Published in final edited form as:
Alcohol Clin Exp Res. 2010 August ; 34(8): 1363–1375. doi:10.1111/j.1530-0277.2010.01220.x.

Pharmacologic dissociation between impulsivity and alcohol drinking in High Alcohol Preferring mice

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Abstract

Background—Impulsivity is genetically correlated with, and precedes addictive behaviors and alcoholism. If impulsivity or attention is causally related to addiction, certain pharmacological manipulations of impulsivity and/or attention may affect alcohol drinking, and vice versa. The current studies were designed to explore the relationship among impulsivity, drinking, and vigilance in selectively bred High Alcohol Preferring (HAP) mice, a line that has previously demonstrated both high impulsivity and high alcohol consumption. Amphetamine, naltrexone and memantine were tested in a delay discounting (DD) task for their effects on impulsivity and vigilance. The same drugs and doses were also assessed for effects on alcohol drinking in a two-bottle choice test.

Methods—HAP mice were subjected to a modified version of adjusting amount DD using 0.5 sec and 10 sec delays to detect decreases and increases, respectively, in impulsive responding. In 2 experiments, mice were given amphetamine (0.4, 0.8 or 1.2 mg/kg), naltrexone (3 and 10 mg/kg), and memantine (1 and 5 mg/kg) before DD testing. Another pair of studies used scheduled access, two-bottle choice drinking to assess effects of amphetamine (0.4, 1.2, or 3.0 mg/kg), naltrexone (3 and 10 mg/kg), and memantine (1 and 5 mg/kg) on alcohol consumption.

Results—Amphetamine dose-dependently reduced impulsivity and vigilance decrement in DD, but similar doses left alcohol drinking unaffected. Naltrexone and memantine decreased alcohol intake at doses that did not affect water drinking, but had no effects on impulsivity or vigilance decrement in the DD task.

Conclusions—Contrary to our hypothesis, none of the drugs tested here, while effective either on alcohol drinking or impulsivity, decreased both behaviors. These findings suggest that the genetic association between drinking and impulsivity observed in this population is mediated by mechanisms other than those targeted by the drugs tested in these studies.

Keywords

Stimulants; behavioral economics; ethanol; animal model; pharmacotherapy

Introduction

Impulsivity is correlated with addiction in users of virtually all drugs of abuse (Bickel et al., 1999; Coffey et al., 2003; Hoffman et al., 2006; Kirby et al., 1999; Mitchell, 1999; Petry, 2001a; Quednow et al., 2007; Simons et al., 2005). Interestingly, addictive behaviors that are not drug-based also correlate with impulsivity, such as compulsive gambling (Petry, 2001b), overeating (Braet et al., 2007; Weller et al., 2008), and serial sex offences (Baltieri and Andrade, 2008). Increasingly, impulsivity is thought to be a necessary component of addiction (de Wit and Richards, 2004; Goldstein and Volkow, 2002), and to be involved in all phases of human addiction (de Wit and Richards, 2004; Perry and Carroll, 2008). Furthermore, individual differences in impulsivity predict drug use in animals (Perry et al., 2005; Poulos et al., 1995). As impulsivity may underlie addictive behaviors, this behavior may be an important target of therapeutic interventions. Therefore, a better understanding of the neural circuits and neurochemistry that promote impulsive behavior may provide better treatment of addiction disorders and clinical outcomes.

Impulsivity is a complex behavioral phenotype, which has many meanings and components. The focus of the current studies is impulsive choice, also called “cognitive impulsivity”, which can be differentiated from motor impulsivity (Mitchell et al., 2005; Winstanley et al., 2004). Similar to the pathology of addiction, impulsive choice is specifically defined as the choosing of a smaller immediate reward to the exclusion of a larger delayed reward (Rachlin and Green, 1972). This definition may be experimentally assessed by using a task called delay discounting (DD), which has been used extensively in both humans and animals (Bickel et al., 1999; Richards et al., 1997). The DD task is widely used in both human and animal studies, and the task is similar between species, lending good face validity to assessments of impulsivity in experimental animal models. Impulsivity in the DD task is defined as the extent to which time degrades the subjective reward-value of the delayed reinforcer. To assess how delay to reinforcer affects its subjective value, reinforcer size is pitted against reinforcer delay in a concurrent choice task. Assessment of aversion to delay in DD can be made by manipulating either reinforcer amount or delay to reinforcer, depending on the paradigm used. When changing reinforcer amount within sessions (adjusting amount procedure), delays can be manipulated across sessions to generate discounting curves (Richards et al., 1997; Wilhelm and Mitchell, 2008) although delay discounting has also been assessed using a single delay (Richards et al., 1999). Use of pairs of delays - that is, short and long delays - may enhance sensitivity to manipulations that would cause increases or decreases, respectively, in impulsivity (Gregory Madden, personal communication).

Human alcoholics and addicts discount delayed rewards more steeply than controls (Madden et al., 1997; Mitchell et al., 2005; Mitchell, 1999), as do ethanol-naïve mice and rats bred for high alcohol preference (Oberlin and Grahame, 2009; Wilhelm and Mitchell, 2008). These data suggest that neural and genetic mechanisms involved in differences in alcohol consumption are the same mechanisms that lead to differences in impulsivity. Furthermore, these results indicate the potential to treat high alcohol seeking behavior by intervening at the level of impulsivity, to the extent that one considers this trait to be an endophenotype related to the etiology of some forms of alcoholism. In other words, drugs that reduce impulsivity could also have effects on alcohol consumption. In the following studies, we explore the pharmacologic relationship between impulsivity and alcohol drinking in two

ways. First, we assess amphetamine, which has been shown to decrease impulsivity as measured in delay discounting, by examining its effects on both impulsivity and free choice alcohol consumption. Second, we assess effects on delay discounting of memantine and naltrexone, again examining the effects of these drugs during free choice alcohol consumption. In these studies, we seek to maximize the relevance of our findings to an alcohol abusing population by utilizing a selectively bred High Alcohol Preferring (HAP) line of mice. Previous results have shown that this line both drinks large amounts of alcohol freely and shows a high degree of impulsivity (Grahame and Grose, 2003; Oberlin and Grahame, 2009).

HAP mice have been selectively bred for high alcohol consumption over four weeks of free-choice access to 10% ethanol and water. HAP mice do not have to be food or water deprived to drink ethanol, they will drink unsweetened ethanol in the range of 19-24 g/kg per day, and they prefer ethanol to water at a ratio of ∼80% (Behm et al., 2003; Grahame et al., 1999b). HAP mice achieve pharmacologically relevant Blood Alcohol Concentrations (BAC) following free-choice access to ethanol and water (Grahame and Grose, 2003; Grahame et al., 1999a).

The existing literature assessing the pharmacological relationship between impulsivity and alcohol consumption is not wholly in agreement, partly because studies on impulsivity and drinking utilize differing populations and doses of drugs. Generally speaking, the drugs that most consistently reduce impulsivity are psychostimulants that enhance monoaminergic transmission, such as amphetamine and methylphenidate. The majority of research indicates that amphetamine reduces impulsivity in DD tasks (de Wit et al., 2002; Floresco et al., 2008; Isles et al., 2003; van Gaalen et al., 2005; Wade et al., 2000; Winstanley et al., 2003), although amphetamine has increased impulsivity in some studies (Evenden and Ryan, 1996; Helms et al., 2006). There is poor consensus about the effect of amphetamine on ethanol drinking. Amphetamine reduced responding for ethanol at some doses (Pfeffer and Samson, 1985a; Pfeffer and Samson, 1985b), and selectively reduced ethanol drinking when combined with fenfluramine (Yu et al., 1997). Other rat studies, however, have shown no consistent effect of amphetamine on ethanol consumption (Hubbell et al., 1991; Linseman, 1990) or responding for ethanol (Slawecki et al., 1997), or have shown increased ethanol consumption when administered continuously (Levy and Ellison, 1985; Potthoff et al., 1983). At present, we are unaware of any previous studies that have examined amphetamine on both impulsivity and ethanol consumption in mice or humans, or any studies assessing its effects on voluntary alcohol consumption in mice or in humans.

Naltrexone is an opioid antagonist that decreases alcohol drinking in humans (Bouza et al., 2004; Lapham et al., 2008; O'Brien et al., 1996) and ethanol reinforcement along with place preference in inbred C57 mice (Middaugh and Bandy, 2000; Middaugh et al., 2000). The endogenous opioid system is thought to be important in mediating ethanol's rewarding effects (Froehlich et al., 1990), and as such it is believed that naltrexone decreases the rewarding value of ethanol via opioid antagonism (Gianoulakis, 2001; Modesto-Lowe and Fritz, 2005). Although naltrexone is viewed as a general opioid antagonist, it is more potent at μ-opioid than δ-opioid receptors (Takemori and Portoghese, 1984). However, both of these receptor classes appear to be important in mediating ethanol reward (Froehlich et al., 1991). Naltrexone's effects on impulsivity are less clear, as it had no effect in rats at doses up to 10 mg/kg (Kieres et al., 2004) or in human alcoholics (Mitchell et al., 2007). Although naltrexone did not appear to modulate impulsivity in the Kieres et al. (2004) study, it was not tested in a selected high-drinking population, which is more analogous to human alcoholism. Mitchell et al. (2007) did test naltrexone in a human alcoholic population and found no reliable effect on discounting. However, only abstinent alcoholics were used in this study, i.e. a self-selected group. Alcohol-dependent humans are a diverse group with

different subtypes and likely different etiologies (Johnson et al., 2000; Leggio et al., 2009), and it may well be that alcoholics who become sober are different in some ways than those who do not. Therefore it would be attractive to test pharmacotherapies for effects on impulsivity in the same population in which efficacy at reducing alcohol preference is concurrently demonstrated.

Memantine is a N-Methyl-D-Aspartate (NMDA) antagonist that reduced craving in alcohol dependent humans (Bisaga and Evans, 2004; Krupitsky et al., 2007), decreased alcohol drinking (Muhonen et al., 2008), or had no effect (Evans et al., 2007). In animal models, memantine decreased ethanol drinking in rats (Piasecki et al., 1998) without affecting intake of other fluids. Memantine may impinge on ethanol reward by reducing activity in the mesolimbic dopamine pathway; which is richly innervated by glutamate afferents (Geisler et al., 2007; Kelley et al., 1982). The authors are not aware of any published studies that assessed DD with memantine, although one recent study did indicate that a different NMDA antagonist, ketamine, increased impulsive responding in the 5-choice serial reaction time assay (Oliver et al., 2009).

Amphetamine generally reduces impulsivity, which demonstrates an important role of dopamine systems in impulsive choice. The importance of dopamine systems in alcohol drinking is well-established, as are opioidergic and glutamatergic afferent pathways (Koob, 1992; McBride et al., 1999; Mendez and Morales-Mulia, 2008; Tzschentke and Schmidt, 2003). The role of opioidergic and glutamatergic systems in modulating impulsive choice has been investigated to a lesser degree than alcohol drinking, but evidence shows that both systems can modulate impulsivity (Pattij et al., 2009; Sukhotina et al., 2008).

Conceptually related to impulsivity, impaired attention has also been linked to drug abuse (Cairney et al., 2007; Lane et al., 2007; Mackin et al., 2005) and may be neurologically related to impulsive choice and addiction. A longitudinal study in humans found that attentional impairment/executive deficit predicted later substance use, even when controlling for other factors (Tapert et al., 2002). The association between impaired attention/vigilance and addiction is further strengthened by the high rate of comorbidity of attention-deficit/hyperactivity disorder (ADHD) and addiction (Eyre et al., 1982; Schubiner et al., 2000). During the 60 minute concurrent choice sessions for assessment of DD, HAP mice show a greater increase in reaction time (RT) for emission of the nosepoke that initiates the lever choice component of the task compared to Low Alcohol Preferring mice (Oberlin and Grahame, 2009). These data suggest that high genetic load for alcohol drinking in alcohol-naive animals may also be linked to vigilance impairment during tasks that require sustained attention.

To explore the pharmacologic relationship between impulsivity, high alcohol consumption, and vigilance/attention, we will test the following specific predictions, based on the hypothesis that there are shared mechanisms underlying impulsivity and high alcohol consumption: 1) Doses of amphetamine that decrease impulsivity as measured by DD performance and enhance attention as measured by vigilance decrement should decrease alcohol consumption in selectively bred HAP mice in a behaviorally selective manner. 2) Drugs that decrease alcohol consumption in HAP mice should also decrease impulsivity as measured by DD.

Materials and Methods

All work was performed in accordance with, and approved by, the Indiana University School of Medicine IACUC.

Animals

Mice were HAP1 and HAP2 mice born in the IUPUI School of Science Animal Care Facility. Mice were individually housed in polycarbonate cages (27.9 × 9.5 × 12.7 cm) with Cellsorb bedding, at an ambient temperature of 21 ± 1°C and lights on from 2200 to 1000. All mice had ad lib access to food. Water access was restricted to 2 hours per day, immediately after testing, for delay discounting (experiments 1 and 3). In those experiments, mice were transported in a light shielded transporter to the testing room; the mice were tested between 1100 and 1600, and were always tested in the dark. In experiments 2 and 4 mice always had access to water and were tested in the homecage between 1200 and 1300.

Experiment 1 used 15 male and 15 female HAP1 mice (generation 33) that were an average of 177 ± 1 days old at the beginning of drug testing. Eight of these mice had previous experience with ethanol drinking in an unrelated experiment, while the other 22 were ethanol-naive. Experiment 2 used 27 male and 22 female HAP1 mice (generation 36) that were an average of 61 ±2 days old at the beginning of drug testing. Experiment 3 used 20 male and 20 female HAP2 mice (generation 28) that were an average of 116 ± 2 days old at the beginning of drug testing. Experiment 4 used 25 male and 19 female HAP2 mice (generation 22) that were 119 ± 2 days old at the beginning of the study.

Apparatus

The apparatus used in experiments 1 and 3 consisted of 16 identical operant chambers that measured 21.6 × 19.7 × 12.7 cm inside, with two sides constructed of clear acrylic and two sides of aluminum (Med Associates, St. Albans, VT). The operant chamber was contained in a sound- and light- attenuated box that was equipped with a fan for ventilation and background noise. An LED/nose-poke infrared detector was centered on the 19.7 cm side at 6.3 cm above the floor, and illumination of that LED signaled the beginning of a trial. Below the LED/nose-poke detector was the sipper access hole, through which the sipper descended when mice were being reinforced. The sipper tube was a 10 ml graduated plastic serological pipette fitted with a stainless steel tip (Ancare, Belmont, NY.) The sipper tube could be extended into the box for varying amounts of time, which allowed precise control of sipper access. The sipper tube was filled with a solution of 0.0316% (w/v) saccharin solution that served as the reinforcer. At the end of each session, consumption volumes were visually read from the tube with a resolution of ±0.1 ml. Levers were mounted 2.5 cm above the floor on either side of the sipper tube opening. Each lever had an LED 2.3 cm above it signaling that the lever was active (that is, reinforcement was available on that lever). Control of the operant chambers and collection of data were performed via the MedPC IV software and MedPC interface cards on a PC compatible computer. Experiments 2 and 4 were performed in the homecage using the same type of sipper tubes as used in DD assessment.

Drugs

All drugs were administered with an injection volume of 10 ml/kg i.p. We selected doses of amphetamine that could be expected to reduce impulsivity based on previous studies (Isles et al., 2003). Amphetamine sulfate (Sigma-Aldrich St. Louis, MO) was dissolved in isotonic saline to concentrations of 0.04, 0.08, 0.12, or 0.30 mg/ml. Naltrexone HCl (Sigma-Aldrich St. Louis, MO) and memantine HCl (Acros Organics, Morris Plains, NJ) were dissolved in isotonic saline to concentrations of 0.3 and 1.0 mg/ml, and 0.1 and 0.5 mg/ml for each drug, respectively. Naltrexone doses of 3 and 10 mg/kg were selected based on previous studies that showed reduction in ethanol drinking at 3 and 10 mg/kg doses in rats (Linseman, 1989) and reduction in responding for ethanol at doses of 0.3 to 2.7 mg/kg in mice (Middaugh et al., 2000). Memantine doses of 1 and 5 mg/kg were selected based on previous studies that showed reduction in the alcohol deprivation effect at 4.8 mg/kg (Holter et al., 1996).

Additionally, a dose of 3.75 mg/kg prevented alcohol dependence (Kotlinska, 2001), and 7.5 mg/kg blocked cocaine conditioned place preference (Kotlinska and Biala, 2000). In DD testing, drugs were administered immediately before testing to insure that plasma concentrations were high during the middle of the test, which is similar to other studies (van Gaalen et al., 2005; Winstanley et al., 2003). For homecage drinking, drugs were administered 30 minutes before testing. All drug doses were calculated as the salt of the free base.

Procedure

Experiments 1 and 3: Delay Discounting

The time course of each trial is illustrated in figure 1. The procedure was a slightly modified version of a previously reported DD task (adjusting amount procedure) and has been previously described (Richards et al., 1997). Briefly, the center nosepoke cue light is illuminated until the mouse initiates the trial by nosepoking. After the nosepoke, the center light goes dark, and the lights illuminate above both left and right levers, signaling availability of a choice. Both lights remain illuminated until a lever press is recorded. Once a lever press is made, the non-chosen lever light extinguishes, while the light above the elected lever remains illuminated, and the sipper containing saccharin solution descends into the drinking position. One lever was always assigned to delayed reinforcement and the other was assigned to immediate reinforcement. A lever press on the delay side resulted in delivery of the standard, 2 second reward after the programmed delay interval, during which time the light above the delay lever remained illuminated. An immediate-side lever press resulted in delivery of the adjusting reward without any programmed delay. The immediate, adjusting side was set to 1 second access time (half the standard reward) at the beginning of the session. The subsequent access time on the immediate side was adjusted depending on the subject's choice such that an immediate choice resulted in a decrease of immediate reward sipper access time by 0.2 seconds, and a delay choice resulted in an increase of immediate reward sipper access time by 0.2 seconds. The adjustment increment, 0.2 seconds, was 20% of the initial adjusting side amount. As the value of the immediate reinforcer increased or decreased, the mice titrate to a value subjectively equivalent to the 2 second standard reward available on the delay side. Therefore, the adjusted amount of the immediate side provides an estimate of the subjective valuation of the delayed reward by the end of the session. The adjusted amount of the immediate side was limited to 2 seconds so that it never became larger than the amount on the delayed side, as experience with very large immediate rewards might interfere with mice being able to reliably assess reward magnitude. Thus the range of adjustment was always between 0 and 2 seconds sipper access time. To expose the mice regularly to both immediate and delayed reinforcers, a forced trial was instituted after two consecutive selections of the same lever where only the twice-unselected lever was active after a nosepoke. Additionally, there was no adjustment of the immediate reinforcer resulting from forced trials.

Mice were shaped according to a protocol previously described (Oberlin and Grahame, 2009) with the addition of training at either short or long delays prior to drug administration. After the zero delay criterion had been met in the last stage of shaping, mice were assigned to one of two groups, 0.5 sec (short) or 10 sec (long) delay. The purpose of this assignment was to gain sensitivity to drugs that decrease indifference points (that is, increase impulsivity) in the short delay group, and increase indifference points (that is, decrease impulsivity) in the long-delay group. Group assignment was balanced across zero delay indifference point and sex. Mice then had to meet the new criterion of mean indifference points of ≥ 1.4 and ≤ 0.6 seconds access time for 0.5 sec or 10 sec delay, respectively. The 0.5 sec and 10 sec delay criterion applied to 3 out of 4 days' consecutive performance. When mice had met this criterion, drug administration commenced. Drug dose assignment was

based on a Latin Square design, balanced across Delay, Sex, and Run Order. There were no washout days between drug doses. Experiment 1 tested amphetamine at doses of 0.4, 0.8, and 1.2, and mg/kg, while experiment 3 tested naltrexone (3 & 10 mg/kg), memantine (1 & 5 mg/kg) and amphetamine (1.2 mg/kg).

Indifference points for each mouse were determined by taking the median adjusted amount for the last 20 choice trials completed, and then averaging those values across 3 sessions within a given dose. Sessions were limited to 1 hour or 60 choice trials, whichever came first. All daily data from mice that completed fewer than 20 trials on a day were excluded. If a mouse did not complete ≥ 20 trials on at least 1 out of 3 sessions at a drug dose, that mouse was excluded from the experiment for non-performance. Drug doses were administered for 3 consecutive days.

Experiments 2 & 4: Homecage Drinking

All mice were tested in the dark, with injections beginning at 1200 for experiment 2 and at 1600 for experiment 4. Injections were administered 30 minutes before ethanol access. Thirty minutes after drug administration, plain water was replaced with two graduated tubes that contained tap water plus 0.1% (w/v) saccharin (WS) and ethanol 8% (v/v) plus 0.1% (w/v) saccharin (ES). Saccharin was added to both solutions to increase overall palatability, but it also had the effect of reducing ethanol preference while maintaining ethanol as the sole difference between the two available solutions. Preference ratios close to 50% allow equivalent sensitivity to drug effects on consumption of ethanol specifically, vs. fluid intake in general, which is especially important when interpreting effects of drugs that cause general decreases in intake of palatable fluids, such as amphetamine (Wolgin, 1983). WS and ES tubes remained on the homecage for 30 minutes. Volumes were read from the tubes before and after the access period to a resolution of 0.1 ml, and consumption was calculated from these. The position of the tubes was alternated daily to balance the effect of side preference. Mice were tested for 4 consecutive days; 2 baseline (saline), then 2 drug days. Mice were initially balanced for baseline drinking, then assigned to drug dose groups. Dose groups were assigned between-subjects. Drinking scores were calculated as the mean of the two drug days. Mice that drank less than 0.45 g/kg/30 minutes in the first two baseline days were not included in the assessment of drug effect. Given the metabolic rate of alcohol in these mice this level of consumption would not be expected to yield a blood alcohol level above zero (Grahame et al., 1999b), meaning that decreases in intake brought about by potential pharmacotherapies would not be pharmacologically relevant. Experiment 2 tested amphetamine at doses of 0.4, 1.2, and 3 mg/kg. Experiment 4 used one cohort of mice and tested naltrexone (3 and 10 mg/kg) in one week, then memantine (1 and 5 mg/kg) 28 days later.

For Experiment 4, an ethanol fade-in procedure was employed to gradually habituate the mice to ethanol. The ethanol ramp-up procedure was as follows: the first three days, only one tube containing 0.1% (w/v) saccharin was used; for the next three run days, the tube had 5% (v/v) ethanol added to it; for the next two run days and all subsequent days, two tubes were used [one contained 5% ethanol and 0.1% saccharin (ES), and the other contained only 0.1% saccharin in tap water WS)]; for the next two days, the ethanol concentration was elevated to 7%. Pilot data with ethanol concentrations ranging from 8 to 12% showed that 8% (v/v) produced the lowest variability, so that was the final concentration used to assess drug effects.

After experiment 4, while doing an unrelated experiment in our lab, we found that stable ethanol drinking could be achieved in a much shorter time frame. Therefore for experiment 2 there was no ramp-up procedure. Instead, the induction procedure was simplified to 3 days

of habituation to saline injections with just homecage water access, then 4 days of WS and ES (8% v/v) access with no injections, and finally drug testing starting on the eighth day.

Data Analysis

All data were sorted in Microsoft Excel (Redmond, WA) and statistical analyses were performed using SPSS 15.0 (Chicago, IL). All within-subjects analyses employed Huynh-Feldt corrections as appropriate. Differences were considered significant when $p < 0.05$ for all analyses. For delay discounting data, delay groups were analyzed separately, a priori.

Exp. 1 (DD & amphetamine)

Mean indifference points were analyzed with a Dose (saline, 0.4, 0.8, 1.2 mg/kg) X Sex mixed ANOVA; paired t-tests were performed as appropriate. Reaction time data were pooled within subject in 10-trial bins, and medians for each subject at each dose were derived. Response latencies longer than 30 seconds were excluded as omissions. To better estimate the vigilance decrement within-subject, the RT from the first 10 trials was subtracted from the last 10 in the absence of a baseline difference.

Exp. 2 (homecage drinking & amphetamine)

Univariate Dose X Sex ANOVA was used to detect differences in ethanol intake and total consumption. In the presence of a main effect of Dose, t-tests were conducted against saline. Data were collapsed in the absence of a significant interaction.

Exp. 3 (DD & naltrexone, memantine, amphetamine)

Data were analyzed in the same manner as experiment 1, except that due to different drug classes being tested, each drug was analyzed separately. Although the purpose of this experiment was to test naltrexone and memantine, a single efficacious dose of amphetamine (1.2 mg/kg) was included as a positive control.

Exp. 4 (homecage drinking & naltrexone and memantine)

The same type of analysis was used as in experiment 2, except that t-tests in baseline drinking were conducted between assessments of naltrexone and memantine to assess the possibility of carryover effects.

Results

Briefly, amphetamine had expected effects on both impulsivity and vigilance, while leaving ethanol intake relatively unaffected. Neither naltrexone nor memantine affected impulsivity or vigilance decrement, yet they both behaviorally selectively decreased ethanol drinking.

Effect of Amphetamine on DD and homecage drinking

In experiment 1, 8 (3 from 10 sec and 5 from 0.5 sec delay group) out of 30 mice (26.6%) were excluded a priori for not meeting baseline criteria. Of the remaining 22 mice, 10 sessions (3% of total) were excluded for non-completion of 20 trials. The mice that had prior ethanol experience were compared to the other subjects in their delay group and were not found to be different in baseline indifference points (ps > 0.69). To assess possible baseline changes over the course of drug administration, saline was given for 3 sessions following drug. Pre-saline did not differ from post-saline in indifference points (ps > 0.50), therefore pre- and post-saline were combined for subsequent analyses. Dose Order did not affect adjusted amounts ($p > 0.28$), so data were collapsed across Dose Order.

In the 0.5 sec group, an Amphetamine Dose (saline, 0.4, 0.8, 1.2 mg/kg) X Sex ANOVA revealed no main effects of Dose or Sex (*p*s > 0.35) nor interaction in indifference points ($p = 0.50$). In the 10 sec group, the same analysis revealed a main effect of Dose $F(2.9, 29.0) = 4.34$, $p = 0.012$, but no main effect of Sex (p = 0.83) or interaction ($p = 0.56$). Paired t-tests to saline revealed an increase in indifference point at the 1.2 mg/kg dose $t(11) = 3.32$, $p = 0.007$, but only a trend at the 0.8 mg/kg dose ($p = 0.08$). These data are shown in panels A and B in figure 2. Because amphetamine dose order was counterbalanced, we were able use an overall ANOVA across days to examine overall changes in sensitivity to drug with repeated administration. There was no change in adjusted amount across days, $p > 0.19$. The increase in adjusted amounts in the 10 sec group combined with the lack of a drug effect in the 0.5 sec group show that amphetamine decreased impulsivity in these mice.

Experiment 2 assessed the effect of amphetamine on homecage drinking. Three mice were excluded for drinking < 0.45 g/kg/30 minutes during the two baseline days. Univariate Amphetamine Dose (saline, 0.4, 1.2, 3.0 mg/kg) X Sex ANOVA revealed a main effect of Dose $F(3, 38) = 10.78$, $p < 0.001$ on ethanol drinking, but no main effect or interactions with Sex (*p*s > 0.94). Follow-up t-test revealed that the 3.0 mg/kg dose differed $t(22) = 5.82$, $p < 0.001$ from saline. To assess whether or not the reduction in ethanol was specific to ethanol, a Dose X Sex ANOVA was performed on total consumption. A main effect of Dose $F(3, 38) = 11.25$, $p < 0.001$ was detected, with no main effect or interaction with Sex (*p*s > 0.54). Follow-up t-tests revealed that the 3.0 mg/kg dose differed from saline $t(22) = 7.33$, $p < 0.001$. Therefore amphetamine reduced all fluid consumption at the high dose, and had no effect at lower doses. These data are shown in figure 2, panels C and D.

Effects of naltrexone on DD and homecage drinking

In experiment 3, 3 mice were excluded a priori for not meeting baseline criteria. Additionally, 8 mice died for unknown reasons (5 from 0.5 sec and 3 from 10 sec). Of the remaining mice, one was excluded for failure to complete at least 20 trials on at least one of the three days in each drug condition. These exclusions left 28 mice for analyses. The criteria were the same as detailed in experiment 1, and resulted in an exclusion rate of 7.3% based on behavioral criteria. Pre-saline did not differ from post-saline in indifference points (*p*s > 0.12), so pre and post saline were collapsed for subsequent analyses.

Analyses of naltrexone's effect on impulsivity was performed with mixed Naltrexone Dose (saline, 3, 10 mg/kg) X Sex ANOVA on indifference points. In the 0.5 sec group, no main effects or interactions were detected (*p*s > 0.11) as pictured in figure 3 panel A. In the 10 sec group, no main effect of Dose or interaction was detected (*p*s > 0.30), shown in figure 3 panel B, but a main effect of Sex was detected $F(1, 14) = 5.68$, $p = 0.032$. Collapsed across Dose, females were shown to be less impulsive than males $t(14) = 2.38$, $p = 0.32$; mean ± SEM indifference point for females was 0.26 ± 0.042 and for males it was 0.12 ± 0.029.

The positive control, 1.2 mg/kg amphetamine, increased adjusted amount (data not shown in figure) $F(1, 14) = 4.88$, $p = 0.044$ from a saline indifference point of 0.25 ± 0.046 to the amphetamine indifference point of 0.52 ± 0.102. Naltrexone did not modify indifference points either up or down, so therefore did not appear to change impulsivity. The replication of the amphetamine effect suggested that the task was sensitive to potential drug effects on impulsive responding.

Experiment 4 assessed the effect of naltrexone on homecage drinking. Seven subjects (15.9%) were excluded for low baseline drinking. Dose (saline, 3, 10 mg/kg) X Sex ANOVA on ethanol intake revealed a main effect of Dose $F(2, 31) = 7.00$, $p = 0.003$, but no main effect or interaction with Sex (*p*s > 0.08). T-tests against saline revealed that the 3 mg/kg dose reduced ethanol intake $t(23) = 2.43$, $p = 0.023$, as did the 10 mg/kg dose $t(22) =$

3.10, $p = 0.005$. To determine if the reduction of ethanol intake was selective for ethanol, we performed a Dose X Sex ANOVA on total fluid consumption. No main effects or interactions were detected (ps > 0.22), which demonstrates a selective effect of naltrexone on ethanol consumption. These data are illustrated in figure 3 panels C and D.

Effects of memantine on DD and homecage drinking

Memantine and impulsivity were also assessed in experiment 3, so the exclusions and analyses were as described for naltrexone.

Analyses of memantine's effect on impulsivity was performed with mixed Memantine Dose (saline, 1, 5 mg/kg) X Sex ANOVA on indifference points. In the 0.5 sec group, no main effects or interactions were detected (ps > 0.26) as pictured in figure 4 panel A. Similarly, in the 10 sec group, no main effects or interactions were detected (ps > 0.10), shown in panel B. Memantine, like naltrexone, did not modify indifference points either up or down, so therefore did not appear to change impulsivity.

Experiment 4 assessed the effect of memantine on homecage drinking. A t-test of baseline ethanol drinking did not reveal any change from the baseline of naltrexone ($p = 0.92$). Memantine Dose (saline, 1, 5 mg/kg) X Sex ANOVA on ethanol intake revealed a main effect of Dose $F(2, 30) = 4.58$, $p = 0.018$ and Sex $F(1, 30) = 6.99$, $p = 0.013$, but no interaction ($p > 0.81$). T-tests against saline revealed that the 5 mg/kg dose reduced intake $t(22) = 2.82$, $p = 0.010$, but the 1 mg/kg dose did not ($p = 0.24$). To determine if the reduction of ethanol intake was selective for ethanol, we performed a Dose X Sex ANOVA on total fluid consumption. No main effects or interactions were detected (ps > 0.22), which suggests a selective effect of memantine on ethanol consumption. These data are illustrated in figure 4, panels C and D.

Drug effects on vigilance decrement

Response latency, the time from when the center cue light illuminates to when the mouse makes a center nosepoke response, can be regarded as a measure of how well the mouse is attending. Typically, reaction time (RT) gets longer as a session progresses, which is called vigilance decrement (Koelega, 1993). The difference between RT at the beginning of the session and the end of the session can be used as a measure of sustained vigilance or attention, such that large increases indicate poor sustained vigilance/attention.

Amphetamine (experiment 1)—To assess the possibility of a drug effect on omissions, an Amphetamine Dose (saline, 0.4, 0.8, 1.2 mg/kg) X Sex ANOVA was conducted on number of trials with response latency greater than 30 seconds. There were no main effects of Dose or Sex (ps > 0.07), but an interaction of Dose X Sex was detected $F(3, 30) = 3.82$, $p = 0.022$. Follow-up t-tests by Sex within Dose revealed no differences (ps > 0.15).

An Amphetamine Dose (saline, 0.4, 0.8, 1.2 mg/kg) X Sex ANOVA conducted on the first bin (trials 1 through 10) did not reveal any Dose effects on the baseline (ps > 0.17) in either delay group from experiment 1. Group RT means by 10-trial bin are shown in table 1. As individual mice complete different numbers of trials on different days, a more precise measurement of vigilance decrement can be obtained by subtracting the RT during the first trials from the RT during the last trials within-subjects and within-session. Thus, an ANOVA was performed on the values derived by subtracting the first 10 trials' RT from the last 10. In the 0.5 sec group, a Dose X Sex ANOVA revealed a main effect of Dose $F(3, 24) = 3.92$, $p = 0.021$ and a strong trend of Sex ($p = 0.052$), but no Dose X Sex interaction ($p = 0.69$). Follow-up paired t-tests to saline revealed that only the 1.2 mg/kg dose reduced the vigilance decrement $t(9) = 2.44$, $p = 0.037$. In the 10 sec group, a Dose X Sex ANOVA

revealed a main effect of Dose $F(3, 30) = 3.55$, $p = 0.026$, but no main effect or interaction with Sex (ps > 0.12). Follow-up paired t-tests showed that all three doses showed reduced vigilance decrement relative to saline ts(11) > 2.45, ps < 0.033 (figure 5). These data are consistent with an enhancement of sustained vigilance/attention in both delay groups, with the 10 sec group being more sensitive to reduced decrement.

Amphetamine (experiment 3)—An Amphetamine Dose (saline, 1.2 mg/kg) X Sex ANOVA on omissions in the 0.5 sec group revealed no main effect of Dose or interaction with Sex (ps >0.20), but a main effect of Sex was detected $F(1, 10) = 7.62$, $p = 7.62$ such that males made less omissions (30 ± 2.04) than females (35 ± 1.39). In the 10 sec group the same analysis detected a main effect of Dose $F(1, 14) = 9.41$, $p = 0.008$ such that the 1.2 mg/kg dose led to less omissions vs. saline (29.8 ± 2.61 vs. 40.6 ± 2.08 respectively), but no effects of Sex (ps > 0.36).

Amphetamine Dose (saline, 1.2 mg/kg) X Sex ANOVA on RT difference detected a decrease in vigilance decrement in the 0.5 sec group $F(1, 10) = 26.22$, $p < 0.001$, and an interaction trend of Sex ($p = 0.066$), but no main effect of Sex ($p = 0.95$). The mean ± SEM vigilance decrement was 5.79 ± 0.77 and 2.87 ± 0.70 seconds for saline and amphetamine, respectively. In the 10 sec delay group, no main effects or interactions were detected (ps > 0.30).

Naltrexone—RT data for experiment 3 were analyzed in the same manner as in experiment 1. No effects of naltrexone on omissions were detected (ps > 0.06). A Naltrexone Dose (saline, 3, 10 mg/kg) X Sex mixed ANOVA on RT differences did not detect main effects or interactions in either the 0.5 or 10 second delay groups (ps > 0.17), data not shown.

Memantine—No effects of memantine on omissions were detected (ps > 0.16). Memantine Dose (saline, 1, 5 mg/kg) X Sex mixed ANOVA on RT difference did not detect main effects or interactions in either the 0.5 or 10 second delay groups (ps > 0.21), data not shown.

Discussion

In these experiments, we were able to show that amphetamine decreased impulsivity and generally increased vigilance, but was without behaviorally selective effects on alcohol consumption. On the other hand, naltrexone and memantine, both of which decreased alcohol consumption in HAP mice, did not affect either impulsivity or vigilance. Overall, within the limits imposed by the drugs we tested here, these findings do not support our hypothesis that there would be a pharmacological relationship between impulsivity and vigilance/attention on the one hand, and ethanol consumption on the other. However, these findings do not speak to the previously demonstrated genetic relationship impulsivity and vigilance/attention have with ethanol consumption (Oberlin and Grahame, 2009). That is, impulsivity and drinking are genetically and therefore neurophysiologically related, but presumably via mechanisms that do not overlap with pathways affected by amphetamine, naltrexone, or memantine.

Even so, results provided pharmacological validation of both the DD and alcohol drinking procedures used here. In the DD studies, long (10-sec) delays were used to detect amphetamine-mediated decreases in impulsivity in a selected population of mice previously shown to be impulsive relative to a low-drinking population. Unfortunately, we did not test a drug that is known to increase impulsivity, but we might expect to decrease adjusted amounts in the 0.5 sec delay group in that case. Granted, drugs that increase impulsivity

would inform the utility of this assay, although would be expected to be of little clinical interest.

A procedural difference in drug administration between the drinking paradigm and the DD task that should be noted is that drugs were administered 30 minutes before limited ethanol access, but immediately before the DD task. As we calculate indifference points from choice behavior in the last 20 trials, the data that is most important in determining indifference points is obtained in the last half of the session, i.e. minutes 30 to 60. This procedural difference makes the behaviorally relevant time period roughly equivalent in both tasks.

Consistent with a trait difference in impulsive subjects, it has also been shown that amphetamine is more efficacious in decreasing impulsivity in more impulsive individuals (Winstanley et al., 2003). Given this potential interaction between high impulsivity and stimulant efficacy, it may be more clinically relevant to assess impulsivity in a model of addiction or alcoholism, such as we did here by testing its effects on the more impulsive High Alcohol Preferring mice.

The possibility remains that naltrexone and memantine may alter impulsivity and/or vigilance, but that we simply used ineffectual doses, or our assay was not sensitive to small changes in impulsivity. These concerns are somewhat mitigated by several factors. First, we tested amphetamine in conjunction with memantine and naltrexone, and were able to detect its anticipated actions on both impulsivity and vigilance decrement. Second, at least in the case of naltrexone, our findings agree with earlier studies that tested rats and humans (Kieres et al., 2004; Mitchell et al., 2007). Finally, both naltrexone and memantine at these doses affected drinking in HAP mice, suggesting that we are sensitive to some effects of these drugs at the doses used presently, but that they are without actions in this version of the delay discounting task. Overall, these results indicate that a current pharmacotherapy for alcoholism, naltrexone, does not affect impulsivity, and likely has its actions on drinking via an alternative mechanism.

Consistent with this conclusion, there is considerable evidence that both naltrexone and memantine diminish drug reward in rodents. Naltrexone blocked conditioned place preference (CPP) to ethanol (Middaugh et al., 2000), morphine (Olmstead and Burns, 2005; Piepponen et al., 1997), and cocaine (Bilsky et al., 1992; Suzuki et al., 1992), but interestingly not amphetamine (Haggkvist et al., 2009). Similarly, memantine blocked CPP expression and reinstatement with morphine (Popik et al., 2006; Ribeiro Do Couto et al., 2004; Ribeiro Do Couto et al., 2005), and cocaine (Kotlinska and Biala, 2000; Maldonado et al., 2007). The current drinking data are largely in agreement with previous findings in humans (Bisaga and Evans, 2004; Bouza et al., 2004; Krupitsky et al., 2007; O'Malley et al., 2002; Volpicelli et al., 1992). If naltrexone and memantine selectively modulate the rewarding value of ethanol or cues paired with ethanol, but leave mechanisms underlying impulsive choice unaffected, then we might expect little change in a task like DD. All the while, we may expect decreases in alcohol intake under the influence of these medications. Arguably, the best strategy to maintain sobriety for the purposes of treatment might be to affect both of the mechanisms involved in the (presumably impulsive) choice to drink, as well as those involved in the rewarding effects of alcohol. The literature on opioid and glutamatergic modulation of impulsivity is scant, but it could well be that only subsets of receptor families modulate impulsivity and alcohol drinking in parallel. Further research into this issue will hopefully elucidate those relationships.

Vigilance decrement is sometimes reported as a measure of the loss of sustained attention (Pattyn et al., 2008; Shimizu et al., 2008; Whyte et al., 1995). Our finding that amphetamine reduces vigilance decrement is consistent with previous reports (Grilly, 2000), although

measured here using a different task. That this effect was observed in both the 0.5 and 10 sec delay groups, at least in experiment 1, indicates that this measure of vigilance/attention is stable and replicable, and that it can be measured in this version of the DD task. Our data show that vigilance decrement can be measured in the absence of an effect on impulsivity, as in the 0.5 sec group, yet they suggest that attention and impulsivity are related. This idea is supported by the well-established history of ADHD treatment with stimulants (Stevenson and Wolraich, 1989).

In experiment 2, amphetamine did not have behaviorally selective effects on ethanol drinking, consistent with other studies showing that systemically-administered amphetamine did not selectively reduce ethanol drinking (Hubbell et al., 1991; Linseman, 1990) or responding for ethanol in rats (Slawecki et al., 1997). However, amphetamine did reduce responding for ethanol at some doses (Pfeffer and Samson, 1985a; Pfeffer and Samson, 1985b), and selectively reduced ethanol drinking when combined with fenfluramine (Yu et al., 1997). Our findings agree with the large literature on amphetamine's anorectic effects (Foltin, 2000; Gibson and Booth, 1988; Wolgin, 1983). Therefore it appears that attention and impulsivity can be modulated together by psychostimulants, but that attention and/or impulsivity do not directly modulate ethanol drinking via mechanisms affected by amphetamine.

The current data show that the DD task programmed with discrete short and long delays is sensitive to pharmacological manipulations that decrease impulsivity. The observed efficacy of amphetamine in decreasing impulsivity in HAP mice implies a key role of catecholaminergic systems in regulating impulsive behavior. Additionally, the dual modulation of impulsivity and vigilance decrement suggests common underlying mechanisms. This idea is supported by numerous human studies showing impairments of executive function, working memory, visuospatial ability, and attention in alcoholics (Beatty et al., 1996; Brandt et al., 1983; Sullivan et al., 2000; Sullivan et al., 1997). Human studies such as these may be confounded by drug history. That said, better measurements of the relationship of cognitive impairment to later alcoholism are made by family history and longitudinal studies. One study that tested family history positive teens found no impairment on attentional measures (Barnow et al., 2007), but when multigenerational or higher familial alcoholism density are used as factors, attentional impairment can be detected (Corral et al., 2003; Corral et al., 1999). An 8-year longitudinal study with high-risk youths found that attentional impairment/executive functioning predicted later substance use, even when controlling for intake substance involvement, gender, education, conduct disorder, family history, and learning disabilities (Tapert et al., 2002). These findings are also consistent with our previous findings of a larger vigilance decrement in selected high drinking mice versus low drinking mice (Oberlin and Grahame, 2009), but inconsistent with the present results suggesting that improvements in impulsivity and vigilance do not decrease alcohol consumption.

We note that our use of a stability criterion decreased variability, at the cost of restricting the applicability of these findings to the large majority of HAP mice whose behavior fell within the limits we imposed. Furthermore, we applied a ceiling of 2 s to our adjusted amounts, the same reinforcer magnitude as the delayed reward, to avoid presenting mice with a choice of a larger reinforcer immediately vs. a smaller reinforcer presented after a delay. This parameter prevents us from measuring a side bias, so we elected to assign the large reinforcer to the initially less preferred lever. However, because we utilized two groups, that is, the long and short delay groups, each of which were equivalent with respect to any bias effects but which differed greatly in adjusted amounts, we feel the drug effects measured here aren't affected by potential side bias issues.

In summary, drugs that selectively reduce ethanol drinking in HAP mice, naltrexone and memantine, do not appear to modulate impulsive choice in HAP mice. While amphetamine reduces impulsivity and decreases vigilance decrement, it does not selectively reduce alcohol drinking. It remains to be seen whether there are drugs that affect both impulsivity and alcohol consumption. The list of pharmacologic agents tested here was by necessity short, and the current findings should not in any way be construed to rule out the idea that a search for medications that decrease impulsivity would have beneficial effects on alcoholism. To the extent that impulsivity lies at the core of multiple forms of addictive behavior, our hope would be that compounds that decrease impulsive behavior would have positive outcomes not just on excessive drinking, but also potentially comorbid afflictions of drug abuse, gambling, and other ultimately self-injurious behaviors. For example, the stimulant modafinil has shown positive actions on pathological gambling in impulsive gamblers (Zack and Poulos, 2008) , and in symptoms of attention deficit disorder in children with ADHD (Biederman et al., 2005; Boellner et al., 2006) as well as showing promise with psychostimulant abusers (Hart et al., 2008; Shearer et al., 2009). Future studies (and an ongoing NIDA-sponsored clinical trial; identifier NCT00142818) might assess whether it would have the hoped-for effects on both impulsivity and alcohol and cocaine consumption in dependent individuals.

Acknowledgments

Supported by AA13483 to NJG, AA016430 to BGO, and AA07611 to David Crabb. Memantine HCl was a gift of Pfizer Pharmaceuticals.

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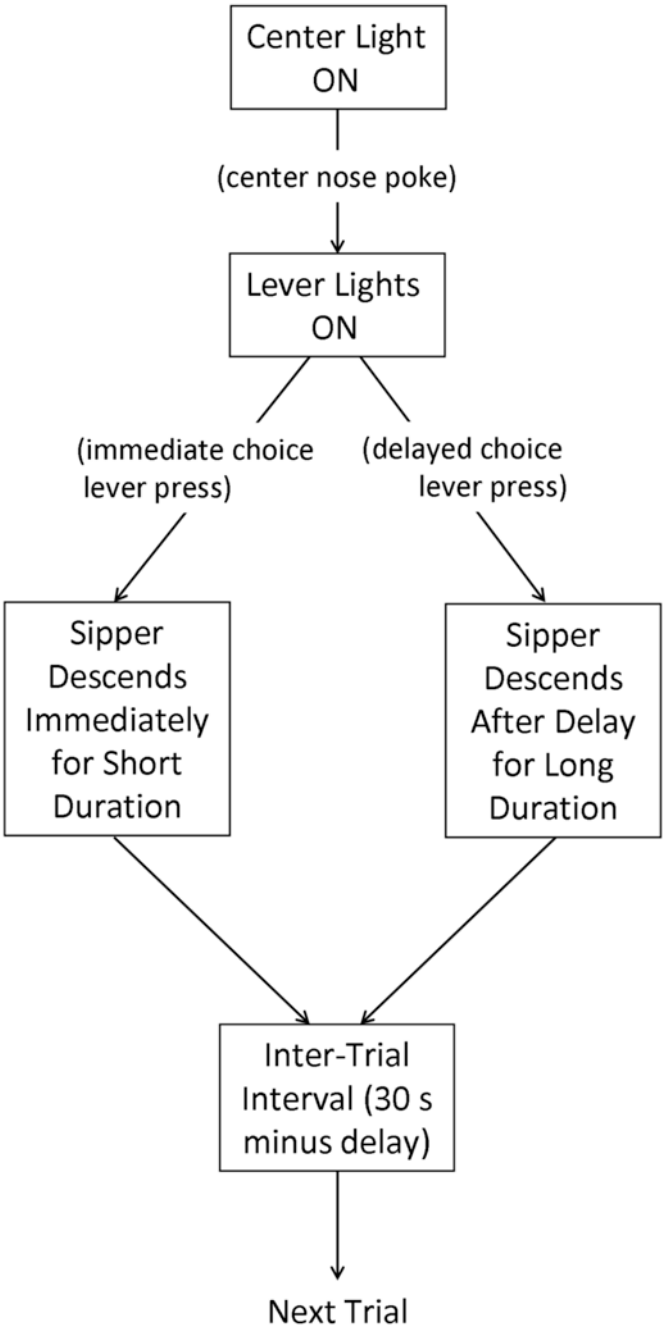

Figure 1.
Shown are cues and contingencies for the completion of one trial. The text in parentheses show the operant responses required to proceed to the next step for delay discounting experiments 1 and 3. The sipper tube contains 0.0316% (w/v) saccharin solution.

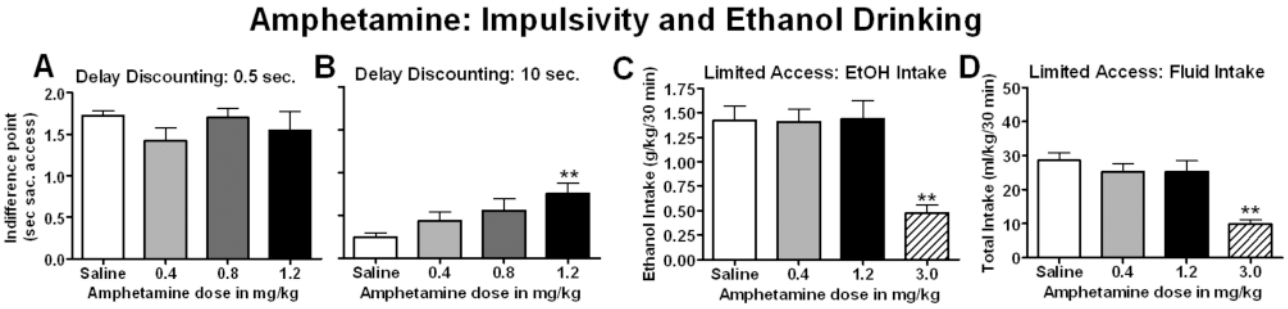

Figure 2.

A. Mean (± SEM) indifference points, measured as seconds of saccharin access, for the 0.5 sec Delay Group (n=10) from experiment 1. Increased shading indicates increasing amphetamine dose. All mice in both groups received 3 doses of amphetamine (0.4, 0.8 and 1.2 mg/kg) plus saline. Note that decreased indifference points represent increased impulsivity, and increased indifference points reflect decreased impulsivity. **B**. Indifference points from experiment 1 in the 10 sec Delay Group (n=12) indicate that the high dose of amphetamine reduces impulsivity. **C**. Ethanol drinking was decreased by the 3.0 mg/kg dose of amphetamine in experiment 2 (n=46, group ns=10-12), but it was a non-specific effect, as illustrated by decreased total consumption in panel **D**. Note that 3.0 mg/kg was not tested in DD. **p ≤ 0.01, compared to saline.

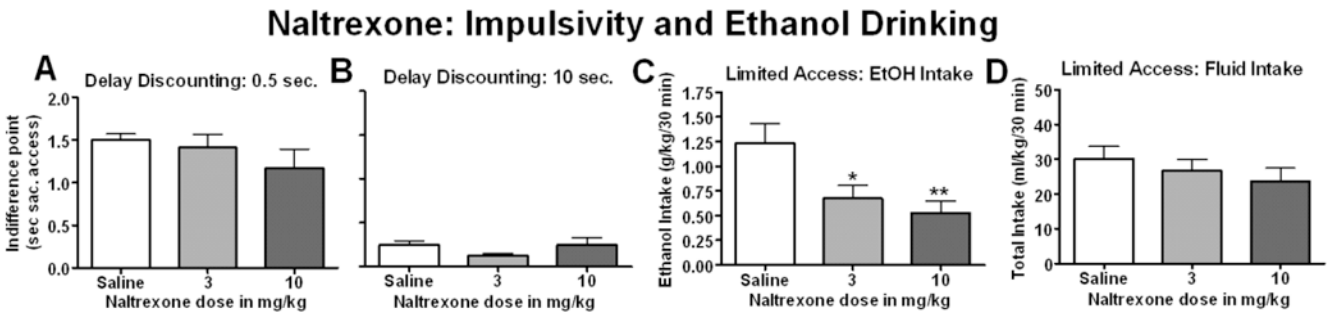

Figure 3.

A. Mean (± SEM) indifference points, measured as seconds of saccharin access, for the 0.5 sec Delay Group (n=12) from experiment 3. Increased shading indicates increasing naltrexone dose. All mice in both groups received 2 doses of naltrexone (3 & 10 mg/kg) plus saline. **B**. No differences were detected in indifference points from experiment 3 in the 10 sec Delay Group (n=16). **C**. Ethanol drinking was decreased by the 3 and 10 mg/kg dose of naltrexone in experiment 4 (n=37, group ns=12-13). **D**. Naltrexone did not affect total consumption, which suggests a selective effect on ethanol drinking. *$p < 0.05$, **$p \leq 0.01$, compared to saline.

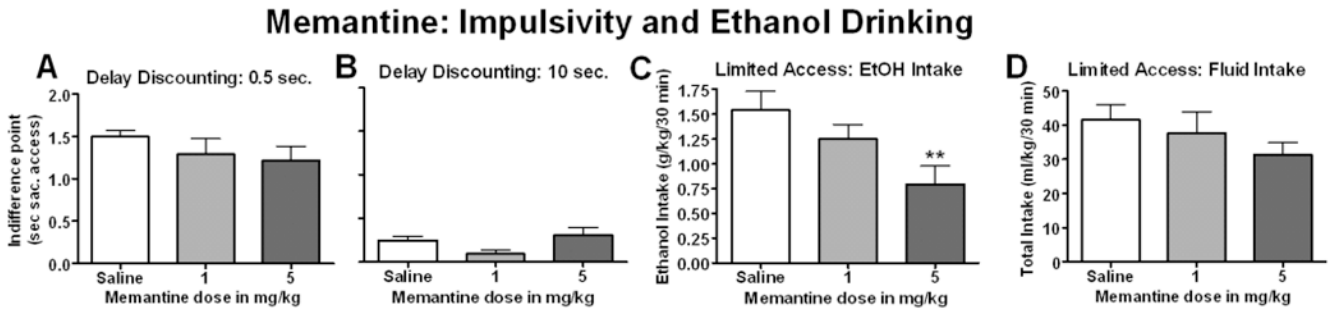

Figure 4.

A. Mean (± SEM) indifference points, measured as seconds of saccharin access, for the 0.5 sec Delay Group (n=12) from experiment 3. Increased shading indicates increasing memantine dose. All mice in both groups received 2 doses of memantine (1 & 5 mg/kg) plus saline. **B**. No differences were detected in indifference points from experiment 3 in the 10 sec Delay Group (n=16). **C**. Ethanol drinking was decreased by the 5 mg/kg dose of memantine in experiment 4 (n=36, group ns=12). **D**. Memantine did not affect total consumption, which suggests a selective effect on ethanol drinking. **p ≤ 0.01, compared to saline.

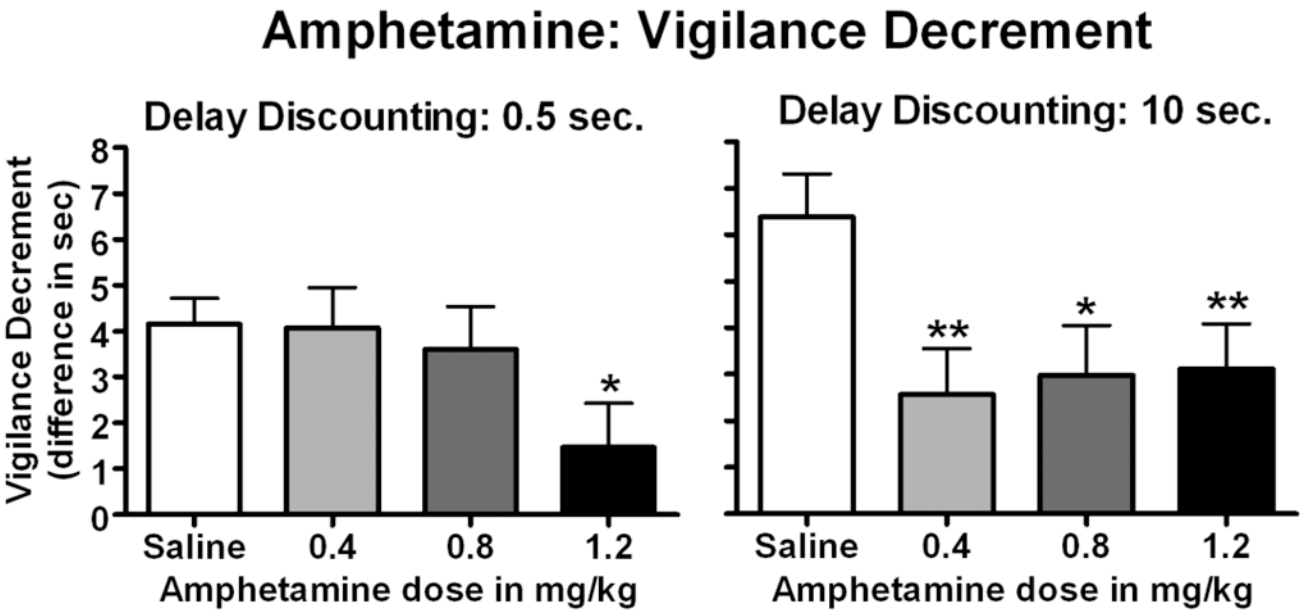

Figure 5.

Mean (± SEM) vigilance decrement in the 0.5 sec delay group (left panel, n=10) and the 10 sec delay group (right panel, n=12) from experiment 1. All mice in both groups received 3 doses of amphetamine (0.4, 0.8 and 1.2 mg/kg) plus saline, indicated by increased shading. Vigilance decrement is derived by subtracting the median RT of the first 10 trials from the last 10 within-subject. Smaller last 10 - first 10 differences indicate reduced vigilance decrement throughout the session, which indicates that vigilance/attention is remaining more focused. *$p < 0.05$, **$p \leq 0.01$, compared to saline.

Table 1

Mean ± SEM Reaction Time by Trial bin and Amphetamine in Experiment 1

Delay	Dose	Trials 1 to 10		Trials 11 to 20		Trials 21 to 30		Trials 31 to 40		Trials
0.5 sec	Saline	1.71	0.18	1.65	0.15	2.81	0.27	4.02	0.44	5.15
	0.4	2.28	0.46	2.27	0.37	3.70	0.76	4.85	0.56	5.96
	0.8	2.29	0.33	3.16	0.71	3.79	0.64	4.55	0.66	5.19
	1.2	2.96	0.90	2.62	0.39	4.16	0.58	3.79	0.65[a]	3.50
10 sec	Saline	3.18	0.42	4.30	0.62	5.28	0.94	7.40	1.07	9.60
	0.4	4.67	0.94	4.45	0.91	5.06	1.47	6.60	1.12	6.40
	0.8	3.81	0.57	4.17	0.80	3.92	0.50	5.36	0.98	6.07
	1.2	4.08	0.77	4.58	0.70	4.81	1.02	3.53	0.43[a]	5.09

[a]Three subjects did not complete greater than 30 trials at the 1.2 mg/kg dose (1 in 0.5s and 2 in 10s group)