Altered Growth Hormone Secretory Dynamics in Prepubertal Males with Constitutional Delay of Growth

JAMES R. KERRIGAN, PAUL M. MARTHA, Jr.,[1] JOHANNES D. VELDHUIS, ROBERT M. BLIZZARD, AND ALAN D. ROGOL

Department of Pediatrics [R.M.B., J.R.K., P.M.M., A.D.R.], Internal Medicine [J.D.V.], and Pharmacology [A.D.R.], NSF Science and Technology Center for Biological Timing [J.R.K., A.D.R., J.D.V.], University of Virginia Health Sciences Center, Charlottesville, Virginia 22908

ABSTRACT. We have used the technique of deconvolution analysis to determine if abnormalities in growth hormone (GH) secretion or metabolic clearance underlie the observed alterations in circulating hormone concentrations in a group of seven prepubertal males with constitutional delay of growth (SHORT-DBA). The results were compared with data obtained from 13 healthy, short prepubertal males (SHORT) and 11 healthy prepubertal male subjects of normal stature (NORMAL). Although the mean 12-h overnight GH production rates were invariant among the groups (8.0 ± 1.0 *versus* 7.3 ± 0.7 *versus* 6.7 ± 1.2 μg/L, NORMAL *versus* SHORT *versus* SHORT-DBA for all comparisons), different secretory mechanisms were operative. The secretory burst half-duration (time interval of the secretory event at half-maximal amplitude) of the SHORT-DBA subjects (26 ± 1 min) was greater (p = 0.02) than that of the SHORT group (20 ± 1 min); values for both the SHORT and SHORT-DBA subjects were indistinguishable from that of NORMAL controls (22 ± 2). Both the mass of GH released per secretory episode and the maximal rate of hormone secretion were less (p ≤ 0.02 and p < 0.01, respectively) for the SHORT-DBA subjects [16 ± 2 μg/unit of body distribution volume (L_v) and 0.6 ± 0.1 μg/L_v/min, respectively] compared with those of the NORMAL (26 ± 2 μg/L, and 1.1 ± 0.1 μg/L_v/min, respectively) and SHORT (28 ± 4 μg/L, and 1.3 ± 0.2 μg/L_v/min, respectively) groups; values for the latter two groups were indistinguishable. Given the dominant association of GH pulse amplitude with normal childhood growth, the present findings suggest a possible GH secretory mechanism underlying the suboptimal growth in a subset of prepubertal males with constitutional delayed growth. (*Pediatr Res* 33: 278–283, 1993)

Abbreviations

GH, growth hormone
SDS, standard deviation score
SHORT, short, prepubertal male subjects
NORMAL, prepubertal males of normal stature

SHORT-DBA, prepubertal male subjects with constitutional delay of growth
BA-SDS, bone age standard deviation score
SRIH, somatotropin release-inhibiting hormone
GHRH, growth hormone–releasing hormone
L_v, body distribution volume

The GH secretory status of children with disordered growth has been the focus of numerous investigations. Many such studies have assessed endogenous GH levels in children with short stature. Some short children have abnormalities of circulating GH concentration profiles according to some (1–6) but not other investigators (7, 8). The apparent discrepancies between these studies include issues such as the inclusion of different control groups; use of an objective, validated hormone pulse detection program; and the use of different GH assays. Any or all of these factors, as well as others, may contribute to the differing results.

The mechanism(s) subserving the observed alterations of serum GH concentration profiles in children with subnormal growth are not known. As such, none of the studies described has assessed specific variations in GH secretion and metabolic clearance. To assess alterations in either secretion or clearance, we have used the technique of deconvolution analysis (9) in a group of children with previously defined abnormalities of endogenous GH concentrations. Deconvolution analysis, or convolution modeling, represents a mathematical technique that, when applied to hormone data series, provides subject-specific estimates of the neurosecretory events and of hormone clearance (10, 11). Assuming that GH secretion occurs in a repetitive, burst-like fashion, convolution modeling characterizes these bursts of pituitary hormone release by their frequency of occurrence, the mass of hormone secreted, the rate of hormone secretion, and the duration of the secretory process. Estimates of hormone production and subject-specific clearance rates can be derived simultaneously from deconvolution analysis. The results of our analysis provide new insight into the altered GH physiology that characterizes some short prepubertal males with constitutional delay of growth.

SUBJECTS AND METHODS

Subjects. Thirty-one prepubertal children were enrolled in this study. None had received prior treatment with growth promoting agents. All participants had prepubertal sexual development. None had evidence of systemic disease, intrauterine growth retardation, dysmorphic features, or previous CNS irradiation. Body mass indices (12) were within ± 2.0 SDS for skeletal age

for all subjects. The clinical characteristics of all subjects have been reported previously (6).

Thirteen healthy boys with a height SDS of −2.0 or less composed the SHORT group. All had BA within ± 2.0 SDS based on chronologic age. The SHORT-DBA group was composed of seven healthy male subjects with a height SDS of −2.0 or less and bone age SDS of −2.0 or less for chronologic age. Subjects in both the SHORT and SHORT-DBA groups had GH concentrations of >10 μg/L after pharmacologic testing. Eleven healthy males composed the NORMAL group. All had height SDS, weight SDS, and BA SDS within ± 2.0 for chronologic age.

Auxologic measurements were normalized according to the data of Tanner and Davies (13). Pubertal staging was based on genital development according to the method of Marshall and Tanner (14). Skeletal maturation and SDS were determined according to the method of Tanner et al. (15).

Protocol. The study was approved by the Human Investigation Committee at the University of Virginia and was performed in at institution's General Clinical Research Center. Participants were informed of the details of the investigation. Legal consent and assent were then provided by the parents or legal guardians and the children, respectively.

An i.v. catheter with heparin lock was inserted into a forearm vein at least 2 h before sampling. Venous blood samples were obtained every 20 min via the indwelling catheter beginning at 2000 h and continuing through 0800 h. Subjects were allowed normal activity and were provided caffeine-free meals and snacks.

Assays. Serum GH concentrations were determined in duplicate by an immunoradiometric assay (Nichols Institute, San Juan Capistrano, CA) using the supplied horse-serum matrix. The limit of assay detection is 0.5 μg/L with intra- and interassay coefficients of variation of ≤8.0 and ≤10.0%, respectively. All samples obtained from a given subject were measured in a single assay run to avoid interassay variability. Plasma IGF-I concentrations were determined using a double-antibody RIA kit (Nichols Institute).

Deconvolution analysis. Based on the premise that GH and other anterior pituitary hormones are secreted in a burst-like fashion and that hormone elimination occurs at subject-specific metabolic clearance rates (9), we used deconvolution analysis to estimate the following dynamic measures of GH secretion and removal: *1)* number and positions in time of the secretory episodes, *2)* secretory burst half-duration (duration of the secretory episode at half-maximal amplitude), *3)* amplitude (maximal secretory rate in each secretory burst, and *4)* GH half-life corresponding to a disappearance rate constant. Multiple-parameter deconvolution analysis assumes that the simultaneous operation of these four sets of parameters gives rise to the circulating GH concentrations (9). The mass of GH secreted per episode was calculated as the integral (area) of the deconvolution-resolved secretory burst. The 12-h GH production rate was calculated as the product of the average mass of hormone secreted per burst and the total number of secretory bursts. An assumption of multiple-parameter deconvolution analysis is that each secretory burst can be approximated statistically by a gaussian distribution of release rates. No constitutive secretion was necessary to model the present experimental data.

Statistical analyses. Group values were compared using one-way analysis of variance with Duncan's multiple-range test. Secretory parameters were log-transformed because they are not normally distributed (10). Univariate linear regression analysis was used to assess correlations. Statistical significance was accepted at a *p* value of <0.05. Results are reported as mean ± SEM.

RESULTS

The clinical characteristics of all the study groups are displayed in Table 1. The average chronologic and skeletal ages were

Table 1. *Clinical characteristics of study participants**

	NORMAL	SHORT	SHORT-DBA
CA (y)	9.0 ± 0.3	9.5 ± 0.5	10.4 ± 1.0
BA (y)	8.2 ± 0.4	9.1 ± 0.6	7.6 ± 0.8
BA SDS	−0.8 ± 0.8[a]	−0.4 ± 0.2[a]	−2.6 ± 0.2[b]
Height SDS	0.1 ± 0.3[a]	−2.6 ± 0.2[b]	−3.1 ± 0.2[b]
GV SDS	1.0 ± 0.7[a]	−1.2 ± 0.4[b]	−1.8 ± 0.6[b]

* Values (mean ± SEM) within a row without identical superscripts differ statistically (*p* ≤ 0.03). CA, chronologic age; BA, bone age; GV, growth velocity.

indistinguishable among the groups. Skeletal age, expressed as SDS, was significantly (*p* < 0.001) less (by experimental design) for the SHORT-DBA group compared with those of both other groups. Values for height SDS and growth velocity SDS for both the SHORT and SHORT-DBA groups were significantly (*p* < 0.001 and *p* < 0.01, respectively) less than those of the NORMAL subjects but indistinguishable from each other.

Typical profiles obtained by deconvolution analysis are shown in Figure 1; a representative reconvolved serum GH concentration *versus* time graph and a GH secretory rate versus time curve are illustrated for each group. The numerical results of deconvolution analysis for the three study groups are listed in Table 2.

The secretory burst half-duration (time interval of the secretory event at half-maximal amplitude) of the SHORT-DBA subjects (26 ± 1 min) was greater (*p* = 0.02) than that of the SHORT group (20 ± 1 min); values for both the SHORT and SHORT-DBA subjects were indistinguishable from those of the NORMAL controls (22 ± 2). Both the mass of GH released per secretory episode and the maximal rate of hormone secretion were less (*p* ≤ 0.02 and *p* < 0.01, respectively) for the SHORT-DBA subjects (16 ± 2 μg/L$_v$ and 0.6 ± 0.1 μg/L$_v$/min, respectively) compared with those of the NORMAL (26 ± 2 μg/L$_v$ and 1.1 ± 0.1 μg/L$_v$, respectively) and SHORT (28 ± 4 μg/L$_v$ and 1.3 ± 0.2 μg/L$_v$/min, respectively) groups; values for the last two groups were indistinguishable. The mean 12-h serum GH concentrations, secretory burst frequencies, and 12-h GH production rates [expressed as mass of GH per unit of body distribution volume (L$_v$), mass of GH per unit of body surface area, or mass of GH/kg of body mass] were indistinguishable among the study groups. Comparisons of secretory burst frequency, mass of GH released per secretory burst, maximal rate of hormone secretion, and GH production rate are depicted in Figure 2. Endogenous GH half-life estimates were indistinguishable among the study groups; the derived estimates are in general agreement with independently obtained values in adults and children (16–20).

Shown in Table 3 are the results of linear-regression analysis for several GH secretion characteristics and BA SDS for all subjects combined. Significant correlations were observed between secretory burst half-duration (*r* = −0.41, *p* = 0.02), the mass of GH released per secretory episode (*r* = 0.43, *p* = 0.02), and maximal rate of GH secretion attained within a burst (amplitude) (*r* = 0.46, *p* = 0.01) *versus* BA SDS. The relationships between BA SDS and the mass of GH released per secretory burst and the rate of GH secretion are illustrated in Figure 3. No significant relationship was observed between GH production rate (*r* = 0.24, *p* = 0.20) and BA SDS.

DISCUSSION

Subnormal concentrations of GH released spontaneously over 12 to 24 h have been observed in some children with short stature (1–6). In particular, diminished GH pulse amplitudes occur in some healthy, short children. The significance of this finding is suggested by the data of Hindmarsh et al. (21) who observed a positive curvilinear relationship between the amplitude of circulating GH pulses and linear growth velocity. Most recently, these same investigators have obtained data that support the concept that the rate of change of endogenous GH concentrations
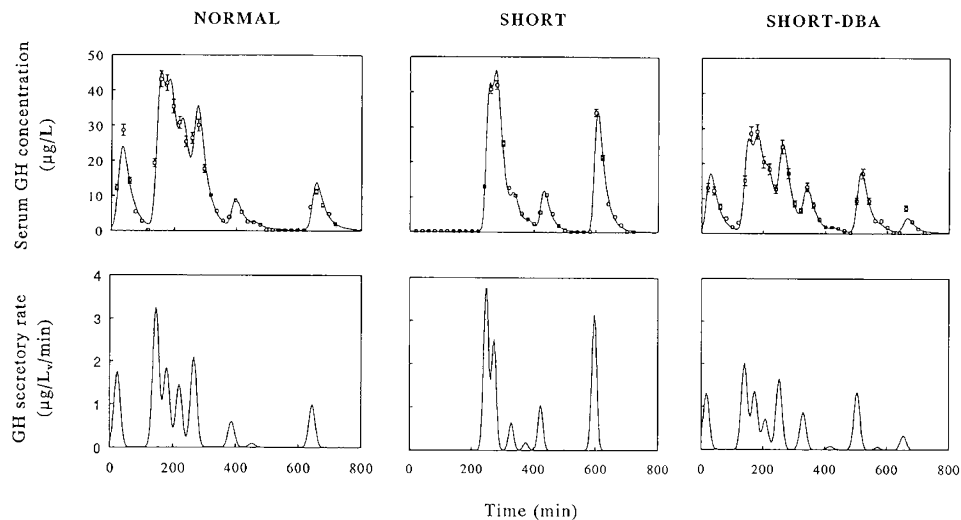
Fig. 1. Shown in this composite figure are data from a representative subject in each of the three study groups: one control (the two graphs on the left), one short boy with normal skeletal development (the two graphs in the center), and a child with short stature and delayed bone age (the two graphs on the right). The vertical axes for the three graphs in each row have identical ranges of values. The *upper panels* depict the deconvolution-predicted curves and the measured serum GH concentrations (shown as *open boxes* with *vertical error bars* representing the intrasample SD); the deconvolution-derived curves closely approximate the experimental data points. The *bottom panels* illustrate the distinct GH secretory bursts as estimated by deconvolution analysis and are represented as secretory rate *vs* time.

Table 2. *Characteristics of GH secretion, GH half-life, and plasma IGF-I levels**

	NORMAL	SHORT	SHORT-DBA
Mean 12 h serum GH concentration (μg/L)	8.0 ± 1.0	7.3 ± 0.7	6.7 ± 1.2^{NS}
Secretory burst half-duration (min)	$22 \pm 2^{a,b}$	20 ± 1^a	26 ± 1^b
No. of secretory bursts/ 12 h	8.2 ± 0.6	8.8 ± 0.7	11.0 ± 1.4^{NS}
Mass of GH released per burst (μg/L$_v$)	26 ± 2^a	28 ± 4^a	16 ± 2^b
Maximal rate of GH secretion per burst (μg/L$_v$/min)	1.1 ± 0.1^a	1.3 ± 0.2^a	0.6 ± 0.1^b
GH production rate (μg/L$_v$ $\times$ 12 h)	214 ± 26	225 ± 24	178 ± 29^{NS}
GH production rate (μg/m^2 $\times$ 12 h)	476 ± 57	461 ± 47	366 ± 57^{NS}
GH production rate (μg/kg $\times$ 12 h)	17 ± 2	18 ± 2	14 ± 2
Half-life (min)	22 ± 2	20 ± 2	26 ± 1
IGF-I (IU/mL)†	0.90 ± 0.13 (0.34–1.77)	0.60 ± 0.06^a (0.22–1.10)	0.65 ± 0.12^a (0.22–1.18)

* Values (mean ± SEM) within a row without identical superscripts differ statistically ($p < 0.04$). Superscript NS denotes no significant difference.

† Values in parentheses represent the range of IGF-I concentrations.

is an important signal for the control of growth (22). As such, these findings underscore the important role of the pulsatile pattern of GH secretion in the modulation of normal childhood growth. However, the precise role and characteristics of pituitary GH secretion and metabolic clearance of the GH molecule in the modulation of growth in otherwise healthy short children has not been fully addressed.

We have therefore applied deconvolution analysis to determine if alterations in pituitary GH secretion and the consequent hormone production rate or in hormone clearance exist in a group of healthy, short, prepubertal males. Multiple-parameter deconvolution analysis is a computerized mathematical technique that, when applied to deconvolutional hormone concentration *versus* time series, provides subject-specific estimates of

hormone secretion and elimination characteristics. Thus, the application of this mathematical technique provides mechanistic insight into the kinetics of the secretory events and the metabolic clearance of the GH molecule.

In the present study, average circulating levels of GH did not differ among the groups. Different mechanisms of hormone secretion, however, were existent. In the short subjects with delayed skeletal maturation, the average duration of GH secretory episodes was prolonged compared with the other short subjects. This abnormality has also been observed recently in young girls with Turner's syndrome (23). A diminished mass of GH released per secretory episode and a decreased average maximal rate of hormone secretion were observed in the same subjects. Although a trend toward decreased 12-h GH production rates was observed for the SHORT-DBA group, the results did not achieve statistical significance. The prolonged duration of secretion and trends toward a greater secretory burst frequency and a lengthened hormone half-life, both of which have been recognized in prepubertally aged girls with Turner's syndrome (above), would contribute to increased circulating GH concentrations. The decreased mass of hormone released per burst and diminished rate of GH release, however, would result in lowered GH levels. The net result of these simultaneously acting mechanisms is an invariant average concentration of spontaneously circulating GH and unaltered GH production rates.

The findings of the present study provide some insight into the pathophysiology of altered GH secretion and suboptimal growth in a subset of healthy, prepubertal males with constitutional delayed growth. The pulsatile pattern of GH secretion arises from episodic increases and decreases in the release and subsequent action of GHRH and SRIH on the somatotrope (24, 25). In the simplest interpretation of available data, the amount of GHRH released determines the amount of GH released per secretory episode and the pattern of SRIH action determines the frequency and duration of the GH secretory bursts (26–28).

The findings of the present study support the concept that a relative deficiency of the amount of GHRH released per burst (but not the indirectly inferred frequency of GHRH bursts) plays an important role in the altered GH secretion observed in prepubertal males with constitutional delay of growth. In support of this concept are the diminished mass of GH released per burst and a decreased maximal rate of hormone release. Although these findings might also be explained by heightened SRIH tone,
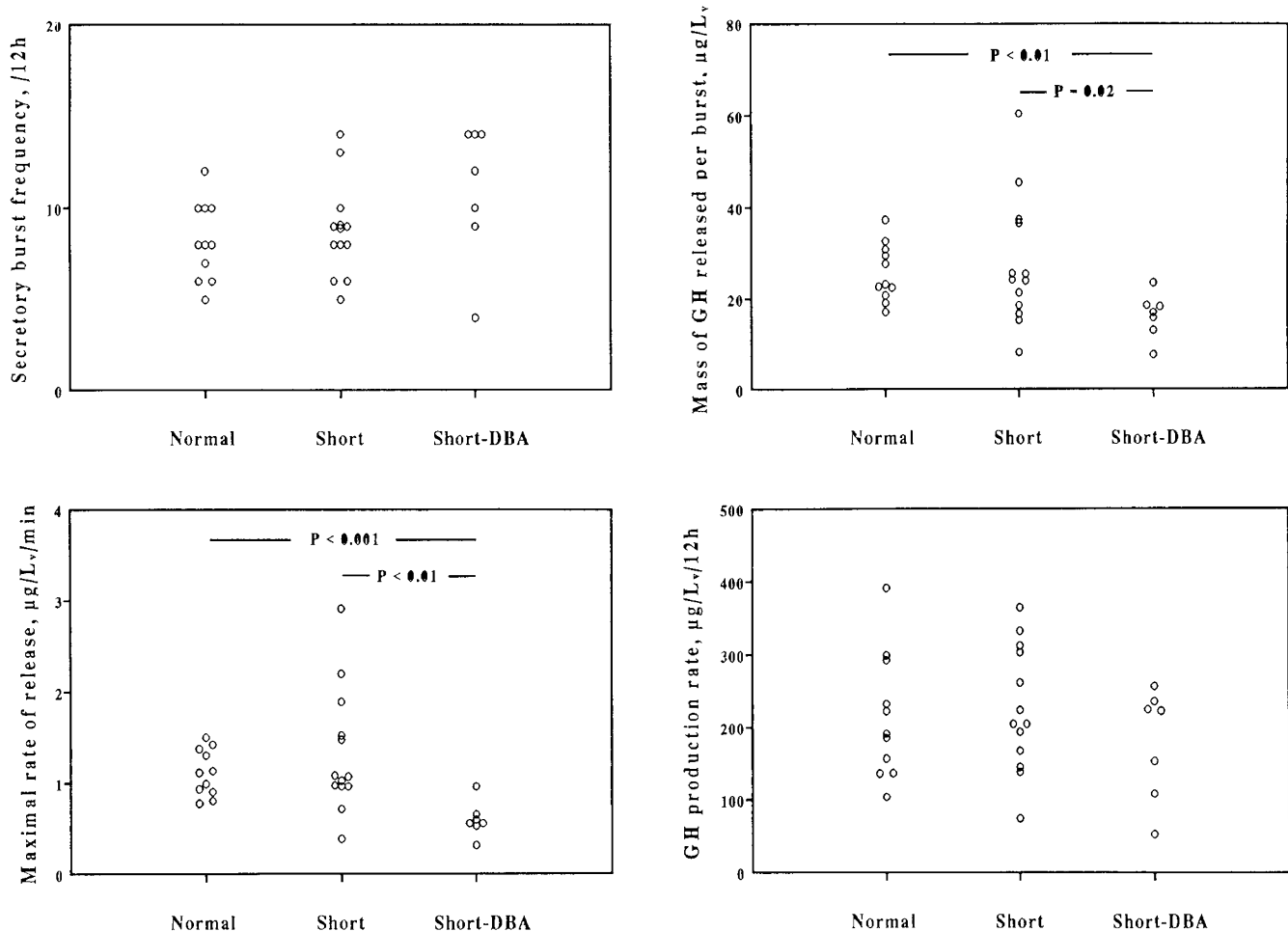
Fig. 2. Illustrated in this composite figure are comparisons (among the three study groups) of GH secretory burst frequency (*top left panel*), mass of GH released per burst (*top right panel*), amplitude or maximal rate of GH secretion attained within bursts (*bottom left panel*), and 12-h GH production rate (*bottom right panel*). Statistically different group values are denoted by connecting lines with the respective p values.

Table 3. *Correlation analysis of selected GH secretory burst characteristics and BA SDS of all study subjects*

	Correlation coefficient	p value
Secretory burst half-duration (min)	−0.41	0.02
Mass of GH released per secretory episode (μg/L$_v$)	0.43	0.02
Rate of GH secretion (μg/L$_v$/min)	0.46	0.01
GH production rate (μg/L$_v$/12 h)	0.24	0.20

additional evidence in support of altered GHRH action is derived from presumptive inhibition of SRIH secretion by β-adrenergic blockade. Spontaneous release of GH fails to rise after administration of atenolol, a β-adrenergic blocking agent, to healthy, prepubertal males with constitutional delay of growth (29). These data suggest that perturbed GHRH action, rather than disturbance of SRIH effect, plays a critical role in the altered GH secretion in prepubertal males with constitutional delayed growth. The increased secretory burst duration, however, may not be due entirely to altered GHRH action. There are likely direct GHRH-SRIH interactions within the hypothalamus (30). The consequence of a disruption of these normal interactions may be manifested as altered rate and/or duration of hormone secretion and, conceivably, altered frequency of GH secretory episodes. Of interest, an increased frequency of low-amplitude GH secretory bursts has been described recently as a statistically positive predictor of clinical linear-growth responses to GH administration in Turner's syndrome (31).

The sex-steroid hormones are known to significantly alter GH secretion (32, 33). By definition, subjects with constitutional delayed growth and adolescence have a prolonged period of relative sex-steroid hormone insufficiency. One may speculate that the apparent (and relative) deficiency of GHRH in our subjects with constitutional delay is the result of this suboptimal action of gonadal steroid hormones in the prepubertal period. In support of such a relationship is the ability of very small doses of estrogen to increase GH secretion 2- to 3-fold in prepubertal girls with Turner's syndrome (34). Administration of androgen to young males with constitutional delay of growth and adolescence results in augmented GH secretion (35). Specifically, both the mass and maximal rate of GH released per secretory episode were increased in these subjects. Saggese *et al.* (36) have recently reported decreased circulating concentrations of GHRH in prepubertal subjects with constitutional delayed development. No such abnormality was observed in these subjects during adolescent development, a time of augmented sex-steroid hormone levels. No alterations in peripheral SRIH concentrations were observed. Although of interest, the precise relevance of such measurements to changes in the levels of GHRH and SRIH in hypophyseal portal blood remains to be tested.

Recently, Veldhuis *et al.* (37) used deconvolution analysis to quantitate pituitary GH secretion and circulating GH half-life in a group of healthy, prepubertal males with idiopathic short stature. No differences were noted, however, for any characteristics of hormone secretion or of the estimated, subject-specific half-lives. Although no apparent mathematical relationship was observed between various specific quantitative parameters of GH
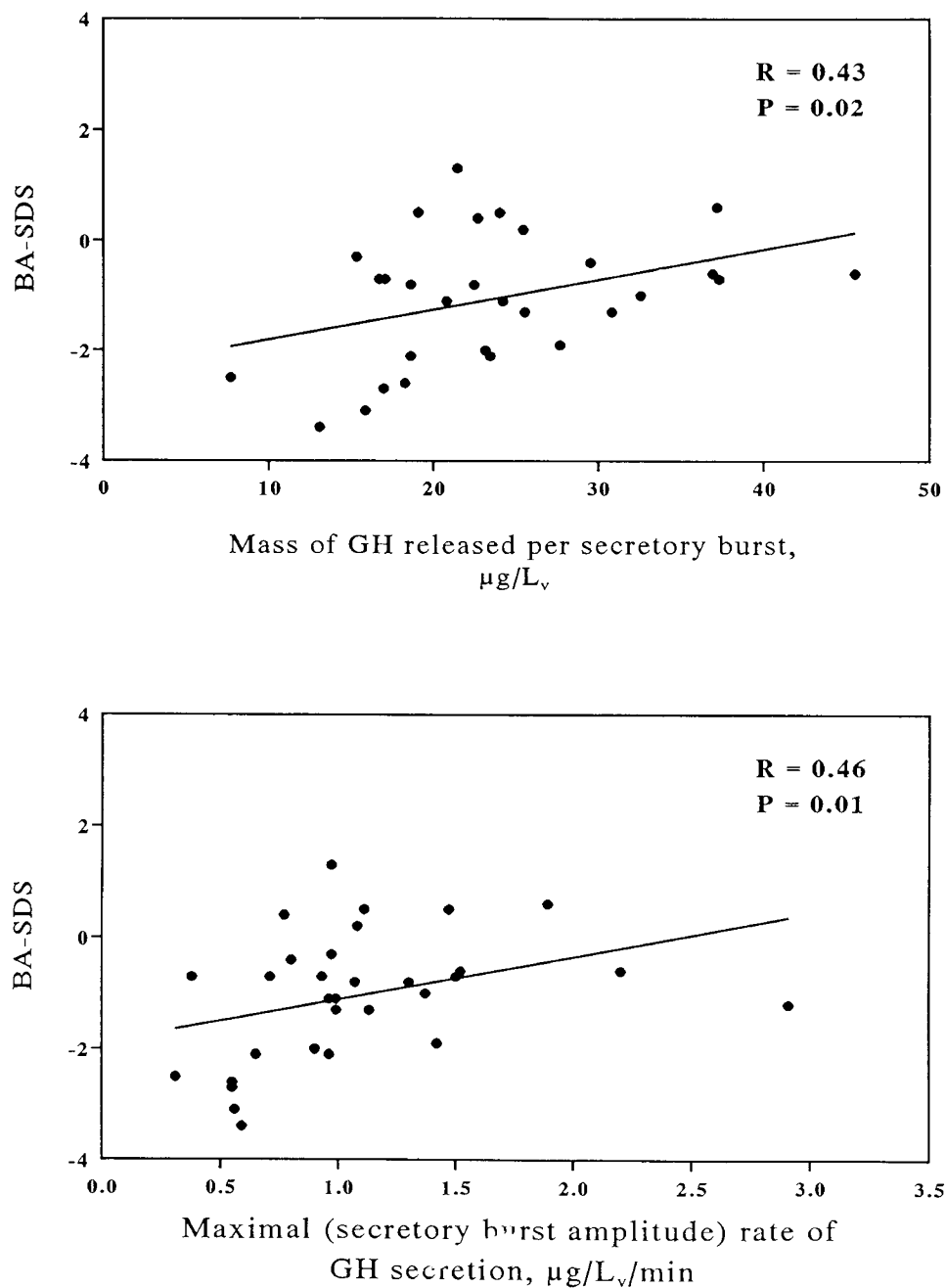
Fig. 3. Relationships (as determined by univariate linear regression analysis) between skeletal maturation (expressed as BA SDS) and the mass of GH released per secretory burst (top panel) and the rate of GH secretion (bottom panel) are illustrated. The respective correlation coefficients and p values are displayed in the upper right corner of each graph.

secretion and skeletal age, those subjects with significantly delayed bone ages were not evaluated separately and constituted a small percentage of the group. Thus, inferences concerning the mode of GH secretion in subjects with constitutional delayed growth and development in that study are not possible.

In summary, 12-h overnight GH production rates for healthy, short, prepubertal males did not differ from values for control subjects of normal stature. In a subset of short boys with constitutional delay of growth (i.e. those short boys with significantly delayed bone age), however, several characteristics of GH secretion were altered; among these were decreased mass of hormone released per secretory burst, prolonged GH secretion episodes, and diminished maximal rate of GH secretion attained within each burst. The frequency of GH secretory burst and the endogenous GH half-life were invariant. The observed alterations in GH secretory dynamics may underlie the suboptimal growth in

some prepubertal males with constitutional delay of growth and provide insight into the neuroendocrine mechanisms subserving such altered GH physiology.

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