Sympathetic Augmentation in Hypertension
Role of Nerve Firing, Norepinephrine Reuptake, and Angiotensin Neuromodulation

Markus P. Schlaich, Elisabeth Lambert, David M. Kaye, Zygmunt Krozowski, Duncan J. Campbell, Gavin Lambert, Jacqui Hastings, Anuradha Aggarwal, Murray D. Esler

Abstract—There is growing evidence that essential hypertension is commonly neurogenic and is initiated and sustained by sympathetic nervous system overactivity. Potential mechanisms include increased central sympathetic outflow, altered norepinephrine (NE) neuronal reuptake, diminished arterial baroreflex dampening of sympathetic nerve traffic, and sympathetic neuromodulation by angiotensin II. To address this issue, we used microneurography and radiotracer dilution methodology to measure regional sympathetic activity in 22 hypertensive patients and 11 normotensive control subjects. The NE transport inhibitor desipramine was infused to directly assess the potential role of impaired neuronal NE reuptake. To evaluate possible angiotensin sympathetic neuromodulation, the relation of arterial and coronary sinus plasma concentrations of angiotensin II to sympathetic activity was investigated. Hypertensive patients displayed increased muscle sympathetic nerve activity and elevated total systemic, cardiac, and renal NE spillover. Cardiac neuronal NE reuptake was decreased in hypertensive subjects. In response to desipramine, both the reduction of fractional transcardiac $^{3}$H$^{1}$NE extraction and the increase in cardiac NE spillover were less pronounced in hypertensive patients. DNA sequencing analysis of the NE transporter gene revealed no mutations that could account for reduced transporter activity. Arterial baroreflex control of sympathetic nerve traffic was not diminished in hypertensive subjects. Angiotensin II plasma concentrations were similar in both groups and were not related to indexes of sympathetic activation. Increased rates of sympathetic nerve firing and reduced neuronal NE reuptake both contribute to sympathetic activation in hypertension, whereas a role for dampened arterial baroreflex restraint on sympathetic nerve traffic and a peripheral neuromodulating influence of angiotensin II appear to be excluded. (Hypertension. 2004;43:169-175.)

Key Words: hypertension, essential ■ catecholamines ■ sympathetic nervous system ■ norepinephrine ■ angiotensin II

Although there is growing evidence that essential hypertension is commonly neurogenic and is initiated and sustained by overactivity of the sympathetic nervous system, the precise causal mechanisms leading to sympathetic augmentation in hypertensive subjects are still poorly understood. Among others, possible mechanisms include increased sympathetic nerve firing rates, altered neuronal norepinephrine (NE) reuptake, diminished arterial baroreflex buffering of sympathetic nerve traffic, and facilitation of NE release by neurohumoral factors such as angiotensin II. These possibilities, however, have not yet been conclusively tested for in humans.

To further address some of these issues, we combined microneurography, to measure sympathetic nerve firing rates, with relevant radiotracer methodology to comprehensively study systemic and regional kinetics of NE and its intraneuronal and extraneuronal metabolites. To directly assess whether decreased neuronal NE reuptake contributes to increased NE spillover, we studied the effects of the NE transport inhibitor desipramine on NE reuptake and spillover. We hypothesized that if neuronal NE reuptake was impaired in essential hypertension, blockade of the NE transporter would result in a less pronounced effect on both the reduction in uptake and the increase in spillover of the neurotransmitter in hypertensive subjects. These effects would be most prominent in the heart, where NE disposition particularly depends on neuronal NE reuptake.

If alterations in NE transport indeed contribute to sympathetic augmentation, it seemed plausible to test for variations in the NE transporter gene. Whether diminished arterial baroreflex control of sympathetic nerve traffic may contribute to sympathetic overactivity was also assessed. Given the accumulating evidence for a tissue renin-angiotensin system in humans, which potentially interacts with the sympathetic nervous system by facilitating norepinephrine release, we also tested the hypothesis that local angiotensin...
II levels in the heart may contribute to sympathetic activation. We thought that in the assessment of these possibilities, combining various measurements in the same subjects would provide the most direct test of their potential mechanistic role in essential hypertension.

**Methods**

**Subjects**

We studied 22 patients with essential hypertension (EH) and 11 age- and weight-matched healthy normotensive control subjects (NT). Previous use of antihypertensive therapy was reported in 10 of 22 hypertensive subjects. Antihypertensive therapy was discontinued for at least 4 weeks before the study was commenced. Participants did not follow any specific dietary guidelines. Blood pressure (BP) readings were taken according to WHO recommendations. The usual BP readings were confirmed by measurement with a Finapres BP monitor (Datex-Ohmeda2300) during microneurography and by intra-arterial BP measurement during the catheter study. Written informed consent was obtained from all participants before the study. The study protocol was approved by the Alfred Hospital Ethics Review Committee.

**General Procedure**

The study was commenced after an overnight fasting period with abstinence from smoking, alcohol, tea, and coffee for at least 12 hours before the experiment.

**Microneurography**

Multunit postganglionic sympathetic nerve activity (MSNA) was recorded through the use of microneurography in the peroneal nerve, as described previously. After an acceptable nerve recording site was obtained, which was possible in 29 participants (NT, 9; EH, 20), MSNA was recorded for 20 minutes. MSNA was expressed as burst frequency (bursts/min) and burst incidence (bursts/100 heartbeats).

**Assessment of Spontaneous Arterial Baroreflex Control of MSNA**

Over a 3- to 5-minute resting period, diastolic pressures of individual cardiac cycles were grouped in intervals of 2 mm Hg, and, for each interval, the percentage of diastoles associated with a sympathetic burst was plotted against the mean of the pressure interval (threshold diagram), as previously described. Muscle sympathetic bursts were advanced by 1.3 seconds to compensate for baroreflex delay. The sensitivity or reflex gain was defined as the slope of the regression line.

**Catheterization Protocol**

A tracer infusion of 3H-labeled NE (levo–7–3H NE, specific activity of 11 to 25Ci/mmol; New England Nuclear) was given through a peripheral vein at 0.6 to 0.8 μCi/min, after a priming bolus of 12 μCi, for the measurement of NE kinetics by isotope dilution, as described previously. Total NE spillover to plasma was measured in all subjects. Regional NE spillover rates were measured by catheterization of the region of interest from the heart (coronary sinus, CS) in 31 participants (NT, 10; EH, 21) and the kidney (right renal vein) in 25 subjects (NT, 9; EH, 16). Simultaneously, arterial and CS blood samples were drawn for determination of angiotensin I and II concentrations in 28 subjects (NT, 10; EH, 18). Renal plasma flow was determined from the steady-state clearance and renal extraction of p-aminohippurate. After initial sampling from the various sites, the neuronal NE reuptake inhibitor desipramine was infused through a peripheral vein for 20 minutes at a dose of 0.3 mg/kg body wt in 29 subjects (NT, 11; EH, 18), and measurements of NE kinetics for the heart and the whole body were repeated.

**Biochemical Analysis**

Plasma concentration of neurochemicals was determined by high-performance liquid chromatography with electrochemical detection. Angiotensin I and II blood concentrations were measured by high-performance liquid chromatography–based radioimmunoassay.

**Genetic Testing**

Blood was collected and DNA extracted, following standard protocols. Seventeen hypertensive patients and 9 normotensive control subjects were analyzed for the Gly478Ser mutation by 3′ RACE reaction and sequencing. Furthermore, the entire coding region and flanking intron sequences of the NET gene was sequenced in 3 patients in whom NE reuptake was severely impaired and who displayed a strong family history of essential hypertension. All 14 coding exons and adjoining intronic sequences were amplified with the use of primers annealing to intronic sequences 30 to 100 bp from exon/intron boundaries; sequencing was performed with the use of specific primers in the forward and reverse directions.

**Statistical Analysis**

Results are presented as mean±SD. Two-sided probability values are given throughout the text. A 2-sided probability value of <0.05 was considered to indicate statistical significance. Statistical comparisons of groups were assessed by 1-way ANOVA or Kruskal-Wallis ANOVA on ranks for data that were not normally distributed. Serial within-group comparisons were subjected to repeated-measures ANOVA. Relations between variables were determined by linear regression analysis. The data were processed with the use of the software package SigmaStat for Windows 2.03 (SPSS Inc.).

**Results**

Clinical characteristics of the study cohort are summarized in Table 1. Hypertensive subjects displayed an increase in
sympathetic neural discharge, as indicated by higher sympathetic nerve firing rates to the skeletal muscle vasculature (Figure 1), but this was not explicable in terms of any reduction in arterial baroreflex dampening of sympathetic nerve firing. As expected, assessment of the arterial baroreflex control of MSNA revealed that there was an inverse relation between MSNA and diastolic BP in both normotensive subjects and hypertensive patients. Sympathetic baroreflex diagrams indicated that the baroreflex gain, signified by the increase in MSNA per millimeter of mercury decrease in diastolic BP, was similar in both groups (NT, 3.94 ± 1.08% versus EH, 3.60 ± 0.46%; P NS).

Total systemic and cardiac NE kinetics are detailed in Table 2. Whole-body and cardiac NE spillover were substantially increased in hypertensive subjects (fractional extraction of [3H]NE: NT, 0.70 ± 0.12 versus EH, 0.57 ± 0.15; P < 0.05), which was accompanied by a reduced concentration of the intraneuronal tritiated metabolite [3H]DHPG in CS plasma in hypertensive patients (NT, 47.8 ± 15.6 versus EH, 31.3 ± 14.2 dpm/min; P < 0.01). Cardiac spillover of endogenous DHPG was significantly less in EH than in NT (NT, 93 ± 29 versus EH, 58 ± 37).

Cardiac neuronal NE reuptake was significantly reduced in hypertensive subjects (fractional extraction of [3H]NE: NT, 0.70 ± 0.12 versus EH, 0.57 ± 0.15; P < 0.05), which was accompanied by a reduced concentration of the intraneuronal tritiated metabolite [3H]DHPG in CS plasma in hypertensive patients (NT, 47.8 ± 15.6 versus EH, 31.3 ± 14.2 dpm/min; P < 0.01). Cardiac spillover of endogenous DHPG was significantly less in EH than in NT (NT, 93 ± 29 versus EH, 58 ± 37).

Table 2. Total Systemic and Cardiac Norepinephrine Plasma Kinetics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>NT (n=11)</th>
<th>EH (n=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial NE plasma concentration, pg/mL</td>
<td>181±66</td>
<td>262±113*</td>
</tr>
<tr>
<td>Coronary sinus NE plasma concentration, pg/mL</td>
<td>211±122</td>
<td>371±203*</td>
</tr>
<tr>
<td>Fractional transcardiac [3H] NE extraction</td>
<td>0.70±0.12</td>
<td>0.57±0.15*</td>
</tr>
<tr>
<td>Coronary sinus plasma flow, mL/min</td>
<td>81.4±18.0</td>
<td>89.0±29.2</td>
</tr>
<tr>
<td>Cardiac NE spillover, ng/min</td>
<td>11.7±6.3</td>
<td>23.5±16.1*</td>
</tr>
<tr>
<td>Total systemic NE spillover, ng/min</td>
<td>229±140</td>
<td>388±136*</td>
</tr>
<tr>
<td>NE plasma clearance, mL/min</td>
<td>1519±335</td>
<td>1592±442</td>
</tr>
<tr>
<td>[3H] NE infusion time, min</td>
<td>113±21</td>
<td>109±26</td>
</tr>
<tr>
<td>[3H] NE infusion rate, dpm/min×10⁶</td>
<td>4.5±2.6</td>
<td>4.1±2.2</td>
</tr>
</tbody>
</table>

Data are expressed as mean±SD. NE indicates norepinephrine. *P<0.05 vs NT.

Figure 1. A, Representative recording of MSNA by microneurography in a normotensive and a hypertensive subject, with simultaneous recording of the ECG and BP. B, Grouped data for MSNA expressed as burst incidence (bursts/100 heartbeats), demonstrating a significant increase in EH compared with NT subjects.

Figure 2. Rates of NE spillover into plasma for the body as a whole (A), the heart (B), and the kidney (C) in EH and NT subjects.
Mean arterial plasma concentration of the extraneuronal metabolite of NE, MHPG, was elevated in hypertensive subjects (NT, 2494 ± 571 versus EH, 3768 ± 1368 pg/mL; P < 0.05). Evidence for an impairment of neuronal NE reuptake was not only present for the heart but also for the body as a whole. The ratio of the plasma concentration of the intraneuronal metabolite DHPG to that of NE was lower in hypertensive subjects (Figure 3A). Furthermore, the arterial plasma concentration of the intraneuronal metabolite of tryptated NE, 3[H]DHPG, was significantly lower in hypertensive patients (NT, 50.8 ± 16.8 versus EH, 26.0 ± 14.5 dpm/min; P < 0.01) (Figure 3B).

Indicative of the drug’s propensity to inhibit central sympathetic outflow, desipramine infusion lowered total body NE spillover to a similar extent (≈25% to 30%) in both groups. However, total body NE spillover still remained higher in hypertensive subjects (Figure 4A). In the heart, desipramine elicited a more pronounced reduction in the fractional extraction of 3[H]NE in normotensive subjects than in hypertensive subjects (NT, −0.56 ± 0.14 versus EH, −0.35 ± 0.10; P < 0.01) (Figure 4B). Cardiac spillover of NE after desipramine infusion increased only in normotensive subjects, to a value similar to that of hypertensive subjects, to a value similar to that of hypertensive subjects (NT, 23.5 ± 12.9 versus EH, 25.3 ± 12.7 ng/min, P = NS) (Figure 4C). The less pronounced effect of NE transport blockade on cardiac NE disposition in hypertensive subjects is also mirrored by the changes in the ratio of cardiac to total body NE spillover, which was similar at baseline but significantly lower in hypertensive subjects after administration of desipramine (Figure 4D).

Screening of our study population for the Gly478Ser missense substitution (G1432A) in the NET gene revealed that none of the subjects displayed this single nucleotide polymorphism. All subjects displayed G at nucleotide 1432. Further genetic analysis was performed on 3 patients in whom NE reuptake was severely impaired. No mutations were observed that change the activity of the NE transporter. All 3 patients displayed the exon 9 G1287A and intron 9 G1389–9A polymorphisms. In addition, 2 patients had the intron 7 A1148–13C allele and 1 patient the exon 2 T296C polymorphism, which changes a threonine to an isoleucine. All alleles were present as heterozygotes. All variants have previously been reported, and there is no evidence that they affect activity of the transporter.

Arterial and CS plasma concentrations of angiotensin I and II were similar in both groups (CS angiotensin II: NT, 50 ± 16.8 versus EH, 40 ± 14.5 ng/mL; P < 0.05). Evidence for an impairment of neuronal NE reuptake was not only present for the heart but also for the body as a whole. The ratio of the plasma concentration of the intraneuronal metabolite DHPG to that of NE was lower in hypertensive subjects (Figure 3A). Furthermore, the arterial plasma concentration of the intraneuronal metabolite of tritiated NE, 3[H]DHPG, was significantly lower in hypertensive patients (NT, 50.8 ± 16.8 versus EH, 26.0 ± 14.5 dpm/min; P < 0.01) (Figure 3B).

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5.8±4.0 versus EH, 3.8±3.1 fmol/mL; P=NS), as was the angiotensin II/angiotensin I ratio, an index of rate of conversion of angiotensin I to angiotensin II in the coronary circulation (NT, 0.56±0.17 versus EH, 0.54±0.22 fmol/fmol; P=NS) (Figure 5). No correlation was evident between CS plasma angiotensin I or II concentrations and any indexes of total or regional NE spillover. Similarly, there was no relation between angiotensin II levels and cardiac NE reuptake (r=0.04; P=NS).

**Discussion**

In the present study, we comprehensively investigated the role of major mechanisms that could contribute to increased rates of NE spillover to plasma in hypertensive subjects, a hallmark of neurogenic essential hypertension. By combining radiotracer methodology, microneurography, and regional angiotensin II measurements, our study revealed that both increased rates of sympathetic nerve firing and a reduction of cardiac neuronal NE reuptake contribute substantially to increased spillover of NE from the heart in hypertensive subjects. The reduction in neuronal NE reuptake was not explicable in terms of any variations detected in the NE transporter gene. In contrast, neither reduced arterial baroreflex buffering of sympathetic activity nor angiotensin II sympathetic neuromodulation appear to be primarily involved in sympathetic activation.

Systemic administration of desipramine results in central sympathoinhibition. Yet, in the heart, where NE reuptake is of particular importance in overall NE disposition, the net effect is an increase in NE spillover, at least in healthy control subjects. In the present study, we exploited these properties of desipramine to directly test the hypothesis that alterations in neuronal NE reuptake in hypertensive patients contributes to sympathoexcitation.

We were able to demonstrate that the increase in cardiac NE spillover in hypertensive subjects was due, at least in part, to impaired cardiac neuronal NE reuptake. The evidence for this in essential hypertension was the reduced fractional extraction of plasma 3[H]NE in transit through the heart, a reduction in the concentration of the intraneuronal metabolite of tritiated NE, 3[H]DHPG, in CS plasma, a reduction in the cardiac spillover of endogenous DHPG, and the presence of a higher arterial plasma concentration of MHPG, consistent with increased substrate availability for extraneuronal uptake (U2) and subsequent extraneuronal metabolism by catechol O-methyltransferase in hypertensive subjects. A potential confounding effect of alterations in myocardial blood flow could be excluded, since the mean CS plasma flow was similar in the two groups both before and after desipramine infusion.

The response to blockade of NE reuptake with desipramine lent further support to this notion of impaired neuronal NE reuptake in that in hypertensive subjects, the reduction in the fractional extraction of 3[H]NE across the heart and the increase in cardiac spillover of NE were significantly less pronounced than in normotensive subjects. Furthermore, in normotensive subjects after desipramine, there was an increase in the ratio of cardiac to total body NE spillover, which reflects the balance between central sympathoinhibition and local blockade of transmitter reuptake, indicative of a greater capacity in normotensive subjects for pharmacological NE reuptake block in the sympathetic nerves of the heart. Similarly, our results provide evidence for impairment of neuronal NE reuptake for the body as a whole in hypertensive subjects, as reflected by a reduced ratio of the intraneuronal metabolite DHPG to that of plasma NE and by a lower arterial plasma concentration of 3[H]DHPG, which is produced in sympathetic nerves from tritiated NE after neuronal reuptake. Plasma whole-body clearance of NE was similar.
in hypertensive patients and healthy subjects, but this is
dependent on hemodynamic influences and therefore less
useful for assessing neuronal NE reuptake in normotensive
and hypertensive subjects.13

Our findings indicate that the elevated spillover of NE
from sympathetic nerves present in hypertensive subjects
appears to depend on a variety of neural mechanisms,
including increased sympathetic nerve firing rates and im-
paired neuronal NE reuptake. A recent systematic search
for variations in the human NE transporter gene identified 13
naturally occurring DNA sequence variants, 5 of which were
missense substitutions.17 Among these, only the Gly478Ser
variant displays a substantial reduction in the affinity for its
natural substrate, NE, when expressed in COS-7 cells, indi-
cating that the glycine in position 478 is part of a substrate
recognition domain.8 The reduced removal of released NE
from the synaptic cleft by reuptake through the Gly478Ser
variant might cause an increase in the synaptic concentrations
of the neurotransmitter and might therefore be operational in
disease states characterized by elevated NE concentrations,
such as heart failure and essential hypertension.8 Screening
of our study population for the Gly478Ser missense substitution
did not reveal this single nucleotide polymorphism in any of
our subjects. In an attempt to further explore potential genetic
influences, we sequenced all 14 exons of the NE transporter
gene in 3 hypertensive subjects with biochemical evidence
of severely impaired NE reuptake in addition to a strong
family history of essential hypertension. Again, no nucleotide
sequence variants were present that would result in changes
to NE transporter activity.16 Although our hypertensive sub-
jects were well characterized in terms of phenotypic evidence
of reduced neuronal NE reuptake and an association with
 genetic alterations would have been most likely to be evident
in these subjects, our sample size may not be sufficient to
exclude a potential contribution of sequence variability in the
human NE transporter gene to increased levels of NE in
hypertensive subjects. Furthermore, we cannot exclude the
possibility that mutations in regulatory sequences in promoter
or enhancer regions may play a role. These issues warrant
further investigation.

Whether baroreceptor modulation of sympathetic efferents
to blood vessels is altered in essential hypertension is con-
troversial.5,20,21 Given these uncertainties, it is reasonable to
argue that an impaired baroreceptor restraint of sympathetic
nerve traffic might be one mechanism of the sympathetic
overactivity present in essential hypertension. We assessed
spontaneous arterial baroreflex control of MSNA in our
normotensive and hypertensive subjects, finding that the gain
of the MSNA arterial baroreflex was similar in the two
groups. Thus, from our observations, it seems unlikely that a
dampening of arterial baroreflex restraint on sympathetic
nerve traffic underlies the sympathetic overactivity present
in our hypertensive subjects. This is in line with a previous
report demonstrating that baroreflex modulation of vasomo-
tor tone is preserved in borderline hypertension.20

Despite evidence from animal and human studies to sup-
port the hypothesis of a functional cardiac renin-angiotensin
system,9 a functional effect on the cardiac sympathetic nerves
in humans remains to be determined. Whether angiotensin II
contributes to sympathetic activation in human essential
hypertension has not yet been adequately investigated. Stud-
ies in the spontaneously hypertensive rat suggest that ACE
inhibition increases cardiac neuronal reuptake of catechol-
amines, probably by a direct activation of the NE transport-
er.22 To assess whether mechanisms such as these may be
operative in human hypertension, and, if present, whether
they are confined to the heart, we measured angiotensin II
concentrations in CS and arterial blood in our normotensive
and hypertensive subjects and tested for a relation with total
systemic and cardiac sympathetic tone. There was no detect-
able difference in angiotensin I or II concentration or in
estimated ACE activity between the two groups. No relation
was evident between any parameters of sympathetic activity,
either systemically or in the heart, and CS or arterial angio-
tensin II levels. Furthermore, indexes of cardiac and systemic
NE reuptake did not correlate with plasma angiotensin II
levels. Thus, angiotensin II does not appear to contribute
substantially to either increased NE release or reduced NE
reuptake in our hypertensive study population, which is in
line with a previous report.23

**Perspectives**

Despite increasing evidence for an important contribution
of neurogenic mechanisms to essential hypertension,1,2 the
precise causal mechanisms leading to sympathetic augmentation
in hypertensive subjects remain unclear. Our comprehensive
assessment of potential mechanisms revealed that increased
rates of sympathetic nerve firing and reduced neuronal NE
reuptake both contribute to sympathetic activation in hyper-
tension, whereas a role for dampened arterial baroreflex
restraint on sympathetic nerve traffic and a peripheral
neuro-modulating influence of angiotensin II appear to be excluded.
Our finding of an increased sympathetic activity was obtained
from a small homogenous hypertensive cohort and further
supports the notion that sympathetic overactivity plays an
important role in the underlying cause of essential hyperten-
sion. However, our data cannot necessarily be extrapolated to
the entire hypertension population. Whether the described
mechanisms can be targeted therapeutically needs to be
assessed in further studies.

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