Could platelet activating factor play a role in developmental dyslexia?

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Source: This work was supported by the Dyslexia Research Trust.

Summary

Post-mortem studies by Galaburda and colleagues on the brains of developmental dyslexics found characteristic neuronal abnormalities: ectopias, microgyria, and fewer large-soma cells in sensory thalamus. An association between dyslexia and immune dysfunction has also been proposed. We describe a mechanism which may explain these observations. Platelet-activating factor (PAF) is a pro-inflammatory lipid implicated in neurological disorders. We propose that PAF may also be involved in dyslexia.

Keywords: ectopias, platelet activating factor, neuroimmune, neurodevelopmental

Introduction: neuronal abnormalities in dyslexic brains

Ectopias and microgyria are cortical abnormalities linked to disordered neuronal migration. Ectopias ('brain warts') are localised disruptions in which neurons appear to have extruded from the pial membrane following a rupture of that membrane. They may result from damage to the fetal blood brain barrier, which ruptures the limiting pial membrane, allowing neurons to project into the extra-cerebral space beyond their normal termination zones (1). Microgyria are miniature fissures in the cortical surface. They likely result from damage to cells in the immediate vicinity of the small blood vessels penetrating the brain perpendicular to the cerebral surface.

Cortical abnormalities have been associated with many neurodevelopmental disorders. Ectopias in particular have been linked with developmental dyslexia by the work of Galaburda and colleagues (2). In post-mortem human brains, they found a significantly increased incidence of ectopias and microgyria in dyslexic as opposed to control brains, particularly in the left temporal lobe (3).

Analyses of the sensory thalamus in the same post-mortem tissue suggest that there are also abnormalities in this region. In the lateral geniculate nucleus, for example, the normal division into magnocellular (large-soma) and parvocellular (small-soma) neurons is clear-cut. In the dyslexic brains, the LGN layers have been shown to be disordered (4). In the medial geniculate nucleus, an overall shift towards smaller cell sizes was observed (5).

Dyslexia and immune dysfunction

The idea of a link between dyslexia and immune dysfunction was notably made by Geschwind, Behan and Galaburda (6-9) in the 1980s, who related dyslexia, and immune dysfunction and handedness to testosterone levels during fetal development. Although aspects of their hypothesis are controversial, reviewed by various authors in (10), several studies support the claim that in at least some individuals dyslexia may be associated with a higher risk of immune dysfunction of some sort (11-13).

In these individuals, it has been hypothesised that dyslexia may result from an immune challenge in midgestation - around the time of neuronal migration - interacting with a pre-existing genetic weakness to produce relatively subtle and extremely variable effects on neuronal development and connectivity. Stein has suggested that these effects preferentially target large-soma neurons such as those found in the magnocellular visual system (14), which are preferentially involved in fast processing of dynamic stimuli. Taylor and Richardson (15) have proposed mechanisms whereby this could occur.

Puzzles in dyslexia

The traditional account of developmental dyslexia views it as a phonological deficit. Such an account leaves a number of puzzling questions unresolved. Many dyslexics show signs and symptoms in many other functional domains than pure phonology, for example visual symptoms (16) and working memory (17). There is also considerable individual variation, leading some authors to suggest that subtypes of dyslexia may

exist (11, 18), although this remains controversial. Dyslexia is also highly comorbid with other DSM-IV disorders such as attention deficit disorder.

Of course, the phonological hypothesis specifies only a functional abnormality (phonological processing) and says nothing about how this function might come to be abnormal. Thus it does not exclude the possibility of a brain-based explanation of dyslexia (19). Some such physiological account is needed to explain the neuroanatomical abnormalities noted by Galaburda and colleagues. In addition, explanations are required for associations between dyslexia and immune dysfunction - including Lahita's finding that mothers with systemic lupus erythematosus (SLE) have a higher than expected incidence of dyslexic sons (20). There is also mounting evidence of disrupted fatty acid metabolism in dyslexics, including signs of fatty acid deficiency (21, 22) and raised cytosolic phospholipase A2 (PLA2) (23).

Platelet-activating factor

To explain these various observations, a mechanism is needed which relates immune function, neuronal function and fatty acid biochemistry. We propose that this mechanism may involve raised levels of platelet-activating factor (PAF: 1-0-alkyl-2-acetyl-sn-glycero-3-phosphocholine), a powerful pro-inflammatory lipid and vasopermeabiliser which is neurotoxic in excess and which is a product of the arachidonic acid cascade mediated by PLA2. PAF has been implicated in a number of neurological disorders, including multiple sclerosis and schizophrenia (24, 25). If PAF is relevant to dyslexia, two questions arise. Firstly, how could raised levels of

PAF generate the neuronal abnormalities observed in dyslexic brains? Secondly, how might raised levels of PAF come about?

Raised PAF levels could stimulate brain inflammation, leading to ectopias

PAF is a powerful neuroimmune mediator. One consequence of raised PAF levels would be an increase in leucocyte adhesion at the blood brain barrier. This would stimulate inflammatory reactions, including increased upregulation of inflammatory genes and production of inflammatory products such as oxygen radicals, cyclo-oxygenase-2, interleukin-1 beta and tumour necrosis factor alpha (26-29). An analogy here is with multiple sclerosis (MS). PAF is increased in the plasma and cerebrospinal fluid (CSF) of MS patients: levels correlate with the numbers of gadolinium-enhancing lesions (markers of blood brain barrier injury) seen on these patients' MRIs (24). The study of Callea and colleagues (24) found two species of PAF in both plasma and CSF of MS patients: C16:0 was higher in plasma, while C18:0 was higher in CSF. The authors suggest that C16:0 may originate from peripheral leucocytes activated during the immune response, while C18:0 may originate from neurons and glia, both of which produce PAF in response to, respectively, neurotransmitters such as NMDA, and tumor necrosis factor alpha.

At its weakest point, surrounding capillaries which penetrate the cortical surface, the blood brain barrier thins to a single layer of cerebral endothelial cells. These cells have a pivotal role in the initiation and regulation of inflammation in ischaemia (30). Leucocyte adhesion to endothelial cells in cerebral blood vessels occurs by a process known as juxtacrine signalling (27). This is mediated by PAF via a G-protein coupled

receptor (27). Increased PAF leads to increases in leucocyte stickiness (measured by the number of cells rolling along or adhering to venular endothelium) and transmigration (24). Antagonists to the PAF receptor decrease leucocyte adhesion to the vascular wall and migration across a cytokine-stimulated endothelium (27).

Initially, weak interactions between cell surface selectins help to bind the leucocyte as it rolls along the cerebral endothelium without activating the leucocyte. In the cerebral endothelial cell, PAF is then translocated to the cell surface, where it binds to PAF receptors on the surface of the leucocyte, tethering it more firmly (27). This upregulates expression of CD11 and CD18 integrins on the leucocyte surface. These integrins then bind to ligands such as ICAM-1 on the endothelial cell, strengthening the adhesion still further. PAF is known to increase the expression of adhesion molecules in the endothelial cells of the umbilical vein, and in human eosinophils (31).

As well as stimulating leucocyte adhesion, PAF is a powerful vasopermeabiliser. Increased blood brain barrier permeability would allow leucocytes and inflammatory products to penetrate the brain parenchyma more easily (30), facilitating inflammatory reactions within cortical tissue. These various effects of PAF could damage or even destroy localised regions of the blood brain barrier, which normally forces the termination of neuronal migration. Instead of stopping when they reach the pial membrane, therefore, neurons would continue through the gap, forming an ectopia. Whether and what extent ectopias were formed would depend on the degree to which PAF was transiently increased, and also on when the increase occurred relative to neuronal migration.

Raised PAF levels could kill cells, leading to microgyria

High levels of PAF are known to be neurotoxic and gliotoxic; increased synthesis of PAF occurs during seizures and neural injury (32, 33). Mice genetically deficient in PLA2, the enzyme which provides free fatty acids for conversion to PAF, had less damage following cortical ischaemia than control mice (34). PAF binding to platelets in stroke patients correlates with neuronal damage and neurological impairment (35). Since microglia are thought to modify neuronal processes constantly by phagocytosis, an intact blood brain barrier may be essential to prevent the resulting antigenic fragments from stimulating circulating lymphocytes (36). The neurotoxic effects of PAF could destroy tissue in the vicinity of the damaged capillaries, creating microgyria. As with ectopias, one would expect the formation of microgyria during fetal development to have a deleterious effect on the efficiency of brain processing in later life.

Raised PAF levels could affect overall cell size, leading to fewer large-soma cells

PAF in neurons is known to facilitate the induction of activity and phosphorylation of p38 and other MAP kinases (37, 38). In primary hippocampal cell cultures, PAF acts downstream of the glutamate analogue kainate, which can induce neurotoxicity (37, 39). In human monocytes, inhibiting cytosolic PLA2 attenuates the activation of MAP kinase (28). Among their numerous effects, these enzymes modulate microtubule-associated proteins and hence microtubule dynamics (15). The drugs KT5720 and U-98017, which appear to have a microtubule-stabilising effect via inhibition of MAP

kinase, have been shown in chinese hamster ovary cells to significantly affect the cytoskeleton, increasing microtubule length and overall cell size (40). This suggests that overactive MAP kinase could reduce microtubule length and cell size, resulting in fewer large-soma neurons. As noted above, such an effect has been seen in the medial geniculate nucleus of dyslexic brains (5). The relative lack of large-soma neurons could preferentially affect the processing of fast, rapidly changing visual and auditory stimuli, two areas of perception in which dyslexics have been shown to have deficits (41-43).

Fatty acid deficiency could contribute to the problem

The lipolytic enzyme PLA2 acts on phospholipid bilayers - the major constituents of cell membranes - to remove the fatty acid at the sn-2 position (44). It is the rate-limiting enzyme in the metabolic cycle which generates free fatty acids (FFAs), which can then be used in various intracellular and extracellular pathways - for example, as retrograde messengers (arachidonic acid), or for making prostaglandins to use in inflammatory responses. FFAs are not normally left in the free state for long, because of their ability to generate potent bioactive molecules such as PAF and leukotrienes. Instead, they are reincorporated into the cell membrane by reuptake enzymes, completing the cycle (44).

The PLA2 cascade is normally tightly controlled. The limited activity of PLA2, the presence of antioxidants such as Vitamin C and superoxide dismutase, and the action of reuptake enzymes such as acyl-CoA lysophospholipid acyltransferase (ACLAT) and fatty acid coenzyme-A ligase (FACL-4) prevent overly high concentrations of

bioactive molecules accumulating. However, in certain circumstances the PLA2 metabolic cycle may become unstable, leading to a positive feedback spiral in which the highly active molecules created as products of that cycle further damage the phospholipid membranes. For example, activation of PAF's G protein coupled receptor, for example by plasma PAF, facilitates the activity of PLA2. PAF biosynthesis may also be stimulated by the intracellular mobilisation of calcium, which can be induced in some cell types by oxidative stress (45).

Overactive PLA2 could deplete fatty acid availability, affecting neuronal growth

Raised PLA2 levels in the fetus could lead to a depletion of the membrane-bound fatty acids recruited by PLA2 for PAF synthesis on demand, since these fatty acids will be converted to the free form (32), and hence to other products. In the longer term, this depletion of fatty acids, the materials required to build phospholipid cell membranes, could have important effects on cell membrane viability. A fatty acid deficit in would likely have a greater impact on larger cells because they have a greater surface area. Low concentrations of fatty acids have been shown to reduce the size of erythrocytes, while higher concentrations increase red blood cell diameter (46). If there were a deficit in membrane building materials, one would expect that some of the cells which would otherwise become large (magnocellular) neurons might instead be size-restricted, and would therefore look more like parvocellular neurons. The availability during development of dietary polyunsaturated fatty acids, particularly arachidonic acid and docosahexaenoic acid, has been shown to affect brain growth, visual acuity and learning ability (47-49).

If the problem is with a lack of fatty acids during fetal development, then the timing of such a lack could be important. Neuronal migration and synaptogenesis are prominent during the second trimester of gestation. Although the fetus is a very efficient parasite, a severe lack of the relevant polyunsaturated fatty acids in the mother's diet could starve the fetus of the materials needed to build neuronal processes. Free fatty acids are rapidly either reincorporated into the phospholipid membrane or converted to other products; this free pool is enhanced by dietary fatty acid intake. There is evidence that the magnocellular visual pathway matures earlier than its parvocellular counterpart (50). It is possible that such a difference could potentially be reflected in differential vulnerability to low dietary fatty acid levels, depending on the time during fetal development at which that deficit occurred.

The extent of the fatty acid depletion would depend on various factors. These include: the efficacy of the reuptake mechanisms which reincorporate free fatty acids into phospholipid membranes, the presence of antioxidants, which protect against fatty acid loss, and the dietary supply of fatty acids and their substrates (the essential fatty acids linoleic and linolenic acid).

How might raised levels of PAF come about?

It is possible that in some cases the effects of raised PAF could be restricted to the fetal phase. Earlier we remarked upon Lahita's observation that the sons of mothers with systemic lupus erythematosus have a higher-than-expected incidence of learning disabilities. SLE is one of a number of autoimmune disorders are characterised by a high level of serum PAF. A study of patients with active SLE found detectable plasma

levels of PAF and reduced levels of platelet activating factor acetylhydrolase (PAFAH), the enzyme which inactivates PAF. Patients with inactive SLE, and healthy controls, did not show these effects (51). It is possible that during pregnancy this lipid could cross the placenta and raise levels of fetal plasma PAF. Thus even a fetus which had, by chance, not inherited the alleles associated with increased risk for SLE could be transiently affected by PAF. If this is correct, we would expect that disorders such as multiple sclerosis, which is also characterised by high PAF (24), would show the same association with dyslexia in offspring as observed for SLE by Lahita (20).

However, developmental dyslexia is thought to have a considerable genetic component (52). If as we have speculated raised levels of PAF are involved, this could be due to some genetic abnormality in the enzymes which synthesise or degrade PAF. If so, the effects of this abnormality might be exerted both during fetal development -- leading to the generation of ectopias, for example -- and later on in life. Environmental variability (for example, in the availability of polyunsaturated fatty acids) could contribute to the huge variability of the dyslexic phenotype.

The idea that PAF might still be overproduced in the adult is interesting, given the wealth of functions in which PAF is now thought to be involved. As well as having vasopermeabilising and immune functions, PAF may participate in synaptic plasticity. Bazan and colleagues have suggested that PAF can serve as a retrograde messenger in long-term potentiation (53), a neuronal process hypothesised to underlie some forms of memory. They have shown that the synthetic PAF analogue methylcarbamyl-PAF (mc-PAF), which is resistant to enzymatic degradation, is memory enhancing: post-

training intrahippocampal injections of mc-PAF reduced the escape latencies of rats in a Morris water maze task, compared with controls. Injections of lyso-PAF had no effect, while PAF antagonists such as BN 52021 and BN 50730 significantly impaired memory (54).

One contributor to raised levels of PAF could be a genetic abnormality in the enzymes which synthesise this lipid. As noted above, raised levels of PLA2 have been found in dyslexic subjects (23). Some forms of PLA2 have been mapped to chromosome 1p34-1p36.4 (55). This site has been linked to dyslexia (see Table 1). Another possibility is that the inactivating enzymes which normally reincorporate the free fatty acids into the phospholipid membrane, thus preventing their conversion to PAF, could be underactive. One of these enzymes, ACLAT, has been mapped to chromosome 6p21.3 (56), a site repeatedly linked to dyslexia (see Table 1).

A third possibility, suggested by Horrobin (D. Horrobin, personal communication), is that an abnormality in coenzyme A-independent transacylase (CoAIT) may be involved. This enzyme is central to the remodelling pathway which is largely responsible for PAF release from inflammatory cells (57). Initially fatty acids such as arachidonic acid are incorporated into a specific phospholipid subclass -- the phosphatidylcholine pool -- in these cells. Remodelling, which is an essential precursor for the production of lipid mediators such as PAF, allows the movement of arachidonate between phospholipid subclasses, and hence the enrichment of particular phospholipid fractions. For example, in mast cells arachidonate must move into an ethanolamine phospholipid subclass before it can be released by Group II PLA2. CoAIT mediates this remodelling process. It has been shown in macrophages that

CoAIT is highly selective for arachidonate and produces a higher percentage of polyunsaturated acylated products than the other two enzymes (coenzyme A dependent transacylase and acyl coenzyme A acyltransferase) known to be involved in remodelling. Inhibitors of CoAIT inhibit remodelling and attenuate the production of PAF and arachidonic acid release (58).

CoAIT is especially interesting because it seems to be essential for the full development of normal immune and inflammatory responses. Furthermore, Horrobin and Bennett (59) have proposed that a genetic abnormality leading to excess activity of CoAIT could be one of the genes of major effect involved in unipolar depression. Major depression is characterised by elevated levels of proinflammatory cytokines such as interleukin-6, and administration of cytokines to human subjects can result in severe depressive symptoms, leading to the 'inflammatory response system activation model' of depression proposed by Maes and colleagues (60). Overactivation of CoAIT, by enriching the 'inflammatory' phospholipid pool in arachidonic acid, would likely enhance immunological activity in various ways, including the production of proinflammatory cytokines and PAF.

Yet another possibility is dysfunction of platelet-activating factor acetylhydrolase (PAFAH), the enzyme responsible for degrading PAF. In mouse fetus, PAFAH activity is correlated with neuronal migration (61). This enzyme has three subunits: alpha, beta and gamma. The beta subunit is also known as LIS 1 because heterozygous mutation or deletion of this subunit is associated with Type I lissencephaly, a severe disorder of neuronal migration (62). Hence PAF may be involved in neuronal migration (during the second trimester of gestation). A genetic

abnormality which decreased the efficiency of PAFAH could result in PAF overactivity. The most common brain isoform of this PAF-inactivating enzyme, PAFAH(Ib), has three subunits: α (mapped to chromosome 17p13.3), β (mapped to chromosome 11q23) and γ (mapped to chromosome 19q3.1) (56, 63, 64). These sites have not been linked to dyslexia to date. PAFAH(II) has been mapped to chromosome 1p34.3, and plasma PAFAH to chromosome 6p21.1 (56). These sites have been linked to dyslexia (see Table 1).

Table 1: Linkage for dyslexia

Chromosome	Markers	References
6p22-6p21	(between D6S422 and D6S291)	(65-68) c.f. (69)
15pter-qter	(in the region of D15S143)	(66)
1p36-1p34		(70)
2p15-2p16	(between D2S2352 and D2S1337)	(71)

Predictions

A number of predictions follow from our hypothesis. These include:

There should be a positive association between some maternal autoimmune disorders, such as SLE and multiple sclerosis, and dyslexia in the children, particularly if the syndrome is active/acute during pregnancy. This has been indicated for SLE (20). However, immune disorders in which PAF is not implicated should not show an

association with dyslexia. If this is the case, relationships between dyslexia and immune dysfunction will depend on the type of immune problem studied, perhaps helping to account for the conflicting findings so far. Since PAF affects the cerebral vasculature and blood brain barrier, we would also predict associations between dyslexia and neurovascular disorders such as migraine and stroke.

PAF is a potent vasopermeabiliser. We would therefore predict a negative association between developmental dyslexia and high blood pressure. To our knowledge this has not yet been assessed.

There should be higher concentrations of ectopias, in dyslexia, in regions with high concentrations of NMDA receptors. PAF synthesis is mainly agonist-stimulated. In neurons, therefore, the effects of PAF should be clearest in cells in which PLA2 is concurrently being stimulated by an agonist, such as glutamate via the PLA2-coupled NMDA receptor. One might therefore expect higher concentrations of ectopias in areas with high concentrations of NMDA receptors, such as the temporal lobe (72); this has been observed (3).

Nutritional supplementation with polyunsaturated fatty acids during pregnancy or later in life may reduce the incidence and severity of dyslexia. In particular, enhancing the ratio of omega-3 to omega-6 fatty acids may help alleviate some symptoms by affecting PAF production, for example in immune cells (73). Effects of diet on dyslexia may also be detectable (for example starvation in pregnancy should heighten risk for dyslexia in the child). It has been suggested that the apparent rise in reading disability, and other highly comorbid disorders such as ADHD, in the West

during the last thirty years may be influenced by the increasing ratio of saturated to unsaturated dietary fat (74). However, we note that extreme fatty acid deficiency may contribute to more severe cognitive deficits. In such cases the affected individual may not be diagnosed as dyslexic.

Summary and Conclusions

We have proposed that at least some dyslexics may be affected during fetal development by raised levels of PAF. This neuroimmune mediator is ideally placed to mediate several puzzling and apparently disparate aspects of dyslexia. As we have outlined, its effects are likely to be highly variable and depend on complex environmental factors, including dietary intake of fatty acids during pregnancy and levels of maternal PAF. In addition, dyslexics could be particularly susceptible to the effects of PAF for a number of genetically based reasons.

If this hypothesis is valid, it generates a number of testable predictions. It also has important implications for the treatment and prevention of developmental dyslexia. If the hypothesis is not valid, we nevertheless believe that it is important because it demonstrates a way in which the immune system, fatty acid biochemistry and neuronal biochemistry could interact. The final story will almost certainly turn out to be more complicated than the one told in this article (for example, we have not discussed the role of cytokines). Nevertheless, we hope that our hypothesis may stimulate discussion on the role of physiological factors -- specifically immune function and fatty acid metabolism -- in dyslexia. Perhaps it may even contribute to a more general acceptance that neurodevelopmental disorders such as dyslexia are not

just cognitive phenomena, but involve the interaction of numerous complex physiological systems in the brain.

Acknowledgments

Our grateful thanks to Angela Vincent and David Horrobin for their help.

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