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Different Mechanisms for K^+-Induced Relaxation in Various Arteries

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$[K^+]_o$ can be increased under a variety of conditions including subarachnoid hemorrhage. The increase of $[K^+]_o$ in the range of 5~15 mM may affect tensions of blood vessels and cause relaxation of agonist-induced precontracted vascular smooth muscle (K^+-induced relaxation). In this study, effect of the increase in extracellular K^+ concentration on the agonist-induced contractions of various arteries including resistant arteries of rabbit was examined, using home-made Mulvany-type myograph. Extracellular K^+ was increased in three different ways; from initial 1 to 3 mM, from initial 3 to 6 mM, or from initial 6 to 12 mM. In superior mesenteric arteries, the relaxation induced by extracellular K^+ elevation from initial 6 to 12 mM was the most prominent among the relaxations induced by the elevations in three different ways. In cerebral arteries, the most prominent relaxation was produced by the elevation of extracellular K^+ from initial 1 to 3 mM and a slight relaxation was provoked by the elevation from initial 6 to 12 mM. In superior mesenteric arteries, K^+-induced relaxation by the elevation from initial 6 to 12 mM was blocked by Ba^{2+} (30 μM) and the relaxation by the elevation from 1 to 3 mM or from 3 to 6 mM was not blocked by Ba^{2+}. In cerebral arteries, however, K^+-induced relaxation by the elevation from initial 3 to 6 mM was blocked by Ba^{2+}, whereas the relaxation by the elevation from 1 to 3 mM was not blocked by Ba^{2+}. Ouabain inhibited all of the relaxations induced by the extracellular K^+ elevations in three different ways. In cerebral arteries, when extracellular K^+ was increased to 14 mM with 2 or 3 mM increments, almost complete relaxation was induced at 1 or 3 mM of initial K^+ concentration and slight relaxation occurred at 6 mM. TEA did not inhibit Ba^{2+}-sensitive relaxation at all and NMMA or endothelial removal did not inhibit K^+-induced relaxation. Most conduit arteries such as aorta, carotid artery, and renal artery were not relaxed by the elevation of extracellular K^+. Among conduit arteries, trunk of superior mesenteric artery and basilar artery were relaxed by the elevations of $[K^+]_o$. These data suggest that K^+-induced relaxation has two independent components, Ba^{2+}-sensitive and Ba^{2+}-insensitive one and there are different mechanisms for K^+-induced relaxation in various arteries.

Key Words: Ba^{2+}-sensitive K^+-induced relaxation, Ba^{2+}-insensitive K^+-induced relaxation, Cerebral arteries, Superior mesenteric artery, Conduit artery

INTRODUCTION

Although most arteries constrict in response to the large increase of extracellular K^+ concentration in more than 30 mM, the moderate increase of extracellular K^+ in the range of 6~15 mM relaxes vascular smooth muscle (Kuschinsky et al, 1972; McCarron & Halpern, 1990). Extracellular K^+ can be increased under a variety of conditions such as subarachnoid hemorrhage. In brain, activated neuronal cells can release K^+, which enters and depolarizes neighboring astrocytes resulting in K^+ release from other regions of astrocytes (Sykova, 1983; Newman, 1986; Paulson & Newman, 1987). K^+ re-

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leased by active neurons may be sufficient to cause K^+-induced relaxation of cerebral blood vessels, and this may be a factor linking cerebral blood flow to local neuronal metabolism.

As the relaxation by the elevation of extracellular K^+ (K^+-induced relaxation) is blocked by Ba^{2+} and/or ouabain and not by blockers of ATP-sensitive K^+ channel and Ca^{2+} channel, it could be suggested that external K^+-induced relaxation is caused by stimulation of the electrogenic Na^+-K^+ pump and/or by the activation of inward rectifier K^+ current (McCarron & Halpern, 1990; Quayle et al, 1993). McCarron & Halpern (1990) reported that there are two distinct components in K^+-induced dilation; the first consisted of transient dilations blocked by ouabain but not by Ba^{2+} or Cs^{2+} at low K^+ concentrations and the second maintained ouabain-, Ba^{2+}-, and Cs^{2+}-senstive dilation at higher concentrations.

Most studies about ion channels in smooth muscle cells isolated from conduit arteries and resistant arteries demonstrated that ion channels in resistant arteries might differ from those in conduit arteries (Nelson et al, 1991). Inward rectifier K^+ channels, which are known to evoke K^+-induced relaxation, may exist in smooth muscle cells in small arteries but not in large arteries, suggesting that there may be different mechanisms for K^+-induced relaxation in various arteries including conduit arteries. The concentration of K^+ in cerebrospinal fluid seems to be different from that of K^+ in plasma. Davson et al (1987) reported that the concentration of K^+ in cerebrospinal fluid was 2.9 mM, 67 % of that of K^+ in plasma. This report suggested that concentration of K^+ in cerebrospinal fluid and extracellular fluid in brain is significantly lower than that of K^+ in plasma and extracellular fluid in other space except brain. From this report, we hypothesized that there is a difference between the effects of extracellular K^+ elevation in the arteries exposed to CSF and others.

Therefore, in this study, we tried to confirm the two components in the K^+-induced relaxation and then investigated whether there are different mechanisms for the K^+-induced dilation in various arteries including resistant arteries.

METHODS

Animal preparation

Rabbits of either sex, weighing about 2.5 kg, were killed by exsanguination from the femoral artery under sodium pentobarbital (40 mg/kg) anesthesia. The basilar artery, middle cerebral artery, superior mesenteric artery, carotid artery, renal artery, and aorta were excised and immersed in Krebs Ringer bicarbonate solution at room temperature and cleaned by removing connective tissues surrounding the vessels.

Recording of isometric contraction

Mechanical responses were recorded from the ring segments (3.0~4.0 mm) using home-made myograph similar to the Mulvany type myograph (Fig. 1). A wire or rod made by stainless steel or tungsten was used to mount arterial rings of small arteries or conduit arteries. Each ring from small arteries was threaded onto two pieces of 40~60 μm stainless or tungsten wire. One from conduit arteries was threaded onto two pieces of 120 μm stainless or tungsten wire. One wire was anchored in organ chamber (1 ml) and the other connected to a mechano-transducer (Grass, FT-03), which was connected to a three dimensional manipulator. The rings were mounted under optimal resting tensions (0.6~2 g) and the muscle chamber was perfused with Krebs Ringer bicarbonate solution maintained at 36.5°C, at a constant flow rate of 2.5 ml/min using peristaltic pump. The optimal resting tensions were determined by comparing the tensions developed by 30 mM K^+ solution under different resting tensions. The tissues were equilibrated for 60 min at the optimal resting tension in order to develop maximal tension in response to high-K^+ solution.

Experimental protocols

Extracellular K^+ was increased in three different ways; from initial 1 to 3 mM, from initial 3 to 6 mM, or from initial 6 to 12 mM. Vessels were incubated at the initial concentration of extracellular K^+ for more than 30 min, and then contracted by the combined treatment with histamine 10^{-5} M and phenylephrine 10^{-5} M. When the contraction reached a steady state, extracellular K^+ was elevated according to the experimental protocols. In some experiments using cerebral arteries, extracellular K^+ was increased from initial 1, 3, or 6 mM to 14 mM with 2~3 mM increments. In some experiments, endothelium was removed by gentle rubbing with cotton ball

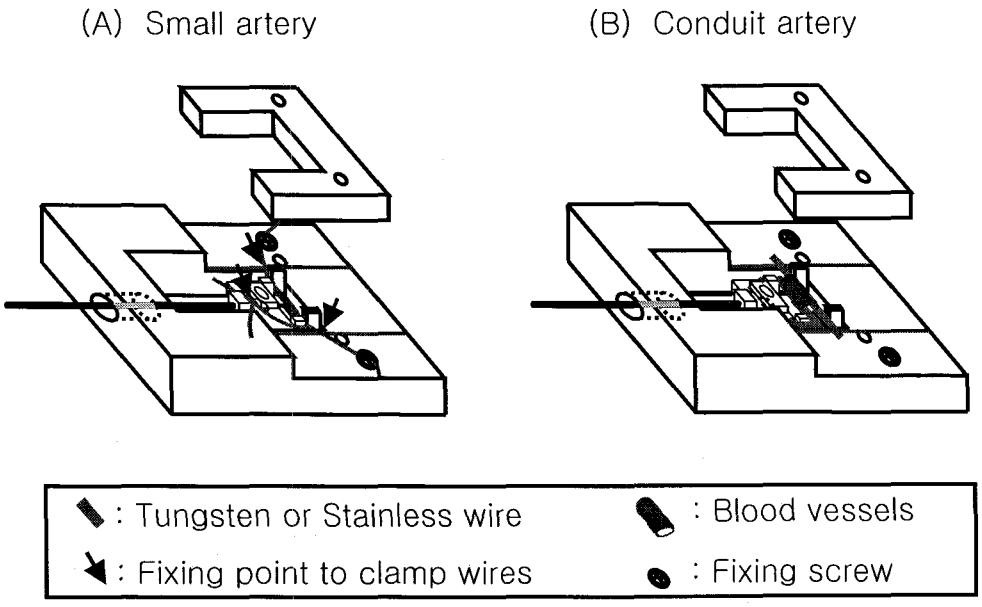

Fig. 1. A schematic representation of the home-made myograph by Suh et al. Wire ends are wrapped around fixing screws, so that the screws tighten the wires. And then, the wires are compressed by lucite plate.

and removal of endothelium was verified by the loss of ACh-induced endothelium-dependent relaxation.

Solutions and drugs

The ionic composition of Krebs Ringer bicarbonate solution was as follows (in mM): NaCl 118.3, KCl 4.7, $MgSO_4$ 1.2, KH_2PO_4 1.2, $CaCl_2$ 2.5, $NaHCO_3$ 25.0, CaEDTA 0.016, and glucose 11.1. The solution was aerated with 95% O_2-5% CO_2 (pH 7.3-7.4). K^+ concentration was adjusted by substituting Na^+ with K^+ or K^+ with Na^+. N^G monomethyl-L-arginine (NMMA) was purchased from RBI, USA. All other chemicals and drugs used in this study were purchased from Sigma Chemical Co. (USA).

Statistics

Experimental values were expressed as means ± SEM for n separate experiments. Statistical significances were determined using unpaired Student's t-test, and probabilities of less than 5% ($p<0.05$) were considered significant.

RESULTS

Conduit arteries

Carotid artery, aorta, renal artery, and trunk of superior mesenteric artery were contracted by the combined application of 10^{-5} M histamine and 10^{-5} M phenylephrine. When extracellular K^+ was elevated at the steady state of contraction, carotid artery or renal artery showed no or slight relaxation with the elevation (Fig. 2). On the contrary to these arteries, trunk of superior mesenteric artery was relaxed by the elevation and the magnitudes of the relaxation were different according to how to elevate extracellular K^+. When extracellular K^+ was elevated from initial 1 to 3 mM, the arterial ring was relaxed a little. But, when extracellular K^+ was elevated from initial 3 to 6 mM or from 6 to 12 mM, the arterial ring was markedly relaxed. The relaxation by the elevation from 1 to 3 mM or from 3 to 6 mM was not inhibited by the treatment with Ba^{2+}, whereas Ba^{2+} inhibited completely the relaxation by the elevation from 6 to 12 mM. These data indicate that some of conduit arteries, such as superior mesenteric artery, can be relaxed by the elevation of extracellular K^+ and there are two components in K^+

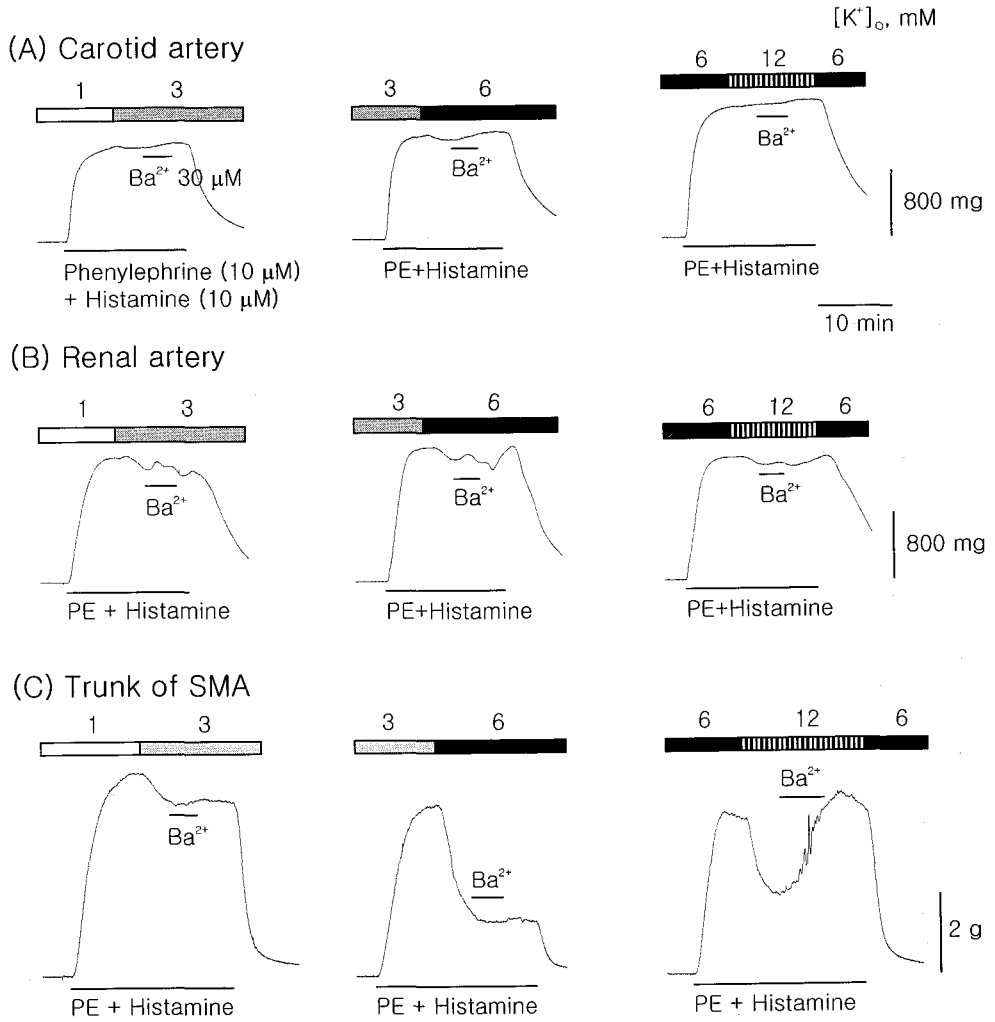

Fig. 2. Representative recordings showing the effect of extracellular K^+ elevation on the contraction induced by the combined application of 10 μM phenylephrine and 10 μM histamine in carotid artery (A), renal artery (B), and trunk of superior mesenteric artery (C). Conduit arteries such as aorta, carotid artery, and renal artery showed no or slight relaxation with the elevation, whereas trunk of superior mesenteric artery was markedly relaxed.

-induced relaxation; Ba^{2+}-sensitive and Ba^{2+}-insensitive one.

Branches of superior mesenteric artery

K^+-induced relaxation was recorded in the second-order branches (proximal) and the third- or fourth-order branches (distal) of superior mesenteric artery (Fig. 3, & Fig. 5). K^+-induced relaxations evoked in these branches of superior mesenteric artery were similar to that of trunk of superior mesenteric artery. The arterial ring was relaxed with the elevation of extracellular K^+ and the magnitude of the relaxation was dependent on how to elevate extracellular K^+. In the branches, almost complete relaxation was produced by the elevation of extracellular K^+ from 6 to 12 mM, whereas the elevation of extracellular K^+ from initial 1 to 3 mM induced a partial relaxation. Among the relaxations induced by the extracellular K^+ elevations in three different ways, the extracellular K^+ elevation from initial 1 to 3 mM induced the smallest relaxation. The relaxation by elevation of extracellular K^+ from 6 to 12 mM was completely blocked by Ba^{2+}, and the inhibitory effect of Ba^{2+}

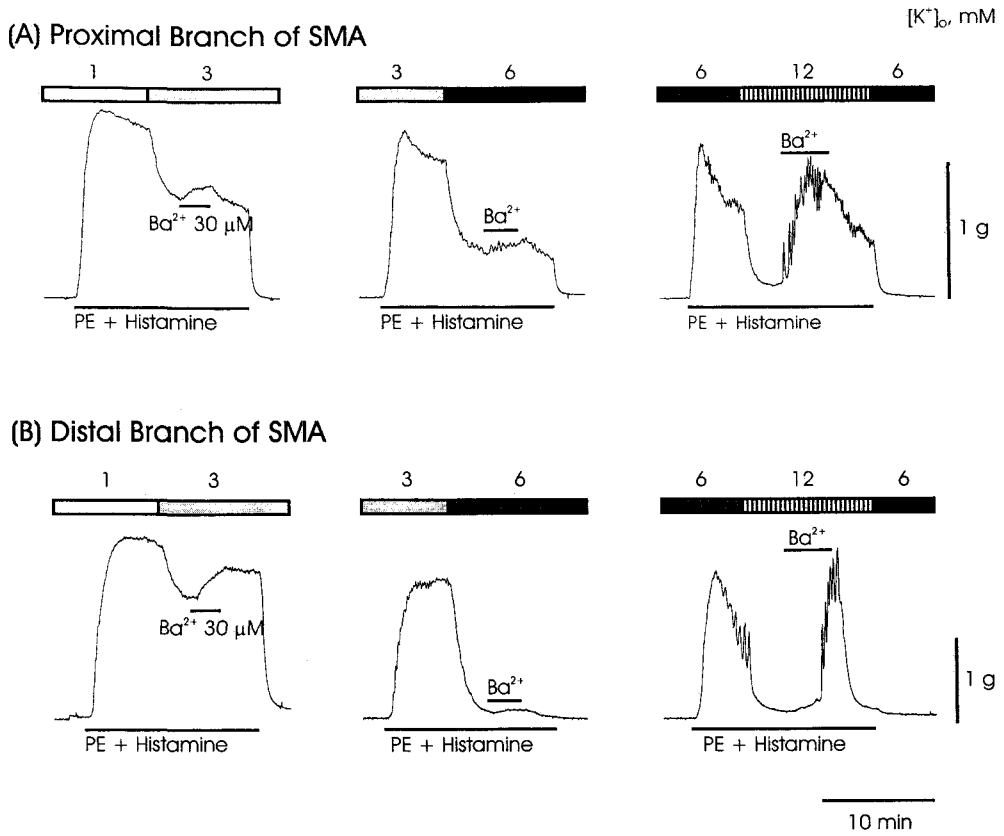

Fig. 3. Representative recordings showing K^+-induced relaxation in branches of superior mesenteric artery (SMA). Branches of superior mesenteric artery were relaxed by the elevation of extracellular K^+. In these arteries, the elevation extracellular K^+ from initial 6 to 12 mM provoked the greatest relaxation among the three kinds of the elevations. The relaxations by the elevation of extracellular K^+ from 1 to 3 mM or from 3 to 6 mM was not blocked by Ba^{2+}, whereas the relaxation by elevation from 6 to 12 mM was completely blocked by Ba^{2+}.

was reversible. The increased tension by the application of Ba^{2+} was re-decreased by the removal of Ba^{2+}. However, the relaxation by the elevation of extracellular K^+ from 1 to 3 mM or from 3 to 6 mM was not blocked by Ba^{2+} (Fig. 3), but by ouabain (Fig. 6B). When extracellular K^+ was increased from 3 to 6 mM, the magnitude of the relaxation was similar to that of the relaxation by the increase of extracellular K^+ from 6 to 12 mM. But, the relaxation was not inhibited by the application of Ba^{2+}. These data indicate that in superior mesenteric arteries, the elevation of extracellular K^+ from higher extracellular K^+ concentration provokes greater K^+-induced relaxation than the elevation of extracellular K^+ from lower extracellular K^+ concentration does.

The Ba^{2+}-sensitive relaxation was not blocked by the treatment with 1 mM TEA (Fig. 6C). When extracellular K^+ was elevated from 6 to 12 mM, the contraction by phenylephrine and histamine was almost completely relaxed in the branch of superior mesenteric artery. By the application of Ba^{2+}, the relaxation was completely blocked and the tension of the branch was recovered to the level of initial contraction. The recovered tension was re-decreased by the elimination of Ba^{2+}. When TEA was applied after the artery was relaxed by the elevation, TEA did not inhibit the relaxation at all. In additional series of experiments, we pretreated the artery with TEA for 5 minutes before the application of phenylephrine and histamine. When the contraction induced by phenylephrine and histamine was reached a steady state, extracellular K^+ was increased from 6 to 12 mM. With the increase of $[K^+]_o$, K^+-induced relaxation was provoked and the pretreatment with TEA did not

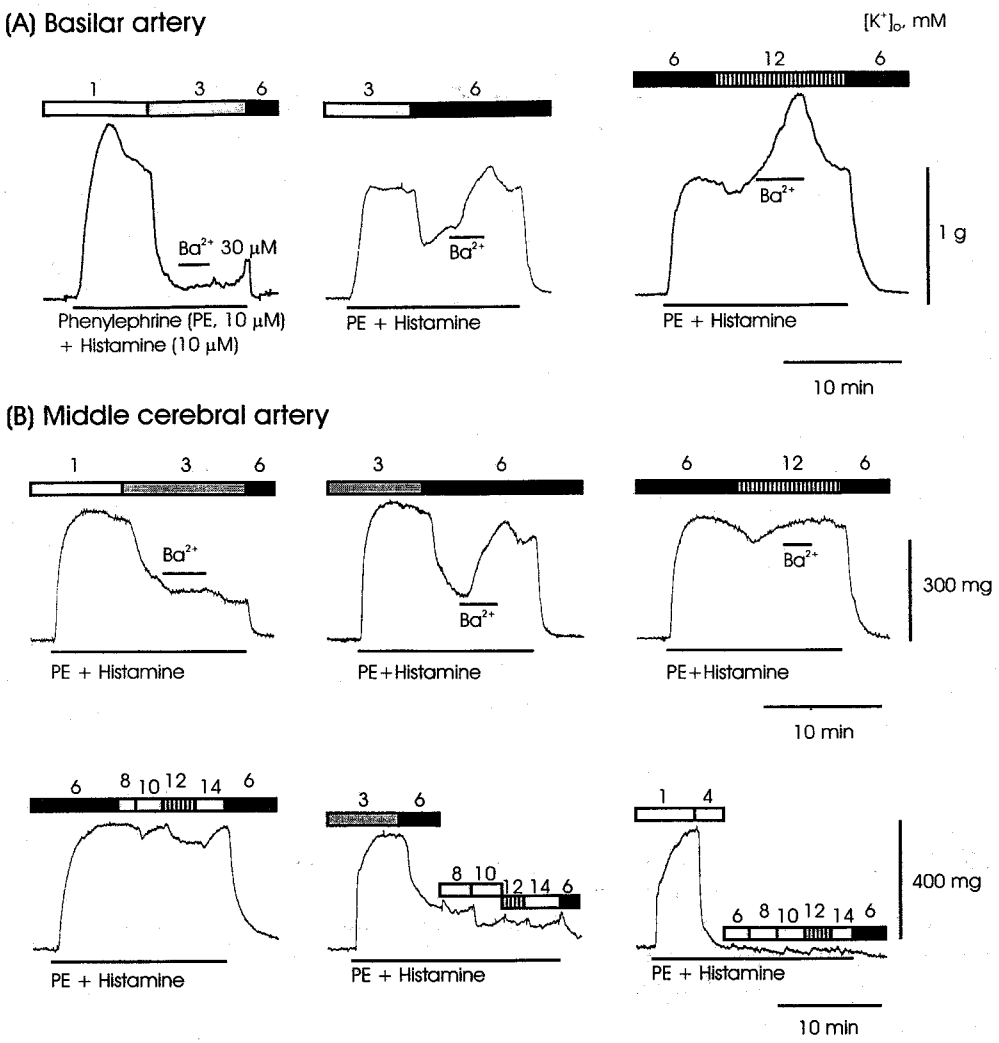

Fig. 4. Representative recordings showing K^+-induced relaxation in basilar artery (A) and branch of middle cerebral artery (B). On the contrary to the K^+-induced relaxations in branches of superior mesenteric artery, cerebral arteries showed no or slight relaxations with the elevation of extracellular K^+ from 6 to 12 mM and the relaxation by the elevation from 3 to 6 mM was completely inhibited by 30 μM Ba^{2+}. However, the elevation of extracellular K^+ from 1 to 3 mM or from 3 to 6 mM relaxed the arteries remarkably and the relaxation was not blocked by Ba^{2+}. When extracellular K^+ was elevated to 14 mM with 2 or 3 mM increments, the magnitude of the relaxation was dependent on the initial K^+ concentration. When the initial concentration was 6 mM, the arterial ring was not or slightly relaxed with the elevation. However, when the initial concentration was 1 or 3 mM, the arterial ring was almost completely relaxed with the elevation of extracellular K^+.

inhibit the relaxation. On the contrary to TEA, the relaxation was completely inhibited by the treatment with Ba^{2+}.

Cerebral arteries

Basilar artery and branch of middle cerebral artery were used to record K^+-induced relaxation in cerebral arteries (Fig. 4 & Fig. 5). Cerebral arteries, which were contracted by the combined application of histamine and phenylephrine, were relaxed by the elevation of extracellular K^+, but the responses were different from those of superior mesenteric artery. In these cerebral arteries, K^+-induced relaxations were

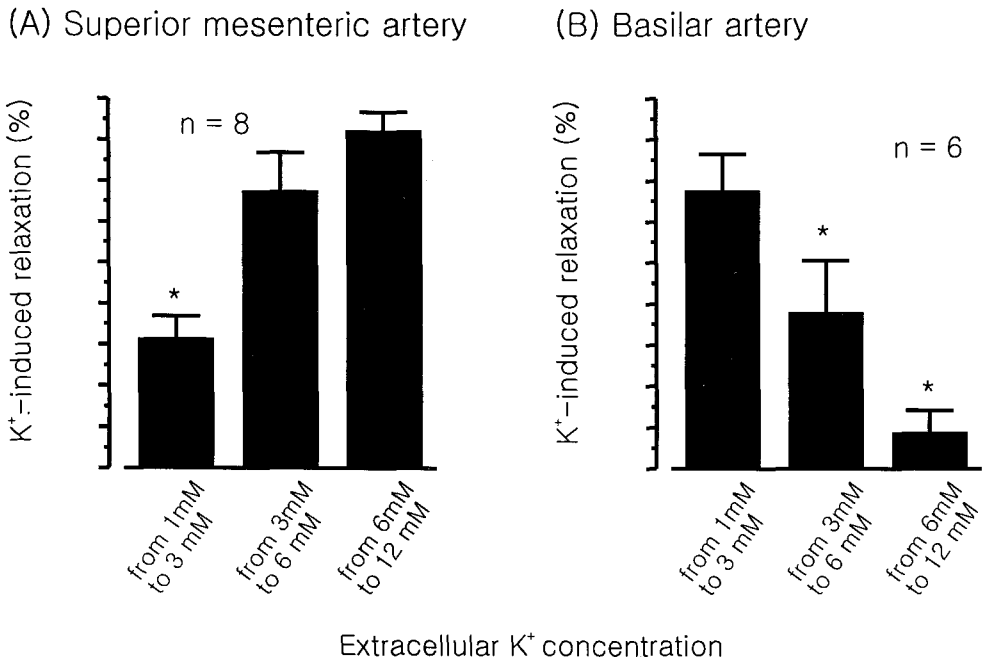

Fig. 5. Effect of the elevation of extracellular K^+ on the contraction in branch of superior mesenteric artery (A) and basilar artery (B). The data were expressed as relative % relaxation against the contraction by the combined application of histamine (10^{-5} M) and phenylephrine (10^{-5} M). Each bar represents the mean value and the vertical bar the SEM. * indicates $p<0.05$ between the relaxation by the elevation of extracellular K^+ from 1 to 3 mM and that by the elevation from 3 to 6 mM or between that by the elevation from 3 to 6 mM and that by the elevation from 6 to 12 mM.

produced by the elevation of extracellular K^+ from 1 to 3 mM. The relaxations were not inhibited by the application of 30 μM Ba^{2+} but by 10 μM ouabain (Fig. 6A). When extracellular K^+ was increased from 3 to 6 mM, K^+-induced relaxation was completely inhibited by Ba^{2+}. In superior mesenteric artery, the relaxation by elevation of extracellular K^+ from initial 3 to 6 mM was not inhibited by Ba^{2+}. When extracellular K^+ was elevated from initial 6 to 12 mM, cerebral arteries showed no or slight relaxation. These data indicate that in cerebral arteries, the elevation of extracellular K^+ from lower extracellular K^+ concentration evokes greater K^+-induced relaxation than the elevation of extracellular K^+ from higher extracellular K^+ concentration does.

When extracellular K^+ was elevated to higher concentration to induce the K^+-induced relaxation, the magnitude of relaxation was dependent on the initial K^+ concentration (Fig. 4B). When the extracellular K^+ was elevated from 6 to 14 mM by 2 mM increment, the tension of middle cerebral artery was not or slightly relaxed. However, when the extracellular K^+ was elevated from 1 or 3 mM to 14 mM by 2 or 3 mM, the tension of middle cerebral artery was markedly relaxed.

The role of endothelium on K^+-induced relaxation

As reported that there is inward rectifier K^+ channel in endothelial cells (Himmel et al, 1994; Pennefather & Decoursey, 1994), it could be suggested that endothelial cells might contribute $Ba2^+$-sensitive K^+-induced relaxation. In arteries with small diameter such as distal branch of superior mesenteric artery, it was quite difficult to get rid of endothelium without damage of underlying smooth muscle by rubbing with tungsten wire. Therefore, we tried to determine the role of endothelium-derived NO in K^+-induced relaxation by using nitro-L-arginine or NMMA (Fig. 7). After nitro-L-arginine (10^{-4} M) or NMMA (10^{-5} M) was pretreated for 30 minutes, superior mesenteric artery was contracted by the combined application of phenylephrine and histamine. With the elevation of extracellular K^+, the

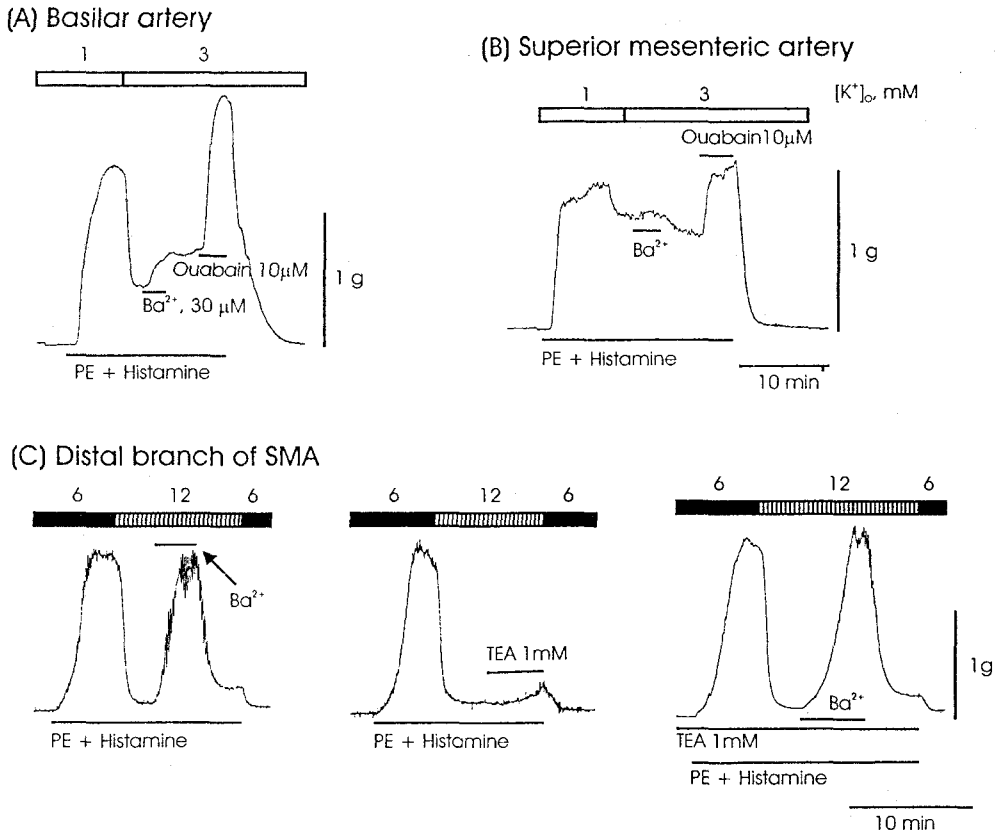

Fig. 6. Representative recordings showing the effects of ouabain (A and B) and TEA (C) on K^+-induced relaxation. 10 μM of ouabain inhibited K^+-induced relaxation completely, but 1 mM of TEA did not inhibit the relaxation.

artery was relaxed and the K^+-induced relaxation was not inhibited by the pretreatment with nitro-L-arginine or NMMA. In arteries with rather large diameter, such as proximal branch of superior mesenteric artery, it was possible to get rid of endothelium without damage of underlying smooth muscle by gentle rubbing. The arteries with endothelium and without endothelium were contracted by phenylephrine and histamine. The artery with endothelium was relaxed by the application of acetylcholine, whereas the artery without endothelium was not relaxed by the ACh application. The artery without endothelium was relaxed by the elevation of extracellular K^+ from initial 6 to 12 mM, and the relaxation was blocked by the application of 30 μM Ba^{2+}. These findings were quite similar to those recorded in the artery with endothelium. These data suggest that smooth muscle cells contribute K^+-induced relaxation.

DISCUSSION

This study confirmed the previous report that there are two components in the K^+-induced relaxation and firstly demonstrated that there are different mechanisms for the K^+-induced relaxation in various arteries. Although most of conduit arteries were not relaxed by the elevation of extracellular K^+, trunk of superior mesenteric artery and basilar artery were relaxed by the elevation. These data indicate that K^+-induced relaxation can be evoked in some of conduit arteries. In superior mesenteric artery, the greatest relaxation was evoked by the elevation of extracellular K^+ from initial 6 mM, the highest extracellular K^+ among the three experimental protocols, which was Ba^{2+}-sensitive relaxation. On the contrary, cerebral arteries showed slight or no relaxation by the elevation from initial 6 mM and were relaxed in the greatest magnitudes by the elevation of from initial 1 mM, the lowest extracellular K^+ among the three

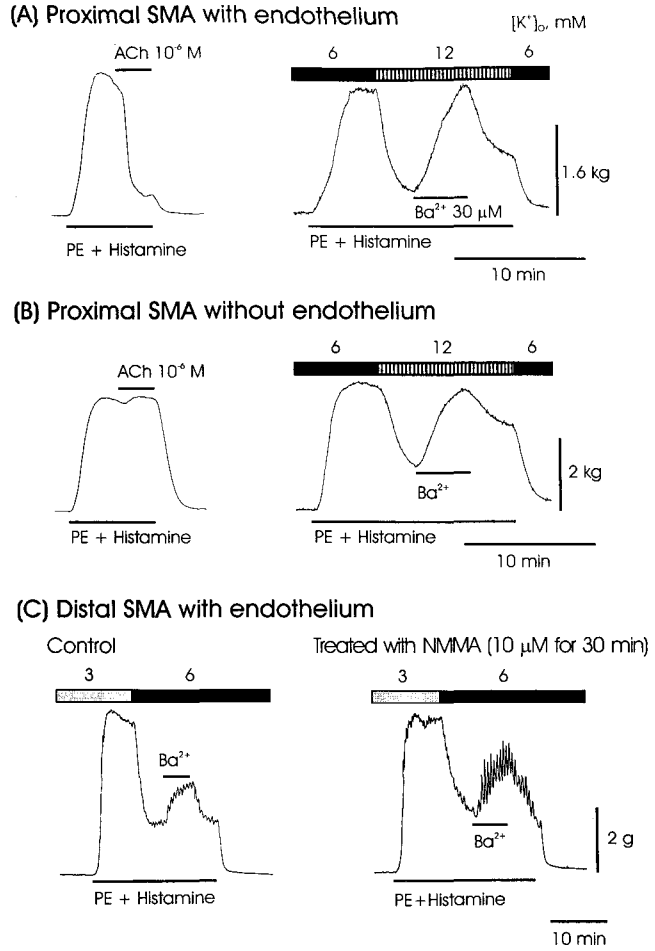

Fig. 7. Representative recordings showing the effect of denudation of endothelium (A and B) or NMMA (C) on K^+-induced relaxation. K^+-induced relaxation could be evoked even in the arterial ring without endothelium and the magnitude of the relaxation was not decreased by the pretreatment with 10 μM NMMA.

protocols, which was Ba^{2+}-insensitive relaxation. From these data, it could be suggested that there are different mechanisms for the K^+-induced relaxation between superior mesenteric artery and cerebral arteries.

In this study, K^+-induced relaxation has two components, which can be distinguished by the sensitivity to Ba^{2+}. At lower K^+ concentration (initial 1 mM), the relaxation induced by K^+ elevation was not blocked by the application of Ba^{2+}. At higher K^+ concentration (initial 6 mM), the relaxation was completely blocked by the application of Ba^{2+}. At the intermediate concentration (initial 3 mM), the effect of Ba^{2+} was dependent on the arteries tested. In the branches of superior mesenteric artery, Ba^{2+} had no effect, whereas Ba^{2+} inhibited K^+-induced relaxation completely in cerebral arteries. From these data, it could be suggested that there are two components, Ba^{2+}-sensitive and Ba^{2+}-insensitive ones, in K^+-induced relaxation. This finding is consistent with the finding by McCarron & Halpern (1990). However, they reported that the Ba^{2+}-insensitive relaxation, which was evoked at low K^+ concentration ($<$ 5 mM), is transient. In their report, the dilation at low K^+ concentration was followed by slow reconstriction and the tension was returned to initial level within 10 minutes. In the present study, all of the relaxations were not transient but persistent for more than 10 minutes.

K^+-induced relaxation can be evoked by the stimulation of Na^+-K^+ pump and/or by the activation of inward rectifier K^+ current (Webe & Bohr, 1978; Edwards et al, 1988; McCarron & Halpern, 1990). Considering that *Kd* for the activation by external K^+ is in the range of 1~2 mM (Whittam & Ager, 1964; Rang & Ritchie, 1968) and that the magnitude of the relaxation by the elevation of extracellular K^+ can be used as an indirect method to evaluate Na^+-K^+ pump activity (Webe & Bohr, 1978), Na^+-K^+ pump can be activated by the elevations of extracellular K^+ shown in the experimental protocols. Ba^{2+} did not inhibit Na^+-K^+ pump (Nelson et al, 1980) and the Ba^{2+}-insensitive relaxation was blocked by ouabain. These findings suggest that the Ba^{2+}- insensitive relaxation might be evoked by the stimulation of Na^+-K^+ pump. Compared with the Ba^{2+}-insensitive relaxation, which is evoked by the elevation of extracellular K^+ at lower concentration, Ba^{2+}-sensitive relaxation is evoked by the elevation of extracellular K^+ at higher concentration. As inward rectifier K^+ channels are blocked by 30 μM Ba^{2+} at concentration that inhibits K^+-induced relaxation, Ba^{2+}-sensitive relaxation is suggested to be evoked by the activation of inward rectifier K^+ current. These data are consistent with the findings by Edwards et al (1988) and by McCarron & Halpern (1990).

On the contrary to the suggestion, 10 μM of ouabain blocked not only Ba^{2+}-insenstive relaxation but also Ba^{2+}-sensitive relaxation. As Ba^{2+}-insensitive relaxation is evoked by the stimulation of Na^+-K^+ pump, the relaxation can be inhibited by blocking Na^+-K^+ pump with ouabain. However, the blocking mechanism for Ba^{2+}-sensitive relaxation by ouabain is uncertain. One of the possible mechanisms

was suggested by McCarron & Halpern (1990). Briefly, inward rectifier K^+ channels are very steeply voltage dependent, closing on depolarization, and ouabain depolarizes vascular smooth muscle. Consequently, ouabain could inhibit Ba^{2+}-sensitive relaxation indirectly by closing the inward rectifier K^+ channels through depolarizing membrane potential. But TEA, which also depolarizes vascular smooth muscle by blocking K^+ channels, did not block Ba^{2+}-insensitive relaxation at all. Therefore, it is still in doubt whether depolarization of membrane potential can inhibit Ba^{2+}-sensitive relaxation indirectly.

In basilar and middle cerebral artery, Ba^{2+}-sensitive relaxation was evoked by the elevation of extracellular K^+ from initial 3 to 6 mM and there was no relaxation by the elevation from initial 6 to 12 mM. However, in branches of superior mesenteric artery, K^+-induced relaxation was evoked by the elevation from initial 6 to 12 mM. The relaxation by elevation from initial 6 to 12 mM was blocked by Ba^{2+}, but Ba^{2+} did not block the relaxation by elevation from initial 3 to 6 mM. These data indicate that the inward rectifier channels in cerebral arteries are activated by the elevation of extracellular K^+ from initial 3 to 6 mM and those in superior mesenteric artery are activated by the elevation from initial 6 to 12 mM. Therefore, it could be suggested that the characteristics of inward rectifier K^+ channel in cerebral arteries are different from those in superior mesenteric artery.

Middle cerebral artery was markedly relaxed by the elevation of extracellular K^+ from initial 1 or 3 mM to 14 mM, but slightly relaxed by the elevation from initial 6 to 14 mM. Similar data were reported in basilar artery (Suh et al, 1998). These data indicate that the most important determinant of K^+-induced relaxation in cerebral arteries is initial K^+ concentration. Considering K^+ concentration of cerebrospinal fluid was reported to be 2.9 mM (Davson et al, 1987), the increase of extracellular K^+ will induce a profound effect on cerebrovascular blood flow via Ba^{2+}-sensitive component.

Although K^+-induced relaxation was not inhibited by the removal of endothelium or by the pretreatment with nitro-L-arginine, the possible involvement of endothelium is difficult to exclude. If endothelium plays a minor role in K^+-induced relaxation and smooth muscle cells play a major role, K^+-induced relaxation cannot be affected by the removal of endothelium or by the inhibition of NO production. Therefore, as K^+-induced relaxation was not inhibited by the removal of endothelium or by the inhibition of NO production, it could be suggested that K^+-induced relaxation is almost exclusively contributed by vascular smooth muscle, and if any, endothelium plays a minor role in the relaxation.

In conclusion, we provided the first evidence that there are different mechanisms for K^+-induced relaxation in various arteries. We demonstrated that extracellular K^+ concentration to evoke Ba^{2+}-sensitive K^+-induced relaxation in cerebral arteries is lower than that in superior mesenteric artery and the major determinant of K^+-induced relaxation in cerebral arteries is initial K^+ concentration. Comparative characterization of inward rectifier K^+ channels in superior mesenteric artery and cerebral artery is required to define more precisely the mechanisms for K^+-induced relaxation in the arteries. Our results are consistent with the hypothesis that there is a difference in the effect of extracellular K^+ elevation between the arteries in CSF and others.

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