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Forum Minireview

Pharmacology in Health Foods: Effects of Arachidonic Acid and Docosahexaenoic Acid on the Age-Related Decline in Brain and Cardiovascular System Function

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Abstract. Arachidonic acid (ARA) and docosahexaenoic acid (DHA) are major constituents of cell membranes and play important roles in preserving physiological and psychological function. Recently, data from several studies have indicated that impairments in long-term potentiation (LTP), the process underlying plasticity in synaptic connections, are associated with a decrease in membrane ARA and DHA in aged rats; and treatment of aged rats with either of these polyunsaturated fatty acids (PUFAs) reverses age-related decrease in LTP and the decrease in membrane fatty acid concentration. This review focuses on our recent findings concerning the effects of ARA and DHA on the age-related decline in the function of the brain and cardiovascular system. ARA supplementation decreased P300 latency and increased P300 amplitude of event-related potentials in healthy elderly men. Cognitive impairments in patients with mild cognitive impairment (MCI) and patients with organic brain lesions were significantly improved with ARA and DHA supplementation. ARA and DHA supplementation also increased coronary flow velocity reserve in elderly individuals; this suggests beneficial effects of PUFAs on coronary microcirculation. In conclusion, ARA and DHA may be beneficial in preventing and/or improving age-related declines in brain and cardiovascular system function.

Keywords: arachidonic acid, docosahexaenoic acid, age-related decline, brain function, cardiovascular system, health food

1. Introduction

The importance of arachidonic acid (ARA) and docosahexaenoic acid (DHA) was originally established in infant neurodevelopment. These fatty acids are supplied by breast milk and rapidly accumulate in the brain during the first postnatal year. Reports of enhanced intellectual development in breastfed children and reports linking polyunsaturated fatty acid (PUFA) deficiency with neurodevelopmental disorders have stressed the physiological importance of ARA and DHA in the nervous systems.

Data from several recent studies have indicated that impairments in long-term potentiation (LTP), the process underlying plasticity in synaptic connections, is associated with a decrease in membrane PUFAs, specifically ARA and DHA, in aged rats (1 – 5). Treatment of aged rats with either of these PUFAs has been shown to reverse age-related decrease in LTP and decrease in membrane fatty acid concentrations (1 – 5). These findings suggest that ARA and DHA are important not only for infants but also for the nervous systems of the elderly.

DHA-enriched triacylglycerol (TAG) oil from fish oil is commercially available. It is expected that highly purified oils rich in ARA will be widely used not only in infant formulas but also in nutritional products and food supplements. In the last few decades, advances in microbiological technology have enabled supplementation of TAG oil with ARA (6). Safety studies on ARA-enriched TAG oil obtained from *Mortierella alpina* have been conducted using healthy subjects in the USA (1.5 g/day for 50 days) and in Japan (838 mg/day for 4 weeks). Both studies found that supplementation with ARA-enriched TAG safely increases ARA concentrations in blood

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plasma and erythrocytes (7 – 10).

In this review, I propose the possible administration of ARA and/or DHA as nutritional products and food supplements to prevent or improve age-related decline in brain and cardiovascular function.

2. Dietary ARA preserves synaptic plasticity in aged rats

In a study by McGahon et al. (1), a group of aged and young rats received an experimental diet supplemented with ARA and γ-linolenic acid, while the remaining aged and young rats received a control diet supplemented with corn oil. The rats that received the experimental diet exhibited a marked induction of sustained LTP, while the rats given the control diet failed to exhibit LTP induction.

We examined whether synaptic plasticity was preserved in aged rats fed an ARA-containing diet. Young (2-month-old) and 2 groups of aged (2-year-old) male Fischer-344 rats were given either a control diet or a diet containing ARA-enriched TAG for at least 3 months. Aged rats receiving the ARA-supplemented diet tended to perform better in the Morris water maze task than did aged rats receiving control diet. LTP induced by titanic stimulation was recorded from 300-μm-thick hippocampal slices with a 36-channel multi-electrode array positioned at the dendrites of CA1 pyramidal neurons. The degree of potentiation after 1 h in aged rats given the ARA diet was comparable to that of young control rats. Phospholipid analysis revealed that ARA and DHA were the major fatty acids in the hippocampus of aged rats. There were correlations between the behavioural measure and the changes in excitatory postsynaptic potential slope and between the physiologic measure and the total amount of ARA in the hippocampus (11).

3. ARA supplementation decreases P300 latency and increases P300 amplitude of event-related potentials in healthy elderly men

Event-related potentials (ERPs) have been used to non-invasively evaluate neurophysiologic disturbances associated with aging and neurodegenerative disorders. The most intensively investigated ERP measure in aging has been the P300 component (12). P300 latency reflects changes in neural activity in development and aging. A meta-analysis of P300 findings in normative aging studies by Polich (13) suggested that P300 latency could provide useful information on the cognitive changes associated with aging. During childhood and adolescence, P300 latency is inversely correlated with age and is positively correlated with age during adulthood; P300 amplitude tends to decrease with age (14, 15). These findings suggest that cognitive function may be evaluated by determining P300 latency and amplitude.

We examined the effects of ARA on age-related ERP changes in 25 healthy elderly men. This study was performed using a double-blind crossover design. The subjects were given daily capsules containing either 600 mg ARA-enriched TAG (240 mg ARA) or 600 mg olive oil as the inactive placebo. The capsules were administered for 1 month. ERPs were measured before ARA supplementation and after 1 month of supplementation; P300 latency and amplitude were also measured. P300 latency was significantly shorter, and P300 amplitude was significantly higher in the subjects receiving ARA than in subjects receiving olive oil (Table 1). Subjects receiving ARA also exhibited a significant increase in ARA content in serum phospholipids (Table 2). These findings suggest that supplementing with ARA can improve cognitive dysfunction in healthy elderly men (16).

4. Dietary ARA and DHA supplementation alleviates cognitive dysfunction

Rodent cognitive function can be assessed by examining learning behaviours, while human cognitive function is clinically estimated by neuropsychological testing. Previous neuropsychological assessments of cognitive deficits suffered from a lack of appropriately designed testing batteries for screening numerous human subjects quickly but accurately. However, the repeatable battery for the assessment of neuropsychological status (RBANS) is becoming the standard screening testing battery because it was designed to assess global neuropsychological functions in a short period of time (17). RBANS precisely estimates 5 cognitive domains of interest: immediate memory, visuospatial/constructional ability, language, attention, and delayed memory. We have evaluated the effects of ARA and DHA supplementation on cognitive dysfunctions of the patients with mild cognitive impairments (MCI), organic brain lesions (organic), or Alzheimer's disease (AD), using the Japanese version of RBANS (18).

The subjects included 21 patients with MCI, 10 patients with organic brain lesions, and 8 patients with AD. Cognitive function was evaluated at 2 time points: prior to and 90 days after supplementation with 240 mg/day ARA and 240 mg/day DHA. MCI patients supplemented with ARA and DHA showed a significant improvement in the immediate memory and attention score. In addition, patients in the organic group showed a significant improvement in immediate and delayed memory after ARA and DHA supplementation. However, there were no significant improvements in any of the scores in AD

Table 1. Changes of P300 latency and P300 amplitude with ingested oils

	OO-group			ARA-group		
	Before ingestion	After ingestion	Δ value	Before ingestion	After ingestion	Δ value
P300 latency (ms)	385.5 ± 26.7	387.4 ± 32.1	1.9 ± 14.1	391.1 ± 29.7	381.0 ± 30.5	−10.1 ± 15.9*
P300 amplitude (μV)	9.7 ± 3.7	9.4 ± 3.3	−0.3 ± 1.4	9.0 ± 4.1	9.8 ± 3.6	0.8 ± 1.7*

OO-group, the subjects ingested olive oil capsules; ARA-group, the subjects ingested arachidonic acid–enriched triglyceride capsules. Each value is the mean ± S.D. ANOVA including the factors sequence, period, and treatment was conducted to evaluate changes from the baseline in P300 latency and P300 amplitude. *$P < 0.05$.

Table 2. Changes of fatty acid contents (μg/ml) in serum phospholipids with ingested oils

	Fatty acid	Fatty acid content (μg/ml) in OO-group			Fatty acid content (μg/ml) in ARA-group		
		Before ingestion	After ingestion	Δ value	Before ingestion	After ingestion	Δ value
16:0	Palmitic acid	402.7 ± 54.1	422.7 ± 74.6	20.0 ± 65.0	415.3 ± 63.7	420.8 ± 84.2	5.5 ± 61.8
18:0	Stearic acid	237.8 ± 36.0	248.9 ± 45.9	11.1 ± 38.0	243.2 ± 40.2	255.6 ± 47.9	12.4 ± 39.5
18:1 n-9	Oleic acid	141.6 ± 34.8	146.2 ± 43.5	4.6 ± 28.7	146.4 ± 33.1	145.3 ± 42.4	−1.2 ± 31.9
18:2 n-6	Linoleic acid	287.2 ± 49.4	291.9 ± 60.8	4.6 ± 58.5	286.0 ± 74.9	294.6 ± 58.8	8.6 ± 67.3
20:3 n-6	DGLA	32.1 ± 8.2	29.1 ± 6.4	−3.0 ± 6.9	28.3 ± 9.5	29.9 ± 8.1	1.6 ± 10.7
20:4 n-6	ARA	138.9 ± 27.7	135.7 ± 24.7	−3.2 ± 15.3	137.9 ± 32.0	175.6 ± 37.5	37.7 ± 26.2***
18:3 n-3	α-Linolenic acid	3.1 ± 1.5	2.7 ± 2.0	−0.3 ± 1.6	2.9 ± 1.8	2.7 ± 2.2	−0.2 ± 2.3
20:5 n-3	EPA	61.3 ± 28.6	66.8 ± 33.2	5.6 ± 25.3	73.5 ± 32.8	60.5 ± 28.4	−13.0 ± 20.3*
22:6 n-3	DHA	141.3 ± 26.1	141.3 ± 35.0	0.0 ± 29.8	151.1 ± 33.3	149.7 ± 37.4	−1.5 ± 24.8
	Total fatty acids	1550.6 ± 222.7	1589.8 ± 279.2	39.2 ± 247.5	1591.6 ± 246.8	1642.4± 309.6	50.8 ± 240.2

DGLA, dihomo-γ-linolenic acid; ARA, arachidonic acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid. OO-group, the subjects ingested olive oil capsules; ARA-group, the subjects ingested ARA-enriched triglyceride capsules. Each value is the mean ± S.D. ANOVA including the factors sequence, period, and sample was conducted to evaluate changes from the baseline in fatty acid contents in serum phospholipids. *$P < 0.05$, ***$P < 0.001$.

patients. These data suggest that ARA and DHA supplementation can improve cognitive dysfunction of the patients with MCI and organic brain lesions (19).

5. Effects of dietary ARA supplementation on age-related changes in endothelium-dependent vascular responses in rats

It has been reported that dietary ARA supplementation can alleviate age-related neural dysfunction in aged rats (1, 6). However, little is known about the involvement of membrane ARA in age-related cardiovascular dysfunction. The purpose of the following study was to determine whether supplementing the diet of aged rats with ARA could improve age-related cardiovascular dysfunction.

Young (2-month-old) and aged (22-month-old) male Fisher-344 rats were randomly separated into a control diet group (young control, YC; old control, OC) and an ARA-containing diet group (young ARA, YA; old ARA, OA). After a 2-month feeding period, vascular responses were evaluated using aortic rings denuded of the endothelium or with intact endothelium. Vasoconstriction responses to phenylephrine (α_1-adrenoceptor agonist) were augmented in the endothelium-intact rings from the OC group compared with those of YC and YA groups, although this augmentation was significantly suppressed by dietary ARA supplementation. There were no significant differences in vascular responses to phenylephrine in endothelium-denuded rings among the 4 groups. Acetylcholine (ACh)-induced, endothelium-dependent vasorelaxation was attenuated in the OC and OA groups compared with those in the YC and YA groups. ARA supplementation slightly enhanced ACh-induced vasorelaxation in aged rats. ACh-induced vasorelaxation correlated very well with aortic ARA concentrations in aged rats, but not in young rats. There were no significant differences in endothelium-independent vasodilator responses to sodium nitroprusside in any of the groups. These findings suggest that dietary ARA supplementation improves age-related endothelial dysfunction that leads to various cardiovascular diseases (20).

Table 3. Coronary flow data PUFA supplement

	Baseline	1 Month after	3 Months after
PUFA supplement			
Diastolic mean velocity, cm/s			
at rest	17 ± 7	17 ± 7	17 ± 17
hyperaemia	62 ± 20	65 ± 20	73 ± 19*
Coronary flow velocity reserve	3.85 ± 1.04	4.01 ± 0.99	4.46 ± 0.95*
Placebo			
Diastolic mean velocity, cm/s			
at rest	16 ± 6	16 ± 5	16 ± 4
hyperaemia	59 ± 12	59 ± 13	64 ± 12
Coronary flow velocity reserve	3.98 ± 0.83	3.95 ± 0.79	4.04 ± 0.82

PUFA, polyunsaturated fatty acid. Each value is the mean ± S.D. Two-way repeated-measures analysis of variance. *$P < 0.01$.

6. ARA and DHA supplementation increases coronary flow velocity reserve (CFVR) in Japanese elderly individuals

Epidemiological studies have suggested that consumption of dietary PUFAs decreases the risk of cardiovascular events (21, 22). Based on epidemiological evidence and clinical studies, the dietary intake of n-3 fatty acids, such as α-linoleic acid and fish oils, has been suggested to counteract atherosclerosis and to have anti-inflammatory, antithrombotic, and anti-arrhythmic effects (23, 24). A recent study showed that the decline in membrane ARA concentrations is reversed by supplementation of ARA (1), whereas another recent study showed that n-6 PUFA neither counteracts nor augments the cardiovascular benefits of a modest intake of n-3 PUFA (25). The purpose of the study was to evaluate the effects of ARA and DHA on coronary circulation in elderly individuals using CFVR measurements by transthoracic Doppler echocardiography (TTDE). CFVR is considered a useful physiological index of coronary circulation (26). Recent developments in TTDE allow for non-invasive estimation of CFVR (27).

A double-blind, placebo-matched study of 28 Japanese elderly individuals (19 men, 9 women; mean age 65 years) was conducted to compare the effects of PUFAs (ARA, 240 mg/day; DHA, 240 mg/day) and placebo on CFVR. Coronary flow velocity (CFV) of the left anterior descending coronary artery was measured by TTDE at rest and during hyperaemia to determine CFVR.

There were no significant differences in CFV at rest or during hyperaemia or in baseline CFVR in the 2 groups. After 3 months of PUFA supplementation, CFV during hyperaemia was significantly higher in the PUFA-supplemented group than in the placebo group, although no significant differences were found in resting CFV between the 2 groups. Thus, CFVR significantly increased with PUFA consumption (Table 3).

Three months of PUFA supplementation increased CFVR in Japanese elderly individuals, suggesting that PUFAs have beneficial effects on coronary microcirculation (28).

7. Conclusion

These data suggest that ARA and/or DHA may be beneficial in preventing and improving age-related decline of brain and cardiovascular system function.

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