Review

Cadherins and catenins at synapses: roles in synaptogenesis and synaptic plasticity

Jyothi Arikkath and Louis F. Reichardt

Department of Physiology, University of California San Francisco, Rock Hall, Room 284A, Mission Bay, 1550 Fourth Street, San Francisco, CA 94158-2611, USA

Synapse formation involves reciprocal interactions between cells resulting in formation of a structure optimized for efficient information transfer. Recent work has implicated constituents of the cadherin–catenin cell-adhesion complex in both synapse formation and plasticity. In this review, we describe recent interesting discoveries on mechanisms of cadherin complex function, in addition to regulating adhesion, that are relevant for understanding the role of this complex in synaptogenesis and plasticity. We describe how this complex acts via (i) recruitment/stabilization of intracellular partners; (ii) regulation of intracellular signaling pathways; (iii) regulation of cadherin surface levels, stability and turnover; (iv) stabilization of receptors; and (v) regulation of gene expression. These exciting discoveries provide insights into novel functional roles of the complex beyond regulating cell adhesion.

Introduction

Synapses of the central nervous system are specialized asymmetric cell-adhesion junctions that mediate directional information transfer. Pre- and postsynaptic compartments are morphologically distinct with specialized functional roles. Presynaptic terminals contain synaptic vesicles and machinery for neurotransmitter release, whereas postsynaptic sites include neurotransmitter receptors and a variety of scaffolding and signaling proteins. Together, these molecules ensure rapid and directional information transfer. Moreover, the synaptic compartments are dynamic, allowing for synaptic modulation in response to neural activity, a property believed to underlie the ability of the nervous system to learn and retain memory [1,2]. The processes that underlie synapse assembly, maintenance and plasticity need to be precisely regulated during development and in response to synaptic activity to optimize functioning of synapses and neural circuits.

In this review, we focus on the role of a cell-adhesion complex, the cadherin–catenin complex, in synapse morphogenesis and plasticity within the mammalian central nervous system. This complex has been extensively studied in epithelial cells. It is becoming increasingly clear that it also has very interesting functional roles in neurons. Several studies indicate that components of the complex regulate multiple aspects of synapse morphogenesis and plasticity. Many of the insights obtained in epithelia concerning mechanisms through which adhesion and signaling by the cadherin complex are regulated appear to be useful in understanding the functions of these complexes in synapse formation, function and plasticity [3].

Contact-mediated adhesion in synaptogenesis

The formation of a synapse requires target recognition followed by recruitment of pre- and postsynaptic elements in precise apposition (Figure 1). Synapse morphogenesis is initiated by formation of contacts between filopodia that arise from dendrites and axon segments, followed by contact stabilization and acquisition of appropriate pre- and postsynaptic elements, together with spine maturation at many excitatory synapses. Synaptic maturity is characterized by morphological and molecular specializations in both compartments that are optimized for fast and efficient information transfer.

In central neurons, the majority of excitatory synapses are formed on dendritic spines. Dendritic spine density, morphology and size are important regulators of their roles in information transfer, learning and memory [4]. The ability of spines to regulate shapes and content in response to synaptic activity is vital for their function. Regulation of cadherin-complex-associated functions contributes to spine morphogenesis, plasticity and function [5,6].

The cadherin–catenin cell-adhesion complex

The cadherin family is composed of more than 80 members in a single species that has been classified into several subfamilies, including classical cadherins, protocadherins, Fat cadherins, CNRs and seven-pass transmembrane cadherins [7]. This review is restricted to classical cadherins. The roles for cadherins and catenins, cytosolic partners of cadherins, in regulating cell adhesion in epithelial cells have been extensively explored. It is now clear that these proteins regulate synaptogenesis and plasticity in central neurons. More interestingly, the cadherin–catenin complex regulates synapses through both cell-adhesion-dependent and -independent mechanisms.

Structurally, classical cadherins, the type I and II cadherins, include a series of five extracellular repeat structures which bind calcium, a single transmembrane domain and an intracellular tail. The cadherin repeats mediate *cis* and *trans* interactions leading to homophilic *cis* and *trans*

Corresponding author: Reichardt, L.F. (louis.reichardt@ucsf.edu).

0166-2236/$ – see front matter doi:10.1016/j.tins.2008.07.001 Available online 4 August 2008

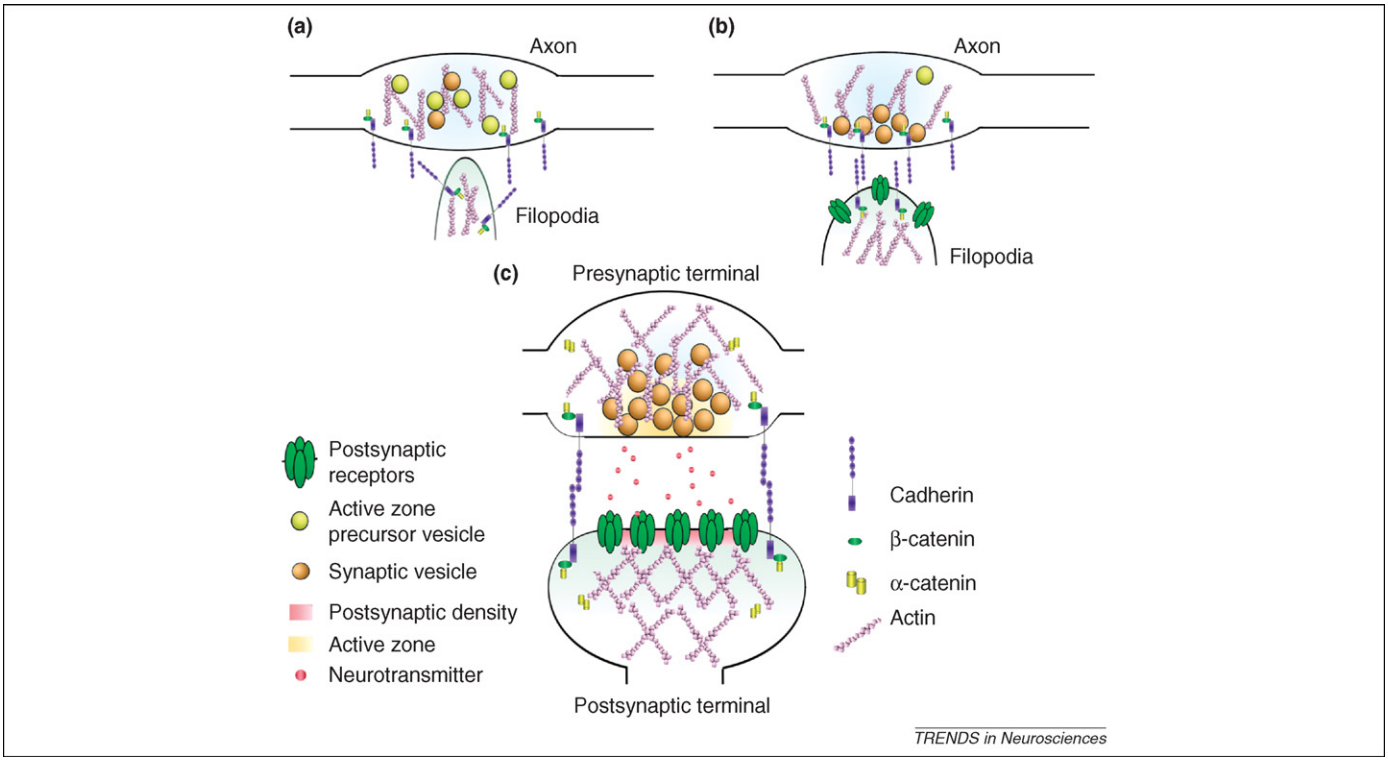

Figure 1. Schematic representation of hippocampal excitatory synapse formation and localization of the cadherin–catenin complex at different stages. **(a)** Synaptogenesis is initiated by the formation of nascent contacts between dendritic filopodia and axons. At these stages, N-cadherin in distributed evenly along the synaptic structure. This is followed by **(b)** contact stabilization and clustering of cadherin and **(c)** maturity. A mature synapse is characterized by a stable presynaptic terminal that contains vesicles primed for neurotransmitter release and a postsynaptic density that contains the receptors and scaffolding proteins. In the adult, cadherin is localized to distinct regions bordering the mature active zone, termed as the *puncta adherentia*. Both β-catenin and α-catenin are known to colocalize with cadherin at these junctions. Recent studies in nonneuronal cells indicate that the binding of α-catenin to β-catenin and actin are mutually exclusive, with the monomer form having a higher affinity for β-catenin and the dimer having a higher affinity for actin. Although p120ctn and δ-catenin are known to be at synapses, their localization at the electron microscope level and during development is unclear.

cadherin dimerization [8]. Cytoplasmic domains of cadherins include binding sites for a variety of proteins, including catenins. The catenins are cytosolic proteins that can be subdivided into three separate groups – two β-catenin-like proteins (β-catenin and plakoglobin), three α-catenins and four p120catenin-related proteins. The distal region of cadherin cytoplasmic domains includes a binding site for β-catenin, whereas the membrane proximal region contains a binding site for members of the p120ctn family that includes δ-catenin, ARVCF and p0071. α-Catenins bind the complex via interactions with β-catenin (Figure 2).

Structurally, β-catenin includes N- and C-terminal regions flanking a series of 12 armadillo (arm) repeats [9]. Cadherins bind to β-catenin and plakoglobin via an extended groove formed by the arm repeats. The C-terminal domain of β-catenin includes a transcriptional activation motif. The PDZ motif at the C terminus of β-catenin interacts with a variety of synapse-associated PDZ-domain-containing proteins.

Three α-catenins, encoded by different genes, have been characterized. These include αE-catenin, predominantly expressed in epithelia; αN-catenin, restricted to neural tissue; and αT-catenin, expressed in the heart. α-Catenins contain several regions that are homologous to domains in vinculin and include N- and C-terminal regions flanking an M (adhesion modulation) domain [10]. They are not structurally related to other catenins. The N-terminal regions include β-catenin-binding and dimerization domains. The C-terminal regions include an actin-binding site. In addition, α-catenin binds several actin-binding proteins, including vinculin, eplin, α-actinin and formins, proteins that promote F-actin polymerization [10]. In addition, α-catenin inhibits Arp2/3-mediated actin polymerization. Hence, α-catenin can regulate the actin cytoskeleton by multiple mechanisms.

The structures of p120ctn family members share some similarity with that of β-catenin with a central domain that includes nine armadillo repeats plus N- and C- terminal flanking sequences [9,11]. The armadillo repeat region includes the cadherin-binding site and a putative nuclear localization signal. In addition, δ-catenin, ARVCF and p0071 include a C-terminal PDZ-binding motif. p120ctn and δ-catenin function as RhoGDIs (guanine dissociation inhibitor); p120ctn also binds p190RhoGAP. p120ctn binds the cytoplasmic tyrosine kinase Fer which, through phosphorylation, stabilizes interactions between cadherins and β-catenin [12]. p120ctn and δ-catenin bind kaiso, suppressing its ability to repress transcription [13].

Until recently, the cadherin–catenin complex was believed to link cadherins to the actin cytoskeleton via binding of β-catenin to α-catenin, which in turn links to the actin cytoskeleton. By contrast, recent studies have demonstrated that α-catenin binds to β-catenin or F-actin in a mutually exclusive manner [14,15], with the monomeric form preferentially binding β-catenin and the homodimeric form preferentially binding F-actin. As α-catenin