Tachykinin-Induced Contractions in the Circular Muscle of Guinea Pig Ileum†

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ABSTRACT—Actions of substance P (SP, 10^{-9} to 10^{-6} M), neurokinin A (NKA, 10^{-9} to 10^{-6} M) and neurokinin B (NKB, 10^{-10} to 10^{-6} M) in the circular muscle of guinea pig ileum were investigated in segment and strip preparations, in which methacholine produced similar contractions. In the segment preparations, three tachykinins produced repeatedly occurring twitch-like contractions. Their efficacies were similar with the same maximal contractions, but their potencies were different (NKB > NKA = SP). Latency (38 sec) was observed before the initiation of contractions in response to NKA, but not to SP or NKB. Atropine (10^{-6} M) and tetrodotoxin (3×10^{-7} M) did not affect NKA-induced contractions, but inhibited SP- and NKB-induced contractions; the dose-response curves for SP and NKB were rightwardly shifted by atropine. The treatment with atropine brought out latency in the responses for NKB. In the strip preparations, SP did not substantially induce contractions, but NKA and NKB produced twitch-like contractions after latent periods of 28 and 36 sec, respectively. The efficacy of NKA was similar to that in segment preparations, while that of NKB was much lower in strip preparations. Unlike in segment preparations, atropine did not inhibit contractions induced by the two tachykinins in strip preparations. These results suggest that tachykinins induce contractions through myogenic and neurogenic mechanisms, the latter of which may be inoperative in strip preparations.

Keywords: Substance P, Neurokinin A, Neurokinin B, Circular muscle, Ileum (guinea pig)

Substance P (SP), neurokinin A (NKA) and neurokinin B (NKB) are structurally related peptides that are members of a family of biologically active peptides known as tachykinins. A number of studies have indicated that SP and NKA are contained in the gastrointestinal tract, playing the role of excitatory neurotransmitters in the myenteric plexus of many gastrointestinal tissues (1-3, reviews). It has been demonstrated that exogenously applied SP and NKA produced powerful contractions in the longitudinal muscle of guinea pig ileum (4-7).

Tachykinins have also been thought to be responsible for contractions in the circular muscle of guinea pig small intestine (8-10). In spite of being important for understanding the genesis of propulsive activity and peristalsis, analysis of receptors responsible for tachykinin actions in the circular muscle has not been performed until recently. By using strip preparations of guinea pig ileal circular muscle, Maggi et al. (11) and Bartho et al. (12) have investigated the actions of tachykinin agonists and antagonists. Their results indicate that three subtypes of tachykinin receptors, NK_1, NK_2 and NK_3, are present in the circular muscle of guinea pig ileum, and they mediate tachykinin-induced contractions in different manners: Activation of NK_1-receptors produces partly neurogenic and largely myogenic contractions; NK_2-receptors mediate totally myogenic contractions; and NK_3-receptors mediate totally neurogenic contractions.

We found, as is to be shown in the present study, that SP had much more capability to induce contractions in the circular muscle of guinea pig ileum in segment preparations than in strip preparations. In the two types of preparations, however, no significant difference was observed in methacholine-induced contractions. In the present study, we investigated the actions of tachykinins in the circular muscle of guinea pig ileum to compare the two types of preparations, with the aim of clarifying the mechanisms of tachykinin-induced contractions.

† Part of the present study has been reported at the 66th Annual Meeting of The Japanese Pharmacological Society (1993).

MATERIALS AND METHODS

General procedures

After male guinea pigs (300 to 500 g) were killed by a blow on the head, the ileum was removed. The terminal portion of approximately 10 cm from the ileocolonic junction was discarded, and the remaining portion (approximately 30 cm in length) was immersed in a cold Krebs solution pre-oxygenated with a mixture of 95% O_2 and 5% CO_2. The composition of the Krebs solution used was as follows: 140 mM NaCl, 6 mM KCl, 2 mM $CaCl_2$, 1 mM $MgCl_2$, 1 mM NaH_2PO_4, 20 mM $NaHCO_3$, 5 mM HEPES and 11 mM glucose.

Measurement of contractions in segment preparations

The methods to record contractions of the circular muscle in segment preparations were described before (13, 14). An aluminum tube holder, which had a small rectangular window opened in the middle region, was put into the lumen of the ileal segment (2 to 3 cm), and the segment was fixed with thread covering the window to the holder. The holder with the segment was horizontally set in an organ bath containing Krebs solution (25 ml). The lumen of the segment was continuously infused from the oral side with Krebs solution through a silicon tube connected to the oral end of the aluminum tube. The Krebs solution bathing the segment and that used for infusing the lumen of the segment were maintained at 35℃ and continuously bubbled with a gas mixture of 95% O_2 and 5% CO_2. A small hook tied to a thread was fastened onto the ileal surface over the window of the holder, and the other end of the thread was connected to a strain gauge (UL-10GR; Shinkoh, Nagano). A resting tension of 0.2 g was applied, and contractions were isometrically measured. For electrical transmural stimulations, one of a pair of platinum wire electrodes that were connected to an electric stimulator (SEN 3301; Nihon Kohden, Tokyo) was placed inside the lumen, and the other was placed outside the segment. After equilibration for at least 60 min, transmural stimulations by 100 electrical pulses (0.05-msec duration, 50 V, 10 Hz) were applied to the segment preparation. These stimulations induced an "on" contraction and an "off" contraction (14), and the amplitude of the "on" contraction was used to quantitate agonist-induced contractions.

Measurement of contractions in strip preparations

In some experiments, contractions of circular muscle were investigated in strip preparations to compare its responses with those in the segment preparation. Strip preparations were made as follows: A 3- to 4-cm ileal segment was opened along the mesentery and was held flat with many fine pins on a silgard-bedded petri dish with the mucosa down. A strip (8-mm-long and 2-mm-wide) was dissected along the axis of the circular muscle. The strip preparation was horizontally set in a silgard-bedded, 5-ml organ bath. One end of the preparation was fixed on the bottom with a pin, and the other end was connected to a strain gauge (the same model as described above) via a thread to record contractions isometrically. Strip preparations were loaded with a resting tension of 0.2 g and were allowed to equilibrate for 60 min at 35℃, during which the villi of the mucosa were shed off with repeated changes of the bathing solution. For electrical transmural stimulations, two platinum wire electrodes connected to the electric stimulator were placed on the sides of the preparation. After equilibration, transmural stimulations with 100 electrical pulses (0.2-msec duration, 50 V, 10 Hz) were applied to the strip preparation. These stimulations, like in the segment preparation, produced "on" and "off" contractions that were abolished by 3×10^{-7} M tetrodotoxin (N. Suzuki et al., unpublished results). The amplitude of the "on" contraction induced was used to quantitate the amplitudes of agonist-induced contractions.

Drugs

The drugs used in the present study were as follows: methacholine chloride, tetrodotoxin, SP, NKA, NKB (all from Sigma Chemical Co., St. Louis, MO, USA); atropine sulfate (Wako Pure Chemicals, Osaka); CP-96,345 (Pfizer Inc., Groton, CT, USA); and FK224 (Fujisawa Pharmaceutical Co., Osaka). Applications of all drugs were addressed to the Krebs solution bathing ileal segments and strips in the organ baths. Tachykinins were applied at intervals of 15 to 20 min, and this maneuver did not provoke tachyphylaxis with any tachykinin. Applications of receptor antagonists were carried out 15 min prior to applications of agonist drugs.

Statistical analyses

Results are shown as values of the mean ± S.E.M. for quantitative analysis in the present study. Statistical analysis was carried out with Student's paired or non-paired *t*-test. A difference was considered to be significant when P was less than 0.05.

RESULTS

Contractions induced by methacholine in two types of preparations

Contractions were induced by more than 10^{-7} M methacholine in the circular muscle of guinea pig ileum in both segment and strip preparations. As shown in the insets of Fig. 1, contractions were elicited immediately at their application of methacholine, reached their peak

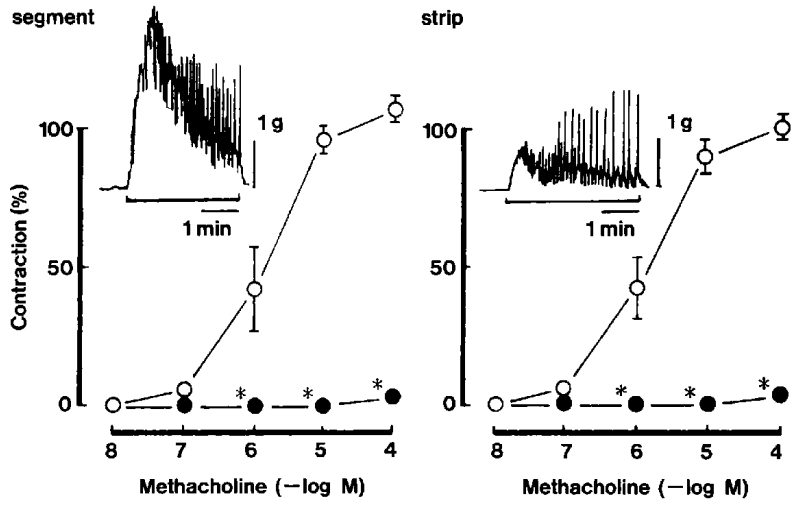

Fig. 1. Dose-response curves for methacholine in the circular muscle of guinea pig ileum in segment and strip preparations in the absence (○) and presence of 10^{-6} M atropine (●). Insets are the actual traces of 10^{-5} M methacholine-induced contractions. Ordinate: the amplitude of contractions presented as a percent of electrical transmural stimulation (100 pulses)-induced contractions, abscissa: −log M concentration of methacholine. The number of preparations tested is 6 and 5 for segment and strip preparations, respectively. Vertical bars represent standard errors. *Significantly different from responses in the absence of atropine ($P<0.05$).

and then decayed with repeatedly occurring twitch-like contractions. The dose-response curves shown in Fig. 1 were constructed by using the peak amplitudes during the initial rising phase. The maximal responses to methacholine were as large as those induced by transmural stimulations in the two types of preparations. Sensitivity to methacholine was similar in the two types of preparations; pD_2 was 5.9 ± 0.24 (mean±S.E.M., n=6) for the segment preparations and 5.8 ± 0.31 for the strip preparations (n=5). Methacholine-induced contractions were almost abolished by 10^{-6} M atropine in both types of preparations (Fig. 1).

Contractions induced by tachykinins in two types of preparations

Contractions in the circular muscle in response to SP, NKA and NKB showed both similarities and dissimilarities between the segment and strip preparations and also

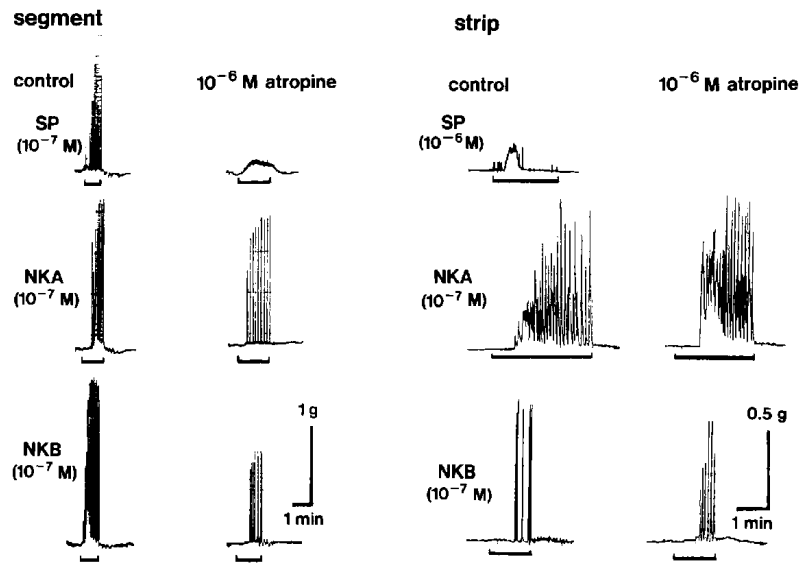

Fig. 2. Traces illustrating the contractions induced by tachykinins in the circular muscle of guinea pig ileum in segment and strip preparations in the absence (control) and presence of 10^{-6} M atropine. The concentration of tachykinins was 10^{-7} M, except for SP tested in strip preparations (10^{-6} M). SP, substance P; NKA, neurokinin A; NKB, neurokinin B.

among the tachykinins. Typical traces for the contractions induced by the three tachykinins at 10^{-7} M (10^{-6} M SP in the strip preparation) are illustrated in Fig. 2.

In the segment preparations, contractions induced by the three tachykinins were composed of repeatedly occurring twitch-like contractions superimposed on small tonic contractions. However, the onset of contractions was clearly different between NKA and the other two tachykinins. SP and NKB produced twitch-like contractions shortly and immediately after the applications, respectively; in response to SP, small phasic contractions were induced prior to repetitive twitch-like contractions. In contrast to the rapid onset of actions for these two tachykinins, there was a considerable latent period (about a half minute) before contractions were initiated after the application of NKA (Fig. 2). The latent periods for the three tachykinins are summarized in Table 1.

In the strip preparations, SP did not produce detectable contractions at 10^{-7} M and induced small phasic contractions at 10^{-6} M (Fig. 2). NKA and NKB at 10^{-7} M, like in segment preparations, induced twitch-like contractions in strip preparations. There was latency observed for both tachykinins in strip preparations before contractions were induced (Fig. 2). The latent periods for the two tachykinins in the strip preparation were similar to that for NKA in the segment preparation (Table 1).

Figure 3 shows the dose-response curves for the three tachykinins in the segment and strip preparations. They were constructed by using the peak amplitudes of the twitch-like contractions induced by each concentration of tachykinins, with amplitudes being presented as a percent of that induced by the electrical tranmural stimulations (see Materials and Methods). In the segment preparation, amplitudes of the maximal responses induced by the three tachykinins were similar, all being as large as those of the contractions induced by electrical stimulations. However,

Table 1. Latent periods for substance P-, neurokinin A- and neurokinin B-induced contractions in the absence and presence of atropine in the circular muscle of guinea pig ileum in segment and strip preparations

	Segment (sec)	Strip (sec)
Substance P		
control	1.20±1.20	ND
atropine	0.00±0.00	ND
Neurokinin A		
control	38.40±8.82	28.80±1.20
atropine	34.80±5.50	26.40±3.06
Neurokinin B		
control	0.00±0.00	36.00±6.63
atropine	45.60±7.25	25.50±4.50

Values are the mean±S.E.M. of 6 segment and strip preparations. Concentrations of tachykinins are 10^{-7} M and that of atropine is 10^{-6} M. ND, not determined.

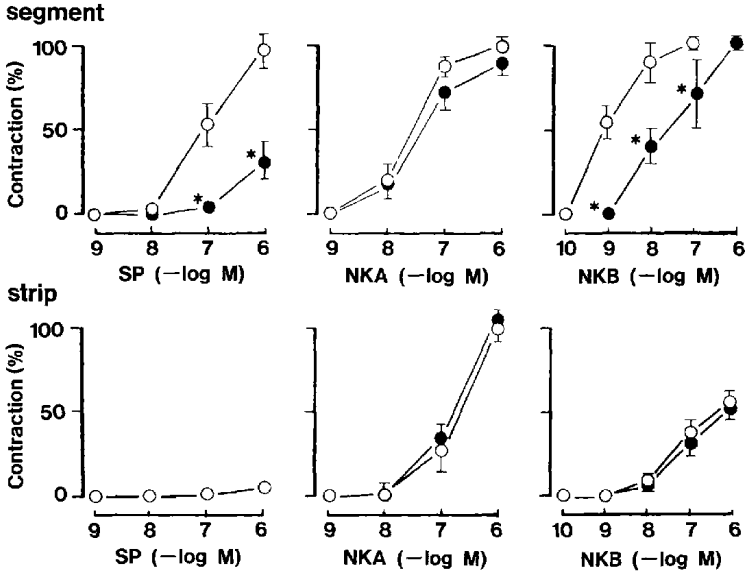

Fig. 3. Dose-response curves for tachykinins in the circular muscle of guinea pig ileum in segment and strip preparations in the absence (○) and presence of 10^{-6} M atropine (●). Ordinate: the amplitude of contractions presented as a percent of electrical transmural stimulation (100 pulses)-induced contractions, abscissa: −log M concentration of tachykinins. SP, substance P; NKA, neurokinin A; NKB, neurokinin B. The number of preparations tested is 6 for both the segment and strip preparations. Vertical bars represent standard errors. *Significantly different from responses in the absence of atropine ($P<0.05$).

potencies of the three tachykinins were different; the rank order as determined by pD_2 was: NKB (8.8 ± 0.28) > NKA (7.4 ± 0.24) = SP (7.0 ± 0.22, $n = 6$ for all tachykinins). In the strip preparation, SP at less than 10^{-7} M did not produce contractions; small contractions were produced at 10^{-6} M, whereas NKA and NKB dose-dependently (10^{-8} to 10^{-6} M) induced contractions (Fig. 3). Effects of the higher doses were not examined for any tachykinin because of the cost for using large amounts of tachykinins. Hence, maximal contractions may not be attained in the experiments with the strip preparation. Even if this is taken into account, the amplitudes of the maximal contractions induced by NKB looked at most about half of those by NKA in the strip preparation (Fig. 3). Unlike in the segment preparation, potencies of NKA and NKB were similar in the strip preparation. It is obvious from the dose-response curves that the potency of NKB was much lower in the strip preparation than in the segment preparation.

Effects of atropine on tachykinin-induced contractions

Tachykinin-induced contractions were differently affected by 10^{-6} M atropine in the two types of preparations. In the segment preparation, 10^{-7} M SP- and NKB-induced contractions were almost completely and by half inhibited by atropine, respectively, but NKA-induced contractions were not significantly affected by atropine (Fig. 2). In the presence of atropine, latency was observed for the NKB-induced contractions as well as for NKA (Fig. 2), the length of which was similar to that for NKA in the absence of atropine (Table 1).

As shown in Fig. 3, the dose-response curve for SP was shifted to the right by 10^{-6} M atropine in the segment preparation. Whether or not the maximal response for SP was affected by atropine could not be examined because of the reason mentioned before. The dose-response curve for NKA was not affected by atropine, whereas that for NKB was shifted to the right by atropine with no changes in the maximal response.

In the strip preparation, atropine did not significantly affect contractions induced by either NKA or NKB as illustrated in the contraction traces and the dose-response curves (Figs. 2 and 3). The latent periods for NKA and NKB were unaffected by atropine (Table 1). The effects of atropine on SP-induced contractions were not examined in the strip preparation since SP did not substantially induce contractions except for a high dose of 10^{-6} M.

Effects of tetrodotoxin on tachykinin-induced contractions in the segment preparation

The foregoing results that atropine inhibited contractions induced by SP and NKB in the segment preparation indicate that neural mechanisms are responsible for the contractions in response to tachykinins. This was assessed by using tetrodotoxin in the segment preparation. Tetrodotoxin at 3×10^{-7} M almost abolished 10^{-7} M SP-induced contractions to 4% of the control and inhibited 10^{-7} M NKB-induced contractions to 56% of the control (Fig. 4). NKA (10^{-7} M)-induced contractions were not affected by tetrodotoxin. Tetrodotoxin at 3×10^{-7} M completely inhibited the contractions induced by electrical transmural stimulations, whereas it did not affect 10^{-5} M methacholine-induced contractions (Fig. 4).

Effects of CP-96,345 and FK224 on tachykinin-induced contractions in the presence of atropine

In the presence of atropine, three tachykinins still induced contractions in the segment preparation (Figs. 2 and 3). The following experiments were performed to investigate which subtype of tachykinin receptors was responsible for the atropine-resistant contractions. In these experiments, 10^{-7} M CP-96,345 and 10^{-5} M FK224 were used as an antagonist for NK_1-receptors (15) and as a dual antagonist for NK_1- and NK_2-receptors (16, 17), respectively. The effectiveness of these antagonists in blocking tachykinin receptors at the concentrations used was discussed previously (14).

Figure 5 shows that 10^{-7} M CP-96,345 slightly inhibited the SP-induced contractions in the presence of 10^{-6} M atropine, while it did not affect the contractions induced by the other two tachykinins. FK224 at 10^{-5} M almost completely inhibited the atropine-resistant contractions for the three tachykinins.

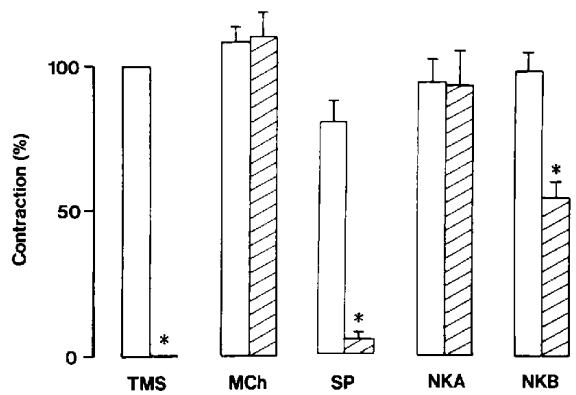

Fig. 4. Effects of 3×10^{-7} M tetrodotoxin (TTX) on contractions induced by electrical transmural stimulations (TMS, 100 pulses), 10^{-5} M methacholine (MCh), 10^{-7} M substance P (SP), 10^{-7} M neurokinin A (NKA) and 10^{-7} M neurokinin B (NKB) in the circular muscle of guinea pig ileum in segment preparations. The amplitude of contractions is presented as a percent of electrical transmural stimulation (100 pulses)-induced contractions. The number of preparations tested is 6 for each treatment. Vertical bars represent standard errors. *Significantly different from the control ($P < 0.05$). □ Control, ▨ 3×10^{-7} M TTX.

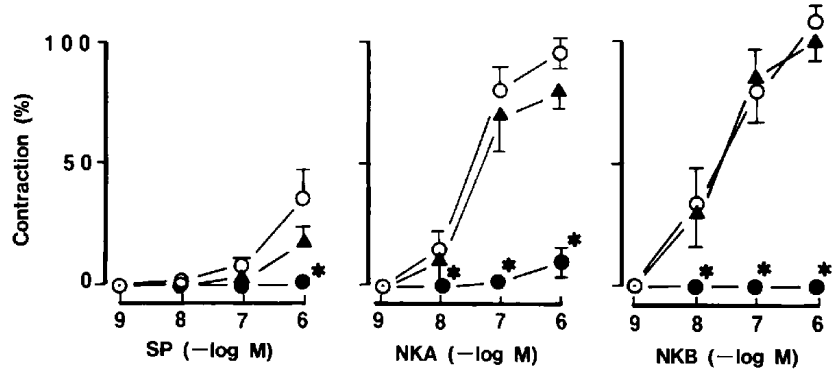

Fig. 5. Effects of 10^{-7} M CP-96,345 and 10^{-5} M FK224 on the dose-response curves for tachykinins in the presence of 10^{-6} M atropine in the circular muscle of guinea pig ileum in segment preparations. ○, Control contractions in the presence of 10^{-6} M atropine; ▲, 10^{-7} M CP-96,345 in the presence of 10^{-6} M atropine; ●, 10^{-5} M FK224 in the presence of 10^{-6} M atropine. Ordinate: the amplitude of contractions presented as a percent of electrical transmural stimulation (100 pulses)-induced contractions, abscissa: −log M concentration of tachykinins. SP, substance P; NKA, neurokinin A; NKB, neurokinin B. The number of preparations tested is 6 for each treatment. Vertical bars represent standard errors. *Significantly different from the control ($P<0.05$).

DISCUSSION

The present results have shown that contractions in response to tachykinins are not necessarily the same in the circular muscle of guinea pig ileum in the segment and strip preparations. While SP and NKB produced large contractions with high potencies in the segment preparation, these tachykinins produced much smaller contractions in the strip preparation. It is unlikely that weak actions of the two tachykinins in the strip preparation are due to damages in the circular smooth muscle cells, since the strip preparation could contract in response to methacholine and NKA in the same manner as the segment preparation.

SP is thought to be the physiological transmitter for NK_1-receptors in many tissues including the longitudinal muscle of guinea pig ileum (1–3), but it can also activate NK_2- and NK_3-receptors with lower potencies than NK_1-receptors (18). The results that SP-induced contractions were inhibited by atropine and tetrodotoxin to a large and nearly complete extent, respectively, in the segment preparation indicate that these contractions are for the most part neurogenic. There is ample evidence that activation of NK_3-receptors causes a release of acetylcholine and also possibly tachykinins from the myenteric plexus neurons in guinea pig ileum (5, 19, 20). SP may indirectly produce contractions in the circular muscle through the activation of NK_3-receptors, thereby releasing endogenous acetylcholine and tachykinins in the segment preparation. It seems likely that the released tachykinins activate NK_2-receptors, contributing to the neurogenic component of SP-induced contractions, since the atropine-resistant contractions were abolished by FK224, while they were only slightly reduced by CP-96,345. This result also indicates that NK_1-receptors play a minor role in SP-induced contractions in the segment preparation.

Weak actions of SP in the strip preparation may be due to impairments of the neural functions carried out in the myenteric plexus, which seems not to be well-preserved in the strip preparation. It is likely that in the strip preparations, neural connections are much more liable to being disrupted in the synapses and axons due to their small size and the preparation method, resulting in some loss of neural functions in the strip preparations. Accordingly, if actions of SP and other tachykinins depend on the maintenance of proper neural functions, the responses induced by tachykinins would be much reduced or lost in the strip preparation. A similar low SP efficacy to induce contractions or to affect membrane potentials in the circular muscle of guinea pig ileum has been reported in strip preparations by Fujisawa and Ito (21) and Bauer and Kuriyama (22).

Some investigators, however, reported eminent actions of SP to induce contractions in strip preparations (9, 11). In fact, Maggi et al. (11) have reported that the potency of SP to induce contractions was as high as that of NKA in their strip preparations. The reasons for such a large variability in the actions of SP in strip preparations are not clear. It seems possible that contractions of circular muscle are easily affected by artificial factors, such as loaded tensions or procedures employed to make the strip preparations.

In the segment and strip preparations, large contractions were induced by NKA; the amplitudes of the maximal contractions were as large as those induced by electrical transmural stimulations in both types of preparations. In the two types of preparations, the contractions were not affected by either atropine or tetrodotoxin. In the seg-

ment preparation, NKA-induced contractions were not inhibited by 10^{-7} M CP-96,345, but were abolished by 10^{-5} M FK224 in the presence of atropine. These results indicate that NKA-induced contractions are mostly myogenic and are mediated largely by activation of NK_2-receptors located in the circular smooth muscle cells.

NKB has been demonstrated to activate NK_3-receptors in preference to NK_1- and NK_2-receptors (5, 18, 23). In the segment preparation, the contractions induced by NKB were partly inhibited by atropine and tetrodotoxin. Atropine rightwardly shifted the dose-response curve for NKB without changing the maximal contractions in the segment preparation. In the strip preparations, on the other hand, the dose-response curve for NKB was not affected by atropine. While NKB was much more potent than SP and NKA in the segment preparation, the potency of NKB in the strip preparation was similar to that of NKA, being much lower than that in the segment preparation. These results indicate that in the segment preparation, NKB-induced contractions are composed of a neurogenic component, mediated possibly by NK_3-receptors, and a myogenic component. The myogenic component may be due to activation of NK_2-receptors, since FK224, but not CP-96,345, abolished the contractions in the presence of atropine. In the strip preparations, by contrast, NKB-induced contractions are composed of only a myogenic component, mediated largely by NK_2-receptors. The difference in the actions of NKB in the two types of preparations may plausibly derive from different preservation of neural functions, like the case of SP as described above.

In the segment preparation, NK_2-receptors may also be partly responsible for the NKB-induced neurogenic contractions through the action of endogenous tachykinins released. Relative magnitudes of the maximal contractions for NKB, as quantified by electrical transmural stimulation-induced contractions, were much larger in the segment preparation than in the strip preparation, and they were not reduced by atropine in the segment preparation. It seems that in the segment preparation, NKB releases endogenous tachykinins from the myenteric neurons as a result of the activation of NK_3-receptors and that the tachykinins released, activating NK_2-receptors, may contribute to producing larger maximal contractions.

It was noticed in the present results that there was a latency of around 30 sec, before contractions were induced by NKA in the segment and strip preparations. A similar latent period was observed for NKB-induced contractions in the strip preparation. In the segment preparation, the treatment with atropine brought out the latency for NKB. As discussed above, these contractions with latency may be myogenic and are thought to be mediated by NK_2-receptors. The latent periods do not seem to reflect the time it takes for the applied tachykinins to diffuse into the inner circular smooth muscle cell layers, since methacholine did induce contractions immediately after the application in the circular muscle. Slow occurrence of contractions in response to NKA has also been reported in rat duodenum (24) and rat urinary bladder (25). Harada et al. (26) have reported longer latency in the electrophysiological responses in *Xenopus* oocytes mediated by NK_2-receptors than by NK_1-receptors, which were expressed with injections of appropriate exogenous mRNAs. These facts indicate that the latency is not a specific characteristic in the circular muscle of guinea pig ileum, but rather a common quality in NK_2-mediated responses in many tissues. There is ample evidence that the three subtypes of tachykinin receptors, NK_1, NK_2 and NK_3, are G protein coupled, activation of which all leads to inositol phospholipid hydrolysis (see 3, 18 for reviews). The long latency for the NK_2-mediated responses may imply that the intramembrane and intracellular events thought to take place following the binding of agonists with NK_2-receptors, such as coupling to G proteins and activation of relevant enzymes, are controlled in a different manner from those for NK_1- and NK_3-receptors.

A possible physiological role of the latency in guinea pig ileum is that contractions in the two muscle layers (longitudinal and circular) take place in a temporally coordinated manner so that they may not interrupt the contractions of one another in response to the tachykinins released from the myenteric neurons. Histochemical, biochemical and molecular studies have provided evidence that SP and NKA are contained in the same neurons, conceivably including motoneurons, in the myenteric plexus of the small intestine (27–30). It would be then supposed that, when these motoneurons are excited, contractions occur immediately in longitudinal muscle as a result of the activation of NK_1-receptors by the released SP and NKA, while in circular muscle, contractions take place after some delay, because of the slow onset of reactions after the activation of NK_2-receptors by the released NKA, thereby enabling the occurrence of temporally organized contractions in the two muscle layers.

In summary, the present results have shown that actions of tachykinins in the guinea pig ileal circular muscle are not necessarily the same in segment and strip preparations; in the latter preparations, some of the neural functions may be lost, leading to failure in neurally mediated actions of tachykinins. In the segment preparations, tachykinin actions are in general accounted for by the previously suggested role for the three subtypes of tachykinin receptors in the guinea pig ileum (11). NK_2- and NK_3-receptors are largely involved in the myogenic and neurogenic actions of tachykinins, respectively, while the role of NK_1-receptors is low.

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