

Anxious and Depressive Disorders and Their Comorbidity: Effect on Central Nervous System Noradrenergic Function

Oliver G. Cameron, James L. Abelson, and Elizabeth A. Young

Background: Although comorbidity of anxiety with depression is common, investigations of physiologic abnormalities related specifically to comorbidity are rare. This study examined relationships of DSM-IV-defined depression, anxiety, and their comorbidity to noradrenergic function measured by blunting of the growth hormone (GH) response to the alpha2 adrenoreceptor agonist (and imidazoline receptor agent) clonidine and by blood pressure and symptom responses.

Methods: Fifteen subjects with pure social anxiety or panic disorder, 15 with pure major depression, and 18 with both depression and anxiety were compared with healthy control subjects matched for age and gender. Other factors known to affect GH (weight, menstrual status, prior antidepressant, or other drug exposure) were controlled.

Results: Anxiety produced GH blunting, but depression was associated with normal GH responses. The comorbid state did not affect results beyond the impact of anxiety. Preclonidine stress-related GH elevations were observed, to the greatest degree in anxious subjects. Relevant symptom, but not blood pressure, changes were significantly associated with blunting.

Conclusions: With use of pure depression and anxiety groups and careful control of other factors known to affect GH, these results demonstrate central nervous system noradrenergic dysfunction in anxiety disorders. In contrast to less rigorously controlled studies, noradrenergic function in depression was normal.

Key Words: Anxiety, clonidine, comorbidity, depression, growth hormone, noradrenergic
toms by adrenergic blockade (Lader 1988; Tyrer 1988), and the
intimate involvement of CNS noradrenergic systems including the
 locus cenereus in fear (Bremner et al 1996; Sullivan et al 1999;
Tanaka et al 2000)—with none of these factors directly involved
in depression—all suggest that adrenergic functions including
that measured by GH responses to clonidine are directly related
to anxiety but not depression. To test this hypothesis, individuals
comorbid for major depression and an anxiety disorder were
studied, along with individuals with pure major depression or a
pure anxiety disorder. All were compared to specifically matched
control subjects. Based on possible confoundings recognized in
the GH depression literature, including comorbidity, as well as
research documenting involvement of noradrenergic systems in
anxiety (Cameron and Nesse 1988; Johnson and Lydiard 1995;
Ressler and Nemeroff 2000; Sullivan et al 1999) and anxiety-
associated functions (e.g., apprehension, arousal, attention, nov-
elty, stress; Aston-Jones et al 1999; Koob 1999; Robbins 1984;
Stanford 1995), we hypothesized that abnormal brain noradren-
ergic function, as indicated by GH blunting to clonidine, imply-
ing diminished postsynaptic alpha2 adrenoreceptor effects,
would be associated with anxiety but not depression. What roles
symptom severity and the presence of comorbidity per se play in
GH blunting were also investigated.

Methods and Materials

Subjects
Ninety-six subjects were recruited by advertisement, includ-
ing 15 with an anxiety disorder without depression (anxiety
 group), 15 with major depression without an anxiety disorder
(depression group), 18 with both disorders (comorbid group),
and 48 individually age and gender matched control subjects.
Diagnoses were made according to DSM-IV criteria with a
Structured Clinical Interview (SCID) interview by an experienced
research nurse. Subjects with pure disorders did not reach
present or past criteria within 2 years for the other disorder, and
the pure disorder was always primary, whereas comorbid indi-
viduals either met criteria for both disorders currently or within
the past year. Control subjects never had any psychiatric disor-
ders themselves or in any first-degree relatives. Subjects with
pure or comorbid anxiety had predominant anxiety diagnoses of
social phobia or panic disorder. Most were naive to psychotropic
medications; five had received an selective serotonin reuptake
inhibitor. All were medication free for at least 9 months. Obese
subjects (body mass index ≥ 30) or those with any eating
disorder or a recent weight loss averaging more than 1 kg/week
were excluded, as was anyone under 18 or over 50. Female
subjects were premenopausal and were studied within 10 days of
the onset of menstruation. The University of Michigan Medical
Center IRB approved the study. All subjects gave written in-
formed consent.

Procedures
Subjects were admitted to the Clinical Research Center at 7:30
AM. They were studied at bed rest with an intravenous catheter
for clonidine infusion and blood sampling. Automated measure-
ment of blood pressure (BP), blood sampling, and completion of
self-rated visual analogue scales (VAS; “drowsy” rating) were
performed before clonidine administration, and after 15, 30, 60,
90, and 120 min. Clonidine (Duracon R), 2.0 μg/kg, was
administered intravenously over 5 min by infusion pump, start-
ing at 9:00AM. Preclonidine measurements were done for GH at
30, 15, and 1 min before clonidine, for BP at 60 and 10 min
before, and for VAS ratings at 10 min before. The State and Trait
Anxiety Inventories (STAI) were completed at 8:50 AM and the
Hamilton Depression and Anxiety Rating Scales and the Sheehan
Disability Scale between 9:30 and 10:30 AM. Separated by at least
2 days before or after this study, each subject had a Trier Social
Stress Test (TSST; Kirschbaum et al 1993), involving performance
of a 5-min speech and a difficult mathematical subtraction task
with time pressure in front of an audience of three “experts”
(procedure detailed in Young et al 2004). Analyzed also were the
STAI State and three VAS ratings (“nervous,” “anxious,” “fearful”)
obtained during the TSST immediately before the social chal-
lenge. Order did not affect results of either study.

Blood samples for GH (ng/mL) and somatomedin-C (ng/
ML) were stored on ice for a maximum of 30 min, then plasma
was separated and frozen at –70°C. Growth hormone was
assayed by Nichols IRMA method (interassay coefficient of
variation of 6.8%). Somatomedin-C was assayed locally by
radioimmunoassay.

Data Analyses
Area under the curve (AUC) was calculated by trapezoidal
approximation for relevant data points. Distributions of untrans-
formed data were approximately normal and log-transformation
did not visibly affect normality, so raw data were used in all
analyses except AUC. In addition to repeated-measures data,
patients were compared with control subjects on GH peak
change scores, calculated as highest GH level postclonidine
always either 9:30 or 10:00 AM minus last GH level before
clonidine administration (9:00 AM).

Hypotheses were tested using t tests and analyses of variance
(ANOVA), including repeated measures (RM-ANOVA) with co-
variance (RM-ANCOVA). Because GH levels were measured both
before and after clonidine and because GH measurements after
clonidine were timed to start before a robust response and to end
after the response was complete, interaction tests of each RM-
ANOVA and RM-ANCOVA, testing for nonparallel levels between
groups over time (e.g., a blunted GH clonidine response), were
used as the main hypothesis tests. Because age and gender can
affect GH levels and patient groups could not be closely matched
on these variables, and because assay variability over time can
affect results, analyses always compared patients with their
individually matched control subjects, with subject and matched
control always assayed in the same batch. Regressions were used
to assess relationships of preclonidine to postclonidine GH
levels, and relationships of age, weight, and symptom ratings to
GH levels.

First, the hypothesis that patients (regardless of diagnosis)
differed from control subjects was examined by comparing all
patients combined with all control subjects. Then, to dissect the
relative contributions of anxiety, depression, and the comorbid
state to any GH blunting, two approaches were used. First, each
of the DSM-IV-defined pure anxiety, pure depressed, and comor-
bid groups were compared with their respective control subjects.
The comorbid patients were then subdivided into two groups,
based on predominant symptoms, to identify the disorder more
severely affecting the subject at time of study. All comorbid
subjects except one could be assigned a predominant diagnosis,
based on the more symptomatic or dysfunction-producing diag-
nosis, for the DSM-IV-defined qualifying duration of symptoms—
for example, 2 weeks for a major depressive episode or 1 month
for panic disorder. All patients with predominant anxiety (n =
23) were compared with their control subjects and all with
predominant depression (n = 24) to theirs.
9:00 AM, GH levels for patients and control subjects were responses following clonidine. (Immediately before clonidine, at first two of three baseline samples and their blunted GH release was evident in all three analyses (F = 8.2, df = 7, 196 for anxiety, F = 3.5, df = 7, 196 for depression, F = 9.7, df = 7, 231 for comorbid; p < .0001 for anxiety and comorbid, p < .002 for depression). The clonidine-by-group interaction was significant RM-ANOVAs comparing each diagnostic group (pure anxiety, pure depression, comorbid) to respective control subjects showed the following (Figure 2): A clonidine effect on GH release was evident in all three analyses (F = 8.2, df = 7, 196 for anxiety, F = 3.5, df = 7, 196 for depression, F = 9.7, df = 7, 231 for comorbid; p < .0001 for anxiety and comorbid, p < .002 for depression). The clonidine-by-group interaction was significant.

The three control groups for the three DSM-IV-defined diagnostic groups did not differ significantly from each other.

### Results

#### Subject Characterization

Table 1 contains age, gender, weight, diagnosis, and clinical rating scale scores, including ANOVA and post hoc comparison results. Matching ensured that all group comparisons included only groups that had matched age and gender distributions. There were no meaningful group differences in body weight. Social phobia was the predominant anxiety disorder diagnosis. Hamilton Depression, Hamilton Anxiety, STAI State, STAI Trait, TSST STAI-State, and Sheeian Disability scores all differed significantly across groups. Except for the TSST STAI-State, ratings for the depression and comorbid groups always exceeded the anxiety group. For all three, TSST VAS scores, anxious, comorbid, and depressed groups differed significantly from control subjects (range for overall F scores: 9.05–15.4, all p < .0001), but not each other for “nervous” and “anxious,” whereas for “fearful,” the comorbid group differed from all others (which did not differ from each other).

#### GH Response to Clonidine

The RM-ANOVA comparing all patients to all control subjects (Figure 1) showed a highly significant main effect of clonidine (i.e., repeated-measure: F = 19.11, df = 7, 651, p < .0001), reflecting robust GH release in response to clonidine. The clonidine-by-group interaction was significant (F = 2.48, df = 7, 651, p = .016) due to both some elevation in GH in patients at the first two of three baseline samples and their blunted GH responses following clonidine. (Immediately before clonidine, at 9:00 AM, GH levels for patients and control subjects were approximately equal.) The main effect of group was not significant in this or any subsequent GH RM-ANOVA comparing patient groups to control subjects.

### Table 1. Subject Characteristics of the Pure Depression, Pure Anxiety, Comorbid, and Control Groups (mean ± SD, where applicable)

<table>
<thead>
<tr>
<th></th>
<th>Depression</th>
<th>Comorbid</th>
<th>Anxiety</th>
<th>All Control Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>15</td>
<td>18</td>
<td>15</td>
<td>48</td>
</tr>
<tr>
<td>Age (years)</td>
<td>28.7 ± 7.7</td>
<td>23.2 ± 5.5</td>
<td>25.4 ± 8.5</td>
<td>26.0 ± 7.1</td>
</tr>
<tr>
<td>Gender (F:M)</td>
<td>6:9</td>
<td>13:5</td>
<td>8.7</td>
<td>27.21</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>70.9 ± 13.4</td>
<td>67.1 ± 7.6</td>
<td>70.3 ± 13.9</td>
<td>68.7 ± 12.1</td>
</tr>
<tr>
<td>Anxiety Diagnoses</td>
<td>0</td>
<td>18</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Panic disorder</td>
<td>0</td>
<td>5</td>
<td>3</td>
<td>0</td>
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<td>Social phobia</td>
<td>0</td>
<td>13</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Depression Diagnoses</td>
<td>15</td>
<td>18</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Melancholic</td>
<td>7</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nonmelancholic</td>
<td>8</td>
<td>14</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hamilton Depression Rating&lt;sup&gt;a&lt;/sup&gt;</td>
<td>19 ± 4.0</td>
<td>12.7 ± 6.7</td>
<td>3.3 ± 3.4</td>
<td>5 ± .9</td>
</tr>
<tr>
<td>Hamilton Anxiety Rating&lt;sup&gt;a&lt;/sup&gt;</td>
<td>13.8 ± 5.5</td>
<td>12.4 ± 7.0</td>
<td>5.8 ± 7.0</td>
<td>.7 ± 7.0</td>
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<tr>
<td>STAI-Trait&lt;sup&gt;b&lt;/sup&gt;</td>
<td>50.4 ± 11.2</td>
<td>53.3 ± 8.3</td>
<td>40.1 ± 11.0</td>
<td>27.1 ± 5.2</td>
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<tr>
<td>STAI-State&lt;sup&gt;b&lt;/sup&gt;</td>
<td>42.0 ± 14.1</td>
<td>50.3 ± 12.1</td>
<td>34.1 ± 7.4</td>
<td>25.0 ± 4.3</td>
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<tr>
<td>TSST STAI-State&lt;sup&gt;b&lt;/sup&gt;</td>
<td>35.4 ± 9.3</td>
<td>45.6 ± 9.4</td>
<td>43.2 ± 11.1</td>
<td>28.6 ± 8.6</td>
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<tr>
<td>Sheehan Scale&lt;sup&gt;c&lt;/sup&gt;</td>
<td>17.9 ± 5.7</td>
<td>20.6 ± 7.0</td>
<td>9.0 ± 6.5</td>
<td>1.4 ± 1.1</td>
</tr>
</tbody>
</table>

<sup>a</sup>Analysis of variance (ANOVA): F = 137.9, p < .0001 for group; by Fisher protected least significant difference (PLSD), p < .05 for all group contrasts.

<sup>b</sup>ANOVA: F = 46.3, p < .001 for group, by Fisher PLSD, p < .05 for control subjects versus depression, anxiety, and comorbid groups; depression versus anxiety groups; and comorbid versus anxiety groups.

<sup>c</sup>ANOVA: F = 59.3, p < .0001 for group; by Fisher PLSD, p < .002 for control groups versus depression, anxiety, and comorbid groups; depression versus anxiety groups; and comorbid versus anxiety groups.

ANOVA: F = 40.9, p < .0001 for group; by Fisher PLSD, p < .05 for all group contrasts.

ANOVA: F = 19.7, p < .0001 for group; by Fisher PLSD, p < .05 for all group contrasts except anxiety versus comorbid groups.

ANOVA: F = 91.1, p < .0001 for group; by Fisher PLSD, p < .05 for all contrasts except depression versus comorbid groups.

STAI, State and Trait Anxiety Inventory; TSST, Trier Social Stress Test.

**Figure 1.** Comparison of growth hormone (GH) levels (mean ± SE) for all anxious, depressed, and comorbid subjects combined (“patients”: n = 48) to all individually age- and gender-matched control subjects (n = 48) before and after intravenous clonidine (2.0 µg/kg) administration at 9:00 AM. x axis: discrete time points of GH sampling; y axis: GH levels (ng/mL). See Results for statistical analyses.
only in the pure anxiety group ($F = 2.58, df = 7,196, p = .015$), because only the pure anxiety group showed clearly blunted GH responses following clonidine compared with control subjects.

The pure depressed group had normal GH clonidine responses (interaction $F = .71, df = 7,196, p = .66$). The comorbid group, like pure depression, did not show significantly abnormal GH responses (interaction $F = .70, df = 7, 231, p = .67$); however, in the comorbid group GH responses appear to be intermediate, between clear blunting seen in pure anxiety and normal responses seen in pure depression.

To further evaluate the source of blunting, patients in the comorbid group were divided according to predominant diagnosis. All patients with predominant anxiety (pure plus comorbid) were compared with their control subjects, and all with predominant depression (pure plus comorbid) were compared with theirs. The RM-ANOVA for predominant anxiety showed the robust effect of clonidine on GH ($F = 11.20, df = 7, 301, p < .0001$). It also showed a significant clonidine-by-group interaction ($F = 3.19, df = 7, 301, p = .003$), due to highly blunted GH responding in the anxious patients (Figure 3). The parallel

![Figure 2. Comparison of growth hormone levels for anxious subjects (upper panel, "pure anxiety": $n = 15$), depressed subjects (middle panel, "pure depression": $n = 15$), and subjects comorbid for anxiety and depression (lower panel, "comorbid": $n = 18$) to respective matched control subjects ($n$ = that for patient group for each comparison). Other details same as Figure 1.](image1)

![Figure 3. Comparison of growth hormone levels for predominantly anxious subjects (upper panel, "predominant anxiety patients": $n = 23$) and predominantly depressed subjects (lower panel, "predominant depression patients": $n = 24$) to respective matched control subjects ("matched control subjects": $n$ = that for patient group for each comparison). Other details same as Figure 1.](image2)
RM-ANOVA comparing patients with predominant depression with their control subjects showed the clonidine effect (F = 9.34, df = 7, 322, p < .0001), but the clonidine-by-group interaction was not significant (F = .49, df = 7, 322, p = .84) because of very similar GH responses in depressed patients and control subjects. Interaction terms for RM-ANCOVAs, using the 8:30 AM pre-clonidine GH levels as covariates (time of maximum baseline difference across groups), remained significant for pure anxiety and predominant anxiety analyses (F = 2.13 and 2.98, p = .042 and .005, respectively), but not for the all-patient comparison (F = 1.42, p = .19). Anxious subjects were divided into social phobia and panic disorder subgroups. Inspection of results (not shown) indicated comparable blunting, but subgroups were too small to reach significance.

In summary, patients overall showed abnormal GH clonidine responses. Blunting was clearly associated with anxiety and not with depression. To verify results, paired t tests compared patient groups to matched control subjects on peak GH clonidine response (change scores). Comparison of predominant anxiety subjects to control subjects reached significance (t = 2.87; df = 44; p = .03), and comparison of pure anxiety patients to control subjects showed a strong trend (t = 1.99; df = 28; p = .06). In contrast, comparisons of predominantly depressed (t = .55; df = 40; p = .60) and pure depressed (t = .52; df = 28; p = .61) to their respective control groups did not approach significance.

Because blunting of GH clonidine responses in depression was reported in prior studies as specific to melancholia, effect of the presence or absence of melancholia on GH response was examined. All patients with depression were compared with their control subjects, dividing the depressed group into those with melancholia and those without. No significant group differences were detected (mean ± SD, ng/mL, for postclonidine peak: melancholia = 5.37 ± 4.26; nonmelancholia = 3.97 ± 4.20; control subjects = 5.27 ± 4.97).

Figures 2 and 3 suggest that GH levels declined across the baseline period in anxious patients, but considerably less so in nonanxious patients. Exploring this further, RM-ANOVAs were performed including the three samples before clonidine (8:30, 8:45, and 9:00 AM). Over this baseline period, all comparisons with control subjects involving pure anxiety subjects (groupings: all patients; all anxiety, including all comorbid; predominant anxiety; and pure anxiety) showed significant time effects (F range: 4.18–9.82; df range: 2, 56–2, 188; all p ≤ .02) because of declining values in patients from 8:30 to 9:00 AM. None of the comparable comparisons that did not include pure anxiety subjects (groupings: pure depression; all depression, including all comorbid; predominant depression; comorbid only) showed similar statistically significant time effects. For the anxiety-predominant analysis, the interaction term was also significant (F = 3.09; df = 4, 184; p < .02), indicating that the GH level decline was significantly greater in predominantly anxious patients than in their control subjects.

To determine the relationship of GH levels before and after clonidine, regressions were performed for 8:30 AM and 9:00 AM GH levels with peak change score and with postclonidine AUCs. Of primary interest was the question of whether higher pre-clonidine levels predict reduced GH release following clonidine. In regressions including all 96 subjects, GH levels at 8:30 and 9:00 AM were significantly predictive of postclonidine GH secretion (AUC: R = .22, p = .03; and R = .36, p = .0004, respectively); however, higher levels before clonidine were associated with higher levels after. Baseline levels were also positively predictive of postclonidine peak GH, although this was only significant for 9:00 AM (R = .23, p = .006).

To determine whether blunted GH responses were due to persistently increased GH secretion, resulting in increased negative feedback, 8:30 AM somatotropin-C was measured. For pure depression and control subjects, results (mean ± SD, ng/mL) were 234 ± 24 and 221 ± 12; for comorbid, 283 ± 35 and 342 ± 42, and for pure anxiety, 292 ± 24 and 273 ± 21. All differences were nonsignificant.

Regression analyses confirmed that neither age nor weight had any impact on GH responses, using either AUC or peak change score results. Across all 96 subjects, a large gender effect was observed. In an RM-ANOVA with two independent variables, gender and diagnosis, the main effect of gender was highly significant (F = 17.5, df = 1, 92, p < .0001), due to much higher overall GH levels in female subjects; however, the clonidine-by-diagnosis interaction effect was also significant (F = 2.17, df = 7, 637, p = .03), due to reduced GH responses in both male and female patients relative to their same-gender control subjects. There were no other significant interactions. Thus, blunted GH responses seen in patients were independent of gender. Additionally, ANOVAs with gender and diagnosis, using GH peak change scores, found no gender effect, indicating that gender differences were due to group differences in GH baselines, not GH clonidine responses.

Regressions determined whether dimensional ratings of anxiety (STAI and Hamilton Anxiety Scores) on the same day as the clonidine study would predict GH results (8:30 and 9:00 AM levels, AUC, or peak change score). None significant. The pure anxiety group had the clearest GH blunting, but also significantly lower scores on anxiety rating scales. Examination of the relationship between depression severity (using Hamilton Depression scores) and GH measures showed no significant correlations, looking at all subjects together or patients alone (all R = .1). In contrast, TSST STAI State regressions with GH AUC showed significant negative associations within the predominant anxiety group (R = .47, p = .022) and within the pure plus comorbid anxiety group (R = .42, p = .014), but not within the normal or depressed groups.

**BP and “Drowsy” Responses to Clonidine**

Effects of clonidine on sedation (VAS “drowsy”) and BP (systolic [SBP] and diastolic [DBP]) were assessed, with RM-ANOVAs comparable to those run on GH data. Predictably, both SBP and DBP fell significantly over time in response to clonidine (F = 27.7 and 48.5, df = 9, 846 for both, both ps < .0001, for main effect of time), but patients and control subjects did not differ in BP levels or clonidine responses. There were no significant interactions for either SBP or DBP in comparisons of all patients to all control subjects or any subgroup to matched control subjects.

There was the expected rise and then fall in drowsiness in all subjects in response to clonidine (F = 15.1, df = 6, 552, p < .0001). All patients rated themselves as more drowsy, compared with all control subjects (F = 9.58, df = 1, 94, p < .003); however, clonidine had similar (i.e., parallel) patterns of effect on drowsiness ratings in patients and control subjects (no significant interaction). There were no significant interactions for drowsiness for any patient subgroup compared with matched control subjects.

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Discussion

The primary goal of this study was to explore relative contributions of anxiety, depression, and their comorbidity to the blunted GH clonidine responses reported in previous research in patients with major depression and various anxiety disorders. Results support the hypothesis that the presence of anxiety per se (specifically, panic disorder and social phobia, of sufficient symptom number, severity, and chronicity to qualify for DSM-IV diagnoses) accounts for GH blunting. In this study, pure depression was associated with a normal GH response. The comorbid state did not affect results beyond the impact of anxiety. Thus, in past studies of depression, failure to exclude subjects with comorbid anxiety could have contributed to the blunting reported; however, lack of significant blunting in a sizeable group with documented depressive–anxious comorbidity in this study suggests that comorbidity alone probably does not fully explain past positive results reported in the depression literature. Many prior depression studies did not adequately control for gender, age, weight, menstrual phase, menopausal status, and prior recent tricyclic antidepressant exposure. This study indicates that with appropriate control subjects (as described in Methods) and exclusion of anxious comorbidity, depression itself is not associated with abnormal GH clonidine responses. Also, based on rating scales, overall syndrome severity (anxiety, depression, and disability scores on clonidine study day) was least among patient groups for anxious subjects, indicating that acute severity per se did not produce blunting. Furthermore, within the comorbid group, the observed nonsignificant blunting appeared to be due to individuals who were predominantly anxious, suggesting that these individuals might be different pathophysiologically from those with predominant depression.

Reports in the depression literature have suggested that GH blunting might be linked to melancholia (Amsterdam et al 1989b; Checkley et al 1984; Matussek et al 1980). In this study, individuals with melancholic depression showed no greater blunting than nonmelancholic patients. Using symptom ratings, despite several intervening days, TSST STAI State ratings for anxious subjects were negatively correlated with GH AUC. In contrast, anxiety ratings for the anxious subjects were lower during the clonidine procedure, and no relationships with any GH measures were seen. Furthermore, significant relationships were not observed for nonblunted depressed subjects with anxiety ratings, nor for any subjects with depression ratings, during clonidine. Thus, a measure that partly reflects depression severity—melancholia—is not associated with blunting, whereas elevated anxiety—produced here by the TSST—is negatively correlated with GH response to clonidine, but only in those individuals with chronic, impairing anxiety that passes the DSM-IV diagnostic threshold.

Blunted GH clonidine responses have traditionally been interpreted as reflecting abnormal alpha2 adrenoreceptor function (Siever et al 1981), but clonidine also binds to imidazoline receptors, which could be implicated in GH blunting. As expected, clonidine produced significant BP decreases, but no interaction effects were observed. Because hypotensive effects of clonidine are thought to be mediated by imidazoline receptors, lack of effects of diagnosis on BP response implies normal imidazoline receptor responsibility to clonidine in all groups and lends support to the hypothesis of abnormality of alpha2 adrenoreceptors. One prior study (Piletz et al 1996) reported normal imidazoline binding in generalized anxiety.

Sedative effects of clonidine are believed to be mediated by alpha2 adrenoreceptors. Drowsiness ratings demonstrated higher levels for all disorders combined than for control subjects. This pattern was true for individual patient groups as well; however, differences were as large before clonidine as after, indicating that the effect observed was not specifically differential sensitivity to the sedative effects of clonidine. Thus, in this study, sedative responses to clonidine do not provide evidence for or against any abnormality of alpha2 adrenoreceptor function.

Normal somatomedin-C levels indicate that a chronic abnormality of GH axis activity, leading to abnormal feedback effects, was not a mechanism responsible for the blunting observed. In contrast, a significant association between GH levels and elevated anxiety symptoms, in those with anxiety disorders only, indicates that chronic or recurrent anxiety symptoms (or both) are probably associated with changes in either receptor function (“subsensitivity,” “downregulation”) or other functional characteristics of the GH control system involving relevant receptors.

Separate analyses of baseline data suggested that anxious patients, in addition to showing blunted GH clonidine responses, might also have had higher GH levels following intravenous catheter insertion and study initiation. Evidence for this was not robust; patients in the pure anxiety group did not show significantly elevated GH levels relative to their matched control subjects at any specific preclonidine time point. They did have the highest initial preclonidine GH levels, however, and showed declines in GH levels across the baseline period that were considerably steeper than seen in other groups. Patients in the predominant anxiety disorder group were the only ones who showed significantly greater declines across the baseline period than matched control subjects. Evidence from prior research demonstrates that GH is acutely responsive to stress (Abplanalp et al 1977; Brown and Heninger 1975; Kosten et al 1984; Noel et al 1976; Rose and Hurst 1975), and GH elevations have been observed in anxious individuals without drug administration. Anxiety patients might have had greater GH reactivity to study conditions (e.g., fear or novelty) than nonanxious patients. Consistent with the hypothesis that this GH elevation is circumstance-related, resting GH levels in panic disorder are not abnormal (Abelson et al 2005). Future research addressing this issue is needed before drawing firm conclusions. If such hyperreactivity is present in anxiety patients, it might represent a phenomenon (noradrenergic or nonnoradrenergic) separate from whatever mechanism produces GH blunting, because there was no significant relationship between baseline GH levels and degree of blunting following clonidine.

The data showed a substantial gender effect on baseline GH levels, with women showing higher levels than men, both before and after clonidine. This finding supports the importance of always using control subjects matched for gender (and other relevant factors) in GH studies. Careful use of specifically matched control subjects and reliance on analyses that compared patients with their specific control group ensured that this gender effect could not influence any of the reported diagnosis-related effects.

One caveat in interpreting these results is the use of DSM-IV definitions of pure depression and pure anxiety. Milder, nonexclusionary symptoms of the other pure disorder might have been present in either or both pure diagnostic group. Our results nonetheless indicate that the DSM-IV definitions used identified groups different in a physiologically meaningful way. Second is use of the categorization “predominant.” Although “principal Axis I diagnosis” is specified as a categorization by the SCID and
defined as the main focus of clinical attention or the reason for the clinical encounter, it is not commonly used in research studies. Thus, predominant, defined for this study as the disorder having greater negative impact as judged by both subject and investigators, has not yet been shown to be a reliable and valid rating; however, as with the first caveat, it did identify groups that differed in a meaningful way. Third, unlike some (but not all) prior studies, no placebo control subjects were used. Fourth, this study involved only one measure of brain noradrenergic activity. No conclusion can be made regarding the status of brain noradrenergic function other than that assessed by GH responses to the alpha2 adrenergocceptor agonist clonidine, mediated by GH-releasing hormone and somatostatin, and potentially involving other receptors and neurotransmitters (where the source of any identified functional abnormality might actually reside) in addition to this noradrenergic system (Frohman et al 1992; Reichlin 1989).

These results for panic disorder and social phobia are consistent with findings from prior studies demonstrating that the pathophysiology of several anxiety disorders within the DSM-IV diagnostic schema involve noradrenergic (and other) brain circuits controlling GH release, including alpha2 adrenergocceptors. Particularly, they support prior evidence for noradrenergic abnormalities in social phobia (Gelernter et al 2004; Stein et al 1992; Tancer et al 1993). Although the benefit of serotoninergic activity drugs in social phobia implies serotonin involvement (Fedoroff et al 2001; Van Ameringen et al 2003), they do not necessarily act at the primary site of physiologic dysfunction, and their effectiveness is not evidence against involvement of other systems. Further research is needed to determine which anxiety disorders demonstrate consistent evidence for noradrenergic dysfunction.

We hypothesized and observed that, with proper study design, major depression would not be associated with a blunted GH response; however, because many prior depression studies did report such blunting, this finding requires careful replication before full acceptance. Multiple factors in prior depression studies probably contributed to the blunting seen. GH elevation in anxiety disorders due to novelty or stress (or both) also requires replication.


