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Literature Review: The Role of NRXN-3 and Neurexin-3 Proteins in the Mechanisms of Schizophrenia

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ABSTRACT

Schizophrenia is a neuropsychiatric disorder which affects more than 26 million people worldwide, impacting thought and perception. A combination of neural, genetic, and environmental factors make up its etiology. The gene NRXN3 has been studied for its role in the symptoms and development of schizophrenia. NRXN3 translates into 2 postsynaptic proteins which are involved with synapse formation: alpha and beta neurexin-3. Neurexin-3 proteins play a role in synapse formation, differentiation, plasticity, and regulation of inhibitory and excitatory synapses, all of which are impacted in schizophrenia. Further investigation of NRXN3 and its role in schizophrenia may lead to the development of more efficient and antipsychotic and therapeutic medications for patients.

Introduction

Schizophrenia is a neuropsychiatric disorder that affects more than 26 million people across the globe [15]. Schizophrenic people are 6-7 times more likely to experience unemployment than unaffected ones and are consequently more likely to experience homelessness [15, 2]. Schizophrenic individuals, even when treated with antipsychotics and psychotherapies, have life expectancies of 15-20 years lower than unaffected individuals [15]. Heavy stigma surrounding the condition is one key reason for this.

The International Classification of Diseases (ICD) characterizes schizophrenia as a disorder that affects thoughts and perception [19]. There are six main subtypes of schizophrenia: residual, simple, paranoid, hebephrenic, catatonic, and undifferentiated. According to the ICD, common symptoms of schizophrenia are hallucinations, delusional perception, and thought disorders including thought echo, broadcasting, withdrawal, and insertion [19]. These symptoms are placed into two categories: positive and negative. Positive symptoms display abnormal function of the brain and include hallucinations and delusions [8]. Negative symptoms, on the other hand, are present typically, but are reduced or absent in schizophrenic brains. Common negative symptoms are lack of motivation and social isolation [8].

Schizophrenia is caused by a combination of environmental, neural, and genetic factors. Symptoms result from dysfunctions in the brain, sometimes caused by abnormal neurotransmitters involved with higher order processing in the temporal lobe, basal ganglia, orbital frontal cortex, and thalamus [15]. The most common altered neurotransmitter in theories about schizophrenia's etiology is dopamine.. The "dopamine hypothesis" of schizophrenia suggests that hypoactive transmission of dopamine in the prefrontal cortex and hyperactive transmission in the mesolimbic areas can cause schizophrenia [5]. This theory is supported by the observation that antipsychotic medications used to treat schizophrenia: they block the dopamine D2/3 receptor, which in turn blocks transmissions of dopamine [22].

A combination of several mutated and dysfunctional gene families is also involved with schizophrenia. One such family is NRXN, comprised of the α and β components of NRXN1, NRXN2, and NRXN3. The

NRXN family produces neurexins, proteins which connect neurons at their synapses to regulate the formation of synapses and signaling that occurs through them [20]. Because disruption of connectivity in the brain is a defining factor of schizophrenia NRXN and neurexins are of great relevance to schizophrenia [23]. This paper focuses on the role of NRXN3 and its alpha and beta protein isoforms in schizophrenia.

NRXN3 Gene

According to the National Library of Medicine, the NRXN3 gene, also known as C14orf60, is located on chromosome 14 on the band 14q24.3-q31.1 [29]. It is the largest of the NRXN genes, spanning approximately 1.8 Mb [18]. NRXN3 translation can begin at an upstream or a downstream promoter, resulting in the formation of 2 type-1 membrane protein isoforms [41, 29]: neurexin-3α and neurexin-3β. Neurexin-3 proteins are located in the presynaptic regions of neurons and are involved with synaptic adhesion, synaptic differentiation, and transmission of nerve impulses [30]. NRXN3 is expressed all over the brain, including in the midbrain, caudate, putamen, and hippocampus [17]. During development, NRXN3 is mainly expressed in the cerebral cortex [41].

Neurexin-3 Protein Structure

Neurexin-3α has a N-terminal signal peptide and 6 laminin-neurexin-sex (LNS) hormone demains, followed by O-linked sugar modification sequences, a cysteine loop, and a sequence of 55-56 serine and threonine residues [41, 37]. In addition to a N-terminal signal peptide and 6 LNS domains, neurexin-3β also contains β-neurexin specific sequences that splice into α-neurexin's N-terminal sequence of its LNS6 domain. Thus, neurexin-3β is essentially an N-terminally truncated neurexin-3α with a specific N-terminal sequence [37]. Both neurexins additionally have a transmembrane region (TMR) that allows them to bind to presynaptic membranes [17].

NRXN3 has 6 alternative splice sites in neurexin-3α (SS1-6) and 2 in neurexin-3β (SS4-5) [18, 41]. Thus, there are 1000+ possible transcriptional variants that can be formed through post-translational alternative splicing, each with unique roles [41]. Some are covered in this paper.

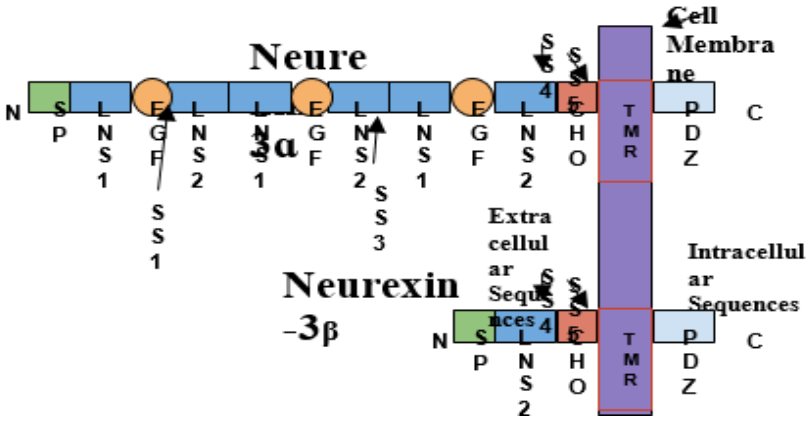

Figure 1. Structure of Neurexin-3α and Neurexin-3β

Synapse Formation

A synapse is a gap between neurons, consisting of presynaptic terminals at axonal ends and postsynaptic terminals across a synaptic cleft [6]. Synapses are where neurons can be connected and nerve impulses be transmitted.

During synapse development, a presynaptic neurexin binds to postsynaptic protein--typically neuroligin, but sometimes cerebellin, neurexophilin, or dystroglycan--and forms a trans-synaptic complex [36, 30]. Neurexin-neuroligin complexes are also involved in formation and regulation of inhibitory and excitatory synapses [7]. Neurexins are necessary for function, regulation, and development of synapses [30]. Dysregulation in the properties and development of synapses, as a result of mutations in genes like NRXN3, underlie altered neuronal function in neuropsychiatric disorders such as schizophrenia and autism spectrum disorder [38].

Synaptic Plasticity

Synaptic plasticity is the ability of neurons to modify the strengths of their connections in response to stimuli and is crucial for learning, memory, and post-damage reorganization [40]. Due to the role of neurexins in forming synapses and maintaining plasticity, it can be inferred that harmful modification to their structure can lead to modified connectivity within the brain. Disruptions in connectivity have been proposed as markers of schizophrenia [9]. In fact, schizophrenic symptoms such as episodic memory deficits, anomalies in synapse and axon formation, and malfunction of hippocampal circuitry suggest aberrant neuronal plasticity as the underlying mechanism [3]. The very nature of symptoms like hallucinations, disorganized speech, and delusions supports point to deficits in instantaneous processing, suggesting that specifically short-term plasticity is affected in schizophrenia [9]. In addition, a study viewing cortical connectivity found reduced LTP-like plasticity in the posterior parietal and frontal cortices of schizophrenic brains in comparison to control subjects. Dysconnectivity between the brain and the parietal lobe contributes to disorganization symptoms of schizophrenia such as unpredictable emotional responses and bizarre-seeming behaviors [12].

N-Methyl-D-Aspartate-Receptors (NMDARs)

NMDAR-mediated calcium entry is essential to short-term and long-term plasticity and synaptic communication. Hypofunctional NMDARs alter calcium influx and consequently affect plasticity and cellular signaling [31]. Emerging evidence shows that altered NMDA-dependent plasticity, along with failures of self-monitoring, causes schizophrenic delusions. Cognitive and negative symptoms are also related to synaptic plasticity; if abnormal plasticity prevents patients from learning from and adapting to social experiences, apathy and social withdrawal will ensue [34]. Additionally, antagonism of the glutamatergic NMDA-receptor complex, which typically stimulates synaptogenesis and regulates neuronal migration, is associated with schizophrenic abnormalities including reduced synaptic connections and abnormal neuronal migration [16]. Alternatively spliced SS4+ neurexin-3 proteins block postsynaptic LTP dependent on NMDARs [11].

Neurotransmission and Action Potentials in KO Mice

A KO mice study investigated the removal α-neurexins role in coupling Ca2+ channels to presynaptic membranes and found that neurotransmitter release was impaired [27]. A similar study found that the deletion of α-neurexins caused reduced neurotransmitter release at excitatory and inhibitory synapses, leading to early death of triple mutants and many double-KO mice, revealing the role of alpha-neurexins in functional neurotransmission [32]. This deletion also decreased Ca2+ currents and revealed that Ca2+-dependent exocytosis at synapses is dependent on α-neurexins [27]. These findings suggest that mutations in neurexin-3α would result in altered transmission of neurotransmitters like GABA and dopamine, which are known to be associated with schizophrenia. Alpha neurexins are also necessary for neurotransmission at neuromuscular junctions [32]. A study observing the neuromuscular junctions of mice found that in α-neurexin double knockouts, the amount of acetylcholine released per nerve impulse from motor nerve terminals was reduced. Reduced acetylcholine levels

play a role in schizophrenic symptoms including visual and auditory hallucinations and sensory gating deficit [10].

Conditional deletion of NRXN3 in the olfactory bulb caused a ~60% decrease in GABA receptor mediated inhibitory responses, and these inhibitory synapses could only be saved with a neurexin-3α protein. These results suggest that neurexin-3α and 3β play major roles in the regulation of inhibitory and excitatory responses, respectively [1].

AMPARs (Excitatory Synapses)

In the CNS, AMPARs bind to glutamate and transmit postsynaptic excitatory currents. Neurexin-neuroligin complexes regulate AMPAR-mediated excitatory responses. Alternatively spliced neurexin-3β (SS4+) reduces the number of postsynaptic AMPARs and increases AMPAR-endocytosis in hippocampal synapses of mice. Conditional deletion of NRXN3 was found to decrease postsynaptic AMPARs, regulating excitatory synapses [41]. AMPAR modulators have been found to improve cognitive function in schizophrenia, suggesting the role of abnormal AMPARs in schizophrenia [13].

Additionally, AMPARs assist with regulation of anti-homeostatic plasticity by responding to changes in the strength of excitatory inputs by upscaling or downscaling neuronal excitability. Neurexins with altered functions may alter the expression or function of AMPARs and could thus explain reduced plasticity and connectivity in schizophrenic brains [33].

GABARs (Inhibitory Synapses)

Postsynaptic GABARs interact with GABA released from presynaptic membranes to control hyperpolarization of GABAergic neurons. This interaction inhibits neurotransmission and reduces neuronal excitability. GABARs inhibit learning and memory and are involved with brain development. Among the 3 types of GABARs, neurexin-3 most prominently affects $GABA_A$Rs [41].

Overexpression of NRXN3 can suppress GABAergic synaptic transmission [18]. Altered inhibition results in impaired neural oscillations, which typically instill temporal relationships between neuronal responses and allow for proper memory, consciousness, and perception. Dysfunctional oscillations are thought to contribute to the generation of cognitive deficits and other related schizophrenic symptoms. Reduction in synaptic connectivity is also a means by which deficits in oscillations can occur [21]. On the other hand, neurexin deletion at the Calyx of Held was found to counteract $GABA_B$-receptor-induced inhibition of presynaptic Ca2+ channels in a study with mice [25].

GABAergic neurons in the hippocampus contain high amounts of NRXN3 mRNA. NRXN3β typically binds to neuroligin-2 in inhibitory synapses. Contrary to expectations, however, an experiment manipulating NRXN3 in hippocampal culture did not affect inhibitory synaptic transmission [4].

Mutations

NRXN3 mutations play a role in increasing the likelihood of schizophrenia and other psychiatric disorders. The table below shows some of the recently studied mutations and the effects they had on the affected individuals:

NRXN3 mutations and their studied results:

Mutation	Effects
a. Deletion of NRXN3 (and NRXN1 and	Loss of function of presynaptic GABAb-receptors at the

NRXN2)	Calyx of Held [41]
b. De novo interstitial deletion of 5.5 Mb of 14q24-q32 (includes NRXN3)	Haploinsufficiency of neurexin-3 proteins (basis of some cognitive defects in schizophrenia), developmental delay, epilepsy [28]
c. NRXN3 deletion	NRXN3 haploinsufficiency; motor and language delay; schizophrenia [39]
d. Monoallelic frameshift variant at the 15th amino acid after the signal sequence	Symptoms including intellectual impairment, schizophrenia, delusion, and persecutory ideas [14]

Discussion

Most studies investigating NRXN3's association with schizophrenia use KO mice models because of their feasibility. While these models are useful, they do not fully match human models and provide limited information. Only ~3 of the few dozen papers cited by this review discussed human experiments, and those were studies of specific Chinese families and populations [18, 24, 39]. Furthermore, there is little focus on NRXN3 in studies.While the functions of alpha-neurexins and beta-neurexins of NRXN1 and NRXN2 have been thoroughly studied, little is known about their unique role in NRXN3. For this reason, parts of this review and other published papers can merely describe their general function. Further experiments focusing on NRXN3 with larger, more diverse populations are needed to better understand its role in the etiology of schizophrenia to develop more efficient treatment.

There is no cure for schizophrenia at present, but first and second-generation antipsychotics (SGA) can alleviate symptoms [26, 34]. Second-generation antipsychotics are prescribed more than first-generation antipsychotics due to less associated parkinson-like extrapyramidal side effects, although they are associated with metabolic adverse effects such as dyslipidemia and diabetes mellitus [34]. However, antipsychotics mostly target positive symptoms, leaving patients with cognitive and residual negative symptoms. As a result, only 10-30% of schizophrenia patients experience limited benefits from treatment [26]. All antipsychotics work by antagonizing dopamine receptors. Additional research on NRXN3 and related genes could lead to the development of antipsychotics with more efficient mechanisms.

Almost 30% of individuals with schizophrenia are resistant to current medications, and so development of atypical therapies is a large focus in the world of neuropsychiatric research. One is asenapine transdermal patches, which were approved in 2019 and have been shown as effective in reducing both positive and negative symptoms while improving tolerability and avoiding dysgeusia and hypothesis, which are associated with sublingual asenapine [26, 42]. Additionally, researchers believe NMDAR dysfunction, caused by abnormal neurexins, should be targeted by therapeutic intervention and prevention in early stages due to its role in early stages of schizophrenia which may also cause GABA and dopamine deficits [31]. Overall, further studies of NRXN3 in schizophrenia is crucial to understand its relationship and develop more efficient medications.

Conclusion

The relationship between neurexin-3 proteins and schizophrenia is not abundantly clear, however there is a valid correlation. Therefore, more research, specifically in human brain tissue, must be conducted in order to

gain additional evidence to better understand this relationship. Studying NRXN3 on a deeper level could contribute to currently sparse knowledge of the genetic etiology of schizophrenia and could thus be used to develop more efficient medications, improving the lives of schizophrenic people.

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