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$GABA_B$ receptor agonist only reduces ethanol drinking in light-drinking mice

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ABSTRACT

Baclofen, a $GABA_B$ agonist, reduces ethanol intake in animals and humans, but the contrary or no effect was also reported. Our previous study demonstrated that mice characterized as “loss of control over ethanol intake” had different Gabbr1 and Gabbr2 transcription levels, which express, respectively, the $GABA_{B1}$ and $GABA_{B2}$ subunits in brain areas related to addictive behavior. In the present study, we tested baclofen on ethanol intake in mice exposed to the free-choice paradigm. Adult male Swiss mice, individually housed, had free access to three bottles: ethanol (5% and 10%) and water. The protocol had four phases: acquisition (AC, 10 weeks), withdrawal (W, 4 cycles during 2 weeks of 2 day-free-choice and 2 day-only-water), reexposure (RE, 2 weeks), and adulteration of ethanol solutions with quinine (AD, 2 weeks). Mice characterized as “loss of control” (A, $n=11$, preference for ethanol in AC and maintenance of ethanol intake levels in AD), heavy (H, $n=11$, preference for ethanol in AC and reduction of ethanol intake levels in AD), and light (L, $n=16$, preference for water in all phases) drinkers were randomly distributed into two subgroups receiving either intraperitoneal injections of all doses of baclofen (1.25, 2.5, and 5.0 mg/kg, given each dose twice in consecutive days) or saline, being exposed to free-choice. Fluid consumption was measured 24 h later. Baclofen reduced ethanol intake in group L. In group H a reduction compared to AC was observed. Group A maintained their high ethanol intake even after baclofen treatment. Activation of the $GABA_B$ receptor depends on the precise balance between the $GABA_{B1}$ and $GABA_{B2}$ subunits, so the disproportionate transcription levels, we reported in group A, could explain this lack of response to baclofen. These data highlight the importance to test baclofen in individuals with different ethanol drinking profiles, including humans.
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1. Introduction

The modulatory role of the γ-aminobutyric acid (GABA) system, mainly $GABA_B$ receptors, has recently been related to addiction. Numerous observations indicate that the tonic activation of $GABA_B$ receptors abolishes the reinforcement effects of morphine, cocaine, and ethanol (Brebner et al., 2002; Filip et al., 2007; Maccioni et al., 2008). However, selective antagonists of these receptors did not alter the dose range of intravenously self-administered cocaine (Filip et al., 2007) or the expression of morphine-induced place preference (Tsuji et al., 1996). The role of increased dopamine in the nucleus accumbens in rewarding and locomotor effects of several drugs of abuse are well established (Koob and Bloom, 1988). Some evidence suggests the involvement of $GABA_B$ receptor in controlling dopamine efflux in the nucleus accumbens: the systemic administration of baclofen, a selective $GABA_B$ receptor agonist, decreased nucleus accumbens dopamine efflux in rats trained to self-administer amphetamine (Brebner et al., 2005) by a mechanism involving the stimulation of $GABA_B$ receptors located on cell bodies in ventral tegmental area (VTA) dopamine neurons that project to the nucleus accumbens (Liang et al., 2000).

Numerous preclinical and clinical studies have demonstrated that $GABA_B$ receptor agonists suppress ethanol-related behaviors (Addolorato et al., 2000, 2002; Bechtholt and Cunningham, 2005; Colombo et al., 2000, 2002, 2003a, 2003b; Knapp et al., 2007; Heilig and Egli, 2006; Maccioni et al., 2005, 2008; Moore and Boehm, 2009; Walker and Koob, 2007). For example, in rats, baclofen inhibited the acquisition of ethanol consumption and the ethanol-induced conditioned place preference, decreased ethanol-induced motivational properties and withdrawal symptoms (such as anxiety-related behaviors), promoted abstinence, increased ethanol intake in a drinking-in-the-dark procedure, and reduced ethanol consumption in Sardinian ethanol-preferring rats. Although most data have shown that baclofen suppresses ethanol consumption, few studies in animals have reported that specific doses of baclofen increased ethanol self-administration (Czachowski et al., 2006; Petry, 1997) and ethanol intake (Smith et al., 1992, 1999). Although ethanol consumption was increased in C57BL/6J mice after repeated baclofen administration in the drinking-in-the-dark procedure (Moore et al., 2007), when microinjection of

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baclofen was administered into the anterior ventral tegmental area a reduced binge-like ethanol intake was observed in the same strain (Moore and Boehm, 2009). In humans, a recent clinical study reported no effect of baclofen treatment on ethanol consumption (Garbutt et al., 2010), although recently Muzyk et al. (2012) reported that patients treated with baclofen experienced higher rates of abstinence and lower anxiety scores.

Our previous study showed that the genes that encode the $GABA_{B1}$ and $GABA_{B2}$ subunits (*Gabbr1* and *Gabbr2*, respectively) were differentially expressed only in mice that continued consuming ethanol in large quantities even when adding quinine to ethanol solutions (named here as "loss of control" mice or group A) using this same three-bottle free-choice paradigm (Ribeiro et al., 2010, 2012). Only mice classified as group A showed increased *Gabbr1* and *Gabbr2* transcription levels in cerebral areas proposed to be related to drug taking and drug seeking (Kalivas and Volkow, 2005; Everitt and Robbins, 2005) suggesting that these genes may be related to ethanol addiction.

Considering that (*i*) $GABA_B$ receptors appear to be involved in ethanol related behaviors, (*ii*) some discrepancies have been reported in the literature concerning the relationship between $GABA_B$ receptors and ethanol consumption, (*iii*) differences in *Gabbr1* and *Gabbr2* transcription levels were found in mice with different ethanol intake phenotypes, and (*iv*) our validated ethanol consumption model provides an alternative approach to the study of addictive behaviors, the present study investigated the effect of baclofen treatment on ethanol consumption in mice with different intake profiles.

2. Material and methods

2.1. Animals

Seventy locally bred, naive, male Swiss mice weighing 20–30 g and aged 45 days at the beginning of the experiment were housed individually in cages measuring 20 × 30 × 20 cm in a temperature-controlled room (22 ± 2 °C) maintained on a 12 h/12 h light/dark cycle (lights on at 0700 h). Food was available *ad libitum* (Purina Laboratories, Brazil). The animals were weighed weekly. The experiment began after a 1-week acclimation period. All animal maintenance, care, and treatment procedures were controlled and approved by the Ethics Committee for Animal Experimentation of the Setor de Ciências Biológicas, Universidade Federal do Paraná (process no. 23075.105451/2009-19; approved November 10, 2009).

2.2. Drugs

Ethanol solutions (10% and 5%, v/v) were prepared for oral administration by diluting ethanol P.A. (Vetec Laboratories, Bronx, NY, USA) with tap water every other day (to control for ethanol evaporation). Adulterated ethanol solutions were prepared with 0.005 g/L of quinine hydrochloride. Baclofen hydrochloride solutions (RBI, Natick, MA, USA) were prepared for intraperitoneal administration by diluting with saline (0.1 mL/10 g).

2.3. Experimental design

2.3.1. Extended chronic ethanol intake

A group of mice ($n = 60$) had 24 h access to three bottles (inverted 25 mL graduated cylinder with sipper tube) containing 10% and 5% (v/v) ethanol and tap water for 10 weeks (acquisition phase, AC). Over the next 2 weeks, mice were submitted to four cycles of ethanol withdrawal (withdrawal phase, W), consisting each cycle of 2 days with access to water (W1, W2, W3 and W4) followed by 2-day free access to ethanol solutions and water (aW1, aW2 and aW3). For the following 2 weeks, they again had free access to the ethanol solutions and water (reexposure phase, RE). At the end of this period, the ethanol solutions were adulterated with quinine and offered to the animals for a further 2-week period (adulteration phase, AD). The quinine concentration (0.005 g/L) was chosen based on dose–response curve data previously performed in our lab (Fachin-Scheit et al., 2006) and recently confirmed by us (data not shown here). The analysis of the dose–response curves showed that 0.005 g/L reduced significantly the water intake when quinine was added without causing a total inhibition of intake, while higher concentrations (0.01 and 0.05 g/L) caused totally inhibition, *i.e.* a ceiling effect The positions of the bottles were changed on alternate days when the fluid intake was measured volumetrically. A separate group of ethanol naive control animals ($n = 10$) only had access to water. At the end of the exposition to the 3-bottle free choice paradigm, the mice were classified into groups based on their individual patterns of ethanol preference and consumption. Firstly, we evaluated the preference between total ethanol intake (mL) and water consumption during each phase for each mouse. Those mice preferring water during all phases were classified as "light-drinker" (group L). Those mice preferring ethanol during AC were, then, evaluated regarding their individual ethanol consumption (g/kg/day) along the phases: those ones maintaining [*i.e.*, no significant decrease] the ethanol intake when ethanol solutions were added quinine (AD phase) were classified as "loss of control" (group A); and those ones with decreased ethanol consumption during the AD phase compared to AC phase were classified as "heavy-drinker" (group H). The animals that did not conform strictly to any of these patterns were excluded from subsequent analyses.

2.3.2. Baclofen treatment

Firstly, we assessed the effect of baclofen on the ambulation in open field test in the dose range of 0.6–10.0 mg/kg (dose–response curve). Naïve male Swiss mice (15/dose) received acutely i.p. injections of baclofen (0.6; 1.25; 2.5; 5.0 or 10.0 mg/kg) or saline 30 min before their exposition to the open field test accordingly to the methodology described by Boerngen-Lacerda and Souza-Formigoni (2000). Each animal was placed in the center of the arena and its ambulation in the central area and in the peripheral area (number of squares invaded) was recorded for 5 min. From the obtained curve we chose the three doses used to treat the classified groups.

After the last day of the AD phase, the animals spent 4 days in abstinence, with access only to water. After the classification of mice, they were randomly distributed to receive either: (I) baclofen (each animal received i.p. injections of all doses of baclofen: B1.25 = 1.25 mg/kg, B2.5 = 2.5 mg/kg, B5.0 = 5.0 mg/kg) or (II) saline (SAL; each animal received i.p. saline injections during the period of baclofen treatment). Each animal assigned to the baclofen treatment (I) received all baclofen doses administered using a Latin square design. Each dose was administered twice on 2 consecutive days, and mice had free access to ethanol and water. Between the administrations of the different doses, an interval of 4 days was given, during which the animals had access only to water. The saline-treated mice (II) were subjected to the same conditions and the same experimental design as the baclofen-treated groups, except the baclofen treatment. Access to the solutions of ethanol and water (free-choice) was allowed 30 min after the injection of baclofen or saline. Ethanol and water consumption was then quantified after 24 h of the injection. The 10 animals from the ethanol naive control group were randomly distributed into two groups designated to receive the same doses of baclofen and then to have access only to water (III) or to 3-bottle free choice (IV). The procedure (I) was designed to assess the baclofen effect on ethanol intake in each different intake-profile group; the procedure (II) to assess the saline effect on ethanol intake in each different intake-profile group; the procedure (III) to assess the baclofen effect on water intake in a control group and the procedure (IV) to assess the baclofen effect on initial ethanol intake in a control group.

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