Title:	Regulation of Metabotropic Glutamate Receptor Internalization and Synaptic AMPA Receptor Endocytosis by the Postsynaptic Protein Norbin
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Abstract:	Group I mGluRs have diverse functions in some fundamental neuronal processes, including modulation of synaptic plasticity; and dysregulation of these receptors could lead to various neuropsychiatric disorders. Trafficking of Group I mGluRs plays critical roles in controlling the precise spatiotemporal localization and activity of these receptors, both of which contribute to proper downstream signaling. Using “molecular replacement” approach in hippocampal neurons derived from mice of both sexes, we demonstrate a critical role for the postsynaptic density protein Norbin in regulating the ligand-induced internalization of Group I mGluRs. We show that Norbin associates with protein kinase A (PKA) through its N-terminus and anchors mGluR5 through its C-terminus, both of which are necessary for the ligand-mediated endocytosis of mGluR5, a member of the Group I mGluR family. A point mutation (A687G) at the C-terminus of Norbin inhibits the binding of Norbin to mGluR5 and blocks mGluR5 endocytosis. Finally, we demonstrate an important mechanism by which Norbin regulates mGluR-mediated AMPAR endocytosis in hippocampal neurons, a cellular correlate for mGluR-dependent synaptic plasticity. Norbin, through its PKA-binding regions, recruits PKA to AMPARs on activation of mGluRs; and deletion of the PKA-binding regions of Norbin inhibits mGluR-triggered AMPAR endocytosis. We further report that Norbin is important specifically for the mGluR-mediated AMPAR endocytosis, but not for NMDAR-dependent AMPAR endocytosis. Thus, this study unravels a novel role for Norbin in the internalization of mGluRs and mGluR-mediated AMPAR endocytosis that can have clinical relevance to the function of Group I mGluRs in pathologic processes.
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