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Comparative Studies of Sulpiride and Classical Neuroleptics on Induction of Catalepsy, Locomotor Activity, and Brain Dopamine Metabolism in Mice

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FUJIWARA, H. *Comparative studies of sulpiride and classical neuroleptics on induction of catalepsy, locomotor activity, and brain dopamine metabolism in mice.* PHARMACOL BIOCHEM BEHAV 41(2) 301-308, 1992.—The effects of the peripheral administration of sulpiride on the induction of catalepsy, the vertical (VMA) and horizontal (HMA) locomotor activities, and on the dopamine metabolism in the limbic system, striatum, and nucleus accumbens were examined using mice up to 7.5 h after administration of drugs. These effects were compared to those of pimozide and haloperidol. Sulpiride (1.25-160 mg/kg, IP) clearly induced catalepsy similar to pimozide (0.0625-4 mg/kg, IP) and haloperidol (0.0375-0.3 mg/kg, IP). During the induction of catalepsy, the intensity was the strongest at 4.5 h after administration and the ED_{50} value showed 11.5 mg/kg at that time. However, a moderate dose of sulpiride at 10-20 mg/kg did not show the induction of a dose- and time-dependent catalepsy. During the locomotor activity, the VMA was significantly inhibited at 1.5 h and 6 h after administration of pimozide (0.25 mg/kg, IP) and haloperidol (0.075 mg/kg, IP) as compared to the control group, while the HMA was significantly inhibited at 1.5 h after administration of sulpiride (40 mg/kg, IP) and pimozide (0.25 mg/kg, IP). Subsequently, in the dopamine metabolism, sulpiride, pimozide, and haloperidol: 1) considerably accelerated the turnover in the dopamine metabolism in three distinct brain areas; 2) increased the levels of the DOPAC, HVA, and 3-MT even 6 h after administration, as well as at 1.5 h after administration; and 3) decreased the levels of dopamine in the nucleus accumbens at 1.5 h after administration. These results indicate that sulpiride displays a mode of action different from pimozide and haloperidol with regard to the induction of catalepsy, but not with regard to the locomotion and brain dopamine metabolism.

Sulpiride Pimozide Haloperidol Catalepsy Locomotion Dopamine metabolism Mouse

ALTHOUGH the classical neuroleptics have been established as valuable agents for treatment of psychosis, a major drawback to the clinical use of these drugs has been the concurrent development of the extrapyramidal side effects such as parkinsonism and tardive dyskinesia (10,44). It is indeed difficult to confirm the antipsychotic activity of drugs in the experiment using animals; however, the activity of drugs generally can be predicted from their ability to induce cataleptic response and to block stereotyped behavior induced by the dopamine agonists (3). All classical neuroleptics possess the ability to produce these activities in animals, and this ability is clearly related to the antipsychotic activities in man (18). However, much interest has been focused on drugs with the antipsychotic activity and on drugs that do not produce the induction of the extrapyramidal side effects.

The substituted benzamide sulpiride has been shown to possess the property clearly differing from the classical neuroleptics (4,26,33,39), because it induces less extrapyramidal side effects while possessing the antipsychotic effect (10,12,28,41). These properties of sulpiride can be characterized by being partly due to the preferential action on the dopamine receptors in the mesolimbic dopamine system (11,24,27,34). Moreover, it is reported that when sulpiride is peripherally given, less induction of the extrapyramidal side effects, especially catalepsy, is caused by the poor penetration into the central nervous system of sulpiride (17,33,35,37,42).

Recently, Achiron et al. (1) reported that the long-term administration of sulpiride has induced symptoms such as parkinsonism and tardive dyskinesia in patients, and they advised caution in inducing the extrapyramidal side effects with the clinical use of sulpiride.

On the other hand, it is reported that in experiments with mice and rats sulpiride induces marked catalepsy when administered intracerebroventrically (17,33,43,44); however, two different reports were obtained when sulpiride was administered peripherally: one where sulpiride induces catalepsy (9,10,12, 13,25,28,32,41), and the other where catalepsy is difficult to induce (2,14,17,18,20,22,26,36,37,43,45) with regard to the induction of the extrapyramidal side effects.

The present study was conducted to clarify whether periph-

eral administration of sulpiride to mice induces catalepsy. Furthermore, the influence of the difference in the administration time of sulpiride on the induction of catalepsy, spontaneous locomotor activity, and brain dopamine metabolism was compared with those of the classical neuroleptics, pimozide and haloperidol.

METHOD

Animals

Male ddY mice, weighing 22–25 g, purchased from the Shizuoka Laboratory Animal Center (Hamamatsu, Japan), were used throughout the studies. They were housed in groups of 10–12 mice in standard breeding cages in an animal room kept on a 12L:12D cycle (light: 700–1900, dark: 1900–700) at a temperature of 23 ± 2°C and a humidity at 60 ± 5% for at least 7 days before use, and allowed free access to water and food except during testing procedures.

Assessment of Catalepsy

An assessment of catalepsy was performed by placing both front limbs of the mouse over a 3.8-cm high horizontal metal bar, 2 mm in diameter, for intervals of 1.5, 3, 4.5, 6, and 7.5 h after the administration of drugs. Thus, the mouse was forced to rest on its hind legs only. The duration of this abnormal posture was measured repeatedly, and if the mouse maintained this posture for over 30 s it was regarded as a positive sign of catalepsy.

In the preliminary examination, mice receiving sulpiride but not pimozide and haloperidol were found to be oversensitive to the stimuli from the outside environment. Therefore, in the assessment of catalepsy the mice were handled more carefully, quietly, and gently in manner.

Measurement of Locomotor Activity

Locomotor activity was measured using 10 sets of apparatus developed by Itoh et al. (23). The apparatus can divide the activity of each mouse into the vertical (VMA) and horizontal (HMA) locomotor activities and measure the activities of 10 mice at the same time. Measurement was carried out for 30 min at both 1.5 and 6 h after the administration of drugs. Seven days before the beginning of the experiment, the tails of the mice under ether anesthesia had been cut at about 5 mm from the root because the motion of their tails adversely affects the VMA and HMA counts when measuring their locomotor activities.

Brain Dopamine and Its Metabolites

The mice were sacrificed at 1.5 and 6 h respectively, after administration of a drug by microwave irradiation for 8 s (Model RE-3000, 1 kW at 2450 MHz Sharp Company, Osaka, Japan). Their brains were then removed and dissected according to the Glowinski and Iversen method (15) into the limbic system, striatum, and nucleus accumbens on an ice-chilled glass plate. The dissected tissues were quickly frozen on dry ice, weighed and stored at −80°C until extraction. According to the method of Murai et al. (30) for extraction, the tissues were homogenized with an ultrasonic cell disruptor (60 W, 50% pulsed power for 10 s, Model 200, Branson, Danbury, CT) in a 200-μl volume of ice-cooled 0.1 M perchloric acid containing 0.1 mM EDTA for the striatum and in a 120-μl volume for the limbic system and nucleus accumbens, respectively. Homogenates were centrifuged at 12000 × *g* for 10 min at 4°C and the supernatants filtered through a 0.45-μm filter (Type HV, Nihon Millipore, Yonezawa, Japan). A 20-μl portion of the clear filtrates was injected into the HPLC-ECD system. The HPLC system consisted of a delivery pump (L-5000, Yanagimoto, Japan), an analytical column (EICOMPAK, 250 × 4.6 mm, Eicom, Japan), and a guard column (Eicom). The electrochemical detector (VMD-501, Yanagimoto, Japan) with a graphite electrode (WE-3G, Eicom) was used at a voltage setting of +0.83 V vs. a Ag/AgCl reference electrode. The mobile phase was 0.02 M sodium acetate/0.0125 M citric acid buffer, pH 3.92, containing 16% methanol, 0.0033% heptanesulfonic acid, and 0.1 mM EDTA. The flow rate was set to 2.1 ml/min with a column temperature of 23°C.

The following four kinds of dopamine-related substances were measured: dopamine (DA), 3,4-dihydroxyphenylacetic acid (DOPAC), 3-methoxy-tyramine (3-MT), and homovanillic acid (HVA).

Drugs

The following drugs were employed: sulpiride (Dogmatyl, Fujisawa Yakuhin Kogyo, Japan), pimozide (Orap, Fujisawa Yakuhin Kogyo, Japan), and haloperidol (Serenace, Dainippon Pharmaceutical Company, Japan). Sulpiride and pimozide were extracted as pure powder in our laboratory and dissolved in 0.1 M tartaric acid to a concentration of 1 mg/ml. The drugs were further diluted and adjusted to the desired concentration with a sterile saline solution and then injected intraperitoneally at a volume of 0.05 ml/10 g body weight.

Statistics

The data obtained was analyzed by one-way analysis of variance (ANOVA) and subsequently by Dunnett's test or the Litchfield-Wilcoxon method.

RESULTS

Induction of Catalepsy

Effect of increasing the dose of sulpiride on induction of catalepsy. Sulpiride, as well as pimozide and haloperidol, as shown in Fig. 1, induced catalepsy. The incidence of catalepsy increased depending on the doses of sulpiride, except for the incidence of catalepsy of almost the same levels with no relation to the doses at 6 and 7.5 h after administration of sulpiride. However, the catalepsy in the mice that were administered pimozide and haloperidol increased depending on the doses at the times after administration.

Time-course in the incidence of catelepsy after administration of sulpiride. The incidence of catalepsy in mice which were administered a relatively low dose of sulpiride at 1.25, 2.5, and 5 mg/kg, as shown in Fig. 2, increased slightly both 3 and 4.5 h after administration, whereas the incidences of catalepsy in the mice which were administered a large dose of sulpiride at 40, 80, and 160 mg/kg came to almost near 100% at both 1.5 and 4.5 h after administration. However, the incidences of catalepsy in the mice which were administered a moderate dose of sulpiride at 10 and 20 mg/kg maintained the level of about 50% between 1.5 and 7.5 h after administration.

On the other hand, the incidences of catalepsy in the mice administered low doses of pimozide at 0.0625 and 0.25 mg/kg or haloperidol at 0.0375 and 0.075 mg/kg increased slightly during the observation period, while the incidences of cata-

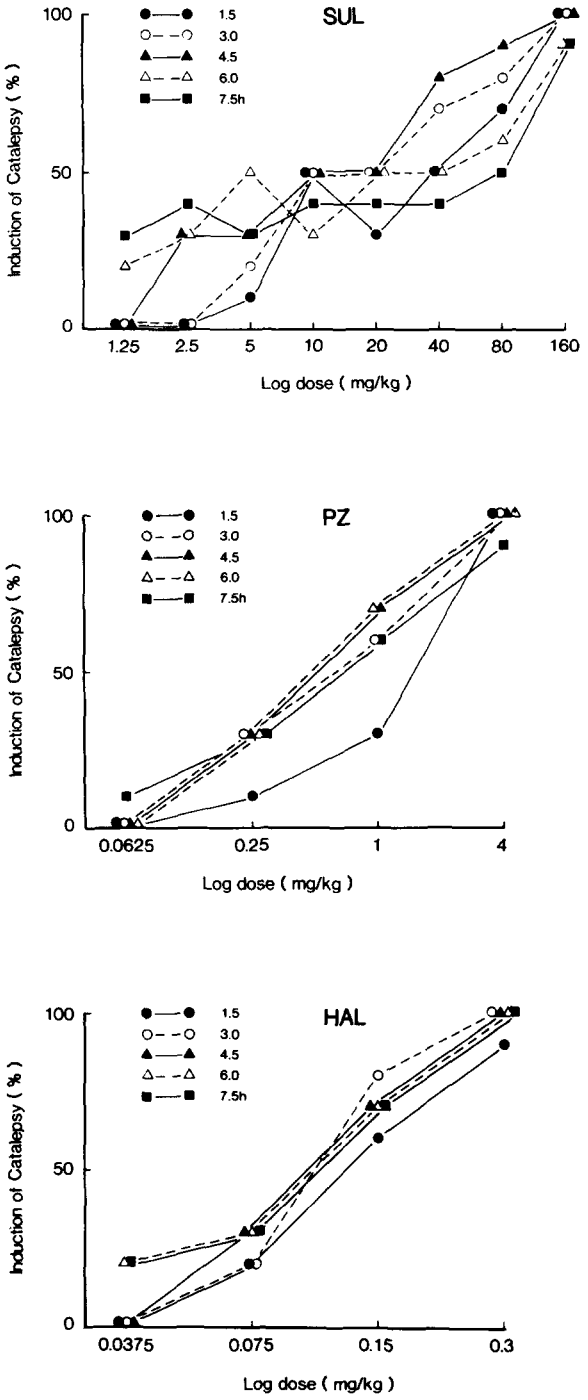

FIG. 1. Dose-response curves of the incidence of catalepsy at each time after IP administration of sulpiride (SUL), pimozide (PZ), and haloperidol (HAL) in mice (n = 10). The incidence of catalepsy was assessed at 1.5, 3, 4.5, 6, and 7.5 h after IP administration of the drugs.

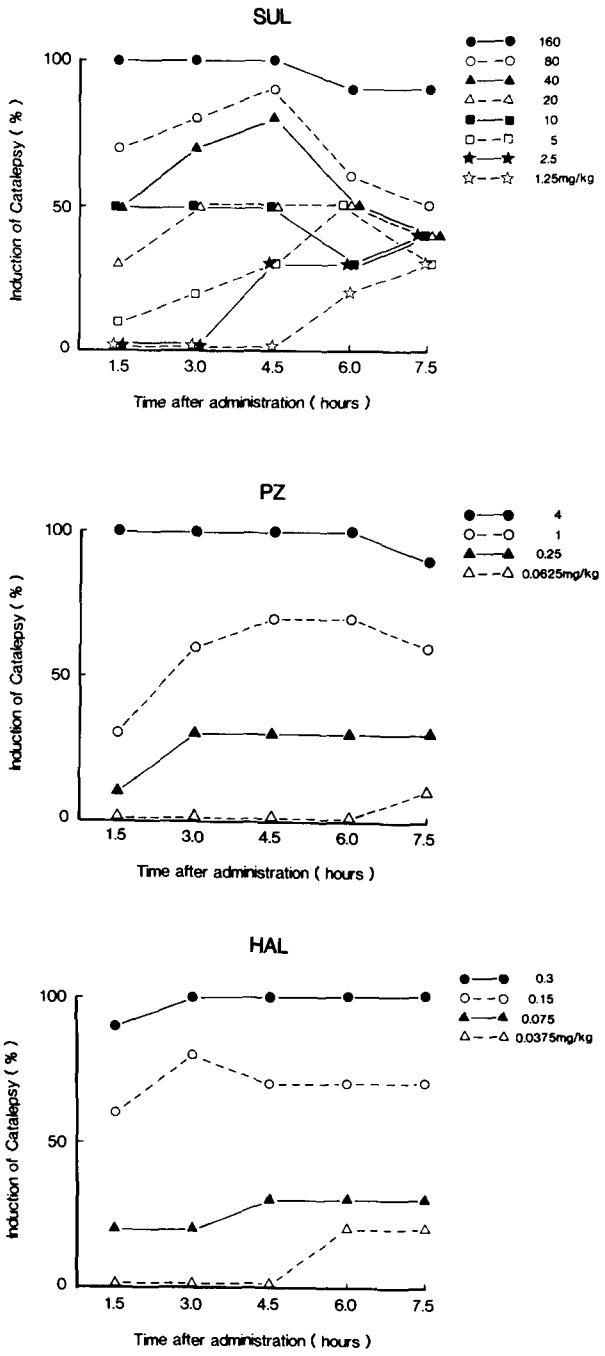

FIG. 2. Time courses of the incidence of catalepsy after IP administration of sulpiride (SUL), pimozide (PZ), and haloperidol (HAL) at each dose in mice (n = 10).

TABLE 1

VALUES OF ED_{50} AND 95% CONFIDENCE LIMITS IN THE INDUCTION OF CATALEPSY AT 1.5, 4.5, AND 6 H AFTER IP ADMINISTRATION OF SULPIRIDE, PIMOZIDE, AND HALOPERIDOL IN MICE

Drug	ED_{50} (95% confidence limits) (mg/kg)		
	1.5 h	4.5 h	6.0 h
Sulpiride	21.4 (10.5-44.0)	11.5 (5.7-22.9)	18.7 (7.5-46.3)
Pimozide	2.6 (0.5-14.0)	0.5 (0.2-1.1)	0.5 (0.2-1.1)
Haloperidol	0.13 (0.08-0.19)	0.12 (0.08-0.18)	0.11 (0.06-0.20)

Litchfield-Wilcoxon method was used for data analysis.

lepsy in the mice administered large doses of pimozide at 4 mg/kg or haloperidol at 0.15 and 0.3 mg/kg maintained the same high level between 1.5 and 7.5 h after the administration. Thus, the time-course in the incidence of catalepsy in mice which were administered sulpiride showed a pattern different from those administered pimozide and haloperidol.

Value of 50% effective dose (ED_{50}) in the induction of catalepsy by sulpiride. The value of ED_{50} in the induction of catalepsy by sulpiride, as shown in Table 1, was 11.5 mg/kg at 4.5 h after administration. This value was about 100 times more than the ED_{50} value in haloperidol, which showed a similar level of 1.5, 4.5, and 6 h after administration. Furthermore, the ED_{50} values at either 1.5 or 6 h after administration of sulpiride were about twice the value after 4.5 h.

The value of ED_{50} during the induction of catalepsy by pimozide was the same level at both 4.5 and 6 h after administration, and this value was about five times that of the value observed after 1.5 h.

Effect of Sulpiride on Spontaneous Locomotor Activity

Effect of sulpiride on VMA. In mice with sulpiride levels of 5 and 40 mg/kg, the VMA, as shown in Fig. 3., showed no change at both 1.5 and 6 h after administration, whereas with pimozide at a 0.25 mg/kg level and haloperidol at a 0.075 mg/kg level the VMAs significantly decreased at both 1.5 and 6 h after administration as compared with those of the control group.

Effect of sulpiride on HMA. In mice with 40 mg/kg sulpiride, the HMA, as shown in Fig. 3, significantly decreased 1.5 h after administration, as well as in mice with 0.5 mg/kg pimozide as compared with that of the control group, but the decreased HMA was restored 6 h after administration.

On the other hand, the HMA in mice with 5 mg/kg sulpiride showed a level similar to that of the control group either 1.5 or 6 h after administration, as well as the levels of the HMAs in mice with pimozide at 0.0625 mg/kg or haloperidol at 0.0375 and 0.075 mg/kg levels.

Effect of Sulpiride on Dopamine and Its Metabolites

DA. In the limbic system and nucleus accumbens, but not in the striatum, the levels of DA in mice with 40 mg/kg sulpiride showed a significant decrease 1.5 h after the administration as compared with that of the control group, while the levels of DA in mice with 5 and 20 mg/kg sulpiride were similar to those of the control group in three distinct brain areas (Fig. 4).

In each distinct brain area in mice with pimozide (in the striatum at both 1.5 and 6 h after 1 mg/kg administration and in the nucleus accumbens at 1.5 h after 1 mg/kg administration) and haloperidol (in the nucleus accumbens at 1.5 h after 0.075 mg/kg administration and 6 h after 0.0375 mg/kg administration), the levels of DA, as shown in Fig. 4, showed, in part, a significant decrease as compared with those of the control group.

DOPAC and HVA. In the limbic system, striatum, and nucleus accumbens, the levels of DOPAC and HVA in mice with sulpiride, as shown in Figs. 5 and 6, increased depending on the dose at both 1.5 and 6 h after administration. However, the levels of DOPAC in three distinct brain areas became lower 6 h after administration than after 1.5 h (Fig. 5). On the other hand, the levels of HVA in the limbic system and nucleus accumbens, as shown in Fig. 6, showed a similar degree at both 1.5 h and 6 h after administration, whereas the levels of HVA in the striatum was higher 6 h after administration than after 1.5 h. The levels of DOPAC and HVA in three distinct brain areas of mice with pimozide and haloperidol showed a dose-dependent increase at both 1.5 h and 6 h after administration, as well as those with sulpiride (Fig. 5). Especially, the levels of DOPAC in three distinct brain areas of mice with 1 mg/kg pimozide and in the striatum of mice with 0.15 mg/kg haloperidol showed a marked increase 1.5 h after administration. Furthermore, the levels of DOPAC in three

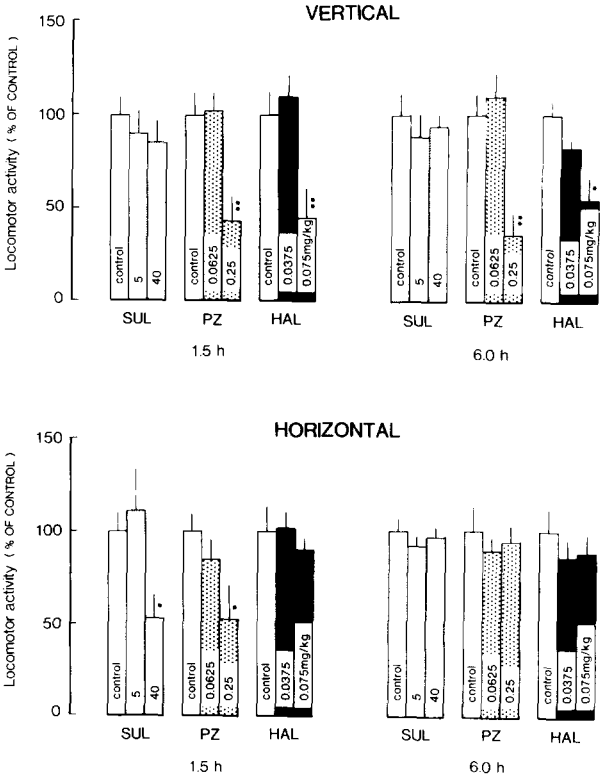

FIG. 3. Vertical (upper) and horizontal (lower) locomotor activities at 1.5 and 6 h after IP administration of sulpiride (SUL), pimozide (PZ), and haloperidol (HAL) at each dose in mice (n = 10). Each vertical bar represents the mean ± SEM of the total counts for 30 min. Statistical comparison between the drugs and vehicle-treated groups was performed by one-way ANOVA followed by Dunnett's test: $*p < 0.05$, $**p < 0.01$.

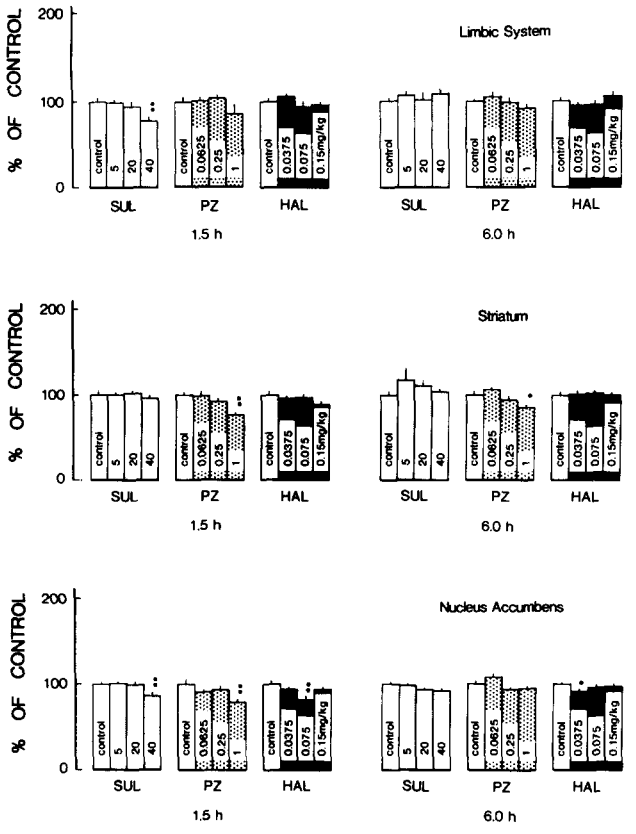

FIG. 4. Levels of dopamine in the limbic system, striatum, and nucleus accumbens at 1.5 and 6 h after IP administration of sulpiride (SUL), pimozide (PZ), and haloperidol (HAL) at each dose in mice (n = 10). Each vertical bar represents the mean ± SEM of the dopamine contents in the distinct brain areas. Statistical comparison between the drugs and vehicle-treated groups was performed by one-way ANOVA followed by Dunnett's test: $*p < 0.05$, $**p < 0.01$.

distinct brain areas of mice with pimozide and haloperidol were much lower 6 h after administration than at 1.5 h. However, the levels of HVA were of the same degree at both 1.5 and 6 h after administration (Fig. 6).

3-MT. In the striatum of mice with sulpiride, the levels of 3-MT, as shown in Fig. 7, showed a dose-dependent increase 1.5 h after administration, but did not show a dose-dependent increase 6 h after administration. The levels of 3-MT in the striatum of mice with pimozide also showed the same tendency as that of sulpiride. The levels of 3-MT in the striatum of mice with haloperidol showed a dose-dependent increase that kept a similar level at both 1.5 and 6 h after administration (Fig. 7).

DISCUSSION

There is conflict as to whether sulpiride of the selective D_2 antagonist, which is one of the large number of substituted benzamides, induces catalepsy because there are two different reports: One says sulpiride induces catalepsy in mice and rats (9,10,12,13,25,28,32,41) and the other says it does not (2,14, 17,18,20,22,26,36,37,43,45). However, it has become clear that in the present study sulpiride ranging from 1.25–160 mg/kg induces catalepsy in mice, as does pimozide, which possesses the specific antidopaminergic action, and haloperidol, which possesses the dopamine D_1/D_2 receptor blocking action (5,8,21). In addition, the induction of catalepsy by sulpiride was observed even 6 h after administration. However, fluctuation with time on the incidence of catalepsy in mice administered sulpiride showed a tendency different from that of the sedative mice with pimozide and haloperidol. This difference was also evident in that the mice with sulpiride displayed a lively struggle when handled because they had become oversensitive to the stimuli from their outside environment. There-

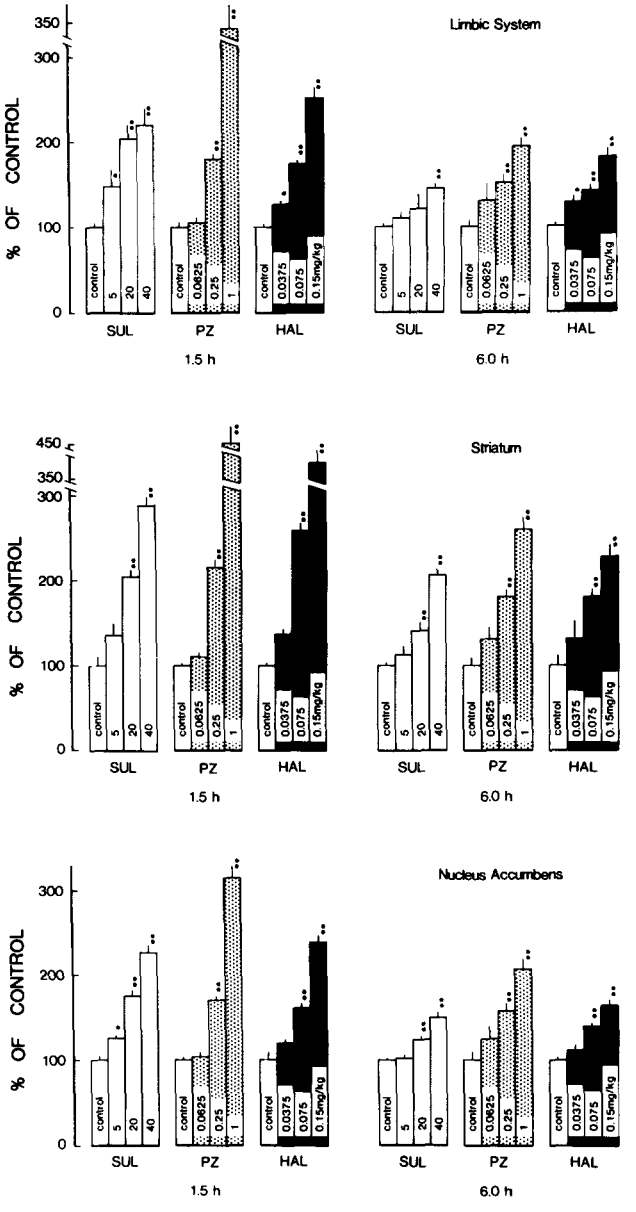

FIG. 5. Levels of DOPAC in the limbic system, striatum, and nucleus accumbens at 1.5 and 6 h after IP administration of sulpiride (SUL), pimozide (PZ), and haloperidol (HAL) at each dose in mice (n = 10). Each vertical bar represents the mean ± SEM of the DOPAC contents in the distinct brain areas. Statistical comparison between the drugs and vehicle-treated groups was performed by one-way ANOVA followed by Dunnett's test: $*p < 0.05$, $**p < 0.01$.

fore, such a working action of sulpiride in animals may have led to the inconsistent results of whether sulpiride induces catalepsy.

On the other hand, it is reported that catalepsy markedly develops in the intracerebroventricular administration of sulpiride (5,17,18,27,33,40,43), and that catalepsy is difficult to develop in the peripheral administration of sulpiride (2,14, 17,18,20,22,26,36,37,43,45) because sulpiride has a hard time penetrating the blood-brain barrier (1,5,17,18,26,33,35,37,40, 42). However, it is suggested that sulpiride passes through the blood-brain barrier, because it was observed that in the present study sulpiride induced catalepsy even during peripheral administration, and further influenced brain dopamine metabolism, as will be described later.

In mice administered sulpiride, the incidence of catalepsy

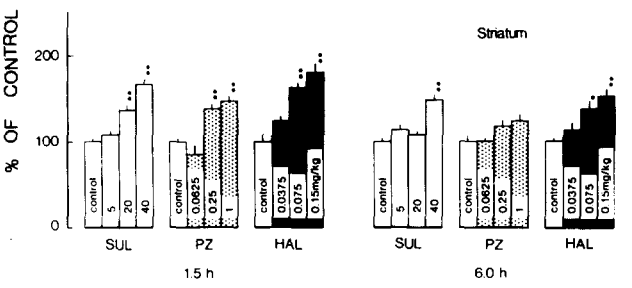

FIG. 7. Levels of 3-MT in the striatum at 1.5 and 6 h after IP administration of sulpiride (SUL), pimozide (PZ), and haloperidol (HAL) at each dose in mice (n = 10). Each vertical bar represents the mean ± SEM of the 3-MT contents in the striatum. Statistical comparison between the drugs and vehicle-treated groups was performed by one-way ANOVA followed by Dunnett's test: $*p < 0.05$, $**p < 0.01$.

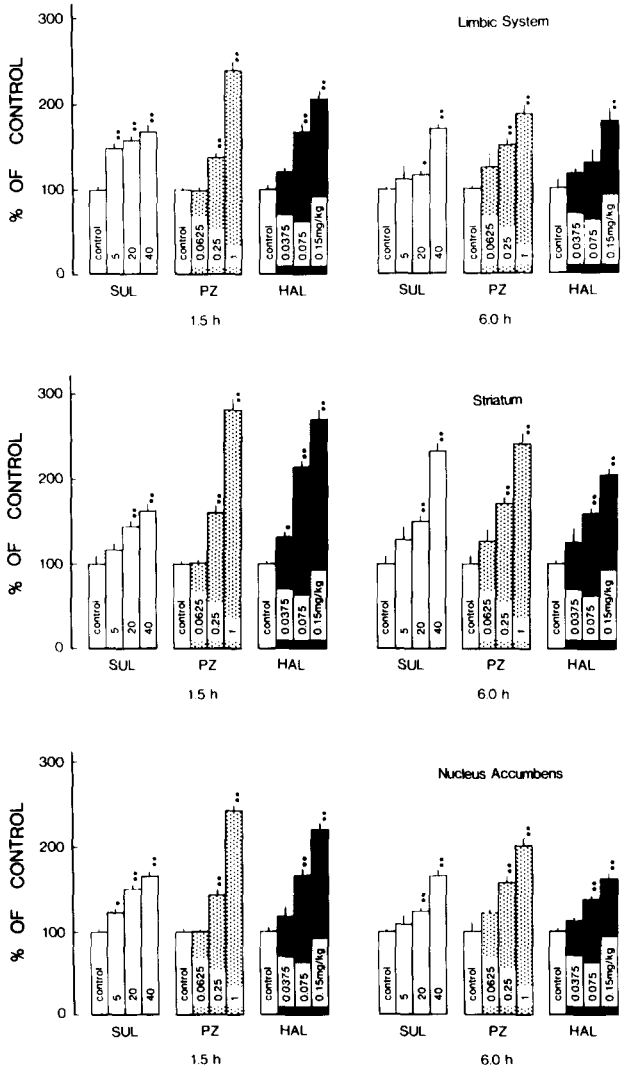

*FIG. 6. Levels of HVA in the limbic system, striatum, and nucleus accumbens at 1.5 and 6 h after IP administration of sulpiride (SUL), pimozide (PZ), and haloperidol (HAL) at each dose in mice (n = 10). Each vertical bar represents the mean ± SEM of the HVA contents in the distinct brain areas. Statistical comparison between the drugs and vehicle-treated groups was performed by one-way ANOVA followed by Dunnett's test: $*p < 0.05$, $**p < 0.01$.

was the highest at 4.5 h after administration and, at the same time, the value of ED_{50} was 11.5 mg/kg. This value of sulpiride is about 100 times as high as the ED_{50} value in the incidence of catalepsy in mice administered haloperidol at the same time and about 30–40 times the value of pimozide. This agrees with the proportion for dosage in the clinical use of sulpiride, pimozide, and haloperidol.

Moreover, at 7.5 h after administration of sulpiride the incidences of catalepsy in mice with doses ranging from 1.25–80 mg/kg showed almost similar values, independent of the doses. Also, in the case of sulpiride at 10 and 20 mg/kg, the incidences of catalepsy showed almost similar values until 7.5 h after administration, independent of time. These results of sulpiride observed in the present study differ from those of pimozide and haloperidol, which showed the induction of catalepsy depending upon the dose and the time, and it appears that this fact was not reported.

In general, it is considered that blockage of the dopamine receptors by neuroleptics changes the intracellural function and increases the number of receptors at the receptor sites, and that from these results the receptors become oversensitive. In addition, because a change in the receptors even affects the activity of the cholinergic neurons, a connection between the dopaminergic and cholinergic neurons becomes imbalanced (7,29). Thus, it is suggested that sulpiride, which leads the dopamine D_2 receptors to become hypersensitive, may be effective for a symptom such as oral dyskinesia (8) but ineffective for a symptom such as parkinsonism (13). Furthermore, it is said that sulpiride generally is difficult to blame for inducing the extrapyramidal side effects (4,5,18,33,39), although it has been recently reported that in the clinic the extrapyramidal side effects such as parkinsonism and tardive dyskinesia did develop in patients who had a long-term administration of sulpiride (1). Therefore, the induction of extrapyramidal side effects by sulpiride seems to bear some relation to a mode of action different from pimozide and haloperidol (4,18,33,39). This is also supported by the differences that appeared in the fluctuation of time on the incidence of catalepsy by three neuroleptics used in this study.

Subsequently, there has been a difference in reports with regard to the effect of sulpiride on spontaneous locomotor activity: A relatively large dose of sulpiride inhibits this activity (16,33) or does not inhibit it (19). In the present study, a relatively large dose 40 mg/kg of sulpiride significantly inhibited the HMA only 1.5 h after administration, but a low dose

of sulpiride had no influence on the VMA and HMA. This is in agreement with the reports by Bjerkenstedt et al. (5), Helmeste (16), Ögren et al. (33), and Usuda and Maeno (40).

On the other hand, although it is reported that a low dose of pimozide stimulates spontaneous locomotor activity (19) and a large dose inhibits it, a low dose of pimozide inhibited the VMA and HMA in the present study. This disagreed with the results by Horikomi and Fujita (19). Also, a low dose of haloperidol inhibited only the VMA. In general, inhibition of the spontaneous locomotor activity induced by the classical neuroleptics is discussed in relation to the antipsychotic effect; however, it is thought that the mechanism of the dopamine action in the nucleus accumbens plays an important role in spontaneous locomotor activity (7).

In the experiment on the effect of classical neuroleptics in the brain dopamine metabolism the neuroleptics decreased the DA levels (18,21,31,33,38). In the present study, sulpiride at 40 mg/kg in the limbic system and nucleus accumbens, pimozide at 1 mg/kg in the striatum and nucleus accumbens, and haloperidol at 0.075 mg/kg in the nucleus accumbens significantly decreased DA levels. In a word, sulpiride decreased the DA levels of the nucleus accumbens, as well as that by pimozide and haloperidol. These results perhaps reveal the correlation of action between the inhibition of spontaneous locomotor activity by sulpiride and its antipsychotic effect. However, a correlation between the inhibition of the DA levels by sulpiride and the induction of catalepsy could not be determined.

The levels of DOPAC and HVA, which are metabolites of DA, in three distinct brain areas showed a dose-related increase by sulpiride, which agrees with the former reports, as well as increases by pimozide and haloperidol (18,21,31, 33,38). Furthermore, the levels of 3-MT, which is related to a release of DA, showed a dose-related increase by sulpiride, as well as that by pimozide and haloperidol. In addition, three neuroleptics activated a dose dependency in the metabolism of DA even 6 h after administration, and also stimulated a biosynthesis and release of DA, as shown by the results from Carlsson and Lindqvist (6). These findings show that neuroleptics block the dopamine receptors and affect the regulatory mechanism of the DA metabolism, which is located on the receptor sites in the dopaminergic neurons, and remarkably accelerate a turnover in the DA metabolism by the feedback mechanism. Moreover, a correlation between the changes in the DOPAC, HVA, and 3-MT levels in three distinct brain areas by sulpiride and the induction of catalepsy could not be determined, as reported by Zetterström et al. (45).

In conclusion, it was observed that sulpiride, which has selective D_2 receptor-blocking action, induced catalepsy even by a peripheral administration of a low dose and inhibited spontaneous locomotor activity. In addition, even 6 h after administration of sulpiride, as well as at 1.5 h, sulpiride considerably accelerated a turnover in the DA metabolism in three distinct brain areas.

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