A Patient with a Prolactinoma Associated with an Aldosterone Producing Adrenal Adenoma: Differences in Dopaminergic Regulation of PRL and Aldosterone Secretion

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Abstract. A patient with a rare combination of prolactinoma and aldosterone producing adrenal adenoma (APA) was reported in relation to studies concerning dopaminergic regulation of PRL and aldosterone secretion. The patient is a 38-year-old female with plasma PRL and aldosterone concentrations (PAC) of 563 ng/ml and 54 ng/dl, respectively. A bolus of 10 mg of metoclopramide significantly increased plasma PRL in 6 normal subjects and in 4 patients with APA, whereas the responses were blunted in 7 patients with prolactinoma and in our patient. The response of aldosterone to metoclopramide was less than that of PRL, but similar in all studied subjects, indicating that the dopaminergic inhibition of aldosterone secretion is less than that of PRL in normal subjects and did not change in patients with APA or prolactinoma. Oral administration of 2.5 mg of bromocriptine suppressed plasma PRL significantly in all the subjects studied, but did not produce any consistent changes in PAC. Discrepancies in the response of PRL and aldosterone to metoclopramide and to bromocriptine suggest a difference in the dopaminergic regulation of PRL and aldosterone secretion in both normal subjects and patients with prolactinoma and APA. It is unlikely that reduced dopaminergic inhibition is the basis for hypersecretion of PRL and aldosterone in our patient.

Key words: Prolactinoma, APA, Bromocriptine, Metoclopramide. (Endocrinol Japon 39: 169–176, 1992)
Materials and Methods

Case report

The patient was a 38-year-old female with increased plasma PRL (563 ng/ml) and a pituitary macroadenoma on computerized tomographic scan (CT). The results of pituitary function tests, summarized in Table 1, indicate that reserves are partially impaired. Serum PRL levels did not significantly change in response to administration of TRH. The patient also had hypertension (210/110 mmHg) associated with suppressed levels of plasma renin activity (PRA, 0.1 ng/ml/h), and an elevated plasma aldosterone concentration (PAC, 54 ng/dl) after overnight recumbency while consuming an unrestricted diet. PRA remained suppressed even after intravenous administration of 40 mg of furosemide and standing for 2 h (0.2 ng/ml/h before and 0.2 ng/ml/h after). A solitary adenoma was found in the left adrenal gland on CT and magnetic resonance imaging (MRI). These data supported the diagnosis of a prolactinoma associated with an APA.

The course after admission is summarized in Fig. 1. Nifedipine, a calcium channel blocker, lowered blood pressure to 150/90 mmHg, while PRL and PAC remained high. After initiation of bromocriptine therapy (5.0 to 7.5 mg/day), plasma PRL levels decreased strikingly and attained normal levels within 2–3 weeks. Although PAC tended to decrease after initiation of bromocriptine treatment, it remained high in sharp contrast to that of PRL. Bromocriptine did not alter the response of PAC to intravenous injection of furosemide followed by standing for 2 h (36.8 ng/dl before and 38.2 ng/dl after). Intravenous injection of synthetic 1–24 ACTH resulted in a rise

Table 1. Pituitary function test

<table>
<thead>
<tr>
<th>Test</th>
<th>normal</th>
<th>basal level</th>
<th>before</th>
<th>max.</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT*</td>
<td>GH (ng/ml)</td>
<td>5</td>
<td>1.5</td>
<td>0.1</td>
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<tr>
<td></td>
<td>Cortisol (ng/dl)</td>
<td>4.5–24</td>
<td>20.5</td>
<td>28.8</td>
</tr>
<tr>
<td>TRH</td>
<td>TSH (mU/ml)</td>
<td>0.2–0.4</td>
<td>2.0</td>
<td>24.7</td>
</tr>
<tr>
<td>PRL</td>
<td>(ng/ml)</td>
<td>15</td>
<td>479</td>
<td>555</td>
</tr>
<tr>
<td>LH-RH</td>
<td>LH (mU/ml)</td>
<td>1.5–12.7</td>
<td>6.8</td>
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</tr>
<tr>
<td></td>
<td>FSH (mU/ml)</td>
<td>3.2–10.2</td>
<td>5.6</td>
<td>7.4</td>
</tr>
</tbody>
</table>

* ITT: Insulin Tolerance Test.

Fig. 1. Clinical course of the patient with a prolactinoma and an APA.
in plasma aldosterone of 16.0 ng/dl before and 91.3 ng/dl during bromocriptine treatment. A left adrenalectomy was performed one month after admission and a golden yellow adenoma, 16 × 9 × 8 mm in size, was extirpated with normal adjacent adrenal tissues. The histological findings were compatible with the diagnosis of APA. The serum potassium concentration, PAC, and blood pressure were normal within 2 weeks after surgery. Plasma PRL remained suppressed and there was a marked reduction in the size of the pituitary tumor on brain CT and MRI with continued administration of bromocriptine after adrenalectomy. Menstruation resumed about 2 months after surgery.

Metoclopramide test

A metoclopramide test was performed in this patient and in 6 normal subjects (25–48 yr), 7 patients (18–51 yr) with prolactinoma (aldosterone samples were not available from 4 of 7 normal subjects), and 7 patients (30–58 yr) with APA. All patients and normal subjects were studied while they were consuming a diet unrestricted in sodium after an overnight fast, and following assumption of a supine position for at least 1 h prior to basal sampling. A bolus of 10 mg of metoclopramide was injected intravenously between 0900 h and 0930 h. Plasma samples were obtained before and 30 min after injection, since published reports [7] and our preliminary studies have shown that both PRL and PAC reach their peak values 30 min after intravenous injection of metoclopramide.

Bromocriptine test

The changes in plasma PRL and aldosterone concentrations in response to bromocriptine administration were examined in this patient, 5 normal subjects (aldosterone samples were not available from 2 of these 5 subjects), 5 patients with prolactinoma and 4 patients with APA. Bromocriptine (2.5 mg) was administered orally at 0900 h. Plasma samples for assay of PRL and aldosterone were obtained at 0, 2, 4, and 6 h. In addition samples were obtained from some patients at 1, 8, 12 and 24 h. The study conditions were the same as those for the metoclopramide test except that all patients and normal subjects were allowed to have a light meal at the time of bromocriptine administration to minimize gastrointestinal symptoms.

Plasma was separated immediately and stored at −20°C until the assay. The hormones were determined by radioimmunoassay with commercially available kits. PRL and aldosterone kits were obtained from Eiken ICL (Tokyo, Japan) and PRA kits were obtained from Dainabot RI Laboratories (Tokyo, Japan). Normal values for PRL, aldosterone and PRA were 2–20 ng/ml, 2.2–15 ng/dl and 0.5–3.0 ng/ml/h. The inter- and intra-assay variations for all of the assays were within 10%. Statistical analysis was performed by ANOVA followed by Duncan’s multiple range test.

Results

The responses of PRL and aldosterone concentrations to metoclopramide are shown in Figs. 2 and 3, respectively, and the maximal percent changes are shown in Fig. 5. Plasma PRL levels increased significantly in normal subjects (M±SD, 1146±198%) and in patients with APA (615±360%), while the response was blunted in the present patient (126%) and in patients with prolactinoma (118±30%). The responses of aldosterone to metoclopramide at 30 min were 156±43% in normal subjects, 174±60% in patients with prolactinoma, 154±30% in patients with APA, and 140% in the present patient.

The acute effects of bromocriptine on PRL and aldosterone levels are shown in Fig. 4 and percent changes at 6 h are shown in Fig. 5. Plasma levels of PRL were suppressed by a single administration of 2.5 mg of bromocriptine to 12±5% of the basal levels in normal subjects, 27±9% in patients with prolactinoma and 23±5% in patients with APA. No significant differences were observed among the 3 groups. Bromocriptine suppressed our patient’s plasma PRL from 563 ng/ml to 51 ng/ml (9%) with the lowest value at 6 h.

In contrast to changes in plasma PRL levels, bromocriptine did not produce any significant changes in PAC in normal subjects (92±11%) or in patients with prolactinoma (83±39%), although mean levels tended to decrease. Bromocriptine administration was followed by large fluctuations of plasma aldosterone levels in 2 of 4 patients with APA. PAC decreased after 1 h and then peaked at 2 and 4 h and subsequently fell to below the basal level at 6 h in the present patient. There were no
Fig. 2. PRL levels before and 30 min after iv administration of 10 mg of metoclopramide to 6 normal subjects, 7 patients with prolactinoma and 7 patients with APA. The points connected by a dashed line indicate the results for the patient described in this report.

Fig. 3. PAC before and 30 min after iv administration of 10 mg of metoclopramide to 6 normal subjects, 3 patients with prolactinoma and 6 patients with APA. The points connected by a dashed line indicate the results for the patient described in this report.
DOPAMINE ON PRL AND ALDOSTERONE

Fig. 4. Changes in plasma levels of PRL and aldosterone after oral administration of 2.5 mg of bromocriptine to 5 patients with prolactinoma ( ), 4 patients with APA ( ) and the present patient ( ). The shadow area includes the mean ± SD for normal subjects.

Discussion

The results of the present study demonstrate that there are differences in the response of PRL and aldosterone to metoclopramide as well as to bromocriptine in normal subjects and in patients with prolactinoma or APA and in one patient with a prolactinoma and an APA.

The aldosterone responses to metoclopramide were significantly lower than the responses of PRL to metoclopramide in normal subjects and in patients with APA. Assessing metoclopramide response as an index of the extent of dopaminergic inhibition, the findings suggest that dopaminergic inhibition is less important in determining the secretion of aldosterone than in determining the secretion of PRL in normal subjects.

Fig. 5. Maximal responses of PRL (above) and aldosterone (below) to (a) metoclopramide and (b) bromocriptine in all patients and normal subjects studied. The mean maximal responses for each group are indicated by short horizontal lines. The significance of differences between groups are shown (*, P<0.01; NS, not significant).
and in patients with APA. These observations are similar to those made in earlier studies of normal subjects [9-14]. The small aldosterone release in response to metoclopramide seen in normal subjects and in patients with APA was similar to that seen in our patient and in patients with prolactinoma.

In contrast to the results in normal subjects and patients with APA, the maximal percentage response of PRL to metoclopramide was significantly attenuated in patients with prolactinoma and also was minimal in our patient, indicating that the dopaminergic inhibition of PRL secretion is reduced in patients with prolactinoma. Diminished response of PRL to metoclopramide was reported earlier in patients with prolactinoma and in patients with hypothalamic lesions [15, 16]. Impaired tubero-infundibular dopaminergic neurons or an increased turnover of dopamine in the hypothalamus and/or pituitary have been postulated to explain these findings.

There have been some inconsistencies concerning the changes in dopamine tone modulating aldosterone secretion in patients with APA: both increased [17, 18] and unchanged [19, 20, 21] dopamine tone have been reported. The results of the present study showed that the responses of plasma aldosterone to metoclopramide in patients with APA are approximately the same as those in normal subjects, suggesting that dopaminergic tone is not greatly altered in the adrenals of patients with APA.

In addition to the results obtained with metoclopramide, there were differences in the responses of PRL and aldosterone to the administration of bromocriptine. Our results together with most earlier reports [1, 2, 7] show some degree of suppression of PRL in response to bromocriptine in all normal subjects and patients studied. Dopamine receptors in the pituitary gland have been well characterized in ligand-binding studies [22, 23] and PET analysis [24]. DA-2 receptors have been found on normal lactotrophs and in prolactinoma tissues [22, 23]. The affinity and the concentration of binding sites in pituitary adenomas were roughly the same as those in normal lactotrophs. More recently, gene expression of DA-2 receptor has been demonstrated by in situ hybridization [25].

In contrast, there was relatively little effect of bromocriptine on aldosterone secretion in any of the patients or normal subjects studied. Most earlier reports describe a discrepancy between the responses of PRL and aldosterone to bromocriptine [26, 27, 28, 29]. While plasma aldosterone concentrations at times varied after bromocriptine administration to normal subjects and patients with prolactinoma and APA, no consistent changes were observed. Since changes in PRA and in serum potassium levels were not associated with changes in plasma aldosterone levels after bromocriptine administration, the renin-angiotensin system and changes in serum potassium concentrations could not account for the variations observed in the plasma aldosterone concentration. Changes in ACTH levels cannot be ruled out as a cause for the observed changes in plasma aldosterone levels.

Although both adrenal and pituitary DA receptors have been reported to be of the DA-2 type [22, 23, 30, 31], Carey et al. [11, 12] have suggested that the differences in response could be attributed to differences in the subtypes of dopamine receptors on the adrenals and the pituitary. A recent study with receptor gene expression reported that no DA-2 receptors or dopamine- and adenylylcylclosis-regulated phosphoprotein (DARPP-32), a presumptive marker for D-1-receptive neurons, were found in the adrenal cortex of rats, though DA-2 receptors were found in the adrenal medulla of these animals [25]. DA receptors in the adrenal cortex may be few in number and/or different in type from those in the pituitary.

The lower aldosterone response to metoclopramide and the poor suppression of aldosterone by bromocriptine compared to the response and suppression of PRL, may be attributed to less dopaminergic innervation and fewer dopaminergic receptors in the adrenals compared to the pituitary. Dopaminergic regulation of PRL and aldosterone must be independent of each other in normal subjects, in patients with APA, and in prolactinoma. It would seem physiologically appropriate for regulation of aldosterone and PRL release to be independent. Dopamine is the most potent physiological PRL release inhibiting factor, while many factors other than dopamine such as the renin-angiotensin system, potassium, and ACTH regulate the secretion of aldosterone.

In our patient the changes in PRL and aldosterone in response to metoclopramide and bromocriptine, respectively, were similar to those in patients with prolactinoma and with APA, respect-
tively. It is unlikely that reduced dopaminergic inhibition is the basis for hypersecretion of PRL and aldosterone in our patient. The coexistence of a prolactinoma and an APA found in this case may be coincidental.

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