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TITLE

HUMAN MEMBRANE GUANYLATE CYCLASES: UNDERSTANDING THE STRUCTURAL BASIS OF RECEPTOR-LIGAND INTERACTIONS AND APPROACHES TO DRUG DESIGN

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Membrane guanylate cyclases (GCs) are multifunctional transmembrane receptor proteins that respond to extracelluar stimuli by synthesis of cGMP. So far, seven different GCs, GC-A to GC-G, were identified in humans. GC-C, for example, is a key regulator of electrolyte concentration in the intestine, the kidneys, and pancreas, and GC-C, like many other, if not all, GCs, is the target of peptide hormones. The GC-C ligands are guanylin (GN) and uroguanylin (UGN). In addition, GC-C is targeted by heat stable toxin STa from enterotoxigenic E. coli (ETEC). Binding of either ligand leads to cGMP-dependent inhibition of Na^+/H^+ exchange and activation of the cystic fibrosis transmembrane conductance regulator. In comparison to the endogenous peptide hormones GN and UGN, however, STa binds to GC-C about two orders of magnitude more tightly and, as an effect, causes diarrhea that is manifested as traveler's disease in industrialized nations but is a major cause of child deaths in developing countries, with nearly 400 thousand victims aged 5 or younger per year according to WHO estimates. We are currently studying the conformation of the GC-C ligands GN, UGN, and STa, the conformation of their prohormones as well as the conformation of the extracelluar domain of GC-C, mainly using nuclear magnetic resonance (NMR) and fluorescence spectroscopy. The major aim of our research is to understand the interactions of the ligands with the receptor in atomic detail and use this knowledge as a basis for the rational design of STa antagonists and scavengers.