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Review article

Functions of synapse adhesion molecules neurexin/neuroligins and neurodevelopmental disorders

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ABSTRACT

Neurexins and neuroligins are two distinct families of single-pass transmembrane proteins localized at pre- and postsynapses, respectively. They trans-synaptically interact with each other and induce synapse formation and maturation. Common variants and rare mutations, including copy number variations, short deletions, and single or small nucleotide changes in neurexin and neuroligin genes have been linked to the neurodevelopmental disorders, such as autism spectrum disorders (ASDs). In this review, we summarize the structure and basic synaptic function of neurexins and neuroligins, followed by behaviors and synaptic phenotypes of knock-in and knock-out mouse of these family genes. From the studies of these mice, it turns out that the effects of neurexins and neuroligins are amazingly neural circuit dependent, even within the same brain region. In addition, neurexins and neuroligins are commonly involved in the endocannabinoid signaling. These finding may provide not only insight into understanding the pathophysiology, but also the concept for strategy of therapeutic intervention for ASDs.

Contents

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1. Introduction

The neurodevelopmental disorder is a term for brain disorders with mental distortion that affect children and the condition persists throughout patient's lives. Autism spectrum disorders (ASDs) are a most common form of neurodevelopmental disorders characterized by impairments in social interaction and social communication, and repetitive and restricted patterns of behavior. Recent statistics reveals the prevalence of ASDs is up to 2–3% of all population and boys are four times higher than girls (Christensen et al., 2016; Huguet et al., 2013). Some behavioral interventions, such as Developmental Individual-differences Relationship-based (DIR) floor time, have been proven to be effective for some cases of ASDs, nevertheless, no pharmacological treatments are available for ASDs (Pajareya and Nopmaneejumruslers, 2011). Although the etiology of ASDs is largely unknown, the genetic components have been suggested to be involved in the disorder. While single causative genes for syndromic ASDs have been identified, it seems to be more intricate to narrow down to single genes account for non-syndromic ASDs. It is reasonable to conceive that the cause for the most of the non-syndromic ASDs is essentially polygenic. Common variations and rare mutations, including copy number variations, short deletions, small and single nucleotide variations, in genes functioning at synapses in the brain have been frequently identified from the patients with ASDs. SFARI Gene run by Simon Foundation (https://gene.sfari.org/autdb/Welcome.do) and Autism Kb (http://autismkb.cbi.pku.edu.cn/) run by Pekin University are two major online database for autism risk genes. They scrutinize the literature and score the candidate risk genes in accordance with the strength of linkage to ASDs. Neurexins and neuroligins are among a few gene families of which all members are listed and highly scored in the database (Table 1). In addition, neuroligins are the first genes of which single point mutations have been linked to non-syndromic ASDs by studies in human genetics and mouse models.

In this review, we summarize our knowledge on neurexins and neuroligins from the aspect of the structures and basic functions of the proteins, the phenotypes in behavior and synaptic function in knock-in and knock-out mouse of these molecules as models of ASDs.

2. Structures and functions of neurexins and neuroligins

Neurexins and neuroligins are both single-pass transmembrane proteins localized at pre- and postsynapses, respectively. Neurexins are originally isolated as α-latrotoxin receptors (Ushkaryov et al., 1992). Neurexin family has three genes in mammals all of which have two independent promoters that produce longer α- and shorter β-form (Missler et al., 1998). α-Neurexins contain six laminin/neurexin/sex hormone-binding globulin (LNS) domains and three epidermal growth factor (EGF)-like repeats in their extracellular region and a short cytoplasmic tail with protein 4.1 binding sequence in the middle and class II PDZ binding sequence at their carboxy-terminus (Fig. 1). β-Neurexins have a short β-specific sequence in their N-terminal region but share the remaining part encompassing from last LNS domain to carboxy-terminal with α-neurexins (Fig. 1). Five alternative splice sites (ss1–ss5) have been known for all neurexin genes and the combination of the presence or absence of insertion in these splice sites produces nearly 4000 isoforms of neurexin proteins (Tabuchi and Sudhof, 2002). Later on, one additional alternative splice site within the coding region of fourth LNS domain was discovered in neurexin-1 and -2 (Treutlein et al., 2014). Although this resides between ss2 and ss3, it is referred to as sixth splice site (ss6) (Fig. 1).

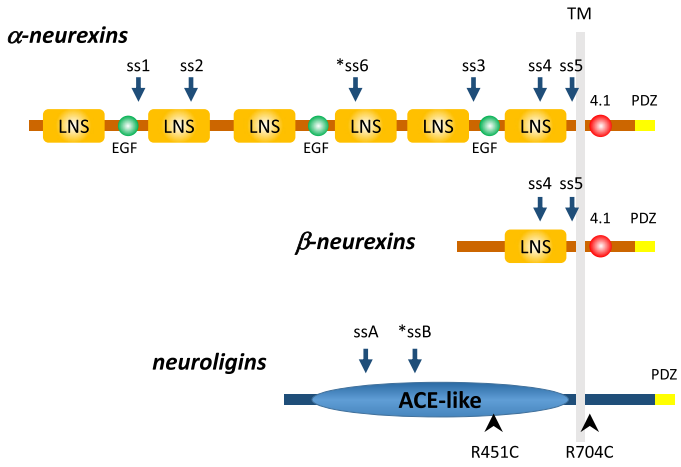

Fig. 1. Domain structure of neurexins and neuroligins.
Allows indicate alternative splicing sites (*ss6 in neurexin is not found in neurexin-2. ssB in neuroligin is found only in neuroligin-1). Arrowheads in neuroligins indicate single amino acid mutations identified in human ASD patients and introduced in the knock-in mice as animal models for ASD (R451C and R704C). LNS: laminin/neurexin/sex hormone-binding globulin-domain, EGF: epidermal growth factor-like repeats, 4.1: protein 4.1 binding sequences, PDZ: PDZ domain binding sequence, ACE-like: acetylcholinesterase-like domain, TM: transmembrane region.

Neuroligins are originally isolated as binding partners for β-neurexins (Ichtchenko et al., 1995). Five genes encoding neurexins have been identified in the human genome (NLGN1, NLGN2, NLGN3, NLGN4X and NLGN4Y) (Craig and Kang, 2007). Proteins of all members contain an acetylcholinesterase-like domain in the extracellular region and a short cytoplasmic tail with class I PDZ binding sequence at the carboxy-terminus (Fig. 1). Neuroligins have an alternative splice site within acetylcholinesterase-like domain coding region (ssA) (Fig. 1). Neuroligin-1 has one additional alternative splice site after ssA also within the acetylcholinesterase-like domain (ssB) (Fig. 1). In the beginning, it was considered that the only β-neurexins lacking insertion in ss4 could bind neuroligins, but later on, it turned out that β-neurexins containing exon in ss4 or α-neurexins lacking exon in ss4 can also bind neuroligin-1 without insertion in ssB (Boucard et al., 2005). Neuroligin proteins are localized and function at postsynapses as a dimer (Comoletti et al.,

Table 1
Neurexin/neuroligin genes and the strength of association with ASD scored by SFARI Gene and Autism Kb.

Gene symbol	Protein name	Chromosome band	SFARI score[a]	Autism Kb score[b]
NRXN1	Neurexin-1	2p16.3	2	28
NRXN2	Neurexin-2	11q13.1	4	16
NRXN3	Neurexin-3	14q24.3-q31.1	3	3
NLGN1	Neuroligin-1	3q26.31	4	13
NLGN2	Neuroligin-2	17p13.1	NA	3
NLGN3	Neuroligin-3	Xq13.1	2	26
NLGN4X	Neuroligin-4X	Xp22.32-p22.31	3	38
NLGN4Y	Neuroligin-4Y	Yq11.221	4	12

[a] SFARI score indicates as follows; 1: high confidence, 2: strong confidence, 3: suggestive evidence, 4: minimal evidence, 5: hypothesized, S: syndromic, NA: not available.
[b] Higher number in Autism Kb Score indicates stronger association with ASD.