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Review

Arachidonic acid and other unsaturated fatty acids and some of their metabolites function as endogenous antimicrobial molecules: A review

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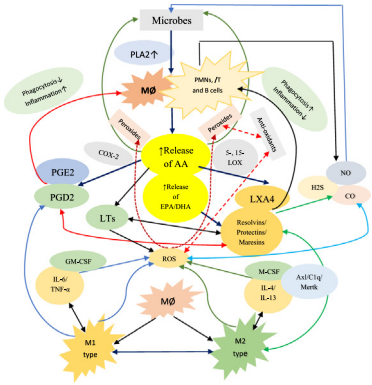
GRAPHICAL ABSTRACT

Scheme showing relationship among M1 and M2 macrophages, cytokines, bioactive lipids, eicosanoids and ROS.



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ABSTRACT

Our body is endowed with several endogenous anti-microbial compounds such as interferon, cytokines, free radicals, etc. However, little attention has been paid to the possibility that lipids could function as antimicrobial compounds. In this short review, the antimicrobial actions of various polyunsaturated fatty acids (PUFAs, mainly free acids) and their putative mechanisms of action are described. In general, PUFAs kill microbes by their direct action on microbial cell membranes, enhancing generation of free radicals, augmenting the formation of lipid peroxides that are cytotoxic, and by increasing the formation of their bioactive metabolites, such as prostaglandins, lipoxins, resolvins, protectins and maresins that enhance the phagocytic action of leukocytes and macrophages. Higher intakes of α-linolenic and cis-linoleic acids (ALA and LA respectively) and fish (a rich source of eicosapentaenoic acid and docosahexaenoic acid) might reduce the risk pneumonia. Previously, it was suggested that polyunsaturated fatty acids (PUFAs): linoleic, α-linolenic, γ-linolenic (GLA), dihomo-GLA (DGLA), arachidonic (AA), eicosapentaenoic (EPA), and docosahexaenoic acids (DHA) function as endogenous anti-bacterial, anti-fungal, anti-viral, anti-parasitic, and immunomodulating agents. A variety of bacteria are sensitive to the growth inhibitory actions of LA and ALA *in vitro*. Hydrolyzed linseed oil can kill methicillin-resistant *Staphylococcus aureus*. Both LA and AA have the ability to inactivate herpes, influenza, Sendai, and Sindbis virus within minutes of contact. AA, EPA, and DHA induce death of *Plasmodium falciparum* both *in vitro* and *in vivo*. Prostaglandin E1 (PGE1) and prostaglandin A (PGA), derived from DGLA, AA, and EPA inhibit viral

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replication and show anti-viral activity. Oral mucosa, epidermal cells, lymphocytes and macrophages contain and release significant amounts of PUFAs on stimulation. PUFAs stimulate NADPH-dependent superoxide production by macrophages, neutrophils and lymphocytes to kill the invading microorganisms. Cytokines induce the release of PUFAs from cell membrane lipid pool, a potential mechanism for their antimicrobial action. AA, EPA, and DHA give rise to lipoxins (LXs), resolvins, protectins, and maresins that limit and resolve inflammation and have antimicrobial actions. Thus, PUFAs and their metabolites have broad antimicrobial actions.

Introduction

It is evident that our body is constantly exposed to various pathogenic organisms and so our tissues need to be endowed with antimicrobial molecules to protect and ward off these exogenous potentially hazardous organisms. Some of these endogenous antimicrobial compounds include: interferon, cytokines, free radicals, etc., that are also yet times have harmful actions on various tissues. For instance, cytokines when produced in excess may cause tissue damage and sepsis. But relatively little attention is paid to the observation that certain lipids could have antimicrobial actions and thus, may serve as endogenous antibiotic-like actions. The importance of these antimicrobial lipids lies in the fact that they are present in all tissues of the body.

It is known that *Staphylococcus aureus* and coagulase-negative staphylococci, group A streptococci are present on normal human skin but do not cause any infection that could be attributed to the susceptibility of these bacteria to the action of skin surface lipids, especially unsaturated fatty acids. This is supported by the observation that group A streptococcus exposed to oleic acid (OA, 18:1n-9) showed decreased survival within 5 min of exposure showing condensation of the nucleoid and distortion of the streptococcal surface by numerous clumps and blebs indicating the ability of this fatty acid to alter the integrity of the cell membrane with loss of ribonucleic acid but not DNA [1]. M protein, located on the surface fimbriae of group A streptococci, is antiphagocytic in nature. Hence, the M− but not the M+ streptococci are not well phagocytized. On the other hand, oleic acid-killed and heat-killed streptococci (both M+ and M−) were readily phagocytized, while M+ streptococci killed by ultraviolet irradiation were inefficiently phagocytized. An extract of M protein reduced the bactericidal capacity of oleic acid, indicating that oleic acid may bind to and alter the M protein of group A streptococci and thus, enhance phagocytosis [2]. In addition, oleic acid enriched mouse peritoneal macrophages showed 3–4-fold greater erythrophagocytic capacity compared to palmitic acid-enriched macrophages [3].

Macrophage AA has antimicrobial actions

Our lungs are constantly exposed to various viruses, bacteria and fungal elements through inhaled air. Hence, efficient mechanisms are needed to protect lungs from various infections. For this purpose, alveolar macrophages need to have efficient mechanism of inducing antimicrobial action. It is known that Staphylococci in the alveoli are killed predominantly by macrophages [4–7]. Paradoxically, alveolar macrophages have poor chemotactic and phagocytic ability compared with peritoneal macrophages [8–10] and have weak intracellular killing activity *in vitro* [11,12]. Studies evaluating intraalveolar killing of staphylococci by use of a bronchoalveolar lavage technique revealed that inhaled staphylococci are killed mainly outside alveolar macrophages. Further studies in search of these extracellular bactericidal factors for pneumococci revealed that the surfactant fraction (55,000-g pellet) of leukocyte-free lavage of rats and other animal species contain heat and trypsin resistant factors that are rapidly bactericidal and lytic for pneumococci *in vitro* [12] and complete characterization of these extracellular bactericidal activity was found to reside in the surfactant lipids that can be stored at −70 °C in chloroform and stable indefinitely. The most anti-pneumococcal activity was found to reside in the most highly unsaturated acid namely arachidonic acid (AA, 20:4n-6). Other unsaturated fatty acids: linoleic, oleic, and palmitoleic also showed anti-bacterial activity but were less potent compared to AA. AA was found to be active against gram-positive and gram-negative bacteria [13–17], fungi [18,19], and enveloped viruses, including influenza [20–22]. The ability of unsaturated fatty acids including AA is further supported by the observation that polyunsaturated free fatty acids and lysolecithin in the small intestine of pigs can prevent proliferation of *Clostridium welchii* [23]. Human fecal lipids contain a mixture of long chain free fatty acids such as C16:0, C I8:1, C18:2, and C 20 or more, which are bactericidal for gonococci [24]. The mechanism of the antimicrobial action of AA seems to be by inducing leakage and even lysis of bacterial cell membranes [25,26] as well as various cellular metabolic effects, including but not limited to inhibition of respiratory activity, effects on transportation of amino acids, and uncoupling of oxidative phosphorylation [27–30].

These results suggest that alveolar macrophages release AA and other unsaturated fatty acids into the alveolar fluid that, in turn, exert their antimicrobial action and thus, protect lungs from various infective organisms. There is no reason to believe that this is not so even with macrophages in other body cavities and organs. Extending this argument further, it is reasonable to propose that even leukocytes including macrophage-like cells in various organs, T and B lymphocytes (in addition to their adaptive immune response) under some well-defined conditions may release unsaturated fatty acids to bring about their antimicrobial actions to protect from various infections. This could be one of the fundamental mechanisms employed by human body to protect itself from the onslaught of various microbes. It is noteworthy that even HIV could be inactivated by unsaturated fatty acids especially, AA [31].

Fatty acids can damage plasma membranes and thus, bring about their lethal effects on phytoplankton: chlorophytes (*Chlorella vulgaris Beij* and *Monoraphidium contortum* (Thur.) Kom.-Legn.) and a cyanobacterium *(Anabaena* P-9). When these organisms were treated with fatty acids, an elevation of extracellular potassium (K+) was detected in the culture medium, indicating leakage of intracellular K+ because of damage to the plasma membranes [32].

Phospholipase A(2) is an endogenous antibiotic

Type-IIA secreted phospholipase A(2) (sPLA(2)-IIA) releases AA from the cell membrane phospholipids. This implies that sPLA (2)-IIA could serve as a potent bactericidal protein. This enzyme is present in animal and human biological fluids at concentrations sufficient to kill bacteria. In fact, human recombinant sPLA(2)-IIA-induced release of PUFAs can kill Gram-positive bacteria at concentrations as low as 1.1 ng/ml. This property is ascribed to the preference of sPLA(2)-IIA for anionic phospholipids such as

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