Cuauhtemoc Ulises Gonzalez

Mimicking neuronal synapse cell-cell contacts in HEK cells leads to ligand-induce activity in orphan Delta receptors

Ionotropic glutamate delta receptors are neuronal membrane receptors that have been implicated in multiple motor and neurocognitive functions such as ataxia, autism, schizophrenia, and retarded speech. Delta receptors belong to the family of ligand-activated ionotropic glutamate receptors. However, unlike its family members, Delta receptors have not been shown to evoke ligand-induced currents and have been thought to be primarily structural elements. Delta receptors are localized in the postsynaptic membrane and have been found to make junction with the presynaptic membrane through interactions with soluble extracellular protein, cerebellin (Cbln), which in turn binds to presynaptic membrane protein, Neurexin1β. Interruption of this interaction leads to a decrease in synaptic long-term depression which is thought to be due to the loss of structural integrity. We show that Delta receptors can be activated by glycine and D-serine and that this opening of ion channel is stabilized through cell-to-cell interactions with Cbln and NRXN1β. Furthermore, we have established that this is due to Neurexin1β and Cbln acting as biological cross-linkers by holding the extracellular domains together, thus allowing for efficient transfer of the ligand-binding conformational changes towards the transmembrane segments and inducing channel opening. This was further verified using chemical linkers at the amino-terminal domain. Together, these findings conclude Delta receptors have a role as ligand-induced channels in neurons and presents opportunities in developing drugs that can modulate this activity directly.