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Multipathway modulation of exercise and glucose stress effects upon GH secretion in healthy men

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ABSTRACT

Objective. Exercise evokes pulsatile GH release followed by autonegative feedback, whereas glucose suppresses GH release followed by rebound-like GH release (feedforward escape). Here we test the hypothesis that age, sex steroids, insulin, body composition and physical power jointly determine these dynamic GH responses.

Methods. This was a prospectively randomized glucose-blinded study conducted in the Mayo Center for Advancing Translational Sciences in healthy men ages 19–77 years (N = 23). Three conditions, fasting/rest/saline, fasting/exercise/saline and fasting/rest/iv glucose infusions, were used to drive GH dynamics during 10-min blood sampling for 6 h. Linear correlation analysis was applied to relate peak/nadir GH dynamics to age, sex steroids, insulin, CT-estimated abdominal fat and physical power (work per unit time).

Results. Compared with the fasting/rest/saline (control) day, fasting/exercise/saline infusion evoked peak GH within 1 h, followed by negative feedback 3–5 h later. The dynamic GH excursion was strongly (R^2 = 0.634) influenced by (i) insulin negatively (P = 0.011), (ii) power positively (P = 0.0008), and (iii) E_2 positively (P = 0.001). Dynamic glucose-modulated GH release was determined by insulin negatively (P = 0.0039) and power positively (P = 0.0034) (R^2 = 0.454). Under rest/saline, power (P = 0.031) and total abdominal fat (P = 0.012) (R^2 = 0.267) were the dominant correlates of GH excursions.

Conclusion. In healthy men, dynamic GH perturbations induced by exercise and glucose are strongly related to physical power, insulin, estradiol, and body composition, thus suggesting a network of regulatory pathways.

Abbreviations: GH, growth hormone; CT, computed tomography; E_2, estradiol; GHRH, growth hormone releasing hormone; GHRP, growth hormone releasing peptide; Mayo IRB, Mayo Institutional Review Board; ECG, electrocardiography; T, testosterone; LH, luteinizing hormone; FSH, follicle stimulating hormone; Mayo CTSA, Mayo Center for Advancing Translational Sciences; IGF-I, insulin-like growth factor 1; IGFBP-3, insulin-like growth factor-binding protein 3; TSH, thyroid stimulating hormone; AVF, abdominal visceral fat; TAF, total abdominal fat; ANOVA, analysis of variance; SEM, standard error of mean; BMI, body mass index; IGBP-1, insulin-like growth factor-binding protein 1.

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1. Introduction

Aging reduces pulsatile GH secretion, including the amount of GH secreted over 24 h and per burst [1,2]. Intercurrent acute illness, sex-steroid depletion, adiposity, sedentarism, hypothermia, hypothyroidism, type II diabetes mellitus and other chronic diseases often decrease GH secretion further [3,4]. However, major unresolved mechanistic issues remain, including how daily negative and positive regulators coordinately control GH secretion.

The secretion of GH has been investigated extensively under highly standardized laboratory conditions over the last five decades [5,6]. Typical interventions include insulin-induced hypoglycemia, administration of L-DOPA, naloxone, clonidine, propranolol, L-arginine, GHRH and/or GHRPs, oral glucose, parenteral somatostatin, GH-receptor antagonists, GH itself to induce autofeedback, L-thyroxine, selected neuropharmacologic agents and calibrated exercise paradigms intended to probe, if possible, individual endocrine and neurotransmitter pathways [7–13]. Outcomes of such single-agent studies along with data in laboratory animals suggest the existence of more complex interactions, which comprise presumptively interlinked feedforward (stimulatory) and feedback (inhibitory) connections [5]. A theoretic projection is that aggregate (joint) interactions, rather than any single pathway, mediate day-to-day GH production [6]. A corollary postulate is that coordinated GH-axis interactions are secondarily modulated by various internal (*e.g.* body composition, age, sex steroids) and external (*e.g.* glucose exposure, exercise) factors.

GH production in healthy individuals is principally pulsatile, especially (>85%) overnight in the fasting state [14]. Pulsatile GH secretion preferentially induces anabolic and so-called male-pattern gene expression in liver, muscle and adipose tissue, most evidently in laboratory animals but also in the human [15]. Accordingly, impoverished GH pulsatility – observed in obesity, the metabolic syndrome, hyperinsulinism, aging, cachexia, the overfed state and protracted critical illness – could have important catabolic implications [16].

Understanding day-to-day factors that supervise GH pulsatility remains difficult, although interactions among such regulatory factors are likely to be particularly relevant to models of chronic hyposomatotropism. A testable hypothesis is that components of an individual's day-to-day phenotype, *viz.* age, degree of adiposity, physical fitness, insulin and sex-steroid availability, interact with acute hour-by-hour regulators, such as the GH pulse-stimulating effect of exercise and the GH pulse-suppressing effect of glucose. The present investigation provides an initial test of this thesis.

2. Methods

2.1. Overall Design

This study assessed GH secretion during fasting/rest/saline (FRS) infusion compared with that in response to a physical stressor (GH feedforward and feedback induced by submaximal exercise, defined as fasting/exercise/saline [FES]) and a common metabolic stressor (transient glucose elevation, fasting/rest/iv glucose [FRG]) in healthy men in a within-subject cross-over design single-blinded to glucose *vs* saline infusion. Each man served as his own control.

2.2. Subjects

Healthy community-dwelling volunteers provided written, witnessed informed consent approved by Mayo IRB. Participants were required to pass baseline wellness screening, which included medical history, physical exam, and blood chemistries to test hepatic, renal, metabolic, endocrine and hematologic functions. Exercise screening comprised 12-lead ECG monitoring during maximal cycle ergometry at the Mayo Cardiovascular Health Center. Allowable ages were 18–80 years.

2.3. Exclusion Criteria

Individuals unable or unwilling to provide written voluntary consent for any reason including cognitive decline or mental illness were excluded. Volunteers with orthopedic limitations, hypertension, diabetes mellitus, cardiovascular disease, cancer, sleep apnea, pulmonary disease, weight loss (>2 kg in 6 wk), drug or alcohol abuse, psychiatric disability, hematological disorders, acute or chronic inflammatory conditions, renal insufficiency, hepatic disease, neoplasm, anemia, chronic infections, including viral hepatitis or HIV, and subjects receiving systemic medications were excluded. Allowable exposures were replacement thyroid hormone, laxatives, antacids, ophthalmic solutions, diuretics, or skin preparations. Hypogonadism (serum total T < 240 ng/dL, LH > 12 IU/L and/or FSH > 16 IU/L), glucocorticoid use, and transmeridian travel (over 3 time zones) in the 10 days prior were also disallowed.

2.4. Protocol

Eligible volunteers were admitted to the Mayo Center for Advancing Translational Sciences (CTSA) the evening before blood sampling. Beginning at 1900 h, subjects remained supine and fasting except for water, diet soda, and other non-caloric and non-caffeinated fluids. The next day, blood was sampled from an arm vein every 10 min from 0700 to 1300 h for GH and every 30 min for plasma glucose. This 6-h block permitted 1 h of baseline sampling before one of three interventions: fasting/rest/saline (FRS), fasting/exercise/saline (FES) or fasting/rest/iv glucose (FRG) during the interval 0800–0900 h, followed by 5 additional hours of sampling. FRS comprised 0800 h bolus iv saline injection (25 mL) over 3 min. FRG comprised 0800 h iv injection of 25 mL of dextrose 50% over 3 min. FES comprised sequential bouts of 7 min of bicycle ergometer at 65% peak work alternating with 2 min of bilateral arm curls. Curls began at 20 pounds and decreased to 15, 10 or 5 pounds as necessary to sustain one complete curl every 2 sec (1 sec for the upswing and 1 sec for the downswing using a metronome). This was followed by a 1-min rest and blood sample. The mixed-exercise sequence was conducted in the Energy Balance Core Laboratory of the CTSA with a physician in attendance.