

臨床利用分野

Division of Clinical Application

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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) 天然薬物（特に魚油中の DHA・EPA）の臨床的有効性について
- 2) 炎症反応に伴って起こる摂食行動障害の機構解析とその制御
- 3) 脂肪吸収を抑制する和漢薬および食品成分

◇研究概要

- I) EPA・DHA が行動あるいは各種疾患に及ぼす影響を疫学調査あるいは介入試験で検討する。
- II) 炎症反応に伴って起こる摂食行動障害におけるシクロオキシゲナーゼ代謝産物および炎症性サイトカインの役割の解明
- III) 炎症反応に伴って起こる摂食行動障害の和漢薬による制御とその機構解析
- IV) マウスを用いた脂肪負荷後の血中中性脂肪上昇を評価する実験系を確立した。これに有効な和漢薬および食品成分を検索する。

◇著書

- 1) Okuyama H., Ichikawa Y., Sun Y., Hamazaki T., Lands W.E.M.: Prevention of coronary heart disease. From the cholesterol Hypothesis to $\omega 6/\omega 3$ Balance. Simopoulos AP(eds) Vol 96, World rev nutri diet. Basel, karger, 2006.

◇原著論文

- 1) Hamazaki K., Itomura M., Hamazaki T., and Sawazaki S.: Effect of cooking plant oils on recurrent aphthous stomatitis: a randomized, placebo-controlled, double-blind trial. *Nutrition*, 22:534-538, 2006.

OBJECTIVE: One-third of the total population seems to develop minor recurrent aphthous stomatitis (RAS) during their lifetime. However, well-controlled dietary intervention studies to prevent minor RAS are very rare. The objective of the present study was to investigate whether the prevalence of RAS decreased with perilla oil (rich in alpha-linolenic acid). **METHODS:** Thirty subjects (8 men and 22 women) who had minor RAS at least once a month were randomly allocated to a soybean oil group or a perilla oil group in a double-blind manner (experimental phase) after a run-in phase of 4 mo during which subjects used a reference oil, the most popular cooking oil in Japan, or a 50/50 mixture of soybean oil and rapeseed oil. During the experimental phase, subjects were asked to use soybean oil or perilla oil as the sole cooking oil for 8 mo. Blood samples were collected at the start and end of the experimental phase for fatty acid analysis of total plasma phospholipid fraction. Occurrence and needed days for healing of minor RAS were recorded during the two phases and compared. **RESULTS:** alpha-Linolenic acid concentrations in the plasma phospholipid fraction increased significantly in both groups during the experimental phase to a similar extent. The prevalence of minor RAS in the experimental phase decreased significantly in both groups compared with the run-in phase to a similar extent, without intergroup differences. **CONCLUSION:** Perilla oil, which is rich in alpha-linolenic acid, was not superior to soybean oil in preventing minor RAS. There was a possibility that avoiding rapeseed oil might be beneficial for prevention of minor RAS.

- 2) Nishizawa H., Hamazaki K., Hamazaki T. Fujioka S., and Sawazaki S.: The relationship between tissue RBC n-3 fatty acids and pulse wave velocity. *in vivo*, 20:307-310, 2006.

Abstract: Consumption of n-3 fatty acids is well-known to prevent deaths from coronary heart disease. However, not many studies have investigated the effects of n-3 fatty acids on arteriosclerosis in free living subjects. The pulse wave velocity between the brachia and ankles (baPWV) of 161 healthy male subjects was measured and the fatty acid composition of the total phospholipid fraction of their red blood cells (RBC) analyzed. There was a significant inverse correlation between the eicosapentaenoic acid concentrations in the RBC phospholipid fraction and baPWV of the subjects after adjustment for age, pulse rate and diastolic pressure, or further for body mass index, smoking status, diabetes and the ratio of low-density cholesterol to high-density cholesterol. Although baPWV values may not directly indicate arteriosclerosis, the present study suggests that long-term n-3 fatty acid intake is beneficial for the vascular system.

- 3) Hamazaki K., Higashihara E., Terachi T., Takada H., Matsuda T., Kawakita M., Fuse H., Hamazaki T., Kameyama S., Masai M., Chiba Y., Tokunaga M., Furuya Y., Okegawa T., Murota T., Kawa G., and Itomura M.: The effect of eicosapentaenoic acid on prostate-specific antigen. *in vivo*, 20:397-401, 2006.

Abstract: The "Study of EPA Effects on Prostate Cancer" (SEEP) Group has been conducting a clinical

trial with patients who underwent radical prostatectomy. The main purpose of the SEEPIC is to evaluate whether eicosapentaenoic acid (EPA) prevents prostate cancer (PC) recurrence. As the surrogate marker of recurrence, the prostate-specific antigen (PSA) level was measured. However, if EPA affects the PSA values independently of PC, PSA may not be a good marker of recurrence in the event of EPA treatment. Thus, in the present study, whether EPA affected the PSA values was investigated using non-PC volunteers. Twenty men, of at least 50 years of age, were recruited, mostly from hospital staff. The volunteers were randomly allocated either to the EPA group or the control. The subjects in the EPA group were administered EPA-ethyl ester a dose of 2400 mg/day for 12 weeks, whereas the controls were administered none. Fasting blood samples were obtained before the start of EPA administration and 4 and 12 weeks later. The EPA concentrations in erythrocytes increased in all the subjects in the EPA group (174+/-96%) with no significant changes in the control group (8.5+/-14.0%). There were no significant differences between the two groups in the serum PSA levels, allowing the conclusion that the PSA is an appropriate surrogate marker of recurrence in prostate cancer.

4) Hamazaki K., Itomura M., Sawazaki S., and Hamazaki T.: Fish oil reduces tooth loss mainly through its anti-inflammatory effects? *Med. Hypotheses*, 67:868-870, 2006.

Abstract: Competing at several steps of arachidonic acid metabolism, n-3 fatty acids reduce production of highly active prostaglandins and leukotrienes and exert anti-inflammatory effects. They are also experimentally shown to be anti-osteoporotic. Periodontitis is responsible for most tooth loss in adult populations. If enough n-3 fatty acids are provided, periodontitis with alveolar bone resorption may be controlled, and tooth loss may be prevented. In fact, n-3 fatty acid administration lowered prostaglandin E(2) production, tooth movement and alveolar bone resorption in animal experiments. Aggression, which may be related with tooth loss, was also controlled with fish oil. Our cross-sectional data supported our hypothesis. We recruited 256 men (22-59 y of age) and 95 women (22-66 y), counted the numbers of their remaining teeth, and analyzed the fatty acid composition of the total phospholipid fraction of RBCs. The beta-coefficient of the numbers of remaining teeth and EPA concentrations in the fraction was 0.89 (per 1% EPA, p=0.007) after adjustment for 9 possible confounding factors. Long-term intervention studies with fish oil planned in the future should be able to test our hypothesis by just adding another very simple endpoint in those studies: tooth loss during the intervention period. This hypothesis may explain the linkage between periodontitis/tooth loss and coronary heart disease.

5) Fujioka S., Hamazaki K., Itomura M., Huan M., Nishizawa H., Sawazaki S., Kitajima I., and Hamazaki T.: The effects of eicosapentaenoic acid-fortified food on inflammatory markers in healthy subjects — a randomized, placebo-controlled, double-blind study. *J. Nutr. Sci. Vitaminol.*, 52:261-265, 2006.

Abstract: Epidemiological studies showed that habitual fish intakes were associated with lower blood inflammatory markers. In the present study the effects of a fish oil-containing food on inflammatory markers were investigated in healthy, mostly middle-aged subjects (59 men and 82 women) with normal to mildly elevated triglyceride levels. Study subjects were randomly allocated to two groups in a double-blind manner; one group ingested an eicosapentaenoic acid (EPA)-rich fish oil-fortified drink (0.60 g EPA+0.26 g docosahexaenoic acid/d. EPA group, n=68) for 12 wk. The rest of the subjects took a placebo (control group, n=73). Plasma levels of high sensitivity C-reactive protein (hs-CRP) and soluble tumor necrosis factor-receptors 1 and 2 (sTNF-Rs 1 and 2) were measured at the start and end of intervention. EPA concentrations in the total RBC phospholipid fraction significantly increased by 79% in the EPA group at the end of the study, and they changed very little in the control group (+0.68%). The inflammatory markers did not change in either group. It is likely that fish oil does not change hs-CRP or sTNF-Rs 1 or 2 in subjects without active inflammation.

- 6) Naoi K., Kogure S., Saito M., Hamazaki T., and Watanabe S.: Differential effects of selective cyclooxygenase (COX)-1 and COX-2 inhibitors on anorexic response and prostaglandin generation in various tissues induced by zymosan. *Biol. Pharm. Bull.* 29:1319-1324, 2006.

ABSTRACT: We have shown that anorexic response is induced by intraperitoneal injection of zymosan in mice, although the role of prostaglandins in this response is relatively unknown as compared with lipopolysaccharide (LPS)-induced anorexic response. Indomethacin (0.5 and 2.0 mg/kg), a non-selective cyclooxygenase (COX) inhibitor, as well as meloxicam (0.5 mg/kg), a selective COX-2 inhibitor, but not FR122047 (2.0 mg/kg), a selective COX-1 inhibitor, attenuated zymosan-induced anorexia. Zymosan injection elevated COX-2 expression in brain and liver but not in small intestine and colon. Meloxicam (0.5 mg/kg) and FR122047 treatment (2.0 mg/kg) similarly suppressed the generation of brain prostaglandin E2 (PGE2) and peritoneal prostacyclin (PGI2) upon zymosan injection. PGE2 generation in liver upon zymosan injection was suppressed by meloxicam (0.5 mg/kg) but not by FR122047 treatment (2.0 mg/kg). Our observations suggest that COX-2 plays an important role in zymosan-induced anorexia, which is a similar feature in LPS-induced anorexic response. However, non-selective inhibition by selective COX-1 and COX-2 inhibitors of brain PGE2 generation upon zymosan injection does not support the role of COX-2 expressed in brain in zymosan-induced anorexic response. PGE2 generation in liver may account for peripheral role of COX-2 in zymosan-induced anorexic response.

◇総説

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- 2) 浜崎智仁, 糸村美保: リノール酸摂取の問題点—昨年9月に脂質栄養学会で行われたシンポジウムを受けて, *脂質栄養学*, 15(1), 15-26, 2006.

◇学会報告 (*: 特別講演, シンポジウム, ワークショップ等)

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- 2) Zhang W., Xia R., Nagasawa T., Hamazaki K., Terashima Y., Sun Y., and Hamazaki T.: The fatty acid content of forty-four kinds of fish available in Dalian-city and Hangzhou-city, China. 7th Congress of the International Society for the Study of Fatty Acids and Lipids. 2006, 7. 23-28, Cairns.
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- 4) Hamazaki K., Syafruddin D., Tunru I.S., Azwir M.F., and Hamazaki T.: Effect of fish oil on Malaria infection and behavior: A placebo-controlled, double-blind test in Indonesian children. 7th Congress of the International Society for the Study of Fatty Acids and Lipids. 2006, 7.23-28, Cairns.
- 5) Higashihara E., Itomura M., Matsuda T., Hamazaki T., and for the Research Group of "Study of EPA Effect on Prostate Cancer"(SEEPC): Does EPA decrease recurrence rates in radically operated prostate cancer patients? A randomized controlled trial. 7th Congress of the International Society for the Study of Fatty Acids and Lipids. 2006, 7.23-28, Cairns.
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- 7) Hamazaki T.: Fish oil and behavior. 1st International Congress for Medical Use of Functional Foods. 2006,11.16-17, Tokyo.

- 8) 寺島嘉宏, 浜崎景, 糸村美保, ホワンミンミン, 澤崎茂樹, 小林悟, 浜崎智仁.: 麻黄附子細辛湯と補中益気湯のインフルエンザ抗体価に対する影響について, 第 23 回和漢医薬学大会, 2006,8.26-27, 岐阜.
- 9) 浜崎景, Syafruddin, Tunru I.S., Azwir M.F., 浜崎智仁: 魚油が小学生のマラリア感染と行動に及ぼす影響: インドネシアでの二重盲験試験, 第 15 回大会日本脂質栄養学会, 2006,9.1-2, 岐阜.
- 10) 渡路子, 浜崎景, 平田豊明, 浜崎智仁, 大久保善朗.: 統合失調症の急性期症状と n-3 系不飽和脂肪酸, 第 15 回大会日本脂質栄養学会, 2006,9.1-2, 岐阜.
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- 12) 斉藤正隆, 渡辺志朗.: デキサメタゾンによる LPS 誘発性の摂食行動障害を抑制するが、ザイモサン誘発性の摂食行動障害を抑制しない -脳内 IL-6 応答系との関連. 日本薬学会北陸支部平成 18 年度第 2 回総会, 2006, 11.12, 富山.
- 13) 山田泰広, 山本亮, 渡辺志朗.: Indomethacin 投与により誘発される消化管出血, 貧血およびショック反応に及ぼすオウゴンエキスの影響. 日本薬学会北陸支部平成 18 年度第 2 回総会, 2006, 11.12, 富山.

◇その他

資料等

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- 3) 浜崎智仁: 「コレステロールは高い方がいい!」. 第 39 回食品新素材研究会, (社) 菓子総合技術センター, 2006, 2.22, 東京.
- 4) 浜崎智仁: 講義「呼吸, 消化, 血液の働きについて」. 黒部市三日市小学校, 2006, 7.3, 黒部.
- 5) 浜崎智仁: 講義「人や動物の体, 人や動物の体の素晴らしさや不思議について考える」. 上市町立宮川小学校, 2006, 7.14, 上市町.
- 6) 浜崎智仁: 「n-3 系脂肪酸と行動」, 若手栄養学研究者の集い第 40 回夏期研修会, 2006, 8.5, 富山.
- 7) 浜崎智仁: 「魚がなくなる日」, 第 15 回大会日本脂質栄養学会 市民公開講座「地球, 食, 健康」, 2006.9.2, 岐阜.
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- 9) 浜崎智仁: 「心筋梗塞の危険因子ーコレステロールはあまり関係ないー」, 医療ルネサンス北陸フォーラム, 読売新聞社, 富山県国民健康保険団体連合会, 2006, 10.24, 富山.
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◇共同研究

国内

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◇研究費取得状況

- 1) 富山県受託研究、和漢薬・バイオテクノロジー研究（分担：渡辺志朗）「消化管をターゲットとした新しい和漢薬製剤の開発」、（分担課題）
- 2) 脂肪吸収の調節および摂食障害を改善する和漢薬の探索とその機構の解析 研究拠点形成費補助金（COEプログラム）（分担：渡辺志朗）

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卒業論文：

山本 亮：非ステロイド抗炎症剤誘発性の消化管出血に対するオウゴン含有漢方方剤の影響

修士論文：

藤岡俊太郎：Indomethacin の投与により誘発される摂食障害に伴う炎症反応の解析

山田泰広：Indomethacin の毒性反応に対する黄芩および黄芩含有漢方方剤の影響