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SITES OF DEFECTIVE REGULATION OF PROLACTIN SECRETION IN CHRONIC RENAL FAILURE

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Summary

The possible sites of the defective regulation of prolactin secretion in chronic renal failure (CRF) were evaluated in 30 CRF patients not undergoing dailysis by stimulating prolactin secretion with cimetidine acting at a supra-pituitary site and thyrotrophin-releasing hormone (TRH) acting on pituitary lactotropes. In the patients who underwent both tests (n=20) three groups were obtained. In the first group (n=9), patients did not respond to either test, in the second group (n=6), patients responded only to TRH and in the third group (n=5) patients responded to both tests. Glomerular filtration rate (GFR) was lower in the first compared with the second group ($p<0.01$) and in the second compared with the third group ($p<0.05$). A positive correlation was found between GFR and maximal prolactin change from baseline in all patients with both cimetidine and TRH stimulation. The results indicate that the supra-pituitary dysfunction seems to precede the pituitary defect during progression of renal failure.

Introduction

Several groups of investigators have reported that plasma prolactin is elevated in patients with renal failure [1–3]. Although a primary role for the kidney in prolactin metabolism has been shown, the hyperprolactinaemia observed in CRF is not simply due to stress or to an inability of the kidney to degrade or clear this hormone from the circulation [3–7]. It has been suggested that uraemia adversely affects the function of either the hypothalamus or the pituitary gland.

This study evaluates the site of defective regulation of prolactin secretion at different degrees of chronic renal failure. Our results show that hypothalamic dysfunction seems to precede the pituitary defect during progression of renal failure.

Patients and methods

Thirty patients (21 men and 9 women) with CRF not undergoing dialysis were studied in order to evaluate basal prolactin and prolactin response to cimetidine and TRH stimulation. Mean age was 43±11 years in males and 43±12 in females (mean±SD). No patient was diabetic and none showed signs of pituitary or central nervous system dysfunction. Basal prolactin and response to cimetidine and TRH stimulation were also evaluated in 14 normal subjects, seven males aged 40±9 and seven females aged 42±10 years. GFR, assessed by endogenous creatinine clearance, was 29±17ml/min in males and 25±18ml/min in females. Both tests were administered following at least 12 hours bed rest and any drug was discontinued during four days before. The interval between the two tests was, at least, two days.

Cimetidine test (30 cases): 200mg of cimetidine were injected rapidly in a forearm vein (time 0). Blood samples for prolactin determination were obtained at the following times -15′, 0′, +10′, +20′, +30′, +45′, +60′, +90′.

Thyrotrophin-releasing hormone test (20 cases): 200μg of synthetic thyrotrophin (Biodata, Milan) were injected rapidly in a forearm vein. Blood samples for prolactin determination were obtained at the same intervals as in the cimetidine-test. Prolactin was assessed by Radioimmunoassay Technique (RIA, Biodata, Milan). Normal range was, according to this technique, 5–15ng/ml in males and 5–20ng/ml in females. Both tests were considered positive when plasma prolactin, following stimulation with cimetidine or TRH, doubled from the baseline as observed in normal subjects (100% increase).

Statistical evaluation was performed by unpaired 't' test and one way analysis of variance (Duncan test).

Results

Abnormal high basal prolactin values were observed in 19 per cent males and 22 per cent females. Males and females with hyperprolactinaemia showed a GFR less than 15 and 10ml/min respectively. A significant negative correlation was observed, in all patients, between GFR and log basal prolactin ($p<0.05$). This relationship confirms the finding of hyperprolactinaemia in the patients with the lowest GFR. Patients who underwent both cimetidine and TRH stimulation (20 cases) were divided into three groups according to the response to the tests (Table I). In the first group (n=9), patients did not respond to any test and mean GFR was 13±7ml/min. Six of nine patients showed basal hyperprolactinaemia. In the second group (n=6), patients responded only to TRH stimulation and mean GFR was 38±11ml/min. In the third group (n=5), patients responded to both cimetidine and TRH stimulation and mean GFR was 54± 10ml/min. No patient, in the second and third group, showed basal hyperprolactinaemia. GFR was significantly lower in the first versus second group ($p<0.01$), in the second versus third group ($p<0.05$) and in the first versus third group ($p<0.01$).

TABLE I

Groups	Number	Sex	Age (years)	Renal Disease	GFR (ml/min)	Urea (mg/dl)	Basal prolactin (ng/ml)	% patients with prolactin> baseline
I Group	9	6 M 3 F	45±7	4 CGN 1 HNS 1 IN 1 PLC 2 UKN	13±7	164±66	27±20	67
II Group	6	6 M – F	43±16	3 CGN 1 HNS 1 PLC 1 UKN	38±11	82±16	8±1	–
III Group	5	3 M 2 F	34±10	4 CGN 1 HNS	54±10	51±5	5±2	–

CGN Chronic glomerulonephritis
HNS Hypertensive nephrosclerosis;
IN Interstitial nephropathy
PLC Polycystic kidney disease
UKN Unknown

GFR I vs II group $p<0.01$; I vs III group $p<0.01$; II vs III group $p<0.05$

A significant positive correlation was found, in all patients, between GFR and maximal prolactin change from baseline with both cimetidine ($p<0.01$) and TRH ($p<0.001$) stimulation (Figure 1).

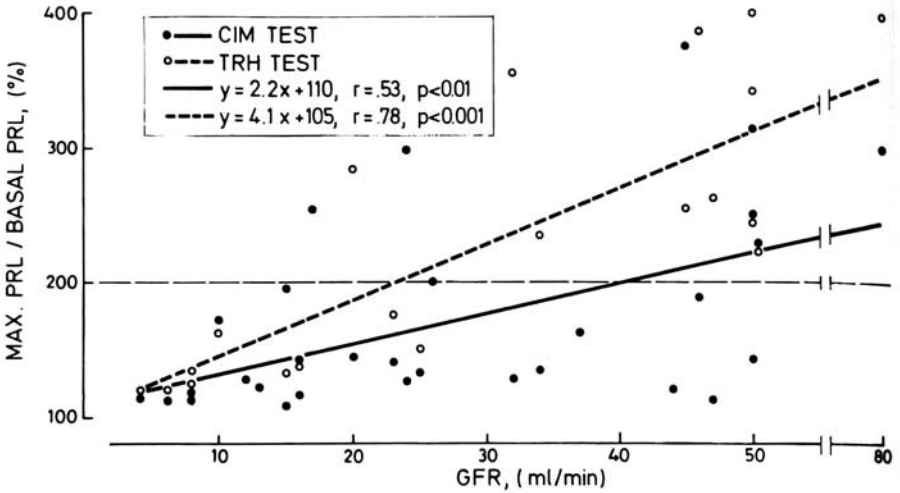

Figure 1. Relationship between GFR and maximal prolactin change from baseline. Normal response to both tests above 200 per cent line

Discussion

Previous studies have shown a decreased prolactin suppression by dopaminergic agents and a blunted response to TRH in chronic uraemic and haemodialysis patients [3,5,7]. These data indicated a generalized defect in hypothalamic-pituitary regulation in CRF. In this study we tested prolactin response to two drugs stimulating prolactin secretion with different mechanisms: TRH acting directly on pituitary lactotropes and cimetidine whose prolactin-releasing activity has been suggested to be dependent on blockade of H_2-histaminic receptors in the central nervous system [8].

Our data confirms that uraemia is associated with a defective regulation of prolactin secretion and shows that this occurs in the early phase of CRF and even in the presence of normal basal prolactin. The blunted response to cimetidine associated with a normal response to TRH in those patients with intermediate reduction of renal function suggest that an altered central regulation of prolactin secretion precedes the pituitary defect.

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