

## 臨床利用分野

## Division of Clinical Application

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### ◇研究目的

脂質代謝制御を基盤とした漢方薬および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) 非ステロイド性抗炎症剤による小腸粘膜傷害に対する漢方薬および食餌脂肪酸の影響
- 3) 脂肪の消化管内での代謝反応に対する作用を指標とした漢方薬の薬効評価
- 4) 炎症反応に伴って起こる摂食行動障害における炎症性メディエーターの役割の解析
- 5) 動物胆汁の発展的利用のための安全性および有効性の確認

### ◇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による漢方薬の検討。
- II) 非ステロイド性抗炎症剤による小腸粘膜傷害が漢方薬および n-3 系脂肪酸より制御される機構を、脂質メディエーターの産生変化から明らかにする。
- III) 動物胆汁製剤の用途を発展させる一案として、それに n-3 系脂肪酸を配合した製剤を提案した。それをメタボリックシンドロームにおける脂質代謝異常の改善に有用であるか否かを動物実験にて評価している。
- IV) ザイモサン誘発性摂食行動障害モデルを用いて、局所炎症反応に伴う脳神経系応答反応における脂質性メディエーターの役割を解析している。

### ◇著書

- 1) Hamazaki T., Kirihara Y.: Correlation between low cholesterol levels and high all-cause mortality-results from meta-analysis in Japan-, In what areas are traditional / alternative medicimes useful? Hamazaki T., Nagasawa T., Okuyama H.(ed.) 19-27, Proceedings of 11th International Symposium on Traditional Medicine in Toyama 2007, 2008.
- 2) Hamazaki T., Okuyama H.: The Japanese Experience. High Cholesterol is Not an Important Risk Factor of All-Cause Mortality, Wild-Type Food in Health Promotion and Disease Prevention. The

Columbus Concept, Fabien De Meester, Ronald Ross Watson (ed.) 21-28, Humana Press INC. Totawa, New Jersey, 2008.

- 3) Awale S., Hamazaki T., Kadowaki M., Saiki I., Tezuka Y., Kadota S.: Chapter 4 Commonly Encountered diseases in Traditional Medicine, Myanmar Traditional Medicine Handbook. MINISTRY OF HEALTH Department of Traditional Medicine, 99-120, 2008.

#### ◇原著論文

- 1) **Itomura M., Fujioka S., Hamazaki K., Kobayashi K., Nagasawa T., Sawazaki S., Kirihara Y., and Hamazaki T.: Factors Influencing EPA+DHA Levels in Red Blood Cells in Japan. *in vivo*. 22: 131-136, 2008.**

**Abstract:** The blood eicosapentaenoic and docosahexaenoic acid (EPA+DHA) concentration is an important inverse risk factor for sudden cardiac death. However, it is not known what kinds of factors influence the EPA+DHA levels in the total phospholipid fraction in red blood cells (RBC EPA+DHA) in Japan, who regularly eat more fish with increasing age. Four hundred and fifty-six healthy individuals (320 men and 136 women, 18 to 70 years old) were recruited between 2002 and 2005. RBC EPA+DHA were measured by gas chromatography and questionnaires were administered. Multivariate analysis indicated that there were significant correlations between RBC EPA+DHA and (i) dietary EPA+DHA (beta=0.31), (ii) age (beta=0.33), (iii) gender (beta=-0.15) and (iv) physical activity (beta=-0.11) but not with body mass index or smoking.

- 2) **Kirihara Y., Hamazaki K., Hamazaki T., Ogushi Y., Tsuji H., and Shirasaki S.: The Relationship between Total Blood Cholesterol Levels and All-cause Mortality in Fukui City, and Meta-analysis of This Relationship in Japan. *J. Lipid Nutr.* 17: 67-78, 2008.**

**Abstract:** Summary: Shirasaki published a Japanese paper about the relationship between total cholesterol levels and all-cause mortality in Fukui City, Japan. His cholesterol data were not grouped according to ordinal 20mg/dL (0.52 mmol/L) intervals. In the present study, we re-calculated his data for meta-analysis. The relative risk (RR) of all-cause mortality adjusted for age and sex showed a decreasing trend with total cholesterol levels (p for trend <0.0001). In order to summarize the relationship between total cholesterol and all-cause mortality, literature describing this relationship in Japan was collected mainly using computer search engines. Literature published before 1995 was excluded. Reports with the total number of study subjects smaller than 5,000 were also excluded. Five reports were found suitable for meta-analysis of cholesterol levels and all-cause mortality. Meta-analysis revealed that the RR in the <160 mg/dL (<4.14 mmol/L) group [RR=1.71 (1.41, 2.08)] was significantly higher than in the reference group [160-199 mg/dL (4.14-5.17 mmol/L)], and that the RRs in the 200-239 mg/dL (5.18-6.21 mmol/L) group [RRs=0.83 (0.74, 0.94)] and  $\geq 240$  mg/dL ( $\geq 6.22$  mmol/L) group [0.78 (0.65, 0.95)] were significantly lower than in the reference group when both men and women were combined. We suggest that Japanese subjects with cholesterol levels  $\geq 240$  mg/dL ( $\geq 6.22$  mmol/L) should not be regarded as hypercholesterolemic or dyslipidemic except when having some genetic disorders like familial hypercholesterolemia because they are in the safest ranges in terms of all-cause mortality.

- 3) **Hamazaki K., Din Syafruddin., Insan S Tunru., Marina F Azwir., Puji BS Asih, Sawazaki S., and Hamazaki T.: The effect of docosahexaenoic acid-rich fish oil on behavior, school attendance rate and malaria infection in school children –a double-blind, randomized, placebo-controlled trial in Lampung, Indonesia. *Asia Pac J Clin Nutr.* 17: 258-263, 2008.**

**Abstract:** BACKGROUND: There are only a very limited number of reports of intervention studies on the effects of fish oil on behavior in normal school children. OBJECTIVE: To observe the effects of fish oil on behavior and school attendance rates in school children. DESIGN: Fourth to sixth graders (mostly 9-12 years of age) of an elementary school in Lampung Province, Indonesia, were randomly divided into either a docosahexaenoic acid (DHA) group (n=116) or a control group (n=117) in a double-blind manner. The subjects in the DHA group took 6 fish oil capsules per day (0.65 g DHA and 0.10 g eicosapentaenoic

acid (EPA)/day) for 3 months. Controls took soybean oil capsules. Two questionnaires were administered and blood was taken at the start and end of the study. Two questionnaires were administered at the start and end of the study: Hostility-Aggression Questionnaire for Children (HAQ-C) and Barratt Impulsiveness Scale, version 11 (BIS-11), for measurement of aggression and impulsivity, respectively. Attendance was recorded during the study period. **OUTCOMES:** The concentrations of DHA and EPA in the phospholipid fraction in red blood cells were significantly increased in the DHA group. Behavior checked with HAQ-C or BIS-11 did not show any differences between groups. However, the odds ratio of inability to attend school regularly during the study period was 0.40 (95%CI: 0.23-0.71) in the DHA group compared with controls ( $p=0.002$ ). **CONCLUSIONS:** DHA-rich fish oil may improve the school attendance rate of children in Lampung, Indonesia.

- 4) **Hamazaki T., Shimokawa H., Terashima Y., Itomura M., Hamazaki K., Nagasawa T., Yamamoto J., and Jun Wu.: The Fatty Acid Composition of Red Blood Cells in Mildly Demented Dogs and of Commercially Available Dog Foods in Japan. J. Lipid Nutr. 17: 163-171, 2008.**

**Abstract:** Summary: In order to investigate the relationship between the fatty acid composition of the dogs' tissue and dementia, we compared the fatty acid composition of red blood cells (RBCs) between 15 mildly demented dogs and 15 normal controls ( $\geq 10$  years old). In the mildly demented dogs polyunsaturated fatty acids (PUFA) were significantly decreased and the ratios of arachidonic acid to total PUFA (AA/PUFA) were significantly increased compared with normal dogs. AA/PUFA ratios had a significant correlation with dementia scores of 30 dogs ( $r=0.48$ ). Dog food analysis showed that the average n-6 fatty acids/n-3 fatty acids ratios, a parameter influencing AA/PUFA ratios in tissues, were very high in pellet-type dog foods ( $n=20$ , the ratios=12). In conclusion, high AA/PUFA values in RBCs might be a risk factor of mild dementia in dogs. It seems not prudent to provide AA supplements to mildly demented dogs.

- 5) **Higashihara E., Nutahara K., Horie S., Muto S., Hosoya T., Hanaoka K., Tuchiya K., Kamura K., Takaichi K., Ubara Y., Itomura M., and Hamazaki T.: The effect of eicosapentaenoic acid on renal function and volume in patients with ADPKD. Nephrol Dial Transplant. 23: 2847-2852, 2008.**

**Abstract:** BACKGROUND: Soy protein ameliorates rat polycystic kidney disease with concomitant renal enrichment of omega3-polyunsaturated fatty acids. A study was conducted to examine the effects of eicosapentaenoic acids (EPA) on renal volume and function in patients with autosomal dominant polycystic kidney disease (ADPKD). METHODS: Non-azotemic patients were randomized to either a control group ( $n = 20$ ) or an EPA group ( $n = 21$ ). EPA capsules (2.4 g/day) were administered in the EPA group for 2 years. Twenty-four hours of urine was collected for the creatinine clearance (Ccr) measurement every year. At baseline and 24 months, fatty acid compositions in erythrocytes were measured and computerized tomographies were obtained for calculation of renal volume by the modified ellipsoid and volumetric methods. RESULTS: In the EPA group, the EPA concentration (1.80 +/- 0.99 versus 4.40 +/- 1.79 area%,  $P < 0.001$ ) and the omega3/omega6 ratio in the erythrocyte increased, but docosahexaenoic acid (DHA) (6.76 +/- 1.19 versus 5.64 +/- 1.45 area%,  $P < 0.010$ ) concentration decreased. Ccr decreased by 8.5 +/- 9.5 and 9.0 +/- 13.0 ml/min/1.73 m<sup>2</sup>/2 years in the control and EPA groups, respectively (NS). The increases in renal volume calculated by either method were not significantly different between the two groups. CONCLUSIONS: A beneficial effect of EPA on renal function and kidney volume in ADPKD patients could not be confirmed in the present study. Administration of EPA with DHA supplementation and/or longer intervention might be necessary to demonstrate preventive effects of omega3-polyunsaturated fatty acids on progression of ADPKD.

- 6) **Itomura M., Terashima Y., Hamazaki K., Inoue K., Shirato N., Shibahara N., and Hamazaki T.: The Effects of a New Kanpo Formula, Hogen-ou, on Psychological Distress and**

**Low-Grade Inflammation — A Placebo-Controlled Double-Blind Study. *Current Topics In Nutraceutical Research.* 6:145-148, 2008.**

**Abstract:** We manufactured a new kampo formula, Hogen-ou (HGO), a combination of Hogento (Baoyuantang in Chinese) and Bezoar bovis, expecting that HGO might be able to control stress. Apparently healthy volunteers were allocated either to the active (the HGO group, n=22) or to the placebo group (n=25) in a double-blind manner. Subjects in the HGO group took 3g of HGO per day for 12 weeks; those in the placebo group took indistinguishable placebo. At weeks 0 (the start of the study), 4, 8, 12 (the end of the study), the 30-item version of the General Health Questionnaire (GHQ-30) was administered. Blood samples were also collected. Blood chemistry including high-sensitivity C-reactive protein (hs-CRP) was assessed; blood cells were counted. There were no changes in GHQ-30 between two groups. No changes were detected in blood chemistry either. However, leukocyte counts were significantly lowered in the HGO group compared with the placebo group. We suggest that HGO had anti-inflammatory effects on low-grade inflammation in apparently healthy subjects.

- 7) **Yoshizumi K., Murota K., Watanabe S., Tomi H., Tsuji T., and Terao J.: Chiisanoside is not absorbed but inhibits oil absorption in the small intestine of rodents. *Biosci. Biotechnol. Biochem.* 72:1126–1129, 2008.**

**Abstract:** Chiisanoside is the main component of *Acanthopanax sessiliflorus* leaves. Simultaneous administration of chiisanoside resulted in a decrease in the plasma TG level and increase of undigested TG in the intestinal lumen after oil gavage to mice. This suggests that chiisanoside has the potential to prevent obesity as a lipase inhibitor which suppresses fat absorption in vivo.

- 8) **Watanabe S., Yamada Y., Dobashi K., and Saito M.: Scutellariae Radix augments ulceration but attenuates proinflammatory cytokine and chemokine gene induction in the small intestine during indomethacin-induced enteropathy in mice. *J. Trad. Med.* 25:55-59, 2008.**

**Abstract:** Our previous report described the enhancement of intestinal bleeding and anemia associated with indomethacin (INDO)-induced enteropathy in mice by oral administration of *Scutellariae Radix* (SR) extract. We here demonstrate that SR extract enhanced ulceration but attenuated the elevation of expression levels of interleukin (IL)-1 $\beta$ , IL-6 and CCL2 gene transcripts in small intestine during INDO-induced enteropathy. Our observations further support that INDO-induced enteropathy is aggravated by the oral administration of SR extract. This effect of SR extract may be due to the modulation of immune-inflammatory processes possibly through the suppression of proinflammatory cytokine and chemokine induction.

- 9) **Dobashi K., Ohkoshi E., Fujii Y., Nagai M. and Watanabe S.: Scutellariae Radix aggravates diclofenac sodium-induced enteropathy in mice. *J. Trad. Med.* 25:81-86, 2008.**

**Abstract:** We have reported that the oral administration of water extract of *Scutellariae Radix* (SR) enhances small intestinal ulceration and intestinal bleeding in the experimental enteropathy induced by subcutaneous injections of indomethacin (INDO) in mice. The present study was carried out to examine whether SR extract or SR-containing Kampo formula exerts similar effects in diclofenac sodium (Dic)-induced enteropathy in mice. We found that small intestinal ulceration and fecal hemoglobin (Hb) excretion in Dic-treated mice were enhanced by SR extract. However, such effects were not induced by pure baicalin (> 97%, w/w). OrenGEDOKUTO (OGT) did not enhance small intestinal ulceration but significantly enhanced fecal Hb excretion in Dic-treated mice. Our observations suggest a possibility that SR-containing Kampo formulas could aggravate non-steroidal anti-inflammatory drug-induced enteropathy.

- 10) **Saito M. and Watanabe S.: Differential modulation by dexamethasone treatment of lipopolysaccharide- and zymosan-induced hypophagia in mice. *Pharmacol. Biochem. Behav.***

90: 428-433, 2008.

**Abstract:** The treatment of experimental animals with lipopolysaccharide (LPS) induces behavioral depression, in which the central and peripheral inductions of proinflammatory cytokines are proposed to play an important role. We have shown that the intraperitoneal injection of zymosan, composed of insoluble particles prepared from yeast cell walls, can induce behavioral depression assessed as hypophagia in mice, although the role of proinflammatory cytokines in this response has not yet been investigated. We have also shown that the subcutaneous injection of the corticoid, dexamethasone (Dex), a potent inhibitor of cytokine production, is effective in attenuating hypophagia in LPS-treated mice. The attenuated response was associated with the suppression of the gene induction of proinflammatory cytokines (i.e., IL-1beta, IL-6 and TNFalpha) in the brain and liver. In contrast, no significant induction of proinflammatory cytokine genes was observed in the brain or liver during zymosan-induced hypophagia; the subcutaneous injection of Dex did not attenuate zymosan-induced hypophagia but its intraperitoneal injection did. Thus, zymosan-induced hypophagia was less responsive to a subcutaneous injection of dexamethasone than LPS-induced hypophagia, which may be due to the limited role of systemic inflammation in this response. An important role of localized, rather than systemic, inflammation in zymosan-induced hypophagia was suggested, although the role of local proinflammatory cytokines remains to be clarified.

#### ◇総 説

- 1) Hamazaki T., Hamazaki K.: Fish oils and aggression or hostility. *Prog lipid res.* 47: 221-232, 2008.
- 2) 浜崎智仁, 糸村美保: 飽和脂肪酸→コレステロール→冠動脈疾患を再検する Reconsideration of the Sequence of Saturated Fatty Acids, Cholesterol and Coronary Heart Disease in Japan. *オレオサイエンス* 8: 429-436, 2008.
- 3) 浜崎智仁, 糸村美保: 第1部機能性食品成分, 第16章不飽和脂肪酸の健康効果, 第9節 n-3系脂肪酸と行動, *食品機能性の科学*, 544-547, 2008.
- 4) 浜崎景, 浜崎智仁: 第9章ブレインフード系, 第3節臨床現場におけるブレインフードの応用, *アンチエイジング・ヘルスフードー抗加齢・疾病予防・健康長寿延長への応用一*, 243-249, 2008.
- 5) 渡辺志朗, 奥山治美: 第16章第7節 不飽和脂肪酸の健康効果 n-3系脂肪酸の抗炎症, 抗アレルギー作用, *食品機能性の科学*, 538-541, 2008.

#### ◇学会報告 (\*: 特別講演, シンポジウム, ワークショップ等)

- \* 1) Hamazaki T. : The high omega-3/high cholesterol' healthy diet. 6th International Congress on the Columbus Concept. 2008, 10, 6-9, Geneva.
- \* 2) Hamazaki T. : Clinical Trials of Omega3 Fatty Acid containing Food Administration on Symptoms of Attention-Deficit/Hyperactivity Disorder – our experience and others. 2nd WFSBP Asia-Pacific Congress. 2008, 9, 11-13, Toyama.
- 3) Hamazaki T., Suzuki N., Widyowati R., Miyahara T., Kadota S., Ochiai H., Hamazaki K.: The Effect of n-9 Eicosatrienoic acid. 8th Congress of the International Society for the Study of Fatty Acids and Lipids. 2008, 5, 17-22, Kansas City.
- 4) Hamazaki K., Terashima Y., Itomura M., Sawazaki S., Inagaki H., Kuroda M., Tomita S., Hirata H., Hamazaki T. : N-3 Fatty Acids and Survival of Hemodialysis Patients. 8th Congress of the International Society for the Study of Fatty Acids and Lipids. 2008, 5, 17-22, Kansas City.
- 5) Hamazaki-Fujita N., Kosuge H., Yomoda S., Itomura M., Terashima Y., Hamazaki K., Hamazaki T. : Relationship Between Fatty Acids in RBCs and Skin Conditions. 8th Congress of the International Society for the Study of Fatty Acids and Lipids. 2008, 5, 17-22, Kansas City.
- \* 6) 浜崎智仁 : 脂質と精神, 日本脂質栄養学会サテライトシンポジウム「脳機能・行動・神経症に影響を与える脂質栄養」2008.9.7, 大阪.

- \* 7) 浜崎智仁：血清コレステロール値（あるいは LDL-コレステロール値）に上限をもうけることはほとんど無意味，第 17 回大会日本脂質栄養学会，シンポジウム「コレステロールを多方面から考えるー日本動脈硬化学会との合同シンポジウムー」2008.9.6, 大阪.
- 8) 浜崎景, 寺島嘉宏, 糸村美保, 澤崎茂樹, 稲垣均, 黒田昌宏, 富田新, 平田仁, 浜崎智仁：透析患者において n-3 系多価不飽和脂肪酸が生命予後に及ぼす影響，第 17 回大会日本脂質栄養学会，2008.9.5-6, 大阪.
- 9) 渡辺志朗, 山田泰広, 土橋一輝, 斎藤正隆：オウゴンエキスがインドメタシンにより誘発される小腸における粘膜傷害と炎症性サイトカインの遺伝子発現に及ぼす影響，日本薬学会第 128 年会，2008. 3.26-28, 横浜.
- \* 10) 渡辺志朗, 土橋一輝：オウゴンエキスがジクロフェナクナトリウムにより誘発される小腸粘膜傷害に及ぼす影響，第 25 回和漢医薬医学会大会 2008.8.30-31, 大阪.

#### ◇その他

- 1) Inagaki H, Satoh T, Kamiya K, Mori T, Nomura T, Hamazaki T, and Hamazaki K.: (Letter to the editor) Simplest method to prevent rust formation at the nipple connecting the hemodialysis console and dialysate tube. Cllinical Nephrology. 70:185-186, 2008.
- 2) Hamazaki T., Hamazaki K. Letters to the Editor Why so thin? Eur J Clin Nutr. 62: 1252-1254, 2008.
- 3) 浜崎智仁：低コレステロールは危険メタ分析で研究結果を裏付け，実業之富山，4:49, 2008.
- 4) 浜崎智仁：「コレステロール値は高いと死ににくい」，青淵（渋沢栄一祈念財団），26-28, 2008.
- 5) 浜崎智仁：「コレステロール下げる必要はない！高いほうが長生きできる！」，安心，8 月号 130-133, 2008.
- 6) 浜崎智仁：研究室から，脂質の研究をする，富薬 9 号 30 巻 No.230, p6.

#### ◇共同研究

##### 国内

- 1) 岩崎基：国立がんセンター，「多目的コホートにおける血液を用いた脳卒中・心筋梗塞のコホート内症例・対照研究，2006, 9-
- 2) 芝原章：大阪府立大学，「トランス脂肪酸投与と脳の脂肪酸構成」，2007,12-
- 3) 奥山治美：金城学院大学，「脂質栄養と性差に関するオープンリサーチ，2007,10-
- 4) 山田幸雄：株式会社広貫堂「メタボリックシンドロームの改善に有効な n-3 系脂肪酸および動物胆配合一般用家庭薬品の開発研究」2007, 7-

##### 海外

- 1) 夏瑢：浙江中医学院，「血中脂肪酸と骨折とのコホート研究」，2005, 1-
- 2) Taslim N.A.：ハサヌディン大学，「骨粗鬆症と脂肪酸」，2005, 2-
- 3) 夏瑢：浙江中医学院，「n-3 系脂肪酸と睡眠時無呼吸症候群」，2005,11-

#### ◇海外調査

- 1) 浜崎智仁：国際協力機構（JICA），短期派遣専門家業務 ミャンマー伝統医療プロジェクト，2008, 3, 18-26, 2008, 11,29-12,10, ミャンマー

#### ◇研究費取得状況

- 1) 多目的コホートでの血液脂肪酸構成から見た心筋梗塞・脳卒中の症例・対照研究，平成

- 20年度文部科学省科学研究費基盤(C) (代表：浜崎智仁)
- 2) 脂質栄養と性差に関するオープンリサーチ, 私大学術研究高度化事業 (分担：浜崎智仁)
  - 3) 中高年者疾患に有効な富山県ブランド生薬および和漢薬方剤の開発研究, 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)
  - 4) 脂肪分解促進作用に基づく熊胆の合成代替品の開発を目指した基礎的検討, 富山第一銀行奨学財団助成事業 (代表：渡辺志朗)
  - 5) メタボリックシンドロームの改善に有効な n-3 系脂肪酸および動物胆配合一般用家庭薬品の開発研究, 新商品・新事業創出公募事業, 富山県新世紀産業機構機構 (分担：渡辺志朗)
  - 6) 天然薬物の遺伝子解析等に基づく標準化, 知的クラスター創成事業(Ⅱ) 広域化プログラム (分担：渡辺志朗)

#### ◇研究室在籍者

学部3年生：吉田康彦

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大学院修士1年：石川宏則

大学院医学研究科4年：寺島嘉宏

技術補佐員：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) 2008.4-2008.9)

山崎美保(ポリエン・プロジェクト(有) 2008.4-2009.3)

#### ◇学位(修士, 博士) 取得者

卒業論文：

阿部将平：動物胆汁がジクロフェナクナトリウムにより誘発される小腸粘膜傷害に及ぼす影響

亀井貴志：サポニン含有生薬の膵リパーゼ活性に及ぼす影響

博士論文：

斎藤正隆：サイモサンにより誘発される摂食抑制における炎症反応の役割の解析