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Title:	A critical role of snx1 and hrs in the trafficking of metabotropic Glutamate receptor 5 (mglur5)
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Abstract:	<p>Metabotropic glutamate receptor 5(mGluR5) is a member of the group I family of metabotropic Glutamate Receptors (mGluRs) which are G-Protein Coupled Receptors (GPCRs) activated by the amino acid glutamate (the most abundant excitatory neurotransmitter in the Central Nervous System (CNS). Group I mGluRs (which consists of mGluR1 and mGluR5) have been implicated previously in various forms of synaptic plasticity including learning and memory as well as in several neuropsychiatric disorders like Fragile X Syndrome (FXS), autism etc. They are predominantly positively coupled to the Gαq-linked pathway, which generates diacylglycerol (DAG), and inositol- 1,4,5-triphosphate (IP$_3$). The normal signaling of these receptors depends on their precise positioning in specific regions of the neuron. Receptor trafficking regulates not only the spatio-temporal localization of the receptors but also their activity. Despite this obvious significance, very little is known about the cellular and molecular machineries which control the trafficking of these receptors in the CNS. Sorting Nexin 1(SNX1) which is the founding member of the sorting nexin family of proteins, is a component of the retromer complex that is involved in the retrograde transport of endocytosed cargo from the endosomes to the Trans-Golgi Network (TGN). However numerous reports have suggested that SNX1 can also control the trafficking of receptors through other pathways: SNX1 controls the lysosomal degradation of Protease-Activated Receptor 1(PAR1), Epidermal Growth Factor Receptor (EGFR) and the recycling of the P2Y$_1$ receptor. SNX1 has also been reported to interact with the cytoplasmic tails of group I mGluRs in vitro. Considering these existing literature, our lab decided to investigate the role of SNX1 in the trafficking of group I mGluRs, if any. It has been previously reported by Dr. Rohan Sharma that overexpression of dominant-negative SNX1 or knockdown of endogenous SNX1 resulted in the rapid recycling of mGluR1 and also this recycling via the rapid recycling route did not allow the resensitization of the receptor. However whether SNX1 plays any role in the trafficking of the other member of the group I mGluR family, mGluR5 has not been investigated yet. Work done in GPCRs in the past few decades has taught us that every GPCR is unique and not a single GPCR can serve as a model for all GPCRs. The work presented in this thesis shows that absence of SNX1 does not yield any significant endocytosis of mGluR5 at 30 min post ligand application. However whether this observed absence in endocytosis is due to a block in endocytosis of mGluR5 or due to the fast recycling of these receptors (as observed in the case of mGluR1) is subject to further investigation. It has also been reported previously that SNX1 regulates the trafficking of mGluR1 through the interaction with Hrs (hepatocyte growth factor-regulated tyrosine kinase substrate), a protein that has been implicated in both signaling and vesicular trafficking of endocytosed cargo proteins. I have designed the shRNA against Hrs to study the role of Hrs, if any, in the ligand-mediated trafficking of mGluR5. The role of Hrs in the trafficking of mGluR5 will be investigated in future.</p>
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