Lipids and schizophrenia

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Lipid neurochemistry is now an important focus in schizophrenia research. Reports of abnormalities in brain lipids in schizophrenia appear widely in the medical and lay press. Disordered brain fatty acid metabolism was first postulated to play a part in the pathophysiology of schizophrenia by Horrobin (1977) and lately there is evidence that new treatments could follow (Mellor *et al*, 1996; Puri *et al*, 1998). At first glance the unlikeliness of this approach is striking. Lipids are ubiquitous; they are essential to life, forming the membranes that bound individual cells. Two polyunsaturated fatty acids (PUFAs) are essential components of the human diet. These essential fatty acids are linoleic acid and α-linolenic acid. Each has 18 carbon atoms. They head up two series of PUFAs through repeated elongation and desaturation (Fig. 1). All PUFAs are stored in phospholipids, such as phospatidyl ethanolamine, within cell membranes. They play a role in membrane structure and can be released by phospholipase A_2 and related enzymes. These free PUFAs are precursors of many compounds important to the healthy function of nervous tissue, including glycolipids, cholesterol esters, sphingolipids, thromboxanes, leucotrienes and prostaglandins (Fig. 2). The compound produced depends upon the combination of the specific PUFA and the enzyme pathway. Polyunsaturated fatty acids constitute about 20% of the dry weight of brain and, of these, arachidonic acid and docosahexaenoic acid account for about 70%.

Some severe neurological syndromes are determined by genetic abnormalities in enzymes that degrade or remodel brain lipids. Major dysfunction of lipid metabolism reduces life expectancy. The childhood cerebral form of adrenoleucodystrophy is symptomatic early, and death supervenes two years from onset. Milder forms of adrenoleucodystrophy have a later onset, a more chronic course and are compatible with life but cerebral function is impaired. They are of relevance to schizophrenia research. Variants of the leucodystrophies respond to Lorenzo oil (Moser, 1993), a rape-seed derivative and one of the first synthetic 'nutripharms' (nutrients used pharmacologically, usually in ultra-high dosage). By analogy, an apparently relatively minor lipid dysfunction could lead to the symptoms of schizophrenia. Nutripharms are 'naturally' appealing to the general public and to patients. A Mental Health Foundation survey (reported by D. Brindle, in *The Guardian*, 22 February 1997) revealed that 85–97% of psychiatric patients found alternative therapies (including dietary and natural supplements) helpful, compared with 70% for drug treatment and electroconvulsive therapy. The potential market for nutripharms in psychiatry may have hastened investigation of lipid dysfunction hypotheses in schizophrenia.

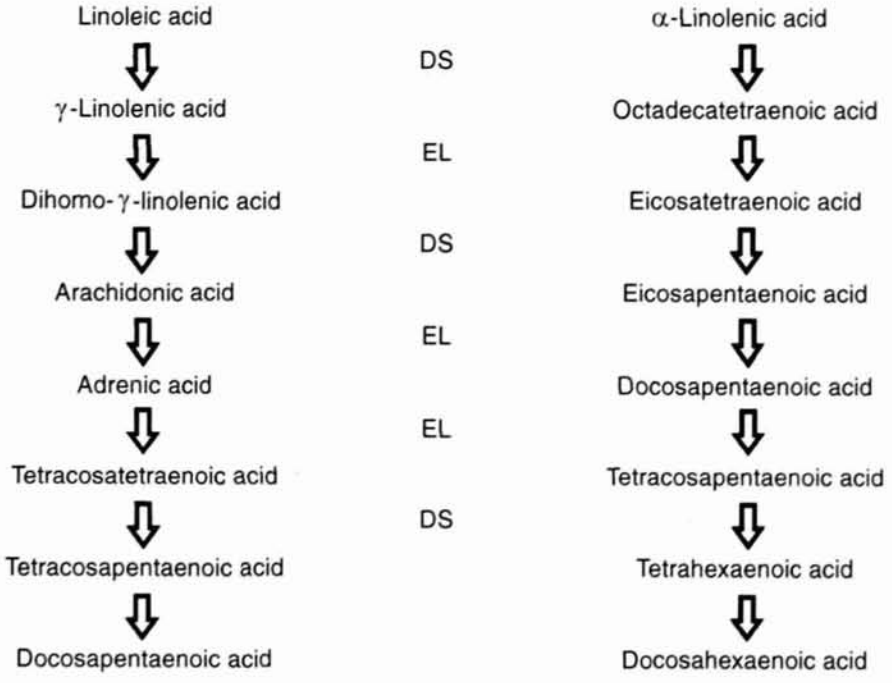

Fig. 1 Linoleic acid- and α-linolenic acid-derived series of polyunsaturated fatty acids, showing enzymes of desaturation (desaturase, DS) and elongation (elongase, EL).

ABNORMAL LIPID METABOLISM IN SCHIZOPHRENIA

There is some evidence of abnormal lipid metabolism in schizophrenia beyond what is attributable to drugs, diet and lifestyle. Horrobin (1977) postulated that schizophrenia could arise from a deficiency within the eicosanoid system in which prostaglandins are major constituents. He reviewed much circumstantial support for his hypothesis. For example, he cited historical evidence that subjects with schizophrenia, compared with those not suffering from schizophrenia, are less likely to display a significant inflammatory reaction to typhoid vaccination. Prostaglandins and related compounds are potent substances that are difficult to study *in vivo* in schizophrenia because of their extremely short half-lives and their presence at very low concentrations. They are synthesised and degraded at their site of action. Direct measurement in the central nervous system is impractical, except at post-mortem. Horrobin *et al* (1991) analysed the phospholipid composition of frontal and cerebellar cortex at necropsy in a comparison

https://doi.org/10.1192/bjp.174.2.101 Published online by Cambridge University Press

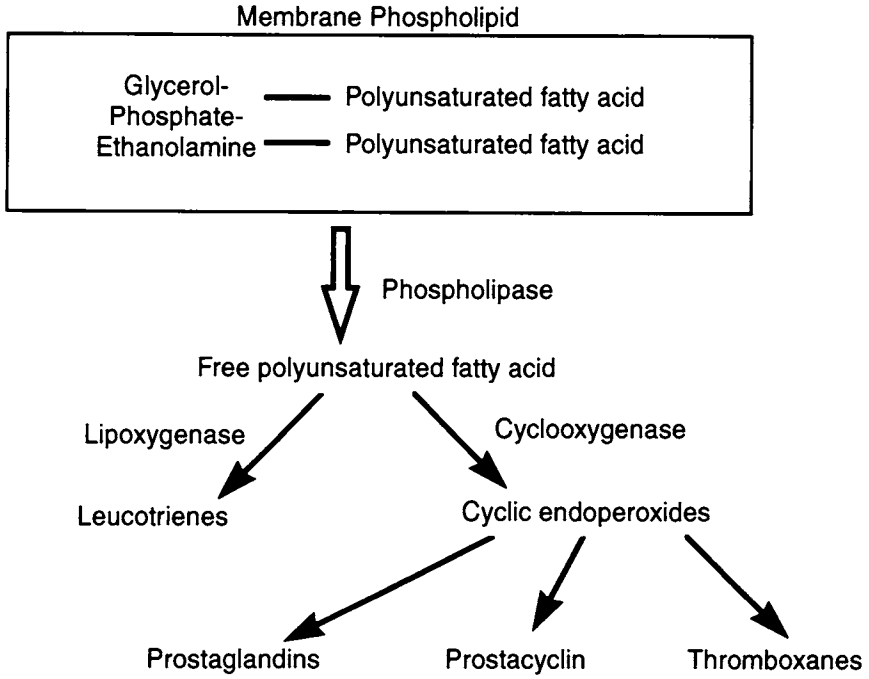

Fig. 2 Polyunsaturated fatty acid release from storage in membrane phospholipids and involvement in eicosanoid synthesis.

between seven subjects with schizophrenia and seven healthy controls. Arachidonic acid concentrations in the frontal lobes were significantly lower in the subjects with schizophrenia. Cerebellar tissue showed no significant differences. Horrobin *et al* (1991) argued that the patients' cerebellar results controlled for dietary and medication effects. Post-mortem artefacts could not be excluded and storage conditions were not uniform.

There are two approaches *in vivo* to the measurement of brain lipid metabolism: bioassay and measurement in peripheral cell models. Expediency and convenience have forced choices for modelling central nervous system structures in this way, but there is some evidence to support the use of a red blood cell membrane model to study lipid pathology in psychiatric disease. Makrides *et al* (1994) measured PUFA concentrations in cell membranes from cerebral cortex and erythrocytes from infants at necropsy to assess the effects of breast- and bottle-feeding. They found a significant correlation between the lipid profiles of cerebral cortex and erythrocyte. Caution is required. Carlson *et al* (1986) studied red cell and neuronal membrane PUFAs in newborn rats under a variety of dietary conditions. Although changes in membrane PUFA concentrations were not significantly different between the two cell types, absolute concentrations did differ significantly.

LIPID METABOLISM MEASURED BY BIOASSAY

Early studies of prostaglandin function in schizophrenia used bioassay. A prostaglandin-mediated system is measured indirectly by stimulating 'upstream' and recording the effect 'downstream'. Abdulla & Hamadah (1975) treated platelet suspensions with adenosine bisphosphate, which stimulates arachidonic acid release from phospholipids. Platelet enzymes convert arachidonic acid to prostaglandins in normal subjects inducing platelet aggregation; in schizophrenia aggregation is reduced. This finding fits with the hypothesis that prostaglandin activity is reduced in schizophrenia.

LIPID METABOLISM MEASURED IN THE PERIPHERY

Measurement of prostaglandin precursors in peripheral cell models provides an indirect measurement of prostaglandins. The assumption underlying this method is that increases (or decreases) in precursor lead to increased (or decreased) synthesis. This has some validity in terms of biochemical equilibria. It explains the action of medicines such as L-dopa in Parkinson's disease. Fischer *et al* (1992) compared platelet membrane PUFA concentrations in 16 subjects with schizophrenia and six controls and found lower concentrations in those with schizophrenia. They found a strong negative correlation between PUFA concentrations and antipsychotic drug dose, and postulated that lowered lipids in subjects with schizophrenia may be due to antipsychotic medication. However, this part of their analysis lacked the power to establish a relationship.

Glen *et al* (1994) compared 68 subjects with schizophrenia and 259 controls and found that erythrocyte membrane arachidonic acid and docosahexaenoic acid were lower in those with schizophrenia. They also reported that their cohort with schizophrenia fell into two groups; there was a bimodal distribution of PUFAs, not present in the control group. Approximately three-quarters of the subjects with schizophrenia shared the control group's Gaussian distribution, while the remaining quarter showed a distinct, lower distribution pattern. Peet *et al* (1994) reported similar findings but they went one step further; they looked at PUFA peroxidation products. These were elevated in the subjects with schizophrenia and were correlated negatively with arachidonic acid. They suggested that lowered arachidonic acid may be due to increased breakdown. None of these reports included data on diet or medication.

LIPID METABOLISM MEASURED IN BRAIN

The most exciting developments in lipid neurochemistry to date are direct measurements of phospholipid in the living brain using functional magnetic resonance imaging (fMRI), specifically ^{31}P-MRI. Pettegrew *et al* (1991) used fMRI to examine brain phospholid metabolism. They compared a first-episode drug-free cohort with schizophrenia with a control group and found significantly raised phosphodiester concentrations, suggesting increased breakdown by phospholipase A_2, and decreased phosphomonoesters, which could suggest lowered phospholipid synthesis in schizophrenia. Stanley *et al* (1995) reported similar findings with drug-treated and drug-free groups of subjects with schizophrenia and normal controls. These enquiries involved small numbers and studies were restricted

https://doi.org/10.1192/bjp.174.2.101 Published online by Cambridge University Press

to the dorsolateral prefrontal cortex. Although the results are not open to simple interpretation, they remain landmark studies of brain lipid metabolism in schizophrenia. They provide consistent results, apparently independent of drug effect, and have encouraged many research groups to begin studies on lipid metabolism in psychiatric disorders, especially on possible causes of excess phospholipid breakdown.

RELEVANCE TO CAUSAL HYPOTHESES OF SCHIZOPHRENIA

Genetics and neurodevelopment

There are likely to be large genetic and environmental contributions to the causes of schizophrenia and examination of the effects of specific genes on neurodevelopment may prove productive (Jones & Murray, 1991). Gene–diet interaction early in neurodevelopment (McGill *et al*, 1996) may uncover genetically determined abnormalities in lipid metabolism of causal importance in the later onset of schizophrenia. Neurodevelopmental studies underline the importance of an adequate dietary content of essential fatty acids for the integrity of brain structures (Crawford, 1993). Maternal arachidonic acid and docosahexaenoic acid are important determinants of foetal brain size, possibly through their effects on synaptic outgrowth and remodelling (Hess *et al*, 1993). In the case of two PUFAs, eicosapentaenoic acid and docosahexaenoic acid, adequate dietary content contributes to the functional integrity of the brain and may explain the putative advantages of breast milk (which contains both eicosapentaenoic acid and docosahexaenoic acid) over formula feeds (which do not) in both verbal and performance intelligence (Lucas *et al*, 1992).

In prostaglandin synthesis, phospholipase A_2 is the rate-limiting enzyme. It catalyses the release of PUFAs from phospholipids and is involved in synaptic outgrowth. Inhibition of phospholipase A_2 delays neuritic outgrowth, and administration of phospholipase A_2 will prevent neuritic retraction (Smalheiser *et al*, 1996). Mixed reports suggest either increased (Gattaz *et al*, 1987) or normal (Albers *et al*, 1993) phospholipase A_2 activity in subjects with schizophrenia compared to controls. Such variations require careful investigation. Ross *et al* (1997) addressed these inconsistencies and asked whether different investigators had measured different subtypes of phospholipase A_2. They found that calcium-independent phospholipase A_2 activity was increased in the group with schizophrenia but calcium-dependent activity was normal, thus explaining the discrepancies of previous studies. These findings may also prove relevant to the role of phospholipase A_2 in synaptic remodelling; Negre-Aminou *et al* (1996) demonstrated that calcium-independent (but not calcium-dependent) phospholipase A_2 is enriched in the nerve growth cone compared to other parts of the foetal brain. Huttenlocher (1979) reported late maturational changes in normal brain, which occur mostly in late childhood and early adolescence and result in a marked reduction in synaptic density. These stages in neurodevelopment, when cellular changes occur at a high rate over a short time, represent 'critical periods'. During critical periods, the nervous system is likely to be especially susceptible to environmental and other insults. Increased phospholipase A_2 activity, if maintained in the neuritic outgrowth, could lead to a failure of 'synaptic pruning' and, potentially, predispose to the later onset of schizophrenia. There is also some evidence that antipsychotic medication reduces phospholipase A_2 activity to normal (Gattaz *et al*, 1987). These findings suggest a pathway open to diverse influences (genes, nutrition, toxins and experiences), which may account for disparate findings in schizophrenia and integrate competing causal models derived from pharmacology, epidemiology and clinical observation.

The fMRI and phospholipase A_2 data taken together encouraged enzyme geneticists to include regulators of lipid metabolism among candidate genes for schizophrenia. Hudson *et al* (1996) studied a poly-A repeat polymorphism associated with the gene for phospholipase A_2. They found that larger alleles were enriched in subjects with schizophrenia and suggested that these alleles may influence expression of the phospholipase A_2 family of genes, thus affecting phospholipase A_2 activity. Although Price *et al* (1997) failed to replicate these findings, the regulation of phospholipase A_2 activity rather than the structure of the phospholipase A_2 gene family may prove to be of critical relevance.

Neurotoxicity

One of the more plausible of the many hypotheses of schizophrenia is that endogenous reactive oxygen species, released during normal respiration, damage nucleic acids and lipids, as has been shown in cancer (Duthie *et al*, 1996). This mechanism could reveal or amplify latent 'pre-schizophrenic' genetic abnormalities. Increased peroxidation could also account for the lowered PUFA concentrations seen in schizophrenia. McCreadie *et al* (1995) measured lipid peroxide and vitamin E in the blood of subjects with schizophrenia and controls. They found that subjects with schizophrenia have significantly higher lipid peroxide and lower vitamin E concentrations than controls matched for age, gender and smoking status. Patients who smoke show the effect more markedly. They could detect no effect of medication.

LIPID METABOLISM AND DISEASE

The importance of lipid metabolism in disease is beyond doubt. Cardiovascular mortality is reduced by lifestyle improvements such as cessation of smoking, increased exercise and better diet. The case remains to be established that lipids play an important role in the pathogenesis of psychiatric disorders. Important questions remain. The reliability and validity of many lipid measurements are not well proven; storage and handling effects are poorly studied. Diet is likely to be of major importance in determining lipid composition of cell membranes, possibly at two stages: around the time of measurement and during neurodevelopment. This would imply potential for gene–diet interaction *in utero* and during early childhood (McGill *et al*, 1996). There may be influences of psychological stressors on lipid measures, possibly mediated by hormonal mechanisms (especially adrenal and thyroid); endocrine function is known to be altered in acute psychosis (Whalley *et al*, 1989).

Medication and smoking effects are yet to be explored fully. Even so, the evidence of lipid dysfunction is compelling enough to postulate that PUFA and antioxidant supplements will help to relieve schizophrenia. Puri *et al* (1998) report a single case of schizophrenia responding to supplementation with eicosapentaenoic acid. There is evidence that better diet and cessation of smoking have a beneficial effect on lipid metabolism (Brown *et al*, 1991). Reduced dietary cholesterol consumption decreases the risk of heart disease.

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Enrichment with micronutrients such as eicosapentaenoic acid (Puri *et al*, 1998) may be helpful in schizophrenia, as Lorenzo oil can be in adrenoleucodystrophy (Moser, 1993). Improved maternal nutrition during pregnancy and breast-feeding may help to prevent neurodevelopmental abnormalities, much as folic acid supplementation in pregnancy reduces the incidence of spina bifida.

Molecular genetic techniques are likely to prove informative in the study of causes of schizophrenia. The evidence presented here supports the case for inclusion of genes concerned with the regulation of brain lipid metabolism in studies of families with schizophrenia in high density. Abnormalities in lipid metabolism may prove relevant to understanding neurodevelopmental abnormalities in schizophrenia and how obstetric complications and malnutrition increase its risk. Potentially, advances in lipid neurochemistry in schizophrenia will improve the choice of novel therapeutic strategies to ameliorate the public and personal burden of schizophrenia.

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(First received 30 March 1998, final revision 26 October 1998, accepted 2 November 1998)

https://doi.org/10.1192/bjp.174.2.101 Published online by Cambridge University Press