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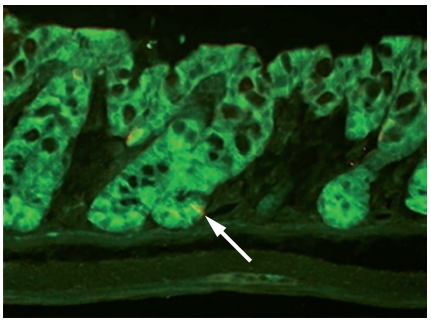
MOTILITY

Searching for 5-HT$_4$ receptors in the colonic mucosa

Study results confirm that 5-HT$_4$ receptors are expressed in the colonic mucosa. Moreover, the findings reveal that activation of these receptors promotes colonic motility and helps alleviate visceral pain. Thus, specifically targeting these colonic receptors might be a useful approach to treat constipation. "5-HT$_4$ agonists that are formulated to stay in the lumen—nonabsorbable or coated so they are released only in the colon—might be an effective way of treating constipation and visceral pain, without the risk of systemic adverse effects," notes corresponding author Gary Mawe.

5-HT$_4$ receptor agonists (for example, mosapride) promote colonic motility and can be used in the management of constipation. However, a number of these agents were removed from the market owing to safety concerns, and just how these agents exert their effects is unclear.

In this study, intestinal samples from animal models and humans were found to widely express 5-HT$_4$ receptors. By using transgenic mice in which green fluorescent protein expression was under the control of the 5-HT$_4$ receptor promoter, the researchers could determine in which particular cells this receptor was expressed. "We were astounded to find that essentially all of the epithelial cells in the mouse large intestine fluoresced green," says first author Jill Hoffman.



Distal colon of a 5-HT$_4$(BAC)-eGFP mouse. Cells expressing the 5-HT$_4$ receptor are shown in green, red indicates immunoreactivity for serotonin, the arrow indicates an enterochromaffin cell. Courtesy of G. M. Mawe.

The investigators went on to confirm that stimulation of these colonic 5-HT$_4$ receptors led to mucus, fluid and mucosal 5-HT secretion. Whereas administration of 5-HT$_4$ receptor agonists resulted in accelerated propulsive motility and reduced visceral hypersensitivity (the effects being most potent with intracolonic administration), these effects were blocked by 5-HT$_4$ receptor antagonists.

Mawe acknowledges that more work is needed to verify the motility-promoting effects of colonic 5-HT$_4$ receptors *in vivo*. "We would also like to determine the mechanisms that are actually responsible for the motility and antinociceptive actions of lumenally-administered 5-HT$_4$ agonists," he adds.

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Original article Hoffman, J. M. *et al.* Activation of colonic mucosal 5-HT$_4$ receptors accelerates propulsive motility and inhibits visceral hypersensitivity. *Gastroenterology* doi:10.1053/j.gastro.2011.12.041