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Omega-3 Polyunsaturated Fatty Acids in the Treatment of Schizophrenia

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Abstract: Most studies have shown reduced levels of polyunsaturated fatty acids, particularly docosahexaenoic acid and arachidonic acid, in the cell membranes of red blood cells from schizophrenic patients. This has led to research interest in the possible therapeutic benefits of omega-3 fatty acids in schizophrenia. There is evidence from double-blind placebo-controlled trials that omega-3 fatty acids might prevent conversion from a prodromal state into first episode psychosis, and reduce the antipsychotic drug requirement in first episode patients. Results in chronic and acutely relapsing schizophrenia have been mixed. The problems associated with single nutrient studies are discussed. Nutrients are normally ingested in complex combinations, and they interact with each other in their normal metabolic and physiological functions. It is likely that optimal nutritional treatment will involve complex combinations of nutrients, preferably as part of a healthy balanced diet rather than by using supplements. However, such approaches have been little evaluated in mental health.

Introduction

The phospholipid hypothesis of schizophrenia, originally developed by David Horrobin and his colleagues (1, 2), proposed that a variety of mental health problems could result from abnormalities of the phospholipid structure of neuronal membranes. Since polyunsaturated fatty acids (PUFA) are major structural components of cell membrane phospholipid, a great deal of research interest has been focussed on the possible role of these fatty acids in mental health. This review will focus on the available evidence relating to the role of omega-3 fatty acids in schizophrenia.

The Role of Omega-3 Fatty Acids

Omega-3 fatty acids are primarily obtained from dietary sources. An outline of the metabolism of omega-3 fatty acids is shown in Figure 1. The parent of this class of fatty acids is A-linolenic acid (ALA). This fatty acid cannot be synthesized by humans, so it is termed an essential fatty acid. The omega-3 fatty acids which have been investigated most in relation to mental health are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Although these fatty acids can be synthesized from ALA, the meta-

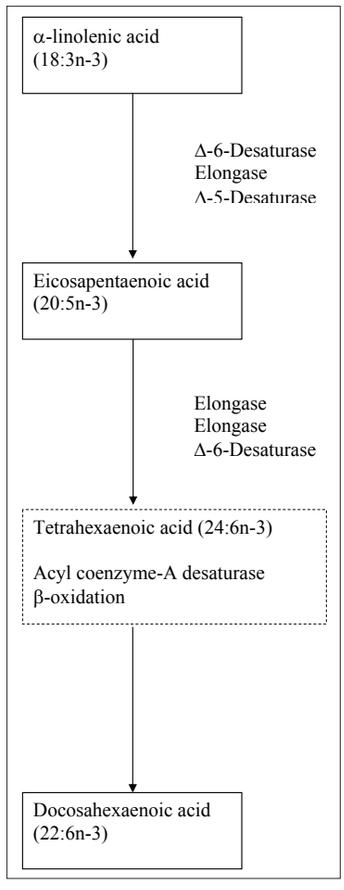

Figure 1. An outline of the metabolic pathway for omega-3 fatty acids.

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bolic pathway is not very efficient (3) so that in practice most EPA and DHA comes from dietary sources, particularly fish.

DHA is a major omega-3 polyunsaturated fatty acid in the phospholipid of neuronal cell membranes (4). EPA, in contrast, is not present in neuronal cell membranes. Because of this, DHA and EPA have different physiological effects on neuronal function. Thus, there is good evidence that changing the DHA content of neuronal cell membranes can alter densities of dopamine, serotonin and muscarinic receptors in brain (5). EPA can affect neuronal function because it is an important precursor of eicosanoids and modulator of cytokines which have neurotransmitter and neuromodulatory effects (6). Omega-3 fatty acids can also modify the expression of genes, including several genes which are important for brain function (7). It has been shown that maternal omega-3 fatty acid deficiency leads to long term over expression of dopamine receptor genes in the offspring (8).

Omega-3 Fatty Acids in Schizophrenia

It has been shown repeatedly that schizophrenic patients have reduced cell membrane levels of polyunsaturated fatty acids, particularly DHA and arachidonic acid (AA) (9). Most studies were conducted on cell membranes from red blood cells (RBC). RBC membrane levels of PUFA are regarded as a reflection of brain levels; it has been shown that the two correlate significantly in adult humans (10). Some of the early studies may have been confounded by extraneous factors. For example, there is evidence that smoking leads to reduced levels of PUFA in RBC membranes and it is well known that a higher proportion of schizophrenic patients smoke relative to the general population (11). Also, there is a tendency for RBC membrane levels of DHA and AA to diminish during storage, and this happens more rapidly in samples from schizophrenic patients than in those from healthy controls (12), possibly because the blood of schizophrenic patients is under increased oxidative stress. Because of that, samples need to be stored at -80°C rather than the standard -20°C (13). Some recent studies, taking account of these confounders, have still reported low levels of DHA and AA in RBC membranes from schizophrenic patients. However, a recent study found no reduction of either DHA or AA in large groups of unmedicated schizophrenic patients from India and from Malaysia (9). Therefore, reduced RBC levels of DHA are not a necessary or inevitable association with schizophrenia but perhaps may modify the presentation and course of the illness.

Omega-3 PUFA in the Treatment of Schizophrenia

An early open-label study of omega-3 PUFA in schizophrenia reported significant improvement in both schizophrenic symptoms and tardive dyskinesia (TD) (14). These beneficial effects were confirmed in early double blind placebo controlled trials (15). There was also an indication from these early studies that EPA was more effective than DHA, and as a result subsequent studies have focussed on EPA.

The results of all double blind placebo controlled studies of omega-3 fatty acids treatment in schizophrenia are summarized in Table 1. It has been divided into studies including young people at ultra-high risk of developing psychosis, those who have developed a first episode of psychosis, and those patients who have established chronic schizophrenia. The only placebo controlled trial in ultra-high risk subjects provided evidence that an EPA rich omega-3 preparation can reduce the risk of these subjects developing overt psychosis (16). Two studies have been conducted in first episode patients. In the first study (15) EPA enriched oil or corn oil placebo was given to unmedicated patients for three months. The primary outcome measure was whether or not the patients required treatment with antipsychotic drugs. All 12 patients on placebo, but only eight out of 14 on EPA, required these drugs during the three months study period. The patients in this study were older than a usual first episode group (mean 33 years) and the duration of psychosis averaged around six years. Some had been treated previously. Therefore, this was not a representative first episode group. A recent study (17) used EPA or placebo as an add-on to existing treatment with risperidone. Although the primary analysis based on symptom ratings showed no difference between EPA or placebo treated patients, secondary analysis showed that the EPA treated patients were on a lower dose of

risperidone by the end of the study. Thus, both these studies can be interpreted as showing an antipsychotic-sparing effect of omega-3 fatty acid treatment. Studies in chronic schizophrenia have given much more mixed results, with three studies reporting benefits from EPA enriched oil in either the primary or secondary analysis of data, two studies showing no benefit from EPA over placebo, and one study in acutely relapsing schizophrenia showing that EPA alone led to a significantly worse outcome than placebo treatment. In all of these studies, EPA rich oil was given in addition to existing antipsychotic medication. In the study by Bentsen (18), the apparently detrimental effect of the EPA was reversed when antioxidant medication was given in addition. One study (19) showed a marked benefit for EPA treatment in the subgroup of patients who were already being treated with clozapine.

Table 1. *Double-Blind Placebo-Controlled Studies of Omega-3 PUFA in Schizophrenia*

Authors	Study Design	Primary analysis	Secondary analysis
High Risk			
Amminger & Schafer (16)	Mono; EPA rich oil vs placebo	EPA>placebo	
First Episode			
Peet et al. (15)	Mono; 2g: EPA vs placebo	EPA>placebo for antipsychotic drug requirement	
Berger et al. (17)	Add-on; 2g: EPA vs placebo	EPA=placebo	EPA>placebo for antipsychotic dose
Chronic Schizophrenia			
Peet et al. (15)	Add-on; 2g: EPA vs DHA vs placebo	EPA>placebo	EPA>DHA
Fenton et al. (20)	Add-on; 3g: EPA vs placebo	EPA=placebo	
Peet & Horrobin (19)	Add-on; 1, 2 & 4g: EPA vs placebo	EPA=placebo	EPA(2g)>placebo in clozapine subgroup
Emsley et al. (21)	Add-on; 3g: EPA vs placebo	EPA>placebo	
Bentsen (18)	Add-on; 2g: EPA vs antioxidants vs combination vs placebo	EPA<placebo	EPA+antioxidants =placebo
Emsley et al. (22)	Add-on; 2g: EPA vs placebo	N/A (Primary analysis for effect on tardive dyskinesia)	EPA=placebo

Explanation of abbreviations: Add-on is the addition of omega-3 PUFA to current antipsychotic medication; mono is single therapy with omega-3 fatty acids. Primary analysis is the statistical analysis for the hypothesized main effect; secondary analysis relates to secondary hypotheses or post-hoc statistical analysis.

The Problem of Single Nutrient Studies

When treating schizophrenia, psychiatrists are accustomed to the idea that it is better to use a single drug rather than polypharmacy. The same approach is taken when investigating potential new treatments. Nutritional treatments are different. Nutrients are normally ingested in complex combinations, and in normal physiology they act synergistically. Either deficiency, or excess, of a particular nutrient can have harmful effects (23). In schizophrenia, there is evidence for benefits, not only from omega-3 PUFA, but also from other nutrients. These include the "homocysteine-lowering" vitamins (folate, B_6, B_{12}) (24), and the antioxidant vitamins (25).

There is good evidence that the "homocysteine-lowering" vitamins are important for omega-3 PUFA metabolism. Vitamin B_6 is a co-factor for enzymes in the metabolic chain shown in Figure 1. Rats fed high quantities of ALA (the parent omega-3 fatty acid) but low levels of vitamin B_6 showed significantly higher levels of ALA but lower levels of EPA and DHA than control animals which were not vitamin B_6 deficient (26). This was associated with a marked reduction in the activity of Δ_6-desaturase and the first enzyme of the β-oxidation pathway (acyl-CoA oxidase), both of which are involved in the metabolic pathway of omega-3 PUFA (Figure 1). Rats which are deficient in folic acid have significantly reduced plasma and platelet membrane levels of omega-3 PUFA (27), and the administration of folic acid leads to an increase in omega-3 PUFA levels in plasma and in RBC and platelet membranes, relative to control animals (28). There is also evidence that omega-3 fatty acids can influence homocysteine levels. While short-term studies of the effects of omega-3 fatty acids supplementation on homocysteine levels have given mixed results (29), a more recent long-term study showed that homocysteine levels are significantly reduced after one year of omega-3 PUFA treatment relative to the effects of corn oil in patients who have suffered an acute myocardial infarction (30). Li et al. (31) found a significant inverse relationship between plasma homocysteine levels and phospholipid DHA levels in healthy male subjects.

Antioxidant vitamins may also be important with regard to omega-3 PUFA levels. It is well recognized that oxidative stress will reduce cell membrane levels of DHA and other PUFA (32), and there is evidence that vitamin E supplementation can increase RBC membrane levels of DHA and other PUFA (33).

The possible importance for mental health of these synergistic effects of micronutrients is demonstrated by preliminary and as yet unpublished findings from placebo controlled trials. A recent study (34) reported that the apparently detrimental effects of EPA on the symptoms of chronic schizophrenia were reversed when the EPA was given together with antioxidant vitamins. In depression, there is evidence that EPA is effective only in those patients who have an adequate folic acid status (Horrobin, unpublished). Nutritional practitioners commonly use combinations of homocysteine-lowering and antioxidant vitamins, omega-3 fatty acids and other micronutrients in the supplementary treatment of schizophrenia. However, the efficacy of these combinations has been very little researched.

Research in the area is further compromised by the ethical requirement to administer nutritional treatment in addition to an established treatment such as an antidepressant, rather than using an unproven nutritional supplement as the sole treatment. However, now that we have increasing efficacy data from "add-on" studies, it is becoming ethically acceptable to conduct nutrient-only studies under some circumstances.

The Nutritional Status of Schizophrenic Patients

There have been several studies showing that people with a diagnosis of schizophrenia eat a diet which is even worse than that of the general population. Their diet is high in saturated fat and sugar, and low in polyunsaturated fats and in fresh fruit and vegetables. Therefore, they consume low levels of omega-3 fatty acids, folic acid and antioxidant vitamins, and excessive quantities of unhealthy foods (35–38). This may explain the common biochemical findings of high homocysteine levels, low omega-3 fatty acid levels, and high oxidative stress (39) in these patients. A recent study showed a positive correlation between dietary fish fat intake and levels of folate and vitamin B_{12} in a group of schizophrenic patients, which confirms that many patients suffer from multiple nutritional deficiencies (40).

Implications

Given what we know about nutrient interactions and the multiple deficiencies which occur in schizophrenic patients, it is not surprising that single nutrient studies have given mixed results. It is likely that the optimal nutritional treatment for schizophrenia will involve increasing the intake of multiple nutrients. It is also significant that schizophrenic patients are known to suffer from increased risks of cardiovascular disease (41) and diabetes (42). It is likely that both genetic and lifestyle factors play a role in this increased physical morbidity, but nutritional factors including lack of omega-3 fatty acids are probably of particular importance (43, 44). The same nutrients that have been implicated in mental health including omega-3 fatty acids, homocysteine-lowering vitamins and antioxidants, have also been highlighted as essential to physical well-being (45, 46). We contend that nutritional management should be an integral part of the treatment of people suffering their first episode of psychosis, with the aim of reducing subsequent physical morbidity and mortality and the likelihood that the mental state will also benefit from good nutrition. Our own practice is to carry out a full nutritional assessment on every patient who presents with first episode psychosis. This is conducted by a nutritionist using a diet diary, and the dietary information is analyzed using the WISP software package version 3.0 (Tinuvel software, Warrington, U.K.). This is followed by detailed nutritional feedback aimed at increasing dietary intake of nutrients which are important for mental and physical health, and reducing the dietary intake of harmful nutrients including saturated fat and sugar. In the initial phases of treatment, we use supplements which include omega-3 fatty acids and multivitamin and mineral combinations which include homocysteine-lowering and antioxidant vitamins. These are given as commercially available prescribed supplements which contain 1g of omega-3-acid esters (EPA 460mg, DHA 380mg), folic acid 400 micrograms, cyanocobalamin 3 micrograms, pyridoxine 2mg, ascorbic acid 60mg, vitamin E 10mg, as well as a variety of other vitamins, minerals and trace elements. However, the main aim of nutritional therapy is to encourage patients to eat a more balanced, healthy diet as part of their normal lifestyle.

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