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REVIEW

Regulation and postsynaptic binding of neurexins – drug targets for neurodevelopmental and neuropsychiatric disorders

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Abstract **Neurexins (NRXNs) have been linked to neurodevelopmental and neuropsychiatric disorders and have become attractive drug targets. They are transmembrane neuronal adhesion molecules and play important roles in the formation and differentiation of synapses and synaptic activity. Many postsynaptic binding partners of NRXNs have been identified. The interactions between NRXNs and postsynaptic binding partners can be regulated by alternative splicing, synaptic activity, and RNA binding proteins. The postsynaptic interactive partners may compete with each other for NRXN binding. The expression of NRXNs can also be regulated transcriptionally and post-transcriptionally. Genetic polymorphism may affect the function and expression of NRXNs. In this review, we will summarize the recent advance in these areas. Understanding the biology of neurexin signaling is essential for developing neurexin-based drugs.**

Keywords alternative splicing, neurexins, neurodevelopmental disorders, neuropsychiatric illness, post-synaptic interactive partners, regulation, synapse

Introduction

Neurexin (NRXN) was first discovered in 1992 by the 2013 Nobel Laureate Thomas Südhof during studies to identify receptors for α-latrotoxin, the toxin component of the venom from black widow spiders (Ushkaryov et al., 1992). Neurexins are characterized as type I membrane proteins and known as synapse-organizing proteins (Südhof, 2008; Krueger et al., 2012). There are three *NRXN* genes in the mammalian genome, *NRXN1*, *NRXN 2* and *NRXN 3*, and each has an upstream promoter and a downstream promoter to drive transcription of two major kinds of protein isoforms: a long α-neurexin (α-NRXN) and a short β-neurexin (β-NRXN), respectively (Tabuchi and Südhof, 2002). All these six primary transcripts from the three *NRXN* genes are subject to extensive alternative splicing. NRXNs have acquired particular attention because alterations and mutations in *NRXNs* genes have been linked to autism spectrum disorders (ASD), learning disability, schizophrenia and other neurodevelopmental/neuropsychiatric disorders (Südhof, 2008; Yan et al., 2008; Kirov et al., 2009; Rujescu et al., 2009; Ching et al., 2010; Duong et al., 2012; Büna et al., 2013; Curran et al., 2013).

NRXNs are essential in modulating synaptic activity in the central and peripheral nervous system (Missler et al., 2003; Sons et al., 2006; Zhang et al., 2010), and play important roles in the formation and differentiation of synapses (Dean et al., 2003; Graf et al., 2004; Nam and Chen, 2005). NRXNs are mostly found at presynaptic membrane as synaptic cell adhesion molecules. Binding of NRXNs to postsynaptic binding partners are important for synapse formation, stablization and functional maturation (Uemura et al., 2010; Soler-Llavina et al., 2011; Kwon et al., 2012). Cocultures of primary neurons and non-neuronal cells transfected with NRXNs have shown that NRXNs can stimulate the *de novo* formation of functional synapses (Graf et al., 2004). From triple- knockout mouse models it was found that mice lack all α-NRXNs die at birth due to major deficits in synaptic function (Missler et al., 2003). The loss of one or more α-NRXN isoforms reduced Ca^{2+} currents, severely impaired spontaneous and evoked neurotransmitter release at excita-

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tory and inhibitory synapses (Missler et al., 2003; Kattenstroth et al., 2004; Etherton et al., 2009). Homozygous *Nrxn1α* knockout mice displayed core symptoms of neurodevelopmental disorders including altered social approach, reduced social investigation, and reduced locomotor activity in novel environments, as well as increased aggressiveness in male mutants (Grayton et al., 2013). In addition, *Nrxn1β* mutant mice showed impaired glutamatergic transmission in pyramidal cortical neurons (Rabaneda et al., 2014). On the other hand, constitutive expression of NRXN-3 (SS4 +) produced a selective decrease in postsynaptic AMPA-receptor (but not NMDA-receptor) level and enhanced postsynaptic AMPA-receptor endocytosis. Constitutive inclusion of SS4 in presynaptic NRXN-3 abrogated postsynaptic AMPA receptor recruitment during NMDA-receptor-dependent long-term potentiation (LTP) (Aoto et al., 2013). These results highlight the importance of NRXN isoforms in synaptic homeostasis.

Until now, over 500 research articles associated with NRXNs have been published. A detailed description of the structure of NRXNs and their postsynaptic binding partners, particular for NRXN to neuroligins (NLGNs), can be found in other excellent review articles (for examples, Dean and Dresbach, 2006; Lisé and El-Husseini, 2006; Craig and Kang, 2007; Bang and Owczarek, 2013; Reissner et al., 2013; Bourne and Marchot, 2014). Here we summarized the research data in addition to more recent results, and focused more on the factors that regulate NRXNs' postsynaptic binding and gene expression. We address four aspects: (i) structure, splicing and location of α- and β-NRXNs; (ii) trans-synaptic binding partners; (iii) regulation of postsynaptic binding and gene expression, and (iv) association of the NRXNs with neurodevelopmental and neuropsychiatric diseases.

Structure, splicing and location of α- and β-NRXNs

Each NRXN gene encodes two major protein isoforms: α-NRXN and β-NRXN, which share a single transmembrane region and a short cytoplasmic tail at the C terminus, but differ in the N-terminal extracellular sequences. α-NRXNs are composed of a large extracellular domain, which contains an N-terminal signal peptide followed by a cassette which is repeated three times, and an O-linked sugar attachment sequence. This cassette includes 2 LNS (laminin, nectin, sex-hormone binding globulin) domains and an epidermal growth factor-like (EGF) domain arranged LNS-EGF-LNS. LNS domains are commonly found in adhesion molecules. β-NRXNs are essentially truncated version of α-NRXNs with a short unique N terminus and only one LNS domain in its extracellular domain (Fig. 1). The cytosolic domains of all NRXNs have a potential endoplasmic retention signal, a cytoskeleton integrating protein 4.1 and PDZ binding motif that is required for trafficking of NRXNs (reviewed by Reissner et al., 2013).

Most NRXNs are differentially spliced at five sites: SS1 to SS5. The SS1 is located between the EGF1 and LNS2 domains; SS2 within the LNS2, SS3 within the LNS4, SS4 within the LNS6 and SS5 within the O-glycosylation region next to the transmembrane domain. The SS1, SS2 and SS3 are specific to α-NRXNs, whereas SS4 and SS5 are shared by β-NRXNs. The alternatively spliced sequences for SS1 to SS4 are highly homologous among the three NRXNs, whereas those of SS5 differ among NRXNs (Reissner et al., 2013). For example, the SS5 encompasses only 3 amino acids in NRXN1, but 194 residues in NRXN2, and 247 residues in NRXN3. The SS5 in NRXN3 also contains an in-frame stop codon, effectively, producing secreted NRXN3 isoforms with SS5 + (Ushkaryov and Südhof, 1993; Ullrich et al., 1995). Recently, Treutlein et al. (2014) identified a novel but abundantly transcribed alternatively spliced exon of *NRXN1α* and *NRXN3α* (referred to as alternatively spliced sequence 6 (SS6)) which is absent from *NRXN2*. This exon encodes a 9-residue insertion in the flexible hinge region between the fifth LNS domain and the third EGF-like sequence. The SS6 is evolutionarily conserved in zebrafish and macaque *NRXN* genes and is not yet incorporated into the genome databases. The function of the novel splice variants containing SS6 is largely unclear.

It seems that α- and β-NRXNs perform essential but rather different functions. An artificial synaptogenesis assay suggests α-NRXNs are primarily expressed by GABAergic synapses, whereas β-NRXNs can be found both in glutamatergic and GABAergic synapses (Chih et al., 2006; Kang et al., 2008; Bang and Owczarek, 2013). At GABAergic synapses, NRXN-1α is highly diffused along developing axons and slightly enriched at the presynaptic membrane, whereas NRXN-1β is strictly localized to presynaptic buttons and anchored at termini, likely through binding to post synaptic interactive partners such as Neuroligins (Fu and Huang, 2010).

Postsynaptic binding partners of NRXNs

Synapse assembly, function, specificity and stability are mediated by trans-synaptic interactions between cell adhesion molecules (Waites et al., 2005; Williams et al., 2010). NRXNs are synaptic cell adhesion molecules and binding to their postsynaptic partners is essential for their function. It has been shown that NRXNs bind to multiple postsynaptic cell-adhesion molecules through the N-terminal extracellular domain, these partners include neuroligins, LRRTMs, CIRL1/latrophilin-1, cerebellin 1, dystroglycan, neurexophilin, calsyntenin-3 and GABA receptors (Fig. 2).

Neuroligins: binding to α- and β-NRXNs dependent on alternative splicing

Neuroligins (NLGNs) are well-studied binding partners of

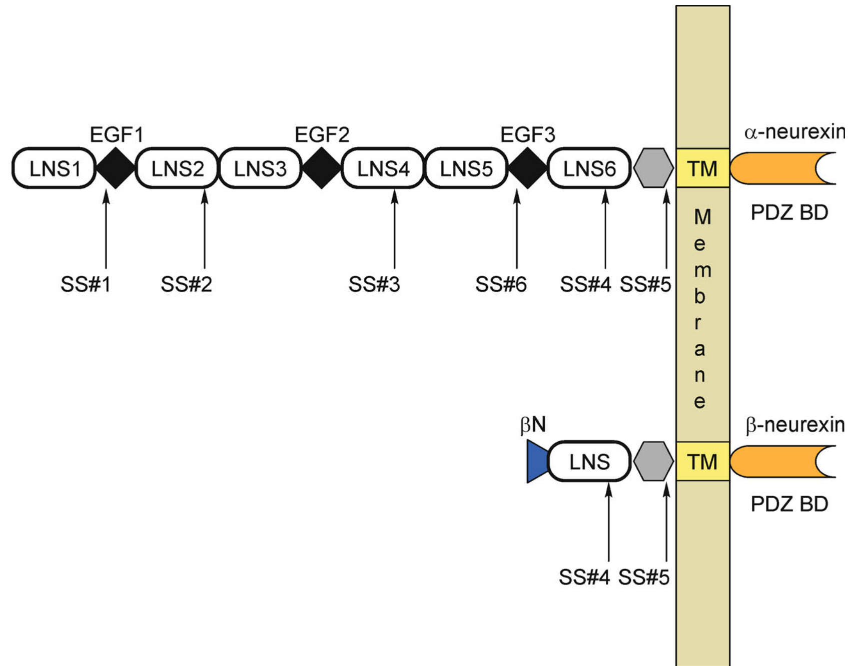

Figure 1 Structure organization of α-neurexin and β-neurexin. Neurexins are transmembrane proteins with a single path transmembrane helix (TM) and a pre-synaptic tail of PDZ-domain binding sites (PDZ BD). The extracellular domain of the α-neurexin contains 3 repeats of a cassette of LNS-EGF-LNS followed by a highly glycosylated region (gray hexagon). The β-neurexin contains a unique 87aa at the N terminus, a LNS domain and a glycosylated region in its extracellular domain. Arrows indicate positions of five conserved splice sites (SS#1 to SS#5) and a newly identified splice site (SS#6). LNS: laminin, nectin, sex hormone binding globulin; EGF: epidermal growth factor-like domain.

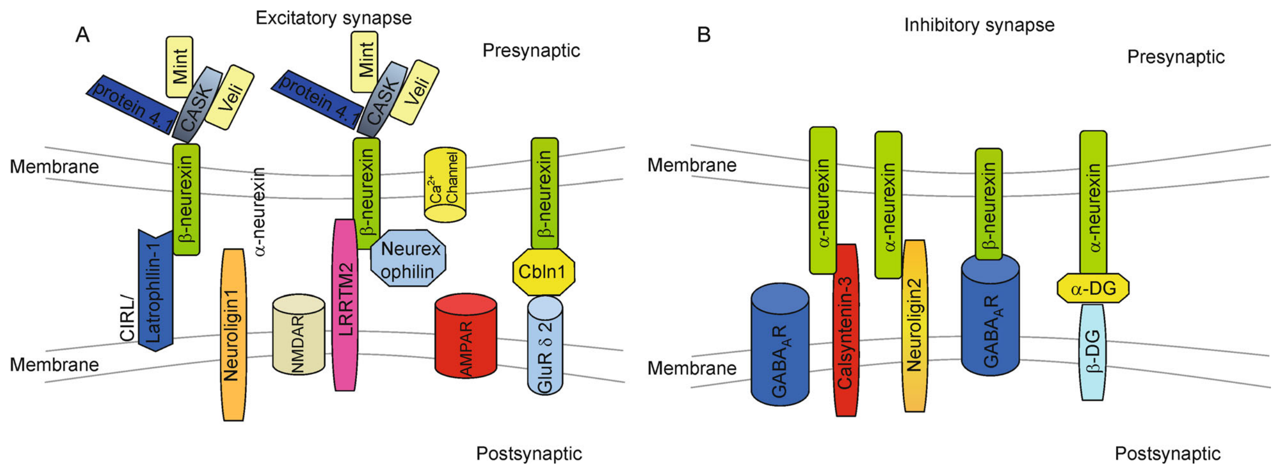

Figure 2 Schematic diagram of excitatory (A) and inhibitory (B) synapses of the neurexins (α-neurexin and β-neurexin) with their binding partners. Presynaptic neurexins are synapse-organizing proteins which bind to specific receptors in the postsynaptic membrane at the synaptic cleft. (A) In the excitatory synapses, binding partners of neurexins including neuroligins, LRRTM2, Neurexophilin, CIRL/ latrophilin-1 and Cbln1. Cbln1 bridges the binding of neurexins and GluRδ2. Intracellularly, neurexins interact with CASK/Mint/Veli/ protein 4.1, and mediate the activation of Ca^{2+} channels. Postsynaptic binding partners regulate neurotransmitter receptors: AMPAR and NMDAR. (B) In the inhibitory synapses, binding partners of neurexins including neurolingins, Dystroglycan (complex of α-DG and β-DG) and Calsyntenin-3. These binding partners modulate inhibitory synapse by mediation of $GABA_AR$ which is the major inhibitory neurotransmitter receptor, and neurexins also can directly interact with $GABA_AR$. LRRTM2: Leucine-rich repeat transmembrane neuronal protein 2; Cbln1: Cerebellin 1 precursor protein; GluRδ2: δ2 glutamate receptor; CASK: calcium/calmodulin-dependent serine protein kinase; Mint: Munc18 interacting protein; Veli: vertebrate Lin 7; AMPAR: AMPA receptor; NMDAR: NMDA receptor; $GABA_AR$: $GABA_A$ receptor.

NRXNs. NLGNs are localized at the postsynaptic membrane in neurons (Südhof, 2008). In mammals, there are four *Nlgn* genes (*Nlgn1-4*), and two of which, *Nlgn3* and *Nlgn4*, are localized on the X chromosome. In humans, a fifth *NLGN5* gene is located on the Y chromosome which encodes a protein similar to NLGN4, therefore it is termed *NLGN4Y*. NLGN1 is exclusively localized to glutamatergic excitatory, whereas NLGN2 and NLGN4 localize to GABAergic/glycinergic inhibitory synapses. NLGN3 appears to be present in both synapses (Song et al., 1999; Varoqueaux et al., 2004; Budreck and Scheiffele, 2007; Hoon et al., 2011; review see Bourne and Marchot, 2014). In rodents, Nlgn2 can also be found in the pancreas (Suckow et al., 2008) and uterus (Kang et al., 2004) as well as in the brain. In humans, NLGN1 and NLGN2 proteins are thought to be brain-specific, whereas the transcripts of both NLGN3 and NLGN4 are also detected in peripheral tissues (Philibert et al., 2000; Bolliger et al., 2001; review see Bang and Owczarek, 2013).

NLGNs also are type I transmembrane proteins, comprised of several functional domains including a cleaved signal peptide, an AChE homologous domain, an carbohydrate attachment region, a single transmembrane domain and a short C-terminal tail containing a type I PDZ binding motif (Ichtchenko et al., 1995; reviewed by Lisé and El-Husseini, 2006). The AChE homologous domain is the major extracellular domain of NLGNs. It lacks cholinesterase activity but mediates binding to NRXNs (Craig and Kang, 2007). All *NLGN* mRNAs, with an exception of the *NLGN4*, can be alternatively spliced at a canonical position (SSA) in the AChE homologous region, and *NLGN1* has an additional splice site B (SSB) within this region. NLGNs and NRXNs both have relatively short intracellular domains that terminate in PDZ-domain binding sites, which link with other synaptic proteins (reviewed by Bourne and Marchot, 2014; Craig and Kang, 2007).

The binding between NLGNs and NRXNs is controlled by alternative splicing of both *NLGNs* and *NRXNs* genes (Dean and Dresbach, 2006). NLGNs binds to α- and β- NRXNs at LNS6 domain, where the SS4 locates (Reissner et al., 2013). α-NRXNs containing an insert at site 4 (SS4 +) can only bind NLGN2, whereas α-NRXN lacking SS4 (SS4 −) as well as β-NRXNs (SS4 +) preferentially interact with NLGN without an insert at site B (SSB −). β-NRXNs (SS4 −) can binds all NLGN (SSA −/+ and SSB −/+), but NLGN (SSB −) only binds β-NRXNs (SS4 −) (Dean et al., 2003; Boucard et al., 2005; Chih et al., 2006; Graf et al., 2006) (reviewed by Bang and Owczarek, 2013). Since NRXN (SS4 −) and NRXN (SS4 +) exhibit distinct affinities for different isoforms of NLGNs, they create a 'splice code' of interactions, perhaps, also a code of communication between neurons (Aoto et al., 2013).

The functions of NLGNs depend on specificity of NRXNs binding (Bang and Owczarek, 2013). The localization and alternative splicing of NLGNs may be functionally relevant. For example, NLGN1 is essential for LTP in young CA1 neurons of hippocampus, where extracellular domain of NLGN1 (SSB +) has been previously shown to determine specificity of NRXN binding. NLGN2 is associated with inhibitory synapses and preferentially binds to α-NRXN, which, in turn, induces GABAergic post-synaptic differentiation (Graf et al., 2004; Chih et al., 2006; review see Runkel et al., 2013). Substantial evidence highlights that the NLGNs and NRXNs play important roles in the regulation of the neuronal excitation/inhibition (E/I) balance (Levinson and El-Husseini, 2005; Südhof, 2008). The NLGN:NRXN complex is also suggested to play critical roles in the maintenance and function of excitatory glutamatergic and inhibitory GABAergic synapses (Südhof, 2008; van der Kooij et al., 2014). In addition, mutations in *Nlgns* transgenic mice caused alterations in the E/I balance and abnormal social behaviors (Tabuchi et al., 2007; Hines et al., 2008; Jamain et al., 2008; Blundell et al., 2010; reviewed by van der Kooij et al., 2014).

LRRTMs and CIRL1/latrophilin-1: binding to α- and β- NRXNs (SS4-)

Leucine-rich repeat transmembrane (LRRTM) neuronal proteins, as postsynaptic binding partners of NRXNs, bind to the α- and β-NRXNs specifically lacking an insert at SS4 (SS4–) (Siddiqui et al., 2010). There are 4 genes (*LRRTM1-4*) that are selectively expressed in neurons. There are involved in synapse formation or maintenance (Laurén et al., 2003; Linhoff et al., 2009). For example, LRRTM2 selectively induces excitatory synapse formation in the artificial synapse-formation assay, and increases excitatory synapse density in transfected neurons (Ko et al., 2009). Knockdown (KDs) of LRRTMs individually or in combinations in cultured hippocampal neurons did not decrease synapse numbers, but triple KDs (TKD) of LRRTMs and NLGN3 induced a 40% loss of excitatory but not inhibitory synapses. These results suggest that these two NRXN binding partners, LRRTMs and NLGNs, act redundantly to maintain excitatory synapses (Ko et al., 2011).

CIRL/latrophilin-1 is a neuronal adhesion molecule that can also directly bind to NRXNs specifically lacking an insert at SS4 (SS4–) (Boucard et al., 2012). CIRL/latrophilin-1 belongs to the GPCR (G- protein- coupled receptor) family and is expressed almost exclusively in neurons (Sugita et al., 1998). Latrophilin 1 is the major brain receptor for alpha-latrotoxin, which also binds to NRXNs and strongly stimulates neuronal exocytosis. It may control synapse maturation, exocytosis, release of calcium from intracellular stores and release of neurotransmitters. The functions of latrophilins may be determined by their interactions with respective ligands. CIRL/latrophilin-1 may compete with NLGN1 for NRXNs binding. Cell adhesion assays revealed that interaction of NRXNs and CIRL/latrophilin-1 produces a stable intercellular adhesion complex and their interaction can be trans-cellular (Boucard et al., 2012). However, the

physiological importance of the interaction of NRXN with CIRL/latrophilin-1 remains unclear.

Cerebellin 1: binding to α- and β-NRXNs (SS4 +)

Cerebellin 1 precursor protein (Cbln1) is a glycoprotein, secreted from presynaptic granule neurons. It bridges the pre- and post-synaptic membranes by binding to NRXNs on cerebellar granule neurons and δ2 glutamate receptor (GluRδ2) on cerebellar Purkinje cells (Hirai et al., 2005) and is essential for formation and stability of excitatory synapses (Hirai et al., 2005; Matsuda et al., 2010).

Matsuda and Yuzaki (2011) showed that Cbln1 and its family member Cbln2 can bind α- and β-NRXN carrying the splice site 4 insert (SS4 +) and induce synaptogenesis in cerebellar, hippocampal and cortical neurons *in vitro*. Cbln1 is involved in synaptogenesis, presumably by competing with NLGN1 lacking the splice sites A and B, but not with LRRTM2, possibly by sharing the presynaptic NRXN (SS4 +). However, unlike NRXNs/NLGNs or NRXNs/LRRTMs, the interaction between NRXN1β (SS4 +) and Cbln1 was insensitive to extracellular Ca^{2+} concentrations.

Dystroglycan: binding to α- and β-NRXNs (SS2-/SS4-)

Dystroglycan is a cell surface protein that is composed of two invariable subunits, an extracellular α subunit and a transmembrane β subunit (Ibraghimov-Beskrovnaya et al., 1992). α-Dystroglycan is a secreted glycoprotein that binds to LNS domain-containing proteins such as NRXNs, whereas the β-Dystroglycan is composed of a single transmembrane region and a cytoplasmic tail which binds to Dystrophin (Sugita et al., 2001; Sassoè-Pognetto et al., 2011). Dystroglycan interact with α-NRXNs at LNS2 and LNS6, or β-NRXNs, and require a splice insert-free at the LNS domains (SS2–, SS4–) (Sugita et al., 2001).

Dystroglycan affects embryonic development since its deletion leads to early embryonic lethality (Hemler, 1999; Henry and Campbell, 1998, 1999). Dystroglycan and dystrophin are expressed abundantly in neurons. The dystrophin-dystroglycan complex is present in a subset of GABAergic synapses, for example in cerebellar Purkinje cells (Briatore et al., 2010; Tian et al., 1996). Although the function of dystroglycan is not well understood, binding to NRXNs may suggest that it functions in mediating trans-synaptic interaction.

Neurexophilin and calsyntenin-3: the specific α-NRXN tran-synaptic interactors

Neurexophilins (Nxph) are secreted peptides encoded by at least four genes (Petrenko et al., 1996; Missler and Südhof, 1998). *Nxph1*, *3* and *4* are expressed in brain of rat, mouse and human, whereas *Nxph2* mRNA is detected at low levels in rat and human peripheral tissues, and at high levels in bovine brain (Missler et al., 1998a; Missler and Südhof, l998). Although NRXNs are synthesized throughout the brain in all excitatory and inhibitory neurons (Ullrich et al., 1995), in situ hybridization of *Nxph* revealed that it is expressed in selected inhibitory interneurons of the adult brain (Petrenko et al., 1996) and in migratory interneuron precursors (Batista-Brito et al., 2008). The binding of NRXNs to trans-synaptic partners are mediated by the LNS2 (with SS2 + or SS2 –) and LNS6 domains (with SS4 + or SS4 –) (Reissner et al., 2013). Nxph binds α-LNS2 domain independently of other alternative splicing (Missler et al., 1998b; Born et al., 2014).

The function of Nxph is largely unknown, but it is reported that Nxph is restricted to neuronal subpopulations (Petrenko et al., 1996, Beglopoulos et al., 2005), mainly inhibitory neurons (Born et al., 2014). Each *Nxph* single-knockout mouse shows normal brain morphology. However, the increased startle responses and impaired motor coordination of the *Nxph3* knockout mice indicate that Nxphs may have a role in specific circuits (Beglopoulos et al., 2005; Craig and Kang, 2007). Recently, Born et al. (2014) found that mice lacking *Nxph1*, showed an impairment of $GABA_B$ receptor ($GABA_BR$)-dependent short-term depression of inhibitory synapses in the nucleus reticularis thalami, a region where Nxph1 is normally expressed at high levels. An inverse phenotype to the genetic deletion of *Nxph1* can be observed, when Nxph1 is ectopically expressed at excitatory terminals in the neocortex. These transgenic mice showed a reduced short-term facilitation which might be modulated by $GABA_BR$. Consistently, the reduction of facilitation could be rescued through blockage of presynaptic $GABA_BR$ and postsynaptic $GABA_AR$, which suggested that Nxph1 is able to recruit or stabilize the GABA receptors. Thus, these data suggest that Nxph1 plays an instructive role in synaptic short-term plasticity and the configuration with GABA receptors.

Recently, it was reported that Calsyntenin-3 is a specific α-NRXN interactor (Pettem et al., 2013; Um et al., 2014). Calsyntenin-3, also known as Alcadein-b (Alzheimer-related cadherin-like protein b), is a brain-specific transmembrane protein with extracellular cadherin and LNS domains which are subject to ectodomain shedding (Pettem et al., 2013). Calsyntenin-3 is expressed highly by interneurons throughout the hippocampus and cortex and at lower levels by many pyramidal neurons. Pettem et al. (2013) found that the transmembrane form of calsyntenin-3 may lead to both excitatory and inhibitory presynapse differentiation in contacting axons. They showed that calsyntenin-3 specifically binds α-NRXN but not β-NRXN, with cell-based binding and recruitment assays and pull-down from brain. However, Um et al. (2014) showed that Calsyntenin-3 did not directly bind to NRXNs, although α-NRXNs are components of a calsyntenin-3 complex mediating presynaptic differentiation. Further studies are required to elucidate these complexes.

$GABA_A$Rs: directly interacting with NRXN in a Ca^{2+}-independent manner

GABA is the major inhibitory neurotransmitter which acts primarily via $GABA_A$ receptors ($GABA_A$Rs). $GABA_A$Rs possess a pentameric structure formed from multiple subunits. These subunits exhibit discrete expression profiles. Most native receptors are comprised of two α, two β and a single γ, δ, or ε subunit (Gunn et al., 2014).

NRXNs can directly bind to the extracellular domains of $GABA_A$Rs. Zhang et al. (2010) found that overexpression of NRXNs in neurons selectively suppressed GABAergic synaptic transmission without decreasing GABAergic synapse numbers. This suppression was conducted in a NLGN-independent but cell-autonomous manner. Furthermore, NRXNs were found to directly and stoichiometrically bind to $GABA_A$Rs. Binding of $GABA_A$α1-receptor to NRXN was Ca^{2+}-independent, and a mutation in the NRXN Ca^{2+} binding sequence that blocks NLGN1 binding had no effect on $GABA_A$α1-receptor binding. This suggests that NRXNs may decrease GABAergic synaptic responses by interacting with $GABA_A$Rs. Taken together, different NRXNs isoforms appear to have different affinity with different binding partners. Since NRXNs may show different functions by interacting with different binding partners, it is necessary to understand the expression profile of the NRXNs isoform in distinct types of excitatory and inhibitory synapses.

Regulation of expression of NRXNs isoforms

Regulation of alternative splicing

The binding affinity of NRXNs to most postsynaptic partners is dependent on the splice form. Alternative splicing of NRXNs is highly regulated through synaptic activity, RNA binding proteins and neuroanatomic regions.

Synaptic activity

Synaptic activity can regulate NRXNs' alternative splicing. Iijima et al. (2011) altered membrane depolarization by stimulating cultured granule cells through addition of 25 mM potassium chloride. They found that *NRXN1* (*SS4 –*) mRNA was increased accompanied by a decrease in the *NRXN1* (*SS4 +*) and total *NRXN1* transcript. They also found that each of transcripts from the three *NRXN* genes (*NRXN1, NRXN2* and *NRXN3*) showed a similar response to depolarization. Depolarization did not dramatically alter exon incorporation at the neighboring SS3 or SS5. The result suggested that alternative splicing of *NRXN* might be depolarization-dependent, and that activity-dependent splicing regulation may be splicing site-specific. Furthermore, blocking voltage-gated calcium channels by pharmacological inhibitors abolished the splicing shifts caused by depolarization. Application of the CaMK inhibitors KN-62 and KN-93 also abolished the depolarization-induced increase in the NRXN1 (SS4 –) isoform, which suggested that alternative splicing of *NRXN1* was calcium- and CaMKIV-dependent.

RNA binding proteins

Activity-dependent alternative splicing is mediated by RNA binding proteins (Iijima et al., 2011, 2014; Ehrmann et al., 2013). The RNA binding proteins Sam68, SLM2 and SLM1 have been found to control a panel of splicing targets that encode important synaptic proteins (Ehrmann et al., 2013). Alternative splicing of NRXN1-3 has been reported to be regulated by Sam68, SLM1 and SLM2. SAM68 is a member of the STAR (Signal Transduction and Activation of RNA) family of RNA binding proteins containing a single KH-domain (Volk et al., 2008). Two SAM68-like mammalian proteins, SLM1 and SLM2 have been identified, and they share 70%–80% amino acid identity with SAM68 in their RNA binding domains (Di Fruscio et al., 1999; Iijima et al., 2011). SAM68 is required for depolarization-dependent alternative splicing of NRXN1. The depolarization-dependent alternative splicing shift at *NRXN1* and *NRXN3 SS4* was impaired in $SAM68^{-/-}$ neurons compared with a significant upregulation of the *NRXN1 SS4* splice variant in ($SAM68^{+/-}$) neurons (Iijima et al., 2011). However, SAM68 did not exhibit significant activity toward NRXN2 (SS4), whereas SLM1 and SLM2 induced exon skipping in NRXN2 (Iijima et al., 2014). SLM1 and SLM2 are expressed in largely segregated neuronal populations. For example, in the cerebellum, SLM1 is highly concentrated in Purkinje cells, whereas SLM2 marks interneurons in the inner granular and molecular layer. Thus, SLM1 and SLM2 are restricted to subpopulations of neurons in the brain (Iijima et al., 2014). Distribution of SLM1 and SLM2 proteins *in vivo* is strikingly non-overlapping. These data suggest that SLM1 and SLM2 are well suited to regulate neuronal alternative splicing programs in a cell type–specific manner, in conjunction with NRXNs (Iijima et al., 2014).

Neuroanatomic location

Alternative splicing of NRXNs may be regionally regulated. Aoto et al. (2013) found that the three *NRXN* genes were expressed at comparable levels in different brain regions, and exhibited a coordinated but differential pattern of SS4 alternative splicing. Some brain regions, e.g., striatum and cerebellum, expressed primarily (about 90%) SS4 + forms of all three NRXNs. Other brain regions, e.g., cortex and hippocampus, expressed similar abundance of SS4 + and SS4 – forms of NRXN1 and NRXN2, but primarily the SS4 – form of NRXN3 (about 90%). These data suggest that NRXNs alternative splicing may be related to regional function of the brain, although its biologic significance has

not been thoroughly established (Aoto et al., 2013). Conditional knockout of specific isoforms may provide answers.

Developmental regulation

The expressions of NRXNs are developmentally regulated. Pregno et al. (2013) showed that in postnatal (P) day P5–P21, NRXN was found practically in all GABA synapses, whereas in the mature cerebellum (> P30) of mice, NRXN was below detectable levels at inhibitory synapses (labeled for the $GABA_AR$ α1 subunit). They isolated synaptosomes from cerebella of P15 and adult (> P30) mice, and found considerably higher NRXN levels in juvenile than in adult mice. The white matter and neuronal connectivity are largely established during this early postnatal period. These results suggest that NRXNs are present in developing GABA synapses, but are downregulated at the end of the synaptogenic period.

The expressions of binding partners of NRXNs are also regulated according to developmental stage. For example, the NLGN1-3 proteins are expressed at moderate levels in newborn mice, but upregulated during postnatal development to 2 – 3 fold higher levels in adult mice (Varoqueaux et al., 2006). Knockdown of LRRTM1 and LRRTM2 at P0 (when synapses are forming) selectively reduced AMPA receptor-mediated synaptic currents, however, knockdown of LRRTMs at P21 (when synapses are largely mature) did not alter excitatory transmission (Soler-Llavina et al., 2011). These results suggested that expression of NRXNs and their binding partners are developmental regulated in relation to their function.

Binding interference

When binding to NRXNs, some post-synaptic partners may interfere and/or compete with the binding of other potential partners. For example, as reviewed above, Nxph1 interacts with LNS2 of α-NRXNs, α-dystroglycan interacts with both LNS2 and LNS6 of α-NRXNs (SS2 – or SS4 –), whereas NLGN2 interacts with LNS6 (SS4 +/–) of α-NRXNs (Lévi et al., 2002; Born et al., 2014). NLGN2 can form a physiologically relevant trans-synaptic complex with NRXN at inhibitory synapses (Varoqueaux et al., 2004; Fu and Huang, 2010). α-NRXN1 can also bind with either α-dystroglycan or with Nxph1 at inhibitory synapses. These binding partners are mutually exclusive, despite the fact that the binding sites for Nxph1 and α-dystroglycan do not overlap (Reissner et al., 2014). The Nxph1/α-NRXN1 complex was not able to interact with α-dystroglycan, therefore, the presence of Nxph1 may sterically constrain physical binding of α-dystroglycan to α-NRXN. It was also reported that a triple complex of α-NRXN/NLGNs/α-dystroglycan is unlikely to occur in brain, although α-dystroglycan and NLGN differentially interact with LNS2 and LNS6 respectively. Binding of α-dystroglycan at LNS2 can prevent interaction of NLGN at LNS6 with or without splice insert in SS4, presumably by sterically hindering each other in the conformation of α-NRXN.

Some interactors may compete for overlapping binding regions. It is reported that LRRTMs and NLGN1 have a highly overlapping binding sites on NRXN, and the affinity of NRXN (SS4 –) to LRRTMs is of the same range as NRXN: NLGN binding affinity (Siddiqui et al., 2010). However, LRRTM2 and NLGN1 cannot bind simultaneously to β-NRXN1 (Ko et al., 2009). In addition, Cbln1 was reported to compete with NLGN1(A-B-), but not LRRTM2 for synaptogenesis, possibly by sharing the NRXN (SS4 +) (Matsuda and Yuzaki, 2011). These results suggest that interference and competition exist among the NRXN postsynaptic partners, which may be required for diverse function of NRXN signaling. In support of this, Soler-Llavina et al. (2011) found that knockdown of LRRTM1 and LRRTM2 selectively reduced AMPA receptor-mediated synaptic currents. Triple knockdown of NLGN3/LRRTM1/LRRTM2 in NLGN1 knockout mice yielded greater reductions in AMPA and NMDA receptor- mediated currents. These results show that the NRXN postsynaptic partners LRRTMs and NLGNs *in vivo* are part of a functionally dynamic cell adhesion network that regulates excitatory synaptic transmission, and that these proteins redundantly contribute to maintenance of synaptic function (Soler-Llavina et al., 2011).

Transcriptional and post-transcriptional regulation on NRXNs

Expression of NRXNs can be regulated at transcriptional and post-transcriptional levels. Epigenetic regulation has been reported to pay a role for the transcriptional regulation of NRXNs. Methyl-CpG binding protein 2 (MeCP2) is a transcriptional regulator in brain (Chahrour et al., 2008), and *Nrxn1 – 3* and *Nlgn1 – 3* expression levels are almost simultaneously decreased at day 7 and increased at day 20 in brains of mice lacking MeCP2 (Runkel et al., 2013). The 5′-regions of *Nrxn1* and *Nlgn2* which bind to MeCP2 contain two CpG-rich elements that show distinct methylation. These CpG islands affect transcriptional activity in luciferase reporter gene assays. In addition, microRNAs (miRNAs) may also regulate expression of *NRXN*. Fan et al. (2014) identified a novel miRNA (miR-NID1) processed from the intron 5 of human *NRXN1*, and show that expression levels of NRXN1 and α-NRXN1 are negatively correlated with the levels of miR-NID1.

Environmental factors may affect the expression of NRXNs. For example, Fang et al. (2013) subjected rats to immobilization stress for 2 h/day for 7 days. Immobilization stress significantly decreased many expression of many proteins include β-NRXN. If the rats were exercised on the treadmill at a speed of 15 m/min, 30 min/day for 5 days, the decreased expression of these proteins was significantly

attenuated. These results suggest that treadmill exercise reverses stress-induced changes in the rat hippocampus and may induce a functional reconnection of hippocampal synapses that mediate antidepressant actions.

NRXNs are reported to be post-transcriptionally regulated. NRXNs are proteolytically processed at glutamatergic synapses by presenilins (PS), the catalytic components of the γ-secretase complex that mediates the intramembraneous cleavage of several type I membrane proteins. Inhibition of PS/γ-secretase induces a significant accumulation of neurexin C-terminal fragment (CTFs) in cultured rat hippocampal neurons and mouse brain (Saura et al., 2011).

NRXNs intracellularly interact with the PDZ-domain protein CASK (Hata et al., 1996). In cytoplasm, CASK interacts stoichiometrically with Mint-1 and Velis that may be involved in organizing synapses (Borg et al., 1998; Butz et al., 1998). CASK associates with neurexin1 and protein-4.1 and forms a trimeric complex. This complex is a potent nucleator of actin polymerization (Biederer and Sudhof, 2001). Mukherjee et al. (2008) found that the CASK CaM-kinase domain could directly phosphorylate the NRXN-1 C-terminal-tail, and that this activity was strongly inhibited by Mg^{2+}. β-NRXN phosphorylation was also increased > 2-fold when synaptic activity-driven divalent ion fluxes were suppressed. Since CASK is inhibited by divalent ions, enhanced NRXN phosphorylation upon synaptic inactivation is strongly suggestive of CASK kinase activity. Indeed, β-NRXN phosphorylation was reduced by nearly 40% in CASK-knockout neurons. These data suggest that CASK physiologically bind NRXNs in neurons leading to phosphorylation, and this phosphorylation is regulated by the synaptic activity-driven fluxes of divalent ions. However, it should be mentioned that in the absence of CASK, the significant phosphorylation of neurexin-1 can still be detected, suggesting that there are other kinases involved.

Association of NRXN with neurodevelopmental and neuropsychiatric illness

The neurexin-neuroligin pathway is proposed to regulate the neuronal connectivity bidirectionally and to play a major role in cognitive diseases. Compelling genetic data suggest that NRXN pathway is a common risk factor for a range of neurodevelopmental disorders, including mental retardation, developmental delay, ASD, schizophrenia and epilepsy. For example, medical record reviews of subjects with *NRXN1* deletion revealed a variable clinical phenotype including ASD, mental retardation, language delays and hypotonia (Ching et al., 2010). Mutations in neurexins (*NRXN1, NRXN2 and NRXN3*) and neuroligins (*NLGN1, NLGN3* and *NLGN4*) genes have been identified in patients with ASD (Jamain et al., 2003; Comoletti et al., 2004; Laumonnier et al., 2004; Feng et al., 2006; Szatmari et al., 2007; Kim et al., 2008; Yan et al., 2008; Gauthier et al., 2011; Camacho-Garcia et al., 2012; Liu et al., 2012; Vaags et al., 2012), mental retardation (Ching et al., 2010, Camacho-Garcia et al., 2012; Millson et al., 2012), and schizophrenia (Walsh et al., 2008; Kirov et al., 2009, Rujescu et al., 2009, Gauthier et al., 2011).

Kim et al. (2008) analyzed two ASD patients with chromosomal abnormalities and found both breakpoints disrupted *NRXN1* gene. Subsequently, they sequenced *NRXN1* coding exons in a cohort of 114 ASD and 478 non-ASD controls, and identified seven novel heterozygous variants (L18Q, G35, G304, L748I, A1055, G1325, P1458) in the ASD cohort. High density genotyping of 2 large cohorts of 1771 ASD cases and 2539 controls confirmed rare exonic deletions of *NRXN1* in ASD (Bucan et al., 2009). Deletions and mutations in *NRXN1* have been found in patients with severe mental retardation, autistic behavior, epilepsy, and breathing anomalies (Zweier et al., 2009).

Kirov has analyzed copy number variations in 93 individuals with schizophrenia and 372 controls using array comparative genomic hybridization, and identified *NRXN1* deletion (2p16.3) and 15q13.1 duplication as two genetic causal factors in schizophrenia (Kirov et al., 2008). A meta-analysis in 8789 schizophrenia cases and 42054 controls showed an excess of *NRXN1* deletions (> 100 kb) in patients compared to control (Kirov et al., 2009). A case-control association study was conducted to examine copy number variants in 2977 schizophrenia patients and 33746 controls from seven European populations, this found that *NRXN1* (but not *NRXN2* or *NRXN3*) is associated with schizophrenia. A significant enrichment of the *NRXN1* disruption was found in schizophrenia: 66 deletions and 5 duplications of *NRXN1* were identified in 2977 cases, compared to 49 deletions and 3 duplications in 33746 controls (Rujescu et al., 2009). Significantly, NRXN1 and a member of the superfamily of neurexin-like proteins CNTNAP2 were identified as major risk for schizophrenia and bipolar disorder in a recent pathway analysis of 3 large genome-wide association studies from International Schizophrenia Consortium, Genetic Association Information Network and Wellcome Trust Case Control Consortium (O'Dushlaine et al., 2011).

NRXN1 binding partners are also linked with many psychiatric disorders, especially ASD. The NLGN3 R451C point mutation was found in Swedish brothers with autism and Asperger syndrome, and the NLGN3 D396X truncation in another set of Swedish brothers (Jamain et al., 2003). NLGN4 and NLGN4Y mutations associated with heritable autism and mental retardations include NLGN4 R87W (Zhang et al., 2009), G99S, K378R, V403M and R704C point mutations (Yan et al., 2005), NLGN4 D429X truncation mutation (Laumonnier et al., 2004), NLGN4 exon 4 deletion (Talebizadeh et al., 2006), exons 4–6 deletion (Lawson-Yuen et al., 2008) and NLGN4Y I679V mutation (Yan et al., 2008). A genome-wide copy number variation analysis also shows that NLGN1 is linked to autism (Glessner et al., 2009).

These data overwhelmingly suggest that perturbation of neurexin cell adhesion pathway is central to neurodevelop-

mental and neuropsychiatric illness, and this is the most significant common pathway associated with ASD, epilepsy, schizophrenia and learning disability.

Conclusions

Accumulating genetic evidence suggest that the NRXN pathway is widely implicated in neurodevelopmental and neuropsychiatric illness. In this review, we focused on the regulation of NRXNs expression and extracellular binding and function, which are dynamically regulated, and can be affected by genetic, epigenetic and environmental factors. Our understanding of the biology of NRXN signaling may be facilitated by the generation and characterization of human stem cell disease models, which may be useful for drug development.

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Compliance with ethics guidelines

Yicheng Ding, Linda Howard, Louise Gallagher and Sanbing Shen declare that they have no conflict of interest. This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

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