Endocrine, Cardiovascular, and Behavioral Effects of Intravenous Protirelin in Patients With Panic Disorder

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• **The effects of protirelin administration on the anterior pituitary release of thyrotropin and prolactin were examined in 26 patients with panic disorder and 22 healthy volunteers. There were no differences observed in hormonal responses to protirelin between patients and controls. However, higher Beck Depression Inventory scores were associated with smaller baseline-corrected maximal changes in thyrotropin responses. Cardiovascular responses to protirelin did not differ between a subgroup of 15 patients with panic disorder and 15 age- and sex-matched healthy controls. Although protirelin produced robust increases in heart rate and blood pressure, only one patient with panic disorder experienced a panic attack during the infusion. The hormonal findings suggest that the presence of depressive symptoms may have a significant impact on various indexes of neuroendocrine responsivity and should be taken into consideration when looking at biologic measures in patients with panic disorder. The cardiovascular and behavioral findings do not support the hypothesis that all panic-producing stimuli are nonspecific and suggest that the induction of physical stimuli may be insufficient to produce panic attacks even in susceptible individuals.**

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A rich clinical and experimental lore exists to suggest a potential relationship between thyroid disease and psychiatric disorder.[1-3] Perhaps the most extensively studied aspect of this relationship has been the investigation of the hypothalamic-pituitary-thyroid (HPT) axis in psychiatric patients, ie, examining the thyrotropin (TSH) response to protirelin (thyrotropin-releasing hormone).[4-7] The TSH response to protirelin has been most intensively studied in depressed patients, with the finding that abnormally low responses occur in approximately 25% to 30% of depressed patients.[4] However, blunted TSH responses to protirelin have also been noted in mania,[8] alcoholism,[9] cocaine and phencyclidine abuse,[10] anorexia nervosa and bulimia nervosa,[11-14] and borderline personality disorder.[15]

Recently, several independent investigators have also reported a blunted TSH response to protirelin in patients with panic disorder (PD).[16-18] These studies have found reduced TSH responses to protirelin (using a cutoff of <7 mU/L to define a blunted response) in 33%,[16] 40%,[17] and 33%[18] of their patients with PD, respectively, all in fairly small patient samples (n=12, 20, and 9, respectively). In addition, the frequent reports of thyroid abnormalities in patients with panic attacks,[19-25] although counterbalanced by a number of negative reports,[26-31] provide a further rationale for the more detailed study of the HPT axis in these individuals.

As a consequence of our ongoing interest in the overlap between PD and major depression,[16,32-37] we have come to appreciate the potential complexity of this interrelationship. Many studies of biologic indexes in PD have failed to account for the variables of illness severity, concurrent depressive symptoms, and dietary and medication factors to the same degree as recent biologic studies in depressive disorders. Yet it is becoming increasingly clear that these factors may all have significant impact on the findings. For example, a recent study[38] suggests that urinary free cortisol may be elevated in "complicated" PD (ie, with depression or severe phobic avoidance) but not in uncomplicated PD.

Conversely, a recent report[39] has suggested that in patients with major depression, the presence of panic attacks is associated with significantly reduced TSH responses to protirelin. This latter finding implies that "blunting" may actually be more a feature of panic than of depression. Thus, to shed further light on this topic, we sought to reexamine the dynamic status of the HPT axis in PD by conducting a study of neuroendocrine responses to protirelin in a large, completely

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new sample of patients with PD and normal control (NC) subjects, attending carefully to the issues of diet, illness severity, complicated vs uncomplicated panic, and family history. In view of protirelin's robust effects in increasing heart rate and blood pressure in animals[40-47] and humans,[48-50] we elected also to examine the cardiovascular responses to protirelin and the potential anxiogenic or panic-producing effects of this stimulus.

SUBJECTS AND METHODS

Subjects

Subjects were recruited and the study was completed in its entirety during the 18-month period from March 1987 through September 1988. Patients and controls were recruited and studied concurrently. No subject (ie, patient or control) in this study was included in a prior report of protirelin testing in PD[16] from our group; ie, this study represents an entirely new cohort of subjects. All subjects gave written informed consent for the study.

Subjects were evaluated by a research psychiatrist (M.B.S.) with the aid of a semistructured interview derived from the Schedule for Affective Disorders and Schizophrenia–Lifetime version (modified for the study of anxiety disorders).[51] The patient group consisted of 26 individuals who met *DSM-III-R* criteria for PD; 12 (46%) also had agoraphobia. No patient with PD met concurrent *DSM-III-R* criteria for major depression since this was a specific exclusion criterion, although patients had variable histories of major depression, which were documented. Twenty-one of the patients with PD were outpatients and 5 were inpatients. The 5 inpatients were hospitalized because they lived too far from the National Institutes of Health, Bethesda, Md, to participate as outpatients, not on the basis of illness severity. The control group consisted of 22 healthy individuals who were free of past or present psychiatric illness as determined by the same Schedule for Affective Disorders and Schizophrenia interview with the research psychiatrist. All subjects received a thorough physical examination and ancillary tests (electrocardiogram, complete blood cell count, 20-factor automated blood chemistry analysis, triiodothyronine, thyroxine, free thyroxine, TSH, antimicrosomal and antithyroglobulin antibody titers, urinalysis) and were determined to be in good health. Any subject (patient or control) with a history of thyroid disease was excluded from the study.

Methods

All subjects were medication free for a minimum of 2 weeks before testing. Subjects followed a low-monoamine diet for 72 hours before testing and were also caffeine free for this duration. We thought that particular attention to caffeine intake was warranted because methylxanthines such as caffeine may reduce TSH secretion[52,53] and also because patients with PD are behaviorally hypersensitive to caffeine.[54-56] Conceivably, patients with PD might also differ in their anterior pituitary sensitivity to methylxanthines,[56] and so, although unproved, we sought to remove the effects of caffeine consumption as a potential confounding variable. To the best of our knowledge, this has not been controlled for in prior protirelin studies in psychiatric patients.

Behavioral ratings were obtained in the patients with PD during the week before protirelin testing. These consisted of the Zung Anxiety Scale (ZAS),[57] the 21-item Hamilton Rating Scale for Depression (HRSD),[58] the Sheehan Patient-Rated Anxiety Scale,[59] the Spielberger State-Trait Anxiety Inventory State Form,[60] and the Beck Depression Inventory (BDI).[61] Healthy controls had the ZAS completed before protirelin testing to reflect their anxiety in the week before testing. A subset (n = 10) of healthy controls also had the BDI completed. Some of these measures are reported with differing sample sizes, which reflect missing data.

The prior course of illness, including lifetime history of major depression, was systematically recorded as described elsewhere.[37] Family history of depression in first-degree relatives was ascertained only by questioning each patient with PD; the criterion for a "positive" history was that the individual described had received treatment for the depression.

After an overnight fast, subjects reported at 9 AM to the outpatient clinic. They were instructed that the procedure was likely to elicit only minor subjective effects, if any. Protirelin testing was performed with 500 μg of protirelin with sampling at 15-minute intervals over 60 minutes as per standard protocol and as described elsewhere.[16] Pulse and blood pressure were measured (Critikon Dinamap Vital Signs Monitor, Tampa, Fla) at 5-minute intervals for 30 minutes before protirelin infusion, and then 1, 6, and 11 minutes after the infusion. Symptoms following protirelin administration (ie, nausea, urge to void, feeling hot or flushed, heart racing or palpitations, feeling anxious or nervous) were recorded as absent, mild, or severe. Those subjects who reported feeling anxious or nervous during the infusion were immediately asked to elaborate on the degree of similarity to their naturally occurring panic attacks. This was used, along with further systematic inquiry about each specific *DSM-III-R* panic symptom, to determine whether the subject had experienced a "panic attack." The occurrence of three panic symptoms in a crescendo fashion, along with the requirement that the patient describe the experience as being "moderately or very similar" to their "naturally occurring" attacks, was deemed necessary to qualify as a panic attack for this study.

The concentration of TSH was measured by an immunoradiometric assay (IRMA, Serono Diagnostics, Norwell, Mass) with a sensitivity of 0.1 mU/L and an intra-assay coefficient of variability of less than 2.0%, and with an interassay coefficient of variability of less than 6.0% for TSH values above 2 mU/L and less than 9.0% for TSH values less than 2 mU/L. Prolactin (PRL) was measured by radioimmunoassay[62] with a sensitivity of 1.6 μg/L and intra-assay and interassay coefficients of variability of 10.4% and 12.2%, respectively.

Statistics

Endocrine and cardiovascular data were analyzed using an analysis of variance with repeated measures; in these analyses, a significant diagnosis × time interaction would be indicative of a difference between patients with PD and healthy controls. In the case of the endocrine data (ie, TSH and PRL responses to protirelin), none of the analyses revealed a significant diagnosis × time interaction, and so these analyses will not be presented in the "Results" section in the interest of brevity. Baseline-corrected maximal changes (Δ_{max} values) were calculated for each endocrine measure, and comparisons were made between the two diagnostic groups using Student's t test for parametrically distributed data and the Mann-Whitney U test for nonparametric data, where appropriate. Areas under the TSH and PRL response curves (ie, from 0 to 60 minutes) were also calculated. However, since we observed that Δ_{max}TSH and area under the curve for TSH correlated at $r = .99$ ($P < .0001$), and Δ_{max}PRL and area under the curve for PRL correlated at $r = .99$ ($P < .0001$), we have opted to report all the data in the more familiar Δ_{max} format.

Pearson Product-Moment Correlation Coefficients (r) and multiple regression analyses, when indicated, were used to examine relationships among selected measures. Categorical data were examined using Fisher's Exact Test or the χ^2 test.

All data are expressed as mean ± SD. Two-tailed tests are used unless otherwise specified. Values at $P < .05$ are considered statistically significant, but values between $P = .05$ and $P = .10$ are specifically reported; values at $P \geq .10$ are reported as not significant (NS).

RESULTS

Clinical and behavioral characteristics of the subjects are detailed in Table 1. The mean age and gender distribution of the patients with PD did not differ significantly from those of the healthy controls. As expected, the patients with PD scored significantly higher than the NC subjects on the ZAS and the BDI.

Thyrotropin Response to Protirelin

Baseline TSH (ie, mean of the −15- and 0-minute values before protirelin infusion) and Δ_{max}TSH did not differ between patients with PD and NC subjects (Table 2 and Fig 1). However, when men and women were examined separately, the Δ_{max}TSH values tended to be lower in the men with PD than the male NC subjects (Table 2). It should be noted, however, that while they were of comparable mean ages, the male PD subgroup had more subjects over 40 years of age (5 of 10 subjects) than did the male NC subgroup (2 of 9 subjects). The

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Table 1.—Clinical and Behavioral Characteristics of Subjects*

	Panic Disorder (n=26)	Normal Control (n=22)
Clinical Characteristics		
Age, y (range)	35.6±8.1 [21-48]	34.0±9.2 [22-57]†
Gender, M/F	10 (38)/16 (62)	9 (41)/13 (59)†
Age of men, y (range)	35.8±9.8 [21-47]	33.7±10.6 [25-57]†
Age of women, y (range)	35.5±7.1 [24-48]	34.2±8.6 [22-46]†
Age at onset, y	28.4±8.7	. . .
Duration, y	7.5±5.7	. . .
History of MDE	14 (54)	. . .
First-degree FH of depression	8 (32)	. . .
With agoraphobia	12 (46)	. . .
Behavioral Ratings		
Zung Anxiety	44.5±8.9	27.0±2.9‡
Beck Depression Inventory	5.7±5.4	1.2±2.4§
Sheehan Patient-Rated Anxiety Scale	26.6±11.9	. . .
Hamilton Depression Rating Scale (21 item)	10.3±4.7	. . .
Spielberger State-Trait Anxiety Inventory State Form	46.5±11.5	. . .
Panic attacks per week	0.43±0.79	. . .

*MDE indicates major depressive episode; FH, family history. Values are mean±SD or number (percent). Range is indicated by values in brackets.
†Not significant for comparison of groups.
‡Mann-Whitney $U=2.50$, n=47, $P<.00005$.
§Mann-Whitney $U=48.50$, n=36, $P<.005$.

Table 2.—Neuroendocrine Responses to Protirelin in Male and Female Subjects*

	Normal Control	Panic Disorder
TSH Responses		
Baseline TSH, mU/L, all subjects	1.42±0.68 (22)	1.44±0.55 (26)
Δ_{max} TSH, mU/L		
All subjects	17.0±7.4 (22)	16.2±7.4 (26)
F only	16.1±6.1 (13)	19.8±8.0 (16)
M only	18.9±8.9 (9)	11.1±4.7 (10)†
M age >40 y	15.1±4.7 (2)	9.4±5.7 (5)
"Blunted" TSH responses, all subjects	0/22 (0%)	3/26 (12%)
"Abnormal" TSH responses, all subjects	0/22 (0%)	2/26 (7.7%)
PRL Responses		
Baseline PRL, μg/L		
All subjects	5.7±2.3 (22)	4.7±1.9 (26)
F only	6.2±1.8 (13)	4.5±1.7 (16)‡
M only	4.9±2.8 (9)	4.9±2.3 (10)
Δ_{max} PRL, μg/L		
All subjects	36.5±17.5 (22)	39.4±27.2 (26)
F only	44.4±17.9 (13)	47.7±29.8 (16)
M only§	25.2±8.7 (9)	26.2±16.1 (10)

*TSH indicates thyrotropin; Δ_{max}, maximal change from baseline; and PRL, prolactin. Except as indicated, values are mean±SD (number of subjects). Except as indicated, differences are not significant. Blunted TSH response is defined as Δ_{max} TSH below 7 mU/L; abnormal TSH response is defined based on 95% confidence interval in normal controls of Δ_{max} TSH of 3.6 to 31.8 mU/L.
†Male controls vs male patients with panic disorder, Mann-Whitney $U=65.5$, n=19, $P<.10$.
‡Female controls vs female patients with panic disorder, Mann-Whitney $U=158.5$, n=29, $P<.02$.
§All female vs all male subjects, Mann-Whitney U test=116.5, n=48, $P<.0008$.

Δ_{max}TSH values did not differ significantly between women with PD and NC women (Table 2).

Conceptually, comparison of mean responses between groups might mask a subpopulation of subjects with abnormal responses. Several authors[4,6] have therefore suggested the use of thresholds to define an abnormal response. Using either the customary literature cutoff of Δ_{max}TSH below 7 mU/L to define a blunted response[4] or the 95% confidence interval from our own healthy control group (Δ_{max}TSH from 3.6 to 31.8 mU/L) to define an "abnormal" (ie, high or low) response, the patients with PD failed to differ from the NC subjects in their rates of blunted or abnormal TSH responses to protirelin (Table 2).

PRL Response to Protirelin

Baseline PRL value did not differ between patients with PD and NC subjects, although baseline PRL was lower in women with PD than in female healthy controls (Table 2). Patients with PD and NC subjects also exhibited similar Δ_{max}PRL values (Table 2 and Fig 2). When examined separately by gender, this response was seen to be higher in women than in men but did not differ between male patients with PD and male controls or between female patients with PD and female controls (Table 2).

Relationship Between Basal and Stimulated Values

There were no relationships observed between age and either basal or protirelin-stimulated TSH or PRL values (NS). In both diagnostic groups, Δ_{max}TSH was positively correlated with baseline TSH (PD: $r=.55$, $P<.005$; healthy controls: $r=.85$, $P<.0001$; Fig 3). The Δ_{max}PRL was not significantly correlated with baseline PRL in either diagnostic group. The Δ_{max}TSH did not correlate significantly with Δ_{max}PRL in either diagnostic group.

Relationship of Endocrine Responses to Protirelin and Clinical Variables

The endocrine responses to protirelin did not differ between patients with PD with vs without a lifetime history of major depression, with vs without a first-degree family history of depression, or with vs without extensive phobic avoidance (ie, agoraphobia; all NS).

In the healthy controls, neither ZAS nor BDI correlated significantly with any endocrine measure. In the patients with PD, there were no significant correlations between any endocrine measure and the ZAS, Patient-Rated Anxiety Scale, HRSD, or Spielberg State-Trait Anxiety Inventory State Form. However, in the patients with PD, there were significant negative correlations between BDI scores and baseline TSH ($r=-.52$, $P<.01$), and between BDI scores and Δ_{max}TSH ($r=-.60$, $P<.002$; Fig 4). (While the data in Fig 4 might suggest that the latter correlation was influenced by several outlying data points, it should be noted that this correlation remained highly significant even when Δ_{max}TSH values were log-transformed [$r=-.69$, $P<.0001$].) For the patients with PD, multiple regression analysis showed that baseline TSH values and BDI scores both contributed significantly to the prediction of Δ_{max}TSH values according to the following equation:

$$\Delta_{max}\text{TSH} = -0.64(\text{BDI}) + 4.77(\text{Baseline TSH}) + 13.2$$

Cardiovascular Responses to Protirelin

Measurement of cardiovascular responses to protirelin were available for only the last 17 patients with PD and 19 healthy controls who participated in this study. Because of the variability in cardiovascular measures that occurs with age, it was thought that these responses would be best compared in a tightly age- and sex-matched group.

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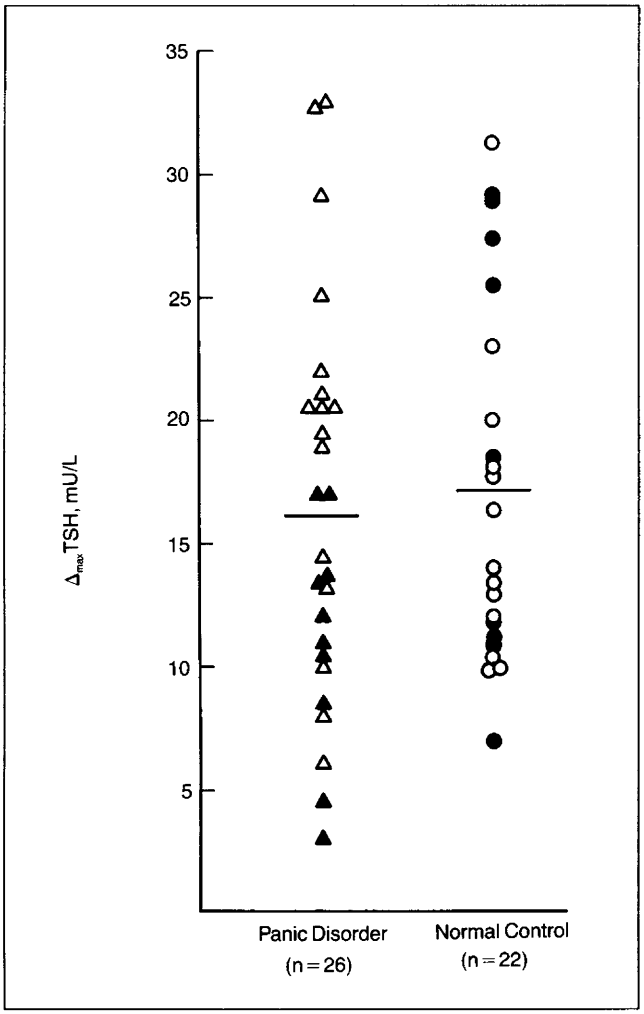

Fig 1.—Thyrotropin (TSH) responses to protirelin (expressed as maximal change from baseline [Δ_{max}TSH]) in 26 patients with panic disorder (triangles) and 22 healthy controls (circles) (solid triangles and circles represent male subjects and open triangles and circles, female subjects). The horizontal lines represent group means.

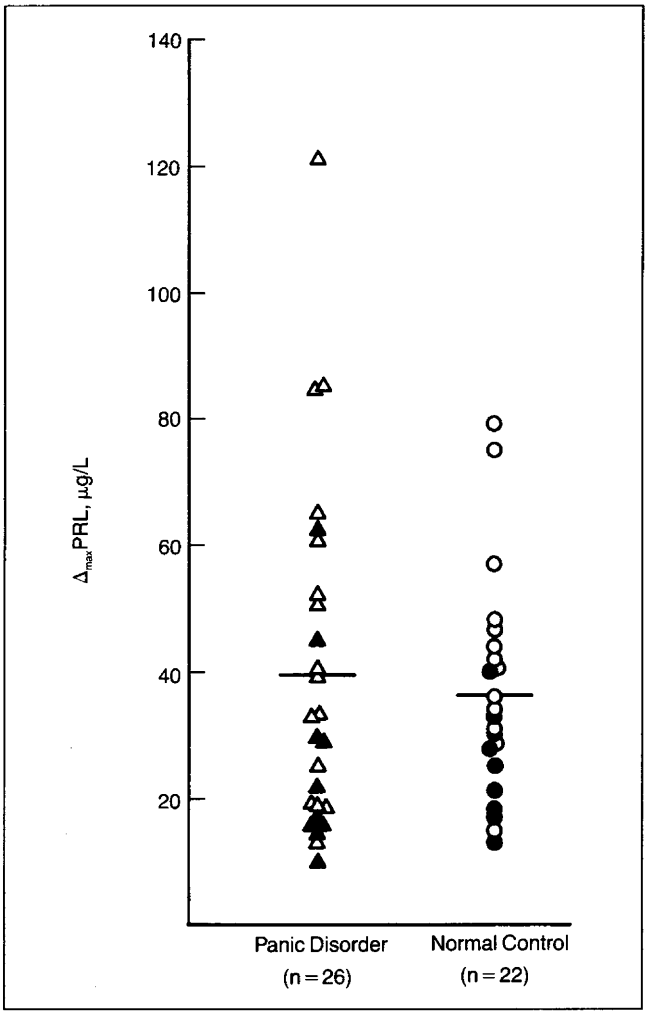

Fig 2.—Prolactin (PRL) responses to protirelin (expressed as maximal change from baseline [Δ_{max}PRL]) in 26 patients with panic disorder (triangles) and 22 healthy controls (circles) (solid triangles and circles represent male subjects and open triangles and circles, female subjects). The horizontal lines represent group means.

Consequently, we will report herein the results in 15 patients with PD and 15 age- (within 5 years) and sex-matched controls. It should be noted, however, that the results in the larger sample did not differ in any respect from the results presented herein.

The mean age of the 15 patients with PD (9 women and 6 men) was 33.1 ± 6.4 years (range, 24 to 47 years), and the mean age of the 15 NC subjects (9 women and 6 men) was 33.1 ± 8.0 years (range, 22 to 46 years). The cardiovascular responses to protirelin are given in Table 3. It can be seen that each measure showed a robust increase at 1 minute following protirelin administration, with a return to baseline within the next 10 minutes. However, there were no differences observed in the magnitude or patterns of response between the patients with PD and the NC subjects (Table 3). Figure 5 presents these findings as change scores from baseline to 1 minute. The mean responses did not differ between groups (Student's t tests, NS), but the variance of the diastolic pressor response to protirelin was greater in the patients with PD than the healthy controls (Levene's F test, $F' = 3.96$, $P < .02$). There were no significant correlations observed between any behavioral or neuroendocrine measure and any of the cardiovascular measures in either diagnostic group.

Panic Attacks After Protirelin

Side effects were similar in both subject groups, with 38% of patients and 36% of controls describing mild or moderate nausea, 67% of patients and 77% of controls complaining of an urge to void, 21% of patients and 41% of controls feeling hot or flushed, and 21% of patients and 32% of controls noting heart racing or palpitations. In terms of "anxiety or nervousness," 18% of the healthy controls reported this as being mild or moderate, compared with 25% of the patients with PD. One of these patients with PD described her anxiety as being moderately similar to her "panicky feelings," but she did not experience enough associated symptoms nor was her attack intense enough to qualify as a panic attack. One additional patient with PD experienced severe anxiety during the protirelin infusion and met criteria for a panic attack 12 minutes after the protirelin had been administered. This consisted of fearfulness, tachycardia, shortness of breath, tremulousness, and a desire to flee. The patient rated this experience as "very similar" to her naturally occurring panic attacks.

Thus, despite the fact that protirelin induced robust (15% to 25%) increases in heart rate and mean arterial pressure, only one patient experienced a panic attack and one other patient experienced a less-intense panic-like event.

COMMENT

Neuroendocrine studies of patients with affective illness have been widely employed in the past decade and have

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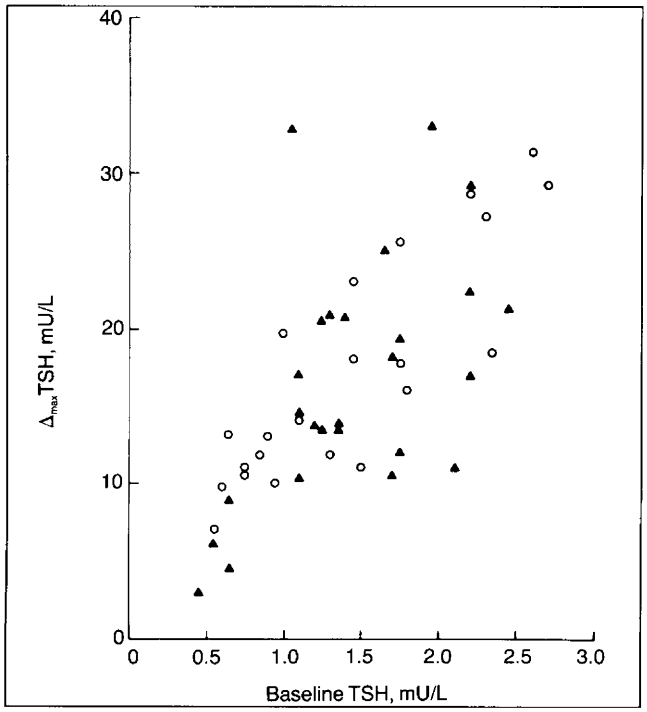

Fig 3.—Relationship between baseline thyrotropin (TSH) values (ie, before protirelin infusion) and maximal change from baseline (Δ_{max}TSH) in patients with panic disorder (triangles; $r = .55$, $P < .005$) and healthy controls (circles; $r = .85$, $P < .0001$).

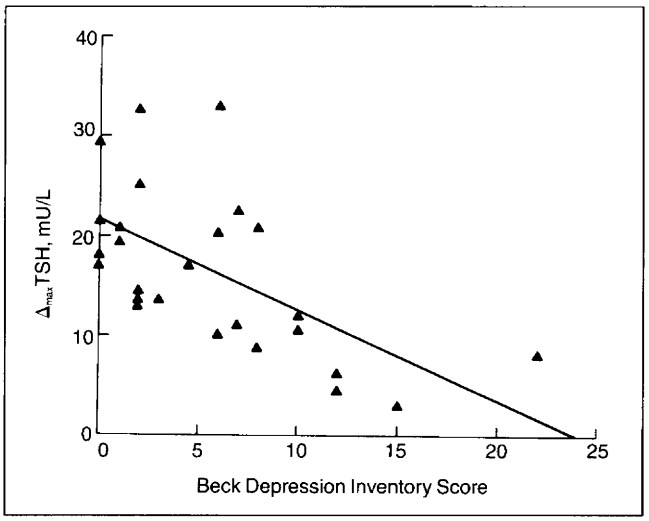

Fig 4.—Relationship between Beck Depression Inventory scores and maximal change from baseline in thyrotropin (Δ_{max}TSH) in 26 patients with panic disorder ($r = .60$, $P < .002$).

contributed significantly to our understanding of the pathophysiology of these disorders. However, while early enthusiasm for these neuroendocrine tests ran high, we have gradually come to realize that the complexities in interpretation of these results cannot be overstated. A good example of this is the dexamethasone suppression test.[68] Initially, it was believed that the dexamethasone suppression test could be of use in the diagnosis of depression,[63] but, as clinical experience grew, this expectation could not be sustained.[64,65] Eventually, the intricacies of the response to the dexamethasone suppression test were unveiled, including the influences of age,[66] weight changes,[67] medications,[68] depressive severity or quality,[69] and possibly diet.[70] More recently, the amazing subtleties of such influences as variations in dexamethasone kinetics[71,72] have been factored into this complex, ever-changing equation. Thus, while initial hopes about the simplicity and utility of these tests have not been realized, they have been replaced by an appreciation for the many ways in which these systems may be influenced.

We would draw a historical and theoretical parallel of the evolution described above to our present findings with protirelin administration in PD. While initial studies[16-18] found an increase in abnormal TSH responses to protirelin, these earlier studies did not control for a number of potentially important factors. In this study, using a carefully selected population of patients with PD and a control population of age- and sex-comparable healthy volunteers, we were unable to replicate the findings of abnormal TSH responses to protirelin in PD.

Factors Potentially Influencing TSH Responses to Protirelin

We found no differences in TSH response to protirelin in patients with PD as compared with healthy controls, regardless of whether mean responses or operationally defined rates of abnormal responses were analyzed. We did find, however, a trend toward lower mean TSH responses to protirelin in men with PD compared with normal men or women. However, this may have been an artifact of having several male patients with PD with relatively high BDI scores. Alternatively, this finding may relate to the greater number of men over the age of 40 years in the PD group; men over 40 years old are known frequently to exhibit low TSH responses to protirelin.[73] Unfortunately, our sample size for NC subjects was not large enough to allow the calculation of normative ranges by gender, leaving us unable to be certain about the explanation for this finding.

Among other factors that influenced the TSH response to protirelin was the basal TSH value, which correlated well with Δ_{max}TSH (Fig 3). This suggests that with the use of an immunoradiometric assay that has good sensitivity at the lower spectrum of TSH values,[74] the assessment of basal TSH values may provide a great deal of information toward predicting protirelin-stimulated responses. This finding confirms those of other recent studies.[75,76]

In this study, the BDI (but none of the behavioral measures of anxiety) was negatively correlated with Δ_{max}TSH in the patients with PD (Fig 3). While speculative, this observation might suggest that the TSH response to protirelin may be related to the degree of current depression. The possible influence of concurrent depressive symptoms on biologic indexes such as 3-methoxy-4-hydroxyphenylglycol[77] or urinary free cortisol[38] in patients with PD has also recently been noted, and our findings would be compatible with those observations. While BDI scores correlated with Δ_{max}TSH, HRSD scores did not. We believe that this is because, in our experience and that of others,[77] the HRSD scores in patients with PD tend to reflect questions involving primarily psychic and somatic anxiety, rather than depression, per se. The BDI may therefore represent a worthwhile measure to use along with the HRSD in future biologic studies of patients with PD. In this regard, it is noteworthy that the mean BDI score in our previous study[16] was 13.3, compared with 5.7 in this study, perhaps explaining the higher incidence of blunted responses in our initial study. The BDI scores were not published for the other two studies that demonstrated a blunted TSH response to protirelin in smaller samples of patients with PD.[17,18]

A recent study by Gillette et al[39] further addresses the issue

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Table 3.—Cardiovascular Responses to Protirelin in 15 Patients With PD and 15 Age- and Sex-Matched Healthy Controls*

	Systolic BP, mm Hg		Diastolic BP, mm Hg		Heart Rate, Beats/min	
Time, min	PD	Control	PD	Control	PD	Control
−10	115.7±9.3	113.0±8.3	66.5±9.1	67.1±6.8	58.6±10.4	60.0±5.9
−5	115.5±10.8	111.9±7.3	64.3±10.5	64.7±7.7	59.5±7.8	60.3±5.5
0	116.9±10.4	113.8±7.4	62.8±11.2	66.4±7.8	63.1±12.6	61.1±6.1
1	124.2±11.1	126.9±9.6	77.1±10.7	78.0±7.4	71.7±11.2	69.1±9.5
6	121.1±9.9	119.2±10.9	67.9±10.9	66.5±8.7	59.6±11.7	59.0±7.2
11	117.8±9.3	113.8±13.5	64.6±11.5	66.8±7.3	59.2±9.5	58.5±6.2
ANOVA, main effect						
Diagnosis						
F	0.5		0.1		0.1	
df	1,28		1,28		1,28	
P	NS		NS		NS	
Time						
F	16.5		22.2		18.9	
df	5,140		5,140		5,140	
P	<.0001		<.0001		<.0001	
Diagnosis × time						
F	1.2		0.66		0.6	
df	5,140		5,140		5,140	
P	NS		NS		NS	

*Values are mean ± SD, except for statistics. PD indicates panic disorder; BP, blood pressure; ANOVA, analysis of variance; and NS, not significant.

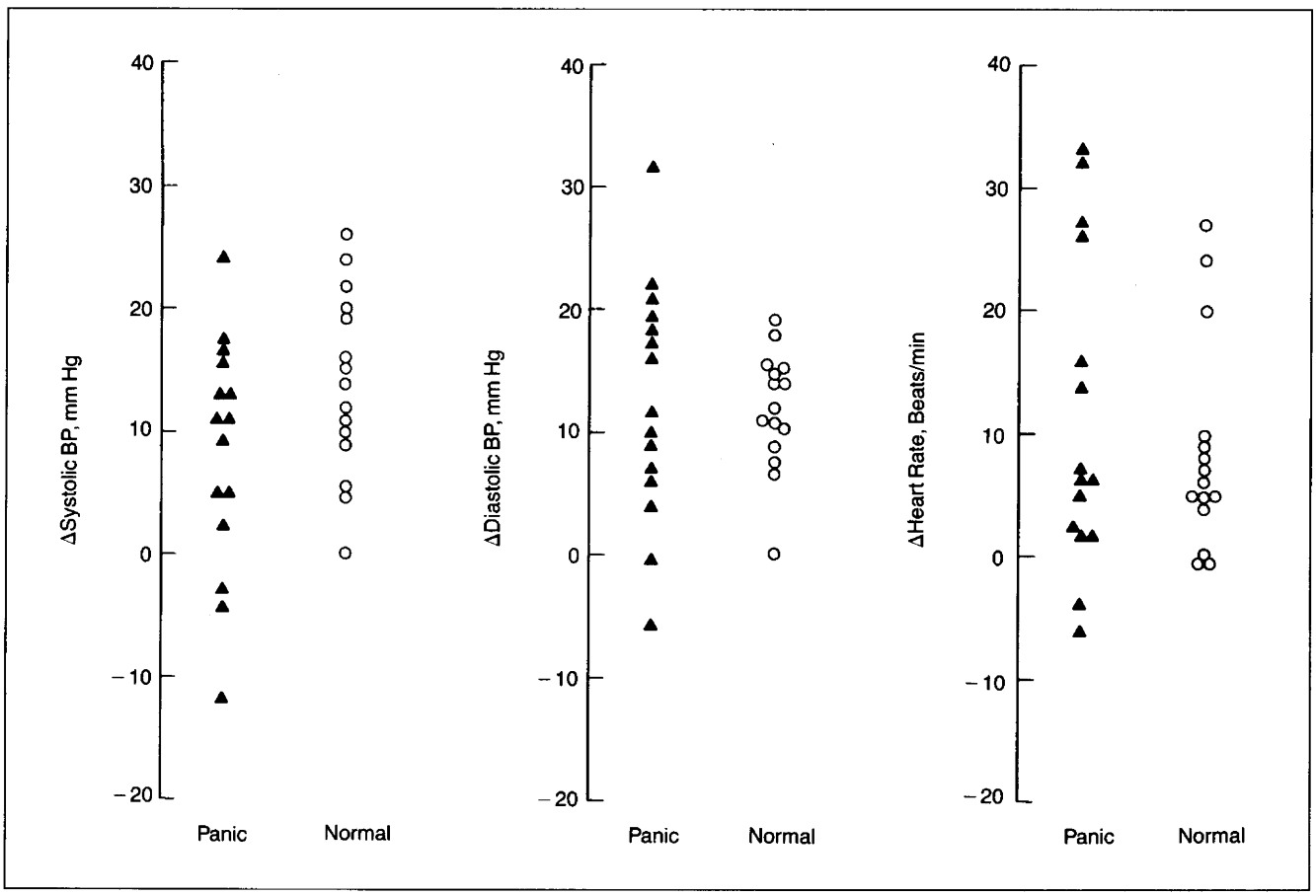

Fig 5.—Cardiovascular responses to protirelin in 15 patients with panic disorder and 15 age- and sex-matched healthy controls. Values plotted represent the change (Δ) from baseline (before protirelin infusion) to 1 minute (after protirelin infusion) for each value measured. BP indicates blood pressure.

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of TSH responsivity to protirelin in patients with both depression and panic. In their study, patients with major depression and panic attacks had smaller TSH responses to protirelin than depressed patients without panic attacks. Taken together, our observations and those of Gillette et al[39] might suggest that while either PD or major depression may be associated with blunted TSH responses to protirelin, it is the combined or interactive influence of the two factors that yields the highest rates of blunting. This hypothesis remains to be tested in future studies that meticulously document the phenomenology of the subjects. Because patients with PD may frequently suffer from low-grade dysthymia or otherwise atypical depression that does not meet *DSM-III-R* severity criteria for a major depressive episode, diagnostic assessment to characterize the presence of such syndromes in these patients may serve to clarify this issue.

PRL Responses to Protirelin

Our initial study[16] was the only other investigation to assess PRL responses to protirelin in patients with PD and healthy controls. In this study,[16] the mean PRL response was lower in women with PD (n = 6) than in healthy women (n = 6; 10 vs 25 μg/L). In our present study, while we did find the expected greater PRL response to protirelin in women than in men,[78] we did not find that female patients with PD had lower PRL responses than their same-sexed healthy controls. The significance of these discrepant findings is unclear, particularly since the PRL response to protirelin has been variably reported to be normal, exaggerated, or blunted in patients with major depressive illness.[79] Variations in menstrual cycle phase at the time of testing may have contributed to the differential results, but this remains speculative.

Cardiovascular Responses to Protirelin

While our neuroendocrine findings tend to refute the hypothesis of abnormalities in HPT axis functioning in PD, examination of the cardiovascular responses to protirelin may provide us with insight into different areas of potential pathophysiologic relevance to PD. It is known that intravenous protirelin elevates pulse and blood pressure in humans at doses comparable with those used in this study (500 μg).[48-50] While the precise mechanism of this effect remains unclear, it appears that a central noradrenergic or cholinergic mechanism that then secondarily stimulates adrenomedullary epinephrine secretion may be involved, with the net effect being the provision of an adrenergic stimulus.[40-47] In this study, we observed that the intravenous administration of protirelin resulted in rapid and robust chronotropic and pressor effects in patients with PD and healthy controls. However, patients with PD had cardiovascular responses comparable with those of their age- and sex-matched controls. Uncertainties about the cardiovascular mechanism of action of protirelin make it a less-than-optimal probe for evaluating the physiology of PD. Nonetheless, the failure to see differences in cardiovascular reactivity between patients with PD and controls would suggest that patients with PD are not nonspecifically "hyperreactive" to stimuli that perturb the autonomic nervous system.

Effect of Protirelin on Panic Attacks

Several elegant arguments have been put forth suggesting that patients with PD are hypersensitive to autonomic or other physical stimuli, or misperceive and misattribute these physical sensations.[80-82] These hypotheses propose that a key element in the provocation of panic attacks under natural and experimental conditions is the induction of somatic stimuli, which the patient with PD then perceives in a particular fashion and responds to with the conditioned behavior of a panic attack. Some authors have argued that panic-producing substances such as lactate have their effects not through any direct biologic mechanism, but rather through an indirect mechanism involving secondary cognitive processing and response to an "interoceptive stimulus."[82,83] In this study, despite the fact that intravenous protirelin produced abrupt and substantial increases in heart rate and blood pressure that are comparable in magnitude with those elicited by several other panic-producing agents,[55,84-86] only one patient with PD reported experiencing anything akin to a naturally occurring panic attack. This rate of panic induction is even lower than that reported for placebo infusions.[87]

Accordingly, the low rate of panic responses to protirelin and its attendant cardiovascular stimulation would be at variance with a purely interoceptive conditioning model for PD. As reviewed and discussed elsewhere,[88] our negative findings are consistent with other studies in which the nonspecific effects of pain[89] or hypoglycemia[90,91] failed to induce panic attacks in patients with PD, despite eliciting somatic symptoms. Conversely, our observations would seem to suggest that there is some specificity to panic-producing stimuli such as lactate,[92] caffeine,[55,56] or carbon dioxide,[86] and that the production of somatic sensations that are often associated with spontaneous panic attacks (increased heart rate, for example[93]) is insufficient to produce a panic attack in susceptible individuals in a laboratory setting. On the other hand, our patients were prepared for a rather mundane neuroendocrine test and did not receive instructions that the protirelin had a likelihood of inducing a panic attack. Thus, the effects of expectancy bias and preparedness inherent in this study design may have had a protective effect in mitigating against the induction of panic. In future investigations with protirelin, it would be interesting to manipulate the research environment in a systematic fashion to assess these questions more directly. In this regard, a recent report has demonstrated that the perception of control over the panic-producing effects of carbon dioxide inhalation substantially modified the panic-producing capacity of this particular stimulus.[94] These variables must be more intensely scrutinized in future panic challenge studies[88] to allow us to assess the relative impact (and interaction) of this complex array of cognitive and physiologic cues to panic.

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