

## 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の漢方薬による制御の機構の解明
- 3) 脂肪吸収の調節を指標とした漢方薬の評価と臨床応用
- 4) 炎症反応に伴って起こる摂食行動障害におけるアラキドン酸代謝物の役割の解析

### ◇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 (NSAIDs) による小腸粘膜傷害がオウゴンにより増悪される機構を明らかにするために研究を行っている。また NSAIDs による小腸粘膜傷害を軽減する漢方薬の開発を目指す。
- III) 熊胆の脂肪分解促進作用を担う有効成分を見出し、その情報をもとに代替熊胆を開発することを目指す。
- 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する。

## ◇原著論文

- 1) **Kobayashi K., Hamazaki K., Fujioka S., Terao K., Yamamoto J., and Kobayashi S.: The effect of n-3 PUFA/ $\gamma$ -cyclodextrin complex on serum lipids in healthy volunteers ? a randomized, placebo-controlled, double-blind trial. *Asia Pac J. Clin. Nutr.*, 16: 429-434, 2007.**

**OBJECTIVES:** This study was carried out to examine whether serum triglyceride concentrations were decreased by administration of n-3 polyunsaturated fatty acid (PUFA)/ $\gamma$ -cyclodextrin ( $\gamma$ -CD) complex-containing capsules as reported previously with n-3PUFA without  $\gamma$ -CD. **STUDY DESIGN:** A placebo-controlled double-blind study with healthy subjects (n=35) and hypertriglyceridemic subjects (n=7) of 35-66 years of age was performed. The subjects were randomized to a group (n-3 group) supplemented with n-3PUFA/ $\gamma$ -CD-containing capsules (660 mg EPA + 280 mg DHA/day) or a control group supplemented with capsules containing essentially no n-3 PUFA for 8 weeks with stratification by sex, age, and serum triglyceride levels in a double blind manner. Fasting blood samples were obtained at the start of administration and 4 and 8 weeks afterward. **RESULTS:** EPA concentrations in the total phospholipid fraction of red blood cells increased significantly in all subjects in the n-3 group, whereas no changes were seen in the control group. Triglyceride levels were significantly decreased (-17%) in the n-3 group compared with the control group at week 8. The following serum lipids did not significantly change over time: total-cholesterol, low-density lipoprotein-cholesterol and high-density lipoprotein-cholesterol. Only two subjects in the n-3 group guessed at the end of the study that their capsules were active. **CONCLUSION:** n-3 PUFA/ $\gamma$ -CD complex lowered triglyceride levels in normal and slightly hypertriglyceridemic subjects. There was a possibility that  $\gamma$ -CD might at least partly cover the smell and aftertaste of fish oil.

- 2) **Hamazaki K., Sawazaki S., Itomura M., Huan M., Shibahara N., Kawakita T., Kobayashi S., Hamazaki T.: No effect of a traditional Chinese medicine, Hochu-ekki-to, on antibody titer after influenza vaccination in man: A randomized, placebo-controlled, double-blind trial. *Phytomedicine*, 14: 11-14, 2007.**

**BACKGROUND:** It was shown that a traditional Chinese medicine, Hochu-ekki-to (HET), had adjuvant effects in influenza vaccination in an animal experiment. This, however, could not be assessed in a clinical study. **METHODS:** Thirty-two healthy subjects were randomly assigned to two groups (control and HET groups) in a double-blind manner. HET subjects (n=17) took 7.5 g of HET/day for two weeks; control subjects took the same amount of indistinguishable placebo. Then subjects were vaccinated against influenza (H1N1, H3N2 and B/Shandong). Hemagglutinin titers and natural killer (NK) activity were measured at weeks 0, 1, 2, 4, and 12. **RESULTS:** Antiinfluenza titers against the three viruses were increased continuously for the first two weeks and leveled off. However, there were no significant differences in any titers between the two groups. NK activity peaked at week 2 without any inter-group differences. **CONCLUSION:** We could not find any adjuvant effects of HET in this experimental condition.

- 3) **Terashima Y., Hamazaki K., Itomura M., Huan M., Shibahara N., Kobayashi S., Hamazaki T.: Effect of traditional Chinese medicine, maobushisaishinto, on the antibody titer after influenza vaccination : A randomized, placebo-controlled, double-blind trial. *J. trad. Med.*, 24: 59-66, 2007.**

**Background:** It was shown that a traditional Chinese medicine, maobushisaishinto (MBST), had adjuvant effects on influenza vaccination in an animal experiment and an open trial in elderly subjects. **Purpose:** To examine the adjuvant effects of MBST in a closer clinical experiment. **Methods:** Forty-seven healthy subjects between 20 and 71 y of age were randomly assigned to two groups (control and MBST groups) in a double-blind manner. The subjects in the MBST group (n=23) took 1.68g spray-dried powder

of MBST/day for two weeks; the rest (control subjects, n=24) took the same amount of indistinguishable placebo. Then subjects were vaccinated against influenza viruses (A/H1N1, A/H3N2 and B). Serum hemagglutination inhibition titers were measured at weeks 0, 1, 2, 4, and 12. Results: The titers against the three viruses were increased continuously for the first two weeks and leveled off. However, MBST was not superior to placebo in any titers. Conclusion: We could not find any adjuvant effects of MBST in this experimental condition.

- 4) **Kumasaka R., Nakamura N., Yamabe H., Osawa H., Shirato K., Shimada M., Murakami R., Fujita T., Okumura K., Hamazaki K. and Hamazaki T.: Fatty acid composition of plasma and kidney in rats with anti-thy1.1 nephritis. *in vivo*, 21: 77-80, 2007.**

**BACKGROUND:** n-3 Polyunsaturated fatty acids (PUFA) are reported to ameliorate atherosclerotic and inflammatory diseases because they compete with arachidonic acid and reduce its inflammatory metabolites. In the present study, the fatty acid composition of plasma and kidney in rats with anti-Thy1.1 nephritis was investigated. **MATERIALS AND METHODS:** A group of male Wister rats weighing about 200 g was injected with anti-Thy1.1 antibody (1.25 mL/kg) through their tail veins (nephritis group). Rats in the control group were injected with saline. Five days after the injection, urinary protein levels were determined. All rats were then sacrificed and fatty acid composition of plasma and kidney were analyzed. **RESULTS:** Eicosapentaenoic acids (EPA) levels in the kidney phospholipid (PL) fraction in the nephritis group were significantly lower than those in the control group (0.67 +/- 0.06 mol% vs. 0.96 +/- 0.06 mol%,  $p < 0.05$ ). EPA levels in the plasma PL fraction in the nephritis group were also significantly lower than those in the control group (0.38 +/- 0.05 mol% vs. 0.59 +/- 0.03 mol%,  $p < 0.05$ ). Urinary protein levels 5 days after the injection were inversely correlated with EPA levels in the kidney PL fraction ( $r^2 = 0.65$ ,  $p = 0.01$ ). These results suggested that decreased EPA levels in the kidney PL fraction might play an important role in anti-Thy1.1 nephritis.

- 5) **Yamada Y., Yamamoto R. and Watanabe S.: Scutellariae Radix enhances but Scutellariae Radix-containing Kampo formulas, Orengedokuto and San'oshashinto, prevent intestinal bleeding associated with indomethacin-induced enteropathy in mice. *J. Trad. Med.*, 24: 128-136, 2007.**

A single subcutaneous injection of indomethacin (INDO) in mice induced enteropathy characterized as ulceration in small intestine, which was associated with the elevation of fecal hemoglobin (Hb) content and the decrease in Hb and total protein concentration in blood. Oral administration of Scutellariae Radix (SR) (500 mg/kg) enhanced fecal Hb excretion but did not affect the decrease in blood Hb and total protein concentration in INDO-treated mice. In contrast, administration of two SR-containing kampo formulas, Orengedokuto (OGT) and San'oshashinto (SST) at 1100 mg/kg, which contained nearly the same amounts of baicalin as SR extracts at 500 mg/kg, markedly suppressed INDO-induced intestinal bleeding and blood loss. Plasma INDO concentration was not changed by the administration of SR, OGT or SST. The present study suggests that OGT and SST are useful for limiting complications such as intestinal bleeding and blood loss associated with INDO-induced enteropathy. However, possible harmful effects of other SR-containing kampo formulas on INDO-induced enteropathy remain to be investigated.

## ◇総説

- 1) 寺島嘉宏, 浜崎智仁: 魚油の行動に対する生理活性と応用. *Food Style* 21, 5月号 42-44, 2007.
- 2) 浜崎景, 浜崎智仁: 魚油の行動・精神への影響(1) n-3系多価不飽和脂肪酸と攻撃性について. *臨床栄養*, vol. 111(3), 284-285, 2007.
- 3) 浜崎景, 浜崎智仁: 魚油の行動・精神への影響(2) n-3系脂肪酸と精神疾患について. *臨床栄養*, vol. 111(5), 596-597, 2007.

## ◇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) Hamazaki T.: Fish oil and hostility/aggression in humans. International Mini-Symposium on Lipid Nutrition Affecting Brain Functions and Behavior, 2007. 10.23, Nagoya.
- \* 3) Hamazaki T.: Revisiting an “old-fashioned” conventional diet therapy ? reduction in egg consumption-. The 11th International Symposium on Traditional Medicine in Toyama 2007, 2007. 10.25-26, Toyama.
- \* 4) Hamazaki T.: The relationships between docosahexaenoic acid intake and brain function have been investigated. The 39th conference of Asia-Pacific Academic Consortium for Public Health, 2007. 11.22-25, Saitama.
- \* 5) 浜崎智仁: 魚油と行動. 第22回日本静脈経腸栄養学会ランチョンセミナー, 2007. 2. 9, 愛媛.
- \* 6) 浜崎智仁: コレステロールと総死亡—むしろ高い方が安全—. 第16回大会日本脂質栄養学会市民公開講座「健康長寿と脂質栄養」2006. 8. 31-9. 1, 島根.
- 7) 斎藤正隆, 渡辺志朗: LPS およびザイモサンにより誘導される摂食行動障害に対するTLR4の変異とデキサメタゾンの影響. —脳内 IL-6 応答系との関連: 日本薬学会第127年会, 2007. 3. 30, 富山.
- 8) 山田泰広, 山本亮, 渡辺志朗: インドメタシンにより誘導される消化管出血および貧血に及ぼすオウゴンおよびオウゴン含有漢方方剤の影響: 日本薬学会第127年会, 2007. 3. 28, 富山.
- 9) 斎藤正隆, 渡辺志朗: LPS およびザイモサン投与に伴う摂食行動障害および炎症性サイトカイン発現の比較: 第1回日本薬学会北陸支部, 2007. 7. 7, 石川.
- 10) 斎藤正隆, 渡辺志朗: ザイモサン投与による摂食行動障害および血中コルチコステロンの増加におけるIL-6の役割: 第2回日本薬学会北陸支部, 2007. 11. 11, 石川.

## ◇その他

### 資料等

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- 2) 浜崎智仁: 特別寄稿「n-3系脂肪酸に関わる臨床試験, 特に行動面について」10年の歩み DHA・EPA 協議会, 41-42, 2007.
- 3) 浜崎智仁, 桐原祐子: コレステロール値と日本人の総死亡率の関係—鶏卵はコレステロールが多いけれど安全—. 養鶏の友9月号, 20-23, 2007.
- 4) 浜崎智仁: 85センチ以上でも大丈夫「メタボリック」異議あり他. 丈夫がいいね健康にいい話, 北日本新聞社編集局偏健康BOOK シリーズ2, 72-74, 2007.
- 5) 浜崎智仁: 狭心症・心筋梗塞・脳梗塞の元凶「動脈硬化」を撃退するコレステロール健康法. 健康365, 5:20-23, 2007.
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- 7) 浜崎智仁: シリーズ油脂の知識とn-3系脂肪酸 VOL. 1 代謝と疫学. VOL. 2 疾患への応用. VOL. 4 胎児への影響. 大塚製薬工場.

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- 2) 浜崎智仁: 臨床栄養に関わる最新動向—コレステロール, 肥満, 魚油など—. H19年度実践栄養学科「総合講座」, 女子栄養大学, 2007, 6. 6, 坂戸.
- 3) 浜崎智仁: ヒトの行動に及ぼす魚油の影響. 食と消化器: 蓼科シンポ2007, 2007. 7. 25, 蓼科.

- 4) 浜崎智仁：ひとの体. 理数大好きモデル地域事業第6学年理科学習, 片口小学校, 2007, 9:21, 射水.

## ◇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) 吉積一真：株式会社ファンケル総合研究所, 「マンシュウウコギ葉由来サポニンである chiisanoside の脂肪吸収抑制作用に関する研究, 2007, 6-

### 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) 孫月吉：大連医科大学神経精神医学, 「血中脂肪酸と自殺未遂のコホート研究, 2005, 7-
- 4) 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-

## ◇研究費取得状況

- 1) 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)
- 2) 特定疾患進行性腎障害に関する調査研究, 厚労省科学研究費補助金 (分担：浜崎智仁)
- 3) 富山大学学長裁量経費, 「第11回国際伝統医薬シンポジウム」
- 4) 消化管をターゲットとした新しい和漢薬製剤の開発, 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) 漢方薬および構成生薬が非ステロイド性抗炎症剤により誘発される小腸粘膜傷害に及ぼす影響, 研究拠点形成費補助金 (21世紀COEプログラム) (分担：渡辺志朗)

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## ◇学位 (修士, 博士) 取得者

卒業論文：

土橋一輝：非ステロイド性抗炎症剤誘発性の消化管出血に対する黄連解毒湯の影響

博士論文：

桐原祐子：総コレステロール値と総死亡率の関係—福井市健診データと日本人におけるメタアナリシス—