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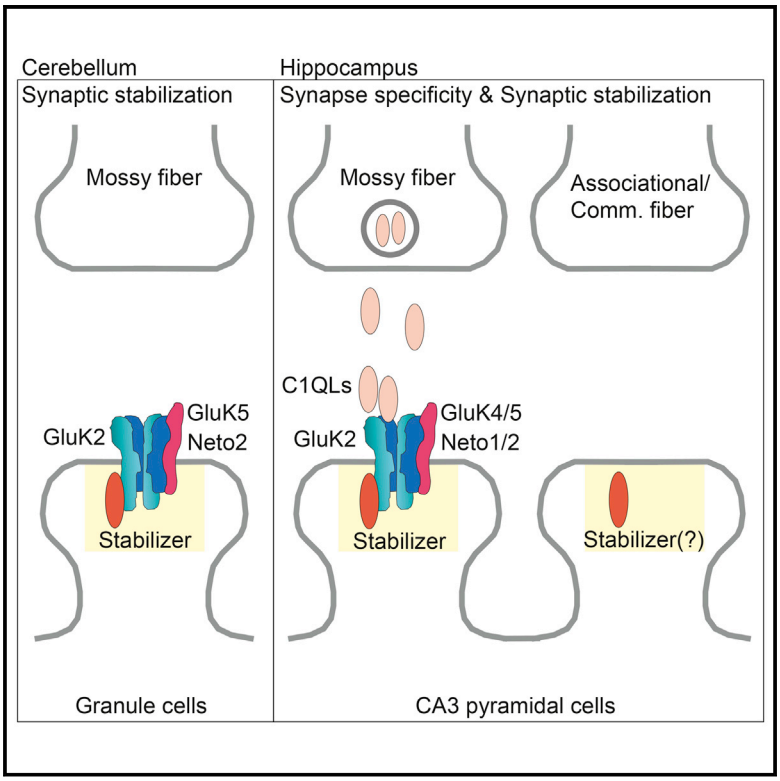
Cell Reports

Distinct Subunit Domains Govern Synaptic Stability and Specificity of the Kainate Receptor

Graphical Abstract



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In Brief

Synaptic communication between neurons requires neurotransmitter receptors to be localized precisely to the correct synapse type. Straub et al. identify two distinct mechanisms that lead to input-specific synaptic localization of the kainate receptor complex in the brain.

Highlights

- The GluK2 cytoplasmic domain mediates synaptic stabilization
- Surface kainate receptor activity depends on GluK2 but not its cytoplasmic domain
- The extracellular domain of high-affinity GluK subunits mediates synaptic specificity
- Input-specific synaptic localization of kainate receptors is mediated by two mechanisms

Straub et al., 2016, Cell Reports *16*, 531–544
July 12, 2016 © 2016
http://dx.doi.org/10.1016/j.celrep.2016.05.093

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Distinct Subunit Domains Govern Synaptic Stability and Specificity of the Kainate Receptor

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http://dx.doi.org/10.1016/j.celrep.2016.05.093

SUMMARY

Synaptic communication between neurons requires the precise localization of neurotransmitter receptors to the correct synapse type. Kainate-type glutamate receptors restrict synaptic localization that is determined by the afferent presynaptic connection. The mechanisms that govern this input-specific synaptic localization remain unclear. Here, we examine how subunit composition and specific subunit domains contribute to synaptic localization of kainate receptors. The cytoplasmic domain of the GluK2 low-affinity subunit stabilizes kainate receptors at synapses. In contrast, the extracellular domain of the GluK4/5 high-affinity subunit synergistically controls the synaptic specificity of kainate receptors through interaction with C1q-like proteins. Thus, the input-specific synaptic localization of the native kainate receptor complex involves two mechanisms that underlie specificity and stabilization of the receptor at synapses.

INTRODUCTION

Proper synaptic communication requires correct localization of neurotransmitter receptors to specific postsynaptic sites. Glutamate is the major excitatory transmitter in the vertebrate brain, and three classes of ionotropic glutamate receptors (kainate, AMPA, and NMDA) mediate the vast majority of synaptic transmission at excitatory synapses. Whereas most excitatory synapses contain AMPA- and NMDA-type receptors, kainate-type glutamate receptors (KARs) only localize to select synapses (Contractor et al., 2011; Darstein et al., 2003; Foster et al., 1981; Isaac et al., 2004; Monaghan and Cotman, 1982; Nicoll and Schmitz, 2005; Petralia et al., 1994). This restricted localization of KARs is apparent in the hippocampal stratum lucidum where mossy fiber axons projecting from dentate gyrus granule neurons form complex synapses with CA3 neurons (Castillo et al., 1997; Contractor et al., 2003; Darstein et al., 2003; Mulle et al., 1998; Petralia et al., 1994; Vignes and Collingridge, 1997). In contrast, KARs are found at all synapses in the cerebellum, where granule cells receive input from only one type of excitatory afferent, the mossy fiber (Yan et al., 2013). Mechanisms underlying these synaptic differences remain unclear.

KARs in the brain form a tripartite hetero-oligomeric complex consisting of the low-affinity GluK1–3 and high-affinity GluK4/5 KAR subunits along with Neto auxiliary subunits. Because KAR-mediated transmission is absent in primary cultured hippocampal neurons (Lerma et al., 1993), studying synapses in vivo using mouse gene-targeting approaches has been particularly useful in identifying KAR components required for synaptic localization and function. Knockout of the primary low-affinity subunit GluK2 abolishes KAR currents as well as localization of receptors (Mulle et al., 1998; Yan et al., 2013). In addition, GluK2 KO mice exhibit reduced expression of other components of the native KAR complexes, GluK4/5 and Neto1/2 (Christensen et al., 2004; Nasu-Nishimura et al., 2006; Ruiz et al., 2005; Straub et al., 2011; Zhang et al., 2009). In Neto1 KO mice, synaptic expression of KARs is unchanged at hippocampal mossy fiber-CA3 cell synapses, while the decay kinetics of the current are dramatically faster (Straub et al., 2011). In mice in which both Neto1 and Neto2 are ablated (Neto1/2 DKO) or mice in which both high-affinity subunits are knocked out (GluK4/5 DKO), KARs are reduced in the post-synaptic density (PSD) (Fernandes et al., 2009; Wyeth et al., 2014). In addition, GluK4/5 DKO mice lack KAR-mediated synaptic currents at mossy fiber synapses despite no obvious difference in the surface expression of the GluK2 subunit (Fernandes et al., 2009). Because dysregulation in multiple steps of receptor biogenesis, including protein expression, surface expression, synapse specific localization, and synaptic stabilization can affect synaptic activity of KARs, it remains unclear which components of the receptor complex contribute to synaptic stabilization and synapse-specific localization of KARs in the brain.

In this study, we used a gene-targeting approach to elucidate the mechanisms of synapse-specific localization of KARs by