Cyclooxygenase-Dependent Alterations in Substance P-Mediated Contractility and Tachykinin NK$_1$ Receptor Expression in the Colonic Circular Muscle of Patients with Slow Transit Constipation

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ABSTRACT

Tachykinins are important neurotransmitters regulating intestinal motility. Slow transit constipation (STC) represents an extreme colonic dysmotility with unknown etiology that predominantly affects women. We examined whether the tachykinin system is involved in the pathogenesis of STC. Isolated sigmoid colon circular muscle from female STC and control patients was studied using functional and quantitative reverse transcriptase-polymerase chain reaction methods. A possible alteration of neurotransmission was investigated by electrical field stimulation (EFS) and ganglionic stimulation by dimethylphenylpiperazinium (DMPP). Substance P (SP)-mediated contractions in circular muscle strips were significantly diminished in STC compared with age-matched control ($P < 0.001$). In contrast, contractile responses to neurokinin A, the selective tachykinin NK$_2$ receptor agonist, [Lys$^5$,MeLeu$^6$Nle$^9$]NKA(4–10), and acetylcholine were unaltered in STC. The reduced responses to SP in STC were fully restored by indomethacin, partially reversed by tetrodotoxin (TTX), but unaffected by atropine or hexamethonium. The restoration by indomethacin was blocked by the NK$_1$ receptor antagonist CP99994 [(2$^S$,3$^S$)-3-(2-methoxybenzylamino)-2-phenylpiperidine] and TTX. In STC colonic muscle, there was a significant increase of NK$_1$ receptor mRNA expression, but no difference in NK$_2$ mRNA level. DMPP generated biphasic responses, relaxation at lower and contraction at higher concentrations. Although the responses to DMPP were similar in STC and control, an altered contractile pattern in response to EFS was observed in STC circular muscle. In conclusion, we postulate that the diminished contractile response to SP in STC is due to an increased release of inhibitory prostaglandins through activation of up-regulated NK$_1$ receptors. Our results also indicate some malfunction of the enteric nervous system in STC.

The tachykinins substance P (SP) and neurokinin (NK) A are important neurotransmitters regulating many gastrointestinal functions, including motility (Holzer and Holzer-Petsche, 1997). SP and NKA occur primarily in intrinsic enteric neurons, where they are colocalized with acetylcholine. We have shown previously that these natural tachykinins are potent spasmogens in human intestine, although the selective NK$_1$ receptor agonist [Pro$^9$]SP is an ineffective contractile agent (Warner et al., 2000; Liu et al., 2002). Using selective antagonists, we showed that NK$_2$ receptors on smooth muscle mediate contraction by SP and by NKA (Warner et al., 2000; Liu et al., 2002; Burcher et al., 2008). However, there are also facilitatory NK$_1$ receptors on cholinergic neurons that make a minor contribution to the SP-induced contraction (Liu et al., 2002). Although immunohistochemical and autoradiographic studies have shown that NK$_1$ receptors are localized to smooth muscle, interstitial cells of Cajal (ICC), and enteric neurons (Goode et al., 2000; Liu et al., 2002; Boutaghou-Cherid et al., 2006), NK$_1$ receptors seem uncoupled to contractile mechanisms (Liu et al., 2002), and their roles in the control of human intestinal motility remain to be determined.

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ABBREVIATIONS: SP, substance P; NK, neurokinin; ICC, interstitial cell(s) of Cajal; STC, slow transit constipation; PG, prostaglandin; COX, cyclooxygenase; EFS, electrical field stimulation; DMPP, dimethylphenylpiperazinium; ACh, acetylcholine; SR48968, (S)-N-methyl-N-[4-acetylaminono-4-phenylpiperidino]-2-(3,4-dichlorophenyl) butylbenzamide; CP99994, (2S,3S)-3-(2-methoxybenzylamino)-2-phenylpiperidine; TTX, tetrodotoxin; ANOVA, analysis of variance; RT, reverse transcription; PCR, polymerase chain reaction; QC, quantitative competitive; idRNA, internal deleted cRNA; IQR, interquartile range.
motility remain unclear. However, SP and NK₁ receptors are involved in gastrointestinal immune functions, with NK₁ receptors expressed on a variety of immune cells (Koon and Pothoulakis, 2006). The tachykinin system also has been implicated in the pathophysiology of functional gastrointestinal disorders. Furthermore, results from the clinical trials with the NK₂ receptor antagonist neotanepitant have shown promise in reducing gut motility and pain in patients with irritable bowel syndrome (Lecci et al., 2006).

Slow transit constipation (STC) is a chronic and debilitating functional colonic dysmotility that is unrelated to systemic disorders or pelvic floor dysfunction (Knowles and Martin, 2000; Knowles et al., 2001). The adult form of STC is found almost exclusively in young to middle-aged women (Lubowski et al., 1996; Knowles and Martin, 2000). The pathophysiological basis of STC is poorly understood. In pediatric STC, changes in NK₂ receptors but not in cholinergic transmission were reported (Stanton et al., 2003). However, the etiology and disease process of adult STC differs from pediatric STC; this occurs in males and females, and the onset of the disease is typically in infancy to early childhood (Sutcliffe et al., 2004).

In some of the studies of adult STC, a reduction in the cell volume or number of ICC has been reported in STC (He et al., 2000; Wedel et al., 2002), but others failed to detect any abnormalities in ICC, despite the selection of highly symptomatic individuals (Toman et al., 2006). It also was suggested that decreased number and size of colonic enteric neurons may play a role (He et al., 2000; Knowles and Martin, 2000; Wedel et al., 2002). A recent study, using novel smooth muscle markers and transmission electron microscopy, revealed abnormalities linked to the smooth muscle contractile apparatus in patients with STC and idiopathic megacolon (Wedel et al., 2006). Most recently, there has been a report that abnormal levels of PGs and cyclooxygenase (COX)-2 may be associated with the impaired motor function in STC patients (Cong et al., 2007).

Results on involvement of tachykinin immunoreactivity in STC have been rather variable, with levels of SP like immunoreactivity increased (Sjölund et al., 1997), decreased (Tzavela et al., 1996; Porter et al., 1998), or unchanged (Dolk et al., 1990). Functional data investigating colonic motility and enteric signaling in STC are sparse. One study showed an increased contractility of isolated colon circular muscle to selective NK₂ receptor agonists in male STC patients compared with control, but the cholinergic component remained unchanged (Menzies et al., 2001). In contrast, other studies demonstrated a hyporesponsiveness to tachykinin and acetylecholine stimulation (Mitolo-Chiappa et al., 1998, 2001; Tomita, 2008) and a reduced relaxation response to vasoactive intestinal peptide (Tomita, 2008). The aim of this study was to investigate whether there were changes in STC in tachykinin-mediated circular muscle contraction and responses to electric field stimulation (EFS) and the ganglionic nicotinic receptor agonist dimethylphenylpiperazinium (DMPP). Using the COX inhibitor indomethacin, we have provided insights into possible mechanisms underlying such changes.

### Materials and Methods

#### Patients and Specimens

Sigmoid colon segments were obtained from 27 female patients (median age, 48.5; range, 19–73 years) undergoing subtotal colectomy with ileorectal anastomosis for STC. These STC patients represented severe cases that were resistant to conventional laxative treatment (Wong and Lubowski, 2007). Control sigmoid colon segments (resected during surgery for carcinoma, taken 10–15 cm from the tumor) were obtained from 29 female patients (median age, 48; range, 30–72). Patients who had obstruction or had undergone radiation therapy or chemotherapy were excluded from the study.

Small pieces of specimens were collected directly into the RNA-later solution and used for RNA extraction. Other specimens (approximately 4 cm in length) were collected into carbon-gassed ice-cold Krebs-Henseleit solution, transported to the laboratory on ice at the day of surgery, and dissected within 4 h of arrival. The mucosa, submucosa, and serosa were dissected away, and the circular muscle bands were then separated from the taenia coli. The dissected circular muscle was placed in fresh Krebs-Henseleit solution, stored overnight at 4°C, and used for functional studies the next day. This project was approved by the Human Ethics Committees of the University of NSW and the St. George Hospital.

#### Functional Studies

Circular muscle bands were cut into 4 × 8-mm strips and suspended under 1-g tension in 2-mL siliconized glass organ baths containing Krebs-Henseleit solution at 37°C and aerated with carbogen. Muscle tension was recorded isometrically using Grass FTO3C force transducers and recorded by Polygraph computer program (Mr. E. Crawford, University of New South Wales, NSW, Australia). After 60 min of equilibration with periodic washing, acetylecholine (ACh; 10 mM) was added into each bath to induce maximal muscle contraction, and this was repeated at the end of each experiment. ACh was then washed out, and the muscle strips were allowed to rest 60 min before further experiments. A single concentration-response curve was obtained from each strip, as described previously (Liu et al., 2002; Burcher et al., 2008). All muscle strips were weighed at the end of each experiment. The mean (±S.E.M.) weights of strips used for SP studies were 54.9 ± 3.6 mg for control and 64.0 ± 5.5 mg for STC (P > 0.05, unpaired Student’s t test).

#### Responses to Agonists

Discrete concentration-response curves were constructed for ACh, SP, NKA, the NK₂ receptor selective antagonist GMPP, and the ganglionic nicotinic receptor agonist DMPP, with ascending concentration sequences. Each concentration was left in contact with the tissue for 4 to 6 min before washing, and a 30- to 60-min agonist-free rest period was given to avoid tachyphylaxis.

#### Responses to SP in the Presence of Inhibitors

To determine mechanisms underlying changes seen in STC tissues in response to SP, discrete concentration-response curves to SP were constructed in the presence of the NK₁ receptor antagonist SR49868 (0.1 μM), the NK₂ receptor antagonist CP99994 (0.1 μM), atropine (1 μM), hexamethonium (100 μM), tetrodotoxin (TTX, 1 μM), indomethacin (1 μM), indomethacin (1 μM) plus CP99994 (0.1 μM), or indomethacin (1 μM) plus TTX (1 μM). All inhibitors were added to the bath 30 min before the addition of SP, except SR49868, which was added 2 h before tissues were exposed to SP. These experiments were performed using a paired design.

#### Activation of Enteric Nerves by EFS

Circular muscle strips were positioned between two platinum rings in 2-mL organ baths and equilibrated under a rest tension of 1 g for 60 min. Muscle tension was recorded isometrically as described above. The maximal contraction was induced with 10 mM ACh. After washout of ACh, the muscle strips were allowed to equilibrate for a further 60 min. EFS was conducted at supramaximal voltage with pulses of 1-ms duration at frequencies of 0.5, 1, 2.5, 5, 10, 20, and 40 Hz in trains lasting 10s. In some strips, EFS was carried out in the presence of atropine (1 μM) and/or TTX (1 μM).

#### Data Analysis

Contractile responses to agonists or to EFS were measured in grams and then expressed as a percentage of the maximal response to 10 mM ACh in each strip. The agonist potencies were expressed as pEC₅₀ (–log EC₅₀), and the maximal response (E₉₀) to NKA and [Lys⁵,MeLeu⁹,Nle¹⁰]NKA(4–10) was defined as the response achieved at 10 μM. The maximal responses to ACh and SP did not seem to have been reached at the...
highest concentration of agonist used; the apparent $E_{\text{max}}$ for ACh was taken at 10 mM and that for SP at 100 nM.

**TABLE 1**

<table>
<thead>
<tr>
<th>Agonist</th>
<th>pEC$_{50}$ Control</th>
<th>pEC$_{50}$ STC</th>
<th>$E_{\text{max}} %$ Control</th>
<th>$E_{\text{max}} %$ STC</th>
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<tr>
<td>ACh</td>
<td>3.28 ± 0.34 (23)</td>
<td>3.22 ± 0.39 (14)</td>
<td>0.38 ± 0.05 (21)</td>
<td>0.38 ± 0.05 (21)</td>
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<tr>
<td>SP</td>
<td>6.14 ± 0.13 (28)</td>
<td>5.35 ± 0.06*** (27)</td>
<td>62.8 ± 9.22% (18)</td>
<td>45.0 ± 2.30%*** (21)</td>
</tr>
<tr>
<td>NKA</td>
<td>7.43 ± 0.09 (26)</td>
<td>7.36 ± 0.10 (14)</td>
<td>60.6 ± 3.47% (25)</td>
<td>58.0 ± 4.58% (13)</td>
</tr>
<tr>
<td>NKA analog</td>
<td>7.51 ± 0.12 (25)</td>
<td>7.31 ± 0.16 (15)</td>
<td>63.5 ± 3.57% (24)</td>
<td>57.9 ± 4.35% (15)</td>
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**Results**

**Functional Studies in Sigmoid Colon Circular Muscle Strips: Response to Agonists.** Contractile responses to ACh, SP, NKA, and [Lys$_5$,MeLeu$_9$,Nle$_{10}$]-NKA(4–10) were purchased from Auspep (Melbourne, Australia). CP99994 was obtained from Dr. M. Snider (Pfizer, Groton, CT), SR48968 from Dr. X. Emonds-Alt (Sanofi-Synthelabo, Montpellier, France). Stock solutions of peptides were made in 0.01 M acetic acid containing 1% β-mercaptoethanol and stored in aliquots at −20°C. ACh, indomethacin, atropine, TTX, DMPP, and hexamethonium were purchased from Sigma-Aldrich (St. Louis, MO). AmpliScribe T7 High Yield Transcription Kit was purchased from Astral Scientific Pty Ltd (Caringbah, Australia), TRIzol reagent was from Invitrogen (Carlsbad, CA), and the Access RT-PCR system was from Promega (Madison, WI).

There were no age-related changes in the maximal response to SP in either control or STC circular muscle strips (Fig. 3). Furthermore, age-related changes were completely absent with respect to maximal responses to ACh, NKA, and [Lys$_5$,MeLeu$_9$,Nle$_{10}$]-NKA(4–10) (data not shown).

**Response to SP in STC in the Presence of Inhibitors.** To determine mechanisms underlying reduced circular muscle contractile responses to SP in STC (Fig. 2B), the effects of...
various inhibitors were investigated in paired studies. The contractile responses to SP were almost abolished by pre-treating tissues with the selective NK₂ receptor antagonist, SR48968 (0.1 μM; Fig. 4A), but were unaffected by the NK₁ receptor antagonist, CP99994 (0.1 μM; Fig. 4B). This was similar to our previously published observation in the control (Liu et al., 2002), suggesting an NK₂ (rather than NK₁) receptor-mediated contractile response to SP in this tissue.

Atropine (1 μM, Fig. 4C) and hexamethonium (100 μM, Fig. 4D) had no effect on responses to SP in STC. TTX (1 μM, Fig. 4E) showed a small enhancement of responses at 10 μM SP. A notable result was the enhancement by indomethacin (1 μM, Fig. 4F) of contractile responses to SP. In other words, responses to SP in STC were fully restored to the control level in the presence of indomethacin.

The mechanism of this effect of indomethacin was further studied. TTX (1 μM) abolished the potentiation by indomethacin at lower concentrations of SP (10⁻⁴ M and less) and partially inhibited its effect at the highest SP concentration (10⁻³ M) (Fig. 4G). CP99994 (0.1 μM) totally abolished the
indomethacin-induced increase in responses at all concentrations of SP (Fig. 4H).

**Response to DMPP.** The ganglionic nicotinic receptor agonist, DMPP, produced a biphasic response in circular muscle strips. Responses were characterized by very small net relaxations at lower concentrations (10^-7-10^-4M); these were significantly different from baseline tension. At the highest concentration (10^-3M), there was no net contraction, equivalent to 8% of ACh maximal response. Responses were no different between control and STC strips (Fig. 5).

**Response to EFS.** EFS usually induced contraction, although in some control and STC strips, EFS caused an initial relaxation at low frequencies. In control strips, EFS elicited frequency-dependent increases in contractions, ranging from relaxation at low frequencies. In control strips, EFS elicited though in some control and STC strips, EFS caused an initial reduction; these were unrelated to the stimulation frequency (22–33% ACh maximal contraction). In STC, atropine and TTX almost completely abolished responses to EFS. In comparison with control (Fig. 6C), at lower frequencies (0.5–5 Hz), the contractile amplitudes were higher in STC than in control, but contractile responses of STC to higher frequency stimulation (10–40 Hz) were greatly reduced compared with control.

**QC-RT-PCR.** NK1 and NK2 receptor mRNA expression levels were measured in the sigmoid colon circular muscle of STC patients, compared with age-matched controls. As shown in Fig. 7A, there was a 2.6-fold increase in NK1 receptor mRNA expression in STC. The NK2 receptor mRNA was expressed at similar levels in STC and control (Fig. 7B). No age-related differences in expression of NK1 or NK2 receptor mRNA were seen, for either control or STC data.

**Discussion**

Several important findings have resulted from this study. First, SP-mediated contractions of female colonic circular muscle strips were significantly diminished in STC, compared with age-matched control. Second, this reduction was reversed by indomethacin in STC, suggesting changes in COX in this disorder. Third, NK1 receptors appear implicated, because: 1) CP99994 antagonized the effect of indomethacin, and responses to EFS were reduced by atropine (1 μM) but not further reduced by TTX (1 μM), *P < 0.05, one way ANOVA; B, EFS-evoked contractions in STC circular muscle were unrelated to stimulation frequency and were reduced by atropine (1 μM); TTX (1 μM) showed no further significant reduction; *, *P < 0.05; **, **P < 0.01; ***, **P < 0.001, one-way ANOVA. C, at lower frequencies (0.5–5 Hz), the contractile amplitudes were higher in STC than in control (P < 0.05, two-way ANOVA). However, contractile responses to higher frequency stimulation (10–40 Hz) were greatly reduced in STC compared with control (P < 0.01). Points represent the mean ± S.E.M. of n individual patients.

Mechanisms are also likely to be involved because TTX also antagonized the effect of indomethacin, and responses to EFS were markedly altered in STC.

The reduction of contractility to SP seen in STC was not due to its action on NK2 receptors, which are primarily responsible for mediating the direct component of SP-induced contractile responses (Warner et al., 2000; Liu et al., 2002; Burcher et al., 2008). Contractile responses to NKA and to the selective NK2 receptor agonist, [Lys⁵,MeLeu⁹,Nle¹⁰]-NKA(4–10), were unaltered in STC. Furthermore, ACh-induced contractions also remained unchanged, indicating that the attenuation of SP responses was unrelated to nonspecific diminished responsiveness of smooth muscle. A minor component(s) of the SP contractile response is independent of NK2 receptors and involves NK1 receptors associated with neuronal and/or immune cell mechanisms (Fig. 8). We suggest that this indirect NK1 receptor-mediated component is unmasked and/or amplified in STC, and its activation by SP
results in a net relaxation of colonic smooth muscle (Fig. 8). This hypothesis is supported by the increased expression of NK₁ receptor mRNA in STC, whereas NK₂ receptor mRNA remained unchanged.

Constitutive COX-1 and COX-2 are widely expressed in normal human colon smooth muscle, myenteric ganglia, and ICC, and in the mucosa (Fornai et al., 2005; Bernardini et al., 2006; Burcher et al., 2008). Prostanoids play many roles in normal gut function, being involved in mucosal protection and repair, regulation of blood flow, mucosal secretion, and motility. We previously reported that in normal human colon circular muscle, contractile responses to SP were unaffected by indomethacin (Liu et al., 2002). However, a novel finding of the present study was that the mechanism of the attenuated response to SP in STC seems to be related to the COX system. This result is consistent with a recent study (Cong et al., 2007) showing that abnormal levels of PGs and COX-1 and COX-2 occur in female patients with STC. They found that the reduced spontaneous motility in STC was associated with a reduction of contractile PGs, thromboxane A₂ and PGF₂α (Cong et al., 2007), and an increase of PGE₂, known to relax colonic circular muscle (Bennett et al., 1981; Botella et al., 1995).

Our studies in STC circular muscle found that the indomethacin-induced reduction of contractile responses to SP (Fig. 4F) was blocked by the NK₁ receptor antagonist CP99994 (Fig. 4H). Thus, we hypothesize that the STC-susceptible indirect component of the SP response is due to an increased release of inhibitory PGs, through activation of NK₁ receptors (Fig. 8). Neuronal mechanisms may also be involved, since TTX reversed the attenuated responsiveness to SP in STC. TTX also (as well as CP99994) blocked the indomethacin-induced potentiation of contractile response to SP. We suggest that SP caused an indirect muscle relaxation, via activation of neuronal NK₁ receptors that mediate the release of an inhibitory mediator(s) (suggested to be PGs) from postganglionic enteric neurons and other cell types (Fig. 8). This is consistent with literature findings that COX enzymes are expressed in myenteric ganglia and involved in inhibitory modulation of cholinergic motor functions in normal human colon (Fornai et al., 2005; Bernardini et al., 2006).

Although there is no functional evidence for the participation of NK₁ receptors in human colon circular muscle contraction, NK₁ receptors are present on the circular muscle, ICC, enteric ganglia, nerve fibers, and vascular endothelial cells of the human colon (Goode et al., 2000; Renzi et al., 2000; Liu et al., 2002). We postulate that the NK₁ receptor is closely associated with COX enzymes in the human colonic myenteric ganglia and/or muscularis externa. The restoration of contractility by SP revealed that an imbalance in prostanooid production seems to be related to the pathophysiology of STC.

Our finding that EFS-evoked contractions were increased at lower frequency and reduced at higher frequency in STC compared with control may reflect an impaired enteric motor function in STC. Unlike the control, EFS-evoked contractions in STC were similar in amplitude and unrelated to stimulation frequency. Similar to the control, the EFS-induced contractions in STC were mainly cholinergic in origin, and in some strips, an initial relaxation was seen at low frequencies. In the intestine, the inhibitory motor neurons release a combination of at least three transmitters, nitric oxide (NO), ATP, and vasoactive intestinal peptide, but in circular muscle of the human colon, NO is the principal inhibitory transmitter (Boeckxstaens et al., 1993; Keef et al., 1993). It is possible that dysfunctions of both inhibitory and excitatory neurotransmission occur in STC. It has been shown that STC patients display a loss of enteric neurons, partially because of increased apoptosis (Bassotti et al., 2006). A reduced release of [³H]ACh in response to EFS in STC taenia coli muscle strips and decreased choline acetyltransferase in colonic myenteric neurons of STC have been demonstrated (Burleigh, 1988; Wattchow et al., 2008). Conversely, increased NO synthase-positive neurons and activities are associated with STC (Tomita et al., 2002; Wattchow et al., 2008). Our result is in agreement with the study by Mitolo-Chieppa et al. (2001) performed in male STC circular muscle, which shows that EFS-induced relaxation of SP-precontracted muscle strips is reduced at 0.5 Hz (ATP mediated) and enhanced at 4 Hz (NO) mediated compared with control, suggesting an abnormality in NO and ATP release. Therefore, we cannot rule out that the reduced contractile amplitudes at higher frequency may be attributed to (or partially attributed to) the excessive NO production in STC.

In animals, DMPP induces relaxation of rat distal colon by a purinergic and a nitricergic mechanism and causes guinea pig ileum contraction by increase of ACh output, through stimulation of nicotine receptors situated on myenteric ganglia (Börjesson et al., 1997; Galligan, 1999). In human colon, the dual effects of DMPP on circular muscle activity do not seem to have been reported. At lower concentrations, the net effect was a slow relaxation indicating the release of inhibitory neurotransmitters, whereas at the highest concentration, the output of excitatory neurotransmitters predominated. In contrast to our EFS results, responses to DMPP were unaltered in STC. The results are difficult to interpret because any alteration in enteric neurotransmission may be masked by opposing inhibitory and excitatory actions. One explanation is that DMPP has a relatively limited action, activating ganglionic motor neurons, whereas EFS activates mixed populations of all axons and nerve terminals.
A recent study suggests that a defective expression of proteins associated with the smooth muscle contractile apparatus may be involved in the pathogenesis of STC (Wedel et al., 2006). Immunostaining for smooth muscle myosin heavy chain, smoothelin, and histone deacetylase 8 was homogenous in normal colon smooth muscle but was either absent or greatly reduced in STC smooth muscle (Wedel et al., 2006). No abnormality of smooth muscle contractile apparatus was observed in our study because the contractile responses to NKA and ACh, both of which are via direct myogenic mechanisms, were unchanged in STC. However, because both the receptor subtypes involved (tachykinin NK1 and muscarinic M3 receptors) use the same second messenger pathway, G protein-coupled inositol trisphosphate and calcium, the occurrence of other specific defects of smooth muscle contractile mechanisms in STC cannot be excluded.

In summary, SP-mediated circular muscle contractions were significantly diminished in STC, whereas contractile responses to NKA and ACh were unaltered. An important and original finding is that reduced contractile responses to SP in STC were restored by indomethacin to the normal control level, suggesting a role of prostanoids in the pathogenesis of STC. The restoration by indomethacin was blocked by the NK1 receptor antagonist CP99994 and by TTX. We also found that STC circular muscle strips showed an altered contractile pattern in response to electric nerve stimulation, supporting the theory of an impaired function of the enteric nervous system in STC. In conclusion, the reduction in magnitude of contractile responses to SP in STC may be due to an increased release of inhibitory PGs from possibly neuronal sites, via up-regulated NK1 receptors.

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References


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