

## 臨床利用部門

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### ◇研究目的

天然薬物の臨床利用を目指して、以下のテーマについて研究している 1. n-3 系脂肪酸の抗ストレス作用と抗炎症作用, 2. n-3 系脂肪酸の欠乏が行動に及ぼす影響, 3. 必須脂肪酸欠乏症の時に体内で積極的に合成されるアラキドン酸アナログであるミード酸の抗炎症作用, 4. 漢方方剤が脂質メディエーターに及ぼす影響。

### ◇研究概要

1. n-3 系脂肪酸の一つ DHA の抗ストレス作用を利用して、小学生に DHA を投与することにより、敵意性が制御できるかを研究する目的で現在準備中。  
口内炎のよくできるボランティアに家庭用の油を全てシソ油 (n-3 系が多い) か大豆油にしてもらい、口内炎の発生頻度を調べる。第一回の 6 ヶ月間の介入試験では、大きな口内炎はシソ油で有意に減少している。規模を 2 倍以上にして第 2 回目を準備中。
2. LPS 投与による motivated behavior の減弱が、n-3 系脂肪酸含有飼料を給餌しておくことにより抑えられることが判明した。
3. DHA あるいはミード酸をエサに加えることで、マウスの腹腔にマクロファージにおけるロイコトリエンあるいは PAF の産生が低下することが判明した。
4. 抗アレルギー作用があるとされる漢方方剤に脂質メディエーターの産生抑制作用があるか否かを現在検討中。

## ◇著 書

- 1) Editors: Michel Lagarde, Arthur A. Spector, Claudio Galli, Tomohito Hamazaki, Howard R. Knapp. *Fatty Acids and Lipids from Cell Biology to Human Disease. Proceedings of the 3rd congress of the international society for the study of fatty acids and lipids (ISSFAL). Lipids, vol.34, 1999. Supplement/AOCS PRESS.*
- 2) 浜崎智仁 : *The Health Benefits of DHA and EPA. Supervised by : Hiramitsu Suzuki, Ph.D., Tomohito Hamazaki, M.D., Ph.D. and Kazunaga Yazawa, Ph.D. DHA&EPA Association, 2000.*
- 3) 浜崎智仁 : 「脂質と癌」奥山治美・小林哲幸・浜崎智仁編 (脂質栄養学シリーズ3 学会出版センター), 2000.
- 4) 浜崎智仁 : 二重盲検法を用いたヒトでの機能評価. *食品機能研究法. 3-3-13 : 310-317, 2000.*

## ◇原 著

- 1) **Yokoyama A., Hamazaki T., Ohshita A., Kohno N., Sakai K., G.D Zhao, Katayama H., Hiwada K.: Effect of Aerosolized Docosahexaenoic Acid on a Mouse Model of Atopic Asthma. *Int Arch Allergy Immunol. 123:327-332, 2000.***

**Abstract :** *Background:* Docosahexaenoic acid (DHA) found in fish oil is known to depress inflammation-related mediators. We investigated a novel delivery method of tridocosahexaenoyl-glycerol (DHA-TG). *Methods:* BALB/c mice (6-8 wk old) were primed intraperitoneally with ovalbumin and Al(OH)<sub>3</sub> on days 0 and 7, and with aerosolized ovalbumin on day 7. Primed mice were challenged by repeated exposure to aerosolized ovalbumin on days 15-17. Just before each aerosolized ovalbumin exposure, mice were also exposed to aerosol of emulsified DHA-TG or soybean oil, or saline (days 7,15-17). Bronchial hyperresponsiveness (BHR) to methacholine was measured, and bronchoalveolar lavage fluid was obtained at 24 hr after the last challenge (day 18). Lungs were histologically examined. *Results:* Bronchoalveolar lavage fluid of saline-treated mice showed an increased cellularity with predominant eosinophils. Exposure to DHA-TG significantly reduced the total cell number and the eosinophils percentage in lavage fluid, whereas soybean oil did not. *Conclusion:* DHA but not soybean oil exposure reduced BHR and cell infiltration to bronchovascular bundles. This type of DHA administration could be studied in clinical trials.

- 2) **Kato M., Nagata Y., Tanabe A., Ikemoto A., Watanabe S., Kobayashi T., Fujii Y., and Okuyama H.: Supplementary Treatment of Atopic Dermatitis Patients by Choosing Foods to Lower the N-6/N- 3 Ratio of Fatty Acids. *Journal of Health Science, 46(4): 241-250, 2000.***

**Abstract:** In- and outpatients with atopic dermatitis and their families were advised to lower the n-6/n-3 ratio of fatty acids of patients' foods throughout one year. Basic nutritional recommendations were to eat traditional Japanese foods, that is, more seafood than meat, and to omit all kinds of high-linoleic acid (n-6) vegetable oils and their products (including fried cookies); use of perilla oil as a cooking oil with a very low n-6/n-3 ratio was advised. Topical steroidal anti-inflammatory drugs were used at the same time but were decreased toward the 3rd month of treatment. The n-6/n-3 ratio of serum lipids decreased significantly, atopic dermatitis area and severity index (ADASI) decreased dramatically and blood eosinophil counts decreased significantly, but the levels of serum IgE, total protein, total cholesterol, hemoglobin, calcium and iron were relatively unchanged. Kampo medicines were also used for some patients with weak constitution, but beneficial effects have been neither proved nor disproved during the year of treatment. Infants were more susceptible to this treatment than adults. Although a longer-term follow-up is necessary, the method was found to be promising and safe for the treatment of atopic dermatitis.

- 3) **Miyazaki M., Takemura N., Watanabe S., Hata N., Misawa Y., Okuyama H.: Dietary Docosahexaenoic acid ameliorates, but rapeseed oil and safflower oil accelerate renal injury in stroke-prone spontaneously hypertensive rats as compared with soybean oil, which is associated with expression for renal transforming growth factor- $\beta$ , fibronectin and renin. *Biochimica et Biophysica Acta. 1483:101-110, 2000.***

**Abstract :** We have noted that n-3 fatty acid-rich oils, such as fish oil, perilla oil and flaxseed oil as well as ethyl docosahexaenoate (DHA) prolonged the survival time of stroke-prone spontaneously hypertensive rats (SHRSP) rats by ~10% as compared with linoleate (n-6)-rich safflower oil. Rapeseed oil with a relatively low n-6/n-3 ratio unusually shortened the survival time by ~40%, suggesting the presence minor components unfavorable to SHRSP rats. This study examined the effects of dietary oils and DHA on renal injury and gene expression related to renal injury in SHRSP rats. Rats fed rapeseed oil- and safflower oil-supplemented diets developed more severe proteinuria than those fed soybean oil-supplemented diet used as a control, but there were no significant differences in blood pressure. In contrast, the DHA-supplemented diet inhibited the development of proteinuria and suppressed hypertension. The mRNA levels for renal TGF- $\beta$ , fibronectin and renin were higher in the rapeseed oil and safflower oil groups after 9 weeks of feeding of the experimental diet than in the soybean oil and DHA groups. The fatty acid composition of kidney phospholipids was markedly affected by these diets. These results indicate that the renal injury observed in the groups fed safflower oil with a high n-6/n-3 ratio and rapeseed oil with presumed minor components is accompanied by increased expression of the TGF- $\beta$ , renin and fibronectin genes, and that dietary DHA suppresses renal injury and gene expression as compared with soybean oil.

4) **Watanabe S., Katagiri K., Onozaki K., Hata N., Misawa Y., Hamazaki T., Okuyama H.: Dietary docosahexaenoic acid but not eicosapentaenoic acid suppresses lipopolysaccharide induced interleukin-1  $\beta$  mRNA induction in mouse spleen leukocytes. Prostaglandins, Leukotrienes and Essential Fatty Acids. 62(3):147-152, 2000.**

**Summary :** Mice were fed a diet supplemented either with beef fallow (BT), BT plus ethyl eicosapentaenoate (EPA) or BT plus ethyl docosahexaenoate (DHA) for 9 weeks. EPA and DHA supplementation increased the content of the respective fatty acid in spleen leukocyte lipids, which was associated with the reduction in the arachidonate content. IL-1  $\beta$  mRNA induction upon lipopolysaccharide (LPS) stimulation in spleen leukocytes in the DHA diet group was significantly lower than in the BT diet group, but the EPA diet was without any significant effect. The amount of prostaglandin E2 (PGE<sub>2</sub>) released from LPS-stimulated spleen leukocytes was significantly lower in both the EPA and DHA groups than in the BT group. Thus, dietary EPA and DHA inhibited arachidonate metabolism similarly but had different effects on IL-1  $\beta$  mRNA in mouse spleen leukocytes.

◇ **総 説**

- 1) 浜崎智仁 : DHA で学級崩壊やキレの問題に迫れるか? FOOD STYLE 21 vol.3 : 51-54, 2000.
- 2) 浜崎智仁 : EPA と DHA -最近の研究.健康と環境. 15 : 76-83, 2000.

◇ **学会報告**

- 1) Hamazaki T.: Anti-Stress Effects of DHA. Chemistry and Healty Promotion. 2nd International Conference on Food Factors. 1999, 12/12-17, Kyoto.
- 2) Nakamura N., Hamazaki T., Yamazaki K., Urakaze M., Sawazaki S., Satoh S., Fujikawa M., Ohta M., Okuda K and Kobayashi M.: Effects of Eicosapentaenoic Acids on Remnatn-Like Patients Cholesterol Concentrations and Plasma Fatty Acid Composition in Patients with Diabetes Mellitus. 4th Congress of the International Society for the Study of Fatty Acids and Lipids. 2000. 6/4-9, Tsukuba.
- 3) Nakamura N., Hamazaki T., Johkaji H., Minami S., Yamazaki K., Urakaze M., Sawazaki S., Satoh A., Fujikawa M and Kobayashi M.: Effects of Cilostazol on Serum Lipid Concentrations and Plasma Fatty Acid Cmposition in Diabetic Patients with Peripheral Vessel Diseases. 4th Congress of the International Society for the Study of Fatty Acids and Lipids. 2000, 6/4-9, Tsukuba.
- 4) F.A. Wallace, P.C. Calder and Hamazaki T.: The Effects of Dietary DHA on the Immune Response of Stressed and Unstressed Mice. 4th Congress of the International Society for the Study of Fatty Acids and Lipids. 2000, 6/4-9, Tsukuba.

- 5) M. Wannasirindr, Itomura M., A. Thienprasert and Hamazaki T. : Polyunsaturated Fatty Acids Composition in Heroine Addicts. 4th Congress of the International Society for the Study of Fatty Acids and Lipids. 2000, 6/4-9, Tsukuba.
- 6) A. Thienprasert, Itomura M., Hamazaki T., K. Kheovichai, S. Samuhaseneetoo, Nagasawa T and Watanabe S.: The Effect of Docosahexaenoic Acid on Aggression / Hostility in Elderly Subjects : A Placebo-Controlled Double-Blind Study. 4th Congress of the International Society for the Study of Fatty Acids and Lipids. 2000, 6/4-9, Tsukuba.
- 7) Nakamura N., Hamazaki T., Sawazaki S. and Kobayashi M.: HMG-COA Reductase Inhibitors and Plasma Polyunsaturated Fatty Acid Profile. 4th Congress of the International Society for the Study of Fatty Acids and Lipids. 2000, 6/4-9, Tsukuba.
- 8) Hamazaki T.: The Effect of DHA on Hostility. 4th Congress of the International Society for the Study of Fatty Acids and Lipids. 2000, 6/4-9, Tsukuba.
- 9) Hamazaki T.: Docosahexaenoic acid and Hostility- A New Area of Research. (Keynote speaker) Japan Oil Chemists' Society American Oil Chemists' Society World Congress 2000. Joint with the 39th Annual Meeting of JOCS. (JAWC2000) 2000, 10/22-27, Kyoto.
- 10) Hamazaki T.: The Effects of Hostility. Workshop on the Essentiality of and Dietary Reference Intakes (DRIs) for Omega-6 and Omega-3 Fatty Acids. 1999, 4, USA.
- 11) Hamazaki T.: The Control of Hostility by Fish Oil. The 3rd International Symposium on Recent Advances In Natural Products Research and 1999 Korea · Japan Joint Symposium. 1999, 11, Korea.
- 12) 道志勝, 渡辺志朗, 浜崎智仁, 秋元健吾, 木曾良信 : ミード酸含有脂質の給餌がマウスにおける脂質性ケミカルメタボリックシンドローム産生に及ぼす影響 : 日本薬学会120年会 2000, 3/29-31, 岐阜.
- 13) 糸村美保, 渡辺志朗, 浜崎智仁 : 短期間の DHA 給餌が若齢および老齢ラットの血清・肝臓の脂質含量に及ぼす影響 : 日本脂質栄養学会第9回大会 2000, 9/8-9, 東京.
- 14) 渡辺志朗, 浜崎智仁 : 低リノール酸—高ドコサヘキサエン酸食がマウスの脳内 2-アラキドノイルグリセロール含量に及ぼす影響. 第73回日本生化学会, 2000, 10/11-14, 横浜.
- 15) Du C-Y, Sato A., Watanabe S., Ikemoto A., Fujii Y. and Okuyama H. : Survival rates and tissue lipid contents affected by dietary fat and oils with different degree of unsaturation and n-3/n-6 ratio in mice. : 4th Congress of the International Society for the Study of Fatty Acids and Lipids, 2000, 6/4-9, Tsukuba.
- 16) Watanabe S., Doshi M., Hamazaki T., Akimoto K. and Kiso Y. : Dietary mead acid (20:3n-9)- containing fungal lipids reduce tissue arachidonate content and leukotriene generation in mice. : 4th Congress of the International Society for the Study of Fatty Acids and Lipids, 2000, 6/4-9, Tsukuba.
- 17) Itomura M., Akiyama M., Watanabe S and Hamazaki T.: Change in the Plasma Phospholipid Fatty Acid Composition After Intake of DHA-Enriched Eggs for Three Months in Elderly Subjects. 4th Congress of the International Society for the Study of Fatty Acids and Lipids. 2000, 6/4-9, Tsukuba.

#### ◇その他

- 1) 浜崎智仁 : 魚油 EPA・DHA の働き. ヘルシスト. 137 : 26-29, 1999.
- 2) 浜崎智仁 : 心身両面に影響を及ぼす EPA/DHA 魚油. AERA MooK 食生活学がわかる. 54-55, 2000.
- 3) 浜崎智仁 : 「DHA 関連記事」1999, 12-2000, 3 共同通信加盟各紙 8 件.
- 4) 浜崎智仁 : 「自殺・抑うつ魚嫌いに顕著」2000, 5/27, 読売新聞.
- 5) 浜崎智仁 : 「ISSFAL2000 関連記事」2000, 6/15, ヘルスライフビジネス.
- 6) 浜崎智仁 : 「魚油は心血管死を防げるか日本で大規模試験始まる」2000, 8月号. サイエス.
- 7) 浜崎智仁 : 「DHA 関連記事」2000, 8月号. Nikkei Medical.
- 8) 浜崎智仁 : DHA と敵意性. ここまでわかった! 高齢者のための健康的で豊かな食生活/科学技術庁生活者ニーズ対応研究課題高齢社会に向けた食品機能の総合的解析とその利用に関する研究/農林水産省

食品総合研究所・科学技術庁. P12, 2000.

- 9) 浜崎智仁, 澤崎茂樹: 敵意性制御効果を示す食品成分の探索. 高齢社会に向けた食品機能の総合的解析とその利用に関する研究. 科技庁研究開発局成果報告書 H9-11. 177-185, 2000.
- 10) 浜崎智仁: 和漢の窓から「精神障害と魚」2000, 7/29, 読売新聞.
- 11) 浜崎智仁: 「ISSFAL2000関連記事」2000, 8/3, Medical Tribune.
- 12) 浜崎智仁: 「ISSFAL2000関連記事」2000, 8/30, 読売新聞.

#### ◇講演

- 1) 浜崎智仁: 「魚の油と心の落ち着き」東京都社会福祉協議会, 2000, 2/23, 東京.
- 2) 浜崎智仁: 「魚嫌いは自殺する」和漢研夏期セミナー 2000, 8, 富山.
- 3) 浜崎智仁: 「油と健康」富山県栄養士会, 2000, 9/18, 富山.
- 4) 浜崎智仁: 「魚の油健康-ドコサヘキサエン酸 (DHA) が情動に及ぼす影響」岐阜県小中学校教育研究会, 2000, 10/20, 岐阜.
- 5) 浜崎智仁: 「魚の油-心疾患から精神疾患-」会津若松医師会, 2000, 10/27, 福島.
- 6) 浜崎智仁: 「魚の油と健康」スリーティグループQC発表会, 2000, 11/11, 富山.
- 7) 浜崎智仁: 「 $\omega$ 3系脂肪酸の栄養学的意義」函館病院薬剤師会, 2000, 11/17, 函館.
- 8) 浜崎智仁: 「魚の油-心疾患から精神疾患-」京都実地医家の会, 2000, 11/26, 京都.

#### ◇非常勤講師

浜崎智仁: 富山短期大学食物栄養学科 講義「臨床栄養学」2000, 10/15.-2001, 1/24. 富山.

#### ◇研究費取得状況

- 1) 学術研究費助成 (立仁会) (代表: 浜崎智仁): 200千円
- 2) 富山県受託研究費「和漢薬・バイオテクノロジー研究」(分担: 浜崎智仁), 「生体防御に有効な和漢薬の開発研究」, 384千円
- 3) 科学研究費補助金 (基盤研究(C)(2)) (代表: 浜崎智仁), 「 $\alpha$ -リノレン酸によるアフタ性口内炎の予防研究 (二重盲検法)」, 2,200千円
- 4) (社) 大日本水産会, 水産物消費改善推進事業補助金 (代表: 浜崎智仁), 「ドコサヘキサエン酸 (DHA) 含有食品が児童に及ぼす影響の研究」, 4,000千円
- 5) 教育研究学内特別経費「アトピー性皮膚炎モデルに有効な漢方方剤の作用と作用機序および活性成分の研究」(分担: 浜崎智仁), 1,200千円
- 6) 科学研究費補助金 (奨励研究(A)) (代表: 渡辺志朗) 「食餌 n-3 系不飽和脂肪酸がII型糖尿病に及ぼす影響とその機構の解析」, 600千円
- 7) 教育研究学内特別経費「富山ブランド家庭薬に配合される生薬資源の確保と評価」(分担: 渡辺志朗), 1,000千円

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