Abnormal Noradrenergic Function in Posttraumatic Stress Disorder

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• To evaluate possible abnormal noradrenergic neuronal regulation in patients with posttraumatic stress disorder (PTSD), the behavioral, biochemical, and cardiovascular effects of intravenous yohimbine hydrochloride (0.4 mg/kg) were determined in 18 healthy male subjects and 20 male patients with PTSD. A subgroup of patients with PTSD were observed to experience yohimbine-induced panic attacks (70% [14/20]) and flashbacks (40% [8/20]), and they had larger yohimbine-induced increases in plasma 3-methoxy-4-hydroxyphenylglycol levels, sitting systolic blood pressure, and heart rate than those in healthy subjects. In addition, in the patients with PTSD, yohimbine induced significant increases in core PTSD symptoms, such as intrusive traumatic thoughts, emotional numbing, and grief. These data were consistent with a large body of preclinical data that indicated that uncontrollable stress produces substantial increases in noradrenergic neuronal function. We discuss the implications of these abnormalities in noradrenergic functional regulation in relation to the long-term neurobiological sequelae of severe uncontrollable stress and the pathophysiological relationship between PTSD and other anxiety disorders, such as panic disorder.

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Although only recognized as a distinct diagnostic entity in 1980, current data suggest that posttraumatic stress disorder (PTSD) is a disorder of considerable prevalence and morbidity.[1,2] Despite the high prevalence of PTSD, there has been comparatively little research directed toward understanding its pathophysiology. Studies that focus on elucidating the neurobiological changes that occur in the brain following severe psychological trauma are only now being initiated.

The dearth of clinical neurobiological research on PTSD stands in sharp contrast to the preclinical body of investigation that has identified large and long-term functional changes in a variety of brain neuronal systems as a result of stress. The effects of stress on brain noradrenergic function have been particularly well studied. For example, stress, especially uncontrollable stress, produces an elevated sense of fear and anxiety and causes regional increases in norepinephrine turnover in the locus ceruleus (LC), limbic regions (hypothalamus, hippocampus, and amygdala), and cerebral cortex.[3,4] In addition, a series of investigations have shown that uncontrollable stress results in an increased responsiveness of LC neurons to excitatory stimulation that is associated with a reduction in α_2-adrenergic autoreceptor sensitivity.[5,6]

Recent clinical investigations suggest that a subgroup of patients with chronic PTSD may exhibit abnormalities in noradrenergic function. Twenty-four–hour urine norepinephrine excretion has been reported as significantly increased, while platelet α_2-adrenergic receptor number and lymphocyte adenylate cyclase activity have been reported as significantly decreased compared with that in controls.[7-10] This decrease in receptor number and adenylate cyclase activity may represent an adaptive downregulation in response to persistently elevated levels of circulating catecholamines. Furthermore, propranolol hydrochloride and clonidine hydrochoride, which act by decreasing noradrenergic transmission, appear to diminish a number of PTSD symptoms.[11,12] These findings are consistent with psychophysiological studies that show that veterans with chronic PTSD respond with abnormal elevations of blood pressure and heart rate when exposed to combat-associated stimuli, such as gunfire.[13-19]

The purpose of the present investigation was to evaluate further the relationship between the regulation of noradrenergic function and PTSD. This was done by using a yohimbine hydrochloride challenge paradigm that has previously demonstrated evidence for abnormal regulation of noradrenergic function in patients with panic disorder.[20-22] Yohimbine activates noradrenergic neurons by blocking the α_2-adrenergic autoreceptor and, thereby, produces a variety of biochemical, behavioral, and cardiovascular effects.[20-22]

SUBJECTS AND METHODS

Patients

Twenty male patients gave voluntary written informed consent for their participation in the study. They were treated as inpatients in the National Center for PTSD, located in the Department of

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From the National Center for Post Traumatic Stress Disorder, West Haven (Conn) Veterans Affairs Medical Center (Drs Southwick, Krystal, Morgan, Johnson, Nagy, Nicolau, and Charney), and the Department of Psychiatry, Yale University School of Medicine, New Haven, Conn (Drs Southwick, Krystal, Morgan, Johnson, Nagy, Heninger, and Charney).

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Veterans Affairs Medical Center at West Haven, Conn. Each patient met *DSM-III-R* criteria for chronic PTSD, using the Structured Clinical Interview for *DSM-III-R*, and they had a Mississippi Posttraumatic Stress Disorder Scale score of greater than 107. Vietnam combat experience was verified by military records, including the DD214 (an official military document of service). The mean (±SEM) severity of PTSD on the Mississippi Scale was 129.5±2.0 (n=17).[23] All diagnoses were finalized by a consensus diagnostic team. On admission to the study, nine patients and eight patients also met current *DSM-III-R* criteria for panic disorder and major depression, respectively. Eighty percent of patients met lifetime *DSM-III-R* diagnostic criteria for major depression, 60% for lifetime panic disorder, and 85% for lifetime alcohol dependence. The mean (±SEM) age was 41±3 years. The mean (±SEM) weight of the patients was 83±12 kg. All patients were drug free for a minimum of 4 weeks before the first test session. Exclusion criteria included organic mental disorders, neurological disorders, such as seizures, cardiovascular disease, including hypertension, history of myocardial infarction, or significant electrocardiographic abnormalities, and serious medical illnesses, such as diabetes and chronic hepatitis.

Healthy Subjects

Eighteen healthy male subjects were recruited from responses to advertisements and from referrals by other healthy subjects, and they all gave voluntary, written, informed consent for their participation in the study. The healthy subjects were determined to be free of mental disorder on the basis of a structured psychiatric interview, and none of the subjects reported a history of mental illness in first-degree relatives. None of the healthy subjects reported that they were taking any psychoactive medication for the 4 weeks before the study. The mean (±SEM) age of the healthy subjects was 28±9 years. The mean (±SEM) weight of the healthy subjects was 82±15 kg.

None of the patients and healthy subjects in the study reported a history of serious medical illness, and they all had normal results on physical examination, electrocardiogram, and laboratory tests of renal, hepatic, pancreatic, hematopoietic, and thyroid function.

PROCEDURES

In a double-blind fashion, patients and healthy subjects received either an intravenous infusion of yohimbine hydrochloride (0.4 mg/kg) or saline solution during 10 minutes in a randomized balanced order. Except for the research pharmacist, all investigators and raters were blind to infusion. The interval between test days was generally between 4 and 7 days.

The patients and healthy subjects arrived on the Neurobiological Studies Unit by 8:30 AM of each test day. For each test day, subjects fasted overnight for 10 hours and remained in the fasting state during the test day until approximately 2 PM. They were supine with their heads elevated during most of the 5-hour test day. They stood only to use the bathroom and to permit recording of their standing blood pressure and pulse rate. They were not permitted to sleep. Blood was sampled from an intravenous cannula in a forearm vein that was kept patent with a normal saline solution. The intravenous cannula was in place for at least 60 minutes before blood samples were obtained for determination of free 3-methoxy-4-hydroxyphenylglycol (MHPG) and cortisol levels. Blood samples were obtained for determining plasma-free MHPG and cortisol levels at 15 and 0.5 minutes before the dose and at 40, 60, 120, and 180 minutes after the dose. Sitting and standing blood pressure and pulse rate were measured in the usual clinical fashion with a mercury sphygmomanometer at 15 and 0.5 minutes before and 20, 40, 60, 120, and 180 minutes following the dose.

A series of self-report behavioral ratings were administered 15 minutes before and 20, 60, 120, and 180 minutes after the yohimbine or placebo dose. The Panic Attack Symptom Scale (PASS) was administered to assess the effects of yohimbine on panic attack symptoms. This scale consisted of 27 items that included the 13 *DSM-III-R* panic attack symptoms (eg, sweating, chest pain or discomfort, fear of dying). Each symptom was rated on a four-point scale (1=not present, 2= mild, 3=moderate, and 4=severe). Scores on this scale can range from a minimum of 27 to a maximum of 108. A PTSD symptom scale was developed and used to measure the effects of yohimbine on specific symptoms associated with PTSD. This scale was only administered to the patients with PTSD and consisted of 14 items (intrusive traumatic thoughts, flashback, startle, hypervigilant, out of body, distant from people, emotionally numb, difficulty with concentrating, guilt, anger, grief, helpless, hopeless, and sad). Each symptom was rated on a five-point scale (1=not present, 2=mild, 3=moderate, 4=severe, and 5=worst ever). The possible scores on this scale can range from a minimum of 14 to a maximum of 70.

Careful attention was directed toward an accurate assessment of whether yohimbine induced a panic attack or a flashback in the healthy subjects or patients with PTSD. To determine whether the subject had a panic attack or a flashback during test sessions, each patient and healthy control were evaluated by a research psychiatrist (S.M.S. or J.H.K.) and a research nurse who was blind to medication status. This evaluation was based on direct clinical observation and the patient's self-report.

The following criteria had to be satisfied to qualify as a panic attack: (1) In comparison with baseline, yohimbine had to produce an increase in severity on four or more *DSM-III-R* panic attack symptoms that were assessed on the PASS. (2) The patient must have reported a crescendo increase in severe subjective anxiety of at least 25 mm from baseline on a 100-mm visual analogue scale for anxiety.[20-22] (3) Based on a structured interview that was completed during the test session by the research nurse, the symptoms that were reported by the patient following drug administration had to meet *DSM-III-R* criteria for a panic attack. (4) For patients with a history of panic attacks, the drug-induced anxiety state had to be very similar to a naturally occurring panic attack in relation to intensity and specific symptoms. (5) There must have been consensual agreement of the two research psychiatrists (S.M.S. and J.H.K.) that a panic attack had occurred based on information from above and from nursing notes that documented a rapid increase in anxiety and fear characteristic of naturally occurring panic attacks.

To be classified as a flashback, the following criteria had to be met: (1) The patient must have reexperienced a past traumatic event during the course of drug or placebo infusion. (2) The reexperiencing must have involved one or more sensory modalities (hearing, seeing, smelling, tasting, and/or feeling). (3) For patients with a history of flashbacks, the drug-induced reexperiencing state must have been very similar to a naturally occurring flashback. (4) There must have been consensual agreement of the two research psychiatrists (S.M.S. and J.H.K.) that a flashback had occurred.

Biochemical Methods

Blood samples were kept on ice for a maximum of 1 hour before separation of plasma in a refrigerated centrifuge. The plasma specimens then were frozen at −70°C until assay. Preparation of the sample for MHPG analysis was carried out according to a modified version of the method of Dekirmenjian and Maas[24] and Maas et al.[25] Quantitation of the plasma-free MHPG level was carried out by selected ion monitoring, as described elsewhere, using a quadruple mass spectrometer that was equipped with a gas chromatographic inlet system[24,25] (intra-assay and interassay coefficients of variation [CVs] were 6% and 11%, respectively). The plasma cortisol level was measured by using radioimmunoassay kits (Baxter Travenol Diagnostics, Inc, Incstar Corp, Stillwater, Minn); intra-assay and interassay CVs were 3% and 5%, respectively. To reduce the variance in method, plasma specimens were assayed in duplicate. The individual values that were reported were the means of the two values that were obtained from these specimens. The subjects, research nurse, and laboratory staff were blind to the sequence of the yohimbine and placebo doses.

Data Analysis

The data were entered into computer files and analyzed by using standard Statistical Analysis System and Biomedical Data Processing programs. The effects of yohimbine on plasma MHPG and cortisol levels, cardiovascular parameters, and behavioral ratings in patients and healthy subjects were initially evaluated by using an analysis of variance (ANOVA) with repeated measures. This allowed an assessment of the statistical significance of the main effects of diagnosis (patients vs healthy controls), drug (placebo vs yohimbine), and time of measurement (changes over the time points that were sampled). A central question of the data analysis was whether the patients reacted differently to yohimbine than the healthy subjects. In the ANOVA, this was manifest in the interaction of diagnosis with drug, diagnosis with time, and, most important, diagnosis with drug and time. The one remaining interaction of drug and time simply indicated the significance of the drug effect over time for the sample as a whole.

The significant interactions with diagnosis were further evaluated with *t* tests that were used to determine how and when the patients differed from healthy subjects in their response to yohimbine. This was primarily done by subtracting the baseline value from the value at each time point on the variable of interest. This resulted in a change score at each time point following placebo or yohimbine administration. Subtracting the change following placebo administration from that following yohimbine administration enabled an estimate of the net yohimbine effect (eg, yohimbine-placebo difference).

The net peak change for each variable following yohimbine administration was measured by subtracting the baseline score from the peak score following yohimbine administration. The peak change value for yohimbine minus the peak change value for placebo gave a net peak value of the yohimbine effect. Pearson correlation coefficients were calculated to evaluate the relationships among net peak biochemical, behavioral, and cardiovascular effects of yohimbine in both the healthy subjects and patients. The correlation coefficients that were calculated did not reveal a relationship between age and yohimbine effects in either patients or healthy subjects. Results were reported as the mean±SEM. Two-tailed tests of significance were used.

RESULTS

Anxiogenic Effects of Yohimbine

Panic Attacks and Flashbacks.—Yohimbine produced panic attacks in 14 (70%) and flashbacks in eight (40%) of the 20 patients with PTSD. Each of the eight patients who reported flashbacks following yohimbine had panic attacks at the same time. None of the healthy subjects experienced yohimbine-induced panic attacks or flashbacks. No panic attacks occurred after placebo administration in either the patients with PTSD or healthy subjects. Only one subject, a patient with PTSD, had a flashback following placebo.

In many patients, the panic attacks and flashbacks that were produced by yohimbine were intense and vivid. Below, we report two cases that exemplify the nature of the yohimbine-induced panic attacks and flashbacks.

Case 1.—The first patient is a 41-year-old, divorced, marine Vietnam combat veteran who had a long history of PTSD. In Vietnam, he saw heavy combat and participated in atrocities. Since the war, he had suffered from PTSD with marked psychosocial dysfunction. On evaluation, he met *DSM-III-R* criteria for PTSD but not for panic disorder. The patient experienced a panic attack on the active yohimbine infusion day but not on the placebo infusion day. On the active yohimbine infusion day, 10 minutes after the start of the infusion, the patient suddenly experienced intense fear, shortness of breath, diaphoresis, intense tremulousness and shaking, nausea, palpitations, hot and cold flashes, and light-headedness. Although he reported vivid memories of combat, he did not have a flashback.

Case 2.—The second patient is a 47-year-old veteran who served as a helicopter gunner in Vietnam. He flew dozens of combat missions and witnessed many deaths. He was wounded on two separate occasions. For the past 20 years, he has suffered from severe PTSD. On evaluation, he met *DSM-III-R* criteria for both PTSD and panic disorder. During the challenge test, his response to placebo infusion was relatively uneventful. However, on the active yohimbine treatment day, the patient experienced both a panic attack and a flashback. During the flashback, the patient was highly agitated and described a helicopter crashing into flames. He could see the flames, hear the crash, and smell the smoke. He appeared to be in a dissociated state, responding as if the traumatic episode was occurring in the present.

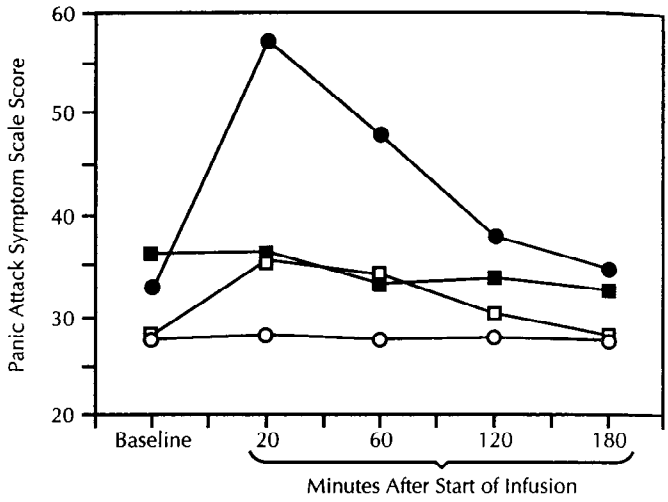

Fig 1.—*Effects of yohimbine hydrochloride and placebo on scores of the Panic Attack Symptom Scale in healthy subjects (n=17) and patients with posttraumatic stress disorder (n=18). The mean change from baseline after yohimbine administration minus the mean change from baseline after placebo administration (defined as the yohimbine-placebo difference) is significantly greater in patients with posttraumatic stress disorder than in healthy subjects at 20 minutes (P<.001) and 60 minutes (P<.05). Open circles indicate healthy subjects/placebo; open squares, healthy subjects/yohimbine; closed squares, patients with posttraumatic stress disorder/placebo; and closed squares, patients with posttraumatic stress disorder/yohimbine.*

Panic Attack Symptom Scale.—As shown in Fig 1, consistent with the panicogenic effects of yohimbine, the patients with PTSD had larger increases on the PASS than the healthy subjects following yohimbine treatment. In the patients with PTSD ($F=16.49$; $df=4, 68$; $P<.001$) and healthy subjects ($F=9.10$; $df=4, 64$; $P<.001$), there was a significant drug and time interaction. A highly significant drug and time and diagnosis interaction was also seen ($F=6.12$; $df=4, 4, 132$; $P<.001$). The yohimbine-placebo difference at 20 and 60 minutes was significantly greater in the patients compared with that in the healthy controls. The patients with PTSD who reported panic attacks had greater yohimbine-induced increases on the PASS than the other patients at every time point, but given the small sample size, this failed to reach statistical significance.

PTSD Scale.—As shown in Fig 2, yohimbine increased PTSD symptoms in the patients as indicated by substantial increases on the total score of the PTSD scale. The ANOVA revealed a significant drug and time interaction ($F=4.92$; $df=4, 76$; $P<.01$), which was reflected in significant yohimbine-placebo differences at 20 ($t=10.2$, $df=19$, $P<.01$) and 60 ($t=8.0$, $df=19$, $P<.05$) minutes following drug administration.

Analysis of the specific symptoms that were rated on the PTSD scale revealed significant drug and time interactions for intrusive thoughts ($F=6.20$; $df=4, 64$; $P<.001$), emotionally numb ($F=3.05$; $df=4, 64$; $P<.05$), guilt ($F=3.02$; $df=4, 64$; $P<.05$), grief ($F=3.47$; $df=4, 64$; $P<.05$), distant from people ($F=2.94$; $df=4, 64$; $P<.05$), helplessness ($F=3.03$; $df=4, 64$; $P<.05$), difficulty with concentrating ($F=4.86$; $df=4, 64$; $P<.01$), and flashback ($F=2.49$; $df=4, 64$; $P=.05$). There were significant yohimbine-placebo differences for each of these symptoms, except for helplessness and flashback at 20 min-

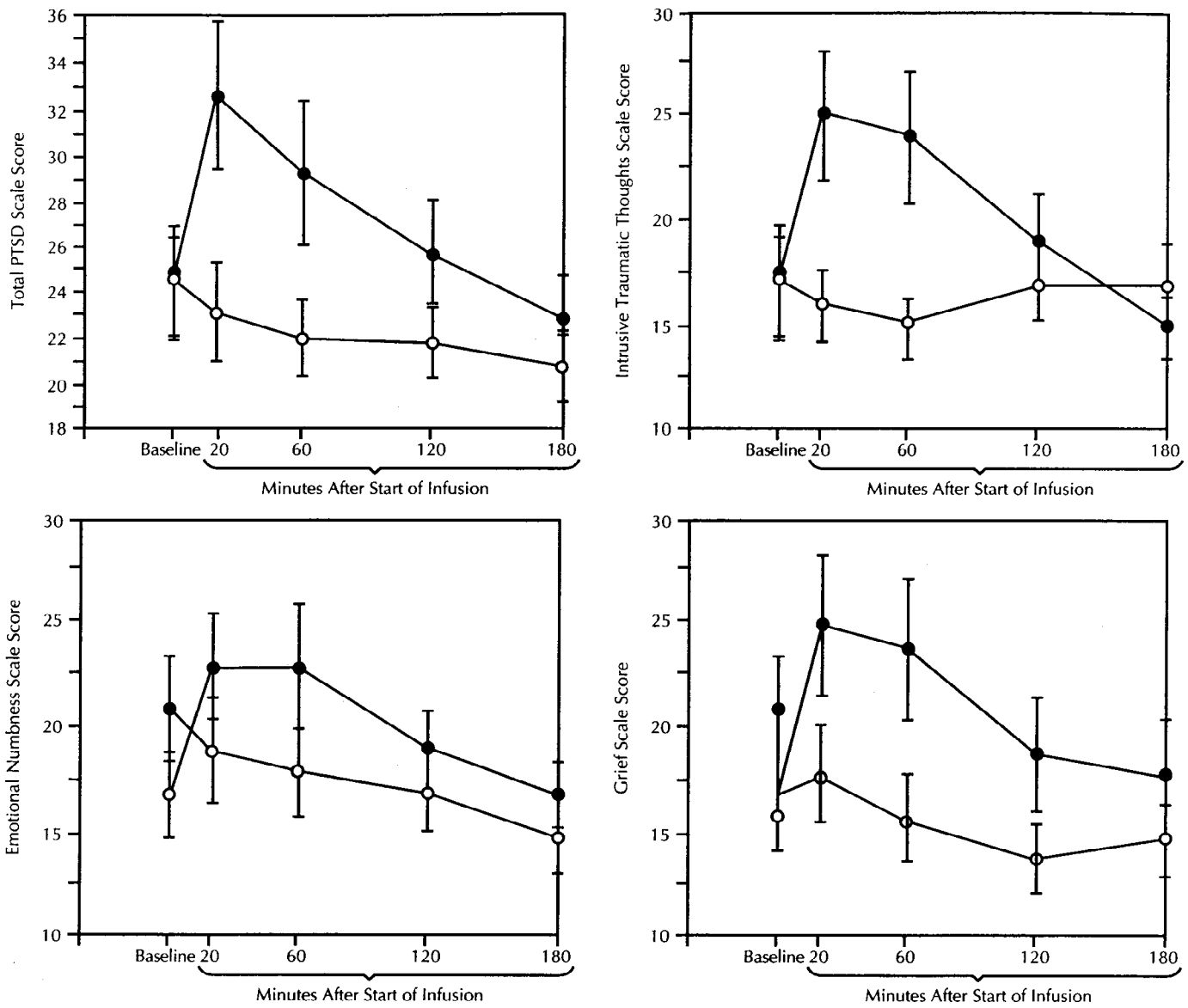

Fig 2.—*Effects of yohimbine hydrochloride (closed circles) and placebo (open circles) on total score and individual symptom scores of the Posttraumatic Stress Disorder (PTSD) Scale in patients with PTSD (n=20). The mean change from baseline after yohimbine administration was greater than the mean change from baseline after placebo administration (P<.05 and P<.01 at 20 and 60 minutes after the start of the infusion, respectively).*

utes. Significant yohimbine-placebo differences were also seen for other symptoms, such as intrusive thoughts, emotionally numb, grief, and difficulty with concentrating, at 60 minutes.

Biochemical Effects of Yohimbine

Yohimbine Effects on Plasma MHPG Levels.—As given in the Table, the ANOVAs that examined the effects of yohimbine on plasma MHPG levels showed a significant drug and time interaction in both healthy subjects (F=3.0; *df*=4, 60; *P*<.02) and in the patients with PTSD (F=14.2; *df*=4, 72; *P*<.001). Significant yohimbine-placebo–induced increases were observed at all time points within each group.

The patients with PTSD had greater increases in plasma MHPG levels after receiving yohimbine than the healthy subjects. A significant diagnosis and drug and time interaction was observed in the comparison of the patients with PTSD with the healthy subjects (F=2.7; *df*=4, 4, 132; *P*<.05). Significant differences in the yohimbine-placebo difference were identified between the patients with PTSD and the healthy subjects at every time point that was measured (Table). The values for the yohimbine-placebo difference in plasma MHPG levels at 180 minutes for each healthy subject and patient with PTSD are illustrated in Fig 3. The patients who experienced yohimbine-induced panic attacks or flashbacks had numerically greater yohimbine-placebo differences than the patients who did not, but this failed to reach statistical significance on the ANOVA or Student's *t* tests. Baseline plasma MHPG levels were not different between the patients with PTSD and healthy subjects.

There was a significant correlation between baseline MHPG levels and peak effects of yohimbine on MHPG levels in the patients with PTSD (*r*=.66, *P*<.01) but not in the healthy subjects (*r*=.24, *P*=.35). In both the healthy subjects (*r*=.68, *P*<.01) and patients with PTSD (*r*=.61, *P*<.01), there was a significant correlation between the baseline PASS score and the baseline MHPG concentration. Moreover, there was a significant correlation between peak effects of yohimbine on plasma MHPG levels and the PASS in the patients with PTSD (*r*=.54, *P*<.05) but not in the healthy subjects (*r*=.18, *P*=.53). With regard to PTSD-specific

The Effect of Intravenous Yohimbine and Placebo on Plasma-Free MHPG Levels in Healthy Subjects and Patients With PTSD*

Group and Drug	Baseline		MHPG Level Change From Baseline After Dose, ng/mL							
			40 min		60 min		120 min		180 min	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
Healthy subjects (n=16)										
Placebo	3.7	0.3	0.3	0.2	0.2	0.1†	0.4	0.2†	0.7	0.2
Yohimbine hydrochloride	3.5	0.2	1.1	0.2‡	1.3	0.3‡	1.4	0.3‡	1.2	0.1‡
Yohimbine-placebo difference	...	...	0.8	0.3§	1.1	0.3‖	1.0	0.4§	0.5	0.2
Patients with PTSD (n=19)										
Placebo	4.1	0.4	0.1	0.1	0.1	0.1	0.2	0.1	0.4	0.1¶
Yohimbine	4.1	0.4	1.8	0.3‡	2.5	0.4‡	2.6	0.5‡	2.3	0.5‡
Yohimbine-placebo difference	...	...	1.6	0.3#**	2.4	0.5#**	2.4	0.4#**	1.9	0.4#††

*MHPG indicates 3-methoxy-4-hydroxyphenylglycol; PTSD, posttraumatic stress disorder. Baseline values are given as the means from two samples obtained 15 and 0.5 minutes before drug administration. The yohimbine-placebo difference is calculated as follows: (value for time point after yohimbine administration minus baseline) minus (value for time point after placebo administration minus baseline).

†$P<.05$, change from baseline (except where indicated, all P values in this table were determined by two-tailed paired t tests).

‡$P<.001$, change from baseline.

§$P<.05$, change from baseline, yohimbine vs placebo.

‖$P<.01$, change from baseline, yohimbine vs placebo.

¶$P<.01$, change from baseline.

#$P<.001$, change from baseline, yohimbine vs placebo.

**$P<.05$, yohimbine-placebo difference, patients with PTSD vs healthy subjects (Student's t test, two tailed).

††$P<.01$, yohimbine-placebo difference, patients with PTSD vs healthy subjects (Student's t test, two tailed).

symptoms, although there was not a significant relationship between baseline scores on the PTSD symptoms scale and baseline MHPG levels (r=.29, P=21), there was nearly a significant correlation between peak effects of yohimbine on plasma MHPG levels and the PTSD symptom scale in the patients with PTSD (r=.41, P=.08).

Yohimbine Effects on Cortisol Levels.—The ANOVA that assessed the effects of yohimbine on plasma cortisol levels in the healthy subjects revealed a highly significant drug and time interaction (F=11.121; df=4, 68; $P<.001$). Significant yohimbine-placebo differences were seen at 40 (7.0±2.1, t=3.29, df=17, $P<.01$) and 60 (7.7±2.1, t=3.58, df=17, $P<.01$) minutes. The ability of yohimbine to increase the plasma cortisol level in the patients with PTSD was similar to that in the healthy subjects. The drug and time interaction was also highly significant (F=11.39; df=4, 76; $P<.001$), and significant yohimbine-placebo differences occurred at 40 (7.9±1.7, t=4.73, df=19, $P<.001$), 60 (8.6±1.9, t=4.43, df=19, $P<.001$), and 120 (5.5±1.5, t=3.65, df=19, $P<.01$) minutes.

There were no significant differences between the patients with PTSD and healthy subjects in the cortisol response to yohimbine. The diagnosis and drug and time interaction was not significant, and at no time point were the yohimbine-placebo differences significantly different between the two groups. Similar analyses indicated that the patients with PTSD who reported yohimbine-induced panic attacks or flashbacks had cortisol responses to yohimbine that were not different than those of the healthy subjects.

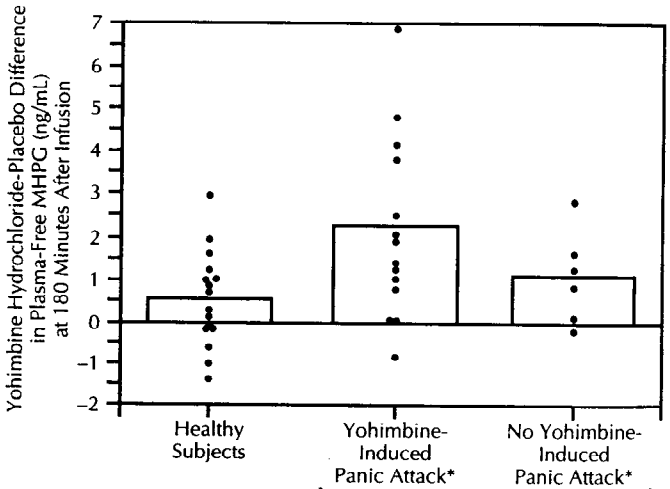

Fig 3.—*Yohimbine hydrochloride–placebo difference in plasma-free 3-methoxy-4-hydroxyphenylglycol (MHPG) at 180 minutes after infusion in healthy subjects, patients with posttraumatic stress disorder (PTSD), and patients with PTSD without yohimbine-induced panic attacks. Asterisk indicates P<.01, patients with PTSD who had yohimbine-induced panic attacks compared with healthy subjects.*

Effects of Yohimbine on Blood Pressure and Heart Rate

Blood Pressure.—Highly significant drug and time interactions for sitting and standing systolic and diastolic blood pressures were observed in the healthy subjects. The significant mean yohimbine-placebo increases in sitting systolic blood pressure occurred at 40, 60, and 120 minutes and ranged from 10 to 14 mm Hg. Significant yohimbine-placebo increases in standing systolic blood pressures were seen at 40 and 120 minutes and ranged from 6 to 19 mm Hg. There were also significant yohimbine-placebo increases in sitting diastolic blood pressure at 40 and 60 minutes, ranging from 6 to 9 mm Hg, and in standing diastolic blood pressure at 40, 120, and 180 minutes, ranging from 5 to 10 mm Hg.

Yohimbine had robust effects on blood pressure in the patients with PTSD. Significant drug and time interactions were found for each of the four blood pressure measurements. There were significant yohimbine-placebo increases from baseline in sitting and standing systolic blood pressures at all time points after the dose, ranging from 11 to 31 mm Hg. There were also significant yohimbine-placebo increases in sitting diastolic blood pressure at 40, 60, and 120 minutes and standing diastolic blood pressure at 40 and 60 minutes, ranging from 5 to 11 mm Hg.

The patients with PTSD who reported panic attacks had greater changes in blood pressure than the healthy subjects. Analysis of the effects of yohimbine on blood pressure revealed a significant diagnosis and drug and time interaction for sitting systolic blood pressure when these patients with PTSD were compared with the healthy subjects (F=4.13; df=4, 4; $P<.01$). A yohimbine-placebo increase in sitting systolic blood pressures at 40 minutes (35±3 vs 14±4 mm Hg, t=3.98, df=30, $P<.001$) was significantly

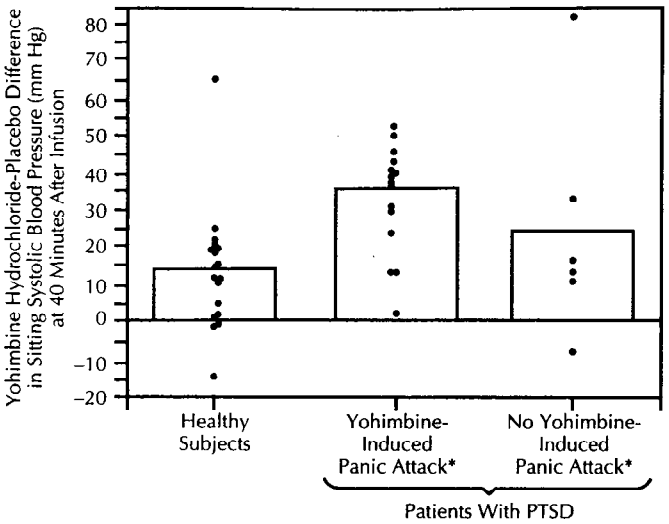

Fig 4.—*Yohimbine hydrochloride–placebo difference in sitting systolic blood pressure at 40 minutes after infusion in healthy subjects, patients with posttraumatic stress disorder (PTSD) who had yohimbine-induced panic attacks, and patients with PTSD without yohimbine-induced panic attacks. Asterisk indicates P<.005, patients with PTSD who had yohimbine-induced panic attacks compared with healthy subjects.*

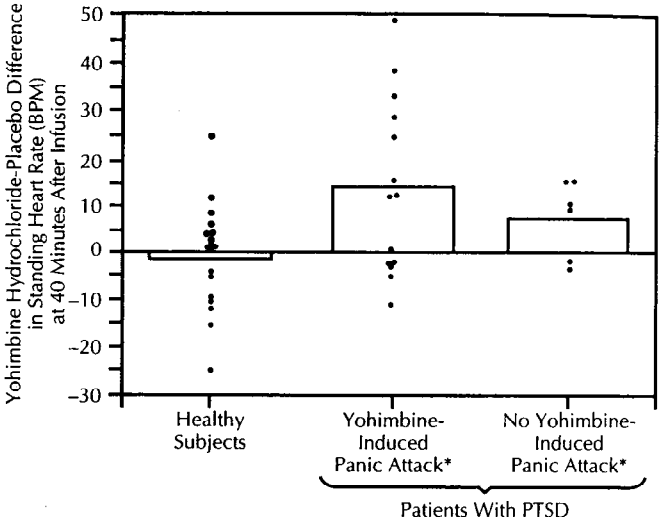

Fig 5.—*Yohimbine hydrochloride–placebo difference in standing heart rate at 40 minutes after infusion in healthy subjects, patients with posttraumatic stress disorder (PTSD) who had yohimbine-induced panic attacks, and patients with PTSD without yohimbine-induced panic attacks. BPM indicates beats per minute; asterisk, P<.01, patients with PTSD who had yohimbine-induced panic attacks compared with healthy subjects.*

different between these patients and the healthy subjects (Fig 4). No such differences were observed between the healthy subjects and the patient group with PTSD as a whole. There was no significant correlation between baseline or peak yohimbine effects on plasma MHPG levels and any of the blood pressures in either the healthy subjects or patients with PTSD.

Heart Rate.—Yohimbine did not produce significant effects on either sitting or standing heart rate (in beats per minute) in healthy subjects. In contrast, in the total patient group with PTSD, significant drug and time interactions were observed for sitting ($F=2.47$; $df=4, 4, 76$; $P=.05$) and standing ($F=4.42$; $df=4, 4, 76$; $P<.01$) heart rate. Significant yohimbine-placebo increases in heart rate were found at 40, 60, and 120 minutes for sitting heart rate, and at all time points for standing heart rate.

The patients with PTSD who reported panic attacks appeared to have a greater increase in heart rate than the healthy subjects. This was reflected in significant diagnosis and drug and time interactions between these patients with PTSD and healthy subjects for both sitting ($F=2.79$; $df=4, 4, 120$; $P<.05$) and standing heart rate ($F=2.71$; $df=4, 4, 120$; $P<.05$). These patients with PTSD had significantly greater yohimbine-placebo increases in sitting heart rate at 60 (12±4 vs 3±3, $P<.05$) and 120 minutes (12±3 vs 2±3, $P<.01$), and standing heart rate at 40 (14±5 vs −0.5±3, $P<.01$) and 120 minutes (12±3 vs 2±3, $P<.05$) than the healthy subjects. There was a diagnosis (PTSD vs healthy) and drug and time interaction for standing heart rate that approached significance ($F=2.32$; $df=4, 4, 120$; $P=.06$). The values for the yohimbine-placebo difference in standing heart rate (in beats per minute) at 40 minutes are shown in Fig 5. The patients with PTSD and panic disorder had a significantly ($P<.05$) higher sitting (78±2 vs 67±2) and standing (87±3 vs 73±2) baseline heart rate than the healthy subjects.

There was a significant correlation between peak yohimbine effects on sitting heart rate ($r=.72$, $P<.001$) and standing heart rate ($r=.56$, $P<.02$) and MHPG levels in the patients with PTSD, but not in the healthy subjects.

COMMENT

The findings of the present investigation using intravenous yohimbine as a probe of peripheral and central noradrenergic reactivity provide further support for sympathetic nervous system dysregulation in patients with chronic PTSD. It is thought that the anxiogenic properties of yohimbine are mediated through its ability to increase presynaptic noradrenergic activity by antagonizing the α_2-adrenergic autoreceptor.[20-22] An abnormal sensitivity of presynaptic noradrenergic neuronal reactivity in our patients compared with that in normal subjects is suggested by the more than twofold greater elevation of the plasma MHPG level following yohimbine administration. In the present investigation, this increase in noradrenergic reactivity appeared to be related to symptoms of both anxiety and PTSD as there was a significant positive correlation between peak yohimbine effects on the PASS and MHPG levels and a similar trend between peak yohimbine effects on the PTSD symptom scale and MHPG levels.

Yohimbine-induced increases in the plasma MHPG level most likely reflect increases in both central and peripheral norepinephrine turnover. Preclinical studies have shown that yohimbine readily crosses the blood-brain barrier and, once in the brain, blocks α_2-adrenergic autoreceptors in noradrenergic systems. A portion of brain MHPG then crosses the blood-brain barrier and appears in plasma.[21] The remainder of the yohimbine-induced increase in the plasma MHPG level (approximately 60% to 70%) is derived from norepinephrine that is released by peripheral sympathetic neurons.[26]

Although yohimbine has effects on multiple neurotransmitter systems,[27] its primary action is on the noradrenergic system. The use of yohimbine as a probe to assess brain noradrenergic function was recently supported in a study of healthy subjects that demonstrated that yohimbine, in doses comparable with those in the present study, significantly increased cerebrospinal fluid norepinephrine levels.[28] Since norepinephrine concentrations in cerebrospinal fluid are not influenced by norepinephrine that is released from peripheral sympathetic neurons, this investigation provided more direct neurochemical evidence that yohimbine activates brain noradrenergic neurons in humans.

The effects of yohimbine on blood pressure and heart

rate do not provide a specific index of noradrenergic function. The ability of yohimbine to increase blood pressure may be due to either presynaptic or postsynaptic noradrenergic receptor effects or the balance between the two. There is a considerable body of preclinical data indicating that norepinephrine has stimulatory effects on blood pressure. On the other hand, there is also evidence that postsynaptic α_2-receptors have inhibitory actions on blood pressure regulation.[29-34] The ability of yohimbine to produce greater increases in blood pressure in the patients with PTSD may be due to a yohimbine-induced increase in norepinephrine release, a subsensitivity of postsynaptic α_2-receptors, or the abnormal regulation of these receptors by other neuronal systems. The greater heart rate elevations that were produced by yohimbine in the patients who experienced yohimbine-induced panic attacks may also relate to dysfunction of either presynaptic or postsynaptic α_2-adrenergic receptors.

The specificity of increased responsiveness to yohimbine in patients with PTSD is supported by findings from recent investigations that have shown that yohimbine does not produce similar effects in patients with schizophrenia, major depression, generalized anxiety disorder, or obsessive-compulsive disorder.[35-38] However, our research group and others[20-22] have found that patients with panic disorder also exhibit potentiated behavioral, biochemical, and cardiovascular responses to yohimbine. In fact, careful inspection of the data from the current study and from the previous work with patients with panic disorder reveals highly similar responses to yohimbine in the two patient groups, suggesting that these two disorders may share a common neurobiological abnormality that is related to altered sensitivity of the noradrenergic system.

Importantly, 45% (9/20) of our patients with PTSD also met criteria for comorbid panic disorder. Because of the high frequency of yohimbine-induced panic attacks in patients with panic disorder, it might be argued that the response in our patients with PTSD was due to the existence of comorbid panic disorder rather than PTSD per se. In a lactate infusion study by Rainey et al,[39] six of seven patients with PTSD had panic attacks, and all seven patients had flashbacks. However, the six patients who had lactate-induced panic attacks met comorbid criteria for panic disorder, making it impossible to know if the attacks were due to PTSD or co-occurring panic disorder, since it is known that patients with panic disorder tend to be sensitive to the effects of intravenous lactate.[40-43] In the present study, however, 43% (6/14) of the patients with PTSD who had yohimbine-induced panic attacks did not meet comorbid criteria for panic disorder. These patients had yohimbine increases in the plasma MHPG level, blood pressure, and heart rate that were similar to those of the other patients with PTSD who experienced yohimbine-induced panic attacks. On the other hand, the likelihood of having a yohimbine-induced panic attack was markedly increased (89% [8/9]) in patients who met criteria for both PTSD and panic disorder.

In patients with PTSD, the diagnostic distinction between PTSD and panic disorder may be artificial. Panic disorder is generally believed to be familial in origin with a prevalence of 1% to 5% in the general population.[44] In a separate investigation that involved the first-degree relatives of all subjects with PTSD who were enrolled in the present study, preliminary findings suggested that panic disorder is no more frequent in the family members of these patients than in the general population.[45] The relatively low incidence of panic disorder in the families of these patients stands in sharp contrast to the 45% rate among the patients themselves. These findings suggest that the panic symptoms that are seen in patients with PTSD and comorbid panic disorder are not genetic in origin. Instead, like the core PTSD symptoms, many of these panic symptoms may result from traumatic stress exposure. Since panic disorder and PTSD appear to share a common abnormality of the noradrenergic system, it may be that patients who meet criteria for both PTSD and panic disorder have a more pronounced abnormality of this system.

NEURAL MECHANISMS OF PTSD AND NORADRENERGIC FUNCTION

A striking effect of yohimbine was its ability to increase the severity of the core symptoms associated with PTSD, such as intrusive traumatic thoughts, emotional numbing, and grief (Fig 2). This may, in part, be due to the involvement of noradrenergic systems in the mechanisms by which memories of traumatic experiences remain indelible for decades and are easily reawakened by a variety of stimuli and stressors.

Indeed, the strength of traumatic memories may relate to the degree to which certain neuromodulatory systems are activated by the traumatic experience.[46-48] Experimental and clinical investigations have demonstrated that memory processes are susceptible to modulating influences after the information has been acquired.[49] Of relevance to the current investigation, stimulation of noradrenegic receptors on the amygdala after a learning experience has memory-enhancing effects.[46,47] Activation of the LC-norepinephrine system that projects to the amygdala, by frightening and traumatic experiences, may facilitate the encoding of memories associated with the experiences. Moreover, it is possible that reproducing a neurobiological state (noradrenergic hyperactivity in specific brain regions) similar to the one that existed at the time of the memory encoding can elicit the traumatic memory.

The involvement of noradrenergic neurons in the neural mechanisms of fear conditioning and behavioral sensitization may relate to the behavioral effects of yohimbine. There is a body of evidence indicating that an intact noradrenergic system may be necessary for the acquisition of fear-conditioned responses. In animals, conditioning of noradrenergic neurons can be induced by environmental stimuli that are previously paired with aversive stimuli.[50,51] For example, neutral stimuli that have been paired with inescapable shock produce increases in brain norepinephrine metabolism and behavioral deficits similar to that elicited by shock alone. Similarly, in humans, recrudescence of traumatic memories (eg, intrusive traumatic thoughts) in response to simple sensory phenomena, such as specific smells, sounds, and cognitive stimuli that are circumstantially associated with the original trauma,[52-55] may occur via fear conditioning associated with activation of noradrenergic neurons.

The noradrenergic system also appears to be involved in behavioral sensitization, a process that may be related to the initiation and maintenance of certain PTSD symptoms. In animals, repetitive stress can cause an increase in stress-related behaviors and in the synthesis of norepinephrine as reflected by increased tyrosine hydroxylase, dopamine β-hydroxylase activity, and synaptic levels of

norepinephrine metabolites.[56-58] Thus, when animals that have been repetitively shocked are reexposed to a lower shock, norepinephrine release and turnover are greater than that expected.[56,57] Similarly, the exaggerated MHPG response to yohimbine in patients with PTSD may, in part, be explained by a noradrenergic system that has become sensitized. From a cognitive and behavioral perspective, patients with PTSD who have been exposed to repeated stressors often respond to mild or moderate subsequent stress with exaggerated behavioral responses (eg, marked anxiety and panic- and PTSD-specific symptoms) that are more appropriate for emergency situations.

Although the present study implicates the noradrenergic system in the pathophysiology of PTSD, many other neurobiological systems, such as dopamine, serotonin, opiate, and the hypothalamic-pituitary-adrenal axis, are also critically involved.[59] For example, there is accumulating evidence that under stressful conditions, corticotropin-releasing factor (CRF) and norepinephrine may participate in a mutually reinforcing feedback loop: intracerebroventricular infusion of CRF increases norepinephrine turnover in several forebrain areas,[60] CRF in a dose-dependent fashion increases the firing rate of LC-norepinephrine neurons,[61] and stress that activates norepinephrine neurons markedly increases CRF concentrations in the LC.[62] Moreover, it has recently been demonstrated that infusion of CRF into the LC is anxiogenic and produces significant increases in the norepinephrine metabolite 3,4-dihydroxyphenylglycol in forebrain areas, such as the amygdala and hypothalamus.[63] Similarly, the opiate, dopamine, and serotonin systems may be involved in PTSD both independently and in conjunction with changes in noradrenergic function due to functional interactions.[64]

It is unclear whether the findings of the present study apply to non–combat-traumatized populations or to populations of recently traumatized individuals with acute PTSD. Furthermore, the degree to which these responses would be seen in non–treatment-seeking combat veterans, both with and without PTSD, awaits future study.

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References

1. Kulka RA, Schlenger WE, Fairbank JA, Hough RL, Jordan BK, Marmar CR, Weiss DS. *Trauma and the Vietnam War Generation.* New York, NY: Brunner/Mazel Inc; 1990.

2. Browne A, Finkelhor D. Impact of child sexual abuse: a review of the research. *Psychol Bull.* 1986:99:66-77.

3. Glavin GB. Stress and brain noradrenaline: a review. *Behav Neurosci Rev.* 1985;9:233-243.

4. Tsuda A, Tanaka M. Differential changes in noradrenaline turnover in specific regions of rat brain produced by controllable and uncontrollable shocks. *Behav Neurosci.* 1985;99:802-817.

5. Simson PE, Weiss JM. Altered activity of the locus coeruleus in an animal model of depression. *Neuropsychopharmacology.* 1988;1:287-295.

6. Simson PE, Weiss JM. Responsiveness of locus coereuleus neurons to excitatory stimulation is uniquely regulated by alpha-2 receptors. *Psychopharmacol Bull.* 1988;24:349-354.

7. Kosten TR, Mason JW, Giller EL. Sustained urinary norepinephrine and epinephrine elevation in posttraumatic stress disorder. *Psychoneuroendocrinology.* 1987;12:13-20.

8. Yehuda R, Southwick SM, Giller EL. Urinary catecholamine excretion and severity of PTSD symptoms in Vietnam combat veterans. *J Nerv Ment Dis.* 1992;180:321-325.

9. Perry BD, Giller EL, Southwick SM. Altered platelet alpha$_2$-adrenergic binding sites in posttraumatic stress disorder. *Am J Psychiatry.* 1987;144:1511-1512.

10. Lerer B, Ebstein RP, Shestatsky M, Shemesh Z, Greenberg D. Cyclic AMP signal transduction in posttraumatic stress disorder. *Am J Psychiatry.* 1987;144:1324-1327.

11. Kolb LC, Burris BC, Griffiths S. Propranolol and clonidine in the treatment of post traumatic stress disorders of war. In: van der Kolk BA, ed. *Post-Traumatic Stress Disorder: Psychological and Biological Sequelae.* Washington, DC: American Psychiatric Press Inc; 1984:98-105.

12. Kinzie JD, Leung P. Clonidine in Cambodian patients with post traumatic stress disorder. *J Nerv Ment Dis.* 1989;177:546-550.

13. Orr SP. Psychophysiologic studies of post traumatic stress disorder. In: Giller EL, ed. *Biological Assessment and Treatment of Post Traumatic Stress Disorder.* Washington, DC: American Psychiatric Press Inc; 1990:75-90.

14. Blanchard EB, Kolb LC, Pallmeyer TP, Gerardi RJ. A psychophysiological study of posttraumatic stress disorder in Vietnam veterans. *Psychiatr Q.* 1982;54:220-229.

15. Blanchard EB, Kolb LC, Gerardi RJ, Ryan P, Pallmeyer TP. Cardiac response to relevant stimuli as an adjunctive tool for diagnosing post-traumatic stress disorder in Vietnam veterans. *Behav Ther.* 1986;17:592-606.

16. Malloy PF, Fairbank JA, Keane TM. Validation of a multimethod assessment of posttraumatic stress disorders in Vietnam veterans. *J Consult Clin Psychol.* 1983;51:488-494.

17. Kolb LC. The post traumatic stress disorders of combat: a subgroup with a conditioned emotional response. *Mil Med.* 1984;149:237-243.

18. Pallmeyer TP, Blanchard EB, Kolb LC. The psychophysiology of combat-induced posttraumatic stress disorder in Vietnam veterans. *Behav Res Ther.* 1986;24:645-652.

19. Pitman RK, Orr SP, Forgue DF, deJong JB, Claiborn JM. Psychophysiologic assessment of post-traumatic stress disorder in Vietnam combat veterans. *Arch Gen Psychiatry.* 1987;44:970-975.

20. Charney DS, Heninger GR, Breier A. Noradrenergic function in panic anxiety: effects of yohimbine in healthy subjects and patients with agoraphobia and panic disorder. *Arch Gen Psychiatry.* 1984;41:751-763.

21. Charney DS, Woods SW, Goodman WK, Heninger GR. Neurobiological mechanisms of panic anxiety: biochemical and behavioral correlates of yohimbine-induced panic attacks. *Am J Psychiatry.* 1987;144:1030-1036.

22. Gurguis GNM, Uhde TW. Plasma 3-methoxy-4- hydroxyphenylethylene glycol (MHPG) and growth hormone responses to yohimbine in panic disorder patients and normal controls. *Psychoneuroendocrinology.* 1990;15:217-224.

23. Keane TM, Caddell JM, Taylor KL. Mississippi scale for combat-related posttraumatic stress disorder: three studies in reliability and validity. *J Consult Clin Psychol.* 1988;56:85-90.

24. Dekirmenjian H, Maas JW. MHPG in plasma. *Clin Chim Acta.* 1974;52:203-208.

25. Mass JW, Hattox SE, Roth RH. The determination of a brain arteriovenous difference for 3-methoxy-4-hydroxyphenylethyleneglycol (MHPG). *Brain Res.* 1976;118:167-174.

26. Kopin IJ, Gordon EK, Jimerson DC, Polinsky RJ. Relation between plasma and cerebrospinal fluid levels of 3-methoxy-4-hydroxy-phenylglycol. *Science.* 1983;219:73-75.

27. Scatton B, Zirkivic B, Devek J. Antidopamine properties of yohimbine. *J Pharmacol Exp Ther.* 1980;215:494-499.

28. Peskind ER, Veith RC, Dorsa DM, Gumbrecht G, Raskind MA. Yohimbine increases cerebrospinal fluid and plasma norepinephrine but not arginine vasopressin in humans. *Neuroendocrinology.* 1989;50:286-291.

29. Rudolph CD, Kaplan SI, Ganong WF. Sites at which clonidine acts to affect blood pressure and the secretion of renin, growth hormone and ACTH. *Neuroendocrinology.* 1980;31:121-128.

30. Reid IA, Ahn JN, Trinh T, et al. Mechanism of suppression of vasopressin and adrenocorticotropic hormone secretion by clonidine in anesthetized dogs. *J Pharmacol Exp Ther.* 1984;229:1-8.

31. Shimizu K. Effect of α_1- and α_2-adrenoceptor agonists and antagonists on ACTH secretion in intact and in hypothalamic dealerenated rats. *Jpn J Pharmacol.* 1984;36:23-33.

32. Kobinger W. α-Adrenoceptors in cardiovascular regulation. In: Ziegler MG, Lake CR, eds. *Norepinephrine.* Baltimore, Md: Williams & Wilkins; 1984:307-326.

33. Tung CS, Onnora CO, Robertson D, et al. Hypertensive effect of yohimbine following selective injection into the nucleus tractus solitarii of normotensive rats. *Brain Res.* 1983;227:193-195.

34. Bosquet P, Schwartz J. Alpha-adrenergic drugs: pharmacological tools for the study of the central vasomotor control. *Biochem Pharmacol.* 1983;32:1439-1465.

35. Glazer WM, Charney DS, Heninger GR. Noradrenergic function in schizophrenia. *Arch Gen Psychiatry.* 1987;44:898-904.

36. Heninger GR, Charney DS, Price LH. α_2-Adrenergic receptor sensitivity in depression: the plasma MHPG, behavioral, and cardiovascular responses to yohimbine. *Arch Gen Psychiatry.* 1988;45:718-726.

37. Charney DS, Woods SW, Heninger GR. Noradrenergic function in generalized anxiety disorder: effects of yohimbine in healthy subjects and patients with generalized anxiety disorder. *Psychol Res.* 1989;27:173-182.

38. Rasmussen SA, Goodman WK, Woods SW, Heninger GR, Charney

DS. Effects of yohimbine in obsessive-compulsive disorder. *Psychopharmacology (Berl).* 1987;93:308-313.
39. Rainey JM, Aleen A, Ortiz A, Yeragami V, Pohl R, Bereliou R. A laboratory procedure for the induction of flashbacks. *Am J Psychiatry.* 1987; 144:1317-1319.
40. Fyer AJ, Liebowitz MR, Gorman JM, Davies SO, Klein DF. Lactate vulnerability of remitted panic patients. *Psychiatry Res.* 1985;14:143-148.
41. Liebowitz MR, Fyer AJ, Gorman JM, Dillon D, Appleby I, Levy G, Anderson S, Levitt M, Palij M, Davies SO, Klein DF. Lactate provocation of panic attacks, I: clinical and behavioral findings. *Arch Gen Psychiatry.* 1984;41:764-770.
42. Liebowitz MR, Gorman JM, Fyer AJ, Levitt M, Dillon D, Levy G, Appleby I, Anderson S, Palij M, Davies SO, Klein DF. Lactate provocation of panic attacks, II: biochemical and physiological findings. *Arch Gen Psychiatry.* 1985;42:709-719.
43. Rainey JM, Frohman CE, Warner K, Bates S, Pohl R, Yeragani V. Panic anxiety and lactate metabolism. *Psychopharmacol Bull.* 1985;21:434-437.
44. Crowe RR. The genetics of panic disorder and agoraphobia. *Psychiatr Dev.* 1985;2:171-186.
45. Nagy L, Marikangas K, Southwick S, Docherty N, Dan E, Harkness L, Charney D. Family relationship between panic and PTSD. In: Program and abstracts of the 144th Annual Meeting of the American Psychiatric Association; May 11-16, 1991; New Orleans, La. Abstract NR182.
46. McGaugh JL. Involvement of hormonal and neuromodulatory systems in the regulation of memory storage. *Annu Rev Neurosci.* 1989;2:255-287.
47. McGaugh JL. Significance and remembrance: the role of neuromodulatory systems. *Psychol Sci.* 1990;1:15-25.
48. Pitman RK. Post-traumatic stress disorder, hormones, and memory. *Biol Psychiatry.* 1989;26:221-223.
49. Squire LR. Mechanisms of memory. *Science.* 1986;232:1612-1619.
50. Cassens G, Kuruc A, Roffman M, Orsulak P, Schildkraut JJ. Alterations in brain norepinephrine metabolism and behavior induced by environmental stimuli previously paired with inescapable shock. *Behav Brain Res.* 1981;2:387-407.
51. Rasmussen K, Marilak DA, Jacobs BL. Single unit activity of the locus coeruleus in the freely moving cat, I: during naturalistic behaviors and in response to simple and complex stimuli. *Brain Res.* 1986;371:324-334.
52. Litz BT, Keane TM. Information processing in anxiety disorders: application to the understanding of post-traumatic stress disorder. *Clin Psychol Rev.* 1989;9:243-257.
53. McNally RJ, Luedke DL, Besyner JK, Peterson RA, Bohm K, Lips OJ. Sensitivity to stress relevant stimuli in post traumatic stress disorder. *J Anxiety Dis.* 1987;1:105-116.
54. VanDyke C, Zilberg NJ, MacKinnon JA. Post traumatic stress disorder: a thirty year delay in a World War II veteran. *Am J Psychiatry.* 1985;142: 1070-1073.
55. Solomen Z, Garb K, Bleich A, Grupper D. Reactivation of combat-related post traumatic stress disorder. *Am J Psychiatry.* 1987;144:51-55.
56. Anisman H, Sklar LS. Catecholamine depletion upon reexposure to stress: mediation of the escape deficits produced by inescapable shock. *J Comp Psychol.* 1978;93:610-625.
57. Irwin J, Ahluwalia P, Anisman H. Sensitization of norepinephrine activity following acute and chronic footshock. *Brain Res.* 1986;379:98-103.
58. Nisenbaum LK, Zigmund MJ, Sved AF, Abercrombie ED. Prior exposure to chronic stress results in enhanced synthesis and release of hippocampal norepinephrine in response to a novel stressor. *J Neurosci.* 1991;11: 1478-1484.
59. Krystal JH, Kosten TR, Perry BD, Southwick S, Mason JW, Giller EL Jr. Neurobiological aspects of PTSD: review of clinical and preclinical studies. *Behav Ther.* 1989;20:177-198.
60. Dunn AJ, Berridge CW. Corticotropin-releasing factor administration elicits a stresslike activation of cerebral catecholaminergic systems. *Pharmacol Biochem Behav.* 1987;27:685-691.
61. Valentino RJ, Foote SL. Corticotropin-releasing hormone increases tonic but not sensory-evoked activity of noradrenergic locus coeruleus neurons in unanesthetized rats. *J Neurosci.* 1988;8:1016-1025.
62. Chappell PB, Smith MA, Kilts CD, Bissette G, Ritchie J, Anderson C, Nemeroff CB. Alterations in corticotropin-releasing factor-like immunoreactivity in discrete rat brain regions after acute and chronic stress. *J Neurosci.* 1990;6:2908-2914.
63. Butler PD, Weiss JM, Stout JC, Nemeroff CB. Corticotropin-releasing factor produces fear-enhancing and behavioral activating effects following infusion into the locus coeruleus. *J Neurosci.* 1990;10:176-183.
64. Redmond DE Jr. Studies of the nucleus locus coeruleus in monkeys and hypotheses for neuropsychopharmacology. In: Meltzer HY, ed: *Psychopharmacology: The Third Generation of Progress.* New York, NY: Raven Press; 1987:967-975.