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Review article

Red blood cell polyunsaturated fatty acids measured in red blood cells and schizophrenia: A meta-analysis

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ABSTRACT

Alterations of polyunsaturated fatty acids (PUFA) in schizophrenia have been reported, but there is substantial variation in the findings. We performed a systematic review and meta-analysis for docosapentaenoic acid (DPA), docosahexaenoic acid (DHA), linoleic acid (LA), and arachidonic acid (AA). We identified 18 studies which compared PUFA in the erythrocyte cell membrane between patients with schizophrenia and controls. A total of 642 patients (169 were antipsychotic-naïve) and 574 controls participated in these studies. We found suggestive evidence that the levels of DPA (C22:5n3) and DHA (C22:6n3) are decreased both in patients currently being treated with antipsychotic medication and antipsychotic-naïve patients. Our findings furthermore suggest that the levels of LA (C18:2n6) are decreased in the medicated subgroup, but not in the antipsychotic-naive group. Finally, we found decreased levels of AA (C20:4n6), most convincingly in antipsychotic-naive patients. Taken together, there is substantial evidence that decreased levels of DPA (C22:5n3), DHA (C22:6n3), and AA (C20:4n6) are associated with the schizophrenia syndrome, apart from a possible influence of antipsychotic medication. Given the large heterogeneity in results, these conclusions should be interpreted cautiously.

Contents

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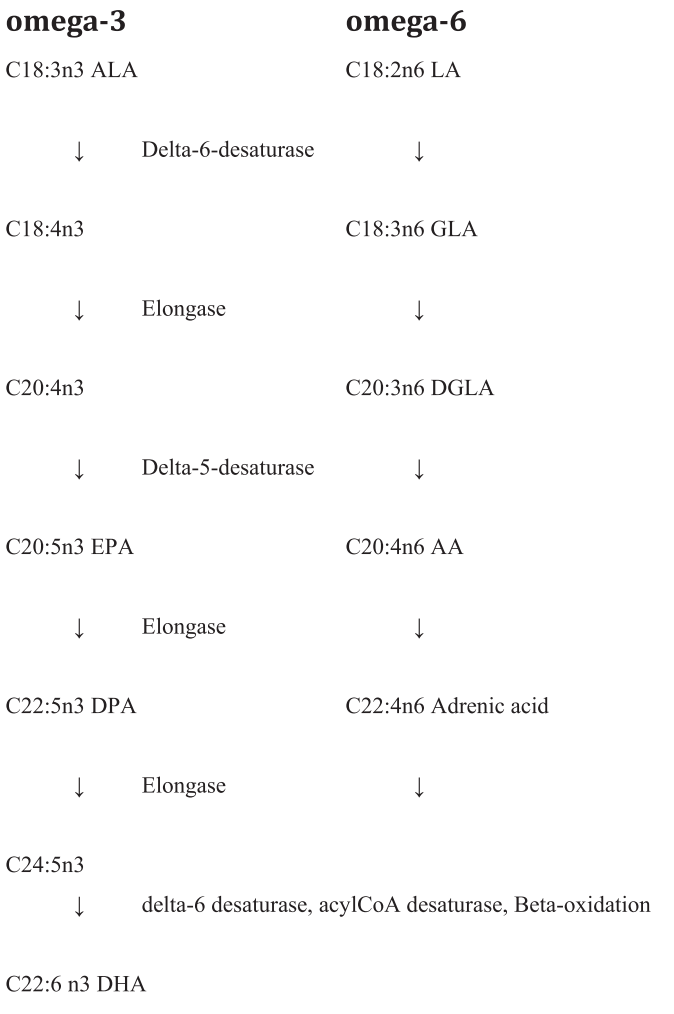
1. Introduction

Schizophrenia is among the most severe and impairing conditions. With a lifetime prevalence exceeding 1.25% (0.87% for schizophrenia, 0.32% for schizoaffective disorder, 0.07% for schizophreniform disorder) these disorders are a major public health concern (Perälä et al., 2007). Data accumulated over the last decades have led to the concept of the schizophrenia syndrome as a neurodevelopmental disorder originating from multiple maturational brain processes, involving proliferation, migration, arborization (circuit formation) and myelination, which together with environmental influences negatively impact on cortical brain maturation (Insel, 2010).

One of the factors that are thought to be involved in schizophrenia are disturbances in the metabolism of fatty acids. Polyunsaturated fatty acids (PUFA) contain two or more double bonds. The position of the first double bond classifies the PUFA as either omega-3 or omega-6. The most prominent omega-6 PUFA are arachidonic acid (AA, C20:4n6) and linoleic acid (LA, C18:2n6). Major omega-3 PUFA are eicosapentaenoic acid (EPA, C20:5n3), docosahexaenoic acid (DHA, C22:6n3) and alpha-linolenic acid (ALA, C18:3n3). In this article we use DPA for C22:5n3 only, and not for C22:5n6. For an overview, see Fig. 1.

Several lines of converging evidence have been put forward to support the notion that fatty acid metabolism plays a role in schizophrenia. A range of clinical and biochemical observations led Horrobin (1994, 1998) to formulate the so-called 'membrane hypothesis of schizophrenia' suggesting that schizophrenia is a disorder in which the metabolism and structure of membrane phospholipids are abnormal, not just in the brain, but also in other tissue (Horrobin et al., 1994; Horrobin 1998). Specifically, Horrobin (1994, 1998) indicated lower plasma essential fatty acids in schizophrenia patients, with similar findings in twins, and with twins concordant for schizophrenia showing greater abnormalities than those who were discordant. Moreover, brain essential fatty acids levels were shown to be abnormal in schizophrenia patients (for an overview of findings, see Horrobin et al., 1994). Studies involving post-mortem brain tissues of patients with schizophrenia supported the membrane hypothesis. They showed that PUFA deficits seen in peripheral tissue can also be observed



ALA = Alpha-linolenic acid, LA = Linoleic acid, GLA = Gamma-linolenic acid, DGLA = Dihomogamma-linolenic acid, EPA = Eicosapentaenoic acid, AA = Arachidonic acid, DPA = docosapentaenoic acid, DHA = Docosahexaenoic acid

Fig. 1. Metabolism of omega-3 and omega-6 fatty acids.