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Opposite Effects Induced by Low and High Doses of Apomorphine on Single-Trial Passive Avoidance Learning in Mice

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ICHIHARA, K., T. NABESHIMA AND T. KAMEYAMA. *Opposite effects induced by low and high doses of apomorphine on single-trial passive avoidance learning in mice.* PHARMACOL BIOCHEM BEHAV **30**(1) 107–113, 1988.—The effects of apomorphine (0.0125–1 mg/kg, SC), a dopamine (DA) agonist, on passive avoidance learning were assessed in mice which received brief and long foot-shocks in a training test. At low doses, apomorphine stimulates DA autoreceptors. With a shock of brief duration, apomorphine at a low dose (0.05 mg/kg), enhanced the avoidance learning when it was administered 20 min before the training test or the retention test. At high doses, apomorphine stimulates postsynaptic DA receptors. With a shock of long duration, apomorphine at a high dose (1 mg/kg), impaired the avoidance learning when it was administered 20 min before the training test or the retention test. However, apomorphine (0.05 and 1 mg/kg) given immediately after the training test did not have any effect on the avoidance behavior with shocks of either brief or long durations. Apomorphine-induced enhancement of passive avoidance learning was antagonized by sulpiride, but not by haloperidol. These results show that apomorphine induced the opposite effects on the passive avoidance learning depending on the dose or on the reinforcement intensity and suggest that the central DA system may play an important role in modulating memory processes.

Presynaptic DA receptors Postsynaptic DA receptors Apomorphine Passive avoidance learning Memory

ALTHOUGH numerous investigators have suggested that learning and memory can be modified by drugs which affect the central dopamine (DA) neuronal system [5, 6, 8, 11, 14–16, 22, 23], it is not clear whether activation of DA receptors facilitates or impairs learning and memory. The discrepancy between the results may be mainly due to the task employed for evaluation of learning and memory and/or due to the characteristics of the drugs used for the test. Moreover, since it has been widely accepted that DA neuronal activity is regulated by the presynaptic DA receptors, termed autoreceptors [1, 19, 20], it may be necessary to investigate the role of DA neurons not only at postsynaptic DA receptors but also at DA autoreceptors in order to clarify the involvment of DA neuronal systems in learning and memory.

In a passive avoidance task, an activation of postsynaptic DA receptors has reportedly induced an impairment of learning [6, 11, 23]. Thus, it should be possible that an inactivation of DA neurons may enhance the passive avoidance learning. This prompted us to investigate whether the reduction of dopaminergic transmission by stimulation of DA autoreceptors modulates learning of the passive avoidance task. For that purpose, the effects of apomorphine at low doses (thought to preferentially stimulate DA autoreceptors [10,29]) and at a high dose (thought to stimulate postsynaptic DA receptors [3]) were studied using a single-trial passive avoidance task in mice.

In the present study, the effects of the drug on the passive avoidance task were also investigated at both weak and strong reinforcement intensities. When the avoidance behavior with a weak reinforcement was to be investigated, and when the avoidance behavior with a strong reinforcement was to be investigated, electric foot-shocks were delivered for a brief duration and for a long duration in the training test, respectively.

GENERAL METHOD

SUBJECTS

Male mice of ddY strain (Shizuoka Laboratory Animal Center, Japan), weighing 28–33 g were used as subjects. The animals were housed in stainless-steel cages, under standard conditions (23±1°C, 50±5% humidity, 8 a.m./8 p.m. light dark cycle) with free access to water and food. Following adaptation to laboratory conditions for at least 3 days, they were used for the experiment.

DRUGS

Apomorphine hydrochloride (APO; Sigma) was dissolved in 0.9% saline solution containing 1 mg/ml ascorbic acid to

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prevent oxidation. Haloperidol (Dainippon) and sulpiride (Sigma) were initially dissolved in a 10% (v/v) lactic acid solution of the minimum volume and diluted with distilled water. Apomorphine was injected SC, and haloperidol and sulpiride were injected IP in volumes of 10 ml/kg.

APPARATUS

The passive avoidance apparatus consisted of a Plexiglas rectangular inner box (30×30×40 cm high) with a steel-rod grid floor (30 parallel steel rods, 0.3 cm in diameter set 1.0 cm apart) and a semi-sound-proof wooden outer box (35×41×91 cm high) with a 15 W illumination lamp in it. A wooden platform (4×4×4 cm) was set in the center of the grid floor. Intermittent electric shocks (ES; 1 Hz, 0.5 sec, 60 V DC) were delivered to the grid floor by an isolated stimulator (Nihon Koden, Japan). The animals received electric shocks in the range of 0.24–0.6 mA since the resistance varied between 100 and 250 kΩ.

PROCEDURES IN TRAINING AND RETENTION TESTS

Training Test

Each mouse was placed gently on the wooden platform and then, when the mouse stepped down from the platform and placed all its paws on the grid floor, the intermittent ES was delivered continuously for 3 sec or 15 sec. The step-down latency was measured with a stopwatch.

Retention Test

Twenty-four hr after the training test, each mouse was placed on the platform again, and the step-down latency was measured with a stopwatch as passive avoidance behavior. An upper cut-off time of 300 sec was set.

STATISTICAL ANALYSIS

The data were expressed in terms of medians and interquartile ranges and analyzed using a Kruskal-Wallis nonparametric one-way analysis of variance; further statistical analyses for individual groups were done with a two-tailed Mann-Whitney U-test. The criterion for statistical significance was $p<0.05$ in all statistical evaluations.

EXPERIMENT 1

Effects of APO on the passive avoidance behavior in mice which received brief and long shocks in the training test were investigated.

METHOD

APO was given to mice during different time periods of learning and memorizing the passive avoidance task: before the training test, after the training test and before the retention test.

Passive Avoidance Behavior With a Brief Shock

In the training test, mice received ES for 3 sec. The retention test was performed 24 hr after the training test. In Experiment A, mice were injected SC with saline or APO (0.0125, 0.025, 0.05, 0.1 and 1 mg/kg) 20 min before the training test. In Experiment B, mice were injected SC with saline or APO (0.0125, 0.025, 0.05, 0.1 and 1 mg/kg) immediately after the training test. In Experiment C, mice were injected SC with saline or APO (0.05 mg/kg) 20 min before the retention test in order to investigate the effect of APO on retrieval of memory. This dose of APO was the most effective dose in mice in Experiment A (see Table 1, Experiment A). Hence, APO (0.05 mg/kg) was used as the low dose in the following experiments.

Passive Avoidance Behavior With a Long Shock

In the training test, mice received ES for 15 sec. The retention test was performed 24 hr after the training test. In Experiment A, mice were injected SC with saline or APO (0.05,0.25 and 1 mg/kg) 20 min before the training test. In Experiment B, mice were injected SC with saline or APO (0.05, 0.25 and 1 mg/kg) immediately after the training test. In Experiment C, mice were injected SC with saline or APO (1 mg/kg) 20 min before the retention test in order to examine the effect on retrieval of memory.

Retention Performance of Non-Shocked Mice

In the training test, mice did not receive ES. The retention test was performed 24 hr after the training test as described above. APO (0.05 and 1 mg/kg) was given SC to mice 20 min before the retention test.

Effect of APO on the Vocalization Threshold

The vocalization threshold with ES was measured using the passive avoidance testing apparatus without the platform. The shock intensity was manually raised stepwise from 20 V (step: 20, 30, 40, 50, 60, 70 and 80 V; shock duration: one sec; inter-shock interval: 10 sec) until a vocalization was observed. Mice were given saline or APO (0.05 and 1 mg/kg) SC 20 min before the test.

RESULTS AND DISCUSSION

The results of all three experiments in the passive avoidance behavior of mice that received a brief shock are persented in Table 1. Starting twenty minutes after the injection of APO (0.0125–1 mg/kg) or saline, mice were trained to engage in passive avoidance. There was a significant drug-effect on the step-down latencies in the retention test, $H(5)=26.04$, $p<0.001$ (Kruskal-Wallis test) and analysis for the individual group using a Mann-Whitney U-test showed that the treatment with APO (0.025, 0.05 and 0.1 mg/kg) significantly prolonged the step-down latencies of mice compared to those of the saline-treated animals (see Experiment A). Lower (0.0125 mg/kg) and higher (1 mg/kg) doses of APO, however, had no effect on the step-down latencies in the retention test ($p>0.05$, Mann-Whitney U-test, see Experiment A). These treatments with APO (0.0125–1.0 mg/kg) prior to the training test did not affect the step-down latencies of mice in the training test, $H(5)=8.39$, $p>0.05$ (Kruskal-Wallis test, see Experiment A). As shown in Table 1, Experiment B, there was no significant difference in the step-down latencies in the retention test among all groups injected with APO (0.0125–1 mg/kg) and saline immediately after the training test, $H(5)=5.16$, $p>0.05$ (Kruskal-Wallis test). When APO (0.05 mg/kg) was given to mice 20 min before the retention test, there was a small but significant ($p<0.05$, Mann-Whitney U-test) increase in the step-down latencies in the retention test compared to those of the saline-treated animals (see Experiment C), although in mice which did not receive the foot-shock (the non-shocked group), there was no significant difference in the step-down latencies in the retention test between the APO-treated and the saline-treated animals ($p>0.05$, Mann-Whitney U-test, see Experiment C).

TABLE 1

EFFECT OF APOMORPHINE ON THE STEP-DOWN LATENCIES OF PASSIVE AVOIDANCE TASK IN MICE RECEIVED A BRIEF SHOCK IN THE TRAINING TEST

Treatment	N	Dose (mg/kg)	Latency to Step-Down (sec) Training Test	Retention Test
Exp. A				
Shocked group				
Saline	15	—	6.0 (4.0–9.0)	35.0 (28.0–134.0)
Apomorphine	15	0.0125	5.0 (4.0–6.0)	39.0 (24.0–120.0)
	15	0.025	8.0 (4.0–9.0)	150.0 (59.0–300.0)*
	15	0.05	8.0 (4.0–12.0)	197.0 (81.0–300.0)†
	15	0.1	8.0 (6.0–10.0)	163.0 (88.0–300.0)*
	15	1.0	6.0 (4.0–8.0)	29.0 (17.0–92.0)
Exp. B				
Shocked group				
Saline	12	—	8.0 (5.3–12.5)	38.0 (26.3–127.8)
Apomorphine	12	0.0125	7.5 (6.3–9.8)	42.0 (25.5–122.8)
	12	0.025	7.0 (4.3–10.8)	51.5 (25.5–105.5)
	12	0.05	7.0 (5.3–8.0)	27.0 (14.5–131.0)
	12	0.1	6.5 (5.0–9.0)	39.5 (24.8–121.5)
	12	1.0	9.0 (6.3–10.8)	72.5 (49.0–150.8)
Exp. C				
Shocked group				
Saline	17	—	5.0 (4.0–9.5)	23.0 (14.0–76.5)
Apomorphine	17	0.05	6.0 (4.0–8.0)	77.0 (31.5–196.5)*
Non-shocked group				
Saline	13	—	6.0 (4.0–8.5)	4.0 (4.0–6.0)
Apomorphine	13	0.05	7.0 (5.0–8.0)	6.0 (4.0–8.0)

Mice were given apomorphine SC 20 min before (Exp. A) and immediately after (Exp. B) the training test, while mice were given it SC 20 min before the retention test (Exp. C). In the training test, the animals were delivered the electric shock for a brief duration (3 sec). Each value represents the median and interquartile ranges. *$p<0.05$, †$p<0.01$ compared to the corresponding saline-treated group (Mann-Whitney U-test).

The results of all three experiments in the passive avoidance behavior of mice that received a long shock are presented in Table 2. When APO (0.05, 0.25 and 1 mg/kg) was given to mice 20 min before the training test, there was a significant drug-effect on the step-down latencies in the retention test, $H(3)=28.46$, $p<0.001$ (Kruskal-Wallis test) and analysis of individual groups using a Mann-Whitney U-test showed that the treatment with APO (0.25 and 1 mg/kg) significantly shortened the step-down latencies of mice compared to the results for the saline-treated animals (see Experiment A). However, the step-down latencies of mice treated with a lower dose (0.05 mg/kg) of APO did not significantly differ from those of the saline-treated animals in the retention test ($p>0.05$, Mann-Whitney U-test, see Experiment A). The treatment with APO prior to the training test did not significantly affect the step-down latencies of mice in the training test, $H(3)=2.99$, $p>0.05$ (Kruskal-Wallis test, see Experiment A). As shown in Table 2, Experiment B, there was no significant difference in the step-down latencies of the retention test among all groups given APO (0.05, 0.25 and 1 mg/kg) and saline immediately after the training test, $H(3)=3.92$, $p>0.05$ (Kruskal-Wallis test). Furthermore, we examined the effects of the highest dose (1 mg/kg) of APO on the step-down latencies in the retention test when APO was given to mice 20 min before the retention test. The APO-treated group showed a significant decrease in the step-down latencies compared to those of the saline-treated group ($p<0.01$, Mann-Whitney U-test, see Experiment C). In the non-shocked group, however, APO at the highest dose (1 mg/kg) did not affect the step-down latencies in the retention test ($p>0.05$, Mann-Whitney U-test, see Experiment C).

The change in animals' response to ES in the training test could influence the passive avoidance behavior. Since effect of APO on the passive avoidance learning might be resulted from the change in response to ES, effect of APO on the vocalization threshold with ES was measured. As shown in Table 3, APO (0.05 and 1 mg/kg) did not significantly alter the vocalization thresholds in mice.

As for the doses of APO used in this study, the low and high doses would stimulate DA autoreceptors and postsynaptic DA receptors, respectively [7, 10, 28–30]. Low doses of APO enhanced the passive avoidance behavior of mice that received a brief shock and high doses of APO impaired it of mice that received a long shock when APO was administered before the training test or the retention test. These effects produced by APO cannot be related to alteration of the response to ES because APO did not significantly alter the vocalization and flinch-jump (data not shown) thresholds in mice with electric foot-shock at the doses and at the time after administration we employed. Recently,

TABLE 2

EFFECT OF APOMORPHINE ON THE STEP-DOWN LATENCIES OF PASSIVE AVOIDANCE TASK IN MICE RECEIVED A LONG SHOCK IN THE TRAINING TEST

Treatment	N	Dose (mg/kg)	Latency to Step-Down (sec) Training Test	Retention Test
Exp. A				
Shocked group				
Saline	15	—	7.0 (4.0–10.0)	184.0 (88.0–300.0)
Apomorphine	15	0.05	7.0 (6.0–8.0)	221.0 (111.0–300.0)
	15	0.25	7.0 (5.0–10.0)	70.0 (33.0–138.0)†
	15	1.0	5.0 (4.0–10.0)	32.0 (16.0–57.0)†
Exp. B				
Shocked group				
Saline	15	—	7.0 (5.0–11.0)	126.0 (118.0–190.0)
Apomorphine	15	0.05	6.0 (4.0–10.0)	136.0 (101.0–201.0)
	15	0.25	8.0 (6.0–10.0)	101.0 (47.0–254.0)
	16	1.0	6.0 (4.0–8.0)	87.0 (43.0–153.0)
Exp. C				
Shocked group				
Saline	15	—	7.0 (6.0–90)	190.5 (92.0–300.0)
Apomorphine	16	1.0	7.0 (5.0–8.0)	55.5 (30.3–184.0)*
Non-shocked group				
Saline	13	—	6.0 (4.0–8.0)	5.0 (4.0–7.0)
Apomorphine	13	1.0	5.0 (4.0–8.0)	6.0 (5.0–9.0)

Mice were given apomorphine SC 20 min before (Exp. A) and immediately after (Exp. B) the training test, while mice were given it SC 20 min before the retention test (Exp. C). In the training test, the animals were delivered the electric shock for a long duration (15 sec). Each value represents the median and interquartile ranges. *$p<0.05$, †$p<0.01$ compared to the corresponding saline-treated group (Mann-Whitney U-test).

Paalzow and Paalzow [17] have reported that APO-induced alteration of sensitivity to pain in the vocalization test in rats. However, our data in mice confirmed the effect of APO on pain threshold reported by previous authors [17] even in different species, since at the dose and at the time after administration we employed, the vocalization threshold did not change. It is unlikely that mice do not learn the passive avoidance behavior because of a general motor incapacity: First, there was no indication of a lack of motor coordination since APO-treated mice showed the same degree of wall climbing and locomotion compared to the control mice. Second, APO did not change the step-down latencies in the training test and the step-down latencies of non-shocked animals in the retention test. Therefore, it seems that modification of the passive avoidance behavior induced by APO is due to effects on memory-related processes.

EXPERIMENT 2

The experiments were carried out to investigate whether the facilitation of the passive avoidance learning induced by APO (0.05 mg/kg) is antagonized by DA receptor blocking agents.

METHOD

Antagonistic Effects of Haloperidol and Sulpiride on the Effects of APO

In Experiment A, the effects of haloperidol or sulpiride alone on the passive avoidance learning were investigated in mice that received a brief shock in the training test. Mice were injected IP with haloperidol (0.0125, 0.025, 0.05 and 0.1 mg/kg) or sulpiride (10, 20 and 40 mg/kg) 60 min before the training test. The retention test was performed 24 hr after the training test. In Experiment B, mice were injected with halo-

TABLE 3

EFFECTS OF APOMORPHINE, HALOPERIDOL AND SULPIRIDE ON THE VOCALIZATION THRESHOLDS WITH ELECTRIC FOOT-SHOCK IN MICE

Treatments	N	Dose (mg/kg)	Vocalization Threshold (V)
Saline	10	—	40.0 (40.0–42.5)
Apomorphine	10	0.05	40.0 (40.0–42.5)
	10	1	50.0 (40.0–50.0)
Vehicle	10	—	45.0 (40.0–50.0)
Haloperidol	10	0.05	40.0 (37.5–40.0)
	10	0.1	40.0 (30.0–40.0)
Sulpiride	10	20	40.0 (40.0–50.0)
	10	40	45.0 (30.0–50.0)

Mice were given apomorphine SC, haloperidol IP and sulpiride IP 20 min, 60 min and 60 min before the test, respectively. Each value represents the median and interquartile ranges. Kruskal-Wallis test: $H(2)=5.41$, $p>0.05$ (for apomorphine-treated group); $H(4)=3.92$, $p>0.05$ (for haloperidol- and sulpiride-treated group).

TABLE 4

EFFECTS OF HALOPERIDOL AND SULPIRIDE ON THE STEP-DOWN LATENCIES OF PASSIVE AVOIDANCE TASK IN MICE RECEIVED A BRIEF SHOCK IN THE TRAINING TEST (EXP. A)

Treatment	N	Dose (mg/kg)	Latency to Step-Down (sec) Training Test	Retention Test
Vehicle	15	—	5.0 (4.0–7.0)	58.0 (26.0–102.0)
Haloperidol	15	0.0125	6.0 (4.0–8.0)	70.0 (24.0–117.0)
	15	0.025	6.0 (4.0–9.0)	94.0 (42.0–136.0)
	15	0.05	5.0 (4.0–7.0)	155.0 (92.0–220.0)†
	15	0.1	9.0 (6.0–12.0)*	203.0 (162.0–300.0)†
Vehicle	15	—	6.0 (4.0–70)	41.0 (27.0–63.0)
Sulpiride	15	10.0	7.0 (4.0–11.0)	35.0 (20.0–97.0)
	15	20.0	7.0 (4.0–8.0)	54.0 (31.0–103.0)
	15	40.0	5.0 (4.0–6.0)	136.0 (72.0–278.0)†

Mice were given haloperidol and sulpiride IP 60 min before the training test. In the training test, the animals were delivered the electric shock for a brief duration (3 sec). Each value represents the median and interquartile ranges. *$p<0.05$, †$p<0.01$ compared to the corresponding vehicle-treated group (Mann-Whitney U-test).

TABLE 5

EFFECTS OF SULPIRIDE AND/OR APOMORPHINE ON THE STEP-DOWN LATENCIES OF PASSIVE AVOIDANCE TASK IN MICE RECEIVED A BRIEF SHOCK IN THE TRAINING TEST (EXP. B)

Treatment	N	Dose (mg/kg)	Latency to Step-Down (sec) Training Test	Retention Test
Vehicle	14	—	5.0 (4.0–9.0)	28.0 (19.0–55.0)
Apomorphine	14	0.05	8.0 (6.0–11.0)	137.0 (79.0–300.0)*
Sulpiride	14	20	5.0 (4.0–7.0)	47.0 (18.0–100.0)
Sulpiride + Apomorphine	14	20 0.05	7.0 (4.0–10.0)	44.0 (27.0–176.0)†

Mice were given sulpiride IP and apomorphine SC 60 min and 20 min before the training test, respectively. In the training test, the animals were delivered the electric shock for a brief duration (3 sec). Each value represents the median and interquartile ranges. *$p<0.01$ compared to the vehicle-treated group, †$p<0.05$ compared to the apomorphine-treated group (Mann-Whitney U-test).

peridol or sulpiride 60 min before the training test at the dose which did not alter the avoidance behavior, and then mice were challenged with APO (0.05 mg/kg SC) 20 min before the training test.

Effects of Haloperidol and Sulpiride on the Vocalization Threshold

The vocalization threshold with ES was measured by the same method described in Experiment 1. Mice were given haloperidol and sulpiride IP 60 min before the test.

RESULTS AND DISCUSSION

First of all, the effects of halperidol or sulpiride alone on the passive avoidance behavior were examined (Experiment A). In the haloperidol-treated groups, there was a significant drug-effect on the step-down latencies in the retention test, $H(4)=25.25$, $p<0.001$ (Kruskal-Wallis test). Like haloperidol, there was a significant drug-effect on the step-down latencies in the retention test in the sulpiride-treated animals, $H(3)=14.30$, $p<0.01$ (Kruskal-Wallis test). Analysis of the individual group using the Mann-Whitney U-test showed that treatment with haloperidol (0.05 and 0.1 mg/kg) or sulpiride (40 mg/kg) significantly prolonged the step-down latencies of mice compared to those of the vehicle-treated animals (Table 4). At the effective doses in the passive avoidance learning, neither haloperidol nor sulpiride significantly altered the vocalization thresholds in mice (Table 3).

Haloperidol and sulpiride facilitated the passive avoidance learning at higher doses, which seems to be due to a blocking of postsynaptic DA receptors. This result was in agreement with that obtained from low doses of APO, suggesting that a reduction of dopaminergic transmission enhances the passive avoidance learning.

The suitable doses which did not affect the avoidance behavior by themselves were used for Experiment B. As

TABLE 6

EFFECTS OF HALOPERIDOL AND/OR APOMORPHINE ON THE STEP-DOWN LATENCIES OF PASSIVE AVOIDANCE TASK IN MICE RECEIVED A BRIEF SHOCK IN THE TRAINING TEST (EXP. B)

Treatment	N	Dose (mg/kg)	Latency to Step-Down (sec)	
			Training Test	Retention Test
Vehicle	15	—	5.0 (4.0–7.0)	37.0 (25.0–179.0)
Apomorphine	15	0.05	7.0 (4.0–9.0)	171.0 (98.0–300.0)*
Haloperidol	15	0.025	7.0 (6.0–8.0)	83.0 (57.0–199.0)
Haloperidol + Apomorphine	15	0.025 0.05	8.0 (6.0–9.0)	146.0 (93.0–300.0)*

Mice were given haloperidol IP and apomorphine SC 60 min and 20 min before the training test, respectively. In the training test, the animals were delivered the electric shock for a brief duration (3 sec). Each value represents the median and interquartile ranges. *$p<0.01$ compared to the vehicle-treated group (Mann-Whitney U-test).

shown in Tables 5 and 6, the pretreatment with sulpiride (20 mg/kg) 60 min before the training test significantly antagonized the enhancement induced by the low dose (0.05 mg/kg) of APO in the passive avoidance learning, while the pretreatment with haloperidol (0.025 mg/kg) failed to antagonize it. The pretreatment with haloperidol (0.05 mg/kg or more) or with sulpiride (40 mg/kg or more) significantly prevented the impairment of the passive avoidance learning induced by the high dose (1 mg/kg) of APO (data not shown).

Sulpiride, at a lower dose which failed to affect the passive avoidance learning by itself, antagonized the facilitation of the passive avoidance learning induced by the low dose of APO, but haloperidol did not. These findings may indicate that sulpiride can clearly distinguish DA autoreceptors from postsynaptic DA receptors due to its ability to bind to DA autoreceptors at lower doses. This suggestion is consistent with previous data which demonstrate that sulpiride acts strongly on presynaptic DA receptors [18,26]. Haloperidol has been reported to antagonize APO-induced hypomotility [10, 16, 31]. Therefore, the role of dopaminergic neuronal systems in learning and memory would differ essentially from that in motor function. Further investigation is necessary to elucidate the difference of antagonistic effects between sulpiride and haloperidol on APO-induced facilitation of the passive avoidance learning and hypomotility.

GENERAL DISCUSSION

If memory could be defined as the retention of information, this information needs to be acquired (learning) and recalled (retrieval). In our study, the passive avoidance learning of mice was altered by APO when administered before the training test or the retention test. Hence, it is conceivable that APO affects learning and retrieval stages of memory by modulation of the DA neuronal system. This finding is strongly supported by several other reports on the impairment of the passive avoidance learning by the activation of dopaminergic neurons [6, 11, 23, 24].

The control animals trained with a shock of long duration exhibited a better avoidance learning (step-down latency: 126.0–190.0 sec, Table 2) than the control animals trained with a shock of brief duration (step-down latency: 23.0–38.0 sec, Table 1). The difference of step-down latency between control groups is caused by different reinforcement intensities and seems to be related to a degree of memorizing the passive avoidance learning. APO changed the degree of memory formed by each reinforcement intensity. Our results suggest that, in mice trained with brief shock, APO at the low doses (0.025–0.1 mg/kg) increases the degree of memory to the level of that in mice trained with long shock. In addition, APO at the high doses (0.25 and 1.0 mg/kg) decreases the degree of memory in the later group to the level of that in the former group. The differential effects of low and high doses of APO using different shock durations may be related to a floor or ceiling effects. Activation of central DA receptors is known to disrupt latent inhibition [27] or latent learning [2]. Szechtman [33] has reported that APO (1.25 mg/kg) interrupts mating by shifting attention from the female to some other stimuli in the environment. These reports suggest that overactivation of central DA receptors may interfere with the animals' awareness of their environment and may disrupt selective attention to the environmental stimulus. In addition, Sara [21] has reviewed the noradrenergic modulation of selective attention in the memory retrieval process. He has reported that the intracerebroventricular injection of APO (10 μg) facilitates memory retrieval with increasing forebrain NE activity in the spontaneous maze-forgetting paradigm, and he has suggested that the increase of NE activity should enhance selective attention. Haloperidol increases the locus coeruleus (LC) NE neuron firing by blocking the putative inhibitory input to the LC from the ventral tegmentum A10 dopaminergic area [25]. Systemic administration of neuroleptic drugs enhances NE release in the rat cortex as a result of an increase in LC activity [13]. Taken together, we were led to the hypotheses that (1) reduced dopaminergic transmission through a stimulation of DA autoreceptors should increase the LC NE neuron firing and, as a result, the selective attention may be enhanced and that (2) stimulation of postsynaptic DA receptors, of course, should produce the opposite effect through a decrease in the LC NE neuron firing. This hypothesis seems to offer a plausible explanation for APO-induced alteration in the passive avoidance behavior in the case of both brief and long foot-shock. Thus, the change in dopaminergic transmission may affect the learning of simple tasks such as single-trial passive avoidance tasks by modulating selective attention to rein-

forcer. However, other mechanisms regarding APO-induced modulation in memory processes, for instance, a cholinergic-dopaminergic link [4,12], or interaction between opiates and dopaminergic neurons [9,32] may exist.

In conclusion, APO showed opposite effects on the learning of the passive avoidance task in mice in a dose-related manner, namely, facilitation and impairment were observed at a low dose and a high dose, respectively. The appearance of those effects depended on the duration of foot-shock in the training test. The present data suggest that the central dopaminergic system may be able to modulate memory processes through mainly affecting the process of attention.

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