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ORIGINAL

RELATIONSHIP BETWEEN THE ACTIVITY OF PLASMA DOPAMINE-BETA-HYDROXYLASE AND THE DURATION OF DIABETES MELLITUS

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SUMMARY

Plasma DBH activity was studied in a group of 50 normal individuals, a group of 53 diabetics diagnosed less than 2 years ago (G1) and a group of 49 diabetics diagnosed more than 10 years ago (G2). The enzyme activity was significantly different in the 2 groups, G1 having the lower activity and G2 the highest. We interpret our results accepting that in G1 the damage of noradrenergic terminals allows less DBH to be liberated to the blood, whereas in G2 DBH reuptake by damaged sympathetic nerves is the predominant lesion, having as a result a prolonged persistence of the enzyme in the plasma.

RESUMO

Relação da actividade plasmática da dopamina-beta-hidroxilase com a duração da diabetes mellitus

Estudou-se a actividade da DBH do plasma em 50 indivíduos normais, 53 diabéticos com menos de dois anos (G1) e 49 com mais de 10 anos de diagnóstico da doença (G2). A actividade da DBH é significativamente diferente nos dois grupos, sendo a mais elevada em G2. Os resultados são interpretados aceitando que no grupo G1 as lesões das terminações noradrenérgicas reduzem a quantidade de DBH libertada para o plasma, ao passo que no grupo G2 a recaptação da DBH pelos nervos simpáticos lesados é a lesão predominante, de que resulta a manutenção do enzima no plasma durante mais tempo com a duração da diabetes mellitus.

INTRODUCTION

Plasma dopamine-beta-hydroxylase (DBH) results from exocytosis of noradrenergic terminals, and its activity has been used as a parameter of sympathetic nerve function.[1-2] A small percentage of normal individuals is characterized by low plasma DBH activity, a trait inherited through a recessive gene.[3-4]

The administration of 6-hydroxydopamine to rats induces a chemical neuropathy, accompanied by a drastic reduction of plasma DBH activity.[1]

It might be expected that plasma DBH activity would be reduced in cases of diabetic neuropathy due to destruction of sympathetic nerve endings. Noth et al[5] found extremely low values of plasma DBH in 4 cases of diabetic neuropathy.

In a previous paper[6] we measured plasma DBH activity in 100 diabetic patients and found no significant difference in comparison to a normal population. Also there was no correlation between enzyme activity, degree of neuropathy, insulin treatment, and type of diabetes. The only important finding consisted in the difference of the distribution curves for DBH activity: gaussian for normal individuals, irregular and wider for diabetics.

In the present paper we analyse plasma DBH activity in relation to the time of evolution of diabetes.

MATERIAL AND METHODS

The human material consisted of 50 controls (M = 22, F = 28) 53 diabetics (M = 24, F = 29) whose disease was diagnosed less than 2 years ago, and 49 diabetics (M = 24, F = 25) diagnosed more than 10 years ago. The age ranges of the 3 groups were approximately the same. Cases of hypertension were avoided (diastolic BP > 100 or systolic BB > 170 mmHg). Patients were attending regularly the Diabetes Outpatients Clinic of the Hospital de Santa Maria.

Blood was obtained by venipuncture, and placed in a heparinized centrifuge tube. It was centrifuged at 4000 r.p.m. for 10 minutes, plasma was separated and frozen at −20 °C (in this condition the enzyme is stable for 2 months).[7]

DBH activity was measured within a week by the method of Nagatsu and Udenfriend[7] in which Tyramine is converted into Octopamine, followed by conversion to p-hydroxybenzaldehyde, which is measured at 330nm. Reagents used were obtained from Sigma Chem. Co (fumarate, catalase, octopamine, tyramine-HCl, N-ethylmaleimide).

Pargiline was an offer of Abbott Lab, USA.

Assays were run in duplicate, with the respective blank, in which the enzyme is inactivated by heat. Blanks of octopamine were used. The reproducibility of the method was good, with less than 5 % standard error. DBH activity is ex-

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TABLE 1 **Plasma DBH activity (I.U.) in 50 normal individuals, 53 diabetics < 2 years, and 49 diabetics > 10 years (mean ± st. deviation).**

	N.°	DBH		t.	p
Normals	50	76,31 ± 50,95	N/diab < 2y	1,251	—
Diabetics < 2 y	53	63,58 ± 51,29	N/diab > 10y	1,648	—
Diabetics > 10y	49	96,18 ± 66,86	diab < 2y/ > 10y	2,747	< 0,01

pressed in international units (micromoles octopamine formed/minute/liter of plasma at 37 °C).

RESULTS

Table 1 shows the results obtained for plasma DBH activity in the 3 groups studied. Diabetics of short duration have the lowest values, and diabetics of long duration the highest, normals being in the middle.

The 2 groups of diabetics differ significantly at the level of 0,01. In Figure 1 we have the distribution of DBH activities, which confirm the tendency for short term diabetics to have lower values and for long term diabetics to have higher values, as compared to normals.

DISCUSSION

In our previous study[6] we found no difference between normal individuals and diabetics for plasma DBH. This is now understandable, since cases of short duration would tend to compensate the cases of long term diabetes. Considering the fact that exocytosis depends on the functional and structural integrity of the noradrenergic system, these results are difficult to interpret.

Berkowitz et al[8-9] studying rats rendered diabetic by streptozotocin or alloxan, found an elevation of plasma DBH, which increases with time, reaching a maximum after 7 months, when DBH activities were 6 times the inicial values.

Recently Hurs et al[10] administered purified DBH to streptozotocin diabetic rats and verified that it remains more elevated than in controls. This was due to a higher concentration of protein and not to the alteration of the kinetic properties of the enzyme. There is then a smaller clearance of DBH in diabetic rats.

DBH is a glycoprotein, and axonal transport of glycoproteins is decreased in streptozotocin diabetics rats.

The same happens after galactose administration, due to structural, biochemical and functional alterations of axonal nerve endings.[11-12]

We may interpret our results as follows: initially damage of noradrenergic terminals would result in a smaller quantity of DBH liberated to the plasma, but reuptake would be normal.

Later on, there would be a decrease in reuptake of the enzyme by noradrenergic endings. This would result in a longer permanence of the enzyme in plasma.

One last point deserves comment. The two groups of diabetics were of approximately the same age range. When we revised the cases, we noticed that cases of long term diabetes were for the most part juvenile onset diabetes, whereas in our cases of short term diabetes adult onset diabetes predominated. Up to what extent this fact could interfere with our data deserves a further study.

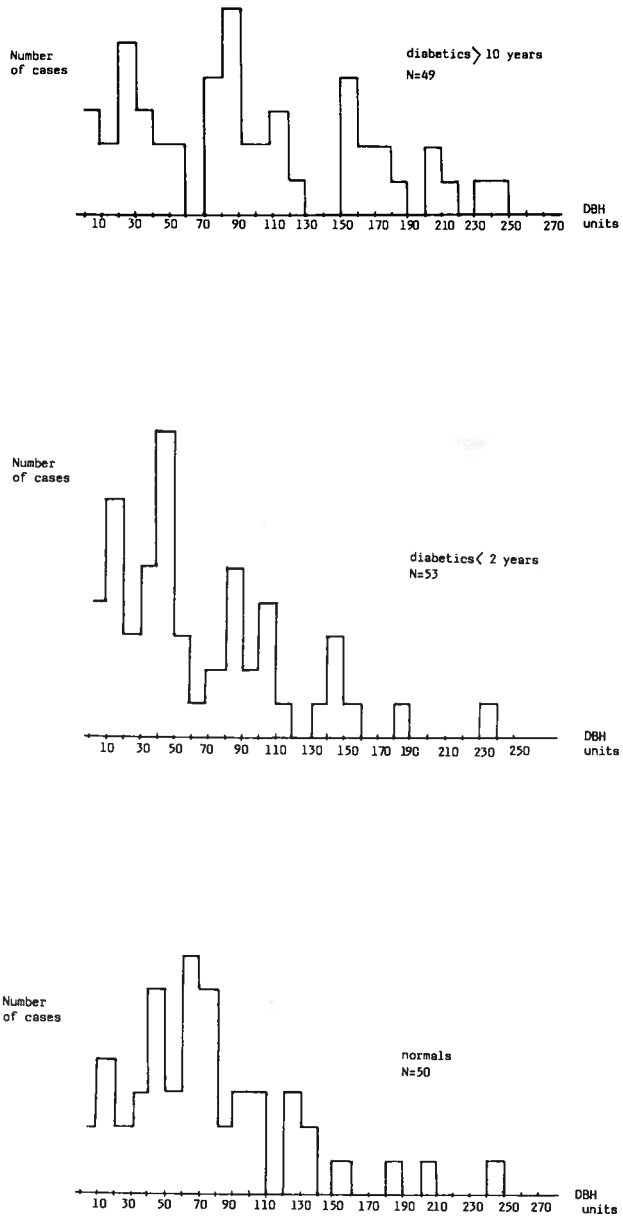

Figure 1: Distribution of plasma DBH activities in normal individuals, cases of short term diabetes and cases of long term diabetes, showing the tendency for the first to accumulate on a lower activity group and the second to accumulate on the higher activity side.

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