Prolonged signaling of backbone-modified glucagon-like peptide-1 analogues with diverse receptor trafficking

Brian P. Cary,[1,2,3]

[1]Department of Chemistry, University of Wisconsin − Madison, 1101 University Avenue, Madison, Wisconsin 53706, United States [2]Drug Discovery Biology Theme, Monash Institute of Pharmaceutical Sciences, Monash University, Parkville, Victoria, Australia. [3]ARC Centre for Cryo-Electron Microscopy of Membrane Proteins, Monash Institute of Pharmaceutical Sciences, Monash University, Parkville, Victoria, Australia

The glucagon-like peptide-1 (GLP-1) receptor, an important target for the treatment of type 2 diabetes and obesity, signals at the cell surface and from intracellular compartments. Here, we present two GLP-1 analogues with increased cyclic-AMP signaling duration compared to the native hormone. Both analogues bind the receptor with higher affinity than GLP-1. Despite similarly elevated affinities and cAMP activities, the two analogues show markedly different abilities to induce intracellular receptor trafficking. Structure-activity relationship studies show that a cyclic-beta amino acid at position 18 is critical for the prolonged signaling behavior we observed. Cryo-electron microscopy and molecular dynamics simulations analysis reveals structural details of the interactions between the ligands and full-length receptor.