Pharmacology Biochemistry & Behavior, Vol. 23, pp. 1013–1018, 1985. © Ankho International Inc. Printed in the U.S.A. 0091-3057/85 $3.00 + .00

Effects of Psychoactive Drugs on Conditioned Avoidance Response in Mongolian Gerbils (*Meriones unguiculatus*): Comparison With Wistar Rats and dd Mice

HISASHI KURIBARA AND SAKUTARO TADOKORO

Division for Behavior Analysis, Behavior Research Institute, Gunma University School of Medicine 3-39-22 Showa-machi, Maebashi 371, Japan

Received 15 October 1984

KURIBARA, H. AND S. TADOKORO. *Effects of psychoactive drugs on conditioned avoidance response in Mongolian gerbils* (Meriones unguiculatus): *Comparison with Wistar rats and dd mice.* PHARMACOL BIOCHEM BEHAV **23**(6) 1013–1018, 1985.—In order to examine applicability of Mongolian gerbils as experimental animals in the field of behavioral pharmacology, the acquisition process of a discrete lever-press avoidance response and effects of psychoactive drugs thereon were studied. The results were compared with those in Wistar rats and dd mice. The gerbils learned the avoidance response much better than the rats and mice. The response rates established were higher in an order of the mice, the gerbils and the rats. Methamphetamine (0.13–1 mg/kg SC), cocaine (2.5–20 mg/kg SC) and morphine (1.3–10 mg/kg SC) facilitated the gerbils' avoidance response, i.e., eliciting a dose-dependent increase in the response rate and a slight increase in the avoidance rate. In contrast, chlorpromazine (0.5–4 mg/kg SC), haloperidol (0.025–0.2 mg/kg SC), pilocarpine (1–8 mg/kg SC), physostigmine (0.05–0.4 mg/kg SC), pentobarbital (5–20 mg/kg SC) and diazepam (0.5–2 mg/kg SC) suppressed the gerbils' avoidance response, i.e., eliciting a dose-dependent decrease in both the response and avoidance rates. Atropine (1.3–10 mg/kg SC) decreased only the response rate without a marked change in the avoidance rate. Scopolamine (0.031–0.5 mg/kg SC) did not produce a marked change in the avoidance response. The qualitative changes in the avoidance response in the gerbils were similar with those in the rats and mice after administration of central stimulants, antipsychotics, cholinergic agonists, central depressant and antianxiety drug, though the sensitivities were different. In particular, the gerbils showed a high sensitivity to the avoidance-suppressing effect of diazepam. The qualitative changes in the gerbils' avoidance response were different from those in the rats and mice after administration of cholinergic antagonists and narcotic drug, particularly after the latter drug.

Mongolian gerbils Wistar rats dd Mice Discrete avoidance response Acquisition processes
Central stimulants Antipsychotics Cholinergic agonists Cholinergic antagonists
Central depressant Antianxiety drug Narcotic drug

IN the field of behavioral pharmacology, mice and rats have been commonly used as the experimental animals. Recently, however, Mongolian gerbils (*Meriones unguiculatus*) have sometimes taken a share in this field. Since the history of this species as the experimental animal is much shorter than mice and rat, characteristics of the behaviors and drug-induced changes in the behaviors have not been established. Particularly, effects of psychoactive drugs on conditioned avoidance response, which have been studied using mice [16–19] or rats (cf. [28]), have not been studied in gerbils, even though characters of gerbils' avoidance response were investigated by many researchers [6–8, 22, 24, 25].

In this experiment, we investigated not only acquisition process of discrete lever-press avoidance response [11,13], but also effects of various types of psychoactive drugs on the avoidance response in gerbils. The results were compared with those in Wistar rats and dd mice. These two species have been considered to be excellent in acquisition of the avoidance response [13–15, 18, 19].

METHOD

Animals

The experimental animals used were 13 male gerbils, 21 male Wistar rats and 54 male dd mice. These animals were provided by breeding colony of Institute of Experimental Animal Research, Gunma University School of Medicine. The gerbils had been housed in groups of 3–5 in Plexiglas cages of 35 (W) × 25 (D) × 15 (H) cm with wooden-flake floor mat (White Flake: Charles River Japan Inc., Atsugi). The mice had been housed in groups of 8–10 in aluminum cages of 30 (W) × 20 (D) × 10 (H) cm with the floor mat. The rats were housed in groups of 3–5 in stainless steel wire mesh cages of 35 (W) × 25 (D) × 20 (H) cm. Solid diet (MF:

Oriental Yeast Co., Tokyo) and tap water were freely given to the animals except during times of avoidance sessions.

The breeding room was artificially illuminated by fluorescent lamps on a 12 hr light-dark schedule (light period; 6:00–18:00), and the room temperature was regulated to 22 ± 2°C.

Training of the animals in the discrete avoidance situation was started at the age of 10 weeks. At that time, the gerbils, rats and mice weighed 55–70 g, 280–320 g and 28–32 g, respectively.

Apparatus

The experimental chambers for gerbils and mice, 18 (W) × 9 (D) × 10 (H) cm, and for rats, 24 (W) × 20 (D) × 19 (H) cm, were made of acrylfiber and aluminum boards. A stainless steel lever of 2 cm in width, and 3.5 cm or 5 cm in length, vertically arranged, was set in the side wall of the chamber for gerbils or mice, respectively. A stainless steel lever of 3 cm in width and 3.5 cm in length, horizontally arranged, was set in the side wall of the chamber for rats. When a gerbil, a rat and a mouse pressed the lever with a force of more than 5 g, 10 g and 1.5 g, respectively, a microswitch attached to the lever was activated, and was recorded as a response. The behavior-controlling and data-recording apparatus (GT 7705 and GT 7715, respectively: O'hara and Co. Ltd., Tokyo) were the same with those used in previous experiments [16–19].

Discrete Avoidance Schedule

The temporal factors of the discrete avoidance schedule [11,13] were an intertrial interval of 25 sec and a warning duration of 5 sec. The warning signal was a pure tone of 800 Hz. The shock was an electric current of 100–150 V, 0.5 mA, 50 Hz AC, and was given for 3 sec during the training sessions and for 0.3 sec during drug-testing sessions. During the training sessions, an escape contingency was considered. The indices of the avoidance response were a response rate (lever-presses/min) and an avoidance rate (number of avoidance responses/number of avoidance trials) during the session.

Each avoidance session, consisting of 1 hr per day, was held every other day during the period of training and every day during the period of drug testing. After 10–15 sessions of a routine training procedure [16,18], the animals which achieved a critical level of avoidance rate (equal to or higher than 75%) were selected as good performing animals. The drug tests were carried out only using the good performing animals. All the avoidance tests were held between 9:00–18:00.

Drugs and Administration Schedules

The drugs tested were methamphetamine HCl (MAP: Philopon; Dainippon Pharm. Co., Osaka), cocaine HCl (COCA: Takeda Pharm. Co., Osaka), chlorpromazine HCl (CPZ: Contomin Inj.; Yoshitomi Pharm. Co., Osaka), haloperidol (HPD: Cerenace Inj.; Dainippon Pharm. Co.), pilocarpine HCl (PILO: Sigma Chemical Co., St. Louis, MO), physostigmine H_2SO_4(PHYSO: Sigma Chemical Co.), atropine H_2SO_4 (AT: Sigma Chemical Co.), scopolamine HBr (SCP: Sigma Chemical Co.), pentobarbital Na (PB: Nembutal Inj.; Abbott Lab., North Chicago, IL), diazepam (DZ: Cercine Inj.; Takeda Pharm. Co.) and morphine HCl (MOL: Takeda Pharm. Co.). PB and DZ were diluted in 5% propylene glycol vehicle, and the other drugs were dissolved or diluted in physiological saline vehicle. The doses administered (presented in Figs. 2–4) were shown in terms of the salt forms. Each volume administered was fixed to 1 ml/100 g body weight to gerbils and mice, and 1 ml/kg body weight to rats. All the drugs were administered SC immediately before start of the avoidance sessions, and the avoidance response of each animal was observed for 1 hr thereafter. The drug-testing sessions were held twice a week (generally Wednesday and Saturday), and the days before saline or propylene glycol was administered as the control sessions. On the other days except on Sunday, the avoidance response was observed without any treatment to check stability of the avoidance response. The orders of the drugs tested were at random among the animals. The doses of each drug administered proceeded from the lower to the higher in half of the animals and the reversed order in the other half of the animals. In each drug testing, 10–40 animals were used.

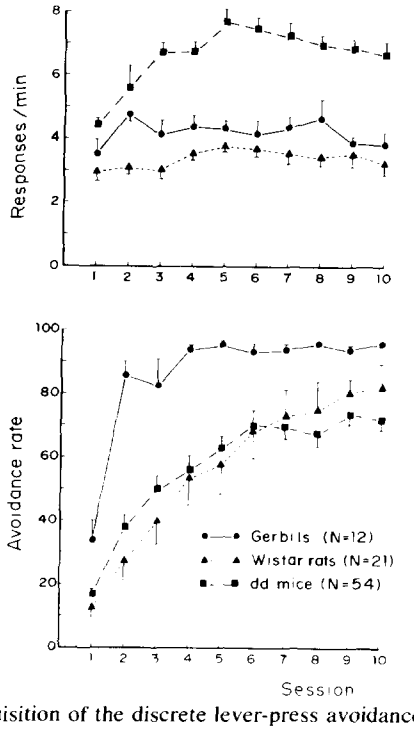

FIG. 1. Acquisition of the discrete lever-press avoidance response (intertrial interval=25 sec and warning duration=5 sec) in Mongolian gerbils, Wistar rats and dd mice. Each session consisted of 1 hr training (120 avoidance trials) per day. Upper panel: The mean response rate (lever-presses/min) with SEM. Lower panel: The mean avoidance rate (number of avoidance responses/number of avoidance trials) with SEM.

Statistical Analysis

Differences in means for the data were made with Student's t test. When p values were equal to or less than 0.05, they were considered to be significant difference. Comparisons between rats and mice have been reported in previous papers [16,17]. Therefore, the statistical comparisons of gerbils vs. rats, and gerbils vs. mice were carried out.

RESULTS

Acquisition of the Avoidance Response

One of the gerbils showed an avoidance rate of higher

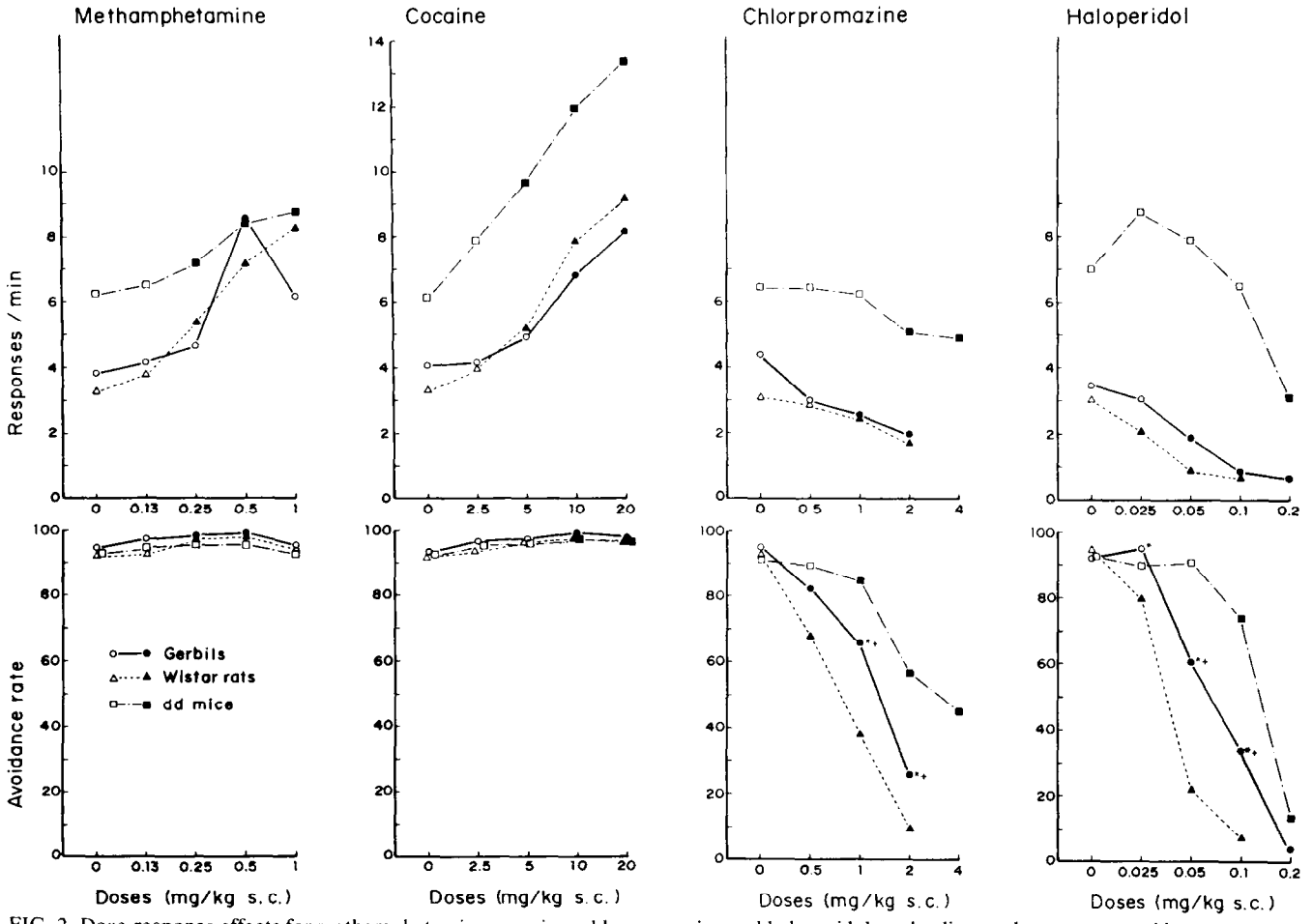

FIG. 2. Dose-response effects for methamphetamine, cocaine, chlorpromazine and haloperidol on the discrete lever-press avoidance response in Mongolian gerbils, Wistar rats and dd mice. Dose 0 denotes administration of physiological saline which was carried out on the days preceding the drug administration. The avoidance response was observed for 1 hr immediately after the administration of the drugs or saline. Upper panel: The mean response rates. Lower panel: The mean avoidance rates. Closed symbols indicate significant difference as compared with the control value (dose=0) within the species ($p<0.05$). * and +: Significant difference as compared with the values in the rats and mice, respectively, after the administration of the same drug dose ($p<0.05$). Ten to 40 animals were used in the experiment.

than 90% after the 3rd session. However, this animal exhibited not only much higher response rate (40–80/min) than the other gerbils but also an unstable response rate after the 5th session. Therefore, the data from this animal were excluded in calculation of mean values.

Figure 1 shows acquisition processes of the discrete avoidance response in the gerbils, Wistar rats and dd mice in terms of the response rate (upper panel) and the avoidance rate (lower panel). The gerbils rapidly learned the avoidance response, and 12/12 showed an avoidance rate of higher than 90% and a stable response rate of 3–5/min within 4 sessions of the training. The rats and mice gradually learned the avoidance response. On the 10th session, the rats and mice demonstrated mean avoidance rates of about 80% and 70%, respectively. When the training was continued until 15 sessions, the mean avoidance rates in the rats and mice achieved to 90% and 80%, respectively, and 19/21 of the rats and 43/54 of the mice showed avoidance rate of higher than 75%. These animals were considered to be good performing animals, and were used in the drug testing. The response rates established after the training were higher in order of the mice > gerbils > rats.

Effects of Psychoactive Drugs

Figures 2–4 show dose-response effects for MAP (0.13–1 mg/kg SC), COCA (2.5–20 mg/kg SC), CPZ (0.5–2 or 4 mg/kg SC) and HPD (0.025–0.1 or 0.2 mg/kg SC) (Fig. 2), for PILO (1–4 or 8 mg/kg SC), PHYSO (0.05–0.2 or 0.4 mg/kg SC), AT (1.3–10 mg/kg SC) and SCP (0.031–0.5 mg/kg SC) (Fig. 3), and for PB (4–20 mg/kg SC), DZ (0.5–2 or 4 mg/kg SC) and MOR (1.3–10 mg/kg SC) (Fig. 4), respectively.

MAP and COCA, central stimulants, facilitated the avoidance response, i.e., eliciting a marked increase in the response rate and a slight increase in the avoidance rate. After MAP, the highest increase in the response rate was observed when 0.5 mg/kg was administered to the gerbils, and 1 mg/kg to the rats and mice. After COCA, the highest increase in the response rate was observed when 20 mg/kg was administered to the three species. The avoidance rate slightly, but significantly increased after MAP 0.25–0.5 mg/kg in the gerbils and rats, and after COCA 10–20 mg/kg in the three species. There was no remarkable difference in the changes in the avoidance rate among the three species after administration of MAP and COCA.

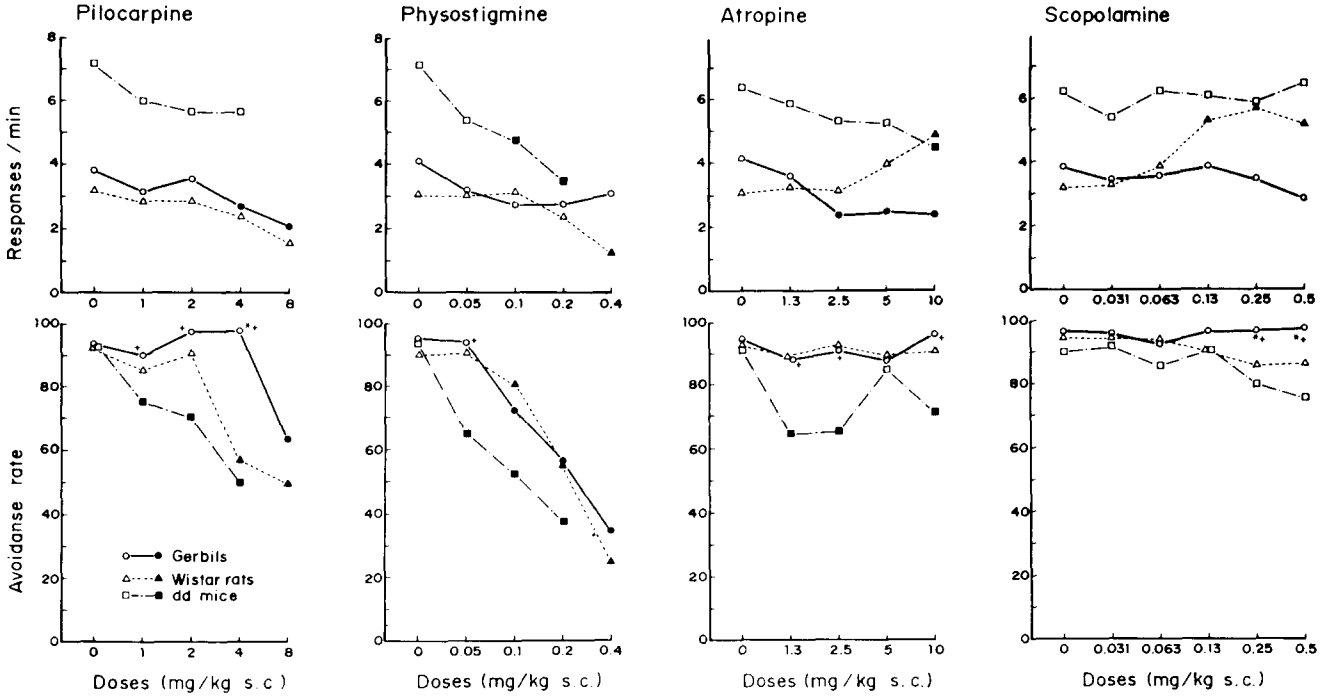

FIG. 3. Dose-response effects for pilocarpine, physostigmine, atropine and scopolamine on the discrete lever-press avoidance response in Mongolian gerbils, Wistar rats and dd mice. The data are shown in the same way as in Fig. 2.

Both CPZ and HPD, antipsychotic drugs, suppressed the avoidance response, eliciting a dose-dependent decrease in both the response and avoidance rates. However, there were species differences in the sensitivity to the avoidance suppressing effects. The dose-response curves of the avoidance rate revealed that the sensitivity to CPZ and HPD was higher in an order of the rats>gerbils>mice.

PILO and PHYSO, muscarinic-cholinergic agonists, suppressed the avoidance response. The dose-response curves of the avoidance rate revealed that the sensitivity to PILO was higher in an order of the mice>rats>gerbils, and to PHYSO in an or of the mice>gerbils≒rats.

AT, a muscarinic-cholinergic antagonist, at the higher doses, slightly but significantly decreased the response rate in the gerbils and mice, while increased it in the rats. No marked change in the avoidance rate was observed after administration of AT to the gerbils and rats. However, the mice exhibited a significant decrease in the avoidance rate after 1.3, 2.5 and 10 mg/kg of AT. SCP, another muscarinic-cholinergic antagonist, did not produce a marked change in the response rate in the gerbils and mice, while it increased it in the rats when doses of 0.13 or more were administered. The gerbils and rats did not exhibit a marked change in the avoidance rate after SCP. However, the mice tended to show a slight decrease in the avoidance rate after SCP at the higher doses.

PB and DZ, a central depressant and an antianxiety drug, respectively, suppressed the avoidance response, eliciting a dose-dependent decrease in the response and avoidance rates except for the response rate in the rats after DZ.The rats did not show a significant change in the response rate after DZ. The dose-response curves of the avoidance rate revealed that the sensitivity to PB was higher in an order of the gerbils>rats>mice, and to DZ in an order of the gerbils>rats ≒ mice. In particular, the gerbils demonstrated much higher sensitivity to the avoidance-suppressing effect of DZ than the other two species.

MOR, a narcotic drug, facilitated the avoidance response in the gerbils, eliciting a dose-dependent increase in the response rate and a slight increase in the avoidance rate at doses of 2.5–5 mg/kg. In contrast, MOR suppressed the avoidance response in the rats and mice, eliciting a dose-dependent decrease in both the response and avoidance rates in the rats, and a dose-dependent decrease in the avoidance rate without a marked change in the response rate in the mice.

DISCUSSION

First, the present experiment demonstrated that gerbils readily learn the discrete lever-press avoidance response. The acquisition speed was much faster and the avoidance rate established is higher than those of Wistar rats and dd mice, which have been considered to show a good avoidance response [13–15, 18, 19]. This result is identical with that reported by Powell *et al.* [25] that the learning of free-operant lever-press avoidance response was superior in the gerbils than in albino and hooded rats. On the other hand, Osborne *et al.* [22] reported that gerbils learned a discrete shuttle avoidance response almost in the same speed as in rats, and that the former showed a longer warm-up period than the latter.

Mean response rate established in the gerbils was about 3.5/min, which was slightly higher and much lower than those in Wistar rats and dd mice, respectively. This result suggests that the gerbils as well as the rats can discriminate fairly well the warning signal.

In order to study effects of psychoactive drugs on avoidance responses, a repetition of training of animals is

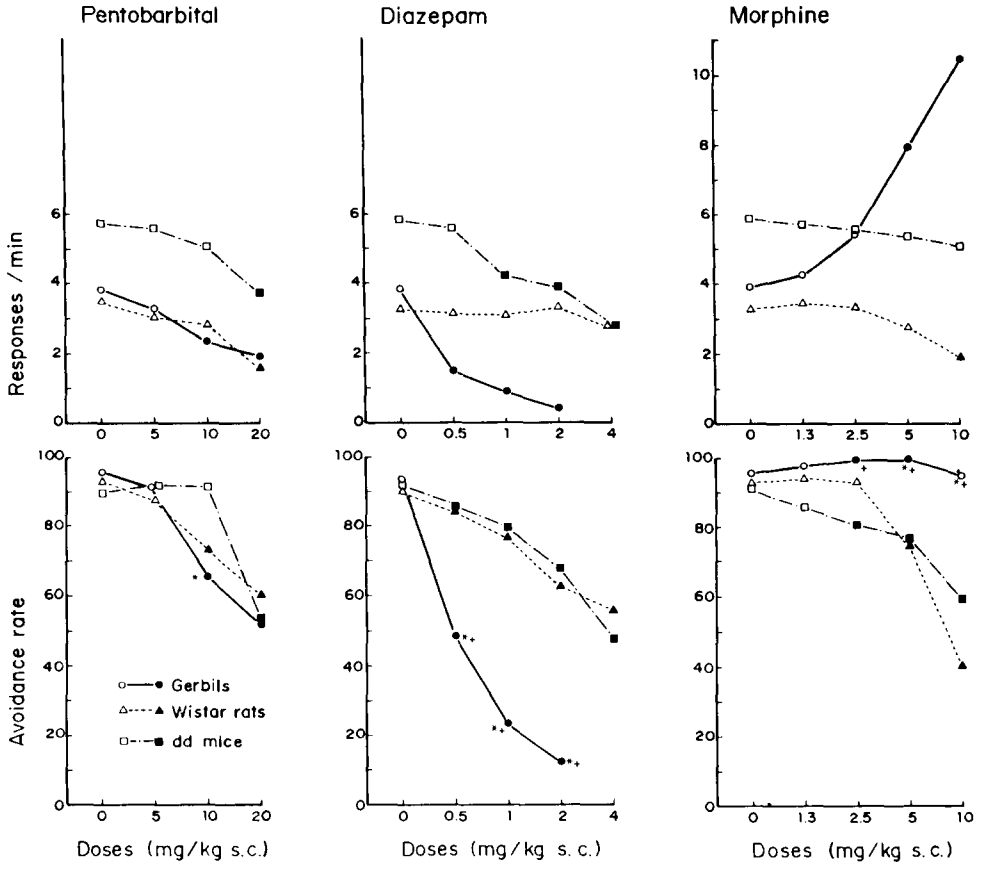

FIG. 4. Dose-response effects for pentobarbital, diazepam and morphine on the discrete lever-press avoidance response in Mongolian gerbils, Wistar rats and dd mice. The data are shown in the same way as in Fig. 2. However, in the experiments of pentobarbital and diazepam, 5% propylene glycol was administered on the control sessions (dose=0).

required until an establishment of a high level of the avoidance rate and a stable response rate. A rapid acquisition of conditioned lever-press avoidance response in the gerbils suggests that this species has an advantage as the experimental animal in the avoidance test.

The qualitative and quantitative change in the avoidance response in the gerbils was identical with those in the rats and mice after central stimulants. However, the gerbils showed a lower response rate after MAP 1 mg/kg than after 0.5 mg/kg. The reason for this result is not explained clearly. However, it has been reported that higher doses of amphetamines sometimes disrupt conditioned behaviors [3,20].

When antipsychotics, cholinergic agonists, central depressant and antianxiety drug were administered, the suppression of the avoidance response in the gerbils were qualitatively identical with those in the rats and mice. However, there were differences in the quantitative changes dependent on the types of drugs. The characters of the avoidance-suppressing effects are different among these drugs. The effects of antipsychotics and cholinergic agonists appear through catecholaminergic (in particular dopaminergic) and cholinergic systems in the brain, respectively [10]. General depressant and antianxiety drugs show sedative effect as well as muscle-relaxing effect. It is therefore considered that the neural activities of the brain in the gerbils are different from those in the rat and mice. It is also considered that the gerbils show an extremely high sensitivity to sedative and muscle-relaxing effects of central depressant and antianxiety drugs. Francis *et al.* [5] and Pettijohn [23] also reported that the gerbils demonstrated a higher sensitivity than rats to the behavior suppressing effects of PB and alcohol, respectively.

On the other hand, the gerbils demonstrated qualitatively different changes in the avoidance response from those of the rats and mice after administration of cholinergic antagonists. This result also suggests different neural activities of cholinergic systems in the brain among three species.

The most interesting result obtained was the changes in the avoidance response after administration of narcotic drug. It has been reported that narcotic drugs show both behavior facilitating and suppressing effects through affecting catecholaminergic [1, 12, 21, 26, 27], cholinergic [4,21] and serotonergic [2, 9, 12, 21, 26, 29] systems in the brain. A dose-dependent increase in the response rate observed in the gerbils after administration of MOR suggests that the species easily reflects the behavior, in particular avoidance facilitating effect of MOR. However, dd mice showed a marked increase in the ambulatory activity after MOR [19], though this species shows a marked suppression of the avoidance response. It can be considered that the avoidance response and ambulatory activity are mediated by different neural systems. A further study is required to find a correlation between changes in the avoidance response and ambulatory

activity after administration of psychoactive drugs.

In summary, the present experiments demonstrated that the gerbils sometimes show a different change in the avoidance response from those in rats and mice after administration of psychoactive drugs. The species difference may be mainly due to difference in the neural activities in the brain. However, we did not examine a neurochemical study in the present experiment. A further study is required to elucidate behavioral as well as neurochemical and neurophysiological characteristics of the gerbils.

ACKNOWLEDGEMENT

We thank Mr. M. Shinoda (Institute of Experimental Animal Research, Gunma University School of Medicine) for supplying Mongolian gerbils.

REFERENCES

1. Buxbaum, D. M., G. G. Yarbrough and M. E. Carter. Biogenic amines and narcotic effects. I. Modification of morphine-induced analgesia and motor activity after alteration of cerebral amine levels. *J Pharmacol Exp Ther* **185:** 317–327, 1973.
2. Cheney, D. L. and A. Goldstein. The effect of p-chlorophenylalanine on opiate-induced running, analgesis, tolerance and physical dependence in mice. *J Pharmacol Exp Ther* **177:** 309–315, 1971.
3. Demellweek, C. and A.-J. Goudie. Behavioural tolerance to amphetamine and other psychostimulants. The use for considering behavioural mechanisms. *Psychopharmacology (Berlin)* **80:** 287–307, 1983.
4. Domino, E. F. and A. Wilson. Effects of narcotic analgesic agents and antagonists on rat brain acetylcholine. *J Pharmacol Exp Ther* **184:** 18–32, 1973.
5. Francis, N., E. Marley and J. D. Stephenson. Effects of spiperone on self-stimulation and other activities of the Mongolian gerbils. *Br J Pharmacol* **63:** 43–49, 1978.
6. Galvani, P. F., M. T. Twitty and K. M. Foster. Intermittent reinforcement and intertrial interval effects on shuttlebox avoidance in the gerbil. *Bull Psychon Soc* **5:** 225–227, 1975.
7. Galvani, P. F. Effects of percentage of shock avoidance on avoidance behavior in gerbils. *Bull Psychon Soc* **7:** 548–550, 1976.
8. Galvani, P. F. and M. T. Twitty. Effects of interval and exteroceptive feedback duration on discriminative avoidance acquisition in the gerbil. *Anim Learn Behav* **6:** 166–173, 1978.
9. Giarman, N. J. and G. Pepeu. Drug induced change in brain acetylcholine. *Br J Pharmacol* **19:** 226–234, 1962.
10. Goodman, L. S. and A. Gilman. *The Pharmacological Basis of Therapeutics, 4th edition.* New York: The MacMillan Company, 1970.
11. Hoffman, H. S., M. Fleshler and H. Chorney. Discriminated bar press avoidance. *J Exp Anal Behav* **4:** 309–316, 1961.
12. Hollinger, M. Effects of reserpine, α-methyl-p-tyrosine, p-chlorophenylalanine, and pargyline on levorphanol induced running activity in mice. *Arch Int Pharmacodyn* **179:** 419–424, 1969.
13. Kuribara, H., K. Ohashi and S. Tadokoro. Rat strain differences in the acquisition of conditioned avoidance responses and in the effects of diazepam. *Jpn J Pharmacol* **26:** 725–735, 1976.
14. Kuribara, H., T. Hayashi, K. Ohashi and S. Tadokoro. Methodological problems in observing learning and memory by operant conditioning in rats. In: *Neurobiological Basis of Learning and Memory*, edited by Y. Tsukada and B. W. Agranoff. New York: John Wiley and Sons, Inc., 1980, pp. 213–232.
15. Kuribara, H. Behavioral characteristics of F344/DuCrj (Fischer) strain rats: Spontaneous motor activity and acquisition of conditioned avoidance responses. *Exp Anim* **29:** 327–333, 1980 (abs. in English, and text in Japanese).
16. Kuribara, H. and S. Tadokoro. Comparison of susceptibilities to the effect of antipsychotic drugs on lever-press avoidance responses between mice and rats. *Jpn J Pharmacol* **33:** 1127–1133, 1983.
17. Kuribara, H. and S. Tadokoro. Differences in cholinergic agonist- and cholinergic antagonist-induced changes in avoidance responses between dd mice and Wistar rats. *Jpn J Psychopharmacol* **3:** 159–166, 1983.
18. Kuribara, H. and S. Tadokoro. Conditioned lever-press avoidance response in mice: Acquisition processes and effects of diazepam. *Psychopharmacology (Berlin)* **82:** 36–40, 1984.
19. Kuribara, H. and S. Tadokoro. Strain differences in lever-press avoidance response in mice: Acquisition processes of discrete avoidance response and effects of psychotropic drugs. *Jpn J Psychopharmacol* **4:** 29–30, 1984 (text in Japanese).
20. McMillan, D. E. and J. D. Leander. Effects of drugs on schedule-controlled behavior. In: *Behavioral Pharmacology*, edited by S. D. Glick and J. Goldfarb. St. Louis: The C. V. Mosby Company, 1976, pp. 85–139.
21. Oliverio, A. Genetic factors in the control of drug effects on the behaviour of mice. In: *The Genetics of Behaviour*, edited by J. H. F. Van Abeelen. Amsterdam: North-Holland Pub. Company, 1974, pp. 375–395.
22. Osborne, G. L., W. F. Caul and R. Vanstrum. Avoidance differences between rats and gerbils. *Anim Learn Behav* **4:** 151–159, 1976.
23. Pettijohn, T. F. Effects of alcohol and caffeine on wheel running activity in the Mongolian gerbil. *Pharmacol Biochem Behav* **10:** 339–341, 1979.
24. Powell, R. W. and L. Palm. Analysis of warm-up effects during avoidance in the Mongolian gerbil. *Bull Psychon Soc* **9:** 329–332, 1977.
25. Powell, R. W., M. D. Curley and L. J. Palm. A comparison of signaled vs. unsignaled free-operant avoidance in Mongolian gerbils and domesticated rats. *Bull Psychon Soc* **12:** 415–418, 1978.
26. Racagni, G., F. Cattabeni and R. Paoletti. A biochemical analysis of strain differences in narcotic action. In: *Animal Models in Psychiatry and Neurology*, edited by I. Hanin and Z. Usdin. Oxford: Pergamon Press, 1977, pp. 315–319.
27. Rethy, C. R., C. B. Smith and J. E. Villarreal. Effects of narcotic analgesics upon the locomotor activity and brain catecholamine content of the mouse. *J Pharmacol Exp Ther* **176:** 472–479, 1971.
28. Seiden, L. S. and L. A. Dykstra. *Psychopharmacology, a Biochemical and Behavioral Approach.* New York: Van Nostrand Reinhold Company, 1977.
29. Yarbough, G. G., D. M. Buxbaum and E. Sanders-Bush. Biogenic amines and narcotic effects. II. Serotonin turnover in the rat after acute and chronic morphine administration. *J Pharmacol Exp Ther* **185:** 328–335, 1973.