SERUM DOPAMINE- β -HYDROXYLASE ACTIVITY IN ESSENTIAL HYPERTENSION AND IN CHRONIC RENAL FAILURE WITH HYPERTENSION

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Elevated serum DBH (dopamine- β -hydroxylase) activity was found in essential hypertension. The elevated level was not reduced when blood pressure was brought to normotensive level by administration of thiazide or rauwolfia. In contrast, serum DBH activity was low in both normotensive and hypertensive patients treated on prolonged hemodialysis. However, there was no correlation between serum DBH activity and blood pressure level. It was suggested that the pathogenesis of high blood pressure might be different between essential hypertension and hypertension with chronic renal failure, and that measurement of serum DBH activity might help for clinical differentiation of essential hypertension from certain forms of secondary hypertension.

IT IS not clear whether activity of the sympathetic nervous system contributes to increased blood pressure in patients with essential hypertension,^{1,2} but in essential hypertension high urinary excretion of noradrenaline,^{1,3} high plasma catecholamine concentrations⁴⁻⁶ and high serum dopamine- β -hydroxylase (DBH) levels have been reported.⁷⁻¹⁰ DBH converts dopamine to noradrenaline in the sympathetic nerve endings, and both DBH and noradrenaline are released into the circulation from the sympathetic nerve endings when sympathetic nerves are stimulated.¹¹⁻¹⁴ Therefore, serum DBH protein or its activity may be considered as an index of sympathetic nerve activity.^{10,14-16} On the contrary, it has been reported that serum DBH activity has little correlation with blood pressure level and can not be a satisfactory index of sympathetic nerve activity.¹⁷ In this study, the

serum DBH activity was determined in patients with essential hypertension and hypertension with renal failure to investigate the correlation between blood pressure and serum DBH activity.

MATERIALS AND METHODS

Blood pressure was measured in the supine position by arm-cuff auscultatory method. The subjects were adults and classified as follows. (1) normotensive control: Normotensive healthy faculty staff. (2) Essential hypertension: Patients with blood pressures over 160 mmHg systolic and over 90 mmHg diastolic, but without proteinuria, glucosuria, and abnormal values of blood urea nitrogen and serum electrolytes. The subjects in this class were diagnosed as essential hypertension (stage I or II of WHO classification) and included these treated with thiazide or rauwolfia. (3) Chronic renal failure: Patients with high blood urea nitrogen of over 30 mg/100 ml and with chronic nephritis or being treated on hemodialysis.

The venous blood samples were centrifuged at $10,000 \times g$ for 10 min at 0°C . The serum was collected and stored at -20°C . Serum DBH

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TABLE I SERUM DBH ACTIVITY IN ESSENTIAL HYPERTENSION

Groups	No. of Cases	Blood pressure mmHg		DBH activity nmoles/min/ml
		Systolic	Diastolic	
N	57	118 ± 1.7	71 ± 1.7	8.7 ± 0.4
H _{uh}	23	194 ± 5.4*	102 ± 2.0*	10.4 ± 0.7*
H _{th}	16	174 ± 4.8*	104 ± 1.8*	10.0 ± 0.2*
H _{tn}	12	135 ± 2.1	86 ± 1.3	10.3 ± 0.6*
H _{rh}	9	187 ± 8.8	107 ± 4.0*	9.6 ± 1.0
H _{rn}	7	138 ± 4.6	83 ± 2.6	10.3 ± 0.5*

N: Normotensive control. H: Essential hypertension. H_{uh}: Untreated patients with hypertension. H_{th}: Thiazide treated patients with lowered blood pressure, but still at hypertensive level. H_{tn}: Thiazide-treated patients who became normotensive.

H_{rh}: Rauwolfia-treated patients with lowered blood pressure, but still at hypertensive level. H_{rn}: Rauwolfia-treated patients who became normotensive.

Values are mean ± SEM.

* Significance of difference was compared between N group and H_{uh}, H_{th}, H_{tn}, H_{rh}, or H_{rn} group, respectively ($p < 0.05$).

activity was assayed by the method of Weinshilboum and Axelrod^{15,18}. In principle tyramine is β -hydroxylated to octopamine by serum DBH, and the octopamine is converted to ¹⁴C-N-methyl-octopamine by phenylethanolamine-N-methyl-transferase in the presence of S-adenosyl-L-methionine-methyl-¹⁴C. The DBH activity was determined by the radioactivity of ¹⁴C-N-methyl-octopamine.

RESULTS

The blood pressure of the untreated essential hypertension cases (H_{uh} in Table I) was significantly higher than that of the normotensive control. The serum DBH activity of the untreated patients was 10.4 ± 0.7 (SEM) nmoles/min/ml, which was significantly higher (approximately 20%) than that of normotensive controls (8.7 ± 0.4 nmoles/min/ml). This high serum DBH activity in essential hypertension remained unchanged, even the blood pressure was reduced to normotensive level by the administration of antihypertensive drugs such as thiazide or rauwolfia (Table I). Serum DBH activity decreased slightly in the group of rauwolfia-treated patients (H_{rn} in Table I), though the blood pressure remained high.

In renal failure due to chronic nephritis, serum DBH activity of patients with high blood pressure treated by antihypertensive drugs was lower than that of normotensive patients (Table II). In patients treated on hemodialysis, the DBH activity was lower in both normotensive and hyper-

tensive patients. There was no positive correlation between the DBH activity and the blood pressure level in patients with renal failure on hemodialysis.

DISCUSSION

It was found that the mean serum DBH activity in essential hypertension was significantly increased as compared with normotensive control, in spite of great individual variations^{7-10,16,19}. Furthermore, it was shown that decrease of blood pressure by thiazide or rauwolfia treated did not cause a decrease in the serum DBH activity in essential hypertension. Therefore, it would seem that sympathetic nerve activity is higher in patients with essential hypertension. However, regulation of blood pressure level may be due to not only by sympathetic nerve activity but also by some other factors, such as cellular electrolyte balance in vascular smooth muscle and renin-angiotensin system. When large dose of rauwolfia was administered to decrease the blood pressure in group H_{rn}, DBH activity was lowered, probably by the rauwolfia reducing the storage and release of noradrenaline and DBH in the sympathetic nerve endings.

In chronic nephritis with renal failure (Group R_{dh}), serum DBH activity was low, when treated with large doses of drugs, such as rauwolfia, α -methyl dopa, bethanidine and hydralazine. These drugs may reduce storage and release of noradrenaline and DBH from the sympathetic nerve endings, however the high blood pressure in

TABLE II SERUM DBH ACTIVITY IN RENAL FAILURE WITH HYPERTENSION

Groups	No. of patients	Blood pressure mmHg		Blood urea nitrogen mg/100ml	DBH activity nmoles/min/ml
		Systolic	Diastolic		
R_n	5	130 ± 4.5	80 ± 4.0	33 ± 1.0	7.0 ± 1.2
R_h	5	$175 \pm 11.4^*$	98 ± 3.7	$55 \pm 6.4^*$	7.0 ± 1.7
R_{dh}	5	$191 \pm 19.1^*$	$106 \pm 5.1^*$	$58 \pm 10.1^*$	$4.9 \pm 1.4^*$
D_n	7	120 ± 4.8	69 ± 1.5	89 ± 9.4	4.2 ± 1.0
D_h	9	$187 \pm 8.2^*$	$103 \pm 4.1^*$	79 ± 9.0	4.0 ± 0.6
D_{dh}	6	$184 \pm 4.6^*$	$103 \pm 7.1^*$	75 ± 6.5	3.7 ± 0.4

R : Renal failure in chronic nephritis. R_n : Untreated normotensive patients. R_{dh} : Patients with antihypertensive drugs with hypertension. D : Patients treated on hemodialysis.

D_n : Untreated normotensive patients. D_h : Untreated hypertensive patients. D_{dh} : Patients treated with antihypertensive drugs, but still hypertensive.

Values are mean $\pm$ SEM.

* Significance of difference was compared between R_n group and R_h or R_{dh} group, and between D_n and D_h or D_{dh} group, respectively ($p < 0.01$).

this group was not lowered. In cases on hemodialysis, abnormally low DBH activity was found in both normotensive and hypertensive patients. There was no positive correlation between serum DBH activity and blood pressure level in renal failure and those on hemodialysis. There is a possibility that the sympathetic nerve activity may be decreased in this type of hypertension. Depressed baroreceptor activity is suggested to exist in neuropathy of the autonomic nervous system by prolonged hemodialysis²⁰ and autonomic nerve dysfunction is most probably due to the generalized neuropathy of the uremic syndrome²¹. Tyler pointed out the presence of peripheral nerve damage and a failure of the transport system between the nerve cell body and distal ramifications of the axonal system²². Low serum DBH activity in patients treated on prolonged hemodialysis might be caused by decreased catecholamine storage in the sympathetic nerve ending due to impaired transport system of autonomic nerves in chronic renal failure. However, further studies are necessary to determine the mechanism of development of low serum DBH activity.²³

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REFERENCES

1. KOCH-WESER, J.: Sympathetic activity in essential hypertension. *New Engl. J. Med.* 288: 627, 1973.
2. PEART, W. S.: Catecholamines and hypertension. *Pharmacol. Rev.* 18: 667, 1966.
3. NESTEL, P. J. & ESLER, M. D.: Patterns of catecholamine excretion in urine in hypertension. *Circ. Res.* 27: Suppl. II: 75, 1970.
4. ENGELMAN, K., PORTNOY, B., & SJOERDSMA, A.: Plasma catecholamine concentrations in patients with hypertension. *Circ. Res.* 27: Suppl. I: 141, 1970.
5. DeQUATTRO, V., & CHAN, S.: Raised Plasma catecholamines in some patients with primary hypertension. *Lancet April* 15: 806, 1972.
6. LOUIS, W. J., DOYLE, A. E., & ANAVEKAR, S.: Plasma norepinephrine levels in essential hypertension. *New Engl. J. Med.* 288: 599, 1973.
7. GEFFEN, L. B., RUSH, R. A., LOUIS, W. J., & DOYLE, A. E.: Plasma dopamine β -hydroxylase and norepinephrine amounts in essential hypertension. *Clin. Science* 44: 617, 1973.
8. SCHANBERG, S. M., STONE, R. A., KIRSHNER, N., GUNNELLA, J. C., & ROBINSON, R. R.: Plasma dopamine β -hydroxylase: A possible aid in the study and evaluation of hypertension. *Science* 183: 523, 1974.
9. GEFFEN, L. B., RUSH, R. A., LOUIS, W. J., & DOYLE, A. E.: Immunoassay of chromogranins in tissue perfusates and plasma. *Life Science* 13: (4): xlii, 1973.
10. GEFFEN, L.: Serum dopamine- β -hydroxylase as an index of sympathetic function. *Life Science* 14: 1593, 1974.
11. KAUFMAN, S., & FRIEDMAN, S.: Dopamine- β -hydroxylase. *Pharmacol. Rev.* 17: 71, 1965.
12. GEFFEN, L. B., & LIVETT, B. G.: Synaptic vesicles in sympathetic nerve. *Physiol. Rev.* 51: 98, 1971.
13. GEWIRTZ, G. P., & KOPIN, I. J.: Release of

- dopamine- β -hydroxylase with norepinephrine during cat splenic nerve stimulation. *Nature* 227: 406, 1970.
14. WEINSHILBOUM, R. M., THOA, N. B., JOHNSON, D. G., KOPIN, I. J., & AXELROD, J.: Proportional release of norepinephrine and dopamine- β -hydroxylase from sympathetic nerves. *Science* 174: 1349, 1971.
 15. WEINSHILBOUM, R. & AXELROD, J.: Serum dopamine- β -hydroxylase activity. *Circ. Res.* 28: 307, 1971.
 16. WETTERBERG, L., ÅBERG, H., ROSS, S. B., & FRÖDEN, Ö.: Plasma dopamine- β -hydroxylase activity in hypertension and various neuropsychiatric disorders. *Scand. J. Clin. Lab. Invest.* 30: 283, 1972.
 17. HORWITZ, D., ALEXANDER, R. W., LOVENBERG, W., & KEISER, H. R.: Human serum dopamine- β -hydroxylase. Relationship to hypertension and sympathetic activity. *Circ. Res.* 32: 594, 1973.
 18. NAGATSU, T.: Dopamine- β -hydroxylase in serum. Active and inactive forms of a serum enzyme. *Seikagaku* 46: 53, 1974 (in Japanese).
 19. YASHIMA, O.: Studies on serum dopamine- β -hydroxylase activity. *Folia Endocrinol. Jap.* 49: 48, 1973 (in Japanese).
 20. LAZARUS, J. M., HAMBERS, C. L., LOWRIE, E. G., & MERRILL, J. P.: Baroreceptor activity in normotensive and hypertensive uremic patients. *Circulation* 42: 1015, 1973.
 21. KERSH, E. S., KRONFIELD, S. J., UNGER, A., POPPER, R. W., CANTOR, S., & COHN, K.: Autonomic insufficiency in uremia as a cause of hemodialysis-induced hypertension. *New Engl. J. Med.* 290: 650, 1974.