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Regulatory Role of Adrenal Medulla and Renin-Angiotensin System in Sympathetic Neurotransmission in Spontaneously Hypertensive and Normotensive Rats

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ABSTRACT

To assess the role of adrenal medulla and renin-angiotensin system in the regulation of sympathetic neurotransmission, the pressor response to PNS was evaluated in pithed SHR and normotensive WKY or SDR with or without adrenal demedullation and/or enalapril pretreatment.

Three weeks after adrenal demedullation, MAP and the heart rate of demedullated rats were similar to their corresponding sham-operated groups. The pressor response to PNS was frequency-dependent, and blocked by prazosin. In contrast to the normotensive rats, in SHR, the pressor response to PNS was attenuated in demedullated rats as compared with sham-operated rats. However, the attenuation of PNS-induced pressor responses in demedullated SHR was not observed in enalapril-treated SHR.

The adrenal demedullation in SHR did not affect the plasma and aortic catecholamine contents in spite of the decreased catecholamine contents of adrenal gland, nor ACE activity in aortic strips. But, in WKY rats, the aortic catecholamines, especially epinephrine, contents as well as ACE activity were increased by adrenal demedullation.

These results suggest that the facilitatory role of adrenal medulla in sympathetic neurotransmission depends upon the activation of renin-angiotensin system, and that the compensatory regulation of renin-angiotensin system takes place in normotensive rats but not in SHR.

Key Words: Adrenal Demedullation, Renin-Angiotensin System, Catecholamines, Sympathetic Neurotransmission, Spontaneously Hypertensive Rats

Abbreviations: PNS, preganglionic nerve stimulation; SDR, Sprague-Dawley rats; MAP, mean arterial pressure; ACE, angiotensin converting enzyme

INTRODUCTION

The spontaneously hypertensive rats (SHR), developed by Okamoto and Aoki (1963), has been considered a suitable animal model to study the pathophysiology of essential hypertension. Though a specific cause for the elevated arterial pressure has not been defined (Oparil, 1988), the involvement of the sympathetic nervous system (Coote and Sato, 1977; Cheng and Shibata, 1980) and the renin-angiotensin system (Niarchos *et al*, 1979; Sweet *et al*, 1981) has been clearly established using a variety of physiological and pharmacological approaches.

The result that bilateral adrenal demedullation fo juvenile SHR reduced the vascular response to

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sympathetic nerve stimulation provided that adrenaline has a faciliatory role in sympathetic neurotransmitter release (Borkowski and Quinn, 1983). On the other hand, the activation of vascular renin-angiotensin system results in a facilitation of neurotransmission in mesenteric vascular preparations of SHR (Kawasaki, 1984).

After sympathectomy of normotensive rats, the blood pressure is maintained at nearly normal levels mainly through an activation of the renin-angiotensin system (Julien *et al*, 1990), implying that the compensatory control mechanism exists between sympathetic nervous system and renin-angiotensin system. This finding led to the question whether the compensation between sympathetic nervous system and renin-angiotensin system takes places in SHR or not There have been few studies on the role of adrenal medulla and renin-angiotensin system in the regulation of sympathetic neurotransmission in spontaneously hypertensive and normotensive rats

To assess the role of adrenal medulla and renin-angiotensin system in the regulation of sympathetic neurotransmission, the pressor response to PNS, with catecholamines level and ACE activity, was evaluated in pithed SHR and normotensive WKY or SDR with or without adrenal demedullation and/or enalapril pretreatment.

MATERIALS AND METHODS

Adrenal demedullation

Nine or ten week-old male SHR and normotensive rats of Sprague-Dawley and Wistar-Kyoto strains were used. Each strain was divided into two groups. One group was subjected to bilateral adrenal demedullation via a flank incision under sodium pentobarbital anesthesia (35 mg/kg, i.p). The adrenal gland was exposed , a small incision was made in the cortex and the whole medulla was removed by a gentle squeeze with a forceps. The other group was sham-operated, i.e., everything, except adrenal demedullation, was performed.

Enalapril pretreatment

In a separate experiment, to evaluate the role of renin-angiotensin system in the regulation of sympathetic neurotransmission, enalapril, at a daily dose of 10 or 25 mg/kg, was administered via tap water for 2 weeks from one week after surgery.

Increase in blood pressure to preganglionic nerve stimulation

Three weeks after surgery, the rats were anesthetized with sodium pentobarbital (35 mg/kg, i. p.). The left femoral artery and vein were cannulated for blood sampling and transfusion, respectively, and right jugular vein for drug administration. The right carotid artery was also cannulated for measuring the arterial pressure and heart rate by means of a strain gage coupler and a biotacheometer coupler, respectively, connected to pressure transducer. The blood pressure and heart rate were recorded on a physiograph (Narco Biosystems, U.S.A.).

After tracheostomy, the rats were pithed according to the method of Gillespie *et al.* (1970). Briefly, the copper rod, insulated except stimulating region, was inserted through the orbit and foramen magnum, down the spinal column, to the sacral vertebra. A stainless steel needle was inserted under the skin of the shoulder to serve as reference electrode. Immediately, artificial ventilation with positive pressure of 12~13 cm H_2O, 1 : 2 inspiration:expiration ratio and 50 beats/min (V5 Kg, Narco Biosystems) was conducted. *d*-Tubocurarine (1 mg/kg, i.v.) was administered after pithing to prevent muscle contractions during preganglionic nerve stimulation. Body temperature was kept within the normal range (about 37° C) by means of a tungsten lamp

Blood samples for catecholamines level were collected from femoral artery and same amount of blood from donor rats was supplied via femoral vein. The increase in MAP was elicited by sympathetic stimulation (10 sec, 1 ms, 20 V at an interval of 5 min) of level T_7 to T_9 at various frequencies (2, 4, 8 and 16Hz).

Catecholamines assay

Plasma catecholamines level and aortic and adrenal catecholamines contents were determined by the method described in preceding report (Kim *et al.*, 1992).

Determination of angiotensin converting enzyme activity

The method accorded to Neels *et al.* (1983). Serum (20 μl) and aortic homogenates (50 μl) were incubated in 100 μl buffered substrate solution (17 mM HGG, 30 mM HEPEG, 168 mM sodium chloride, 223 mM sodium sulfate, pH 8.0) at 37° C, to which sodium tungstate (100 g/L; 100 μl) and dilute H_2SO_4 (334 mM; 100 μl) were added after 30 min to stop the reaction After vortex-mixing and adding 1 ml of water, the solution was centrifuged for 10 min at 200×*g*.To 500 μl of the supernatant, borate buffer (100 mM, pH 9.6; 1 ml) and 2,4,6-trinitrobenzene sulfonic acid solution (60 mM ; 10 μl) were added. About 30 minutes later, the absorbance at 420 nm wavelength (Spectrophotometer, Gilford 2600) was read against a serum blank, prepared by adding the deproteinizing agents followed by serum to the substrate solution. The calibration curve was prepared by first adding the deproteinizing agents and serially diluted Gly-Gly standard solution to the substrate solution, then following procedure described previously.

Statistical analysis

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

Drugs

Drugs used were *d*-tubocurarine, norepinephrine bitartrate, epinephrine, dopamine, dihydroxybenzylamine, alumina, Hippuryl-glycyl-glycine, Glycyl-glycine, 2,4,6-trinitrobenzene sulfonic acid and 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (Sigma, USA); heparin (Choongwae Pharm Co., Korea) and enalapril maleate (donation from Choongwae Pharm. Co.). All other reagents were analytical grade.

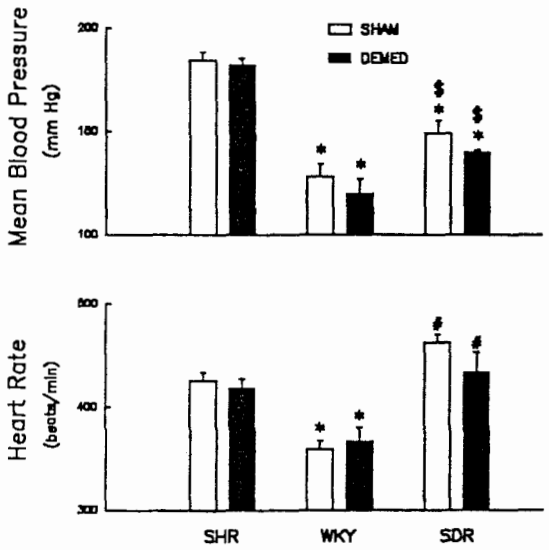

Fig. 1. Mean arterial blood pressure and heart rate in the anesthetized spontaneously hypertensive rats (SHR), normotensive Wistar Kyoto (WKY) and Sprague-Dawley rats (SDR) which had been demedullated or sham-operated 3 weeks before. Each column and bar represents mean± SE of 5 to 15 rats. *P<0.01, significantly different from those of spontaneously hypertensive rats. #P<0.01; $P<0.05, significantly different from those of Wistar Kyoto rats. No significant difference between sham and corresponding demedullated groups (ANOVA).

RESULTS

Effect of Adrenal Demedullation on Blood Pressure and Heart Rate

The adrenal demedullation, three weeks later, did not affect the mean arterial blood pressure and heart rate of the anesthetized SHR nor of the normotensive Wistar Kyoto and Sprague-Dawley rats (Fig. 1). The mean arterial blood pressure of SHR were higher than that of normotensive Wistar Kyoto and Sprague-Dawley rats (P<0.01). Of the normotensive rats, the mean arterial blood pressure of Sprague-Dawley rats were higher than that of Wistar Kyoto rats (P<0.05).

Table 1. Mean blood pressure and heart rate, before and after pithing, in the anesthetized spontaneously hypertensive rats, normotensive Wister Kyoto and Sprague-Dawley rats which had been demedullated or sham-operated 3 weeks before

	Mean blood pressure(mm Hg)		Heart rate(beats/min)	
	SHAM	DEMEDULLATED	SHAM	DEMEDULLATED
Spontaneously Hypertensive rats				
before	184±4	182±3	425±8	418±9
pithed	48±2	44±2	341±13	328±15
Wistar Kyoto rats				
before	128±6**	120±7**	359±8**	367±13**
pithed	43±4	41±4	276±32	303±29
Sprague-Dawley rats				
before	149±6**$	140±1**$	462±8**##	434±19**##
pithed	46±5	46±4	312±18	348±8$

Values are means±SE of 5 to 15 rats. **P<0.01, significantly different from those of spontaneously hypertensive rats.##P<0.01; $P<0.05, significantly different from those of wistar Kyoto rats.

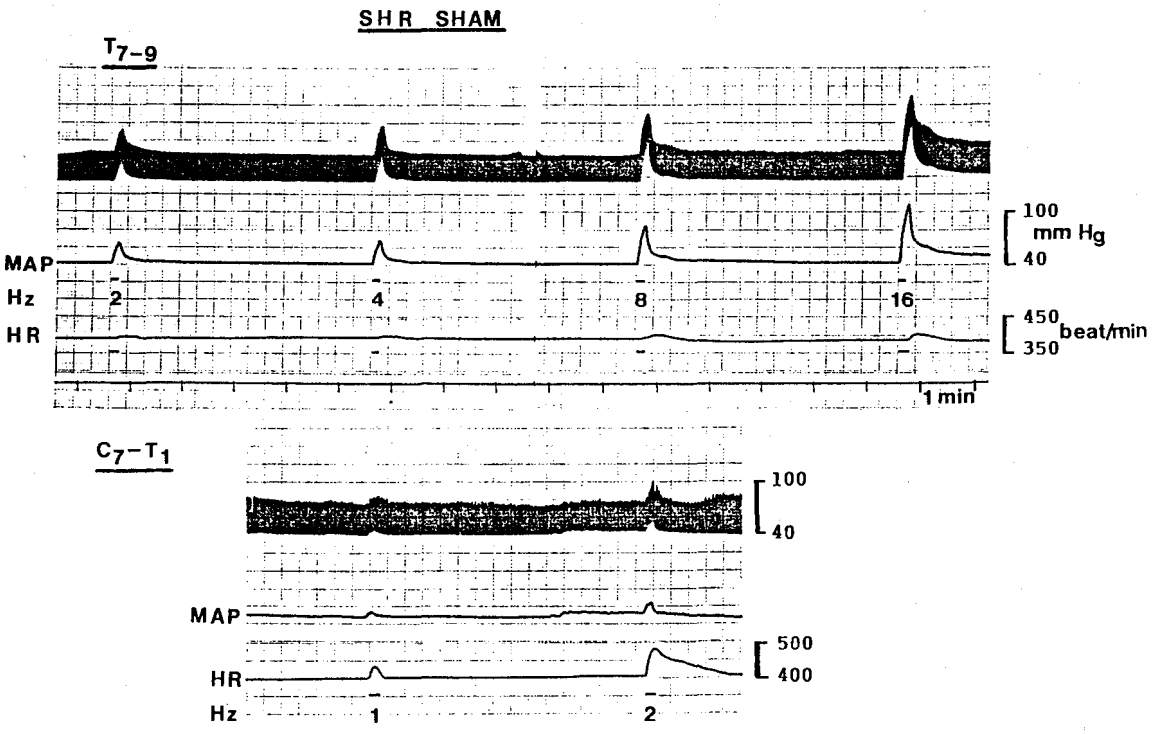

Fig. 2. Typical recording of the increase in mean arterial pressure (MAP) and heart rate (HR) in the response to preganglionic nerve stimulation (20 V, 1 ms, for 10 s at 5 min intervals) in the spontaneously hypertensive rats (SHR) which had been sham-operated 3 weeks before. The stimulatory frequency was varied (2, 4, 8and 16Hz). Stimulation at $T_{7\sim9}$ produced a spike-and-wave appearance in the blood pressure and a small delayed increase in heart rate. In contrast, stimulation at C_7-T_1 increased the heart rate but had minimal effect on the blood pressure.

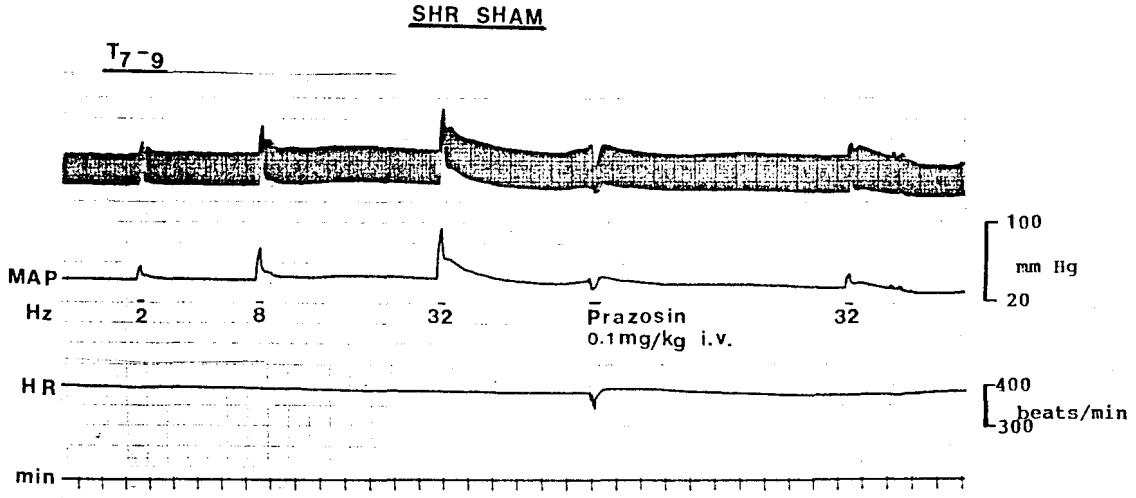

Fig. 3. Typical recording of the increase in mean arterial pressure (MAP) and little change in heart rate (HR) in the response to preganglionic nerve stimulation (20 V, 1 ms, for 10 s at 5 min intervals) in the spontaneously hypertensive rats (SHR) which had been sham-operated 3 weeks before. The stimulatory frequency was varied (2, 8, 32 and 32Hz). The response was blocked by prazosin (0.1 mg/kg, i.v.)

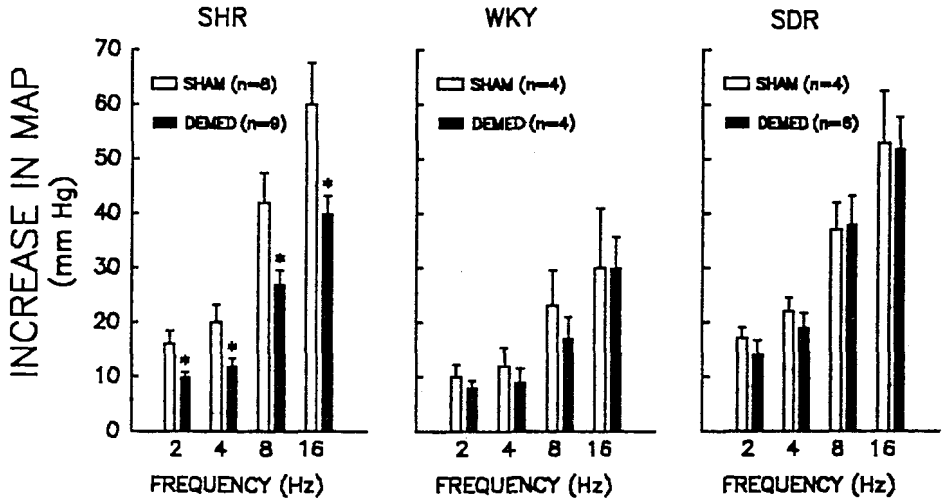

Fig. 4. The increase in mean arterial pressure (MAP) in the response to preganglionic nerve stimulation (20 V, 1 ms, for 10 s at 5 min intervals) in the spontaneously hypertensive rats, normotensive Wistar Kyoto and Sprague-Dawley rats which had been demedullated or sham-operated 3 weeks before. The stimulatory frequency was varide (2, 4, 8 and 16Hz). Each column and bar represents mean±SE. The number of rats used is given in parentheses. *$P<0.05$, significantly different from corresponding sham.

Pressor responses to preganglionic nerve stimulation

In pithed rats, the blood pressure were markedly diminished to similar level regardless of a difference in an initial level of blood pressure, which was not affected by adrenal demedullation (Table 1). When seventh to ninth thoracic preganglionic

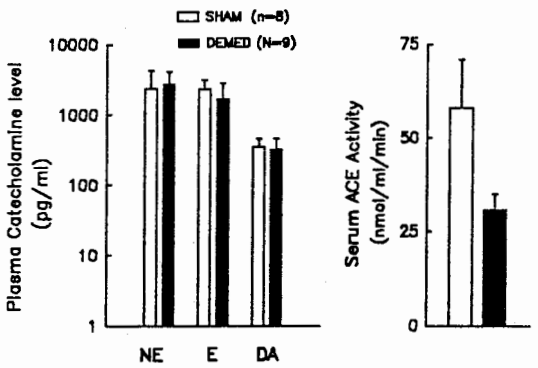

Fig. 5. The plasma catecholamines (norepinephrine, epinephrine, and dopamine) levels and the serum angiotensin converting enzyme activity of SHR. Each column and bar represents mean ±SE. No significant difference was found.

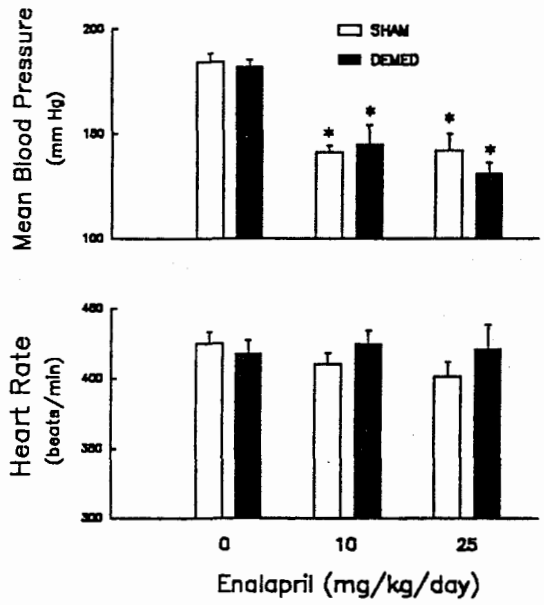

Fig. 6. Effect of enalapril (0, 10 and 25 mg/kg/day for 2 weeks) on resting mean arterial blood pressure (MAP) and heart rate in the spontaneously hypertensive rats (SHR) which had been demedullated or sham-operated 3 weeks fefore. Each column and bar represents mean±SE of 5 to 15 rats. *P<0.01, significantly different from those of no treatment. No significant difference between sham and corresponding demedullated groups (ANOVA).

nerve were stimulated (20 V, 1 msec pulses for 10 sec at 5min intervals) in the pithed rats, the pressor responeses were frequency-dependently (2,4,8 and 16 Hz) increased without change in the heart rate (Fig. 2). Prazosin(0.1 mg/kg, iv), an α_1-antagonist, nearly abolished the pressor responses to preganglionic nerve stimulation (Fig. 3). Adrenal demedullation attenuated the pressor responses to preganglionic nerve stimulation in SHR, but not in normotensive Wistar Kyoto and Sprague-Dawley rats (Fig. 4)

Plasma catecholamines levels and serum angiotensin converting enzyme activity in spontaneously hypertensive rats

Adrenal demedullation did not alter the plasma catecholamines levels in the anesthetized SHR but decreased the angiotensin converting enzyme activity (Fig. 5).

Effect of Enalapril pretreatment on the sympathetic neurotransmission

The blood pressure of SHR which were administered enalapril (10 or 25 mg/kg/day) for 2 weeks was markedly diminished ($P<0.01$), and similar with that of normotensive rats (Fig. 6). Adrenal demedullation did not affect the blood pressure of enalapril-treated SHR. The attenuation of pressor response to preganglionic nerve stimulation by adrenal demedullation in pithed rats was not found in enalapril-treated SHR (Fig. 7)

Aortic angiotensin converting enzyme activity

The aortic ACE activity of SHR which were administered enalapril (10 or 25 mg/kg/day) for 2 weeks was markedly diminished ($P<0.01$), but not affected by adrenal demedullation (Fig. 8). The aortic ACE activity of normotensive Wistar Kyoto rats was lower than that of SHR, but significantly increased by adrenal demedullation ($P<0.05$)

Aortic and adrenal catecholamines contents

Adrenal demedullation decreased the adrenal catecholamines contents in SHR, normotensive Wistar Kyoto rats, and enalapril-treated SHR, but had no effect on aortic catecholamines contents.

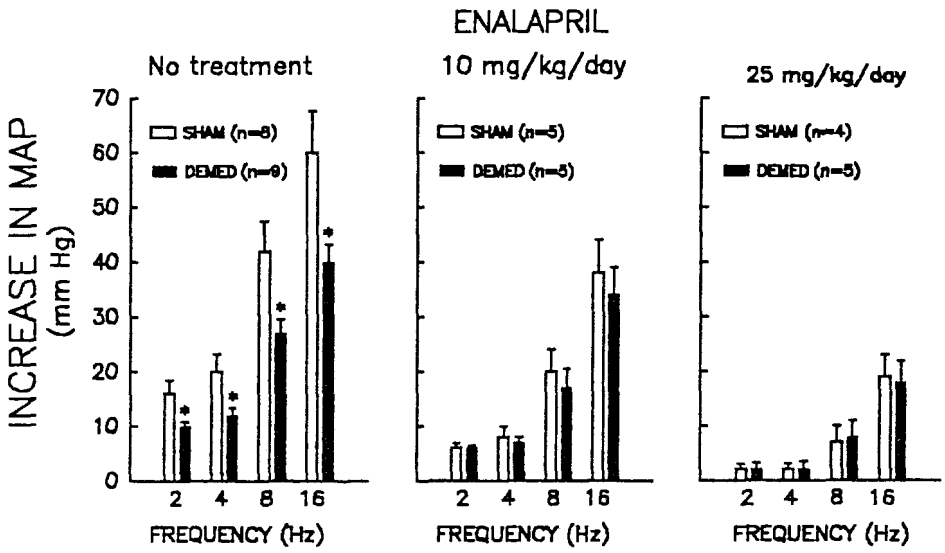

Fig. 7. The increase in mean arterial pressure (MAP) in the response to preganglionic nerve stimulation (20V, 1 ms, for 10 s at 5 min intervals)in the enalapril (10 or 25 mg/kg/day for 2 week)-spontaneously hypertensive rats which had been demedullated or sham-operated 3 weeks before. The stimulatory frequency was varied (2, 4, 8 and 16Hz). Each column and bar represents mean±SE. The number of rats used is given in parentheses. No significant difference between sham and corresponding demedullated groups.

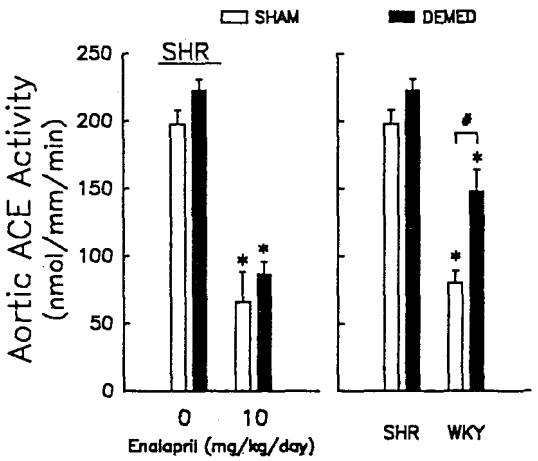

Fig. 8. The aortic angiotensin converting enzyme (ACE) activity of spontaneously hypertensive rats (SHR) treated with enalapril (10 mg/kg/day) or not, and normotensive Wistar Kyoto rats(WKY). Each column and bar represents mean±SE. *P<0.01, significantly different from corresponding untreated spontaneously hypertensive rats. # P<0.05 significant difference between sham and demedullated WKY.

Enalapril pretreatment decreased all the adrenal and aortic catecholamines contents except aortic epinephrine content, which were not affected by adrenal demedullation. By adrenal demedullation of Wistar Kyoto rats, the aortic catecholamines contents were increased while the adrenal catecholamines contents were decreased (Table 2).

DISCUSSION

The pressor response to preganglionic nerve stimulation (PNS) in pithed rats was attenuated by adrenal demedullation in spontaneously hypertensive rats (SHR), but not in normotensive rats nor in enalapril-treated SHR, suggesting that the adrenal medulla and the renin-angiotensin system play an important role in the development of hypertension. The blood pressure of SHR is similar to that of normotensive rats until 5 weeks, then increases to reach plateau around 16~20 weeks (Okamoto and Aoki, 1963). We used SHR

Table 2. Aortic and adrenal norepinephrine(NE), epinephrine(EP) and dopamine(DA) contents in control and enalapriltreated spontaneously hypertensive rats and normotensive Wistat Kyoto rats which had been demedullated or sham-operated 3 weeks before

	Aortic contents(pg/mm ring)		Adrenal contents(ng/pair)	
	SHAM	DEMEDULLATED	SHAM	DEMEDULLATED
SHR (Spontaneously hypertensive rats)				
NE	41±10	46±15	15433±5128	864±412
EP	341±112	312±117	12991±4378	817±317
DA	45±26	41±26	845±229	61±28
Enalapril (10 mg/kg/day)-treated SHR				
NE	40@	39@	3212±230	212±13
EP	24@	29@	2804±72	95±18
DA	9@	22@	230±4	21±8
Enalapril (25 mg/kg/day)-treated SHR				
NE	ND	ND	4528±449	169±45
EP	ND	ND	3285±376	63±11
DA	ND	ND	425±55	17±1
Wistar Kyoto rats				
NE	53@	78@	3993±1552	176±24
EP	1.4@	3.8@	6396±2844	110±27
DA	6.6@	7.1@	281±58	53±33

Values are means±SE of 5 to 11 preparations.
@, Determinations of pooled samples. ND, not determined
Statistical differences was not shown for clarity.

at the age of 12~13 weeks which nearly developed hypertension. Adrenal demedullation, in SHR, did not affect on the mean arterial blood pressure and heart as well as plasma catecholamines level, but slightly decreased serum ACE activity. These observations were not consistent with the finding that adrenal demedullation of juvenile SHR (4 weeks) attenuated the development of hypertension (Borkowski and Quinn 1983). In contrast to our experiment, they have demedullated young rats instead of adult animals. Ontogenically peripheral sympathetic nerves have innervated during preweanling period (Kirby and McCarty, 1987; Mills and Smith, 1986), suggesting that adrenal demedullation, after development of hypertension, altered the sympathetic nervous systems functionally without affecting the maturation and development.

The experiment that the pressor responses to PNS in the pithed rats, first reported by Gillespie *et al.* (1970), has been considered as a sort of an in vivo model devoid of centrally mediated cardiovascular reflexes. This experimental model enables to stimulate the localized segments of the spinal nerves. Stimulation of 7th to 9th thoracic spinal nerves which innervate mesenteric resistance vessels produced increase in blood pressure and a little change in heart rate. The pressor response to PNS was frequency-dependent increase (2,4,8 and 16Hz), and was nearly abolished by prazosin. Thus, the PNS-induced pressor response appears to involve α_1 receptor stimulation by endogenous norepinephrine.

There are two types of adrenergic receptors on prejunctional membrane to control norepinephrine release, facilitation by β-receptors and inhibition by α-receptors (Stjarne and Brundin, 1975). Application of exogenous epinephrine influenced the activation of both inhibitory α- and facilitatory β-receptors, whereas release of endog-

enous epinephrine from stores conditioned to the activation of the facilitatory β-adrenoceptors only (Schwartz and Eikenburg, 1988). Adrenaline-induced enhancement of the blood pressure response to sympathetic nerve stimulation in adrenal demedullated pithed rats has been ascribed to the fact that adrenaline of adrenal medullary origin acts as endogenous agonist at prejunctional β-adrenoceptors mediating a facilitation of neuronal noradrenaline release (Tarizzo and Dahlof, 1989). There were, however, some conflicting evidences to argue against the presence and the role of prejunctional β-receptors. Failure of propranolol to inhibit the epinephrine-induced enhancement of responses to sympathetic nerve simulation in the rat mesenteric vascular bed indicates that β-adrenoceptors do not play a role in the epinephrine-induced potentiation of responses to sympathetic nerve stimulation in the rat mesenteric vascular bed preparation (Falckh *et al.*, 1990). Lack of presynaptic modulation by isoprenaline of ^{3}H-noradrenaline release from rabbit isolated ear artery (Abrahamsen and Nedergaard, 1991) raise the question about the role of presynaptic β-receptor.

However, their reports are in conflict with our results: Under pithing PNS-induced pressor responses attenuated in demedullated SHR in contrast with in demedullated mormotensive WKY and SDR, which indicates that endogenous epinephrine may stimulate presynaptic β-receptor in SHR rather than normotensive rats. Taken together, the role of preganglionic β-receptors seems to depend upon the level of blood pressure. However, it is still difficult to conclude that the enhanced sympathetic neurotransmission in the hypertension is exclusively due to the role of preganglionic β-receptors.

Angiotensin not only has the actions to constrict vascular smooth muscle and to secrete adrenal corticosteroid hormones, but also enhances transmitters release during sympathetic nerve stimulation (Hughes and Roth, 1971; Kawasaki *et al.*, 1982; 1984) The dissociation between the blood pressure lowering response to ACE inhibitors and their inhibitory effects on serum ACE (Cohen and Kurz, 1982) leads to controversy regarding the contribution of the circulating renin-angiotensin system in regulating blood pressure, relative to the role of a functional tissue renin-sngiotensin system. Tissue renin-angiotensin system is more closely related to the regulation of blood pressure than is the circulating one (Weishaar *et al.*, 1991)

In our experiment, the aortic ACE activity of normotensive WKY was significantly increased by adrenal demedullation while that of SHR was not affected by adrenal demedullation. The findings lead us propose plausible explanation; the renin-angiotensin system of SHR can not be activated any more while that of normotensive rats can be activated further more on the basis of following hypothesis that the renin-angiotensin system of SHR is in a genetically maximally activated statse while that of normotensive rat is in a basal state. This explanation can also be supported by our observation that increased ACE activity of demedullated normotensive Wistar Kyoto rats was still lower than those of SHR, and by the report that sympathectomized rats maintain their blood pressure at nearly normal levels probably through an activation of the renin-angiotensin system (Julien *et al.*, 1990).

In consistent with hypernoradrenergic innervation in the vasculature of the SHR (Head, 1989), aortic epinephrine and dopamine, but not norepinephrine, contents of SHR were markedly higher than those of normotensive Wistar Kyoto rats. In addition, epinephrine and dopamine were markedly decreased by enalapril pretreatment relative to aortic norepinephrine content. Of the aortic catecholamines contents, epinephrine content was most closely related to the resting blood pressure and the pressor responses to PNS, implying the role of epinephrine to facilitate sympathetic neurotransmission in hypertension through activation of presynaptic β-receptors (Stjarne and Brundin, 1975; Dahlof, 1981; Majewski *et al.*, 1981)

It is difficult to differentiate whether decreased angiotensin II synthesis in vasculature by enalapril or decreased epinephrine content normalized the blood pressure and attenuated the pressor responses to PNS in enalapril-treated SHR. In consideration of the result from perfusion experiment using mesenteric vascular beds (Kawasaki *et al.*, 1984), sympathetic neurotransmission is, at least in part, under the control of renin-angiotensin system.

Recently independent tissue renin-angiotensin

system has been found in adrenal gland and vascular tissues following brain, kidney, testis and heart (Rosenthal *et al.*, 1984; Campbell, 1987), indicating that locally generated angiotensin II has a more important biological significance to regulate local tissues than does circulating angiotensin. In the vascular tissues, angiotensin II induces smooth muscle cell proliferation (Daemen *et al.*, 1991) and increases smooth muscle isoactin expression (Turla *et al.*, 1991) as well as increases sympathetic nerve activity (Matsukawa *et al.*, 1991). Chromaffin cell membrane of adrenal gland has angiotensin II receptors (Ferrario *et al.*, 1991), which means that angiotensin II has a regulatory role in the synthesis and secretion of catecholamines. The reason why tissue epinephrine content was, relative to other catecholamines, selectively decreased by enalapril remains to be elucidated.

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=국문초록=

선천성 고혈압 흰쥐와 정상혈압 흰쥐의 교감신경성 신경전달에 미치는 부신수질 및 Renin-Angiotensin계의 역할

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선천성 고혈압 흰쥐(SHR)와 정상혈압 흰쥐에서 교감신경성 신경전달에 미치는 부신수질 및 renin-angiotensin계의 역할을 알아보기 위해, 부신수질을 제거하거나 angiotensin 변환 효소 억제제를 장기간 처치한 뒤 중추신경계가 파괴된 상태에서 절전신경을 자극했을 때 나타나는 승압반응과 대동맥의 catecholamine농도 및 angiotensin 변환 효소 활성도의 변화를 비교 검토하였다.

부신수질을 제거하더라도 중추신경계를 파괴하기 전후의 혈압에는 영향을 주지 못했으며, 절전신경 자극에 의한 승압반응은, 자극 주파수에 의존적으로 증가하였으며 prazosin 전처치로서 거의 완전히 억제되었다.

정상혈압 흰쥐에서와는 달리, 선천성 고혈압 흰쥐에서는 부신수질을 제거했을 때는 절전신경 자극에 의한 승압반응이 부신수질을 제거하지 않는 군(이하 대조군)에 비하여 유의하게 약화되었다. SHR에서 부신수질 제거로 부신 catecholamine 함량은 현저히 감소되었고, 혈청의 angiotensin 변환 효소 활성도는 감소되는 경향을 나타내었다. 그러나 혈장 및 대동맥 절편의 catecholamine 함량, 대동맥 절편의 angiotensin 변환 효소의 활성도는 대조군과 유의한 차이가 없었다. 그러나 WKY에서는 부신수질이 제거된 군에서 대동맥 절편의 angiotensin 변환 효소의 활성도와 catecholamine함량이 대조군에 비해 유의하게 증가되어 있었다.

Enalapril처치에 의해서 선천성 고혈압 흰쥐 평균 혈압은, 부신 catecholamine 함량 및 대동맥 절편의 angiotensin 변화 효소의 활성도와 함께 현저히 저하되어 정상혈압 흰쥐와 유사하였다. 그리고 선천성 고혈압 흰쥐에서 부신수질의 제거로 절전신경 자극에 의한 승압반응이 대조군에 비하여 약화되는 현상은 enalapril을 처치하였을 때는 관찰되지 않았다.

이상의 결과로 미루어보아 교감신경성 신경전달을 항진시키는 부신수질의 작용은 renin-angiotensin계의 활성화에 의존적이었으며, 부신수질의 제거로 정상혈압 흰쥐에서는 renin-angiotensin계가 보상적인 조절이 일어났으나, 선천성 고혈압 흰쥐에서는 보상적인 조절이 일어나지 않았다.