Interaction of Osmotic and Nonosmotic Stimuli in Regulation of Vasopressin Secretion in Hypoosmolar State of Man

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Abstract. Vasopressin (AVP) secretion is principally under osmotic regulation, which is altered by nonosmotic stimuli. It is known that the manner of osmotic regulation of AVP secretion in hypoosmolar state of man consists of four types. The types have (A) random changes in plasma AVP without relation of plasma osmolality; (B) plasma AVP secretion correlated closely to plasma osmolality with a low osmotic threshold for AVP release; (C) nonsuppressible AVP secretion with normal osmotic release of AVP; (D) no abnormalities in AVP secretion. In this study, we found an entirely different type of AVP secretion from the above types in six patients with hyponatremia resulting from various causes during infusion of 5% hypertonic saline. To clarify the mechanism underlying the AVP secretion, we analyzed the interaction between osmotic and nonosmotic stimuli of AVP secretion in these patients. Despite hyponatremia, plasma AVP levels in all patients were not suppressed, which was attributed at least in part to the presence of nonosmotic stimuli for AVP release. These stimuli include nausea, hypotension, blood volume contraction, glucocorticoid deficiency or their combinations. Hypertonic saline infusion increased both serum sodium concentrations and plasma osmolality, although to subnormal levels, and concomitantly, alleviated some of the nonosmotic stimuli for AVP release formerly present in these patients. However, plasma AVP concentrations decreased rapidly during the infusion and reached the nadir in all patients. This phenomenon may be due to alleviation of nonosmotic stimuli for AVP release. Thus, the findings indicate that the potentiating effect of nonosmotic stimuli for AVP secretion may modify the osmotic regulation of AVP secretion in hypoosmolar state, resulting in the type of AVP secretion in this study.

Key words: Hyponatremia, Vasopressin, Osmoregulation, Osmotic and nonosmotic stimuli

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VASOPRESSIN (AVP) secretion is primarily under the control of osmotic stimuli and secondarily under the control of nonosmotic stimuli [1-7]. As plasma osmolality rises above the osmotic threshold, AVP secretion increases by an amount that closely correlates with the level of plasma osmolality, but in the hypoosmolar state of man the forms of AVP secretion vary. Robertson et al. first described four patterns of osmotic regulation of AVP secretion based on the infusion of hypertonic saline [2, 8]. The first type consists of large and erratic changes in plasma AVP without relation of plasma osmolality. In the second type, the plasma AVP secretion is correlated closely to plasma osmolality with an abnormally low osmotic threshold for AVP release. In the third type, AVP secretion is constant and of a nonsuppressible type with otherwise normal osmotic release of AVP. In the fourth type, there are no detectable

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abnormalities in AVP secretion.

In this study, we found an entirely different type of AVP secretion from the above in six patients with hyponatremia resulting from various causes during infusion of hypertonic saline. This type shows that plasma AVP levels progressively decreased and correlated conversely with increased levels of plasma osmolality. To clarify the mechanism underlying the AVP secretion, we analyzed the interaction between osmotic and nonosmotic control systems of AVP secretion in these patients.

Subjects and Methods

Patients

Informed consent was obtained from the family of all subjects. Five men and a woman, aged 62–83 yr, were admitted to the Nagaoka Red Cross Hospital because of weakness, anorexia, vomiting or consciousness disturbance (Table 1). Laboratory examinations showed hyponatremia with decreased plasma osmolality in all of them. Underlying disease of the patients were secondary adrenal insufficiency in two, pulmonary tuberculosis associated with or without acute pneumonia in three, and small cell lung cancer in one patient. The condition of one (No. 5) of the patients with pulmonary tuberculosis and acute pneumonia was complicated with non-insulin-dependent diabetes mellitus. Both patients with adrenal insufficiency (Nos. 1 and 2) were shown subsequently not to respond to a bolus in injection of synthetic CRH, with a rise in plasma ACTH and cortisol levels, whereas the secretory capacities of other pituitary hormones were normal, prompting a diagnosis of isolated ACTH deficiency.

On or during admission, all patients had disturbed consciousness ranging in degree from confusion to coma (Table 2). One patient (No. 2) had hyponatremia and tachycardia in the emergency room and one patient (No. 6) had severe tachycardia and a confused state 27 days after admission. Before finding hyponatremia, three patients (Nos. 1 to 3) were suffering from severe nausea and vomiting, which was difficult to manage with anti-emetic drugs. Clinical assessment provided evidence of extracellular fluid volume contraction in four (Nos. 1, 2, 4 and 5), and volume contraction was absent in one patient (No. 3) (Table 1). Patient 6 had pitting edema. Three patients in the former group had lost 3.0 to 5.5 kg in weight when they had hyponatremia. Both physical and laboratory examinations showed that all patients had normal cardiac, renal and thyroid functions. Plasma levels of ACTH and cortisol were normal in all but two, who had secondary adrenal insufficiency.

Patient 3 had received irradiation before admission, and was treated with prednisolone for associated radiation pneumonitis at the time of the study. Patient 4 was treated with anti-tuberculosis drugs, and patients 5 and 6 with antibiotics for acute pneumonia. In patient 6, 35 to 185 ml per day of pleural effusion was drained through drainage tube in the right pleura. Patients 1 and 2 had never been treated with glucocorticoid for adrenal insufficiency before. All patients had

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age(yr)</th>
<th>Sex</th>
<th>Body weight loss (kg)*</th>
<th>Skin turgor</th>
<th>Mucous membrane</th>
<th>Others</th>
<th>Underlying diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>65</td>
<td>M</td>
<td>0</td>
<td>decreased</td>
<td>dry</td>
<td></td>
<td>ACTH deficiency</td>
</tr>
<tr>
<td>2</td>
<td>71</td>
<td>M</td>
<td>4.7</td>
<td>decreased</td>
<td>dry</td>
<td></td>
<td>ACTH deficiency</td>
</tr>
<tr>
<td>3</td>
<td>63</td>
<td>M</td>
<td>0</td>
<td>normal</td>
<td>moist</td>
<td></td>
<td>Small cell lung cancer</td>
</tr>
<tr>
<td>4</td>
<td>76</td>
<td>F</td>
<td>3</td>
<td>decreased</td>
<td>dry</td>
<td></td>
<td>Pulmonary tuberculosis</td>
</tr>
<tr>
<td>5</td>
<td>83</td>
<td>M</td>
<td>3</td>
<td>increased</td>
<td>dry</td>
<td></td>
<td>Pulmonary tuberculosis</td>
</tr>
<tr>
<td>6</td>
<td>74</td>
<td>M</td>
<td>5.5</td>
<td>pitting edema</td>
<td>moist</td>
<td>Drainage into rt. pleura due to pleural effusion</td>
<td>Pulmonary tuberculosis</td>
</tr>
</tbody>
</table>

n.d., not determined; NIDDM, non-insulin-dependent diabetes mellitus. *Body weight lost during the period between the day before and the day when hyponatremia was found.
received iv infusion of isotonic fluid for more than one week before or during admission, which was not effective in improving either the hyponatremia or clinical condition. Average daily intake of water ranged from 1.2 to 2.91, and that of sodium from 100 to 180 mmol.

Patients 1 and 2 were recovered following the administration of hydrocortisone, patient 3 following the administration of demeclocycline, and patients 4 and 5 after receiving fludrocortisone acetate, and patient 6 died the next day after the saline infusion due to an unknown cause.

**Hypertonic saline infusion**

As the patients had severe hyponatremia, hypertonic saline was infused in an effort to correct hyponatremia. This was safe and effective in hyponatremic patients as reported [9-12] and changes in plasma AVP levels during the infusion were concomitantly studied in all patients. Before hypertonic saline was infused, two patients (Nos. 2 and 5) were in a coma, two patients (Nos. 1 and 4) in a stupor and two patients (Nos. 3 and 6) in a state of confusion (Table 2). In addition, two patients (Nos. 1 and 3) had nausea. The patients were kept in a recumbent position for at least 60 min before and throughout the infusion. All medications had been withdrawn until the completion of the study. After taking a control blood sample, 5% saline was infused iv at a rate of 0.05 ml/kg-min for 2 h through a cannula inserted into an antecubital vein. Blood samples were collected every 30 min from an antecubital vein in the opposite arm. An aliquot of blood samples was used for the determinations of hematocrit, osmolality, electrolytes, urea nitrogen, creatinine, uric acid, total protein and glucose. The remaining blood was transferred to a chilled tube containing edetic acid, and the plasma was stored at -20 °C for subsequent measurements of AVP. The blood pressure and heart rate were monitored at 5 min intervals during the infusion with an automatic sphygmomanometer.

**Laboratory analysis**

Plasma AVP concentrations were measured by RIA with kits supplied by Mitsubishi Chemical Co. (Tokyo, Japan) after extraction of AVP with a reverse phase C18 silica cartridge (Waters Associates, Milford, MA), as described previously [9-12]. The mean (± SD) recovery of AVP from plasma was 87.1 ± 10.4%, and the sensitivity of the assay was 0.1 pmol/l. The coefficients of variation averaged 11.4% for intraassay error and 12.1% for interassay error. The mean (± SD) plasma AVP concentration in 19 healthy subjects receiving ad libitum water and sodium was 1.15 ± 0.24 pmol/l.

PRA and aldosterone concentrations were estimated by RIA with commercial kits. Changes in blood volume (BV) were determined from the changes in hematocrit (Hct) by the formula BV2/BV1=Hct1/Hct2 which assumes no changes in circulating erythrocyte volume. Apparent total body water (TBW) deficits were calculated from changes in body weight on the assumption that TBW is 60% of body weight.

### Table 2. Change in hemodynamics, nausea and consciousness before and 2 h after 5% saline infusion into six hyponatremic patients

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Heart rate Before After Percent change</th>
<th>Mean blood pressure Before After Percent change</th>
<th>Hematocrit Before After Percent change in blood volume</th>
<th>Nausea Before After</th>
<th>Consciousness Before After</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>62</td>
<td>72</td>
<td>16</td>
<td>91</td>
<td>83</td>
</tr>
<tr>
<td>2</td>
<td>95</td>
<td>74</td>
<td>-22</td>
<td>64</td>
<td>97</td>
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<td>3</td>
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<td>17</td>
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<td>91</td>
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<td>60</td>
<td>70</td>
<td>17</td>
<td>93</td>
<td>97</td>
</tr>
<tr>
<td>5</td>
<td>72</td>
<td>83</td>
<td>15</td>
<td>79</td>
<td>67</td>
</tr>
<tr>
<td>6</td>
<td>104</td>
<td>122</td>
<td>17</td>
<td>83</td>
<td>72</td>
</tr>
</tbody>
</table>

*Percent change in blood volume was calculated by the method described in the text. n.d., not determined.
Table 3. Serum and urinary sodium levels with their related variables, plasma osmolality, PRA, and plasma concentrations of aldosterone and vasopressin (AVP) in six patients in the present study

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sodium (mmol/l)</th>
<th>Osmolality (mOsm/kg)</th>
<th>Urea nitrogen (mmol/l)</th>
<th>Creatinine (µmol/l)</th>
<th>Uric acid (µmol/l)</th>
<th>Total protein (g/l)</th>
<th>PRA (ng/l·s)</th>
<th>Aldosterone (pmol/l)</th>
<th>AVP (pmol/l)</th>
<th>Sodium (mmol/l)</th>
<th>Osmolality (mOsm/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>116</td>
<td>229</td>
<td>2.1</td>
<td>53</td>
<td>172</td>
<td>67</td>
<td>0.06</td>
<td>55</td>
<td>4.1</td>
<td>179</td>
<td>395</td>
</tr>
<tr>
<td>2</td>
<td>106</td>
<td>223</td>
<td>2.3</td>
<td>53</td>
<td>178</td>
<td>66</td>
<td>0.06</td>
<td>50</td>
<td>4.8</td>
<td>115</td>
<td>372</td>
</tr>
<tr>
<td>3</td>
<td>109</td>
<td>225</td>
<td>3.2</td>
<td>71</td>
<td>71</td>
<td>62</td>
<td>0.22</td>
<td>n.d.</td>
<td>8.6</td>
<td>159</td>
<td>556</td>
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<tr>
<td>4</td>
<td>119</td>
<td>231</td>
<td>5.7</td>
<td>44</td>
<td>89</td>
<td>54</td>
<td>0.33</td>
<td>224</td>
<td>6.3</td>
<td>120</td>
<td>421</td>
</tr>
<tr>
<td>5</td>
<td>101</td>
<td>223</td>
<td>2.1</td>
<td>35</td>
<td>89</td>
<td>54</td>
<td>0.19</td>
<td>&lt;28</td>
<td>11.5</td>
<td>100</td>
<td>544</td>
</tr>
<tr>
<td>6</td>
<td>110</td>
<td>226</td>
<td>3.6</td>
<td>35</td>
<td>54</td>
<td>50</td>
<td>7.28</td>
<td>n.d.</td>
<td>10.1</td>
<td>125</td>
<td>572</td>
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<tr>
<td>Normal</td>
<td>135–146</td>
<td>280–295</td>
<td>3.5–6.5</td>
<td>50–110</td>
<td>120–420</td>
<td>60–80</td>
<td>0.30–1.14</td>
<td>220–430</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

n.d., not determined.

**Statistical analyses**

Values in the text and tables are shown as the mean ± SD. Paired t test was used for statistical evaluation. Regression lines were obtained by the least squares method. P<0.05 was considered significant.

**Results**

**Hyponatremia and related variables**

All patients had severe hyponatremia with decreased plasma osmolality (Table 3). Despite hyponatremia, urinary sodium excretion persisted with urine osmolality exceeding plasma osmolality. Plasma levels of urea nitrogen, creatinine and uric acid were normal or subnormal in all patients. Three patients (Nos. 4 to 6) had hypoproteinemia. PRA was clearly increased in one patient (No. 6), but was subnormal in four and normal in the remaining one. The patient (No. 5) who also had non-insulin-dependent diabetes mellitus had hyperkalemia (>5.0 mmol/l in plasma potassium) and low PRA with a undetectable plasma aldosterone concentration. The plasma AVP level in relation to plasma osmolality was extremely high in all patients.

**Hypertonic saline infusion**

Hypertonic saline infusion increased both serum sodium concentrations and plasma osmolality, although to subnormal levels, in all patients (Fig. 1), resulting in amelioration of the clinical condition (Table 2). Nausea diminished in two patients (Nos. 1 and 3). Four patients (Nos. 1 to 3 and 5) regained consciousness and comprehended spoken words after the infusion. The results suggest that the nausea and disturbed consciousness in these patients were largely due to brain edema consequent to hyponatremia. Further, a partial correction of the extracellular fluid deficit by the infusion may have been responsible for the clinical improvement in some. Patient 4 had low-grade fever, which persisted during the infusion. Patient 6 had moderate hypoxia. The arterial blood gas analysis done at the end of the infusion in this patient did not show any improvement in the hypoxia. Patterns of plasma AVP responses to hypertonic saline infusion in individual patients were essentially the same (Fig. 1). Initially, plasma AVP levels were high, but began to decrease during the infusion and reached the nadir at the end of the infusion. There was a significant negative correlation between plasma AVP and plasma osmolality in each patient (r=0.80 to 0.98 P<0.01). In none of the subjects, however, the plasma AVP concentration suppressed to undetectable levels. There was no significant change in the mean serum concentrations of urea nitrogen, creatinine, uric acid and glucose. One patient (No. 2) who had hypotension and tachycardia before the infusion had decreased heart rate after the infusion, while five patients had increased heart rate (Table 2). Mean blood pressure in patient 2 increased
All patients in the present study had severe hyponatremia with decreased plasma osmolality. Despite the hyponatremia, plasma AVP levels were not suppressed. In two patients (Nos. 1 and 2), high plasma AVP and consequent hyponatremia may have primarily resulted from glucocorticoid deficiency. In secondary adrenal insufficiency, a loss of hypotonic suppression of the osmostat for AVP release, which may be occasioned by glucocorticoid deficiency per se, causes persistent AVP secretion [10]. The association of nausea in patient 1, hypotension and tachycardia in patient 2, and hypovolemia in patients 1 and 2, respectively, may have augmented AVP secretion further, because both are potent nonosmotic stimuli for AVP release [2, 13].

In three patients (Nos. 4 to 6), the nature of the nonosmotic stimulus of AVP secretion is less clear. Their normal to low PRA, plasma urate and creatinine as well as their increased urinary sodium excretion are suggestive of normal or increased total body water due to a primary abnormality in the inhibitory control of AVP secretion (i.e., the syndrome of inappropriate antidiuretic hormone secretion; SIADH). Nevertheless, there are no definitive proofs of euvolemia or hypervolemia since these laboratory data could result from other factors such as normal aging [14, 15], hyporeninimic hypoaldosteronism (patient 5) and hypovolemic hyponatremia in patients with miscellaneous diseases [12, 16–18]. In addition, these patients had weight loss as well as an increase in PRA in one of them, and sodium supplement or mineralocorticoid therapy after the saline infusion study eventually corrected the clinical state and hyponatremia in these patients. These findings, therefore raise the possibility of an underlying hypovolemic stimulus [12, 18], even though SIADH could be present. These patients had hypoproteinemia. The deficiency in plasma protein induces the shift of water from blood to extracellular tissue, developing hypoplastic hypovolemia [19]. In the hypoplastic hypovolemia, hypertension occurs due to constriction of blood vessels to compensate for the hypovolemia and results in hypotension by suppressing or blocking the increase in vasomotor

Discussion

noticeably after the infusion, but in three patients Nos. 1, 5 and 6 it decreased (Table 2). Hematocrit in individual patients decreased after the infusion, and the calculated blood volume increased by 6 to 18% of pre-infusion values, patient 2 having the lowest value and patient 1 the highest (Table 2).

After the infusion, the hyponatremia was improved by treatment with drugs and plasma AVP levels relative to plasma osmolality were normalized (Fig. 1).
tone [20]. The fact that blood pressure decreased after the infusion of hypertonic saline in these patients (Nos. 1, 5 and 6) indicates that hypoplastic hypovolemia may be present, although patient 6 had no clinical sign of dehydration. Judging from body weight changes, these three patients had apparent deficits of 14 to 22% in total body water before the infusion. Because of a shift of water into the cells due to concomitant hyponatremia, the deficits in extracellular fluid and blood volume would have been much greater, which may strongly stimulate AVP release, provided that the serum sodium level is normal [2].

The clinical features of the remaining patient (No. 3), on the other hand, fulfilled the diagnostic criterion of SIADH [21]. In fact, demeclocycline was subsequently shown to be effective in correcting hyponatremia in this patient. Persistent severe nausea and vomiting, in addition, may have stimulated AVP secretion, which in turn accelerated hyponatremia. All our patients therefore had hyponatremia with increased AVP secretion, which might have been induced primarily or secondarily by a variety of nonosmotic stimuli for AVP release, although the etiology of hyponatremia differed from patient to patient.

Hypertonic saline infusion increases both serum sodium and plasma osmolality, and concomitantly improved the clinical state of most patients in this study. This includes the diminishment of nausea, the normalization of blood pressure and heart rate, and the recovery of consciousness. In this regard, great care should be taken to avoid rapid correction of hyponatremia by the hypertonic saline infusion, particularly in children and young women, since central pontine myelinolysis develops following the rapid correction [22]. With these changes, plasma AVP levels began to decrease shortly after the initiation of the infusion and progressively declined thereafter. Decreased plasma AVP levels, therefore, may be attributed to a weakening of the nonosmotic stimuli for AVP release present before hypertonic saline infusion.

The interaction between the osmotic and nonosmotic control systems of AVP secretion in the hypoosmolar state of man is not well established, chiefly because of methodological difficulties. In early studies, a downward resetting of the threshold as well as increased sensitivity of AVP secretion to osmotic stimulus, when hypovolemia or hypotension is present, was demonstrated in patients with isolated aldosterone deficiency and in healthy subjects [8, 23]. Such a potentiating effect of hypovolemia on osmotic secretion of AVP was not observed in our patients, but on the other hand the plasma AVP level decreased with the increased plasma osmolality after a partial correction of volume contraction. It may be argued that serum sodium concentrations and plasma osmolality after hypertonic saline infusion in these patients were too low to permit an osmotic stimulus. Since, however, an increase in plasma osmolality to nearly normal threshold levels of AVP secretion does not induce premature AVP release in patients with hyponatremia after intracranial bleeding [12], this is unlikely. The difference may be due to a different change in plasma volume. The view of Leaf and Frazier [24] that volume regulatory influence on AVP secretion takes precedence over osmoregulatory influences appears to be correct, insofar as the former reaches as extreme. In rats, a decrease in plasma osmolality potentially inhibits AVP secretion [5, 6], and this is also indicated by the fact that hypothalamic AVP mRNA is reduced to unmeasurable levels in the hypoosmolar rats [25]. Multiple nonosmotic stimuli may in part override the inhibition in hypoosmolar state, if the stimuli are sufficiently strong, resulting in this type of AVP secretion. To evaluate the plasma AVP value in patients with hypoosmotic hyponatremia, we need to know the complex interactions of osmotic and nonosmotic stimuli in the regulation of AVP secretion.

Finally, the clinical features of some patients in the present study were almost indistinguishable from those of SIADH. This may be due to a lack of sensitive and specific means in identifying the extracellular fluid volume status. Of several parameters of fluid homeostasis, high PRA and low urinary sodium concentrations may be the most useful predictors for the presence of hypovolemic hyponatremia [26], but PRA may not be increased in elderly patients such as those included in the present study [12, 14, 15, 18]. Urinary sodium excretion may be high in hypovolemic hyponatremia due to salt wastage by the kidneys. A careful evaluation is necessary to determine the cause of hyponatremic disorders in elderly subjects [12, 18].
HYPONATREMIA AND AVP SECRETION

References