Prolactin Secretion in Patients with Idiopathic Diabetes Insipidus

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Abstract. It has been demonstrated that hyperprolactinemia is sometimes present even in patients with idiopathic diabetes insipidus (DI). In this study, we examined the responses of serum prolactin (PRL) to hypertonic saline infusion and TRH injection in 11 patients with idiopathic DI diagnosed by clinical examinations. Serum sodium in these patients (147.5±3.2 mEq/L) was significantly higher at baseline than in normal subjects (139.7±2.4 mEq/L). The plasma arginine vasopressin (AVP) level was significantly lower in DI (0.42±0.24 pg/ml) at baseline than in normal subjects (2.53±1.03 pg/ml). However, the serum PRL level in both groups did not differ significantly except in one patient with idiopathic DI (35.6 ng/ml). There was no significant correlation between the basal serum sodium and basal serum PRL in either group. After an infusion of hypertonic saline, the serum sodium level gradually increased to 155.6±3.4 mEq/L in DI and to 146.5±4.3 mEq/L in the normal subjects. However, this increase did not affect PRL secretion in either group. PRL response to TRH was essentially normal in all patients with idiopathic DI. These results indicate that the secretion of PRL is not generally affected by chronic mild hypernatremic hypovolemia in the patients with idiopathic DI.

Key words: Vasopressin, Hyperprolactinemia, Diabetes insipidus, Hypernatremia.

HYPERPROLACTINEMIA is often caused by pituitary adenomas, certain medications or the destruction of tissue in the hypothalamic region. In patients with idiopathic diabetes insipidus (DI), there is no apparent organic lesion in the hypothalamus or pituitary. However, mild hyperprolactinemia is sometimes present even in patients with idiopathic DI [1, 2].

Recent data have revealed important interactions between prolactin release and the posterior pituitary. In rats, acute or chronic posterior pituitary lobectomy produces an increase in plasma prolactin [3, 4, 5].

On the other hand, it is well known that prolactin physiologically regulates the water and electrolyte balance in teleost fish [6]. Although Buckman et al. [7] reported that prolactin secretion was regulated by plasma osmolality in normal subjects, subsequent studies indicated that prolactin secretion is not affected by the change in plasma osmolality in normal hydrated man [8]. However, in the chronic dehydrated state induced by a deficiency of arginine vasopressin (AVP), it is not known whether the regulation of prolactin secretion is modified by mild hypovolemic hypernatremia or not.

Considering these findings, we designed a study to evaluate prolactin secretion in patients with idiopathic DI to ratiocinate the mechanism underlying its occasional increase.

Materials and Methods

Nine normal volunteers (three men and six
women, 19–23 yr) and eleven patients with idiopathic DI were studied. Idiopathic DI was
diagnosed by measuring plasma AVP during hypotonic saline infusion [9]. Radiological ex-
amination (skull radiography and CT) and magnetic resonance imaging were simultaneously con-
ducted. The secretion of prolactin and/or AVP was studied by means of hypotonic saline infusion and
the injection of thyrotropin-releasing hormone (TRH). No patients took any medications prior to
the study.

Hypertonic saline infusion
The secretion of AVP and prolactin following
the infusion of 5% saline at a rate of 0.05
ml/kg/min for 120 min was determined in the
morning after dehydration for at least 4 h in 9
normal subjects and 11 patients with idiopathic DI.
Blood samples were taken every 20–30 min during
the infusion.

TRH test
The patients received 500 µg of TRH (Tanabe
Seiyaku Company Ltd., Tokyo, Japan) adminis-
tered intravenously after resting for 30 min and
fasting for 12 h. Blood sampling for prolactin
measurement was done every 30 min until 2 h
after injection.

Plasma AVP was assayed with a radioimmunoas-
say kit provided by the Mitsubishi Petrochemical
Co. (Tokyo, Japan) after extraction using Sep-pak
C18 [10]. Serum prolactin was measured with a
radioimmunoassay kit (Prolactin Kit Daiichi II)
provided by the Daiichi Radioisotope Labs., Ltd.
(Tokyo, Japan). Serum sodium was measured by
flame photometry. Values (mean ± SD) were
analyzed statistically by using the unpaired Student’s t-test. Correlation coefficients were calcu-
lated by least squares analysis.

Results
The plasma level of AVP prior to the infusion of
hypotonic saline (baseline value) was significantly
(p<0.001) lower in patients with idiopathic DI
(0.42±0.24 pg/ml) than in normal subjects
(2.53±1.03 pg/ml) (Table 1). In contrast, baseline
serum sodium was significantly (p<0.001) higher
in patients with idiopathic DI (147.5±3.2 mEq/L)
than in normal subjects (139.7±2.4 mEq/L).
Although the baseline serum prolactin level did
not differ significantly between the controls and
the patients with idiopathic DI, one patient (case 2)
with DI had an abnormally high prolactin level
(35.6 ng/ml). Under basal conditions, no signi-
cificant correlation was found between serum pro-
lactin and serum sodium, or between serum
prolactin and plasma AVP.

After the infusion of hypotonic saline for 120

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>s-Na (mEq/L)</th>
<th>s-PRL (ng/ml)</th>
<th>p-AVP (pg/ml)</th>
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</thead>
<tbody>
<tr>
<td>1. E. M.</td>
<td>F</td>
<td>28</td>
<td>146</td>
<td>8.9</td>
<td>0.40</td>
</tr>
<tr>
<td>2. C. H.</td>
<td>F</td>
<td>22</td>
<td>147</td>
<td>35.6</td>
<td>0.10</td>
</tr>
<tr>
<td>3. H. N.</td>
<td>M</td>
<td>9</td>
<td>147</td>
<td>9.0</td>
<td>0.38</td>
</tr>
<tr>
<td>4. S. I.</td>
<td>F</td>
<td>46</td>
<td>152</td>
<td>19.7</td>
<td>0.62</td>
</tr>
<tr>
<td>5. Y. K.</td>
<td>M</td>
<td>50</td>
<td>153</td>
<td>4.7</td>
<td>0.38</td>
</tr>
<tr>
<td>6. T. A.</td>
<td>M</td>
<td>57</td>
<td>144</td>
<td>16.4</td>
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</tr>
<tr>
<td>7. M. Y.</td>
<td>M</td>
<td>18</td>
<td>145</td>
<td>20.8</td>
<td>0.76</td>
</tr>
<tr>
<td>8. K. I.</td>
<td>M</td>
<td>22</td>
<td>145</td>
<td>17.3</td>
<td>0.15</td>
</tr>
<tr>
<td>9. K. Y.</td>
<td>M</td>
<td>36</td>
<td>144</td>
<td>5.1</td>
<td>0.36</td>
</tr>
<tr>
<td>10. U. Y.</td>
<td>F</td>
<td>63</td>
<td>150</td>
<td>10.0</td>
<td>0.25</td>
</tr>
<tr>
<td>11. Y. N.</td>
<td>M</td>
<td>37</td>
<td>150</td>
<td>15.8</td>
<td>0.32</td>
</tr>
</tbody>
</table>

Patients (n=11) 147.5 ± 3.2a 14.8 ± 8.9 0.42 ± 0.24

Normal subjects (n=9) 139.7 ± 2.4 17.5 ± 3.4 2.53 ± 1.03

Values are the mean ± SD.
a: p<0.001 vs. normal subjects.
min, the serum sodium level increased gradually in normal subjects from the baseline value (139.7±2.4 mEq/L) to 146.5±4.3 mEq/L. Consequently, the plasma AVP level rose from 2.53±1.03 pg/ml to 8.56±1.46 pg/ml. However, the serum prolactin level was unaffected by the hypertonic saline stimulation (17.5±3.4 ng/ml before the infusion vs. 17.9±5.6 ng/ml afterwards) (Fig. 1).

In patients with idiopathic DI, the serum sodium level rose from 147.5±3.2 mEq/L to 155.6±3.4 mEq/L, and this increase caused a small increase in plasma AVP from 0.42±0.24 pg/ml to 0.79±0.34 pg/ml. However, the serum prolactin level did not change significantly following hypertonic saline infusion (14.7±9.9 ng/ml vs. 14.8±8.9 ng/ml) similar to the results in normal subjects (Fig. 1).

In the normal subjects and in the patients with idiopathic DI, the relationships between the levels of serum sodium and serum prolactin during the infusion of hypertonic saline indicated a weak but not significant negative correlation (r = -0.149 in normal subjects and -0.165 in patients with idiopathic DI) (Fig. 1). In one patient whose basal prolactin level exceeded the normal range, serum prolactin progressively decreased to 24.1 ng/ml with the increase in serum sodium.

The response of prolactin to TRH injection in patients with idiopathic DI is shown in Table 2. Individual variations in prolactin response to TRH

Table 2. Serum prolactin response to TRH in patients with idiopathic diabetes insipidus

<table>
<thead>
<tr>
<th>Case</th>
<th>Serum prolactin (ng/ml)</th>
<th>0</th>
<th>30</th>
<th>60</th>
<th>90</th>
<th>120 min</th>
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<tr>
<td>2</td>
<td>26.3</td>
<td>87.5</td>
<td>77.5</td>
<td>54.1</td>
<td>44.6</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>10.6</td>
<td>32.4</td>
<td>25.9</td>
<td>19.9</td>
<td>15.3</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>16.9</td>
<td>129.5</td>
<td>179.6</td>
<td>128.3</td>
<td>97.4</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>6.9</td>
<td>36.0</td>
<td>18.1</td>
<td>10.6</td>
<td>7.1</td>
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</tr>
<tr>
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<td>9.5</td>
<td>30.0</td>
<td>24.3</td>
<td>17.2</td>
<td>15.2</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>ND*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>21.6</td>
<td>82.0</td>
<td>64.7</td>
<td>48.0</td>
<td>43.5</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>9.3</td>
<td>71.8</td>
<td>64.7</td>
<td>35.7</td>
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<tr>
<td>10</td>
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<td>59.3</td>
<td>43.3</td>
<td>26.5</td>
<td>15.4</td>
<td></td>
</tr>
</tbody>
</table>

a: Not determined.
were seen, but these responses were essentially normal in all patients with idiopathic DI [11]. One patient (case 2) whose baseline prolactin was increased (three different measurements: values of 35.6, 33.1, 26.3 ng/ml, respectively) did not indicate a marked response to TRH.

**Discussion**

In patients with idiopathic DI, several reports have shown that inexplicable hyperprolactinemia is sometimes observed [1, 2]. In this study, one of the eleven patients with idiopathic DI also had mild hyperprolactinemia. Generally, in patients with DI, thirst and polydipsia compensate for the polyuria induced by AVP deficiency. The present study shows that this compensation is often incomplete. Thus, mild chronic dehydration is present in most patients with DI before appropriate treatment is initiated. Prolactin is known to be a physiological regulator of water and electrolyte metabolism in teleost fish [6]. The role of prolactin in the metabolism of water and electrolytes in man received attention following the initial report by Buckman et al. [7]. However, almost all of the subsequent studies suggest that prolactin does not play an important role in water and electrolyte metabolism in normal hydrated humans [8, 12].

We designed this study to determine whether the secretion of prolactin would be affected by the chronic hypernatremic hypovolemia present in patients with idiopathic DI. Firstly, the acute hyperosmolar increase induced by hypertonic saline infusion failed to stimulate prolactin secretion not only in the normal subjects studied but also in the patients with DI. Secondarily, the prolactin response to TRH was essentially normal in patients with idiopathic DI. These findings suggest that the function in lactotropes is generally unaffected by chronic hyperosmotic hypovolemia in the AVP-deficient state.

The reason for the increased prolactin at the baseline in one patient described is uncertain. However, recent studies strongly suggest that the posterior pituitary plays an important role in prolactin secretion. Ben-Jonathan et al. [3, 4, 5] reported that posterior pituitary lobectomy significantly increases plasma prolactin in rats. It is conceivable that in this species dopamine contained in the posterior pituitary partially suppresses prolactin release from the anterior pituitary; thus the dopamine neuron in the posterior pituitary could be affected directly or indirectly in the case of hypothalamo-neurohypophyseal dysfunction.

**References**

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