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Effects of a Dopamine D_3 Receptor Ligand, BP 897, on Acquisition and Expression of Food-, Morphine-, and Cocaine-induced Conditioned Place Preference, and Food-seeking Behavior in Rats

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The present study addressed the role of dopaminergic D_3 receptors (D_3R) in motivational processes in rats. The effects of the selective D_3R partial agonist, BP 897 (0.25–1 mg/kg, i.p.), on the establishment and the expression of conditioned place preference (CPP) supported by food, morphine (4 mg/kg, s.c.), or cocaine (2 mg/kg, s.c.) were investigated using an unbiased, one-compartment, place-conditioning procedure. When administered alone, BP 897 (0.05–2 mg/kg, i.p.) did not support CPP; on the contrary, conditioned place avoidance (CPA) was observed at 1 mg/kg, suggesting that this dose of BP 897 could be perceived as aversive. When given before each cocaine injection during the conditioning phase, BP 897 (1 mg/kg) prevented the establishment of CPP, and a single administration of BP 897 (0.5 and 1 mg/kg) before the test session impaired the expression of cocaine CPP. In contrast, neither the establishment nor the expression of food- and morphine-CPP were significantly altered by BP 897 (up to 1 mg/kg), whereas the full but less selective D_3/D_2R agonists, 7-OH-DPAT (0.5–2 μg/kg, s.c.) and quinelorane (1 μg/kg, s.c.), prevented the acquisition of food CPP. In a within-session extinction schedule of lever pressing for food, BP 897 (0.06–2 mg/kg) was ineffective in potentiating response reinstatement induced by the noncontingent delivery of two food pellets, in contrast with quinelorane and 7-OH-DPAT where previous studies showed to be efficient in this respect (Duarte *et al*, 2003). These results indicate that BP 897 has no positive appetitive value on its own, and that a moderate degree of stimulation of D_3R is not sufficient to modulate food-primed food-seeking behavior or alter incentive motivation for food, morphine, and/or their associated cues. However, D_3R are likely involved in the perception of the rewarding value of cocaine and cocaine-paired cues. This suggests that the appetitive effects of cocaine are subserved by mechanisms different, at least in part, from those of morphine and food, and that D_3R play a role only in the former.

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INTRODUCTION

Research targeting DA receptor subtypes has supported different roles for $D_{1\text{-like}}$ (D_1, D_5) and $D_{2\text{-like}}$ (D_2, D_3, D_4) receptors in the ability of rewards to elicit appetitive behavior, and pharmacological studies indicated that D_3 receptors (D_3R) might be one important component in the regulation of the reinforcing effects of drugs of abuse. For instance, in rats trained to self-administer cocaine, D_3R-preferring agonists (7-OH-DPAT, quinelorane, PD 128,907) enhanced the reinforcing efficacy of this drug and D_3R-preferring antagonists (*l*-nafadotride, (+)-AJ 76, (+)-UH 232) had the opposite effect (Caine and Koob, 1993, 1995; Richardson *et al*, 1993; Smith *et al*, 1995; Parsons *et al*, 1996; Caine *et al*, 1997, 1999), although a more selective D_3R antagonist, SB-277011-A, was inactive in this respect (Di Ciano *et al*, 2003). The D_3R-preferring agonists were self-administered (Caine and Koob, 1993; Parsons *et al*, 1996); they induced conditioned place preference (CPP) (Mallet and Beninger, 1994; Chaperon and Thiébot, 1996; Khroyan *et al*, 1997; but see Khroyan *et al*, 1995; Rodríguez de Fonseca *et al*, 1995), and/or they generalized from the *d*-amphetamine or the cocaine stimulus effects in drug-discrimination tasks (Acri *et al*, 1995; Bevins *et al*, 1997; Baker *et al*, 1998; Garner and Baker, 1999), indicating that the stimulation of D_3R may exert reinforcing effects and induce some of the subjective effects of psychostimulants.

However, initially claimed to be highly selective for D_3R (as measured by binding studies on CHO cells expressing recombinant rat or human receptors), most of the available

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ligands exhibit low selectivity ratio for rats native D_3R *vs* D_2R *in vitro* (for a review, see Levant, 1997), and serious doubts exist with respect to their *in vivo* selectivity. Therefore, a preferential involvement of this receptor subtype in appetitive processes remains questioned. In fact, D_2R antagonists, but not D_3R-preferring antagonists, blocked CPP supported by 7-OH-DPAT (Beninger *et al*, 1999), impaired rats' ability to discriminate 7-OH-DPAT from saline (Christian *et al*, 2001), and induced a rightward shift of the dose–effect function for cocaine self-administration (Caine *et al*, 2002). The stimulus generalization produced by 7-OH-DPAT in rats trained to discriminate *d*-amphetamine or cocaine from saline, was partially impaired by the D_2/D_3R nonselective antagonist, eticlopride (Bevins *et al*, 1997), but was not blocked by the D_3R-preferring antagonist, PNU-99194A (Baker *et al*, 1998). Likewise, quinelorane maintained self-administration behavior when substituted for cocaine in wild-type mice, but not in mice lacking D_2R, suggesting that D_2R are necessary for quinelorane self-administration (Caine *et al*, 2002). Thus, the behavioral effects of D_2/D_3R agonists can be often explained by an action at D_2R, and the role of D_3R in their motivational effects needs to be more clearly delineated.

Interestingly, using BP 897, a ligand that displays a higher preference ratio for D_3 over D_2 receptors ($\sim$70-fold, as measured at recombinant human receptors, and $\sim$20-fold, in functional assays (Pilla *et al*, 1999)), recent studies gave more direct evidence for an involvement of D_3R in reward-related processes. *In vivo*, BP 897 acts as a D_3R partial agonist or antagonist, at low doses, and as a weak D_2R antagonist at doses above 10 mg/kg (Pilla *et al*, 1999; Wood *et al*, 2000; Wicke and Garcia-Ladona, 2001). It was not self-administered by cocaine-experienced rats and monkeys, did not generalize from cocaine or *d*-amphetamine discriminative stimulus in rats, and did not support CPP in mice (Pilla *et al*, 1999; Beardsley *et al*, 2001; Francès *et al*, 2003), indicating that it is devoid of positive reinforcing potential. In rats trained in a second-order schedule of cocaine self-administration, BP 897 was shown to reduce operant responses maintained by the presentation of a conditioned stimulus previously associated with cocaine infusion, but failed to affect responding once cocaine was delivered (Pilla *et al*, 1999). Likewise, BP 897 antagonized the *expression* of conditioned locomotor activity induced by environmental stimuli previously paired with cocaine or amphetamine, but did not affect drug-induced hyperactivity (Aujla *et al*, 2002; Le Foll *et al*, 2002). Thus, it has been suggested that the D_3R-preferring ligand, BP 897, does not alter the perception of the appetitive effects of psychostimulants, but more likely impairs the association between environmental cues and drug effects. Therefore, D_3R might play an important role in mediating incentive motivational effects of stimuli previously associated with drugs of abuse, such as cocaine or amphetamine.

The present study investigated whether D_3R may also regulate the appetitive component of natural reinforcers (food) or other abused drugs (opiates). This was performed in rats subjected to place conditioning, a procedure that allows to assess the *perception* by animals of the appetitive value (rewarding or aversive) of a primary reinforcer, in its absence (Carr *et al*, 1989; Tzschentke, 1998). We examined whether BP 897 interfered with the establishment or the expression of CPP supported by food or morphine, and by cocaine, as a reference compound. The effects of the full but less selective D_3/D_2R agonists, 7-OH-DPAT and quinelorane, were also investigated on the acquisition of food CPP. In addition, the capacity of BP 897 to modulate *food-seeking* behavior has been evaluated in a reinstatement procedure, using a within-session extinction schedule of lever pressing for food, during which nonreinforced responses were reinstated by noncontingent delivery of food pellets.

MATERIALS AND METHODS

Animals

The experiments were carried out on male Wistar AF rats (CERJ, Le Genest, France). Rats to be subjected to place conditioning weighed 200 g at the beginning of the experiments and were drug- and test-naive. For the reinstatement procedure, rats weighed 100 g upon their arrival and ca 350 g at the time of the test sessions. All the animals were housed eight per cage ($40 \times 40 \times 18\,cm^3$) under standard conditions (12 h light–dark cycle, with light on at 0730; room temperature $21 \pm 1^{\circ}C$), with free access to water in their home cage. At 1 week prior to the beginning of the conditioning, rats were placed on a daily schedule of food restriction (see details below), which was maintained until the end of the study. The experiments were conducted in agreement with the institutional guidelines for use of animals and their care, in compliance with national and international laws and policies (Council directive no. 87–848, October 19, 1987, Ministère de l'Agriculture et de la Forêt, Service Vétérinaire de la Santé et de la Protection Animale, permissions no. 0299 to MH and no. 0597 to MHT).

Place-Conditioning Procedure

Apparatus. The experiments were conducted in a one-compartment apparatus, using an unbiased experimental design, as previously described (Guyon *et al*, 1993; Chaperon and Thiébot, 1996). The rats were trained and tested in four black, wooden open fields ($76 \times 76 \times 50\,cm^3$) located in a dimly lit room supplied with a continuous masking noise. The floor of each open field was covered with removable quadrants made of wire mesh or rough Plexiglas, which were the only discriminative stimuli in the apparatus. These textures were chosen on the basis of previous studies indicating that naive rats exhibited no unconditioned preference for one of them. Video cameras, placed 200 cm above the open fields, were connected to controlling and recording equipment, located in an adjacent room.

Experimental procedure. During the week prior to the experiments, rats were handled, weighed, and habituated to the drug administration procedure by receiving an intraperitoneal (i.p.) or subcutaneous (s.c.) injection of saline daily. Animals to be subjected to drug CPP were provided daily with 20 g/rat of standard chow (Stérilisable 113, UAR, Villemoisson, France) and rats to be subjected to food-induced CPP were given 13 g/rat/day and were also provided with a small quantity of 70 mg sucrose pellets (Formula F, Noyes Company Inc., Lancaster, NH, USA) in their home cage, to be familiarized with this food.

The general, unbiased, procedure consisted of two phases: conditioning and testing. In the conditioning phase, each rat was subjected to eight 30-min sessions (two sessions per day, 4-h apart, unless otherwise specified) during which they had unrestricted access to the entire surface of one open field whose floor was covered with four quadrants of the same texture. The drugs tested were administered before the afternoon sessions, paired with one floor texture. Saline was injected (same route, same pretreatment time) before the morning sessions, paired with the other floor texture. For food-induced place preference, weighed quantities of both sucrose pellets ($\sim$5 g) and four pieces of usual rat chow ($\sim$10 g) were evenly distributed on the four quadrants of the open field, before the afternoon conditioning sessions. During these sessions, the open fields were also provided with a bottle of water. The amounts of sucrose and usual food consumed by each rat during each of these sessions were measured separately. Our previous unpublished data indicated that rats given free access to both chow and sucrose pellets during conditioning sessions exhibited more consistent place preference during the test session than rats given chow or sucrose (or a variety of other palatable foods) alone. Food and water were not available during the morning conditioning sessions. Food– or drug-texture pairings were counterbalanced so that for half of the rats food or drug was associated with the wire mesh floor, and for the other half food or drug was associated with the Plexiglas floor.

The testing phase took place the day following the last conditioning session (except where otherwise specified). The rats were subjected to a single 20-min test session in the open field whose floor was covered by two quadrants of the saline-paired texture and two quadrants of the drug- or food-paired texture. The quadrants of the same texture were positioned diagonally opposite to each other. The time spent on each texture was scored from the videotapes by an experimenter blind to the pairing conditions. Rats were considered to be on a floor quadrant when their four paws were on that quadrant. Half of the time spent on the dividing lines was added to the total time spent on the saline- and drug- or food-paired textures. The number of quadrants crossed during the test session was also recorded.

Experiment 1: Ability of BP 897 to support place conditioning: BP 897 (0.05–2 mg/kg), or vehicle (Tween in saline) for the control group, was administered i.p., 30 min before the afternoon conditioning sessions. Animals of all groups received saline i.p., 30 min before the morning conditioning sessions. Rats were given no injection before the test session.

Experiment 2: Effects of BP 897 on the establishment and the expression of food-induced conditioned place preference: For the establishment of food-induced place conditioning, BP 897 (0.05–1 mg/kg, i.p.), or its vehicle for the control group, was injected 30 min before each conditioning session with food present in the open fields. All the rats received saline (i.p.), 30 min before each alternate conditioning session without food. Rats were given no injection before the test session.

For the expression of food-induced place conditioning, all the rats received an i.p. injection of Tween in saline (ie the vehicle to BP 897), 30 min before the conditioning sessions with food, and saline before the alternate sessions without food. BP 897 (0.05–1 mg/kg, i.p.), or its vehicle for the paired control group, was administered only once, 30 min before the test session. Food and water were not provided in the open fields during the test session.

Experiment 3: Effects of 7-OH-DPAT and quinelorane on the establishment of food-induced conditioned place preference: 7-OH-DPAT (0.5–8 μg/kg, s.c.), quinelorane (0.25–4 μg/kg, s.c.), or their vehicle for the control groups, were injected 30 min or immediately before each conditioning session with food, respectively. All the rats received saline (s.c., same pretreatment time) before each alternate conditioning session without food. Rats were given no injection before the test session; food and water were not provided in the open fields during this session.

Experiment 4: Effects of BP 897 on the establishment and the expression of morphine-induced conditioned place preference: During the conditioning phase, all the rats were given morphine (4 mg/kg, s.c.) immediately before the afternoon sessions, and saline (s.c.) immediately before the morning sessions.

For the establishment of morphine-induced place conditioning, BP 897 (0.25–1 mg/kg, i.p.), or its vehicle for the control group, was administered 30 min before the morphine-paired conditioning sessions, and all rats received saline (i.p.) 30 min before the sessions without morphine. Rats were given no injection before the test session.

For the expression of morphine-induced place conditioning, all the rats received an i.p. injection of Tween in saline (ie the vehicle to BP 897), 30 min before the morphine-paired conditioning sessions and saline (i.p.) before the alternate sessions without morphine. BP 897 (0.25–1 mg/kg, i.p.), or its vehicle for the paired control group, was administered only once, 30 min before the test session. Morphine was not injected before the test session.

Experiment 5: Effects of BP 897 on the establishment and the expression of cocaine-induced conditioned place preference: For cocaine-induced CPP, rats were subjected to a single conditioning session per day, in order to limit tissue necrosis due to daily cocaine-induced vasoconstriction. Immediately before the conditioning sessions, all the rats were administered cocaine (2 mg/kg, s.c.) and, on alternate days, saline (s.c.) according to a counterbalanced design. The test session took place 48 h after the last cocaine injection.

For the establishment of cocaine-induced place conditioning, BP 897 (0.25–1 mg/kg, i.p.), or its vehicle for the control group, was administered 30 min before each cocaine-paired conditioning session, and all rats received saline (i.p.) 30 min before the sessions without cocaine. Rats were given no injection before the test session.

For the expression of cocaine-induced place conditioning, all the rats received an i.p. injection of Tween in saline (ie the vehicle to BP 897), 30 min before the cocaine-paired conditioning sessions, and saline (i.p.) before the alternate sessions without cocaine. BP 897 (0.25–1 mg/kg, i.p.), or its vehicle for the paired control group, was administered only

once, 30 min before the test session. Cocaine was not injected before the test session.

Reinstatement Procedure

Apparatus. The experiments were conducted in four standard ventilated, sound-attenuated operant chambers (Campden Instruments Ltd, Cambridge, UK). Each cage ($24 \times 22 \times h20$ cm) was fitted with a grid floor, white stimulus lights (24 V; 3 W), and a food magazine located between two levers. The operant schedules were automatically controlled and the behavioral data were collected by an Acorn computer with software written in Arachnid version of BASIC (CeNeS Cognition, Cambridge, UK), located in an adjacent room.

General procedure. The experiments were performed using food-restricted rats (13 g/day/rat) as previously described (Duarte *et al*, 2003). Briefly, the animals were trained to press the right lever according to a fixed ratio 1 (FR_1) schedule of food delivery (45 mg pellets, F 0165, Bioserv, Frenchtown, NJ, USA). The left lever was always inactive. The light located above the right lever provided the sole illumination of the chamber. Then, rats were subjected to 1-h daily sessions divided into two successive nonsignaled components, a 15-min *rewarded component*, during which each right lever press delivered one food pellet and initiated a 10-s time out (TO) period, signaled by light off (FR_1: $TO_{10\,s}$), followed by a 45-min *extinction component* during which the right lever presses were no longer rewarded (although they generated the lever '*click*' and the 10-s light off stimuli associated with responding, as during the rewarded component). The numbers of 'appropriate' right lever presses in the presence of the 'light on' cue (ie presses rewarded during the initial 15-min component and then nonrewarded), right lever presses during the 'light off' TO periods, and left lever presses were recorded every minute. During the extinction component, the lever pressing progressively diminished and, after about five sessions, rats emitted less than five responses during the last 40 min of the session.

Rats were habituated to the injection procedure by receiving saline (i.p.), 5 min after the beginning of the extinction component. After stabilization of response, drug studies were initiated. For each test session, rats were divided into four groups of 8–9 animals, matched according to their performance during the last training session, defined as baseline. Matching was performed on the number of 'appropriate' right lever presses during the 46–60 min time interval of the extinction component, and the numbers of food-reinforced responses and TO right lever presses, during the 15-min rewarded component. During the test session, two pellets were noncontingently delivered at the end of the 45th minute, accompanied by food-paired stimuli (activation of the food dispenser and 10-s light off).

Experiment 6: Effect of BP 897 on the reinstating effect of noncontingent food pellet delivery: BP 897 (0.06–2 mg/kg), or its vehicle, was administered i.p. at the 20th min of the test session, and two pellets were noncontingently delivered at the 45th min. The entire dose range was studied in the course of two test sessions, performed 2 weeks apart, in the same series of rats. Eight additional training sessions were performed in the intervening days. Rats were given vehicle, 0.06, 0.125, or 0.25 mg/kg of BP 897 prior to the first test session, and vehicle, 0.5, 1, or 2 mg/kg of BP 897 prior to the second test session. This experimental design reduced the risk of a carry-over effect due to administration of a large dose of BP 897 first, and then a smaller one. In order to control for a possible sequence effect, as much as allowed by matching conditions, rats from one treatment group in the first test session were evenly distributed within the four treatment groups in the second test session.

Drugs

Cocaine-HCl, morphine-HCl (Coopération Pharmaceutique Française, Melun, France), ($\pm$)-7-OH-DPAT-HBr (($\pm$)-7-hydroxy-2-(di-*n*-propylamino) tetralin) (Research Biochemicals Inc., Natick, USA), and quinelorane (Eli Lilly, Indianapolis, USA) were dissolved in saline (0.9% NaCl) and administered s.c. BP 897 (1-(4-(2-naphtoylamino)butyl)-4-(2-methoxyphenyl)-1A-piperazine HCl) (Bioprojet, Paris, France) was suspended with one drop of Tween 80 in distilled water and administered i.p. Drugs and their respective vehicle for control groups were injected in a volume of 5 ml/kg. The doses are expressed as base or salt, as appropriate.

Statistical Analyses

Place conditioning. The results are expressed as the mean ($\pm$ SEM) difference between the time (in seconds) spent on the floor texture previously paired with BP 897, food, morphine, or cocaine, and the time spent on the unpaired texture (time difference). In each group, place conditioning was assessed by comparing the time spent on the texture previously paired with BP 897, food, morphine, or cocaine, with the time spent on the unpaired texture, using paired Student's *t*-test (two-tailed). Overall drug effects on the time differences were analyzed by one-way analysis of variance (ANOVA) with the dose of the drug studied (BP 897, 7-OH-DPAT or quinelorane) as an independent factor. Planned comparisons of time differences between drug treatment groups and their respective controls were then made using two-tailed Dunnett's *t*-test. The mean quantities of sucrose and usual food consumed during each conditioning session (experiments 2 and 4), were analyzed by one-way ANOVAs. The entire dose ranges of BP 897 alone (experiment 1), 7-OH-DPAT, and quinelorane (experiment 2), were studied in the course of two independent experiments; a vehicle control group of rats was associated to each individual experiment; the 0.5 and 1 mg/kg doses of BP 897 and the 2 μg/kg dose of 7-OH-DPAT were also tested twice. In each case, there were no statistically significant differences between control performance, and the results of both experiments were grouped for global analysis. This accounts for the between-group differences in the number of animals included in these dose-range studies.

Reinstatement procedure. The results were expressed as the mean ($\pm$ SEM) number of right lever presses performed in the presence of the 'light on' signal, during the 46–60 min period of the extinction component. There were no

statistically significant differences between the test performance of control groups to the two successive test sessions; thus, the results of both experiments were grouped for overall analysis. Results were analyzed by one-way ANOVA with the dose of BP 897 as an independent factor. Within-group comparisons to baseline response, recorded during the corresponding period of the previous training session, were made using two-tailed paired Student's *t*-test.

RESULTS

Experiment 1: Ability of BP 897 to Support Place Conditioning (Figure 1)

Control rats (given saline before the morning conditioning sessions and vehicle before the afternoon sessions) exhibited individual preference for either floor texture, but the mean time spent on the paired texture during the 1200-s test session was 602 ± 45 s (lower and upper 95% confidence intervals ($CI_{95\%}$): 488, 715 s). This indicates that there was no unconditioned preference for either floor texture, as shown in previous studies (Guyon *et al*, 1993; Chaperon and Thiébot, 1996).

Rats given the 1 mg/kg dose of BP 897 spent significantly less time on the paired texture than on the unpaired texture ($t = 3.09$; $p < 0.01$). The ANOVA indicated that BP 897 (0.05–2 mg/kg) induced no overall change in time differences ($F_{4,91} = 1.21$; $p = 0.31$), and planned comparisons to the control group confirmed that none of the tested doses of BP 897 induced a significant effect (largest Dunnett's $t = 2.01$; $0.05 < p < 0.10$). These results indicate that BP 897 supported conditioned place aversion at the 1 mg/kg dose only, and that there was no dose-related effect. The number of quadrants crossed during the test session was not modified by BP 897 administered before the conditioning sessions ($F_{4,91} < 1$) (not shown).

Experiment 2: Effects of BP 897 on the Establishment and the Expression of Food-Induced Conditioned Place Preference (Figure 2)

The time spent on the food-paired texture by vehicle-injected rats during the test session was 710 ± 43 s ($CI_{95\%}$: 616, 805 s) in the establishment experiment, and 725 ± 52 s ($CI_{95\%}$: 610 s, 840 s) in the expression experiment. The comparisons with the corresponding time spent on the unpaired texture indicated a significant preference for the floor texture previously paired with food ($t = 2.56$ and 2.38, respectively; $p < 0.05$). As indicated by significant differences between the times spent on the paired and unpaired textures, food CPP was also observed in rats given BP 897 (0.05–1 mg/kg) administered at the acquisition stage (lowest $t = 2.27$; $p < 0.05$), or as a single injection before the test session (lowest $t = 2.19$; $p = 0.05$). Accordingly, the ANOVAs indicated no significant main effect of BP 897 on the time differences (both $F_{3,44} < 1$).

The quantities of sucrose pellets and usual food eaten during the conditioning phase were not changed by BP 897 (not shown). The number of quadrants crossed during the test session was not modified by BP 897 administered before either the four conditioning sessions ($F_{3,44} = 2.80$; NS) or the test session ($F_{3,44} < 1$) (not shown).

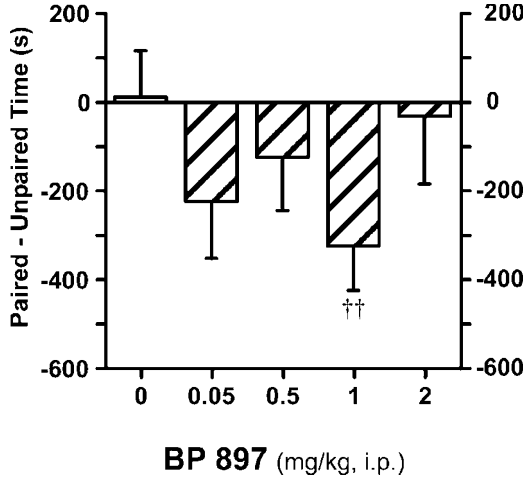

Figure 1 Place conditioning supported by BP 897 alone (experiment 1). Histograms represent the mean (± SEM) difference between the time (seconds) spent on the floor texture previously paired with BP 897 and the time spent on the unpaired texture, during the 20-min test session. Positive and negative values indicate preference and aversion for the paired texture, respectively. BP 897 was injected i.p., 30 min before each of the four afternoon conditioning sessions. Rats were drug-free during the test session. Number of rats per group and 95% lower and upper confidence intervals ($CI_{95\%}$): 0 mg/kg ($n = 24$): −224, +231 s; 0.05 mg/kg ($n = 12$): −540, +117 s; 0.5 mg/kg ($n = 24$): −369, +133 s; 1 mg/kg ($n = 24$): −528, −105 s; 2 mg/kg ($n = 12$): −414, +371 s. $^{††}p < 0.01$; time spent on the BP 897-paired texture *vs* unpaired texture (paired Student's *t*-test). The ANOVA did not reveal significant overall effect ($F_{4,91} = 1.21$).

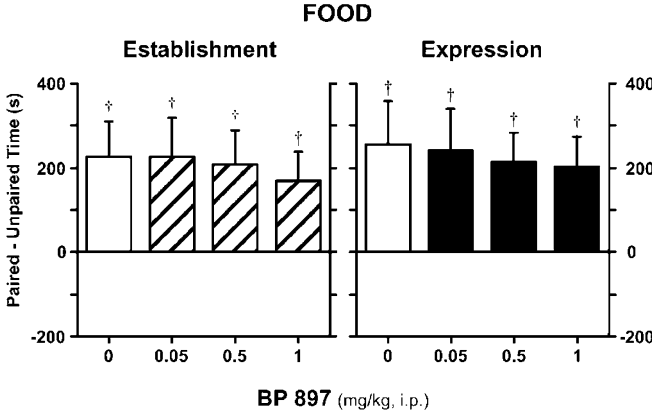

Figure 2 Effects of BP 897 on the establishment and the expression of conditioned place preference induced by food (experiment 2). Histograms represent the mean (± SEM) difference between the time (seconds) spent on the floor texture previously paired with food and the time spent on the unpaired texture, during the 20-min test session. Positive values indicate preference for the food-paired texture. BP 897 (i.p.), or its vehicle, was administered either 30 min before each of the four food-paired conditioning sessions, for the establishment of CPP, or only once, 30 min before the test session, for the expression of CPP. During the test session, food was not present in the open fields. $CI_{95\%}$: acquisition ($n = 12$ rats per group) – 0 mg/kg: +31, +410 s; 0.05 mg/kg: +7, +432 s; 0.5 mg/kg: +16, +388 s; 1 mg/kg: +9, +318 s. Expression ($n = 12$ rats per group) – 0 mg/kg: +19, +481 s; 0.05 mg/kg: −15, +499 s; 0.5 mg/kg: +47, +369 s; 1 mg/kg: +30, +362 s. $^{†}p < 0.05$; time spent on the food-paired texture *vs* unpaired texture (paired Student's *t*-test). The ANOVAs did not reveal significant overall effect of BP 897 (both $F_{3,44} < 1$).

Experiment 3: Effects of 7-OH-DPAT and Quinelorane on the Establishment of Food-Induced Conditioned Place Preference (Figure 3)

The time spent on the food-paired texture by control rats to the 7-OH-DPAT and quinelorane experiments was 726 ± 20 ($CI_{95\%}$: 684, 768 s) and 699 ± 28 s ($CI_{95\%}$: 640, 757 s), respectively. Comparisons with the corresponding time spent on the unpaired texture indicated a significant preference for the floor texture previously paired with food ($t = 6.18$ and 3.51, respectively; $p < 0.01$).

In rats given 7-OH-DPAT before food-paired conditioning sessions, whatever the dose (0.5–4 μg/kg), such a preference for the paired texture was no longer observed. The ANOVA indicated that 7-OH-DPAT induced an overall modification of the time differences ($F_{5,73} = 3.14$; $p < 0.02$), and planned comparisons to controls showed that the establishment of food CPP was disrupted at the doses of 0.5 μg/kg ($t = 2.72$; $p < 0.05$), 1 μg/kg ($t = 2.60$; $p < 0.05$), and 2 μg/kg ($t = 3.34$; $p < 0.01$), but not at higher doses (4 and 8 μg/kg). Prepairing injections of 7-OH-DPAT had no consequence on the number of quadrants crossed during the test session ($F_{5,73} = 1.18$; NS), and did not modify the quantities of sucrose pellets and usual food consumed during conditioning sessions ($F_{5,73} = 1.68$ and 1.94, respectively; NS) (not shown).

In rats given quinelorane before food-paired conditioning sessions, whatever the dose (0.25–2 μg/kg), the preference for the food-paired texture no longer existed. The ANOVA indicated only a trend towards a main effect of quinelorane on time differences ($F_{5,66} = 1.64$; $p = 0.16$). However, planned comparisons to the control group showed that the establishment of food CPP was abolished in rats given the 1 μg/kg dose ($t = 2.80$; $p < 0.05$). Prepairing injections of quinelorane had no consequence on the number of quadrants crossed during the test session ($F_{5,66} = 1.11$; NS) (not shown). Data reported in Table 1 indicate that quinelorane induced overall changes of sucrose pellets and usual food consumed during conditioning sessions ($F_{5,66} = 2.95$; $p < 0.02$; and 2.58; $p < 0.05$, respectively), but there were no significant doses × sessions interactions. Comparisons with quantities eaten by control rats indicated a quinelorane-induced increase in the usual food consumed, which reached the critical level of statistical significance ($p < 0.05$) at the 2 μg/kg dose only. Sucrose intake was marginally reduced by quinelorane, and this effect was inconsistent across the doses and the sessions.

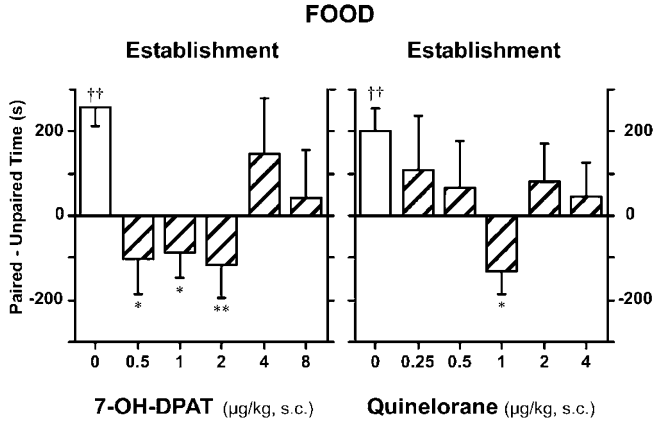

Figure 3 Effects of 7-OH-DPAT and quinelorane on the establishment of conditioned place preference induced by food (experiment 3). Histograms represent the mean (± SEM) difference between the time (seconds) spent on the floor texture previously paired with food and the time spent on the unpaired texture, during the 20-min test session. Positive and negative values indicate preference and aversion for the food-paired texture, respectively. 7-OH-DPAT (s.c.) or quinelorane (s.c.), or their vehicle, were injected 30 or 0 min, respectively, before each of the four food-paired conditioning sessions. During the test session, rats were drug-free and food was not present in the open fields. $CI_{95\%}$: 7-OH-DPAT – 0 μg/kg ($n = 20$): +168, +355 s; 0.5 μg/kg ($n = 10$): −295, +106 s; 1 μg/kg ($n = 10$): −224, +67 s; 2 μg/kg ($n = 19$): −299, +99 s; 4 μg/kg ($n = 10$): −168, +450 s; 8 μg/kg ($n = 10$): −252, +329 s. Quinelorane – 0 μg/kg ($n = 22$): +80, +322 s; 0.25 μg/kg ($n = 10$): −190, +397 s; 0.5 μg/kg ($n = 10$): −203, +323 s; 1 μg/kg ($n = 10$): −291, +14 s; 2 μg/kg ($n = 10$): −136, +286 s; 4 μg/kg ($n = 10$): −149, +232 s. $^{††}p < 0.01$; time spent on the food-paired texture *vs* unpaired texture (paired Student's *t*-test). $^{*}p < 0.05$; $^{**}p < 0.01$ *vs* the associated control group given food alone (Dunnett's *t*-test after ANOVA).

Experiment 4: Effects of BP 897 on the Establishment and the Expression of Morphine-induced Conditioned Place Preference (Figure 4)

The time spent on the texture paired with morphine (4 mg/kg) by vehicle-injected rats during the test session was 807 ± 77 s ($CI_{95\%}$: 638, 976 s) in the establishment experiment, and 769 ± 74 s ($CI_{95\%}$: 600, 937 s) in the expression experiment. Comparisons with the corresponding time spent on the unpaired texture indicated a significant preference for the floor texture previously paired with morphine ($t = 2.70$ and 2.26, respectively; $p < 0.05$).

Rats given BP 897 (0.25 or 0.5 mg/kg) at the acquisition stage also exhibited morphine CPP, as indicated by significant differences between the times spent on the paired and unpaired textures (0.25 mg/kg: $t = 2.19$; $p = 0.05$; 0.5 mg/kg: $t = 2.21$; $p < 0.05$), whereas rats given the 1 mg/kg dose no longer exhibited preference for the morphine-paired texture ($t = 0.92$; NS). Morphine CPP was also observed in rats given a single injection of BP 897 (0.25–1 mg/kg) before the test session, as revealed by significant differences between the times spent on the paired and unpaired textures (lowest $t = 2.34$; $p < 0.05$). Accordingly, the ANOVAs showed no significant main effect of BP 897 on the time differences, whenever it was administered at the conditioning stage ($F_{3,44} = 0.42$; NS) or before the test session ($F_{3,36} = 0.55$; NS), indicating that the effects of BP 897 were not dose-related.

In these two experiments, BP 897 did not modify the number of quadrants crossed during the test session (both $F < 1$) (not shown).

Experiment 5: Effects of BP 897 on the Establishment and the Expression of Cocaine-induced Conditioned Place Preference (Figure 5)

The time spent on the texture paired with cocaine (2 mg/kg) by vehicle-injected rats during the test session was 773 ± 50 s ($CI_{95\%}$: 659, 887 s) in the establishment experiment, and 826 ± 60 s ($CI_{95\%}$: 690, 962 s) in the expression experiment. Comparisons with the corresponding time spent on the unpaired texture indicated a significant

Table 1 Effects of Quinelorane on Sucrose and Usual Food Intake During the Four Food-Texture Pairing Sessions (experiment 3)

	Mean (± SEM) food intake (g) during conditioning sessions			
Quinelorane (μg/kg, s.c.)	**# 1**	**# 2**	**# 3**	**# 4**
Sucrose				
Vehicle	1.75 ± 0.25	2.76 ± 0.27	3.02 ± 0.28	2.69 ± 0.24
0.25	2.14 ± 0.34	2.75 ± 0.50	2.34 ± 0.21	3.03 ± 0.48
0.5	1.22 ± 0.34	2.09 ± 0.29	2.53 ± 0.38	3.02 ± 0.42
1	0.92 ± 0.20	1.95 ± 0.41	1.79 ± 0.33†	1.94 ± 0.31
2	0.97 ± 0.37	1.69 ± 0.47	2.20 ± 0.46	1.85 ± 0.40
4	1.08 ± 0.30	1.56 ± 0.49†	1.84 ± 0.51	1.63 ± 0.35†
$F_{5,66}$	= 2.64; $p < 0.05$	= 1.91; NS	= 1.97; NS	= 2.81; $p < 0.05$
Usual food				
Vehicle	3.26 ± 0.26	3.54 ± 0.19	3.21 ± 0.16	3.67 ± 0.20
0.25	3.32 ± 0.23	4.02 ± 0.33	4.03 ± 0.22	4.09 ± 0.22
0.5	3.72 ± 0.31	4.01 ± 0.27	4.01 ± 0.38	3.97 ± 0.45
1	4.01 ± 0.32	4.39 ± 0.53	3.45 ± 0.67	4.20 ± 0.42
2	3.79 ± 0.39	4.46 ± 0.40†	4.66 ± 0.36*	5.29 ± 0.39**
4	3.22 ± 0.22	4.03 ± 0.36	4.06 ± 0.45	4.24 ± 0.36
$F_{5,66}$	= 1.16; NS	= 1.31; NS	= 2.37; $p < 0.05$	= 2.98; $p < 0.02$

Quinelorane was injected immediately before each 30-min conditioning session with food ($n = 22$ in control group; $n = 10$ in all treated groups). *$p < 0.05$; **$p < 0.01$; $^{\dagger}0.05 < p < 0.10$ *vs* associated control group (Dunnett's *t*-test after ANOVA).

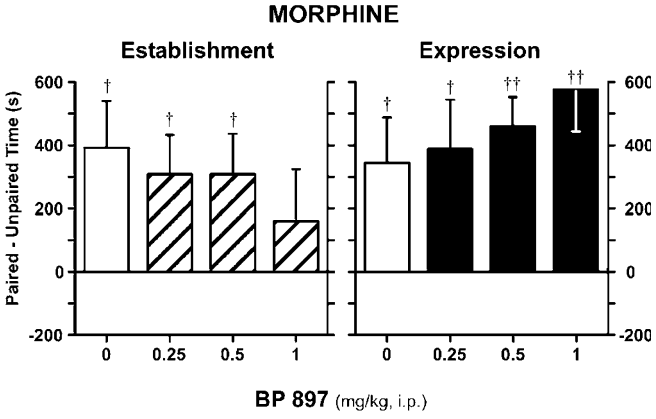

Figure 4 Effects of BP 897 on the establishment and the expression of conditioned place preference induced by morphine (experiment 4). Histograms represent the mean (± SEM) difference between the time (s) spent on the floor texture previously paired with morphine (4 mg/kg, s.c.) and the time spent on the unpaired texture, during the 20-min test session. Positive values indicate preference for the morphine-paired texture. BP 897 (i.p.), or its vehicle, was administered either 30 min before each of the four morphine-paired conditioning sessions for the establishment of CPP, or only once, 30 min before the test session, for the expression of CPP. $CI_{95\%}$: acquisition ($n = 12$ rats per group) – 0 mg/kg: +55, +716 s; 0.25 mg/kg: −1, +609 s; 0.5 mg/kg: +1, +598 s; 1 mg/kg: −215, +522 s. Expression ($n = 10$ rats per group) – 0 mg/kg: +1, +674 s; 0.25 mg/kg: −13, +744 s; 0.5 mg/kg: +233, +670 s; 1 mg/kg: +276, +860 s. $^{\dagger}p < 0.05$; time spent on the morphine-paired texture *vs* unpaired texture (paired Student's *t*-test). The ANOVAs did not reveal significant overall effect of BP 897 ($F_{3,44}$ and $F_{3,36} < 1$).

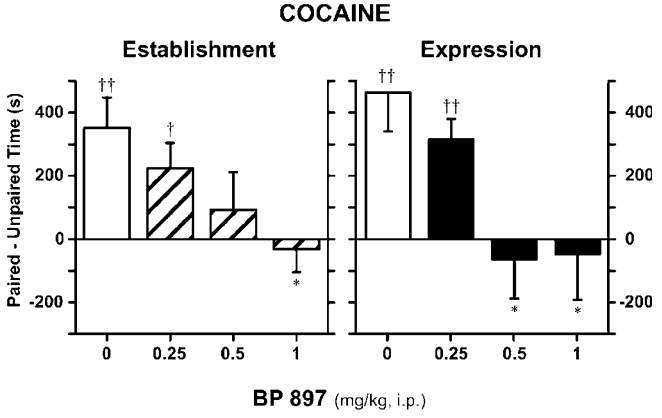

Figure 5 Effects of BP 897 on the establishment and the expression of conditioned place preference induced by cocaine (experiment 5). Histograms represent the mean (± SEM) difference between the time (s) spent on the floor texture previously paired with cocaine (2 mg/kg, s.c.) and the time spent on the unpaired texture, during the 20-min test session. Positive and negative values indicate preference and aversion for the cocaine-paired texture, respectively. BP 897 (i.p.), or its vehicle, was administered either 30 min before each of the four cocaine-paired conditioning sessions, for the establishment of CPP, or only once, 30 min before the test session, for the expression of CPP. $CI_{95\%}$: acquisition – 0 mg/kg ($n = 10$): +119, +574 s; 0.25 mg/kg ($n = 10$): −12, +454 s; 0.5 mg/kg ($n = 9$): −197, +370 s; 1 mg/kg ($n = 10$): −194, +147 s. Expression ($n = 10$ rats per group) – 0 mg/kg: +181, +725 s; 0.25 mg/kg: −144, +466 s; 0.5 mg/kg: −366, +252 s; 1 mg/kg: −380, +299 s. $^{\dagger}p < 0.05$; $^{\dagger\dagger}p < 0.01$; time spent on the cocaine-paired texture *vs* unpaired texture (paired Student's *t*-test). *$p < 0.05$ *vs* the associated control group given cocaine alone (Dunnett's *t*-test after ANOVA).

preference for the floor texture previously paired with cocaine ($t = 3.44$ and 3.77, respectively; $p < 0.01$).

Rats given the 0.25 mg/kg dose of BP 897 also exhibited morphine CPP, as indicated by significant differences between the times spent on the paired and unpaired textures, whenever the treatment was administered at the conditioning stage ($t = 2.20$; $p < 0.05$) or before the test session ($t = 4.28$; $p < 0.01$). On the contrary, rats given the 0.5 and 1 mg/kg doses, either during acquisition or before expression, no longer exhibited preference for the cocaine-paired texture (all $t < 1$). The ANOVA calculated on data obtained in the establishment experiment indicated only a trend towards a main effect of BP 897 on time differences ($F_{3,35} = 2.53$; $p = 0.07$). Nevertheless, planned comparisons to the control group revealed that the establishment of cocaine CPP was abolished in rats given the 1 mg/kg dose ($t = 2.61$; $p < 0.05$). The ANOVA calculated on data obtained in the expression experiment, showed an overall effect of BP 897 on time differences ($F_{3,36} = 4.28$; $p = 0.01$), and planned comparisons to the control group indicated that this was due to the 0.5 and 1 mg/kg doses that abolished the expression of cocaine CPP ($t = 2.93$ and 2.84, respectively; $p < 0.05$).

In these two experiments, BP 897 did not modify the number of quadrants crossed during the test session (both $F < 1$) (not shown).

Experiment 6: Effect of BP 897 on the Reinstating Effect of Noncontingent Food Pellet Delivery (Table 2)

During training sessions, rats usually emitted no more than one response on the right lever in the final 15-min interval of the extinction component. Two food pellets noncontingently delivered at the 45th minute reinstated nonreinforced right lever presses during 3–4 min after food collection. In control rats, this effect was small, but statistically significant, compared to individual responses recorded during the 46–60-min time interval of the preceding training session ($t_{15} = 4.18$; $p < 0.01$). BP 897 (0.06–2 mg/kg) administered at the 20th minute of the test session induced no overall modification of the number of nonrewarded lever presses emitted after the noncontingent pellet delivery ($F_{6,61} < 1$). Whatever the drug condition, response on the left (inactive) lever remained at a near-zero level after noncontingent pellet delivery (not shown).

Table 2 Effect of BP 897 on the Priming Effect of Two Noncontingent Pellets Delivered at the 45th Minute of the Test Session, on Nonreinforced Right Lever Presses During the Following 15 min (experiment 6)

		Number of nonreinforced right lever presses in the 46–60-min time interval (mean ± SEM)	
BP 897 mg/kg	***n***	**Baseline session, no pellet**	**Test session, two free pellets**
Vehicle	16	0.63 ± 0.15	4.81 ± 0.98††
0.06	9	0.56 ± 0.24	4.33 ± 0.76
0.125	8	0.56 ± 0.38	6.63 ± 0.96
0.25	8	0.56 ± 0.38	4.00 ± 0.87
0.5	9	0.78 ± 0.46	5.33 ± 1.09
1	9	0.89 ± 0.56	3.33 ± 0.94
2	9	0.89 ± 0.61	3.56 ± 0.87

BP 897 was injected i.p., at the 20th minute of the test session. Baseline session refers to the preceding training session (all rats given saline at the 20th minute, no free pellet). *n* = number of rats per group. $^{\dagger\dagger}p < 0.01$; in vehicle control rats, test session *vs* baseline (paired Student's *t*-test). ANOVA did not reveal the overall effect of BP 897 during the test session.

Discussion

The main finding of the present study is that BP 897, a selective D_3R ligand with partial agonist or antagonist activity *in vivo*, impairs the CPP induced in rats by cocaine, but not that supported by food or morphine.

On its own, BP 897 did not support CPP. This result is in keeping with data from self-administration and drug discrimination studies, showing that BP 897 has no positive appetitive value and does not share the stimulus effects of psychostimulants (Pilla *et al*, 1999; Beardsley *et al*, 2001). On the contrary, a trend towards conditioned place avoidance (CPA) was observed, an effect also obtained at the same dose (1 mg/kg) by Gyertyán and Gál (2003), whereas, in mice, BP 897 was reported to induce neither CPP nor CPA (Francès *et al*, 2003). Preclamol, a partial agonist at D_2 autoreceptors, and the D_3R antagonists, *l*-nafadotride (~10-fold selective for rat D_3R over D_2R, *in vivo* (Griffon *et al*, 1995)), U-99194A (~20-fold selective for D_3R *vs* D_2R expressed in CHO cells (Waters *et al*, 1993)), and SB-277011-A (>100-fold selective for rat D_3R over D_2R expressed in CHO cells (Reavill *et al*, 2000)), seem devoid of incentive properties (Chaperon and Thiébot, 1996; Kivastik *et al*, 1996; Boyce and Risinger, 2002; Vorel *et al*, 2002; Gyertyán and Gál, 2003). However, in other studies, U-99194A has been shown to support CPP (Kling-Petersen *et al*, 1995; Gyertyán and Gál, 2003). On the other hand, numerous convergent studies indicated that distinct to BP 897, D_3R full agonists shared with D_1/D_2 nonselective and D_2 selective agonists the capacity to establish CPP (Hoffman and Beninger, 1988; Papp, 1988; Mallet and Beninger, 1994; Kling-Petersen *et al*, 1995; Khroyan *et al*, 1997), although some inconsistencies also exist in this respect (Rodríguez de Fonseca *et al*, 1995; Khroyan *et al*, 1997; Gyertyán and Gál, 2003). In fact, D_3R-preferring agonists may exhibit biphasic effects on place conditioning. For instance, in the range of very low doses claimed to be D_3-selective (Pritchard *et al*, 2003), 7-OH-DPAT supported CPA, whereas CPP occurred at larger doses (Chaperon and Thiébot, 1996). It has been proposed that these agonists induce CPA by activating inhibitory D_3 (or D_2) autoreceptors, thereby reducing DA outflow, and CPP when they also stimulate postsynaptic D_2R (Chaperon and Thiébot, 1996). The CPA observed at the 1 mg/kg dose of BP 897 could be subserved by similar selective (but moderate) activation of D_3R-related inhibitory mechanisms, whereas CPP did not appear at a larger dose due to the higher selectivity of BP 897 for D_3R and/or its low antagonist activity at D_2R (although the doses reported to interact with D_2R *in vivo* are much above those used in the present study (Pilla *et al*, 1999)). As a whole, the absence of positive appetitive effect of partial agonists

indicates that a low intrinsic activity is not sufficient for activating the D_3 or other $D_{2\text{-like}}$ receptors involved in reward processes.

BP 897 did not alter food CPP, whenever it was administered at the acquisition or the expression phase, and did not modify the quantities of food consumed during the conditioning sessions. Thus, BP 897 seems to interfere with neither the perceived appetitive value of food nor the capacity of the food-paired cues to elicit approach behavior in the absence of food. These results are reminiscent of those obtained with D_3R-preferring antagonists, since SB-277011-A (10 mg/kg) did not disrupt the expression of food-CPP (Vorel *et al*, 2002) and *l*-nafadotride (0.5–1 mg/kg) did not prevent the establishment of food CPP, whereas a lower dose (0.125 mg/kg) facilitated the development of food CPP (Chaperon and Thiébot, 1996). By contrast, 7-OH-DPAT and quinelorane, which exhibit full intrinsic agonist activity, but poor D_3/D_2 selectivity (preference ratio <10, for D_3 over D_2 rat native receptors (Levant, 1997)), prevented the establishment of food CPP, in the μg/kg dose range. During the conditioning sessions, quinelorane modified rats' choice between sucrose and regular chow (whose intake was decreased and increased, respectively), but this effect was marginal and neither dose-related nor consistent across the conditioning sessions. In addition, food consumption was not affected by 7-OH-DPAT. Therefore, the impairment of the establishment of food CPP by these full agonists unlikely resulted from primary actions on feeding behavior, but very probably involved stimulus–reward associations. Interestingly, the doses of 7-OH-DPAT (0.5–2 μg/kg) and quinelorane (1 μg/kg) active to prevent food CPP were in the range of their ED_{50} for inhibition of DA neuron firing in the ventral tegmental area and/or substantia nigra (Liu *et al*, 1994; Kreiss *et al*, 1995; Lejeune and Millan, 1995; Wicke and Garcia-Ladona, 2001). Since the latter effect has been claimed to be more closely related to drug affinity at D_3 than D_2 receptors (Kreiss *et al*, 1995), this supports a preferential role for D_3R in the action of very low doses of full $D_{2\text{-like}}$ agonists. Therefore, the prevention by 7-OH-DPAT and quinelorane of food CPP can be tentatively explained by a reduction of dopaminergic transmission via a D_3R-mediated blockade of DA neuron firing, a selective activation of $D_{2\text{-like}}$ autoreceptors responsible for negative feedback control of DA release, and/or a preferential stimulation of postsynaptic D_3R (relative to D_2R) that exerts a negative control upon D_1/D_2R-mediated activation of reward systems. The potentiation of food CPP by a low dose of nafadotride (Chaperon and Thiébot, 1996) could rely upon inverse mechanisms. On the other hand, a moderate degree of stimulation of D_3R (or a relative blockade of otherwise stimulated D_3R) by BP 897 does not seem sufficient to interfere with dopaminergic transmission in reward-related pathways and modify the perception by rats of the incentive value of food and food-associated cues.

In the reinstatement procedure of extinguished response for food, the noncontingent delivery of two food pellets during the extinction component resulted in a modest recovery of nonrewarded response, as already reported (McFarland and Kalivas, 2001; Duarte *et al*, 2003). Such a priming effect, initially observed with drugs, has been proposed as an operational measure of seeking behavior, that is, enhanced motivation for the reinforcer (Carroll and Comer, 1996; Meil and See, 1996; Shalev *et al*, 2002). Drug- and food-priming effects can be differentially modulated by dopaminergic drugs (Self *et al*, 1996; Khroyan *et al*, 2000; Alleweireldt *et al*, 2002; Vorel *et al*, 2002; Duarte *et al*, 2003). However, the present study shows that over a large range of doses, BP 897 did not interfere with the reinstating effect of food priming. Previous results indicated that nafadotride was also ineffective, whereas low doses of 7-OH-DPAT and quinelorane potentiated food-primed food-seeking responses. The latter effect, which disappeared at larger doses, has been related to a preferential activation of D_3R, although an involvement of D_2R cannot be ruled out (Duarte *et al*, 2003). Thus, distinct to full agonists, BP 897 did not interact with the dopaminergic processes triggered by the unexpected delivery of food and its consumption, which are responsible for food-seeking behavior.

In the present study, BP 897 did not dose-dependently block the establishment or the expression of CPP supported by morphine (4 mg/kg), indicating that BP 897 neither altered the perceived appetitive value of morphine, nor impair the capacity of environmental cues reliably associated with this opiate to elicit approach behavior. However, rats given the 1 mg/kg dose no longer exhibited preference for the morphine-paired texture, suggesting that BP 897 might marginally reduce the appetitive valence of morphine. Alternatively, since CPA was observed at this dose, it cannot be excluded that BP 897 had nonspecifically interfered with the establishment of morphine CPP by producing a counterbalanced aversive effect during the conditioning sessions. Accordingly, BP 897 administered before the test session tended to lengthen (albeit non-significantly) the time spent on the texture previously paired to morphine, as if rats would seek the environment that was rewarding to counteract the malaise induced by BP 897 during the test session. However, such a possibility seems very unlikely since BP 897 did not tend to favor the expression of CPP supported by food or cocaine. Distinct to the present results, a study conducted in mice indicated that environmental cues previously paired with morphine (16 mg/kg) coadministered with BP 897 (0.1 and 0.5 mg/kg) were preferred to cues associated with morphine alone, suggesting that under these particular pairing conditions, BP 897 *enhanced* the perception by animals of the motivational strength of morphine (Francès *et al*, 2003). Data from a variety of pharmacological or genetic studies investigating the role of D_3R in opiate incentive learning are also rather variable and contradictory. In mice, the D_3R-preferring antagonist, PNU-99194A, prevented CPP induced by morphine, 16 mg/kg (Francès *et al*, 2003), but not 40 mg/kg (Manzanedo *et al*, 2001). In rats, the D_3R antagonist, SB-277011-A (10 mg/kg), blocked both the establishment and the expression of heroin CPP (Ashby Jr *et al*, 2003). At odds with these results, the D_3R gene deletion *potentiated* the incentive effect of morphine as indicated by a 10-fold leftward shift of the dose–effect function for morphine CPP in D_3R knockout mice (Narita *et al*, 2003). Finally, the D_3/D_2R full agonists, 7-OH-DPAT (5 and 10 mg/kg) and quinelorane (0.1 mg/kg), *potentiated* morphine stimulus effects in mice (Francès *et al*, 2003), whereas, in rats, 7-OH-DPAT impaired morphine (1 mg/kg) CPP (Rodríguez de Fonseca *et al*, 1995). In the latter study, the expression of conditioning was blocked by a low dose (10 μg/kg) of

7-OH-DPAT, but curiously, the acquisition was impaired by doses (0.25 and 5 mg/kg) 100–5000-fold higher than those that prevented food CPP (present study), and which were in the range of those supporting CPP on their own, probably through a stimulation of postsynaptic D_2R (Mallet and Beninger, 1994; Chaperon and Thiébot, 1996). Altogether, these results suggest that D_3R may be a component for the modulation of brain reward systems ensuring the perception of the incentive value of opiates, but the exact direction of their influence seems largely to depend on the intrinsic activity and the doses of the D_3R ligands considered, on the dose of morphine used to establish CPP, on the species, and/or on the specific experimental conditions. Clearly, this point deserves further investigations.

BP 897 dose-dependently impaired both the establishment and the expression of CPP induced by cocaine. Since rats experienced conditioning and test sessions in a different drug state (cocaine + BP 897 *vs* no drug, or cocaine *vs* BP 897), it cannot be excluded that a state-dependent learning participated in this effect, even though there is scarce evidence to suggest a crucial role for such a phenomenon in CPP produced by stimulants and opiates (for discussion see Carr *et al*, 1989). However, since CPP supported by food or morphine was not (or only marginally) altered by BP 897, it seems very unlikely that state dependency could account for the reversal of cocaine-CPP by BP 897. In keeping with a study showing that BP 897 reduced the discriminative stimulus effect of cocaine in mice (Beardsley *et al*, 2001), the present results suggest that this D_3R partial agonist attenuated the perception of the appetitive value of cocaine by rats. By contrast, Gyertyán and Gál (2003) reported no blockade of the establishment of cocaine (10 mg/kg) CPP by BP 897 (0.5–1 mg/kg). With regard to antagonists, SB-277011-A (1–10 mg/kg), injected at either the acquisition or the expression phase, abolished cocaine (15 mg/kg) CPP (Vorel *et al*, 2002), and the $D_{2\text{-like}}R$ antagonist, haloperidol (0.03–0.1 mg/kg), impaired the expression of cocaine (10 mg/kg) CPP (Adams *et al*, 2001). However, other studies reported no reduction of cocaine CPP by SB 277011-A (5–20 mg/kg), PNU 99194A (12–24 mg/kg), and nafadotride (1 mg/kg), given at the conditioning phase (Gyertyán and Gál, 2003), raclopride (0.03–0.1 mg/kg, pretest) (Adams *et al*, 2001), and sulpiride (50–100 mg/kg, preconditioning or pretest) (Cervo and Samanin, 1995). Likewise, agonists may apparently exert variable effects. A rightward shift in the dose–response curve of CPP induced by cocaine (3.75–30 mg/kg) was reported with 7-OH-DPAT (0.1 mg/kg); in particular this moderate dose, devoid of appetitive effect on its own, completely prevented CPP normally supported by the lowest dose of cocaine tested, indicating that 7-OH-DPAT *reduced* the incentive effect of cocaine (Khroyan *et al*, 1999). The $D_{2\text{-like}}R$ *partial* agonist, preclamol (8 mg/kg, a rather high dose), attenuated the acquisition of cocaine CPP, whereas the *full* agonist, quinpirole, at a low dose (0.05 mg/kg) supposed to act selectively at $D_{2\text{-like}}$ autoreceptors, was devoid of any effect (Kivastik *et al*, 1996). Thus, here again, depending on the studies, results are quite contradictory, and suggest a nonexclusive role of D_3R in the perception of the incentive value of cocaine and cocaine-associated stimuli by rats.

Interestingly, in the present study, a single injection of BP 897 (0.5 and 1 mg/kg) before the test session, abolished the *expression* of cocaine CPP, whereas it was devoid of any effect on the expression of CPP supported by morphine or food. The *establishment* of cocaine CPP was also completely prevented by BP 897, at 1 mg/kg, while the effect of 0.5 mg/kg was nonsignificant. Only a trend toward reduction of the acquisition of morphine-CPP was observed with the 1 mg/kg dose, and the establishment of food-CPP was not prevented by BP 897. Thus, D_3R-related processes might be differentially involved in the ability of reinforcers to control approach behavior, depending on the reinforcer itself (food, opiates, stimulants), and on whether control is exerted by the primary reinforcer (acquisition phase) or by paired cues (expression phase). Even though the dose range for selectivity of BP 897 on expression *vs* acquisition of cocaine-CPP appears quite narrow at best, the present results are reminiscent of those reported in a second-order schedule of self-administration. Indeed, BP 897 (0.5 and 1 mg/kg) reduced lever pressing maintained by the presentation of cocaine-paired cues before any cocaine infusion, but not once the rats had received cocaine (Pilla *et al*, 1999). In this respect, BP 897 differed from a D_3R antagonist since SB-277011-A reduced response for the conditioned stimuli both under drug-free condition and after cocaine infusion (Di Ciano *et al*, 2003). On the other hand, as observed in the present study for acquisition and expression of morphine- and food-CPP, BP 897 (0.5–1 mg/kg) did not modify operant responding maintained by the presentation of conditioned cues that had been associated with sucrose or heroin self-administration, both before and after the delivery of the primary reinforcer (a lower dose (0.05 mg/kg), however, reduced response after heroin infusion) (Pilla *et al*, 2001). In addition, BP 897 (0.1–1 mg/kg) dose-dependently reduced the reinstatement of extinguished response induced by the presentation of stimuli previously paired with cocaine infusion (Cervo *et al*, 2003), but did not alter response for cocaine self-administration (Pilla *et al*, 1999). Altogether, these results might indicate that the conditioned motivational properties of cocaine-paired cues are more vulnerable to the BP 897 partial agonist activity at D_3R, than are the motivational properties of cocaine itself. Accordingly, it seems possible to reduce the motivation for drug-paired cues at BP 897 doses that do not interfere with the primary drug-related reward. The blockade of the hyperactivity induced by cocaine conditioned cues by BP 897, but not by cocaine itself, might rely on similar processes (Aujla *et al*, 2002; Le Foll *et al*, 2002). On the other hand, BP 897 seems totally devoid of effect on the motivational properties of food, cues paired to food or to opiates, although with regard to the primary effect of cocaine and opiates, the action of BP 897 could appear to be a matter of degree rather than selectivity *vs* cocaine (present results, Pilla *et al*, 2001).

Dopaminergic transmission in the mesocorticolimbic pathways involved in cocaine-related reward processes is under the control of several key components: (i) presynaptic modulation of DA release through D_2 and/or D_3 autoreceptors (Gobert *et al*, 1995), (ii) postsynaptic modulation of D_1/D_2R-mediated transmission via inhibitory postsynaptic D_3R (Kling-Petersen *et al*, 1995; Xu *et al*, 1997), and/or (iii) D_3R-mediated modulation of DA reuptake (Zapata and Shippenberg, 2002). Since the ligands used in the studies reported above exhibit differential

affinities and efficacies at D_3R and D_2R, the apparent contradictory data might result from differences in activation, blockade, or alteration of any of these intervening factors, superimposed onto the intrinsic effect of cocaine on extracellular DA concentrations in corticolimbic areas. Furthermore, the reward pathways involved in the primary appetitive properties of cocaine probably differ, at least in part, from those activated by secondary reinforcers (cocaine-paired cues). This is exemplified by the reported differences in neurotransmitter and receptor systems involved in the establishment *vs* the expression of cocaine CPP (Cervo and Samanin, 1995), and by regional dissociation in conditioned DA release in response to cocaine and cocaine cues (Ito *et al*, 2000; Weiss *et al*, 2000). In addition, cocaine inhibits reuptake of not only DA, but also serotonin (5-HT) and noradrenaline (NA) (Kuhar *et al*, 1991), and enhanced DA, 5-HT, and NA transmissions contribute to its net motivational valence (Hall *et al*, 2002). Since BP 897 exhibits nanomolar affinities for $5\text{-}HT_{1A}$ receptors (where it acts as a partial agonist), for D_2R, and for α_{1A} and α_{2A} adrenergic receptors (where it acts as an antagonist) (Pilla *et al*, 1999; Cussac *et al*, 2000), it cannot be excluded that these effects participate in the blockade by BP 897 of the CPP induced by cocaine and cocaine cues, while taking no or only a minor part in CPP supported by food and morphine.

In conclusion, the present study shows that BP 897 reduces the perception of the appetitive value of cocaine and the acquired incentive value attributed to stimuli reliably paired to cocaine. This effect likely involves a D_3R-mediated process, since BP 897 exhibits a reasonable selectivity for D_3 relative to D_2R. On the other hand, D_3R do not seem significantly involved in the establishment or the expression of morphine- and food-CPP, while $D_{2\text{-like}}$ autoreceptors appear to exert a control upon these processes (at least when food CPP is considered). However, although BP 897 is more D_3R-selective than most other available compounds, behavioral data must be interpreted with caution, since it exerts partial agonist activity and is endowed with a complex receptor-binding profile. Nevertheless, the present results are in keeping with studies indicating that different neurobiological mechanisms subserve the appetitive value of food and drugs of abuse, and that opiates and cocaine activate neuronal circuits that are in part different (Chang *et al*, 1998; Miyazaki *et al*, 1998; Carelli *et al*, 2000).

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