Dissociation of pituitary glycoprotein response to releasing hormones in chronic renal failure

Derek LeRoith1, Gabriel Danovitz2, Stefan Trestian3 and Irving M. Spitz3

Departments of Medicine1 and Nephrology2, Soroka Medical Center, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva and Department of Endocrinology and Metabolism3, Shaare Zedek Medical Center, Jerusalem

Abstract. The LH, FSH and TSH response to LRH and TRH has been evaluated in patients with chronic renal failure. Basal gonadotrophins were elevated in 3 out of 6 males; one of 4 pre-menopausal females had increased basal LH. Exaggerated LH responses to LRH were noted in 4 out of 6 males and one of 4 females; FSH responses were increased in 3 of these males. One male and one female had attenuated LH and FSH responses to LRH. Both testosterone and oestriadiol levels were reduced. In 5 out of 6 subjects tested both pre- and post-dialysis there was a greater LH and FSH response to LRH following dialysis. This suggests the presence of a dialysable toxin which is inhibiting the gonadotrophin response to LRH. Gonadotrophin levels remained elevated during 4 h of dialysis suggesting prolongation of the metabolic clearance rate. Despite low T3 levels, TSH response to TRH (200 μg) was only elicited in 2 of 6 cases. However, all 3 responded to 500 μg and 2 out of 3 to 1000 μg TRH, the third showing an attenuated response. TSH levels also remained persistently elevated in the responders. Dialysis however, failed to improve the relative TSH non-responsiveness to TRH.

In conclusion the data has shown that there is a dissociation in glycoprotein hormone responses to releasing hormones in uraemia. Whereas the gonadotrophs retain their responsiveness to LRH, the thyrotrophs appear to be more effected by the uraemic process and demonstrate an impaired response to TRH.

Derangement of the hypothalamic-pituitary-target organ axes have been documented in patients with chronic renal failure. Abnormalities have been described in the response of thyrotrophin (TSH) to thyrotrophin releasing hormone (TRH), in thyroidal hormonal synthesis, plasma hormonal binding of thyroid hormones and the peripheral generation of triiodothyronine (T3), from thyroxine (Lim et al. 1977; Ramirez et al. 1976; Spector et al. 1976). Controversy exists with regard to the TSH response to TRH. Lim et al. (1977) failed to show a response to 400 μg TRH, though Gonzales-Barcena et al. (1973), using 800 μg, did demonstrate a response. Low testosterone levels and exaggerated luteinizing hormone (LH) and follicle stimulating hormone (FSH) responses to luteinizing hormone-releasing hormone (LRH) are generally seen in uraemic patients (Van Kammer et al. 1978; Holdsworth et al. 1977; Distiller et al. 1975). However although Holdsworth et al. (1977) demonstrated a relationship between the low testosterone levels and exaggerated LH responses, Distiller et al. (1975) failed to confirm this. In contrast, Lim & Fang (1975) showed that in some cases low testosterone levels were associated with low LH levels and high testosterone levels had high LH levels. Dialysis was shown not to influence the gonadotrophin hyperresponsiveness by Distiller et al. (1975). However, as yet the effect of acute dialysis on the TSH response to TRH has not been reported.

In this study we have evaluated the pituitary glycoprotein hormone responses to LRH and TRH in the same uraemic subjects to determine whether there is a relationship between the gonadotrophin and TSH responses. We have used increasing doses of TRH and evaluated the response to releasing hormones before and after dialysis.

Address reprint requests: I. M. Spitz MD., Department of Endocrinology and Metabolism, Shaare Zedek Medical Center, Jerusalem, Israel.
Design of the Study

Nine male and 7 female patients with end-stage renal failure were studied. The ages of the males ranged from 22–46 years and of the females from 24–53 years (2 females were in the post-menopausal age group). All females were amenorrhoeic and the males all complained of decreased libido. Three males and 2 females were receiving digoxin, propranolol or a methyl dopa. Haemodialysis was performed for 4 h, 3 times weekly with a recirculating single pass dialyser using coils with a membrane area of 1 m² or 1.5 m². Informed consent for each study was obtained from every patient.

The following protocols were used:

1. LRH administration

a) Six males and 4 pre-menopausal females were studied after an overnight fast with free fluid intake. Sixty min prior to dialysis, 2 baseline samples were taken during a 15 min equilibration period. LRH 100 µg was then administered iv as a bolus and blood samples were taken at 10 min intervals for 60 min for LH and FSH estimations. Dialysis was then commenced and a further blood sample taken at the end of the 4 h dialysis period.

b) In order to assess the effect of dialysis on the response of LH and FSH to LRH, 3 males and 3 females (2 post-menopausal) were challenged with 100 µg LRH immediately post-dialysis. The response in the same patient was compared to a second dose of LRH given 42 h later, immediately preceding the subsequent dialysis. After each dose of LRH, blood samples were taken as detailed above.

All subjects had estimations of testosterone (males) and oestradiol-17ß (females) from pooled basal samples taken prior to LRH administration.

2. TRH administration

The TSH response to 200 µg TRH was evaluated in 3 males and 3 females prior to dialysis. The patients were then rechallenged immediately following the same dialysis with a further dose of 200 µg TRH. Three additional patients (2 females and one male) received 500 µg pulses and three (2 males and one female) received 1000 µg TRH pulses. Periodic blood sampling was performed for 30 min after TRH and then again at the end of the dialysis period. In all subjects basal samples were taken for estimation of total T₄, T₃ as well as T₃ resin uptake. The free thyroxine index (FTI) was computed and used as an indirect measurement of free thyroxine levels (Solomon et al. 1976).

Controls

Twelve males (aged 22 to 48) and 5 females (aged 22 to 40 years) were similarly challenged with 100 µg LRH and 200 µg TRH. The females were tested during the follicular phase of the menstrual cycle.

Methods

Serum FSH, LH, TSH, testosterone and oestradiol-17ß were determined as described previously (Spitz et al. 1977). Pituitary FSH, LH, TSH as well as their respective antisera were kindly supplied by the National Pituitary Agency, National Institute of Arthritis, Metabolism and Digestive Diseases (NIAMDD). TSH standard as well as the 2nd International Reference Preparation for Human Menopausal Gonadotrophins (2nd IRP HMG), which was used as a standard for both LH and FSH, were supplied by the National Institute for Biological Standards and Control, London. When hormone levels were high, appropriate dilutions were performed so that all results were read on the sensitive part of the standard curve. T₄, T₃ and T₃ resin uptakes were measured by commercial kits (Amersham). In order to avoid inter-assay variations, all samples, including those taken pre- and post-dialysis from a single subject, were measured in the same assay.

Results

Gonadotrophins

Mean ± SEM basal LH and FSH levels in the male controls were 11.0 ± 1.6 and 6.7 ± 0.8 mIU/ml, respectively. Corresponding levels in the females were 14.5 ± 4.5 and 4.9 ± 2.8 mIU/ml. As can be

<table>
<thead>
<tr>
<th>Case No.</th>
<th>LH (mIU/ml)</th>
<th>FSH (mIU/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Basal</td>
<td>Peak</td>
</tr>
<tr>
<td>1 a</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>1 b</td>
<td>50</td>
<td>63</td>
</tr>
<tr>
<td>2 a</td>
<td>40</td>
<td>151</td>
</tr>
<tr>
<td>2 b</td>
<td>25</td>
<td>182</td>
</tr>
<tr>
<td>3 a</td>
<td>4.0</td>
<td>170</td>
</tr>
<tr>
<td>3 b</td>
<td>5.5</td>
<td>274</td>
</tr>
<tr>
<td>4 a</td>
<td>40</td>
<td>103</td>
</tr>
<tr>
<td>4 b</td>
<td>50</td>
<td>124</td>
</tr>
<tr>
<td>5 a</td>
<td>120</td>
<td>345</td>
</tr>
<tr>
<td>5 b</td>
<td>160</td>
<td>560</td>
</tr>
<tr>
<td>6 a</td>
<td>230</td>
<td>360</td>
</tr>
<tr>
<td>6 b</td>
<td>310</td>
<td>500</td>
</tr>
</tbody>
</table>

a = pre-dialysis.
b = post-dialysis.
Cases 1–3 male patients; 4–6 female patients. See text for details.
seen in Fig. 1, 3 out of 6 male uraemic patients had elevated basal LH and FSH levels (+2 s.d. above the mean of the controls). In the case of the female patients, basal LH levels were significantly elevated in only one of the 4 pre-menopausal cases and none showed elevated FSH levels. Peak LH and FSH responses to LRH in control males were 50.0±6.1 and 9.9±1.2, and in the female controls, 93.2±12.0 and 27.2±3.1 mIU/ml, respectively. In the uraemic patients, peak LH responses were significantly elevated in 4 of 6 males and FSH in 3 of 6 males (Fig. 1). In the 4 pre-menopausal females, only one case had exaggerated LH responses and none showed exaggerated FSH responses (Fig. 1). One male and one female (Fig. 1) failed to demonstrate LH and FSH responses to LRH and in addition, one female showed an absent FSH response only.

In the group which received LRH prior to dialysis only, the LH and FSH levels at the end of 4 h of dialysis remained markedly elevated. In the controls, however, gonadotrophin values had decreased by 120 min.

The effect of dialysis in 6 uraemic subjects is shown in Table 1. There was no difference in basal levels in the 2 tests. However, with the exception of one FSH response, peak gonadotrophin responses to LRH were greater when the LRH was given post-dialysis than pre-dialysis. The two post-menopausal females (cases 5 and 6) had high basal gonadotrophins and exaggerated responses to LRH. The increased response post-dialysis was especially evident in cases 1, 3, 5 and 6 though significantly greater \( (P = 0.05) \) in the group as a whole when calculated by the Wilcoxon-Rank sum test for paired samples.

The range of serum testosterone in control males was 3.5—11.0 ng/ml. In female controls, oestradiol-17β was 33–70 pg/ml during the follicular phase of the menstrual cycle. Testosterone levels were low in 4 of the 9 male uraemias (2.1—3.1 ng/ml) and normal in the remainder. Oestradiol-17β levels were low in 3 out of the 4 pre-menopausal females (18.0–28.0 pg/ml) and in both post-menopausal females.

**TSH (Fig. 2)**

There was no difference in basal levels between the patients (2.2—6.0 μU/ml) as compared to the controls (1.0—5.9 μU/ml). Following the administration of 200 μg TRH, peak responses in the male controls were 12.6±2.0 μU/ml and 24.8±8.2 μU/ml in the female controls. By 120 min levels had decreased to 6.7±1.1 and 16.4±4.5 μU/ml, respectively. In the uraemics, only 2 patients, both males, responded normally with peaks of 13.0
μU/ml. In both cases the levels remained elevated for the 4 h dialysis period. All were challenged with 200 μg TRH post-dialysis. The same 2 subjects again demonstrated a response although the remaining 4 were still unresponsive (data not shown). In contrast, all 3 patients tested responded to 500 μg TRH and 2 out of 3 to 1000 μg. The one female had a reduced peak TSH response of 5.0 μU/ml after 1000 μg TRH. Total T₄ levels ranged from 4.2–11.5 μg/100 ml, which was similar to control levels which ranged from 3.3–11.5 μg/100 ml. T₃ levels, in contrast, were reduced in the patients ranging from 52.0–140.0 ng/100 ml (m ± SEM = 83.6 ± 7.4) compared to 112–230 ng/100 ml in the controls ($P = 0.05$). T₃ resin uptakes ranged from 37–47.0% which was similar to the normal range (40–55%). The FTI in uraemics was 3.8 ± 1.2 (range 2.1–8.3), which was normal when compared to controls 4.2 ± 0.8 (range 2.0–7.5). There was no correlation between T₃ and T₄ levels and the responses of TSH to TRH.

**Discussion**

Several factors may be involved in the pathogenesis of the abnormal hormonal metabolism in patients with end-stage renal disease on chronic dialysis. These include altered secretion of hormones at the hypothalamic, pituitary or target organ level, a decrease in the peripheral metabolism of these hormones with reduced metabolic clearance rate (MCR) due to the impaired renal function, or a combination of these factors. The change in MCR may be consequent to a lack of renal tissue itself or related to uraemic toxins affecting the various enzyme systems involved in hormonal degradation.

Many of our uraemic subjects had elevated basal gonadotrophin levels and exaggerated responsiveness to LRH. Similar exaggerated responses have been demonstrated previously (Holdsworth et al. 1977; Distiller et al. 1975). This indicates primary gonadal involvement with lack of appropriate steroidal feedback. In fact many of the patients demonstrated low testosterone and oestradiol-17β levels. Further evidence for gonadal involvement is spermatogenic damage on testicular biopsy and a lack of testosterone response to hCG (De Kretser et al. 1974). The view that the hypothalamic-pituitary axis is most likely unaffected in uraemia, is supported by the finding of normal LH response to clomiphene (Stewart-Bentley et al. 1974) and suppression of LH by testosterone (Holdsworth et al. 1977).

Despite the exaggerated gonadotrophin responses to LRH in most of our subjects, one male and one female showed attenuated responses, suggesting that in some uraemic subjects there may be primary hypothalamic-pituitary involvement. In addition, when compared to pre-dialysis, the LH and FSH responses to LRH were even further increased following dialysis in 5 of the 6 cases tested. This suggests the existence of a dialysable toxin which may be partially inhibiting gonadotrophin release (Schreiner 1975). The persistently elevated gonadotrophin levels at the end of 4 h of dialysis in those subjects who received LRH before dialysis, indicate that in addition to increased secretion there is decreased MCR, which may also contribute to elevated basal and exaggerated gonadotrophin responsiveness.
The results of the thyroid hormone levels in our uraemic cases are similar to those described previously (Lim et al. 1977; Ramirez et al. 1976; Spector et al. 1976). The low T₃, with normal T₄ and T₃ resin uptake and FTI levels, may be a reflection of reduced peripheral conversion of T₄ to T₃. This is supported by the elevated levels of serum reverse T₃ described by Lim et al. (1977). Thyroid uptake of radioactive iodine is increased by TSH stimulation suggesting normal thyroid gland function (Silverberg et al. 1973). In normal control subjects, maximum TSH response to TRH occurs with 400 μg TRH (Snyder & Utiger 1972). However, all normal subjects respond to 200 μg TRH. In the present series only 2 of 6 responded to 200 μg, all 3 responded to 500 μg and 2 out of 3 to 1000 μg TRH, the third having an attenuated response. This shift of the dose-response curve to the right indicates an alteration of the sensitivity of the thyrotroph.

Lim et al. (1977) failed to demonstrate a response to 400 μg, whereas Gonzalez-Barcena et al. (1973) showed a response in their cases to 800 μg TRH. It is of interest that the non-responsiveness existed despite the low T₃ levels. In this situation there are usually high basal TSH levels and an exaggerated TSH response to TRH. This refractoriness has been noted in starvation and other non-thyroidal illnesses and may be regarded as an adaptive mechanism in the catabolic state in an attempt to limit the wastage of hypermetabolism (Portnay et al. 1974; Burger et al. 1976). A similar situation may conceivably exist in chronic renal failure. In these same patients we have also demonstrated an impaired prolactin response to TRH (LeRoith et al. 1979). This indicates that the lactotroph and thyrotroph are similarly affected by the uraemic process. As with the gonadotrophins, stimulated TSH levels remained elevated throughout the dialysis suggesting reduced MCR for TSH. However, in contrast to the gonadotrophins, no change in the TSH responsiveness to TRH was seen post-dialysis.

In conclusion it has been demonstrated that in uraemia there is a dissociation of the pituitary glycoprotein hormone response to releasing hormones. The uraemic state presumably affects thyrotrophs as well as gonadotrophs. The latter retain their responsiveness although this may be improved following dialysis. The thyrotrophs in contrast are not affected by 200 μg TRH and only respond to larger doses of this releasing hormone.

Acknowledgments

We wish to thank Hoffman La Roche (Switzerland) for the generous gift of LRH and TRH; Z. Shemesh and H. Gershman for technical assistance and H. Menachemson for typing this manuscript. This study was supported in part by grants from the Chief Scientist’s Office, Israel Ministry of Health (IMS) and the Center for Absorption in Science, the Ministry for Immigrant Absorption, State of Israel (IMS, DLR).

References


Received on May 1st, 1979.