Kor J Physiol (1996) 30(1), 21~31

Effect of Blood Pressure on the Endothelium-Dependent Contraction in Rat Aorta

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=ABSTRACT=

To investigate the mechanisms of increased endothelium-dependent contraction by acetylcholine in hypertensive rats, the relationship between endothelium-dependent contraction by acetylcholine and blood pressure was studied in spontaneously hypertensive rats (SHR), one-kidney, one clip Goldblatt hypertension (1K,1C-GBH) rats, and Wistar-Kyoto rats (WKY). SHR were treated orally with enalapril or nicardipine in order to prevent development of hypertension or suppress the developed hypertension. 1K,1C-GBH rats were made by renal artery stenosis with contralateral nephrectomy in 8 week-WKY.

1. Endothelium-dependent contractions by acetylcholine (10^{-6}~10^{-5} M) in SHR were significantly greater than those in WKY.

2. Chronic treatment with enalapril or nicardipine reduced the endothelium-dependent contraction in SHR

3. The degree of reduction of endothelium-dependent contraction was greater in SHR which was prevented from developing hypertension than in SHR of which high blood pressure was suppressed.

4. In aortic rings from 1K,1C-GBH rats, endothelium-dependent contractions by acetylcholine were augmented as compared with WKY.

5. There is good relationship between the value of blood pressure and magnitude of endothelium-dependent contraction.

Thus, it is suggested that increased endothelium-dependent contraction in hypertensive rats may be due to the high blood pressure and endothelium-dependent contraction may not be a cause of the initiation of hypertension in SHR.

Key Words: Blood pressure, Endothelium-dependent contration, Hypertension, Vascular endothelium

INTRODUCTION

It is well known that acetylcholine causes endothelium-dependent vasorelaxation in several vessels of normotensive animals. These vasorelaxation was due to release of endothelium-derived relaxing factor (EDRF). Soon after endothelium-dependent relaxation was discovered, observations were reported that the presence of endothelial cells augmented rather than inhibited contractile responses of certain blood vessels (Luscher & Vanhoutte, 1990). This was an indication that endothelium might also produce contracting factor under certain conditions. Endothelium-dependent vasoconstriction can be stimulated by naturally occurring substances (e.g.

acetylcholine, arachidonic acid, norepinephrine, prostaglandin H_2, thrombin), pharmacological agents (e.g. calcium ionophores, nicotine, high K^+), physical forces (stretch, pressure), and hypoxia. The nature of the endothelium-derived contracting factor (EDCF) has not been identified so far. However, it appears to be an unstable product of cyclooxygenase that stimulates thromboxane A_2/prostaglandin H_2 receptors on vascular smooth muscle (Auch-Schwelk et al, 1989, 1990; Kato et al, 1990).

Chronic hypertension is associated with structural (De Chastonay et al, 1983; Peach & Loeb, 1987) and functional changes of the vascular endothelium (Lockette et al, 1986; Luscher & Vanhoutte, 1986; Mayhan et al, 1987; Luscher et al, 1988; Tesfamariam & Halpern, 1988). Acetylcholine causes the simultaneous release of EDRF and EDCF in aorta from spontaneously hypertensive rats (SHR) (Luscher & Vanhouttte, 1986; Luscher et al, 1986). The concomitant release of EDCF from SHR aorta leads to reduced endothelium-dependent relaxations when compared with aorta from Wistar-Kyoto (WKY) rats (Luscher & Vanhouttte, 1986). In the aorta of hypertensive rats, antihypertensive treatment improves endothelium-dependent relaxation, indicating that endothelial dysfunction in hypertension is reversible (Luscher et al, 1987). Elevation of intraluminal pressure in a perfused artery evokes vasoconstriction, which can be prevented by removal of the endothelium (Rubanyi, 1988). Bioassay studies have demonstrated that pressure-induced endothelium-dependent contraction in feline cerebral arteries mediated diffusible factors (Harder et al, 1989). Therefore, it is possible that the reason of greater endothelium-dependent contraction in SHR may be due to a secondary effect by increase in blood pressure.

Above reports give us the possibility that chronic exposure of aortas to high blood pressure cause the endothelial dysfunction and increased endothelium-dependent contraction by acetylcholine is due to a secondary change by an increase of blood pressure in hypertensive animals. Therefore, the present study was designed to investigate the effect of blood pressure on endothelium-dependent contraction by acetylcholine in the aortas from hypertensive and normotensive rats.

METHODS

Animals

All experiments were performed on male 16~20 weeks old spontaneously hypertensive rats (SHR) and Wistar-Kyoto (WKY) rats. To evaluate the effect of prevention of the development of hypertension on endothelium dependent contraction in SHR, 6 week-old SHR received oral dosage of nicardipine (120 mg/kg/day), a dihydropyridine calcium antagonist, or enalapril (30 mg/kg/day), an angiotensin converting enzyme inhibitor, for 10 weeks. To evaluate the effect of suppression of hypertension on endothelium dependent contraction in SHR with established hypertension, 15 week-old SHR received oral dosage of nicardipine (120 mg/kg/day) or enalapril (30 mg/kg/day) for 5 weeks. Administrations of enalapril or nicardipine were stopped 72~96 hours prior to experiment to avoid direct effect of those drugs. To evaluate the effect of high blood pressure on endothelium-dependent contraction in normotensive rats, 8 week-old WKY rats received surgery to become one-kidney one clip Goldblatt hypertension (1K, 1C-GBH) rats. Rats were anesthetized with ether during operation. Then left renal artery was ligated with silk threads, where stainless steel wire (0.3 mm in diameter) was initially positioned with thread and later gently removed; and the contralateral kidney was surgically removed.

Measurement of the blood pressure (BP)

The systolic blood pressure of the rats was monitored weekly using the tail-cuff method for indirect blood pressure measurement. The rats were

pre-warmed for 10 minutes in rat holder by placing them on a hot plate with its surface temperature of 35°C. Since the rats have been preconditioned to the BP measurement procedure, they became sedated within 10 minutes of being restrained in the rat holder. The cuff of 15 mm in width was used and was placed at the base of the rat tail. A electro-sphygmomanometer (PE-300, Narco-Biosystems, Houston, Texas, USA) was used to keep the various parameters such as inflation and deflation rates and systolic blood pressure was monitored. For each rat, three consecutive readings were taken and averaged to obtain the individual blood pressure.

Measurements of isometric tension on isolated aortic rings

The rats were decapitated, thoracic aorta was quickly isolated and adhering adventitia and remaining fat were removed under a stereoscopic microscope. The aorta was left to recover for 2 hours at room temperature. The aorta was then carefully cut into rings (3~4 mm wide). The aortic rings were then mounted vertically between stainless hooks in a thermostatically controlled organ bath containing 50 ml of the Tris-buffered Tyrode's solution containing (mM): NaCl 158, KCl 4, $CaCl_2$ 2, $MgCl_2$ 1, Glucose 6, and Tris 5 (pH 7,4 at 35°C). Organ bath solution was maintained at 35 ℃ and continuously bubbled with 100% O_2. The hook anchoring the upper end of the rings were connected to the lever of a force transducer (F-60, Narco-Bio system, Houston, Texas, USA) and the rings were suspended under a tension of 2 g. Each preparation was allowed to equilibrate for at least one hour. Isometric tension was recorded on a strip chart recorder (Coles Parmer Instrument Co, Chicago, Illinois, USA).

The removal of endothelium from aortic rings was done by gently rubbing the intimal surface with a cotton ball. And successful removal of the endothelium was confirmed later by the inability of acetylcholine (10^{-6} M) to induce relaxation.

Statistical analysis

Differences in various parameter were compared by using Student's t-tests procedure. Correlation between blood pressure and endothelium-dependent contraction was analyzed by a pearson correlation analysis using the statistical analysis system (SAS). P values of less than 0.05 were considered to be statistically significant.

Drugs

The following drugs were used: acetylcholine, norepinephrine and L-nitroarginine methyl ester were purchased from Sigma Chemicals Company. Enalapril and nicardipine were donated by Choong-Wae pharmaceutical company (Daejeon, Korea) and Dong-A pharmaceutical company (Daejeon, Korea). Nicardipine was dissolved in 30% polyethylene glycol (Fluka). All concentrations are expressed as final molar (M) bath concentrations.

RESULTS

Blood pressure and body weight

Systolic blood pressure (SBP) was higher in SHR than in WKY through the entire observation period from 6 to 20 weeks (Fig. 1). SBP increased with age in each strain. However, the rate of increase of SBP of SHR was greater than that of WKY. After 8 weeks, SBP of SHR began to rise and reached a plateau at 12 weeks of age. At 20 weeks, SBP of SHR and WKY were 200±5.2 mmHg and 127.0± 3.4 mmHg, respectively (Fig. 1).

Development of hypertension was prevented by chronic antihypertensive treatment with enalapril or nicardipine in young SHR (Fig. 1). SBP of 16 week-old SHR, treated with antihypertensive drug from 6 weeks of age, were 110±4.2 mmHg (with enalapril) and 141±6.7 mmHg (with nicardipine). A reduction of SBP of SHR treated with enalapril or nicardipine persisted for at least 3 days after drugs were withdrawn. In established hypertension, hyper-

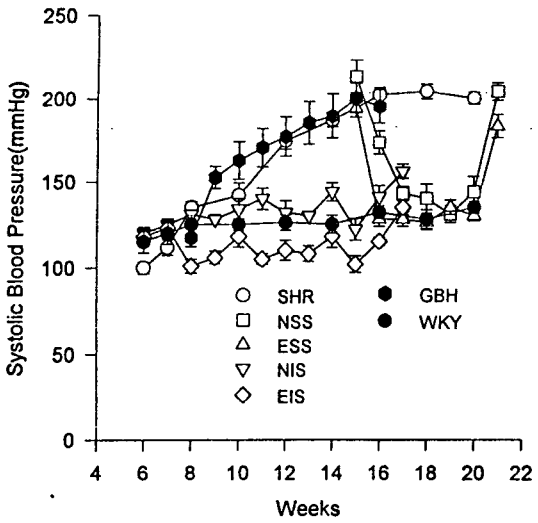

*Fig. 1. Changes of systolic blood pressure in spontaneously hypertensive rats (SHR), normotensive Wistar-Kyoto rats (WKY) and one-kidney, one-clip Goldblatt hypertensive rats (GBH). NSS indicates SHR treated with nicardipine from 15 weeks to 20 weeks; NIS, SHR treated with nicardipine from 6 weeks to 16 weeks; ESS, SHR treated with enalapril from 15 weeks to 20 weeks; EIS, SHR treated with enalapril from 6 weeks to 16 weeks. Data are given as mean±SEM obtained from 5 ~10 animals. * Blood pressure was measured in conscious rats by the tail-cuff method*

tension was markedly suppressed by antihypertensive treatment with enalapril or nicardipine. SBP of 20 week-old SHR, treated with antihypertensive drug from 15 weeks of age, were 130±3.2 mmHg (with enalapril) and 144±7.9 mmHg (with nicardipine). A reduction of SBP of SHR treated with enalapril or nicardipine did not persist, that is, SBP was immediately increased after drugs were withdrawn. SBP of 20 week-old SHR were 183± 7.0 mmHg (with enalapril) and 194±5.7 mmHg (with nicardipine) after withdrawal of antihypertensive drug for 4 days.

In 1K, 1C-GBH rats, SBP was sharply increased for 4 weeks after operation and then reached plateau after next 4 weeks. SBP of 1K,1C-GBH at 10, 12, 14, 16 weeks were 170±11.6, 185.0±13.1, 200.0± 8.9, 195.1±10.3 mmHg, respectively, which were significantly greater than those of WKY (Fig. 1). The body weights of each strains of rats at various ages are shown in Table 1. Body weights of untreated SHR and WKY were 303.8±6.2, 292.0±5.8g, respectively, which were not significantly different between both strains. Body weights of SHR treated with enalapril or nicardipine from old age (15 weeks of age) were not significantly different from those of untreated SHR. However, body weights of SHR treated with enalapril or nicardipine from young age (6 weeks of age) were significantly lower than those

Table 1. Body weights in the several groups of spontaneously hypertensive rats and Wistar- Kyoto rats

Groups	Body weight (g)	Groups	Body weight (g)
SHR groups		WKY groups	
SHR(n=10)	303.8±6.2	WKY (n=6)	292.0±5.8
NSS(n=9)	319.3±11.4	1K,1C-GBH (n=6)	251.7±15.4†
NIS (n=7)	202.1±14.7†		
ESS (n=5)	282.3±10.4		
EIS (n=5)	255.6±9.8†		

SHR indicates spontaneously hypertensive rats; WKY, Wistar-Kyoto rats; 1K,1C-GBH, one-kidney, one-clip Goldblatt hypertensive rats; NSS, SHR treated with nicardipine from 15 weeks to 20 weeks; NIS, SHR treated with nicardipine from 6 weeks to 16 weeks; ESS, SHR treated with enalapril from 15 weeks to 20 weeks; EIS, SHR treated with enalapril from 6 weeks to 16 weeks. Data are given as mean±SEM. † P< 0.05 vs untreated SHR; ‡P<0.05 vs untreated WKY

of untreated SHR ($p<0.05$). Body weights of 1K, 1C-GBH rats were also significantly lower than those of WKY ($p<0.05$).

Endothelium-dependent contraction

To study endothelium-dependent contraction in several groups, the rings with intact endothelium were pretreated with 10^{-4} M L-nitroarginine methyl ester (L-NAME), an inhibitor of nitric oxide synthase, and cumulative doses of acetylcholine (ACh) (10^{-7} to 10^{-5} M) were added. Aortic rings were pretreated with L-NAME for 20 minutes before acetylcholine administration. In some rings, L-NAME caused contractions by itself. When the L-NAME-induced contractions exceeded more than 0.5g, the data were discarded to keep basal tone levels comparable between experimental groups. To confirm that ACh-induced contraction after pretreatment with L-NAME was endothelium-dependent contraction, ACh-induced contraction in the aortic rings with intact endothelium was compared with that without endothelium. As shown in Fig. 2 A,B, when the endothelium was removed from the aortic rings, ACh did not induce any contraction, indicating that the contractile response was an endothelium-dependent response (Fig. 2 A, B).

When the production of EDRF was inhibited by L-NAME, ACh induced endothelium-dependent contraction in the aortic rings of SHR and WKY in a concentration-dependent manner ($10^{-7}\sim10^{-5}$ M) (Fig. 3). The amplitude of endothelium-dependent contraction was expressed as percentage of norepinephrine (NE) (10^{-6}M)-induced contraction in both strains. Endothelium-dependent contraction in

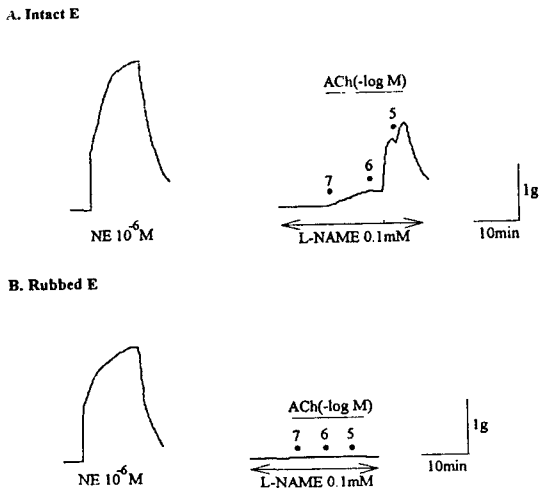

Fig. 2. Typical tracings of acetylcholine (ACh)-induced contraction in the aorta with endothelium (Intact E, A) or without endothelium (Rubbed R, B) of spontaneously hypertensive rats. After the aortic rings with intact endothelium were pretreated with 0.1 mM L-nitroarginine methyl ester (L-NAME), an inhibitor of nitric oxide synthase, and cumulative doses of acetylcholine (10-7 to 10-5 M) was added.

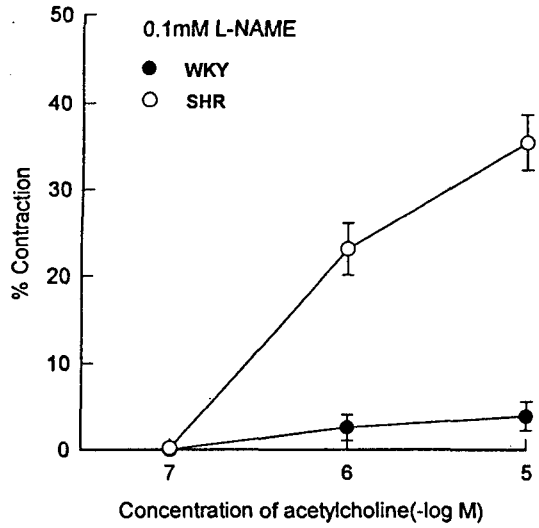

Fig. 3. Endothelium-dependent contraction induced by acetylcholine in the aortic rings with intact endothelium of spontaneously hypertensive rats (SHR) and Wistar-Kyoto rats (WKY). After the aortic rings with intact endothelium were pretreated with 10^{-4} M L-nitroarginine methyl ester (L-NAME), an inhibitor of nitric oxide synthase, and cumulative doses of acetylcholine ($10^{-7}\sim10^{-5}$ M) were added. Data are given as mean±SEM. % Contraction was expressed as percent contraction of norepinephrine (10^{-6} M)-induced contraction.

the aortic rings of SHR was significantly greater than that of WKY over the concentration range (10^{-6} ~ 10^{-5} M) (2.1±1.3 vs 23.1±2.3% at 10^{-6} M, 3.1± 1.5 vs 34.2±2.6% at 10^{-5} M).

Effect of prevention of hypertension on the endothelium-dependent contraction

To prevent the rat from developing hypertension, SHR was treated orally with enalapril or nicardipine from early age, 6 weeks of age, to 16 weeks. At 6 weeks of age, blood pressure of SHR did not rise. Therefore, this group of SHR have never been exposed to high blood pressure until we did experiment. We compared endothelium-dependent contraction of untreated SHR to that of enalapril- or nicardipine-treated SHR. Endothelium-dependent contraction by acetylcholine in the aortic rings of SHR treated with enalapril (13.0±4.4%) or nicardipine (11.9±4.1%) was significantly lesser than that of untreated SHR (34.2±2.6%) at 10^{-6} M of acetylcholine ($p<0.001$). Magnitude of endothelium-dependent contraction of treated SHR was found to lie between the contractions of age-matched untreated SHR and WKY (Fig. 4). The reduction of endothelium-dependent contraction in enalapril-treated SHR was not significantly different from that in nicardipine-treated SHR ($p>0.2$).

Effect of suppression of hypertension in established SHR on the endothelium-dependent contraction

To evaluate the effect of suppression of hypertension in established SHR on the endothelium-dependent contraction, we compared endothelium-dependent contraction of untreated SHR to that of high blood pressure-suppressed SHR. To suppress the established hypertension, the rats were treated orally with enalapril or nicardipine from old age, 15 weeks of age, to 20 weeks. At 15 weeks of age, blood pressure of SHR reached the maximal pressure. Therefore, the rats were exposed to high blood pressure for long time before treatment of antihypertensive drug. Endothelium-dependent contraction induced by acetylcholine in the aortic rings of SHR treated with enalapril (19.5±2.9%) or nicardipine (21.5±3.0%) was significantly lesser than that of untreated SHR (34.2±2.6%) at 10^{-6} M of acetylcholine ($p<0.05$). The magnitude of endothelium-dependent contraction was found to lie between the contractions of age-matched untreated SHR and WKY (Fig. 5). However, the degree of reduction of endothelium-dependent contraction in SHR which was prevented from developing hypertension was greater than in SHR of which high blood pressure was suppressed. There was no significant difference in reduction of endothelial

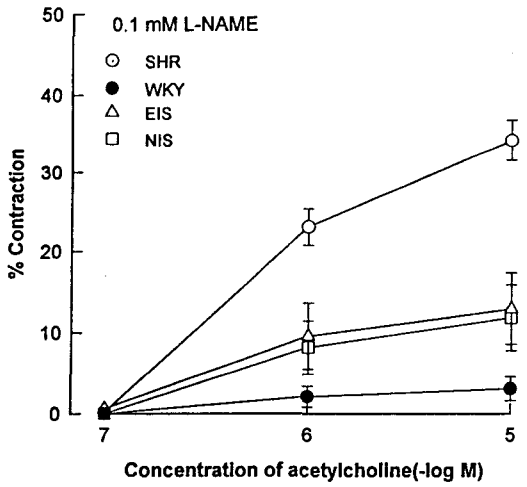

Fig. 4. Endothelium-dependent contraction induced by acetylcholine in the aortic rings with intact endothelium of untreated spontaneously hypertensive rats (SHR) and SHR treated with enalapril or nicardipine. After the aortic rings with intact endothelium were pretreated with 10^{-4} M L-nitroarginine methyl ester (L-NAME), an inhibitor of nitric oxide synthase, and cumulative doses of acetylcholine (10^{-7}~10^{-5} M) were added. EIS; SHR treated with enalapril from 6 weeks to 16 weeks, NIS; SHR treated with nicardipine from 6 weeks to 16 weeks. Data are given as mean±SEM. % Contraction was expressed as percent contraction of norepinephrine (10^{-6} M)-induced contraction.

dependent contraction between enalapril treated-SHR and nicardipine-treated SHR ($p>0.2$).

Effect of secondary hypertension in WKY on the endothelium-dependent contraction

To evaluate the effect of secondary hypertension in WKY on the endothelium-dependent contraction, endothelium-dependent contraction by acetylcholine was studied in the aortic rings of 1K,1C-GBH rats and WKY. Endothelium-dependent contraction induced by acetylcholine in aortic rings in 1K,1C-GBH rats ($26.2\pm6.5\%$) was significantly greater than that of WKY ($3.1\pm1.5\%$) at 10^{-6} M of acetylcholine (Fig. 6).

The relationship between blood pressure and the degree of endothelium-dependent contraction

In order to evaluate the relationship between blood pressure and the degree of endothelium-dependent contraction, the degree of endothelium-dependent contraction was plotted as a function of SBP. Except groups of which high blood pressure was suppressed by antihypertensive treatment in established SHR, all groups of rats was included in this Fig. 7. Coefficient of correlation between systolic blood pressure and the degree of endothelium-dependent contraction is 0.66 ($p<0.001$). The value is close to the regression line of the

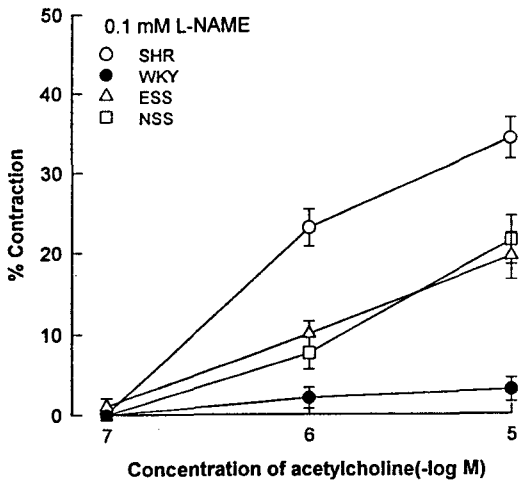

Fig. 5. Endothelium-dependent contraction induced by acetylcholine in the aortic rings with intact endothelium of untreated spontaneously hypertensive rats (SHR) and SHR treated with enalapril or nicardipine. After the aortic rings with intact endothelium were pretreated with 10^{-4} M L-nitroarginine methyl ester (L-NAME), an inhibitor of nitric oxide synthase, and cumulative doses of acetylcholine ($10^{-7}\sim10^{-5}$ M) were added. ESS; SHR treated with enalapril from 15 weeks to 20 weeks, NSS; SHR treated with nicardipine from 15 weeks to 20 weeks. Data are given as mean±SEM. % Contraction was expressed as percent contraction of norepinephrine (10^{-6} M)-induced contraction.

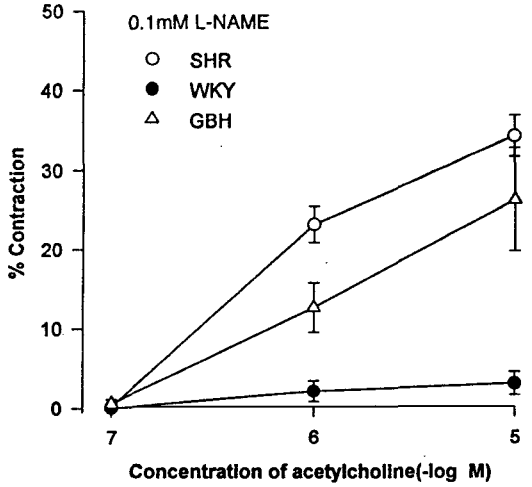

Fig. 6. Endothelium-dependent contraction induced by acetylcholine in the aortic rings with intact endothelium of Wistar-Kyoto rats (WKY) and one-kidney one clip Goldblatt hypertensive rats (GBH). After the aortic rings with intact endothelium were pretreated with 10^{-4} M L-nitroarginine methyl ester (L-NAME), an inhibitor of nitric oxide synthase, and cumulative doses of acetylcholine (10^{-7} to 10^{-5} M) were added. Data are given as mean±SEM. % Contraction was expressed as percent contraction of norepinephrine (10^{-6}M)-induced contraction.

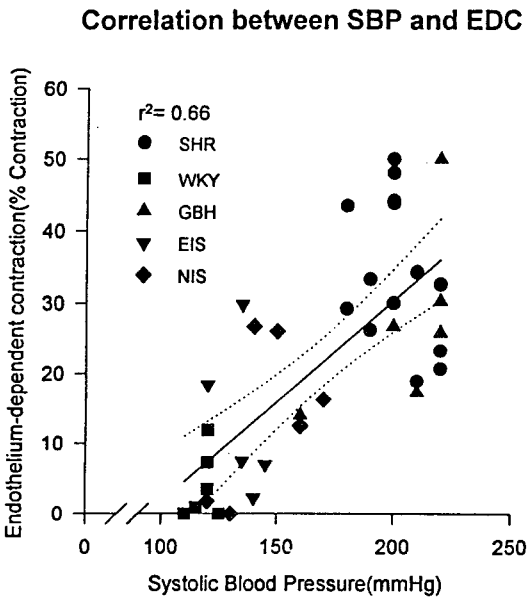

Fig. 7. Correlation between systolic blood pressure and endothelium-dependent relaxation in the several groups. Endothelium-dependent contraction was induced by 10^{-5} M acetylcholine and expressed as percentage of the contraction induced by 10^{-6} M norepinephrine. Regression lines were also indicated with area of 99% reliability. Coefficient of correlation was 0.66 ($p<0.001$).

relationship between blood pressure and the degree of endothelium-dependent contraction.

DISCUSSION

Systolic blood pressure increased gradually during the growth of both WKY and SHR. However the rate of increase of systolic blood pressure in SHR was greater than that of WKY. After 8 weeks of age, systolic blood pressure of SHR was significantly greater than that of WKY. This finding suggested that expression of hypertension might be started in about 8 weeks, although the mechanism of expression of hypertension was still unknown. In the present study, the development of hypertension was prevented by chronic antihypertensive treatment in young SHR as it has been reported previously (Ferrone & Antonaccio, 1979; Freslon & Giodicelli, 1983; Hefti et al, 1986; Harrap et al, 1990). A reduction of systolic blood pressure of SHR treated with enalapril or nicardipine persisted for at least 3 days after drugs was withdrawn. In established hypertensive rat, blood pressure was markedly suppressed by antihypertensive treatment with enalapril or nicardipine. However, a reduction of systolic blood pressure did not persist, that is, systolic blood pressure was immediately increased after drugs were withdrawn. The implication of this observation is that antihypertensive treatment must be initiated before the full expression of hypertension in SHR in order to achieve the maximal effect with antihypertensive treatment.

It was known that one-kidney, one-clip Goldblatt hypertension was considered a non-renin-dependent model of hypertension because it had normal or low level of circulating renin (Freeman et al, 1979; Leener & Myers, 1984) and hypertension was caused by fluid retention (Ledingham & Cohen, 1963; Bianchi et al, 1970) and the increase of peripheral resistance (Ledingham & Cohen, 1963; Guyton et al, 1974). In 1K, 1C-GBH rats, SBP was sharply increased for 4 weeks after surgical operation and then reached plateau after next 4 weeks. SBP in 16 week-old 1K, 1C-GBH rats was similar to that in untreated SHR. Therefore, we choose 1K,1C-GBH rats for evaluation the effect of high blood pressure on endothelium-dependent contraction.

Body weight of untreated SHR and WKY was not significantly different. However, body weights of SHR treated with enalapril or nicardipine from early age were significantly lower than that of untreated SHR. Those of 1K, 1C-GBH rats were also significant lower than those of WKY. The lower body weight of SHR which was prevented from developing hypertension and 1K, 1C-GBH rats may have been due to psychological stresses during drug administration or Goldblatt procedure and/or the disturbances in their calcium metabolism (in the

case of nicardipine).

Endothelial cells modulate underlying vascular smooth muscle tone by releasing EDRF and EDCF (Furchgott, 1983; Gryglewski et al, 1988; Furchgott & Vanhoutte, 1989; Vanhoutte, 1989). Chronic hypertension is associated with functional and structural change in vascular endothelium. Endothelial dependent relaxation is decreased in hypertensive rat. The decrease in endothelium-dependent relaxation in SHR aorta was not due to the change in the production of cGMP, a mediator of endothelium-dependent vasorelaxation (Rapoport & Murad, 1983; Furchgott, 1984), or to the change in the response of smooth muscle to EDRF. We previously reported that the vasorelaxation by 8-bromo-cGMP in the aortic rings of SHR was similar to that of WKY rats (Park et al, 1994). Similar results have been reported in the SHR aorta (Shirasaki et al, 1986) and in stroke-prone SHR mesenteric artery (Tesfamariam & Halpern, 1988). Under the condition that endothelium-dependent contractile response was inhibited by cyclooxygenase (Luscher & Vanhoutte, 1986) and thromboxane A_2/endoperoxide receptor antagonists in SHR, endothelium-dependent relaxation in SHR was not so decreased compared with that in WKY. Therefore, it is suggested that impaired endothelial function in SHR may have been the result from concomitant release of EDCF.

Endothelium-dependent relaxation to acetylcholine, which was depressed in SHR, as described in several previous studies, was dramatically improved after antihypertensive treatment (Luscher et al, 1987; Bossaller et al, 1992; Rubanyi et al, 1993). The relationship between the systolic blood pressure and the endothelium-dependent relaxation by acetylcholine has been reported in the WKY, SHR, stroke prone SHR, and malignant SHR aorta (Sunano et al, 1989). It showed that the decrease in endothelium-dependent relaxation correlated well with the elevation of blood pressure. However, the effect of chronic antihypertensive therapy in SHR and the effect of secondary hypertension in WKY on the endothelium-dependent contraction by acetylcholine are not still clear. Iwama et al (1992) investigated the relation between the blood pressure and endothelium-dependent contraction by using different age group of SHR and reported that there was close relation between the endothelium-dependent contraction and blood pressure. They are speculating that some genetic factor may promote the increase of both EDCF and blood pressure simultaneously. In any case, increased production of EDCF may be a deteriorating factor in increasing blood pressure. However, whether the increase in production of EDCF is a cause or a results of hypertension is of interest, but this cannot be determined from previous report alone.

In the present study, when the production of EDRF was inhibited by L-NAME, ACh induced endothelium-dependent contraction in aortic rings from both strains in a concentration-dependent manner. The aortic rings from SHR developed significantly greater contraction than those from WKY. Chronic treatment of antihypertensive drug restored the endothelial function. Antihypertensive drugs reduced the rise in arterial blood pressure and led to an identical improvement of endothelial function. This finding suggested that the development of endothelium-dependent contraction in the aorta of SHR may be due to secondary change of endothelial function by hypertension. If endothelium-dependent contraction in SHR was due to genetic factor not due to high blood pressure, this contraction must not be induced in secondary hypertension, such of 1K,1C-GBH rats and increased endothelium-dependent contraction in SHR must not be restored by chronic treatment of antihypertensive drug. Endothelium-dependent contraction by acetylcholine in aortic rings of 1K,1C-GBH rats was significantly greater than that of WKY. This finding suggested that endothelium-dependent contraction in the aorta of 1K,1C-GBH rats may be induced by chronic exposure to high blood pressure. The degree of

inhibition of endothelium-dependent contraction by antihypertensive treatment in young SHR was significantly greater than that in old SHR with established hypertension. It may be due to already impaired endothelial function by the chronic exposure to high blood pressure for about 8 weeks. Therefore, blood pressure must be the most important determinant in the endothelial function.

Thus it can be concluded that endothelium-dependent contraction can not be the cause of the initiation of hypertension, although it may be able to accelerate the elevation of blood pressure. Endothelium-dependent contraction in hypertensive rats may be due to high blood pressure.

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