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Understanding the role of synaptopodin and the spine apparatus in Hebbian synaptic plasticity – New perspectives and the need for computational modeling

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ABSTRACT

Synaptopodin (SP) is a proline-rich actin-associated protein essential for the formation of a spine apparatus (SA) in dendritic spines. The SA consists of stacks of smooth endoplasmic reticulum (sER) contiguous with the meshwork of somatodendritic ER. Spines of SP-deficient mice contain sER but no SA, demonstrating that SP is necessary for the assembly of ER cisterns into the more complex SA organelle. Although the SA was described decades ago, its function was difficult to investigate and remained elusive, in part because reliable markers for the SA were missing. After SP was identified as an essential component and a reliable marker of the SA, a role of SP/SA in hippocampal synaptic plasticity could be firmly established using loss-of-function approaches. Further studies revealed that SP/SA participate in the regulation of Ca^{2+}-dependent spine-specific Hebbian plasticity and in activity-dependent changes in the spine actin cytoskeleton. In this review we are summarizing recent progress made on SP/SA in Hebbian plasticity and discuss open questions such as causality, spatiotemporal dynamics and complementarity of SP/SA-dependent mechanisms. We are proposing that computational modeling of spine Ca^{2+}-signaling and actin remodeling pathways could address some of these issues and could indicate future research directions. Moreover, reaction-diffusion simulations could help to identify key feedforward and feedback regulatory motifs regulating the switch between an LTP and an LTD signaling module in SP/SA-containing spines, thus helping to find a unified view of SP/SA action in Hebbian plasticity.

1. Introduction

Correlations between synaptic input and postsynaptic firing lead to long-lasting modifications of synaptic strength (Abbott & Nelson, 2000). This synapse-specific form of synaptic plasticity is also known as "Hebbian"-plasticity (Brown, Kairiss, & Keenan, 1990; Lisman, Grace, & Duzel, 2011) and encompasses both long-term potentiation (LTP) as well as long-term depression (LTD), the two classical plasticity phenomena linked to learning and memory (Sweatt, 2016). The molecular machinery of Hebbian synaptic plasticity has been studied for many years and is arguably the best decoded form of synaptic plasticity (Bliss & Cooke, 2011; Caporale & Dan, 2008). Of note, in spite of the large number of molecules able to modulate LTP (Sanes & Lichtman, 1999), only two molecular steps appear to be crucial, i.e. both necessary and sufficient, for the induction of LTP (Nicoll & Roche, 2013). These include (i) the activation of NMDA receptors which triggers the influx of Ca^{2+} and (ii) activation of CaMKII (Herring & Nicoll, 2016; Lisman, Yasuda, & Raghavachari, 2012). After its induction the persisting expression of LTP, i.e. the long-term strengthening of the synapse, requires the activation of a spine-specific effector machinery, which executes the molecular changes that eventually result in increased synaptic strength. For this strengthening the polymerization of actin filaments, an increase in spine volume and the fast recruitment of postsynaptic AMPA receptors appear to be important (Herring & Nicoll, 2016). Since Synaptopodin (SP) and the spine apparatus (SA) have also been implicated in the regulation of LTP (Deller et al., 2003; Jedlicka et al., 2009), spine Ca^{2+} signaling (Fifková, Markham, & Delay, 1983; Korkotian, Frotscher, & Segal, 2014; Korkotian & Segal, 2011; Vlachos et al., 2009), actin-modulation (Okubo-Suzuki, Okada, Sekiguchi, & Inokuchi, 2008; Vlachos et al., 2009; Wang, Dumoulin, Renner, Triller, &

Abbreviations: SP, synaptopodin; SA, spine apparatus; CaMKII, Ca^{2+}/calmodulin-dependent kinase II; LTP, long-term potentiation; LTD, long-term depression; VGCC, voltage-gated Ca^{2+} channels; sER, smooth endoplasmic reticulum; PKA, protein kinase A.

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Specht, 2016) and local protein synthesis (Pierce, Mayer, & McCarthy, 2001; Pierce, van Leyen, & McCarthy, 2000), we propose that SP/SA are an important part of this downstream effector machinery. The stacking may result in a more efficient form of sER, suggesting that the SA may in fact be a form of "optimized" sER for purposes of spine-specific synaptic plasticity. In this review we discuss the role of SP/SA in Hebbian plasticity in the hippocampus and will discuss recent studies, which provide first experimental evidence for such a concept. Computational modeling may be an important next step to understand the functional consequences of sER stacking and may help to identify promising new research directions.

2. Synaptopodin - an essential component and marker of the spine apparatus organelle

SP is a 100-kDa proline-rich actin-associated protein (Asanuma et al., 2005; Mundel et al., 1997) which is highly (but not exclusively) expressed in telencephalic neurons of the hippocampus, cerebral cortex, striatum and olfactory bulb (Fig. 1; Bas Orth et al., 2005; Mundel et al., 1997). In the hippocampus it appears postnatally (Czarnecki, Haas, Bas Orth, Deller, & Frotscher, 2005) and is found in a characteristic region- and lamina-specific distribution pattern in the adult brain (Deller, Merten, Roth, Mundel, & Frotscher, 2000; Deller et al., 2006; Bas Orth et al., 2005; Fukazawa et al., 2003). By analyzing single GFP-labeled neurons stained for SP we could show that the layer-specific percentage of SP-positive spines ranges between 37% (outer molecular layer of the dentate gyrus) and 14% (stratum oriens of CA1, Bas Orth et al., 2005). Ultrastructural analysis revealed that SP is tightly associated with the SA (Deller et al., 2000) and SP deletion and rescue experiments demonstrated that SP is not only associated with but in fact an essential component needed for the formation of a SA (Fig. 1C–E; Deller et al., 2003; Vlachos et al., 2013). The SA is a unique organelle within dendritic spines (Fig. 1A and B) that consists of stacked cisterns of sER interdigitated by electron dense material (Fig. 1C; Gray, 1959). In dendrites of neurons sER constitutes a meshwork of tubules, vesicles and cisterns (Berridge, 1998). The SA is connected to a side branch of the dendritic ER network which extends into some but not all spines. Based on their ER content three groups of spines were distinguished in the hippocampus: a first subset of spines, typically small spines, contains no sER; a second group of spines has cisterns, tubules or vesicles of sER; a third subset of spines, typically large spines, contains closely packed stacks of sER forming the SA (Chirillo, Bourne, Lindsey, & Harris, 2015; Deller et al., 2000; Spacek & Harris, 1997). In SP-deficient mice sER containing spines are still abundant, but no SAs are found (Fig. 1D), suggesting that SP is an essential component of the dense material that "glues" the cisterns together and assembles the sER into the organelle (Deller et al., 2003).

3. Evidence for an involvement of SP/SA in Hebbian synaptic plasticity

Early ultrastructural studies detected Ca^{2+} in the cisterns of the SA providing the very first evidence that the SA might be involved in Ca^{2+} trafficking and, possibly, synaptic plasticity (Fifková et al., 1983). Similarly, SP was hypothesized to play a role in synaptic plasticity based on observations of an increased SP mRNA as well as protein expression following LTP induction in vivo (Fukazawa et al., 2003; Yamazaki, Matsuo, Fukazawa, Ozawa, & Inokuchi, 2001). Experiments with SP-deficient mice provided the first direct evidence that SP is required for the formation of the SA (Fig. 1) and supported the involvement of SA/SP in the regulation of LTP, learning and memory (Fig. 2; Deller et al., 2003). The lack of SP/SA led to deficits in LTP at hippocampal Schaffer collateral synapses (Fig. 2A)

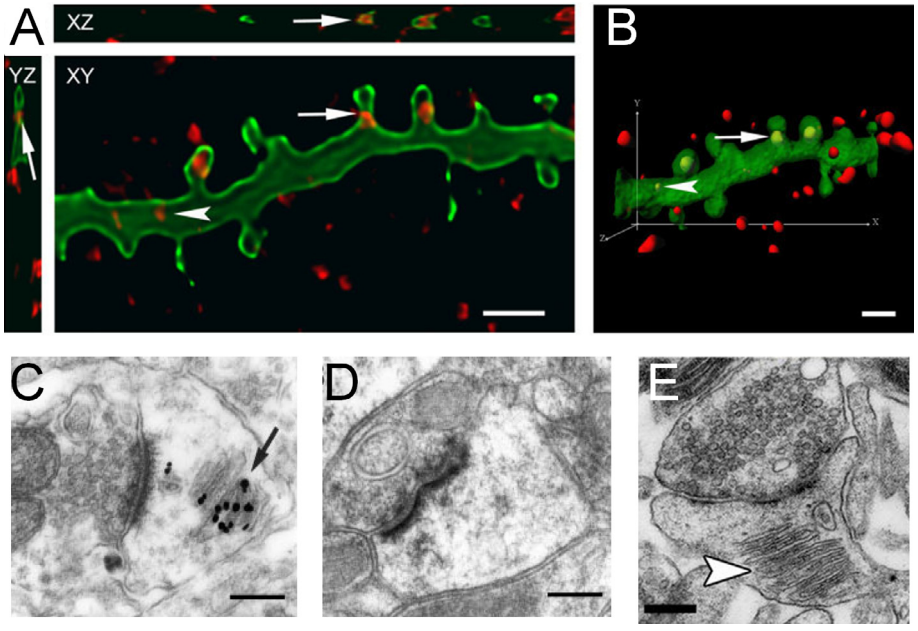

Fig. 1. Synaptopodin (SP) is required for the formation of the spine apparatus (SA). (A) SP is found in a subpopulation of spines. A confocal image of a GFP-labeled (green) segment from a pyramidal cell dendrite (hippocampus, CA1) shows SP-positive clusters in spine heads, spine necks (arrows) and sporadically also in dendrites (arrowhead). (B) 3D-image of the dendritic segment from A depicting intracellular SP clusters (yellow). (C) An electron microscope image of a SA (arrow) in a wild-type (SP-expressing) mouse. Note that the SA (arrow) is composed of stacks of endoplasmic reticulum cisterns stacked together by dense material which is immunopositive for SP (Deller et al., 2003). ER cisterns of the SA are connected to the network of dendritic smooth endoplasmic reticulum. (D) Spines in SP-deficient mice lack the SA indicating that SP is essential for assembling the SA organelle (Deller et al., 2003). (E) Expression of GFP-tagged SP rescued the formation of the SA in SP-deficient neurons in organotypic slice culture preparations (Vlachos et al., 2013). Scale bar: A, B: 1 μm, C, D, E: 0.2 μm. (A, B – from Bas Orth et al., 2005 (copyright (2005) Wiley-Liss, Inc.); C, D – from Deller et al., 2003 (copyright (2003) National Academy of Sciences, U.S.A.); E – from Vlachos et al. (2013)). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)