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Review article

Neuroligins, synapse balance and neuropsychiatric disorders

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ABSTRACT

Neuroligins are postsynaptic adhesion molecules that are involved in the regulation of synapse organisation and function. Four neuroligin proteins have been identified (neuroligin 1, 2, 3, 4), which are differentially enriched in the postsynaptic specialisation of synapses. Neuroligin 1 is localised on excitatory (glutamatergic) synapses, whereas neuroligin 2 is located on inhibitory (GABAergic/glycinergic) synapses. Neuroligin 3 and 4 are present on both types of synapses. Recent data indicate that neuroligins are involved in synapse maturation and specification. Because of their synaptic localisation and function, neuroligins control the balance between excitatory and inhibitory synapses. Animal studies with neuroligin transgenic mice showed the involvement of neuroligin 1 in memory formation, and neuroligin 2, 3 or 4 in social behaviour. Interestingly, genetic analysis of humans showed a mutation in the neuroligin 2 gene in schizophrenic patients, while mutations in neuroligin 3 or 4 genes were found in autism.

Contents

Neuroligin family

Neuroligins are postsynaptic transmembrane adhesion proteins that are comprised of several domains including a cleaved signal peptide, a cholinesterase-like domain, a carbohydrate attachment region, a single transmembrane domain, and a short C-terminal tail containing a type I PDZ-binding motif (for review see Sudhof [1]).

Abbreviations: ASDs, autism spectrum disorders; GABA, γ-aminobutyric acid; LTP, long-term potentiation; mEPSC, miniature excitatory postsynaptic current; mIPSC, miniature inhibitory postsynaptic current; NMDA, N-methyl-D-aspartate; PSD-95, postsynaptic density protein-95; sPSC, spontaneous postsynaptic current.

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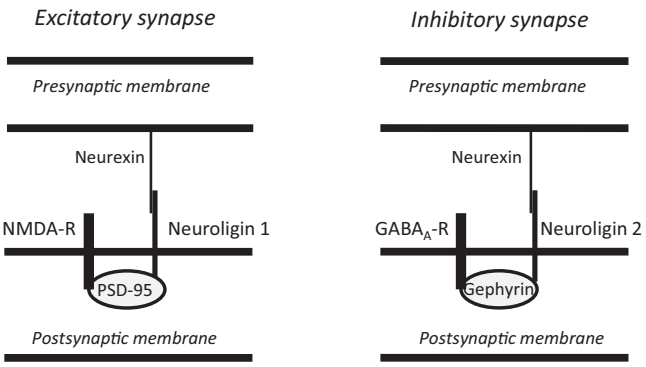

Fig. 1. Schematic illustration of neuroligin binding with neurexin (presynaptic membrane) and postsynaptic scaffolding proteins (PSD-95, gephyrin).

Neuroligin proteins have been found in several species, including humans, rodents, and chickens. Five genes encoding neuroligin proteins have been identified in the human genome (NLGN1, NLGN2, NLGN3, NLGN4, NLGN4Y), and at least four genes coding neuroligin family members have been known in rodents (NLGN1-4). Sequence comparisons indicate that neuroligins 1, 3, and 4 are more similar to each other than to neuroligin 2 [1,2].

Neuroligins link the presynapse to the postsynaptic density by binding through the extracellular cholinesterase-like domain to their presynaptic partners, neurexins, in an alternative splice-dependent manner. At the postsynaptic portion, neuroligins bind by their C-terminus with the third PDZ domain of a postsynaptic scaffold protein, such as the postsynaptic density protein-95 (PSD-95), which anchors a variety of signalling molecules and surface receptors [1–3] (Fig. 1). It has been suggested that the extracellular domain of neuroligin is sufficient to induce the assembly of functional presynaptic terminals, while the intracellular domain is required for terminal maturation [4].

Several findings indicate that neuroligins are present at developing and mature synapses of the brain and play an important role in synapse organisation and function [1,3,5]. They were initially thought to be required for synapse formation [6], but recent findings indicate their crucial involvement in synapse maturation and specification [7]. It was found that neuroligins are differentially enriched in the postsynaptic specialisations of synapses, and they are found on either excitatory or inhibitory synapses.

Neuroligins at the excitatory synapses

Neuroligin 1 proteins are exclusively localised on excitatory synapses [8]. This observation is supported by the facts that the neuronal localisation, subcellular distribution and developmental expression of this protein are connected with the excitatory postsynaptic marker protein PSD-95 and N-methyl-D-aspartate (NMDA) receptor (Fig. 1). Moreover, electron microscopy study demonstrated that only asymmetric synapses contain neuroligin 1, and immunofluorescence labelling showed that neuroligin 1 colocalises with glutamatergic but not with γ-aminobutyric acid (GABA)-ergic synapses [8]. An in vitro study also showed the coaggregation of neuroligin 1 with PSD-95 (scaffold protein of excitatory synapses), but not gephyrin (scaffold protein of inhibitory synapses) in cultured neurons [9]. A similar effect was observed for neuroligin 3 and neuroligin 4, which suggests that these two proteins are also expressed on excitatory synapses [9]. Additional studies confirmed the presence of neuroligin 3 on glutamatergic synapses in the brain and coimmunoprecipitation studies revealed the occurrence of neuroligin 1–neuroligin 3 complexes in the brain extracts [10].

Neuroligins at the inhibitory synapses

Neuroligin 2 is known to be constitutively and selectively present at inhibitory postsynaptic specialisations [11]. Neuroligin 2 is localised at both GABA-ergic and glycinergic inhibitory synapses [12,13]. Neuroligin 2 preferentially binds the inhibitory synapse scaffold protein gephyrin through a conserved cytoplasmic motif [13], and it is able to cluster $GABA_A$ receptors [14] (Fig. 1). In addition to neuroligin 2, neuroligin 3 and 4 were also found at inhibitory synapses [10,15]; however, they are not specific markers for inhibitory synapses (see above). Neuroligin 3 was observed at GABA-ergic synapses [10], while neuroligin 4 was localised at glycinergic synapses [15].

Excitatory and inhibitory synapse balance

Proper brain function is based on a balance between excitation and inhibition, which are mainly mediated by two major neurotransmitters, glutamate and GABA, respectively. The total number of synapses formed and ratio of excitatory to inhibitory synaptic inputs a neuron receives are factors critical for determining neuronal excitability [16]. Molecules that are involved in the control of a balance between excitatory and inhibitory synapse formation are important for proper neuronal excitability and function. Several findings indicate that neuroligins are involved in both excitatory and inhibitory synapse maturation and specificity, and they are able to control the balance between excitatory and inhibitory synapse formation [5]. An in vitro study showed that the suppression of single (neuroligin 1 or 2 or 3) or multiple neuroligin isoform (neuroligins 1–3) expression in cultured rat hippocampal neurons results in a loss of excitatory and inhibitory synapses. However, electrophysiological analysis demonstrated a predominant reduction of inhibitory synaptic function and alteration in normal excitatory/inhibitory balance in hippocampal neurons [6]. The largest changes in inhibitory synaptic transmission than excitatory transmission were also observed in an electrophysiological study in neuroligin knockout mice [7]. It was found that the deletion neuroligins 1–3 dramatically changed the balance between glutamatergic and GABAergic/glycinergic spontaneous postsynaptic currents (sPSC) in brainstem neurons, with a strong decrease in GABAergic/glycinergic sPSC, without affecting the total synapse numbers [7]. In contrast, exogenous neuroligin 1 increased both excitatory and inhibitory presynaptic contacts and the frequency of miniature excitatory and inhibitory postsynaptic currents (mEPSC and mIPSC, respectively) in the cultured hippocampal neurons [17]. Thus, the above data indicate that the proper level of neuroligin proteins seems to be an important factor in the control of the excitatory and inhibitory balance in the brain, and the decrease in neuroligin levels mainly influence the inhibitory transmission.

The fact that all single neuroligin knockout mice as well as all combinations of double neuroligin knockouts were viable, whereas neuroligin 1–3 triple knockout mice died shortly after birth, may indicate a significant degree of functional redundancy among neuroligins [7]. The above observation was also confirmed by the results from an in vitro study showing that the overexpression of all neuroligin isoforms is able to stimulate the formation of both excitatory and inhibitory terminals [6]. On the other hand, the study with transgenic mice showed that the overexpression of neuroligin 1 increased the maturation of excitatory synapses [18]. However, there were no differences in the number and size of glutamatergic and GABAergic hippocampal synapses in neuroligin 1 knockout mice when compared to wild-type animals [19]. In contrast, a decrease in GABAergic but not glutamatergic transmission was found in neuroligin 2 knockout mice [12,13]. The role of neuroligin 2 in the control of inhibitory synapse function was also