Lack of effect of chronic hypocalcaemia on serum prolactin response to chlorpromazine

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Abstract. The effects of chronic hypocalcaemia on serum basal and chlorpromazine-stimulated prolactin (Prl) levels were studied in 16 patients with idiopathic or secondary hypoparathyroidism. These results were compared with the results of other chlorpromazine stimulation tests which were made in the normocalcaemic state after treatment with vitamin D, and in normal subjects.

In hypocalcaemic and normocalcaemic states (mean serum Ca 5.8 ± 0.24 mg/dl and 9.5 ± 0.11 mg/dl, respectively) basal Prl levels were within the normal range and during stimulation the maximal stimulated levels in each state were not significantly different from each other. Also, the mean serum Prl levels obtained from a control group were not different from values in the normocalcaemic state.

It is concluded that chronic hypocalcaemia does not inhibit Prl secretion and low serum parathyroid hormone levels do not affect basal and chlorpromazine-stimulated Prl secretion.

Recent studies have suggested that cations, especially Ca++ play an important role in the synthesis and release of anterior pituitary hormones (Vale et al. 1967; Samli & Geschwind 1968; Wakabayashi et al. 1969; Kraicer et al. 1969; Jutisz & DelaLlosa 1970; MacLeod & Fontham 1970; Parsons 1970; Gautvik & Tashjian 1973). In addition, it has been reported that the production and secretion of prolactin (Prl) by rat adenohypophysis in vitro, are also dependent upon calcium ions (Parsons 1969, 1970; Gautvik & Tashjian 1973; Wakabayashi et al. 1973; White et al. 1981).

Few data are available about the effect of acute changes of plasma calcium levels on Prl secretion. Recently, an increase in plasma Prl levels during parathyroid hormone (PTH) infusion (Isaac et al. 1978) and a significant decrease of Prl levels after administration of salmon calcitonin (CT) (Carman & Wyatt 1977; Isaac et al. 1980) have been demonstrated in man. An inhibitory effect of calcium infusions on serum Prl levels in children and adults has been observed in other investigations (Ajlouni & El Khateeb 1981; Kruse & Kracht 1981). It has also been found that hypocalcaemia produced by human CT injection might cause a small increase in serum Prl levels (Stevenson et al. 1977).

The results of these investigations, suggesting that calcium may also be involved in Prl synthesis and secretion in man, prompted us to study the effect of chronic hypocalcaemia on basal and chlorpromazine-stimulated serum Prl levels.

Material and Methods

Sixteen patients with idiopathic or secondary hypoparathyroidism were studied, 12 women and 4 men (age range 22–45 years).

The serum creatinine and urea nitrogen concentrations were within normal range in all patients and they were taking no other drug affecting serum Prl levels. Serum calcium (Ca) levels were low and phosphate (P) levels were increased.

Chlorpromazine was used to stimulate the secretion of Prl. It is known that chlorpromazine stimulates Prl secretion by blocking dopamine receptors.

A single im injection of chlorpromazine in a dose of 50 mg was used to stimulate serum Prl levels. Blood samples were obtained before injection and at 30, 60, 90, 120, 180, 240 min afterwards.

After the completion of this experiment vitamin D₃ treatment was given to the patients. When a normocal-
caemic state was obtained, the chlorpromazine stimulation test was repeated in the same manner. The laboratory data of the patients are summarized in Table 1.

To assess the effect of low PTH levels on serum Prl concentrations, 7 normal subjects were investigated as a control group with the same study protocol.

All samples from each subject were analyzed for Prl in duplicate in the same assay in order to eliminate any inter-assay variations. At least a 2-fold rise of basal serum Prl concentrations following chlorpromazine administration was the criterion for a normal response (Friesen et al. 1972).

Total serum Ca was determined with an atomic absorption spectrophotometer and serum Prl was assayed with a specific homologous radioimmunological method (Sinha et al. 1973) 'IRE Prolactin Radioimmunoassay Kit'.

The sensitivity of the assay was 34 ± 5 µU/ml. Data were analyzed statistically by Student's t-test and the Mann-Whitney U test. P-values greater than 0.05 were considered non-significant in this study.

Results

The mean values of total serum Ca and inorganic phosphate and basal Prl levels, in the hypocalaemic state, as shown in Table 1, were 5.8 ± 0.24 mg/dl, 6.06 ± 0.45 mg/dl and 278 ± 40 µU/ml, respectively.

During the chlorpromazine stimulation test, serum Prl concentrations reached their maximum levels at 60 min, the mean level being 2043 ± 371 µU/ml (P < 0.001).

After treatment, the mean total serum Ca level rose to 9.5 ± 0.11 mg/dl, and the mean serum P level fell to 4.75 ± 0.24 mg/dl (P < 0.001) reaching the normal range. The mean basal serum Prl level was 296 ± 63 µU/ml and during the stimulation test the peak level was 2011 ± 451 µU/ml (P < 0.01) and the maximal increase also occurred at 60 min (Table 2).

In hypocalcaemic and normocalcaemic states, basal serum Prl levels were within the normal range and maximally stimulated levels in each state were not significantly different from each other. Additionally, the maximal increments occurred at the same time (60 min) in each condition. The mean serum Prl levels obtained from the control group were also not different from values in the normocalcaemic state (Table 2).

<table>
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<th>Patients</th>
<th>Hypocalcaemic state</th>
<th>Normocalcaemic state</th>
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<tbody>
<tr>
<td></td>
<td>Ca (mg/dl)</td>
<td>P (mg/dl)</td>
</tr>
<tr>
<td>1</td>
<td>4.9</td>
<td>5.3</td>
</tr>
<tr>
<td>2</td>
<td>4.3</td>
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</tr>
<tr>
<td>3</td>
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<tr>
<td>16</td>
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</table>

Mean ± se 5.8 ± 0.24 6.0 ± 0.45 278 ± 40 9.5 ± 0.11 4.7 ± 0.24 296 ± 63
Table 2.
Serum Prl levels (µU/ml) (mean ± se) during chlorpromazine stimulation tests on three occasions.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Patients with hypoparathyroidism</th>
<th>Control group</th>
<th>P-value¹</th>
<th>P-value²</th>
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<tbody>
<tr>
<td></td>
<td>Hypocalcaemic state</td>
<td>Normocalcaemic state</td>
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<tr>
<td>0</td>
<td>278 ± 40</td>
<td>296 ± 63</td>
<td>NS</td>
<td>294 ± 99</td>
</tr>
<tr>
<td>30</td>
<td>1639 ± 385</td>
<td>1395 ± 349</td>
<td>NS</td>
<td>1244 ± 94</td>
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<tr>
<td>60</td>
<td>2043 ± 371</td>
<td>2011 ± 451</td>
<td>NS</td>
<td>1880 ± 793</td>
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<tr>
<td>90</td>
<td>1712 ± 297</td>
<td>1473 ± 278</td>
<td>NS</td>
<td>1624 ± 652</td>
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<tr>
<td>120</td>
<td>1866 ± 368</td>
<td>1413 ± 247</td>
<td>NS</td>
<td>1562 ± 629</td>
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<td>180</td>
<td>1566 ± 301</td>
<td>1383 ± 246</td>
<td>NS</td>
<td>1564 ± 695</td>
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<td>240</td>
<td>1207 ± 211</td>
<td>1192 ± 247</td>
<td>NS</td>
<td>1038 ± 165</td>
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</table>

¹ Significance of differences between hypocalcaemic and normocalcaemic states.
² Significance of differences between normocalcaemic state and control group.
NS: non significant.

Discussion

Calcium ions are necessary for Prl synthesis and/or secretion by the rat adenohypophysis in vitro, and act as an intracellular mediator (Parsons 1969, 1970; Gautvik & Tashjian 1973; Tashjian et al. 1978; Moriarty & Leuschcn 1981; White et al. 1981).

Investigations concerning the effect of acute or chronic changes of serum calcium on Prl secretion in man are scant. An acute infusion of parathyroid extract produced a parallel increase in plasma Prl in normal man and the mechanism of this increment was an increase in Prl secretion (Isaac et al. 1978; Castro et al. 1980). According to Isaac et al. (1978) this effect of PTH was the result of antagonism between PTH and dopamine either at the hypothalamic or pituitary level or due to increased intracellular concentrations of Ca in the Prl-producing cells. It is not yet known clearly whether there is a regulatory function of PTH on the physiological secretion of Prl or not. However, the absence of elevated serum Prl levels in primary hyperparathyroidism (Castro et al. 1980) suggested that the Prl response to acute infusion of parathyroid extract was a pharmacological rather than a physiological effect of PTH.

In another study, a marked decrease in basal serum Prl levels and in Prl response to TRH injection was observed when salmon CT was administered iv in healthy subjects and in patients with hyperprolactinaemia (Isaac et al. 1980). This effect did not appear to be due to alterations in serum Ca, because during this experiment serum Ca concentrations fell only slightly. In addition, chronic hypocalcaemia per se was found to have no major effect on Prl and TSH responses to TRH in normal subjects (Carlson & Brickman 1977). In a previous study, Carman & Wyatt (1977) have also reported a striking decrease in serum Prl after salmon CT injections; but the degree of reduction has not been correlated with the size of the hypocalcaemic effect of CT. Likewise, the physiological role of this effect of CT is not still known.

In man, an inhibitory effect of acute hypercalcaemia produced by Ca infusion on serum Prl levels was first demonstrated in children and adults (Ajlouni & El Khateeb 1981; Kruse & Kracht 1981). This inhibitory effect has also been demonstrated in rats and was directly proportional to the degree of hypercalcaemia achieved (Sowers et al. 1980). Kruse & Kracht (1981) considered this inhibitory effect to be mediated by Ca-induced dopamine release from the hypothalamus, because Ca enhances the release of dopamine from in vitro suspension of striatal dopamine-storing vesicles (Philippu & Heyd 1970). Similarly, a stimulatory effect of iv Ca on growth hormone (GH) levels in normal man (Ajlouni & Hagen 1975) supports this speculation, since GH is stimulated by an increase
of dopaminergic activity. It was unclear if the Ca-induced Prl inhibition was an action of superphysiological serum Ca levels, or whether serum Ca levels within the normal range could produce the same endogenous inhibition of Prl secretion.

The effect of chronic hypercalcaemia on serum Prl levels was studied in patients with primary hyperparathyroidism (Adams et al. 1979; Castro et al. 1980) and their serum Prl levels were found to be within the normal range.

According to the results of this study chronic hypocalcaemia also has no effect on serum basal and stimulated Prl levels in man. Comparable conclusions were obtained by Carlson & Brickman (1977) and Carlson et al. (1977). They studied the effect of chronic hypocalcaemia on Prl responses to TRH in patients with pseudohypoparathyroidism and with surgical hypoparathyroidism and found that hypocalcaemia (mean serum Ca was 6.76 ± 0.30 mg/dl) produced no impairment in pituitary Prl secretion in response to TRH (Carlson et al. 1977). In another study, they reported two families with pseudohypoparathyroidism. Several members of these families had isolated Prl deficiency both in the basal state and after stimulation with TRH and chlorpromazine. But this impairment Prl secretion was not returned to normal by correction of hypocalcaemia and they suggested that Prl deficiency in these patients might be a result of an autoimmune process i.e. antilactotroph antibodies.

This study supports these earlier reports that chronic hypocalcaemia alone does not inhibit Prl secretion. Because chlorpromazine was used to stimulate the secretion of Prl in this study, it can be suggested that chronic hypocalcaemia has no direct effect on pituitary lactotrophs or on dopaminergic activity.

This study provides another confirmation that low serum PTH levels in man do not affect basal and stimulated Prl secretion. Similar results, showing no relationship between PTH and Prl have been obtained by others (Carlson & Brickman 1977; Adams et al. 1979; Brickman et al. 1981).

References


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