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Inhibition of neuronal dopamine uptake by some antiallergic drugs

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Abstract

The effects of 10 antiallergic drugs (astemizole, azelastine, ebastine, emedastine, epinastine, ketotifen, oxatomide, terfenadine, pemirolast and tranilast) on neuronal dopamine uptake were examined. Some drugs examined showed a concentration-dependent inhibition of [^{3}H]dopamine uptake into synaptosomal preparations of the rat striatum. The inhibition constant (K_i) values were 231–876 nM for ebastine, terfenadine, oxatomide and astemizole. The specific binding of [^{3}H] (1-[2-(diphenylmethoxy)ethyl]-4-(3-phenylpropyl)piperazine) (GBR12935) to the rat striatal membranes was also inhibited by these antiallergic drugs. There was a good correlation between the degrees of inhibition of [^{3}H]dopamine uptake and [^{3}H]GBR12935 binding. Then, the behavioral excitement induced by L-DOPA (100 mg/kg, s.c.) plus pargyline hydrochloride (80 mg/kg, i.p.) in mice was significantly enhanced by i.p. treatment with ebastine (10 mg/kg) and astemizole (5 mg/kg). These results suggest that the neuronal dopamine uptake is inhibited by some antiallergic drugs, especially ebastine.

Keywords: Antiallergic drug; Dopamine uptake; [^{3}H]GBR12935 binding; Ebastine; Astemizole; Oxatomide; Terfenadine

1. Introduction

Antiallergic drugs such as ketotifen, oxatomide and terfenadine inhibit the degranulation of mast cells and block the receptors for various chemical mediators including histamine H_1 receptors. It has been shown in vitro that histamine H_1 receptor antagonists inhibit the neuronal uptake of monoamines (Coyle and Snyder, 1969; Lidbrink et al., 1971; Brown and Vernikos, 1980; Tuomisto and Tuomisto, 1980). We previously reported that most histamine H_1 receptor antagonists inhibit the dopamine turnover in the mouse brain, probably due to the inhibition of the neuronal uptake of dopamine (Oishi et al., 1994). These results suggest an involvement of some antiallergic drugs in dopamine uptake systems. However, there has been only a preliminary report on this matter (Fügner et al., 1988). In the present study, therefore, we examined the effects of 10 antiallergic drugs on the [^{3}H]dopamine uptake into brain synaptosomes and the binding of [^{3}H](1-[2-(diphenylmethoxy)ethyl]-4-(3-phenylpropyl)piperazine) (GBR12935), a selective ligand for the dopamine transporter to brain membranes. We also studied the behavioral profiles regarding the inhibition of dopamine uptake by the antiallergic drugs which showed positive effects in the first in vitro experiments. For this purpose, we examined the potentiating effects of these drugs on the L-DOPA-induced behavioral excitement of mice, which had been shown for some histamine H_1 receptor antagonists (Sato et al., 1996).

2. Materials and methods

2.1. Animals

Male Sprague–Dawley rats weighing 250–350 g (Kyushu University Laboratory Animal Center, Fukuoka, Japan) and male ddY mice weighing 25–35 g (Seiwa Experimental Animals, Fukuoka) were used for the in vitro and in vivo experiments, respectively. They were housed for at least a week before the experiments in a room controlled at 22 ± 2°C and lighted from 0600 to 1800 h. Food and water were given ad libitum.

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2.2. Chemicals

[^{3}H]Dopamine (22.2 Ci/mmol) and [^{3}H]GBR12935 (40 Ci/mmol) were purchased from Dupont-NEN (Boston, MA, USA). 1-[2-[bis(4-fluorophenyl)methoxy]ethyl]-4-(3-phenylpropyl)piperazine dihydrochloride (GBR12909), chlorpheniramine maleate, L-DOPA and pargyline hydrochloride were purchased from Sigma Chemical (St. Louis, MO, USA) and haloperidol was from Wako Pure Chemical Industries (Osaka, Japan). Astemizole (Mochida Pharmaceutical, Tokyo, Japan), azelastine (Eisai, Tokyo), ebastine (Dainippon Pharmaceutical, Osaka), epinastine (Nippon Boehringer Ingelheim, Kawanishi, Japan), emedastine (Kanebo, Tokyo), ketotifen (Novartis Pharma, Tokyo), oxatomide (Kyowa Hakko Kogyo, Tokyo), terfenadine (Shionogi, Osaka), pemirolast (Tanabe Pharmaceutical, Osaka) and tranilast (Kissei Pharmaceutical, Tokyo) were kindly donated by the respective pharmaceutical companies. All chemicals used were at least of guaranteed reagent grade.

For the experiments in vitro, each drug tested was first dissolved in dimethyl sulfoxide at 10 mM and diluted with the incubated medium. For the behavioral experiments, each antiallergic drug was suspended in 0.5% carboxymethyl cellulose sodium (CMC).

2.3. [^{3}H]dopamine uptake

Rats were killed by decapitation and the brain was removed immediately. The corpus striatum was dissected according to the method of Glowinski and Iversen (1966). The dopamine uptake was measured according to the method described by Richelson and Pfenning (1984). The tissue was homogenized with 25 ml ice-cold 0.3 M sucrose containing 11 mM glucose and centrifuged for 10 min at $1000 \times g$. The supernatant was centrifuged for 20 min at $10\,000 \times g$. After the supernatant was discarded, the crude synaptosomal pellet was resuspended in Krebs Ringer bicarbonate buffer, pH 7.4 at 37°C. After 800 μl of the synaptosomal suspension was preincubated in a tube for 5 min at 37°C, 100 μl of various concentrations of tested drugs and 100 μl of 100 nM [^{3}H]dopamine (final concentration: 10 nM) were added. The nonspecific uptake was defined as the uptake at 0°C. After 5-min incubation, the sample was filtered through Whatman GF/C glass-fiber filters under a vacuum to stop the uptake. The filters were removed and placed in scintillation vials containing 10 ml of aqueous counting scintillant (ACS-II, Amersham, Arlington Heights, IL, USA). The radioactivity was measured by liquid scintillation spectrometry after the sample was left standing overnight. The effect of each concentration of the drugs was tested with three different samples. The data shown are the means of three separate experiments. The IC_{50} values were provided from the formula of sigmoid curve calculated using a software program (DeltaGraph PRO3, DeltaPoint, Monterey, CA, USA), and then the inhibition constant (K_i) values were calculated from the following equation: $K_i = IC_{50}/(1 + [S]/K_m)$. Here, $[S]$ is the concentration of [^{3}H]dopamine (10 nM) and K_m is the Michaelis–Menten constant for the uptake process, which was obtained from the Scatchard plot of the uptake of [^{3}H]dopamine in the concentrations ranging 0.04–2.3 pmol/mg protein performed in the separate experiment. The Hill coefficient values were determined from the Hill plot.

2.4. [^{3}H]GBR12935 binding

The [^{3}H]GBR12935 binding to the dopamine transporter was evaluated according to the method of Nakachi et al. (1995) with minor modifications. The rat corpus striatum was homogenized with 25 ml of ice-cold 50 mM Tris–citrate buffer (pH 7.4 at 4°C) containing 120 mM NaCl and 4 mM $MgCl_2$. The homogenate was centrifuged for 20 min at $45\,000 \times g$, and the pellet was stored at −80°C until the experiment. The pellet was resuspended and centrifuged under the same condition three times. To the final suspension (800 μl) was added 100 μl of 10 or 100 μM of the drugs tested (final concentration: 1 or 10 μM), and the binding reaction was started by the addition of 100 μl of 100 nM [^{3}H]GBR12935 (final concentration: 10 nM). After a 60-min incubation at 0°C, the sample was filtered through Whatman GF/C glass-fiber filters under a vacuum to stop the binding. The radioactivity of the filter was measured as described in the [^{3}H]dopamine uptake experiment. The nonspecific binding was defined as the binding in the presence of 30 μM GBR12909. Three separate experiments consisting of four different samples each were performed.

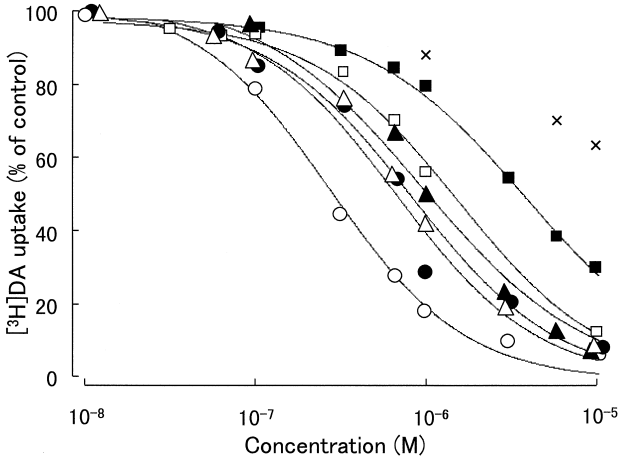

Fig. 1. Effects of antiallergic drugs on the [^{3}H]dopamine uptake into synaptosomal preparations of the rat striatum. After preincubation for 5 min, the synaptosomal suspension was incubated with various concentrations of drugs and 10 nM of [^{3}H]dopamine for 5 min at 37°C. The nonspecific uptake was defined as the uptake at 0°C. Each result represents the mean of three separate experiments with three different samples. ○ Ebastine, ● terfenadine, △ oxatomide, ▲ astemizole, □ chlorpheniramine, ■ azelastine, × epinastine.

Table 1
Inhibition constant (K_i) values and Hill coefficients for the blockade of [^{3}H]dopamine uptake into the rat striatal synaptosomes by antiallergic drugs

Antiallergic drugs	K_i (nM)	Hill coefficient
Astemizole	876	1.27
Azelastine	3289	0.87
Ebastine	231	1.10
Emedastine	> 10000	
Epinastine	> 10000	
Ketotifen	> 10000	
Oxatomide	676	1.00
Terfenadine	556	1.03
Pemirolast	> 10000	
Tranilast	> 10000	
Chlorpheniramine	1395	0.89

The K_i values were calculated from the following equation: $K_i = IC_{50}/(1+[S]/K_m) = IC_{50}/(1+10/91.14)$.

2.5. Behavioral excitement induced by L-DOPA plus pargyline in mice

As reported previously (Sato et al., 1996), mice were injected with pargyline hydrochloride (80 mg/kg, i.p.) 15 min before the administration of L-DOPA (100 mg/kg, s.c.). Four antiallergic drugs which showed K_i values less than 1 μM for [^{3}H]dopamine uptake were injected i.p. immediately after the L-DOPA administration. Each mouse was observed in an individual wire mesh cage (20 × 15 × 15 cm), and the degree of the behavioral excitement was scored 90 min after the L-DOPA administration as follows: 0, almost normal; 1, piloerection or tail up; 2, moderate aggressive hypermotility; 3, marked aggressive hypermotility during almost all of the observation period (5 min); 4, stereotyped sniffing or biting.

2.6. Statistical analysis

The significance of the behavioral data was evaluated by the Kruskal–Wallis test followed by the Mann–Whitney *U*-test for individual comparisons using a statistical analysis software program (StatView, Abacus Concepts, Berkeley, CA).

3. Results

3.1. Effects of antiallergic drugs on [^{3}H]dopamine uptake into the striatal synaptosomes

Fig. 1 shows the inhibition curves of the antiallergic drugs in concentrations of 10–10 000 nM for [^{3}H]dopamine uptake (10 nM) into synaptosomal preparations of the rat striatum. The effect of chlorpheniramine, dopamine and nomifensine was also examined for comparison. Table 1 shows the K_i values and Hill coefficients calculated from the results indicated in Fig. 1. The K_i values of dopamine and nomifensine were 98 and 31 nM, respectively (data not shown). Ebastine most potently inhibited the [^{3}H]dopamine uptake among the 10 antiallergic drugs (K_i = 231 nM). This potency was about six times that of chlorpheniramine. Terfenadine, oxatomide and astemizole were less potent than ebastine; the K_i values were 556, 676 and 876 nM, respectively. Azelastine had about half the potency of chlorpheniramine (K_i = 3289 nM). Emedastine, epinastine, ketotifen, pemirolast and tranilast showed little influence on the [^{3}H]dopamine uptake even at 1 μM (Fig. 1).

3.2. Effects of antiallergic drugs on [^{3}H]GBR12935 binding to the rat striatal membranes

Table 2 shows the inhibitory effects of the 10 antiallergic drugs at 1 and 10 μM on the [^{3}H]GBR12935 binding and [^{3}H]dopamine uptake. At 10 μM, ebastine inhibited the [^{3}H]GBR12935 binding almost completely (98%). Terfenadine, astemizole and oxatomide showed 80–90% inhibition, and azelastine and epinastine showed about 50%

Table 2
Percentages of the specific [^{3}H]dopamine uptake and [^{3}H]GBR12935 binding in the rat striatal preparation in the presence of 1 and 10 μM of each antiallergic drug

Antiallergic drug	1 μM		10 μM	
	[^{3}H]dopamine	[^{3}H]GBR12935	[^{3}H]dopamine	[^{3}H]GBR12935
Ebastine	16.6 ± 4.0	31.7 ± 0.6	4.6 ± 1.9	1.8 ± 1.3
Astemizole	49.7 ± 1.5	58.6 ± 2.1	5.8 ± 1.3	10.8 ± 4.5
Terfenadine	27.9 ± 2.5	42.8 ± 1.5	6.8 ± 0.2	10.5 ± 2.8
Oxatomide	41.2 ± 8.3	60.9 ± 4.2	7.1 ± 3.7	18.1 ± 2.3
Azelastine	79.3 ± 4.2	80.5 ± 2.1	28.9 ± 2.4	46.7 ± 6.3
Epinastine	88.1 ± 3.0	76.8 ± 4.9	63.4 ± 4.1	50.8 ± 2.2
Ketotifen	94.0 ± 2.0	9.3 ± 2.7	87.8 ± 1.2	81.6 ± 5.7
Emedastine	94.8 ± 2.2	85.2 ± 4.0	87.9 ± 5.2	82.1 ± 1.4
Pemirolast	96.5 ± 2.2	89.5 ± 3.1	93.6 ± 2.3	99.7 ± 3.4
Tranilast	95.4 ± 3.5	92.9 ± 3.6	95.2 ± 2.3	93.0 ± 0.8

The [^{3}H]GBR12935 binding was measured by the incubation with 10 nM of this ligand for 60 min. The nonspecific binding was defined as the binding in the presence of 30 μM GBR12909. Each result represents the mean ± S.E.M. of three separate experiments with four different samples.

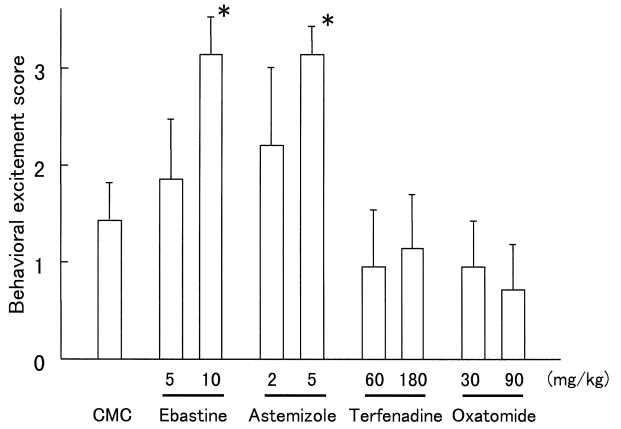

Fig. 2. Effects of some antiallergic drugs on behavioral excitement induced by pargyline plus L-DOPA. Mice were injected with pargyline hydrochloride (80 mg/kg, i.p.) 15 min before treatment with antiallergic drugs (i.p.) plus L-DOPA (100 mg/kg, s.c.) and observed 90 min later. Each value represents the mean score ± S.E.M. of 8–10 animals. $* P < 0.05$ as compared with the CMC-treated group.

inhibition of the [^{3}H]GBR12935 binding. Emedastine, ketotifen, pemirolast and tranilast had less influence on the [^{3}H]GBR12935 binding. There were high correlation between the inhibitory effects of [^{3}H]GBR12935 binding and [^{3}H]dopamine uptake in the presence of 1 and 10 μM of each antiallergic drug ($r = 0.978$ and $r = 0.971$, respectively).

3.3. Effects of astemizole, ebastine, oxatomide and terfenadine on the behavioral excitement induced by L-DOPA plus pargyline in mice

We examined the effects of four antiallergic drugs on L-DOPA-induced behavioral excitement in mice to confirm behaviorally their inhibitory action on the dopamine uptake. The effect of nomifensine was also examined for comparison. In mice treated with saline, nomifensine 2.5 mg/kg and 5.0 mg/kg, the behavioral scores were 1.2 ± 0.3, 2.2 ± 0.8 and 3.7 ± 0.3. In mice with nomifensine (5.0 mg/kg) simultaneously, the scores were significantly increased. In mice treated with 0.5% CMC simultaneously, the behavioral scores were 1.42 ± 0.40 (Fig. 2). However, in the mice treated with astemizole (5 mg/kg) and ebastine (10 mg/kg) simultaneously, the scores were significantly increased. Oxatomide and terfenadine showed no significant influence on the L-DOPA-induced behavioral excitement.

4. Discussion

The inhibitory effect of some histamine H_1 receptor antagonists on neuronal dopamine uptake has been reported in vitro (Coyle and Snyder, 1969; Tuomisto and Tuomisto, 1980). We previously obtained in vivo neurochemical evidence for the inhibition of dopamine uptake by histamine H_1 receptor antagonists including chlorpheniramine (Shishido et al., 1991; Oishi et al., 1994). Behavioral evidence of this action has also been obtained in some experiments, such as in schedule-controlled responding in monkeys (Bergman and Spealman, 1988), conditioned place preference in rats (Suzuki et al., 1990) and L-DOPA-induced behavioral excitement in mice (Sato et al., 1996).

In the present study, we examined the effects of antiallergic drugs which has been frequently used in clinic. The results obtained indicated that some antiallergic drugs have an inhibitory influence on the neuronal dopamine uptake, similar to some histamine H_1 receptor antagonists. Four antiallergic drugs (ebastine, terfenadine, oxatomide, astemizole) inhibited the [^{3}H]dopamine uptake with K_i values less than 1 μM. The potencies of these drugs were much higher than that of chlorpheniramine ($K_i = 1395$ nM). The inhibitory effects of antiallergic drugs on the dopamine uptake were confirmed by the binding study of [^{3}H]GBR12935, a specific ligand for dopamine transporter (Andersen, 1987). In this experiment, the antiallergic drugs inhibited the binding similar to the [^{3}H]dopamine uptake. Although the competition for [^{3}H]GBR12935 binding is not defining only the dopamine transporter (Akunne et al., 1994), these results support the notion that some antiallergic drugs have an affinity to dopamine transporters to various degrees. However, the relationship between these effects and their chemical structures of antiallergic drugs as well as histamine H_1 receptor antagonists (Oishi et al., 1994) is not clear.

The behavioral experiment was performed to examine the in vivo effects of the antiallergic drugs with a relatively potent inhibition of dopamine uptake. In our previous report (Sato et al., 1996), we confirmed that this behavioral excitement is inhibited by a specific dopamine receptor antagonist, pimozide. In addition, this behavior was significantly enhanced by nomifensine in the present experiment.

The L-DOPA-induced behavioral excitement was significantly enhanced by ebastine and astemizole, but not by terfenadine or oxatomide. The lack of effect of terfenadine may be due to its poor penetration to the brain (Leeson et al., 1982); whereas that of oxatomide may be due to its antagonistic effect on dopamine receptors. Leysen and Gommeren (1986) reported that oxatomide binds D_2-receptors with the potency of about the half that of chlorpromazine. However, Ohmori et al. (1983) did not observe an extrapyramidal syndrome such as catalepsy in mice or rats treated with oxatomide even at high doses. In the clinical evaluation of this medicine, the frequency of the extrapyramidal side effects is known to be low. These results, taken together, suggest that the blockade of dopamine receptors and the inhibition of dopamine uptake, both induced by oxatomide, functionally negate each other.

Astemizole is known as an antiallergic drug devoid of central effects (Awouters et al., 1983). However, Laduron et al. (1982) reported that the occupation rate of histamine H_1 receptors in the cerebellum of guinea pigs by astemizole is about 80% at 5 mg/kg, p.o., although the rate is about 10% at doses less than 1 mg/kg. The present results also suggest the central effect of astemizole at high doses. Ebastine showed the most potent inhibition of dopamine uptake among the drugs examined. The potency was about six times that of chlorpheniramine. These results suggest the interaction between antiallergic drugs, especially ebastine and dopamine-related medicines. For instance, the drug dependence on codeine is enhanced by a concomitant treatment with chlorpheniramine, probably due to the dopaminergic mechanism (Suzuki et al., 1990). Therefore, long-term treatment with ebastine may enhance the drug dependence on various opioids.

In conclusion, we clarified the inhibition of dopamine uptake by some antiallergic drugs. Attention should be paid to such interactions, especially when these medicines are used at high doses and for a long period.

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