Supplemental Information Guide.In

Supplemental Table 1. CryoEM data collection, refinement and model parameters

Supplemental Table 2. Effect of GLP-1R mutations on cell surface expression and cAMP signalling.

Supplemental Table 3. GLP-1R systems prepared for MD and simulated in the present work.

Supplemental Data Video 1. Different hydration of polar networks within the GLP-1R transmembrane (TM) domain. In the GLP-1R:TT-OAD2 Gs complex (left), structural water molecules form stable hydrogen bonds with the N320$^{5.50}$ side chain and the Y241$^{3.44}$ backbone atoms as well with E364$^{6.53}$. The bound GLP-1 (right) stabilizes a water molecule network in the proximity of the peptide N-terminal residues H7 and A8 as well of Y152$^{1.47}$, T391$^{7.46}$, R190$^{2.60}$, E364$^{5.53}$.

Supplemental Data Video 2. TT-OAD2 interactions lead to reorganisation and stabilisation of the central polar network via a distinct mechanism to GLP-1. The GLP-1R:TT-OAD2 interactions modify the hydrogen bond network between TM1 and TM2. Left; GLP-1 (brown ribbon representation) residue 3 (D^{9}) (white stick) forms an ionic interaction (red dotted lines) with R190$^{2.60}$, which is involved in key hydrogen bonds with N240$^{3.43}$ (in turn interacting with S186$^{2.56}$). At the top of TM2, K197$^{2.67}$, D198$^{2.68}$, and Y145$^{1.40}$ are stabilized in polar interactions (red dotted lines). Right; The TT-OAD2 (brown stick and transparent van der Waals surface) binding triggers the reorganization of the interaction network at the top of TM1 and leads the Y148$^{1.43}$ and Y152$^{1.47}$ to make contact and form hydrogen bond interactions with the R190$^{2.60}$. The ECL3 of the GLP-1R:TT-OAD complex was removed for clarity.