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Contents

One-carbon metabolism and depression

Kim *et al* concluded that lower levels of folate and vitamin B_{12} and raised homocysteine may be risk factors for late-life depression.[1] We propose to include polyunsaturated fatty acids (PUFAs) in future studies that will test the potential role of one-carbon metabolism in the aetiology and persistence of depression, for several reasons. First, because one-carbon metabolism is intimately linked with PUFA metabolism.[2] The methionine–homocysteine cycle produces methyl groups for the synthesis of phosphatidylcholine from phosphatidylethanolamine catalysed by phosphatidylethanolamine methyltransferase. Phosphatidylcholine is critical for the delivery of important PUFAs such as docosahexaenoic acid (DHA; C22:6n-3) from the liver to the plasma and distribution to peripheral tissues. The phosphatidylcholine/phosphatidylethanolamine ratio also modulates the activity of Delta-5 and Delta-6 desaturases involved in n-3 and n-6 PUFA synthesis. Moreover, plasma homocysteine was significantly inversely correlated with DHA, total n-3 PUFAs and the n-3/n-6 PUFA ratio in healthy males.[3] Second, these findings are relevant for psychiatry, as PUFAs – particularly DHA and arachidonic acid – are key 'building stones' that are required for healthy functioning of nerve and brain cells. In patients with recurrent depression, a decrease in n-3 PUFAs in erythrocyte membranes was found together with a significant positive association between the sum of plasma n-6 PUFAs and homocysteine.[4] There is also increasing evidence from cross-sectional studies and randomised controlled trials supporting the notion that an impaired PUFA metabolism is directly linked to the onset of depression.[5,6] Third, both an impaired one-carbon and an impaired PUFA metabolism might explain the positive associations between depression and metabolic syndrome (a cluster of risk factors for cardiovascular disease). Patients with depression are at risk for all components of metabolic syndrome. Interestingly, metabolic syndrome is associated with a rise in plasma homocysteine levels and a decrease in DHA in plasma and cell membranes. Based on these findings, our opinion is that for a proper understanding of underlying mechanisms linking one-carbon metabolism and depression, homocysteine, folate and B-vitamins should be measured in conjunction with dietary and laboratory analyses of PUFAs.

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Authors' reply: As Assies & Pouwer appropriately point out, there has been growing evidence for an underlying metabolic link between the key components of one-carbon metabolism and PUFAs both in depression and dementia.[1] However, we do not fully agree with their recommendation for measuring these factors in combination. Our reasons are as follows. One of the main potential mood stabilising effects of PUFAs in depression is thought to be their dampening action against abnormal intracellular signal transduction by (a) inhibiting G-protein-mediated and phospholipase-C-mediated hydrolysis of crucial membrane phospholipids;[2] (b) modulating the influx of calcium ions;[3] and (c) reducing the activity of protein kinase C.[4] In addition, PUFA actions are closely related to inflammatory and immune pathways, which are also potentially important in the pathogenesis of depression.[5] Compared with these more established findings, the evidence for relationships between one-carbon metabolism and PUFAs in depression is relatively scant. For these reasons, we cannot recommend measuring PUFAs in the context of one-carbon metabolism at the present time, particularly for clinical purposes. However, we do feel that Assises & Pouwer's suggestions should encourage future animal and clinical studies on these interesting research issues.

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Risk of harm after psychological intervention

In their trial of cognitive–behavioural therapy (CBT) and family intervention for relapse prevention in psychosis,[1] Garety *et al* state: 'There were no differences between the groups, in either [the no-carer or carer] pathway, in the primary outcomes of

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