Contrasting negative-feedback control of endogenously driven and exercise-stimulated pulsatile growth hormone secretion in women and men

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Abstract:

GH represses its own secretion via rapid and reversible feedback exerted at key hypothalamic loci. The primary mechanisms include stimulation of somatostatin release and inhibition of GHRH outflow. Autoinhibition is prominent in the adult male rat but diminutive in the female animal. The sex contrast reflects important differences in central neuropeptide signaling in this species. No comparable insights into gender-specific control of GH autofeedback are available in the human. To examine this issue, we quantitated acute recombinant human (rh)GH-induced inhibition of baseline (resting) and aerobic exercise-stimulated GH secretion in healthy young men (n = 8) and early follicular-phase women (n = 6). Each subject underwent four fasting, morning inpatient infusion studies in a prospectively randomized, placebo-controlled, double-blind, within-subject cross-over design. The feedback paradigm comprised 6-min bolus iv infusion of saline or rhGH (10 μg/kg) followed in 120 min by rest or submaximal aerobic (individually calibrated) bicycle ergometry for 30 min. Concomitantly, blood was sampled every 10 min for 6 h, and sera were submitted to immunochemiluminometric GH assay (sensitivity 0.005 μg/liter). Biexponential deconvolution analysis was applied to estimate stimulated GH secretory-burst mass (μg/liter per 90 min after onset of exercise or rest). Women and men had statistically comparable serum estradiol but unequal testosterone concentrations. Repeated-measures ANOVA documented a significant three-way interaction among gender, stimulus type (rest or exercise), and feedback status (saline or rhGH injection) in determining GH secretory-burst mass ($P = 0.008$). There were prominent two-factor interactions among gender and exercise ($P < 0.001$); gender and rhGH-induced negative feedback ($P = 0.002$); and exercise and rhGH feedback ($P = 0.006$). Gender comparisons disclosed that women, compared with men, maintain 20-fold higher GH secretory-burst mass at rest ($P < 0.001$); 40-fold less stimulation of pulsatile GH release by exercise than rest ($P < 0.001$); and 20-fold greater inhibition of GH secretory-

burst mass by rhGH than saline at rest ($P < 0.05$). Observed feedback contrasts by sex were specific, inasmuch as gender did not affect absolute estimates of exercise-stimulated GH secretion (μg/liter/90 min); nadir GH concentrations (μg/liter) enforced by rhGH infusion; and the time latency (min) to manifest maximal inhibition after rhGH injection.

In summary, the present clinical investigation unmasks: 1) markedly greater fractional feedback inhibition of pulsatile GH secretion by rhGH in young women than men; and 2) partial resistance of the aerobic-exercise stimulus to GH autofeedback in both women and men. We postulate that sex-steroid-specific control of somatostatin and GHRH outflow may mediate the former gender contrasts, whereas unknown (gender-independent) factors may determine the capability of exercise to significantly antagonize GH autoinhibition.

Keywords: endocrinology | women | men | GH autonegative feedback | aerobic exercise

Article:

The pulsatile mode of GH secretion is the principal (>85%) component of GH production in healthy individuals (1, 2). Discrete secretory bursts are stimulated by GHRH, putatively amplified by endogenous ghrelin, and inhibited by somatostatin and IGF-I (3–7). In addition, a pulse of GH exerts rapid autonegative feedback via cognate receptors in the hypothalamus before inducing a detectable rise in systemic IGF-I concentrations (8–12). Mechanistic analyses in the adult male rat indicate that GH autofeedback drives periventricular somatostatin release and represses arcuate-nucleus GHRH outflow (1, 2, 13). Dissipation of the GH pulse relieves heightened somatostatin secretion and triggers rebound-like GHRH release, thereby putatively inducing the next GH secretory burst (1, 2). According to this experimental platform, cycles of reversible autoinhibition drive recurrent high-amplitude pulses (12, 14). Pulsatile GH output induces masculine patterns of growth and target-tissue gene expression in the rodent (8, 15, 16).

The amplitude of GH pulses and the efficacy of GH autofeedback differ vividly by sex in the laboratory rodent (1, 2). In particular, the adult female rat maintains low-amplitude GH pulses and exhibits significant resistance to autoinhibition, whereas the male animal generates high-amplitude GH bursts and manifests strong GH autofeedback (17). On the other hand, whether or how gender determines GH autoregulation in the human is not known. A gender contrast, if present clinically, may differ diametrically from that observed in the experimental animal. This consideration arises because the amplitude of GH concentration peaks and the mass of GH secreted per burst are consistently higher in women than comparably aged men (18–21). Recent biomathematical modeling paradigms forecast that endogenous renewal of high-amplitude GH secretory bursts requires recurrent cycles of autofeedback (12, 14). If valid in the human, this precept would predict that GH-autofeedback efficacy is greater in women than men.

Acute aerobic exercise evokes prominent GH secretion in the young adult (22). Gender comparisons indicate that low-intensity (but not maximal aerobic) exercise stimulates greater GH release in young women than men (23–29). The mechanisms subserving this sex difference are not known. However, the exercise stimulus may be unique in partially overcoming endogenous

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Abbreviations: GHRP, GH-releasing peptide; rh, recombinant human; S, saline; VO2 peak, peak oxygen consumption.

GH autofeedback. In fact, two or three consecutive bouts of exercise fail to damp subsequent GH pulsatility (30–32).

Based on the foregoing issues, the present study tests the interlinked hypotheses that gender governs susceptibility to controlled acute GH-specific autonegative feedback in the healthy young adult and that the exercise stimulus is relatively resistant to rhGH-enforced autoinhibition, especially in women.

Subjects and Methods

Clinical protocol

Volunteers provided a detailed medical history and underwent a complete physical examination, after giving written informed consent approved by the Institutional Review Board. Inclusion criterion comprised healthy young adults who undertook recreational aerobic exercise three or four times per week. Eight men and six women participated. Characteristics were (men) age 26 ± 0.5 yr, height 181 ± 1.0 cm, weight 82 ± 1.6 kg, and peak oxygen consumption (VO_2 peak) 44 ± 1.2 ml/kg·min; and (women) age 22 ± 0.5 yr, height 164 ± 1.0 cm, weight 60 ± 1.2 kg, and VO_2 peak 32 ± 1.6 ml/kg·min. Exclusion criteria included pregnancy, breast-feeding, age 35 yr or more, steroid or hormone use, substance abuse, clinical depression, acute or chronic systemic illness, endocrinopathy, hepatorenal disease, diabetes mellitus, anemia (hematocrit < 38%), exposure to neuro- or psychoactive medications within five biological half-lives, recent transmeridian travel, shift work, weight gain or loss (exceeding 6 pounds in the preceding 6 wk), and failure to provide informed consent.

The lactate threshold was estimated in each volunteer in a preliminary session by graded bicycle ergometry, as reported earlier (28). Thereby, the intensity of the subsequent 30-min exercise stimulus was set at an *a priori* constant load midway between that associated with the individual lactate threshold and volitional fatigue (VO_2 peak). Total work and expended calories (per nonprotein respiratory exchange ratio) were calculated in each 30-min exercise session. Heart rate and blood lactate concentrations were assessed every 10 min during exercise. In resting sessions, subjects remained supine.

Autonegative feedback paradigm

Women were studied during the early follicular phase (d 2–8) once or twice (and no more often than three times) in a single menstrual cycle. Volunteers were admitted to the General Clinical Research Center (GCRC) on four separate occasions (two rest and two exercise) in prospectively randomized order at least 2 d apart. To obviate nutritional confounds, participants ingested a constant meal at 1800 h the evening before, which contained 500 kcal (60% carbohydrate, 20% protein, and 20% fat). Subjects then remained fasting overnight and until 1330 h the next day. Use of coffee, alcohol, and tobacco was disallowed in the GCRC.

Figure 1 schematizes the paradigm of saline *vs.* recombinant human (rh)GH infusion and rest *vs.* exercise applied here. To allow simultaneous sampling and infusion, two forearm venous catheters were inserted contralaterally at 0600 h. Blood samples (1.5 ml) were withdrawn every

10 min for a total of 6 h from 0730 to 1330 h. After a 30-min baseline, a single dose of rhGH (10 μg/kg) or saline (S) was infused iv as a 6-min squarewave pulse. Thereafter, blood was sampled every 2.5 min for 10 min (0800–0810 h) and every 5 min for 50 min (0810–0900 h) for kinetic analyses, followed by every 10 min for 4.5 additional h (0900–1330 h). Exercise was initiated 120 min after double-blind iv injection of saline or rhGH (1000–1030 h). This feedback paradigm suppresses spontaneous and GHRH and GH-releasing peptide (GHRP)-2-stimulated GH secretion by approximately 2-fold in the adult (9, 33).

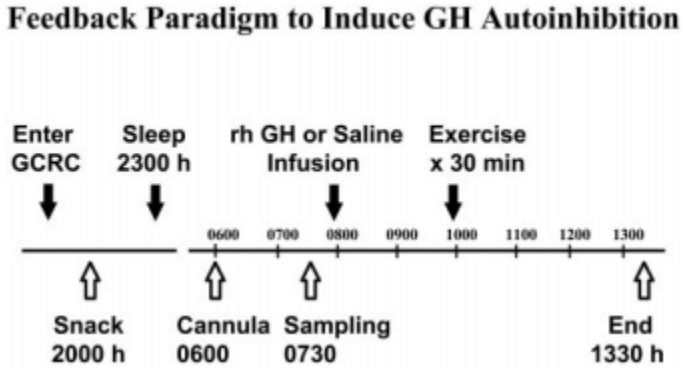

Figure 1. Schema of combined infusion, exercise and sampling protocol to quantitate rhGH-induced feedback inhibition of resting and exercise-stimulated GH secretion in young women and men. Fasting subjects received an iv infusion of S or rhGH (10 μg/kg over 6 min) at time 30 min to enforce autonegative feedback. Endogenous GH release was stimulated 120 min later by rest or aerobic exercise. Blood was withdrawn at 10-min intervals for a total of 6 h beginning 30 min before S/rhGH injection.

Assays

GH concentrations were measured in duplicate in each sample by ultrasensitive immunochemiluminescence assay (Nichols Institute, San Juan Capistrano, CA) (34, 35). The double-monoclonal antibody configuration detects predominantly 22-kDa GH with 34% cross-reactivity with 20-kDa GH (36). Sensitivity is 0.005 μg/liter at three SDs above the zero-dose tube. No samples in the present study contained less than 0.015 μg/liter GH. The median intraassay and interassay coefficients of variation are 5.8% and 6.7%, respectively. For deconvolution analysis (below), the concentration-dependence of the intraassay variance was modeled as a power function using replicates contained in the entire set of samples from all four admissions in any given subject (see *Deconvolution Analysis*, below). Concentrations of total testosterone and estradiol were quantitated by solid-phase RIA (Diagnostic Products, Los Angeles, CA) on the four fasting 0800 h sera collected in each subject. Mean intra- and interassay coefficients of variation were, respectively, 6.9 and 8.3% (total testosterone) and 5.9 and 9.1% (estradiol) (37).

Deconvolution analysis

Pulsatile GH secretion was quantitated by multiparameter deconvolution analysis (38, 39). The outcome measure is the summed mass of GH secreted in bursts (μg/liter per 90 min) after onset of the rest or exercise intervention. The deconvolution technique used published biexponential

kinetics of endogenous GH disappearance in healthy adults, *i.e.* a rapid-phase half-life of 3.5 min, a slow-phase half-life of 20.8 min, and a fractional (slow/total) decay amplitude of 0.63 (40). The deconvolution procedure accounts for unequal within-session basal (nonpulsatile) GH secretion, overlapping GH pulses, and continued decay of GH concentrations across the observational interval (41, 42). The foregoing approach obviates technical confounding of secretion estimates due to use of only the absolute peak, incremental peak, and/or integrated GH concentration (28, 39, 43). The same methodology was used to estimate GH kinetics over the 120 min including and after injection of rhGH, except that the slow-phase (second) component of biexponential decay was estimated analytically in each session. The distribution volume of exogenous GH (liters per kilogram) was computed as the quotient of the dose (10 μg/kg) and the deconvolution-calculated mass of infused rhGH (micrograms per liter).

Statistical procedures

Statistical comparisons of the derived measure, GH secretory-burst mass, were made on logarithmically transformed data to limit heterogeneity of variance. The model was three-way (2 × 2 × 2 factorial) repeated-measures ANOVA (44). This structure includes each of gender (two factors), rest or exercise (two factors), and S or rhGH injection (two factors). Thereby, we examined overall significance of a three-way effect and key two-way interactions, *viz.* gender and negative feedback (primary hypothesis); feedback and exercise (corollary postulate); and, gender and exercise (incidental) as putative determinants of induced GH release. Parameters of the statistical model were estimated by restricted maximum likelihood. *Post hoc* contrasts in means were based on Fisher's restricted least significantly different criterion with an overall (experiment-wise) type I error rate of 0.05 (45). For statistical purposes, the relative response (fold-effect of stimulated over placebo or fold-difference by gender) is represented as the geometric mean ratio with 95% statistical confidence intervals. Absolute GH secretory-burst mass (μg/liter per 90 min) is cited as the arithmetic mean ± SEM.

Results

Fasting resting (saline-infused) 6-h integrated serum GH concentrations averaged 940 ± 248 (809) and 454 ± 153 (251) μg/liter × min in women and men, respectively ($P < 0.05$). Fasting (0800 h) concentrations (mean of four admissions/subject) of testosterone (nanograms per deciliter) were 47 ± 8 and 589 ± 44 ($P < 0.001$) and estradiol (picograms per milliliter) 40 ± 4 and 25 ± 4 (P = NS) in women and men, respectively.

Figure 2 depicts mean 6-h GH concentration-time series (micrograms/liter) obtained by 10-min sampling before, during, and after injection of S or rhGH at rest and after exercise in women (Fig. 2A) and men (Fig. 2B). Insets (*right*) show an expanded y-axis scale to visualize suppressed GH concentrations due to time-delayed inhibition by injected rhGH.

ANOVA disclosed a significant three-factor interaction among gender, exercise, and rhGH infusion in determining GH secretory-burst mass ($P = 0.008$). Further statistical analyses revealed two-factor interactions among gender and exercise ($P < 0.001$); gender and rhGH feedback ($P = 0.002$); and exercise and rhGH feedback ($P = 0.006$).

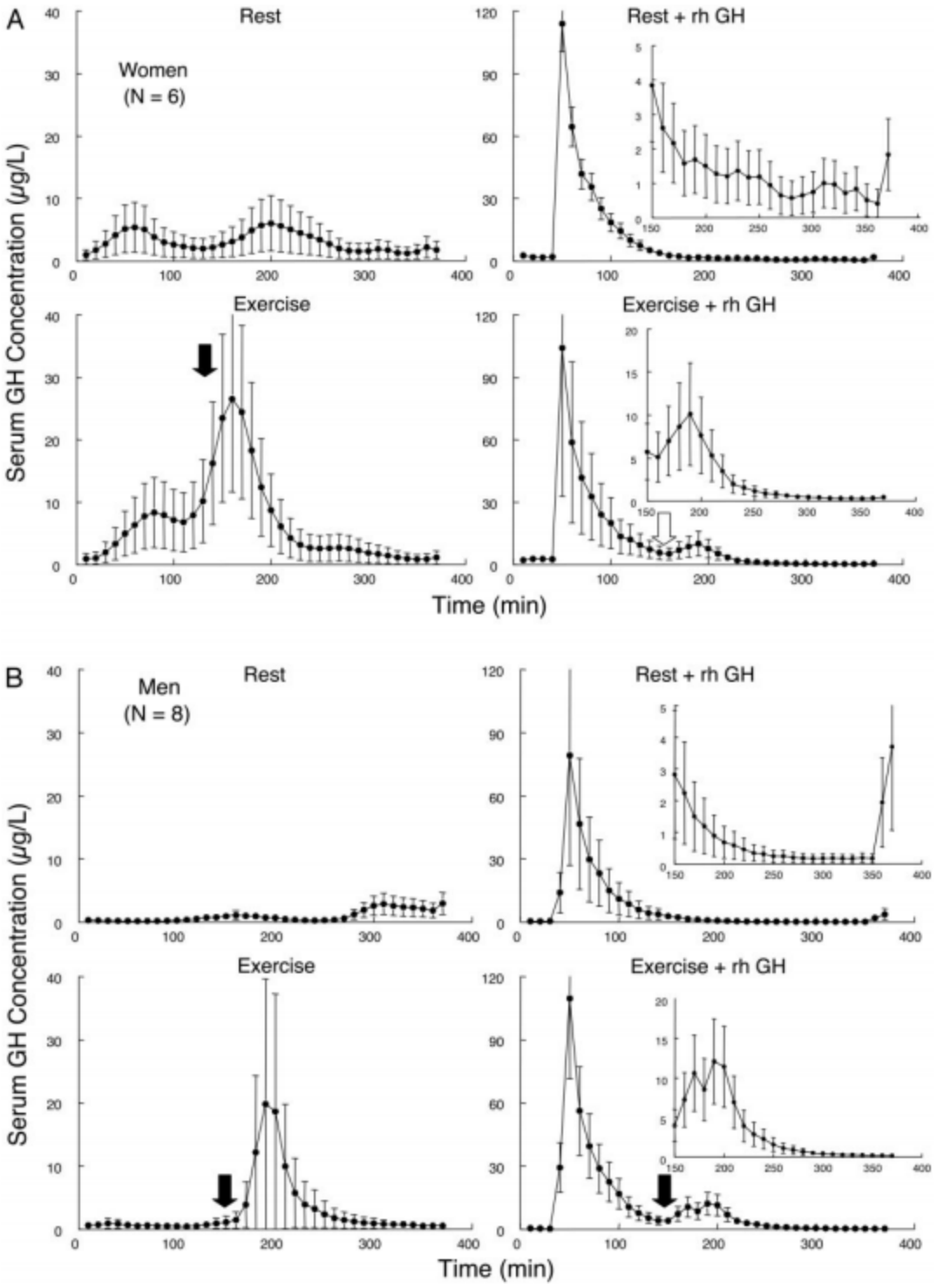

Fig. 2. Mean (±SEM) GH concentrations (y-axis) monitored every 10 min before, during, and after iv infusion of S or rhGH (time 30 min, x-axis) followed by rest or aerobic exercise (time 150 min, *boldface arrow*). Data are given separately in healthy young women (A) and men (B). Expanded y-axis insets (*right*) show suppressed GH concentrations after rhGH infusion during the stimulus interval of rest or exercise [150–370 min after the onset of blood sampling (Fig. 1)]. Each value is the cohort-specific mean ± SEM (n = 6 women, n = 8 men).

Figure 3 summarizes absolute estimates (±SEM) of GH secretory-burst mass (micrograms/liter/90 min) and Fig. 4, A and B, the relative (fold) (and 95% statistical confidence intervals) responses to exercise and rhGH. *Post hoc* statistical contrasts (protected at overall experiment-wise $P < 0.05$) revealed that at rest: (a) during saline infusion, women maintained a 20-fold (95% confidence interval 5.8, 66) higher absolute mass of GH secreted in bursts than men ($P < 0.001$; Fig. 3); and (b) rhGH (compared with S) infusion suppressed GH secretory-burst mass in women by 51-fold (8, 329; $P \leq 0.001$) and in men by 2.6-fold (1.4, 5.0; $P = 0.008$; Fig. 4A). According to these outcomes, women at rest are approximately 20-fold more susceptible to fractional autoinhibition by rhGH of GH burst mass than men at rest ($P < 0.05$). Absolute maximal suppression of GH release was comparable by gender; *viz.* nadir GH concentrations (micrograms per liter) induced by rhGH infusion were 0.15 ± 0.027 (0.13) and 0.14 ± 0.046 (0.12) in women and men, respectively (Fig. 3, *upper*). The timing of the nadir (minutes after the rhGH injection) was similar in women [315 ± 14 (325)] and men [321 ± 11 (340)].

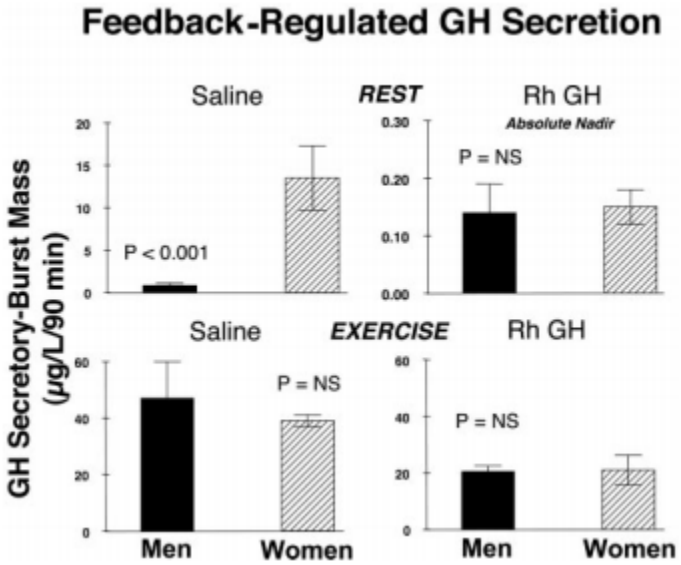

Fig. 3. Deconvolution-based quantitation of the mass of GH secreted in pulses (micrograms per liter per 90 min) at rest (*top*) and after exercise (*bottom*) after iv infusion of S or rhGH. Absolute nadir serum GH concentrations (micrograms per liter) induced by S and rhGH infusion at rest are summarized in the *upper right subpanel*. Data are the mean ± SEM (n = 8 men, n = 6 women). *P* values denote gender contrasts. *P* = NS defines $P > 0.05$.

After S infusion, aerobic exercise stimulated burst-like GH secretion by 1.8 (0.3, 11)-fold in women (*P* = NS) and 75 (35, 120)-fold in men ($P < 0.001$) over that observed at rest ($P < 0.05$ by gender; Fig. 4B). Mean exercise-induced absolute GH secretory-burst mass (micrograms per liter per 90 min; Fig. 3, *lower*) was similar in women and men. Simple peak GH concentrations (micrograms per liter) were also independent of gender at 21 ± 4.1 (women) and 18 ± 5.7 μg/liter (men) (*P* = NS, see *Materials and Methods* caveat).

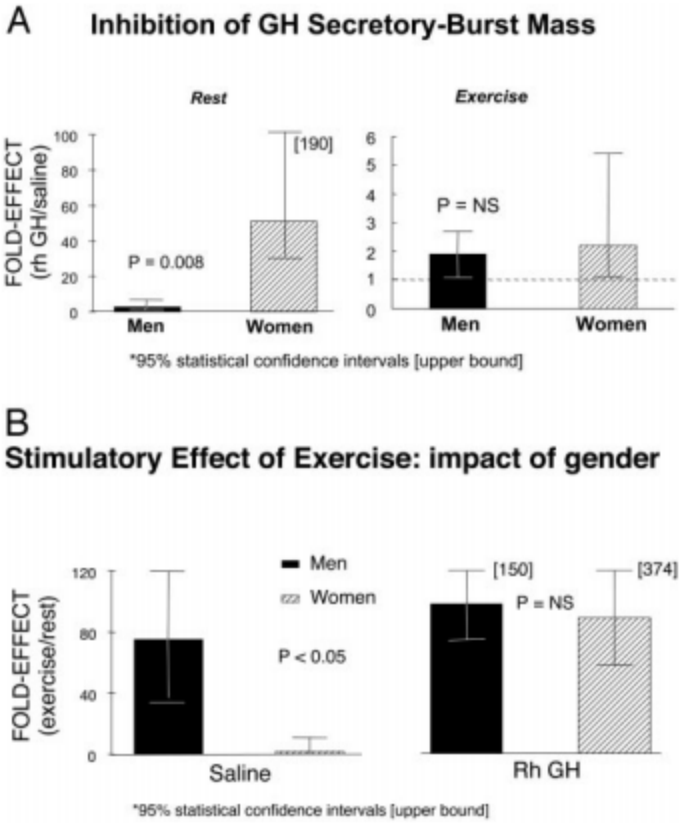

Fig. 4. A, Relative (fold-) suppression of GH secretory-burst mass by injection of rhGH, compared with S at rest (*left*) and in response to acute aerobic exercise (*right*). Values are the mean (and 95% statistical confidence intervals). B, Relative (fold-) stimulatory effect of exercise, compared with rest, on the mass of GH secreted after iv infusion of S or rhGH (Fig. 1).

Compared with sequential saline infusion and exercise, consecutive rhGH injection and exercise reduced GH secretory-burst mass by 3.2 ± 1.1 (2.2)-fold in women ($P = 0.043$) and 2.1 ± 0.39 (1.9)-fold and men ($P = 0.049$) (P = NS by gender). Thus, significant negative feedback operates during exercise. However, despite prior injection of rhGH, exercise stimulated GH secretion markedly, compared with the rhGH/rest intervention in both women and men (Fig. 3, lower). In fractional terms, rhGH/exercise increased GH secretory-burst mass by 90-fold (12, 374) ($P < 0.001$) in women and 98-fold (48, 150) ($P < 0.001$) in men (P = NS by gender) over that observed after rhGH/rest; Fig. 4B). Absolute GH secretory-burst mass after sequential rhGH injection and exercise did not differ by gender (Fig. 3).

The slow-phase half-life of decay of injected rhGH (based on within-subject means of two determinations) was 20 ± 1.64 (19) min in women and 18 ± 0.74 (18) min in men (P = NS). The estimated distribution volume of infused GH (milliliters per kilograms) was 59 ± 8.2 (61) in women and 62 ± 9.3 (63) in men [P = NS]. The lack of a gender difference in apparent distribution volume is relevant because GH secretory-burst mass is expressed as micrograms GH released per unit distribution volume (liter).

Table 1 summarizes exercise-associated work completed, kilocalories expended (per nonprotein respiratory exchange ratio), and end-exercise VO_2 in men and women. Men completed more

work, expended more energy, and maintained higher end-exercise VO_2 than women (each $P < 0.01$). Bolus iv infusion of 10 μg/kg rhGH before exercise did not alter any of the foregoing measures.

TABLE 1. Total work, kilocalories expended, and end-exercise VO_2 in men and women

	Total work (kJ)		Total kcal		End-exercise VO_2 (liter/min)		End-exercise %	
	Men[a]	Women	Men[a]	Women	Men[a]	Women	Men	Women
Saline	326 ± 35	163 ± 26	418 ± 36	215 ± 29	2.9 ± 0.2	1.4 ± 0.2	84 ± 23	73 ± 13
rhGH (10 μg/kg)	319 ± 38	163 ± 26	413 ± 34	205 ± 25	2.8 ± 0.2	1.5 ± 0.2	82 ± 23	72 ± 10

[a] $P < 0.005$ by gender; $P > 0.05$ for each comparison of the within-gender response to saline *vs.* rhGH infusion (n = 8 men; n = 6 women).

Discussion

The present clinical investigation is unique in examining composite control of pulsatile GH secretion by gender, autonegative feedback, and aerobic exercise in healthy young adults. Statistical comparisons established that all three of gender, GH autofeedback, and exercise jointly determine GH secretory-burst mass. Specifically, gender and GH autoinhibition, gender and exercise, and GH autorepression and exercise interact significantly as paired determinants of GH secretory-burst mass. *Post hoc* analyses disclosed three salient gender-related contrasts, wherein: 1) women maintain higher absolute GH secretory-burst mass at rest than men; 2) women sustain markedly greater rhGH-induced fractional suppression of GH secretion at rest than men; and 3) men manifest greater fractional stimulation by exercise (over rest) than women. The foregoing gender-related distinctions are specific in that women and men did not differ by way of absolute nadir GH concentrations enforced by GH autofeedback; the time delay to maximal feedback inhibition; the absolute mass of GH secreted after exercise with or without GH autofeedback; and the half-life or distribution volume of infused rhGH.

The precise mechanisms mediating gender-related control of GH autofeedback are not known. The mean serum estradiol concentration was similar in young men and in women evaluated in the early follicular phase of the menstrual cycle, whereas the total testosterone concentration was 12-fold higher in men. A plausible postulate is that gender-related differences in *in situ* hypothalamo-pituitary synthesis of estradiol and/or reduced androgen from available testosterone substrate modulates autofeedback actions in the GH axis. If the basic mechanisms that transduce GH-specific feedback drive of somatostatin outflow and reciprocal repression of GHRH release are analogous among species (1, 2, 17, 46), then a reasonable conjecture is that a pulse of (exogenous) GH stimulates somatostatin secretion more and/or inhibits GHRH secretion less in young women than comparably aged men (Fig. 5).

The genesis of higher amplitude GH pulses (and higher mean serum GH concentrations) in women than men is not established (47). In experimental contexts, recovery from GH autofeedback requires concomitant somatostatin withdrawal and rebound (burst-like) GHRH secretion (1, 2, 11, 15, 16, 48). Analogously in biomathematical models, negative feedback that enforces a prominent valley is followed by burst-like release of GHRH and GH. Such cycles are able to sustain recurrent, self-renewing, high-amplitude pulses of GH (12, 49) (see first part of text). In clinical contexts, GH pulse amplitude in the female exceeds that in the male throughout late puberty, young adulthood, and menopause (18–21) and doubles in the preovulatory phase of

the menstrual cycle (50, 51). Collectively, these observations suggest that sex steroids modulate autofeedback-dependent pulsatile GH secretion.

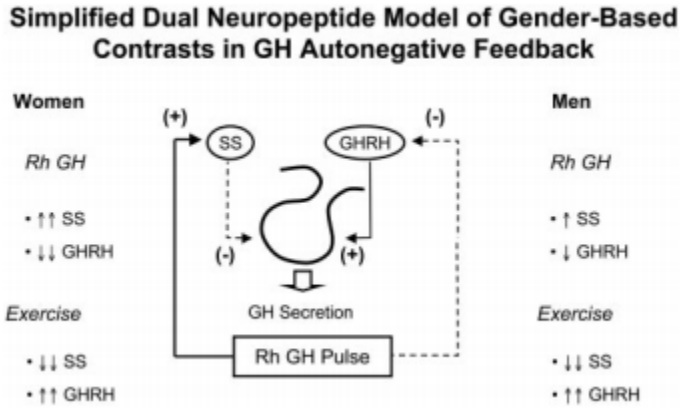

Fig. 5. Simplified schema of hypothesized mechanisms mediating gender-related contrasts in GH-induced autoinhibition.

The 20-folder greater mass of GH secreted per burst in fasting women than men studied at rest (Fig. 3) is consistent with an earlier report of approximately 70-fold higher single-random serum GH concentrations in fasting ambulatory young women than men, as determined by high-sensitivity immunofluorometric assay (52). Twenty-four-hour integrated GH concentrations and GH secretion rates are often 2-fold higher in women than men (18–21). Whereas near-maximal (present data) or maximal aerobic exercise stimulates GH secretion equally by gender (53), low-intensity exercise elicits greater GH release in women than men (27, 29). The present inference that fractional GH autofeedback is potentiated in women, compared with men, is concordant with each of the foregoing gender contrasts (27, 29, 47, 52, 53).

Investigations of sex steroid-dependent regulation of pulsatile GH release have unveiled specific mechanisms by which estrogen *per se* augments the amount of GH secreted per burst. For example, in postmenopausal women, short-term supplementation with oral estradiol, compared with placebo: 1) blunts suppression of GH release by low doses of somatostatin-14 (54); 2) amplifies submaximal stimulation by rhGHRH-1,44-amide (55); 3) potentiates near-maximal drive by GHRP-2; and 4) attenuates rhGH-induced feedback on GHRP-2 (but not the resting, exercise or GHRH)-evoked GH secretion (33, 49). Far less is known about the central neuropeptidyl actions of testosterone in the human somatotropic axis. In principle, actions of testosterone would depend on relative *in situ* hypothalamo-pituitary conversion to estradiol (stimulatory) or 5 α-reduced testosterone (inactive or slightly inhibitory) (1, 47, 56).

A recent clinical analysis disclosed 2- to 3-fold greater GH-specific fractional feedback repression and rebound-like recovery GH secretion in midpubertal than prepubertal boys or young men (9). Comparable quantitation of postsuppression rebound GH release was not possible during the present sampling duration. However, absolute maximal suppression (nadir serum GH concentrations) did not differ by gender. This finding could indicate that rhGH-induced stimulation of maximal somatostatin outflow and/or concomitant inhibition of GHRH release is comparable in women and men.

The present study shows that near-maximal aerobic exercise significantly opposes exogenous GH autoinhibition in both women and men. In fact, despite enforced GH feedback, exercise induced a 90- to 98-fold increase in pulsatile GH release over that observed after rhGH injection at rest. Nonetheless, compared with exercise alone, rhGH infusion suppressed the exercise response significantly (by 2.1- to 3.2-fold) and equivalently by gender. Therefore, feedback resistance is partial, rather than complete. The current data potentially explain the apparent absence of response down-regulation during successive bouts of exercise (30–32). If GH autoinhibition is mediated by stimulation of somatostatin release and inhibition of GHRH outflow (first part of text), then aerobic exercise may overcome autoinhibition by muting somatostatin and/or augmenting GHRH release. The present data do not distinguish between these two mechanisms or exclude the operation of both.

In summary, in the absence of an exercise stimulus, young women exhibit significantly greater susceptibility to fractional inhibition by rhGH-induced autofeedback than men. According to current regulatory concepts, this sex contrast would be consistent with gender-associated modulation of GH-specific stimulation of somatostatin and/or repression of GHRH secretion. On the other hand, women and men manifest marked (but not complete) resistance of the exercise stimulus to GH autoinhibition. Further studies will be required to elucidate putatively central neuropeptidyl interactions that mediate the foregoing gender distinctions and transduce substantial feedback resistance by exercise.

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