Pharmacology of the guanylate cyclase-C agonist Linaclotide

Linaclotide is a 14-amino acid, minimally bioavailable peptide agonist of Guanylate Cyclase-C (GC-C) approved for treatment of adult patients with Irritable Bowel Syndrome with Constipation and Chronic Idiopathic Constipation. Linaclotide stimulation of GC-C expressed on the intestinal epithelium initiates signaling pathways resulting in improvement of spontaneous bowel movement and symptoms of abdominal pain. The effect of linaclotide on bowel movements is hypothesized to be a result of increased fluid secretion mediated by elevated intracellular cGMP levels following linaclotide binding to GC-C. Previous studies in enterocytes demonstrate that cGMP activates PKGII, leading to phosphorylation of CFTR and NHE3, both located on the apical membrane of enterocytes. PKGII phosphorylation alters the activity and cellular localization of both transporters and results in increased intraluminal concentrations of Cl⁻, HCO3⁻ and Na⁺ ions, generating an electrolyte gradient that drives the passive efflux of water into the lumen, thereby accelerating transit. The effects of linaclotide on abdominal pain are hypothesized to be mediated by extracellular cGMP, which decreases the activity of pain-sensing nerves in nonclinical models. Linaclotide stimulation of rat colonic mucosa induces cGMP efflux from both the apical and the basolateral membrane. Efflux of cGMP from the apical membrane is mediated by Multidrug Resistance Protein 4 (MRP4). Inhibition of MRP4-dependent cGMP efflux by MK571 results in accumulation of intracellular cGMP and increased transepithelial ion current, induced by linaclotide. In summary, these data suggest the presence of a novel, previously unrecognized mechanism that functionally couples the secretory GC-C/cGMP pathway to spatially restricted modulation by apical MRP4.

Biography

Boris Tchernychev received his MSc degree in Biophysics from the Department of Biology of Moscow State University. After completing his PhD in Biochemistry at the Weizmann Institute of Science and his Post-doctoral training in the laboratory of B Furie (Beth Israel Deaconess Medical Center), he joined the biotech industry where he spent the last 10 years supporting multiple drug discovery and development programs in different therapeutic areas. At present, he is a Principal Investigator at Ironwood Pharmaceuticals, where his research is focused on further understanding the secretory and pain inhibitory mechanisms of the FDA-approved drug LINZESS (Guanylate Cyclase-C agonist linaclotide).

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