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n-3 Polyunsaturated fatty acids and autoimmune-mediated glomerulonephritis

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A B S T R A C T

Consumption of n-3 polyunsaturated fatty acids (PUFAs) found in fish oil suppresses inflammatory processes making these fatty acids attractive candidates for both the prevention and amelioration of several organ-specific and systemic autoimmune diseases. Both pre-clinical and clinical studies have been conducted to determine whether fish oils containing the n-3 PUFAs docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) can be used in the prevention and treatment of immunoglobulin A nephropathy (IgAN) and lupus nephritis. In a toxin-induced mouse model that mimics the early stages of IgAN, n-3 PUFA consumption suppresses aberrant interleukin (IL)-6-driven IgA production and mesangial IgA immune complex deposition by impairing phosphorylation of upstream kinases and activation of transcription factors essential for IL-6 gene transcription. n-3 PUFAs can also suppress production of anti-double-stranded DNA IgG antibodies and the resultant development of lupus nephritis in the NZBW F1 mouse and related models. These effects have been linked in part to impaired expression of proinflammatory cytokines and adhesion molecules as well as increases in antioxidant enzymes in kidney and immune organs. Several recent clinical trials have provided compelling evidence that n-3 PUFA supplementation could be useful in treatment of human IgAN and lupus nephritis, although some other studies suggest such supplementation might be without benefit. Future investigations employing genomics/proteomics and novel genetically altered mice should provide further insight into how n-3 PUFAs modulate these diseases as well help to identify clinically relevant biomarkers. The latter could be employed in future well-designed, long-term clinical studies that will resolve current controversies on n-3 PUFA efficacy in autoimmune-mediated glomerulonephritis.

1. Introduction

Inflammation is the normal host response to infection or injury that mediates immune elimination of pathogens and tissue repair [1]. Inflammatory processes include increased production of cytokines, chemokines, nitric oxide and eicosanoids by the innate immune system in conjunction with altered leukocyte homing, all of which can greatly impact acquired immunity. Aberrant inflammatory responses not only evoke acute injury, as exemplified by endotoxic shock, but contribute significantly to chronic autoimmune diseases. The capacity of dietary n-3 polyunsaturated fatty acids (PUFAs) found in fish oil to suppress inflammation-associated processes has made them attractive candidates for both the prevention and amelioration of a variety of organ-specific and systemic diseases [2,3]. This review specifically discusses pre-clinical and clinical studies of the efficacy of n-3 PUFAs in prevention and treatment of autoimmune-mediated kidney diseases.

2. n-3 PUFAs, inflammation and immune response

Since mammals require but cannot synthesize fatty acids with double bonds distal to the ninth carbon atom, long chain PUFAs are essential to their diet [4]. Linoleic acid (18:2n-6) is a major PUFA found in oils derived from plant seeds such as corn or safflower. Linoleic acid can be elongated and desaturated to yield arachidonic acid (20:4n-6; AA). The action of Δ15-desaturase in plants converts linoleic acid to α-linolenic acid (18:3n-3) which can be elongated to

Abbreviations: PUFAs, polyunsaturated fatty acids; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; IgAN, immunoglobulin A nephropathy; PGs, prostaglandins; LTs, leukotrienes; COX, cyclooxygenase; ESRD, end-stage renal disease; CKD, chronic kidney disease; SLE, systemic lupus erythematosus; DON, deoxynivalenol; CREB, cAMP response element binding; C/EPBβ, CCAAT/enhancer binding protein β; NF-κB, nuclear factor κB; IC, immune complexes; hnRNA, heteronuclear nuclear RNA; PKR, RNA-activated protein kinase; AA, arachidonic acid; HSP, Henoch-Schonlein purpura; SLE, systemic lupus erythmatosus; NZBW F1, New Zealand Black White (F1) mouse; BXSB, C57BL/6 *x* satin beige mice; DHA-E, DHA ethyl ester; EPA-E, EPA ethyl ester; SLAM-R, Systemic lupus activity measure

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eicosapentaenoic acid (20:5n-3; EPA) and docosahexaenoic acid (22:6n-3; DHA). These latter conversions to EPA and DHA occur slowly in mammals but are carried out readily by marine algae. Transfer of EPA and DHA from these algae through the food chain to fish makes fish oil the primary source of highly unsaturated n-3 PUFAs in the human diet as well as dietary supplements [5]. A CDC-NHIS survey determined that 11.7% of US adults (26 million individuals) consume n-3 PUFA supplements [6].

The capacity of n-3 PUFAs to modulate immune function and suppress inflammatory responses has been reviewed extensively [1,3,7,8]. n-3 PUFAs suppress proinflammatory cytokine production, lymphocyte proliferation, cytotoxic T cell activity, natural killer cell activity, macrophage-mediated cytotoxicity, neutrophil/monocyte chemotaxis, MHCII expression and antigen presentation. Evidence that these cellular effects indeed impact immune function in vivo is reflected in n-3 PUFA attenuation of mediator production, leukocyte homing, delayed-type hypersensitivity, allograft rejection and acute inflammatory responses in experimental animals in which human inflammation and autoimmune diseases are modeled. n-3 PUFAs appear to mediate these pleiotropic effects via both eicosanoid-dependent and eicosanoid-independent pathways.

Eicosanoids are oxygenated and biologically active metabolites that include prostaglandins (PGs) and leukotrienes (LTs) synthesized by the cyclooxygenase (COX) and 5-lipooxygenase pathway, respectively. Immune cells produce eicosanoids a process which is in part influenced by the PUFA composition of the cell membrane [2,3]. The eicosanoid PGE_2, a COX metabolite of AA, can be proinflammatory and modulate cytokine production. The 4-series LTs, lipooxygenase metabolites of AA, have chemotactic properties, promote inflammation and upregulate proinflammatory cytokine production. EPA and DHA competitively inhibit oxygenation of AA by COX and 5-lipoxygenase. EPA is also able to serve as substrate for both COX-2 and 5-lipoxygenase. n-3 PUFAs thus dramatically alter eicosanoid profiles by (1) decreasing membrane AA levels; (2) inhibiting generation of proinflammatory eicosanoids (2 series PGs and 4-series LTs); (3) promoting production of EPA metabolites (3 series PGs and 5 series LTs) and (4) suppressing COX-2 and 5-lipooxygenase expression. Recent elegant studies have demonstrated that n-3 PUFAs convert to a novel series of lipid mediators termed resolvins and protectins that can elicit protective and beneficial effects [9,10]. These mediators attenuate inflammation in a number of models, with the lipid autacoid resolvin E1 being extremely potent [11,12].

There is increasing recognition that eicosanoid-independent mechanisms play a critical role in n-3 PUFA suppression of inflammatory gene expression. Proposed mechanisms include (1) alteration of transcription factor activity or abundance as has been described for PPAR, LXR, NNF-4, NF-κB, AP-1 and CREB [4,13,14]; (2) interference with activity of critical second messenger-regulated kinases such as PKA, PKC, CaMKII, AKT and mitogen-activated protein kinases [15–17]; (3) changes in membrane lipid/lipid raft composition that alter G-protein receptor or tyrosine-kinase linked receptor signaling [18–23] and (4) interference with membrane receptors such as the TLR family [24,25].

Taken together, these anti-inflammatory and immunomodulating activities have led to the evaluation and application of n-3 PUFAs for prevention and treatment of inflammatory and autoimmune diseases. Of particular interest here are those studies that have focused on the kidney.

3. Chronic kidney disease and autoimmune-mediated glomerulonephrides

The kidney's primary function is to remove excess metabolic waste products and water from the blood [26,27]. Damage to the glomeruli, the basic filtration units of the kidney, impairs this critical function. Glomerular damage can result from a kidney-specific disease or be a reflection of a broader systemic disease. Partial loss of kidney function is referred to as renal failure whereas total and permanent loss of kidney function is termed end-stage renal disease (ESRD). Both glomerular inflammation and tissue scarring, classified as glomerulonephritis and glomerulosclerosis, respectively, can contribute to ESRD. Kidney disease symptoms include proteinuria, haematuria, reduced glomerular filtration rate (GFR), low blood protein (hypoproteinemia) and oedema. Damage to the glomeruli can evoke varying degrees of renal failure. In chronic kidney disease (CKD), irreversible loss of kidney function typically occurs over a protracted period of time (>10 years).

Manifestations of CKD can range from relatively mild renal insufficiency to ESRD requiring dialysis or transplantation. Nearly 16% of persons above 20 years old in the US have CKD with over 300,000 individuals undergoing dialysis each year [28,29]. CKD can specifically result from autoimmune diseases, infection, high blood pressure and diabetes, and vasculitis. Given that inflammation plays a significant role in autoimmune glomerulonephritides, it is not surprising that n-3 PUFAs have been extensively evaluated relative to their preventative and therapeutic properties in these diseases. Two of the most important causes of human autoimmune glomerulonephritis are immunoglobulin A nephropathy (IgAN) and systemic lupus erythematosus (SLE) and are therefore the focus of this review.

4. n-3 PUFA and IgAN

4.1. Disease characteristics

IgAN is an autoimmune disease which has as its diagnostic hallmark diffuse mesangial deposition of IgA in kidney glomerulus frequently accompanied by haematuria. It has been estimated that IgAN affects almost 1% of the population and yet the diagnosis is often missed [30]. IgAN is extremely common worldwide accounting for up to 50% of glomerulonephropathies in Japan, 20–35% in Europe and 5–10% in North America [31,32]. It has been estimated that IgAN is the most common glomerulonephritis and cause of ERSD in young adult Caucasians in the US [33]. Nearly 150,000 people in the US are diagnosed with IgAN with 4000 new cases occurring each year [34]. Approximately 25% IgAN patients progress to renal failure within 25 years [30].

The fundamental abnormality in IgAN lies within the IgA system and not the kidney since IgA deposition in IgAN patients recurs after renal transplantation [35]. An overly robust IgA response to mucosal infections and dietary antigens in terms of quantity, size (primarily polymeric), glycosylation status and immune complex formation is believed to contribute to IgAN [36–39]. Cases of IgA nephropathy vary with regard to clinical presentations, clinical and histopathologic risk factors for progressive renal disease, and time course [40]. While no consensus exists on how to best treat human IgAN, approaches include angiotensin-converting enzyme blockade, corticosteroids, cyclosporine, anticoagulants, antiplatelet drugs, phenytoin and tonsillectomy [40,41]. Epidemiologic studies suggest that negative association exists between tissue levels of n-3 PUFAs and IgAN [42] whereas a positive association exists for n-6 PUFAs [43] suggesting possible benefits to dietary supplementation with n-3 PUFAs. Both animal models and clinical studies have been used to evaluate the effectiveness of n-3 PUFAs in direct and adjuvant treatments for IgAN.