

## 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) 動物胆による脂質代謝活性の修飾機構の解析とその臨床利用

### ◇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) 異なる動物種由来の胆汁の脂質代謝に対する影響が大きく異なることを明らかにした。この機構をリポドミクス解析と遺伝子発現解析法を組み合わせるために研究を進めている。

### ◇著書

- 1) 奥山治美, 浜崎智仁, 大榎陽一他策定委員編著者:「長寿のためのコレステロールガイドライン 2010 年版」, 日本脂質栄養学会・コレステロールガイドライン策定委員会監修, 中日出版社, 名古屋, 2010.

### ◇原著論文

- 1) **de Lorgeril M., Salen P., Abramson J., Dodin S., Hamazaki T., Kostucki W., Okuyama H., Pavy B., Rabaeus M.: Cholesterol lowering, cardiovascular diseases, and the rosuvastatin-JUPITER controversy: a critical reappraisal. Arch Intern Med., 170: 1032-6, 2010.**

**Abstract:** BACKGROUND: Among the recently reported cholesterol-lowering drug trials, the JUPITER (Justification for the Use of Statins in Primary Prevention) trial is unique: it reports a substantial decrease in the risk of cardiovascular diseases among patients without coronary heart disease and with normal or low cholesterol levels. METHODS: Careful review of both results and methods used in the trial and comparison with expected data. RESULTS: The trial was flawed. It was discontinued (according to prespecified rules) after fewer than 2 years of follow-up, with no differences between the 2 groups on the most objective criteria. Clinical data showed a major discrepancy between significant reduction of nonfatal stroke and myocardial infarction but no effect on mortality from stroke and myocardial infarction. Cardiovascular mortality was surprisingly low compared with total mortality-between 5% and 18%-whereas the expected rate would have been close to 40%. Finally, there was a very low case-fatality rate of myocardial infarction, far from the expected number of close to 50%. The possibility that bias entered the trial is particularly concerning because of the strong commercial interest in the study.

CONCLUSION: The results of the trial do not support the use of statin treatment for primary prevention of cardiovascular diseases and raise troubling questions concerning the role of commercial sponsors.

- 2) **Lai YC., Hamazaki K., Yoshizawa K., Kawanaka A., Kuwata M., Kanematsu S., Hamaazki T., Takada H. and Tsubura A.: Short-term Pregnancy Hormone Treatment of N-Methyl-N-nitrosourea-induced Mammary Carcinogenesis in Relation to Fatty Acid Composition of Serum Phospholipids in Female Lewis Rats. *in vivo*, 24: 553-560, 2010.**

**Abstract:** AIM: Short-term oestrogen and progesterone treatment (STEPT) mimics the pregnancy hormone milieu. This study compared the development of N-methyl-N-nitrosourea (MNU)-induced mammary cancer in female Lewis rats that received STEPT in early or later life. **MATERIALS AND METHODS:** Rats in Groups 1 and 2 received a single intraperitoneal injection of 50 mg/kg MNU at 4 weeks old. Pellets containing 0.5 mg 17 $\beta$ -estradiol and 32.5 mg progesterone (EP) were subcutaneously implanted in rats in Group 1 during 6-9 weeks old. Rats in Groups 3 and 4 received 50 mg/kg MNU at 22 weeks old and again at 23 weeks old. EP pellets were implanted in rats in Group 3 during 24-27 weeks old. At the time of EP removal and 8 weeks afterward, 4 randomly selected rats in each group were sacrificed for blood sampling. The fatty acid composition of serum phospholipids was measured by capillary gas chromatography. The remaining rats were sacrificed when they developed mammary tumours  $\geq$ 1 cm in diameter or at the termination of the experiment, which was at 18 weeks old for Groups 1 and 2 and at 64 weeks old for Groups 3 and 4. Mammary cancer was histologically confirmed. **RESULTS:** Group 1 had a significantly suppressed incidence of mammary cancer compared to Group 2 (7% vs. 90%), whereas the cancer incidence in Group 3 was similar to that of Group 4 (50% vs. 56%). Rats in Group 1 had significantly smaller n-6/n-3 polyunsaturated fatty acid (PUFA) ratios and higher levels of docosahexaenoic acid (DHA) than those in Group 2 at the time of EP removal but not 8 weeks after EP removal. Neither the PUFA ratios nor the DHA levels differed between Groups 3 and 4 at any time. These data suggest that the age at which STEPT is administered is important, since its mammary cancer-suppressing potential was lost in aged animals. **CONCLUSION:** DHA and the n-6/n-3 PUFA ratio may play a crucial role in mammary cancer suppression by STEPT.

- 3) **Higashihara E., Itomura M., Terachi T., Matsuda T., Kawakita M., Kameyama S., Fuse H., Chiba Y., Hamazaki T., Okegawa T., Tokunaga M., Murota T., Kawa G., Akashi T., Hamazaki K., and Takada H.: Effects of Eicosapentaenoic Acid on Biochemical Failure after Radical Prostatectomy for Prostate Cancer. *in vivo*, 24: 561-566, 2010.**

**Abstract:** AIM: To study the effects of eicosapentaenoic acid (EPA) on prostate-specific antigen (PSA) failure in prostate cancer patients who underwent prostatectomy. **PATIENTS AND METHODS:** Sixty-two prostate cancer patients whose PSA levels were less than 0.2 ng/ml 3 months after surgery were randomized to either an EPA group (n=32) or a control group (n=30). EPA (2.4 g/day) was administered in the EPA group for 2 years. PSA was measured every two months. **RESULTS:** The EPA concentration increased but the docosahexaenoic acid concentration decreased significantly ( $P < 0.001$ ) in erythrocytes. The PSA recurrence rates during a mean follow-up of 53.8 months were not different between the two groups ( $p = 0.16$ ). **CONCLUSION:** A longer and/or larger intervention or docosahexaenoic acid supplementation might be necessary to identify significant preventive effects of mega-3 polyunsaturated fatty acids on PSA recurrence.

- 4) **Watari M., Hamazaki K., Hirata T., Hamazaki T., Okubo Y.: Hostility of drug-free patients with schizophrenia and n-3 polyunsaturated fatty acid levels in red blood cells. *Psychiat Res.*, 177: 22-26, 2010.**

**Abstract:** Many reports suggest that n-3 polyunsaturated fatty acids (PUFAs) influence the symptoms of psychiatric disorders. Moreover, it has also been reported that n-3 PUFAs control aggression and hostility. Acute symptoms of schizophrenia such as aggression can be a formidable clinical problem resulting in hospitalization. However, few investigations have determined the relationships between acute symptoms of drug-free schizophrenia and n-3 PUFAs. We recruited 75 inpatients with acute drug-free schizophrenia admitted to Chiba Psychiatric Medical Center, an emergency psychiatric hospital. Blood was sampled immediately after admission. The red blood cell (RBC) fatty acid composition and hostility score of

Positive and Negative Syndrome Scale (PANSS) scores were measured. Multiple regression analysis showed that the concentrations of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), and the ratio of EPA/arachidonic acid (AA) in RBC showed significant negative correlations with the hostility score of PANSS scores after adjustment for age and sex. AA, on the other hand, showed significant positive correlations. The tissue n-3 PUFA and n-6 PUFA levels were negatively and positively associated with the hostility score of PANSS scores, respectively, suggesting possible effects of PUFA levels on hostile behavior in patients with schizophrenia.

- 5) **Ogura T., Takada H., Okuno M., Kitade H., Matsuura T., Kwon M., Arita S., Hamazaki K., Itomura M., Hamazaki T.: Fatty Acid Composition of Plasma, Erythrocytes and Adipose: Their Correlations and Effects of Age and Sex. *Lipids*, 45: 137-144, 2010.**

**Abstract:** The composition of fatty acids in abdominal subcutaneous adipose tissue and the correlation of fatty acid values of plasma and erythrocytes had not been reported in Japan. The aim of the present study was to investigate the fatty acid composition and correlation of plasma and erythrocyte phospholipids (PL) and adipose triacylglycerols (TG) in 75 adult patients admitted for non-malignant diseases. We also examined the relationship of n-3 and n-6 polyunsaturated fatty acid (PUFA) with patients' characteristics. The total n-3 PUFA were 11.2, 11.8 and 1.9%, and the ratios of n-6/n-3 were 2.41, 1.87 and 8.20 in plasma and erythrocyte PL and adipose TG, respectively. There were the highest correlations for total n-3 PUFA and the n-6/n-3 ratio between plasma and erythrocyte PL and adipose TG. There was a positive correlation between n-3 PUFAs and age, but a negative correlation was found between n-6 PUFAs and age. There was no significant difference in the values of PUFAs in plasma and erythrocyte PL and adipose TG between men and women. The patients with cholesterol cholecystolithiasis showed a significantly lower proportion of eicosapentaenoic acid in plasma and erythrocyte PL than those of the other patients. Our findings suggest that PUFA in plasma and erythrocyte PL may be good biomarkers and more acceptable for studying participants than adipose TG.

- 6) **Zhang W., Xia R., Nagasawa T., Sun Y., Hamazaki K., Wu J., and Hamazaki T.: The Fatty Acid Composition of Fish Consumed in Dalian-and Hangzhou-City, China. *J Lipid Nutr.*, 19: 103 -110, 2010.**

**Abstract:** There was essentially no database on the fatty acid composition of fish available in China. Twenty-seven kinds of fish and 20 kinds were purchased in Dalian- and Hangzhou-city, China, respectively, and edible part was analyzed for the fatty acid composition. Three kinds of fish were purchased in both cities, but they contained markedly different amounts of n-3 polyunsaturated fatty acids (PUFA). Those kinds of fish in Hangzhou-city had more n-3 PUFA than those in Dalian-city. This was probably because fish were purchased in winter in Hangzhou-city and in summer in Dalian-city. Our data were limited in terms of the area and season of catch, and the number of species. However, our database would serve as the starting point for the fatty acid composition study of Chinese fish.

- 7) **Watanabe S. and Tsuneyama K.: A triglyceride-lowering effect of cattle bile is associated with elevation of cholesterol levels and liver injury in mice. *J Trad Med.*, 27: 179-185, 2010.**

**Abstract:** Since cholic acid (CA) has been demonstrated to suppress triglyceride (TG) synthesis, cattle bile (CB) constituted mainly of CA may exert a TG-lowering effect. However, harmful effects of CB such as elevation of cholesterol (Cho) levels and hepatotoxicity are also assumed to be induced. In this study, we demonstrated that diets containing CB at 0.5 and 1.0 % (w/w) reduced TG levels in blood and liver of mice, which was associated with the elevation of Cho levels in blood and liver and liver injury. Our results suggest that practical use of CB as a TG-lowering agent is not recommended.



## ◇総 説

- 1) 浜崎智仁：「長寿のためのコレステロールガイドライン」は何をめざすか？ 臨床栄養，117: 730-731, 2010.
- 2) 稲寺秀邦，浜崎智仁：Cholesterol Controversy: LDL-コレステロールの基準値をめぐる，日衛誌，65: 506-515, 2010.
- 3) 浜崎智仁：コレステロールの新しい観点，高崎医学，60: 29-43, 2010.
- 4) 浜崎景，浜崎智仁：PUFA と認知症，特集 認知症と機能性食品，Functional Food，3: 205-211, 2010.
- 5) 浜崎智仁，糸村美保：低炭水化物食の意義，脂質栄養学，19: 59-63, 2010.
- 6) 浜崎景，松岡豊，浜崎智仁，稲寺秀邦： $\omega$ 3 系多価不飽和脂肪酸の精神への影響，精神科，17: 520-527, 2010.

## ◇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.: Effect of Omega 3 on Chronic Stress Response. Science in Nutrition 2<sup>nd</sup> International Congress. 2010, 3, 5-6, Rome. (Invited lecture)
- 2) Matsuoka Y., Nishi D., Yonemoto N., Hamazaki K., Hashimoto K., and Hamazaki T. : Omega -3 Fatty acids for secondary prevention of posttraumatic stress disorder following accidental injury: an open-label pilot study. 9<sup>th</sup> Conference of the International Society for the Study of Fatty Acids and Lipids (ISSFAL 2010). 2010, 5, 29-6, 2, Maastricht.
- 3) Hamazaki T., Nagasawa T., Hamazaki K., Itomura M.: Mead Acid Inhibits Angiogenesis - An in vitro study -. 9<sup>th</sup> Conference of the International Society for the Study of Fatty Acids and Lipids (ISSFAL 2010). 2010, 5, 29- 6, 2, Maastricht.
- 4) Nina Hamazaki-Fujita, Hamazaki K., Tohno H., Itomura M., Terashima Y., Hamazaki T., Yomoda S.: Polyunsaturated Fatty Acids and Blood Circulation in the Forebrain during Mental Arithmetic Task. 9<sup>th</sup> Conference of the International Society for the Study of Fatty Acids and Lipids (ISSFAL 2010). 2010, 5, 29-6, 2, Maastricht.
- \* 5) 浜崎智仁：n-3 系脂肪酸と敵意性の制御，第 83 回日本薬理学会年会，2010, 3, 16-18，大阪。(招待講演)
- \* 6) 浜崎智仁：コレステロール理論に対する批判的総論，日本脂質栄養学会 19 回大会，2010, 9, 3-4，犬山。(招待講演)
- \* 7) 浜崎智仁：学術シンポジウム，コレステロール低下薬による介入試験の質，第 48 回日本医療・病院管理学会学術総会，2010, 10, 15-16，広島。
- 8) 石川宏則，渡辺志朗：動物胆汁の投与がマウスにおけるジクロフェナクナトリウムによる小腸粘膜傷害に及ぼす影響，日本薬学会第 130 年会，2010, 3, 28-30，岡山。
- 9) 渡辺志朗，常山幸一：牛胆がマウスにおけるトリグリセリドとコレステロールの代謝に及ぼす影響，日本薬学会第 130 年会，2010, 3, 28-30，岡山。
- 10) 渡辺志朗，湖間戸俊輔，米山惇志：牛胆およびコール酸の脂質代謝に及ぼす影響のリピドミクス解析，第 27 回和漢医薬学会，2010, 8, 28-29，京都。
- 11) 雪永玲美，田中謙，渡辺志朗，小松かつ子：鶏血籐の脂肪吸収に与える影響，第 27 回和漢医薬学会，2010, 8, 28-29，京都。
- 12) 太田裕子，田中謙，渡辺志朗，川筋邦夫：シツリシの男性ホルモン増強効果，第 27 回和漢医薬学会，2010, 8, 28-29，京都。
- 13) 澤田啓介，根橋佳奈，大蔵直樹，渡辺志朗，厚味巖一：トランス脂肪酸は脂肪細胞をインスリン抵抗性とする，第 33 回日本分子生物学会年会 第 83 回日本生化学会大会合同大会，2010, 12, 10，神戸。
- 14) 神保沙織，志村佑介，守田雅志，渡辺志朗，今中常雄：ABCD1 欠損マウス由来アストロサイトをを用いた ALD 分子病態の検討，第 33 回日本分子生物学会年会 第 83 回日本生化学会大会合同大会，2010, 12, 10，神戸。

## ◇その他

- 1) 浜崎智仁：講演「コレステロールは人体にとってもビッグファーマにとってもあまりに重要ーポスト・バイオックス・スキャンダルとは？」島根大学大学院，2010, 8, 20, 島根.
- 2) 浜崎智仁：講演「コレステロールは高いほうが死なない」島根大学公開講座，2010, 8, 21, 島根.
- 3) 浜崎智仁：特別講演司会，第1回精神栄養研究会，2010, 11, 3, 東京.
- 4) 浜崎智仁：講演，農食健美クラブ，「今後重要な意味をもつエゴマ油とは」，2010, 9, 13, 富山.
- 5) 浜崎智仁：講演，健康・長寿研究談話会第4回アカデミックサロン，「低炭水化物食とその周辺」，2010, 6, 25, 東京.
- 6) 浜崎智仁：「だんわしつ」コレステロール厚労省記者クラブ会見，実業之富山，7: 37, 2010.
- 7) 浜崎智仁：現行のコレステロール基準は方向転換が必要，コレステロールの新しい考え方を示す，月刊新医療，431:19, 2010.
- 8) 浜崎智仁：コレステロール問題で動脈硬化学会に反論，週刊日本医事新報，4514: 48, 2010.
- 9) 奥山治美，浜崎智仁他：活動報告，「脂質栄養」オープン・リサーチ・センター 2007-9 年度中間報告の要約，金城学院大学消費生活科学研究所「研究所紀要」，14, 31-35, 2010.

## ◇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) 今中常雄：富山大学大学院医学薬学部研究部，「ペルオキシゾーム異常による極長鎖脂肪酸の蓄積の機構解明」，2009, 4-
- 5) 井上誠：愛知学院大学大学院薬学研究科，「特徴的脂質含有植物および動物由来生薬の脂質代謝に及ぼす影響～リピドミック解析を介した内在性および外来性核内受容体リガンドの探索～」
- 6) 能勢充彦：名城大学薬学部，「漢方処方における甘草配合の意義に関する基礎的研究 ～甘草配合漢方処方の胆汁酸誘発肝障害に及ぼす影響～」
- 7) 厚味巖一：帝京大学薬学部，「トランス脂肪酸による脂肪細胞のインスリン耐性形成の分子機構」2009, 10-

### 国外

- 1) 夏瑢：浙江中医薬大学，「血中脂肪酸と骨折とのコホート研究」，2005, 1-
- 2) 夏瑢：浙江中医薬大学，「n-3 系脂肪酸と睡眠時無呼吸症候群」，2005, 1-

## ◇研究費取得状況

- 1) アラキドン酸補給の安全性に関する研究，平成 22 年度厚生労働科学研究費補助金，食品の安心・安全確保推進事業（代表：浜崎智仁）
- 2) 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 22 年度文部科学省科学研究費基盤(C)（代表：浜崎智仁）
- 3) 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）
- 4) 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）

- 5) メタボリックシンドロームの改善に有効な牛胆配合 OCT の開発研究, 地域イノベーション創生事業 (分担: 渡辺志朗)

#### ◇研究室在籍者

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#### ◇学位 (修士, 博士) 取得者

修士論文: 石川宏則: 熊胆および牛胆が Diclofenac sodium による誘発される小腸粘膜傷害に及ぼす影響