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Short communication

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.

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

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present study determined how a prior binge-drinking history influences the affective valence of MA in relation to this stimul ant'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 apparati 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