α- and β-Adrenergic Receptor Mechanisms in Spontaneous Contractile Activity of Rat Ileal Longitudinal Smooth Muscle

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Gastrointestinal motility is influenced by adrenergic modulation. Our aim was to identify specific subtypes of adrenergic receptors involved in inhibitory mechanisms that modulate gut smooth muscle contractile activity. Muscle strips of rat ileal longitudinal muscle were evaluated for spontaneous contractile activity and for equimolar dose-responses (10^{-7} to 3×10^{-5} M) to the adrenergic agents norepinephrine (nonselective agonist), phenylephrine (α_1-agonist), clonidine (α_2-agonist), prenalterol (β_1-agonist), ritodrine (β_2-agonist), and ZD7114 (β_3-agonist) in the presence and absence of tetrodotoxin (nonselective nerve blocker). Norepinephrine (3×10^{-5} M) inhibited 65 ± 6% (mean ± SEM) of spontaneous contractile activity. The same molar dose of ritodrine, phenylephrine, or ZD7114 resulted in less inhibition (46 ± 7%, 31 ± 5%, and 39 ± 3%, respectively; $P < 0.05$). The calculated molar concentration of ZD7114 needed to induce 50% inhibition was similar to that of norepinephrine, whereas higher concentrations of phenylephrine or ritodrine were required. Clonidine and prenalterol had no effect on contractile activity. Blockade of intramural neural transmission by tetrodotoxin affected the responses to ritodrine and phenylephrine (but not to norepinephrine or ZD7114), suggesting that these agents exert part of their effects via neurally mediated enteric pathways. Our results suggest that adrenergic modulation of contractile activity in the rat ileum is mediated primarily by muscular β_3-, β_2-, and α_1-receptor mechanisms; the latter two also involve neural pathways. (J GASTROINTEST SURG 2005;9:227–235)

KEY WORDS: Contractility, motility, ileum, rat, in vitro, adrenergic, adrenergic receptor, α-adrenergic receptors, β-adrenergic receptors

Coordination and modulation of gastrointestinal motor activity are dependent on the interaction of two complex neural inputs: the enteric nervous system, which is completely intrinsic within the bowel wall, and the central nervous system, sending its influences through the extrinsic nerves to the gut (vagal, sympathetic).[1] Interactions between the central nervous system and the enteric nervous system are important in gastrointestinal responses to stress, eating, and behavior.[2]

Vagal motor pathways modulate mainly the upper gastrointestinal tract and the distal colon and rectum. In the small bowel, vagal inputs are supplied to myenteric neurons.[3] These enteric neurons influence the generation of motor patterns.

The intestinal sympathetic nervous system consists of nerve cell bodies located in the prevertebral ganglia with their postganglionic fibers entering the gut. No adrenergic nerve cell bodies are present in the gut wall.[1] Most, if not all, sympathetic postganglionic fibers affecting motility are thought to synapse in the enteric nervous system and not directly on smooth muscle cells. Indeed, adrenergic nerves do not synapse directly on nonsphincter muscle cells in the gut.[4]

Presented in part at the Forty-Third Annual Meeting of The Society for Surgery of the Alimentary Tract, San Francisco, California, May 19–22, 2002 (poster presentation).

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Supported by Nycomed AG Switzerland, Ethicon, Switzerland, and the Swiss National Science Foundation (B.M.B.; Nr. 31-61583.00).

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1091-255X/05/$—see front matter
doi:10.1016/j.gassur.2004.05.012

Despite the predominant, direct adrenergic input to the enteric nervous system, we found strong, adrenergically mediated inhibitory motor mechanisms in rat jejunum and ileum occurring preferentially at the level of these smooth muscle cells rather than in the enteric nervous system[5,6]; these effects appeared to be independent of input from the enteric nervous system.

Therefore, one approach to target gastrointestinal motility disorders through adrenergic pathways would be to direct the pharmacologic therapy at the receptors occurring in the gut on smooth muscle cells. To date, therapeutic approaches targeting adrenergic pathways in the gastrointestinal tract have not been very successful, in part because of substantial cardiovascular side effects of the agents used.[7]

Therefore, mechanisms involved in modulating contractile activity of the gut mediated by specific subtypes of adrenergic receptors are of considerable interest. Our first aim was to identify which adrenergic receptor subtypes mediate inhibition of spontaneous contractile activity. Second, we wanted to determine if these receptor-specific mechanisms were mediated at the level of the smooth muscle and/or via the enteric nervous system. Our hypothesis was that both α_1- and β_2-receptor mechanisms mediate the inhibitory responses and that these mechanisms are active directly at the level of the smooth muscle and not indirectly via effects mediated through the enteric nervous system.

METHODS

Preparation of Tissue

Procedures and animal care were performed according to the guidelines of the Department of Agriculture of the Canton of Bern, Switzerland. Male Wistar rats were used in all experiments. Anesthesia was achieved with intraperitoneal sodium pentobarbital (5 mg/100 g; Abbott Laboratories, North Chicago, IL). A 5-cm segment of the ileum was removed beginning 2 cm orad to the ileocecal valve and stored in cold Krebs-Ringer buffer (concentration in mM: NaCl 118.3, KCl 4.7, $CaCl_2$ 2.5, $MgSO_4$ 1.2, KH_2PO_4 1.2, $NaHCO_3$ 25.0, calcium disodium edetate 0.26, and glucose 11.1). The distal end of the specimen was marked.

Recording of Contractile Activity

The segment of the distal ileum was immersed in chilled, modified Krebs-Ringer bicarbonate solution and opened along the mesenteric border. The tissue was pinned flat in a Petri dish, and eight full-thickness muscle strips per rat were prepared in the direction of the longitudinal muscle. Silk loops were tied at both ends of the strips. The muscles were suspended vertically in 5-ml organ chambers (Radnoti Glass Technology Inc., Monrovia, CA) filled with modified Krebs-Ringer bicarbonate solution maintained at 37.5° C and bubbled with 95% O_2 and 5% CO_2 (Carbagas, Bern, Switzerland). The lower end of the muscle strip was connected to a fixed glass hook in the chamber, and the upper end was attached to a noncompliant force transducer (Radnoti Glass Technology Inc.), thereby allowing measurement of isometric force.

Experimental Design

After an equilibration period of 80–90 minutes with change of the buffer solution every 20–25 minutes, each strip was stretched incrementally at 10- to 15-minute intervals to its optimal length (L_o). L_o is defined as the length beyond which further stretching did not increase the amplitude of spontaneous contractions. The entire experiment was then performed at this L_o; strips without spontaneous activity were not used (2% of all muscle strips).

After recording of baseline spontaneous activity, one substance was administered per chamber in a cumulative manner every 10 minutes. Norepinephrine (NE) was chosen as the nonselective adrenergic agonist; phenylephrine and clonidine as α_1- and α_2-selective agonists; and prenalterol, ritodrine, and ZD7114, as β_1-, β_2-, and β_3-selective agonists, respectively. Drugs were added in cumulative doses (10^{-7} to 3×10^{-5} M) every 10 minutes. The highest dose used was 3×10^{-5} M according to our previous work using only NE.[5,6] One chamber contained a control strip to confirm stable activity during the duration of the experiment, and the final chamber contained a spare strip.

After the dose-response experiment, the chambers were washed 4 times with modified Krebs-Ringer buffer. When spontaneous contractions returned to baseline activity, tetrodotoxin (TTX; 10^{-6} M) was added to every chamber. TTX is thought to abolish most all enteric neural input by blocking neuronal sodium channels. After a 15- to 20-minute equilibration, the same dose-response experiment was repeated in each chamber with the same agonist.

At the conclusion of the experiment, the length of each strip between the two ties of silk loops and wet weight was measured.

Data Analysis

Total spontaneous contractile activity was quantified as the integral of the generated force ($g \times$ time as total area under the contractile curve) measured

for 5 minutes at L_o, whereas responses to adrenergic agonists were quantified by measuring the integral of force for 5 minutes immediately after drug administration. The integral of force was calculated by computerized methodology using special software (AcqKnowledge, Biopac Systems, Inc., Goleta, CA), normalized per millimeter squared of cross-sectional area (CSA) for each muscle strip.

The CSA was calculated using the following equation:

$$\text{CSA (mm}^2\text{)} = \text{Tissue wet weight (mg)/Tissue length (mm)} \times \text{Tissue density (mg/mm}^3\text{)}$$

Tissue length and weight were measured at the end of the experiment, and smooth muscle tissue density was assumed to be 1.05 mg/mm.[3,8]

The dose-response curve for each agonist was obtained by defining spontaneous contractile activity as 100%. To quantify these dose-response curves, the negative of the natural log (In) of the equipotent concentration that caused a 50% response (EC_{50}) was estimated for each agonist based on the dose-response curve. A greater EC_{50} represents a smaller concentration of an agonist needed to induce 50% inhibition of spontaneous activity.

Values are presented as mean ± SEM. Student's *t* tests with a Bonferroni correction were used to compare the effects of each specific agonist with spontaneous activity at all doses and with the respective effect of NE. The effect of TTX on spontaneous activity, on EC_{50}, and on each dose of the respective agonist was evaluated in the same way.

Drugs

L-Phenylephrine hydrochloride, clonidine hydrochloride, ritodrine hydrochloride, and norepinephrine bitartarate salt were purchased from Sigma (St. Louis, MO). Prenalterol and ZD7114 hydrochloride were purchased from Astra Zeneca (Södertälje, Sweden). TTX was purchased from Juro (Luzern, Switzerland).

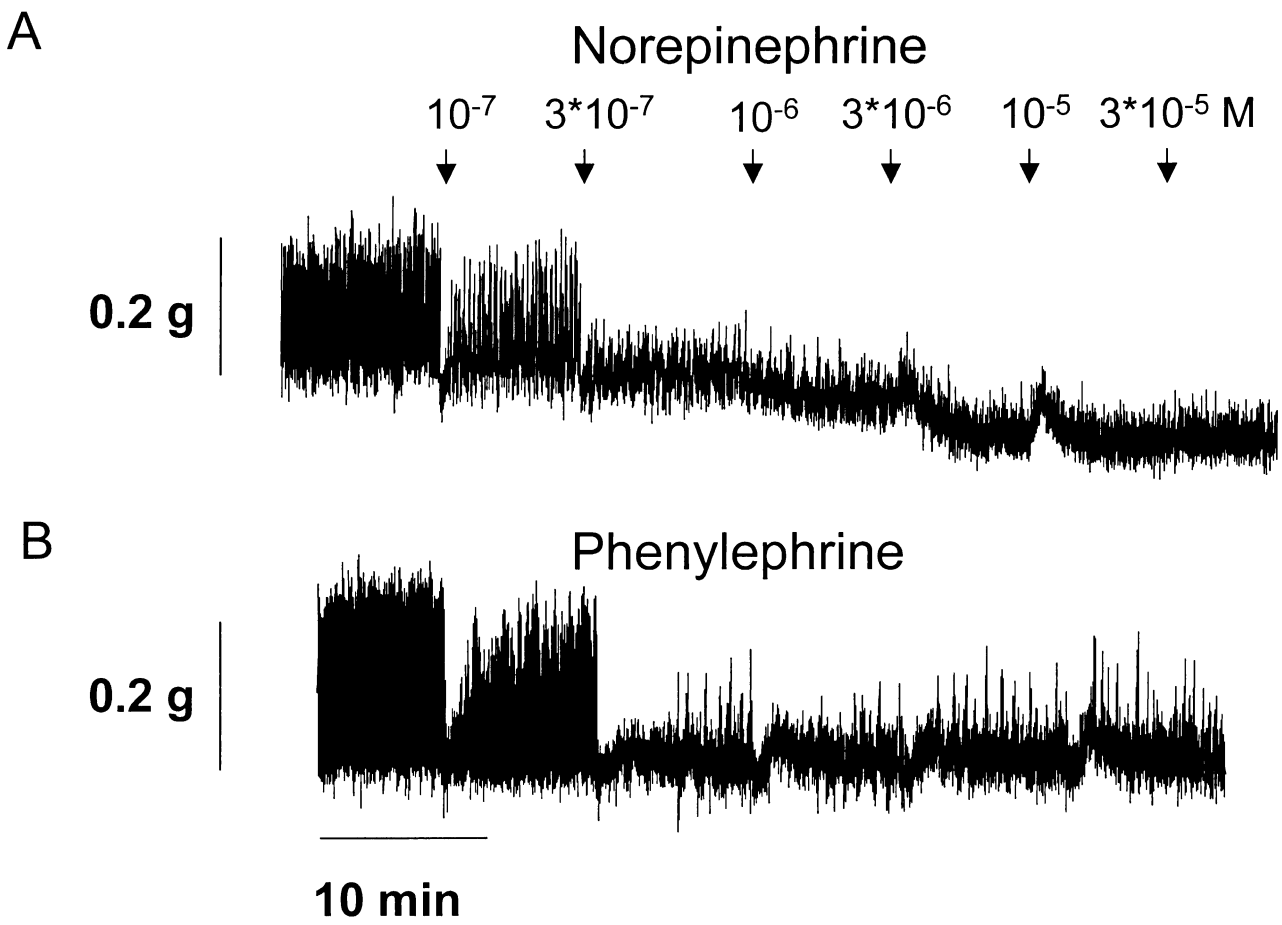


Fig. 1. Effect of norepinephrine (**A**) and phenylephrine (α_2) (**B**) on spontaneous activity. Cumulatively administered molar doses of agents caused a dose-dependent decrease in contractile activity.

RESULTS

Spontaneous Contractile Activity

Spontaneous phasic contractile activity was recorded shortly after suspending the muscle strips in the organ chambers. After the addition of TTX (after the first adrenergic dose-response experiments, washout, and restoration of spontaneous activity), contractile activity was reduced slightly from 77 ± 8 to 73 ± 8 (g/5 min/mm^2; $P < 0.01$).

Effect of Nonselective Adrenergic Stimulation

In all strips treated with NE, the amplitude and the baseline tone were reduced in a dose-dependent manner, whereas the frequency of contractions remained unchanged. At the higher doses, an initial increase in basal tone was observed (Fig. 1A). Inhibition of spontaneous contractile activity induced by the highest dose of norepinephrine (3×10^{-5} M) was $65 \pm 6\%$. Blocking all neural activity within the bowel wall with TTX (10^{-6} M) did not change the dose-response to NE (Table 1) nor the effect of the highest dose of NE on baseline tone (Table 2).

Effect of α-Agonists

Phenylephrine (α_1-agonist) inhibited contractile activity by reducing the amplitude but not the basal tone in a dose-dependent fashion (Fig. 1B). However, the EC_{50} was less than that for NE, and the inhibition (at 3×10^{-5} M) was less compared with an equimolar dose of norepinephrine (Table 1; Figs. 1, 2A). TTX had no effect on α_1-receptor–mediated inhibition induced by phenylephrine. However, if only changes in baseline tone were analyzed, TTX slightly increased the change of baseline tone induced by the highest dose of phenylephrine (3×10^{-5} M; $35 \pm 5\%$ versus $43 \pm 4\%$, $P < 0.05$; Table 2). Clonidine (α_2-agonist) with and without TTX had no demonstrable effect on contractile activity.

Table 2. Reduction of baseline tone induced by adrenergic agonist without or with tetrodotoxin (TTX; 10^{-6} M)

	Response to 3×10^{-5} M dose*	
	Without TTX	With TTX
Norepinephrine	75 ± 9	80 ± 6
Phenylephrine, α_1	35 ± 5	$43 \pm 4^{\dagger}$
Clonidine, α_2	7 ± 4	20 ± 4
Prenalterol, β_1	26 ± 4	32 ± 6
Ritodrine, β_2	66 ± 8	$45 \pm 6^{\dagger}$
ZD7114, β_3	58 ± 7	60 ± 7

*Values represent percent (mean ± SEM; n ⩾ 8 rats) reduction of baseline (one after the highest dose of agonist (3×10^{-5} M) compared with baseline tone before dose-response experiment (100%).
$^{\dagger}P < 0.05$ compared with without TTX.

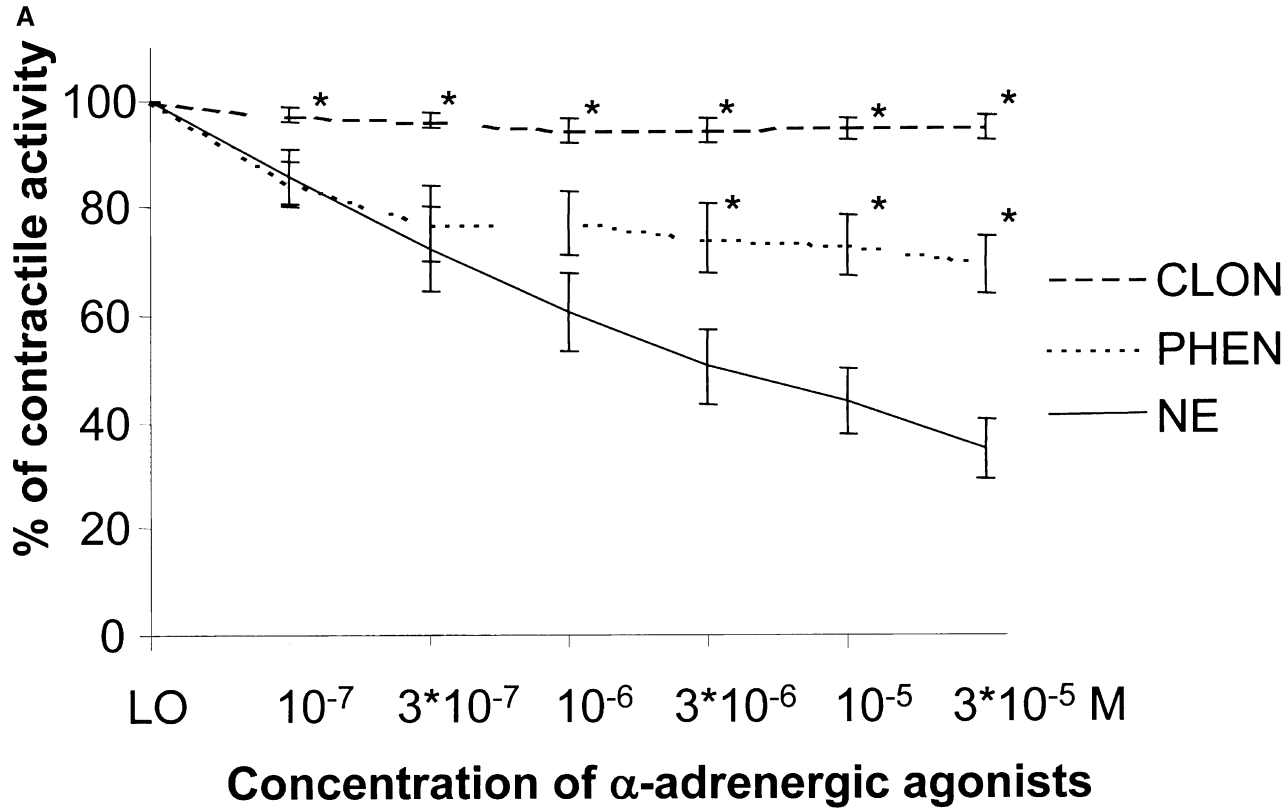
Effect of β-Agonists

Differing effects of the three β-adrenergic agonists were noted. Prenalterol (β_1-agonist) with or without TTX had no effect. In contrast, ritodrine (β_2-agonist) and ZD7114 (β_3-agonist) both induced a marked, dose-dependent effect with inhibitions of $39 \pm 3\%$ and $46 \pm 7\%$ at 3×10^{-5} M doses, respectively (Table 1, Figs. 2B, 3). TTX did not influence the dose-response of ZD7114 (β_3-agonist), but TTX reduced the inhibitory effect of 3×10^{-5} M ritodrine (β_2-agonist) from $46 \pm 7\%$ to $35 \pm 6\%$ ($P < 0.05$); the EC_{50}, however, did not change (Table 1). This decrease in inhibition seems to be due primarily to a lesser reduction in the basal tone (Fig. 4). Ritodrine (3×10^{-5} M; β_2-agonist) reduced basal tone by

Table 1. Inhibitory effect of selective adrenergic agonists on rat ileal longitudinal muscle without and with tetrodotoxin (TTX; 10^{-6} M)

	Response to 3×10^{-5} M dose*		EC_{50}	
	Without TTX	With TTX	Without TTX	With TTX
Norepinephrine	$65 \pm 6^{\dagger}$	$70 \pm 5^{\dagger}$	5 ± 0.3	5.3 ± 0.7
Phenylephrine, α_1	$31 \pm 5^{\dagger\ddagger}$	$30 \pm 6^{\dagger\ddagger}$	$1.5 \pm 0.7^{\ddagger}$	$2.3 \pm 1.2^{\ddagger}$
Clonidine, α_2	$5 \pm 3^{\ddagger}$	$13 \pm 7^{\ddagger}$	NA	NA
Prenalterol, β_1	$9 \pm 4^{\ddagger}$	$15 \pm 2^{\dagger\ddagger}$	NA	NA
Ritodrine, β_2	$46 \pm 7^{\dagger\ddagger}$	$35 \pm 6^{\dagger\ddagger\S}$	$3.5 \pm 0.4^{\ddagger}$	$3.0 \pm 0.6^{\ddagger}$
ZD7114, β_3	$39 \pm 3^{\dagger\ddagger}$	$42 \pm 4^{\dagger\ddagger}$	4.4 ± 0.6	4.4 ± 0.4

EC_{50} = calculated negative log of molar value resulting in 50% inhibition of spontaneous activity; NA = not applicable, because no inhibition was seen.
*Values given as percent inhibition, mean ± SEM; n ⩾ 8 rats.
$^{\dagger}P < 0.005$ compared with norepinephrine.
$^{\ddagger}P < 0.06$ compared with spontaneous activity before adding respective drug.
$^{\S}P < 0.05$ compared with same dose without TTX.



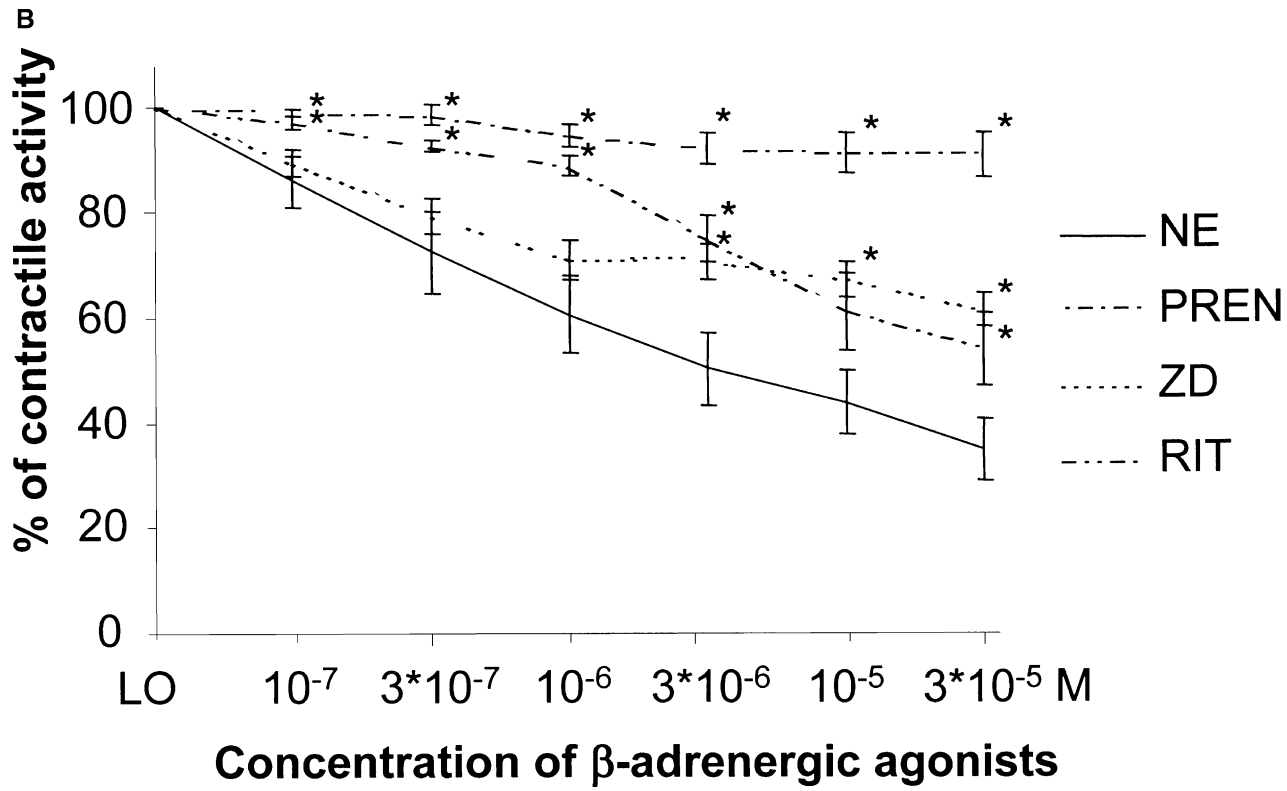


Fig. 2. Dose-responses of (**A**) clonidine (CLON) (α_1) and phenylephrine (PHEN) (α_2) and of (**B**) prenalterol (PREN) (β_1), ritodrine (RIT) (β_2) and ZD7114 (ZD) (β_3) compared with norepinephrine (NE). Values given as mean ± SEM; n = 9 rats. *$P < 0.05$ versus NE.

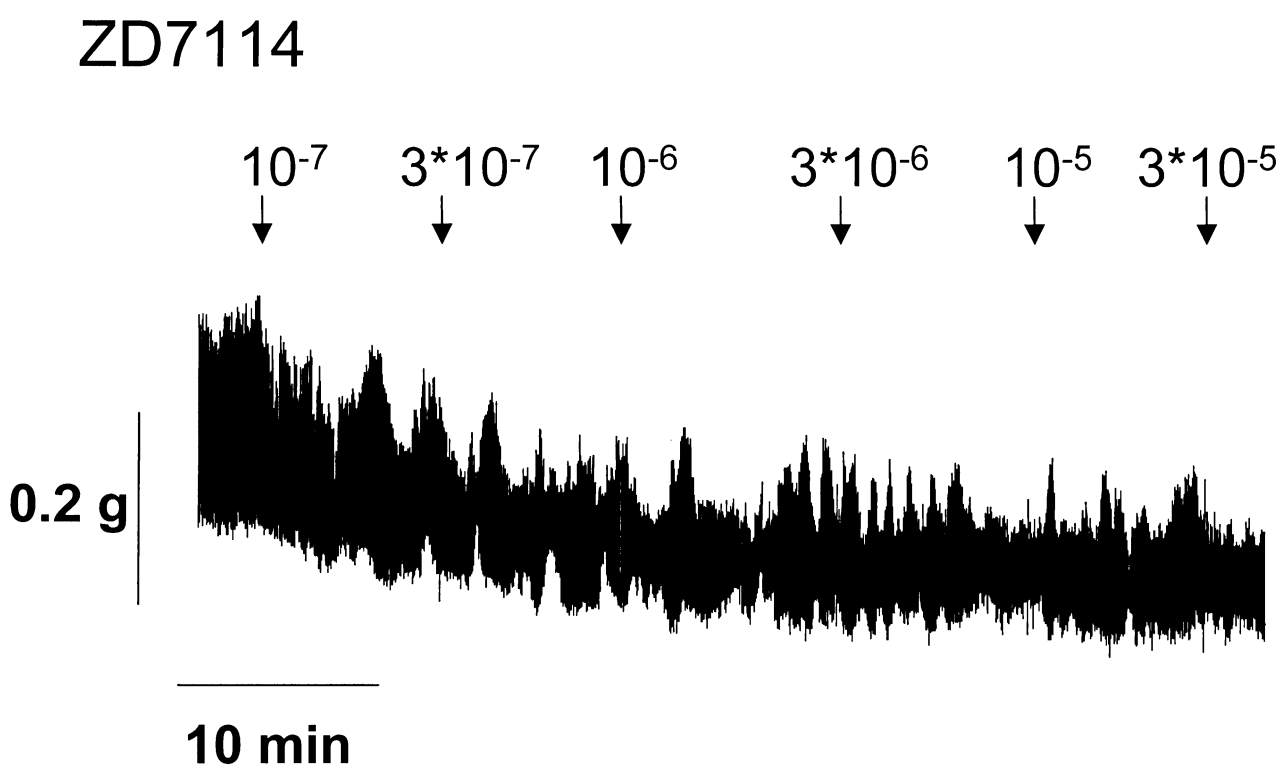


Fig. 3. Effect of ZD7114 (β_3) on spontaneous activity. ZD7114 was administered cumulatively and caused a dose-dependent decrease in basal tone and thus in contractile activity.

66 ± 8%. In the presence of TTX, the reduction in baseline tone was smaller (45 ± 6%, $P < 0.05$).

The EC_{50} for ZD7114 did not differ from the EC_{50} of NE (4.4 ± 0.6 versus 5.0 ± 0.3), suggesting a similar molar inhibitory effect by ZD7114. The EC_{50} of ritodrine and NE (3.5 ± 0.4 versus 5.0 ± 0.3, $P < 0.05$) differed; the dose-response curve for ritodrine was shifted to the right, compared with NE (Fig. 2B).

DISCUSSION

Our study was designed to characterize the involvement of specific adrenergic α_1-, α_2-, β_1-, β_2-, or β_3-receptor mechanisms in the inhibition of contractile activity of longitudinal smooth muscle in the rat ileum. These contractile responses are of particular interest, because modulation of gut motility via adrenergic pathways may represent a novel therapeutic target for motility disorders. This pharmacologic approach would require identification of specific receptor subtype mechanisms such that effects on intestinal contractile function can be targeted, possibly minimizing or even avoiding cardiovascular side effects.

Our main findings were that α_2- and β_1-receptor mechanisms do not appear to be involved in the adrenergic modulation of gut contractile activity in the rat, neither directly on the smooth muscle cells nor indirectly via the enteric nervous system. In contrast, α_1, β_2, and β_3 pathways reproduced, in part, the inhibition induced by norepinephrine, a nonselective, global adrenergic agonist. Blocking enteric neural activity within the muscle strip (with TTX 10^{-6} M) partially reduced the response of β_2-receptor and slightly increased the response of α_1-receptor stimulation, suggesting involvement of enteric neural mechanisms.

The involvement of α_1- but not α_2-receptors in the control of motor activity in the rat ileum is of special interest, because in general not much is known about the role of α-receptors in intestinal contractility. A case report of a patient with pheochromocytoma in whom paralytic ileus was treated successfully with the α-receptor antagonist phentolamine and later with prazosin (selective α_1-receptor agonist)[9] suggests that α-mechanisms may be involved in human small bowel contractile activity, whereas in an in vitro study in human tissue, α_2 pathways did not seem to play a role.[10] Therefore, it seems likely that in control of human small bowel contractility, α-adrenergic influence is dependent on α_1-receptors. This would be in accordance with our

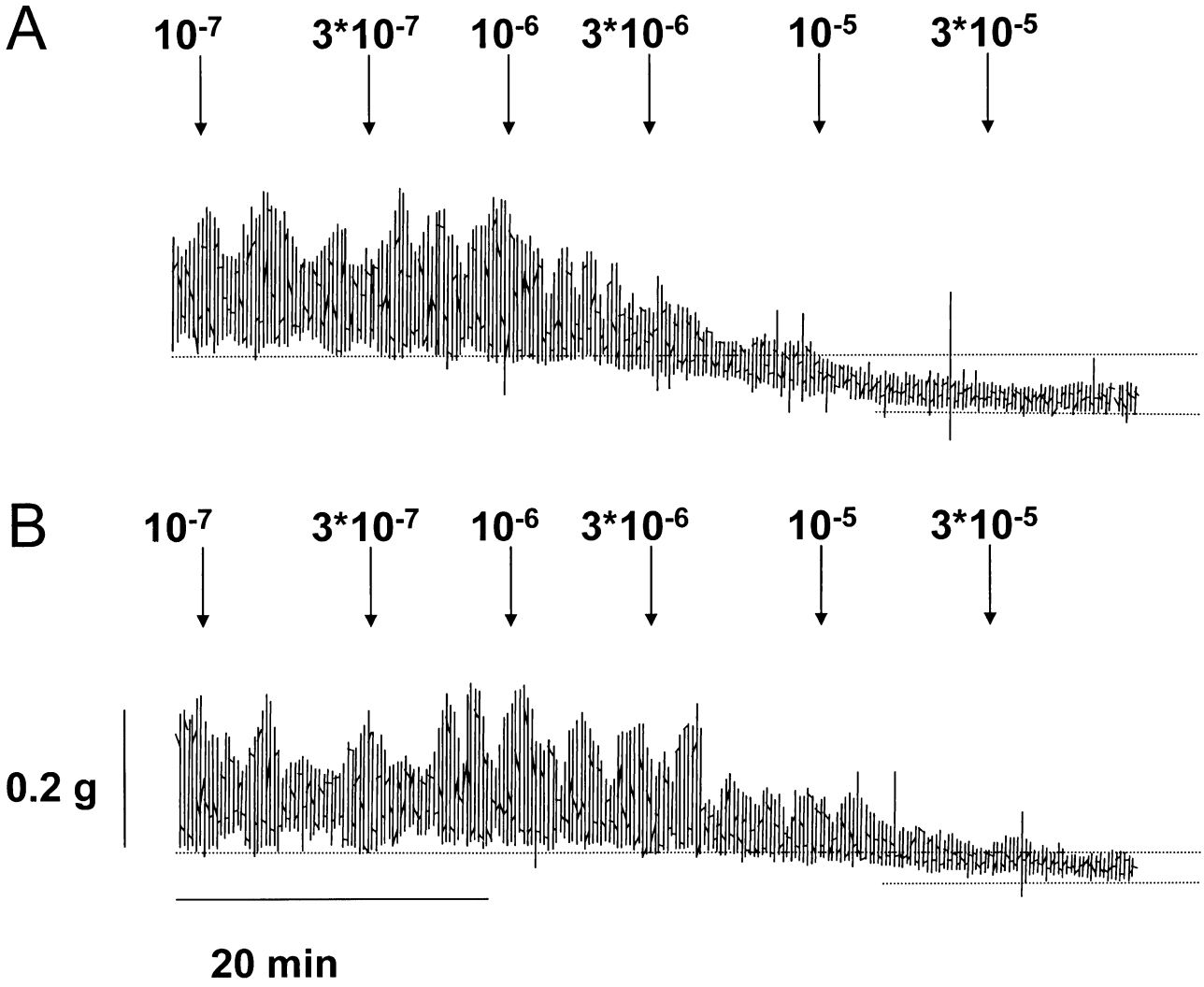


Fig. 4. (**A**) Effect of ritodrine (β_2) on spontaneous activity. Ritodrine was administered cumulatively and caused a dose-dependent decrease in contractile activity. (**B**) In presence of tetrodotoxin, the dose-dependent reduction in basal tone was smaller, thus reducing the overall inhibitory effect induced by ritodrine.

results in rat ileum where α_1 mechanisms but not α_2 pathways appear to influence contractile properties in vitro. However, in the gut of other species, the role of α-receptors is different: in guinea pig ileum, both α_1- and α_2-receptors mediate inhibition,[11] and in canine and mouse ileum and in rat colon, only α_2, not α_1, inhibitory mechanisms have been described.[12–14] In rabbit, α_1 mechanisms can be part of inhibitory pathways in other anatomic regions of the gut such as jejunum[15] and duodenum.[16] Because of marked species differences, broad generalizations between species must be made with caution.

Inhibitory mechanisms mediated by β_2-adrenergic receptors were identified in our study. This finding is consistent with results in rabbit ileum,[17] whereas in canine ileum, β_2 pathways had no influence on contractile activity.[12]

β_3-Receptors have been of particular interest because they seem to be abundantly present in gastrointestinal tissue.[18,19] Our results are in accordance with the data of Brown and Summers,[20] who showed that β_3 pathways play a major role in the inhibition of rat ileum. In guinea pig ileum, contractile activity is also inhibited by β_3-receptor stimulation,[21] whereas canine ileum does not seem to be influenced by β_3-receptors.[12]

As discussed earlier, β_2- and β_3-receptor–specific inhibition plays a role in inhibiting contractile activity, whereas β_1-receptor mechanisms do not appear to be involved in the inhibition of longitudinal muscle of the rat ileum. Our latter finding contrasts with data from Brown and Summers,[20] who reported a slight effect of β_1-receptor mechanisms in rat ileum. Differences in the muscle layers investigated and in

the experimental protocols, such as different substances that were used and conduction of the experiment in precontracted muscle strips, may explain some of these differences. We have shown previously that different contractile responses in circular versus longitudinal muscle layers are as important as are differences between anatomic regions of jejunum versus ileum.[22,23] In an in vivo study in canine ileum that supports our results, β_1-receptors were found to not be important.[12]

In our experiments, we tried to distinguish between muscle-related mechanisms and pathways involving the enteric nervous system, because under pathologic conditions, adrenergic mechanisms might be compromised at either level of control.[5,24,25] None of the specific adrenergic α_2-, β_1-, or β_3-receptor mechanisms were TTX sensitive, and therefore the pathways seem to be independent of the enteric nervous system. Interestingly, part of the β_2 and α_1 inhibition in our experiments appears to be modulated by presynaptic mechanisms. Blockade of neural β_2 mechanisms by TTX resulted in a lesser inhibition of contractile activity. This neurally mediated effect appears to occur via a reduction in baseline tone rather than a reduction in phasic activity. In contrast, the α_1-adrenergic effect appears to be related to a slight increase in baseline tone. The physiologic relevance of these findings as seen in our in vitro measurement of isometric contractions is not yet known. In other study designs, the distinction between muscle or neurally mediated inhibition was not made.[17] However, it is conceivable that part of the gastrointestinal motility disorders in neurologic diseases such as diabetic neuropathy or other postneurotomy syndromes (e.g., postvagotomy gastroparesis) are linked with an impaired modulation of contractile activity via β_2 and α_1 mechanisms. Thus, further studies are required.

CONCLUSION

Because none of the specific pathways alone reached the degree of inhibition achieved by NE, we conclude that adrenergic inhibition in rat ileum may be an additive effect of the three specific adrenergic mechanisms noted to inhibit contractile activity (α_1, β_2, and β_3). This concept of the involvement of several receptors in inhibitory mechanisms is supported by previous results in rabbit ileum[17] and by studies in human colon by Manara et al.[26] Possibly, the known plasticity of the gut may allow one receptor to take over for another receptor under various conditions. Hutchinson et al.[27] showed that β_1-adrenoceptors may compensate for β_3-adrenoceptors in adrenoceptor-mediated relaxation of ileal muscle from β_3-adrenoceptor knock-out mice, and Susulic et al.[28] Suggest that "cross-talk" might exist between β_3-adrenoceptors and β_1-adrenoceptor gene expression.

Our results, when compared with the literature, underline the high degree of variability not only in regional dependent differences (anatomic and muscle layer) but also between species. It is of interest that α_1-receptor mechanisms (but not α_2 pathways) played a role in our rat ileum study. The scarce data from the literature suggest a similar constellation of contractile α mechanisms in human small bowel. If this similarity is confirmed in the future, the rat ileum might be attractive to further model α_1 pathways in pathologic states.

For β_2- and β_3-receptors, species differences are evident as well, but we do not have comparable data for human ileum. Species differences, especially for β_3 pathways, would be of interest, because these receptors are abundantly present not only in adipose tissue but also in gastrointestinal tissue and therefore are of interest for the study of gastrointestinal motility.[29,30] To our knowledge the role of β_3-receptors in human contractility has not been carefully investigated in vitro.

Because of the species differences of adrenoceptor distribution and function, choosing the right animal model is crucial. This has been noted for cardiovascular studies[17] and will be the same for contractile studies of the gastrointestinal tract.

The authors thank Dr. M. G. Sarr for his valuable input to the manuscript.

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