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**Long-chain polyunsaturated fatty acids and the pathophysiology of myalgic
encephalomyelitis (chronic fatigue syndrome)**

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Abstract

Evidence is put forward to suggest that myalgic encephalomyelitis, also known as chronic fatigue syndrome, may be associated with persistent viral infection. In turn, such infections are likely to impair the ability of the body to biosynthesize *n*-3 and *n*-6 long-chain polyunsaturated fatty acids by inhibiting the delta-6 desaturation of the precursor essential fatty acids alpha-linolenic acid and linoleic acid. In turn, this would impair the proper functioning of cell membranes, including cell signalling, and have an adverse effect of the biosynthesis of eicosanoids from the long-chain polyunsaturated fatty acids dihomo- γ -linolenic acid, arachidonic acid and eicosapentaenoic acid. These actions might offer an explanation for some of the symptoms and signs of myalgic encephalomyelitis. A potential therapeutic avenue may be offered by bypassing the inhibition of the enzyme delta-6-desaturase by administering both virgin cold-pressed non-raffinated evening primrose oil and eicosapentaenoic acid. The former would supply gamma-linolenic acid and lipophilic pentacyclic triterpenes. The gamma-linolenic acid can readily be converted into dihomo- γ -linolenic acid and thence arachidonic acid, while triterpenes have important free radical scavenging, cyclooxygenase and neutrophil elastase inhibitory activities. Furthermore, both arachidonic acid and eicosapentaenoic acid are, at relatively low concentrations, directly virucidal.

The aetiology of myalgic encephalomyelitis (chronic fatigue syndrome) is currently not known. In this paper, evidence is adduced to show the key role of certain long-chain polyunsaturated fatty acids in the pathophysiology of this illness. First, evidence is provided which suggests a viral aetiology. Second, the effects of such viral infections on the human biosynthetic pathways for long-chain polyunsaturated fatty acids is considered. Third, the subsequent effects on membrane phospholipids and the immune system are described. Finally, therapeutic implications are outlined.

VIRAL AETIOLOGY

Several converging lines of evidence point to a viral aetiology for myalgic encephalomyelitis.

First, many clinical features of epidemics of myalgic encephalomyelitis-like illnesses such as the Los Angeles County Hospital epidemic of 1934 and the Royal Free Hospital epidemic of 1955 are consistent with viral infections.[1]

Second, immune system changes in myalgic encephalomyelitis tend to point to reduced NK cell activity, reduced Th1 cell activity, increased Th2 cell activity and increased Tc cell activity.[1-6] These findings are consistent with a pre-existing long-term viral infection. Although these findings are also consistent with an autoimmune response, there is little consistent evidence to support this possibility in myalgic encephalomyelitis.

The third line of evidence relates to blood fatty acid levels. As we shall see in the next two sections, viral infections can impair the ability of the mammalian body to biosynthesize long-chain polyunsaturated fatty acids from their short-chain precursors. In their baseline comparison of erythrocyte membrane fatty acid levels between 63 patients (with what was then termed postviral fatigue syndrome) and 32 normal volunteers, Behan *et al.* found significantly lower levels of arachidonic acid and adrenic acid and of the total *n*-6 polyunsaturated fatty acids.[7] A more recent study using the Oxford Criteria for diagnosis found a significantly lower level of eicosapentaenoic acid in patients with chronic fatigue syndrome.[8]

The fourth line of evidence comes from proton neurospectroscopy studies. As we shall see in the next section, viral infections can prevent the body from biosynthesizing long-chain polyunsaturated fatty acids. In turn, this impairs the biosynthesis of membrane phospholipid molecules in the brain, since long-chain polyunsaturated fatty acids are key components at the Sn2 position of these molecules. This leads to a reduced incorporation of the polar head group choline in these molecules (at the Sn3 position). Hence we should expect to see evidence of a raised level of free choline in the brain, which can be assessed using proton neurospectroscopy.[9] This is indeed the finding from the first two systematic proton neurospectroscopy studies thus far published in myalgic encephalomyelitis or chronic fatigue syndrome, namely the one by our group and that by the Glasgow group then headed by Chaudhuri.[10,11] Furthermore, a Japanese case series of three children with juvenile myalgic encephalomyelitis has also reported a raised level of the choline peak on proton neurospectroscopy.[12]

The most recent evidence comes from an elegant study by Jonathan Kerr's group.[13] They studied gene expression in peripheral blood mononuclear cells in 25 patients with chronic fatigue syndrome compared with 25 normal blood donors matched for age, gender and geographical location. One of their findings was upregulation of the

mitochondrial translation initiation factor EIF4G1 transcript variant 5, a result which is consistent with a persistent virus infection.

EFFECTS ON BIOSYNTHETIC PATHWAYS FOR LONG-CHAIN POLYUNSATURATED FATTY ACIDS

The first step in humans in the biosynthesis of *n*-6 long-chain polyunsaturated fatty acids from the 18-carbon short-chain essential fatty acid precursor linoleic acid is catalyzed by the enzyme delta-6-desaturase.[1] Similarly, the biosynthesis of *n*-3 long-chain polyunsaturated fatty acids from the 18-carbon short-chain essential fatty acid precursor alpha-linolenic acid is also catalyzed by delta-6-desaturase.[1] Back in 1935, Stoesser reported that acute viral infections were associated with a reduction in the levels of long-chain polyunsaturated fatty acids.[14] That the cause of this was the ability of many viral species to inhibit the delta-6 desaturation of the precursor short-chain essential fatty acids was discovered four decades later by Dunbar and Bayley.[15,16].

EFFECTS ON MEMBRANE PHOSPHOLIPIDS AND THE IMMUNE SYSTEM

The fundamental building block of the lipid bilayers of outer cell membranes and of many intracellular organelles is the phospholipid molecule. Based on a three-carbon glycerol backbone, in normal membranes the middle carbon (the Sn2 position) should have a long-chain polyunsaturated fatty acid attached to it. This is usually either the *n*-6 long-chain polyunsaturated fatty acid arachidonic acid or the *n*-3 long-chain polyunsaturated fatty acid docosahexaenoic acid. Attached ultimately to the Sn3 position is a polar head group, such as choline, ethanolamine, serine or inositol. As a result of viral, or other, inhibition of delta-6-desaturase, an inadequate supply of the long-chain polyunsaturated fatty acids is available for incorporation into membrane phospholipid molecules. Thus the ratio of anabolism to catabolism of membrane phospholipids can be expected to alter in an adverse direction. In turn, so far as the brain is concerned, this may be expected to have an unfavourable effect on neurotransmission; for example it has been demonstrated that minor changes in fatty acid structure in a very small proportion of membrane phospholipids can lead to profound changes in the tertiary and quaternary structures of membrane proteins, and in the functioning of such proteins.[17,18]

As mentioned above, changes in free choline can be measured *in vivo* using proton neurospectroscopy. Changes in membrane phospholipid metabolism may also be indexed using 31-phosphorus neurospectroscopy.[9]

In addition to the adverse effects on membrane structure and functioning caused by delta-6-desaturase inhibition, there are also negative consequences with respect to the biosynthesis of eicosanoids, such as prostaglandins, leukotrienes and thromboxanes, since these require long-chain polyunsaturated fatty acids such as arachidonic acid and eicosapentaenoic acid as their precursors.[1] In turn, this can compromise the functioning of the immune system.

THERAPEUTIC IMPLICATIONS

Inhibition of delta-6-desaturase can be bypassed by administering a combination of evening primrose oil, which supplies the *n*-6 long-chain polyunsaturated fatty acid gamma-linolenic acid, from which dihomo- γ -linolenic acid and arachidonic acid can be biosynthesized, and the *n*-3 long-chain polyunsaturated fatty acid eicosapentaenoic acid.

A further advantage of giving this combination relates to the finding that arachidonic acid and eicosapentaenoic acid, in addition to being precursors of many eicosanoids, are also directly virucidal at relatively low levels, for example inactivating lipid-enveloped viruses.[19,20] Furthermore, the antiviral actions of interferon may also require its activation of the conversion, catalyzed by cyclooxygenase, of dihomono- γ -linolenic acid and arachidonic acid into eicosanoids.[21]

If administering this regime, there are advantages in using virgin, cold-pressed non-refined evening primrose oil rather than the more commonly available refined preparation, as the former is rich in lipophilic pentacyclic triterpenes, which have free radical scavenging, cyclooxygenase and neutrophil elastase inhibitory properties.[22]

CONCLUSION

There is evidence that myalgic encephalomyelitis or chronic fatigue syndrome may be associated with a persistent viral infection. Such an infection could adversely impact on the biosynthesis of long-chain polyunsaturated fatty acids and therefore on membrane structure and functioning and the production of eicosanoids. Administration of long-chain polyunsaturated fatty acids may offer a potential therapeutic route.

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