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Essential fatty acids and acquired immunodeficiency syndrome

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Summary

Acquired immunodeficiency syndrome (AIDS) is caused by human immunodeficiency virus (HIV) that is characterized by profound immunodeficiency, opportunistic infections and Kaposi's sarcoma. As yet no effective therapy is available for AIDS, though retroviral drugs are able to prolong life and contain HIV proliferation to some extent. I propose that essential fatty acids (EFAs) and their metabolites could be useful in the prevention and management of AIDS. Linoleic acid (LA) and arachidonic acid (AA) inactivate enveloped viruses, linolenic acid-enriched macrophages are markedly tumoricidal, EFAs activate macrophages and neutrophils and induce free radical generation; and cytokines bring about some of their actions by inducing the release of EFAs; gamma-linolenic acid (GLA) and eicosapentaenoic acid (EPA) prevent genetic damage and have tumoricidal actions as well; and are relatively non-toxic when administered orally or parenterally over long periods of time. In view of this, I suggest that further studies with regard to the role of GLA, AA, EPA and/or docosahexaenoic acid (DHA) in the pathobiology of AIDS needs to be performed. It is also proposed that possible use of these fatty acids in the prevention and treatment of AIDS needs serious consideration.

key words: acquired immunodeficiency syndrome • essential fatty acids • enveloped viruses • cytokines • cachexia

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BACKGROUND

AIDS is caused by HIV [1]. It is estimated that the progression from initial infection to AIDS may take anywhere between 10–12 years. The hallmark of AIDS is a reduction in the number of CD4⁺ cells. On the other hand, some individuals who have been exposed to HIV infection remain apparently uninfected; they do not possess antibodies to HIV, and neither HIV nor its nucleic acids can be detected in their blood [2]. These individuals exhibit HIV-specific lymphoproliferation or cytotoxic T lymphocyte (CTL) activity. Based on these evidences, Salk et al. [2] suggested that the goal of immunization to prevent or control HIV infection should be activation of the cell-mediated, rather than antibody-mediated, arm of the immune system.

Because not all patients harboring HIV develop AIDS, there must be some host factor(s) that may play an important role in determining the response of a patient to an exposure to HIV. In addition, many patients with AIDS are wasted and the occurrence of opportunistic infections and tumors is preceded by weight loss and asthenia that in part is attributed to excess production of pro-inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α). Is it possible that there are some critical host factor(s) that have not been looked at or investigated that may have an important role in the treatment of AIDS? A cure may very well come from an approach that has not been considered yet. Finding such an approach will require open mindedness, a willingness to challenge accepted dogma, and a fresh look at AIDS. I propose that one of the host factor(s) that has not been closely looked at is the possible role of essential fatty acids (EFAs) and their metabolites in AIDS.

ESSENTIAL FATTY ACIDS

There are two main families of EFAs, the ω -6 derived from cis-linoleic acid (LA, 18: 2 ω -6) and the ω -3 from α -linolenic acid (ALA, 18: 3 ω -3). LA and ALA are present in our diet and their metabolism is given in Figure 1. The enzymes Δ^6 and Δ^5 desaturases and elongases involved in EFA metabolism are controlled by genetic, hormonal, and nutritional factors [3–5]. LA and ALA are EFAs; they cannot be made by the body, are essential nutrients, and hence, have to be obtained in the diet [4]. On the other hand, gamma-linolenic acid (GLA, 18: 3 ω -6), dihomo-GLA (DGLA, 20: 3 ω -6), and arachidonic acid (AA, 20: 4 ω -6) derived from LA and eicosapentaenoic acid (EPA, 20: 5 ω -3) and docosahexaenoic acid (DHA, 22: 6 ω -3) derived from ALA are termed as long-chain polyunsaturated fatty acids (PUFAs) and are non-essential fatty acids. But in the absence of LA and ALA; GLA, DGLA, AA, EPA, and DHA perform many of their (LA and ALA) functions and hence, are also called as functional EFAs. For easy reference and understanding all these fatty acids are referred to as EFAs.

There are many factors that modulate the activities of desaturases and elongases involved in the metabolism of EFAs [3–5]. Saturated fats, cholesterol, trans-fatty acids formed by vegetable oil processing, alcohol, adrenaline, and glucocorticoids inhibit Δ^6 and Δ^5 desaturases. Pyridoxine, zinc, and magnesium are necessary co-factors for normal Δ^6 desaturase activity. Insulin activates Δ^6 desaturase whereas diabetics have reduced Δ^6 desaturase activity. The activity of

Δ^6 desaturase falls with age. Oncogenic viruses and radiation inhibit Δ^6 desaturase activity and this may have relevance to the role of EFAs in AIDS.

ENVELOPED VIRUSES, IMMUNE RESPONSE AND EFAs

Kohn et al. [6] showed that LA and AA inactivate animal enveloped viruses such as myxoviruses, paramyxoviruses, arboviruses, and herpes viruses within minutes of contact. The viruses lost their infectivity under the influence of unsaturated free fatty acids when used at a concentration of 5–25 μ g/ml, a concentration that can be achieved in the plasma by oral supplementation of fatty acids. At these concentrations, the fatty acids are not harmful to animal host cells *in vitro*. These EFAs could disintegrate the viral envelope and thus, the viruses became ineffective. On the other hand, naked viruses such as polio, and SV40 are not affected by these fatty acids. GLA, EPA, and DHA may also possess similar capacity to inactivate HIV, which is incidentally an enveloped virus. Furthermore, both prostaglandin E₁ (PGE₁) and PGA₁ derived from DGLA have been shown to inhibit viral replication and act as anti-viral compounds [7,8].

Interferon (IFN) and other cytokines such as interleukin-1 (IL-1), IL-2, IL-6, and tumor necrosis factor- α (TNF- α) activate phospholipase A₂ (PLA₂) and induce the release of unsaturated fatty acids [9–16] and free radicals [17–19] in a variety of cells including tumor cells [20–24], and inhibitor studies suggested that the response is not mediated by a metabolite [17,20,22]. Gallagher and Curtis [25] showed that reactive oxygen intermediates stimulate lymphocytes mitotically, and activate human peripheral blood dendritic cells [26]. It is interesting to note that decreased oxidative burst activity of monocytes was observed in asymptomatic and symptomatic HIV-infected individuals [27–29].

Nitric oxide (NO), which is also a free radical, is produced by a variety of cells including leukocytes, endothelial cells, monocytes, macrophages, dendritic cells, Kupffer cells, and glial cells. Constitutive NO produced by endothelial cells is a vasodilator and has beneficial actions, whereas inducible NO (iNO) produced by macrophages and other immunocytes is cytotoxic to both normal and tumor cells. It is believed that excess production of NO (iNO) could be responsible for the neuronal damage seen in AIDS. NO regulates immune response [30] and is essential to inactivate HIV. It is possible that defective production of NO in the cells that are infected by HIV and its (NO) excess production in neuronal cells are responsible for the progression of the disease and central nervous system manifestations. NO is known to inhibit HIV, inactivate HIV-1 encoded protease and reverse transcriptase *in vitro* [31]. In this context, it is interesting to note that EFAs have the ability to enhance endothelial (constitutive) NO [32], and inhibit iNO generation, and show anti-inflammatory actions [33].

Schlager et al. [34,35] demonstrated that mouse peritoneal macrophages can be activated by linolenic acid (ALA) and that cytokine activation of macrophages is accompanied by 2 to 3 fold increase in their linolenic acid content over the control. They also showed that linolenic acid-enriched macrophages are markedly tumoricidal. Based on these studies, it is reasonable to suggest that cytokines and EFAs (and their metabolites) activate neutrophils, macrophages and

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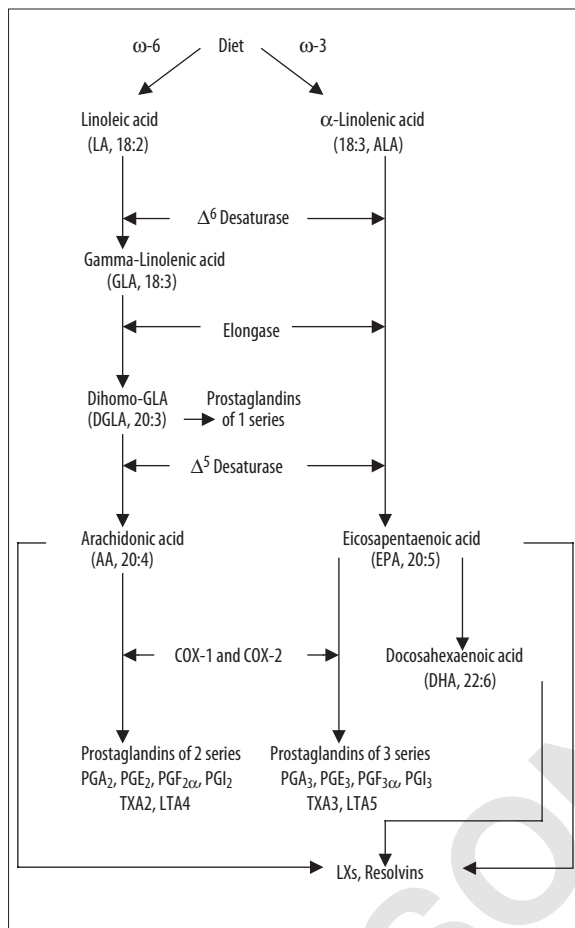


Figure 1. Scheme showing metabolism of essential fatty acids and their metabolites. Resolvins are a group of substances formed from AA, EPA, and DHA that have anti-inflammatory action and inhibit leukocyte migration. Resolvins are involved in the resolution of inflammation.

NK cells and these activated cells release free radicals and NO to produce their cytotoxic action on tumor and virus-infected cells.

EFAs AND TUMOR CELLS

Earlier my colleagues and I showed that GLA, AA, EPA, and DHA have selective tumoricidal actions both *in vitro* and *in vivo* [22,36–40]. Several others confirmed these findings [23,24,41–48]. These fatty acids seem to bring about their tumoricidal action by enhancing free radical generation in the tumor cells, whereas the formation of their cyclo-oxygenase and lipoxygenase products are not necessary for their selective cytotoxic action on tumor cells [20,22,46].

In addition, GLA and EPA have anti-mutagenic actions as well [49–51]. Prostaglandin E_1 (PGE_1) derived from DGLA (that in turn is formed from GLA), prevented genetic damage induced by radiation, benzo (a) pyrene and diphenylhydantoin. This suggests that presence of adequate amounts of GLA and EPA in the cells protects them from the DNA-damaging actions of various mutagens and carcinogens. Hence, it is likely that damage to DNA cannot be prevented and tumor cells are not eliminated when cells are de-

ficient in EFAs. This may lead to an increase in the risk of cancer [52].

ANTI-INFLAMMATORY LIPOXINS AND RESOLVINS FROM EFAs

AA not only forms precursor to pro-inflammatory compounds such as TXs and LTs and beneficial PGI_2 but also gives rise to LXs (see Figure 1). In the presence of non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin; AA, EPA and DHA are converted to form aspirin-triggered 15 epimer LXs (ATLs) that are potent inhibitors of polymorphonuclear neutrophils (PMNs)-mediated injury and acute inflammation [53,54]. Acetylation of cyclo-oxygenase-2 (COX-2) by aspirin prevents the formation of prostanoids, but the acetylated enzyme remains active *in situ* to generate 15R-hydroxyeicosatetraenoic acid (15R-HETE) from AA that is released and converted by activated PMNs to the 15-epimeric LXs. These LXs have potent anti-inflammatory properties [54–56]. This cross-talk between endothelial cells and PMNs that leads to the formation of 15R-HETE and its subsequent conversion to 15-epimeric LXs by aspirin-acetylated COX-2 is a protective mechanism to prevent local inflammation by regulating the motility of PMNs, eosinophils, and monocytes [57–59]. Furthermore, endothelial cells oxidize AA (and possibly EPA and DHA) via P450 enzyme system to form 11,12-epoxy-eicosatetraenoic acid(s) that blocks endothelial cell activation [60].

Studies revealed that beneficial 15R-HETE and 15-epimeric LXs are formed not only from AA but that EPA and DHA may also form precursor to similar compounds. Activated human endothelial cells, pulsed with EPA and treated with aspirin, converted EPA to 18R-HEPE, 18-HEPE, and 15R-HEPE. Similar to the ability of PMNs to convert aspirin triggered, COX-2 derived 15R-HETE to 15-epi-LXA₄ and EPA to 5-series LXs, activated human PMNs converted 18R-HEPE to 5,12,18R-triHEPE and 15R-HEPE to 15-epi-LXA₃ by their 5-lipoxygenase. Both 18R-HEPE and 5,12,18R-triHEPE inhibited LTB_4 -stimulated PMN transendothelial migration similar to 15-epi-LXA₄. 5,12,18R-triHEPE effectively competed with LTB_4 for its receptors and inhibited PMN infiltration suggesting that it can suppress LT-mediated responses if present in adequate amounts at the sites of inflammation.

Murine brain cells expressing COX-2, when treated with aspirin, transformed enzymatically DHA to 17R series of hydroxy DHAs (HDHAs) that, in turn, is converted enzymatically by PMNs to di- and tri-hydroxy containing docosanoids [61]. Similar small molecular weight compounds (similar to HDHAs) are generated from AA and EPA. Thus, 15R-hydroxy containing compounds are formed from AA, 18R series from EPA, and 17R-hydroxy series from DHA (see Figure 1). All these compounds have potent anti-inflammatory actions and are involved in resolution of the inflammatory process and hence have been termed as “resolvins” (Rvs). Resolvins inhibit cytokine generation, leukocyte recruitment, leukocyte diapedesis, and exudate formation and are potent suppressors of inflammation. This is supported by the observation that resolvins inhibit brain ischemia-reperfusion injury [62]. Based on these observations, it is likely that formation of adequate amounts of lipoxins and resolvins from EPA and DHA (and possibly from AA) inhibit inflammation and prevents damage to tissues that may have relevance to the role of EFAs in the pathobiology of AIDS.

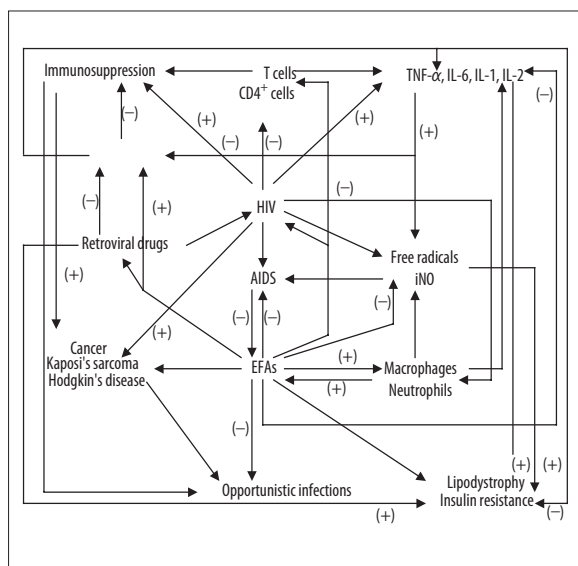


Figure 2. Scheme showing possible relationship between HIV, AIDS, and EFAs. (-) Indicates inhibition of activity, process or synthesis. (+) Indicates increase in activity, process or synthesis. HIV induces apoptosis of CD4⁺ cells and thus causes immunosuppression that leads to opportunistic infections and increased incidence of cancer in patients with AIDS. Retroviral drugs suppress adiponectin production and causes lipodystrophy and insulin resistance. Patients with AIDS have low plasma concentrations of EFAs, increased levels of TNF- α , and produce decreased amounts of free radicals. EFAs inactivate enveloped viruses, suppress TNF- α production, have antibiotic-like actions, activate macrophages and neutrophils, selectively kill tumor cells, and thus, may ameliorate AIDS and its associated manifestations. For further details see text.

EFAs AND AIDS

It is evident from the preceding discussion that EFAs and their metabolites inactivate enveloped viruses, prevent damage to DNA and eliminate tumor cells when present in adequate amounts in the cells. These fatty acids activate macrophages, neutrophils, and NK cells and induce the generation of free radicals and NO to bring about their tumoricidal and anti-bacterial, anti-viral and anti-fungal actions [63]. Even cytokines such as TNF- α , IFN, and ILs seem to bring about most, if not all, of their actions by inducing their release of EFAs and their metabolites. Presence of adequate amounts of various EFAs in the target tissues may also ensure production of sufficient concentrations of LXs and resolvins that are essential for resolving inflammation. In view of this, it is likely that a deficiency of EFAs increases the susceptibility of an individual to various infections including HIV (Figure 2). The finding that plasma concentrations of ω -6 and ω -3 EFAs and their metabolites are significantly lower in patients with AIDS [64–66] supports this proposal.

TESTING THE HYPOTHESIS AND CONCLUSIONS

Based on the preceding discussion, it is hypothesized that AIDS is more common in individuals who have a relative deficiency of EFAs. In other words, a quantitative or qualitative deficiency of EFAs renders an individual more susceptible to

develop AIDS [67]. If the proposals made here are true, it is likely that plasma, red blood cell (RBC) membrane and tissue concentrations of EFAs, and LXs and resolvins will be low in patients with AIDS. It is possible that the plasma/RBCs concentrations of EFAs and LXs and resolvins may be normal in some, if not all. This does not necessarily counter the arguments presented here since the concentrations of these fatty acids and LXs and resolvins are more likely to be low in the affected tissues rather than in the plasma and RBCs. Hence, it is necessary that the concentrations of EFAs, LXs and resolvins should be measured in the biopsy specimens of the tissues. It is essential to study the effect of various EFAs, LXs, and resolvins on the survival of HIV to determine which of the EFAs are the most effective in inactivating the virus.

EFAs have other actions that could be of benefit in AIDS. For instance, EFAs, LXs and resolvins suppress IL-1, IL-2, IL-6, and TNF- α production by T cells [68–71], and thus function as endogenous anti-inflammatory molecules. IL-1, IL-6, and TNF- α have been shown to stimulate HIV proliferation *in vitro* [72]. Thus, one mechanism by which EFAs suppress HIV replication is by inhibiting the production of these cytokines in addition to their ability to directly inactivate the virus. Wasting seen in patients with AIDS is due to excess production of TNF and other pro-inflammatory cytokines [73]. EPA, and other EFAs are known to ameliorate cachexia induced by TNF in animal tumor models [74,75]. Since EFAs have anti-bacterial, anti-parasitic, anti-viral, and anti-fungal actions [6,63,76–81], this may explain why opportunistic infections are common in patients with AIDS (this is in addition to the immunosuppression seen in them), suggesting that supplementation of EFAs may prevent these infections. I propose that EFAs by themselves and/or in combination with various anti-retroviral agents may be useful in the treatment of AIDS. Currently available retroviral agents induce lipodystrophy and insulin resistance and this has been associated with increased levels of TNF- α and decreased concentrations of adiponectin [82,83]. EFAs are known to prevent/reverse insulin resistance [84–86] by decreasing TNF- α levels and possibly, by enhancing adiponectin levels. Thus, EFAs are also predicted to be useful in preventing and/or reversing some of the side effects of retroviral drugs. Parenteral solutions of EFAs can be prepared easily for administration to patients. EFAs are relatively non-toxic, inexpensive, and are readily available for use in the clinic. Before embarking on such clinical studies obviously more studies are needed to know the role of EFAs and their metabolites in AIDS. If this hypothesis is true, oral or parenteral administration of these fatty acids may help to prevent, retard the progression or cure AIDS.

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