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# Modulation of peristalsis by neurotensin in isolated guinea-pig intestinal segments

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**Abstract**

Neurotensin (1–100 nM) produced an inhibitory effect and an excitatory effect on the peristaltic activity elicited by intraluminal distension using the Trendelenburg method or the intraluminal perfusion method in isolated segments of guinea-pig small intestine. The relative contribution of these effects to the overall effect varied from one region to another of the small intestine. In the Trendelenburg preparation, the excitatory effect was found to be accompanied by a decrease in the threshold intraluminal pressure required to trigger a peristaltic reflex. A substantial difference between the jejunum and the ileum was noted in that neurotensin-induced stimulation of peristaltic activity was observed in a smaller number of the segments in the jejunum than in the ileum. A nonpeptide neurotensin receptor antagonist, SR 48692, 2-[(1-(7-chloro-4-quinolinyl)-5-(2,6-dimethoxyphenyl)pyrazol-3-yl)carbonylamino]tricyclo(3.3.1.1.$^{3,7}$)decan-2-carboxylic acid (90 nM), abolished both the inhibitory and excitatory effects. Apamin (10 nM) abolished the inhibitory effect. From these results, neurotensin appears to exert both excitatory and inhibitory actions, via its receptors sensitive to SR 48692, on peristaltic activity in guinea-pig small intestine. The excitatory action varies with an increasing gradient toward the terminal end of the small intestine, and the inhibitory action involves apamin-sensitive mechanism.

*Keywords:* Neurotensin; Peristalsis; Small intestine, guinea-pig; Apamin

## 1. Introduction

Neurotensin is largely located in the neural (Schultzberg et al., 1980) and non-neural (Orci et al., 1976; Polak et al., 1977; Helmstaedter et al., 1977; Sundler et al., 1977) elements of the intestine, particularly in the small intestine (Carraway and Leeman, 1976) and exerts potent actions on the intestinal smooth muscle activity. Given these findings, many reports suggest a possible role for the peptide as a neurotransmitter (Kitabgi and Vincent, 1981; Goedert et al., 1984; Komori et al., 1986), a circulating hormone (Carraway et al., 1980; Theodorsson-Norheim and Rosell, 1983) or a modulator of intestinal motor activity (Kitabgi and Vincent, 1981). However, no plausible physiological function has been ascribed to intestinal neurotensin. In a previous paper (Ohashi et al., 1994), we found that neurotensin exerts a direct action to contract the longitudinal and circular smooth muscles of guinea-pig small intestine, in addition to its well-documented indirect action brought about by the release of acetylcholine from cholinergic nerves (Kitabgi and Freychet, 1978, 1979; Kitabgi, 1982; Huidobro-Toro and Way, 1982), and enhances the voltage-dependent inward $Ca^{2+}$ current in ileal smooth muscle cells. Thus, part of the contractile effect of the peptide is due to its direct action. Neurotensin also exerts an apamin-sensitive inhibitory action to relax longitudinal and circular smooth muscles or inhibit muscarinic receptor-mediated contraction in circular smooth muscle (Ohashi et al., 1994).

We have now investigated the effect of neurotensin on the peristaltic reflex as a first step in determining whether endogenous neurotensin participates in the regulation of the physiological functions of the intestine.

## 2. Materials and methods

Guinea-pigs of either sex, weighing 300–500 g, were stunned and bled to death. The duodenal, jejunal (between 5 and 15 cm and between 15 and 25 cm, respectively, from the gastroduodenal junction) and ileal (between 10 and 30 cm from the ileocaecal junction) regions of the small

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intestine were excised, from which intestinal segments (5–6 cm long) were cut and used for recording peristaltic activity.

For recording initiation of peristaltic activity in response to distension by a pressure rise in the lumen, two different methods were used, namely the Trendelenburg method (Trendelenburg, 1917) and a modified method of Bülbring and Lin (1958). In the former method, each segment was set up in a 50-ml organ bath filled with Tyrode solution (composition, mM: NaCl 137.0, KCl 2.7, $NaH_2PO_4$ 0.4, $NaHCO_3$ 12.0, $MgCl_2$ 2.0, $CaCl_2$ 2.0 and glucose 5.6), which was aerated and maintained at 37 ± 1°C. The ligated oral end of the intestinal segment was attached by thread to a force-displacement transducer (Nihon Kohden, SB-1T) and the isometric tension developed longitudinally was picked up by the transducer, amplified by a preamplifier (Nihon Kohden, RP-3), and recorded on a potentiometric recorder (Hitachi, 561). The anal end of the segment was connected via a Y-shaped glass tube to a reservoir to elicit changes in intraluminal pressure and to an electromanometer (Nihon Kohden, LPU-0.1) to record changes in intraluminal pressure. Desired distensions were achieved by intraluminal pressures brought about by changing the difference in water level between the organ bath and the reservoir. Outputs from the electromanometer associated with changes in the intraluminal pressure of the intestinal segment were coupled through a preamplifier (Nihon Kohden, RP-3) to a potentiometric recorder (Hitachi, 561). In the other method, each intestinal segment was set up horizontally in a 40-ml organ bath containing Tyrode solution maintained at 37 ± 1°C and perfused at a rate of 10 ml/min, using a roller pump. The oral end was connected to one terminal of a fine inflow cannula and the other terminal was connected via a fine, flexible tube to a reservoir of Tyrode solution. The inflow cannula was attached by thread to a mechano-electrotransducer in the same way as described above for recording tension changes in the longitudinal axis of the segment. The anal end was connected to an outflow cannula of a Y-shaped glass tube. One terminal of the glass tube was connected to an electromanometer (Nihon Kohden, LPU-0.1) and another was used for the outlet of intraluminal perfusate. Intraluminal perfusion was at a rate of 0.4 ml/min, using another roller pump, with Tyrode solution aerated and pre-heated to 37 ± 1°C. The perfusate was collected via the outlet tube in a beaker, the water level of which was kept constant using an aspirator. Desired distensions of the segment were obtained by changing the water level of the beaker. Outputs from the electro-mechanotransducer and electromanometer were preamplified and recorded in the same way as used for the former method.

The drugs used were bovine neurotensin (Peptide Institute, Osaka, Japan), a neurotensin receptor antagonist, SR 48692, 2-[(1-(7-chloro-4-quinolinyl)-5-(2,6-dimethoxyphenyl)pyrazol-3-yl)carbonylamino]tricyclo(3.3.1.1.$^{3,7}$)decan-2-carboxylic acid (kindly supplied by Sanofi Research), and apamin (Sigma). The stock solutions of all drugs were dissolved in distilled water, made up at 1000 or more times higher concentrations than those used for the experiments, and stored at −20°C. A certain amount of the concentrated drug solution was added to the organ bath and/or the reservoir to give the final desired concentration. The addition of a drug to the organ bath was made at a time when the reservoir solution containing the drug reached the organ bath. The drug was washed away by replacing the bathing solution with fresh solution.

Means are expressed ± S.E.M. The statistical significance was evaluated by using Student's *t*-test for paired samples and Fisher's exact probability test for unpaired samples. *P* values of 0.05 or less were considered significant.

## 3. Results

Distension by a pressure rise in the lumen of an intestinal segment elicited strong, repetitive increases in the intraluminal pressure. Each response was considered to represent a peristaltic response, since it was associated with elongation of the intestinal segment in its longitudinal direction and a strong wave of contractile activity in the circular muscle which was propagated in the anal direction with propulsion of the intraluminal solution.

### *3.1. Experiments using the Trendelenburg method*

#### *3.1.1. Relationship between the peristalsis frequency and the intensity of the distension stimulation*

The number of peristaltic waves occurring during distension stimulation for 3 min (peristalsis frequency) increased in one segment from the jejunum and ileum as the stimulus intensity was increased. However, in the duodenum, when distension stimulation was achieved with intraluminal pressures higher than 10 mm $H_2O$, a full response, which resulted from a peristaltic wave propagating from the oral end to the anal end of the intestinal segment, was not obtained, and contractile waves in the circular muscle were generated at different regions with varied intervals and some of them disappeared before they reached the anal end. Fig. 1 shows the mean peristalsis frequencies evoked by distension stimuli at four different intensities. The mean peristalsis frequency evoked at one stimulus intensity was significantly larger than that evoked at the next lower stimulus intensity. This figure also shows that the peristalsis frequency at a given distension stimulus varied, with a decreasing gradient from the duodenum to ileum. Peristaltic waves were not necessarily generated with a constant interval over the entire period of distension stimulation. They increased progressively in discharge interval (Fig. 2C) and in some segments they finally disappeared (Fig. 2A). However, the peristaltic responses of one segment from the jejunum and ileum were consistent and

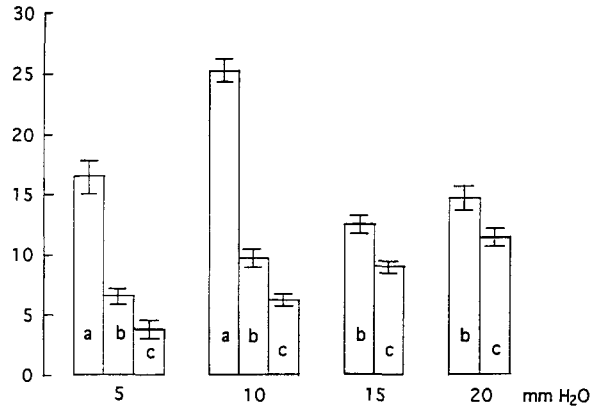


Fig. 1. Relationship between the peristalsis frequency and intraluminal pressure in intestinal segments isolated from guinea-pig small intestine. Peristalsis was induced using the Trendelenburg method. Ordinate, the peristalsis frequency expressed as the number of peristaltic waves occurring during distension stimulation for 3 min. Abscissa, the intraluminal pressure (mm $H_2O$). a, in duodenal segments; b, in jejunal segments; c, in ileal segments. Each column represents the mean ± S.E.M. (vertical line) of 7–18 measurements. The mean peristalsis frequency evoked at one stimulus intensity was significantly larger than that evoked at the next stimulus intensity on the left side, and it was also significantly different between different regions of the small intestine.

reproducible for more than 90 min, when the same distension stimulation was repeated at 4-min intervals.

### 3.1.2. *Effect of neurotensin on peristaltic responses*

The effect of neurotensin on peristaltic responses was examined in jejunal and ileal segments.

Neurotensin (1–100 nM), when applied to the bathing medium 30 s before a distension stimulus and not removed, decreased the discharge rate of peristaltic waves or blocked generation of the waves in jejunal segments. In 20 out of 24 jejunal segments, the inhibitory effect of neurotensin was transient even in the continued presence of neurotensin, and it was observed with the first stimulation after neurotensin application in 12 out of the 20 segments, and occurred in the other 8 segments with the second or later stimulations (Fig. 2A). In the remaining segments, the neurotensin effect was sustained until removal of the drug. The neurotensin effect varied in extent and duration from one segment to another from the same region of the small intestine of different animals (animal to animal variation). A segment in which discharge of peristaltic waves had been abolished by neurotensin responded to a slightly stronger distension by repetitive discharge of peristaltic waves.

Neurotensin exerted an excitatory action on the peristaltic activity in the majority of ileal segments (Fig. 2B). In general, the excitatory effect was transient so that the discharge rate of peristaltic waves was accelerated during the first minute or so of the first distension stimulation after neurotensin application. However, the peristalsis frequency measured during the entire period of distension, as with all other measurements, was not significantly changed, suggesting that the excitatory effect may be followed by an inhibitory effect. Fig. 2C shows that neurotensin lowered the threshold intraluminal pressure needed to trigger a peristaltic reflex in an ileal segment. Similar results were

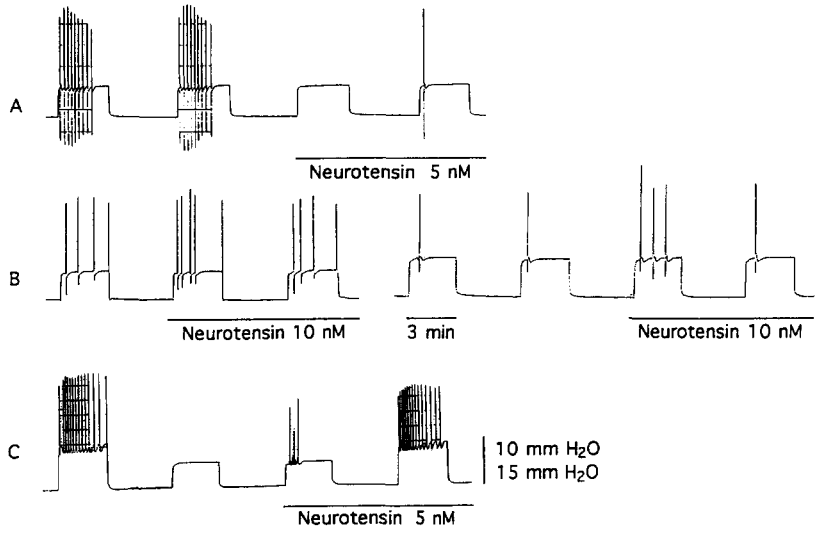


Fig. 2. The effect of neurotensin on the peristaltic responses to distension stimulation. Peristalsis was induced usin the Trendelenburg method. Distension stimulation (3 min) was given every 4 min. A, inhibition of the peristaltic response in a jejunal segment. Neurotensin (5 nM) was applied by adding it to the bathing medium 30 s prior to the third distension stimulation (7 mm $H_2O$). B, stimulation of the peristaltic response. Neurotensin (10 nM) was applied by adding it to the bathing medium 30 s prior to the second distension stimulation (7 mm $H_2O$, left trace) or the third distension stimulation (10 mm $H_2O$, right trace). C, the effect of neurotensin on the threshold intraluminal pressure to trigger peristaltic reflex. Distension stimulation was given at different pressures (10 and 15 mm $H_2O$) in the absence and presence of neurotensin (5 nM). See that the distension stimulation (10 mm $H_2O$) is strong enough to trigger peristaltic reflex in the presence of neurotensin. Time calibration in B also applies to A and B. Pressure calibrations in C are 10 mm $H_2O$ for A and B, and 15 mm $H_2O$ for C. A, B and C, records from four different ileal segments.

obtained in other five ileal segments. In approximately 30% of ileal segments, neurotensin exerted an inhibitory action alone.

### 3.2. Experiments using an intraluminal perfusion method

In the experiments using the Trendelenburg method, neurotensin was found to have an excitatory effect as well as an inhibitory effect on peristaltic activity. It is, however, very difficult to evaluate these effects precisely, because they, especially the excitatory effect, were transient and sometimes truncated by the inhibitory effect, the contribution of both effects to the overall effect is not known, and enzymatic breakdown of neurotensin should be taken into account. To overcome some of these difficulties, an intraluminal perfusion method was used in the following experiments to obtain a continuous discharge of peristaltic waves.

#### 3.2.1. Regional difference in the discharge rate of peristaltic waves

Intraluminal perfusion resulting in distension of an intestinal segment by an increase of the intraluminal pressure to 15 mm $H_2O$ induced a continuous discharge of peristaltic waves for more than 2 h. On generation of each peristaltic wave, a rapid decrease in tension in the longitudinal axis of the intestinal segment occurred as a result of its elongation in the longitudinal direction, due to contraction of the circular muscle layer along the entire length of the segment. Before generation of the next peristaltic wave, the tension in the longitudinal axis developed slowly and then rapidly to reach a critical level. The discharge rate, which was expressed as the number of peristaltic waves occurring in 4 min, varied from one intestinal segment to another, even though the segments were from the same region. The average discharge rate of $8.1 \pm 0.7$ (range 4 to 14) in 22 jejunal segments was significantly greater than that of $4.5 \pm 0.2$ (range 3 to 7) in 28 ileal segments, indicating the existence of an oral gradient in peristalsis frequency. This was true for jejunal and ileal segments isolated from one animal.

#### 3.2.2. Effect of neurotensin on the discharge rate of peristaltic waves

Neurotensin (10 and 100 nM), when applied via the bathing medium for 10 min, exerted a stimulatory action and an inhibitory action on the peristaltic activity. Both the stimulatory effect and the inhibitory effect were concentration dependently increased, but their intensities varied from one intestinal segment to another. Responses to neurotensin were grouped into three patterns, consisting of an increase followed by a decrease of the discharge rate of the peristaltic waves (Fig. 3A), an increase alone (Fig. 3B) and a decrease alone (Fig. 3C). An increase of the discharge rate was usually accompanied by an increased rate of tension development in the longitudinal axis (Fig. 3B) and a small reduction of the maximal intraluminal pressure

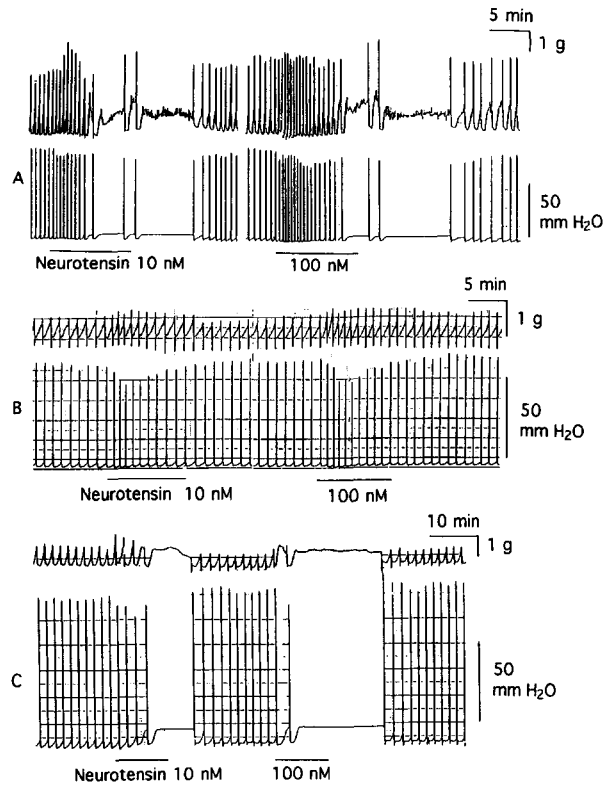


Fig. 3. Different patterns of the effect of neurotensin on the peristalsis in ileal segments in response to distension stimulation (15 mm $H_2O$) by using an intraluminal perfusion method (0.4 ml/min). The bathing medium was continuously renewed at a rate of 10 ml/min. Neurotensin (10 and 100 nM) was applied via the bathing medium for 10 min. Changes in isometric tension in the longitudinal axis (upper trace) and in intraluminal pressure (lower trace) were simultaneously recorded. A, a biphasic effect, an increase followed by a decrease in the discharge rate of peristaltic waves. B, an excitatory effect, an increase in the discharge rate of peristaltic waves. C, an inhibitory effect, a decrease in the discharge rate followed by cessation of peristaltic waves.

evoked by individual peristaltic waves (Fig. 3B and Fig. 4A). Table 1 presents the number of intestinal segments showing these patterns. A substantial difference between the jejunum and the ileum was seen in that stimulation of peristaltic activity was induced in a smaller fraction (segments showing an increase alone and an increase followed by a decrease in the discharge rate of peristaltic waves) of segments and the activity was less pronounced in the jejunum. In jejunal segments, the number of segments showing an increase in peristaltic activity at 10 and 100 nM neurotensin was 10/22 (45.5%) and 12/15 (80.0%), respectively, and this was 28/35 (80.0%) and 15/17 (88.2%) in ileal segments. However, this concentration-dependent difference was statistically significant only in the jejunum. The number of peristaltic waves discharged in 4 min was measured just before and after neurotensin application. The number was increased significantly to $128.9 \pm 3.2\%$ (mean $\pm$ S.E.M., $n = 10$) and $126.9 \pm 3.8\%$ ($n = 12$) by neurotensin at 10 and 100 nM, respectively, in jejunal segments and to $139.1 \pm 4.5\%$ ($n = 28$) and $153.6 \pm 7.1\%$ ($n = 15$) in ileal segments.

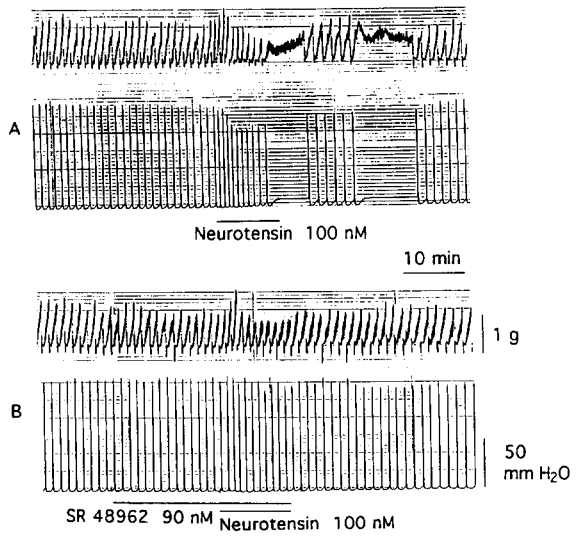


Fig. 4. The effect of SR 48692, a nonpeptide neurotensin receptor antagonist, on the biphasic effect of neurotensin (100 nM) in an isolated ileal segment. Peristalsis was induced by distension stimulation (15 mm $H_2O$) using an intraluminal perfusion method (0.4 ml/min). The bathing medium was continuously renewed at a rate of 10 ml/min. SR 48692 (90 nM) was applied 15 min before neurotensin application and continued to be present. See blockade of both the excitatory effect and the inhibitory effect. A and B, records from the same ileal segment.

### 3.2.3. *Effect of a neurotensin receptor antagonist, SR 48692, on neurotensin-induced changes of the discharge rate of peristaltic waves*

A nonpeptide neurotensin receptor antagonist, SR 48692, was added to the bathing medium to give a concentration of 90 nM, which is about 20 times higher than the $pA_2$ concentration for the neurotensin-induced intracellular $Ca^{2+}$ mobilization in a cell line from human colon carcinoma (HT-29) (Gully et al., 1993). The peristaltic activity remained almost unaltered after application of the antagonist, but neurotensin (100 nM), applied 15 min or so later, had little or no effect on the peristaltic activity in four segments from each of the jejunum and ileum (Fig. 4). The inhibitory effect of SR 48692 was apparently irreversible.

Table 1
Response patterns to neurotensin (NT), namely an increase followed by a decrease in the discharge rate of the peristaltic waves (I+D), an increase alone (I) and a decrease alone (D)

| NT (nM) | Total ($n$) | Response patterns | | | |
|---|---|---|---|---|---|
| | | (I+D) ($n$) | (I) ($n$) | (D) ($n$) | Fraction of (I)+(I+D) (%) |
| Jejunum | | | | | |
| 10 | 22 | 4 | 6 | 12 | 10/22 (46) |
| 100 | 15 | 7 | 5 | 3 | 12/15 (80) |
| Ileum | | | | | |
| 10 | 35 | 16 | 12 | 7 | 28/35 (80) |
| 100 | 17 | 7 | 8 | 2 | 15/17 (88) |

The peristalsis was induced by distension stimulation (15 mm $H_2O$) using an intraluminal perfusion method (0.4 ml/min). The bathing medium was continuously renewed at a rate of 10 ml/min. NT was applied via the bathing medium for 10 min. $n$, the number of intestinal segments.

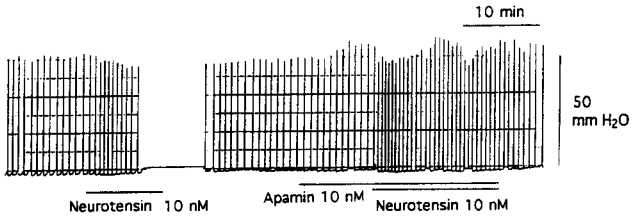


Fig. 5. The effect of apamin on the biphasic response to neurotensin (10 nM) in an isolated ileal segment. Peristalsis was induced by distension stimulation (15 mm $H_2O$) using an intraluminal perfusion method (0.4 ml/min). The bathing medium was continuously renewed at a rate of 10 ml/min. Apamin (10 nM) was applied 10 min before neurotensin application and continued to be present. See blockade of the inhibitory effect of neurotensin with apamin.

### 3.2.4. *Effect of apamin on neurotensin-induced inhibition of the discharge rate of peristaltic waves*

Apamin, a blocker of $Ca^{2+}$-activated $K^+$ channels with a small conductance, has been shown to block a fast nonadrenergic, noncholinergic inhibitory junction potential elicited by electrical stimulation of intramural nerves (Niel et al., 1983; Bywater and Taylor, 1986). In our previous paper (Ohashi et al., 1994), neurotensin-induced relaxation in the longitudinal and circular muscles of guinea-pig ileum was abolished by apamin. When apamin was added to the bathing medium to give a concentration of 10 nM, which was strong enough to block the responses mentioned above, it had little or no appreciable effect on peristalsis. Fig. 5 shows the effects of neurotensin in the absence and presence of apamin. Application of neurotensin (100 nM) after apamin produced an acceleration of the discharge rate of peristaltic waves without producing an inhibitory effect. The selective inhibition by apamin of the inhibitory effect of neurotensin was observed in all six segments from the jejunum or ileum tested. The effect of apamin was reversible as it decreased with time after apamin removal, but the response to neurotensin was not completely restored at 60 min (the longest time observed).

## 4. Discussion

The neurotensin-induced inhibition of peristaltic responses is characterized by its predominance in the jejunum compared to the ileum, its selective abolition by apamin, and its being overcome readily by distension with a slightly stronger intensity. Neurotensin causes the release of γ-aminobutyric acid (GABA), substance P and acetylcholine from neural elements in the guinea-pig intestine (Kitabgi and Freychet, 1979; Monier and Kitabgi, 1980; Huidobro-Toro and Way, 1982; Nakamoto et al., 1987). It is, therefore, possible that neurotensin acts by releasing a substance from neural elements, the action of which is to

suppress peristaltic activity, and this effect is blocked by apamin. Recently, apamin has been reported to abolish the fast nonadrenergic noncholinergic inhibitory junction potential probably mediated by ATP (Bywater and Taylor, 1986; Crist et al., 1992) but not the slow nonadrenergic noncholinergic inhibitory junction potential in which vasoactive intestinal peptide (VIP) and nitric oxide (NO) or a related substance are suggested to be involved (He and Goyal, 1993). Apamin abolished the relaxation of guinea-pig ileum longitudinal muscle caused by ATP but not that caused by noradrenaline and nitroprusside, which forms NO (Ohashi et al., 1994). Thus the apamin-sensitive inhibition of intestinal peristalsis could be mediated by endogenous ATP but not by either noradrenaline, VIP or NO. However, neurotensin has been suggested to be incapable of releasing ATP from neural elements in longitudinal muscle strips from the guinea-pig ileum as the neurotensin-induced relaxation is unaffected after desensitization of ATP receptors (Ohashi et al., 1994).

Neurotensin directly acts to produce relaxation of the circular muscle of the guinea-pig ileum as a result of membrane hyperpolarization (Yamanaka et al., 1987) and prevents carbachol from producing contraction (Ohashi et al., 1994). The mechanical and membrane responses to neurotensin were all abolished by apamin. The musculature of the intestine constitutes one of the elements involved in peristalsis, and the contractile activity of the circular muscle causes a rise in the intraluminal pressure, to propel the intestinal content. Cholinergic neurons are considered to serve as a terminal neuron in the peristaltic reflex which supplies the musculature, since atropine strongly impairs peristalsis (Kosterlitz and Lees, 1964). Thus, the apamin-sensitive responses to neurotensin observed previously in the musculature probably play a role in the inhibitory effect of neurotensin on peristalsis. Furthermore, $Ca^{2+}$-activated $K^+$ channels of small conductance would be involved in mediating the inhibitory effect of neurotensin (Blatz and Magleby, 1986; Capiod and Ogden, 1989), although no evidence has been provided for the existence of this type of $K^+$ channel in intestinal smooth muscle cells. ATP produces relaxation and hyperpolarization of intestinal smooth muscles probably through activation of a type of $K^+$ channels and apamin can block the response to ATP. The type of $K^+$ channel blocked by apamin and its relevance to the neurotensin-induced inhibition of peristaltic activity needs clarifying.

The excitatory effect of neurotensin on the peristaltic activity that increases the discharge rate of peristaltic waves in response to intraluminal distension was observed more frequently in the lower region of the small intestine, suggesting the existence of an aboral gradient for this action of neurotensin. The fraction of intestinal segments exhibiting an excitatory response to neurotensin increased significantly in the jejunum but not in the ileum when the neurotensin concentration was increased from 10 nM to 100 nM. This result can be explained by assuming that the excitatory effect is normally counteracted by the inhibitory effect and that it is unmasked in some jejunal segments only at 100 nM neurotensin because at this concentration the excitatory effect is increased to such a level that it can overcome transiently the inhibitory effect. This explanation is supported by the finding that the inhibitory effect was readily overcome by a slight increase in distension stimulation and that its abolition by apamin potentiated the excitatory effect. In addition, there is no reason to assume that the balance between the opposite effects is identical in all regions of the small intestine and is independent of the concentration of neurotensin.

It is possible that the observed difference in the effects of neurotensin resulted from a difference in its enzymatic breakdown, especially with the Trendelenburg method in which the bathing medium was not renewed. The membrane depolarization produced by neurotensin has been shown to be sustained, until washout, in the longitudinal muscle of the avian rectum, when the muscle preparation is perfused continuously with the solution containing the peptide (Komori et al., 1992). This may well be true in the present experiments with the intraluminal perfusion preparations, although the activity and distribution of enzyme(s) which can cleave neurotensin in segment preparations would be different from those measured under the conditions used in electrophysiological experiments.

Our previous experiments with longitudinal muscle strips (Ohashi et al., 1994) have shown that the direct action of neurotensin in mediating the slow contraction is seen in the presence of atropine and observed with an aboral gradient along the intestine. The contraction is probably due to an increase in the discharge rate of action potentials without there being a change in membrane potential (Yamanaka et al., 1987). Every peristaltic wave evoked by reflex, by intraluminal distension, was preceded by a slow rise in tension in the longitudinal axis of the intestine. These observations raise the possibility that neurotensin may act directly on the longitudinal muscle layer to accelerate the rate of rise in tension in the longitudinal axis of the intestine, resulting in an increase in the discharge rate of peristaltic waves. An indirect action of neurotensin would also lead to stimulation of peristaltic activity. Neurotensin has been demonstrated to cause the release of substance P and acetylcholine in the guinea-pig intestine (Kitabgi and Freychet, 1979; Monier and Kitabgi, 1980; Huidobro-Toro and Way, 1982; Nakamoto et al., 1987), which both act as stimulants on the longitudinal muscle layer. With the Trendelenburg method, neurotensin reduced the minimum distension that can cause the discharge of peristaltic waves, suggesting that neurotensin may render stretch receptors for peristalsis more sensitive to distension stimulation, i.e., a smaller distension is required for activation of the stretch receptors in the presence of neurotensin. This is supposed to play a positive role in peristaltic activity.

Whether neurotensin acts directly or indirectly, the in-

hibitory and excitatory effects on peristaltic activity were abolished by SR 48962, a nonpeptide antagonist for the neurotensin receptor. A question arises whether or not these effects are mediated via separate subtypes of neurotensin receptor, since the existence of subtypes of neurotensin receptor has been suggested in many smooth muscle types (Huidobro-Toro and Yoshimura, 1983; Huidobro-Toro and Zhu, 1984; Mule et al., 1992). If separate subtypes of neurotensin receptor are responsible for the excitatory and inhibitory effects on peristaltic activity in guinea-pig small intestine, SR 48962 should be a nonselective antagonist, and the difference in neurotensin responses along the entire length of the small intestine could be attributable to an unidentical distribution of the two types of neurotensin receptor.

Intestinal neurotensin, if released from its storage sites by a physiological or pathophysiological stimulation, may be implicated via activation of SR 48962-sensitive receptors in the regulation of peristalsis in the small intestine. Its predominant effect is inhibitory in the upper small intestine in which higher peristaltic activity is inherent, but excitatory in the lower small intestine in which lower peristaltic activity is inherent. This relationship between the effect of neurotensin and peristaltic activity might be true in the large intestine, since in previous studies, an increase in colonic activity was observed after intravenous infusion of neurotensin in humans (Calam et al., 1983), cats (Hellstrom and Rosell, 1981) and dogs (Bueno et al., 1985).

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