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Can perinatal supplementation of long-chain polyunsaturated fatty acids prevents schizophrenia in adult life?

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Summary

It is suggested that perinatal supplementation of long-chain polyunsaturated fatty acids (LCPUFAs) especially; eicosapentaenoic and docosahexaenoic acids prevent schizophrenia in the adult. I propose that schizophrenia could be a low-grade systemic inflammatory disease with its origins in the perinatal period, probably triggered by maternal infection in a genetically susceptible individual that leads to excess production of pro-inflammatory cytokines both in the mother and the fetus. These cytokines, in turn, induce damage to the fetal neurons leading to the adult onset of schizophrenia. I suggest that maternal infection perse interferes with the metabolism of essential fatty acids (EFAs) resulting in deficiency of LCPUFAs that are known to have neuroprotective action. Alternatively, decreased formation of LCPUFAs as a result of decreased activity of D6 and D5 desaturases (due to prematurity) can result in neuronal damage due to the absence/decrease in the neuroprotective LCPUFAs. This is supported by the observation that LCPUFAs suppress the production of pro-inflammatory cytokines, have anti-inflammatory and neuroprotective actions. Furthermore, LCPUFAs are essential for brain growth and development. If this hypothesis is true, it implies that perinatal supplementation of appropriate amounts of LCPUFAs in the right combination is helpful in the prevention of schizophrenia in adult life.

key words: **schizophrenia • essential fatty acids • long-chain polyunsaturated fatty acids • cytokines • interleukin • tumor necrosis factor • neuron • dopamine • neuroprotection**

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BACKGROUND

Schizophrenia is common and is characterized by delusions, hallucinations, disorganized speech (e.g., frequent derailment or incoherence), grossly disorganized or catatonic behavior, negative symptoms, i.e., affective flattening, alogia, or avolition, and social/occupational dysfunction. Despite many years of research, the exact cause and aetiopathogenesis of schizophrenia is not clear. It has been suggested that the symptoms of schizophrenia may result from altered neuronal membrane structure and metabolism [1]. Dysregulation of the inflammatory response system has also been linked to pathophysiology of schizophrenia [2]. There is reasonable evidence in support of these two proposals.

PRENATAL IMMUNE EVENTS, CYTOKINES, AND SCHIZOPHRENIA

Recent studies suggested that mice born to mothers who had respiratory tract infection at mid-gestation show features of schizophrenia [3]. This coupled with the observation that prenatal immune challenge disrupts sensorimotor gating in adult rats that was reversed by antipsychotics and that serum levels of interleukins-2 (IL-2) [4] and IL-6 were increased suggests that prenatal immune events may play a role in the aetiopathogenesis of schizophrenia [5]. Several recent studies suggested that there are specific immunological abnormalities in schizophrenia.

Serum and cerebrospinal fluid (CSF) IL-2, IL-6, IL-8 and tumor necrosis factor-α (TNF-α) levels are elevated in patients with schizophrenia [6–10]. Relapse-prone patients, examined both while medicated and after drug withdrawal, had significantly higher levels of CSF IL-2 than patients who did not relapse [6] and the use of risperidone was associated with augmented IL-10 (a suppressor of Th_1 response) and decreased interferon-γ (IFN-γ) production [11] suggesting that measurements of cytokines can be used to predict disease progression and response to treatment. Similarly, both haloperidol and perazine decreased the release of IL-1β and TNF-α from monocytes of schizophrenic patients the concentrations of which were elevated before treatment compared to the control [9]. These results suggest that pro-inflammatory cytokines play a significant role in the pathogenesis of schizophrenia. This is supported by the fact that IL-2 treatment induced behavioral changes can be completely blocked by a selective dopamine D1 receptor antagonist (SCH 23390) or by a relatively high dose of a D2 antagonist (sulpiride) [12] suggesting that IL-2 induces and/or increases psychiatric abnormalities by causing aberrations in central dopaminergic transmission. Further, embryonic day 18 rat cortical cultures exposed to IL-1β, IL-6 and TNF-α showed dose-dependent decreases in the number of neurons immunoreactive for MAP-2 antibody, suggesting decreased neuronal survival [13]. Furthermore, pro-inflammatory cytokines can interfere with the actions of various neurotransmitters that, in turn, result in the development of features of schizophrenia [14]. These data suggest that injury; infection and inflammation-induced increase in pro-inflammatory cytokines during gestational period have the potential to cause injury to fetal neurons that in turn increase their risk of schizophrenia. This may explain the high incidence of schizophrenia associated with maternal infection during pregnancy, the maternal viral infection animal model of schizophrenia developed [3], and why prenatal immune challenge causes schizophrenia [4]. Significant correlations observed between plasma IL-2 and homovanillic acid (HVA), IL-2 and psychopathology assessed by the Scale for the Assessment of Positive and Negative Symptoms (SAPS), and HVA and SAPS during the acute state of schizophrenia and IL-6 and SANA and duration of illness lends further support to the role of cytokines in schizophrenia [12]. These results suggest that methods designed to suppress the production of pro-inflammatory cytokines and the use of neuroprotective agents could be of significant benefit in schizophrenia.

POLYUNSATURATED FATTY ACIDS AND SCHIZOPHRENIA

Reduced levels of membrane LCPUFAs: docosahexaenoic acid (DHA, 22: 6 ω-3), eicosapentaenoic acid (EPA, 20:5 ω-3) and arachidonic acid (AA, 20:4 ω-6), and increase levels of peroxidation products have been observed in schizophrenics [15–17]. However, the reductions in levels of both AA and DHA were much smaller in medicated versus never-medicated patients [16] and the LCPUFA (especially those of AA and DHA) levels were much higher in chronic medicated patients than drug-naïve first-episode patients [18]. It is likely that antipsychotics increase the levels of LCPUFAs in schizophrenia and thus, brings about their beneficial actions. LCPUFAs suppress the production of pro-inflammatory cytokines IL-2, IL-6 and TNF-α both *in vitro* and *in vivo* [19–22]. Oral supplementation of EPA is useful in schizophrenia [23–26]. The beneficial effects of EPA in schizophrenia could be due to its ability to suppress the production of pro-inflammatory cytokines. In addition, EPA, DHA and AA have potent neuroprotective and cytoprotective actions and prevent apoptosis of neurons [27–30].

Maternal feeding of DHA and AA alters dopaminergic and serotoninergic neurotransmitters in frontal cortex caused by a linolenic and α-linolenic acid deficient diet in formula-fed piglets [31]. When pregnant rats were fed a diet rich in DHA, the newborn brain dopamine was inversely related to phosphatidylethanolamine DHA and phosphatidylserine DHA, but positively related to phosphatidylcholine AA. It was also observed that maternal dietary fatty acids could alter fetal brain growth cone and neurotransmitters involved in neurite extension, target finding and synaptogenesis [32].

TESTING THE HYPOTHESIS AND CONCLUSIONS

I propose that injury, infection and inflammation increase the production of pro-inflammatory cytokines during pregnancy both in the mother and the fetus that in turn damage the developing fetal brain by inducing apoptosis of developing neurons, alter the balance between dopaminergic and serotoninergic neurons and predispose them to develop schizophrenia in adult life. Alternatively, since DHA, EPA and AA have neuroprotective action and suppress the production of pro-inflammatory cytokines, it is likely that sub-clinical deficiency of these fatty acids causes enhanced production of pro-inflammatory cytokines due to the absence of their (LCPUFAs) negative feed back control on their (cytokines) synthesis and action. Sub-clinical deficiency of LCPUFAs itself could be due to exposure to increased amounts of pro-inflammatory cytokines such as

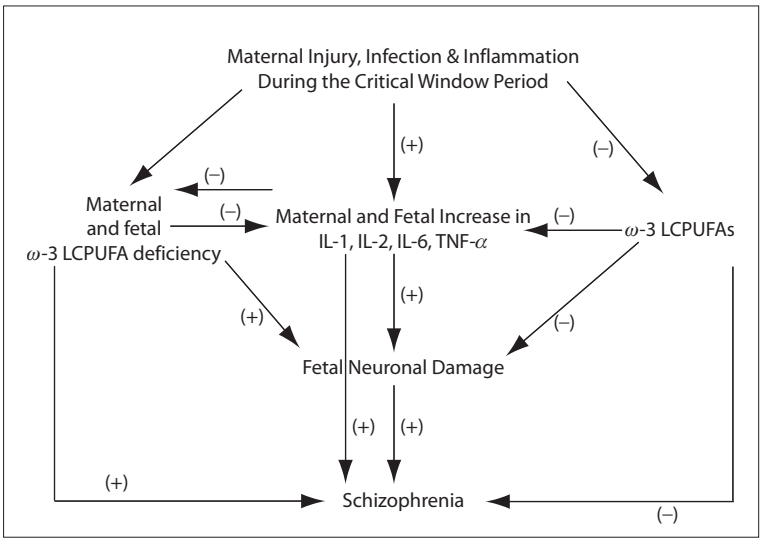

Figure 1. Scheme showing possible interaction(s) between LCPUFAs, maternal infection, injury, and inflammation, fetal neuronal damage and schizophrenia and bipolar disorders. (+) Indicates increase in the synthesis/action or the disease process. (–) Indicates decrease in the synthesis/action or decrease in the incidence of the disease.

IL-1, IL-2, IL-6, TNF-α. This is supported by the observation that short-term exposure of human endothelial cells to TNF-α caused marked alteration in the LCPUFA profile and LCPUFA content of total phospholipids decreased [33]. Presence of injury, infection and inflammation in the pregnant mother will lead to an increase in the production of pro-inflammatory cytokines both in the mother and the fetus that in turn suppress the production of various LCPUFAs in the maternal and fetal tissues, especially in the fetal neurons, and this may render the fetal brain susceptible to the cytotoxic action of cytokines. It was reported that LCPUFAs (especially gamma-linolenic acid and eicosapentaenoic acid) have cytoprotective and genoprotective actions [34–36]. This suggests that decreased levels of LCPUFAs may render the fetal brain more susceptible to the cytotoxic actions of cytokines. Hence, supplementation of LCPUFAs to high-risk pregnant and lactating mothers prevents/postpones the development of schizophrenia in their progeny (Figure 1). LCPUFAs are essential for normal growth and development of brain and memory formation [37–40] It is observed that fewer schizophrenic patients than normal were breast-fed [41,42]. The beneficial effect of breast-feeding in the prevention of schizophrenia can be attributed to the presence of significant amounts of LCPUFAs in human breast milk.

The present proposal can be tested by studying the effect of maternal supplementation of LCPUFAs (especially EPA, DHA, and AA in the ratio 1:6:9, the ratio in which they are present in human breast milk [37]) on prenatal immune activation in response to maternal infection and subsequent development of features consistent with schizophrenia in neurodevelopmental models of schizophrenia [3,4,43]. It is predicted that plasma levels of AA, EPA, and DHA will be low in these animal models of schizophrenia, and supplementation of LCPUFAs will blunt elevation of pro-inflammatory cytokines and prevents pathology of schizophrenia. It is suggested that maternal supplementation of LCPUFAs and/or to newborn during the critical period of brain growth prevents development of schizophrenia in later life. This hypothesis also implies that a combination of currently available anti-schizophrenic drugs and LCPUFAs will be more beneficial than either alone.

One of the major criticisms of the present proposal is that perinatal infections are unlikely to have an impact in adult life especially in the development of an adult diseases such as schizophrenia. In this context, it is interesting to note that there is interplay between the developing organism and the circumstances in which it finds itself. Several studies showed that a given genotype could give rise to different phenotypes, depending on environmental conditions [44]. Such a change in the expression of different phenotypes may include both short-term and long-term changes in physiology and behaviour. It may be mentioned here that such responses to the environment, which includes maternal infections, may be expressed in the fetus rather than in the mother. This may apply to the development of various adult diseases as well. For instance, maternal exposure to glucocorticoids in pregnancy induces hypertension, insulin resistance, obesity and altered muscle mass as well as alterations in the hypothalamic-pituitary-adrenal axis in the adult progeny [45]. Similarly, it is likely that maternal infection leads to excess production of pro-inflammatory cytokines that are neurotoxic resulting in the development of schizophrenia in adult life. The source of these pro-inflammatory cytokines could be infiltrating macrophages, T cells and the neurons themselves [46,47]. Exposure of fetal neurons to such noxious stimulus may render them more susceptible to further damage even by sub-optimal doses of pro-inflammatory cytokines that may explain why in all patients with schizophrenia the concentrations of these cytokines are not uniformly increased. Since brain is rich in LCPUFAs and as they have neuroprotective [27–30] and anti-inflammatory actions [21,22,47], one of the major functions of these fatty acids in the brain could be to protect neurons from the actions of neurotoxic chemicals and insults. This interaction between the mother, fetus and noxious stimuli (including viral infections) may play a critical role in the pathobiology of schizophrenia. Furthermore, triggering such a damage to the fetal neurons by various environmental agents such as maternal viral infection may be induced during sensitive, often brief, periods during development of the brain. Outside these sensitive periods, the influence of the neurotoxic agents may be little or no effect. It is this critical window period during which neuronal damage may occur and predispose the fetus to develop schizophrenia in adult life.

This explains why all maternal viral infections need not necessarily lead or predispose their progeny to develop schizophrenia in adult life. If this hypothesis proves to be true, it may open new avenues of preventing schizophrenia.

REFERENCES:

1. Joy CB, Mumby-Croft R, Joy LA. Polyunsaturated fatty acid (fish oil or evening primrose oil) for schizophrenia. Cochrane Database Syst Rev, 2000; 2: CD001257
2. Boin F, Zanardini R, Pioli R et al: Association between–G308A tumor necrosis factor alpha gene polymorphism and schizophrenia. Mol Psychiatry, 2001; 6: 79–82
3. Shi L, Fatemi S H, Sidwell RW, Patterson PH: Maternal influenza infection causes marked behavioral and pharmacological changes in the offspring. J Neurosci, 2003; 23: 297–302
4. Borrell J, Vela JM, Arevalo-Martin A et al: Prenatal immune challenge disrupts sensorimotor gating in adult rats. Implications for the etiopathogenesis of schizophrenia. Neuropsychopharmacology, 2002; 26: 204–11
5. Editorial. Of mice and mental illness. Nature Neuroscience, 2003, 6: 323
6. Zhang XY, Zhou DF, Zhang PY et al: Elevated interleukins-2, interleukins-6 and interleukins-8 serum levels in neuroleptic-free schizophrenia: association with psychopathology. Schizophr Res, 2002; 57: 247–58
7. Ebrinc S, Top C, Oncul O et al: Serum interlukin 1 alpha and interleukins 2 levels in patients with schizophrenia. J Int Med Res, 2002; 30: 314–17
8. McAllister CG, van Kammen DP, Rehn TJ et al: Increases in CSF levels of interleukins-2 in schizophrenia: effects of recurrence of psychosis and medication status. Am J Psychiatry, 1995; 152: 1291–97
9. Kowalski J, Blada P, Kucia K et al: Neuroleptics normalize increased release of interleukins-1 beta and tumor necrosis factor-alpha from monocytes in schizophrenia. Schizophr Res, 2001; 50: 169–75
10. Maes M, Bocchio Chiavetto L, Bignotti S et al: Increased serum interleukins-8 and interleukins-10 in schizophrenic patients resistant to treatment with neuroleptics and the stimulatory effects of clozapine on serum leukemia inhibitory factor receptor. Schizophr Res, 2002; 54: 281–91
11. Cazzullo CL, Sacchetti E, Galluzzo A et al: Cytokine profiles in schizophrenic patients treated with risperidone: a 3-month follow-up study. Prog. Neuropsychopharmacol. Biol Psychiatry, 2002; 26: 33–39
12. Zalcman SS: Interleukin-2-induced increases in climbing behavior: inhibition by dopamine D-1 and D-2 receptor antagonists. Brain Res, 2002; 944: 157–64
13. Marx CE, Jarskog LF, Lauder JM et al: Cytokine effects on cortical neuron MAP-2 immunoreactivity: implications for schizophrenia. Biol Psychiatry, 2001; 50: 743–49
14. Kim YK, Kim L, Lee MS: Relationships between interleukins, neurotransmitters and psychopathology in drug-free male schizophrenics. Schizophr Res, 2000; 44: 165–75
15. Hibbeln JR, Makino KK, Martin CE et al: Smoking, gender, and dietary influences on erythrocyte essential fatty acid composition among patients with schizophrenia or schizoaffective disorder. Biol Psychiatry, 2003; 53: 431–41
16. Aravindakshan M, Sitasawad S, Debsikdar V et al: Essential polyunsaturated fatty acid and lipid peroxide levels in never-medicated and medicated schizophrenia patients. Biol Psychiatry, 2003; 53: 56–64
17. Assies J, Lieverse R, Vreken P et al: Significantly reduced docosahexaenoic and docosapentaenoic acid concentrations in erythrocyte membranes from schizophrenic patients compared with a carefully matched control group. Biol Psychiatry, 2001; 49: 510–22
18. Khan MM, Evans DR, Gunna V et al: Reduced erythrocyte membrane essential fatty acids and increased lipid peroxides in schizophrenia at the never-medicated first-episode of psychosis and after years of treatment with antipsychotics. Schizophr Res, 2002; 58: 1–10
19. Kumar SG, Das UN, Kumar KV et al: Effect of n-6 and n-3 fatty acids on the proliferation and secretion of TNF and IL-2 by human lymphocytes *in vitro*. Nutrition Res, 1992; 12: 815–23
20. Kumar SG, Das UN: Effect of prostaglandins and their precursors on the proliferation of human lymphocytes and their secretion of tumor necrosis factor and various interleukins. Prostaglandins Leukot Essen Fatty Acids, 1994; 50: 331–34
21. Das UN: Beneficial effect of eicosapentaenoic acid and docosahexaenoic acid in the management of systemic lupus erythematosus and its relationship to the cytokine network. Prostaglandins Leukot Essen Fatty Acids, 1994; 51: 207–13
22. Endres S, Ghorbani R, Kelley VE et al: The effect of dietary supplementation with n-3 polyunsaturated fatty acids on the synthesis of interleukins-1 and tumor necrosis factor by mononuclear cells. N Engl J Med, 1989; 320: 265–71
23. Peet M, Horrobin DF, E-E Multicentre Study Group: A dose-ranging exploratory study of the effects of ethyl-eicosapentaenoate in patients with persistent schizophrenic symptoms. J Psychiatr Res, 2002; 36: 7–18
24. Peet M, Brind J, Ramchand CN et al: Two double-blind placebo-controlled pilot studies of eicosapentaenoic acid in the treatment of schizophrenia. Schizophr Res, 2001; 49: 243–51
25. Puri BK, Richardson AJ, Horrobin DF et al: Eicosapentaenoic acid treatment in schizophrenia associated with symptom remission, normalization of blood fatty acids, reduced neuronal membrane phospholipid turnover and structural brain changes. Int J Clin Pract, 2000; 54: 57–63
26. Mahadik SP, Evans D, Lal H: Oxidative stress and role of antioxidant and omega-3 essential fatty acid supplementation in schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry, 2001; 25: 463–93
27. Lonergan PE, Martin DSD, Horrobin DF, Lynch MA: Neuroprotective effect of eicosapentaenoic acid in hippocampus of rats exposed to γ-radiation. J Biol Chem, 2002; 277: 20804–11
28. Martin DSD, Lonergan PE, Boland B et al: Apoptotic changes in the aged brain are triggered by interleukin-1β-induced activation of p38 and reversed by treatment with eicosapentaenoic acid. J Biol Chem, 2002; 277: 34239–46
29. Kim H-Y, Akbar M, Lau A, Edsall L: Inhibition of neuronal apoptosis by docosahexaenoic acid (22: 6n-3). Role of phosphatidylserine in antiapoptotic effect. J Biol Chem, 2000; 275: 35215–23
30. Kim H-Y, Akbar M, Kim K-Y: Inhibition of neuronal apoptosis by polyunsaturated fatty acids. J Mol Neurosci, 2001; 16: 223–27
31. Owens SP, Innis SM: Docosahexaenoic and arachidonic acid prevent a decrease in dopaminergic and serotoninergic neurotransmitters in frontal cortex caused by a linolenic and α-linolenic acid deficient diet in formula-fed piglets. J Nutr, 1999; 129: 2088–93
32. Innis MS, Owens SP: Dietary fatty acid composition in pregnancy alters neurite membrane fatty acids and dopamine in newborn rat brain. J Nutr, 2001; 131: 118–22
33. Mayer K, Schmidt R, Muhly-Reinholz M et al: *In vitro* mimicry of essential fatty acid deficiency in human endothelial cells by TNFα impact of ω-3 versus ω-6 fatty acids. J Lipid Res, 2002; 43: 944–51
34. Das UN, Devi GR, Rao KP, Rao MS: Prostaglandins and their precursors can modify genetic damage induced by benzo (a,) pyrene and gamma-radiation. Prostaglandins, 1985; 29: 911–20
35. Das UN, Devi GR, Rao KP, Rao MS: Prostaglandins can modify gamma-radiation and chemical-induced cytotoxicity and genetic damage both *in vitro* and *in vivo*. Prostaglandins, 1989; 38: 689
36. Lonergan PE, Martin DSD, Horrobin DF, Lynch MA: Neuroprotective effect of eicosapentaenoic acid in hippocampus of rats exposed to γ-radiation. J Biol Chem, 2002; 277: 20804–11
37. Das UN: The lipids that matter from infant nutrition to insulin resistance. Prostaglandins Leukot Essen Fatty Acids, 2002; 67: 1–12
38. Das UN: Long-chain polyunsaturated fatty acids in the growth and development of the brain and memory. Nutrition, 2003, 19: 62–65
39. Das UN: Can memory be improved? A discussion on the role of *ras*, GABA, acetylcholine, NO, insulin, TNF-α, and long-chain polyunsaturated fatty acids in memory formation and consolidation. Brain Development, 2003; 25: 251–61
40. Makrides M, Neumann M, Simmer K et al: Are long-chain polyunsaturated fatty acids essential nutrients in infancy? Lancet, 1995; 345: 1463–68
41. McCreadie RG: The Nithsdale Schizophrenia Surveys. 16. Breast-feeding and schizophrenia: preliminary results and hypotheses. Br J Psychiatry, 1997; 170: 82–83
42. Amore M, Balista C, McCreadie RG et al: Can breast-feeding protect against schizophrenia? Case-control study. Biol Neonate, 2003; 83: 97–101
43. Zuckerman L, Rehavi M, Nachman R, Weiner I: Immune activation during pregnancy in rats leads to a postpubertal emergence of disrupted latent inhibition, dopaminergic hyperfunction, and altered limbic morphology in the offspring: a novel neurodevelopmental model of schizophrenia. Neuropsychopharmacology, 2003; 28: 1778–89
44. Sultan SE: The promise of ecological developmental biology. J Exp Zool (Mol Dev Biol), 2003; 296B: 1–7

45. Waterland RA, Garza C: Potential mechanisms of metabolic imprinting that lead to chronic disease. Am J Clin Nutr, 1999; 69: 179–97

46. Fricchione GL, Bilfinger TV, Stefano GB: The macrophage and neuropsychiatric disorders. Neurobiol, 1996; 9: 16–29

47. Das UN: A Perinatal Strategy to Prevent Adult Disease: The Role of Long-chain Polyunsaturated Fatty Acids. Kluwer Academic Publishers, Boston, 2002