Effect of Thyrotropin Releasing Hormone (TRH) on HTSH and HGH in Patients with Chronic Renal Failure

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Chronic renal insufficiency has been known for some time to induce various endocrine irregularities. Enlargement of the parathyroid glands due to chronic hypocalcaemia (Shaldon, 1966) and subsequent development of secondary and tertiary hyperparathyroidism is a frequent consequence of chronic renal disease. Similarly, changes of glucose tolerance, which can be corrected by chronic intermittent haemodialysis (Hampers et al, 1966) have been described. In addition high levels of HGH (Samaan & Freeman, 1970), occurrence of gynaecomastia (Lindsay et al, 1967), of exophthalmos (Schmidt et al, 1971) and a depression of gonadal function (Maher et al, 1965) have been observed.

No attempts to evaluate directly disorders of the hypothalamic-pituitary-thyroid axis have so far been reported in patients with chronic renal failure. The synthesis of Thyrotropin Releasing Hormone (TRH) by Gilessen et al (1970) has now provided a tool for the evaluation of the pituitary reserve of HTSH, as we have reported previously for healthy subjects (Waldhäusl, 1971).

This communication presents our studies on the effect of synthetic TRH on the secretion of HTSH and HGH in patients with chronic renal failure due to chronic glomerulonephritis, both in the undialysed state and on regular dialysis treatment (RDT).

METHODS AND SUBJECTS

Table I gives a review of the clinical data obtained in the patients studied. Both groups showed similar blood pressures and renal function. There was no evidence of thyroid disorder as evaluated by $T_3$ resin sponge uptake (The Radiochemical Centre, Amersham) and serum thyroxin (Murphy, 1969). Euthyroid subjects, as judged by $^{131}I$ uptake, $T_3$-uptake and by determination of serum thyroxin served as controls. Patients on RDT were dialysed twice weekly.

Human Thyrotropin Stimulating Hormone (HTSH) was estimated by the
Table I. Review of the clinical data obtained in patients with chronic renal failure: (A) undialysed, and (B) on regular dialysis treatment (RDT)

<table>
<thead>
<tr>
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<th>A 5</th>
<th>B 5</th>
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<tbody>
<tr>
<td>BP (syst/diast)</td>
<td>153 ± 13 / 83 ± 8.6 mm Hg</td>
<td>151 ± 3.3 / 92 ± 3.7* mm Hg</td>
</tr>
<tr>
<td>BUN</td>
<td>79.8 ± 7.3 mg/100 ml</td>
<td>119 ± 6.3* / 62.5 ± 4.2** mg/100 ml</td>
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<tr>
<td>Creatinine</td>
<td>10.4 ± 1.1 mg/100 ml</td>
<td>16 ± 0.6* / 9.8 ± 0.6**mg/100 ml</td>
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<tr>
<td>Na⁺</td>
<td>138.8 ± 6.1 mMol</td>
<td>137.6 ± 1.7* mMol</td>
</tr>
<tr>
<td>K⁺</td>
<td>5.05 ± 0.4 mMol</td>
<td>5.8 ± 0.37* mMol</td>
</tr>
<tr>
<td>HCO₃⁻</td>
<td>20.7 ± 1.1 mMol</td>
<td>13.9 ± 1.5* mMol</td>
</tr>
<tr>
<td>T₃⁻uptake</td>
<td>93 ± 6.8%</td>
<td>96.6 ± 3.9*%</td>
</tr>
<tr>
<td>T₄ (Murphy-Pattee)</td>
<td>6.1 ± 1.2 μg/100 ml</td>
<td>7.5 ± 0.5* μg/100 ml</td>
</tr>
</tbody>
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* before dialysis  
** after dialysis


Synthetic TRH (RO 086 270) was a gift of Hofmann - La Roche and was administered twice intravenously at doses of 400 μg. The interval between two injections was 2 hours.

RESULTS AND DISCUSSION

The main side effects observed from TRH administration were a feeling of frequency and heat in the genital area. This phenomenon is rarely observed by healthy subjects and occurs mainly in patients with severe metabolic disorders as chronic renal failure or myxoedema and seems to be mainly a pharmacological effect of TRH.

Figure 1 shows the effect of TRH (400 μg) on the serum concentration of HTSH and on serum thyroxin in healthy subjects. The maximal increase of HTSH occurred in this group 20 - 30 minutes after the administration of TRH. The serum concentration of HTSH returned to baseline levels 2 hours after the injection; 6 - 12 hours after the administration of TRH, a rise in serum thyroxin was observed. This effect provides additional evidence for the specificity of TRH for the release of HTSH. Injection of 2 x 400 μg TRH caused a more pronounced increase of HTSH following the first dose than during period II (Figure 2). This observation appears to indicate a limited secretory reserve of HTSH in healthy subjects.

Slightly elevated basal values of HTSH were found in patients on RDT. The effect of TRH (2 x 400 μg) on the serum concentration of HTSH, however, was diminished during both periods in patients on RDT when compared with
Figure 1. Effect of TRH (400 μg iv) on HtSH (μU/ml) and serum thyroxin (T4) in healthy subjects. Changes in T4 are expressed in % of basal value (n = 5)

Figure 2. Effect of TRH (2 x 400 μg) on the serum concentration of HtSH (μU/ml) in healthy subjects (n = 6)
Figure 3. Effect of TRH (2 x 400 μg) on the serum concentration of HTSH (μU/ml) in patients on RDT (n = 5). (Controls as Figure 2)

Figure 4. Effect of TRH (2 x 400 μg) on the secretion of HTSH in undialysed patients with chronic renal failure. (Controls as Figure 2)
the control group (Figure 3). This finding seems to indicate a reduced response by the pituitary to TRH in this group.

Undialysed patients with long standing renal disease and with similar clinical data as those reported for the group on RDT displayed however, a diverse pattern of response of HTSH release following TRH injection. Basal levels of HTSH and response of HTSH to TRH were within the normal range in 3 of 5 subjects. Two patients with both normal and increased basal levels of HTSH showed an exaggerated secretion of HTSH after administration of TRH (Figure 4). The serum concentration of HTSH reached its highest value after the second administration of TRH and was in the same range as those reported in patients with primary myxoedema (Waldhäusl, 1971). The serum concentrations of HTSH did not return to baseline levels during the two recorded periods. Basal T₃ uptake and serum thyroxin of these patients were in the normal range. A disturbance in pituitary function similar to that seen in chronic human malnutrition (Zubiran & Gomez-Mont, 1953) seems possible in these patients.

The concentration of HGH in serum was higher in patients with chronic renal failure than in healthy subjects (Figure 5), as also has been reported by Samaan and Freeman (1970). The elevated serum concentrations of HGH might be related to the catabolic state and to the increase of some essential (Young & Parsons, 1970) and non-essential amino acids in patients with chronic renal failure (Gulyassy et al, 1968). A small increase of HGH can be found after the administration of TRH in patients with chronic renal failure.

![Figure 5. Effect of TRH (2 x 400 μg) on the serum concentration of HGH in controls (n = 6) and patients with chronic renal failure (undialysed, n = 5, ---; and on RDT, n = 5, ----)](image-url)
both undialysed and when on RDT. A considerable variability of response of HGH to TRH was however found in healthy subjects. No relationship between the dose of TRH and the change of HGH in serum became apparent in this group (Waldhäusl, 1971). This finding suggests that the release of HGH after the administration of TRH is non specific. Similarly, Best et al. (1968) have shown that even the infusion of sodium chloride induces an increased serum concentration of HGH.

CONCLUSIONS

It appears that patients with chronic renal failure on RDT display a diminished response to TRH as far as HTSH is concerned. An exaggerated response of HTSH to TRH however can be found in some undialysed patients with chronic renal failure, but without any apparent thyroid disorder. In addition elevated serum concentrations of HGH are observed in subjects with chronic renal failure. The fact that TRH causes a different response of HTSH in healthy subjects and in patients with chronic renal failure, both undialysed and on RDT, indicates that the involved severe metabolic disorders interfere with the secretory reserve of the pituitary for HTSH.

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