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Prior binge-drinking history promotes the positive affective valence of methamphetamine in mice

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Abstract

An alcohol use disorder is a major predisposing factor for methamphetamine (MA) abuse. Further, MA-alcohol co-abuse is a risk factor for treatment discontinuation and non-compliance in MA-dependent individuals. No effective treatment exists for MA addiction, let alone treatments directed at those suffering from MA-alcohol addiction co-morbidity. Thus, it is imperative that we develop high-throughput animal models to study the biobehavioral interactions between MA and alcohol of relevance to the etiology and treatment of co-abuse. To this end, we reported that a history of binge alcohol-drinking [5,10, 20 and 40% (v/v); 2 h/day for 10–14 days] reduces MA reinforcement and intake, but it augments MA-preference and intake when drug availability is behaviorally non-contingent. To reconcile this apparent discrepancy in findings, we employed a comparable 2-week binge-drinking paradigm as that employed in our previous studies followed by place-conditioning procedures (4 pairings of 0.25, 0.5, 1, 2 or 4 mg/kg MA, i.p.). This was meant to determine how a prior binge-drinking history impacts the affective valence of MA and sensitivity to MA-induced psychomotor-activation/ sensitization. Prior binge-drinking history blunted spontaneous locomotor activity and shifted the MA dose place-preference function upwards of water drinking controls. The potentiation of MA-conditioned reward by prior binge-drinking history was independent of any alcohol effects upon the locomotor-activating or –sensitizing effects of MA. Based on these results we propose that the reduced MA reinforcement reported previously by our group likely reflects a compensatory response to an increased sensitivity to MA's positive subjective effects rather than increased sensitivity to the drug's psychomotor-activating effects.

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Contributors

The authors all declare that they have each either materially participated in the research and/or article preparation. EKF and KKS designed the studies, EKF conducted the studies, KKS analyzed the data and EKF and KKS composed the report. Both authors edited the report and have approved the final version for submission.

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Conflict of interest

No conflict declared.

Keywords

Methamphetamine; Binge-drinking; Alcohol use disorder; Place-conditioning; Reward; Sensitization; Psychomotor activity

1. Introduction

Globally, there exists a high prevalence of methamphetamine (MA) addiction and alcoholism co-morbidity (e.g., UN Office on Drugs and Crime, 2015). In fact, recent excessive alcohol consumption is associated with a 4–5-fold greater incidence of co-abuse (Brecht et al., 2007; Bujarski et al., 2014; Chen et al., 2014; Furr et al., 2000; Herbeck et al., 2013; O’Grady et al., 2008; Sattah et al., 2002). Further, co-abuse is a risk factor for treatment discontinuation and non-compliance in MA-dependent individuals (Brecht et al., 2005). This later fact presents a serious socioeconomic concern, as the treatment admission rate for MA use is rising annually world-wide (UN Office on Drugs and Crime, 2015).

While a number of psychopharmacological mechanisms might account for the high prevalence of MA-alcohol co-abuse, an alcoholic beverage potentiates MA’s positive subjective effects and can augment MA-craving in human subjects (Bershad et al., 2015; Kirkpatrick et al., 2012a,b; Mendelson et al., 1995). Consistent with these data from humans, drug-naïve C57BL/6J (B6) mice prefer to consume a mixed solution of MA and alcohol over either alone (Fultz et al., 2017), and alcohol-experienced B6 mice exhibit greater oral MA intake than alcohol-naïve animals (Fultz et al., 2017). However, in both rats (Winkler et al., 2016) and mice (Fultz et al., 2017) a prior and/or concurrent history of alcohol-drinking blunts MA-directed responding and intake under operant-conditioning procedures. This argues that alcohol experience *reduces* MA reinforcement. This being said, binge-drinking history shifts the dose-response function for oral MA intake in mice to the left of MA-naïve controls (Fultz et al., 2017). Thus, while prior binge-drinking history reduces the MA’s reinforcing efficacy, it increases sensitivity to MA’s positive motivational properties.

As a reduction in operant behavior can reflect an increase or a decrease in sensitivity to the positive subjective effects of a drug, the present study determined how a prior binge-drinking history influences the affective valence of MA in relation to this stimulant’s effects upon psychomotor activity and its sensitization. Based on the results of human studies (Bershad et al., 2015; Kirkpatrick et al., 2012a,b; Mendelson et al., 1995), it was hypothesized that the reduction in MA reinforcement observed in alcohol-experienced animals reflects increased sensitivity to the positive affective and/or psychomotor-activating properties of MA.

2. Materials and methods

2.1. Subjects

Subjects were adult (8–10 weeks old) male C57BL/6J (B6) mice, obtained either from the Jackson Laboratory (Sacramento, CA; cohorts 1–2) or the Psychological and Brain Sciences vivarium at UCSB (cohorts 3–5). The mice, bred in-house, were raised under a 12-h regular light cycle (lights on: 0700 h) until approximately 10 days prior to the onset of drinking

procedures, at which time they were transferred to an adjacent colony room under a 12-h reverse light cycle (lights on: 2200 h). B6 mice from the Jackson Laboratory were allowed 10 days to acclimatize to the reverse-cycle housing conditions prior to the onset of drinking procedures. After the final day of drinking, mice were transferred back to the regular light cycle and allowed to re-acclimatize for 10 days prior to CPP testing. This was done to lower the spontaneous activity of the animals and augment the probability of detecting MA-induced locomotor hyperactivity. Mice were housed in groups of 4 on a ventilated rack and only separated from their cagemates during experimental procedures, which were all approved by the Institutional Animal Care and Use Committee of the University of California Santa Barbara and conducted in accordance with the Guide to the Care and Use of Laboratory Animals (2014).

2.2. Binge-alcohol drinking procedures

This study employed the same 2-week, 4-bottle-choice (5, 10, 20 and 40% alcohol, v/v) version of the Drinking-in-the-Dark (DID) binge alcohol-drinking paradigm as that employed in our prior study of MA-alcohol interactions (Fultz et al., 2017). At approximately 1 h prior to bottle presentation (which occurred at 3 h into the dark phase of the cycle), mice were transferred to a dark, non-colony testing room and singly housed in their respective drinking cages to habituate the animals to the testing environment (e.g., Fultz et al., 2017; Lee et al., 2016, 2017a,b). The amount of alcohol consumed following a 2-h period was calculated as function of the animals' body weight using changes in bottle weight and corrected for spillage induced by bottle handling. Animals were weighed weekly. Water-drinking animals served as controls.

2.3. MA place-conditioning

The procedures and apparatus used to induce place-conditioning and to monitor locomotor activity and compartment preference were identical to those described in prior reports (for details, see Lominac et al., 2014, 2016; Szumlinski et al., 2017) with the following exceptions: (1) mice in the present study mice underwent two conditioning sessions per day for a total of 4 days during which the saline-conditioning sessions occurred in the morning (starting ~0900 h) and the MA-conditioning sessions in the mid-afternoon (starting ~1400 h), and (2) mice were conditioned with one of five MA doses (0.25, 0.5, 1, 2 or 4 mg/kg, IP; vol = 10 ml/kg).

2.4. Statistical analyses

A one-way ANOVA was conducted on the average total alcohol intake exhibited during the 2-week drinking period to ensure equivalent alcohol intake across the different conditioning-doses. The total distance traveled during the Pre- and Post-Tests was analyzed using a History X Dose X Test ANOVA with repeated measures on the Test factor. The total distance traveled in response to an acute injection of MA was analyzed using a History X Dose ANOVA, and the total distance traveled during the conditioning sessions was analyzed using History X Dose X Injection ANOVAs with repeated measures on the Injection factors (4 levels). These were performed separately for saline- and for MA-conditioning sessions. The difference in the total distance traveled from the 1st to the 4th conditioning session was analyzed separately for saline (Habituation) and for MA (Sensitization) using History X

Dose ANOVAs. The time spent in the SAL- versus MA-paired compartment was analyzed using a History X Dose X Side ANOVA with repeated measures on the Side factor, and the presence of conditioning was confirmed using paired *t*-tests (SAL- versus MA-paired side) separately for each group.

3. Results

3.1. Alcohol intake

The alcohol intakes exhibited by the B6 male mice slated to receive the different MA doses were nearly identical at the outset of conditioning (one-way ANOVA, $p = 0.95$). On average, mice consumed 5.50 ± 0.19 g/kg alcohol in 2-h. Prior studies in our lab and others have correlated these intakes to BACs above 100 mg/dl (Fultz et al., 2017; Lee et al., 2016, 2017a; Rhodes et al., 2005).

3.2. Spontaneous locomotor activity

Prior binge-drinking history reduced the spontaneous locomotor activity expressed during both the pre- and post-conditioning tests (Fig. 1A) [History effect: $F(1.83) = 6.72$, $p = 0.01$; Test effect: $F(1.83) = 71.12$, $p < 0.0001$; interaction: $p = 0.29$. There was no MA Dose effect or interaction, p 's > 0.20]. Prior binge-drinking history reduced the spontaneous locomotor activity expressed during both the pre- and post-conditioning tests when mice were conditioned with saline as well (Fig. 1B) [History effect: $F(1.75) = 4.68$, $p = 0.03$; no History interactions, p 's > 0.60]. Although MA did not influence the distance traveled during the post-conditioning test, group differences in saline-induced locomotion were observed between the groups of mice receiving the different doses of MA, but this effect did not depend upon prior drinking history [Dose X Saline Injection: $F(12,225) = 2.39$, $p = 0.006$]. This interaction reflected greater locomotion during the 2nd saline-conditioning session in mice receiving 4 mg/kg MA versus the other dose groups (data not shown) [Dose effect: $F(4.84) = 3.72$, $p = 0.008$; LSD post-hoc tests, p 's < 0.04]. No other effect of intervening MA-conditioning was observed on the locomotion expressed during any of the other saline-conditioning sessions (univariate ANOVAs, p 's > 0.07). No group differences were observed in the extent to which the saline-induced locomotion habituated over the course of conditioning (Fig. 1C; History X Dose ANOVA, p 's > 0.10).

3.3. MA-induced changes in locomotor behavior

Comparison of the acute locomotor response to MA (i.e., the total distance traveled during the first MA-conditioning session) indicated lower locomotor activity, overall, in alcohol-experienced versus water control animals (Fig. 2A) [History effect: $F(1.84) = 6.27$, $p = 0.014$; Dose effect: $F(4.84) = 21.15$, $p < 0.0001$; History X Dose: $p = 0.16$]. However, there was no statistically significant effect of prior alcohol drinking history upon the change in MA-induced locomotor activity observed across the four MA-conditioning sessions [Dose X MA Injection: $F(12,225) = 6.28$, $p < 0.0001$; no main History effect or interactions: all p 's > 0.11]. Indeed, an analysis of the dose-response function for MA-induced locomotor sensitization (i.e., difference in locomotion expressed from MA-conditioning session 1–4) failed to indicate any influence of prior drinking history upon this measure (Fig. 2B) [Dose effect: $F(4.84) = 9.94$, $p < 0.0001$; no History effect or interaction: p 's > 0.50].

3.4. MA-induced place-conditioning

The dose-response function for MA-induced place-conditioning was shifted upwards in alcohol-experienced mice (Fig. 2C) [History X Side: $F(1,75) = 10.51$, $p = 0.002$; no Dose effect or interactions: p 's > 0.18]. While the 0.25 mg/kg MA dose did not elicit place-conditioning in either group (paired-samples t -tests, p 's > 0.15), 0.5, 2.0 and 4.0 mg/kg MA elicited a place-preference only in alcohol-experienced mice [for alcohol-experienced mice, at 0.5 mg/kg: $t(9) = 2.45$, $p = 0.04$; at 2 mg/kg: $t(7) = 3.67$, $p = 0.008$; at 4 mg/kg: $t(7) = 3.53$, $p = 0.01$; for water mice, all p 's > 0.10]. The 1.0 mg/kg MA dose elicited a place-preference in both drinking groups [for water, $t(7) = 3.17$, $p = 0.02$; for alcohol, $t(7) = 3.22$, $p = 0.02$].

4. Discussion

A prior binge-drinking history promoted the expression of a MA-conditioned place-preference independent of effects upon drug-induced locomotor sensitivity. These findings are in line with the epidemiological data indicating that recent excessive alcohol consumption increases risk for methamphetamine co-abuse (Brecht et al., 2007; Bujarski et al., 2014; Chen et al., 2014; Furr et al., 2000; Herbeck et al., 2013; O'Grady et al., 2008; Sattah et al., 2002) and complement our recent discovery that a comparable history of binge-drinking augments oral MA intake by mice under limited-access conditions (Fultz et al., 2017). Together, this collection of data suggests that the increased MA addiction risk imparted by excessive drinking reflects, at least in part, a potentiation of the positive motivational/affective valence of MA.

The fact that prior binge-drinking experience shifted the entire MA dose-conditioning function upwards indicates a greater efficacy of MA to elicit conditioned reward in alcohol-experienced individuals. Although the average CPP Score elicited by conditioning with the 1, 2 and 4 mg/kg MA doses was comparable in water controls, only the 1 mg/kg MA dose was sufficient to elicit a significant place-preference in these animals. This attests to the variability in responding at the higher doses tested. These observations are in line with prior reports indicating that B6 mice exhibit conditioned reward when injected with 1 mg/kg MA (Chen et al., 2014), while both the direction and magnitude of the conditioned response to 2 mg/kg MA are quite variable in this mouse strain (Szumlinski et al., 2017). However, it should be noted that despite assaying across a 10-fold range of MA doses, none of the MA doses tested in the present study elicited a significant conditioned place-aversion in our animals. Thus, it remains to be determined whether or not the drinking-induced shift upwards in the dose-response function for place-conditioning extends to higher MA doses with negative motivational/affective valence. Furthermore, to the best of our knowledge, no published report has examined the influence of the circadian cycle upon the expression of MA-induced place-conditioning; however, the expression of cocaine-conditioned reward is reported to be greater in mice tested during the light versus dark phase of the cycle (Kurtuncu et al., 2004). Although we have demonstrated previously that prior binge-drinking promotes oral MA intake and preference under modified "Drinking-in-the-Dark" procedures, it remains to be determined whether or not the magnitude of the binge-induced

potentiation of MA-conditioned reward would be greater or different in mice tested during the dark phase of the circadian cycle.

Nevertheless, it is clear from our results that prior binge-drinking experience does not increase MA-induced psychomotor activation or sensitization at any of the doses tested. These negative results are particularly informative as the propensity to consume a drug is typically inversely related to behavioral sensitivity to the drug's psychomotor effects in both humans (e.g., Cruikshank and Dryer, 2009; Schuckit et al., 2012; Sheridan et al., 2009) and laboratory animals (e.g., Davis and Riley, 2010; Shabani et al., 2011). Although the fact that prior binge-drinking history shifted the dose-response function for acute MA-induced locomotion downward might be interpreted as drug cross-tolerance, the failure of prior binge-drinking history to influence the MA-induced locomotor hyperactivity expressed throughout the remainder of conditioning or this drug's psychomotor-sensitizing properties argues against drug cross-sensitization or cross-tolerance of MA's psychomotor-activating effects as mechanisms contributing to the potentiation of MA reward observed herein. Although drug self-administration procedures are considered the gold-standard in the addiction field, study outcomes are subject to many interpretational confounds that require complementary approaches to resolve (Sanchis-Segura and Spanagel, 2006). Indeed, the very limited extant literature pertaining to MA-alcohol interactions in drug-taking (Fultz et al., 2017; Winkler et al., 2016) provides an excellent example of how behavior manifested under operant-conditioning procedures is insufficient to fully understand the psychopharmacological mechanisms underpinning drug-taking behavior.

The reduction in MA reinforcement reported previously in alcohol-experienced rats (Winkler et al., 2016) and mice (Fultz et al., 2017) has been speculated to reflect cross-tolerance of MA's positive subjective effects (Winkler et al., 2016) or a cross-sensitization of MA's psychomotor-sensitizing, anxiogenic and/or positive subjective effects (Fultz et al., 2017). Based on the observations that prior alcohol-experience (1) augmented MA intake under limited-access procedures in the home-cage and (2) shifted the dose-response function for oral MA intake under operant-conditioning procedures to the left of alcohol-naïve controls (Fultz et al., 2017), we argued previously in favor of the latter mechanism as a major contributory factor. The present results for both place-conditioning and locomotor activity support this assertion within the MA dose-range tested.

Interestingly, however, the alcohol-experienced mice in the present study exhibited blunted spontaneous locomotor reactivity during all phases of the place-conditioning study relative to alcohol-naïve controls. Whether or not this blunted activity reflects alcohol withdrawal-induced lethargy or changes in emotionality cannot be delineated from the design of the present experiment. However, we have amassed considerable evidence indicating that our 2-week binge-drinking paradigm augments negative affect in mice without consistently influencing various measures of locomotor activity (Lee et al., 2016, 2017a,b). Thus, the possibility exists that the increased efficacy of MA to elicit reward in alcohol-experienced mice may relate, in part, to a reversal of the negative affective state produced by alcohol withdrawal. This possibility will be explored directly in future studies.

Notwithstanding a characterization of the interaction between alcohol-experience and high-dose MA, we suggest that a prior and/or concurrent history of alcohol-drinking induces plasticity within neural circuits that drive the positive subjective effects of MA. Based on the results of recent biochemical studies linking MA addiction vulnerability to elevated indices of nucleus accumbens glutamate (Szumlinski et al., 2017), we propose that this alcohol-induced neuroplasticity involves accumbens glutamate. Indeed, repeated alcohol experience (both injected and ingested) is well-characterized to sensitize both pre- and post-synaptic indices of glutamate transmission within the nucleus accumbens (c.f., Bell et al., 2016). This raises the testable hypothesis that an alcohol-induced sensitization of nucleus accumbens glutamate transmission augments sensitivity to the positive motivational/affective valence of MA, possibly accounting for the increased risk for MA addiction in individuals with a prior history of excessive alcohol consumption.

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Fig. 1.

Summary of the effects of a prior history of binge alcohol-drinking upon spontaneous locomotor activity. (A) Distance traveled during the 15-min pre- and post-conditioning tests by mice with a prior 2-week history of water (Water) or binge alcohol-drinking (Alcohol). (B) Distance traveled during each of the 15-min saline conditioning sessions. (C) Difference in the distance traveled from the first to the fourth saline conditioning session. The data represent the mean $\pm$ SEMs of the number of mice indicated in parentheses in Panel B. *indicates a main History effect (ANOVA, $p < 0.05$); +indicates main Test effect (ANOVA, $p < 0.05$).

Fig. 2.

Summary of the effects of a prior history of binge alcohol-drinking upon MA-induced changes in behavior. (A) Distance traveled during each of the 15-min MA-conditioning sessions exhibited by mice with a prior 2-week history of water (Water) or binge alcohol-drinking (Alcohol). (B) Dose-response function for the difference in the distance traveled from the first to the fourth MA-conditioning session. (C) Difference in the time spent in the MA- versus saline-conditioned chamber on the post-conditioning test (CPP Score in sec). The data represent the mean $\pm$ SEMs of the number of mice indicated in parentheses in Panel A. *indicates a main History effect (ANOVA, $p < 0.05$); +indicates a place-preference (one-sample t -tests, p 's < 0.05).