Potentiation of L-Dopa-Induced Behavioral Excitement by Histamine H₁-Receptor Antagonists in Mice

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ABSTRACT—Effects of histamine H₁-receptor antagonists on L-dopa-induced behavioral excitement were examined in mice to confirm behaviorally the inhibition of dopamine uptake by these compounds. L-Dopa (100–300 mg/kg, s.c.) combined with pargyline hydrochloride (80 mg/kg, i.p.) caused a dose-dependent behavioral excitement. The marked excitement induced by L-dopa (300 mg/kg) plus pargyline was significantly inhibited by pimozide (0.1–1 mg/kg, s.c.), a selective dopamine antagonist. Tripelennamine (10 mg/kg, s.c.), d-chlorpheniramine (1 and 2 mg/kg, s.c.), homochlorcyclizine (2 and 5 mg/kg, s.c.), diphenhydramine (2 and 5 mg/kg, s.c.) and mepyramine (2 and 5 mg/kg, s.c.) each markedly enhanced the moderate behavioral excitement induced by L-dopa (150 mg/kg) plus pargyline. These findings are behavioral evidence for inhibition of dopamine uptake by H₁ antagonists, which has been suggested by neurochemical studies.

Keywords: Histamine H₁-receptor antagonist, Dopamine uptake, L-Dopa

Histamine H₁-receptor antagonists have various actions in addition to H₁-blocking action. Most H₁ antagonists show antimuscarinic action, and some of these possess local anesthetic activity. In vitro experiments have shown that some H₁ antagonists inhibit the neuronal uptake of dopamine, 5-hydroxytryptamine and noradrenaline (1–3). We have examined the effects of H₁ antagonists on monoamine turnovers in the mouse brain to evaluate the in vivo effects on monoamine uptake, and our data suggested that most H₁ antagonists inhibit the dopamine uptake to various degrees (4, 5). In this study, we tried to obtain behavioral evidence for inhibition of dopamine uptake by H₁ antagonists. For this purpose, we examined the effects of some H₁ antagonists on the L-dopa-induced behavioral excitement in mice.

Male ddY mice weighing 28–35 g (Seiwa Experimental Animals, Fukuoka) were used. For at least one week before the experiments, they were housed in a room controlled at 22 ± 2°C and lighted between 6:00 a.m. and 6:00 p.m. Food and water were given ad libitum. All experiments were performed between 11:00 a.m. and 5:00 p.m.

All the animals were injected with pargyline hydrochloride (80 mg/kg, i.p.) 15 min before s.c. administration of L-dopa. To examine the effect of pimozide, it was injected simultaneously with L-dopa. To examine the effects of various H₁ antagonists, they were injected i.p. immediately after L-dopa (150 mg/kg). Each of the animals was observed in an individual wire mesh cage (20 × 15 × 15 cm), and the degree of behavioral excitement was scored as follows: 0, no behavioral excitement; 1, piloerection or tail up; 2, moderate aggressive hypermotility; 3, marked aggressive hypermotility during almost all the observation period (5 min); 4, stereotyped sniffing or biting. Data were analyzed by the Kruskal-Wallis test followed by the Mann-Whitney U-test.

Pargyline hydrochloride, tripelennamine hydrochloride and homochlorcyclizine dihydrochloride (Sigma Chemical Co., St. Louis, MO, USA); pimozide (Fujisawa Pharmaceutical Co., Osaka); d-chlorpheniramine maleate (Yoshitomi Pharmaceutical Co., Osaka); diphenhydramine hydrochloride (Tanabe Pharmaceutical Co., Osaka); and mepyramine maleate (ICN Pharmaceuticals, Plainview, NY, USA) were each dissolved in 0.9% saline. L-Dopa (Nacalai Tesque, Kyoto) was suspended in 0.5% carboxymethyl cellulose. All drugs were administered in a volume of 0.1 ml per 10 g body weight. The dose of salt-form drugs is expressed as weight of the salts.

In the preliminary experiments, L-dopa (100–300
mg/kg, s.c.) plus pargyline caused a dose-dependent behavioral excitement. At 300 mg/kg, most animals showed maximum scores 90 and 120 min after treatment. As shown in Fig. 1, pimozide, even at 0.1 mg/kg, i.p., significantly inhibited the behavioral excitement induced by L-dopa (300 mg/kg) plus pargyline. The inhibitory effect was more marked at 0.3 and 1.0 mg/kg.

In the mice treated with L-dopa (150 mg/kg) plus pargyline, the behavioral scores were about 1 from 15 to 90 min after treatment (Fig. 2). However, in mice treated with tripelemamine simultaneously, the scores were markedly higher and maximum in almost all animals 120 min after treatment.

Fig. 1. Effect of pimozide on behavioral excitement induced by pargyline plus L-dopa. Mice were injected with pargyline hydrochloride (80 mg/kg, i.p.) 15 min before treatment with L-dopa (300 mg/kg, s.c.) plus i.p. injection of saline (○) or pimozide (0.1 mg/kg, ●; 0.3 mg/kg, □; 1.0 mg/kg, ▲). Each value is the mean score ± S.E.M. of 7 animals. *P<0.05, **P<0.01, as compared with the corresponding saline-injected control.

Fig. 2. Effect of tripelemamine on behavioral excitement induced by pargyline plus L-dopa. Mice were injected with pargyline hydrochloride (80 mg/kg, i.p.) 15 min before treatment with L-dopa (150 mg/kg, s.c.). Saline (○), tripelemamine (10 mg/kg, ●) or tripelemamine plus pimozide (0.3 mg/kg, □) was injected i.p. simultaneously with L-dopa. Each value is the mean score ± S.E.M. of 7 animals. **P<0.01, as compared with the corresponding saline-injected control. ***P<0.01, as compared with the corresponding tripelemamine-injected group.
after treatment. This potentiation was completely inhibited by pimozide (0.3 mg/kg). Figure 3 shows the scores of behavioral excitement 90 min after L-dopa (150 mg/kg) plus pargyline with or without the H₁ antagonist. The scores were significantly increased by d-chlorpheniramine (1 and 2 mg/kg), diphenhydramine (2 and 5 mg/kg), homochlorcyclizine (5 mg/kg) and mepyramine (5 mg/kg). Each H₁ antagonist alone at any of the doses used had little influence on the behavior (data not shown).

In the present study, we examined the effects of an H₁ antagonist on L-dopa-induced behavioral excitement in mice to confirm behaviorally the inhibition of dopamine uptake by these compounds shown in neurochemical studies (2–5). L-Dopa (100–300 mg/kg) combined with pargyline caused a dose-dependent increase in behavioral excitement, in good agreement with the observation by Plotnikoff et al. (6). At 300 mg/kg, L-dopa caused a severe excitement including stereotypy. This excitement was dose-dependently inhibited by pimozide, a selective dopamine receptor antagonist. Therefore, the L-dopa-induced behavioral excitement observed in this study may be mainly mediated by activation of the dopaminergic system.

In in vitro studies, H₁ antagonists such as diphenhydramine and chlorpheniramine have been reported to inhibit the neuronal uptake of dopamine (7). In this study, L-dopa-induced behavioral excitement was markedly potentiated by tripelennamine and this potentiation was completely inhibited by pimozide, suggesting the involvement of the dopaminergic system. The L-dopa-induced excitement was also potentiated by d-chlorpheniramine, diphenhydramine, homochlorcyclizine, and mepyramine which has no antimuscarinic activity (8). This is consistent with our previous suggestion that these H₁ antagonists significantly inhibit dopamine uptake in vivo when evaluated as inhibition of dopamine turnover in the mouse brain (4, 5). The present findings together with the previous findings strongly suggest that various H₁ antagonists enhance the function of the dopaminergic system in the brain.

Suzuki et al. (9, 10) reported that the opioid conditioned place preference is potentiated by H₁ antagonists and abolished by dopamine D₁-receptor antagonists. This phenomenon may be due to the inhibition of dopamine uptake by H₁ antagonists. The enhancement of dopaminergic function by H₁ antagonists may contribute to an addiction to H₁ antagonists combined with opioids, such as “T’s and blues”, a combination of pentazocine and tripelennamine (11, 12). These effects may also partly contribute to their anti-parkinsonism activity. The interaction between H₁ antagonists and dopamine related compounds should also be given attention.
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REFERENCES


