



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

Basant K Puri

J. Clin. Pathol. published online 25 Aug 2006;
doi:10.1136/jcp.2006.042424

Updated information and services can be found at:
<http://jcp.bmjournals.com/cgi/content/abstract/jcp.2006.042424v1>

These include:

Rapid responses

You can respond to this article at:
<http://jcp.bmjournals.com/cgi/eletter-submit/jcp.2006.042424v1>

Email alerting service

Receive free email alerts when new articles cite this article - sign up in the box at the top right corner of the article

Notes

Online First contains unedited articles in manuscript form that have been peer reviewed and accepted for publication but have not yet appeared in the paper journal (edited, typeset versions may be posted when available prior to final publication). Online First articles are citable and establish publication priority; they are indexed by PubMed from initial publication. Citations to Online First articles must include the digital object identifier (DOIs) and date of initial publication.

To order reprints of this article go to:
<http://www.bmjournals.com/cgi/reprintform>

To subscribe to *Journal of Clinical Pathology* go to:
<http://www.bmjournals.com/subscriptions/>

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

BK Puri

MRC Clinical Sciences Centre, Imperial College London, Hammersmith Hospital,
London UK

Correspondence to:

Professor BK Puri, MRI Unit, Hammersmith Hospital, Du Cane Road, London W12

0HS, England, UK

basant.puri@csc.mrc.ac.uk

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-refined 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.

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**:3306-3313.
3. Klimas NG, Salvato FR, Morgan R, *et al*. Immunologic abnormalities in chronic fatigue syndrome. *J Clin Microbiol* 1990;**28**:1403-1410.
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**:116-120.
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**:451-454.
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**:209-216.
8. Warren G, McKendrick M, Peet M. The role of essential fatty acids in chronic fatigue syndrome. *Acta Neurol Scand* 1999;**99**:112-116.
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**:145-147.
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**:224-226.
11. Chaudhuri A, Condon BR, Gow JW, *et al*. Proton magnetic resonance spectroscopy of basal ganglia in chronic fatigue syndrome. *Neuroreport* 2003;**14**: 225-228.

12. Tomoda A, Miike T, Yamada E, *et al.* Chronic fatigue syndrome in childhood. *Brain Dev* 2000;**22**:60-64.
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**:826-832.
14. Stoesser AV. Effect of acute infection on iodine number of serum fatty acids. *Proc Soc Exp Biol Med* 1935;**32**:1326-1327.
15. Dunbar IM, Bayley JM. Enzyme deletions and essential fatty acid metabolism in cultured cells. *J Biol Chem* 1975;**250**:1152-1154.
16. Bayley JM. Lipid metabolism in cultured cells. In: F Snyder (ed.) *Metabolism in Mammals, Volume II*. Plenum Press, New York 1977, pp. 352-364.
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**:1432-1439.
18. Cordero-Erausquin M, Marubio LM, Klink R, *et al.* Nicotinic receptor function: new perspectives from knockout mice. *Trends Pharmacol Sci* 2000;**21**:211-217.
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**:116-118.

"The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, an exclusive licence (or non-exclusive for government employees) on a worldwide basis to the BMJ Publishing Group Ltd and its Licensees to permit this article (if accepted) to be published in JCP and any other BMJ PGL products to exploit all subsidiary rights, as set out in our licence."