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Persistent GHRH-Induced PRL Secretion in Cushing's Syndrome, Obesity and Exogenous Hypercortisolism*

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Endogenous Cushing's syndrome, obesity and chronic glucocorticod treatment are characterized by blunted GH secretion. The administration of GHRH is capable of stimulating a small but significant PRL increase in normal subjects. The current study was designed to determine plasma PRL levels in response to GHRH, studied in three different situations characterized by a blunted GH secretion.Obese patients (n = 6) with a weight over 30 % of ideal body weight, patients with active Cushing's syndrome, and normal volunteers treated with dexamethasone 22 mg *per os* over two days before the pituitary challenge were studied. As a control group 18 normal subjects of similar age and sex were studied. GH and PRL was determined at intervals after GHRH (1 μg/kg). GHRH-induced GH secretion was markedly reduced in patients with obesity, patients with endogenous Cushing's syndrome and volunteers treated with dexamethasone. In contrast, GHRH-induced PRL secretion was not affected in these three clinical situations. In summary, in three situations characterized for an impairment of the somatotroph cell, due to a primary intrinsic defect or to a functional hypothalamic alteration, there is a persistent GHRH-induced PRL secretion, suggesting that prolactin could be released by mammosomatotrophs that function normally in spite of hyposomatotropism.

Key words: Prolactin, GHRH, Hyposomatotropism, Obesity, Hypercortisolism.

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GHRH is a potent stimulus of GH secretion (11, 16). In addition, several studies have shown that GHRH is capable of inducing a small but significant PRL

increase in normal subjects (9, 17), supporting the hypothesis that GHRH may be a physiological regulator of PRL release (12).

Endogenous Cushing's syndrome, obesity and chronic glucocorticod treatment are characterized by impeded GH secretion. In fact, GHRH-induced GH secretion is blunted in these three situations (4, 6, 14).

The current study was designed to determine plasma PRL levels in response to GHRH, studied in three different situations characterized by a blunted GH secretion.

Materials and Methods

This study was carried out on 36 subjects. Six were newly diagnosed patients with Cushing's syndrome (4 women, 2 men, aged 26-49), selected because they were not obese (within 15-20% of ideal body weight). Six were obese patients (6 women, aged 20-41), they weighed over 30 % of ideal body weight, as determined by the Fogarty Center Conference on Obesity (3). All obese patients had normal ovarian cycle, and none had diabetes mellitus or other medical problems or was taking any drugs. A third experiment was performed by administering normal volunteers 22 mg, p. o. of dexamethasone (Dex) over 48 h before GHRH, (2 mg every 6 h seven times, and a final dose of 8 mg was administered 12 h before GHRH). Normal controls were 18 subjects, within 10 % of ideal body weight, of similar age and sex as the experimental groups. All normal controls had normal ovarian cycles, and none had diabetes mellitus or other medical problems or was taking any drugs. Approval for this study was obtained from the Hospital Committee, and all subjects provided informed consent.

Each subject was tested with GHRH (1 μg/kg i. v. at 0 min, no more than 100 μg/subject, GRF 1-29; Serono Spain). Tests were done with the subjects recumbent after an overnight fast. An indwelling catheter was placed in a forearm vein and kept patent with a slow infusion of 0.9 % NaCl. This was followed by the administration of GHRH at 0 min. Blood samples were obtained at appropriate intervals.

Human plasma hormone was measured by commercial kits, GH by kits from Biomerieu (Spain; 6.8 % intraassay coefficient of variation) and PRL by RIA (Corning, USA, 4.5 % intraassay coefficient of variation). All samples from each patient or volunteer were assayed at the same time. The statistical evaluation of the groups was carried out by nonparametric tests (Wilcoxon rank test) for paired data. The statistical level of significance was set at $p < 0.05$.

Results

GHRH administratlon to normal subjects induced a clear-cut increase in circulating GH levels, with a peak of 10 ± 2 μg/L at 45 min (fig. 1). Its administration to patients with Cushing's syndrome did not significantly modify GH levels at any time point, in contrast, induced a small significant PRL peak in control subjects and in Cushing's syndrome patients (9 ± 0.8 μg/L and 9 ± 1 μg/L, respectively). GHRH administration to obese subjects induced a small increase in circulating GH levels, with a peak of 4 ± 0.4 μg/L at 15 min, which was significantly lower than the response in normal subjects. In contrast it induced a small significant PRL

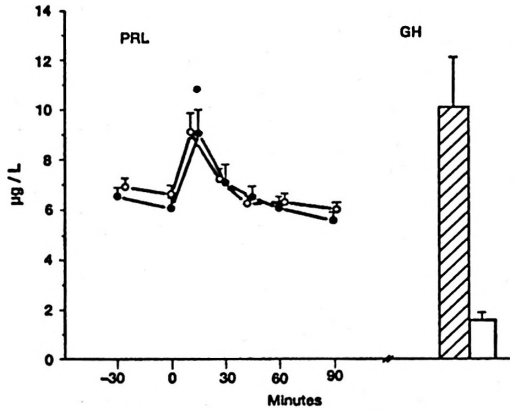

Fig. 1. *Serum concentration (mean ± SD) of PRL and peak GH in a group of Cushing's syndrome patients (o) and normal controls (•) after GHRH administration.*
*p < 0.05 versus 0 min in both conditions.

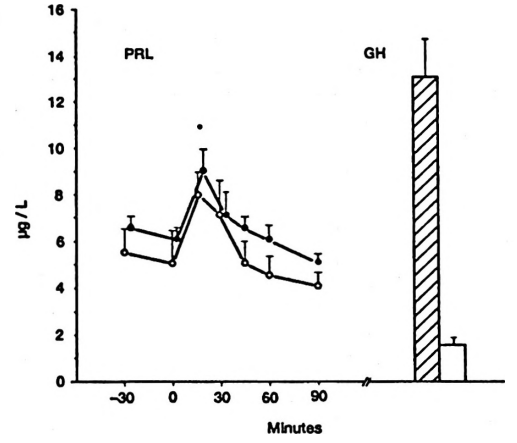

Fig. 2. *Serum concentration (mean ± SD) of PRL and peak GH in a group of obese patients (o) and normal controls (•) after GHRH administration.*
*p < 0.05 versus 0 min in both conditions.

peak (9 ± 0.8 µg/L) in control subjects, similar to the PRL peak (8 ± 1 µg/L) in obese patients (fig. 2).

In volunteers treated with 22 mg *per os* of Dex over 48 h GHRH administration did not significantly modify mean circulating GH levels at any time point, nevertheless it induced a small significant PRL peak (6.8 ± 0.9 mg/L) in Dex treated subjects, similar to the PRL peak (9 ± 0.8 mg/L) in control subjects (fig. 3).

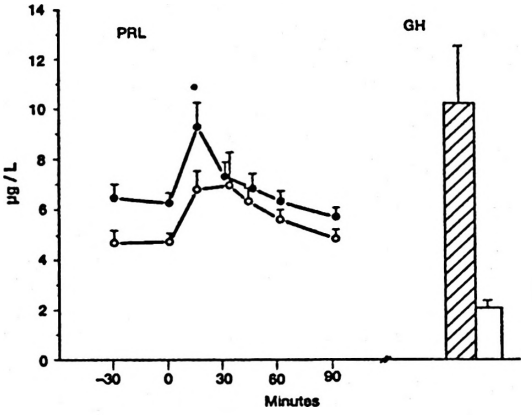

Fig. 3. *Serum concentration (mean ± SD) of PRL and peak GH in a group of volunteers treated with 22 mg Dex over 48 hours (o) and normal controls (•) after GHRH administration.*
*p < 0.05 versus 0 min in both conditions.

Discussion

The present results show that in three situations associated with an impairment of normal GH secretion, such as Cushing's syndrome, obesity and exogenous hypercortisolism, there is a persistence of GHRH-induced PRL secretion.

In obese patients the GH response to provocative stimuli such as hypoglycemia, L-dopa, arginine infusion, physical exercise, opioid administration, sleep, and GHRH is blunted (6, 18, 20). PRL secretion has been studied in obese subjects in response to different stimuli such as insulin hypoglycemia, arginine infusion, TRH, and fenfluramine, the results being inconclusive as some have found a decreased (5, 14, 19) while others a normal (1, 7) PRL secretion in obesity.

Stimulated GH release is blocked in active Cushing's syndrome (10). In fact, GH secretion after GHRH administration was completely blocked in patients with active Cushing's syndrome and in normal subjects previously treated for 48 hours with Dex (4). PRL secretion has been studied in 36 untreated patients with Cushing's syndrome of different etiologies and a normal TRH induced PRL secretion has been found in most patients (8).

Our data have shown that GHRH elicited a small but significant PRL increase in normal subjects. These findings support the hypothesis that GHRH may be a physiological regulator of PRL release and raises the possibility that PRL secretion is regulated by several hormones of hypothalamic origin (9, 17). In agreement with these data a recent case of congenital gigantism due to GHRH excess has shown a markedly increased plasma PRL. The pituitary tissue removed at transphenoidal and transfrontal operations showed not only somatotroph, but also lactotroph and mammosomatotroph massive hyperplasia (21). The mechanisms by which GHRH causes PRL release in normal subjects and in these three states of pathological hyposomatotropism are unclear. One possible mechanism would be the action of GHRH on lactotrophs, a second possible explanation is that PRL release originates from mammosomatotrophs present in the normal pituitary.

Studies done in vitro have assessed the secretory behaviour of mammosomatotroph and mixed somatotroph-lactotroph adenomas. Incubation with GHRH increased the release of GH and PRL by all tumors, the response of mammosomatotrophs was similar for GH and PRL, but in the mixed somatotroph-lactotroph adenomas the response was greater for GH than PRL (2). KASHIO *et al.* have shown with a mammosomatotroph cell line derived from adult rat pituitaries in culture that the stimulation of GH and PRL release in these cells by adenylate cyclase-related agents was comparable to that for GH secretion in mature somatotrophs but much greater than that of PRL release in mature lactotrophs (13). These data suggest that GHRH-induced PRL secretion is due mainly to its effect on the mammosomatotroph cell.

Our results are in agreement with the previous data because in three situations characterized by an impairment of the somatotroph cell, due to a primary intrinsic defect or to a functional hypothalamic alteration, there is a persistent GHRH-induced PRL secretion, suggesting that prolactin could be released by mammosomatotrophs that function normally in spite of hyposomatotropism.

F. CORDIDO, R. PEINO y T. MARTÍNEZ-RAMONDE. *Secreción persistente de PRL tras la administración de GHRH en el síndrome de Cushing, la obesidad y el hipercortisolismo exógeno*. Rev. esp. Fisiol. (J. Physiol. Biochem.), 50 (3), 139-144, 1994.

Se estudian, tras la administración de GHRH, los niveles de prolactina en tres situaciones patológicas caracterizadas por el bloqueo de la secreción de GH: Pacientes obesos con un sobrepeso superior al 30 % sobre el peso ideal, pacientes con síndrome de Cushing activo y voluntarios normales tratados con dexametasona 22 mg p. o. durante dos días antes del estímulo hipofisario. El grupo control está formado por 18 sujetos normales de similar edad y sexo. La GH y la prolactina se determinan a intervalos tras GHRH (1 µg/kg). La respuesta de GH tras GHRH se reduce significativamente en los tres grupos de pacientes (n = 6 en cada uno) no variando la de prolactina. Se concluye que en tres situaciones caracterizadas por una afectación de la célula somatotropa, debido a un defecto intrínseco o funcional hipotalámico, persiste la respuesta de

prolactina a GHRH, sugiriendo que la prolactina puede ser secretada por células mamosomatotropas que funcionan normalmente a pesar de la situación de hiposomatotropismo.

Palabras Clave: Prolactina, GHRH, Hiposomatotropismo, Obesidad, Hipercortisolismo.

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