

## Plasma Norepinephrine and Dihydroxyphenylglycol in Essential Hypertension

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The aim of the present study was to examine whether essential hypertension is associated with altered plasma concentrations of dihydroxyphenylglycol, the principal presynaptic metabolite of norepinephrine. Forearm venous plasma dihydroxyphenylglycol and norepinephrine were determined at rest and during graded orthostasis in 47 normotensive control subjects and 58 outpatients with essential hypertension. There was no group difference in age. At supine rest as well as during sitting and standing, hypertensive subjects had plasma norepinephrine concentrations similar to those in normotensive control subjects, but plasma dihydroxyphenylglycol concentrations were higher than those in normotensive control subjects. Both groups showed a linear relation between plasma dihydroxyphenylglycol (ordinate) and plasma norepinephrine (abscissa). The resulting regression line was steeper ( $p < 0.02$ ) and its ordinate intercept higher ( $p < 0.01$ ) in hypertensive than in control subjects. Eleven normotensive and 14 hypertensive subjects were also tested 3 hours after desipramine (1.5 mg/kg orally) was administered to inhibit neuronal norepinephrine reuptake. The drug did not alter plasma norepinephrine, but did reduce plasma dihydroxyphenylglycol and did abolish plasma dihydroxyphenylglycol responses to upright posture in both groups of subjects. The mean plasma dihydroxyphenylglycol concentration observed in the presence of desipramine again was higher in the hypertensive than in the control group ( $p < 0.01$ ) and closely agreed, in both groups, with the dihydroxyphenylglycol concentration given by the ordinate intercept of the dihydroxyphenylglycol versus norepinephrine regression line in the absence of desipramine. Thus, the desipramine-resistant and desipramine-sensitive component of plasma dihydroxyphenylglycol (i.e., dihydroxyphenylglycol formed from vesicular norepinephrine leaking out of the transmitter stores and from synaptic norepinephrine subsequent to neuronal recapture, respectively) appear to contribute to the elevated plasma dihydroxyphenylglycol concentration in essential hypertension. (*Hypertension* 1991;17:546–552)

The available evidence indicates a role of the sympathetic nervous system in the development and maintenance of primary hypertension both in humans and spontaneously hypertensive rats (SHR).<sup>1–7</sup> Despite this widely held view, the plasma norepinephrine concentration, which has been used as a measure of sympathetic tone, is not consistently elevated above normal in patients with essential hypertension.<sup>8,9</sup> However, even plasma norepinephrine levels within the normal range are inappropriately high when the high blood pressure in these individuals is taken into consideration. This

may indicate a reduced baroreceptor reflex sensitivity<sup>10,11</sup> or an enhanced density of noradrenergic innervation in vascular tissues.<sup>6</sup>

In 1981, Vlachakis and Alexander<sup>12</sup> studied the plasma concentrations of norepinephrine and its primary metabolites normetanephrine and dihydroxyphenylglycol (DOPEG) in SHR and Wistar-Kyoto (WKY) control rats. They found in SHR increased plasma normetanephrine and DOPEG concentrations, whereas plasma norepinephrine levels did not differ from those in WKY rats. The authors concluded that the high plasma levels of norepinephrine metabolites observed in SHR may reflect increased norepinephrine metabolism and turnover resulting from overactivity of the sympathetic nervous system. In a clinical trial involving 12 normotensive control and 12 essential hypertensive subjects, we also found higher than normal plasma DOPEG levels in the hypertensive group.<sup>13</sup> This prompted us to determine

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plasma norepinephrine and DOPEG concentrations in larger groups of normotensive and essential hypertensive subjects, during both recumbency and graded orthostatic stress. DOPEG was chosen instead of normetanephrine because DOPEG is the principal norepinephrine metabolite of presynaptic origin<sup>14-17</sup> and because a method is available in our laboratory by which DOPEG and norepinephrine can be measured simultaneously in a single plasma sample.<sup>18</sup> Moreover, DOPEG penetrates cell membranes and tissues with ease<sup>19</sup> and exhibits a high plasma clearance and a very short plasma half-life,<sup>20,21</sup> so that changes in its presynaptic formation are fairly quickly reflected by changes in its plasma concentration.

### Methods

#### Subjects

Forty-seven normotensive control subjects (20 women and 27 men, aged 21-65 years) and 58 patients with essential hypertension (26 women and 32 men, aged 18-74 years) were studied. The control subjects were healthy volunteers who had unremarkable medical histories, normal physical examinations, and upright (10 minutes sitting) systolic and diastolic blood pressures less than 140/90 mm Hg (standard sphygmomanometer). The majority of the control subjects (35 of 47) were neither medical personnel nor laboratory staff. The hypertensive subjects were outpatients in whom secondary forms of hypertension had been excluded on investigation. They all had, on at least three occasions, upright (10 minutes sitting) diastolic blood pressures in excess of 90 mm Hg (standard sphygmomanometer) and were either previously untreated for hypertension or else had discontinued any antihypertensive medication for 2 weeks before testing. All subjects had been instructed not to smoke or drink coffee for 12 hours before blood sampling and gave their informed consent to the study protocol, which was approved by the local Ethics Committee.

#### Study Protocol

Patients and control subjects were investigated between 9:00 AM and 11:00 AM. An intravenous cannula was inserted into an antecubital vein and then was flushed with saline. After a 30-minute period of recumbency, blood pressure and heart rate were recorded with an automatic device (Dinamap 1846 SX, Critikon, Norderstedt, FRG), and blood samples (10 ml) were taken for determination of plasma norepinephrine and DOPEG. Subjects were then asked to sit quietly without talking for 30 minutes and, thereafter, to stand quietly in place without talking for a further 30 minutes. At the end of the periods of sitting and standing, blood pressure and heart rate measurements as well as blood sampling were repeated. The test procedure was repeated at least 2 days later in 11 normotensive control and 14 hypertensive subjects who volunteered to repeat the test but at 3 hours after oral adminis-

TABLE 1. Characteristics of Participants

Variable	Normotensives (n=47)	Hypertensives (n=58)
Age (yr)	40.1±13.4	43.9±13.7
Sex (m/f)	27/20	32/26
Body weight (kg)	71.1±9.9	80.2±12.8*
Height (cm)	171.4±7.4	171.8±9.1
Heart rate (beats/min)	67±8	71±11†
Systolic blood pressure (mm Hg)	122±12	175±21*
Diastolic blood pressure (mm Hg)	76±9	106±11*

Values are arithmetic means±SD. Heart rate (pulse counting) and blood pressure (standard sphygmomanometer) were measured with the subjects sitting (10 minutes). Heart rate and blood pressure values in hypertensive subjects are based on mean observations made on three separate occasions.

For comparison between groups: \* $p < 0.01$ ; † $p < 0.05$ .

tration of 1.5 mg/kg desipramine. The test consisted of 30 minutes of supine rest followed by 30 minutes of quiet standing; observations were made and blood samples were taken at the end of both 30-minute periods. The dose of desipramine used here has been shown to produce a high degree of inhibition of neuronal norepinephrine uptake.<sup>22-25</sup>

#### Assay Procedure

Blood was collected in ice-cold, K<sub>2</sub>EDTA-containing tubes and chilled on ice. The plasma was separated by centrifugation at 4°C, and plasma samples of 1 ml were mixed with 0.5 ml of a solution containing 1.0% Na<sub>2</sub>EDTA as well as 1.25% Na<sub>2</sub>SO<sub>3</sub> and were then stored at -80°C until assayed. Plasma concentrations of norepinephrine and DOPEG were determined in duplicate after adsorption onto Al<sub>2</sub>O<sub>3</sub> and desorption with 0.1 mol/l HClO<sub>4</sub> by reversed-phase, high-performance liquid chromatography and electrochemical detection as described previously.<sup>18</sup> The analytical recoveries of norepinephrine (75-85%) and DOPEG (65-75%) from plasma were evaluated in each individual assay. The results were corrected accordingly.

#### Statistics

Results are presented as arithmetic means, and unless stated otherwise, SEM values or 95% confidence limits are given. Regression lines relating plasma DOPEG to plasma norepinephrine were calculated by the method of least squares. Correlations were analyzed by computing Spearman's rank correlation coefficients ( $r_s$ ). The significance of differences was assessed by the *U* test according to Wilcoxon, Mann-Whitney (between-subject observations), and Wilcoxon's signed rank test (within-subject observations).<sup>26</sup> Values of  $p < 0.05$  were taken to indicate statistical significance.

### Results

The descriptive characteristics of the normotensive control and hypertensive groups are summarized in Table 1. Besides the group differences with respect to blood pressure, mean heart rate and mean body

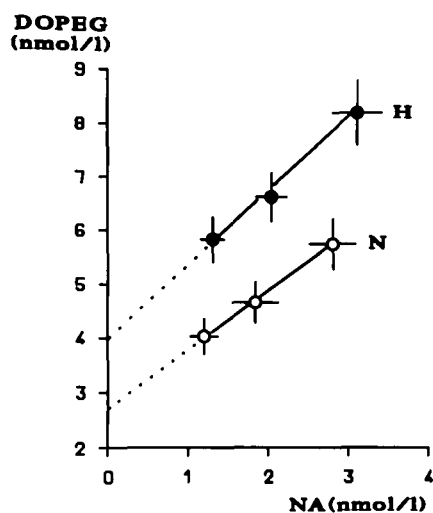


FIGURE 1. Plotting of relation between plasma dihydroxyphenylglycol (DOPEG) and plasma norepinephrine concentrations in normotensive control subjects (N) and essential hypertensive subjects (H). Three data points indicate (from left to right) results obtained after 30 minutes of recumbency, 30 minutes of sitting, and 30 minutes of standing, respectively. Shown are arithmetic means ( $\pm 95\%$  confidence limits) from 47 normotensive and 58 hypertensive subjects as well as regression lines calculated from mean group results. Although there were no hypertensive-normotensive differences in plasma norepinephrine, the differences in plasma DOPEG were highly significant ( $p < 0.01$ ). NA, norepinephrine.

weight were higher in the hypertensive than in the normotensive group. There was no statistically significant group difference in age. After 30 minutes of supine rest, plasma norepinephrine was significantly correlated with age in the normotensive group ( $r_s = 0.353$ ;  $n = 47$ ;  $p < 0.02$ ) but not in the hypertensive group ( $r_s = 0.183$ ;  $n = 58$ ;  $p > 0.1$ ). There was no correlation between plasma DOPEG and age in either the control or the hypertensive group.

Orthostatic stress due to 30 minutes of standing increased heart rate and diastolic blood pressure in normotensive subjects (by  $10 \pm 1$  beats/min and  $10 \pm 2$  mm Hg, respectively;  $n = 47$ ; mean  $\pm$  SEM) and hypertensive subjects (by  $15 \pm 1$  beats/min and  $13 \pm 2$  mm Hg, respectively;  $n = 58$ ) but did not alter systolic blood pressure in either group of individuals. The pretreatment with desipramine had no effect on blood pressure at rest, but increased heart rate at rest in normotensive (by  $13 \pm 4$  beats/min;  $n = 11$ ) and hypertensive subjects (by  $13 \pm 3$  beats/min;  $n = 14$ ). The drug also tended to increase heart rate responses and to reduce diastolic blood pressure responses to standing in both groups of subjects.

The results of the measurements of plasma norepinephrine and DOPEG obtained after 30 minutes of recumbency, sitting, and standing are depicted in Figure 1. At supine rest as well as during sitting and standing, hypertensive subjects had plasma norepinephrine concentrations that, although tending to be higher, did not differ from those in the control sub-

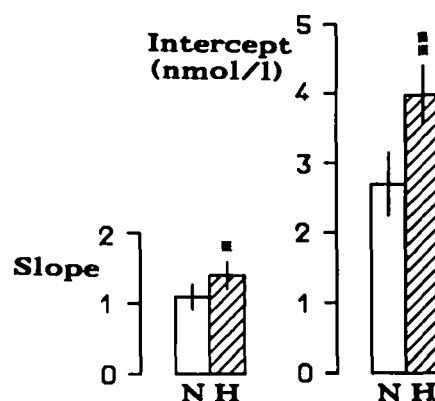


FIGURE 2. Bar graphs showing slope and ordinate intercept of regression line relating plasma dihydroxyphenylglycol (DOPEG) to plasma norepinephrine (see Figure 1) in 47 normotensive control (N) and 58 essential hypertensive (H) subjects. Results were obtained by the method of least squares in each individual subject. Shown are arithmetic means  $\pm 95\%$  confidence limits. Asterisks indicate group differences: \* $p < 0.02$ ; \*\* $p < 0.01$ .

jects. However, under all three conditions, hypertensive subjects exhibited higher plasma DOPEG concentrations than did normotensive subjects (Figure 1). There was no group difference with respect to the plasma norepinephrine responses to upright posture: the increase in plasma norepinephrine ( $\Delta$ NE) induced by sitting and that induced by changing the position from sitting to standing amounted to  $0.636 \pm 0.099$  and  $0.973 \pm 0.105$  nmol/l, respectively, in normotensive subjects and to  $0.727 \pm 0.060$  and  $1.068 \pm 0.094$  nmol/l, respectively, in hypertensive subjects. The increase in plasma DOPEG ( $\Delta$ DOPEG) induced by sitting was likewise similar in the two groups (normotensive subjects,  $0.636 \pm 0.104$  nmol/l; hypertensive subjects,  $0.787 \pm 0.101$  nmol/l), whereas the  $\Delta$ DOPEG produced by changing the position from sitting to standing was higher in hypertensive subjects than in control subjects ( $1.598 \pm 0.150$  versus  $1.087 \pm 0.145$  nmol/l;  $p < 0.02$ ).

Figure 1 illustrates a linear relation between plasma DOPEG and plasma norepinephrine in both groups of subjects. This is likewise substantiated by the observation that the ratio of  $\Delta$ DOPEG/ $\Delta$ NE induced by sitting and that induced by changing the position from sitting to standing were virtually identical both in normotensive ( $0.807 \pm 0.676$  versus  $0.795 \pm 0.493$ ) and hypertensive subjects ( $1.596 \pm 0.303$  versus  $1.551 \pm 0.251$ ). Therefore, the three data points (see Figure 1) obtained in each subject were used to calculate individual ordinate intercepts and slopes of the regression of plasma DOPEG on plasma norepinephrine by the method of least squares. The results indicate steeper slopes and higher ordinate intercepts in hypertensive than in normotensive subjects (Figure 2).

The results obtained in those 11 normotensive control and 14 hypertensive subjects who were given

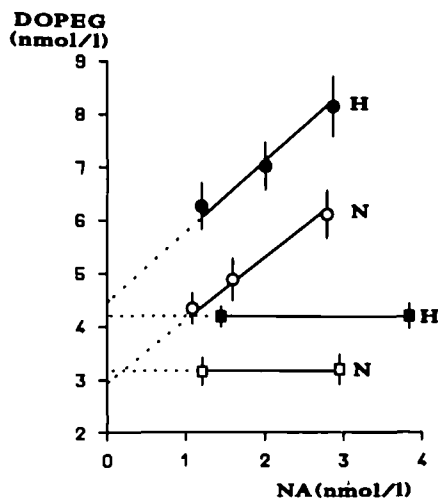


FIGURE 3. Plotting of relation between plasma dihydroxyphenylglycol (DOPEG) and plasma norepinephrine concentrations in 11 normotensive (N) (open symbols) and 14 hypertensive (H) (filled symbols) subjects both under control conditions (circles) and 3 hours after oral administration of 1.5 mg/kg desipramine (squares). Data points obtained in absence of desipramine represent (from left to right) results after 30 minutes of recumbency, 30 minutes of sitting, and 30 minutes of standing, respectively, whereas those obtained in the presence of desipramine show results after 30 minutes of recumbency (left point) and 30 minutes of standing (right point). Shown are arithmetic mean  $\pm$  SEM for plasma DOPEG. The hypertensive-normotensive difference in plasma DOPEG was statistically significant both in the absence and presence of desipramine ( $p < 0.01$ ). NA, norepinephrine.

desipramine are shown in Figure 3. Desipramine did not alter plasma norepinephrine concentrations and had no effect on the plasma norepinephrine response to upright posture in either group of subjects. The standing-induced  $\Delta$ NE observed in the absence and presence of desipramine was  $1.698 \pm 0.208$  and  $1.745 \pm 0.329$  nmol/l, respectively, in normotensive subjects and  $1.663 \pm 0.196$  and  $2.396 \pm 0.529$  nmol/l, respectively, in hypertensive subjects. By contrast, desipramine reduced plasma DOPEG at supine rest (by  $1.152 \pm 0.142$  and  $2.071 \pm 0.306$  nmol/l in normotensive and hypertensive subjects, respectively;  $p < 0.02$ ) and abolished the plasma DOPEG response to upright posture (i.e., decreased the standing-induced  $\Delta$ DOPEG in normotensive and hypertensive subjects, from  $1.791 \pm 0.206$  to  $0.046 \pm 0.087$  and  $1.895 \pm 0.270$  to  $0.022 \pm 0.086$  nmol/l, respectively). The average plasma DOPEG concentration observed in the presence of desipramine was lower in normotensive than in hypertensive subjects ( $3.183 \pm 0.267$  versus  $4.201 \pm 0.209$  nmol/l;  $p < 0.01$ ); these values did not differ from the corresponding ordinate intercepts of the regressions of plasma DOPEG on plasma norepinephrine in the absence of desipramine ( $2.933 \pm 0.212$  versus  $4.442 \pm 0.312$  nmol/l;  $p < 0.01$ ) (Figure 3). In other words, the group difference with respect to plasma DOPEG persisted after

pretreatment with desipramine. When the desipramine-resistant plasma DOPEG is expressed in percent of the total plasma DOPEG observed at supine rest, there was no difference between normotensive ( $73.2 \pm 2.7\%$ ) and hypertensive subjects ( $69.0 \pm 3.4\%$ ).

The results of Figure 3 indicate that the ordinate intercept of the regression line relating plasma DOPEG to plasma norepinephrine reflects that part of plasma DOPEG that remains after desipramine administration. If this is accepted, individual regression lines can be used to calculate, for the total of the two groups, the desipramine-sensitive amount of plasma DOPEG as well as the proportion characterizing the desipramine-resistant part of plasma DOPEG at any given plasma norepinephrine concentration. The results obtained at a norepinephrine concentration of 1.25 and 3.0 nmol/l (i.e., the overall mean plasma norepinephrine of all subjects at supine rest and during standing, respectively) show that the desipramine-sensitive plasma DOPEG was smaller in normotensive than in hypertensive subjects ( $1.297 \pm 0.082$  versus  $1.740 \pm 0.116$  nmol/l at rest and  $3.177 \pm 0.200$  versus  $4.177 \pm 0.278$  nmol/l during standing;  $p < 0.02$  for both differences) and that the percent contribution of the desipramine-resistant DOPEG to total plasma DOPEG was very much the same in the two groups ( $66.8 \pm 2.6\%$  versus  $68.0 \pm 2.2\%$  at rest and  $48.5 \pm 2.6\%$  versus  $49.8 \pm 2.4\%$  during standing).

### Discussion

In vitro experiments with various tissue preparations have shown that the primary norepinephrine metabolite DOPEG is formed predominantly through the actions of presynaptic monoamine oxidase and aldehyde reductase (i.e., within noradrenergic neurones).<sup>14-17</sup> According to these results, there are two sources of DOPEG formation: 1) DOPEG formed from norepinephrine leaking out of the transmitter storage vesicles into the axoplasm ("leakage source") and 2) DOPEG formed from synaptic norepinephrine after its uptake or reuptake into the neurone ("reuptake source"). Although the latter source of DOPEG formation runs dry when neuronal uptake is blocked by, for example, desipramine, the former does not. On the other hand, the leakage source of DOPEG formation is stimulated by the acute inhibition of vesicular uptake (i.e., by reserpine-like drugs) but abolished after depletion of the norepinephrine stores by these agents.

Recent evidence suggests that these considerations also apply to the in vivo condition (i.e., to DOPEG that appears in circulating plasma of rats,<sup>20,27,28</sup> rabbits,<sup>21,29,30</sup> and humans<sup>23-25</sup>). In these in vivo studies, which disclosed very few species differences, changes in plasma DOPEG were linearly related to changes in plasma norepinephrine when the sympathetic activity was varied by administration of clonidine, yohimbine, or vasodilator drugs (animals and humans), or by graded orthostasis (humans). Irrespective of whether the sampling site was peripheral venous (human), mixed-central venous (human, rabbit), or

arterial (rabbit, rat), the slope of the regression line relating plasma DOPEG (ordinate) to plasma norepinephrine (abscissa) was about unity. After administration of desipramine, plasma DOPEG was reduced and increases in plasma DOPEG induced by increases in norepinephrine release were abolished; the plasma concentration of DOPEG then observed did not change with plasma norepinephrine and was virtually identical with the ordinate intercept of the regression of plasma DOPEG on plasma norepinephrine under control conditions. Thus, increases in plasma DOPEG associated with increases in norepinephrine release originate entirely from neuronally recaptured norepinephrine (i.e., from the reuptake source of DOPEG formation), whereas the DOPEG concentration remaining after desipramine administration is independent of the extent of norepinephrine release and reflects that part of plasma DOPEG that is derived from the leakage source of DOPEG formation.

The present results confirm these *in vivo* observations and provide evidence to show that patients with essential hypertension have elevated plasma DOPEG concentrations both at supine rest and during upright posture. This hypertensive-normotensive difference in plasma DOPEG was more pronounced the higher the plasma norepinephrine concentration during orthostasis, and the difference persisted after administration of desipramine. In other words, the desipramine-sensitive and the desipramine-resistant components of plasma DOPEG (which are reflected by the slope and intercept of the regression of plasma DOPEG on plasma norepinephrine, respectively) contributed to the observed hypertensive-normotensive difference in plasma DOPEG. These results strongly suggest that the enhanced DOPEG appearance in plasma of essential hypertensive subjects originates from both the reuptake source and the leakage source of DOPEG formation.

It has been proposed that the plasma DOPEG concentration obtained by extrapolation of the linear relation between plasma DOPEG and plasma norepinephrine to zero plasma norepinephrine stems, at least in part, from noradrenergic neurones within the central nervous system.<sup>31</sup> This has been questioned and thoroughly discussed by Eisenhofer and coworkers.<sup>20</sup> These authors pointed out that a significant contribution by the central nervous system to the plasma pool of DOPEG should result in the plasma DOPEG after desipramine administration to be significantly lower than the plasma DOPEG at zero plasma norepinephrine. The present results show these two values of plasma DOPEG to be virtually identical both in hypertensive and normotensive subjects. Thus, the hypertensive-normotensive difference in plasma DOPEG observed here appears to be derived predominantly from peripheral sources of presynaptic DOPEG formation. Of these peripheral sources, the contribution by the sympathetic nerves supplying the forearm vasculature is probably over-

represented because arteriovenous increments in plasma DOPEG across the forearm (from which venous blood was sampled) of 6–10%<sup>23,25</sup> indicate some net formation of DOPEG in the forearm circulation.

Our conclusion that essential hypertension is associated with an enhanced DOPEG formation requires certain assumptions. These include a lack of difference between the hypertensive and normotensive control groups in 1) the total-body plasma clearance of DOPEG, 2) the fractional forearm extraction of arterial DOPEG, and 3) possible changes in the plasma clearance and forearm extraction of DOPEG induced by upright posture. Unfortunately, the evidence available to verify these assumptions is very limited indeed. A reduced plasma DOPEG clearance in essential hypertension would lead to an increase in the desipramine-sensitive as well as desipramine-resistant component of plasma DOPEG and, thus, could help to explain our results. However, although nothing is known about the plasma clearance of DOPEG in humans, several authors have demonstrated not only the plasma clearance of norepinephrine to be similar in hypertensive and normal subjects,<sup>22,32–34</sup> but also those of epinephrine<sup>35</sup> and isoprenaline.<sup>34</sup> That is why we consider it rather unlikely that hypertensive and normotensive subjects differ substantially with respect to the plasma clearance of DOPEG. As far as assumptions 2 and 3 are concerned, we are not aware of any report dealing with hypertensive-normotensive differences related to these assumptions. Therefore, the following discussion will neglect possible sources of error introduced by our inability to validate the above assumptions and will concentrate on identifying possible reasons for the enhanced DOPEG formation in essential hypertension.

One possible explanation for the increased DOPEG formation in our group of hypertensive subjects is a defect in the amine transport system associated with the transmitter storage vesicles. A deficiency in vesicular function would increase both the net leakage of norepinephrine from the storage vesicles and the proportion of neuronally recaptured norepinephrine that is transformed to DOPEG and thus account for the observed increase in the desipramine-resistant and desipramine-sensitive component of plasma DOPEG. Results obtained in the isolated rat vas deferens,<sup>36</sup> the conscious rat,<sup>20</sup> and the anesthetized rabbit<sup>21</sup> show that about 25% of the recaptured norepinephrine is metabolized to DOPEG. An increase in this percentage and an increase in vesicular norepinephrine net leakage would cause the norepinephrine stores to eventually run empty unless the vesicular dysfunction is counterbalanced by an increase in norepinephrine synthesis. Although there is little, if any, direct evidence in essential hypertension,<sup>1,5</sup> a hastened norepinephrine turnover has been demonstrated in various types of animal hypertension.<sup>1</sup>

The observed enhancement in the plasma DOPEG concentration of hypertensive subjects may likewise be a consequence of an increased efficiency of neuronal norepinephrine reuptake. This would cause the desipramine-sensitive DOPEG formation to increase but leave the desipramine-resistant component unaltered. There is circumstantial evidence consistent with the view that the capacity of neuronal uptake is increased in essential hypertension. Cocaine, also an inhibitor of neuronal uptake, produces a more pronounced leftward shift of the concentration-effect curve to norepinephrine in small subcutaneous arteries from patients with essential hypertension than in the same kind of vessels from normotensive control subjects.<sup>37,38</sup> An enhanced cocaine-induced supersensitivity to norepinephrine was also demonstrated in small mesenteric arteries from SHR.<sup>39</sup> The sensitizing effect of cocaine on the contractile responses to norepinephrine is known to be dependent on the density of noradrenergic innervation.<sup>40</sup> Therefore, the results quoted above<sup>37-39</sup> may well be interpreted to mean that both human essential hypertension and spontaneous hypertension in the rat are associated with an increased noradrenergic innervation of vascular tissue. In fact, the evidence obtained in SHR points toward a hypernoradrenergic innervation of vascular tissue in this animal type of primary hypertension.<sup>6</sup> An enhanced density of sympathetic innervation would explain not only the increase in the desipramine-sensitive component of DOPEG formation (see above) but also the increase in the desipramine-resistant DOPEG formation, since the available number of storage vesicles from which norepinephrine leakage can occur is likely to be increased under this condition. Moreover, although a larger number of nerve varicosities is expected to bring about a larger release of norepinephrine, the enhanced capacity of neuronal reuptake will tend to reduce the norepinephrine spillover into plasma and, thus, mask the anticipated increase in plasma norepinephrine. This could be why we and others<sup>8,9</sup> did not find significantly elevated plasma norepinephrine concentrations in essential hypertension. It is proposed that an increase in norepinephrine release from more densely innervated resistance vessels is best reflected by an increase in DOPEG formation.

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