Abstract

The responses of the adenohypophyseal hormones to metoclopramide (MCP) were evaluated in hyperprolactinemic women with various radiological findings on the sella turcica. Serum PRL concentrations significantly increased after MCP administration in normal women, hyperprolactinemic patients with normal sella and patients with microadenoma, but not in macroadenoma patients with and without suprasellar expansion (SSE). The PRL response to MCP administration was significantly lower in hyperprolactinemic patients than in normal women. Serum TSH concentrations significantly increased after MCP administration in each group of subjects. The TSH response to MCP was significantly higher in patients with normal sella and patients with microadenoma than in normal women. However, the responses of PRL and TSH to MCP were not significantly different between patients with normal sella and patients with microadenoma. Therefore, they were not considered useful in distinguishing tumorous from nontumorous hyperprolactinemia. Serum LH concentrations significantly increased after MCP administration in patients with normal sella, patients with microadenoma and macroadenoma patients without SSE, but not in normal women or macroadenoma patients with SSE. The LH response to MCP was significantly higher in patients with microadenoma than in patients with normal sella. Serum FSH concentrations significantly increased after MCP administration only in patients with microadenoma. The different responses of the adenohypophyseal hormones to MCP in hyperprolactinemic women with various radiological findings on the sella turcica may be explained by the difference in the hypothalamic dopamine activity and in the impairment of the hypothalamic-pituitary system due to pituitary tumor.

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FSH and TSH in hyperprolactinemic women, but not in normal women (Quigley et al., 1979; Quigley and Yen, 1980; Seki et al., 1982). These findings were interpreted as indicating an increased hypothalamic DA activity in hyperprolactinemic women (Quigley et al., 1979), and an MCP test was considered useful for the functional evaluation of the adenohypophysis in hyperprolactinemic women (Seki et al., 1982). However, Andersen and Tabor (1982) failed to observe any consistent abnormality in either the TSH or LH response after MCP administration in hyperprolactinemic women. Pathophysiological states in hyperprolactinemic women are diverse (Boyar et al., 1974), and the pituitary pathology differs in each woman with hyperprolactinemia. Therefore, the inconsistent responses of the adenohypophyseal hormones to MCP in hyperprolactinemic women may be accounted for by the difference in the pituitary pathology in each patient. The responses of the adenohypophyseal hormones to MCP have not heretofore been compared with pituitary pathology in the same patients with hyperprolactinemia, however. In the present study, the responses of PRL, TSH, LH and FSH to MCP were evaluated in hyperprolactinemic women with various radiological findings of the sella turcica to better understand the hypothalamic-pituitary function in hyperprolactinemic women.

Materials and Methods

The subjects of this study were 12 normal women during the early follicular phase and 27 hyperprolactinemic-amenorrheic women (Table 1). Radiological examinations for pituitary tumor were performed in hyperprolactinemic women with plain skull X-ray, tomography of the sella turcica and CT scan (GE CT/T, section thickness of 1.5 mm). Pituitary tumor was radiologically identified in 18 of the 27 hyperprolactinemic women (9 microadenomas and 9 macroadenomas). Suprasellar expansion (SSE) was recognized in 5 of the 9 patients with macroadenoma. After the MCP test, five of the 9 patients with microadenoma and 9 of the 9 patients with macroadenoma were operated on. In all of the patients who were operated on, radiological diagnosis of pituitary tumor was confirmed. All subjects were free from any medication for at least 6 weeks prior to examination. Starting at 0900 h

Table 1. Clinical and basal hormone data (mean±SE) in normal women during the early follicular phase and hyperprolactinemic-amenorrheic patients with normal pituitary fossa and pituitary tumor.

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Normal Women (N=12)</th>
<th>Normal Fossa (N=9)</th>
<th>Microadenoma without SSE (N=9)</th>
<th>Macroadenoma with SSE (N=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>26.2±2.0</td>
<td>30.1±2.3</td>
<td>31.8±1.1</td>
<td>25.8±3.6</td>
</tr>
<tr>
<td>Weight (in % of IBW)</td>
<td>102.0±3.2</td>
<td>100.4±2.8</td>
<td>105.0±3.7</td>
<td>99.9±5.7</td>
</tr>
<tr>
<td>FSH (ng/ml)</td>
<td>331.0±25.1</td>
<td>270.4±31.8</td>
<td>263.0±20.6</td>
<td>246.5±20.6</td>
</tr>
<tr>
<td>LH (ng/ml)</td>
<td>89.1±9.0</td>
<td>81.0±14.8</td>
<td>99.0±22.5</td>
<td>107.0±19.5</td>
</tr>
<tr>
<td>PRL (ng/ml)</td>
<td>9.1±1.3</td>
<td>103.0±11.4</td>
<td>111.6±20.4</td>
<td>219.0±92.1</td>
</tr>
<tr>
<td>TSH (μU/ml)</td>
<td>4.0±0.5</td>
<td>3.9±0.5</td>
<td>4.4±0.7</td>
<td>2.3±0.3</td>
</tr>
<tr>
<td>T4 (μg/ml)</td>
<td>6.2±0.4</td>
<td>6.7±0.4</td>
<td>6.9±0.5</td>
<td>7.5±0.8</td>
</tr>
<tr>
<td>E2 (pg/ml)</td>
<td>42.1±1.7</td>
<td>32.8±4.5</td>
<td>28.1±4.2</td>
<td>24.5±1.8</td>
</tr>
</tbody>
</table>

SSE=suprasellar expansion.
IBW=ideal body weight.
1 p<0.05 vs normal women.
2 p<0.01 vs normal women.
3 p<0.001 vs normal women.
to 1000 h, each subject received 10 mg of MCP as an iv bolus after two baseline samples had been obtained. Additional blood samples were obtained at 15, 30, 60, 120 and 180 min after MCP administration. Serum FSH, LH, TSH, estradiol (E2) and thyroxine (T4) concentrations were measured by radioimmunoassay with the CIS radioimmunoassay kits. FSH and LH concentrations were expressed in terms of ng LER 907/ml. Serum PRL concentrations were measured by radioimmunoassay with the radioimmunoassay kit purchased from the Daiichi Radioisotope Laboratory, Japan. The intra- and interassay coefficients of variation were less than 10% in each radioimmunoassay. FSH, LH, TSH and PRL were determined on all samples, E2 and T4 on baseline samples only. Mean basal concentrations were obtained by averaging two baseline samples collected prior to MCP administration. The area under the curve (AUC) was calculated by the trapezoid integration method.

Statistical analyses were performed using paired and unpaired Student’s t-test.

Results

Mean basal concentrations of FSH, LH, TSH and T4 in hyperprolactinemic women were not significantly different from those in normal women except for significantly lower FSH and LH concentrations in macroadenoma patients with SSE (Table 1). Mean basal concentrations of E2 were significantly lower in hyperprolactinemic women than in normal women (Table 1). Serum PRL concentrations significantly increased after MCP administration in normal women, hyperprolactinemic patients with normal sella and patients with microadenoma, but not in macroadenoma patients with and without SSE (Fig. 1). Serum PRL concentrations were significantly higher at 15, 30, 60, 120 and 180 min after MCP administration in normal women, at 15, 30 and 60 min in

Fig. 1. Serum PRL and TSH levels (mean±SE) before and after MCP administration in normal women during the early follicular phase and in hyperprolactinemic-amenorrheic patients with normal pituitary fossa and pituitary tumor (microadenoma, macroadenoma without SSE and macroadenoma with SSE).

*p<0.05, **p<0.01 and ***p<0.001 vs basal hormone concentrations.
Table 2. The mean (±SE) area under the curve (AUC) of PRL, TSH and FSH after MCP in normal women during the early follicular phase and hyperprolactinemic-amennorrheic patients with normal pituitary fossa and pituitary tumor.

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Normal Women (N=12)</th>
<th>Normal Fossa (N=9)</th>
<th>Microadenoma (N=9)</th>
<th>Macroadenoma without SSE (N=4)</th>
<th>Macroadenoma with SSE (N=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRL (ng/ml×min)</td>
<td>16379.8±2160.1</td>
<td>5583.6±1838.3</td>
<td>2639.1±577.4</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>TSH (μU/ml×min)</td>
<td>102.9±29.9</td>
<td>729.2±254.8</td>
<td>962.0±176.8</td>
<td>139.3±89.4</td>
<td>118.8±29.7</td>
</tr>
<tr>
<td>LH (ng/ml×min)</td>
<td>—</td>
<td>1310.9±1615.2</td>
<td>5625.6±1313.2</td>
<td>4500.0±1775.0</td>
<td>—</td>
</tr>
<tr>
<td>FSH (ng/ml min)</td>
<td>—</td>
<td>—</td>
<td>6414.2±1367.7</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

SSE = suprasellar expansion.

1 p<0.01 vs normal women.
2 p<0.001 vs normal women.
3 p<0.01 vs microadenoma.
4 p<0.001 vs microadenoma.

Fig. 2. Serum LH and FSH levels (mean ±SE) before and after MCP administration in normal women during the early follicular phase and in hyperprolactinemic-amennorrheic patients with normal pituitary fossa and pituitary tumor (microadenoma, macroadenoma without SSE and macroadenoma with SSE).

* p<0.05, ** p<0.01 and *** p<0.001 vs basal hormone concentrations.
patients with normal sella, and at 15 and 30 min in patients with microadenoma when compared to the basal concentrations (Fig. 1). The mean AUC of PRL was significantly lower in patients with normal sella and those with microadenoma than in normal women (Table 2). However, it was not significantly different between patients with normal sella and patients with microadenoma. Serum TSH concentrations significantly increased after MCP administration in each group of subjects (Fig. 1). Serum TSH concentrations were significantly higher at 15, 30, 120 and 180 min after MCP in normal women, at 15, 30 and 60 min in patients with normal sella, at 15, 30, 60, 120 and 180 min in patients with microadenoma, at 30 min in macroadenoma patients without SSE and at 60 min in macroadenoma patients with SSE when compared to the basal concentrations (Fig. 1). The mean AUC of TSH was significantly higher in patients with normal sella and those with microadenoma than in normal women, but not in macroadenoma patients with and without SSE (Table 2). It was not significantly different between patients with normal sella and those with microadenoma. Serum LH concentrations significantly increased after MCP in patients with normal sella, patients with microadenoma and macroadenoma patients without SSE, but not in normal women and macroadenoma patients with SSE (Fig. 2). Serum LH concentrations were significantly higher at 30 min after MCP administration in patients with normal sella, at 15, 30 and 60 min in patients with microadenoma and at 15 and 30 min in macroadenoma patients without SSE when compared to the basal concentrations (Fig. 2). The mean AUC of LH was significantly higher in patients with microadenoma than in patients with normal sella (Table 2). However, the mean AUC of LH in macroadenoma patients without SSE was not significantly different from that in patients with normal sella nor that in patients with microadenoma. Serum FSH concentrations significantly increased after MCP administration in patients with microadenoma, but not in other groups of subjects (Fig. 2). Serum FSH concentrations were significantly higher at 15, 30, 60 and 120 min after MCP in patients with microadenoma when compared to the basal concentrations (Fig. 2).

**Discussion**

Although the responses of the adenohypophyseal hormones to MCP have previously been studied in hyperprolactinemic women with microadenoma and those with normal sella (Quigley et al., 1979; Quigley and Yen, 1980; Seki et al., 1982; Anderson and Tabor, 1982), there are no reported studies which evaluate the responses of the adenohypophyseal hormones to MCP in hyperprolactinemic women with macroadenoma. Further, comparison has not been made of the responses of the adenohypophyseal hormones to MCP between hyperprolactinemic patients with normal sella and those with microadenoma. The present study represents the first attempt to evaluate the responses of the adenohypophyseal hormones to MCP in the same hyperprolactinemic patients with various radiological findings of the sella turcica. Positive responses of FSH and LH to MCP were observed in hyperprolactinemic patients with microadenoma, but not in normal women. The TSH response was greater, and the PRL response was lower in these patients than in normal women. These findings are in general agreement with the results of Quigley et al. (1979) and Quigley and Yen (1980), and support the contention that hypothalamic DA activity is increased in hyperprolactinemic patients with microadenoma. The TSH and PRL responses to MCP in hyperprolactinemic patients with normal sella were qualitatively and quantitatively similar to those in patients with microadenoma. Therefore, the responses of TSH
and PRL to MCP are not considered useful for distinguishing tumorous from non-tumorous hyperprolactinemia. The FSH response to MCP was absent in hyperprolactinemic patients with normal sella, and the LH response was significantly smaller in these patients than in patients with microadenoma. This may probably reflect different hypothalamic DA activity in these patients. However, it is not clear now whether positive FSH response and greater LH response to MCP indicate the existence of microadenoma since the number of subjects was rather small.

In macroadenoma patients without SSE, the TSH response to MCP was smaller than in patients with microadenoma, but the LH response was similar to that in patients with microadenoma. In patients with macroadenoma, not only hyperprolactinemia per se but also morphological alterations in the hypothalamic-pituitary system caused by a large pituitary tumor may influence the secretion of the adenohypophyseal hormones, since the LH response to luteinizing hormone releasing factor and the GH response to insulin-induced hypoglycemia were, in our previous study (Seki et al., 1984), found to be impaired in patients with macroadenoma when compared to patients with microadenoma. It is of interest that only the LH response to MCP was not impaired in macroadenoma patients without SSE compared to that in patients with microadenoma. Because the number of subjects was small, the LH response to MCP in macroadenoma patients without SSE should be further evaluated.

In macroadenoma patients with SSE, no significant changes in FSH, LH and PRL were discernible after MCP administration. This most likely reflects the marked impairment of the hypothalamic-pituitary system due to the large pituitary tumor and SSE since basal concentrations of FSH and LH were also significantly lower in these patients than in normal women. However, it is to be noted that positive response of TSH to MCP was observed in each group of subjects including macroadenoma patients with SSE. Therefore, dopaminergic inhibition of TSH release appears to be operative both in normal women and in hyperprolactinemic women irrespective of the morphological alterations of the pituitary fossa, though the degree of inhibition differs.

References


