Pharmacology Biochemistry & Behavior, Vol. 17, pp. 425–429, 1982. Printed in the U.S.A.

Strain Differences to the Effects of Central Acting Drugs on Sidman Avoidance Response in Wistar and Fischer 344 Rats

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Received 24 November 1981

KURIBARA, H. *Strain differences to the effects of central acting drugs on Sidman avoidance response in Wistar and Fischer 344 rats.* PHARMAC. BIOCHEM. BEHAV. 17(3) 425–429, 1982.—Effects of methamphetamine (MAMP), chlorpromazine (CPZ), pilocarpine (PILO) and scopolamine (SCOP) on Sidman avoidance response (response-shock interval=30 sec, and shock-shock interval=5 sec) were investigated in male rats of Wistar and Fischer 344 strains. The results were compared between the two strains. Both the Wistar and Fischer 344 rats acquired the Sidman avoidance response well and exhibited almost the same baseline response rate (lever-presses/min) of about 6/min and shock rate (number of shocks delivered/min) of about 0.27/min. MAMP and SCOP facilitated the avoidance response with an increase in the response rate and a decrease in the shock rate. CPZ and PILO suppressed the avoidance response with a decrease in the response rate and an increase in the shock rate. The Wistar rats were less sensitive to the avoidance facilitating effect of MAMP, and more sensitive to the avoidance suppressing effect of CPZ than the Fischer 344 rats. In contrast, the Wistar rats were less sensitive to the avoidance suppressing effect of PILO, and more sensitive to the avoidance facilitating effect of SCOP than the Fischer 344 rats. These results suggest that the neural activities of both catecholaminergic and muscarinic-cholinergic systems are different between the Wistar and Fischer 344 rats, and that the two strains rats respond differently to central acting drugs.

Sidman avoidance Strain differences Wistar rats Fischer 344 rats Methamphetamine
Chlorpormazine Pilocarpine Scopolamine

IN a previous paper, it was reported that the Fischer 344 strain rats rapidly acquired the conditioned avoidance response on Sidman and discriminated avoidance situations, and that the baseline levels of both the response rate and avoidance or shock rate achieved were almost identical with those of the Wistar strain rats [6]. Therefore, it is expected that the Fischer 344 rats would be suitable subjects for behavioral studies, particularly for avoidance tests, for assessment of central acting drugs. However, different strains of rats may show different changes in behavior after administration of drugs. Recently, Lloyd and Stone [7] reported that methylxanthines-induced self-injurious behavior was frequently observed in the Fischer 344 rats, while rarely seen in the Wistar rats. It is, therefore, considered that the Fischer 344 rats respond differently to central acting drugs from the Wistar rats. However, there have been few studies on the effects of central acting drugs on conditioned avoidance response in the Fischer 344 rats.

The present experiment studies the effects of several drugs, which affect central catecholaminergic and muscarinic-cholinergic systems, on the Sidman avoidance response [9] in the Wistar and Fischer 344 rats. The experimental results were considered in terms of the differences between of the two strains of rats.

METHOD

Animals

Twelve male rats of the Wistar strain, and twelve male rats of the Fischer 344 strain served as subjects in this experiment. The Wistar and Fischer 344 rats were provided by the breeding colony of Gunma University Medical School, and The Charles River Japan Inc., Atsugi, respectively, at an age of 4 weeks. Groups of 3 rats were housed in stainless steel wire mesh cages of 25 (W) × 40 (D) × 20 (H) cm with a free access to a solid diet (MF: Oriental Yeast Co., Tokyo) and tap water except during the period of avoidance session of 1 hr per day. The breeding room was artificially illuminated by fluorescent lamps on a 12-hr light-dark schedule (light on at 6:00, and light off at 18:00), and the room temperature was regulated to 23±2°C. Humidity was not controlled.

Training of the animals under the Sidman avoidance situation was started from 10 weeks of age.

Sidman Avoidance Situation

The two sets of operant chambers, the behavior-controlling and data-recording apparatus used in the present experiment were of the same as those used in a previous

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experiment [6]. Each animal received the avoidance test in either of the two chambers throughout the training and drug testing sessions.

The Sidman avoidance schedule consisted of two temporal parameters of response-shock interval=30 sec and shock-shock interval=5 sec. The shock was an electric current of 150 V, 1.0 mA, 50 Hz AC, which was given to the rat by passing it through the stainless steel floor grid of the operant chamber for 0.3 sec. Each avoidance session consisted of 1 hr performance per day, and was held every other day during the period of training, and every day during the period of drug tests. The indices of rat's avoidance responses were response rate (lever-presses/min) and shock rate (number of shocks delivered/min). When all the rats achieved to exhibit a critical shock level of less than 0.5/min and displayed a stable response rate for several consecutive sessions, the drug tests were started.

Drugs

The drugs used and the doses given were methamphetamine HCl (MAMP: Philopon; Dainippon) 0.13, 0.25, 0.5 and 1.0 mg/kg; chlorpromazine HCl (CPZ: Contomin Inj.; Yoshitomi) 0.25, 0.5, 1.0 and 2.0 mg/kg; pilocarpine HCl (PILO: Sigma) 1.0, 2.0, 4.0 and 8.0 mg/kg; and scopolamine HBr (SCOP: Sigma) 0.063, 0.13, 0.25 and 0.5 mg/kg. The drugs were dissolved in a physiological saline vehicle, and the doses were expressed in the salt forms. Each injection volume was fixed to 1.0 ml/kg, and was given SC immediately before the start of sessions. The drug testing sessions were held twice a week (generally Wednesday and Saturday). The day before each drug test session the same dose volume of the saline vehicle was given alone as a control injection. On the other days the rat's avoidance response was observed without injection of the drugs or the saline vehicle to check stabilities of the baseline response and shock rates.

The drug tests were performed in an order of MAMP, CPZ, PILO and SCOP. During each drug test the doses given were changed randomly in each animal. The rat's avoidance response was observed for 1 hr after the drug administration. The data obtained during the first 20 min of each session were not included in the analysis in order to eliminate both warm-up effects and the individual variability in latency of minimum drug induced responses.

Statistical Analysis

The data were statistically analyzed by a two-factor analysis of variance (ANOVA). The first factor consisted of 5 levels of drug treatment (including saline as dose 0). The second factor was the rat strain (2 levels: Wistar and Fischer 344). In cases of significant overall F-scores, individual differences of the response and shock rates within and between the Wistar and Fischer 344 rats were assessed statistically by Student's t-test. They were considered significantly when p value was equal or less than 0.05.

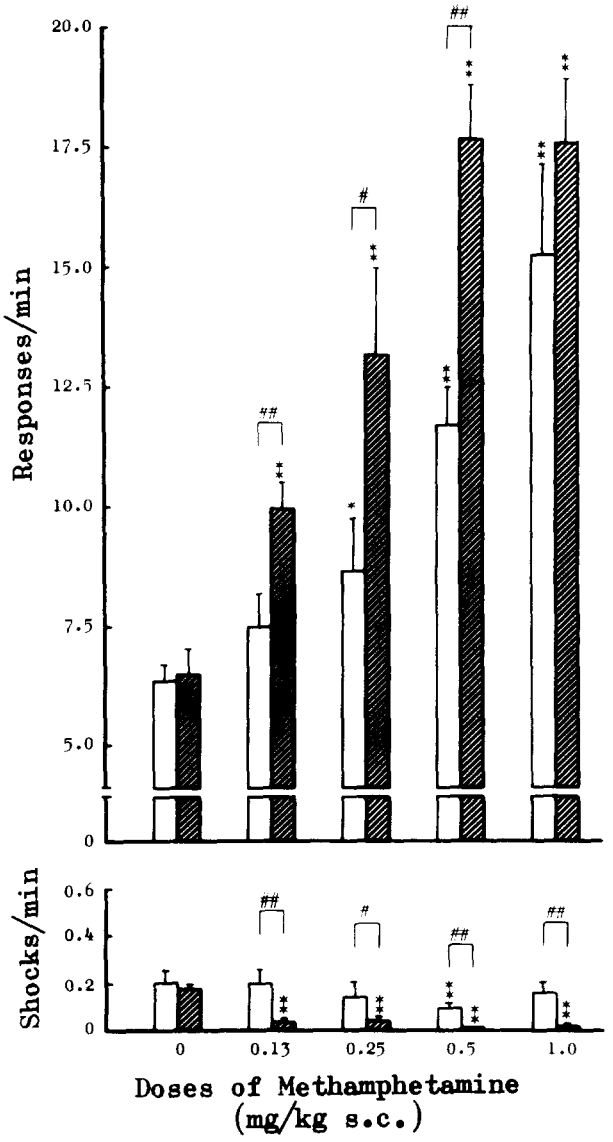

FIG. 1. Changes in mean response rate (upper panel) and shock rate (lower panel) on the Sidman avoidance situation in the Wistar and Fischer 344 strain rats after SC administration of methamphetamine 0.13–1.0 mg/kg. Open and hatched bars indicate the results in the Wistar and Fischer 344 strain rats, respectively. Each horizontal line attached to each bar indicates the standard error of the mean value of 12 rats. *Indicates statistically significantly different from the saline vehicle administered control value within each strain rats ($p<0.05$). **$p<0.01$. #Indicates statistically significantly different between the Wistar and Fischer 344 strain rats after the same dose of methamphetamine ($p<0.05$). ##$p<0.01$.

RESULTS

After 10–15 training sessions, all animals in both strain achieved a stable behavioral baseline of the avoidance response. The mean response and shock rates ±SE of 12 animals in the 16th–20th sessions were 5.91±0.23/min and 0.29±0.05/min, respectively, in the Wistar rats, and 6.20±0.31/min and 0.25±0.03/min, respectively, in the Fischer 344 rats. There was no significant difference in these value between the strains.

Slight variations in the baseline response and shock rates were observed during the drug testing period of more than 4 months. However, these variations were not statistically significant within and between the strains.

Figure 1 shows changes in the mean response rate (upper panel) and the shock rate (lower panel) after MAMP in the Wistar rats (open bars) and in the Fischer 344 rats (hatched

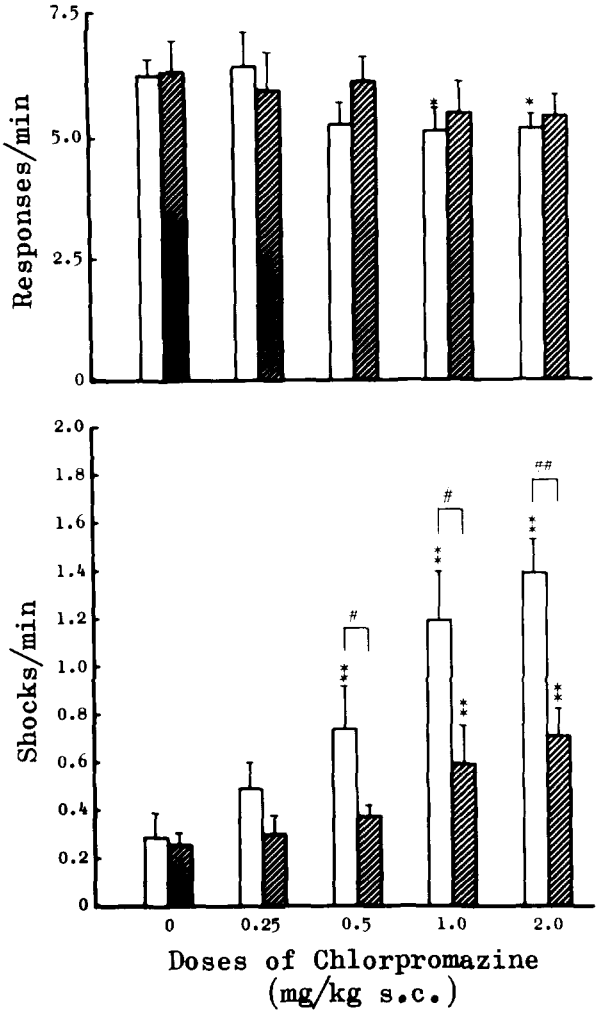

FIG. 2. Changes in mean response and shock rate on the Sidman avoidance situation in the Wistar and Fischer 344 strain rats after SC administration of chlorpromazine 0.25–2.0 mg/kg. The data are expressed in the same way as in Fig. 1.

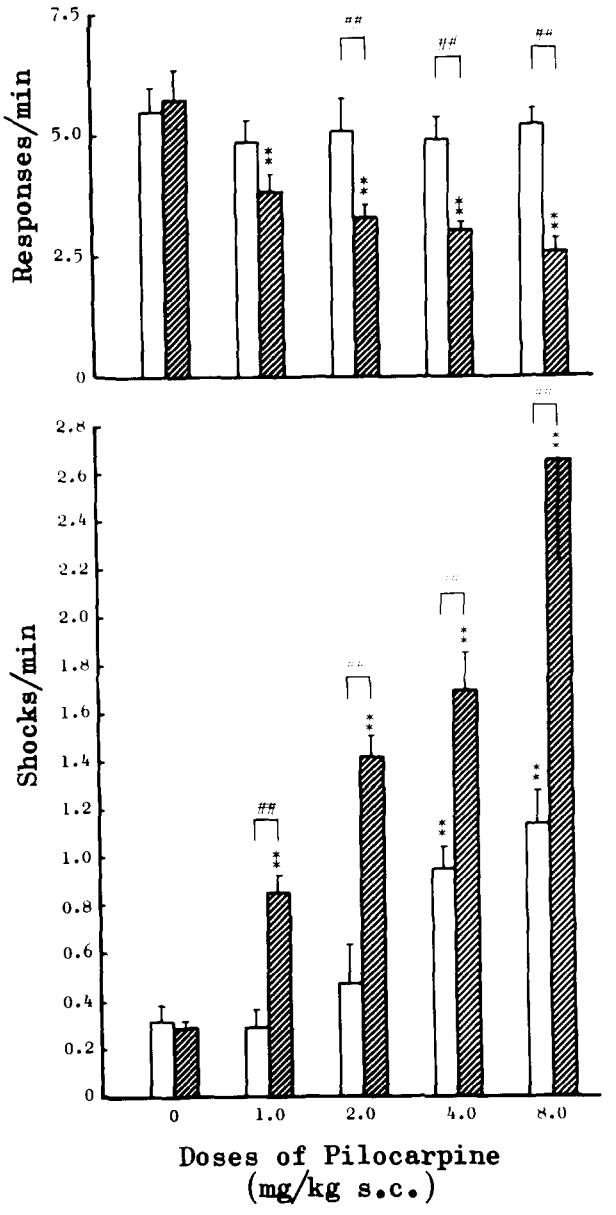

FIG. 3. Changes in mean response and shock rates on the Sidman avoidance situation in the Wistar and Fischer 344 strain rats after SC administration of pilocarpine 1.0–8.0 mg/kg. The data are expressed in the same way as in Figs. 1 and 2.

bars). MAMP showed a dose-dependent increase in the response rate and a decrease in the shock rate in both the strains. ANOVA revealed a significant dose-effect relation, and between strain differences for the response rate: $F(4,110)=65.23$, $p<0.001$ for drug treatment, and $F(1,110)=8.29$, $p<0.01$ for strain, and for the shock rate: $F(4,110)=22.94$, $p<0.001$ for drug treatment, and $F(1,110)=7.35$, $p<0.01$ for strain. In the Wistar rats, the response rate after MAMP 0.25–1.0 mg/kg were significantly higher than the saline administered control response rate ($p<0.05$ or 0.01, Student's t-test), and the shock rate after 0.5 mg/kg was significantly lower than the control shock rate ($p<0.05$). In the Fischer 344 rats, the changes in both response and shock rates after the administration of more than 0.13 mg/kg of MAMP were significantly different from the control values ($p<0.01$). The Wistar rats exhibited significantly lower response rate than the Fischer 344 rats after MAMP 0.13–0.5 mg/kg ($p<0.05$ or 0.01). The Wistar rats demonstrated a significantly higher shock rate than the Fischer 344 rats after MAMP 0.13–1.0 mg/kg ($p<0.05$ or 0.01).

Figure 2 shows changes in the response and shock rates in the Wistar and Fischer 344 rats after CPZ administration. CPZ slightly decreased the response rate, but increased markedly the shock rate. ANOVA revealed a slight significant dose-effect relation for the response rate, $F(4,110)=2.81$, $p<0.05$ for drug treatment, and a marked significant dose-effect relation, and between strain difference for the shock rate: $F(4,110)=75.24$, $p<0.001$ for drug treatment, and $F(1,110)=9.18$, $p<0.01$ for strain. The response rates in the Wistar rats after CPZ 1.0–2.0 mg/kg were significantly lower than the saline administered control value ($p<0.05$). The

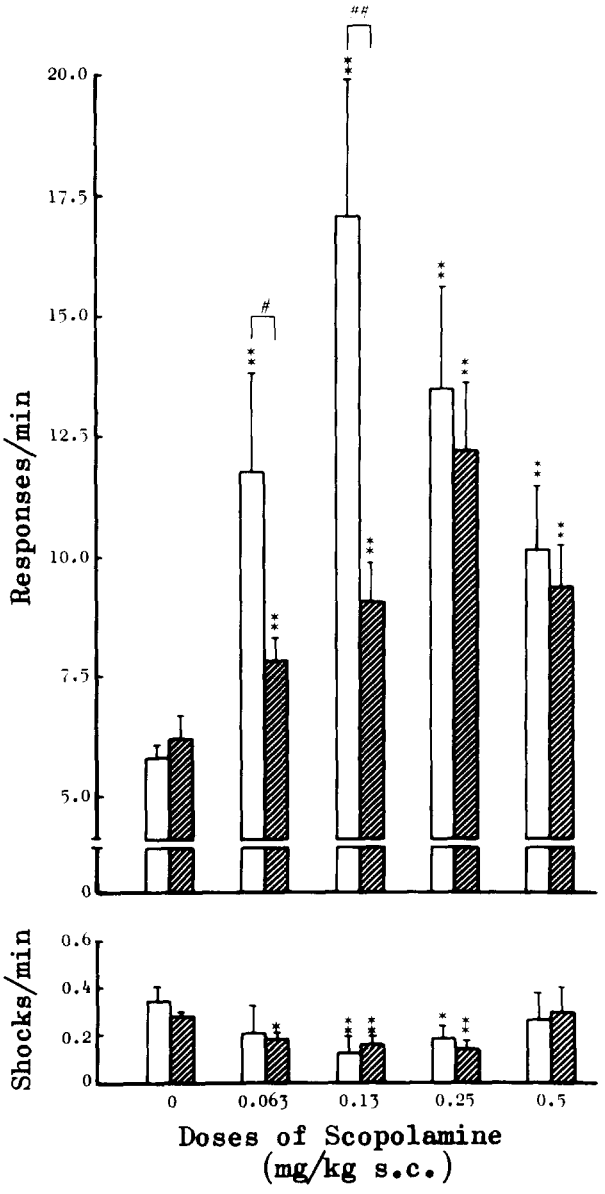

FIG. 4. Changes in mean response and shock rates on the Sidman avoidance situation in the Wistar and Fischer 344 strain rats after SC administration of scopolamine 0.063–0.5 mg/kg. The data are expressed in the same way as in Figs. 1, 2 and 3.

shock rates after CPZ doses of more than 0.5 mg/kg in the Wistar rats and those after 1.0 and 2.0 mg/kg in the Fischer 344 rats were significantly higher than the control values ($p<0.01$). No marked difference in the response rates was observed between the Wistar and Fischer 344 rats after CPZ 0.25–2.0 mg/kg. However, the Wistar rats exhibited significantly higher shock rate than the Fischer 344 rats after CPZ 0.5–2.0 mg/kg ($p<0.05$ or 0.01).

Figure 3 shows changes in the response and shock rates in the Wistar and Fischer 344 rats after PILO. PILO 1.0–8.0 mg/kg did not produce a marked change in the response rate in the Wistar rats, but there was a dose-dependent decrease in the response rate in the Fischer 344 rats. ANOVA revealed a significant dose-effect relation, and between strain differences for the response rate: $F(4,110)=3.92$, $p<0.01$ for drug treatment, and $F(1,110)=7.95$, $p<0.01$ for strain, and for the shock rate: $F(4,110)=121.02$, $p<0.001$ for drug treatment, and $F(1,110)=12.51$, $p<0.01$ for strain. The response rates in the Fischer 344 rats after 1.0–8.0 mg/kg were significantly lower than the saline vehicle administered control value ($p<0.01$). PILO induced a dose-dependent increase in the shock rate, and the rates in the Wistar rats after 4.0–8.0 mg/kg and those in the Fischer 344 rats after 1.0–8.0 mg/kg were significantly higher than the control values ($p<0.01$). The response rates in the Fischer 344 rats were significantly lower than those in the Wistar rats after PILO 2.0–8.0 mg/kg ($p<0.01$). The shock rates in the Fischer 344 rats were significantly higher than those in the Wistar rats after PILO 1.0–8.0 mg/kg ($p<0.01$).

Figure 4 shows changes in the response and shock rates in the Wistar and Fischer 344 rats after administration of SCOP. SCOP markedly increased the response rate and tended to decrease the shock rate. ANOVA revealed a significant dose-effect relation, and between strain difference for the response rate: $F(4,110)=41.74$, $p<0.001$ for drug treatment, and $F(1,110)=10.09$, $p<0.001$ for strain, and a slight significant dose-effect relation for the shock rate, $F(4,110)=2.74$, $p<0.05$ for drug treatment. The response rate in the Wistar and Fischer 344 rats after SCOP 0.063–0.5 mg/kg were significantly higher than the saline administered control values ($p<0.01$). However, the maximum increase in the response rate was observed in the Wistar rats after 0.13 mg/kg and in the Fischer 344 rats after 0.25 mg/kg. The shock rates in the Wistar rats after 0.13–0.25 mg/kg and in the Fischer 344 rats after 0.063–0.25 mg/kg were significantly lower than the control values ($p<0.05$ or 0.01). The Wistar rats exhibited significantly higher response rates than the Fischer 344 rats after SCOP 0.063–0.13 mg/kg ($p<0.05$ or 0.01). However, there was no marked difference in the shock rate between the two strains throughout the drug doses tested.

DISCUSSION

The changes in the Sidman avoidance response in rats after the administration of MAMP, CPZ, PILO and SCOP observed in the present experiment were consistent with data previously reported by Kuribara, and Kuribara and Tadokoro [4,5], and many workers (for example, see [8]). MAMP and SCOP facilitated the Sidman avoidance response with an increase in the response rate and a decrease in the shock rate, while CPZ and PILO suppressed the avoidance response with a decrease in the response rate and an increase in the shock rate. However, the mechanisms for the production of similar behavioral changes after MAMP and SCOP, and CPZ and PILO are different. MAMP stimulates the central catecholaminergic systems through an increase in the catecholamine release and an inhibition of the catecholamine reuptake at the synapses, while SCOP blocks the muscarinic-cholinergic receptors [2]. In contrast, CPZ blocks the catecholaminergic receptors, while PILO is one of the direct muscarinic-cholinergic agonists [2]. That is, the changes in avoidance response, either of facilitation or suppression, are produced through catecholaminergic systems after MAMP and CPZ, and through muscarinic-cholinergic systems after SCOP and PILO. It is, therefore, considered that the central catecholaminergic and muscarinic-cholinergic systems facilitate and suppress, respectively, the rat's conditioned avoidance response.

In addition, the present experiment demonstrated that, although the Wistar and Fischer 344 rats exhibited almost the same baseline response and shock rates during the no drug and/or saline vehicle administered sessions, there were marked differences between the two strains in the changes in response and shock rates after MAMP, CPZ, PILO and SCOP. Here, the Wistar rats were less sensitive to the avoidance facilitating effect of MAMP than the Fischer 344 rats, while the Wistar rats were more sensitive to the avoidance suppressing effect of CPZ than the Fischer 344 rats. In contrast, the Wistar rats were less sensitive to the avoidance suppressing effect of PILO and more sensitive to the avoidance facilitating effect of SCOP than the Fischer 344 rats. The strain differences of rat's behaviors and of the drug effects may be due to differences of the central neural activities. In fact, Coyle, Jr. *et al.* [1] reported strain differences among RHA (Roman high avoidance), RLA (Roman low avoidance) and Sprague-Dawley rats not only in the brain dopamine-β-hydroxylase activity and in the catecholamine turnover rates but also in the acquisition processes of the conditioned avoidance response and in the effects of d-amphetamine on it. Kuribara *et al.* [3] also reported strain differences among the Wistar, Sprague-Dawley and Holtzman rats concerning the acquisition processes and the baseline performances achieved under the Sidman and discriminated avoidance situations and the effects of diazepam on the avoidance response in these strains of rats.

The results obtained by the present experiment are somewhat different from those obtained by Coyle, Jr. *et al.* [1], and the previous results of Kuribara *et al.* [3]. This is because, the Wistar and Fischer 344 rats demonstrated almost identical acquisition processes and baseline response and shock rates on the Sidman avoidance situation [6]. One of the reasons for the observed difference in sensitivities to MAMP, CPZ, PILO and SCOP between the Wistar and Fischer 344 rats is likely due to different neural activities of both catecholaminergic and muscarinic-cholinergic systems between the two strains. Lloyd and Stone [7] reported, from the methylxantines-induced behavioral changes, that the Fischer 344 rats showed a higher sensitivity of the dopamine receptors than the Wistar rats. Wolf *et al.* [10] also reported that the Fischer 344 rats showed higher affinity for dopamine binding than the Zivic-Miller CD rats and the Fischer 344 rats demonstrated higher avoidance percentage than the Zivic-Miller CD rats. However, it is not clear why the Fischer 344 rats exhibit more sensitivity to both the catecholaminergic and muscarinic-cholinergic stimulating drugs, MAMP and PILO, and conversely less sensitivity to the blockers, CPZ and SCOP, than the Wistar rats.

The present results suggest that the rat strain differences must be considered for assessment of drug effects on the rat's avoidance response.

ACKNOWLEDGEMENTS

I thank Prof. S. Tadokoro, M. D., Ph. D. for his helpful discussions and suggestions on this paper, and also thank The Charles River Japan Inc., Atsugi for supplying me the Fischer 344 strain rats.

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