

Eicosapentaenoic Acid (EPA): An Antiinflammatory ω -3 Fat With Potential Clinical Applications

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INTRODUCTION

The potential benefit for including ω -3 (n-3) fatty acids in the normal diet has been supported by clinical evidence of reduced cardiovascular disease for people consuming a diet containing deep-water fish and fish oil.¹ Evaluation of Eskimos, whose diets derive a large portion of dietary calories from ω -3-containing fish, demonstrated a significantly lower rate of cardiovascular disease-associated mortality and malignancies compared to Western populations.² Further evidence in support of ω -3 fatty acid dietary consumption is derived from experimental studies demonstrating eicosapentaenoic acid (EPA)-mediated antiinflammatory and anticachexiogenic benefits.^{3,4}

Proinflammatory cytokines (specifically tumor necrosis factor [TNF] and interleukin-1 [IL-1]) are the proximal secondary pathway mediators of the multistep cascade that regulates the metabolic response to inflammation after a primary pathway stimulus, (injury, infection, malignancy, etc.).⁵ It is generally accepted that the prolonged and inappropriate production and release of proinflammatory cytokines result in clinically evident metabolic abnormalities of anorexia, weight loss, and lean body mass catabolism that as a whole describe the syndrome of cachexia.^{5,6}

A logical approach to attenuate the development of cachexia, and in particular cancer-associated cachexia, would be to reduce or inhibit the propagation of secondary pathway intermediates such as proinflammatory cytokines and arachidonic acid (AA) metabolism intermediates (prostaglandins, prostacyclins, thromboxanes, etc.). Therefore, in our evaluation of new therapies for the treatment of patients with cancer-associated cachexia it would be ideal to use

a readily available low-cost and non-toxic agent that would reduce the production and release of inflammatory mediators. In support of this effort, several experimental and clinical studies have demonstrated a benefit for consuming a diet supplemented specifically with EPA, one of the primary ω -3 fatty acids found in fish oils. In animal models and for patients with progressive malignancy, EPA supplementation promotes weight maintenance, improves food intake, inhibits tumor growth, and may improve survival. These observations suggest a potential role for EPA in the clinical management of patients with progressive malignancy and justify the need for clinical trials. Exciting as these early observations have been, much work remains to be done. In the present paper the significant evidence supporting the role for EPA as a potential agent for the treatment of cancer-associated cachexia is presented.

MATERIALS AND METHODS

Animal Studies

The role of fish oils for the treatment of cancer-associated cachexia in rodent models was investigated by substituting the carbohydrate component of the diet with fish oils. Using the colon adenocarcinoma (MAC16) model, which produces weight loss and reduction in both total body fat and body weight, without a reduction of food intake, fish-oil-fed rodents demonstrated a significant reduction in the rate of tumor growth and body weight loss.³ In this study, an increase in body mass was associated with increased total body fat and muscle mass, suggesting that fish oil is non-toxic and an effective anticachectic agent with antitumor activity.³

The antitumor and antiinflammatory effects observed with fish oils appear to be specific to EPA and not to all ω -3 fatty acids. In comparing the effect of EPA to that of γ -linolenic acid (GLA) in the MAC16 mouse model, Tisdale and colleagues demonstrated that EPA effectively inhibited both host weight loss and tumor growth rate in a dose-dependent manner.⁷ Optimal effects were observed at an EPA dose of 1.25–

2.5 g/kg body weight. In contrast, GLA-treated animals had both a significantly lower weight loss and increased tumor growth, with moderate benefit observed at a dose of 5 g/kg, at which toxicity was also observed.⁷ These experiments effectively demonstrated that EPA has an important role in body weight maintenance and inhibition of tumor progression. Animals treated with EPA demonstrated a prolonged overall survival that was approximately doubled compared to GLA-treated animals. EPA treatment also significantly reduced protein degradation without an effect on protein synthesis, although animals not receiving EPA demonstrated both decreased protein synthesis and increased skeletal muscle degradation.⁷

Clinical Evidence

More recently, data derived from rodent models have been applied to patients with progressive pancreatic cancer, a malignancy noted for the development of profound anorexia and cachexia.⁸ Patients with unresectable pancreatic adenocarcinoma consumed two cans per day of a fish oil-enriched nutritional supplement in addition to their normal food intake. The supplement contained 310 kcal, 16.1 g protein, and 1.09 g EPA. During follow-up, patients were assessed for weight, body composition, dietary intake, resting energy expenditure (REE), and performance status. Patients consuming the EPA-enriched supplement had significant weight gain at 3 and 7 wk of the study. Their dietary intake was increased significantly by almost 400 kcal day, REE per kg body weight and, per-kg lean body mass fell significantly. Performance status and appetite were also significantly improved. This study suggests that an EPA-enriched supplement may attenuate the progression of cachexia in patients with advanced pancreatic cancer.⁸

Mechanism(s) of Action

EICOSANOID INTERMEDIATES. The complete antiinflammatory mechanism(s) of action of EPA are not yet defined; however, it is known that EPA is readily incorporated

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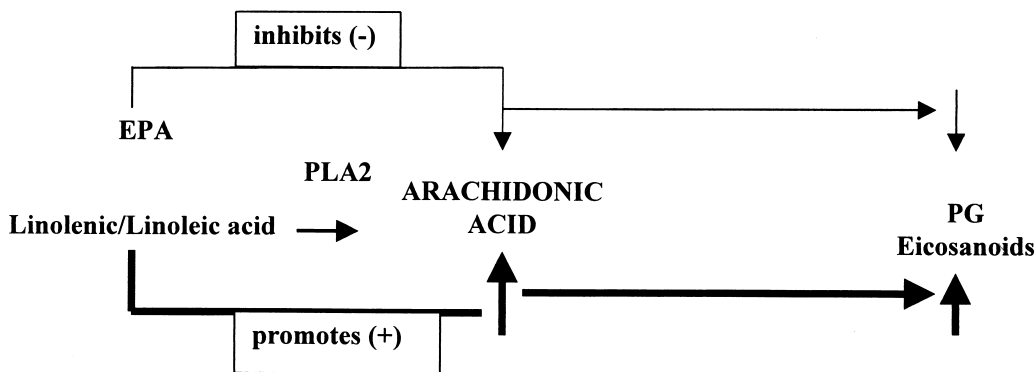


FIG. 1. EPA reduces phospholipase A2 (PLA2) synthesis of arachidonic acid (AA), subsequently replacing macrophage cellular membrane AA. Linolenic and linoleic acids are essential fatty acids necessary for AA synthesis. AA metabolic intermediates through the cyclooxygenase and lipoxygenase pathways result in prostaglandin (PG) and related (eicosanoid) product production.

into cellular membranes.⁹ Linolenic and linoleic acids are the essential fatty acids required for the production of AA, which is subsequently metabolized, forming eicosanoid metabolites (prostaglandins, prostacyclins, etc.) (Fig. 1). Incorporation of EPA into the cell membrane alters the fatty acid composition as well as the biochemical activity within the cellular membrane. These changes, in turn, lead to changes in the eicosanoid intermediates and proinflammatory cytokines produced by the cell membrane from AA.^{9,10}

Experimental evidence from cell culture,^{9,10} and rodent¹¹ and human^{12,13} clinical studies suggests that one mechanism of action for EPA-mediated reduction of proinflammatory cytokine production occurs

through the substitution of EPA for AA, with resultant decreased cytokine and prostanoid production.⁹ In rodent tumor studies, inhibition of PGE2 production by indomethacin leads to improved weight maintenance and prolongs survival.^{14,15} These observations suggest, though do not prove, that inhibition of PGE2 and proinflammatory cytokines may influence pathways that potentially affect survival for patients with progressive malignancy, possibly through reducing the progression of cachexia. An alternative explanation for the beneficial effects of blocking PGE2 production is related to the fact that PGE2 is immunosuppressive. Hence, decreased PGE2 production, in response to fish oil

feeding, may translate into improved immunologic defense by the host against cancer.

NFKB REGULATION. The protective benefits of EPA may be related to its ability to modulate inflammatory and immunologic pathways at the molecular level. Recent *in vitro* and animal studies have shown that EPA decreases transcription of the TNF gene by decreasing translocation of nuclear factor- κ b (NF κ b), a transcriptional regulatory element, from the cytoplasm to the nucleus.¹⁰ This fish oil effect on decreased NF κ b transcriptional activity appears to be caused by an alteration in the affinity of NF κ b for I κ b- α as a direct result of decreased phosphorylation of the I κ b complex.^{10,16} Decreased I κ b- α phosphorylation decreases NF κ b translocation to the nucleus, which results in less NF κ b binding to the promoter region of proinflammatory cytokine genes, thereby decreasing transcription of these mediators (Fig. 2).

Collectively, these studies suggest a potential role of EPA as an effective anti-cachexia and antiinflammatory agent. However, a better understanding of the mechanism(s) whereby EPA modulates immunoinflammatory pathways is necessary before therapeutic strategies using EPA as a supplemental or primary therapy are applied to patients. To date, the data on EPA as an effective, non-toxic, and affordable agent to fight cancer are extremely positive. For this reason, clinical investigations exploring

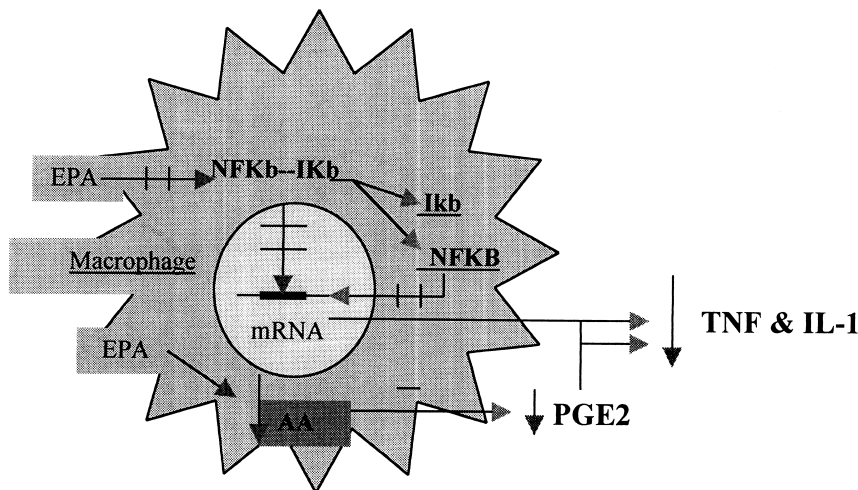


FIG. 2. EPA incorporates into the macrophage cell membrane (CM), replacing arachidonic acid (AA), thus reducing CM AA content. Decreased PGE2 production occurs as a function of decreased AA availability. EPA inhibits TNF gene transcription by preventing NF κ b-I κ b dissociation, preventing NF κ b translocation into the nucleus. As a consequence, overall TNF and IL-1 synthesis and release are reduced.

the utility of ω -3 fatty acids, such as EPA are not only justified but strongly encouraged.

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