Age-Related Blunting of Growth Hormone Secretion During Exercise May Not Be Solely Due to Increased Somatostatin Tone

Taylor J. Marcell, Robert A. Wiswell, Steve A. Hawkins, and Kyle M. Tarpenning

Age-related declines in growth hormone (GH) secretion may result from augmented somatostatin (SRIH) tone and/or diminished GH-releasing hormone (GHRH) secretion. We assessed GH release during exercise without and with pyridostigmine (PYR), which indirectly suppresses SRIH. GH levels were measured throughout exercise and recovery in 12 young men (mean ± SEM, 20.8 ± 0.4 years) and seven old men (66.1 ± 1.9). The area under the GH curve (GH-AUC) was greater in young versus old men during a short-term maximal exercise test (12.9 ± 2.8 *v* 1.5 ± 0.2 ng · min^{-1} · mL^{-1}, *P* = .002) and a 1-hour 60% maximal (submaximal, 10.0 ± 1.5 *v* 3.0 ± 1.0 ng · min^{-1} · mL^{-1}, *P* = .001) cycle exercise bout. PYR increased the GH-AUC in young and old men during maximal (20.9 ± 5.2 *v* 4.9 ± 1.8) and submaximal (12.3 ± 1.6 *v* 4.7 ± 1.5) exercise (*P* < .05). The greater GH response to maximal versus submaximal exercise suggests a role for adrenergic modulation of GHRH during exercise. However, the failure of PYR to restore the responses of the old to those of the young suggests that increased SRIH tone does not completely explain the age difference in GH secretion during exercise.

GROWTH HORMONE (GH) secretion in humans follows a nocturnal rhythm that is dynamically regulated, and differs between genders.[1,2] The primary hypothalamic regulators of GH secretion are GH-releasing hormone (GHRH), which stimulates GH secretion, and somatostatin ([SRIH] somatotropin release–inhibiting hormone), which inhibits GH secretion. Within the hypothalamus, other neurotransmitter systems, which include the cholinergic-muscarinic, adrenergic, and other pathways, modulate both GHRH and SRIH secretion.[3-6]

In humans, peak values of GH are usually achieved during the first 4 hours of sleep. In aging, there is a reduced peak and total GH secretion that occurs at rest, during sleep,[7,8] and in response to stimulation such as exercise. The reduction in total GH secretion with increasing age is primarily a result of decreased amplitude of the nocturnal GH pulses,[9] which decline at a rate of approximately 14% per decade.[10] The decreased pituitary secretion of GH during aging has been attributed primarily to alterations in hypothalamic control of GH release, with some studies implicating an age-related increase in hypothalamic SRIH tone[11-13] as the most important mechanism leading to suppressed GH secretion.

Advancing age is associated with other relevant neuroendocrine changes. For example, skeletal muscle adrenergic receptor sensitivity is diminished in older adults.[14] Therefore, the decreased GH response to an exercise stimulus in the elderly might result, in part, from a decreased sensitivity to adrenergic stimulation, and not entirely from increased SRIH. The purpose of this experiment was to explore the involvement of SRIH in the age-related reduction in the GH response to exercise. Specifically, we assessed the extent to which pharmacological suppression of SRIH tone with pyridostigmine bromide (PYR), an acetylcholine esterase inhibitor, could augment the exercise-induced GH response of old versus young men.

SUBJECTS AND METHODS

Subject Selection

Twelve young (20.7 ± 0.4 years) and seven old (66.1 ± 1.9 years, mean ± SEM) non-obese men with a body mass index (BMI) less than 30 kg · m^2 served as subjects. All men were recruited from the Southern California area and were community-dwelling, ambulatory, and free from metabolic, endocrine, cardiac, or other physical diseases that would have excluded them from participating in exercise. The subjects signed an informed-consent document approved by the Human Subjects Committee at the University of Southern California, Los Angeles.

Treatment Trials

During the first visit, the subjects completed a clinical interview, health history questionnaire, and resting examination including height, weight, 12-lead electrocardiogram (EKG), blood pressure by auscultation, and body composition analysis via dual-energy x-ray absorptiometry ([DEXA] QDR-1500; Hologic, Waltham, MA). Each subject performed two tests of maximal aerobic capacity ($\dot{V}O_2$max) and two submaximal exercise assessments. Each test was performed once following placebo or oral administration of 120 mg PYR, a dose used previously in similar studies.[15] A common side effect of PYR, gastrointestinal (GI) distress, occurred in approximately 10% of the subjects on PYR and in fewer than 5% of the subjects on placebo. The GH exercise response of men reporting GI distress was not significantly different from the response of the mean without this complaint, nor was this occurrence age-dependent. The subjects completed the four exercise tests on separate nonconsecutive days. All testing was performed between 8 and 11 AM following an overnight fast. PYR alone has been previously noted not to increase basal GH levels at rest after 30 minutes. Therefore, we administered PYR 30 minutes before exercise to prevent an elevation in endogenous baseline GH secretion.

Graded Exercise Test

Subjects were fasted overnight. At 8 AM, we inserted an indwelling catheter into the antecubital vein. Thirty minutes before performing the maximal graded exercise test, a resting blood sample was drawn and PYR or placebo was administered by mouth. Exercise was performed on a manually braked stationary Monark (818E; Varberg, Sweden) bicycle ergometer using a ramped protocol while maintaining a cadence of 50 rpm. This protocol began at a resistance of 25 W (1 Kpm) for 1 minute, with an increase of 12.5 W (0.5 Kpm) every minute thereafter until the subject was unable to maintain a minimum cadence of 40 rpm

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and was at a point of volitional fatigue. During exercise, the expired volume of oxygen ($\dot{V}O_2$) and carbon dioxide (CO_2) was measured breath-by-breath via open-circuit indirect calorimetry for determination of the maximal oxygen capacity using a SensorMedics (Vmax 29; Yorba Linda, CA) system. The analyzers were calibrated daily for volume and concentration with known gases. Subjects were also monitored by a 12-lead EKG (Q750B; Quinton, Bothell, WA) throughout exercise. Blood samples were obtained before, at maximum, and at 5 and 15 minutes postexercise. A physician was present during the maximal exercise tests of the older individuals per the American College of Sports Medicine (ACSM) guidelines.

Prolonged Exercise

Subjects were tested following an overnight fast as previously described. Submaximal exercise was performed at a cadence of 50 rpm on a manually braked Monark (818E) bicycle ergometer for 1 hour at an intensity corresponding to 60% of the subject's previously measured $\dot{V}O_2$max. Oxygen consumption was monitored continuously throughout exercise, with periodic removal of the mask to allow for water consumption. Within the first 5 minutes of exercise, the intensity on the bicycle ergometer was increased until 60% $\dot{V}O_2$ max steady-state oxygen consumption was obtained. Intensity was adjusted as needed throughout the 1-hour exercise to maintain 60% $\dot{V}O_2$ output. Data were collected continuously for 5 minutes prior to blood sampling, and the results are expressed as the $\dot{V}O_2$ for minutes 15, 30, 45, and 60, respectively. Venous blood was obtained immediately before (minute 0), at 15-minute intervals throughout (15, 30, 45, and 60 minutes), and 15 minutes (75 minutes) postexercise. Heart rate (HR) telemetry (Polar CIC, Port Washington, NY) was used to record the HR every 15 minutes throughout exercise.

Sample Collection

Serum GH concentrations were determined by ^{125}I radioisotopic assay (RIA) using commercially available kits (DPC, Los Angeles, CA), with all samples from a single subject determined within the same assay. The interassay precision was 5.0% ± 0.3% (mean ± SEM). The RIA methodology measures the major circulating isoforms (20 kd and 22 kd) of GH, and its extraction separates all bound GH, therefore measuring total GH levels. A dose-response curve of radioactivity versus concentration was generated with a personal computer using a regression analysis program (Table Curve 2D; Jandel, Mountain View, CA) based on known concentrations of a standard. The resulting quadratic equation was used to determine patient sample concentrations. The minimal detectable dose was 0.2 $\mu g \cdot L^{-1}$, and this value was used if a patient sample was less than this lower limit.

Data Analysis

Basal GH values were determined by averaging the initial concentrations measured at rest during all four visits. Peak hormone values during maximal and submaximal testing were determined for each subject individually by visual observation. GH data were also evaluated as the total area under the curve (AUC) by the method of trapezoidal integration. In brief, trapezoidal integration is performed by averaging the concentration of hormone between each pair of successive time points, multiplying the mean value by the difference in time for that period. $[(X_1 + X_2)/2 \cdot (time_1 - time_2)]$, and summing the interval values obtained. For each experimental trial, the AUC from 0 to 15 minutes postexercise was determined. This value was then corrected for time by dividing by total exercise time (which varied during maximal and was fixed during submaximal at 75 minutes). Oxygen consumption measurements were monitored by a breath-to-breath system; maximal and 15, 30, 45, and 60 minute values were determined by averaging the minute values. For $\dot{V}O_2$ max, the two highest consecutive 30-second values at the end of exercise were averaged to represent the maximum. For submaximal values, minute values were averaged for a 5-minute period prior to and including the minute of interest.

Statistics

All data were entered into a personal computer, and statistical analysis was performed with the Statistical Package for Social Sciences (SPSS 7.0, Chicago, IL). Descriptive characteristics were analyzed using unpaired *T* tests. Differences between trials were analyzed using a two (age) by two (condition) ANOVA with repeated measures for time and Tukey post hoc analyses, controlling for normality of data distribution. Significance was set a priori at *P* less than .05 using a one-tailed hypothesis to reduce the chance of a type II error.

RESULTS

Subject Characteristics

Characteristics of the 12 young and seven older men are shown in Table 1. Although the young and old men were considered non-obese as judged by established norms,[16] the older men tended to be heavier, with a nonsignificantly greater BMI than the younger men. The older men had a higher percentage of body fat and regional trunk fat as assessed by DEXA ($P < .05$). Lean body mass (LBM) did not differ between young and old men.

Metabolic Response

Absolute (liters per minute) and relative (milliliters per kilogram per minute) $\dot{V}O_2$max and maximal HR were greater in young versus old men ($P < .05$). Neither resting nor maximal HR values differed between the control and PYR trials for either the young or old men (Table 2). $\dot{V}O_2$max values (averaged from the two trials) for young (43 $mL \cdot kg^{-1} \cdot min^{-1}$) and old (28 $mL \cdot kg^{-1} \cdot min^{-1}$) men would be classified as average according to the age-adjusted norms.[17] Total work and time to exhaustion were also greater in the young men ($P < .05$), with an average time to reach the maximum greater than 10 minutes in both the young and old men. In the old men only, total work and maximal exercise time were slightly greater during the PYR versus control trial ($P < .05$).

Maximal Exercise GH

Basal values for GH tended to be greater in the young versus old men (2.3 ± 0.7 *v* 1.1 ± 0.2 $\mu g \cdot L^{-1}$, $P = .08$), but this was not statistically significant. Basal GH values were not significantly related to maximal aerobic capacity, body weight, or LBM ($r = .45$, NS; data not shown). In response to maximal exercise (Fig 1), young men exhibited GH values that increased progressively from basal, peaked at 5 minutes following

Table 1. Subject Characteristics of the Young and Old Men (mean ± SEM)

Characteristic	Young ($n = 12$)	Old ($n = 7$)
Age (yr)	20.8 ± 0.4* (18-24)	66.1 ± 1.9 (60-76)
Height (in)	70.32 ± 0.96	70.71 ± 0.97
Weight (kg)	77.43 ± 4.03	89.86 ± 8.84
BMI (kg/m^2)	24.1 ± 0.9	27.8 ± 2.6
% Fat (DEXA)	15.3 ± 1.2*	23.7 ± 1.9
LBM (kg)	62.47 ± 2.86	63.74 ± 5.07
Trunk fat (kg)	4.90 ± 0.61*	12.15 ± 2.47

*$P < .05$ *v* old.

Table 2. Metabolic Parameters From the Maximal Graded Exercise Test for Young and Old Men (mean ± SEM)

Parameter	Young (n = 12)	Old (n = 7)
VO_2 (L/min)		
Control	3.35 ± 0.14*	2.35 ± 0.21
PYR	3.25 ± 0.16*	2.54 ± 0.22
$\dot{V}O_2$ (mL/kg/min)		
Control	44.01 ± 1.94*	27.32 ± 3.02
PYR	42.42 ± 1.86*	29.30 ± 2.95
RER		
Control	1.06 ± 0.02*	1.12 ± 0.03
PYR	1.05 ± 0.02*	1.15 ± 0.01
HR (bpm)		
Control	188 ± 2*	155 ± 5
PYR	182 ± 3*†	152 ± 7
Work (kp)		
Control	4.87 ± 0.21*	3.54 ± 0.15
PYR	4.81 ± 0.21*	3.68 ± 0.18†
Time (min)		
Control	15.6 ± 0.7*	10.7 ± 0.6
PYR	15.6 ± 0 8*	11.3 ± 0.8†

*P < .05 v old.
†P < .05 v control.

cessation of exercise, and remained elevated at 15 minutes into the postexercise recovery period. In contrast, in the old men, GH secretion did not increase above basal levels until 15 minutes postexercise. The total GH-AUC response of the young men was significantly greater than the basal value during maximal exercise (76.2 ± 27.8 v 407.8 ± 92.2 $\mu g \cdot L^{-1}$, P = .005). However, in the old men, the total GH-AUC was not significantly above the baseline value during maximal exercise (31.2 ± 5.1 v 40.6 ± 7.2 $\mu g \cdot L^{-1}$; Fig 2). Hence, the exercise response of the young men was 10-fold greater than the exercise response of the old men (P = .003). When the GH-AUC was expressed relative to the individual's time to reach maximal exercise (GH-AUC $\cdot$ min^{-1}), the exercise GH-AUC value for the young men (12.86 ± 2.77 $\mu g \cdot L^{-1} \cdot min^{-1}$) remained 8.6-fold greater than that for the old men (1.49 ± 0.22 $\mu g \cdot L^{-1} \cdot min^{-1}$, P = .002), despite the differences in the time to reach maximal in the young versus old men.

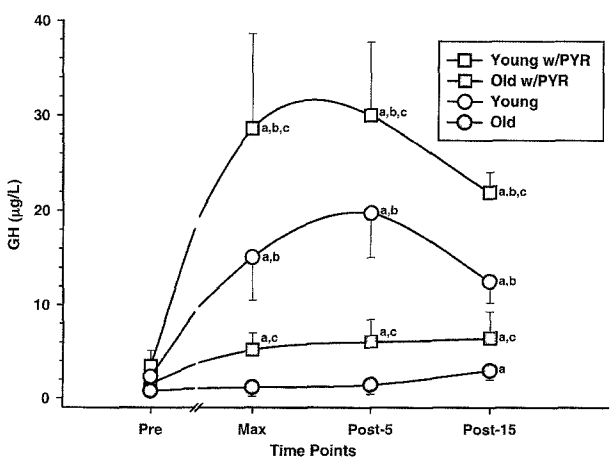

Fig 1. GH concentration during the maximal exercise test for both young and old men without and with coadministration of 120 mg PYR. a, value > basal; b, young > old; c, PYR > control, (P < .05). Values are the mean ± SEM.

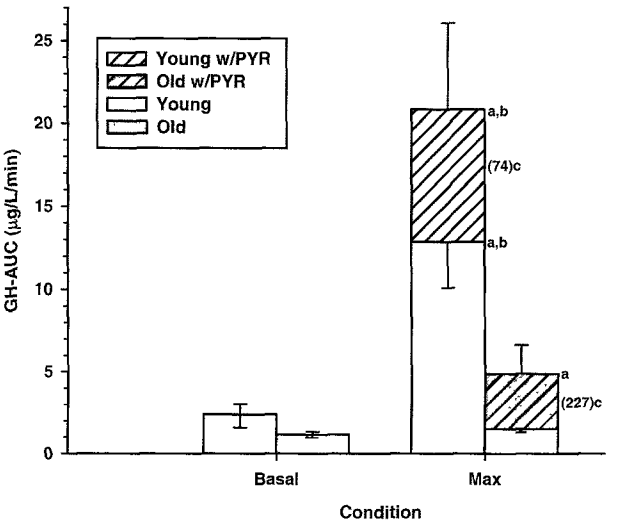

Fig 2. GH-AUC during the maximal graded exercise test and following the 15-minute recovery period (adjusted for total exercise time) for both young and old men. Hatched bars represent the increase in GH-AUC with coadministration of 120 mg PRY 30 minutes prior to exercise. a, = value > basal; b, young > old; c, PYR > control (P < .05). Values are the mean ± SEM. Numbers in parentheses are the percent increase in GH-AUC following PYR treatment.

PYR administered 30 minutes before maximal exercise augmented the GH-AUC above that found during the maximal exercise control trial by 74% for the young men (22.43 ± 5.46 $\mu g \cdot L^{-1} \cdot min^{-1}$, P = .01) and 224% for the old men (4.87 ± 1.77 $\mu g \cdot L^{-1} \cdot min^{-1}$, P = .03). Despite the greater relative increase in GH following PYR in the old men, GH-AUC $\cdot$ min^{-1} remained 4.3-fold greater in young versus old men (P = .012).

Submaximal Exercise Metabolic Response

Submaximal oxygen consumption (liters per minute) did not differ between the control and PYR trials in either the young or old men. Exercise workloads were also similar between trials in the young, and were slightly lower during the PYR trial in the old men. Workloads equated to 61.7% and 61.8% of maximal oxygen consumption for the control and PYR trials, respectively, in the young men, and 64.0% and 64.1%, respectively, in the old men. There were no significant differences between the relative percentage of maximal workload performed in the control and PYR trials for young or old men. Similarly, there was no difference in the relative percentage of workload performed between the young and old men, although the young worked at a higher absolute oxygen consumption and workload.

The HR increased to a plateau and then did not change significantly during the remaining 1 hour of exercise. HRs were higher in young men compared with old men. PYR during exercise resulted in a significantly lower HR at each time point as compared with the control period in both young and old men.

Submaximal Exercise GH

In response to the 1-hour submaximal exercise, GH concentrations increased significantly in the young men by 15 minutes

and continued to increase progressively until 60 minutes (Fig 3). However, in the old men, GH concentrations did not increase until 30 minutes into exercise and were elevated only until 45 minutes, after which they slowly began to decrease (Fig 4). In the young men, the time-adjusted (75 minutes) exercise GH-AUC was significantly greater than basal (2.27 ± 0.75 *v* 9.95 ± 1.53 $\mu g \cdot L^{-1} \cdot min^{-1}$, $P = .001$). The exercise response of the old men was also significantly elevated above basal (1.15 ± 0.17 *v* 2.95 ± 0.99 $\mu g \cdot L^{-1} \cdot min^{-1}$, $P = .05$). Thus, the GH response of the young men to submaximal exercise was 3.4-fold greater than that of the old men ($P = .001$).

During the submaximal exercise + PYR trial, GH-AUC was augmented 24% in the young men (12.34 ± 1.63 $\mu g \cdot L^{-1} \cdot min^{-1}$, $P = .24$, NS) and 59% in the old men (4.69 ± 1.54 $\mu g \cdot L^{-1} \cdot min^{-1}$, $P = .03$) as compared with the control submaximal exercise trial. Again, PYR administration did not eliminate the age difference (2.6-fold, $P = .004$) in GH-AUC $\cdot$ min^{-1} during the prolonged submaximal aerobic exercise. However, the absolute magnitude of the change in GH-AUC (ie, delta) between the control and PYR trial was not significantly different between the young and old men (179.27 ± 145.98 *v* 130.62 ± 76.42 $\mu g \cdot L^{-1}$, respectively, $P = .76$).

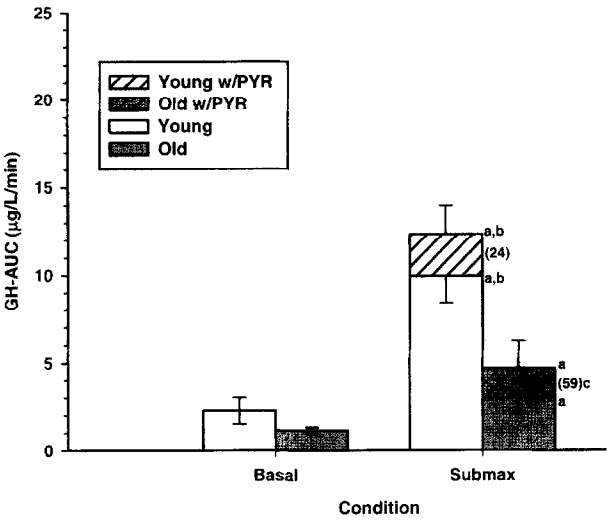

Fig 4. GH-AUC during the 1-hour submaximal bicycle exercise and following the 15-minute recovery period (adjusted for total exercise time) for both young and old men. Hatched bars represent the increase in GH-AUC with coadministration of 120 mg PYR 30 minutes prior to exercise. a, value > basal; b, young > old; c, PYR > control ($P < .05$). Values are the mean ± SEM. Numbers in parentheses are the percent increase in GH-AUC following PYR treatment.

DISCUSSION

In the current study, GH secretion was significantly blunted in the older men in comparison to their younger counterparts during either short-duration maximal or prolonged submaximal exercise of comparable relative intensity. The same phenomenon has been observed following an acute bout of resistive weight-lifting exercise.[1,18-20] PYR administration increased total GH secretion during exercise in both the young and old men, but did not eliminate age-related differences in GH levels. The current data could be interpreted to suggest several possible mechanisms related to the age-related blunting in exercise-induced GH secretion. These include increased SRIH tone with age, decreased cholinergic inhibition of SRIH, decreased adrenergic drive stimulating GHRH, or possibly a decreased sensitivity of the pituitary to GHRH stimulation.

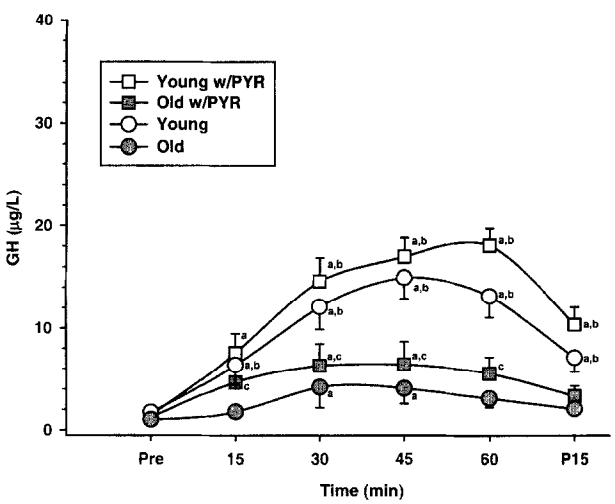

Fig 3. OGH concentration during the 1-hour submaximal bicycle exercise bout for both young and old men without and with coadministration of 120 mg PYR 30 minutes prior to exercise. a, value > basal; b, young > old; c, PYR > control ($P < .05$). Values are the mean ± SEM.

A frequently cited hypothesis in the literature is that aging animals may have greater hypothalamic SRIH tone.[11-13,21] If this were the primary mechanism suppressing GH, then blocking the effect of SRIH should restore youthful levels of GH secretion. Administration of PYR, which inhibits central acetylcholine esterase activity, thus prolonging endogenous acetylcholine activity, has been demonstrated to suppress the majority of SRIH tone at the doses used in this study.[22,23] Thus, if the increase in SRIH tone fully accounts for the decrease in GH response with age, then PYR administration should eliminate the age-related difference in GH secretion. In the current study, there was a greater fractional increase in the GH-AUC following PYR coadministration during exercise in older versus younger men. However, the absolute magnitude of the change in the GH-AUC between the control and PYR trial was not different between the young and old men, suggesting that PYR was equally effective in both groups in counteracting SRIH inhibition of GH secretion. The finding that significant differences in GH release between young and old men persist after suppression of SRIH release by PYR administration is consistent with the concept that an increase in SRIH tone does not completely explain the age-associated blunting of exercise-induced GH secretion.

Alternatively, it is possible that the sensitivity of SRIH secretion to cholinergic inhibition is decreased with age. If there is a decrease in the cholinergic neuron number and/or sensitivity within the median eminence in older adults, this could produce

resistance to cholinergic inhibition of SRIH and result in incomplete suppression of SRIH tone by PYR.

If the GH response to exercise were solely mediated by an increase in cholinergic suppression of SRIH tone as concluded by one study in young men,[24] then after pharmacologic inhibition of SRIH via PYR, there should not be any additional increase in GH secretion during exercise. However, our findings demonstrate that GH secretion during exercise + PYR was greater than during PYR or exercise alone, which suggests the operation of some additional stimulus to GH secretion during exercise, possibly an adrenergic pathway. These findings are consistent with the hypothesis that a feed-forward adrenergic stimulation of GH secretion occurs during exercise.[5] In the current study, the blunting of the GH secretory response in the elderly to both cholinergic stimulation (PYR only) and exercise (which, as already noted, may be partly mediated by adrenergic stimulation) as compared with their younger counterparts is a novel finding, and may suggest a role for a reduction of both cholinergic and adrenergic mechanisms in aging. These results further suggest that a decrease in the sensitivity of pituitary somatotropes to these signaling mechanisms could explain the blunted absolute peak GH response in the older population, a phenomenon observed during exercise alone and during exercise + PYR.

During submaximal exercise + PYR, the HR was reduced, while the total workload was not different and did not vary relative to the control trial. PYR, an acetylcholine esterase inhibitor, could reduce the parasympathetic nervous system via acetylcholine, thus suppressing the HR by increasing parasympathetic drive (increased vagal tone). However, the possibility that an increase in GH secretion could improve work efficiency requires further elucidation. The reduced HR of the older men versus younger men is a frequently observed phenomenon in aging, which was not altered by PYR treatment and may be due to an alteration in the contractile apparatus of the heart.[25] During the maximal testing in the seven old men, there were slightly longer exercise times with coadministration of PYR as compared with the control trial, possibly due to the fact that the PYR tests were conducted after the control tests, as these were used to screen the subjects for health risks (ie, order of testing). This order-of-testing effect potentially could have obscured our results by reducing age-related differences in post-PYR GH levels. However, we observed significant age differences in GH levels following maximal testing regardless of drug or placebo intervention. Thus, any order-of-testing effect was inconsequential.

In summary, serum GH levels increased as a result of both maximal and submaximal exercise, but the magnitude of increase was considerably less and occurred later in healthy older versus younger men. Pretreatment with PYR was associated with an augmentation in both peak and total integrated GH secretion in both age groups. However, PYR did not restore the GH response of the old to the level observed in the young men. These results suggest that increased SRIH tone does not completely explain the age-related decrease in GH secretion during exercise. Our finding of a greater GH response to maximal versus submaximal exercise is also consistent with a possible role for adrenergic modulation of GHRH or direct pituitary GH secretion. Future studies using larger populations and varying doses of PYR could shed further light on these issues.

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