Dopamine β-Hydroxylase Deficiency
A Genetic Disorder of Cardiovascular Regulation

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Dopamine β-hydroxylase (DBH) deficiency is a genetic disorder in which affected patients cannot synthesize norepinephrine, epinephrine, and octopamine in either the central nervous system or the peripheral autonomic neurons. Dopamine acts as a false neurotransmitter in their noradrenergic neurons. Neonates with DBH deficiency have had episodic hypothermia, hypoglycemia, and hypotension, but survivors sometimes cope relatively well until late childhood when overwhelming orthostatic hypotension profoundly limits their activities. The hypotension may be so severe that clonic seizures supervene. Most currently recognized patients are young or middle-aged adults. The diagnosis is established by the observation of severe orthostatic hypotension in a patient whose plasma norepinephrine/dopamine ratio is much less than one. *(Hypertension 1991;18:1-8)*

N orepinephrine and epinephrine are the most critical determinants of minute-to-minute neural regulation of local vascular tone and thus arterial pressure. Moreover, they are also involved in the regulation of autonomic outflow at the level of the brain stem and spinal cord. This outflow has an important influence on cardiac, renal, and vascular function. In the periphery, the effects of norepinephrine generally result in the elevation of blood pressure, but within the central nervous system this neurotransmitter often depresses sympathetic outflow, yielding a fall in blood pressure. Thus, any factor that alters the synthesis of norepinephrine and epinephrine can perturb blood pressure regulation at several interacting levels.

The enzyme dopamine β-hydroxylase (DBH) (EC 1.17.14.1) is required for conversion of dopamine to norepinephrine (and thus epinephrine), but tyrosine hydroxylase rather than DBH is the rate-limiting step in norepinephrine synthesis under almost all circumstances in humans (Figure 1). Even in situations of high sympathetic activation, such as prolonged treadmill exercise, norepinephrine and epinephrine remain the predominant circulating catecholamines, with minimal step-up in plasma dopamine levels. This indicates that in healthy subjects under ordinary circumstances, DBH activity is sufficient for the needs of autonomic cardiovascular regulation.

Recently we and others² have recognized that there are occasional circumstances in which neuronal DBH activity is inadequate. The syndrome of severe DBH deficiency² is a dramatic example of such a case. The survival of individuals with an essentially complete absence of norepinephrine into adulthood strongly suggests that individuals with partial enzyme deficiency will also be found. Unlike previously described forms of autonomic failure, this disorder has been localized to a discrete enzymatic defect, which has enabled investigators to approach its treatment more rationally than has heretofore been possible. Recognition of the disorder has also led to greater understanding of autonomic control of the circulation.

**Dopamine β-Hydroxylase**

DBH catalyzes the conversion of dopamine to norepinephrine.⁴⁻⁵ It is unique among the catecholamine-synthesizing enzymes in that it is located almost exclusively in the chromaffin granules of the adrenal medulla and the large dense-core synaptic vesicles of noradrenergic neurons.⁶ It is found in both peripheral and central noradrenergic and adrenergic neurons. DBH exists in both the dimeric and tetrameric forms, with two copper atoms per monomeric subunit.⁷⁸ The four subunits are linked by disulfide bridges into two dimers, which are joined to each other by noncovalent bonds. The copper is essential for enzyme activity. DBH also requires molecular oxygen and ascorbic acid for enzyme activity. DBH is not substrate-specific, since it oxidizes almost any phenylethylamine to its corresponding...
phenylethanolamine (including the hydroxylation of tyramine into octopamine) and converts the \( \alpha \)-methyldopa metabolite \( \alpha \)-methyldopamine to \( \alpha \)-methyl-norepinephrine. The \( K_m \) of this enzyme for dopamine is approximately \( 5 \times 10^{-3} \) M. 9

Vesicular DBH occurs in both a soluble and a membrane-bound form. 10 These are present in approximately equal amounts. The soluble enzyme is released into the synaptic cleft at the time of vesicular exocytosis and is presumably the source of the enzyme present in blood. Much recent study has gone into the identification of the differences between these two forms. 11 Current evidence suggests that both forms of DBH originate from a single gene and that the soluble form is derived from the membrane bound form. 12 There is evidence that neither glypiation 13 nor retained signal peptide 14 can account fully for the membrane-binding characteristic of the enzyme.

The sequence of DBH complementary DNA (cDNA) was reported by Lamouroux et al 15 in 1987. The cDNA was cloned from a human pheochromocytoma expressing high levels of DBH activity. The corresponding polypeptide chain contained 603 amino acids corresponding to an unmodified protein of 64,862 Da, preceded by a cleaved signal peptide of 25 residues. Kobayashi and coworkers 16 subsequently showed that there is a single DBH gene of approximately 23 kb and that it is composed of 12 exons, with exon 12 providing two alternative polyadenylation sites. Restriction analysis of the positive DBH clones revealed two types of DBH cDNA, type A (2.7 kb) and type B (2.4 kb). The ratio of type A and B messenger RNAs (mRNAs) in the pheochromocytoma was 5:1. Four clones were selected for further analysis. Sequencing of the cDNA inserts demonstrated that type A cDNA (DBH-1) differed from type B cDNA (DBH-2) by an additional 300 nucleotides in the 3' untranslated region, the former set of clones being 2.7 kb. The clones in each set differed from each other at six nucleotides found in various portions of the cDNA (Table 1). This was the first published data for polymorphism at the DBH locus at the molecular level, although other restriction endonuclease restriction fragment length polymorphisms have subsequently been reported. Transcription regulatory sites such as TATA, CCAAT, CACCC, and GC boxes were identified in the 5' flanking region as were sequences homologous to glucocorticoid and cyclic AMP response elements. 16 It is not known if the primary structure of DBH reported by Lamouroux et al 15 is Type A or B, but it cannot be grouped with either set of cDNAs published by Kobayashi et al. 16 Furthermore, the nucleotide difference reported at position 910 would cause an amino acid change (Ala versus Ser), and there is also a change from Arg to Cys at position 1,642, which corresponds to Kobayashi's position 1,603.

Serum DBH activity assays have been widely used during the past 25 years. 17 They are based on the enzymatic conversion of a substrate (e.g., tyramine) into a corresponding product (e.g., octopamine) by

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<th>DBH Nucleotide</th>
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Among the four currently published (presumably normal) dopamine \( \beta \)-hydroxylase sequences, there are seven nucleotides at which differences are noted. Only two of these (910 and 1,603) are at sites that result in different amino acids. Kobayashi 1,2 and Kobayashi 3,4 represent the four clones sequenced by these investigators. 16 They also sequenced the clone from the Maniatis genomic library. 16

![Figure 1](http://hyper.ahajournals.org/fig/1.png) Schematic diagram shows synthesis of norepinephrine and epinephrine. All these enzymatic steps take place in the cytoplasm except for conversion of dopamine to norepinephrine. Dopamine \( \beta \)-hydroxylase is confined to the neurotransmitter vesicles.
DBH, taking advantage of the non-substrate specificity of the enzyme. Inhibitors of DBH are normally present in serum but can be inactivated by N-ethylmaleimide or by copper sulfate.9 In addition to serum DBH activity measurements, the actual amount of enzyme present can be determined by radioimmunoassay.18 When antibodies to homologous protein are used, there is usually an excellent correlation between immunoreactive DBH and DBH enzymatic activity.

It was hoped that measurements of serum DBH could be used to assess adrenergic and noradrenergic function in humans. However, it is now recognized that the wide interindividual variation in enzyme activity observed in humans is mostly due to a genetic trait. Furthermore, within individuals, acute changes in adrenergic function result in changes in DBH activity that are small in magnitude in comparison with changes in plasma catecholamine values. These facts have dampened enthusiasm for the use of serum DBH as a measure of acute alterations in adrenergic activity in humans.19

Biochemical genetic studies of the 1970s and early 1980s using these assays documented polymorphism in DBH in apparently healthy individuals. Serum DBH enzymatic activity and immunoreactive protein increase from low levels in young children to high levels in most adults, but levels of both remain low in a minority.20 Fifty to seventy percent of the variance in basal human serum DBH activity results from this genetic variation in DBH levels. In linkage studies this trait has been mapped to chromosome 9q34, the region containing the gene for DBH.21-23 In addition, approximately 8% of a randomly selected population was found to have a thermolabile form of serum DBH that exhibited familial aggregation.24 This thermostability is a characteristic of the DBH molecule itself and depends on an interaction with oxygen. Although one would expect such a characteristic to derive from the structural DBH gene, thermostability has not been mapped to 9q34.

Although in the vast majority of individuals there is a good correlation between serum immunoreactive and enzymatic DBH levels, some persons have a disparity.19 These individuals have much higher amounts of immunoreactive material than enzymatic DBH activity. This disparity may reflect changes in the active site and could indicate subclinical impaired function. There is clearly a familial aggregation of this trait.

**Clinical Presentation of Dopamine β-Hydroxylase Deficiency**

In 1986, we reported a congenital syndrome characterized by severe orthostatic hypotension, noradrenergic failure, and ptosis of the eyelids.2 This disorder was simultaneously recognized in the Netherlands.3 Based on a battery of biochemical and physiological tests, it was determined that this disorder was due to a deficiency of DBH. The characteristics of patients with DBH deficiency are distinct from previously recognized forms of autonomic dys-
tension, hypoglycemia, and hypothermia have occurred. The causes of hypoglycemia and hypothermia are not fully understood at present, but epinephrine has a well-characterized calorigenic effect in animals, and excessive dopamine may reduce temperature in animals. Vomiting occurred four times in the first year of life in one patient. The hypoglycemia and hypothermia have also been seen primarily in the first year of life. Sometimes seizures have occurred, probably because of hypoglycemia or hypotension.

As children, DBH-deficient patients have had a markedly reduced ability to exercise because of postural hypotension occurring with exertion. The syncope associated with this postural hypotension has led to trials of anticonvulsive medications, even though the electroencephalogram did not suggest a seizure disorder.

Symptoms have generally worsened considerably in late adolescence and early adulthood. Patients complain of profound orthostatic hypotension, especially early in the day and during hot weather or after alcohol ingestion. There is greatly reduced exercise tolerance, ptosis of the eyelids, nasal stuffiness, and focal cerebral and cerebellar degeneration. The patients with DBH deficiency so far described have had such striking abnormalities in catecholamine metabolism that they are readily distinguishable from patients with all other known disorders. The combination of minimal or undetectable plasma norepinephrine with a fivefold to 10-fold elevation of plasma dopamine is probably pathognomonic of the disorder (Table 4). Indeed, perhaps the only other disorder in which plasma dopamine exceeds plasma norepinephrine is Menkes kinky hair disease, a dramatic illness associated with profound mental retardation.

The Menkes syndrome is an X-linked recessive disorder characterized by early growth retardation, short stature, and focal cerebral and cerebellar degeneration. Survival beyond 10 years is rare, and brain damage is usually severe even in these individuals.

DBH deficiency would probably have been recognized earlier were it not for the fact that most
medical centers tend to measure norepinephrine and epinephrine but not dopamine in the evaluation of patients with autonomic dysfunction. Without comparative details about the levels of norepinephrine and dopamine and the patterns of their respective metabolites, the special nature of the enzymatic defect in this disorder can be entirely missed. Such patients were probably considered to have an atypical form of the Bradbury-Eggleston syndrome or idiopathic orthostatic hypotension. In addition, commonly used radioenzymatic methods for catecholamine determinations have the disadvantage of a low, but significant, crossover of dopamine into epinephrine. Because of normally low levels of dopamine, this is usually of minor practical importance. However, in a setting of elevated dopamine levels, as present in DBH deficiency, a proportion of dopamine may be erroneously measured as epinephrine.

Plasma dopamine levels in DBH-deficient subjects approximate plasma norepinephrine levels in normal subjects, but with greater variability. This is believed to occur because dopamine, rather than norepinephrine, is being stored and released by noradrenergic neurons in DBH-deficient subjects. For this reason, plasma dopamine levels respond to various stimuli that would elicit an increase in plasma norepinephrine levels in normal subjects. Thus, for example, a change from supine to upright posture will double or triple the plasma dopamine level. Likewise, the administration of a central suppressant of sympathetic activity such as clonidine will greatly reduce the plasma dopamine level. Plasma dopamine levels have thus been shown to be greatly elevated by insulin hypoglycemia, edrophonium, tyramine, tilt, and upright posture. Perhaps because of high levels of dopamine, plasma prolactin is low in this disorder.

It is noteworthy that plasma dopa levels are also raised twofold to threefold while the enzyme dopa decarboxylase is also normal in plasma.

Metabolites of norepinephrine that have been measured have been low or absent in plasma, urine, and cerebral spinal fluid (CSF). Conversely, dopamine metabolites such as homovanillic acid and 3-methoxytyramine are raised. Determination of whether norepinephrine exists at all in patients with DBH deficiency must await further investigations and improvements in assay methodology. A low, but apparently detectable, level of vanillyl mandelic acid was found in the urine of three patients and a low, but detectable, level of MHPG was found in the CSF of another patient. In other patients, these metabolites have been below the limits of detection of the assay. Whether these reflect genuine differences in pathology or the limitations of the respective assays remains to be seen.

Skin biopsy results reported in three subjects have not stained for DBH, but tyrosine hydroxylase was present in all. In the two subjects in whom data have been reported, neuropeptide Y, calcitonin gene-related peptide, substance P, and vasoactive intestinal peptide have all been present.

Physiological tests of autonomic function also provide diagnostic information of great specificity. Autonomic tests that measure sympathetic noradrenergic and adrenergic function are uniformly abnormal. Cold pressor testing (immersion of a hand in ice water for 1 minute) causes either a fall or no change in blood pressure. Isometric handgrip exercise (sustained handgrip for 3 minutes) fails to significantly increase blood pressure. The Valsalva maneuver results in a profound fall in blood pressure together with an increase in heart rate reflecting parasympathetic withdrawal. The phase IV overshoot of the Valsalva maneuver does not occur. Hyperventilation causes a fall in blood pressure, as is also the case in patients with the Bradbury-Eggleston syndrome. In contrast to the absence of sympathetic activation, the presence of sweating underscores the integrity of sympathetic cholinergic fibers. Moreover, parasympathetic function is preserved since these patients have normal sinus arrhythmia. This selective sympathetic noradrenergic impairment is quite characteristic of DBH deficiency. Other forms of autonomic failure demonstrate both sympathetic and parasympathetic involvement.

DBH deficiency shares many pharmacological features of other forms of autonomic failure. There is a severalfold hypersensitivity to α1-adrenergic receptor agonists and β-adrenergic receptor agonists. This is also found in other forms of autonomic failure and represents a compensatory receptor upregulation as a result of the chronic relative depletion of catecholamines. This phenomenon is analogous to other forms of "denervation hypersensitivity." Tyramine is an indirect-acting pressor amine that will induce norepinephrine release from adrenergic nerve terminals. Tyramine, in intravenous doses of 2–3 mg, will raise plasma norepinephrine and blood pressure in normal subjects and in patients with other types of autonomic failure, but no blood pressure elevation occurred even with 6–8 mg of tyramine in DBH-deficient subjects. Plasma dopamine, instead of norepinephrine, is increased following the administration of tyramine in these patients.
Propranolol, a β-adrenergic receptor antagonist, does not lower the basal heart rate in these patients, but pindolol, a β-antagonist with sympathomimetic properties, raises heart rate significantly. Intravenous atropine raises heart rate by 40–60 beats per minute. The respiratory arrhythmia that occurs in the baseline state in DBH deficiency disappears with the administration of atropine. Taken together, these observations imply normal parasympathetic, but defective sympathetic, control of heart rate. Pindolol, a β-adrenergic receptor antagonist with some sympathomimetic activity, raises heart rate. It is also of interest that atropine elicits a much more pronounced pressor effect in DBH-deficient subjects than in normal subjects.2,3

Clonidine acts on α2-adrenergic receptors or imidazole receptors in the brain stem to reduce sympathetic outflow and lower blood pressure.24 It can also exert peripheral pressor effects by stimulation of vascular α2-adrenergic receptors.38 DBH-deficient patients have no fall in seated mean arterial pressure after the administration of clonidine, probably reflecting the fact that in these patients, blood pressure is not maintained by sympathetic tone. On the contrary, dramatic increases in blood pressure are seen with higher doses of this agent. It is noteworthy that the heart rate decreases in DBH-deficient patients after the administration of clonidine, even though blood pressure does not fall, consistent with the postulated central parasympathetic role in clonidine-induced bradycardia.

Finally, direct measurements of sympathetic nerve traffic to the vasculature of the skeletal muscle have been carried out using microneurography in a patient with DBH deficiency.39 They confirm that sympathetic neural traffic is present and regulated in a qualitatively normal fashion. Dopamine β-Hydroxylase Deficiency: Therapy

DBH-deficient patients have been difficult to treat using standard therapeutic approaches for autonomic failure. Most have failed empirical therapy with anticonvulsant agents before diagnosis of orthostatic hypotension. Fludrocortisone, at dosages of 0.1–0.8 mg daily, has been used to raise blood pressure with some benefit,2 but marked orthostatic hypotension still occurs. Likewise, indomethacin (50 mg four times daily) has been of limited benefit in raising blood pressure in these subjects; furthermore, one patient had aggressive ideation on this drug.30 Monoamine oxidase inhibition (tranylcypromine) has produced paranoid thinking.30 There has been some pressor response to phenylpropanolamine (25 mg and 50 mg), presumably owing to the denervation hypersensitivity of the patients’ vascular α-adrenergic receptors.30

Because both plasma dopa and dopamine levels were elevated in DBH-deficient patients, the vasodepressor effects of dopamine, either through direct vasodilatation or by means of a diuretic effect at the level of the kidney, were proposed as possible explanations for the striking severity of low blood pressure in these patients.40,41 It was hypothesized that if dopa and dopamine were reducing blood pressure in DBH-deficient subjects, the administration of metyrosine (α-methyl-para-tyrosine) might prove therapeutic.28

In normal subjects, metyrosine blocks tyrosine hydroxylase, the enzyme leading to the synthesis of dopa. This results in reduced levels of dopamine and norepinephrine, and therefore blood pressure falls, particularly when the subject is in the upright posture. We hypothesized that our patients might have such high dopamine levels that paradoxical pressor effects might occur. Because metyrosine is a depressor in healthy individuals, a failure of metyrosine to affect blood pressure, or a reduction in blood pressure with metyrosine, would not support a contribution of dopamine to the low blood pressure in our patients. Conversely, a rise in blood pressure with metyrosine would suggest that dopa and dopamine were indeed exerting depressor effects and that these effects could be attenuated by an agent that reduced manufacture and release of dopamine. In the event, metyrosine given in doses used to treat pheochromocytoma exerted a dramatic pressor effect, which appeared to correlate with the metyrosine-associated reduction in urinary dopamine excretion.28

In spite of this initially favorable response to metyrosine, much more experience with it will be required before it can be recommended for treatment. Patients receiving metyrosine experienced significant sedation; one patient experienced a marked dystonic reaction,28 but fortunately responded promptly to a 10 mg intravenous dose of diphenhydramine.

In an effort to achieve more specific therapy, we explored the use of dihydroxyphenylserine (DOPS) in these patients.42 We administered DOPS in the hope that it would result in an endogenous conversion (by dopa decarboxylase) of the drug to norepinephrine. We believed this might occur because DBH is not needed for the conversion of DOPS to norepinephrine and, thus, this enzyme could be bypassed in the patients in whom it is defective. We hypothesized that there would be an increase in plasma norepinephrine following the administration of DOPS.

The administration of DOPS to patients with DBH deficiency has resulted in dramatic increases in blood pressure and concomitant restoration of plasma and urinary levels of norepinephrine toward normal.42,43 There has been an associated modest decline in dopamine levels, as though the provision of norepinephrine to extraneuronal sites might be reducing the activity of tyrosine hydroxylase through feedback inhibition. The increase in plasma norepinephrine was highly correlated with the increase in mean arterial blood pressure. Standing time was greatly increased after administration of DOPS.

We could not be certain whether de novo synthesis of norepinephrine from DOPS occurred in neuronal tissues or in extraneuronal tissues, since dopa decarboxylase activity is present in many extraneuronal tissues.
However, long-term treatment with DOPS in this disorder is associated with intraneuronal restoration of norepinephrine, which is released on assuming the upright posture. Thus, DOPS in DBH deficiency appears to be far more effective than any other therapy for any form of autonomic dysfunction.31,41,42,44

**Dopamine β-Hydroxylase Deficiency: Implications**

Although DBH deficiency is probably a rare disease in adults, it could be more common in the perinatal period. Medical histories of DBH-deficient patients include near fatal illness during the neonatal period due to hypotension, hypoglycemia, and hypothermia. We suspect that many DBH-deficient infants succumb undiagnosed at this point, never reaching childhood and adulthood.

Before recognition of DBH deficiency, it was assumed that humans could not live without norepinephrine. Yet, stretching current assay methodology to the limit, it is not certain that any norepinephrine at all is present in the severely affected individuals we have studied; if it is present in plasma, it is less than 1% of normal.45 Because norepinephrine and its receptor sites have long been postulated to play a role in a number of psychiatric disorders, the generally normal or near-normal mood and mental status of DBH-deficient subjects so far encountered have elicited great interest among investigators in the areas of depression and schizophrenia.

Shortly after DBH was recognized as an important step in catecholamine synthesis, attempts were made to treat hypertension with DBH inhibitors. Disulfiram (Antabuse, Wyeth-Ayerst Laboratories, Philadelphia, Pa.), a copper chelator, was early recognized to inhibit DBH.32 Early clinical studies also demonstrated that fusaric acid and its precursor bupicomide could lower blood pressure in hypertensive subjects and decrease serum DBH activity.9 However, tachycardia and increased excretion of urinary catecholamines were observed. This apparent contradiction can be explained by the fact that fusaric acid apparently stimulates the release of catecholamines from the adrenal gland. More specific and potent DBH inhibitors are currently being tested as antihypertensive agents. As in our patients, inhibition of DBH after the administration of SKF 102698 to rats results in a decrease in plasma and tissue norepinephrine associated with an increase in dopamine levels.46 Also, as our results with metyrosine suggest, the hypotensive effects of specific DBH inhibitors may be related to both a decrease in norepinephrine and an increase in dopamine with its attendant vasodilatory and natriuretic effects.

The presence of such a severe deficit in neurotransmitter synthesis encourages us to continue to search for other disorders of neurotransmitter synthesis.47-48 If DBH deficiency is compatible with life, it seems likely that phenylethanolamine-N-methyl transferase (PNMT) deficiency, a postulated defect in the synthesis of epinephrine, would also be compatible with life. Indeed, it is possible that in the adult, PNMT deficiency would be a relatively subtle abnormality. Because current methods for measuring epinephrine at most institutions are not sensitive into the low-normal range, it is likely that PNMT-deficient patients would be easily missed. However, recognizing them could be important since they might be subject to significant β-adrenergic hypersensitivity and hypoglycemia in infancy.

Finally, DBH deficiency provides us with the unique opportunity to study the role of dopamine not only in this disorder but also in other forms of orthostatic hypotension. It also provides a model that may help us to determine, in general, dopamine's role in cardiovascular control in humans.40 In normal subjects, the presence of norepinephrine would obscure the interpretation of any intervention aimed at modulating dopamine synthesis or action. Our preliminary results suggest that increased endogenous dopamine is not only a simple marker of the enzymatic defect but that it exerts a tonic depressor effect, perhaps in relation to its vasodilatory effect, or more importantly, due to its natriuretic properties.

Most importantly, perhaps, DBH deficiency and its successful treatment by DOPS encourages us to hope that other autonomic disorders may one day also yield to genuinely effective therapeutic interventions.

**References**


**KEY WORDS** dopamine • dopamine-β-hydroxylase • autonomic nervous system • noradrenaline • genetic hypertension • catecholamines • sympathetic nervous system • orthostatic hypotension
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