Shah, N., W. S. Evans, and J. D. Veldhuis. Actions of estrogen on pulsatile, nyctohemeral, and entropic modes of growth hormone secretion. Am. J. Physiol. 276 (Regulatory Integrative Comp. Physiol. 45): R1351–R1358, 1999.—The neuroendocrine mechanisms by which estradiol drives growth hormone (GH) secretion in the human are poorly defined. Here we investigate estrogen’s specific regulation of the 24-h pulsatile, nyctohemeral, and entropic modes of GH secretion in healthy postmenopausal women. Volunteers (n = 9) received randomly ordered placebo versus estradiol-17β (1 mg micronized steroid twice daily orally) treatment for 7–10 days and underwent blood sampling at 10-min intervals for 24 h to capture GH release profiles quantitated in a high-sensitivity chemiluminescence assay. Pulsatile GH secretion was appraised via deconvolution analysis, nyctohemeral GH rhythms by cosinor analysis, and the orderliness of GH release patterns via the approximate entropy statistic. Mean (±SE) 24-h serum GH concentrations approximately doubled on estrogen treatment (viz., from 0.31 ± 0.03 to 0.51 ± 0.07 μg/l; P = 0.033). Concomitantly, serum insulin-like growth factor-I (IGF-I), luteinizing hormone, and follicle-stimulating hormone concentrations fell, whereas thyroid-stimulating hormone and prolactin levels rose (P < 0.01). The specific neuroendocrine action of estradiol included 1) a twofold amplified mass of GH secreted per burst, without significant changes in basal GH release, half-life, pulse frequency, or duration; 2) augmented amplitude and mesor of the 24-h rhythm in GH release, with no alteration in acrophase; and 3) greater disorderliness of GH release (higher approximate entropy). These distinctive and dynamic reactions to estrogen are consistent with partial withdrawal of IGF-I’s negative feedback and/or accentuated central drive to GH secretion.

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SEX-STEROID HORMONES impact secretory activity of the human somatotropic [growth hormone (GH)] axis in puberty, across the normal menstrual cycle, during the menopause, and in various (primary) hypogonadal states in men and women (1, 3–5, 8–10, 38). In boys, the pubertal rise in serum testosterone concentrations correlates with higher mean (24 h) serum GH and insulin-like growth factor (IGF-I) concentrations (20). In men, testosterone concentrations also correlate positively with integrated GH concentrations. In girls, pubertal nighttime increases in serum GH concentrations parallel a rise in estradiol secretion (39), and, in menstruating young women, serum GH concentrations fluctuate by twofold across the menstrual cycle concomitantly with varying estradiol concentrations (8). In the preovulatory phase, plasma IGF-I and GH concentrations increase simultaneously, which would support a notion of increased central GH axis drive at this time in the female (21). Conversely, in estrogen-unreplaced postmenopausal individuals, serum GH concentrations decline significantly, but can be stimulated by oral estrogen or equivalent dose transdermal estrogen replacement (10). Thus available indirect clinical observations indicate that sex-steroid hormones, namely both (aromatizable) androgens and estrogen (7, 34, 37), enhance GH axis secretory activity (12, 34). However, the neuroendocrine mechanisms in the human that mediate increased GH secretion in an estrogen-replete milieu are not well defined (25).

The specific impact of estrogen on each of the neuroendocrine mechanisms that regulate output of the GH axis has not been investigated systematically. These include 1) the underlying pulsatile secretory activity of the GH axis, as distinguished from the serum GH concentration values, which jointly reflect hormone secretion and half-life (27); 2) the recently recognized low basal (interpulse) GH secretion rates, as detected recently by an ultrasensitive chemiluminescence GH assay (33); 3) the 24-h rhythmicity of GH release (14, 28), which reflects a true circadian component and a sleep-activity cycle-related diurnal variation (28); and 4) the pattern regularity or moment-to-moment orderliness of GH release, e.g., as quantified recently by the approximate entropy (ApEn) statistic. To our knowledge, the specific impact of estradiol on each of these primary quantifiable facets of GH neuroregulation remains unknown in postmenopausal women.

Here we applied three new analytic strategies to evaluate the specific neuroendocrine mechanisms of estrogen action on the human female GH axis: 1) deconvolution analysis of ultra-high-sensitivity serum GH measurements over 24 h to quantitate both the pulsatile and basal modes of GH secretion; 2) cosinor analysis to appraise the 24-h rhythmicity of GH release; and 3) the ApEn statistic to assess objectively the orderliness or regularity of the GH secretory process. These complementary approaches jointly disclosed highly specific mechanisms by which estrogen drives increased 24-h serum GH concentrations in women.

METHODS

Clinical protocol. Nine healthy postmenopausal women, ages 53–71 yr and body mass index 23–27 kg/m², who had experienced clinical menopause at least 2 years before study,
provided written informed consent approved by the Human Investigation Committee of the University of Virginia Health Sciences Center. All volunteers were unmedicated, had received no hormone replacement therapy for at least 6 wk, and had a normal medical history, physical examination, and screening chemistry tests of hematological, renal, metabolic, endocrine, and hepatic function. There was no recent acute illness, chronic disease, psychiatric disorder, recent medications within 5 biological half-lives, transmeridian travel within 2 wk, or significant weight change (2 kg or more within 10 days). Estrogen was administered orally as 1.0 mg 17β-estradiol (micronized) or placebo twice daily for 7–10 days in a randomly ordered within-subject crossover design.

The blood sampling protocol consisted of sample removal from a forearm vein at 10-min intervals for 24 h beginning at 0800 after admission and adaptation to the General Clinical Research Center the evening before. Volunteers received an isocaloric diet consisting of three meals provided at 0800, 1200, and 1700.

Assays. Serum GH concentrations were measured in each sample in duplicate by a fully automated ultrasensitive GH chemiluminescence assay (modified Nichols Luma Tag human GH assay; sensitivity 0.005 µg/l) with human recombinant GH (22 kDa) as assay standard, as described previously (18). The median inter- and intra-assay coefficients of variation were <7.5%. All 145 GH samples in each admission were assayed together. Serum estradiol, follicle-stimulating hormone (FSH), luteinizing hormone (LH), thyroxine, thyroid-stimulating hormone (TSH), and IGF-I concentrations were measured in a single 24-h pool of serum from each subject in duplicate by RIA or immunoradiometric assay (33).

Deconvolution analysis. Deconvolution analysis was used to estimate subject-specific measures of pulsatile GH secretion and half-life (27, 31). Daily pulsatile GH secretion rates are the product of secretory burst frequency and the mean mass of GH released per pulse. Basal secretion represented the interpulse (basal) component of the GH release profile. Deconvolution analysis was carried out at 95% joint statistical confidence intervals for all calculated secretory burst amplitudes (25, 33), with the technician blinded to the randomized order of the placebo versus estradiol treatments.

Nyctohemeral (24 h) rhythmicity. Diurnal rhythmicity of serum GH concentrations was appraised using cosinor analysis, as described earlier (29).
Statistical analyses. Given nonnormality of calculated hormone secretory measures, differences between placebo and estrogen-treatment deconvolution measures were assessed using a paired two-tailed nonparametric (Wilcoxon) test. Mean and integrated (24 h) serum GH or estradiol concentrations were compared across treatment by a paired two-tailed Student's t-test. Results are presented as means ± SE (median). Statistical significance was construed for a P value <0.05.

ApEn. ApEn was used as a scale- and model-independent statistic complementary to (and distinct from) pulse or cosinor analysis (22, 35). ApEn quantifies the serial orderliness or regularity of the hormone (GH) release process. Normalized ApEn parameters of m = 1 (series length) and r = 20% (threshold) of the intraseries standard deviation were used, as previously described (23). ApEn is hence designated ApEn (1,20%), which quantifies the regularity of subordinate (nonpulsatile) patterns in the hormone profile (35). Higher absolute ApEn values at equal series lengths and parameter values denote greater relative disorderliness or irregularity of patterns of hormone release, as observed recently for GH in acromegaly (15) and for the female compared with the male GH axis (23).

RESULTS

Serum estradiol concentrations rose 25-fold during estradiol treatment (Table 1). Figure 1 illustrates individual 24-h serum GH concentration profiles in three women each studied during randomly ordered placebo (control) or estradiol treatment. Estrogen treatment increased the mean (24 h) serum GH concentration by 1.65-fold (P = 0.033) and commensurately augmented the 24-h integrated serum GH concentration (P = 0.031; Table 1).

Deconvolution analysis revealed that estradiol selectively increased the mass of GH released per individual secretory burst, which rose in seven of nine individuals studied (see Fig. 2a for individual values). In particular, GH secretory burst mass rose by a mean of 1.82-fold (P = 0.023). The increase in GH burst mass was due to a corresponding increase in GH secretory event amplitude (Fig. 2B). This action of estradiol was highly specific, because, as shown in Table 1, basal GH secretion, half-life of GH, GH pulse frequency, interburst
The present clinical experiments reveal highly distinctive regulatory actions of estradiol on the older female human GH-IGF-I axis on each of three quantifiable facets of GH neuroregulation, i.e., the pulsatile, nycrohemeral, and entropic modes of GH release. Oral estrogen repletion in postmenopausal women increased mean (24 h) serum GH concentrations by ~1.65-fold by specifically enhancing the mass of GH secreted per pulse, as estimated in this context for the first time by deconvolution analysis. In contrast, the basal (interpulse) GH secretion rate, GH half-life, GH pulse frequency, interburst interval, and duration of GH secretory events remained unaltered. Estrogen treatment also approximately doubled the amplitude and mesor of the 24-h rhythm of GH release, without altering its interval, and half-duration (duration at half-maximal amplitude) of GH secretory pulses did not change significantly.

Table 1 also summarizes the partitioning of total (24 h) GH secretion in basal and pulsatile components. The daily total and pulsatile (but not basal) GH secretion rates increased significantly during estradiol replacement therapy. The percentage of total daily GH secretion that was pulsatile did not change, namely, 87 ± 12 (control) vs. 91 ± 17% (estrogen) [P = not significant (NS)].

Cosinor analysis of 24-h (nyctohemeral) rhythmicity of serum GH concentrations revealed that estrogen elicited a significant increase in the amplitude of the 24-h rhythm (one-half the difference between the maximal 24-h value and the nadir) (Fig. 3). In particular, the cosine amplitude of serum GH concentrations during estrogen treatment rose by 2.5-fold (P = 0.0020). Concomitantly, the mesor (average serum GH concentration about which the 24-h rhythm varies) rose by 1.5-fold (P = 0.0013). In contrast, the acrophase (the time of occurrence of the maximal serum GH concentration) was unchanged during estrogen administration and occurred at 0422 clock time ± 42 min (control) vs. 0512 clock time ± 40 min (estriadiol) (P = NS).

Plasma IGF-I concentrations declined in response to estrogen treatment, as shown in Fig. 4. Mean plasma IGF-I was 174 ± 12 (170) during placebo and 130 ± 12 (127) µg/l on estradiol replacement (P = 0.0028). In parallel, serum LH and FSH concentrations fell as predicted, whereas prolactin and TSH levels rose in response to estrogen treatment (Table 1).

ApEn was used to quantify the orderliness of GH release patterns over 24 h. Higher ApEn denotes greater disorderliness or irregularity of serial hormone measurements. ApEn rose from 0.572 ± 0.058 (0.537) to 0.801 ± 0.092 (0.836) (P = 0.0059), as illustrated for the nine individual subjects in Fig. 5. This change indicates a significant loss of pattern consistency within the GH release profile during estrogen replacement.

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Timing (acrophase). Concomitantly, estrogen markedly reduced the regularity (orderliness or serial reproducibility) of GH release patterns. Accordingly, estradiol impacts physiological neuroregulation of the human GH axis in a particular threefold manner, namely, to 1) augment the amount of GH secreted per unit distribution volume per GH pulse, 2) amplify the 24-h rhythmicity of GH release, and 3) reduce the orderliness of GH secretory patterns. To our knowledge, these collective mechanistic inferences are new in both the human and experimental animal.

The serum concentration of GH is governed by three principal kinetic factors acting simultaneously, namely, underlying GH secretion rates (both basal and pulsatile), the GH distribution volume, and the half-life of GH (32). Here we used deconvolution analysis to separately estimate these relevant parameters. This analysis revealed that the basal (interpulse) GH release rate and GH half-life are unaffected by estrogen status, whereas the calculated amount of GH secreted in a pulsatile manner is stimulated by 1.8-fold. If estrogen has a minimal (if any) effect on the plasma GH distribution volume, then these data indicate that estrogen augments the total pulsatile mass of GH secreted daily.

An earlier study showing estrogen's stimulation of serum GH concentration peak heights did not implement deconvolution methods to delineate specific effects of estrogen on GH secretory pulse mass, duration, basal secretion rate, or half-life (10). Indeed, the higher serum GH concentration heights reported earlier by us and others in response to estrogen treatment might have reflected any one (or more) of the following mechanisms: 1) increased GH secretory burst amplitude, 2) prolonged GH secretory burst duration, 3) heightened basal (interpulse) GH release, and/or 4) an extended GH half-life. By deconvolution analysis, we now show that estrogen solely augments GH secretory burst amplitude and (hence) mass.

GH secretory burst amplitude, and thereby the mass of GH secreted per pulse, is controlled reciprocally by hypothalamic GH-releasing hormone (GHRH) drive and somatostatin's inhibition of responsive somatotroph cells (12). Intrapituitary factors and various cosecretagogues of GH (e.g., putative endogenous GH-releasing peptide (GHRP)-like effectors that synergize with GHRH) also may modulate GH secretory activity (12). No available clinical studies yet distinguish definitively between estrogen's augmentation of hypothalamic GHRH drive and/or attenuation in somatostatin restraint. However, unaltered GH pulse frequency defined by intensive 24-h blood sampling (19.8 ± 1.1 GH pulses/day in control vs. 20.2 ± 1.0 bursts/day in the same estradiol-treated women) in our view would argue for unchanging somatostatin tone. This inference is based on the ability of clinical conditions that are probably associated with somatostatin withdrawal, such as

Fig. 3. Nyctohemeral (24 h) rhythmicity of serum GH concentrations in 9 postmenopausal women treated for 7–10 days with oral placebo or estradiol. Amplitudes (top) and mesors (mean, bottom) of 24-h serum GH concentration rhythm are given. Data are means ± SE (n = 9 women).

Fig. 4. Plasma insulin-like growth factor (IGF)-I concentrations in 9 individual postmenopausal women after placebo (control) versus during oral estradiol replacement for 7–10 days. Data are presented as defined in Fig. 2.

Fig. 5. Approximate entropy (ApEn) of 24-h serum GH concentration profiles in 9 postmenopausal women during placebo versus oral estradiol replacement for 7–10 days. Higher ApEn denotes greater irregularity or disorderliness of GH release, e.g., as observed in puberty (34). Data are presented as defined in Fig. 2.
as starvation or deep sleep, to accelerate detectable GH pulse frequency in the human (12, 16, 17). Conversely, short-term somatostatin infusion in young men suppresses GH pulse frequency (2). Thus we hypothesize that augmented hypothalamic GHRH release, enhanced secretion of other putative GH cosecretagogues, and/or recruitment of relevant intrapituitary mechanisms singly or jointly underlie estrogen’s amplification of GH secretory burst mass.

Some clinical studies indicate that the responsiveness of somatotrophs to GHRH stimulation correlates positively with serum estradiol concentrations, is reduced by ovariectomy, and enhanced by estrogen repletion (reviewed in Refs. 12 and 26). In a preliminary study in postmenopausal women, estrogen enhanced the slope of the GHRP-2 dose-responsive stimulation of GH secretion. In the rat, some experimental evidence favors the hypothesis that estrogen enhances GHRH release and/or actions, although such data do not include direct hypothalamo-pituitary portal venous sampling data (12). On the other hand, there is little evidence for major actions of estradiol directly on somatotroph cells.

The 24-h rhythmicity of serum GH concentrations is well established and appears to reflect combined true circadian and diurnal (sleep-activity) effects, e.g., GH release during sleep onset and in stages III and IV (deep) sleep (17). Although we did not assess sleep stages, estrogen augmented the amplitude of 24-h rhythmicity of GH release by approximately twofold, as assessed by cosinor analysis. The timing of maximal GH levels (which occurred during the hours of sleep) was unaltered by estrogen treatment. Thus this sex steroid maintains the physiological pattern of nyctohemeral GH release, albeit at a greater absolute amplitude.

The percentage of total daily GH secretion that was pulsatile (–87% in control) did not change significantly during estrogen treatment (viz., 91%). This new observation in women should be distinguished from impressions in the rodent, in which basal (interpulse) serum GH concentrations are higher in the female than male (12). Indeed, in the male rat, serum immunoreactive GH concentrations between distinct pulses fall to undetectable values (36). To obviate this assay problem, here we used an ultrasensitive chemiluminescence-based GH assay, which detects serum GH concentrations at all times in men, children, and women (present data and Refs. 10, 18, 19, and 33). This assay thus provides the first appraisal to our knowledge of the impact of estradiol, if any, on deconvolution-calculated basal interpulse GH secretion. Whereas an early clinical study also used a chemiluminescence GH assay in older estrogen-treated women (10), serum GH concentration profiles were evaluated by a discrete peak-detection method [cluster (30)]. This analytic strategy fails to dissect interpulse serum GH concentrations into their three separate and confounding origins, namely 1) patient-specific GH half-life, 2) basal GH secretory rates, and 3) all prior pulsatile GH secretion, factors of which jointly control the interpulse basal serum GH concentration (27, 31, 32). Here, by way of deconvolution analysis, we show that estrogen increases the interpulse serum GH concentration specifically by doubling the mass of GH secreted within individual pulses and in fact does not increase GH’s interpulse basal secretory rate, pulse frequency, or half-life.

The moment-to-moment orderliness of GH release can be quantified by the ApEn statistic (23, 35). This statistical tool measures the tendency of subpatterns to recur within data series. Higher ApEn values denote reduced orderliness or diminished reproducibility of serial measurements (22). ApEn is distinct from and complementary to conventional pulse and cosinor analyses by distinguishing degrees of serial consistency (or process randomness) within time series (35). ApEn vividly identifies greater disorderliness of GH release by pituitary tumors and in the normal female compared with male (15, 23). Of mechanistic significance, ApEn appears to serve as a barometer of altered feedback regulation within an axis (34, 35). Thus our finding that estradiol increases the ApEn of 24-h GH release profiles implies that this sex steroid controls GH-IGF-I axis feedback activity. A comparable rise in ApEn of GH release occurs in normal puberty in boys, during replacement with aromatizable (but not nonaromatizable) androgen in young men (11, 34), and in response to continuous GHRP-2 infusions in women or pulsatile GHRH infusions in men (19, 24). On the basis of mathematical considerations (22), the rise in GH ApEn in these settings likely predicts significantly altered feedback control of the hypothalamic-somatotroph unit, i.e., greater strength and/or complexity of relevant regulatory signals (e.g., GHRH, somatostatin, IGF-I, GH itself, or putative endogenous GHRPs, etc.).

Plasma IGF-I concentrations typically fall during oral estrogen replacement as observed here, but decline less consistently during transdermal estrogen treatment (10). Reduced IGF-I levels may reflect estrogenic inhibition of hepatic GH action, as inferred in the rabbit and human (6), and mechanistically (by withdrawal of negative feedback) would tend to amplify GH secretion, as in fasting-stimulated GH secretion (13). However, fasting evokes multiple other complex metabolic changes in addition to the decline in IGF-I, and in fasting both GH secretory burst amplitude and frequency rise (16). In contrast, here we show that estrogen treatment in women only elevates GH secretory burst mass, which speaks against a mechanism of augmented GH secretion due solely to IGF-I feedback withdrawal. Indeed, in other estrogen-enriched contexts such as female puberty, the preovulatory phase of the menstrual cycle, premenopausal women compared with men, and estrogen-treated castrate baboons, estrogen can stimulate a rise in both plasma GH and IGF-I concentrations (4, 21, 25, 39). In these several contexts, simultaneous elevations of GH and IGF-I concentrations support a notion of central GH-IGF-I axis activation by estrogen. Further clinical experiments will be helpful to clarify the relative postulated roles of decreased circulating IGF-I concentrations versus accentuated hypothalamic drive to GH secretion in mediat-
ing estrogen’s augmentation of GH pulse mass, disorderly GH release patterns, and heightened 24-h rhythm in the human.

Perspectives

Sex differences in the neuroregulation of GH secretion are prominent in many animal species and also quantifiably evident in the human (12). In the rodent, the impact of sex hormone withdrawal is reversed by either estradiol or 5α-dihydrotestosterone replenishment, whereas in the human, estrogen or an aromatizable androgen is required (34). Hence, a species difference emerges here that is based on mechanisms that are not yet defined. Even so, further studies in experimental animals using hypothalamic-pituitary portal blood sampling would be helpful in assessing sex steroid actions more directly on both GHRH and somatostatin release, as well as on the secretion of relevant cosecretagogues, such as galanin, neuropeptideY, putative GHRPs, etc., which control GH pulse activation. Such analyses may aid in partially explicating our experimental findings in the human of estrogen’s selective stimulation of GH pulse mass. Further pertinent clinical investigations would also be helpful, such as an appraisal of postulated alterations in GH and/or IGF-I’s feedback control of the GH axis. This suggestion arises in view of the heightened disorderliness of GH secretion delineated here, as reflected in the rise in ApEn of GH release, in the estrogen-sufficient milieu. Clinical and animal studies should be helpful jointly in assessing estrogen’s hypothesized control of true circadian (suprachiasmatic nucleus)-based GH rhythmicity versus regulation of daily sleep-activity rhythms of 24-h GH release. The present demonstration of specific threefold neuroregulatory actions of estrogen on the human GH-IGF-I axis (namely, altered pulsatile, entropic, and 24-h rhythmic modes of GH release) thus unveils new experimental issues in integrative physiology in both the human and animal.

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