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Psychomotor-activating effects mediated by dopamine D_2 and D_3 receptors in the nucleus accumbens

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Abstract

The contribution made by specific dopamine receptor subtypes to the induction of motor behaviors has not been firmly established. Here, we first characterized the behavioral effects induced by a D_2-class receptor agonist, bromocriptine, following injections into the nucleus accumbens (Acb). Bromocriptine showed an atypical D_2-class receptor agonist profile, having no observable effect on a range of motor behaviors. However, when coadministered with the D_1-class receptor agonist SKF 38393, bromocriptine showed a typical D_2-class receptor agonist profile, enhancing locomotor activity and suppressing spontaneous yawning. We then administered the dopamine receptor antagonists L-741 626 and nafadotride, which possess relative selectivity for D_2 and D_3 receptors, respectively, prior to injections of dopamine agonists into the Acb. Nafadotride significantly reduced the locomotor-enhancing effects elicited by the coadministration of SKF 38393 and the D_2-class receptor agonist (+)-PD 128907 into the Acb, and also attenuated the effects induced by the combination of SKF 38393 and bromocriptine, although not significantly so. L-741 626 mildly attenuated the locomotor effects elicited by both drug combinations. Taken together, these results suggest that both D_2 and D_3 receptors in the Acb contribute to the expression of heightened psychomotor activation.

Keywords: Nucleus accumbens; Dopamine receptors; D_2; D_3; Bromocriptine; (+)-PD 128907; L-741 626; Nafadotride; Behavior

1. Introduction

The mesolimbic and nigrostriatal dopamine systems and their target receptors play a significant role in the expression of a wide variety of motor behaviors. Two families of dopamine receptors have been differentiated; the D_1-class, which includes the D_1 and D_5 receptors, and the D_2-class, which includes the D_2, D_3, and D_4 receptors [35,36,39]. Members of the family of D_2 receptors share a high degree of sequence homology and similar pharmacological profile. Of these, one of the most studied in recent years has been the D_3 receptor. Localization studies suggest that the expression of D_3 receptors is prominent in limbic-based circuits that modulate affect and motivated behavior, including the islands of Calleja and the nucleus accumbens (Acb) [16,27,37,38]. Given that the expression of the dopamine D_3 receptor in the limbic system is high, this receptor site has been postulated as a potential target for therapeutic intervention in schizophrenia [24,25,37] and substance abuse [1,17,40,41].

Pharmacological evidence suggests that dopamine D_3 receptors exert inhibitory actions on psychomotor functions. (+)-PD 128907, pramipexole, and 7-OH-DPAT, compounds with relative selectivity for dopamine D_3 receptors, reduce locomotor activity and induce sedation and yawning over a wide dose range [2,5,11,14]. Conversely, D_3 receptor-preferring antagonists stimulate locomotor behavior ([19,29,34], but see Ref. [12]), while D_2 receptor-preferring antagonists inhibit motor activity [30,31]. However, pharmacological studies are not supported by behavioral studies on mice lacking D_3 receptors. The behavioral effects induced by D_3 receptor agonists, including decreased locomotor activity and hypothermia, are identical in wild-type and D_3 receptor-mutant mice [8,43,44]. At the functional level, therefore, studies on the functions of the D_3 receptor have been inconclusive.

We have previously characterized the behavioral effects of quinpirole and (+)-PD 128907, drugs with some selectivity for the D_3 receptor, following injections into the Acb,

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and we have shown that the effects of these agonists critically depend on the level of activation of D_1-class receptors [10,11]. In the present experiments, we first administered the ergot compound bromocriptine into the Acb to compare its behavioral effects to those induced by microinjections of quinpirole and (+)-PD 128907. Second, we tested whether the behavioral effects of bromocriptine can be modified by concurrent administration of a D_1-class receptor agonist. Third, we examined the relative contributions of D_2 and D_3 receptors to the locomotor-enhancing effects induced by coadministration of D_1-class and D_2-class receptor agonists into the Acb. In this case, we administered antagonist drugs with relative selectivity for D_2 or D_3 receptors prior to cocktail injections of D_1-class and D_2-class receptor agonists into the Acb. The results are discussed in terms of the relative contribution of D_2 and D_3 receptors to motor behavior.

2. Materials and methods

2.1. Animals and surgery

All experiments were conducted in accordance with the Animals (Scientific Procedures) Act, 1986 and associated guidelines approved by the University of Oxford. Wistar rats weighing 200–275 g were housed under stable conditions, with rat chow and tap water available ad lib. Rats weighing 250–325 g at the time of surgery were anesthetized with Avertin at a dose of 1 ml/100 g IP, and placed in a dual stereotaxic apparatus (Stoelting, Avondale, IL). The skull was exposed, and a hole was drilled centered at midline, 1.6 mm anterior to bregma. Three stainless steel mounting screws supported the cannulation assembly. Guide cannulae of 23 gauge were bilaterally lowered into the brain and placed 2 mm above the Acb. Coordinates for the guide cannulae were (in mm): A–P 1.6, L 1.4, D–V 4.7 [32]. Dental acrylic was carefully applied, and wire stylets were inserted into the guides to prevent clogging.

2.2. Microinjections, drugs, and histology

Animals were allowed at least 5 days to recover from surgery. For intracerebral infusions, wire stylets were removed, and microinjection needles of 31 gauge were inserted into the guides. Needles protruded 2 mm beyond the guide cannulae, and were connected via polyethylene tubing to Hamilton microsyringes driven by a pump (SP250i, World Precision Instruments, UK). Microinjections were made bilaterally into the Acb at a rate of 1 μl/min, in a volume of 0.5 μl per side. Needles were left in place for an additional 1 min to allow for diffusion of the drugs. At least 48 h elapsed between injections.

As a D_2 receptor agonist, we chose the ergot compound bromocriptine because it shows a ca. 7-fold preference for D_2 vs. D_3 receptors [19,37]. As a D_3 receptor agonist, we chose the benzopyranoxazine (+)-PD 128907 [*R*-(+)-4,4*a*,10*b*-tetrahydro-4-propyl-2*H*,5*H*-(1)benzopyrano(4,3-*b*)-1,4-oxacin-9-ol] because it is the most selective agonist for the D_3 receptor in binding studies (>200-fold) and functional tests (>50-fold) [3,4,33]. As a D_3 receptor antagonist, we selected nafadotride (*N*((*n*-butyl-2-pyrrodinyl)methyl)-1-methoxy-4-cyano naphtalene-2-carboxamide), a potent, partially selective drug that displays a 10-fold selectivity for the dopamine D_3 receptor in binding studies and in the mitogenesis test [19,33]. We selected L-741 626 [3-(4-(4-chloro)phenyl-4-hydropiperidino)-methyl)indole] as the D_2 receptor antagonist. L-741 626 shows an ca. 10-fold selectivity for D_2 vs. D_3 receptors [6,9]. SKF 38393 was used as the D_1-class receptor agonist, as in our previous studies [11].

Bromocriptine (Tocris Cokson, UK) was dissolved in 50% propylene glycol at doses of 0.05, 0.5, 5, and 50 μg/0.5 μl, and SKF 38393 (Sigma-RBI, USA) was dissolved in 0.1% ascorbic acid and administered at a dose of 0.5 μg/0.5 μl ($n = 11$). This dose of SKF 38393 has been shown to be inactive behaviorally following injections into the Acb [11]. The combinations of SKF 38393 (0.5 μg/0.5 μl) plus bromocriptine (50 μg/0.5 μl) and of SKF 38393 (0.5 μg/0.5 μl) plus (+)-PD 128907 (5 μg/0.5 μl) (Sigma-RBI) were administered as cocktails into the Acb, 15 min after the systemic (IP) administration of the dopamine receptor antagonists L-741 626 (Merck, Sharp and Dohme, UK) (0.25 and 0.5 mg/kg; $n = 18$) or nafadotride (Bioproject,

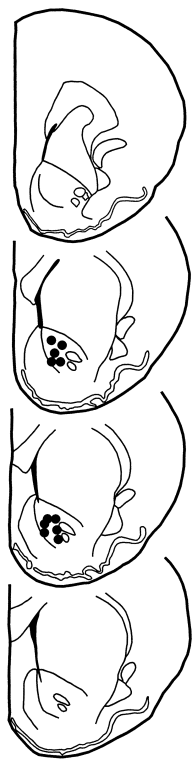

Fig. 1. Reconstruction of microinjection sites in the Acb (Experiment 1) on modified serial sections from Paxinos and Watson [32].

France) (0.5 and 1 mg/kg; $n = 17$). Nafadotride was dissolved in water, and L-741 626 was dissolved in 25% polyethylene glycol. Intracerebral and systemic control injections were made with the appropriate solvents, and found to be behaviorally inactive. In each experiment, injections were administered in a counterbalanced fashion (six injections per experiment). Upon completion of the experiments, animals were deeply anesthetized with an overdose of pentobarbital (Sagatal) and perfused with isotonic saline followed by 10% formal saline. The brains were removed and postfixed in a 30% sucrose solution. Coronal 40 μm sections cut in a sliding microtome were stained with cresyl violet. Placements were verified, and drawn for each individual animal on modified sections of Paxinos and Watson [32]. All injection sites were confined within the Acb (see Figs. 1–3). Tissue damage was minimal in all cases considered.

2.3. Behavioral procedures, measures, and statistics

Behavioral procedures were as described previously [10,11]. The test apparatus consisted of a rectangular, transparent perspex box (46 cm long, 21 cm wide, and 24 cm deep) placed in the center of the test room. Observations were carried out with a video camera connected to a video recorder. Rats were first preexposed to the observation chamber for a period of 10 min. Wire stylets were then removed and rats received a sham microinjection (needles did not protrude beyond the guide cannulae, and no infusion was made). Each rat was then observed for 20 min. On test days, we carried out the same procedure, but drugs were administered. Videotapes were examined blind to the experimental conditions, and behavioral elements were scored during the 20 min postinjection period. In Experiment 1, the following behavioral categories (each representing different combinations of related responses) were selected: (a) rearing, episodes of rearing in the center and the periphery of the arena; (b) crossovers, crosses through a line dividing the experimental apparatus into two halves; (c) grooming behavior, including scratching and licking of the body, body gnawing, face washes, and paw nibbling; (d) oral behavior, episodes of oral behavior not directed at any stimulus, including vacuous, low-frequency chewing, tremulous high-frequency chewing, mouth movements, tongue protrusions, and facial tremors; and (e) yawning behavior. In the experiments with the antagonists (Experiments 2 and 3), we only measured locomotor activity (crossovers), because this response was the most sensitive behavioral parameter in these and in previous studies [10,11]. The results

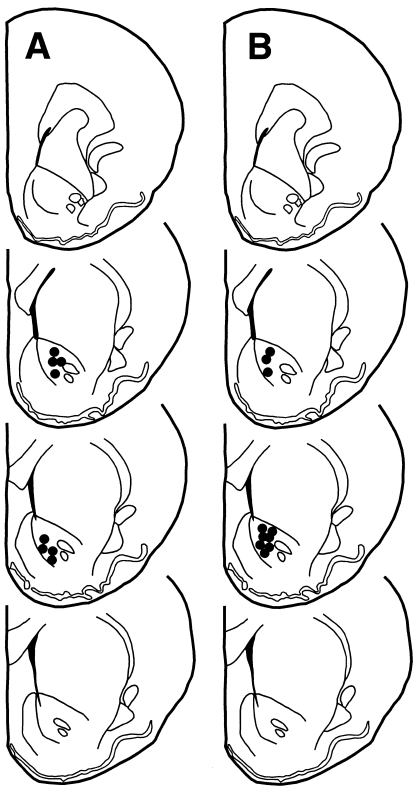

Fig. 2. Reconstruction of microinjection sites in the Acb (Experiment 2) on modified serial sections from Paxinos and Watson [32]. (A) Experiment with SKF 38393 plus (+)-PD 128907 and L-741 626; (B) experiment with SKF 38393 plus bromocriptine and L-741 626.

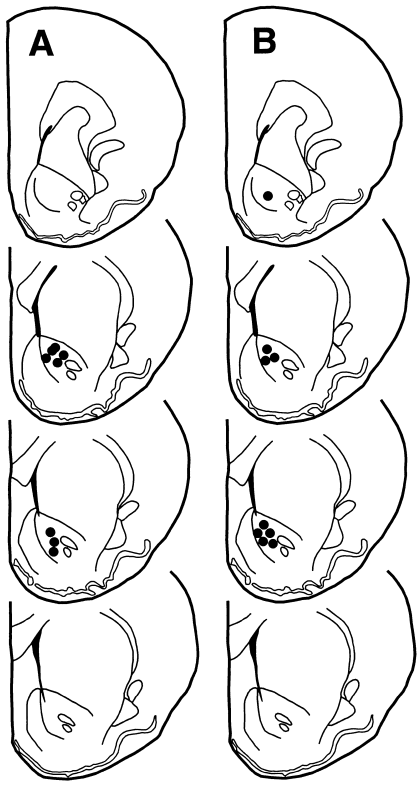

Fig. 3. Reconstruction of microinjection sites in the Acb (Experiment 3) on modified serial sections from Paxinos and Watson [32]. (A) Experiment with SKF 38393 plus (+)-PD 128907 and nafadotride; (B) experiment with SKF 38393 plus bromocriptine and nafadotride.

were analyzed by analysis of variance (ANOVA) followed by Newman–Keuls tests, where required. Levels of sedation were analyzed with the Friedman test for k-correlated samples.

3. Results

3.1. Experiment 1: behavioral effects induced by bromocriptine and by SKF 38393 plus bromocriptine following injections into the Acb (Table 1)

3.1.1. Sniffing

Bromocriptine injections into the Acb did not induce significant changes in sniffing behavior. The ANOVA showed no effect of drug, $F(4, 40) = 0.269$, $p < 0.869$. There was no significant effect induced by the coadministration of SKF 38393 plus bromocriptine into the Acb, $F(1, 20) = 1.948$, $p < 0.178$. This treatment only produced a mild increase in sniffing responses.

3.1.2. Rearing

Rearing behavior was not significantly affected by bromocriptine infusions into the Acb. ANOVA indicated no effect of drug, $F(4, 40) = 0.283$, $p < 0.888$. However, the coadministration of SKF 38393 plus bromocriptine into the Acb increased rearing significantly, $F(1, 20) = 11.738$, $p < 0.003$. The increase in rearing behavior produced by the coadministration of SKF 38393 and bromocriptine was smaller than that induced by amphetamine or by the coadministration of SKF 38393 and quinpirole into the Acb under similar experimental conditions [10,11].

3.1.3. Locomotion

Locomotor activity was not altered by bromocriptine microinfusions into the Acb at any dose. The effect of drug was not significant, $F(4, 40) = 0.224$, $p < 0.923$. However, the combined treatment with SKF 38393 and bromocriptine increased locomotor activity significantly, $F(1, 20) = 16.545$, $p < 0.001$. In this behavioral model, the increase in locomotor activity elicited by injections of SKF 38393 plus bromocriptine into the Acb was approximately 2.5-fold smaller than that induced by coadministration of SKF 38393 plus quinpirole into the Acb [11].

3.1.4. Grooming

ANOVA showed no effect of bromocriptine injections into the Acb on grooming behavior. The effect of drug was not statistically significant, $F(4, 40) = 1.135$, $p < 0.354$. Grooming behavior was not significantly modified by the coadministration of SKF 38393 and bromocriptine into the Acb, $F(1, 20) = 0.249$, $p < 0.623$.

3.1.5. Oral behaviors

ANOVA showed no effect of drug, $F(4, 40) = 1.898$, $p < 0.130$, indicating that bromocriptine did not induce a significant increase in oral behaviors. There was only a tendency for the middle doses to increase oral behaviors.

Table 1
Effects of bromocriptine microinjections into the Acb and interactions with SKF 38893

	0	0.05	0.5	5	50	SKF–Br
Sniffing (total)	28.9±3.9	25.5±2.8	27.5±2.3	27.4±3.5	28.5±2.8	33.5±3.0
Upward	0.9±0.2	0.7±0.4	2.0±1.3	0.3±0.2	1.5±0.4	2.2±0.8
Downward	28.0±3.8	24.8±3.1	25.5±2.2	27.1±3.6	27.0±2.8	31.3±3.3
Rearing (total)	20.0±3.1	22.6±5.2	23.5±3.8	20.3±4.5	23.8±4.0	37.9±7.2**
Centre	1.6±0.6	2.3±0.9	4.1±1.4	1.7±0.8	2.7±1.0	3.0±1.8
Periphery	18.4±2.7	20.3±4.6	18.9±2.5	18.6±3.7	21.1±3.5	34.9±5.8
Crossovers	15.7±2.6	15.1±3.0	16.4±1.6	14.4±2.7	16.5±2.7	29.7±4.8**
Stillness	1.2±0.5	1.4±0.5	2.1±0.6	1.9±0.5	2.1±0.5	0.3±0.2
Grooming (total)	10.3±2.2	8.5±1.7	12.3±2.2	7.5±1.6	10.1±2.5	9.1±2.0
Scratch/lick	4.8±1.1	4.6±1.0	5.9±1.2	3.5±0.8	5.6±1.5	4.4±1.1
Gnawing	1.1±0.4	0.4±0.2	1.4±0.4	0.9±0.4	0.9±0.3	0.4±0.3
Face wash	4.0±0.8	3.1±0.7	4.1±0.7	2.5±0.6	3.4±0.8	4.3±0.9
Paw nibbling	0.4±0.2	0.5±0.3	0.9±0.5	0.5±0.4	0.1±0.1	0.0±0.0
Oral (total)	19.8±4.2	25.1±8.5	26.2±5.0	32.8±5.9	16.7±3.1	21.8±5.9
Tremulous chewing	3.5±1.2	4.9±1.7	4.1±1.2	6.1±1.0	2.6±0.5	2.4±0.9
Vacuous chewing	2.2±0.9	4.0±2.3	4.5±1.4	5.9±1.9	1.5±0.7	5.2±1.3
Mouth movements	5.5±1.1	5.3±1.2	7.0±1.4	8.0±1.1	7.5±1.0	6.2±1.3
Tongue protrusions	3.4±1.1	3.3±1.1	4.1±0.7	2.7±0.5	1.3±0.5	2.7±1.1
Facial tremor	5.2±1.7	7.6±3.3	6.5±1.9	10.1±2.3	3.7±1.3	5.3±1.9
Yawning	3.9±1.1	2.7±1.4	2.5±0.7	3.5±1.0	2.0±0.7	0.5±0.4**
Sedation	1.5±0.3	1.5±0.3	1.9±0.4	1.6±0.3	1.6±0.3	1.1±0.1

Behavioral responses (means+SEM) elicited by microinjections of bromocriptine (in μg per side) and of SKF 38393 plus bromocriptine (SKF–Br) into the Acb.

* $p < 0.05$.

** $p < 0.01$ (from controls).

Injections SKF 38393 plus bromocriptine into the Acb produced no significant effects on oral behaviors, $F(1, 20) = 0.191$, $p < 0.667$.

3.1.6. Yawning

Bromocriptine infusions into the Acb had no effect on yawning, as indicated by ANOVA, $F(4, 40) = 1.008$, $p < 0.415$. However, the combination of SKF 38393 and bromocriptine significantly attenuated spontaneous yawning following infusion into the Acb, $F(1, 20) = 10.785$, $p < 0.004$.

3.1.7. Sedation

Bromocriptine did not induce sedation at any dose (Friedman's $\chi^2 = 1.67$, $p < 0.90$).

3.2. Experiment 2: effects of L-741 626 on locomotor activity induced by combinations of SKF 38393 plus (+)-PD 128907 or SKF 38393 plus bromocriptine (Table 2)

3.2.1. L-741 626 treatment followed by SKF 38393–(+)-PD 128907

ANOVA indicated the presence of a drug effect, $F(5, 35) = 3.256$, $p < 0.016$. The coadministration of SKF 38393 plus (+)-PD 128907 produced a significant increase in locomotor activity (226% relative to baseline). Within the dose range selected, L-741 626 was devoid of effects on locomotor activity when administered alone. Moreover, L-741 626 did not significantly suppress the increase in locomotor activity induced by coadministration of SKF 38393 plus (+)-PD 128907 into the Acb, but there was a slight attenuation of this effect.

Table 2
Effects of nafadotride and L-741 626 on hyperlocomotor effects induced by coactivation of D_1-class and D_2-class receptors in the Acb

	Vehicle	Nafa 0.5	Nafa 1.0
SKF–PD	36.3±6.6**	26.9±3.9	16.8±3.8***
Vehicle	11.8±1.8	11.9±2.1	10.8±2.1
	Vehicle	L 0.25	L 0.5
SKF–PD	29.4±5.1*	21.1±5.7	20.2±4.5
Vehicle	9.0±1.9	7.1±2.1	9.9±2.5
	Vehicle	Nafa 0.5	Nafa 1.0
SKF–Br	28.5±3.7**	25.9±3.9	17.7±3.1
Vehicle	11.3±2.1	11.0±1.7	12.1±2.1
	Vehicle	L 0.25	L 0.5
SKF–Br	26.1±2.9*	22.1±3.6	16.8±2.4
Vehicle	13.2±1.8	11.4±1.8	10.2±1.7

Locomotor effects (crossovers, means+SEM) induced by SKF 38393 plus bromocriptine (SKF–Br) and by SKF 38393 plus (+)-PD 128907 (SKF–PD) and modulation by L-741 626 (L, mg/kg) and nafadotride (Nafa, mg/kg).

* $p < 0.05$.

** $p < 0.01$ (from controls).

*** $p < 0.05$ (from SKF–Br or SKF–PD).

3.2.2. L-741 626 treatment followed by SKF 38393–bromocriptine

A significant drug effect, $F(5, 40) = 3.576$, $p < 0.009$, was found in the ANOVA. The injection of SKF 38393 plus bromocriptine elicited a significant increase in locomotor activity (98% relative to controls). At the doses selected, L-741 626 was without effect on locomotor activity when administered alone. The antagonist drug attenuated the locomotor activity induced by infusions of SKF 38393 plus bromocriptine into the Acb, but this suppression did not reach overall significance.

3.3. Experiment 3: effects of nafadotride on locomotor activity induced by combinations of SKF 38393 plus (+)-PD 128907 or SKF 38393 plus bromocriptine (Table 2)

3.3.1. Nafadotride treatment followed by SKF 38393–(+)-PD 128907

ANOVA revealed a significant effect of drug, $F(5, 35) = 3.563$, $p < 0.010$. As described previously [1], SKF 38393 plus (+)-PD 128907 induced hypermotility shortly after its administration into the Acb. Relative to controls, SKF 38393 plus (+)-PD 128907 produced a significant increase in locomotor activity (212% relative to controls). Post hoc comparisons indicated that nafadotride dose dependently suppressed the effect induced by SKF 38393 plus (+)-PD 128907 at doses that did not affect locomotor activity when administered alone (in combination with control injections into the Acb).

3.3.2. Nafadotride treatment followed by SKF 38393–bromocriptine

ANOVA showed a significant effect of drug, $F(5, 45) = 4.633$, $p < 0.002$. SKF 38393 plus bromocriptine produced a significant enhancement of locomotor activity (152% relative to controls). Nafadotride, which also failed to affect locomotor activity when given alone in this experiment, produced a nonsignificant attenuation of the locomotor effects elicited by microinjections of SKF 38393 plus bromocriptine into the Acb.

4. Discussion

4.1. Typical and atypical behavioral profiles induced by bromocriptine injections into the Acb: dependence on D_1-class receptor activation

Bromocriptine exhibits the typical behavioral profile of a D_2-class receptor agonist following systemic administration. Bromocriptine suppresses spontaneous locomotion at low doses, but it induces hypermotility and stereotyped behaviors at high doses [18,23]. The expres-

sion of some bromocriptine-induced behavioral effects depends on D_1-class receptor activation. In rats exposed to α-methyl-*p*-tyrosine plus reserpine, the locomotor-enhancing effects of bromocriptine are not evident, but these can be reinstated by concurrent administration of behaviorally inactive doses of the dopamine D_1-class receptor agonist SKF 38393 [20,21]. Studies on the effects of bromocriptine following injections into the Acb have produced conflicting results. Bromocriptine decreased rat locomotor behavior in the open field [26] and inhibited mouse spontaneous climbing behavior following direct injections into the Acb [13]. In activity cages, however, bromocriptine induced no changes in locomotor activity [23]. Using a similar measure of locomotor activity and a wider dose range, the present experiments confirm the findings of Jenkins and Jackson [23] and extend their observations to other activity-related measures, including sniffing and rearing. In this regard, considering the ability of quinpirole and (+)-PD 128907 to suppress locomotor activity following injections into the Acb [10,11], bromocriptine is an atypical D_2-class receptor agonist.

Bromocriptine induces sedation and yawning responses following administration of low systemic doses [42,45]. In the present experiments, however, bromocriptine injections into the Acb failed to elicit yawning or sedation at any of the doses tested. In addition, bromocriptine produced only a weak tendency to increase oral activity. In this respect, bromocriptine also shows an atypical profile, because these behaviors are elicited by injections of quinpirole and (+)-PD 128907 into the Acb [10,11]. These atypical effects of bromocriptine could be due to its complex pharmacological profile. Binding studies have shown that bromocriptine has a high affinity for noradrenergic α_1 and α_2 receptors, and for serotonin 5-HT_{1a} receptors [22]. Moreover, microdialysis studies have shown that bromocriptine increases 5-HT turnover, and reduces extracellular levels of acetylcholine and dopamine in the striatum [15,22]. Thus, interactions with neurotransmitter systems other than the dopamine system may contribute to the atypical D_2-class receptor agonist profile of bromocriptine following intracerebral injections.

Previous studies suggest that D_1-class receptors may play a permissive role in the locomotor-stimulant effects of bromocriptine following systemic administration [20,21]. In our study, the combination of SKF 38393 and bromocriptine enhanced locomotor activity and suppressed spontaneous yawning responses. These two effects are also observed following amphetamine treatment or coadministration of SKF 38393 and quinpirole into the Acb [10,11]. The present experiments indicate that activation of dopamine D_1-class receptors at the level of Acb alters the effects of bromocriptine in a way such that the behavioral output clearly reflects D_1-class/D_2-class receptor interactions. With regard to these interactions, bromocriptine behaves as a typical D_2-class receptor agonist.

4.2. Studies with nafadotride and L-741 626 suggest a contribution of D_2 and D_3 receptors in the Acb to the induction of enhanced locomotor behavior

To study whether D_2 and/or D_3 receptors play a role in the enhanced locomotor stimulation induced by combinations of SKF 38393 and either bromocriptine or (+)-PD 128907, the antagonist drugs L-741 626 and nafadotride were administered before injections of the agonist drugs. The results showed that the locomotor response elicited by SKF 38393 plus (+)-PD 128907 was effectively blocked by nafadotride at doses that do not produce functional blockade of D_2 receptors [28] (J.-C. Schwartz, personal communication), while L-741 626 was less effective. These results suggest that D_3 receptors synergize with D_1-class receptors and contribute to the expression of behavioral hyperactivity. Nafadotride also attenuated the hyperactivity induced by SKF 38393 plus bromocriptine, although not significantly so. In the present experimental conditions, nafadotride was without effect on locomotor activity. Previously, however, stimulatory effects of nafadotride on locomotor activity have been observed in well-habituated rats [34], although this finding has not been replicated [12]. In the present experiments, we did not detect any stimulatory effects of nafadotride on locomotor behavior.

At the doses tested, L-741 626 attenuated the responses to (+)-PD 128907 and bromocriptine following coadministration with SKF 38393, but the magnitude of this attenuation did not reach statistical significance. Considering the overall results obtained with the antagonist L-741 626, it seems that slightly higher doses would have blocked the locomotor effects of both SKF 38393 plus bromocriptine and SKF 38393 plus (+)-PD 128907. In fact, previous studies have shown that some physiological effects of (+)-PD 128907 are readily blocked by L-741 626 [6,9], suggesting that (+)-PD 128907 could lack selectivity for the D_3 receptor in vivo. Moreover, (+)-PD 128907 elicits locomotor suppression and hypothermia both in wild-type and D_3-mutant mice [8,44], but not in D_2 knock-outs [7]. This evidence should be carefully considered when reaching conclusions regarding the behavioral functions of the D_3 receptor. In our study, low doses of nafadotride significantly attenuated the locomotor effects of the combination of SKF 38393 and (+)-PD 128907, suggesting that both D_2 and D_3 receptors in the Acb synergize with D_1-class receptors for the induction of enhanced locomotor stimulation. This evidence, however, should be evaluated with a wider range of more potent and selective agonists and antagonists for D_3, relative to D_2, receptors.

5. Conclusions

The results of this study indicate that bromocriptine induces atypical D_2-class receptor-mediated behavioral effects following administration into the Acb. However,

in combination with a D_1-class receptor agonist, bromocriptine displays the typical functional profile of a D_2-class receptor agonist. The present observations further indicate that antagonists with relative selectivity for D_2 or D_3 receptors are able to attenuate the motor effects induced by coadministration of a D_1-class receptor agonist and either bromocriptine or (+)-PD 128907 into the Acb. These results suggest that in the presence of sufficient D_1-class receptor activation, which critically modulates D_2-class receptor-mediated behavioral responses at the level of the Acb [11], D_2 and D_3 receptors in the Acb may contribute in similar ways to the expression of heightened psychomotor arousal.

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