Therapeutic potential of allosteric modulators for the treatment of gastrointestinal motility disorders.

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Abstract

Gastrointestinal motility is tightly regulated by the enteric nervous system (ENS). Disruption of coordinated ENS activity can result in dysmotility. Pharmacological treatment options for dysmotility include targeting of G protein-coupled receptors (GPCRs) expressed by neurons of the ENS. Current GPCR-targeting drugs for motility disorders bind to the highly conserved endogenous ligand binding site and promote indiscriminate activation or inhibition of the target receptor throughout the body. This can be associated with significant side-effect liability and a loss of physiological tone. Allosteric modulators of GPCRs bind to a distinct site from the endogenous ligand, which is typically less conserved across multiple receptor subtypes and can modulate endogenous ligand signalling. Allosteric modulation of GPCRs that are important for ENS function may provide effective relief from motility disorders while limiting side-effects. This review will focus on how allosteric modulators of GPCRs may influence gastrointestinal motility, using 5-HT, ACh, and opioid receptors as examples.

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