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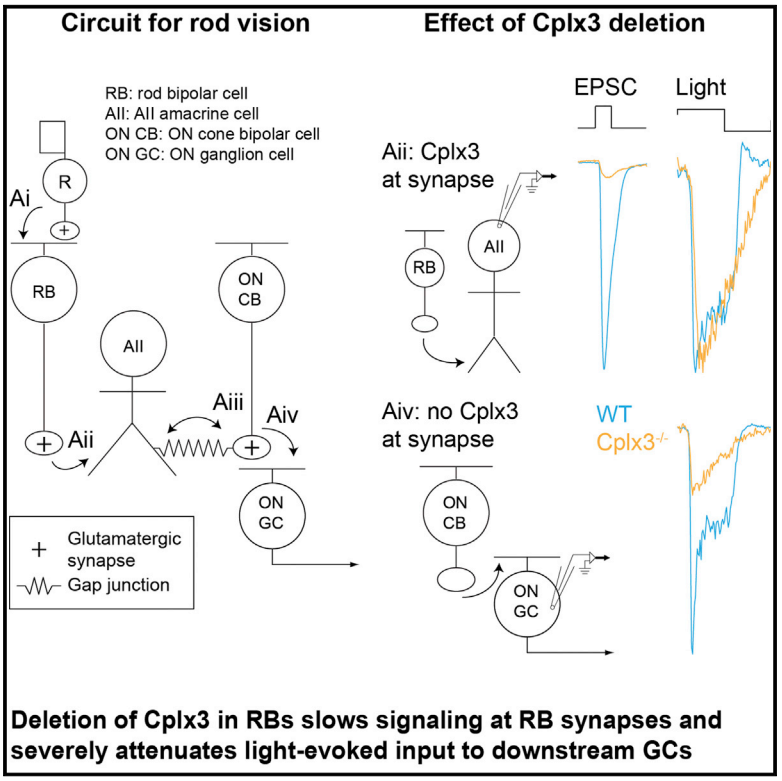
Complexin 3 Increases the Fidelity of Signaling in a Retinal Circuit by Regulating Exocytosis at Ribbon Synapses

Graphical Abstract



Deletion of Cplx3 in RBs slows signaling at RB synapses and severely attenuates light-evoked input to downstream GCs

Highlights

- Cplx3 boosts fast phasic transmitter release while suppressing asynchronous release
- Transmission at rod bipolar cell ribbon synapses is sluggish in absence of Cplx3
- Sustained depolarization of postsynaptic interneurons degrades light-evoked signaling

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In Brief

Mortensen et al. link complexin-3-dependent synaptic dynamics at rod bipolar cell ribbon synapses to downstream retinal circuit function during rod-mediated vision. In the absence of complexin 3, enhanced asynchronous release from rod bipolar cells depolarizes the postsynaptic network and hinders transmission at synapses onto retinal ganglion cells.

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Complexin 3 Increases the Fidelity of Signaling in a Retinal Circuit by Regulating Exocytosis at Ribbon Synapses

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SUMMARY

Complexin (Cplx) proteins modulate the core SNARE complex to regulate exocytosis. To understand the contributions of Cplx to signaling in a well-characterized neural circuit, we investigated how Cplx3, a retina-specific paralog, shapes transmission at rod bipolar (RB)→AII amacrine cell synapses in the mouse retina. Knockout of Cplx3 strongly attenuated fast, phasic Ca^{2+}-dependent transmission, dependent on local [Ca^{2+}] nanodomains, but enhanced slower Ca^{2+}-dependent transmission, dependent on global intraterminal [Ca^{2+}] ([Ca^{2+}]$_I$). Surprisingly, coordinated multivesicular release persisted at Cplx3$^{-/-}$ synapses, although its onset was slowed. Light-dependent signaling at Cplx3$^{-/-}$ RB→AII synapses was sluggish, owing largely to increased asynchronous release at light offset. Consequently, propagation of RB output to retinal ganglion cells was suppressed dramatically. Our study links Cplx3 expression with synapse and circuit function in a specific retinal pathway and reveals a role for asynchronous release in circuit gain control.

INTRODUCTION

Neural circuit function depends critically on mechanisms that link presynaptic depolarization to the postsynaptic response. A key component of this process is the coupling between presynaptic Ca^{2+} influx and exocytosis (Kaeser and Regehr, 2014; Kavalali, 2015; Rizo and Xu, 2015; Schneggenburger and Rosenmund, 2015). Several proteins alter the Ca^{2+} sensitivity of exocytosis and allow one nerve terminal to sustain multiple modes of transmission, i.e., spontaneous (independent from Ca channel opening), phasic (time locked to presynaptic Ca^{2+} influx), and asynchronous (driven by residual [Ca^{2+}]$_I$ after closure of Ca channels) (Kaeser and Regehr, 2014; Kavalali, 2015; Schneggenburger and Rosenmund, 2015).

Understanding the functions of proteins that modulate exocytosis is critical in assessing contributions of these transmission modes to synaptic signaling. The complexin (Cplx) family of proteins apparently contributes to the diversity of exocytotic modes: Cplxs bind to the core SNARE complex and lower the free-energy barrier to membrane fusion, thereby increasing the efficiency of Ca^{2+}-dependent exocytosis; also, Cplxs might act as brakes on spontaneous fusion to preserve vesicles in a release-ready state (Trimbuch and Rosenmund, 2016).

We assessed the role of the retina-specific isoform Cplx3 in regulating transmitter release from rod bipolar cells (RBs), which serve as a model system for studying ribbon synapses, the specialized synapses of excitatory neurons in primary sensory structures (Matthews and Fuchs, 2010). Paired voltage-clamp recordings from presynaptic RBs and postsynaptic AII amacrine cells (AIIs) reveal multiple release modes—phasic, tonic, asynchronous, and spontaneous—in excitatory postsynaptic currents (EPSCs) recorded in AIIs (Mehta et al., 2014; Singer and Diamond, 2003). Among the known Cplxs, RBs express only Cplx3 (Landgraf et al., 2012; Reim et al., 2009; Vaithianathan et al., 2015), and in mice lacking Cplx3, we reveal the role that Cplx3 plays at RB→AII synapses and the influence that its synaptic function has on light-evoked circuit output to retinal ganglion cells (GCs) (Demb and Singer, 2015).

RESULTS

Loss of Cplx3 from RBs Severely Attenuates Phasic Exocytosis

Localized [Ca^{2+}]$_I$ changes originating from single Ca channel openings ([Ca^{2+}]$_I$ "nanodomains") evoke synchronized, phasic release from RBs (Jarsky et al., 2010). Such [Ca^{2+}]$_I$ changes