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Mobility of Calcium Channels in the Presynaptic Membrane

Highlights

- Calcium channels (VDCC) are mobile yet confined within the presynaptic membrane
- Intracellular Ca^{2+} chelation by BAPTA or EGTA reduces VDCC mobility
- Increasing VDCC surface expression by $\alpha 2\delta 1$ leaves synaptic VDCC density unaffected
- Simulations suggest mobility-dependent equalization of synaptic release probability

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In Brief

By single-molecule tracking, Schneider et al. demonstrate the dynamic organization of presynaptic calcium channel populations in hippocampal neurons. The data suggest that channel mobility promotes cooperativity of calcium influx and serves as a potential means to control vesicle release probability.

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Mobility of Calcium Channels in the Presynaptic Membrane

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SUMMARY

Unravelling principles underlying neurotransmitter release are key to understand neural signaling. Here, we describe how surface mobility of voltage-dependent calcium channels (VDCCs) modulates release probabilities (P_r) of synaptic vesicles (SVs). Coupling distances of <10 to >100 nm have been reported for SVs and VDCCs in different synapses. Tracking individual VDCCs revealed that within hippocampal synapses, ~60% of VDCCs are mobile while confined to presynaptic membrane compartments. Intracellular Ca^{2+} chelation decreased VDCC mobility. Increasing VDCC surface populations by co-expression of the α2δ1 subunit did not alter channel mobility but led to enlarged active zones (AZs) rather than higher channel densities. VDCCs thus scale presynaptic scaffolds to maintain local mobility. We propose that dynamic coupling based on mobile VDCCs supports calcium domain cooperativity and tunes neurotransmitter release by equalizing P_r for docked SVs within AZs.

INTRODUCTION

The molecular architecture of active zones (AZs) ensures the precision and adjustability of synaptic vesicle (SV) release. This involves a tight coupling of presynaptic voltage-dependent calcium channels (VDCCs) and calcium sensor proteins on docked SVs. Experimentally, differential shaping of intracellular calcium domains by chelators such as EGTA and BAPTA has been used to assess channel-sensor coupling and modeling has led to various testable hypotheses (Eggermann et al., 2012). Protein-protein interactions that directly or indirectly link VDCCs to SVs are described (Catterall, 1999; Davydova et al., 2014; Kaeser et al., 2011; Liu et al., 2011; Wong et al., 2014). However, the precise modalities of channel-sensor coupling, in particular its dynamic aspects, remain unclear. Tight coupling of 10–20 nm was uncovered for cortical GABAergic Schaffer collateral and glutamatergic cerebellar synapses (Bucurenciu et al., 2008; Schmidt et al., 2013). In this scenario, a single channel opening can trigger vesicular fusion and release probabilities (P_r) may be rather uniform as long as channels are evenly distributed within AZs and exceed the number of docked vesicles (Ermolyuk et al., 2013; Holderith et al., 2012; Scimemi and Diamond, 2012). Loose coupling of 100 nm along with higher VDCC numbers were reported for other types of synapses and probably contributes to presynaptic plasticity (Borst and Sakmann, 1996; Meinrenken et al., 2002; Vyleta and Jonas, 2014). P_r even varies considerably between synapses in single axons, i.e., for a given type of synapse. Such fluctuations can result from differences in the number of readily releasable SVs but also from synapse-specific rates of Ca^{2+} influx due to maturation- or plasticity-related differences in the subtype composition, activity state, local density, and positioning of Ca^{2+} channels (Holderith et al., 2012; Ermolyuk et al., 2012; Li et al., 2007; Reid et al., 1997).

Assuming a low to moderate density of VDCCs within AZs, we wondered whether VDCC mobility contributes to a dynamic mode of channel-sensor coupling. Using single particle tracking-photoactivated localization microscopy (sptPALM), we monitored mEOS2-tagged α1 calcium channel subunits at high spatio-temporal resolution in cultured hippocampal neurons. We found that a substantial fraction of $Ca_V2.1$ (P/Q)- and $Ca_V2.2$ (N)-type channels is mobile within presynaptic areas. We assessed various parameters for their impact on channel mobility and found that it is largely unaffected by α2δ1 subunit-mediated increase in synaptic VDCC abundance and by an acute depletion of the readily releasable pool (RRP) of SVs. In contrast, intracellular calcium chelation uncovered Ca^{2+}-dependent regulation of channel mobility. To integrate these findings, we performed computational modeling, which suggests that the interplay between channel densities, mobility, and Ca^{2+} influx