The Effect of Blood Volume Changes Accompanying Isotonic Circumstances on Plasma Antidiuretic Hormone Levels in Normal Subjects

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Changes in plasma ADH levels were investigated in human male subjects whose blood volume was altered under isotonic circumstances. Blood volume was reduced by ambulation and increased by isotonic saline infusion in an overnight dehydrated state, and determinations were made on plasma ADH levels, plasma osmolality and hematocrit values. Plasma ADH levels were clearly affected by the small changes in blood volume, and significantly negative correlation was found between plasma ADH levels and the percent changes in blood volume under isotonic circumstances. From these findings, it was concluded that ADH release in human subjects is also controlled by the changes of the blood volume factor in addition to osmotic stimuli.

Key Words: Plasma ADH, Blood volume, Isotonic circumstances

The secretion of antidiuretic hormone (ADH) seems to be regulated by blood pressure, plasma osmolality and plasma volume through the baroreceptor,^{1, 2)} osmoreceptor^{1, 3, 4)} and volume receptor,^{4, 5)} respectively. Since the significant relation of plasma osmolality and plasma ADH level was elucidated by Verney (1947),⁶⁾ numerous investigations^{1, 3, 4, 7-10)} have supported this relationship. In addition, in human subjects it has been shown that changes in plasma osmolality is one of the important factors in the control of ADH release.^{1, 3, 10)} On the other hand, many investigators have demonstrated in experimental animals that the reduction of blood volume by hemorrhage or other procedures and the expansion of it by several methods result in an augmentation and suppression of ADH release, respectively.^{1, 4, 5, 7, 11-18)} Thus, it has been nearly established that ADH release is also controlled by the change of blood volume in animal

experiments. In human studies, however, the influence of the volume factor on ADH secretion has been controversial,^{8-10, 19-22)} and this problem still remains unclear.

In the present study, in order to clarify the effect of alteration of blood volume without change in plasma osmolality on ADH secretion in human subjects, two experimental approaches were carried out. One approach was blood volume reduction by ambulation and the other was blood volume elevation by isotonic saline infusion. Plasma ADH levels were measured in both states.

MATERIALS AND METHODS

All of the subjects were healthy males, ranging in age from 18 to 40 years, admitted to our hospital for a medical examination. They received a regular diet containing 200 mEq/day of sodium and 75 mEq/day of potassium.

An ambulation test was performed in six cases

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of overnight dehydrated subject after supine rest for 60 minutes or more in the early morning. The blood samples were obtained from the antecubital vein immediately before and 30, 60 and 120 minutes after the initiation of posture change. In these samples, plasma ADH level, plasma osmolality and the hematocrit value were determined.

Intravenous infusion of 0.9% isotonic saline was performed via the right antecubital vein at a rate of 1000 ml/60 minutes for 60 minutes in 7 overnight dehydrated subjects in a supine position after 30 minutes or more of rest in the early morning. Blood samples were drawn from the left antecubital vein. The following samples were obtained immediately before infusion, at 30 (500 ml infused) and 60 minutes at the time of infusion (1000 ml infused), and 30 minutes and 60 minutes after the completion of the infusion (90 minutes and 120 minutes after the initiation of the infusion, respectively), for the determination of plasma ADH levels, plasma osmolality and hematocrit values.

The blood sample was taken by a heparinized disposal plastic syringe and immediately drawn into a capillary tube for hematocrit determination, and the remainder was centrifuged at 3000 rpm for 15 minutes at 4°C. The plasma was carefully aspirated and an aliquot was taken for determination of osmolality. The remaining plasma was stored at -20°C until extraction and assay for ADH. Plasma ADH was determined by heterologous radioimmunoassay using anti-lysine-vasopressin antiserum and ^{125}I -arginine vasopressin as previously reported.³⁾ The assay procedure could detect plasma ADH at concentrations as low as 1.0 pg/ml in samples of 0.6 ml and did not cross-react with oxytocin. ADH extraction from the plasma was performed by cold acetone. Osmolality was measured in fresh plasma by freezing point determination (Osmette S Osmometer). Change in blood volume (B) was estimated from the change in hematocrit value (Ht) by the standard formula, $(B_2/B_1) = (Ht_1/Ht_2) \times 100$ which assumes no change in the circulating erythrocyte volume.

Statistical Analysis: A statistical analysis was performed with Student's t-test for paired data.

Correlations were determined by linear regression analysis using the method of least square.

RESULTS

The changes of plasma ADH, plasma osmolality and hematocrit during a 2 hour ambulation are shown in Fig. 1. Hematocrit values were clearly elevated at 30 minutes and gradually increased up to 120 minutes after the start of ambulation. Changes in blood volume calculated from hematocrit values were $5.3 \pm 0.4\%$, $6.0 \pm 0.7\%$ and $6.4 \pm 0.6\%$ (mean $\pm$ SEM) at 30, 60 and 120 minutes, respectively. Plasma osmolality did not show any change during ambulation. Plasma ADH level immediately before the ambulation was 4.4 ± 0.3 pg/ml, and this level gradually increased significantly during the ambulation ($p < 0.05$) in all subjects.

As shown in Fig. 2, during the isotonic saline infusion, hematocrit values were clearly reduced at 30 minutes (500 ml infused) and reached the

Fig. 1. Effect of 2-hour-ambulation on plasma ADH level, plasma osmolality and hematocrit value in 6 normal subjects. Vertical lines indicate the standard error of the mean. Asterisks represent significant difference from the control levels ($p < 0.05$).

lowest value at 60 minutes after the initiation of infusion (1000 ml infused), followed by a gradual elevation after the completion of infusion. The elevation rates of blood volume were $10.4 \pm 1.0\%$, $13.4 \pm 1.2\%$, $10.0 \pm 1.9\%$ and $8.1 \pm 1.2\%$ at 30, 60, 90 and 120 minutes after the start of infusion, respectively. Plasma osmolality showed no change throughout the experimental course. Plasma ADH levels during the isotonic saline infusion decreased significantly with the elevation of blood volume, and the lowest value (2.5 ± 0.4 pg/ml) was found at 60 minutes (1000 ml infused), followed by an increase with the reduction of blood volume.

Fig. 3 shows the correlation between plasma ADH levels and changes in blood volume at each point of posture change and isotonic saline infusion, of which both did not show any changes in plasma osmolality. The response of plasma ADH level to blood volume change showed a statistically significant linear relationship ($r =$

Fig. 2. Effect of isotonic infusion for 60 minutes on plasma ADH level, plasma osmolality and hematocrit value in 7 normal subjects. Time (minutes) on horizontal axis means those after the initiation of infusion. Vertical lines indicate standard error of the mean. Asterisks indicate significant difference from the control levels ($p < 0.05$).

Fig. 3. Correlation between plasma ADH levels and percent changes of blood volume in the individual determinations observed during the ambulation and the isotonic saline infusion tests under isotonic circumstances.

0.780, $p < 0.001$).

DISCUSSION

It is well known in animal experiments that blood volume should be one of the important regulating factors of ADH release through the volume receptor.^{1, 6, 8-16} In human subjects, however, results reported from many laboratories^{8-10, 19-22} regarding this regulatory system have been controversial, and no definitive explanation has been established. In this study, under isotonic circumstances, it was clearly demonstrated that reduction of blood volume from a basal state, increased plasma ADH levels, and that expansion of it, decreased plasma ADH levels in normal human subjects. Moreover, a significant negative correlation was observed between plasma ADH levels and changes of blood volume. These results suggest that ADH release was easily affected by the least bit of change in blood volume.

In this study, it was also shown that the regression curve of plasma ADH levels versus the alteration in blood volume was a linear one, while Robertson et al.¹ observed exponential nature in the response curve of ADH release in rats. This may be due to the small range of blood volume depletion or expansion in our study.

Recently, the pathophysiological role of ADH has generated interest in hypertensive diseases²³⁻²⁶ and edematous diseases.^{27, 28} However, there are a number of unsolved problems and no definitive explanation for the patho-

physiological role of ADH in these diseases is established. As a result of the present study, it might be emphasized that the regulation of ADH release through the volume factor should also be considered in investigating the physiological and pathophysiological role of ADH in various diseases, in addition to the factors of the plasma osmolality and blood pressure.

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