Low Growth Hormone Response to Growth Hormone–Releasing Hormone in Child Depression

Ronald E. Dahl, Boris Birmaher, Douglas E. Williamson, Lorah Dorn, James Perel, Joan Kaufman, David A. Brent, David A. Axelson, and Neal D. Ryan

Background: This study examined growth hormone (GH) response to growth hormone–releasing hormone (GHRH) in a large sample of depressed children compared with normal control children. Within-subject comparisons were also performed in control subjects to examine test–retest reliability and in depressed children comparing episode versus clinical recovery.

Methods: The sample included depressed children (n = 82) and normal control children (n = 55) group-matched for age, gender, and pubertal status; the mean ages were 11.2 ± 1.7 and 11.2 ± 1.8 years, respectively. We gave GHRH (0.1 mcg/kg) at 9 AM, and serum GH levels were determined every 15 min from 230 min through 190 min of the GHRH infusion. A subgroup of normal control subjects (n = 11) repeated the protocol for test–retest reliability within a 2-month interval. A subgroup of depressed children (n = 20) were restudied off all medications following full clinical remission from depression.

Results: The mean GH response to GHRH was significantly lower in the depressed group (8.7 ng/mL ± SEM 0.9) compared with normal control children [12.2 ng/mL ± SEM 1.3; t(135) = 2.59, p = .01 effect size 0.44]. The test–retest reliability of GH response to GHRH was stable (intraclass correlation = .93 for mean post-GH). The GH response to GHRH remained low in subjects restudied during clinical remission from depression.

Conclusions: Depressed children show low GH response to GHRH. The measure appears to be reliable, and the low GH response continues following clinical remission. Further studies are needed to explore the mechanism and relative specificity of this finding. Biol Psychiatry 2000; 48:981–988 © 2000 Society of Biological Psychiatry

Key Words: Depression, growth hormone, growth hormone–releasing hormone, development, children, adolescents

Introduction

Progress in understanding affective disorders over the past decade increasingly has focused attention on questions of maturational influences on biological systems of interest. There has been considerable interest in 1) the effects of early adverse experiences on later expression of affective dysregulation, 2) the increasing rates of depression during adolescent development, 3) the emergence of gender differences in rates of depression during adolescent development, and 4) changes across childhood, adolescence, adulthood, and geriatrics in specific domains, such as symptom profile, clinical course, genetic influences, and treatment response. Broadly speaking, this work has yielded some areas of maturational continuity, as well as areas of developmental variation (Angold et al 1998; Birmaher et al 1996a, 1996b; Garber et al 1993; Harrington et al 1994; Kovacs 1996; Puig-Antich et al 1993; Rao et al 1995; Ryan et al 1987).

This theme of both similarities and differences across child, adolescent, and adult depression also has been evident in psychobiologic studies. For example, HPA-axis alterations and electroencephalogram (EEG) sleep changes associated with depression show considerable maturational variance (Dahl 1996; Dahl et al 1991a, 1991b, 1992, 1994, 1996; Emslie et al 1994). In contrast, low growth hormone (GH) response to pharmacologic challenges seen in association with depression has shown relative continuity across development, including depressed samples ranging from prepubertal children through old age (Jarrett et al 1990, 1994; Lesch et al 1987, 1989; Meyer et al 1991; Puig-Antich et al 1984c, 1984d; Ryan et al 1988, 1994; Siever et al 1992).

There is also preliminary evidence that this low GH persists after clinical recovery (in a medication-free state) in depressed children (Puig-Antich et al 1984d) and following treatment for depression in adults (Jarrett et al 1994).

Recently, our research group has found that low GH response to growth hormone–releasing hormone is also evident in children and adolescents with no personal history of depression but with high rates of affective
illness in their families (Birmaher et al 2000). These results have been considered within an emerging model based on the hypothesis that low GH response to GHRH represents a stable trait marker for affective illness—a marker evident before the onset of depression, persisting across episode and recovery, and independent of age and maturational changes.

The studies reported in this paper address the basic foundation for further investigations of this model, focusing on three specific aims: 1) to extend earlier findings of low GH response to GHRH by comparing a large sample of depressed children and well-matched control subjects with careful assessment of psychiatric and family history data, 2) to examine the reliability of GH responses to physiologic stimuli (within-subject test–retest reliability), and 3) to examine GH responses after clinical recovery within a subset of depressed children studied initially during a depressive episode.

Methods and Materials

Phase 1 and Phase 2 Studies

The data described in this paper include GH data collected in two similar studies. The research facility, most of the personnel, GH assay procedures, and design of the study up to and including the GHRH test were identical. Phase 1 of the study included a larger number of neuroendocrine tests after the GHRH test; a later phase of the study had a shorter neuroendocrine protocol. The GHRH data from n = 36 children with major depressive disorder (MDD) n = 18 normal control subjects from phase 1 studies were included in a preliminary report (Ryan et al 1994). All of the phase 2 data are new, and there is no overlap with any previously reported GH data. The methods for the GHRH test measures and protocol were identical across studies, and analyses were performed showing that there was no effect of phase on any of the GH measures being examined, thus the data were combined across phase 1 and phase 2 studies to maximize the power to examine covariates and subgroup effects.

Recruitment and Inclusion–Exclusion Criteria

Depressed children were recruited from the inpatient and outpatient clinics at Western Psychiatric Institute and Clinic, University of Pittsburgh Medical Center. Normal control children were recruited through advertisement and personal contacts. Informed consent to participate in the study was obtained in accordance with the University of Pittsburgh Institutional Review Board guidelines. Inclusion criteria common for all subjects were that they be 7 to 15 years of age and medically healthy. Children in the depressed cohort were required to meet DSM-III-R criteria for MDD. Additional exclusion criteria for the MDD cohorts only included 1) concurrent DSM-III-R diagnosis of anorexia nervosa, bulimia nervosa, autism, schizoaffective disorder, or schizophrenia and 2) MDD chronologically secondary to conduct disorder.

For the normal control subjects only, additional inclusion criteria included 1) no lifetime history of any psychiatric disorder and 2) low familial risk for affective illness. In this study, low familial risk for affective disorder was operationally defined as having no first-degree relative with a lifetime episode of any affective disorder or schizophrenia spectrum illness; no second-degree relative with a lifetime history of recurrent, bipolar, or psychotic depression, schizoaffective disorder, or schizophrenia; and no more than 20% of second-degree relatives with a single episode of MDD.

Exclusion criteria for both groups were 1) significant medical illnesses, 2) medications (except acetaminophen) within 2 weeks of the study, 3) inordinate fear of needles, 4) obesity (weight greater than 150% of ideal body weight) or severe growth failure (weight or height less than 3% of the National Health Statistic Curve), and 5) mental retardation or the presence of a specific learning disability.

DIAGNOSTIC ASSIGNMENT. Diagnostic assessments of the depressed cohorts were completed by research assistants who administered the Present Episode (Chambers et al 1985) and Epidemiologic (Orvaschel and Puig-Antich 1987) versions of the semistructured diagnostic interview, the Schedule for Affective Disorders and Schizophrenia for School-Aged Children (K-SADS). The diagnosis of MDD was made using DSM-III-R criteria, with the presence of all positive symptoms confirmed by a child psychiatrist or psychologist. For normal control subjects, if an initial telephone screen of the family indicated preliminary eligibility and interest, the child’s lifetime history of psychiatric symptomatology was assessed using only the K-SADS-E (Orvaschel and Puig-Antich 1987). All symptom ratings were made by interviewing the parent(s) first, then interviewing the child. All children who participated in the study were reinterviewed using a short version of the K-SADS at the time of the psychobiological studies to confirm presence of depressive symptomatology.

All interviews were carried out by trained research clinicians blind to the subject’s clinical status under the supervision of child psychiatrists (DA, BB) or a child psychologist (JK). Interrater reliability for all diagnoses for our studies has been $k \geq .70$. Socioeconomic status (SES) was measured using the Hollingshead four-factor index (Hollingshead 1975).

GHRH TEST. Following a visit and orientation to the laboratory, children and family members arrived in the lab to begin the psychobiological study at 5 PM. The sleep–neuroendocrine laboratory is furnished with many age-appropriate materials, including books, art supplies, board games, entertainment videos, and computer games. Children are given considerable individual attention from staff with years of experience conducting biological studies with children. On a rating scale completed immediately after finishing the psychobiological studies, the majority of children who participated in this and other studies conducted in the lab rated the experience as “very positive” (Dahl and Ryan 1999). An intravenous line was placed within the first hour of the study, and children are then free to play interactive games, watch movies, and so forth for the rest of the evening. Before bedtime, EEG leads were placed for standard sleep recordings. On the
following morning, baseline blood samples for GH were obtained through the indwelling catheter at 8:30, 8:45, and 9:00 AM. Immediately following the 9:00 AM draw, children received an infusion of 1.0 mcg/kg of GHRH over 2 min. There were no significant side effects of any sort related to the GHRH test. Children generally showed no signs of behavioral reaction of any kind. A physician was in attendance throughout the procedure. Following GHRH administration, blood samples for GH were obtained every 15 min for a total of 90 min. The child remained fasting from bedtime (of the previous evening) until completion of the GHRH test.

**BLOOD SAMPLES AND GH ASSAYS.** Blood samples were collected in plastic tubes containing edetic acid (EDTA) then centrifuged immediately in a refrigerated centrifuge. Plasma was separated and stored at −80°C until assayed. Human growth hormone levels were measured on a 50 μL plasma sample, run in duplicate. A modified version of the double antibody 125 I radioimmunoassay procedure developed by Diagnostic Products Corporation (Los Angeles) was used for these determinations. To increase the sensitivity of the assay to 0.5 ng/mL of growth hormone from that of the straight kit procedure, the amount of antibody was decreased, and a longer, sequential incubation of the antibody and radiolabeled antigen was used. Subjects’ duplicates with a coefficient of variation exceeding 5.0% were retested. The range for the intraassay variation of subjects’ duplicates was 0.00 to 4.98% CV, with a mean of 0.87% CV. Interassay variation ranged from 20.15% CV (mean of 2.47 ng/mL) to 13.68% CV (mean of 12.31 ng/mL).

**Statistical Analyses**

Sample characteristics were compared using analyses of variance, χ2, and Fisher’s exact tests as appropriate. Problem with missing hormonal data were minimal, with only a few subjects missing one or two data points. Analyzing the data with and without linear interpolation to fill in the occasional missing values yielded similar results, therefore only the interpolated data are reported. Before conducting any analyses, summary variables for the hormonal measures and clinical rating scales were examined for normality using the Shapiro and Wilks’ W statistic. The data were subject to log or square root transformation where no transformation normalized the data, nonparametric tests were used. The following summary values were used to characterize children’s GH responses: baseline, peak, and mean post-GH. The baseline values were computed by determining the mean of the three GH specimens taken at −30, −15, and 0 min preinfusion. The peak value represents the highest value postinfusion, and the mean post-GH values were the average of samples from +15 through +90 min. (The GH levels by 90 min were back to a level that was not significantly different from baseline.) A comparison using total GH, as computed by determining the area under the curve with all GH values obtained from 0 to 90 min post-GH using the trapezoidal rule revealed identical group comparisons; only the mean values are reported here.

**Table 1. Demographic Characteristics in Depressed and Low-Risk Children**

<table>
<thead>
<tr>
<th>Variable</th>
<th>MDD (n = 82)</th>
<th>NC (n = 55)</th>
<th>Statistic</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>11.2 ± 1.7</td>
<td>11.2 ± 1.8</td>
<td>t(135) = 0.11</td>
<td>ns</td>
</tr>
<tr>
<td>Gender (F/M)</td>
<td>29/53</td>
<td>22/33</td>
<td>χ² = 0.14</td>
<td>ns</td>
</tr>
<tr>
<td>Race (W/B/O)</td>
<td>66/15/1</td>
<td>49/3/3</td>
<td>Fisher exact test</td>
<td>.0314</td>
</tr>
<tr>
<td>SES</td>
<td>39.2 ± 13.9</td>
<td>47.8 ± 11.1</td>
<td>t(127) = 3.68</td>
<td>.0003</td>
</tr>
<tr>
<td>BMI</td>
<td>19.4 ± 3.6</td>
<td>18.8 ± 4.1</td>
<td>t(135) = 1.20</td>
<td>ns</td>
</tr>
</tbody>
</table>

Values are means ± SDs. MDD, major depressive disorder; NC, normal controls; Subjects; F/M, female/male; W/B/O, white/black/other; SES, socioeconomic status; BMI, body mass index.

**Reliability Study**

To assess the test–retest reliability of the GHRH test, the protocol was repeated in 11 normal control subjects within 1 to 2 months after the initial study.

**Recovery Study**

In the clinical follow-up of the depressed sample, subjects were invited to participate in a repeat study when they had recovered from the depressive episode. To be considered recovered, depressed children were required to be fully remitted for 8 consecutive weeks (Frank et al 1991) and medication free for at least 8 weeks. At the time of these analyses, n = 20 subjects had been restudied in the same protocol following remission and had their data compared with the findings from GH data obtained in the depressed state.

**Results**

There were no significant group differences in age, gender, body mass index, or Tanner stage of sexual maturation (Table 1). The groups were significantly different in SES [39.2 ± SD 13.9 vs. 47.8 ± SD 11.1; t(127) = 3.68, p = .0003]. Because SES was significantly different between MDD and control groups, this variable was examined in relation to the summary GH measures and was not found to be a significant covariate for any of the GH measures. There were also no significant differences in GH responses between male and female subjects in any of these analyses; thus, male and females subjects were combined for all comparisons. Analyses examining pubertal status (Tanner stage) also showed no significant effect on GH response to GHRH.

**Depressed versus Normal Control Subjects**

Baseline GH measures (−30 −15, and 0 min before GHRH infusion) were not different between groups (0.4 ng/mL ± SEM 0.05 vs. 0.4 ± 0.05). Following infusion of GHRH, the depressed subjects (n = 82) secreted signif-
Significantly less GH than control subjects ($n = 55$) as measured by peak levels [13.9 ng/mL ± SEM 1.4 vs. 19.5 ng/mL ± SEM 2.1; $t(135) = 2.6, p = .02$], and mean levels postinfusion [8.7 ng/mL ± SEM 0.9 vs. 12.2 ± 1.3; $t(135) = 2.6, p = .01$; Figure 1 and Table 2]. The effect size for the between-group differences in GH response based on the entire sample ($n = 82$ MDD subjects; $n = 55$ control subjects) was 0.44; the effect size when examining only the independent replication sample ($n = 46$ MDD subjects; $n = 37$ control subjects) was 0.39.

**GH Results in Relation to Severity and Other Clinical Symptoms**

We examined GH response to GHRH in relation to clinical symptoms, including prior episodes of depression (15% of the sample had a history of a past episode of depression), duration of depression (mean duration was 42.4 ± 36.8 weeks), severity of depression (mean depression 12 score from the K-SADS was 31.4 ± 5.7), and comorbid symptoms of anxiety symptoms (53% of the depressed sample had current or past anxiety). None of these analyses showed any significant effect on GH response to GHRH within the MDD sample.

**Test–Retest Reliability**

The GH response to GHRH showed an intraclass correlation (ICC) = .89 (peak) and $r = .93$ (mean post) within the 11 subjects who underwent repeat testing within 2 months (Figure 2).

**GH Responses following Clinical Recovery**

On restudy in a medication-free state, GH responses were not significantly different than their previous values obtained during the episode of MDD; mean GH post-GHRH was 9.21 ± 10.82 versus 8.10 ± 7.61 [$t(19) = 0.36$, ns] and peak GH post-GHRH was 13.40 ± 14.78 versus 13.72 ± 12.82 [$t(19) = 0.07$, ns] in depressed and remitted states respectively. As shown in Figure 3, the GH response in the MDD-recovered group ($n = 20$) remained significantly lower than the GH response in the control group.

**GH Responses in Relation to Hypothalmic–Pituitary–Adrenal Axis Measures**

The subjects in this study had also undergone measurements of cortisol and corticotropin (baseline and following corticotropin-releasing hormone challenge); analyses comparing summary hypothalmic–pituitary–adrenal axis

---

**Table 2. Demographic Characteristics and Growth Hormone Response to GHRH and during Baseline in Depressed and Low-Risk Children**

<table>
<thead>
<tr>
<th>Variable</th>
<th>MDD ($n = 82$)</th>
<th>NC ($n = 55$)</th>
<th>Statistic</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GHRH</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0.4 ± 0.05</td>
<td>0.4 ± 0.05</td>
<td>$t_{135} = 0.32$</td>
<td>ns</td>
</tr>
<tr>
<td>Postinfusion</td>
<td>8.7 ± 0.9</td>
<td>12.2 ± 1.3</td>
<td>$t_{135} = 2.59$</td>
<td>.0107</td>
</tr>
<tr>
<td>Peak postinfusion</td>
<td>13.9 ± 1.4</td>
<td>19.5 ± 2.1</td>
<td>$t_{135} = 2.55$</td>
<td>.0119</td>
</tr>
</tbody>
</table>

All between-group comparisons on growth hormone were done using log-transformed growth hormone values; reported growth hormone values are means ± SEMs. MDD, major depressive disorder; NC = normal control subjects; GHRH, growth hormone–releasing hormone.
measures and GH measures revealed no significant correlations within the MDD or control samples.

Discussion

Because of the challenges in recruitment and performing biological studies in children, psychobiological studies in child psychiatry typically entail small clinical and control samples. There is also an inherent bias toward publishing studies that have found group differences, compared with small-sample “negative” studies that are less likely to be written-up and published. This classic “file-drawer problem” is particularly concerning in the arena of child psychiatry.

Large controlled studies and independent replications are infrequent but essential to moving the field forward. This article establishes a large, independent replication of low GH response to pharmacologic stimulation associated with child depression, which was first reported in Puig-Antich’s seminal papers (Puig-Antich et al 1984a, 1984b, 1984c, 1984d). By examining a large sample of depressed children ($n = 82$) selected over a 10-year interval in a well-controlled study, the data in this article establish strong support for the hypothesis that low GH response to GHRH represents a neuroendocrine marker of affective illness in children. Our study also establishes good test-retest reliability for the measure, and demonstrates continuity of low GH response to GHRH in depressed children in clinical remission.

There are also several limitations to these data to be considered. One issue that has not been addressed is the specificity of the finding to depression. It is possible that low GH is associated more generally with psychiatric or emotional difficulties in childhood. Few studies have examined GH responses to pharmacologic challenge in other child psychiatric disorders. A recent study in children with anxiety using a clonidine challenge (Sallee et al 1998) reported increased GH responses in the anxious children compared with control subjects. The sample in that study also included children with obsessive-compulsive disorder, as well as other anxiety disorders. Furthermore, studies in adult samples have generally reported low GH responses to several types of pharmacologic challenge, in depression and anxiety disorders (Coplan et al 1997; Holsboer 1995; Uhde et al 1986) including generalized anxiety disorder (Abelson et al 1991) social phobia (Tancer et al 1993), and panic disorder (Charney et al 1987; Coplan et al 1997, in press; Nutt 1989; Rapaport et al 1989). Many of the pharmacologic challenges in adult studies, however, (particularly clonidine and yohimbe challenges) were based on the assumption that researchers were evaluating the integrity of noradrenergic sensitivity and that GH was simply a marker.

Focusing more specifically on GHRH stimulation studies in psychiatry, a critical review by (Skare et al 1994) discussed four replications showing low GH response to GHRH in adult depression, as well as two failures to replicate. These authors summarized the promising results but raised several concerns, including 1) the variability of GH response among control subjects, 2) the need to consider the age and gender of the subjects, 3) the lack of uniformity of procedures and measures, and 4) absence of data in adult studies regarding the test–retest reliability within subjects. It is important to note that among the controlled studies reviewed in that paper, the sample sizes ranged from $n = 7$ to $n = 19$ subjects with depression and the total number of depressed adults is only $n = 80$ (combining all studies). In contrast, our study contained $n = 82$ depressed children and $n = 55$ control subjects. In addition, we performed reliability tests, examined the influences of age and gender carefully, and used uniform procedures based on previous studies.

One study of GHRH in depressed adults (Gann et al 1995) published after the Skare review reported no differences in GH response to GHRH; however, the sample contained only $n = 12$ MDD subjects and $n = 12$ control subjects and reported the GH was $645 \pm 770$ (area under the curve) in the MDD subjects and $1031 \pm 279$ in the control subjects. Thus, that “negative” paper actually found lower GH response to GHRH in the MDD group with an effect size of 0.67 (comparable to our results) and likely failed to find significant group differences because of the small samples.
Effects on Growth

The functional significance of lower GH response regarding growth processes is unclear. There were no significant differences in height or weight between groups, and preliminary measures of height velocity were not different between groups. It is possible that any difference in GH regulation in response to GHRH challenge is not reflected in overall GH production or IGF-1 levels, and that it does not have any functional impact on growth. On the other hand, these effects may be subtle and below the threshold of detection over short intervals of time because Pine et al reported a slight but statistically significant reduction in expected adult height in the follow-up of children with anxiety disorders, but only in the females (Pine et al 1996).

Functional Significance and Mechanism of Action

Since our finding is stable following clinical recovery, one possibility is that this represents some type of early “scar” marker related to having had a depressive episode; however, other work by our research group (Birmaher et al 2000) shows evidence of low GH in children at high familial risk of depression but without any clinical signs of depression. In that study, the mean GH response in the nondepressed “high-risk” sample (n = 64) was 8.6 ng/mL ± 1.1, similar to the MDD sample (n = 82) 8.7 ng/mL ± 0.9 with both groups significantly different from the normal control subjects without family loading for depression (n = 55) at 12.2 ng/mL ± 1.3. Taken together, these data are consistent with a model that low GH response to GHRH represents a “trait” marker associated with the risk or vulnerability toward depression. Further, the absence of any significant relationship of GH response to severity of depression or duration of depression is also consistent with the concept of a trait marker.

Another possibility is that early stress or adverse social experiences early in life may alter GH regulation and confer greater risk of depression. Some animal studies have found low GH response in monkeys and rodents that were exposed to maternal separation early in life. Champoux et al 1989 reported low GH responses to pharmacologic challenge in nursery-reared infant rhesus macaques at 37 days of age compared with mother-reared control subjects (the nursery-reared monkeys also showed higher rates of depressive like behaviors later in life (Champoux et al 1989). Coplan et al (1998), studying bonnet macaques raised in variable foraging demand (VFD) conditions (Rosenblum et al 1994), found low GH response to clonidine infusion in the VFD offspring that showed high rates of anxious social behaviors and low exploration. These VFD offspring were also found to have elevated cerebrospinal fluid somatostatin (GH-inhibiting peptide) (Coplan et al 1998). Most recently Plotsky’s research group (Mason et al 1998) found blunted GH response to clonidine infusion in rodents that had experienced 180-min maternal separations early in life compared with handled control rats. Taken together, the animal data are consistent with the concept that low GH responses are associated with early social stress, anxious behavioral patterns, or both across several species.

Holsboer, drawing from findings in adult depression and from animal work, has presented a model whereby the mechanism of GH changes seen in depression may be mediated by alterations in central corticotropin-releasing factor (Holsboer 1995). Coplan et al (in press) reported results consistent with this link by showing that GH response to clonidine in the VFD monkeys was significantly correlated with corticotropin-releasing factor in the cerebrospinal fluid of these monkeys.

Clearly, there are several important mechanistic questions regarding the changes in GH response associated with depression and possibly with the risk for depression early in life. Promising preliminary results from a nonhuman primate model showing stable individual differences in GH response to GHRH and clonidine in young monkeys and a correlation between low GH response and low behavioral reactivity in a stranger-approach condition (K. Coleman et al, unpublished data) present one promising approach to explore the underlying mechanisms.

Summary

Low GH response to GHRH appears to be a trait marker of depression that is evident and stable early in development. The mechanism and functional significance of this marker requires further investigation. Progress in understanding these findings will likely require both clinical and basic investigations into the neurobehavioral systems underpinning these alterations in GH regulation, including developmental and genetic influences and the possible effects of early adverse experiences.

This work was supported by National Institute of Health Grant Nos. PO1-MH41712 (NDR and colleagues) and KO2-MH01362 (RED). This line of investigation was originally initiated under the direction of the late Joaquin Puig-Antich, to whom this article is dedicated. The authors wish to extend our appreciation to Laura Trubnick and her staff in the Sleep Laboratory, Stacy Stull and the staff of the Neuroendocrine Laboratory, the clinical interviewers, and the children and families who made this study possible.

References


Hollingshead A (1975): *Four-Factor Index of Social Status*. New Haven, CT: Yale University, Department of Sociology.


Jarrett DB, Miewald JM, Kupfer DJ (1990): Recurrent depression is associated with a persistent reduction in sleep-related growth hormone secretion. *Arch Gen Psychiatry* 47:113–118.


