Clinical Interventions in Aging

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ORIGINAL RESEARCH

Effect of the Casein-Derived Peptide Met-Lys-Pro on Cognitive Function in Community-Dwelling Adults Without Dementia: A Randomized, Double-Blind, Placebo-Controlled Trial

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Naoki Yuda[1]
Miyuki Tanaka[1]
Koji Yamauchi[1]
Fumiaki Abe[1]
Izumi Kakiuchi[2]
Kyoko Kiyosawa[2]
Mitsunaga Miyasaka[2]
Naoki Sakane[3]
Masahiko Nakamura[4]

[1]Food Ingredients and Technology Institute, Morinaga Milk Industry Co., Ltd., Zama, Kanagawa, Japan; [2]Department of Nursing, Matsumoto Junior College, Matsumoto, Nagano, Japan; [3]Division of Preventive Medicine, Clinical Research Institute, National Hospital Organization Kyoto Medical Center, Kyoto, Japan; [4]Matsumoto City Hospital, Matsumoto, Nagano, Japan

Background: Preventative measures have recently been taken to reduce the incidence of Alzheimer's disease worldwide. We previously showed that Met-Lys-Pro (MKP), a casein-derived angiotensin-converting enzyme inhibitory peptide with the potential to cross the blood–brain barrier, attenuated cognitive decline in a mouse model of Alzheimer's disease. However, the effect of MKP on cognitive function improvement in humans remains unknown. This exploratory study sought to investigate whether MKP intake could improve cognitive function in adults without dementia.

Methods: A total of 268 community-dwelling adults without dementia participated in this 24-week randomized controlled trial. Participants were randomly allocated to the MKP (n = 134) or placebo (n = 134) group. The MKP group received four tablets daily, each containing 50 μg MKP, while the placebo group received four dextrin tablets containing no detectable MKP for 24 weeks. Scores on the Japanese version of the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog) were used as the primary outcome to compare cognitive function between the MKP and placebo groups. The study products were also evaluated for safety.

Results: The intention-to-treat analysis showed that there was no significant difference between the groups in terms of the ADAS-cog total score. Orientation, as measured by the respective ADAS-cog subscale, was significantly improved compared to placebo at 24 weeks post-MKP administration (P = 0.022). No serious adverse events due to MKP intake were observed.

Conclusion: To the best of our knowledge, this is the first study to report the effects of MKP on human cognition. These preliminary results suggested the safety of daily MKP intake and its potential to improve orientation in adults without dementia. Further clinical studies are needed to confirm the present findings and the benefits of MKP on cognitive function.

Keywords: humans, MKP, cognition, cognitive dysfunction, orientation, Alzheimer's disease

Introduction

As global life expectancy rises, the growth in the number of older adults with dementia is unprecedented. The number of individuals living with dementia is predicted to increase from 47 million in 2015 to 132 million by 2050.[1] Alzheimer's disease (AD) is the most common cause of dementia. Cholinesterase inhibitors and N-methyl D-aspartate receptor antagonists have been approved for

Correspondence: Naoki Yuda
Food Ingredients and Technology Institute, Morinaga Milk Industry Co., Ltd., 1-83, 5-Chome, Higashihara, Zama, Kanagawa, Japan
Tel +81 46 252 3051
Fax +81 46 252 3017
Email n-yuda@morinagamilk.co.jp

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the treatment of AD in many countries.[2] Although these drugs provide a moderate treatment effect, they do not completely alter the condition.[3,4] Prevention and care for AD have become urgent worldwide issues. AD progresses for many years before symptoms appear; and when symptoms become clinically apparent, the condition is too advanced for treatment.[5,6] Therefore, taking preventative measures before the onset of clinical symptoms is recommended.[7–9]

Recently, it was suggested that centrally active angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers may lower AD risk or slow its progression, independent of their blood-pressure-lowering effect.[10,11] The activity of ACE is elevated in the brains of patients with AD.[12] Angiotensin II generated by ACE may promote oxidative stress and neuroinflammation, leading to neurodegeneration and brain aging.[13,14] However, several clinical studies have shown that centrally active ACE inhibitors, which cross the blood–brain barrier, prevent the process of neurodegeneration leading to dementia and the incidence of AD.[11,15-17]

Food-derived peptides have been identified as ACE inhibitors.[18] We have previously identified a novel antihypertensive tripeptide, Met-Lys-Pro (MKP), derived from bovine casein.[19] MKP exhibited relatively strong ACE inhibitory activity in vitro (IC_{50} = 0.43 μM), and orally administrated MKP was absorbed into the plasma and reduced blood pressure (BP) in spontaneously hypertensive rats.[20] Moreover, a randomized, double-blind, placebo-controlled, parallel group trial revealed that daily MKP intake is a safe and effective systolic BP (SBP) lowering treatment for individuals with high-normal BP or grade 1 hypertension.[21]

As MKP exhibited relatively strong ACE inhibitory activity, we examined its potential effects on cognitive function. The results showed that oral administration of MKP significantly attenuated cognitive decline in a mouse model of AD.[22] Additionally, the autoradiography data showed that orally administrated[14] C-MKP was distributed in the brain.[22] Therefore, we hypothesized that MKP may act as a centrally active ACE inhibitor and therapeutic agent for cognitive function.

Improving cognitive function by the daily ingestion of effective food ingredients at a pre-AD stage may either prevent or delay the onset of AD.[23] Thus, we sought to conduct a 24-week, randomized, double-blind, placebo-controlled trial to investigate the ability of MKP to improve cognitive function in a population of community-dwelling adults without dementia. Since they represent a population at risk of developing clinical AD, but constitute a group in whom the preclinical disease is believed to be at an early enough stage to still respond to intervention, middle-aged and elderly individuals without dementia were recruited for the study.[6] We used the scores of the Japanese version of the cognitive subscale of the AD Assessment Scale (ADAS-cog)[24,25] as the primary outcome. ADAS-cog is one of the most frequently used instruments to evaluate general cognitive function in clinical trials. To the best of our knowledge, this is the first study to evaluate the effects of MKP on human cognition. Therefore, we used ADAS-cog in this study to broadly examine the effects of MKP on cognitive function. As secondary outcomes, we assessed participants using the Revised Hasegawa's Dementia Scale (HDS-R),[26] the Japanese version of the Montreal Cognitive Assessment (MoCA-J),[27,28] and the eight-item Short-Form Health Survey (SF-8).[29] We also evaluated the safety of MKP.

Methods

Participants

Adult volunteers living in Matsumoto, Japan, and the surrounding areas were recruited through website announcements, advertisements, and mailed invitations. Recruitment was conducted from April to June 2018. The inclusion criteria were as follows: age ≥ 40 years and an HDS-R score of 21–30. The exclusion criteria were as follows: 1) history or presence of dementia; 2) suspected dementia; 3) mental disorders such as schizophrenia and depression; 4) serious diseases of the brain, liver, kidney, heart, lung, gastrointestinal tract, blood, or metabolism; 5) serious allergies to medicine or food; 6) pregnancy, lactation, or pregnancy planning during the study period; 7) ineligibility due to physician's diagnosis based on participant background, physical examination, and interview.

Procedures

The trial was conducted in Matsumoto between June 2018 and February 2019. To investigate the impact of regular MKP intake on cognitive function in community-dwelling adults without dementia, a 24-week randomized, double-blind, placebo-controlled trial was conducted. The study lasted 24 and 2 weeks for treatment and post-treatment observation, respectively. Efficacy assessments were obtained at baseline, week 12, and week 24.

Eligibility was assessed on the basis of interviews, physical examination (BP, height, body weight), self-reported data from health and lifestyle questionnaires, the Geriatric Depression Scale (GDS)[30,31] score, and the HDS-R score. Individuals with scores ≥ 7 on the GDS or ≤ 20 on the HDS-R were excluded from participation. Eligible participants were randomly assigned to receive MKP or placebo tablets in a 1:1 ratio by a person not directly involved in the study using computer-generated lists of random numbers via the randomly permuted block method. The participants, physician, researchers assessing outcomes, and researchers conducting statistical analyses were blinded to the treatment group allocation over the study duration.

The MKP-containing tablets were prepared using casein hydrolysate manufactured by the Morinaga Milk Industry (Tokyo, Japan).[19] The participants in the MKP and placebo groups received four tablets daily, each containing 50 μg MKP in 0.25 g casein hydrolysate, and 0.25 g dextrin with no detectable MKP, respectively. MKP and placebo tablets were matched for appearance.

All participants were encouraged to continue with their usual daily activities and diet throughout the study period. The participants were also asked to maintain a record using diaries, which included items related to supplementation of study products, illness, use of medications or other nutritional supplements, and hospital visits. Study staff interviewed participants before and throughout the study to ensure their compliance with these lifestyle requirements based on the participant diaries. Treatment compliance was assessed by counting the number of tablets returned at the time of the final study visit and inspecting participant diaries.

Outcome Measures

The primary outcome measure was the ADAS-cog score.[24,25] The test, which yields a score ranging from 0 (no errors) to 70 (maximum impairment), assesses memory, language, praxis, and orientation and is composed of 11 subscales (word recall, spoken language ability, comprehension of spoken language, word-finding difficulty, following commands, naming objects and fingers, constructions, ideational praxis, orientation, word recognition, and recall of test instructions) to evaluate general cognitive function.

The secondary outcome measures were the HDS-R, MoCA-J, and SF-8 scores. In Japan, the HDS-R is a neuropsychological battery commonly used for the screening of dementia.[26] Individuals with scores of ≤ 20 out of 30 are diagnosed with suspected dementia. The MoCA-J is a useful screening tool for detecting mild cognitive impairment (MCI).[27,28] The cut-off point of the test for MCI and AD is 25/26 out of 30. To correct for the educational background, 1 point is added for participants with a total score of < 30 and an educational background of < 12 years. The ADAS-cog and MoCA-J were performed at baseline and after 12 and 24 weeks of supplementation. The HDS-R was performed at baseline and after 24 weeks of supplementation. The participants self-reported assessment of physical and mental health at baseline and week 24 was obtained using the SF-8.[29] The Mental Component Summary (MCS) and Physical Component Summary (PCS) scores were calculated.

Safety Monitoring

All intervened participants were monitored throughout the study for adverse events (AEs) and side effects. Safety monitoring comprised a questionnaire that assessed general health and occurrence of any health-related events. The relation of AEs to ingestion of the study products was determined by the physician while remaining blinded to group allocation. The severity of AEs was evaluated according to the Common Terminology Criteria for Adverse Events version 4.0 JCOG/JSCO.

Sample Size

The effect size (d) of the ADAS-cog total score at 24 weeks after MKP intake was estimated to be 0.40. The sample size required to detect a mean ADAS-cog total score difference at $\alpha = 0.05$ and power = 0.90 by the unpaired t-test was calculated at 133 study participants per group, making up a total of 266 study participants. The target sample size was calculated using G*Power 3.1.9.2 (Heinrich Heine Universitat, Dusseldorf, Germany). Considering a 10% dropout rate, approximately 150 participants per group needed to be recruited.

Statistical Analysis

The statistical analysis was based on the intention-to-treat population, which included all randomly assigned participants with at least one observation. Missing data were handled by the available case analysis. Data are presented as means (along with standard deviations). The baseline characteristics of the study groups were compared with the use of the Fisher's exact test for categorical variables and the unpaired t-test for continuous variables. We assessed the continuous variables of efficacy using the analysis of

covariance models to adjust for baseline values, using the week 24 values as the dependent variables. The cognitive test data were also analyzed according to age, MoCA-J score, or medication status by dividing the participants into predefined subgroups. Age was divided by 65, the standard for elderly people in Japan. The MoCA-J score was divided by 26, the standard for suspected MCI. Medication status was divided by whether the participants were using regular medication; temporary medication, such as for colds, was not included. Safety analyses were carried out based on summary listings of AEs, with the Fisher's exact test used for pairwise comparisons. All comparisons were two-tailed, and the statistical significance level was set to $P < 0.05$. All analyses were performed using IBM SPSS Statistics version 23 (IBM Corp., Armonk, NY, USA).

Results

Participants

From a total of 468 participants screened for the study, 268 were enrolled and randomly allocated into the MKP (n = 134) and placebo (n = 134) groups (Figure 1). Out of the 268 enrolled participants, 256 and 253 remained enrolled in the study for 12 weeks and until the end of the study period, respectively. Three randomized participants withdrew before the intervention for personal reasons unrelated to the trial and 12 (six in the MKP and the placebo group, respectively) discontinued; nine (six and three in the MKP and the placebo group, respectively) dropped out during the intervention period due to personal reasons unrelated to the trial, and three (all in the placebo group) due to AEs unrelated to the treatment. The overall dropout rate was 5.6% (15

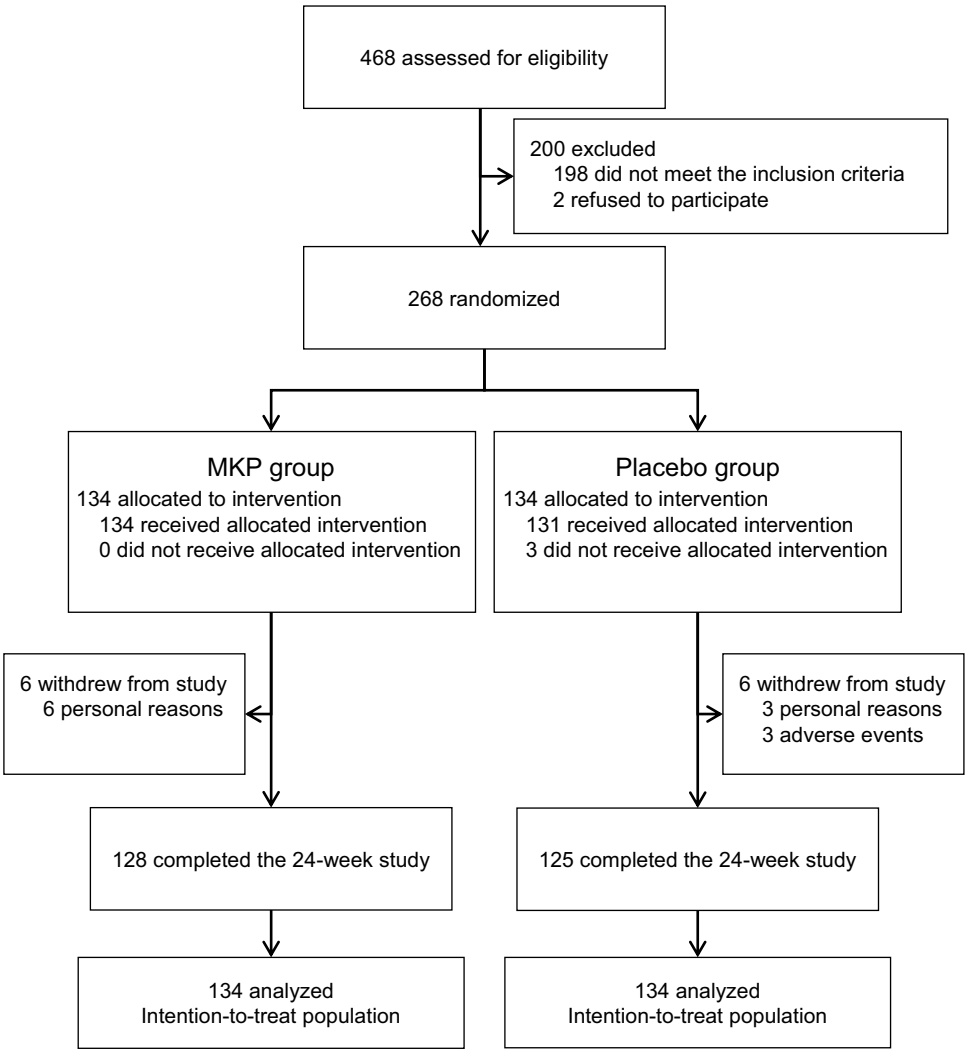

Figure 1 Study flow diagram.
Abbreviation: MKP, Met-Lys-Pro.

of 268). The compliance rates were 96.7% and 96.5% in the MKP and placebo group, respectively, with the difference being nonsignificant. Table 1 shows the baseline characteristics, including sex, age, BP, body mass index (calculated as weight in kg divided by height in m^2), education years, and SF-8, GDS, ADAS-cog, MoCA-J, and HDS-R scores. The two groups did not differ significantly in the baseline demographic variables. In the overall population, the mean age was 68.3 years, the mean ADAS-cog score was 4.1, the mean MoCA-J score was 25.8, and the mean HDS-R score was 28.6. Considering the cut-off threshold of the MoCA-J score (25/26), 58% of all enrolled participants were considered cognitively healthy, and 42% were considered as having a suspected MCI.

Outcomes

A summary of the cognitive test data at baseline and after 12 and 24 weeks is presented in Table 2. After 24 weeks, there was no significant MKP treatment effect on the ADAS-cog total score compared to placebo. Orientation of the participants in the MKP group, as measured by the respective ADAS-cog subscale, significantly improved (P = 0.022, d = 0.30). There were no significant differences between the groups in the other cognitive variables.

We performed a subgroup analysis of age, MoCA-J score, and medication status. The analysis results are shown in Tables 3–5. The study of the subgroup of elderly participants (age ≥ 65 years) revealed a statistically significant treatment effect between the two groups with regard to construction (P = 0.049, d = 0.28) and orientation (P = 0.039, d = 0.34), as measured by the respective subscales of the ADAS-cog (Table 3). There were no significant differences between the groups in terms of other cognitive variables in the subgroup analysis by age. The P values for the interaction between treatment and age were 1.000 for construction and 0.869 for orientation. The study of the subgroup of cognitively healthy participants (MoCA-J score ≥ 26) revealed a statistically significant treatment effect for orientation (P = 0.029, d = 0.37) and HDS-R score (P = 0.033, d = 0.37) between the two groups (Table 4). There were no significant differences between groups in terms of the other cognitive variables in the subgroup analysis by MoCA-J score. The P values for the interaction between treatment and MoCA-J scores were 0.181 for orientation and 0.140 for the HDS-R score. The analysis of the subgroup "without medication" revealed a statistically significant treatment effect for orientation (P = 0.003, d = 0.62) between the two groups (Table 5). There were no significant differences between the groups in terms of the other cognitive variables in the subgroup analysis by medication status. The P value for the interaction between treatment and medication status was 0.235 for orientation. Table 6 presents the MCS and PCS values of SF-8 before and after daily intake of MKP or placebo. There was no significant MKP treatment effect on SF-8 compared to placebo.

Table 1 Baseline Characteristics of the Participants

Characteristics	MKP (n = 134)	Placebo (n = 134)
Male/female, n	43/91	42/92
Age, years [range]	68.1 (8.4) [43–92]	68.5 (8.0) [46–88]
SBP, mmHg	126.1 (13.2)	127.2 (14.4)
DBP, mmHg	71.4 (9.4)	73.5 (10.5)
BMI, kg/m^2	23.0 (2.9)	22.5 (3.0)
Education, years	13.2 (1.7)	13.0 (1.8)
SF-8 (PCS)	61.7 (8.1)	62.3 (7.2)
SF-8 (MCS)	51.8 (5.5)	52.1 (4.7)
GDS	1.6 (1.6)	1.5 (1.5)
ADAS-cog [range]	4.1 (2.2) [0.3–12.3]	4.1 (2.1) [0.3–10.0]
MoCA-J [range]	25.8 (2.8) [18–30]	25.9 (2.9) [16–30]
HDS-R [range]	28.7 (1.5) [23–30]	28.6 (1.3) [23–30]

Note: Data represent numbers or means (with standard deviations).
Abbreviations: MKP, Met-Lys-Pro; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; SF-8, Short Form-8; PCS, Physical Component Summary; MCS, Mental Component Summary; GDS, Geriatric Depression Scale; ADAS-cog, cognitive subscale of the Alzheimer's Disease Assessment Scale; MoCA-J, Japanese version of the Montreal Cognitive Assessment; HDS-R, Revised Hasegawa's Dementia Scale.

Safety

As shown in Table 7, there was no significant difference between the groups in the incidence of AEs during the 24 weeks of treatment and 2 weeks of post-treatment observation. In total, 306 AEs were reported by the 243 participants throughout the study; 145 were reported by 114 participants in the MKP group and 161 by 129 participants in the placebo group. Upper respiratory infection was the most common AE (32.1% in the MKP vs 33.6% in the placebo group, P = 0.896). No AE was related to the study products.

Discussion

In recent years, the search for the best strategy to reduce AD incidence and prevalence in cognitively healthy individuals at a risk of developing AD has attracted marked attention.[8] In fact, a considerable body of epidemiological evidence supports that modifiable lifestyle-related factors are associated with the development of pre-dementia and dementia

Table 2 Summary of the Cognitive Tests in the Intention-to-Treat Population

	Group	Baseline	Week 12	Week 24	*P* value	ES (*d*)
Number of participants	M P	134 134	129 127	128 125		
ADAS-cog total score	M P	4.08 (2.17) 4.10 (2.10)	3.94 (2.14) 4.21 (2.38)	3.18 (1.88) 3.43 (2.10)	0.302	0.12
Word recall	M P	2.33 (1.17) 2.40 (1.22)	2.69 (1.27) 2.87 (1.47)	1.85 (1.16) 1.93 (1.13)	0.635	0.08
Spoken language ability	M P	0.01 (0.09) 0.00 (0.00)	0.00 (0.00) 0.00 (0.00)	0.00 (0.00) 0.00 (0.00)	NA	NA
Comprehension of spoken language	M P	0.00 (0.00) 0.00 (0.00)	0.00 (0.00) 0.00 (0.00)	0.00 (0.00) 0.00 (0.00)	NA	NA
Word-finding difficulty	M P	0.00 (0.00) 0.00 (0.00)	0.00 (0.00) 0.00 (0.00)	0.00 (0.00) 0.00 (0.00)	NA	NA
Following commands	M P	0.28 (0.48) 0.31 (0.55)	0.29 (0.52) 0.23 (0.42)	0.27 (0.46) 0.22 (0.42)	0.299	0.11
Naming	M P	0.00 (0.00) 0.00 (0.00)	0.01 (0.09) 0.00 (0.00)	0.00 (0.00) 0.00 (0.00)	NA	NA
Constructions	M P	0.09 (0.42) 0.10 (0.30)	0.02 (0.12) 0.03 (0.18)	0.01 (0.09) 0.08 (0.41)	0.054	0.24
Ideational praxis	M P	0.09 (0.42) 0.04 (0.29)	0.03 (0.28) 0.09 (0.44)	0.03 (0.28) 0.02 (0.18)	0.625	0.07
Orientation	M P	0.10 (0.32) 0.13 (0.38)	0.08 (0.32) 0.11 (0.34)	0.05 (0.26) 0.15 (0.38)	0.022*	0.30
Word recognition	M P	1.18 (1.06) 1.13 (1.00)	0.83 (0.88) 0.88 (0.99)	0.97 (0.94) 1.01 (1.01)	0.677	0.04
Recall of test instructions	M P	0.01 (0.09) 0.01 (0.09)	0.00 (0.00) 0.00 (0.00)	0.00 (0.00) 0.01 (0.09)	0.313	0.13
MoCA-J	M P	25.82 (2.83) 25.87 (2.91)	26.36 (2.61) 26.18 (2.64)	27.34 (2.24) 27.14 (2.50)	0.417	0.08
HDS-R	M P	28.67 (1.50) 28.57 (1.34)		28.18 (2.04) 28.08 (1.99)	0.885	0.05

Notes: Data represent numbers or means (with standard deviations). *$P < 0.05$ (vs placebo). *P* values were derived by the analysis of covariance (the scores at week 24 were adjusted for the baseline score).

Abbreviations: M, Met-Lys-Pro; P, placebo; ADAS-cog, cognitive subscale of the Alzheimer's Disease Assessment Scale; MoCA-J, Japanese version of the Montreal Cognitive Assessment; HDS-R, Revised Hasegawa's Dementia Scale; ES, effect size; NA, not available because scores of both groups at week 24 were 0.

syndromes in later life.[32] Furthermore, several healthy dietary plans and food compositions have preventive effects on cognitive decline.[23,33-35] The present study showed that MKP supplementation may have the potential to improve orientation in community-dwelling adults without dementia, with good tolerability, and no treatment-related AEs, during the 24 weeks of treatment and 2 weeks after treatment. In addition, although our data were exploratory, the results of the pre-specified subgroup analyses suggested that the benefits of MKP may be more likely to appear in elderly individuals aged ≥ 65 years, those with healthy cognitive function, and those who do not use regular medications. Therefore, this study's results suggested that MKP may be effective in treating individuals in the preclinical stage of AD or dementia, especially elderly people who are not suffering from any disease. Orientation is the ability to correctly identify one's own location in space and time and serves as a useful indicator of cognitive decline.[36]

Table 3 Subgroup Analysis of the Cognitive Tests by Age

	Group	Age < 65 Years		Age ≥ 65 Years	
		Baseline	Week 24	Baseline	Week 24
Number of participants	M P	33 35	32 32	101 99	96 93
ADAS-cog total score	M P	3.35 (2.25) 3.09 (1.67)	2.88 (1.80) 2.68 (1.33)	4.32 (2.10) 4.45 (2.12)	3.28 (1.91) 3.69 (2.25)
Word recall	M P	1.81 (1.12) 1.97 (0.96)	1.75 (1.19) 1.86 (0.91)	2.50 (1.14) 2.54 (1.27)	1.88 (1.15) 1.96 (1.20)
Spoken language ability	M P	0.00 (0.00) 0.00 (0.00)	0.00 (0.00) 0.00 (0.00)	0.01 (0.10) 0.00 (0.00)	0.00 (0.00) 0.00 (0.00)
Comprehension of spoken language	M P	0.00 (0.00) 0.00 (0.00)	0.00 (0.00) 0.00 (0.00)	0.00 (0.00) 0.00 (0.00)	0.00 (0.00) 0.00 (0.00)
Word-finding difficulty	M P	0.00 (0.00) 0.00 (0.00)	0.00 (0.00) 0.00 (0.00)	0.00 (0.00) 0.00 (0.00)	0.00 (0.00) 0.00 (0.00)
Following commands	M P	0.30 (0.47) 0.29 (0.57)	0.31 (0.47) 0.16 (0.37)	0.28 (0.49) 0.31 (0.55)	0.26 (0.46) 0.25 (0.43)
Naming	M P	0.00 (0.00) 0.00 (0.00)	0.00 (0.00) 0.00 (0.00)	0.00 (0.00) 0.00 (0.00)	0.00 (0.00) 0.00 (0.00)
Constructions	M P	0.00 (0.00) 0.03 (0.17)	0.00 (0.00) 0.00 (0.00)	0.12 (0.48) 0.12 (0.33)	0.01 (0.10)* 0.11 (0.48)
Ideational praxis	M P	0.03 (0.17) 0.00 (0.00)	0.00 (0.00) 0.00 (0.00)	0.11 (0.47) 0.05 (0.33)	0.04 (0.32) 0.02 (0.21)
Orientation	M P	0.18 (0.46) 0.09 (0.37)	0.03 (0.18) 0.06 (0.25)	0.07 (0.26) 0.14 (0.38)	0.06 (0.28)* 0.18 (0.42)
Word recognition	M P	1.02 (1.20) 0.69 (0.62)	0.79 (1.03) 0.60 (0.60)	1.23 (1.00) 1.28 (1.07)	1.03 (0.90) 1.16 (1.09)
Recall of test instructions	M P	0.00 (0.00) 0.03 (0.17)	0.00 (0.00) 0.00 (0.00)	0.01 (0.10) 0.00 (0.00)	0.00 (0.00) 0.01 (0.10)
MoCA-J	M P	26.79 (2.13) 27.09 (2.63)	27.66 (1.94) 28.25 (1.34)	25.50 (2.97) 25.44 (2.89)	27.24 (2.33) 26.76 (2.70)
HDS-R	M P	28.79 (1.14) 28.74 (1.07)	29.28 (0.96) 29.41 (1.07)	28.63 (1.60) 28.51 (1.42)	27.81 (2.18) 27.62 (2.03)

Notes: Data represent numbers or means (with standard deviations). *$P < 0.05$ (vs placebo). Data were analyzed by the analysis of covariance (the scores at week 24 were adjusted for the baseline score).

Abbreviations: M, Met-Lys-Pro; P, placebo; ADAS-cog, cognitive subscale of the Alzheimer's Disease Assessment Scale; MoCA-J, Japanese version of the Montreal Cognitive Assessment; HDS-R, Revised Hasegawa's Dementia Scale.

Therefore, systematic dietary supplementation with MKP may be a promising intervention toward safe and improved orientation before the onset of AD or dementia.

We previously described the effect of MKP, an ACE inhibitory peptide with the potential to cross the blood–brain barrier, on cognitive function in an AD mouse model induced by intracerebroventricular injection of amyloid-β (Aβ) 42 using the Morris water maze.[22] In addition, the hippocampus was collected after behavioral testing, and inflammatory cytokine and nicotinamide adenine dinucleotide phosphate oxidase subunit expression were measured.[22] Consequently, daily administration of casein hydrolysate containing MKP markedly attenuated Aβ42-induced cognitive decline and reduced Aβ42-induced tumor necrosis factor-α, monocyte chemoattractant protein-1, inducible nitric oxide synthase, $p47^{phox}$, and $gp91^{phox}$ expression. A clinicopathological study of

Table 4 Subgroup Analysis of the Cognitive Tests by MoCA-J Score

	Group	MoCA-J < 26		MoCA-J ≥ 26	
		Baseline	Week 24	Baseline	Week 24
Number of participants	M P	57 55	54 52	77 79	74 73
ADAS-cog total score	M P	5.25 (2.10) 5.19 (1.96)	4.15 (2.10) 4.17 (2.09)	3.22 (1.79) 3.34 (1.85)	2.48 (1.34) 2.90 (1.95)
Word recall	M P	2.93 (1.09) 2.95 (1.13)	2.44 (1.20) 2.31 (1.15)	1.89 (1.02) 2.01 (1.13)	1.41 (0.91) 1.66 (1.04)
Spoken language ability	M P	0.02 (0.13) 0.00 (0.00)	0.00 (0.00) 0.00 (0.00)	0.00 (0.00) 0.00 (0.00)	0.00 (0.00) 0.00 (0.00)
Comprehension of spoken language	M P	0.00 (0.00) 0.00 (0.00)	0.00 (0.00) 0.00 (0.00)	0.00 (0.00) 0.00 (0.00)	0.00 (0.00) 0.00 (0.00)
Word-finding difficulty	M P	0.00 (0.00) 0.00 (0.00)	0.00 (0.00) 0.00 (0.00)	0.00 (0.00) 0.00 (0.00)	0.00 (0.00) 0.00 (0.00)
Following commands	M P	0.39 (0.53) 0.33 (0.55)	0.30 (0.50) 0.31 (0.47)	0.21 (0.44) 0.29 (0.56)	0.26 (0.44) 0.16 (0.37)
Naming	M P	0.00 (0.00) 0.00 (0.00)	0.00 (0.00) 0.00 (0.00)	0.00 (0.00) 0.00 (0.00)	0.00 (0.00) 0.00 (0.00)
Constructions	M P	0.14 (0.35) 0.15 (0.36)	0.00 (0.00) 0.13 (0.60)	0.05 (0.46) 0.06 (0.25)	0.01 (0.12) 0.04 (0.20)
Ideational praxis	M P	0.14 (0.58) 0.02 (0.13)	0.02 (0.14) 0.04 (0.28)	0.05 (0.22) 0.05 (0.35)	0.04 (0.35) 0.00 (0.00)
Orientation	M P	0.19 (0.44) 0.29 (0.53)	0.11 (0.37) 0.23 (0.47)	0.03 (0.16) 0.01 (0.11)	0.01 (0.12)* 0.10 (0.30)
Word recognition	M P	1.43 (1.13) 1.44 (1.02)	1.29 (1.19) 1.14 (0.84)	0.99 (0.96) 0.91 (0.93)	0.74 (0.62) 0.92 (1.12)
Recall of test instructions	M P	0.02 (0.13) 0.02 (0.13)	0.00 (0.00) 0.00 (0.00)	0.00 (0.00) 0.00 (0.00)	0.00 (0.00) 0.01 (0.12)
MoCA-J	M P	23.09 (1.84) 22.96 (1.96)	26.13 (2.50) 25.83 (2.85)	27.84 (1.34) 27.90 (1.28)	28.23 (1.52) 28.08 (1.71)
HDS-R	M P	28.07 (1.72) 28.02 (1.52)	27.00 (2.39) 27.50 (2.20)	29.12 (1.12) 28.95 (1.05)	29.04 (1.15)* 28.49 (1.72)

Notes: Data represent numbers or means (with standard deviations). *$P < 0.05$ (vs placebo). Data were analyzed by the analysis of covariance (the scores at week 24 were adjusted for the baseline score).

Abbreviations: M, Met-Lys-Pro; P, placebo; ADAS-cog, cognitive subscale of the Alzheimer's Disease Assessment Scale; MoCA-J, Japanese version of the Montreal Cognitive Assessment; HDS-R, Revised Hasegawa's Dementia Scale.

patients with AD found that spatial and temporal disorientations were associated with neurofibrillary tangle densities in the Brodmann areas 7 and 23, and the CA_1 field of the hippocampus.[37] Although the precise nature of the relationship between MKP and neurofibrillary tangles remains unknown, MKP may improve orientation by improving hippocampal function.

In this study, the ADAS-cog was used as the primary endpoint. Although the ADAS-cog is the gold standard for confirming general cognitive function in AD trials, it has been suggested to be less sensitive in individuals with normal cognitive function and MCI.[38] In this study, the effect size of MKP intake on the ADAS-cog total score was estimated to be 0.40, whereas the actual effect size

Table 5 Subgroup Analysis of the Cognitive Tests by Medication Status

	Group	Without Medication		With Medication	
		Baseline	Week 24	Baseline	Week 24
Number of participants	M P	56 52	51 43	78 82	77 82
ADAS-cog total score	M P	4.01 (2.28) 3.80 (2.21)	3.05 (1.96) 3.05 (1.99)	4.13 (2.10) 4.29 (2.01)	3.27 (1.84) 3.62 (2.14)
Word recall	M P	2.29 (1.18) 2.23 (1.16)	1.75 (1.26) 1.81 (1.13)	2.36 (1.17) 2.50 (1.25)	3.27 (1.84) 2.00 (1.13)
Spoken language ability	M P	0.00 (0.00) 0.00 (0.00)	0.00 (0.00) 0.00 (0.00)	0.01 (0.11) 0.00 (0.00)	0.00 (0.00) 0.00 (0.00)
Comprehension of spoken language	M P	0.00 (0.00) 0.00 (0.00)	0.00 (0.00) 0.00 (0.00)	0.00 (0.00) 0.00 (0.00)	0.00 (0.00) 0.00 (0.00)
Word-finding difficulty	M P	0.00 (0.00) 0.00 (0.00)	0.00 (0.00) 0.00 (0.00)	0.00 (0.00) 0.00 (0.00)	0.00 (0.00) 0.00 (0.00)
Following commands	M P	0.29 (0.49) 0.25 (0.56)	0.25 (0.48) 0.16 (0.37)	0.28 (0.48) 0.34 (0.55)	0.29 (0.45) 0.26 (0.44)
Naming	M P	0.00 (0.00) 0.00 (0.00)	0.00 (0.00) 0.00 (0.00)	0.00 (0.00) 0.00 (0.00)	0.00 (0.00) 0.00 (0.00)
Constructions	M P	0.13 (0.57) 0.12 (0.32)	0.00 (0.00) 0.05 (0.21)	0.06 (0.25) 0.09 (0.28)	0.01 (0.11) 0.10 (0.49)
Ideational praxis	M P	0.11 (0.45) 0.00 (0.00)	0.02 (0.14) 0.00 (0.00)	0.08 (0.39) 0.06 (0.36)	0.04 (0.34) 0.02 (0.22)
Orientation	M P	0.07 (0.26) 0.13 (0.40)	0.00 (0.00)** 0.16 (0.37)	0.12 (0.36) 0.12 (0.36)	0.09 (0.33) 0.15 (0.39)
Word recognition	M P	1.13 (1.10) 1.05 (1.02)	1.03 (1.05) 0.85 (0.93)	1.21 (1.03) 1.18 (0.99)	0.93 (0.86) 1.10 (1.05)
Recall of test instructions	M P	0.00 (0.00) 0.02 (0.14)	0.00 (0.00) 0.02 (0.15)	0.01 (0.11) 0.00 (0.00)	0.00 (0.00) 0.00 (0.00)
MoCA-J	M P	26.55 (2.43) 26.79 (2.52)	27.59 (2.33) 27.65 (2.01)	25.29 (3.00) 25.29 (3.00)	27.18 (2.17) 26.88 (2.70)
HDS-R	M P	28.64 (1.33) 28.79 (1.27)	28.37 (2.02) 28.47 (1.87)	28.69 (1.33) 28.43 (1.37)	28.05 (2.06) 27.88 (2.03)

Notes: Data represent numbers or means (with standard deviations). **$P < 0.005$ (vs placebo). Data were analyzed by the analysis of covariance (the scores at week 24 were adjusted for the baseline score).

Abbreviations: M, Met-Lys-Pro; P, placebo; ADAS-cog, cognitive subscale of the Alzheimer's Disease Assessment Scale; MoCA-J, Japanese version of the Montreal Cognitive Assessment; HDS-R, Revised Hasegawa's Dementia Scale.

was 0.12 (Table 2). Therefore, it may be necessary to use more sensitive neuropsychological tests for cognitively healthy individuals and individuals with MCI to investigate the impact of MKP on cognitive function in more detail.

We previously reported that regular MKP intake was a safe and effective SBP-lowering treatment for individuals with high-normal BP or grade 1 hypertension in clinical trial.[21] In this study, BP was measured only at baseline; thus, the relationship between the MKP effect on orientation and BP was not elucidated. Alternatively, other tests using the AD mouse model showed that MKP intake did not affect BP.[22] Besides, BP before intervention in the present participants was not high (Table 1). Therefore, this

Table 6 Summary of the SF-8 in the Intention-to-Treat Population

	Group	Baseline	Week 24	*P* value
Number of participants	M P	134 134	128 125	
SF-8 (PCS)	M P	61.97 (7.63) 62.31 (7.15)	62.90 (8.16) 62.41 (8.17)	0.263
SF-8 (MCS)	M P	51.90 (5.12) 52.01 (4.75)	50.92 (5.32) 50.48 (5.59)	0.233

Notes: Data represent numbers or means (with standard deviations). *P* values were derived by the analysis of covariance (the scores at week 24 were adjusted for the baseline score).
Abbreviations: SF-8, Short Form-8; M, Met-Lys-Pro; P, placebo; PCS, Physical Component Summary; MCS, Mental Component Summary.

Table 7 Intervened Participants with Adverse Events by System Organ Class

System Organ Class	MKP	Placebo	*P* value
	(n = 134)	(n = 131)	
	n (%)	n (%)	
Infections and infestations	52 (38.8)	54 (41.2)	0.708
Nervous system disorders	16 (11.9)	14 (10.7)	0.847
Gastrointestinal disorders	13 (9.7)	15 (11.5)	0.693
Musculoskeletal and connective tissue disorders	7 (5.2)	9 (6.9)	0.615
Respiratory, thoracic and mediastinal disorders	5 (3.7)	8 (6.1)	0.408
General disorders and administration site conditions	2 (1.5)	1 (0.8)	1.000
Injury, poisoning and procedural complications	2 (1.5)	2 (1.5)	1.000
Cardiac disorders	1 (0.7)	1 (0.8)	1.000
Immune system disorders	1 (0.7)	2 (1.5)	0.619
Neoplasms benign, malignant and unspecified	1 (0.7)	2 (1.5)	0.619
Renal and urinary disorders	1 (0.7)	0 (0.0)	1.000
Reproductive system and breast disorders	1 (0.7)	0 (0.0)	1.000
Skin and subcutaneous tissue disorders	1 (0.7)	5 (3.8)	0.117
Ear and labyrinth disorders	0 (0.0)	1 (0.8)	0.494

Note: *P* values were derived by the Fisher's exact test.
Abbreviation: MKP, Met-Lys-Pro.

result may be independent of the effect of MKP on BP. In the future, to clarify this mechanism of action, it will be crucial to examine how MKP intake affects BP and cognitive function.

Our study had several further limitations. First, considering the effects observed in this trial, the sample size might have been too small to fully evaluate the effect of MKP intake on cognitive function in adults without dementia. In addition, the intervention period was limited to a 24-week period and a single MKP-dose protocol. Furthermore, the MKP impact on patients with manifested dementia remains unknown. It may be necessary to conduct a larger-scale, longer-duration, and multi-dose intervention to detect the MKP effects on adults with and without dementia.

Conclusion

To the best of our knowledge, this is the first study to report the effects of MKP, a casein-derived ACE inhibitory peptide with the potential to cross the blood–brain barrier, on human cognitive function. The results of the present study suggested the safety of daily MKP intake and its potential to improve orientation in adults without dementia. However, this study was exploratory. Therefore, further studies are warranted to confirm these findings and the beneficial effects of MKP on cognitive function.

Data Sharing Statement

The datasets used in the present study are available from the corresponding author on reasonable request.

Ethics Approval and Informed Consent

The study protocol was examined and approved by the institutional review board and the Ethics Committee of Matsumoto Junior College (approval code: 201704). The study was conducted in accordance with the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research Involving Human Subjects (Ministry of Education, Culture, Sports, Science and Technology; Ministry of Health, Labor and Welfare, Japan). After receiving a detailed explanation regarding the study objectives and procedures, all participants provided written informed consent and were informed that they were free to withdraw at any time without obligation. This trial was registered at the University Hospital Medical Information Network Clinical Trials Registry as UMIN000032833 on June 1, 2018.

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Disclosure

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