Invited Reviews for the 2008 Hirosi Kuriyama Award

5-Hydroxytryptamine_4 receptor agonists and colonic motility

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Abstract

5-Hydroxytryptamine (5-HT) released from enterochromaffin cells regulates gastrointestinal function in either an excitatory or inhibitory manner. 5-HT_3 and 5-HT_4 receptors in the gut have been the focus of clinical studies on the management of gastrointestinal motility disorders. 5-HT stimulates intestinal propulsive reflexes through 5-HT_4 receptors. 5-HT_4 receptor agonists can stimulate upper or lower gut motility, depending on their selectivity and affinity. In the guinea pig colon, the distribution of 5-HT_4 receptors in the myenteric plexus and circular muscle layer differs between the proximal and distal regions. 5-HT stimulates intestinal motility via excitatory neurons while causing relaxation of the circular muscle via 5-HT_4 receptors. In the light of these findings on the distribution of 5-HT_4 receptors, the effects of receptor agonist compounds could vary depending on the species of experimental animal and the anatomical region studied.

Key words: 5-hydroxytryptamine, receptor agonists, colon, 5-HT_4 receptor distribution

Introduction

5-Hydroxytryptamine (5-HT) is an important neurotransmitter in both the brain and the gut. About 95% of 5-HT is found in the gastrointestinal (GI) tract and is involved in GI secretion and motility (Kim and Camilleri, 2000). Most 5-HT is stored in, and released from enterochromaffin (EC) cells that are distributed throughout the gut mucosa. 5-HT is also contained in serotonergic neurons in the enteric nervous system. 5-HT interacts with seven different receptor subtypes, five of which are found in the GI tract, namely 5-HT_1, 5-HT_2, 5-HT_3, 5-HT_4, and 5-HT_7 receptors (De Maeyer et al., 2008). 5-HT_4 receptors have been investigated as a major therapeutic target for management of GI motility disorders, and 5-HT_4 receptor agonists have been shown to have potent prokinetic effects in the GI tract (Gershon and Tack, 2007). The focus of this review is on the novel 5-HT_4 receptor agonists and their function in colonic motility.

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5-HT and the peristaltic reflex

5-HT stimulates the intestinal propulsive reflexes through 5-HT\textsubscript{4} receptors (Grider \textit{et al.}, 1998; Jin \textit{et al.}, 1999). In the gut, mucosal sensory stimulation induces release of 5-HT from enterochromaffin cells (Fig. 1) (Jin \textit{et al.}, 1998). Released 5-HT stimulates intrinsic primary afferent neurons (IPAN) via 5-HT\textsubscript{4} receptors (Kim and Camilleri, 2000). The intrinsic pathway includes calcitonin gene related peptide (CGRP) neurons in the enteric nervous system (Grider \textit{et al.}, 1998). Intrinsic CGRP neurons relay ascending contraction via excitatory neurotransmitters, and descending inhibitions via inhibitory neurotransmitters (Grider \textit{et al.}, 1998; Jin \textit{et al.}, 1999). 5-HT\textsubscript{4} receptors therefore play an important role in intestinal motility through triggering of the peristaltic reflex.

Distribution and function of 5-HT\textsubscript{4} receptors in the colon

Many immunohistochemical studies have reported on the distribution of 5-HT\textsubscript{4} receptors in the gut, including the colon. 5-HT\textsubscript{4} receptors are present in the myenteric plexus and in muscle layers, both in the guinea pig and human colon (Sakurai-Yamashita \textit{et al.}, 1999). In the guinea pig colon, the density of 5-HT\textsubscript{4} receptors is remarkably higher in the myenteric plexus than in the muscle layers (Sakurai-Yamashita \textit{et al.}, 1999). In the myenteric and submucosal plexus, the majority of 5-HT\textsubscript{4} receptors are present in intrinsic primary afferent neurons (IPANs) (Pool \textit{et al.}, 2006). In particular, 5-HT\textsubscript{4} receptors are restricted to the presynaptic area (Gershon, 2004). Drugs targeting 5-HT\textsubscript{4} receptors are thought to function by stimulating neurotransmitter
release at presynaptic sites, and activating IPAN-initiating peristaltic reflexes. In the human colon, 5-HT₄ receptors are relatively evenly distributed in the myenteric plexus and muscle layers compared to the guinea pig colon (Sakurai-Yamashita et al., 1999). 5-HT₄ receptors mediate relaxation in smooth muscle cells as well as contraction via excitatory neurons (Briejer and Schuurkes, 1996; Mclean and Coupar, 1996; Sakurai-Yamashita et al., 1999). The different distributions of 5-HT₄ receptors in humans and guinea pigs could explain the different responses of isolated gut preparations.

**Different functions of the proximal and distal colon**

The main functions of the proximal and distal colon are different; the function of the proximal portion is storage, while the function of the distal portion is propulsion of contents (Bassotti et al., 1999). 5-HT₄ receptor immunoreactivity has been observed in the duodenum, small intestine, and in both the proximal and distal colon. More specifically, receptors were identified only in the enteric plexus, the interstitial cells of Cajal and smooth muscle cells, but not in the mucosa, mucosal nerves, or epithelial cells (Liu et al., 2005). Theoretically, 5-HT₄ agonists can affect the whole gut wherever 5-HT₄ receptors are found, with their exact effect depending on the distribution of receptors. Until now, the majority of studies have evaluated the effect of 5-HT₄ agonists on the functions of the upper or lower gut in various animal studies. In humans, 5-HT₄ receptor distribution in the upper and lower gut has not yet been evaluated, and should be addressed in the future. The localization of 5-HT₄ receptors in the human colon shows the same pattern as that in the guinea pig (Sakurai-Yamashita et al., 1999). 5-HT₄ receptors are more densely distributed in the myenteric plexus in the proximal colon than in the distal colon (Kim et al., 2008). However, in circular muscle, the receptors are more abundant in the distal colon than in the proximal colon. This supports the classic thesis that the excitatory or inhibitory response of intestinal motility to 5-HT₄ receptor agonists depends on the anatomical region as well as the species (Ford and Clarke, 1993).

**The effect of 5-HT₄ receptor agonists on colonic motor function**

Many full or partial 5-HT₄ receptor agonists have been evaluated as prokinetics of the GI tract in *in vitro* and *in vivo* studies. Cisapride and metoclopramide are considered to stimulate primarily upper GI motor activity, although there are conflicting results on their prokinetic effects in the colon (De Ponti and Malagelada, 1998; De Mayer et al., 2008). Two novel enterokinetic compounds are tegaserod, a partial agonist, and prucalopride, a full agonist (Grider et al., 1998; Briejer et al., 2001). Both have been proposed as agents for chronic constipation. Prucalopride appears to stimulate the colon more selectively without influencing gastric or small bowel function (Bouras et al., 1999). Renzapride stimulates the entire length of the colon (Nagakura et al., 1996).

Mosapride citrate, a selective 5-HT₄ receptor agonist, has been reported to stimulate upper gastrointestinal motility without affecting colonic motility (Mine et al., 1997). It increased gastric emptying in rats, and stimulated gastric motor activity in conscious dogs (Yoshida et al., 1997).
Mosapride did not affect the colonic motor index in conscious dogs, and showed a relatively high EC_{50} value, indicating low affinity for the distal colon in guinea pig (Mine et al., 1997). In the isolated guinea pig colon, mosapride augmented only segmental contraction in the proximal portion, and failed to induce peristaltic acceleration (Tsubouchi et al., 2003). However, mosapride increased the amplitude of proximal colonic motility in conscious guinea pigs, measured by a force transducer recording contractions of the circular muscle of the proximal colon (Inui et al., 2002). This result differed from the primary data on mosapride (Table 1). We also found that mosapride significantly increased contractile amplitude in the proximal colon, coinciding with rapid transit (Kim et al., 2008). This increased contraction might physiologically expel the proximal stored contents into the distal portion. To date, mosapride is still used for management of upper gut dysfunction such as functional dyspepsia. However, consensus needs to be established on the net prokinetic property of mosapride on colonic motility, especially in humans.

<table>
<thead>
<tr>
<th>Year</th>
<th>Animal</th>
<th>Portion</th>
<th>Result</th>
<th>Significant dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1991</td>
<td>Conscious dog</td>
<td>Ascending</td>
<td>Not affect</td>
<td>0.2–1.0 mg/kg, i.v.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Descending</td>
<td>Not affect</td>
<td>0.2–1.0 mg/kg, i.v.</td>
</tr>
<tr>
<td>1997</td>
<td>Conscious dog</td>
<td>Proximal</td>
<td>Not affect</td>
<td>0.1–3 mg/kg, i.v.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Distal</td>
<td>Low affinity</td>
<td></td>
</tr>
<tr>
<td>2001</td>
<td>Isolated guinea pig</td>
<td>Distal</td>
<td>Inactive</td>
<td>Not present</td>
</tr>
<tr>
<td>2003</td>
<td>Isolated guinea pig</td>
<td>Proximal</td>
<td>Segmental contraction ↑</td>
<td>0.1–10 µM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Distal</td>
<td>Peristaltic contraction ↓</td>
<td>10 µM</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Segmental contraction ↑</td>
<td>1–10 µM</td>
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<td></td>
<td></td>
<td></td>
<td>Peristaltic contraction ↓</td>
<td>10 µM</td>
</tr>
<tr>
<td></td>
<td>Conscious dog</td>
<td>Ascending</td>
<td>Not affect</td>
<td>0.3–3 mg/kg, i.v.</td>
</tr>
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<td>Not affect</td>
<td>0.3–3 mg/kg, i.v.</td>
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References


5-HT4 receptors on colonic motility


