PITUITARY-THYROID FUNCTION IN SPIRONOLACTONE TREATED HYPERTENSIVE WOMEN

By
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ABSTRACT

Four weeks high dose spironolactone treatment (Aldactone® Searle, 100 mg q. i. d.) significantly enhanced the TSH (Δ max. 8.5 ± 4.1 vs. 4.6 ± 3.1 μU/ml, P < 0.05) and T₃ (Δ max. 32 ± 27 vs. 11 ± 16 ng/100 ml, P < 0.05) responses to an intravenous TRH/LH-RH bolus injection in 6 eumenorhoeic euthyroid hypertensive women, without affecting basal serum TSH, T₃ or T₄ levels or the basal and stimulated LH, FSH and prolactin values (P > 0.10). The mean serum testosterone, 17-hydroxyprogesterone and oestradiol levels were also similar before and during therapy. Spironolactone, possibly by virtue of its antiandrogenic action, may exert its enhancing effect on pituitary-thyroid function by modulating the levels of receptors for TRH in the thyrotrophs or by altering the T₃ receptor in the pituitary permitting a greater response to TRH.

High dose spironolactone therapy amply has been reported to be associated with sexual and gonadal disturbances in both men and women (Spark & Melby 1968; Levitt 1970; Loriaux et al. 1976; Rose et al. 1977; Caminos-Torres et al. 1977). One of the possible mechanisms by which spironolactone might exert these effects is by its strong antiandrogen action (Menard et al. 1974; Basinger & Gittes 1974; Corvol et al. 1975; Rijka et al. 1977), which has been shown to be almost comparable to that of cyproterone acetate (Corvol et al. 1975). In addition to their antiandrogenic action both steroids share progestational activities (Hertz & Tullner 1958; Hamada et al. 1963; Schreiber & Roháková 1971). Cyproterone acetate recently has been demonstrated to enhance thyroid gland
function in rats by a hitherto unknown mechanism (Schreiber & Roháčová 1971). In view of its resemblance to cyproterone acetate, it seemed worthwhile to study the effect of spironolactone on pituitary-thyroid function. Therefore in addition to pituitary-gonadal function, thyrotrophin reserve was studied in 6 pre-menopausal eumenorrhoeic hypertensive women before and during spironolactone treatment. The data on the influence of spironolactone on the pituitary-gonadal axis have been reported elsewhere in more detail (Smals et al. 1978b).

MATERIALS AND METHODS

High doses of spironolactone (Aldactone®, Searle, 100 mg q. i. d. orally) were administered as the only drug for 4 weeks to 6 euthyroid women (age 37 ± 9.9 years) with essential hypertension (mean systolic and diastolic blood pressure 160 ± 12 and 100 ± 16 mmHg) with regular menstrual cycles (21 to 28 days). Control studies in each patient started at day 6, 8, 13, 18, 19 and 20 of their respective cycles. Between 8 and 10 a.m. on the control day and on the last day of spironolactone therapy blood samples

![Graph](image)

**Fig. 1.**

Mean serum LH, FSH, testosterone, 17-hydroxyprogesterone and oestradiol levels (± SEM) before (white rectangles) and after (black rectangles) 4 weeks of spironolactone therapy in 6 euthyroid hypertensive women.
Fig. 2.

Mean serum LH, FSH and prolactin increments (± SEM) in response to a TRH/LH-RH bolus injection before (○—○) and after (●—●) 4 weeks of spironolactone therapy in 6 euthyroid hypertensive women.

were collected at -15 and 0 min before and at 5, 10, 15, 30, 60 and 90 min after an iv bolus injection of thyrotrophin releasing hormone (TRH) TRF Roche®, 200 µg) and luteinizing hormone-releasing hormone (LH-RH, Hoechst®, 100 µg) for the assay of LH, FSH and prolactin, TSH, T₃ and T₄. In addition on the control day and on the last day of spironolactone therapy blood samples were taken at time 0 for the assay of 17-hydroxyprogesterone (17-OHP) testosterone (T) and oestradiol (Oe₂). Serum TSH, T₃, T₄, LH, FSH, prolactin, testosterone, 17-hydroxyprogesterone and oestradiol levels were measured by radioimmunoassay (Smals et al. 1976a, 1977, 1978a). All samples from one patient were run in the same assay. Statistical analysis was performed by using Wilcoxon's signed rank test.
Table 1.
Mean basal serum TSH, T₃ and T₄ levels before and during spironolactone therapy in 6 hypertensive women.

<table>
<thead>
<tr>
<th>Time (min before TRH/LH-RH injection)</th>
<th>Before spironolactone treatment</th>
<th>During spironolactone treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>TSH (uU/ml)</td>
<td>2.5 ± 0.7</td>
<td>2.6 ± 0.9</td>
</tr>
<tr>
<td>T₃ (ng/100 ml)</td>
<td>157 ± 25</td>
<td>140 ± 18</td>
</tr>
<tr>
<td>T₄ (µg/100 ml)</td>
<td>8.2 ± 1.2</td>
<td>7.4 ± 0.8</td>
</tr>
</tbody>
</table>

**RESULTS**

High dose spironolactone therapy lowered supine systolic (−25 ± sd 13) and diastolic (−15 ± sd 4 mmHg) blood pressure in 4 of the patients, but did not influence blood pressure in the 2 others.

The effects of spironolactone treatment on the mean basal serum LH, FSH, testosterone, 17-hydroxyprogesterone and oestradiol levels and on the mean stimulated serum LH and FSH levels are given in Figs. 1 and 2. No statistically significant differences were found between the basal or stimulated values (P > 0.10). The mean basal prolactin levels were also similar before and during treatment (7.1 ± 3.2 vs. 4.7 ± 2.0 ng/ml) (P > 0.10) and exhibited a comparable response to the releasing hormone administration (Fig. 2).

The effects of high dose spironolactone treatment on pituitary-thyroid function are given in Table 1 and Fig. 3.

The mean basal serum TSH levels at −15 and 0 min before and during treatment did not differ significantly from each other (P > 0.10). Probably due to haemodilution on changing from the erect to the recumbent position for the test, in 5 of the 6 patients basal serum T₃ and T₄ levels were lower at time 0 as compared to time −15 min, both before and after treatment (Table 1). No statistically significant difference could be demonstrated between the mean T₃ and T₄ values at −15 and 0 min before and during therapy (P > 0.10).

Simultaneous TRH/LH-RH administration increased serum TSH levels in all patients, the maximum increases being achieved at about the same time before and during spironolactone therapy (30 ± 0 and 28 ± 8 min). During spironolactone administration, however, the mean TSH increments at 10, 15 and 30 min (Fig. 1) and the maximum TSH increases (8.5 ± 4.1 vs. 4.6 ± 3.1
Serum TSH, T₃, and T₄ increments after intravenous TRH/LH-RH injection (time 0) before and after 4 weeks of spironolactone treatment. The vertical bars indicate the SEM, the asterisks statistically significant differences in hormone levels (P < 0.05) between the treated and untreated periods.

μU/ml) were almost twice the pre-treatment increments (P < 0.05). The mean serum T₃ increases between 0 and 90 min also were significantly higher during therapy (32 ± 27 ng/100 ml) than before spironolactone administration (11 ± 16 ng/100 ml (P < 0.05)). The mean serum T₄ increments did not differ significantly (0.25 ± 0.6 vs. 0.30 ± 0.6 μg/100 ml) before and during therapy (P > 0.10).

DISCUSSION

High dose spironolactone therapy for 4 weeks did not affect basal or stimulated gonadotrophin and prolactin levels or basal testosterone, 17-hydroxypro-
gesterone or oestradiol values, making a systemic change in menstrual cycle phase due to therapy highly unlikely (Smals et al. 1978b).

Spironolactone treatment also did not affect basal serum $T_3$, $T_4$ or TSH levels in 6 euthyroid, hypertensive women. This finding is in accordance with data of Caminos-Torres et al. (1977) who also failed to demonstrate any consistent change in basal serum $T_3$, $T_4$ or TSH levels in healthy men taking similar doses of spironolactone for as long as 24 weeks.

In the present study high dose spironolactone therapy augmented the pituitary TSH and thyroid $T_3$ response to TRH in all patients studied, despite virtually unchanged basal levels of these hormones. An almost analogous physiologically occurring enhancement of the pituitary-thyroid response has been observed in pre-pubertal girls and in normal women who show higher TSH and even $T_3$ responses to TRH than pre-pubertal boys and men, despite almost similar basal serum TSH, $T_3$ and $T_4$ values (Faglia et al. 1973; Noel et al. 1974; Smals et al. 1976b; Tenore et al. 1977).

The reason for the enhanced pituitary and thyroid responsiveness to TRH during spironolactone therapy is not clear.

Firstly, the augmented response might be the consequence of alterations in circulating levels of oestradiol, which has been reported to increase pituitary reserve and sensitivity to TRH both in pituitary cell cultures (Miller et al. 1977) and in laboratory animals (de Léan et al. 1977), men (Faglia et al. 1973) and women (Ramey et al. 1975). Such higher circulating oestrogen levels also could provide an explanation for the higher TSH response to TRH in women than in men (Faglia et al. 1973; Noel et al. 1974; Smals et al. 1976a; Tenore et al. 1977). In the patients from the present study, however, mean serum oestradiol levels were equal before and during spironolactone therapy (Smals et al. 1978b). Therefore the hypothesis of spironolactone induced oestrogen mediated increase in TSH reserve was rejected. An intrinsic oestrogenic action of spironolactone can not be excluded although unaltered basal and stimulated levels of LH and FSH do not favour such hypothesis.

The second possibility, by which spironolactone might influence pituitary-thyroid function is by its intrinsic progestagenic activity (Hertz & Tullner 1958). Ramey et al. (1975) reported an augmented TSH response to TRH in women receiving oral contraceptive steroids containing both oestrogens and progestagens, whereas Delitala et al. (1973) found an enhanced TSH response in the luteal phase. Both effects, however, may be due to the synchronous increase of oestrogen levels. In fact in vitro studies using cell cultures of ovine pituitaries did not show any enhancing effect of physiological amounts of progestagens on TSH production in contrast to oestradiol (Miller et al. 1977).

A third possible mechanism by which spironolactone may alter pituitary-thyroid function might be through its diuretic action and/or by changes in serum electrolytes. Recently acute intravenous spironolactone administration has been
shown to induce histologic and chemical evidence of increased glandular hormonogenesis in rats (Cuparencu et al. 1975). A similar response pattern was observed after administration of other diuretics. In men, however, chronic treatment with mercurial or thiazide diuretics never has been reported to affect thyroid function (Cuparencu et al. 1975; DeGroot et al. 1975).

The fourth possibility by which spironolactone might influence pituitary-thyroid function is by its antiandrogenic action which is comparable to that of cyproterone acetate as both steroids are equally potent in displacing dihydrotestosterone from the cytoplasmatic and nuclear receptor (Corvol et al. 1975). In male rats, cyproterone acetate has been shown to increase thyroid weight and radioiodine uptake by an unknown mechanism (Schreiber & Roháková 1971). Very recently Lumb (1978) reported on changes in thyroid gland histology occurring in rats already after 4 weeks of high dose (up to 250 mg/kg body weight) spironolactone treatment: increased height and granularity of the cells lining the colloid were observed in the presence of diminished colloid volumes. On the strength of these observations it is suggested that both antiandrogens cyproterone acetate and spironolactone influence pituitary-thyroid function in a similar hitherto unknown way, e.g. by modulating the levels of receptors for TRH in the pituitary thyrotrophs or by altering the T₃ receptor in the pituitary permitting a greater response to TRH.

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REFERENCES


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