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Regulation of the Deleterious Effects of Binge-Like Exposure to Alcohol during Adolescence by α7 Nicotinic Acetylcholine Receptor Agents: Prevention by Pretreatment with a α7 Negative Allosteric Modulator and Emulation by a α7 Agonist in Alcohol-Preferring (P) Male and Female Rats

Zachary A. Rodd[1,2,*], **Sheketha R. Hauser**[1,2], **H. Scott Swartzwelder**[1,2], **R. Aaron Waeiss**[1,2], **Debomoy K. Lahiri**[1,2], **Richard L. Bell**[1,2]

[1]Department of Psychiatry, Institute of Psychiatric Research, Indiana University School of Medicine, Indianapolis, IN 46202.

[2]Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, N.C., USA

Abstract

Rationale and Objectives—Binge-like alcohol consumption during adolescence associates with several deleterious consequences during adulthood including an increased risk for developing alcohol use disorder (AUD) and other addictions. Replicated preclinical data has indicated that adolescent exposure to binge-like levels of alcohol results in a reduction of choline acetyltransferase (ChAT) and an upregulation in the α7 nicotinic receptor (α7). From this information, we hypothesized that the α7 plays a critical role in mediating the effects of adolescent alcohol exposure.

Methods—Male and female P rats were injected with the α7 agonist AR-R177779 (AR) once during 6 time points between post-natal days (PND) 29–37. Separate groups were injected with the α7 negative allosteric modulator (NAM) dehydronorketamine (DHNK) 2 hours before administration of 4 g/kg EtOH (14 total exposures) during PND28–48. On PND75 all rats were

*Address Correspondence to: Zachary A. Rodd, Ph.D., Neuroscience Research Building, 320 W. 15th Street, Suite 300B, Indianapolis, IN 46202-2266 USA, zrodd@iupui.edu, 1-317-278-3003.

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given access to water and ethanol (15 and 30%) for 6 consecutive weeks (acquisition). All rats were then deprived of EtOH for 2 weeks and then alcohol was returned (relapse).

Results—Administration of AR during adolescence significantly increased acquisition of alcohol consumption during adulthood and prolonged relapse drinking in P rats. In contrast, administration of DHNK prior to binge-like EtOH exposure during adolescence prevented the increase in alcohol consumption observed during acquisition of alcohol consumption and the enhancement of relapse drinking observed during adulthood.

Discussion—The data indicate that α7 mediates the effects of alcohol during adolescence. The data also indicate that α7 NAMs are potential prophylactic agents to reduce the deleterious effects of adolescent alcohol abuse.

Keywords

Alcohol-preferring (P) rats; alcohol; ethanol; adolescence; acquisition; relapse; addiction

INTRODUCTION

In US adolescents, the most commonly utilized drug of abuse is alcohol (Johnston et al., 2004). Despite a legal drinking age of 21, 11% of all alcohol consumed in the US is by individuals aged 12 to 20 (OJJDP, 2005). Over 90% of US adolescent alcohol consumption occurs in the form of binge drinking (OJJDP, 2005). High school students report high levels of binge-drinking within the past two weeks (Johnston et al., 2004).. Binge-drinking in high school is associated with an increased rate of binge-drinking in college and a propensity for frequent binge-drinking (19–25% report more than 3 episodes of binge drinking per week; Wechsler et al., 1995, 2000).

Age of first drink and the propensity to have binge EtOH drinking episodes during adolescence correlates with an increase in alcohol involvement, heavier drinking bouts, arrests for driving with ability impaired, and an increased rate of alcohol dependence during adulthood (Hingson et al., 2008; Chou and Pickering, 1992). Epidemiological studies show a 1.3 to 1.6 times increased rate of alcohol dependence in individuals who initiate alcohol use before the age of 15 (Dawson et al., 2008).

The adolescent brain is in neuro-developmental flux and is characterized by rapid growth, reorganization, and pruning of neurons throughout adolescence (c.f., Geidd, 2004). Adolescent alcohol exposure can disrupt this normal remodeling of cortical and limbic regions (Spear, 2000). Replicable effects of adolescent alcohol consumption on the adult brain include a hyper-dopaminergic response to stimuli, reduction in choline acetyltransferase (ChAT), alterations in neuroimmune function, and non-specific modulation of epigenetic factors (Spear and Swartzwelder, 2014; Mullholland et al., 2018; Swartzwelder et al., 2019).

The reduction in ChAT is not specific to adolescent alcohol exposure and is similarly reduced following nicotine, opioid, and cocaine exposure (Abreu-Villaca et al., 2004; Wilson et al., 1994; Robinson et al., 1993). Despite the convergent data sets indicating that ChAT expression is reduced following adolescent alcohol exposure, there has been a general

lack of research examining compensatory alterations in nicotinic receptors. Recent data from our laboratory has indicated that voluntary EtOH intake during adolescence in P rats results in a leftward and upward shift in the dose-response curve (increased sensitivity) for the ability of nicotine microinjected into the posterior ventral tegmental area (VTA) to stimulate dopamine (DA) release in the nucleus accumbens shell (AcbSh) during adulthood (Waeiss et al., 2019). Similarly, AIE treatment during adolescence in Wistar and P rats reduced the concentration of EtOH required (increased sensitivity) to support EtOH self-administration directly into the posterior VTA during adulthood (Hauser et al., 2019). An analysis of DA and acetylcholine related genes expression in adulthood following AIE exposure in male and female Wistar rats indicated that there was a reduction in the expression of the cholinergic muscarinic 1 receptor, α4, and α5 nicotinic acetylcholine receptors (NAchRs) and the D3 DA receptor, but an increase in the expression of α7 in both male and female rats (Hauser et al., 2019). Similar results occurred in P rats that voluntarily consumed EtOH during adolescence as indicated by an increase in the protein levels of the α7 subunits and an increase in α7 immunohistochemical expression in the posterior VTA during adulthood (Waeiss et al., 2019).

EtOH directly alters the actions of the α7 receptor (Dyson et al., 2013). The α7 is unique in multiple manners. The α7 is the only known receptor that has exerted evolutionary pressures on organisms to evolve innate regulatory factors of that system. In humans, evolutionary pressure has produced a chimeric gene (CHRFAM7A) that is a partial duplicate of the CHRNA7 (α7 receptor), but the protein coded by the CHRFAM7A gene acts as an innate negative allosteric modulator of α7 (Araud et al., 2011). A two- base pair deletion in the CHRFAM7A gene results in a pronounced increase in susceptibility to development of schizophrenia (Akbarian and Kundakovic, 2015). Genes similar to CHRFAM7A may have independently emerged in other species (e.g. raptors; Tessier et al., 2018). The α7 is the only known dual ionotropic and metabotropic receptor detected to date. Specifically, α7 is both a fast action/quickly desensitized ligand-gated ion channel (increase Ca2+ influx) and a long-acting G-protein coupled receptor (Gαq which promotes the sustained release of Ca2+ in the neuron; Kabbani and Nichols, 2018). In addition, α7 desensitization is much shorter than other NAchRs and is typified by a fast recovery period (King et al., 2018). Therefore, activation of α7 is a primary candidate for a critical site of action for adolescent alcohol consumption to produce persistent neuroadaptation.

Experimenter-administered Alcohol Intermittent Exposure (AIE) protocol results in equivalent exposure to EtOH in subjects and blood alcohol levels that exceed the binge-drinking threshold (c.f., Vetreno et al., 2014). The amount administered during AIE treatment is a supra-physiological dose and there could be tangential effects not observed during voluntary EtOH binge-drinking during adolescence (c.f., Rodd et al., 2020). The level used in the current experiments (4 g/kg) is the median EtOH dose for AIE treatment and has been shown to have face and ecological validity (c.f., Crews et al., 2019). Therefore, the AIE protocol, although possessing limitations, is a functional model to produce equivalent binge-like levels of alcohol exposure in rodents. The current experiments determined the effects of an α7 agonist administered daily during early adolescence on adult alcohol consumption. Similar to humans, early adolescent exposure to alcohol has more effects on adult alcohol consumption than later adolescent exposure (Saalfield and Spear, 2015; Spear, 2018). Also,

an experiment was conducted to determine if pretreatment with an α7 NAM would affect AIE-induced potentiation of adult alcohol consumption. Dehydronorketamine (DHNK) is a metabolite of ketamine but is lacking glutamatergic effects (Moaddel et al., 2013). DHNK has no reported abuse liability and is a selective α7 NAM (binding to α3β4 IC_{50} > 200 μM; Moaddel et al., 2013). A NAM does not reduce the activity of a receptor; NAMs prevents the increase or decrease activity of a receptor produced by ligands (Goodman and Gillman, 2011). The DHNK concentrations used in the reported studies were comparable to concentrations of DHNK shown not to influence locomotor activity or other variables (Salat et al. 2015). The use of an α7 nicotinic receptor NAM is beneficial to use in adolescent subjects because it does not alter the normal activity of a receptor. Inhibition of α7 (or reduction in the genetic expression of α7 subunits) during adolescence impairs cognitive performance during adulthood (Tanaka et al., 2015). In contrast, a α7 nicotinic receptor NAM should not produce that negative side effect.

METHODS

Subjects

The alcohol-preferring (P) rats used in the current experiments were from the standard P stock maintained by the Animal Breeding Core of the Indiana University Alcohol Research Center (IUARC). Animals used in this study were maintained in facilities fully accredited by the Association for the Assessment and Accreditation of Laboratory Animal Care. All research protocols were approved by the IUSM Institutional Animal Care and Use Committee (IUSM IACUC) and were in accordance with the guidelines of the Institutional Care and Use Committee of the National Institute on Drug Abuse, the NIH, and the Guide for the Care and Use of Laboratory Animals (2011).

Effects of exposure to the α7 agonist AR-R17779 during early adolescence on adult EtOH consumption

Adolescent male (n = 14) and female (n = 13) P rats were exposed to the α7 nicotinic receptor agonist, AR-R17779 (AR; Tocris) on PND 29, 30, 33, 35, 36, and 37. The doses of SR-R17779 was 0 (saline controls), 3 or 10 mg/kg (all drugs administered i.p.). AR is a highly selective α7 nicotinic receptor agonist with no or minimal affinity for all other examined receptors (Mullen et al., 2000). The doses of AR employed are typical for peripheral administered studies and results in observed alterations in specific behaviors (Levin et al., 1999). All rats were group housed between PND 26 and 73 (adulthood). Subjects only received treatment with AR_on the days specified. Experiment Timeline is provided in Figure 1 (top panel).

Effects of pretreatment with an α7 NAM dehydronorketamine prior to binge-like exposure during adolescence on adult EtOH consumption

There were 5 treatment groups. Adolescent male (n = 24) and female (n = 26) P rats were used in the experiment. The AIE exposure began on PND 28. Rats were given 4 g/kg alcohol (25% v/v; gavage) every Monday, Tuesday, Thursday and Friday (4 days a week; 3 days with no alcohol exposure) from post-natal day 28–48. Control (CON) groups received an equivalent volume administration of water. In the AIE groups, rats were injected (i.p.) with 0

(saline), 10 or 50 mg/kg of the α7 nicotinic receptor NAM dehydronorketamine (DHNK; Santa Cruz biotechnology) 2 hours prior to AIE exposure. CON groups received (i.p.) injections of saline or 50 mg/kg DHNK 2 hours prior to water gavage exposure. All rats were group housed between post-natal day 48 and 73 (adulthood). Pretreatment and gavage administration occurred during PND 28, 29, 30, 31, 34, 35, 37, 39, 40, 41, 44, 45, 47, and 48. Subjects were not exposed to DHNK any time after PND48. Experiment Timeline is provided in Figure 1 (bottom panel).

Measurement of bottle weights for the Adult EtOH consumption component was done blind to adolescent treatment condition.

Adult EtOH consumption

All rats were placed into individual hanging steel cages on PND 73 and allowed to acclimate for 48 hours prior to EtOH intake testing. Each hanging cage was equipped with an unanchored plastic perch (8 cm x 18 cm x 0.5 cm). Rats used the perch to rest and sleep. This perch greatly reduces the negative effects of being house in the hanging cage. Food and water were available *ad libitum* to all animals throughout the experiment. Ethyl alcohol (190 proof; McCormick Distilling Co., Weston, MO) was diluted to 15% and 30% (v/v) then provided continually beginning on PND 75 until the conclusion of the experiment.

All rats received 6 weeks of continual access to the EtOH solutions. All rats were then deprived of EtOH for 2 weeks. Relapse drinking was accessed through use of the alcohol deprivation effect (ADE). The ADE is a well-established phenomenon in which rats (or humans) consume more alcohol during EtOH re-exposure compared to baseline level of intake (Rodd et al., 2004). After the 2-week deprivation period, EtOH was again made available to all rats (both 15 and 30%).

Statistical Analysis

All statistical analyses followed the procedures/flowchart indicated by Keppel and Zedeck (1986). Briefly, the experiments examining the acquisition of alcohol consumption utilized the dependent measure of average weekly alcohol intake. The overall analyses were mixed factor ANOVAs with between subject factors of drug dose and EtOH exposure history (when applicable) and a within subject factor of Week. The statistical analyses surveying relapse drinking examined the average EtOH intake for the three days prior to deprivation and daily EtOH intake values following re-exposure. Post-hoc comparisons for between subject factors were performed with Tukey's b analyses. The Tukey's b post-hoc comparison is a modified Tukey post-hoc comparison that reduces the prohibitive penalty for unequal sample size. There is a single assumption of ANOVAs that cannot be violated. The statistical integrity of ANOVAs is greatly reduced when the assumption of 'Independence of Measure' is violated (Kepple and Zeddeck, 1986). Therefore, within subject variables should not be treated like between subject variables and analyzed with forced ANOVAs and inappropriate post-hoc analyses. Proper within subject post-hoc analyses are t-tests and orthogonal contrasts (Keppel and Zeddeck, 1986). Given the general lack of understanding of orthogonal contrasts, we are reporting only the findings from t-test analyses. Concerns of Type I error rate inflation is eliminated by the proper reading of Rodgers (1967). We adhere

to the replicated finding that Type 1 error rate inflations is $\Psi_i (i = 1, \ldots, J-1)$, and not Bonferroni improper estimate. Given the effect size of the current data set there is no likelihood of Type 1 error rate inflation for any reported analyses (c.f., Rodgers and Roberts, 2012; Roberts, 2011).

RESULTS

Exposure to the α7 Agonist AR-R17779 during early adolescence on adult EtOH consumption only at the highest dose

The overall statistical analysis performed on the dependent measure of average daily alcohol intake for each week revealed a Week x Sex x Dose interaction (Figure 2; $F_{2,21} = 4.59$; $p = 0.022$). For both weeks, there was a significant effect of AR dose on alcohol intake ($F_{2,21}$ values > 24.58; $p < 0.0001$). In female rats (top panel) there was a significant effect of AR on adult alcohol consumption for the first two weeks of alcohol drinking ($F_{2,10}$ values > 9.6; $p < 0.005$). Post-hoc comparisons (Tukey's b) indicated that during the 1st week of alcohol access female P rats (Fig. 2) administered 10 mg/kg AR during early adolescence consumed more alcohol than rats administered saline or 3 mg/kg AR during adolescence. During the 2nd week of alcohol access, post-hoc comparisons indicated that rats treated with 10 mg/kg AR during early adolescence consumed more alcohol than rats treated with 3 mg/kg AR which consumed more than saline treated rats (10 mg/kg > 3 mg/kg > saline; $p< 0.05$). In male rats (Fig. 2, bottom panel) there was a significant effect of AR on adult alcohol consumption during weeks 1 and 2 ($F_{2,11} = 21.1$; $p < 0.001$). Post-hoc comparisons indicated that during the 1st and 2nd weeks of alcohol access, male rats administered 10 mg/kg AR during early adolescence consumed more alcohol than rats administered saline or 3 mg/kg AR ($p < 0.05$).

Baseline alcohol consumption was determined by average intake during the last 3 days prior to deprivation. Overall analysis indicated a significant Day x Dose x Sex interaction term (Figure 2; $F_{8,84} = 3.18$; $p = 0.003$). Reducing the interaction term by examining effects as a factor of Sex was performed utilizing established statistical procedures. In female rats (Fig. 3, top panel) there was a significant Day x Dose interaction term ($F_{8,40} = 5.9$; $p < 0.001$). There was no group difference in the amount of EtOH consumed during the last 3 days of baseline intake ($p = 0.624$). Individual ANOVAs indicated that during re-exposure days 1–3 there were significant group differences ($F_{2,10}$ values > 4.98; $p < 0.031$). Post-hoc comparisons (Tukey's b; $p < 0.05$) revealed that on Day 1 of EtOH re-exposure the group of rats treated with 10 mg/kg AR consumed more alcohol than the 3 mg/kg group. During the 2nd re-exposure day, rats administered 10 mg/kg AR consumed more alcohol than rats administered saline. Each group differed significantly from each other on re-exposure day 3 (10 mg/kg > 3 mg/kg > Saline). Within subject analysis indicated that rats administered Saline during adolescence displayed an increase in EtOH consumption during the 1st re-exposure day compared to baseline level intake. Evidence for an ADE was observed in rats treated with 3 mg/kg (2 days) and 10 mg/kg (3 days).

The expression of an ADE was reduced in males compared to females (Fig. 3, bottom panel). Statistically, there was a Day x Dose interaction ($F_{2,11} = 2.67$; $p = 0.017$). There were no significant group differences between the AR male groups during re-exposure days 1–4

($p > 0.083$). Within subject analysis indicated that male rats administered Saline or 3 mg/kg AR during adolescence displayed elevated levels of EtOH intake during the 1st re-exposure day compared to baseline intake ($p < 0.05$). Evidence of an ADE was detected during re-exposure days 1–3 in rats administered 10 mg/kg AR during adolescence.

Effects of pretreatment with an α7 NAM dehydronorketamine prior to binge-like exposure during adolescence on adult EtOH consumption

We observed no differences between AIE and CON rats for body weight during adolescence (data not shown), no loss of subjects, no signs of stress during the procedure, and no observed behavioral effects of gavage.

The overall statistical analysis performed on the dependent measure of average daily alcohol intake for each week revealed a Week x Dose interaction ($F_{4,40} = 3.42$; $p = 0.017$). Overall, pretreatment with DHNK blocked the ability of adolescent alcohol exposure to increase alcohol consumption during adulthood (Figure 4). In female rats (Fig. 4, top panel) there was a significant effect of DHNK dose during adolescence on the average weekly alcohol intake in adulthood during the first and second weeks of alcohol access ($F_{4,21} = 3.42$; $p < 0.027$). Post-hoc comparisons (Tukey's b) indicated that rats exposed to the AIE protocol drank significantly more alcohol during the 1st and 2nd week of alcohol access compared to all other groups. In male rats (Fig. 4, bottom panel) there was a significant effect of DHNK administration during adolescence on the ability of the AIE treatment to enhance alcohol drinking during adulthood ($F_{4,19}$ values > 8.91; $p < 0.001$). Post-hoc comparisons indicated that during the 1st and 2nd week of alcohol access, male rats pretreated with saline prior to AIE exposure consumed more alcohol than all other groups. The data indicated that 1) exposure to the high dose of DHNK did not alter alcohol drinking during adulthood (CON – 50 mg/kg DHNK), indicating a lack of abnormal developmental actions, 2) adolescent alcohol exposure increased adult alcohol consumption in both males and females (AIE – Saline), and 3) pretreatment with 10 or 50 mg/kg DHNK blocked the deleterious effects of adolescent alcohol exposure (Figure 3).

DHNK pretreatment altered the enhancement in relapse drinking produced by AIE exposure (Fig. 5). The overall analysis indicated significant Day x Sex ($F_{4,160} = 3.44$; $p < 0.001$) and Day x Dose ($F4_{,160} = 7.25$; $p < 0.0001$), but no Sex x Day x Dose interaction ($p = 0.96$). Given a priori considerations, we decomposed the interaction term by examining Day and Dose in each sex. In female rats (Fig. 5, top panel) there was a significant Day x Dose interaction term ($F_{4,76} = 4.3$; $p < 0.001$). There was no group difference during baseline intake ($F_{4,21} = 0.104$; $p = 0.98$). During the first three re-exposure days there were significant group differences in alcohol intake ($F_{4,21}$ values > 5.28; $p < 0.004$). Post-hoc comparisons (Tukey's b) indicated that the AIE – Saline group consumed more alcohol than all other groups.

Given that this analysis was a within subject procedure, we performed paired t-tests to determine within group alterations from baseline consumption. Adolescent rats given control water gavage exposure (CON – Saline and CON – 50 mg/kg DHNK) displayed a significant increase in alcohol drinking during the 1st re-exposure day. Adolescent EtOH exposure potentiated alcohol relapse drinking. The AIE – Saline and AIE-50 mg/kg DHNK expressed

an increase in alcohol consumption during the first three re-exposure days. Rats in the AIE – 10 mg/kg DHNK expressed an increase in alcohol consumption (compared to baseline during the 1st re-exposure day).

In males rats (Fig. 5, bottom panel) there were a similar Day x Dose interaction term ($F_{16, 76}$ =3.8; $p < 0.001$). There were no group differences in baseline EtOH consumption ($p = 0.71$). There were significant group differences during re-exposure days 1–3 ($F_{4, 19}$ values > 4.03; $p < 0.016$). Post-hoc comparisons (Tukey's b) indicated that the AIE – Saline group consumed more alcohol than all other groups during re-exposure days 1–3. Within subject analysis indicated that there was a significant increase in alcohol consumption from baseline intake during re-exposure days 1–3 in the AIE – Saline group. Rats in the CON – Saline and AIE – 10 mg/kg DHNK groups displayed increase in drinking during the 1st re-exposure day. Rats in the CON – 50 mg/kg and AIE – 50 mg/kg groups did not display an ADE.

DISCUSSION

Our data indicate that early adolescent exposure to the α7 agonist AR enhanced the acquisition (Fig. 2) and relapse (Fig. 3) EtOH consumption in adulthood in male and female rats. In addition, limited exposure to AR during adolescence produced parallel alterations in adult EtOH drinking as were previously observed following voluntary adolescent EtOH consumption (McKinzie et al., 1996; Rodd-Henricks et al., 2002a,b; Toalston et al., 2015) or experimenter administered EtOH during adolescence (Amodeo et al., 2017, 2018; Spear, 2018; Figs. 4 and 5). It is premature to state that exposure to a α7 agonist during adolescence results in identical adult consequences as adolescent EtOH consumption/exposure, since binge-like EtOH exposure (AIE) is highly likely to have broader and more extensive consequences in adolescent brains than α7 agonists. For example, EtOH is a powerful solvent while AR is not, EtOH can result in hypothermia while AR does not, EtOH is metabolized into biologically active compounds that can have potentially damaging effects while AR does not, etc. Nevertheless, our data suggest that α7 is a potential critical site for adolescent EtOH consumption/exposure to produce the persistent deleterious consequences on adult alcohol consumption.

The increase in adult EtOH consumption induced by adolescent alcohol exposure (enhanced acquisition and relapse drinking) can be prevented by pretreatment with an α7 NAM (Figs. 4 and 5). Thus, an α7 NAM can prophylactically prevent unknown processes (presumably mediated by α7) in the adolescent brain, such as those that produces the persistent neuroadaptations that alter EtOH consumption/reward during adulthood (Hauser et al., 2019; Toalston et al., 2014). The negative effects of adolescent alcohol consumption on adult alcohol dependence are compounded in individuals with a family history of alcoholism (Agrawal et al., 2009; Jacobus et al., 2009). Specifically, a family history of alcoholism interacts with the age of onset of drinking to significantly increase the rate of adult AUD (Agrawal et al., 2009). A family history of AUD also significantly increased alteration in white matter integrity (factional anisotropy) observed following adolescent binge alcohol consumption (Jacobus et al., 2009). Therefore, the ability of an α7 NAM to prevent the deleterious consequences of adolescent binge-like EtOH exposure in the most established

animal model for genetic predisposition to consume excessive alcohol (P rats) adds to the ecological validity of the current findings.

A primary goal of adolescent alcohol research is to develop pharmacotherapeutics to mediate the negative consequences of adolescent alcohol consumption, and α7 NAMs may be the first candidate compound class with sufficient supporting evidence to justify more extensive research to develop an efficacious treatment. Furthermore, adolescent alcohol consumption is associated with many additional adult disorders (addiction-related and not) that are regulated by α7. Adolescent alcohol drinking is linked to increased adulthood use of opioids, cannabis, and other drugs of abuse (Anthony & Petronis 1995). Particularly, for nicotine, adolescent binge drinking enhances the likelihood of smoking during adolescence by 88% as well as during adulthood (Best et al. 2000). Conversely, individuals who do not engage in binge drinking have lower rates of smoking during adolescence and adulthood (Bobo & Husten 2000). There is an obvious role for α7 in regulating nicotine dependence (Jackson et al., 2017). Alterations in α7 receptor levels or function mediate the actions of opioids (Gu et al., 2017) and thus could influence opioid use disorder. Opioids directly bind to α7 (Zhang et al., 2015) and methadone is an agonist at α7 (Talka et al., 2015). Similar to the 5HT3 receptor, cocaine and cocaine metabolites bind directly to α7 (Francis et al., 2001). Administration of α7 receptor agonists and antagonists bi-directionally alters the actions of cocaine within the mesolimbic dopamine system (Zanetti et al., 2007). Therefore, upregulation of the α7 receptor in the mesolimbic dopamine system following adolescent alcohol consumption/exposure (Hauser et al., 2019; Waeiss et al., 2019) could be an important biological basis for alcohol consumption in adolescence to increase the propensity of developing addictions to these drugs during adulthood. However, extensive research will be required to develop the use of α7 NAMs to prevent the deleterious actions of adolescent alcohol exposure on adulthood addictions.

Addiction researchers need to expand the interpretations of their research. Persistent alterations within the brain caused by drug use/exposure mitigate behaviors/disease states beyond addiction. Excessive adolescent alcohol consumption also links to an increased propensity to develop depression, anxiety disorders, schizophrenia, Alzheimer's disease (AD), Parkinson's disorder (PD), other dementia-related Illnesses, and auto-immune diseases during adulthood (Harwood et al., 2010; Schwarzinger et al., 2018; Langballe et al., 2015; Coleman et al., 2019). Dysregulation of the α7 receptor system associates with schizophrenia (Akbarian and Kundakovic, 2015), AD (Ma and Qian, 2019), PD (Quik et al., 2015), and dementia-related Illnesses (Deutsch et al., 2014, Nikiforuk et al., 2016). Therefore, any neuroprotection due to treatment with an α7 NAM could prevent such dysregulation in the adult α7 receptor system produced by excessive alcohol consumption which would increase the risk of these disorders.

The α7 is the primary receptor to regulate the peripheral and neuronal immune system, primarily through the JAK/STAT pathway, although other pathways play a role. Alterations in the α7 receptor system are associated with an increase in psoriasis, rheumatoid arthritis, and systemic lupus erythematosus (Kalkman and Feuerbach, 2016). Excessive adolescent alcohol consumption promotes psoriasis (Phan et al., 2018), rheumatoid arthritis (Zaccardelli et al., 2019), and systemic lupus erythematosus (van Weelden et al., 2016). The

neuroprotection produced by an α7 NAM could prevent the dysregulation in the adult α7 receptor system and reduce the likelihood of psoriasis, rheumatoid arthritis, and systemic lupus erythematosus in adulthood.

There have been few studies in which the effects of adolescent EtOH consumption/exposure have been 'reversed'. Gabapentin can normalize the deficits in delta power, but not theta power, during slow-wave sleep produced by adolescent EtOH vapor exposure (Ehlers et al., 2018a), as well as AIE-induced increases of NMDA receptor-mediated current amplitude in CA1 pyramidal neurons (Swartzwelder et al, 2017). Donepezil can reverse AIE-induced decreases in dendritic spine density and expression of the Fmr1 gene in the hippocampus (Mulholland et al., 2018). The effects of Donepezil (e.g., neuroprotection against toxins, regulation of the neuroimmune system, alterations in the genetic expression of other systems) are primarily thought to be through increased activity of the a7 system (Takada-Takatori et al., 2008; Russo et al., 2017).

The Donepezil and Gabapentin studies may have produced temporary relief from the neuroadaptations produced by exposure to binge-like levels of EtOH during adolescence (longitudinal studies not conducted). Therefore, an α7 NAM may be a potential therapeutic for the prevention of the effects of adolescent EtOH consumption/exposure, and Gabapentin and Donepezil may be potential rescue pharmacotherapeutics for the treatment of adolescent EtOH exposure if there had been no prophylactic intervention during adolescent/young adult alcohol consumption.

The differences in the philosophical approach to the treatment of adolescent alcohol exposure can be illustrated by an analogy: is it easier to protect an egg from damage or to try to reconstruct exactly a pulverized egg? The addiction field has thus far focused on elucidating the long-term consequences of adolescent drug use and has sought pharmacological targets to attempt to repair a destroyed egg. In contrast, prophylactic treatments that protect a developing brain against the effects of adolescent EtOH (e.g., α7 NAM) is a kin to preventing harm/damage to the egg. We would assert that it is morally and ethically beneficial to attempt to prevent harm occurring in humans who have experimented with drugs during adolescence.

The present study has implications beyond alcoholism and addiction. For example, heavy alcohol consumption is associated with a faster rate of cognitive decline in AD patients, suggesting that they may hasten the progression of AD. Alcohol drinking habits might alter the course of AD (Heymann et al., 2016). At the cellular level, astrocytic α7 nAChR upregulation detected in the AD brains is closely associated with deposits of the amyloid beta-peptde (Aβ) (Ren et al, 2019). Brain parenchyma deposition of Aβ, which is derived from APP, is one of the major hallmarks of AD, and thus an important drug target (Bailey et al, 2011). Interestingly, astrocytic α7 activation inhibits Aβ aggregation through the PI3K/Akt signaling pathway (Ren et al, 2019). Further, P-rat, used in the present work, had been a useful model to understand how alcohol and APP expression affect development. Indeed, APP plays an important role in the early development of the rat brain, and the alcohol-preferring trait may influence APP processing in the developing brain (Lahiri et al., 2002). In addition, chronic psychosocial stress exacerbates the impairment of synaptic

plasticity in an animal model of AD (Alkadhi et al., 2011). Our future work will include testing NAMs in AD and related disorders using different cellular and animal models. Understanding how adolescence alcohol exposure, chronic stress, via the APP pathway, affects AD pathogenesis would be a fruitful direction of research. In this context, leveraging α7 NAMs as potential prophylactic agents to reduce the harmful effects of adolescent alcohol *as well as* late-life cognitive disorders would be extremely significant.

To conclude, the α7 system has many sites of action in the human body and mediates numerous behaviors and disorders. α7 is a unique target of inquiry for adolescent alcohol exposure because the α7 receptor is directly acted upon by EtOH and it mediates a number of the behavioral/physiological consequences of adolescent EtOH exposure. We are not proposing that the α7 receptor is the only neurotransmitter system regulating the effects/consequences of adolescent EtOH exposure, but our current data does suggest a direct regulation of a key adult consequence (adult alcohol consumption). It will take years of extensive research to satisfy the scientific requirements to confirm that α7 NAMs are valid pharmacotherapeutics for the prophylactic treatment against the effects in adulthood of adolescent alcohol consumption. However, the successful establishment of α7 NAMs as valid pharmacotherapeutics would be pointless without a comparable shift in social norms about honestly addressing drug use in adolescence and young adults. One must first admit to a condition before one bothers to treat it. It is hoped that given a functional treatment for adolescent alcohol use there will be a cultural shift (comparable to condom prevention of sexually transmitted disease/pregnancies) in societies to protect the young.

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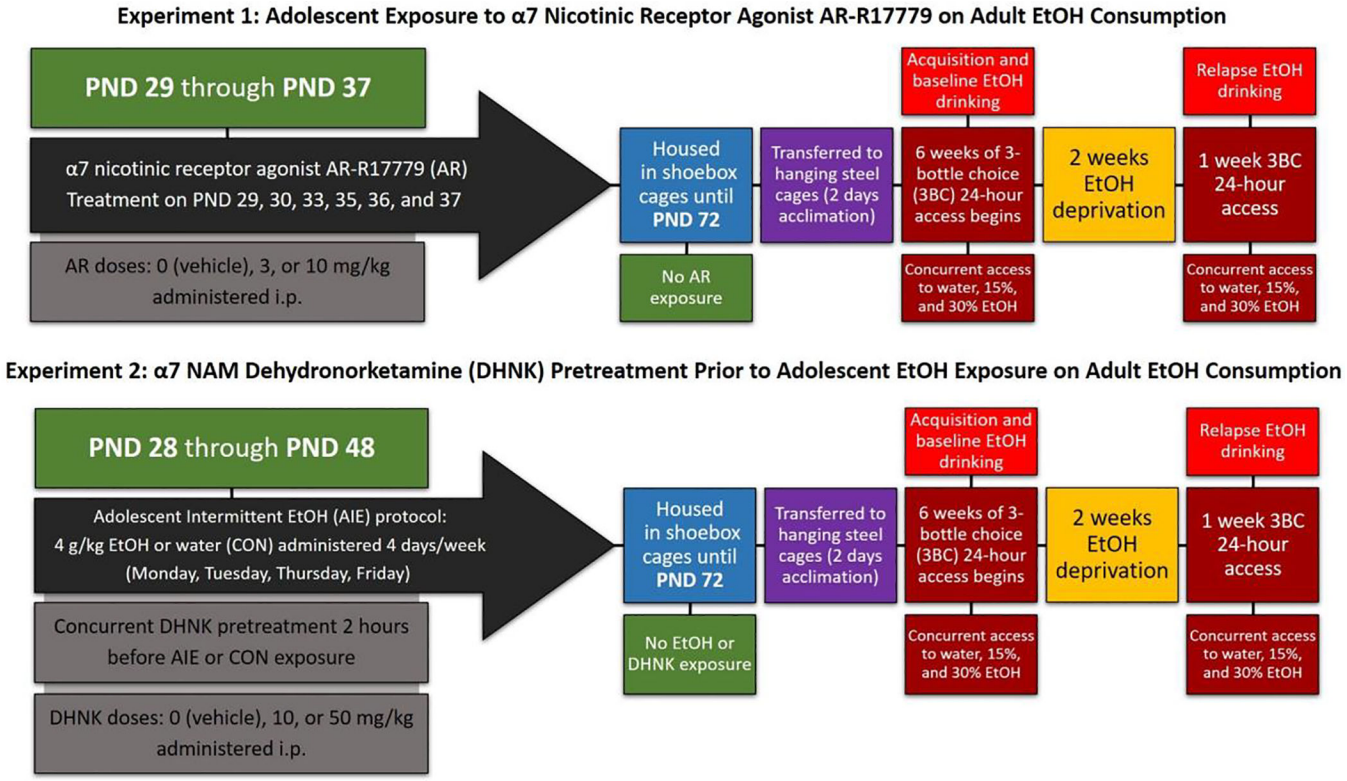

Figure 1.

Depicts the experiment timeline for the a7 agonist (AR, top panel) and DHNK (bottom panel) used in the current experiments.

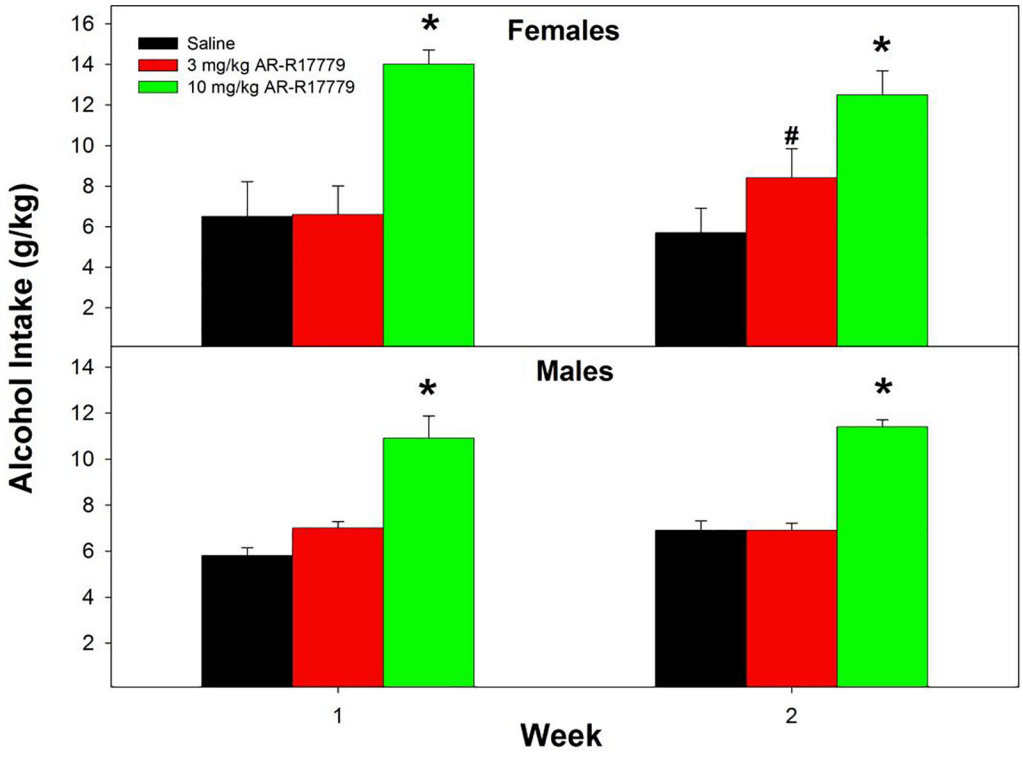

Figure 2.

Depicts the average alcohol intake in female (top) and male (bottom) rats administered AR-R17779 during adolescence on adult alcohol consumption. * indicates 10 mg/kg AR-R17779 > 3 mg/kg and saline. # indicates 3 mg/kg > saline.

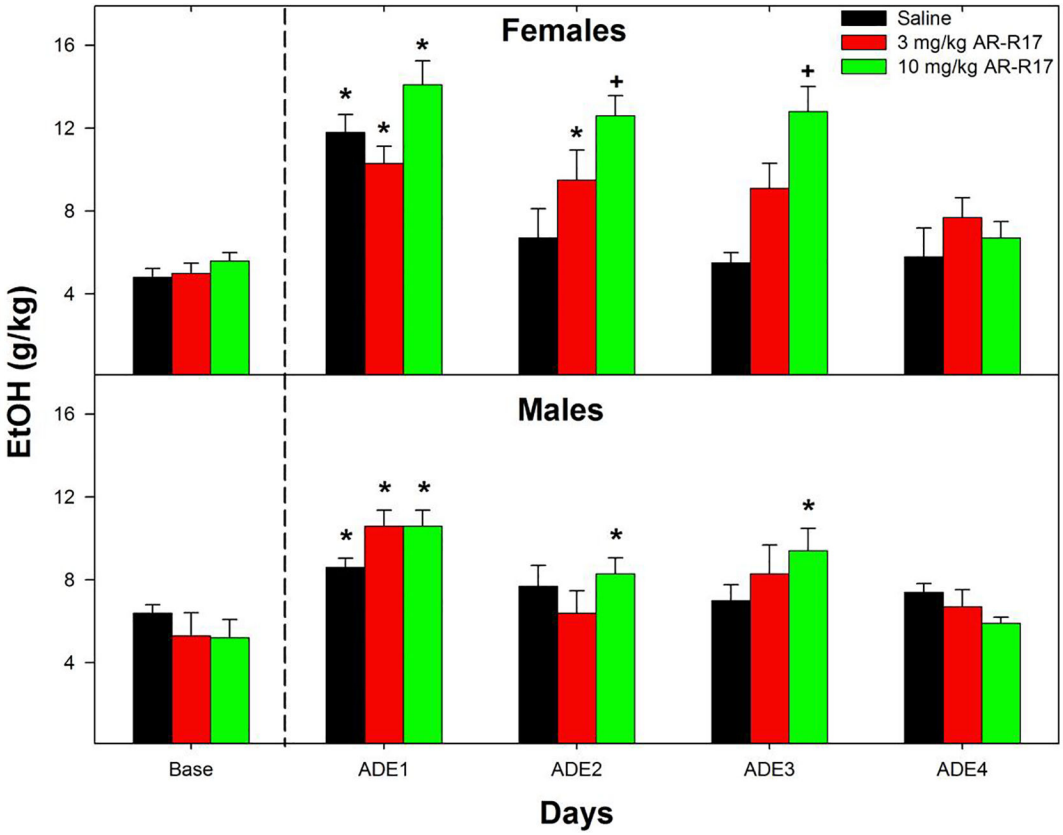

Figure 3.

Depicts the mean (+ SEM) for female (top) and male (bottom) alcohol-preferring (P) rats during relapse EtOH drinking. * indicates EtOH consumption exceeds baseline intake.+ indicates that rats administered 10 mg/kg AR-R177779 during adolescence consumed more alcohol than saline controls.

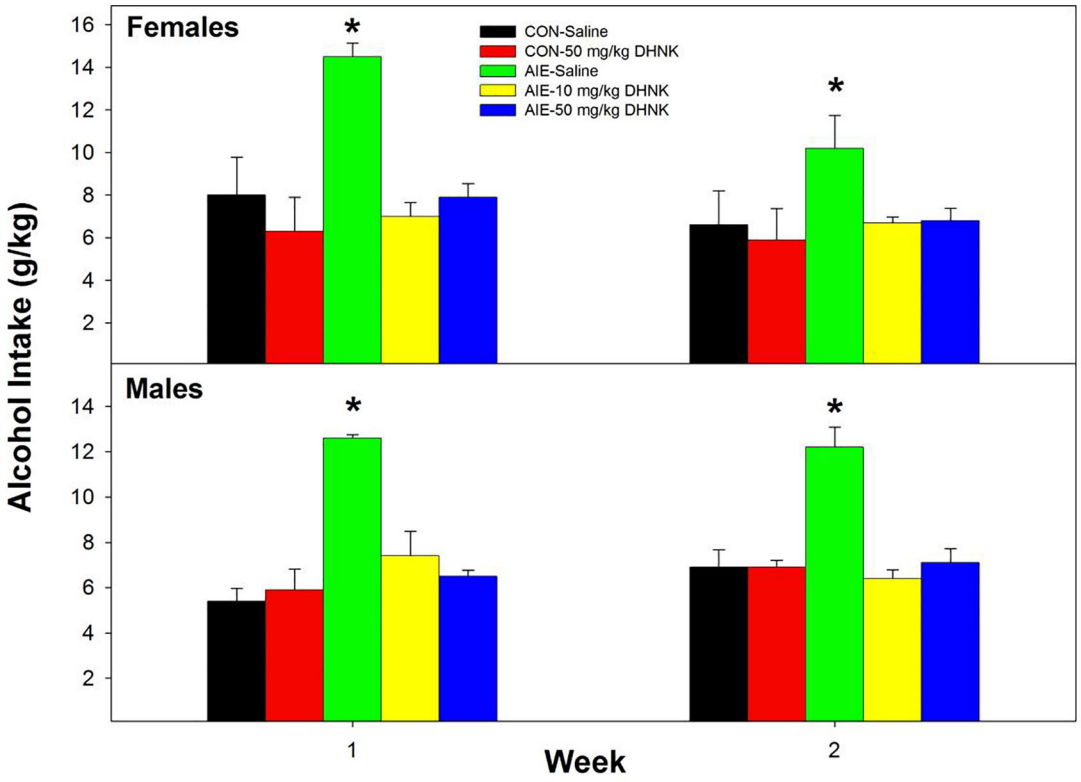

Figure 4.

Depicts the average alcohol intake in male (top) and female (bottom) rats administered DHNK 2 hours prior to AIE or CON treatment during adolescence.* indicates AIE-Saline rats consumed more alcohol than all other groups.

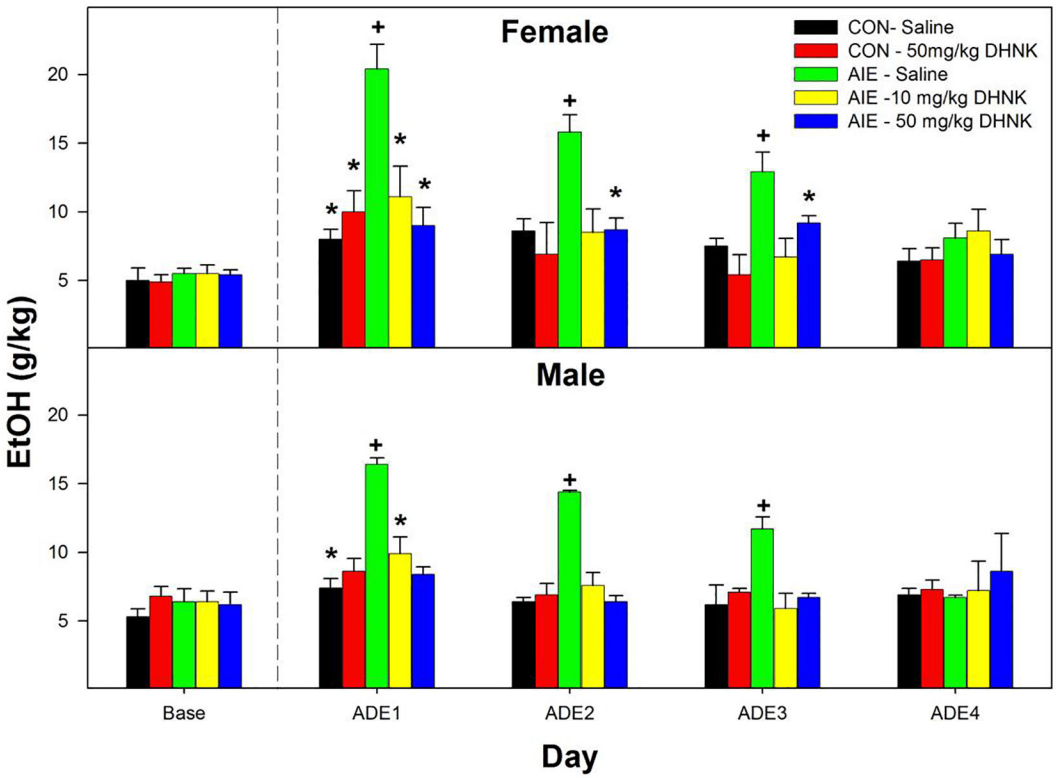

Figure 5.

Depicts the mean (+ SEM) for female (top) and male (bottom) alcohol-preferring (P) rats during relapse EtOH drinking. * indicates EtOH consumption exceeds baseline intake.+ indicates that rat pretreated with saline prior to AIE exposure (AIE - Saline) consumed more alcohol than any other group.