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Long-Term Treatment with Enalapril Depresses Endothelin and Neuropeptide Y-induced Vasoactive Action in Spontaneously Hypertensive Rats

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ABSTRACT

This study was designed to evaluate the responses of cardiovascular system to endothelin (ET) and neuropeptide Y (NPY) in 12 week-old SHR treated with or without enalapril (ENP) for 6 weeks.

The diastolic blood pressure and heart rate were lower in ENP-treated SHR than in control. The pressor response to intravenous, but not intracerebroventricular, ET or NPY was attenuated by ENP treatment. The chronotropic action induced by electrical stimulation was attenuated by ENP or ET. The negative chronotropic action of ET was blocked by yohimbine.

The increase in aortic tension induced by electrical field stimulation (EFS) was depressed in ENP-treated group as compared with non-treated group, and enhanced by ET, but not NPY, in the non-treated group. The ET-induced increase in tension was enhanced by removal of endothelium in the control group but not in ENP-treated group.

The plasma concentration of norepinephrine and ET-induced increase in concentration of norepinephrine and epinephrine in plasma were decreased in ENP-treated group.

These results suggest that preventive effect of enalapril on the development of hypertension may result from depressing vasoactive action of endothelin and neuropeptide Y, and sympathetic neurotransmission at peripheral nervous system.

Key Words: Enalapril, Endothelin, Neuropeptide Y, Spontaneously Hypertensive Rats, Cardiovascular Responses

Abbreviations: ET, endothelin; NPY, neuropeptide Y; SHR, spontaneously hypertensive rats; ENP, enalapril; EFS, electrical field stimulation.

INTRODUCTION

It has been well known that angiotensin II raises blood pressure via direct constriction of the smooth muscle of the arteriole and facilitates the release of catecholamines by sympathetic nerve stimulation (Hughes and Roth, 1971). In addition, recently discovered endogenous peptides, endothelin (ET. Yanagisawa *et al.*, 1988; Mortensen *et al.*, 1990) and neuropeptide Y (NPY. Tatemoto, 1982; Edvinsson *et al.*, 1984; 1987) have a potent activity of increase in blood pressure. Interestingly, blood level of ET is higher in patients with essential hypertension than in normotensive subjects (Saito *et al.*, 1990).

Angiotensin converting enzyme (ACE) inhibitors can attenuate the manifestation of neurogenic hypertension (Longo *et al.*, 1989), and the development of normotension into hypertension in growing SHR (Huh *et al.*, 1991), however, little affect to deoxycorticosterone acetate-induced hypertension in rats (Douglas *et al.*, 1979). In patients with essen-

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tial hypertension, the antihypertensive effect of ACE inhibitor is not positively related to plasma renin activity (Wilson *et al.*, 1991).

These facts provide the possibility that antihypertensive effect induced by ACE inhibitors may result from any other action on a certain factor in addition to inhibitory action on ACE.

In this study, it was aimed to investigate the influence of treatment with enalapril in growing SHR on the responses of cardiovascular system-changes of blood pressure and contractility of isolated aortic strip-to ET and NPY under various conditions.

MATERIALS AND METHODS

Enalapril treatment

Male SHR of 3 weeks old were obtained from Korea Research Institute of Chemical Technology, and divided into 2 groups when matured with 6 weeks: One was treated with enalapril at a dosage of 3 mg/kg/day for 6 weeks via tap water, and the other control rats were given drug-free tap water. All rats were made free access to the food and water. To confirm developing hypertension, the systolic blood pressure was checked by the tail-cuff technique with electrosphygmography (Narco Biosystems).

In vivo study

SHR was anesthetized with urethane 1 g/kg intraperitoneally, the left carotid artery was cannulated for measuring the arterial pressure, and bilateral jugular veins for drugs admini-stration. Blood pressure (BP) was measured via pressure transducer connected to DC preamplifier, and heart rate (HR) by tachograph, and then the changes of BP and HR were recorded on polygraph (Model 79E, Grass Co.).

The central effect of ET or NPY was conducted according to method of Sohn *et al.* (1989) by using stereotaxic instrument (David Co.). To examine the peripheral effect of ET or NPY, pithed model were prepared according to the method of Gillespie *et al.*, (1970) as follows: Bilateral vagus nerves of rats pretreated with d-tubocurarine (1 mg/kg, i.p.) were cut, the rats were pithed by insertion of steel rod, and immediately artificial ventilation with tidal volume of 1 ml/100 g, 40~50 strokes/min (Respirator; model V5 Kg, Narco Biosystems) was conducted.

In pithed rat, the increase in DBP elicited by sympathetic stimulation (10 sec, 1 ms, 40 V), and in HR by cardiac nerve stimulation (10 sec, 0.5 ms, 20 V) were in frequency-dependent manner. An interval of 8~9 minutes was imposed between stimulation periods to allow full recovery of responses. To determine catecholamine levels in plasma, blood samples were collected from femoral artery and same amount of blood from donor rats was supplied via femoral vein.

In vitro study

The rats were decapitated and the thoracic aorta was rapidly removed, cleaned of connective tissue and cut into ring segments (4 mm in length). The endothelium was carefully denuded or not at need. These strips were suspended in a Krebs-Henseleit solution bubbled with 95% O_2 and 5% CO_2 and kept at 37°C. The composition (mM) of the solution in organ bath were: NaCl, 115.0; KCl, 4.7; $CaCl_2$, 2.5; $MgCl_2$, 1.2; $NaHCO_3$, 25.0; KH_2PO_4, 1.2; dextrose, 10.0.

The preparations were equilibrated for 120 min under 1 g resting tension. Isometric tension was measured by means of force displacement transducers (Myograph F-60, Narco Biosystems). Electrical field stimulation was provoked by stimulator (Model SI-10, Narco Biosystems) for 10 sec, 50 ms with 80 V.

Assay of catecholamines in plasma or the heart

One ml (in nonpithed SHR) or 0.5 ml (in pithed SHR) of blood was transferred immediately to ice-cold centrifuge tubes containing 50 ul of 0.9% NaCl with 100 units/ml heparin and 50 ul of 4 mM $NaHSO_3$, and centrifuged on Centrikon T-124 (Kontron Ins.) at 12000 g for 10 min at 4°C. Approximately 40 mg of left ventricle tissue was homogenized in 0.1 M perchloric acid solution contained with 0.5% Na_2EDTA, and centrifuged at 11000 g for 15 min at 4°C. In order to determination of catecholamine levels in blood and cardiac muscle, supernatents were kept in 0.1 M perchloric acid with 4 mM $NaHSO_3$ at −20°C, and then each of the sample was stirred in alumina with Tris buffer (pH 8.6), and the alumina was washed twice, and elutes catecholamines from alumina by 0.1 M perchloric acid, it was detected with electrochemi-

cal detector (M 460, Waters) connected to HPLC system by means of Nova-Pack C_{18} reverse phase column. The mobile phase consisted of 0.15 M NaH_2PO_4, 0.1 mM EDTA, 1 mM octane sulfonic acid and 2% methanol (pH 3.3), and was pumped at speed of 1 ml/min at +0.63 V with glassy carbon electrode.

Statistical analysis

Data were expressed as mean±S.E. The statistical significance of all results was evaluated by Student's t-test or MANOVA (multiple analysis of variance) test using SPSS/PC$^+$ program. Differences were considered significant when P values were less than 0.05.

Drugs

Drugs used were neuropeptide Y and endothelin (Peninsula Co., USA); d-tubocurarine, yohimbine, norepinephrine bitartrate, epinephrine, dopamine, and dihydroxybenzylamine (Sigma Co., USA); potassium chloride (Junsei Co., Japan), heparin (Choongwae Pharm. Co., Korea) and enalapril maleate (donation from Choongwae Pharm. Co). All drugs were dissolved in saline for in vivo study, and in distilled water for in vitro study.

RESULTS

Resting BP and HR of SHR treated with enalapril

Long-term treatment with enalapril (3 mg/kg/day for 6 weeks) prevented growing SHR from developing hypertension as the rat grew older (Fig. 1-b). In control and enalapril-treated groups, the rate of body weight gain was similar at 6 and 12 weeks of age (Fig. 1-a). Irrespective of pithing resting DBP and HR under anesthesia was decreased in enalapril-treated group as compared with corresponding control (Table 1).

Cardiovascular response of pithed and non-pithed SHR to ET and NPY

As indicated in Fig. 2, the increase in DBP induced by ET 30 or 100 nmol/kg i.v. in pithed SHR (Fig. 2-b) as well as ET 100 nmol/kg i.v. in non-pithed SHR (Fig. 2-c) was attenuated in the enalapril treatment when compared with control. However, initial vasodepressive action produced by intravenous ET (Fig. 2-c) and increase in DBP

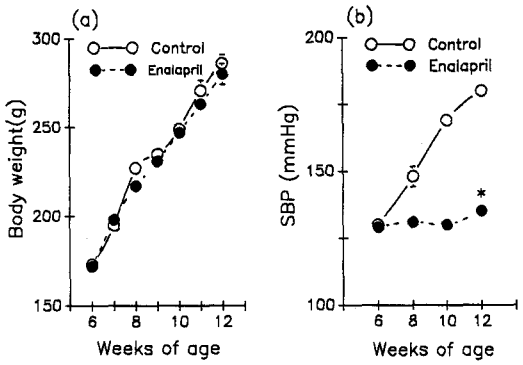

Fig. 1. Changes of body weight(a) and systolic blood pressure(SBP; b) under treatment with enalapril in growing SHR. Body weight or SBP were measured every 1 or 2 week by tail cuff method from 6th week of age. Enalapril(3 mg/kg/day) was administered via tap water *ad libitum* for 6 weeks. * $P<0.01$ compared with control curve.

Table 1. Resting value of diastolic blood pressure(DBP) and heart rate(HR) before or after pithing in SHR

Group	n	DBP(mmHg)	HR(beats/min)
Before pithing			
Control	18	119.8±3.4	410.6±6.5
Enalapril	20	80.7±3.2*	383.7± 7.1*
After pithing			
Control	11	44.7±2.3	382.7± 8.0
Enalapril	10	36.4±1.1*	348.4±10.4*

Enalapril(3 mg/kg/day) was treated for 6 weeks through tap water. n; the number of animals used. Each value represents mean± S.E. * $P<0.05$, * $P<0.01$ compared with control.

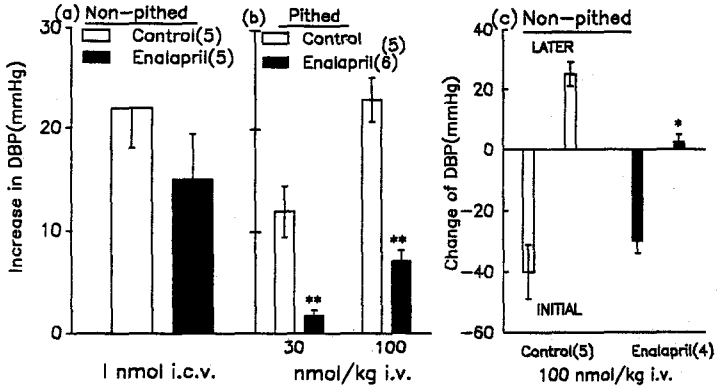

Fig. 2. Intracerebroventricular(i.c.v.), in-travenous(i.v.) effect of endothelin in pithed(b) and non-pithed(a,c) SHR. The columns show the mean with S.E. shown by vertical bars. The number of animals is expressed in parentheses. *, $P<0.05$ and **, $P<0.01$ compared with control.

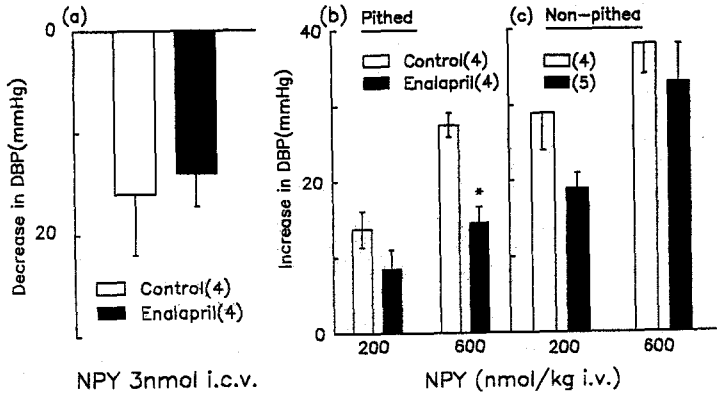

Fig. 3. Intracerebroventricular(i.c.v.; a) or intravenous(i.; b, c) effect of neuropeptide Y(NPY) in pithed(b) and non-pithed(a, c) SHR. The columns show the mean with S.E shown by vertical bars. The number of animals is expressed in parentheses. * $P<0.01$ compared with control.

by ET 1 nmol i.c.v. (Fig. 2-a) were not affected by enalapril treatment.

In the course of experiment designed to test NPY, the decrease in DBP induced by NPY 3 nmol i.c.v. (Fig. 3-a), and the increase in DBP in NPY 200 or 600 nmol/kg i.v. (Fig. 3-c) in non-pithed SHR were little influenced by enalapril treatment. However, the increase in DBP by NPY 600 nmol/kg i.v. (Fig. 3-b) in pithed SHR was attenuated by enalapril treatment.

Effect of ET on the increase in heart rate or in tension induced by electrical stimulation

When the preganglionic cardiac nerve in pithed SHR non-treated with ENP was stimulated with 1 ms duration for 10 sec, HR was increased in a frequency-dependent manner without any change of BP. The frequency-dependent increase in HR was significantly diminished by enalapril treatment (Fig. 4-a). The increase in heart rate induced by electrical stimulation (1.5 Hz) was diminished by

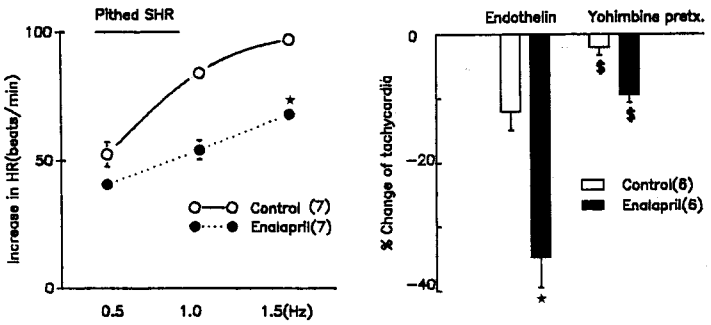

Fig. 4. Effect of endothelin on electrical stimulation-induced chronotropy in pi-thed SHR. a; Chronotropic response was elicited by stimulation of cardiac accelerator nerve with 0.5, 1 or 1.5 Hz for 10 s, 0.5 ms with 20 V in pithed SHR. b; Endothelin(10 nM/kg, i.v.) was administered 10 min before, and yohimbine(1 mg/kg, i.v.) was administered 15 min before electrical stimulation with 1.5 Hz. The columns show the mean with S.E shown by vertical bars. The number of animals is expressed in parentheses. * $P<0.01$ compared with control. $ $P<0.01$ compared with endothelin-treated group.

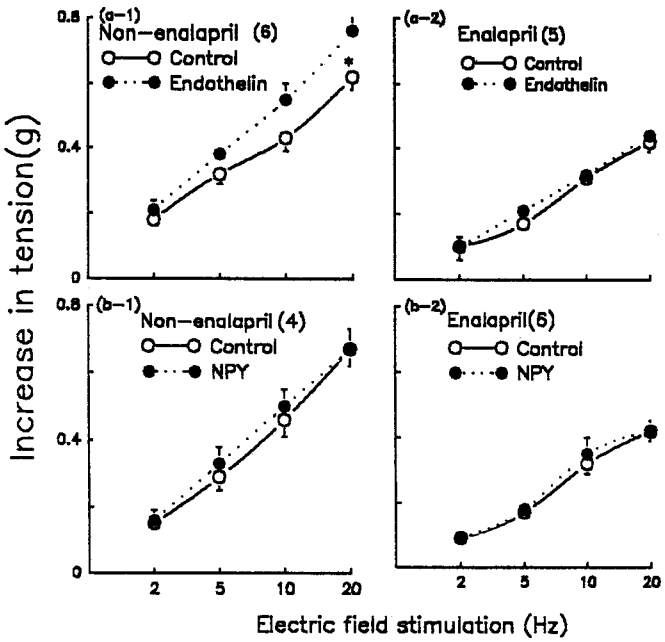

Fig. 5. Effect of endothelin(a-1, a-2, top) or NPY(b-1, b-2, bottom) on the frequency-dependent increment of tension under the electrical field stimulation in the isolated aorta. Each point indicate mean±S.E. Endothelin(0.1 nM) or NPY(1 nM) was treated 10 min before field stimulation which was conducted for 10 sec, 50 ms with 80 V. The number of animals is expressed in parentheses. * $P<0.01$ compared with control curve.

pretreatment with ET (10 nmol/kg i.v.), which was more remarkable in enalapril-treated group. The diminution with ET in both groups was blocked by yohimbine (1 mg/kg, 15 min before), α_2-receptor antagonist (Fig. 4-b).

Influence of enalapril on the electrical field stimulation (EFS)-induced increase of tension in isolated aortic strip in the presence of ET and NPY

In the isolated aorta, EFS (80 V, 50 ms, 10 sec) increased muscle tension frequency-dependently (Fig. 5). The increase of tension in enalapril-treat-

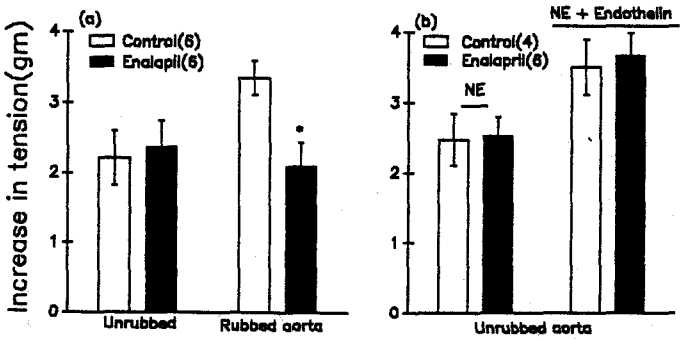

Fig. 6. Influence of endothelium or norepinephrine or ET-induced vasoconstricition of aorta. a; Endothelium of the aorta was rubbed or not. Endothelin(1.5 nM) was administered in the absence(a) or presence(b) of norepinephrine(NE). The columns show the mean with S.E shown by vertical bars. The number of animals is expressed in parentheses. * $P<0.05$ compared with control.

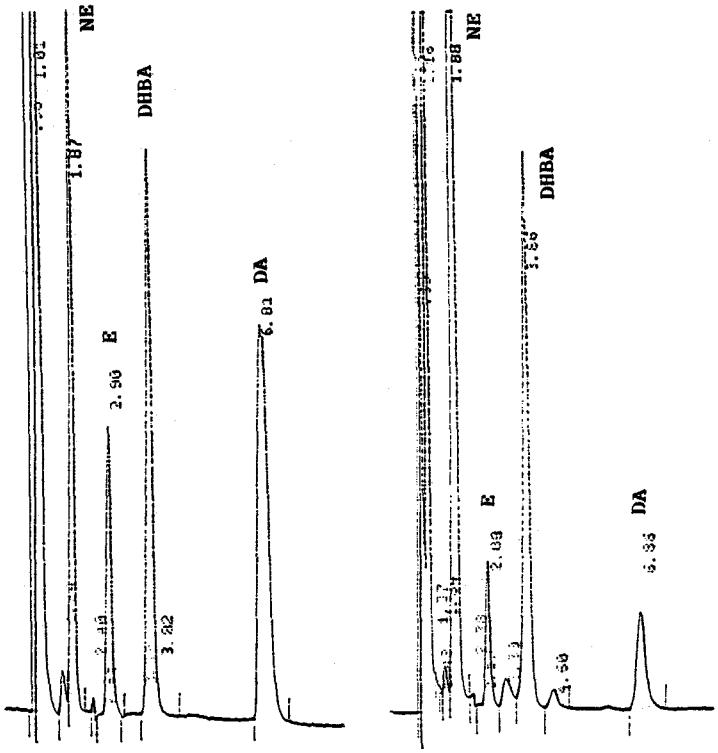

Fig. 7. Reversed phase HPLC separation of the catecholamines(norepinephrine; NE, epinephrine; E, dopamine; DA), of standard(left) and left ventricle tissue(right) obtained with Nova-Pak C^{18} column and electrochemical detection at +0.63 V with a glassy carbon electrode. Mobile phase contains 0.1 mM EDTA, 1 mM octane sulfonic acid, 2% methanol, and 0.15 M sodium phosphate(pH 3.3). Dihydroxybenzylamine (DHBA) was used as internal standard. Flow rate was 1 ml/min and controller sensitivity was 1.5 nA.

ed groups (Fig. 5-a-2 and 5-b-2) was attenuated as compared with those in non-enalapril-treated groups (Fig. 5-a-1 and 5-b-1). Endothelin (0.1 nM) pretreatment strengthened the increase in tension by EFS in non-enalapril-treated group (Fig. 5-a-1), but not in enalapril-treated group (Fig. 5-a-2). However, NPY (1 nM) did not alter the increase in muscle tension by EFS in both groups (Fig. 5-b-1 and 5-b-2).

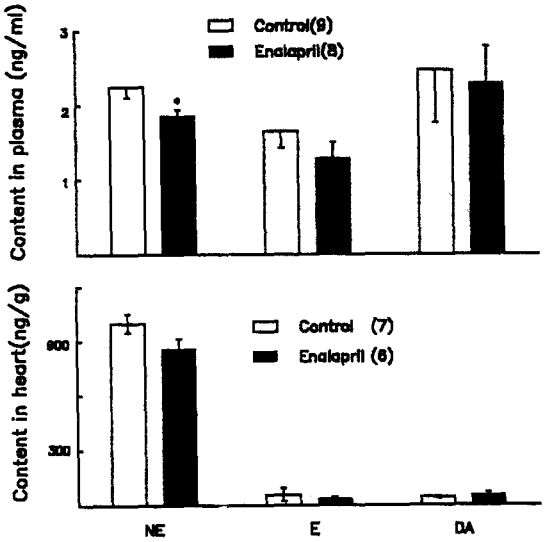

Fig. 8. The concentrations of catecholamines(NE; norepinephrine, E; epinephrine, DA; dopamine) in the plasma and cardiac tissue of SHR. The columns show the mean with S.E shown by vertical bars. The number of animals is expressed in parentheses. *P<0.05 compared with control.

Influence of endothelium or norepinephrine on the ET-induced vasoconstriction in aortic strips

In the presence of endothelium, the vasoconstriction by ET (1.5 nM) was not changed by enalapril treatment. In the absence of endothelium, however, the vasoconstriction by ET was attenuated by enalapril treatment (Fig. 6-a). The additive action of ET (1.5 nM) and norepinephrine (NE, 0.1 μM) on vasoconstriction was unaffected by enalapril treatment (Fig. 6-b).

Effects of ET and enalapril on catecholamine levels in plasma and cardiac muscles

Fig. 7 showed a representative reversed phase HPLC separation of catecholamine from standard solution (left) and left ventricle tissue of the heart (right) by means of electrochemical detector. The contents of NE in plasma and cardiac muscle were lower in enalaparil-treated group than those in control; in plasma (pg/ml), 2235±145 versus 1856 ±85 (Fig. 8-a); in the heart (ng/g), 1001±51 versus 860±56 (Fig. 8-b). The content of neither epinephrine (E) nor dopamine (DA) was changed in both

Table 2. Effect of endothelin(ET) on plasma catecholamines levels in non-pithed and pithed SHR

Groups \ Contents(pg/ml)	NE	E	DA
Non-pithed SHR			
Control(5)			
Before	2306±246	1265±105	1484±556
After ET	3417±675*	1857±131*	2035±912
Enalapril(5)			
Before	1839±105[a]	1266±275	926±237
After ET	2516±387*[b]	1280±265b	1186±437
Pithed SHR			
Control			
Before	847	182	130
After ET	2064	405	119
Enalapril			
Before	707	40	65
After ET	697	107	117

Blood sampling(1 ml; non-pithed or 0.5 ml; pithed) was conducted 10 min before or after endothelin injection(i.c.v. or i.v.; pithed) via femoral artery. The number of animals is expressed in parentheses. Each value represents mean±S.E. * P<0.01 compared with non-ET. a; P<0.05, b; P<0.01 compared with each of the control group. The value of pithed SHR represents mean of seven experiments.

of the groups.

In non-pithed SHR, the contents of NE and E in control rats as well as the content of NE but not E in enalapril-treated group were increased by ET 1 nmol/kg (i.c.v. 10 min after; Table 2-upper). In pithed SHR, NE was increased by i.v. ET in control, but not in enalapril-treated group (Table 2-lower), and E was increased by i.v. ET in control and enalapril-treated groups. Inhibitory effect resulted from enalapril treatment on the ET-induced increment of NE in plasma was more pronounced in pithed SHR than in non-pithed SHR (% of decrease; 66 vs 26).

DISCUSSION

Endogenous angiotensin II facilitates hemodynamic response induced by electrical stimulation in pithed rats (Kaufman and Vollmer, 1985) and bilateral nephrectomy suppresses the electrical stimultion-induced hypertension in pithed SHR (Hatton and Clough, 1982). The reports lead to possibility that angiotensin-converting enzyme inhibitor, enalapril, acts on neurotransmission at peripheral nervous system, or that it inhibits action of endogenous substance released by electrical stimulation.

Cardiovascular function of pithed rats is maintained under the absence of tonic sympathetic discharge and active renin-angiotensin system (Vollmer *et al.*, 1984) and so the pithed animal model has been used to rule out effects of central nervous system.

Enalapril treatment prevented SHR from the development of hypertension without changing body weight. Under non-pithed conditions, even under the pithed conditions as described above, the decrease in resting DBP and HR was shown in SHR treated with enalapril as compared with corresponding control.

The inhibitory effect of enalapril may result from the decrease in total peripheral resistance (Cody, 1984) via inhibition to the activity of voltage-dependent calcium channels (Sada *et al.*, 1989) and to angiotensin II-mediated facilitation of adrenergic neurotransmission (Kawasaki *et al.*, 1982; 1984).

The increase in DBP by intravenous injection of ET in pithed rats was attenuated by enalapril treatment, but the increase by intracerebroventricular injection in non-pithed rats was little affected. This result shows the facts that the increase in peripheral resistance by ET itself (le Monnier de Gouville *et al.*, 1990) can be elicited from its peripheal and central action, however, inhibitory effect of enalapril on ET-induced increase in DBP may be caused mainly by peripheral action. Intravenous injection of ET produced changes in blood pressure consisting of two phases in non-pithed rats; initial transient hypotension was followed by increase in blood pressure. Enalapril treatment markedly inhibited the increment of blood pressure, but little affected on the initial hypotension which seems to be caused by the release of rANF (Winquist *et al.*, 1989) and EDRF (Warner *et al.*, 1989), and to be mediated by ET receptor (le Monnier de Gouville *et al.*, 1990).

Possible role of NPY in essential hypertension may be proposed by following reports; NPY is released by sympathetic stimulation i.e. cold stress or bicycle exercise (Chamber *et al.*, 1989), and NE and NPY enhance the contractile response elicited by electrical field stimulation of peripheral sympathetic nerve (Ekblad *et al.*, 1984); The content of NPY in sympathetic neuron is increased in hypertensive rat (Gurusinghe *et al.*, 1990). However, report dealing with the effect of NPY on the renin-angiotensin system in SHR is rare.

Enalapril treatment did not affect on lowering DBP by i.c.v. injection of NPY. The treatment markedly inhibited on the increase in DBP by iv injection of NPY at high dose (600 nmol/kg) in pithed SHR, however, little affected on the increase in DBP by iv injection of NPY even at high dose in non-pithed SHR. This result provides possibility that NPY-induced increase in DBP may not be closely related to additive action of NPY on angiotensin II- or norepinephrine-induced vasoconstriction (Huge and Roth, 1971). This possibility seems to be supported by the evidence that NPY enhances purinergic and adrenergic response by EFS of the rabbit ear artery (Saville *et al.*, 1990).

The decrease of DBP by i.c.v. injection of NPY may be caused by activation of alpha-2 receptor (Chen *et al.*, 1988), and the increase in DBP by i.c.v. injection of ET may be caused, at least in part, by catecholamine release to periphery (Ouchi *et al.*, 1989). In our result, the central effect by ET and NPY was little affected by enalapril treatment. The ineffectiveness can provides a possible action of enalapril which is difficult to penetrate into the

CNS, or difference between action of enalapril on the CNS and site of action of ET or NPY on it.

In pithed SHR, the inhibitory effect of enalapril on positive chronotropy provoked by cardiac nerve stimulation was enhanced by ET, which was pronouncedly attenuated by yohimbine. It shows the evidence that the enhanced inhibitory action by ET may be caused by alpha-2 receptor-mediated endogenous feedback inhibition. The feedback inhibition is more developed in normotensive than in hypertensive rats (de Jonge *et al.*, 1983). This report leads to presumption that ACE inhibitor-induced antihypertensive action can augment the cardioinhibitory activity of ET via alpha-2 receptor activation in SHR.

On the basis of this presumption, inhibitory effect of enalapril on ET-induced increase in DBP seems to be related to possibility that enalapril can potentiate ET-induced alpha-2 receptor activation. However, further studies into this problem are necessary.

Hypertension may be due to an increased facilitatory or a decreased inhibitory modulation of vascular adrenergic neurotransmission (Cheng and Shibata, 1980) and vascular renin-angiotensin system (Kawasaki *et al.*, 1984). This assumption may lead to explanation for the fact that EFS-induced contraction is more pronounced in SHR than in WKY (Tabuchi *et al.*, 1990).

EFS-induced increae in aortic muscle tension was inhibited in SHR treated with enalapril as compared with in non-treated SHR. The effect may be related to inhibitory actions of enalapril on the activity of voltage-dependent calcium channel (Sada *et al.*, 1989; Huh *et al.*, 1991) and on angiotensin II-mediated facilitation to adrenergic neurotransmission (Kawasaki *et al.*, 1982; 1984).

NPY enhances contractile response elicited by EFS in peripheral sympathetic nerve (Ekablad *et al.*, 1984), and it enhances the response of non-adrenergic and adrenergic nerve to EFS in ear artery (Saville *et al.*, 1990). NPY-induced vascular smooth muscle contraction requires extracellular calcium (Franco-cerda, 1989) However, NPY did not enhance EFS-induced activity of an increase in tension regardless of enalapril treatment. Our results suggest that EFS-mediated contraction of aortic strips may be resistance to NPY-induced smooth muscle contraction.

ET inhibits norepinephrine efflux by periarterial nerve stimulation (Tabuchi *et al.*, 1990) and it increase intracellular calcium concentration (Simon and Dame, 1990) via production of IP_3 (Huang *et al.*, 1989). EFS-induced increase in tension was enhanced by the presence of ET in non-treated with enalapril. The result may be related to increasing intracellular calcium concentration induced by ET (Huang *et al.*, 1989). However, ET did not affect to EFS-induced action in enalpril-treated SHR. This unresponsiveness of aortic strips from enalapril treatment to ET is likely concerned with the possibility that inhibitory action of enalapril on activity of voltage-operated calcium channel (Sada *et al.*, 1989; Huh *et al.*, 1991) can result in lowering intracellular calcium concentration, or that enalapril may, at least in part, inhibit binding of ET to receptor (Monier *et al.*, 1990) Further possibility is that enalapril inhibits angiotensin II-induced catecholamine release (Hugh and Roth 1971) or adrenergic neurotransmission (Kawasaki *et al.*, 1982; 1984). This description is in accordance with our result in the pithed and nonpithed SHR that ET increased plasma catecholamine level, which was lowered by enalapril treatment, especially more significant lowering in pithed SHR than in non-pithed SHR.

In rubbed aortic ring strips, ET-induced contraction was significantly decreased by the enalapril treatment, but not in unrubbed arotic strips. This result required further study on a possible action that unknown any component in endothelium can interfere with inhibitory action of enalapril in the strips itself. In addition, ET-induced increase in tension may be disturbed by EDRF on the basis of our result that ET-induced action was enhanced in rubbed aortic strips as compared with the action in unrubbed strips.

In conclusion, although the precise mechanism of inhibitory action of enalapril on developing hypertension in SHR remains to be elucidated, three possible actions seem to be derived from our results; First, additional evidence favoring enalapril-induced antihypertensive action via angiotensin converting enzyme inhibition is likely that NPY- and especially ET-induced increase in blood pressure may inhibited by enalapril at peripheral nervous system. Second, enalapril may attenuate release of catecholamines from peripheral nervous system or sympathetic neurotransmission. Third, enalapril may inhibit tension of aortic smooth muscle via decrease in calcium utilization, which is unrelated to NPY-induced calcium

utilization in contrast to ET-induced action.

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=국문초록=

선천성 고혈압흰쥐에서 Endothelin과 Neuropeptide Y에 의한 심혈관계 반응에 Enalapril 장기처치가 미치는 영향

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선천성 고혈압 흰쥐(SHR)에서 endothelin-1(ET)과 neuropeptide Y(NPY) 투여에 의한 심혈관계 반응에 미치는 enallapril 장기처치의 영향을 검토하였다.

생후 6주의 SHR에 enalapril(3 mg/kg/day)을 6주간 투여하였을 때 고혈압 발현이 현저히 억제되었다(이하 enalapril 처치군). Enalapril 처치군에서 ET 및 NPY에 의한 승압반응이 현저히 억제되었지만, ET 측뇌실투여에 의한 혈압상승 및 NPY측뇌실 투여로 야기되는 혈압하강효과에는 영향이 없었다.

뇌척수제거 흰쥐에서 전기적 자극으로 야기되는 빈맥효과는 enalapril처치나 ET투여로 억제되었는데, ET의 작은 α_2-수용체 길항제인 yohimbine 전처치로 봉쇄되었다.

SHR의 적출 대동맥에서 전기자극 빈도수에 따르는 수축반응이 ET 전처치로 항진되었으나 NPY 전처치로는 차이가 없었다. 전기자극 빈도수에 따른 수축반응은 enalapril투여한 군의 것이 투여하지 않은 군의 것에 비하여 약화되었다. ET투여에 의한 혈중 norepinephrine의 증가작용이 enalapril처치로 감소되었으며, 이러한 감소작용이 뇌척수제거 흰쥐에서 현저하였다.

위의 결과로 미루어 고혈압흰쥐에 enalapril을 장기처치함으로써 고혈압 발현을 효과적으로 억제할 수 있으며, 이는 ET 및 NPY에 의한 승압반응 및 교감신경말단의 신경전달과정의 억제가 관여될 수도 있을 것 같다.