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Binge-like ingestion of a combination of an energy drink and alcohol leads to cognitive deficits and motivational changes

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ABSTRACT

The combination of alcohol with an energy drink (ED) is believed to contribute to risky alcohol-drinking behaviors, such as binge drinking. However, the long-term effects on cognition and reward function that are caused by the repeated binge-like ingestion of alcohol and EDs are still poorly known. The present study examined the effects of a history of repeated exposure to alcohol and/or an ED on short-term memory and alcohol-seeking behavior. Male Wistar rats were given daily intragastric administration of alcohol (3.4 g/kg) combined or not with an ED (10.71 ml/kg) for 6 consecutive days. The rats were tested for locomotion 15 min after the first intragastric treatment. Short-term memory was assessed in the novel object recognition and social discrimination tests 2–3 days after the last intragastric administration. The rewarding effect of alcohol was tested 1–3 weeks following the last intragastric administration in a conditioned place preference paradigm. The acute binge-like ingestion of alcohol decreased locomotor activity, whereas the combination of alcohol and an ED increased locomotion in the first minutes of assessment. Alcohol exposure produced cognitive deficits in both the object recognition and social discrimination tests, and adding the ED to the alcohol solution did not modify these effects. The combination of alcohol and the ED increased alcohol-induced conditioned place preference. Thus, a history of binge-like alcohol exposure combined with the ED caused subsequent cognitive deficits and increased alcohol seeking behavior, and such behavioral effects might contribute to the progression to alcohol abuse disorders.

1. Introduction

Binge drinking, which can result in blood alcohol levels of 0.08 g/dl within 2 h, has been popularized worldwide in recent decades. This drinking pattern has been shown to produce cognitive deficits and motivational alterations following repeated alcohol exposure (Bechara et al., 2001; Harper and Matsumoto, 2005; Stephens and Duka, 2008; Sprow and Thiele, 2012; Cippitelli et al., 2014; Townshend et al., 2014). The combination of alcoholic beverages and energy drinks (EDs) has been suggested to favor binge drinking because of increased palatability (e.g., the sweet taste) and the common misconception that EDs antagonize the depressant effects of alcohol.

Energy drinks contain several substances that can potentially affect behavior, including caffeine, taurine, inositol, sugars, vitamin B, and glucuronolactone. Caffeine has been reported to enhance cognitive performance, prevent memory impairments (Takahashi et al., 2008; Duarte et al., 2009; Cunha and Agostinho, 2010; Espinosa et al., 2013), and potentiate alcohol-induced dopamine release (Ferré, 1997; Ferré and O'Brien, 2011). Taurine appears to decrease alcohol aversion in rats that are given high doses of alcohol (Aragon et al., 1992; Quertemont et al., 1998; Olive, 2002). Furthermore, taurine decreases glutamatergic excitotoxic effects and prevents cellular death (El Idrissi and Trenkner, 1999; Wu and Prentice, 2010). Therefore, we hypothesized that the addition of an ED to an alcohol solution would prevent alcohol-induced cognitive deficits while increasing sensitivity to its rewarding effects.

The goal of the present study was to test alcohol abstinence-associated changes in short-term memory and rewarding effects in animals that were exposed to a binge-like pattern of administration of alcohol combined or not with an ED.

2. Materials and methods

2.1. Animals

Ninety-eight adult (8–9 weeks old) and five juvenile (21–28 days old) male Wistar rats were obtained from the Federal University of Santa Catarina animal facility and maintained in collective plastic cages (five rats per cage) in a room with controlled temperature (21 ± 2 °C) and under a 12 h/12 h light/dark cycle (lights on at 7:00 AM). Chow and water were freely available except during

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behavioral testing. The local Committee on Animal Care and Use approved all of the procedures (protocol no. PP00816/CEUA).

2.2. Drugs

Alcohol (99.5%, v/v, Synth, SP, Brazil) was diluted in tap water or an energy drink (Red Bull) to a final concentration of 40% (w/v). For conditioned place preference (CPP), alcohol was diluted with saline to 15% (w/v).

2.3. Intragastric treatment

This protocol was adapted from Kuzmin et al. (2012). The rats were fasted for 3 h and given alcohol (3.4 g/kg) daily by gavage combined or not with the ED (10.71 ml/kg; Ferreira et al., 2004) for 6 consecutive days. This dose of alcohol has been shown to yield blood alcohol levels > 0.15 g/dl (Walker and Ehlers, 2009) and cause cognitive deficits following repeated alcohol exposure (Kuzmin et al., 2012). The control group received equivalent volumes of tap water via intragastric administration.

2.4. Locomotor activity

Activity cages (Insight, São Paulo, Brazil) were used to evaluate horizontal locomotion (crossovers). The equipment consisted of an acrylic square box (50 × 50 × 48 cm) that was placed on a metallic base equipped with 16 infrared photocells positioned around the box. A computer that was linked to the activity cages recorded the speed and distance traveled. The rats were individually placed in the center of the cage 15 min after fluid administration on day 1. Locomotion was assessed for 30 min in a dimly lit room (~10 lx).

2.5. Object recognition test

This protocol was adapted from Pires et al. (2009) to assess short-term memory function. The experiment was performed over 2 days, starting on the second day after the last intragastric administration (i.e., memory assessment occurred on the third day following the last alcohol exposure). Each animal was individually habituated to an open field (100 cm × 100 cm, made of wood and covered with a thick plastic layer) for 10 min, 24 h prior to the first presentation of the objects (A and A′). The time spent touching or sniffing objects A and A′ was recorded for 5 min. The animals were returned to their home cages for 30 min and then placed back in the open field for the object recognition test (B and A) for another 5 min. Objects A and A′ were identical plastic bottles with some transparency, whereas object B was opaque, had a different color, and had a slightly different shape from object A. Both objects were placed 20 cm away from the walls and parallel to each other. The test was conducted in a dimly lit room (~10 lx). The discrimination index was calculated according to the following equation: discrimination index = [(exploration time [s] of novel object)/(exploration time [s] of novel + familiar objects)] × 100.

2.6. Social discrimination test

This test was based on Watson et al. (2012) and also used to assess short-term memory function. Twenty-four hours after the last intragastric administration, the rats were individually housed until testing. The test was conducted on the third day following the last intragastric administration and consisted of two steps. First, a juvenile rat, marked on the tail, back, or head with black dye, was placed in the adult rat cage for 5 min (juvenile 1). The time spent sniffing or following the juvenile rat by the adult rat was recorded. Thirty minutes later, the familiar juvenile rat and a novel juvenile rat were simultaneously placed into the adult rat cage for 5 min (juvenile 2). The test was conducted in a dimly lit room (~10 lx). The social discrimination index was calculated according to the following equation: discrimination index = [(investigation time [s] of novel juvenile)/(investigation time [s] of familiar + novel juvenile)] × 100.

2.7. Conditioned place preference

This protocol was adapted from Pandolfo et al. (2009). The test was performed between 1–3 weeks following the last intragastric administration. The apparatuses consisted of four identical rectangular wooden boxes covered with Formica, composed of three compartments: two larger compartments (30 cm × 25 cm × 40 cm) with distinct visual and tactile stimuli and a smaller central compartment (15 cm × 25 cm × 40 cm). Openings on the walls of the central compartment provided access to the larger compartments. The time spent in each compartment was recorded for 10 min and used to calculate the index of preference: Δ time spent (s) in the alcohol-paired compartment in the pre- and postconditioning trials. The protocol lasted a total of 13 days: 2 days preconditioning (the time spent was based on second-day exploration), 10 days conditioning (5 days with alcohol and 5 days with saline), and 1 day postconditioning. During the pre- and postconditioning trials, the animals had access to all of the chambers. The conditioning trials consisted of administering 1 g/kg alcohol (15%, w/v, i.p.) alternated with saline (i.p.) every 24 h. Alcohol conditioning was performed in the least-preferred compartment. The rats that showed baseline preference (≥85%) or aversion (≤15%) for any of the compartments were excluded from the experiment (De Carvalho et al., 2010). In our experimental conditions, we know that 20 conditioning trials with alternate injections of alcohol (1 g/kg) and saline are needed to produce significant CPP (De Carvalho, unpublished data). Because our hypothesis was that the binge-like ingestion of alcohol mixed with the ED would increase the rewarding effects of alcohol, we adapted the protocol to "suboptimal" CPP conditions (i.e., only 10 conditioning trials).

The same rats that were used for the memory tests were subsequently used for CPP. All of the animals were randomly split into two subgroups. Half of the animals received injections of saline in both compartments throughout the conditioning trials to verify that the previous procedures and testing (i.e., intragastric treatment and memory tests) had no effect on CPP. The other half of the animals received injections of alcohol in one compartment alternated with saline in the other compartment of the apparatus for conditioning. The sessions were performed in a dimly lit room (~10 lx).

2.8. Statistical analysis

All of the results are expressed as mean ± SEM. One- or two-way analysis of variance (ANOVA) with or without repeated-measures was used to analyze the data as described in each test. When a significant effect or interaction was found in the ANOVA, multiple comparisons were performed using the Bonferroni post hoc test. The accepted level of significance for all of the tests was $p \leq 0.05$. All of the statistical analyses were performed using GraphPad Prism 6.0 software.

3. Results

Fig. 1 shows the effects of acute treatment (i.e., first intragastric administration) with alcohol and/or the ED on locomotor activity. The repeated-measures ANOVA revealed a significant time × group interaction for distance traveled ($F_{15,225} = 4.7$, $p < 0.0001$; Fig. 1A) and locomotion speed ($F_{15,225} = 4.7$, $p < 0.0001$; Fig. 1B). The post hoc comparisons indicated that the rats that received alcohol + ED exhibited increases in distance and speed in the first 5 min of testing compared with all of the other groups ($p < 0.05$). Rats that received the ED only exhibited increases in distance and speed from 10 to 25 min compared with rats that received alcohol only ($p < 0.05$).