (Gonzales et al., 2004). Ethanol exerts its reinforcing properties through this pathway by increasing dopamine (DA) release in the NAc. Previous studies indicate that ethanol dose-dependently increases accumbal DA levels through activation of nAChRs in the VTA (Chatterjee and Bartlett, 2010; Davis and De Fiebre, 2006; Ericson et al., 2003). In contrast, withdrawal effects of ethanol are influenced by cholinergic activity in the habenula-interpeduncular pathway (McLaughlin et al., 2017; Perez et al., 2015). In sum, modulating nAChR function in brain regions related to drug reward and withdrawal can lead to changes in ethanol responses.

Generally, nAChRs have been implicated in many of ethanol's behavioral responses including consumption (Feduccia et al., 2012; Hendrickson et al., 2010; Kamens et al.,

2010b; Kamens et al., 2018; Steensland et al., 2007), reward (Liu et al., 2013b; Powers et al., 2013), ataxia (Kamens et al., 2010a; Taslim et al., 2008), sedation (Bowers et al., 2005; Kamens et al., 2010a; Kamens et al., 2012), and locomotor activation (Kamens et al., 2009; Kamens and Phillips, 2008; Larsson et al., 2002) in rodent models. Human genetics work complements these findings. For example, polymorphisms in nAChR genes have been associated with alcohol dependence (Hoft et al., 2009; Sherva et al., 2010), consumption (Landgren et al., 2009), frequency of use (Coon et al., 2014), level of response (Choquet et al., 2013), initial response (Ehringer et al., 2007), and the onset of use (Schlaepfer et al., 2008). These data provide a compelling argument that this receptor system should be examined as a potential target for AUD treatments. To identify relevant literature for this review, we searched PubMed using the following keywords: *nAChR*, *ethanol*, *alcohol*, and *behavior*. This review synthesizes the research on nAChR involvement in alcohol-related behaviors by examining findings from pre-clinical research, focusing specifically on results from genetically modified animals and pharmacological treatments.

2.1 The implication of involvement of nAChRs with non-specific pharmacological tools

Mecamylamine (MEC; Inversine®) is an FDA approved medication used to treat hypertension that acts as a non-selective, non-competitive nAChR antagonist (Bacher et al., 2009). At anti-hypertensive doses (30–90 mg/day), it can cause several adverse side effects such as nausea, drowsiness, and fainting (Shytle et al., 2002). Consistent with these adverse effects seen clinically, in rodent models, high doses of MEC alter ethanol behaviors but also have non-specific effects. For example, MEC (6–8 mg/kg) decreases both ethanol (10%) and sucrose (5%) self-administration in male C57BL/6J mice (Ford et al., 2009). These doses also decrease locomotor activity, a finding replicated with MEC (4 mg/kg) in Long Evans rats (Hetzler and Bauer, 2013). Therefore, similar to observations in humans, high doses of MEC seem to have adverse or non-specific effects, which limit its therapeutic potential.

Research with lower doses of MEC has observed mixed results for the treatment of AUD (Petrakis et al., 2018; Young et al., 2005). For example, a short-term clinical study showed that MEC (15 mg/day) reduced ratings of alcohol stimulation and reported a trend for decreased alcohol choice (Young et al., 2005). In contrast, long-term treatment with MEC (10 mg/day, 12 weeks) did not affect the number of heavy drinking days (Petrakis et al., 2018). In addition to the length of treatment, these differences could also be attributed to the level of alcohol use within the study population, healthy volunteers versus alcohol dependent subjects, respectively. In male C57BL/6J mice, lower doses of MEC (0.5–3 mg/kg) reduce choice ethanol consumption, preference (Farook et al., 2009), and binge-like drinking (Hendrickson et al., 2009). These studies found that MEC decreased ethanol intake without altering water, total fluid intake (Farook et al., 2009), or sucrose consumption (Hendrickson et al., 2009). Consistent with these findings, in male Wistar rats, low doses of MEC (1.25 and 2.5 mg/kg) decreased ethanol operant self-administration (Kuzmin et al., 2009). This work using low MEC doses in rodents supports the general involvement of nAChRs in modulating ethanol consumption and its motivational effects. These data also highlight the importance of dose tested to avoid non-specific effects.

In addition to work on ethanol consumption, other research has demonstrated that MEC attenuates ethanol-induced locomotor stimulation, reward, reinstatement, and neuronal responses. Work in DBA/2J mice has shown that MEC (1–4 mg/kg) reduces ethanol-induced locomotor stimulation without altering general activity (Kamens and Phillips, 2008). Bhutada et al. showed a similar attenuation of ethanol-induced locomotor stimulation in male Swiss mice. This group further extended this work and demonstrated a reduction in the acquisition and expression of ethanol-induced locomotor sensitization (Bhutada et al., 2010). Finally, important work has been done with ethanol conditioned place preference (CPP). Here, intracerebroventricular administration of MEC decreased acquisition, expression, and reinstatement of ethanol CPP in male Swiss mice (Bhutada et al., 2012). These results suggest that MEC, and therefore nAChRs, can alter both acute and chronic ethanol responses. In complementary work, the effect of MEC (3 mg/kg) on ethanol-induced neuronal activation in C57BL/6J mice was measured by c-Fos expression. Here, MEC significantly reduced c-Fos expression in dopaminergic VTA cells following acute ethanol administration (Hendrickson et al., 2009). Further, in C57BL/6J and DBA/2J mice MEC reduces ethanol-induced DA release in the NAc (Yorgason et al., 2015). Taken together, these data suggest that MEC reduces ethanol consumption and behavioral responses to systemically administered ethanol, possibly through its ability to block ethanol activation of dopaminergic neurons in the VTA (Blomqvist et al., 1993; Ericson et al., 1998; Hendrickson et al., 2009).

Given the non-selectivity of MEC at nAChRs, it is difficult to know which receptor(s) drive these effects (Papke et al., 2001). Next, this review examines the influence of specific nAChR subunits on various ethanol responses. There are eight nAChR subunits commonly found in the mammalian brain. We first describe the results with subunits that form the most common brain nAChRs, the homomeric $\alpha 7$ and heteromeric $\alpha 4\beta 2$ receptors. The final five subunits are located in two distinct gene clusters and thus are described in this way.

2.2 $\alpha 7$ nAChRs

$\alpha 7$ nAChRs are the most common homomeric nicotinic receptor found in the brain (Drisdell and Green, 2000). Mice lacking this subunit ($\alpha 7$ knockout; KO) consume significantly less ethanol than wildtype (WT) mice, but similar amounts of water, quinine, and saccharin (Kamens et al., 2010b). Bowers and colleagues examined the influence of the $\alpha 7$ subunit on other ethanol-related behaviors in KO mice. Here, null mutant $\alpha 7$ mice were more sensitive to ethanol-induced sedation, hypothermia, and acute ethanol-induced locomotor stimulation compared to WT animals (Bowers et al., 2005). No genotype-dependent differences were found on acoustic startle reflex, pre-pulse inhibition of the acoustic startle reflex, or ethanol metabolism (Bowers et al., 2005). Interestingly, $\alpha 7$ KO mice exhibit enhanced ethanol-induced cortical neurotoxicity relative to WT (de Fiebre and de Fiebre, 2004). Overall, these results with genetically modified mice suggest that $\alpha 7$ nAChRs modulate several ethanol responses, including consumption, sedation, hypothermia, ethanol-induced locomotor stimulation, and neurotoxic effects.

To target $\alpha 7$ nAChRs pharmacologically, methyllycaconitine citrate, an $\alpha 7$ nAChR antagonist, has been used. Using this drug, Larsson et al. found that methyllycaconitine (2

mg/kg) did not alter ethanol-induced locomotor stimulation or ethanol-induced DA overflow in the NAc of male NMRI mice (Larsson et al., 2002). Further, work using C57BL/6J mice found that a range of methyllycaconitine doses (5–10 mg/kg) did not affect binge-like ethanol consumption in a 2h drinking-in-the-dark (DID) assay (Hendrickson et al., 2009). These findings are inconsistent with the results from KO mice. These conflicting results could be attributed to the lack of $\alpha 7$ in the KO animals throughout development or compensation from other nAChR subunits. A second possibility is that doses of methyllycaconitine tested were too low, but these same doses block nicotine responses in animal models (Iha et al., 2017; Markou and Paterson, 2001).

2.3 $\alpha 4\beta 2$ nAChRs

$\alpha 4\beta 2$ nAChRs are the most widely expressed heteromeric nicotinic receptors found in the brain and thus have been studied for their involvement in both behavioral and physiological ethanol responses. Liu et al. examined ethanol-induced activation of midbrain dopaminergic neurons from $\alpha 4$ KO mice and Leu'9 Ala knock-in animals expressing a hypersensitive $\alpha 4$ subunit (Liu et al., 2013a). They found that at concentrations of ethanol that produce intoxication (100 mM), dopaminergic activation was significantly reduced in $\alpha 4$ KO mice relative to WT animals. In contrast, low levels of ethanol were sufficient to activate dopaminergic neurons in Leu'9 Ala mice, but not in WT mice. These results suggest that activation of $\alpha 4$ -containing nAChRs is important for ethanol-induced neuronal firing. In parallel, behaviorally, $\alpha 4$ KO mice do not exhibit CPP at rewarding ethanol doses, whereas Leu'9 Ala mice exhibited CPP at sub-rewarding doses (Liu et al., 2013a). These results are in line with the physiological changes observed and demonstrate that the $\alpha 4$ nAChR subunit is involved in ethanol reward sensitivity.

Research has also examined the effect of the $\beta 2$ subunit on ethanol behaviors and neuronal responses. Dawson and colleagues found that $\beta 2$ KO mice were more resilient to the sedative-hypnotic effects of ethanol and exhibited reduced ethanol-induced anxiety relative to WT mice (Dawson et al., 2013). In contrast, the absence of this subunit does not alter ethanol-induced locomotor depression, hypothermia, or ethanol consumption (Dawson et al., 2013; Kamens et al., 2010b). Physiologically, $\beta 2$ KO mice exhibit decreased spontaneous activity of DA neurons relative to WT mice but have similar DA activity in response to ethanol (Tolu et al., 2017). Together, this work suggests that the $\beta 2$ subunit is involved in the sedative-hypnotic and anxiolytic effects of ethanol, but provides no evidence for its involvement in ethanol consumption.

In contrast to the work in genetically modified animals, there is relatively strong support for $\alpha 4\beta 2$ nAChR involvement in ethanol consumption with pharmacological manipulations. Interestingly, $\alpha 4\beta 2$ nAChR full agonist (sazetidine-A) (Zwart et al., 2008), partial agonist (varenicline (Rollema et al., 2007), cytisine (Radchenko et al., 2015)), and antagonist (AP-202) (Wu et al., 2017) all decrease ethanol intake or self-administration. The most widely studied $\alpha 4\beta 2$ nAChR modulator is varenicline, an FDA approved medication for smoking cessation (Ebbert, 2010). Varenicline reduces ethanol consumption in mice (Hendrickson et al., 2010, 2011; Kamens et al., 2010b; Kamens et al., 2018; Patkar et al., 2016), rats (Bito-Onon et al., 2011; Feduccia et al., 2014; Froehlich et al., 2017; Sotomayor-

Zárate et al., 2013; Steensland et al., 2007), and nonhuman primates (Kaminski and Weerts, 2014). Although many studies have replicated this finding, one study using male Marchigian Sardinian alcohol-preferring rats found no effect of varenicline on ethanol consumption (Scuppa et al., 2015). This finding lead the authors to hypothesize that this strain may be less sensitive to varenicline's effects. Interestingly, results using operant self-administration paradigms have been mixed with increased, decreased, and no change in responding being reported in male rats (Czachowski et al., 2018; Funk et al., 2016; Ginsburg and Lamb, 2013; Randall et al., 2015). The results from animal studies are largely in line with data from a randomized clinical trial that demonstrates that varenicline, in combination with psychosocial intervention, reduces heavy drinking in males with AUD and comorbid smoking (O'Malley et al., 2018). In most cases, this reduction in consumption was specific for ethanol, but in a few cases, this drug reduced (Kamens et al., 2018; Shariff et al., 2016) or increased (Wouda et al., 2011) the consumption of sweet tastants. Similar results were observed with another $\alpha 4\beta 2$ partial agonist, cytisine. This drug reduced ethanol consumption and preference in a 2BC drinking paradigm using male C57BL/6J mice (Sajja and Rahman, 2013) and in a binge-drinking paradigm (Hendrickson et al., 2009).

In addition to consumption of alcohol, another important aspect of AUD is the vulnerability to relapse. For example, when exposed to an alcohol cue heavy drinkers report craving. In animal models, varenicline has been shown to reduce both cue- and context-induced relapse (Lacroix et al., 2017; Wouda et al., 2011). These findings are in agreement with a human laboratory experiment where participants treated with varenicline show less craving following an alcohol cue-exposure (Roberts et al., 2017). Together these data provide strong support for $\alpha 4\beta 2$ partial agonist as a potential pharmacotherapy for AUD.

Similar reductions in ethanol intake have been found with other $\alpha 4\beta 2$ nAChR drugs. For example, high doses of sazetidine-A, a full agonist that desensitizes $\alpha 4(2)\beta 2(3)$ nAChRs, reduces binge-like ethanol intake in C57BL/6J mice without altering sucrose intake (Touchette et al., 2018). In contrast, in alcohol-preferring P rats, sazetidine-A reduced ethanol consumption, but also decreased saccharin intake (Rezvani et al., 2010). Further, sazetidine-A reduces the reinstatement of ethanol preference following a 4 day abstinence period in P rats (Rezvani et al., 2010) and withdrawal signs in C57BL/6J mice (Hendrickson et al., 2009).

Data from $\alpha 4\beta 2$ nAChR antagonists have provided mixed results. AP-202, a potent $\alpha 4\beta 2$ nAChR antagonist, reduces oral ethanol self-administration without altering food self-administration in male Sprague Dawley rats (Cippitelli et al., 2018). Unfortunately, the dose of AP-202 that influences self-administration also reduces general locomotor activity. When models of reinstatement were examined, AP-202 had no effect on cue- or stress-induced relapse (Cippitelli et al., 2018). While AP-202 reduced ethanol self-administration, dihydro- β -erythroidine (DH β E), a second $\alpha 4\beta 2$ antagonist, did not affect ethanol consumption in either a binge-like ethanol intake assay in C57BL/6J mice (Hendrickson et al., 2009) or an intermittent-access 2BC paradigm in male Wistar rats (Chatterjee et al., 2011; Lê et al., 2000). The effects of DH β E on ethanol self-administration have yielded inconsistent findings. In male Wistar rats, systemic administration of a high (4 mg/kg), but not low (1–2 mg/kg), dose of DH β E reduces ethanol (5%) operant self-administration; however, it also

reduces inactive lever pressing at this dose (Kuzmin et al., 2009). In Sprague Dawley rats, a high (8 mg/kg) dose of DH β E did not alter ethanol self-administration (Cippitelli et al., 2018). There are a few reasons why inconsistent results may have occurred with α 4 β 2 antagonist. These include the potency of the drug at the receptor, non-equivalent doses, or the potential of spurious results.

In addition to examining the role of these receptors in ethanol consumption and self-administration, several other behaviors have been examined. For example, in adult C57BL/6J mice, varenicline (2 mg/kg) increases the sedative and ataxic effects of ethanol (Kamens et al., 2010a). This effect on ethanol sedation may be age-specific as varenicline did not affect ethanol-induced sedation in adolescent C57BL/6J mice (Kamens et al., 2018). Importantly, these potential age-specific differences are not likely due to changes in metabolism as prior studies have found no effect of varenicline on ethanol metabolism in adult (Gubner et al., 2014; Gulick and Gould, 2008; Kamens et al., 2010b) or adolescent mice (Kamens et al., 2018). In terms of ethanol reward, Gubner et al. found no significant influence on acquisition or expression of ethanol-induced locomotor sensitization or CPP. This group did observe that varenicline attenuates ethanol-induced locomotor stimulation at high (2 mg/kg) doses, but these effects appear to be nonspecific because it also decreases general locomotion (Gubner et al., 2014). There are at least two ways that a drug could reduce ethanol consumption. It could either increase the aversive effects or diminish the rewarding effects of ethanol. Together these data suggest the former explanation. Interestingly, varenicline has also been reported to enhance alcohol sedation in human studies and potentiate negative subjective effects (Childs et al., 2012; Fucito et al., 2011). These data align with the animal findings.

Few of the other α 4 β 2 nAChR drugs have been used to examine other ethanol behavioral responses. There are inconsistent results on the effect of DH β E on ethanol-induced DA release. One study found that DH β E decreases ethanol-induced DA release in the NAc of male C57BL/6J and DBA/2J mice (Yorgason et al., 2015); however, another study showed no effect in male NMR mice (Larsson et al., 2002). Further, treatment with a range of DH β E doses (0.5–2 mg/kg) did not alter ethanol-induced locomotor stimulation in mice (Kamens and Phillips, 2008; Larsson et al., 2002). These findings are in-line with earlier reviewed studies where DH β E did not consistently alter ethanol self-administration.

2.4 α 5 α 3 β 4 nAChRs

The α 5, α 3, and β 4 gene cluster is located on human chromosome 15 and mouse chromosome 9. To understand the contributions of these nAChR subunits, animal models have manipulated all three genes together and individually. The TgCHRNA5/A3/B4 transgenic mice overexpress the human *CHRNA5*, *CHRNA3*, and *CHRNA4* genes (Gallego et al., 2012a). Gallego and colleagues utilized these mice to assess the genetic contributions of this cluster on many ethanol-related phenotypes. They found that male TgCHRNA5/A3/B4 mice consume significantly less ethanol (3–20%) in a 2BC drinking paradigm relative to WT mice, while there were no differences in tastant consumption. In contrast, the transgenic overexpressing mice showed no difference in ethanol-induced ataxia, sedation, hypothermia, or withdrawal severity relative to WT animals (Gallego et al.,

2012b). These findings suggest that increased expression of these receptor subunits appears to have a specific effect on ethanol consumption. However, it is unclear if increased expression of all three subunits is required or if one or a combination of these subunits drives this effect.

A complementary approach to the transgenic model has utilized genetically modified animals where a single subunit is removed. Work by Santos and colleagues showed that male $\alpha 5$ KO mice displayed increased ethanol-induced sedation and ataxia compared to WT animals, but showed no difference in ethanol metabolism or binge-like ethanol consumption over a range of ethanol concentrations (5–30%) (Santos et al., 2013). These results for ethanol-induced ataxia and sedation are in contrast to results from the Tg*CHRNA5/A3/B4* transgenic mice that exhibited no changes in these behavioral measures. Both Gallego et al. and Santos et al. used the rotarod and loss of righting reflex paradigm (LORR) to measure ethanol-induced ataxia and sedation, respectively. The ethanol drinking results also differ between the Gallego et al. and Santos et al. studies. Gallego et al. measured choice ethanol consumption in a 24 h 2BC paradigm, whereas Santos et al. measured binge-like ethanol consumption with a 4 h limited access DID paradigm. DID assesses heavy binge-like drinking (Thiele and Navarro, 2014) while 2BC assesses chronic ethanol consumption and preference (Tabakoff and Hoffman, 2000). These data suggest that the $\alpha 5$ nAChR subunit is involved in ethanol-induced motor incoordination and sedation but does not appear to contribute to binge-like drinking in male mice.

Homozygous mice lacking the $\alpha 3$ nAChR subunit are neonatal lethal (Xu et al., 1999), so prior research has examined heterozygous $\alpha 3$ mice to probe the role of this receptor subunit in ethanol behaviors. Heterozygous *Chrna3* null mutant mice (*Chrna3* +/–) had reduced locomotor sedation in response to acute ethanol exposure compared to WT mice (Kamens et al., 2009). This research suggests that the $\alpha 3$ subunit is involved in the acute locomotor response to ethanol, which is related to dopaminergic activity and the drug's euphoric effects (Beckstead and Phillips, 2009).

$\beta 4$ KO mice have been used to examine both physiological and behavioral changes in response to ethanol. Tolu and colleagues used $\beta 4$ KO mice to assess DA neuron firing in the VTA following ethanol. They found that $\beta 4$ KO mice displayed reduced DA activity in response to ethanol compared to WT mice, without altering spontaneous activity. Behaviorally, $\beta 4$ KO mice consume significantly more ethanol than WT mice at high ethanol concentrations (10–15%), but no differences were observed at lower concentrations (3–6%) (Tolu et al., 2017). Interestingly, Kamens and colleagues found no difference in ethanol-induced ataxia, sedation, metabolism, or consumption when $\beta 4$ KO mice were compared to WT animals (Kamens et al., 2017b). The differing results could be attributed to several factors. First, Tolu et al. used a 24 h 2BC paradigm to measure choice consumption, whereas Kamens et al. used a 4 h DID paradigm, which may capture a different pattern of ethanol consumption. Additionally, Tolu et al. found differences in ethanol consumption when presented with 10–15% ethanol concentrations, but Kamens et al. used a higher ethanol concentration (20%). Together, these findings suggest that the $\beta 4$ subunit influences dopaminergic response to ethanol in the VTA, but these neurobiological changes may only alter ethanol preference and not heavy drinking.

Compared to the Tg*CHRNA5/A3/B4* transgenic animal model, the results from the *Chrn4* KO mice are the only ones to recapitulate the drinking results. Specifically, the transgenic animal model that overexpressed the genes in this cluster had reduced ethanol consumption relative to WT mice. Consistent with this finding, *Chrn4* KO mice demonstrated increased ethanol consumption in the 2BC model. These findings suggest that *Chrn4* may be important for choice ethanol consumption, but future research should confirm this hypothesis.

Research using both $\alpha 3\beta 4$ nAChR partial agonists and antagonist has provided support for the involvement of these receptors in ethanol behaviors. Three $\alpha 3\beta 4$ nAChR partial agonists have been tested, CP-601932, PF-4575180, and AT-1001. Treatment with both CP-601932 and PF-4575180 reduce both operant ethanol (10%) self-administration and ethanol (20%) consumption in a 24 h intermittent 2BC paradigm. Neither drug changed responding for or consumption of sucrose, but the highest dose of PF-4575180 increased water intake (but with no overall effect on total fluid consumption) (Chatterjee et al., 2011). Work in Sprague Dawley rats has shown that a high dose (3 mg/kg) of AT-1001 reduces operant ethanol self-administration, but also reduces responding for food (Cippitelli et al., 2015a). Due to these nonspecific findings, a lower dose (1.5 mg/kg) of AT-1001 was examined. This low AT-1001 dose had no effect on ethanol self-administration or cue-induced reinstatement. Additionally, it did not precipitate reinstatement (Cippitelli et al., 2015b, 2015a). In contrast, it did decrease stress-induced reinstatement, suggesting a role for $\alpha 3\beta 4$ nAChRs in stress precipitated ethanol behaviors. While these data provide support for the role of $\alpha 3\beta 4$ nAChRs in ethanol consumption, it also highlights again the importance of considering dose.

18-Methoxycoronaridine's (18-MC) primary mechanism of action is as an $\alpha 3\beta 4$ nAChR antagonist (Glick et al., 2000; Glick and Maisonneuve, 2000). Prior work using alcohol-preferring rats has shown that 18-MC decreases ethanol consumption (Rezvani et al., 2016, 1997). Consistent findings in C57BL/6J mice showed that a high dose (30 mg/kg) of 18-MC reduces binge-like ethanol consumption without altering tastant intake, metabolism, or ethanol-induced sedation (Miller et al., 2019). Other work has examined the effects of 18-MC on ethanol-induced locomotor stimulation and sensitization. Here, 18-MC did not alter ethanol-induced locomotor stimulation or basal locomotor activity, but the 30 mg/kg 18-MC dose reduced ethanol-induced sensitization in male and female DBA/2J mice (Miller and Kamens, In Press). Sensitization models neural adaptations underlying the development of drug dependence (Steketee and Kalivas, 2011), so the ability of 18-MC to disrupt this process supports the clinical potential of this drug.

2.5 $\alpha 6\beta 3$ nAChRs

The $\alpha 6$ and $\beta 3$ subunits are located adjacent to one another on chromosome 8 in both humans and mice. These adjacent genes are highly expressed in the striatum, a brain region implicated in drug reinforcement and reward (Champtiaux et al., 2003). To study the $\alpha 6$ subunit, receptor hypersensitive and null mutant mice were examined, but these models have not always provided convergent information. Engle and colleagues used mice with a hypersensitive $\alpha 6$ subunit ($\alpha 6L9'S$ mice) to examine if this change altered AMPAR function in VTA neurons exposed to ethanol. Hypersensitive $\alpha 6L9'S$ mice require lower ethanol

concentrations to enhance AMPAR function than WT mice (Engle et al., 2015). In addition to these physiological differences, male and female hypersensitive $\alpha 6$ mice exhibit increased binge-like ethanol consumption and display ethanol CPP at a lower dose than WT animals (Powers et al., 2013). Female hypersensitive mice consume significantly more ethanol at low (3–6%) concentrations compared to WT mice. This difference was not observed in male mice or at higher concentrations (Powers et al., 2013). Taken together, these studies suggest that $\alpha 6$ -containing nAChRs are important for modulating physiological responses to ethanol, consumption, and reward.

Parallel work has used $\alpha 6$ KO models to examine the involvement of this subunit in ethanol reward sensitivity. Liu and colleagues found that unlike WT mice, $\alpha 6$ KO mice did not exhibit increased activity of VTA dopaminergic neurons in response to ethanol (Liu et al., 2013b). These results complement the work using the hypersensitive $\alpha 6$ model and further implicate nAChRs containing this subunit as a modulator of ethanol-induced changes in VTA firing. Multiple groups have tested $\alpha 6$ KO mice for sensitivity to ethanol traits. Guildford et al. found that $\alpha 6$ KO mice only develop CPP at a low (2 g/kg) ethanol dose, whereas WT mice exhibit CPP at higher doses (2–5 g/kg) (Guildford et al., 2016). This general trend was replicated by a second group, albeit that the effective doses were lower (Steffensen et al., 2018). Mice lacking the $\alpha 6$ subunit did not differ in binge-like ethanol consumption nor the acute locomotor response to ethanol relative to WT animals (Guildford et al., 2016). Similar results were independently replicated by a second group, who showed that $\alpha 6$ KO mice exhibit enhanced ethanol-induced sedation but did not differ in 2BC ethanol consumption or ethanol-induced ataxia relative to WT mice (Kamens et al., 2012). The differences found between the hypersensitive and KO mice may be due to compensatory mechanisms of nAChRs observed in $\alpha 6$ KO mice (Champtiaux et al., 2002). Together, data from genetically modified animals provides support for $\alpha 6$ in the rewarding effects of ethanol, but the influence of this subunit in ethanol consumption is not conclusive in these models.

Although there are mixed results for the involvement of $\alpha 6$ -containing nAChRs in ethanol consumption, pharmacological tools provide support for the involvement of these receptors in ethanol behaviors. α -conotoxins are a family of neurotoxic peptides that act as competitive antagonists of nAChRs (Arias and Blanton, 2000). One conotoxin that targets $\alpha 6$ -containing nAChRs is α -conotoxin MII [H9A; L15A]. This compound attenuates ethanol-induced DA release in the NAc in response to low, but not high, concentrations of ethanol in C57BL/6J and DBA/2J mice (Yorgason et al., 2015). However, due to neurotoxic effects, conotoxins are unsafe for clinical use. Recent work with N,N-decane-1,10-diyl-bis-3diiodide (bPiDI), a selective $\alpha 6\beta 2$ antagonist, has further supported the role of these receptors (Wooters et al., 2011). bPiDI reduces ethanol self-administration in alcohol-preferring rats (Srisontiyakul et al., 2016) and binge-like ethanol consumption in C57BL/6J mice (H. M. Kamens et al., 2017a). This reduction in consumption is independent of changes in metabolism, ataxia, or sedation (H. M. Kamens et al., 2017a). Although bPiDI effects ethanol consumption, bPiDI had no effect on cue-induced reinstatement of ethanol seeking, suggesting this receptor likely is not involved in relapse (Srisontiyakul et al., 2016). The effects of bPiDI on locomotor activity and tastant consumption seem to be species-specific. For example, work in alcohol-preferring rats suggests that bPiDI does not alter

locomotor activity or sucrose self-administration (Srisontiyakul et al., 2016). In contrast, work in C57BL/6J mice suggests that bPiDI reduces saccharin consumption and locomotor activity (Kamens et al., 2017a). Overall, $\alpha 6$ -containing nAChRs may be involved in ethanol consumption, but it is possible that drugs that target these receptors may have nonspecific effects.

Work with bPiDI suggests that targeting $\alpha 6\beta 2$ receptors can reduce ethanol consumption. Studies using $\beta 2$ KO mice observed no changes in ethanol consumption, so the effects observed with bPiDI may be driven by the $\alpha 6$ subunit. This hypothesis would be consistent with data from the $\alpha 6$ hypersensitive animals, but not the KO model. Future work is needed to test this hypothesis.

In contrast, less research has examined the role of the $\beta 3$ nAChR subunit in ethanol-related behaviors. We know of a single study that examined choice ethanol consumption, ethanol-induced ataxia, and sedation in $\beta 3$ KO mice (Kamens et al., 2012). In this paper, no differences in ethanol behaviors were observed. Thus, there is currently no evidence for a role of the $\beta 3$ nAChR subunit in ethanol behaviors, but it has not been exhaustively studied. To the best of our knowledge, no drugs specifically target nAChRs containing a $\beta 3$ subunit.

3.1 Conclusions and directions for future research

Given the public health burden of alcohol use, it is crucial to continue to investigate novel therapeutics for this disease. The current manuscript reviews literature showing that nAChRs are involved in many ethanol-related behaviors. To date, the most promising nAChRs to target for therapeutics appear to be $\alpha 4\beta 2$, $\alpha 3\beta 4$, and $\alpha 6\beta 2$.

3.2 Ligand specificity

This review was organized by nAChR subunit, which may make interpretation of the present work difficult. This is because pharmacological interventions interact with the whole receptor, and generally not a specific subunit. For example, AP-202, is a selective $\alpha 4\beta 2$ antagonist (Wu et al., 2017). It is possible that the effects of this drug may be attributed to the $\alpha 4$ or $\beta 2$ subunit, or a combination of both. Further research should combine genetically engineered mice with pharmacological agents to gain a better understanding of the mechanism of action. For example, such work has been conducted with varenicline. Here, data have shown the importance of the $\alpha 4$ nAChR subunit in varenicline's reduction of ethanol consumption (Hendrickson et al., 2011, 2010), but the removal of the $\beta 2$ subunit did not affect this behavior (Kamens et al., 2010b).

A limitation to the current review is the potential overlap among ligands used and how they are characterized. In this review, we classified each drug under the receptor for which it has the highest specificity. For example, varenicline is a high affinity partial agonist at $\alpha 4\beta 2$ nAChRs, but it is also known to interact with other nAChRs and 5-HT₃ receptors at high doses (Coe et al., 2005; Rollema et al., 2007). Therefore, these other receptors may modulate effects on ethanol consumption. This is true for not only varenicline, but other drugs reviewed here as well.

3.3 Functional compensation

In this review we present data from genetically modified animals and pharmacological manipulations that do not always align. In addition to ligand specificity, a second consideration that could account for divergent results is compensatory changes in genetically modified animals. For example, in $\alpha 6$ KO animals, α CtxMII-resistant [3 H]epibatidine binding has been shown to be upregulated in the striatum compared to WT animals (Champtiaux et al., 2002). Although other studies have found no compensation in nAChR KO animals (Marubio et al., 1999; Picciotto et al., 1998; Ross et al., 2000), it remains possible compensatory changes have occurred in these mice that have yet to be observed or tested.

3.4 Overall conclusions

Alcohol misuse creates an alarming economic and health burden in the United States, and the low efficacy of current therapeutics drives further research into the mechanisms underlying alcohol-related behaviors. This review examined genetic and pharmacologically manipulated rodent models to isolate the contributions of specific nAChR subunits in ethanol-related behaviors. Overall, these findings support cholinergic therapeutics as a focus of future drug development for AUD. These data also highlight the need for the generation of specific ligands that may treat alcoholism with minimal side effects.

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