Drug Effects on Cognitive Function in Mice Determined by the Non-Matching to Sample Task Using a 4-Arm Maze

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ABSTRACT—A new task for the analysis of drug effects on the cognitive function in mice was investigated using a 4-arm maze with three selectable arms. Each trial consisted of a forced run either to the right or left arm containing a food pellet, which was changed for each trial, followed by a free-choice run after a delay (0–120 sec). The correct response was to turn to the arm 180 degrees opposite from the forced one. Entrance into the center arm in the free-choice run, which was called the non-reward response, was not reinforced at any time. As the delay became longer, correct responses decreased, but non-reward response errors remained unchanged in the well-trained mice. Without increasing the non-reward response, scopolamine and atropine, but not methylscopolamine, decreased the correct response in a delay-dependent manner at a low dose range, while diazepam did so in a delay-independent manner. Physostigmine ameliorated scopolamine-induced impairment in performance, but had less effect on the delay-induced decrease in the correct response. Other tested drugs (chlorpromazine, haloperidol, apomorphine, phentolamine, propranolol, lithium chloride, ketamine, and caffeine) had no significant effect on performance. These results suggest that CNS muscarinic blockades and diazepam treatment selectively attenuate working memory in different ways.

A rodent model of dementia is necessary to develop antidementia drugs such as cognitive enhancers, cerebral metabolism activators, or drugs which retard the progression of dementia. Recently, senescence-accelerated prone mice (SAM) have been noted as likely candidates for an aging model with learning and memory deficit (1), but simple and reliable memory tests have not been established in mice. Therefore, there is not much information about specific drug effects on memory in mice, although many researchers have reported about drug effects on cognitive functions in rodents.

In a memory test at the animal level, Honig (2) proposed a new memory classification consisting of 'reference' and 'working' memory. The reference memory is defined as information based on trial-independent invariant stimulus-response contingencies, and the working memory defined as information based on trial-dependent contingencies that varied from trial to trial. The passive and active avoidance responses in rats and mice were first chosen as screening methods for cognitive enhancers. Successful performance of these tasks depended mainly on the reference memory. On the other hand, the radial maze task
and the non-matching to sample task using a T-maze have been frequently used on rats to test working memory. However, these common methods could not easily detect the specific effects of drugs on memory subtypes, since both reference and working memories were responsible for the correct performance of these tasks. Accordingly, special schedules or apparatus were needed to differentiate between reference and working memory. For example, in the radial maze task, separation of reference and working memory became possible because food pellets were placed only in the arms fixed beforehand (3). On the other hand, we had to use another simultaneous discrimination task for separating reference memory in the T maze.

In this study, mice were trained by the non-matching to sample task, which easily distinguishes reference and working memories due to the procedure in the 4-arm maze with 3 selectable arms. Each trial of this task consisted of a forced run either to the right or left arm, which was changed for each trial, followed by a free-choice run. The correct response was to turn to the arm 180 degrees opposite from the forced one. Accordingly, this new task required judgment based on both reference and working memory for correct performance, because the center arm choice was not reinforced at any time, and the correct side arm (right or left) was changed for each trial. After the indices of reference and working memories in this task were characterized according to delay-dependency, drug effects on performance were analyzed to confirm the validity of this task as a method for the assessment of drug effects on memory.

MATERIALS AND METHODS

Animals

The subjects were 19 male Slc : ddY mice obtained at 4 weeks of age. The present study began when the mice were 6 weeks old and continued for 5 months. Throughout the experiment the mice were caged with free access to water in an air-conditioned animal room (23 ± 2°C and 60 ± 20% humidity) that was illuminated from 6:00 – 18:00. They were maintained on a restricted feeding schedule so that they would be in a state of hunger; specifically, they were given 3 g of solid feed (MF, Oriental Yeast Co., Tokyo) after everyday training. The training occurred during the daylight period of the L:D cycle.

Apparatus

Behavioral testing was conducted in a wooden 4-arm maze with a starting runway (length = 160 mm, width = 78 mm) and 3 selectable arms (length = 240 mm, width = 56 mm). Side walls (120 mm high) extended the length of each arm. The center arm had a white-painted sidewall and a floor made of wood; the right arm had a horizontal black-and-white striped sidewall and a floor which was covered with a celluloid sheet; and the left arm had a black sidewall and a floor which was covered with a sheet of sandpaper. A start box (length = 100 mm, width = 78 mm, height = 120 mm) was attached to the end of the starting runway. Small plastic cups, mounted at the end of each arm, served as receptacles for reinforcers. Guillotine doors were inserted at the exit of the start box and at each arm entrance. The room housing the maze was always filled with masking noise from a motor fan.

Behavioral procedure

Acquisition training: For 2 days before the start of training, mice in a state of hunger were individually placed in the startbox of the maze, and then permitted to explore the inside of the maze. A food pellet (20 mg precision pellet, O’hara & Co., Ltd., Tokyo) was put in each food cup, and all the doors were opened. This adaptation was continued until the mice finished 3 pellets. After adaptation, the mice started training on the non-matching to sample task.

Each trial consisted of forced and free-choice runs (Fig. 1). A forced run either to the right or left arm with a food pellet was followed by a free-choice run. A correct re-
response (CR) was to turn to the arm 180 degrees opposite from the forced arm, and this was rewarded with a food pellet. Following an incorrect response (IR) (that is, entering the forced arm), an animal was permitted to re-select other arms without reinforcement. Entrance into the center arm, which was designated as the non-reward response (NR), consisting of entrance into the center arm, was never rewarded. S: start box, ○: food tray with a food pellet, ●: food tray without a food pellet.

was changed for each trial according to the Gellermann series (1933). As a general rule, each day's training, conducted under a 0-sec delay condition, consisted of 5 trials, and the selected forced arm ratio was 5:5 between the right and left arm in 10 trials every 2 days (5 trials per day). The mice were given such training 5 days a week until they showed a CR rate of more than 80%.

**Delay training:** The effect of delay on this task was investigated in 15 mice showing a CR rate greater than 80% (another 4 mice were used in the preliminary experiment). Delay was defined as the time interval from re-entry to the startbox after finishing eating a pellet in the forced run to the opening of the door in the free-choice run. The mice waited in the startbox during the delay period. Five conditions of 0, 15, 30, 60 and 120-sec intervals were adopted; and the training, consisting of 10 trials (2 trials after each delay) in a day, was carried out twice on alternate days. The 5 delays were randomly arranged in all mice. In the day between the delay test, the mice had no training.

**Drug test training:** At first, 4 trials under a 0-sec delay were given as a training warm up, and then drug administration was followed by test training with 10 trials. In the 10 trials, the selected forced arm ratio was 5:5 between the right and left arms, and 2 delays of 0 and 30 sec for all drugs except physostigmine and caffeine (0 and 60 sec) were inserted in random order. The 19 mice showing a CR rate greater than 80% were randomly divided into two groups. One group (n = 10) was assigned scopalamine (SCO), atropine (ATO), physostigmine (PHY), SCO + PHY, haloperidol (HAL), propranolol (PRO), and apomorphine (APO); the other group (n = 9) was given methylscopolamine (MSCO), diazepam (DZ), chlorpromazine (CPZ), phentolamine (PHE), lithium (LI), ketamine (KET), and caffeine (CAF) in this order. The dose range of each drug was determined by behavioral observation following preliminary administration of the drug in other mice.

The following selected drugs and doses were
subcutaneously administered: scopolamine hydrobromide (Tokyo Kasei Kogyo, Tokyo): 0.05, 0.1, 0.2, and 0.4 mg/kg; atropine sulfate (Nacalai Tesque, Kyoto): 5, 10, and 20 mg/kg; scopolamine methylbromide (Tokyo Kasei Kogyo): 0.2 and 0.4 mg/kg; diazepam (Cercine Inj., Takeda Chemical Ind., Osaka): 0.5, 1, 2, and 4 mg/kg; haloperidol (Cerenace Inj., Dainippon Pharm, Osaka): 0.05, 0.1, and 0.2 mg/kg; chlorpromazine hydrochloride (Contomine Inj., Yoshitomi Pharm., Osaka): 0.5 and 1 mg/kg; phentolamine mesylate (Regitin Inj., Ciba-Geigy (Japan), Takarazuka): 10 and 20 mg/kg; propranolol hydrochloride (Inderal Inj., I.C.I. Pharm.-Sumitomo, Osaka); lithium chloride (Nacalai Tesque): 50 and 100 mg/kg; and ketamine hydrochloride (Ketalar Inj., Sankyo, Tokyo). Physostigmine sulfate (Tokyo Kasei Kogyo), apomorphine hydrochloride (Sigma Chemi., St. Louis, MO), and caffeine (Nacalai Tesque) were intraperitoneally administered at doses of 0.025, 0.05, and 0.1 mg/kg, 0.1, 0.2, and 0.4 mg/kg and 10, 20, and 40 mg/kg, respectively. The combined effect of SCO and PHY was observed following the co-administration of SCO 0.2 mg/kg, s.c. and PHY 0.025, 0.05, or 0.1 mg/kg, i.p. All the drugs without APO were administered 10 min before the start of the test; APO was administered immediately before. DZ was diluted by 5% propylene glycol, and the others were dissolved in or diluted by a physiological saline. Each vehicle corresponding to the test drug was administered in the control test. As a general rule, the doses of each drug administered proceeded from lower to higher in half of the animals and in the reverse order in the other half. Testing of each drug was done twice a week; and on the other days (except holidays), the mice were trained under 0-sec delay without any treatment to maintain stable performance in the task. The following indices of drug effects were adopted in this task: CRs at each delay, NRs, and running time (RT), which was defined as time spent in the forced run from the startbox to the food cups. When more than 20 sec of RT was observed in the forced run, the trial was stopped and considered to be impossible. Drug-induced changes in appearance were also carefully observed.

Statistical analysis

Changes of response rates depending on the training and the delay were analyzed using ANOVA. The two overall mean values of CR rates and RTs between the control and each drug treatment test were statistically compared by the Wilcoxon matched-pairs rank test (two-tailed). Regarding NR rates, when the mean value difference between the control and the treatment was more than 15%, it was judged to be significant for convenience, since a 0% mean value in NR rate was frequently observed in the group of well-trained mice.

RESULTS

Figure 2 shows the acquisition process of the non-matching to sample task (5 trials/day under 0-sec delay condition) in the 4-arm maze in 10 mice (the other 9 mice were trained in other preliminary schedules). During the training process, the mice showed an increase in CR and a decrease in NR. These changes were shown to be significant (F5,54 = 10.75, P < 0.01 and F5,54 = 16.81, P < 0.01, respectively, for rates X blocks of 10 trials) by ANOVA. The IR rate was less than 20% in the early stage of training, and this tendency continued throughout the training. All mice tested learned this task well, showing a more than 80% CR rate and less than 5% NR rate within 60 trials. CR rates decreased depending on delay (F4,70 = 8.35, P < 0.01 by ANOVA) to 55% for the 120-sec delay. On the other hand, any delay inserted did not increase NR, i.e., delay-induced errors were almost IR (Fig. 3).

Figures 4–6 show the effects of SCO, MSCO, and ATO on task performance under two delay conditions (0 and 30 sec). Vehicle treated mice exhibited CR rates of more than 90% and 70–80% with 0 and 30-sec delays, respectively. NR rates of less than 5% were observed with all delays. RTs were 1.5–3.0
Fig. 2. Acquisition process of non-matching to sample task (delay = 0 sec, intertrial interval = 60 sec) in the 4-arm maze in mice. The training session started after habituation to the apparatus and consisted of 5 trials per day. In this figure, each point represents the choice rate of 10 trials per 2 days; thus the acquisition process for a period of 12 days is indicated. ●: correct response, ○: non-reward response, ■: incorrect response.

Fig. 3. Effect of interval between a forced-sample and free-choice run (delay) on non-matching to sample task in the 4-arm maze in mice. Mice (n = 10) were tested under 5 delay conditions for 2 days (10 trials per day). Each point represents the choice rate of 40 observations. Two broken lines of 50 and 33.3%, respectively, show the chance level in two and three choice situations. ●: correct response, ○: non-reward response.

Fig. 4. Effect of scopolamine on non-matching to sample task under delays of 0 and 30 sec in the 4-arm maze in mice. Scopolamine was administered 10 min before the start of a test session consisting of 10 trials. A delay of either 0 or 30 sec was assigned to half of the 10 trials and each trial was carried out in random order. Each point represents the mean with S.E. of 10 mice. *P < 0.05, **P < 0.01, significant difference from the control (dose = 0) by the Wilcoxon matched-pairs rank test (two-tailed). ●: correct responses for 0 sec delay, ○: correct responses for 30 sec delay, ■: non-reward responses, ●: running time.
sec. The same results were obtained in all vehicle treated mice in other tests.

SCO dose-dependently decreased the CR rates in both 0 and 30-sec delays in the following way. Significant decreases were observed at 0.4 mg/kg in the 0-sec delay, and at 0.1, 0.2, and 0.4 mg/kg in the 30-sec delay. No significant change of NR was obtained with any SCO doses. The RT was increased dose-dependently, and significant changes were observed at 0.1, 0.2, and 0.4 mg/kg of SCO. Characteristic symptoms such as dysphagia appeared with all tested doses of SCO, and the mice were unable to eat because of severe inhibition of salivary secretion at more than 0.4 mg/kg. MSCO (0.2 and 0.4 mg/kg) produced a significant increase in RT and a slight increase in NR. However, there was no significant change in CR in spite of severe dysphagia from MSCO. ATO (5–20 mg/kg) impaired performance in a similar pattern to SCO, but its doses were about 50 times larger than those of SCO.

Figures 5 and 6 show the effects of PHY under 0 and 60-sec delay conditions and the effects of PHY combined with SCO (0.2 mg/kg) under 0 and 30-sec delay conditions, respectively. In the saline control, the CR rate with the 60-sec delay was less than with the 30-sec delay. The decrease in CR with a 60-sec delay was slightly ameliorated by 0.05 mg/kg of PHY. However, 0.1 mg/kg of PHY did not have such an effect, and it increased

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**Fig. 5.** Effect of methylscopolamine on non-matching to sample task in the 4-arm maze in mice. The data are shown in the same way as in Fig. 4.

**Fig. 6.** Effect of atropine on non-matching to sample task in the 4-arm maze in mice. The data are shown in the same way as in Fig. 4.
the NR slightly. RT increased significantly and dose-dependently after PHY (0.025–0.1 mg/kg), and performance became impossible at a dose of more than 0.1 mg/kg because of sedation. On the other hand, the disturbed performance caused by SCO was reversed by
treatment with PHY. This effect of PHY reached a maximum at 0.05 mg/kg and disappeared at 0.1 mg/kg.

As shown in Fig. 9, DZ decreased the CR rate regardless of delay time, and significant changes were observed at 1, 2, and 4 mg/kg with a 0-sec delay and at 2 and 4 mg/kg with a 30-sec delay. On the other hand, NR was never influenced by any dose of DZ. RT was significantly shortened by 0.5 mg/kg of DZ, but unchanged at all other doses of DZ. More than 4 mg/kg of DZ caused ataxia, which prohibited the mice from performing the task. On the other hand, one case in which 0.5 mg/kg of DZ was administered showed delay-dependent impairment in CR (100–80% in 0–30 sec delay in the control and 100–40% in DZ); and one case in which 1 mg/kg of DZ was administered showed an increase of 30-sec delay CR rate (60% in the control and 100% in DZ), although the 0 sec delay CR rate decreased (100% in the control and 80% in DZ). The disturbed performance by DZ was characterized by the mice preferring either the right or left arm position regardless of the direction of the forced run.

The other drugs (HAL, CPZ, APO, PHE, PRO, LI, KET, and CAF) had no significant effect on CR rates when delays of 0 and 30 sec (or 60 sec) were used or on NR at doses which could be tested in this study, although RTs were significantly increased by HAL, CPZ, APO, PHE, PRO, and KET (data not shown).

**DISCUSSION**

Correct performance in the non-matching to sample task in the 4-arm maze requires both working and reference memories as proposed by Honig (2), because the correct arm (right or left side) is alternated trial by trial and the non-reward center arm is fixed throughout the training. There is a difference in the temporal aspect of working memory between the present task and the Olton-type radial maze tasks, i.e., in the former, performance was markedly disturbed by delay, while the latter is delay-resistant (4). In this connection, the working memory required in the present task might involve short-term memory more than it does in the radial maze task. A typical method for assessment of short-term memory in rodents is the non-matching to sample task using a T-maze (5). However, reference and working memory can not be distinguished in this

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**Fig. 9.** Effect of diazepam on non-matching to sample task in the 4-arm maze in mice. The data are shown in the same way as in Fig. 4.
task, since either the impairment in retrieval of reference memory or an acquisition deficit in working memory will produce a bad performance. Recently, Olton et al. (6) developed a modified T-maze task that tests working and reference memory separately. In this method, rats must clear a simultaneous right-left discrimination task (rats could pass only on one side), which requires only reference memory at one choice point in a stem of the T maze; then they must perform a non-matching to sample response at another choice point at a corner. By contrast, in the present task there was only one choice point where reference and working memory were simultaneously used in producing a correct response.

The following discussion explains the characteristics of the present task. Most of the mice easily learned this task within 60 trials. In the early stage of training, NR response errors were frequently observed, which implied that learning of reference information was in progress. On the other hand, mice did not commit much IR at the beginning. This might result from the spontaneous alterations which are habitual in the rodent's feeding behavior (7). This habit is considered to be of great advantage to this task because the non-matching to sample response, as well as the radial maze task, requires a win-shift strategy in which animals must avoid the previous choice to conduct a correct performance. The well-trained mice hardly showed NR and IR under a 0-sec delay condition, having a CR rate of greater than 90% as a result. Insertion of a 30 or 60-sec delay between the forced and sample runs decreased the CR rate to 60-80%, which was still a higher level than chance. Therefore, both augmental and decremental working memory can be tested in this task. Of course, a delay condition can be freely selected according to whether the augment or decrement factor in working memory is anticipated after drug administrations. In the present study, two pairs of delay (0 and 30 sec for all drugs except PHY and CAF or 0 and 60 sec for PHY and CAF) were used separately.

It is not clear whether SCO, a typical muscarinic antagonist, has a positive effect on memory, although it is known to induce amnesia in humans and animals (8, 9). Specific inhibitory effects of SCO on memory have been reported by several workers (10-12). On the other hand, Kirk et al. (13) and Spenser et al. (14) concluded that SCO did not affect the time-dependent process of retention in working memory in rats. In the present study, SCO produced a delay-dependent deficit in CR at 0.1-0.2 mg/kg, and a delay-independent deficit at 0.4 mg/kg. However, 0.2 mg/kg of SCO produced a quantitatively different effect on 0-sec delay CR (see Figs. 4 and 8). This result suggests that this dose of SCO may be the border where SCO affects the acquisition of working memory. Consequently, subtle differences in experimental conditions (e.g., drug history and intraperitoneal injection of saline) may influence the results. Test doses of SCO did not produce NR. Viscardi and Heise (9) reported that impaired performance observed at 0-sec delay in a delayed discrimination task implied an acquisition deficit, while a retention deficit was suggested if impaired performance was observed at a delay-inserted condition but not at 0-sec delay. According to their idea, the present results suggest that SCO disrupts the retention process in working memory at 0.1 and 0.2 mg/kg and the acquisition process in working memory at 0.4 mg/kg, but it does not affect acquired reference memory in mice. However, Furukawa and Iwasaki (5) suggested that SCO impaired both working and reference memory in rats by comparing SCO effects on delayed matching to sample and non-matching to sample tasks using the T maze. At present, it is unclear what causes these differences in SCO effect on reference memory. It is necessary to examine it resolutely under various conditions (species of animals, doses of drugs, schedule, apparatus, etc.). At this point, the drug effect on memory should not be generally discussed apart from experimental conditions. MSCO produced dysphasia similarly to SCO, but did not
change the CR rate significantly. On the other hand, a few mice avoided entering the reward arms because of a dysphasia-induced decrease in motivation. Such behavior is thought to increase NR. Whether the drug penetrates the CNS or not may produce such a difference in effect between SCO and MSCO. ATO produced a delay-dependent decrease of the CR rate at doses of 5 and 10 mg/kg, which were about 50 times higher than those of SCO, and high doses (20 mg/kg) of ATO decreased the CR rate at 0 delay without NR error. The similarity of effects between SCO and ATO suggests that the central muscarinic blockade impairs the retention of working memory in mice.

PHY, a choline esterase inhibitor, is said to improve learning and memory in humans and animals (15, 16). In this task under the 60-delay condition, 0.05 mg/kg of PHY increased CR by about 10%, but 0.1 mg/kg of PHY impaired the performance. This biphasic pattern is similar to that of the clinical effect of PHY (15). It has also been reported that PHY antagonizes SCO-induced impairment in the cognitive function (10, 17). The present study proved that PHY ameliorated the performance deficit attributed to SCO (0.2 mg/kg). However, this anti-SCO effect of PHY was observed only at 0.05 mg/kg. These results show that the effective range of PHY against memory deficit is narrow, and overdosage may actually impair cognitive function in reverse because of its toxic effect.

Amnesia in humans induced by benzodiazepine-type anxiolytics such as DZ has been noted as either a side effect of daily usage or a beneficial effect in surgical operations (18). DZ impaired the performance of the present task differently than SCO. DZ induced a delay-independent decrease in CR without NR. In addition, mice treated with DZ but not SCO showed position preference for either the right or left arm. Furthermore, at the doses used, DZ produced no elongation of RT at all. These results suggest that DZ impairs the acquisition process in memory. Similar results have been reported in delayed discrimination tasks in rats (12). However, the analysis of individual data showed the possibility that 0.5 mg/kg of DZ causes a delay-dependent impairment of CR, but 1 mg/kg of DZ induced an increase in 30 sec delay CR. It is unclear whether these minor cases were phenomena particular to peculiar individuals.

The other drugs (HAL, CPZ, APO, PHE, PRO, LI, KET, and CAF) tested in this study had no significant effect on performance in this task. This result suggests that these drugs may not have a specific or marked effect on the memory of mice, at least in acute administration. As these drugs have been reported to affect the cognitive function in some cases, a further experiment was required to elucidate the essential effect of these drugs on memory.

The above results show that the effects of specific drugs on memory can be simultaneously examined using the present task. Because most behaviors in animals are based on an excellent cooperation between the working and reference memory, this method may be more practical than other conventional learning and memory tasks. However, the present finding that NR as an index of reference memory was not markedly affected by any drug treatment must be further discussed. Avoidance of the non-reward center arm can be achieved by trial-independent information based on either declarative or procedural memory (19). The present results suggest the possibility that suppression of NR during the period of drug tests might be maintained by the procedural memory, which is well-maintained in patients with amnesia. Accordingly, further analysis of drug effects on the learning process will be required to elucidate the characteristics of memory type as they affect the performance of the present task.

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