

Agonist-receptor Interactions and Conformational Changes in the GluR6 Ligand Binding Domain

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Recent crystal structures of the isolated ligand binding domain of the kainite receptor subunits have shown that it undergoes a graded cleft closure conformational change upon agonist binding to the protein, with the extent of cleft closure correlating to the efficacy of the agonist. At this time, however, there is no structure available for the apo state of the kainite receptor subunit and the structures for the antagonist bound forms show varying degrees for the cleft opening. Hence, the extent to which the cleft is open in the resting state, and therefore the extent of cleft closure conformational change due to agonist binding relative to the apo state, is still largely unknown. We have used a fluorescence resonance energy transfer (FRET) based method to determine the distance between domain 1 and domain 2 in the apo, and various agonists bound states of the GluR6 subunit of the receptor and thus established the extent of cleft closure due to agonist binding to this protein relative to the apo state. We have also investigated the agonist:protein interactions using Fourier transform infrared spectroscopy and established that the interactions at the amine group of the agonist is correlated to the extent of activation. These studies show that the kainite receptors not only have similar conformational changes as that observed for the AMPA receptor subtype of the glutamate receptors, they are also similar at the level of chemical interactions that control the extent of activation.