Basal, Pulsatile, Entropic, and 24-Hour Rhythmic Features of Secondary Hyperprolactinemia Due to Functional Pituitary Stalk Disconnection Mimic Tumoral (Primary) Hyperprolactinemia

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ABSTRACT

Under physiological conditions, PRL secretion is regulated precisely by various stimulating and inhibiting factors. Hyperprolactinemia may arise as a primary consequence of a PRL-secreting pituitary adenoma. Secondary hyperprolactinemia (SH) may emerge in patients with hypothalamic disease, hypophyseal stalk compression, or suprasellar extension of a (nonlactotrope) pituitary adenoma. The latter may reflect diminished delivery of dopamine or other inhibitory factors to normal lactotropes. We hypothesized that diurnal and ultradian rhythms of PRL secretion would differ in secondary (e.g., hypothalamic) and primary (e.g., tumoral states) hyperprolactinemia (PH), assuming that the underlying pathophysiology differs. To test this clinical postulate, we investigated the patterns of 24-h PRL release in eight patients with SH associated with functional hypothalamo-pituitary disconnection and in eight patients with PH attributable to microprolactinoma. Data in each group were compared with values in healthy gender-matched controls. PRL time series were obtained by repetitve 10-min blood sampling, followed by high-precision immunofluorometric assay. PRL concentration profiles were analyzed by the complementary tools of model-free discrete peak detection, wave-form-independent deconvolution analysis, cosinor regression, and the approximate entropy metric to quantify pulsatile, basal, 24-h rhythmic, and pattern-dependent (entropic) PRL secretion.

Patients with tumoral hyperprolactinemia (PH) showed a 2-fold higher 24-h mean serum PRL concentration than patients with SH (62 ± 13 µg/L vs. 30 ± 6.9 µg/L, respectively, P = 0.029). Estimated PRL pulse frequency (events/24 h) was similar in the two patient groups (18.5 ± 0.7 vs. 17.6 ± 0.8; P = 0.295) but elevated over that in euprolactinemic controls (P < 0.0001 for both). Deconvolution analysis disclosed a mean daily PRL secretion rate of 790 ± 170 µg in PH patients vs. 380 ± 85 µg in SH patients (P = 0.030). Nonpulsatile PRL secretion comprised nearly 70% of total secretion in both patient groups and 50% in controls (P < 0.0001). Cosinor analysis revealed similar acrophases in all three study cohorts. The mean skewness of the statistical distribution of the individual PRL sample secretory rates was reduced, compared with controls (P < 10⁻⁶ for each), but equivalent in SH and PH patients (0.83 ± 0.12 vs. 0.78 ± 0.08, respectively), denoting a loss of the normal spectrum of low- and higher-amplitude secretion rates. Approximate entropy, a regularity statistic, was markedly elevated in both patient groups over controls (P < 10⁻⁶ for each) and was slightly higher in PH patients than in SH patients (1.639 ± 0.029 vs. 1.482 ± 0.067, P = 0.048).

In summary, patterns of PRL secretion in PH and SH states exhibit an equivalently increased frequency of PRL pulses, a comparably marked rise in nonpulsatile (basal) PRL secretion. Despite overlap, the regularity of PRL release patterns is disrupted even more profoundly in PH (tumoral), compared with SH. Assuming that the orderliness of serial PRL output monitors normal integration within a feedback-controlled neurohormone axis, then the more disorderly patterns of tumoral PRL secretion point to greater regulatory disruption in PH. The latter may reflect abnormal secretory behavior associated with lactotrope neoplastic transformation and/or isolation of the tumor cell mass from normal hypothalamic controls. (J Clin Endocrinol Metab 86: 1562–1567, 2001)

PRL SECRETION is regulated by a composite of stimulatory and inhibitory factors derived from the hypothalamus (e.g., dopamine), the systemic circulation (e.g., estradiol), and the pituitary gland itself (e.g., autocrine and paracrine signals). Implicitly, the foregoing ensemble of effectors governs the orderly, physiologically pulsatile, and 24-h rhythmic secretion of PRL (1). Hyperprolactinemia emerges in several physiological states (such as pregnancy and lactation) and in diverse pathophysiological contexts, including stress, uremia, treatment with dopaminergic antagonists, prolactinomas, and various lesions that interfere with the transport of hypothalamic factors regulating PRL release. For example, infiltrative or destructive hypothalamic processes and interruption of the pituitary stalk can diminish the availability of dopamine to the pituitary gland and elicit secondary hyperprolactinemia (SH), presumptively associated with otherwise normal lactotropes (2–4). Conversely, tumoral or primary hyperprolactinemia (PH) is driven by autonomous PRL secretion, which (by analogy with other neuroendocrine tumors) would be expected to show distinc-
tive dysregulation of pulsatile, 24-h rhythmic, and/or entropic (pattern-dependent) output (5–10).

The present study tests the latter prediction by comparing ultradian, nyctohemeral (diurnal), and entropic features of PRL release in patients with PH and SH.

Subjects and Methods

Subjects

The patient cohort comprised eight individuals with SH (four men and four women; mean age, 46 yr; range, 32–66 yr) and eight with PH (mean age, 35 yr; range, 24–43 yr). The diagnosis of SH required sustained hyperprolactinemia unassociated with renal or hepatic disease, drug use, primary hypothyroidism, undue stress, pregnancy, or lactation. Clinically, a nonsecretory pituitary tumor (below) with suprasellar extension was demonstrated by magnetic resonance imaging (MRI) (seven patients), or primary hypothalamic disease was present (one patient). Immunohistochemical investigation of the adenoma was possible in six patients, two of whom exhibited no hormone staining, and four exhibited PSH β-subunit staining. None showed detectable PRL immunoreactivity. One patient received nonsurgical treatment with quinagolide, which normalized PRL but did not decrease the suprasellar extension, as observed by yearly MRI scans over 6 yr (11). Thyroxin levels were in the low-normal range in five SH patients with an adenoma, and subnormal in two others, who were subsequently substituted with T₄ before the sampling studies were performed. A delayed response of TSH to iv TRH administration was found in all six investigated patients. Testosterone levels were decreased in two male patients, and serum estradiol was low in one premenopausal woman. Delayed LH increase to GnRH was present in all subjects. In two other patients, GH and ACTH (cortisol) responses to insulin-induced hypoglycemia and GHRH and CRH were both investigated. In these subjects, the GH and ACTH responses to hypoglycemia were subnormal, in contrast to the normal increase of these hormones to direct pituitary stimulation. One of these subjects subsequently received hydrocortisone substitution.

The diagnosis of PH required secondary amenorrhea, galactorrhea, elevated serum PRL concentration, and a MRI diagnostic of a pituitary microadenoma (i.e., tumor diameter less than 1 cm). Three patients underwent adenomectomy and immunohistochemistry confirmation of tumoral PRL. Staining was negative for ACTH, GH, TSH, intact gonadotropins, and their subunits. In the group of SH patients, 2 women were receiving stable estrogen replacement, and 3 men had received hydrocortisone substitution. Two PH patients with secondary amenorrhea were taking estrogen before the correct diagnosis of prolactinoma was made. Twelve healthy men and 15 healthy women (mean age, 43 yr; range, 21–77 yr) with normal body mass indexes served as controls for comparison with the SH patients (SH controls), and 15 women in this group (mean age, 45 yr; range, 21–77 yr) served as controls for PH patients (PH controls). Premenopausal controls were studied in the follicular phase of the menstrual cycle.

In SH patients, sampling studies were generally carried out shortly before surgery; and in PH patients, before dopaminergic drug therapy was started. An indwelling iv cannula was inserted in a forearm vein, 60 min before sampling began, and blood samples were withdrawn at 10-min intervals, starting at 0900 h, for the next 24 h. Subjects were free to ambulate but not to sleep during the daytime. Meals were served at 0800, 1230, and 1730 h. Lights were turned off between 2200 and 2400 h. No electroencephalogram sleep recording was performed. Plasma samples were collected on ice in heparinized tubes and centrifuged at 4 °C.

Assays

Plasma PRL concentrations were measured in duplicate with a sensitive and precise time-resolved fluoroimmunoassy (Wallac, Inc. Oy, Turku, Finland). The standards were calibrated against the World Health Organization 3rd International Standard for PRL 84/500 (to convert μg/L to mU/L, multiply by 36). The limit of detection (defined as 2 sds above the mean zero standard) was 0.04 μg/L. The intraassay coefficient of variation varied from 2.0–3.3%, in the assay range from 3.0–80 μg/L, with a corresponding interassay coefficient of variation of 3.4–6.2%. All samples from one individual were run in the same batch.

Analytical techniques

Pulsatile PRL release was quantitated by discrete peak detection, using the Cluster program. Criteria included a 2-cluster size to test for significant upstrokes and downstrokes in the data (two samples in both the test nadir and in the test peak) and critical t statistics of 2.0 for both an increase and decrease to constrain the false-positive rate to less than 5% on signal-free noise (12, 13). The following peak features were quantified: the total number of PRL concentration peaks per 24 h, peak duration (min), maximal peak height (highest PRL concentration attained in the peak), incremental peak height (amplitude) above preceding nadir, incremental peak area, and interpulse valley and nadir PRL concentrations.

A waveform-independent deconvolution technique (Pulse) was used to estimate sample PRL secretion rates without model assumptions (14, 15). To this end, the two-component half-life for PRL was recalculated, by nonlinear regression, using the original data set in healthy controls of Sievertsen et al. (16). The half-life of the fast component was 18.4 ± 4.0 min; and that of the slow component, 139 ± 25 min. The fractional
TABLE 1. Discrete pulse detection applied to 24-h plasma prolactin concentration profiles in hyperprolactinemic patients and euprolactinemic controls

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Prolactinoma (PH)</th>
<th>Controls</th>
<th>P value</th>
<th>Secondary hyperprolactinemia (SH)</th>
<th>Controls (SH)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-h mean conc (µg/L)</td>
<td>61.9 ± 13.0*</td>
<td>4.8 ± 0.5</td>
<td></td>
<td>29.8 ± 6.9</td>
<td>4.3 ± 0.3</td>
<td>2.44 × 10⁻⁵</td>
</tr>
<tr>
<td>24-h integrated conc (mg/L-24 h)</td>
<td>89.1 ± 18.8*</td>
<td>7.0 ± 0.8</td>
<td></td>
<td>42.9 ± 9.9</td>
<td>6.2 ± 0.5</td>
<td>2.41 × 10⁻⁵</td>
</tr>
<tr>
<td>Peaks (no./24 h)</td>
<td>18.5 ± 0.7</td>
<td>12.4 ± 0.6</td>
<td></td>
<td>17.6 ± 0.8</td>
<td>12.9 ± 0.5</td>
<td>4.14 × 10⁻⁵</td>
</tr>
<tr>
<td>Peak width (min)</td>
<td>54.9 ± 2.5</td>
<td>85.6 ± 6.2</td>
<td></td>
<td>58.4 ± 3.9</td>
<td>81.1 ± 3.9</td>
<td>0.005</td>
</tr>
<tr>
<td>Peak height (µg/L)</td>
<td>67.1 ± 14.1b</td>
<td>5.7 ± 0.5</td>
<td></td>
<td>320 ± 7.1</td>
<td>5.1 ± 0.3</td>
<td>1.41 × 10⁻⁸</td>
</tr>
<tr>
<td>Peak amplitude (µg/L)</td>
<td>8.4 ± 1.6c</td>
<td>2.1 ± 0.2</td>
<td></td>
<td>4.0 ± 0.7</td>
<td>1.8 ± 0.2</td>
<td>6.67 × 10⁻⁵</td>
</tr>
<tr>
<td>Peak area (µg/L/min)</td>
<td>315 ± 60</td>
<td>121 ± 22</td>
<td></td>
<td>169 ± 40</td>
<td>104 ± 13</td>
<td>0.049</td>
</tr>
<tr>
<td>Nadir conc (µg/L)</td>
<td>56.9 ± 12.1*</td>
<td>3.5 ± 0.4</td>
<td></td>
<td>27.3 ± 6.4</td>
<td>3.2 ± 0.2</td>
<td>1.75 × 10⁻⁸</td>
</tr>
</tbody>
</table>

Values are the mean ± SEM. Blood samples were withdrawn at 10-min intervals for 24 h in 8 women with a microprolactinoma (PH), 8 patients (4 men and 4 women) with secondary hyperprolactinemia (SH), 27 SH-controls (12 men and 15 women), and 15 PH-controls. Significance was determined by the Student’s t test. Significant statistical differences between PH and SH patients were: *P = 0.047, b P = 0.043, c P = 0.028. conc, Concentration.

TABLE 2. Deconvolution analysis of basal (nadir), pulsatile, and total 24-h PRL secretion in patients and controls

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PH patients</th>
<th>Controls (PH)</th>
<th>SH patients</th>
<th>Controls (SH)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nadir secretion (µg/L)</td>
<td>590 ± 130</td>
<td>31 ± 4.1</td>
<td>285 ± 75</td>
<td>25 ± 2.5</td>
<td></td>
</tr>
<tr>
<td>Pulsatile secretion (µg/L)</td>
<td>200 ± 138</td>
<td>32.5 ± 3.5</td>
<td>96 ± 17</td>
<td>30 ± 2.4</td>
<td></td>
</tr>
<tr>
<td>Total secretion (µg/L)</td>
<td>790 ± 170</td>
<td>63 ± 7</td>
<td>380 ± 85</td>
<td>58 ± 4.5</td>
<td></td>
</tr>
<tr>
<td>Nonpulsatile secretion (%)</td>
<td>74 ± 2.4</td>
<td>49 ± 2.1</td>
<td>73 ± 2.9</td>
<td>49 ± 1.6</td>
<td></td>
</tr>
</tbody>
</table>

Values are the mean ± SEM. Blood samples were withdrawn at 10-min intervals for 24 h in eight women with a microprolactinoma (PH patients), eight patients with secondary hyperprolactinemia (SH patients), and the respective control groups. Statistical difference was determined by the unpaired Student’s t test. P values for comparisons between patients and the control groups were less than 0.0001. Significant differences between PH and SH patients were: *P = 0.029, b P = 0.011.

TABLE 3. Cosinor analysis of the 24-h rhythmic release of PRL

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PH patients</th>
<th>Controls (PH)</th>
<th>P value</th>
<th>SH patients</th>
<th>Controls (SH)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesor (µg/L)</td>
<td>61.9 ± 13.0*</td>
<td>4.8 ± 0.5</td>
<td>1.6 × 10⁻¹⁰</td>
<td>29.8 ± 6.9</td>
<td>4.3 ± 0.3</td>
<td>2.1 × 10⁻¹⁵</td>
</tr>
<tr>
<td>Amplitude (µg/L)</td>
<td>4.7 ± 0.6</td>
<td>2.6 ± 0.5</td>
<td>0.06</td>
<td>3.5 ± 0.9</td>
<td>2.1 ± 0.3</td>
<td>0.12</td>
</tr>
<tr>
<td>Acrophase (h ± min)</td>
<td>05:16 ± 56</td>
<td>03:37 ± 42</td>
<td>0.32</td>
<td>04:54 ± 35</td>
<td>04:16 ± 26</td>
<td>0.51</td>
</tr>
<tr>
<td>Relative amplitude</td>
<td>7.3 ± 0.5</td>
<td>54.7 ± 7.4</td>
<td>1.4 × 10⁻⁴</td>
<td>11.4 ± 1.7</td>
<td>49.7 ± 4.8</td>
<td>1.8 × 10⁻⁸</td>
</tr>
</tbody>
</table>

Values are the mean ± SEM. Blood samples were withdrawn at 10-min intervals for 24 h in 8 women with a microprolactinoma (PH), 8 patients (4 men and 4 women) with secondary hyperprolactinemia (SH), 27 SH controls (12 men and 15 women), and 15 PH controls. Significance was determined by the Student’s t test. Significant statistical differences between PH and SH patients were: *P = 0.029, b P = 0.011.

Contribution of the slow component to the overall decay amplitude was 49.5 ± 15%. The following secretory measures were estimated: basal (no significant variation in consecutive sample secretion rates), pulsatile (nonzero secretion flanked by successive positive and negative first derivative changes at P < 0.05), and total (basal pulsatile) daily secretion rates.

Cosinor analysis was performed to quantitate the diurnal variation of plasma PRL concentrations in our patients. The following parameters were calculated: mesor (mean value around which the 24-h oscillation occurs), amplitude (one-half the difference between the highest and lowest value), and the acrophase (time of maximum concentration).

The irregularity of serial hormone measurements was quantitated by the approximate entropy (ApEn) statistic using parameter choices of m = 1 (pattern length) and r = 20% of the so of the individual subject’s hormone concentration time-series as the threshold (17, 18). This set of parameter choices provides a normalized (concentration-independent) ApEn measure with high statistical replicability, sensitivity, and validity for series of this length.

Statistical analysis

Results

Figure 1 illustrates 24-h plasma PRL concentration profiles obtained by sampling blood every 10 min in one PH patient, one SH patient, and one control subject. PRL release was pulsatile and varied diurnally in all subjects. Cluster analysis documented 2-fold higher PRL concentration-dependent parameters in PH than in SH patients; viz. 24-h mean and integrated plasma PRL concentrations, maximal peak height, incremental peak amplitude, peak area, and interpeak valley and nadir concentrations (see Table 1). PH patients exhibited 12-fold higher 24-h mean and integrated PRL concentrations, nadir values, and maximal PRL peak heights and 3- to 4-fold higher incremental peak amplitudes and peak areas than controls. SH patients maintained 7-fold higher 24-h mean and integrated PRL concentrations, nadir concentrations, and maximal peak heights and 2-fold increased incremental peak amplitudes and peak areas over controls. PRL peak frequency and duration were comparable in the two patient groups: i.e. the peak frequency for PH and SH patients was, respectively, 18.5 ± 0.7 vs. 17.6 ± 0.8 per 24 h (P = 0.395), and peak duration was 55 ± 2.5 vs. 58 ± 3.9 min (P = 0.490). Both PRL peak frequencies exceeded control values.
Deconvolution analysis disclosed significantly elevated daily PRL secretion in PH (13-fold) and SH (8-fold) patients (Table 2). Nonpulsatile (basal) PRL secretion approximated 70% of total secretion in the two patient groups, compared with 50% in controls ($P \leq 10^{-6}$). Cosinor analysis revealed similar acrophases and amplitudes of 24-h rhythmic PRL release in all three study cohorts (Table 3). The mesor was elevated in both patient groups but higher in PH than in SH patients. The fractional amplitude (ratio of amplitude/mesor, expressed as a percentage) was lower in PH than SH patients, $P = 0.011$ (Fig. 2).

The statistical distribution of individual sample secretory rates in patients and controls was quantitated by the relative skewness of the corresponding histograms. Skewness values were similar in PH and SH patients ($0.78 \pm 0.09$ vs. $0.83 \pm 0.12$, respectively; $P = 0.747$) but less than in corresponding controls [PH controls, $3.35 \pm 0.40$; SH controls, $3.61 \pm 0.28$; $P < 10^{-5}$ for each (Figs. 3 and 4)]. The foregoing loss of skewness in PH and SH denotes reduced secretory rate variability about the mean in both hyperprolactinemic states, i.e., blunting of expected occasional high and low extremes observed in the normal subjects.

PRL secretion in PH patients was more irregular than that in SH patients, as quantified by higher ApEn values ($1.639 \pm 0.029$ and $1.482 \pm 0.067$, respectively, $P = 0.048$). ApEn values in both patient groups were remarkably higher than those in respective controls (PH controls, $0.813 \pm 0.079$; and SH controls, $0.841 \pm 0.055$; $P < 10^{-6}$ for each). There was complete separation between values in PH patients and controls (Fig. 5).

**Discussion**

Very little is known about the neuroregulatory pathophysiology of PH and SH. To our knowledge, this is the first clinical study to quantitate detailed distinctions between the dynamics of PH (tumoral) and SH, and also establish substantive similarities. To this end, we compared PRL release properties in eipituitary hyperprolactinemic patients with PH and SH along with gender-specific controls, using a high-precision immunofluorometric assay of 24-h plasma PRL concentrations obtained by repetitive (10-min) blood sampling. PRL time series were then analyzed via statistically independent, but thematically complementary, techniques to evaluate basal, pulsatile, 24-h rhythmic and entropic (pattern-sensitive) features. Thereby, we could identify both common and distinct alterations in PRL secretion in the two hyperprolactinemic groups. Daily PRL secretion was elevated in both PH and SH groups and was about 2-fold higher in the former. Both groups maintained markedly increased basal (i.e. nonpulsatile) and pulsatile PRL secretion, blunting of the normal dispersion of sample secretion rates, and an elevated 24-h rhythmic (cosine) mesor with normal acrophase. Each of the foregoing secretory abnormalities in PH and SH also occurs in the tumoral hypersecretion associated with aldosteronoma, acromegaly, and Cushing's disease (6, 9, 19). Indeed, the single distinguishing dynamic between PH and SH was the more disorderly secretory pattern associated with tumoral hyperprolactinemia.

We observed an increase in PRL pulse frequency in patients with PH and SH. The latter finding contrasts with that of Samuels et al. (20). The higher precision of immunofluorometric assay (compared with immunoradiometric assay) a more intensive sampling paradigm, and/or our choice of gender- and age-matched controls might contribute to this difference. Based on analogy with the GH axis, both secondary (i.e. fasting-associated) and tumoral (e.g. acromegaly) hormone hypersecretion can elevate secretory burst frequency, possibly because of, respectively, withdrawal of hypothalamic somatostatin release and tumoral autonomy (5, 19, 21, 22). Thus, it is conceivable that SH mutes activity of a hypothalamic inhibitory factor that normally restrains PRL pulse frequency, and/or that microadenomas in PH sustain a relatively autonomous high-frequency of (irregular) PRL secretory events.

Most endocrine glands signal via episodic hormone release (23, 24). Pulsatile-like hormone release is also evident in vitro, although at accelerated pulse frequencies and reduced amplitudes (25–27). Thus, low-frequency and high-

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**Fig. 2.** Mesor (cosine-derived) values and fractional (%) amplitudes of the 24-h plasma PRL concentration rhythms in patients and controls.
amplitude in vivo pulsatility likely requires intra- and interglandular synchronization (28). Partial preservation of normal PRL pulsatility mechanisms by microadenomas, and/or escape from putative hypothalamic frequency restraint in SH, could thus account for the marked overlap in their secretory properties.

PRL secretion is regulated by an array of apparently stimulatory and inhibitory factors. Reported agonists include TRH, vasoactive intestinal polypeptide, GnRH, dopamine, angiotensin II, antidiuretic hormone, and PRL-releasing peptide (29, 30). PRL-releasing peptide is expressed in the hypothalamus and the pituitary gland, including in PRL- (and GH-) secreting adenomas. Which of these (or other) regulatory factors would best account for the present observations is not clear, because dopaminergic blockade does not accelerate PRL pulse frequency (31). Likewise, the imperfect correlation between pulsatile PRL and TSH release would question the primacy of TRH in driving joint PRL pulsatility (32). To our knowledge, few data exist to define further the precise mechanisms of putative PRL pulse-frequency control in the human.

Both PH and SH patients maintained a normal PRL acrophase, suggesting preserved coupling of lactotrope output to central nervous system sleep-wake cycle and/or circadian timing systems. Our finding for PRL is comparable with that for GH and ACTH in many, but not all, patients with acromegaly or Cushing’s disease (6, 19). However, available studies have not excluded more subtle disruption of true circa-
dian periodicity or phase, evaluated in the absence of environmental time cues or with sleep-wake cycle reversal. The ApEn statistic was used to monitor the minute-to-minute reproducibility of PRL release patterns. This metric quantitates nonpulsatile and noncircadian features of hormone secretion (33). Both hyperprolactinemic groups manifested elevated PRL ApEn, which in principle would denote loss of coordinate feedback and/or feedforward control within the lactotrophic axis. The generally higher PRL ApEn values quantitated here in PH, than in SH, agree with data in other tumoral or autonomous states, such as for GH in acromegaly, ACTH in Cushing’s disease, and aldosterone in aldosteronoma (5, 6, 19), as well as sustained exogenous secretagogue drive (34, 35).

In summary, the present clinical investigation establishes certain common neuroendocrine alterations in PH and SH; e.g. increases in basal, pulsatile, entropic, and 24-h rhythmic PRL secretion. In addition, we observe more prominently greater process irregular PRL secretion patterns in tumoral PH than SH, pointing to greater loss of coordinate neurosecretory control by the microadenoma. Impaired secretory-pattern regulation in prolactinomas may reflect neoplasia-associated secretory autonomy rather than any space-occupying effect, because SH associated with larger nonsecretory tumors with suprasellar extension does not manifest equivalent feedback disarray.

References
29. Lamberts SWJ, MacLeod RM. 1990 Regulation of prolactin secretion at the level of the lactotroph. Physiol Rev. 70:279–318.