(n-3) Fatty Acids and Infectious Disease Resistance

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ABSTRACT The current view of the manner in which (n-3) polyunsaturated fatty acids (PUFA) affect the immune system is centered on their ability to alter cytokine production and secondarily to diminish eicosanoid biosynthesis. The purpose of this article is to review the evidence that (n-3) PUFA affect host infectious disease resistance. Although there have been a few human clinical trials involving (n-3) PUFA and human infectious disease, the data are equivocal and the study designs confounded by the simultaneous inclusion of other immunonutrients (i.e., arginine and nucleotides) with the (n-3) PUFA. Thus, this review focuses on animal feeding trials that include an in vivo challenge of the host with a live infectious agent. Host survival and pathogen clearance are the most common endpoints measured in these studies. The data suggest that (n-3) PUFA can both improve and impair host resistance to a number of pathogens. However, the data are still quite limited in breadth and depth. For those pathogens for which data exist, the number of published studies in general does not exceed two or three. Emphasis is placed on defining important microbiological and immunological differences in various host-pathogen interactions that might help explain the incongruity in the findings published to date. The authors believe that direct examination of (n-3) PUFA on human infectious disease resistance is warranted.


KEY WORDS: • (n-3) fatty acids • fish oil • infectious disease • infection • bacteria

Interest in the potential health benefits of long-chain (n-3) polyunsaturated fatty acids (PUFA) arose from epidemiologic studies with Greenland Eskimos (1). The researchers noted the remarkably low incidence of death from ischemic heart disease in this population despite the consumption of diets that were traditionally high in fat and cholesterol. The paradox was explained later to be a consequence of the high (n-3) PUFA intake by these people. Since then, numerous studies have documented the protective role of (n-3) PUFA in fish oils, i.e., eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), against cardiovascular (2,3) and inflammatory/autoimmune diseases (4–6). However, the health benefits of consuming (n-3) PUFA may come at a price. Before the reported beneficial effects of high (n-3) PUFA intake, epidemiologists had noted a high incidence of tuberculosis in native Eskimos (7). In this population, however, separating the relative contribution of crowded living conditions, inadequate public health measures and nutritional factors on the high incidence of tuberculosis is problematic (8).

Thousands of people in the United States are supplementing their diets with (n-3) PUFA, typically in the form of fish oil pills. The motivation to do this for many comes from the potential beneficial effects that (n-3) PUFA have on risk factors associated with cardiovascular disease (e.g., reduced blood triglycerides, improved platelet function, reduced cardiac arrhythmias). Additionally, people are using (n-3) PUFA supplements as part of self-directed efforts to treat one or more inflammatory conditions (e.g., Crohn’s disease, arthritis, psoriasis). Over the past decade, evidence from clinical studies with hospitalized trauma and cancer patients has led several researchers to suggest that the immunomodulatory effects of (n-3) PUFA consumption might improve infectious disease resistance.

The conclusions from a recent meta-analysis of data from these human clinical trials using “immunonutrition” suggest that giving an (n-3) PUFA-supplemented enteral nutrition product (e.g., Impact, Sandoz Nutrition, Minneapolis, MN) may reduce nosocomial infection and sepsis rates in some patient populations (9). Unfortunately, because of the combination of nutrients (i.e., arginine, nucleotides and (n-3) PUFA) in the enteral formula used in all of these human studies, it is difficult to discern how much of the reported effects are attributable to (n-3) PUFA. To our knowledge, direct examination of the effect of (n-3) PUFA alone on infectious disease resistance of healthy humans remains unexamined.

The primary purpose of this article is to present a critical review of the evidence that (n-3) PUFA independently affect infectious disease resistance. In the absence of useful human data on this topic, our focus will be on research using various animal models. On the basis of Medline searches covering 1966 through 2001, we identified 30 original research articles that contained data relating to the feeding of (n-3) PUFA...
followed by an in vivo challenge with an infectious agent. There are nearly an equal number of papers published that report an adverse effect of (n-3) PUFA on host infectious disease resistance as those that do not show an effect or show a beneficial effect. Host survival, pathogen clearance, and eicosanoid or cytokine production are the most frequent end points reported. This review is organized according to the type of infectious challenge (i.e., pathogen). We believe that an appreciation of the interplay between pathogen and host is critical in interpreting the data from such studies. Furthermore, predicting how any nutrient might affect resistance to a given pathogen will require a deeper understanding of this interaction. Thus, we attempted to provide the reader with some rudimentary information about host-pathogen interactions.

**Infectious disease resistance**

Infectious diseases are illnesses caused by microbial pathogens, such as bacteria, viruses, fungi and parasites. The normal healthy host encounters many microorganisms on a daily basis; however, only occasionally do they cause disease. Physical barriers such as skin, mucus, tears, saliva and stomach acid all help prevent entry of infectious agents. However, when these fail, the host must rely on the immune system to recognize and destroy the pathogen.

The immune response involves many different types of cells and varies according to the nature of the invading organism. It is also composed of temporally disparate responses. The early host response is rapid and nonspecific. This response is mediated by chemicals [e.g., antibacterial peptides, nitric oxide (NO) and lysozyme] and a variety of cells, such as macrophages, polymorphonuclear cells, dendritic cells, natural killer cells (NK) and γδ T cells. These all make up the innate immune system. As time progresses, the immune response shifts to the adaptive phase. This phase involves the development of antigen-specific effectors (i.e., cytotoxic T cells and antibody-secreting plasma cells). Cells of the innate immune system play a key role in shaping the adaptive response in large part through the secretion of an array of proinflammatory mediators such as interleukin (IL)-1β, tumor necrosis factor (TNF)-α, prostaglandin (PG)E2 and leukotriene (LT)B4 in response to the pathogen. Among other things, these mediators trigger the expression of adhesion molecules and chemokines that result in the trafficking of immune cells to the site of infection. Cytokines produced by cells of the innate immune system also play a critical role in the early expansion and differentiation of antigen-specific lymphocytes and later in maintaining the adaptive response. Figure 1, adapted from Janeway et al. (10), illustrates the temporal course of a typical acute infection.

In a process that is poorly understood, some effectors cells become memory cells. True "immunity" is characterized by a more rapid and effective response upon reexposure to the same agent. This immunity, often referred to as immunologic memory, involves recognition of a pathogen by memory B and T cells and their subsequent activation without the requirement for costimulation. This pathogen-specific recognition is followed by rapid (i.e., 1–2 d) activation and expansion of memory cells into effector cells that quickly clear the infection. Understanding the cellular and molecular processes underlying the development of immunologic memory is currently an area of intense research.

In this review, we will discuss three important aspects of microbial pathogenesis: toxins, evasion mechanisms and finally whether a microbe resides intracellularly or extracellularly during a host infection. Where a pathogen locates has a tremendous effect on the type of immune response that is required by the host to successfully rid itself of the invader. For example, all viruses are obligate intracellular pathogens. They absolutely require cells for their survival and growth. Many other disease-causing agents (e.g., Salmonella, Listeria, Shigella, Bordetella, Plasmodium, Candida and mycobacterium) are facultative intracellular pathogens, that is, they are able to grow both on artificial media and inside cells. Living inside cells affords the pathogen many benefits, such as access to the host cell's nutrients and biosynthetic machinery as well as protection from certain antimicrobial effector molecules (e.g., antibodies, lysozyme). Successful host defense against intracellular pathogens usually involves activation of professional phagocytes and the generation of cytotoxic CD8+ T-lymphocytes capable of selectively killing pathogen-infected host cells. In contrast, effective control of most extracellular pathogens involves the generation of pathogen-specific antibodies. Finally, many pathogens contain or secrete toxins (endo- and exotoxin, respectively) that play a major role in infectious disease and the nature of the host's response to that pathogen. Thus, in the face of such diversity from the pathogens, it is likely that nutritional modulation of the host immune system will not affect host defense against all pathogens in the same manner and to the same extent.

During the course of infection, tissue damage is often unavoidable and it may be a direct result of the pathogen and/or a result of the host's response to the infective agent. Pathogens can damage host tissues in a variety of ways (11). Some pathogens are directly cytopathic. For example, viruses destroy the cells they infect after using the cells' own machinery to replicate. Other pathogens, such as Staphylococcus aureus and Streptococcus pyogenes synthesize and secrete exotoxins that can lead to an acute-onset illness known as toxic shock syndrome. Severe tissue damage can occur as an indirect consequence of the host's response to the infection. For example, many pathogens contain endotoxins [e.g., lipopolysaccharide (LPS), lipoteichoic acid]; they trigger a massive inflammatory response that in turn can cause local tissue damage. Unchecked production of these potent inflammatory mediators can lead to systemic problems as well, such as multiorgan failure and death as seen in some septic patients. Further, destruction of infected host cells (i.e., cell cytotoxicity) is the intended and natural consequence of a cell-mediated immune

**FIGURE 1** A schematic representation of the temporal nature of the host immune response to invasion by a pathogenic microorganism. [Adapted from Janeway et al. (10).]
response to intracellular pathogens (e.g., *Salmonella*, mycobacterium, *Listeria*, all viruses). Other ways in which the host's immune response to some pathogens can lead to tissue damage include immune complex formation and the generation of antibodies or effector cells that cross-react with normal host tissues (e.g., the link between rheumatic carditis and group A streptococcus). Thus, it is conceivable that nutrients that diminish host inflammatory responses, such as (n-3) PUFA, may reduce tissue damage and improve survival against gram-negative bacteria. In contrast, the diminished inflammation due to (n-3) PUFA may reduce the generation of cell-mediated immunity (12), which in turn could compromise host resistance to gram-positive intracellular pathogens.

*(n-3) PUFA and the immune response*

The initial concern over the potential adverse effect of consuming of a diet rich in (n-3) PUFA on host immunity arose from the observations that these nutrients tend to suppress in vivo and in vitro immune responses. For example, Virella and co-workers (13) demonstrated that consumption of (n-3) PUFA (~3 g/d) reduced some elements of T and B cell function in humans. The two most frequently reported alterations in human immune cell function associated with (n-3) PUFA are reduced lymphocyte proliferation in conjunction with impaired IL-2 biosynthesis and reduced production of proinflammatory cytokines, such as TNF-α and IL-1β. Such immunoinhibitory actions of (n-3) PUFA have been reported for immune cells isolated from humans and a variety of animals including mice, rats, dogs, pigs and chickens. These data have been the subject of several reviews (14–17). More recently, (n-3) PUFA have been shown to inhibit immune cell NO production (18). Endogenous NO plays an important role as an antimicrobial agent in professional phagocytes (19). Together these ex vivo and in vitro data suggest that dietary (n-3) PUFA could impair host defense against infectious agents. However, such in vitro data may not be predictive of actual clinical outcomes when a host is challenged with a pathogen. Thus, we believe that improving our understanding of how (n-3) PUFA may affect infectious disease resistance requires the study of a host's response to an intact infectious agent.

*(n-3) PUFA and host survival*

In many studies of infectious disease resistance, the primary data collected are host survival statistics. In *Table 1*, we summarize all of the studies in which laboratory animals were fed a diet rich in (n-3) PUFA and survival was measured after an experimental challenge with a live pathogen. Collectively these data suggest that (n-3) PUFA from fish oils can have both beneficial as well as adverse effects on host survival after an infectious challenge. It is unclear why so much inconsistency exists.

From a nutritional perspective, the amount of (n-3) PUFA consumed, length of feeding before the immune challenge and specific (n-3) PUFA fed (chain length and desaturation, source) are all factors that might affect the outcome. Yet, there is a surprising amount of similarity in this aspect of the research described in *Table 1*. Most studies involved rodents fed ~0.2 g/d of (n-3) PUFA from fish oils (i.e., a mixture of EPA and DHA) for 4–5 wk before the infection.

A more likely reason for the variability in outcomes is a consequence of differences in the following: 1) nature of the pathogen, 2) dose administered, 3) route of administration and 4) genetic components of resistance in the host (e.g., species, mouse strain). Although survival is clearly the most important clinical end point, it may not necessarily be a complete indicator of host immunity. Failure to survive an infection may be a consequence of too little or too much of a host immune response. The magnitude of the immune response is very dependent on antigen load (i.e., challenge dose). In many of the studies summarized in *Table 1*, survival after the intentional introduction of a pathogenic organism is most likely related to the challenge dose. In some cases, the use of very high challenge doses may abrogate dietary treatment effects. In our experience, this was true for the effect of fish oil on survival during murine listeriosis.

The underlying mechanism(s) by which (n-3) PUFA affect infectious disease resistance remain unclear. As stated previously, most efforts to define which elements of the host defense system that (n-3) PUFA modulate during an infectious challenge have focused on changes in proinflammatory eicosanoid and cytokine production. The potential involvement of these proinflammatory mediators may be particularly important during infection with gram-negative pathogens. The literature is replete with nutrition intervention studies that measure in vivo and in vitro proinflammatory mediator production after a LPS challenge. Whether such studies are predictive of changes in clinically important end points (e.g., pathogen clearance, survival) is unclear. Thus, we have chosen to exclude from this review studies that used LPS as a surrogate for gram-negative bacteria, but we have included those using the actual bacteria.

*(n-3) PUFA and gram-negative bacteria*

The only gram-negative bacteria evaluated in (n-3) PUFA feeding trials are *Bacteroides* spp., *Escherichia coli*, *Klebsiella* spp., *Salmonella* spp. and *Pseudomonas aeruginosa*. Most of these organisms are part of a large collection of gram-negative bacilli which make up the normal flora of the large intestine and colon of humans and animals. In general, they cause disease when they acquire certain virulence factors that allow them to overcome nonspecific host defense mechanisms or gain entry into sterile areas of the body (e.g., gun shot to the abdomen, burns, urinary tract infections).

(n-3) PUFA consumption is associated with reduced proinflammatory mediator production induced by a LPS injection (16,20,21). Such changes are often associated with clinical benefits. For example, (n-3) PUFA supplementation either via diet or parenteral emulsion administration enhanced survival of guinea pigs after a challenge with LPS (22). In humans, (n-3) PUFA consumption (~1–2 g/d for 6–8 wk) had a modest beneficial effect on the pyrogenic (fever-inducing) response to an intramuscular injection of *Salmonella typhi* vaccine (23). It is unfortunate that these authors missed the opportunity to assess diet treatment on vaccine efficacy. Chu et al. (24) reported that (n-3) PUFA reduce the binding of LPS to a human monocyte cell line (THP-1 cells) via a reduction in CD14 expression. If their findings can be reproduced in vivo, then this could explain in part how (n-3) PUFA reduce proinflammatory cytokine production in response to an LPS challenge. In addition to diminishing the production of pyrogenic cytokines, such as TNF-α and IL-1β, (n-3) PUFA have been reported to reduce the host's responsiveness to these mediators (25). Therefore, it is possible that (n-3) PUFA consumption would improve survival after an actual challenge with gram-negative bacteria.

In 1992 Blok et al. (26) reported just such an effect in female C57Bl/6 mice after an intramuscular injection with *Klebsiella pneumonia*. However, when the challenge dose was increased 10-fold from $0.5 \times 10^7$ to $0.5 \times 10^8$ colony-forming
units (cfu), the beneficial effect of (n-3) PUFA was abrogated. Treatment of mice with indomethacin did not affect survival. Thus, the authors proposed that improved survival due to (n-3) PUFA was not mediated by changes in PG production.

A year later, Johnson et al. (27) reported that (n-3) PUFA supplementation of male Sprague-Dawley rats improved their survival from bacterial peritonitis. In addition to their normal diets, rats were fed 1 mL of MaxEPA oil (~40% combined EPA and DHA), linoleic acid or sterile saline by gavage daily for 2 wk before the infection. The infection was initiated via cecal ligation and puncture (CLP). The resulting infection was most likely caused by a combination of enteric bacteria, including B. fragilis and E. coli. Both of these gram-negative bacteria can synthesize capsules that protect them from phagocytosis, which in turn contributes to their pathogenesis. Further, this infection is associated with abscess formation and considerable inflammation. A more recent study by Lanza-Jacoby and co-workers (28) confirmed that (n-3) PUFA from fish oil can enhance survival rates of rats after infection via CLP. In this study, a jugular catheter was placed in male Sprague-Dawley rats 4 d before CLP and constantly infused with saline while they continued to consume a standard nonpurified diet. Thirty minutes post-CLP, (n-3) PUFA, (n-6) PUFA from soybean oil or saline was administered parenterally until death or the end of the study on d 5. These authors also reported that (n-3) PUFA, but not (n-6) PUFA, prevented or diminished infection-induced changes in immune cell function, including proliferation and PGE2, IL-2, IL-10 and transforming growth factor (TGF)-β biosynthesis.

One (n-3) PUFA supplementation study was published in which E. coli was the sole pathogen (29). Unlike the previous two studies that used CLP to establish an infection, this study involved tracking the translocation of radiolabeled E. coli after their instillation into the gut of male Sprague-Dawley rats. These authors found that replacing 20% surface area burn that was then seeded with the bacteria. The authors conducted three independent survival experiments with 10 mice/diet treatment group in each study. However, it is unfortunate that they tested only a single challenge dose for each pathogen. A few years earlier, another team of researchers had also reported that (n-3) PUFA consumption did not affect the survival of mice challenged with P. aeruginosa (32). This study will be mentioned several more times in this review because the authors examined host resistance to several other pathogens, including murine cytomegalovirus, yeast (i.e., Candida albicans) and Listeria monocytogenes, a gram-positive bacteria. Although this was one of the earliest and most comprehensive examinations into the potential adverse effect of (n-3) PUFA on infectious disease resistance, the results of this study should be considered with caution. The autoimmune-prone mice that they used (i.e., NZB × NZW F1) do not have a normal immune system (33,34). A recent report indicated that macrophages from several autoimmune-prone mice, including the NZB × NZW strain, have defective IL-12 biosynthesis (35). At least for some pathogens, this finding could be particularly important because of the central role that IL-12 plays in the host defense against intracellular pathogens (36).

The effects of (n-3) PUFA on host response to gram-negative bacteria have not always translated into a benefit for the host. For example, Chang and co-workers (37) gave an oral challenge of Salmonella typhimurium (virulent 779-SmS strain) to female Swiss Webster mice that had been fed various high fat diets for 4 wk. Mice fed the (n-3) PUFA rich diet (fish oil) not only showed poorer survival, but also diminished bacterial clearance from the spleen compared with mice fed the low PUFA (i.e., coconut oil) or high (n-6) PUFA (corn oil) diets. An important strength of this study was that the researchers used the same challenge route (i.e., oral) that this pathogen normally uses to gain entry into the host. Unfortunately, they did not include any measure of host immunity or inflammatory response (e.g., cytokines or eicosanoids). Later that same year, there was another report on the effect of dietary (n-3) PUFA and resistance to S. typhimurium (31). However, unlike the previous study, these researchers did not find a significant effect of (n-3) PUFA on the survival of female CF1 mice after an i.p. challenge with 108 cfu of S. typhimurium (strain unknown). Although there are minor differences in the nutritional elements of these two studies (e.g., menhaden oil vs. MaxEPA; 4 vs. 3 wk of diet treatment before challenge), it seems unlikely that they explain the disparity in these findings. More likely explanations are the differences in the challenge route used in these two studies (i.e., oral vs. i.p.), strain of bacteria or mouse strain.

In summary, evidence suggests that (n-3) PUFA are capable of affecting host resistance to gram-negative bacteria. (n-3) PUFA-mediated changes in the host have proven to be both beneficial and detrimental. However, the existing studies have been somewhat narrow in scope, with survival as the primary focus. Additional studies with gram-negative bacteria that focus more on the key elements of the host’s immune response against these pathogens are warranted. Careful attention should be given to the dose and route of infectious challenge. In future studies, efforts should be made to extend the coverage of bacteria previously studied to include some additional important human pathogens.

(n-3) PUFA and gram-positive bacteria

Although we found nine original research articles describing how or whether dietary (n-3) PUFA alter host response to gram-positive bacteria, only three pathogens were examined: Staphylococcus aureus, Group B Streptococcus sp. and Listeria.
### Summary of published data regarding the effect of (n-3) polyunsaturated fatty acids

<table>
<thead>
<tr>
<th>Authors and Citation</th>
<th>Year</th>
<th>Animal and Strain</th>
<th>Pathogen</th>
<th>Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rubin et al. (32)</td>
<td>1989</td>
<td>Female mice (NZB × W)F₁ (n = 5/dose)</td>
<td>Gram-negative (LPS⁺) bacteria</td>
<td>Pseudomonas aeruginosa (10⁵-10⁶ cfu)</td>
</tr>
<tr>
<td>Peck et al. (30)</td>
<td>1990</td>
<td>Female mice BALB/c</td>
<td>Pseudomonas aeruginosa (10⁵-10⁶ cfu)</td>
<td>i.p.</td>
</tr>
<tr>
<td>Blok et al. (26)</td>
<td>1992</td>
<td>Female mice C57Bl/6 (n = 10/trt)</td>
<td>Klebsiella pneumonia (0.5 × 10⁴ - 0.5 × 10³)</td>
<td>i.m.</td>
</tr>
<tr>
<td>Clouva-Molyvdas et al. (31)</td>
<td>1992</td>
<td>Female mice CF₁ (n = 30/trt for each pathogen)</td>
<td>Salmonella typhimurium (10⁴ cfu)</td>
<td>i.p.</td>
</tr>
<tr>
<td>Chang et al. (37)</td>
<td>1992</td>
<td>Female mice Swiss Webster (n = 24/trt)</td>
<td>Salmonella typhimurium (6 × 10⁶ cfu)</td>
<td>P.o.</td>
</tr>
<tr>
<td>Johnson et al. (27)</td>
<td>1993</td>
<td>Male rats Sprague-Dawley (n = 9–12/trt)</td>
<td>GI flora (not given)</td>
<td>CLP</td>
</tr>
<tr>
<td>Lanza-Jacoby et al. (28)</td>
<td>2001</td>
<td>Male rats Sprague-Dawley (n = 8/trt)</td>
<td>GI flora (not given)</td>
<td>CLP</td>
</tr>
<tr>
<td>Barton et al. (38)</td>
<td>1991</td>
<td>Male rats Sprague-Dawley (n = 12–14)</td>
<td>Gram-positive, exotoxin-producing bacteria</td>
<td>Staph. aureus (10⁹) with Bacteroides fragilis (10⁹)</td>
</tr>
<tr>
<td>Rayon et al. (41)</td>
<td>1997</td>
<td>Neonatal rats Sprague-Dawley (n = 80/trt)</td>
<td>Streptococcus Group B (3 × 10⁹ cfu)</td>
<td>i.p.</td>
</tr>
<tr>
<td>Rubin et al. (32)</td>
<td>1989</td>
<td>Female mice (NZB × W)F₁ (n = 5/dose)</td>
<td>Intracellular, gram-positive bacteria</td>
<td>Listeria monocytogenes (10⁵-10⁷ cfu)</td>
</tr>
<tr>
<td>Fritsche et al. (47)</td>
<td>1997</td>
<td>Female mice C3H/HeN (SPF) (n = 12)</td>
<td>Listeria monocytogenes (10⁵-10⁷ cfu)</td>
<td>i.p.</td>
</tr>
<tr>
<td>de Pablo et al. (49)</td>
<td>2000</td>
<td>BALB/c mice (n = 10)</td>
<td>Listeria monocytogenes (10⁶ cfu)</td>
<td>i.v.</td>
</tr>
<tr>
<td>Rubin et al. (32)</td>
<td>1989</td>
<td>Female mice (NZB × W)F₁ (n = 5/dose)</td>
<td>Viruses</td>
<td>Cytomegalovirus (CMV) (10⁴-10⁷ cfu)</td>
</tr>
<tr>
<td>Fernandes et al. (62)</td>
<td>1992</td>
<td>SPF weanling female C57Bl/6 mice (n = 40)</td>
<td>Murine leukemia virus (LpBM5 MuLV) (5 × 10⁵ PFU)</td>
<td>Not given</td>
</tr>
<tr>
<td>Byleveld et al. (60)</td>
<td>1999</td>
<td>Male mice BALB/c (SPF)</td>
<td>Influenza log₁₀ 5 cfu (n = 3–24 depending on time point)</td>
<td>Intranasal</td>
</tr>
<tr>
<td>Levander et al. (63)</td>
<td>1989</td>
<td>CD₁ Swiss male mice</td>
<td>Protozoa</td>
<td>Plasmodium yoelli</td>
</tr>
<tr>
<td>Blok et al. (26)</td>
<td>1992</td>
<td>Female mice C57Bl/6</td>
<td>Plasmodium berghei</td>
<td>i.v. with infected RBC</td>
</tr>
</tbody>
</table>

1 Abbreviations used: cfu, colony forming units; CLP, cecal ligation and puncture; DHA, docosahexaenoic acid; en%, energy percent; EPA, eicosapentaenoic acid; GI, gastrointestinal; IFN, interferon; Ig, immunoglobulin; IL, interleukin; i.m., intramuscular; i.p., intraperitoneal; i.v., intravenous; LD₅₀, dose at which 50% mortality occurs; LPS, lipopolysaccharide (n-3) PUFA, (n-3) polyunsaturated fatty acids; p.o., peroral; PG, prostaglandin; SPF, specific pathogen-free; TGF, transforming growth factor; trt, treatment.

2 (n-3) PUFA intakes are estimates based on the following assumptions: mice consumed 60–80 kJ metabolizable energy (ME)/d, whereas rats consumed between 120 and 140 kJ ME/d; if not specified, fish oils contained 25% (n-3) PUFA; MaxEPA contains 40% (n-3) PUFA.

3 Effect of (n-3) PUFA intake on survival is indicated by arrows: ↑, increase; ↓, decrease; ↔, no effect.
fatty acids on host survival from an experimental infection

<table>
<thead>
<tr>
<th>Dietary treatments</th>
<th>(n-3) PUFA intake and duration</th>
<th>Survival</th>
<th>Other effects of (n-3) PUFA</th>
</tr>
</thead>
<tbody>
<tr>
<td>46 en% fat beef tallow or menhaden fish oil</td>
<td>−0.2 g/d 4–5 wk</td>
<td>⇨</td>
<td>LD$_{50}$ = $\sim 10^7$ Time to death &lt; 1 d No diet trt effects. No effect with 5% fat diets; Adding antioxidants to diets did not abrogate the (n-3) PUFA effect.</td>
</tr>
<tr>
<td>10 and 40 en% safflower oil or MaxEPA</td>
<td>−0.3 g/d for 40% MaxEPA diet and ~0.1 g/d for 10%</td>
<td>↓</td>
<td>55–70% mortality for S. typhimurium; 10–30% mortality for P. aeruginosa.</td>
</tr>
<tr>
<td>Purified diet 30 en% corn oil 30% palm oil 28% fish oil (+2% corn oil)</td>
<td>−0.18 g/d 6 wk</td>
<td>↑</td>
<td>No diet effect at higher challenge dose; indomethacin trt did not affect survival.</td>
</tr>
<tr>
<td>No fat, low fat, 5 and 40 en% coconut oil oleic acid safflower oil MaxEPA</td>
<td>−0.3 g/d for 40% MaxEPA diet and −0.05 g/d for 5% diet</td>
<td>⇨</td>
<td>Majority (68%) of deaths occurred within 48 h of CLP, none from either (n-3) PUFA supplemented group. (n-3) PUFA supplemented rats had no deaths until 72–96 h (4/22 total)</td>
</tr>
<tr>
<td>40 en% corn oil coconut oil fish oil</td>
<td>−0.2 g/d 2–3 wk</td>
<td>↓</td>
<td>Spleen clearance was also reduced by (n-3) PUFA ↓</td>
</tr>
<tr>
<td>Purified diet EFA-deficient MaxEPA, linoleic acid or normal saline</td>
<td>1.0 mL/d MaxEPA 2 wk</td>
<td>↑</td>
<td>50% of the FO infused rats survived to 120 h vs. 12% of SO and none of the saline. FO reduced PGE$<em>2$, IL-10 and TGF$</em>\beta$ production, reduced T cell proliferation, maintained IL-2 levels.</td>
</tr>
<tr>
<td>25 en% fat: soybean oil; 1:1 fish oil (FO): soybean oil (SO)</td>
<td>2.2 mL/h parenteral 30 min after CLP through death or 120 h</td>
<td>↑</td>
<td>All deaths occurred within 48 h; Survivors remained ill.</td>
</tr>
<tr>
<td>15 en% safflower oil or fish oil via a gastrostomy tube 22 en% fat via the dams diet: corn oil fish oil</td>
<td>−0.2 g/d 5 days</td>
<td>↑</td>
<td>All deaths occurred within 48 h;</td>
</tr>
<tr>
<td>46 en% fat beef tallow fish oil</td>
<td>−0.2 g/d 4–5 wk</td>
<td>⇨</td>
<td>LD$_{50}$ = $\sim 10^6$ Time to death = 4–5 d No diet trt effects. No diet from the spleen, but not liver, was delayed; at low dose, all mice survived.</td>
</tr>
<tr>
<td>40 en% fat lard soybean oil fish oil</td>
<td>−0.2 g/d 4–5 wk</td>
<td>↓</td>
<td>All mice died within 7 d.</td>
</tr>
<tr>
<td>5 en% fat (control) 40 en% fat: hydrogenated coconut oil; olive oil; fish oil</td>
<td>−0.2 g/d; 4–5 wk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>46 en% beef tallow or 46% menhaden oil</td>
<td>−0.2 g/d* 4–5 wk</td>
<td>⇨</td>
<td>LD$<em>{50}$ = $4 \times 10^5$ for tallow LD$</em>{50}$ = $8 \times 10^5$ for fish oil Time to death = 5–7 d No diet trt effects. Calorie restriction and fish oil increased survival; No effect on T cell proliferation; FO reduced PGE$<em>2$ production (~60%). Delayed viral clearance (d 1 and 5) Reduced sera IgG (d 7 only) Reduced lung IgA (d 7 only) Reduced lung IFN$</em>\gamma$ (d 5 and 7)</td>
</tr>
<tr>
<td>5% corn oil; 5% CO with 40% en restriction; 20% corn oil; 20% fish oil 6 en% sunflower oil w/34% beef tallow or 34% fish oil</td>
<td>−0.2 g/d 8 wk</td>
<td>↑</td>
<td>Because all diets had 5% fish oil, these data only show that addition of $100$ mg/kg of vitamin E to a fish oil diet abrogated the beneficial effects of high (n-3) PUFA intake.</td>
</tr>
<tr>
<td>5% menhaden oil w/ or w/o 100 mg/kg of vitamin E</td>
<td>−0.03 g/d 4 wk</td>
<td>↑</td>
<td>No diet effect on parasitemia (%RBC infected)</td>
</tr>
<tr>
<td>Nonpurified diet 30 en% corn oil 30% palm oil 28% fish oil (+2% corn oil)</td>
<td>−0.18 g/d 6 wk</td>
<td>↑</td>
<td>Indomethacin trt did not affect survival on parasitemia. Vitamin E status not determined.</td>
</tr>
</tbody>
</table>
monocytogenes. The first two release exotoxins and are among the most common and clinically important bacteria in human medicine. S. aureus is an extracellular pathogen; thus protective immunity involves pathogen-specific antibodies [especially immunoglobulin (Ig)A at mucosal surfaces] and antimicrobial peptides. The pathology that these agents cause depends on the site of infection. For example, S. aureus in the skin leads to boils, in the GI tract to diarrhea, whereas in the blood it leads to toxic shock syndrome and death.

In 1991 Barton and co-workers (38) reported that rats fed a diet enriched with (n-3) PUFA had decreased mortality in a sepsis model that involved a S. aureus challenge. Male Sprague-Dawley rats were fed a liquid diet via a gastrostomy tube containing 15 en% as either safflower oil or a 10:1 mixture of menhaden oil and safflower oil for 5 d before the establishment of the infection. Rats were infected by intrabdominal implantation of a sterile fecal-agar pellet that had been inoculated with S. aureus (10^11) and Bacteroides fragilis (10^8). Rats fed the fish oil–containing liquid diet had a slightly better survival rate (35%, 5/14) than those fed safflower oil (16%, 2/12), but this difference was not significant (P > 0.05). Regardless of dietary treatment, survivors continued to appear ill throughout the 7-d follow-up period. Because all deaths occurred within 48 h of the infectious challenge, the authors speculated that diet-induced changes in eicosanoid production occurred within 48 h of inoculation. Pups suckling dams fed salmon oil at 7 d of age. Mortality depended on the site of infection. For example, S. aureus is a food-borne pathogen in humans that causes serious life-threatening infections in the very young, very old and the immunocompromised. Listeria monocytogenes has been an extremely useful tool for elucidating the mechanisms for immunity to intracellular bacteria (42,43). In mice, the course of infection is rapid and reproducible with sterile clearance or death occurring by d 7 after initial introduction of the bacteria; [see Fig. 2, adapted from Kaufmann et al. (44)]. Cell-mediated immunity plays a critical role in host defense against L. monocytogenes infections. CD4+ and CD8+ T lymphocytes are thought to work cooperatively toward resolution of primary infection, but with CD8+ cytotoxic T lymphocytes playing a greater role in long-term protective immunity. A more detailed review of the host immune response associated with intracellular bacteria can be found elsewhere (44).

The first report in the literature regarding L. monocytogenes resistance and dietary (n-3) PUFA was the study by Rubin et al. (32). These researchers did not find an effect of dietary fish oil on host resistance to a number of pathogens, including L. monocytogenes. As mentioned previously, their use of the autoimmune-prone NZB × NZW F1 mice is problematic. Two other studies that involved (n-3) PUFA and L. monocytogenes also should be interpreted with some caution. In these studies, mice were provided an enteral product that was enriched with a modest amount of (n-3) PUFA (i.e., 0.17 g of EPA and DHA/L). Resistance to L. monocytogenes was either unaffected

FIGURE 2 The three stages of the host response to Listeria monocytogenes: At each stage, the cells fulfill two functions: first, they express effector functions that directly interfere with bacterial growth; second, they perform regulatory functions that influence the other two stages. Abbreviations used: DC, dendritic cell; MP, macrophages; PMN, polymorphonuclear granulocyte; NK, natural killer cells; γδ T cells; Th1, T helper 1 cell (CD4 or CD8 phenotype); IL, interleukin; TNF, tumor necrosis factor; IFNγ, interferon-γ. [Adapted from Kaufmann (44)].
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(45) or slightly improved (46). However, the presence of other immunomodulating components (e.g., arginine, RNA) in this enteral product makes it difficult to ascribe these effects to the (n-3) PUFA.

We conducted a series of experiments to examine the effect of feeding mice a diet rich in (n-3) PUFA from fish oil on resistance to L. monocytogenes. In our studies, weanling female C3H/HeN mice were fed experimental diets containing one of three fat sources (20 g/100 g): lard (low PUFA), soybean oil [(n-6) PUFA] or a mixture (9:1) of menhaden oil and corn oil [(n-3) PUFA]. After 4 wk, mice were given various doses of live L. monocytogenes (ATCC strain 43249) by i.p. injection. Those fed the (n-3) PUFA diet had significantly delayed bacterial clearance as well as decreased survival (47). In follow-up experiments, we reported that (n-3) PUFA–fed mice had lower levels of serum IL-12 and IFNγ at 24 h postinfection than (n-6) PUFA– or low PUFA–fed mice. Consistent with lower circulating IFNγ and lower spleen IFNγ mRNA, (n-3) PUFA–fed mice also had fewer IFNγ-producing cells in their spleen compared with the (n-6) PUFA–fed group (48). A recent report from another laboratory (49) confirmed our findings that high (n-3) PUFA intake reduces survival and bacterial clearance after a challenge with L. monocytogenes.

Thus, it appears that (n-3) PUFA can improve host response to two different exotoxin-secreting, gram-positive bacteria sufficiently to enhance host survival. In these studies, death from these organisms usually occurred rapidly (e.g., within 48 h). Much of the tissue damage associated with these pathogens is from host-derived mediators. In many respects, host response to exotoxin-secreting pathogens is similar to that with gram-negative bacteria. Thus the ability of (n-3) PUFA to improve survival in such infections may reflect their effect on the host’s ability to strike the proper balance between the necessary vs. excessive production of various proinflammatory mediators. In contrast, most of the data with L. monocytogenes, a gram-positive, food-borne pathogen, suggest that (n-3) PUFA can diminish host resistance to this bacteria. This impairment seems to be related to the ability of (n-3) PUFA to diminish the production of certain key cytokines (i.e., IL-12 and IFNγ) that play essential roles in host defense against intracellular pathogens, such as L. monocytogenes.

(n-3) PUFA and bacteria that do not gram stain

This group includes a number of clinically important intracellular pathogens, but only one has been the subject of a (n-3) PUFA investigation, i.e., Mycobacterium tuberculosis. This organism causes tuberculosis in millions of people worldwide and is responsible for ∼3 million deaths annually (50). The disease is characterized by a long incubation period, a protracted disease course and dormancy. It has been estimated that one third of the world’s population is infected with M. tuberculosis. Most of these individuals harbor M. tuberculosis within granulomas in their lungs, held in check by T cells and macrophages. Such carriers remain asymptomatic until their immune system weakens and reactivation of dormant M. tuberculosis occurs (44).

We have identified two studies in which the effect of dietary (n-3) PUFA was examined in a M. tuberculosis challenge. In the first study, specific pathogen–free male guinea pigs were fed one of three experimental diets that differed primarily in fatty acid composition (51). One diet (control) was rich in saturated fatty acids and devoid of (n-3) PUFA, whereas the other two experimental diets were rich in (n-6) PUFA or (n-3) PUFA from safflower or fish oil, respectively. After 13 wk, guinea pigs received an intramuscular injection of 180 cfu M. tuberculosis (strain H37Rv, ATCC 35837). Seven weeks after infection, the number of viable organisms in the spleen of (n-3) PUFA-fed guinea pigs was significantly higher than in those fed the other two diets. A few years later, these same authors conducted another feeding trial and reported very similar findings (52). Together, these data suggest that (n-3) PUFA reduce host resistance to mycobacterium infection. These experimental data are consistent with the epidemiologic findings in native Greenlanders and Alaskans (i.e., Eskimos) who were found to have a high (n-3) PUFA intake (53) and a high incidence of tuberculosis (7,54). However, many factors other than (n-3) PUFA intake may have contributed to the elevated incidence of tuberculosis in this population (8).

In summary, the experimental animal data and human epidemiologic data suggest that (n-3) PUFA may impair host resistance to M. tuberculosis. These findings may have great importance from a public health perspective because millions of people are currently infected, chronically with M. tuberculosis and the incidence of tuberculosis is rising. Furthermore, the incidence of multidrug-resistant strains of M. tuberculosis is increasing at an alarming rate. The data from the L. monocytogenes research along with these more limited data with M. tuberculosis raise an important public health question. Are people who are currently infected with M. tuberculosis, but asymptomatic (i.e., TB carriers) at increased risk of reactivating their disease upon (n-3) PUFA supplementation?

(n-3) PUFA and viral infections

We identified eight research articles that describe how dietary (n-3) PUFA influence host responses to a challenge with a variety of viruses, including influenza A, vaccinia, murine cytomegalovirus (CMV), and a murine retrovirus, LpBM5 murine leukemia virus (MuLV) that mimics human HIV. Viruses are obligate intracellular pathogens because they require the use of the host’s cellular machinery for their own replication. As intracellular pathogens, only a cell-mediated immune response will effectively eliminate viral infections from the host. However, most disease-causing viruses have one or more mechanisms for interfering with the host’s immune response to the infection. Small viruses such as influenza A and retroviruses evade the immune system by constantly changing their envelope glycoproteins. DNA viruses such as vaccinia and CMV express proteins that hinder the host’s immune response. For example, vaccinia viruses secrete proteins that inhibit complement activation, and bind and neutralize cytokines, specifically TNF-α, IL-1β and IFNγ (55). CMV express proteins that down-regulate the expression of major histocompatibility complex class I molecules and diminish antigen presentation (56), thus blocking antigen-specific killing of virally infected host cells by CD8+ cytotoxic T lymphocytes.

Only a single report exists regarding (n-3) PUFA and host response to CMV infection. In 1989 Rubin et al. (32) found that compared with beef tallow, feeding autoimmune-prone NZB × NZW mice (n-3) PUFA from fish oil did not affect survival after a lethal challenge with murine CMV. In addition to the previously mentioned shortcoming of using autoimmune-prone mice for infectious disease studies, another weakness in their approach was the use of CMV as an acute infectious agent. In humans as well as in animals, primary infection by CMV is generally asymptomatic and the virus persists within the host for a lifetime. However, impairment in host immune status from stress, trauma, aging or HIV infection can all reactivate CMV and disease onset. Thus, a more
relevant and interesting experimental design would have been to infect the mice with a low dose of CMV, wait several weeks, then feed them (n-3) PUFA and look for diet-induced differences in the reactivation of the virus after trauma or stress. Knowing whether (n-3) PUFA might increase the likelihood of CMV reactivation could be an important public health issue because 60–100% of the human population have been infected with human CMV (57).

In 1989 Fritsche and Johnston (58) reported that feeding female BALB/c mice a diet high in linoleic acid (~10 en% 18:3(n-3), from linseed oil) enhanced viral-specific cell-mediated cytotoxicity after a live challenge with vaccinia virus. This effect was transient in that greater cytotoxicity was observed at 6 d, but not at 3 or 9 d after the primary challenge. In a follow-up experiment, it was shown that unlike linoleic acid, a diet rich in (n-3) PUFA from fish oil did not enhance viral-specific cytotoxic activity at least compared with mice fed a corn oil–containing diet (59).

Influenza A virus is a pathogen of great relevance in human medicine. Byleveld and co-workers (60,61) recently published two studies that suggest that dietary (n-3) PUFA can diminish host defense against this pathogen. In 1999 they fed male BALB/c mice one of two nutritionally complete diets that differed only in fat source, i.e., fish oil or beef tallow (20 g/100 g). After 2 wk, mice were given 10^5 plaque-forming units (PFU) of influenza A virus (H3N2 strain) via nasal instillation. Their use of a route that mimics the natural site of entry for this pathogen is one of the major strengths of this study. Viral clearance, production of several key antiviral cytokines (i.e., interferons α, β and γ) and the concentration of total and virus-specific immunoglobulins (i.e., IgG and IgA) in the sera and lungs were assessed at 3 h, 1, 2, 5 and 7 d postchallenge. These researchers found that viral titers were significantly higher in fish oil–fed mice at 1 and 5 d postchallenge. At d 5 and 7 postchallenge, IFNγ concentrations were lower in the lungs of mice fed fish oil. At d 7, the beef tallow group had significantly higher virus-specific IgG titers in serum and higher IgA titers in their lung lavage samples than mice fed the fish oil diets. In the follow-up study (61), a similar diet and intranasal challenge regimen was followed but the researchers looked at different end points, including cytotoxicity and T cel proliferation. At d 5 postchallenge, virus-specific cytotoxic activity was significantly lower in the fish oil–fed mice compared with the beef tallow–fed mice (i.e., 20 vs. 40% specific lysis at an effector to target ratio of 50:1). Diet groups did not differ in the nonspecific cytotoxicity of lung macrophages or NK cells. Although these data suggest that high (n-3) PUFA intake may impair acquired cell-mediated immunity against influenza A virus, it is important to note that all mice successfully cleared the virus.

Two reports suggest that dietary (n-3) PUFA delay the progression of a murine retrovirus-induced immunodeficiency syndrome that mimics human AIDS. In the first study (62), the authors fed C57BL/6 mice experimental diets with either 5 or 20% fat, in which the primary source of fat was either corn oil or fish oil. After 4 wk, mice were injected with the murine retrovirus (LpBM5 MuLV). They reported that mice fed the 20% fish oil diet survived significantly longer than mice fed the 20% corn oil diet. A study by Xi et al. (20) was similar to the one described above. For example, the same strain of mice was used and the diets were either 20% corn or fish oil. Many of the characteristic changes in immune function associated with the retrovirus infection were not as diminished in mice fed the high (n-3) PUFA diet compared with mice fed the corn oil diet. Data such as these might encourage some HIV+ patients to supplement their diets with (n-3) PUFA. However, it is premature to make such a recommendation in part because these fatty acids may adversely affect host resistance to several opportunistic pathogens as described above.

In summary, (n-3) PUFA may affect host antiviral defense in both positive and negative ways. The data are too limited to speculate on the underlying mechanism(s) that might help explain the difference in outcomes. However, in general, the magnitude of the (n-3) PUFA effect appears to be much smaller for antiviral than antibacterial responses. It would be interesting to examine the response of these mice to a secondary viral challenge in both vaccinia and influenza studies. Little is known about how transient differences in a primary immune response may affect the quality of the memory response to a subsequent infection by the same pathogen. Further studies investigating the potential effect of (n-3) PUFA on host antiviral defense seem warranted. However, care should be taken to design these studies to include pathogens of clinical relevance and to employ inoculation protocols that mimic natural routes of infection (i.e., via lungs or gastrointestinal tract).

(n-3) PUFA and parasitic infections

Parasites are divided into two major groups, protozoan, consisting of a single eukaryotic cell, and multicellular helminths (worms). Of the protozoan parasites, Plasmodium is of greatest clinical importance. Several species of Plasmodium infect RBC, causing malaria, which is the number one killer among infectious diseases worldwide. It is estimated that over half of the world’s population is at risk for malaria and that between 1 and 2 million of the ~500 million new cases each year are fatal.

Of the infectious disease models, the effect of (n-3) PUFA on host resistance to infection from P. berghei or P. falciparum, the causative agents of malaria, is the most consistent and best understood from a mechanistic perspective. In 1989 Levander and co-workers (63) showed that feeding male CD1-Swiss mice a diet deficient in vitamin E and containing 5% menadione oil afforded significant protection from infection against challenges with either of two strains of P. berghei. They monitored parasitemia and survival through 60 d postinfection. Regardless of strain, (chloroquine-sensitive or resistant), when the vitamin E–deficient diet was combined with 5% fish oil, it dramatically improved host survival. Mice that had been infected with the faster growing chloroquine-sensitive strain but fed the (n-3) PUFA–enriched, vitamin E–deficient diet had a survival rate of 90% vs. 10% in the group fed the control diet. Similarly, mice challenged with the slower growing, chloroquine-resistant strain and fed the (n-3) PUFA–enriched, vitamin E–deficient had a 64% survival rate compared with a 0% survival rate when the control diet was fed.

Several possible mechanisms for the antimalarial activity of (n-3) PUFA have been explored. Because the in vivo administration of indomethacin had no effect on the development of cerebral malaria or parasitemia, it was concluded that (n-3) PUFA were probably not working through changes in PG production. Data from Blok et al. (26) and Vreden and co-workers (64) do not support an important role for (n-3) PUFA–mediated changes in cytokine production as the primary means by which host response to P. berghei is affected. That (n-6) as well as (n-3) PUFA inhibit parasitemia both in vivo and in vitro suggested that fatty acids were acting directly on the pathogen. Kumaratilake et al. (65) demonstrated that of the fatty acids tested, only PUFA, both (n-6) and (n-3), inhibited parasite growth in vitro. This inhibition was dependent on concentration as well as on the degree of fatty acid...
unsaturation and chain length. It was also shown that the addition of scavengers of reactive oxygen species or antioxidants reduced the ability of PUFA to kill P. falciparum and that the addition of oxidized fatty acids enhanced their ability to kill the parasite. Thus, for this infectious disease, the data strongly suggest that (n-3) PUFA can improve host survival by directly affecting parasite survival, independent of any changes in the host’s immune system.

Blok et al. (26) showed that overt vitamin E deficiency was not required for (n-3) PUFA to positively affect antimalarial resistance. In their study, female Swiss mice were supplemented with fish oil or palm oil via gastric instillation for an undefined length of time before being infected with 10⁷ erythrocytes parasitized with P. berghei. Fish oil–supplemented mice had increased survival compared with mice fed palm oil. Parasitemia in mice supplemented with fish oil was also lower at d 9 postinfection. In a second experiment, these researchers demonstrated that compared with corn oil, dietary fish oil (15 g/100 g) increased the survival of mice challenged with P. berghei. Unfortunately, the vitamin E status of these mice was not assessed. However, consumption of fish oil is generally associated with significant reductions in hepatic and plasma vitamin E concentrations, whereas immune cell vitamin E status is preserved (66). Therefore, these data are still consistent with a model in which the effect of (n-3) PUFA on parasitemia was mediated by enhancing oxidative stress in situ (i.e., in the RBC, where P. berghei resides in mammalian infection).

There are two reports that dietary (n-3) PUFA from fish oil reduce the severity of coccidiosis in chickens. Coccidiosis is a parasitic disease that is common in poultry and is caused by the protozoan parasite Eimeria tenella. Allen and co-workers (67) reported that the inclusion of 2.5 or 5% fish oil in the diet of chickens reduced the severity of gastrointestinal tract lesions after an experimental Eimeria challenge. In 1997 Korver et al. (68) showed that the normal growth-depressing effects of an Eimeria infection could be completely abrogated by the inclusion of 4% fish oil in the diet. This latter study provided some evidence that the beneficial effect of fish oil might occur in a 5-lipoxygenase (5-LO)–dependent manner. Specifically, inclusion of a 5-LO inhibitor in the control diet mimicked the effect of fish oil in terms of preventing the weight loss associated with Eimeria infection. In contrast, the 5-LO inhibitor had no additional effect when added to the diets containing fish oil. Thus, these authors concluded that fish oil, i.e., (n-3) PUFA, had a beneficial effect on the host response to this parasite by reducing the production of an endogenous 5-LO metabolite, possibly the proinflammatory eicosanoid, LTB₄. Only a single study has been published that examined the effect of (n-3) PUFA on host resistance to helminths. Helminths are a large and diverse group of parasitic worms that include tapeworms, roundworms and flukes. They are a prominent cause of disease in tropical countries with overcrowded living conditions and inadequate public sanitation. The diseases caused by helminths depend on the type and developmental form of parasite. In most cases, the mature form (worm) does not produce severe disease. However, eggs and larvae of some helminths can cause life-threatening disease. Protective immunity against helminth infection is mediated by antibody-dependent cellular cytotoxicity. This response involves IgE, IgA, macrophages and eosinophils as effectors. Olive et al. (69) found that dietary fish oil did not affect the susceptibility of rats to an intragastric infection with Trichinella spiralis, a nematode commonly found in muscle tissue from infected pigs. Specifically, they found that feeding rats a diet containing ~10 g/100 g fish oil did not affect the primary in vivo or secondary ex vivo response against this parasite. Among the strengths of this study was the introduction of the pathogen by the route that would occur naturally (i.e., by mouth). Unfortunately, the assessment of the host immune response to this infection was quite limited as were the number of subjects used in this study.

In summary, (n-3) PUFA can have a direct cytoxic action on the malaria-causing pathogen, Plasmodium spp. This cytotoxicity involves the induction of oxidative damage and thus can be enhanced or diminished by either decreasing or increasing the intake of antioxidant nutrients such as vitamin E and selenium. Beneficial effects of (n-3) PUFA intake have been reported for the protozoan parasite responsible for coccidiosis in poultry (i.e., Eimeria). The data suggest that it was the ability of (n-3) PUFA to diminish 5-LO metabolite production that was central to the clinical benefits observed in this infection.

Conclusions

There is a compelling body of data that dietary (n-3) PUFA can modulate inflammatory and immune responses in laboratory animals and in people. In contrast, the data that (n-3) PUFA affect host infectious disease resistance are more limited and equivocal. However, we contend that the body of evidence presented in this review suggests that further testing would be prudent. Although it is difficult to obtain precise data, the number of people supplementing their diets with (n-3) PUFA may be in the tens or hundreds of thousands. Most are hoping to improve the quality and or length of their lives with these supplements. The time has come to improve our fundamental and mechanistic understanding of how (n-3) PUFA affect host responses to a wider variety of important human pathogens.

LITERATURE CITED


