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Visual function, fatty acids and dyslexia

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Summary There is mounting evidence that developmental dyslexia is a neurodevelopmental disorder which involves abnormalities of fatty acid metabolism, particularly with respect to certain long-chain highly unsaturated fatty acids (HUFAs). Psychophysical evidence also strongly suggests that dyslexics may have visual deficits as well as phonological problems. Specifically, these visual deficits appear to be related to the magnocellular pathway, which is specialized for processing fast, rapidly-changing information about the visual scene. It remains unclear how these two aspects of dyslexia — fatty acid processing and visual magnocellular function — could be related. We propose some hypotheses — necessarily speculative, given the paucity of biochemical research in this field to date — which address this question. © 2000 Harcourt Publishers Ltd

INTRODUCTION

Developmental dyslexia is a multifactorial disorder which appears to involve a number of additional signs and symptoms, as well as problems with reading. These signs are symptoms include visual deficits and evidence of abnormal metabolism of certain long chain highly unsaturated fatty acids (HUFAs). In this paper, we explore how these two aspects of dyslexia could be related. Dyslexia has only recently been accepted as a neurological syndrome, with a basis in the brain. Little research has been done into it biochemical aspects as yet, so the proposals put forward in this paper must necessarily be speculative. However, it is suggested that research to elucidate the basis of the well-documented visual abnormalities in dyslexia should include further investigations of fatty acid metabolism.

VISUAL DEFICITS AND DYSLEXIA

As reviewed by John Stein in this volume and elsewhere,[1] dyslexics have visual as well as phonological problems.[2,3] Their visual difficulties include problems with night-vision,[4] visual instability – dyslexics often report that when reading 'letters move about on the page' – and motion perception.[5,6] Such problems seem particularly related to the visual magnocellular processing pathway,[7] which is compared of large cells with large-diameter axons and fast channel kinetics.

In primates, the visual system appears to be divided into two functionally distinct pathways: the magnocellular and the parvocellular.[8] The magnocellular pathway appears to mediate functions which require rapid processing of dynamic stimuli, such as motion perception: it is specialized for the fast detection of and orientation to changing events in the visual scene. The parvocellular pathway is slower and specialized for the processing of visual details such as form and colour, which allow objects to be identified. This functional division allows the brain to concentrate processing resources where they are needed. Processing the entire visual scene to the level of detail required for object identification (the level provided by the fovea) would take more time and resources than even the human brain has available.

Given the nature of visual symptoms in dyslexia, it has been suggested that a selective deficit in the larger cells which make up the magnocellular pathway could be involved in development dyslexia (1). If these cells were damaged of dysfunctional in some way, the magnocellular system would be less efficient at detecting and

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processing rapidly, changing stimuli. This would generate the kinds of features, such as unusually high thresholds for detecting coherent motion, which have been observed in developmental dyslexia.[9]

HUFAS AND THE BRAIN

Fat in the form of phospholipid, is the major constituent of cell membranes. These membranes consist of a phospholipid bilayer, with the phospholipid molecule having a fatty acid attached to the second atom in its carbon-chain backbone (the SN-2 position). Each cell continually renews and repairs its phospholipid membranes by way of a metabolic cycle which strips the fatty acids from the SN-2 position, generating free fatty acids, and then reincorporates free fatty acid back into the membranes.[10,11] The rate-limiting enzyme in this cycle is cytosolic phospholipase A2 (PLA_2), which converts membrane-bound fatty acids to the free form. It has recently been shown[12] that dyslexics have abnormally high levels of PLA_2 in their blood plasma, suggesting that the way they process fatty acids may be unusual.

To service this metabolic cycle, cells require a supply of HUFAs. Arachidonic acid (AA), dihomogamma-linolenic acid (DGLA), docosohexanoic acid (DHA) and eicosapentanoic acid (EPA) are especially important for the normal development of brain structure and function, and appear to be developmentally regulated.[13] In adults, these can be synthesized from their precursors., alpha-linolenic acid and linoleic acid, although it is not clear how efficient synthesis is, nor how much this may be subject to individual variation. In the fetal and early postnatal period the infant is dependent on intake of the preformed fatty acids from the mother's placenta or breast milk.

There is controversy over the exact effects of fatty acid deficiency on the developing brain. For a summary of the recent literature see Ref. 14. Fatty acids have been implicated in myelinogenesis, since postnatal malnutrition and fatty acid deficiency result in hypomyelination.[15,16] There have been suggestions that fatty acid supplementation may improve the symptoms of multiple sclerosis patients[15] and patients with generalized peroxisomal disorders, who also suffer problems with myelin. In one such study, for example, DHA was found to be severely decreased in patients with generalized peroxisomal disorders. Supplementing their diet with DHA ethyl ester normalized DHA blood levels within weeks and significantly improved brain myelin images.[17]

Studies in term and preterm infants are inconsistent with respect to cognitive development.[18] However, visual function does appear to be enhanced by supplementation with omega-3 HUFAs[19] or a mixture of AA and DHA.[20] DHA has been shown to be an essential requirement of rat photoreceptors in vitro and is equally vital for normal retinal development in humans.[20,21] There is evidence that the maturation of visual evoked potentials may be slower in preterm infants who receive infant formula without HUFAs than in those whose formula is supplemented with fatty acids (22). In addition, the content of both free AA and free DHA in human retina is positively correlated with age. This accumulation of polyunsaturated fatty acids may reflect an alteration in their processing in the retina, perhaps due to increased oxidative stress.[23] Furthermore, a recent study suggests that the degenerative disorder Bietti crystalline dystrophy, which involves progressive night-blindness, is linked to a lack of certain fatty acid binding proteins which specifically bind to fatty acids of the omega-3 series.[24] In other words, fatty acids appear to be essential for the proper development of some aspects of brain function, especially in the visual system.

HUFAS AND DYSLEXIA

As noted earlier, and discussed in other papers in this volume, there is mounting evidence of an association between dyslexia and abnormal fatty acid metabolism,[10,25,26] including higher than normal levels of the enzyme PLA_2 which converts membrane-bound fatty acids to the free form. Phospholipid metabolism has also been shown to be abnormal in dyslexic brains in vivo, compared with controls.[27] It is not clear yet whether a genetic abnormality may give rise to the higher levels of PLA_2, with consequent abnormal fatty acid processing, or whether the initial deficit(s) may be in some other aspect of fatty acid metabolism.

The major question which remains is: how could an abnormality in the processing or provision of HUFAs selectivity affect visual magnocellular neurons? There are various ways in which this could occur.

EFFECTS OF LOW HUFA LEVELS ON CELL SIZE AND BRAIN DEVELOPMENT

A selective deficit in the materials (fatty acids) required to build phospholipid cell membranes would be likely to have a comparatively 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.[28] 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. This is interesting in light of the fact that a higher proportion of smaller cells than usual has been observed both in the

lateral geniculate nucleus and in the medial geniculate nucleus of dyslexia brains post-mortem.[29,30]

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 HUFAs in the mother's diet could starve the fetus of the materials needed to build neuronal processes. There is evidence that the magnocellular visual pathway matures earlier than its parvocellular counterpart.[31] It is possible that such a difference could potentially be reflected in differential vulnerability to low HUFA levels, depending on the time during fetal development at which that deficit occurred.

As noted above, fatty acid composition affects the efficiency of visual pathways. In the retina, DHA in particular is essential for normal function. Radiolabelling studies indicate very high conservation of DHA in both the retina and the brain, while substitution studies with other phospholipids suggest that DHA is optimal for retinal transduction. For example in terms of its effects on the kinetics of metarhodopsin II-G protein coupling in the photoreceptors.[32] DHA seems to optimize the singalling sensitivity of the visual pathway at the retinal level. Low levels of DHA can therefore be expected to decrease the efficiency of visual processing.

SPECIFIC MAGNOCELLULAR CELL SURFACE ANTIGENS

It has been suggested that magnocellular neurons may be selectively susceptible to damage by environmental factors because of specific cell surface antigens they carry.[33-35] One candidate is the major histocompatibility complex (MHC) Class I, which is an important regulator of immune function. MHC I is encoded in the region of chromosome 6p21.3. A region repeatedly linked to dyslexia.[36,37] There have been suggestions that dyslexics have a higher than normal incidence of immunological problems, but this remains controversial.

EFFECT OF PHOSPHOLIPIDS ON THE CYTOSKELETON

Phospholipids are known to interact with the neuronal cytoskeleton, a major determinant of cell size and shape.[38] Assembly of cellular microtubules, which form the 'bones' in the cytoskeleton, facilitates larger overall cell size, and is also important for the development of connectivity – the extension of axons and dendrites. It is regulated by numerous cytoskeletal proteins, such as the microtubule-associated proteins (MAPs), and enzymes, such as mitogen-associated protein kinase (MAPK), which are developmentally regulated.[39]

The interactions between phospholipids and the cytoskeleton are complex and not fully understood. Microtubule-associated protein 1B (MAP1B), a major neuronal cytoskeletal protein, binds to acidic phospholipids, such as phosphatidylserine, but not to neutral phospholipids, such as phosphatidylcholine.[40] Phosphoinositol inhibits microtubule assembly by binding to microtubule-associated protein 2 (MAP2) at a single high-affinity site.[41] Phosphatidyl ethanolamine is also associated with MAPs and stimulates microtubule assembly in vitro.[42] facilitating a larger cytoskeleton. Phospholipids do therefore seem able to affect microtubule assembly and hence cell size, so abnormalities in the levels of phospholipids could be relevant to the formation of large neurons.

MAPs are thought to be essential for normal brain development. Mice deficient in MAP1B die during embryogenesis if they are homozygous.[43] Heterozygotes show abnormal dendritic structure in the retina, hippocampus, olfactory bulb and cerebellar Purkinje cells. Behavioural effects include lack of visual acuity and motor abnormalities, a finding intriguingly reminiscent of the problems experienced by some dyslexics. It is possible that abnormal connectivity in the retina and cerebellum in particular could be relevant to dyslexia: the cerebellum is a major receiver of visual magnocellular information and plays an important role in rapid information processing.[44] Of course, there are dangers in extrapolating between species. Nevertheless, the mouse is considered a good model for many aspects of neuronal function, and comparative data in humans are currently lacking.

The phosphorylation of MAPs, which is regulated by protein kinases such as mitogen-associated protein kinase (MARK), also appears to be critical fro brain function. For example, the phosphorylation of MAP1B is considered essential for synapse formation.[40] a process which occurs both during fetal development and throughout life. Abnormal hyperphosphorylation of the smaller-weight MAP tau is known to play a role in disease states. For example, abnormally hyperphosphorylated tau is the major component of neurofibrillary tangles in Alzheimer's disease.[45] Tau promotes microtubule assembly and stability, facilitating greater overall cell size. Phosphatidylserine appears to reduce tau's capacity for phosphorylation by MARK,[46] suggesting that this phospholipid may protect against the development of the hyperphosphorylated disease state. MAPK is thus an important regulator of cytoskeletal function, and hence of both cell size and connectivity.

The drugs KT5720 and U-98017, which appear to have a microtubule-stabilizing effect similar to that of taxol, do not, unlike taxol, act directly on tubulin, the major component of microtubules. When applied to Chinese

hamster ovary cells, KT5720 and U-98017 significantly affect the cytoskeleton, increasing microtubule length and overall cell size.[38]

Their effects appear to occur via inhibition of the activity of MAPK. This suggests that overactive MAPK, as well as potentially over-phosphorylating tau, could have the effect of reducing microtubule length and cell size, resulting in more 'parvocellular' neurons. As noted above, such an effect has been seen in both the lateral and the medial geniculate nucleus of dyslexic brains.[29,30]

Given this, it is interesting that the gene for MAPK, which appears to be developmentally, regulated, has been localized to chromosome 6p21.3,[47] a candidate locus for dyslexia.[36,37] One intriguing consequence of this speculative line of thought is that there could, if MAPK is involved in developmental dyslexia, be a possible association between this disorder and Alzheimer's disease. To our knowledge, no such association has yet been investigated.

To summarize, the cytoskeleton is a major determinant of cell size. Phospholipids interact with the cytoskeletal MAPs which regulate microtubule assembly and stability. It is possible that abnormal levels of phospholipids, due to abnormal fatty acid processing or provision, may occur in dyslexia, either during development or in the adult. These could affect connectivity, particularly in the retina and cerebellum, via effects of cytoskeletal components. It is also possible that MAPK, which by phosphorylating MAPs reduces their efficacy in synapse formation, neurite outgrowth and microtubule assembly, could be overactive in dyslexia. This could result in subtly altered connectively which might particularly affect areas sensitive to magnocellular input, such as the cerebellum, together with a lower proportion of larger, 'magnocellular' neurons.

SUMMARY AND CONCLUSIONS

At present far too little is known about the roles of phospholipids and essential fatty acids in the developing brain to be able to make any firm statements about how essential fatty acid deficiency could be involved in dyslexia Yet there are suggestive pointers towards such as involvement, both from behavioural studies and from biochemical assays. There is also good evidence for visual problems in dyslexia, which seem particularly related to the visual magnocellular pathway. At present, it is probably fair to say that there is no firm evidence linking visual magnocellular function with fatty acid abnormalities, although there is substantial and mounting evidence of the importance of fatty acids to visual function in general. It is also probably fair to say that evidence for a specific link with the magnocellular system has not been looked for at the biochemical level. We have explored some ways in which a deficit in the processing of the essential materials that make up cell membranes could affect the development of cells in the brain. It is at least possible that some such interactions would have a more severe effect on larger cells.

Despite the current paucity of research into the biochemistry of dyslexia, this is a fast-growing field. It is still at an early stage, and in need of specific theories. Once those theories emerge, however (and they are already emerging), there is a wealth of research into biochemical mechanisms already available. Much more remains to be discovered about the interaction of phospholipids with the components of the cytoskeleton, and the role of microtubule-associated proteins in neurodevelopment. However, much is already known, and biochemistry, whether of lipids, microtubule, or other relevant areas, is an established field with well-developed experimental techniques. Tapping this expertise should assist researchers interested in the biochemistry of dyslexia to make rapid progress in understanding the basis of this complex neurodevelopmental disorder.

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