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Dietary supplementation of arachidonic and docosahexaenoic acids improves cognitive dysfunction

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Abstract

Age-dependent increase of peroxidation of membrane fatty acids such as arachidonic acid (ARA) and docosahexaenoic acid (DHA) in neurons was reported to cause a decline of the hippocampal long-term potentiation (LTP) and cognitive dysfunction in rodents. Although supplementation of ARA and DHA can improve LTP and cognitive function in rodents, their effects in humans are unknown. The present work was undertaken to study whether ARA and DHA have beneficial effects in human amnesic patients. The subjects were 21 mild cognitive dysfunction (12 MCI-A with supplementation and 9 MIC-P with placebo), 10 organic brain lesions (organic), and 8 Alzheimer's disease (AD). The cognitive functions were evaluated using Japanese version of repeatable battery for assessment of neuropsychological status (RBANS) at two time points: before and 90 days after the supplementation of 240 mg/day ARA and DHA, or 240 mg/day of olive oil, respectively. MCI-A group showed a significant improvement of the immediate memory and attention score. In addition, organic group showed a significant improvement of immediate and delayed memories. However, there were no significant improvements of each score in AD and MCI-P groups. It is suggested from these data that ARA and DHA supplementation can improve the cognitive dysfunction due to organic brain damages or aging.
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Keywords: Arachidonic acid; Docosahexaenoic acid; Cognitive dysfunction; Aging; Organic brain lesion

1. Introduction

Ageing is often associated with decline of cognitive functions. In the experimental animals, cognitive function can be evaluated by long-term potentiation (LTP) or behavior test (Bliss and Lomo, 1973; McKernan and Shinnick-Gallagher, 1997; Rogan et al., 1997). Compared with young rats, aged animals usually show a significant decrease of LTP. This decline of LTP was reflected on the behavioral deficits on the Morris water maze test (Kotani et al., 2003; Rosenzweig et al., 1997). Such decline of cognitive functions may be partly due to the age-dependent decrease of membrane $n-6$ polyunsaturated fatty acid (PUFA), especially arachidonic acid (ARA) that is abundant in the hippocampal neurons (Lynch et al., 1994; McGahon et al., 1997; Murray and Lynch, 1998a; Soderberg et al., 1991). Even if the dietary intake of ARA is unchanged, the concentration of ARA in the neuronal membrane may decrease because of the increase of ARA peroxidation with ageing. Accordingly, it seems to be reasonable that water maze performance and synaptic plasticity can be improved with ARA dietary supplementation in the aged rats (Kotani et al., 2003; Murray and Lynch, 1998b). It is likely

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that membrane ARA is indispensable for the maintenance of cognitive function in the aged rats.

On the other hand, docosahexaenoic acid (DHA) is one of the $n-3$ major PUFA that is abundant in the brain and retina. DHA is not only associated with learning-memory and vision (Birch et al., 2000; Carlson and Werkman, 1996), but also is useful for the prevention of ischemic brain damages by means of anti-thrombotic effect (Tsukada et al., 2000). DHA in the brain is known to show an age-dependent decrease like ARA (McGahon et al., 1999).

In humans, decreased cerebral concentration of ARA and DHA are seen with aging and Alzheimer's disease (Soderberg et al., 1991). The cognitive deficits are well known to be associated not only with ageing or Alzheimer's disease, but also with various organic brain diseases such as cerebral infarction, hemorrhage and traumatic brain injuries. Until now, there have been very few effective treatments for the cognitive dysfunction due to ageing, organic brain lesions, or Alzheimer's disease. Certain medicine can merely delay the progress of symptoms, but is not sufficient for improving these cognitive impairments.

The cognitive functions of rodents were assessed by the learning behaviors, while human cognitive function was clinically estimated by the neuropsychological test. Previous neuropsychological assessments of cognitive deficits suffered a lack of appropriately designed test batteries for quickly but precisely screening many human subjects in the clinical practice. However, the repeatable battery for the assessment of neuropsychological status (RBANS) is nowadays becoming a standard screening test battery, because it was designed to assess global neuropsychological functions in a brief administration time (Randolph et al., 1998). Using RBANS, one can precisely estimate five cognitive domains of interest: immediate memory, visuospatial/constructional ability, language, attention, and delayed memory.

Here, we have evaluated the effect of ARA and DHA supplementation upon cognitive dysfunctions due to ageing, organic brain lesions or Alzheimer's disease, using a Japanese version of RBANS neuropsychological test (Yamashima et al., 2002).

2. Methods

2.1. Participants

A total of 40 out-patients of Minami-gaoka Hospital with a chief complaint of amnesia were initially registered in this study. However, one subject with ARA and DHA supplementation dropped out from the study for complaining mild diarrhea in the initial few days. In the end, the remaining 39 patients participated in this study.

Out of 39 patients studied, 21 patients (12 male, 9 female, 68.1 ± 6.3 years old, mean $\pm$ S.D.) were diagnosed as mild cognitive impairment (MCI) according to the modified criteria of Petersen et al. (1999). We made diagnosis of MCI according to the results of the total score of 12 indexes being less than mean minus 1.5 S.D. These MCI patients were randomly subdivided into two groups: one for ARA and DHA supplementation (MCI-A; nine male, three female, 66.9 ± 7.0 years old), while the other for placebo (MCI-P; three male, six female, 69.7 ± 5.2 years old).

Ten patients (four male, six female, 57.5 ± 12.4 years old) had organic brain lesions (organic) such as cerebral infarction, hemorrhage, or traumatic brain injuries with a history of more than 5 years after onset. These patients showed a healed cerebral apoplexy or contusions on magnetic resonance imaging (MRI), and showed a sustained decline in memory lasting more than 5 years. Eight patients (three male, five female, 67.0 ± 6.3 years old) were diagnosed as early Alzheimer's disease (AD) according to the NINCDS-ADRDA and the NINDS-AIREN criteria. AD patients did not have anti-dementia agents before and during PUFA supplementation.

Here MCI-P is a control group of MCI-A, while AD is actually a control of organic group for assessing effects of the present supplementation. Because MCI-P group showed no improvement after supplementation as shown in the results, placebo study of the organic and AD groups was omitted. The patients of MCI-A, organic and AD groups were administrated with 240 mg/day of ARA and the same amount of DHA supplements for 90 days. This administration period was based on the reports of the previous animal experiments by Lynch et al. (1994), Kotani et al. (2003), and Okaichi et al. (2005). In contrast, MCI-P group was administrated 240 mg/day of olive oil. The neuropsychological assessments were done before and after the supplementation, using "Forms A–A" or "Forms A–B" batteries of RBANS.

Investigators performing the RBANS under the instructions of neurologist (NM) and/or neurosurgeon (TY) were blind to the patient's status (i.e. criteria, and the prior neuropsychological test data). All patients were recruited from the out-patient clinic at the Minami-gaoka hospital (Kanazawa, Japan). They gave their informed consent to participate in this study, and had given a comprehensive neuropsychological test battery, which usually took approximately 30 min to complete. This clinical study was done with the approval of the ethical committee of Minami-gaoka Hospital (Kanazawa, Ishikawa, Japan), and the clinical study protocol was based on the tenets of the Declaration of Helsinki.

2.2. Fatty acid supplementation

Commercially available Aravita (Suntory Ltd., Osaka, Japan) contains 40 mg/capsule of ARA and DHA, and 0.16 mg/capsule of asthaxanthin (anti-oxidant of PUFA). Placebo capsule contains 40 mg/capsule of olive oil (major content is oleic acid). Because each subject was administrated 6 capsules/day, daily intake of ARA and DHA, or olive oil was 240 mg, respectively. Both groups showed no change of the serum chemistry data after the 90 days supplementation.

2.3. Neuropsychological assessment

The Japanese version (Yamashima et al., 2002) of RBANS (Randolph et al., 1998) was used. The RBANS comprises of 12 sub tests ((1)–(12)) that are used to calculate five domains of cognitive functions. These comprise of immediate memory ((1) list learning and (2) story learning); visuospatial/constructional ((3) figure copy and (4) line orientation); language ((5) picture naming and (6) semantic fluency); attention ((7) digit span and (8) coding); delayed memory ((9) list recall, (10) list recognition, (11) story recall, and (12) figure recall).

Each index scores was expressed by standard score (T). T can be calculated by the following formula:

$$T = 10\left(\frac{x_a - \bar{x}}{\partial}\right) + 50$$

where x_a is the individual patient's score, $\bar{x}$ the mean value, and ∂ is the standard deviation of generation to whom the patient belongs.

Normal control for the standardization of the Japanese version of RBANS consisted of subjects ranging in their 20s to the 80s (Yamashima et al., 2002) (Fig. 1).

2.4. Statistical analysis

Analysis of variance was used to determine whether there were significant differences in each index score among the four groups. When significant main effects could be detected, multiple post hoc comparisons were performed using Fisher's restricted least difference. The differences in RBANS score between pre- and post-supplementation were evaluated statistically by the paired t-test. A p value of less than 0.05 was considered significant. The statistical analyses were performed with SPSS for windows (version 11.5, SPSS Inc., Chicago, IL, USA).

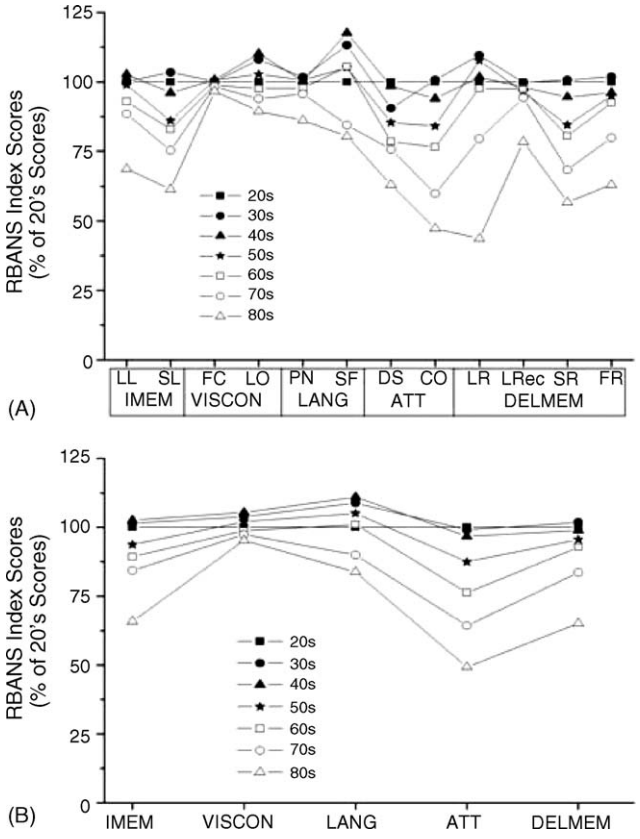

Fig. 1. Standard score profiles of Japanese version of RBANS indexes from 20s to 80s age groups. (A) Both the immediate and delayed memory indexes show an age-dependent decrease. The average score of the 3rd decade was estimated as 100, then the percentile score of the each age group was shown for each 12 subtest indexes. (B) Comparison of the five domain indexes among the different age groups from 20s to 80s. The total participants are 292 normal subjects without any abnormality on the magnetic resonance imaging. LL, list learning; SL, story learning; FC, figure copy; LO, line orientation; PN, picture naming; SF, semantic fluency; DS, digit span, CO, coding; LR, list recall; LRec, list recognition; SR, story recall; FR, figure recall; IMEM, immediate memory; VISCON, visuospatial/constructional; LANG, language; ATT, attention; DELMEM, delayed memory.

3. Results

3.1. RBANS test

Standard score profiles of Japanese version of RBANS indexes were collected from 292 normal subjects, as summarized in Fig. 1. Scores of the 12 subtests in the normal population were shown in Fig. 1A, while those of the five cognitive domains were shown in Fig. 1B. Index scores of the normal population showed an age-dependent decrease, especially in immediate memory, attention and delayed memory indexes. As the score showed a decrease especially over 7th decade, aged subjects over 50 years old were focused as an MCI group in this study.

Form A of RBANS was done for the assessment before the supplementation, while either Form A or B was randomly used for the assessment after the supplementation. As clearly shown in the data of the MCI-P group, no significant practice effect (carry-over effect) were seen for both immediate (Fig. 3) and delayed (Fig. 5) memories regardless of the test battery forms used after the supplementation.

3.2. Representative cases

A 60-year-old male (Fig. 2A, left) suffered from subarachnoid hemorrhage due to the ruptured aneurysm of middle cerebral artery 10 years ago. Since clipping surgery until now, this patient has been complaining of memory impairment. After dietary ARA and DHA supplementation, however, both the immediate and delayed memory seemed to be remarkably improved (Fig. 2B). The delayed memory has recovered almost to the average level (RBANS score of 50) of the same

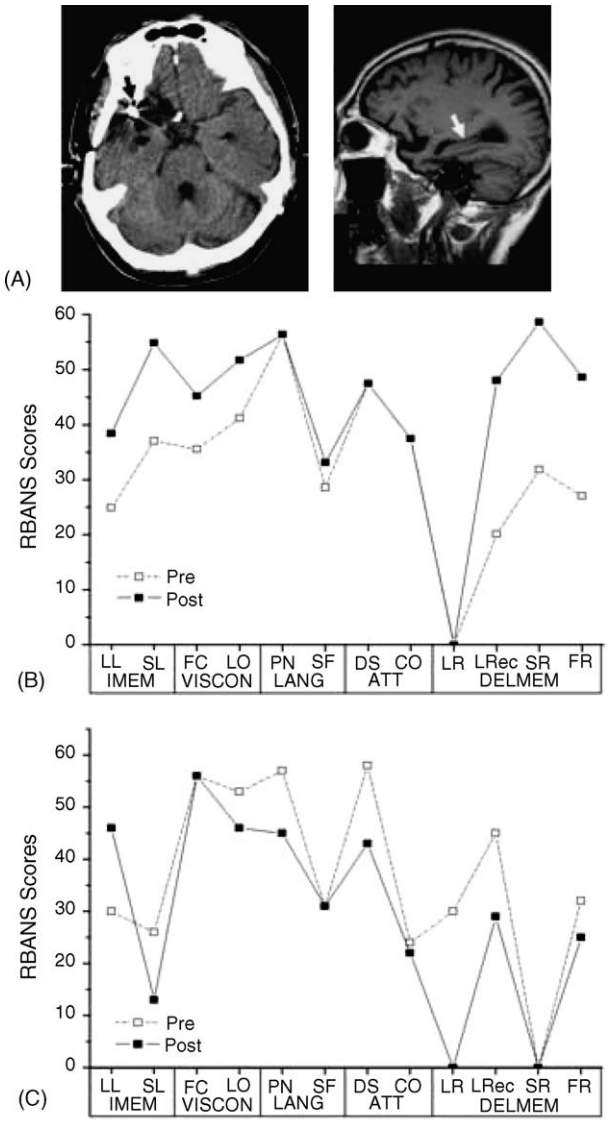

Fig. 2. Representative cases: (A) computed tomography scanning image of organic brain lesion (left) and magnetic resonance image of Alzheimer's disease (right). Black arrow (left) indicates hemostatic clip of the cerebral aneurysm, while white arrow (right) indicates hippocampus with mild atrophy. (B and C) RBANS score before (dotted line) and after (line) 240 mg/day of PUFA (ARA and DHA) supplementation for 90 days. (B) Impairment of the immediate and delayed memories was seen as long as 10 years after subarachnoid hemorrhage of 60-year-old male. The RBANS scores, however, showed a significant recovery after the supplementation. (C) Each index score showed no significant changes after the AEA and DHA supplementation in a 76-year-old female who was diagnosed as early AD.

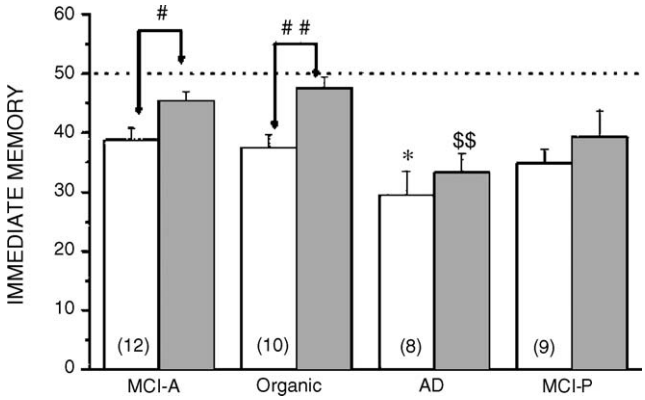

Fig. 3. Comparison of the immediate memory domain between pre- and post-PUFA supplementation in each groups. The AD group showed a significantly lower score compared with the mild cognitive impairment (MCI-A) group before and after the supplementation. Both the MCI-A ($^{\#}p < 0.0$l) and organic brain lesion (organic, $^{\#\#}p < 0.01$) groups showed a significant improvement. MIC-P group showed no significant changes by supplementation. $^{*}p < 0.05$ vs. MCI-A without supplementation, $^{\$\$}p < 0.01$ vs. MCI-A with supplementation. Score of 50 indicates average scores of standard data. Open bars: before supplementation; shaded bars: after supplementation.

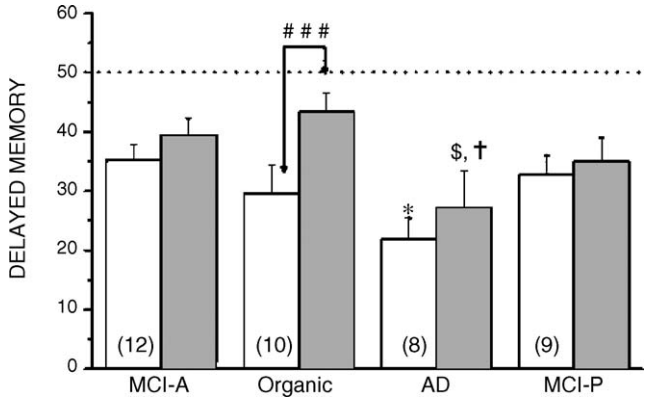

Fig. 5. Comparison of the delayed memory domain. The AD ($^{*}p < 0.05$) group showed a significantly worse score from the MCI-A before supplementation. Among the four groups, the organic group exceptionally showed a significant ($^{\#\#\#}p < 0.00$l) improvement after PUFA supplementation. In contrast, there were no significant effects of supplementation in the MCI-A, MCI-P and AD groups. $^{\$}p < 0.05$ vs. MCI-A with supplementation, $^{\dagger}p < 0.05$ vs. organic with supplementation. Open bars: before supplementation; shaded bars: after supplementation.

generation. In particular, the indexes of story learning, story recall and figure recall were improved.

A 76-year-old female (Fig. 2A, right) was diagnosed as early Alzheimer's disease according to NINCDS-ADRDA, because of the severe impairment of the RBANS index of the memory and language (Randolph et al., 1998). MRI showed mild atrophy of the hippocampus. Each index except for list learning showed rather deterioration even after the ARA and DHA supplementation (Fig. 2C). These two cases showed a remarkable contrast in the effect of ARA and DHA.

3.3. Effect of supplementation

Each RBANS index scores before and after the dietary PUFA supplementation was multiple-compared among the four test groups (MCI-A, MCI-P, organic and AD). Prior to the supplementation, the immediate memory score of MCI-A did not show a significant difference with the MCI-P and organic groups, but with AD (pre, $p < 0.05$; post, $p < 0.01$). Effect of the PUFA supplementation on immediate memory was confirmed in both the MCI-A ($p < 0.01$) and organic ($p < 0.01$) groups (Fig. 3). On the contrary, no significant changes were observed in the MCI-P and AD groups after the supplementation. The visuospatial/construction and language scores showed no significant improvement in any groups by the supplementation (data not shown). Although there was no significant improvement of the attention score in the MCI-P, organic and AD groups, only the MCI-A group showed a significant ($p < 0.05$) improvement. The AD group showed a significantly low ($p < 0.01$) score, compared to the remaining three groups (Fig. 4). No significant improvement of the delayed memory was observed in the MCI-A, MCI-P and AD groups. The AD group showed a significantly ($p < 0.05$) worse score compared to the MCI-A group before and after the supplementation. Although the delayed memory score of the organic group was worse than MCI-A before supplementation, it was significantly ($p < 0.001$) improved after the supplementation (Fig. 5). All of the 10 subjects of the organic group unexceptionally showed certain degrees of improvement.

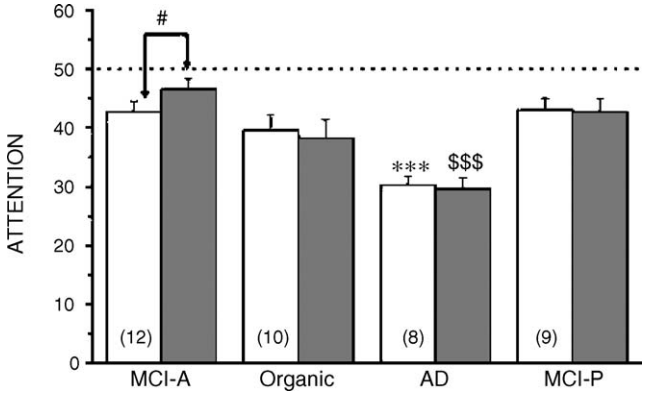

Fig. 4. Comparison of the attention domain. Only the MCI-A group showed a significant ($^{\#}p < 0.05$) improvement of attention. The remaining groups showed no improvement after the PUFA supplementation. The AD group showed significantly low scores before and after supplementation compared with MCI-A group. $^{***}p < 0.01$ vs. MCI-A without supplementation, $^{\$\$\$}p < 0.01$ vs. MCI-A with supplementation. Open bars: before supplementation; shaded bars: after supplementation.

4. Discussion

In this protocol, we studied whether dietary PUFA supplementation can improve cognitive dysfunction. Cognitive functions of the four groups (MCI-A, MCI-P, organic and AD) were evaluated by the Japanese version of RBANS neuropsychologjcal test (Yamashima et al., 2002), before and after the PUFA supplementation. The immediate memory score of the AD group being significantly lower than MCI-A, showed no improvement (Fig. 3). However, the immediate memories of the

MCI-A and organic groups were significantly improved after the supplementation. Intriguingly, the delayed memory score of the organic group improved to the same level of MCI-A after the supplementation (Fig. 5). Solfrizzi et al. reported that intake of high monounsaturated fatty acid such as olive oil was protective against age-related cognitive decline (Solfrizzi et al., 1999). In this study, however, the Placebo group showed no significant improvement of cognitive functions by the supplementation of 240 mg/day of olive oil. Not only the MCI-P but also AD groups showed no improvement after the supplementation of ARA and DHA.

The present human data are compatible with the previous rodent data showing that the dietary PUFA supplementation can improve impairment of hippocampus-dependent cognitive function, as revealed by LTP and water maze task (Kotani et al., 2003; McGahon et al., 1997; Okaichi et al., 2005). The underlying physiological functions such as the regulation of membrane-bound enzymes, control of ionic channel activity and maintenance of various types of receptors, were considered to depend on the membrane fluidity (Yehuda et al., 2002; Zs-Nagy, 1997). Solfrizzi et al. also suggested that unsaturated fatty acid can preserve cognitive functions because it can maintain the structural integrity of neuronal membrane (Solfrizzi et al., 1999). Lu et al. (2001) demonstrated that LTP was induced by a rapid insertion of new AMPA receptors into the dendritic membrane and also by an increased clustering of AMPA receptors at the surface of membranes. The age-dependent decrease in the synaptic plasticity and the transmitter release in hippocampus should be caused by the decrease of membrane fluidity that may disturb rapid insertion and clustering of AMPA receptors. Such membrane fluidity is actually based on the intra membranous concentration of PUFA (Lynch and Voss, 1994). Since the neurotransmitter release requires fusion of the synaptic vesicle with the synaptic membrane, decrease of the membrane fluidity may impair the synaptic transmission (Martin et al., 2002; Muccioli et al., 1996). Although hippocampal neurons in AD show irreversible damages in NMDA receptors to induce and maintain normal LTP, those in MCI-A conceivably retain some potentials for the neural network remodeling. Daw et al. reported that treatment with phorbol ester induced the insertion of AMPA type glutamate receptors into the plasma membrane (Daw et al., 2000). Scheuer et al. demonstrated that piracetam improved cognitive performance in the aged rats by restoring neurochemical deficits (Scheuer et al., 1999). They observed a positive effect of piracetam on NMDA receptor density in hippocampus due to the improvement of membrane fluidity, which might be associated with the positive effects on the cognitive performance.

Recently, adult neurogenesis is well-known to occur in the subventricular zone and the dentate gyrus of hippocampus (Song et al., 2002a; Song et al., 2002b; Tonchev et al., 2003). Interestingly, the rate of adult neurogenesis can be up-regulated by physical exercise and certain drugs (van Praag et al., 1999). Manev et al. and Uz et al. demonstrated that 5-lipoxygenase which is an enzyme involved in the metabolism of arachidonic acid into leukotrienes, was necessary to support the proliferation of neuronal precursors (Manev et al., 2001; Uz et al., 2001). These results suggest that 5-lipoxygenase and/or arachidonic metabolites might be related to adult neurogenesis. Recently, Hama et al. reported that ARA, with the aid of protein kinase C (PKC), may contribute to trigger synaptogenesis and the signal propagation as diffusible intracellular messengers (Hama et al., 2004). Synaptogenesis in the adult brain is regulated by local astrocytes through PKC signaling. Accordingly, it is likely that the improvement of cognitive functions after the ARA supplementation might be due to the improved membrane fluidity that can affect neurogenesis and/or synaptogenesis.

DHA is also known to be crucial for the maintenance and restoration of neural membrane function (Champeil-Potokar et al., 2004; Horrocks and Farooqui, 2004). Especially, astrocytes being essentially important for the neurotransmission and neuroprotection, require DHA to restore the $n-3$/$n-6$ PUFA balance in their membrane phospholipids (Champeil-Potokar et al., 2004). The amount of DHA in the astrocyte membrane may be a key factor affecting the cognitive and sensitive components, and changing the lipid signaling by the release of ARA and production of eicosanoids (Yehuda et al., 1998). Although the increase of the regional cerebral blood flow (rCBF) in response to the vibrotactile stimulation was significantly lower in the somatosensory cortex of aged monkeys compared to young monkeys, supplementation of DHA may increase rCBF as reported previously (Tsukada et al., 2000). Namely, DHA might be directly involved in improvements not of the synaptic plasticity and cognitive function, but of the membrane function and rCBF.

In summary, there were some reports suggesting the effect of $n-3$ fatty acids such as EPA and DHA on cognitive functions in human subjects (Boston et al., 2004; Horrocks and Yeo, 1999), but very few reports have focused on the effect of $n-6$ fatty acids. The present pilot study of ARA and DHA supplementation showed remarkable memory improvements in the human patients with organic brain lesion or MCI. We speculate that such improvements are conceivably due to both the neuronal circuit remodeling by the possible up-regulation of synaptogenesis and/or neurogenesis with the aid of ARA, and the improvement of the membrane function and rCBF by DHA.

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