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Contractile and Electrical Responses of Guinea-pig Gastric Smooth Muscle to Bradykinin

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=ABSTRACT=

The nonapeptide bradykinin has been shown to exhibit an array of biological activities including relaxation/contraction of various smooth muscles. In order to investigate the effects of bradykinin on the contractility and the electrical activity of antral circular muscle of guinea-pig stomach, the isometric contraction and membrane potential were recorded. Also, using standard patch clamp technique, the Ca^{2+}-activated K currents were recorded to observe the change in cytosolic Ca^{2+} concentration.

0.4 μM bradykinin induced a triphasic contractile response (transient contraction-transient relaxation-sustained contraction) and this response was unaffected by pretreatment with neural blockers (tetrodotoxin, atropine and guanethidine) or with apamin. Bradykinin induced hyperpolarization of resting membrane potential and enhanced the amplitude of slow waves and spike potentials. The enhancement of spike potentials was blocked by neural blockers. Both the bradykinin-induced contractions and changes in membrane potential were reversed by the selective B_2-receptor antagonist (Nα-adamantaneacetyl-D-Arg-[Hyp, Thy, D-Phe]-bradykinin). In whole-cell patch clamp experiment, we held the membrane potential at -20 mV and spontaneous and transient changes of Ca-activated K currents were recorded. Bradykinin induced a large transient outward current, consistent with a calcium-releasing action of bradykinin from the intracellular calcium pool, because such change was blocked by pretreatment with caffeine. Bradykinin-induced contraction was also blocked by pretreatment with caffeine. From these results, it is suggested that bradykinin induces a calcium-release and contraction through the B_2 receptor of guinea-pig gastric smooth muscle. Enhancement of slow wave activity is an indirect action of bradykinin through enteric nerve cells embedded in muscle strip.

Key Words: Bradykinin, Gastric smooth muscle, Guinea-pig, Caffeine

INTRODUCTION

It has been reported that many kinds of endogenous peptides found in neural or endocrine cells act as neurotransmitters or hormones. However, some endogenous peptides are not stored in the cytoplasm but are found in the plasma as inactive precursor substances. They are degraded into active peptides by enzymes activated by various physiologic stimuli, and these active peptides play their own regulatory role. Angiotensin and plasma kinins are examples of such endogenous peptides.

Plasma kinins are formed from two kinds of kininogen (high molecular weight (HMW) kininogen and low molecular weight (LMW) kininogen) through the action of kallikrein. Bradykinin is form-

ed from HMW kininogen and kallidin is produced from LMW kininogen. Their half lives are quite short (~15 sec) and they are mainly metabolized in the liver and lung circulation (Douglas, 1985). Bradykinin is a potent vasodilator while it induces complex contractile responses in other kinds of smooth muscles. Physiological roles of the plasma kinin system are not yet fully understood. However, as their activation induces major symptoms of inflammatory responses, it is thought that the kinins participate in the 'defense and repair' processes (Dray & Perkins, 1993).

Previously, workers have studied the effect of bradykinin on the contractility of gastrointestinal smooth muscles (Walker & Wilson, 1979; Boschcov et al, 1984; Dusser et al, 1988; Hall & Morton, 1991; Ransom et al, 1992) but not on the guinea-pig antral circular muscle. In this study, we observed contractile responses of guinea-pig antral circular muscles to bradykinin and found the Ca-releasing action of bradykinin on single myocytes isolated from antral circular muscle layer.

MATERIALS AND METHODS

Cell isolation

Guinea-pigs of either sex weighing 300~350 g were exsanguinated after being stunned. The stomach was isolated and cut in the longitudinal direction along the lesser curvature in phosphate-buffered Tyrode solution. The antral part of stomach was cut and the mucosal layer was separated from the muscle layers. The circular muscle layer was dissected from the longitudinal layer using fine scissors and made into small segments (2~3 mm). These segments were incubated in a medium modified from the Kraft-Brühe (K-B) medium (Isenberg & Klöckner, 1982) for 30 min at 4℃. Then, they were transferred to nominal Ca^{2+}-free physiological salt solution (PSS) containing 0.1% collagenase (Böhringer Mannheim or Wako), 0.05% dithiothreitol, 0.1% trypsin inhibitor and 0.2% bovine serum albumin and incubated for 15~25 min at 35℃. After digestion, the supernatant was discarded and softened muscle segments were transferred again to the modified K-B medium and single cells were dispersed by gentle agitation with a wide-bored glass pipette. Isolated gastric myocytes were kept in the modified K-B medium at 4℃ until use. All experiments were carried out within 12 hours of harvesting cells and performed at room temperature.

Measurement of membrane currents: Isolated cells were transferred to a small chamber (400 μl) on the stage of an inverted microscope (IMT-2, Olympus, Japan). The chamber was perfused with physiological salt solution (PSS, 2~3 ml/min). Glass pipettes with a resistance of 2-4 MΩ were used to make a gigaseal of 5-10 GΩ. Standard whole cell patch clamp techniques were used (Hamill et al, 1981).

An Axopatch-1C patch-clamp amplifier (Axon instruments, Burlingame, USA) was used to record membrane currents and command pulses were applied using an IBM-compatible AT computer and pCLAMP software v.5.51 (Axon Instrument, Burlingame, USA). The data were filtered at 5 kHz and displayed on a digital oscilloscope (PM 3350, Phillips, Netherlands), a computer monitor, and a pen recorder (Recorder 220, Gould, Cleveland, USA).

Measurement of isometric contractions and intracellular recording of the electrical activity: Muscle strips (2~3 mm wide, 10~12 mm long) from the proximal part of the antrum were cut parallel to the circular fibers, and mounted on silicon rubber in a 2 ml horizontal chamber. The strip was pinned out at one end with tiny pins and the other end was connected to a force transducer to record the isometric contractions. The strip was constantly perfused at a rate of 2~3 ml/min with CO_2/bicarbonate-buffered Tyrode solution. Electrical activities were recorded by means of glass microelectrodes filled with 3 M KCl (tip resistance of 40~80 MΩ and

drawn by a chart recorder (MX-6, Device Ltd, Britain). Field stimulation was applied transmurally to stimulate intramural nerves by using a pair of platinum wires (0.5 mm in diameter) placed on both sides of the preparation. Electrical current pulses of 0.05~0.1 ms in duration and 10~50 V in intensity were applied from an electric stimulator (Grass S-88). The glass microelectrode was put into the tissue about 0.3 mm apart from platinum electrode.

Solutions

Phosphate-buffered Tyrode solution contained (in mM) NaCl 147, KCl 4, $MgCl_2$ 1, $CaCl_2$ 1.8, NaH_2PO_4 0.42, Na_2HPO_4 1.81, glucose 5.5, pH 7.3. CO_2/bicarbonate buffered-Tyrode solution contained (in mM) NaCl 116, KCl 5.4, $CaCl_2$ 1.5, $MgCl_2$ 1, $NaHCO_3$ 24, glucose 5 (pH 7.3 ~ 7.4, bubbled with 5% CO_2-95% O_2). Ca^{2+}-free PSS contained (in mM) NaCl 135, KCl 5, $MgCl_2$ 1, glucose 5, HEPES (N-[2-hydroxyethyl]piperazine-N'-[2-ethanesulfonic acid]) 5, and the pH was adjusted to 7.3 with Tris. PSS contained 1.8 mM $CaCl_2$. All other components were as in the Ca^{2+}-free PSS. Modified K-B solution contained (in mM) L-glutamate 50, KCl 50, taurine 20, KH_2PO_4 20, $MgCl_2$ 3, glucose 10, HEPES 10, EGTA (ethyleneglycol-bis(β-aminoethyl ether)-N,N, N/,N/-tetraacetic acid) 0.5 and pH was adjusted to 7.3 by KOH. To record voltage-activated K currents, the pipette solution was composed of (in mM) K-aspartate 100, MgATP 5, di-tris-creatine phosphate 5, KCl 20, $MgCl_2$ 1, EGTA 10, HEPES 5, pH was adjusted to 7.3 by KOH. All the potassium in the pipette solution was exchanged with Cs and TEA (20 mM) in order to block the K current when recording voltage-gated Ca current. All drugs used in these experiments were purchased from Sigma.

Statistical analysis

All values are expressed as mean ± SEM and statistical analysis was not used generally because the resultant analysis was a qualitative comparison between data groups. The figures cited in this article are representitive examples selected after confirmation of the same results.

RESULTS

Effects of bradykinin on spontaneous contractions of antral circular muscle

Bradykinin showed a highly potent inotropic effect on this smooth muscle. 10^{-10}M bradykinin increased the amplitude of spontaneous contractions (data not shown). At higher concentration (0.04 μM), bradykinin typically induced a fast transient increase of basal tone and spontaneous contractions (first phase of bradykinin effect) and subsequently decreased the size of spontaneous contractions (second phase). Such a phasic response was followed by a sustained potentiation of spontaneous contractions and increased basal tone (third phase, Fig. 1 & Table 1). Throughout the experiments shown

Table 1. Effects of bradykinin (0.04 μM) on the isometric contractions of circular muscle of guinea-pig stomach

	mean	SEM
% increase of the amplitude of spontaneous contractions at first phase of bradykinin effect	184%	65.3
% decrease of the amplitude of spontaneous contractions at second phase of bradykinin effect	94.5%	30.0
% increase of the amplitude of spontaneous contractions at third phase of bradykinin effect	268%	35.9
maximal increase of basal tone induced by bradykinin	267 mg	51.2

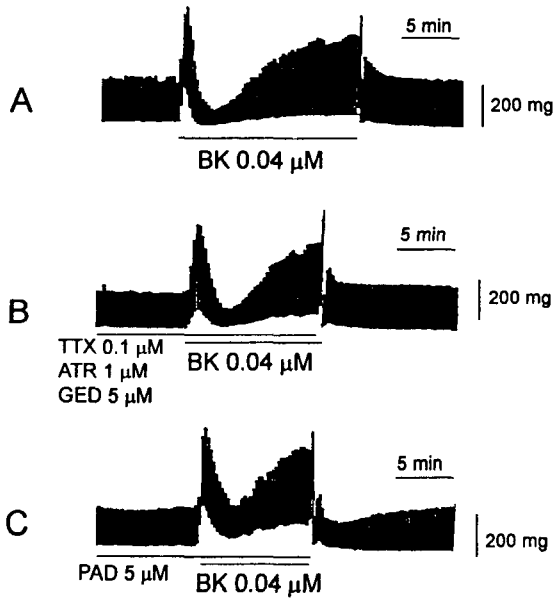

Fig. 1. Effects of bradykinin on the isometric contractions of guinea-pig gastric smooth muscle.
A. Bradykinin induced characteristic contractile responses, which are composed of a rapid contraction-transient relaxation-slowly developing contraction. B. Bradykinin-induced contraction was not changed by pretreatment with tetrodotoxin (TTX, 0.1 μM), atropine (ATR, 1 μM) and guanethidine (GED, 5 μM). C. Phosphoramidone (PAD, 5 μM), a neutral endopeptidase inhibitor, also had no effect on the contraction.

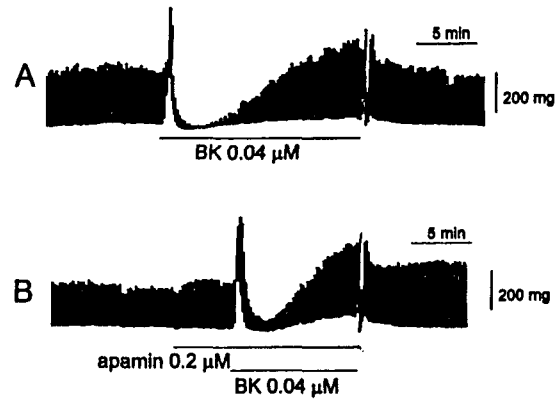

Fig. 2. Effects of apamin on the bradykinin-induced contraction.
With apamin-pretreatment (0.2 μM), spontaneous contractions were slightly enhanced. Bradykinin still showed a characteristic phasic contractile response (B) which was similar to the control (A).

here, 0.04 μM bradykinin was used to elicit the contractile or electrical response of smooth muscle cells. Bradykinin-induced contractile response was not significantly changed by pretreatment with tetrodotoxin (0.1 μM), atropine (1 μM) and guanethidine (5 μM, Fig. 1 B, n=3). In Fig. 1 C, it was tested whether the transient relaxation might have been caused by the activity of endopeptidase (Dusser et al, 1988). Characteristic phasic contractile response to bradykinin was not changed by pretreatment with phosphoramidon (5 μM), a neutral endopeptidase inhibitor (n=2).

In the experiment of Fig. 2, it was tested whether apamin, a potassium channel blocker, could change the transient inhibitory response to bradykinin, as has been reported in rat duodenum (Hall & Morton, 1991). However, apamin (0.2 μM) could not change the basic pattern of response induced by bradykinin in this gastric smooth muscle (n=4).

To identify the source of Ca^{2+} necessary for the bradykinin-induced contractile response, the effect of nifedipine or caffeine was observed. Nifedipine and caffeine were used as an L-type Ca channel blocker and a Ca-releasing agent from sarcoplasmic reticulum, respectively (Endo, 1977; Iino et al, 1988). As can be seen in Fig. 3, caffeine-pretreatment could block the bradykinin-induced contraction almost completely while pretreatment with nifedipine could not block the contractile response by bradykinin (n=3).

Effects of bradykinin on membrane potential and slow waves of gastric smooth muscle

Using the conventional intracellular microelectrode technique, the membrane potential and slow waves were recorded and the isometric tension was measured simultaneously. Slow waves of about 20 mV amplitude were recorded and the resting

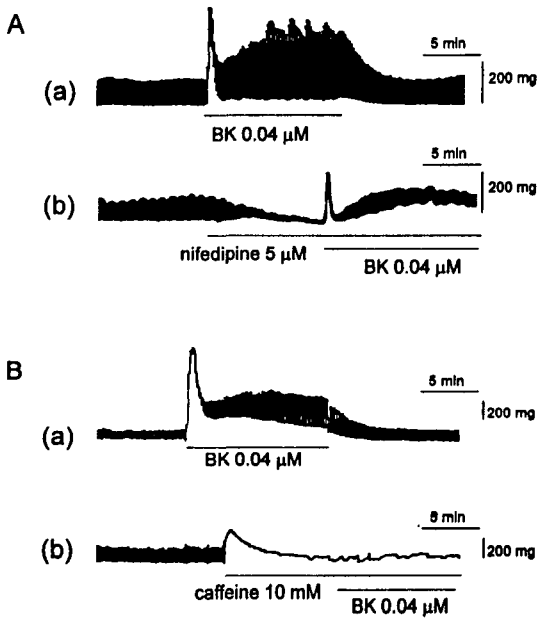

Fig. 3. Role of calcium in the bradykinin-induced contraction
A. Nifedipine, a Ca channel blocker, abolished spontaneous contractions and under these conditions bradykinin still induced a typical contractile response of muscle strip. B. Bradykinin could not induce the contractile response at all following pretreatment with caffeine, a chemical known to deplete the stored Ca in sarcoplasmic reticulum.

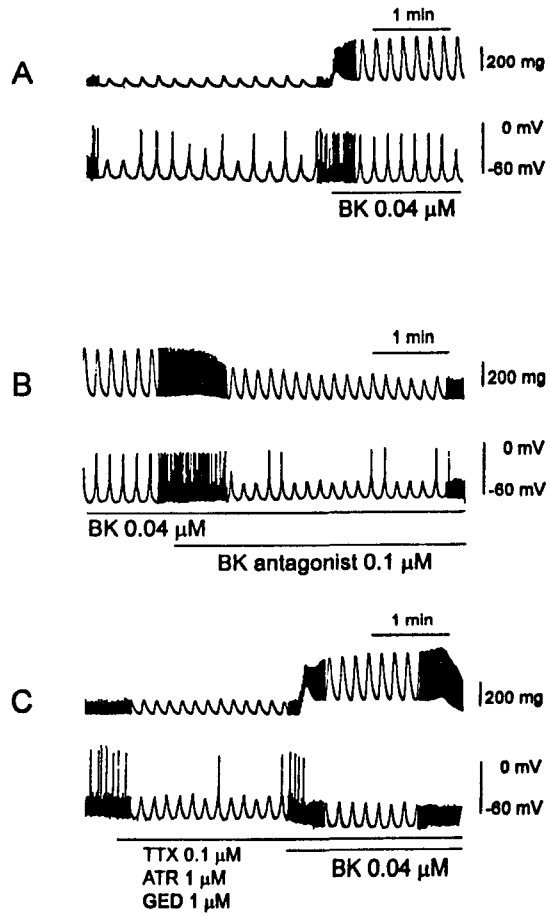

Fig. 4. Effects of bradykinin on membrane potential and slow waves of gastric smooth muscle.
Slow waves were recorded, of approximately 20 mV in amplitude, with a resting membrane potential of −61mV. On the peak of each slow wave, single or multiple spike potentials or abortive spikes were observed. A. Bradykinin increased the size of spike potentials and hyperpolarized the resting membrane potential. B. Application of a peptide antagonist to B_2-type bradykinin receptor reversed both the electrical and mechanical changes induced by bradykinin. C. Pretreatment with tetrodotoxin (TTX), atropine (ATR) and guanethidine (GED) prevented the enhancement of spike potentials by bradykinin while the hyperpolarization became more prominent.

membrane potential was around -60 mV. On the peak of each slow waves, single or multiple spike potentials were observed occasionally (Fig. 4A).

Bradykinin increased the number and size of spike potentials (8 out of 13 experiments) while inducing hyperpolarization of resting membrane potential (2.5 ± 0.39 mV, n=13). The amplitude of slow waves was increased ($110 \pm 3.75\%$, n=13) and the spontaneous contractions were potentiated at the same time (Fig. 4A). These changes in membrane potential and mechanical contraction were reversed by addition of a B_2-type antagonist for bradykinin receptor (Nα-adamantane acetyl-D-Arg-[Hyp, Thy, D-Phe]-bradykinin, Rigoli et al, 1990) (n=2, Fig, 4B).

To rule out an indirect effect of bradykinin on the membrane potential through the enteric nervous sy-

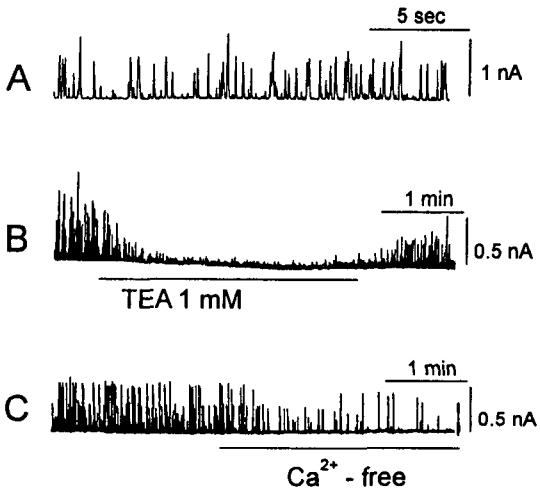

Fig. 5. Spontaneous transient outward currents (STOCs) recorded from gastric myocytes.
A. The membrane potential of gastric myocyte was clamped at -20 mV with pipette solution composed of high potassium and low concentration of EGTA(0.1 mM). Spontaneous transient outward currents (STOCs) were observed. B. STOCs were blocked by the applicaiton of tetraethylammonium (TEA, 1 mM). C. Elimination of calcium from bath solution decreased the size and frequency of STOCs.

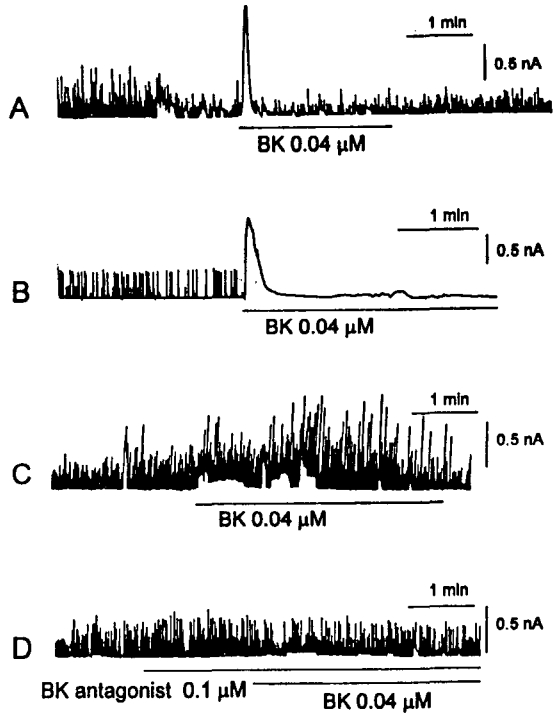

Fig. 6. Effects of bradykinin on the Ca-activated K currents recorded from a single gastric myocyte.
Bradykinin induced a large transient outward current and the following STOCs were suppressed or abolished (A, B). In some cases, sustained increase of STOCs were observed (C). Above changes were blocked by pretreatment with a peptide antagonist to bradykinin receptors (D).

stem, the same muscle strip was pretreated with tetrodotoxin (0.1 μM), atropine (5 μM) and guanethidine (5 μM) and a comparison was made. In these conditions, enhancement of spike potential by bradykinin was completely blocked while the hyperpolarization process was more pronounced (n=2, Fig. 4C). The contractile response was not affected by these neural blockers as was already shown in Fig. 1B. With a single pretreatment with atropine, bradykinin-induced enhancement of spike potential was not elicited and only the hyperpolarization of resting membrane potential was observed (n=2, data not shown).

Effects of bradykinin on the Ca-releasing activity of single gastric myocytes

Isolated gastric myocytes were voltage clamped (at -20 mV) using standard patch-clamp technique in the whole-cell configuration and dialyzed by an high K pipette solution containing a low concentration (0.1 mM) of EGTA. Spontaneous transient outward currents (STOCs) were observed (Fig. 5A). STOCs are thought to be due to the simultaneous opening of Ca^{2+}-activated K channels in response to sudden and cyclic discharges of Ca ion from internal stores (Benham & Bolton, 1986) as they were eliminated by treatment with caffeine (10 mM, deplete the stored Ca, Fig. 7 A & B) or TEA (1 mM, sensitively block the large conductance Ca-activated K channels at this concentration, Fig. 5B). Their

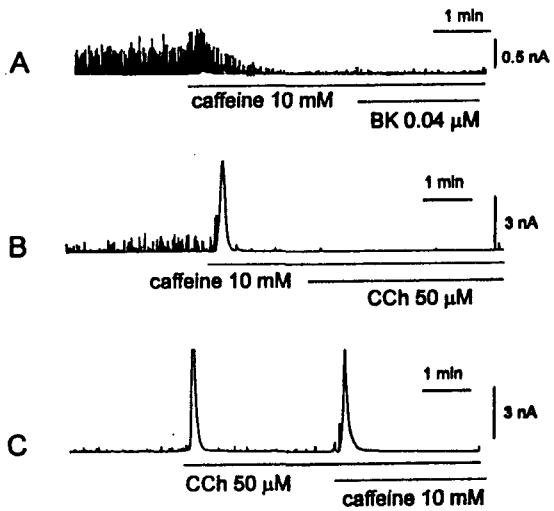

Fig. 7. Effects of caffeine on the increase of Ca-activated K currents induced by bradykinin or CCh.
Caffeine induced a similar large transient increase in Ca-activated K current (A, B & C) and after that increase, bradykinin and CCh (50 μM) could not induce any change of outward current (A & B). Caffeine still could induce a transient increase of outward current after the CCh-induced transient current (C). Membrane potential was held at 0 mV for the experiments in B and C.

frequency was sharply decreased by Ca^{2+}-free bath solution (Fig. 5C).

Recording STOCs under these conditions, externally applied bradykinin induced a large transient increase of outward current (Fig. 6A & B, 6 out of 14 cases of experiments) or occasionally, sustained increase of STOCs and outward current was observed (Fig. 6C, 2 out of 14 cases of experiments). Such changes in ionic currents were blocked by the same bradykinin antagonist used in Fig. 4B (Fig. 6D, n= 3). Caffeine induced a transient increase of STOCs (Fig, 7A) or a large outward current (Fig. 7B & C) and suppressed the subsequent generation of STOCs. In these conditions, both the bradykinin-induced and the CCh-induced current response were blocked by pretreatment with caffeine (Fig. 7A & B, n=2 & 3, respectively).

DISCUSSION

This study shows the effects of bradykinin on the contractility of antral circular muscle of guinea-pig stomach and the Ca-releasing activity of bradykinin in these gastric myocytes. A typical contractile response to bradykinin can be characterized by a sequence of transient contraction-various levels of transient relaxation-sustained increase of spontaneous contraction.

At first, it was tested whether bradykinin acts directly on its own receptors in smooth muscle cells or indirectly through the enteric nervous cells. In organ bath studies, bradykinin-induced contraction of gastric smooth muscle is not sensitive to neural blockers (Fig. 1) and therefore, does not appear to involve the myenteric plexus. Results in Fig. 4 and Fig. 6 show that both the bradykinin-induced contraction and the bradykinin-induced Ca-release were blocked by an analogue of bradykinin which acts as the antagonist for the bradykinin receptor. These results clearly indicate that bradykinin acts directly on the smooth muscle cells. However, different responses of membrane potential depending on the presence of neural blockers, especially cholinergic antagonists, suggest a possibility that bradykinin has an indirect action on the membrane potential and the generation of spike potentials. Goldstein et al (1983) have reported that bradykinin can release acetylcholine from longitudinal muscle-myenteric plexus preparations. As it is well known that muscarinic activation induces depolarization of membrane potential and promotes the generation of spike potentials in gastrointestinal smooth muscle (Bolton, 1979) through the activation of a nonselective cationic current (Benham et al, 1985; Kim et al, 1995), bradykinin could enhance the generation of spike potentials through modulation of the cholinergic nerve fibers embedded in these muscle preparations.

The membrane receptors that mediate the action

of bradykinin have been categorized as being either of the B_1 or B_2 type. These two classes are distinguished on the basis of their relative affinities for des-Arg kinins which exhibit significant activity at B_1 receptors while being virtually inactive at B_2 receptors (Rigoli & Barabe, 1980). By now, it is widely known that, predominantly physiological and pathological responses to bradykinin involve B_2 receptors.

It has been reported that the two primary signal transduction mechanisms linked to B_2 receptors are stimulation of phosphoinositide hydrolysis and eicosanoid biosynthesis (Yano et al, 1984; Miller, 1987; Ransom et al, 1992). We mainly focused upon the Ca-releasing action of bradykinin as bradykinin induced a large and transient contractile response in this gastric smooth muscle. Actually, bradykinin induced a large oscillation of Ca-activated K current which reflects the transient increase of cytosolic Ca concentration (Fig. 6, 7). Both the contractile response and the Ca-release response were blocked by pretreatment with 10 millimolar caffeine (Fig. 3, 7). It is well known that the inositol triphosphate (IP_3) released from the hydrolysis of phophoinositide induces Ca-release from the sarcoplasmic reticulum of various cells (Berridge & Irvine, 1984) including smooth muscle cells (Bolton & Lim, 1989). ACh or CCh, the most common IP_3 releasing agonists used in gastrointestinal myocyte, also induced similar Ca-releasing responses in this myocyte and those actions were also blocked by caffeine (Fig. 7). Although separate receptors on the membrane of sarcoplasmic reticulum are responsible for the Ca-releasing activities of IP_3 and caffeine (IP_3 receptor and ryanodine receptor, respectively), many other reports suggest that both receptors exist in single myocytes and that the Ca store of smooth muscle cells consists of at least two compartments, one with Ca-induced Ca release (CICR) which is sensitive to caffeine or ryanodine, and the other with IP_3-induced Ca release (IICR) mechanism (Endo, 1977; Iino et al, 1988; Ganitkevitch & Isenberg, 1992). In this gastric myocyte, the CCh-induced Ca-release was blocked by the pretreatment with caffeine while the caffeine-induced Ca release was not blocked by CCh (Fig. 7). From this model of the compartmentalization of the Ca pool in single myocytes, this result suggests that the IICR compartment is functionally included in the CICR compartment by way of the distribution state of IP_3 receptors and ryanodine receptors on SR membrane. Bradykinin seems to have stimulated the production of IP_3 like others have reported in guinea-pig ileum (Ransom et al, 1992), and this IP_3-mediated Ca-release seems to have induced characteristic contractile response in guinea-pig gastric smooth muscle.

REFERENCES

Benham CD, Bolton TB & Lang RJ (1985) Acetylcholine activates an inward current in single mammalian smooth muscle cells. *Nature (London)* **316,** 345-347

Benham CD & Bolton TB (1986) Spontaneous transient outward currents in single visceral and vascular smooth muscle cells of the rabbit. *J Phyiol (London)* **381,** 385-406

Berridge MJ & Irvine RF (1984) Inositol trisphosphate, a novel second messenger in cellular signal transduction. *Nature (London)* **312,** 315-321

Bolton TB (1979) Mechanism of action of transmitters and other substances on smooth muscle. *Physiol Rev* **59(3),** 606-718

Bolton TB & Lim SP (1989) Properties of Ca stores and transient outward currents in single smooth muscle cells of rabbit intestine. *J Physiol (London)* **409,** 385-401

Boschcov P, Paiva ACM, Paiva TB & Shimuta SI (1984) Further evidence for the existence of two receptor sites for bradykinin responsible for the diphasic effect in the rat isolated duodenum. *Br J Pharmacol* **83,** 591-600

Douglas W (1985) Polypeptides-angiotensin, plasma kinins, and others. In Goodman & Gilman (ed) *Goodman and Gilman's The Pharmacological Basis of Therapeutics,* chapter 27. Macmillan Comp, New York, p639-659

Dray A & Perkins M (1993) Bradykinin and inflam-

matory pain. *TINS* **16(3),** 99-104

Dusser DJ, Nadel JA, Sekizawa K, Graf PD & Borson DB (1988) Neutral endopeptidase and angiotensin converting enzyme inhibitors potentiate kinin-induced contraction of ferret trachea. *J Pharmacol Exp Ther* **244(2),** 531-536

Endo M (1977) Calcium release from the sarcoplasmic reticulum. *Physiol Rev* **57,** 71-108

Ganitkevitch VYa & Isenberg G (1992) Caffeine-induced release and reuptake of Ca^{2+} by Ca^{2+} stores in myocyte from guinea-pig urinary bladder. *J Physiol (London)* **458,** 99-117

Goldstein DJ, Ropchak TG, Keiser HR, Atta GJ, Argiolas A & Pisano JJ (1983) Bradykinin reserves the effect of opiates in the gut by enhancing acetylcholine release. *J Biol Chem* **258,** 12122-12124

Hall JM & Morton KM (1991) Bradykinin B_2 receptor evoked K^+ permability mediates relaxation in the rat duodenum. *European J Pharmacol* **193,** 231-238

Hamill OP, Marty A, Neher B, Sakmann N & Sigworth EJ (1981). Improved patch-clamp technique for high resolution current recording from cells and cell free membrane patches. *Pflügers Arch* **391,** 85-100.

Iino M, Kobayashi T & Endo M (1988) Use of ryanodine for functional removal of the calcium stores in smooth muscle cells of the guinea-pig. *Biochem Biophys Res Commun* **152,** 417-422

Isenberg G & Klöckner U (1982) Calcium tolerant ventricular myocytes perpared by pre-incubation in a "KB-medium". *Pflügers Arch* **395,** 6-18

Kim SJ, Ahn SC, So I & Kim KW (1995) Quinidine blockade of the carbachol-activated nonselective cationic current in guinea-pig gastric myocytes. *Br J Pharmacol* **115,** 1407-1414

Miller RJ (1987) Bradykinin highlights the role of phospholipid metabolism in the contrrrrol of nerve excitability. *TINS* **10,** 226-228

Ransom RW, Goodman CB & Young GS (1992) Bradykinin stimulation of phosphoinositide hydrolysis in guinea-pig ileum longitudinal muscle. *Br J Pharmacol* **105,** 919-924

Rigoli D & Barabe J (1980) Pharmacology of bradykinin and related kinins. *Pharmacol Rev* **32,** 1-45

Rigoli D, Rhaleb NE, Dion S & Drapeau G (1990) New selective bradykinin receptor antagonists and bradykinin B_2 receptor characterization. *TIPS* **11,** 156-161

Walker R & Wilson KA (1979) Prostaglandins and the contractile action of bradykinin on the longitudinal muscle of rat isolated ileum. *Br J Pharmacol* **67,** 527-533

Yano K, Higashida H, Inoue R & Nozawa Y (1984) Bradykinin-induced rapid breakdown of phosphatidylinositol 4,5-bisphosphate in neuroblastoma × glioma hybrid NG108-15 cells. *J Biol Chem* **259,** 10201-10207