Pharmacology Biochemistry and Behavior, Vol. 58, No. 4, pp. 899–902, 1997

0091-3057/97 $17.00 + .00

ELSEVIER

PII S0091-3057(97)00052-X

Chronic Haloperidol Administration Does Not Block Acute Nicotine-Induced Improvements in Radial-Arm Maze Performance in the Rat

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Received 21 August 1996; Revised 7 January 1997; Accepted 4 February 1997

LEVIN, E. D. *Chronic haloperidol administration does not block acute nicotine-induced improvements in radial-arm maze performance in the rat.* PHARMACOL BIOCHEM BEHAV **58**(4) 899–902, 1997.—Nicotine has been found to improve cognitive performance in a variety of tasks including the radial maze. Nicotine has also been shown to promote the release of a variety of neurotransmitters including dopamine (DA). DA has been found to be important for nicotine's reinforcing effects. DA involvement with nicotine's cognitive effects is unclear. In the current study, the effects of acute nicotine injections (0, 0.1, 0.2, or 0.4 mg/kg) were examined on radial-arm maze performance in rats given chronic infusions the DA antagonist haloperidol (0, 0.2, or 0.6 mg/kg/day). Chronic haloperidol infusion was not found to attenuate the memory improvement caused by acute nicotine injection. In fact, the dose-related nicotine-induced memory improvement was clearer in the haloperidol-treated groups than in controls. This is similar to the effect of nicotine we saw in human subjects given chronic doses of haloperidol. Our previous studies demonstrated significant nicotinic–DA interactions with regard to memory function. The current results suggest that in the DA–nicotinic relationship DA stimulation is not necessary for the memory improvement caused by nicotine. © 1997 Elsevier Science Inc.

Haloperidol Nicotine Memory Radial-arm maze

NICOTINE has complex variety of neural and behavioral effects. Currently, it is not clear which of its neural effects are necessary for which of its effects on behavioral function. Nicotine and nicotinic agonists have been shown in a variety of studies to improve memory function (8,14). The neural basis for this effect is currently not known.

One likely mechanism for nicotine effects on cognition is its action as an indirect dopaminergic (DA) agonist. Nicotine, via presynaptic actions, potentiates the release of a variety of transmitters including DA (32). Nicotine also stimulates the activity of DA cells in the midbrain (3,11). Acute nicotine-induced DA release appears to be important for nicotine's reinforcing effects (4–6), its locomotor stimulant effects (2,25, 26), nicotine-induced increased vacuous chewing (30) and nicotine-induced hypothermia (33). In contrast, the antinociceptive effect of nicotine does not seem to require DA activation (7). It is not known if DA activation is necessary for the cognitive facilitation caused by acute nicotine.

Memory improvement is a well-documented effect of nicotine. It is clear that there are important nicotinic–DA interactions with regard to memory function. It is not clear how much this effect has in mediating nicotine effects on cognitive function. Nicotine has been found in a variety of studies to improve cognitive function in rats, monkeys, and humans (8,14). Nicotine-induced facilitation of shock avoidance learning seems to be dependent on stimulation of DA receptors (1). Nicotine-induced DA activation also seems to be important for its effects in blocking latent inhibition (9,12). However, there is recent evidence from Gray's laboratory (10) that nicotine is effective in improving memory performance in a water maze task even after 6-hydroxydopamine lesions of the nucleus accumbens, showing that at least this DA system is not necessary for nicotine effects on memory.

In a series of studies, we have found that nicotine given acutely or chronically can improve working memory performance on the radial-arm maze (RAM) (14,21). In contrast, the nicotinic antagonist mecamylamine can impair working memory performance in the RAM (16). Acute nicotine can reverse the memory impairment caused by the partial D_1 agonist SKF 38393 (18) and add to the memory improvement caused by the D_2/D_3 agonist quinpirole (18). Nicotine can act together with the nonspecific DA agonist pergolide to im-

prove RAM memory performance (15). In contrast, the amnestic effect of the nicotinic antagonist mecamylamine is reversed by quinpirole (20) and is potentiated by the selective D_2 antagonist raclopride (23) or the nonselective DA antagonist haloperidol (22). Thus, there are important interactions of nicotinic and DA systems with regard to memory. The necessity of dopaminergic stimulation for the expression of nicotine effects on memory performance are just now being determined. Chronic D_2 blockade with raclopride infusion was not seen to attenuate the chronic nicotine-induced memory improvement (17). But is not clear whether DA stimulation is necessary for acute nicotine effects.

DA receptor blockers are classically given to schizophrenics to control their psychoses. One of the most widely used antipsychotics, haloperidol, potently blocks D_2 receptors and has some effects in blocking the D_1 receptor as well (31). It is effective at controlling the positive symptoms of schizophrenia (29), but causes a motor slowing (bradykinesia) (29) and cognitive slowing (bradyphrenia) (13). In a recent study with schizophrenics we found that haloperidol significantly impairs nonverbal working memory and mental rotation processing speed (13). Interestingly, nicotine-administered skin patches significantly improve working memory performance and processing speed in patients with moderate or high doses of the antipsychotic drug haloperidol.

The current study was conducted to further investigate the relationship of nicotinic and DA systems with regard to memory function. This study was designed to determine whether DA mechanisms are essential for acute nicotine effects in improving working memory performance.

METHOD

Subjects

Female Sprague–Dawley rats (Zivic-Miller, Allison Park, PA) were used in the current study. They were housed in groups of two to three. The rats were given ad lib access to water; however, their weights were maintained at 80–85% of their free-feeding levels. They were fed daily after testing. All rats were on reverse 12-h light/12-h dark cycle, and testing occurred during the dark phase.

Radial-arm Maze

The maze was made of wood painted black and consisted of a center platform 35 cm in diameter, and eight extending arms (10 × 80 cm). The maze was elevated 30 cm from the floor and was located in a room with many extramaze visual cues. Food cups, located at the ends of each of the arms, were baited with half of a Kellogg's Froot Loops. All arms were baited prior to testing and no arm was rebaited after testing began. The maze was wiped off with a towel between rats. Prior to testing the rat was placed in an opaque cylinder, approximately 30 cm in diameter, that was placed in the central area of the maze for 10 s. Timing began after the cylinder was lifted and the rat was free to explore. Arm choices were recorded after all four rat paws crossed completely into the arm. The rat had a maximum of 300 s to find all the reinforcers. If the rat reentered an arm, it was counted as an error. This procedure tested working memory, that is, memory for cues encountered during a specific trial of a task (28). The measure of choice accuracy was entries to repeat, the number of correct entries made before an error was made. The measure of response latency was seconds per entry, the total length of the session, divided by the number of entries made.

Chronic Haloperidol Treatment

After 18 sessions of acquisition training on the radial-arm maze the rats were anesthetized with ether and subcutaneously implanted with osmotic minipumps (Alzet Model 2ML4). They were removed 4 weeks later while the rats were under the same anesthetic. Pumps were filled with haloperidol HCl dissolved in saline in a concentration to deliver approximately 0, 0.2, or 0.6 mg/kg/day calculated as the weight of the salt. Controls were implanted with identical pumps filled with the vehicle. There were 24 rats in the study with 8 in each of the three groups.

Acute Nicotine Treatment

Each of the rats was administered nicotine ditartrate (SC) 20 min before testing in a volume of 1 ml/kg. Doses of 0, 0.1, 0.2, and 0.4 mg/kg (doses given as a function of the salt weight) were given in a counterbalanced order over weeks 3 and 4 of haloperidol infusion and weeks 1 and 2 after withdrawal. Each dose was given two times, once during haloperidol administration and once after withdrawal. Drug injections were given twice per week with at least 3 days between injections. Between injections the rats were tested once without injections.

Data Analysis

The response accuracy (entries to repeat) and response latency (seconds per entry) data were assessed by analysis of variance for repeated measures. The cutoff for significance was $p < 0.05$, two-tailed. The between-subjects factor was chronic haloperidol dose level (0, 0.2, and 0.6 mg/kg/day). Within-subjects factors were test period (during and after haloperidol administration) and acute nicotine dose (0, 0.1, 0.2, and 0.4 mg/kg).

RESULTS

Neither the low (0.2 mg/kg/day) nor the high (0.6 mg/kg/day) haloperidol doses were found to significantly impair choice accuracy in the radial-arm maze. During the chronic haloperidol infusion phase of the study, the control rats averaged 6.86 ± 0.63 entries to repeat, rats given 0.2 mg/kg/day of haloperidol averaged 6.12 ± 0..58 entries to repeat, and rats given 0.6 mg/kg/day of haloperidol averaged 5.75 ± 0.75 entries to repeat when saline injections were given. Acute nicotine injections caused a significant linear dose-related improvement, $F(1, 60) = 4.83$, $p < 0.05$, during the period of chronic haloperidol administration. There was no evidence for chronic haloperidol administration diminishing the effects of acute nicotine. In fact, the nicotine-induced memory improvement was more evident in the groups administered haloperidol than in controls (Fig. 1). No significant nicotine or haloperidol effects on response latency were seen during the haloperidol administration phase.

After the minipumps were removed, acute nicotine dose–effect functions were once again assessed. As in the earlier phase of the study, there was a significant linear nicotine dose-related improvement in choice accuracy, $F(1, 60) = 4.00$, $p < 0.05$. There was no significant effect of previous haloperidol treatment either as a main effect or as an interaction with nicotine treatment (Fig. 2). As in the earlier phase, no significant nicotine or haloperidol effects on response latency were seen during the haloperidol withdrawal phase.

In the overall analysis of data during and after haloperidol administration there was a highly significant linear nicotine

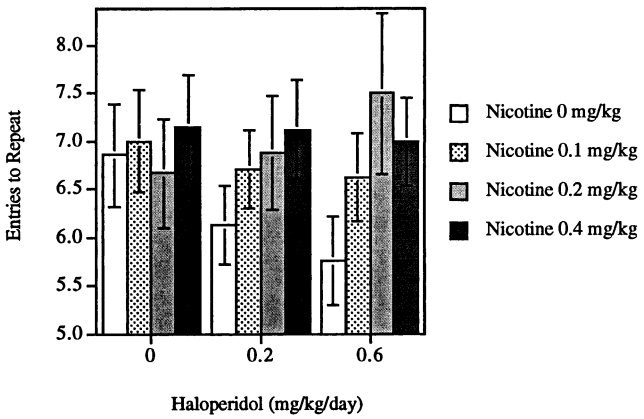

FIG. 1. Acute nicotine effects on radial-arm maze choice accuracy during chronic haloperidol infusion (mean ± SEM).

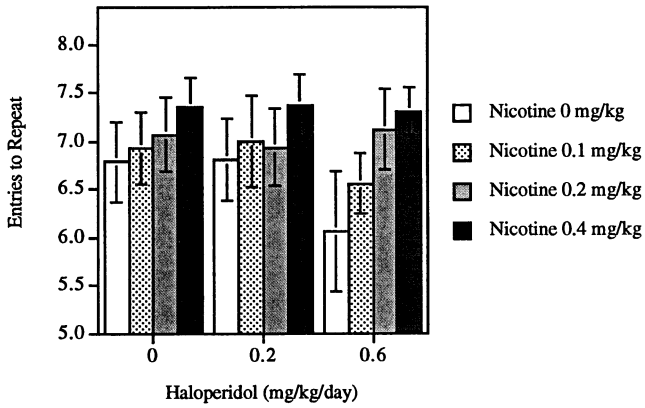

FIG. 3. Acute nicotine effects on radial-arm maze choice accuracy during and after chronic haloperidol infusion (mean ± SEM).

dose-related choice accuracy improvement, $F(1, 60) = 9.24$, $p < 0.005$. The overall analysis did not detect any differential effect of nicotine during and after haloperidol administration. Figure 3 shows the acute nicotine effects on choice accuracy performance for the haloperidol treatments averaged for the periods during and after haloperidol administration. The main effect of haloperidol or test period (during or after haloperidol) was not significant.

DISCUSSION

Acute nicotine caused a significant linear dose-related improvement in working memory performance in the radial-arm maze. This effect was not diminished in rats administered chronic doses of the DA receptor blocker haloperidol. The full effect of acute nicotine improving choice accuracy in the radial-arm maze was seen in the rats chronically administered haloperidol. These results support the hypothesis that the degree of DA activation is not necessarily related to the degree of nicotine-induced improvement in working memory function.

It is possible that the effects of nicotine on memory performance may be blocked by higher doses of haloperidol. Given the sedative effects of haloperidol, certainly a high enough dose would nonspecifically block nicotine effects on memory performance by blocking response. The haloperidol doses used in the current study were selected to be at or below the threshold for motor effects to avoid the potential nonspecific effects of sedation. The dose range in the current study has been found by our laboratory and others to have defined neurobehavioral effects. Ohno et al. (27) found a chronic infusion dose of 0.3 mg/kg/day of haloperidol to cause hypoactivity during a 30-min session in an activity monitor. They also found that the ED_50 for blocking methamphetamine (2 mg/kg)-induced hyperactivity was a SC dose of 0.187 mg/kg of haloperidol. Four days after withdrawal from 2 weeks of haloperidol infusion at 0.3 mg/kg/day dose there was a significantly enhanced stereotypy caused by apomorphine (0.1 mg/kg). McMillen (24) found using the same dose of haloperidol (0.3 mg/kg/day) for 2 weeks caused a significant elevation in striatal DOPAC concentrations to approximately 50% above control levels. This dose of chronic haloperidol also significant blunted the rise in DOPAC caused by an acute injection of haloperidol (0.1 mg/kg). We have previously found this dose range of chronic haloperidol to cause a transient RAM choice accuracy deficit (19). Although in the current study the haloperidol effect was not significant, the haloperidol dosed groups did have lower mean choice accuracy scores than controls when the rats were given saline injections. The statistical power of the current study may have too low to demonstrate a significant effect.

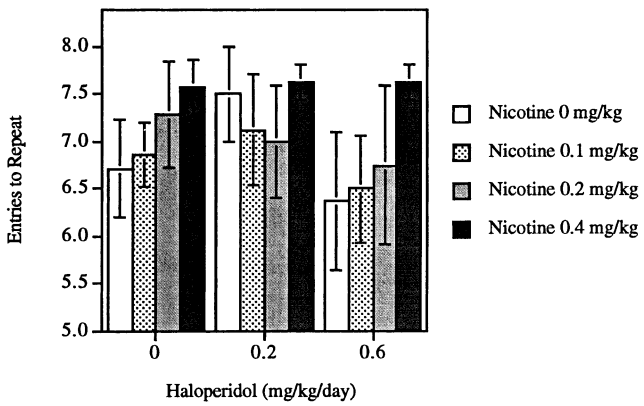

FIG. 2. Acute nicotine effects on radial-arm maze choice accuracy after with chronic haloperidol infusion (mean ± SEM).

There are clearly important nicotinic-DA relationships with regard to working memory performance. Nicotine attenuates D_1 agonist-induced memory deficits and adds to D_2 agonist memory improvements (18). The nicotinic antagonist mecamylamine causes memory impairments that are reversed by D_2 agonist treatment (20) and are potentiated by D_2 (23) or general DA antagonist treatment (22). The current results do not discount the important nicotinic–DA relationships. They do, however, suggest that DA activation is not required for nicotine-induced memory improvement.

The current results are quite similar to our recent results in schizophrenics (13). In that study, as in this one, nicotine-induced memory improvements were clearly seen despite the presence of chronic haloperidol administration. The greater nicotine effect in subjects given haloperidol was even clearer in the human study. This may have been due to the fact that generally higher doses of haloperidol were given, enough to cause mild Parkinsonian effects.

In summary, these results demonstrate that nicotine-induced improvements are clearly seen even with concurrent administration of haloperidol a DA blocker. Although certain nico-

tine effects such as reinforcement seem to require DA activation, the memory-enhancing effects of nicotine do not appear to be diminished by DA receptor blockade.

ACKNOWLEDGEMENTS

This research was supported by a grant from the Council for Tobacco Research-USA.

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