Case Report

Reflex Control of Sympathetic Nerve Activity in Dopamine β-Hydroxylase Deficiency

Robert F. Rea, Italo Biaggioni, Rose M. Robertson, Virginia Haile, and David Robertson

Patients with autonomic failure secondary to dopamine β-hydroxylase deficiency lack the enzyme activity necessary for the conversion of dopamine to norepinephrine in sympathetic nerve terminals and the adrenal medulla. These patients have virtually undetectable norepinephrine and epinephrine in plasma and cerebrospinal fluid. The presence of intact sympathetic nerve activity in these patients has been suggested by the enhanced release of dopamine (but not norepinephrine) in response to maneuvers that augment sympathetic outflow in normal subjects. In the present study, we recorded sympathetic nerve traffic by using microneurography in a patient with dopamine β-hydroxylase deficiency and measured sympathetic neural responses to static exercise, the cold pressor test, and pharmacological alterations of blood pressure. At rest, sympathetic nerve activity was abundant and was modulated in a normal manner by handgrip (+278%), the cold pressor test (+169%), hypotension induced with isoproterenol (+102%), and hypertension induced with phenylephrine (~85%). These results provide the first electrophysiological evidence for intact regulation of sympathetic neural outflow in a patient with dopamine β-hydroxylase deficiency and suggest that central norepinephrine and epinephrine pathways believed essential for the control of sympathetic neurotransmission in humans may be supplanted by alternative redundant mechanisms. (Hypertension 1990;15:107–112)

Dopamine β-hydroxylase (DβH) is the enzyme responsible for conversion of dopamine to norepinephrine in the adrenal medulla as well as in noradrenergic nerve terminals located in the brain and peripheral sympathetic nerves. Deficiency of this enzyme, first recognized as a distinct clinical entity by investigators in the United States and the Netherlands in the 1980s, is manifested clinically by isolated failure of noradrenergic neurotransmission. Patients with this syndrome have orthostatic hypotension and ptosis but have normal sweating and normal respiratory variation of heart rate that indicate normal sympathetic cholinergic and parasympathetic autonomic function.

Biochemically these patients are characterized by essentially undetectable norepinephrine and epinephrine and greatly elevated dopamine in plasma and cerebrospinal fluid. Plasma levels of dopamine but not norepinephrine increase in response to assumption of upright posture suggesting that dopamine is released from noradrenergic nerve terminals during maneuvers associated with reflex increases of sympathetic nerve activity.

We report evidence from intraneural recordings of sympathetic nerve traffic for normal modulation of muscle sympathetic nerve activity (MSNA) in a patient with DβH deficiency. This is the first electrophysiological demonstration of intact sympathetic neural outflow in this condition. In addition, these results suggest that there are alternative redundant mechanisms independent of central norepinephrine and epinephrine that control sympathetic neural outflow in humans.

Methods

The patient is a 42-year-old white male of Dutch, Scots-Irish, and Cherokee ancestry. He has suffered from lifelong severe orthostatic hypotension, ptosis, nasal stuffiness, and impotence due to retrograde ejaculation. His episodes of orthostatic hypotension...
had in the past occasionally led to grand mal seizures for which he had been treated with phenytoin without notable success. He was unable to do any work that required him to stand. However, growth and maturation were unimpaired physically or mentally.

Prior functional autonomic testing showed a 46 mm Hg orthostatic drop in systolic blood pressure with a 6 beat/min increase in heart rate. Systolic blood pressure did not rise with cold pressor testing (normal=10 mm Hg) and rose only 5 mm Hg with isometric handgrip (normal=15 mm Hg). During the Valsalva maneuver, there was no phase IV overshoot of blood pressure. Sweating was intact. The patient had a history of intermittent atrial fibrillation, but when sinus rhythm was present there was normal respiratory variation of heart period.

Plasma, urine, and cerebrospinal fluid catecholamine levels were determined by catechol-O-methyltransferase radioenzymatic assay6,7 and subsequently by high-performance liquid chromatography with electrochemical detection in laboratories at Vanderbilt University and the National Institutes of Health. Norepinephrine and epinephrine were virtually absent in plasma and cerebrospinal fluid (<5 pg/ml) and in urine (<2 μg/24 hr). Dopamine was greatly increased in venous plasma (318 pg/ml) and cerebrospinal fluid (107 pg/ml) (see Table). Plasma dihydroxyphenylglycol (DHPG), which is derived from intraneuronal deamination of axoplasmic norepinephrine, was 10 pg/ml or less (normal 1,292±113 pg/ml, mean±SEM) indicating further the virtual absence of neuronal norepinephrine. In a recent study of catecholamine levels in patients with autonomic failure, DHPG levels averaged 1,338±89 pg/ml in 22 patients with multiple system atrophy and 627±101 pg/ml in eight patients with pure autonomic failure.8 Thus, the plasma catecholamine screen is unique in D/3H deficiency. Biochemical evidence for the integrity of catecholamine release mechanisms was shown by an increase in dopamine on assumption of the upright posture (70%) and after tyramine infusion (37%).

**Sympathetic Nerve Recordings**

Multunit, postganglionic muscle sympathetic nerve activity was recorded with a tungsten microelectrode inserted percutaneously into the right peroneal nerve posterior to the fibular head. Evidence that this activity represents efferent sympathetic neural discharge includes 1) interruption of the activity by local nerve block proximal but not distal to the recording site, 2) elimination of the activity by ganglionic block-ade, and 3) transmission velocity approximately 1 m/sec. Details regarding the technique and its validation have been published previously.9

**Other Measurements and Protocol**

The patient was studied after a 3-day period without any medications. He had been off dihydroxyphenylserine7 for several months. The diet during this 3-day period contained 150 meq sodium and 80 meq potassium. Blood pressure was measured in the left arm with a sphygmomanometer by a single observer. Heart rate was derived from the electrocardiogram.

After placement of an intravenous cannula, electrocardiographic leads, and the microneurographic electrodes, the subject lay quietly for 10 minutes. The following interventions were performed with several minutes of rest interspersed to allow return of heart rate, blood pressure, and nerve activity to baseline levels: 1) cold pressor testing (left hand immersion in ice water for 1 minute), 2) phenylephrine (25 μg i.v.) injection, 3) isometric handgrip at 30% of maximum voluntary contraction for 2 minutes, and 4) isoproterenol (0.1 μg i.v.) injection.

All experimental procedures were approved by the Vanderbilt University Institutional Review Board. The patient gave written informed consent for the performance of these studies.

**Analysis of Data**

Sympathetic bursts in the integrated neurogram were identified by their characteristic morphology and relation to R waves in the electrocardiogram. MSNA is expressed in burst frequency (bursts/min) and total activity (units/min = burst frequency x mean burst amplitude). MSNA during each intervention was compared with the immediately preceding control period.

**Results**

The cardiac rhythm was atrial fibrillation with an average ventricular response of 80 beats/min. The baseline supine blood pressure was 83/52 mm Hg.

Resting MSNA was abundant and averaged 46 bursts/min (Figure 1). Total activity varied among control periods because of spontaneous oscillations of burst frequency and occasional shifts of electrode position that altered the amplitude of the recorded discharge. However, electrode position was stable for the duration of each individual intervention and its immediately preceding control period.

Several lines of evidence indicate that these burst discharges in our patient represent muscle sympathetic nerve traffic. First, the bursts were tightly coupled to the cardiac rhythm.9 After a long R-R interval, there was a burst of greater amplitude and duration (Figure 1). This phenomenon has been described previously in patients with cardiac arrhythmias10 and has been ascribed to the lower diastolic pressures associated with longer R-R intervals. Second, a brief period of held expiration provoked increases in burst frequency and amplitude. This response has been attributed in normal subjects

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**Table. Normal Values for Catecholamines**

<table>
<thead>
<tr>
<th></th>
<th>Plasma (μg/ml)</th>
<th>Urine (μg/24 hrs)</th>
<th>CSF (μg/ml)</th>
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</thead>
<tbody>
<tr>
<td>Norepinephrine</td>
<td>226±20</td>
<td>42±10</td>
<td>50–400</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>30±8</td>
<td>26±8</td>
<td>4–30</td>
</tr>
<tr>
<td>Dopamine</td>
<td>26±11</td>
<td>196±64</td>
<td>0–30</td>
</tr>
</tbody>
</table>

Values for plasma and urine are mean±SEM. CSF, cerebral spinal fluid.
to activation of sympathoexcitatory chemoreceptors and withdrawal of sympathoinhibitory pulmonary afferent inputs. Third, there was no neural response to emotionally arousing stimuli such as a loud noise. Sympathetic outflow to skin (which comprises sudomotor as well as vasoconstrictor impulses), but not muscle sympathetic outflow, increases in response to arousal.

During the final 30 seconds of the cold pressor test, burst frequency increased 85% and total activity increased 169% compared with control levels. Despite this, there was virtually no change in systolic blood pressure (Figure 2).

During the final 30 seconds of static handgrip, burst frequency increased 150% and total activity increased 278% from control levels. Again, despite substantial increases in MSNA, blood pressure remained constant (Figure 3).

After intravenous injection of phenylephrine (25 \( \mu \)g) to stimulate arterial baroreceptors, blood pressure increased to 101/64 mm Hg. Accompanying this rise in blood pressure was a 63% decrease in burst frequency and an 85% decrease in total activity (Figure 4).

After intravenous injection of isoproterenol (0.1 \( \mu \)g) to inhibit arterial baroreceptors, blood pressure fell to 70/49 mm Hg. Burst frequency increased 29% and total activity increased 102% (Figure 5).

**Discussion**

These experiments provide electrophysiological evidence of intact sympathetic neural outflow in a patient with autonomic failure secondary to DiH deficiency. In addition, the results demonstrate that this outflow is modulated in this patient in a qualitatively normal manner by static exercise, arterial baroreceptor reflexes, and the cold pressor test.

In normal human subjects, plasma norepinephrine levels correlate with directly recorded MSNA both in the resting state and during pharmacological changes of arterial pressure. Before this report, the presence of intact sympathetic neural outflow in DiH deficiency despite virtually undetectable plasma and...
cerebrospinal fluid levels of norepinephrine was suggested by enhanced release of dopamine but not norepinephrine with tyramine, orthostatic stress, hypoglycemia, and ganglionic stimulation and suppression of basally elevated dopamine levels with head down tilt and clonidine.\textsuperscript{3,4,15} The present experiments provide confirmatory evidence of intact resting postganglionic MSNA in this disorder. Our experiments do not, however, permit conclusions regarding sympathetic neural outflow to territories other than muscle vascular beds.

In normal subjects, the cold pressor test produces pronounced increases in MSNA as well as systolic blood pressure. The mechanism of this reflex is unclear but probably involves peripheral cutaneous afferents as well as central neural mechanisms.\textsuperscript{16} In the present study, there was a brisk sympathetic neural response to immersion of the left hand in ice water, but this was unassociated with increases in systolic blood pressure. Interestingly, heart rate increased from 80 to 86 beats/min. It has been suggested that the tachycardia associated with the cold pressor test is mediated by sympathetic noradrenergic stimulation of the heart because it can be prevented by pretreatment with propranolol.\textsuperscript{16} Although the patient presented here was in atrial fibrillation, his responses suggest that the mechanism of tachycardia during cold stimulation may not be strictly noradrenergic sympathetic in origin. Parasympathetic withdrawal or sympathetic dopaminergic stimulation of the heart might explain this tachycardia. The latter seems unlikely because in a previous study\textsuperscript{3} \(\beta\)-adrenergic blockade did not uncover any ongoing \(\beta\)-adrenergic receptor stimulation of the
heart despite greatly elevated plasma dopamine. It is possible, however, that during major increases in sympathetic outflow sympathetic dopaminergic acceleration of the dominant cardiac pacemaker might occur.

MSNA increased during static handgrip, but there was no associated increase in blood pressure. There was an associated increase in heart rate from 80 to 90 beats/min. This is consistent with the concept that increases in heart rate early in exercise are mediated by parasympathetic withdrawal rather than through sympathetic stimulation of the heart.17 The lack of increase in blood pressure despite an increase in heart rate was puzzling because increases of cardiac output secondary to increases in heart rate should increase blood pressure. There are two possible explanations. First, the magnitude of increase in MSNA during handgrip was the greatest seen during any maneuver performed in the present study. It is possible that a surge of dopamine was released during this heightened neural discharge and produced vasodilation. Second, hyperventilation decreases arterial pressure in patients with autonomic failure.3 It is possible that increases in ventilation associated with physical effort buffered the expected increases in arterial pressure.

There were pronounced increases and decreases of blood pressure after administration of small doses of phenylephrine and isoproterenol, respectively, and these changes of blood pressure were accompanied by directionally opposite changes of MSNA. During isoproterenol administration, the discharge of arterial baroreceptors decreases as arterial pressure falls resulting in disinhibition of sympathetic outflow. This increase in MSNA could be buffered in part by an increase in the discharge of cardiopulmonary receptors concomitant with an increase in cardiac contractility. During phenylephrine administration, arterial and central venous pressures increase resulting in sympathoinhibition by both arterial and cardiopulmonary receptors. In normal subjects, similar doses of these medications would produce virtually no changes of blood pressure. Such hyperresponsiveness to α- and β-adrenergic receptor stimulation has been reported previously in DβH deficiency.34 In normal subjects, increases and decreases of blood pressure are buffered in part by modulation of sympathetic outflow and vascular tone. Our patient demonstrated intact baroreceptor reflex regulation of MSNA but had exaggerated blood pressure responses at least in part because baroreceptor reflex regulation of vascular tone was impaired.

Central norepinephrine and epinephrine mechanisms have long been thought to play an important role in control of peripheral sympathetic function.18 There has been speculation that epinephrine or phenylethanolamine-N-methyltransferase neurons arising in the retrofacial portion of the nucleus paragigantocellularis lateralis (Cl area) might constitute an important component of the bulbospinal tract stimulatory outflow to the peripheral sympathetic nervous system.19,20 A role of these neurons in the action of centrally acting α2 agonists has been suggested.21,22 The presence of intact postganglionic sympathetic nerve traffic without biochemical evidence for the presence of central norepinephrine or epinephrine as well as qualitatively normal reflex modulation of MSNA in our patient suggests that alternative redundant mechanisms may be present for the control of sympathetic outflow by bulbospinal tract neurons in humans.

Our conclusions regarding the role of central catecholamines in sympathetic neurotransmission are based on the assumption that cerebrospinal fluid levels of epinephrine and norepinephrine and their metabolites are reliable markers of brain levels of

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**TABLE 1.** Responses to isoproterenol injection (see text). HR, heart rate; BP, blood pressure; MSNA, muscle sympathetic nerve activity.

<table>
<thead>
<tr>
<th>Condition</th>
<th>HR</th>
<th>BP</th>
<th>MSNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>80</td>
<td>81/50</td>
<td>720 units, 28 bursts</td>
</tr>
<tr>
<td>Isoproterenol 0.1 μg I.V.</td>
<td>82</td>
<td>70/49</td>
<td>1460 units, 36 bursts</td>
</tr>
</tbody>
</table>

**FIGURE 5.** Responses to isoproterenol injection (see text). HR, heart rate; BP, blood pressure; MSNA, muscle sympathetic nerve activity.
these compounds. We believe this is reasonable given the virtual absence of both these catecholamines and their metabolites in our patient\textsuperscript{7} and undetectable levels of D\textsubscript{3}H both in plasma and cerebrospinal fluid reported in other patients with D\textsubscript{3}H deficiency.\textsuperscript{3,4,15} It might also be argued that dopamine in central "norepinephrine" and "epinephrine" neurons in D\textsubscript{3}H deficiency could stimulate \(\alpha\)- and \(\beta\)-adrenergic receptors and function as a substitute neurotransmitter. However, it is noteworthy that in a previous study\textsuperscript{3} peripheral \(\alpha\)-blockade and peripheral \(\beta\)-blockade did not uncover any detectable ongoing \(\alpha\)- or \(\beta\)-adrenergic receptor stimulation.

In summary, we have provided electrophysiological evidence for the presence of intact sympathetic neural outflow to the muscle circulation in a patient with isolated failure of noradrenergic neurotransmission due to D\textsubscript{3}H deficiency. We have also demonstrated qualitatively normal modulation of this activity by a number of reflex stimuli and have documented a dissociation between neural and neuroeffector responses to these stimuli. These data provide new insight into the role of catecholamines in cardiovascular control mechanisms in humans.

References

Key Words • dopamine-\(\beta\)-hydroxylase • sympathetic nervous system • catecholamines • microneurography • nucleus tractus solitarii
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