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Research article

Behavioral effects of the combined use of alcohol and energy drinks on alcohol hangover in an experimental mice model

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ABSTRACT

In last few years it has been a significant increase in the consumption of alcohol combined with energy drink. The aim of this work was to study the effect of this mixture in motor and affective behaviors during an alcohol hangover episode. Male Swiss mice received one of the following treatments: saline + sucrose; saline + energy drink; ethanol + sucrose; ethanol + energy drink. Ethanol dose was 3.8 g/kg BW (i.p.) and energy drink dose was 18 ml/kg BW (gavage) at ZT1 (8 am) (ZT: Zeitgeber time; ZT0: 7 am; lights on). The behavioral tests used were tight rope test to determine motor coordination; hanging wire test to study muscular strength; elevated plus maze and open field tests to evaluate anxiety like-behavior and locomotor activity. Tests were carried out at basal point that matched with lights onset and every 6 h up to 18 h after treatments. Hangover onset was established at ZT7 when blood alcohol concentration (BAC) was almost zero. Our results showed that the mixture of alcohol and energy drink altered significantly motor skills. Specifically, a significant decrease was observed in the performance of the animals in the tightrope and hanging wire tests in groups treated with the mixture of alcohol and energy drink. A significant impairment in the anxiety-like behavior was observed mainly at the beginning of alcohol hangover. These findings suggest that energy drink added to alcohol extends motor disabilities observed during an alcohol hangover episode in comparison with animals that received alcohol alone.

1. Introduction

Mixing alcohol with highly caffeinated energy drinks (AmED) has become increasingly popular among teenagers and young adults due to the prevailing view that the stimulant properties of energy drinks (ED) decrease the depressant effects of alcohol, leading individuals to believe they are less drunk and can drink more or for longer periods of time [1,2]. AmED may produce a false sense of confidence that induces to the drinker to carry out risk tasks [3–5]. Thus, the co-consumption of ED and alcohol has become a topic of concern and an increasingly important public health problem [6,7].

Alcohol hangover (AH) refers to the combination of cognitive and physical symptoms experienced the day after a single episode of heavy drinking, starting when blood alcohol concentration approaches zero [8,9]. Otherwise, the effects of alcohol hangover could overlap with withdrawal symptoms [9,10]. The hangover is an important issue in light of ED and alcohol co-use because cognitive, emotional and motor functions are negatively affected during AH with significant individual, social and economic consequences [11,12]. In this sense, perhaps the most important aspect is that adolescents believe that ED and alcohol co-use mitigates hangover symptoms which could play a role in motivation to consume this mixture, highlighting that this age group may be at particularly high risk for consequences arising from AmED consumption[13]. Interestingly, Costa et al. [14] have reported that more than a third of ED Australian adolescent consumers (12–18 years) exceed the daily limit of ED considered appropriate for adults (two standard ED/day). In addition, the amount of ED consumed was positively correlated with the presence of negative physiological symptoms and adolescents risk taking.

In humans, AH is characterized by headache, thirst, nausea, vomiting, tremors, diarrhea, sleepiness, fatigue, diminution in motor coordination and impaired cognitive functioning [15–17]. In addition, it has been suggested that other alterations such as dehydration, electrolyte imbalances, hypoglycemia, sleep and biological rhythm disturbances are produced by AH [15,18–20]. AH physiopathology is unknown and although several articles discuss a number of hypotheses it remains unclear. Acetaldehyde, the principal metabolite of ethanol, has been suggested as one of the causes of perturbations observed during AH [18]. Maxwell el al. [21] proposed that acetate is responsible of AH headache throughout inflammatory mechanism.

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In experimental animal models it has been demonstrated that during AH there is a decrease in neuromuscular coordination, motor strength and locomotion together with gait variability and slowness in exploratory activity [22]. Also, anxiety-like behavior together with fear related phenotype and depression signs have been shown [23]. Bustamante et al. [24] have related motor performance alterations with mitochondrial dysfunction during AH in mice. Greater locomotor activity, increased anxiety-like behavior, lost their righting reflexes sooner and poorer motor coordination, were observed in mice treated with AmED indicating that alcohol-induced deficits are aggravated by ED [25]. The combined administration of alcohol and ED may trigger rewarding effects in mice that were not stimulated by alcohol alone [26]. Preclinical studies in rodents indicated that adolescents may respond differently than adults to the combination of alcohol with ED. In these sense, adolescent ED consumption was not correlated with changes in adult alcohol intake or preference, suggesting that exposure to large amounts of caffeine does not alter future alcohol intake [27]. In addition, Fritz et al. [28] have reported that caffeine increased binge consumption of alcohol in adolescent and adult mice, but produced additive motor stimulation only in adolescent animals and also later alcohol intake and preference was not influenced by prior consumption history.

On this basis, the aim of the present study was to describe the motor and anxiety-like behavior effects of the AmED when BAC is closed to zero (onset of alcohol hangover). Specifically, we studied the effects of alcohol alone or mixed with ED at high dose on the spontaneous locomotor activity and anxiety-like behavior in mice. For this propose, tightrope, hanging wire, open field and elevated-plus maze (EPM) tests were used to evaluate the interaction produced by the AmED still when the amount of ED consumed exceeds the daily limit considered appropriate for adults.

2. Materials and methods

2.1. Animals

Male Swiss mice (Mus musculus) weighing 30–40 g were acquired from the School of Biochemistry, University of Buenos Aires, and housed in a soundproof room under conditions of controlled temperature (22 ± 2 °C) and humidity, with a 12:12 h light/dark cycle. Standard mice chow and tap water were provided *ad libitum*.

Animal handling, treatments and experimental procedures were reviewed in accordance with the guidelines of the National Institutes of Health (USA) and with Regulation 6344/96 of Argentina's National Drug, Food and Medical Technology Administration (ANMAT). Moreover, the present study had the legal ethical accreditation from Ethics Committee for Laboratory Animal Handling of the School of Medicine from University of Buenos Aires (CICUAL) where the protocol was performed. All efforts were made to minimize suffering and reduce the number of animals used.

2.2. Drugs and experimental procedure

We used Red Bull®, a widely consumed and advertised ED, which composition, according to the manufacturer is:100 ml of Red Bull has 11.3 g of sucrose and glucose, 400 mg of taurine, 32 mg of caffeine, 240 mg of gluconolactone, 20 mg inositol, 7.2 mg of niacin, 2.4 mg of pantenol, 0.4–0.8 mg of vitamins B2/B6/B12, citric acid, caramel coloring, artificial flavoring and sparkling water. ED was administrated by gavage in a dose of 18 ml/kg BW. ED dose was chosen to exceed the daily limit considered appropriate for adults and was calculated considering the injected dose of alcohol and the amount of ED necessary to achieve a relationship between ED and alcohol equivalent to that used by Ferreira et al. (2.4 g/kg EtOH: 10.71 ml/ kg ED) [26]. Ethanol (EtOH) was used at a concentration of 15% (3.8 g/kg BW, i.p.). EtOH dose was previously applied in alcohol-induced hangover animal models [22–24]. The sucrose solution was given by gavage at a dose of 18 ml/kg BW (8.03 kilocalories/kg, isocaloric respect to ED). Animals were randomly divided in four groups: SAL (saline) + SS (Sucrose solution); EtOH + SS; SAL + ED; EtOH + ED. It is important to note that although human beings consume the mixture orally, under our experimental conditions it was not possible. Previously, we had conducted a pilot test and observed that the volume of the mixture required achieving the desired dose of alcohol and energy drink exceeded mice stomach capacity [29] and most of animals showed a backflow of the mixture. This very important physical limitation prevented us to administer the ED by gavage.

2.3. Determination of the onset of hangover

In order to determine the animal's response to ethanol and the onset of hangover, blood alcohol concentrations (BAC) were evaluated for each group of animals. They were decapitated 60, 180 or 360 min after the injection (n = 5 each time point). Blood was collected from the trunk and was measured by gas chromatography. Experiments were conducted in the morning (9:00 am). The criteria used to establish the onset of AH was when BAC was less than or equal to 10% of the maximum value reached.

2.4. Behavioral assessments

Treatments were administrated one hour after lights on: ZT1 (8 am) (ZT: Zeitgeber time). Behavioral tests were carried out at a basal point that matched with lights onset (ZT0: 7 am, 1 h before treatment) and every 6 h after treatment: ZT7 (2.00 pm, when AH began), ZT13 (8 pm, 12 h after treatment) and ZT19 (2 am, 18 h after treatment). (See Fig. 1). Each subject was tested every 6 h in only one behavioral test avoiding multiple tasks for animal groups. Motor performance, motor strength, locomotion and anxiety like-behavior were evaluated at specific times described above, using a battery of different behavioral tests. During experimental procedures, test boxes or the apparatus used for behavioral studies were cleaned with 10% EtOH solution after every individual test session to prevent the next mouse from being influenced by the odors deposited in the urine and feces of the previous mouse.

2.5. Tightrope test

Motor coordination was evaluated with a modified tightrope test [30]. Briefly, the procedure consisted in placing the animal on the middle of a 60 cm long horizontal rope suspended 30 cm above the floor and time was recorded until the animal either reached the end of the rope or fell down during a period of 60 s. A score was assigned accordingly: animals reaching the end of the rope in ≤6 s were given 1 point and an additional point was given for every additional 6 s needed to complete the test. Animals that stayed on the rope for 60 s without reaching the end obtained 11 points. When mice fell down, while test was running, 11 points were assigned and 1 extra point was added for every 6 s before the test ending time (60 s). The test evaluates the motor performance of the animal as a mean of its intrinsic neuromuscular

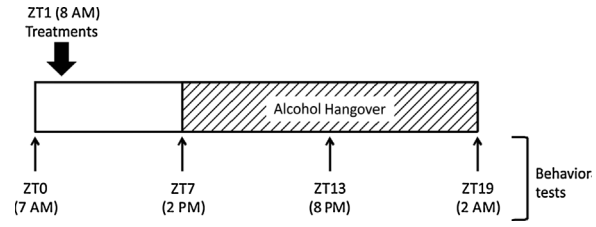

Fig. 1. Timeline and experiments Male mice received different treatments at 8:00 AM. Behavioral tests were performed before (ZT0) and after treatment: ZT7 (when alcohol hangover began), ZT13 and ZT19. Real time figure between brackets. ZT: Zeitgeber time; ZT12: 7:00 PM lights off; photoperiod 12:12 l:D.

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