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Review article

Membrane phospholipid composition, alterations in neurotransmitter systems and schizophrenia

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Abstract

This review addresses the relationship between modifications in membrane phospholipid composition (MPC) and alterations in dopaminergic, serotonergic and cholinergic neurotransmitter systems in schizophrenia. The main evidence in support of the MPC hypothesis of schizophrenia comes from post-mortem and platelet studies, which show that in schizophrenia, certain omega-3 and omega-6 polyunsaturated fatty acid (PUFA) levels are reduced. Furthermore, examination of several biochemical markers suggests abnormal fatty acid metabolism may be present in schizophrenia. Dietary manipulation of MPC with polyunsaturated fatty acid diets has been shown to affect densities of dopamine, serotonin and muscarinic receptors in rats. Also, supplementation with omega-3 fatty acids has been shown to improve mental health rating scores, and there is evidence that the mechanism behind this involves the serotonin receptor complex. This suggests that a tight relationship exists between essential fatty acid status and normal neurotransmission, and that altered PUFA levels may contribute to the abnormalities in neurotransmission seen in schizophrenia.

Keywords: Brain function; Membrane phospholipid composition; Polyunsaturated fatty acid; Schizophrenia; Serotonin; Treatment

Contents

Abbreviations: AA, arachidonic acid; Acb, nucleus accumbens; ACC, anterior cingulate cortex; ADP, adenosine diphosphate; Amg, amygdala; BPRS, brief psychiatric rating score; CA1–3, CA1–3 fields of the hippocampus; CHO, carbohydrate; CPRS, comprehensive psychiatric rating scale; CPUDL, caudate–putamen, dorsolateral; CPUDM, caudate–putamen, dorsomedial; CPUVL, caudate–putamen, ventrolateral; CPUVM, caudate–putamen, ventromedial; Cx, cortex; D_2, dopamine D_2 receptor subtype; DA, dopamine; DAT, dopamine transporter; DG, dentate gyrus; DGLA, dihommo-gamma-linolenic acid; DHA, docosahexaenoic acid; E-E, ethyl eicosapentaenoate; EFA, essential fatty acid; Efamol, evening primrose oil; E-EPA, ethyl eicosapentaenoic acid; EPA, eicosapentaenoic acid; FA, fatty acid; FCx, frontal cortex; GLA, gamma-linolenic acid; HF, hippocampal formation; HPC, hippocampus; 5-HT_{1A}, serotonin 1A receptor subtype; 5-HT_{2A}, serotonin 2A receptor subtype; 5-HT_{2C}, serotonin 2C receptor subtype; 5-HT, serotonin; 5-HTT, serotonin transporter; MPC, membrane phospholipid composition; MUFA, monounsaturated fatty acid; *N*, number of subjects; $n-3$, omega 3; $n-6$, omega 6; PANSS, positive and negative syndrome scale; PET, positron emission tomography; PfCx, prefrontal cortex; PUFA, polyunsaturated fatty acid/s; SANS, scale for the assessment of negative symptoms; SAPS, scale for the assessment of positive symptoms; SF, saturated fat; STR, striatum; $VMAT_2$, vesicular monoamine transporter.

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1. Introduction

Schizophrenia is a debilitating mental disorder characterised by both positive and negative symptoms. Positive symptoms include hallucinations, delusions and thought disorganisation; while the negative symptoms include impaired motivation and decreased emotional expression (Lewis, 2000). The aetiology of schizophrenia remains to be elucidated, though researchers are coming to realise that it is probably multifactorial, involving interactions of many neurotransmitter systems and/or other factors. Some recent hypotheses put forward involve membrane phospholipid composition, glycine, vitamin D, noradrenalin and electrical dysfunction. Evidence from new techniques for investigating schizophrenia in vivo, such has positron emission tomography (PET), add new support to some of the more original hypotheses involving dopamine, serotonin and glutamate abnormalities (Farde, 1997).

Arguments have been put forward that in several cases, polyunsaturated fatty acids (PUFA) could be involved in the aetiology of schizophrenia. These are based on findings of reduced omega-3 ($n-3$) and omega-6 ($n-6$) PUFA (Yao et al., 1994; Arvindakshan et al., 2003), and of abnormalities in phospholipid metabolism in schizophrenia (Pettegrew et al., 1991; Messamore, 2003). The membrane phospholipid composition (MPC) hypothesis of schizophrenia argues that alterations in MPC of the brain, as a direct result of changes in fatty acid levels, affects aspects of brain function, such as neurotransmitter–receptor interaction (Horrobin, 1998).

Chalon et al. (2001) have inferred a link between MPC, neurotransmission and several neuropsychiatric affections. Studies from this group have focussed primarily on aspects of dopamine neurotransmission in an $n-3$ PUFA deficient rat model. Dietary manipulation of MPC from this diet has been shown to increase in D_2 receptor density in the nucleus accumbens, and reduce D_2 receptor density in the frontal cortex. Similar patterns of D_2 density have been reported in schizophrenia (Roth and Meltzer, 2000). Studies have also shown that high PUFA diets can affect serotonin and acetylcholine muscarinic receptor expression in the rat brain (Freund et al., 1986; Farkas et al., 2002; Aïd et al., 2003).

This review does not seek to evaluate all literature published on the membrane phospholipid composition hypothesis of schizophrenia. Rather, the objective of this paper is to determine whether a link between fatty acid abnormalities and alterations in neurotransmitter–receptor interactions in schizophrenia can be substantiated. However, it is worth noting that factors such as oxidative stress and altered immune function have also been related to PUFA defects in schizophrenia, which have been recently reviewed elsewhere (Yao et al., 2001; Yao and van Kammen, 2004).

Literature was obtained by searching the online databases ‘Science Direct’ and ‘Ovid’ using the keywords: ‘membrane phospholipid composition’, ‘essential fatty acids’, ‘serotonin’, ‘dopamine’ and ‘diet’, combined with the term ‘schizophrenia’ and by collecting references therein.

2. Schizophrenia and the MPC hypothesis

2.1. The role of essential fatty acids in the brain

Essential fatty acids (EFAs) such as arachidonic acid from the omega-6 family and docosahexaenoic acid from the omega-3 family, play important roles in neural membranes, once they are incorporated into membrane phospholipids (Fenton et al., 2000). The phospholipid composition of a membrane can influence the activity of ion channels and enzyme activities including Na^+/K^+ ATPase, cAMP and cyclic nucleotide (Bourre et al., 1991). The activity of transporters and receptors is also sensitive to changes in lipid environment (Spector and Yorek, 1985), therefore a change in membrane phospholipid composition may affect neurotransmission (Horrobin, 1998). Arachidonic acid and its derivatives can modulate dopamine release and dopamine receptor activity, as well as serotonin and glutamatergic activity (Skosnik and Yao, 2003).

The ratio of $n-6/n$-3 PUFA incorporated into membrane phospholipids (fluidity) can also influence receptor–ligand interaction, possibly by increasing the availability of binding sites on receptor proteins and/or by increasing receptor concentration in the membrane (Farkas et al.,