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Myelin, copper, and the cuprizone model of schizophrenia

Nicole R. Herring, Christine Konradi

Departments of Pharmacology and Psychiatry and Center for Molecular Neuroscience and Kennedy Center for Research on Human Development, Vanderbilt University, Nashville, Tennessee, 37203

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1. ABSTRACT

In recent years increasing evidence is pointing toward white matter abnormalities in schizophrenia and other psychiatric disorders. The present paper will provide an overview over the role of myelin in cognition and brain function, and its potential involvement in brain disorders. Furthermore, we will examine one particular experimental model for the study of dysmyelination, created by the administration of the toxin cuprizone. Cuprizone, a copper chelator, causes white matter abnormalities in rodents. The administration of cuprizone during specific developmental periods allows for the targeting of specific brain areas for dysmyelination. Thus, cuprizone can be used to study the pathogenesis and pathophysiology of myelin deficiencies in the central nervous system, and its effect on behaviors relevant to psychiatric disorders.

2. INTRODUCTION

Although we tend to believe that intellectual aptitude and brain activity are a consequence of neuronal function, this assumption reflects only a part of the narrative. Non-neuronal cells, and in particular glia, are more than just 'glue' that keeps the neurons together, as their name would make us believe (glia = Greek for 'glue')(1). Here we will focus on one particular type of glia, oligodendrocytes, and their role in schizophrenia and other psychiatric disorders.

The main task of oligodendrocytes is to form myelin, a specialized membrane that is used to insulate axons. Myelinated axons facilitate neuronal performance by increasing the speed of neuronal conductance. As will be outlined below, a strong correlation has been observed

between strength of white matter within a brain area and performance on tasks specific for that brain area. Since white matter is composed of myelinated axons, such findings emphasize the role of myelination in cognitive aptitude.

Cognitive deficits are observed in psychiatric disorders such as schizophrenia, which in itself might not be a strong argument for an involvement of myelin. However, certain characteristics of schizophrenia, such as a parallel between age of onset of the disorder and timing of myelination, together with a proposed 'disconnectivity', have made myelination a compelling target for study in the disorder. Thus, a number of schizophrenia studies have found increased neuronal density in the context of smaller brain volumes and unchanged total neuron numbers, indicating a reduction in neuropil (i.e. myelinated axons); post-mortem studies have shown pathological changes in oligodendrocytes; and diffusion tensor imaging (DTI) studies have shown alterations in fiber bundles. Here we will illustrate findings of myelin abnormalities in schizophrenia and other psychiatric disorders. Moreover, we will take another look at an old hypothesis of schizophrenia, disturbances in copper metabolism, and the potential relationship to myelination. Finally, recent results in rodent studies with the copper chelator cuprizone, and the potential of this model to study the pathophysiology of myelin deficits and their role in schizophrenia-relevant behavioral traits, will be discussed.

3. STRUCTURE AND FUNCTION OF OLIGODENDROCYTES

Oligodendrocytes, the cellular units of oligodendroglia, insulate neuronal axons in the central nervous system by wrapping them with a multilamellar membrane. Unlike their counterparts in the peripheral nervous system, the Schwann cells (figure 1A), oligodendrocytes ensheath up to 60 different axons (2), (Figure 1B). The myelin segments along the axons are interspersed with small gaps, the nodes of Ranvier, where sodium channels are gathered in high density and spatially separated from potassium channels at the paranodal region (3-6). Membrane depolarization can only occur at the nodes of Ranvier, leading to saltatory ('jumping') conductance (7). This setup enables the axon to propagate electrical signals more rapidly and efficiently, to minimize diffusion and to avoid non-specific cross over of signals to unrelated neuronal circuits.

4. MYELIN: A MAJOR PLAYER IN COGNITION AND INTELLECTUAL PERFORMANCE

The quality of cognitive processing is dependent upon effective communication between many different brain areas. Sensory stimuli are compared against each other, crosschecked with past experiences and responses determined by cognitive and emotional modalities. Myelination influences processing speed and strength and plays a vital role in signal propagation. Thus it is not surprising that myelination of brain regions during development corresponds to the progression of specific cognitive functions (8, 9). In typically developing adolescents, white matter coherence correlates with visuospatial, psychomotor, and language skills (10). Prefrontal cortex (PFC) development and myelination correlate with the development of cognitive functions such as executive decision-making and impulse control (11). High verbal intellectual abilities are accompanied by heightened white matter development in late childhood in corresponding brain regions (12). In the adult brain, white matter structure has been correlated with IQ, working memory, attention, aptitude in reading, and musical talent (8, 13-20). Training and experience are capable of changing white matter; for example, the number of hours spent practicing the piano correlates with the organization of fiber tracts in regions associated with musical ability (18). Similarly, training of working memory leads to white matter changes and facilitates connectivity in the corpus callosum, the area that connects both cerebral hemispheres, and other brain areas (21). The inverse is also true; severely neglected children have a significantly smaller corpus callosum (22). Taken together, white matter plays an important role in learning, memory and overall cognitive abilities.

5. EVOLUTION AND ONTOGENY OF MYELIN

5.1. Evolution of myelin

Human oligodendrocytes and myelin sheaths have their developmental origin in vertebrates (23). However, a strong evolutionary pressure toward myelination resulted in the independent appearance of myelin several times in evolution (23-25). All myelin, regardless of species, provides multilamellar membrane wrapping and promotes 'saltatory' conductance (24, 25).

5.2. Embryonic development of oligodendrocytes and oligodendrocyte regeneration in the adult brain

Oligodendrocytes are the last cell type to arise and develop in any brain area, following the generation of neurons and astrocytes. During early rodent brain development precursors of the oligodendrocyte lineage arise predominantly in the ventral ventricular zone of the neural tube, though there is also recent indication for some dorsal sources (26, 27). Oligodendrocytes in the cortex originate from three sources that are sequentially triggered: the medial ganglionic eminence and lateral ganglionic eminence in the embryonic brain, followed by derivation from oligodendrocyte progenitors (OPCs) located directly in the cortex (Figure 2). As the forebrain develops, cells of the oligodendrocyte lineage start to appear in the neuroepithelium of the medial ganglionic eminence, from where they migrate into the forebrain (27). A second wave of oligodendrocyte precursors is derived from the lateral ganglionic eminence. Around birth and thereafter, postnatal and adult OPCs located in the cortex start to generate oligodendrocytes. These OPCs can be activated throughout the organism's lifetime in response to brain injury and pathological conditions (28, 29). In contrast, the corpus callosum, striatum and fimbria fornix receive migrating OPCs from the subventricular zone in adulthood (30).

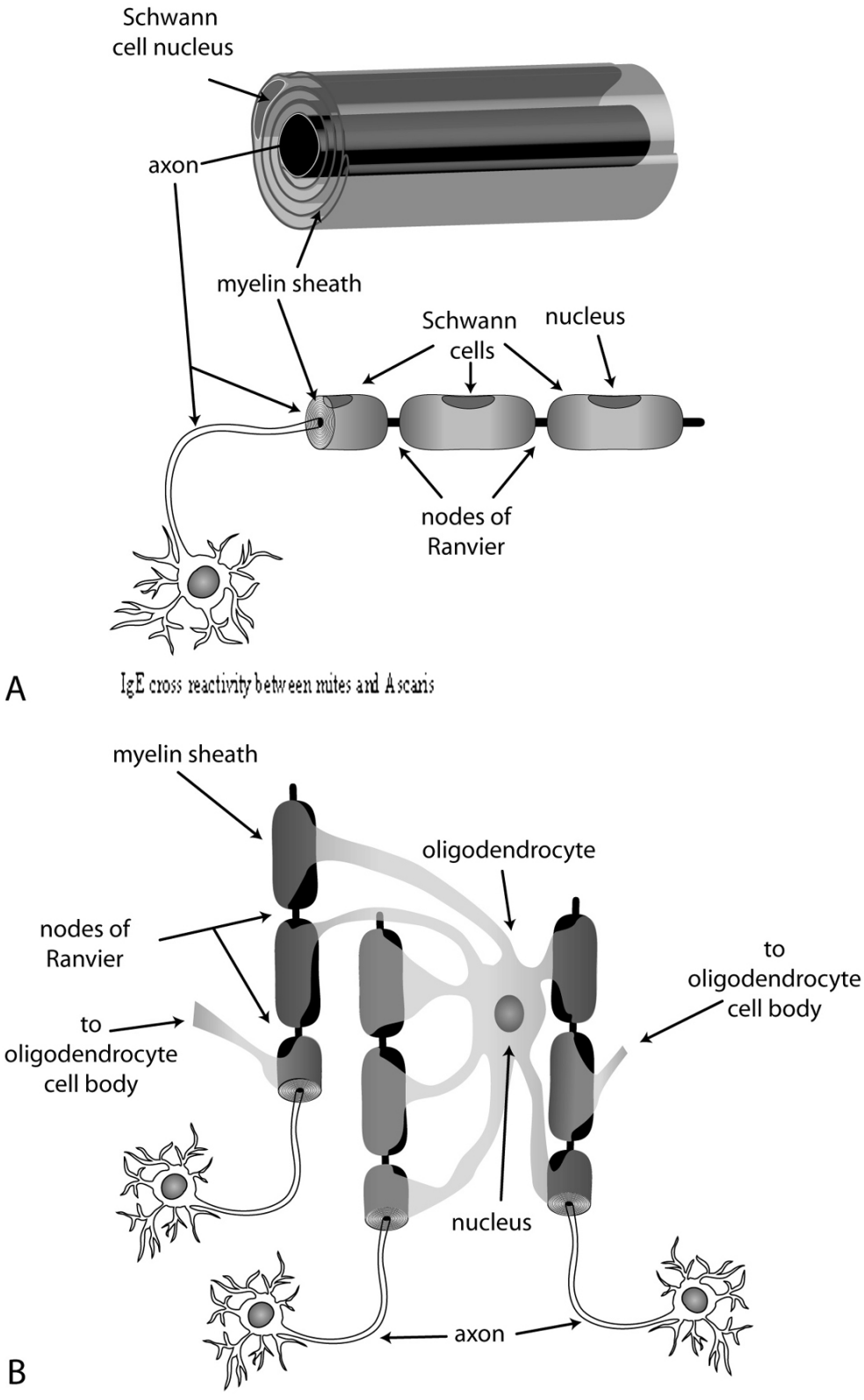

Figure 1. Myelin-producing cells. Schwann cells in the peripheral nervous system (PNS) are individually wrapped around axon segments, A. In the CNS, oligodendrocytes provide numerous myelin segments to a number of different axons, B.

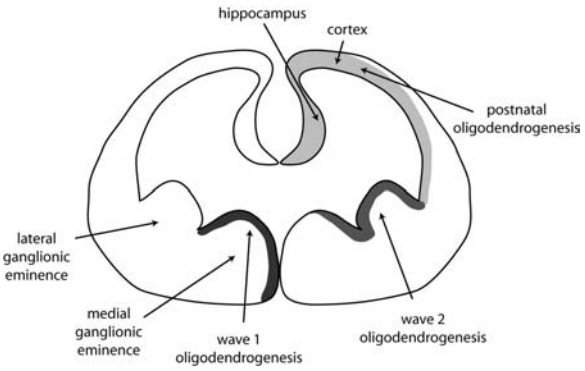

Figure 2. Developmental origin of oligodendrocytes. During embryogenesis in the mouse, oligodendrocytes are first generated in the medial ganglionic eminence, followed by generation in the lateral ganglionic eminence. From there, oligodendrocytes migrate into other brain areas. Around birth and thereafter, OPCs in the cortex and the hippocampus generate oligodendrocytes as needed.

The majority of CNS myelination occurs postnatally and continues into adulthood. For example, a recent longitudinal DTI study in human adolescence showed continued microstructural changes in white matter during late adolescence suggesting ongoing refinement of myelination into adulthood (31). In a similar study it was shown that myelination correlates with the phylogenetic age of brain areas, whereby 'older' areas and projections such as the ones to the brainstem are fully myelinated during adolescence, whereas interhemispheric connections and prefrontal brain areas involved in executive control are still getting myelinated in adulthood (32). Such findings, which have been previously shown in postmortem brains using histological staining techniques (33) suggest that executive control of behavior is still immature in adolescence, raising challenging legal questions about extent of criminal culpability in teenagers and potential for rehabilitation (34). It seems that myelination is an ongoing process into early aging, as gray matter is thinning and white matter increasing up to the fifth decade of life (35).

6. DISORDERS OF MYELIN

Traditionally, myelin alterations have been investigated for their role in pathologic conditions such as multiple sclerosis (MS), leukodystrophies, and other diseases with known white matter pathology (36, 37). More recently, subtle changes in white matter have been found in numerous conditions not traditionally associated with myelin. For example, moderate to severe white matter disturbances accompany cognitive decline in aging and in dementia (38-44). Even in healthy individuals white matter abnormalities are associated with cognitive impairment (42, 45). Myelin alterations have also been found in mental illnesses and drug and alcohol addictions (46-49). These observations have led to an examination of co-morbidities between the more classic demyelination disorders and mental illnesses including addiction.

6.1. Typical demyelinating disorders: multiple sclerosis and leukodystrophies

Multiple sclerosis is an inflammatory demyelinating disease of the central nervous system affecting 1 in 1,000 individuals, with age of onset generally in the early to mid twenties (15-45 years) (50). Symptoms and severity vary individually depending on the location of the white matter lesion(s), with periods of remission interspersed with relapses. The defining characteristics of MS are typically motor-related symptoms such as fatigue and weakness, visual loss, loss of balance, muscle spasms, loss of- or slurred speech, and bowel and bladder incontinence. In addition, symptoms such as cognitive impairment and psychosis are also prevalent (51-53). Cognitive impairment has been observed in 50-70% of MS patients (54) including during the initial demyelinating episode (55), and is progressive throughout the disease (56). The specific location of white matter lesions determines cognitive impairment and decline, as well as the occurrence of dementia (57). Individuals with MS tend to have a higher incidence of psychiatric issues including depression, anxiety, bipolar disorder, and substance abuse (58), which is again associated with lesion location.

Leukodystrophies are hereditary, i.e. caused by genetic mutations that affect myelination. Many leukodystrophies are lysosomal storage disorders leading to progressive degeneration of the white matter, frequently accompanied by psychiatric problems. For example, metachromatic leukodystrophy presents in early adulthood with psychosis, disorganized thoughts and delusions, and is frequently diagnosed as schizophrenia (59-62). Myelin loss is particularly pronounced in the frontal lobe, which explains the psychiatric symptoms and may cause dementia in the later stages of the disease. Interestingly, metachromatic leukodystrophy has been termed 'a valuable model for the study of psychosis' (63).

Cognitive decline with white matter damage is observed not only in demyelinating and genetic disorders of myelin but also in infectious diseases such as HIV, progressive multifocal leukoencephalopathy, traumatic brain injury, and neoplastic white matter tumors (39).

6.2. White matter abnormalities in schizophrenia

Many psychiatric disorders including obsessive-compulsive disorder, ADHD, depression, psychosis, and bipolar disorder are accompanied by myelin deficits (8). Schizophrenia is perhaps the most investigated psychiatric disorder in regard to white matter abnormalities, with the most consistent findings. The disease is characterized by altered perception of reality, most often in forms of disorganized thought processes and speed, auditory, visual, or paranoid hallucinations, and/or social dysfunction. Like MS, schizophrenia has an early peak in age of onset, typically in the late teens to early twenties, and is accompanied by cognitive deficits (64, 65).

Schizophrenia is a systems-wide disorder with genetic and environmental contributions (66, 67). More than one gene is involved, more than one brain area is affected, and communication between brain areas seems

disrupted (68, 69). These features of the disorder are highly compatible with disturbances in myelin, though they do neither elucidate the sequence of events (i.e. primary abnormalities in myelination or secondary adjustment to a pathological event), nor do they exclude that diverse pathological events, including but not limited to myelination, can cause a variety of symptoms collectively referred to as 'schizophrenia'. Following is a summary of experimental approaches and results that highlight white matter abnormalities in schizophrenia.

6.2.1. Post-mortem and imaging studies show myelin abnormalities in schizophrenia

Reductions in neuropil, first found in post-mortem studies, have long been proposed in schizophrenia (70, 71). These reductions suggest a decrease in dendritic spine density as well as a decrease in myelin (72). Ultrastructural post-mortem studies have demonstrated pathological changes in oligodendrocytes in schizophrenia and bipolar disorder (73). Decreased numbers of oligodendrocytes were found in schizophrenia, bipolar disorder, and in major depression, particularly in layer VI of the PFC (74). Oligodendrocytes were reduced around capillaries in the PFC in schizophrenia, as well as around neurons (75, 76). Immunostaining of oligodendrocytes with 2',3'-cyclic nucleotide-3'-phosphodiesterase in the superior frontal gyrus yielded similar results (77).

Multiple structural and functional magnetic resonance imaging (fMRI) studies along with DTI studies have demonstrated white matter abnormalities in schizophrenia including reduced density, altered integrity, changes in white matter volume, myelin/axonal disruption and abnormal organization of fiber tracts (8, 78, 79). The alterations in myelin were present among first-episode psychosis patients, under treatment with atypical or typical antipsychotics, and in drug-free patients, indicating that the white matter changes are not solely a result of length of disease or treatment (80-86). However, length of disease does cause a further decline in white matter organization (87).

A vast number of DTI studies have been carried out in the last couple of years in schizophrenic patients. These studies demonstrated an inverse relationship of DTI fractional anisotropy (FA; a measure of white matter health) with positive symptom scores in association fibers (88), as well as a correlation with memory functions (89). A recent study used DTI to differentiate patients with schizophrenia from healthy volunteers with 98% accuracy (90). In monozygotic twins it was shown that anatomical connectivity in medial PFC is heritable (91). In addition, altered medial frontal white matter integrity was found in non-affected relatives of schizophrenic patients. These findings suggest that reduced white matter integrity in medial frontal regions is associated with the genetic liability to schizophrenia, and that myelin abnormalities can be used as an endophenotype (91).

6.2.2. Microarray- and gene expression studies highlight myelin abnormalities in schizophrenia

A microarray study of gene expression levels in the post-mortem dorsolateral PFC of patients with schizophrenia showed that genes expressed in oligodendrocytes were decreased (92). The group of oligodendrocyte-specific genes included myelin associated glycoprotein, myelin basic protein, proteolipid protein, myelin oligodendrocyte glycoprotein, and others. The findings were confirmed in a number of follow-up studies (93-95). A decrease in oligodendrocyte-specific mRNA levels was also observed in other brain areas (96-101) and in mood disorders (93, 102, 103). No difference in the expression levels of oligodendrocyte transcripts was observed between medicated and unmedicated schizophrenic patients, suggesting that these changes are not secondary to treatment with antipsychotic drugs (92, 101).

6.2.3. Factors important for oligodendrocyte development and myelination are known to be affected in schizophrenia

A large number of factors including guidance cues, growth factors and chemokines are necessary to direct OPC migration, proliferation and maturation (2). Small differences in the level or distribution of these factors can presumably have deleterious effects. During development, the number of axons to be myelinated needs to be carefully matched with an appropriate number of oligodendrocytes. After myelination, oligodendrocytes and axons communicate via complex reciprocal interactions. Here we will mention a few of the factors involved in development and communication that might be of particular relevance to schizophrenia. Abnormalities in gene expression patterns will be excluded and are the subject of a chapter below.

6.2.3.1. Electrical activity

Electrical activity stimulates myelination in the CNS, as shown in studies with pharmacological agents that increase or decrease action potential firing (6, 104). Hypoactivity in neuronal circuits, as has been suggested for the PFC in schizophrenia, might thus lead to deficient myelination, creating a vicious cycle of sub-optimal information transfer in response to incomplete myelination (105).

6.2.3.2. Glutamate

Communication between oligodendrocytes and axons is accomplished by a number of neurotransmitters and receptors, with glutamate playing a particularly critical role (106).

Abnormalities in the glutamate system have been indicated in schizophrenia, leading to the 'glutamate hypothesis' of schizophrenia (107, 108). These abnormalities, predicting a hypofunction in the glutamate system, will impair the coordination between axons and oligodendrocytes. The careful matching of axon number/axon length and oligodendrocyte number/myelin segments could thus be derailed (106).

6.2.3.3. Neuregulin 1 (NRG1) and ErbB4 (v-erb-a erythroblastic leukemia viral oncogene homolog 4):

NRG belongs to a family of epidermal growth factor-like ligands that interact with ErbB receptor tyrosine kinases. Genetic abnormalities in NRG1 and ErbB4 are among the most consistent findings in schizophrenia (109-

112). In the peripheral nervous system (PNS), NRG1 is a critical axonal signal that controls Schwann cell development and myelin sheath thickness (113, 114). Levels of NRG1 type III are a key instructive signal that determines the ensheathment fate of axons (115). Similar functions in the CNS are presumed but not proven to date.

6.2.3.4. Disrupted in schizophrenia (Disc1)

DISC1 was first described as a DNA breakpoint in a large Scottish pedigree with high incidence of schizophrenia, bipolar disorder and other mental illnesses (116, 117). In zebra fish Disc1 is vital for oligodendrocyte development by promoting specification of Olig2-positive cells (118). These defects are comparable to disruption of NRG1 and ErbB signaling. Thus, Disc1 and NRG1 function in common or related pathways to control development of oligodendrocytes. In a rodent model this was further demonstrated that down-regulation of Disc1 results in accelerated differentiation and neuronal integration (28, 119).

6.2.3.5. Reelin (RELN)

A decrease in RELN levels and increased methylation within its promoter region has been associated with schizophrenia in various paradigms (120-123). RELN also plays a role in myelination. It is a secreted extracellular matrix protein which in the PNS regulates Schwann cell-axon interactions (124). In the CNS, RELN is expressed in embryonic and postnatal neurons during periods of neuronal and glial migration (125).

6.2.3.6. Oligodendrocyte lineage transcription factor 2 (OLIG2):

OLIG2 encodes a transcription factor that controls oligodendrocyte development (126). In schizophrenia a significant disease association was found with several markers in the OLIG2 gene (127). Interestingly, an interaction between OLIG2 and ErbB4 was also observed in that sample. A study in Chinese Han schizophrenia patients confirmed an association between schizophrenia and OLIG2 (128), while a study in Japanese patients did not find an association (129).

6.2.3.7. Brain-derived neurotrophic factor (BDNF):

The BDNF gene is a risk factor for schizophrenia, psychosis and mood disorders (130-138), although these findings might not hold up across different populations (139, 140). BDNF knockout mice demonstrated that BDNF plays a role in OPC development in the basal forebrain (141). These findings follow previous studies that demonstrated that BDNF elicits increases in the expression of myelin basic protein in the basal forebrain but not the cortex (142).

6.3. White matter abnormalities in other psychiatric disorders

6.3.1. Mood disorders

Bipolar disorder and major depressive disorder patients have shown myelin abnormalities in postmortem tissue, imaging, and genetic analysis (73, 102, 103, 143, 144). Some of the most consistent findings in bipolar disorder are an increased number of white matter hyperintensities; the underlying mechanism of the hyperintensity is unknown but may be due to demyelination (144). Structural abnormality data have not been consistent with both positive and negative findings, however this most likely reflects subtle changes in white matter structure compared to a global defect in myelin. Most DTI studies in bipolar patients have shown reduced fractional anisotropy and elevated apparent diffusion coefficient in the frontal cortex, corpus callosum, and internal capsule suggesting a loss of connectivity in white matter (143, 144).

6.3.2. Drugs of abuse

Among cocaine addicts, myelin-related genes such as PLP and MOBP are down-regulated in the nucleus accumbens, however genes involved in myelin development such as Olig2 and Sox10 are unaltered (145). Larger white-matter volume and abnormal tract morphology have been observed in chronic methamphetamine users (146-149). The alterations to white matter are present even during the early period of abstinence (150). Cognitive alterations are also present among chronic methamphetamine users including impaired inhibition, information processing, learning and memory, attention and psychomotor speed (151-153). Interestingly, psychiatric symptoms including psychosis, anxiety, suicidal ideation, and hostility are common in methamphetamine-abusing subjects during intoxication and abstinence (154-156).

7. COPPER METABOLISM, THE CUPRIZONE MODEL OF DEMYELINATION, AND THEIR RELEVANCE TO SCHIZOPHRENIA

7.1. Cuprizone and copper

Cuprizone (CPZ; biscyclohexanone oxalyldihydrazone) is a copper (Cu) chelator discovered in the early 1950s (157, 158). CPZ selectively injures oligodendrocytes, but the underlying mechanisms of CPZ-induced demyelination are not well understood. CPZ has been used as a model for MS in mice, but seemed to be without effect in rats. As will be shown below, the latter might not be accurate. Indeed, CPZ can be used to study the effect of oligodendrocyte disruption in the CNS on behaviors relevant for schizophrenia (159).

7.1.1. Role of copper in the CNS

Since CPZ is a Cu chelator, the role of Cu in the CNS deserves a closer look. Copper is an important catalytic and structural cofactor in a wide array of biochemical processes with a narrow range of optimal concentration (160). It has been estimated that 0.2% to 0.5% of the eukaryotic proteome depends on Cu or are involved in Cu management (161). Among the enzymes that use Cu as a co-factor are superoxide dismutase-1 (162), monoamine oxidase (163), dopamine-ß-hydroxylase (dopamine beta-monooxygenase, 164), the cytochrome c oxidase family (165), and cytochrome c oxidase assembly protein (166). Excess Cu is highly toxic requiring a close control of the transport, uptake, release and storage of Cu (167, 168).

It is not known if the chelated Cu is inactivated by CPZ or if it is trapped but still reactive. Thus, CPZ

toxicity might be caused by an increase in Cu, due to a cellular enrichment of Cu-CPZ, or a decrease in Cu, due to inactivation by CPZ. One hint to the dilemma might be that supplemental administration of Cu failed to reduce CPZ-induced toxicity, pointing to Cu being still active (169). However, a review by a group with a strong commitment to CPZ research claims that Cu levels are reduced after CPZ treatment (170). Because neither data nor a specific reference is provided, it is difficult to further assess this statement.

Taken together, while there is no doubt that CPZ is a Cu chelator that affects oligodendrocyte viability in the mouse (see below), the mechanism of action remains largely unknown.

7.1.2. Genetic disorders of copper metabolism

Genetic disorders that are accompanied by too high or too low Cu levels are well known. Wilson's disease is characterized by dramatic build-up of intracellular copper with subsequent neurologic abnormalities (171, 172). MRIs of Wilson's disease patients show abnormalities in extrapyramidal and pyramidal white matter tracts (173). Interestingly, Wilson's patients have a host of psychiatric manifestations from the affective disorder and schizophrenia spectrum, which often precede the diagnosis of Wilson's disease (174-176). In a subgroup of these patients the psychiatric symptoms improve with therapies that lower Cu levels, while other patients respond to antipsychotic drugs (174).

Low Cu levels can be equally damaging (177). The X-linked recessive disorder Menkes' disease is characterized by generalized Cu deficiency (172). Severe neurologic impairment is evident within the first two months after birth and progresses rapidly to decerebration and death (178). Pathological abnormalities include extensive myelin loss (179), which at one point led to the suggestion to group the disorder with leukodystrophies (180). A gene expression microarray study found genes involved in myelination, energy metabolism, and translation to be downregulated (181), and MRI scans showed delayed myelination even in treated patients (182).

7.1.3. Copper levels in schizophrenia

It has long been theorized that excess tissue copper can cause schizophrenia (183). This theory has neither been compellingly demonstrated nor convincingly refuted (184). Most recently, plasma Cu concentrations were shown to be elevated in schizophrenic patients ((185), see also (186) for an earlier reference), and a study of trace metals in scalp hair samples of schizophrenic patients showed an increase in Cu concentrations (187). A caveat of the latter study, pointed out by the investigators, is that most of the patients were poor, middle-aged and divorced. Thus, the alterations might be a consequence nutritional status and socioeconomic factors. On the other hand, a number of studies found no changes in Cu levels. For example, Cu levels in the CSF (188), as well as in post-mortem brains (189) were reported to be normal in schizophrenic patients, and in contrast to the recent study mentioned above (187), a previous study found a *reduction* in Cu in the hair of schizophrenic patients (190). Treatment with antipsychotic drugs may contribute to the increases in Cu levels (191), although some of the initial studies were carried out prior to the introduction of antipsychotic drugs (183).

At this point, we cannot exclude a genetically predisposing difference in Cu metabolism in schizophrenia, though we are far from a convincing proof. For example, ceruloplasmin, a plasma metalloprotein, carries 90 percent of the plasma Cu (192) and, in the brain, is synthesized and released by glia (predominantly astrocytes, 193, 194). In schizophrenia, ceruloplasmin levels are increased in the CNS (195), and correlated with increased Cu levels (196). One could thus imagine a subset of patients with a genetic predisposition that includes altered ceruloplasmin activity in glia and a higher vulnerability when exposed to Cu. Alternatively, Cu dysregulation, if real, could be an epiphenomenon of nutritional status, disease treatment, or due to secondary pathophysiological mechanisms.

7.2. The cuprizone model of demyelination in the mouse

CPZ has been used in mice to model demyelination and remyelination for MS research (170). The first experiments were performed in the 1960s showing microscopic lesions, edema, astrogliosis, and demyelination along with growth retardation (169). CPZ is typically administered in the chow at concentrations of 0.2 – 0.6% with growth retardation occurring in a dose-dependent manner. Different strains of mice have different degrees of demyelination, which could be an indication that genetic factors influence susceptibility to demyelinating diseases (197, 198), although genetic factors might also influence Cu physiology in this model. The corpus callosum and other major white matter tracts have been predominantly investigated in the CPZ model, but other areas such as the cortex (199), hippocampus (200-202), and cerebellum (203-205) have also shown demyelination. Cuprizone decreases the expression of myelin-specific genes *in vivo* (206-208) and retards the differentiation of oligodendrocytes *in vitro* (209). After CPZ treatment in mice, Cu and zinc concentrations increase by over 100% in the brain, with a concomitant decrease in iron (158). During the early stages of exposure to CPZ a decrease in monoamine oxidase and cytochrome c oxidase in the brain and liver of mice is observed (210) along with the development of mega-mitochondria in the liver (211).

Removal of CPZ from the chow allows for remyelination within four to six weeks after onset of exposure, dependent on CPZ dose and the age of the mice. After extended demyelination over 12 weeks, remyelination is either negligible or delayed over weeks of recovery (212, 213). The demyelination-remyelination aspect of the mouse CPZ model is beneficial for the study of the relapsing characteristic of MS.

Not surprisingly, motor deficits are common in mice during CPZ exposure and after withdrawal. These included reduced performance in the rotarod (214) and in wheel running (215, 216). Some open field studies have shown increased exploration in the center together with increased rearing, indicating decreased anxiety (214). However, this has not been repeated in other studies (217).

Of significance to schizophrenia, CPZ impairs spatial working memory in mice, which can be reversed by the antipsychotic drug quetiapine (218). Prepulse inhibition (PPI), a measure of sensory gating known to be disturbed in schizophrenia (219), is also altered in CPZ treated mice (217, 220). Cuprizone-exposed mice display diminished social interaction, another symptom of schizophrenia (221), more time in open arms of the elevated plus maze, and decreased spontaneous alterations in the Y-maze (217).

The timing of CPZ exposure and the age of mice correlate with the severity of the cognitive deficits. Mice exposed to CPZ at an early age (postnatal day 29 -56) display working memory deficits immediately after CPZ treatment and after remyelination, whereas mice exposed at a later age (postnatal day 57-84) display working memory deficits only immediately following CPZ exposure (222). This could indicate that an environmental impact affecting oligodendrocyte development might have long-lasting consequences if happening during childhood or early adolescence, whereas the same impact later in life is of lesser significance.

Many of the behavioral changes can be reversed with antipsychotic drugs co-administered with CPZ exposure (217, 220). Mice with co-administered antipsychotic drugs (haloperidol, clozapine, or quetiapine) do not display the PPI deficits, decreased spontaneous alteration in Y maze, or decreased social interaction exhibited by CPZ-only exposed mice. Moreover, the white matter damage induced by CPZ is attenuated in PFC mice given clozapine or haloperidol and in the hippocampus in mice given clozapine or quetiapine. Overall, the CPZ model in mice is a strong indicator that white matter disturbances can cause behavioral deficits similar to the ones observed in schizophrenia, and that these deficits can be reversed with antipsychotic drugs. The caveat in this model might be the motor complications, but these complications can be overcome with careful titration of CPZ.

7.3. The cuprizone model of demyelination in the rat

Although CPZ works well as a demyelinating agent in mice and is used primarily for studies of MS, it does not seem to be useful as an MS model in rats. Whereas one study showed demyelination in young rats at a high concentration of CPZ (223), other studies did not observe demyelination or decreases in oligodendrocyte numbers (170, 224, 225). We were interested in developing a rat model of demyelination in the CNS that leads to oligodendrocyte disturbances in the CNS without triggering motor symptoms. We chose rats since we were interested in the PFC and PFC-mediated behaviors, and rats have an anatomically well-described PFC with established PFC-mediated behaviors (226-228). Given that CPZ was not an obvious MS trigger in rats, we decided to examine it for possible use as a mildly demyelinating agent in the CNS.

Decreased cognitive ability is recognized as a core feature of schizophrenia (229). Cognitive function is a critical determinant for quality of life of schizophrenic patients and long-term outcome of the disease (230-232). Many of the cognitive deficits are mapped to the PFC with schizophrenic patients performing poorly on the Wisconsin Card Sorting Test (WCST), a test dependent on the PFC (233). Since oligodendrocyte pathology is a well-described feature in schizophrenia (see above), we sought to devise an experiment in which to test if oligodendrocyte deficits in the PFC can explain some of the behavioral deficits observed in schizophrenia.

Based on the human data that show that the PFC is fully myelinated only in the late teens to early twenties, we started low-dose (0.2%) CPZ exposure beginning on postnatal day 29, during the juvenile period in the rat. Our hypothesis was that the oligodendrocytes in this final stage of development in the PFC would be more vulnerable than those that had fully matured in other brain regions. Indeed, rats exposed to moderate concentrations of CPZ during adolescence had a decrease in mRNA transcripts and protein levels of oligodendrocyte-specific genes in the PFC (159), similar to what has been observed in schizophrenia and bipolar disorder in humans. Levels of myelin-related genes were not affected in the striatum and hippocampus, two brain areas that should have been completely myelinated before the age of CPZ exposure. The alterations in myelin-related genes were present in the PFC after two and four weeks of CPZ exposure. In addition to the altered myelin genes, glial fibrillary acidic protein (GFAP) was upregulated in the PFC, indicating an activation of astrocytes.

The behavior of CPZ-treated rats was investigated in the attentional set-shifting task (ASST), a modified version of the WCST which reveals impairments in schizophrenia (233, 234). One phase of the ASST, the extra dimensional shift, is impaired by bilateral lesions of the medial PFC and could thus reveal a decline in PFC function (228, 235). Rats treated for two weeks with CPZ demonstrated an increased difficulty to shift attention from one perceptual dimension to another in the extra dimensional shift phase of the ASST (159), while other, arguably more challenging parts of the task, were not affected. The deficit in only the extra dimensional shift phase (shifting strategies) of the task and not during acquisition and reversal-learning indicates specificity for PFC involvement (228). Importantly, CPZ treated rats did not exhibit locomotor problems and had normal weight gain. Thus, the CPZ model in rats can be used to study developmental windows of vulnerability, as well as the pathogenesis and behavioral consequences of dysmyelination.

8. PERSPECTIVES

Overwhelming evidence supports the conclusion that schizophrenia is accompanied by dysmyelination. Little is known about the factors causing myelin deficits in schizophrenia, though it is reasonable to assume that a number of genetic and environmental factors can target different aspects of oligodendrogenesis, axon-oligodendrocyte interaction, and oligodendrocyte viability.

The CPZ model of dysmyelination in rodents can help to elucidate windows of vulnerability during brain development and the effects of dysmyelination in particular brain areas on aspects of behavior with relevance to schizophrenia.

9. ACKNOWLEDGEMENT

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Abbreviations: ASST: attentional set-shifting task, BDNF: Brain-derived neurotrophic factor , CPZ: cuprizone, Cu: copper, Disc1: Disrupted in schizophrenia , DTI: diffusion tensor imaging, ErbB4 : v-erb-a erythroblastic leukemia viral oncogene homolog 4, fMRI: functional magnetic resonance imaging, GFAP: glial fibrillary acidic protein, MRI: magnetic resonance imaging, MS: multiple sclerosis, NRG1: Neuregulin 1 , OLIG2: Oligodendrocyte lineage transcription factor 2 , OPCs: oligodendrocyte progenitors, PFC: prefrontal cortex, PNS: peripheral nervous system, PPI: prepulse inhibition, RELN : Reelin, WCST: Wisconsin Card Sorting Test

Key Words: Schizophrenia, White Matter, Myelin, Oligodendrocytes, Cuprizone, Copper, Prefrontal cortex, Review

Send correspondence to: Christine Konradi, Vanderbilt University, Department of Pharmacology, MRB 3, Room 8160, 465 21st Avenue South, Nashville TN 37232-8548; USA, Tel. 615-936-1021, Fax 615-936-0484, E-mail: christine.konradi@vanderbilt.edu

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