A Is For . . .

Neuregulin

neuregulins *— Members of the EGF superfamily of growth and differentiation factors that signal through ErbB receptor tyrosine kinases; implicated in the pathogenesis of schizophrenia.*

The neuregulin family of genes consists of four members, *NRG1* to *4*, with more than 15 known isoforms that retain an EGF-like domain. Little is known about the biological functions of the NRG2, 3, and 4 proteins, but NRG1 plays a central role in neural development and synaptic plasticity, as well as in neurotransmission.

Recently, *NRG1* has been identified as a potential susceptibility gene for schizophrenia. In a genome-wide scan of families of schizophrenics in Iceland, Stefansson and colleagues isolated *NRG1* on chromosome 8p, in an area previously linked to the disease in different populations. Subsequent studies in Scottish and Welsh families confirmed the association with *NRG1*, though a Japanese study found no association, which indicates that *NRG1* is not the only gene underlying susceptibility to schizophrenia.

A mutation in the *NRG1* gene has not been identified in schizophrenics, but rather, insertions or polymorphisms may lead to the disease. In a recent study, the ratios of three NRG1 mRNA isoforms were found to be altered in the dorsolateral prefrontal cortex of schizophrenic patients. In animal experiments, mice lacking one copy of the *Nrg1* gene showed behavioral abnormalities, including hyperactivity, that are similar to those seen in schizophrenics.

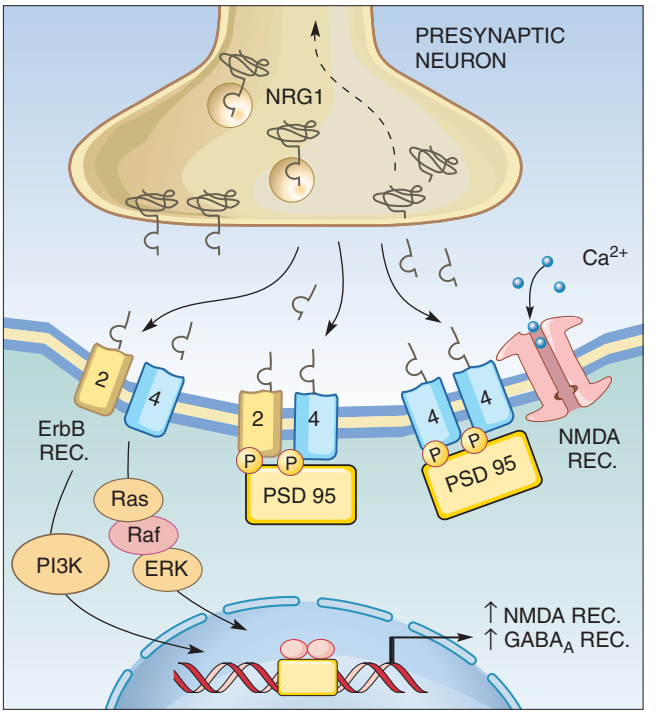
There are three ways in which NRG1 is proposed to be involved in the pathogenesis of schizophrenia, which also relate to the existing glutaminergic and neurodevelopmental theories of schizophrenia.

First, NRG1 signaling through erbB affects neuronal migration, primarily by promoting radial glia formation and differentiation. In the cerebral cortex, NRG1-erbB signals induce elongation of cortical radial glia fibers, which act as neuronal precursors and migratory guides, and accelerate neuronal growth. Defects in signaling during brain development could lead to alterations in neuronal migration, with disruption of cortical connectivity and resulting cognitive and behavioral effects. Defects in brain architecture in schizophrenia have been observed in some (but not all) studies.

Second, NRG1-erbB signaling promotes oligodendrocyte differentiation and CNS myelination. Defects in NRG1-erbB signaling could result in alterations in oligodendrocyte development and abnormal myelination, which have been described in the prefrontal cortex and other brain areas of schizophrenics. Hypomyelination may lead to reduced or irregular neural transmission, which could lead to altered perception and emotional states characteristic of schizophrenia.

Finally, NRG1 affects expression of neurotransmitter receptors in the CNS, including the NMDA-glutamate, $GABA_A$, and acetylcholine receptors. Defects in NRG1 function affecting one or more of these receptors may lead to altered excitatory and/or inhibitory neurotransmission, altering information processing. Effects on these neurotransmitter systems would be consistent with the glutaminergic theories of schizophrenia pathogenesis.

Outside the nervous system, NRG1 has been implicated in an aggressive phenotype of tumors that express erbB2, including breast and lung cancers, and in the heart, where erbB2 is important in development and function of the myocardium.



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NRG1 is brought to the synaptic cleft by vesicle transport. After proteolytic processing, its extracellular domain migrates across the cleft and binds to ErbB receptors on the postsynaptic neuron, activating downstream signaling cascades (forward signaling). Activated heterodimers of ErbB2 and ErbB4 can activate the Ras/Raf/Erk pathway, resulting in upregulation of NMDA and $GABA_A$ receptors. NRG1 also may activate ErbB receptors co-localized with postsynaptic densities (PSD 95), which transduce a signal to NMDA receptors resulting in its posttranslational modification. The intracellular portion of NRG1 is translocated back to the presynaptic nucleus, affecting expression of apoptosis regulators.

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Hreinn Stefansson, V. Steinthorsdottir, T.E. Thorgeirsson, et al: Neuregulin 1 and schizophrenia. *Annals of Medicine* 36:62-71, 2004.

Gabriel Corfas, K. Roy, and J.D. Buxbaum: Neuregulin 1-erbB signaling and the molecular/cellular basis of schizophrenia. *Nature Neuroscience* 7:575-580, June 2004.