ABSTRACT

G protein-coupled receptors (GPCRs) have long been recognized as essential membrane receptors mediating a vast array of functions in eukaryotes. GPCRs have more complex signaling than originally envisioned due to the fact that GPCRs can associate to form homomeric complexes or associate with other GPCRs to form heteromeric complexes. Allosteric communication within complexes influences the range of receptor function. Cannabinoid receptor 1 (CB1) and dopamine receptor 2 long (D2L) are GPCRs that are co-localized in specific neuronal populations in the basal ganglia. These receptors play crucial roles in the coordination of movement. I hypothesized that CB1 and D2L receptors associate in heteromeric complexes and that CB1 and D2L ligands promote bidirectional allosteric interactions within heteromeric complexes. I confirmed that CB1 and D2L receptors form homodimers and that each homodimer was coupled to a Gαi protein. CB1 and D2L receptors formed higher order oligomeric complexes; the minimum functional heteromeric complex was composed of a CB1 and D2L homodimer each coupled to a Gαi protein. Activation of either CB1 or D2L receptors by the agonists, arachidonyl-2-chloroethylamide (ACEA) or quinpirole, respectively, resulted in fast and transient conformational changes among CB1, D2L and Gαi proteins indicative of receptor activation. Treating cells co-expressing CB1 and D2L receptors with both ACEA and quinpirole switched CB1 and D2L receptors coupling and signaling from Gαi to Gαs, enhanced β-arrestin1 recruitment and co-internalization. The high-affinity D2L receptor antagonist, haloperidol, was also able to switch CB1 coupling from Gαi to Gαs but, unlike D2L agonists, haloperidol inhibited β-arrestin1 recruitment to CB1 and inhibited complex internalization. Allosteric interactions within CB1/D2L heteromers were ligand dose-dependent and bidirectional. CB1/D2L heteromers were detected in the globus pallidus of C57BL/6J mice. Chronic exposure to the cannabinoid CP 55,940 increased CB1/D2L heteromers while the D2 antagonist haloperidol reduced CB1/D2L heteromers in the globus pallidus of C57BL/6J mice indicating that functional heteromers existed in vivo and were affected by chronic drug exposure. The concept of bidirectional allosteric interaction within CB1/D2 heterotetramers has significant implication for the understanding of the complex physiology and pharmacology of CB1 and D2L receptors.