Increased Norepinephrine Spillover Into the Jugular Veins in Essential Hypertension

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In essential hypertension sympathetic nerve firing is commonly increased. A central nervous system origin has been presumed but not tested directly. To estimate cerebral norepinephrine release in essential hypertension, spillover of norepinephrine into the cerebrovascular circulation was measured by isotope dilution, with high internal jugular venous sampling. Norepinephrine was released into the cerebrovascular circulation in both hypertensive patients and healthy volunteers and was present after administration of the ganglion blocker trimethaphan and in patients with sympathetic nervous failure, indicating that brain neurons and not cerebrovascular sympathetic nerves were the probable source. Although differing among hypertensive patients, norepinephrine spillover on average was higher in the hypertensive patients (153±41 pmol/min) than in healthy subjects (59±12 pmol/min; p<0.05), and was elevated in six of 17 patients, in whom the accompanying whole body norepinephrine spillover rate was higher than in the remaining 11 patients (p<0.01). To test for a possible link between brain norepinephrine release and human sympathetic nervous function, the effect of the tricyclic antidepressant desipramine (0.3 mg/kg i.v.) on both brain and whole body norepinephrine spillover was measured in healthy volunteers. Desipramine lowered the cerebrovascular spillover of norepinephrine, its precursor dihydroxyphenylalanine, and its metabolite dihydroxyphenylglycol by 50-80% and produced a mean fall of 35% in whole body norepinephrine spillover. One interpretation of these results is that human sympathetic nerve firing is dependent on norepinephrine release within the brain and that increased cerebral norepinephrine release may possibly be present in some patients with essential hypertension, underlying their higher sympathetic nerve firing rates. (Hypertension 1992;19:62-69)

Estimation of the regional overflow of the major sympathetic nervous system neurotransmitter norepinephrine from individual organs provides a useful clinical measure of organ-specific sympathetic nervous function. This is because the rate at which norepinephrine spills into the venous drainage of individual organs is in general proportional to their rate of sympathetic nerve firing.1 Regional norepinephrine spillover measurements of this kind provide evidence that the sympathetic nervous outflow to the kidneys and heart is commonly increased in patients with essential hypertension.1 Demonstration of an elevated firing rate in recordings directly performed on muscle sympathetic nerves2-3 provides additional evidence of sympathetic nervous hyperactivity in human hypertension.

The underlying mechanism of this change is unclear. Clinical, epidemiological, and experimental laboratory research does provide some suggestion that behavioral and psychosocial factors may be involved.4-6 Since central nervous system (CNS) noradrenergic mechanisms are of importance in the regulation of the sympathetic nervous system,7-11 another rather more direct experimental approach might be to attempt to study norepinephrine release within the CNS in essential hypertension. A role in cardiovascular regulation has been ascribed to a number of CNS noradrenergic cell groups including the A6 (locus ceruleus), A5, and A2 nuclei.8 It is now well established that substantial innervation of the preganglionic sympathetic neurons in the intermediolateral column of the spinal cord originates from the A5 and subceruleus noradrenergic cell groups.9 It

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might perhaps be helpful to measure norepinephrine overflow from the brain, with sampling from the internal jugular vein, analogous to the measurement of norepinephrine spillover from peripheral organs, to seek underlying abnormalities in CNS noradrenergic cardiovascular control in primary hypertension. Reports of an elevated norepinephrine concentration in cerebrospinal fluid in essential hypertension provide an additional impetus to do this. The existence of a blood–brain barrier to monoamines, however, that blocks the passage of neurotransmitters between the bloodstream and the brain would invalidate any efforts to assess CNS norepinephrine release using measurements of norepinephrine spillover to plasma. Although there are strong grounds for believing that such an impediment to norepinephrine passage from the bloodstream to the brain exists, the evidence supporting the existence of a barrier to norepinephrine movement in the reverse direction, from the brain to the circulation, is less compelling. In an early study in rats, Glowinski and coworkers reported that 25% of tritiated norepinephrine injected into the lateral cerebral ventricle reached the systemic circulation unchanged. An active transport system, in fact, may exist in the cerebral microcirculation, facilitating the outward transport of norepinephrine from the brain. Based on these considerations, measurements of norepinephrine overflow into the cerebrovascular circulation might prove useful as an index of norepinephrine release in the brain.

In the present study, we attempted to evaluate the possibility that the activity of cerebral noradrenergic neurons may be altered in essential hypertension. This could be an underlying mechanism of the sympathetic nervous activation commonly present in hypertensive patients. Using radiotracer methodology, we compared the rates of norepinephrine spillover into the cerebrovascular circulation in hypertensive patients and healthy volunteers. To clarify whether norepinephrine appearing in the venous drainage of the brain originates from cerebral noradrenergic neurons or cerebrovascular sympathetic nerves, cerebral norepinephrine spillover was also measured in patients with sympathetic nerve degeneration (idiopathic peripheral autonomic insufficiency) and in a subset of the essential hypertensive patients both before and after administration of the ganglion blocker trimethaphan (Arfonad, Roche Australia, Sydney, Australia). In addition, to explore the possible dependence of peripheral sympathetic function on cerebral norepinephrine release, we assessed the effects of the tricyclic antidepressant desipramine, which has been shown experimentally to reduce CNS norepinephrine release, on both brain and whole body norepinephrine spillover to plasma.

Methods

Subjects

The study population consisted of 26 hypertensive patients (24 men and two women) in whom renal vein catheterization and bilateral renal vein renin sampling was performed, with the results excluding the presence of significant renal artery stenosis. After sampling for the diagnostic renins, a central venous catheter was sited in one or both internal jugular veins, and the research study was conducted. In these essential hypertensive patients, directly recorded intrarterial blood pressure (BP) was 162/92±2/3 mm Hg (mean±SEM), and mean age was 44 years (range, 18–61 years). Other forms of secondary hypertension were excluded by appropriate clinical testing. The hypertensive patients were either previously untreated or, if under treatment, antihypertensive medication was withdrawn at least 4 weeks before the study.

For comparison, we also studied CNS catecholamine overflow in 21 healthy male volunteer subjects of similar age (mean age, 42 years; range, 18–75 years) in all of whom blood pressure was consistently less than 135/85 mm Hg. The healthy research volunteers were recruited from the general community by advertisement and were paid a nominal fee for their services. A detailed clinical health examination was performed on all before their participation in the research study. None of the healthy volunteers were taking any drugs.

The five patients with idiopathic peripheral autonomic insufficiency (mean age, 61 years) had symptomatic postural hypotension. The diagnosis was based on the absence of demonstrable central nervous system disease, a denervation response pattern to the Valsalva maneuver (no heart rate change, substantial blood pressure fall during the period of straining with no late BP recovery or poststraining overshoot of diastolic BP), reduced norepinephrine spillover to plasma during supine rest, markedly reduced extraction of radiolabeled norepinephrine across the heart indicative of sympathetic denervation, and postural hypotension without increase in norepinephrine spillover on head-up tilting.

The study protocol was approved by the Alfred Hospital Ethics Review Committee. All patients and volunteers gave written informed consent before their participation.

Procedures

After overnight fasting, all patients and volunteers received a light standardized breakfast and refrained from drinking caffeinated beverages or smoking cigarettes. The study was performed with the subject in the supine position. Under local anesthesia, a 7F coronary sinus thermodilution catheter (type CCS-74, Webster Lab, Baldwin Park, Calif.) was percutaneously inserted in a brachial vein and advanced under direct fluoroscopic control to the internal jugular vein. The tip of the catheter was placed beyond the mandibular angle, upstream to the point of entry of any venous tributaries from the tissues of the face, to minimize contamination of the cerebral venous effluent. The catheter was used for sampling jugular venous blood and for determination of jugu-
lar blood flow by thermodilution. Bilateral jugular venous sampling was performed in some subjects, either by repositioning this catheter to lie in the other internal jugular vein or by the percutaneous placement of a second catheter. A 21-gauge catheter, placed percutaneously under local anesthesia in a brachial or radial artery, was used for arterial blood sampling and BP monitoring. A venous line inserted into a peripheral vein was used for infusion of tritiated norepinephrine and, in eight subjects, tritiated epinephrine. Measurements were obtained at rest, after intravenous infusion of the ganglion blocker trimethaphan in six hypertensive patients, and after infusion of the tricyclic antidepressant desipramine in nine of the healthy subjects.

**Catecholamine Kinetics**

Tritiated norepinephrine (levo-[3H]-7-norepinephrine, 12-20 Ci/mmol, New England Nuclear, Boston, Mass.) was diluted in 50 ml normal saline and infused intravenously at a rate of 0.35 µCi/min/m² for the duration of the study. Nine healthy subjects received simultaneous infusions of [3H]epinephrine (levo-[N-methyl-3H]epinephrine, 58-69 Ci/mmol, New England Nuclear) infused at the same rate as the [3H]norepinephrine. After reaching steady-state plasma concentration, the rate of release of endogenous norepinephrine (NE) into plasma (the "spill-over rate") was determined as follows:1,20

\[
\text{Total NE spillover rate} = \frac{[3H]\text{NE infusion rate}}{\text{Plasma NE specific radioactivity}} \tag{1}
\]

The fractional extraction of the tracer across the brain was calculated from the relation

\[
\text{CNS } [3H]\text{NE extraction} = \frac{[3H]\text{NE}_a - [3H]\text{NE}_v}{[3H]\text{NE}_a} \tag{2}
\]

Norepinephrine spillover rates into one internal jugular vein were calculated according to the Fick principle from the relation1

\[
\text{Unilateral CNS NE spillover} = \frac{[(\text{NE}_v - \text{NE}_a) + (\text{NE}_a \times \text{NE}_v)] \times \text{JPF}} {\text{JPF}} \tag{3}
\]

where NE_v is the plasma norepinephrine concentration in the jugular vein, NE_a is the arterial plasma norepinephrine concentration, NE is the fractional extraction of plasma tritiated norepinephrine across the brain, calculated according to equation 2, and JPF is the jugular plasma flow. Blood flow was determined by thermodilution.21 Blood and plasma flows were interconverted using the subject's hematocrit.

Determination of the bilateral CNS norepinephrine spillover rate, derived from the sum of norepinephrine spillover rates into the right and left jugular vein, was possible in five healthy subjects and six hypertensive patients.

The net cerebral spillover rate of the norepinephrine precursor dihydroxyphenylalanine (DOPA) was estimated as follows:

\[
\text{CNS DOPA spillover rate} = \frac{[\text{DOPA}_v - \text{DOPA}_a] \times \text{JPF}} {\text{JPF}} \tag{4}
\]

where DOPA_v and DOPA_a represent the jugular venous and arterial DOPA plasma concentrations, respectively, and JPF is the jugular blood flow.

The net cerebral spillover rate of the norepinephrine precursor dihydroxyphenylglycol (DHPG) was estimated from

\[
\text{CNS DHPG spillover rate} = \frac{[\text{DHPG}_v - \text{DHPG}_a] \times \text{JBF}} {\text{JBF}} \tag{5}
\]

where DHPG_v and DHPG_a represent the jugular venous and arterial DHPG plasma concentrations, respectively, and JBF is the jugular blood flow. Plasma flow was used to calculate the CNS spillover of DOPA based on results from this laboratory showing that 86% of exogenous DOPA added to whole blood is recoverable from the plasma compartment. For DHPG spillover calculations, blood flow rather than plasma flow was used, based on results showing rapid equilibration of added DHPG between plasma and red blood cells.22 For both DOPA and DHPG, unlike for norepinephrine, net spillover was calculated since no correction could be made for brain uptake in the absence of infusion of the corresponding tracers.

**Trimethaphan Infusion**

After catecholamine measurements were made at rest, the ganglion blocker trimethaphan was infused at a rate of 0.75–2.0 mg/min (the dose used being that sufficient to reduce supine systolic arterial pressure by 20–30 mm Hg) for 30 minutes in six of the hypertensive patients, and the blood sampling and jugular flow measurements were repeated. In one subject, bilateral jugular venous sampling was performed.

**Desipramine Infusion**

In nine healthy subjects desipramine hydrochloride (Ciba-Geigy, Sydney, Australia) was infused intravenously into a forearm vein, over 30 minutes, in a total dose of 0.3 mg/kg desipramine base. This dose of desipramine has been previously determined to produce near maximal neuronal norepinephrine uptake blockade23 while avoiding side effects such as nausea, which are sometimes seen with higher doses. Arterial and internal jugular venous blood samples were collected at rest and within 30 minutes of completing the infusion in these nine subjects for determination of brain and whole body norepinephrine spillover rates.

**Assay of Endogenous and Radiolabeled Catechols**

Blood samples (5 ml) were transferred immediately to ice-chilled tubes containing EGTA and re-
Statistical Analysis

Data are given as mean±SEM or shown as individual data points. When normally distributed, paired data were analyzed with paired t test. For non-Gaussian distribution, paired observations were evaluated with Wilcoxon's signed rank test. Serial data points were subjected to repeated-measures analysis of variance.

Results

In healthy volunteers, radiolabeled norepinephrine was subject to a significant, but low, level of extraction across the cerebrovascular circulation, 15±3% (mean±SEM). The transcerebral extractions of endogenous and tritiated epinephrine were similar to this (15±5% and 14±7%, respectively). In contrast to the extraction of radiolabeled norepinephrine, a positive venoarterial plasma concentration gradient existed across the brain for endogenous norepinephrine (Figure 1). This isotope dilution of plasma norepinephrine in transcerebral transit was indicative of norepinephrine release into the cerebrovascular circulation.

Spillover of norepinephrine into the left or right internal jugular vein, calculated during [H]norepinephrine infusion, was 59±12 pmol/min in 16 healthy subjects (Table 1). This unilateral norepinephrine spillover was 62±17 pmol/min into the right jugular vein and 49±12 pmol/min into the left jugular vein (Figure 2). Total cerebral norepinephrine spillover measurements, derived from the sum of simultaneously measured right and left jugular vein spillovers, were available in five healthy volunteers. This combined cerebral norepinephrine spillover was 106±29 pmol/min (Figure 3).

Spillover of norepinephrine into the cerebrovascular circulation was evident also in hypertensive patients at a somewhat higher level on the right than on the left (176±53 versus 106±23 pmol/min, p=0.48; Figure 2). Unilateral norepinephrine spillover into the internal jugular vein was higher in hypertensive patients (153±41 pmol/min) compared with the value

### TABLE 1. Cerebral Norepinephrine Kinetics in Hypertensive Patients and Healthy Volunteers

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hypertensive</th>
<th>Control</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=23</td>
<td>n=21</td>
<td></td>
</tr>
<tr>
<td>Plasma norepinephrine (pmol/l)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arterial</td>
<td>1,725±164</td>
<td>1,536±138</td>
<td>NS</td>
</tr>
<tr>
<td>Jugular vein</td>
<td>2,056±306</td>
<td>1,625±144</td>
<td>NS</td>
</tr>
<tr>
<td>Norepinephrine extraction (%)</td>
<td>0.17±0.04</td>
<td>0.15±0.02</td>
<td>NS</td>
</tr>
<tr>
<td>Jugular vein plasma flow (ml/min)</td>
<td>232±14</td>
<td>217±27</td>
<td>NS</td>
</tr>
<tr>
<td>Norepinephrine spillover (pmol/min)</td>
<td>153±41</td>
<td>59±12</td>
<td>0.036</td>
</tr>
</tbody>
</table>

Values are given as mean±SEM.
The present study shows that norepinephrine overflows from the brain into the circulation both in healthy subjects compared with 793 ± 223 pmol/min in hypertensive patients (p = 0.06).

To ascertain whether norepinephrine spillover into the internal jugular veins derived from brain neurons or from the cerebrovascular sympathetic nerves, the ganglion blocker trimethaphan was administered. With a dose of trimethaphan that was sufficient to lower supine systolic blood pressure by 20–30 mm Hg in six hypertensive patients and to reduce the total body norepinephrine spillover rate by approximately 25% (p < 0.05), norepinephrine spillover into the cerebrovascular circulation was unchanged, pointing to probable primacy of brain neurons as the source of the norepinephrine (Figure 4).

This conclusion was supported by observations in five patients with sympaticic nerve degeneration (idiopathic peripheral autonomic insufficiency) in whom the entry of norepinephrine into the cerebrovascular circulation was not reduced (Figure 4) despite markedly subnormal total body norepinephrine spillover (869 ± 177 pmol/min).

In nine healthy subjects infusion of desipramine reduced the cerebrovascular spillover of norepinephrine, DOPA, and DHPG by 50–80%. Unilateral cerebral norepinephrine spillover obtained with sampling from the left (n = 3), right (n = 2), or both (n = 4) internal jugular veins was reduced from 59 ± 18 to 10 ± 4 pmol/min (p < 0.05, paired t test) (Figure 5). A significant decrease was also observed in the spillover of DOPA (from 223 ± 30 to 101 ± 20 pmol/min, p < 0.01) and DHPG (from 188 ± 14 to 38 ± 16 pmol/min, p < 0.01). In these subjects, desipramine produced a mean fall in total spillover of norepinephrine to plasma of 35% (Figure 5).

**Discussion**

The present study shows that norepinephrine overflows from the brain into the circulation both in
These findings are unexpected and in conflict with the conventional view that a "blood-brain barrier" would prevent passage of catecholamines from the brain to the circulation.

The existence of an anatomic and biochemical barrier to movement of a range of solutes across the capillary walls of the brain microcirculation is well established. Although with sudden, extreme elevation of arterial pressure disruption of the blood–brain barrier can occur, gross disruption of the blood–brain barrier was not present here. This was evident from the low (mean 16%) and identical rates of outward movement of radiolabeled norepinephrine in transit through the cerebrovascular circulation in healthy subjects and hypertensive patients, with the transcerebral extraction of tritiated norepinephrine being substantially lower than the fractional extraction of tracer seen across other organs, such as the heart, liver, and skeletal muscle (50–80%). This relative barrier to norepinephrine flux (and also to radiolabeled epinephrine) supports the existing view that there is a substantial impediment to catecholamine movement between the bloodstream and brain.

The extent of any barrier to norepinephrine movement in the reverse direction, from the CNS to the circulation (a brain–blood barrier), has been less studied. Glowinski and coworkers reported that fully 25% of tritiated norepinephrine injected into the lateral cerebral ventricle of rats reached the systemic circulation unchanged. There is, in fact, evidence to suggest that an active transport process may exist in the cerebral microcirculation facilitating outward passage of norepinephrine from the brain. The overflow of norepinephrine into the cerebrovascular circulation we detect could possibly represent such a facilitated unidirectional flux, or perhaps passage of norepinephrine across regions of the brain microcirculation where the blood–brain barrier is known to be deficient.

Another possible means by which CNS norepinephrine...
could enter the circulation is through reabsorption of cerebrospinal fluid, but given that the rate of cerebrospinal fluid reabsorption into the sagittal sinus via the arachnoid villi is no more than 1–2 ml/min,29 and the cerebrospinal fluid norepinephrine concentration approximately 1.2 nM,31 this mechanism could not be responsible for more than a small fraction of the observed CNS norepinephrine spillover.

Since the cerebral arterial tree has well-developed sympathetic innervation,30 it is pertinent to consider whether norepinephrine overflow into the cerebrovascular circulation derives from sympathetic nerves or from brain neurons. The failure of ganglionic blockade with trimethaphan to reduce cerebrovascular norepinephrine spillover suggests that this norepinephrine largely represents transmitter released from brain neurons. Although the ganglionic blockade produced with trimethaphan was substantial, producing a fall in supine systolic blood pressure of 20–30 mm Hg, it was not complete, as indicated by a pattern of partial denervation only with the Valsalva maneuver (some recovery of BP late in the straining phase). That some norepinephrine may have originated from cerebrovascular nerves cannot be excluded with certainty. In dogs, ganglionic blockade with trimethaphan has been reported to decrease the concentration of norepinephrine in cerebrospinal fluid,31 a finding taken to indicate that it is postganglionic sympathetic nerve endings that are the major source of norepinephrine in cerebrospinal fluid. Supporting our concept of a predominantly neuronal origin of the norepinephrine released into the cerebral circulation is the fact that in our patients with idiopathic peripheral autonomic insufficiency who had sympathetic nerves damaged by disease, cerebrovascular norepinephrine spillover was undiminished even though, as expected, total body norepinephrine spillover was markedly reduced. In short, although our data are entirely consistent with a CNS source of the norepinephrine released into the cerebrovascular circulation they do not completely exclude some input from a postganglionic sympathetic source.

We found cerebral norepinephrine spillover to be increased in hypertensive patients, accompanied by 22–122% higher rates of unilateral and bilateral spillover of the norepinephrine precursor DOPA and the norepinephrine metabolite DHPG. The previously reported increase in norepinephrine concentration in cerebrospinal fluid in essential hypertensive patients12,13 appears to be an allied phenomenon. As discussed, it is unlikely that the mechanism of the increased CNS norepinephrine spillover in hypertensive patients is a disruption of the blood–brain barrier caused by the elevated arterial pressure. The more likely cause is that the rate at which norepinephrine is released as a neurotransmitter within the brain is increased, and the higher cerebrovascular norepinephrine spillover in hypertensive patients is a consequence of higher CNS norepinephrine release. The elevation in norepinephrine spillover is probably not simply a response to higher pressures because in secondary forms of hypertension, cerebrospinal fluid norepinephrine concentration appears to be normal.13 Since noradrenergic mechanisms of cardiovascular control exist within the CNS,7–11 it is pertinent to ask whether these may possibly be deranged in essential hypertension, with elevated cerebral noradrenergic activity contributing to the blood pressure elevation.

Norepinephrine is widely distributed in the brain and in the gray matter of the spinal cord. In subcortical areas of the brain, norepinephrine-containing cells are assorted into nuclei and located in different areas classified as A1 to A7.8,32 The largest group of norepinephrine-containing neurons, estimated to account for not less than 50% of the norepinephrine in the brain, is the locus ceruleus (A6), located in the pons near the wall of the fourth ventricle.33 Electrophysiological and anatomic studies carried out in animals provide evidence of a connection between pressor hypothalamic and bulbar noradrenergic nuclei involved in cardiovascular regulation and sympathetic preganglionic neurons in the thoracolumbar cord, relayed in part via the rostral ventral medulla.7–11,13,24 Given this relation, the question arising from our finding of increased cerebral norepinephrine spillover in hypertensive patients is whether increased cerebral norepinephrine release in bulbar and hypothalamic noradrenergic centers important in cardiovascular regulation may be responsible for the elevated peripheral sympathetic nerve firing and norepinephrine spillover observed in some essential hypertensive patients.1–3,35

To search for a possible link between norepinephrine release in the brain and peripheral sympathetic nervous function, we made use of the tricyclic antidepressant desipramine. Desipramine has been shown in experimental animals to reduce neuronal firing and norepinephrine release in several cerebral noradrenergic nuclei.14,15 Our experience here is that acute dosing with desipramine reduces norepinephrine spillover from the human brain and that of its precursor DOPA and its metabolite DHPG. And further, this reduction in brain norepinephrine turnover was accompanied by a fall in sympathetic nerve firing, as indicated by the substantial reduction in the overall rate of spillover of the transmitter to plasma. This sympathoinhibitory action of desipramine we observed has been well documented.36–38 The effects of desipramine, a reduction in CNS norepinephrine spillover accompanied by lowered sympathetic nerve firing, in some respects represent the converse of the common findings in essential hypertension, increased sympathetic activity associated with evidence of elevated CNS norepinephrine release, and suggest a dependence in both contexts of peripheral sympathetic nerve firing rates on the activity of CNS noradrenergic neurons.

The biological basis of the increased sympathetic nerve firing present in some patients with essential hypertension, particularly in the early developmental phase,1 is obscure. It has sometimes been thought of as psychosomatic in nature, and perhaps attributable to psychosocial stress5 or behavioral patterns such as
the inordinate suppression of hostility.\textsuperscript{39} Our study provides evidence of a possible link between human cerebral noradrenergic activity and the prevailing level of sympathetic nervous outflow and suggests that increased sympathetic nerve firing rates present in a proportion of patients with primary human hypertension, whatever the initiating mechanism, may possibly derive from increased norepinephrine release in the brain.

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**Key Words** • autonomic dysfunction • norepinephrine • brain • sympathetic nervous system • central nervous system • trimethaphan • desipramine
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