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Pharmacology Biochemistry and Behavior, Vol. 54, No. 1, pp. 235–239, 1996

0091-3057/96 $15.00 + .00

SSDI 0091-3057(95)02131-0

Indirect Dopamine Agonists Effects on Despair Test: Dissociation From Hyperactivity

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VAUGEOIS, J.-M., D. POUHÉ, F. ZUCCARO AND J. COSTENTIN. *Indirect dopamine agonists effects on despair test: Dissociation from hyperactivity.* PHARMACOL BIOCHEM BEHAV **54**(1) 235–239, 1996.—Both dexamphetamine and the pure dopamine reuptake inhibitor GBR 12783 elicit a stimulation of locomotion and increase swimming activity in the behavioral despair test in mice. The dopamine D_1 dopamine receptor antagonist SCH 23390 dose dependently (7.5–30 μg/kg SC) antagonized the stimulant locomotor effect of both drugs but did not prevent their antiimmobility effect on the behavioral despair test. The D_2 dopamine receptor antagonist haloperidol dose dependently (12.5–50 μg/kg IP) antagonized the effects of dexamphetamine on both locomotor activity and behavioral despair test. By contrast, haloperidol inhibited the effects of GBR 12783 in the forced swimming test but not on locomotion. It is concluded that indirect dopamine agonists are effective on the behavioral despair test independently of a stimulation of locomotor activity. Their effects on the despair test depend on the stimulation of D_2 but not D_1 dopamine receptors.

Behavioral despair test Indirect dopamine agonists D_1, D_2 dopamine receptors Motor activity Mice

THE BEHAVIORAL despair test is claimed to detect drugs with antidepressant activity (25). The test is easy to perform (i.e., measurement of an immobility time during a short period) but has a few drawbacks in terms of sensitivity and specificity. For instance, selective serotonin reuptake inhibitors that are effective antidepressants are not regularly detected by this test (4). On the contrary, central muscarinic receptor blockers are active in this test (8), but their beneficial effects are less documented than their adverse effects in depressed patients. In addition, amphetaminics are considered as reducing unspecifically the time of immobility in the behavioral despair test because they increase locomotion in rodents (25). As a matter of fact, a drug must reduce immobility in the behavioral despair test at doses that do not stimulate locomotion to be considered as a potential antidepressant.

Antidepressant effects in depressive patients have been reported with the direct dopamine D_2 agonists piribedil (22,27) and bromocriptine (11). Besides these clinical reports, these two drugs and other D_2 dopamine agonists were also shown to be effective on the behavioral despair test (14,26). A recent study also found that a dopamine D_2 receptor mechanism was involved in the rapid eye movement sleep deprivation treatment-induced increase in swimming activity in the mouse behavioral despair test (2). A similar effectiveness was found on the learned helplessness paradigm (18). On the other hand, D_1 dopamine receptor agonists such as SKF 38393, SKF 81297, or A 68930 have been reported to be effective in animal models of depression by some authors (12,17,30) but not others (5,14,18). In the present work we studied the effects of the indirect dopamine agonists dexamphetamine and GBR 12783 on the behavioral despair test. Dexamphetamine is both a dopamine releaser and reuptake blocker (16), whereas GBR 12783 is a pure dopamine reuptake inhibitor (3). We explored the involvement of D_1 and D_2 dopamine receptors in the effects induced by these two drugs. The relationships between the effects of these drugs on locomotor activity and the reduction of the time of immobility were especially examined.

METHOD

Animals

Male Swiss albino CD1 mice, weighing 22–25 g, were purchased from Charles River (Saint Aubin lès Elbeuf, France). CD1 mice were housed in groups of 30 in Makrolon cages (38 × 24 × 18 cm) with free access to water and food (U.A.R., France) and kept in a ventilated room at a temperature of 21 ± 1°C, under a 12 L : 12 D cycle (lights on between 0700 and 1900 h). Experiments were carried out between 0900 and 1700 h.

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Testing Procedures

Mouse behavioral despair test. The apparatus consisted of two Plexiglas cylinders (25 cm height, 10 cm internal diameter) placed side by side in a Makrolon cage (38 × 24 × 18 cm) filled with water (7.5 cm height) at 21–23°C. Two mice were tested simultaneously, but a nontransparent screen placed between the two cylinders prevented mice from seeing each other. Fifteen minutes after the last treatment the mice were put into the cylinders and left there for 6 min. The immobility time was measured during the last 3 min of the test by an observer who was unaware of the drug treatment. A mouse was judged to be immobile when it remained floating in the water, making only those movements necessary to keep its head above water.

Locomotor activity. Locomotor activity was measured with a Digiscan actometer (Omnitech Electronics Inc., Columbus, OH), which monitored the horizontal movements of the animals. The individual compartments (L = 20; W = 20; H = 30 cm) were put in a dimly lit and quiet room. The responses to drugs injected immediately before the test were expressed as number of beams crossed between the 5th and the 35th min after treatments.

Drugs

Dexamphetamine sulfate (La Cooper, Melun, France) was dissolved in saline; GBR 12783 [1-[2-(diphenyl-methoxy)-ethyl]4-(3-phenyl-2-propenyl)-piperazine] (obtained from Pr Robba, Caen, France) was dissolved in distilled water containing 5% dimethyl sulfoxide; haloperidol = Haldol® (Janssen) was diluted in distilled water; SCH 23390 (Schering Corp., Bloomfield, NJ) was dissolved in distilled water containing 5% dimethyl sulfoxide and 5% Cremophor EL (Sigma Chemical Co., St. Louis, MO). All drugs were injected in a volume of 10 ml/kg. Doses always refer to the free bases.

Statistics

Results are expressed as means ± SEM. Analyses of variance (ANOVAs) were used for statistical analysis of the data. When appropriate, Tukey tests were used for making post hoc comparisons. Values of $p < 0.05$ were considered significant.

RESULTS

In preliminary dose-response studies, the administration of the indirect dopamine agonists dexamphetamine or GBR 12783 produced dose-dependent reductions of immobility in the mouse behavioral despair test that were significant at 2 mg/kg SC and 16 mg/kg SC, respectively (data not shown). These doses were, therefore, chosen in the present experiments (Figs. 1 to 4, lower panels). The period of immobility measured 15 min after dexamphetamine was reduced dose dependently in mice pretreated with increasing doses of haloperidol (25, 50, 100, 200 μg/kg IP) 30 min before dexamphetamine (Fig. 1, lower panel).

The effect of GBR 12783 in the despair test was also reversed by pretreatment with haloperidol (Fig. 3, lower panel). Under similar conditions, SCH 23390 (7.5, 15, 30 μg/kg SC) did not modify the effects of dexamphetamine and GBR 12783 in the despair test (Figs. 2 and 4, lower panels). The immobility time was slightly but significantly increased in control animals after acute treatment with a 30 μg/kg SC dose of SCH 23390 (Figs. 2 and 4, lower panels).

The stimulant locomotor effect of dexamphetamine (2 mg/kg SC) was dose dependently suppressed in mice that received increasing doses of haloperidol 30 min before dexamphetamine (Fig. 1, upper panel). On the contrary, there was no significant reduction in the GBR 12783-induced stimulation in locomotor activity in mice injected with haloperidol (Fig. 3, upper panel). Finally, the stimulant locomotor effects of dexamphetamine and GBR 12783 were both dose depen-

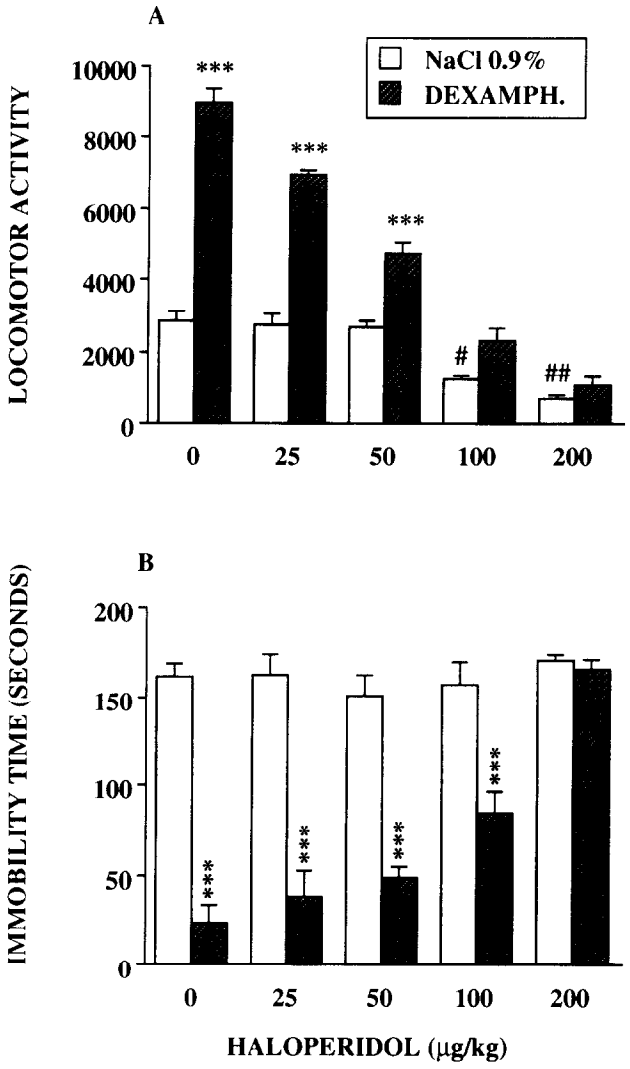

FIG. 1. Effects of haloperidol on stimulation of locomotor activity and antiimmobility response induced by dexamphetamine. Mice were injected with saline (open bars) or increasing doses of haloperidol (25–50–100–200 μg/kg IP) (hatched bars). Thirty minutes later they were injected with saline or dexamphetamine (2 mg/kg SC). Panel A: locomotor activity test. Immediately after the second treatment mice were introduced into the actometers. The horizontal activity was measured for 30 min, after a 5-min period of habituation. Means ± SEM of data from 10 mice per group. ANOVA: $F(9, 90) = 102.3, p < 0.001$. Post hoc comparisons: $\#p < 0.01$; $\#\#p < 0.001$ compared with saline-saline group; $***p < 0.001$ compared with haloperidol (same dose)-saline group. Panel B: behavioral despair test. Pretreated mice received saline or dexamphetamine 15 min before testing. The immobility time was measured during the last 3 min of immersion. Means ± SEM of data from eight mice per group. ANOVA: $F(9, 70) = 34.2$, $p < 0.001$. Post hoc comparisons: $***p < 0.001$ compared with haloperidol (same dose)-saline group.

dently reversed by increasing doses of SCH 23390 (Figs. 2 and 4, upper panels).

DISCUSSION

Beneficial effects of dopamine reuptake blockers and dexamphetamine have been reported in depression [for review, see (7)]. There is also increasing evidence from imaging studies for a role of dopaminergic transmissions in the pathophysiology of depressive disorders (13). In the present study, we have determined the effects of indirect dopamine agonists in one of the many screening procedures that have been used to predict and evaluate the therapeutic potential of drugs in depressive disorders.

If mice are forced to swim in a confined space, they assume an immobile posture after an attempt to escape. This state has been named behavioral despair by Porsolt et al. (25), and it is assumed that the animals have given up hope of escaping.

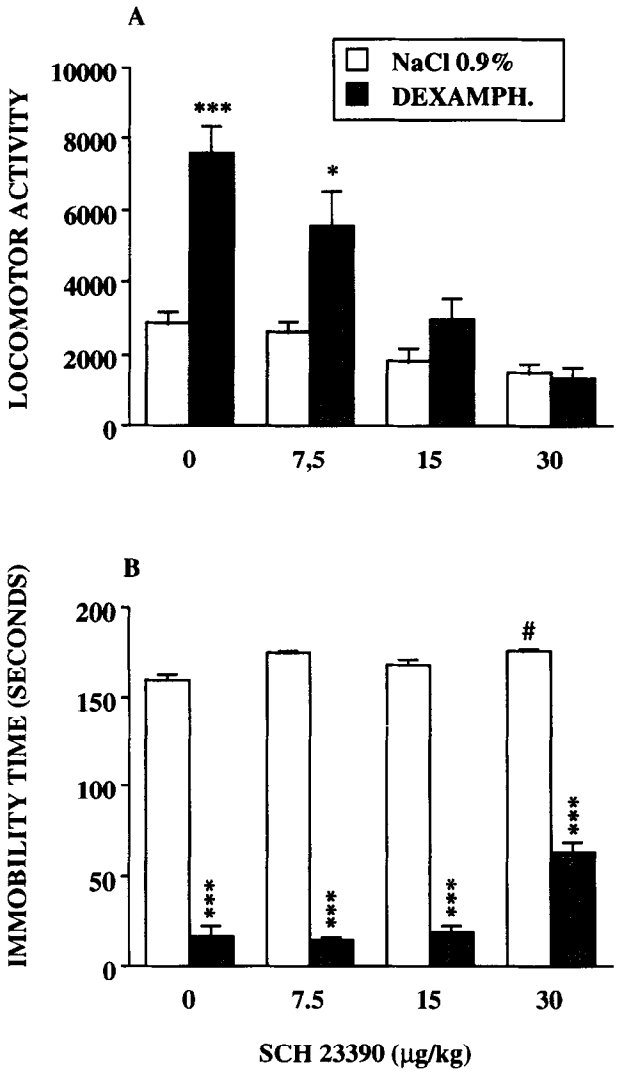

FIG. 2. Effects of SCH 23390 on stimulation of locomotor activity and antiimmobility response induced by dexamphetamine. Mice were injected with vehicle (open bars) or increasing doses of SCH 23390 (7.5–15–30 µg/kg SC) (hatched bars). Thirty minutes later they were injected with saline or dexamphetamine (2 mg/kg SC). Panel A: locomotor activity test. Immediately after the second treatment mice were introduced into the actometers. The horizontal activity was measured for 30 min, after a 5-min period of habituation. Means ± SEM of data from 10 mice per group. ANOVA: $F(7, 72) = 14.7$, $p < 0.001$. Post hoc comparisons: $*p < 0.05$; $***p < 0.001$ compared with SCH 23390 (same dose)-saline group. Panel B: behavioral despair test. Pretreated mice received saline or dexamphetamine 15 min before testing. The immobility time was measured during the last 3 min of immersion. Means ± SEM of data from 10 mice per group. ANOVA: $F(7, 72) = 398.4$, $p < 0.001$. Post hoc comparisons: $\#p < 0.05$ compared with vehicle-saline group; $***p < 0.001$ compared with SCH 23390 (same dose)-saline group.

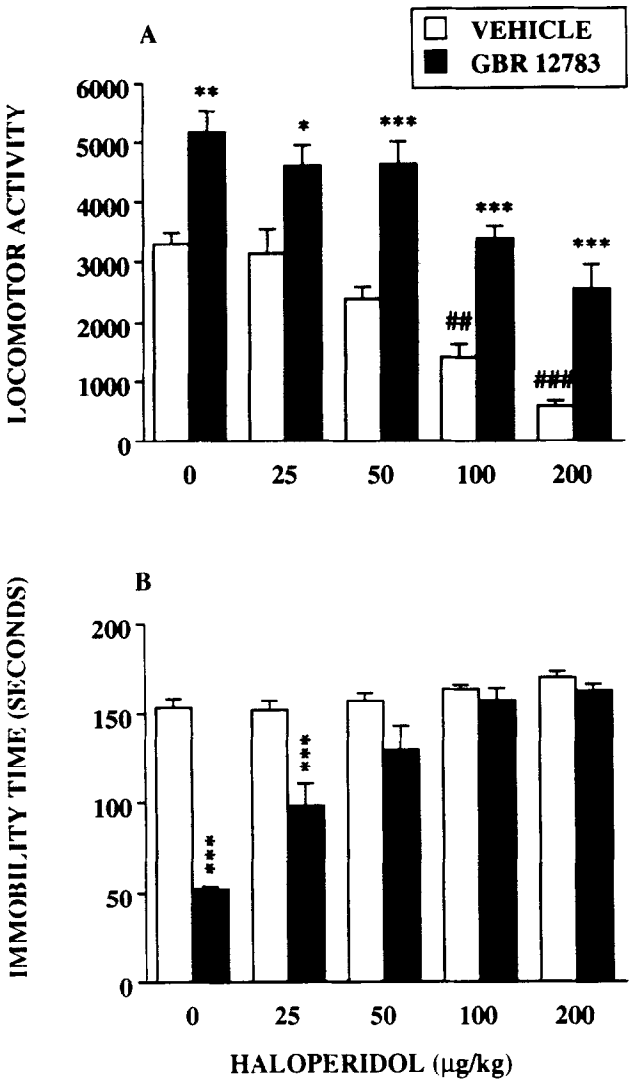

FIG. 3. Effects of haloperidol on stimulation of locomotor activity and antiimmobility response induced by GBR 12783. Same procedure as in Fig. 1 except that GBR 12783 (16 mg/kg) was administered instead of dexamphetamine (2 mg/kg SC). Panel A: locomotor activity test. Means ± SEM of data from nine mice per group. ANOVA: $F(9, 80) = 22.9$, $p < 0.001$. Post hoc comparisons: $\#\#p < 0.01$; $\#\#\#p < 0.001$ compared with saline-vehicle group; $***p < 0.001$ compared with haloperidol (same dose)-vehicle group. Panel B: behavioral despair test. Means ± SEM of data from eight mice per group. ANOVA: $F(9, 70) = 26.5$, $p < 0.001$. Post hoc comparisons: $***p < 0.001$ compared with haloperidol (same dose)-saline group.

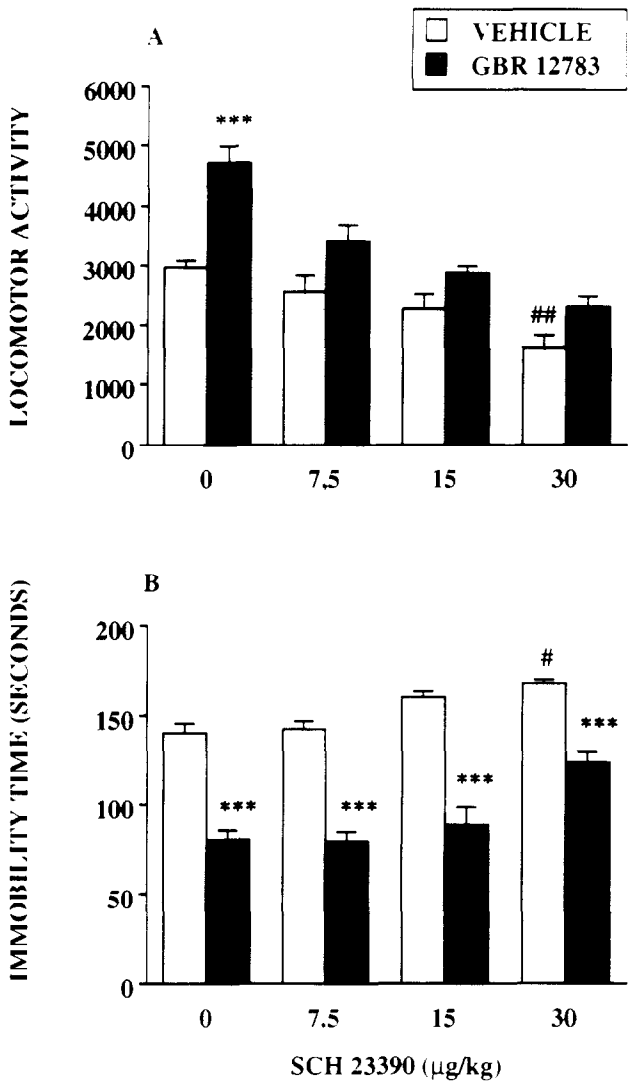

FIG. 4. Effects of SCH 23390 on stimulation of locomotor activity and antiimmobility response induced by GBR 12783. Same procedure as in Fig. 2 except that GBR 12783 (16 mg/kg) was administered instead of dexamphetamine (2 mg/kg SC). Panel A: locomotor activity test. Means ± SEM of data from eight mice per group. ANOVA: $F(7, 56) = 18.0, p < 0.001$. Post hoc comparisons: $\#\#p < 0.01$ compared with vehicle-vehicle group; $***p < 0.001$ compared with SCH 23390 (same dose)-vehicle group. Panel B: behavioral despair test. Means ± SEM of data from 10 mice per group. ANOVA: $F(7, 72) = 35.6$, $p < 0.001$. Post hoc comparisons: $\#p < 0.05$ compared with vehicle-vehicle group; $***p < 0.001$ compared with SCH 23390 (same dose)-vehicle group.

Some false positives have been reported for stimulants, anticholinergics, and a number of other drugs in this test (31). It is clear that antidepressant-induced reduction of immobility cannot be explained by a nonspecific behavioral stimulation, as many antidepressants tend to decrease motor activity (5,6,14). Interestingly, Bulach et al. (9) have already shown that a given dose of phenylethylamine induced an increase in motor activity in mice but did not reduce the immobility behavior in the forced swimming test. However, the positive responses induced by indirect dopamine agonists could result from their motor stimulant effects.

In the present study, acute treatment of mice with dexamphetamine or GBR 12783, two indirect dopamine agonists (15), produced an antiimmobility effect in the behavioral despair test in accordance with previously reported results (15,25). The effects induced by dexamphetamine and GBR 12783 are blocked by haloperidol, a D_2 preferential dopamine receptor antagonist (29). In comparison with haloperidol, the ineffectiveness of the D_1 dopamine receptor antagonist SCH 23390 (19) leads to the conclusion that stimulation of D_2 dopamine receptors but not D_1 receptors is critically involved in the antiimmobility effect. Indeed, D_1 dopamine receptors agonists have been shown previously to be ineffective in the mouse (14) or rat (5) behavioral despair tests. Nevertheless, positive effects of SKF 38393 have been reported when using rats (12,30). The importance of D_1 dopamine receptors in the mechanism of action of antidepressants in rats remains a controversial issue to date (1,17,24). Whatever may be, species-specific phenomena might explain the discrepant results observed concerning D_1 dopamine receptor mechanisms in the rodent models of depression (23). Finally, in accordance with other authors (5), we observed a slight enhancement in the immobility time in control animals after acute treatment with the highest tested dose of SCH 23390. This effect could be linked to its depressant effects on locomotion.

A dose of 2 mg/kg SC of dexamphetamine induced a larger increase in motor activity than a dose of 16 mg/kg SC of GBR 12783, confirming previous results (15). The classical reversal of dexamphetamine-induced hyperkinesia in mice operated by a blockade of D_2 dopamine receptors (28) is dose dependent and virtually total for the highest tested dose of haloperidol (200 μg/kg). On the contrary, there was no antagonism of GBR 12783-induced motor stimulant effect by haloperidol, as previously demonstrated (15). This discrepancy in the action of haloperidol upon dexamphetamine and GBR 12783 effects might result from the different modes of action of these two indirect dopamine agonists [for discussion, see (15)]. The different degree of antagonism caused by haloperidol on dexamphetamine and GBR 12783 effects in the behavioral despair and motor activity tests is, therefore, in favor of a specific action of these drugs in the forced swimming test unrelated to their stimulant effect on locomotor activity.

The reversal of the effects of dexamphetamine or GBR 12783 by SCH 23390 in the locomotor activity test again supports this interpretation. In fact, the stimulation of locomotion in naive rodents requires the simultaneous stimulation of D_1 and D_2 dopamine receptors (21). The antagonism by D_1 dopamine receptor antagonists of the stimulant locomotor effects induced by indirect dopamine agonists has already been reported (10,20).

Stimulants are among the most frequently encountered false positives in animal models of depression (32). Regardless of the difficulty to properly assess in blind clinical trials the efficacy of these drugs in the treatment of depressive disorders, we may ask as pointed out by Willner whether these positive responses are really false (32). Indeed, the procedure used in the present study enabled us to exclude a possible bias in the usual paradigm of behavioral despair test, i.e., a stimulant effect on locomotor activity. When this stimulant effect results from an enhancement of dopamine transmission, the D_1 dopamine receptor antagonist SCH 23390 may be the adequate tool for discriminating a potential antidepressant from a psychostimulant.

ACKNOWLEDGEMENT

This study has been partly supported by DRET contract 92155.

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