PLASMA AND URINARY ADH LEVELS IN PATIENTS WITH ESSENTIAL HYPERTENSION

K. SHIMAMOTO, T. ANDO, Y. NAKAHASHI, T. NAKAO, S. TANAKA, M. SAKUMA* AND M. MIYAHARA

In order to investigate the regulatory system of release and excretion of ADH in essential hypertension, plasma and urinary ADH levels were determined in normal control subjects and patients with essential hypertension. Plasma ADH levels in 42 normal subjects and 53 patients with essential hypertension were $4.5 \pm 0.18$ pg/ml (mean $\pm$ SEM) and $4.0 \pm 0.12$ pg/ml, respectively, and a significant difference was found between the two groups. Urinary ADH excretion was $74.4 \pm 9.5$ ng/day (mean $\pm$ SEM) and $48.0 \pm 8.2$ ng/day in 15 normal subjects and in 17 patients, respectively, and it was significantly lower in the patient group.

In 25 patients, plasma ADH levels were measured immediately upon admission and after a two week bed rest without medication following admission. A significantly negative correlation was observed between the change of mean blood pressure and plasma ADH levels. After two weeks, sodium restriction (Na: 35 mEq and K: 75 mEq, daily) was ordered for 1 week in 17 patients, and a significant elevation of plasma ADH levels and a remarkable lowering of the blood pressure was found. And there was also a significantly negative correlation between the change of mean blood pressure and plasma ADH levels. Since the linear regression line was steeper after sodium restriction than after a two week rest, the elevation of plasma ADH levels induced by sodium restriction may be considered to be affected not only by the blood pressure lowering but also by the decrease of plasma volume.

From these results, it was suggested that the control of ADH release in essential hypertension was maintained normally, and that the baroreceptor might play an important role in regulation of ADH release under these conditions.

It is well known that ADH release is controlled by blood pressure through baroreceptors and plasma osmolality through osmoreceptor and plasma volume through volume receptor. Padfield et al. reported that plasma ADH levels were significantly lower in essential hypertension than in the normal control. However, Khokkar et al. and Freisenhausen et al. found a significantly higher excretion of urinary ADH in this disease.

Thus, there remains an unexplained discrepancy between plasma ADH levels and urinary ADH excretion in essential hypertension.

In this study, therefore, the regulation of ADH release and its excretion in patients with

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The 2nd Department of Internal Medicine, Sapporo Medical College, S-1 W-16, Sapporo, Japan
* Sakuma In Clinic, Kuchian-cho, Abuta-Gun, Hokkaido, Japan

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this disease was evaluated by measuring the plasma and urinary ADH levels.

MATERIALS AND METHODS

Plasma ADH levels and plasma osmolality in an overnight dehydrated state were determined in 42 normal subjects (age from 16 to 70 years) and 53 patients with essential hypertension (age from 18 to 66 years). Before the blood samples were drawn, both the normal subjects and the patients were kept in a recumbent position for 30 minutes.

Urinary ADH excretion was determined in 15 normal subjects (age from 19 to 70 years) and 17 patients with essential hypertension (age from 29 to 56 years). A 24 hour urine sample was collected in a bottle containing 20 ml of concentrated hydrochloric acid. In the patients, all hypotensive drugs were withdrawn at least for 10 days prior to the experiment.

25 patients were kept at rest with a free diet for 2 weeks after admission. And then 17 of these 25 patients were placed on a low sodium diet, containing 35 mEq sodium and 75 mEq potassium daily, for 7 days. Blood samples in an overnight dehydrated state were drawn before and after a 2 week rest, and after 7 days of sodium restriction for the determination of plasma ADH levels and plasma osmolality.

On the day of sampling, blood pressure was measured. The determination of plasma ADH levels was carried out by the radioimmunoassay system reported previously. Urinary ADH levels was directly determined by the same radioimmunoassay method without the procedure of extraction which was used for the measurement of plasma ADH. Plasma osmolality was measured by freezing point determination (Osmette Precision Osmometer, Precision Systems, Framingham, Mass.).

Statistical analysis was performed with the Student's t-test for paired and unpaired data. The values were expressed as mean ± SE.

RESULTS

Mean blood pressure was 84 ± 3 mmHg and 120 ± 3 mmHg in normal subjects and patients with essential hypertension, respectively.
There was no sex difference of plasma ADH levels in the normal control (male; 4.2 ± 0.29, female; 4.6 ± 0.36 pg/ml). And the mean of both sexes was 4.5 ± 0.18, while it was 4.0 ± 0.12 pg/ml in the patients which was significantly lower than the control (P < 0.02) (Fig. 1).

**Fig.3.** Plasma ADH levels before and after a 2 week hospitalization in patients in whom the mean blood pressure decrease was in excess of 5 mmHg (Responder) and less than 4 mmHg (Non-Responder).

**Fig.4.** A correlation between the change in mean blood pressure (Δm-BP) and that in plasma ADH levels (Δ ADH) after a 2 weeks hospitalization.

**Fig.5.** Plasma ADH levels before and after a 1 week sodium restriction period.

Urinary ADH excretion in the patients (48.0 ± 8.2 ng/day) was significantly lower than in the control (74.4 ± 9.5 ng/day) (P < 0.05) (Fig. 2).
Creatinine clearance was $93.0 \pm 7.9$ ml/min in the control and $90.0 \pm 4.3$ ml/min in the patients.

In the study of a 2 week rest following hospitalization, the mean blood pressure was lowered by 5 mmHg or over in 13 patients (Responder), while in the remaining 12 patients it was lowered by less than 4 mmHg or showed no change (Non-Responder). In the 13 responders, plasma ADH levels increased significantly from $4.0 \pm 0.31$ pg/ml to $4.8 \pm 0.23$ pg/ml ($p < 0.01$), while no significant change was seen in the non-responder (from $4.1 \pm 0.26$ pg/ml to $4.3 \pm 0.23$ pg/ml) (Fig. 3), and among these 25 patients, a significantly negative correlation between the change of mean blood pressure ($\Delta$ m-BP) and that of plasma ADH levels ($\Delta$ ADH) ($p < 0.02$) was noted (Fig. 4).

In the study of salt restriction in both responder and non-responder, the mean blood pressure fell from $116 \pm 2$ mmHg to $108 \pm 2$ mmHg and a significant elevation of plasma ADH levels from $4.2 \pm 0.17$ pg/ml to $5.0 \pm 0.32$ pg/ml ($p < 0.01$) was observed (Fig. 5). And there was a significantly negative correlation between the changes of mean blood pressure ($\Delta$ m-BP) and those of plasma ADH levels ($\Delta$ ADH) ($p < 0.05$) (Fig. 6).

Plasma osmolality was $283.4 \pm 0.84$ mOsm/kg and $283.0 \pm 1.0$ mOsm/kg in the normal control and in essential hypertensives, respectively. Thus no significant difference was observed between the two groups. Plasma osmolality before and after hospitalization, and after sodium restriction was $284.1 \pm 1.1$, $283.7 \pm 2.6$ and $283.5 \pm 1.4$ mOsm/kg, respectively, and likewise no significant difference was found among these different states.

DISCUSSION

In the present study, plasma ADH levels were significantly lower in the essential hypertensives than in the normal control. This result was consistent with that reported by Padfield et al. Since ADH release is controlled by blood pressure, there is a possibility that the low plasma ADH levels in the patients is due to the high blood pressure levels in essential hypertension.

In the study of a 2 week rest after hospitalization, plasma ADH levels increased in proportion to the blood pressure drop, and a significantly negative correlation was found between the change of blood pressure and that of plasma ADH levels. In this period, there was not change in plasma osmolality. Our previous study showed that plasma volume increased significantly in patients whose blood pressure fell after hospitalization. Therefore, it is unlikely that the increase of plasma ADH levels in the responder is caused through the osmoreceptor or volume receptor. And it is strongly suggested that ADH release under this condition is regulated by the blood pressure level.

In the study of sodium restriction, a significantly negative correlation was observed between the change in plasma ADH levels and that in mean blood pressure. This finding suggests that the increase of plasma ADH levels by sodium restriction is assumed to be affected by the drop of blood pressure. However, the slope of linear regression line was steeper in sodium restriction when compared with the 2 week hospitalization study. Dustin et al. reported that the blood pressure fall by sodium restriction was associated with plasma volume reduction. Therefore, in sodium restriction, the elevation of plasma ADH levels might be affected not only by the fall of blood pressure but also by the decrease of plasma volume, and the difference of the slope may be due to the difference of the change in plasma volume under these two conditions.

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In addition to plasma ADH levels, the urinary ADH excretion was significantly lower in patients than in the normal subjects. Therefore, our results appear to suggest that ADH release is suppressed in essential hypertensives than in the normal subjects. At the moment, we cannot give a clear explanation of the discrepancy between the results of Khokkar et al. and Freisenhausen et al. and ours. The reason why there exists a discrepancy in the degree of the decrease between plasma and urinary ADH values (about 11% in plasma and 35% in urine) in the patients is so far exactly unknown, though it may be partly due to the smaller number of the subjects examined in urinary ADH excretion.

Our results suggest that the control of ADH release is possibly kept at normal, and that the baroreceptor may play an important role in the regulation of ADH release in essential hypertension under these conditions. And ADH may be considered to have no significant role in the pathogenesis of essential hypertension.

REFERENCE