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Positive allosteric modulation of the $GABA_B$ receptor by GS39783 attenuates the locomotor stimulant actions of ethanol and potentiates the induction of locomotor sensitization

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ABSTRACT

Acute ethanol-induced locomotor stimulation and ethanol-induced locomotor sensitization are two behavioral assays thought to model the rewarding effects of ethanol. Recent evidence suggests that GS39783, a $GABA_B$ positive allosteric modulator, may be effective at reducing both the rewarding and reinforcing effects of several drugs of abuse, including ethanol. The goal of this study was to determine if GS39783 was capable of altering acute ethanol-induced stimulation, and the induction and expression of ethanol-induced locomotor sensitization, without effecting basal locomotion levels. Several doses of GS39783 (ranging from 0 to 100 mg/kg, depending on experiment) were tested on adult male DBA/2J mice in four experiments using 3-day basal locomotion and acute ethanol stimulation paradigms, and 14-day induction and expression of ethanol sensitization paradigms. The results of experiment 1 are in agreement with current literature, suggesting that 30 mg/kg doses of GS39783 and lower do not alter basal locomotor activity. In experiment 2, we found that GS39783 significantly decreased acute ethanol stimulation, but only at the 30 mg/kg dose, supporting our hypothesis and other publications suggesting that $GABA_B$ receptors modulate acute ethanol stimulation. Contrary to our hypothesis, GS39783 did not alter the expression of locomotor sensitization. Additionally, repeated administration of GS39783 in conjunction with ethanol unexpectedly *potentiated* ethanol-induced locomotor sensitization. Further study of GS39783 is warranted as it may be a more tolerable treatment for alcoholism than full agonists, due to its behavioral efficacy at doses that lack sedative side effects. Our results add to current literature suggesting that the $GABA_B$ receptor system is indeed involved in the modulation of ethanol-induced locomotor stimulation and sensitization.

Introduction

Understanding the neuroadaptive mechanisms underlying alcohol reinforcement and reward is an important step in finding therapeutic interventions to counter addiction. Ethanol-induced locomotor stimulation and sensitization models have been used to help elucidate the neuronal regions and pathways involved in addiction. In mice, acute administration of low-to-moderate doses of ethanol induce locomotor stimulation thought to model alcohol-induced euphoria in humans (Humeniuk, White, & Ong, 1993; Koob, 1992; Kornetsky, Bain, Unterwald, & Lewis, 1988; Wise & Bozarth, 1987). When ethanol is administered repeatedly, a robust enhancement in stimulation develops, a phenomenon known as locomotor sensitization (Lessov, Risinger, & Phillips, 2001; Phillips, Dickinson, & Burkhart-Kasch, 1994; Phillips, Huson, Gwiazdon, Burkhart-Kasch & Shen, 1995; Robinson & Berridge, 1993). The neural adaptations involved in locomotor sensitization are thought to modulate alcohol abuse, addiction, and relapse, likely due to an enhancement in the reinforcing and motivational aspects of ethanol (Grahame, Rodd-Henricks, Li, & Lumeng, 2000; Hunt & Lands, 1992; Lessov et al., 2001; Newlin and Thomson, 1991; Schoffelmeer, Vanderschuren, Mulder, Jacobs, & De Vries, 2000).

There are two components to drug-induced sensitization: the induction and expression of sensitization. The induction of sensitization refers to transient neuroadaptive changes that occur during acquisition of sensitization, whereas the expression of sensitization refers to long term neuroadaptive changes induced by repeated drug exposure (Camarini et al., 2010; Phillips et al., 1995; Robinson & Berridge, 1993). Many neurotransmitter systems, including dopamine, serotonin, GABA, corticotrophin releasing factor-1, opioids, and nicotinic acetylcholine, have been implicated in modulating the dissociation of neuroadaptive changes in the induction and expression of sensitization, but their specific actions

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still need to be further elucidated (Bhutada et al., 2010; Broadbent & Harless, 1999; Fee, Sparta, Picker, & Thiele, 2007; Kalivas & Stewart, 1991; Pastor & Aragon, 2006; Umathe et al., 2009).

The GABA receptor system, the central nervous system's major inhibitory neurotransmitter, is postulated as being highly involved in modulating ethanol reinforcement and reward (Koechling, Smith, & Amit, 1991; Vlachou & Markou, 2010). More specifically, $GABA_B$ receptors, located along the mesocorticolimbic ('reward') pathway, have been implicated in modulating the acute and chronic locomotor effects induced by ethanol (Boehm, Piercy, Bergstrom, & Phillips, 2002; Broadbent & Harless, 1999; Ludlow et al., 2009; Phillips & Shen, 1996). For example, when baclofen, a $GABA_B$ agonist, is systemically administered in the presence of ethanol, it has attenuating effects on ethanol-stimulated locomotor activity (Holstein, Dobbs, & Phillips, 2009; Phillips & Shen, 1996). Baclofen has also been found to modulate the induction, as well as expression of sensitization to the locomotor stimulant effects of ethanol (Broadbent & Harless, 1999). However, the clinical efficacy of baclofen might be limited due to sedative side effects (Humeniuk et al., 1993). For example, baclofen has been found to potentiate motor incoordination, muscle relaxation and sedation, as well as to reduce locomotor activity and responding for water (Besheer, Lepoutre, & Hodge, 2004; Holstein et al., 2009). Studies have also shown that tolerance to baclofen develops due to the desensitization of the $GABA_B$ receptor following repeated exposure (Gjoni & Urwyler, 2008; Lehmann, Mattsson, Edlund, Johansson, & Ekstrand, 2003). Thus, pharmacological tools that indirectly facilitate the action of $GABA_B$ receptors might be useful tools used to target this receptor system, while minimizing side effects.

The $GABA_B$ positive allosteric modulator N,N′-dicyclopentyl-2-methylsulfanyl-5-nitropyrimidine-4,6-diamine (GS39783) is thought to be one such pharmacological tool (Urwyler et al., 2003). $GABA_B$ positive allosteric modulators act by binding at sites distinct from the active binding sites of endogenous GABA, and can act synergistically with receptor agonists by increasing the affinity of the $GABA_B$ receptor for GABA (Adams & Lawrence, 2007; Gjoni & Urwyler, 2008; Orru et al., 2005; Urwyler, Gjoni, Koljatic, & Dupuis, 2005). For example, studies have shown that when baclofen and GS39783 are administered together, the efficacy and potency of baclofen is greatly potentiated (Adams & Lawrence, 2007). However, when GS39783 is administered in the absence of exogenous $GABA_B$ activating compounds (ie. ethanol or baclofen), it typically exhibits no intrinsic activity (Adams & Lawrence, 2007; Pin & Prezeau, 2007). In concordance with this notion, studies have shown GS39783 to have no effect on locomotor activity or body temperature when administered alone (Cryan et al., 2004); decreased locomotor activity and hypothermia are side effects of baclofen (Besheer et al., 2004; Cryan et al., 2004). Finally, tolerance does not appear to develop to GS39783 following repeated use, due to its inability to induce desensitization of $GABA_B$ receptors (Gjoni & Urwyler, 2008; Lehmann et al., 2003).

Interestingly, GS39783 has been found to dose-dependently decrease ethanol consumption, ethanol self-administration, and responding for ethanol in rats (Maccioni et al., 2007, 2008). Furthermore, GS39783 has been shown to dose-dependently decrease acute cocaine-induced stimulation, and moderately attenuate the induction and expression of cocaine-induced locomotor sensitization in mice (Lhuillier et al., 2007). However, to our knowledge, no studies have tested the effects of GS39783 on acute ethanol-induced stimulation, or the induction and expression of ethanol-induced locomotor sensitization in mice. Therefore, the goal of this study was to test the effects of GS39783 on acute ethanol-induced locomotor stimulation, as well as the induction and expression of locomotor sensitization, using a well-established behavioral model in mice (Boehm et al., 2002; Holstein et al., 2009; Linsenbardt & Boehm, 2010; Phillips et al., 1994). We hypothesized that GS39783 would dose-dependently attenuate locomotor stimulation, while exhibiting no effects on basal locomotor activity. We also expected to see an attenuation of both the induction and expression of sensitization induced by ethanol.

Materials and methods

Animals

One-hundred and sixty-four 56 day old male DBA/2J mice, purchased from Jackson Laboratories (Bar Harbor, ME), were used in this study. Mice were housed four to a cage, and allowed one week to acclimate to the vivarium before the beginning of each experiment. The vivarium was maintained on a 12 h light/dark cycle with lights off at 7:30 PM. During the entire length of the experiments, all mice were given free access to both water and food (LabDiet 5001 rodent diet) except during behavioral testing. All procedures were approved by the Purdue School of Science Animal Care and Use Committee, and the use of animals followed the Guide for the Care and Use of Laboratory Animals (National Academic Press, 2003).

Ethanol administration

One-hundred and ninety proof ethanol obtained from Pharmco, Inc (Brookfield, CT) was diluted in sterile 0.9% saline solution to a concentration of 20% v/v. This ethanol solution was administered through intraperitoneal (ip) injections in doses of 2.0 and 2.5 g/kg.

Drugs

GS39783 was purchased from Sigma–Aldrich (St. Louis, MO) and suspended in 30 μl Tween 80 and physiological saline in order to create the seven doses (1, 3, 5, 10, 30, 50 and 100 mg/kg) of GS39783 used throughout our experiments. Tween 80 constituted 0.6% of the total solution volume for each dose. The 0 mg/kg (vehicle) dose, used as a control for GS39783, simply contained 30 μl of Tween 80 in physiological saline.

Locomotor activity chambers

Locomotor activity data was collected using the VersaMax Animal Activity Monitoring System (Accuscan Inst, Columbus, OH). Locomotion was detected by interruption of eight pairs of intersecting photocell beams (2 cm above the chamber floor) evenly spaced along the walls of the 40 × 40 cm test chamber. This equipment was situated in sound-attenuating box chambers (inside dimensions, 53 cm across × 58 cm deep × 43 cm high) equipped with a house light and fan for ventilation and background noise.

Experiment 1 — dose response

The purpose of experiment 1 was to test the effects of five doses of GS39783 on basal locomotor activity to find a maximally effective dose (for experiments 2–4) that would not alter basal locomotion, using a standard 3-day stimulation paradigm routinely employed in our lab (Boehm et al., 2002; Boehm, Goldfarb, Serio, Moore, & Linsenbardt, 2008; Linsenbardt & Boehm, 2010). On days 1 (habituation) and 2 (baseline), all mice received an ip saline injection and were then placed back into their home cages. Fifteen minutes later, each mouse was immediately placed into the locomotor activity chambers for 15 min during which time locomotor activity was recorded. On day 3, the mice were pseudo randomly divided into five groups ($n = 11$–12) based on day 2 locomotor activity levels.