Phenotypic Evidence of Faulty Neuronal Norepinephrine Reuptake in Essential Hypertension

Magdalena S. Rumantir, David M. Kaye, Garry L. Jennings, Mario Vaz, Jacqueline A. Hastings, Murray D. Esler

Abstract—Previous reports suggest that neuronal norepinephrine (NE) reuptake may be impaired in essential hypertension, perhaps because of dysfunction of the NE transporter, although the evidence is inconclusive. To further test this proposition, we applied phenotypically relevant radiotracer methodology, infusion of tritiated NE and quantification of NE metabolites, to 34 healthy lean subjects (body mass index <27.0 kg/m²), 19 overweight (body mass index >28.0 kg/m²) but otherwise healthy normotensive subjects, 13 untreated lean patients with essential hypertension, and 14 obesity-related hypertensives. Spillover of NE from the heart was increased in lean hypertensives only (mean±SD 33.4±20.6 versus 16.1±11.7 ng/min in lean normotensives, P<0.05), but this could have resulted from high cardiac sympathetic nerve firing rates, faulty NE reuptake, or both. The arterial plasma concentration of 3-methoxy-4-hydroxyphenylglycol, an extraneuronal metabolite of NE, was elevated in lean hypertensives only (3942±1068 versus 3055±888 pg/mL in healthy subjects, P<0.05). The fractional extraction of plasma tritiated NE in passage through the heart, determined on the basis of neuronal NE uptake, was reduced in lean essential hypertensives (0.65±0.19 versus 0.81±0.11 in healthy subjects, P<0.05). Cardiac release of the tritiated NE metabolite [3H]dihydroxylphenylglycol, produced intraneuronally by monoamine oxidase after uptake of [3H]NE by the transporter, was reduced in lean hypertensives only (992±1435 versus 4588±3189 dpm/min in healthy subjects, P<0.01) These findings suggest that neuronal reuptake of NE is impaired in essential hypertension. Through amplification of the neural signal, such a defect could constitute a neurogenic variant of essential hypertension. In obesity-related hypertension, there was no phenotypic evidence of NE transporter dysfunction. (Hypertension. 2000;36:824-829.)

Key Words: nervous system, sympathetic ■ norepinephrine ■ heart ■ hypertension, obesity

The exact pathophysiology of the sympathetic nervous system remains to be delineated. Available evidence indicates that in a substantial proportion of patients, essential hypertension is neurogenic, with documentation of high rates of spillover of norepinephrine (NE) from the heart and kidneys.1 The increased cardiac and renal spillover of NE is no doubt attributable at least in part to increased sympathetic nerve firing rates, although this cannot be measured directly; clinical microneurographic measurements in hypertensive patients have documented activation of sympathetic efferents in another sympathetic outflow, that to the skeletal muscle vasculature.2

There are additional potential neural mechanisms, however, that could contribute to high intrasynaptic concentrations of NE and increased NE spillover in essential hypertension and to the development and maintenance of neurogenic variants of hypertension, but these have not been definitively investigated. That there might be an increase in the density of sympathetic innervation in human hypertension, as is well documented in the Japanese spontaneously hypertensive rat, remains one such possibility. Facilitation of neuronal NE release by epinephrine released from sympathetic nerves as a cotransmitter and impairment of neuronal NE reuptake after its release from sympathetic nerves are others.

Previous reports from 3 laboratories5–7 suggest that neuronal NE reuptake may be impaired in some patients with essential hypertension, perhaps due to dysfunction of the NE transporter, although the evidence is inconclusive. In these earlier studies, the half-time of the rapid disappearance phase of tritiated NE removal from plasma on termination of an intravenous infusion of the tracer, which is primarily, but not exclusively, dependent on neuronal NE uptake was found to be prolonged in some patients with essential hypertension.5–7 In the present study, we applied more specific radiotracer methods and focused in particular on neuronal processing of tritiated NE by the heart.

We thought that because the disposition of NE after its release is more dependent on neuronal reuptake in the heart than in all other organs,8 incomplete grades of impairment of
NE transporter function would be most likely to be phenotypically evident there. We were encouraged in this line of thinking by the recent description of a missense mutation of the NE transporter gene in a family kindred with the postural tachycardia syndrome \(^9\) in whom the exaggerated reflex increase in heart rate with standing, which is a cardinal feature of the disorder, was due to the NE transporter fault.

We investigated 4 categories of experimental subjects: lean and obese patients with essential hypertension and comparable groups with normal blood pressure. The inclusion of obese people both with and without hypertension was in recognition of the fact that although not all overweight people develop hypertension, the predisposing influences to blood pressure elevation in the obese are unknown. Dysfunction of the NE transporter might be such a predisposing factor, given that obesity-related hypertension does have an important neurogenic element.\(^2\,^{10}\)

**Methods**

Neurochemical indices of the phenotype of impaired neuronal reuptake of NE were studied. The indices chosen for investigation were those previously shown to be sensitive markers of reduced neuronal NE reuptake (U1) into sympathetic nerves and uptake into extraneuronal cells (U2). In the presence of impairment of U1, production of DHPG is reduced and that of MHPG is increased, although the majority of DHPG production derives from NA leaking from the sympathetic vesicles, independent of NA reuptake.\(^10\) MAO indicates monoamine oxidase; COMT, catechol-o-methyltransferase; NMN, normetanephrine.

![Figure 1. Schematic representation of NE (NA) overflow from sympathetic nerves to the circulation (NA Spillover). NA is removed from the circulation (plasma NE clearance) through neuronal uptake (U1) into sympathetic nerves and uptake into extraneuronal cells (U2). In the presence of impairment of U1, production of DHPG is reduced and that of MHPG is increased, although the majority of DHPG production derives from NA leaking from the sympathetic vesicles, independent of NA reuptake.](Image 1)

![Figure 2. Schematic of transcardiac processing of tritiated NE (3H NA). The majority of [3H]NE is removed from plasma via a clearance mechanism that involves neuronal uptake. Within sympathetic nerves, [3H]NE is metabolized into tritiated [3H]DHPG (3H DHPG) by monoamine oxidase (MAO), with some subsequent release into the venous circulation.](Image 2)

Subjects

We studied 80 adults (73 men, 7 women) between the ages of 18 and 65 years who encompassed a wide range of body mass index (BMI) (19.3 to 35.5 kg/m\(^2\)). Participating research volunteers were recruited from the hypertension clinics of the Alfred and Baker Medical Unit of the Alfred Hospital and from the Cardiovascular Risk Assessment Clinic of the Baker Medical Research Institute and, for the overweight normotensive subjects, through use of the database of a weight reduction center (Gutbusters, Melbourne, Australia).

Hypertensive patients constituted a consecutive series of consenting volunteers. Secondary hypertension was excluded in all. For entry, average clinic blood pressure exceeded 150 mm Hg systolic, 90 mm Hg diastolic, or both but was not greater than 200 mm Hg systolic or 125 mm Hg diastolic. None had accelerated hypertension, clinical coronary heart disease, heart failure, a history of stroke, renal insufficiency, or diabetes. The majority were previously unmedicated, or if they had had prior therapy, all drugs had been stopped a minimum of 6 weeks before research testing. Dietary sodium intake was unrestricted, and the obese hypertensives were not on calorie-restricted diets.

All subjects with normal blood pressure underwent careful clinical evaluation and serum biochemistry measurements to exclude hepatic and renal dysfunction. Respondents with a history of incidental disease, a blood pressure of >140/85 mm Hg, and alcohol intakes of >2 standard drinks/d were excluded. The experimental protocol was explained in detail to all participants, and written consent was obtained for the investigation, which was approved by the Ethics Review Committee of the Alfred Hospital.

**General Procedure**

Subjects were studied in the morning while supine with abstinence from smoking, food, tea, and coffee for 12 hours before the experiment. All received a tracer infusion of \(^1\)H-labeled NE (specific activity 11 to 25 Ci/mmol, New England Nuclear) intravenously at 0.6 to 0.8 \(\mu\)Ci/min for the measurement of NE kinetics by isotope dilution.\(^8\,^{11}\,^{12}\) Whole body spillover of NE to plasma was calculated in all subjects (\(n=80\)) from arterial samples obtained via a 21-gauge cannula placed percutaneously under local anesthesia in the brachial or radial artery. Regional plasma NE kinetics was also measured for the heart (\(n=57\)), with coronary sinus venous sampling performed as described previously.\(^8\,^{11}\,^{12}\)

**Biochemical Analysis**

The plasma concentration of neurochemicals was determined with HPLC with electrochemical detection.\(^11\,^{13}\) Timed collection of the
eluate leaving the detection cell with a fraction collector permitted the separation of H-labeled NE and [3H]DHPG for counting with liquid-scintillation spectroscopy.

**Calculation of Whole Body and Cardiac Plasma NE Kinetics and Cardiac [3H]DHPG Spillover**

Whole body rates of NE plasma spillover and clearance were calculated as follows:

\[
\text{NE plasma clearance} = \frac{[\text{H}]\text{NE infusion rate (dpm/min)}}{\text{plasma}[\text{H}]\text{NE concentration (dpm/mL)}}
\]

Total NE spillover = [H]NE infusion rate (dpm/min)

plasma NE specific activity (dpm/pg)

NE spillover from the heart was calculated with the following equation:

Cardiac NE spillover = \((\text{NE}_{a} - \text{NE}_{c}) + (\text{NE}_{a} - \text{NE}_{o})\) - CSPF

where NE\(_{a}\) and NE\(_{c}\) are the arterial and coronary sinus venous plasma concentrations of NE, respectively; NE\(_{a}\) is the fractional extraction of tracer NE across the heart; and CSPF is the coronary sinus plasma flow.

The transcardiac fractional extraction of plasma tritiated NE was calculated as follows:

\[
\text{Fractional transcardiac} \ [\text{H}]\text{NE extraction} = \frac{[\text{H}]\text{NE}_{a}}{[\text{H}]\text{NE}_{a} - [\text{H}]\text{NE}_{c}}
\]

The cardiac spillover of [3H]DHPG was calculated with the Fick principle from the venoarterial plasma [3H]DHPG concentration difference across the heart and the CSBF, as follows:

Cardiac [3H]DHPG spillover = \(\{[\text{H}]\text{DHPG}_{a} - [\text{H}]\text{DHPG}_{c}\} - \text{CSBF}\)

**Retest Reliability of the Measures**

Intra-assay coefficients of variation were 4.6% for plasma NE at a concentration of 200 pg/mL, 5.0% for MHPG at a concentration of 1000 pg/mL, 3.9% for DHPG at a concentration of 1000 pg/mL, 5.3% for H-labeled NE at a concentration of 600 dpm/mL, and 8.2% for [3H]DHPG at a concentration of 40 to 100 dpm/mL. With replicate determinations of whole body and regional NE spillover, there is a high level of reproducibility of the measurements.

Within-day coefficients of variation for total and cardiac NE spillover under resting conditions are 5.9% and 6.2%.

**Statistical Analysis**

Results are presented as mean±SD. Statistical comparisons of groups were assessed with ANOVA or the Mann-Whitney U test for data that were not normally distributed. The null hypothesis was rejected at \(P<0.05\).

**Results**

The general characteristics of the experimental groups are shown in Table 1. The majority of participants were men. All lean hypertensive patients had a BMI of <27 kg/m\(^2\), but overall BMI was higher than that in lean subjects with normal blood pressure, with mean values of 25.1 and 23.1 kg/m\(^2\), respectively \((P<0.05)\). Heart rates and intra-arterial blood pressures directly recorded at rest in the cardiac catheterization laboratory on the test day are included in Table 1. Heart rates in both lean and obese hypertensive groups were elevated compared with those of normotensive subjects (Table 1).

The mean plasma concentration of NE was 45% higher in lean hypertensive subjects than in lean healthy volunteers \((P<0.05)\) (Table 2), and the total NE spillover rate was 20% higher \((difference\ not\ statistically\ significant)\) (Figure 3). Obese normotensive and hypertensive subjects did not differ from healthy subjects in these measurements of whole body NE kinetics. The concentration in arterial plasma of the extraneuronal NE metabolite MHPG was elevated in lean hypertensives only \((3942±1068\ pg/mL)\) compared with that in healthy subjects \((3056±888\ pg/mL)\) (Table 2). The ratio of the plasma concentration of NE to that of its intraneuronal metabolite DHPG, which provides a semiquantitative index of whole body NE neuronal reuptake,\(^8,15\) was higher in lean hypertensives than in healthy controls \((0.30 versus 0.20, P<0.01,\ Figure\ 3)\).

NE spillover from the heart was increased in lean hypertensive patients \((33.4±20.6\ ng/min)\) compared with that in healthy lean subjects \((16.1±11.7\ ng/min, P<0.05,\ Figure\ 3)\). Cardiac NE spillover was significantly higher in lean than in obese hypertensives \((P<0.05,\ Figure\ 3)\). Cardiac NE spillover in the normotensive obese subjects was suppressed compared with that in the lean normotensives \((P<0.05,\ Figure\ 3)\).

Extraction of tritiated NE from plasma during transcardiac passage was reduced in lean patients with hypertension \((65%\ versus\ 81%; P<0.05)\), as was release from the heart of its metabolite, [3H]DHPG, formed intraneuronally via monoamine oxidase (Figure 4). Total NE plasma clearance for the whole body was 18% lower in lean hypertensives than in

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**TABLE 1. Characteristics of Subject Groups**

<table>
<thead>
<tr>
<th>Participant</th>
<th>Age, y</th>
<th>Gender, M/F</th>
<th>BMI, kg/m(^2)</th>
<th>Systolic</th>
<th>Diastolic</th>
<th>Heart Rate, bpm</th>
<th>Infusion Time, min</th>
<th>Infusion Rate, dpm (\times 10^6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lean</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal BP</td>
<td>38.1±17.3</td>
<td>32/2</td>
<td>23.1±2.2</td>
<td>139±16</td>
<td>71±7</td>
<td>63±12</td>
<td>85±23</td>
<td>1.44±0.44</td>
</tr>
<tr>
<td>High BP</td>
<td>42.9±12.2</td>
<td>10/3</td>
<td>25.1±2.7*</td>
<td>165±18*</td>
<td>86±14*</td>
<td>79±15*</td>
<td>71±19</td>
<td>1.32±0.64</td>
</tr>
<tr>
<td>Obese</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal BP</td>
<td>43.6±11.0</td>
<td>19/0</td>
<td>30.2±1.8*</td>
<td>136±14</td>
<td>73±7</td>
<td>61±9</td>
<td>78±31</td>
<td>1.19±0.42*</td>
</tr>
<tr>
<td>High BP</td>
<td>47.6±11.3</td>
<td>12/2</td>
<td>30.5±1.8*</td>
<td>167±10*</td>
<td>91±7*</td>
<td>72±8*</td>
<td>77±27</td>
<td>1.11±0.37*</td>
</tr>
</tbody>
</table>

BP indicates blood pressure. Values are expressed as mean±SD.

\*\(P<0.05\) vs lean normotensive individuals.
healthy subjects ($P=0.059$) (Figure 4). The arterial plasma concentration of [3H]DHPG was 28% lower in lean hypertensives than in healthy lean volunteers ($P=0.09$, Figure 4) and lower still in both obese experimental groups; in the latter cases, this may be attributable to the somewhat lower tritiated NE infusion rates (Table 1). The ratio of the plasma concentrations of tritiated DHPG to tritiated NE was substantially lower in lean hypertensives than in lean healthy subjects (mean 0.041 versus 0.064, $P<0.05$).

**Discussion**

Typical neurochemical consequences of neuronal NE reuptake impairment are facilitation of NE spillover from sympathetic nerves to plasma, reduced clearance of NE from plasma for the body as a whole and by individual organs, and alteration in the pattern of NE metabolites due to reduction in neuronal metabolism and augmentation of extraneuronal metabolism.5,7,8,11,12,15 Neurochemical indices of this type were applied to test for the phenotype of impaired neuronal reuptake of NE in patients with essential hypertension. By amplifying the neural signal, leading to greater concentrations of NE in the synaptic cleft, such a defect in neuronal NE reuptake could constitute a neurogenic variant of essential hypertension.

Previous reports that involved measurement of the whole body plasma kinetics of tritiated NE suggest that neuronal NE reuptake may be impaired in essential hypertension,5-7 although this evidence was inconclusive. In the present study, we applied recently developed, more specific radiotracer methods, including a measure of neuronal processing of tritiated NE by the heart. Because the disposition of NE after its release is more dependent on neuronal reuptake in the heart than in all other organs,8,11 less-than-complete grades of NE transporter dysfunction would be most likely to be phenotypically evident there. In lean patients with essential hypertension, the spillover of NE from the heart was increased, cardiac extraction of radiolabeled NE from plasma was reduced, and the intraneuronal conversion of the tracer to tritiated DHPG within the heart was low, such as to strongly suggest that the intracardiac neuronal uptake of NE was subnormal. These changes noted in the heart were, however, quantitatively less than expected on the basis of total absence of neuronal NE reuptake.8,11

For the whole body, the changes seen were proportionally less than those in the heart. The ratio of the arterial plasma concentration of the intraneuronal metabolite of NE, DHPG, to that of NE and the ratio of the plasma concentrations of tritiated DHPG and tritiated NE, both of which are inversely

**Table 2. NE Plasma Kinetics and NE Metabolites**

<table>
<thead>
<tr>
<th>Participant</th>
<th>NE Plasma Kinetics</th>
<th>NE Metabolites</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NA Plasma Concentration, pg/mL</td>
<td>NA Total Spillover, ng/min</td>
</tr>
<tr>
<td>Lean Normal BP</td>
<td>202±97</td>
<td>547±241</td>
</tr>
<tr>
<td>Lean High BP</td>
<td>293±102*</td>
<td>657±305</td>
</tr>
<tr>
<td>Obese Normal BP</td>
<td>200±89</td>
<td>493±213</td>
</tr>
<tr>
<td>Obese High BP</td>
<td>225±88</td>
<td>587±276</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SD.

*P<0.05 vs lean normotensive individuals.

![Graphs of NE spillover rates for the heart and the whole body in lean and obese subjects with either normal blood pressure (NBP) or high blood pressure (HBP)](image)
related to whole body NE neuronal reuptake, were lower in
lean hypertensives than in healthy subjects. In contrast, the
values for whole body NE spillover (20% increased) and total
plasma NE clearance (18% reduced), although qualitatively
altered in the directions expected on the basis of impairment
of neuronal NE uptake, did not differ significantly from those
found in healthy subjects. This could have resulted from a
partial impairment of neuronal NE reuptake, suggested by a
comparison with total NE plasma clearance values reported
when reuptake is totally absent (plasma clearance 25% to
40% reduced), but it probably also reflects the lesser
importance of NE uptake to overall NE disposition in organs
such as the kidneys and skeletal muscle (compared with the
heart), which make an important contribution to whole body
plasma NE kinetics.

Several potential confounders and limitations must be
considered when evaluating these changes in NE spillover,
disposition, and metabolism in lean hypertensive patients.
The first is the possible relevance of sex, in that most
participating subjects were male, and although it is not our
experience, an influence of sex on sympathetic function and
catecholamine metabolism has been described. Whether our
findings apply equally to female hypertensive patients re-
mains uncertain. A second consideration is that there are
misgivings by some that sympathetic nervous activation in
hypertension might simply represent an alerting response in
the laboratory, perhaps contributed to by anxiety resulting
from the recent diagnostic labeling of a patient as “hyperten-
sive.” This possibility can be definitively excluded, how-
ever, because the pattern of sympathetic activation in lean
hypertensive patients differs materially from that seen in
mental stress responses. The sympathetic nervous activation
present in essential hypertension involves the sympathetic
outflow to skeletal muscle blood vessels, spares the sympa-
thetic innervation of the skin and hepatomesenteric circula-
tion, and is not accompanied by increased adrenal medullary
secretion of epinephrine. None of these apply in mental
stress responses, in which epinephrine secretion is increased
and the sympathetic outflow to skeletal muscle vasculature
typically is unchanged or reduced while skin and hepatomes-
enteric sympathetic activation is present.

A third potential confounding influence concerns the pos-
sibility that undetected dietary sodium restriction voluntarily
adopted by hypertensive participants might have caused the
observed reduction in NE reuptake and increase in cardiac
NE spillover. This is unlikely, because available evidence
indicates that in humans, sodium depletion increases renal,
but not cardiac, NE spillover and actually increases neuronal
NE uptake.

Near-total absence of activity of the neuronal NE trans-
porter was recently reported in a family kindred with the
postural tachycardia syndrome, in which a missense mutation
of the NE transporter gene has been identified. The cardinal
diagnostic features of this condition are exaggerated reflex
increases in heart rate and plasma NE concentration with
standing, attributable in the kindred reported although not in
the majority of patients with the condition to the NE trans-
porter fault. Given that orthostatic intolerance, sometimes
associated with postural hypotension, rather than blood pres-
sure elevation is typical of the disorder, it is pertinent to ask
whether the idea that a defect in neuronal NE reuptake could
cause hypertension remains credible. Probably so, given that
there is evidence of an associated regional sympathetic
neuropathy that involves multiple sites, including the legs and
kidneys (but not the heart), in the postural tachycardia
syndrome, which might be expected to modify the transla-
tion of a neuronal reuptake defect into blood pressure
elevation. Unlike in the postural tachycardia syndrome, in
essential hypertension, sympathetic nerve firing is commonly
increased, and a combination of increased NE release cou-
pled with faulty neuronal NE reuptake would be more likely
to chronically elevate blood pressure.

It is possible that reduced neuronal NE reuptake also exists
in the brain in patients with essential hypertension, such as to
augment forebrain noradrenergic neurotransmission and elev-
ate sympathetic nerve firing rates. Overflow from the brain
of MHPG, the principal extraneuronal central nervous system NE metabolite, is increased ≈3-fold in patients with essential hypertension. Suprabulbar noradrenergic projections to the forebrain activate the sympathetic nervous system. There is good evidence that the stimulation of the sympathetic nervous system present is essential hypertension is, in fact, driven by increased forebrain NE turnover.

In obesity-related hypertension, there was no phenotypic evidence of NE transporter dysfunction. Obese subjects with and without hypertension differ in cardiac NE spillover, which is higher in the hypertensives. Although faulty neuronal reuptake of NE has been proposed as a basis for this differences in cardiac NE spillover, and as a predisposing factor in the development of the hypertension in the obese, a genetic fault that involves the NE transporter in obesity-related hypertension now appears to be excluded.

Screening of a mixed population of blood bank donors and psychiatric patients (with schizophrenia and bipolar affective disorder) recently lead to the identification of 13 DNA sequence variants of the NE transporter gene, of which 5 were interpreted as missense substitutions. Blood pressure status of the subjects with transporter gene mutations was not recorded in this report, and the degree of functional reduction in NE transporter activity associated with individual single nucleotide polymorphisms was not established. In a preliminary screening for these 5 missense substitutions in the NE transporter gene we conducted in 40 hypertensive patients (not the patients described in the present study), none of the substitutions were present. The transporter gene mutation recently described in the postural tachycardia syndrome kindred differs from the 5 identified earlier and is associated with almost total absence of transporter activity. A study in essential hypertension patients that incorporates neurochemical indices of the competency of NE neuronal reuptake such as those used in the present study, coupled with testing for coding region mutations in the transporter gene and functional assessment of any identified DNA sequence variants in an in vitro system, is now clearly needed.

Acknowledgments

This work was supported by a National Health and Medical Research Council of Australia Institute grant to the Baker Medical Research Institute. The authors are grateful to Dr Garry Eggar, Glen Sheffield, and the staff of Gutsbusters for their help in recruiting overweight study participants and to Sr Leoni Johnston, Kaye Varcoe, and Elizabeth Dewar for their skillful technical support in the catheter laboratory.

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Hypertension. 2000;36:824-829
doi: 10.1161/01.HYP.36.5.824

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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