HYPOTENSIVE RESPONSES TO CENTRALLY ADMINISTERED TAURINE IN DOCA-SALT HYPERTENSIVE AND SPONTANEOUSLY HYPERTENSIVE RATS

ATSUSHI INOUE, M.D., HAKUO TAKAHASHI, M.D., LI-CHIK LEE, M.D., SUSUMU SASAKI, M.D.
KAZUO TAKEDA, M.D., MANABU YOSHIMURA, M.D., MASAO NAKAGAWA, M.D.
AND HAMAO IJICHI, M.D.

The present study was designed to investigate the short-term effects of intracerebroventricularly-administered taurine in DOCA-salt hypertensive (DOCA), spontaneously hypertensive (SHR) and their respective normotensive control rats anesthetized with urethane.

Blood pressure, heart rate and sympathetic nerve activity were consistently decreased following the injection of taurine 150 μ g per rat in hypertensive rats as well as in normotensive controls of the two groups. Percent changes from the baselines in blood pressure, heart rate and sympathetic nerve activity were significantly larger in DOCA-salt hypertensive rats than those in sham operated rats. In contrast, percent changes in blood pressure and sympathetic nerve activity were not significantly different between spontaneously hypertensive rats and normotensive wistar kyoto rats.

These results show that the responses of blood pressure, heart rate and sympathetic nerve activity to intracerebroventricular taurine are different between spontaneously hypertensive rats and DOCA-salt hypertensive rats. It appears that augmented vasodepressor responses to taurine in DOCA-salt hypertensive rats, as compared to spontaneously hypertensive rats, are due to enhanced inhibition of the sympathetic outflow.

TAURINE is distributed throughout mammalian tissues, with a large amount present in the brain. Taurine is biosynthesized from cysteine and methionine.¹ Orally-administered taurine is absorbed from the gastrointestinal tract and distributed to many organs, accumulating in the brain by passing through the blood brain barrier.^{2,3} Nara et al.⁴ reported that chronic administration of taurine results in a significant increase of taurine content in the cerebellum,

diencephalon and lower brainstem. They also found a significant taurine-induced reduction of blood pressure in the stroke-prone substrain of SHR (SHR-SP), but not in normotensive Wistar Kyoto rats (WKY) or stroke-resistant SHR (SHR-SR). Furthermore, chronic administration of taurine perorally resulted in a significant increase of taurine content in the hypothalamus, and prevented the development of DOCA-salt hypertension.⁵ These results suggest that altered taurine content in the brain may be implicated in the development of some forms of hypertension; i.e. increased taurine content in the brain induced by chronic administration may retard or prevent development of some forms of hypertension. On the other hand, we⁶ have reported

Key Words:

Taurine
Intracerebroventricular injection
Sympathetic nerve activity
DOCA-salt hypertensive rats (DOCA)
Spontaneously hypertensive rats (SHR)

(Received October 12, 1985; accepted August 5, 1986)

The Second Department of Medicine, Kyoto Prefectural University of Medicine, Kyoto Japan

Mailing address: Atsushi Inoue, M.D., The Second Department of Medicine, Kyoto Prefectural University of Medicine, Kawaramachi-Hirokoji, Kamikyo-ku, Kyoto 602, Japan

TABLE I DEVELOPMENT OF DOCA-SALT HYPERTENSIVE RATS

Variables	Rat	Weeks after Treatment				
	Group	before	1	2	3	4
Body weight (g)	Sham	137 ± 4	163 ± 4	232 ± 7	270 ± 7	286 ± 8
	DOCA	139 ± 3	150 ± 4 ^a	203 ± 7 ^a	234 ± 6 ^a	248 ± 7 ^a
Systolic blood pressure (mmHg)	Sham	104 ± 4	108 ± 3	110 ± 3	124 ± 2	128 ± 2
	DOCA	106 ± 2	106 ± 2	129 ± 5 ^a	155 ± 7 ^a	179 ± 9 ^a
Heart rate (beats/min)	Sham	382 ± 17	381 ± 17	390 ± 7	376 ± 10	412 ± 11
	DOCA	382 ± 6	326 ± 6 ^a	344 ± 8 ^a	356 ± 11	370 ± 17

Sham = sham operated rat, DOCA = DOCA-salt hypertensive rat

Data are expressed as mean ± SEM from 7 sham operated rats and 8 DOCA salt hypertensive rats. Data was compared by using a two tailed t-test: differences at 5% level or less were considered significant. a: significantly different from Sham by using two tailed t-test at the 5% level or less.

that intracerebroventricular (ICV) administration of taurine lowers blood pressure by decreasing the sympathetic nerve outflow in normotensive rats.

The aim of the present study was to investigate the central effects of ICV injections of taurine in DOCA-salt hypertensive rats and spontaneously hypertensive rats and to discuss the underlying mechanism.

MATERIALS AND METHODS

Materials: Male 13- 14-week-old SHR and Wister Kyoto rats (WKY) were purchased from Charles River Japan Laboratories (Kanagawa, Japan). DOCA rats were used 4 weeks after the implantation of deoxycorticosterone acetate. At the time of the experiments, the average body weight in sham operated rats, DOCA rats, and WKY and SHR was 286 ± 6g (n = 7), 248 ± 7g (n = 8), 270 ± 6g (n = 10) and 269 ± 7g (n = 7), respectively.

Development of DOCA-salt Hypertension: Sixteen male Sprague-Dawley rats, weighing 130–150g, were purchased from Nihon Rat Laboratories (Osaka Japan). They were subjected to unilateral nephrectomy from a midline abdominal incision during anesthesia with ketamine hydrochloride (40 mg/kg, Park-Davis Sankyo Pharmaceutical Co.). Half of these rats were treated with deoxycorticosterone acetate in a dose of 150 mg/kg as a Silastic subcutaneous implant and the other half were given a Silastic

implant that did not contain deoxycorticosterone acetate, according to the technique of Ormsbee and Ryan.⁷ All rats were given 1% NaCl solution ad libitum. Systolic blood pressure was measured using a tail-cuff method (Narco Bio-system Inc.) once a week for four weeks.

Animal Preparation: Rats were anesthetized with urethane (120 mg/100g, intraperitoneally) and cannulae were inserted into the femoral artery for blood pressure recording and the femoral vein for drug injections. The cannulae consisted of two parts; 19 gauge tygon tubing 15 cm long with a tip of 26-gauge polyethylene tubing 1.5 cm long. The femoral arterial catheter was connected to a pressure transducer (MVP 290, NEC-Sanei), through which pulsatile and mean pressures were measured. Heart rate was recorded simultaneously by triggering a biotachometer with the pressure signal from the transducer. The trachea was cannulated with polyethylene tubing, PE-240, for artificial ventilation.

Intracerebroventricular Injections: A guide cannula (23-gauge stainless steel tubing 3.0 cm long with a 30 gauge stylet) was inserted into the right lateral ventricle (at stereotaxic coordinates⁸; 5.6 mm anteroposterior, 1.7 mm lateral and 2.0 mm dorsoventral, with the incisor bar set 5 mm above the interaural line). Taurine was administered by inserting an injection cannula (30-gauge stainless tubing) connected to a 50 µl syringe into the guide cannula. Because our previous study demonstrated that ICV injections of taurine 50–200 µg produced dose-dependent depressor

Fig.1. Cardiovascular and sympathetic nerve effects of an ICV injection of taurine, 150 μ g. Left panel indicates a sham operated rat and right panel a DOCA-salt hypertensive rat. From top to bottom, tracings of phasic aortic pressure (mmHg), heart rate (beats/min) and a histogram (spikes/10 sec) are shown. The arrow indicates the ICV injection of taurine. The chart speeds are shown in min on the top of the tracings.

responses in normotensive rats⁶ 150 μ g of taurine was used in this study. Taurine, dissolved in 10 μ l of saline, was delivered manually in 10 sec. At the termination of the experiment, the site of ventricular injection was confirmed with the ICV administration of 10 μ l of Evans blue dye and visual inspection for staining of the lateral and third ventricle. Only data from rats in which staining of the ventricles was observed are reported in this paper.

Recording of Sympathetic Nerve Activity:

To determine whether differences in sympathetic nerve activity could account for the depressor responses and responded bradycardia to ICV administered taurine, abdominal sympathetic nerve activity was recorded. The abdominal plexus was exposed through a left abdominal transverse incision, and the nerve bundle between the cardiac and celiac ganglion was placed over bipolar stainless steel electrode tips (uninsulated tips 1.0 mm apart). Nerves and electrode tips were immersed in vegetable oil to prevent the tissue from drying. To reduce noise during the nerve recording, spontaneous respiratory movements were abolished by paralyzing skeletal muscle with decamethonium bromide (Syncurine, 0.2 mg/100g i.v.) and the rats were ventilated with room air by a ventilator (Ealing Co.). The frequency of the ventilator was set at 70–90 cycles/min and pressure was set at 15–25 cm H₂O to maintain normal pO₂ and pCO₂. Because ganglion blockade would be equivalent to crushing the

nerve bundle to obtain zero activity;²⁵ pentolinium tartrate (Ansolsen, 0.5 mg/100g i.v.) was injected routinely at the end of every experiment. During playback, the low-level control of the window discriminator was set to filter background noise persisting after ganglion blockade. Spike potentials were amplified in two steps (P-15 AC preamplifier, Grass Instrument Co. and Bio-physioamplifier, NEC-Sanei Instrument Co.) monitored on an oscilloscope (Kikusui Electronics) and continuously recorded on a magnetic tape recorder (TEAC Co.) together with the blood pressure. Band-pass of the preamplifier was set to below 3000 Hz. Tapes were later played back into an amplitude analyzer to reduce background noise and the resulting pulses were fed into a spike counter (Dia Medical System Co.) whose output was digitalized and printed out on a recorder (Rectigraph, NEC-Sanei Instrument Co.). Integrated nerve activity for 60 sec at 3, 5, 10, 15 and 20 min following the drug injection was expressed as the percent change from the baseline activity.

Intravenous Injections of Taurine: To examine whether these responses were of central origin or not, taurine 150 μ g was injected intravenously using two rats from each of the four groups.

Statistics: Data were expressed as an average $\pm$ SEM. Data from more than three groups of rats were analyzed using analysis of variance; for F ratios significant at 5% or less, the differences

Fig. 2. Cardiovascular and sympathetic nerve effects of an ICV injection of taurine, 150 μ g. Left panel indicates WKY and right panel SHR. The figure is arranged as in figure 1.

between pairs of mean value were examined using the Dunchan multiple range test. Results obtained from only two groups were evaluated using a two-tailed t-test. Differences at 5% level ($p < 0.05$) or less were considered significant.

RESULTS

Body Weight, Systolic Blood Pressure and Heart Rate in DOCA-salt Hypertensive Rats: As shown in Table I, body weight in DOCA-salt hypertensive rats (DOCA) was significantly smaller than that in sham operated rats (Sham) at 1 week. Implantation of a Silicone mold with deoxycorticosterone acetate gradually but consistently increased the blood pressure. The systolic blood pressure was higher in DOCA rats than in Sham rats at the 2nd, 3rd and 4th weeks. The heart rate was lower in DOCA rats than in Sham rats at 2 and 3 weeks.

Blood Pressure and Heart Rate Responses to ICV Injection of Taurine: Average baselines for arterial mean pressure in Sham rats, DOCA rats, WKY and SHR were 84 ± 3 mmHg, 113 ± 8 mmHg, 82 ± 5 mmHg and 117 ± 9 mmHg, respectively, and those for heart rate were 351 ± 13 beats/min, 344 ± 15 beats/min, 307 ± 17 beats/min and 325 ± 9 beats/min, respectively. As for baselines, both DOCA rats and SHR had significantly higher blood pressure than the respective controls, while heart rates were not different between the hypertensive rats and the respective controls in both groups. Both blood pressure and heart rate were consistently de-

creased following the injection of taurine in all four groups (Figs. 1, 2). After injecting taurine 150 μ g per rat, the blood pressure began to fall gradually within 1 min, showing the maximum response at 5 min in DOCA rats and at 10–15 min in the other three groups. Percent changes of depressor and bradycardic responses in DOCA rats were significantly larger than those in the other three groups. In contrast, percent changes of depressor responses in SHR were not different from those in WKY. Percent changes of bradycardic responses were larger in WKY than those in SHR at 15 min (Table II).

Sympathetic Nerve Responses to ICV Injection of Taurine: The baselines for abdominal sympathetic nerve activity were 313 ± 29 spikes/10 sec in Sham rats, 366 ± 31 spikes/10 sec in DOCA rats, 312 ± 19 spikes/10 sec in WKY and 337 ± 33 spikes/10 sec in SHR, respectively. Average baselines for abdominal sympathetic nerve activity in both DOCA rats and SHT were not different from those of the respective controls. After the injection of taurine, the abdominal sympathetic nerve firing began to decrease corresponding to the simultaneous depressor and bradycardic responses. Percent changes of the sympathetic inhibition in DOCA rats were significantly larger than those in Sham rats, while percent changes in SHR were similar to those in WKY (Table II).

Effects of Intravenous Injections: Intravenous injection of taurine 150 μ g affected neither blood pressure, heart rate nor sympathetic nerve activity (Table III).

TABLE II CARDIOVASCULAR AND SYMPATHETIC NERVE EFFECTS INDUCED BY ICV INJECTION OF TAURINE (150 μ g/rat)

Rat groups	Elapsed time in minutes				
	3	5	10	15	20
% Blood pressure change					
Sham	-12 ± 4	-15 ± 5	-24 ± 4	-27 ± 3	-24 ± 4
DOCA	-29 ± 5^{bcd}	-35 ± 5^{bcd}	-34 ± 4^{cd}	-28 ± 5	-22 ± 5
WKY	-10 ± 4	-14 ± 4	-20 ± 3	-20 ± 3	-15 ± 3
SHR	-6 ± 3	-12 ± 3	-15 ± 3	-15 ± 2	-16 ± 2
F ratios	7.2	6.8	4.6	2.9	1.5
% Heart rate change					
Sham	-6 ± 2	-8 ± 3	-14 ± 3	-14 ± 3	-12 ± 3
DOCA	-22 ± 5^{bcd}	-30 ± 5^{bcd}	-30 ± 3^{bd}	-26 ± 3^{bd}	-22 ± 5^{bd}
WKY	-5 ± 2	-10 ± 3	-24 ± 3	-21 ± 2	-17 ± 2
SHR	-5 ± 2	-10 ± 3	-14 ± 3	-13 ± 3	-11 ± 3
F ratios	8.3	11.8	7.3	5.9	4.2
% Sympathetic nerve activity change					
Sham	-22 ± 5	-32 ± 6	-31 ± 6	-28 ± 6	-21 ± 5
DOCA	-54 ± 6^{bcd}	-57 ± 6^{cd}	-54 ± 8	-50 ± 10	-44 ± 11
WKY	-7 ± 8	-20 ± 9	-44 ± 8	-44 ± 8	-35 ± 10
SHR	-12 ± 11	-21 ± 14	-33 ± 9	-24 ± 8	-15 ± 9
F ratios	7.7	3.8	1.6	2.1	1.9

Sham = sham operated rat, DOCA = DOCA-salt hypertensive rat, WKY = wistar kyoto rat, SHR = spontaneously hypertensive rat.

Data are expressed as mean $\pm$ SEM from 7 sham operated rats, 8 DOCA-salt hypertensive rats, 10 WKY and 7 SHR. In comparing data from different groups, with $f_1 = 3$ and $f_2 = 28$, F ratios equal to or greater than 2.95 are significant at 1%.

b: significantly different from Sham using Dunchans multiple range test at the 5% level or less.

c: significantly different from WKY using Dunchans multiple range test at the 5% level or less.

d: significantly different from SHR using Dunchans multiple range test at the 5% level or less.

DISCUSSION

As previously reported, in normotensive rats,⁶ we found that ICV injections of taurine affected the central nervous system to lower blood pressure, probably by decreasing the sympathetic nerve outflow in Sham-operated rats, DOCA-salt hypertensive rats, WKY and SHR. Our most provocative findings were the different patterns of responses between DOCA rats and SHR; i.e. percent changes of depressor responses and decreases in sympathetic nerve activity in DOCA rats were significantly larger than those in Sham rats, while those percent changes in SHR were not greater than those in WKY. The decreases in abdominal sympathetic nerve activity induced by ICV injections of taurine are of central origin because intravenous injections of taurine 150 μ g affected neither blood pressure, heart rate nor sympathetic nerve activity. ICV injection of

taurine is known to cause depressor responses with bradycardia in cats⁹ and rats.¹⁰ Paakkari et al.¹² suggested that the depressor and bradycardiac response might be related in part to an altered parasympathetic mechanism. In our previous and present studies, we have presented direct evidence that hypotension is associated with the splanchnic sympathetic inhibition. As is well known, the decrease in sympathetic nerve activity leads to a fall in arterial blood pressure; hypotensive effects of both clonidine¹² and alpha-methyldopa¹³ are mediated by the decrease of peripheral sympathetic nerve activity.

However, it is well documented that sympathetic activities to various vascular beds are different. Abdominal sympathetic nerve activity alone was measured in the present study. One of criticisms of sympathetic determination is whether the abdominal sympathetic nerve activity represents the whole sympathetic activity. A direct

TABLE III CARDIOVASCULAR AND SYMPATHETIC NERVE EFFECTS INDUCED BY INTRAVENOUS INJECTION OF TAURINE (150 μ g/rat)

Rats groups	Elapsed time in minutes				
	3	5	10	15	20
<i>Blood pressure change (mmHg)</i>					
Sham	3 $\pm$ 1	1 $\pm$ 1	3 $\pm$ 1	-2 $\pm$ 2	-2 $\pm$ 4
DOCA	1 $\pm$ 1	3 $\pm$ 1	-2 $\pm$ 0	2 $\pm$ 2	-1 $\pm$ 3
WKY	1 $\pm$ 1	-1 $\pm$ 1	2 $\pm$ 2	1 $\pm$ 1	1 $\pm$ 1
SHR	3 $\pm$ 1	1 $\pm$ 3	0 $\pm$ 4	-2 $\pm$ 6	-1 $\pm$ 5
F-ratios	1.3	0.9	0.9	0.4	0.2
<i>Heart rate change (beats/min)</i>					
Sham	3 $\pm$ 3	6 $\pm$ 0	-3 $\pm$ 3	-3 $\pm$ 3	-12 $\pm$ 0
DOCA	3 $\pm$ 3	3 $\pm$ 3	0 $\pm$ 0	0 $\pm$ 0	-6 $\pm$ 6
WKY	3 $\pm$ 3	9 $\pm$ 3	12 $\pm$ 0	3 $\pm$ 9	3 $\pm$ 9
SHR	9 $\pm$ 3	9 $\pm$ 3	3 $\pm$ 3	3 $\pm$ 3	-3 $\pm$ 9
F-ratios	0.2	1.2	0.3	0.5	0.8
<i>% Sympathetic nerve activity change</i>					
Sham	4 $\pm$ 6	3 $\pm$ 5	-1 $\pm$ 8	-5 $\pm$ 9	-5 $\pm$ 7
DOCA	-7 $\pm$ 6	-11 $\pm$ 7	-3 $\pm$ 0	-7 $\pm$ 3	-7 $\pm$ 3
WKY	-5 $\pm$ 2	-1 $\pm$ 2	-6 $\pm$ 7	-2 $\pm$ 4	1 $\pm$ 2
SHR	-4 $\pm$ 2	-4 $\pm$ 2	-6 $\pm$ 2	-9 $\pm$ 7	-1 $\pm$ 4
F-ratios	1.2	1.8	0.2	0.2	1.4

Sham = sham operated rat, DOCA = DOCA-salt hypertensive rat, WKY = Wistar Kyoto rat, SHR = spontaneously hypertensive rat.

Data are expressed as mean $\pm$ SEM from two rats in each group. In comparing data from different groups, with $f_1 = 3$ and $f_2 = 4$, F ratios equal to or greater than 9.3 are significant at 5%.

cause-and-effect relationship between changes in abdominal nerve firing and blood pressure produced either by stimulating various medullary areas electrically^{14,15} or by changing baroreceptor input through different cardiovascular manipulations¹⁶ has been shown in unanesthetized deterebrated cats. And Gootman and Cohen¹⁶ concluded that abdominal sympathetic nerve discharge is a reliable indicator of central sympathetic regulation of blood pressure.

The imbalance between central pressor and depressor mechanisms are present in both SHR and DOCA rats, yet these mechanisms are complicated and are not the same in DOCA rats and SHR.⁴⁶ Although the possibility that penetration of taurine into the cerebral parenchyma is different cannot be denied, dye staining in the lateral and third ventricles showed no difference between DOCA rats and SHR by visual inspection.

Kuriyama et al.¹⁷ reported that taurine reduces the potassium-evoked release of acetylcholine and norepinephrine not only from the cerebral cortex but also from the superior sympathetic

ganglion of the rat. It is considered, then, that taurine may have a physiological role as a neuromodulator to suppress the synaptic release of neuroactive substances in the nervous system.

Central cholinergic neurons are reported to produce pressor responses and therefore attenuation of the cholinergic neurotransmission may decrease blood pressure. But cholinergic mechanisms hardly explain the different pattern of responses in DOCA rats and SHR, because the central cholinergic system may be augmented in both SHR¹⁸ and DOCA rats.¹⁹ On the other hand, it is well documented that the sympathetic nervous system plays an important role in the development and maintenance of DOCA-salt²⁰⁻²² and spontaneous hypertension.²³⁻²⁵ Chen et al.²⁶ reported that plasma norepinephrine and epinephrine in conscious, unrestrained resting DOCA rats are significantly elevated at 28 days after treatment. As for SHR, McCarty et al.²⁷ reported that when SHR and normotensive control rats are transferred to a new cage, both groups have increases in plasma catecholamines

but the increases are greater in SHR. It is common to use two kinds of indices to evaluate the sympathetic nervous system: one is plasma catecholamine and the other is sympathetic nerve discharge. Iriuchijima²⁸ reported increased spontaneous splanchnic discharge in SHR and Takeda²² reported a similar finding in DOCA rats. In this experiment, there was no difference between hypertensive rats and the respective control rats, probably because of variant numbers of nerve fibers measured in individual rats, although DOCA rats and SHR had slightly larger splanchnic discharge than the respective control rats.

The proposed sympathetic hyperactivity is closely related to the central alpha-adrenergic system in DOCA rats and SHR. Yamori et al.^{29,30,35} postulated that the pathogenesis of spontaneous hypertension is related to the dysfunction of the central adrenergic system; this hypothesis is based on findings that the concentration of noradrenaline in the lower brainstem and hypothalamus of SHR is significantly lower than that in WKY. A tendency to delay in noradrenalin turnover in the brainstem in DOCA rats was also detected in this study.³⁵ Furthermore, Nakamura et al.³¹ reported the decrease of noradrenaline turnover in the brainstem in DOCA rats. Reid et al.³² reported that the destruction of central adrenergic neuron with ICV injection of 6-hydroxydopamine (6-HODA) prevents both the development of DOCA-salt hypertension and increase in plasma norepinephrine level. Haeusler et al.³³ reported that ICV injection of 6-HODA in prehypertensive young SHR prevented the progressive elevation of arterial blood pressure. Chalmer et al.³⁴ reported that ICV injection of 6-HODA prevented the development of spontaneous hypertension and DOCA-salt hypertension. In this respect, the central noradrenergic system in DOCA rats and SHR is similar and this difference could not be explained by the different mode of responses produced by ICV injection of taurine, although taurine might modulate the noradrenaline transmission in the central nervous system.

Furukawa et al.³⁷ have shown that angiotensin II injected into the posterior hypothalamus produces pressor responses. And ICV pretreatment with taurine attenuates the pressor responses to angiotensin II in normotensive rats. Although it has not yet been made clear which mechanism is the main contributor in this respect, these pressor mechanisms by angiotensin II are

considered to be the activation of central sympathetic outflow and an increased release of an antidiuretic hormone.³⁸ Suzuki et al.³⁹ showed that pressor mechanisms by ICV angiotensin II are considered to be the activation of renal sympathetic nerve activity and an increased release of an antidiuretic hormone. Weyhenmayer found more cells and fibers staining for angiotensin like immunoreactivity in the brains of both DOCA rats⁴² and SHR⁴³ compared to respective control rats. Okuno et al.⁴⁴ showed that the chronic administration of captopril attenuated the development of spontaneous hypertension; however, these depressor mechanisms are independent of altered fluid and sodium balance and the sympathoadrenal system. We⁴⁵ have indicated that both an angiotensin analogue and captopril failed to reduce blood pressure in mature SHR. These findings suggest that a brain-angiotensin system may contribute to the development but not to the maintenance of spontaneous hypertension. Moreover, the pressor responses produced by ICV injection of angiotensin II are different in DOCA rats and SHR. Yamori et al.⁴⁶ reported that the magnitude of the pressor responses produced by ICV injection of angiotensin II was decreased in SHR compared to WKY. This could be due to the decreased adrenergic activity in the brain of SHR because the ICV clonidine augmented the pressor responses and destruction of central noradrenergic neurons by ICV injection of 6-HODA decreased the magnitude of pressor responses in WKY. However, Matsuguchi et al.⁴⁷ reported that the pressor responses to ICV injections of angiotensin II were greatly augmented and the central renin-angiotensin system might play a important role in DOCA hypertension.

Collectively, because taurine may suppress not only the cholinergic and adrenergic neurotransmission but also the angiotensin II mechanism to decrease blood pressure, the different depressor responses to ICV taurine in DOCA rats and SHR may be due in part to alterations in the renin-angiotensin axis in the brain.

REFERENCES

1. JACOBSEN JD, SMITH LH, Jr: Biochemistry and physiology of taurine derivatives. *Physiol Rev* 48: 424, 1986
2. MINATO A, et al.: Distribution of radioactivity after administration of S³⁵-taurine in rats. *Chem Pharm Bull* 17: 1945, 1969
3. URQUHART N, et al.: Passage of taurine into adult mammalian brain. *J Neurochem* 22: 871,

- 1974
4. NARA Y, et al.: Effect of dietary taurine on blood pressure in spontaneously hypertensive rats. *Biochem Pharmacol* 27: 2689, 1978
5. SATO Y, et al.: The absence of natriuresis in the antihypertensive effect of taurine. *Sulfur Amino Acid* 6: 83, 1983 (in Japanese)
6. INOUE A, et al.: Centrally induced vasodepressor and sympathetic nerve responses to taurine. *Jap Circ J* 49: 1180, 1985
7. ORMSEE HS, RYAN CF: Production of hypertension with deoxycorticosterone acetate-impregnated silicon rubber implants. *Nature* 62: 255, 1970
8. PELLEGRINO L, CUSHMAN AJ: A stereotaxic atlas of the rat brain. Appleton-Centry-Crofts, Inc., New York, 1967
9. BOSQUHART P, et al.: Central cardiovascular effects of taurine: Comparison with homotaurine and muscimol. *J Pharmacol Exp Ther* 219, 213: 15, 1981
10. YAMORI Y, et al.: Pathological role of taurine in blood pressure regulation in stroke-prone spontaneously hypertensive rats (SHR). In the effect of taurine in excitable tissues, ed by SCAFFER SW, STEVEN IB and JAMES JK (MTP), 391, 1981
11. PAAKKARI P, et al.: Mechanism of the inhibitory cardiovascular effects of taurine and homotaurine. *Acta Med Scand* 677(Suppl): 133, 1983
12. SCHMITT H, et al.: Centrally mediated decrease in sympathetic tone induced by 2-(2, 6-dichlorophenylamino)-2-imidazoline. *Eur J Pharm* 2: 147, 1967
13. VAN ZWETEN HW, et al.: Central hypotensive effect of methyldopa. *J Pharm Pharmacol* 20: 409, 1968
14. KAHN N, MILL SE: Centrally evoked sympathetic discharge: A functional study of medullary vasomotor area. *J Physiol* 191: 339, 1967
15. GOOTMAN PM, COHEN MI: Evoked splanchnic potentials produced by electrical stimulation of medullary vasomotor regions. *Exp Brain Res* 13: 1, 1971
16. GOOTMAN PM, COHEN MI: Efferent splanchnic nerve activity and systemic arterial pressure. *Am J Physiol* 219: 897, 1970
17. KURIYAMA K, et al.: Alteration of cerebral taurine in spontaneously hypertensive rats. *J Neurochem* 42: 1600, 1984
18. TAKAHASHI H, et al.: Augmented central cholinergic mechanisms in spontaneously hypertensive rats: Involvement of deranged noradrenergic mechanisms in the brain. *Jap Heart J* 25: 397, 1984
19. TAKAHASHI H, et al.: Centrally-induced vasopressor responses to carbachol are augmented in DOCA-salt hypertensive rats. *Cardiovas Res* 18: 126, 1984
20. DE CHAMPLAIN J, et al.: Catecholamine metabolism in experimental hypertension in the rats. *Circ Res* 20: 136, 1967
21. DE CHAMPLAIN J, et al.: Turnover and synthesis of norepinephrine in experimental hypertension in rats. *Circ Res* 25: 285, 1969
22. TAKEDA K, BUNAG RD: Augmented sympathetic nerve activity and pressor responsiveness in DOCA hypertensive rats. *Hypertension* 2: 97, 1980
23. THOREN P, RICKSTEN SE: Recording of renal and splanchnic sympathetic nerve activity in normotensive and spontaneously hypertensive rats. *Clin Sci* 57: 197, 1979
24. WATANABE JW, et al.: Sympathetic nerve activity: role in regulation of blood pressure in the spontaneously hypertensive rats. *Circ Res* 38(Suppl II): II-21, 1976
25. TAKEDA K, BUNAG RD: Sympathetic hyperactivity during hypothalamic stimulation in spontaneously hypertensive rats. *J Clin Invest* 62: 642, 1978
26. CHEN YF, et al.: Hyperresponsiveness of monoaminergic mechanisms in DOCA/NaCl hypertensive rats. *Am J Physiol* 249: H-71, 1985
27. KOPIN IJ, et al.: Plasma level of noradrenaline. NIH conference. *Annals of Int Med* 88: 671, 1978
28. IRIUCHIJIMA J: Sympathetic discharge rate in spontaneously hypertensive rats. *Jpn Circ J* 14: 350, 1973
29. YAMORI Y, et al.: Norepinephrine metabolism in brainstem of spontaneously hypertensive rats. *Science* 170: 544, 1970
30. YAMORI Y, et al.: Catecholamine metabolism in the central and peripheral nervous system of spontaneously hypertensive rats. *Jap J Constitutional Med* 34: 36, 1971
31. NAKAMURA K, et al.: Experimental hypertension of rats: Reciprocal changes of norepinephrine turnover in heart and brainstem. *Naunyn-Schmiedberg Arch Pharmacol* 268: 125, 1971
32. REID JL, et al.: Central and peripheral adrenergic mechanisms in the development of deoxycorticosterone-saline hypertension in rats. *Circ Res* 37: 569, 1975
33. HAEUSLER G, et al.: Central adrenergic neurons and the initiation and development of experimental hypertension. *Experientia* 28: 1200, 1972
34. CHALMERS IP, et al.: Brain amines and model of experimental hypertension. *Circ Res* 36: 469, 1975
35. YAMORI Y, et al.: Deviation of central norepinephrine metabolism in hypertensive rats. *Jpn Circ J* 37: 1235, 1973
36. YAMORI Y, et al.: Central amine and blood pressure regulation. *Folia Endocrinol Jap* 49: 113, 1973
37. FURUKAWA T, et al.: Central and peripheral effect of sulfur amino acid: Antagonism against central effects of angiotensin. In *Sulfur Amino Acids: Biochemical Aspects*, ed by KURIYAMA K, HUXTABLE RJ, IWATA H, Alan Press Liss Inc, New York, 1983
38. HOFFMAN WE, et al.: Antidiuretic hormone release and the pressor responses to central angiotensin II and cholinergic stimulation. *Neuropharmacol* 16: 463, 1977
39. SUZUKI H, et al.: Mechanism of pressor effects on intraventricular injection of angiotensin II in the rat: Role of vasopressin and renal nerve. *Clin Sci* 63: 275, 1982
40. SHIONO K, SOKABE H: Renin-angiotensin system in spontaneously hypertensive rats. *Am J Physiol* 231: 1295, 1976

41. PHILLIPS MI, et al.: Lowering of hypertension by central saralasin in the absence of plasma renin. *Nature* 270: 445, 1977
42. WEYHENMEYER JA, et al.: Angiotensin II in the brain and brainstem of the DOCA salt hypertensive rat. *Clin Exp Hypertension* A7 73, 1985
43. WEYHENMEYER JA, et al.: Angiotensin-like immunoreactivity in the brain of the spontaneously hypertensive rat. *Hypertension* 4: 514, 1982
44. OKUNO T, et al.: Attenuation of the development of spontaneous hypertension in the rats by chronic central administration of captopril. *Hypertension* 5: 653, 1983
45. TAKAHASHI H, et al.: Endogenous brain angiotensin II-mediated sympathetic nerve responses are not augmented in mature spontaneously hypertensive rats. *Jpn Circ J* 46: 1082, 1982
46. YAMORI Y, et al.: Central amine and blood pressure regulation. *Saishin-igaku* 21: 1019, 1973 (in Japanese)
47. MATSUGUCHI H, et al.: Central mechanisms in DOCA-salt hypertensive rats. *Clin and Exper Hyper* A4(8): 1303, 1982