Intracellular loop 2 (ICL2) connecting transmembrane helices III and VI is the most conserved intracellular loop of the rhodopsin family of GPCRs with respect to length. This intracellular region has been shown to contain binding determinants for β-arrestin, Gα and GRK2. Its importance in GPCR function is further highlighted by human pathologies caused by point mutations within ICL2 in GPR54, vasopressin V2 receptor and the melanocortin 1 receptor.

Crystallographic data have demonstrated the potential of ICL2 to adopt multiple conformations. Crystal structures of the β1AR and the A2A R first demonstrated α-helical portions of ICL2 whereas the β2AR adopted an L-shaped conformation. It has been suggested that an α-helix conformation of ICL2 is associated with the ability to bind β-arrestin and that in general, GPCRs are able to adopt both conformations with varied probability. This dynamic character is highlighted by the dopamine D3 receptor, where ICL2 of only one unit of the asymmetric dimer is resolved indicating structural flexibility in the other.

The role of ICL2 in the structure and function of the vasopressin V1a receptor (V1a R) was investigated using a systematic site-directed mutagenesis approach. Mutant receptor constructs were pharmacologically characterised with respect to agonist and antagonist binding. Signalling capability and cell-surface expression were quantified by inositol phosphates dose-response and ELISA respectively. Together these data indicate the role of key residues of ICL2 in the structure and function of the V1a R.