Adrenergic Function in Patients With Panic Anxiety

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- Increased β-adrenergic receptor sensitivity could account for many aspects of panic disorder. We tested this hypothesis by comparing 14 patients with six normal control subjects. The controls and eight patients had 14 blood samples taken, and heart rate and BP measured, during a four-hour protocol that included supine rest, a posture and isometric exercise stimulus, and a series of up to seven logarithmically increasing bolus intravenous doses of isoproterenol hydrochloride. The other six patients were studied only at rest. Patients had markedly elevated resting heart rate, substantially elevated levels of plasma epinephrine, cortisol, and growth hormone, mildly elevated plasma norepinephrine levels, and decreased heart rate responses to isoproterenol. These results suggest that β-adrenergic receptor response is not increased, and may be decreased, in patients with panic disorder. Receptor down-regulation could result from the increased adrenergic function that these patients demonstrate, even in the absence of panic attacks.

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Several lines of evidence implicate β-adrenergic stimulation in panic attacks. The racing and pounding heartbeats, shortness of breath, sweating, rapid, deep breathing, and chest pain that occur during a panic attack suggest β-adrenergic activation. Tricyclic antidepressants prevent panic attacks, down-regulate β-adrenergic receptors, and decrease β-adrenergic agonist-induced cyclic adenosine monophosphate (cAMP) production. The gradual decrease in receptor number during antidepressant treatment is temporally related to clinical improvement. Imipramine treatment also blocks the panic attacks that lactate infusions otherwise induce in patients with panic disorder. As imipramine treatment is begun, up to 30% of panic disorder patients experience agitation and insomnia. This could be explained by increased adrenergic stimulation of overly responsive adrenergic receptors.

Isoproterenol hydrochloride, a β-adrenergic agonist, causes normal subjects to experience many somatic manifestations of panic, including the sudden onset of shortness of breath, and rapid, pounding heartbeats. Patients with "hyperdynamic β-adrenergic state" or acute "anxiety-like" attacks experience these and other symptoms at low doses of isoproterenol. Propranolol hydrochloride, a β-adrenergic blocker, relieves the somatic signs and symptoms of anxiety and can block isoproterenol-induced anxiety-like symptoms. Short-term propranolol administration does not, however, block lactate-induced panic in susceptible patients. If high doses of propranolol are stopped suddenly, panic symptoms may occur. The fact that patients with panic disorder are at increased risk for mitral valve prolapse syndrome (MVP) is intriguing because patients with MVP have abnormal autonomic function, elevated catecholamine levels, and anxiety-like symptoms. Taken together, these findings implicate the β-adrenergic system in panic disorder and suggest that increased β-adrenergic receptor sensitivity or increased stimulation of the β-adrenergic system. This study tests these competing hypotheses.

METHODS

Fourteen patients with panic attacks were compared with six normal control subjects. All patients had requested treatment at the University of Michigan Anxiety Disorders Clinic, Ann Arbor. The control subjects were recruited by advertisements. Subjects gave written consent and were fully informed about the design of the study, including the effects of isoproterenol and the use of placebo. They were not informed about the protocol, dosages, or order of drug and placebo infusions (Table I). Comprehensive histories, physical and psychiatric examinations, ECGs, and blood studies, including thyroid function tests, excluded subjects with substance abuse, medication use, pregnancy, and endocrine cardiovascular, or potentially confounding medical conditions other than MVP. Patients and controls were of comparable socioeconomic status. Age and sex data (Table 2) are assessed in "Results."

Control subjects had no diagnosable DSM-III axis I psychiatric disorders. Patients with panic attacks all had panic disorder or agoraphobia with panic attacks, as defined by DSM-III, but no other axis I disorders. Patients with clinical depression were excluded. All patients had experienced panic attacks in the previous month, but none had major attacks in the 24 hours before the protocol. Agoraphobic symptoms were mild in these patients, and it was not difficult for them to come to the hospital and participate in the protocol. Patients with panic attacks were included only if the evaluating investigator found the DSM-III diagnosis unequivocal, and a co-investigator concurred, on the basis of the written report and questionnaires. The questionnaires included standard rating scales and a detailed history questionnaire.

Table 1 outlines the experimental protocol. Sessions began at 11:40 AM with a tour of the Clinical Research Center, intended to minimize anxiety and novelty effects. At 11:45 AM, each subject ate a standardized lunch of approximately 650 calories, 420 mL of fluid, and 1 g of sodium. At 1 PM, each subject lay down in bed with the head elevated 45°. A slow intravenous (IV) infusion of normal saline solution was started in each arm, chest ECG leads were attached, and the first blood sample was taken. Blood samples were taken from the IV line without using a tourniquet.

The experimental protocol consisted of a 40-minute baseline period, a ten-minute standing and exercise period, a 19-minute rest period, and a 120-minute period in which a bolus infusion of isoproterenol hydrochloride or normal saline was given every ten minutes (Table I). Baseline blood samples were drawn 20, 30, and 40 minutes after the patients lay down. For six patients, the protocol ended at this point. These patients knew they would not receive drug infusions, and thus provided a control for possible effects of anticipating infusions on preinfusion variables.

Eight patients and the six controls continued with the rest of the protocol. At 1:40 PM, the subject stood; from 1:45 to 1:50 PM, the subject performed isometric exercise by steadily squeezing a tennis ball with the hand opposite the source of the blood specimen. At 1:50 PM, the subject lay down again. Blood samples, BP, and pulse rate were obtained prior to, and at 1, 5, and 10 minutes after standing up. The ECG printout and digital heart rate (HR)
Table 1.—Protocol Outline

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
</tr>
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<tbody>
<tr>
<td>11:40 AM</td>
<td>Tour of Clinical Research Center</td>
</tr>
<tr>
<td>11:45</td>
<td>Standardized lunch</td>
</tr>
<tr>
<td>12:00 PM</td>
<td>Quiet reading time</td>
</tr>
<tr>
<td>1:20</td>
<td>Blood sample 2 (baseline)</td>
</tr>
<tr>
<td>1:30</td>
<td>Blood sample 3 (baseline)</td>
</tr>
<tr>
<td>1:40</td>
<td>Blood sample 4 (baseline), then subject stands up</td>
</tr>
<tr>
<td>1:41</td>
<td>Blood sample 5 (after 1 min standing)</td>
</tr>
<tr>
<td>1:45</td>
<td>Blood sample 6 (after 5 min standing), then subject begins isometric exercises</td>
</tr>
<tr>
<td>1:50</td>
<td>Blood sample 7 (after 10 min standing and 5 min isometric exercise)</td>
</tr>
<tr>
<td>1:51</td>
<td>Subject lies down</td>
</tr>
<tr>
<td>2:05</td>
<td>Blood sample 8 (baseline)</td>
</tr>
<tr>
<td>2:10</td>
<td>Infusion 1 (placebo)</td>
</tr>
<tr>
<td>2:15</td>
<td>Blood sample 9</td>
</tr>
<tr>
<td>2:20</td>
<td>Infusion 2 (0.06 μg isoproterenol hydrochloride)</td>
</tr>
<tr>
<td>2:25</td>
<td>Blood sample 10</td>
</tr>
<tr>
<td>2:30</td>
<td>Infusion 3 (0.125 μg isoproterenol hydrochloride)</td>
</tr>
<tr>
<td>2:40</td>
<td>Infusion 4 (0.25 μg isoproterenol hydrochloride)</td>
</tr>
<tr>
<td>2:45</td>
<td>Blood sample 11</td>
</tr>
<tr>
<td>2:50</td>
<td>Infusion 5 (placebo)</td>
</tr>
<tr>
<td>2:50</td>
<td>Infusion 6 (0.50 μg isoproterenol hydrochloride)</td>
</tr>
<tr>
<td>3:10</td>
<td>Infusion 7 (1.0 μg isoproterenol hydrochloride)</td>
</tr>
<tr>
<td>3:15</td>
<td>Blood sample 12</td>
</tr>
<tr>
<td>3:20</td>
<td>Infusion 8 (placebo)</td>
</tr>
<tr>
<td>3:30</td>
<td>Infusion 9 (2.0 μg isoproterenol hydrochloride)</td>
</tr>
<tr>
<td>3:35</td>
<td>Blood sample 13 (for subjects who received top dose of 2.0 μg)</td>
</tr>
<tr>
<td>3:40</td>
<td>Infusion 10 (4.0 μg isoproterenol hydrochloride)</td>
</tr>
<tr>
<td>3:45</td>
<td>Blood sample 13 (for subjects who received 4.0-μg dose), blood sample 14 (15 min after highest dose, for all subjects)</td>
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</table>

were recorded from one minute before until three minutes after each activity: (a) standing, (b) starting to squeeze the ball, and (c) lying down. When the subject had been supine for 14 minutes, another baseline blood sample was obtained.

From 2:10 PM until 3:40 PM, the subject received nine or ten bolus IV infusions, ten minutes apart. Each subject received three saline placebo infusions and six or seven isoproterenol hydrochloride infusions. Each isoproterenol dose was double the previous dose. Doses were 0.06, 0.12, 0.25, 0.50, 1.0, 2.0, and 4.0 μg, and were administered as a bolus through a rapidly running IV line into an antecubital vein. All doses were in identical syringes containing 1 mL fluid. No additional isoproterenol was given if the HR reached 155 beats per minute or increased more than 35 beats per minute above baseline. To guarantee that data for all subjects were comparable (ie, that all blood specimens were drawn at the same time after the same total isoproterenol dose), the order of infusions was identical for all subjects. A placebo was always the first infusion, and the infusion following the 0.25- and 1.0-μg isoproterenol hydrochloride infusions.

The ECG and digital HR were recorded for one minute before and three minutes after each infusion. Three minutes after each infusion, the subject completed questionnaires about symptoms noted, and recorded a guess as to whether placebo or isoproterenol had been administered. Blood samples were drawn from the IV line five minutes after the first placebo infusion, five minutes after isoproterenol hydrochloride infusions of 0.06, 0.25, and 1.0 μg, and five and 15 minutes after the highest dose was given. Two subjects in each group received 4.0 μg of isoproterenol hydrochloride; for all others the highest dose was 2.0 μg.

All blood samples were placed in chilled tubes at the bedside, catecholamine samples into tubes containing glutathione and ethyleneglycol tetraacetic acid, lactate samples into tubes containing perchloric acid, and all other samples into heparinized tubes. The samples were immediately transported on ice to the adjacent laboratory. Lactate samples were homogenized and assayed promptly using an enzymatic method with lactate dehydrogenase and nicotinamide adenine dinucleotide. For all other measurements, patient and control samples were assayed in the same laboratory in batches that included both groups. Plasma for catecholamine and hormone specimens was separated by cold centrifugation and stored at –80 °C. Norepinephrine and epinephrine concentrations were assayed by a modification of an enzymic single-isotope derivative procedure that is accurate at 20 μg/mL. Plasma insulin levels were measured by radioimmunoassay. Plasma growth hormone (GH) level was assayed by a double-antibody radioimmunoassay with a sensitivity of 0.10 ng/mL. Plasma cortisol level was assayed by a competitive protein-binding technique. Plasma CAMP levels were determined by radioimmunoassay.

The mean and SD for the digital HR values were calculated for each subject for the 60-s periods before each of the nine or ten infusions. The mean for all these periods gave the baseline HR for each subject. Each subject's HR SD was similarly defined as the mean of the corresponding SDs. To conform with prior work and minimize the effect of vagal fluctuations in HR, a maximum baseline HR was defined for each subject as the baseline HR + 1.4 x HR SD. The postinfusion HR peak was defined as the average rate during the shortest three consecutive ECG RR intervals in the period 30 to 90 s after the infusion. A subject's increase in HR at a given isoproterenol dose was the difference between the maximum baseline HR and the postinfusion HR peak. For each subject, a regression line was calculated for postinjection HR increase as a function of isoproterenol dose number, using four or more pairs of values in which the peak HR was at least 10 beats per minute above maximum baseline HR. This method gave higher correlations than comparable calculations using overall baseline HR or using separate baseline HRs for each injection. The chronotropic dose 25 (CD25), the dose of isoproterenol that raised HR 25 beats per minute, was calculated from each subject's regression equation. The relationship between dose number and the actual dose is as follows: dose (μg) = 25 x CD25/40 - 5.

Echocardiographic evaluation was performed after subjects had completed the protocol and begun treatment. Antidepressant treatment is reported to have no effect on echocardiographic findings in patients with panic attacks. Echocardiographic and two-dimensional M-mode echocardiographic records were evaluated blindly by three faculty cardiologists according to standardized criteria. The MVEF was considered present if two of the three cardiologists agreed on the diagnosis.

The eight patients and six control subjects who participated in the entire protocol were compared on all variables. Hormone and lactate data were analyzed with a two-way analysis of variance (ANOVA) with repeated measures (diagnostic group by times). Group comparisons for other dependent variables were assessed with Student's t test. Heart rate data from the infusion study were subjected to a covariance analysis. Data from the six patients who did not receive infusions were separately analyzed using ANOVA and t tests.

RESULTS

No panic episodes or cardiac dysrhythmias occurred during the study. Most subjects were mildly apprehensive at the start, but all

Table 2.—Subject Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Controls (Complete)</th>
<th>Patients (Without Infusions)</th>
</tr>
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<tbody>
<tr>
<td>No.</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Mean age, yr</td>
<td>29.2</td>
<td>34.2</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>4/2</td>
<td>2/6</td>
</tr>
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</table>

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reported little apprehension during the latter part of the session. The three groups of subjects are designated controls, patients, and no-infusion patients. Median Spielberger State Anxiety Scale scores at the initial diagnostic evaluation were, as expected, substantially higher for patients than controls (Table 3). Patients' anxiety levels were also higher than controls' immediately before and immediately after the protocol, but the decline in anxiety during the session was proportional for all groups (Table 3). According to this measure, effects of anticipated were not different for the three groups.

Mean plasma epinephrine level (Fig 1) was significantly higher in patients than in controls throughout the protocol ($F = 7.42, P < .02$; Table 4). Both groups responded to the posture and exercise stimuli with modest parallel elevations. Similar elevations in both groups five minutes after the highest dose of isoproterenol may result from isoproterenol interference with the assay. Patients who were only studied at rest had levels comparable with the other patients and elevated in comparison with controls ($F = 14.08, P < .01$). Compared with normal subjects studied in our laboratory, and elsewhere, the patient groups had baseline epinephrine levels that were substantially higher, and the control group had levels that were somewhat lower.

Although mean plasma norepinephrine levels (Fig 1) were higher for patients than for normal subjects at all times, the difference was small ($F = 4.50, P < .06$; Table 4). Only during the latter part of the protocol did patients have levels consistently elevated above those of controls. The patients who did not receive infusions also had higher levels than controls ($F = 4.19, P < .05$). Baseline norepinephrine levels for both patient groups were higher than in normals studied here and elsewhere; mean levels for the control group were the same as those of other normals.

Because GH levels fluctuate widely, median values are presented (Fig 1), and results were analyzed nonparametrically. During the complete protocol, defining 4.0 nmol/L as an elevated GH level, 24% of all patient values but only 12% of control values were elevated ($x = 3.92, P < .04$). Control values were similar to published norms.

Patients' mean cortisol levels (Fig 1) were almost twice as high as in controls ($F = 12.47, P < .004$; Table 4). Values decreased for both groups during the session, but the difference between groups was consistent. Individual data (not shown) demonstrated that control subjects had relatively stable levels whereas patients had both higher levels and marked declines. Patients studied only at rest had levels similar to normal controls but lower than patients ($F = 17.91, P < .01$). The levels for controls were the same as published norms for the same time of day.

Fig 1.—Mean plasma concentrations during protocol. Times correspond to blood sample numbers in Table 2 (1 to 4 at rest, 5 to 7 standing, 9 to 14 during infusions). Mean values of all 14 times were indicated by open circles for patients, solid circles for controls. Error bars represent the average SEMs for all 14 times. Error bars for growth hormone exceeded scale. Broken line indicates patients (n = 8); dotted line, patients without infusions (n = 6); solid line, controls (n = 6); cAMP, cyclic adenosine monophosphate.

Plasma lactate level (Fig 1) was not significantly different between groups (Table 4). For all groups, levels decreased during the experimental session.

The cAMP assay was not consistently available, and results are presented only for patients (Fig 1). Levels were in the normal range (average for patients was 97.1 pmole/mL; normal values for this assay were below 20 pmole/mL) and were unaffected by isoproterenol, with the possible exception of the highest doses.

The ANOVA summary (Table 4) reveals no significant interaction effects between diagnostic group and times. Thus, there was no consistent tendency for the posture change, exercise, or isoproterenol infusions to differentially affect the groups on any of the variables studied.

Figure 2 shows mean BPs for each group while supine and after standing for one minute. Standing increased both systolic and diastolic pressure for all controls. The fact that patients' mean BP did not increase on standing results from decreases, after standing, in four patients' systolic pressure and in three patients' diastolic pressure.

Mean baseline HR was 25.5 beats per minute faster in patients than in controls: 80.7 vs 53.2 beats per minute ($t = 4.83, P < .001$). To determine if this result was skewed by a few rapid rates, the groups were compared for the slowest one-minute baseline HR determination for each subject. Patients showed a mean slowest baseline HR of 77 beats per minute, controls, a mean of 55.42 beats per minute ($t = 5.71, P < .01$). The difference remained significant ($P < .01$) after excluding the patient with the fastest HR and the control subject with the slowest HR. Ranges for the groups did not overlap; the slowest patient's HR (70.5 beats per minute) was faster than the
fastest control subject (65.1 beats per minute). The minimum resting HRs for the control group are similar to rates in some published reports for waking minimum HRs in young normal subjects, though overall mean supine HRs for control subjects are lower than in some previously reported HRs for panic patients are similar to those observed herein. A comparison of HR increase above baseline in response to standing revealed no differences between the groups. The coefficients of variation for HRs (SD/mean) were not different: 4.9% vs 5.1%.

The HR increase in response to a given dose of isoproterenol was less for patients than for controls. Figure 3 shows HR increase plotted as a function of isoproterenol dose for each subject. At doses of 1.0 and 2.0 μg, the actual highest doses for most subjects, the HR increases of six of the eight patients are below those of all of the controls.

A covariance analysis was used to compare the HR responses of all patients with those of all controls. The dose number was covariance as a function of HR increase above the subject’s maximum baseline HR. The analysis was structured to facilitate group comparison at the CD50. Absolute HR could not be used in this analysis because of the large group differences in baseline HR. The slope of the line fitting all patients’ data was not significantly different from that of the controls (F = 2.54, 0.05 < P < 0.10). Because the CD50 is a stable and reliable indicator of cardiac sensitivity to isoproterenol, the intercepts of each line were analyzed at the CD50. The patient group had a higher CD50 than the control group (F = 5.60, P < 0.02), i.e., they were less sensitive to isoproterenol. Mean CD50 for patients was 2.75 μg; for controls it was 0.91 μg. The mean CD50 for normal subjects studied with similar methods elsewhere was 1.19 μg.

The possibility of a “law of initial values,” or other effect of baseline HR differences on HR responsiveness to isoproterenol, was investigated. The HR increase was plotted as a function of baseline HR for each of four doses of isoproterenol. Regression equations were calculated separately for patients and controls at each dose, giving a total of eight lines. If baseline HR influenced the HR increase at a given dose of isoproterenol, the slopes and correlation coefficients of these lines should be different from 0. The mean slope for the eight regression lines was 0.007, and the mean correlation coefficient was −0.01. This suggests that baseline HR and HR response to isoproterenol are independent, in the HR ranges reported herein.

Both patients and controls correctly identified 67% of the isoproterenol infusions. A dose of 0.25 μg was usually identified correctly as an active substance; a dose of 0.50 μg was consistently identified correctly. Controls more frequently than patients guessed “drug” when placebo was actually administered, 33% vs 21%. In other words, both groups seemed equally sensitive to the hypnotic effects of the drug, and patients did not demonstrate any tendency to be placebo responders.

Three of ten patients and none of three controls available for study had MVPs. Despite the extremely small number, the three patients with MVPs were compared with the seven without MVPs. On CD50, epinephrine, norepinephrine, and cortisol levels, the groups were nearly the same. The two subjects with the highest GH levels both had MVPs. This is likely to be an artifact of the small number. Lower mean lactate levels (0.90 mmol/l = 1.13 mM; t = 1.1; P < 0.29) in patients with MVPs are also of questionable importance.

Because the sex ratios of the groups were unequal (Table 2), the male and female subjects in each group were compared on each variable, to determine if this factor might have affected the results. No significant differences were found, and the nonsignificant differences were such that, if the sex ratios in the groups had been equal, differences between patients and controls could be expected to increase for CD50 and plasma epinephrine levels and to remain unchanged for cortisol and GH. Mean plasma norepinephrine level for female subjects (348 ng/mL) was higher than for male subjects (283 ng/mL) (t = 1.58; P < 0.14), but previous research has not found sex differences in plasma catecholamine levels. Female patients did have higher baseline HRs than male patients, but patients and controls had no overlap in HR ranges. Sex bias cannot account for the differences between groups.

The patients and patients without infusions groups were older (by means of 5 years and 9 years, respectively) than the control group. Age is reported not to affect plasma epinephrine levels, but mean plasma norepinephrine level increases approximately 4 pg/mL/year. This could explain only 25% of the observed norepinephrine group differences.

Characteristics of individual subjects, including mean hormone levels, HR, CD50, and subjective symptoms were analyzed for correlations with each other within diagnostic groups and in the group of all subjects. In controls, baseline HR was significantly correlated only with mean cortisol level (r = −0.87; P < 0.05); for patients, baseline HR was significantly correlated with mean GH level (r = −0.94; P < 0.01) and mean norepinephrine level (r = 0.90; P < 0.01). The CD50 in controls was significantly correlated only with mean epinephrine level during times 1 through 4 (r = −0.82; P < 0.05); for patients it was significantly correlated with no other variable. In neither patients nor controls was CD50 correlated with baseline HR (r = −0.07 and r = 0.16, respectively). These significant correlations may simply reflect the large number of correlations calculated instead of any real relationship between variables.

COMMENT

When compared with normal controls, patients with panic disorder or agoraphobia with panic attacks demon-
strated (a) substantially elevated baseline HR; (b) moderately elevated plasma epinephrine and mildly elevated plasma norepinephrine levels during rest, exercise, and the infusions; (c) elevated plasma GH and cortisol levels; (d) normal plasma cAMP level; (e) equal plasma lactate level; and (f) decreased HR response to isoproterenol. These findings suggest that patients with panic attacks have increased adrenergic activity at times other than during panic attacks, and that their β-adrenergic receptors are not overly responsive, and may, in fact, have decreased sensitivity. Consistent with this interpretation is a recent report that patients with “incapacitating anxiety” have in vitro isoproterenol-stimulated cAMP production that is significantly lower than that of controls.87

These results confirm prior work,9 with respect to epinephrine, though controls from this prior study had higher levels than either controls in this study or published norms.88 Using data from 14 times, patients’ norepinephrine levels were slightly elevated in the present study, in contrast to the prior report of large but statistically insignificant differences.9 The normal cortisol levels reported previously for panic disorder patients9 are at variance with the elevated levels reported here.

The elevated resting HRs in patients with panic attacks require replication and explanation using a protocol designed for that purpose. Extended recordings of HR during various activities and sleep will be necessary. Calculations based on prior work89 show that the epinephrine and norepinephrine elevations in patients reported herein could not increase HR by more than a few beats per minute. Parasympathetic influences are likely to be important.

The elevations of cortisol, GH, and catecholamines suggest acute “stress” as a possible explanation for the differences between groups90;91; however, several observations suggest that this is not correct. Many of these patients are part of a larger ongoing study, in which elevated urinary norepinephrine and epinephrine levels are observed in patients with panic disorder, whether or not a protocol is anticipated the next day (R.M.N. et al, unpublished findings, October 1983). Panic disorder patients in a separate (as yet unpublished) study,92 who only had blood samples taken, had elevated plasma catecholamine levels. Reduced β-adrenergic receptor sensitivity suggests a chronic change in adrenergic stimulation that is unlikely to result from acute “stress.” Patients studied without infusions had GH and catecholamine levels similar to those of patients with infusions, but cortisol levels similar to controls, suggesting that elevated cortisol levels could be related to anticipating infusions. Anxiety changes related to anticipating the session were, however, similar for all groups (Table 8). Finally, the remarkably consistent differences between the groups’ cortisol and catecholamine levels at all 14 times weigh against an acute “stress” explanation, because the procedure was not equally stressful at all 14 times. Although this study included no “professional subjects,” four of the control subjects were familiar with clinical settings. This factor is important for studies involving catecholamines because subjects “familiar with research routines” may have lower plasma levels than inexperienced subjects.93 This does not explain the current findings because patients and patients who were not anticipating infusions had resting catecholamine levels that were substantially higher than norms for a large pool of volunteers studied at the same laboratory, and they were higher than published norms.88 In addition, standing tends to equalize norepinephrine values for experienced and inexperienced volunteers,94 whereas plasma catecholamine levels of patients and controls in this study remained different during standing and isometric exercise.

Because differences in exercise habits might influence these variables, this was assessed for the five controls and ten patients who completed a health history questionnaire, which included questions about exercise. “Regular exercise” was reported by 83% of patients, 75% of patients without infusions, and 100% of controls. “Regular strenuous exercise” was reported by three patients and only one control. Group differences in exercise tolerance are unlikely to have seriously biased the results.

How specific are these findings? People with hypertension, depression, mania, and schizophrenia are also reported to have elevated catecholamine levels.95,96 For depression, physical activity97 or anxiety98 may account for the differences observed. In this study, differences between groups were reliably present on multiple measurements during bed rest. Studies of other anxiety disorders are needed to determine the specificity of these findings. Reliable findings specific for panic disorder might provide clues to the mechanisms that determine susceptibility to panic. These may be quite different from the mechanisms that mediate specific panic symptoms, and the findings reported herein may be only indirectly related to changes that occur during panic attacks. Studies of patients during panic attacks are needed to clarify the autonomic and endocrine changes involved, and their role in the production of panic symptoms. The surprisingly small endocrine changes observed during lactate-induced panic attacks99 suggest that parasympathetic and other mechanisms need to be considered. It is possible that chronic catecholamine excess itself makes people more susceptible to panic. A careful study of patients with pheochromocytoma would test this hypothesis.

The hypothesis that patients with panic attacks might have increased β-adrenergic receptor sensitivity appears to be false, and the alternate hypothesis of increased adrenergic stimulation is supported. Other findings that emerged from this study may suggest new directions that may lead to an understanding of more fundamental abnormalities in patients with panic disorder.

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