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$_4$ 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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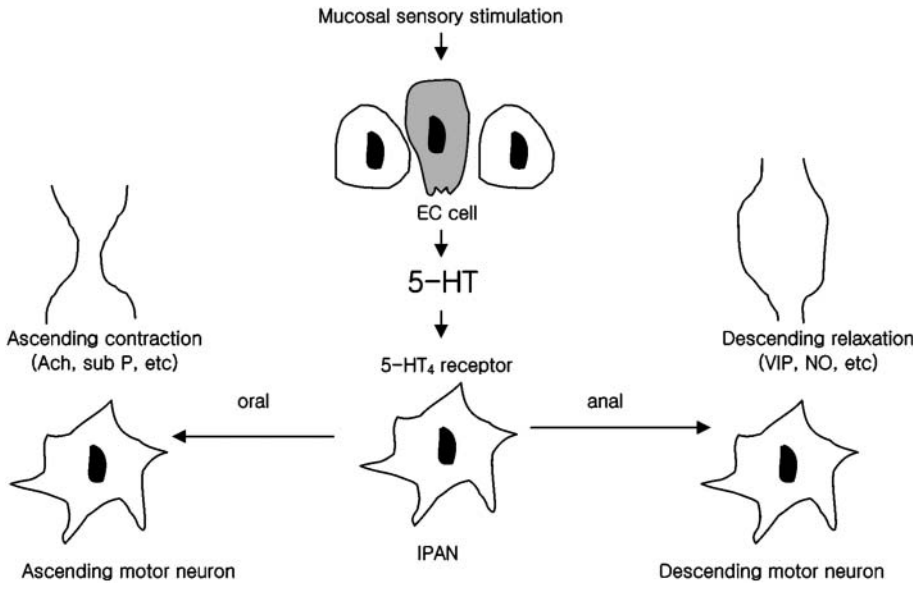

Fig. 1. Scheme of peristaltic reflex via 5-hydroxytryptamine$_4$ receptor. EC cell: enterochromaffin cell, 5-HT: 5-hyroxytryptamine, IPAN: intrinsic primary afferent neuron.

5-HT and the peristaltic reflex

5-HT stimulates the intestinal propulsive reflexes through 5-HT$_4$ receptors (Grider *et al.*, 1998; Jin *et al.*, 1999). In the gut, mucosal sensory stimulation induces release of 5-HT from enterochromaffin cells (Fig. 1) (Jin *et al.*, 1998). Released 5-HT stimulates intrinsic primary afferent neurons (IPAN) via 5-HT$_4$ receptors (Kim and Camilleri, 2000). The intrinsic pathway includes calcitonin gene related peptide (CGRP) neurons in the enteric nervous system (Grider *et al.*, 1998). Intrinsic CGRP neurons relay ascending contraction via excitatory neurotransmitters, and descending inhibitions via inhibitory neurotransmitters (Grider *et al.*, 1998; Jin *et al.*, 1999). 5-HT$_4$ receptors therefore play an important role in intestinal motility through triggering of the peristaltic reflex.

Distribution and function of 5-HT$_4$ receptors in the colon

Many immunohistochemical studies have reported on the distribution of 5-HT$_4$ receptors in the gut, including the colon. 5-HT$_4$ receptors are present in the myenteric plexus and in muscle layers, both in the guinea pig and human colon (Sakurai-Yamashita *et al.*, 1999). In the guinea pig colon, the density of 5-HT$_4$ receptors is remarkably higher in the myenteric plexus than in the muscle layers (Sakurai-Yamashita *et al.*, 1999). In the myenteric and submucosal plexus, the majority of 5-HT$_4$ receptors are present in intrinsic primary afferent neurons (IPANs) (Pool *et al.*, 2006). In particular, 5-HT$_4$ receptors are restricted to the presynaptic area (Gershon, 2004). Drugs targeting 5-HT$_4$ receptors are thought to function by stimulating neurotransmitter

release at presynaptic sites, and activating IPAN-initiating peristaltic reflexes. In the human colon, 5-HT$_4$ receptors are relatively evenly distributed in the myenteric plexus and muscle layers compared to the guinea pig colon (Sakurai-Yamashita *et al.*, 1999). 5-HT$_4$ 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-HT$_4$ 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-HT$_4$ 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-HT$_4$ agonists can affect the whole gut wherever 5-HT$_4$ 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-HT$_4$ agonists on the functions of the upper or lower gut in various animal studies. In humans, 5-HT$_4$ receptor distribution in the upper and lower gut has not yet been evaluated, and should be addressed in the future. The localization of 5-HT$_4$ receptors in the human colon shows the same pattern as that in the guinea pig (Sakurai-Yamashita *et al.*, 1999). 5-HT$_4$ 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-HT$_4$ receptor agonists depends on the anatomical region as well as the species (Ford and Clarke, 1993).

The effect of 5-HT$_4$ receptor agonists on colonic motor function

Many full or partial 5-HT$_4$ receptor agonists have been evaluated as prokinetics of the GI tract in *in vitro* and *in vivo* studies. Cisapride and metocolopramide 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-HT$_4$ 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.*,

Table 1. Different results of the effect of mosapride citrate on proximal and distal colonic motility

Year	Animal	Portion	Result	Significant dose
1991[a]	Conscious dog	Ascending	Not affect	0.2–1.0 mg/kg, *i.v.*
		Descending	Not affect	0.2–1.0 mg/kg, *i.v.*
1997[b]	Conscious dog	Proximal	Not affect	0.1–3 mg/kg, *i.v.*
	Isolated guinea pig	Distal	Low affinity	
2001[c]	Isolated guinea pig	Distal	Inactive	Not present
2003[d]	Isolated guinea pig	Proximal	Segmental contraction ↑	0.1–10 μM
			Peristaltic contraction ↓	10 μM
		Distal	Segmental contraction ↑	1–10 μM
			Peristaltic contraction ↓	10 μM
	Conscious dog	Ascending	Not affect	0.3–3 mg/kg, *i.v.*
		Descending	Not affect	0.3–3 mg/kg, *i.v.*
2002[e]	Conscious guinea pig	Proximal	Amplitude ↑	3–30 mg/kg, *i.g.*
2008[f]	Isolated guinea pig	Proximal	Colonic transit ↑	10^{-8}–10^{-7} M
			Amplitude ↑	10^{-9}–10^{-7} M
	Isolated guinea pig	Distal	Colonic transit ↑	10^{-7} M
			Amplitude ↑	10^{-9} M

a. Yoshida *et al.* (1991); b. Mine *et al.* (1997); c. Kajita *et al.* (2001); d. Tsubouchi *et al.* (2003); e. Inui *et al.* (2002); f. Kim *et al.* (2008).

1989; Yoshida *et al.*, 1991). 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.

References

Bassotti, G., Iantorno, G., Fiorella, S., Bustos-Fernandez, L. and Bilder, C.R. (1999). Colonic motility in man: features in normal subjects and in patients with chronic idiopathic constipation. *Am. J. Gastroenterol.* **94**: 1760–1770.

Bouras, E.P., Camilleri, M., Burton, D.D. and Mckinzie, S. (1999). Selective stimulation of colonic transit by the benzofuran 5-HT_4 agonist, prucalopride, in healthy humans. *Gut* **44**: 682–686.

Briejer, M.R., Prins, N.H. and Schuurkes, J.A. (2001). Effects of the enterokinetic prucalopride (R093877) on colonic motility in fasted dogs. *Neurogastroenterol. Motil.* **13**: 465–472.

Briejer, M.R. and Schuurkes, J.A.J. (1996). 5-HT_3 and 5-HT_4 receptors and cholinergic and tachykininergic neurotransmission in the guinea-pig proximal colon. *Eur. J. Pharmacol.* **308**: 173–180.

De Maeyer, J.H., Lefebvre, R.A. and Schuurkes, A.J. (2008). 5-HT_4 receptor agonists: similar but not the same. *Neurogastroenterol. Motil.* **20**: 99–112.

De Ponti, F. and Malagelada, J.R. (1998). Functional gut disorders: from motility to sensitivity disorders: a review of current and investigational drugs for their management. *Pharmacol. Ther.* **80**: 49–88.

Ford, A.P. and Clarke, D.E. (1993). The 5-HT_4 receptor. *Med. Res. Rev.* **13**: 633–662.

Gershon, M.D. (2004). Review article: serotonin receptors and transporters-roles in normal and abnormal gastrointestinal motility. *Aliment. Pharmacol. Ther.* **20**(S7): 3–14.

Gershon, M.D. and Tack, J. (2007). The serotonin signaling system: from basic understanding to drug development for functional GI disorders. *Gastroenterol.* **132**: 397–414.

Grider, J.R., Foxx-Orenstein, A.E. and Jin, J.G. (1998). 5-Hydroxytryptamine$_4$ receptor agonists initiate the peristaltic reflex in human, rat, and guinea pig intestine. *Gastroenterol.* **115**: 370–380

Inui, A., Yoshikawa, T., Nagai, R., Yoshida, N. and Ito, T. (2002). Effects of mosapride citrate, a 5-HT_4 receptor agonist, on colonic motility in conscious guinea pigs. *Jpn. J. Pharmacol.* **90**: 313–321.

Jin, J.G., Foxx-Orenstein, A.E. and Grider, J.R. (1999). Propulsion in guinea pig colon induced by 5-hydroxytryptaine (HT) via 5-HT_4 and 5-HT_3 receptors. *J. Pharmacol. Exp. Ther.* **288**: 93–97.

Kajita, S., Ito, C., Kawamura, R., Yasuda, S., Isobe, Y. and Fukushima, K. (2001). Pharmacological characterization of a novel 5-HT_4 receptor agonists, TS-951, *in vitro*. *Pharmacol.* **63**: 8–16.

Kim, D.Y. and Camilleri, M. (2000). Serotonin: a mediator of the brain-gut connection. *Am. J. Gastroenterol.* **95**: 2698–2709.

Kim, H.S., Choi, E.J. and Park, H. (2008). The effect of mosapride citrate on proximal and distal colonic motor function in the guinea-pig *in vitro*. *Neurogastroenterol. Motil.* **20**: 169–176.

Liu, M., Geddis, M.S., Wenm Y., Setlikm, W. and Gershon, M.D. (2005). Expression and function of 5-HT_4 receptors in the mouse enteric nervous system. *Am. J. Physiol.* **289**: G1148–G1163.

Mclean, P.G. and Coupar, I.M. (1996). Stimulation of cyclic AMP formation in the circular smooth muscle of human colon by activation of 5-HT_4-like receptors. *Br. J. Pharmacol.* **117**: 238–239.

Mine, Y., Yoshikawa, T., Oku, S., Nagai, R., Yoshida, N. and Hosoki, K. (1997). Comparison of effect of mosapride citrate and existing 5-HT_4 receptor agonists on gastrointestinal motility *in vivo* and *in vitro*. *J. Pharmacol. Exp. Ther.* **283**: 1000–1008.

Nagakura, Y., Kamato, T., Nishida, A., Itom H., Yamano, M. and Miyata, K. (1996). Characterization of 5-hydroxytryptamine (5-HT) receptor subtypes influencing colonic motility in conscioius dogs. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **353**: 489–498.

Poole, D.P., Xu, B., Koh, S.L., Hunne, B., Coupar, I.M., Irving, H.R., Shinjo, K. and Furness, J.B. (2006). Identification of neurons that express 5-hydroxytryptamine$_4$ receptors in intestine. *Cell Tissue Res.* **325**: 413–422.

Sakurai-Yamashita, Y., Yamashita, K., Kanematsu, T. and Taniyama, K. (1999). Localization of the 5-HT_4 receptor in the human and the guinea pig colon. *Eur. J. Pharmacol.* **383**: 281–285.

Tsubouchi, T., Saito, T., Mizutani, F., Yamauchi, T. and Iwanaga, Y. (2003). Stimulatory action of itopride hydrochloride on colonic motor activity *in vitro* and *in vivo*. *J. Pharmacol. Exp. Ther.* **306**: 787–793.

Yoshida, N., Ito, T., Karasawa, T. and Itoh, Z. (1991). AS-4370, a new gastrokinetic agent, enhances upper gastrointestinal motor activity in conscious dogs. *J. Pharmacol. Exp. Ther.* **257**: 781–787.

Yoshida, N., Omoya, H., Oka, M., Furukawa, K., Ito, T. and Karasawa, T. (1989). AS-4370, a novel gastrokinetic agent free of dopamine D_2 receptor antagonist properties. *Arch. Int. Pharmacodyn. Ther.* **300**: 51–67.