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Data Article

Spatial and latent memory data in PS2Tg2576 alzheimer's disease mouse model after memantine treatment

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ABSTRACT

We herein present behavioral data on whether memantine, an adamantane derivative and medical NMDA-receptor antagonist, improves spatial and latent learning deficits in amyloid precursor protein/presenilin 2 double-transgenic mice (PS2Tg2576 mice). In PS2Tg2576 mice, early amyloid-β protein (Aβ) deposition at 2–3 months of age and progressive accumulation at about 5 months of age has been shown. Thus, PS2Tg2576 mice were subjected to Morris water maze (MWM) test for spatial memory and the water-finding test for latent memory testing at ages 3 and 5–6 months. In addition, memantine (30 mg/kg/day, *p.o.*) was administered 3–4 weeks before commencing the behavioral tasks to check for effects on cognitive function. The information provided in this paper adds to the literature and can be used for the selection of animal models and behavioral paradigms for Alzheimer's disease (AD) research.

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Specifications Table

Subject	Neuroscience
Specific subject area	Alzheimer's disease, behavioral neuroscience
Type of data	Image Graph Figure
How data were acquired	Behavioral phenotyping (HomeCageScan, TopScan; CleverSys Inc., Reston, VA) with Morris water maze test and water-finding test.
Data format	Raw data Analyzed data
Parameters for data collection	Three-month-old or 5/6-month-old PS2Tg2576 mice were administered memantine-containing water (30 mg/kg/day) for 3–4 weeks.
Description of data collection	We collected data regarding two types of hippocampus-dependent learning through the Morris water maze and water-finding test using PS2Tg2576 mice after treatment with memantine, which is a promising a drug against Alzheimer's disease.
Data source location	Institution: Tokushima Bunri University City/Town/Region: Sanuki City/ Kagawa Prefecture Country: Japan Latitude and longitude (and GPS coordinates, if possible) for collected samples/data: 34° 19′ 17.40″ N and 134° 10′ 22.80″ E
Data accessibility	Data together with the original publication is available on Mendeley with the DOI: https://doi.org/10.17632/xxrsf4nr7v.2 Repository name: Mendeley Data Data identification number: Direct URL to data: http://dx.doi.org/10.17632/xxrsf4nr7v.3

Value of the Data

- The selection of an appropriate mouse model, behavioral tasks, and the right timing for drug administration is critical to elucidate in an animal model research for Alzheimer's disease. For the present data, we examined the effects of memantine on two different cognitive tasks at two ages in the amyloid precursor protein/presenilin 2 double-transgenic mouse (PS2Tg2576): Alzheimer's disease mouse model.
- These data are useful for investigators researching the pharmacological effects of memantine. Further, this data is also of particular utility for researchers employing PS2Tg2576 mice, and for those using the Morris water maze and water-finding test in behavioral pharmacological studies.
- Moreover, these data provide grounds for future studies on the potential use of PS2Tg2576 mice and the present learning paradigms to explore new drug strategies against neurodegenerative diseases.

1. Data Description

In this report, we present behavioral data on the effects of memantine, an adamantane derivative [1,2], on the Morris water maze and the water-finding tests abilities of amyloid precursor protein/presenilin 2 double transgenic mice (PS2Tg2576 mice) [3,4]. The MWM is a spatial learning test for rodents that relies on distal cues to navigate from a starting position to find a submerged escape platform. On the other hand, the water-finding test is a latent learning paradigm related to attentional processes and the ability to sort visuospatial information.

As indicated in Fig. 1, memantine (30 mg/kg/day) was administered to PS2Tg2576 mice for 3 weeks, and the mice were subjected to the MWM test at the age of 3 or 5–6 months. After the completion of the MWM test, *i.e.* at 4 weeks after the start of administering memantine, the water-finding test was conducted.

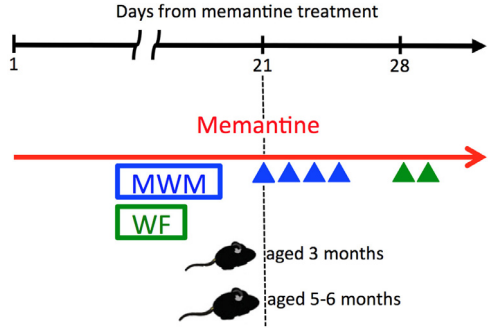

Fig. 1. Experimental design for memantine treatment and behavioral tasks. Black arrows indicate the number of days since the beginning of memantine administration. The first day of administration was designated as Day 1. At Day 14, mice are 3 months old or 5/6 months old. All mice underwent MWM testing for four days (from Day 14 to Day 18). Following the MWM test, the water-finding test was conducted on Day 21 and 22. MWM, Morris water maze.

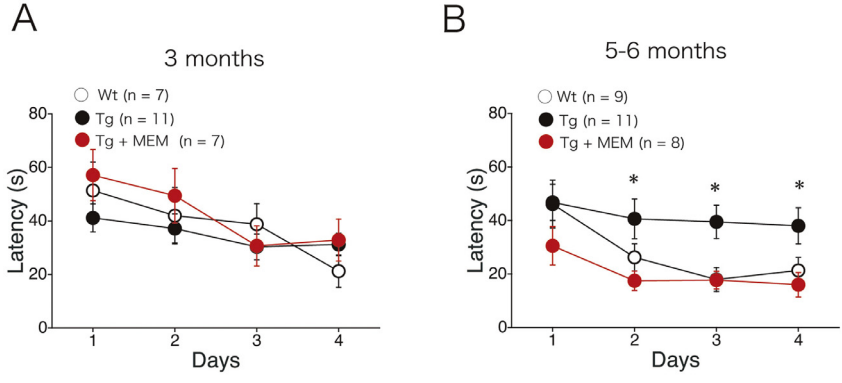

Fig. 2. Data showing spatial-memory deficits in PS2Tg2576 mice after memantine treatment. (A) Escape latencies in the MWM were evaluated in control wild-type mice (Wt, open circle, $n = 7$), PS2Tg2576 mice (Tg, closed circle, $n = 11$), and memantine-treated PS2Tg2576 mice (Tg + MEM, red circle, $n = 7$) aged 3 months. The mean escape latencies during behavioral tests were not significantly different among these three groups. ANOVA revealed no significant interaction effects between sessions and groups ($P = 0.26$; F [6, 66] = 2.24) and no significant group effect ($P = 0.63$; F [2, 22] = 3.44). (B) Escape latencies in the MWM were evaluated in control wild-type mice (Wt, open circle, $n = 9$), PS2Tg2576 mice (Tg, closed circle, $n = 11$), and memantine-treated PS2Tg2576 mice (Tg + MEM, red circle, $n = 8$) aged 5/6 months. ANOVA revealed no significant interaction effects between sessions and groups ($P = 0.58$; F [6, 75] = 0.80), but a significant group effect ($P = 0.0059$; F [2, 25] = 6.34). Post hoc analysis indicated a significant difference in the latency between Wt and PS2Tg2576 mice on Days 3, 4 and 5 ($P = 0.028$, 0.042, 0.040, respectively). However, there was no significant difference between Wt and Tg + MEM groups throughout the entire period. $^{*}P < 0.05$. PS2Tg2576, amyloid precursor protein/presenilin 2 double-transgenic mouse; MWM, Morris water maze; ANOVA, analysis of variance.

Fig. 2 shows MWM escape latency in wild-type, PS2Tg2576, and memantine-treated PS2Tg2576 mice at the ages of 3 and 5/6 months. Fig. 3A is a schematic illustration of the apparatus for the water-finding test. Fig. 3B includes the definitions of the terms: entering latency (EL), finding latency (FL), and drinking latency (DL). Fig. 4A shows EL, FL, DL in wild-type, PS2Tg2576, and memantine-treated PS2Tg2576 mice aged 3 months. In any of the indices, no abnormalities were found in PS2Tg2576 mice compared to wild-type mice. Fig. 4B shows EL, FL, and DL in 5–6 months old wild-type, PS2Tg2576, and memantine-treated PS2Tg2576 mice. Regarding EL, there was no significant difference between the three groups. However, there was a significant difference between wild-type and PS2Tg2576 mice in FL and DL. There was no statistically significant difference between wild-type and memantine-treated PS2Tg2576 mice.

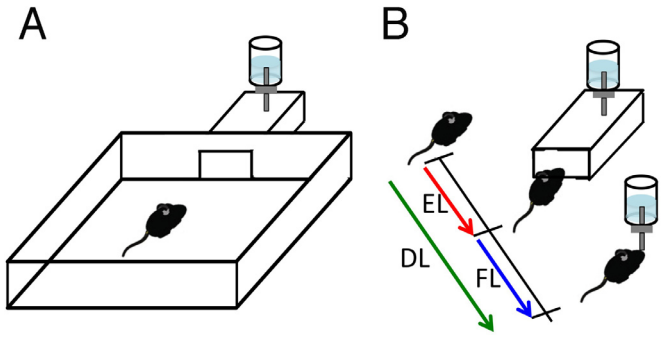

Fig. 3. Schematic illustration of the water-finding test. (A) Schematic diagram of the water-finding test apparatus. The apparatus consisted of a rectangular open field with an alcove. (B) Definitions of entering latency (EL) and finding latency (FL). EL was defined as the period from exploration start until entering the small alcove, and FL as the period from entering the alcove until finding the water pipe. The sum of EL and FL was defined as drinking latency (DL).

2. Experimental Design, Materials and Methods

2.1. Animals

APP/PS2 double transgenic (PS2Tg2576) mice were obtained by crossbreeding Tg2576 mice and PS2 mutant mice as previously reported [3–7]. PS2Tg2576 mice ($n = 37$) and littermate wild-type mice ($n = 17$) aged 3 month or 5–6 months were employed. Males and females were balanced so that there were approximately half of each in each group.

2.2. Drug treatment

PS2Tg2576 mice were experimentally divided into two groups: a memantine-treated group ($n = 15$) and a control group ($n = 22$). The former received 30 mg/kg/day (for details, see Results) memantine (Sigma-Aldrich, USA) orally (via drinking water) for 14 consecutive days, starting 3 weeks before the first behavioral task, the MWM, while the latter drank normal water (See Fig. 1 for details). This dosage and administration method followed have been previously reported previously [8]. The procedure is considered to produce a therapeutic steady-state plasma level of around 1 μM [8]. Wild-type mice were allowed to drink normal water without memantine during the entire experiment.

2.3. Morris water maze (MWM) test

The MWM test was conducted as previously described [9–12]. A gray tank (Eiko Science, Tokushima, Japan), with 120 cm diameter and 34 cm depth, was filled with water till a 25 cm height. A transparent rescue platform (10 cm in diameter) was submerged 0.5 cm below the water surface. The test was started 14 days after drug administration (Fig. 1) and training trials were conducted over 4 days; on each day, four hidden platform trials were performed with at least 1 hour interval between successive trials. The maximum latency allowed was 80 s, and the mouse was required to stay on the platform for >3 s. After each trial, mice remained on the platform for 30 s, after which they were removed from the platform and returned to their home cage. The water was kept at a constant temperature throughout the experiment (24.0 ± 2.0 °C). Performance was monitored and analyzed with an automated video-tracking system (Clever System, Inc., Reston, VA). During the MWM acquisition phase, the platform location remained

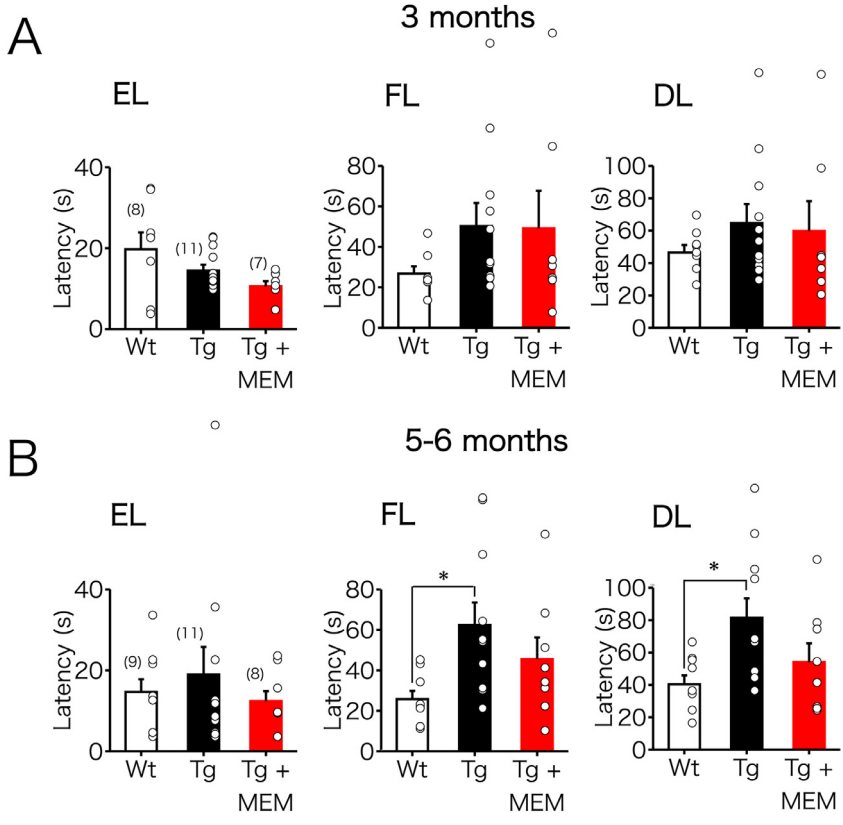

Fig. 4. Data showing a latent memory deficit in PS2Tg2576 mice after memantine treatment. (A) ELs, FLs, and the FLs in test trials (day 2) of the water-finding test were evaluated in control wild-type mice (Wt, open bar, $n = 8$), PS2Tg2576 mice (Tg, closed bar, $n = 11$), and memantine-treated PS2Tg2576 mice (Tg + MEM, red bar, $n = 7$) at the age of 3 months. There was no significant difference among groups in any of the three indexes. (B) ELs, FLs, and the FLs in test trials (day 2) of the water-finding test were evaluated in control wild-type mice (Wt, open bar, $n = 9$), PS2Tg2576 mice (Tg, closed bar, $n = 11$), and memantine-treated PS2Tg2576 mice (Tg + MEM, red bar, $n = 8$) at the age of 5/6 months. In EL, no significant difference was found between the three groups. However, there was a significant difference between Wt and Tg in FL and DL ($P = 0.025$, 0.022, respectively), but no significant difference among all other groups. $^{*}P < 0.05$. Individual data points represent independent mice and data are represented as mean ± SEM. PS2Tg2576, amyloid precursor protein/presenilin 2 double-transgenic mouse; EL, entering latency; FL, finding latency; DL, drinking latency.

constant, and entry points were changed semi-randomly between trials. Mice failing to reach the platform within 80 s were led to the platform with a metal escape scoop.

2.4. Water-finding (WF) test

Four days after the last MWM test session, the water-finding test was conducted. The apparatus and experimental procedures for evaluating latent memory were essentially the same as previously described [9,13]. A schematic diagram is shown as Fig. 2A. Mouse movements were tracked from above with a TopScan (CleverSys, Inc.) video camera system. The apparatus consisted of an open field (40 × 72 × 30 cm) with an alcove (15 × 20 × 10 cm) in the middle of one of the long walls. After each test, the apparatus was cleaned with ethanol. A metal drinking

water bottle of the same type as in the normal cages was inserted in the center of the alcove ceiling at 5 cm (training trial) or 7 cm (test trial) above the floor. In the training test (Day 1), the water bottle was left empty. Animals were not deprived of water.

Each mouse was placed in the starting corner and the elapsed time until the beginning of environmental exploration was recorded as starting latency (SL). The mice were then allowed to explore freely for 3 min. If a mouse did not touch the bottle tube, it was excluded in the subsequent test trials (one mouse was excluded). After the training test, the mice were immediately returned to their cages and did not receive water until the test trial (Day 2). The next day, a test trial was conducted. The latency from the search start to the entry into the small alcove was defined as entering latency (EL). The latency from the first time the mouse entered the alcove to the time it touched the water tube was defined as finding latency (FL), and the sum of EL and FL was defined as drinking latency (DL). If a water tube could not be found within 3 min from the start of the exploration, DL was recorded as 180 s. Test trials were conducted analogous to training trials.

2.5. Statistical analysis

Behavioral data were statistically analyzed with Prism software version 6.0 (GraphPad Software, CA, US). Data obtained in the MWM test were analyzed with a two-way (session $\times$ group) analysis of variance (ANOVA), followed by a post hoc Tukey-Kramer test. Data for the water-finding test were analyzed by Tukey-Kramer multiple comparison test. All data are presented as mean $\pm$ SEM. The significance level was defined at $P < 0.05$.

Ethics Statement

All animal procedures were approved by the Tokushima Bunri University animal ethics committee (approval number: 23P-1) and carried out in accordance with the National Institutes of Health guide for the care and use of laboratory animals.

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Role of the Funding Source

The funding sources had no involvement for the collection, analysis and interpretation of data.

CRediT Author Statement

Masahisa Matsumura: Investigation, Data curation; **Kana Sato:** Investigation; **Takashi Kubota:** Investigation, Data curation; **Yasushi Kishimoto:** Supervision, Writing– Original draft preparation, and Writing– Reviewing and Editing, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships which have or could be perceived to have influenced the work reported in this article.

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