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
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) Hamazaki T : Agrression, Fish Oil, and Noradrenerigic Activity. S. Yehuda and D.I. Mostofsky (eds): Nutrients, Stress, and Medical Disorders. Humana Press INC. 245-252,2005.
2) 浜崎智仁 ： コレステロールは高い方が病気にならない. KK ベストセラーズ. 2005.

◇原著論文

1) **Hamazaki K., Itomura M., Huan M., Nishizawa H., Sawazaki S., Tanouchi M., Watanabe S., Hamazaki T., Terasawa K., and Yazawa K.: Effect of ω-3 fatty acid-containing phospholipids on blood catecholamine concentrations in healthy volunteers: a randomized, placebo-controlled, double-blind trial. *Nutrition,* 21: 705-710, 2005.**

Abstract: Objectives: We previously reported that administration of fish oil rich in docosahexaenoic acid (DHA) increased the plasma ratio of epinephrine to norepinephrine (NE) at rest in young adults who were under chronic stress and that this effect was achieved mainly through depression of NE. However, not many reports have documented the effects of eicosapentaenoic acid (EPA) and DHA on blood catecholamine levels in healthy humans. Therefore, we performed another intervention study to test their effect on catecholamines with healthy subjects under no chronic stress.

Methods: Twenty-one healthy young adults (15 men and 6 women) were randomly assigned to an omega-3 group (n = 9) or a control group (n = 12) in a double-blind manner. Twenty capsules of shellfish-derived lipids containing 762 mg of EPA plus DHA per day were administered to the omega-3 group for 2 mo. The controls took the same amount of placebo capsules. Fasting blood samples after a 30-min rest with a catheter in a forearm vein were obtained at the start and the end of the study for catecholamine measurements.

Results: EPA but not DHA concentrations in red blood cells significantly increased in the omega-3 group compared with the control group ($P < 0.001$). Plasma NE concentrations were significantly decreased in the omega-3 group (from 1.49 +/- 0.39 nmol/L to 1.05 +/- 0.14 nmol/L) compared with the control group (from 1.12 +/- 0.24 nmol/L to 1.39 +/- 0.32 nmol/L) with analysis of covariance ($P < 0.001$). The differences remained significant ($P = 0.01$) even after deletion of three subjects in the omega-3 group who had the highest baseline NE values and one in the control group who had the lowest baseline NE value to nullify a significant baseline differences in NE between groups. **Conclusion:** This study demonstrated that EPA plus DHA supplementation lowered plasma NE concentrations in normal volunteers even at the small dose of 762 mg of EPA plus DHA per day. This effect of EPA plus DHA to lower plasma NE concentrations may be important to understand some of the effects of fish oils on diseases.

2) **Itomura M., Hamazaki K., Sawazaki S., Kobayashi M., Terasawa K., Watanabe S., and Hamazaki T.: The effect of fis oil on physical aggression in schoolchildren –a randomized, double-blind, placebo-controlled trial. *J. Nutr. Biochem.*, 16: 163-171, 2005.**

Abstract: Objectives: The aim of the study was to investigate whether fish oil supplementation affected Japanese schoolchildren's behavior, with changes in aggression over time as the primary endpoint.

Design and subjects: A placebo-controlled double-blind study with 166 schoolchildren 9-12 years of age was performed. The subjects of the fish oil group (n=83) took fish oil-fortified foods (bread, sausage and spaghetti). These foods were provided in amounts such that each subject in the fish oil group had an intake of 3600 mg of docosahexaenoic acid+840 mg of eicosapentaenoic acid (EPA)/week for 3 months. The rest (the controls, n=83) took control supplements. At the start and end of the study, psychological tests were performed to assess their aggression.

Results: Physical aggression assessed by Hostility-Aggression Questionnaire for Children in girls

increased significantly (median: 13 to 15, n=42) in the control group and did not change (13 to 13, n=43) in the fish oil group with a significant intergroup difference (P=.008) with baseline as covariate. The changes in physical aggression scores over time and those of the ratio of EPA/arachidonic acid in RBC (DeltaEPA/AA) were significantly correlated in girls who agreed to blood collection (r=-.53, P=.01, n=23). On the contrary, there were no significant changes in physical aggression in boys. Aggression against others (extraggression) assessed by Picture Frustration Study did not change in the control group (median: 5 to 5) but increased significantly in the fish oil group (4 to 5) with a significant intergroup difference (P=.02) with baseline as covariate. These changes in extraggression might be explained partly by significantly lower baseline values of extraggression in the fish oil group (P=.02) than in the control group. There were no significant correlations between Deltaextraggression and DeltaEPA/AA in blood-sampled children (n=49). Impulsivity of girls assessed by parents/guardians using the diagnostic criteria for attention deficit/hyperactivity disorder of DSM-IV was reduced in the fish oil group (1 to 0) with a significant (P=.008) intergroup difference from the control group (1 to 1). There were no significant correlations between Deltaimpulsivity and DeltaEPA/AA in blood-sampled girls. In males, impulsivity reduced in both groups without any intergroup differences.

Conclusion: There is a possibility that changes in fatty acid nutrition might affect physical aggression especially in girls.

3) **Takenaka M., Kanada S., Hamazaki T., and Watanabe S. : Dietary supplementation with n-3 polyunsaturated fatty acids attenuates the depression of food-motivated behavior during zymosan-induced peritonitis. *Biol. Pharm. Bull.*, 28: 1291-1293, 2005**

Abstract: Peripheral inflammation is accompanied by neurobehavioral alterations such as depression of feeding, exploratory and sexual behavior. Our previous investigation reported that dietary enrichment with n-3 polyunsaturated fatty acids (PUFA) attenuated the depression of food-motivated behavior and social exploration, but not endocrinological and metabolic disturbances in the mice wuith systemic inflammation induced by lipopolysaccharide (LPS). We here demonstrate that dietary n-3 PUFA also attenuate the reduction of food-motivated behavior during zymosan-induced peritonitis in mice without influencing plasma leakage into peritoneum and writhing response. Our results suggest that the common mechanism is involved in the attenuation of depression during systemic and local inflammation by dietary n-3 PUFA.

4) **Saito M., Hamazaki T., Tani T., and Watanabe S.: Bofutsushosan, a traditional Chinese formulation, inhibits pancreatic lipase activity *in vitro* and suppression the elevation of plasma triacylglycerols after oral administration of lipid emulsion. *J. Trad. Med.*, 22: 308-313, 2005**

Abstract: Pancreatic lipase activity measured as fatty acid liberation from lipid emulsion was shown to be inhibited by the addition of Bofutsushosan (BOF) or Daijokito (DJT) extracts at >30mg/ml. The extracts of Orengedokuto (OGT), Chotosan (CTS), Boiogito (BOT) or Shibuto (SBT) were ineffective in inhibiting pancreatic lipase activity upto 60 mg/ml. Mice were orally administered with a lipid emulation in the presence of BOF extracts at 750 and 2250 mg/kg and subsequent elevation of plasma triacylglycerols (TAG) was significantly suppressed as compared with that in the mice which received lipid emulasion alone. However, the addition of DJT extracts did not suppress the elevation of plasma TAG after oral administration of lipid emulsion. Our results suggest that BOF suppress the absorption of ingested fats and this effect could account for the anti-obese effects of BOF.

5) **Morita M., Takahashi I., Kanai M., Okafuji F., Iwashima M., Hayashi T., Watanabe S., Hamazaki T., Shimokawa N., Suzuki Y., Furuya H., Yamada T., and Imanaka T.: Baicalein 5,6,7-trimethyl ether, a flavonoid derivative, stimulates fatty acid β-oxidation in skin fibroblasts of X-linked adrenoleukodystrophy. *FEBS Lett.*, 579: 409-414, 2005**

Abstract: The purpose of the present study is to identify compounds with potential for X-linked adrenoleukodystrohpy (X-ALD) pharmacological therapy. Various plant natural products including flavonoids were tested for their ability to ameliorate the abnormality of very long chain fatty acid (VLCFA) metabolism in cultured skin-fibroblasts from X-ALD patients. Of the compounds tested, baicalein 5,6,7-trimethyl ether (baicalein-tri-Me) was found to be significantly stimulate the VLCFA β-oxidation activity. Furthermore, the incorporation of [1-^{14}C]lignoceric acid into cholesteryl esters was markedly redcued towards the decreased. These results make baicalein-tri-Me a candidate for the therapeutic compounds for X-ALD.

6) **Nakamura N., Kumasaka R., Osawa H., Yamabe H., Shirato K., Fujita T., Murakami R., Shimada M, Nakamura M., Okumura K., Hamazaki K, and Hamazaki T.: Effects of Eicosapentaenoic Acids on Oxidaitive Stress and Plasma fatty Acid Composition in Patients with Lupus Nephritis. *in vivo*, 19: 879-882, 2005.**

Abstract: Eicosapentaenoic acid (EPA) is one of the major components of fish oil, which was reported to have antiatherogenic, anti-inflammatory and immune suppressive effects. In the present study, highly purified EPA was administered to patients with lupus nephritis and the effects of EPA on urinary 8-isoprostane, a reliable marker of oxidative stress, were investigated in these patients. Six outpatients (1 man and 5 women), with lupus nephritis diagnosed by renal biopsy, were entered in the study. We administered 1800 mg EPA ethyl-ester (purity > 95%) daily and examined the urinary 8-isoprostane levels and plasma fatty acid composition before and 3 months after EPA treatment. The urinary 8-isoprostane levels were significantly decreased after the treatment compared with those before the treatment (from 530 +/- 113 pg/mg x Cr to 235 +/- 49 pg/mg x Cr, p = 0.02). The EPA levels in the plasma phospholipid (PL) fraction were significantly increased after the treatment (from 3.30 +/- 0.64 mol% to 8.01 +/- 0.47 mol%, p < 0.001). Arachidonic acid (AA) levels in the plasma PL fraction were significantly decreased after the treatment (from 9.47 +/- 0.28 mol% to 7.33 +/- 0.43 mol%, p < 0.001). The ratios of EPA to AA were significantly increased after the treatment (from 0.35 +/- 0.07 to 1.14 +/- 0.16, p < 0.001). Thus, this preliminary study indicated that EPA might exert beneficial effects on lupus nephritis by decreasing the oxidative stress.

7) **Kobayakawa M., Yamawaki S., Hamazaki K., Akechi T., Inagaki M., and Uchitomi Y.: Levels of omega-3 fatty acid in serum phospholipids and depression in patients with lung cancer. *Br. J. Cancer*, 93: 1329-1333, 2005.**

Abstract: Previous studies suggested that omega-3 fatty acids (FAs) have therapeutic effects against depression, but there is no evidence in the oncological setting. Our preliminary study reported the association between lower omega-3 FA intake and occurrence of depression in lung cancer patients. To explore the association further, the present study examined whether depression was associated with lower levels of omega-3 FAs in serum phospholipids. A total of 717 subjects in the Lung Cancer Database Project were divided into three groups by two cutoff points of the Hospital Anxiety and Depression Scale depression subscale (HADS-D). In all, 81 subjects of the nondepression and minor depression groups (HADS-D<5 and 5<or=HADS-D<or=10, respectively) were selected to match with 81 subjects of the major depression group (HADS-D>10) for age, gender, clinical stage, and performance status. Fatty acids were assayed by gas chromatography and compared among the three matched groups. There were no differences between the major depression group and nondepression group in any FAs. The minor depression group had higher mean levels of docosahexaenoic acid (mean+/-s.d. (%), nondepression: 7.40+/-1.54; minor depression: 7.90+/-1.40; major depression: 7.25+/-1.52, P=0.017). These results suggested that serum FAs are associated with minor, but not major, depression in lung cancer patients.

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6) 斎藤正隆, 浜崎智仁, 谿　忠人, 渡辺志朗：防風通聖散の血中中性脂肪上昇抑制および膵リパーゼ活性阻害作用, 日本薬学会125年会, 2005, 3/29-31, 東京.
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◇共同研究

国内

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◇研究費取得状況

1) 富山医科薬科大学国際交流基金，平成１７年度国際交流推進・研究者派遣事業,（浜崎智仁）
2) 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）
3) 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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修士論文（2005年3月）：
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小林功治：ガンマーシクロデキストリン包接化オメガ３脂肪酸が血清脂質に及ぼす影響