

Mechanism of impaired growth hormone secretion in patients with Cushing's disease

Hideo Takahashi, Hiroshi Bando, Chenyu Zhang, Ryuichi Yamasaki and Shiro Saito

First Department of Internal Medicine, School of Medicine, The University of Tokushima, Tokushima, Japan

Takahashi H, Bando H, Zhang C, Yamasaki R, Saito S. Mechanism of impaired growth hormone secretion in patients with Cushing's disease. *Acta Endocrinol* 1992;127:13–17. ISSN 0001–5598

The function of the growth hormone-releasing hormone (GHRH)-growth hormone (GH) axis in Cushing's disease was studied by monitoring (a) the GH responses to GHRH loading and L-dopa loading, (b) the GHRH response to L-dopa loading, and (c) the daytime profiles of plasma GH concentration. GH release following GHRH and L-dopa was blunted in patients as compared to that in age-matched control subjects. However, GHRH release following L-dopa was similar in patients and controls. The plasma GH levels in four patients measured every 20 min by a highly sensitive immunoradiometric assay for GH showed pulsatile GH secretion at low levels during the observation period. These results indicate that GHRH release from the hypothalamus is preserved in patients with Cushing's disease, and support the hypothesis that glucocorticoid inhibits GH secretion by altering the hypothalamic somatostatin tone.

Hideo Takahashi, First Department of Internal Medicine, School of Medicine, The University of Tokushima, Kuramoto-cho 3-18-15, Tokushima 770, Japan

Patients with Cushing's disease show blunted growth hormone (GH) responses in various provocative tests including insulin-induced hypoglycemia (1, 2), arginine loading (1), and L-dopa loading (3). Smals et al. (4) reported that they also show a reduced GH response to growth hormone-releasing hormone (GHRH). The reason for impaired GH secretion in patients with Cushing's disease is, however, still unknown, and there are no reports of studies on the functional change of their GHRH-GH axis.

We found previously that the GHRH level in the plasma increased before or simultaneously with increase in GH secretion during slow wave sleep or oral L-dopa loading (5), indicating that oral L-dopa should be useful as stimuli in GHRH provocative tests (6). Therefore, in this work, to elucidate the mechanism of impairment of GH secretion in patients with Cushing's disease, we studied the function of their GHRH-GH axis by analysing (a) the GH responses of the patients to GHRH loading and L-dopa loading, (b) the GHRH response to L-dopa loading, and (c) the daytime profile of their plasma GH concentration. Plasma GH was measured with a highly sensitive immunoradiometric assay (IRMA).

Materials and methods

Subjects

As shown in Table 1, one male and six female patients with Cushing's disease (aged 29–51 years) were studied. Cushing's disease was diagnosed on the basis of the

symptoms, laboratory findings and pituitary imaging. Five patients had received no therapy, and two patients had undergone transsphenoidal adenomectomy but with insufficient effect. All the patients had hypercortisolemia. Tests on GHRH loading and L-dopa loading were performed at rest after overnight fasting.

As controls, 10 age-matched subjects (33–51 years) and 12 normal elderly subjects (70–85 years) were also studied.

The study was approved by the Human Subjects Protection Committee, School of Medicine, University of Tokushima, and informed consent was obtained from the patients.

GHRH test

A dose of 100 µg of synthetic GHRH (1–44)NH₂ (GRF Sumitomo 100; Sumitomo Pharmaceutical Co., Osaka, Japan) was administered intravenously and before and 15, 30, 60, 90 and 120 min after its administration blood samples were collected in pre-cooled polypropylene tubes containing 1.2 mg EDTA and 500 KIU aprotinin per ml of blood. The plasma was separated and stored at –40°C until assay of plasma GH concentration.

L-dopa loading test

A dose of 500 mg of L-dopa (Daiichi Pharmaceutical Co., Tokyo, Japan) was given orally and blood samples were collected at 0, 30, 60, 90 and 120 min for determinations of plasma GHRH and GH concentrations.