Atenolol Enhances Growth Hormone Release to Exogenous Growth Hormone-Releasing Hormone but Fails to Alter Spontaneous Nocturnal Growth Hormone Secretion in Boys with Constitutional Delay of Growth¹

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ABSTRACT. We tested the hypothesis that selective β_1 -adrenergic blockade will enhance growth hormone (GH) secretion in boys with constitutional delay of growth in response to both exogenously administered growth hormone-releasing hormone as well as to endogenous GH-releasing hormone pulsations. The study group comprised eight healthy, short, prepubertal boys ranging from 7 $\frac{1}{2}$ to 15 $\frac{1}{2}$ yr old with bone ages delayed 15 to 42 months. All had demonstrated GH levels of greater than 10 ng/ml following a pharmacologic or physiologic stimulus. During two consecutive nights, blood samples were withdrawn every 20 min for GH determination between 2000 and 0800 h. Immediately after each 0800 h blood withdrawal, 1 μ g/kg of GH-releasing hormone (1-40)-OH was administered intravenously to each subject and blood was withdrawn every 15 min for an additional 2 h. During the day before the second overnight sampling period each subject received atenolol, 25 mg orally, at 1030 and 1600 h to induce β -adrenergic blockade. The six subjects in whom β -adrenergic blockade could be documented had enhanced GH release after GH-releasing hormone administration on the atenolol treatment day both in terms of higher peak GH levels achieved ($p < 0.05$) as well as greater total GH secretion (3916 ± 701 versus 5624 ± 986 ng/ml·min, $p < 0.01$). In contrast, there were no differences in endogenous, unstimulated nocturnal GH pulse characteristics between study and control days. In particular, there were no changes in number of GH pulses, mean 12-h GH concentrations, mean GH pulse height, amount of GH secreted in pulses, mean interpulse GH levels, or total area under the GH versus time curve. (*Pediatr Res* 23: 393-397, 1988)

Abbreviations

GH, growth hormone
GHRH, GH-releasing hormone (1-40)-OH
Sm-C, somatomedin-C
BAB, β -adrenergic blockade
CDG, constitutional delay of growth

Catecholamines play a central role in the physiologic control of pulsatile GH secretion. Accumulating evidence indicates that these neuromodulators influence the pattern of GHRH and somatotropin release inhibiting hormone (somatostatin) secretion from the hypothalamus into the hypophyseal portal system. Stimulation of central α -adrenergic receptors causes GH release, most likely by enhanced GHRH secretion (1-6) whereas β -adrenergic receptors mediate a GH inhibitory signal, possibly by stimulating somatostatin release (7-14). α -Adrenergic agonists are capable of stimulating GH release in man (1-6), an effect which is diminished by phentolamine (3, 6, 7). Particularly well studied is clonidine, an α -adrenergic agonist. The GH-stimulating properties of clonidine have proven clinically useful both for the diagnosis of growth disorders (2, 4) and for stimulation of growth velocity in some children with short stature (15-17). Conversely, administration of β -adrenergic blocking agents enhances GH release in response to a variety of stimuli including insulin-induced hypoglycemia (7, 11), exercise (10), glucagon (13), and GHRH (8, 12, 18) but fails to cause GH release in the absence of such stimuli (1, 7, 8).

Recently we showed that administration of the selective β_1 -adrenergic antagonist, atenolol, enhanced the GH response to multiple doses of exogenous GHRH in children with GH deficiency (18). The ability of atenolol to enhance GH release after a single injection of GHRH has also previously been shown in normal adult volunteers (12). Based on the finding that atenolol increases GH release in response to exogenously administered GHRH, we hypothesized that its administration would also augment GH release in response to endogenous nocturnal GHRH pulsations. To investigate this hypothesis we studied the acute effects of atenolol administration on the characteristics of nocturnal GH pulses in a group of prepubertal boys with CDG.

MATERIALS AND METHODS

Study subjects. The study group comprised eight prepubertal boys with a mild to moderate degree of constitutional delay of growth. Clinical and endocrinologic data for these subjects are given in Table 1. All boys were in otherwise good health and were chosen from our group of patients followed in the University of Virginia Pediatric Endocrinology Clinic. Chronologic ages ranged from 7 $\frac{1}{2}$ to 15 $\frac{1}{2}$ yr (mean $\pm$ SEM, 10.3 ± 1.0) with a mean bone age delay of 25.6 ± 4.0 months (range, 15-42 months). Sm-C concentrations determined at 0600 h on study day 1, ranged from 0.5 to 1.18 U/ml. All subjects had short stature (height SD scores -1.4 to -2.8 range; -2.0 ± 0.2 , mean $\pm$ SEM). Their growth velocities determined over at least 6

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Table 1. Clinical and endocrinologic data on study subjects (prepubertal boys)

Subject	Chronologic age (yr)	Bone age (yr)	Ht (cm)	Ht SDS*	Growth velocity (cm/yr)	Growth velocity SDS*	Sm-C (U/ml)
1	10 ¹ / ₁₂	7 ⁶ / ₁₂	122.2	-2.3	3.0†	-2.9	0.62
2	12 ³ / ₁₂	11 ¹ / ₁₂	135.0	-2.0	4.9	-0.1	1.09
3	10 ⁵ / ₁₂	7 ⁰ / ₁₂	128.4	-1.7	6.2	+1.6	1.18
4	15 ⁰ / ₁₂	11 ¹ / ₁₂	145.0	-2.8	8.1	+3.1	0.83
5	7 ³ / ₁₂	6 ⁶ / ₁₂	110.8	-2.3	6.2	+0.5	1.08
6	7 ² / ₁₂	5 ⁶ / ₁₂	112.9	-1.4	5.8	-0.4	0.50
7	9 ⁷ / ₁₂	7 ⁶ / ₁₂	123.8	-1.7	5.0	-0.3	0.64
8	10 ¹⁰ / ₁₂	9 ⁶ / ₁₂	129.2	-1.9	5.0	-0.1	1.10

* SDS (SD scores) based on chronologic age.

† Growth velocity determined over only 4 months in this subject. The velocities in others were determined over at least 6 months.

months were all within 2 SD for bone age (19) with the exception of subject 1. Subject 1 had a growth velocity that appeared to be normal at the time of study based on a measurement from his private pediatrician. However, during 4 months of measurements in our clinic his growth velocity was only 3.0 cm/yr. He failed to return for all subsequent appointments after the 4-month measurement so we do not have growth data at 6 months or later.

All subjects achieved serum GH levels of more than 10 ng/ml in response to a standard pharmacologic or physiologic stimulus. A complete blood count with differential, erythrocyte sedimentation rate, serum chemistry profile, and liver function tests were obtained and judged acceptable for age in all subjects. An ECG was performed and was normal in each boy before his participation. Bone ages were determined by the method of Greulich and Pyle (20) by one of us (P.M.M.) from x-rays of the left hand and wrist.

Study design. After obtaining informed consent from a parent and assent from each boy the subjects were admitted to the University of Virginia Clinical Research Center for approximately 48 h. An intravenous catheter was placed in an upper extremity vein at 1900 h on the first study night. Between 2000 and 0800 h blood was withdrawn every 20 min for GH determinations. At 0831 h an intravenous injection of GHRH (1-40)-OH at a dose of 1 µg/kg was administered to each subject and blood was withdrawn every 15 min for an additional 2 h thereafter. Supine and upright blood pressure and pulse were obtained before and immediately after the GH sampling period. However, during the entire 14.5-h (2000–1030 h) withdrawal period the subjects remained recumbent (with bathroom use as needed) and blood pressure and pulse were monitored hourly.

On the day of the second overnight study, each subject received atenolol in a dose of 25 mg orally at 1030 h and again at 1600 h. GH sampling and GHRH stimulation then proceeded exactly as described for the first night except that some subjects retained their intravenous catheter from the previous night.

Assays. All serum samples were analyzed in duplicate for GH concentration using Nichols Institute Diagnostic human GH immunoradiometric assay kits (San Juan Capistrano, CA). The assay sensitivity was 0.5 ng/ml and the inter- and intraassay coefficients of variation at 4.5 ng/ml were 7.1 and 5.5%. Sm-C determinations were measured by radioimmunoassay as previously described (21).

Pulse analysis. We applied Cluster analysis (22) to the hormone concentration series from all study periods to identify significant excursions (pulses) of hormone concentration. Briefly, Cluster is a computer based pulse detection algorithm which defines a "pulse" as a significant increase followed by a significant decrease in hormone concentration. The program scans the data series in both directions and performs *t*-comparisons between consecutive groups of hormone values ("clusters") to identify all significant increases and decreases. "Significance" is dependent on the variance present within the actual data set. The various *t*-statistics and cluster sizes used are determined by the user in a

manner that constrains the false-positive (type I error) detection rate to a desired level.

We chose our parameters to constrain the false-positive detection rate to less than 5% while minimizing our false-negative (type II error) rate. This was accomplished by analyzing GH concentration data from eight healthy prepubertal subjects (including four who participated in the present study) obtained every 20 min over 24 h using a variety of cluster sizes and *t*-statistics known to be associated with a false-positive detection rate of less than 5% under the conditions present herein (Veldhuis JD, personal communication). The combination of these parameters resulting in the greatest number of pulses detected was, therefore, associated with the lowest false-negative rate. This combination (a one point by one point cluster size and *t*-statistic of 2.32 to test for both significant increases and decreases) was then used for all GH pulse analysis herein.

Mean nocturnal GH concentrations were computed from all 36 GH values between 2000 and 0800 h. Total nocturnal GH secretion is expressed as area under the GH *versus* time curve as determined by trapezoidal reconstruction.

Statistical analysis. Comparisons of data regarding GH secretion on the control day and the day atenolol was administered were performed using the paired Student's *t* test with the exception of peak GH responses to GHRH. For the latter the nonparametric method of Wilcoxon signed rank test was used since the data were not normally distributed. Results are expressed as mean ± SEM. We accepted statistical significance at a level of *p* < 0.05. Data storage and analysis were accomplished in part through use of the University of Virginia GCRC CLINFO laboratory.

RESULTS

The presence of systemic BAB was assumed when there was loss of a significant tachycardic response to upright posture after atenolol administration. This was documented in six of the eight study subjects (subjects 1–6) (Table 1). We could detect no clinical differences between these six and the two who did not have evidence of BAB at the end of the study. We purposely did not attempt to determine the cardiovascular response to postural changes during the period of blood withdrawal to avoid the possibility that the expected catecholamine release in the presence of BAB might result in GH secretion via unopposed α -adrenergic stimulation (23). Thus, we cannot be certain whether subjects 7 and 8 had evidence of BAB earlier in the study period which had waned by the end.

All six subjects who unequivocally achieved BAB showed enhanced GH release in response to intravenous GHRH on the atenolol treatment day when compared to the control day (Figs. 1 and 2). This enhancement took the form of both higher peak GH levels achieved (*p* < 0.05) and greater total GH secretion during the 2-h post-GHRH sampling period (3916 ± 701 versus 5624 ± 986 ng/ml·min, *p* < 0.01). There were no differences in

GH levels during the 90-min baseline sampling period immediately before the GHRH bolus ($p = 0.19$). Subjects 7 and 8, who did not have evidence of BAB, did not show augmented GH release on the atenolol day (data not shown).

In contrast, there were no differences in the pulse characteristics of nocturnal GH secretion between study and control days (Table 2). Specifically, no changes were found in the number of significant increases in GH concentration (GH pulses), mean 12-h GH concentration, mean GH pulse height, amount of GH secreted in pulses, mean interpulse (trough) GH levels, or total nocturnal GH secretion. There were no significant side effects of atenolol reported by any of the subjects.

DISCUSSION

Recent reports have shown that atenolol administration enhances GH release in response to exogenous GHRH in normal

adults (12) and in children with GH deficiency (18). These observations were a logical extension of earlier studies demonstrating the ability of the nonselective β -adrenergic antagonist, propranolol, to augment the GH secretory response to a wide variety of stimuli (7, 8, 10, 11, 13). Although all studies but one (3) failed to show an effect of β -adrenergic antagonists on endogenous GH secretion in the absence of other stimuli, none had sampling periods that included a significant number of spontaneous GH pulses. It is probable that spontaneous GH pulsations in man, as in the rat (14, 24, 25), are under dual control of hypothalamic GHRH and somatostatin. We thus hypothesized that atenolol administration would also augment spontaneous GH secretion. A 12-h nocturnal sampling period was chosen to maximize the detection of a number of spontaneous GH pulses in each subject. It should be noted that our GH values were obtained using an immunoradiometric assay and the absolute values should not be directly compared to those of other inves-

Fig. 1. GH concentration data (mean $\pm$ SEM) from six boys with CDG before (open circles) and after (closed circles) BAB induced by atenolol administration. Ninety min into the sampling period, a $1 \mu\text{g/kg}$ intravenous bolus of GHRH (1-40)-OH was administered to each subject. There was significantly more total GH secretion after GHRH (3916 ± 701 versus $5624 \pm 986 \text{ ng/ml} \cdot \text{min}$, $p < 0.01$) in the presence of BAB.

Fig. 2. Individual GH responses to GHRH ($1 \mu\text{g/kg}$ iv bolus) in six boys with CDG. A, individual peak GH levels achieved in response to GHRH before and after BAB induced by atenolol. B, total GH secreted (area under the GH versus time curve) during the 2 h after GHRH administration in each subject before and after atenolol administration.

Table 2. Spontaneous nocturnal GH secretory characteristics of six boys with CDG before (control) and after BAB induced by atenolol administration

Subject	Study day	Mean GH concentration (ng/ml)	Total 12-h GH secretion (ng/ml $\cdot$ min)	No. GH pulses	Mean GH pulse amplitude (ng/ml)	Mean pulse area (ng/ml $\cdot$ min)	Mean interpulse GH concentration (ng/ml)
1	Control	10.9	7610	4	28.0	1430	8.1
	Atenolol	6.5	4510	6	11.2	546	2.7
2	Control	6.2	4470	6	15.6	486	6.7
	Atenolol	8.6	6210	5	25.8	1208	9.6
3	Control	8.8	6170	5	21.1	855	8.0
	Atenolol	4.7	3320	4	12.5	568	1.6
4	Control	6.0	4310	5	9.3	675	4.5
	Atenolol	4.1	2920	5	7.3	342	4.5
5	Control	9.9	7070	6	23.2	875	7.1
	Atenolol	6.1	4310	6	16.2	565	3.9
6	Control	5.5	3960	4	23.0	730	4.9
	Atenolol	5.2	3740	7	10.5	401	4.3
All subjects (mean $\pm$ SEM)	Control	7.9 $\pm$ 0.9	5600 $\pm$ 640	5.0 $\pm$ 0.4	20.0 $\pm$ 2.7	842 $\pm$ 131	6.6 $\pm$ 0.6
	Atenolol	5.9 $\pm$ 0.7	4170 $\pm$ 480	5.5 $\pm$ 0.4	13.9 $\pm$ 2.7	605 $\pm$ 125	4.4 $\pm$ 1.1
(Significance level, control vs atenolol)		($p = 0.12$)	($p = 0.13$)	($p = 0.49$)	($p = 0.17$)	($p = 0.32$)	($p = 0.21$)

tigators determined by polyclonal radioimmunoassays that may detect different epitopes on the GH molecule.

As expected, atenolol-induced β -adrenergic blockade enhanced GH release after exogenous GHRH in our subjects with constitutional delay of growth. Although our data are the first to show augmented GH release for a selective β_1 -adrenergic antagonist in this population, the results are similar to those of Chihara *et al.* (8) using the nonselective β -adrenergic blocker, propranolol, in a similar group of children (8) and those of Mauras *et al.* (12) in normal men. Several lines of evidence indicate that this GH secretory enhancing effect of β -adrenoreceptor antagonists is due to their interference with hypothalamic somatostatin activity. First, these agents lack the inherent ability to stimulate GH secretion, although they increase the potency of other GH secretagogues (7, 8, 10–13). Second, β -adrenergic agonists have a direct stimulatory effect on GH secretion from rat anterior pituitary cells *in vitro* (26–29), but do not affect subsequent GHRH-stimulated GH release (Krieg RJ, personal communication). In contrast, isoproterenol infusion to intact rats predominantly inhibits subsequent GHRH stimulation, an effect abolished by prior administration of an antiserum to SRIH (Krieg RJ, personal communication). Third, direct application of isoproterenol to slices of rat brain from the amygdaloid complex and preoptic anterior hypothalamic area is capable of stimulating somatostatin release (30). Fourth, β -adrenergic stimulation causes somatostatin release from pancreatic islets (31).

It has been proposed (24) that the observed ultradian rhythm in GH secretion in the rat results from a tonic secretion of both GHRH and somatostatin from the hypothalamus into the hypophyseal portal blood with superimposed, reciprocal, periodic secretory surges of the two peptides. This is supported by the findings of Plotsky and Vale (32) using direct measurement of GHRH and somatostatin levels in the hypophyseal portal circulation. In addition, administration of antiserum to somatostatin elevates trough GH levels in the rat but does not affect GH pulse amplitude (14). These data indicate that somatostatin is responsible for the GH trough levels. In this regard our findings are somewhat surprising. If it is true that BAB inhibits somatostatin secretion, and if hypothalamic control of the pulsatile pattern of GH secretion in the human is analogous to the rat, then it would be expected that the interpulse trough levels in our subjects would have been higher on the atenolol treatment day. We did not find such an effect (Table 2). This elevation would also be expected to affect total 12-h GH secretion (as area under the GH *versus* time curve) and mean 12-h GH concentration but again no differences were found (Table 2). The absence of this anticipated effect may indicate that, in contrast to the rat, hypothalamic somatostatin does not serve a primary role in determining the trough GH levels in our subjects. It is also possible that if we had studied a full 24-h period an effect of atenolol would have emerged. Alternatively, it may be that due to inter- and intraassay variability as well as variability among this small group of subjects we were unable to detect such changes with certainty even if they existed (type II error).

Our results indicate that, in contrast to α -adrenergic agonists (15–17), β -adrenergic antagonists may not have growth promoting therapeutic potential when used alone in children with constitutional delay of growth although only a full therapeutic trial would answer this question with certainty. However, as we have previously suggested (18) they may be useful as adjunctive therapy in combination with other agents, such as GHRH, which stimulate endogenous GH release.

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