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Neural regulation of the interrelation between haustral and taenial motility in the rabbit proximal colon.

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Abstract

Neural regulation of the motility between the haustra and taenia coli was studied in the isolated rabbit proximal colon. Four types of haustral and taenial preparations were used: the haustral strip without the taenia coli (type 1), the haustral strip including the taenia coli (type 2), the L-shaped (taenia-haustra) preparations for recording the haustral (circular) response to taenial stimulation (type 3) and the L-shaped (haustra-taenia) preparation for recording the taenial (longitudinal) response to haustral stimulation (type 4). Field electrical stimulation induced a contractile response in the haustra and taenia coli. Hexamethonium reduced the contraction in type 2, 3 and 4 preparations. The desensitization to serotonin reduced the response in type 2 and 3 preparations. After atropinization, the response in types 1 and 4 was reversed to relaxation, and the response in types 2 and 3 was reversed to relaxation followed by contraction which was reduced or abolished by indomethacin. The responses remaining after atropinization in all types of preparations were not affected by other blocking agents tested or desensitization to neuropeptides. Tetrodotoxin abolished all relaxation and contractile responses in all types of preparations. These results suggest that the indirect contractile response to field stimulation is induced mainly via cholinergic and serotonergic neurons, and that the relaxation is mainly mediated by nonadrenergic noncholinergic neurons. The late haustral contractions after atropine may be caused by endogenous prostaglandin.

KEYWORDS: proximal colon, cholinergic neuron, serotonergic neuron, nonadrenergic noncholinergic neuron, prostaglandin

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Neural Regulation of the Interrelation between Haustral and Taenial Motility in the Rabbit Proximal Colon

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Neural regulation of the motility between the haustra and taenia coli was studied in the isolated rabbit proximal colon. Four types of haustral and taenial preparations were used: the haustral strip without the taenia coli (type 1), the haustral strip including the taenia coli (type 2), the L-shaped (taenia-haustra) preparations for recording the haustral (circular) response to taenial stimulation (type 3) and the L-shaped (haustra-taenia) preparation for recording the taenial (longitudinal) response to haustral stimulation (type 4). Field electrical stimulation induced a contractile response in the haustra and taenia coli. Hexamethonium reduced the contraction in type 2, 3 and 4 preparations. The desensitization to serotonin reduced the response in type 2 and 3 preparations. After atropinization, the response in types 1 and 4 was reversed to relaxation, and the response in types 2 and 3 was reversed to relaxation followed by contraction which was reduced or abolished by indomethacin. The responses remaining after atropinization in all types of preparations were not affected by other blocking agents tested or desensitization to neuropeptides. Tetrodotoxin abolished all relaxation and contractile responses in all types of preparations. These results suggest that the indirect contractile response to field stimulation is induced mainly via cholinergic and serotonergic neurons, and that the relaxation is mainly mediated by nonadrenergic noncholinergic neurons. The late haustral contractions after atropine may be caused by endogenous prostaglandin.

Key words: proximal colon, cholinergic neuron, serotonergic neuron, nonadrenergic non-cholinergic neuron, prostaglandin

In the rabbit, the part of colon oral to the fusus coli has been named as the proximal colon and that of the colon aboral to it, is referred to as the distal colon. The proximal colon is divided into two parts: one has three taeniae coli with the typical formation of haustra between the taeniae, and the other has a single wide taenia covering approximately half of the circumference of the

colonic tube with a single row of haustra completing the circumference (1). The fusus coli acts as a pacemaker of the colon (2, 3). Section of the proximal colon oral to the fusus coli has been shown to reduce markedly the slow wave frequency in the proximal colon. The slow wave frequency in most oral part of the proximal colon was less than that in the distal colon (3). In the proximal colon of the rabbit, three types of contraction have been observed: haustral activity,

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segmental activity and mass peristalses (4). In the haustra coli, Ehrlein *et al.* (5) observed a migrating shallow ring (repetitive contraction).

In the rabbit, the proximal colon from the ileo-cecal valve to the fusus coli is innervated exclusively by the vagus and splanchnic nerves (6).

Although effects of various agents, such as nicotine (7), acetylcholine (9), catecholamine (8-11), serotonin (9) and neuropeptides (12-21), on rabbit colonic motility have been studied, the role of neurons in connecting the haustral and taenial motility has never been investigated. Therefore, aim of this experiment was to examine this particular role.

Materials and Methods

Twenty-three rabbits of both sexes, weighing 1.5-2.5 kg, were used. The proximal colon was removed after urethane anesthesia (1.0 g/kg, i.v.) and placed in aerated Tyrode solution (mM; 145 NaCl, 2.7 KCl, 1.5 CaCl₂, 0.7 MgCl₂, 4.8 NaHCO₃, 0.3 NaHPO₄, 11.1 glucose). After intraluminal contents were rinsed, the proximal colon was separated into four types of preparation: a) the haustral strip without the taenia coli (type 1), b) the haustral strip including the taenia coli (type 2), c) an L-shaped preparation for recording the haustral motility induced by taenial stimulation (type 3), and d) an L-shaped preparation for

recording the taenial motility induced by haustral stimulation (type 4) (Fig. 1). These preparations were placed in a 15-ml organ bath containing Tyrode solution at $36.0 \pm 0.5^\circ\text{C}$, which was aerated with 95 % O₂ + 5 % CO₂. The circular contraction of the haustra and the longitudinal contraction of the taenia coli were recorded with isotonic transducers (TD-112S, Nihon Kohden, Tokyo, Japan) and a pen oscillograph (RJG-3026, Nihon Kohden, Tokyo, Japan). The resting load was 0.5 g. The contractile response induced by electrical stimulation was compared with carbachol (0.3 μM)-induced contraction.

The preparations were equilibrated for 90-120 min and washed out every 30 min. In order to stimulate the enteric neurons of the proximal colon, the preparations were stimulated at 5, 10, 20 Hz, 0.5 msec, maximal current during 20 sec at every 6 to 8 min interval. The blocking agents were added 10-15 min before starting the field stimulation. The desensitization to serotonin and substance P was achieved by administering 3 times the same concentration of drugs 5 min before the field stimulation.

Statistical analysis was performed by means of Student's *t*-test for paired data. Values of $p < 0.05$ were regarded as significant.

The following drugs were used: atropine sulfate (Merck, Darmstadt, West Germany), tetrodotoxin (San-kyo, Tokyo, Japan), pyrilamine hydrochloride (Sigma Chemical Co., St. Louis, USA), guanethidine sulfate (Tokyo Kasei, Tokyo, Japan), cimetidine hydrochloride (Sigma, St. Louis, USA), indomethacin (Japan Merck-Banyu, Tokyo, Japan), hexamethonium bromide (Sigma), serotonin creatinine sulfate (Nakalai Teque, Kyoto, Japan), ketanserin (Janssen, Beerse, Belgium), adrenaline

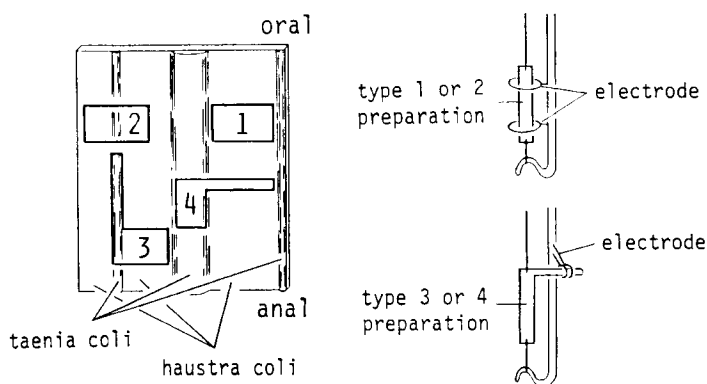


Fig. 1 Schematic drawings of methods and prepared areas. Numbers in the figure indicate the areas used in the respective types of preparations. Type 1 and 2 preparations were stimulated by field electrical stimulation. When the taenia coli was stimulated in the type 3 preparation, the haustral motility was recorded and when the haustra was stimulated in the type 4 preparation, taenial motility was recorded.

bitartrate (Sigma), L-noradrenaline bitartrate (Sigma), L-isoprenaline hydrochloride (Katayama Chem Ltd., Osaka, Japan), phentolamine methanesulfonate (Japan Ciba-Geigy, Takarazuka, Japan), phenylephrine hydrochloride (Sigma), propranolol hydrochloride (Sigma), carbamylcholine chloride (Katayama, Chem.), acetylcholine chloride (Wako Pure Chemical Fud., Ltd., Osaka, Japan), 1, 1-dimethyl-4-phenylpiperazinum iodide (DMPP) (Aldrich, Milwaukee, WIS., USA), (+)-bicuculline (Sigma), 5-aminovaleic acid (Sigma), capsaicin (Sigma), naloxone hydrochloride (Sigma), substance P (Peptide Inst., Osaka, Japan), neurotensin (Peptide Inst.), met-enkephalin (Peptide Inst.) and somatostatin (Peptide Inst.).

Results

Effects of field stimulation on four types of strip preparations separated from the proximal colon. Electrical field stimulation (5, 10, 20 Hz, 0.5 msec, maximal current) induced a contractile response in all 4 types of preparations. In these

preparations, the contractile response was increased by stimulation (5, 10 and 20 Hz) in an intensity dependent manner. After termination of field stimulation, the spontaneous contraction in type 1 was reduced or disappeared in every case, while in type 2 and type 3 preparations, the spontaneous contraction decreased after the stimulation but did not disappear. Field stimulation of the haustra (type 4) induced a contraction of the taenia coli followed by a relaxation in most preparations. The responses in type 3 and 4 preparations were abolished by cutting the haustra or taenia that is connected to the site of stimulation by the electrode.

Effects of atropine on the contractile response induced by field stimulation and influences of other drugs on the remaining response after application of atropine. In type 2 and 3 preparations, the haustral contractile response was reversed to a relaxation by atropine, which was followed by a contraction. The haustral contraction

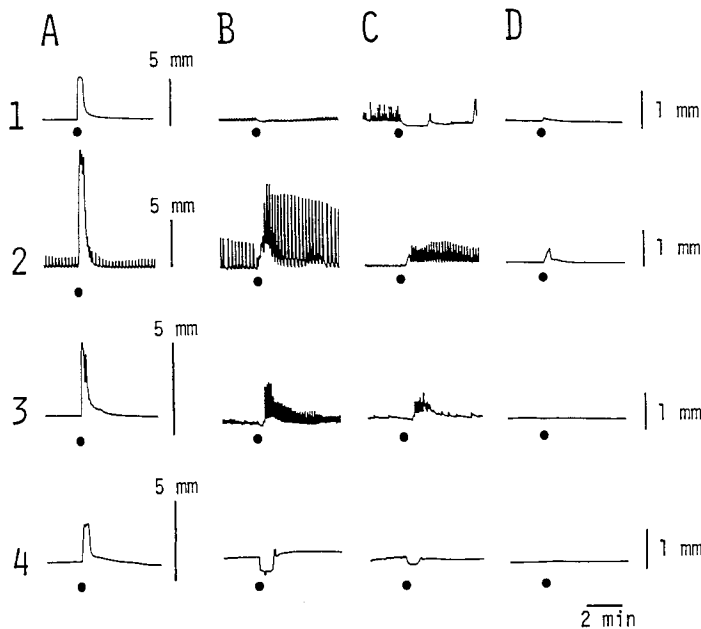


Fig. 2 Effects of atropine, guanethidine, indomethacin and tetrodotoxin on the response induced by field stimulation. A, control; B, after $1\mu\text{M}$ atropine and $1\mu\text{M}$ guanethidine; C, after atropine, guanethidine and $2.8\mu\text{M}$ indomethacin; D, after atropine, guanethidine, indomethacin and $0.32\mu\text{M}$ tetrodotoxin. ●, 20 Hz, 0.5 msec, maximal current. Numbers (1-4) on the left indicate the types of preparations.

in type 1 and the taenial contraction in type 4 were reversed to relaxation (Fig. 2B). These relaxations which remained after atropine were not abolished by guanethidine ($1\mu\text{M}$), pyliramine ($1\mu\text{M}$), bicucullin ($1, 5\mu\text{M}$), 5-aminovaleric acid ($1, 5\mu\text{M}$), cimetidine ($1\mu\text{M}$), ketanserin ($1, 3\mu\text{M}$), or hexamethonium ($10\mu\text{M}$), while the contraction remaining after atropine with guanethidine was reduced or abolished by indomethacin ($1, 10\mu\text{M}$) in type 2 and 3 preparations (Fig. 2C). The relaxation and contractile responses remaining after indomethacin were both abolished by tetrodotoxin ($0.32, 1.6\mu\text{M}$) in type 3 and 4 preparations (Fig. 2D).

Effects of hexamethonium (C_6) on the contractile response induced by field stimulation in all 4 types of preparations. C_6 ($10\mu\text{M}$) had no effect on the spontaneous motility and tone in all

4 types of preparations. After treatment with C_6 , the contractile response (10 Hz) in type 1 preparations was reduced to about 90 % of the control value ($p > 0.05$) (Fig. 3B-1 and 4A-1). In type 2 preparation, the contractile response was also decreased to about 90 % of the control ($p < 0.05$) (Fig. 3B-2 and 4A-2). In type 3 preparation, the contractile response was reduced to 75 % of the control ($p < 0.05$) (Fig. 3B-3 and 4A-3). In type 4, the contractile response was reduced to 20 % of the control ($p < 0.05$) (Fig. 3B-4 and 4A-4).

Effects of desensitization to serotonin, substance P and capsaicin on the contractile response to field stimulation. Serotonin ($0.1, 5\mu\text{M}$) and substance P ($50\text{--}100\text{ nM}$) induced contractile responses in all 4 types of preparations, which were reduced by atropine ($1\mu\text{M}$) but not by guanethidine ($1\mu\text{M}$).

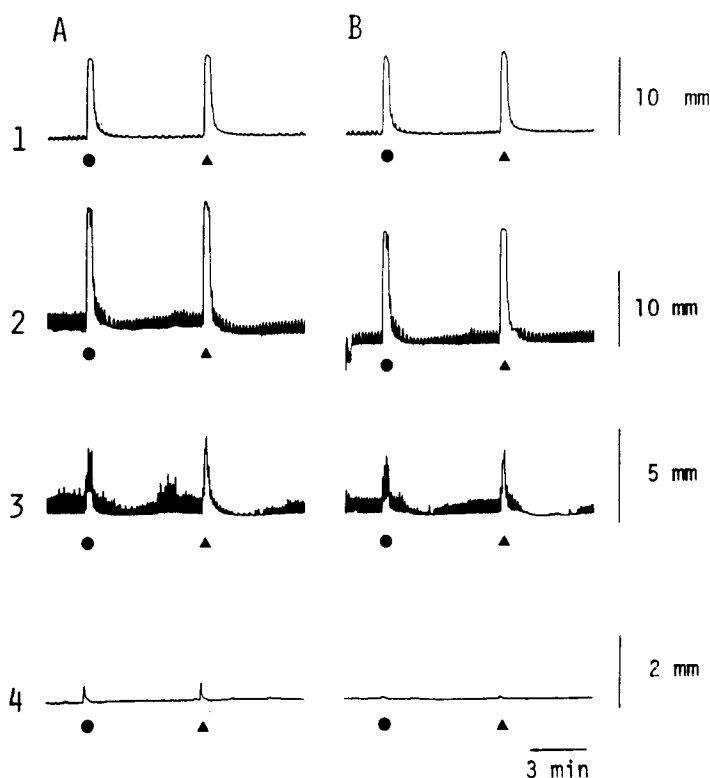


Fig. 3 Effects of hexamethonium on the contractile response induced by field electrical stimulation.

A, control; B, after hexamethonium bromide ($10\mu\text{M}$); ●, 10 Hz , 0.5 msec maximal current; ▲, 20 Hz , 0.5 msec maximal current. Numbers on the left indicate the types of preparations.

Desensitization to serotonin was achieved in all 4 types of preparations by applying serotonin ($5\mu\text{M}$) 3 times. Unlike in type 1 preparation, the type 2 showed that the contractile response induced by field stimulation was decreased by serotonin-desensitization ($p < 0.05$) (Fig. 4C-2). In type 3 preparation, the contractile response was reduced by serotonin-desensitization to about 18 % of the control ($p < 0.05$) (Fig. 4C-3). In type 4 preparation, the contractile response showed a tendency to decrease after serotonin-desensitization, but the effect did not reach a significant level (Fig. 4C-4). After application of

C_6 , additional serotonin-desensitization reduced the contractile response in type 2 and 3 preparations.

Desensitization to substance P was achieved in all 4 types of preparations by application of substance P (50 or 100nM) 3 times. The resultant application revealed that the spontaneous phasic contraction was larger than the control contraction in all types of preparations. In type 2, 3 and 4 preparations, the contractile response was influenced by substance P-desensitization, but the difference between the control and the post-desensitization response was not significant (Fig.

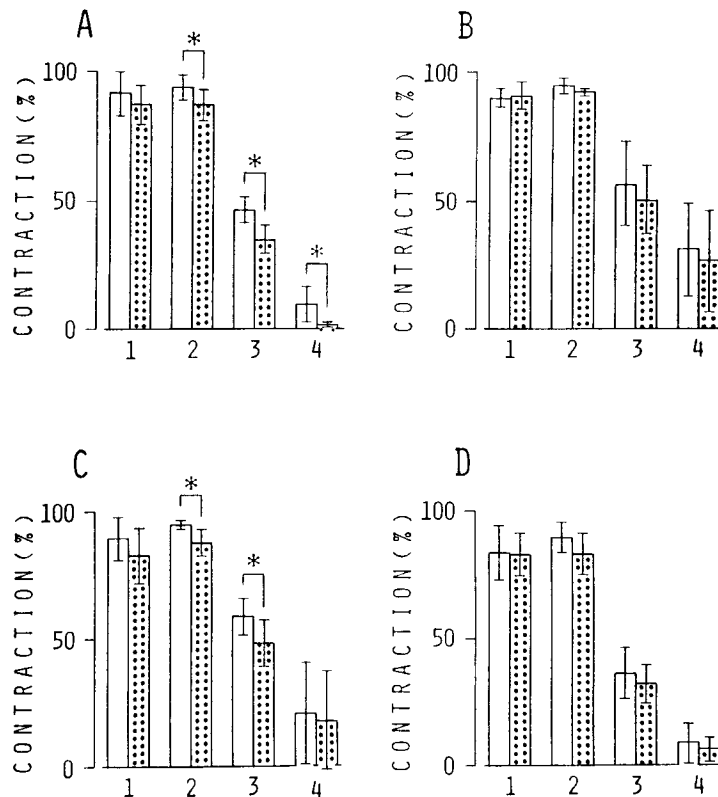


Fig. 4 Effects of hexamethonium, guanethidine, desensitization to serotonin or substance P on the contractile response induced by field electrical stimulation.

1, haustra; 2, haustra including taenia coli; 3, L-shaped type 3 preparation, in which haustral motility was induced by taenial stimulation; 4, L-shaped type 4 preparation, in which taenial motility was induced by haustral stimulation. Open column, field stimulation-induced contraction (10 Hz, 0.5 msec, maximal current); Dotted column, after treatment with $10-30\mu\text{M}$ hexamethonium (A) ($n = 7$), $10\mu\text{M}$ guanethidine (B) ($n = 5$), desensitization to $5\mu\text{M}$ serotonin (3 times) (C) ($n = 7$) and $0.5\mu\text{M}$ substance P (3 times) (D) ($n = 7$).

Vertical bars in each column indicate SD. The contraction induced by field stimulation in all preparations was calculated as percentages of carbachol-induced contraction ($0.3\mu\text{M}$). *, $p < 0.05$ compared with control.

4).

Capsaicin ($3\mu\text{M}$) had an effect similar to substance P-desensitization in all 4 types of preparations, regarding contractile response to field stimulation. After atropinization, these excitatory effects were not observed in any preparation.

Effects of some autonomic agents, polypeptide and other blocking agents. Phenylephrine ($1\mu\text{M}$) and isoprenaline ($1\mu\text{M}$) induced relaxation of the haustral (circular) strip which was antagonized by phentolamine ($1\mu\text{M}$) and propranolol ($1\mu\text{M}$), respectively. Adrenaline ($1\mu\text{M}$) and nor-adrenaline ($1\mu\text{M}$) caused relaxation of the haustra which was abolished by the combination of phentolamine ($1\mu\text{M}$) and propranolol ($1\mu\text{M}$). Acetylcholine ($0.5\mu\text{M}$) induced an atropine ($1\mu\text{M}$)-sensitive contraction. DMPP ($10\mu\text{M}$) caused a contraction which was antagonized by hexamethonium ($10\mu\text{M}$).

Neurotensin (50nM) induced contractions, and met-enkephalin (0.1 and $0.5\mu\text{M}$) produced relaxation which was antagonized by naloxone ($1\mu\text{M}$). Desensitization to neurotensin or somatostatin did not at all affect the contractile response induced by field stimulation in any preparation.

The contractile and relaxant responses induced by field stimulation were not affected by cimetidine, naloxone, bicucullin or phentolamine in any preparation. The contractile responses by field stimulation in type 1 and 2 preparations were neither reduced nor increased by treatment with guanethidine ($1\mu\text{M}$) ($p > 0.05$) (Fig. 4B-1,2). In type 3 and 4 preparations, the contractile response showed a tendency to be reduced after treatment with guanethidine ($1\mu\text{M}$) ($p > 0.05$) (Fig. 4B-3,4).

Discussion

In the present experiment, the neural control of the interrelation of motility of the haustra and taenia coli was studied in the isolated rabbit proximal colon.

Field stimulation induced a contractile response of the haustral circular muscle in type 1 and 2 preparations, whereas it produced a contractile response in the haustra and taenia coli, respectively, in type 3 and 4 preparations. The contractile responses in type 2,3,4 preparations were inhibited by hexamethonium. These results suggest that the increase in the haustral and taenial motility by field stimulation is mediated via the presynaptic cholinergic neurons in the myenteric plexus, which activate nicotinic receptors of postsynaptic neurons via the release of acetylcholine.

Leander *et al.* (14) observed substance P immunoreactive neurons in the myenteric plexus of the guinea-pig colon. Substance P induced a contractile response in the gut (13, 14, 16, 17), which was reduced by atropine (16). These previous reports suggest that some of the contractile action of substance P is mediated via the cholinergic neurons and the remaining contractile action is due to its direct effect on the intestinal smooth muscle. It has been suggested that the peristalses induced by raising the intraluminal pressure of the guinea-pig ileum after atropinization is caused by endogenous substance P (22-25). The results of the present experiments is consistent with those of other authors and indicate that in the rabbit haustra substance P increases the motility of the smooth muscle of the colon partly by direct stimulation of the muscle and partly via the activation of presynaptic cholinergic neurons.

It has been known that capsaicin acts on the primary afferent nerves resulting in the depletion of endogenous substance P (26-28). In all types of preparations, the amplitude and frequency of the spontaneous phasic contraction was increased by capsaicin. Similar phenomena were observed after substance P-desensitization. However, after atropinization capsaicin induced no excitatory response in all types of preparations. These results suggest that the excitatory response to capsaicin is the result of the activation of cholinergic neurons in the myenteric plexus by the sub-

stance P released from primary afferent nerve fibers.

In the present experiment, serotonin induced contractions in all types of preparations. These contractile responses to serotonin in the haustra and taenia coli were inhibited by atropine. After administration of C_6 , the serotonin-desensitization reduced the haustral contraction induced by field stimulation in type 2 and 3 preparations but not in types 1 and 4. These results suggest that the haustral contractile response to field stimulation is mediated partly via serotonergic interneurons in the myenteric plexus which act as a nerve pathway from the taenia to the haustra, but not vice versa. Consequently, it is also suggested that the contractile response to serotonin is partly due to its direct action on the smooth muscle. In the guinea-pig small intestine and colon (12,13), serotonergic neurons in the myenteric plexus have been hypothesized to act as interneurons for regulation of circular muscle motility.

Prostaglandins induced a contractile response by directly acting on smooth muscle cells, and indomethacin reduced the contraction which was indirectly induced by coaxial electrical stimulation and prevented by pretreatment with guanethidine (29). Prostaglandins regulate the parasympathetic activity by inhibition of noradrenaline release from sympathetic nerves (29). The ileal motility under the resting condition is maintained by the basal prostaglandin synthesis (30, 31). The prostaglandin synthesis was blocked by indomethacin (32–34). In the present experiment, the contraction remaining after the combined treatment with atropinization and guanethidine was reduced or abolished by indomethacin. Therefore, the contraction remaining may be induced by prostaglandins released from myenteric neurons or activation of prostaglandin synthesis in neurons or smooth muscles. In type 2 and type 3 preparations, this contraction remaining after atropinization was abolished by tetrodotoxin, but not by other blocking agents tested and desensitization to other peptides. In type 1 and 4 preparations, electrical field stimulation caused no contractile

response after atropinization. Therefore, it is suggested that the contraction observed after atropine and guanethidine treatment resulted from the increased prostaglandin synthesis. The synthesis caused by seems to be caused by electrical field stimulation in neurons whose nerve fibers are projected to the haustra from cell bodies located in the taeniae coli. However, the present experimental results provide no direct evidence of the increased release of endogenous prostaglandins from nerve endings in the myenteric plexus. The inhibitory response after atropine was abolished by tetrodotoxin and not by other blocking agents tested. It is possible that the inhibitory response was induced via nonadrenergic noncholinergic neurons in the myenteric plexus. VIP (10, 14, 15, 20), CGRP (35, 36) or galanin (37) may be neurotransmitters of these neurons involved in these inhibitory and excitatory responses.

Enkephalin induced the relaxation which was blocked by naloxone in all types of preparations. The relaxation induced by enkephalin was due to an inhibition of neuronal acetylcholine release (21) which was confirmed in the present experiment. Moreover the contraction induced by enkephalin in the cat distal colon was caused by the inhibition of VIP release from myenteric neurons (20).

Adrenaline, phenylephrine and isoprenaline induced the relaxation of the taenia and haustra which was abolished by phentolamine and/or propranolol. The phenylephrine-induced contraction of the guinea-pig small intestine (38) and the adrenaline-and isoprenaline-induced relaxation of the rabbit (9) and dog (10) proximal colon were abolished by α - and β -adrenergic blocking agents, respectively. Adrenergic neurons inhibit presynaptic cholinergic neurons via α_2 -adrenoceptors in the cat colon (11). The relaxation induced by α - and β -agonists may be due to the direct stimulation of β -adrenoceptors on the muscle cells and the activation of presynaptic α_2 -adrenoceptors on nerve fibers, as reported by Gills (11).

It is concluded that to attain coordinated activities of longitudinal and circular muscles, the

excitation of longitudinal muscles is conducted to the circular muscles via presynaptic cholinergic, serotonergic or substance P-containing neurons and the excitation of the circular muscles is conducted to longitudinal muscles via cholinergic neurons in the myenteric plexus. The late contractile response of the haustra by field stimulation of the taeniae may be induced by endogenous prostaglandins released from myenteric neurons which innervate circular muscles. The inhibitory responses of longitudinal muscles produced by field stimulation of circular muscles or inhibitory responses of circular muscles to longitudinal muscle stimulation may be mediated via nonadrenergic noncholinergic neurons. Enkephaliner-gic and adrenergic neurons seem to act as inhibitory neurons to longitudinal and circular muscles of the proximal colon.

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