Pergamon

Pharmacology Biochemistry and Behavior, Vol. 52, No. 4, pp. 837-840, 1995

0091-3057/95 $9.50 + .00

0091-3057(95)00165-4

BRIEF COMMUNICATION

Pergolide Interactions With Nicotine and Pilocarpine in Rats on the Radial-Arm Maze

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Received 6 October 1994

LEVIN, E. D. *Pergolide interactions with nicotine and pilocarpine in rats on the radial-arm maze.* PHARMACOL BIOCHEM BEHAV **52**(4) 837-840, 1995.—Antagonists of nicotinic and muscarinic acetylcholinergic (ACh) receptors have significant interactions with dopaminergic (DA) ligands with regard to radial-arm maze choice accuracy. The current studies examined the interactions of agonists of nicotinic and muscarinic ACh receptors with the DA agonist pergolide. Pergolide given in a range from 0.03-1.0 mg/kg had no detectable effect on radial-arm maze choice accuracy when given alone. With this dose range there was a linear increase in response latency. Pergolide had significant interactive effects with the nicotinic and muscarinic agonists nicotine and pilocarpine. Given together with nicotine, pergolide produced a significantly elevated linear increase in accuracy relative to when it was given alone. With pilocarpine, pergolide had an inverted U-shaped effect improving choice accuracy at low to moderate doses of 0.03 and 0.1 mg/kg. These results support previous findings of DA-ACh interactions with regard to radial-arm maze choice accuracy. Combined DA-ACh treatment may be a useful treatment of cognitive dysfunction.

Acetylcholine Dopamine Nicotinic Muscarinic Radial-arm maze Nicotine Pilocarpine Pergolide

DOPAMINE (DA) and acetylcholine (ACh) systems seem to have important interactions with regard to cognitive function. A variety of studies from our laboratory and others have found that DA ligands have significant interactions with ACh agonist and antagonist effects on memory performance (16). The current studies were conducted to further investigate DA-ACh relationships important for cognitive function.

Baratti and co-workers (1) found that the passive avoidance memory facilitation caused by posttrial injections of the muscarinic ACh agonist oxotremorine was blocked by the DA antagonist haloperidol. Following up this work, Gasbarri et al. (5) found that specifically the D_2 antagonist sulpiride but not the D_1 antagonist SCH 23390 blocked oxotremorine-induced improvement in passive avoidance memory. Recently, it has been found that increasing DA activation indirectly by administration of the MAO-B inhibitor L-deprenyl can attenuate the scopolamine-induced impairment in the Morris water maze (23).

We have conducted a series of studies to investigate the impact on radial-arm maze working memory performance of DA interactions with nicotinic and muscarinic ACh systems. Nicotinic-DA interactions seem to be primarily mediated via D_2 receptors. The nicotinic antagonist mecamylamine causes a radial-arm maze choice accuracy deficit that is potentiated by the DA antagonist haloperidol (19). More specifically, the D_2 antagonist raclopride, but not the D_1 antagonist SCH 23390, has been found to potentiate the mecamylamine-induced deficit (20). Consistent with the involvement of D_2 receptors, the mecamylamine-induced choice accuracy deficit was found to be reversed by the D_2/D_3 agonist quinpirole but not the D_1 agonist SKF 38393 (13).

Muscarinic-DA interactions, on the other hand, seem to be primarily mediated via D_1 receptors. The radial-arm maze choice accuracy deficit caused by the muscarinic antagonist scopolamine is attenuated by the DA antagonist haloperidol (18). More specifically, the D_1 antagonist SCH 23390, but not the D_2 antagonist raclopride, has been found to reverse the scopolamine-induced deficit (9). Interestingly, the scopolamine-induced deficit is also reversed by the partial D_1 agonist SKF 38393 (14). The D_2/D_3 agonist quinpirole had no significant interactive effect with scopolamine.

There are interactions of DA ligands with ACh agonists as well. Nicotine has been found in our laboratory and others to improve choice accuracy performance [for a review see (10)].

A recent study indicated that the D_2/D_3 agonist quinpirole potentiates this improvement (12). The current studies were conducted to examine the interactions of nicotinic and muscarinic agonists with the general DA agonist pergolide, which has agonist actions at D_1, D_2, and D_3 receptors (4). The generality of pergolide effect may aid in its effectiveness in conjunction with both nicotinic and muscarinic agonists.

METHODS

Subjects

Young adult female Sprague–Dawley strain rats (Zivic-Miller, Allison Park, PA) were used in the present experiments. There were 11 rats in Study 1 and 12 rats in Study 2. They were housed in groups of two to four in plastic cages with pine shavings. They had ad lib access to water and were fed daily after testing such that their weights were kept at 80–85% of free-feeding levels.

Radial-Arm Maze Training

Behavioral testing was conducted on a radial eight-arm maze constructed of wood and painted black. The central arena was 50 cm in diameter, and eight 10 × 60 cm arms extended radially; food cups were located 2 cm from the distal end of each arm. The maze was positioned 30 cm above the floor in a testing room containing many extra-maze visual cues.

We used an overlearned radial-arm maze task so that choice accuracy could be more clearly measured against a stable baseline with minimal changes due to additional learning. The rats were tested one session/day for 3–5 days/week. Before the session, each arm of the maze was baited with a third to a half piece of sugar-coated cereal (Kellogg's Froot Loops®, Battle Creek, MI). At the beginning of the session, the rat was placed in a circular plastic ring in the central platform; after 10 s, the ring was lifted and the rat was allowed to walk freely through the maze. Arm choices were recorded when the rat had placed all of its paws beyond the threshold at the proximal end of the arm. Because the reinforcements were not replaced during the session, only the first entry in each arm was rewarded. Subsequent reentries were scored as errors. The session continued until the rat had entered all eight arms or 5 min had elapsed. The choice accuracy measure was the number of entries until an error was made (entries to repeat). The response duration measure was the total session duration divided by the number of arms entered (seconds per entry).

Drug Administration

After the 24 sessions of acquisition, the rats were given drug challenges. In both experiments the rats were administered doses of 0, 0.03, 0.1, 0.3, and 1.0 mg/kg of pergolide mesylate (Lilly, Indianapolis, IN) either alone or together with an ACh agonist. In Study 1, a dose of 0.2 mg/kg of the nicotinic ACh agonist nicotine ditartrate (Sigma, St. Louis, MO) was given. In Study 2, a dose of 1 mg/kg of the muscarinic ACh agonist pilocarpine hydrochloride (Sigma) was given. The drug doses are a function of the weight of the salt. They were dissolved in 0.9% sterile saline, which was administered by itself for control injections. Injections were given subcutaneously in a volume of 1 ml/kg, 20 min before testing. The experiments used a repeated measures counterbalanced design. The pergolide doses were selected according to previous work by Fuller and Clemens (4). Doses of nicotine and pilocarpine were selected on the basis of our previous study showing these doses to improve choice accuracy in this radial-arm maze task (15).

Data Analysis

The choice accuracy and response latency data were assessed by analyses of variance for repeated measures. As planned comparisons, the dose-effect functions of pergolide with and without nicotine or pilocarpine were characterized by analyses of linear and quadratic trends (8). The Huynh–Feldt (6) correction for nonsphericity was used for these analyses of repeated measures.

RESULTS

When given alone, the DA agonist pergolide had no significant effect on choice accuracy in the radial-arm maze. The data from the pergolide doses from the two studies are shown in Table 1. There was a significant dose-related linear increase in response latency [$F(1, 88) = 11.80, p = 0.005$]. Compared with saline, there was a 52% increase in response latency with the highest dose of pergolide (1.0 mg/kg). In contrast to the lack of effect of pergolide on choice accuracy, there were significant interactions between pergolide and both the muscarinic ACh agonist pilocarpine and the nicotinic ACh agonist nicotine.

Study 1

The interaction of pergolide and nicotine with regard to choice accuracy in the radial-arm maze is shown in Fig. 1. There were no significant main effects of nicotine or pergolide. However, there was a significant interaction of nicotine × linear trend of pergolide dose [$F(1, 10) = 4.94, p = 0.05$]. The interaction of nicotine × quadratic trend was not a significant. Pergolide, when given with nicotine, caused a dose-related improvement in choice accuracy. In contrast, pergolide without nicotine caused a dose-related decline in performance. There were no significant effects seen with response latency in this experiment.

Study 2

The interactive effects of pergolide and pilocarpine on choice accuracy are shown in Fig. 2. There were no significant main effects of either pergolide or pilocarpine, but they did interact significantly. There was a significant interaction of nicotine × the quadratic trend for pergolide dose [$F(1, 11) = 7.53, p = 0.02$]. The interaction of nicotine × linear trend for pergolide dose was not significant. When given together with 1 mg/kg pilocarpine, pergolide showed a significant quadratic trend [$F(1, 44) = 7.17, p = 0.02$], consisting of an inverted U-shaped function. Pergolide alone showed no significant linear or quadratic trends.

In terms of response latency, there was a highly significant linear trend [$F(1, 44) = 64.58, p = 0.0001$] of pergolide, progressively slowing in response with increasing dose. This was seen both with and without the addition of pilocarpine. There was a significant interaction of pilocarpine × pergolide with the quadratic trend [$F(1, 11) = 5.56, p = 0.04$]. Separate analyses of the quadratic trend with and without pilocarpine showed that there was no significant quadratic trend of pergolide without pergolide, but there was a significant quadratic trend with pilocarpine [$F(1, 44) = 5.98, p = 0.02$], reflecting a positively accelerating slope with increasing doses of pergolide given with pilocarpine.

TABLE 1
EFFECT OF PERGOLIDE ON RADIAL-ARM MAZE

	Pergolide (mg/kg)				
	0	0.03	0.1	0.3	1.0
Entries to repeat	6.91 ± 0.31	6.26 ± 0.38	6.52 ± 0.32	6.44 ± 0.36	6.35 ± 0.31
Seconds per entry	22.1 ± 4.1	25.5 ± 2.9	31.0 ± 5.9	32.6 ± 3.3	33.7 ± 3.1

DISCUSSION

The general DA agonist pergolide had no discernible effect on radial-arm maze choice accuracy when given alone. However, it had significant interactions with both pilocarpine and nicotine. These interactions support the importance of DA agonist interactions that we have seen previously with ACh antagonists [for review see (16)]. Previous results showed that both nicotinic and muscarinic blockade-induced radial-arm maze choice accuracy deficits could be attenuated by DA agonists. Specifically, the deficit caused by the nicotinic antagonist mecamylamine was attenuated by quinpirole, a D_2/D_3 DA agonist (13) and the deficit caused by the muscarinic antagonist scopolamine could be attenuated by SKF 38393, D_1 DA agonist (14). Because pergolide has agonist effects at D_1, D_2, and D_3 receptors (4), it is not surprising that it potentiates the choice accuracy improvements caused by both nicotinic and muscarinic agonists. Also supporting these DA-ACh interactions is our recent finding with the same radial-arm maze task of an additive effect of nicotine and the D_2/D_3 agonist quinpirole in improving choice accuracy (12).

In the current studies, the doses of nicotine (0.2 mg/kg) and pilocarpine (1 mg/kg) did not affect choice accuracy when given alone. In previous studies, we did find these doses of nicotine (15,17) and pilocarpine (15) to improve choice accuracy in the same task. However, in those experiments the rats were not performing at as high levels of accuracy as the rats in the current study. In a recent study of the effects of ICV nicotine administration (2), we tested rats performing at high and low levels of choice accuracy and found that nicotine significantly improved performance in rats with low levels of choice accuracy, but not with rats with high levels of choice accuracy. Also important may be possible carryover effects of intercurrent injections of pergolide on nicotine actions.

Neuropharmacologic studies have provided evidence for close DA-ACh interactions in areas of the brain important for memory function. DA and ACh systems have reciprocal interactions in both the cortex and hippocampus. Either D_1 or D_2 agonists have been found significantly to increase ACh release in the hippocampus (7). D_1 but not D_2 agonists were found to increase ACh release in the cortex (3). ACh manipulation also affects DA systems. Memo and co-workers found that administration of the muscarinic ACh antagonist scopolamine significantly decreased DA metabolism in both the hippocampus and frontal cortex, but not the striatum. The decreases in DA metabolism paralleled scopolamine-induced memory deficits in passive avoidance both in terms of dose and duration.

Further studies should assess the precise relationship between regional differences in DA-ACh relationships and functional consequences on memory performance. Local infusion studies may help determine the anatomic systems critically involved; they would also be useful in determining the importance of drug effects on other processes such as liver metabolism and cerebral blood flow, which may have indirect effects on memory performance.

The results from the current studies provide not only additional evidence concerning the interactions of DA and ACh systems involved with cognitive function, but also suggestions concerning possible combination DA-ACh therapies to counteract cognitive dysfunction. Further investigation is clearly needed. Neither the pergolide-nicotine nor the pergolide-

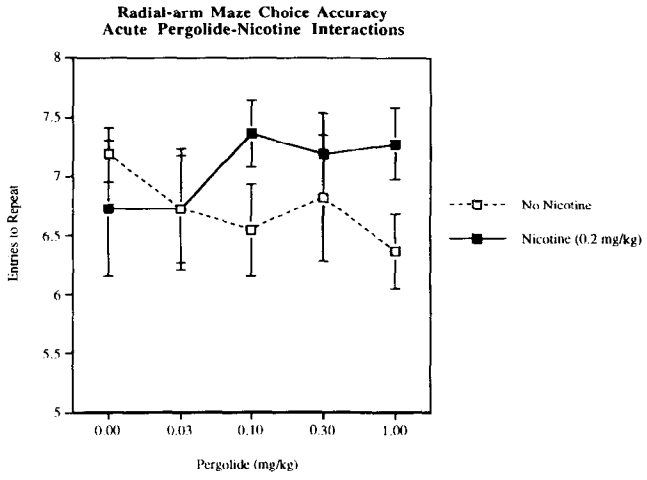

FIG. 1. Interactive effects of nicotine and pergolide on choice accuracy in the radial-arm maze.

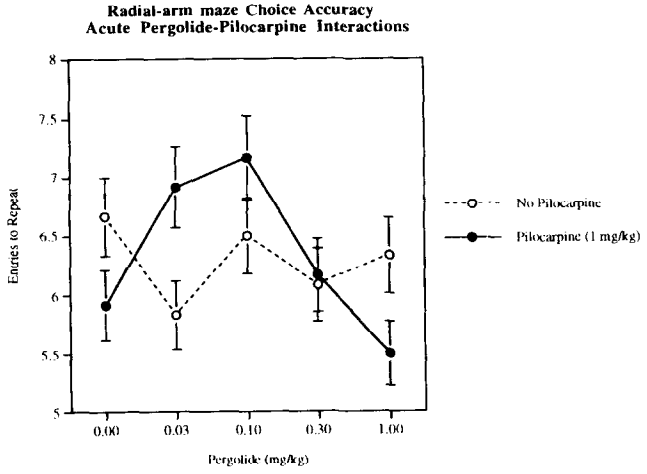

FIG. 2. Interactive effects of pilocarpine and pergolide on choice accuracy in the radial-arm maze.

pilocarpine-induced improvements in choice accuracy were very dramatic. However, they do indicate that such mutually enhancing effects are possible. To determine the maximal possible improvement, future studies should further examine the dose-response of the interactions of these drugs as well as the interactions of other DA and ACh agonists. It is important also to determine the interactions of chronic DA-ACh agonist treatment given that chronic treatment would be necessary for treatment of human cognitive disorders such as Alzheimers disease.

These interactions should also be evaluated in animal models of memory dysfunction. There is a good chance that combined therapy would be effective, because we have found that both DA and ACh agonists individually are effective in attenuating the choice accuracy impairments seen after lesions of the medial basalocortical projection (11,21,22). Further investigation should determine whether combined DA-ACh agonist treatment will improve memory performance in experimental animals and humans with cognitive dysfunction.

ACKNOWLEDGEMENTS

These studies were supported by a grant from the Council for Tobacco Research-USA. The author thanks Sandra Briggs and Channelle Christopher for their help with testing the rats.

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