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Short communication

Clozapine reconstructed: Haloperidol's ability to reduce alcohol intake in the Syrian golden hamster can be enhanced through noradrenergic modulation by desipramine and idazoxan

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ABSTRACT

Background: Alcohol use disorder commonly occurs in patients with schizophrenia. Most antipsychotic drugs do not lessen alcohol use; although the atypical antipsychotic clozapine has been shown to reduce alcohol use in patients with schizophrenia, its toxicity severely limits its use in patients. With an eye toward creation of a safer clozapine-like drug, we have investigated the pharmacological basis of the clozapine's effects on alcohol drinking in the Syrian golden hamster. In this animal, as in patients with schizophrenia, clozapine reduces alcohol drinking while the typical antipsychotic haloperidol does not. We have suggested that clozapine decreases alcohol drinking due to its weak dopamine D2 receptor blockade, its potent norepinephrine α-2 receptor antagonism, as well as its ability to elevate plasma norepinephrine.
Methods: We recreated a clozapine-like drug to reduce alcohol drinking in the Syrian golden hamster by combining low dose haloperidol with a norepinephrine α-2 receptor antagonist, idazoxan, and a norepinephrine reuptake inhibitor, desipramine. Hamsters were given free access to water and alcohol (15% v/v) and were treated daily with each drug or with the three-drug combination for 23 days.
Results: The drug combination reduced alcohol drinking and preference significantly as compared to vehicle or to haloperidol, idazoxan or desipramine, while not altering food-intake or body-weight.
Conclusion: These findings suggest that that haloperidol, which does not reduce alcohol drinking in patients with schizophrenia or the hamster, if combined with idazoxan and desipramine (producing a drug combination that mimics aspects of clozapine's pharmacology) is able to reduce alcohol drinking in the hamster.

1. Introduction

Alcohol use disorder (AUD) is 3 times more prevalent in patients with schizophrenia (SCZ) compared to the general population; over 30% of patients with SCZ have an AUD (Regier et al., 1990). Although patients with SCZ tend to consume only moderate amounts of alcohol on a regular basis, even this moderate, but regular, use substantially increases the morbidity of SCZ (Drake and Mueser, 1996). AUD in patients with SCZ is associated with poor treatment response, treatment non-compliance (Owen et al., 1996), relapse and hospitalization (Drake and Mueser, 1996; Gupta et al., 1996), as well as violence (Bartels et al., 1991; Swanson et al., 1990) and suicide (Allebeck et al., 1987; Harkavy-Friedman and Nelson, 1997). There are few treatment options available to control AUD in this difficult-to-treat population; to date, the atypical antipsychotic clozapine (CLOZ) is the only antipsychotic shown to reduce alcohol drinking in patients with SCZ (Drake et al., 2000; Green et al., 2008, 1999; Lee et al., 1998; Zimmet et al., 2000). Unfortunately, CLOZ is only used infrequently because of its toxic side-effect profile.

Our group and others have proposed that patients with SCZ may have a dysregulated brain reward circuit that underpins their alcohol use, and that alcohol may transiently improve the functioning of this circuit (Chambers, 2007; Green et al., 1999). Furthermore, we have also proposed that CLOZ, because of its broad-spectrum effects, including its weak dopamine (DA) D2 receptor antagonism,

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potent norepinephrine (NE) α-2 antagonism and ability to increase levels of norepinephrine in plasma and brain [through possible NE reuptake inhibition ability (Yoshimura et al., 2000)], may also improve the functioning of this circuitry and thereby limit alcohol/other substance use (Chau et al., 2011; Green et al., 2004, 2008, 1999). We have noted that typical antipsychotics, such as HAL, are not able to decrease alcohol drinking in patients with SCZ (Green et al., 2004), and we have suggested that this may be due, in part, to their potent dopamine D2 receptor antagonism, which may itself produce a reward deficit (Grace, 1991).

We have performed a series of experiments in the alcohol-drinking Syrian golden hamster, deconstructing CLOZ into its pharmacological components, with an eye toward developing medication combinations that, like CLOZ, might limit alcohol drinking in patients with SCZ. The hamster is an appropriate animal with which to assess the potential ability of medications to limit alcohol drinking in patients with schizophrenia, for the following reasons: (a) like patients with schizophrenia who tend to drink regular but moderate amounts of alcohol, the hamster consumes alcohol on a regular basis, achieving moderate blood alcohol levels, and does not develop physiologic withdrawal (Ferris et al., 1998; Harris et al., 1979; Keung et al., 2000); and (b) like patients with schizophrenia, this animal reduces its alcohol consumption when treated with CLOZ, but not when treated with HAL (Green et al., 2004). Data from our hamster studies have strongly suggested that CLOZ's actions are, indeed, contributed to by its weak dopamine D2 receptor blockade, as well as its modulation of noradrenergic signaling in the brain via both NE reuptake inhibition and α-2 receptor antagonism (Chau et al., 2011; Gulick et al., 2014). Based on these data, we hypothesized that combining a low dose of HAL (to mimic the weak DA D2 receptor blockade of CLOZ) with desipramine (DMI; a NE reuptake inhibitor) and idazoxan (IDAZ; a NE α-2 receptor antagonist) would replicate the effects of CLOZ, and reduce alcohol drinking and preference in the Syrian golden hamster. Findings from this study can further advance our understanding of the mechanisms of action of CLOZ, and moreover, may shed light on the development of new medications that can limit alcohol drinking in patients with SCZ and, potentially, in those with AUD alone.

2. Materials and methods

2.1. Animals

Adult, male Syrian golden hamsters *(Mesocricetus auratus*; 100–130 g; Harlan Inc., Indianapolis, IN) were individually housed and maintained on a 12 h/12 h light/dark cycle with ad libitum access to food and water. Hamsters were given free access to two drinking bottles (water and 15% alcohol [v/v]); the positions of the two bottles were rotated daily to prevent positional preference), and food. A technician, blinded to the experimental conditions, measured fluid intake every 24 h, food intake every 48 h, and body-weight every 4 days. Once the hamsters achieved a steady baseline level of alcohol intake, drug treatment began. All injections were performed 1–2 h prior to the start of the dark cycle to avoid any immediate locomotor effects of the drugs on alcohol intake. All experiments were carried out in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals (NIH Publications No. 80-23) revised in 1996 and approved by the Institutional Animal Care and Use Committee of Dartmouth College.

2.2. Procedures

Thirty-four hamsters were given access to separate bottles of water and 15% v/v alcohol for 12 days prior to randomization into 5 groups based on baseline alcohol intake (g/kg; $n = 7–8$ per group); baseline alcohol intake was calculated using the last 4 days of the initial 12-day period of access to alcohol. The groups were subsequently treated daily for 23 days with either: vehicle (VEH); 0.02 mg/kg HAL; 1.5 mg/kg IDAZ; 5 mg/kg DMI; or the combination of all three drugs. All hamsters received free access to food, water, and alcohol during treatment.

2.3. Drugs

HAL, IDAZ and DMI were purchased from Sigma Aldrich (St. Louis, MO). All drugs were dissolved in 0.5 N acetic acid, with the volume adjusted in the 0.5 M sodium acetate vehicle solution (pH 5.5). All drug and VEH solutions were injected subcutaneously (2 ml/kg body-weight).

2.4. Data analysis

Alcohol intake (g/kg), alcohol preference, food-intake (g/kg), and body-weight (g) data were analyzed using a two-way repeated measures analysis of co-variance (RMANCOVA), using time (measured in days) and drug treatment as independent variables and the last four days of alcohol drinking prior to treatment as covariates. The main effects between treatment groups were compared in a pair-wise manner using a Bonferroni confidence interval adjustment. When the analysis indicated that a significant time by treatment interaction was observed, pairwise comparisons between groups were made using the Bonferroni adjustment to help interpret time by treatment interactions from the RMANOVAs; adjustment to p-values was carried out separately at each day. Data are expressed as mean (M) ± standard error of the mean (SEM) and significance was set at $p < 0.05$.

3. Results

3.1. Combining a low dose of haloperidol with idazoxan and desipramine reduces alcohol intake

A two-way repeated measures ANOVA (RMANOVA) indicated no effect of time, but a significant effect of treatment $F(6, 33) = 20.237$, $p < 0.001$, and a significant time by group interaction, $F(132, 9726) = 1.378$, $p < 0.01$, on alcohol intake in the hamster (Fig. 1A). Post-hoc pairwise comparisons showed that the combination of HAL, IDAZ and DMI resulted in significantly lower alcohol intake compared to VEH, as well as compared to HAL, IDAZ or DMI alone ($p < 0.05$). In particular, the combination group differed significantly from VEH on days 3–10, 15, 17, 19 and 22; from HAL alone on days 2–11, 13–19 and 22; from DMI alone on days 8, 13 and 22; and from IDAZ alone on days 2–10, 13–17 and 19–22 ($p < 0.05$). Interestingly, while HAL and DMI alone were not significantly different from VEH, they did differ significantly from each other, possibly due to a somewhat transient reduction seen in alcohol drinking with DMI alone combined with a potential increase in alcohol drinking due to HAL alone.

3.2. Combination of low dose haloperidol, idazoxan and desipramine significantly reduces alcohol preference

A two-way repeated measures ANOVA (RMANOVA) indicated no effect of time, but a significant effect of treatment $F(6, 33) = 12.465$, $p < 0.001$, and no time by group interaction, on alcohol preference (Fig. 1B). Post-hoc pairwise comparisons showed that the combination of HAL, IDAZ and DMI resulted in significantly lower alcohol preference compared to VEH, as well as compared to HAL, IDAZ or DMI alone ($p < 0.05$).

3.3. Combination of low dose haloperidol, idazoxan and desipramine increases water intake, but does not alter food-intake or body-weight

First, a two-way repeated measures ANOVA (RMANOVA) indicated a significant effect of time $F(22, 660) = 1.823$, $p < 0.05$, a significant effect of treatment $F(6, 30) = 16.607$, $p < 0.001$, but no time by group interaction, on water intake (Fig. 1C). Post-hoc pairwise comparisons showed that the combination of HAL, IDAZ and DMI resulted in significantly higher water intake compared to VEH, as well as compared to HAL, IDAZ or DMI alone ($p < 0.05$). These results suggest a compensatory increase in water drinking in response to a decrease in alcohol drinking, consistent with our previous studies in the hamster (Chau et al., 2010; Green et al., 2004).

Second, a two-way repeated measures ANOVA (RMANOVA) indicated a significant effect of time $F(132, 770) = 5.848$, $p < 0.01$, but