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Toward a Better Understanding of…

PSD95 Translation Is Differentially Regulated by Cell Surface Versus Intracellular mGluR5 in Striatal Neurons

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Metabotropic glutamate receptor 5 (mGluR5) is a glutamate-activated, G-protein-coupled receptor that plays an important role in neuronal development, synaptic plasticity, learning, and memory. Recently, mGluR5 has been shown to oppose the Fragile X Mental Retardation protein, FMRP, which functions as an mRNA translational suppressor. Most studies so far focused on the role of cell surface mGluR5. However, up to 90% of mGluR5 is intracellular, located on either the endoplasmic reticulum or nuclear membrane. We have shown that active intracellular mGluR5 generates unique cellular responses in striatal neurons, inducing long, sustained Ca\textsuperscript{2+} responses leading to the activation of MEK-extracellular signal-regulated kinase (ERK1/2) pathways. Other signaling pathways downstream of mGluR5 activation implicate the mammalian target of rapamycin (mTOR) cascade, which controls initiation of cap-dependent translation. Growing evidence indicates that dysregulation of the mTOR signaling cascade is associated with human diseases, including cancer, diabetes, autism, and Fragile X Syndrome. Previously, the mTOR pathway studies have only examined the role of cell surface mGluR5; this study shows that both cell surface and intracellular mGluR5 lead to the activation of the PI3K-Akt-mTOR-S6K pathway in striatal neurons. In addition, eukaryotic elongation factor 2 (eEF2) which modulates the elongation step of protein synthesis is also phosphorylated by both cell surface and intracellular mGluR5. The focus of this research is an important mTOR and MEK target postsynaptic density protein 95 (PSD95), a scaffolding protein that forms clusters of receptors or ion channels at post-synaptic sites. PSD95 is upregulated by intracellular but not cell surface mGluR5 in striatal neurons. The mGluR5-induced upregulation of PSD95 is MEK-ERK and translation-dependent but PI3K-Akt-mTOR-S6K and transcription-independent. In summary, these studies suggest a major role for intracellular mGluR5 in the regulation of synaptic plasticity, and might lead to novel strategies for disorders such as Fragile X syndrome, anxiety, addiction, and Parkinson disease.