JPP Journal of Pharmacy and Pharmacology

JPP 2009, 61: 367–373

Received August 26, 2008
Accepted December 12, 2008
DOI 10.1211/jpp/61.03.0012
ISSN 0022-3573

Research Paper

Effect of TZP-201, a novel motilin receptor antagonist, in the colon of the musk shrew (*Suncus murinus*)

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Abstract

Objectives Motilin is the main gut peptide that stimulates propulsive motility in the upper gastrointestinal (GI) tract. Motilin receptors exist in the colon but little is known about their functional role, and species-dependent differences present a major obstacle to understanding the physiological significance and potential therapeutic implications of motilin receptors in the colon. Our study aimed to define whether a motilin receptor is functionally expressed in the colon of the Asian musk (or house) shrew (*Suncus murinus*) and to investigate the effect of a novel motilin receptor antagonist, TZP-201.

Methods GI tissue (gastric antrum, small intestine and colon) was isolated from male shrews and the effects of a motilin receptor agonist [Nle^{13}]motilin and the antagonist TZP-201 on contractile activity and mucosal electrogenic transport of water and electrolytes were investigated *in vitro*.

Key findings [Nle^{13}]motilin induced a moderate increase in spontaneous contractility in the stomach and no significant changes in the small intestine; a marked increase in contractility was found in the colon. Motilin-induced contractions in the colon were abolished by tetrodotoxin or atropine, and dose-dependently inhibited by 0.01–10 μM TZP-201. Neither [Nle^{13}]motilin nor TZP-201 had any effect on basal mucosal transport.

Conclusions Shrew colon expresses a functional motilin receptor that induces contractile activity by the activation of enteric cholinergic neurons. TZP-201 inhibited motilin-induced colonic contractions. Motilin antagonists may represent a new approach for the treatment of GI motility disorders characterised by hypercontractility.

Keywords colonic contraction; motilin; motilin receptor antagonist TZP-201; musk shrew

Introduction

Motilin is a 22-amino acid peptide hormone secreted by enterochromaffin cells in the mucosa of the upper gastrointestinal (GI) tract.[1,2] Motilin is a regulator of gastroduodenal motility during the interdigestive period.[3,4] The effects of motilin are due to the activation of G-protein-coupled receptors expressed by smooth muscle cells and enteric nerves throughout the GI tract of mammalian species,[5,6] including humans.[7,8] The genes for motilin receptors in different species evolved from a common ancestral gene, becoming species dependent; orthologues are found in rabbits and humans,[7,9] but there are no functional motilin genes in rats and mice.[10,11] The absence of a functional motilin receptor in the rodent GI tract is a disadvantage in the profiling of motilin ligands, since rats and mice are commonly used in preclinical research. Most recently, the motilin gene of the Asian musk (or house) shrew (*Suncus murinus*), a small insectivore, has been cloned and has high sequence homology with the genes of other mammalian species, including the human gene.[12]

Since the discovery of motilin, researchers have sought to develop synthetic motilin receptor agonists with gastroprokinetic effects that could be used in the treatment of diseases related to GI dysmotility.[13,14] It has also been proposed that motilin receptor antagonists may have potential therapeutic benefits in the treatment of hypermotility disorders associated with diarrhoea. For example, Simrén *et al*.[15] suggested that motilin-mediated alterations in colonic motility may play a pathophysiological role in irritable bowel syndrome (IBS), since patients with IBS show higher interdigestive and postprandial

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levels of plasma motilin compared with healthy control patients. Similar results were reported by Fukudo and Suzuki,[16] who showed a significant increase in colonic motility and motilin levels during a psychological stress paradigm in patients with IBS but not in healthy controls. Furthermore, oral administration of the selective competitive motilin receptor antagonist MA-2029 to rabbits was found to inhibit motilin-induced colonic contractions and visceral pain.[17]

The current study had two related aims. The first was to determine whether the house musk shrew, maintained at laboratory conditions, expresses functional motilin receptors and is a suitable model for laboratory investigation of the GI effects of motilin. The musk shrew was selected as a test model on the basis of identification of motilin-secreting enteroendocrine cells in the proximal intestine.[18] The second aim was to use isolated preparations from the shrew colon to investigate the effects of a novel motilin receptor antagonist, TZP-201, on contractility and mucosal secretion. TZP-201 belongs to a new class of macrocyclic antagonists of the human motilin receptor[19] and is currently under development (patents WO2004/111077 and WO2008/033328). The targeted indications for TZP-201 are chemotherapy-induced diarrhoea and diarrhoea associated with IBS. We used in-vitro methods. Specifically, muscle contractility was recorded from isolated preparations suspended in organ baths under isometric conditions, and electrogenic epithelial transport of water and electrolytes was studied electrophysiologically in mucosal sheets mounted in modified Ussing chambers. The experiments demonstrated that the musk shrew might serve as a new animal model to characterise the selective activity of TZP-201 as a motilin receptor antagonist, which suppressed colonic contractions without having an effect on epithelial secretion. Overall the results from this in-vitro study suggest that TZP-201 has a therapeutic potential for the treatment of motility-related diarrhoea.

Materials and Methods

Animals

Healthy adult (5–7 months old) house musk shrews (*S. murinus*) weighing 40–70 g were supplied from a breeding colony at the University of Virginia, Charlottesville, Virginia, USA. Musk shrews do not live in social groups and behave aggressively when placed together; animals were therefore housed individually in Plexiglas cages, with pine shaving and shredded paper for bedding.[20] Temperature was kept constant at 21°C and a 12 h light–dark cycle was maintained throughout the study. Food (Purina Cat Chow) and water were available *ad libitum*. The animals were acclimatised to the facility for at least 1 week before the study.

All experiments complied with the National Institutes of Health Guide for Care and Use of Laboratory Animals, and were approved by the Animal Care and Use Committees of the University of Oklahoma Health Sciences Center and the Veterans Affairs Medical Center in Oklahoma City, Oklahoma, USA.

Solutions and drugs

The modified Krebs bicarbonate solution contained (in mM): NaCl 120.0, KCl 6.0, $MgCl_2$ 1.2, NaH_2PO_4 1.2, $CaCl_2$ 2.5, $NaHCO_3$ 14.4 and glucose 11.5. The solution was gassed continuously with 95% O_2/5% CO_2 and the pH was in the range 7.2–7.3. The motilin receptor agonist [Nle^{13}]motilin (norleucine^{13} analogue of porcine/human motilin) was obtained from Calbiochem (San Diego, CA, US). Carbamylcholine chloride (carbachol), atropine sulfate and tetrodotoxin were obtained from Sigma Chemical Co. (St Louis, MO, US). TZP-201.HCl was supplied by Tranzyme Pharma Inc. (Sherbrooke, QC, Canada).

Stock solutions of TZP-201 were made in DMSO, stored at 4°C and diluted in distilled water before each experiment. The concentration of the TZP-201 stock was 10 mM and the final concentration of DMSO in the organ bath was in the range 0.01–0.1%.

The other drugs were dissolved in deionised distilled water and fresh solutions were prepared on the day of experiment. Drugs were added to the baths in volumes less than 1% of the total bath volume.

Contractile activity of isolated preparations

On the day of experiment the animals were euthanised by carbon dioxide inhalation and the entire GI tract was harvested and placed in ice-cold Krebs buffer aerated with 95% O_2/5% CO_2.

Compared with rats, mice, guinea-pigs and rabbits, the GI tract of the shrew is relatively short and does not have an anatomically distinguished caecum. In a series of pilot experiments to define whether exogenous motilin has an effect in the GI tract of the shrew, the stomach, small intestine and colon of the harvested GI tract were separated and cleaned of intraluminal content. The stomach was cut along the small curvature and pinned flat to the bottom of a Silgard-covered dish filled with continuously aerated Krebs buffer. Full-thickness strips (10 mm long, 2–3 mm wide) from the gastric antrum were excised in the direction of the circular muscle. The duodenum (10–12 mm from the lower oesophageal sphincter area), small intestine and colon (4–5 cm proximal to the colorectal region) were flushed gently with Krebs buffer and whole-segment preparations (approximately 10 mm long) were dissected and mounted vertically to record contractile activity in the direction of the longitudinal muscle layer. Six animals were used for the pilot experiments; two preparations from each anatomical region were isolated from each animal. A total of 34 shrews were used in the main study to investigate the effect of [Nle^{13}]motilin and the antagonist activity of TZP-201 against motilin-induced contractions in isolated colonic segments (four segments from each animal).

All preparations were initially loaded with 1 g tension, and contractile activity under isometric conditions was recorded using a Radnoti 8 chamber organ bath system (Radnoti Glass Technology, Inc., Monrovia, CA, US). The preparations were allowed to equilibrate for 90 min, during which the Krebs solution was changed every 15 min. Optimal tension was achieved at the end of the equilibration period by increasing the

resting tension by loading at 0.2 g increments until the contractile responses induced by 0.1 μM carbachol no longer increased in amplitude. Contractile activity at optimal tension was recorded continuously using a PowerLab/400 data acquisition system (AD Instruments, Inc., Colorado Springs, CO, US).

Epithelial transport of water and electrolytes

Twelve animals were used for investigations of colonic epithelial transport; three or four mucosal sheets were isolated from the colon of each animal. The colonic mucosal sheets were dissected free from the external muscle and were mounted in modified Ussing chambers (0.6 cm^2 window opening) for electrophysiological recording (World Precision Instruments Inc., Sarasota, FL, US). The luminal and serosal sides of the preparations were bathed with Krebs buffer aerated with 95% O_2/5% CO_2 and maintained at 37°C. Two pairs of agar–salt bridge electrodes connected to voltage–current clamp apparatus (EVC 4000, World Precision Instruments) were used to measure the potential difference (PD) and the short-circuit current (Isc). Basal PD was lumen-negative and measured in mV; basal Isc was measured in μA and normalised for 1 cm^2 of the mucosal area. Electrical conductance (G), expressed as mS/cm^2, was calculated according to Ohm's law from the open-circuit PD and Isc. The Isc was recorded continuously throughout the experiment using a PowerLab/400 data acquisition system (AD Instruments).

Data analysis and statistics

The contractile effects of [Nle^{13}]motilin were expressed relative to the effect of 0.1 μM carbachol. Drug-induced changes in mucosal secretion were compared with the secretory effect of 1 μM carbachol added to the serosal bathing solution.

Data are presented as means ± SEM; *n* refers to the number of preparations isolated from different animals. All data sets showed normal distribution. The significance of the effects induced by multiple concentrations of TZP-201 or [Nle^{13}]motilin was assessed using one-way analysis of variance or the non-parametric Kruskal–Wallis test, as appropriate. Individual differences between drug- and vehicle-treated groups were assessed for statistical significance by Dunnett's or Dunn's post hoc test. Differences were considered significant at $P < 0.05$. The antagonist potency of TZP-201 was evaluated from the IC50 value, which is the concentration that produced 50% inhibition of the maximal contraction induced by [Nle^{13}]motilin. IC50 was determined by non-linear regression using Prism software (GraphPad Software, Inc., La Jolla, CA, US).

Results

Contractile effects of [Nle^{13}]motilin

A series of pilot experiments was performed to define whether motilin receptor activation induces contractile activity in the GI tract of the shrew. Contractile activity was recorded from smooth-muscle preparations isolated from the stomach, duodenum, small intestine and colon. Following a period of equilibration, all muscles maintained low basal tone (0.1–0.5 g), with phasic contractions developing spontaneously throughout the 3–4 h recording period. Addition of [Nle^{13}]motilin (0.1–1 μM) to the bathing solution dose-dependently increased the spontaneous contractions in all GI regions except for the small intestine. At 0.3 μM [Nle^{13}]motilin produced 80–100% of the maximal effect induced by 1 μM [Nle^{13}]motilin. The effect of 0.3 μM [Nle^{13}]motilin investigated for a 10 min treatment period was reversible and reproducible following a 45 min washout period. Table 1 summarises the time course of the changes in basal contractile activity induced by 0.3 μM [Nle^{13}]motilin in the gastric antrum, duodenum, small intestine and colon, expressed as percentage of the contraction induced by 0.1 μM carbachol. The effects of [Nle^{13}]motilin reached a maximum within the first 3–4 min, then gradually declined during the 10 min treatment period.

[Nle^{13}]motilin-induced contractions in the colon

The amplitude of contractions induced in the colon by a single application of 0.3 μM [Nle^{13}]motilin was 56.3 ± 6.2% of the amplitude of contractions induced by 0.1 μM carbachol in the same preparation. We examined the site of action of motilin in the shrew colon by measuring the contractile response to [Nle^{13}]motilin in the presence of tetrodotoxin, a neurotoxin that prevents neuronal conduction by acting as a sodium channel blocker. The contractile effect of [Nle^{13}]motilin was abolished by pretreatment with tetrodotoxin (1 μM) in all six preparations tested (Figure 1), implicating motilin receptors located on enteric nerves in the contraction of the shrew colon. In a different series of experiments, the contractile effects of [Nle^{13}]motilin as well as the reference acetylcholine agonist, carbachol, were similarly inhibited in the presence of atropine (1 μM), indicating that the motilin effect involves activation of cholinergic enteric neurons (Figure 2).

Table 1 Changes in spontaneous contractile activity induced by 0.3 μM [Nle^{13}]motilin in isolated gastrointestinal preparations

Preparation	*n*	[Nle^{13}]motilin-induced contraction				
		0–1 min	1–2 min	2–3 min	3–4 min	4–5 min
Gastric antrum	4	21.3 ± 11.9	30.2 ± 11.2	30.7 ± 13.9	18.9 ± 9.5	12.5 ± 4.7
Duodenum	6	5.6 ± 2.2	9.8 ± 2.9	11.6 ± 5.6	15.4 ± 2.2	9.3 ± 3.3
Small intestine	5	3.6 ± 1.4	4.1 ± 1.9	3.5 ± 2.1	2.8 ± 0.9	5.2 ± 2.3
Colon	4	27.7 ± 6.6	46.5 ± 4.4	51.3 ± 2.2	46.9 ± 6.6	38.3 ± 6.7

Values are means ± SEM, expressed as percentage of the contractile response to 0.1 μM carbachol.

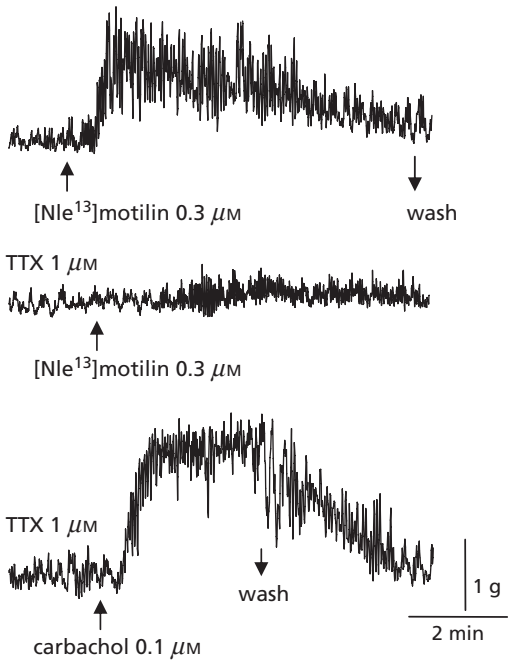

Figure 1 Contractile activity induced by [Nle^{13}]motilin and the effect of tetrodotoxin. The traces illustrate the contractile effect of [Nle^{13}]motilin in an untreated colonic segment (upper trace) and the lack of motilin-induced effect in the presence of tetrodotoxin (TTX) (middle trace). The viability of the preparation was confirmed by the contractile response induced by carbachol in the presence of TTX (lower trace).

Efficacy of TZP-201 against [Nle^{13}]motilin-induced colonic contractions

The efficacy of TZP-201, an antagonist of the human motilin receptor,[19] against the contractile response induced by [Nle^{13}]motilin was investigated in colonic segments. To avoid desensitisation of the motilin receptor, each colonic preparation was subjected to two challenges with 0.3 μM [Nle^{13}]motilin: one in the absence and one in the presence of TZP-201, with multiple washings and a 60 min washout. Under these conditions, the response to [Nle^{13}]motilin was reproducible and no differences were found between the effects obtained in the absence or presence of the vehicle.

In the presence of increasing concentrations of TZP-201 (0.01–10 μM), a dose-dependent inhibition of [Nle^{13}]motilin-induced contractions was observed, with a log IC50 of −7.16 ± 0.32 (Figure 3). Administration of TZP-201 alone to the bathing solution had no significant effect on the spontaneous activity of the preparations and did not cause a change in the magnitude of contractions induced by 0.1 μM carbachol. For example, the contractions induced by carbachol in the presence of the highest concentration of TZP-201 (10 μM) were equal to 94.9 ± 9.5% of carbachol responses obtained in the absence of TZP-201 (n = 6).

Effects of [Nle^{13}]motilin and TZP-201 on colonic mucosal transport of water and electrolytes

A separate series of experiments was performed to investigate whether activation or inhibition of motilin receptors affects electrogenic epithelial transport of ions and water across

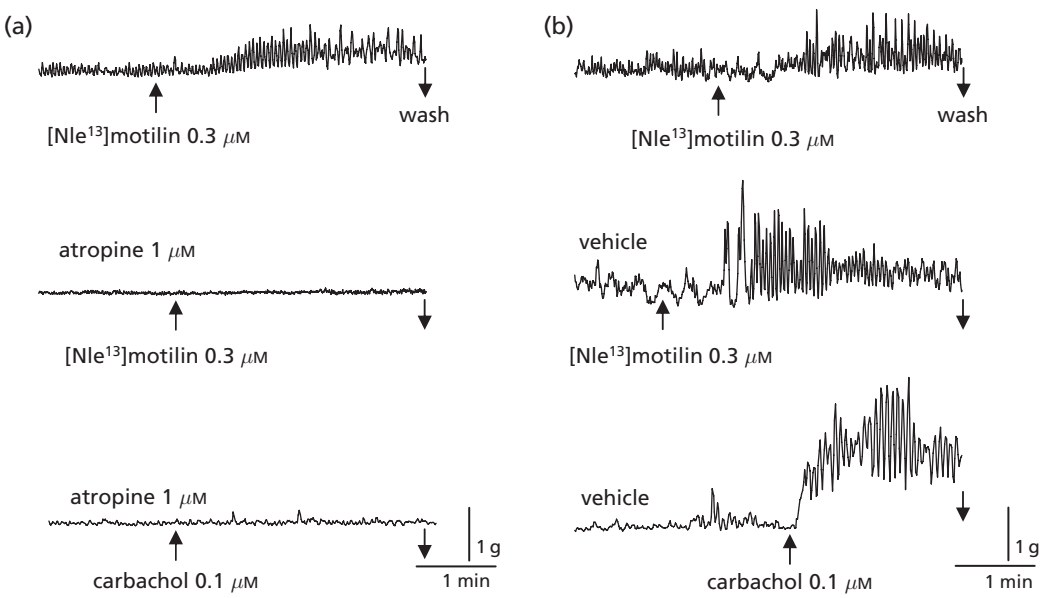

Figure 2 The effect of atropine on [Nle^{13}]motilin-induced contractile activity. (a) Inhibition of the contractile response of colonic segments to [Nle^{13}]motilin by atropine, which blocks muscarinic cholinergic receptors and prevents the effect of carbachol. A 1 h washout period was allowed between the first and second applications of [Nle^{13}]motilin to avoid desensitisation of motilin receptors; atropine treatment was applied during the last 15 min of the washout. (b) The specific cholinergic mechanism of [Nle^{13}]motilin-induced contractions was confirmed by time-matched control experiments performed in colonic segments pretreated with the vehicle of atropine (10 μl deionised distilled water).

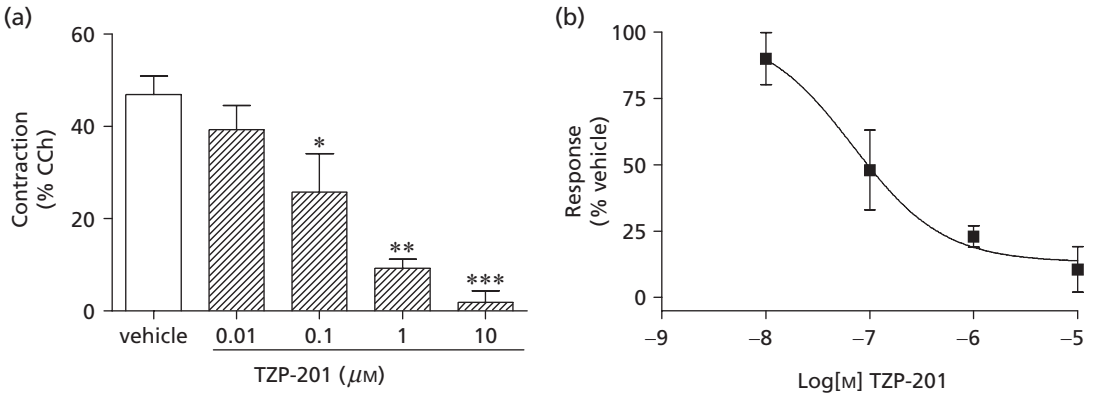

Figure 3 The effect of TZP-201 on [Nle^{13}]motilin-induced contractile activity. (a) Concentration-dependent inhibition of the contractile response of isolated colonic segments induced by 0.3 μM [Nle^{13}]motilin in the presence of increasing concentrations of TZP-201 (0.01–10 μM). Responses are expressed as percentage of the contraction induced by 0.1 μM carbachol (CCh) in each preparation (means of 4–6 experiments). *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ vs vehicle (Kruskal–Wallis non-parametric multiple comparison followed by Dunn's post hoc test). (b) Antagonist potency of TZP-201 against the effect of [Nle^{13}]motilin in the colon. Effects in the presence of TZP-201 are expressed as a percentage of the control effect induced in the presence of the vehicle (0.1% DMSO). The EC50 is −7.16 ± 0.32.

mucosal sheets isolated from the shrew colon. Basal PD and Isc were measured following a period of equilibration, after which [Nle^{13}]motilin or TZP-201 were added to the buffer bathing the serosal surface of the mucosal sheet and changes in Isc were measured. Each preparation was subjected to treatment with increasing concentrations of TZP-201 or a single concentration of [Nle^{13}]motilin. To confirm the viability of the tissue at the end of the experiment, carbachol (10 μM) was added to induce a secretory response, measured as an increase in basal Isc. [Nle^{13}]motilin (0.3, 3 or 10 μM), even at the highest concentration, had no significant effect on basal PD and Isc, and did not cause a change in electrical conductance (Table 2).

The experiments investigating the effect of TZP-201 (0.1, 1 or 10 μM) on epithelial transport showed no significant changes in basal PD, Isc and electrical conductance (Table 2). Furthermore, the carbachol-induced increase in Isc was 142 ± 13 μA/cm^2 in the absence of TZP-201, versus 170 ± 25 μA/cm^2 in the presence of 10 μM TZP-201, suggesting that even the highest concentration TZP-201 had no significant inhibitory effect on the secretory response to carbachol.

Table 2 Effect of [Nle^{13}]motilin or TZP-201 on epithelial transport of electrolytes and water in isolated colonic mucosa

Treatment	PD (mV)	Isc (μA/cm^2)	G (mS/cm^2)
Effects of [Nle^{13}]motilin or carbachol			
Vehicle	–3.3 ± 0.6	124 ± 18	44.8 ± 10.4
[Nle^{13}]motilin, 3 μM	–3.5 ± 0.7	126 ± 18	44.1 ± 10.8
[Nle^{13}]motilin, 10 μM	–3.2 ± 0.9	131 ± 27	45.3 ± 3.3
Carbachol, 10 μM	–3.9 ± 0.6	209 ± 31**	56.0 ± 6.4*
Effects of TZP-201 or carbachol			
Vehicle	–3.0 ± 0.5	134 ± 27	44.7 ± 7.5
TZP-201, 0.1 μM	–3.3 ± 0.6	137 ± 26	45.4 ± 7.7
TZP-201, 1 μM	–3.4 ± 0.4	142 ± 31	45.4 ± 7.9
TZP-201, 10 μM	–3.4 ± 0.5	145 ± 32	46.3 ± 8.1
Carbachol, 10 μM	–4.0 ± 0.2	219 ± 35*	57.3 ± 7.1*

Basal potential difference (PD), short circuit current (Isc) and electrical conductance (G) were measured in the absence and presence of increasing concentrations of [Nle^{13}]motilin or TZP-201 in the bathing solution. Carbachol was added at the end of the experiment to confirm the viability of the tissue. Values are means ± SEM from 8–13 preparations. *$P < 0.05$, **$P < 0.01$ vs vehicle (one-way analysis of variance followed by Dunnett's test for multiple comparisons).

Discussion

Compared with rabbits and guinea pigs, which express functional motilin receptors, the GI tract of the shrew lacks a pronounced caecum and more closely resembles the anatomy and GI function of dogs and humans. In addition, the shrew expresses an emetic reflex and responds with retching and vomiting to cisplatin treatment; it therefore provides an excellent model for investigating the antiemetic potential of motilin receptor antagonists and agonists in both acute and delayed chemotherapy-induced emesis.

Our pilot studies in the GI tract of the shrew showed that [Nle^{13}]motilin induced transient increases in muscle tension, similar to the effect of motilin or [Nle^{13}]motilin reported by Jarvie *et al.* in isolated rabbit gastric antrum circular muscles.[21] Moreover, recordings of colonic contractile activity in the rabbit *in vivo* showed a similar increase in the frequency and amplitude of spontaneous contractions that developed immediately after an i.v. infusion of motilin and lasted about 15 min.[17] In the shrew, the effect of 0.3 μM [Nle^{13}]motilin was most pronounced in the colon, followed by the gastric antrum and the duodenum. These anatomical differences in the functional response to motilin in the shrew are consistent with the motilin receptor distribution found in binding assays on rabbit GI tissue homogenates, where the receptor population was reported to be maximal in the colon, followed by the duodenum and gastric antrum.[22]

Studies in various species, including humans, have demonstrated that the contractile effect of motilin is induced

by activation of motilin receptors located on smooth muscle cells and/or on enteric nerves innervating the smooth muscle.[23–28] Motilin receptors were found at very high concentrations in the rabbit colon, with specific motilin receptor subtypes identified in nerves and muscles.[22] In our study tetrodotoxin abolished the contractile effect of [Nle^{13}] motilin in all six preparations. The contractile effects of [Nle^{13}]motilin were also inhibited in the presence of atropine. Taken together, these data suggest that, in the shrew, motilin induces contraction of the colon via excitation of enteric cholinergic neurons and the activation of smooth muscle muscarinic cholinoreceptors. An enteric pre-junctional site of action of motilin has been described previously in rabbit circular muscle isolated from the gastric antrum.[9,29] In humans, motilin receptor-mediated facilitation of cholinergic neurotransmission has been associated with coordinated gastric contractions and increased gastric emptying.[25] Specific motilin receptor subtypes have been identified in enteric nerves and muscles of the rabbit colon.[22] In contrast to its effect in the shrew, motilin was found to cause direct excitatory effects mediated by smooth muscle motilin receptors in circular muscles isolated from the human or rabbit colon.[21,30,31] The difference between the neuronal and smooth muscle sites of motilin action defined in the colon of shrews or rabbits and humans is likely to reflect species-dependent differences. However, data from the shrew refer to the effect of motilin on the longitudinal muscle, whereas studies in the rabbit and human colon refer to contractions of the circular muscle; thus, the difference could be due to differences in the mechanisms regulating the activity of longitudinal and circular colonic smooth muscle layers.

TZP-201 (0.01–10 μM) produced dose-dependent inhibition of [Nle^{13}]motilin-induced contractions, whereas addition of TZP-201 alone had no significant effect on the spontaneous activity of the preparations and did not cause a change in the magnitude of contractions induced by 0.1 μM carbachol. Taken together, these results suggest that TZP-201 blocks [Nle^{13}]motilin-induced contractions of the shrew colon by specific antagonism of the motilin receptor. The log IC50 value determined in our study corresponds with the potent binding activity of TZP-201 in competitive binding experiments at the human motilin receptor,[19] and TZP-201 appears to have a similar potency across the human and shrew receptor orthologues.

In the experiments looking at colonic mucosal transport of water and electrolytes, [Nle^{13}]motilin, even at the highest concentration, had no significant effect on basal PD and Isc, and did not cause a change in electrical conductance. TZP-201 had no significant effect on basal PD, Isc or electrical conductance, or on the secretory response to carbachol. These observations are consistent with evidence that motilin receptors do not appear to regulate epithelial secretion in isolated mucosal sheets that retain the submucosa but are devoid of the myenteric plexus. However, in an intact animal, intestinal contractions are reflexly coupled to epithelial chloride secretion;[32] it is therefore possible that inhibition of motilin-induced contractions may suppress epithelial chloride secretion indirectly and ameliorate the symptoms of motility-driven diarrhoea.

Conclusions

We have demonstrated that motilin receptors are functionally expressed in the GI tract of the shrew. Specifically, [Nle^{13}] motilin induced a neurally mediated increase in colonic contractility by activating motilin receptors on enteric cholinergic neurons. However, [Nle^{13}]motilin had no effect on basal epithelial transport of water and electrolytes in isolated colonic mucosal sheets. TZP-201, a potent antagonist of the human motilin receptor, caused dose-dependent inhibition of [Nle^{13}]motilin-induced contractions but did not alter basal epithelial transport or the transient secretory response induced by carbachol. Taken together, the results suggest that motilin receptors may regulate colonic motility but are not directly involved in the regulation of epithelial secretion. The *in vitro* efficacy of the synthetic motilin receptor antagonist TZP-201 against motilin-induced contractions in the colon suggests that TZP-201 has therapeutic potential to alleviate the symptoms of motility-related diarrhoea related to colonic hypermotility but without direct effects on the secretory response.

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

Funding

This research was supported by Tranzyme Pharma, Sherbrooke, QC, Canada.

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