Title:	Understanding the Role of Ubiquitination in the Constitutive Endocytosis of Group I Metabotropic Glutamate Receptors
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Abstract:	This study seeks to augment our understanding of how the activity of Group I metabotropic glutamate receptors (mGluRs) is regulated in the absence of glutamate. Trafficking of these receptors after glutamate-binding, has been extensively studied, but not much is known about their ligand-independent endocytic-trafficking. I also investigated if ubiquitination, one of the major post-translational modification, regulates constitutive endocytosis of these receptors. mGluRs are GPCRs that have the capacity to trigger several signaltransduction cascades in a cell and are major targets of GPCR-directed pharmacotherapy. Group I mGluRs are pertinent for neurodevelopment, circuit formation, synaptic plasticity, neurodegeneration and induction of reactive astrocytes. Deficiencies in these diverse functions lead to an array of neurological and neurodegenerative disorders. Compelling studies have shown that exaggerated signalling through mGluR5 lead to cognitive and syndromic features characteristic Fragile X syndrome. In fact, mGluR5 antagonists revert phenotypes of Fragile X syndrome. These receptors play a definite role in maintaining the excitation-inhibition balance in the neural circuits. Consequently, the loss of mGluR signalling can have devastating effects including inefficient synaptic plasticity, culminating in loss of learning and memory. In this study, I determined if mGluR1 and mGluR5 undergo ligand-independent (constitutive) endocytosis in the heterologous cell line, HEK293 and mouse primary hippocampal neurons. Further, I was interested to see if ubiquitination is involved in the constitutive trafficking of these receptors. My data suggest that both group I mGluRs undergo constitutive endocytosis in primary neurons and this process is regulated by ubiquitination. Upon pharmacologically inhibiting the ubiquitin activating enzyme E1, these receptors remain on the cell surface. I also observed that the mutant form of mGluR1 which lacks a critical Lysine residue at the C-terminal end, undergoes constitutive endocytosis, despite not undergoing internalization upon ligand binding. This suggests that ligand-independent endocytosis perhaps occurs through a pathway, not involved in the ligand-mediated internalisation of mGluR1. Therefore, my study adds to our understanding of the basal level endocytosis of these receptors, which is crucial for normal homeostatic brain function.
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