Mucosal 5-HT4 Receptors: A Novel Therapeutic Target in Colitis

We have previously shown that 5-HT4 receptors are expressed in colonic epithelium, and 5-HT4 agonists produce physiological responses such as mucus secretion from goblet cells, chloride secretion from enterocytes, and serotonin release from enterochromaffin cells. These responses may have protective actions in the colon in conditions like colitis. To test this hypothesis, we induced colitis in CD-1 mice using 4% DSS (w/v) in drinking water or a single enema of TNBS (7.5mg/mL in 50% ethanol) and treated mice with the 5-HT4 receptor agonist, Tegaserod (1mg/kg), Tegaserod plus the 5-HT4 antagonist, GR113808, or vehicle. Animals were treated during (days 1-7) or following (days 7-15) the development of colitis. To test the effect of this treatment on propulsive motility, TNBS treated guinea pigs were administered tegaserod on days 1-7, and distal colon motility and inhibitory junction potentials (IJPs) were measured. Inflammation was evaluated by Disease Activity Index (DAI), Macroscopic Damage Scores (MDS), and histological damage scores. We found that treatment with Tegaserod reduced the severity of colitis in the 7d DSS model compared to vehicle treated inflamed animals as measured by DAI (p<0.05), MDS (p<0.01) and H&E scores (p<0.001), and we were able to block these effects with GR113808. In the 15d paradigm, recovery from colitis was accelerated. Furthermore, Tegaserod treatment protected colonic motility and IJPs in inflamed guinea pigs. Taken together, these data suggest that activation of mucosal 5-HT4 receptors reduces the development of, and speeds recovery from, inflammation.

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