

臨床利用部門

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◇研究目的

天然薬物の臨床利用を目指して、1. イソフラボノイドの一つ daidzin の抗酒効果、2. n-3 系脂肪酸の抗ストレス作用と抗炎症作用、3. 必須脂肪酸欠乏症の時に体内で積極的に合成されるアラキドン酸アナログであるミード酸の抗炎症作用。

◇研究概要

1. Daidzin を含む大豆抽出物の抗酒効果を検討中。配糖体の方が効果が強いとの報告があるため、配糖体のまま吸収させる方法（エマルジョンにして口経投与）を検討する。
2. n-3 系脂肪酸の抗ストレス作用については、この巻の総説を参照されたい。現在高齢者での DHA の抗ストレス効果（敵意性制御効果）およびその作用機序を検討中である。抗炎症作用についてはボランティア20名以上で α -リノレン酸を多く含むしそ油と対照の大豆油で口内炎の予防研究を1年がかりの二重盲検法で検討中（現在7ヶ月目）である。
3. ミード酸の抗炎症作用の基礎的研究として、各種サイトカインの合成に対する影響を検討中。

◇著 書

- 1) 澤崎茂樹, 浜崎智仁: EPA 製剤. 「高脂血症・動脈硬化」, 萩原俊男, 斉藤 康, 馬淵宏編, pp16-17, 先端医学社, 東京, 1998.

◇原 著

- 1) Hamazaki T., Sawazaki S., Nagao Y., Kuwamori T., Yazawa K., Mizushima Y., and Kobayashi M.: Docosahexaenoic acid does not affect aggression of normal volunteers under nonstressful conditions. A randomized, placebo-controlled, double-blind study. *Lipids*, 33 : 663-667, 1998.

ABSTRACT: We previously found that docosahexaenoic acid (DHA) intake prevents aggression enhancement at times of mental stress. In the present study we investigated changes in aggression under nonstressful conditions. Forty-six students of two universities took either DHA-rich fish oil capsules containing 1.5 g DHA (DHA group: 13 males and 9 females) or control oil capsules containing 97% soybean oil plus 3% of another fish oil (control group: 11 males and 13 females) for 3 mon in a double-blind fashion. At the start and end of the study they took an aggression-estimating test (P-F Study) without a stressor component. DHA (5.9 to 8.5%, $P < 0.001$) and eicosapentaenoic acid (0.7 to 1.5%, $P < 0.001$) increased in red blood cell phospholipids in the DHA group, while linoleic acid increased slightly (8.3 to 9.1%, $P < 0.002$) in the soybean oil control group. In the control group, measured aggression levels decreased from 34.8 to 29.4% ($P < 0.005$), whereas they remained stable in the DHA group (33.5 to 33.8%). The intergroup differences (-5.4 vs. 0.3%) were marginally significant ($P \leq 0.05$). Aggression levels were stable in the DHA group whether there was stressor (as previously shown) or not. This effect of DHA appears to be interesting, considering the reported association between a low intake of n-3 fatty acids and depression.

- 2) Nakamura N., Hamazaki T., Kobayashi M., Ohta M., and Okuda K.: Effects of eicosapentaenoic acids on remnant-like Particles, cholesterol concentrations and plasma fatty acid composition in patients with diabetes mellitus. *in vivo*, 12 : 311-314, 1998.

ABSTRACT: Remnant lipoproteins are transient metabolites from chylomicron and/or very low density lipoproteins (VLDL), and remnant hyperlipoproteinemia has recently been reported to be a risk factor for atherosclerosis. Eicosapentaenoic acid (EPA), a major component of fish oil, has the following effects: anti-platelet aggregation, vaso-dilation, anti-inflammation, hypotriglyceridemia, and therefore has potential anti-atherosclerotic effects. We measured serum of remnant-like particle cholesterol (RLP-C) concentrations, and investigated the effects of EPA on serum RLP-C concentrations in patients with diabetes mellitus. Ten patients with non-insulin dependent diabetes mellitus were treated with 900-1800 mg EPA ethyl-ester daily for 3 months. We investigated serum RLP-C concentrations and plasma fatty acid composition before and after the administration of EPA. Serum RLP-C concentrations were significantly decreased 3 months after the administration of EPA (from

14.5±5.3 mg/dL to 3.3±0.8 mg/dL, $P < 0.01$). Plasma EPA concentrations and the ratios of EPA to arachidonic acids (AA) were significantly increased during the same period (from 86.2±12.4 mg/L to 194.6±27.3 mg/L, $P < 0.01$, from 0.571±0.074 to 1.242±0.163, $P < 0.01$, respectively). Serum RLP-C concentrations were inversely correlated with the ratios of EPA to AA in plasma ($r = -0.516$, $P < 0.05$). These results suggested that administration of EPA was effective on remnant hyperlipoproteinemia which was a risk factor for atherosclerosis.

3) Mizushima Y., Sassa T., Hamazaki T., Fujishita T., Oosaki R. and Kobayashi M.: Diuretic response to cyclophosphamide in rats bearing a matrix metalloproteinase-9-producing tumour. *Brit. J. Cancer*, 78 : 1030–1034, 1998.

Summary: When cyclophosphamide (CY) (100–120 mg kg⁻¹) was administered intravenously (i.v.) to normal F-344 rats, oliguria occurred over the 5-day observation period. Conversely, in rats bearing matrix metalloproteinase-9 (MMP-9) producing 13762NF mammary adenocarcinoma (MTLn3 clone), polyuria occurred chiefly during the first 24 h after CY treatment. In parallel with urine volume, a decrease in the urinary excretion of N-acetyl-beta-D-glucosaminidase (NAG) was observed during the first 5 days after CY treatment in normal rats, but it increased in MTLn3-bearing rats. No elevation in blood urea nitrogen (BUN) or serum creatinine (Cr) values was observed for either group. Both urine volume and urinary excretion of NAG after CY treatment were lower in rats bearing the MTC clone (lower production of MMP-9) than for those bearing the MTLn3 clone. In the case of treatment with cisplatin (CDDP, 4–6 mg kg⁻¹), urine volume, urinary NAG excretion and BUN and serum Cr values all increased in normal rats and were all found to be higher in MTLn3-bearing rats than in normal rats. The diuretic response to these drugs in tumour-bearing (TB) rats may be associated with MMP-9 produced by the tumour cells. This report suggests that the nephrotoxicity due to anti-cancer drugs may change when the drugs are used for the treatment of patients bearing a MMP-9-producing tumour.

4) Andoh T., Nagasawa T., Satoh M. and Kuraishi Y.: Substance P induction of itch-associated response mediated by cutaneous NK₁ tachykinin receptors in mice. *J. Pharmacol. Exp. Ther.*, 286 : 1140–1145, 1998.

ABSTRACT: Our experiments were conducted to determine whether substance P (SP) would elicit an itch sensation mediated by mast cells in mice. An intradermal injection of SP (10–135 μg site⁻¹) into the rostral back of the ICR mouse dose-dependently produced scratching of the injected site. The SP- (135 μg site⁻¹ = 100 nmol site⁻¹) induced scratching was inhibited by capsaicin (repeated administration) and naloxone; features being similar to itch in humans. SP elicited scratching in mast cell-deficient (WBB6F1 W/W^v) mice as well as control (+/+) mice. Pretreatment with compound 48/80 produced similar degrees of inhibition of SP-induced scratching in mast cell-deficient mice as well as control +/+ and ICR mice. Intradermal injections of the NK₁ receptor agonist GR73632 produced dose-dependent scratching, while the NK₂ agonist GR64349 and the NK₃ agonist senktide were without

effects. SP-induced scratching was inhibited by the NK₁ receptor antagonists spantide and L-668,169, but not by the NK₂ antagonist L-659,877. The results suggest that scratching of the mouse induced by an i.d. injection of SP is itch-associated response. The SP action may be mediated at least partly by cutaneous NK₁ receptors, and mast cells may not be key factors in SP-induced itching.

5) 佐藤一哉, 山崎奈穂子, 倉石 泰, 長澤哲郎: 麻黄附子細辛湯の抗侵害受容作用における下行性セロトニン作動神経系の関与. 痛みと漢方. 8: 33-37, 1998.

要旨: 漢方方剤麻黄附子細辛湯 (TJ-127) の鎮痛作用の発現機序を明らかにする目的で, RCS 負荷ラットを用いて TJ-127 の抗侵害受容作用を検討し, さらに下行性抑制系の関与を調べた。RCS 性痛覚過敏ラットにおいて TJ-127 (30-300 mg/Kg, p.o.) は, 用量依存的な抗侵害受容作用を示した。また, TJ-127 の抗侵害受容作用は, セロトニン神経毒 5,7-DHT の脊髄クモ膜下腔内注射 (i.t.) により有意に減弱し, 5-HT_{1/2} 受容体拮抗薬 methysergide (30nmol/rat), cyproheptadine (3nmol/rat), methysergide (30nmol/rat) の i.t. に注射によっても有意に減弱した。カテコラミン神経毒 6-OHDA は TJ-127 の最大効果を有意に抑制したが, α -アドレナリン受容体拮抗薬 phentolamine (100nmol/rat) は有意に抑制しなかった。以上の結果より TJ-127 の抗侵害受容作用に少なくとも一部下行性セロトニン神経系が関与するが, 下行性ノルアドレナリン神経系の関与は少ないことが示唆される。

◇総説及びその他

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- 2) Hamazaki T.: (シンポジウム) DHA and Hostility in Japanese Students. The XVI Congress of the World Association for Social Psychiatry. 1998, 8, Vancouver.
- 3) Hamazaki T.: (招待講演) Hostility and noradrenergic changes in double-blind placebo-controlled intervention trials. NIH Workshop on Omega-3 Essential Fatty Acids and Psychiatric Disorders. 1998, 9, Bethesda.
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- 5) 浜崎智仁: EPA とDHA の静注で一体何が起こるか. 第13回日本静脈・経腸栄養研究会,

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- 6) 安東嗣修, 長澤哲郎, 中村布美枝, 王 政文, 倉石 泰: アレルギー及びサブスタンスP誘発痒み関連反応のグルココルチコイドによる抑制. 第71回日本薬理学会年会, 1998, 3, 千葉.
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- 3) 浜崎智仁: 「国際脂肪酸脂質学会日本開催へ」1998, 6/25, 食品化学新聞.
- 4) 浜崎智仁: 談論自由席「平静さ保つ DHA/魚を食べて摂取を」1998, 7/14, 北日本新聞.
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- 7) 浜崎智仁: 健康食「脂肪の取り方」1998, 11/25, 週間朝日.
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◇共同研究

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◇非常勤講師

浜崎智仁: 帯広畜産大学生物資源科学科 講義「魚の油-心筋梗塞と精神疾患」, 1999, 3/5, 帯広.

◇研究費取得状況

- 1) 科学技術庁科学技術振興調整費 (代表: 浜崎智仁): 「高齢者の敵意性抑制効果を有する食品成分の探索」(第2年度) 16,696千円

- 2) 五峯ライフサイエンス (代表: 浜崎智仁), 「高齢者でのドコサヘキサエン酸が敵意性に及ぼす影響」, 600千円
- 3) 平成10年度富山第一銀行奨学財団 (代表: 浜崎智仁): 「ドコサヘキサエン酸による禁煙」, 400千円
- 4) 国際研究集会派遣研究遣旅費 (浜崎智仁): 「第3回脂肪酸と脂質の国際会議リヨン (フランス)」
- 5) 国際研究集会派遣研究遣旅費 (浜崎智仁): 「第16回世界社会精神医学会, バンクーバー (カナダ)」

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