The Effect of Docosahexaenoic Acid on Aggression in Young Adults

A Placebo-controlled Double-blind Study

Tomohito Hamazaki,* Shigeki Sawazaki,* Miho Itomura,‡ Etsuko Asaoka,*‡ Yoko Nagao,§ Nozomi Nishimura,§ Kazunaga Yazawa,‖ Toyomi Kuwamori,¶ and Masashi Kobayashi*

**The First Department of Internal Medicine, Toyama Medical and Pharmaceutical University, Toyama 930-01; ‡Toyama Medical and Pharmaceutical University, School of Medicine; §Yokkaichi University, Junior College, Yokkaichi 512; ‖Sagami Chemical Research Center, Kanagawa 229; and ¶Toyama Women's Junior College, Toyama 930-01, Japan*

Abstract

41 students took either docosahexaenoic acid (DHA)-rich oil capsules containing 1.5–1.8 grams DHA/day (17 females and 5 males) or control oil capsules containing 97% soybean oil plus 3% fish oil (12 females and 7 males) for 3 mo in a double-blind fashion. They took a psychological test (P-F Study) and Stroop and dementia-detecting tests at the start and end of the study. The present study started at the end of summer vacation and ended in the middle of mental stress such as final exams. In the control group extraggression (aggression against others) in P-F Study was significantly increased at the end of the study as compared with that measured at the start ($\Delta = +8.9\%$, $P = 0.0022$), whereas it was not significantly changed in the DHA group ($\Delta = -1.0\%$). The 95% CI of differences between the DHA and control groups were −16.8 to −3.0%. DHA supplementation did not affect the Stroop and dementia-detecting tests. Thus, DHA intake prevented extraggression from increasing at times of mental stress. This finding might help understand how fish oils prevent disease like coronary heart disease. (*J. Clin. Invest.* 1996. 97:1129–1133.) Key words: coronary heart disease • P-F Study • fish oil • Stroop test • mental stress

Introduction

Docosahexaenoic acid (DHA)[1] is found in the phospholipid fraction of the brain as a major polyunsaturated fatty acid and the major n-3[2] fatty acid (1). The depletion of n-3 fatty acids from diets through two generations appears to affect the brain and retinal functions of animals. Neuringer et al. (2) reported that the deprivation of n-3 fatty acids in rhesus monkeys during gestation and postnatal development caused subnormal visual acuity at 4–12 wk of age and prolonged recovery time of the dark-adapted electroretinogram after saturating flash. They suggested that dietary n-3 fatty acids are essential for normal prenatal and postnatal development of the retina and brain. It seems that the higher functions of the brain more complex than simple visual acuity are also affected by n-3 fatty acids. According to Yamamoto et al. (3), the deprivation of n-3 fatty acids through two generations decreased the correct response ratio in a brightness-discrimination-learning test in spontaneous hypertensive rats and normotensive Wistar rats. The reports described above (2, 3) all indicate important effects of DHA (or n-3 fatty acids) on the central nervous system functions during prenatal and postnatal periods. However, to our knowledge, it is not known whether supplemental DHA has any effects on the higher functions of the brain in young adults.

Fish oils influence many physiological and pathophysiological aspects of the human and animal body (4–7). However, there are very few behavioral studies using n-3 fatty acids. So, our purpose of the present study is to determine whether DHA, one of the major n-3 fatty acids in fish oils, has any effects on aggression. We also checked whether the speed of judgment was modulated by DHA intake.

Methods

Subjects. The purpose and plan of the present study was explained to two classes of university students to recruit volunteers; one was a fourth-year class of Toyama Medical and Pharmaceutical University, and the other was a second-year class in Yokkaichi University. The total number of 53 nonsmoking students of Toyama Medical and Pharmaceutical University (21–30 yr of age [median 22], 16 females and 19 males) and Yokkaichi University (19–20 yr of age, 18 females and no males) volunteered to enter into two parallel trials. Those subjects had been judged healthy through physical examinations and interview by physicians and by blood tests 3–4 mo before the entry to the study. The subjects did not regularly take any drugs. They were randomly divided into control and DHA groups in a double-blind fashion (Table I). Written informed consent was obtained from each subject, and the study was approved by the ethical committee of Toyama Medical and Pharmaceutical University.

Study design and oils. The design of the study is shown in Fig. 1. The study took place in the two universities on the same protocol

Address correspondence to Tomohito Hamazaki, M.D., Ph.D., The First Department of Internal Medicine, Toyama Medical and Pharmaceutical University, 2630 Sugitani, Toyama-shi, Toyama 930-01, Japan. Phone: 764-34-2281 x2504; FAX: 764-34-5025.

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1. *Abbreviations used in this paper:* CHD, coronary heart disease; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid.

2. n-3 defines the number of the carbon at which the last double bond is located.

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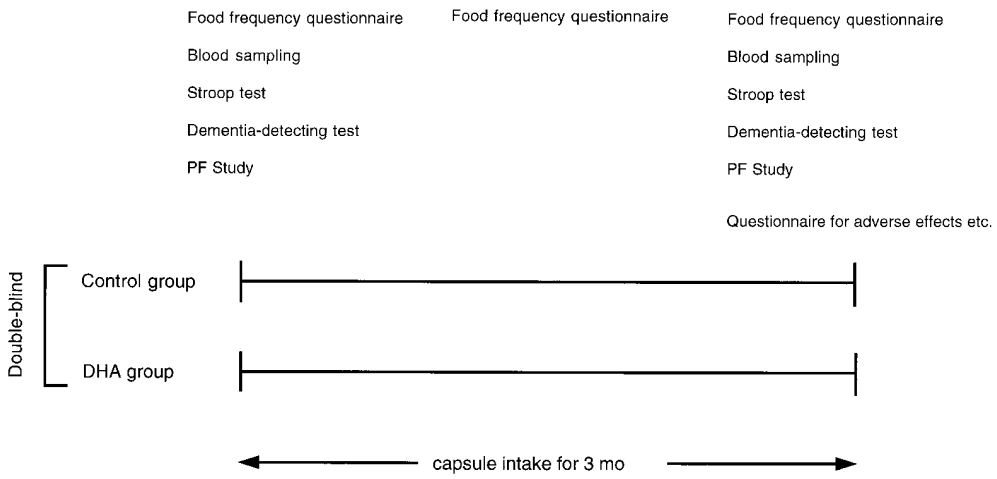

Figure 1. Design of the present study.

with common manuals beginning and ending on the same days. Subjects were asked to fill out food frequency questionnaires three times during the study and another questionnaire about adverse effects of capsules at the end of the study. We periodically counted remaining capsules to monitor capsule intake. Fasting blood was taken for analysis of the fatty acid composition of the total serum fatty acid fraction (8). Mental and psychological tests were performed at the start and end of the study.

All subjects were asked to keep their body weight and physical activity as constant as possible and not to change their food custom during the study. They were also asked to take 10–12 capsules containing either DHA-rich fish oil for the DHA group or control oil for the control group for 3 mo. The number of capsules to take was decided according to subjects' body weight; 10 capsules for $\leq$ 50 kg, 11 for $\leq$ 55 and 12 for $>$ 55. Each capsule contained 300 mg of oil with 0.3% α-tocopherol. The fish oil used for the DHA group contained 49.3% (wt/wt) DHA, 6.7% eicosapentaenoic acid (EPA), 9.0% palmitic acid, 7.3% oleic acid, 3.3% arachidonic acid, 3.2% palmitoleic acid 2.3% stearic acid and others. Consequently, subjects in the DHA group ingested 1.5–1.8 grams DHA/day from capsules. The control oil was a mixture of 97% soybean oil and 3% another fish oil that had been deodorized only partially. The composition of the control oil was 54.1% linoleic acid, 22.3% oleic acid, 10.8% palmitic acid, 6.8% α-linolenic acid, 3.7% stearic acid, 0.5% DHA and others. We added fish oil to the base of the control oil (soybean oil) to make the control oil smell sightly fishy.

P-F Study, and Stroop and dementia-detecting tests. P-F Study was originally developed by Rosenzweig (9). We used the adult form of the Japanese version (10). This psychological test consisted of 24 pictures illustrating frustration. Subjects were asked to look at pictures and describe their first reactions (replies) with a couple of sentences. Their reactions were regarded as aggression (assertiveness), and aggression was analyzed according to its direction (extraggression, aggression against others; intraggression, aggression against self; and imaggression, aggression against nobody).

Stroop test was a test to measure accuracy and speed of instantaneous judgment of the meaning of a color-meaning word written in a different color. We created a new version for our own purpose. All subjects were asked to write down, in one of the two Japanese alphabet systems (hiragana), the meaning or color of up to 168 color meaning words, written in Chinese characters or English in different colors, in 5 min. They took the same Stroop test at both start and end of the study.

Dementia-detecting test was originally created by Kaneko et al. (11) for assessing the degree of early dementia of elderly people. We revised it for students to assess the higher functions of the brain. This test required two kinds of ability at the same time, namely to pick out certain indicated letters from several sentences composing a short story and understand the story itself. There were 10 such stories in our revised test; each story had different instructions about which kind of letters to pick out and put a circle on, and a different question about the story. All subjects were asked to answer as many questions

Table I. The Number of Subjects at the Start and Selection of Subjects to Analyze

	Control group			DHA group		
		Toyama Yokkaichi			Toyama Yokkaichi	
Number of subjects at randomization	8F	9M	9F	8F	10M	9F
Exclusion steps						
Dropout	1F*	1M				
Significant body weight changes	1F (−4 kg)	1M (+7 kg)			1M (−4.5 kg)	
Insufficient capsule intake ($<$ 70%)			2F		1M	
Smoking					1M	
Decrease in DHA in serum‡ (applied to the DHA group only)	–	–	–		2M	
Final number of subjects to analyze	6F§	7M	7F	8F	5M	9F

*This control dropped out of the study just after randomization was completed and not during the capsule intake period. ‡This step was carried out without any knowledge other than fatty acid analysis after the double-blind code was broken. §Furthermore, another control female was excluded from the analysis of P-F Study and Stroop test because of improper performance at those tests. Consequently, there were 19 controls for analysis of P-F Study and Stroop test.

Table II. Summary of Stroop and Dementia-detecting Tests

Tests	Groups	Changes in scores: Start → End	Intra-group differences	Two-way ANOVA
Stroop test (100%)	Control (n = 19)	51.1±12.7→59.3±14.6*	8.2±7.2	
				P = 0.52 (P = 0.47)§
	DHA (n = 22)	50.8±11.4→57.4±15.2‡	6.6±8.3	
Dementia-detecting test (100%)‖	Control (n = 20)	49.1±9.9→57.9±8.7	8.7±5.2	
				P = 0.94 (P = 0.80)§
	DHA (n = 22)	46.6±8.0→55.5±9.1	8.9±3.8	

Scores of Stroop and dementia-detecting tests were compared between before and after 3 mo of capsule administration. There were no significant differences between the control and DHA groups. No significant differences were observed at the start of the study. Full mark is described in brackets. Significant differences from the values at the start are indicated by *P = 0.0001 and ‡P = 0.0013. §P value with site-effect adjustment. ‖Statistical significance of intra-group differences was not calculated because questions in the test at the end of the study were different from those at the start.

as possible in 7 min. The stories used at the start of the study were replaced with different ones at the end of the study.

These three tests written above were carried out after breakfast. Rating of these tests was blindly done by three testers (M.I., E.A. and N.N.) independently throughout the study. There was essentially no discrepancy in ratings of P-F Study among the three testers. However, on rare occasions of discrepancy they discussed to reach a consensus.

Statistical analysis. StatView (version 4.0) was used for statistical analysis. Data are expressed as means±SD. Two-way ANOVA was applied for P-F Study, Stroop test and dementia-detecting test. Paired t-test was used for intra-group differences between the end and start of the study. Unpaired t-test was also used for the comparison of food intake between the two groups. With regard to P-F Study, statistical analysis was performed for each subgroup (Toyama or Yokkaichi) as well as for the whole group. Otherwise analysis was performed only for the whole group because there were not any marked differences between the two subgroups. Site-effect-adjusted P-values were calculated by two-way ANOVA of the differences between the end and start of the study using the two factors of sites and capsules. P less than 0.05 was taken as significant.

Results

Exclusion of improper subjects. As shown in Table I, there were two dropouts in the control group. We excluded 4 controls and 5 DHA subjects for various reasons (Table I). One control subject of Toyama did not properly follow the instructions of the last P-F Study and Stroop test, so we could not

Table III. Changes in Extraggression (P-F Study) after 3 Mo of Capsule Administration

Groups	Start	End	Differences	Two-way ANOVA
Toyama subgroup				
Control (n = 12)	36.6±11.6	→42.0±9.5*	5.4±9.7	
				P = 0.018
DHA (n = 13)	30.9±7.8	→26.9±9.7	−4.0±8.8	
Yokkaichi subgroup				
Control (n = 7)	32.3±7.9	→47.0±7.1‡	14.8±13.7	
				P = 0.080
DHA (n = 9)	32.2±14.1	→35.6±15.8	3.5±10.2	
Total				
Control (n = 19)	35.0±10.3	→43.9±8.8§	8.9±11.9	
				P = 0.0063 (P = 0.0029)‖
DHA (n = 22)	31.4±10.5	→30.5±13.0	−1.0±9.9	

Extraggression was calculated in the two groups at the start and end of the study. There were no significant differences at the start between the control and DHA groups in Toyama and/or Yokkaichi. *P = 0.077; ‡P = 0.029; §P = 0.0022 (comparison with values at the start). ‖P value with site-effect adjustment.

Table IV. Changes in the Fatty Acid Composition (weight%) in the Total Serum Fatty Acid Fraction

	Groups			
	Control (n = 20)		DHA (n = 22)	
Fatty acids	Start	End	Start	End
16:0	23.6±2.5	22.9±1.2	24.1±2.5	22.8±1.9*
18:0	8.2±1.5	8.2±0.8	8.4±1.5	8.5±0.8
18:1 (n-9)	18.0±3.6	18.6±2.5	18.2±3.1	16.4±2.5*
18:2	31.1±3.7	32.3±4.2	31.8±3.2	29.9±3.9
20:4	5.9±1.3	5.6±1.2	5.8±1.5	6.7±1.6
20:5 (EPA)	1.5±1.7‡	1.3±0.9	0.9±0.4	2.5±1.1§
22:6 (DHA)	3.6±1.3	3.5±1.1	3.1±0.5	6.1±1.6§

Volunteers ingested 3.0–3.6 grams of either control oil (97% soybean oil + 3% fish oil) or DHA-rich oil (50% DHA) for 3 mo. Fatty acid composition was analyzed in the total serum fatty acid fraction. *$P < 0.05$; §$P < 10^{-5}$(compared with values at the start), ‡because of one outlier (8.0%), the EPA average in the control group was nonsignificantly higher than that of the DHA group at the start.

score her performance at those tests. However, her performance was otherwise proper; therefore, she was excluded only from analysis of those two tests.

Adverse effects. 10 subjects out of the 20 control subjects complained of minor adverse effects. Also, 10 subjects out of 22 DHA subjects complained of minor adverse effects. These adverse effects in both groups were transient except for four subjects. Acne (2 subjects) and itching (1) in the control group and a trend toward obesity (1) in the DHA group continued throughout the study although those effects were not too serious to discontinue capsule intake.

Stroop and dementia-detecting tests. There were no significant inter-group differences with regard to Stroop or dementia-detecting test. Changes in scores in the two groups are shown in Table II.

P-F Study. P-F Study did not detect any extremely deviated individuals at either checkpoint.

Changes in extraggression are shown in Table III. In controls extraggression percentage tended to increase ($P = 0.077$ by paired t-test, and $P = 0.018$ by two-way ANOVA) in Toyama and significantly increased ($P = 0.029$ by paired t-test, but $P = 0.08$ by two-way ANOVA) in Yokkaichi, whereas that in the DHA group was unchanged in both subgroups. In case of combination of two subgroups, extraggression percentage did not change in the total DHA group ($\Delta = -1.0\%$), whereas that in the total control group significantly increased ($\Delta = +8.9\%$). The 95% CI of differences between these two changes were −16.8 to −3.0%.

The increase in extraggression in the control group was set off by decreases in imaggression ($\Delta = -4.5\%$) and in intraggression ($\Delta = -4.4\%$) since the total of these three kinds of aggression was 100% (all directions of aggression).

Serum fatty acids and lipid intake from food. Changes in the major fatty acids of the total serum fatty acid fraction are shown in Table IV. The DHA concentrations of the DHA group just doubled following DHA capsule intake.

The daily intake of lipids was not different between the two groups as shown in Table V.

Table V. Lipid Intake from Daily Food

Lipids		Control group (n = 20)	DHA group (n = 22)
DHA	(grams/day)	0.22±0.09	0.23±0.09
EPA	(grams/day)	0.10±0.06	0.11±0.06
linoleic acid	(grams/day)	11.8±7.3	11.7±4.3
n-6/n-3		7.3±1.3	7.2±1.5
Total lipid	(grams/day)	49.1±21.7	53.0±15.5

Lipid intake of each subject was calculated by averaging three sets of data from food-frequency questionnaires performed at the start, middle and end of the study. There were no significant differences between the two groups.

Discussion

The speed of judgment was not modulated by DHA intake. However, extraggression seemed to be stabilized by DHA. We started the present study on September 4, 1994, around the end of summer vacation, and we ended the study on December 4, 1994. In Toyama there were term exams in pathology for all subjects around December 4, and these exams were probably the toughest of all. In Yokkaichi, all subjects had to finish their graduation thesis (the toughest trial of all) by the middle of December. Consequently, December 4 was one of the busiest and most frustrated days for both Toyama and Yokkaichi subjects. On the other hand, September 4 was still within summer vacation. According to the frustration-aggression hypothesis (12), frustration enhances readiness to get aggressive against external trigger-factors. Consequently, it is naturally understandable why extraggression percentage was significantly increased in the control group. In this context, the stability in extraggression percentage in the DHA group indicates aggression-controlling effects of DHA.

ANOVA for extraggression percentage, site-effect adjusted or not, indicated a very significant difference. The inter-group differences were significant in Toyama (−4.0–5.4 = −9.4%) and had a tendency in Yokkaichi (+3.5–14.8 = −11.3%). These two inter-group differences were very similar. Taken together, the finding on extraggression strongly indicates that the aggression-controlling effects of DHA were not observed merely by chance.

According to Nakashima et al. (13), the dietary α-linolenate/linoleate balance affected general behavior of mice as well as sensitivities to drugs known to affect behavior. Moreover, in the experiments performed by the same group (3), rats on an α-linolenate–rich diet performed better at a brightness-discrimination test than did n-3 fatty acid-deficient rats in terms of the correct response ratio; however, the number of all responses, whether correct or incorrect, was apparently greater in n-3 fatty acid-deficient rats than in n-3 fatty acid-fed rats, which suggests that the n-3 fatty acid depletion might enhance aggression. Although our control subjects were not depleted of n-3 fatty acids, their findings in rats (3) are similar to ours in the sense that n-3 fatty acids controlled aggression. Mills et al. (14) reported that EPA, another major n-3 fatty acid in fish oils attenuated blood pressure increase during isolation stress in rats. Their study is also similar to ours in attenuation of the stress-induced reactions.

More than half of the subjects were females in the present

study. Extraggression might be influenced by menstruation. There were at least 12 female subjects in one group with regard to P-F Study, and the duration of the study was exactly 3 mo. Consequently, it is likely that the effect of menstruation was averaged in case of comparison between the two groups and minimized if compared between the start and end of the study. In fact, there were no marked differences in performance between females and males at any tests (data not shown).

The oil contained in control capsules was very small (3.0–3.6 grams/day) and had to be well covered by daily intake of lipids in the control group (Table V). Consequently, it is highly unlikely that fatty acids contained in control capsules influenced the performance at P-F Study. Theoretically there might be a remote possibility that control capsules might have something toxic other than fatty acids. However, this assumption is most unlikely because of the following reasons. (*a*) Control capsules contained only usual soybean and fish oils on market and 0.3% α-tocopherol. (*b*) Peroxide values of the oil in control capsules stored at room temperature were very low and similar to those of the fish oil of DHA capsules when compared even 4 mo after the end of the study (data not shown). (*c*) The questionnaire for adverse effects carried out at the end of the study showed no difference between the two groups. (*d*) Performance at the mental tests other than P-F Study, that need deep concentration and quick and correct judgment, was essentially the same in both groups.

According to the Western Collaborative Group Study (15), the death rate from coronary heart disease (CHD) of Type A subjects, whose behavior pattern is characterized by enhanced aggression (16) including time urgency and hostility (17), was more frequent than that of type B. However, it is now recognized that only hostility-related aspects of Type A are coronary prone, and that hostility may be a risk factor of all-cause mortality as well (17). On the other hand the effects of fish oils on CHD death is well-known (18–21), and as described above DHA appears to have aggression-controlling effects. Consequently, it is possible that fish oils prevent CHD through controlling hostility. However, this hypothesis must be tested by the studies of fish oils especially focused on hostility.

In conclusion, DNA intake prevents aggression enhancement at times of mental stress. We believe that this effect of DHA is important for understanding how fish oils prevent disease like CHD.

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