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Methamphetamine-alcohol interactions in murine models of sequential and simultaneous oral drug-taking

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ABSTRACT

Background: A high degree of co-morbidity exists between methamphetamine (MA) addiction and alcohol use disorders and both sequential and simultaneous MA-alcohol mixing increases risk for co-abuse. As little preclinical work has focused on the biobehavioral interactions between MA and alcohol within the context of drug-taking behavior, we employed simple murine models of voluntary oral drug consumption to examine how prior histories of either MA- or alcohol-taking influence the intake of the other drug.

Methods: In one study, mice with a 10-day history of binge alcohol-drinking [5,10, 20 and 40% (v/v); 2 h/day] were trained to self-administer oral MA in an operant-conditioning paradigm (10–40 mg/L). In a second study, mice with a 10-day history of limited-access oral MA-drinking (5, 10, 20 and 40 mg/L; 2 h/day) were presented with alcohol (5–40% v/v; 2 h/day) and then a choice between solutions of 20% alcohol, 10 mg/L MA or their mix.

Results: Under operant-conditioning procedures, alcohol-drinking mice exhibited less MA reinforcement overall, than water controls. However, when drug availability was not behaviorally-contingent, alcohol-drinking mice consumed more MA and exhibited greater preference for the 10 mg/L MA solution than drug-naïve and combination drug-experienced mice. Conversely, prior MA-drinking history increased alcohol intake across a range of alcohol concentrations.

Discussion: These exploratory studies indicate the feasibility of employing procedurally simple murine models of sequential and simultaneous oral MA-alcohol mixing of relevance to advancing our biobehavioral understanding of MA-alcohol co-abuse.

1. Introduction

The prevalence of methamphetamine (MA) and alcohol co-abuse is high, with MA ranking 3rd as the illicit drug most co-abused in individuals with alcohol-use disorders (AUDs) (e.g., UN Office on Drugs and Crime, 2015). Conversely, the percentage of current MA users that report alcohol co-abuse (a.k.a. mixing) ranges from 34 to 99% (e.g., Brecht et al., 2007; Celentano et al., 2008; Furr et al., 2000; O'Grady et al., 2008; Sattah et al., 2002). Prior AUD history is a major predisposing factor for MA abuse, with recent excessive alcohol consumption associated with a 4–5-fold greater incidence of co-abuse (e.g., 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 co-abuse is a risk factor for treatment discontinuation and non-compliance in MA-dependent individuals (Brecht et al., 2005). This latter fact is particularly serious as primary MA use accounts for ~30% of all addiction treatment admissions in the U.S. (SAMHSA, 2009, 2012), the world-wide treatment admission rate for MA use is rising annually (UN Office on Drugs and Crime, 2015) and currently, there exists no effective treatment for MA addiction, let alone addiction co-morbidity.

In humans, the increased MA abuse risk observed in problem drinkers reflects, in part, alcohol's ability to potentiate MA's stimulant-related subjective effects (Bershad et al., 2015; Kirkpatrick et al., 2012a; Mendelson et al., 1995). Of direct relevance here, prescription MA (Desoxyn) has high abuse liability (NIDA, 2013) and oral MA administration at doses of 20 or 40 mg (i.e., 0.33 or 0.66 mg/kg) elicit positive subjective effects in current stimulant abusers (e.g., Kirkpatrick et al., 2012b) and MA-alcohol co-abusers (c.f., Bershad et al., 2015;

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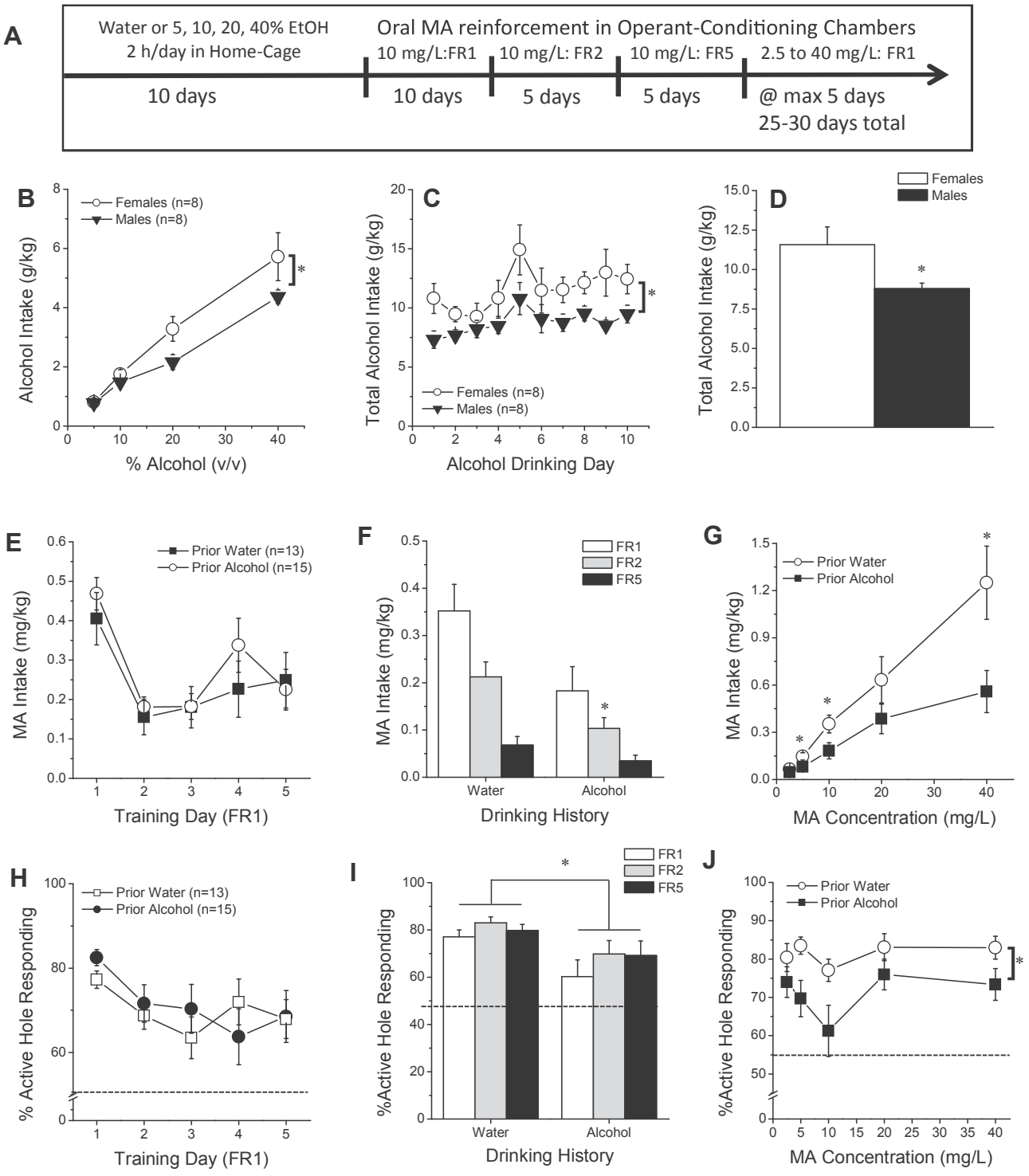

Fig. 1. Summary of the effects of a prior history of binge alcohol-drinking upon MA reinforcement. (A) Procedural time-line for Experimental 1. During the alcohol-drinking phase of this experiment, females exhibited: (B) a shift upwards in the dose-response function for alcohol intake; (C) consistently higher levels of daily total alcohol intake; and (D) greater average total alcohol intake, than their male counterparts. For panels B-D,]* indicates a main Sex effect (ANOVA, $p < 0.05$). (E) When compared to water-drinking controls (Prior Water), male and female mice with a prior history of binge alcohol-drinking (Prior Alcohol) exhibited comparable MA intake during the first week of operant-conditioning, when 10 mg/L MA served as the reinforcer. (F) Although the intake of 10 mg/L MA dropped precipitously in both groups with increasing response demand, alcohol-experienced mice exhibited lower intake under the FI20 and FR2 schedules of reinforcement, relative to water controls. (G) The dose-response function for MA intake was shifted downwards, but to the left, of water controls. (H) No effect of prior alcohol history was observed upon the percentage of total responses directed at the active hole (% Active Hole Responding) during the initial 5 days of operant-conditioning. (I) However, alcohol-experienced mice exhibited lower response allocation with increasing response demand and (J) the dose-response function for response allocation was shifted downwards in alcohol-experienced mice, relative to water controls. The data represent the mean ± SEMs of the number of mice indicated in parentheses. For panels E-J,]* indicates a main Binge History effect ($p < 0.005$); *$p < 0.05$ vs. Prior Water (tests for simple main effects).‘.

Kirkpatrick et al., 2012a, 2012b). In these populations, an alcoholic beverage increases ratings of “good drug effect”, “drug liking” and “desire to take drug”, over that produced by oral MA alone (Bershad et al., 2015; Kirkpatrick et al., 2012a). Thus, both sequential and simultaneous MA-alcohol mixing increases risk for co-abuse in humans. Yet, there is little biobehavioral research into the sequelae of MA-