REVIEW

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

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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 biosynthesise n-3 and n-6 long-chain polyunsaturated fatty acids by inhibiting the δ-6 desaturation of the precursor essential fatty acids—namely, α-linolenic acid and linoleic acid. This would, in turn, impair the proper functioning of cell membranes, including cell signalling, and have an adverse effect on 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 could be offered by bypassing the inhibition of the enzyme δ-6-desaturase by treatment with virgin cold-pressed non-raffinated evening primrose oil, which would supply γ-linolenic acid and lipophilic pentacyclic triterpenes, and with eicosapentaenoic acid. The γ-linolenic acid can readily be converted into dihomo-γ-linolenic acid and thence arachidonic acid, while triterpenes have important free radical scavenging, cyclo-oxygenase and neutrophil elastase inhibitory activities. Furthermore, both arachidonic acid and eicosapentaenoic acid are, at relatively low concentrations, directly virucidal.

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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 disease. Firstly, evidence suggesting a viral aetiology is provided. Secondly, the effects of such viral infections on the human biosynthetic pathways for long-chain polyunsaturated fatty acids are considered. Thirdly, 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.

Firstly, 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]

Secondly, immune system changes in myalgic encephalomyelitis tend to point to reduced natural killer cell activity, reduced Th1 cell activity, increased Th2 cell activity and increased cytotoxic T cell activity.[1–6] These findings are consistent with those of 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 described later, viral infections can impair the ability of the mammalian body to biosynthesise long-chain polyunsaturated fatty acids from their short-chain precursors. In the baseline comparison of erythrocyte membrane fatty acid levels among 63 patients (with what was then termed postviral fatigue syndrome) and 32 normal volunteers, Behan *et al*[7] found considerably lower levels of arachidonic acid, adrenic acid and the total n-6 polyunsaturated fatty acids. Warren *et al*[8] used the Oxford Criteria for diagnosis and found a considerably lower level of eicosapentaenoic acid in patients with chronic fatigue syndrome.

The fourth line of evidence comes from proton neurospectroscopy studies. As described in the next section, viral infections can prevent the body from biosynthesising long-chain polyunsaturated fatty acids. In turn, this impairs the biosynthesis of membrane phospholipid molecules in the brain, as 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 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 on myalgic encephalomyelitis or chronic fatigue syndrome—one by our group[10] and the other by the Glasgow group then headed by Chaudhuri.[11] Furthermore, in their report of a Japanese case series of three children with juvenile myalgic encephalomyelitis, Tomoda *et al*[12] have also reported a raised level of the choline peak on proton neurospectroscopy.[12]

The most recent evidence comes from an elegant study by Kaushik *et al*.[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, sex and geographical location. One of their findings was up regulation of the mitochondrial translation initiation factor EIF4G1 transcript variant 5: a result that 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 catalysed by the enzyme δ-6-desaturase.[1] Similarly, the biosynthesis of n-3 long-chain polyunsaturated fatty acids from the 18-carbon short-chain essential fatty acid precursor α-linolenic acid is also catalysed by δ-6-desaturase.[1] Back in 1935, Stoesser[14] reported that acute viral infections were associated with a reduction in the levels of long-chain polyunsaturated fatty acids. That the cause of this reduction was the ability of many viral species to inhibit the δ-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 phospholipid molecule is the fundamental building block of the lipid bilayers of outer cell membranes and of many intracellular organelles. Based on a 3-carbon glycerol backbone, in normal membranes, the middle carbon (the Sn2 position) should have a long-chain polyunsaturated fatty acid attached to it, which is usually either the n-6 arachidonic acid or the n-3 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 δ-6-desaturase, an inadequate supply of the long-chain polyunsaturated fatty acids is available for incorporation into the membrane phospholipid molecules. Thus the ratio of anabolism to catabolism of membrane phospholipids can be expected to change in an adverse direction. In turn, as far as the brain is concerned, this may be expected to have an unfavourable effect on neurotransmission—for example, it has been shown that minor changes in fatty acid structure in a 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 the membrane phospholipid metabolism may also be indexed using phosphorus-31 neurospectroscopy.[9]

In addition to the adverse effects on membrane structure and functioning caused by inhibition of δ-6-desaturase, there are also negative consequences with respect to the biosynthesis of eicosanoids, such as prostaglandins, leucotrienes and thromboxanes, as 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 δ-6-desaturase can be bypassed by treatment with a combination of evening primrose oil, which supplies the n-6 long-chain polyunsaturated fatty acid γ-linolenic acid, from which dihomo-γ-linolenic acid and arachidonic acid can be biosynthesised, and the n-3 long-chain polyunsaturated fatty acid eicosapenteanoic acid.

A further advantage of treatment with 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, by inactivating lipid-enveloped viruses.[19 20] Furthermore, the antiviral actions of interferons may also require the activation of the conversion, catalysed by cyclo-oxygenase, of dihomo-γ-linolenic acid and arachidonic acid into eicosanoids.[21]

In administering this regimen, it is more advantageous to use virgin, cold-pressed non-raffinated evening primrose oil rather than the more commonly available refined preparation, as the virgin evening primrose oil is rich in lipophilic pentacyclic triterpenes, which have free radical scavenging, cyclo-oxygenase and neutrophil elastase inhibitory properties.[22]

Take-home messages

- Myalgic encephalomyelitis (chronic fatigue syndrome) may result from a persistent viral infection.
- It is worthwhile trying a course of ultra-pure EPA with virgin evening primrose oil in patients.
- A daily dose of between two and eight VegEPA capsules should be tried for at least 3 to 6 months.
- Vitamin cofactors which may be helpful when using fatty acid treatment include biotin, niacin, folic acid, vitamin B6, vitamin B12 and vitamin C.
- Mineral cofactors which may be helpful when using fatty acid treatment include selenium, zinc and magnesium.

CONCLUSION

Evidence suggests that myalgic encephalomyelitis or chronic fatigue syndrome may be associated with a persistent viral infection. Such an infection could adversely affect the biosynthesis of long-chain polyunsaturated fatty acids and therefore the membrane structure, functioning and production of eicosanoids. Treatment with long-chain polyunsaturated fatty acids may offer a potential therapeutic route.

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REFERENCES

1 **Puri BK**. *Chronic fatigue syndrome*. London: Hammersmith Press, 2005.
2 **Caligiuri M**, Murray C, Buchwald D, *et al*. Phenotypic and functional deficiency of natural killer cells in patients with chronic fatigue syndrome. *J Immunol* 1987;**139**:3306–13.
3 **Klimas NG**, Salvato FR, Morgan R, *et al*. Immunologic abnormalities in chronic fatigue syndrome. *J Clin Microbiol* 1990;**28**:1403–10.
4 **Tirelli V**, Pinto A, Marotta G, *et al*. Clinical and immunologic study of 205 patients with chronic fatigue syndrome: a case series from Italy. *Arch Intern Med* 1993;**153**:116–20.
5 **Visser J**, Blauw B, Hinloopen B, *et al*. CD4 T lymphocytes from patients with chronic fatigue syndrome have decreased interferon-gamma production and increased sensitivity to dexamethasone. *J Infect Dis* 1998;**177**:451–4.
6 **Skowera A**, Cleare A, Blair D, *et al*. High levels of type 2 cytokine-producing cells in chronic fatigue syndrome. *Clin Exp Immunol* 2004;**135**:294–302.
7 **Behan PO**, Behan WMH, Horrobin D. Effect of high doses of essential fatty acids on the postviral fatigue syndrome. *Acta Neurol Scand* 1990;**82**:209–16.
8 **Warren G**, McKendrick M, Peet M. The role of essential fatty acids in chronic fatigue syndrome. *Acta Neurol Scand* 1999;**99**:112–16.
9 **Puri BK**. Proton and 31-phosphorus neurospectroscopy in the study of membrane phospholipids and fatty acid intervention in schizophrenia, depression, chronic fatigue syndrome (myalgic encephalomyelitis) and dyslexia. *Int Rev Psychiatry* 2006;**18**:145–7.

10 **Puri BK**, Counsell SJ, Zaman R, *et al*. Relative increase in choline in the occipital cortex in chronic fatigue syndrome. *Acta Psychiatr Scand* 2002;**106**:224–6.
11 **Chaudhuri A**, Condon BR, Gow JW, *et al*. Proton magnetic resonance spectroscopy of basal ganglia in chronic fatigue syndrome. *Neuroreport* 2003;**14**:225–8.
12 **Tomoda A**, Miike T, Yamada E, *et al*. Chronic fatigue syndrome in childhood. *Brain Dev* 2000;**22**:60–4.
13 **Kaushik N**, Fear D, Richards SCM, *et al*. Gene expression in peripheral blood mononuclear cells from patients with chronic fatigue syndrome. *J Clin Pathol* 2005;**58**:826–32.
14 **Stoesser AV**. Effect of acute infection on iodine number of serum fatty acids. *Proc Soc Exp Biol Med* 1935;**32**:1326–7.
15 **Dunbar IM**, Bayley JM. Enzyme deletions and essential fatty acid metabolism in cultured cells. *J Biol Chem* 1975;**250**:1152–4.
16 **Bayley JM**. Lipid metabolism in cultured cells. In: F Snyder, eds. *Metabolism in mammals*.Vol II. New York: Plenum Press, 1977:352–64.
17 **Witt MR**, Nielsen M. Characterisation of the influence of unsaturated free fatty acids on brain GABA/benzodiazepine receptor binding in vitro. *J Neurochem* 1994;**62**:1432–9.
18 **Cordero-Erausquin M**, Marubio LM, Klink R, *et al*. Nicotinic receptor function: new perspectives from knockout mice. *Trends Pharmacol Sci* 2000;**21**:211–17.
19 **Sands J**, Auperin D, Snipes W. Extreme sensitivity of enveloped viruses, including herpes simplex, to long-chain unsaturated monoglycerides and alcohols. *Antimicrob Agents Chemother* 1979;**15**:67–73.
20 **Horowitz B**, Piet MP, Prince AM, *et al*. Inactivation of lipid-enveloped viruses in labile blood derivatives by unsaturated fatty acids. *Vox Sang* 1988;**54**:14–20.
21 **Karmazyn M**, Horrobin DF, Manku MS, *et al*. Interferon fever. *Lancet* 1977;**2**:307.
22 **Puri BK**. The clinical advantages of cold-pressed non-raffinated evening primrose oil over refined preparations. *Med Hypotheses* 2004;**62**:116–18.