Renin-Hyporesponsiveness in Essential Hypertension Dissociation Between Plasma Renin and Catecholamines or Aldosterone Following Furosemide

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Summary. The influences of sequential stimulation with upright posture and sodium depletion by intravenous furosemide on blood levels of norepinephrine, epinephrine, dopamine, renin and aldosterone was studied in 26 normal subjects and 45 patients with borderline (N=20) or established (N=25) essential hypertension. Basal 24-h urinary sodium, norepinephrine and epinephrine excretion rates and basal (supine) plasma catecholamine, renin and aldosterone levels and the body sodium-volume state were comparable between the three groups. Assumption of the upright posture for 10 to 60 min caused significant increases in plasma norepinephrine (P<0.001), epinephrine (P<0.001) or dopamine (P<0.05) levels. Upright plasma catecholamine concentrations were similar in normal and hypertensive subjects and they were not modified further by furosemide. In contrast upright posture as well as furosemide induced each a successive significant (P<0.02) increase in plasma renin and aldosterone levels. Furosemide-stimulated plasma renin was significantly (P<0.05) lower in patients with established hypertension than in normal or borderline hypertensive subjects; however, plasma aldosterone levels were comparable. These findings suggest that renin release induced by furosemide is not mediated by increased adrenergic activity. Consequent...
The sympathetic nervous system and the renin-angiotensin-aldosterone axis are both activated by upright posture, the former acutely within seconds to minutes [1,2] and the latter more slowly within minutes to hours [3]. Furthermore, reduction in sodium intake to less than 3 g/day causes parallel increases in the plasma levels of renin and aldosterone as well as in plasma and urinary catecholamines [2,4,5]. This suggested that renin release during upright posture or sodium depletion is partly mediated by a rise in adrenergic nervous activity. However, another stimulus of renin release [6,7], namely acute administration of potent diuretics caused only a mild increase in plasma norepinephrine [8], while urinary norepinephrine excretion was reported to remain unchanged [9]. This raises the question whether the sympathetic and the renin-angiotensin systems may be dissociated under certain conditions. The recent development of sensitive radioenzymatic methods [10] has provided the necessary basis for the evaluation of circulating norepinephrine as well as epinephrine and dopamine levels.

It has been postulated that subtle abnormalities in plasma renin and catecholamine levels may play a pathogenic role in essential hypertension. Considering age as a factor, circulating renin, norepinephrine and epinephrine are normal in the majority of such patients [11-14]. However, subgroups with increased or decreased values have been described [15-17]. Certain authors related the abnormalities in circulating renin to parallel variations in adrenergic nervous activity [18,19], but this concept is not generally accepted [8]. Stimulation by upright posture and the acute administration of a potent diuretic have been used as a sensitive approach for detection of altered renin release in essential hypertension [6,7,20]. The present study was undertaken to assess the responses of plasma norepinephrine, epinephrine, dopamine, renin and aldosterone levels to upright posture and to acute salt depletion by furosemide in normal subjects and patients with borderline or established essential hypertension.

Subjects and Methods

Twenty-six normal subjects and 45 patients with benign essential hypertension were studied. The normal subjects included eight females and 18 males, ranging in age from 20 to 68 years (mean 39±17 ±SD years). All were normal volunteers in good health, with a blood pressure consistently below 140/90 mm Hg. The hypertensive patients included 11 females and 34 males, ranging in age from 18 to 65 years (mean 43±14 years). Secondary hypertension was excluded by the usual tests. Hypertension was always benign, and no patient had congestive heart failure or relevant renal functional impairment (plasma creatinine >1.3 mg/100 ml). Antihypertensive drugs were withdrawn four weeks before study and replaced by placebo tablets. Based on blood pressure values obtained under placebo conditions, the patients were divided into 20 with borderline hypertension as defined by blood pressure ranging from 141/91 mm Hg to 159/94 mm Hg and sometimes below [21]; and 25 with established hypertension (>160/95 mm Hg). Mean ages in the two hypertensive subgroups were 39±16 and 45±11 years, respectively.

To avoid very high sodium intake, subjects were instructed to ingest a normal diet but without very salty foods or adding salt to their food [14]. Following the oral administration of approximately 60 µCi of 24Na between 8:00 and 8:30 A.M., a 24 h urine was collected for the determination of 23Na, 24Na, potassium, creatinine, norepinephrine and epinephrine excretion rates. At the end of the collection period, blood pressure, pulse rate, plasma sodium, potassium, creatinine, renin activity (PRA), aldosterone (PA), norepinephrine (PNE), epinephrine (PE) and dopamine (PD) levels, exchangeable body sodium and blood volume were measured between 8 and 9 A.M. after one hour of recumbancy, according to our standard procedure [14,22]. Indwelling intravenous cannulas were inserted at least 30 min before the initial blood sampling.

Blood pressure, pulse rate, PNE, PE and PD were again determined following 10 min of passive standing and 60 min of ambulation, PRA and PA were obtained following 60 min of passive standing and 60 min of ambulation. The patients then emptied their bladder and furosemide, 0.45 mg/kg body weight was injected intravenously; measurements of blood pressure, pulse rate, PRA, PA, PNE, PE and PD were repeated after an additional hour of ambulation, and urine collected during this hour was used for determination of sodium, potassium, creatinine, norepinephrine and epinephrine excretion rates.

Blood pressure was measured using standard cuff and sphygmomanometer. Each blood pressure was the mean of three recordings. The mean blood pressure was calculated as the sum of the diastolic (disappearance of sounds) and one third of the pulse pressure. Plasma and urinary sodium and potassium concentrations were determined by flame photometer, creatinine levels by autoanalyzer, PRA [23] and PA [24] by radioimmunoassay and catecholamines in urine with a fluorometric [25] and in plasma with a radioenzymatic method [10], as described previously from this laboratory [14,26]. For t-test and regression analysis, the natural logarithm transformation of PRA, PA, PNE, PE and PD values or of norepinephrine and epinephrine excretion rates was used.

Results

Basal Conditions

Mean age was similar in the 26 normal subjects and the 20 patients with borderline hypertension (39±17 ±SD yr and 39±16 yr, respectively) and it was only slightly and not significantly higher in the 25 patients with established hypertension (45±11 yr).