Potentiation of sulpiride-induced prolactin secretion by sodium deprivation in man

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Abstract. Previous studies suggest that prolactin is not an important osmoregulatory hormone in man, while aldosterone is well known to be important in osmoregulation. The present investigation was undertaken to ascertain whether serum osmotic changes affect pituitary prolactin secretion following sulpiride administration. Five normal subjects were placed on a constant isocaloric diet with different sodium content. Serum prolactin and aldosterone level were measured by specific radioimmunoassay. The basal serum level of prolactin was unaffected by changes in sodium content of the diet, in contrast to the basal level of aldosterone. On the other hand, the maximum levels of serum prolactin in response to sulpiride (50 mg, im) were significantly higher on a low sodium diet (3 g of salt/day) than on a control diet (12–15 g of salt/day). When the content of diet changed from low salt to high salt (25 g of salt/day), sulpiride-induced prolactin response decreased, though it was not significantly lower than that on a control diet. However, sulpiride administration could not stimulate aldosterone secretion under any of the various sodium contents of the diet.

The present study provides evidence that lowering of serum osmolarity stimulates serum prolactin response to sulpiride administration in man and this response is not modulated by aldosterone secretion.

Although both prolactin and aldosterone have been well known to regulate osmolarity in lower vertebrate species and prolactin has been reported to stimulate aldosterone, clinical observations in man have not supported the possibility that prolactin might be involved in these roles. Buckman & Peake (1973) and Buckman et al. (1973) reported that oral water load or hypotonic saline infusion suppressed serum prolactin concentrations in normal subjects or patients with functional galactorrhea. In contrast, Adler et al. (1975) and Baumann et al. (1977) failed to find any effect of the intravenous injection of either hypotonic or hypertonic saline on plasma prolactin level in man. Wartofsky et al. (1975) also reported that basal or TRH-stimulated plasma prolactin was not altered by water loading in hypothyroid patients. Furthermore, Holland et al. (1977) could not find any evidence for a possible role of prolactin in stimulating aldosterone. Thus, they concluded that prolactin was not an important osmoregulatory hormone in man.

It has been postulated that sulpiride could be used in the dynamic functional exploration of pituitary prolactin release in man (Mancini et al. 1976; Mori et al. 1977). The present study was undertaken to examine the question of whether serum osmotic changes might affect pituitary prolactin secretion in response to sulpiride administration in man.

Materials and Methods

Five normal male volunteers (aged 42 to 48 years) participated in the study. They were placed on a constant
isocaloric diet. The study was divided into three phases: phase I, control sodium diet (12–15 g of salt/day) for 7 days; phase II, on a low sodium diet (3 g of salt/day) for 3 days; and phase III, a high sodium diet (25 g of salt/day) for 4 days. Blood and urine samples were taken between 08.30 and 09.00 in the morning and the end of each phase. Fifty mg of sulpiride (supplied by Fujisawa Pharmaceutical Co., Japan) was then injected im and further blood samples were taken at 30, 60, 90, and 120 min. Sera were separated by centrifugation and kept frozen at −20°C until assay.

Serum and urine electrolyte concentrations were measured by flame photometry. Serum osmolarity was determined by freezing-point depression. Serum prolactin was measured by radioimmunoassay (RIA) using a CEA-IRESORIN’s prolactin kit according to the method of Reuter et al. (1976). Serum aldosterone was measured by RIA using a Dainabot aldosterone RIA kit according to the method of Ogihara et al. (1977). The assay sensitivities in the prolactin kit and the aldosterone kit were 50 μU/ml (40 IU of the hormone preparation compared to 1 mg of NIH (1)) and 50 pg/ml, respectively. All samples were done in duplicate and assayed at the same time. The coefficients of intra-assay variation of prolactin and aldosterone were 6.2 and 9.7%, respectively. Statistical analysis of the data was performed using Student’s t-test.

### Results

The serum sodium concentration, serum osmolarity, and urinary sodium to potassium ratio during treatment with a control sodium diet were 144.8 ± 0.5 mEq/l, 283.2 ± 3.1 mOsm/l and 6.1 ± 0.5, respectively. After sodium deprivation, these parameters fell significantly (Table 1). However, no

<table>
<thead>
<tr>
<th>Diet</th>
<th>Serum osmolarity (mOsm/l)</th>
<th>Serum Na (mEq/l)</th>
<th>Urinary Na/K</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control Na</td>
<td>283.2 ± 3.1</td>
<td>144.8 ± 0.5</td>
<td>6.1 ± 0.5</td>
</tr>
<tr>
<td>Low Na</td>
<td>271.2 ± 3.1*</td>
<td>138.0 ± 0.9*</td>
<td>2.0 ± 0.5**</td>
</tr>
<tr>
<td>High Na</td>
<td>299.0 ± 7.0</td>
<td>144.8 ± 0.2</td>
<td>5.8 ± 0.5</td>
</tr>
</tbody>
</table>

Each value represents the mean ± SEM of 5 determinations. Significant difference vs. controls:

* P < 0.05.

** P < 0.02.

Changes in serum prolactin level before and after administration of sulpiride are shown in Fig. 1. The basal serum prolactin level was not altered by the changes in sodium content of the diet (the basal level of prolactin on a control diet, a low sodium diet and a high sodium diet: 398.7 ± 85.9, 428.3 ± 55.8, and 369.4 ± 70.0 μU/ml, respectively.). Administration of sulpiride markedly elevated the serum prolactin in all subjects studied. The maximum level of prolactin in response to sulpiride was achieved at 30 min which was significantly higher on a low sodium diet than on a control diet (4738.3 ± 364.0 vs. 3401.4 ±396.1 μU/ml, P < 0.05). When subjects were exposed to a high sodium diet instead of a low sodium diet, this elevated prolactin response returned to approximately control value (3203.1 ± 331.0 μU/ml). Basal aldosterone level was significantly elevated in a low sodium diet and slightly decreased in a high sodium diet compared to a control diet. Sulpiride administration, however, could not increase aldosterone secretion and rather decreased it (Table 2).

### Discussion

Most investigators (Adler et al. 1975; Wartofsky et al. 1975; Baumann et al. 1977) failed to observe discernible changes in serum prolactin level after water load, hypotonic and hypertonic saline infusion, in contrast with the data reported by Buckman & Peake (1973) and Buckman et al. (1973).
The result of the present study indicates that lowering of serum osmolarity stimulates serum prolactin response following sulpiride administration (Fig. 1). There are some experimental supports for the concept that hypotonicity might increase, rather than decrease, prolactin secretion. Labella et al. (1975) reported that prolactin release into medium rose, when bovine pituitary glands were incubated in hypotonic saline. Similarly, Ensor & Ball (1972) observed that prolactin was secreted at a high rate in fresh water for teleost fish, but at a very low rate in sea water. In addition, Relkin & Adachi (1973) found that sodium deprivation produced increased plasma prolactin level in the rat. It would appear reasonable that a condition associated with low serum osmolarity and serum sodium concentration could result in a compensatory rise in serum prolactin.

Aldosterone is known to be of major importance in the regulation of sodium and water metabolism. In addition, aldosterone secretion has been reported to be possibly stimulated by prolactin (Lichtenstein et al. 1976; Melby et al. 1966; Edwards et al. 1975; Solyom 1974). Lichtenstein et al. (1976) mentioned that ovine prolactin stimulated aldosterone production from rat adrenals in vitro. Human placental lactogen, possessing many characteristics of prolactin, has been reported to enhance aldosterone secretion in man (Melby et al. 1966). Bromocriptine has been reported to inhibit the diuretic induced plasma aldosterone secretion, possibly by inhibition of prolactin secretion (Edwards et al. 1975). In view of this considerable evidence suggesting a possible role of prolactin in stimulating aldosterone, the serum aldosterone level was evaluated in our experiments. As shown in Table 2, changes of sodium diet caused an alternation of the basal level of aldosterone. However, sulpiride administration could stimulate prolactin secretion but not aldosterone secretion, and rather decreased aldosterone levels, although metoclopramide, resembling the structure of sulpiride, has been reported to stimulate both prolactin and aldosterone secretion (Norbiato et al. 1977). These results indicate that the action of sulpiride is different from that of metoclopramide in regard to aldosterone secretion, although both substances seem to have dopaminergic antagonist action. On basis of the above evidence, the present studies also suggest that prolactin elevation does not induce aldoste-
rone secretion and that potentiation of sulpiride-induced prolactin secretion in sodium deprivation is not modulated by aldosterone secretion.

Basal serum prolactin level was not affected by sodium deprivation (Fig. 1) in agreement with previous reports (Adler et al. 1975; Wartofsky et al. 1975; Baumann et al. 1977). This provides evidence that osmolarity may modulate the anterior pituitary lactotrophs' response to a prolactin-releasing substance. Therefore, the magnitude of the prolactin response to sulpiride may be an indicator of basal prolactin level in situations in which basal prolactin concentrations would be expected to be altered.

The serum prolactin response to sulpiride during treatment in a high sodium diet was definitely lower than that in a low sodium diet, but not significantly lower than that in a control sodium diet. As normal subjects have been reported to tend to show an escape phenomenon from the high sodium concentration (Sealey et al. 1969), serum sodium and osmolarity in a high sodium diet may not be able to increase compared with those in a control sodium diet. However, it is conceivable that serum prolactin response to sulpiride would certainly decrease, if the doses of duration while on a high sodium diet were sufficient to increase serum sodium concentration and serum osmolarity.

The acute stimulatory effect of sulpiride on serum prolactin level was also confirmed in our present study (Mancini et al. 1976; Mori et al. 1977). The action of sulpiride on prolactin secretion has been assumed to be exerted at the hypothalamus, possibly by acting against the dopaminergic mechanism (Mori et al. 1977; MacLeod & Robyn 1977), although the possibility that its effect is exerted directly at the pituitary level cannot be excluded (Debeljuk et al. 1974).

Table 2.

<table>
<thead>
<tr>
<th>Diet</th>
<th>0 min</th>
<th>30 min</th>
<th>60 min</th>
<th>90 min</th>
<th>120 min*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control Na</td>
<td>99.8 ± 8.3**</td>
<td>70.2 ± 8.1</td>
<td>71.0 ± 8.7</td>
<td>70.6 ± 7.5</td>
<td>88.2 ± 14.9</td>
</tr>
<tr>
<td>Low Na</td>
<td>179.8 ± 23.8***</td>
<td>123.8 ± 17.8***</td>
<td>134.2 ± 27.0</td>
<td>131.6 ± 27.8</td>
<td>128.0 ± 23.4</td>
</tr>
<tr>
<td>High Na</td>
<td>84.2 ± 4.2</td>
<td>73.2 ± 9.5</td>
<td>62.0 ± 4.5</td>
<td>70.6 ± 6.7</td>
<td>67.0 ± 5.0</td>
</tr>
</tbody>
</table>

* The time after administration with sulpiride.
** Each value (pg/ml) indicates the mean ± SEM of 5 subjects.
*** Significant difference vs. control sodium diet (Control Na): P < 0.05.

References


