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Endogenous lipid activated G protein-coupled receptors: Emerging structural features from crystallography and molecular dynamics simulations

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ABSTRACT

Class A G-protein coupled receptors (GPCRs) are thought to have a common topology that includes seven transmembrane alpha helices (TMHs) that are arranged to form a closed bundle. This bundle forms the ligand binding pocket into which ligands are commonly thought to enter via the extracellular milieu. This ligand approach direction makes sense for GPCRs that have small positively charged ligands, such as the beta-2-adrenergic or the dopamine D2 receptor. However, there is a growing sub-group of Class A GPCRs that bind lipid-derived endogenous ligands, such as the cannabinoid CB_1 and CB_2 receptors (with endogenous ligands, N-arachidonoylethanolamine (anandamide) and sn-2-arachidonylglycerol (2-AG)) and the $S1P_{1-5}$ receptors (with endogenous ligand, sphingosine-1-phosphate). Even the widely studied Class A GPCR, rhodopsin, binds a highly lipophillic chromophore (11-cis-retinal). For these receptors, ligand approach from the extracellular milieu has seemed unlikely given that the ligands of these receptors readily partition into lipid or are actually synthesized in the lipid bilayer. The recent X-ray-crystal structure of the sub-type 1 sphingosine-1-phosphate receptor ($S1P_1$) provides important information on the key structural variations that may be the hallmarks for a Class A GPCR that binds lipid-derived ligands. These include an extracellular domain that is closed off to the extracellular milieu and the existence of an opening between transmembrane helices that may serve as a portal for ligand entry via the lipid bilayer. This review examines structural aspects that the cannabinoid receptors may share with the $S1P_1$ receptor based upon sequence homology. This review also examines experimental and simulation results that suggest ligand entry via a lipid portal is quite likely for this emerging sub-group.

G protein-coupled receptors (GPCRs) are integral membrane proteins that serve as very important links through which cellular signal transduction mechanisms are activated. Class A GPCRs (rhodopsin-like) are thought to have a common topology that includes seven transmembrane alpha helices (TMHs) that are arranged to form a closed bundle. This bundle forms the ligand binding pocket into which ligands are commonly thought to enter via the extracellular milieu. This ligand approach direction makes sense for GPCRs that have small positively charged ligands, such as the beta-2-adrenergic or the dopamine D2 receptor. However, there is a growing sub-group of Class A GPCRs that bind lipid-derived endogenous ligands, such as the cannabinoid CB_1 and CB_2 receptors (Devane et al., 1988; Munro et al., 1993) (with endogenous ligands, N-arachidonoylethanolamine (anandamide) (Devane et al., 1992) and sn-2-arachidonylglycerol (2-AG))(Mechoulam et al., 1995) and the $S1P_{1-5}$ receptors (Chun, 1999, 2005; Chun et al., 1999, 2000; Sanchez and Hla, 2004; Zhang et al., 1999) (with endogenous ligand, sphingosine-1-phosphate) (Choi et al., 2011; Graler, 2010; Hla and Brinkmann, 2011). Even the widely studied Class A GPCR, rhodopsin, binds a highly lipophillic chromophore (11-cis-retinal) (Palczewski et al., 2000). For these receptors, ligand approach from the extracellular milieu has seemed unlikely given that the ligands of these receptors readily partition into lipid or are actually synthesized in the lipid bilayer.

The recent X-ray-crystal structure of the sub-type 1 sphingosine-1-phosphate receptor ($S1P_1$) (Hanson et al., 2012) provides important information on the key structural variations that may be the hallmarks for a Class A GPCR that binds lipid-derived ligands. These include an extracellular domain that is closed off to the extracellular milieu and the existence of an opening between transmembrane helices that may serve as a portal for ligand entry via the lipid bilayer. This review examines structural aspects that the cannabinoid receptors may share with the $S1P_1$ receptor based upon sequence homology. This review also examines experimental and simulation results that suggest ligand entry via a lipid portal is quite likely for this emerging sub-group.

Abbreviations: MD, molecular dynamics; 2-AGPI, 2-arachidonoyl-sn-glycero-3-phosphoinositol; POPC, 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine; AEA, N-arachidonoylethanolamine; TMH, transmembrane helix; GPCR, G protein-coupled receptor; EDG, endothelial differentiation gene; LPA, lysophosphatidic acid; S1P, spinghosine-1-phosphate.

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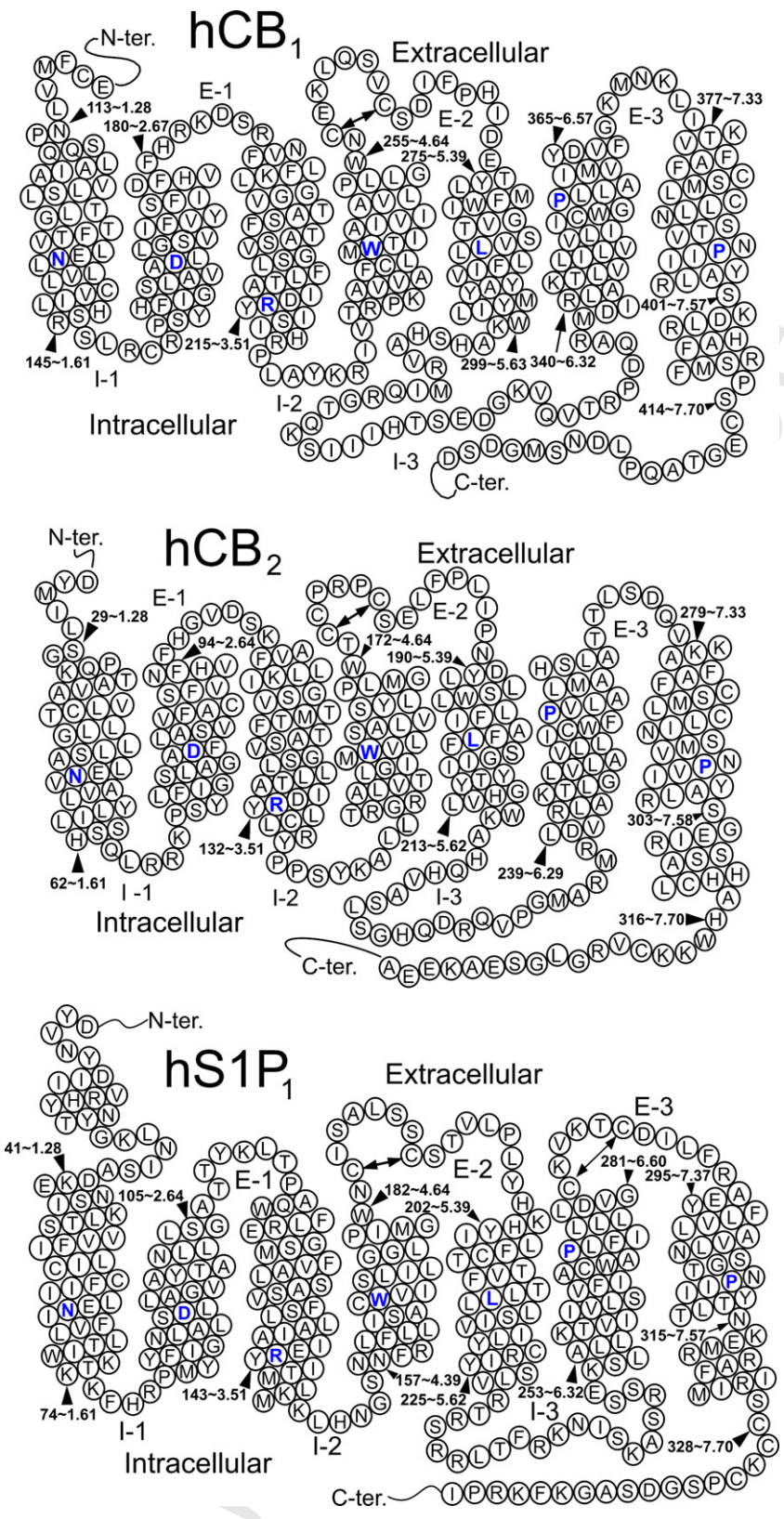

Fig. 1. The sequences of the human CB_1, CB_2 and $S1P_1$ receptors are illustrated here in helix net diagrams.

1. Cannabinoid receptors: ligands and signalling

1.1. CB_1 receptor

The cannabinoid CB_1 and CB_2 receptors (see Fig. 1) belong to the Class A (rhodopsin (Rho) family) of G-protein coupled receptors (GPCRs). CB_1 was initially cloned from a rat cerebral cortex cDNA library (Matsuda et al., 1990) and early sequence analyses revealed that this receptor had highest homology with the endothelial differentiation gene (EDG) receptor family (now split into the lysophosphatidic acid (LPA) receptors and the

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