The Role of Vasopressin in Essential Hypertension
Plasma Levels and Effects of the V1 Receptor Antagonist OPC-21268 During Different Dietary Sodium Intakes
Yuhei Kawano, Hiroaki Matsuoka, Toshio Nishikimi, Shuichi Takishita, and Teruo Omae

To study the role of vasopressin (VP) in essential hypertension, we examined plasma levels of VP and blood pressure (BP) response to an orally active V1 receptor antagonist, OPC-21268, in hypertensive patients on diets with different sodium contents. Plasma VP was determined in 12 normotensive subjects and 12 patients with mild essential hypertension on a regular sodium diet, and in eight hypertensive patients on a high sodium (250 mmol/day) and a low sodium (25 mmol/day) diet. BP response was examined for 4 h after single oral administration of OPC-21268 (100 mg) or placebo in eight patients on the regular diet, and in six patients on the high and low sodium diets. In four patients on the regular diet, the effects of OPC-21268 on the baroreflex control of heart rate were also examined with intravenous injections of methoxamine. Plasma VP did not differ between the normotensive and hypertensive subjects. Levels of VP in the plasma was higher in the high sodium than in the low sodium period, but the difference was not significant. BP and heart rate did not change significantly after administration of OPC-21268 or placebo under either condition. OPC-21268 also failed to lower BP in salt-sensitive patients on the high sodium diet. The baroreceptor reflex sensitivity was not modified by the administration of OPC-21268. Our results suggest that VP does not play an important role in mild essential hypertension through its action on the V1 receptors regardless of dietary sodium intake. Am J Hypertens 1997;10:1240 –1244 © 1997 American Journal of Hypertension, Ltd.

KEY WORDS: Hypertension, vasopressin, V1 receptor antagonist, sodium, baroreceptor reflex.

Vasopressin (VP) constricts blood vessels via its action on V1 receptors and decreases urinary water excretion via V2 receptors.1 The release of VP is regulated mainly by changes in osmolality that are dependent on sodium (Na) concentration, although nonosmotic mechanisms such as arterial and cardiopulmonary baroreceptor reflexes are also involved.2 VP may play an important role in the development and maintenance of salt-dependent and malignant forms of hypertension, such as deoxycorticosterone acetate (DOCA)-salt hypertension, reduced renal mass–salt hypertension, and that in stroke-prone spontaneously hypertensive rats (SHR).1,3 The role of VP in the relationship between salt and hypertension was also supported by our previous study of intracerebroventricular hypertonic...
NalCl. Vasopressin is also known to influence the baroreceptor reflex. However, the role of VP in human hypertension has not been clarified in detail. Results regarding plasma VP levels in hypertensive patients are not consistent, with high levels in some studies but normal or low levels in others. In a study using a peptide V1 antagonist, significant decreases in blood pressure (BP) were not observed in hypertensive subjects. The possible involvement of VP in the altered baroreceptor reflex in hypertensive patients is also not clear.

OPC-21268 is an orally active nonpeptide V1 antagonist. This agent can antagonize the vasoconstrictive action of exogenous VP in humans and has been used to study the role of endogenous VP in pathophysiological conditions. To investigate the possible role of VP in essential hypertension, we examined plasma levels of VP and the effects of OPC-21268 on BP in hypertensive patients with special reference to dietary Na intake. We also studied the effects of OPC-21268 on the baroreflex control of heart rate.

**Methods**

**Subjects** Sixteen patients with mild essential hypertension were included in this study. The patients consisted of nine men and seven women, aged from 32 to 66 years (53 ± 3 years, mean ± SE). All of the subjects had systolic BP above 140 mm Hg or diastolic BP above 90 mm Hg on three different occasions, and none had serious cardiac, renal, hepatic, or neurological disorders. All antihypertensive drugs were withdrawn for at least 2 weeks before the study. Twelve healthy normotensive subjects (36 ± 2 years) also participated in this study to determine plasma VP on an ordinary diet.

**Protocol** The study protocol was approved by the Clinical Research Committee of our institute, and informed consent was obtained from each subject. Plasma levels of VP were determined in 12 hypertensive patients and 12 normotensive subjects on a regular salt diet (120 to 170 mmol/day). In the eight hypertensive patients, plasma VP level was measured at the end of the 7-day high-salt period (250 mmol/day) and the 7-day low-salt period (25 mmol/day). Blood samples were obtained after 30 min of bed rest in the morning. BP was measured twice before blood sampling.

Effects of OPC-21268 on BP and heart rate were examined in eight hypertensive patients on the regular salt diet, and in six patients on the high- and low-salt diets. OPC-21268 was given orally at a dose of 100 mg in the morning. This dose has been demonstrated to block the vasoconstriction caused by exogenous VP in humans. It has been shown that the mean $t_{max}$ of this agent is 0.5 to 1.5 h and the mean plasma half life is 1 to 2 h after single oral administration in normal subjects. BP and heart rate were measured every 10 min from 30 min before until to 240 min after administration. On another day, BP was measured before and after administration of placebo in each individual.

The baroreflex control of heart rate was investigated in four hypertensive patients on the regular salt diet. BP and electrocardiograms were monitored continuously. Sixty minutes after oral administration of OPC-21268 (100 mg) or placebo, reflex bradycardia was examined following intravenous injections of methoxamine (2 to 32 µg/kg), an α1 agonist. Sensitivity of the baroreceptor reflex was determined from the changes in systolic BP and R-R interval.

**Measurements** Intermittent measurement of BP was performed by the Korotokoff method using an electronic device (BP-201, Nippon Colin, Komaki, Japan). Continuous noninvasive BP monitoring was carried out with a Jentow-7700 (Nippon Colin) based on arterial tonometry. Blood samples were centrifuged immediately, and aliquots were stored at −20°C until assay. Plasma VP and renin activity (PRA) were determined by radioimmunoassay. Serum and urinary Na concentrations were measured with a biochemical autoanalyzer.

**Data Analysis** All data are expressed as means ± SEM. Paired and unpaired Student’s $t$ tests were used for comparisons between pairs of groups. Analysis of variance for repeated measures was used to examine the time-related changes in BP and heart rate. Linear regression analysis was employed to determine individual baroreflex sensitivity. A value of $P < .05$ was considered statistically significant.

**Results**

**Plasma VP Level** Hypertensive patients on the regular salt diet had higher BP than did normotensive subjects (147 ± 3/90 ± 3 vs 117 ± 2/73 ± 2 mm Hg, $P < .001$), but their plasma VP was normal (1.2 ± 0.3 vs 1.4 ± 0.3 pg/mL).

Levels of BP, serum and urinary Na, PRA, and plasma VP in hypertensive patients on the low-salt and the high-salt diets are shown in Table 1. BP, plasma osmolality, serum Na concentration, and urinary Na excretion were significantly higher, and PRA was markedly lower in the high-salt period than in the low-salt period. The difference in plasma VP level was not significant.

Four patients showed the difference in mean BP between the high- and the low-salt periods $> 10$ mm Hg. In these salt-sensitive patients, plasma VP level tended to be higher in the high-salt period than in the low-salt period ($1.8 ± 0.4$ vs $1.1 ± 0.2$ pg/mL, $P < .1$).
The level of plasma VP in four non–salt-sensitive patients was 1.0 ± 0.3 and 0.9 ± 0.2 pg/mL, respectively.

**Effects of OPC-21268 on BP** Figure 1 shows the time courses of changes in BP before and after oral administration of OPC-21268 and placebo in hypertensive patients on the regular salt diet. BP was 141 ± 5/83 ± 3 mm Hg before administration, and 140 ± 5/85 ± 4, 141 ± 5/84 ± 3, and 142 ± 6/83 ± 4 mm Hg at 1, 2, and 4 h after administration of OPC-21268, respectively. No significant changes in BP were observed in either period. Plasma concentration of VP did not change significantly after administration of OPC-21268.

The effects of OPC-21268 on BP in the low-salt and high-salt periods are also shown in Figure 1. In the low-salt period, BP was 137 ± 5/83 ± 4, 138 ± 5/83 ± 3, 137 ± 5/82 ± 3, and 135 ± 5/80 ± 3 mm Hg at 0, 1, 2, and 4 h, respectively. Mean values for the high-salt period were 143 ± 4/86 ± 3, 140 ± 3/85 ± 3, 140 ± 5/84 ± 4, and 140 ± 5/83 ± 4 mm Hg, respectively. Average systolic BP before and after administration of placebo was 137 ± 3, 138 ± 3, 137 ± 4, and 135 ± 5 mm Hg in the low-salt period, whereas it was 143 ± 5, 139 ± 3, 139 ± 4, and 142 ± 5 mm Hg in the high-salt period. Although BP was higher in the high-salt than in the low-salt period, there were no significant changes in BP or heart rate under any of the conditions examined here.

In three salt-sensitive patients, mean changes in BP after administration of OPC-21268 were −2.3 ± 1.2/−2.0 ± 1.7 mm Hg in the high-salt and −0.3 ± 3.5/0 ± 2.0 mm Hg in the low-salt period. These values for three non–salt-sensitive patients were −2.7 ± 2.0/−2.3 ± 2.8, and −1.0 ± 2.5/−1.7 ± 3.2 mm Hg, respectively.

### TABLE 1. LEVELS OF BLOOD PRESSURE, SERUM AND URINARY SODIUM, PLASMA RENIN ACTIVITY, AND VASOPRESSIN ON LOW- AND HIGH-SALT DIETS IN EIGHT HYPERTENSIVE SUBJECTS

<table>
<thead>
<tr>
<th>Variable</th>
<th>Low Salt</th>
<th>High Salt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>137 ± 4</td>
<td>146 ± 4*</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>86 ± 3</td>
<td>91 ± 3*</td>
</tr>
<tr>
<td>Serum Na (mmol/L)</td>
<td>139.8 ± 0.4</td>
<td>141.7 ± 0.4*</td>
</tr>
<tr>
<td>Urinary Na (mmol/day)</td>
<td>19 ± 3</td>
<td>224 ± 11‡</td>
</tr>
<tr>
<td>Plasma osmolality (mOsm/L)</td>
<td>290 ± 2</td>
<td>293 ± 2*</td>
</tr>
<tr>
<td>Plasma renin activity (ng/mL/h)</td>
<td>4.8 ± 1.1</td>
<td>0.8 ± 0.2†</td>
</tr>
<tr>
<td>Plasma vasopressin (pg/mL)</td>
<td>1.0 ± 0.2</td>
<td>1.4 ± 0.3</td>
</tr>
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* P < .05; †P < .01; ‡P < .001.

**Effects of OPC-21268 on the Baroreceptor Reflex** Baseline BP and heart rate were not affected by administration of OPC-21268. The baroreflex sensitivity after administration of OPC-21268 (8.5 ± 1.0 msec/mm Hg) was not significantly different from that following treatment with placebo (8.1 ± 0.8 msec/mm Hg).

**DISCUSSION**

In the present study, plasma VP levels were similar between hypertensive and normotensive subjects, and the nonpeptide V<sub>1</sub> receptor antagonist OPC-21268 did not produce any significant changes in BP or heart rate in the hypertensive subjects. These results suggest that VP does not play an important role in mild essential hypertension. Our results are consistent with those reported by Bussien et al, who showed normal plasma VP level and no effects of a peptide V<sub>1</sub> receptor an-
tagonist on BP, heart rate, or skin blood flow in patients with mild essential hypertension. Morton and Padfield reported that plasma VP was lower in patients with benign essential hypertension than in normal subjects, although patients with malignant hypertension had higher VP levels. Moreover, patients with the syndrome of inappropriate antidiuretic hormone secretion (SIADH) usually do not have hypertension. These studies do not support the role of VP in human hypertension.

Elevated plasma VP and the depressor response to V₁ receptor antagonists have been observed in models of salt-dependent hypertension and malignant hypertension. It has been shown that OPC-21268 lowers BP in DOCA-salt hypertensive rats and stroke-prone SHR, although this agent failed to decrease BP in Dahl salt-sensitive rats and ordinary SHR. There have also been a few reports suggesting the involvement of VP in the relationship between salt intake and hypertension in man. Cowley et al. observed higher plasma VP levels in hypertensive subjects compared with normotensive controls, and higher plasma VP in hypertensive subjects with high urinary Na excretion than in those with low Na excretion. Skjøttø et al. reported increased plasma VP in low renin essential hypertension, which is known to be salt-sensitive. In our study plasma VP was slightly higher in the high-salt than in the low-salt period, but difference was not significant and the level in the high-salt period remained within the normal range. Administration of OPC-21268 did not lower BP in either the high- or low-salt period, or in either salt-sensitive or non–salt-sensitive subjects. Our results suggest that VP may not contribute to the salt-induced BP elevation in hypertensive patients.

It is reasonable to assume that plasma VP increases with high salt intake because Na concentration determines plasma osmolality, which is a powerful regulator of VP secretion. However, increased VP and stimulated water intake caused by high-salt intake act to decrease the elevated Na concentration and VP secretion. In this study, serum Na concentration was higher in the high-salt than in the low-salt period, but the difference was only 2 mmol/L. We observed previously that intracerebroventricular hypertonic NaCl elevated plasma VP acutely but not chronically. The depressor effect of a V₁ antagonist was evident in the early but not in the late phase of hypertonic NaCl infusion.

The results presented here do not exclude the possibility of a minor role of VP in the salt-related BP elevation in essential hypertension. BP in hypertensive patients was not extremely high and changes in BP caused by the high Na intake were not remarkable in our study. Significant increases in plasma VP and some effect of the V₁ antagonist might be observed in patients with severe hypertension or with marked salt sensitivity. It is possible that the dose and duration of OPC-21268 treatment used in this study were not sufficient to produce the depressor effect. However, we observed no changes in BP during 7 days of treatment with this agent (100 mg taken three times daily) in a small group of hypertensive patients (unpublished observation). Vasopressin may also raise BP through its renal effects via V₂ receptors. Our results do not support this possibility because plasma levels of VP were normal in hypertensive patients on a high-sodium diet.

It is well known that the arterial baroreflex control of heart rate is blunted in essential hypertension. It has also been shown that VP influences the arterial baroreceptor reflex. Cowley et al. showed that VP sensitizes the baroreflex regulation of heart rate because intravenous VP causes marked bradycardia with relatively small BP elevation. Brooks reported that a V₁ receptor antagonist depressed the reflex tachycardia induced by sodium nitroprusside in dogs. On the other hand, VP may act to suppress the baroreflex control of sympathetic outflow, as Nishida and Vishops observed inhibition of the reflex changes in renal sympathetic nerve activity by VP in rabbits. Although the effects of VP on the baroreflex appear to be complex, V₁ receptor antagonists may be useful tools to study the possible role of VP in the baroreflex in essential hypertension. In our study, OPC-21268 did not affect the reflex bradycardia induced by intravenous methoxamine or the baseline BP or heart rate in hypertensive patients. Our results are consistent with those reported by Goldsmith, who observed that administration of small doses of VP did not influence the changes in BP, heart rate, or forearm blood flow during baroreceptor unloading studies in normal subjects. Therefore, VP may not play a role in the baroreceptor reflex, under normal conditions, in patients with essential hypertension as well as in normotensive subjects.

In conclusion, the present study suggests that VP does not play an important role in the maintenance of BP in patients with mild essential hypertension regardless of dietary sodium intake. Vasopressin also appears not to modulate the arterial baroreflex control of heart rate in hypertensive subjects under usual conditions.

REFERENCES


