

Growth Hormone Secretion in Children and Adolescents at High Risk for Major Depressive Disorder

Boris Birmaher, MD; Ronald E. Dahl, MD; Douglas E. Williamson, PhD; James M. Perel, PhD; David A. Brent, MD; David A. Axelson, MD; Joan Kaufman, PhD; Lorah D. Dorn, PhD; Stacy Stull, MS; Uma Rao, MD; Neal D. Ryan, MD

Background: Decreased growth hormone (GH) response to pharmacologic stimulation has been found in children and adolescents during an episode of major depressive disorder and after recovery. In this study, we sought to determine whether GH secretion is similarly altered in children and adolescents who had never experienced depression but were at high risk of developing depression.

Methods: Subjects were 8 through 16 years of age and selected for high- and low-risk status according to familial loading for mood disorders. Sixty-four high-risk and 55 low-risk healthy subjects participated in the study, which assessed the following GH measures: (1) GH before growth hormone-releasing hormone (GHRH) infusion, every 15 minutes for 30 minutes; (2) GH response after intravenous infusion of GHRH (0.1 µg/kg), every 15 minutes for 90 minutes; and (3) nocturnal GH every 20 minutes from 9 PM until morning awakening.

Results: After stimulation with GHRH, the high-risk subjects secreted significantly less GH compared with the low-risk healthy controls (effect sizes for mean and peak GH, 0.52 [$P=.007$] and 0.40 [$P=.04$], respectively). In contrast, there were no between-group differences in the pre-GHRH and nocturnal GH secretion levels. Exposure to recent stressors was not associated with GH secretion.

Conclusions: Taken together with previous evidence of decreased GH after GHRH infusion in acutely depressed and recovered children, these results indicate that the decreased GH response found in high-risk subjects may represent a trait marker for depression in children and adolescents.

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DECREASED GROWTH hormone (GH) secretion in response to pharmacologic stimulation with various substances has been reported in children and adolescents with major depressive disorder (MDD).^{1,2} Similarly, decreased GH secretion after stimulation has been reported in most studies of adults with MDD.^{3,4} Overall, the results of these studies are consistent in suggesting that GH secretion is decreased after pharmacologic stimulation among depressed subjects across the age span. In contrast, studies^{1,3-9} evaluating the 24-hour baseline or nocturnal secretion of GH in acutely depressed children, adolescents, and adults have yielded inconsistent results.

Since these pharmacologic stimulation studies were conducted while the subjects were depressed, it is unclear whether the decreased GH response is a function of the depressive condition or also can be found in susceptible individuals prior to the onset of depression. Although a few studies in children and adolescents^{2,10,11} and

adults^{7,12-16} reported persistently abnormal GH secretion patterns after recovery from a depressive episode, these findings could be secondary to the effects of a prior depressive episode (a "scar" effect). What has yet to be examined is whether GH is decreased before the onset of the depression, consistent with its role as a trait marker. Therefore, we evaluated the GH secretion patterns before and after the administration of growth hormone-releasing hormone (GHRH) in children and adolescents who had never been depressed but were at high risk of developing depression. This group was chosen because the best predictor of future development of MDD is a familial history of mood disorders.^{17,18} Moreover, this strategy has been successfully used to demonstrate the presence of other biological alterations in subjects who had never been depressed but were at high risk for depression.¹⁹⁻²⁴

Based on the literature,^{1,2,17,19-24} we hypothesized that subjects at high risk of developing MDD would show a decreased GH response to GHRH stimulation compared with low-risk healthy controls. In addition,

From the Department of Psychiatry, University of Pittsburgh School of Medicine, Western Psychiatric Institute and Clinic, Pittsburgh, Pa.

SUBJECTS AND METHODS

SUBJECTS

Sixty-four high-risk and 55 low-risk healthy children and adolescents (mean [SD] age, 10.9 ± 1.7 years) (18 subjects [15%] of the total sample were younger than 12 years) were recruited via advertisement and through parents with mood disorders who attended the outpatient mood disorders clinic. The high-risk subjects were slightly younger, had lower Tanner stage scores, and had lower socioeconomic class compared with the low-risk healthy subjects (**Table 1**). There were no between-group differences in sex, ethnicity, and body mass index (BMI).

Before participating in the study, subjects and their parents were required to sign assents and informed consents, respectively, in compliance with the requirements of the University of Pittsburgh Institutional Review Board.

High-risk subjects were required to have at least 1 first-degree and at least 1 second-degree relative with a history of childhood-onset, recurrent, bipolar, or psychotic depression. In addition, the high-risk subjects were required never to have had a lifetime episode of any mood disorder.

Low-risk healthy subjects were required to have had no lifetime psychiatric disorders; no first-degree relatives with a lifetime episode of any mood or psychotic disorder; no second-degree relatives with a lifetime history of childhood-onset, recurrent, psychotic, or bipolar depression or schizo-affective or schizophrenic disorder; and no more than 20% of second-degree relatives with a lifetime single episode of MDD.

Other exclusionary criteria for both high-risk and low-risk healthy subjects included the use of any medication with central nervous system effects within the past 2 weeks (no subjects were taking serotonin reuptake inhibitors, stimulants, or other antidepressant medications), significant medical illness, extreme obesity (weight greater than

150% of ideal body weight) or growth failure (height or weight below the third percentile), IQ of 70 or less, and inordinate fear of intravenous needles.

MEASUREMENTS

Subjects' lifetime DSM-III-R²⁹ psychiatric symptoms were assessed using the Schedule for Affective Disorders and Schizophrenia for School Aged Children—Epidemiological Version,³⁰ with both the child and parent(s) or guardian(s) serving as informants. Dimensional assessment of symptoms were ascertained using the Child Behavior Checklist.³¹

To determine familial loading for mood disorders, first- and second-degree relatives were interviewed using the Schedule for Affective Disorders and Schizophrenia for School Aged Children—Epidemiological Version for relatives aged 6 to 18 years and the Schedule for Affective Disorders and Schizophrenia—Lifetime Version³² for adult relatives. Adult first- and second-degree relatives unavailable for direct interview were assessed indirectly using a modified version of the Family History Interview,³³ with the child's parent(s) and other available relatives serving as informant(s). All lifetime diagnoses among relatives were made according to the best-estimate procedure³⁴ based on DSM-III-R criteria. All interviews were carried out by trained research clinicians blind to the subject's clinical status under the supervision of the investigators. Interrater reliability for all diagnoses was good ($\kappa \geq 0.70$). Socioeconomic status was measured using the Hollingshead 4-factor index.³⁵

Negative life events that occurred during the year before the interview were assessed using a modified version of the Coddington's Life Events Record.³⁶ Events were classified into those that were dependent on (eg, arguments) or independent (eg, death of a relative) of the child's behavior.³⁶ Current parent-child, peer-child, and mother-father relationships (warmth, tension) and child's school performance were evaluated using the Psychosocial Schedule.³⁷

tion, since offspring of depressed parents are exposed to more stressful environments when compared with offspring of healthy controls^{17,18} and since it has been shown that stress may affect GH secretion in humans²⁵⁻²⁷ and animals,^{2,28} we explored the effects of recent stresses on GH secretion.

RESULTS

All subjects participated in the GHRH stimulation probe. However, due to methodologic problems (eg, intravenous catheter problems), only 57 high-risk and 48 low-risk healthy subjects were included for the nocturnal GH secretion analyses. There were no significant demographic, Tanner stage, and BMI differences between subjects whose data were and were not included in the nocturnal GH studies.

Within the high-risk group, 21 subjects (33%) had 1 or more of the following lifetime nonaffective psychiatric disorders: oppositional defiant disorder (10 subjects), attention-deficit/hyperactive disorder (13 subjects), or separation anxiety disorder (2 subjects with disruptive disorder). Compared with the high-risk sub-

jects without psychiatric disorders, the high-risk subjects with psychiatric disorders had lower socioeconomic status (38.7 ± 10.8 [class III]³⁵ vs 45.6 ± 12.9 [class IV]³⁵, $t_{62} = 2.10$, $P = .04$) and were more likely to be African American (14.3% vs 0.0%, Fisher exact test, $P = .03$). There were no age, sex, Tanner stage, or BMI differences between the high-risk subjects with or without psychiatric disorders. Therefore, the analyses of the results were performed with and without the subjects with nonaffective psychiatric disorders.

There were no significant differences in the GH levels between the high-risk and low-risk healthy subjects before the administration of GHRH (**Table 2**). After the administration of GHRH, the high-risk and low-risk healthy controls showed increased secretion of GH, but the magnitude of the increase was markedly less in the high-risk group (**Figure**, Table 2). Adjusting for age, sex, BMI, Tanner stage, and their interactions, the high-risk subjects still showed significantly lower mean and peak GH than the low-risk healthy controls (effect sizes for mean and peak GH levels, 0.52 [$P = .007$] and 0.40 [$P = .04$], respectively). These results were unchanged after controlling for the pre-GHRH baseline GH levels.

Tanner stage of sexual development was assessed by the investigators through physical examination using the method described by Marshall and Tanner.^{38,39} The percentage of agreement for Tanner classification was 90% or higher. For purposes of the analyses, Tanner stage was dichotomized as prepubertal (I/II) or postpubertal (\geq III). The BMI was calculated as the weight in kilograms divided by the square of height in meters.

BIOLOGICAL PROCEDURES AND ASSAYS

This study was part of a comprehensive psychobiological investigation of childhood MDD initiated in 1987 by the late Joaquim Puig-Antich, MD, in which other baseline hormones (eg, cortisol), hormonal challenge probes (eg, cortisol and prolactin responses after the administration of 5-hydroxytryptophan), and sleep electroencephalogram were measured with the method described previously.^{1,2,6,19,40} Briefly, after admission to the Child Sleep Laboratory around 5 PM, an intravenous catheter was placed in an antecubital vein and kept open through a constant drip of isotonic sodium chloride solution. During the first night ("adaptation night"), the catheter was left in place, but no blood was drawn. The next morning, around 9 AM, 3 baseline blood samples for GH were obtained every 15 minutes. Thereafter, subjects were given 1.0 μ g/kg of GHRH intravenously for 2 minutes, and blood samples for GH were obtained every 15 minutes for 90 minutes. There were no significant side effects of any kind related to this probe. On the second night, plasma samples for nocturnal baseline GH secretion were drawn every 20 minutes from 9 PM until the subject awoke the following morning.

Blood samples were collected in EDTA tubes and centrifuged, and plasma was stored at -80°C until assayed. The GH radioimmunoassay variability is described elsewhere.^{1,2,6} Somatostatin was measured only in a subgroup of subjects (high risk, 18; low risk and healthy, 19), using

methods similar to Arimura and colleagues,⁴¹ on the pooled blood samples collected during sleep. The mean interassay variation of this latter assay was 10.7% coefficient of variation at a spiked value of 50 g/L (range, 42.4-62.0 g/L).

STATISTICAL ANALYSIS

The high-risk and low-risk healthy groups were compared using analysis of variance (ANOVA), χ^2 test, and Fisher exact tests as appropriate. The problem of missing data was minimal, with only 0.3% missing. Measurements were examined for normality using the test of Shapiro and the Wilks W statistic. Nonnormally distributed data were normalized using logarithmic transformation. There were no outliers. ANOVA was used to examine the nocturnal GH secretion, the mean GH levels before GHRH administration, and the peak and mean GH levels after GHRH administration. Regression analyses were used to test effects of group status on GH secretion after the administration of GHRH, adjusting for pre-GHRH GH baseline levels, age, sex, BMI, Tanner stage, socioeconomic status, and their interactions. Correlations between cortisol, somatostatin, family loading for mood disorders, and negative events with GH secretion were analyzed using Pearson or Spearman correlations. All values are reported as mean \pm SD. All *P* values are based on 2-tailed tests with a 2-tailed α of .05.

Before analyzing the between-group differences for GH secretion, the correlations among demographic characteristics, Tanner stage, BMI, and GH secretion patterns were examined. Both age and BMI were negatively correlated with GH secretion after GHRH administration ($r = -0.16$ to -0.41 , $P \leq .05$). Both BMI and Tanner stage were negatively correlated with nocturnal GH secretion ($r = -0.35$, $P = .001$; $r = -0.21$, $P = .03$, respectively). Therefore, these characteristics, as well as sex, were controlled for in all statistical analyses.

Table 1. Characteristics of High-Risk and Low-Risk Healthy Control Subjects*

Characteristics	High Risk (n = 64)	Low Risk (n = 55)	Statistic	<i>P</i>
Age, mean \pm SD, y	10.3 \pm 1.6	11.2 \pm 1.8	$t_{117} = 2.86$.005
Sex, F/M	23/41	22/33	$\chi^2 = 0.07$.80
Ethnicity, white/nonwhite	61/3	49/6	Fisher exact test	.30
SES, mean \pm SD	43.1 \pm 12.5 (Class IV)	47.8 \pm 11.1 (Class IV)	$t_{113} = 2.09$.04
BMI, mean \pm SD, kg/m ²	18.2 \pm 2.8	18.8 \pm 4.1	$t_{117} = 0.67$.50
Tanner stage				
Breast/genital (I-II/ \geq III)	59/5	42/13	Fisher exact test	.02
Pubic hair (I-II/ \geq III)	59/5	40/15	Fisher exact test	.006

*SES indicates socioeconomic status (Hollingshead³⁶); BMI, body mass index.

To evaluate whether the high-risk subjects with psychiatric disorders accounted for the between-group differences, we repeated these analyses, excluding the high-risk subjects with psychiatric disorders. High-risk subjects without psychiatric disorders continued to show significantly lower GH response to GHRH infusion compared with the low-risk healthy subjects (adjusted mean, 7.9 \pm 1.3 μ g/L vs 12.5 \pm 1.2 μ g/L, $t_{113} = 2.75$, $P = .007$, effect size = 0.58;

adjusted peak, 13.8 \pm 2.2 μ g/L vs 20.2 \pm 1.9 μ g/L, $t_{113} = 2.23$, $P = .03$, effect size = 0.46). Moreover, there were no significant differences in any GH variable between the high-risk subjects with and without psychiatric disorders.

There were no significant group differences between the high-risk and low-risk healthy subjects in the nocturnal mean GH secretion level, even after adjusting for the effects of age, sex, BMI, and Tanner stage (Table

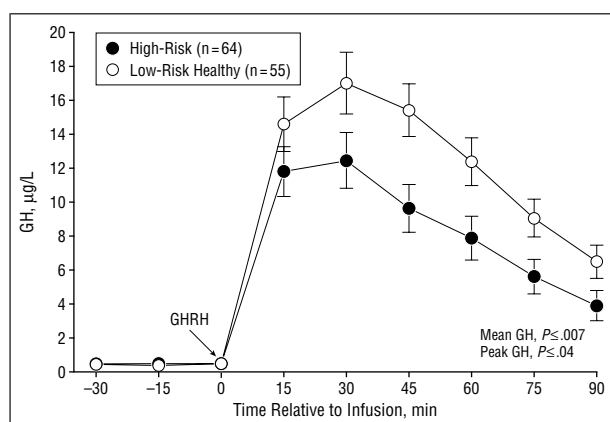
Table 2. Growth Hormone (GH) After Growth Hormone-Releasing Hormone (GHRH) and Nocturnal GH Secretion in High-Risk and Low-Risk Healthy Subjects*

	High Risk	Low Risk	Statistic†	P
GH secretion after GHRH				
Baseline GH pre-GHRH, µg/L‡	0.5 ± 0.7	0.4 ± 0.4	$t_{113} = 0.41$.68
Post-GHRH, µg/L	8.9 ± 8.1	12.2 ± 10.0	$t_{113} = 2.74$.007
Peak, µg/L	15.8 ± 13.7	19.5 ± 15.7	$t_{113} = 2.09$.04
Nocturnal GH secretion				
Nocturnal GH, µg/L	3.3 ± 2.3	3.6 ± 3.4	$t_{99} = 0.27$.78

*Results are presented as mean ± SD. For GH secretion after GHRH, sample sizes were 64 high-risk and 55 low-risk subjects. For nocturnal GH secretion, sample sizes were 57 high-risk subjects and 48 low-risk subjects.

†Statistical tests were performed on the logarithm of the mean values adjusted for age, sex, body mass index, and Tanner stage.

‡Before GHRH secretion.



Growth hormone (GH) response to growth hormone-releasing hormone (GHRH).

2). Since most studies of MDD across ages have reported alterations in GH during the first 3 hours of sleep,^{7,16,42,43} we restricted our analyses of GH secretion of the high-risk vs low-risk healthy groups to this period and failed to find any differences.

There were no significant differences in the nocturnal GH secretion among the high-risk subjects without psychiatric disorders (n=39), the high-risk subjects with psychiatric disorders (n=18), and the low-risk healthy controls (n=48) (3.6 ± 2.7 µg/L vs 3.2 ± 2.6 µg/L vs 3.5 ± 2.7 µg/L, respectively; $F_{2,102} = 0.93$, $P = .4$).

There were no significant correlations between dimensional measures of anxiety and depression (measured by the Child Behavior Checklist) and GH secretion patterns ($\rho = 0.03-0.14$, $P = .23-.76$).

Since somatostatin and cortisol inhibit the release of GH,⁴⁴ we explored the effects of these hormones on GH variables. Somatostatin showed a nonsignificant negative correlation with nocturnal GH secretion ($\rho = -0.16$, $P = .33$) and, contrary to our expectations, was positively correlated with the mean and peak GH secretion after GHRH ($r = 0.44$ [$P = .003$] and $r = 0.37$ [$P = .01$], respectively). In contrast, no significant correlations were found between any GH variables and cortisol secretion ($\rho = -0.10$ to 0.16 , $P = .2-.03$).

There were no significant correlations among the total, independent, and dependent negative life events and family and peer relationships with the GH measurements ($\rho = -0.13$ to 0.05 , $P = .11-.5$). There were no significant differences in GH secretion between subjects living with both parents compared with those living with only 1 parent ($P = .14-.97$).

There were no significant associations between the family loading for anxiety disorders and any GH variable (for the mean and peak GH response to GHRH, $F_{1,114} = 0.98$ [$P = .32$] and 0.28 [$P = .6$], respectively). By definition, the high-risk subjects had high family loading for lifetime mood disorders. Therefore, the overall effects of family loading for mood disorders could not be examined. However, we were able to explore the effects of living with a mother with lifetime MDD (n=52) vs no MDD (n=13), a father with lifetime MDD (n=25) vs no MDD (n=40), and living with both parents with MDD (n=20) vs no parents with lifetime MDD (n=8) within the high-risk subjects. No significant findings for any GH variable were found based on parental lifetime mood disorders.

COMMENT

In this study, we found that after stimulation with GHRH children and adolescents at high risk of developing MDD secreted significantly less GH compared with the low-risk healthy controls. There were no between-group differences in the baseline GH secretion levels before GHRH administration and nocturnal GH secretion. Also, there were no effects of cortisol, somatostatin, family loading for anxiety disorders, recent environmental stressors, and living with 1 or both parent(s) on any GH measurement. However, high-risk children and adolescents showed a similar degree of blunted GH response to GHRH to already depressed children and adolescents also studied in our laboratory² (mean GH response, 8.6 ± 1.1 µg/L vs 8.7 ± 0.9 µg/L; peak GH response, 15.2 ± 1.8 µg/L vs 13.8 ± 1.4 µg/L). These findings, together with the decreased GH levels after GHRH administration found in acutely depressed patients across the age span¹⁻⁴ and after recovery from depression,^{2,7,10-16} suggest that the dysregulation of the GH response to GHRH might be a trait marker that antedates the onset of a depressive episode. To prove this hypothesis, longitudinal clinical follow-up of the high-risk subjects with low and normal GH responses to GHRH is warranted.

Before considering the implications of this study, it is important to emphasize that our results need to be considered in light of the following limitations. Because only 15% of the sample were adolescents, our results pertain mainly to prepubertal children. The instruments used to evaluate the effects of environmental stressors on the GH secretion may not have been sufficiently sensitive^{27,36} and only assessed recent stressors. Finally, peripheral measures of somatostatin and cortisol do not necessarily reflect the activity of these substances in the brain.

The mechanisms by which the GH response to GHRH is decreased in children and adolescents at high risk of developing depression are not clear. The neurotransmitter systems that have been associated with the

pathogenesis of MDD^{17,40} have also been implicated, at least in part, in the regulation of GH^{28,44-46} and the pathogenesis of depression-like symptoms in animals.^{28,47-50} Studies in children^{25,26,51,52} and both young and mature animals^{44,53-58} exposed to stress have shown abnormal basal GH secretion and decreased GH secretion in response to stimulation that appear to be partially mediated by central serotonergic and noradrenergic mechanisms.^{28,44,46,50,56-58} In contrast with the persistent reduction in GH secretion after stimulation found in subjects who had recovered from depression across the life span,^{2,7,10-16} the biological changes triggered by stress appear to be reversible when the stress is removed (eg, the child is placed in a supportive environment^{25,26,59} or the animal is returned to the mother^{28,46,50,59,60}) or in animals when antidepressants have been administered.^{47,48,61,62} However, some animals appear to show long-term changes in behavior and neuroendocrine response to exposure to early stresses into adulthood,^{28,53,62} which may, in part, be genetically mediated.^{53,63} In our study, we did not find any effects of recent stresses on the secretion of GH, but it is possible that the high-risk subjects may have been exposed to events that occurred before the time in which the stresses were measured in this study (eg, abuse).

Other studies have also shown that infants, children, and adolescents who had never been depressed but who are at high risk of developing MDD present biological abnormalities,¹⁹⁻²⁴ including changes in cortisol and prolactin secretion after the administration of 5-hydroxytryptophan,¹⁹ similar sleep architecture abnormalities as their depressed parents,²² and left-right brain frontal hemisphere asymmetry on their electroencephalograms.^{20,21,24} Also, adult subjects without prior depressive episodes but with a family history of MDD have been reported to have a greater worsening in mood after tryptophan depletion compared with those without positive family histories,⁶⁴ low cerebrospinal fluid 5-hydroxyindoleacetic acid levels,^{65,66} altered hypothalamic-pituitary-adrenal responses,²³ and sleep electroencephalographic abnormalities.⁶⁷ Some of these biological abnormalities appear to be markers not only for the risk to develop depression but also for recurrences of depression among adolescents⁶⁸ and adults,^{69,70} emphasizing the importance of biological studies in populations at high risk of developing psychiatric disorders.

In summary, children and adolescents at high risk for depression showed decreased GH secretion after GHRH administration compared with low-risk healthy controls, which parallels the findings among children and adolescents with an acute episode of MDD and after recovery.^{1,2,10,11} The results of this study suggest that decreased GH response to GHRH may be a trait marker for MDD and that the mechanisms that control the secretion of GH may be already altered before the first depressive episode. Ongoing follow-up of subjects included in this study will help clarify whether decreased GH response to GHRH, maturational development, and ongoing exposure to stress separately or together predict the development of first-onset MDD. Differentiating between a genetic basis for this trait vs a marker of early stress in these families warrants further study.

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Corresponding author: Boris Birmaher, MD, Western Psychiatric Institute and Clinic, 3811 O'Hara St, Pittsburgh, PA 15213 (e-mail: birmaherb@msx.upmc.edu).

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