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Review

# The neuregulin signaling pathway and schizophrenia: From genes to synapses and neural circuits

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ABSTRACT

Numerous genetic linkage and association studies implicate members of the Neuregulin-ErbB receptor (NRG-ErbB) signaling pathway as schizophrenia "at risk" genes. An emphasis of this review is to propose plausible neurobiological mechanisms, regulated by the Neuregulin-ErbB signaling network, that may be altered in schizophrenia and contribute to its etiology. To this end, the distinct neurotransmitter pathways, neuronal subtypes and neural network systems altered in schizophrenia are initially discussed. Next, the review focuses on the possible significance of genetic studies associating NRG1 and ErbB4 with schizophrenia, in light of the functional role of this signaling pathway in regulating glutamatergic, GABAergic and dopaminergic neurotransmission, as well as modulating synaptic plasticity and gamma oscillations. The importance of restricted ErbB4 receptor expression in GABAergic interneurons is emphasized, particularly their expression at glutamatergic synapses of parvalbumin-positive fast-spiking interneurons where modulation of inhibitory drive could account for the dramatic effects of NRG-ErbB signaling on gamma oscillations and pyramidal neuron output. A case is made for reasons that the NRG-ErbB signaling pathway constitutes a "biologically plausible" system for understanding the pathogenic mechanisms that may underlie the complex array of positive, negative and cognitive deficits associated with schizophrenia during development.

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## 1. Introduction

Schizophrenia is a complex psychiatric disorder generally characterized by positive symptoms that include hallucinations, running thoughts and delusions, as well as negative symptoms such as social withdrawal and lack of affect. Deficits in working memory are also associated with the disorder. The combined effects of multiple susceptibility genes, with small effects from individual genes, are believed to contribute to the risk of developing schizophrenia (rev. [63]). The degree of concordance for schizophrenia in monozygotic twins has been reported to be between 50% and 80%, indicating that, while genetic background is important, genetic liability on its own is not sufficient to cause schizophrenia. It is generally accepted that genetic liabilities in combination with environmental contributions during development, such as frequency of cannabis use, infection or stress during gestation, stress during parturition and paternal age at conception, increase the likelihood of developing schizophrenia later in life (rev. [89,105]). While the positive symptoms of the illness (i.e., psychosis) frequently become apparent in the second decade of life, schizophrenia is generally considered a neurodevelopmental disorder (rev. [89,121,6]). The late onset of symptoms are thought to arise from earlier developmental alterations, such as deficits in neuronal migration, maturation of neuronal processes, deficits in synaptic pruning and myelination of selective axonal tracts projecting to frontal cortical areas (rev. [94]), which in turn can affect synaptic connectivity. Therefore, a future challenge in understanding the neurobiological deficits in schizophrenia is to functionally dissect the molecular, cellular, synaptic and neural circuits that contribute to the complex array of positive, negative and cognitive deficits, in particular the cognitive deficits that ultimately have the highest impact in the lives of persons with schizophrenia.

### 1.1. Neurotransmitter systems and genes implicated in schizophrenia

#### 1.1.1. Multiple neurotransmitter systems are implicated in schizophrenia

Several lines of evidence on the neurochemical changes that may underlie the deficits observed in schizophrenia strongly implicate disturbances in glutamatergic and dopaminergic neurotransmission (rev. [149,83,156,17,55,124]), as well as GABAergic interneurons (rev. [11,90,96]). Human and animal studies using *N*-methyl-D-aspartate (NMDA) receptor competitive antagonists, such as ketamine and PCP, suggest that hypofunction of NMDA receptors may underlie the functional deficits observed in schizophrenia (rev. [124,73,116,72]; see article by Javitt et al. (this issue)). The glutamate hypofunction hypothesis of schizophrenia originated from the observation that NMDA receptor antagonists elicit cognitive deficits in healthy individuals that are similar to the positive (i.e., hallucinations) and negative (i.e., social withdrawal) symptoms observed in persons diagnosed with schizophrenia (rev. [26]); however, it has been suggested that the effects observed with PCP could result from its partial agonism on D2-type dopamine receptors and interference with dopaminergic transmission [129]. An extension of the glutamate hypofunction hypothesis emphasizes the selective reduction of NMDA receptor activity in GABAergic interneurons (rev. [10,11,90,116,54]). Although these pharmacological and genetic findings primarily implicate NMDA receptors, it is important to note that, because of the intimate functional interactions between NMDA and AMPA receptors, in particular the requirement for membrane depolarization by AMPA receptors to relieve the voltage-sensitive magnesium block of NMDA receptors, perturbations in either receptor type might be expected to contribute to glutamate hypofunction.

A role for altered dopaminergic transmission in schizophrenia, predominantly the positive symptoms of the disorder, was supported initially by the observation that most antipsychotics are dopamine D2-type receptor antagonists or partial agonists (see [17,77]). This hypothesis has been revised recently to account for the positive and negative symptoms resulting from dopamine imbalances and for the cortical hypofrontality observed in schizophrenia, and proposes that cortical hypoglutamatergia enhances subcortical hyperdopaminergia and cortical hypodopaminergia (see [83,107]). Importantly, it is difficult to assign the systemic effects of drugs targeting dopamine receptors specifically to this neurotransmitter system, because there is extensive cross-talk between dopamine and glutamatergic or GABAergic neurotransmission both at a neural systems level [107], as well as by indirect and direct physical interactions between distinct types of receptors (rev. [18]). Dopamine receptor activation regulates glutamate and GABA neurotransmission at synapses by regulating ion channel properties and subcellular targeting of receptors [19,41,66,67,127,133,153]. Direct physical interactions have been reported, in particular between dopamine D1 and NMDA receptors [87,35,128]. The reciprocal interactions between glutamate, GABA and dopamine neurotransmission at the system, cellular and molecular level make it difficult to directly assign imbalances in any one transmitter system to deficits observed in schizophrenia and stress the importance of genetics for identifying the heritable underling neurobiological liabilities that contribute to the risk of developing the disorder. While there have been numerous studies reporting association of genes involved in the synthesis, degradation and binding of different neurotransmitters with schizophrenia (see below), replication of these findings have been few and genome wide association studies have not borne out a clear link between neurotransmitter-associated genes and the etiology of schizophrenia. It is thus conceivable that genes that subserve a modulatory rather than an effector role in the dopamine, glutamate and GABA neurotransmission pathways significantly contribute to increased risk for schizophrenia (see below).

#### 1.1.2. Neuronal network activity is altered in schizophrenia

Numerous studies suggest that neuronal circuitry and network activity, in particular gamma oscillations, are altered in schizophrenia (see [54,134–136,58]). The synchronization of neuronal network activity in the human cortex and hippocampus at gamma frequencies (30–80 Hz) is important for cognition, learning and memory [30]. Gamma oscillations in rodents have been recorded *in vivo* [14,28] and their frequency is modulated by GABAergic basket cells, as suggested by studies performed in acute slices where gamma oscillations are induced by either carbachol or kainate [36,100]. Studies performed in hippocampal slices showed that the power (amplitude) and frequency of carbachol- and kainate-induced gamma oscillations are driven by the complex recurrent network of the CA3 area and rely on the interplay of fast inhibitory and fast excitatory synaptic neurotransmission [36]. The power of gamma oscillations in subjects diagnosed with schizophrenia is reduced [79,155], and the regional reaction time phase-lock of oscillations is correlated with either positive or negative symptoms [136]. Also of importance is the repeated observation that GABAergic fast-spiking interneurons and expression of GAD67, the rate limiting enzyme in the GABA synthesis pathway, are reduced in parvalbumin-expressing interneurons in postmortem brains from affected individuals, suggesting that specific neural circuits may be associated with schizophrenia ([3,157,158]; see [54]). Altered functionality of parvalbumin-expressing interneurons, which provide perisomatic innervation to pyramidal neurons, may account for the observed reduction in neural network oscillations that are important for working memory [90,134]. Of significance, we recently reported that the Neuregulin-