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Anxiogenic-like Effects Induced by Stimulation of Dopamine Receptors

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SIMON, P., C. PANISSAUD AND J. COSTENTIN. *Anxiogenic-like effects induced by stimulation of dopamine receptors.* PHARMACOL BIOCHEM BEHAV **45**(3) 685–690, 1993.—We considered the increase in latency for entering into a white-lightened compartment from a black one as an index of anxiety for Swiss albino mice. This has been validated with several reference anxiogenic drugs [pentylenetetrazole, yohimbine, dexamphetamine, and methyl-β-carboline-3-carboxylate (β-CCM)]. On this test, the effects of various indirect or direct dopamine (DA) agonists have been investigated, as well as the respective involvement of D_1 and D_2 dopamine receptors. Dexamphetamine, the specific DA uptake inhibitor 1-[2-(diphenylmethoxy)-ethyl]4-(3-phenyl propenyl)-piperazine (GBR 12783), and the mixed DA/norepinephrine uptake inhibitor *N*-[1-(2-benzo(*b*)thiophenyl)-cyclohexyl]piperidine (GK 13) dose dependently increased the entering latency. This effect was shared by the D_2 DA agonist RU 24926. The partial agonist of D_1 DA receptors SK&F38393 had a significant although moderate efficacy. Their association led at best to an additive synergy. The antagonist of D_1 DA receptors SCH23390 shortened the entering latency. The anxiogenic effect of GBR 12783 was antagonized by haloperidol and SCH23390. It is concluded that an anxiogenic-like effect is linked to an increase in dopaminergic transmission involving both D_1 and D_2 dopamine receptors.

Anxiety Dopamine Dopamine agonists Dopamine receptors Mouse

MOST of the tests used in psychopharmacology for the assessment of anxiety in rodents are particularly adapted to detect anxiolytic activities. In general, animals are exposed to anxiogenic conditions, either a novel environment (elevated plus-maze, social interaction test, open field) or a conflict situation (Vogel punishment drinking test or Geller-Seifter test) (9, 10,13,17,25). Because these tests could constitute models of human anxiety, they have been widely used in the study of anxiolytic properties of many compounds, especially the benzodiazepines. An easy test to perform is the two-compartment exploratory test. The apparatus used consists of two compartments, one black and one white, communicating by a small opening. The rodent is introduced into the more anxiogenic location (white compartment); then, the delay to enter the black compartment is measured. This delay is increased by anxiolytic agents (5). As our purpose was to measure anxiogenic effects, we inverted the test (i.e., the mouse was introduced into the black compartment). Thus, the more anxiogenic location is not imposed directly, and the higher the degree of anxiety the longer should be the time before entering the white compartment. This reasoning is based upon the natural aversion of mice for a bright environment, which may be tempered by a tendency to explore a new environment ("curiosity"). In addition, the duration of the first stay in the white compartment has been measured. This last parameter might be influenced, among other components, by anxiety and locomotor activity. Originally, the test has been validated with several reference anxiogenic drugs: yohimbine (3,14,20), pentylenetetrazole (11), dexamphetamine (13), and methyl-β-carboline-3-carboxylate (β-CCM) (18). The obvious effect of dexamphetamine, shared by other indirect catecholamine agonists, prompted us to investigate the involvement of dopaminergic transmissions on this response and determine the respective roles of D_1 and D_2 receptors in this respect.

METHOD

Animals

Male Swiss albino mice (Charles River CD1, Saint Aubin lès Elbeuf, France) weighing 20–25 g were used. They were kept under standard conditions: constant temperature (22 ± 1°C), a 12 L : 12 D cycle (light from 8:00 a.m.–8:00 p.m.), food and water ad lib up to the time of the experiment, 20 mice per cage (40 × 25 × 18 cm). The experiments were carried out between 10:00 a.m. and 5:00 p.m. Animals were introduced in the room where experiments were performed at least 1 h before their beginning. This room was weakly illuminated. Animals were isolated in small individual cages for at least 30 min before the administration of the tested drugs.

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Test Apparatus

The test apparatus consisted of an enclosure with two compartments, each measuring 32 × 22 × 18 cm. One compartment was dark (painted black and covered). The other compartment, not covered, was painted white and strongly lit by a 100-W incandescent lamp set 50 cm above its floor. The compartments communicated by an opening (5 × 5 cm) located at the base of the median part of the separating wall.

Testing Procedure

White compartment to black compartment paradigm. The animal was introduced into the white compartment (the head turned to a corner of the wall opposed to the aperture). A chronometer was started and stopped when the mouse entered for the first time obviously in the black compartment (all four paws in it). At this time, a second chronometer measured the duration of the first stay in the black compartment.

Black compartment to white compartment paradigm. Immediately after introduction of the mouse into the black compartment (the animal looking at a corner of the wall opposed to the aperture), the cover was applied, a first chronometer was started, and stopped when the animal entered for the first time obviously into the white compartment (all four paws in it). At this time, a second chronometer measured the duration of the first stay in the white compartment. If the mouse did not leave the dark chamber during the first 6 min, the experimentation was conventionally stopped. On the contrary, if the mouse entered immediately the white compartment (latency < 5 s) this measure was cancelled.

Locomotor Activity

Locomotor activity was measured with a Digiscan actometer (Omnitech Electronics Inc., Columbus, OH). The individual boxes (20 × 20 × 30 cm) were put in a dimly lit room. The horizontal activity was expressed by the total number of beams crossed by mice between the 5th and 35th min after the treatment.

Statistics

Statistical comparisons of different groups to a control group were made by use of Student's *t*-test. An analysis of variance (ANOVA) followed by a Duncan test were used for multiple comparisons. Two-way ANOVAs were used to show interactions.

Drugs

Yohimbine HCl (C.P.F., Melun, France) and pentylenetetrazole (Sigma Chemical Co., St. Louis, MO) were dissolved

TABLE 1

EFFECTS OF PENTYLENETETRAZOLE, YOHIMBINE, (+)AMPHETAMINE, AND β-CCM ON THE ENTERING LATENCY AND FIRST-STAY DURATION IN THE WHITE COMPARTMENT

	White Compartment-Entering Latency (seconds)	White Compartment First-Stay Duration (seconds)
Pentylenetetrazole (mg/kg, SC)		
0	21 ± 3	10.5 ± 1
6.25	41 ± 5	12 ± 2
12.5	88 ± 9*	14 ± 2.5
25	127 ± 27*	11 ± 1.5
50	173 ± 27*	12 ± 2
Yohimbine (mg/kg, SC)		
0	19 ± 3	9 ± 2
0.50	19 ± 4	12 ± 2.5
1	54 ± 23	12 ± 3.5
2	150 ± 25*	10 ± 2
4	281 ± 51*	16.5 ± 3.5
(+)Amphetamine (mg/kg, SC)		
0	31 ± 5	8 ± 1
1	37 ± 11	9 ± 2
2	144 ± 56*	6 ± 2
4	316 ± 70*	3.5 ± 1.5*
β-CCM (mg/kg, SC)		
0	32 ± 4	7 ± 0.5
1	159 ± 24*	9.5 ± 2

Mice were injected SC with saline or increasing doses of pentylenetetrazole (6.25, 12.5, 25, and 50 mg/kg), yohimbine (0.5, 1, 2, and 4 mg/kg), (+)amphetamine (1, 2, and 4 mg/kg), or β-CCM (1 mg/kg). They were isolated in small individual cages during 30 min; then, they were gently introduced into the black compartment. Means ± SEM of 7–12 mice per group. Multiple comparisons: pentylenetetrazole, $F = 12.26$, $p < 0.001$; yohimbine, $F = 16.7$, $p < 0.001$; amphetamine, $F = 8.67$, $p < 0.001$.

*$p < 0.05$ as compared to the saline-injected group.

in distilled water. Dexamphetamine sulfate (C.P.F.), *N*-[1-(2-benzo(*b*)thiophenyl)-cyclohexyl] piperidine (GK 13), (a generous gift from Dr. Kamenka, Montpellier, France), SK&F38393 (Bioblock Scientific, Illkirch, France), and β-CCM (Bioblock) were dissolved in saline. 1-[2-(Diphenylmethoxy)-ethyl]4-(3-phenyl propenyl)-piperazine, (GBR 12783) (kindly synthesized by Prof. Robba and Dr. Lancelot, Faculty of Pharmacy, Caen, France) was dissolved in dimethyl sulfoxide (DMSO) and diluted in distilled water (final concentration: 5%). RU 24926 (Roussel UCLAF, Romainville, France) and SCH23390 (Schering Corp., Bloomfield, NJ) were dissolved in distilled water containing 5% DMSO and 5% Cremophor EL (BASF, Ludwigshaffen, Germany). Haloperidol (Haldol, Janssen Pharmaceutica, Beerse, Belgium) and diazepam (Valium, Roche, Basel, Switzerland) were diluted in saline.

All drugs were injected in a volume of 10 ml/kg. Doses always refer to the free bases.

RESULTS

Effects of Reference Anxiogenic Drugs

Black compartment to white compartment paradigm. Pentylenetetrazole from 6.25 mg/kg SC increased significantly and dose dependently the latency for entering the white compartment. At no tested dose, up to 50 mg/kg, was there a significant reduction in the duration of the first stay in the white compartment. Similar results were obtained with yohimbine from 2 mg/kg SC. Dexamphetamine from 2 mg/kg SC induced similar effects but with a tendency to reduce the first-stay duration in the white compartment, which was significant for the 4-mg/kg dose. The β-carboline derivative β-CCM (1 mg/kg) increased the white compartment-entering latency whereas the white compartment first-stay duration was not modified (Table 1).

White compartment to black compartment paradigm. Pentylenetetrazole (50 mg/kg), (+)amphetamine (4 mg/kg), or β-CCM (1 mg/kg) were not able to modify significantly the black compartment-entering latency. In contrast, yohimbine (4 mg/kg) increased this latency. Concerning the black compartment first-stay duration, this parameter was increased by the four tested drugs (Table 2).

Effects of Indirect Catecholamine Agonists

GBR 12783 from 5 mg/kg IP increased significantly and dose dependently the latency in entering the white compartment. At no tested dose, up to 10 mg/kg, was there a significant reduction in the duration of the first stay in the white compartment, although a tendency was observed. Similar results were obtained with GK 13 from 2.5 mg/kg IP (Table 3).

Effects of Direct Agonists of D_1 and D_2 Dopamine Receptors

Increasing doses of the D_1 agonist SK&F38393 (5, 10, and 20 mg/kg) induced an increase of the white compartment-entering latency, the maximum being apparently reached between 10 and 20 mg/kg: In saline controls, the entering latency was 36 ± 3.5 s (n = 66) and reached 63 ± 8 s (n = 40) in SK&F38393 5-mg/kg SC- ($p < 0.01$), 96.5 ± 13.5 s in SK&F38393 10-mg/kg SC- ($p < 0.001$), and 113 ± 15 s (n = 25) in SK&F38393 20-mg/kg SC-treated mice ($p < 0.01$). The D_2 agonist RU 24926 increased dose dependently the latency in entering the white compartment from 250 μg/kg SC (Table 4). In addition, it increased significantly the length of the first-stay duration in the white compartment. Considering the influence of the 500-μg/kg dose of RU 24926 on the locomotor activity of mice, we observed a significant decrease (−35%): The locomotor activity (number of crossed beams) was in controls 4,048 ± 205 and in RU-24926 treated mice 2,621 ± 180 ($p < 0.001$). Associating with 10 mg/kg SK&F38393 increasing doses of RU 24926 (125–500 μg/kg),

TABLE 2

EFFECTS OF PENTYLENETETRAZOLE, YOHIMBINE, (+)AMPHETAMINE, AND β-CCM ON THE ENTERING LATENCY AND FIRST-STAY DURATION IN THE BLACK COMPARTMENT

	Black Compartment-Entering Latency (seconds)	Black Compartment First-Stay Duration (seconds)
Pentylenetetrazole (mg/kg, SC)		
0	26 ± 8	123 ± 38
50	17 ± 1.5	269 ± 47*
Yohimbine (mg/kg, SC)		
0	16.5 ± 2	21 ± 3
4	43 ± 8†	192.5 ± 50†
(+)Amphetamine (mg/kg, SC)		
0	14 ± 2	65.5 ± 19.5
4	11 ± 3	249 ± 54†
β-CCM (mg/kg, SC)		
0	18.5 ± 4.5	50.5 ± 13.5
1	19.5 ± 4.5	145.5 ± 41*

Mice were injected SC with saline, pentylenetetrazole (50 mg/kg), yohimbine (4 mg/kg), (+)amphetamine (4 mg/kg), or β-CCM (1 mg/kg). They were isolated in small individual cages during 30 min; then, they were gently introduced into the white compartment. Means ± SEM of 8–10 mice per group.

*$p < 0.05$, †$p < 0.01$, ‡$p < 0.001$ as compared to the saline-injected group.

TABLE 3

EFFECTS OF THE DOPAMINE UPTAKE INHIBITORS GK 13 AND GBR 12783 ON THE ENTERING LATENCY AND FIRST-STAY DURATION IN THE WHITE COMPARTMENT

	White Compartment-Entering Latency (seconds)	White Compartment First-Stay Duration (seconds)
GK 13 (mg/kg, IP)		
0	22.5 ± 4.0	7.0 ± 1.5
2.25	43.5 ± 13.0	8.5 ± 2.0
5	89.0 ± 11.0*	4.5 ± 0.5
10	151.5 ± 27.5*	4.5 ± 1.0
GBR 12783 (mg/kg, IP)		
0	54.5 ± 15.5	12.5 ± 2.0
2.5	83.5 ± 16.5	11.5 ± 1.5
5	163.5 ± 25.5*	9.0 ± 1.5
10	288 ± 37*	7.5 ± 1.5

Mice were injected IP with saline or increasing doses of GK 13 (2.5, 5, and 10 mg/kg) or GBR 12783 (2.5, 5, and 10 mg/kg). They were isolated in small individual cages during 30 min; then, they were gently introduced into the black compartment. Means ± SEM of 9–11 mice per group. Multiple comparisons (for the white compartment-entering latency parameter): GK 13, $F = 12.3$, $p < 0.001$; GBR 12783, $F = 17.4$, $p = 0.001$.

*$p < 0.05$ as compared to the saline-injected group.

we observed that the resultant effect corresponded at best to an addition of their respective effect [no significant interaction, $F(2, 54) = 2.84$].

Effects of D_1 and D_2 Dopamine Receptors Antagonists or Diazepam on the Anxiogenic Effect of GBR 12783

The preferential D_2 dopamine receptor antagonist haloperidol, administered IP at the 50-μg/kg dose, antagonized the increase of the latency in entering the white compartment induced by GBR 12783 (10 mg/kg, IP) (Table 5). A pretreatment (15 min, SC) with the specific D_1 dopamine receptor antagonist SCH23390, at the 20-μg/kg dose, significantly reduced the high latency in entering the white compartment induced by GBR 12783 (10 mg/kg, IP) administered 30 min before testing. In this experiment, SCH23390, intrinsically, did not significantly reduce the latency in entering the white compartment; however, a tendency was observed. Further, pooled data indicate that whereas in saline controls this latency was 55 ± 8 s it was 32 ± 3 s in SCH23390 (15 μg/kg, SC) (means ± SEM of, respectively, 60 and 55 mice; $p < 0.001$). A 7.5-μg/kg dose was ineffective whereas the results obtained with a 30-μg/kg dose were similar to those obtained with the 15-μg/kg dose (not shown). A pretreatment with diazepam (2.5 mg/kg, SC) did not significantly reduce ($p > 0.05$) the latency in entering the white compartment. This treatment performed 30 min before IP administration of GBR 12783 (10 mg/kg) reduced significantly this latency (Table 5).

DISCUSSION

The results presented in this study show that the increase of the latency in entering the white compartment could be related to a behavior approaching human anxiety. This is suggested by the efficacy of reference anxiogenic drugs yohimbine, pentylenetetrazole, (+)amphetamine, and β-CCM. This reticence to enter the white compartment can be explained by the natural aversion that rodents have for a new environment (the so-called "neophobia"). Several tests have been based upon this neophobia, such as the delayed food intake by deprived rats when foods are presented in a new environment (1,24). In addition, this reticence likely depends upon their aversion for bright environments, which can inhibit some behaviors, as it has been shown on "social interaction" (10). The present test is quick and easy to perform and it may be easily automated (that is now in development). A drawback may lie

TABLE 4

EFFECTS OF SK&F38393, RU 24926, AND THEIR ASSOCIATION ON THE ENTERING LATENCY AND FIRST-STAY DURATION IN THE WHITE COMPARTMENT

	White Compartment-Entering Latency (seconds)	White Compartment First-Stay Duration (seconds)
Saline	39 ± 8	8 ± 1
SK&F38393 (10 mg/kg)	74 ± 33	7 ± 1
RU 24926		
125 μg/kg	86 ± 30	11 ± 2
250 μg/kg	137 ± 38*	21 ± 4*
500 μg/kg	230 ± 41*	17.5 ± 4*
SK&F38393 (10 mg/kg) + RU 24926 (125 μg/kg)	73 ± 33	13 ± 2
SK&F38393 (10 mg/kg) + RU 24926 (250 μg/kg)	149 ± 41*	20 ± 3
SK&F38393 (10 mg/kg) + RU 24926 (500 μg/kg)	269 ± 39.5	19 ± 12

Mice were injected SC with saline, SK&F38393 10 mg/kg, or increasing doses of RU 24926 (125, 250, and 500 μg/kg) or coinjected with SK&F38393 (10 mg/kg) and the same increasing doses of RU 24926. After injection, they were isolated in small individual cages and then gently introduced into the black compartment. Means ± SEM of 10–15 mice per group. Multiple comparisons (for the white compartment-entering latency parameter): RU 24926, $F = 7.49$, $p < 0.001$; SK&F38393 + RU 24926, $F = 10.6$, $p < 0.001$.

*$p < 0.05$ as compared to the saline-injected group.

TABLE 5

EFFECTS OF HALOPERIDOL, SCH23390, AND DIAZEPAM ON THE INCREASE IN THE WHITE COMPARTMENT-ENTERING LATENCY ELICITED BY GBR 12783

	White Compartment-Entering Latency (seconds)	*n*
Saline + saline	57 ± 9	46
Saline + GBR 12783 (10 mg/kg)	166 ± 25*	32
Haloperidol (25 μg/kg) + Saline	84 ± 19	32
Haloperidol (50 μg/kg) + saline	80 ± 19	28
Haloperidol (25 μg/kg) + GBR 12783 (10 mg/kg)	93 ± 23†	22
Haloperidol (50 μg/kg) + GBR 12783 (10 mg/kg)	63 ± 19‡	25
Saline + saline	59 ± 14	16
SCH23390 (20 μg/kg) + saline	39 ± 5	20
Saline + GBR 12783 (10 mg/kg)	180 ± 32*	20
SCH23390 (20 μg/kg) + GBR 12783 (10 mg/kg)	79 ± 23†	16
Saline + saline	60 ± 21	16
Diazepam (2.5 mg/kg) + saline	51 ± 18	16
Saline + GBR 12783 (10 mg/kg)	207 ± 38§	15
Diazepam (2.5 mg/kg) + GBR 12783 (10 mg/kg)	80 ± 32‡	15

Mice were injected IP with saline or haloperidol (25 or 50 μg/kg) 30 min before IP administration of saline or GBR 12783 (10 mg/kg), or injected SC with saline or SCH23390 (20 μg/kg) 15 min before IP administration of saline or GBR 12783 (10 mg/kg), or injected SC with saline or diazepam (2.5 mg/kg) 30 min before IP administration of saline or GBR 12783 (10 mg/kg). The test was performed 30 min after the last injection. Means ± SEM of 19–46 mice per group.

*$p < 0.001$, §$p < 0.01$ as compared to the saline/saline-injected group.

†$p < 0.05$, ‡$p < 0.01$ as compared to the saline/GBR-12783 injected group.

in an increased latency to enter the white compartment related to a motor incapacitation or a sedation and not to an anxiogenic effect. This bias can be tested by observing treated animals, eventually measuring their locomotor activity, and measuring the duration of their first stay in the white compartment. An increase of this duration would correspond to an anxiolytic effect if it goes with a short latency in entering the white compartment. On the contrary, an increase of the white compartment first-stay duration would correspond to a sedative effect or a motor incapacitation if it goes with a high latency in entering the white compartment.

We cancelled the data obtained for mice that escape the black compartment in less than 5 s. This unusual response was observed in an aleatory manner (unrespective of treatments) in less than 5% of tested animals. We made the hypothesis that this case concerns a running-away reflex by animals that did not integrate the environmental cues and therefore cannot elaborate an adapted response.

In the classical paradigm that considers the black compartment-entering latency, saline-injected animals entering latency is brief (15–20 s). Therefore, its shortening by anxiogenic drugs should be difficult to evidence. As a matter of fact, none of the four tested reference anxiogenic agents significantly shortened this latency. On the contrary, using the inverted paradigm we evidenced for each of these drugs a statistically significant, dose-dependent, and large increase in the white compartment-entering latency.

The marked increase in entering latency into the white compartment elicited by (+)amphetamine, a catecholamine uptake inhibitor (8) that is also a potent dopamine releaser (4), was shared by drugs that are only catecholamine uptake inhibitors: GK 13 and GBR 12783 (2,6,23). Whereas GK 13 inhibits neuronal uptake of both norepinephrine and dopamine, GBR 12783 is selective of the dopamine uptake. Therefore, the involvement of dopaminergic transmissions appears likely. This is confirmed by the antagonism of the GBR 12783 effect by both the D_2 preferential dopamine receptor antagonist haloperidol (19) and the specific D_1 dopamine receptor antagonist SCH23390 (15,16). To substantiate the involvement of D_1 and D_2 dopamine receptors in this effect, we tested direct agonists of both types of dopamine receptors. The D_1-specific agonist SK&F38393 (21) induced a moderate anxiogenic-like effect. The D_2-specific agonist RU 24926 (7) in a more evident dose-dependent manner shared this apparent anxiogenic property. However, in the range of effective doses it reduced the locomotor activity, which might unspecifically account for the delay in entering the white compartment. In addition, this was accompanied by an increase in the first-stay duration in the white compartment. The association of the D_1 agonist SK&F38393 with the D_2 agonist RU 24926 did not result in a potentiation, but at the best revealed an additivity of their intrinsic effects. Considering the effect of dopamine receptor antagonists, we observed that the D_1 antagonist SCH23390 reduced the latency in entering the white compartment, which could result from the decrease in a dopaminergic tonus involving D_1 receptors. On the contrary, we observed no intrinsic

anxiogenic-like effects with the preferential dopamine receptor antagonist haloperidol. The suppression by the reference anxiolytic diazepam of the GBR 12783-induced increase in entering latency constitutes a supplementary reason to consider that this entering latency might depend upon an anxious state. In this view, it appears that anxious states underlined by an increase in dopamine transmission may be reduced by benzodiazepine anxiolytic agents.

Because the greatest care must be taken in transposing animal responses to a psychological state such as anxiety, one must insist on the fact that this increased aversion for the strongly lit environment elicited by dopamine agonists might not be necessarily generalized to other stressful situation.

In conclusion, it appears that a basal dopaminergic tonus, by stimulating D_1 receptors, induces a mild anxious-like state that is suppressed by the D_1 antagonist SCH23390. Increasing the dopamine transmissions obviously aggravates the anxious level, which involves both D_1 and D_2 receptors, the benzodiazepine anxiolytic diazepam (12) being able to antagonize this anxiogenic-like effect.

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