International Review of Psychiatry, April 2006; 18(2): 85–98

Routledge
Taylor & Francis Group

Bioactive lipids in schizophrenia

GREGOR E. BERGER[1], STEFAN SMESNY[2], & G. PAUL AMMINGER[3]

[1]*ORYGEN Youth Health and ORYGEN Research Centre, Department of Psychiatry, University of Melbourne, Australia,* [2]*Department of Psychiatry, University of Jena, Jena, Germany, and* [3]*Department of Child and Adolescent Psychiatry, Medical University of Vienna, Austria*

Summary
Bioactive lipids, in particular arachidonic acid (AA), are vital for monoaminergic neurotransmission, brain development and synaptic plasticity. Phospholipases A2 (PLA2) are key-enzymes in AA metabolism and are activated during monoaminergic neurotransmission. Reduced membrane AA levels, and an altered activity of PLA2 have been found in peripheral membranes of drug-naïve patients with schizophrenia with some conflicting results in more chronic patient populations. Furthermore, *in vivo* brain phosphorus-31 magnetic resonance spectroscopy suggests reduced lipid membrane precursors (phosphomonoesters) and increased membrane breakdown products (phosphodiesters) in drug-naïve or early treated first-episode schizophrenia patients compared to age-matched controls or chronic populations and these changes were correlated with peripheral red blood cell membrane AA levels. We postulate that processes modulating membrane lipid metabolism are associated with psychotic illnesses and might partially explain the mechanism of action of antipsychotic agents, as well as experimental agents such as purified ethyl-eicosapentaenoic acid (E-EPA). Recent supplementation trials suggest that E-EPA is a modestly effective augmentation treatment resulting in reduced doses of antipsychotic medication in acutely ill patients with schizophrenia (but not in residual-type schizophrenia). This review investigates the role of bioactive lipids in schizophrenia and its treatment, as well as its potential use in prevention.

What are bioactive lipids?

Bioactive lipids are long chain fatty acids (LCFAs) that are released during neuronal signalling and act as lipid second messengers. The human body has lost the capacity to synthesize these molecules *de novo*, what fore they are termed 'essential fatty acids (EFAs)'. There are two series of fatty acids that are classified as essential, the n-3 and n-6 series. The terms n-6 and n-3 are synonymous with omega-6 and omega-3, and indicate the location of the last double bond, counted from the carbon tail. Linoleic acid (LA, 18 : 2, n-6) and alpha-linolenic acid (α-LA, 18 : 3, n-3) are the parent compounds of the two series, both with 18 carbon atoms. The n-3 and n-6 EFAs compete for the same enzymes (desaturases, elongases, phospholipases) and cannot be interconverted (i.e., n-3 cannot be transformed into n-6 EFA and *vice versa*). The ratio between unsaturated (including the EFAs) and saturated fatty acids determine the structure and fluidity of cell membranes, which in turn modulates ion channel function, receptor activity, and neurotransmitter release (Farooqui, Horrocks, & Farooqui, 2000).

In their inactive form, bioactive lipids are usually bound to glycerophospholipids (GPLs). The GPLs of the brain, in particular those located in synaptic membranes, have a much higher concentration of bioactive lipids then other cell membrane GPLs (Agranoff, Joyce, & Hajra, 1998). There are different types of GPLs and each type of GPL in a given tissue has a characteristic bioactive lipid composition. For example, white matter phosphatidylethanolamine (PtdEtn) contains 3% docosahexaenoic acid (DHA), whereas grey matter PtdEtn contains 24% DHA. 'Derived LCFAs' can be synthesized from their essential parent C-18 compounds in low amounts, however a substantial proportion are obtained directly from diet (e.g., fish [Sinclair, Murphy, & Li, 2000; Torres, Mira, Ornelas, & Melim, 2000], and breast milk [Cunnane, Francescutti, Brenna, & Crawford, 2000]).

Bioactive lipids, synaptic functioning and brain development

Arachidonic acid (AA) is the most common lipid second messenger in the brain and precursor of a

Correspondence: Gregor E. Berger, MD FMH Psych (CH), ORYGEN Research Centre (EPPIC), Senior Lecturer Department of Psychiatry, University of Melbourne, Locked Bag 10, 35 Poplar Rd, VIC 3052, Australia. Tel.: +61 3 9342 2800. Fax: +61 3 9387 3003. E-mail: gregor@unimelb.edu.au

ISSN 0954–0261 print/ISSN 1369–1627 online/06/020085–14 © Institute of Psychiatry
DOI: 10.1080/09540260600583072

range of derivates, called the eicosanoids. Docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) are further bioactive lipids that have been identified to act as lipid second messengers. AA (20 : 5, n-6), DHA (22 : 5, n-3) and EPA (20 : 5, n-3) are important for monoaminergic neurotransmission, brain development and synaptic functioning (Bazan, 2005; Piomelli et al., 1991). Excitable membranes such as synaptic membranes or the retina have a particularly high concentration of these EFAs. It is now becoming apparent that EFAs such as AA, DHA or EPA and their products (eicosanoids) such as prostaglandins, thromboxanes, prostacyclins and leukotrienes are essential for processes such as neuronal migration, pruning and synaptic plasticity (Bazan, 2005; Bazan, Packard, Teather, & Allan, 1997), processes proposed to be dysfunctional in schizophrenia (Mirnics, Middleton, Stanwood, Lewis, & Levitt, 2001; DeLisi, 1997; Keshavan, Anderson, & Pettegrew, 1994; Feinberg, 1990; 1982). In addition, AA linked with ethanolamine as anandamide, or esterified with glycerol, is an endogenous ligand for the brain cannabinoid receptors (Devane & Axelrod, 1994), a receptor system proposed to be involved in the pathogenesis of schizophrenia and other neuropsychiatric disorders (Glass, 2001).

Bioactive lipids in major mental illnesses

What does epidemiology tell us?

As bioactive lipids are essential, one can postulate that major nutritional deficits of EFA interferes with normal brain development and nerve functioning (Innis, Sprecher, Hachey, Edmond, & Anderson, 1999), in particular during pregnancy and early childhood, implying that EFA deficits may be of importance for the onset of schizophrenia (Brown et al., 1996). In line with this speculation is the observation that breastfeeding (rich in EFA) exerts a protective role against the development of schizophrenia and related disorders (McCreadie, 1997; Peet, Poole, & Laugharne, 1999). The positive studies (Peet et al., 1999; McCreadie, 1997) selected 'high-risk babies' with other predisposing factors, such as a family history of schizophrenia, very premature birth, birth complications, viral infections, or extreme forms of malnutrition, whereas the negative studies were population-based (Leask, Done, Crow, Richards, & Jones, 2000; Sasaki et al., 2000). These discrepancies may imply that EFA and breastfeeding as protective factors may only be of relevance as protective factors in 'at risk groups' and less relevant for the normal populations. Further investigations using carefully designed large scale case-control studies or longitudinal studies in 'high-risk populations' (selective prevention [Mrazek & Haggerty, 1994]) seem warranted.

A retrospective analysis (Christensen & Christensen, 1988) correlating the course and outcome figures from the International Pilot Study of Schizophrenia (IPSS; Jablensky, 2000) with the national dietary characteristics of the eight participant countries suggested that the outcome was better in those countries where the diet contained less saturated (animal) and more polyunsaturated fats (e.g., vegetables and seafood). The study compared population-based inventories (IPSS and dietary database) which may result in false positive associations and that there are many confounding factors that may be able to explain the proposed associations. It is well known that patients with schizophrenia live an unhealthy lifestyle (increased intake of saturated fats, lower intake of EFA, increased cigarette consumption and alcohol use, less exercise and more obesity). Therefore it remains unclear if the reduced intake of EFAs has a direct negative impact on the course of the illness (Brown, Birtwistle, Roe, & Thompson, 1999) or represents only an epiphenomenon. This raises the question of whether the postulated associations may be better explained by common underlying variables such as more urban living, migration or stress (Mahadik, Mulchandoni, Mahabaleshwar, & Ranjekar, 1999) and not diet alone.

The lower incidence of depression in populations with high intake of marine or sea fish (rich in n-3 fatty acids) provides further support for the importance of life time intake of EFA and proneness to mental illness (Lichtermann, Ekelund, Pukkala, Tanskanen, & Lonnqvist, 2001; Stoll, 2001; Hibbeln, 1998) although there are some conflicting results (Hakkarainen et al., 2004; Ness et al., 2003; Suzuki et al., 2004). Future outcome studies in major mental illness should consider dietary factors as potential co-factors that have to be taken into account to investigate to what extent life time diet may explain the variation in outcome.

Excess of bioactive lipids in rheumatoid arthritis—a potential protective factor?

The negative association between rheumatoid arthritis (RA) and major mental illnesses, in particular schizophrenia, gives further evidence for the involvement of EFAs and its derivates in the pathophysiology of major mental disorders (Horrobin, 1977; Mellsop, 1972). Rheumatoid arthritis is associated with an overproduction of AA, its derivates and platelet-activating factor (PAF) (Heleniak & O'Desky, 1999). A meta-analysis of 16 published data sets (Oken & Schulzer, 1999) encompassing over 70,000 patients with schizophrenia and over

350,000 patients with other major psychiatric conditions estimated that the rate of RA in patients with major psychiatric disorders was less than a third compared to the general population. The relative risk of RA in schizophrenia versus the general population was estimated to be even lower at around 10%. These findings are in keeping with the hypothesis that bioactive lipids are important modulators for major mental illness, in particular schizophrenia.

Impaired niacin sensitivity, a potential indicator of abnormal monoaminergic neurotransmission?

Anecdotal clinical reports of impaired pain and temperature perception, decreased tendency to develop fever and inflammation and an impairment of the facial flush response to niacin stimulation (Horrobin, 1977) resulted in the suggestion that schizophrenia is associated with a deficit in AA-derived prostaglandins (Heleniak & O'Desky, 1999). Arachidonic acid is released via G-protein coupled activation of phospholipases (e.g., in the context of D2 activity; Piomelli et al., 1991). The oral intake of niacin (nicotinic acid, vitamin B3) in normal volunteers also induces an activation of this pathway and a dose-dependant flush reaction of the face and upper body that is mainly mediated via prostaglandin D2 (Morrow, Awad, Oates, & Roberts, 1992). This unwanted effect is well known to patients with hypercholesterolemia who sometimes prefer to take niacin due to its anti-lipolytic effects instead of other cholesterol lowering drugs (Morgan, Capuzzi, & Guyton, 1998). Early studies reported a reduced flush response in some patients with schizophrenia (Horrobin, 1977; Hoffer, 1969) and its restoration after remission of psychosis (Horrobin, 1980). Attempts to quantify the flush reaction using methodologies such as measuring (malar) skin temperature changes (Fiedler, Wolkin, & Rotrosen, 1986) or plethysmography to measure blood flow (Rybakowski & Weterle, 1991; Wilson & Douglass, 1986) had mixed results. Hudson and colleagues (1997) used thermo-coupled sensors to measure the skin temperature relative to the core body and ambient room temperature after oral intake of 200 mg niacin. They demonstrated that 42.9% of patients with schizophrenia had no change in temperature, whereas 94% of patients with bipolar disorder and 100% of normal controls did. In addition, the lack of flushing was associated with low levels of AA in red cell membranes (Glen et al., 1996).

The development of a topical variant of the niacin flush test resulted in a considerable progress. Skin erythema and oedema were assessed in five-minute steps on the basis of an ordinate four point rating scale (0 = no response to 4 = maximal cutaneous erythema; oedema = yes/no) after topical application of four different concentrations of niacin (0.1 M, 0.01 M, 0.001 M and 0.0001 M). Using the topical niacin skin test, a zero or mini-mal niacin response was reported in 83% of medicated schizophrenia patients and 23% of controls with the greatest degree of differentiation at 0.01 M niacin (Ward, Sutherland, Glen, & Glen, 1998). Shah and colleagues (2000) replicated these findings using a scoring system that integrated the oedema, and this was able to separate patients with schizophrenia from normal controls in all but the lowest niacin concentration (0.0001 M), independent of antipsychotic drug-treatment.

Two recent studies confirmed that at least a subgroup of patients with schizophrenia has impaired niacin sensitivity (Messamore, Hoffman, & Janowsky, 2003; Tavares, Yacubian, Talib, Barbosa, & Gattaz, 2003). New strategies to quantify the skin response after topical niacin stimulation via optical reflection spectroscopy (ORS) (Smesny et al., 2003) or via blood flow duplex sonography (Messamore et al., 2003) enabled the investigation of niacin sensitivity on the basis of quantitative measures and confirmed significantly diminished niacin sensitivity as compared to controls. However, the quantification revealed a non-linear response curve due to the emergence of the oedema in strong responders (Smesny et al., 2003). Our own group, using a semi-quantitative, descriptive assessment scale that integrates erythema, oedema and time course to assess the overall flush reaction confirmed previous results. Using this scale we were able to separate normal controls from first episode psychosis patients with a sensitivity of 81% and a specificity of 81.5% (Berger et al., 2002). Normal controls had a unimodal distribution, whereas first episode patients showed a bimodal distribution supporting a previous report suggesting a bimodal distribution of AA levels in patients with schizophrenia (Glen et al., 1994). Only about 40–50% of patients demonstrated a reduced niacin sensitivity implying that the niacin skin test is not a diagnostic marker. However, the question rises if niacin sensitivity is able to define a phenotype encompassing a dysfunctional bioactive lipid metabolism. The observation that phospholipid alterations have been present before the onset of any psychotic symptoms (Keshavan et al., 1997) and the presence of niacin insensitivity in non-affected offspring of patients with schizophrenia (Horrobin & Bennett, 1999; Keshavan, Stanley, Montrose, Minshew, & Pettegrew, 2003; Waldo & Freedman, 1999) are supportive of this suggestion. Thus, another potential role of the niacin skin test may be given by the prediction of transition to psychosis in patients at risk for psychosis or in the prediction of

relapse in repeatedly ill patients. Indirect support that this may be the case comes from the observation that reduced membrane fluidity seems to be predictive of relapse in schizophrenia (Yao, van Kammen, & Welker, 1994a). Also membrane fluidity is associated with membrane content of AA levels, a more precursor of niacin sensitivity regulating prostaglandins (Yao, van Kammen, & Welker, 1994b).

Direct measurement of bioactive lipids in schizophrenia and related disorders

The clinical observation of impaired prostaglandin mediated processes (see above) and niacin sensitivity (see above) in conjunction with EFA abnormalities in the cerebrospinal fluid (Farstad, 1966) and peripheral cell membranes (Fenton, Hibbeln, & Knable, 2000) of patients with schizophrenia, lead to the formulation of the membrane hypothesis of schizophrenia (Horrobin, 1998). A review of 15 published studies (Fenton et al., 2000) concluded that there was a depletion of EFA, in particular AA, in red cell, thrombocyte, and fibroblast membranes of patients with schizophrenia, which was thought to be independent of drug treatment (Yao, van Kammen, & Gurklis, 1996). Primate studies confirm that peripheral membrane AA levels correlates with AA levels of nerve cell membranes (Connor, Neuringer, & Lin, 1990). A recent study in first episode schizophrenia patients associated peripheral AA levels with membrane breakdown products using 31phosphorus spectroscopy (31P-MRS) (Yao, Stanley, Reddy, Keshavan, & Pettegrew, 2000b). Reductions in AA levels have also been found in post mortem brains of patients with schizophrenia, relative to normal control brains (Horrobin, Manku, Hillman, Iain, & Glen, 1991; Yao, Leonard, & Reddy, 2000a). A defective uptake of AA into membrane GPLs (Yao et al., 1996) or an increased breakdown of membrane lipids (oxidative damage) (Herken et al., 2001; Mahadik, Mukherjee, Scheffer, Correnti, & Mahadik, 1998; Peet, Laugharne, Mellor, & Ramchand, 1996) have been proposed as a possible pathomechanism.

Phospholipases A2, key-metabolizing enzymes of bioactive lipids

Phospholipases A2 (PLA2) are key enzymes in regulating the AA content in the cell membrane, as well as the release and production of bioactive lipids in general. The group of phospholipases A2 (PLA2) consists of a broad range of enzymes (the PLA2 superfamily) defined by the ability to catalyse the hydrolysis of the middle (sn-2) ester bond of substrate GPL. As breakdown products, mainly EFAs (e.g., AA) and lysophospholipids (e.g., lyso-platelet-activating factor (lyso-PAF) are released (Six & Dennis, 2000). Historically, PLA2s were classified by their location (secretory, cytosolic) or by their calcium-requirement, but both classification systems could be misleading and were not always meaningful. The more structured classification is genetically determined and currently contains 11 subgroups based on homologies (Six & Dennis, 2000). Each group may contain multiple homologues further assigned a letter. For example, phospholipase A2 Group 4A (PLA2G4A) and phospholipase A2 Group 4B (PLA2G4B) are evolutionarily related homologues (A and B) within Group 4 (G4). Most of the studies measuring PLA2 activity of patients with schizophrenia to date were carried out before acquisition of this knowledge and used enzymatic essays that often measured several types of PLA2 making interpretation of the results difficult.

Gattaz and colleagues (Gattaz & Brunner, 1996; Gattaz, Schmitt, & Maras, 1995; Gattaz, Hubner, Nevalainen, Thuren, & Kinnunen, 1990) were the first to demonstrate an over-active PLA2 in plasma, serum and platelets of patients with schizophrenia, using a fluorometric methodology that primarily measured a calcium-independent PLA2 (most likely encompassing mainly the cytosolic 85kDa group IVA PLA2). Ross, Hudson, Erlich, Warsh, and Kish (1997) demonstrated that contradictory findings in previous reports (Hudson, Gotowiec, Seeman, Warsh, & Ross, 1999; Ross et al., 1997; Gattaz et al., 1995; Albers, Meurer, Marki, & Klotz, 1993; Noponen et al., 1993; Gattaz et al., 1990; Gattaz, Kollisch, Thuren, Virtanen, & Kinnunen, 1987) could be explained by different PLA2 assays used (the negative studies used an assay based on bacterial antibodies). In keeping with reductions of membrane AA in schizophrenia, an increased calcium-independent PLA2 activity has also been demonstrated in post mortem brain tissue of the temporal cortex of patients with schizophrenia (Ross, Turenne, Moszczynska, Warsh, & Kish, 1999). In contrast, calcium-dependent PLA2 activity was decreased by 27–29% in the temporal and prefrontal cortex and by 44% in the putamen, relative to controls (although it is known that PLA2 is inhibited by neuroleptic medication (Gattaz et al., 1987). In a very recent study comparison of calcium-independent PLA2 activity in blood serum of first episode and chronic schizophrenia patients with corresponding matched control groups revealed significantly increased iPLA2 activity only in first episode patients (Smesny et al., 2005) suggesting that these processes may be particularly relevant for the early phase of schizophrenia and related disorders. Similar alterations in PLA2 activities

have been found in other psychiatric and neurological conditions (Noponen et al., 1993).

PLA2 gene variations and schizophrenia

Allelic association studies of PLA2 genes using case-control and transmission disequilibrium tests provide conflicting results. The majority of association studies to date investigated the promotor and Ban1 region of PLA2G4A. Hudson et al. (1996) investigated the promotor Poly(A) variant (an adenine repeat) and reported 10 size alleles, termed A1–A10, ranging from 41–60 repeats in length. They reported an association between the alleles A7–A10 with schizophrenia (Hudson et al., 1996) using a case-control and a transmission model. Interestingly, niacin insensitivity was greater in patients with the A7–A10 alleles (Hudson, Wei, Lee, & Peet, 1996). Later studies found associations between schizophrenia and a Poly(A) allele (Frieboes et al., 2001; Doris et al., 1998; Price, Fox, St Clair, & Shaw, 1997). Ramchand, Wei, Lee, & Peet (1999) investigated deletions of promotor CA repeats and found no significant association with schizophrenia. Furthermore a range of studies found associations of a PLA2 gene variant in the 1st intron of PLA2G4A, rs10798059 (BanI) with schizophrenia under both case control and Transmission Disequilibrium Test models (Wei & Hemmings, 2004; Pae et al., 2004; Peet et al., 1998; Wei, Lee, & Hemmings, 1998), however five consecutive studies could not replicate any association between the BanI locus and schizophrenia (Tao et al., 2005; Junqueira, Cordeiro, Meira-Lima, Gattaz, & Vallada, 2004; Wei & Hemmings, 2004; Yu et al., 2004; Chowdari et al., 2001). An investigation using micro-satellite markers across the chromosome region containing PLA2G4A makes it unlikely that the associations are due to linkage disequilibrium with a nearby gene (Wei & Hemmings, 2004). Even less conclusive are association studies for other PLAs such as PLA2G6A. A variant in the fourth intron of PLA2G6A rs4375 has been associated with schizophrenia using both a case/control and a Transmission Disequilibrium model in a Brazilian population (Junqueira et al., 2004). In conclusion, there is very limited understanding of the different genetic variants of different types of PLA2s and psychotic illnesses (Frieboes et al., 2001; Hudson et al., 1996; Junqueira et al., 2004). There is a need to investigate the role of PLA2 gene variants in schizophrenia in a more systematic way to understand possible pathophysiological implications, for example, interactions of PLA2 gene variations, responses characteristic to anti-psychotics and environmental variables such as cannabis abuse (containing arachidonic acid).

Lipoproteins, the transport vehicles for bioactive lipids

Lipoproteins, in particular ApoD, ApoE and ApoL have received increasing attention in neuropsychiatric disorders, in particular schizophrenia (Sutcliffe & Thomas, 2002). ApoD as a transport molecule of AA has been researched in schizophrenia. ApoD which is mainly bound to high density proteins and found in high abundance in the brain, is differentially expressed in different brain regions (Thomas, Dean, Scarr, Copolov, & Sutcliffe, 2003) and its expression is induced by atypical anti-psychotics such as clozapine (Dean et al., 2003). Increased levels of ApoD levels have been reported in post mortem prefrontal cortex (Thomas, Dean, Pavey, & Sutcliffe, 2001b) and in plasma of drug-naïve schizophrenia patients (Mahadik, Khan, Evans, & Parikh, 2002). These data indicate that the ApoD increase probably predates the onset of illness. The increase in ApoD after clozapine treatment may be indicative that clozapine's superior efficacy may be partially mediated via induction of ApoD. What is unclear is if gene variants of ApoD may increase the risk for schizophrenia or be related to poor outcome. There is some evidence that ApoE (Dean et al., 2003; Schurhoff et al., 2003) and ApoL may be linked to the illness itself and be important for the understanding of associations between aberrant bioactive lipid signalling and major mental illnesses (Mahadik et al., 2002).

Altered glycerophospholipid (GPL) membrane composition in schizophrenia

Whereas the evidence for reduced EFAs, increased activity of the calcium-independent PLA2 (probably the cytosolic 85 kDa group IVA PLA2), decreased activity of calcium dependent PLA2 and altered lipid transport proteins (ApoD) seems to be quite robust, measures of GPL composition of the cell membrane seem to be less conclusive (Ripova, Strunecka, Nemcova, & Farska, 1997; Keshavan, Mallinger, Pettegrew, & Dippold, 1993; Rotrosen & Wolkin, 1987). Initial reports found a marked increase in phosphatidylserine (PtdSer) (up to 50%) and a decrease in phosphatidylethanolamine (PtdEtn) (9–47%) and phosphatidylcholine (Henn, 1980; Stevens, 1972) leading to the proposal that the ratio of PtdEtn to PtdSer might be a biochemical marker for schizophrenia (Keshavan et al., 1993; Ripova et al., 1997; Rotrosen & Wolkin, 1987), although two groups (Hitzemann, Hirschowitz, & Garver, 1984; Lautin et al., 1982) failed to replicate these findings. Significantly lower amounts of PtdEtn and PtdCho were found in post mortem brain tissue from patients with schizophrenia (Yao et al., 2000b), even after accounting for potential confounds.

Longitudinal GPL analysis of peripheral cell membranes in first episode drug-naïve patients and non-affected first degree relatives in combination with measurement of enzyme activities (e.g., phospholipases), An EFA analysis and 31-phosphorus MRS would be required to further elucidate the underlying pathomechanism behind these membrane abnormalities.

Membrane chemistry assessed by 31 phosphorus MR spectroscopy (31P-MRS)

Advances in brain imaging have allowed measurement of *in vivo* brain lipid metabolites using 31P-MRS. There are two important peaks from the phosphorus spectrum—the phosphomonoesters (PMEs) and phosphodiesters (PDEs) enabling the *in vivo* assessment of brain membrane abnormalities. The PME sum-peak includes the resonances of phosphatidylethanolamine (PtdEth) and phosphatidylcholine (PtdCh) peak (associated with cell membrane precursors). The PDE sum-peak can be separated into resonances of glycerophosphatidylcholine (GPCh) and glycerophosphatidylethanolamine (GPEth), although they represent only about 15% of the total peak area. The PDEs are associated with the breakdown products of the cell membrane. The remaining broader underlying signals (membrane bound phospholipids that are less mobile and probably of lysosomal and peroxisomal origin) most likely arise from intracellular phospholipids (Potwarka et al., 1999). The role of 31P-MRS in the investigation of high-energy metabolites (Kegeles, Humaran, & Mann, 1998; Vance et al., 2000) and other methodological aspects (Keshavan, Stanley, & Pettegrew, 2000) are reviewed elsewhere.

In a landmark study, Pettegrew et al. (1991) demonstrated decreased PMEs and increased PDEs in the prefrontal cortex of drug-naïve first-episode patients, indicative of a higher cell membrane turnover in emerging psychotic disorders. This pattern may also be present before the onset of psychosis (Keshavan, Pettegrew, Panchalingam, Kaplan, & Bozik, 1991). Reduced PMEs and increased PDEs have also been identified in the temporal lobes of drug-naïve first-episode patients (Fukuzako et al., 1999a). Thus, the previously described alterations of the cell membrane in peripheral cells and post mortem brain tissue have also been demonstrated *in vivo*, in early stages of schizophrenia. Indeed, first-episode drug-naïve psychosis patients showed a strong correlation between elevated *in vivo* brain PDEs in prefrontal cortex and low red cell membrane AA levels in red cell membranes, suggesting that alterations in peripheral tissue are closely related to *in vivo* brain membrane alterations (Yao et al., 2002) supporting the notion of the presence of membrane abnormalities in schizophrenia throughout the body (Horrobin, 1996).

Stanley et al. (1995) examined whether this pattern was present at different illness stages by examining three groups: drug-naïve, newly diagnosed medicated and chronic medicated patients with schizophrenia. The PMEs were lower in all three groups when compared to age- and sex-matched control groups. However, PDEs were only increased in drug naïve and newly diagnosed medicated patients, implying a higher membrane phospholipid turnover at the onset of illness. Another explanation for this finding may be that antipsychotics inhibit the breakdown of membrane phospholipids (Fukuzako et al., 1999b). Using proton-decoupling in chronic medicated patients with schizophrenia, Potwarka et al. (1999) unexpectedly found that the glycerol-3-phosphoethanolamine (GPEth) peak, and glycerol-3-phosphocholine (GPCh) peak were both normal, but the broader underlying phospholipid peak (probably lysosomal or peroxisomal) was higher, potentially suggesting excessive pruning (Keshavan et al., 1994) or excessive apoptotic activity (Ferri & Kroemer, 2001). However, this has yet to be replicated, with the only similar study assessing the parietal rather than the prefrontal cortex (Bluml et al., 1999) not describing this broad underlying peak.

EFA supplementation studies in schizophrenia

Initial supplementation studies in chronic schizophrenia patients used formulae with a majority of omega-6 EFA and did not identify any beneficial effect on symptomatology (Vaddadi, Gilleard, Mindham, & Butler, 1986; Wolkin, Jordan, Peselow, Rubinstein, & Rotrosen, 1986). However, in a further study in psychiatric patients ($n = 48$) suffering mainly from chronic schizophrenia (81.3%) with neuroleptica-associated tardive dyskinesia (TD), Vaddadi, Courtney, Gilleard, Manku and Horrobin (1989) used 12 capsules of Efamol per day, each containing 360 mg of linoleic acid and 45 mg gamma-linolenic acid in a double-blind placebo-controlled eight months trial with cross-over after four months. They found evidence of EFA deficiency, in particular of arachidonic acid and docosahexenoic acid. The EFA deficiency was bigger in cases with high levels of TD. Unexpected was the clinically relevant mean improvement of 20–30% in the psychopathology during the Efamol treatment compared to the placebo treatment as measured with the Comprehensive Psychopathological Rating Scale (CPRS) ($F = 18.45$; $df = 1.30$; $p < 0.002$). The cognitive improvement as measured with the Wechsler Memory scale ($F = 7.06$; $df = 1.29$; $p < 0.012$) and for

the Simpson's dyskinisia scores ($F = 4.32$; $df = 1.36$; $p < 0.05$) were significant however the effects were rather small to be of major clinical significance. The effects for the Abnormal Involuntary Movement Scale were not significant.

An open-labelled trial including 20 patients with chronic schizophrenia was indicative that 10 g of an Omega-3 enriched oil (1 g of MaxEPA contains 171 mg of eicosapentaenoic acid, and 114 mg of docosahexanoic acid) improved positive and negative symptoms, though only negative symptoms reached statistical significance (Mellor, Laugharne, & Peet, 1996; Rudin, 1981). The Cohen's d effect size with Hedges Adjustment of this open-labelled trial was quite big with 0.93 (95% CI 0.27–1.58). However, such an effect size has to be treated very cautiously, given the lack of a control group and the experience of large placebo effects in other placebo-controlled omega-3 fatty acid supplementation trials in chronic population (Peet et al., 2002). However, forward multiple regression does indeed suggested that changes in RBC membrane total n-3 fatty acids were associated with changes in total PANSS scores, in fact accounting for 28% of the variance. Whilst negative symptoms showed significant clinical improvement, no significant relationship to changes in fatty acid levels were found in this analysis. Similar findings were also observed in another small open-label study using 1g of an EPA-enriched oil (Kirunal; EPA: DHA = 3 : 1) per day in 10 chronic, symptomatic patients with schizophrenia (Shah, Vankar, Telang, Ramchchand, & Peet, 1998). The key limitation of all these studies was that they were not masked (double blind), however, the correlation between symptomatic improvement and normalization of EFA metabolites is suggestive that the effects are not only explained by rater bias or placebo effect.

On the basis of these preliminary results, Peet, Brind, Ramchand, Shah and Vankar (2001) conducted a double-blind, randomized, placebo-controlled pilot study in symptomatic patients with chronic schizophrenia ($n = 45$), which was devised to compare the effects of an EPA-enriched oil (Kirunal®), a DHA-enriched oil (Doconal®) and a placebo oil. After treatment, the total PANNSS score of the EPA-treated group was significantly lower then that of the placebo group ($t = 2.1$ $p = 0.05$). The Cohen's d effect size with Hedges Adjustment was 0.57 (95% CI −0.17–1.31). Using ANCOVA for repeated measures (thus taking baseline differences into account), there was a significant treatment effect favouring EPA over DHA on the positive PANSS score ($F = 5.24$; $p = 0.03$). The advantage became even more obvious if a 25% cut-off score was used showing a significant group effect (Kruskal-Wallis one-way ANOVA, $\chi^2 = 7.6$ $p = 0.02$). Pair-wise comparison using Chi-square tests showed a significant difference between EPA and DHA ($\chi^2 = 6.57$; $p = 0.04$) and between EPA and placebo ($\chi^2 = 6.75$; $p = 0.04$).

Consequently, Peet and colleagues (2001) undertook another randomized double-blind placebo-controlled study comparing 2 g of EPA enriched oil/day with 2 g mineral oil supplementation as an initial sole treatment. The treating doctors were instructed to withhold neuroleptic treatment as long as possible. After the study period of 12 weeks, only 66% of the patients in the EPA arm were started on neuroleptic medication (haloperidol), compared with 100% of those in the placebo arm (Fisher's Exact test EPA versus placebo $p < 0.02$). Furthermore total days on haloperidol were significantly lower in the EPA-treated group (35.1 [34.7] days versus 65.3 [18.9] days; $p < 0.02$), and despite this, patients of the EPA group showed a greater improvement in PANSS total ($p < 0.02$) and PANSS positive scores ($p < 0.05$). Calculation of effect sizes is not justified in this study as the distribution of antipsychotic background treatment is not equal between the two groups.

Fenton and colleagues (2001) undertook the first fully independent double-blind placebo-controlled randomized trial in chronic patients with chronic residual type schizophrenia ($n = 87$) that was supported through the Stanley Medical Research Centre. The patients had a mean age of 40 (range 18–65), an average duration of illness of 20 years and were supplemented with 3 g purified EPA/placebo daily for a period of sixteen weeks. The placebo-controlled randomized trial showed no between group differences for either psychopathological parameters, or for cognitive functioning. There are several possibilities to explain the lack of efficacy in this well-designed trial in comparison with the Peet trials. The selection of patients was different. In the Fenton trial, patients had chronic residual type schizophrenia, whereas in the Peet trials, patients were either unmedicated or had an acute psychotic episode. The likelihood of change using a pure augmentation strategy in residual type chronic schizophrenia group is rather low. Furthermore, in the Fenton trial, they were on a fixed dose of antipsychotic background medication, a large proportion were treated with atypical medication, whereas in the Peet trials, a large proportion of patients were on typical antipsychotic medication. The key advantage of the Fenton trial was that it was a trial that was supported by a non-benefit organization, whereas the Peet trials were supported by the manufacturer of the purified E-EPA.

In a dose-ranging exploratory study including 115 patients with DSM-IV schizophrenia, Peet et al. (2002) investigated 1, 2, and 4 g of E-EPA versus placebo. The mean age in all four groups was in the

late 30th with a wide range. Patients were treated with a range of antipsychotic medications. Only the clozapine treated patients showed a beneficial effect at all three doses of E-EPA augmentation compared to placebo PANSS total and sub-scores, as well as MADRS scores (e.g., percentage changes from baseline to last assessment for 2 g E-EPA −26.6% versus placebo −6%, $p = 0.004$). However, the numbers per cell were very low (<10 patients per group!) There was a positive correlation between improvement on rating scales and rise in red blood cell arachidonic acid concentrations. Finally, the triglyceride levels in the patients on clozapine improved more in the 2 g and 4 g E-EPA-treated group compared to the placebo treated group ($p = 0.02$) (Peet et al., 2002). Calculation of effect sizes was not possible as no standard deviations were provided.

Emsley et al. (2002) conducted a second independent placebo-controlled trial using 3 g of E-EPA versus 3 g of a placebo oil in sub-acute patients with schizophrenia ($n = 40$) with high rates of TD and showed a beneficial effect of 3 g EPA over placebo. For the PANSS total score the difference between the groups was statistically significant in favour of the E-EPA group (mean = 12.6 [SD = 14.0] versus 3.1 [SD = 13.3]) ($t = 2.20$, $df = 38$, $p = 0.03$), and this difference remained significant after controlling for effects of dietary EPA, medication, duration of illness, and gender. The Cohen's d effect sizes for E-EPA in this study were 0.68 (95% CI 0.04–1.32). Furthermore, the E-EPA group showed a significantly greater reduction in Extrapyramidal Symptom Rating Scale dyskinesia scores at 12 weeks ($t = 2.82$, $df = 38$, $p = 0.008$). A possible explanation for the contradictory findings may be the selection of patients (sub-acute to chronic versus residual-type schizophrenia) or the presence of high rates of TD in the latter study.

Limitations

There are several limitations evident in the treatment studies reported to date. Different combinations and doses of oils, some with higher quantities of parent EFA compounds and others with different n-3/n-6 ratios, make interpretation difficult. Some studies used a sample of chronic highly treatment-resistant patients with TD, while other studies used unmedicated acutely ill schizophrenia patients. Ethnic or dietary factors may also be a confounding factor (the studies with the strongest effects were carried out in India). Neuroleptic treatment has also been heterogeneous. In addition, the effects of sex steroids on EFA metabolism, susceptibility of EFA to oxidation (from smoking, starvation, and stress), developmental factors (e.g., birth complications, breast-feeding), the dependency of EFA metabolism on age (e.g., loss of desaturase activity), and environmental factors (e.g., cannabis use) should also to be considered in future studies. While diet might also have a confounding effect, this would be unlikely, as the amount of EFA supplementation used in clinical trials (usually 1–10 g n-3 EFA/day) is much higher than the dietary intake, even if fish were consumed on a daily basis (a fish meal of 100 g smoked Atlantic Salmon has around 200 mg EPA [Nichols, Virtue, Mooney, Elliot, & Yearsley, 1998], which is around 10% of the amount of EPA used in clinical trials).

Discussion and conclusions

A general reduction of cell membrane AA levels in peripheral (e.g., red blood cells, fibroblasts) and post mortem brain tissue, the increased activity of calcium-independent PLA2 (most likely the cytosolic, group IVA PLA2) and the increased *in vivo* membrane turn-over measured with 31P-MRS in drug-naïve first episode schizophrenia support the notion of a membrane pathology at the onset of illness. The findings are less conclusive in chronic illness. The underlying pathology of these findings is still speculative but may be related to an increase in apoptotic activity in the context of axonal and dendritic pruning and loss of (synaptic) glial cells (Berger, Wood, & McGorry, 2003), or be due to a dysfunction in lipid metabolising enzymes, lipid transport proteins that may manifest if environmental factors such as increased oxidative stress and cannabis abuse interact with a genetic vulnerability. While differences might be expected at different illness stages, no longitudinal studies have been performed examining bioactive lipids from the onset of the illness to more chronic stages. At least cross-sectional comparison of PLA2 activity (Smesny et al., 2005), niacin sensitivity and *in vivo* 31P-MRS (Smesny et al., 2005; Stanley et al., 1995) between first episode and chronic schizophrenia patients and matched controls support the notion of a stage dependency of membrane lipid changes. While the membrane breakdown could be influenced by antipsychotic treatment (Fukuzako et al., 1999b), the first-episode studies in neuroleptic-naïve patients (Pettegrew et al., 1991) indicate that medication effects do not explain the observed membrane changes at the on-set of illness.

Tools, such as the niacin skin test as a marker of AA availability, blood and breath analyses (Phillips, Erickson, Sabas, Smith, & Greenberg, 1995) may be important to further explore the relevance of lipid chemistry in subtyping psychotic disorders (Hudson et al., 1999). Stratification using such biological markers may enable to identify subgroups that benefit

form potential new treatments such as selective enzyme inhibitors (selective iPLA2 inhibitors, COX 2 inhibitors; Muller et al., 2004) or agents that target molecules relevant for lipid metabolism (e.g., expression of apolipoprotein D; Thomas et al., 2001a). More recent gene expression studies further support that a range of differentially expressed lipid genes may be important for the pathogenesis of schizophrenia (Davis et al., 2003; Hakak et al., 2001).

The available preliminary data from intervention studies provide some limited support for the notion that purified EPA is a modestly effective augmentation treatment to antipsychotic medication in acute schizophrenia at doses of 1–3 grams/day. However, the largest, well designed independent multi-centre study in patients with established schizophrenia and residual symptoms using 3 grams EPA/day failed to demonstrate such an effect. It is unclear if this is related to the selection of residual type schizophrenia patients on stable medication potentially masking the effects of E-EPA, or if the smaller scale studies were prone to statistical errors. Most studies have used EPA as an adjunct to neuroleptic medication with only one small controlled study initially starting acute schizophrenia patients on EPA alone (Peet et al., 2001).

The question of specificity of the findings and any proposed interventions needs to be addressed. Controlled clinical trials indicate that omega-3 fatty acids may be beneficial either as sole or an augmentation treatment in a range of neuropsychiatric conditions with conflicting results (Schachter et al., 2005). Controlled trails in individuals with childhood disorders such as dyslexia or attention deficit and hyperactivity disorders (Richardson & Montgomery, 2005), major depression (Su, Huang, Chiu, & Shen, 2003; Nemets, Stahl, & Belmaker, 2002; Peet & Horrobin, 2002; Puri, Counsell, Richardson, & Horrobin, 2002b), bipolar disorder (Stoll et al., 1999), borderline personality disorder (Zanarini & Frankenburg, 2003), and incarcerated young males (Gesch, Hammond, Hampson, Eves, & Crowder, 2002) suggest that omega-3 fatty acids may modulate mood, impulsivity and aggression, while more robust effects have been associated with the treatment of movement abnormalities in Huntington's disease (Vaddadi, Soosai, Chiu, & Dingjan, 2002; Clifford et al., 2002; Puri, et al., 2002a; Puri et al., 2005).

After five published small to medium scale placebo-controlled studies investigating the short-term effects of purified E-EPA in schizophrenia (four positive and one negative), the authors believe that two further large-scale studies in first-episode non-affective psychosis are needed. A short-term trial (e.g., six weeks) investigating its effects on time to remission, hospitalization time and antipsychotic dose, preferably in first episode schizophrenia (eventually restricted to an inpatient setting). The second and probably clinically more relevant study is a large scale relapse prevention study (e.g., one to two years) in the early course of schizophrenia with number of relapses and treatment adherence as primary outcome measures, and the investigation of the effects of E-EPA on metabolic tolerability of antipsychotic medication as secondary outcome measures. A postulated modest effect of EPA may manifest better in relapse prevention studies than in the acute phase of illness or in chronic stable patients, where already effective antipsychotic treatments or chronicity of illness may mask its modest effects. Such studies seem to be warranted, given the preclinical evidence of its neuroprotective potential at moderate doses (Lonergan, Martin, Horrobin, & Lynch, 2002). Furthermore future studies need to address the socio-economic implications of such an augmentation strategy. Finally, besides efficacy, tolerability and socio-economic reasons, we should also consider the potential effects on compliance by supplying our patients with a combination product that integrates atypical antipsychotic agents with natural ingredients such as E-EPA given the low adherence rates to psychotropic medications in serious mental illness. Such studies would ultimately determine if E-EPA has a place in the treatment of non-affective FEP.

Acknowledgments

This work was supported by the ORYGEN Research Centre, that received funding for related projects by an NHMRC project grant (IDs: 209062), a NHMRC program grant (McGorry et al.) and the Colonial Foundation, Melbourne Australia. Dr Gregor Berger received further support from the Swiss National Science Foundation and M. & W. Lichtenstein Foundation (University of Basel), the Stanley Medical Research Centre, the University of Melbourne, and Melbourne Health. The first author wants to thank the late David Horrobin, Matcheri Keshavan, Patrick McGorry, Malcolm Peet, Krishna Vaddadi (Monash University) and Stephen Wood for their ongoing support and encouragement over the last couple of years in progressing his ideas around the importance of lipid biology for schizophrenia. We want to thank Richard Cotton and Matthew Law for their support to understand the complexity of the genetics of PLA2s genes. There are no conflicts of interest of any of the authors.

References

Agranoff, B. W., Joyce, A. B., & Hajra, A. K. (1998). Lipids. In G. J. Siegel, & B. W. Agranoff (Eds.), *Basic neurochemistry: Molecular, cellular and medical aspects* (6th ed., pp. 47–68). Philadelphia: Lippincott-Raven Publishers.

Albers, M., Meurer, H., Marki, F., & Klotz, J. (1993). Phospholipase A2 activity in serum of neuroleptic-naive psychiatric inpatients. *Pharmacopsychiatry*, *26*(3), 94–98.

Bazan, N. G. (2005). Lipid signaling in neural plasticity, brain repair, and neuroprotection. *Molecular Neurobiology*, *32*(1), 89–103.

Bazan, N. G., Packard, M. G., Teather, L., & Allan, G. (1997). Bioactive lipids in excitatory neurotrans-mission and neuronal plasticity. *Neurochemistry International*, *30*(2), 225–231.

Berger, G. E., Wood, S. J., Pantelis, C., Velakoulis, D., Wellard, R. M., & McGorry, P. D. (2002). Impli-cations of lipid biology for the pathogenesis of schizophrenia. *Australia & New Zealand Journal of Psychiatry*, *36*(3), 355–366.

Berger, G. E., Wood, S. J., & McGorry, P. D. (2003), *Psychopharmacology Bulletin*, *37*, 79–101.

Bluml, S., Tan, J., Harris, K., Adatia, N., Karme, A., Sproull, T., et al. (1999). Quantitative proton-decoupled 31P MRS of the schizophrenic brain *in vivo*. *Journal of Computer Assisted Tomography*, *23*(2), 272–275.

Brown, A. S., Susser, E. S., Butler, P. D., Richardson Andrews, R., Kaufmann, C. A., & Gorman, J. M. (1996). Neurobiological plausibility of prenatal nutritional deprivation as a risk factor for schizophrenia. *Journal of Nervous and Mental Disorders*, *184*(2), 71–85.

Brown, S., Birtwistle, J., Roe, L., & Thompson, C. (1999). The unhealthy lifestyle of people with schizophrenia. *Psychological Medicine*, *29*(3), 697–701.

Chowdari, K. V., Brandstaetter, B., Semwal, P., Bhatia, T., Deshpande, S., Reddy, R., et al. (2001). Association studies of cytosolic phospholipase A2 polymorphisms and schizophrenia among two independent family-based samples. *Psychiatric Genetics*, *11*(4), 207–212.

Christensen, O., & Christensen, E. (1988). Fat consumption and schizophrenia. *Acta Psychiatrica Scandinavica*, *78*(5), 587–591.

Clifford, J. J., Drago, J., Natoli, A. L., Wong, J. Y., Kinsella, A., Waddington, J. L., et al. (2002). Essential fatty acids given from conception prevent topographies of motor deficit in a transgenic model of Huntington's disease. *Neuroscience*, *109*(1), 81–88.

Connor, W. E., Neuringer, M., & Lin, D. S. (1990). Dietary effects on brain fatty acid composition: The reversibility of n-3 fatty acid deficiency and turnover of docosahexaenoic acid in the brain, erythrocytes, and plasma of rhesus monkeys. *Journal of Lipid Research*, *31*(2), 237–247.

Cunnane, S. C., Francescutti, V., Brenna, J. T., & Crawford, M. A. (2000). Breast-fed infants achieve a higher rate of brain and whole body docosahexaenoate accumulation than formula-fed infants not consuming dietary docosahex-aenoate. *Lipids*, *35*(1), 105–111.

Davis, K. L., Stewart, D. G., Friedman, J. I., Buchsbaum, M., Harvey, P. D., Hof, P. R., et al. (2003). White matter changes in schizophrenia: Evidence for myelin-related dysfunction. *Archives in General Psychiatry*, *60*(5), 443–456.

Dean, B., Laws, S. M., Hone, E., Taddei, K., Scarr, E., Thomas, E. A., et al. (2003). Increased levels of apolipoprotein E in the frontal cortex of subjects with schizophrenia. *Biological Psychiatry*, *54*(6), 616–622.

DeLisi, L. E. (1997). Is schizophrenia a lifetime disorder of brain plasticity, growth and aging? *Schizophrenia Research*, *23*(2), 119–129.

Devane, W. A., & Axelrod, J. (1994). Enzymatic synthesis of anandamide, an endogenous ligand for the cannabinoid receptor, by brain membranes. *Proceedings of the National Academy of Sciences of the USA*, *91*(14), 6698–6701.

Doris, A., Wahle, K., MacDonald, A., Morris, S., Coffey, I., Muir, W., et al. (1998). Red cell membrane fatty acids, cytosolic phospholipase-A2 and schizophrenia. *Schizophrenia Research*, *31*(2–3), 185–196.

Emsley, R., Myburgh, C., Oosthuizen, P., & van Rensburg, S. J. (2002). Randomized, placebo-controlled study of ethyl-eicosapentaenoic acid as supplemental treatment in schizo-phrenia. *American Journal of Psychiatry*, *159*(9), 1596–1598.

Farooqui, A. A., Horrocks, L. A., & Farooqui, T. (2000). Glycerophospholipids in brain: Their metabolism, incorporation into membranes, functions, and involvement in neurological disorders. *Chemistry and Physics of Lipids*, *106*(1), 1–29.

Farstad, M. (1966). Determination of fatty acids in cerebrospinal fluid. V. The fatty acid content in the total lipids of cerebrospinal fluid in psychiatric patients. *Scandinavian Journal of Clinical and Laboratory Investigations*, *18*(3), 343–346.

Feinberg, I. (1990). Cortical pruning and the development of schizophrenia. *Schizophrenia Bulletin*, *16*(4), 567–570.

Feinberg, I. (1982). Schizophrenia: Caused by a fault in programmed synaptic elimination during adolescence? *Journal of Psychiatric Research*, *17*(4), 319–334.

Fenton, W. S., Dickerson, F., Boronow, J., Hibbeln, J. R., & Knable, M. (2001). A placebo-controlled trial of omega-3 fatty acid (ethyl eicosapentaenoic acid) supplementation for residual symptoms and cognitive impairment in schizophrenia. *American Journal of Psychiatry*, *158*(12), 2071–2074.

Fenton, W. S., Hibbeln, J., & Knable, M. B. (2000). Essential fatty acids, lipid membrane abnormalities, and the diagnosis and treatment of schizophrenia. *Biological Psychiatry*, *47*, 8–21.

Ferri, K. F., & Kroemer, G. (2001). Organelle-specific initiation of cell death pathways. *Nature Cell Biology*, *3*(11), E255–E263.

Fiedler, P., Wolkin, A., & Rotrosen, J. (1986). Niacin-induced flush as a measure of prostaglandin activity in alcoholics and schizophrenics. *Biological Psychiatry*, *21*(13), 1347–1350.

Frieboes, R. M., Moises, H. W., Gattaz, W. F., Yang, L., Li, T., Liu, X., et al. (2001). Lack of association between schizo-phrenia and the phospholipase-A(2) genes cPLA2 and sPLA2. *American Journal of Medical Genetics*, *105*(3), 246–249.

Fukuzako, H., Fukuzako, T., Hashiguchi, T., Kodama, S., Takigawa, M., & Fujimoto, T. (1999a). Changes in levels of phosphorus metabolites in temporal lobes of drug-naive schizophrenic patients. *American Journal of Psychiatry*, *156*(8), 1205–1208.

Fukuzako, H., Fukuzako, T., Kodama, S., Hashiguchi, T., Takigawa, M., & Fujimoto, T. (1999b). Haloperidol improves membrane phospholipid abnormalities in temporal lobes of schizophrenic patients. *Neuropsychopharmacology*, *21*(4), 542–549.

Gattaz, W. F., & Brunner, J. (1996). Phospholipase A2 and the hypofrontality hypothesis of schizophrenia. *Prostaglandins Leukotrienes and Essential Fatty Acids*, *55*(1–2), 109–113.

Gattaz, W. F., Schmitt, A., & Maras, A. (1995). Increased platelet phospholipase A2 activity in schizo-phrenia. *Schizophrenia Research*, *16*(1), 1–6.

Gattaz, W. F., Hubner, C. V., Nevalainen, T. J., Thuren, T., & Kinnunen, P. K. (1990). Increased serum phospholipase A2 activity in schizophrenia: A replication study. *Biological Psychiatry*, *28*(6), 495–501.

Gattaz, W. F., Kollisch, M., Thuren, T., Virtanen, J. A., & Kinnunen, P. K. (1987). Increased plasma phospholipase-A2 activity in schizophrenic patients: Reduction after neuroleptic therapy. *Biological Psychiatry*, *22*(4), 421–426.

Gesch, C. B., Hammond, S. M., Hampson, S. E., Eves, A., & Crowder, M. J. (2002). Influence of supplementary vitamins, minerals and essential fatty acids on the antisocial behaviour of young *adult prisoners. Randomised, placebo-controlled trial. British Journal of Psychiatry*, *181*, 22–28.

Glass, M. (2001). The role of cannabinoids in neurodegenerative diseases. *Progress in Neurology, Psychology and Biological Psychiatry*, *25*(4), 743–765.

Glen, A. I., Cooper, S. J., Rybakowski, J., Vaddadi, K., Brayshaw, N., & Horrobin, D. F. (1996). Mem-brane fatty acids, niacin flushing and clinical parameters. *Prostaglandins Leukotrienes and Essential Fatty Acids*, *55*(1–2), 9–15.

Glen, A. I., Glen, E. M., Horrobin, D. F., Vaddadi, K. S., Spellman, M., & Morse-Fisher, N. (1994). A red cell membrane abnormality in a subgroup of schizophrenic patients: Evidence for two diseases. *Schizophrenia Research*, *12*(1), 53–61.

Hakak, Y., Walker, J. R., Li, C., Wong, W. H., Davis, K. L., Buxbaum, J. D., et al. (2001). Genome-wide expression analysis reveals dysregulation of myelination-related genes in chronic schizophrenia. *Proceedings of the National Academy of Sciences of the USA*, *98*(8), 4746–4751.

Hakkarainen, R., Partonen, T., Haukka, J., Virtamo, J., Albanes, D., & Lonnqvist, J. (2004). Is low dietary intake of omega-3 fatty acids associated with depression? *American Journal of Psychiatry*, *161*(3), 567–569.

Heleniak, E., & O'Desky, I. (1999). Histamine and prostaglandins in schizophrenia: Revisited. *Medical Hypotheses*, *52*(1), 37–42.

Henn, F. A. (1980). The biological concepts of schizophrenia. In C. Baxter & T. Melnachuk (Eds.), *Perspectives in Schizophrenia Research* (p. 209). NewYork: Raven Press.

Herken, H., Uz, E., Ozyurt, H., Sogut, S., Virit, O., & Akyol, O. (2001). Evidence that the activities of erythrocyte free radical scavenging enzymes and the products of lipid peroxidation are increased in different forms of schizophrenia. *Molecular Psychiatry*, *6*(1), 66–73.

Hibbeln, J. R. (1998). Fish consumption and major depression. *Lancet*, *351*(9110), 1213.

Hitzemann, R., Hirschowitz, J., & Garver, D. (1984). Membrane abnormalities in the psychoses and affective disorders. *Journal of Psychiatric Research*, *18*(3), 319–326.

Hoffer, A. (1969). Adverse effects of niacin in emergent psychosis. *Journal of the American Medical Association (JAMA)*, *207*(7), 1355.

Horrobin, D. F., & Bennett, C. N. (1999). The membrane phospholipid concept of Schizophrenia. In W. F. Gattaz & H. Haefner (Eds.), *Search for the Causes of Schizophrenia. Balance of the Century* (Vol. IV, pp. 261–279). Darmstadt: Springer.

Horrobin, D. F. (1998). The membrane phospholipid hypothesis as a biochemical basis for the neurode-velopmental concept of schizophrenia. *Schizophrenia Research*, *30*(3), 193–208.

Horrobin, D. F. (1996). Schizophrenia as a membrane lipid disorder which is expressed throughout the body. *Prostaglandins Leukotrienes and Essential Fatty Acids*, *55*(1–2), 3–7.

Horrobin, D. F., Manku, M. S., Hillman, H., Iain, A., & Glen, M. (1991). Fatty acid levels in the brains of schizophrenics and normal controls. *Biological Psychiatry*, *30*(8), 795–805.

Horrobin, D. F. (1980). Prostaglandins and schizophrenia. *Lancet*, *1*(8170), 706–707.

Horrobin, D. F. (1977). Schizophrenia as a prostaglandin deficiency disease. *Lancet*, *1*(8018), 936–937.

Hudson, C. J., Gotowiec, A., Seeman, M., Warsh, J., & Ross, B. M. (1999). Clinical subtyping reveals significant differences in calcium-dependent phospholipase A2 activity in schizophrenia. *Biological Psychiatry*, *46*(3), 401–405.

Hudson, C. J., Lin, A., Cogan, S., Cashman, F., & Warsh, J. J. (1997). The niacin challenge test: Clinical manifestation of altered transmembrane signal transduction in schizophrenia? *Biological Psychiatry*, *41*(5), 507–513.

Hudson, C. J., Kennedy, J. L., Gotowiec, A., Lin, A., King, N., Gojtan, K., et al. (1996). Genetic variant near cytosolic phospholipase A2 associated with schizophrenia. *Schizophrenia Research*, *21*(2), 111–116.

Innis, S. M., Sprecher, H., Hachey, D., Edmond, J., & Anderson, R. E. (1999). Neonatal polyunsaturated fatty acid metabolism. *Lipids*, *34*(2), 139–149.

Jablensky, A. (2000). Epidemiology of schizophrenia: The global burden of disease and disability. *European Archives in Psychiatry & Clinical Neuroscience*, *250*(6), 274–285.

Junqueira, R., Cordeiro, Q., Meira-Lima, I., Gattaz, W. F., & Vallada, H. (2004). Allelic association analysis of phospholipase A2 genes with schizophrenia. *Psychiatric Genetics*, *14*(3), 157–160.

Kegeles, L. S., Humaran, T. J., & Mann, J. J. (1998). In vivo neurochemistry of the brain in schizophrenia as revealed by magnetic resonance spectroscopy. *Biological Psychiatry*, *44*(6), 382–398.

Keshavan, M. S., Stanley, J. A., Montrose, D. M., Minshew, N. J., & Pettegrew, J. W. (2003). Prefrontal membrane phospholipid metabolism of child and adolescent offspring at risk for schizophrenia or schizoaffective disorder: An *in vivo* 31P MRS study. *Molecular Psychiatry*, *8*, 316–323.

Keshavan, M. S., Stanley, J. A., & Pettegrew, J. W. (2000). Magnetic resonance spectroscopy in schizophrenia: Methodological issues and findings-part II. *Biological Psychiatry*, *48*(5), 369–380.

Keshavan, M. S., Montrose, D. M., Pierri, J. N., Dick, E. L., Rosenberg, D., Talagala, L., et al. (1997). Magnetic resonance imaging and spectroscopy in offspring at risk for schizophrenia: Preliminary studies. *Progess in Neuropsychopharmacology & Biological Psychiatry*, *21*(8), 1285–1295.

Keshavan, M. S., Anderson, S., & Pettegrew, J. W. (1994). Is schizophrenia due to excessive synaptic pruning in the prefrontal cortex? The Feinberg hypothesis revisited. *Journal of Psychiatric Research*, *28*(3), 239–265.

Keshavan, M. S., Mallinger, A. G., Pettegrew, J. W., & Dippold, C. (1993). Erythrocyte membrane phos-pholipids in psychotic patients. *Psychiatry Research*, *49*(1), 89–95.

Keshavan, M. S., Pettegrew, J. W., Panchalingam, K. S., Kaplan, D., & Bozik, E. (1991). Phosphorus 31 magnetic resonance spectroscopy detects altered brain metabolism before onset of schizophrenia. *Archives in General Psychiatry*, *48*(12), 1112–1113.

Lautin, A., Cordasco, D. M., Segarnick, D. J., Wood, L., Mason, M. F., Wolkin, A., et al. (1982). Red cell phospholipids in schizophrenia. *Life Sciences*, *31*(26), 3051–3056.

Leask, S., Done, D. J., Crow, T. J., Richards, M., & Jones, P. (2000). No association between breast-feeding and adult psychosis in two national birth cohorts. *British Journal of Psychiatry*, *177*, 218–221.

Lichtermann, D., Ekelund, J., Pukkala, E., Tanskanen, A., & Lonnqvist, J. (2001). Incidence of cancer among persons with schizophrenia and their relatives. *Archives in General Psychiatry*, *58*(6), 573–578.

Lonergan, P. E., Martin, D. S., Horrobin, D. F., & Lynch, M. A. (2002). Neuroprotective effect of eicosapentaenoic acid in hippocampus of rats exposed to gamma-irradiation. *Journal of Biology & Chemistry*, *277*(23), 20804–20811.

Mahadik, S. P., Khan, M. M., Evans, D. R., & Parikh, V. V. (2002). Elevated plasma level of apolipoprotein D in schizophrenia and its treatment and outcome. *Schizophrenia Research*, *58*(1), 55–62.

Mahadik, S. P., Mulchandoni, M., Mahabaleshwar, H. V., & Ranjekar, P. K. (1999). Cultural and socio-economic differences in dietary intake of essential fatty acids and antioxidants: Effects on the course and outcome of schizophrenia. In M. Peet, I. Glen & D. Horrobin (Eds.), *Phospholipid Spectrum Disorder in Psychiatry* (pp. 167–179). Carnforth, UK: Marius Press.

Mahadik, S. P., Mukherjee, S., Scheffer, R., Correnti, E. E., & Mahadik, J. S. (1998). Elevated plasma lipid peroxides at the onset of non-affective psychosis. *Biological Psychiatry*, *43*(9), 674–679.

McCreadie, R. G. (1997). The Nithsdale Schizophrenia Surveys. 16. Breast-feeding and schizophrenia: Preliminary results and hypotheses. *British Journal of Psychiatry*, *170*, 334–337.

Mellor, J. E., Laugharne, J. D. E., & Peet, M. (1996). Omega-3 fatty acid supplementation in schizophrenic patients. *Human Psychopharmacology*, *11*, 39–46.

Mellsop, G. W. (1972). Schizophrenia and rheumatoid arthritis. *Australia & New Zealand Journal of Psychiatry*, *6*(4), 214.

Messamore, E., Hoffman, W. F., & Janowsky, A. (2003). The niacin skin flush abnormality in schizophrenia: A quantitative dose-response study. *Schizophrenia Research*, *62*(3), 251–258.

Mirnics, K., Middleton, F. A., Stanwood, G. D., Lewis, D. A., & Levitt, P. (2001). Disease-specific changes in regulator of G-protein signalling 4 (RGS4) expression in schizophrenia. *Molecular Psychiatry*, *6*(3), 293–301.

Morgan, J., Capuzzi, D., & Guyton, J. (1998). A new extended-release niacin (Niaspan): Efficacy, tolerability, and safety in hypercholesterolemic patients. *American Journal of Cardiology, 82* (*12A*), 29U–34U; discussion 39U–41U.

Morrow, J. D., Awad, J. A., Oates, J. A., & Roberts IInd, L. J. (1992). Identification of skin as a major site of prostaglandin D2 release following oral administration of niacin in humans. *Journal of Investigative Dermatology*, *98*(5), 812–815.

Mrazek, P. J., & Haggerty, R. J. (1994). New directions in definition. In P. J. Mrazek & R. J. Haggerty (Eds.), *Reducing Risks for Mental Disorders. Frontiers for preventive Intervention Research* (pp. 19–29). Washington, DC: National Academy Press.

Muller, N., Ulmschneider, M., Scheppach, C., Schwarz, M. J., Ackenheil, M., Moller, H. J., et al. (2004). COX-2 inhibition as a treatment approach in schizophrenia: Immunological considerations and clinical effects of celecoxib add-on therapy. *European Archives in Psychiatry & Clinical Neuroscience*, *254*(1), 14–22.

Nemets, B., Stahl, Z., & Belmaker, R. H. (2002). Addition of omega-3 fatty acid to maintenance medication treatment for recurrent unipolar depressive disorder. *American Journal of Psychiatry*, *159*(3), 477–479.

Ness, A. R., Gallacher, J. E., Bennett, P. D., Gunnell, D. J., Rogers, P. J., Kessler, D., et al. (2003). Advice to eat fish and mood: A randomised controlled trial in men with angina. *Nutrition & Neuroscience*, *6*(1), 63–65.

Nichols, P. D., Virtue, P., Mooney, B. P., Elliot, N. G., & Yearsley, G. K. (1998). Seafood the good Food. The oil (fat) content and composition of Australian commercial fishes, shellfishes and crustaceans. Marine Research.

Noponen, M., Sanfilipo, M., Samanich, K., Ryer, H., Ko, G., Angrist, B., et al. (1993). Elevated PLA2 activity in schizophrenics and other psychiatric patients. *Biological Psychiatry*, *34*(9), 641–649.

Oken, R. J., & Schulzer, M. (1999). At issue: Schizophrenia and rheumatoid arthritis. The negative association revisited. *Schizophrenia Bulletin*, *25*(4), 625–638.

Pae, C. U., Yu, H. S., Lee, K. U., Kim, J. J., Lee, C. U., Lee, S. J., et al. (2004). BanI polymorphism of the cytosolic phospholipase A2 gene may confer susceptibility to the development of schizophrenia. *Progress in Neuropsychopharmacology & Biological Psychiatry*, *28*(4), 739–741.

Peet, M., & Horrobin, D. F. (2002). A dose-ranging study of the effects of ethyl-eicosapentaenoate in patients with ongoing depression despite apparently adequate treatment with standard drugs. *Archives in General Psychiatry*, *59*(10), 913–919.

Peet, M., Brind, J., Ramchand, C. N., Shah, S., & Vankar, G. K. (2001). Two double-blind placebo-controlled pilot studies of eicosapentaenoic acid in the treatment of schizophrenia. *Schizophrenia Research*, *49*(3), 243–251.

Peet, M., Poole, J., & Laugharne, J. (1999). Breastfeeding, neurodevelopment, and schizophrenia. In M. Peet, I. Glen & D. Horrobin (Eds.), *Phospholipid Spectrum Disorder in Psychiatry* (pp. 159–166). Carnforth, UK: Marius Press.

Peet, M., Ramchand, C. N., Lee, J., Telang, S. D., Vankar, G. K., Shah, S., et al. (1998). Association of the Ban I dimorphic site at the human cytosolic phospholipase A2 gene with schizophrenia. *Psychiatric Genetics*, *8*(3), 191–192.

Peet, M., Laugharne, J. D., Mellor, J., & Ramchand, C. N. (1996). Essential fatty acid deficiency in eryth-rocyte membranes from chronic schizophrenic patients, and the clinical effects of dietary supplementation. *Prostaglandins Leukotrienes and Essential Fatty Acids*, *55*(1–2), 71–75.

Pettegrew, J. W., Keshavan, M. S., Panchalingam, K., Strychor, S., Kaplan, D. B., Tretta, M. G., et al. (1991). Alterations in brain high-energy phosphate and membrane phospholipid metabolism in first-episode, drug-naive schizophrenics. A pilot study of the dorsal prefrontal cortex by *in vivo* phosphorus 31 nuclear magnetic resonance spectroscopy. *Archives in General Psychiatry*, *48*(6), 563–568.

Phillips, M., Erickson, G. A., Sabas, M., Smith, J. P., & Greenberg, J. (1995). Volatile organic compounds in the breath of patients with schizophrenia. *Journal of Clinical Pathology*, *48*(5), 466–469.

Piomelli, D., Pilon, C., Giros, B., Sokoloff, P., Martres, M. P., & Schwartz, J. C. (1991). Dopamine activation of the arachidonic acid cascade as a basis for D1/D2 receptor synergism. *Nature*, *353*(6340), 164–167.

Potwarka, J. J., Drost, D. J., Williamson, P. C., Carr, T., Canaran, G., Rylett, W. J., et al. (1999). A 1H-decoupled 31P chemical shift imaging study of medicated schizophrenic patients and healthy controls. *Biological Psychiatry*, *45*(6), 687–693.

Price, S. A., Fox, H., St Clair, D., & Shaw, D. J. (1997). Lack of association between schizophrenia and a polymorphism close to the cytosolic phospholipase A2 gene. *Psychiatric Genetics*, *7*(3), 111–114.

Puri, B. K., Leavitt, B. R., Hayden, M. R., Ross, C. A., Rosenblatt, A., Greenamyre, J. T., et al. (2005). Ethyl-EPA in Huntington disease: A double-blind, randomized, placebo-controlled trial. *Neurology*, *65*(2), 286–292.

Puri, B. K., Bydder, G. M., Counsell, S. J., Corridan, B. J., Richardson, A. J., Hajnal, J. V., et al. (2002a). MRI and neuropsychological improvement in Huntington disease following ethyl-EPA treatment. *NeuroReport*, *13*(1), 123–126.

Puri, B. K., Counsell, S. J., Richardson, A. J., & Horrobin, D. F. (2002b). Eicosapentaenoic acid in treatment-resistant depression. *Archives in General Psychiatry*, *59*(1), 91–92.

Ramchand, C. N., Wei, J., Lee, K. H., & Peet, M. (1999). Phospholipase A2 Gene Polymorphism and associated Biochemical Alterations in Schizophrenia. In M. Peet, I. Glen & D. Horrobin (Eds.), *Phospholipid Spectrum Disorder in Psychiatry* (pp. 31–39). Carnforth, UK: Marius Press.

Richardson, A. J., & Montgomery, P. (2005). The Oxford-Durham study: A randomized, controlled trial of dietary supplementation with fatty acids in children with developmental coordination disorder. *Pediatrics*, *115*(5), 1360–1366.

Ripova, D., Strunecka, A., Nemcova, V., & Farska, I. (1997). Phospholipids and calcium alterations in platelets of schizophrenic patients. *Physiological Research*, *46*(1), 59–68.

Ross, B.M., Turenne, S., Moszczynska, A., Warsh, J. J., & Kish, S. J. (1999). Differential alteration of phospholipase A2 activities in brain of patients with schizophrenia. *Brain Research*, *821*(2), 407–413.

Ross, B. M., Hudson, C., Erlich, J., Warsh, J. J., & Kish, S. J. (1997). Increased phospholipid breakdown in schizophrenia. Evidence for the involvement of a calcium-independent

phospholipase A2 [see comments]. *Archives in General Psychiatry*, *54*(5), 487–494.

Rotrosen, J., & Wolkin, A. (1987). Phopholipid and prostaglandin hypotheses of schizophrenia. In H. Meltzer (Ed.), *Psychopharmacology. The Third Generation of Progress* (pp. 759–764). New York: Raven Press.

Rudin, D. O. (1981). The major psychoses and neuroses as omega-3 essential fatty acid deficiency syndrome: Substrate pellagra. *Biological Psychiatry*, *16*(9), 837–850.

Rybakowski, J., & Weterle, R. (1991). Niacin test in schizophrenia and affective illness. *Biological Psychiatry*, *29*(8), 834–836.

Sasaki, T., Okazaki, Y., Akaho, R., Masui, K., Harada, S., Lee, I., et al. (2000). Type of feeding during infancy and later development of schizophrenia. *Schizophrenia Research*, *42*(1), 79–82.

Schachter, H., Kourad, K., Merali, Z., Lumb, A., Tran, K., Miguelez, M., et al. (2005). Effects of omega-3 fatty acids on mental health. (No. 116). Rockville, MD: Prepared by University of Ottawa Evidence-based Practice Center, Under Contract No. 290-02-0021.

Schurhoff, F., Krebs, M. O., Szoke, A., Loze, J. Y., Goldberger, C., Quignon, V., et al. (2003). Apolipoprotein E in schizophrenia: A French association study and meta-analysis. *American Journal of Medical Genetics*, *119B*(1), 18–23.

Shah, S. H., Vankar, G. K., Peet, M., & Ramchand, C. N. (2000). Unmedicated schizophrenic patients have a reduced skin flush in response to topical niacin [letter]. *Schizophrenia Research*, *43*(2–3), 163–164.

Shah, S. H., Vankar, G. K., Telang, S. D., Ramchchand, C. N., & Peet, M. (1998). Eicosapentanoic acid (EPA) as an adjunct in the treatment of schizophrenia. *Schizophrenia Research*, *29*, 158.

Sinclair, A. J., Murphy, K. J., & Li, D. (2000). Marine lipids: Overview 'news insights and lipid composi-tion of Lyprinol'. *Allergies & Immunology (Paris)*, *32*(7), 261–271.

Six, D. A., & Dennis, E. A. (2000). The expanding superfamily of phospholipase A(2) enzymes: Classification and characterization. *Biochimica Biophysica Acta*, *1488*(1–2), 1–19.

Smesny, S., Kinder, D., Willhardt, I., Rosburg, T., Lasch, J., Berger, G., et al. (2005). Increased calcium-independent phospholipase A2 activity in first but not in multi-episode chronic schizophrenia. *Biological Psychiatry*, *57*(4), 399–405.

Smesny, S., Berger, G., Rosburg, T., Riemann, S., Riehemann, S., McGorry, P., et al. (2003). Potential use of the topical niacin skin test in early psychosis—a combined approach using optical reflection spectroscopy and a descriptive rating scale. *Journal of Psychiatric Research*, *37*(3), 237–247.

Stanley, J. A., Williamson, P. C., Drost, D. J., Carr, T. J., Rylett, R. J., Malla, A., et al. (1995). An *in vivo* study of the prefrontal cortex of schizophrenic patients at different stages of illness via phosphorus magnetic resonance spectroscopy [published erratum appears in *Archives of General Psychiatry* 1995 Oct; 52 (10) : 799] [see comments]. *Archives of General Psychiatry*, *52* (5), 399–406.

Stevens, J. D. (1972). The distribution of the phospholipid fractions in the red cell membrane of schizophrenics. *Schizophrenia Bulletin*, *6*, 60–61.

Stoll, A. L. (2001). Fish consumption, depression, and suicidality in a general population. *Archives of General Psychiatry*, *58*(5), 512–513.

Stoll, A. L., Severus, W. E., Freeman, M. P., Rueter, S., Zboyan, H. A., Diamond, E., et al. (1999). Omega 3 fatty acids in bipolar disorder: A preliminary double-blind, placebo-controlled trial [see comments]. *Archives of General Psychiatry*, *56*(5), 407–412.

Su, K. P., Huang, S. Y., Chiu, C. C., & Shen, W. W. (2003). Omega-3 fatty acids in major depressive disorder. A preliminary double-blind, placebo-controlled trial. *European Journal of Neuropsychopharmacology*, *13*(4), 267–271.

Sutcliffe, J. G., & Thomas, E. A. (2002). The neurobiology of apolipoproteins in psychiatric disorders. *Molecular Neurobiology*, *26*(2–3), 369–388.

Suzuki, S., Akechi, T., Kobayashi, M., Taniguchi, K., Goto, K., Sasaki, S., et al. (2004). Daily omega-3 fatty acid intake and depression in Japanese patients with newly diagnosed lung cancer. *British Journal of Cancer*, *90*(4), 787–793.

Tao, R., Yu, Y., Zhang, X., Guo, Y., Shi, J., Xie, L., et al. (2005). Cytosolic PLA2 genes possibly contribute to the etiology of schizophrenia. *American Journal of Medical Genetics & Neuropsychiatric Genetics*, *137*(1), 56–58.

Tavares, H., Yacubian, J., Talib, L. L., Barbosa, N. R., & Gattaz, W. F. (2003). Increased phospholipase A2 activity in schizophrenia with absent response to niacin. *Schizophrenia Research*, *61*(1), 1–6.

Thomas, E. A., Dean, B., Scarr, E., Copolov, D., & Sutcliffe, J. G. (2003). Differences in neuroanatomical sites of apoD elevation discriminate between schizophrenia and bipolar disorder. *Molecular Psychiatry*, *8*(2), 167–175.

Thomas, E. A., Danielson, P. E., Nelson, P. A., Pribyl, T. M., Hilbush, B. S., Hasel, K. W., et al. (2001a). Clozapine increases apolipoprotein D expression in rodent brain: Towards a mechanism of neuroeptic pharmacotherapy. *Journal of Neurochemistry*, *76*, 789–796.

Thomas, E. A., Dean, B., Pavey, G., & Sutcliffe, J. G. (2001b). Increased CNS levels of apolipoprotein D in schizophrenic and bipolar subjects: Implications for the pathophysiology of psychiatric disorders. *Proceedings of the National Academy of Sciences of the USA*, *98*(7), 4066–4071.

Torres, I. C., Mira, L., Ornelas, C. P., & Melim, A. (2000). Study of the effects of dietary fish intake on serum lipids and lipoproteins in two populations with different dietary habits. *British Journal of Nutrition*, *83*(4), 371–379.

Vaddadi, K. S., Soosai, E., Chiu, E., & Dingjan, P. (2002). A randomised, placebo-controlled, double blind study of treatment of Huntington's disease with unsaturated fatty acids. *NeuroReport*, *13*(1), 29–33.

Vaddadi, K. S., Courtney, P., Gilleard, C. J., Manku, M. S., & Horrobin, D. F. (1989). A double-blind trial of essential fatty acid supplementation in patients with tardive dyskinesia. *Psychiatry Research*, *27*(3), 313–323.

Vaddadi, K. S., Gilleard, C., Mindham, R., & Butler, R. (1986). A controlled trial of prostaglandin E1 precursor in chronic neuroleptic resistant schizophrenic patients. *Psychopharmacology (Berlin)*, *88*(3), 362–367.

Vance, A. L., Velakoulis, D., Maruff, P., Wood, S. J., Desmond, P., & Pantelis, C. (2000). Magnetic resonance spectroscopy and schizophrenia: What have we learnt? *Australia & New Zealand Journal of Psychiatry*, *34*(1), 14–25.

Waldo, M. C., & Freedman, R. (1999). Neurobiological abnormalities in the relatives of schizophrenics. *Schizophrenia Research*, *33*(6), 491–495.

Ward, P. E., Sutherland, J., Glen, E. M., & Glen, A. I. (1998). Niacin skin flush in schizophrenia: A preliminary report. *Schizophrenia Research*, *29*(3), 269–274.

Wei, J., & Hemmings, G. P. (2004). A study of a genetic association between the PTGS2/PLA2G4A locus and schizophrenia. *Prostaglandins Leukotrienes and Essential Fatty Acids*, *70*(4), 413–415.

Wei, J., Lee, K. H., & Hemmings, G. P. (1998). Is the cPLA2 gene associated with schizophrenia? *Molecular Psychiatry*, *3*(6), 480–481.

Wilson, D. W., & Douglass, A. B. (1986). Niacin skin flush is not diagnostic of schizophrenia. *Biological Psychiatry*, *21*(10), 974–977.

Wolkin, A., Jordan, B., Peselow, E., Rubinstein, M., & Rotrosen, J. (1986). Essential fatty acid supplementation in tardive dyskinesia. *American Journal of Psychiatry*, *143*(7), 912–914.

Yao, J. K., Stanley, J. A., Reddy, R. D., Keshavan, M. S., & Pettegrew, J. W. (2002). Correlations between peripheral polyunsaturated fatty acid content and *in vivo* membrane phospholipid metabolites. *Biological Psychiatry*, *52*(8), 823–830.

Yao, J. K., Leonard, S., & Reddy, R. D. (2000a). Membrane phospholipid abnormalities in postmortem brains from schizophrenic patients. *Schizophrenia Research*, *42*(1), 7–17.

Yao, J. K., Stanley, J. A., Reddy, R. D., Keshavan, M. S., & Pettegrew, J. W. (2000b). Correlation between RBC fatty acids and 31P MRS brain measures in schizophrenia. *Society for Biological Psychiatry*, *47*, 41.

Yao, J. K., van Kammen, D. P., & Gurklis, J. A. (1996). Abnormal incorporation of arachidonic acid into platelets of drug-free patients with schizophrenia. *Psychiatry Research*, *60*(1), 11–21.

Yao, J. K., van Kammen, D. P., & Welker, J. A. (1994a). Red blood cell membrane dynamics in schizophrenia. I. Membrane fluidity. *Schizophrenia Research*, *11*(3), 209–216.

Yao, J. K., van Kammen, D. P., & Welker, J. A. (1994b). Red blood cell membrane dynamics in schizophrenia. II. Fatty acid composition. *Schizophrenia Research*, *13*(3), 217–226.

Yu, Y. Q., Tao, R., Wei, J., Xu, Q., Liu, S. Z., Ju, G. Z., et al. (2004). No association between the PTGS2/PLA2G4A locus and schizophrenia in a Chinese population. *Prostaglandins Leukotrienes and Essential Fatty Acids*, *71*(6), 405–408.

Zanarini, M. C., & Frankenburg, F. R. (2003). Omega-3 fatty acid treatment of women with borderline personality disorder: A double-blind, placebo-controlled pilot study. *American Journal of Psychiatry*, *160*(1), 167–169.