Function and regulation of serotonin receptors mediating peristalsis in the normal and inflamed colon.

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Abstract

Chronic digestive disorders such as Inflammatory Bowel Disease (IBD) and Irritable Bowel Syndrome (IBS) are associated with alterations in key elements of serotonin (5-HT) signaling pathways in the gastrointestinal tract, and 5-HT3 and 5-HT4 receptors represent the most effective targets for the treatment of functional gastrointestinal disorders. While much is known about how serotonergic agents affect gut function, critical gaps in our knowledge have limited the ability to develop safe and effective strategies involving 5-HT4 agonists for the treatment of constipation, as well as precluded our understanding of how inflammation-induced changes in 5-HT signaling affect peristaltic reflex activity. The objectives of this research proposal are to elucidate the mechanisms by which 5-HT4 agonists promote colonic propulsive motility and to test whether 5-HT receptor expression and function are altered by intestinal inflammation. The hypotheses to be tested in the proposed studies are (1) that 5-HT4 receptors promote motility by activating 5-HT release from enterochromaffin cells in the mucosal layer of the colon, and (2) increased bioavailability of 5-HT resulting from intestinal inflammation leads to a compensatory downregulation of 5-HT receptors, resulting in decreased peristaltic activity in the inflamed region. In Specific Aim 1, we will use a motility assay, intracellular recording, RT-PCR, and amperometry to test whether peristaltic activity can be triggered and enhanced by activation of 5-HT4 receptors in the colonic mucosa. Previous studies have established that 5-HT levels are increased in the mucosa of the inflamed colon, but nothing is known about the resulting impact on 5-HT receptors. In Specific Aim 2, we will use two models of intestinal inflammation, TNBS and Citrobacter rodentium, to determine if inflammation, and the associated elevation in 5-HT, leads to decreased expression of 5-HT receptors in the colonic mucosa. We will also test whether altered 5-HT receptor expression contributes to the changes in propulsive motility previously documented in colitis. Additionally, we will test whether site-specific administration of 5-HT4 receptor agonists can restore function in the inflamed colon. These studies will contribute new knowledge regarding the roles of 5-HT receptors in normal and disordered gastrointestinal motility, and yield valuable information regarding potential pharmacotherapeutic strategies to facilitate the peristaltic reflex in chronic digestive disorders.