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## Abstract

Effects of noradrenaline (NA) on the isolated rectal circular muscle of the cats were studied in comparison with the effects on the internal anal sphincter (IAS). NA ( $10^{-8}$ - $10^{-7}$  g/ml) caused tonic contraction in four of 15 strips of the rectum taken from 15 animals, and in all 15 strips of the IAS. Phenylephrine also induced rectal and IAS contraction. Rectal contraction induced by NA was resistant to phentolamine, yohimbine, propranolol, hexamethonium and tetrodotoxin, but blocked by atropine. IAS contraction induced by NA was resistant to propranolol, atropine, hexamethonium and tetrodotoxin, but blocked by phentolamine and yohimbine. It is suggested that an atropine-sensitive excitatory adrenergic mechanism other than the excitatory alpha-adrenergic mechanism exists in the rectal circular muscle.

**KEYWORDS:** gastrointestinal motility, rectum, noradrenaline, adrenergic receptors, muscarinic receptor.

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## ATROPINE-SENSITIVE, TETRODOTOXIN-RESISTANT CONTRACTION INDUCED BY NORADRENALINE IN ISOLATED CAT RECTUM

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*Abstract.* Effects of noradrenaline (NA) on the isolated rectal circular muscle of the cats were studied in comparison with the effects on the internal anal sphincter (IAS). NA ( $10^{-8}$ - $10^{-7}$ g/ml) caused tonic contraction in four of 15 strips of the rectum taken from 15 animals, and in all 15 strips of the IAS. Phenylephrine also induced rectal and IAS contraction. Rectal contraction induced by NA was resistant to phentolamine, yohimbine, propranolol, hexamethonium and tetrodotoxin, but blocked by atropine. IAS contraction induced by NA was resistant to propranolol, atropine, hexamethonium and tetrodotoxin, but blocked by phentolamine and yohimbine. It is suggested that an atropine-sensitive excitatory adrenergic mechanism other than the excitatory  $\alpha$ -adrenergic mechanism exists in the rectal circular muscle.

*Key words:* gastrointestinal motility, rectum, noradrenaline, adrenergic receptors, muscarinic receptor.

Noradrenaline usually inhibits gastrointestinal motility, while the drug induces a contractile response mediated by  $\alpha$ -adrenergic receptors in the sphincter and other parts of the gastrointestinal tract (1-10).

In this investigation, it was found that noradrenaline caused contraction of the isolated rectal circular muscle of cats. The action of noradrenaline on this muscle was studied pharmacologically in comparison with that in the internal anal sphincter.

### METHODS

Cats of both sexes, weighing 1.4 to 3.1 kg, were anesthetized with pentobarbital sodium (30 mg/kg given intraperitoneally). The rectum with the internal anal sphincter (IAS) was removed, opened along the mesenteric border, and emptied. It was pinned with the mucosal side up on a cork board in a bath of Tyrode solution equilibrated with 95 % O<sub>2</sub>-5 % CO<sub>2</sub> at 37 °C. The Tyrode solution had the following composition (mM): NaCl, 145; KCl, 2.7; CaCl<sub>2</sub>, 1.5; MgCl<sub>2</sub>, 0.7; NaHCO<sub>3</sub>, 4.8; NaH<sub>2</sub>PO<sub>4</sub>, 0.3 and glucose, 11.1. The mucosal and submucosal layers were removed. Strips, each 3 cm long and 5 mm wide, were taken from the IAS and the rectum 3 to 5 cm oral to the anal margin. Strips were cut 90 ° to the oral-anal axis. They were fixed in 15 ml Tyrode solution equilibrated with 95 % O<sub>2</sub>-5 % CO<sub>2</sub> at 37 °C. The longitudinal contraction of the strips was recorded with an isotonic transducer using a penoscillo-

graph. Thus, mainly contraction of the circular muscle layer was recorded. After a 2 h control period, the drug effects were examined. The following drugs were used: acetylcholine chloride, 1-noradrenaline bitartrate, phenylephrine hydrochloride, dl-isoprenaline bitartrate, phentolamine methanesulphonate, yohimbine hydrochloride, propranolol hydrochloride, atropine sulphate, hexamethonium bromide and tetrodotoxin. All concentrations shown refer to the concentrations of salts.

### RESULTS

Acetylcholine ( $10^{-8}$ - $10^{-6}$ g/ml) produced contraction of the rectum, but was not effective in the IAS. Noradrenaline (NA) caused contraction of the isolated rectum in 4 of 15 strips taken from 15 animals, and relaxation in the other 11 strips, while NA caused only contraction of the internal anal sphincter in all 15 strips. The threshold dose was  $10^{-8}$ g/ml in the rectum, and the contractile response increased with increasing NA concentration (Fig. 1). The IAS contracted when the

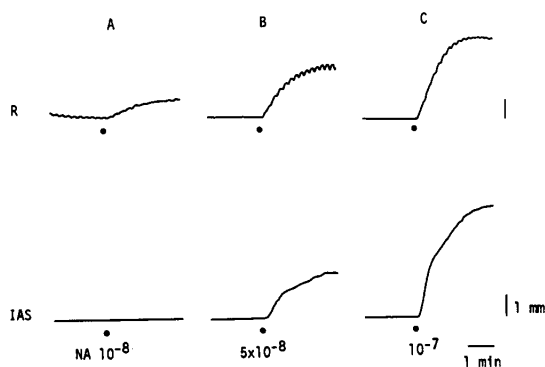


Fig. 1. Effect of noradrenaline (NA) on the rectal circular muscle (R) and the internal anal sphincter (IAS) in the cat. Noradrenaline was administered at  $10^{-8}$  in A,  $5 \times 10^{-8}$  in B and  $10^{-7}$ g/ml in C, respectively.

NA concentration was above  $5 \times 10^{-8}$ g/ml. Phenylephrine, an  $\alpha$ -adrenoceptor agonist, induced a contractile response in the rectum and IAS in doses above  $5 \times 10^{-8}$ g/ml. The effect of the drug in the rectum was weaker than in the IAS. Thus, the contractile response in the IAS was attributed to stimulation of excitatory  $\alpha$ -adrenergic receptors by NA.

The  $\alpha$ -adrenoceptor antagonists, phentolamine ( $10^{-7}$ g/ml) and yohimbine ( $10^{-7}$  –  $4 \times 10^{-6}$ g/ml) did not affect NA-induced contractions of the rectum, although the IAS contraction induced by NA was abolished by these antagonists (Figs. 2, 3). The NA-induced contractile response in the rectum and IAS was augmented in preparations pretreated with the  $\beta$ -adrenoceptor antagonist propranolol ( $10^{-7}$  –  $10^{-6}$ g/ml) (Fig. 3). This augmentation may have resulted from blockade of the NA action on the  $\beta$ -adrenoceptors, stimulation of which causes relaxation of the rectum and IAS. Rectal relaxation induced by NA in 11 strips was abolished by a combination of the  $\alpha$ - and  $\beta$ -adrenoceptor antagonists phentolamine and propranolol.

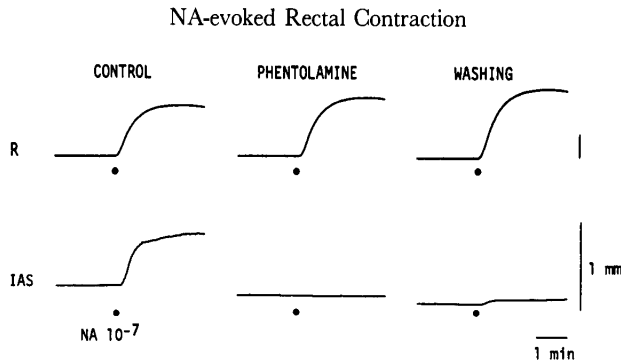


Fig. 2. Effect of phentolamine ( $10^{-7}$ g/ml) on contractions of the rectum (R) and the internal anal sphincter (IAS) induced by noradrenaline (NA,  $10^{-7}$ g/ml).

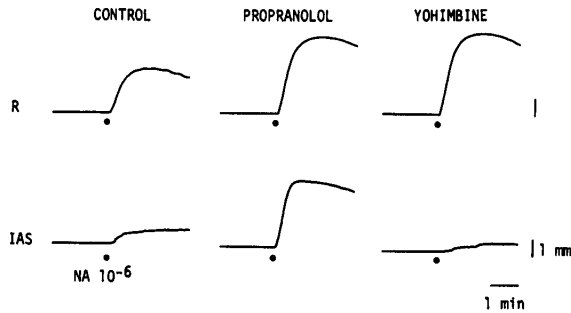


Fig. 3. Effect of propranolol ( $5 \times 10^{-7}$ g/ml) and yohimbine ( $4 \times 10^{-6}$ g/ml) on contractions of the rectum (R) and the internal anal sphincter (IAS) induced by noradrenaline (NA,  $10^{-6}$ g/ml).

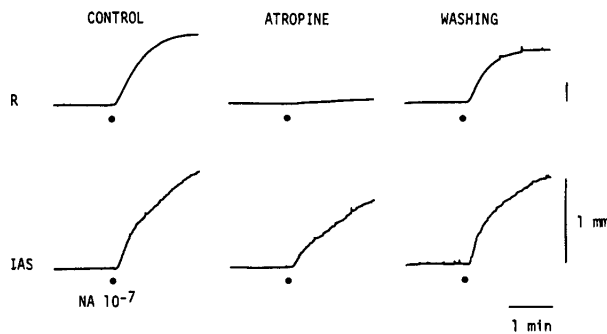


Fig. 4. Effect of atropine ( $5 \times 10^{-8}$ g/ml) on contractions of the rectum (R) and the internal anal sphincter (IAS) induced by noradrenaline (NA,  $10^{-7}$ g/ml).

To reveal whether a cholinergic mechanism is involved in NA-induced rectal contraction, the effects of a cholinergic receptor antagonist and neuron blockers were studied. As shown in Fig. 4, the rectal contraction induced by NA ( $10^{-7}$  –  $10^{-6}$ g/ml) was blocked by pretreatment with atropine ( $5 \times 10^{-8}$ g/ml) and also

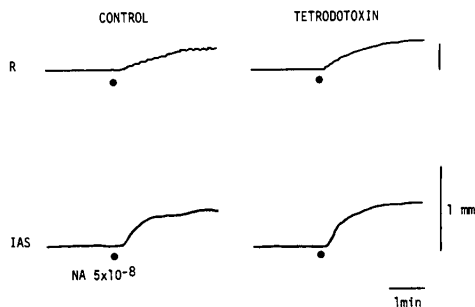


Fig. 5. Effect of tetrodotoxin ( $10^{-7}$ g/ml) on contractions of the rectum (R) and the internal anal sphincter (IAS) induced by noradrenaline (NA,  $5 \times 10^{-8}$ g/ml).

was reduced to the level before NA application by treatment with atropine ( $5 \times 10^{-7}$ g/ml). After washing the strips, the contractile response to NA recovered completely. On the other hand, the NA-induced IAS contraction was not affected by atropine. The ganglion blocker hexamethonium ( $10^{-5}$ g/ml) and the neuron blocker tetrodotoxin ( $10^{-7}$ g/ml) had no effect on the contractile response in the rectum and IAS induced by NA (Fig. 5).

#### DISCUSSION

Although mainly inhibitory  $\alpha$ -adrenergic receptors have been identified in gastrointestinal smooth muscles (1), excitatory  $\alpha$ -adrenergic receptors have been found in the terminal ileum (2, 3) and jejunum and ileum (4) in guinea pigs, esophagus of guinea pigs and cats (5-7), opossum duodenum (8), human sigmoid colon (9), and IAS of vervet monkeys (10). Adrenaline, NA and adrenergic agonists cause contractions by acting on the excitatory  $\alpha$ -adrenergic receptors in the smooth muscles. In the present experiments, NA produced contractions of the rectal circular muscles in strips taken from 4 out of 15 cats and contractions of the IAS muscles in all strips. As the IAS contraction was abolished by the  $\alpha$ -antagonists phentolamine and yohimbine, this response was caused by the  $\alpha$ -adrenoceptor-stimulating action of NA as reported in the monkey by Reyner (10). On the other hand, the rectal contraction induced by NA could not be attributed to NA action on excitatory  $\alpha$ -adrenergic receptors, since adrenergic  $\alpha$ -antagonists phentolamine and yohimbine did not affect the NA-induced rectal contraction. Rectal contraction induced by NA was abolished by the muscarinic antagonist atropine, but the IAS contraction was not. However, it is not thought that rectal contraction is mediated by release of acetylcholine from the myenteric nerve endings as proposed by Mizutani, *et al.* (4), since ganglion blockage by hexamethonium and neuron blockage by tetrodotoxin did not diminish the contractions. All rectal and IAS strips were prepared at the same time, by the same procedure and from the same animals. IAS strips responded to NA and other drugs used in the present experiments in the same manner as previously reported by Reyner (10). Therefore, the conditions of the rectal smooth muscle should be physiologically the same as in the IAS.

An adrenergic mechanism, which is not related to excitatory  $\alpha$ -adrenergic receptors and is linked with atropine-sensitive cholinergic receptors, may exist in the rectal smooth muscle and result in muscle muscarinic receptor excitation and contraction.

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