Lack of Correlation Between Serum Dopamine-β-Hydroxylase Activity and Blood Pressure in Middle-aged Men

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SUMMARY The activity of serum dopamine-β-hydroxylase (DBH) was measured in 1194 asymptomatic middle-aged men with diastolic blood pressure ranging from 75 to 125 mm Hg during the baseline examination of a multifactorial intervention program for primary prevention of coronary heart disease. No correlation was present between serum DBH activity and systolic \((r = -0.01, \text{NS})\) or diastolic \((r = +0.02, \text{NS})\) blood pressure. No significant differences in serum DBH activity was observed between individuals with blood pressure in the lower, middle or upper deciles. Serum DBH activity was similar in subjects with normal blood pressure, in individuals with widely fluctuating blood pressure and in patients with fixed hypertension. The results suggest that serum DBH activity cannot be used as an aid in the diagnosis of essential hypertension of middle-aged men. (Hypertension 1: 47–52, 1979)

KEY WORDS • serum DBH • sympathetic nervous system • blood pressure • essential hypertension

OVERACTIVITY of the sympathetic nervous system has long been implicated in the pathogenesis of essential hypertension.\(^1\)\(^\text{-}^8\) Evaluation of the role of sympathetic nerve activity has, however, been hampered by the lack of convenient methods for assessing its function. Dopamine-β-hydroxylase (DBH), the enzyme that converts dopamine to norepinephrine, is present in the synaptic vesicles of postganglionic sympathetic neurons.\(^4\) The release of norepinephrine from the nerve endings is accompanied by the simultaneous release of the soluble portion of DBH.\(^5\)\(^,\)\(^6\) In contrast to catecholamines, which immediately undergo axonal uptake, DBH persists in the circulation with a much longer half-life.\(^7\) Therefore, it has been suggested that plasma DBH activity might be a valuable indicator of the activity of the sympathetic nervous system.

Studies on serum DBH activity in hypertensive patients have produced highly conflicting results.\(^7\)\(^,\)\(^8\) The level of DBH activity has been reported by several authors to be abnormally high both in fixed and labile hypertension, whereas in other studies, no consistent change has been observed. The reason for the contradiction is not yet known, although it has become evident that the activity and the amount of serum DBH is determined mainly by genetic factors.\(^1\)\(^,\)\(^9\)

In the present study we have measured the serum DBH activity in 1194 middle-aged men during the baseline examination of a multifactorial intervention study for primary prevention of coronary heart disease. The data were analysed in several ways in an attempt to reveal correlations between DBH activity and systolic or diastolic blood pressure in subjects with normal blood pressure or labile or fixed hypertension.

Methods

Altogether 1194 males, aged from 40 to 54 years, were examined. The participants were executives who had volunteered for a controlled trial of multifactorial primary prevention of coronary heart disease. They were selected from 3625 men because of the presence of one or more of the following seven risk

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TABLE 1. Relationship Between Serum DBH Activity and Systolic and Diastolic Blood Pressure in Men with Normal Blood Pressure or with Borderline or Overt Hypertension

<table>
<thead>
<tr>
<th>Diastolic BP (mm Hg)</th>
<th>Mean serum DBH activity (µmoles/1/min)</th>
<th>Correlation coefficient (r) between serum DBH activity and BP</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 90</td>
<td>28.9 ± 0.8</td>
<td>-0.05, +0.01</td>
</tr>
<tr>
<td>91–100</td>
<td>29.6 ± 0.8</td>
<td>+0.02, -0.02</td>
</tr>
<tr>
<td>≥ 101</td>
<td>29.2 ± 0.9</td>
<td>-0.01, +0.01</td>
</tr>
</tbody>
</table>

Abbreviations: DBH = dopamine-β-hydroxylase; BP = blood pressure.

TABLE 2. Serum dopamine-β-hydroxylase (DBH) Activity in Subjects with Different Smoking Habits

<table>
<thead>
<tr>
<th>Smoking status</th>
<th>No. of subjects</th>
<th>Serum DBH activity* (µmoles/1/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never smoked</td>
<td>380</td>
<td>30.7 ± 1.0</td>
</tr>
<tr>
<td>Ex-smokers</td>
<td>401</td>
<td>29.2 ± 0.8</td>
</tr>
<tr>
<td>Current smokers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 10 cigarettes/day</td>
<td>413</td>
<td>27.5 ± 0.8</td>
</tr>
<tr>
<td>11–20 cigarettes/day</td>
<td>58</td>
<td>29.0 ± 0.8</td>
</tr>
<tr>
<td>≥ 21 cigarettes/day</td>
<td>103</td>
<td>27.1 ± 1.5</td>
</tr>
<tr>
<td>pipe or cigar</td>
<td>96</td>
<td>26.8 ± 1.7</td>
</tr>
</tbody>
</table>

*Mean ± SEM.

Factors: 1) serum cholesterol > 7.0 mmoles/l; 2) serum triglycerides > 1.7 mmoles/l; 3) blood glucose in 1-hr glucose tolerance test (1 g of glucose per kg of body weight) > 9.0 mmoles/l; 4) relative body weight > 120%; 5) systolic blood pressure > 160 mm Hg; 6) diastolic blood pressure > 95 mm Hg; or 7) smoking > 10 cigarettes/day. All subjects with symptomatic coronary heart disease, cerebrovascular disease and antihypertensive or hypolipidemic medication were excluded from the study.

Blood pressure was measured at two separate occasions in the sitting position. The first measurement was carried out by a registered nurse in the municipal health center. The second was performed by one of us 10 minutes after the beginning of the first office visit. Those 297 subjects who had high blood pressure (either systolic blood pressure > 160 or diastolic blood pressure > 95 mm Hg) at both occasions were considered to have “fixed” hypertension and were subjected to more detailed studies (serum creatinine and potassium, urinary sediment and, in selected cases, urography and adrenocortical function tests). Patients with secondary hypertension were excluded from the study. The difference between the measurements taken by the nurse and by the physician was used as an index of the “lability” of blood pressure in some of the analyses. It was assumed that the first visit to the doctor’s office would result in a higher activity of the sympathetic nervous system than the more casual examination carried out by the nurse in the health center.

Venous blood samples for the measurement of serum lipids and glucose were withdrawn at 8:00 a.m. after an overnight fast. Serum cholesterol was assayed by the method of Huang et al. and serum triglyceride and glucose by a Technicon Auto-analyzer. (Technicon Instruments Corp., Tarrytown, N.Y.).

Blood samples for the determination of serum DBH activity were obtained in the afternoon in non-fasting state. Earlier studies have demonstrated that the activity of serum DBH remains essentially stable during the daytime but decreases somewhat during the sleeping hours. The activity of DBH was measured by the spectrophotometric method of Nagatsu and Udenfriend. Serum samples were stored at -25°C for 3–12 months before the essay. In separate experiments it was shown that the decay in the enzyme activity at -25°C was 5–7% per year and that freezing and thawing did not influence the activity. The small decay was ignored in the calculation of the results. Mean, SD, SEM and regression were calculated by a computer program. Statistical difference was tested by Student's t test or paired t test.

Results

The mean activity of serum DBH in 1194 men was 29.2 µmoles/1/min. The distribution of the values (fig. 1) was slightly skewed to the right as reported earlier. No activity or very low activity (less than 5 µmoles/1/min) was recorded in 53 subjects (4.6%) but these subjects did not form a separate subgroup in the frequency distribution histogram as was reported by Weinshilboum for children. No trend toward a bimodal distribution at the higher enzyme levels was found. This observation is in agreement with the results of Horwitz et al. and Weinshilboum et al., but differs from the experience of Schanberg et al. and Ogawa et al.

No correlation was present between the activity of serum DBH and systolic or diastolic blood pressure (r = -0.01 and + 0.02, respectively; NS). Lack of any consistent relationship is further substantiated by the results shown in figure 2. No significant difference in serum DBH activity was seen between the subjects with systolic or diastolic blood pressure in the lower, middle or upper deciles. Finally, no correlation between DBH activity and blood pressure was observed in the subgroup when the study population was divided into quintiles on the basis of DBH activity.

In an attempt to correlate the serum DBH level to the "lability" of the sympathetic nervous system activity, we analyzed the correlation between serum DBH activity and the difference in systolic blood pressure recording obtained by the registered nurse under basal conditions and by the physician during the first office visit. The difference varied from -4 mm Hg to 65 mm Hg and was more than 10 mm Hg in ap-
proximately 50% of the subjects. As shown in figure 3, no correlation was, however, observed between serum DBH level and the lability of blood pressure estimated in this way.

It has been reported that a positive correlation exists between serum DBH activity and diastolic blood pressure in patients with borderline hypertension, but not in subjects with normal or definitely elevated blood pressure. In an attempt to confirm this observation we studied the relationship between DBH activity and systolic and diastolic blood pressure in three subgroups with diastolic pressure 90 mm Hg or less, 91-100 mm Hg and 101 mm Hg or more. However, DBH activity and blood pressure recordings did not correlate in any of the three groups (table 1).

No correlation was present between serum DBH activity and the level of serum cholesterol ($r = -0.01$, NS), serum triglycerides ($r = +0.07$, NS), 1-hr glucose tolerance test ($r = +0.02$, NS) or relative body weight ($r = +0.06$, NS). Lack of any consistent relationship was further confirmed by analyzing the mean DBH activity in decile classes formed on the basis of risk-factor levels.

The mean DBH activity was somewhat lower in current smokers than in subjects who had never smoked ($p < 0.05$; table 2). A similar observation has been reported by Takahashi et al. and may be due to hemodilution caused by nicotine-induced antidiuresis. The difference between ex-smokers and those subjects who had never smoked was not statistically significant.

According to Dunnette and Weinshilboum, very low serum DBH activity is inherited as a recessive autosomal gene. About 5% of the American population may be homozygous in regard to "low DBH activity gene." To analyze whether the subjects presumably homozygous for the low-activity gene might differ from the rest of the population, we compared the mean levels of systolic and diastolic blood pressure, serum cholesterol and triglycerides, and height and relative body weight in participants with serum DBH activity less than 5 μmoles/min (53 subjects, 4.6%) to the respective values in the rest of the group. No difference in any of these parameters was found between subjects with very low, normal or high serum DBH activity.

Discussion

No correlation was observed in the present investigation between serum dopamine-β-hydroxylase activity and blood pressure in 1194 asymptomatic men with diastolic pressure ranging from 75 to 125 mm
A positive correlation between plasma DBH (assayed by radioimmunoassay with a heterologous antibody) and blood pressure was observed also by Geffen et al. and Louis et al. Furthermore, the same investigators reported a positive correlation between serum DBH and serum catecholamine concentration and urinary catecholamine excretion, which they considered as evidence for the role of sympathetic nervous system overactivity in the pathogenesis of essential hypertension.

On the other hand, in agreement with our results, several other groups have failed to establish the presence of high serum DBH activity in subjects with various types of hypertension. Horwitz and his associates studied 90 subjects with normal blood pressure and 78 patients with borderline or established hypertension but did not find any difference in serum DBH activity between the groups. No correlation between serum DBH activity and blood pressure was observed by Weinshilboum in school children or in adolescent subjects 13 to 18 years of age. Lack of correlation has been reported also by several other investigators on the basis of experience obtained from smaller groups of patients. Furthermore, a recent study by Lake et al. did not reveal any relationship between plasma DBH activity and plasma catecholamine concentration in over 350 subjects with normal or mild to moderate hypertension.

Stone and his associates have suggested that elevation of plasma DBH is typical for labile hypertension, whereas the values are less abnormal in subjects with fixed hypertension. Similarly, Alexander et al. reported a correlation between serum DBH activity and diastolic blood pressure in patients with borderline or labile hypertension, but not in subjects with normal blood pressure or established hypertension. Despite these differences the mean level of serum DBH activity was similar in their three groups. Since these studies suggested that serum DBH activity might be inappropriately high in labile or borderline hypertension, we analyzed our data in several ways to define subgroups of subjects with labile hypertension or with high activity of the sympathetic nervous system. However, no correlation was found between serum DBH levels and systolic or diastolic blood pressure in subjects with diastolic blood pressure between 91–100 mm Hg. Furthermore, the level of DBH activity did not differ between individuals with small and large fluctuations in systolic or diastolic blood pressure.

The discrepancies between our findings and other...
investigations reporting a relationship between serum DBH levels and blood pressure are not easy to explain. However, at least two alternative interpretations should be considered. One of the major differences resides in the characteristics of the study populations. Positive correlations between the serum DBH level and blood pressure have been observed mostly in small groups of patients attending clinics specialized for treatment of hypertension. Yet, studies in less selected populations, such as our group, have usually failed to confirm the relationship. Thus, it is still possible (although less probable in our opinion) that serum DBH might be elevated in subgroups of hypertensive individuals with particular characteristics that lead to more detailed clinical studies.

The conflicting results might also arise from methodological differences. The assay system of Nagatsu and Udenfriend,18 which was used, has been shown to give parallel results with other major techniques for the measurement of DBH activity.14 On the other hand, a positive correlation between the serum DBH contents and blood pressure has been reported by a group using radioimmunoassay with anti-sheep DBH antibody and sheep antigen.44, 46 No correlation was observed between blood pressure and serum activity of DBH. It was suggested by these authors that their assay system is capable of identifying fragments that reflect the activity of the sympathetic nerve system better than the large active enzyme. Their results have not, however, been confirmed, and later studies have demonstrated a direct relationship between enzyme activity and immunoreactive DBH with both immunoprecipitation16 and radioimmunoassay using homologous antigen and antibody.28 Thus, it is unlikely that differences between various assay techniques would provide an explanation for such discrepancies in experimental results.

The present data strongly suggest that high serum DBH activity is not associated with essential hypertension in middle-aged men. Conversely, the individuals with low or non-existent serum DBH activity do not seem to differ from the rest of the population in regard to blood pressure or any other characteristic studied in the present investigation. Lack of correlation between serum DBH level and blood pressure may be interpreted in several ways. The variation due to genetic factors has been shown to be a major determinant of serum DBH activity4, 17 and is likely to conceal the influence of quantitatively minor factors. In fact, procedures that increase sympathetic nerve activity may alter the serum DBH level, but the changes are small in comparison to the effects of age and heredity.8, 40 We should also emphasize that the role of the sympathetic nervous system in the pathogenesis of primary hypertension is still disputed. Although disturbed regulation of sympathetic nerve activity has been suggested to be common in young patients (aged between 18 and 35 years),8, 41 sympathetic overactivity may not be the only cause of essential hypertension in the age-groups represented in the present study. Our results strongly suggest that serum DBH activity is of little use in the assessment of essential hypertension in middle-aged men.

References
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