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Single and repeated baclofen treatment attenuates the discriminative stimulus effects of morphine in rats

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ABSTRACT

The $GABA_B$ agonists block the rewarding properties of opiates. However, the role of $GABA_B$ receptors in the discriminative properties of these drugs has received little attention. In this line, the present study was performed to investigate the effects of acute (Experiment 1) and chronic (Experiment 2) pretreatment with baclofen on the discriminative stimulus effects of morphine. Rats were trained to discriminate morphine (5 mg/kg i.p.) from saline under a two-lever fixed-ratio schedule of food reinforcement. Experiment 1: a morphine generalization curve was obtained under standard conditions in control and baclofen (1 and 2 mg/kg i.p.) pretreated animals. Acute baclofen pretreatment attenuated morphine-lever responding and response rate at both doses. Experiment 2: the animals were randomly divided in two groups and a morphine generalization curve was obtained in daily consecutive test sessions before (TEST1) and after (TEST2) chronic saline (Group I) or chronic baclofen (2 mg/kg) (Group II) administration. As expected, chronic saline pretreatment was ineffective, while chronic baclofen pretreatment attenuated the stimulus properties of morphine, without modifying the rate-decreasing effect of the drug.The data support a role for GABAergic neurotransmission in the discriminative effects of opiates and demonstrate that a short-term treatment with baclofen is useful for decreasing the sensitivity to narcotic cue.

1. Introduction

Several lines of evidence support the hypothesis that the mesocorticolimbic dopamine system has a role in mediating opiate discrimination (Krivsky et al., 2006; Shaham and Stewart, 1995) as well as opiate reinforcement (Bardo, 1998). However, the dopaminergic system is only one component of the neural circuitry underlying the behavioural properties of opiates. $GABA_B$ receptors have been found both in the nucleus accumbens (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). Actually, intra-ventral tegmental area administration of the $GABA_B$ agonist baclofen decreases extracellular dopamine in the NA and in the medial prefrontal cortex (Westerink et al., 1998). Therefore, activation of $GABA_B$ receptors localized on dopaminergic and glutamatergic neurons in the VTA is expected to modulate the motivational as well the discriminative properties of opiates by regulating mesolimbic circuitry and its afferent inputs. In this regard it is worth noting that the $GABA_B$ agonist baclofen blocks the rewarding effect of morphine, as measured by conditioned place preference (Kaplan et al., 2003; Tsuji et al., 1996), and heroin self-administration (Brebner et al., 2002; Xi and Stein, 1999) (see Filip and Frankowska, 2008 for a review). However, the role of $GABA_B$ receptors in the discriminative properties of opiates has received little attention. Actually, the only available study, to our knowledge, has given conflicting results, since selective inhibition of GABA reuptake, but not inhibition of GABA transaminase or direct stimulation of $GABA_A$ and $GABA_B$ receptors, attenuated the discriminative stimulus effects of heroin in rats (Solecki et al., 2005). Thus, the present study was performed to further investigate the effects of a $GABA_B$ agonist (baclofen) on the discriminative stimulus effects of morphine.

Medications to treat addictive disorders are administered chronically (Montoya and Vocci, 2008); thus, since the effect of acute and chronic drug treatments may differ (Matto and Allikmets, 1999), a further experiment was performed to evaluate the effect of repeated baclofen on the discriminative stimulus effects of morphine in rats. In this case, as usual (Emmett-Oglesby, 1990; Wood et al., 1984), training was halted during the chronic baclofen treatment.

2. Materials and methods

The Principles of Laboratory Animal Care (NIH publication No. 85-23, revised 1985) were followed. The experimental protocol was approved by a local bioethical committee, whereas the University Veterinary Service controlled the procedures and animal comfort.

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2.1. Subjects

Fourteen male Sprague–Dawley rats (Harlan Italy), experimentally naive, weighing 275–300 g at the beginning of the experiments, served as subjects. They were housed two to three to a cage, under standard laboratory conditions (lights on 07:00–19:00 h; temperature 22 ± 1 °C, humidity 65%). Water was freely available; food was restricted to 36 or 54 g per cage, depending on the number of rats, given at 19:00 h; all animals exhibited a uniform gain in weight, thus confirming the suitability of the feeding regimen.

2.2. Apparatus

The experimental chambers were six custom-made operant chambers (20 × 20 × 30 cm), equipped with two response levers located on opposite sides of the same wall (left and right lever) and a food tray, mounted between the two levers, for 45 mg food pellets as reinforcers. A force of approximately 20 g was required to depress the lever microswitch. Each box was enclosed in a sound-insulated and ventilated compartment. A 3 W light bulb mounted on the top of the chamber provided a low-level illumination during the trials. A 5TI programmable control system (Texas Instruments Incorporated, Johnson City, TN, USA) and a microcomputer (IBM) were used to control schedule contingencies and to record data.

2.3. Procedure

2.3.1. Preliminary training

Rats were trained (5 days per week) to respond on either lever in a two-lever food-reinforced operant task according to a tandem VI 60-FR15 schedule; during this phase only one lever (left or right alternatively) was available in the experimental chambers.

2.3.2. Discrimination training and testing

In this phase both levers were made available. Sessions took place 5 days per week. Reinforcers were obtained by pressing the injection-appropriate lever; responses on the inappropriate lever had no programmed consequences. For half the rats the left lever (L) was designated as the morphine correct lever and the right lever (R) as the saline correct lever; this was reversed for the remaining animals. Treatments (5 mg/kg of morphine or 2 ml/kg of saline) were administered according to the following two sequences, which were presented alternatively: LRRLL and RLLRR. The subjects were placed in the operant chambers 30 min after the treatment and were allowed to respond for 30 min. Test sessions began when a subject reached the training criterion (≥80% of total responses before the first reinforcer made on the correct lever, on at least 10 out of 11 consecutive daily training sessions). On test sessions the 15th cumulative response to occur on a given lever (selected lever) produced the first food pellet; subsequent responding was reinforced throughout the trial (30 min) for pressing that lever (Colpaert et al., 2007).

2.3.3. Experiment 1: effect of baclofen and morphine co-administration on the discriminative stimulus effects of morphine

Tests were conducted once or twice per week, with training sessions scheduled on the intervening days. For each animal a test session was run only if, during the two most recent training sessions, at least 80% of total responses before the first reinforcer was made on the correct lever. Baclofen was administered at doses (1 and 2 mg/kg) that do not significantly affect spontaneous motor activity (Bartoletti et al., 2004; Hotsenpiller and Wolf, 2003; Woo et al., 2001). The drug was administered both alone and in combination with a full range of morphine doses (0.6–5.0 mg/kg; $n = 10$–14/dose); the preinjection time (15 min) was chosen based upon earlier studies from our laboratory (Bartoletti et al., 2004, 2005). The sequence of testing was randomized for each animal to control for drug history effects (Kohut et al., 2009).

2.3.4. Experiment 2: effect of repeated baclofen treatment on the discriminative stimulus effects of morphine

Following Experiment 1, training was resumed for three weeks; therefore, two rats were excluded for the study, due to pour discriminative performance. Then, the animals were randomly divided in Groups I and II (see Table 1). For both groups training was halted and saline was administered daily in the home cage for 10 days (days 1–10). Then, a morphine generalization curve was obtained in four daily consecutive test sessions (TEST1, days 11–14); the sequence of treatments was randomized for each animal. Subsequently, discrimination training was resumed for 2 weeks (days 17–28) and then halted again for 10 days. During this period (days 29–38), Groups I and II received daily injections of saline and baclofen (2 mg/kg) respectively. Finally, a morphine generalization curve was obtained once more in four daily consecutive test sessions (TEST2, days 39–42), the sequence of treatments being randomized for each animal.

2.4. Drugs

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

2.5. Statistical analysis

The test sessions generated data on the following variables: (1) percentage of drug-appropriate responses; (2) response rate (i.e. the total number of responses made on both levers during the entire session), expressed as a percentage of the response rate during the most recently preceding saline training session; (3) FRF value, defined as the sum of responses made on either lever before the first reinforcement occurred; (4) % RSL, percentage of responses on the selected lever, based on responses made after lever selection occurred.

Increased FRF values and increased responding on the nonselected lever have been considered as possibly related to disruptive effects of the test drug on discriminative performance (Koek et al., 1995; Koek, 1999; Gaiardi et al., 2001). Thus, if animals simultaneously exhibited high FRF values (FRF>17) and low percentages of responses on the selected lever (% RSL<90), data were omitted from calculations. Given the moderate suppressing effect of baclofen on bar pressing activity, no "rate-dependent" exclusion criteria were used.

As regards Experiment 1, a two factor (morphine, baclofen) ANOVA, followed by a Dunnett *t* test, was used to analyze both drug-lever responding and response rate; all the data were included in the analysis. As regards Experiment 2, a subject within each group was measured under both TEST1 and TEST2 and after all doses of morphine. Thus, data relative to Groups I and II have been separately analyzed as a TEST × morphine factorial design with subjects as blocks. Data from one rat (Group I, TEST1, 1.2 mg/kg morphine) met the exclusion criterion and were removed from the analysis. All the statistical analyses were run on BMDP/PC (release 7.01).

Table 1
Experiment 2—schedule of drug treatment.

Group	*N*	Days				
		1–10	11–14	17–28	29–38	39–42
I	6	SAL	TEST1	TRAINING	SAL	TEST2
II	6	SAL	TEST1	TRAINING	BCF	TEST2

3. Results

3.1. Experiment 1: effect of baclofen co-administration on the discriminative stimulus effects of morphine

The effects of baclofen co-administration on the discriminative stimulus effects of morphine are shown in Fig. 1. As regards drug-lever responding, the ANOVA revealed significant effects of morphine [$F(3,135)=7.73$, $P<0.01$] and baclofen [$F(2,135)=5.97$, $P<0.01$], but no morphine × baclofen interaction ($F<1$). Further comparisons indicated that baclofen significantly attenuates morphine-lever responding at both doses (1 mg/kg: $t_{135}=2.32$, $P<0.05$; 2 mg/kg: $t_{135}=3.14$, $P<0.01$). The ANOVA relative to response rate revealed a significant effect of morphine [$F(3,135)=10.14$, $P<0.01$] and baclofen [$F(2,135)=23.69$, $P<0.01$], but no morphine × baclofen interaction [$F(6,135)=1.37$, P = NS]. Further comparisons indicated that baclofen significantly attenuates response rate at both doses (1 mg/kg: $t_{135}=2.45$, $P<0.05$; 2 mg/kg: $t_{135}=6.87$, $P<0.01$).

3.2. Experiment 2: effect of repeated baclofen treatment on the discriminative stimulus effects of morphine

Morphine generalization curves obtained in Group I rats after the first (TEST1) and second (TEST2) repeated treatment with saline (see Table 1) are shown in Fig. 2a.

As regards drug-lever responding, the ANOVA revealed a significant effect of morphine [$F(3,34)=13.93$, $P<0.01$], but no TEST effect ($F<1$) or morphine × TEST interaction ($F<1$). Likewise, the ANOVA relative to response rate indicated a significant effect of morphine [$F(3,34)=9.54$, $P<0.01$], but no TEST effect ($F<1$) or morphine × TEST interaction ($F<1$).

Thus, also in the present conditions (discriminative training halted during saline repeated treatment and daily consecutive test sessions), morphine generalization curve appears very stable.

Morphine generalization curves relative to Group II are shown in Fig. 2b. In this case, TEST2 was performed after a repeated treatment with baclofen (see Table 1).

As regards drug-lever responding, the ANOVA revealed significant morphine [$F(3,35)=12.55$, $P<0.01$] and TEST [$F(1,35)=8.11$, $P<0.01$] effects, but no morphine × TEST interaction ($F<1$). Moreover, the ANOVA relative to response rate indicated a significant effect of morphine [$F(3,35)=13.88$, $P<0.01$], but no TEST effect ($F<1$) or morphine × TEST interaction ($F<1$). Thus, repeated baclofen treatment shifts the morphine generalization curve to the right, but does not modify the rate-decreasing effect of the drug.

4. Discussion

Baclofen co-administration reduced the potency of morphine as a discriminative stimulus. The data are in keeping with previous reports supporting the role of GABAergic neurotransmission in the reinforcing (Brebner et al., 2002; Kaplan et al., 2003; Tsuji et al., 1996; Xi and Stein, 1999, 2000, 2002) and discriminative (Solecki et al., 2005) effects of opiates. Actually, Solecki et al. (2005) found that the enhancement of GABAergic transmission by GABA uptake inhibitors potently reduces heroin discriminative stimulus; however, a 0.5 mg/kg dose of baclofen was ineffective and higher amounts of the drug (1.25–2.5 mg/kg) could not be used, due to their completely suppressing effect on bar pressing activity. This was not the case in the present experiment; actually, no data met the exclusion criterion. On the other hand, Solecki et al. (2005) trained Wistar rats to discriminate heroin from saline under a two-lever fixed-ratio schedule of water reinforcement; thus, methodological differences (strain, type of reinforcer, reinforcement schedule, etc.) possibly explain the lower suppressing effect of baclofen on bar pressing activity we observed in the present experiment.

As regards Experiment 2, the data indicate that 10 day pauses in discrimination training before tests are not detrimental to discriminative performance (see Group I) and suggest that repeated baclofen treatment reduces the potency and, possibly, the efficacy (see the plateau of dose–effect curves and the lack of a morphine × TEST interaction) of morphine as a discriminative stimulus, without modifying the rate-decreasing effect of the drug. Since tests have been conducted at least 24 h after the last baclofen treatment, the results are unlikely due to any direct effect of the drug during the experimental session. In this regard it is worth noting that a repeated treatment with baclofen does not induce any significant change in the responsiveness to the locomotor effect of morphine in drug naive animals (Bartoletti et al., 2007; Woo et al., 2001); similar results have been obtained with amphetamine as the challenge drug (Bartoletti et al., 2004, 2005).

VTA appears to be critical in mediating the discriminative effects of morphine, since small doses of morphine (1–3 μg) administered into the VTA proved sufficient to produce generalization to the systemic cue (3.0 mg/kg s.c.) (Shoaib and Spanagel, 1994); moreover, intra-VTA naloxone decreased the near-100% morphine-appropriate responding produced by the s.c. training dose of morphine to approximately 55% (Krivsky et al., 2006). As already reported, several data suggest that $GABA_B$ receptor activation in the VTA inhibits mesolimbic dopaminergic transmission. Baclofen, when administered directly into the VTA in rats, decreases somatodendritic dopamine release in this area (Klitenick et al., 1992) and extracellular dopamine

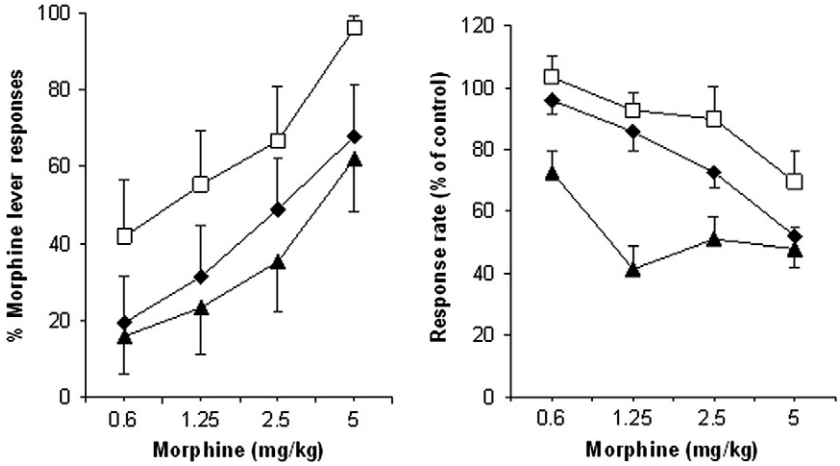

Fig. 1. Effect of baclofen and morphine co-administration on the discriminative stimulus effects of morphine. Percentages of morphine-appropriate responses (left panel) and response rates (right panel) following morphine administered with saline (□) or with two doses of baclofen (♦, 1 mg/kg; ▲, 2 mg/kg) in rats trained to discriminate 5 mg/kg morphine from saline. Each point represents the mean of 10–14 observations ± SEM.

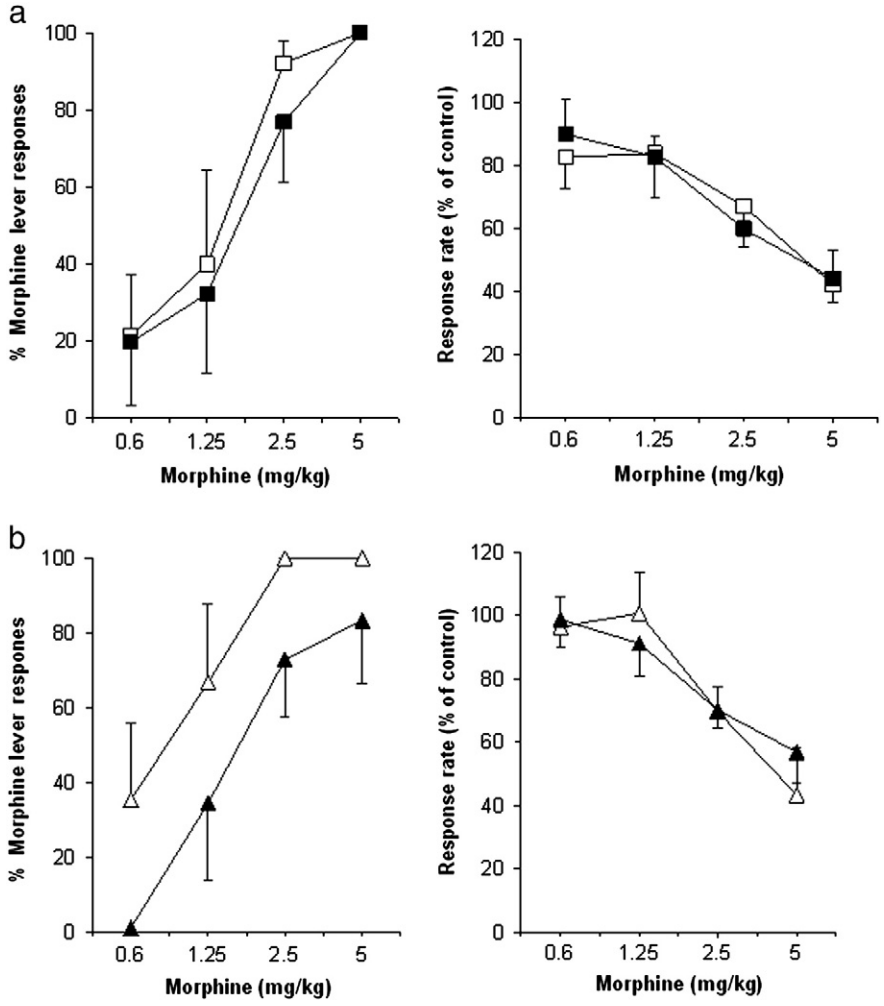

Fig. 2. (a) Morphine generalization curves in rats trained to discriminate 5 mg/kg morphine from saline and repeatedly treated with saline (TEST1 □; TEST2 ■). Morphine-appropriate responses (left panel) and response rate (right panel). Each point represents the mean of 5–6 observations ± SEM. (b) Morphine generalization curves in rats trained to discriminate 5 mg/kg morphine from saline and repeatedly treated with saline (TEST1 Δ) or with baclofen (TEST2 ▲). Morphine-appropriate responses (left panel) and response rate (right panel). Each point represents the mean of 6 observations ± SEM.

levels in the NA (Westerink et al., 1998). Furthermore, systemic administration of baclofen, at the dose used in the present experiment, does not elicit any change in basal dopamine levels in the nucleus accumbens, but dose-dependently reduces morphine-evoked dopamine release in NA (Fadda et al., 2003). Consistently, intra-accumbal infusion of the selective $GABA_B$ receptor antagonist 2-hydroxysaclofen (1 and 10 nmol), which does not alter basal dopamine efflux in the NA, enhances the endomorphin-1(25 nmol)-induced dopamine efflux (Saigusa et al., 2008).

The mechanism by which repeated baclofen treatment decreases the sensitivity to narcotic cue is not clear. However, the data are fairly reminiscent of chronic baclofen induced decrease in the motility effects of morphine in morphine-experienced animals (Bartoletti et al., 2007) and of amphetamine in amphetamine-experienced animals (Bartoletti et al., 2004). In this regard it is worth noting that Bonci and Williams (1996) described a common change in synaptic regulation of dopamine cells in the VTA after a chronic treatment with either morphine or cocaine. Actually, D1 receptor activation augmented the amplitude of a $GABA_B$ inhibitory post-synaptic potential (IPSP) in saline controls, but caused an inhibition of the $GABA_B$ IPSP in drug-experienced animals. Thus, the possibility remains that a repeated baclofen treatment might reverse a common $GABA_B$ related change in synaptic regulation of dopamine cells in the VTA. Further experiments are necessary to verify such a hypothesis.

On the whole, the data support a role for GABAergic neurotransmission in the discriminative effects of opiates and demonstrate that a short-term treatment with baclofen is useful for decreasing the sensitivity to narcotic cue. Thus, the present data add to the available evidences suggesting that modulators of $GABA_B$ receptors, such as baclofen, have potential as adjunct treatments to aid in the initiation of abstinence, maintenance of abstinence, and prevention of cue-related relapse (Tyache et al., 2010). In this regard it is worth noting that baclofen prevented heroin-induced reinstatement of heroin-seeking behaviour in rats (Spano et al., 2007); moreover, in a randomized, double-blind, placebo-controlled clinical trial the same drug was significantly superior to placebo in terms of retention in treatment, opiate withdrawal syndrome and depressive symptoms (Assadi et al., 2003). On the other hand, baclofen is considered a promising medication for alcohol (Johnson, 2008), inhalant (Muralidharan et al., 2008) and cigarette dependence (Franklin et al., 2009) (for a review see Froestl, 2010).

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