Korean J. of Pharmacology
Vol. 28, No. 1, pp. 61-74, 1992

Influence of Blockade of Sympathetic Nervous System, Renin-Angiotensin System, and Vasopressin System on Basal Blood Pressure Levels and on Pressor Response to Norepinephrine, Angiotensin II, and Vasopressin

Haeng Nam Chung

Department of Pharmacology, Chonnam University Medical School, Kwangju, Korea

ABSTRACT

Influence of the blockade of the three major pressor systems—sympathetic nervous system (SNS), renin-angiotensin system (RAS) and vasopressin system—on the pressor responsiveness to norepinephrine (NE), angiotensin II (AII), and vasopressin (VP) as well as on basal blood pressure (BP) levels was investigated in urethane-anesthetized rabbits. To block the SNS and RAS, chlorisondamine (CS) and pirenzepine (PZ), sympathetic ganglionic blockers, and enalapril (ENAL), an inhibitor of angiotensin converting enzyme, respectively were used. And for suppressing the VP system bremazocine (BREM), a kappa opiate receptor agonist shown to suppress plasma levels of VP, was employed.

Each of CS (0.4 mg/kg), ENAL (2 mg/kg), and BREM (0.25 mg/kg) produced almost same levels of steady hypotensive state. The hypotensive effect of BREM was significantly attenuated by desmopressin, a synthetic VP-like analogue, suggesting the hypotension being at least in part due to suppression of plasma levels of VP. CS, ENAL, and BREM elicited further fall of the BP which had been lowered by ENAL or BREM, CS or BREM, and CS or ENAL, respectively. The hypotension produced by both CS and PZ together with either of ENAL or BREM was more marked than that produced by the three drugs other than CS.

CS potentiated the pressor response not only to NE but to AII and VP. The pressor effect of AII was increased by ENAL and BREM, too. The pressor response to VP was also enhanced by BREM. Blockade of α-adrenergic receptors with phentolamine or phenoxybenzamine potentiated the pressor response to AII and that to VP.

The results on basal BP levels indicate that the three major pressor systems are all participating in control of BP, but SNS has the greatest potential for supporting BP. The finding that blockade of one of the pressor systems induced enhanced pressor responsiveness to the pressor hormone of that particular system as well as to the pressor hormone(s) of the other systems(s) provides evidence for important interactions among the three major pressor systems.

Key Words: Rabbit blood pressure, Sympathetic nervous system, Renin-angiotensin system, Vasopressin system, Chlorisondamine, Pirenzepine, Enalapril, Bremazocine, Norepinephrine, Angiotensin II, Vasopressin.

INTRODUCTION

Arterial blood pressure (BP) is maintained by three major pressor systems: the sympathetic nervous system (SNS), the renin-angiotensin system (RAS) and the vasopressin system. The contributions of these systems to the maintenance of BP have frequently been evaluated by observing the

effect on BP of pharmacological agents that block each of the systems. It has been repeatedly shown that blockade of one of the pressor systems activates the other uninhibited systems. For example, sympathetic ganglionic blockade increases the contribution of RAS and vasopressin(VP) to the maintenance of BP, the treatment with an angiotensin converting enzyme inhibitor leads to the increased contribution of SNS and VP, and so forth (Houck *et al.*, 1983; Brand *et al.*, 1988; Jacob *et al.*, 1988; Hasser and Bishop 1988; Cornish *et al.*, 1990). Also, it has been demonstrated that change in the physiological state of an animal which activates a particular system may increase the contribution of that system in sustaining BP. Thus, dehydration or hemorrhage, for example, results in increased contribution of VP to the BP maintenance (Ryan *et al.*, 1989; Aisenbrey *et al.*, 1981; Andrews *et al.*, 1981; Fejes-Toth *et al.*, 1985; Schwartz and Reid 1981, 1983), whereas sodium depletion increases the contribution of RAS(Kopelman *et al.*, 1983; Samuels *et al.*, 1976).

Previous studies in our laboratory have demonstrated in rabbits that the pressor effects of both norepinephrine (NE) and angiotensin II (AII) were potentiated by blockade of SNS with hexamethonium or chlorisondamine (Ahn 1970; Lim 1971). Also, it has been shown that blockade of RAS with captopril resulted in an enhanced response to another pressor hormone VP in rats(Spertini *et al.*, 1981), and that the pressor responses to VP and NE were greater and more prolonged in VP-deficient Brattleboro rats than in normal rats (Laycock and Lightman 1989). These findings may suggest that when one of the pressor systems has been inhibited, the responsiveness of that system as well as the other uninhibited systems to their appropriate pressor hormones may increase, contributing to the maintenance of BP. The possibility of this interpretation was examined in this study. To produce blockade of the SNS and RAS, chlorisondmaine (CS) and pirenzepine(PZ), sympathetic ganglionic blockers, and enalapril(ENAL), an inhibitor of angiotensin converting enzyme, respectively were employed. And to block the VP system bremazocine (BREM), a kappa opiate receptor agonist shown to suppress plasma levels of VP (Leander *et al.*, 1985), was used.

METHODS

Rabbits of either sex, weighing between 1.8 and 2.2 kg, were anesthetized with sc urethane (1 g/kg). The animal was fastened supine and the trachea was canulated. The left femoral artery was canulated and the arterial blood pressure was recorded on the ink writing recorder (Gould Instruments Inc, model 3400) through the pressure transducer (Statham P23XL). Blood pressure (BP) was expressed as diastolic BP (mean±SE, mmHg) in this paper.

In 8 rabbits changes of BP were observed for 4 hr (ar room temperature 20~23°C) during which 0.5 ml/kg of saline (27~30°C) was injected every 20 min. At the time of the canulation of the femoral artery, about 1 hr after anesthesia, BP ranged from 79 to 87 mmHg but BP declined gradually, reaching to 68 to 74 mmHg (range of decrease: 8~18 mmHg) within 1hr. For about 3 hr thereafter each rabbit maintained comparatively steady BP levels, showing a variation of from an increase of 4 mmHg to a decrease of 6 mmHg. Based on these data the experiment started at least 1hr after the canulation, i. e., 2 hr after anesthesia.

Drugs were injected into the left ear vein in a volume of 0.5 ml/kg, and infusion of drugs were into the right ear vein at a rate of 0.1 ml/kg/min.

The animals in which the pressor action of DMPP was examined were bilaterally vagotomized by cutting the vagal nerve trunks at the level of the neck 1hr before the experiment.

Magnitude of the pressor response was expressed in two ways. In case of NE and AII difference between the preinjection BP level and the maximum BP level achieved by an injection of these agents (mmHg) was taken. In case of VP, in addition to this difference, the duration, time (sec) from beginning of rise of BP till return to a half of the rise, was also measured.

Drugs. Chlorisondamine chloride (Ciba), enalapril maleate (Merck Sharp & Dohme), bremazocine HCl (RBI), desmopressin acetate (Sigma), pirenzepine dihydrochloride (Sigma), norepinephrine bitartrate (Sigma), angiotensin I (Sigma), angiotensin II (Sigma), vasopressin (Sigma), phentolamine methanesulfonate (Ciba), phenoxybenzamine hydrochloride (RBI), [d(CH_2)$_5$ Tyr (Me)]-arginine-vasopressin (Sigma) and saralasin

(Sigma) were used. The drugs were dissolved in saline. All doses are expressed as weight of salt when they are salt.

The Student's t-test was used in analysing the results statistically.

RUSULTS

Changes of basal BP levels by CS, ENAL, BREM, and PZ

CS (0.4 mg/kg). As seen in Figs 1 and 4, BP fell abruptly following administration but was partly restored in the next one or two min, and then showed a slight gradual decline. The BP level was almost unvaried during from 10 to 60 min after CS. The restorative response which was followed by the abrupt fall was hardly seen in the rabbits pretreated with PZ.

ENAL (2 mg/kg). BP showed a gradual decline, reaching the lowest point at about 30~60 min following injection, and then a gradual recovery (Fig. 2).

BREM (0.25 mg/kg). BP fluctuated for about 1 hr following administration (Fig. 3-A). BP levels fell gradually and reached its nadir at about 2 hr after BREM.

To examine whether the BP-lowering response to BREM was due to the suppression of plasma levels of VP, effect of desmopressin, a synthetic VP-analogue, on the action of BREM was examined. Desmopressin(0.2 μg/kg) did not cause any change in BP for 2 hr in 4 rabbits tested. After simultaneous administration of BREM and desmopressin BP declined gradually as in rabbits given BREM alone. However, the magnitude of the fall of BP was significantly smaller (Fig. 3-B). And at about 4 hr after the simultaneous administration BP was restored to the original level, whereas BP remained lowered in rabbits given BREM alone.

Baseline BP at 30 min after CS, that at 30~60 min after ENAL and that at 2 hr after BREM were nearly same (BP level columns in Tables 1~4).

PZ (1 mg/kg). This drug did not cause change of BP.

The doses per kg employed in this study were CS 0.4 mg, ENAL 2 mg, BREM 0.25 mg and PZ 1 mg.

CS and ENAL, CS and BREM, ENAL and BREM. CS, ENAL, and BREM elicited further decline of the BP which had been lowered by ENAL or BREM, CS or BREM, and CS or ENAL, respectively. Basal BP levels after combined treatment with CS and ENAL, those after CS and BREM, and those after ENAL and BREM were almost similar, which were significantly lower

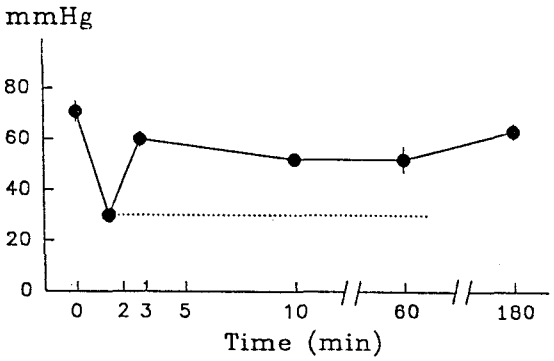

Fig. 1. Change of BP following CS. Each dot (mean± SE) was obtained form 8 rabbits. At 0 time CS (0.4 mg/kg) was injected. BP showed an abrupt fall (at about 2 min following injection) followed by marked restorement (at about 3 min) and then a gradual slight decline. Refer to Fig. 4. In about 3 hr BP returned nearly to the level of before CS. After treatment with PZ little restorement following an abrupt fall was seen (dotted line).

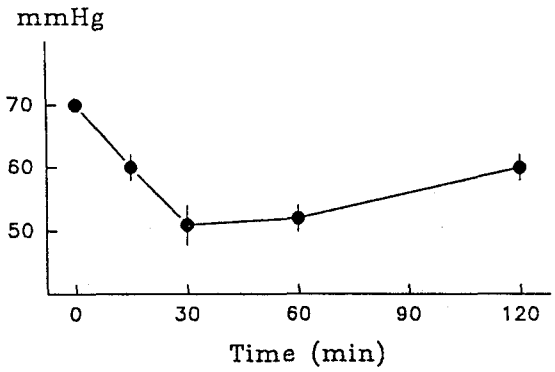

Fig. 2. Change of BP following ENAL. Each dot (mean ±SE) was obtained from 5 rabbits. AT 0 time ENAL (2 mg/kg) was injected. BP showed a gradual decline, reaching the lowest point at about 30 min, and then a gradual recovery.

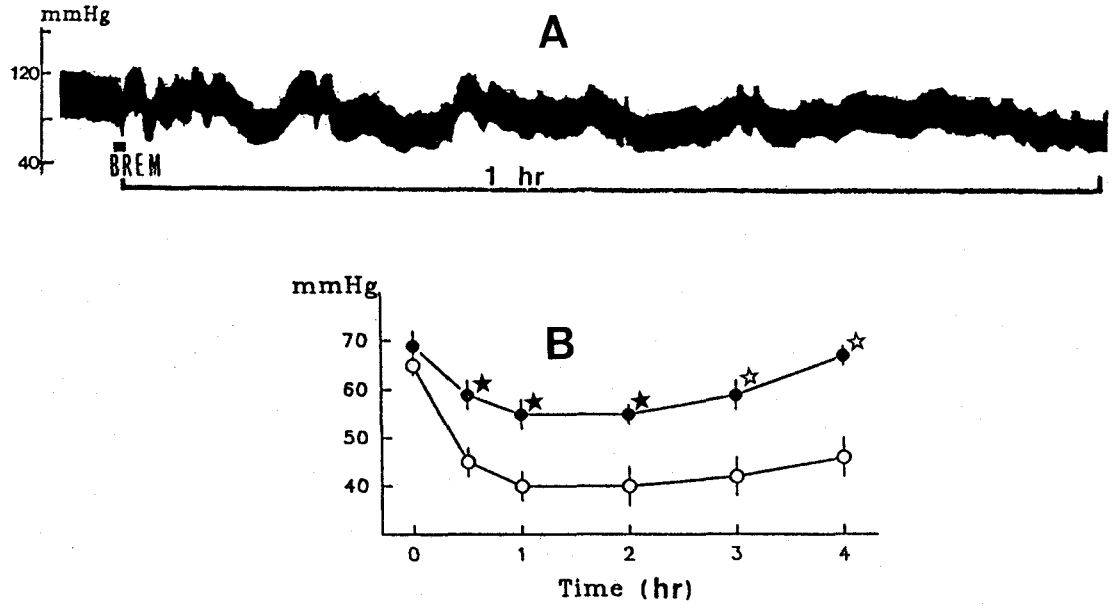

Fig. 3. [A] Change of BP for 1 hr following BREM (0.25 mg/kg) in a rabbit. Fluctuation of BP was noted.
[B] Change of BP following BREM (lower curve), and BREM and desmopressin(upper curve).
Lower curve: At 0 time BREM (0.25 mg/kg) was injected. Each dot (mean±SE) was obtained form 6 rabbits. BP showed a gradual decrease, reaching its nadir at about 1~2 hr, and then a gradual recovery.
Upper curve: At O time BREM (0.25 mg/kg) and desmopressin (0.2 μg/kg) were injected. Each dot (mean±SE) was obtained from 10 rabbits. BP showed a gradual decrease as in rabbits treated with BREM alone. However, magnitude of the decrease was markedly less. When compared two values at the corresponding time (0.5, 1, 2, 3, 4 hr) on the lower and upper curve, each difference was significant(★ $p<0.01$, ☆ $p<0.001$).

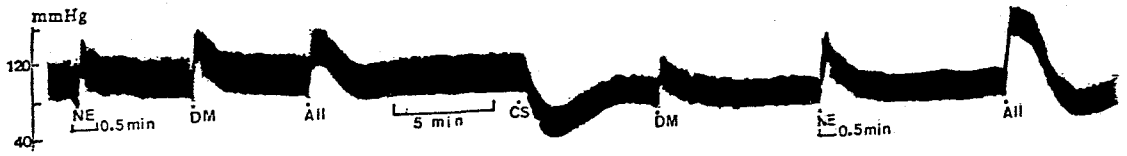

Fig. 4. Effect of CS (0.4 mg/kg) on pressor responses to NE (3 μg/kg), AII (0.3 μg/kg) and DMPP (DM, 100 μg/kg) in a rabbit. The drugs were injected as indicated. The tracing was continuous one. The speed of tracing was faster for 0.5 min when injecting NE. Note that pressor responses to NE and AII were greater after CS, while those to DMPP smaller.

than those after CS, ENAL or BREM alone (Tables 1~4).

CS and PZ, ENAL and PZ, BREM and PZ. PZ potentiated the hypotensive effect of CS, and PZ produced a hypotensive response when given after CS. But PZ was without effect on the hypotension by ENAL and BREM, and vice versa (Tables 1, 4).

As shown above, the hypotensive potency of BREM was not different between rabbits pretreated with CS, ENAL, or PZ alone, but rabbits which had been given CS together along with PZ or ENAL, which showed very low BP, responded

Table 1. Influence of ENAL, BREM, and PZ in magnitude of BP fall by Chlorisondamine (0.4 mg/kg) in rabbits

Pretreatment	n	BP level before CS	Magnitude of BP fall[#]
None	8	74±4	22±2
ENAL	6	56±3**	25±4
BREM	6	55±4**	24±1
PZ	8	73±4	37±2***
BREM followed by ENAL	7	36±4***	22±2
ENAL followed by PZ	4	54±5*	28±4
BREM followed by PZ	4	60±3*	26±2
BREM followed by ENAL and then PZ	7	40±3***	20±2

Numerals: mean±S.E mmHg.

[#] Difference of BP level at about 30 min after CS and that before CS.

*, ** and *** denote significant difference from none-group: *, $p<0.05$; **, $p<0.01$; ***, $p<0.001$.

Doses per kg: ENAL 2 mg, BREM 0.25 mg, PZ 1 mg.

Time of pretreatment: EREM 2 hr, ENAL 30 min, PZ 10 min before CS.

BP level after pretreatment with 'BREM followed by ENAL' was significantly lower than that of after 'ENAL'($p<0.01$) and that of after 'BREM' ($p<0.01$).

Table 2. Influence of CS, BREM, and PZ on magnitude of BP fall by Enalapril (2 mg/kg) in rabbits

Pretreatment	n	BP level before ENAL	Magnitude of BP fall [#]
None	11	74±4	17±1
CS	8	58±2***	22±4
BREM	6	52±4**	16±2
PZ	4	72±4	17±4
CS followed by PZ	4	31±3***	16±5
BREM followed by PZ	4	56±4**	20±5
BREM followed by CS	4	32±3***	14±2
BREM followed by CS and then PZ	6	30±3***	16±3

[#] Difference of BP level before ENAL and that at about 30 min after ENAL. Time of pretreatment: BREM 2 hr, CS 30 min, PZ 10 min before ENAL. Other legends are the same as in Table 1.

BP level after pretreatment with 'BREM followed by CS' was significantly different form that of after 'BREM'($p<0.01$) and that of after 'CS' ($p<0.001$).

BP level after pretreatment with 'CS followed by PZ' was significantly different form that of after 'CS' ($p<0.001$).

with less marked hypotension (Table 3).

BP levels of rabbits treated with three drugs among CS, ENAL, BREM and PZ. BP levels of rabbits treated with BREM plus CS plus PZ, and ENAL plus CS plus PZ were 30±3 mmHg(n=6) and 30±3 mmHg(n=8), respectively, showing almost no difference. These values, however, were significantly different from the value(40±3 mmHg, n=7) obtained from rabbits treated with BREM plus ENAL plus PZ($p<0.05$), suggesting greater potency of combination of CS and PZ in producing hypotension.

Table 3. Influence of CS, ENAL, and PZ on magnitude of BP fall by Bremazocine (0.25 mg/kg) in rabbits

Pretreatment	n	BP level before BREM	Magnitude of BP fall #
None	6	68±2	23±3
CS	8	54±3**	17±2
ENAL	4	58±1**	15±6
PZ	4	72±3	24±4
CS followed by PZ	4	38±3***	9±2**
ENAL followed by CS	8	35±5***	11±3*
ENAL followed by PZ	4	54±4*	17±4
ENAL followed by CS and then PZ	8	30±3***	9±2**

Difference of BP level before BREM and that at about 2 hr after BREM. Time of pretreatment: ENAL 45min,, CS 15 min, PZ 10 min before BREM. Other legends are the same as in Table 1.

BP level after pretreatment with 'ENAL followed by CS' was significantly different from that of 'after CS' ($p<0.01$) and that of 'after ENAL' ($p<0.01$).

BP level after pretreatment with 'CS followed by PZ' was significantly different from that of after 'CS' ($p<0.001$).

Table 4. Influence of CS, ENAL, and BREM on magnitude of BP fall by Pirenzepine (1 mg/kg) in rabbits

Pretreatment	n	BP level before PZ	Magnitude of BP fall #
None	8	65±3	2±1
CS	14	46±3***	11±3**
ENAL	4	53±3**	1±1
BREM	4	47±4**	1±1
ENAL followed by CS	4	35±3***	10±3**
BREM followed by CS	4	34±4***	10±2**
BREM followed by ENAL	4	38±4***	2±1
BREM followed by ENAL and then CS	8	33±4***	9±3**

Difference of BP level before PZ and that at about 10 min after PZ. Time of pretreatment: BREM 2 hr, ENAL 45 min, CS 30 min before PZ. Other legends are the same as in Table 1.

BP level after pretreatment with 'BREM followed by ENAL' was significantly different from that of 'after ENAL' ($p<0.01$) and that of 'after BREM' ($p<0.05$).

BP level after pretreatment with 'ENAL followed by CS' was significantly different from that of 'after ENAL' ($p<0.01$) and that of 'after CS' ($p<0.01$).

BP level after pretreatment with 'BREM followed by CS' was significantly different from that of 'after BREM' ($p<0.05$) and that of 'after CS' ($p<0.01$).

Influence of CS, ENAL, and BREM on pressor response to NE, AII, and VP

CS. At about 5 min after CS administration, when BP fell and remained lowered, responses to NE, AII, and VP were enhanced (Table 5, Fig. 4) and these enhanced responses persisted until at least 3hr after CS. The pressor response to DMPP was inhibited by CS (Fig. 4).

Table 5. Influence of CS, ENAL, and BREM on pressor responses to NE (3 μg/kg), AII (0.3 μg/kg) and VP (50 ml. U./kg) in rabbits

Pretreatment	Initial BP(mmHg)	Magnitude of BP rise#			
		NE height(mmHg)	AII height(mmHg)	VP height(mmHg)	VP duration(sec)
None	68±2 (37)	23±1 (37)	20±1 (34)	17±1 (12)	110±8
CS	55±4 (16)	57±3*** (8)	48±4*** (8)	29±4** (10)	208±25**
ENAL	56±3 (22)	27±2 (11)	28±1*** (11)	20±1 (13)	93±12
BREM	49±4 (24)	26±1 (12)	35±3*** (12)	24±2** (12)	226±17***
CS+ENAL	29±3 (20)	49±3*** (9)	61±4*** (9)	32±4** (12)	229±20***
CS+BREM	31±4 (20)	54±5*** (10)	58±3*** (10)	30±3*** (10)	297±30***
ENAL+BREM	40±4 (26)	28±3 (13)	30±1*** (7)	23±2* (12)	206±18***
CS+ENAL+BREM	29±3 (29)	48±3*** (29)	66±1*** (12)	36±2*** (28)	375±34***

Numerals: mean±SE mmHg(number of expts).

#Magnitude of BP rise: see Methods.

*, ** and *** denote significant difference from the corresponding none-group: *, $p<0.05$; **, $p<0.01$; ***, $p<0.001$.

In AII column the value after 'CS+ENAL' was significantly different from the value 'after CS' ($p<0.05$) and that 'after ENAL' ($p<0.001$).

In AII column the value after 'CS+BREM' was significantly different from the value 'after CS' ($p<0.05$) and that 'after BREM' ($p<0.001$).

In VP-duration column the value after 'CS+BREM' was significantly different from the value 'after CS' ($p<0.05$) and that 'after BREM' ($p<0.05$).

ENAL. At about 30 min after ENAL administration the response to AII became greater, while the responses to NE and VP remained unchanged (Table 5). This potenitation of AII response persisted at least for 2 hr.

The pressor response to angiotenisn I 3 μg/kg, a rise of 41±3 mmHg from preinjection level of 70± 7 mmHg in 9 rabbits, was reduced to that of 5± 1 mmHg from 64±5 mmHg at about 5min after ENAL. This reduction continued at least for 2 hr, as well.

BREM. At about 1 hr after BREM administration no change was observed in the effect of three pressor agents. At 2 hr the response to AII and VP became increased while that to NE remained unaltered. In the VP response both the increase of the magnitude of rise in BP and the prolongation of the duration of the rise were observed (Fig. 5, Table 5).

PZ. No change in the response to the three drugs was observed.

CS and ENAL. AII produced more marked increase of BP in rabbits treated with CS and ENAL than in animals treated with CS or ENAL alone (Table 5).

CS and BREM. The enhanced response to AII and VP after CS and after BREM was further increased by BREM and by CS, respectively (Table 5).

ENAL and BREM. The enhanced response to AII after ENAL and BREM was not further augmented by BREM and ENAL, respectively (Table

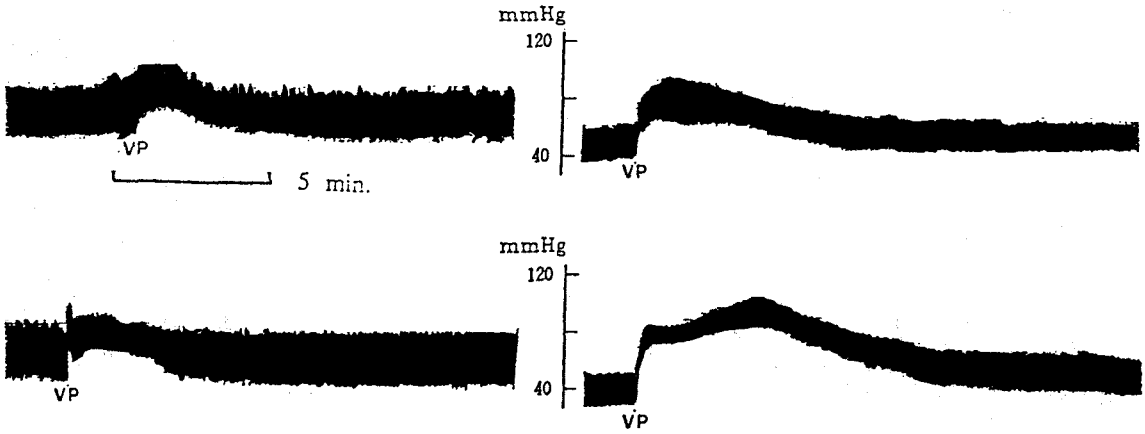

Fig. 5. Effect of BREM (0.25 mg/kg) and CS (0.4 mg/kg) on pressor responses to VP (50 mI. U. /kg) in rabbits. Left panels: control response. Upper right panel was obtained 2 hr after BREM, and right lower 2 hr after BREM and 30 min after CS.

Table 6. Effect of phentolamine (1 mg/kg, PA) and phenoxybenzamine(5 mg/kg, PBZ) on pressor responses to NE, AII, and VP in rabbits

	NE (3 μg/kg)		AII @(0.3 or 1 μg/kg)		VP(50 mI.U./kg)	
	Preinjection BP level	Pressor # response	Preinjection BP level	Pressor # response	Preinjection BP level	Pressor # response
			Phentolamine(n=6~8)			
before	74±2	27±3	70±2	35±2	67±2	20±1
after PA						
ca 10 min	44±3	5±1***	54±5	43±2*	47±4	31±1*
ca 20 min	47±7	13±2**	52±5	28±3	49±5	20±2
ca 2 hr	56±6	17±2*	58±5	29±2	55±5	21±2
			Phenoxybenzamine(n=5)			
before	73±2	24±3	72±3	18±1	70±3	17±2
after PBZ						
ca 30 min	47±4	=0***	46±3	30±3**	44±4	33±3**
ca 3 hr	37±5	=0***	37±5	24±2*	39±5	37±3***
					[59±2	30±2]**

Numerals: mean±SE mmHg.

#Magnitude of BP rise in height as in Table 5.

@doses of AII were 1 μg/kg in PA experiments and 0.3 μg/kg in PBZ experiments. Responses to pressor agents were examined at indicated time.

*, ** and *** denote significant difference from the before-value on the same column (*, $p<0.05$; **, $p<0.001$; ***, $p<0.001$).

In bracket, result of experiments from the rabbits whose BP levels were raised by infusion of AII(0.2 μg/kg/min).

Table 7. Relations of pressor response to NE, AII and VP with initial BP

	Range of preinjection BP level (mmHg)		
	16~29	30~39	40~54
NE(3 μg/kg)	38±4☆	61±4	36±2
	(15)	(12)	(5)
AII(0.3 μg/kg)	68±3	74±3***	46±1
	(15)	(11)	(3)
VP(50 mI.U./kg)	28±3☆	48±2**	35±3
	(11)	(8)	(9)

The result was obtained from rabbits treated with 3 agents; CS, ENAL and BREM.
Numerals: magnitude of BP rise in height, mean±SE mmHg (number of expts).
*** and **: significant difference from the values on '40~54' mmHg on the same rank (***, $p<0.001$; **, $p<0.01$).
☆: Significant difference from the values on '30~39' mmHg on the same rank ($p<0.001$).

5).

CS, ENAL, and BREM. In rabbits treated with these three drugs, the NE response was not different from that in rabbits treated with CS alone. The response to AII was almost same as that in rabbits treated with either of CS and ENAL or CS and EREM. VP, in these rabbits, tended to produce more marked pressor response, although not statistically significant, than in the rabbits treated with CS and BREM (Table 5).

Effect of α-adrenergic antagonist, AII-receptor antagonist, and vasopressinergic antagonist on pressor reponses to NE, AII, and VP

Experiments in rabbits treated with phentolamine (Table 6): Phentolamine depressed the BP level. At about 10 min after phentolamine the response to NE was markedly inhibited, whereas the response to AII and VP was significantly increased. During the next 2 hr the response to NE was gradually restored, and that to AII and VP became smaller, returning to the original response.

Experiments in rabbits treated with phenoxybenzamine (Table 6): To further ascertain the potentiating effect of the α-adrenergic antagonist on the pressor response to AII and VP, experiments were performed with phenoxybenzamine. During the period of complete inhibition of the NE pressor effect, the pressor effect of AII and VP was markedly increased.

To investigate the influence of initial BP levels on the pressor response to VP, the BP level before injection of VP was raised with AII and the response was examined. As shown in Table 8 (in bracket), the potentiating effect of phenoxybenzamine remained unchanged under the raised BP level.

Experiments in rabbits treated with saralasin: Infusion of saralasin (6 μg/kg/min) did not affect basal BP levels. During the infusion the pressor response to AII(1 μg/kg) was markedly inhibited, from the control rise of 37±2 mmHg (n=4) to 7±1 mmHg. The infusion did not modify the pressor response to NE and VP.

Experiments in rabbits treated with [d(CH$_2$)$_5$ Try(Me)]-AVP: After [d(CH$_2$)$_5$ Tyr(Me)]-AVP (20 μg/kg) basal BP levels were not varied. The pressor response to VP was almost completely blocked (from a rise of 21±2 mmHg to 2±1 mmHg, n=7), and the response to NE and AII remained unchanged.

§ Relationship of the magnitude of the pressor response with the initial BP

Since it has been shown that, within limits, the pressor response to the pressor agents frequently bears an inverse relationship to the initial BP (Wilder 1962) the enhanced pressor response shown in the present study might simply be the result of the lowered BP by the blockers. So this possibility was examined.

Observations in rabbits treated with three drugs: CS, ENAL and BREM: Rabbits treated with these three drugs showed low BP, ranging form 16 to

Table 8. Influence of elevation of initial BP on pressor responses to NE, AII and VP in CS-treated rabbits

	NE (3 μg/kg)		AII (0.3 μg/kg)		VP(50 mI.U./kg)	
	Preinjection BP level	Pressor # response	Preinjection BP level	Pressor # response	Preinjection BP level	Pressor # response
before CS	74±3	22±4	74±3	20±3	72±3	22±2
after CS[@] (before infusion)	44±4	42±3	46±5	46±2	44±6	35±2
during infusion of						
NE	78±4	–	73±5	40±4[ns]	78±2	28±3[ns]
AII	88±5	40±2[ns]	84±3	–	82±3	28±3[ns]
VP	85±8	41±2[ns]	80±5	46±7[ns]	68±2	–

Numerals: mean± SE (mmHg) of 4 to 5 expts.

[#] Magnitude of BP rise in height as in Table 5.

[@] At about 10 min after CS responses to pressor agents were checked, and then infusion of NE (1.2 μg/kg/min), AII (0.06 μg/kg), and VP (10 mI. U./kg/min) were performed. During the infusion responses to pressor agents were checked again.

ns: no significant difference from the value 'after CS' on the same column.

54 mmHg. These rabbits were arbitrarily divided into three groups depending on the initial level of BP, and responses to three pressor agents were scrutinized.

As shown in Table 7, rabbits showing the BP level of between 30 and 39 mmHg responded with greater rise than those between 40~54 mmHg. When BP was from 16 to 29 mmHg response to NE and VP became smaller, whereas the response to AII was little varied.

Experiments in CS-treated rabbits: To further investigate dependence of the magnitude of the response on initial BP the low BP level of CS-treated rabbits was raised by infusion of NE, AII or VP, and responses to NE, AII and VP were examined. As shown in Table 8, in CS-treated rabbits, even when the BP was raised, the three pressor drugs produced almost same degree of pressor response.

DISCUSSION

Blockade of SNS. There will be no dispute that CS and PZ block the SNS by acting on the nicotinic and muscarinic synapses in the sympathetic ganglia to produce hypotension (Yoo 1989).

Blockade of RAS. Angiotensin converting enzyme (ACE) inhibitors such as captopril and ENAL are commonly used for the inhibition of the RAS. Despite the fact the ENAL has to be converted to its active diacid form (Patchett *et al.*, 1980), this conversion does not limit the use of ENAL as an experimental tool (Tomlinson *et al.*, 1990). In the present experiment the pressor response to angiotensin I was inhibited soon after administration of ENAL, indicating the inhibition of ACE in the rabbit. ENAL was successfully used as a blocker of RAS in elucidating the central pressor action of muscarine in the rabbit(Lee 1991).

The hypotension following ACE inhibition, however, is not simply related to the reduction in plasma AII levels (Mento and Wilkes 1987). The participation of other factors such as bradykinin (Erdos and Skidgel 1987), inhibition of local AII production (Unger *et al.*, 1986), and production of vasodilator prostaglandins (Dusing *et al.*, 1983; Swartz *et al.*, 1980) has been suggested.

Blockade of VP system. BREM and other kappa opioid agonists have frequently been reported to produce the suppression of plasma levels of VP by inhibiting VP release from the pituitary (Leander *et al.*, 1985; Slizgi and Ludens 1982). Leander *et al.* (1985) has shown that desmopressin, a synthetic VP-like analogue, blocked the diuretic effect of BREM. In our laboratory the same result was obtained from anesthetized hydrated rabbits(unpublished data). In the present experiment BREM caused hypotension and the hypotension was sig-

nificantly attenuated by desmopressin (Fig. 3), suggesting the association of the cardiovascular effect of BREM with action site(s) of desmopressin. Although desmopressin is commonly known as a specific V_2-receptor agonist, the drug too has pressor activity, even though weak, and is characterized by its long duration of action (Varva *et al.*, 1968, 1974; Pliska 1985). The partial inhibition by desmopressin of the hypotension due to BREM, therefore, could be interpreted as that the suppression of plasma VP levels induced by BREM caused loss of vasoconstriction being induced by V_1-receptors participating in the maintenance of BP (Malayan *et al.*, 1980; Montani *et al.*, 1980), resulting in hypotension.

On the other hand, however, Salas *et al.* (1989) suggested that the diuretic effect of BREM was dissociated from the cardiovascular response. Some authors also have shown that the hypotension by BREM and related kappa-opiate agonists in anesthetized animals was due to reduction of the sympathetic outflow via peripheral opioid receptors (Feuerstein and Faden 1982; Laurent and Schmitt 1983; Ensinger *et al.*, 1986).

SNS, RAS, and VP system in supporting basal BP levels. PZ produced no hypotension but it did when given in the presence of CS (Table 4), and CS produced more marked fall of BP in the presence of PZ (Table 1). These findings indicate the participation of the synaptic muscarinic receptors in supporting BP under the blockade of the synaptc nicotinic receptors. The magnitude of the hypotensive effect of CS without PZ, of ENAL, and of BREM, with the doses employed in this study, was almost same, and each of these three drugs elicited further fall of the BP which had been lowered by either of the other two drugs (Tables 1～3). These results show that SNS, RAS, and VP system are all participating in control of BP and that the magnitude of the effect of the sympathetic ganglionic nicotinic activity on the maintenance of BP is comparable with either that of RAS and of VP system. The hypotension induced by both CS and PZ together with ENAL or BREM was more marked than that produced by the combination of the three drugs other than CS, suggesting greater potency of SNS in producing hypotension.

Depressor potency of BREM became weaker under the influence of CS (Table 3). This might imply the participation of the SNS in its hypotensive effect (Feuerstein and Faden 1982; Laurent and Schmitt 1983; Ensinger *et al.*, 1986).

Potentiation by blockers of pressor responses to NE, AII, and VP. In the present study the blockade of SNS by CS potentiated the pressor responses not only to the pressor hormone of SNS−NE−but to the pressor hormones of the other two pressor systems, AII and VP. In a similar way, the blockade of VP system by BREM caused the increased responses to VP and AII. The blockade of RAS augmented only the response to AII, but the response to VP in rabbits treated with three drugs; CS, BREM, and ENAL tended to be greater, although not significant, than in rabbits treated with CS and BREM, suggesting increased responsiveness to VP by ENAL. These findings may suggest that the three pressor systems display important interactions to maintain normal BP. About the mechanism(s) of these interactions no satisfactory explanation has been provided. There is, however, increasing evidence to support the view that BP is continuously regulated not only by the SNS but also a variety of hormones (Laycock and Lightman 1989; Burnier and Brunner 1983; Feuerstein *et al.*, 1984; Poole *et al.*, 1978; Peach 1977).

Potentiation by α-antagonists of pressor effects of VP and AII. The potentiation by phentolamine and phenoxybenzamine of the pressor effects of AII and VP (Table 6) can be interpreted as the same way as the potentiation by CS. The potentiation by α-antagonists of the pressor action of VP has been shown in the rat (Erker and Chan 1977; Dekanski 1952). Supek *et al.* (1962) also reported in the dog that chlorpromazine, as an α-antagonist, potentiated the responses to both VP and AII. The mechansim of the potentiating action has not been established. It is suggested that this action is not specifically related to the chemical structure of the antagonists, but most probably is related to α-adrenergic blocking activity (Erker and Chan 1977; Supek *et al.*, 1962).

Relationship of the magnitude of the pressor response with the initial BP. Table 7 shows that pressor responses to NE, AII and VP when the inital BP was between 30～39 mmHg were greater than when BP was between 40～54 mmHg, suggesting an inverse relationship of the pressor effect with the initial BP. When BP was further lowered (16～29 mmHg), however, the response to NE and VP became smaller, whereas that to AII remained un-

altered, showing that the causal agent to produce the pressor action plays a role. Table 8 clearly demonstrates that the potentiation by CS of the pressor effect of the three pressor hormones is not related to the lowered initial BP. Similarly the potentiation by phenoxybenzamine of the pressor response to VP could be observed when the initial BP was raised (Table 6).

Acknowledgement. The author wishes to thank Prof. Yung In Kim, Department of Pharmacology, Chonnam University Medical School, Kwangju, Korea, and Prof. Toshimitsu Uchiyama, Department of Pharmacology, Toho University School of Medicine, Tokyo, Japan, for their invaluable advice and assistance during the course of this work.

REFERENCES

Ahn KS: *Modification of pressor effects of norepinephrine and angiotensin by ganglioplegics in rabbits. Chonnam MJ 7: 411-420, 1970*

Aisenbrey GA, Handelman WA, Arnold P, Manning M and Schrier RW: *Vascular effects of arginine vasopressin during fluid deprivation in the rat. J Clin Invest 67: 961-968, 1981*

Andrews CE Jr and Brenner BM: *Relative contributions of arginine vasopressin and angiotensin II to maintenance of systemic arterial pressure in the anesthetized water-deprived rat. Circ Res 48: 254-258, 1981*

Brand PH, Metting PJ and Brittion SL: *Support of arterial blood pressure by major pressor systems in conscious dogs. Am J Physiol 255: H483-H491, 1983*

Burnier M and Brunner HR: *Pressor responses of rats to vasopressin: effect of sodium, angiotensin, and catecholamines. Am J Physiol 244: H 253-H 258, 1983*

Cornish KG, Barazanji MW and Iaffaldano R: *Neural and hormonal control of blood pressure in conscious monkeys. Am J Physiol 258: H 107-H 112, 1990*

Dekanski J: *The quantitative assay of vasopressin. Brit J Pharmacol Chemother 7: 567-572, 1952*

Dusing R, Scherhag R, Landsberg G, Glanzer K and Kramer HJ: *The converting enzyme inhibitor captopril stimulates prostacyclin synthesis by isolated rat aorta. Eur J Pharmacol 91: 501-504, 1983*

Ensinger H, Hedler L, Szabo B and Starke K: *Bremazocine causes sympathoinhibition and hypotension in rabbits by activating peripheral K-receptors. J Cardiovasc Pharmacol 8: 470-475, 1986*

Erdos EG and Skidgel RA: *The angiotensin I-converting enzyme. Lab Invest 56: 345-348, 1978*

Erker EF and Chan WY: *The site and the mechanism of phenoxybenzamine potentiation of the pressor response to oxytocin and vasopressin: In vivo and isolated aortic strips studies. J Pharmacol Exp Ther 202: 287-293, 1977*

Fejes-Toth G, Naray-Fejes-Toth A and Ratge D: *Evidence against role of antidiuretic hormone in support of blood pressure during dehydration. Am J Physiol 249: H 42-H 48, 1985*

Feuerstein G and Faden AI: *Differential cardiovascular effects of mu, delta and kappa opiate agonists at discrete hypothalamic sites in the anesthetized rat. Life Sic 31: 2197-2200, 1982*

Feuerstein G, Zerbe RL and Faden AI: *Central cardiovascular effects of vasotocin, oxytocin and vasopressin in conscious rats. J Pharmacol Exp Ther 228: 348-353, 1984*

Hasser EM and Bishop VS: *Neurogenic and humoral factors maintaining arterial pressure in conscious dogs. Am J Physiol 255: R 693-R 698, 1988*

Houck PC, Fiksen-Olsen MJ, Britton SL and Romero JC: *Role of angiotensin and vasopressin on blood pressure of ganglionic blocked dogs. Am J Physiol 244: H 115-H 120, 1983*

Jacob HJ, Barres CP, Machado BH and Brady MJ: *Studies on neural and humoral contributions to arterial pressure lability. Am J Med Sci 295: 341-345, 1988*

Kopelman RI, Dzau VJ, Shimabukuro S and Barger AC: *Compensatory response to hemorrhage in conscious dogs on normal and low salt intake. Am J Physiol 244: H 351-H 356, 1983*

Laurent S and Schmitt H: *Central cardiovascular effects of K-agonists dynorphin-(1-13) and ethylketocyclazocine in the anesthetized rat. Eur J Pharmacol 96: 165-169, 1983.*

Laycock JF and Lightman SL: *Cardiovascular interactions between vasopressin, angiotensin and noradrenaline in the Brattleboro rat. Br J Pharmacol 96: 347-355, 1989*

Leander JD, Zerbe RL and Hart JC: *Diuresis and suppression of vasopressin by kappa opioids: Comparison with mu and delta opioids and clonidine. J Pharmacol Exp Ther 234: 463-469, 1985*

Lee CK: *Pressor action of intracerebroventricular nicotine and muscarine in the rabbit. Korean J Pharmacol 27: 21-31, 1991*

Lim DW: *Chlorisondamine, bretylium and guanethidine on the pressor action of angiotensin. Chonnam MJ 8: 457-466, 1971*

Malayan SA, Ramsay DJ, Keil LC and Reid IA: *Effects of increases in plasma vasopressin concentration on plasma renin activity, blood pressure, heart rate, and plasmal corticosteroid concentration in conscious dogs. Endocrinology 107: 1899-1904, 1980*

Mento PF and Wilkes BM: *Plasma angiotensins and blood pressure during converting enzyme inhibition. Hyperten-*

sion 9 (Suppl III): III42-III48, 1987

Montani JP, Liard JF, Schoun J and Mohring J: *Hemodynamic effects of exogenous and endogenous vasopressin at low plasma concentrations in conscious dogs. Circ Res 47: 346-355, 1980*

Patchett AA, Harris E and Tristram EW: *A new class of angiotensin-converting enzyme inhibitors. Nature 288: 280-283, 1980*

Peach MJ: *Renin-angiotensin system: Biochemistry and mechanisms of action. Physiol Rev 57: 313-370, 1977*

Poole CJM, Frankel HL, Williams TDM and Lightman SL: *Neuroendocrine control of vasopressin secretion and its effect on blood pressure in subjects with spinal cord transections. Brain 110: 727-736, 1987*

Pliska V: *Pharmacology of Deamino-D-Arginine vasopressin. In: diabetes inspidus in man: frontiers of hormone research, edited by Zernichow P and Robinson AG. Basal: Karger, Vol 13, p 278-291, 1985*

Ryan KL, Thornton RM and Proppe DW: *Vasopressin contributes to maintenance of arterial blood pressure in dehydrated baboons. Am J Physiol 256: H 486-H 492, 1989*

Salas SP, Roblero J, Ureta H and Huidobro-Toro JP: *Diuretic effect of bremazocine, a kappa-opioid with central and peripheral sites of action. J Pharmacol Exp Ther 250: 992-999, 1989*

Samuels AI, Miller ED, Fray Jr JCS, Haber E and Barger AC: *Renin angiotensin antagonists and the regulation of blood pressure. Federation Proc 35: 2512-2520, 1976*

Schwartz J and Reid IA: *Effect of vasopressin blockade on blood pressure regulation during hemorrhage in conscious dogs. Endocrinology 109: 1778-1780, 1981*

Schwartz J and Reid IA: *Effect of vasopressin blockade on blood pressure regulation in conscious water-deprived dogs. Am J Physiol 244: R 74-R77, 1983*

Slizgi GR and Ludens JH: *Studies on the nature and mechansim of the diuretic activity of the opioid analgesic ethylketocyclazocine. J Pharmacol Exp Ther 220: 585-591, 1982*

Spertini F, Brunner HR, Waeber B and Gavras H: *The opposing effects of chronic angiotensin-converting enzyme blockade by captopril on the responses to exogenous angiotensin II and vasopressin vs. norepinephrine in rats. Cir Res 48: 612-618, 1981*

Supek Z, Uroic B, Gjuris V and Marijan N: *The effect of adrenergic blocking agents and of chlorpromazine on blood pressure increase by vasopressin and angiotensin. J Pharm Pharmacol 14: 284-287, 1962*

Swartz SL, Williams GH, Hollenberg NK, Levine L, Dluhy RG and Moore TJ: *Captopril-induced changes in prostaglandin production. Relationship to vascular responses in normal man. J Clin Invest 65: 1257-1264, 1980*

Tomlinson KC, Gardiner SM and Bennett T: *Hypotensive effects of angiotensin II analogues and angiotensin converting enzyme inhibitors in water-deprived Brattleboro rats. J Cardiovasc Pharmacol 15: 562-568, 1990*

Unger T, Ganten D and Lang RE: *Tissue converting enzyme and cardiovascular actions of convering enzyme inhibitors. J Cardiovasc Pharmacol 8 (Suppl 10): S75-S81, 1986*

Varva I, Machova A, Holelek V, Cort JH, Iaoral M and Sorm F: *Effect of a synthetic analogue of vasopressin in animals and in patients with diabetes insipidus. Lancet II: 948-952, 1968*

Varva I, Machova A and Krejci I: *Antidiuretic action of 1-Deamino-[8-D-Arginine]-vasopressin in unanesthetized rats. J Pharmacol Exp Ther 188: 241-247, 1974*

Wilder J: *Basimetric approach (law of inital value) to biological rhythms. Ann NY Acad Sic 98: 1211-1220, 1962*

Yoo H: *Depressor action of atropine and pirenzepine in the rabbit. Chonnam J Med Sci 2: 79-89, 1989*

= 국문초록 =

교감신경계, Renin-Angiotensin계, Vasopressin계의 차단이 혈압 및 Norepinephrine, Angiotensin II 및 Vasopressin의 승압효과에 미치는 영향

전남대학교 의과대학 약리학교실

정 행 남

마취가토에서 혈압유지에 중요한 역할을 하고 있는 교감신경계, renin-angiotensin계, vasopressin계를 차단하였을때의 혈압자체의 변동과 *norepinephrine* (NE), angiotensin II (AII) 및 vasopressin (VP)의 승압효과의 변동을 조사하였다. 교감신경계와 renin-angiotensin계의 차단에는 각각 교감신경절 차단약인 chlorisondamine (CS)과 pirenzepine (PZ), angiotensin 변환효소억제약인 enalapril (ENAL)를 사용하였다. VP계의 차단에는 혈장 VP농도를 하강시킴이 알려져 있는 kappa opioid 수용체의 작용약인 bremazocine (BREM)을 사용하였다.

CS (0.4 mg/kg), ENAL (2 mg/kg), BREM (0.25 mg/kg)은 각각 비슷한 정도의 저혈압상태를 일으켰다. BREM에 의한 저혈압은 VP와 같은 효과를 가진 합성약인 desmopressin으로 유의하게 길항되었으며 BREM에 의한 저혈압이 적어도 일부 혈장 VP농도의 하강과 관계있음을 시사하였다. CS는 ENAL 또는 BREM으로 하강된 혈압을, ENAL은 CS 또는 BREM으로 하강된 혈압을, BREM은 CS 또는 ENAL로 하강된 혈압을, 더욱 하강시켰다. CS, PZ 그리고 ENAL 또는 CS, PZ 그리고 BREM에 의한 저혈압은 CS이외의 세약물에 의한 저혈압보다 심하였다.

CS는 NE에 의한 승압효과 뿐만아니라 AII와 VP의 승압효과도 강화시켰다. AII의 승압효과는 또 ENAL과 BREM으로도 증대되었다. VP의 승압효과는 BREM으로도 강화되었다. α-수용체의 길항약인 phentolamine과 phenoxybenzamine은 AII와 VP승압효과를 강화시켰다.

3승압계 차단이 혈압자체에 미치는 실험결과는 3계가 모두 혈압조절에 관여하고 그 중에서도 교감신경계가 가장 큰 역할을 하고 있음을 가리키고 있다. 한 승압계의 차단하에서, 그 계의 승압 hormone 뿐만아니라 다른 계의 승압 hormone의 승압효과도 증대됨은 이 3승압계가 긴밀한 상호작용을 하고 있는 증거이다.