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Elevated Growth Hormone Secretory Rate in Premature Infants: Deconvolution Analysis of Pulsatile Growth Hormone Secretion in the Neonate

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ABSTRACT. Premature infants have higher circulating concentrations of growth hormone (GH) than term infants. Previous investigations of these differences have used sampling frequencies of every 30 min with subsequent application of pulse detection algorithms, such as the CLUSTER program, to assess serum GH pulse parameters. To determine differences in GH secretory rates or GH $t_{½}$ values between premature and term infants, we have sampled 11 neonates at 15-min intervals. We performed deconvolution analysis of the resultant plasma GH values to estimate GH secretory and clearance parameters. Five premature infants (gestational age range 24–34 wk) and six term infants (gestational age range 38–42 wk) were sampled every 15 min for 6 h. All subjects had indwelling arterial catheters. GH was measured (in duplicate) by RIA using 10 μL of plasma. Premature infants had higher secretory burst amplitudes (2.2 ± 0.13 μg/L/min *versus* 1.4 ± 0.27 μg/L/min, $p = 0.02$), higher production rates (product of the total number of bursts and the mean mass of GH secreted per burst, 811 ± 173 μg/L/6 h *versus* 283 ± 77 μg/L/6 h, $p = 0.03$), and a higher mass of GH per secretory burst (106 ± 25 μg/L *versus* 38 ± 11 μg/L, $p = 0.049$) than term infants. The integrated plasma GH concentration exhibited a strong trend toward a higher value in the premature infants (18 100 ± 800 μg/L *versus* 10 200 ± 2 700 μg/L, $p = 0.067$). There were no differences between GH secretory burst frequency (7.8 ± 0.2 pulses/6 h *versus* 7.7 ± 0.6 pulses/6 h), GH $t_{½}$ (20 ± 4 min *versus* 24 ± 6 min), half-duration of burst (the time elapsed at half-maximal amplitude, 45 ± 11 min *versus* 25 ± 4 min), or mean interval between peaks (48 ± 2 min *versus* 48 ± 3 min) comparing the premature and term groups, respectively. In summary, we have demonstrated an elevation in GH secretory burst amplitude, GH production rate, and the mass of GH secreted per burst in premature compared with term infants. Because the estimated GH $t_{½}$ is similar between these two groups, amplified secretion rather than decreased clearance accounts for the differences in circulating GH concentrations. We suggest that the augmented GH secretory activity in premature infants reflects an increase in hypothalamic GH-releasing hormone activity and/or reduced somatostatin tone. (*Pediatr Res* 32: 286–290, 1992)

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Abbreviations

GH, growth hormone
GA, gestational age
GHRH, growth hormone-releasing hormone
SRIF, somatostatin

GH is first detectable in the human fetal pituitary by 9 wk of gestation (1). The physiologic importance of GH for growth prenatally is unclear. Several investigators have documented higher GH concentrations in fetuses and premature infants compared with term infants by measuring GH in either single serum samples from aborted fetuses (1) or single cord blood samples (2). A similar phenomenon has been well documented in fetal sheep (3). With the discovery that GH secretion after birth is intermittent (4), investigators have more recently examined these pulsatile parameters in fetal and early life. Bassett and Gluckman (5) have measured ovine fetal circulating GH concentrations every 20 min for 3 h and demonstrated significantly higher hormone levels than in full-term neonatal sheep. Miller *et al.* (6) measured human plasma GH concentrations every 30 min over a 12-h period in 15 premature and eight term infants and found a strong trend toward higher GH concentrations in the premature group.

To date it has not been possible to determine whether this observed increase in GH concentration in premature infants relative to term infants is secondary to increased secretion of GH or rather is a result of decreased GH clearance. Moreover, the neuroendocrine mechanism for increased secretion might entail amplified GH secretory burst amplitude or frequency, or both. We have measured and compared GH concentrations at frequent intervals in premature and term human infants and have applied deconvolutional modeling to differentiate GH secretory from clearance function. We also evaluated changes in the frequency, amplitude, mass, and/or duration of underlying GH secretory bursts.

MATERIALS AND METHODS

Subjects. Eleven infants from the neonatal intensive care units at The University of Virginia (10 subjects) and the University of

California-Irvine (one subject) were recruited for the study. Protocols were approved by the Human Investigation Committee at each institution. Eligibility criteria included the following: age between 24 and 96 h, preexisting indwelling arterial cannulas, and minimal or no ventilatory support. Informed parental consent was obtained for all subjects. Infants with congenital anomalies and infants receiving vasopressor drugs were excluded.

Infants were sampled for GH (0.1 mL of blood per sample) every 15 min for a 6-h period and one for IGF-I (0.1 mL blood). Glucose and hematocrit determinations were made twice. The total amount of blood taken during the 6-h study was 2.8 mL. No infant had been fed before the study and all were receiving i.v. glucose and electrolyte-containing fluids. Parenteral nutrition was not given during the study.

Assays. Blood samples were centrifuged at 12 500 rpm for 3 min, and the plasma was removed and stored in labeled plastic vials on ice. Samples for IGF-I were collected in 0.4-mL vials containing EDTA. Upon completion of the 6-h study period, all samples were stored at −80°C until analysis.

GH was measured in heparinized plasma by a modification of a double-antibody RIA (Diagnostic Products, Los Angeles, CA) using 10 μL of plasma. This sample was diluted with 40 μL of kit standard to attain the requisite 50 μL of assay volume, and samples were run in duplicate. The range of detectability for these diluted samples in this assay was 1.0–30 μg/L. The values of these diluted samples were then determined by multiplying by 5. The intraassay coefficient of variation and interassay coefficient of variation were 6.2 and 7.3%, respectively.

IGF-I was measured in EDTA plasma after separation of IGF-I from its binding proteins using octadecasilyl-silica cartridges (C18 Sep Pak; Waters, Milford, MA). The serum samples were not acid-chromotographed, and total IGF binding protein was not determined. IGF-I kits were purchased from Nichols Institute (San Juan Capistrano, CA). The intraassay coefficient of variation and interassay coefficient of variation were 1.1 ± 0.7% (± SD) and 11%, respectively.

Deconvolutional modeling. Previously, neonatal pulsatile GH characteristics have been assessed using pulse detection algorithms (6) such as CLUSTER (7, 8). This program analyzes observed GH concentrations over time (Fig. 1, *top panel*). The circulating GH concentration at any given point in time can be described by a convolution integral, which reflects assay accuracy and simultaneous GH secretion and clearance (Fig. 2). To determine true GH secretory parameters and to estimate GH clearance function from this convolution integral (Fig. 2, *right panel*), we have used deconvolutional modeling. This computerized analysis has been described previously (9). It separates secretory (Fig. 2, *left panel*) and clearance function (Fig. 2, *middle panel*) in each subject. Figure 1 (*middle panel*) shows a continuous curve, which represents expected GH concentrations if discrete GH secretory bursts had occurred as predicted by deconvolution analysis. Figure 1 (*bottom panel*) shows the presumptively gaussian secretory bursts that were predicted by this analysis. Parameters with statistical confidence intervals for each burst including amplitude (maximal rate of secretion within a burst), half-duration (the time elapsed at half-maximal amplitude), temporal positions, and GH $t_{½}$ can then be determined. No interburst secretory activity was required to model the present data. The mass of GH secreted per burst (the area under the curve of the secretory burst), the GH production rate (product of the total number of bursts and the mean mass of GH released per burst), and the mean time interval between bursts were also determined.

Statistics. Unpaired two-tailed *t* tests were performed on the following GH deconvolution parameters: secretory burst amplitude, production rate, mass of GH per secretory burst, integrated plasma GH concentrations, GH $t_{½}$, and half duration of secretory burst. Because of departures from normality as defined by the Wilkes-Shapiro statistic, the GH secretory burst frequency and mean interval between bursts were analyzed using the Wilcoxon rank sum test. Data are reported as the mean ± SEM. Significance was accepted at $p < 0.05$.

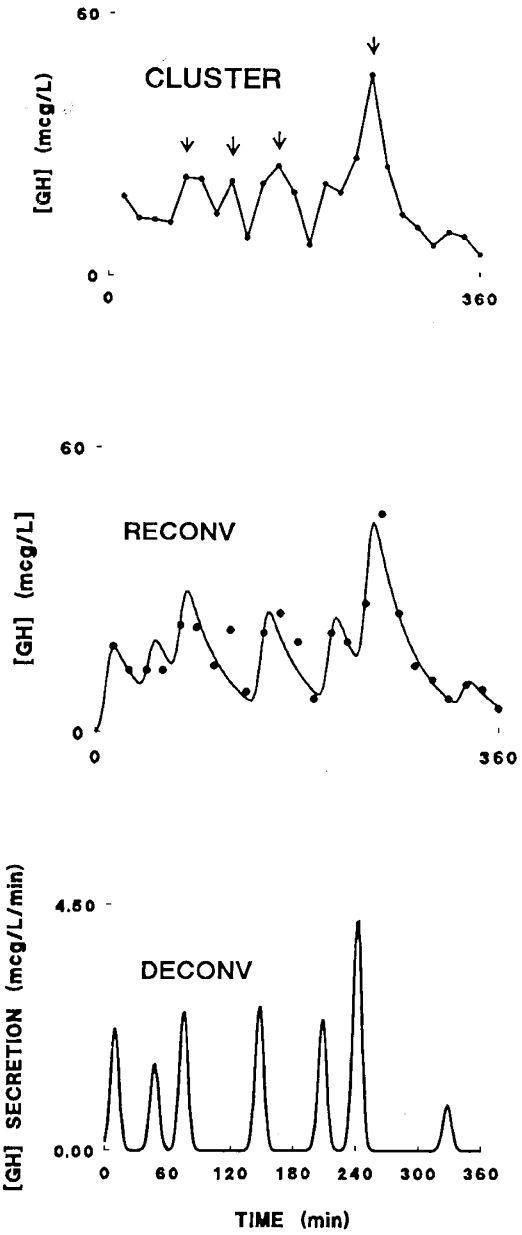

Fig. 1. Schema of GH secretion. *Top panel* shows results of CLUSTER analysis of plasma GH concentrations over time (*arrows* denote peaks). *Middle panel* depicts GH concentrations as above, in addition to reconvolved fit of these data as predicted by deconvolution analysis. *Bottom panel* reveals computer-identified GH secretory bursts, which account for observed GH concentrations.

RESULTS

Growth, demographic, diagnostic, and clinical summaries for the five preterm and six term infants studied are shown in Table 1. All infants were clinically stable; most preterm infants with mild, resolving respiratory distress syndrome had received intratracheally at least one dose of calf lung surfactant extract. The term infants had a variety of pulmonary-cardiovascular conditions requiring treatment, but none was receiving more than 62% O_2 by hood at the time of the study. All of the preterm infants were of appropriate height and weight for GA as determined by Ballard examination. One of the term infant's weight was at the 5th percentile for his GA and another infant's weight

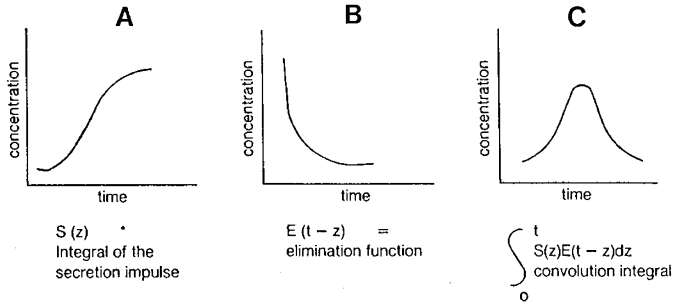

Fig. 2. Schematic illustration of deconvolutional modeling. Hormonal concentrations at any given point in time (*C*) reflect the effects of prior and simultaneous secretory impulses (*A*) and endogenous subject-specific metabolic clearance (*B*). Reprinted from Pediatr Res 28:626, 1990 with permission of the International Pediatric Research Foundation, Inc.

was greater than the 95th percentile for GA. Neither infant required more than physiologic amounts of glucose to maintain a normal circulating glucose concentration. The average age at study for the preterm infants was 67.6 ± 4.3 h and for the term infants, 53.8 ± 9.4 h. All but one were receiving ampicillin and gentamicin at the time of the study, but none had positive blood cultures.

Family history was negative for growth hormone deficiency or short stature.

Figure 3 displays secretory rate *versus* time of two representative subjects (subject 1, a 25-wk GA premature infant and subject 6, a 38-wk GA term infant).

Premature infants had higher secretory burst amplitudes (2.2 ± 0.13 μg/L/min *versus* 1.4 ± 0.27 μg/L/min, $p = 0.02$), higher production rates (811 ± 173 μg/L/6 h *versus* 283 ± 77 μg/L/6 h, $p = 0.03$), and a greater mass of GH per secretory released burst (106 ± 25 μg/L *versus* 38 ± 11 μg/L, $p = 0.049$). The integrated plasma GH concentration exhibited a strong trend toward a greater value in the premature infants (18 100 ± 800 μg/L *versus* 10 200 ± 2 700 μg/L, $p = 0.067$). There were no differences between GH secretory burst frequency (7.8 ± 0.2 pulses/6 h *versus* 7.7 ± 0.6 pulses/6 h), GH $t_{1/2}$ (20 ± 4 min *versus* 24 ± 6 min), half-duration of bursts (45 ± 11 min *versus* 25 ± 4 min), or mean interval between secretory burst (48 ± 2 min *versus* 48 ± 3 min) in the premature and term groups, respectively (Table 2).

The IGF-I concentrations in the premature and term groups [11.5 ± 1.2 ng/mL (1.50 nmol/L) and 27.1 ± 7.5 ng/mL (3.5 nmol/L), respectively] suggest a trend ($p = 0.09$) toward lower IGF-I concentrations in the premature group.

DISCUSSION

Our comparison of pulsatile GH secretion parameters between premature and term neonates shows higher secretory burst amplitudes, production rates, and mass of GH released per secretory burst in the premature infants. These changes were specific, inasmuch as the calculated GH $t_{1/2}$ values did not differ between the two groups. The GH $t_{1/2}$ values of 20 and 24 min for premature and term infants, respectively, are similar to those reported for normal adult men (18.9 min) (10) and for children (19 min) (11). These values differ from the mean GH $t_{1/2}$ of 12 min, estimated in four term infants by Cornblath *et al.* (2), who found a range of 11–14 min. This discrepancy may reflect a difference in the $t_{1/2}$ of exogenous, cadaveric GH and our estimate of endogenous GH. Additionally, Faria *et al.* (10) recommended measurements of four or five $t_{1/2}$ values to best determine GH $t_{1/2}$. To our knowledge, estimates of GH $t_{1/2}$ in premature infants have not previously been determined. The present data indicate that the high circulating GH concentrations observed in premature infants are a result of greater pituitary secretion rather than decreased metabolic clearance.

Pituitary GH secretion is regulated by hypothalamic secretion of GHRH and SRIF (12). Gluckman and Parsons (13) have demonstrated that GH secretion in fetal lambs requires an intact hypothalamus. An increase in GHRH or a decrease in SRIF secretion could explain the elevated GH levels in the premature infant. Inasmuch as all plasma GH concentrations were detectable, decreased SRIF inhibitory tone with or without augmented amounts of GHRH released per pulse, and/or enhanced somatotroph cell responsiveness to GHRH, could account for our findings.

Kaplan *et al.* (1) have proposed that elevated fetal GH concentrations result from an immaturity of hypothalamic control of the pituitary somatotroph. Alternatively, decreased inhibition of hypothalamic function could explain this increased stimulation of the pituitary by the hypothalamus in the premature infant. A known inhibitor of hypothalamic and pituitary function regulating GH secretion by somatotrophs is IGF-I (14, 15). We found a tendency toward lower total IGF-I levels in the premature group. These data support previous findings of studies with greater numbers of subjects that total IGF-I concentrations are lower in premature infants (6, 16, 17) or in fetal porcine models (18). Thus the lower levels of total IGF-I in premature infants could result in less inhibitory feedback on the hypothalamopituitary unit, resulting in augmented GH secretion from the pituitary.

Inasmuch as the majority of IGF-I in humans is complexed to IGF binding proteins, particularly IGF binding protein-3 (19), these proteins may play an important role in this pathway. IGF binding protein-3 concentrations rise from the neonatal period through puberty (20). Miller *et al.* (6) have shown that premature

Table 1. *Individual subject clinical data**

Subject no.	GA (wk)	Wt (kg)	Length (cm)	Age (h)	Sex	Race	Diagnosis
Premature							
1	25	0.65	33	66	M	C	RDS
5	24	0.65	31	54	F	C	RDS, PDA
8	34	2.38	45	69	M	C	RDS
9	34	2.17	45	81	F	C	RDS
11	34	2.55	50	68	M	C	RDS
Term							
2	40	3.18	49	38	M	B	Mec Asp, mild
3	41	3.93	50	39	M	B	Mec Asp, mild
4	40	2.35	45	69	M	B	PPHTN, mild
6	38	3.67	53	94	M	C	RDS, pneumonia
7	42	3.26	48	43	F	Am Indian	Resolved pneumothorax
10	38	3.76	52	40	F	H	Mec Asp; PPHTN, mild

* Abbreviations: RDS, respiratory distress syndrome; PPHTN, persistent pulmonary hypertension; PDA, patent ductus arteriosus; Mec Asp, meconium aspiration; B, black; C, Causasian; H, Hispanic.

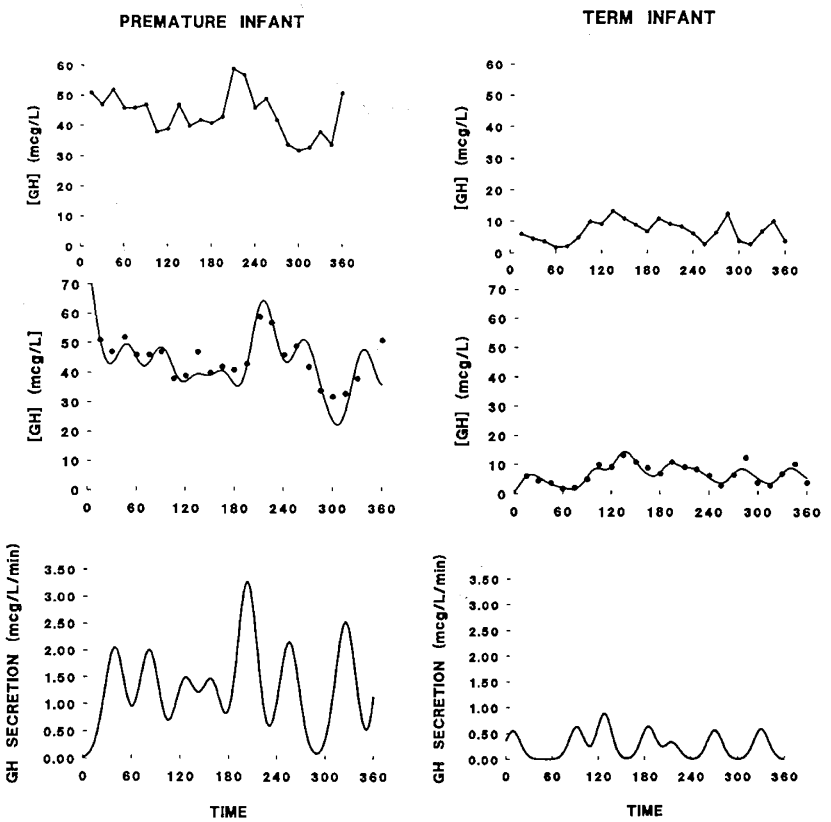

Fig. 3. GH secretory profiles of two representative subjects (a 25-wk gestation premature male infant on the left and a 38-wk term male infant on the right). *Top panel* depicts observed plasma GH concentrations (μg/L) over time (min), plotted using CLUSTER. *Middle panel* shows discrete GH concentrations as above, in addition to reconvolved fit of these data predicted by deconvolution analysis shown by the *continuous line*. *Bottom panel* represents deconvolved secretory bursts over time, which account for observed GH concentrations (secretory rate, μg/L/min *vs* time).

Table 2. *GH secretory burst parameters**

	Premature	Term
Amplitude (μg/L/min)	2.2 ± 0.1†	1.4 ± 0.3
Production rate (μg/L/6 h)	811 ± 173†	283 ± 77
GH mass/burst (μg/L)	106 ± 25†	38 ± 11
Integrated serum [GH] (μg/L)‡	18 100 ± 800	10 200 ± 2 700
Burst frequency (pulses/6 h)	7.8 ± 0.2 (8)	7.7 ± 0.6 (7)
$t_{½}$ (min)	20 ± 4	24 ± 6
Half-duration of burst (min)	45 ± 11	25 ± 4
Mean peak interval (min)	48 ± 2 (45)	48 ± 3 (53)

* Comparison of GH secretory burst parameters (mean ± SEM) between the premature infant and term infant groups. Median values are shown in parentheses for parameters analyzed nonparametrically.

† Statistically significant between-group differences ($p < 0.05$).

‡ [GH], GH concentration.

infants have significantly lower IGF binding protein-3 concentrations than do term infants. Additionally, IGF binding protein-2, which is present in greatest concentration prenatally, and increases with development in the fetal pig (21), may also affect this pathway.

Tanner (22) has suggested an inhibitory influence of IGF-I on GH secretion in general. Decreased IGF-I feedback on the neonatal hypothalamopituitary unit ultimately resulting in elevated circulating GH concentrations in the premature infant may be accounted for by an additional explanation. Specifically, GH traditionally results in an elevation of IGF-I concentrations, yet the opposite is found in premature infants. Exceptions to this rule are also found in several pathophysiologic conditions including Laron-type dwarfism, which is associated with abnormality of the GH receptor (23), and starvation states (24, 25). Relative quantitation of the GH receptor can be indirectly obtained by measurement of GH binding protein, a putative GH receptor degradation product. GH binding protein concentrations are low in human premature infants (26) compared with their term counterparts. These data suggest that the altered GH axis in the premature infant may result primarily from an immaturity of the GH receptor, specifically a lower receptor number.

In summary, we have investigated the pulsatile nature of GH secretion in premature and term infants by frequent blood sampling. Application of deconvolutional modeling to these data has shown that the elevated circulating GH concentrations found in premature infants are a result of increased pulsatile GH secretion, with a greater mass of GH secreted per burst, not decreased GH clearance. In view of the present body of neonatal GH data, we suggest that decreased tissue actions of GH and reduced IGF-I negative feedback may explain the physiologic state of accentuated GH secretion in the premature newborn.

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