Kor J Physiol (1991) 25(2), 147-158

Excitatory Influences of Noradrenaline on the Spontaneous Contractions and Electrical Activity of Antral Circular Muscle of the Guinea-pig Stomach

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= ABSTRACT =

The effects of noradrenaline on the spontaneous contraction recorded from a strip of mucosa-free antral circular muscle were studied in the guinea-pig stomach, and the changes in slow waves and membrane resistance were analyzed in order to elucidate the mechanism for the excitatory response to noradrenaline. Electrical responses of circular muscle cells were recorded using glass microelectrodes filled with 3 M KCl. Electrotonic potentials were produced to estimate membrane resistance by the partition stimulating method. All experiments were performed in tris-buffered Tyrode solution which was aerated with 100 % O_2 and kept at 35°C. The results obtained were as follows:

1) The spontaneous contractions were potentiated dose-dependently by the application of noradrenaline.

2) Through the experiments using adrenoceptor-blockers, the strong excitatory effect via α-adrenoceptors and the weak inhibitory efffect via β-adrenoceptors were noted.

3) Noradrenaline produced hyperpolarization of membrane potential, and increases in the amplitude and the maximum rate of rise of slow waves.

4) In the presence of apamin, Ca-dependent K channel blocker, the characteristic hyperpolarization was not developed. However, the excitatory effect of noradrenaline on spontaneous contraction remained.

5) Membrane resistance was reduced during the hyperpolarized state by the application of noradrenaline, and the change of membrane resistance and the hyperpolarized state were completely abolished by apamin.

From the above results, following conclusions could be made:

Excitatory responses to noradrenaline result from the dominant α-excitatory, and the weak β-inhibitory action of noradrenaline.

Hyperpolarization of membrane potential by noradrenaline is due to the activation of Ca-dependent K channel.

Key Words: Antral circular muscle, Noradrenaline, Slow wave, Membrane resistance, Apamin

Received Oct. 13, 1991; Accepted Nov. 28, 1991.

This study was supported by in part by the Research Grant from Dankook University, 1991.

INTRODUCTION

Myogenic oscillatory potentials (slow waves) and spike potentials with or without overshoot are recorded in the smooth muscle cells of guinea-pig stomach, especially in the antrum (Tomita, 1981). The antrum generates slow waves and spontaneous contractions (El-Sharkawy et al, 1978; Komori & Suzuki, 1986). There is evidence that slow waves originate in the circular and longitudinal muscle layers independently (Kuriyama et al, 1970; Ohba et al, 1975, 1977). In general, large contractions occur when Ca spike potentials occur (action potential contractions). However, small contractions can occur in association with slow waves on which no action potentials are superimposed (slow wave contractions) in the mammalian gastrointestinal tract (Szurszewski, 1975; Sanders, 1983; Rhee & Kim, 1987).

The electrical responses of gastric smooth muscle cells to intramural nerve stimulation are complex, and cholinergic excitatory junction potentials (ejp), adrenergic inhibitory junction potentials (ijp), non-adrenergic, non-cholinergic ejps and non-adrenergic, non-cholinergic ijps have all been described (Kuriyama et al, 1970; Tomita, 1981). In the guinea-pig stomach, a cholinergic ejp can be recorded in the fundus and a non-adrenergic, non-cholinergic ijp is shown both in the antrum and in the atropinized fundus (Komori & Suzuki, 1986).

Endogenous catecholamines are essential as humoral regulators of smooth muscle function. They have inhibitory and excitatory effects on mechanical activity, not only by a direct action on smooth muscle cells but also by an indirect action on the nervous elements innervating them. Studies of exogenously applied catecholamines are similarly complicated. The direct action on the smooth muscle cells, which possess both α- and β-receptors, can produce similar or dissimilar mechanical responses. Excitation is mediated by α-receptors, while inhibition can be mediated by α- as well as β-receptors. Which of these two reactions dominates, varies from tissue to tissue. Indirect actions include the depression by catecholamines on the activity of intrinsic nerves, causing inhibition, for example by reducing acetylcholine release. It has been reported that an inhibitory action of catecholamines on stomach smooth muscle is mediated by both α- and β-receptors: the rabbit, the rat, and the guinea-pig (Bailey, 1971; Ito & Kuriyama, 1975). On the other hand, there are other evidences that stimulation of the α-receptor produces excitatory responses in the rabbit intestine, in the rat colon, in the rat stomach, in the rabbit stomach, and in the guinea-pig stomach (Bailey, 1971; Yamaguchi & Tomita, 1974).

The present experiments were undertaken to clarify the mechanisms underlying the excitatory action of noradrenaline on the spontaneous contractions of antral circular strips from guinea-pig stomach.

METHODS

Albino guinea-pigs of either sex, weighing 200~250 g, were stunned and bled. The stomach was isolated and cut in the longitudinal direction along the lesser curvature. The contents of the stomach were removed and the mucosal layers were separated from the muscle layers in the phosphate-buffered Tyrode solution at room temperature. Strips of circular muscle (2 mm wide, 20 mm long) were isolated together with the longitudinal layer, and mounted in an experimental chamber with tiny pins. The chamber (about 2 ml of volume) was made with Lucite plate, and the tissues were superfused with warmed (35°C) tris-buffered Tyrode solution, at a flow rate of 2~3 ml/min.

The ionic compositions of phosphate-buffered and tris-buffered Tyrode solutions

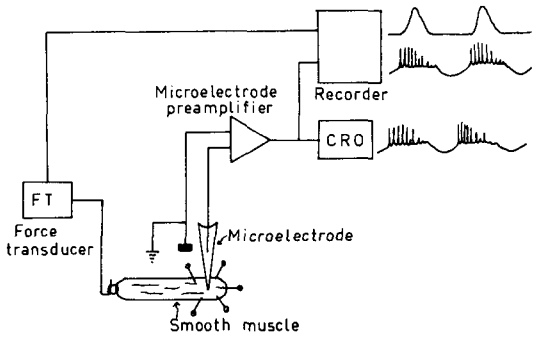

Fig. 1. A schematic representation of the isometric contraction and the electrical activity recording systems. The isometric contraction was recorded through a tension transducer from the smooth muscle preparation. And the microelectrode puncture technique for intracellular recording of the electrical activities was employed in this experiment.
CRO: Cathode Ray Oscilloscope
ME: Microelectrode

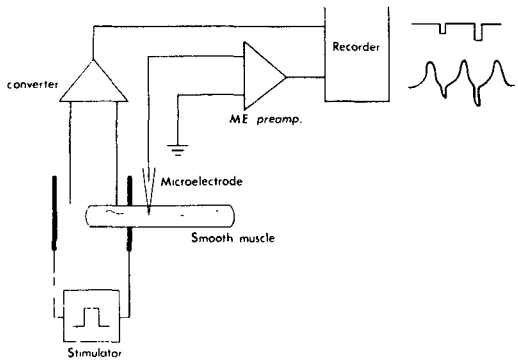

Fig. 2. A diagram of the partition stimulating method. The muscle chamber is divided by one of the stimulating electrodes into two compartments, stimulating(left) and recording (right). The electrotonic potentials were produced by the current stimulations.
IV converter: current-voltage converter

were as follows respectively (mM): Phosphate-buffered Tyrode, NaCl 147, KCl 4, $CaCl_2 \cdot 2H_2O$ 2, $MgCl_2 \cdot 6H_2O$ 1.05, $NaH_2PO_4 \cdot 2H_2O$ 0.42, $Na_2HPO_4 \cdot 12H_2O$ 1.81, glucose 5.5; tris-buffered Tyrode, NaCl 147,KCl 4, $CaCl_2 \cdot 2H_2O$ 2, $MgCl_2 \cdot 6H_2O$ 1.05, tris • HCl 5, glucose 5.5). The solutions were gassed with 100% O_2 and the pH of the solution was maintained at 7.35.

Spontaneous contractions were measured isometrically by use of tension transducer (Grass FT-03) at the optimal length obtained from length-tension curve. Electrical responses of smooth muscle cells were recorded by means of glass microelectrodes of tip resistance 40~80 MΩ and filled with 3 M KCl (Fig. 1). Smooth muscle tissues were stimulated by the partition stimulating method (Abe & Tomita, 1968) through a Grass S 88 stimulator, to produce electrotonic potentials (Fig. 2). Mechanical and electrical responses of smooth muscle cells were displayed simultaneously on a pen-writing recorder (Device physiograph).

Drugs used were apamin (Sigma), atropine sulfate (Sigma), guanethidine sulfate (Tokyo Kasei), (−)-isoproterenol (+)-bitartrate salt (Sigma), L-norepinephrine bitartrate (Sigma), L-phenylephrine-HCl (Sigma), phentolamine (Regitine, Ciba), DL-propranolol-HCl (Sigma), and tetrodotoxin (TTX, Sankyo).

RESULTS

Effects of noradrenaline on spontaneous contractions

Mechanical responses of antral circular smooth muscle were recorded during the application of noradrenaline. As shown in Figure 3, noradrenaline, which was administered cumulatively, potentiated the amplitude of the antral spontaneous contractions from the concentration of 10^{-7} M in a dose-dependent manner. The amplitude of tonic contraction increased dose-dependently by noradrenaline, while that of phasic contraction showed the initial increase followed by

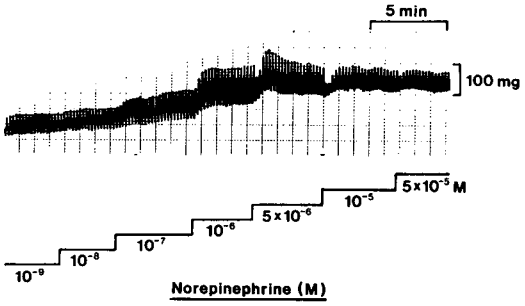

Fig. 3. Effect of norepinephrine on the spontaneous contractions recorded from the antral strip of without mucosa.

Norepinephrine, which was administered cumulatively, potentiated the amplitude of the antral spontaneous contractions in a dose-dependent manner.

The excitatory effect appeard about at the concentration of 10^{-7} M and increased in parallel with the increase in norepinephrine concentration. Note that the amplitude of tonic contraction increased dose-dependently by norepinephrine, while that of phasic contraction showed the initial increase followed by the subsequent gradual decrease, especially at a higher concentration.

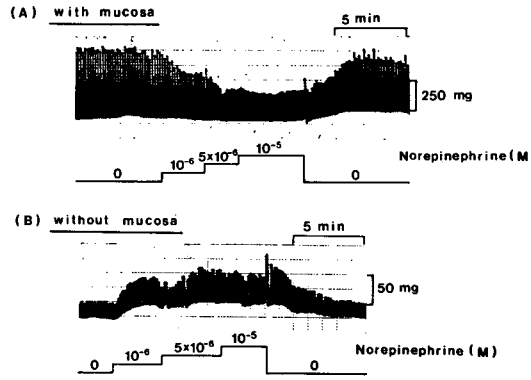

Fig. 4. Comparison of the norepinephrine effect on the antral strip of circular muscle having intact mucosa (A) with that on the mucosa-free strip (B) in the guinea-pig.

Note that in the strip of circular muscle with intact mucosa the amplitude of spontaneous contractions was suppressed dose-dependently by the administration of norepinephrine, whereas in the mucosa-free strip the effect of norepinephrine on the spontaneous contractions was excitatory in a dose-dependent manner.

the subsequent gradual decrease, biphasic pattern especially at a higher concentration. Figure 4 shows that the gastric mucosa influences upon the noradrenaline-induced gastric motility. The spontaneous contractions recorded from antral circular muscle strip with intact mucosa were suppressed dose-dependently by the application of noradrenaline (Fig. 4A), whereas those from the mucosa-free strip were potentiated in a dose-dependent manner (Fig. 4B). The excitatory action of noradrenaline on the spontaneous contractions was not affected even in the presence of TTX (3×10^{-7} M), guanethidine (5×10^{-6} M), and atropine (10^{-6} M), indicating that the excitatory effect of noradrenaline is developed mainly via direct action on smooth muscle cells (Fig. 5A).

Figure 5B & C show that the effect via α-adrenoceptors is excitatory, while that via β-adrenoceptors is slightly inhibitory: Typical noradrenaline-induced excitatory response was markedly suppressed by the application of phentolamine, α-blocker whereas that was rather slightly potentiated by propranolol, β-blocker. Myogenic spontaneous contractions of antral circular muscle were remarkably potentiated by the administration of α-agonist, phenylephrine (5×10^{-5} M) and its effect was completely antagonized by α-blocker, phentolamine (5×10^{-6} M) (Fig. 6B). In contrast, the spontaneous contractions were suppressed by β-agonist, isoprenaline (5×10^{-6} M) and the suppressed contractions were recovered to normal level by β-blocker, propranolol (5×10^{-6} M) (Fig. 6C).

In Ca^{2+}-free Tyrode solultion containing 0.1 mM EGTA, the excitatory response to noradrenaline was not developed (Fig. 7B). This result indicates that extracellular Ca^{2+}

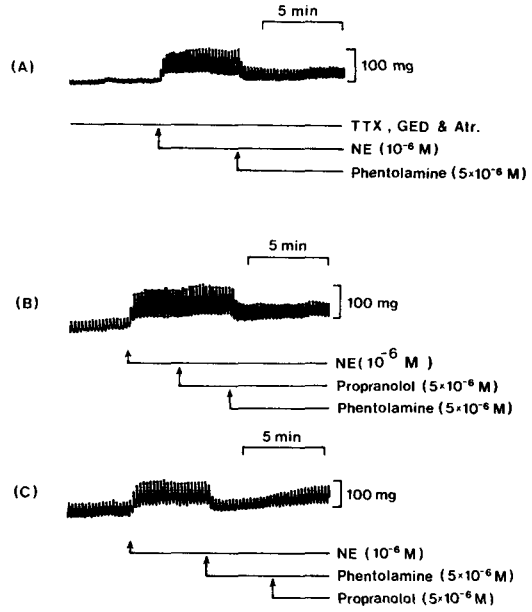

Fig. 5. The strong excitatory effect of norepinephrine (NE) via α-adrenoceptors and the week inhibitory effect via β-adrenoceptors on the spontaneous contractions recorded from the antral strip of circular muscle without mucosa.

The excitatory effect of NE on the spontaneous contractions was produced even in the presence of TTX (3×10^{-7} M), guanethidine (5×10^{-6} M), and atropine (10^{-6} M) (A).

Note that the effect via α-adrenoceptors was excitatory while that via β-adrenoceptors was slightly inhibitory (B & C).

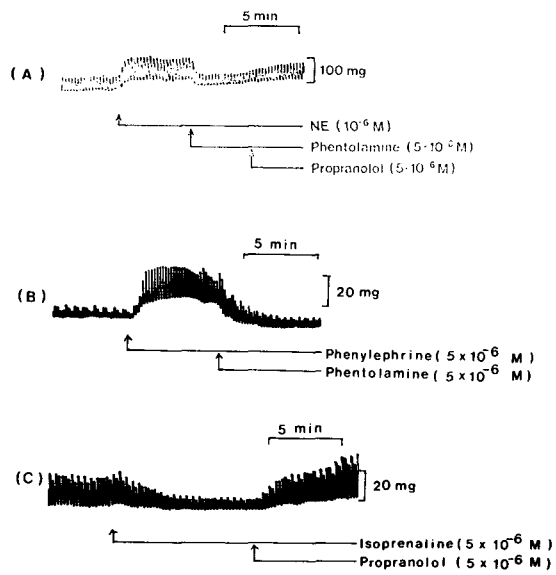

Fig. 6. The excitatory effect via α-adrenoceptors and the inhibitory effect via β-adrenoceptors on the spontaneous contractions recorded from the antral strip of circular muscle without mucosa in the guinea-pig.

Spontaneous contractions were markedly potentiated by the administration of α-agonist, phenylephrine (5×10^{-5} M) and its effect was completely antagonized by α-blocker, phentolamine (5×10^{-6} M) (B). In contrast to the excitatory action of phenylephrine, the spontaneous contractions suppressed by β-agonist, isoprenaline (5×10^{-6} M) and the suppressed contractions were recovered to normal level by β-blocker, propranolol (5×10^{-6} M) (C).

plays an important role as a major Ca^{2+} source in potentiating the spontaneous contractions.

Effects of noradrenaline on myogenic slow waves

Figure 8 shows the characteristic actions of noradrenaline to spontaneous contractions and slow waves recorded simultaneously from a strip of antrtal circular muscle of guinea-pig stomach. After the administration of noradrenaline remarkable changes in slow waves were observed: Hyperpolarization of the membrane potential, the increases in the amplitude and the maximum rate of rise of slow waves (steep and tall slow waves) were developed. It is very interesting to observe the sequential changes between spontaneous contractions and slow waves: Prior to the start of hyperpolarization, the precedent increase in tonic contraction is developed. Representative no-

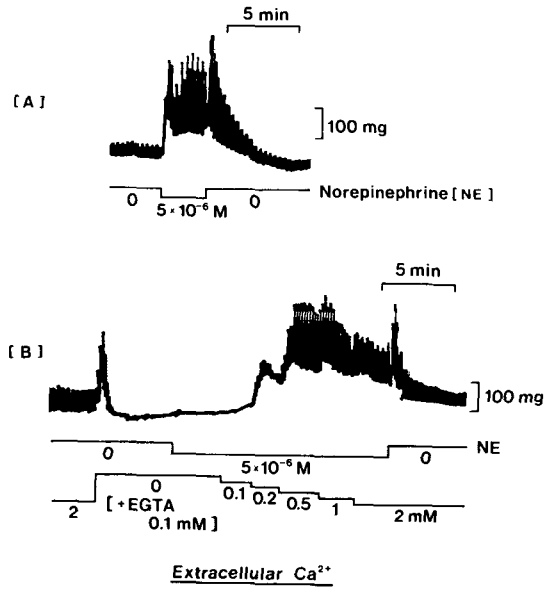

Fig. 7. Effect of extracellular Ca^{2+} on the excitatory action of norepinephrine (NE) to the spontaneous contractions of a strip of the antral circular muscle in the guinea-pig.
Note that in Ca^{2+}-free Tyrode's solution containing 0.1 mM EGTA the excitatory response to norepinephrine was not developed (B).

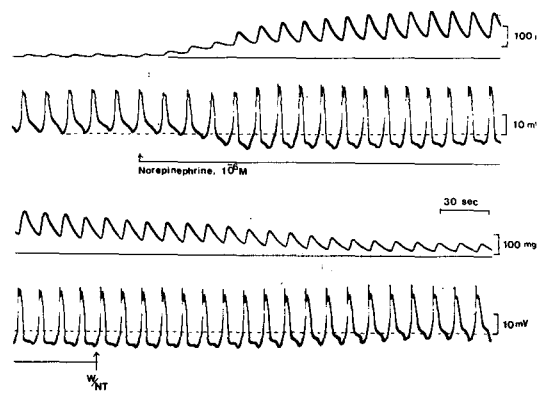

Fig. 8. The characteristic actions of norepinephrine (NE) to spontaneous contractions and slow waves recorded simultaneously from a strip of antral circular muscle in the guinea-pig.
The observed changes in slow waves after the administration of NE were hyperpolarization of the membrane potential, and the increases in the amplitude and the maximum rate of rise of slow waves.
Note that sequential changes in spontaneous contractions and slow waves: In prior to the start of hyperpolarization, the precedent increase in tonic contraction was developed.

radrenaline-induced changes in slow waves are shown in Figure 9A & B. Noradrenaline (10^{-5} M) potentiated the amplitude of slow wave from 15 mV at control state to 30 mV and the maximum rate of rise from 7 mV/sec to 34 mV/sec, respectively. The resting membrane potential, which was -60 mV at control state, was hyperpolarized to -73 mV after the application of noradrenaline. These noradrenaline-induced changes in slow waves were completely antagonized by the administration of phentolamine (10^{-5} M): The amplitude was reduced to normal level from 28 mV to 15 mV, and the maximum rate rise from 35 mV/sec to 7 mV/sec, respectively. Resting membrane potential was also returned to normal control level from -67 mV to -60 mV.

The effect of α-agonist, phenylephrine on the slow waves was compared with that of β-agonist, isoprenaline in a strip of antral circular muscle of guinea-pig stomach (Fig. 10A & B). Phenylephrine (5×10^{-6} M) produced the changes in slow waves similar to those induced by noradrenaline: Hyperpolarization of membrane potential, and tall and steep slow waves. However, no remarkable changes in slow waves were observed in spite of the reduction of contrction amplitude after the application of isoprenaline (5×10^{-6} M).

Apamin is a component of bee venom, which is known to block the Ca-dependent K channel selectively (Banks et al, 1979).

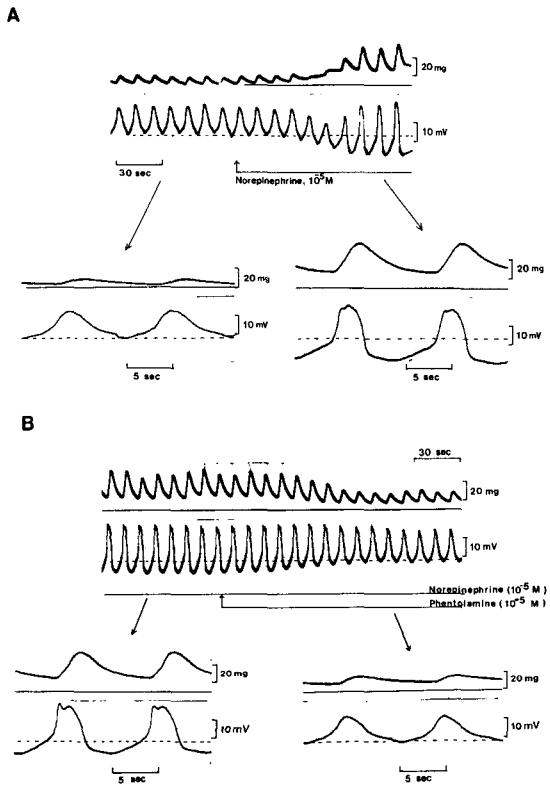

Fig. 9. Antagonistic influences of norepinephrine (NE) and phentolamine upon the slow waves recorded from a strip of the antral circular muscle in the guinea-pig.

NE (10^{-5} M) potentiated the amplitude and the maximum rate of rise of the slow waves: The amplitude of slow waves increased from 15 mV at control state to 30 mV and the maximum rate of rise from 7 mV/sec to 34 mV/sec, respectively. The resting menbrane potential, which was -60 mV at control state, was hyperpolarized to -73 mV after application of NE (A).

These characteristic NE-induced changes in slow waves were completely antagonized by the admini-stration of phentolamine(10^{-5} M): The amplitude was reduced to normal level from 28 mV to 15 mV, and the maximum rate of rise from 35 mV/sec to 7 mV/sec, respectively. Resting menbrane potential was also returned to normal control level from -67 mV to -60 mV (B).

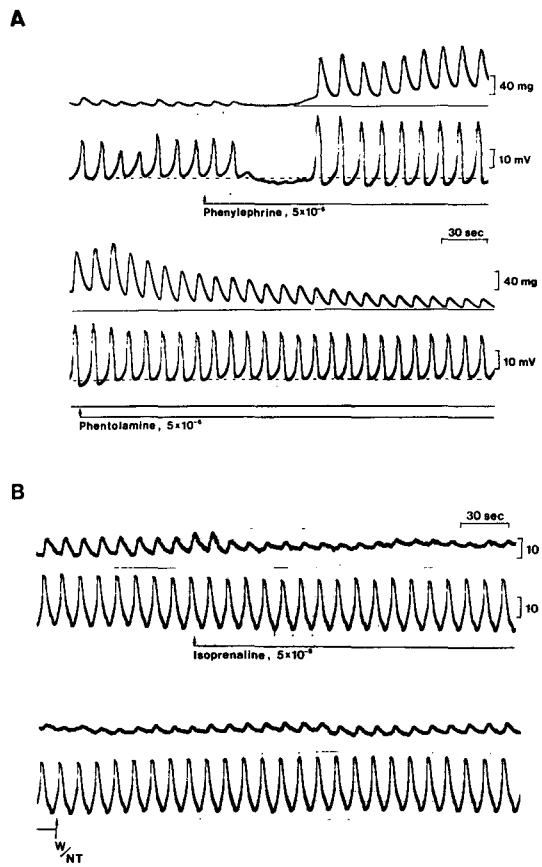

Fig. 10. Comparison of the effect of phenylephrine (PE) with that of isoprenaline(IP) on the slow waves recorded from a strip of antral circular muscle in the guinea-pig.

Phenyleprine (5×10^{-6} M) produced the changes in slow waves similar to those induced by NE: Hyperpolarization of the membrane potential, and tall and steep slow waves (A).

However, no remarkable changes in slow waves were observed after the application of isoprenaline (5×10^{-6} M) (B).

Even at a low concentration (10^{-8} M) apamin blocked the ijps induced by the stimulation of purinergic nerves and also ATP-induced hyperpolarization (Vladimirova & Shuba, 1978; Shuba & Vladimirova, 1980). Figure 11 shows the effects of apamin on the characteristic noradrenaline-induced chan-

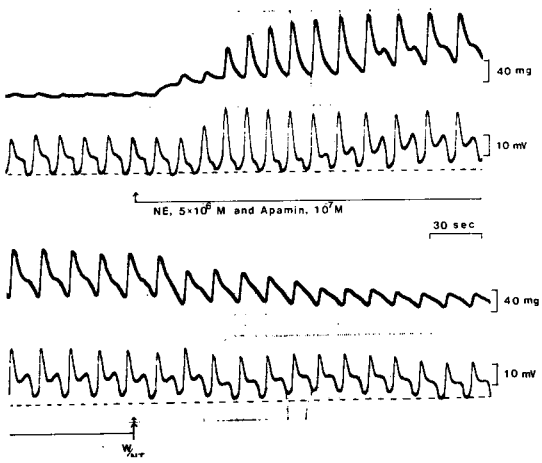

Fig. 11. Effects of apamin on the characteristic NE-induced changes in slow waves and spontaneous contractions recorded from a strip of antral circular muscle in the guinea-pig.

NE (5×10^{-6} M) containing apamin (10^{-7} M) revealed the excitatory contractile responses similar to those of NE only.

However, the characteristic hyperpolarization of membrane potential was blocked completely in the presence of apamin.

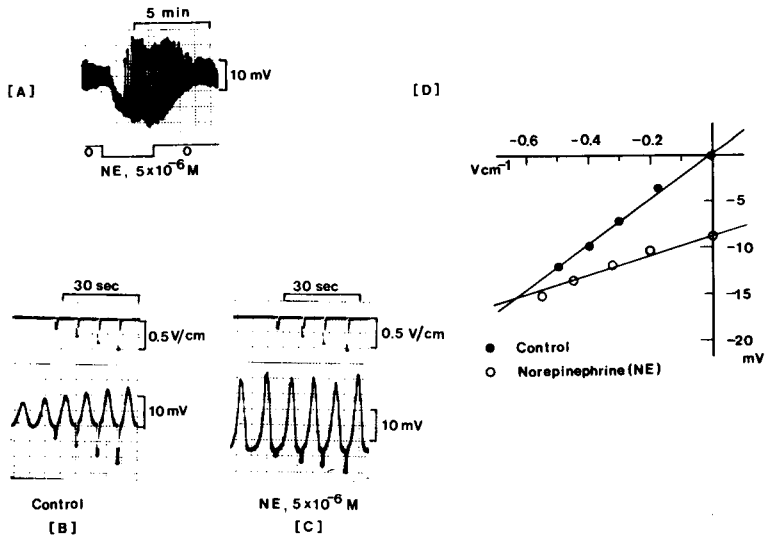

Fig. 12. Electrotonic potentials produced by 4 different intensities of inward current pulse (1 sec in duration) recorded from an antral circular muscle cell of the guinea-pig.

(A) Slow speed tracing of slow wave after application of NE (5×10^{-6} M).

(B) Control recordings of electrotonic potentials in the absence of NE.

(C) Recordings taken after application of NE.

(D) Current-voltage relationship. The amplitude of the electrotonic potential was plotted against the intensity of the current shown by V cm^{-1}.

Vertical axis: Membrane potential change measured from the resting membrane potential. Negative value indicated hyperpolarization.

All responses were recorded from the same cell with intracellular microelectrode which was located 0.1~0.2 mm apart from the stimulating electrode. Note that the current-voltage relationship revealed a marked decrease in the slope after the membrane was hyperpolarized by NE (5×10^{-6} M).

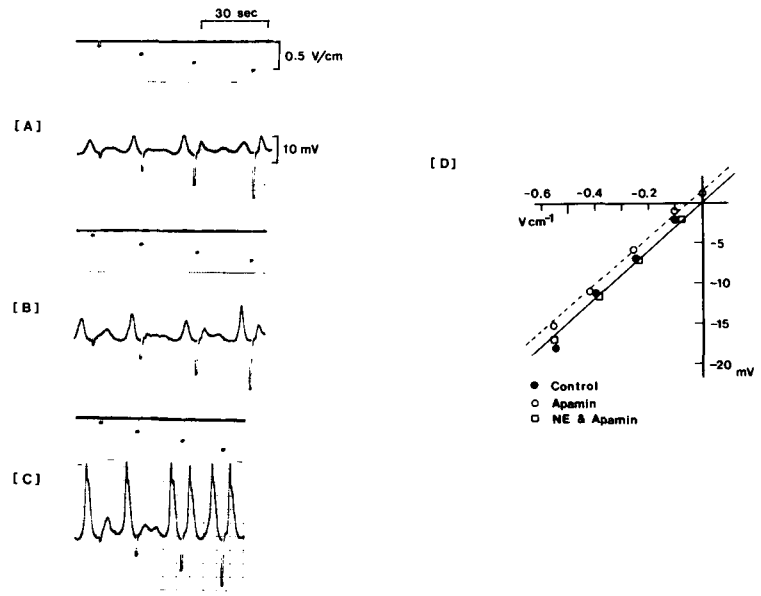

Fig. 13. Electrotonic potentials recorded before and after application of apamin and norepinephrine (NE) to an antral circular muscle cell of the guinea-pig.
(A) Control recordings before application of apamin and NE.
(B) Recordings taken after application of apamin (10^{-7} M) only for 10 min.
(C) Recordings taken after application of NE (5×10^{-6} M) and apamin(10^{-7} M) for 5 min.
(D) Current-voltage relationship.
Note that the current-voltage relationship showed a similar slope to that of the control.

ges in slow waves and spontaneous contractions recorded from a strip of antral circular muscle of guinea-pig stomach. Noradrenaline (5×10^{-6} M) containing apamin (10^{-7} M) revealed the excitatory contrctile responses similar to those of noradrenaline alone. However, the characteristic hyperpolarization of membrane potential was blocked completely in the presence of apamin, indicating that noradrenaline-induced hyperpolarization is associated with Ca-dependent K channel.

Effects of noradrenaline on membrane conductance

The effects of noradrenaline on the membrane conductance of smooth muscle cells were estimated from changes in the amplitude of electrotonic potentials produced by the partition stimulating method.

The electrical length constant of the smooth muscle tissues of the guinea-pig stomach is about 1.4 mm (Kuriyama et al, 1970), therefore the electrotonic potentials were recorded in close proximity to the stimulating electrodes (less than 0.2 mm), to allow noradrenaline-induced changes in membrane resistance to be estimated from changes in amplitude of the electrotonic potentials (Hodgkin & Rushton, 1946).

Figure 12 shows that the current-voltage relationship reveals a marked decrease in the slope after the membrane was hyperpolarized by noradrenaline (5×10^{-6} M), thus indicating that the noradrenaline-induced hyperpolarization is associated with a decrease in membrane resistance. The cur-

rent-voltage relationship obtained from the recordings taken after the application of noradrenaline and apamin, showed a similar slope to that of the control (Fig. 13D).

DISCUSSION

The present experiments have demonstrated that in the antral circular strips without mucosa, noradrenaline enhances the tonic contraction dose-dependently while the phasic contraction shows the initial increase followed by subsequent gradual decrease, biphasic pattern especially at a higher concentration (Fig. 3). These events occurred even in the presence of TTX, atropine and guanethidine, indicating that they are induced mainly through the direct action on smooth muscle cells. In Ca^{2+}-free Tyrode solution containing 0.1 mM EGTA, the excitatory response to noradrenaline was not developed and that was initiated in parallel with the extracellular addition of Ca^{2+}. This result suggests that extracellular Ca^{2+} plays an important role as a major Ca^{2+} source in developing the excitatory effect of noradrenaline on spontaneous contractions.

According to the report of Yamaguchi & Tomita (1974), the responses of noradrenaline to spontaneous contractions of guinea-pig stomach showed three types: Type I, simple contraction; Type II, an initial relaxation followed by a large contraction; Type III, simple relaxation. The proportions of each type among the three kinds of contractile responses are different between the muscle layers: In circular muscle layer, type I 71%, type II 8%, and type III 21%, while in the longitudinal muscle layer type I 0%, type II 4%, and type III 96%. Present study using the antral circular strips without mucosa showed only type I response to noradrenaline.

In the guinea-pig stomach there are probably two types of relaxation. Alpha relaxation was more dominant in the circular muscles and β relaxation in the longitudinal muscles. However, contractions in both muscles were mediated through α effects. The circular muscle is more sensitive to the β effect (Yamaguchi & Tomita, 1974). In the present experiment, α-excitatory, β-inhibitory responses of noradrenaline were confirmed (Fig. 5 & 6). However, it was impossible to observe definite α-inhibitory response of noradrenaline.

The influences of gastric mucosa upon the catecholamine-induced gastric motility of guinea-pig stomach were reported firstly in the strip of longitudinal muscle by Bailey (1971), and also in the circular muscle with intact mucosa noradrenaline suppressed the spontaneous contractions while in mucosa-free circular muscle the spontaneous contractions were potentiated dose-dependently by the application of noradrenaline. The results of the present study using the strips of antral circular muscle have shown the same ones obtained from the strips of longitudinal muscle (Fig. 4). Gerschon (1967) found that for the intact stomach isolated from the guinea-pig, the removal of nervous influences with tetrodotoxin did not reduce the inhibitory responses to noradrenaline. In experiments on the isolated whole stomach, noradrenaline produce mainly the inhibitory response, i.e. reduction of intraluminal pressure (guinea-pig, kitten, rat and mouse). The other possibility is that in the experiment using whole stomach the basal tension of stomach muscle may be kept high so that relaxation would be more easily detectable than contractions (Yamaguchi & Tomita, 1974). From the present study and other results (Bailey, 1971), it is evident that gastric mucosa plays a some role in noradrenaline-induced gastric motility. However, it remains to be clarified how the mucosa influences upon the noradrenaline-induced gastric motility.

In the present study, noradrenaline induced three characteristic changes in slow

waves: Hyperpolarization of membrane potential, increase in the amplitude of slow wave and also increase in the maximum rate of rise of slow wave (tall and steep slow waves) (Fig. 8 & 9). Since apamin is known to be a specific Ca-dependent K channel blocker (Meech, 1974; Meech & Standen, 1975; Banks et al, 1979), we used apamin to observe the relationship between noradrenaline-induced hyperpolarization and Ca-dependent K channel. From the results that apamin blocked the noradrenaline-induced hyperpolarization and the hyperpolarization was associated with the increase in ionic conductance of the smooth muscle, noradrenaline-induced hyperpolarization is likely to be due to the activation of Ca-dependent K channel. According to the simultaneous recordings of spontaneous contractions and slow waves, the tonic contraction was initially potentiated prior to the changes in slow waves by the application of noradrenaline, and then hyperpolarization occurred. Prior to the appearance of the hyperpolarization, tonic contractions were potentiated and large phasic contractions were followed by tall and steep slow waves on the hyperpolarized membrane potential, indicating that noradrenaline increases intracellular Ca^{2+} concentration via Ca influx and increased intracellular Ca activates the Ca-dependent K channel and produces hyperpolarization.

It is concluded that in the guine-pig stomach, noradrenaline produces excitatory effects on mucosa-free antral circular smooth muscle cells, typified by hyperpolarization of membrane potential and increases in slow wave amplitude and steepness. These responses of noradrenaline result from the dominant α-excitatory and the weak β-inhibitory actions.

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