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Membrane potential of mesenteric artery from carvedilol-treated spontaneously hypertensive rats

Keiichi Shimamura [a,*], Fumiko Sekiguchi [b], Kyoko Matsuda [b], Kazuo Yamamoto [a], Shoko Tanaka [b], Satoru Sunano [b], Tomoko Shibutani [c], Hiroo Hashimoto [c], Makoto Tanaka [c]

[a] *Research Institute of Hypertension, Kinki University, 377-2 Ohno-higashi, Osaka-Sayama, Osaka 589, Japan*
[b] *Faculty of Pharmaceutical Sciences, Kinki University, 3-4-1 Kowakae, Higashi-osaka, Osaka 577, Japan*
[c] *Tokyo R&D Center, Daiichi Pharmaceutical Co., Ltd., 16-13 Kita-Kasai 1-Chome, Edogawa-ku, Tokyo 134, Japan*

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Abstract

The effects of chronic treatment of stroke-prone spontaneously hypertensive rats (SHRSP) with carvedilol, an antihypertensive agent which has both α- and β-adrenoceptor-blocking actions, on membrane potential and relaxation of mesenteric resistant artery were studied. Five-week old SHRSP were treated with carvedilol for three months. At 16 weeks, the resting membrane potential of arteries from carvedilol-treated SHRSP was more negative than that of arteries from untreated SHRSP. The magnitude of acetylcholine-induced hyperpolarization in arteries from carvedilol-treated SHRSP was not different from that of arteries from untreated SHRSP. In the presence of noradrenaline, the membrane potential of arteries from carvedilol-treated SHRSP was more negative than that of arteries from untreated SHRSP. The membrane potential of arteries from carvedilol-treated SHRSP in the presence of noradrenaline and acetylcholine was more negative than that of arteries from untreated SHRSP. The acetylcholine-induced relaxation in noradrenaline-precontracted preparations from carvedilol-treated SHRSP was greater than that in preparations from untreated SHRSP and was smaller than that in preparations from Wistar Kyoto rats. Scanning electronmicroscopy showed that carvedilol-treatment decreased the structural abnormalities of the endothelium of arteries from SHRSP. These results indicate that chronic carvedilol treatment made the membrane potential of smooth muscle more negative and improved endothelial function in the mesenteric artery of SHRSP, which may contribute to the antihypertensive effect of carvedilol. © 1998 Elsevier Science B.V.

Keywords: Carvedilol; Spontaneously hypertensive rat, stroke-prone (SHRSP); Mesenteric artery; Smooth muscle; Endothelium; Membrane potential; Noradrenaline

1. Introduction

The splanchnic circulation contributes to the control of systemic blood pressure, mainly by regulation of mesenteric blood flow (Kreulen and Keef, 1989). Therefore, the mesenteric small artery has been studied to gain an understanding of the peripheral resistance (Mulvany and Aalkjaer, 1990; Christensen and Mulvany, 1993).

One of the regulatory factors in the contraction of arterial smooth muscles is the membrane potential (Nelson et al., 1990) and the effects of neurohumoral substances on the membrane potential of the mesenteric artery have been examined (Kuriyama et al., 1995). Acetylcholine induces endothelium-dependent hyperpolarization in mesenteric arteries (Bolton et al., 1984) and the endothelium-dependent hyperpolarization contributes to relaxation in precontracted mesenteric arteries (Adeagbo and Triggle, 1993). It is also reported that the endothelium-dependent hyperpolarization produced by acetylcholine is reduced in mesenteric artery of hypertensive rats (Fujii et al., 1992).

In aorta, chronic antihypertensive treatment prevents functional abnormalities in smooth muscle and endothelium in hypertensive rats (Nigro et al., 1989; Clozel et al., 1990; Sunano et al., 1997). However, little information is available on the effect of chronic antihypertensive treatment on membrane electrical activity in small arteries. We are interested if chronic antihypertensive treatment changes the membrane potential of resistant arteries from genetically hypertensive rats.

Because hypotensive treatment via one mechanism activates compensatory processes that increase blood pressure,

* Corresponding author. Tel.: +81-723-660221/3317; fax: +81-723-660206.

antihypertensive treatment with a combination of drugs that act by different mechanisms has been proposed to be successful (Rahn, 1987). Recently, agents with multiple actions have been introduced for antihypertensive treatment (Prichard, 1992). Carvedilol is an α_1-adrenoceptor-blocking agent with β-adrenoceptor-blocking activity (Sponer et al., 1987; Hashimoto et al., 1988, 1991; Dunn et al., 1997). It has been reported that chronic carvedilol treatment reduces cardiac and renal tissue damage in stroke-prone spontaneously hypertensive rats (SHRSP) (Barone et al., 1996). In the present experiment, we used carvedilol for the preventative antihypertensive treatment of SHRSP.

2. Materials and methods

2.1. Animals

SHRSP and Wistar Kyoto rats (WKY) were originally obtained from Dr. Okamoto (Okamoto et al., 1974) and bred successively in our animal facility. The animals were kept under the conditions of 25°C, 50% humidity and the light and dark cycle of 12 h.

Male SHRSP and WKY were used in the present study. The systolic blood pressure of rats was measured every week by means of the tail-cuff method from 5 to 16 weeks of age. Prior to the measurement, the rats were warmed at 40°C for 5 min.

Treatment of SHRSP with carvedilol was started at the age of 5 weeks and continued until the rats were 16 weeks old. The drug was mixed with chow, changing the dose. The amount of drug administered was estimated from the weight of drug-mixed chow consumed by the rats. The dose was changed to keep the systolic blood pressure of the treated SHRSP below 200 mmHg. The dose was increased from 30 mg/kg per day (5–7 weeks old) to 60 mg/kg per day (8–9 weeks old) and to 120 mg/kg per day (10–16 weeks old). Further increases in the doses were not made because the animals lost their appetite and weight.

Untreated-SHRSP ($n = 30$), carvedilol-treated SHRSP ($n = 21$) and WKY ($n = 30$) were killed at the age of 16 weeks. For in vitro physiological studies, they were killed by bleeding from the neck under anesthesia with ethyl ether and mesenteric arteries were excised. Second-order branches of the mesenteric artery were used for membrane potential recording experiments or for mechanical recordings (10–20 rats, respectively).

2.2. Membrane potential recordings

Arterial preparations of 5 mm long were mounted in a 1 ml chamber with insect pins as previously reported (Shimamura et al., 1997). Special attention was paid so as not to stretch the preparation too much (Osol, 1995). The chamber was superfused continuously (3 ml/min) with aerated Tyrode's solution of the following composition (in mM): NaCl, 137; KCl, 5.4; $CaCl_2$, 2.0; $MgCl_2$, 1.0; $NaHCO_3$, 11.9; NaH_2PO_4, 0.4 and glucose, 5.6. The solution was kept at 37°C and aerated with a gas mixture of 95% O_2 and 5% CO_2. A glass capillary electrode (Hilgenberg 1.2 mm, Germany) was made by a puller (PA81, Narishige, Tokyo) and filled with 3 M KCl (tip resistance 40–80 MΩ). The electrode was impaled into the smooth muscle from the adventitial side. Membrane potential was monitored with an oscilloscope (VC-10, Nihon-kohden, Tokyo). The data were stored in a data recorder (RMG-5304, Nihon-kohden). Impalement was considered to have been successful when a sharp drop in potential and recovery of potential were observed at the beginning and end of the recordings.

2.3. Mechanical recordings

Ring preparations of 1.5 mm width were mounted in 5 ml organ bathes filled with the Tyrode's solution at 37°C and aerated with a gas mixture of 95% O_2 and 5% CO_2. High-K-Tyrode's solution was made by replacing NaCl in the solution with equimolar KCl. Two stainless wires (diameter 50 μm) were inserted in the lumen and the tension changes of the preparations were measured isometrically with a force-displacement transducer (Minebea, Karuizawa, Japan) under a stretch tension of 1 mN. Preparations were equilibrated for at least 30 min in the modified Tyrode's solution. The experiments were started after two successive high-K (50 mM) contractions were recorded. Preparations were contracted with 5×10^{-6} M of noradrenaline and acetylcholine was applied during the tonic contraction. At the end of experiments, the preparations were relaxed by addition of 10 μM verapamil and 100 μM papaverine and the changes in tension were measured from this relaxed level.

2.4. Scanning electron microscopy

The surface structure of the endothelium of mesenteric arteries was examined by scanning electron microscopy. In three rats from each group, the vena cava was cut under ethyl ether anesthesia and animals were perfused with the modified Tyrode's solution via the left ventricle at a pressure of 70 mmHg for 10 min. The perfusing solution was then changed to 2.5% glutaraldehyde in phosphate buffer (pH 7.4). The mesenteric artery was dissected and preparations were made from five second-order branches from each animal. Preparations were opened lengthwise and pinned on a Teflon sheet. The tissue was postfixed in 1% osmic acid solution in 0.1 M phosphate buffer at room temperature. The tissue was dehydrated through graded ethanol, critical point-dried in CO_2 and sputter-coated with

gold–palladium and examined under a scanning electron microscope (Hitachi S-800, Japan). After a general examination at low magnification, detail was examined, taking photographs of four different spots at a magnification of $\times 1000$ in each preparation.

2.5. Drugs

Drugs used in the present experiment were acetylcholine · HCl (Wako, Osaka, Japan), carvedilol (Daiichi, Tokyo), noradrenaline bitartrate (Sigma, St. Louis, MO), nitro-L-arginine (Aldrich, Milwaukee, USA), papaverine · HCl (Wako, Osaka, Japan), indomethacin (Wako) and verapamil · HCl (Ei-sai, Osaka, Japan).

2.6. Statistics

Obtained data are expressed as means ± S.E. with the number of animals in parentheses. The Levene test showed that the variance in each group was similar, so the parametric one-way analysis of variance (ANOVA) was used to assess differences among data. Post-hoc analysis was performed with Tukey's test (SPSS 7.5, SPSS, Chicago, USA). *P*-values lower than 0.05 were considered to be statistically significant.

3. Results

3.1. Body weight of the rats

The body weight of the rats at 16 weeks of age was 232 ± 9.1 g ($n = 30$) and 336 ± 5.3 g ($n = 30$) in untreated SHRSP and WKY, respectively. This difference was statistically significant ($P < 0.05$). The body weight of carvedilol-treated SHRSP was 249 ± 3.9 g ($n = 21$) and was not different from that of untreated SHRSP.

3.2. Blood pressure of animals

The blood pressure of untreated SHRSP aged 5 weeks was already significantly higher than that of WKY and rose steeply with age and reached a high plateau level at 12 weeks of age (Fig. 1). The blood pressure at the age of 16 weeks was 245.8 ± 2.9 mmHg ($n = 28$). The blood pressure of carvedilol-treated SHRSP was not different from that of untreated SHRSP at 5–7 weeks of age. It was lower than that of untreated SHRSP aged 8 weeks (3 weeks after starting the treatment) ($P < 0.05$). At age 16 weeks, the blood pressure of the carvedilol-treated SHRSP was 199.8 ± 1.9 mmHg ($n = 21$) and was lower than that of untreated SHRSP ($P < 0.05$). The increase in blood pressure of WKY with age was not prominent and the blood pressure at 16 weeks of age was 135.3 ± 1.2 mmHg ($n = 29$).

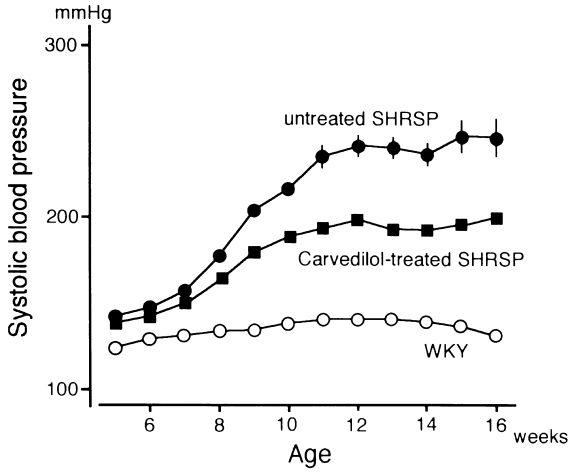

Fig. 1. Age-dependent changes in systolic blood pressure in untreated SHRSP (solid circle), carvedilol-treated SHRSP (solid square) and WKY (open circle). Mean ± S.E. for 21–29 rats. S.E.'s for WKY and carvedilol-treated SHRSP were smaller than a side or diameter of each symbol.

3.3. Membrane potential of smooth muscle in mesenteric artery

In normal Tyrode's solution, smooth muscle of mesenteric artery showed a stable membrane potential. The resting membrane potential of arteries from untreated SHRSP, carvedilol-treated SHRSP and WKY was -58 ± 0.9 mV ($n = 7$), -67 ± 1.8 mV ($n = 11$) and -64 ± 2.0 mV ($n = 13$), respectively. The membrane potential of arteries from carvedilol-treated SHRSP was more negative than that of arteries from untreated SHRSP ($P < 0.05$) and was comparable with that of arteries from WKY.

When acetylcholine was applied to the perfusate, the membrane potential hyperpolarized immediately and the maximal hyperpolarization was observed within 1 min (Fig. 2A). The amplitude of the acetylcholine-induced hyperpolarization of the membrane potential was concentration dependent. The hyperpolarization attained the maximum amplitude at 3×10^{-7} M in all of the groups (Fig. 2B). The maximal hyperpolarization induced by acetylcholine in arteries from carvedilol-treated SHRSP (8.4 ± 0.7 mV, $n = 11$) or untreated SHRSP (7.0 ± 1.6 mV, $n = 7$) was smaller than that in arteries from WKY (12 ± 0.6 mV, $n = 13$) ($P < 0.05$). The maximal hyperpolarization induced by acetylcholine in arteries from carvedilol-treated SHRSP was not different from that in arteries from untreated SHRSP. However, in the presence of acetylcholine 3×10^{-7} M, the membrane potential of preparations from carvedilol-treated SHRSP (-75.1 ± 2.2 mV, $n = 11$) was more negative than that of preparations from untreated SHRSP (-66.4 ± 1.5 mV, $n = 7$) ($P < 0.05$) and was comparable to that of preparation from WKY (-76.0 ± 1.6 mV, $n = 13$).

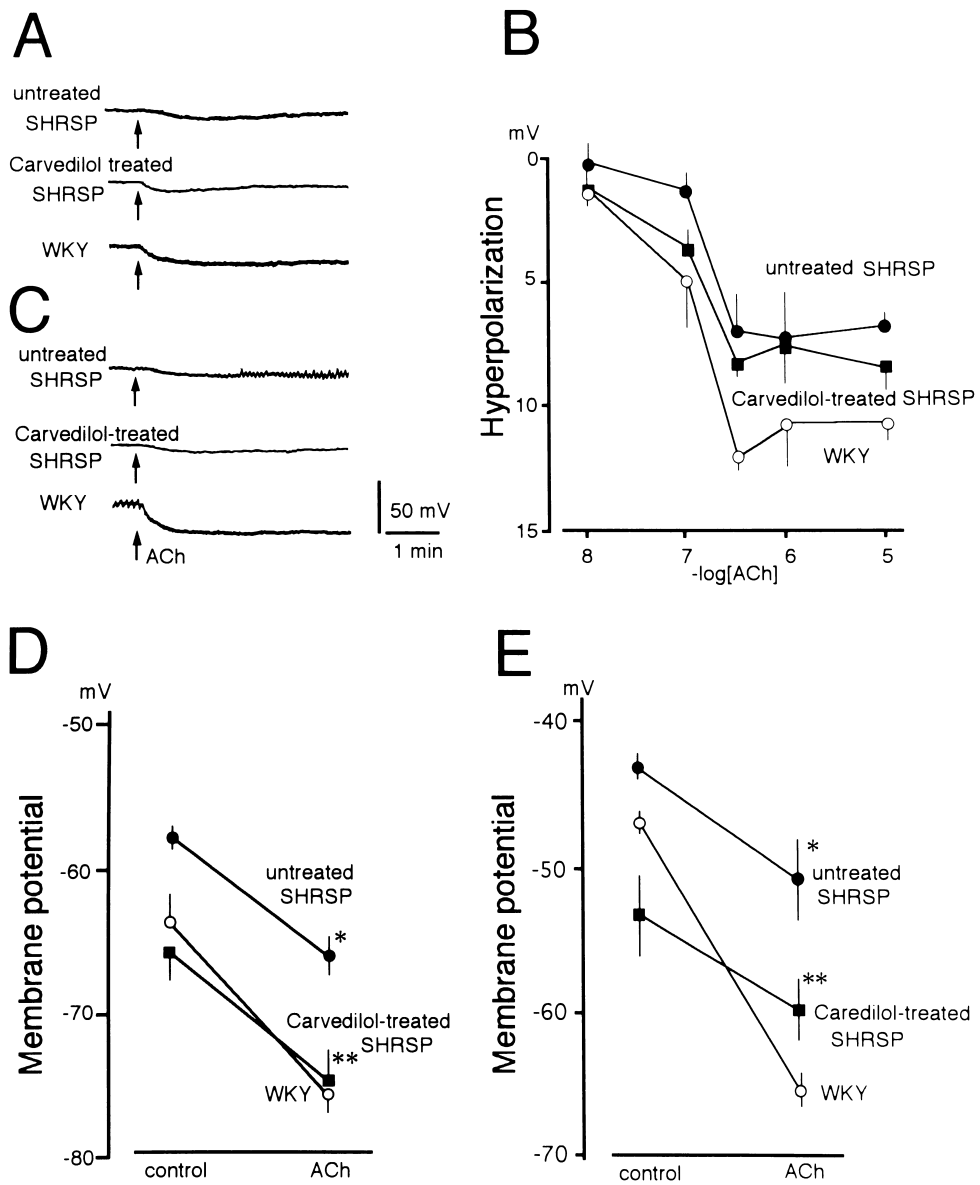

Fig. 2. Smooth muscle membrane potential recordings in the mesenteric arteries from untreated SHRSP, carvedilol-treated SHRSP and WKY. (A) Typical recording traces of smooth muscle membrane potential in mesenteric arteries from 16-week old rats in normal Tyrode's solution. From top to bottom; untreated SHRSP, carvedilol-treated SHRSP and WKY. Resting membrane potential was -57, -60 and -70 mV, respectively. Acetylcholine 3×10^{-7} M was applied at each arrow. Vertical and horizontal calibrations are the same as (C). (B) A concentration–response curve for acetylcholine-induced hyperpolarization in rat mesenteric arteries in normal Tyrode's solution. Untreated SHRSP (solid circle), carvedilol-treated SHRSP (solid square) and WKY (open circle). Mean $\pm$ S.E. for 5–13 rats. (C) Typical recording traces of smooth muscle membrane potential in mesenteric arteries from 16-week old rats in the presence of noradrenaline 5×10^{-6} M. From top to bottom; untreated SHRSP, carvedilol-treated SHRSP and WKY. Membrane potential before acetylcholine application was -44, -48 and -46 mV, respectively. Acetylcholine 3×10^{-7} M was applied after each arrow. (D) Summary of membrane potential before (control) and after application of acetylcholine 3×10^{-7} M (ACh) in the normal Tyrode's solution. Untreated SHRSP (solid circle), carvedilol-treated SHRSP (solid square) and WKY (open circle). Mean $\pm$ S.E. for 7–13 rats. Asterisks indicate significant difference from WKY (*) or from untreated SHRSP (**) in the presence of 3×10^{-7} M acetylcholine. (E) Summary of membrane potential before (control) and after application of acetylcholine 3×10^{-7} M (ACh) in the presence of noradrenaline 5×10^{-6} M. Symbols are same as in (D). Mean $\pm$ S.E. for 8–9 rats.

When noradrenaline 5×10^{-6} M was applied, depolarization of the membrane potential was observed. The membrane potential of preparations from untreated SHRSP, carvedilol-treated SHRSP and WKY in the presence of noradrenaline 5×10^{-6} M was -43 ± 0.9 mV ($n = 8$), -53 ± 2.8 mV ($n = 9$) and -48 ± 1.0 mV ($n = 8$), respectively. The membrane potential of arteries from carvedilol-treated SHRSP in the presence of noradrenaline 5×10^{-6} M was more negative than that of arteries from untreated SHRSP ($P < 0.05$). In the presence of noradrenaline, acetylcholine 3×10^{-7} M hyperpolarized the membrane of arteries from untreated SHRSP, carvedilol-

treated SHRSP and WKY (Fig. 2C) by 9.7 ± 3.4 mV ($n = 8$), 6.6 ± 1.3 mV ($n = 9$) and 17.8 ± 1.3 mV ($n = 8$), respectively. There was no difference in the magnitude of hyperpolarization between arteries from carvedilol-treated SHRSP and untreated SHRSP. In the presence of acetylcholine 3×10^{-7} M, the membrane potential of preparations from carvedilol-treated SHRSP was -60.0 ± 2.7 mV ($n = 9$) and more negative than that of preparations from untreated SHRSP (-50.7 ± 3.6 mV, $n = 8$) ($P < 0.05$). The membrane potential before and after acetylcholine 3×10^{-7} M application in the absence or presence of noradrenaline 5×10^{-6} M is summarized in Fig. 2(D) and (E), respectively.

To study the mechanism underlying the less negative membrane potential in SHRSP preparations, the membrane potential was recorded in the presence of indomethacin (10^{-5} M) and nitro-L-arginine (10^{-4} M). Noradrenaline (5×10^{-6} M) depolarized the membrane potential to -60.3 ± 2.1 mV ($n = 5$) and -42.7 ± 1.4 mV ($n = 5$) in preparations from WKY and SHRSP, respectively ($P < 0.05$). Acetylcholine (3×10^{-7} M) hyperpolarized the membrane by 16.6 ± 1.7 mV ($n = 5$) and 11.6 ± 1.3 mV ($n = 5$) in preparations from WKY and SHRSP, respectively. The membrane potential in the presence of acetylcholine was -77.0 ± 1.3 mV ($n = 5$) and -54.4 ± 1.7 mV ($n = 5$) in preparations from WKY and SHRSP, respectively. The magnitude of hyperpolarization in preparations from SHRSP was smaller than preparations from WKY ($P < 0.05$) and the membrane potential in the presence of acetylcholine was less negative in SHRSP preparations ($P < 0.05$).

3.4. Endothelium-dependent relaxation

Endothelium-dependent relaxation was examined by applying acetylcholine to preparations precontracted with noradrenaline at a submaximal concentration (5×10^{-6} M). Preparations from untreated SHRSP were relaxed by acetylcholine dose-dependently up to 10^{-7} M and then tended to contract again as the concentration of acetylcholine increased to 10^{-4} M. In WKY, the relaxation increased dose-dependently up to 10^{-7} M and no contraction was observed until 10^{-4} M. The acetylcholine-induced relaxation in preparations from carvedilol-treated SHRSP was greater than that in preparations from untreated SHRSP ($P < 0.05$) when the acetylcholine concentration was higher than 10^{-8} M (Fig. 3).

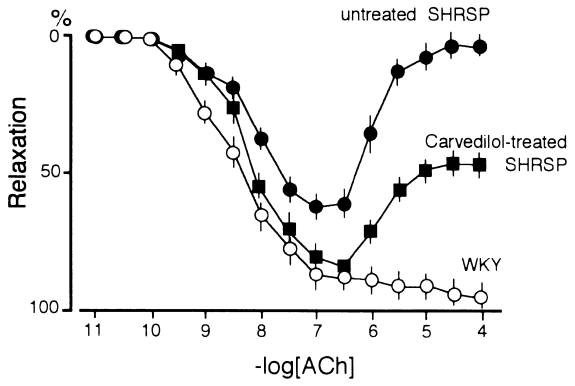

Fig. 3. A dose–response curve for acetylcholine-induced relaxation in rat mesenteric artery contracted by noradrenaline 5×10^{-6} M. Untreated SHRSP (solid circle), carvedilol-treated SHRSP (solid square) and WKY (open circle). Mean ± S.E. for 14–15 rats.

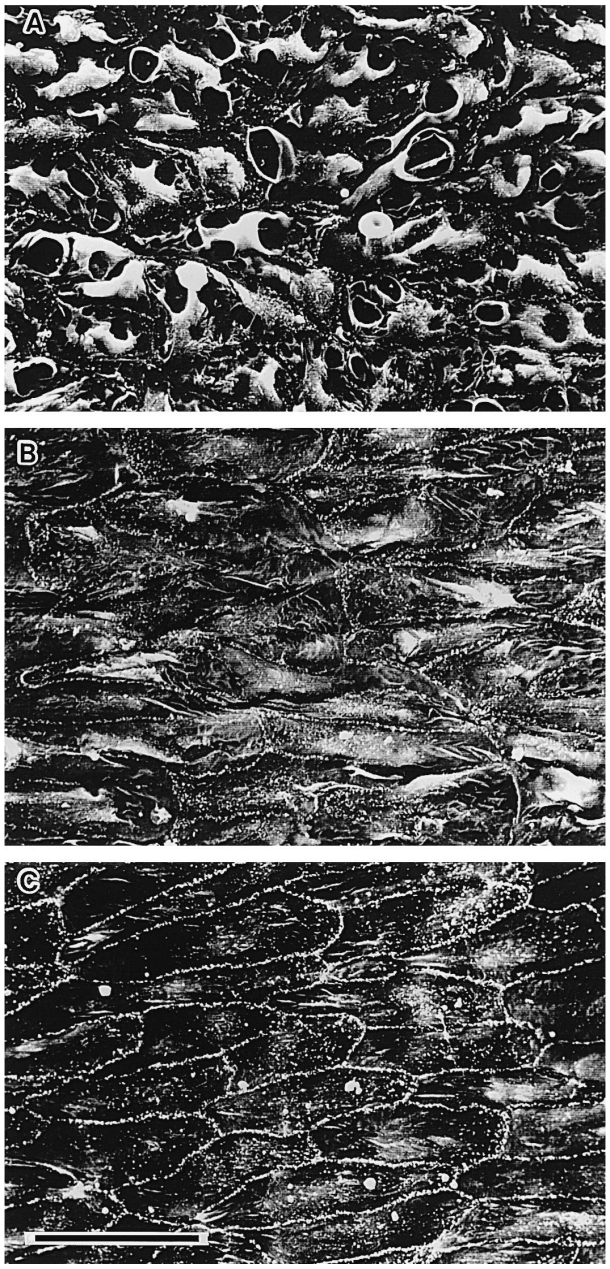

Fig. 4. Scanning electron-micrographs of the endothelial surface of mesenteric arteries from untreated SHRSP (A), carvedilol-treated SHRSP (B) and WKY (C). The calibration bar in the micrograph of WKY (C) indicates 30 μm length in (A), (B) and (C). Note the rough surface with crater formation in untreated SHRSP (A).

3.5. Structural changes of endothelium

Scanning electron microscopy showed that the endothelial surface of mesenteric arteries from untreated SHRSP was irregular and rough, and protrusions toward the lumen and crater formation were often observed. Treatment with carvedilol attenuated these abnormal changes and kept the surface relatively flat and smooth (Fig. 4). Mesenteric arteries from WKY showed a well-organized flat pavement pattern of endothelial cells.

4. Discussion

4.1. Membrane potential of mesenteric artery

The present study demonstrated that the membrane potential of smooth muscle cells in a second-order branch of mesenteric artery from SHRSP is less negative than that from WKY, as has been previously reported in main branch of the mesenteric artery (Fujii et al., 1992). The mechanism underling the difference in the membrane potential has not been clarified yet and little information is, therefore, available about the effect of chronic antihypertensive treatment on the membrane potential. Since the membrane potential of the smooth muscle of SHRSP mesenteric artery changed to a more negative level, close to that of WKY mesenteric artery, after treatment with carvedilol, the change in hypertensive arteries is secondary to the hypertension or related to carvedilol-sensitive mechanisms. As the membrane potential of the vascular smooth muscle cells in the arteries of hypertensive rats was less negative, contractions mediated by electromechanical coupling would be more easily induced in hypertensive rats (Cheung, 1989). In addition, a less negative resting membrane potential enhances the increase in $[Ca]_i$ through the inositol 1,4,5-trisphosphate-mediated mechanism and facilitates contraction (Ganitkevich and Isenberg, 1993).

It is reported that carvedilol inhibits the norepinephrine-induced depolarization and nerve-mediated slow depolarization by its postsynaptic α-adrenoceptor blocking action. It also inhibits the isoproterenol-induced increase in amplitude of excitatory junction potentials by its presynaptic β-adrenoceptor-blocking action (Seki et al., 1988). However, it did not change the resting membrane potential of arterial smooth muscle when it was applied acutely in vitro. In the present experiment, it was shown that the membrane potential of the smooth muscle of mesenteric arteries from SHRSP recovered to a level close to that of arteries from WKY after chronic treatment with carvedilol. The mechanism of the recovery, however, remains uncertain in the present experiment.

The application of acetylcholine hyperpolarized the smooth muscle membrane of arteries from both WKY and SHRSP. This hyperpolarization has been shown to be mediated by endothelium-derived hyperpolarizing factor (EDHF) and potassium channels (Hashitani and Suzuki, 1997). Although we can not exclude the possibility that nitric oxide contributed to the hyperpolarization, it has been shown that the hyperpolarization elicited by acetylcholine is not mediated by nitric oxide in rat small artery (Garland and McPherson, 1992).

The amplitude of the hyperpolarization elicited by acetylcholine in preparations from untreated SHRSP was significantly smaller than that of preparation from WKY. A similar difference was reported previously for first-order branch of mesenteric arteries from hypertensive rats (Fujii et al., 1992). In that study, the reduction of the hyperpolarization was attributed to the reduced release of EDHF, since the hyperpolarization elicited by a K^+ channel activator was not altered. The hyperpolarization was not changed by cyclooxygenase inhibition in hypertensive mesenteric artery, indicating that endothelium-derived contracting factor, which is involved in the impairment of the endothelium-dependent relaxation in hypertensive rats (Watt and Thurston, 1989), is not involved in the hyperpolarization.

Treatment of SHRSP with carvedilol did not change the amplitude of the acetylcholine-induced hyperpolarization. However, the hyperpolarized membrane of preparations from carvedilol-treated SHRSP had a more negative potential than that of preparations from untreated SHRSP, due to the more negative resting membrane potential.

Noradrenaline 5×10^{-6} M depolarized the membrane to a similar extent in preparations from SHRSP and WKY as reported previously (Fujii et al., 1992). The membrane potential of preparations from SHRSP in the presence of noradrenaline was less negative than that of preparations from WKY. The difference was also observed in the presence of nitro-L-arginine and indomethacin, indicating that nitric oxide or cyclooxygenase products are not involved in the difference. Noradrenaline depolarized the membrane less in preparations from carvedilol-treated SHRSP, possibly due to its α-adrenoceptor blocking action. In the presence of noradrenaline, the differences in the magnitude of acetylcholine-induced hyperpolarization between preparations from WKY and untreated SHRSP became more prominent. This may be due to the depolarized membrane potential elicited by noradrenarine, which increased the driving force for potassium ion efflux and hyperpolarization. The more negative membrane potential in the presence of noradrenaline and acetylcholine in the preparations from carvedilol-treated SHRSP would explain the greater relaxation of the mesenteric artery described below.

4.2. Relaxation by acetylcholine in mesenteric artery

The acetylcholine-induced relaxation of the noradrenaline-induced contraction of preparations from untreated SHRSP was decreased when compared with that of preparations from WKY. The reduced relaxation of hypertensive

mesenteric artery has been explained by an increased release of contractile substances, which are is sensitive to blockage of the cyclooxygenase pathway of the arachidonic acid cascade (Watt and Thurston, 1989). However, a reduced release of relaxing substances (endothelium-derived relaxing factor (EDRF) and EDHF) might also contribute to the decrease in relaxation. Changes in membrane hyperpolarization may also contribute to the relaxation. Hyperpolarization of the membrane relaxes smooth muscle by reducing Ca-influx through voltage-dependent channels (Garland et al., 1995). In addition, IP_3-mediated contraction of smooth muscle has been reported to be inhibited by membrane hyperpolarization (Itoh et al., 1992). Thus, reduced hyperpolarization, observed under the same conditions as used in the mechanical experiment, may be involved in the impairment of the relaxation in preparations from untreated SHRSP and the increased hyperpolarization of preparations from carvedilol-treated SHRSP could enhance the endothelium-dependent relaxation.

Treatment with carvedilol increased the resting membrane potential of SHRSP mesenteric artery to the level of WKY artery. Although the amplitude of the hyperpolarization produced by acetylcholine was not restored, the membrane potential during acetylcholine-induced hyperpolarization was similar to that elicited in preparations from WKY. This would contribute to the relaxation of the preparation.

4.3. Morphological changes in the endothelial surface

The endothelial surface of untreated SHRSP mesenteric artery was rough, as demonstrated by scanning electron microscopy. It is possible that the release of EDRF and EDHF is reduced and the release of contracting substances is increased in the abnormal endothelium. A similar abnormality has been reported in aorta from hypertensive rats, and these endothelial structural changes were prevented by chronic antihypertensive treatment (Clozel et al., 1990; Sunano et al., 1993). In the present study, it was shown that treatment with carvedilol prevented the structural damage in mesenteric artery endothelium. Protection from high pressure could prevent structural damage of endothelium in the mesenteric artery of SHRSP. The protective mechanism of carvedilol was not defined in the present study. Carvedilol has been shown to have a local anesthetic action (Seki et al., 1988) and an antioxidant action (Yue et al., 1992). It may also be possible that its protective action was mediated by chronic blockade of a sympathomimetic effect.

In conclusion, chronic treatment of hypertensive rats with carvedilol shifts the resting membrane potential and the membrane potential hyperpolarized by acetylcholine to a more negative potential in mesenteric resistance arteries. The treatment also increased the acetylcholine-induced relaxation. These changes may be beneficial in the antihypertensive effect of the drug.

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