Pharmacological Characterization of Adrenoceptors Mediating Contractile and Relaxant Responses to Noradrenaline in the Longitudinal Muscle of Guinea-Pig Ileum

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ABSTRACT. Mechanical responses to noradrenaline (NA) were recorded in longitudinal muscle strips from the terminal and intermediate regions (3–10 cm and 30–40 cm from the ileo-caecal junction, respectively) of the guinea-pig ileum. NA (0.16–1.600 μM) produced a concentration-dependent contraction in the terminal ileum with the EC50 value of 11.9 ± 4.3 μM (n=5). In the intermediate ileum, NA produced relaxation at concentrations ranging from 0.016 μM to 1.6 μM. Responses to NA at 16 μM varied among preparations: no noticeable change in tension, a moderate relaxation and a small contraction. At higher concentrations, NA produced contractile responses and their peak tension increased in a concentration-dependent manner. The contractile effect of NA in the terminal ileum remained unaltered after treatment with propranolol (1.4 μM) or yohimbine (1.1 μM), or a combination of these drugs. In the intermediate ileum, the relaxant effect of NA was markedly reduced or abolished by propranolol (1.4 μM). Yohimbine (1.1 μM) had little effect on NA-induced relaxation. The contractile effect of NA in both the terminal ileum and intermediate ileum was inhibited by prazosin (11 μM), so that the contractions were converted to relaxation or markedly reduced. Propranolol abolished the relaxant responses induced by NA at 0.16 μM, but did not inhibit those induced by NA at 1.6 μM. Methoxamine (0.16–1.600 μM) produced a concentration-dependent contraction in both the terminal ileum and the intermediate ileum. The EC50 was 93.5 ± 28.5 μM (n=8) in the terminal ileum and 83.3 ± 27.7 μM (n=10) in the intermediate ileum. There was no significant difference between the values. The results showed that NA is capable of producing contraction or relaxation in the longitudinal muscle layer of the terminal and intermediate regions of the guinea-pig ileum. The contraction, which is mediated by α1-adrenoceptors, predominates in the terminal ileum, but relaxation, which is mediated by β-adrenoceptors and uncharacterized adrenoceptors, predominates in the intermediate ileum. — KEY WORDS: adrenoceptor, ileum, noradrenaline, smooth muscle.

In the gut of different animals, sympathetic nerve stimulation or exogenous noradrenaline (NA) produces an inhibitory effect on the mechanical and electrical activities in the smooth muscle [1, 14, 16]. Exceptional regions are the pyloric sphincter, the ileo-caecal sphincter and the terminal ileum in which an excitatory effect is elicited. Therefore, in most experiments in which receptor types mediating the actions of sympathomimetic drugs in the small intestine are investigated, the terminal ileum has been discarded.

Although it is well known that NA produces the contraction and relaxation of the smooth muscle of the guinea-pig intestine, adrenoceptors mediating these mechanical responses have still remained elusive. α-adrenoceptors consist of α1-subtype which is exclusively located on the smooth muscle and mediates relaxation or contraction dependent on the intestinal region, and α2-subtype which is located on cholinergic nerve terminals and mediates an inhibitory effect of cholinergic excitatory transmission to the smooth muscle. Recently the existence of α2-subtype in the smooth muscle has been described [5]. β-adrenoceptors are of β1-subtype, although there is some debate. The existence of atypical β-adrenoceptors has recently been suggested [8, 9]. Such adrenoceptors are insensitive to nonselective β-adrenoceptor antagonists such as propranolol, but indistinguishable in the rank order of potency of agonists from β1-adrenoceptors.

Recently, signal transductions to which α1-, α2- and β-adrenoceptors are linked have been investigated in many cell types. Activation of α1-adrenoceptors is associated with an increase in intracellular calcium, and α2-adrenoceptors appear to inhibit adenyl cyclase, whereas β-adrenoceptors activate the enzyme [12]. However, there is no paper dealing with those in intestinal smooth muscle cells.

The experiments designed in the present paper were to establish adrenoceptor-subtypes mediating mechanical responses to noradrenaline, in the longitudinal muscle of the guinea-pig ileum, as a step to investigate mechanisms for signal transduction to which adrenoceptor-subtypes are linked.

MATERIALS AND METHODS

Preparation of ileal muscle strips: Male albino guinea-pig, weighing 300 to 400 g, were killed by exsanguination after a sudden blow on the head. The whole of the ileum was removed and placed in a large, shallow dish filled with Tyrode solution (composition in mM; NaCl 136.9, CaCl2 1.8, KCl 2.7, MgCl2 2.1, NaH2PO4 0.4, NaHCO3 11.9 and glucose 5.6), from which intestinal segments were isolated from the respective regions between 3 and 10 cm (terminal

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region) and between 30 and 37 cm (intermediate region) away from the ileo-caecal junction. The lumen of the intestinal segments was flushed with Tyrode solution to remove the content. The longitudinal muscle layer of each intestinal segment was peeled from the underlying tissue by the method described by Paton and Vizi [19], and a muscle strip (3–5 mm wide and 40–50 mm long) was folded in two at a right angle to the longitudinal axis to prepare a double-layered muscle strip. The ends of the muscle strip were each tied with cotton thread.

Recording of tension changes: The longitudinal muscle strip was mounted vertically in a 3 ml organ bath with one end of it fixed and the other attached by thread to a transducer. The organ bath was filled with Tyrode solution kept at 37°C and continuously aerated. The preparation was allowed to equilibrate for 60 min with an initial tension of 1.2–1.5 g. During this period, its tension reached a sustained and elevated level. Changes in tension were recorded isometrically by a force-displacement transducer (Nihon Kohden, TB-612T) on a pen recorder (Hitachi, 561).

Before starting the experiment, carbachol was repeatedly applied at a submaximal concentration of 0.066 μM to the preparation until a reproducible response was obtained. An adrenergic agonist, noradrenaline (NA) was added to the organ bath in a volume of up to 50 μl to give a desired concentration and allowed to act for 1 to 2 min. The action was terminated by washing 4 to 5 times with fresh Tyrode solution. The interval between successive applications was 10 min. Adrenoceptor-antagonists were added to Tyrode solution in the reservoir and were allowed to act on the preparation for more than 30 min before subsequent application of the agonist. In experiments in which NA was applied repeatedly to one preparation at varied concentrations, carbachol (6.6 μM) or papaverine (250 μM), or both drugs were applied at their supramaximal concentration at the end of the experiment. For calculation of the magnitude of contractile responses or relaxant responses the basal tension just before the first application of NA was used throughout the experiment whether it changed or not. To avoid errors from deterioration, one concentration-response curve for the action of noradrenaline was constructed per one preparation.

Drugs: Drugs used were noradrenaline hydrochloride, methoxamine hydrochloride, propranolol hydrochloride, tetrodotoxin of which all were purchased from Sigma, prazosin hydrochloride, yohimbine hydrochloride, clonidine hydrochloride, carbachol chloride, papaverine hydrochloride and atropine sulfate monohydrate from Wako Pure Chemical Ltd.

Statistical analysis: Means are expressed with ± the standard error of the mean (± S.E.M). The statistical significance was evaluated by Student’s t-test for unpaired and paired samples and p values of 0.05 or less were considered significant.

RESULTS

Mechanical responses to noradrenaline (NA) (0.016–1,600 μM) were observed in longitudinal muscle strips from the terminal and intermediate regions of the guinea-pig ileum. The magnitude of contractile responses and relaxant responses to NA was measured as a change in tension from the basal tension and was normalized for the contractile responses using the magnitude of a contractile response induced by carbachol (6.6 μM) and for the relaxant responses the magnitude of a relaxant response induced by papaverine (250 μM), respectively.

In the terminal ileum, NA produced a rise in tension with a threshold concentration of around 0.16 μM. As NA concentration was increased, the rate of tension development and peak tension of the contractile responses increased, as shown in Fig. 1. The tension reached a peak within 15 sec after NA application and then decayed with a slower time course. Due to the slow time course of the decay phase, the tension was still at an elevated level at the end of NA application (1–2 min). In some cases, the tension response decayed with a decreasing rate after reaching a peak and then attained to a sustained level in tension or caused a transition to a rise in tension again especially when NA was applied at high concentrations. Contractile responses were often preceded by an initial, rapid relaxation. On average, the magnitude of contractile responses to NA (1600 μM) was 92.5 ± 2.7% (mean ± S.E.M, n=5) of that of the carbachol response. Atropine (0.3 μM) and tetrodotoxin (0.1 μM), which were sufficient to abolish contractile responses to carbachol (up to 1.6 μM) and to block nerve excitation, respectively, did not significantly affect the contractile responses to NA. Therefore, the contractile effect of NA appeared to be brought about by its direct

Fig. 1. Mechanical response to noradrenaline (NA) in the terminal and intermediate regions of the ileum. Upper row, responses to NA at six different concentrations (Ⅲ, left to right, 0.016, 0.16, 1.6, 16, 160 and 1600 μM, at start of application of NA), with a contractile response to carbachol (Ⅲ, 6.6 μM CCh) in the terminal ileum. Lower row, responses in the intermediate ileum. Notice the transition from the relaxant response to the contractile response in the intermediate ileum.
action.

The concentration-response curve for the contractile effect was often non-sigmoidal and in many cases, did not reach a clearly defined maximum (Fig. 2). In any case, from the concentration-response curves obtained using the maximum tension produced by 1,600 μM NA as a saturation level (the maximum effect) the concentration of NA required for a half maximum effect (EC\textsubscript{50}) was calculated to be 11.9 ± 4.3 μM (n=5).

In the intermediate ileum, when applied at 0.016 μM, NA produced a small relaxation in less than 10% of preparations, but not any measurable response in others, suggesting its threshold concentration of around 0.016 μM. Relaxant responses increased in magnitude with a saturated level as NA concentration was increased. The saturated level, which was 76.4 ± 8.7% (mean ± S.E.M., n=6) of the maximum relaxation produced by papaverine, was attained by NA at 1.6 μM in three out of six preparations and at 16 μM in other three preparations. Responses to NA at 16 μM varied among preparations, a relaxation (four preparations) and a small contraction (two preparations). This suggests that at a concentration close to 16 μM, NA makes a change in the overall effect from relaxation to contraction. At concentrations higher than 16 μM NA elicited contraction only, and the magnitude of contractile responses increased in a concentration-dependent manner with a maximum value of 86.1 ± 4.0% (n=6) of the contractile response produced by carbachol (Figs. 1 and 2).

**Effect of α1-adrenoceptor blockade with prazosin:** To evaluate an involvement of α1-adrenoceptors in the generation of contractile responses to NA, prazosin (1.1 μM) was applied to block these adrenoceptors. This concentration of prazosin was more than 100 times greater than the concentration derived from its pA2 value (8.5–10.5) for α1 adrenoceptors and was confirmed to be sufficient to block the contractile effect of methoxamine (up to 1.6 μM).

In the terminal ileum, prazosin inhibited the contractile effect and unmasked a relaxant effect of NA. At concentrations ranging between 0.16 μM and 160 μM, NA was effective in producing relaxation with decreased or abolished spontaneous activities in the continued presence of prazosin. The relaxant response increased in magnitude concentration-dependently with a saturation level (160 μM NA), as shown in the Fig. 3. The saturation magnitude was 84.0 ± 5.8% (n=6) of the relaxant response produced by papaverine. In addition, during a period of 2 min of NA application at high concentrations, the relaxation reached a maximum level within 15–30 sec after NA application, remained at this maximum level for 30 sec or so and then started decaying before the end of NA application. The concentration of NA required for a half maximum effect (EC\textsubscript{50}) was 0.42 ± 0.14 μM (n=6).

![Graph of concentration-response curves for the contractile and relaxant effects of noradrenaline (NA) in the terminal and intermediate regions of the ileum.](image)

Fig. 2. Concentration-response curves for the contractile and relaxant effects of noradrenaline (NA) in the terminal and intermediate regions of the ileum. Abscissa: -log concentration of NA. Ordinate: % change in the magnitude of the contractile responses (positive direction) and relaxant responses (negative direction). The magnitude of the contractile response to 6.6 μM carbachol was taken as 100% for the contractile effect and the magnitude of the relaxant response to 250 μM papaverine was taken as 100% for the relaxant effect, in each preparation. □—□, in the terminal ileum; □—□, in the intermediate ileum. Each point represents the mean ± SEM of 6–8 measurements. Responses to NA at 16 μM varied among preparations (contractile responses in two preparations and relaxant responses in four preparations). See text for details.

![Graph of concentration-response curves for the relaxant effect of noradrenaline (NA) after blockade of α1-adrenoceptors by prazosin (1.1 μM) in the terminal and intermediate regions of the ileum.](image)

Fig. 3. Concentration-response curves for the relaxant effect of noradrenaline (NA) after blockade of α1-adrenoceptors by prazosin (1.1 μM) in the terminal and intermediate regions of the ileum. Abscissa: -log concentration of NA. Ordinate: % change in the magnitude of the relaxant responses. The magnitude of the relaxant response to 16 μM NA was taken as 100% in each preparation. ○—○, in the terminal ileum; □—□, in the intermediate ileum. Each point represents the mean ± SEM of 6 measurements. See text for details.
Fig. 4. Characterization of relaxant responses to noradrenaline (NA) after blockade of α1-adrenoceptors by prazosin (1.1 μM) in the terminal and intermediate regions of the ileum. A, responses to NA at three different concentrations with a relaxant response to papaverine (●), left to right, 1.6, 16, and 160 μM, at start of application of NA, ○, 250 μM, at start of application of papaverine) in the intermediate ileum, a, the time taken from the start of NA application to the end of the sustained, maximum level of relaxation (sec), x/b, the rate of decay from the maximum relaxation (%/min). B, summarized effects of NA on a (left) and x/b (right). Open column, in the terminal ileum; hatched column, in the intermediate ileum. Noticed the transition of both variables at 160 μM NA.

For further characterization of relaxations produced by NA at concentrations higher than 1.6 μM, the time taken from the beginning of NA application to the end of the sustained maximum level of relaxation (a, the relaxation duration) and the rate of decay (x/b) were measured, as shown in Fig. 4A. The mean relaxation durations at 1.6, 16 and 160 μM of NA in four separate experiments were 49.5 ± 5.8, 75.0 ± 6.6 and 53.3 ± 5.5 sec, respectively. The decay rates were 33.0 ± 5.6 %/min at 1.6 μM, 14.4 ± 5.0%/ min at 16 μM and 34.6 ± 6.3%/min at 160 μM (Fig. 4B). The results demonstrate some influence on both variables of a superimposed contractile effect which appears again when NA concentration is increased to 160 μM.

In the intermediate ileum, prazosin inhibited the contractile effect of NA. Relaxant responses to NA in the presence of prazosin resembled those obtained in the terminal ileum (see Fig. 3). The concentration-response curves for the relaxant effect in six different preparations gave the mean EC50 of 0.20 ± 0.04 μM, which was not significantly different from that in the terminal region. The maximum magnitude of relaxations produced by NA was 76.4 ± 8.7% of that of the relaxation produced by papaverine. The relaxation duration and the decay rate measured as in the terminal ileum were 66.0 ± 9.0 sec and 20.3 ± 6.1 %/min at 1.6 μM, 99.0 ± 17.4 sec and 8.2 ± 4.7%/min at 16 μM and 71.3 ± 17.2 sec and 38.3 ± 19.4 %/ min at 160 μM (Fig. 4B). The same transition of both variables as that in the terminal ileum took place at 160 μM, because of a superimposed contractile effect of NA.

Effect of α2- and β-adrenoceptor blockers with yohimbine and propranolol: Yohimbine was used for α2-adrenoceptor blockade at 1.1 μM which is more than 10 times greater than the concentration derived from its pA2 value (7.5–9.5) for α2-adrenoceptors. The concentration of yohimbine was high enough to block relaxation produced by clonidine (0.1 μM). Propranolol was used for β-adrenoceptor blockade at 1.4 μM which is more than 100 times greater than the concentration derived from pA2 value (5.5–9.5) for β-adrenoceptors. The concentration of propranolol was effective in blocking relaxations produced by isoprenaline (up to 0.1 μM).

In the terminal ileum, the contractile effect of NA remained unaltered after treatment with yohimbine (n=7) or propranolol (n=10) or a combination of both antagonists (n=5). The concentration-response curve for the contractile effect did not significantly shift under these circumstances, as shown in Fig. 5. The mean values for EC50 and peak magnitude of the responses in the presence of both yohimbine and propranolol were 14.06 ± 3.69 μM (n=5) and 70.2 ± 9.0% (n=5) of that of the contraction produced by carbachol. The EC50 was not significantly different from the control (11.9 ± 4.3 μM, n=5), whereas the maximum magnitude was significantly smaller than the control (92.5 ± 27, n=5).

In the intermediate ileum, the relaxant effect of NA was abolished with propranolol (1.4 μM) in five out of seven preparations. In the remaining two preparations, NA still exert a relaxant effect when applied at concentrations of 0.16 and 1.6 μM. Yohimbine seemed to have a weak inhibitory effect on the relaxant responses to NA.

Adrenoceptors mediating relaxant responses to noradrenaline: Adrenoceptors mediating the relaxant response to NA were more precisely examined in the
Fig. 6. The effects of yohimbine and propranolol on the relaxant responses induced by noradrenaline (NA) in the presence of prazosin (1.1 μM). A, pairs of the responses to NA at two different concentrations (\(
abla\), 0.16 and 1.6 μM, at start of application of NA); a, control; b, in the presence of yohimbine (1.1 μM) and c, in the presence of propranolol (1.4 μM). d, the relaxant response induced by 250 μM papaverine. B, summarized effects of yohimbine alone, propranolol alone, and yohimbine and propranolol. The magnitude of the relaxant response to 250 μM papaverine was taken as 100% in each preparation. Each column represents the mean ± SEM of the measurements indicated by attached numbers. Left column in each pair, control.

presence of prazosin (1.1 μM) to suppress the superimposed contractile effect. Because of the close similarity of the pharmacological profiles of the relaxant responses to NA in the terminal and intermediate regions of the ileum, the description of the results in this section was made without separating between the two different regions. The mean relaxations produced by NA at 0.16 μM (close to an EC_{50} of 0.2–0.4 μM) and 1.6 μM (close to EC_{50}) were 40.4 ± 7.5% (n=8) and 80.3 ± ± 2.9% (n=4), and 35.8 ± 5.0% (n=3) and 69.4 ± 11.7% (n=3) in the absence and presence of yohimbine (1.1 μM), respectively (Fig. 6). The difference between the means at either concentration of NA was not significant, suggesting no involvement of \(\alpha_2\)-adrenoceptors in mediating the relaxant response. Pretreatment with propranolol (1.4 μM) reduced the relaxant response to 0.16 μM NA (40.4 ± 7.5%, n=8) to zero, but did not significantly affect the relaxant response to 1.6 μM NA (74.3 ± 5.3% before and 83.5 ± 2.6% after application of propranolol).

**Contractile responses mediated via \(\alpha_1\)-adrenoceptors:** The contractile response mediated via \(\alpha_1\)-adrenoceptors was studied by methoxamine. As shown in Fig. 7, methoxamine (0.016–1,600 μM) produced a concentration-dependent contraction in both the terminal ileum (Fig. 7A) and the intermediate ileum (Fig. 7B) with a threshold concentration of around 0.16 μM. The mean EC_{50} of 93.5 ± 28.5 μM (n=8) and the magnitude of the contraction produced by methoxamine (1600 μM) of 68.1 ± 6.5% (n=8) in the terminal ileum are not significantly different from the corresponding values of 83.3 ± 27.7 μM (n=10) and 69.8 ± 4.7% in the intermediate ileum. Prazosin (1.1 μM) shifted the concentration-response curves two orders of magnitude to the right. The results rule out the possibility that a regional variation in the density of \(\alpha_1\)-adrenoceptors accounts for the difference in the overall effect of NA.

**DISCUSSION**

The results demonstrated that NA is capable of producing contraction or relaxation in the longitudinal muscle layer of the different regions of the guinea-pig ileum; contraction

Fig. 7. Concentration-response curves for the contractile effect of methoxamine in the terminal and intermediate regions of the ileum. Abscissa: –log concentration of methoxamine. Ordinate: % change in the magnitude of the contractile responses. The magnitude of the contractile response to 1,600 μM methoxamine in the absence of any antagonist was taken as 100% in each preparation. A and B in the terminal ileum and in the intermediate ileum, respectively. ○—○, control; ■—■, in the presence of propranolol (1.4 μM) and yohimbine (1.1 μM), and ■—■, in the additional presence of prazosin (1.1 μM). See text for details.
predominated in the terminal ileum, while relaxation predominated in the intermediate ileum, in agreement with the previous findings [4, 5]. The contractile effect of NA was abolished by prazosin unless NA was applied at much higher concentrations and appears to be mediated via α1-adrenoceptors [4]. The contractile effect remained unaffected after application of TTX, and it can be attributed to the action of NA at α1-adrenoceptors located on the smooth muscle cells. The possibility can be excluded that NA acts on nerve terminals to release an unidentified stimulatory substance independent of nerve impulses, since the contractile effect of NA was preserved in preparations stored at 4°C for 24 hr or more (unpublished observations).

The relaxation produced by NA at a concentration close to the EC50 was abolished by propranolol, suggesting involvement of β-adrenoceptors in mediating the mechanical response. This is compatible with the previous studies [2, 5, 13]. However, at 1.6 μM which is close to the concentration required to produce its maximal effect, the relaxant response to NA remained almost unaltered after treatment with propranolol in the continued presence of prazosin. Unfortunately, propranolol, when used at a higher concentration, reduced the muscle preparation tone so that its effect could not be evaluated with accuracy. Since the NA concentration of 1.6 μM was close to but still below the maximal concentration in producing the relaxant response (see Fig. 3), this finding suggests the existence of adrenoceptors other than β-adrenoceptors which mediate the smooth muscle relaxation. The uncharacterized adrenoceptors would be atypical β-adrenoceptors [8, 9]. Recently, Taneda and Clarke [20] reported the coexistence of atypical β-adrenoceptors with β1-adrenoceptors in the guinea-pig ileum. Atypical β-adrenoceptors are characterized by their resistance to nonselective β-adrenoceptor antagonists including propranolol and the potency order of agonists such as adrenaline (A) and NA are similar to that for β1-adrenoceptors (NA ≡ A).

The relative contributions of the various subtypes of adrenoceptors are of importance in determining the overall effect of NA and they may vary along the ileum. The predominance of the contractile response to NA in the terminal ileum has been related to the greater density or coupling efficacy or both of α1-adrenoceptors relative to those in the intermediate ileum [4, 6]. This idea is not supported by the present finding that there was no apparent difference in the action of methoxamine, a drug with a relatively-selective action on α1-adrenoceptors, on muscle preparations obtained from the different regions of the ileum. Therefore, it seems likely that the same variables of adrenoceptors mediating smooth muscle relaxation account for the regional variation of NA-induced responses. It has been suggested by the mechanical and electrical response to isoprenaline that β-adrenoceptors are distributed homogenously in the ileal smooth muscle [4, 6]. The inhibitory adrenoceptors which are of uncharacterized adrenoceptors seem to be distributed in different density. To resolve this matter, experiments in which the localization and concentration of different adrenoceptor types are determined should be performed using techniques which can quantify and characterize individual adrenoceptor types.

In the smooth muscle of the guinea-pig taenia caeci, in which activation of α2-adrenoceptors causes relaxation, the effect is produced by inhibition of electrical activities through membrane hyperpolarization. The hyperpolarizing effect is due primarily to increase in the membrane conductance. Although activation of Ca2+-dependent K+ channels and also, at least in part, Ca2+-dependent Cl- channels has been suggested to be involved in the hyperpolarizing effect [7, 10, 18], the inhibitory adrenoceptors have not been clearly characterized; they may be of α1-adrenoceptor type or of mixed type of α1- and α2-adrenoceptors. In this present study, the excitatory adrenoceptors present in the ileal longitudinal muscle were found to be of α1-adrenoceptor type. Its activation elicited contraction and the contraction would be associated with the acceleration of discharge of action potentials through depolarization and reduction in the input resistance of the membrane [6]. It is possible that activation of Cl- channels leading to membrane depolarization predominates in the smooth muscle, as in the myometrium [11, 15]. Effects of NA on the activity of ion channels await electrophysiological analysis using patch-clamp techniques.

For the location of α2-adrenoceptors, there have been some debates: these adrenoceptors are located exclusively on cholinergic nerve terminals in the enteric plexuses to inhibit the transmitter (ACh) release resulting from their stimulation [21, 22]. In addition to cholinergic neurons, α2-adrenoceptors may be located on postjunctional sites, namely smooth muscle cells of the intestine [5]. The present findings that part of the relaxation produced by NA or clonidine, was inhibited with yohimbine suggest that it may be attributed to activation of α2-adrenoceptors located on the smooth muscle. This is compatible with the previous reports [2, 5, 13]. Arients and Simonis [3] suggested that in vascular bed, α2-adrenoceptors located on the smooth muscle may not function as postjunctional receptors of the sympathetic innervation but serve as receptors sensitive to primarily to circulating adrenaline and/or NA. However, yohimbine had no significant effect on the relaxant response to NA in the presence of prazosin. Prazosin, at least the concentration used in the present study, might produce blockade of α2-adrenoceptors as well as α1-adrenoceptors.

NA released by adrenergic nerve impulses in the ileum can act on such different types of adrenoceptors located on different tissues to regulate intestinal functions. In general, intestinal motilities are considered to be inhibited by sympathetic nerve stimulation. The present results confirmed the regional difference in the mechanical responses to NA in the longitudinal muscle of the guinea-pig ileum and showed that the regional variation of NA-induced responses is not attributable to the concentration and coupling efficacy of α1-adrenoceptors which mediate the contractile response, but to those of β-adrenoceptors, presumably atypical β-adrenoceptors [8, 9] which mediate the relaxant response. A question arises as to how it plays a potential physiological role in regulating...
ileal functions. In an attempt to gain some insight in this question, studies on the effect of exogenously-applied NA on the peristaltic reflex are in progress using isolated intestinal segments of different regions of the guinea-pig ileum.

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