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Depression and bipolar disorder: relationships to impaired fatty acid and phospholipid metabolism and to diabetes, cardiovascular disease, immunological abnormalities, cancer, ageing and osteoporosis

Possible candidate genes

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Summary Depression and bipolar disorder are two of the commonest illnesses in the developed world. While some patients can be treated effectively with available drugs, many do not respond, especially in the depression related to bipolar disorder. Depression is associated with diabetes, cardiovascular disease, immunological abnormalities, multiple sclerosis, cancer, osteoporosis and ageing: in each case depressed individuals have a worse outcome than non-depressed individuals. In all of these conditions there is now evidence of impaired phospholipid metabolism and impaired fatty acid-related signal transduction processes. Impaired fatty acid and phospholipid metabolism may be a primary cause of depression in many patients and may explain the interactions with other diseases. Several novel gene candidates for involvement in depression and bipolar disorder are proposed.

INTRODUCTION

Depression and bipolar disorder (manic depression) are both very common disorders. The risk of being depressed is rising rapidly in developed countries, for reasons which are unknown although many hypotheses have been proposed.[1] The success rate of drug treatment has not changed for 40 years. About two-thirds of depressed patients experience a 50% or better improvement in symptoms on drug treatment; the others fail to respond and multiple drug treatments do not greatly increase the success rate. The depression of bipolar disorder is the least well managed component of the illness. While mania can usually be brought rapidly under control, depression responds less well.[2–5] This suggests that current theories of depression which are largely based on disordered catecholamine and serotonin metabolism and which have formed the rationale for drug development for 40 years are inadequate to provide a full explanation for the illness.

Another recent research theme has been the evidence of strong associations between depression on the one hand and, on the other, cardiovascular disease, diabetes, immunological abnormalities, multiple sclerosis, cancer and ageing. In these situations it is by no means clear whether the depression is exacerbating the medical disease, the medical disease is exacerbating the depression or whether both are attributable to a third factor involved in both the depression and the other illnesses.

This paper examines the evidence and suggests that the missing factors in the understanding of depression relate to disturbed fatty acid and phospholipid metabolism and to their effects on post-receptor signal transduction mechanisms. It is also suggested that this type of mechanism explains the relationships between depression and the other illnesses.

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DEPRESSION AND OTHER DISEASES

It is evident that depression is associated with a wide range of other diseases.[6–10]

Cardiovascular disease

Large-scale cross-sectional studies have clearly shown that depression is associated with coronary heart disease[11–19] with self-rated palpitations, an indicator of cardiac rhythm disturbances[20] and with increased risk of stroke.[21] Depressed people have 2–4 times as much cardiovascular disease as non-depressed people.

Cardiovascular disease, like any serious illness, might be expected to cause depression but cross-sectional studies can not address the issue of causation. Long-term prospective studies are required to test which condition is predisposing to which. Several such prospective studies have now compared the risk of cardiovascular disease over follow-up periods of between 3 and 30 years in individuals whose psychiatric state was assessed at a time when cardiovascular health was normal.[22–25] The results of all the studies are consistent. Baseline depression is associated with an increased risk of subsequent cardiovascular disease of between two- and five-fold. The effect is greater consistently in men than in women. Thus, the depression is not caused by the cardiovascular disease. Whether the depression causes the cardiovascular disease or whether depression is an early, and cardiovascular disease a late, complication of an underlying metabolic problem remains to be clarified.

The mechanisms of the association remain unknown. Altered autonomic reactivity, increased platelet activity, hypertension and drug treatment have all been postulated as possibilities.[16,26–28] Negative feelings were positively correlated with arterial intima thickness, and also with progression of arterial thickening:[29] the more negative the feelings, the worse was the condition of the arteries.

Thus the relationship between depression and cardiovascular disease is clear. It is also clear that the depression usually precedes the cardiovascular problems but the mechanisms of interaction remain unknown.

Diabetes

The association between diabetes and cardiovascular disease is well known, so it is not surprising that there is also an association between depression and diabetes. In different studies, between 8 and 29% of patients with diabetes have been reported to be depressed, rates considerably higher than in the non-diabetic population.[30–39] There is no agreement as to the nature of the causation. It is clear that depressed patients with diabetes have an impaired quality of life[40] and also that they have an increased risk of developing all the major complications including cardiovascular disease, retinopathy, nephropathy and neuropathy.[8] Treatment can present major problems with respect to the management of both the depression and the diabetes.[30,33,41,42]

The mechanisms of the depression in diabetes remain unknown. In animals the diabetic state influences serotonin receptors.[43] In relatively rare patients, mitochondrial mutations may predispose to both psychiatric disorders and diabetes.[44] As will be discussed later, there is a reasonable basis for the idea that the fatty acid abnormalities in diabetes contribute significantly to the depression.

Immunological and cytokine abnormalities

One of the most interesting recent developments has been the macrophage/cytokine theory of depression, first proposed by Smith[45] and then developed, among others, by Maes and Leonard and their colleagues. Macrophages and other immune system cells are activated by stress and a variety of other mechanisms to generate a range of cytokines, including interferons and interleukins. The activation of these responses is associated with depression. It is not the function of the present paper to review this field in detail since this has recently been done many times.[46–59] There is abundant experimental evidence of elevations of interleukins, interleukin receptors and interferons in patients with major depression.[60–72] Depression is common in atopic disorder.[73–75] Clinical evidence from studies in which interleukins and interferons have been administered to patients, particularly those with cancer, hepatitis and multiple sclerosis, have clearly shown that severe depression and other psychiatric disorders can be precipitated by these agents and can regress on withdrawing treatment.[76–79] Whether this direct causative effect can explain in full the relationship between cytokines and depression remains unknown.

Multiple sclerosis

Depression is a major feature of multiple sclerosis.[80–84] Inappropriate euphoria is also a well known feature of multiple sclerosis and most authors have assumed that the depression is an appropriate reaction to the disease while the euphoria is an indication of brain damage. However, the fluctuating immune status of the patient with multiple sclerosis has features in common with the fluctuating mood states of the person with bipolar disorder. It has been proposed that both disorders represent disordered regulation of a phospholipid-based signal transduction process which predominantly affects neurons directly in bipolar disorder but affects both the immune

system and neurons in multiple sclerosis.[85] As early as 1926, Cottrell and Wilson argued that the mood abnormalities were fundamental to the understanding of multiple sclerosis. Both depression and bipolar disorder are much more common in patients with multiple sclerosis than in the general population and in at least some the psychiatric disorder precedes the diagnosis of multiple sclerosis and so cannot be a reaction to it.[86,87]

Cancer

To be diagnosed with cancer is a sombre event for anyone and it is, therefore, not surprising that most observers have regarded depression as an entirely appropriate psychological reaction. Because of this the condition is frequently underdiagnosed and undertreated.[88,89]

However, recently it has begun to be recognized that much of the depression found in cancer patients is not simply an appropriate psychological reaction but has a biological and biochemical basis. The effects of cytokines such as interferon and interleukin-2 in precipitating depression have already been mentioned: depression is a common side-effect when these drugs are used for cancer treatment. Colony stimulating factor may have a similar effect[90] and many of the chemotherapy and other drugs used in cancer patients are known to cause depression.[88]

Furthermore, cancer is often associated with the stress-type reactions which produce the abnormalities of hypothalamic-pituitary-adrenal function seen in depressed people without cancer.[89,91] Many cancers, and the immunological reactions they evoke, lead to substantial increases in the circulating levels of cytokines such as interleukins and interferons.[92,93] Various cytokines, and related substances, and in particular soluble interleukin 2 receptor alpha, are positively correlated with depression and poor quality of life in cancer patients.[93] These observations strongly suggest that at least some of the depressive illness associated with cancer is not simply an appropriate psychological reaction to the disease, but is induced directly by some of the biochemical changes found in cancer patients.

Ageing

As with cancer, many researchers have regarded depression as an appropriate reaction to the ageing process. Depression is much commoner among older people than among younger ones and some have attributed this in part to the co-morbidity of cardiovascular disease.[11,94–97] However, this is certainly not the whole story because depression is also commoner in older people who do not have cardiovascular disease, and because many old people are not depressed. The possibility, therefore, arises that, as with cancer, some of the depression of the elderly may not be simply a psychological reaction to ageing but may be a consequence of some of the biochemical changes found with ageing. As will be discussed later, changes in fatty acid metabolism may be involved.

DEPRESSION, BIPOLAR DISORDER AND PHOSPHOLIPID-RELATED SIGNAL TRANSDUCTION

Research on unipolar depression has been dominated by the catecholamine and serotonin concepts of disturbed neurotransmitter synthesis, release, reuptake and metabolism, and of neurotransmitter receptor function. These fields are undoubtedly important and the partial successes of the tricyclic antidepressants and the selective serotonin reuptake inhibitors (SSRIs) and related drugs have kept pharmaceutical industry research focussed on the identification of better and safer drugs within these classes. The dominance of industry funding for research in this field has obscured the facts that around 30% of patients with major depression do not respond to any drug, that the definition of response for those who do respond is usually a 50% rather than an 80–100% improvement in rating scale scores, and that in terms of efficacy the current drugs are no better than those introduced in the 1950s.[98]

Given the intensity of research on neurotransmitter hypotheses, we have been either unlucky or unimaginative in not finding better neurotransmitter-based drugs, or alternatively there are other quite different mechanisms which contribute to depression and which remain untouched by current drugs. Although bipolar disorder has attracted much less research interest, other mechanisms have been more seriously considered than is the case with unipolar depression. This is partly because it is well recognized that depression in bipolar disorder is poorly treated[2,3,5] and partly because those drugs which are the mainstay of treatment in bipolar disorder (lithium, valproate and carbamazepine) do not appear to have their primary mode of action at the neurotransmitter or receptor level. Rather they appear to interact with signal transduction systems beyond the receptor. Such signal transduction systems may well represent the most fruitful areas for research in both bipolar disorder and in unipolar depression.

Signal transduction in bipolar disorder

This is not the place for a detailed discussion of this topic which has been well-covered in recent reviews.[4,99–108] In essence, occupation of a neuronal surface receptor frequently changes the configuration of a G-protein associated with the inner side of the phospholipid membrane, or alternatively, directly activates a tyrosine kinase asso-

ciated with the receptor. There are multiple types of G-protein which have many different actions in neurons and other cells. Among these actions are activation and inhibition of cyclic AMP and cyclic GMP formation, modulation of a range of protein kinases which have many different actions, and activation of phospholipases (PL) including PLC, PLD and PLA_2. In bipolar disorder there is good evidence of disturbed membrane and phospholipid metabolism although the precise pinpointing of the specific biochemical problem has proved elusive.[101,109–111]

Part of the problem in research on the biochemistry of bipolar disorder is uncertainty as to whether patients should be studied in the manic, depressive or euthymic stages, and the difficulty of studying a substantial number of relatively uniform patients when the condition may fluctuate so rapidly. Because of this there are far fewer biological studies on bipolar disorder than is the case with unipolar disorder or schizophrenia. Instead, researchers have often attempted to probe bipolar disorder by trying to understand the mechanisms of action of the drugs which work in the illness, notably lithium and valproate.

With regard to valproate, there is no consensus as to the precise action but there are many papers suggesting that it may interact with the PLC/phosphatidylinositol cycle, the G-protein System or the protein kinase system.[102,112] There is consensus as to the view that valproate's main actions do not lie at the neurotransmitter or receptor level, but at the post-receptor signal transduction level.

The situation with lithium is similar although there is more general agreement that a major component of lithium action is likely to relate to inhibition of inositol monophosphatases in the PLC cycle.[100,102,103,113,114] This will inhibit the activity of the PLC cycle which has been postulated to be overactive in bipolar disorder, and will lead to a reduction in the levels of myo-inositol required for the synthesis of phosphatidyl-inositol. This may then secondarily lead to some of the other effects of lithium such as modulation of protein kinase C.[115]

However, none of these theories explains satisfactorily the bipolarity of bipolar disorder or the prevention of both mania and depression by lithium. Some recent observations by Chang et al. at the National Institute of Aging may be more successful in this regard. Chang and colleagues have recently found that lithium is a powerful inhibitor of arachidonic acid (AA) specific PLA_2 in the brain in vivo.[116,117] The particularly appealing features of this observation are that it occurs in the brain and it occurs at lower concentrations of lithium, well within the human therapeutic range, than any other known biochemical effect of lithium. Eighty percent of PLA_2 activity is inhibited at around 0.6 mmolar lithium. The observations suggest that the primary abnormality in bipolar disorder might be activation of PLA_2, leading to increased release of highly unsaturated fatty acids (HUFAs) such as AA, dihomo-gammalinolenic acid (DGLA) and eicosapentaenoic acid (EPA). These fatty acids are all prostaglandin precursors and have 20 carbon atoms. Lithium did not appear to inhibit the release of the 22-carbon, suggesting that the relevant PLA_2 may be one which is docosahexaenoic acid (DHA) specific to AA and closely related fatty acids.[118]

This recent observation parallels similar observations made 20 years ago in which lithium was found to inhibit the release of AA and of DGLA in response to hormonal stimulations.[119,120] Although PLA_2 activity was not measured at the time, these observations are consistent with the observations of Chang et al. on lithium and PLA_2.

These observations also offer a possible basis for the cyclic nature of bipolar disorder and for the prophylactic effect of lithium against both mania and depression. In normal individuals PLA_2 releases AA, DGLA and EPA and some of these fatty acids are converted to the related prostaglandins. Since fatty acids and prostaglandins are consistently being released from normal tissues, it is reasonable to assume that there is a normal, basal level of constant PLA_2 activity. If this PLA_2 activity is enhanced in bipolar disorder, there will an increased rate of formation of the free HUFAs and their derived prostaglandins. This will continue until the relevant compartments have been emptied of their HUFAs. At this point, instead of there being excessive release of HUFAs and PGs, there will be a fall to below normal levels until the HUFA signal transduction compartments can be repleted. Thus, there will be a flip from excess formation of HUFAs and PGs to reduced formation. There is evidence of enhanced PGE_1 production in mania and depressed PGE_1 production in depression which would be consistent with this hypothesis.[121] Lithium, by inhibiting PLA_2 will prevent both the excessive release and the depletion. If the HUFAs and their derivatives are important in regulating mood, this would explain both the mood swings of bipolar disorder and the prophylactic effects of lithium.[85,122–124] Interestingly, in view of the low levels of PGE_1 production by platelets from depressed people, PGE_1 infusions have been found to raise mood.[125]

An overactivity of PLA_2 could also explain the efficacy of dopamine D_2 blockers, of serotonin $5HT_2$ blockers and of lithium in controlling acute mania. Suppose that in mania PLA_2 is overactive because of some abnormality in the signal transduction process. We know from recent studies that much of the physiological drive which maintains PLA_2 activity comes from the occupation of D_2 and 5HT receptors.[126–130] Thus in mania, while PLA_2 activity may be increased because of something happening at the signal transduction level, part of the total PLA_2 activity will still depend on drive coming from D_2 and $5HT_2$ receptors. The direct inhibition of PLA_2 by lithium, or the

indirect reduction of PLA_2 drive by D_2 and $5HT_2$ blockade, will both reduce PLA_2 activity and help to control the mania.

Signal transduction in unipolar depression

There is now a considerable body of evidence which relates fatty acid and prostaglandin blood and tissue levels to depression. Interpretation, however, is not always easy.

The first two papers in this area both reported elevated levels of the n-3 HUFAs, DHA and EPA in depressed patients as compared to controls.[131,132] No other investigators have since reached similar conclusions. The general view is that these papers represent erroneous findings based on inappropriate selection of controls or some other problem. However, it is important that they should not be forgotten.

All subsequent investigators have reported the opposite situation, either an absolute deficit of n-3 HUFAs, or a reduced ratio of n-3 HUFAs to n-6 HUFAs. In 20 patients with major depression, Adams et al.[133] found that red cell EPA levels were inversely related to depression scores, whereas the ratio of AA/EPA in red cells and plasma was positively related to depression scores. DHA levels in either plasma or red cells were not significantly related to depression scores.

In a Belgian population comparing 36 patients with major depression, 14 with minor depression and 24 controls, similar results were obtained.[134] In both phospholipid and cholesterol esters in plasma, patients with major depression had a significantly elevated ratio of AA/EPA. They also exhibited significantly lower levels of EPA. Again DHA levels were not significantly different between the groups. In a follow-up study the same group obtained similar results: plasma levels of both EPA and its precursor alpha-linolenic acid were significantly reduced in major depression, whereas the ratio of AA to EPA was significantly elevated.[135] Again, DHA levels were not significantly different between the groups.

In an elderly population in Japan, similar results were obtained.[136] The blood cell levels of EPA were inversely related to the depression scores whereas the ratio of AA/EPA was positively correlated with depression. Again DHA levels were unrelated to depression.

Two UK studies have shown broadly similar results. In red cell membranes the levels of saturated fats were increased while those of unsaturated fatty acids were decreased.[137] However, the levels of the n-3 EFAs were reduced more than those of n-6 EFAs. When the red cells were incubated with hydrogen peroxide as a pro-oxidant, there was little change in the unsaturated fatty acid concentrations of the patients but a substantial fall in the controls. This raises the possibility that excessive oxidation may contribute to the loss of unsaturated fatty acids in the patients. A second study found very similar results in red cells, with significantly reduced levels of both EPA and DHA.[138] Part of the reason may have been dietary intake since the dietary contents of all the n-3 fatty acids were lower in the patient group than in the controls. However, this is unlikely to explain the extent of the deficits in long-chain n-3 HUFAs. There were inverse relationships between both red cell n-3 fatty acids and dietary n-3 fatty acids and the Beck Depression Inventory. The strongest relationships in the red cells were with α-linolenic acid and DHA, while in the diet the strongest relationships were with α-linolenic acid and total n-3 intake. None of the n-6 EFAs were predictive of the depression score.

There have been recent detailed reviews of the relationships between dietary and blood EFAs and depression and related parameters such as hostility and anxiety.[1,139,140] Salem, Hibbeln and their colleagues have drawn together an impressive body of evidence which indicates that dietary intake of n-3 EFAs can substantially attenuate depression. There have been remarkable and consistent progressive increases in the lifetime prevalence of depression as the present century has progressed. These changes are correlated with progressive falls in the intake of n-3 fatty acids and progressive rises in the ratio of n-6/n-3 fatty acids in the diet and the blood. Moreover, cross comparisons between countries provide similarly consistent data: there are strong inverse relationships between dietary intakes of n-3 fatty acids in a country and the national prevalences of depressive illness. The authors collate considerable evidence indicating that these changes may have important actions on neurotransmitter metabolism, on signal transduction and on ion channels. One particularly striking observation was that total long-chain HUFA levels in plasma were strongly positively correlated with both 5HIAA (the main metabolite of serotonin) and with HVA (the main metabolite of dopamine in human cerebro-spinal fluid). Low levels of CSF 5HIAA are strongly predictive of impulsiveness, hostility and depression. This study, therefore, suggests that the availability of HUFAs may be important in regulating formation of neurotransmitters important in modulation of mood. Consistent with this observation are animal studies which showed the early accumulation of brain tryptophan, followed within a few hours by increases of brain serotonin, in animals fed EPA and DHA.[141]

Two other studies also suggest effects of dietary fatty acids on the brain in humans. In an elderly Dutch population, a high intake of linoleic acid was associated with cognitive impairment, while a high intake of fish (containing n-3 HUFAs) was protective against cognitive impairment[142] at baseline and also against cognitive decline over 3 years. In a study in Greece, adipose tissue long-chain fatty acids were inversely associated with anxiety

suggesting that they may be protective against anxiety as well as against depression.[143]

Depression and prostaglandins

One of the functions of the HUFAs is to give rise to the prostaglandins (PG). Dihomogammalinolenic acid (DGLA) is the precursor for PGs of the 1 series, AA the precursor for 2 series PGs, and EPA the precursor for 3 series PGs. Quantitatively, the 2 series PGs are by far the most abundant although the 1 and 3 series PGs both have important functions.

The reports on 2 series PG levels in blood and saliva in depression have been surprisingly consistent. Almost all studies have found elevated concentrations of 2 series PGs or the related thromboxane in depressed individuals. Lieb et al.[44] were the first to report highly significantly elevated blood concentrations of both PGE_2 and thromboxane B_2 in depression. At about the same time Calabrese et al.[145] also reported elevated blood levels of PGE_2 in depressed patients. More recently, Piccirillo[146] again found elevated thromboxane B_2 concentrations in depression. In saliva Nishino[147] and Ohishi et al.[148] found significantly elevated PGE_2, $PGF_{2\alpha}$ and PGD_2 in patients with depression. Severe depression is also associated with systemic mastocytosis, an illness where circulating prostaglandin levels are very high.[149] Stress also elevates prostaglandin levels.[150] Infusions of prostaglandin may cause depressed mood.[151]

In contrast to the above results, cerebrospinal fluid (CSF) levels of prostaglandins have usually been normal in patients with depression.[152–154] However, levels of CSF PGs are low and measurement is fraught with potential artifacts. One careful study reported strikingly elevated levels of PGE_2 in CSF of depressed as opposed to normal or schizophrenic individuals.[155]

One argument against the idea that PGs may be important in depression is that non-steroidal anti-inflammatory drugs (NSAIDs) do not have obviously psychotropic effects. However, these drugs do not penetrate the brain well and have little effect on brain PG synthesis. When sources of PGs are obviously peripheral and substantial as in polyarthralgia or in mastocytosis, NSAIDs do have clear antidepressant actions.[149,156] More importantly, it is often forgotten that monoamine oxidase inhibitors (MAOIs) are potent inhibitors of PG synthesis which do get into the brain.[157–160] Equally, although tricyclic antidepressants are best known for their effects on neurotransmitter metabolism, they are also powerful antagonists of PG action.[161,162] If these actions of the MAOIs and tricyclics had been discovered first, and if the drug classes had, therefore, been given different names, the whole history of the development of anti-depressants might also have been very different.

PHOSPHOLIPID AND FATTY ACID METABOLISM: EXPLAINING THE ASSOCIATIONS BETWEEN DEPRESSION AND OTHER ILLNESSES

It is clear that in depression there are important abnormalities of fatty acid and eicosanoid metabolism. There are two types of essential fatty acids, the n-*6* derived from dietary linoleic acid and the n-3 derived from dietary alpha-linolenic acid (Fig. 1). The 20 carbon fatty acids of these series, with 3–*6* double bonds, are the ones particularly involved in brain metabolism and also in immunological and inflammatory reactions. This group of compounds is sometimes known as the HUFAs. The most consistent observations in depression are low levels of both n-3 and n-*6* HUFAs in both plasma and red cells. The n-3 depletion is consistently greater than the n-*6* depletion leading to elevations of the n-*6*/n-3, AA/EPA and AA/DHA ratios. These abnormalities are associated with substantial elevations of the formation of 2 series PGs. These observations can help to explain the interactions between depression and the various other illnesses described earlier in this paper.

Cardiovascular disease

As in depression, people at risk of cardiovascular disease have low levels of both n-*6* and n-3 HUFAs in plasma and red cells with the n-3 depletion often being greater than the n-*6* depletion and the n-*6*/n-3 ratio often being elevated. Many papers have reported similar findings. Substantial reviews can be found in References 163 and 164.

Thus cardiovascular disease and depression are linked by similar patterns of plasma and cell membrane fatty acid abnormalities. It is a reasonable hypothesis to propose that both medical and psychiatric clinical problems may be caused by the abnormal biochemistry. The causative role of the biochemistry is supported by animal studies[163,165] and by clinical trials which show significant reductions in mortality in groups given n-3 EFAs as compared to control groups.[166,167] Both cardiovascular disease and depression may be due to reduced levels of long chain n-*6* and n-3 HUFAs and to a reduced ratio of n-3 to n-*6* HUFAs. In people at high risk of heart disease the heart rate is unusually stable: in a randomized trial, n-3 HUFAs were found to induce significantly greater heart rate variability in survivors of myocardial infarction.[168] Depression is also associated with a reduced variability in heart rhythm, supporting the idea that this rate stability in both cardiac disease and may be related to n-3 deficits.[16,169,170] N-3 HUFAs are potent anti-arrhythmic, HDL-raising, anti-thrombotic and triglyceride lowering agents, all of which mechanisms may contribute to their efficacy in people at risk of cardiovascular disease.[163]

It is unfortunate that in none of these studies was the

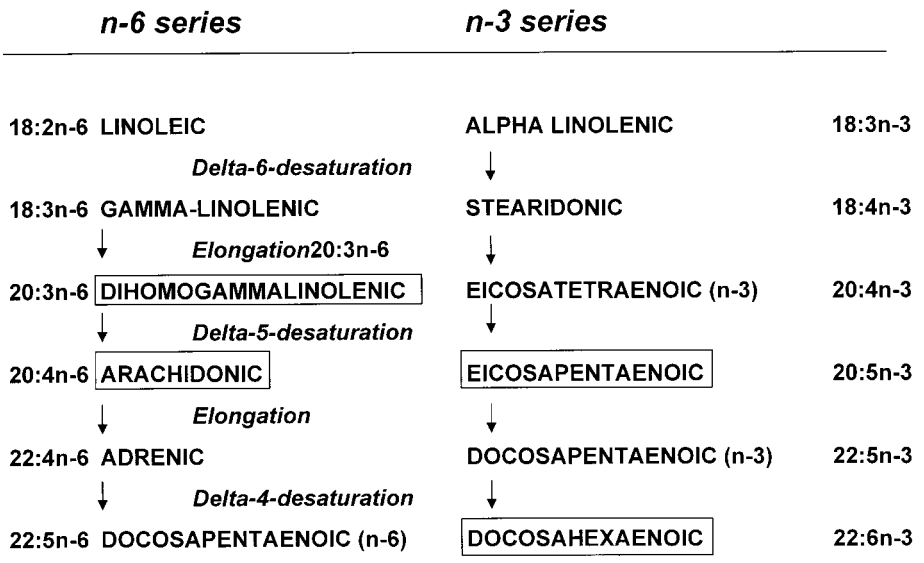

Fig. 1 An outline of the metabolism of n-3 and n-6 essential fatty acids.

effect of n-3 treatment on depression noted. In view of the strong associations between the two disorders, future studies should look seriously at this.

Diabetes

Diabetes is associated with two different important abnormalities in HUFA metabolism.[171–173] First, the conversion of the dietary EFAs, linoleic and α-linolenic acids, through to the HUFAs is impaired at both the Δ-6-desaturase and Δ-5-desaturase levels. This inhibition is particularly clear in insulin-dependent diabetes but less so in type II non-insulin dependent diabetes. The second abnormality is present equally in both types of diabetes and is a major reduction of membrane HUFAs as compared to plasma HUFAs. In diabetes there appears to be an impaired ability to get HUFAs into cells. If patients with depression have low levels of HUFAs, particularly n-3 HUFAs, it is easy to see that the metabolic abnormalities present in diabetes will exacerbate this situation.[171–174]

There is good evidence from both animal and human studies that highly purified preparations of the n-3 HUFA, EPA, have beneficial effects in diabetes. In diabetic rats with nerve damage, EPA was able to restore normal nerve structure and function and to improve the impaired Na/KATPase activity.[175] In Takushima rats, which are believed to provide a model of type II diabetes, EPA was able to prevent or reverse the development of insulin resistance, apparently by being incorporated into skeletal muscle membranes.[176]

In humans with non-insulin-dependent diabetes and nerve damage, a year's treatment with EPA improved clinical symptoms of nerve damage, lowered serum triglycerides, lowered albumin excretion in the urine and dilated the dorsalis pedis artery.[177] EPA over 4 weeks also had desirable cardiovascular and renal effects in diabetic patients with renal damage.[178] There is, therefore, clear evidence that the low levels of n-3 HUFAs in diabetes are producing pathological states which can be reversed by EPA treatment.

Whereas defects in the desaturase enzymes are good candidates for the reduced formation of HUFAs from dietary EFAs, an emerging candidate for the defect in fatty acid transport is the fatty acid translocase (FAT). This was first identified as the cell surface antigen CD36, which interacts with a wide range of factors including collagen, oxidized lipoproteins, anionic phospholipids and red cells parasitized with malaria.[179] CD36 is now known to be identical with a member of the FAT family[180,181] and also with one of the major genes in hypertensive rats which causes insulin resistance, elevated triglycericle levels and hypertension.[182] The defect in CD36 may be able to explain the abnormalities of fatty acid release in hypertensive rats,[183,184] abnormalities which can be corrected by n-3 HUFAs.[183] In isolated human monocytes, EPA and DHA significantly reduced expression of CD36.[185] Since monocytes are believed to be involved in both atherosclerosis and inflammation and since the CD36/FATP entity seems involved in these processes, down regulation by n-3 HUFAs is likely to be desirable.

Immunological abnormalities

There is an enormous literature on the question of fatty acid metabolism and immune function and in this section. I will quote selectively from representative papers. Much

of the interest in this field arose from observations that high doses of fish oil might be able to control human rheumatoid arthritis and other autoimmune diseases.[186–188]

Arising from these observations has come a large body of work at the cell culture, animal model and human levels. In cell culture, proliferation of lymphocytes and other immune and inflammatory cells is suppressed, expression of histocompatability and adhesion molecules is inhibited, and release of tumour necrosis factor, interleukins and interferons is reduced.[189–191] Similar results occur in animals where n-3 HUFAs become incorporated into macrophages and lymphocytes, suppress acute phase responses, diminish antigen presentation and expression of surface molecules, and inhibit TNF, interleukin and interferon production by various cell types.[192–197] The anorexia which can be induced by interleukin-1 and which seems to involve prostaglandins, can be suppressed by fish oils.[198]

Unusually, the results in cell culture and in animals are consistent with substantial numbers of studies in humans. N-3 HUFAs are able to reduce immune and inflammatory cell proliferation, inhibit the formation of interleukins, TNF, interferons and interleukin receptors, inhibit fever and generally suppress immunological overactivity without eliminating valuable responses to infections.[92,199–210]

Much work needs to be done on detailed mechanisms of the effects of the n-3 fatty acids. Among these so far described are inhibition of 2 series PG formation,[198] inhibition of diacylglycerol and ceramide formation,[211] inhibition of protein kinase[212] and inhibition of phospholipase C.[212]

It is clear that many of the immune, inflammatory and cytokine overactive responses which have been described in depression can be suppressed by treatment with n-3 fatty acids. It is, therefore, not unreasonable to hypothesize that the deficits in n-3 HUFAs in depression may contribute to the activation of immunological and inflammatory responses.

Multiple sclerosis

In multiple sclerosis (MS) there is activation of immunological and inflammatory responses, with elevated PG production by cells isolated from the CSF and an association between elevated cytokine production and disease progression.[214,215] At the same time in plasma, red cell and adipose tissue there are deficits of both n-3 and n-6 HUFAs in patients as compared to controls.[216,217] There are only limited data on treatment of MS with n-3 HUFAs but what there is is mildly encouraging.[219] Certainly in MS patients n-3 HUFAs are able to suppress TNF, interleukins and interferons by mononuclear cells.[220] Curiously, a polymorphism of a human brain protein, Pc1 Duarte, is commoner in both MS and in depression than in the general population.[221]

Cancer

Patients with cancers may be profoundly depressed, not just as an appropriate psychological reaction to the disease. One possibility is that the depression could be attributed to the elevated interleukins, interferon and TNF in many types of cancer. A combination of n-3 and n-6 HUFAs has been shown to suppress levels of all these cytokines in patients with colorectal cancer although, unfortunately, no depression scores were noted in this study.[92] Treatment with n-3 HUFAs could prove a novel and safe approach to the treatment of depression in cancer patients.

Age

The main fatty acid abnormality so far identified with ageing is impairment of Δ-6-desaturase and Δ-5-desaturase.[222–225] The desaturases are now known to be highly expressed in brain[226] and so such a failure in desaturation with aging could lead to reduced availability of n-3 and n-6 HUFAs for the brain. This would be expected to exacerbate any deficits arising from other reasons and so lead to an increased risk of depression. In animals at least, the manifestations of brain ageing such as loss of long-term potentiation, loss of normal glutamate release and elevation of interleukin 1β and interleukin converting enzyme (ICE) can all be reversed by the administration of AA with a small amount of DHA.[227,228] Human studies are needed.

Osteoporosis

Not mentioned earlier, reduced bone density has now been shown to be related to depression to a clinically relevant degree.[229,230] There is a great deal of evidence demonstrating that n-3 fatty acids are essential for normal bone and calcium metabolism, that deficits of these fatty acids will lead to osteoporosis and that treatment can be beneficial.[231] The relationship between osteoporosis and depression could thus be explained by an n-3 deficit in both.

WHAT EXPLANATIONS ARE AVAILABLE FOR THE FATTY ACID ABNORMALITIES IN DEPRESSION?

While major depression and the depression of bipolar disorder clearly have at least some abnormalities in common, they also have many important differences. It is, therefore, important to consider them separately.

Bipolar disorder

There is a general agreement that the drugs which are used in bipolar disorder are not primarily acting at the neurotransmitter metabolism or receptor levels. They are believed to be working at the G-protein, protein kinase or other signal transduction level.[99–103] Most work has been done on the mechanism of action of lithium. This has been reported to be acting on protein kinase and on ATPases, but until very recently the consensus pointed strongly to a major effect on the phosphatidyl inositol cycle. This is believed to be overactive, possibly at both the PLC and the inositol monophosphatase levels and the activity is believed to be damped down by lithium inhibition of inositol monophosphatase, thus blocking the formation of free inositol for the regeneration of phosphatidylinositol.[113] This mechanism remains the one which is most widely accepted and one which is likely to be at least partly true.

However, recently lithium at therapeutic, concentrations has been shown to have a strong inhibitory effect on PLA_2, suggesting that this may be its primary mode of action.[116,117] This fits in with old observations on lithium inhibition of hormonal effects on fatty acid release.[122] It also fits in with a whole series of observations drawn together by Hibbeln et al.[232] which suggest that PLA_2 may be overactive in affective disorders.

Thus in bipolar disorder there may be two or three abnormalities in cell signalling at the PLA_2, PLC and inositol monophosphatase levels. All of them will interact to lead to abnormalities in phospholipid and fatty acid signal transduction mechanisms.

Major depression

In major depression there is more clear-cut biochemical evidence of abnormalities in phospholipid and fatty acid metabolism. Much of the evidence about PLA_2 collected by Hibbeln et al.[232] relates to major depression. Although less well documented than its role in bipolar disorder, lithium has therapeutic effects in major depression also, which would be consistent with its inhibition of a PLA_2 excess.

The fatty acid patterns are, however, not easy to interpret on this simple basis. Most PLA_2 enzymes are selective either for HUFAs in general, or have a preferential effect on n-6 HUFAs with a smaller effect on n-3 HUFAs. A simple PLA_2 excess, would therefore be expected to lead to an equal loss of n-3 and n-6 HUFAs or, alternatively, a selective loss of n-6 HUFAs. This is not consistent with the pattern reported by several investigators in major depression. There is a selective depletion of n-3 HUFAs with a relative or occasionally absolute excess of n-6 HUFAs. This could perhaps be explained by a change in the affinity of a PLA_2 so that the enzyme preferentially metabolized n-3 fatty acids, or alternatively by the impact of a second gene.

There is an emerging consensus to the effect that the major psychoses are unlikely to be explained on a single gene base. Either two or three genes of major effect and/or many genes of minor effect may be involved.[233] What might be a good candidate for a second gene in major depression?

We wish to propose Coenzyme A-independent transacylase (CoAIT) as a strong candidate for a second genetic abnormality in major depression. In cells there are many different classes of phospholipids.[234,237] One type has an acyl fatty acid group in the Sn1 position. But other types, known as ether phospholipids have alkyl or alkenyl groups at the Sn1 position. These latter classes are particularly abundant in cells involved in immunity and inflammation and have been much studied in macrophages. Among other things, they act as precursors for platelet activating factor (PAF). It is now clear that activation of these inflammatory cells, and the myriad things associated with activation, such as cytokine release[238] and cytokine activation,[239] are dependent upon the release of AA esterified at the Sn2 position of alkyl or alkenyl phospholipids. This seems to be the pool of AA which is particularly involved in signal transduction processes during inflammation and immune activation. AA is now known to be transferred to the ether phospholipids from acyl-acyl-phospholipids by the enzyme CoAIT (Fig. 2). CoAIT is selective for AA and produces a substantial enrichment of the phospholipid fraction in AA. It transfers the AA to what are known as lysophospholipids, phospholipids which have no fatty acid attached to the Sn2 position because of removal of that fatty acid by PLA_2. CoAIT and PLA_2 seem to be absolutely required for the development of fully competent immunological and inflammatory responses and several novel classes of anti-inflammatory drugs are based on inhibition of CoAIT rather than on inhibition of phospholipases or cyclooxygenases.[240–243]

Thus an excess of activity of CoAIT and of PLA_2 will lead to a relative enrichment of the ether phospholipids in AA, and a substantial increase in the likelihood of immunological and inflammatory reactions. As described in previous sections, this makes sense because of the substantial evidence of immunological activation and cytokine release in major depression. Both the depression and the immunological activation may be caused by the increased PLA_2 and COAIT activity.

Therapeutic implications

These concepts suggest that major targets for drug action in bipolar disorder should be PLA_2, PLC and inositol monophosphatase. Another possible target is DAG kinase,

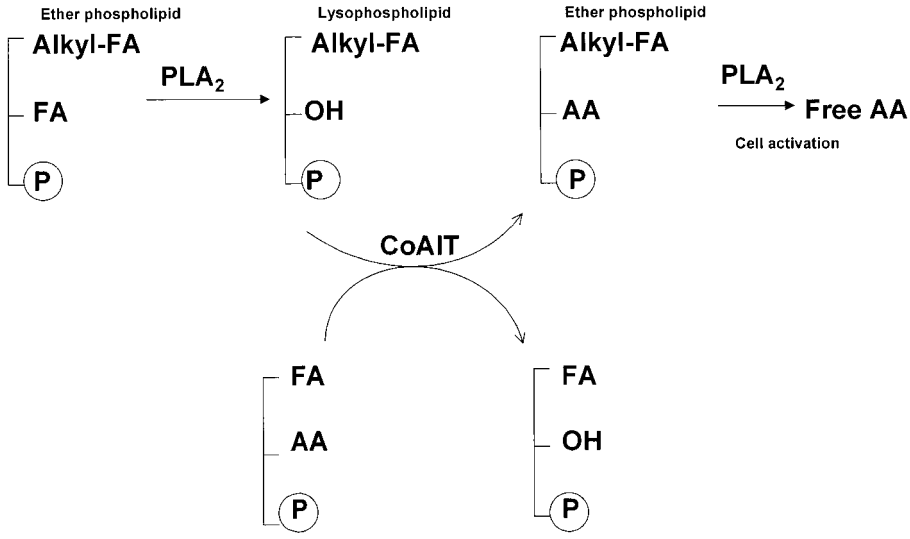

Fig. 2 The CoAIT system which incorporates AA into cellular compartments which are activated in inflammatory and immunological reactions.

an enzyme which also plays an important role in the PLC cycle (Fig. 3). DAG kinase is located on chromosome 4p16, a region associated with bipolar disorder. In major depression, PLA_2 and CoAIT look promising targets for novel drug actions.[244,245]

It is of great interest that the activities of these enzymes may be modulated by the n-3 fatty acid EPA. In the human studies, deficits of EPA have been strongly associated with depression. EPA can inhibit PLA_2,[246] can inhibit PLC,[213] and can compete with AA for the active site of CoAIT. If these enzymes are involved in affective psychoses, then EPA should have therapeutic effects. Since excess PLA_2 is involved in schizophrenia, then EPA should also be of value in this illness.[244,247] It is, therefore, interesting that mixtures of EPA and DHA have been found effective in a randomized trial in treatment-resistant bipolar disorder[248] and that the mass of epidemiological evidence referred to earlier suggests that the n-3 HUFAs will be of value in depression.[1,140] Most people in the field have argued in favour of the prime importance of DHA, mainly because the brain contains large amounts of DHA and only modest amounts of EPA. However, in a randomized study in schizophrenia comparing EPA, DHA and placebo, DHA and placebo were ineffective whereas

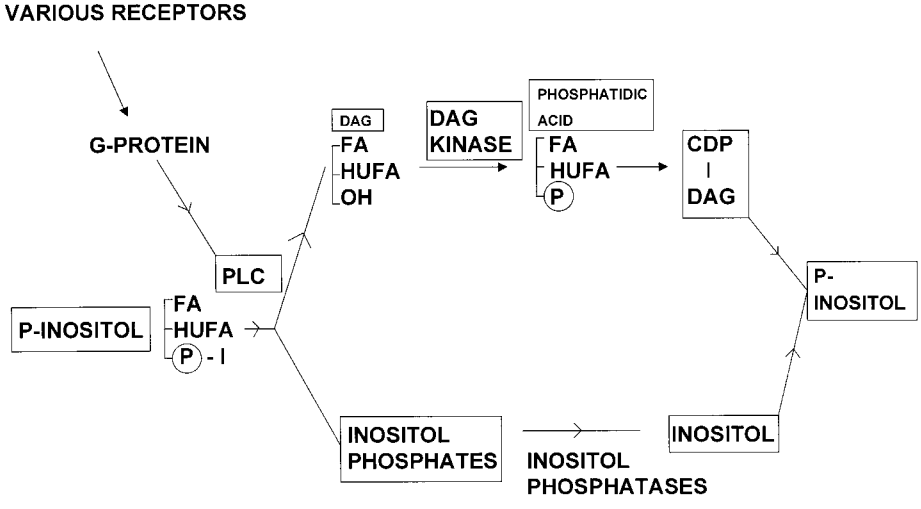

Fig. 3 The PLC signal transduction cycle. Occupation of various receptors activates PLC which splits phosphatidyl-inositol (PI, P-inositol) into DAG and inositol phosphates. DAG and inositol phosphates are highly active signal transduction molecules whose activities must then be terminated by reincorporation into P-inositol by the reactions shown.

EPA produced an improvement comparable to that produced by neuroleptics.[249] At least one type of PLA_2 can be strongly inhibited by EPA but not DHA.[246] Since, as discussed earlier, EPA has been demonstrated to be successful in treating diabetes, inflammatory disorder, cardiovascular disease and related conditions, it makes sense to propose that EPA may be working through a limited number of signal transduction processes which are central to all these illnesses. The association between depression and other illnesses may be dependent upon common signal transduction defects which are corrected by EPA.

A psychosis gene: why some drugs have effects in schizophrenia, bipolar disorder and major depression

Anyone who has experienced the problems of fitting patients into DSM-IV categories knows that there are major overlaps between the clinical syndromes represented by the three common major psychoses. Indeed, it may be very difficult to discriminate between these conditions.[250]

This clinical confusion is matched by genetic confusion. Family studies over several generations often show that a family identified because of a proband with one of the major psychoses, frequently also has members with one or both of the others. It is now thought unlikely that any of these disorders is caused by a single major gene. The familial patterns are often consistent with models which postulate two or three genes of substantial effect, possibly with many more genes of minor effect.[233]

One possibility is that one of the genes of substantial effect is common to all the major psychoses. This would help to account for the overlaps in clinical syndromes and for the multigenerational familial patterns. The other one or two major genes might then be specific to bipolar disorder, schizophrenia and major depression, so accounting for the differences between the syndromes. Many minor genes may further modulate the clinical expression of the disorders.[244]

What might these genes be on the basis of the phospholipid/fatty acid models of psychiatric diseases? Some clues may be generated by the fact that there are drugs which appear to be effective in all three conditions. They are not always thought of as effective in the three conditions but that is more because of their marketing than because of their mechanisms of action. Two examples of different types of drugs which are effective in this way in all three disorders are lithium and combined dopamine and serotonin blockers such as olanzapine or risperidone.

If Chang and colleagues are correct, that inhibition of PLA_2 represents the main action of lithium at therapeutic plasma concentrations, then this provides support for the views that excessive PLA_2 activity, probably of a calcium-independent PLA_2[251] may be common to the three disorders. This explains the effect of lithium, but how does a drug like olanzapine fit in? Olanzapine is a blocker of dopamine D_2 and serotonin 5HT2 receptors. Both D_2 and 5HT2 receptors provide much of the drive to PLA_2 activation in neurons.[126,129,252] Thus olanzapine and related drugs, via the D_2 and $5HT_2$ receptors, are likely to be potent modulators of PLA_2 activity, so explaining why they are effective in all three disorders.

If calcium independent, AA specific PLA_2 represents 'the psychosis gene', then what are the other genes in each of the three conditions? As argued in this and

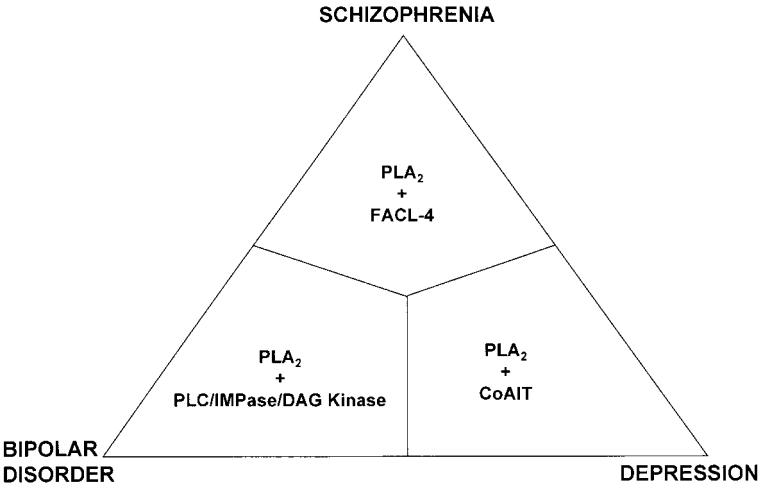

Fig. 4 A possible hypothesis concerning the interactions between the three major psychoses. In all three there may be an abnormality in PLA_2 which might, therefore, be called the psychosis gene. Other genes then contribute to the differences between the three major psychoses.

another paper, the other gene involved in schizophrenia may be one of the FACL family, particularly FACL-4.[243] In bipolar disorder PLC, DAG kinase and inositol monophosphatase are good candidates, while in major depression with its associations with so many other disorders, CoAIT or a related enzyme involved in inflammatory and immune responses might be the key enzyme. The concept is illustrated in Figure 4.

CONCLUSIONS

The new emphasis on signal transduction mechanisms promises to be the beginning of a new paradigm in the understanding of schizophrenia and the affective disorders. The old neurotransmitter metabolism/receptor paradigm has made major contributions but the relative lack of recent success in improving drug efficacy is a sign of paradigm strain. The new concept which incorporates with neurotransmitters and signal transduction offers a hope of progress.

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