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ORIGINAL INVESTIGATION

A $GABA_B$ agonist reverses the behavioral sensitization to morphine in rats

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Abstract
Rationale In laboratory animals, repeated administration of drugs of abuse causes sensitization to their stimulant and rewarding effects. Neuroadaptations underlying sensitization could be related to those that contribute to addictive behaviors. An increased understanding of the molecular mechanisms of sensitization could lead to improved treatments for addiction.
Objectives Since baclofen (BCF) co-administration has been reported to block the development and the expression of motor sensitization to morphine (MOR), the present study examined the hypothesis that a chronic treatment with BCF alone might reverse and/or prevent MOR-induced sensitization.
Methods Rats were first sensitized to MOR (saline or 10 mg/kg MOR i.p.; days 1–10) and then chronically treated with BCF (saline or 2 mg/kg BCF i.p.; days 11–20). Finally, the motility effect of MOR (10 mg/kg i.p.) was assessed 3 and 30 days after the end of BCF treatment. The same rats were again challenged with MOR on day 70, after a further period of saline or MOR treatment (days 51–60).
Results Behavioral sensitization to MOR was observed in control animals but not in rats chronically treated with BCF (days 23 and 50). Thus, BCF completely reversed MOR-induced sensitization, and its effect was long lasting. However, a previous repeated BCF treatment did not prevent the development of sensitization to MOR both in naive and desensitized rats.
Conclusions The present results confirm that γ-aminobutyric acid $(GABA)_B$ receptors play an important role in the expression of motor sensitization to MOR and suggest that $GABA_B$ agonists could be useful for reversing the neuroadaptations related to drug addiction.

Keywords Sensitization · Desensitization · Locomotor activity · $GABA_B$ receptor · Morphine · Baclofen · Rat

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Introduction

Intermittent addictive drug administration results in a progressive enhancement of their psychomotor stimulant effects (Stewart and Badiani 1993). Behavioral sensitization has been linked to the gradual enhancement of drug craving, the main cause of drug relapse (Robinson and Berridge 2003; McSweeney et al. 2005). Thus, the persistence of sensitization (Babbini et al. 1975; Bartoletti et al. 1983) can be viewed as a model for the persistence of drug craving in humans. Rats repeatedly exposed to drugs of abuse consistently show an augmented dopaminergic transmission in the nucleus accumbens (NA) associated with sensitized locomotor responses (Vanderschuren and Kalivas 2000). However, dopaminergic system is only one component of the neural circuitry that mediates behavioral sensitization (Vanderschuren and Kalivas 2000; Tzschentke and Schmidt 2003). γ-aminobutyric acid $(GABA)_B$ receptors have been found both in the NA, one of the main projection sites of the mesolimbic dopamine system, and in the ventral tegmental area (VTA; Kalivas et al. 1990) and may play a primary role in decreasing dopamine release (Klitenick et al. 1992). In fact, intraventral tegmental area administration of the $GABA_B$ agonist baclofen (BCF) decreases extracellular dopamine in the NA and in the medial prefrontal cortex (Westerink et al. 1998). Thus,

activation of $GABA_B$ receptors localized on dopaminergic and glutamatergic neurons in the VTA may modulate the stimulant and motivational properties of drugs of abuse by regulating mesolimbic circuitry and its afferent inputs. In this regard, it is worth noting that the $GABA_B$ agonist BCF, when co-administered with morphine (MOR), blocked the development (Woo et al. 2001; Leite-Morris et al. 2004) and the expression (Leite-Morris et al. 2004) of motor sensitization to MOR. Furthermore, BCF inhibited opiate-induced conditioned place preference (Kaplan et al. 2003).

Based on these findings, we investigated whether manipulating GABAergic transmission might provide a means of reversing processes underlying long-term locomotor sensitization. To this end, we first tested the effects of MOR in rats repeatedly treated with the drug, to determine whether sensitization occurred (experiment 1). Subsequently, MOR sensitized animals were chronically treated with BCF and then challenged with MOR after a short (3 days) and a prolonged (30 days) BCF-free period to be sure that neural changes associated with sensitized behavior were actually reversed and not transiently masked by the $GABA_B$ agonist (experiment 2). Finally, since chronic BCF reversed MOR sensitization, we investigated whether the same treatment could prevent the development of locomotor sensitization when administered in control and in desensitized rats (experiment 3).

Materials and methods

The "principles of laboratory animal care" were followed. The experimental protocol was approved by a local bioethical committee, whereas the University Veterinary Service controlled the procedures and animal comfort.

Subjects

Male Sprague–Dawley rats (Harlan Italy), experimentally naive, weighing 275–300 g at the beginning of the experiment, served as subjects. They were housed three to a cage, under standard laboratory conditions (lights on 07.00–19.00 h; temperature 22±1°C, humidity 65%). Water and food were available *ad libitum*.

Apparatus

Activity was measured using five jiggle-cage actometers already described (Bartoletti et al. 2004). Briefly, the oscillatory movements of the cage were counted by means of solid-state circuits operating printing counters. To obtain a baseline activity high enough to evaluate both stimulant and depressant actions of the drugs, the tests were run during the day, but in the dark (the lights were switched off in the experimental room).

Procedure

Experiment 1: effect of repeated MOR treatment

Four groups of six rats were treated with either saline (2 ml/kg; two groups) or MOR (10 mg/kg; two groups) for 10 days. The dose of MOR was chosen on the basis of other sensitization experiments performed with MOR in rats (Tzschentke and Schmidt 1996; Kratzer et al. 2003). The injections were administered in the animals' home cages to minimize context dependent sensitization. Three days after the end of MOR treatment (day 13), the animals were put into the activity cages for 1 h to acclimatize to the apparatus; then, they were injected with either saline (one saline-pretreated and one MOR-pretreated group) or 10 mg/kg MOR (one saline-pretreated and one MOR-pretreated group) and immediately put again into the actometers. Motility was recorded for 5 h, readings being made at 1 h intervals.

Experiment 2: effect of repeated BCF treatment on the expression of sensitization to MOR

Rats were assigned to one of four groups. Groups II and IV were daily injected with 10 mg/kg MOR for 10 days. Groups I and III were treated with saline (2 ml/kg). On the last day of chronic treatment (day 10), half the animals of groups I/III and Groups II/IV were randomly chosen and challenged with saline (groups I/III) or 10 mg/kg MOR (Groups II/IV). Starting on day 11, rats of groups III and IV received BCF (2 mg/kg) daily for 10 days; rats of groups I and II received saline. The same dose of BCF has been found effective in sensitization experiments performed with amphetamine in rats (Bartoletti et al. 2004, 2005). Three (day 23) and 30 (day 50) days after the end of BCF treatment, all the rats were challenged with 10 mg/kg MOR (see Table 1 for further details and Experiment 1 for the procedure).

Experiment 3: effect of repeated BCF treatment on the subsequent development of sensitization to MOR in 'control' and 'desensitized' rats

Starting on day 51, control (groups III) and desensitized (group IV) rats received MOR (10 mg/kg) daily for 10 days; rats of groups I and II received saline. Ten days after the end of chronic treatment (day 70), the animals were again challenged with 10 mg/kg MOR (see experiment 1 for the procedure).

Table 1 Schedule of drug treatment

Group	Number	Experiment 2						Experiment 3		
		Days								
		1–10	11–20	21–22	23	24–49	50	51–60	61–69	70
I	10	SAL	SAL	–	MOR	–	MOR	SAL	–	MOR
II	10	MOR	SAL	–	MOR	–	MOR	SAL	–	MOR
III	10	SAL	BCF	–	MOR	–	MOR	MOR	–	MOR
IV	10	MOR	BCF	–	MOR	–	MOR	MOR	–	MOR

Drugs

Morphine hydrochloride (Salars, Italy) and BCF (Sigma-Aldrich, Italy) were dissolved in 0.9% NaCl. Both drugs were administered intraperitoneally (2 ml/kg).

Statistical analysis

The data from experiment 1 were analyzed by a three-way (pretreatment, treatment, time) analysis of variance (ANOVA) with repeated-measures on the last factor. Experiment 2 was separately analyzed for each challenge test by a three-way (MOR, BCF, time) ANOVA with repeated-measures on the time factor. Experiment 3 was also analyzed by a three-way ANOVA (MOR, BCF/MOR, time) with repeated-measures on the last factor. Subsequent comparisons were performed by Bonferroni (experiment 1) or Dunnett (experiment 2 and 3) *t* tests. For all the analyses, a square root transformation was used to stabilize the cell variances, as suggested by the Box–Cox diagnostic (Box and Cox 1964).

Results

Experiment 1: effect of repeated MOR treatment

The locomotor response to an MOR challenge in chronically treated rats is shown in Fig. 1. The ANOVA indicated significant 'pretreatment' [$F(1,20)=42.44$, $P<0.01$], 'treatment' [$F(1,20)=45.03$, $P<0.01$] and 'time' [$F(4,80)=8.18$, $P<0.01$] effects and a 'pretreatment × treatment × time' interaction [$F(4,80)=3.51$, $P=0.01$]. Further analysis revealed a significant MOR effect in control animals at the first [$t(100)=2.47$, $P<0.05$] and third [$t(100)=3.20$, $P<0.01$] hour of recording. Moreover, motility values were higher in sensitized than in control MOR treated rats at the first [$t(100)=6.17$, $P<0.01$], second [$t(100)=6.59$, $P<0.01$] and third [$t(100)=3.60$, $P<0.01$] hour of recording. Finally, no significant difference was found at any time between saline challenged groups.

Experiment 2: effect of repeated BCF treatment on the expression of sensitization to MOR

As expected, motility values obtained on the last day of chronic treatment (day 10) were very similar to those previously observed (see experiment 1) in control, saline treated and sensitized, MOR treated animals (data not shown).

Figure 2, top panel, shows the results from the first challenge test (day 23). The ANOVA revealed a significant effect of 'MOR' [$F(1,36)=18.31$, $P<0.01$] and 'BCF' [$F(1,36)=4.52$, $P<0.05$]; moreover the analysis indicated a significant 'MOR × BCF' [$F(1,36)=12.42$, $P<0.01$] but not 'MOR × BCF × time' ($F<1$) interaction. Thus, further comparisons were performed on the data collapsed across

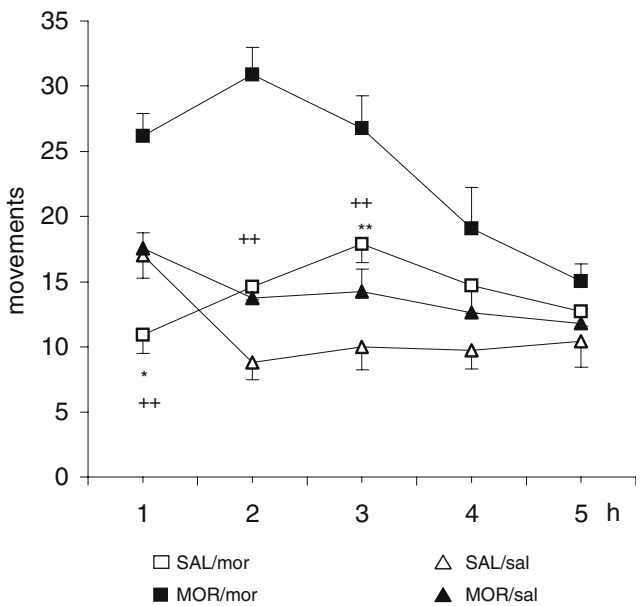

Fig. 1 Locomotor response to saline (*SAL*) or 10 mg/kg morphine (*mor*) 3 days after 10 once-daily injections of SAL or 10 mg/kg MOR. Motility values (see statistical analysis for transformation) are presented as means of 6 values ± SEM for each 1-h interval. (*Asterisk*) $P<0.05$, (*double asterisk*) $P<0.01$ for SAL/mor group vs SAL/sal group; (*double plus signs*) $P<0.01$ for SAL/mor group vs MOR/mor group (Bonferroni *t* test)

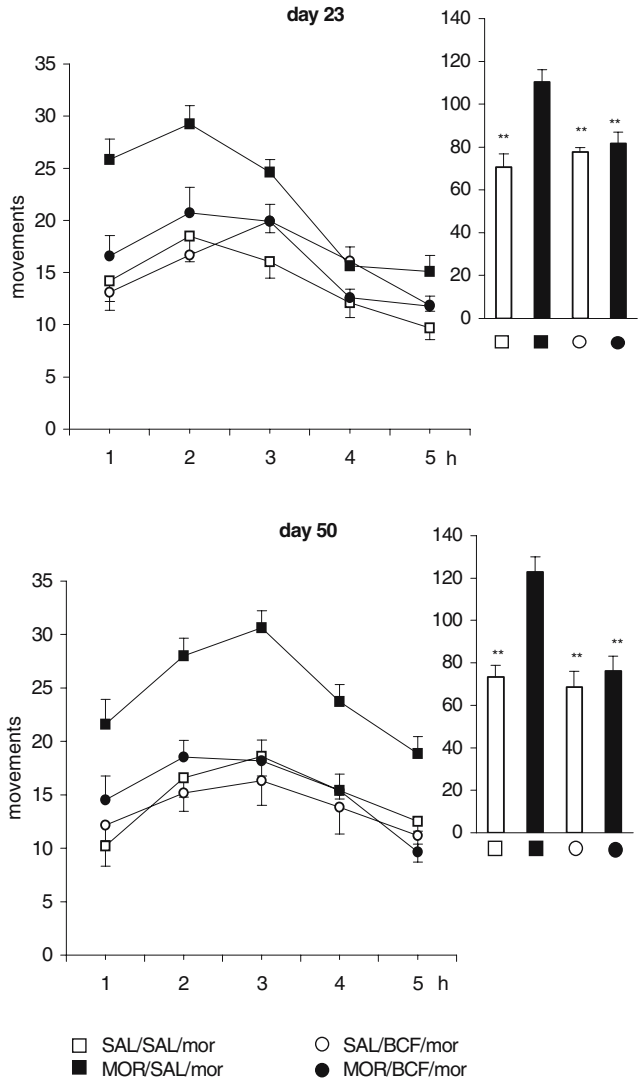

Fig. 2 Effect of repeated treatment with baclofen (*BCF*) (2 mg/kg daily for 10 days) on the expression of the sensitized locomotor response to 10 mg/kg morphine. For each group, capital letters refer to the repeated treatment and small letters to the challenge treatment. Motility values (see statistical analysis for transformation) are presented as means of 10 values ± SEM for each 1-h interval. In bar graphs insert the data are collapsed across time. Statistically different from MOR/SAL group (*double asterisk*) $P<0.01$ (Dunnett *t* test)

times (see Fig. 2, bar graph insert). The comparisons revealed that the MOR/saline(SAL) group had motility values significantly higher than any other group [SAL/SAL: $t(36)=5.52$, $P<0.01$; SAL/BCF: $t(36)=4.53$, $P<0.01$; MOR/BCF: $t(36)=4.00$, $P<0.01$]. Thus, behavioral sensitization to MOR was observed in control animals, but not in rats chronically treated with BCF.

The results from the second challenge test (day 50) were very similar to those relative to the first one (see Fig. 2, bottom panel). The ANOVA revealed a significant effect of 'MOR' [$F(1,36)=17.84$, $P<0.01$) and 'BCF' [$F(1,36)=14.27$, $P<0.01$]. Moreover, the 'MOR × BCF' [$F(1,36)=9.64$, $P<0.01$] but not the 'MOR × BCF × time' [$F<1$] interaction was statistically significant. Further comparisons, performed on the data collapsed across times (see Fig. 2, bar graphs insert), again indicated that the MOR/SAL group had motility values significantly higher than any other group [SAL/SAL: $t(36)=5.18$, $P<0.01$; SAL/BCF: $t(36)=5.66$, $P<0.01$; MOR/BCF: $t(36)=4.87$, $P<0.01$]. Thus, BCF-induced reversal of the sensitized response to MOR was long lasting.

Experiment 3: effect of repeated BCF treatment on the subsequent development of sensitization to MOR in 'control' and 'desensitized' rats

The results are shown in Fig. 3. The ANOVA revealed a significant effect of 'MOR' [$F(1,35)=4.62$, $P<0.05$) but not of 'BCF/MOR' [$F<1$]. Moreover, the analysis indicated a significant 'MOR × BCF/MOR' [$F(1,35)=5.54$, $P<0.05$], but not a 'MOR × BCF/MOR × time' [$F<1$] interaction. Subsequent comparisons, performed on the data collapsed across times, (see Fig. 3, bar graph insert) indicated that MOR/SAL/SAL group had motility values higher than SAL/SAL/SAL group [$t(35)=3.23$, $P<0.01$] but not significantly different from SAL/BCF/MOR group [$t(35)=0.93$, NS] or MOR/BCF/MOR group [$t(35)=1.10$, NS]. Thus, BCF repeated treatment did not prevent the development of locomotor sensitization to MOR both in naïve and desensitized rats.

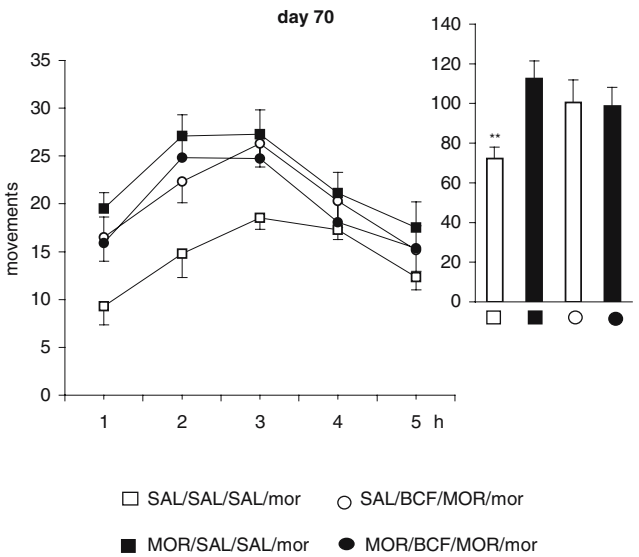

Fig. 3 Effect of repeated treatment with baclofen (2 mg/kg daily for 10 days) on the development of the sensitized locomotor response to 10 mg/kg morphine. For each group, capital letters refer to the repeated treatment and small letters to the challenge treatment. Motility values (see statistical analysis for transformation) are presented as means of 9–10 values ± SEM for each 1-h interval. In bar graphs insert the data are collapsed across time. Statistically different from MOR/SAL/SAL group (*double asterisk*) $P<0.01$ (Dunnett *t* test)

Discussion

The locomotor response to a 10 mg/kg dose of MOR in sensitized rats was the same as repeatedly observed in previous studies (Babbini et al. 1979; Bartoletti et al. 1985). In this regard it is worth noting that, although pretreatment was done in the animals' home cages (to minimize context dependent sensitization), a conditioned locomotor response to the injection ritual could still have developed in the MOR-treated animals. However, this was not the case as no significant difference was found between the locomotor response to saline of control and MOR-treated animals.

As regards experiments 2 and 3, a potential experimental flaw is the fact that all animals got at least three MOR challenges, as a single exposure to 10 mg/kg of MOR has been shown to cause long-lasting changes in psychomotor reactivity and mesolimbic dopamine activity (Vanderschuren et al. 2001). However, data from animals that had never received BCF (groups I and II) were analyzed by a three-way (MOR, challenge session, time) ANOVA with repeated measures on the last factor. The analysis revealed a significant effect of 'MOR' [$F(1,54)=62.59$, $P<0.01$], but not of 'challenge session' ($F<1$), 'MOR × challenge session' ($F<1$) or 'MOR × challenge session × time' ($F<1$); thus, it seems reasonable to rule out that sensitization had occurred as a result of repeated MOR challenges.

The main finding of the present work is that repeated BCF treatment normalizes the sensitized response to MOR. Interestingly, the reversal of sensitization is long lasting, if not permanent, since the animals have been challenged 3 and 30 days after the end of the chronic treatment. The present results are in keeping with previous reports showing that BCF, when co-administered with MOR, blocks the development (Woo et al. 2001; Leite-Morris et al. 2004) and the expression (Leite-Morris et al. 2004) of sensitization to this drug. Other GABA-related compounds modulate the behavioral sensitization to opiates. For instance, the co-administration of a $GABA_A$ agonist (muscimol, THIP) or of a positive allosteric modulator of GABA activity at $GABA_A$ receptors (diazepam, alprazolam) inhibited or attenuated the development (Woo and Kim 2001; Votava et al. 2002; Yoon et al. 2002a,b) but not the expression (Votava et al. 2002) of sensitization to MOR in mice. Furthermore, the co-administration of valproate, which enhances GABA activity within the brain, blocked the development of sensitization to MOR (Li et al. 2004). However, neither single nor multiple administrations of valproate had any effect on the expression of MOR sensitization (Li et al. 2004). In this regard it is worth noting that, in addition to presynaptic effects on GABA release, valproate can potentiate post-synaptic responses, possibly by interaction with the benzodiazepine regulatory site of the $GABA_A$ receptor (Cunningham et al. 2003). On the whole, the data confirm that GABA activity modulates the opiate-induced behavioral sensitization, and suggest that $GABA_B$ receptors play a role in reversing the sensitized response to MOR.

The results of experiment 3 indicate that a repeated BCF treatment does not prevent the development of sensitization to MOR both in MOR naïve and in desensitized rats. The present findings are consistent with previous work, indicating that repeated BCF administration reverses the sensitized response to amphetamine (Bartoletti et al. 2004) but does not prevent its development (Bartoletti et al. 2005). In this regard it is worth noting that a repeated treatment with BCF does not induce any significant change in the responsiveness to acute MOR (present study; Woo et al. 2001) or amphetamine (Bartoletti et al. 2004, 2005). Thus, BCF possibly exerts a specific action in reversing neural changes associated with prolonged opioid treatment.

Sensitization to opioids appears to be associated with enhanced dopamine transmission (for review, see Vanderschuren and Kalivas 2000). BCF, when administered directly into the VTA in rats, decreased somatodendritic dopamine release in this area (Klitenick et al. 1992) and extracellular dopamine levels in the NA (Westerink et al. 1998). Moreover, pretreatment with BCF dose-dependently reduced MOR-evoked dopamine release in the shell of the NA (Fadda et al. 2003). Finally, gamma vinyl GABA, an irreversible GABA-transaminase inhibitor, attenuated or completely abolished heroin-induced increases in NA DA, the effect being likely mediated through $GABA_B$ receptors (Gerasimov et al. 1999). In conclusion, it appears likely that the inhibitory control exerted by $GABA_B$ receptor stimulation attenuates or blocks the increased extracellular dopamine levels observed in the accumbens during long-term sensitization.

The activity of VTA dopaminergic neurons is strongly modulated by glutamatergic afferents (Overton and Clark 1997), and previous studies have shown a relevant involvement of glutamate in behavioral sensitization (for review, see Vanderschuren and Kalivas 2000). In this regard, systemic BCF has been shown to decrease glutamate release in the NA (Hotsenpiller and Wolf 2003), and Harte and O'Connor (2005) demonstrated a selective prefrontal cortical $GABA_B$ receptor-mediated inhibition of glutamate release in the VTA. Thus, $GABA_B$ receptors possibly play a modulatory role on glutamatergic transmission in drug-sensitized subjects.

Chronic exposure to different classes of drugs of abuse results in augmentation of GABA transmission within the VTA during the early withdrawal period (Manzoni and Williams 1999; Giorgetti et al. 2002). This increased GABA tone has been viewed as a compensatory mechanism that is engaged to reduce the excessive glutamatergic drive to DA neurons. Thus, one possibility is that a repeated administration of a $GABA_B$ agonist during the early

withdrawal period reduces the excessive glutamatergic drive to DA neurons and blocks the induction of persistent neuroadaptations in regions receiving dopaminergic input. On the other hand, different abused drugs, including MOR, share the ability to produce long-term potentiation in VTA DA neurons (Saal et al. 2003), and the activation of $GABA_B$ receptors has been reported to promote the susceptibility to depotentiation stimulation in the hippocampus (Huang and Hsu 2004). In conclusion, our findings suggest that a short-term treatment with appropriate agents may reverse the neuroadaptations related to drug sensitization.

Sensitization phenomena are hypothesized to contribute to the development of compulsive drug taking, drug craving and relapse (De Vries et al. 1998; Robinson and Berridge 2003). Thus, present and previous (Bartoletti et al. 2004, 2005) results indicate that $GABA_B$ agonists may offer a rational therapeutic approach to the treatment of poly-drug addiction (e.g., psychostimulants and opioids). In this regard, it is worth noting that BCF decreases stimulus maintained responding for many drugs of abuse, including heroin, cocaine, *d*-amphetamine and nicotine (Brebner et al. 2002b, 2005; Di Ciano and Everitt 2003; Markou et al. 2004; Roberts et al. 1996; Xi and Stein 1999), but not for natural reinforcers (Shoaib et al. 1998). On the other hand, BCF is already approved for use in humans and preliminary clinical data suggest that it can be effective in the treatment of addictive disorders (Brebner et al. 2002a; Colombo et al. 2004; Cousins et al. 2002).

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