Review
TRENDS in Neurosciences Vol.29 No.1 January 2006
Full text provided by www.sciencedirect.com

Neuroligins and neurexins: linking cell adhesion, synapse formation and cognitive function

Camin Dean[1] and Thomas Dresbach[2]

[1]Department of Physiology, University of Wisconsin Medical School, Madison, WI 53706, USA
[2]University of Heidelberg, Institute for Anatomy and Cell Biology II, Heidelberg, D-69120, Germany

Cell adhesion represents the most direct way of coordinating synaptic connectivity in the brain. Recent evidence highlights the importance of a trans-synaptic interaction between postsynaptic neuroligins and presynaptic neurexins. These transmembrane molecules bind each other extracellularly to promote adhesion between dendrites and axons. This signals the recruitment of presynaptic and postsynaptic molecules to form a functional synapse. Remarkably, neuroligins alone can induce the formation of fully functional presynaptic terminals in contacting axons. Conversely, neurexins alone can induce postsynaptic differentiation and clustering of receptors in dendrites. Therefore, the neuroligin–neurexin interaction has the unique ability to act as a bi-directional trigger of synapse formation. Here, we review several recent studies that offer clues as to how these proteins form synapses and how they might function in the brain to establish and modify neuronal network properties and cognition.

Introduction

Brain development and function rely on proper formation, maintenance and modification of connections between neurons. During development, axons are guided towards target dendrites by attractive and repulsive cues. Stable contacts between axons and dendrites result in the formation of functional synapses, which are highly elaborate asymmetric sites of neuron–neuron contact. The presynaptic side of the junction includes: (i) the active zone where neurotransmitter release occurs; (ii) a network of scaffolding proteins known as the cytomatrix of active zones; and (iii) a cluster of neurotransmitter-containing synaptic vesicles. Postsynaptic components include: (i) an accumulation of neurotransmitter receptors directly opposed to the active zone; and (ii) scaffolding proteins. At excitatory synapses these scaffolding proteins are known as the postsynaptic density (PSD); a distinct set of scaffolding proteins are present at inhibitory synapses. For synapses to function, all these components must be recruited and precisely aligned across the synaptic cleft, a 20-nm-wide extracellular space that separates two neurons at synaptic junctions. In view of this architecture, an appealing model of synapse assembly and maintenance invokes heterophilic presynaptic and postsynaptic transmembrane proteins that bind each other in the extracellular space and recruit additional proteins via their intracellular domains. Recently, several molecules, including synaptic cell-adhesion molecule (SynCAM), N-cadherin, neural cell-adhesion molecule (NCAM), Eph receptor tyrosine kinases, and neuroligins and neurexins, have been implicated in synapse formation and maintenance (Craig *et al.*, in this issue). Here, we focus on the roles of two families of heterophilic adhesion molecules, neuroligins and neurexins, in trans-synaptic signaling. In particular, we address three emerging trends: (i) the potential of these two proteins to induce synapse assembly in cultured neurons; (ii) the modes of action of these proteins; and (iii) the implications of the effects of these proteins in the pathogenesis of cognitive disorders.

Corresponding authors: Dean, C. (camin@physiology.wisc.edu), Dresbach, T. (thomas.dresbach@urz.uni-heidelberg.de).
Available online 7 December 2005

Neurexins and neuroligins

Neurexins were discovered as a result of their ability to bind α-latrotoxin, a component of black widow spider venom, which triggers massive neurotransmitter release [1]. Neurexins were hypothesized to act as cell-recognition molecules based on their structure: a single transmembrane region and an extracellular domain that is similar to laminin A, slit and agrin, proteins implicated in axon guidance and synaptogenesis [1,2]. There are three genes that encode α-neurexins and three genes that encode β-neurexins, all of which are expressed predominantly in neurons. α-Neurexins contain six LNS (laminin, nectin, sex-hormone binding globulin) domains commonly found in adhesion molecules. α-Neurexins are important for the localization and function of Ca^{2+} channels and NMDA receptors [3,4]. β-Neurexins are essentially truncated α-neurexins, containing only a single LNS domain.

The binding between neuroligins and neurexins is controlled by alternative splicing of both neuroligin and neurexin genes. For example, unspliced neuroligins can bind β-neurexins but not α-neurexins. Removing an eight-amino-acid sequence from neuroligins by splicing generates isoforms that bind both α-neurexins and β-neurexins, and this binding could be involved in modulating synapse properties [5]. Neuroligin-1 was identified as a result of its ability to bind certain isoforms of all three β-neurexins [6]. Neuroligins only

www.sciencedirect.com 0166-2236/$ - see front matter © 2005 Elsevier Ltd. All rights reserved. doi:10.1016/j.tins.2005.11.003

bind isoforms of β-neurexins that lack an insert at the fourth splice site. Figure 1 shows a schematic of neuroligins and β-neurexins, and outlines structural elements of the neuroligin–β-neurexin interaction.

There are five neuroligin genes in humans and at least three in rodents, with neuroligins-1, -2 and -3 predominantly expressed in the CNS [7–10]. Interestingly, neuroligin-1 and neuroligin-2 are localized postsynaptically at

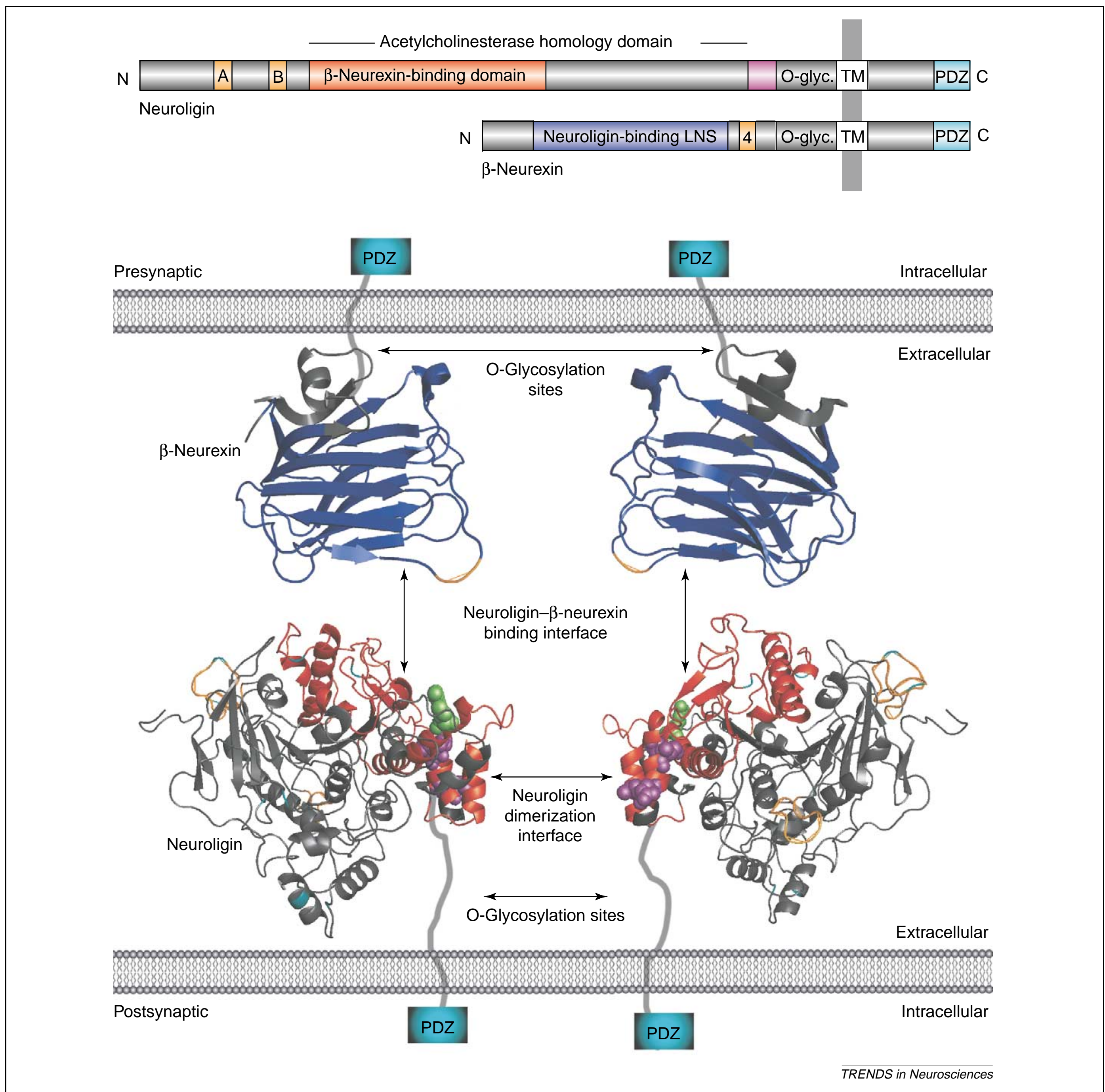

Figure 1. The structure of neuroligins and β-neurexins, showing their interaction domains and the neuroligin dimerization interfaces, which are essential for synaptogenic activity and β-neurexin binding [13]. (Upper panel) β-Neurexins are composed of: (i) an extracellular N-terminal sequence that is specific to β-neurexins, a single LNS domain that is essential for binding neuroligins (blue) [16]; (ii) an O-glycosylation (O-glyc.) region; (iii) a transmembrane (TM) domain; and (iv) a cytoplasmic tail that contains a PDZ-interaction site on the C-terminus. (Lower panel) The crystal structure of putative dimers of β-neurexin-1 [69] reveals that it contains two seven-stranded β-sheets that form a fold that has similarity to lectins, and splice sites that are localized within loops at the edge of the fold (yellow), which might act as a protein-interaction surface. Only β-neurexins that lack an insert at splice site four (yellow) can bind neuroligins. (Upper panel) Neuroligins consist of a large extracellular domain that shares sequence homology with acetylcholinesterase [70]. A structural model of neuroligins based on this domain is shown. Neuroligins contain: (i) two EF-hand motifs in this domain (not shown) [71] that bind Ca^{2+} [14]; (ii) an O-glycosylation region; (iii) a transmembrane domain; and (iv) a cytoplasmic C-terminal tail that contains a PDZ-interaction site [6,7,72]. A portion of the acetylcholinesterase homology domain shown in the neuroligin structure model [13] is necessary for β-neurexin binding and synaptogenic activity (red) [15,73]. Neuroligins contain two splice sites (A and B), an oligomerization domain (purple) and five N-linked glycosylation sites [73,74]. Deglycosylation increases binding to β-neurexin, indicating a possible regulatory role for glycosylation [73]. (Lower panel) Neuroligins contain nine cysteines (turquoise), eight of which form disulfide bonds [74]. Neuroligins oligomerize through a specific interface (purple) [13,73] and mutations in these regions abolish binding to β-neurexins and synaptogenic activity [13]. Residue 473 in neuroligin-1 (green), which corresponds to residue 451 in human neuroligin-3 (mutated in autistic patients), is essential for surface targeting of the protein [19,64,65]. Splice sites are shown in yellow.

Download English Version:

https://daneshyari.com/en/article/4354821

Download Persian Version:

https://daneshyari.com/article/4354821

Daneshyari.com