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Review Article

A BRIEF REVIEW ON FATTY ACIDS ACTS AN IMMUNOMODULATOR

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ABSTRACT:

The fatty acid composition of lymphocytes, and other immune cells, is altered according to the fatty acid composition of the diet and this alters the capacity of those cells to produce eicosanoids, such as prostaglandin E_2, which are involved in immune-regulation. A high fat diet can impair lymphocyte function. Cell culture and animal feeding studies indicate that oleic, linoleic, conjugated linoleic, g-linolenic, dihomo-g-linolenic, arachidonic, a-linolenic, eicosapentaenoic and docosahexaenoic acids can all influence lymphocyte proliferation, the production of cytokines by lymphocytes, and natural killer cell activity. High intakes of some of these fatty acids are necessary to induce these effects. Among these fatty acids the long chain n-3 fatty acids, especially eicosapentaenoic acid, appear to be the most potent when included in the human diet. These effects appear to mediated at the membrane level suggesting important roles of fatty acids in membrane order, lipid propel structure and function, and membrane trafficking. Thus, the fatty acid composition of human immune cells influences their function and the cell membrane contents of arachidonic acid, Eicosapentaenoic acid and docosahexaenoic acids are important. Fatty acids influence immune cell function through a variety of complex mechanisms and these mechanisms are now beginning to be tattered.

KEY WORDS: Polyunsaturated fatty acids (PUFA), Immunomodulator, Immunity.

INTRODUCTION:

In nutrition, polyunsaturated fat, or polyunsaturated fatty acid, are fatty acids in which more than one double bond exists within the representative molecule. That is the molecule has two or more points on its structure capable of supporting hydrogen atoms not currently part of the structure. Polyunsaturated fatty acids can assume a cis or trans conformation depending on the geometry of the double bond.

A fatty acid has a carboxylic acid at one end and a methyl group at the other end. Carbon atoms in a fatty acid are identified by Greek letters on the basis of their distance from the carboxylic acid. The carbon atom closest to the carboxylic acid is the alpha carbon; the next adjacent carbon is the beta carbon, etc. In a long-chain fatty acid the carbon atom in the methyl group is called the omega carbon because omega is the last letter of the Greek alphabet. Omega-3 fatty acids have double bond three carbons away from the methyl carbon, whereas omega-6 fatty acids have a double bond six carbons away from the methyl carbon. (http://wikipedia.org/wiki/Polyunsaturated fat).

THE IMMUNE SYSTEM IN HEALTH AND DISEASE:

The immune system protects the host from environmental infectious agents such as pathogenic bacteria, viruses, fungi, and parasites and from other noxious insults. It also permits tolerance

to self-antigens and to non-threatening environmental agents such as food proteins and commensal gut bacteria. The system has two functional divisions: the innate (or natural) immune system and the acquired (also termed specific or adaptive) immune system. Both components involve various blood-borne factors and cells. Immune cells originate in bone marrow and are found circulating in the bloodstream, organized into lymphoid organs such as the thymus, spleen, lymph nodes and gut-associated lymphoid tissue, or dispersed in other locations. Different immune cell types have highly specialized roles (eg. phagocytosis, antigen presentation, antibody production, destruction of virally infected cells) and acting together they create a coordinated and regulated immune response.

Certain cells of the immune system retain memory of previous immunologic encounters so ensuring a more rapid response upon re-infection. Thus, the four key general roles of the immune system are (Calder. 2008).

- To act as an exclusion barrier
- To discriminate ‘‘self’’ from ‘‘non-self’’ so assuring tolerance
- To eliminate the source of ‘‘non-self’’ antigens
- To retain memory of immunologic encounters

ROLE OF FATTY ACIDS IN IMMUNITY:

The status of the immune system closely aligns with the health of an individual. Malnutrition and metabolic disorders commonly result in decreased food intake, decreased feed efficiency, growth retardation, low uniformity and high mortality. Nutrients from diets provide basic needs to maintain sound animal health. In animal husbandry, genetic selection for rapid growth has compromised immunity in animals since nutrients are allocated for growth (Connor, 2000). Therefore, manipulation of specific nutrients to enhance immunity is of great interest. Fat composition of the diets, along with protein, has a significant role in health through its content of fatty acids, cholesterol, and fat soluble vitamins.

The profound effect of fatty acids on immunity is best exemplified by the Greenland Eskimo paradox. Consumption of large quantities of Eicosapentaenoic acid (EPA) and Docosahexaenoic acid (DHA) from marine products has greatly decreased the incidence of coronary heart disease and stroke among this population (Kremer, 1996; Bruckner, 1997). In addition, evidences have shown that EPA and DHA reduce cholesterol and inhibit atherosclerosis (Chamberlain *et al*. 1991; Sadi *et al*. 1996), inhibit the blood coagulation pathway (Miller, 1998; Mutanen and Freese, 2001), ameliorate symptoms of lung disease by decreasing production of bronchoconstrictive leukotrienes (Schwartz, 2000) and modulates bone growth in animals (Liu and Denbow, 2001). In all cases, eicosanoids and the cytokine, interleukin-1 (IL-1), have been associated with these effects.

Dietary supplement of fish oil rich in EPA and DHA has been shown to suppress IL-1 production and TGF-α in various animal models. Suppression of IL-1 causes a decrease in lymphocyte proliferation, hampering the expression of cell adhesion molecules, and down regulates inflammatory gene nuclear factor kappa (NF-κB) expression (Toborek *et al*., 2002), which leads to decreased indices of inflammation. Among evidence that supports n-3 polyunsaturated fatty acids, (PUFA) ameliorating inflammatory symptoms in autoimmune diseases, the EPA in marine lipids that are metabolized to the less bioactive eicosanoids is the most promising evidence. The 3 series of prostaglandin and 5 series of leukotriene are produced from EPA. PGE3 has pro-inflammatory activity similar to that of PGE2, but it synthesized with a very low efficiency, and leukotriene (LT) B5 has little inflammatory activity compared to LTB4 (James *et al*., 2000). The significance of substitutes of PG and LT families to less bioactive EPA metabolites has been reviewed (Kremer, 1996). Kremer has suggested that 21 supplementation with n-3 PUFA in rheumatic arthritis patients enables the discontinuation of nonsteroidal anti-inflammatory drugs (NSAID).

Among a variety of fatty acids, n-3 and n-6 PUFA have been most extensively studied for their functions in immunity. However, research on the effects of monounsaturated fatty acids on immunity is incomplete. With the popularity and amount being consumed by humans, MUFA (Mono Unsaturated Fatty Acid) has become a center of attention in human health. In Western diets, more than 40% of commercial fats are trans MUFA isomers (Craig-Schmidt *et al*. 2000). A recent study investigating the uptake of individual fatty acids into adipose tissue in relation to their presence in the human diet indicated that MUFA was preferentially absorbed and stored in adipose tissues (Summers *et al*. 2000). The quantity stored in relation to type of fatty acids was MUFA > n-6 PUFA > SAF > n-3 PUFA. It is reasonable to speculate that MUFA could have a greater influence than other classes of fatty acids. Moreover, it has been shown that the consumption of olive oil rich in oleic acid (cis C18:1) decreases the risk for developing rheumatoid arthritis in humans (Linos *et al*., 1991).

In animals, the PUFA content in basal diets usually masks the effects of lipid treatment containing high MUFA such as lard or chicken fat. Therefore, MUFA diets have typically been used as control treatments, or have been reported not to affect various immunological indices. In 1996, Jeffery *et al*. reported an inversed relationship between splenocytes 23 stimulation index and the ratio of oleic to linoleic acid in the diet. Moreover, Yaqoob (1998) reported that MUFA consumption resulted in suppression of proliferation of peripheral blood mononuclear cell stimulated by CON A (Concanavalin A). The host versus graft response to injection of allogenic cells into the footpad of a host was suppressed by fish oil rich in n-3 PUFA, while feeding olive oil rich in oleic acid had a similar but weaker effect in rats (Sanderson *et al*., 1995). In humans, consumption of a MUFA rich diet decreased CAM (Cell adhesion Molecule) expression on peripheral blood mononuclear cells and suppressed NK(Natural Killer) cell activity and cell proliferation (Yaqoob *et al*., 1994). The immunosuppressive effect by dietary lipids is not limited to fish oil containing n-3 PUFA. The n-9, 18:1 oleic acid also exerts an anti-inflammatory property, at least when incorporated into the diet using olive oil.

PRINCIPLE MECHANISM OF IMMUNOMODULATION BY PUFA:

Three modes of PUFA action have been primarily discussed with respected to their immunomodulatory action. First, PUFA of the n-3 series interfere with the biosynthesis of lipid mediator molecules. Eicosanoid messenger molecules such as prostaglandin (PG), leukotrianes (LT), and thomboxans (TX) are usually derived from arachidonic acid (AA) that is librated from membrane n-phospholipids. Metabolism of AA by cyclooxygenase (COX) leads to generation of PG and TX of the 2-series, where, where as metabolism via 5-lipooxygenase gives to, for examples, LT of the 4-series. PUFA of the n-3 series inhibit eicosanoid synthesis from AA and /or give rise to chemically altered molecules .When EPA(Eicosapentaenoic acid) is metabolized instead of AA by the COX(Cyclooxygenase), PG and TX of the 3-series are produced that in some cases have different biological effects, as reviewed in detail elsewhere (Stunlnig., 2003; Calder *et al*., 2002). In addition to directly interfering with enzymes of eicosanolid synthesis PUFA can also expression as shown for COX-2 in monocytes (Calder,

1997). Although n-6 and n-3 PUFA exert clearly different effects on eicosanoids synthesis, the functional outcome of these changes with respect to immunomodulation are often not predicatable due to parallel pro and anti-inflammatory effects and often unknown *in vivo* interaction of the generated messanger molecules. Moreever, due to grea differences (Lee *et al*., 1997) and differences between *in vivo* and *in vitro* eicosanoid production (Lee *et al*., 2003) *in vivo* extrapolations of experimental data have turned out to be extremely difficult.

A second principal mechanism for modulation of immune response by PUFA is by direct alteration of gene expression by modification of transcription factor activity. This can be achived either by direct interaction with ligand-binding transcription factors, so called nuclear receptor or by interference with membrane or cytoplasmic signaling pathways that finally lead to altered transcription factor activation. Peroxide some proliferators activated receptor (PPAR)-γ preferentially binds a verity of PUFA and their derivatives and has been shown to be involved in lymphocyte activation and macrophages differentiation (Morita *et al*., 1983; Knapp, *et al*., 1986; Saito *et al*., 1997). Since PUFA activates PPAR-γ, this could be a mechanism of PUFA mediated immunomodulation. However; PPAR-γ is also activated by the abundant monosturrated FA. In addition to PPAR-γ, PPAR-δ can bind FA, but with even less specificity for PUFA, PPAR-γ is highly abundant in myeloid cells but T lymphocytes, which constitutively express PPAR-α, express PPAR-γ only upon stimulation. Liver X receptor α and β are inhibited by mono and polyunsaturated FA (Yang *et al*., 2000). Retinoid X receptors, the hetero dimer partner for a varity of nuclear receptors including those mentioned above, are activated by DHA with some selectively compared to AA (Clark *et al.*, 2000). However, nuclear receptors generally lack adequate specificity for PUFA to explain PUFA's immunomodulatory effects. Moreover, suppressive effects *in vitro* have mostly been found with rather unselective nuclear receptor ligands so that the impact of nuclear receptor in general and PPAR-γ in particular, on PUFA mediated immunomodulation is doubtful.

DRUGS MODULATED BY PUFA: Prostanoids produced via the action of COX-2 appear central to many inflammatory conditions. In LPS-treated rats however, COX-2 induction alone does not greatly increase

prostanoid production *in vivo*. For this, a second AA liberating stimulus is also required. Thus,only after intravenous injection of bradykinin or exogenous AA was a marked increase in prostanoid formation seen. There is, therefore, synergy between proinflammatory mediators: both induction of COX-2 protein and an increase in the supply of AA are required to greatly enhance prostanoid production. Second, the supply of AA to increase prostanoid production reduces the effectiveness of both currently used nonsteroidal antiinflammatory drugs (NSAIDs) (Diclofenac) and novel COX-2-selective inhibitors (celecoxib) as inhibitors of COX-2 activity.

This clearly indicates that: 1). Increased prostanoid production in inflammation is a two component response: increased COX-2 expression and increased AA supply; 2) The supply of AA to COX-2 determines the effectiveness of NSAIDs. NSAIDs and selective COX-2 inhibitors, therefore, will generally be less effective at more inflamed sites, providing a rationale for the very high doses of NSAIDs required in human conditions such as rheumatoid arthritis (Hamilton *et al*., 1999).

GUIDELINES FOR THE ASSESMENT OF PUFA STATUS:

For the assessment of the essential PUFA status of an individual, the total amount of the various EFA and PUFA in plasma or erythrocyte phospholipids is a useful indicator. It should be realized that the plasma content of essential PUFA does not necessarily guarantee the proper use of these fatty acids by cells and tissues. Therefore, additional status markers are (Hornstra *et al*., 1992) required to reliably assess the functional PUFA status of a given individual. In general, if insufficient essential PUFA are available to meet PUFA requirements, the body starts to synthesize certain fatty acids that are hardly present if the EFA and PUFA status is adequate. Therefore, these fatty acids can be essential PUFA status markers.

The best known marker is Mead acid (C 20:3 n-9). The synthesis of this fatty acid is promoted if there are insufficient concentrations of LA and LNA to meet the need for the synthesis of long-chain PUFA. EPA and DHA inhibit Mead acid synthesis; the presence of Mead acid indicates a general shortage of all essential PUFA. Another suitable indicator of essential PUFA status is the essential PUFA status index, which is the ratio between

all essential PUFA (the sum of all n-3 and n-6 fatty acids) and all nonessential unsaturated fatty acids (the sum of all n-7 and n-9 fatty acids). The higher the essential PUFA status index, the better the essential PUFA status. Finally, if there is a functional shortage of DHA, the body starts to synthesize the most comparable long-chain PUFA of the n-6 family, osbond acid (22:5n-6). Therefore, under steady state conditions, the ratio between DHA and osbond acid is a reliable indicator of the functional DHA status (Neuringer *et al.,* 1986).

CONCLUSION: Human immune cells are typically rich in arachidonic acid and poor in EPA and DHA. Arachidonic acid, EPA and DHA contents can be altered through oral administration of EPA and DHA and the incorporation of EPA and DHA occurs in a dose-dependent manner. These results in a change pattern of production of eicosanoids and probably also of resolvins, although the latter are not well examined in the human context. Changing the fatty acid composition of immune cells also affects phagocytosis, T cell signaling and antigen presentation capability. These effects appear to mediated at the membrane level suggesting important roles of fatty acids in membrane order, lipid raft structure and function and membrane trafficking. Thus, the fatty acid composition of human immune cells influences their function. The cell membrane contents of arachidonic acid, EPA and DHA are important. Fatty acids influence immune cell function through a variety of complex mechanisms and these mechanisms are now beginning to be ragged.

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