Bioinformatic analyses have highlighted an overrepresentation of intrinsic disorder in the intracellular domains of membrane proteins. We have addressed the role of intrinsic disorder in two membrane proteins, the human sodium-proton exchanger 1 (NHE1), a 12 TM-helix protein and the human prolactin receptor (PRLR), which has a single-pass TM-helix. NHE1 and PRLR contain long (<300 residues) intracellular domains (ICD) implicated in regulatory functions involving phosphorylation as well as a number of protein-protein interactions. Sparse structural information is available on the ICDs. We have characterized their membrane proximal and membrane distal parts separately and show that these long C-terminal tails are highly disordered. We have applied conservation analysis to pinpoint basal functional sites. For NHE1 we show that knock-out of one common transient helix identified from NMR chemical shifts analyses and located in proximity to a sequence motif identical in all species, retain NHE1 in the ER. For both proteins we observe distinct differences in their functional roles relative to the proximity to the membrane. For the membrane proximal parts, both proteins show specificity for lipids characteristic of the inside of the plasma membrane. This suggests a regulatory cross-talk between the membrane and the membrane protein.