Oligodendrocyte pathophysiology: a new view of schizophrenia

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Abstract

A recent focus of schizophrenia research is disruption of white-matter integrity as a key facet of this complex disorder. This was spurred, partly, by new imaging modalities, magnetic transfer imaging and diffusion tensor imaging, which showed differences in white-matter integrity and tract coherence in persons with schizophrenia compared to controls. Oligodendrocytes, in particular, have been the subject of increased study after gene microarray analyses revealed that six myelin-related genes specific to oligodendrocytes have decreased expression levels in schizophrenia. Oligodendrocytes have also been shown to be decreased in number in the superior frontal gyrus of subjects with schizophrenia. The MAG knockout mouse, missing a myelin-related gene linked to schizophrenia, may prove to be a useful animal model for the dysmyelination observed in the human disease. Studies currently ongoing on this model have found changes in dendritic branching patterns of pyramidal cells in layer III of the prefrontal cortex. Further characterization of the pathology in these mice is underway.

Introduction

A new focus of research has emerged recently in the field of schizophrenia research. From the dopamine-centred hypotheses that long dominated the field, a new, more complex view has emerged positing that altered brain connectivity plays a critical role in the development of schizophrenia. Several studies have shown increased neuronal density without increased absolute numbers of neurons in a number of brain areas of patients with schizophrenia, implying that cortical volume is reduced in schizophrenia, possibly because of reduced neuropil (Selemon and Goldman-Rakic, 1999). In addition, there is a notable absence of a clear degenerative process in schizophrenia, contrasting sharply with the pathology of neurons seen in other neurological disorders, such as Parkinson's disease or Alzheimer's disease. It has therefore been proposed that it is disorganization of specific white-matter tracts that may result in the functional deficits seen in the disease, including impaired working memory, cognitive deficits, and inappropriate affect.

In fact, this hypothesis is supported by several studies using new brain-imaging modalities. A major advantage of such approaches is that they can be used to study changes in schizophrenia in vivo, allowing investigation of different stages of the disease and providing correlates to post-mortem and animal studies. Magnetic transfer imaging (MTI) measures protons bound to macromolecules included in cell membranes and myelin, and studies using this technique have demonstrated decreased myelin or axonal membrane integrity in the temporal and frontal lobes of subjects with schizophrenia (Foong et al., 2000, 2001; Kubicki et al., 2005). This decrease is particularly correlated with severity of negative symptoms (Foong et al., 2001). Diffusion tensor imaging (DTI) can be used to measure the vectors of water movement in the brain. Because water molecules within white matter move most freely in the direction parallel to the axons, DTI provides a measurement of white-matter tract direction and, by measuring the strength of the direction vector, tract coherence (Davis et al., 2003). Recent DTI studies have demonstrated decreased anisotropy, implying decreased tract coherence, in several major white-matter tracts in persons with schizophrenia (Buchsbaum et al., 1998; Kubicki et al., 2003, 2005; Lim et al., 1999; Sun et al., 2003; Wang et al., 2004). In the thalamus, phosphatidylcholine, the main membrane

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lipid, and sphingomyelin and galactocerebroside, major myelin membrane components, were also found to be decreased in schizophrenia (Schmitt et al., 2004), providing additional evidence for a myelin dysfunction in the disease. Comparison of schizophrenia with other demyelinating diseases such as metachromatic leukodystrophy (MLD) and multiple sclerosis (MS) provides further evidence for the existence of dysmyelination in schizophrenia. When MLD is diagnosed in late adolescence and early adulthood, the age when schizophrenia symptoms often appear, this demyelinating disease can present with psychotic symptoms sometimes indistinguishable from those of schizophrenia (Davis et al., 2003). Likewise, patients with MS who display cognitive and psychiatric symptoms frequently have white-matter lesions in the frontal and temporal lobes, which are the brain regions most implicated in schizophrenia (Davis et al., 2003). This convergence of symptoms among demyelinating diseases affecting the age and brain regions targeted in schizophrenia suggests that a common pathology possibly exists.

The role of oligodendrocytes

As evidence mounted that white-matter tracts are in some way disorganized in schizophrenia, new studies began to shed light on what that precise defect might be. A ground-breaking study used gene microarray analysis to examine gene expression levels in post-mortem dorsolateral prefrontal cortex (PFC) of patients with schizophrenia and matched controls (Hakak et al., 2001). The study's unexpected discovery was that the expression of six myelin-related genes (*MAG*, *MAL*, *CNP*, *HERR3*, *gelsolin*, and *transferrin*) was significantly decreased in post-mortem schizophrenia brains. These genes are all predominantly expressed in oligodendrocytes. These results, later confirmed independently (Tkachev et al., 2003; Peirce et al., 2006 in the case of CNP) and extended to other brain areas (Dracheva et al., 2006), implied that there is a pathology of oligodendrocytes underlying schizophrenia. This pathology is probably region-specific; reduced myelin-related gene expression in schizophrenia has been shown in the PFC (Sugai et al., 2004), hippocampus, superior temporal cortex, and cingulate gyrus (Katsel et al., 2005), but not in the putamen (Dracheva et al., 2006). Intriguingly, the gene *SOX10*, an oligodendrocyte-specific transcription factor, tends to be highly methylated in the brains of persons with schizophrenia, and this correlates with reduced expression of both *SOX10* and other oligodendrocyte-related genes (Iwamoto et al., 2005). These findings may represent an epigenetic indication of oligodendrocyte dysfunction in schizophrenia, although genetic variations in the *SOX10* gene do not appear to affect susceptibility towards the disease (Iwamoto et al., 2006). The myelin oligodendrocyte glycoprotein gene (*MOG*) is another gene potentially involved in schizophrenia. One group reported a weak positive association between *MOG* gene markers and schizophrenia in the Chinese Han population (Liu et al., 2005), while another group failed to find any significant evidence for the *MOG* gene as a susceptibility factor for schizophrenia in the general population (Zai et al., 2005).

Still under debate is the issue of whether these gene expression changes may be due in part to treatment with antipsychotic drugs. Drugs that target dopamine receptors may play a role in altered gene expression patterns, because oligodendrocytes express D_2 and D_3 receptor mRNA and protein at different stages of maturation (Bongarzone et al., 1998; Rosin et al., 2005). Agonists for these receptors provide protection of oligodendrocytes against glutamate toxicity and injury after oxygen/glucose deprivation, while antagonists limit this protection (Rosin et al., 2005). Oligodendrocytes also express *N*-methyl-D-aspartate (NMDA) receptors, which can mediate excitotoxic injury (Matute, 2006). Indeed, administration to rats of phencyclidine, an NMDA receptor antagonist that can induce psychotic symptoms in humans, resulted in altered expression of many genes, including several related to oligodendrocyte lineage (Kaiser et al., 2004). However, several studies of gene expression in human tissue have not indicated a drug-induced effect on gene expression. Tissue from patients with bipolar disorder showed similar oligodendrocyte-related gene expression changes to tissue from patients with schizophrenia, even though bipolar disorder is generally not treated with antipsychotic drugs (Tkachev et al., 2003). Additionally, separate analyses of patients with schizophrenia who were treated and not treated with neuroleptic drugs showed no differences in gene expression changes (Hakak et al., 2001; Iwamoto et al., 2005; Tkachev et al., 2003). In one study, long-tailed macaque monkeys treated with haloperidol for 3 months did show alterations in glia-related genes, but the specific genes affected were not all identical to those altered in humans with schizophrenia (Sugai et al., 2004).

Recent electron microscopy studies have further bolstered the hypothesis of oligodendrocyte pathology in schizophrenia. Studying post-mortem tissue from the PFC and caudate nucleus, Uranova and colleagues (2001) have demonstrated apoptotic oligodendrocytes and damaged myelin sheath lamellae forming
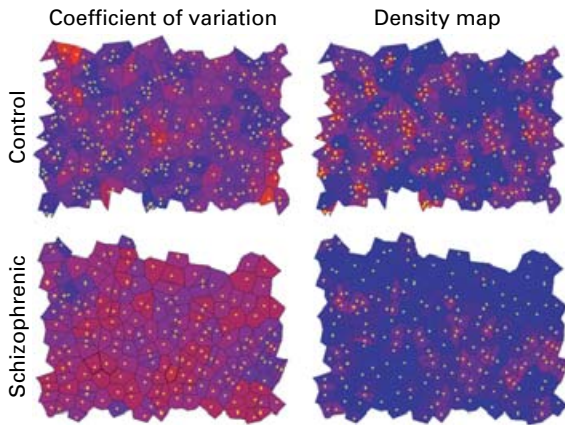
Coefficient of variation   Density map

Figure 1. Voronoi diagrams of the spatial distribution of oligodendrocytes in the white matter under area 9 in a control case and a schizophrenia case. Each polygon is associated with a CNPase-immunoreactive cell. The CV and the local densities are displayed. The schizophrenia patient displays less clustering than the control case. Clustering is revealed by more intense red areas and homogeneity by blue areas. The bottom panel shows a difference in the CV of the spatial distribution of oligodendrocytes in the white matter of area 9 revealing higher homogeneity in schizophrenia. (From Hof et al., 2003.)

concentric lamellar bodies in schizophrenia brains, along with irregularities of heterochromatin and mitochondria in oligodendrocytes. With these results in mind, our group and others undertook to analyse and quantify the pathology of oligodendrocytes and white matter in schizophrenia.

Homogeneous cellular distributions are the exception rather than the rule in nervous tissue, an observation not reflected in simple counts of specific cell types in a given brain area. It is specifically the characteristics of oligodendrocyte spatial distribution, however, that may be relevant to the pathophysiology of schizophrenia. This is particularly significant in the context of exploring the organizational structure of white matter in order to provide a cellular correlate to the decreased anisotropy in schizophrenia observed by DTI. To the end of clarifying possible differences in oligodendrocyte spatial distribution, we utilized a technique using Voronoi tessellation maps (Figure 1) to represent oligodendrocyte distribution in post-mortem material from the superior frontal gyrus of persons with schizophrenia and controls (Hof et al., 2003). Voronoi polygons enclose the region of space that is closest to an oligodendrocyte by drawing lines at mid-distance between neighbouring cells and connecting those lines to form a tessellation of polygons. It is thus the coefficient of variation (CV) of polygon areas that represents the spatial distribution

of oligodendrocytes. A homogeneous cellular distribution will yield polygons of similar sizes with a small CV, while a more heterogeneous distribution will result in very differently sized polygons and a larger CV of polygon area. The CV thus provides an objective estimate of the degree of clustering of oligodendrocytes. When this method was applied to the superior frontal gyrus, the CV of polygon area in controls was 30% higher than in matched subjects with schizophrenia. This indicated a more clustered arrangement of oligodendrocytes in controls, which may perhaps contribute to the greater white-matter tract coherence in controls observed using DTI. In addition, the density of oligodendrocytes, as calculated from these maps, was 28.3% lower in subjects with schizophrenia compared to controls, and there was a clear correlation between decreased CV of spatial distribution and decreased local cell density in schizophrenia brains. Absolute numbers of oligodendrocytes were also significantly decreased in schizophrenia (Figure 2), in both layer III and the white matter underlying area 9, where the decrease reached 27% (Hof et al., 2003), which is comparable to the results obtained from the tessellation analyses. In a separate study of the anterior thalamic nucleus, the number of oligodendrocytes was again found to be reduced in schizophrenia, particularly in males (Byne et al., 2006). These results clearly support the notion that pathology of oligodendrocytes is present in schizophrenia, at least in the frontal gyrus. This region of the PFC has been shown to undergo changes in schizophrenia (Bouras et al., 2001; Rajkowska et al., 1998; Selemon et al., 1995, 1998). The findings of altered oligodendrocytes in this same region may therefore indicate that pathology of white matter contributes to the functional and morphometric changes observed in the disease. We are currently extending these studies to other white-matter areas, including the anterior cingulate gyrus and temporal areas.

Mouse knockout models

An acknowledged disadvantage of studying human post-mortem material is the generally poor quality of the tissue, making it on the whole unsuitable for ultrastructural studies and fine analyses on the single cell level, unless materials can be fixed within a very short post-mortem delay, as was the case in the Uranova et al. (2001) study. Animal models of human diseases provide a way to circumvent the limitations inherent in studying human tissue. The mouse MAG knockout may serve as a putative animal model for schizophrenia. This particular model was chosen in
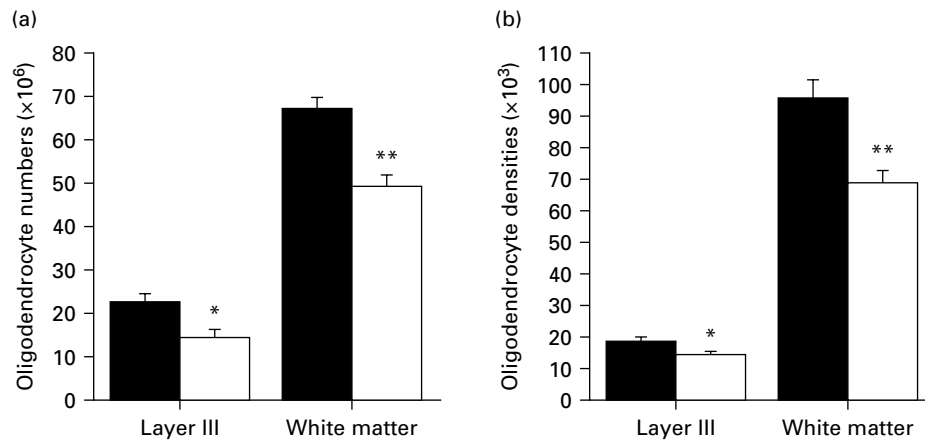
(a)

(b)

Figure 2. (a) A 28.3% decrease in oligodendrocyte total numbers was noted in layer III of area 9 in schizophrenics ($p < 0.01$) and a difference of 27% ($p < 0.01$) in the white matter. (b) Similar decreases in oligodendrocyte densities were also noted. ■, Controls; □, schizophrenics. (From Hof et al., 2003.) Asterisks indicate $p < 0.01$.

light of the gene microarray studies mentioned above that found decreased expression of MAG among the myelin-related genes implicated in schizophrenia (Hakak et al., 2001). MAG has also been found to be a susceptibility gene for schizophrenia in the Chinese Han population (Wan et al., 2005). In addition, MAG is known to interact with neuron membranes and is involved in initiation of myelination in the central nervous system (Montag et al., 1994). MAG has also been shown to enhance oligodendrocyte survival with trophic signals (Weiss et al., 2000). Although the phenotype of the MAG knockout mouse is admittedly mild, with only slight developmental deficits (see, for example, Li et al., 1994, Weiss et al., 2000, 2001), it is unclear how a mouse model of schizophrenia would be expected to behave. Behavioural studies performed on these mice have shown several subtle abnormalities. Mice missing the *MAG* gene are less proficient than wild-type mice in maintaining balance on a rotating cylinder, and they displayed hyperactivity and impaired hindlimb reflex extension (Pan et al., 2005). However, the mutant mice showed no differences in spatial learning and memory or in swimming speed, as demonstrated by a Morris water maze test (Montag et al., 1994). A mouse model missing the CNPase gene has been developed which shows marked pathology: although myelin ultrastructure appears normal, the mice develop axonal swellings and diffuse neurodegeneration resulting in hydrocephalus and early death (Lappe-Siefke et al., 2003). This model may shed light on several neurodegenerative disorders, but it clearly does not represent the primary processes occurring in schizophrenia.
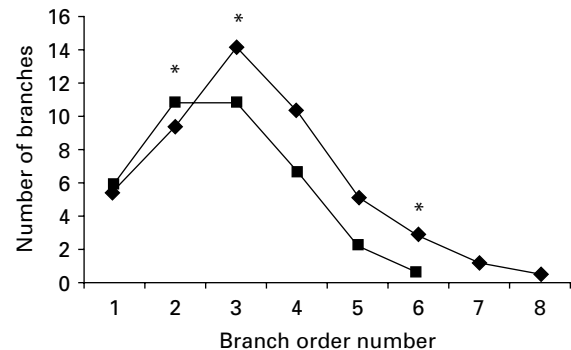

Figure 3. Differences in the dendritic trees of a MAG knockout mouse (–■–) and control (–◆–). Data from the cingulate cortex with three animals in each group show fewer branch numbers throughout the tree, predominating in the third order. Asterisks indicate $p < 0.05$.

Schizophrenia is a disease of disordered thought processes and, as such, is a fundamentally human disease. Although the MAG knockout mouse model cannot be expected to show the behavioural deficits observed in the human disease, it can still provide a vehicle for studying the morphological and anatomical abnormalities that may result from a genetic abnormality known to be linked with schizophrenia. All research performed on mice was approved by the Institutional Animal Care and Use Committee of Mount Sinai School of Medicine.

We are currently examining the repercussions of deficient myelination resulting from absence of the *MAG* gene on the morphology of pyramidal neurons in the frontal cortex of mice at different developmental
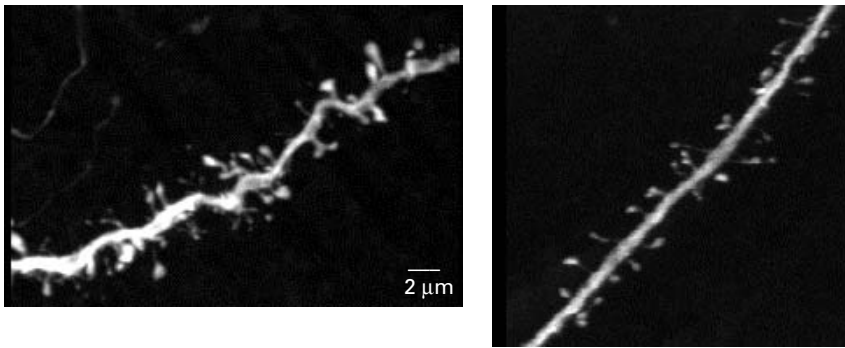
Figure 4. Dendritic spines from a wild-type (left) and MAG knockout mouse (right), with the knockout mouse showing an apparently lower spine density. Neurons are from the frontal cortex and are loaded with Lucifer Yellow. Images were acquired on a confocal laser scanning microscope at a magnification of $100\times$ and represent stacks of $100 \times 100 \times 0.1\ \mu$m images that were tiled together.

stages. These cortical neurons may be the targets of axonal pathways that are affected in schizophrenia, such as the cingulum bundle. Layer III cortical pyramidal neurons may be especially relevant in light of evidence that these neurons are reduced in number in persons with schizophrenia (Selemon et al., 1998). Using a cell-loading approach, we can reconstruct the 3D morphology of these neurons and analyse the geometric complexity of their dendritic arborization, providing an indication of the functional integrity of these neurons. Neuronal morphology and spine densities have been shown to be altered in schizophrenia (Garey et al., 1998; Glantz and Lewis, 2000; Kalus et al., 2000; Pierri et al., 2001), so these studies may help gain a fuller understanding of the disease process.

In a preliminary study, we visualized layer III pyramidal cells in the PFC of MAG knockout and wild-type mice aged 3 months by intracellular loading with Lucifer Yellow and 3D reconstruction. We constructed dendrograms as a measure of neuronal complexity and calculated dendritic spine densities as an indicator of neuronal functional integrity. In young MAG knockout mice, PFC layer III pyramidal cells showed a 25% decrease in total basal dendritic length (D. Segal, unpublished data). The sixth-order dendritic branches were even more affected, with a 65% decrease in length. Also, the number of branches were decreased in the third (23%) and sixth (79%) orders. However, basal dendrites of MAG knockout mice had 15% more second-order branches (Figure 3). In addition, MAG knockout mice had 34% fewer fifth-order apical dendritic branches. These data imply that a disturbance in the organization of myelin due to impaired expression of MAG results in alterations of morphology of PFC layer III pyramidal cells,

particularly with respect to basal dendritic integrity. Such alterations may lead to abnormalities of specific white-matter tracts and affect the prefrontal circuits severely, thereby playing a key role in the development of schizophrenia. Although no significant differences were noted in spine densities between knockout and control mice in the young animals, spine pathology may be more prominent in old mice (Figure 4) as recently demonstrated in a non-human primate model of ageing (Duan et al., 2003). Further analyses at additional time-points will be necessary to assess the age-dependence of such changes.

Planned future studies also include using electron microscopy to examine ultrastructural changes in oligodendrocytes at the single-cell level in this model. Electron microscopy allows for the direct visualization of cell and myelin integrity. If these studies show the same sorts of changes observed in tissue from patients with schizophrenia, it may help validate the use of the MAG knockout mouse as a model for schizophrenia as well as shed new light on the processes that may be occurring in the disease.

Another mouse model for schizophrenia research that has recently been suggested is the QKI (*quaking*) mouse. In the mouse, the Qki protein regulates a kinase inhibitor which is involved in terminal differentiation of oligodendrocytes, and may therefore similarly regulate maturation of oligodendrocytes in humans (Aberg et al., 2006). Indeed, QKI is potentially a regulator of oligodendrocyte-related genes in humans, and has decreased expression levels in schizophrenia (Katsel et al., 2005). The two available mouse mutants, the qk^v and the qk^{e5} mutants, both display the reduced expression of myelin-related genes and dysmyelination that have been noted in schizophrenia (McInnes and Lauriat, 2006). The QKI

mice display severe body tremors and decreased lifespan (McInnes and Lauriat, 2006), traits that are not associated with schizophrenia, so they are probably not accurate models for the disease itself. These mice may, however, provide another system in which to study the various effects of dysmyelination similar to that in the human disorder.

Future directions

Increasingly, parallel evidence from very different lines of research supports the premise that pathophysiology of oligodendrocytes may play a critical role in the development of schizophrenia. It remains to be seen what position oligodendrocytes hold in the cascade of malfunctions that results in the constellation of behavioural deficits seen in the disease. For example, does oligodendrocyte pathophysiology result in the symptoms of schizophrenia, or is there a separate, common basis that has not yet been described? Studies examining the MAG knockout mouse model may shed light on this particular issue, and it remains to conduct behavioural studies of these mice to look for subtle changes that may parallel those seen in the human disease. One plausible possibility that links several areas of schizophrenia research is that AMPA receptor-mediated excitotoxicity damages oligodendrocytes. Decreased functioning of NMDA may lead to compensatory glutamate release that could trigger excitotoxic damage by acting on several ionotropic receptor subtypes (Akbarian et al., 1996; Dracheva et al., 2001; Gao et al., 2000; Olney and Farber, 1995; Theberge et al., 2002). Indeed, oligodendrocytes have excitatory glutamate receptors, and excitatory axons can induce fast AMPA receptor-mediated currents in the cells (Bergles et al., 2000). It has been shown that oligodendrocytes in the forebrain are particularly susceptible to excitotoxic damage (Levine et al., 2001; Matute et al., 1997; McDonald et al., 1998). In addition, gene microarray analyses of tissue from subjects with schizophrenia (Hakak et al., 2001; Mirnics et al., 2000) have found abnormalities of several genes related to receptors and synaptic functions, further bolstering the notion that excitotoxicity and may play an important role in the pathophysiology of schizophrenia, perhaps by damaging oligodendrocytes.

Additionally, the evidence available at present has not indicated whether dysmorphic oligodendrocytes are the cause or result of the dysmyelination evidenced in MTI and DTI findings. Studying different stages of the disease, as well as animal models at different ages, may help elucidate the answer to this particular question. These sorts of studies may also help explain another central issue in schizophrenia research: why do the deficits of schizophrenia first come to light at a peculiar developmental stage? Quantitative and ultrastructural studies may help explain what is actually being measured by DTI, on a cellular level, in the observed decreased anisotropy in persons with schizophrenia. Further investigation of the oligodendrocyte-related disturbances in schizophrenia may also shed light on several other psychiatric conditions. Studies have shown a decrease in mRNA transcripts for oligodendrocyte-specific proteins in the temporal cortex in major depressive disorder (Aston et al., 2005) and in the dorsolateral PFC in bipolar disorder (MacDonald et al., 2006). A study of altered myelination in the hippocampus in schizophrenia and bipolar disorder indicates that there may be a complex interaction between gender, mental illness, and myelination (Chambers and Perrone-Bizzozero, 2004), although the nature and mechanism of these interactions are still unclear. When satisfactory answers are found for these difficult yet essential questions, we will be a great deal closer to a full understanding of schizophrenia and, hopefully, to an effective treatment for this devastating disorder.

Statement of Interest

None.

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