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Review

# Epigenetic mechanisms in schizophrenia

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ABSTRACT

Epigenetic modifications, including DNA methylation, histone modifications, and non-coding RNAs, have been implicated in a number of complex diseases. Schizophrenia and other major psychiatric and neurodevelopmental disorders are associated with abnormalities in multiple epigenetic mechanisms, resulting in altered gene expression during development and adulthood. Polymorphisms and copy number variants in schizophrenia risk genes contribute to the high heritability of the disease, but environmental factors that lead to epigenetic modifications may either reduce or exacerbate the expression of molecular and behavioral phenotypes associated with schizophrenia and related disorders. In the present paper, we will review the current understanding of molecular dysregulation in schizophrenia, including disruption of the dopamine, NMDA, and GABA signaling pathways, and discuss the role of epigenetic factors underlying disease pathology.



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## 1. Introduction

In recent years, many diseases, particularly neuropsychiatric disorders, have been found to be the result of complex interactions between genetic susceptibility and environmental insults (Gavin and Akbarian, 2012; Robertson, 2005; Robertson and Wolffe, 2000; Schanen, 2006; Tsankova et al., 2007). Schizophrenia is a complex and disabling disorder defined by psychotic, affective, and cognitive symptoms. Positive symptoms include hallucinations, psychosis, and mania, while negative symptoms include anhedonia and social withdrawal. Although cognitive functioning is generally intact, working memory may be severely impaired. The onset of the disease typically occurs during late adolescence or early adulthood, a critical period in neurodevelopment that is characterized by activity-dependent synaptic pruning and final maturation of the prefrontal cortex (PFC), the region of the brain that regulates higher cognitive functions such as working memory and emotional control. The positive symptoms in schizophrenia are primarily associated with upregulation of dopamine (DA) signaling throughout the brain, while the negative and cognitive symptoms are caused both by abnormal dopamine signaling and a complicated interaction between GABAergic signaling and hypoactive NMDA function in the

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PFC and hippocampus. At a neuromorphological level, brains from schizophrenic patients exhibit a reduction in the number and complexity of neuronal connections in the cortex, suggesting aberrant synaptic pruning during the late stages of neurodevelopment. Reduced dendritic complexity in the PFC correlates with the cognitive deficits common to schizophrenia.

Despite the global impairment and severity of the disease, there are few effective therapies available, many of which have severe side effects. Antipsychotic drugs primarily target dopamine receptor signaling at the dopamine D2 receptor. In animal models, antipsychotics that target D2 receptors induce dopamine neuron inactivation or block depolarization; treatment with amphetamine increases hyperactivity and other psychosis-relevant behaviors, and treatment with the antipsychotic clozapine reverses these effects (Herrera et al., 2013; Valenti et al., 2011). Recently it has been suggested that hyperactivity of the DA signaling system may be related to reduced inhibitory neuron function in the hippocampus and ventral tegmentum, as selective reduction of parvalbumin interneurons in the hippocampus results in an increase in downstream dopamine neuron activity (Boley et al., 2014; Gilani et al., 2014).

The importance of dopamine signaling in schizophrenia is based on 3 lines of evidence: first, the most effective drugs for schizophrenia are the D2R-targeting antipsychotics, with up to 90% D2 receptor occupancy; second, most patients with schizophrenia are highly sensitive to dopamine agonists, showing an immediate re-emergence of psychosis and other positive symptoms; and third, functional imaging studies have provided overwhelming evidence for dopamine hyperactivity in the brain, even in asymptomatic or drug naive patients (Salavati et al., 2014; Seeman, 2010). Functional imaging has overwhelmingly shown an upregulation of presynaptic striatal dopamine activity, variations in dopaminergic signaling correlated with executive functioning in the prefrontal cortex, and manipulation of dopamine signaling results in network disruption in numerous brain regions including the prefrontal cortex, hippocampus, striatum, basal ganglia, and putamen (Cole et al., 2013; Tan et al., 2007).

Although there is a strong functional association between DA signaling and schizophrenia, genome-wide association studies (GWAS) have not identified statistically significant loci containing dopamine-related genes. Quantitative trait locus and candidate gene mapping have been somewhat more successful, and several particularly strong candidates have been found, including *DISC1*, *NRG1*, and a cluster of GABA-A receptor subunits on chromosome 5 (Gogos and Gerber, 2006). However, many of these studies have failed to replicate, possibly due to population variability, very small effect sizes of risk genes, epistasis, and environmental factors. Because multiple large genome-wide studies have identified a strong overlap between schizophrenia and other major psychiatric disorders, there is now an effort to define studies based on endophenotypes, rather than diagnosis (Consortium, 2013; Craddock and Sklar, 2013). One DA-related representative of the endophenotypic approach is catechol-O-methyltransferase (COMT), which assists in clearing DA from synapses. The COMT Val158Met polymorphism has been well-studied in humans: in control subjects and unaffected siblings of schizophrenic patients, the Val allele is associated with reduced prefrontal DA levels and impaired working memory, particularly during more difficult tasks, but function can be rescued with amphetamine treatment (Tan et al., 2007). In both control and schizophrenic patients, the Val allele negatively impacts both working memory and negative symptoms (Ceaser et al., 2013). Interestingly, a number of studies have shown that COMT interacts with polymorphisms in other schizophrenia risk genes, including AKT, MTHFR, DRD2, DTNBP1 (Tan et al., 2012).

While DA antagonists are largely effective at reducing or eliminating psychotic and hallucinatory symptoms in schizophrenic patients, antipsychotics have little effect on the affective and cognitive symptoms in schizophrenia. Recent research suggests that the interaction of NMDA and GABA signaling in the PFC may also be important to the pathogenesis of the disease. NMDA signaling is required for proper synapse formation and maintenance, particularly during adolescence, but is reduced in schizophrenia, a phenotype known as hypofrontality (Bhatt et al., 2009). In animal models, genetic or pharmacological induction of NMDA hypofunction is known to recapitulate both positive and negative behavioral endophenotypes similar to those observed in schizophrenia. NMDA antagonists can produce a wide array of relevant positive, negative, and cognitive behaviors such as hyperactivity, anhedonia, and social withdrawal in both acute and chronic paradigms, along with including dysregulation in dopamine signaling, interruption of normal inhibitory-excitatory circuitry in the prefrontal cortex, and cognitive defects induced by aberrant prefrontal cortex-hippocampus connectivity (Blot et al., 2013; Neill et al., 2014; Svensson, 2000). Mice engineered to express just 5% of the obligatory NMDAR subunit NR1 display schizophrenia-like behavior, including increased locomotion and stereotypies (Mohn et al., 1999).

NMDA function is significantly impaired in patients with schizophrenia. NMDA, D-cycloserine, and other endogenous NMDAR agonists are reduced in post-mortem prefrontal and striatal tissue from schizophrenia patients, as are the NMDAR subunit NR2 and the downstream NMDA signaling components NRG1 and ERBB4 (Benneyworth et al., 2011; Geddes et al., 2011). NMDA antagonists induce psychosis and cognitive impairment in normal subjects, and exacerbate symptoms in psychiatric patients (Enomoto et al., 2007; Malhotra et al., 1997). Most recently, copy number variant analysis and exome sequencing of patients with schizophrenia show a significant over-representation of mutations in brain development-related genes, particularly genes associated with the NMDA signaling pathway (Gilman et al., 2012; Hall et al., 2014).

The activity of prefrontal glutamatergic neurons is tightly regulated by GABAergic interneurons, and, like NMDA signaling, GABAergic signaling is dysregulated in schizophrenia. Levels of GAD1, the enzyme responsible for synthesizing GABA, are reduced in post-mortem schizophrenic brains, as are a number of genes associated with GABA synthesis and signaling (Hashimoto et al., 2008). Polymorphisms in two GABA-expressed genes downstream from NMDA, NRG1 and ERBB4 are associated with aberrant GABAergic interneuron development and migration, and elimination of the NR1 subunit of the NMDA receptor in a subset of cortical GABAergic interneurons during postnatal development in mice results in a number of behavioral and molecular phenotypes associated with schizophrenia (Belforte et al., 2010; Flames et al., 2004). The most-replicated change is the decrease in the number of parvalbumin (PVALB)-positive interneurons and reduced expression of *PVALB* mRNA (Lewis et al., 2012; Uchida et al., 2014). Parvalbumin neurons are considered crucial to the pathogenesis of schizophrenia, as they are strongly associated with the regulation of NMDA signaling.

A final important aspect in the pathogenesis of schizophrenia is the neurodevelopmental timecourse. Although some symptoms, such as reduced sociability, may be observed in childhood, the onset of schizophrenia generally does not occur until late adolescence or early adulthood. While neurogenesis and massive dendritic connectivity characterize the early postnatal period, the adolescent period is characterized by NMDA-dependent synaptic pruning and the final maturation of the GABA-glutamate circuitry in the prefrontal cortex (Bale et al., 2010). Schizophrenia is believed

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