Pharmacology Biochemistry & Behavior Vol 38 pp 243–246 © Pergamon Press plc 1991 Printed in the U S A 0091-3057/91 $3 00 + 00

Interactive Effects of D_1 and D_2 Agonists With Scopolamine on Radial-Arm Maze Performance

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Received 17 July 1990

LEVIN, E D AND J E ROSE *Interactive effects of D_1 and D_2 agonists with scopolamine on radial-arm maze performance* PHARMACOL BIOCHEM BEHAV **38**(2) 243–246, 1991 —Pharmacological blockade of muscarinic cholinergic (ACh) receptors has been found to impair choice accuracy in a variety of tasks including the radial-arm maze The cognitive impairment caused by the muscarinic antagonist scopolamine is reversed by the dopaminergic (DA) antagonist haloperidol as well as the selective D_1 antagonist SCH 23390 In the current study, interactions were studied between scopolamine and selective agonists of D_1 (SCH 38393) and D_2 (quinpirole) receptors Surprisingly, the D_1 agonist SKF 38393 was found to significantly alleviate the scopolamine-induced choice accuracy deficit In contrast, the D_2 agonist quinpirole was not found to significantly alter the effects of scopolamine on choice accuracy but did have supra-additive effects of increasing choice latency Both the D_1 agonist SKF 38393 and the D_1 antagonist SCH 23390 have been found to reverse the choice accuracy deficit caused by scopolamine and the deficit resulting from lesions of the medial projection from the basal forebrain to the cortex Possible mechanisms for these effects are discussed

Radial-arm maze Scopolamine D_1 D_2 Muscarinic Cholinergic Memory

THE muscarinic acetylcholinergic (ACh) blocker scopolamine impairs choice accuracy performance in a variety of cognitive tasks including the radial-arm maze [for review see (7)] This scopolamine-induced deficit in radial-arm maze choice accuracy can be reversed by dopaminergic (DA) receptor blockade (8, 12, 14) In particular, reversal of the scopolamine-induced deficit can be seen after selective blockade of D_1 dopaminergic receptors with SCH 23390 (8). Selective blockade of D_2 receptors by raclopride was not found to affect the scopolamine-induced deficit (8) Recently, an experiment examined the effectiveness of the D_1 and D_2 agonists and antagonists in counteracting the radial-arm maze choice accuracy impairment caused by knife-cuts of the medial projections from the basal forebrain to the cortex (13) As with scopolamine, SCH 23390 attenuated the experimentally induced choice accuracy deficit caused by this lesion, while the D_2 antagonist raclopride was ineffective. To provide a more complete description of the involvement of D_1 mechanisms with the lesion-induced choice accuracy deficit, the selective D_1 agonist, SKF 38393, was also studied. Surprisingly, this drug also provided attenuation of the choice accuracy deficit caused by the lesion

The current study was conducted to examine the interaction of selective D_1 and D_2 agonists with scopolamine on choice accuracy performance in the radial-arm maze Previous studies have provided two opposite predictions concerning the D_1 agonist. If it acts in the opposite fashion as the D_1 antagonist with regard to scopolamine, it should exacerbate the scopolamine-induced choice accuracy deficit. On the other hand, if it acts in a similar fashion as to knife-cut lesions of the medial basalocortical projections with regard to scopolamine, it should attenuate the scopolamine-induced choice accuracy deficit

METHOD

Subjects

Eleven adult female Sprague-Dawley strain albino rats (Zivic-Miller, Zelienople, PA) were used in the present experiment They were housed in groups of 2–4 in a standard vivarium room on a 12 12-h light dark cycle (lights came on at 6·00). The rats had ad lib access to drinking water but were maintained on a restricted feeding to keep their body weights at 80–85% of free-feeding levels

Apparatus

Behavioral testing of the rats was conducted on a radial 8-arm maze constructed of wood and painted black. It was elevated 30 cm from the floor. The central platform was 50 cm in diameter

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and eight arms (10 × 60 cm) extended radially. Food cups for the reinforcements were located near the distal end of each arm. The maze was located in a testing room which contained many extra-maze visual cues.

Behavioral Procedure

The rats were tested 5 days/week Before each session each of the arms was baited with ⅓ to ½ of a piece of sugar-coated cereal (Kellogg's Froot Loops). To begin the session the rat was placed in a circular plastic ring in the central platform. Then, after 10 seconds, the ring was lifted and the rat was allowed to move freely about the maze Arm choices were recorded when the rat had placed all of its paws past the threshold of the arm. Since the arms were not rebaited during the session, only the first entry was rewarded. Subsequent reentries were counted as errors. The session continued until the rat entered all eight arms or five minutes had elapsed, whichever came first The measure of choice accuracy was the number of entries until an error was made (entries to repeat). The measure of choice latency was the total session latency divided by the number of arms entered (seconds per entry). Drug testing began after asymptotic levels of choice accuracy were achieved (at least 19 sessions)

Drug Administration

All rats received saline, the muscarinic antagonist scopolamine (0 05 or 0.15 mg/kg), the dopamine D_1 agonist SKF 38393 (2 or 4 mg/kg), the D_2 agonist quinpirole (LY 171555) (0.04 or 0.08 mg/kg) and combinations of scopolamine + SKF 38393 and scopolamine + quinpirole. The drug weights are expressed as a function of their salt. They were mixed in 0.9% saline and injected (SC) in a volume of 1 ml/kg, 20 minutes before testing Drugs were administered twice a week with at least two days between injections On the days between injections the rats were tested without drugs. The first phase of the study consisted of testing the effects of both doses of the D_1 and D_2 agonists in combination with the higher dose of scopolamine. Saline and each drug alone were also tested in this phase. The second phase consisted of testing the effects of both doses of the D_1 and D_2 agonists in combination with the lower dose of scopolamine. Saline and the lower dose of scopolamine alone were also tested in this phase Within each phase, each drug dose and combination was tested once in a counterbalanced order Three rats did not make sufficient arm choices after treatment with LY 171555 to provide entries to repeat data They were retested with the same dose and thereupon did provide choice data

Data Analysis

The entries to repeat and seconds per entry measures were evaluated by analyses of variance for repeated measures. Since the study was run in two parts, one examining D_1 and D_2 agonist treatments on the the effects of the higher dose of scopolamine and the other examining D_1 and D_2 agonist treatments on the effects of the lower dose of scopolamine, there were two levels of within subjects variables, scopolamine dose and D_1 or D_2 agonist dose. Analyses compared the effects of the drugs when given alone relative to saline injections. Analyses were then conducted to examine the effects of the doses of either the D_1 agonist SKF 38393 or the D_2 agonist quinpirole in combination with scopolamine relative to scopolamine alone. One rat did not provide entries to repeat data for two of the drug conditions (0 15 mg/kg scopolamine and 0.15 mg/kg scopolamine + 0 08 mg/kg LY 171555) and was not included in the subsequent data analysis.

RESULTS

Choice Accuracy

Neither SKF 38393 nor quinpirole when given alone caused significant alterations of choice accuracy (Fig 1a and b) In contrast, there was a clear scopolamine-induced choice accuracy deficit, $F(1,9) = 22.48$, $p<0.005$, which was dose-related. The lower dose of scopolamine (0.05 mg/kg) caused a moderate deficit (6.10 ± 0.69) relative to its saline control condition ($7\ 60 \pm 0.27$), while the higher scopolamine dose (0.15 mg/kg) caused a more pronounced deficit (5.10 ± 0.48) relative to its saline control condition ($7.50 \pm 0\ 34$) As shown in Fig 1a, the scopolamine-induced deficit was significantly attenuated by coadministration of the D_1 agonist SKF 38393, $F(2,18) = 3.79$, $p<0.05$. Individual comparisons revealed that this effect resulted from the action of the higher dose of SKF 38393 (4 mg/kg) significantly attenuating the impairment of choice accuracy induced by scopolamine, $F(1,9) = 5.61$, $p<0\ 05$. In contrast to the D_1 agonist, the D_2 agonist quinpirole did not provide a significant degree of alleviation of the scopolamine-induced choice accuracy deficit (Fig. 1b). In fact, in combination with the higher (0.15 mg/kg) dose of scopolamine, quinpirole showed a tendency for exacerbating the scopolamine-induced deficit, but this was not significant

Response Latency

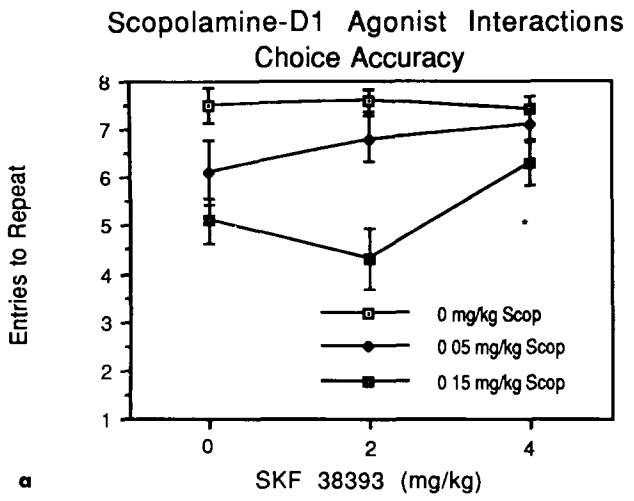
Scopolamine itself caused an increase in choice latency, $F(1,9) = 15.43$, $p<0.005$, an effect which was dose-related (Fig 2a and b) There was no effect of SKF 38393 on choice latency either by itself or in combination with scopolamine (Fig. 2a). Quinpirole did not cause a significant increase in choice latency by itself, but there was a dose-related trend in this direction (Fig 2b). In combination with scopolamine, quinpirole caused a significant increase in choice latency, relative to scopolamine alone, $F(2,18) = 8.53$, $p<0.005$. Both the low, $F(1,9) = 14.46$, $p<0.005$, and the high, $F(1,9) = 23.70$, $p<0\ 001$, doses of quinpirole caused significantly increased choice latency relative to scopolamine alone (Fig. 2b)

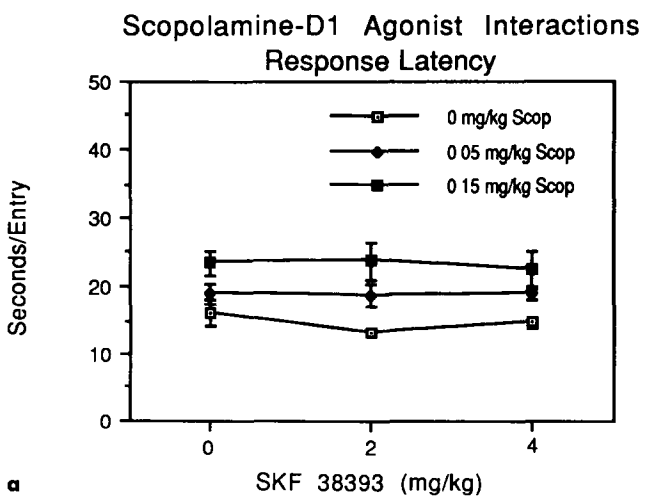
DISCUSSION

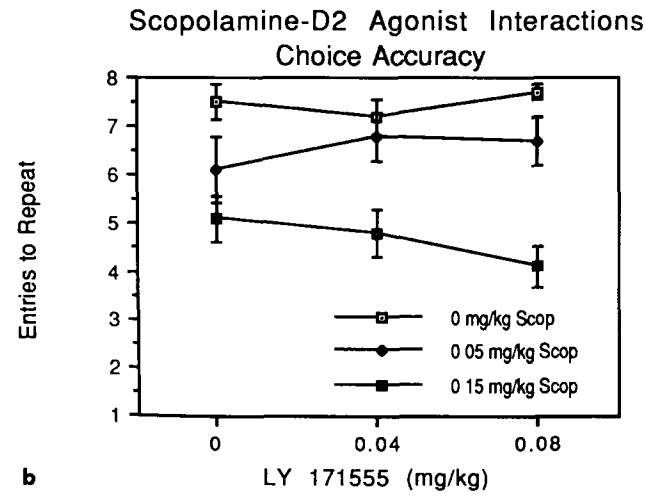
The most important finding of the current study is that the higher dose of the D_1 agonist provided significant attenuation of the scopolamine-induced deficit ($p<0.05$) The deficit caused by the lower scopolamine dose was almost completely reversed and the deficit caused by the higher dose was reduced by about half (Fig. 1a).

In two models of cholinergic hypofunction (lesion of basal forebrain projections and muscarinic receptor blockade) both D_1 agonist and D_1 antagonist treatment have been found to attenuate the choice accuracy deficit (8,13). It is unusual that both an agonist and an antagonist of the same receptor would have a similar therapeutic effect There are several possible explanations for this type of result. Since only one ligand per category has thus far been examined, it is possible that some nondopaminergic side effect of one of the drugs was responsible for its therapeutic effect. It is known that SCH 23390 has antagonistic effects at 5-HT_2 as well as D_1 receptors (1). SCH 23390 may reverse the scopolamine-induced choice accuracy deficit by means of 5-HT_2 blockade Relevant to this hypothesis is the finding that serotonin inhibits ACh release in the hippocampus, an effect which is reversed by 5-HT_2 blockers (17).

It also may be the case that SCH 23390 and SKF 38393 do not act on exactly the same population of D_1 receptors As has been discovered in other transmitter systems, notably the seroto-







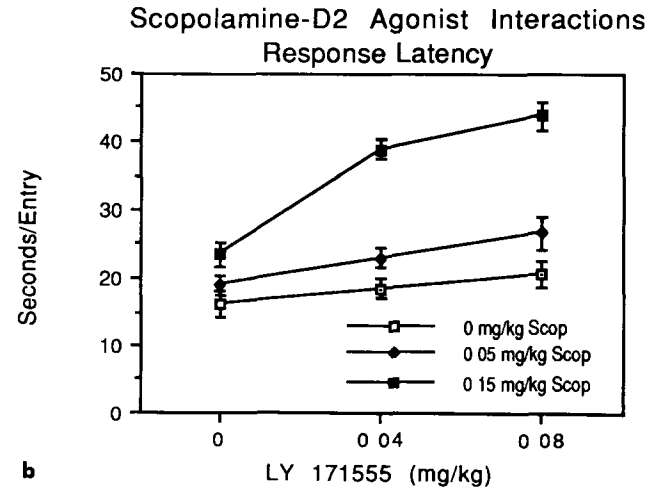


FIG 1 (a) Choice accuracy (entries to repeat), scopolamine interactions with the D_1 agonist SKF 38393 (mean ± standard error of the mean) *$p<0$ 05 Scop +4 mg/kg SKF 38393 vs scopolamine alone (b) Choice accuracy (entries to repeat), scopolamine interactions with the D_2 agonist quinpirole (mean ± standard error of the mean)

FIG 2 (a) Latency (seconds per entry), scopolamine interactions with the D_1 agonist SKF 38393 (mean ± standard error of the mean) (b) Latency (seconds per entry), scopolamine interactions with the D_2 agonist quinpirole (mean ± standard error of the mean)

nergic system, there may be different varieties of receptor subtypes. The observed results could be explained by SKF 38393 preferentially acting at a certain subclass of D_1 receptors and SCH 23390 preferentially acting at others. Inasmuch as these potentially different D_1 receptor subtypes may have different anatomic localization, the known interactions of DA and ACh in two relevant sites provide opposite predictions of whether a D_1 agonist or antagonist should be beneficial in reversing an antimuscarinic effect. In the septum, DA input from the ventral tegmental area (VTA) has inhibitory influence over septohippocampal ACh cells (3,21). Durkin et al (4) found that local administration of the DA antagonist haloperidol to the lateral septum increased the firing rate of septohippocampal ACh neurons This was paralleled by increased activity of hippocampal pyramidal cell activity and accelerated extinction of a conditioned behavioral response This group also found that selective lesions of the DA projections to the septum caused an increase in hippocampal ACh activity, facilitated spontaneous alternation performance and caused improvements in acquisition and reversal of a T-maze spatial discrimination (5). Our previous results would predict that application of SCH 23390 in this area should help overcome anticholinergic effects In the basal forebrain DA fibers from the substantia nigra and VTA provide innervation (6, 18, 22) and appear to exert excitatory influence on the basalocortical ACh projection (2). The current results would predict that application of SKF 38393 in this area should be beneficial in reversing anticholinergic effects. However, our previous finding that SKF 38393 is effective in reversing the choice accuracy deficit produced by a knifecut lesion of the medial cortical projection from the basal forebrain (13)

implies that DA innervation of the basal forebrain is not the only site for the therapeutic effects of the D_1 agonist. Further research is necessary to determine which anatomical substrates are critical for the observed interactions between D_1 and muscarinic ligands. In particular, work is needed to assess the relative importance of D_1 and D_2 receptors in the DA-ACh interactions in the above mentioned sites.

The interactions of D_1 and D_2 systems with ACh mechanisms may be important for the development of treatments of Alzheimer's disease, which is characterized by cholinergic hypofunction (19). The present finding that the D_1 agonist SKF 38393 reverses the cognitive impairment due to muscarinic ACh blockade complements our earlier finding that the D_2 agonist quinpirole reversed the cognitive impairment due to nicotinic ACh blockade (9). Nicotinic ACh receptors have been found to be down-regulated in Alzheimer's disease (23). While evidence for overall muscarinic ACh receptor down-regulation in Alzheimer's disease is more equivocal (19), there is good evidence for selective down-regulation of M2 receptors (16,20). Given the finding that understimulation of nicotinic and muscarinic receptors causes at least additive impairments in cognitive function (10,11), DA treatment for the cognitive decline in Alzheimer's disease should address the understimulation of both types of ACh receptors. In counteracting nicotinic receptor hypofunction, the results using DA drugs are quite straightforward. D_2 stimulation helps overcome the cognitive deficit due to nicotinic blockade (9) and D_2 blockade potentiates the deficit (15), while D_1 ligands have little appreciable interactive effect. In counteracting muscarinic hypofunction the results are more difficult to interpret. It is clear that D_1 systems have interactive effects with muscarinic blockade effects while D_2 systems appear to not have any appreciable interaction. However, full explanation of the surprising finding that both a D_1 agonist and a D_1 antagonist reverse the cognitive deficit from muscarinic blockade awaits further research.

ACKNOWLEDGEMENTS

This research was supported by a grant from the United Way. The authors thank Smith, Kline & French Pharmaceuticals for providing SKF 38393 and Lilly Pharmaceuticals for providing LY 171555, and Elizabeth Carnahan for her assistance in testing the rats.

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NOTE ADDED IN PROOF

Brooderson et al. (24) recently found that the D_1 agonists SKF 38393 and CY 208-243 inhibit dopamine synthesis by a non-D_1 receptor-mediated process. They found that both (+) SKF 38393, which is an effective D_1 agonist, and (−) SKF 38393, its inactive isomer, are effective in reducing dopamine synthesis. The racemic mixture was used in the current study. Suppression of dopamine synthesis by SKF 38393 may be the mechanism by which this drug has similar effects as the D_1 antagonist SCH 23390 in reversing the scopolamine-induced choice accuracy deficit in the radial-arm maze.