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Medium-chain triglycerides tricaprin TC10 and tricaprylin TC8 attenuated HFD-induced cognitive decline in a manner dependent on or independent of GLP-1

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Population aging is the most important social and medical demographic issue worldwide; therefore, healthy aging is important. The increasing prevalence of dementia and cognitive decline are major health concerns. Medium-chain triglycerides (MCTs) have been shown to improve cognitive decline. The present study investigated the effects and mechanisms of action of orally administered MCTs, including tricaprylin (TC8), tricaprin (TC10), and trilaurin (TC12), on cognitive function in mice fed a high-fat diet (HFD). The administration of TC8 and TC10 attenuated cognitive decline. A relationship has been reported between cognitive dysfunction and impaired glucose metabolism. The administration of TC8 and TC10 also reduced blood glucose levels in the glucose tolerance test. Cognitive improvements by MCTs are widely attributed to the ketogenic effect. In the present study, TC8 significantly increased blood ketone concentrations, whereas TC10 did not. On the other hand, TC10 increased the plasma concentration of glucagon-like peptide-1 (GLP-1), the hormone that promotes insulin secretion. The administration of the GLP-1 receptor antagonist, exendin(9–39), blocked the cognitive-enhancing effects of TC10. These results suggest that TC10 improved cognitive function via the GLP-1 receptor. The in vitro experiment indicated that 2-monocaprin (2-MC10), not TC10, stimulated the secretion of GLP-1 and decreased intracellular cAMP concentrations. In conclusion, we herein demonstrated that TC8 and TC10 attenuated cognitive decline through different mechanisms. This is the first study to suggest that TC10 attenuates cognitive decline via GLP-1.

Keywords Medium-chain triglycerides, Cognitive function, Glucose metabolism, GLP-1, Ketone

Medium-chain triglycerides (MCTs) are triglycerides bonded to medium-chain fatty acids (MCFAs) with carbon numbers ranging from 8 to 12 (i.e., caprylic (C8:0), capric (C10:0), and lauric (C12:0) acids). MCTs are easily digested[1], releasing MCFAs, which are transported directly to the liver via the portal vein for absorption; however, migration rates depend on chain lengths[2,3]. Acyl-CoA derived from MCFAs is redirected to the production of ketone bodies[4], thereby increasing blood concentrations of ketone bodies, which are then utilized by some organs, such as the brain, as an alternative energy source to glucose. Therefore, MCTs are characterized by their easy digestion and rapid production of energy. In addition, glucose metabolism was recently reported to be improved after tricaprin (TC10) intake mediated by the GPR84 related to increase in plasma GLP-1 levels in mice[5].

Due to their unique feature of efficient energy production, MCTs are also considered to be beneficial for brain function, with many studies reporting improvements in cognitive function. In clinical studies, the consumption of MCTs improved cognitive function in individuals with mild cognitive impairment[6,7]and enhanced performance in cognitive tasks by healthy young adults[8]. MCTs are also present in the breast milk of mammals[9]. Besides efficient energy production, they have been shown to benefit a baby's brain. Breastfed babies achieved more favorable results in brain development than formula-fed babies, including more mature cerebral white matter and larger regional brain volumes[10–12]. These findings suggest that the significance of MCTs in breast milk lies in

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their positive impact on the brain as signaling molecules. Although a number of studies have demonstrated the positive effects of MCTs on brain function, the mechanisms of action remain unclear.

The brain constantly processes and interprets information obtained externally through the five senses on our surroundings, and manipulates language, calculates, learns, and memorizes based on this information. This is called cognitive function. Cognitive decline has a negative impact on the daily activities of living. It is induced by aging and lifestyle, including dietary habits. The intake of a high-fat diet (HFD) has been shown to induce cognitive decline in both animals[13,14]and humans[15,16]. We previously detected hippocampus-related cognitive decline in mice fed HFD for one week without changes in food intake or body weight[17–19]. In the present study, we used this experimental system to examine the effects of MCTs with different chain lengths of constituent fatty acids, namely, tricaprylin (TC8), tricaprin (TC10), and trilaurin (TC12), on cognitive function and their mechanisms of action.

Materials and methods

Materials

TC8, TC10, and TC12 were purchased from Tokyo Chemical Industry Co., Ltd. (Tokyo, Japan). Exendin(9–39) was purchased from the Peptide Institute Inc. (Osaka, Japan). 1-Monocaprin (1-MC10), 2-monocaprin (2-MC10), and 1,2-dicaprin (1, 2-DC10) were obtained from Olbracht Serdary Research Laboratories (Toronto, Canada).

Animals

Eleven-week-old male ddY mice were purchased from SLC (Shizuoka, Japan). This ddY strain is a closed colony with a rapid growth rate and high reproductive potential and has frequently been used in biomedical research, including behavioral pharmacological tests[20–26]. Rearing conditions were as follows: 23 ± 1℃ on a 12-h light-dark cycle with lights on at 7 am. Each mouse was acclimatized by feeding with the standard rodent diet, MF (Oriental Yeast Co., Ltd., Osaka, Japan). After acclimatization, mice were divided into experimental groups: a HFD-fed group and HFD-fed plus administration of MCTs groups[17,18]. HFD intake was achieved by feeding each group 60 kcal% HFD (D12492, Research Diets Inc., NB, USA) for 7 d. The day of the exchange from MF to HFD was set as day 0. In the last 3 d, 250 mg/mouse TC8, TC10, or TC12 was orally administered to each group. Mice were euthanized by cervical dislocation after the experiment. Animal experiments were conducted in accordance with the Fundamental Guidelines for Proper Conduct of Animal Experiment and Related Activities in Academic Research Institutions under the jurisdiction of the Ministry of Education, Culture, Sports, Science and Technology of Japan, and were approved by the Committee on Animal Experimentation at Kyoto University, Japan. All experiments were approved by the Kyoto University Ethics Committee for Animal Research Use, permission code was R5-13. All experimental procedures were performed in accordance with the ARRIVE guidelines. All efforts were made to minimize the number of animals used and to limit experimentation to what was necessary to produce reliable scientific information.

The novel object recognition test (NORT) and object location test (OLT)

To evaluate cognitive function, NORT was performed on day 7 as previously described[17–19,27] with slight modifications. It consisted of three sessions: habituation, familiarization, and a test session, and all sessions were performed under the condition where light intensity in the middle of the field was 200 lx. The field used in these tests was a square open field (50 × 50 × 50 cm) made of grey 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 in the same experimental apparatus. In the familiarization session, each mouse was released into the field and allowed to explore the two identical objects freely for 20 s of total exploration. The exploration of objects was defined as valid when the animal's nose 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; however, the familiar object was replaced with a novel one. Each mouse explored these objects similarly in the open field for 20 s and the time spent exploring each object was measured. The antagonist, exendin(9–39), was intraperitoneally administered 30 min before the administration of MCTs at a dose of 0.1 mg/kg.

OLT was also performed as previously described[17–19]. OLT was conducted using a similar experimental procedure to that of NORT; however, in the familiarization session, two identical objects were placed in the adjacent corners of the field and each mouse explored these objects. In the test session, one of the two objects was moved to the opposite corner. Each mouse was again released into the field for 20 s of total exploration, and the time spent exploring the familiar object and the moved object was measured. NORT (Fig. 1A, $n = 10–11$; Fig. 4A, $n = 7–8$; B, $n = 5–6$) and OLT (Fig. 1B, $n = 7–9$) were performed 2 h after oral administration.

The oral glucose tolerance test (OGTT) and intraperitoneal insulin tolerance test (IPITT)

Glucose-lowering effects were assessed using OGTT and IPITT on day 7. OGTT was performed as previously reported[17,18,28] with slight modifications. Briefly, glucose solution was orally administered at a dose of 2 g/kg to mice fasted for 18 h. Blood was then collected from the tail vein. Blood glucose levels were immediately measured before and 15, 30, 60, and 90 min after glucose administration using One Touch Ultra View (LifeScan Japan Corp., Tokyo, Japan). MCTs were orally administered 2 h before the administration of glucose (Fig. 2B, C, $n = 8–9$). IPITT was referred to previous report[28]. Insulin (0.5 U/kg) was administered to mice fasted for 6 h, and blood glucose levels were measured before and 15, 30, and 60 min after the administration. Similarly, MCTs were orally administered 2 h before the administration of insulin (Fig. 2A, $n = 9–10$).

Measurement of plasma ketone concentrations

Under sevoflurane anesthesia, blood samples were collected from the fundus 2 h after the administration of MCTs (Fig. 3B, $n = 12–13$). β-ketone concentrations were measured using the electronic handheld device, FreeStyle Precision Neo (Abbott GmbH & Co., Wiesbaden, Germany).

ELISA assay

Blood samples were collected, similarly to 2.5 (Fig. 3A, $n = 10–12$). The LBIS Mouse Insulin ELISA Kit (FUJIFILM Wako Pure Chemical Co., Osaka, Japan) was used to measure insulin concentrations, while the GLP-1 Total ELISA 96-well Plate Assay (EMD Millipore Corp., MA, USA) was employed to assess GLP-1 concentrations according to the manufacturers' instructions.

GLP-1 secretion in STC-1 cells

STC-1 cells were grown in Dulbecco's modified Eagle's medium (Sigma-Aldrich Co., STL, USA) supplemented with 10% fetal bovine serum, 100 IU/mL penicillin, and 100 μg/mL streptomycin in a humidified 5% CO_2 atmosphere at 37 °C. Cells were seeded in 96-well culture plates at a density of 3.3×10^4 cells/well and cultured overnight until 80–90% confluence was reached. Cells were washed twice with PBS to remove culture media and were then exposed to TC10, DC10, and MC10 (100 μM) dissolved in HEPES buffer (140 mM NaCl, 4.5 mM KCl, 20 mM HEPES, 1.2 mM $CaCl_2$, 1.2 mM $MgCl_2$, 10 mM D-glucose, and 0.1% BSA, pH 7.4) containing 0.1% DMSO at 37 °C for 10 min. After the incubation, supernatants were collected, centrifuged at 800 × *g* at 4°C for 5 min to remove remaining cells, and then stored at − 80 °C for the later measurement of GLP-1 concentrations.

Data analysis

All values were expressed as means ± SEM. An analysis of variance (ANOVA) followed by the Student's *t*-test or Dunnett's test was used to assess differences among two or three or more groups, respectively. *P*-values < 0.05 were considered to be significant.

Results

Oral administration of TC8 and TC10 attenuated HFD-induced cognitive decline in mice

The chronic intake of HFD has been reported to reduce cognitive function[29] and we previously demonstrated that the intake of HFD for 1 week exerted similar effects[17–19]. In NORT, the approach time to the novel object was shorter by mice fed HFD for one week than by mice fed the normal diet[17,18]. Orally administered TC8 and TC10 significantly increased approach times to the novel object, whereas TC12 did not (Fig. 1A). The same results were observed in OLT (Fig. 1B). Collectively, these results suggest that TC8 and TC10 attenuated HFD-induced cognitive decline in different two paradigms in mice.

Orally administered TC8 and TC10 decreased blood glucose levels independent of insulin sensitivity

Impaired glucose tolerance is a risk factor for cognitive decline[30,31]. Using mice fed HFD and administered MCTs, we performed OGTT and IPITT to examine changes in glucose tolerance and insulin sensitivity, respectively. Body weight and food intake remained unchanged after three consecutive days of MCTs (Fig. S1A, B). IPITT showed that blood glucose levels were also unchanged (Fig. 2A). In OGTT, TC8 and TC10 both significantly

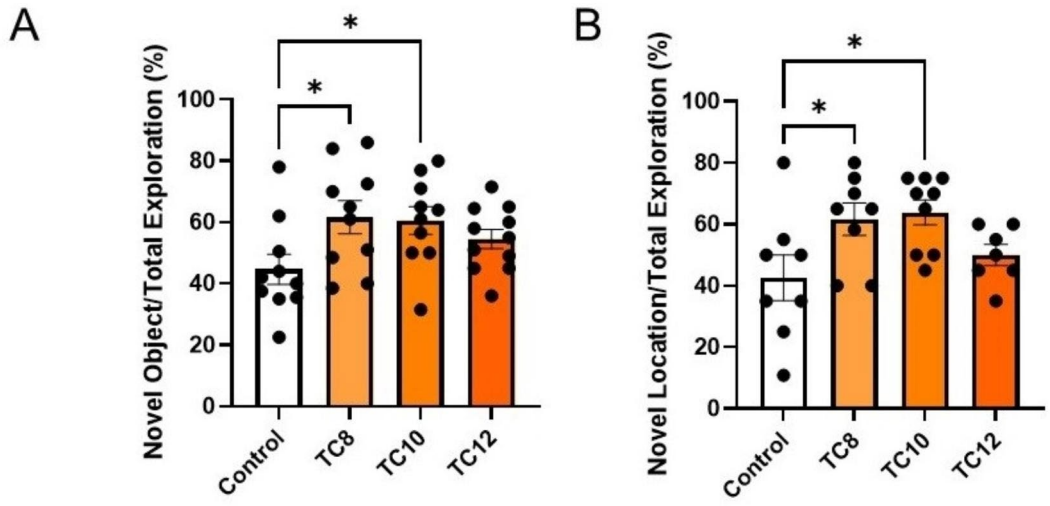

Fig. 1. MCTs attenuated cognitive decline induced by the intake of HFD. Mice were fed HFD for one week and were then orally administered water or MCTs at a dose of 250 mg/mouse (once a day for 3 days). (A) Thereafter, the novel object recognition test (NORT) was performed. (B) The object location test (OLT) was also performed similarly to NORT. All values are means ± SEM (A, $n = 10–11$; B, $n = 7–9$). *$P < 0.05$ vs. the control group.

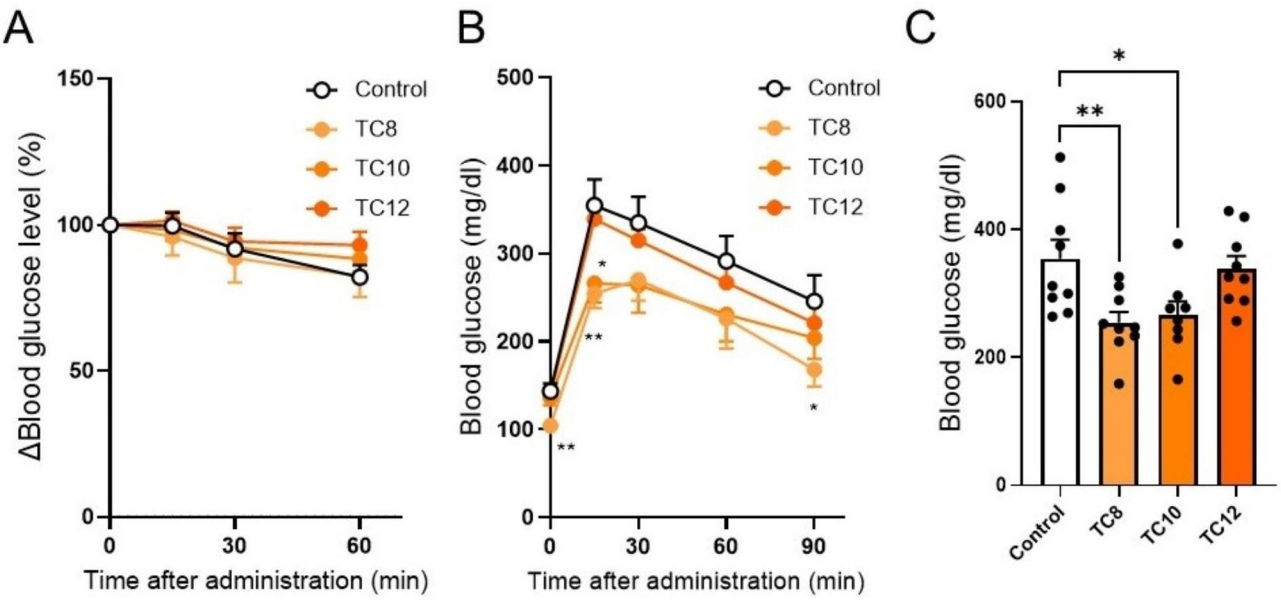

Fig. 2. Effects on blood glucose levels in mice fed HFD. (A) IPITT and (B, C) OGTT were performed. All values are means ± SEM (A, $n = 9–10$; B, C, $n = 8–9$). $^{*}P < 0.05$, $^{**}P < 0.01$ vs. the control group.

reduced blood glucose levels after the glucose injection (Fig. 2B, C). Therefore, these results indicate that TC8 and TC10 improved glucose tolerance and deceased blood glucose levels independent of insulin sensitivity.

TC8 and TC10 increased plasma concentrations of GLP-1

Based on the results obtained from OGTT and IPITT and previous findings[5], which showed that TC10 affected glucose homeostasis through the secretion of GLP-1, we focused on insulin secretion, not sensitivity, and measured the plasma concentrations of insulin and GLP-1, an incretin, which promotes insulin secretion[32]. MCTs did not significantly affect plasma insulin concentrations (data not shown). TC8 and TC10 significantly increased plasma GLP-1 concentrations, whereas TC12 did not (Fig. 3A). These results suggest that TC8 and TC10 stimulated GLP-1 signals to improve glucose metabolism.

The intake of MCTs increases plasma ketone concentrations, and a previous study reported that caprylic acid (C8:0) induced 3- and 6-fold greater increases in blood ketone concentrations than capric acid (C10:0) and lauric acid (C12:0), respectively[33]. We administered MCTs to mice and measured the plasma concentration of β-hydroxybutyrate, the most abundant ketone in blood. Consistent with previous findings[33], the administration

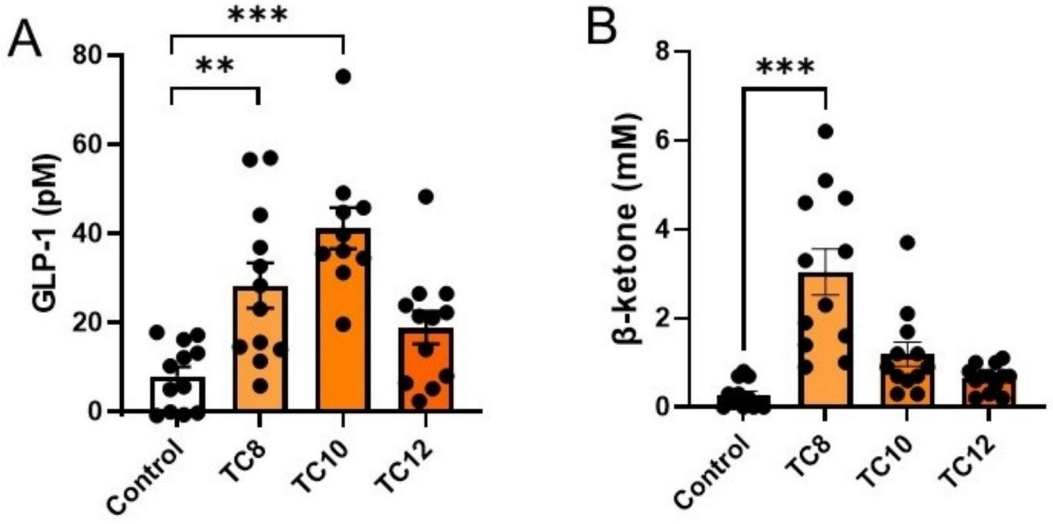

Fig. 3. Changes in blood parameters in mice treated with MCTs. We measured plasma (A) GLP-1 and (B) β-ketone concentrations in mice administered MCTs. All values are means ± SEM (A, $n = 10–12$; B, $n = 12–13$). $^{**}P < 0.01$, $^{***}P < 0.001$ vs. the control group.

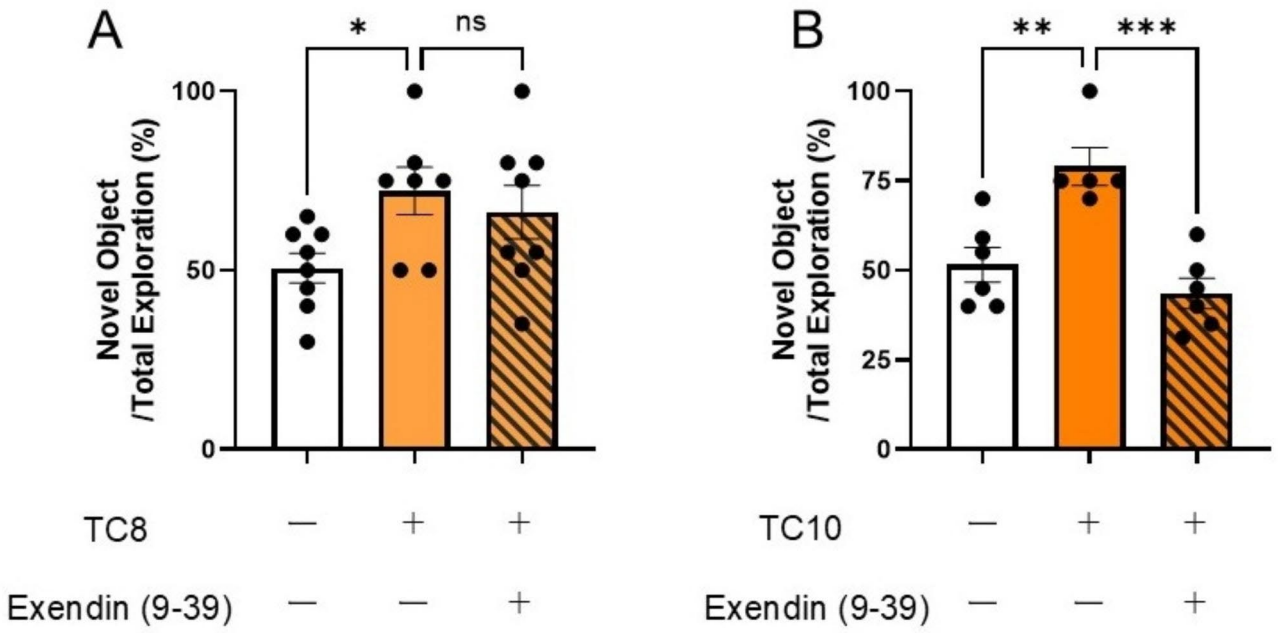

Fig. 4. Exendin(9–39), an antagonist of GLP-1 receptors, abolished the attenuation of cognitive decline by TC10, but not TC8. We performed NORT using mice administered exendin(9–39) (0.1 mg/kg, i.p.) 30 min before the administration of (A) TC8 and (B) TC10. All values are means ± SEM (A, $n = 7–8$; B, $n = 5–6$). $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ vs. the MCT-administered group.

of TC8 significantly increased plasma β-hydroxybutyrate concentrations, whereas TC10 and TC12 did not (Fig. 3B). These results indicate that the administration of MCTs increased the production of ketones, and also that the effects of TC8 may be associated with ketones.

The attenuation of cognitive decline by orally administered TC10 was blocked by a GLP-1 receptor antagonist

Previous studies reported that the GLP-1 analog liraglutide, which is used to treat diabetes, improved cognitive function in humans and animals[34,35]. Therefore, we herein investigated whether exendin(9–39), a GLP-1 receptor antagonist, had an impact on the MCT-induced attenuation of cognitive decline using NORT. We confirmed that intraperitoneally administered exendin(9–39) did not affect the approach time to the novel object at a dose of 0.1 mg/kg (data not shown). Furthermore, it did not change the effects of TC8 (Fig. 4A), but inhibited those of TC10 (Fig. 4B). Therefore, the oral administration of TC10 appeared to attenuate cognitive decline via GLP-1 receptors, which differs from the mechanism of action of TC8.

Discussion

The present study showed that TC8 and TC10 attenuated HFD-induced cognitive decline through different mechanisms of action. Many researchers have investigated the relationship between MCT intake and cognitive function, mainly with a focus on MCTs as an alternative energy source to glucose. Other functions of MCTs, such as their roles as signaling molecules, remain unclear. To elucidate a causal relationship, we examined the effects of the short-term ingestion of MCTs on cognitive decline. The results obtained suggest that TC10 ameliorated cognitive decline via GLP-1 signaling, which is a different mechanism of action from that of TC8.

TC10 attenuated cognitive decline, but did not significantly affect plasma ketone concentrations or hippocampal mitochondria, suggesting a different mechanism of action from that of TC8. GLP-1 receptors are expressed in the brain, including the hippocampus, which is associated with memory[36]. GLP-1 crosses the blood-brain barrier, binds to receptors, and triggers physiological responses[35,37,38]. Peripherally administered GLP-1 analogs, which are commonly used in medical treatment, have been shown to improve cognitive function[34]. These findings suggest that peripherally secreted GLP-1 affects brain function. Based on the results obtained herein, orally administered TC10 appeared to affect brain function via GLP-1 signaling; however, TC10 itself and its degradation products cannot cross the blood-brain barrier. Therefore, GLP-1 may be a mediator between the gastrointestinal tract and brain in the regulation of brain function. To the best of our knowledge, this is the first study to show that TC10 attenuated cognitive decline via GLP-1 signaling, which may contribute to new discoveries regarding improvements in cognitive function.

Triglycerides do not pass through the blood-brain barrier and are rapidly degraded by lipases. We previously reported that a diglyceride produced by the enzymatic digestion of triglycerides exhibited a higher ghrelin secretory capacity[39]. MCTs in which all three constituent fatty acids are MCFAs are not abundant in breast milk, accounting for only 0.8 to 1.1% of all triglycerides. On the other hand, MCTs including one or two MCFA account for approximately 50% of all triglycerides. Therefore, triglycerides comprising MCFAs, which are present

in small amounts in breast milk, or their degradation products may function as signaling molecules rather than as an efficient energy source. Indeed, 2-MC10 stimulated the secretion of GLP-1 (Fig. S4).

The intake of HFD induces not only cognitive decline, but also glucose metabolism disorders, in which blood glucose levels become abnormally high during fasting or after meals. These disorders may occur when the effects of insulin, a unique hormone that lowers blood glucose levels to the normal range, are impaired due to obesity, insulin resistance, or a decreased ability to secrete insulin. Previous studies suggested a relationship between diabetes and cognitive decline[40], and diabetes has been estimated to increase the risk of dementia by approximately 60%[41]. In the present study, TC8 and TC10 also improved glucose metabolism. Therefore, the effects of TC8 may involve ketone synthesis, while those of TC10 involve the secretion of GLP-1; however, further studies are needed to confirm this.

Ketones have been shown to play a critical role in cognitive function because they are an energy source for mitochondria, the primary source of neuronal energy[30]. Mitochondrial function declines with age, is affected by behavioral and environmental factors, and may ultimately lead to Alzheimer's disease[42]. In the present study, TC8 increased plasma ketone concentrations and the concentration of hippocampal mitochondria (Fig. S2), but did not affect the mRNA expression of neurotrophic factors in the hippocampus (Fig. S3). These results indicate that TC8 increased blood ketone concentrations and normalized hippocampal mitochondria function to ameliorate cognitive decline; however, further investigations of its direct effects on the hippocampus are needed.

We found that the administration of TC8 and TC10, which have similar structures, ameliorated cognitive decline via different mechanisms. The mechanisms by which MCTs improve cognition are widely considered to involve improvements in brain metabolism due to the ketogenic effect[43]. However, the present study showed that TC10-induced cognitive improvements were more closely associated with the secretion of GLP-1. The results obtained herein imply that even if MCTs are similar in structure, they may have different and sometimes opposing effects and pathways. It has been suggested that multi-targeted therapeutics may be superior to single-targeted ones[44,45]. Whereas single-targeted agents may cause desensitization and resistance formation, multi-targeted agents potentially have additive and synergistic effects. It seems reasonable that food components, which often exist in mixtures, could exert their effects through multiple pathways. In addition, despite extensive research, the ratios of MCTs that are effective in treatment of cognitive decline have yet to be established. This may be because the optimal ratio depends on the condition of each individual's body, including the brain. The present study provides novel insights into the mechanisms by which MCTs improve cognitive function, which will facilitate their application to the treatment of diabetes and cognitive dysfunction. Further investigations, including longer-term studies and broader data analyses on the detailed mechanism of MCT, will be needed.

Conclusions

TC8 and TC10, which are both MCTs, attenuated cognitive decline and improved glucose metabolism via different mechanisms of action. The administration of TC8 increased plasma ketone concentrations, while that of TC10 promoted the secretion of GLP-1 and ameliorated cognitive decline. This is the first study to suggest that TC10 attenuates cognitive decline in mice via GLP-1 receptor.

Data availability

The original work presented in this study is included in the article/supplementary material. For all other inquiries, contact the corresponding author.

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Author contributions

K. Ohinata supervised and designed the experiments; M. Shobako, K. Kawano, and E. Taniguchi performed the experiments and analyzed the data; M. Shobako and K. Ohinata wrote the paper; and all authors discussed the results and the manuscript.

Declarations

Competing interests

The authors declare no competing interests.

Additional information

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