Potential 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 pimoziide (0.1–1 mg/kg, s.c.), a selective dopamine antagonist. Tripeleennamine (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. admin-

istration of L-dopa. To examine the effect of pimoziide, 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, tripeleennamine hydrochloride and homochlorcyclizine dihydrochloride (Sigma Chemical Co., St. Louis, MO, USA); pimoziide (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

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Fig. 1. Effect of pimozone 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 pimozone (0.1 mg/kg, ●; 0.3 mg/kg, □; 1.0 mg/kg, ■). Each value is the mean score $\pm$ S.E.M. of 7 animals. * $P < 0.05$, ** $P < 0.01$, as compared with the corresponding saline-injected control.

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, pimozone, 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 tripeleppamine simultaneously, the scores were markedly higher and maximum in almost all animals 120 min

Fig. 2. Effect of tripeleppamine 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 (○), tripeleppamine (10 mg/kg, ●) or tripeleppamine plus pimozone (0.3 mg/kg, □) was injected i.p. simultaneously with L-dopa. Each value is the mean score $\pm$ 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 tripeleppamine-injected group.

Fig. 3. Effect of some histamine H_1 -receptor antagonists 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 histamine H_1 -receptor antagonists (i.p.) plus L-dopa (150 mg/kg, s.c.) and observed 90 min later. Each value is the mean score $\pm$ S.E.M. of 6 animals. * $P < 0.05$, ** $P < 0.01$, as compared with the corresponding saline-injected control.

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 H_1 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 H_1 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 H_1 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, H_1 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 tripeleennamine 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 H_1 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 H_1 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 H_1 antagonists and abolished by dopamine D_1 -receptor antagonists. This phenomenon may be due to the inhibition of dopamine uptake by H_1 antagonists. The enhancement of dopaminergic function by H_1 antagonists may contribute to an addiction to H_1 antagonists combined with opioids, such as "T's and blues", a combination of pentazocine and tripeleennamine (11, 12). These effects may also partly contribute to their anti-parkinsonism activity. The interaction between H_1 antagonists and dopamine related compounds should also be given attention.

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REFERENCES

- 1 Lidbrink P, Jonsson G and Fuxe K: The effect of imipramine like drugs and antihistamine drugs on uptake mechanisms in the central noradrenaline and 5-hydroxytryptamine neurons. *Neuropharmacology* **10**, 521–536 (1971)
- 2 Brown PA and Vernikos J: Antihistamine effect on synaptosomal uptake of serotonin, norepinephrine and dopamine. *Eur J Pharmacol* **65**, 89–92 (1980)
- 3 Tuomisto J and Tuomisto L: Effects of histamine and histamine antagonists on the uptake and release of catecholamines and 5-HT in brain synaptosomes. *Med Biol* **58**, 33–37 (1980)
- 4 Shishido S, Oishi R and Saeki K: In vivo effects of some histamine H_1 -receptor antagonists on monoamine metabolism in the mouse brain. *Naunyn Schmiedeberg's Arch Pharmacol* **343**, 185–189 (1991)
- 5 Oishi R, Shishido S, Yamori M and Saeki K: Comparison of the effects of eleven histamine H_1 -receptor antagonists on monoamine turnover in the mouse brain. *Naunyn Schmiedeberg's Arch Pharmacol* **349**, 140–144 (1994)
- 6 Plotnikoff N, Will F, Evans A and Meekma P: PS-2747: A new antidepressant agent. *Arch Int Pharmacodyn Ther* **195**, 330–342 (1972)
- 7 Coyle JT and Snyder SH: Antiparkinsonian drugs: inhibition of dopamine uptake in the corpus striatum as a possible mechanism of action. *Science* **166**, 899–901 (1969)
- 8 Kubo N, Shirakawa O, Kuno T and Tanaka C: Antimuscarinic effects of antihistamines: quantitative evaluation by receptor-binding assay. *Jpn J Pharmacol* **43**, 277–282 (1987)
- 9 Suzuki T, Masukawa Y and Misawa M: Drug interactions in the reinforcing effects of over-the-counter cough syrups. *Psychopharmacology (Berlin)* **102**, 438–442 (1990)
- 10 Suzuki T, Masukawa Y, Shiozaki Y and Misawa M: Potentiation of pentazocine conditioned place preference by tripeleminamine in rats. *Psychopharmacology (Berlin)* **105**, 9–12 (1991)
- 11 Showalter CV and Moore L: Abuse of pentazocine and tripeleminamine. *JAMA* **239**, 1610–1612 (1978)
- 12 Butch AJ, Yokel RA, Sigell LT, Hanenson IB and Nelson ED: Abuse and pulmonary complication of injecting pentazocine and tripeleminamine in tablets. *Clin Toxicol* **14**, 301–306 (1979)