Improving myelin/oligodendrocyte-related dysfunction: a new mechanism of antipsychotics in the treatment of schizophrenia?

Yuan Ren\textsuperscript{1,\textast}, Hanzhi Wang\textsuperscript{2*} and Lan Xiao\textsuperscript{2}

\textsuperscript{1} Department of Clinical Medicine, Chongqing Key Laboratory of Neurobiology, Third Military Medical University, Chongqing, China
\textsuperscript{2} Department of Histology and Embryology, Chongqing Key Laboratory of Neurobiology, Third Military Medical University, Chongqing, China

Abstract

Schizophrenia is a severe psychiatric disorder with complex clinical manifestations and its aetiopathological factors remain unclear. During the past decade, the oligodendrocyte-related myelin dysfunction was proposed as a hypothesis for schizophrenia, supported initially by a series of neuroimaging studies and genetic evidence. Recently, the effects of antipsychotics on myelination and oligodendroglial lineage development and their underlying molecular mechanisms were evaluated. Data from those studies suggest that the antipsychotics-resulting improvement in myelin/oligodendrocyte-related dysfunction may contribute, at least in part, to their therapeutic effect on schizophrenia. Importantly, these findings may provide the basis for a new insight into the therapeutic strategy by targeting the oligodendroglia lineage cells against schizophrenia.

Key words: Antipsychotics, myelination, oligodendrocyte, schizophrenia, white matter.

Introduction

Schizophrenia, with its general stage of onset in either adolescence or young adulthood, is a severe psychiatric disorder with complex clinical manifestations, including psychotic symptoms, affective disturbance and cognitive dysfunction. There is no known single cause of schizophrenia although genetics, early environment, neurobiology, psychological and social processes appear to be important contributors (Jablensky \textit{et al.} 2005; Kirov \textit{et al.} 2005; St Clair \textit{et al.} 2005; Tsuang, 2000). Due to limited understanding in its aetiology, the mainstay of schizophrenia treatment has been to use antipsychotic medications that only relieve its symptoms instead of eliminating its aetiopathological factors. Consequently, most chronic schizophrenia patients cope with symptoms throughout their lives.

In the past decade, several hypotheses concerning the pathogenesis of schizophrenia have been generated and tested. Among them, genetic epidemiology studies showed that variation in the regions of chromosomes 1, 2, 4, 5, 6, 7, 8, 9, 10, 13, 15, 18 and 22, as well as the X chromosome is closely related to schizophrenia (Riley & McGuffin, 2000). Also, genetic predisposition in individuals may determine the symptoms and extent of schizophrenia. Pharmacology studies suggest that dysfunction of neurotransmitters is one of the primary aetiologies of schizophrenia (Hirvonen & Hietala, 2011), while antagonists or selective-agonists of dopamine, serotonin and/or glutamate receptors were developed and used as major antipsychotic drugs (APDs) in clinical practice during recent years. Noticeably, apart from the traditional neurotransmitter hypothesis, several lines of evidence revealed that white matter abnormalities and/or disconnection of neural signalling conduction may also be involved in the pathogenesis of schizophrenia. Concerning the action of APDs on white matter, a recent neuroimaging study using diffusion tensor imaging (DTI) assessed the myelin integrity among normal control and acutely psychotic, drug-free schizophrenics, before and after APD treatment. It was found that a decrease of myelin integrity was partially restored in drug-responding schizophrenic individuals, whereas the poorly responsive schizophrenics did not appear to be related to a disordered myelin (Garver \textit{et al.} 2008). Therefore, it is of interest to identify the underlying mechanism of action of antipsychotics in the development of oligodendroglia and/or myelination and to determine new targets for treatment of schizophrenia.

In this review, we mainly focus on the involvement of oligodendroglial and/or myelin dysfunction in schizophrenia. We also summarize recent progress in related...
vented to identity OPCs (He et al. 2009) with specific bio-markers, NG2, A2B5 and PDGF. Regarding their pro-OLs, premature OLs and mature OLs with specific distinct developmental stages, i.e. OPCs, late precursor cells of the oligodendroglial lineage that includes a series of cell types (OPCs); the latter share a developmental lineage and myelination. Oligodendrocyte precursor cells (OPCs) arise from domains of the ventricular zone of the neural tube and rapidly acquire expression of cell surface antigens characterized by the monoclonal antibodies NG2, A2B5 and PDGFβR. These cells are bipolar with higher proliferation and migration abilities. Following differentiation, these cells acquire expression of oligodendrocyte marker (O4) and are identified as premature oligodendrocytes (OLs). Maturing oligodendrocytes acquire expression of proteolipid protein (PLP) or myelin basic protein (MBP) and so on. Newly generated OLs are vulnerable to cell death. BMP, Bone morphogenetic protein; GalC, galactocerebroside.

aspects, including neuroimaging, human genetic and experimental pharmacologic studies.

**Fig. 1.** Schematic representation of some major cell signalling pathways involved in the development of oligodendroglial lineage and myelination. Mitogen activated protein kinase (MAPK) are a family of Ser/Thr-specific kinases activated by extracellular stimulation through protein phosphorylation. So far four subtypes of MAPK have been discovered in mammalian cells: extracellular signal-regulated kinases 1 and 2 (ERK1/2); JNK/SAPK; p38MAPK; ERK5. Apart from ERK5, the three other subtypes are known to be critical for the formation and development of the oligodendroglial lineage (Fig. 1).

The JNK/SAPK and p38MAPK signalling activation mediate the apoptosis of oligodendroglial lineage cells whereas p38MAPK can also inhibit OPC differentiation and myelin gene expression by regulating parallel MAPK cascades, including JNK and ERK (Chew et al. 2010; Lee et al. 2011). Specifically, ERK signalling is important for both long-term survival and the progressing timing of oligodendroglia differentiation. ERK1/2 signalling is required in vivo for the migration, proliferation and differentiation of the oligodendroglial lineage but not for the survival of OPCs (Newbern et al. 2011). However, in vitro ERK1/2 plays a specific role in the timing of forebrain myelination but is not critical for the proliferation or survival of OPCs (Yaffe-Maricich et al. 2011). Moreover, there are significant differences between ERK1 and ERK2 in OPC development regulation. ERK1 deletion does not affect OL differentiation while the loss of ERK2 results in a delay, but not a complete arrest of OL differentiation (Yaffe-Maricich et al. 2011).

**Notch signalling pathway**

The Notch signalling pathway is a conserved intercellular mechanism that is essential for proper embryonic development in many metazoan organisms. Four different Notch receptors (Notch1–4) and five ligands [Jagged (JAG)1 and 2; D-like 1, 2 and 4] have been characterized in mammalian cells. Notch signalling is also important for OL differentiation and specification (Fig. 1). Activated
by JAG1. Notch1 signalling is permissive for OPC expansion but inhibits differentiation and myelin formation (Zhang et al. 2009). However, another study argued that Notch1 signalling can enhance OL differentiation through a functional ligand of Notch called F3/contactin (Hu et al. 2003). Therefore, the role of Notch1 signalling in OL differentiation is currently controversial and remains to be clarified. Additionally, Notch2 signalling also plays a critical role in triggering the re-myelination programmes of aged cognitively impaired rats (Rowe et al. 2007).

**Canonical Wnt signalling pathway**

The Wnt signalling pathway is a network of proteins controlling cell-cell communication from receptors on the surface of the cell to DNA expression in the nucleus. It is crucial in embryogenesis and cancer genesis, while recent studies have shown that it is also involved in the development of the oligodendroglial lineage (Fancy et al. 2009; Rosenberg & Chan, 2009). Targeting a different step in the Wnt pathway has revealed several influences on OPC proliferation or differentiation; for example, enrichment of the extracellular Wnt-3a protein can block OPC differentiation but not proliferation (Shimizu et al. 2005; Tawk et al. 2011). In cytoplasm, glycogen synthase kinase (GSK)-3β inhibition strikingly increases OL differentiation, which suggests the possibility of communication between GSK-3β and other signalling pathways (Azim & Butt, 2011). Furthermore, constitutive activation of β-catenin in the nucleus exhibits a similar phenomenon to Wnt-3a (Feigenson et al. 2009). In conclusion, canonical Wnt signalling is a profound inhibitor of OL differentiation and myelination (Fig. 1).

**Association of myelin/oligodendrocyte-related dysfunction with schizophrenia**

**Evidence from neuroimaging studies**

The white matter regions underlie the grey matter cortex and are composed of neuronal fibres enclosed by an electrical insulation sheath, called myelin. Magnetic resonance imaging (MRI) can indirectly demonstrate myelinization in vivo using T1-weighted and inversion-recovery sequences to maximize myelin signal and grey/white matter contrast (Koenig, 1991). Using MRI, it has been shown that white matter volume increases in the frontal lobes until age 44 yr while the temporal lobe’s volume starts to decline after age 47 yr in a normal healthy individual (Bartzokis et al. 2001). However, another MRI study from the same group comparing 52 healthy male adults with 35 male schizophrenia patients showed the absence of white matter volume expansion in the patients. These findings suggest that the loss of myelination may be involved in the pathogenesis of schizophrenia (Bartzokis et al. 2003). In line with this notion, a study with MRI T2 relaxation analysis by measuring the water fraction of myelin demonstrated that the myelin thickness in the patients with schizophrenia was reduced about 12% overall (Flynn et al. 2003).

With the unique advantage of determining the precise location of white matter abnormalities, DTI has been widely used to explore the function of white matter. DTI studies in chronic schizophrenics indicate micro-structural abnormalities of the corpus callosum, anterior limbs of the internal capsule, superior longitudinal fasciculus and cingulum, but the results are conflicting regarding which neuronal tracts are affected (Peters et al. 2010). Moreover, a DTI index called fractional anisotropy (FA) has been interpreted to reflect the micro-structural integrity of white matter and its degree of myelination and FA decrease has proved to be closely associated with both the amount of white matter volume loss and the symptoms of schizophrenia (Beaulieu, 2002; Scheel et al. 2012). Other studies have shown that the severity of negative symptoms and cognitive deficits is associated with reduction of white matter volume, indicating that myelin/oligodendrocyte damage is involved in development of negative symptoms and cognitive dysfunction (Barley et al. 2009; Kim et al. 2008).

**Evidence from molecular genetics**

Based on the association between white matter dysfunction and schizophrenia from neuroimaging studies the potential role of white matter, myelin and/or OLs is emerging in the pathophysiology of schizophrenia (Table 1). Microarray analysis using post-mortem dorsolateral prefrontal cortex of schizophrenic patients showed that six myelin/oligodendrocyte-genes (MAL, MAG, CNPase, transferrin, gelsolin and ERBB3) were significantly decreased in elderly chronic schizophrenics (Hakak et al. 2001; Hof et al. 2002). Other studies further identified five additional myelin/oligodendrocyte-related genes (Olig2, Sox10, PLP1, MPZL1 and PMP22) which were shown to be down-regulated in patients with schizophrenia by microarray analysis (Aston et al. 2004; Dracheva et al. 2006; Iwamoto et al. 2005; Tkachev et al. 2003).

In the past 20 yr, gene linkage and association analysis has been employed as a major approach to search for genetic candidates that may account for complex diseases. Several promising candidate genes were discovered for schizophrenia susceptibility; NRG1, G72 and DTNBP1 genes were first identified through this approach (Hall et al. 2004). Notably, among those schizophrenia candidate genes, some are known to be closely correlated with the development of the oligodendroglial lineage, suggesting that myelin/OL-related dysfunction may be involved in schizophrenia. For instance, the DISC1 gene, detected in a large Scottish schizophrenic family with a (1; 11) (q42; q14.3) translocation, has been considered a strong candidate for schizophrenia.
Recently, experiments using zebrafish and DISC1-transgenic mice animal models both demonstrated that DISC1 can cause premature OL differentiation and increased proliferation of OPCs (Katsel et al. 2011; Wood et al. 2009). Highly expressed in the embryonic corpus callosum at a critical time, DISC1 is also involved in the formation of myelin (Osbun et al. 2011). Furthermore, a recent study identified another attractive candidate gene, called K homology domain RNA-binding (QKI) from a large family in Northern Sweden (Aberg et al. 2006). The qkI gene expresses three major alternatively spliced mRNAs (5, 6 and 7 kb) encoding QKI-5, -6 and -7 in the OLs of normal mice (Ebersole et al. 1996). QKI-5 is the only nuclear isoform and it shuttles between the nucleus and cytoplasm, while QKI-6 and -7 are mainly detected in the cytoplasm (Wu et al. 1999). Overexpression of QKI-5 causes nuclear retention of the MBP mRNA in OLs of rodent and further negatively affects MBP protein synthesis (Larocque et al. 2002). Conversely, QKI-6 and -7 bind to p27Kip1 mRNA, resulting in increased levels of the p27Kip1 protein as well as cell-cycle arrest followed by OL differentiation (Larocque et al. 2005). Additionally, both QKI-6 and -7 can initiate new production of myelin via an increase of MAP1B level (Wu et al. 2001). Specifically, QKI-6 can also facilitate oligodendrocyte differentiation and myelination alone by targeting the mRNA of AIP-1, hnRNPA and SIRT2 (Doukhanine et al. 2010; Zhao et al. 2010; Zhu et al. 2012). Collectively, both strong candidate genes for schizophrenia, the DISC1 and QKIs, play a positive role in development of the oligodendroglial lineage, suggesting that mutations of these genes may result in schizophrenia by causing myelin/oligodendrocyte-related dysfunction.

Most recently, molecular genetic-associated study further supported this notion by demonstrating the association of the myelin-related gene with schizophrenia. A single nucleotide polymorphism (SNP; SNP9, rs1049623) for a myelin-related gene, i.e. discoidin domain receptor-1 gene, was found strongly associated with schizophrenia (Roig et al. 2007). Furthermore, one SNP (rs2070106) for CNP was found potentially associated with schizophrenia in the Caucasian population (Voineskos et al. 2008) while the three SNPs (rs12458282, rs2008323, rs721286) for golli-MBP were identified as possibly associated with schizophrenia in the Jewish Ashkenazi population (Baruch et al. 2009). These observations suggest that myelin dysfunction

<table>
<thead>
<tr>
<th>Table 1. Myelin/oligodendrocyte-related gene expression in the brain of patients with schizophrenia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gene</strong></td>
</tr>
<tr>
<td><strong>Microarray</strong></td>
</tr>
<tr>
<td><strong>Cell type</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

Q-PCR, Quantitative polymerase chain reaction; OPC, oligodendrocyte precursor cells.

<sup>a</sup> Data published in Tkachev et al. (2003).
<sup>b</sup> Data published in Dracheva et al. (2006).
<sup>c</sup> Data published in Hakak et al. (2001).
<sup>d</sup> Data published in Aston et al. (2004).
<sup>e</sup> Data published in Iwamoto et al. (2005).

n.a. denotes that genes were not analysed; + denotes that significant difference exists in optional brain regions; – denotes the opposite.
may predispose to schizophrenia across different populations.

A demyelination mouse model for schizophrenia study

Endowed with its specificity to induce damage of OLs and myelin membrane vacuolization, cuprizone (CPZ) has been widely used in establishing demyelination models. After feeding with a CPZ-containing diet for >3 wk, adult C57BL/6 mice will demonstrate demyelination in specific white matter tracts of the brain, including the cerebellar peduncles, corpus callosum and anterior commissure (Komoly, 2005). Recent studies showed that C57BL/6 mice with CPZ-induced demyelination and OL loss developed an array of abnormal behaviours, including deficits in prepulse inhibition, reduced social interaction and impaired spatial working memory (Makinodan et al. 2009; Xu et al. 2009, 2011). Furthermore, CPZ-treated rats display a specific deficit in a prefrontal cortical (PFC)-mediated behavioural paradigm—the ability to shift between perceptual dimensions in the attention set-shifting task—paralleling the Wisconsin card sorting test (Gregg et al. 2009). The CPZ-fed rodents therefore appear as a useful animal model for exploring the role of myelin/oligodendrocyte-related dysfunction in the pathophysiology of schizophrenia.

Impact of antipsychotic drugs on the oligodendroglial lineage cells

The first-line APDs against schizophrenia are divided into two categories, i.e. the first-generation (also known as typical) and the second-generation (also known as atypical) APDs. The typical APDs, represented as haloperidol, mainly work as the antagonist of dopamine D$_1$ and D$_2$ receptors (Creese et al. 1996; Seeman et al. 2005). Typical APDs are effective for alleviating the positive symptoms of schizophrenia; however, undesired side-effects and risk, such as extra-pyramidal symptoms including Parkinson’s syndrome, akathisia and tardive dyskinesia, may negatively impact patients’ quality of life and social function (Leucht et al. 2009). Along with the development in schizophrenia research, dysfunction in neurotransmitters other than dopamine, e.g. glutamate, γ-aminobutyric acid and serotonin (5-HT) has been considered involved in schizophrenia pathogenesis (Meltzer & Massey, 2011; Stone et al. 2007). Most recently, adenosine is also proposed to contribute to schizophrenia endophenotypes (Shen et al. 2012). Therefore, by targeting on non-dopaminergic signalling, the atypical APDs such as clozapine, olanzapine, quetiapine and risperidone have been developed and affect various neurotransmitter receptors, including 5-HT$_1A$ and 5-HT$_2$ D$_1$ and D$_2$, histamine 1 and adrenergic (α$_1$ and α$_2$) receptors (Nemeroff et al. 2002). Compared to the typical APDs, the atypical APDs have superior therapeutic effects on treatment of negative and cognitive symptoms in patients with schizophrenia and less extra-pyramidal side-effects (Glick & Marder, 2005; Kasper et al. 2004; Tandon, 2004; Tandon & Jibson, 2003).

In an attempt to reveal the underlying cellular mechanisms of the therapeutic actions of atypical APDs, studies showed that atypical APDs provide neuroprotective effect in system models of animal or culture cells against various insults (He et al. 2005; Lu et al. 2004; Lu & Dwyer, 2005; Qing et al. 2003; Wang et al. 2005; Wei et al. 2003; Xu et al. 2002). Furthermore, chronic treatment with the atypical APDs was demonstrated to increase the number of new-born cells in the hippocampus, PFC and striatum of adult rats, which may account for the pro-cognition effect and negative symptom relief (Kodama et al. 2004; Wakade et al. 2002; Wang et al. 2004). Recently, a series of studies have shown different effects of APDs on oligodendroglia or myelination.

Haloperidol and oligodendroglial lineage cells

Despite its adverse effects, the typical APD haloperidol is still applied in the treatment of schizophrenia patients with serious positive symptoms. A number of studies suggest that haloperidol treatment leads to expression changes in the myelin/oligodendrocyte-related gene (Farkas et al. 2010; Konopaske et al. 2008; Steiner et al. 2011). Chronic haloperidol treatment was also shown to cause alteration of myelin/oligodendrocyte-related genes in the prefrontal brain of monkeys (Sugai et al. 2004). Adult male mice treated with haloperidol (2 mg/kg.d) for 30 d demonstrated a significantly decreased expression of myelin/oligodendrocyte-related genes including MBP, PLP, MAG, transferrin, UDP-galactose ceramide galactosyltransferase and Claudin 11 (Narayan et al. 2007). Moreover, a chronic haloperidol treatment increased the number of NG2$^+$ OPCs without affecting APC$^+$ OLs in the relevant brain area (Wang et al. 2010), which suggests that the target of haloperidol is quiescent OPCs in the adult brain. Additionally, incubation of haloperidol with cultured OPCs significantly increases the number of OPCs but decreases the number of OLs (Niu et al. 2010). These results suggest that haloperidol can promote the proliferation but inhibit the differentiation of OPCs albeit the mechanism by which haloperidol acts on OPCs remains unclear. Most likely it is mediated by D$_2$ receptors that are only expressed in OPCs and immature OLs (Niu et al. 2010).

Quetiapine and oligodendroglial lineage cells

Among APDs, the atypical APD quetiapine seems unique in terms of its efficacy on genesis of oligodendroglial lineage cells. This is shown by quetiapine which can promote in vitro the differentiation of neural progenitor cells to OLs via activation of ERK1/2 and elevated MBP synthesis and myelination. Also, chronic quetiapine treatment can effectively block myelin breakdown in the
cerebral cortex and against the concomitant spatial working memory impairment in CPZ-induced demyelinated mice (Xiao et al. 2008). Further, quetiapine can prevent or alleviate myelin breakdown and decrease the activation of astrocytes and microglia in CPZ-exposed mice (Zhang et al. 2008). In the chronic demyelinated mice model, quetiapine treatment also promoted remyelination and recovery of spatial working memory impairment (Zhang et al. 2012). Considering the therapeutic effect of quetiapine, particularly in the improvement of cognitive impairment in schizophrenia (Riedel et al. 2007), these observations imply that protecting the white matter from damage may become an effective approach to improve the negative symptoms in schizophrenia.

Olanzapine and oligodendroglial lineage cells

Olanzapine is an atypical APD, similar to quetiapine, which has been widely used for the treatment of schizophrenia and other psychiatric disorders such as depression or bipolar disorder. In a study with the purpose of testing whether olanzapine can affect the genesis of OLs, C57BL/6j mice were treated with olanzapine for 8 wk and bromodeoxyuridine intake for the last 2 wk. It was shown that olanzapine increases the number of oligodendroglial lineage cells, especially due to enhanced differentiation from immature glial progenitors (Yamauchi et al. 2010). In an in vitro study using OPC cultures, it was found that an appropriate concentration of olanzapine can stimulate proliferation but inhibit differentiation of OPCs, due to the increase or decrease of phosphorylated ERK1/2, respectively (Kimoto et al. 2011). Although olanzapine has a higher affinity for the 5-HT receptor over the D₂ receptor, similarly to quetiapine, it affects oligodendroglia differently from how quetiapine does. In this regard, it seems that the effects of APDs on oligodendroglial lineage cells are different from type to type; thus, it may not be simply accounted for by one kind of neurotransmitter receptor. To clarify the underlying mechanism, further well-designed pharmacological studies are needed.

Conclusion and prospects

During the past 10 yr, structural, functional and molecular changes in white matter lesions have become a major focus of interest in exploring the aetiology of schizophrenia. In this review, we discussed the functions and mechanisms of one typical APD (haloperidol) and two atypical antipsychotics (quetiapine and olanzapine) on the survival, genesis, proliferation, differentiation and maturation of the oligodendroglial lineage (Fig. 2). Interestingly, haloperidol and olanzapine stimulate proliferation but inhibit differentiation of OPCs via different molecular mechanisms. Quetiapine, however, is diametrically opposed to the above processes, although it targets the similar receptors as does olanzapine. Therefore, we propose that the improvement of myelin/oligodendrocyte dysfunction by antipsychotic drugs may not rely on canonical neurotransmitters but rather that cross-communication may exist through different molecular mechanisms. Future research strategies should include the investigation of putative molecular mechanisms for the actions of APDs on the oligodendroglial lineage. For instance, in addition to the MAPK (ERK1/2) pathway, the effects described earlier may be mediated by other signal pathways and the interactions between these signal pathways and several transcription factors also deserve to be further studied.

ADPs can be used correctly only if we understand more clearly the molecular mechanisms that they trigger. In the future this should help to generate the discovery of new therapeutic tools by developing OL-directed strategies in schizophrenia. Towards this, the improvement of myelin/OL-related dysfunction by APDs may provide a new insight into the treatment of schizophrenia and other related psychiatric disorders.

Acknowledgements

This work is partly supported by the National Natural Science Foundation of China (NSCF, 31000482), International Science & Technology Cooperation Program of China (2010DFB30820) and Natural Science Foundation Project of Chongqing (CQ CSTC, 2010BB5157).

Statement of Interest

None.
References


Tandon R (2004). Quetiapine has a direct effect on the negative symptoms of schizophrenia. Human Psychopharmacology 19, 559–563.


