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する。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。この機構をリピドミクス解析と遺伝子発現解析法を組み合わせて明らかにするための研究を進めている。

◇著書

1) Okuyama H., Hamazaki T., Ogushi Y.: New Cholesterol Guidelines For Longevity (2010). Healthy Agriculture, Healthy Nutrition, Healthy People. World rev Nutr Diet. by Simopoulos AP(eds), 102: 124-136, Karger, Basel, 2011.
2) 浜崎智仁：コレステロール値が高いほうがずっと長生きできる，講談社α新書，東京，2011.
3) 奥山治美，浜崎智仁，大櫛陽一他策定委員編著者：崔春彦訳，「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，Shinilbooks, Soul Korea, 2011.

◇原著論文

1) **Matsuoka Y., Nishi D., Nakaya N., Sone T., Hamazaki K., Hamazaki T. and Koido Y.: Attenuating posttraumatic distress with omega-3 polyunsaturated fatty acids among disaster medical assistance team members after the Great East Japan Earthquake: The APOP randomized controlled trial. BMC Psychiatry., 11:132-138, 2011.**

Abstract: *Background:* On March 11, 2011, a magnitude 9.0 earthquake, the most powerful ever recorded in Japan, and a massive tsunami struck off the coast of the Sanriku region. A Disaster Medical Assistance Team, a mobile medical team with specialized training that is deployed during the acute phase of a disaster, was dispatched to areas with large-scale destruction and multiple injured and sick casualties. Previous studies have reported critical incident stress (i.e. posttraumatic stress disorder symptoms and depressive symptoms) among rescue workers as well as the need for screening and prevention for

posttraumatic stress disorder. So far we have shown in an open trial that posttraumatic stress disorder symptoms in critically injured patients can be reduced by taking omega-3 fatty acids intended to stimulate hippocampal neurogenesis. *Method/Design:* This study is designed to determine the effectiveness of attenuating posttraumatic distress with omega-3 polyunsaturated fatty acids among Disaster Medical Assistance Team members after the Great East Japan Earthquake, and is named the APOP randomized controlled trial which is currently ongoing. First, we will provide psycho-education on posttraumatic distress, which is common in responders to the Disaster Medical Assistance Team members deployed to the disaster area. Second, observational research will be conducted to evaluate critical incident stress following the completion of medical activities. Third, team members who provide consent to participate in the intervention research will be randomly divided into a group given an omega-3 fatty acid supplement and a group not given the supplements. Outcome will be evaluated at 12 weeks after the supplements are shipped to the team members. *Discussion:* Measures that address critical incident stress in disaster responders are important, but there is no substantial evidence that links such measures with prevention of posttraumatic stress disorder. Thus, any confirmation through this study that the intake of omega-3 fatty acid supplements serves as a simple preventative measure for critical incident stress will be of great significance.

2) **Nakamura N., Kumasaka R., Lu Yong Fu, Fujita T., Murakami R., Shimada M., Shimaya Y., Osawa H., Yamabe H., Okumura K., Hamazaki K., Hamazaki T.: Effect of Tridocosahexaenoyl-Glycerol Emulsion on Proteinuria in Rats with Nephrotoxic Serum Nephritis. Nephron Extra., 1:139-146, 2011.**

Abstract: *Background:* Docosahexaenoic acid (DHA) is one of the n–3 polyunsaturated fatty acids and an important component of cell membrane phospholipids (PL). Nephrotoxic serum (NTS) nephritis was a worldwide model of the Goodpasture syndrome. We investigated the effects of tridocosahexaenoyl-glycerol (DHA-TG) emulsion on proteinuria in rats with NTS nephritis. *Methods:* Sixteen male Wistar rats weighing approximately 200 g were used. Twelve rats were treated with NTS via the tail vein and divided into 3 groups (groups A, B, and C). Another 4 rats treated with saline served as controls (group D). DHA-TG and soybean oil emulsions were intraperitoneally administered to the rats in groups A and B, respectively, 24 h prior to NTS injection, and 0, 1, 2, 3, 4, and 5 days after the injection. Saline was administered to the rats in groups C and D in the same manner. All rats were sacrificed on day 6 to obtain plasma and kidney samples. Analyses of urinary protein levels and fatty acid composition of plasma and kidney as well as histological examination of the kidneys were performed. *Results:* Urinary protein levels in group A were significantly lower than those in group C (35.0 ± 13.3 vs. 79.2 ± 11.8 mg/day on day 5, means ± SE, $p < 0.05$). DHA levels in the PL fraction of the kidneys in group A were significantly increased compared with those in groups B and C. *Conclusions:* These results suggest that the DHA-TG emulsion may have beneficial effects on NTS nephritis in the rat.

3) **Hamazaki K., Terashima Y., Itomura M., Sawazaki S., Inagaki H., Kuroda M., Tomita S., Hirata H., Inadera H., Hamazaki T.: Docosahexaenoic Acid Is an Independent Predictor of All-Cause Mortality in Hemodialysis Patients. Am. J. Nephrol., 33: 105-110, 2011.**

Abstract: *BACKGROUND:* Dietary n-3 polyunsaturated fatty acids (PUFAs), docosahexaenoic acid (DHA) and eicosapentaenoic acid have been shown to reduce cardiovascular mortality. Patients on hemodialysis (HD) have a very high mortality from cardiovascular disease. Fish consumption reduces all-cause mortality in patients on HD. Moreover, n-3 PUFAs, especially DHA levels in red blood cells (RBCs), are associated with arteriosclerosis in patients on HD. The aim of this study was to determine whether DHA levels in RBCs predict the mortality of patients on HD in a prospective cohort study.
METHODS: A cohort of 176 patients (64.1 ± 12.0 (mean ± SD) years of age, 96 men and 80 women) under HD treatment was studied. The fatty acid composition of their RBCs was analyzed by gas chromatography. *RESULTS:* During the study period of 5 years, 54 deaths occurred. After adjustment for 10 confounding factors, the Cox hazard ratio of all-cause mortality of the patients on HD in the highest DHA tertile (>8.1%, 15 deaths) was 0.43 (95% CI 0.21-0.88) compared with those patients in the lowest DHA tertile (<7.2%, 21 deaths). *CONCLUSION:* The findings suggest that the level of DHA in RBCs

could be an independent predictor of all-cause mortality in patients on HD.

4) **Hamazaki-Fujita N., Hamazaki K., Tohno H., Itomura M., Terashima Y., Hamazaki T., Nakamura N., Yomoda S.: Polyunsaturated fatty acids and blood circulation in the forebratin during a mental arithmetic task. Brain Res., 1397:38-45, 2011.**

Abstract: The effects of polyunsaturated fatty acids on human cerebral blood oxygenation have yet to be extensively investigated. In this study, healthy participants (14 men, 40 women) aged between 20 and 49 years were recruited. All female participants entered the trial at the start of their menstrual cycle. Blood was sampled before measuring cerebral blood oxygenation in the prefrontal cortex (PFC) and prior to administering two kinds of questionnaires, the Profile of Mood States (POMS) and a questionnaire regarding participants' arousal level. Blood oxygenation in the PFC was continuously monitored immediately before and during the Uchida-Kraepelin Performance (UKP) test as a mental arithmetic task. Changes in the tissue oxygenation index (the ratio of oxyhemoglobin to oxyhemoglobin+deoxyhemoglobin; TOI, a simplified index for cerebral blood circulation) were measured by near-infrared spectroscopy. Multiple regression analysis was performed with sex, age, smoking and drinking as confounding factors. Eicosapentaenoic acid (EPA) was positively associated with TOI, which was positively associated with arousal level and inversely associated with negative mood (POMS). EPA and docosahexaenoic acid were inversely associated with depression-dejection (POMS) and positively associated with arousal level and overall performance in the UKP test. We suggest that EPA might increase the oxygenation level in the PFC, in turn improving various psychological parameters and performance.

5) **Kobayakawa M., Inagaki M., Fujimori M., Yoshikawa E., Akizuki N., Hamazaki K., Hamazaki T., Akechi T., Tsugane S., Nishiwaki Y., Goto K., Hashimoto K., Yamawaki S., Uchitomi Y.: Serum brain-derived neurotrophic factor and antidepressant-naive major depression after lung cancer diagnosis. Jpn J. Clin. Oncol., 41: 1233-7, 2011.**

Abstract: Previous studies have reported the existence of an association between brain-derived neurotrophic factor and major depression. However, the possible role of brain-derived neurotrophic factor in the pathophysiology of major depression after cancer diagnosis has not yet been investigated. Subjects were collected using the Lung Cancer Database project. Using the cut-off scores on the depression subscale of the Hospital Anxiety and Depression Scale (HADS-D), 81 subjects with depression (HADS-D > 10) and 81 subjects without depression (HADS-D < 5) were selected. The two groups were matched for age, sex, clinical stage and performance status. The serum brain-derived neurotrophic factor levels were measured using an enzyme-linked immunosorbent assay method. The serum brain-derived neurotrophic factor levels were not statistically different between the subjects in the depression group [29.1 (13.6) ng/ml; mean (SD)] and the non-depression group [31.4 (10.6) ng/ml] (P = 0.22). In a stratified analysis by gender, however, the mean serum brain-derived neurotrophic factor level in the depression group tended to be lower than that in the non-depression group among women (n = 24 pairs, P = 0.06). Major depression after cancer diagnosis is not associated with serum brain-derived neurotrophic factor levels.

6) **Ishikawa H., Watanabe S.: Cattle bile aggravates diclofenac sodium-induced small intestinal injury in mice. Evid. Based. Complement. Alternat. Med., doi: 10.1155/2011/315858, 2011.**

Abstract: Cattle bile (CB) has long been used in Japan as an ingredient of digestive medicines. Bile acids are major chemical constituents of CB, and CB ingestion is assumed to affect small intestinal injury induced by nonsteroidal anti-inflammatory drugs (NSAIDs). Mice were fed a diet supplemented with or without CB for 7 days and treated with diclofenac sodium (DIF) to induce small intestinal injury. Lesion formation was enhanced, and PGE2 content and COX expression levels were elevated in the small intestine of DIF-treated mice fed the CB diet compared with those fed the control diet. The administration of a reconstituted mixture of bile acids found in CB enhanced lesion formation in DIF-treated mice. CB administration elevated the contents of CB-derived bile acids in the small intestine, some of which exhibited a high cytotoxicity to cultured intestinal epithelial cells.

These results suggest that the elevated levels of CB-derived cytotoxic bile acids in the small intestine contribute to the aggravation of DIF-induced small intestinal injury. The use of CB may be limited during the therapy of inflammatory diseases with NSAIDs.

◇総　説

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◇学会報告　（*：特別講演，シンポジウム，ワークショップ等）

* 1) 浜崎智仁：トピックレクチャーⅠ「脂質栄養の新しい展開ーコレステロールにどのように対応すべきか」，第 14 回日本病態栄養学会年次学術集会，2011, 1, 15，横浜.

* 2) 浜崎智仁：コレステロールを再考する，日本脂質栄養学会第 20 回大会，2011, 9, 2-3，坂戸.

* 3) 浜崎智仁：教育講演「今なぜコレステロールなのか？」～コレステロールの知られていない面～，第 58 回日本栄養改善学会学術総会，2011, 9, 8-10，広島.

* 4) 浜崎智仁：「コレステロールをどう考えるかー栄養学の変化ー」，第 33 回日本臨床栄養学会総会，第 32 回日本臨床栄養協会総会，第 9 回大連合大会，2011, 10, 28，東京.

5) 浜崎景，稲寺秀邦，浜崎智仁：精神疾患の死後脳扁桃体における脂肪酸組成について，日本脂質栄養学会第 20 回大会，2011, 9, 2-3，坂戸.

6) 渡辺志朗，常山幸一：牛胆は一価不飽和脂肪酸含有コレステロールエステルの優位な蓄積を伴う脂肪肝を誘導する，日本薬学会第 131 年会，2011, 3, 28-31，静岡.

7) 澤田啓介，根橋佳奈，大藏直樹，渡辺志朗，厚味厳一：脂肪細胞でのトランス脂肪酸によるインスリン抵抗性に関する解析，日本薬学会第 131 年会，2011, 3, 28-31，静岡.

8) 渡辺志朗：牛胆の投与によって誘導される脂肪性肝炎様症状に伴う脂質代謝変化の解析，第 12 回 Pharmaco-hematology Symposium，2011, 6, 20，富山.

9) 渡辺志朗，吉田康彦，湖間戸俊輔，浜田雄大，常山幸一：エイコサペンタエン酸がコール酸添加高脂肪食により誘導される脂肪性肝炎様症状に及ぼす影響, 第 84 回日本生化学会，2011, 9, 21-24，京都.

10) 大嶋利之，澤田啓介，根橋佳奈，大藏直樹，渡辺志朗，厚味厳一：トランス脂肪酸は脂肪細胞のインスリン応答性を低下させる，第 84 回日本生化学会，2011, 9, 21-24，京都.

11) 渡辺志朗：牛胆によって誘導される脂質代謝変化と脂肪性肝炎様症状における胆汁酸の役割，第 33 回胆汁酸研究会，2011, 11, 17，大阪.

◇その他

1) Matsuoka Y., Nishi D., Yonemoto N., Hamazaki K., Hamazaki T., Hashimoto K.: Potential Role of Brain-Derived Neurotrophic Factor in Omega-3 Fatty Acid Supplementation to Prevent Posttraumatic Distress after Accidental Injury: An Open-Label Pilot Study. Psychother. Psychosom., 80:310-312, 2011.

2) Hamazaki T., Hashimoto M.: (Forum Minireview) Neuroprotective and Ameliorative Actions of Polyunsaturated Fatty Acids Against Neuronal Diseases — Evidence From basic to Clinical Studies: Preface. J. Pharmacol. Sci., 116(2), 1149, 2011.

3) 大櫛陽一，奥山治美，浜崎智仁：コレステロール値は高いほうが長生きする，産業医学ジャーナル，34(3), 97-101, 2011.

4) 浜崎智仁：女性とコレステロール, ホスファチジルセリン研究会会報, 9(1), 158-159, 2011.

5) 浜崎智仁：講演，「コレステロール理論とは一体なんだったのか？」島根大学医学部，2011, 2, 8，島根.

6) 浜崎智仁：講演，DHA・EPA 協議会第 14 回通常総会「n-3 系脂肪酸に関わる最新の研究と今後の展開について」DHA・EPA 協議会，2011, 5, 20，東京.
7) 浜崎智仁：講演,「今なぜコレステロールなのか」島根大学公開講座，2011, 6, 25，島根.
8) 浜崎智仁：「コレステロール摂取量を増やしても血清コレステロール値は上がらない」，第 58 回日本栄養改善学会学術総会市民公開講座，2011, 9, 10，広島.

◇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, 9-2011, 3.
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, 10-2012, 3.
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-
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6) 三田村俊秀：国立国際医療研究センター研究所,「ヒトマラリア生活環における stearoyl-CoA desaturase の役割に関する研究」，2011, 8-

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-
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◇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 23 年度厚生労働科学研究費補助金，食品の安全確保推進事業（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) リピドミクス解析による漢方薬の新しい脂質代謝制御活性の検出 科学研究費補助金 学術研究助成基金助成金 基盤研究（C）（代表：渡辺志朗）
4) 豚胆の脂質低下作用の機構解析 富山大学産学交流振興会試験研究プロジェクト研究（代表：渡辺志朗）

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