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Fatty acid amides present in Camembert cheese improved cognitive decline after oral administration in mice

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ABSTRACT

Herein, we investigated the effects of Camembert cheese (CC) and its fatty acid contents on cognitive function in mice by employing the object recognition test to evaluate hippocampus-dependent memory. Orally administered CC improved the cognitive decline induced by a high-fat diet. Next, we focused on myristamide (MA), oleamide, and stearamide, which are fatty acid amides produced during the fermentation process of CC. We found that oral administration of MA improved cognitive decline. Notably, an improvement was not observed using myristic acid, a free fatty acid that is not amidated. Thus, fatty acid amidation may contribute to the physiological activity. Moreover, we investigated changes in gene expression related to neurogenesis in the hippocampus. After MA administration, mRNA expression analysis indicated that MA increased hippocampal *brain-derived neurotrophic factor* expression.

1. Introduction

Fermented foods are produced by a metabolic process where food components react with microbial enzymes, creating new molecules that are not found in natural foods (Dimidi et al., 2019; Marco et al., 2017). Fermented foods were initially consumed as preserved foods in numerous cultures (Marco et al., 2017), but they are currently sold worldwide and have recently undergone a surge in popularity as healthy foods. Several groups have stated that fermented foods should be included in dietary guidelines (Chilton et al., 2015; Ebner et al., 2014).

The increasing prevalence of dementia and cognitive decline is one of the major general health concerns, especially considering that the global population is growing and aging. Furthermore, epidemiological studies have indicated that type 2 diabetes is a risk factor for Alzheimer's disease (Matsuzaki et al., 2010; Ohara et al., 2011; Ott et al., 1999). As Alzheimer's disease progresses, severe neurodegeneration and brain dysfunction are developed. Thus, improving mild cognitive impairment (MCI) before neurodegeneration or brain dysfunction is considered important for the prevention of dementia. The ideal approach to preventing cognitive decline is the regular consumption of the proper nutrients derived from everyday foods. For example, the intake of dairy products has been reported to reduce the risk of Alzheimer's disease (Ozawa et al., 2014).

The intake of Camembert cheese (CC) has been reported to increase a neurotrophic factor, which might contribute to improving cognitive decline, in the blood of the elderly (Suzuki et al., 2019). CC is produced from milk that is fermented by white mold (*Penicillium camembert*). Active compounds for improving cognitive function are assumed to exist in fermented cheese. However, the underlying mechanism and active compounds remain to be elucidated.

In this study, we investigated the effect of CC on cognitive function in mice. Furthermore, we tested the effects of fatty acid amides, molecules produced during the fermentation of CC. We found that CC and myristamide (MA) reduce the cognitive decline induced by short-term intake of a high-fat diet (HFD). We also examined the neural stem cell proliferation and expression levels of neurotrophic factors in the hippocampus, which are associated with cognitive function.

Abbreviation: CC, Camembert cheese; MA, myristamide; OA, oleamide; SA, stearamide; HFD, high-fat diet; ORT, object recognition test; *BDNF*, *brain-derived neurotrophic factor*; *NGF*, *nerve growth factor*; *NT-3*, *neurotrophin-3*; *GDNF*, *glial cell line-derived neurotrophic factor*; *EGF*, *epidermal growth factor*; *CNTF*, *ciliary neurotrophic factor*; *FGF-2*, *fibroblast growth factor 2*; *IGF-2*, *insulin-like growth factor 2*; *VEGF*, *vascular endothelial growth factor*.

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2. Materials and methods

2.1. Animals

Male ddY mice (11 weeks old) were purchased from SLC (Shizuoka, Japan). The mice were housed at 23 ± 1 °C using a 12 h light-dark cycle, with lights on at 7 am, and they were acclimatized by feeding them a standard rodent diet, namely MF (Oriental Yeast Co., Ltd., Osaka, Japan), for more than 7 days. After acclimatization, the mice were divided into two experimental groups: the HFD group (control group) and HFD plus fatty acid amide administration group (HFD + fatty acid amide group) (Nagai et al., 2019; Shobako et al., 2023). The HFD was established by feeding each group with a 60 kcal% HFD (D12492, Research Diets Inc., New Brunswick, USA) for 7 days. The date of exchange from the MF to the HFD was set as day 0. For the last 3 days, 8 or 15 g/kg of CC (Meiji Co., Ltd., Tokyo, Japan), 0.1–10 mg/kg of MA (Alfa Aesar, Massachusetts, USA), 10 mg/kg of oleamide (OA) (FUJIFILM Wako Pure Chemical Corp., Osaka, Japan), 10 mg/kg of stearamide (SA) (Cayman Chemical Company, Michigan, USA), and 0.1 or 10 mg/kg of myristic acid (FUJIFILM Wako Pure Chemical Corp., Osaka, Japan) were orally administered in each group. We measured body weight and food intake of mice on day 3. Camembert cheese, containing both white mold surface and inside without bias, was homogenized. Mice were euthanized by cervical dislocation after the experiment. All experiments were approved by the Kyoto University Ethics Committee for Animal Research Use. All efforts were made to decrease the number of animals used and to minimize their stress and pain.

2.2. Object recognition test (ORT) and object location test (OLT)

To evaluate cognitive function, the ORT and OLT were conducted. The ORT was performed on day 7 as previously described (Leger et al., 2013), with slight modification. The ORT consists of three sessions, namely the habituation, familiarization, and test sessions, and all sessions were performed with a light intensity of 200 lx in the middle of an open square field (50 cm × 50 cm × 50 cm) made of gray polyvinyl chloride. Two typical objects were used: a wooden block and a tissue culture flask filled with sand. In the habituation session on day 6, mice were placed in the field without objects for 5 min. The familiarization session was performed 24 h after the habituation session using the same experimental apparatus. In the familiarization session, each mouse was released into the field and allowed to explore the object freely for 20 s of total exploration. Exploration of the object was defined as valid when the animal's nose was directed to the object at a distance of less than 1 cm. After 1 h, the test session was performed. In the session, the mouse was again placed into the field, but the familiar object was replaced with a novel one. Each mouse explored these objects similarly for 20 s of total exploration and the approach time to each object was measured.

Similar to the ORT, the OLT consisted of 3 sessions. In the familiarization session, mice were exposed to 2 identical objects that were placed in 2 selected contiguous corners, whereas during the test session, 1 of the objects was moved to a novel location in the opposite corner respective to the nondisplaced object. Each mouse was again placed into the open field for 20 s of total exploration, and the exploration time for the familiar object and novel location object was measured. The ORT and OLT were performed 2 h after oral administration.

2.3. Concentration of fatty acid amides in CC

The lauramide, palmitamide, MA, SA, and OA contained in CC were quantified by LC-MS/MS using an internal standard method. Each [1–^{13}C,^{15}N]-fatty acid amide was synthesized using [1–^{13}C] labeled fatty acids and ammonia-^{15}N solution (Sigma-Aldrich, USA) as the raw material, and 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride n-hydrate (DMT-MM) (FUJIFILM Wako Pure Chemical, Osaka, Japan) as the condensing agent, which was then purified and used as a stable isotope-labeled internal standard. Frozen CC was homogenized using a Multi-Beads Shocker pulverizer (Yasui Kikai, Osaka, Japan). The cheese was extracted with 10 times the volume of isopropanol (HPLC grade, FUJIFILM Wako Pure Chemical, Osaka, Japan) after adding an internal standard. The measurement was conducted using a Prominence HPLC system (Shimadzu, Kyoto, Japan) equipped with an API 3200 triple quadrupole mass spectrometer (SCIEX, CA, USA).

2.4. RNA preparation and quantitative RT-PCR

The hippocampus was collected 2 h after oral administration. The hippocampus was excised and stored at −80 °C until RNA extraction. Total RNA was extracted using the RNeasy Lipid Tissue Kit (QIAGEN Sciences Inc., Osaka, Japan) and transcribed using the Takara Prime Script RT Master Mix (Takara Bio Inc., Osaka, Japan). For quantitative PCR, we amplified the cDNA using the Light Cycler 96 System (Roche Diagnostics, Mannheim, Germany) with THUNDERBIRD qPCR Mix (TOYOBO Co., Ltd., Osaka, Japan) and each primer set specific for mouse *brain-derived neurotrophic factor* (*BDNF*), *nerve growth factor* (*NGF*), *neurotrophin-3* (*NT-3*), *glial cell line-derived neurotrophic factor* (*GDNF*), *epidermal growth factor* (*EGF*), *ciliary neurotrophic factor* (*CNTF*), *fibroblast growth factor 2* (*FGF-2*), *insulin-like growth factor 2* (*IGF-2*), or *vascular endothelial growth factor* (*VEGF*). The reactions were cycled 40 times with denaturation at 95 °C for 10 s, and annealing and elongation at 65 °C for 60 s. The relative expression level of each mRNA was normalized using the mRNA level of β-actin.

2.5. Statistical analysis

All values are expressed as the means ± SEM. An analysis of variance followed by Student's t-test or Dunnett's test was conducted to assess differences among two or more than two groups, respectively. *P*-values less than 0.05 were considered significant.

3. Results

3.1. CC improved the cognitive decline induced by HFD intake

Chronic HFD intake was shown to reduce cognitive function (Lindqvist et al., 2006), and we previously found that short-term HFD intake decreased cognitive function (Nagai et al., 2019; Shobako et al., 2023). To investigate the effects of milk-related samples on cognitive function in mice, we performed the ORT (Leger et al., 2013) after orally administrating 8 or 15 g/kg of CC. Mice fed with the HFD showed significantly increased approach times to novel objects after receiving 15 g/kg of CC (Fig. 1). These results suggested that CC improved the cognitive decline induced by HFD intake.

3.2. MA improved the cognitive decline induced by HFD intake

Table 1 shows the concentration of fatty acid amides in CC. We focused on MA, OA, and SA. These fatty acid amides were orally administered (10 mg/kg) and their effects were evaluated using the ORT. Oral administration of MA significantly increased the approach time to the novel object (Fig. 2A). In the OLT, another behavior test to evaluate cognitive function, it was confirmed that MA administration significantly increase the approaching time to the object in the novel location (Fig. 2B). We repeated the ORT comparing the effects of MA and OA, and both amide acids increased the approach time to the novel object after oral administration (Fig. S1A). In other words, oral administration of MA and OA improved cognitive decline. This is the first report demonstrating that MA improves cognitive decline in mice.

We also examined the dose dependency of MA (0.1, 1.0, and 10 mg/kg). MA administration increased the approach time in a dose-dependent manner (Fig. 3A). Moreover, we compared the effects of

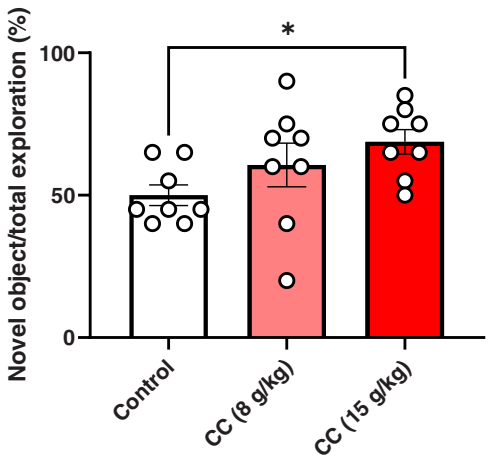

Fig. 1. Mice were fed with an HFD for one week and orally administrated with saline or CC at 8 or 15 g/kg (once a day for 3 successive days). Then, the ORT was performed, showing that CC improved the cognitive decline induced by HFD intake. Each value is the mean ± SEM (n = 8). *$P < 0.05$ vs. the control group.

Table 1
The concentration of fatty acid amides in the CC.

Name	Abbreviation	Fatty acid	Content (μg/g)
Lauramide	LA	C12:0	0.05
Myristamide	MA	C14:0	0.20
Palmitamide	PA	C16:0	0.49
Stearamide	SA	C18:0	0.38
Oleamide	OA	C18:1	0.62

MA with those of myristic acid, a free fatty acid. Myristic acid did not improve the cognitive decline induced by HFD intake (Fig. 3B and S1B), suggesting that amidation supports the improvement of cognitive decline.

3.3. MA increased BDNF expression in the hippocampal mRNA levels

We investigated changes in gene expressions related to neurogenesis in the hippocampus (Fig. 4A–I). *BDNF* is one of the neurotrophic factors that acts on neuroprotection and synaptogenesis. Additionally, it is closely related to learning and memory. *BDNF* mRNA expression levels significantly increased after MA administration, suggesting that MA increases hippocampal *BDNF* expression (Fig. 4A).

4. Discussion

We found that MA, one of the fatty acids amide produced during the fermentation of CC, improved cognitive decline induced by an HFD in a dose-dependent manner, and only a low dosage was required. In contrast, myristic acid, a free fatty acid that is not amidated, did not improve cognitive decline. Thus, amidation may be important to improve cognitive function. In addition, hippocampal *BDNF* mRNA levels were significantly increased after MA administration.

Considering that CC and MA improve the cognitive decline induced by an HFD and CC contains MA, the improvement caused by CC intake may be attributed to MA. Furthermore, not only MA but also OA may contribute to the improvement (Ano et al., 2015a, 2015b) (Fig. 2 and S1A). In addition to our previous report (Nagai et al., 2019), another group showed that dairy food-derived peptides improve cognitive decline (Ano et al., 2018). Therefore, we considered that the physiological function of CC is activated by interactions between fatty acid amides and peptides.

In intervention trials, CC has been reported to significantly increase the levels of neurotrophic factors, which are necessary for neurogenesis and neuronal growth, in older Japanese women with MCI (Suzuki et al., 2019). In animal experiments, CC reduced amyloid-beta (Aβ) in the brain after oral administration in a mice model of Alzheimer's disease (Ano et al., 2015a, 2015b). Moreover, OA, another fatty acid amide found in CC, activated phagocytosis of Aβ by brain microglia and inhibited inflammation in the brain. Although CC was suggested to improve cognitive decline in human intervention studies and animal studies, cognitive behavioral studies have not been implemented. Therefore, we performed ORTs to examine whether cognitive function improved in mice that consumed CC.

OA is synthesized by the amidation of oleic acid using bacterial enzymes (Mandrekar-Colucci et al., 2012). Oleic acid is abundant in dairy products, and ammonia is produced by the fermentation of cheese. Furthermore, fatty acid amides are synthesized from fatty acid and ammonia by enzymatic amidation (Moore et al., 2001). Notably, the

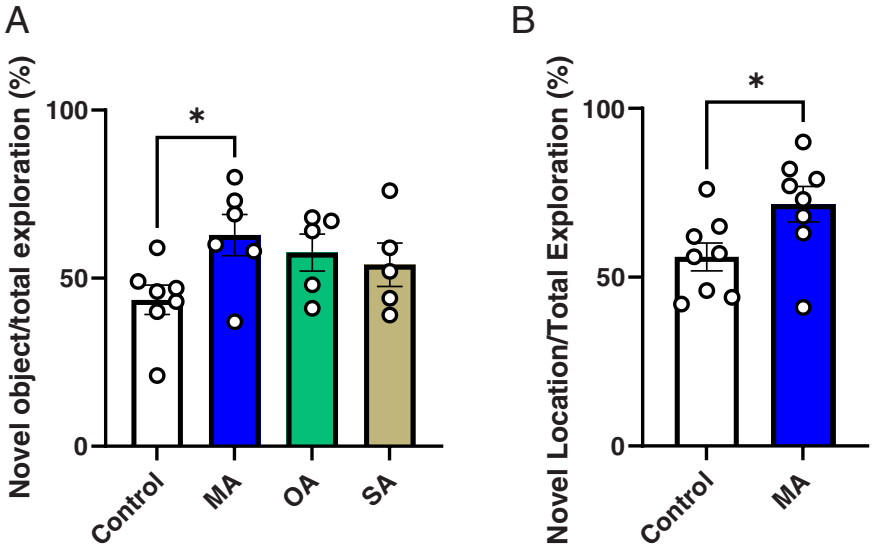

Fig. 2. (A) MA, OA, and SA, the fatty acid amides produced during cheese fermentation, were orally administered at a dose of 10 mg/kg. MA improved the cognitive decline induced by HFD intake. All values are the mean ± SEM (n = 5–7). (B) The OLT, another behavior test to evaluate cognitive function was performed, showing that MA improved the cognitive decline induced by HFD intake. Each value is the mean ± SEM (n = 8). *$P < 0.05$ vs. the control group.

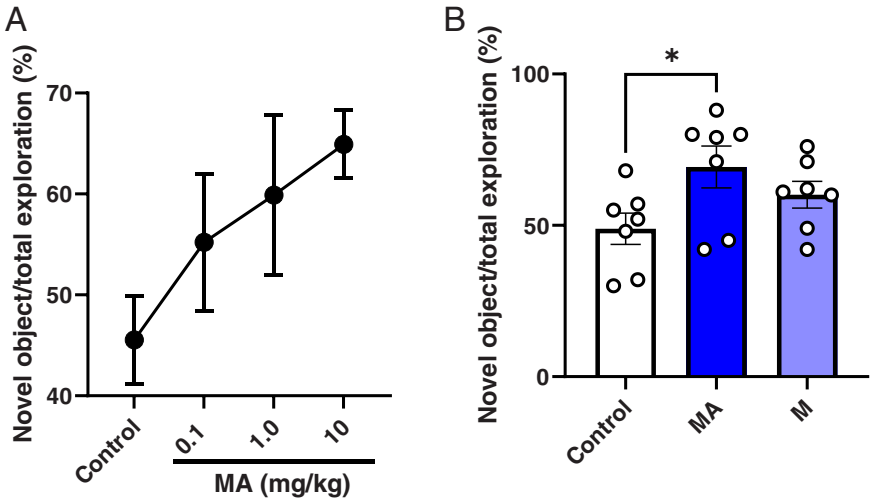

Fig. 3. (A) Dose dependence of the effect of MA on cognitive function, using 0.1, 1.0, and 10 mg/kg doses. The mean approach time to the novel object appeared to be dose-dependent. Each value is the mean ± SEM (n = 5–6). (B) The effect of myristic acid, a free fatty acid that is not amidated. The cognitive decline was not improved using myristic acid. MA and myristic acid were administrated at a dose of 10 mg/kg. All values are the mean ± SEM (n = 7). *$P < 0.05$ vs. the control group.

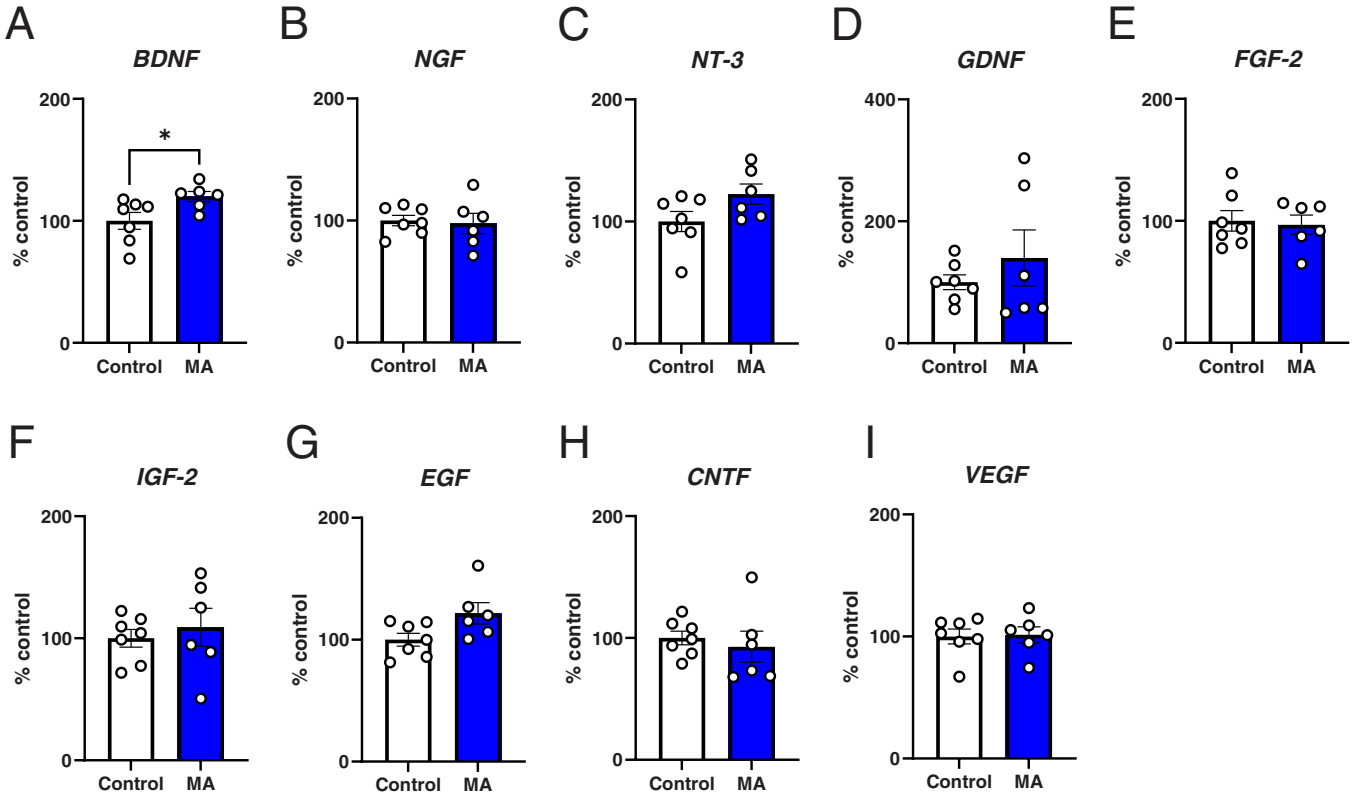

Fig. 4. Changes in the hippocampal mRNA levels of neurotrophic factors after MA administration (A-I). The following neurotrophic factors were measured by quantitative RT-PCR: *BDNF* (A), *NGF* (B), *NT-3* (C), *GDNF* (D), *FGF-2* (E), *IGF-2* (F), *EGF* (G), *CNTF* (H), and *VEGF* (I). All values are the mean ± SEM (n = 6–7). *$P <$ 0.05 vs. the control group.

concentration of MA in CC was measured to be 0.2 μg/g (Table 1), and the concentration of myristic acid was 0.11 g/g (Adamska et al., 2017). Although MA contributed to cognitive function at low concentrations (Fig. S1B), myristic acid did not (Fig. 3B). Therefore, fatty acid amidation during the fermentation process may contribute to the physiological activity. Food intake and body weight were not affected by MA administration, suggesting that the MA-induced cognitive function improvement might be independent of regulation of food intake and growth (Fig. S2).

MA is presumed to signal the brain, but it has not been clarified whether MA directly affects the brain or uses the vagus nerve by acting on intestinal cells. An intestinal receptor, cannabinoid receptor 1, also known as an OA receptor, is a possible candidate for information transmission methods (Dionisi et al., 2012; Leggett et al., 2004; Oh et al., 2010). MA may also be mediated through this receptor. Several food-derived peptides have been reported to mediate serotonin,

dopamine, GABA, and acetylcholine receptors (Mori et al., 2018; Shobako et al., 2023). Therefore, the above receptors are possible receptor candidates for MA. Analysis of the hippocampal neurotrophic factor expression showed that MA administration significantly increased *BDNF* expression in the hippocampus. This is consistent with the increase in blood BDNF concentration, observed in human intervention studies (Suzuki et al., 2019). In the future, the mechanism underlying short-term cognitive improvement will be elucidated by examining phosphorylation of memory-related proteins.

Recently, there has been an increased interest in the relationship between food intake and cognitive function. Previous reports have shown that a diet characterized by a high intake of soybean, vegetables, seaweed, wine, milk, and dairy products, together with a low intake of grain products, reduced the risk of developing dementia (Bigman et al., 2023; Kim et al., 2023; Li et al., 2023). In addition, the risk of developing dementia, especially Alzheimer's dementia, was reduced by a high intake of milk and dairy products (Suzuki et al., 2019). A tripeptide derived from α casein, a major component in bovine milk, was also found to improve the cognitive decline induced by HFD intake (Nagai et al., 2019). The present study showed that the improved cognitive function can be attributed not only to the components of natural foods but also to those of fermented foods. In particular, we found that the fermentation of milk by white mold produces molecules with enhanced physiological activity. Further investigations, including longer-term studies and broader data analyses, will be needed.

In conclusion, we showed that fatty acid amides produced during cheese fermentation improved cognitive decline in mice fed with an HFD, and amidation appears to support this biological activity.

CRediT authorship contribution statement

Kohei Kawano: Data curation, Formal analysis, Investigation, Resources, Validation, Visualization, Writing – original draft, Writing – review & editing. **Maiko Shobako:** Data curation, Formal analysis, Investigation, Resources, Validation, Visualization, Writing – original draft, Writing – review & editing. **Taichi Furukawa:** Formal analysis, Investigation. **Tatsuhiro Toyooka:** Formal analysis, Investigation. **Kousaku Ohinata:** Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Supervision, Validation, Writing – original draft.

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Author contributions

KO supervised and designed the experiments. KK, TF, MS, and TT performed the experiments and analyzed the data. KK, MS and KO drafted the paper. KK and MS wrote and improved the paper. All authors discussed the results and the manuscript.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neures.2024.03.002.

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