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Effects of Specific Dopaminergic Agonists and Antagonists in the Open-Field Test

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BRUHWYLER, J., E. CHLEIDE, J-F. LIÉGEOIS, J. DELARGE AND M. MERCIER. *Effects of specific dopaminergic agonists and antagonists in the open-field test.* PHARMACOL BIOCHEM BEHAV **39**(2) 367–371, 1991.—It has been found that dopaminergic transmission could be involved in some aspects of anxiety. The present study aims to explore this hypothesis further, using specific DA1 (SKF 38393) and DA2 (bromocriptine) agonists or DA1 (SCH 23390), and DA2 (zetidoline) antagonists in the open-field test. The results confirm previous studies indicating that DA1 and DA2 agonists predominantly increase locomotor activity, while DA1 and DA2 antagonists predominantly decrease it. However, at low doses, the four drugs increase the peripheral ambulation score significantly and, with the exception of zetidoline, also increase the central ambulation score. The observations made with zetidoline confirm the hypothesis that a specific presynaptic DA2 antagonism could be a determinant for the disinhibitory effects of low doses of neuroleptics. A collateral action on 5HT transmission is also suggested to explain an hypothetic anxiolytic action of DA agonists and SCH 23390 at lower doses.

DA agonist DA antagonist 5HT antagonism SCH 23390 SKF 38393 Bromocriptine Zetidoline Open field Anxiety Anxiolytic Rat

THE open-field procedure has largely been used to test the anxiolytic potential of drugs. The antagonism between the instinctive tendency to explore and to shun this new environment is mostly evaluated on the basis of the peripheral ambulation score and the central ambulation score into the innermost areas of the open field. Moreover, the number of times the subject defecates allows its emotional reactivity to be assessed (35, 63, 65).

In this test, the effects of anxiolytics like benzodiazepines are generally biphasic with an increase in the peripheral and central ambulation scores for a low dose and a decrease in these scores when a high dose is administered, accompanied by muscular relaxation, ataxia and sedation (11, 12, 19, 23, 54, 63).

Clinical studies have indicated that neuroleptics could relieve anxiety-related symptoms (49), borderline (10) and chronically anxious patients (46,50). In addition, the disinhibitory and anxiolytic properties of neuroleptics have been measured employing various experimental procedures: the open-field test (17), two-compartment test (47), conflict test (22,47), fixed-interval schedule and temporal regulation schedules (13–15). Recently, we reported (11) that sulpiride (a specific DA2 antagonist) and clozapine (a bivalent DA1/DA2 antagonist) could increase the central ambulation and decrease the defecation scores in the open field, even at high doses.

On the other hand, as is the case for dopamine (DA) antagonists, apomorphine (a bivalent DA1/DA2 agonist) in low, subemetic doses has been recommended as an anxiolytic (38). This agent was found to attenuate conflict behavior in rats with a potency over 50 times greater than that of diazepam and chlordiazepoxide (62). All these observations support the hypothesis that DA transmission in certain brain regions could be involved in some aspects of the etiology and expression of anxiety (62).

The present study aims to explore this hypothesis further, using specific DA1 (SKF 38393) and DA2 (bromocriptine) agonists or DA1 (SCH 23390) and DA2 (zetidoline) antagonists in the open-field test.

METHOD

Animals

In total, 160 Wistar rats, 100 to 120 days old and weighing from 350 to 400 g, were used for the experiments. At 50 days old, the subjects had been placed together in cages in groups of 10 and kept under a 12/12 L/D cycle (dark period from 7 a.m. to 7 p.m.). The temperature was maintained constant at 21°C. Food and water were available ad lib. All experiments were undertaken between 10 a.m. and 3 p.m.

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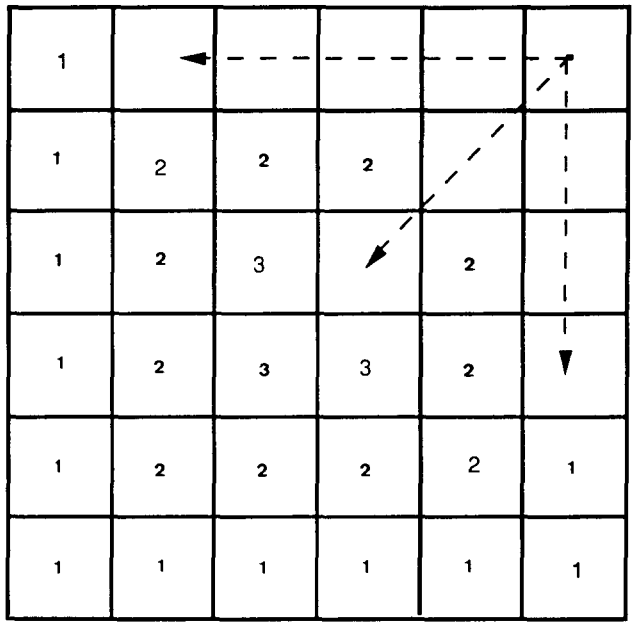

FIG. 1. Schematic representation of the open-field.

Apparatus

The apparatus consisted of a square surface of wood, the sides of which measured 96 cm, surrounded by a 28 cm high wooden wall. The surface, painted white, was divided into 36 squares, the sides of which were 16 cm long. The open field was placed in a ventilated, sound-proof room lighted by a 40-W bulb.

Procedures

Each experimental group consisting of 10 rats received an intraperitoneal injection containing either SCH 23390 (SCH, Research Biochemicals Inc., 0.01, 0.03, 0.1, 0.3 mg/kg), zetidoline (ZETI, Lepetit Research Center, 0.3, 1, 3 mg/kg) or SKF 38393 (SKF, Smith Kline and French, 3, 10, 30 mg/kg) at 30 min before the test, bromocriptine (BROMO, Parlodel®, Sandoz Ltd., 0.3, 1, 3 mg/kg) at 2 hours before the test or an NaCl solution (9/1000) at 30 min before the test. BROMO, ZETI and SKF were dissolved in a physiological solution (NaCl 9/1000). SCH was dissolved in a solution of distilled water and ethanol (92:8). The placebo was injected into 3 groups of 10 subjects. Following drug administration, each rat was carefully placed in a particular square next to the wall and left in the open field for 10 minutes (Fig. 1). During this period, the peripheral ambulation (number of peripheral squares entered), the central ambulation separated into median (class 2) and central (class 3) squares and the number of fecal boluses were measured, always by the same observer working in a simple blind check. The averages obtained for the different parameters and the different groups were compared statistically employing analysis of variance, with the "dose" as the classification criterion, followed by post hoc Newman-Keuls comparisons.

RESULTS

Peripheral Ambulation (Table 1)

The pharmacological treatment was found to be significant ($p<0.01$) for the four drugs [BROMO, $F(3,56)=6.06$; SCH, $F(4,65)=29.93$; ZETI, $F(3,56)=11.08$; SKF, $F(3,56)=15.97$]. With BROMO and SKF, peripheral ambulation was increased at a medium dose ($p<0.01$) and at all doses ($p<0.01$), respectively. In contrast, with SCH and ZETI, the score was increased significantly ($p<0.01$) at low doses and then decreased at high doses, significantly ($p<0.05$) only in the case of ZETI.

Central Ambulation

The effect of the pharmacological treatment on the number of class 2 squares entered was significant for BROMO, $F(3,56)=3.22$, $p<0.05$, SCH, $F(4,65)=8.12$, $p<0.01$ and SKF, $F(3,56)=4.93$, $p<0.01$, but was not significant ($p<0.05$) for ZETI. BROMO increased this score at a medium dose ($p<0.05$) and SCH at the lowest dose ($p<0.01$), while SKF in-

TABLE 1

EFFECTS OF DRUGS ON THE BEHAVIOURAL PARAMETERS IN THE OPEN-FIELD TEST

Drugs	(mg/kg)	Peripheral Ambulation Mean (SD)	Central Ambulation Area 2 Mean (SD)	Central Ambulation Area 3 Mean (SD)	Defecation Mean (SD)
Control		15.1 (17.7)	0.1 (0.3)	0.0 (0.0)	3.2 (3.4)
BROMO	(0.3)	31.9 (29.1)	0.4 (1.3)	0.4 (1.3)	3.4 (2.5)
	(1.0)	57.2 (46.9)†	1.2 (1.5)*	0.0 (0.0)	2.3 (1.2)
	(3.0)	24.6 (24.9)	0.7 (1.6)	0.1 (0.3)	3.1 (1.8)
SKF	(3)	93.0 (51.0)†	1.8 (1.9)*	0.2 (0.6)	1.1 (1.3)*
	(10)	66.5 (32.7)†	1.8 (2.7)*	0.2 (0.6)	0.5 (0.7)*
	(30)	57.3 (50.8)†	0.9 (2.0)	0.0 (0.0)	0.1 (0.3)*
ZETI	(0.3)	40.7 (31.0)†	0.7 (2.2)	0.3 (0.9)	2.9 (1.4)
	(1.0)	1.1 (1.0)	0.0 (0.0)	0.0 (0.0)	3.6 (2.1)
	(3.0)	0.2 (0.4)*	0.1 (0.3)	0.0 (0.0)	4.7 (2.4)
SCH	(0.01)	115.5 (78.0)†	4.4 (6.3)†	0.9 (1.7)†	1.4 (1.6)
	(0.03)	45.0 (32.9)*	0.6 (0.8)	0.0 (0.0)	1.8 (1.9)
	(0.10)	1.4 (1.4)	0.0 (0.0)	0.0 (0.0)	3.5 (3.2)
	(0.30)	1.6 (2.1)	0.0 (0.0)	0.0 (0.0)	2.6 (1.6)

SD = standard deviation; *$p<0.05$; †$p<0.01$.

creased it at low and medium doses ($p<0.05$). The effect of the pharmacological treatment on the number of class 3 squares entered was significant only for SCH, $F(4,65)=4.88$, $p<0.01$. At the lowest dose, SCH increased this parameter significantly ($p<0.01$).

Defecation

The pharmacological treatment was significant ($p<0.01$) for SKF, $F(3,56)=5.72$ and SCH, $F(4,65)=12.58$. SKF reduced the number of fecal boluses in relation to the dose ($p<0.05$). With SCH, the defecation score did not decrease significantly ($p>0.05$).

DISCUSSION

The present results broadly confirm previous studies indicating that DA1 agonists (43,51) and DA2 agonists (5, 33, 34) predominantly increase locomotor activity, while DA1 antagonists (24, 29, 60) and DA2 antagonists (7, 26, 55) predominantly decrease it. However, at low doses (medium dose in the case of BROMO), all the drugs used in this study increased the peripheral ambulation score significantly. The fact that specific DA antagonists could stimulate locomotion corroborates our first reports based on the open-field test in rats (11) and differential reinforcement of the response duration schedule in dogs (13). According to Pich and Samanin (47), the clear preference of low doses of DA2 antagonists for presynaptic DA2 sites could explain such a type of stimulation. The results obtained with ZETI (0.3 mg/kg) largely confirm this hypothesis. Indeed, ZETI is a strong DA2 receptor blocker, devoid of any other effect on neurotransmission, as demonstrated previously in pharmacological and biochemical studies (3,48). It is more surprising to find the same effects with a DA1 antagonist like SCH. However, in our study, the profile of SCH for low doses resembled that of a true anxiolytic like chlordiazepoxide (11, 12, 19, 23, 54, 63), since it increased both the peripheral and the central ambulation scores significantly, together with a nonsignificant decrease in the defecation score. SCH has been shown to display strong affinities for both DA1 and $5HT_2$ receptors (8, 28, 41), while being devoid of anticholinergic and antihistaminergic effects (32,56). Bijak and Smialowski (8) demonstrated that the dose of SCH able to block quipazine (a direct central 5HT agonist)-induced head twitches was low, at about 1.25 μg/kg. In models of anxiety based on fear of open space, e.g., the plus-maze or the open field, quite strong anxiolytic-like effects have been described for $5HT_2$ antagonists like ketanserin (21), ritanserin and cyproheptadine (39). The $5HT_2$ antagonist properties of SCH might contribute to its ability to decrease anxiety. The difference between ZETI and SCH could be linked to such $5HT_2$ affinity since ZETI appears to be devoid of any anti-5HT activity and to show no interaction with $5HT_2$ receptors labelled by ^{3}H-ketanserin in the rat prefrontal cortex and striatum (4).

At higher doses, cataleptic properties of both ZETI (58,61) and SCH (24, 29, 30, 40, 45) predominantly influence the motor behavior. It has been observed that cataleptic subjects tend to defecate more frequently, reflecting an anxiogenic effect of the drug (52,53). However, since no significant effect is demonstrated in defecation, we cannot relate the drop in locomotion to an anxiogenic property of these compounds (7,35).

Anxiolytic-like profiles have also been detected in our studies on SKF and BROMO. They tend to corroborate the attenuation of conflict behavior observed with apomorphine in rats (38,62). A collateral action on 5HT transmission has also been proposed for these substances and could explain their anxiolytic potential (6, 37, 64). BROMO can displace the binding of both $5HT_1$ and $5HT_2$ ligands to cortical membranes and appears to act as a weak antagonist of 5HT-sensitive adenyl cyclase (37). Some contradictions still exist regarding the behavioral effects of SKF. While some researchers agree in recognizing stimulant effects by SKF on grooming and sniffing (2, 9, 33, 42, 44), others have found this agent to exert no effect in normal animals (20, 36, 57). Recent reports differ as to whether episodes of locomotion are [in the rat: (43)] or are not [in the mouse: (59)] induced. Our results indicate that SKF can increase the peripheral and central scores significantly in the rat, when tested in the open field. The anxiolytic profile of SKF could be explained not only by DA stimulation but also by an inhibition of 5HT release, since this has been detected in the substantia nigra (6).

Without further investigations, employing other procedures capable of detecting the anxiolytic potential of substances, it may be premature to draw precise conclusions. However, at least two hypotheses can be proposed to account for the "anxiolytic-like profile" of DA agonists and low doses of DA antagonists. According to Claustre et al. (16) and Ikeda et al. (31), placing a rat in a new environment can increase the release of DA by DA neuron endings. The significant effect observed on the ambulation scores observed with BROMO, SKF and low doses of ZETI and SCH could result from a potentiation of the DA neurotransmission system already stimulated. In this case, the increase in central ambulation scores with SCH, BROMO and SKF could simply be explained by a nonspecific stimulation of general activity. On the other hand, since it is now recognized that buspirone, a potential nonbenzodiazepine anxiolytic compound, acts on both DA and 5HT transmissions (1, 18, 25, 27, 47), the hypothesis that both the DA and 5HT systems could be involved in a "true anxiolytic" effect of DA compounds still remains.

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