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Short communication

Inhibitory actions of various vasorelaxants on the myogenic contraction induced by quick stretch studied in canine cerebral artery

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Abstract

Quick stretch at a rate of 10 cm/s with the amount of 30% of the initial muscle length (= 100%) produced a myogenic contraction in canine cerebral artery. The inhibitory actions of various vasorelaxants on the stretch-induced contraction were investigated. Ca^{2+} channel blockers (nicardipine, D-*cis*-diltiazem) inhibited the stretch-induced contraction by 50–60% at the concentrations which abolished high KCl-induced contraction. Inhibitions of the stretch-induced contraction by nitro-compounds (nitroglycerin, sodium nitroprusside) were about 50%. In contrast, inhibitions by the compounds which activate ATP-sensitive K^+ channels (cromakalim, nicorandil, pinacidil) of the myogenic contraction in response to quick stretch were only 20%. Papaverine totally abolished the stretch-induced contraction. It is likely that all the vasorelaxant compounds tested in the present study except papaverine are beneficial in the sense that they do not suppress the intrinsic myogenic contraction, which may be related to the autoregulation of local blood flow.

Keywords: Stretch-induced contraction; Cerebral artery; Ca^{2+} channel blocker; Nitro-compound; K^+ channel, ATP-sensitive; Blood flow

1. Introduction

Regulation of local blood flow in organs such as heart and brain is an important factor in the maintenance of their normal functions. Arterial blood flow regulation depends on the excitability and contractility of arterial smooth muscle cells. Chemical factors such as neurotransmitters, hormones and autacoids modulate the excitability and contractility of arterial smooth muscle cells. In addition to these chemical factors, mechanical deformation of vascular wall evoked by stretch, stress or stain also affects arterial smooth muscle excitability and contractility. The enhanced vascular tone produced by mechanical stimulation has been considered to be the basis of the myogenic mechanism of the regulation of local blood flow (Bayliss, 1902). Myogenic contraction of vascular smooth muscle is also related to the etiology of circulatory disorders, for instance, hypertension and vasospasm. We have shown that quick stretch, or dynamic stretch produced a delayed contraction in vascular beds isolated from brain, heart, kidney, and somatic periphery of various animal species (Nakayama, 1982; Nakayama et al., 1986, 1989; Tanaka and Nakayama, 1991; Tanaka et al., 1994a,b, 1997).

The vascular contraction produced by quick stretch is myogenic in nature because the vascular contraction in response to quick stretch is not affected by various pharmacological receptor antagonists, tetrodotoxin or removal of endothelium (Nakayama et al., 1989; Tanaka and Nakayama, 1991). In contrast, the vascular contraction produced by static stretch, i.e., slow stretch was endothelium-dependent in some blood vessels (Katusic et al., 1987; Nakayama et al., 1997). Myogenic contraction of arterial smooth muscle in response to quick stretch is greatly influenced by promoters and inhibitors of Ca^{2+} influx or by drugs which affect intracellular Ca^{2+} storage sites (Nakayama, 1982; Nakayama et al., 1986; Tanaka et al., 1994a,b), which implies a relevant role of intracellular free Ca^{2+} in the generation of stretch-induced contraction in vascular smooth muscle. However, there is little information available about the inhibitory actions of vasorelaxants on the stretch-induced contraction other than the drugs which influence the Ca^{2+} mobilization. In the present

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study, we examined the effects of various types of vasorelaxants on the myogenic contraction evoked by quick stretch in canine cerebral artery. The findings show that all the compounds except papaverine do not entirely suppress the myogenic contraction of cerebral artery induced by quick stretch.

2. Materials and methods

2.1. Preparations

Healthy mongrel dogs of either sex weighing 7–15 kg were used. Each animal was maintained on a diet of standard dog chow (Oriental Food, Funabashi, Japan) and looked after for at least 10 days before being used experimentally. The animals were anesthetized with pentobarbital sodium (30 mg/kg, i.v.) and exsanguinated by bleeding from the carotid arteries. A cylindrical segment of the basilar artery (2 cm long) was removed from the proximal portion near the communicating artery (Willis ring). The arteries were cleared of connective tissue and adventitia under a dissection microscope. Helical strips (width, 1 mm; length, 10 mm) about 1 mg in wet weight were prepared. Ring segments about 2 mm wide (0.5 mg in wet weight) were also prepared.

2.2. Mechanical measurement of stretch-induced contraction of artery preparations

Experimental details on stretch activation of the artery were given in earlier publications (Nakayama, 1982; Nakayama et al., 1986, 1989; Tanaka and Nakayama, 1991; Tanaka et al., 1994a,b, 1997). The length of the artery in helical strip was adjusted to 130% of its initial muscle length (= 100%: slack length). The artery was then quickly stretched with an electromagnetic puller which moved a force-transducer (TR-10, Tokyo Koki, Tokyo, Japan) upward. The degree and speed of quick stretch could be varied. Generally, the artery was quickly stretched with the amount of stretch equivalent to 30% of the slack length of the muscle preparation, which gave the total artery muscle length of 160% of the slack length. The rate of stretch was 10 cm/s with a 30-s duration of the stretch stimulation separated by 20-min intervals. Compliance of the transducer was about 2 mm/mN and was less than 1% of the initial muscle length when the artery was maximally contracted by 80 mM KCl or stretched up to 160% of its slack length. The magnitude of the active response to quick stretch was assessed quantitatively: the active mechanical response to quick stretch was obtained by subtracting the area under the passive increase in tension induced by repeated stretches in the medium without Ca^{2+} from the circumscribed area on the recording chart under the stretch-induced total tension increase. This was then divided by the wet weight of the artery. The unit of contractile activity was force × time (g × s) per wet weight of the artery.

Normal Tyrode's solution was continuously bubbled with 97% O_2—3% CO_2 to give a pH of 7.35 at a temperature of 35°C. The high KCl solution was made by substituting NaCl with equimolar KCl. Ca^{2+}-free Tyrode's solution was prepared by omitting Ca^{2+} from Normal Tyrode's solution and adding 0.2 mM EGTA.

2.3. Drugs

Drugs used in the present study and their sources were as follows: *O*,*O*′-bis(2-aminoethyl) ethyleneglycol-*N*,*N*,*N*′-*N*′-tetraacetic acid (EGTA) (Dojin, Kumamoto, Japan); nicardipine hydrochloride, D-*cis*-diltiazem, sodium nitroprusside (Sigma, St. Louis, MO, USA); nitroglycerin (Nippon Kayaku, Tokyo, Japan); cromakalim (Nihon Beecham, Tokyo, Japan); nicorandil (Chugai, Tokyo, Japan); pinacidil (Shionogi, Osaka, Japan); papaverine hydrochloride (Wako, Osaka, Japan). Nicardipine hydrochloride was dissolved in 100% ethanol at the concentration of 10^{-3} M and diluted with the solvent which has the following composition: ethanol:polyethyleneglycol 400:distilled water = 1:1:3 (v/v). Cromakalim was dissolved in 70% ethanol at the concentration of 10^{-2} M and diluted with distilled water. All other drugs were dissolved in distilled water. Molar concentrations in the bathing solution were given for all drugs used.

2.4. Statistical analysis

Data were expressed as the mean value ± S.E.M. Statistical analysis was carried out by means of one-way analysis of variance (ANOVA) followed by the Tukey's multiple comparison test. *P* values less than 0.05 were considered statistically significant.

3. Results

Fig. 1 shows the typical traces representing the inhibitory effects of nicardipine (10^{-7} M) (Fig. 1a) and nitroglycerin (10^{-5} M) (Fig. 1b) on the stretch-induced contraction of cerebral artery segments. The rate, the amount, and the duration of the quick stretch were 10 cm/s, 30% of the slack length (= 100%), and 30 s. Quick stretch of the artery segment produced an initial tension rise. This was soon followed by a decay of tension and then the subsequent delayed contraction. Normally, the delayed contraction in response to quick stretch began to appear 0.7–1.3 s after the completion of the stretch and the tension was maintained, or sometimes gradually decreased during the stretch period for 30 s. A rapid tension decrease was caused by the quick release, which was followed by, in some cases, a moderate tension increase, the so-called 'quick release-induced contraction'. However, in this case,

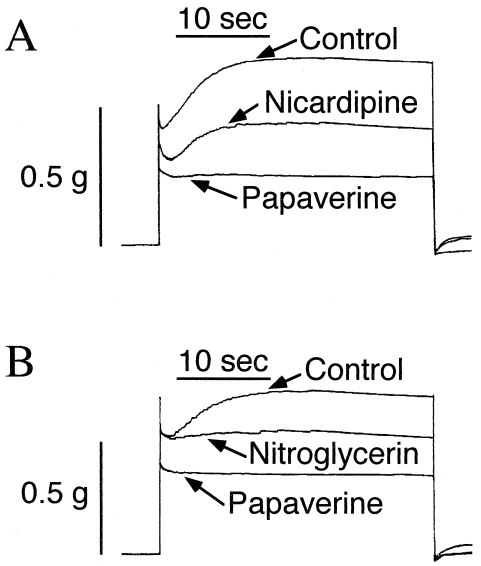

Fig. 1. Mechanical responses to quick stretch and inhibitory effects by vasorelaxants. Active tension was induced by quick stretch at a rate of 10 cm/s up to 160% from 130% of the initial muscle length (=100%) with the stimulation period of 30 s. The cerebral arterial smooth muscle was initially stretched to a standardized length, i.e., 130% of the initial length. Therefore, the total length during the stretch period reached 160% of the initial length. (A) Quick stretch was applied to an arterial segment in the absence and in the presence of nicardipine (10^{-7} M). Nicardipine was present in the bath solution for 60 min. At the end of experiment, stretch-induced contraction was totally eliminated in the presence of papaverine (10^{-4} M). (B) Quick stretch was applied to an arterial segment in the absence and in the presence of nitroglycerin (10^{-5} M). Nitroglycerin was present in the bath solution for 20 min. At the end of experiment, stretch-induced contraction was totally eliminated in the presence of papaverine (10^{-4} M).

reproducible responses were hardly obtainable. Until the next application of quick stretch, i.e., 20 min after the first application of the stretch, muscle tension returned to its basal level. Repeated stretches of the artery segment in the solution without Ca^{2+} or in the presence of 10^{-4} M papaverine (Fig. 1A and B) abolished the stretch-induced contraction.

Incubation of the artery segment in the presence of nicardipine (10^{-7} M) for 60 min suppressed the stretch-induced contraction by about 60% (Fig. 1a). Further incubation of the arterial segment for more than 60 min in the presence of nicardipine (10^{-7} M) did not suppress the stretch-induced contraction any more. This concentration of nicardipine (10^{-7} M) completely inhibited the high KCl (80 mM)-induced arterial contraction.

Incubation of the cerebral artery segment in the presence of nitroglycerin at 10^{-5} M for 20 min suppressed the stretch-induced contraction by about 50% (Fig. 1b). Concentrations of nitroglycerin higher than 10^{-5} M or further incubation more than 20 min did not suppress the stretch-induced contraction any more. For instance, the inhibition of the stretch-induced contraction by 10^{-4} M nitroglycerin was $49.4 \pm 8.7\%$ ($n = 3$).

Fig. 2 summarizes the inhibitory actions of the compounds tested on the stretch-induced contraction of cerebral artery segments. Ca^{2+} channel blockers (nicardipine, 10^{-7} M; D-*cis*-diltiazem, 10^{-5} M) inhibited the stretch-induced contraction by 50–60% ($55.4 \pm 6.7\%$ for nicardipine, $n = 4$; $52.5 \pm 2.1\%$ for D-*cis*-diltiazem, $n = 3$). These concentrations of Ca^{2+} channel blockers abolished high KCl (80 mM)-induced contraction: the inhibition of high KCl-induced contraction by 10^{-7} M nicardipine was $104.9 \pm 4.7\%$ ($n = 6$) and that by 10^{-5} M D-*cis*-diltiazem was $100.9 \pm 3.8\%$ ($n = 5$). Another L-type Ca^{2+} channel blocker, flunarizine, was tested on the stretch-induced contraction. The incubation of the cerebral arterial segment with 10^{-6} M flunarizine for 60 min inhibited the stretch-induced contraction by $53.0 \pm 3.7\%$ ($n = 5$). This concentration of flunarizine (10^{-6} M) inhibited the 80 mM KCl-induced contraction by $97.6 \pm 1.0\%$ ($n = 4$).

Nitro-compounds (nitroglycerin and sodium nitroprusside) suppressed the contraction of the arterial segment in response to quick stretch by 40–50% ($49.5 \pm 9.1\%$ for nitroglycerin, $n = 4$; $41.8 \pm 9.6\%$ for sodium nitroprusside, $n = 4$). The inhibitions of high KCl-induced contraction by these nitro-compounds were $31.2 \pm 3.0\%$ ($n = 5$) for 10^{-5} M nitroglycerin and $36.8 \pm 2.8\%$ ($n = 7$) for 10^{-5} M sodium nitroprusside, respectively.

Inhibition of the stretch-induced contraction by cromakalim (10^{-5} M), nicorandil (10^{-5} M), pinacidil (10^{-5} M), which activate ATP-sensitive K^+ (K_{ATP}) channels, were less than 30%: the inhibitions of stretch-induced contraction by these compounds were $6.8 \pm 4.6\%$ ($n = 3$) for 10^{-5} M cromakalim, $20.0 \pm 6.7\%$ ($n = 5$) for 10^{-5} M

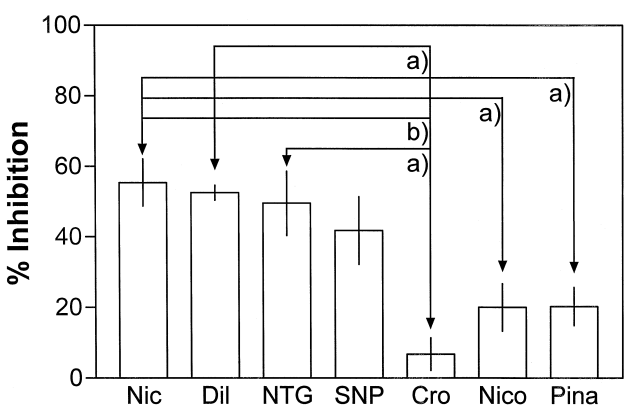

Fig. 2. Inhibitory effects of various vasorelaxants on the cerebral arterial contraction produced by quick stretch. The contractile activity of canine cerebral artery in response to stretch in the absence of test compounds was measured following the method described in Section 2. The inhibitory effects of test compounds were expressed as percent inhibition of the contractile activity in the absence of compounds. Cerebral arterial segments were incubated in the presence of each compounds for 20–60 min. Nic, nicardipine (10^{-7} M); Dil, D-*cis*-diltiazem (10^{-5} M); NTG, nitroglycerin (10^{-5} M); SNP, sodium nitroprusside (10^{-5} M); Cro, cromakalim (10^{-5} M); Nico, nicorandil (10^{-5} M); Pina, pinacidil (10^{-5} M). Bars represent standard error of means (S.E.M.). Statistical significance is indicated by (a) $P < 0.05$ and (b) $P < 0.01$.

nicorandil, and 20.3 ± 5.4% ($n = 4$) for 10^{-5} M pinacidil. The inhibition of KCl (80 mM)-induced contraction by 10^{-5} M cromakalim was 6.9 ± 3.4% ($n = 3$) and that by 10^{-5} M pinacidil was 10.3 ± 2.6% ($n = 3$). Papaverine (10^{-4} M) abolished both stretch-induced contraction and KCl (80 mM)-induced contraction.

To find whether there were significance differences in the inhibition by the various compounds, we analyzed these differences for stretch-induced contraction. There were no significance differences between the inhibition by Ca^{2+} channel blockers (10^{-6} M nicardipine and 10^{-5} M D-*cis*-diltiazem) and that by nitro-compounds (10^{-5} M nitroglycerin and 10^{-5} M sodium nitroprusside) against stretch-induced contraction. Ca^{2+} channel blockers, nicardipine (10^{-6} M) and D-*cis*-diltiazem (10^{-5} M) inhibited the stretch-induced contraction significantly more strongly than did a K_{ATP} opener, 10^{-5} M cromakalim (nicardipine vs. cromakalim, $P < 0.01$; D-*cis*-diltiazem vs. cromakalim, $P < 0.05$). The nicardipine-produced inhibition of stretch-induced contraction was also statistically significant in comparison with the inhibitions by other K_{ATP} openers (10^{-6} M nicardipine vs. 10^{-5} M nicorandil, $P < 0.05$; 10^{-6} M nicardipine vs. 10^{-5} M pinacidil, $P < 0.05$). There was a significance difference between the inhibition of stretch-induced contraction by 10^{-5} M nitroglycerin and that by 10^{-5} M cromakalim ($P < 0.05$).

4. Discussion

In the present study, we examined the inhibitory actions of various vasorelaxants on the cerebral arterial contraction produced by quick stretch. The rank order of the potency of the compounds to inhibit the stretch-induced contraction was as follows: papaverine > Ca^{2+} channel blockers > nitro-compounds ≫ ATP-sensitive K^+ (K_{ATP}) channel openers.

L-type Ca^{2+} channel blockers (nicardipine, D-*cis*-diltiazem, flunarizine) at the concentrations which abolished high KCl (80 mM)-induced contracture suppressed the stretch-induced contraction of canine cerebral artery by 50–60%. We previously showed that by use of fura-2, the inhibitions of stretch-induced contraction by Ca^{2+} channel blockers are accompanied by the same degree of inhibitions of cytosolic Ca^{2+} concentration ($[Ca^{2+}]_i$) changes (Nakayama and Tanaka, 1989). This finding indicates that Ca^{2+} influx from extracellular space through L-type voltage-gated Ca^{2+} channels is partly responsible for the occurrence of the myogenic contraction of cerebral arterial smooth muscle in response to stretch. However, the mechanisms underlying the activation of L-type voltage-gated Ca^{2+} channels by the stretch of vascular smooth muscles are not well understood at present. Membrane stretch has been reported to activate Ca^{2+} permeable cation channels in various types of vascular smooth muscles and cells (Hwa and Bevan, 1986; Christensen, 1987; Lansman et al., 1987; Laher et al., 1988; Yang and Sachs, 1989; Franco and Lansman, 1990; Hazama and Okada, 1990). Thus, increased influx of cation including Ca^{2+} by membrane stretch may cause membrane depolarization, which subsequently activates L-type voltage-gated Ca^{2+} channels. However, our unpublished observation shows that the cerebral arterial contraction produced by quick stretch was not affected by gadolinium (10^{-5} M), which was reported to inhibit stretch channels (Yang and Sachs, 1989; Franco and Lansman, 1990). Thus, it is unlikely that gadolinium-sensitive stretch channels are responsible for inducing the stretch-induced contraction in canine cerebral artery. The detailed mechanisms responsible for the activation of L-type voltage-gated Ca^{2+} channels following vascular smooth muscle stretch should be elucidated in the future.

Our present findings with Ca^{2+} channel blockers also indicate that vascular smooth muscle contraction by quick stretch can be generated even when the L-type voltage-gated Ca^{2+} channels in vascular smooth muscles cells are completely blocked by the Ca^{2+} channel blockers. With regard to the rest of the vascular contraction induced by stretch in the presence of Ca^{2+} channel blockers, our previous findings showed that inositol 1,4,5-trisphosphate (IP_3)-induced Ca^{2+} release mechanism is mainly responsible for the contraction (Tanaka et al., 1994a,b).

Nitro-compounds have been widely used for more than a century for the treatment of circulatory disorders such as coronary vasospasm (Yanagisawa et al., 1989). Nitroglycerin and sodium nitroprusside at the concentration of 10^{-5} M were found to inhibit the stretch-induced contraction by 40–50%. This concentration of nitroglycerin and sodium nitroprusside (10^{-5} M) suppressed 80 mM KCl-induced depolarizing contracture by 30–40%. Therefore, it may be possible that the inhibitions by nitro-compounds against stretch-induced contraction in cerebral artery are partly attributable to the blockade of Ca^{2+} influx through L-type Ca^{2+} channels of cerebral arterial smooth muscle cells (Karaki et al., 1984). However, we cannot rule out the possibility that nitro-compounds suppress the stretch-induced contraction by decreasing the sensitivity of contractile elements to Ca^{2+} without affecting Ca^{2+} influx through L-type Ca^{2+} channels (Yanagisawa et al., 1989), or inhibiting Ca^{2+} release enhanced by arterial stretch (Karaki et al., 1988).

Potassium channel openers such as cromakalim, pinacidil and nicorandil are known to activate ATP-sensitive K^+ (K_{ATP}) channels in a variety of tissues including cardiac and smooth muscles. The compounds which activate K_{ATP} channels are currently used or being developed as antihypertensive and bronchodilating drugs (Lawson, 1996), and thus are thought to be effective against the vascular smooth muscle contractions induced by arterial spasmogens. However, our present study showed that the inhibitions by the compounds which activate K_{ATP} channels of stretch-induced contraction were not so pro-

nounced. There seems to be two possibilities to explain this finding: (1) Quick stretch of the cerebral arterial segments may cause strong membrane depolarization of arterial smooth muscle cells. Thus, such potent membrane depolarization cannot be counteracted by hyperpolarization caused by K_{ATP} channel openers. (2) The density of K_{ATP} channels in canine cerebral arterial smooth muscle cells may not be so high as compared to that in other vascular smooth muscle cells. It is possible that weak inhibitions by K_{ATP} channels openers of stretch-induced contraction is attributable to the mechanisms other than the suppression of Ca^{2+} influx through L-type voltage-gated Ca^{2+} channels due to the membrane hyperpolarization produced by K_{ATP} channels openers (Yamashita et al., 1994).

Nicorandil (10^{-5} M) inhibited the stretch-induced contraction more strongly than cromakalim (10^{-5} M) though the difference of the inhibitions by these two compounds were not statistically significant ($p > 0.05$). Nicorandil indeed possesses K_{ATP} channel opener action, but, is a hybrid compound between nitrates and K_{ATP} channel openers (Taira, 1989; Christiaans and Timmerman, 1996). The greater effectiveness of nicorandil than cromakalim against stretch-induced contraction may be attributable to the nitrate-like action of nicorandil since nitroglycerin was far more effective in inhibiting stretch-induced contraction than cromakalim ($p < 0.05$). Actually, nicorandil-induced action as a nitrate but not as a K_{ATP} opener, was reported in isolated canine large coronary arteries preconstricted with a thromboxane A_2 analogue or 25 mM KCl (Satoh et al., 1991). It is also possible that mechanisms other than blockade of K_{ATP} channels such as the decrease in Ca^{2+} sensitization of contractile elements (Anabuki et al., 1990) is involved in the inhibitory effect of pinacidil (10^{-5} M) on the stretch-induced contraction of canine cerebral artery.

The augmented vascular tone due to the mechanical vascular deformation such as stretch has been the basis of the myogenic mechanism of the regulation of local blood flow (Bayliss, 1902). Ca^{2+} channel blockers, nitro-compounds and K_{ATP} channels openers are now widely used or currently developed as the drugs to treat circulatory disorders such as hypertension and vascular spasm. Our present findings show that these compounds have advantages in the sense that they do not entirely eliminate myogenic vascular responses which may be related to the autoregulation of local blood flow. The loss of myogenic arterial contraction might lead to the dysfunction of the organs in which constant blood supply should be always kept. Furthermore, non-selective dilatation by vasorelaxants of resistance arteries in healthy organs might decrease the blood supply to ischemic portions (steal phenomenon) or cause luxury circulation in healthy portions. Our present findings also imply that the vascular contraction induced by mechanical stimulation such as stretch may become an useful alternative of the vascular contraction induced by high KCl or spasmogens for the evaluation of newly developed compounds against circulatory disorders.

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