Dynamic testing of prolactin and growth hormone secretion in patients with neuroendocrine disorders

E. E. Müller¹, F. Cavagnini³, A. Martínez-Campos², C. Maraschini³, P. Giovannini⁴, A. Novelli and V. De Leo⁵

Department of Pharmacology, University of Milan, First Medical Clinic³, University of Milan, Istituto Neurologico C. Besta⁴, Milan, Italy and Institute of Clinic Obstetrics⁵, University of Siena, Italy

Abstract. Prolactin (Prl) and growth hormone (GH) responses to different pharmacologic probes acting at the central nervous system (CNS) or the anterior pituitary (AP) level were evaluated in patients with distinct neuroendocrine disorders. Thirteen patients with Prl-secreting tumours (PST), 10 acromegals (A) and 8 patients with hypothalamic lesions (HL), as assessed on clinical, radiological and surgical grounds, underwent on separate occasions acute testing with the opioid peptide FK 33-824 (0.5 mg iv), the indirect dopamine (DA) agonist nomifensine (NOM, 200 mg po), the DA receptor antagonist domperidone (DOM, 10 mg iv), TRH (200 μg iv) and insulin (ITT, 0.10–0.15 IU/kg iv). All patients were evaluated pre-surgery and 4 of them also post-surgery. Prl and GH were evaluated by RIA at different time intervals following treatments. Peculiar features of Prl and GH response could be evidenced in the patients as follows: Prl: PST patients did not respond either to stimulation by FK 33-824 (12/13) or to inhibition by NOM, (9/10), but 2/8 and 4/12 of them did respond to DOM or TRH stimulation, respectively; 8/10 A and all of the HL patients did not suppress plasma Prl following NOM, but many of them did respond to FK 33-824 (6/10 A, 5/8 HL) and TRH (9/10 A, 6/8 HL); as for GH, PST patients could be divided into FK 33-824 responders (8/12) and non-responders, whereas in only one of the A and in none of the HL patients a consistent response to the peptide was present; a major difference between A and HL patients was the ability of TRH to elicit a GH rise in the former (8/10) but not the latter (0/6). In conclusion, concomitant application of different CNS- or AP-acting stimuli seems to enable better functional connotation of individual disorders, and hence, provide information of value for the underlying pathophysiology.

Over the past few years, a variety of dynamic tests have been devised or reappraised in prolactin (Prl) research (see Müller et al. 1981, for review). The main objective of these maneuvers was to distinguish between tumourous and non-tumourous hyperprolactinaemia and to advance understanding on the mechanism(s) involved in the control of Prl secretion. Some of these tests have also been used occasionally in other neuroendocrine disorders, such as acromegaly (Müller et al. 1981; Scanlon et al. 1977) or hypothalamic diseases (Crosignani et al. 1980; Kamoi et al. 1981); however, to our knowledge, no attempts have been made of concomitantly evaluating hormonal responses to the different challenges in the aforementioned conditions.

In this study, we have evaluated Prl and growth hormone (GH) responses to some neuroactive agents in patients with prolactinomas, acromegaly and hypothalamic lesions. Our scope was that of a) evidencing a pattern of the Prl and/or GH responses to one or more of the applied stimuli enabling the best diagnostic and/or functional con-
notation of the disease, and b) hopefully providing information of value for the underlying pathophysiology.

Material and Methods

Thirteen patients bearing a prolactinoma (prolactinoma group), 10 patients with active acromegaly (acromegaly group) and 8 with hypothalamic lesions (hypothalamic lesion group) gave their informed consent to participate in this study. All of these patients were off drugs and free of associated diseases known to affect pituitary function. Clinical and laboratory details of these patients are summarized in Table 1. Cases 2–11 of the first group had roentgenographic alterations which were considered unequivocal for the presence of a pituitary tumour (Camanni et al. 1980); 2 of the acromegalic patients (cases 17 and 18) showing typical clinical signs of acromegaly, had plasma GH levels within the normal limits, which were not suppressed after oral glucose and in-

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Sex</th>
<th>Age years</th>
<th>GH (ng/ml)</th>
<th>Prl (ng/ml)</th>
<th>Clinical details</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>32</td>
<td>0.6–0.9</td>
<td>7660–8620</td>
<td>Headache, decreased libido, galactorrhoea, chromophobe adenoma with suprapituitary extension (surgically proven)</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>22</td>
<td>4–4.2</td>
<td>120–190</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>33</td>
<td>0.9–1.1</td>
<td>138–170</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>35</td>
<td>0.5–0.7</td>
<td>81–151</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>21</td>
<td>0.4–0.8</td>
<td>135–250</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>45</td>
<td>1.1–4.1</td>
<td>16.9–39</td>
<td>Oligo-amenorrhoea, galactorrhoea, (except case 5) since 2–8 years.</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>43</td>
<td>0.7–4.5</td>
<td>58–78</td>
<td>Roentgenographic alterations highly presumptive for microprolactinoma</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>26</td>
<td>0.3–6.5</td>
<td>19–54</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>30</td>
<td>0.5–2.8</td>
<td>46–89</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>43</td>
<td>0.4–2.2</td>
<td>75–285</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>27</td>
<td>0.6–1.9</td>
<td>28–48</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>F</td>
<td>15</td>
<td>0.8–1.1</td>
<td>308–369</td>
<td>Primary amenorrhoea, galactorrhoea</td>
</tr>
<tr>
<td>13</td>
<td>F</td>
<td>35</td>
<td>0.7–0.9</td>
<td>162–214</td>
<td>Amenorrhoea, galactorrhoea since 5 years, after unsuccessful surgery for prolactinoma</td>
</tr>
</tbody>
</table>

Acromegaly

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Sex</th>
<th>Age years</th>
<th>GH (ng/ml)</th>
<th>Prl (ng/ml)</th>
<th>Clinical details</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>F</td>
<td>28</td>
<td>23–32</td>
<td>20.5–28</td>
<td>Eosinophilic adenoma (surgically proven)</td>
</tr>
<tr>
<td>14’</td>
<td></td>
<td></td>
<td>0.5–3.5</td>
<td>0.5–11</td>
<td>Post-surgery, uneventful pregnancy and lactation; under replacement therapy with thyroxine and cortone</td>
</tr>
<tr>
<td>15</td>
<td>M</td>
<td>47</td>
<td>18.5–45</td>
<td>6–13</td>
<td>Hypertension, diabetes, eosinophilic adenoma (surgically proven)</td>
</tr>
<tr>
<td>15’</td>
<td></td>
<td></td>
<td>1.9–4.2</td>
<td>7.8–13.2</td>
<td>Post-surgery, remission of diabetes. No replacement therapy</td>
</tr>
<tr>
<td>16</td>
<td>M</td>
<td>54</td>
<td>37–63</td>
<td>177–225</td>
<td>Eosinophilic adenoma (surgically proven)</td>
</tr>
<tr>
<td>16’</td>
<td></td>
<td></td>
<td>5–7.6</td>
<td>25–40.5</td>
<td>Post-surgery, GH and Prl values still high. Replacement therapy with cortone</td>
</tr>
<tr>
<td>17</td>
<td>F</td>
<td>67</td>
<td>2.8–5</td>
<td>3–8.5</td>
<td>In spite of borderline GH levels, clinical signs of acromegaly, sellar enlargement, GH response to TRH and GnRH or OGTT</td>
</tr>
<tr>
<td>18</td>
<td>F</td>
<td>47</td>
<td>3–7.9</td>
<td>12.5–22.3</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>M</td>
<td>45</td>
<td>8.3–11.9</td>
<td>3.1–4.9</td>
<td>Clinical signs of acromegaly since 3–12 years. Sellar enlargement and, except in case 19, clear evidence of endosellar tumour at CT</td>
</tr>
</tbody>
</table>
creased in response to GnRH and/or TRH. Among the patients of the third group two were included (cases 26 and 28) despite normal baseline Prl levels, because of an unequivocal evidence for hypothalamic lesion. Three patients with acromegaly (cases 14', 15', and 16') and 1 patient with a third ventricle dysgerminoma (case 24') were also re-evaluated after surgical removal of the pituitary or brain tumour.

Starting at 8.30–9.00 a.m. and after an overnight fast, patients received, in random order and on separate occasions, 0.5 mg iv FK 33-824 (d-Ala², MePhe⁴, Met(0)⁴-
ol enkephalin, Sandoz, Basel), 200 µg iv TRH (Relefact, Hoechst Italia S.p.A., Milan), 200 mg po, nomifensine (NOM, Alival or Psicronizer, Hoechst Italia S.p.A., Milan), 10 mg iv domperidone (DOM, Motilium, Janssen Pharmaceutica S.p.A., Rome) and, with the exception of the prolactinoma patients, 0.15 or 0.10 IU/kg body weight iv regular insulin (Actrapid, Novo, Copenhagen). Placebo studies were also performed in the majority of the patients. Serial blood samples were obtained from an antecubital vein kept open by a slow saline drip before and for 2 h after FK 33-824, TRH, DOM and insulin

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Sex</th>
<th>Age years</th>
<th>Baseline levels</th>
<th>Clinical details</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>GH (ng/ml)</td>
<td>Prl (ng/ml)</td>
</tr>
<tr>
<td>20</td>
<td>M</td>
<td>49</td>
<td>17–37</td>
<td>3.4–5.8</td>
</tr>
<tr>
<td>21</td>
<td>M</td>
<td>30</td>
<td>125–290</td>
<td>7.7–18.2</td>
</tr>
<tr>
<td>22</td>
<td>F</td>
<td>67</td>
<td>19–24</td>
<td>2.6–9.8</td>
</tr>
<tr>
<td>23</td>
<td>F</td>
<td>59</td>
<td>18–23</td>
<td>35–42</td>
</tr>
</tbody>
</table>

Clinical signs of acromegaly since 8 years. Eosinophilic adenoma (surgically proven)

Hypothalamic lesions

24 F 18 0.4–0.6 30–45   Bulimia, primary amenorrhoea, stunted growth. Dysgerminoma anterior wall 3rd ventricle (surgically proven)

24'   7.5–9  Post-surgery, disappearance of bulimia, appearance of menstrual cycles

25 F 23 0.6–0.8 28.3–37.6 Secondary amenorrhoea since 5 years, galactorrhoea. Diabetes insipidus. Roentgenographic diagnosis of tumour of the floor of the 3rd ventricle. Radiotherapy.

26 M 56 0.3–1.7 5.5–12  Psychic deterioration, obstructive hydrocephalus. Third degree astrocytoma of the anterior wall 3rd ventricle at stereotactic biopsy. Ventricular-peritoneal shunt

27 F 20 1–1.2 16.4–26  Secondary amenorrhoea, diabetes insipidus. Histiocytosis based on tumour shrinkage after glucocorticoids

28 M 40 0.5–7.5 5–11.4 Bitemporal haemorrhage. Aneurism of the anterior communicating artery. Evidence for hypothalamic involvement at CT

29 F 16 0.1–1.8 20–52  Primary amenorrhoea. Prader-Willy syndrome

30 M 14 0.2–3.7 60–69  Clinical signs compatible with dysgerminoma (hypodipsia, hypernatraemia, hypokalaemia, attacks of proximal muscle weakness)

31 M 11 0.8–1.3 17.9–38.2 Bulimia. Short stature. Von Recklinghausen's neurofibromatosis. Glioma of the optic chiasm involving the optic nerves. Extreme reduction of visual capacity
(ITT) injection, and for 5 h following NOM administration. Plasma was separated, frozen and stored at -20°C until assayed. Plasma GH and Prl levels were determined by double antibody RIA (Hales & Randle 1963), using commercial reagents (Dow Lepetit Kit and Biodata Kit, respectively). Sensitivity of GH and Prl assays is 1.5 and 0.4 ng/ml, respectively. Intra- and inter-assay coefficients of variation (CV) were 4 and 7% for Prl and 3.3 and 4.8% for GH. Whenever necessary, in the GH estimation, plasma was diluted 1:2 and 1:10 (1 patient) with the assay buffer; in these conditions, intra-assay CV were 3.8 and 11%, respectively. Likewise, in the Prl assay some plasma samples were diluted 1:3 and 1:15 (1 patient), with intra-assay CV of 12.6 and 16%, respectively. In our laboratory the upper limit of normal for Prl is 20 ng/ml in women during the follicular phase and 15 ng/ml for men; for GH, 0–3 ng/ml in either sex.

Blood glucose in the ITT was determined by Technicon-AutoAnalyzer. The ITT was considered to be adequate when glycaemia was suppressed below 50% of baseline and below 40 mg/dl, in presence of unequivocal signs of hypoglycaemia. In the NOM test, Prl values were expressed as per cent of baseline. Responsiveness to NOM was defined as a mean decrease of at least 30% between 120 and 240 min after drug treatment (Genazani et al. 1980). In hyperprolactinaemic patients, a response to TRH and DOM was considered to be present when at least doubling of baseline Prl value occurred (Jacobs et al. 1973; Kleinberg et al. 1977); the Prl response to FK 33-824 was evaluated by comparison with the hormone pattern in the placebo test. In normoprolactinaemic patients, data were compared with those obtained in healthy age-matched controls: 8 women and 5 men for TRH and 12 women and 7 men for DOM. The same was done for the GH and Prl responses to ITT (7 women and 6 men) and FK 33-824 (6 women and 5 men). Based on these comparisons, responses to different challenges were classified as normal, blunted or absent.

Results

Prolactinomas

Prolactin. Acute administration of FK 33-824 failed to significantly increase plasma Prl concentration in all of the patients but one (case 10), when plasma changes were compared to those occurring during placebo infusion (Fig. 1, up left). Four of 12 patients (cases 5, 6, 8 and 9) displayed a consistent Prl increase (149, 233, 271 and 237%, respectively) following TRH (Fig. 1, middle left), whilst, with one exception (case 7), none of the patients had any suppression of their plasma Prl levels following
NOM (Fig. 1, up right). In 2/8 patients (case 5 and 9), there was, as with TRH, an appreciable Prl increase after DOM (Fig. 1, middle right).

GH. In contrast with its inability to evoke Prl release, FK 33-824 induced a clear cut rise in plasma GH in 8/12 patients (Fig. 1, bottom). Three of 9 patients tested with NOM (case 7, 10 and 13) exhibited a normal GH rise (ΔGH, 10, 9 and 9 ng/ml) (data not shown).

Acromegaly

Prolactin. FK 33-824 caused a clear cut rise in plasma Prl in 6/10 patients (case 14', 15, 17, 18, 22 and 23); a normal Prl response could be noted in case 15 also at post-surgical evaluation, while it was blunted or absent in the remaining 4 cases (Fig. 2, upper left). A Prl rise after TRH was recorded in all of the patients except in case 23, who was responsive to FK 33-824, and in case 16' who did respond to TRH before surgery (Fig. 2, middle left).

At variance with FK 33-824 and TRH, NOM did not affect plasma Prl levels except in cases 17 and 18 in whom a 36.2% and 38.9% Prl decrease, respectively, occurred (Fig. 2, bottom left). DOM was fully effective to increase plasma Prl in case 17, 19 and 22 while it caused a Prl elevation of lesser degree in 5 additional cases (14', 15, 15', 18, 20 and 23) and was completely ineffective in cases 16' and 21 (data not shown). A highly blunted or absent Prl response to an ITT was obtained in 8 acromegalics tested, with the exception of 1 patient who showed a normal Prl rise (data not reported).

GH. In contrast to its effects on Prl, FK 33-824 elicited a significant rise in plasma GH only in case 23 (Fig. 2, up right). TRH caused a GH rise in 8/10 patients evaluated before surgery and in case 16' with persistently high GH levels after surgery, while it was no longer effective in case 15' after successful operation (Fig. 2, middle right). NOM did not affect plasma GH levels except in case 15 where it produced a reduction of plasma hormone levels. The GH-lowering effect of NOM in case 15 was no longer evident following adenomectomy (Fig. 2, bottom right). DOM failed to alter baseline GH levels (data not shown). Cases 15-19, 21 exhibited a GH rise in response to an ITT, while cases 14 and 20 did not. GH responses remained qualitatively similar in 3 of these patients evaluated post-surgery (data not shown).

Hypothalamic lesions

Prolactin. FK 33-824 induced a rise in plasma Prl levels in 5/8 patients (cases 25–28, 30); in case 24, Prl unresponsiveness persisted after removal of a dysgerminoma (Fig. 3, up left). Prl pattern following TRH paralleled that observed after FK 33-824 in cases 25–28 (responders) and in case 29 (non-responder); in contrast, Prl rose in cases 24 and 31 who did not respond to FK 33-824 but not

Fig. 2.
Prl and GH responses to different stimuli in patients with acromegaly.
in case 30, who displayed a moderate response to the opioid (Fig. 3, up middle). DOM increased PRL levels in 4/7 patients (cases 26–28, 31), who were also responsive to TRH, and, with the exception of case 31, to FK 33-824, but failed to do so in cases 24, 29 and 30, of whom the two former also were FK 33-824 non-responders (Fig. 3, up right). NOM was completely ineffective in lowering PRL levels in 8/8 subjects (Fig. 3, bottom right). Absent or highly blunted PRL responses to ITT were present in all patients tested but one (case 30) (data not shown).

**GH.** FK 33-824 (Fig. 3, bottom left) as well as TRH (Fig. 3, bottom middle), and NOM (data not shown) failed to consistently increase plasma GH levels in this patient group; only a slight GH increase was observed in case 30 after FK 33-824 (∆GH, 5.1 ng/ml) and in case 29 following NOM (∆GH, 6.3 ng/ml). GH response to ITT was blunted (case 26, 29 and 30) or absent (cases 24, 25, 27 and 31) in 7 subjects investigated (data not shown).

**Discussion**

In patients with different neuroendocrine disorders, administration of nomifensine (NOM), domperidone (DOM), FK 33-824, TRH and insulin (ITT), enabled us to delineate for each disease peculiar features of PRL and GH responses and provided information of diagnostic and/or pathophysiological relevance.

**Prolactinomas**

Experimental evidence has led to postulate that in patients harbouring a prolactinoma defective tuberoinfundibular DA (TIDA) function underlies the inappropriate PRL secretion (Fine & Frohman 1978; Müller et al. 1981). Supporting this view is the observation that both indirectly acting DA agonists (IADAs), e.g. NOM, and DA receptor antagonists, e.g. DOM, are ineffective to alter baseline PRL levels in most of the patients with prolactinoma (Camanni et al. 1980; Genazzani et al. 1980; Kamoi et al. 1981). In our study, in 9/10
patients with a prolactinoma NOM failed to suppress plasma Prl, while DOM caused more than doubling of baseline Prl levels in 2/8 cases. On the other hand, these same cases and 2 others, out of 12 studied, had increased Prl levels following TRH, thus arguing against the tenet that unresponsiveness to TRH is a functional marker of patients with prolactinomas (Faglia et al. 1977; Barbarino et al. 1979).

Like NOM, FK 33-824 failed to alter plasma Prl in 12/13 patients. This finding is in keeping with the view, derived from animal studies, that endogenous opioids may promote Prl release by decreasing DA metabolism and release at TIDA nerve terminals (Van Loon et al. 1980). The same finding also supports the idea that TIDA neuronal function is defective in these patients (see above).

In contrast to its inability to alter Prl secretion, FK 33-824 induced a definite GH rise in 8/12 patients, which suggests that neurotransmitters others than DA mediate the GH-releasing effect of the peptide (Casanueva et al. 1981a,c). As for the lack of GH response to the opioid of the remaining 4 patients, it must be recalled that such a pattern also was present in 4/11 of control subjects (data not shown).

Acromegaly
An inappropriate hypothalamic secretion of a GH-releasing factor or the existence of a primary GH-secreting neoplasm has been advocated as the most likely cause of acromegaly (Reichlin 1980). In our study, administration of FK 33-824 failed to elicit a rise in plasma GH in 9/10 acromegalics and, interestingly, also was ineffective in 2 cases evaluated after successful surgery. No correlation was found between GH responses to FK 33-824 and TRH. Moreover, in case 15, evaluated after successful adenomectomy, a persisting impairment of the GH response to FK 33-824 was associated with disappearance of the paradoxical GH response to TRH, which was still present in case 16 after unsuccessful surgery. These findings, which expand those by Demura et al. (1981), point to the existence of an impaired hypothalamic control of GH secretion in acromegaly. Furthermore, they reinforce the proposition that the TRH-induced GH rise is related to abnormal TRH recognition sites on tumourous somatotrophs (Faglia et al. 1978) and favour the idea that FK 33-824 releases GH in man via a suprapituitary site of action.

In keeping with the findings of other investigators (Scanlon et al. 1977), NOM failed to alter baseline GH levels in the majority of acromegalic patients, further stressing the view that central catecholaminergic control of GH secretion is defective in this disease (Müller et al. 1977; Van Loon 1979). GH responses to insulin hypoglycaemia displayed by our patients were variable and did not correlate with those obtained in the other dynamic testing of GH secretion.

Regulation of Prl secretion in acromegaly is incompletely understood, though in the majority of reports blunted Prl responses to Prl-releasing stimuli have been observed in normo- or hyperprolactinaemic acromegalics (Spitz et al. 1980). In view of the proposition that FK 33-824 promotes Prl secretion by inhibiting DA turnover in TIDA neurons (Van Loon et al. 1980), our finding that this compound enhanced Prl release in a considerable proportion of acromegalics would indicate a preserved dopaminergic function in the FK 33-824 responders. However, against such conclusion mitigates the observation that only 2/10 patients had suppressed Prl after NOM, and 3/10 responded normally to DOM. Therefore, for the Prl-releasing effect of FK 33-824 an extradopaminergic, namely serotoninergic, mediation (Koenig et al. 1979; Spampinato et al. 1979) or alternatively, a direct pituitary site of action may be envisioned (see also below). In favour of the latter idea is the finding that the direct Prl secretagogue TRH elicited a consistent elevation of plasma Prl in 9/10 patients.

Hypothalamic lesions
Like the acromegalics, patients with organic or functional alterations in the hypothalamus failed to respond with a consistent plasma GH rise to FK 33-824 and, with one exception, to NOM. However, in sharp contrast to acromegalics, there was no GH response to TRH in the 6 subjects investigated. An unexpected result was the ability of FK 33-824 to evoke, as in the acromegalics, a distinct Prl rise in most of these patients, which is in clear contrast to its failure to stimulate GH secretion. Since a hypothalamic site of action has been identified for FK 33-824 in animal studies (Grandison et al. 1980), this unforeseen effect of the peptide calls for its inherent ability to act also at a pituitary site. Inferential support to this proposition is the finding that FK 33-824 stimulates the release of Prl, but not of GH, in rats with mechanical ablation of the hypothalamus (Casanueva et al. 1981b). A direct action of opioid compounds at the lactotrophs to
remove DA tonic inhibition has been proposed by Enjalbert et al. (1979). Consistent with this view, there was in our subjects an almost complete overlapping between the Prl response to FK 33-824 and to DOM, a stimulus whose Prl-releasing effect rests on the modulatory influence by DA on the pituitary lactotrophs. Adequate Prl responsiveness to TRH in most of the patients adds further weight to the idea that their lactotrophs were highly reactive to stimuli. Total refractoriness of our patients and the patients of others to the Prl-lowering effect of NOM (Crosignani et al. 1980; Kamoi et al. 1981), denotes the existence of an alteration solely due to the disrupting effect of the hypothalamic lesion on TIDA pathways. The almost complete lack of the Prl response to ITT present in these subjects, reinforces this view. Finally, it is apparent that though NOM and DOM assess related aspects of DA function, the former is a more rigorous indicator of TIDA function, and this may account for a dissociation in the Prl responsiveness to the two stimuli in some endocrine disorders (Massara et al. 1981; this study).

In conclusion, concomitant application of different CNS- or pituitary-acting stimuli to diseases of the hypothalamo-pituitary system seems to provide better functional connotation of individual disorders. Prl unresponsiveness to FK 33-824 and NOM appears to be the better functional marker in patients with a prolactinoma. Unresponsiveness to NOM is also present in patients with hypothalamic lesions, but most of these cases do respond to FK 33-824. This may be crucial for a diagnostic differentiation from patients with prolactinomas, whenever this is not allowed from clinical and radiologic presentation (Kapcala et al. 1980). Moreover, whilst GH unresponsiveness to FK 33-824 is present in patients with hypothalamic lesions, the peptide releases GH in some patients with prolactinomas. Acromegals share with patients with hypothalamic lesions GH unresponsiveness to FK 33-824 and with the other neuroendocrine disorders Prl unresponsiveness to NOM. However, the TRH-induced GH rise may only be found in some acromegalic patients.

Acknowledgments

The participation to part of these studies of Drs. A. R. Genazzani, C. Invitti, G. Sciliano is gratefully acknowledged. Miss Isabella Zago and Miss Elena Cambié provided secretarial help. These studies were supported in part by special CNR research project 'Control of Neoplastic Growth', sub-project Endocrine Control', Rome, Italy.

References


Received on May 28th, 1984.