Clinical and Epidemiological Study of Eicosapentaenoic Acid (EPA) in Japan

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I. INTRODUCTION

The epidemiological studies of Greenland Eskimos by Dyerberg and Bang indicated that a marine diet rich in ω-3 polyunsaturated fatty acids (ω-3 PUFA) such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) may have anti-thrombotic and anti-atherogenic action and thus decrease the incidence of cerebro- and cardiovascular diseases1). Numerous investigations have been done in order to estimate the role of ω-3 PUFA for the prevention and the treatment of thrombotic disorders. Here we present the summary of our clinical and epidemiological studies in Japan.

II. EPIDEMIOLOGICAL STUDIES IN CHIBA PREFECTURE JAPAN

Between 1978 and 1980, we investigated and compared the dietary intake of fish meat, platelet function, rheological properties of blood and mortality rate due to thrombotic cardiovascular diseases between the residents of fishing and farming villages. Notable finding is that the dietary intake of EPA in the residents of fishing village was nearly 3 times (2.5 g/day) higher than that (0.9 g/day) in the residents of farming village. Decreased platelet aggregability, prolonged bleeding time, increased red cell deformability and decreased whole blood viscosity together with a relatively low mortality rate due to ischemic heart disease were found in the residents of fishing village, in contrast to the residents of farming village in Chiba.

III. ANTI-THROMBOTIC AND HYPOLIPIDEMIC ACTIONS OF EPA IN THE PATIENTS WITH CEREBRO- AND CARDIOVASCULAR DISEASES

On the basis of the epidemiological studies mentioned above, the effect of oral administration of purified EPA ethylester (EPA-E, 1.8 - 2.7 g/day) prepared from sardine oil on platelet and red cell function and on serum lipid profile in 62 patients with various thrombotic disorders were investigated. A significant decrease in platelet aggregability with concomitant reduction in thromboxane B2 (TXB2) formation was noted. Decreased whole blood viscosity and increased red cell deformability was also found. Interestingly a positive correlation between red cell deformability and the content of EPA in red cell was found. A significant reduction in serum levels of total cholesterol and triglycerides in these patients was noted after EPA-E ingestion. As shown in Fig. 1, EPA appears to reduce arachidonic acid (AA) content in plasma membrane, and competitively inhibit AA metabolism at
cyclooxygenase resulting in the reduction of TXA$_2$ formation and decrease platelet aggregability. As for hypolipidemic action of EPA, it may be ascribed to the reduction of hepatic TG production and enhanced elimination of cholesterol via bile acid.

**Figure 1. Proposed in vivo mechanism for anti-platelet effect of EPA**

**IV. ANTI-ATHEROGENIC ACTION OF EPA**

As the process of initiation and development of atheromatous changes in vascular walls, accumulation of lipid-laden macrophages, so-called foam cells, and migration and proliferation of vascular smooth muscle cells (SMC) are two important characteristic features. Recently it has been shown that low density lipoprotein (LDL) can be oxidized at the site of vascular walls. These oxidized LDLs are incorporated into macrophages in an unlimited manner and finally foam cells are formed. In addition, these foam cells and activated platelets produce platelet-derived growth factor (PDGF), which is one of the most potent growth factors to stimulate proliferation of vascular SMC. Based on these background, we performed experiments to reveal effects of EPA-E feeding on the susceptibility of LDL to oxidative modification and the potency of macrophages in producing...
PDGF. The effect of EPA on foam cell formation and SMC proliferation was also investigated.

In EPA-enriched peritoneal macrophages obtained from rat fed with purified EPA-E, a significant decrease in proteolytic degradation of acetyl LDL (AcLDL) and also in the accumulation of cholesteryl ester was noted. Also it was found that the decrease of AcLDL incorporation in EPA-rich macrophages was due to the reduction of scavenger receptor numbers. These results indicate that EPA may have suppressive effect on foam cell formation as shown in Fig. 2.

Figure 2. Suppressive effect of EPA on foam cell formation

In addition, PDGF production was also significantly decreased in EPA-rich rat peritoneal macrophages. Prostacyclin (PGI₂) production was significantly increased in thoracic aorta obtained from rat fed with EPA-E. Furthermore in cultured rat SMC, PGI₂ production was also significantly increased when EPA-triglyceride emulsion was co-cultured with SMC. The enhanced PGI₂ production may be partly explained by activation of cyclooxygenase activity by the lipid peroxides of EPA. When purified EPA-E was orally given to the patients with peripheral vascular diseases, around 60% of cases showed recognizable clinical improvement. These evidences described above may explain the anti-thrombotic action of EPA.

V. ANTI-INFLAMMATORY AND IMMUNOMODULATORY ACTIONS OF EPA

Chronic inflammatory autoimmune diseases such as rheumatoid arthritis, ulcerative colitis or psoriasis are rarely found in Greenland Eskimos. Administration of EPA has been reported to be effective in these diseases.

The incidence of psoriasis in Japan has been steadily increasing and increased levels of LTB₄ and PGE₂ have been found in skin lesions and leukocytes of patients with psoriasis.
In the study conducted by us with cooperation of Department of Dermatology of Chiba University Medical School. Six among 7 patients showed a marked improvement after 3-6 month treatment by 3.6 g/day of purified EPA. By EPA treatment, LTB₄ production in stimulated leukocytes was decreased.

Decrease in arachidonic acid content in plasma membrane, inhibition of arachidonic acid release and inhibition of LTA₄ hydrolase by LTB₅ derived from EPA may be responsible for the reduction of LTB₄ production in EPA-rich leukocytes.

Biological activities of LTB₅ in stimulating leukocyte (chemotaxis, aggregation and lysosomal enzyme release of neutrophil, immune function of mononuclear leukocytes) is much less than those of LTB₄. The effect of EPA on cytokine production and natural killer cell cytotoxicity was also studied. It was found that the production of cytokines such as IL-1 or IL-2 was decreased. And natural killer cell cytotoxicity were apparently suppressed. These anti-inflammatory and immunomodulatory action of EPA may contribute to its beneficial influence on chronic inflammatory autoimmune diseases.

REFERENCES