Upsala J Med Sci 80: 24–26, 1975

Dopamine-β-hydroxylase and Plasma Renin Activity in Twenty Hypertensive Subjects

HANS ÅBERG,[1] HANS HEDSTRAND,[1] LENNART WETTERBERG[2] and SVANTE B. ROSS[3]

From the [1]Department of Medicine, University Hospital, Uppsala, the [2]Department of Psychiatry, Karolinska Institutet, St Görans Hospital, Stockholm, and the [3]Research Laboratories, Astra Läkemedel AB, Södertälje, Sweden

ABSTRACT

Dopamine-β-hydroxylase (DBH), the enzyme responsible for the biosynthesis of noradrenalin from dopamine, was assayed in the blood plasma of 20 men with primary hypertension. At the same time plasma was taken for measurement of plasma renin activity. Renin release as well as the plasma level of DBH is dependent upon the activity of the sympathetic nervous system, at least to some extent. A possible relationship between the two enzymes was therefore investigated. However, no relationship could be found in this series of 20 hypertensive patients. Another aim was to study the levels of DBH in venous and arterial blood simultaneously. No difference in the DBH level was found in venous and in arterial blood in 11 patients undergoing heart catheterization.

The role of the sympathetic nervous system in the pathogenesis of primary hypertension is still unknown. However, the effect of this system on some factors of possible importance for the initiation and/or maintenance of an elevated blood pressure is known. Thus, it is now clear that the renal sympathetic nerves, as well as intrarenal receptors and a number of humoral agents, are involved in the control of renin release (4).

There is a great individual variation of plasma renin activity (PRA) in primary hypertension (3). One of several possible explanations for the great variability is a differing discharge of the renal sympathetic nerves in different individuals. One way of testing this hypothesis could be to determine the level of dopamine-β-hydroxylase (DBH), the enzyme responsible for the biosynthesis of noradrenalin from dopamine. DBH is released in direct relation to sympathetic nervous system activity (14). Both PRA and DBH show a great variability in hypertensives (1, 2).

A comparison between levels of DBH in arterial and venous blood was also made in this study. The large DBH molecule is probably transported from the synaptic cleft mainly via lymphatic drainage to the circulation (1). The difference of the fate of DBH in the circulation compared to renin which rapidly changes in the system is obvious. Differences in the behaviour of the two enzymes in the circulation should be considered when a possible relation of DBH and renin is studied.

MATERIALS AND METHODS

Material A

The material consisted of 20 men with hypertension (diastolic blood pressure of at least 105 mmHg on three occasions). They were selected from a health screening program for 50-year-old men in the City of Uppsala and were drawn consecutively. They had no medication. Most of them were free of symptoms and unaware of their disorder.

Material B

This material consisted of 11 patients (8 men and 3 women with different types of valvular heart disease. The mean age was 51±2.3 (S.E.M.) years (range 22–63).

Methods

In material A the plasma specimen was obtained in the afternoon at a visit to the out-patient »after work» clinic. These subjects were on their regular diet. The venuous sample was taken after the patient had been up and about for several hours and at least 3 hours after a meal.

In material B the plasma samples from vein and artery were taken simultaneously at diagnostic heart catheterization. The patients had fasted during the morning prior to the examination.

DBH was determined according to the method described by Molinoff et al. (8) with the modification that the DBH reaction was performed at pH 5.2 (13). β-phenyl-ethylamine was used as substrate. DBH in plasma is expressed in nmol of phenylethanolamine formed per ml plasma after 20 min incubation. PRA has been measured using a conventional radioimmunoassay technique for generated angiotensin I (Angiotensin I [^{125}I] Radioimmunoassay Kit, New England Nuclear Biomedical Assay Laboratories, Worcester, Mass. 01608, USA). The result reported is the mean of three determinations. PRA is ex-

Table I. *Results of determination of PRA (ng/100 ml/3 h) and of DBH activity (nmol/ml/20 min)*

	No. of cases	Mean±S.E.M.	Range
PRA	20	424±67	132–1 374
DBH	20	219±28	44– 498

pressed in ng per 100 ml plasma after 3 hours' incubation.

The venous sample for the renin activity determination was taken at the same time as DBH in a pre-chilled B-D Vacutainer tube to give approximately 1 ml blood/1 mg EDTA Na_2. The sample was immediately centrifuged in the cold to recover the plasma, which was stored frozen until assayed.

RESULTS

Both DBH activity and PRA showed a wide range of values in the subjects under study (Table I). A regression analysis did not show any significant relationship between plasma DBH and PRA ($r=-0.27$; $y=-0.63x+563$, Fig. 1). On the other hand a few of the highest DBH values are combined with low PRA and four of the highest PRA are combined with low DBH-values. There was no difference between arterial and venous blood with regard to DBH for the total group (Table II). Regression analysis revealed a strong correlation ($r=0.96$; $y_{art}=0.95x_{ven}+11.9$) between DBH in venous and arterial blood. In 2 out of 11 cases there were significant differences in DBH activity levels between the arterial and venous samples. In one case the venous sample had a higher value than the arterial sample ($0.05<p<0.02$) and in the other case the opposite occurred. In the rest no difference was found.

DISCUSSION

As in all other studies there is a wide range of plasma DBH activity (2, 13) in this series. Due to this wide normal range the detection of pathological deviations is difficult. Rush & Geffen have used a radioimmunoassay for DBH, instead of the enzymic assay in the present study, and these authors have found a narrower range of normal values (12). However, even using this technique the individual variation among patients with essential hypertension is large (5).

PRA levels in hypertensives have also a wide range under standardized conditions and these levels are to some extent dependent upon the sodium content of the diet (3). Although the subjects deny any unusual habits concerning salt intake this factor has not been possible to control in this out-patient series.

When measuring PRA it is important to standardize the procedure for collection of the venous sample. As Oparil et al. (9), as well as others, have shown there is a very rapid change of PRA according to altered body position etc. On the other hand DBH has a relatively long circulating half-life. In animal experiments it has been estimated to 3 hours (12). This is the reason for the relatively stable DBH-values (15) and the similar values concomitantly obtained from arterial and venous blood supports this stability. The lack of relationship between PRA and DBH in this study could then be due to different clearance rates from plasma.

One recent study within this field has a different result from ours. DeQuattro & Miura (10) have recently shown by simultaneous determination of PRA and plasma catecholamines in 25 patients with primary hypertension a significant although poor correlation between the two ($r=0.491$, $p<0.05$). The lack of correlation between DBH and renin activity and findings by the authors above is not easy to explain under the suggested proportional release of DBH and noradrenalin from the sympathetic nervous system. The discrepancy could to some extent, however, be explained by different standardization of the experimental circumstances in the two studies. Another explanation may be that the level of plasma DBH although at least partially originating from the sympathetic nervous system is determined also by other factors than the activity of this system (11).

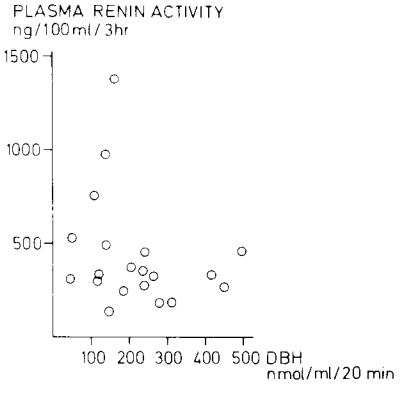

Fig. 1. Relationship between DBH activity and plasma renin activity in the subjects.

Table II. *DBH activity in plasma from artery and vein*

Mean±S.E.M.	No. of cases	DBH (nmol/ml/20 min)	$\frac{DBH_{ven}}{DBH_{art}} \times 100$
Arterial samples	11	178±34	
Venous samples	11	174±35	99±6

In another recent report Geffen et al. (5) found that plasma DBH amounts correlated significantly with those of plasma noradrenalin and diastolic blood pressure in individual patients. These authors conclude that the sympathetic nervous system contributes toward the maintenance of the elevated blood pressure in subjects with essential hypertension. One difficulty in the evaluation of these seemingly different results is that different assay techniques were used (enzymic and radioimmunoassay). The greater validity of plasma DBH measured by the latter method with regard to ability to mirror the sympathetic activity has been advocated (5).

On the other hand Lurvey & deQuattro (7) have found that DBH of hypertensive patients was not increased by furosemide (Lasix®) which was the case in normal volunteers. These authors state from these experiments that different components of sympathetic nerve activity might be involved in the release of DBH and renin. This proposal could explain our findings. The amounts of DBH might reflect the overall sympathetic activity while the renin release is dependent on a more selectively increased renal sympathetic nerve activity. This touches the problem of different receptors.

Finally, one explanation for the different results reported by deQuattro & Miura (10) and our group is the fact that the correlation of sympathetic nerve activity to plasma DBH-level is not as good as to plasma noradrenalin (6).

ACKNOWLEDGEMENT

We thank Mrs Öie Frödén for valuable technical assistance. The work was supported by a grant from "Nationalföreningen mot hjärt- och lungsjukdomar" and grant B-73-21-3371-03 B from the Swedish Medical Research Council.

REFERENCES

1. Åberg, H. E., Hansson, H. E., Wetterberg, L., Ross, S. B. & Frödén, Ö.: Dopamine-β-hydroxylase in human lymph. Life Sci *14:* 65, 1974.
2. Åberg, H., Wetterberg, L., Ross, S. B. & Frödén, Ö.: Dopamine-β-hydroxylase in hypertension. Acta Med Scand *196:* 17, 1974.
3. Brunner, H. R., Laragh, J. H., Baer, L., Newton, M. A., Goodwin, F. T., Krakoff, L. R., Bard, R. H. & Bühler, F. R.: Essential hypertension: renin and aldosterone, heart attack and stroke. New Engl J Med *286:* 441, 1972.
4. Davis, J. O.: What signals the kidney to release renin? Circ Res *28:* 301, 1971.
5. Geffen, L. B., Rush, R. A., Louis, W. J. & Doyle, A. E.: Plasma dopamine-β-hydroxylase and noradrenaline amounts in essential hypertension. Clin Sci *44:* 617, 1973.
6. 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.
7. Lurvey, A. N. & deQuattro, V.: Suppressed responsiveness of serum dopamine beta hydroxylase activity to diuresis and upright posture in patients with primary hypertension. Clin Res *21:* 434, 1973.
8. Molinoff, P. B., Weinshilboum, R. M. & Axelrod, J.: A sensitive enzymatic assay for dopamine-β-hydroxylase. J Pharmacol Exp Ther 78: 425, 1971.
9. Oparil, S., Vassaux, C., Sanders, C. A. & Haber, E.: Role of renin in acute postural homeostasis. Circulation *41:* 89, 1970.
10. deQuattro, V. & Miura, Y.: Neurogenic factors in human hypertension: Mechanism or Myth? Am J Med *55:* 362, 1973.
11. Ross, S. B., Wetterberg, L. & Myrhed, M.: Genetic control of plasma dopamine-β-hydroxylase. Life Sci *12:* 529, 1973.
12. Rush, R. A. & Geffen, L. B.: Radioimmunoassay and clearance of circulating dopamine-β-hydroxylase. Circ Res *31:* 444, 1972.
13. Weinshilboum, R. M., Raymond, F. A., Elveback, L. R. & Weidman, W. H.: Serum dopamine-β-hydroxylase activity: Sibling-sibling correlation. Science *181:* 943, 1973.
14. Weinshilboum, R. M., Thoa, N. B., Johnson, D. G., Kopin, J. J. & Axelrod, J.: Proportional release of norepinephrine and dopamine-β-hydroxylase from sympathetic nerves. Science *174:* 1349, 1971.
15. Wetterberg, L., Åberg, H., Ross, S. B. & Frödén, Ö.: Plasma dopamine-β-hydroxylase activity in hypertension and various neuropsychiatric disorders. Scand J Clin Lab Invest *30:* 283, 1972.

Received September 23, 1974

Address for reprints:

Hans Åberg, M.D.
Department of Medicine
University Hospital
S-750 14 Uppsala 14
Sweden