Increased Plasma Vasopressin in Low Renin Essential Hypertension

INGRID OS, SVERRE ERIK KJELDSEN, JOHN SKJØTÖ, ARNE WESTHEIM, KNUT LANDE, INGVAR AAKESSON, PER FREDERICHSEN, PAUL LEREN, INGVAR HJERMANN, AND IVAR K. EIDE

SUMMARY Baseline plasma vasopressin concentrations were measured in 48 men (all 50 years old) with decreased plasma renin concentration and untreated, sustained essential hypertension and in 29 healthy normotensive men. Mean hypertensive plasma vasopressin concentration was more than twice as high as the corresponding normotensive level (15.7 ± 2.2 [SE] vs 7.5 ± 1.0 pg/ml; p < 0.001). Plasma renin concentration in the hypertensive group was reduced compared with that in the normotensive group (0.28 ± 0.04 vs 0.46 ± 0.06 Goldblatt units × 10^{-4}/ml). These differences appeared despite virtually identical serum osmolality, creatinine clearance, and urinary sodium excretion in the two groups. In the first 38 hypertensive subjects, arterial plasma epinephrine concentrations were significantly increased over those of the first 28 control subjects (99 ± 12 vs 68 ± 6 pg/ml; p < 0.025). In contrast to those with low renin essential hypertension, 35 men with normal renin essential hypertension (all 40 years old) had normal plasma vasopressin levels that were not significantly different from those in a comparable normotensive control group (3.7 ± 0.8 vs 3.5 ± 0.4 pg/ml). Arterial epinephrine concentrations were not significantly different between normal renin subjects and the control group. After 6 weeks of treatment with the nonselective β-adrenergic receptor blocker oxprenolol in 11 subjects with low renin hypertension, blood pressure was reduced and the plasma vasopressin concentration fell from 27.6 ± 6.4 to 13.5 ± 4.2 pg/ml (p < 0.01). After 6 weeks of treatment with the β₁-selective agent atenolol in another 11 men with low renin hypertension, plasma vasopressin level fell from 16.3 ± 3.3 to 13.1 ± 3.1 pg/ml, but this reduction was not significant. In pooled groups treated with β-adrenergic blockade, plasma vasopressin level decreased more the higher its initial concentrations (r = 0.79, p < 0.001, n = 22). These findings suggest that plasma vasopressin is increased in low renin essential hypertension and may be related to sympathetic adrenal overactivity. (Hypertension 8: 506–513, 1986)

KEY WORDS • blood pressure • catecholamines • sodium • osmolality • β-adrenergic blockade • pituitary • antidiuretic hormone

ARGININE vasopressin (AVP) may increase blood pressure primarily by volume retention, but it is also a powerful vasoconstrictive agent, even more potent than angiotensin. It may also participate in cardiovascular regulation, both centrally and peripherally, and stimulate the gain of baroreceptor reflexes. Potentiation of the vasoconstrictor effect of catecholamines has been established.

Arginine vasopressin has been implicated in the pathogenesis of different types of experimental hypertension, especially in the sodium-dependent forms with mineralocorticoid excess. Deoxycorticosterone-salt hypertension will not develop in the Brattleboro rat, which lacks AVP because of a genetic defect. Blockade by either specific antiserum or competitive antagonists of AVP substantially attenuates both the development and severity of preexisting deoxycorticosterone-salt hypertension. Most recently, observations by Haywood et al. point to the sympathetic nervous system and AVP as the critical factors responsible for mediating the hypertension in sodium-dependent hypertension.

In contrast, there are few studies of plasma AVP in human essential hypertension, and these seem controversial. Although both Padfield et al. and Shimamoto et al. found normal AVP levels in essential hypertension, Cowley et al. reported that average levels were almost twice as high in hypertensive patients over 50 years of age as compared with their younger counterparts. There may be several reasons...
for these divergent results, including differences in the materials and subjects examined. In our opinion, since low renin hypertension has been termed volume-dependent and is associated with increased mineralocorticoid activity, the already cited experimental evidence implies that an increase in AVP should most reasonably be sought specifically in the low renin patients. This hypothesis was recently suggested by Skjøtt et al., but is by no means self-evident, since this hormone is a strong vasoconstrictive substance and might rather be increased in the high renin, so-called vasoconstrictor variety of essential hypertension.

The aim of the present study was, first, to test our hypothesis in patients with essential hypertension at different levels of plasma renin and, second, to correlate the concentrations of circulating AVP with the simultaneous sympathetic adrenal tone.

**Subjects and Methods**

**Hypertensive Subjects**

**Low Renin Essential Hypertension**

Forty-eight men, all 50 years old with untreated, sustained essential hypertension of World Health Organization (WHO) Group I classification, were selected from the ongoing Oslo Study of Cardiovascular Diseases. This was a random, examiner-blind selection undertaken by one of us (S.E.K.) according to three inclusion criteria: 1) male sex, 2) age 50 years, and 3) hypertension. Subjects were selected from the checklists of control (untreated) hypertensive subjects, and 50 years of age was chosen to obtain subjects with an average plasma renin concentration (PRC) lower than that of a comparable normotensive control group (see the section on the control group), since the proportion of subjects with low renin is known to increase with age (see Discussion). This selection procedure was completely devoid of any bias or prejudice conveyed by a priori knowledge of already measured data. All chosen subjects completed the study.

Ten years before the present investigation the subjects had systolic blood pressure below 150 mm Hg and diastolic blood pressure above 95 mm Hg. At the time of the present study, they had stable blood pressure above 150/100 mm Hg. Further characteristics, including heart rate, weight, electrolytes and osmolality, are given in Table 1. They had normal electrocardiograms, and their kidney function was normal as estimated by creatinine clearance and urinalysis.

**Normal Renin Essential Hypertension**

Thirty-five men, all 40 years old with untreated, essential hypertension of WHO Group I, were selected from the ongoing Oslo Study of Cardiovascular Diseases. A random selection was undertaken exactly as just described for the low renin subjects by two of us (I.O. and S.E.K.), but the age stratum was changed to 40 years to obtain subjects with an average PRC similar to or higher than that of a comparable normotensive control group, since the proportion of normal or even high renin subjects is known to increase at a lower age than that seen with low renin concentrations (see Discussion). As in the low renin group, this selection took place well ahead of any assays of biochemical parameters (e.g., PRC and AVP). All chosen subjects completed the study.

Two years before the present investigation the subjects had systolic blood pressure between 140 and 170 or diastolic blood pressure above 90 and 100 mm Hg, or both. They were included if diastolic blood pressure had remained stable between 94 and 105 mm Hg on two separate occasions and if systolic blood pressure exceeded 150 mm Hg. Further characteristics, including heart rate, weight, electrolytes, and osmolality, are given in Table 2. They had normal electrocardiograms, and kidney function was normal as estimated by creatinine clearance and urinalysis.

**Normotensive Control Subjects**

The two control groups consisted of twenty-nine 50-year-old and forty-four 40-year-old healthy men drawn from among the normotensive control subjects of the

**Table 1. Characteristics of Low Renin Hypertensive Subjects and Their Normotensive Controls**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hypertensive (n = 48)</th>
<th>Normotensive (n = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>181.2 ± 0.8</td>
<td>181.0 ± 1.1</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>88.1 ± 1.5*</td>
<td>78.9 ± 1.6</td>
</tr>
<tr>
<td>Supine blood pressure (mm Hg)</td>
<td>155 ± 2/107 ± 1</td>
<td>126 ± 1/86 ± 1</td>
</tr>
<tr>
<td>Supine heart rate (beats/min)</td>
<td>64 ± 2†</td>
<td>58 ± 1</td>
</tr>
<tr>
<td>Serum osmolality (mosm/kg)</td>
<td>287 ± 1</td>
<td>286 ± 1</td>
</tr>
<tr>
<td>Serum Na+ (mmol/L)</td>
<td>139.6 ± 0.2‡</td>
<td>138.8 ± 0.3</td>
</tr>
<tr>
<td>Urine Na+ (mmol/24 hours)</td>
<td>175 ± 9</td>
<td>183 ± 13</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min)</td>
<td>142 ± 5</td>
<td>130 ± 5</td>
</tr>
</tbody>
</table>

Values are means ± SE. *p < 0.001, †p < 0.01, ‡p < 0.05, compared with values in normotensive group.

**Table 2. Characteristics of Normal Renin Hypertensive Subjects and Their Controls**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hypertensive (n = 35)</th>
<th>Normotensive (n = 44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>179.5 ± 1.0</td>
<td>178.1 ± 0.9</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>83.5 ± 2.0*</td>
<td>75.9 ± 1.6</td>
</tr>
<tr>
<td>Supine blood pressure (mm Hg)</td>
<td>149 ± 2/98 ± 1†</td>
<td>126 ± 1/80 ± 1</td>
</tr>
<tr>
<td>Supine heart rate (beats/min)</td>
<td>65 ± 2†</td>
<td>57 ± 1</td>
</tr>
<tr>
<td>Serum osmolality (mosm/kg)</td>
<td>284 ± 1</td>
<td>285 ± 1</td>
</tr>
<tr>
<td>Serum Na+ (mmol/L)</td>
<td>138.2 ± 0.3</td>
<td>138.8 ± 0.3</td>
</tr>
<tr>
<td>Na+ excretion (mmol/day)</td>
<td>199 ± 15‡</td>
<td>166 ± 8</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min)</td>
<td>146 ± 7</td>
<td>136 ± 6</td>
</tr>
</tbody>
</table>

Values are means ± SE. *p < 0.01, †p < 0.001, ‡p < 0.05, compared with values in normotensive group.
Oslo Study who, both at present and two years or more previously, had blood pressure below 140/90 mm Hg. Tables 1 and 2 show the characteristics of these normotensive men.

**Protocol**

The study was approved by the local ethics committee, and informed consent was obtained from all subjects. They were examined as outpatients and were able to continue their daily work routine. All were familiar with clinical examination, blood pressure recording, and blood sampling. None were addicted to alcohol or taking any drugs. The examinations were performed in the morning between 0800 and 0900; the participants had been fasting and had abstained from smoking, caffeine, and fluid the last 8 hours before the examination. Only one subject was examined each day, and all were examined by the same two physicians.

The subjects rested supine in a quiet room for 30 minutes before systolic and fifth phase diastolic blood pressure were measured with a mercury sphygmomanometer and heart rate was counted. Immediately thereafter, arterial blood for catecholamine assay was sampled after gentle puncture of the femoral artery in the low renin subjects and their controls and the brachial artery in the normal renin subjects and their controls. In both groups venous blood was drawn from the median cubital vein. The blood samples for AVP, catecholamines, and renin were drawn into ice-chilled tubes containing appropriate anticoagulants and centrifuged at 4°C, and the plasma was frozen at -70°C. A 24-hour urine specimen was collected for urinalysis and determination of sodium excretion and creatinine clearance.

**Intervention Trial**

Twenty-two of the 50-year-old hypertensive subjects were randomly allocated to an examiner-blind study of venous AVP and catecholamines during treatment with either atenolol (n = 11) or oxprenolol (n = 11). The two groups were comparable with respect to creatinine clearance, urinary sodium excretion, serum osmolality, blood pressure and heart rate. Oxprenolol hydrochloride (Trasicor), 80 mg, was given once daily. Atenolol (Tenormin), 50 mg, was given daily for 1 week and then twice daily for the next 5 weeks. Atenolol (Tenormin), 50 mg, was given daily for 1 week and then twice daily for the rest of the 6-week period. On the day of examination, 6 weeks after the intervention began, the morning dose was omitted. The examination took place as previously described.

**Analytical Methods**

The blood samples for AVP were drawn into ice-chilled tubes containing Na₂-ethylenediaminetetraacetic acid (EDTA), 5 to 6 mg/ml blood, according to the method of Fyhrquist et al. 8-Arginine vasopressin was measured by radioimmunoassay according to the method of Hammer as recently described. With this assay, the detection limit of AVP was 0.6 pg per tube. Full-term pregnancy serum was incubated with AVP according to the method of Husain et al. and exerted a degradation of immunoreactive AVP by vasopressinase to below the detection limit. The between-day coefficient of variation was 15% for the complete range of plasma AVP encountered within the present material. As a control for between-day stability, we regularly included a plasma pool slightly above the detection limit and one plasma pool with 20 pg/ml exogenous AVP added for recovery. The overall recovery averaged 67 ± 2%, and all results were corrected for recovery. Buffer blanks carried through the complete procedure had no detectable effect on the final outcome of the assay. The PRC was measured at zero-order kinetics with a surplus of exogenous renin substrate. Plasma catecholamines were determined with a radioenzymatic method as previously reported. In each of these assays, we took care to measure an equal number of hypertensive and normotensive subject plasma samples within each daily setup. Creatinine and electrolytes were determined on a Technicon SMA 12/60 autoanalyzer (Tarrytown, NY, USA) and osmolality on a Fiske OS osmometer (Uxbridge, MA, USA). All assays were undertaken completely examiner-blind.

**Statistics**

The data are presented as means ± SE. Two-tailed statistical analyses were performed with Student’s t test for paired and unpaired comparisons. Correlation coefficients were calculated using the Pearson product-moment formula. Results were considered statistically significant at a p value less than 0.05.

**Results**

**Plasma Vasopressin Concentration and Blood Pressure**

**Low Renin Hypertension**

Mean venous plasma AVP concentration was more than two times higher in the 48 low renin hypertensive subjects than in the 29 normotensive subjects (15.7 ± 2.2 vs 7.5 ± 1.0 pg/ml; p < 0.001; Figure 1). Over 70% of the hypertensive values exceeded the normotensive median of 6.2 pg/ml. This difference appeared despite virtually identical serum osmolality, creatinine clearance, and urinary sodium excretion in the two groups (see Table 1). Over the entire blood pressure range (i.e., normotensive and hypertensive pressures taken together; n = 77), there were statistically significant correlations between plasma AVP and either systolic (r = 0.40, p < 0.001), diastolic (r = 0.41), or mean blood pressure (r = 0.42; Figure 2). The correlations apparently were not linear, however, and most probably should not be calculated as such.

**Normal Renin Hypertension**

No significant difference in AVP concentration appeared between the group with normal renin hypertension and the normotensive control group, either in arterial or venous plasma despite a slightly higher arterial level, which we consider the more sensitive of the two
Venous plasma vasopressin (AVP) levels and plasma renin concentration (PRC) in 50-year-old subjects with low renin essential hypertension (HT) and normotensive controls (NT). Values are means ± SE. GU = Goldblatt units.

Figure 1. Venous plasma vasopressin (AVP) levels and plasma renin concentration (PRC) in 50-year-old subjects with low renin essential hypertension (HT) and normotensive controls (NT). Values are means ± SE. GU = Goldblatt units.

Figure 2. Blood pressure plotted against venous plasma vasopressin (AVP) levels in the pooled groups of 50-year-old hypertensive and normotensive control subjects. Values are means ± SE.

Venous difference of plasma AVP was higher in the hypertensive group (0.8 ± 0.7 vs 0.04 ± 0.21 pg/ml), this difference also was not significant.

Plasma Vasopressin and Renin Concentrations
In the low renin hypertensive group, PRC was considerably reduced (0.28 ± 0.04 Goldblatt units [GU] x 10^{-4}/ml) and averaged only 62% of the concentration in the control subjects (0.46 ± 0.06 GU x 10^{-4}/ml; see Figure 1). Seventy-five percent of the hypertensive values were below the normotensive median of 0.42 GU x 10^{-4}/ml. The low PRC appeared concomitantly with the high AVP levels and despite similar urinary sodium excretion rates. In the normal renin hypertensive group, the average PRC was 0.37 ± 0.05 GU x 10^{-4}/ml and was not significantly different from the 0.35 ± 0.03 GU x 10^{-4}/ml seen in the control group (see Figure 3). No correlation was found between PRC and AVP or between blood pressure and PRC.

Plasma Vasopressin and Catecholamine Concentrations
Low Renin Hypertension
Arterial plasma catecholamines were measured in 38 subjects with low renin hypertension and 28 normotensive controls (Figure 4). Arterial epinephrine concentration was increased in the hypertensive subjects as compared with the normotensive group (99 ± 12 vs 68 ± 6 pg/ml; p < 0.05). A small increment was seen as well for arterial norepinephrine concentration (273 ± 15 vs 250 ± 8 pg/ml), but this difference was not significant. However, arterial norepinephrine concentration correlated positively with heart rate both in the pooled groups (r = 0.44, p < 0.001, n = 66) and in the hypertensive group alone (r = 0.50, p < 0.01, n = 38).
The hypertensive group had a mean heart rate of 64 ± 2 (n = 48) as compared with 58 ± 1 beats/min in the normotensive group (n = 29, p < 0.01).

Normal Renin Hypertension

Arterial epinephrine concentration in the 35 normal renin hypertensive subjects averaged 91 ± 16 pg/ml, which was not significantly higher than the 72 ± 4 pg/ml seen in the 44 normotensive subjects. On the other hand, heart rate averaged 65 ± 2 beats/min in the hypertensive subjects, which was significantly higher than the 57 ± 1 beats/min seen in the normotensive group (p < 0.001). As in the low renin hypertensive subjects, arterial norepinephrine concentrations were slightly, but not significantly, higher in the normal renin subjects than in their corresponding controls (213 ± 10 vs 192 ± 6 pg/ml).

Plasma Vasopressin Concentration and β-Adrenergic Receptor Blockade

Twenty-two subjects with low renin hypertension were randomly allocated to treatment with two different β-blockers. After 6 weeks of treatment with the nonselective β-adrenergic blocker oxprenolol (n = 11), blood pressure was reduced from 162 ± 4/112 ± 2 to 141 ± 5/95 ± 2 mm Hg and AVP decreased from 27.6 ± 6.4 to 13.5 ± 4.2 pg/ml (p < 0.01). With the β1-selective agent atenolol (n = 11), blood pressure was reduced from 162 ± 3/109 ± 3 to 138 ± 3/92 ± 2 mm Hg while AVP levels changed from 16.3 ± 3.3 to 13.1 ± 3.1 pg/ml (NS). The extent of AVP reduction during β-blockade emerging from the pooled data with both blockers increased in parallel with basal plasma AVP levels (r = 0.73, p < 0.001, n = 22; Figure 5).

Although neither of the β-blockers had any effect on norepinephrine or epinephrine concentration, both significantly increased venous plasma-free dopamine concentrations: from 21 ± 3 to 42 ± 2 pg/ml (p < 0.001) for atenolol and from 23 ± 4 to 42 ± 4 pg/ml for oxprenolol (p < 0.02).

Plasma Vasopressin Concentration, Sodium Level, and Weight

Both the low renin and the normal renin hypertensive groups were significantly heavier than their corresponding controls. For both, however, the weight difference from their corresponding control group was similar (see Tables 1 and 2). Since plasma AVP concentration was increased in one and normal in the other of the two hypertensive groups, it is not likely that weight had any appreciable influence on plasma AVP. The low renin hypertensive group had a significant tendency for sodium retention with an increased serum sodium concentration but no increase in urinary sodium excretion (see Table 1). The opposite was true in the normal renin hypertensive group, which had normal serum concentration and increased urinary sodium excretion (see Table 2).

Discussion

Several factors stimulate the secretion of AVP. One of the most important is serum osmolality,26 which was found to be similar in the present study in both hypertensive and normotensive subjects. Potential moderators of AVP secretion are sodium balance15, 27 and age,28 but neither age nor sodium balance could explain the greater than twofold increase in plasma AVP concentration in the low renin hypertensive group as compared with their corresponding control group. Arterial plasma concentrations of epinephrine were increased in the low renin hypertensive group compared with their corresponding control group, as was heart rate. Venous plasma AVP concentrations increased with rising blood pressure.
At first glance, AVP levels in both our low renin hypertensive and control subjects might seem inappropriately high. The AVP levels, however, conform rather precisely with those reported by Cowley et al. To our knowledge, theirs is the only report using age contrasts with some previous reports.

Baseline plasma AVP may be smaller than presently reported. For example, we know from our own study that plasma AVP in normal subjects trebles when age increases from 25 to 50 years. Even between the ages of 40 and 50 years AVP concentration doubled. Moreover, the plasma AVP concentration seen in our 40-year-old control subjects conforms rather precisely to that of 40-year-old normotensive men in a recent study by Cowley et al. Nevertheless, this matter is controversial, and we are aware that other reports suggest the age impact on baseline plasma AVP may be smaller than presently reported.

The present increment in hypertensive AVP levels contrasts with some previous reports. On the other hand, Khokhar and Slater reported that urinary AVP concentration was increased in patients with mild hypertension and Cowley et al. found that hypertensive subjects were hyperresponsive to increased sodium intake, as evidenced by a marked elevation of AVP. One reason for discordance between reports might be differences in the examined hypertensive groups. First, one of the cited studies had a wide within-group age range. As recently shown, plasma AVP concentrations may be significantly influenced by age.

Second, our subjects with high levels of AVP were characterized by low PRC. It has been known for more than 10 years that patients with essential hypertension may be considered as high, normal, or low renin hypertensive. According to early publications, patients with low renin hypertension have higher extracellular fluid volumes than others. The low renin patients accordingly were named volume-dependent. Such volume dependence could be explained by primary renal sodium retention or increased secretion of adrenocortical sodium-retaining substances. Another, quite recently addressed hypothesis is the possibility that increased posterior pituitary release of antidiuretic hormone causes renal water retention in low renin hypertension.

Much of the available experimental evidence seems to support a role for AVP, since several types of experimental hypertension that are volume-dependent either will not develop or will be ameliorated by different modes of AVP inhibition. There is, however, some doubt whether extracellular volume or exchangeable sodium is actually increased in the low renin, so-called volume-dependent hypertension. This variety mostly occurs in the relatively older hypertensive patient, who is not typically hyperkinetic but rather tends to have increased peripheral resistance.

Furthermore, there is also evidence that high renin hypertension is not specifically vasoconstrictive. Rather, this kind of hypertension occurs primarily in the younger patient with a propensity for volume-dependent hyperkinetic hemodynamics (i.e., increased cardiac index and decreased peripheral vascular resistance).

For these reasons, the vasoconstrictive effect of AVP may be of importance even in low renin hypertensive patients and should be looked for specifically in them. In turn, the low renin concentration may well be related to plasma AVP, since this hormone inhibits renin release. An appropriate question would be whether an AVP concentration of approximately 20 pg/ml is sufficient for a direct vasoconstrictive effect on arterial blood pressure. For example, blood pressure is normal in patients with the syndrome of inappropriate secretion of antidiuretic hormone and plasma AVP concentrations of 50 pg/ml. Nevertheless, the patients with this syndrome have increased peripheral vascular resistance due to AVP while normalcy of blood pressure is only preserved by a secondary decrease in cardiac output. Actually, some investigators have found during infusions in dogs that plasma AVP concentrations even below 20 pg/ml will increase peripheral resistance significantly. For blood pressure to rise, a maintained or even increased cardiac output seems necessary against the vasoconstrictive effect of AVP. One mechanism behind maintained cardiac output might well be increased sympathetic drive, which increases both myocardial contractility and cardiac frequency. At these relatively low concentrations AVP probably will act as a hypertensive agent only against a given background of increased sympathetic tone.

Such a background was provided by the low renin hypertensive subjects in the present study. In these subjects, arterial plasma concentrations of epinephrine were increased, heralding a sympathetic adrenal overdrive. We are aware that increased sympathetic tone has been ascribed almost exclusively to high renin patients. Nevertheless, increased sympathetic tone in low renin patients is not without precedence in the literature, and at least two observations support an increased sympathetic drive in our low renin hypertensive subjects. First, they had a significant increment of both arterial epinephrine concentration and cardiac frequency. Second, their blood pressure decreased toward normal during β-adrenergic blockade.

The effect of β-adrenergic blockade may also provide a clue to the cause of increased plasma AVP. According to Knepley and Meyer, β-adrenergic stimulation with isoproterenol increases AVP release. In our hypertensive subjects, arterial plasma epinephrine was the only significantly increased catecholamine, and is the most probable explanation of why β-adrenergic blockade with oxprenolol significantly decreased the plasma AVP concentration. The reason why AVP was reduced only by the β-blocker with intrinsic sympathomimetic activity most probably lies in the fact that, despite a random allocation, the subjects given oxprenolol had considerably higher plasma AVP concentrations than did the group given atenolol. Thus, the extent of AVP reduction during β-adrenergic blockade
closely correlated with the initial level of plasma AVP. Since β-blockers increase plasma dopamine levels and dopamine inhibits AVP release, this might be an alternative explanation of reduced AVP during β-adrenergic blockade. This alternative is not the most likely, however, since dopamine was equally stimulated by the two β-blockers while only oxprenolol significantly reduced the plasma AVP concentration.

Since the higher renin levels predominate in the younger age groups, we had to step down 1 decade of age (i.e., from 50 to 40 years) to find subjects with an average PRC similar to or higher than that of a comparable normotensive control group. This method provided the necessary number of such subjects but demanded in return a new control group, since plasma AVP concentration is markedly influenced by age. Thus, the age step from 50 to 40 years accounts for about a 50% reduction in peripheral plasma AVP. Also, increased sodium intake (as reflected by sodium excretion) is a major stimulus to pituitary AVP release. However, the difference in sodium excretion from 166 to 199 mmol/day with no significant change in serum sodium in the normal renin hypertensive subjects is clearly too small to have a real impact on plasma AVP.

The PRC in the 40-year-old controls was also slightly lower than that in the 50-year-old control subjects. This difference was due to a small drift in our PRC assay through the years 1980 to 1984. Most of this miniature drift took place when a new batch of renin standard was opened in 1983, but this was balanced by the 40-year-old control group, whose members were recruited and examined and whose plasma samples were taken and assayed in parallel with those of the normal renin hypertensive group.

An interesting paradox might be that since low renin hypertension tends to be mineralocorticoid and thereby volume-retaining, the osmotic threshold for AVP release could have been shifted to the right and plasma AVP thereby decreased. According to our results, such a reduction in AVP did not take place, probably because mineralocorticoid activity leads to slightly increased serum sodium (see Table 1), which (if anything) will only stimulate increased AVP release. Furthermore, since AVP was substantially increased in the low renin hypertensive subjects, a decreased serum osmolality probably would have been expected. Nevertheless, serum osmolality remained unchanged as compared with that of the normotensive control subjects, but again this probably was due to increased mineralocorticoid activity, which tended to decrease serum sodium concentrations and thereby restore serum osmolality.

In our opinion, the increased AVP concentration cannot be readily explained by the higher body weight or by the increased dietary salt intake in the hypertensive subjects; there was no correlation between these two variables and blood pressure. Thus, we conclude that plasma AVP is genuinely increased in low renin hypertension.

Acknowledgments

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