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Correlated Synaptic Inputs Drive Dendritic Calcium Amplification and Cooperative Plasticity during Clustered Synapse Development

Highlights

- Synaptic NMDAR activation triggers CICR during early postnatal synapse formation
- NMDAR-CICR coupling controls Ca^{2+} dynamics in space and time
- Correlated inputs drive local cooperative spine plasticity via NMDAR-CICR coupling
- Synapse maturation is clustered along dendrites of CA1 pyramidal cells

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In Brief

Lee et al. show that NMDAR activation triggers CICR exclusively during spine synapse development in CA1 pyramidal cells. This calcium amplification mechanism selects for specific input features along dendrites and spatially regulates synaptic plasticity, likely to shape microscale connectivity patterns of emerging neural circuits.

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Correlated Synaptic Inputs Drive Dendritic Calcium Amplification and Cooperative Plasticity during Clustered Synapse Development

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SUMMARY

The mechanisms that instruct the assembly of fine-scale features of synaptic connectivity in neural circuits are only beginning to be understood. Using whole-cell electrophysiology, two-photon calcium imaging, and glutamate uncaging in hippocampal slices, we discovered a functional coupling between NMDA receptor activation and ryanodine-sensitive intracellular calcium release that dominates the spatiotemporal dynamics of activity-dependent calcium signals during synaptogenesis. This developmentally regulated calcium amplification mechanism was tuned to detect and bind spatially clustered and temporally correlated synaptic inputs and enacted a local cooperative plasticity rule between coactive neighboring synapses. Consistent with the hypothesis that synapse maturation is spatially regulated, we observed clustering of synaptic weights in developing dendritic arbors. These results reveal developmental features of NMDA receptor-dependent calcium dynamics and local plasticity rules that are suited to spatially guide synaptic connectivity patterns in emerging neural networks.

INTRODUCTION

Neural circuit function is tied to the organization of synaptic connectivity between constituent neurons. At the macroscopic level, targeted projections between major brain regions serve as general routes for information flow in the brain. At the level of local circuits, such as in the hippocampus, stereotyped patterns of connectivity also exist to support specialized roles in information processing (Buzsáki and Moser, 2013). Interestingly, recent work has begun to reveal structured connectivity patterns at yet a finer level, along individual dendrites of pyramidal neurons (Druckmann et al., 2014; Kleindienst et al., 2011; Makino and Malinow, 2011; Winnubst et al., 2015). Such microscale features of synaptic connectivity merge with a growing literature on dendritic computation describing nonlinear mechanisms of synaptic integration that depend on the spatial organization of synaptic input along dendrites (London and Häusser, 2005; Major et al., 2013). These dendritic boosting mechanisms enhance the throughput of spatially clustered synaptic activity (Losonczy and Magee, 2006; Mel, 1993; Polsky et al., 2004) and are thought to enhance the computational power of individual neurons (Poirazi and Mel, 2001). Remarkably, recent studies have shown that these dendritic nonlinearities occur during sensory processing in vivo (Lavzin et al., 2012; Palmer et al., 2014; Sheffield and Dombeck, 2015; Smith et al., 2013). One important line of questioning pertains to how neural circuits establish the fine-scale patterns of synaptic connectivity required for these nonlinear forms of integration.

During the first postnatal weeks in the rodent hippocampus, pyramidal neurons develop elaborate dendritic arbors and establish synaptic connections at thousands of dendritic spines (Lohmann and Kessels, 2014). This critical developmental stage offers a prime opportunity for local plasticity mechanisms (Govindarajan et al., 2011; Harvey and Svoboda, 2007; Kleindienst et al., 2011; Makino and Malinow, 2011; Winnubst et al., 2015) to shape the spatial organization and fine-scale patterning of synaptic connectivity in emerging neural circuits. Here, we describe the spatial and temporal features, activation parameters, and developmental profile of a novel local plasticity mechanism mediated by noncanonical NMDA receptor (NMDAR)-dependent calcium signals. Using whole-cell electrophysiological recordings combined with two-photon calcium imaging and glutamate uncaging at CA1 pyramidal neurons, we observed robust spatial and temporal transformations of synaptic calcium signals during spine synapse development. In sharp contrast to triggering the compartmentalized calcium signals commonly observed at spines from older neurons (Koester and Sakmann, 1998; Mainen et al., 1999; Oertner et al., 2002; Sabatini et al., 2002; Yuste and Denk, 1995), we found that NMDAR activation at spines from younger neurons triggered calcium signals that spread locally in dendrites and invaded neighboring spines. These spreading calcium signals involved ryanodine receptor-dependent calcium-induced calcium release (CICR) and were