

臨床利用分野 Division of Clinical Application

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◇研究目的 Aims of the research projects

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) 天然薬物（特に魚油中の DHA・EPA）の臨床的有効性
- 2) 中枢神経系における自然免疫応答の制御機構の解析
- 3) 脂肪吸収に及ぼす和漢薬の影響

◇研究概要 Research projects

- I) 注意欠陥/多動性障害児における二重盲検試験により DHA が集中力をむしろ低下させる可能性があり(対照群では慣れにより検査値が向上したが、DHA 群では変化がない)、DHA は中枢性ノルアドレナリンを抑制している可能性が考えられる。また、二次的症候である攻撃性は、DHA で有意に低下した。これもノルアドレナリンの低下と関連すると思われる。
- II) マウスに LPS を投与することにより起こる摂食行動の低下が n-3 系脂肪酸をあらかじめ与えておくことにより抑制されることを明らかにした。この機構を中枢神経系機能の面から解明する。
- III) LPS やサイトカインおよびその誘導剤を投与したときに起こる摂食行動の低下を中枢神経系における自然免疫応答の指標として、これに対する和漢薬の効果を評価する。
- IV) 食後血中中性脂質の上昇を抑える和漢薬を検索している。

◇著書 Books

- 1) 浜崎智仁, 矢沢一良 : DHA 衝動・攻撃性を抑えうつ症状を改善する, 予防医学の権威がすすめる健康食事典週刊朝日編279-287, 朝日新聞社, 東京, 2004.
- 2) 浜崎智仁 : N-3 系脂肪酸と行動, 機能性脂質のフロンティア, 12-18, シーエムシー出版, 東京, 2004.
- 3) 浜崎智仁 : 監修「コレステロールは高いほうがいい」, マキノ出版, 東京, 2004.

◇原著 Original papers

- 1) **Hirayama S., Hamazaki T., and Terasawa K. : Effect of docosahexaenoic acid-containing food administration on symptoms of attention-deficit/hyperactivity disorder — a placebo-controlled double-blind study. Eur J Clin Nutr., 58: 467-473, 2004.**

Abstract: Objectives: To investigate whether docosahexaenoic acid (DHA) supplementation was able to ameliorate attention-deficit/hyperactivity disorder (AD/HD) symptoms in AD/HD children.

Design and subjects: A placebo-controlled double-blind study with 40 AD/HD (including eight AD/HD-suspected) children of 6-12y of age who were mostly without medication. Subjects of a DHA group (n=20) took active foods containing fish oil (fermented soybean milk, bread rolls and steamed bread; 3.6g DHA/week from these foods) for 2 months, whereas those of a control group (n=20) took indistinguishable control foods without fish oil. The following items were measured at the start and end of the study: (1) attention deficit, hyperactivity and impulsivity (AD/HD-related symptoms according to DSM-IV criteria); (2) aggression assessed by both parents and teachers; (3) visual perception (finding symbols out of a table); (4) visual and auditory short-term memory; (5) development of visual-motor integration; (6) continuous performance; (7) impatience.

Results: Changes in tests 1, 2, 3, 5 and 7 over time did not significantly differ between the two groups. However, visual short-term memory and errors of commission (continuous performance) significantly improved in the control group compared with the changes over time in the DHA group (P=0.02 and 0.001, respectively). Recalculation without AD/HD-suspected subjects (n=4 each group) showed similar P-values with regard to both measures.

Conclusion: DHA supplementation did not improve AD/HD-related symptoms. Treatment of ADHD with fatty acids deserves further investigation, but careful attention should be paid as to which fatty acid(s) is used.

- 2) **Huan M., Hamazaki K., Sun Y., Itomura M., Liu H., Kang W., Watanabe S., Terasawa K., and Hamazaki T. : Suicide attempt and n-3 fatty acid levels in red blood cells: A case control study in China. Biol Psychiatry, 56: 490-496, 2004.**

Abstract: Background: Epidemiologic studies show that low fish intake is a risk factor of suicidality; however, there are no case-control studies investigating suicide attempt risk and tissue n-3 fatty acid levels.

Methods: we recruited 100 suicide-attempt cases and another 100 control patients injured by accidents who were admitted to three hospitals affiliated with Dalian Medical University in Dalian, China. Case and control subjects were matched for age, gender, and smoking status. Those who were inebriated at the time of hospitalization were excluded. Blood was sampled immediately after admission to a hospital. Washed red blood cells (RBCs) were obtained, and the fatty acid composition of the total RBC phospholipid fraction was analyzed by gas chromatography.

Results: Eicosapentaenoic acid (EPA) levels in RBC in the case subjects were significantly lower than those of the control subjects ($.74 \pm .52\%$ vs $1.06 \pm .62\%$, $p < .0001$). when the highest and lowest quartiles of EPA in RBC were compared, the odds ratios of suicide attempt was .12 in the highest quartile (95% confidence interval; .04-.36, p for trend = .0001) after adjustment for possible confounding factors.

Conclusions: our findings suggest that low n-3 fatty acid levels in tissues were a risk factor of suicide attempt. Further studies including intervention with fish oil are warranted.

3) **Watanabe S., Kanada S., Takenaka M., Hamazaki T. : Dietary n-3 fatty acids selectively attenuate LPS-induced behavioral depression in mice. *Physiol Behav.*, 81: 605-613, 2004.**

Abstract: Systemic administration of bacterial lipopolysaccharide (LPS) induces a series of physiological and pathological alterations as well as behavioral depression in experimental animals. These alterations induced by LPS administration are known to be mediated by endogenous cytokines and arachidonate metabolites, which may be modulated by dietary n-3 fatty acids. Mice were fed a diet supplemented with n-3 or n-6 fatty acids for 4 weeks prior to LPS administration. Food-motivated behavior after intraperitoneal administration of LPS as compared with that before LPS administration was significantly depressed in the mice fed with the n-6 fatty-acid-rich diet (47% to 85% reduction; $P < .05$) but not significantly in the mice fed with the n-3 fatty-acid-rich diet. Depression of social exploration by intraperitoneal LPS administration in the n-3 fatty-acid rich diet group (39% reduction vs. vehicle group) was significantly less in the n-6 fatty-acid-rich diet group (76% reduction vs. vehicle group; $P < .05$). The behavioral depressions induced by intracerebroventricular LPS injection were not significantly different between the two dietary groups ($F = .60$). The elevation of serum corticosterone and the hypoglycemic response following intraperitoneal LPS administration were not significantly different between the two dietary groups ($F = .57$ and $P = .43$, respectively). We demonstrate that dietary n-3 fatty acids attenuate behavioral depression in mice peripherally administered with LPS without affecting the increase in serum corticosterone and the decrease in serum glucose concentration.

4) **Doshi M., Watanabe S., Niimoto T., Kawashima H., Ishikura Y., Kiso Y., Hamazaki T.: Effect of dietary-enrichment with n-3 polyunsaturated fatty acids (PUFA) or n-9 PUFA on arachidonate metabolism in vivo and experimentally induced inflammation in mice. *Biol Pharm Bull*, 27: 319-323, 2004.**

Abstract: Mice were fed a diet supplemented with palm oil (control diet), n-3 polyunsaturated fatty acids (PUFA)-, or n-9 PUFA-rich oil for 3 weeks. The n-3 PUFA-rich diet suppressed the generation of both leukotrienes (LT) and prostaglandins (PG), but the n-9 PUFA-rich diet did LT but not PG generation during acute inflammation. Leukocyte accumulation during acute inflammation was not different in the n-3 or n-9 PUFA-rich diet group as compared with the control group. The n-3 PUFA-rich diet but not the n-9 PUFA-rich diet suppressed Freund's adjuvant-induced granuloma formation. The n-9 PUFA-rich diet significantly attenuated galactosamine/lipopolysaccharide-induced liver injury more effectively than the n-3 PUFA-rich diet as compared with the control diet. The present study revealed the differential modification of experimentally induced inflammation in mice by dietary n-3 PUFA and n-9 PUFA, which may be due to their different effects on 5-lipoxygenase and cyclooxygenase metabolism of arachidonic acid during inflammatory processes.

◇ **総説** Review papers

- 1) Hamazaki T.: Relationship between total cholesterol and all cause mortality: is there a need for lowering total cholesterol in the Japanese population? *Current Topics in Nutraceutical Research*, 2: 177-188, 2004.
- 2) 中村典雄, 大沢弘, 山辺英彰, 白戸研一, 中村雅将, 島田美智子, 熊坂隆一郎, 奥村謙, 浜崎景, 浜崎智仁, 村上礼一, 藤田雄: (研究報告) ループス腎炎患者における酸化ストレスマーカーに対するエイコサノイドペンタエン酸の効果について. *Progress in Medicine*, 24: 175-178, 2004.
- 3) 浜崎景, 浜崎智仁: 特集: エビデンスからみた機能性食品の現状3. 抗動脈硬化食品(2) n-3系脂肪酸食品. *栄養 評価と治療*, 21: 47-53, 2004.

◇ **学会報告** Scientific presentation (*: 招待講演)

- * 1) 浜崎智仁: 脂質による行動の変化. 日本農芸化学会2004年度大会シンポジウム, 2004, 3, 広島.
- 2) 浜崎智仁: 公開講演 生活習慣病は予防から. 第53回日本医学検査学会, 2004, 5, 富山.
- 3) 浜崎智仁: 脂質栄養に関する最近の話題. 第41回日本外科代謝栄養学会ランチョンセミナー, 2004, 7, 愛媛.

- 4) 浜崎智仁：パネルディスカッション「高コレステロールははたして危険か」日本脂質栄養学会第13回大会, 2004, 9, 山形.
- 5) Hamazaki T.: n-3 Fatty acids and behavior. International Academy Nutrition and Aging (IANA) Symposium on Nutrition & Alzheimer's Disease, 2004, 10, 東京.
- 6) 浜崎智仁：乳幼児の食・栄養・行動～最近の問題とその対応～. 第26回日本臨床栄養学会パネルディスカッション, 2004, 10, 大阪
- 7) Hamazaki K., Inagaki H., Itomura M., Sawazaki S., Tomita S., Hirata H., Kuroda M., Hamazaki T.: n-3 long-chain polyunsaturated fatty acids in patients under chronic hemodialysis and their pulse wave velocity. 6th Congress of the International Society for The Study of Fatty Acids and Lipids, 2004, 6, Brighton.
- 8) Hamazaki K., Itomura M., Hamazaki T., Watanabe S., Sawazaki S.: Relationship between tissue EPA levels and tooth retention. 6th Congress of the International Society for the Study of Fatty Acids and Lipids, 2004, 6, Brighton.
- 9) 浜崎景, 稲垣均, 糸村美保, 澤崎茂樹, 富田新, 平田仁, 黒田昌宏, 渡辺志朗, 浜崎智仁：血液透析患者における赤血球膜中n-3系高不飽和脂肪酸と脈波伝播速度との関連. 日本脂質栄養学会第13回大会, 2004, 9, 山形.
- 10) ホワンミンミン, 浜崎景, 孫月吉, 浜崎智仁：自殺未遂と赤血球中 n-3 系脂肪酸—大連でのケース・コントロール研究—. 第100回日本精神神経学会, 2004, 5, 札幌.
- 11) Huan M., Hamazaki K., Sun Y., Itomura M., Watanabe S. and Hamazaki T. : Suicide attempt and n-3 fatty acid levels in red blood cells—a case control study in china. 6th Congress of the International Society for the Study of Fatty Acids and Lipids, 2004, 6, Brighton.
- 12) ホワンミンミン, 浜崎景, 糸村美保, 渡辺志朗, 浜崎智仁, 寺澤捷年：自殺未遂と赤血球中 n-3 系脂肪酸—大連でのケース・コントロール研究—. 日本脂質栄養学会第13回大会, 2004, 9, 山形.
- 13) 藤岡俊太郎, 浜崎景, 糸村美保, ホワンミンミン, 西澤弘人, 澤崎茂樹, 柴則子, 北島勲, 渡辺志朗, 浜崎智仁：エイコサペンタエン酸 (EPA) が血中炎症マーカーの及ぼす影響について. 日本脂質栄養学会第13回大会, 2004, 9, 山形.

◇その他 Others

- 1) Hamazaki T, Hirayama S.: (letter) The effect of docosahexaenoic acid-containing food administration on symptoms of attention-deficit /hyperactivity disorder—a placebo controlled double-blind study, *Eur J Clin Nutr.*, 58: 838, 2004
- 2) Hamazaki T: (letter), *Eur J Clin Nutr.*, 58: 1557, 2004.
- 3) Inagaki H., Hamazaki K., Itomura M., Kuroda M. and Hamazaki T. : (Letter to editor) Simplest and realtime screening method of hemodialysis access recirculation. *Clinical Nephrology*, 62: 328-330, 2004.
- 4) 浜崎智仁：EPA・DHAの新しい展開. 岡崎医報, 48, 11-12, 2004.
- 5) 浜崎智仁：講演「コレステロールは高い方が長生きする」. 富山漢方会講演会, 2004, 3, 富山.
- 6) 浜崎智仁：講義「最近の脂質に関する変わった話題-専門家の言うことは信用するな」. 東京海洋大学, 2004, 6, 東京.
- 7) 浜崎智仁：酸化 LDL が真の悪玉. 日本経済新聞, 2004,6
- 8) Hamazaki T: Current advances in behavior and omega 3 fatty acid research. California Walnut Commission Scientific Advisory Council Meeting, 2004,8, USA.
- 9) 浜崎智仁：講演「総死亡率からみたコレステロール値-高くても安全-」近畿大学生涯教育研修会, 2004, 9, 大阪.
- 10) Hamazaki T : The japan society for lipid nutrition recommends to reduce the intake of linoleic acid: a review and critique of the scientific evidence. 3rd International Congress on the Columbus, 2004, 10, Belgium.
- 11) 浜崎智仁：魚の脂肪酸、自殺予防に効果？ 日本経済新聞, 2004, 10

◇共同研究 Co-operative researchs

学内

- 1) 今中常雄：薬学部教授「極長鎖脂肪酸代謝の制御に関する研究」2004.4～

国内

- 1) 東原英二：杏林大学医学部泌尿器科学教授「前立腺癌の再発予防研究」2001.9～
- 2) 日本油脂（株）：「ホスファチジルセリン (PS) の記憶能改善効果に関する研究」2004.7～
- 3) 鈴木信雄：金沢大学「カルシウムの石灰化抑制剤」2004.10～

海外

- 1) Syafruddin, Nurpudji A Taslim：インドネシア・アイクマン研究所, ハサヌディン大学, 「魚油によるマラリア予防の大規模介入試験」2002.6～
- 2) 孫 月吉：中国・大連医科大学神経精神医学教授「交通事故と脂肪酸栄養」2004.4～
- 3) 夏 瑢：中国・浙江中医学院助教授「中高年における血中脂肪酸と骨折」2005.1～

◇研究費取得状況 Acquisition of research funds

- 1) 受託研究費, (株) マルハ (代表：浜崎智仁) 「DAGE が喫煙者の尿中 8-HOd に及ぼす影響について」
- 2) 平成16年度人物交流派遣事業, (財) 国際文化交流事業財団 (浜崎智仁)
- 3) 厚生労働省科学研究費 (分担：渡辺志朗) 「数種の食用油に含まれる微量有害因子に関する研究」
- 4) 研究拠点形成費補助金 (COE プログラム) (分担：渡辺志朗)

◇研究室在籍者 Research Members

学部3年生：中島俊介, 宮川誠一

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大学院後期2年：桐原祐子

大学院医学研究科2年生：西澤弘人

大学院医学研究科4年生：ホワンミンミン

研究支援推進員：武部鎮子

事務補佐員：浜谷裕子

受託研究員：浜崎景 (ポリエン・プロジェクト (有) 2003.4～2005.3)

◇学位 (修士, 博士) 取得者 Academic degrees and theses

卒業研究：

藤岡俊太郎「エイコサペンタエン酸 (EPA) が血中炎症マーカーに及ぼす影響」

山田泰広 「脳における炎症性サイトカイン発現のリボヌクレアーゼプロテクションアッセイによる評価」

修士論文 (2004年3月)：

岡藤文人 「脳内の極長鎖脂肪酸 (VLCFA) 含量に及ぼす食餌中 VLCFA 含量と cuprizone 投与の影響」

斎藤正隆 「漢方方剤の腓リパーゼ活性および脂肪負荷後の血中トリアシルグリセロール上昇に対する作用」

直井一久 「Zymosan 誘発腹膜炎における局所炎症反応と摂食行動障害に対するシクロオキシゲナーゼ阻害剤の影響」

課程博士 (2004年3月)：

ホワンミンミン「Suicide attempt and n-3 fatty acid levels in red blood cells: A case control study in China」医学博士 (富山医科薬科大学)