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RESEARCH ARTICLE

Effect of coadministration of the $GABA_B$ agonist baclofen and the 5-HT_{2C} agonist Ro60-0175 on the expression of amphetamine-induced locomotor sensitization

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Abstract
$GABA_B$ and 5-HT_{2C} agonists are effective in attenuating the behavioral effects of psychostimulants. However, they induce adverse side effects when used in high doses. The previous evidence has suggested that the $5HT_{2C}$ receptor activation effect could be produced by an increased release of GABA in the ventral tegmental area (VTA) and the consequent activation of GABAergic receptors. Therefore, the objective of this study was to evaluate the effects of joint administration of an intermediate dose of the $GABA_B$ agonist baclofen (3.0 mg/kg) with different doses of the $5HT_{2C}$ agonist Ro60-0175 (0.3, 1.0, and 3.0 mg/kg) on the locomotor sensitization expression induced by the repeated administration of amphetamine (1.0 mg/kg). Our results showed an attenuation of the expression of sensitization in a dose-dependent manner with both agonists. In both cases, we observed a complete blockade at the highest dose. In addition, the intermediate dose of baclofen increased the effects of the three doses of Ro60-0175. These results support the role of the joint action of $GABA_B$ and 5-HT_{2C} receptors in the effects of psychostimulants. However, it remains to be explored whether the observed effect can be attributed to receptors located in the VTA or the nucleus accumbens.

Keywords Amphetamine · Locomotor sensitization · Baclofen

Introduction

At the neurobiological level, addictive drugs exert their effects by activating the brain reward system, whose primordial element is the mesolimbic dopaminergic pathway that projects from the ventral tegmental area (VTA) to the nucleus accumbens (nAcc). Psychostimulants such as amphetamine (AMPH) increase the release of dopamine (DA) in the nAcc through the action on DA transporters. There have been attempts to use DA antagonists as pharmacological treatments for addictions; however, because of the side effects associated with the direct manipulation of DA concentrations, alternatives with different mechanisms have been evaluated and involve the manipulation of other neurotransmitters systems with the possibility of indirectly regulating the dopaminergic pathway. Recent suggestions have included the activation of neurotransmitter systems, such as the GABA or serotonin systems.

The $GABA_B$ agonist baclofen (BCF) (2.5–5.6 mg/kg i.p.) has been shown to attenuate self-administration (i.v.) of psychostimulants (Roberts et al. 1996; Roberts and Andrews 1997; Shoaib et al. 1998; Campbell et al. 1999; Brebner et al. 2000, 2005) and other drugs such as nicotine (Fattore et al. 2002). BCF (3.2–5.6 mg/kg i.p.) also reduces the breakpoints generated with progressive ratio schedules reinforced with cocaine (Brebner et al. 2000), and blocks the development and expression of locomotor sensitization induced by morphine (Bartoletti et al. 2007). In addition, we reported that BCF (3.0–5.6 mg/kg i.p.) partially reduces the discriminative signal of AMPH (Miranda et al. 2009), and blocks the development and expression of AMPH-induced locomotor sensitization (3.0–4.0 mg/kg i.p.) (Cedillo and Miranda 2013). The effects of BCF on addiction-related behavior could be mediated by the activation of $GABA_B$ receptors on the DAergic neurons of the VTA. This mediation has been supported by findings that $GABA_B$ receptors are located on the body of the DAergic neurons in the VTA

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(Nagai et al. 1983; Bowery et al. 1987; Johnson and North 1992; Kalivas 1993). However, because of the high distribution of $GABA_B$ receptors in the CNS, the use of high doses of BCF (e.g., 4 mg/kg) induces sedation, hypothermia, and alterations in sexual behavior, which, together with its short half-life, limit its application as a therapeutic agent for addiction treatment in humans.

On the other hand, evidence has shown that $5HT_{2C}$ receptors modulate the behavioral and neurochemical effects of cocaine, since the systemic administration of $5HT_{2C}$ agonists (1.0 mg/kg i.p.) inhibits and antagonists enhance behavioral responses produced by cocaine, such as the locomotor-stimulating effects and the discriminative and reinforcing properties (Filip et al. 2012). This effect may involve the activation of the $5HT_{2C}$ receptors located on cell bodies of the GABAergic interneurons in the VTA; activation of these receptors could increase GABA in the VTA and, consequently, decrease DA release in the nAcc (Devroye et al. 2013; Nocjar et al. 2015). Although $5HT_{2C}$ receptors are currently considered to have the potential to improve treatment for the abuse of and dependence on addictive drugs such as cocaine (Cathala et al. 2015), the activation of these receptors with Ro60-0175 has been shown to have a sedative profile and potential anxiogenic effects at doses exceeding 0.5 mg/kg (Kennett et al. 2000).

In summary, in separate studies, it has been proven that activation of $GABA_B$ and $5HT_{2C}$ receptors in the VTA can modulate the DAergic neurons in the nAcc, and this modulation may be of therapeutic value in the field of addictions. However, the use of high and effective doses of BCF and Ro60-0175 has been shown to produce side effects. These side effects may be reduced using lower doses of both agonists. In line with this, the aim of the present work is to evaluate the effect of the joint administration of an intermediate dose of the $GABA_B$ agonist BCF and low doses of the $5HT_{2C}$ agonist Ro60-0175 on the development of locomotor sensitization induced by the repeated administration of AMPH.

Materials and methods

Animals

A total of 210 male Wistar rats that were 120 days old and weighed 200–250 g at the beginning of the experiment were obtained from the breeding colony of the FES-Iztacala-UNAM, México. They were individually housed in stainless-steel cages with freely available food (Teklad LM485 Rat Diet by Harlan, Mexico City, Mexico) and water, and were maintained under a 12 h light/dark cycle, with the lights turned on at 08:00 h. The room was maintained at a temperature of 21 ± 1 °C. All experiments were conducted during the light phase (11:00–13:00 h). Animal care and handling procedures were performed in accordance with the Official Mexican Norm (NOM-062-ZOO-1999), and the local bioethics committee approved all procedures.

Drugs

The drugs used in these experiments were D-amphetamine sulfate, the $GABA_B$ receptor agonist (±)-baclofen (Sigma-Aldrich, St. Louis, USA), and the 5-HT_{2C} receptor agonist Ro60-0175 (Sigma-Aldrich, St. Louis, USA). The drugs were dissolved in 0.9% saline solution (Pisa, Jalisco, México), freshly prepared daily, and administered to rats via intraperitoneal injection (i.p.) (1 mL/kg).

Apparatus

Locomotor activity was measured with an open-field activity monitoring system (ENV-515 model from Med Associates, St. Albans, USA). Each box (40 × 40 × 30 cm) was equipped with 2 sets of 8 photobeams that were located at 2.5 cm above the surface of the floor on opposite walls to record *x*–*y* ambulatory movements. Photobeam interruptions were recorded and translated by software in real time to yield the horizontal distance traveled (cm), which was the dependent measure used for analysis.

Experimental procedure

Acute effects of BCF and Ro60-0175 on locomotor activity

To investigate the acute effects of BCF and Ro60-0175 on locomotor activity, we conducted an initial experiment. Separate groups of rats ($n = 10$ rats per group) were assessed once in response to the different doses of BCF (0.0, 2.0, 3.0, and 4.0 mg/kg), Ro60-0175 (0.0, 0.3, 1.0, and 3.0 mg/kg), and BCF (3.0 mg/kg) + Ro60-0175 (0.0, 0.3, 1.0, and 3.0 mg/kg).

Effect of the $GABA_B$ agonist BCF, the 5-HT_{2C} agonist Ro60-0175, and the coadministration of the $GABA_B$ agonist BCF, and the 5-HT_{2C} agonist Ro60-0175 on locomotor sensitization expression

The experimental design (Table 1) consisted of 11 sessions. For all sessions, rats were removed from their home cages and introduced into the activity boxes. Each session began with a habituation period of 10 min in the locomotor activity boxes, after which time, the rats were removed from the

Table 1 Experimental design of development and expression of AMPH-induced locomotor sensitization

Group	Habituation	BL	Sensitization development	Rest days	Challenge days	
					S	AMPH
Days	− 1	0	1–5	6–7	8	9
SAL		3S	3S		3S	2S + AMPH (1.0)
AMPH		3S	2S + AMPH (1.0)		3S	2S + AMPH (1.0)
BAC-2.0		3S	2S + AMPH (1.0)		3S	S + BAC (2.0) + AMPH (1.0)
BAC-3.0		3S	2S + AMPH (1.0)		3S	S + BAC (3.0) + AMPH (1.0)
BAC-4.0		3S	2S + AMPH (1.0)		3S	S + BAC (4.0) + AMPH (1.0)
Ro-0.3		3S	2S + AMPH (1.0)		3S	S + Ro (0.3) + AMPH (1.0)
Ro-1.0		3S	2S + AMPH (1.0)		3S	S + Ro (1.0) + AMPH (1.0)
Ro3.0		3S	2S + AMPH (1.0)		3S	S + Ro (3.0) + AMPH (1.0)
BAC-3 + Ro-0.3		3S	2S + AMPH (1.0)		3S	BAC (3.0) + Ro (0.3) + AMPH (1.0)
BAC-3 + Ro-1.0		3S	2S + AMPH (1.0)		3S	BAC (3.0) + Ro (1.0) + AMPH (1.0)
BAC-3 + Ro-3.0		3S	2S + AMPH (1.0)		3S	BAC (3.0) + Ro (3.0) + AMPH (1.0)

Each dose (mg/kg) represents a group ($n = 10$). In some groups, two or three saline injection were used to control de maximum number of injections on the main group

S saline, *2S* 2 saline injections, *3S* 3 saline injections, *AMPH* amphetamine, *BAC* baclofen, *Ro* Ro60-0175, *BL* baseline

activity boxes, were administered drugs or saline, and then returned to the activity boxes, where locomotor activity was recorded for 60 min. For habituation (day − 1) and baseline (day 0) sessions, all rats received three saline injections (i.p.) before introduction into the activity boxes to record their activity for 60 min. During the sensitization development period (days 1–5), all rats, except ten randomly selected rats (SAL group), received AMPH (1.0 mg/kg), and then, their locomotor activity was recorded. The SAL group was administered saline again. Once sensitization developed, on day 6, rats that had been administered AMPH during the 5 previous days were randomly assigned to one of the ten experimental groups. On days 6 and 7, all rats remained in their home cages without manipulation. Finally, two different pharmacological challenges were carried out. For the saline challenge (S challenge) (day 8), rats received three saline injections (i.p.). For the AMPH challenge (day 9), rats received three injections (i.p.) of the drug or drugs to be evaluated depending on the group to which they had been assigned.

Data analysis

Locomotor activity (distance traveled in cm) is expressed as the mean ± SEM. Data obtained during the development of locomotor sensitization were analyzed via two-way ANOVA with repeated measures, with group as factor 1 and day as factor 2. The data obtained during the baseline, testing days, and the acute effects of BCF and Ro60-0175 were analyzed with one-way ANOVA. When the ANOVA results were significant, Tukey's test ($p < 0.05$) was used to perform a posteriori comparisons.

Results

Acute effects of the $GABA_B$ agonist BCF and the 5-HT_{2C} agonist Ro60-0175 on locomotor activity

The results of this experiment are shown in Fig. 1. The data revealed that administration of different doses of

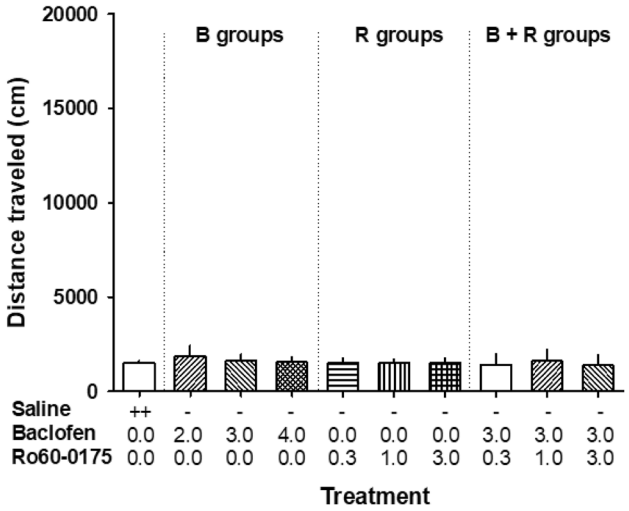

Fig. 1 Results for the acute effects of BCF and Ro60-0175 on locomotor activity. Bars are mean ± SEM of the distance traveled ($n = 10$). All groups received an injection of one of the different doses of baclofen (B groups), one of the different doses of Ro60-0175 (R groups), or the medium dose of BCF plus different doses of Ro60-0175

BCF, Ro60-0175, and BCF + Ro60-0175 did not alter rat locomotor activity ($F[9,99] = 0.690$, $p = 0.716$).

Sensitization development

The development of sensitization is shown in Fig. 2. First, there were no differences between the baseline values from the AMPH and SAL groups ($t[108] = 2.25$, $p = 0.299$). Repeated AMPH administration resulted in the development of locomotor sensitization, while saline administration did not produce any changes. Two-way repeated-measures ANOVA indicated significant differences between groups ($F[1108] = 46.53$, $p = 0.000$), days ($F[4432] = 3.26$, $p = 0.012$), and the interaction group × day ($F[4.432] = 4.58$, $p = 0.001$).

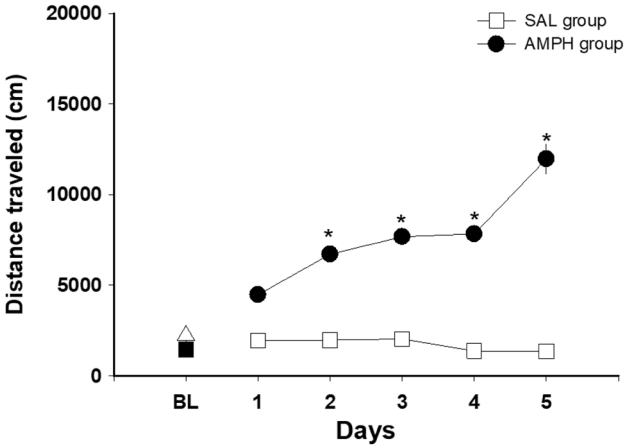

Fig. 2 AMPH-induced sensitization development. Black points are 100 rats mean ± SE. White points mean ± SEM from 10 rats. *Indicate significant differences ($p < 0.05$, Tukey's test)

Effect of sensitization development on the saline challenge

During the saline (S) challenge on day 8 (Fig. 3), no significant differences were found between the groups ($F[10,109] = 1.216$, $p = 0.290$).

Effects of the $GABA_B$ agonist BCF, agonist Ro60-0175, and coadministration of the $GABA_B$ agonist BCF, and the 5-HT_{2C} agonist Ro60-0175 on locomotor sensitization expression

Data obtained with different doses of BCF, different doses of Ro60-0175, and coadministration of BCF and Ro60-0175 are shown in Fig. 4. On day 9, we found that the $GABA_B$ agonist BCF and the 5-HT_{2C} agonist Ro60-0175 dose-dependently decreased the expression of locomotor sensitization produced by repeated AMPH administration, and BCF increased the effect of Ro60-0175 ($F[10,109] = 9.973$, $p = 0.0001$). Multiple comparisons also indicated that the AMPH ($p = 0.035$) and R0.3 ($p = 0.024$) groups were significantly higher than the SAL group. In contrast, we found significant differences between the AMPH and SAL ($p = 0.035$), B4.0 ($p = 0.000$), B3.0 + R0.3 ($p = 0.002$), B3.0 + R1.0 ($p = 0.000$), and B3.0 + 3.0 ($p = 0.000$) groups. A posteriori comparison also showed that the B3.0 group was different from the B3.0 + R3.0 group ($p = 0.045$). The B2.0 group was not different from the AMPH group ($p = 0.413$), but was also not different from the SAL group ($p = 0.991$).

Discussion

The main objective of the present study was to evaluate the coadministration of low doses of the $GABA_B$ agonist BCF and the $5HT_{2C}$ agonist Ro60-0175 on the expression

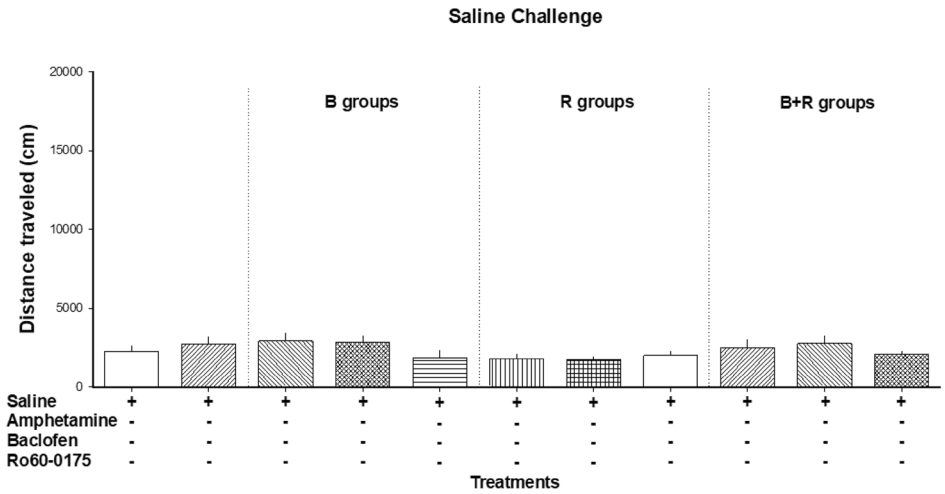

Fig. 3 Results for saline challenge on day 8, after development of AMPH-induced locomotor sensitization. Bars are mean ± SEM of the distance traveled ($n = 10$). All groups received saline injections

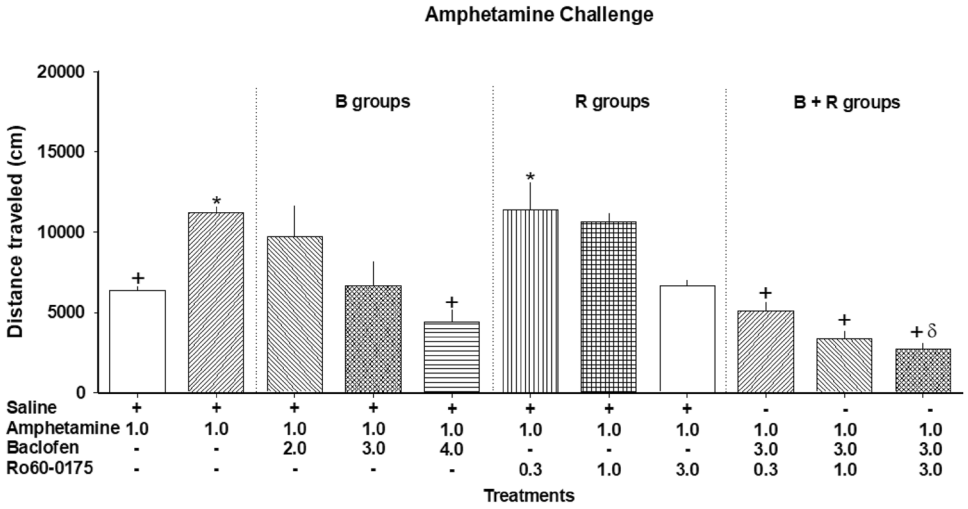

Fig. 4 Results for AMPH challenge on day 9. Bars are mean ± SEM of the distance traveled ($n = 10$). All groups received AMPH injection, AMPH injection plus one of the different doses of baclofen (B groups), AMPH injection plus one of the different doses of Ro60-0175 (R groups) or AMPH plus the medium dose of BCF and different doses of Ro60-0175. *Indicate significant differences with SAL group, $^{+}$significant differences with AMPH group, and $^{\delta}$significant differences with B3.0 group after Tukey's test

of AMPH-induced locomotor sensitization. During the experiments, we observed that the repeated administration of AMPH (1.0 mg/kg) increased the locomotor activity of rats in a progressive way. In addition, both the $GABA_B$ agonist BCF and the 5-HT_{2C} agonist Ro60-0175 prevented the expression of locomotor sensitization in a dose-dependent manner. In the case of BCF, the 4.0 mg/kg dose produced significant differences with respect to the AMPH group. The 2.0 and 3.0 mg/kg doses did not produce significant differences with respect to the AMPH group, but did not produce significant differences with respect to the SAL group. Although the medium and lowest dose of BCF reduced the expression of locomotor sensitization produced by AMPH, it was not able to completely block its expression. In the case of Ro60-0175, we only found differences with the highest dose (3.0 mg/kg). In addition, the effect of all doses of Ro60-0175 was increased by administering the intermediate dose of BCF, and the effect of the combination of the highest doses of both compounds was significantly higher than the effect of 3.0 mg/kg BCF alone.

Our findings are consistent with the previous results in which it has been reported that BCF can prevent both the development (Bartoletti et al. 2005; Cedillo and Miranda 2013) and the expression (Bartoletti et al. 2004; Cedillo and Miranda 2013) of locomotor sensitization produced by AMPH, cocaine (Frankowska et al. 2009), morphine (Bartoletti et al. 2007; Fu et al. 2012), and ethanol (Broadbent and Harless 1999).

Similarly, it has been reported that 5-HT_{2C} receptor pharmacological activation with lorcaserin suppresses the development and expression of heroin-induced behavioral sensitization (Wu et al. 2015).

These results could be explained by the modulation of DA release. In the nAcc, DA is principally released by neurons projecting from the VTA. This DAergic pathway, known as the mesolimbic system, plays an important role in the production of rewarding and motor effects of psychostimulants (Di Chara 1995; Kalivas and Nakumara 1999; Koob 1992). The mesolimbic system has also been implicated in the development and expression of locomotor sensitization (Pierce and Kalivas 1997). In animals that express locomotor sensitization, pre- and postsynaptic neuroadaptations have been found in the nAcc DAergic system (Robinson and Berridge 2000). However, some reports have shown that neural adaptations in DA terminal fields in the nAcc are sufficient for the expression of AMPH sensitization, although an action on DA cell bodies may be required for the induction of AMPH sensitization (Paulson and Robinson 1991). Regardless, DAergic projections from the VTA to the nAcc are thought to be the major component in the development and expression of locomotor sensitization, and there is a clear role of DA release for AMPH-induced sensitization (Vanderschuren and Kalivas 2000).

There is considerable evidence to support the hypothesis that $GABA_B$ receptors are located on the cell bodies of the DAergic neurons in the VTA (Nagai et al. 1983; Bowery et al. 1987; Johnson and North 1992; Kalivas 1993) where they are activated by GABA released from GABAergic interneurons or by nAcc projections. Evidence has shown that BCF infusions in the VTA decreased DA release in the nAcc (Westerink et al. 1996; Yoshida et al. 1994). In addition, it has been shown that BCF infusions in the VTA reduced heroin (Xi and Stein 1999) and cocaine (Shoaib et al. 1998) self-administration under fixed-ratio and progressive ratio schedules (Brebner et al. 2000), as well as the motor activity produced by AMPH (Kalivas et al. 1990). Although the evidence seems to support this mechanism as an explanation of the observed results, there is also evidence of the presence of $GABA_B$ receptors in the nAcc, and this potential influence would have to be analyzed (Pitman et al. 2014).

In the case of the 5-HT_{2C} agonist Ro60-0175, the effect could be due to activation of 5-HT_{2C} receptors located on the cell bodies of GABAergic interneurons in the VTA. 5-HT_{2C} receptor activation could produce excitation of the interneurons and, therefore, an increase in VTA GABA release. This GABA increase would result in a decrease in the DA release in the nAcc (Devroye et al. 2013; Nocjar et al. 2015). This hypothesis is supported by studies in which it has been found that Ro60-0175 infusions (5 µg/0.2 µL) in the VTA can significantly reduce the DA release produced by systemic administration of cocaine (Navailles et al. 2008). In addition, in behavioral studies, it has also been found that Ro60-0175 injections in the VTA can attenuate the locomotor activity increase produced by cocaine, as well as its self-administration (Fletcher et al. 2004). Similar to the reports of $GABA_B$ receptors, there are also reports that indicate the presence of 5-HT_{2C} receptors in the nAcc shell (Navailles et al. 2008).

Finally, with respect to the lack of conditioned locomotion observed in the present experiment, there are conflicting results reported in different papers. Some authors (Vezina and Leyton 2009; Cedillo and Miranda 2013) have reported conditioned locomotor activity; however, there are also authors who have reported that there is no conditioned locomotion (Acosta-García et al. 2017), as in the present results. In this line, some authors have suggested that psychostimulant behavioral sensitization is a composite of conditioned locomotion and increased unconditioned drug responses. While these authors have reported that the conditioned response can be statistically robust, the response was only a very small fraction of the sensitized response (Pinheiro et al. 2011). The expression or absence of conditioned locomotion can be influenced by different factors, such as the number of days of testing or the intensity of the stimulus. This has been the subject of previous investigations (Pinheiro et al. 2011; Vezina and Leyton 2009).

Taken together, evidence shows that the increase in behavioral effects observed after administering the $GABA_B$ agonist BCF and the 5-HT_{2C} agonist Ro60-0175 could be due to the simultaneous stimulation of both types of receptors. These results support the role of $GABA_B$ and 5-HT_{2C} receptors in the behavioral effects of psychostimulants and reaffirm the idea of these agonists as possible therapeutic agents in the treatment of psychostimulant addiction. However, it is still necessary to analyze the actual contribution of the $GABA_B$ and 5-HT_{2C} receptors in the VTA and nAcc.

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Author contributions LNC designed the experiments, wrote the manuscript, and performed experiments RIR performed experiments, JCJ performed experiments, and FM designed and directed the experiments and wrote the manuscript. All of the authors analyzed the data, discussed the results and commented on the manuscript.

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