ORIGINAL ARTICLE

Positron Emission Tomography Measurement of Cerebral Metabolic Correlates of Yohimbine Administration in Combat-Related Posttraumatic Stress Disorder

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Background: We have previously reported an increase in symptoms of anxiety in patients with posttraumatic stress disorder (PTSD) following administration of the β_2-antagonist yohimbine, which stimulates brain norepinephrine release. Preclinical studies show decreased metabolism in the neocortex and the caudate nucleus with high-dose yohimbine-induced norepinephrine release, but low levels of norepinephrine release result in an increase in metabolism in these areas.

Methods: We used positron emission tomography and fludeoxyglucose F 18 to measure brain metabolism in Vietnam combat veterans with PTSD (n=10) and healthy age-matched control subjects (n=10), following administration of yohimbine (0.4 mg/kg) or placebo in a randomized, double-blind fashion.

Results: Yohimbine resulted in a significant increase in anxiety in the patients with PTSD, but not in healthy subjects. There was a significant difference in brain metabolic response to yohimbine in patients with PTSD compared with healthy subjects in prefrontal, temporal, parietal, and orbitofrontal cortexes. Metabolism tended to decrease in patients with PTSD and increase in healthy subjects following administration of yohimbine.

Conclusion: These findings are consistent with our previous hypothesis of enhanced norepinephrine release in the brain with yohimbine in patients with PTSD.

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PSYCHIATRISTS HAVE long hypothesized that alterations in noradrenergic function may underlie the symptoms of combat-related posttraumatic stress disorder (PTSD).[1-3] Observations of the symptoms of combat veterans from earlier wars, including sleep disturbance, hypervigilance, physiological arousal, and exaggerated startle response, led to the use of terms such as "irritable soldier's heart" to describe what would be classified today as PTSD. This syndrome was believed to be related to alterations in catecholamine levels. Several recent investigations have provided evidence for the idea that alterations in catecholamine levels, including norepinephrine levels, may underlie symptoms of PTSD.

Preclinical studies also support a role for norepinephrine in stress.[4-6] Norepinephrine cell bodies, primarily located in the locus caeruleus, release neurotransmitter centrally in cortical and subcortical structures.[7-12] Animal models of stress showed increased firing of the locus caeruleus and increased turnover and release of norepinephrine in these regions,[11,13-28] but increased release of norepinephrine was shown in chronically stressed animals following administration of the α_2-antagonist idazoxan, which stimulates brain norepinephrine release through blockade of the presynaptic α_2-receptor. At the level of the postsynaptic receptor, norepinephrine has a stimulatory effect with binding to α_1-receptors, an inhibitory effect with postsynaptic α_2-receptors, and excitatory and inhibitory effects with binding to postsynaptic β-receptors.[29-32] Pharmacological studies in nonhuman primates using agents that stimulate brain norepinephrine release, including the α-adrenergic blocker phentolamine, and phenylethylamine, showed a dose-dependent effect. These agents increased cerebral blood flow at lower doses, and decreased cerebral blood flow at higher doses.[33,34] Administration to animals of high doses of the α_2-antagonist yohimbine resulted in a decrease in brain metabolism in the frontal, parietal, temporal, postcentral (sensory), and occipital cortex, the caudate nucleus,[35,36] the olfactory cortex, and the sulcal cortex.[35] Electrical stimulation of the

SUBJECTS AND METHODS

SUBJECT SELECTION

The patient group was comprised of 10 Vietnam veterans with a history of combat-related PTSD who were admitted to an inpatient unit for PTSD during a 2-year period who gave informed consent for participation, met the criteria for PTSD based on the Structured Clinical Interview *DSM-III-R* (SCID)[65] (available in 9 of 10 patients), and had a score of more than 107 (consistent with the diagnosis of PTSD) on the Mississippi Scale for Combat-Related PTSD, an instrument for the measurement of PTSD symptoms.[66] Combat exposure was documented using the Combat Exposure Scale, a self-report instrument for the quantitation of level of combat exposure that has documented reliability and validity. Although the Combat Exposure Scale relies on self-report, studies showing a correlation between the score on the Combat Exposure Scale and the level of PTSD symptoms support the validity of this instrument as a measure of combat exposure.[67] That patients had been exposed to combat in Vietnam also was confirmed by the official military record of service in the Vietnam theater when these were available. In the few cases in which they were unavailable, an attempt to verify combat status was made by corroborating history obtained from family members, interviews with experienced psychiatrist clinicians, and a review of the patient's medical records. Patients were excluded if they had a history of meningitis, traumatic brain injury, neurologic disorder, current alcohol abuse, schizophrenia based on *DSM-III-R* criteria, shrapnel or other foreign bodies, human immunodeficiency virus infection, or loss of consciousness for more than 10 minutes. None of the patients had a history of loss of consciousness within the last year. Patients were observed for a 2-month period with frequent toxicology screens for validation of substance- and alcohol-free status. Patients had been medication-free for 4 weeks or more at the time of the study.

Healthy subjects (n=10) were recruited through newspaper advertisements to match the patients for age and sex. Healthy subjects included men between the ages of 18 and 65 years who were physically healthy and without psychiatric disorder as assessed with the SCID for nonpatients or psychiatric interview using SCID-based criteria. Subjects were excluded if they had a history of psychiatric disorder, exposure to extreme psychological stressor based on psychiatric interview, or the exclusion criteria described for the patients. An extreme psychological stressor was defined in accordance with the *DSM-III-R* criteria as an event beyond the range of normal human experience that would be distressing to almost anyone.

There were no differences in demographic variables between the patients and the controls. Mean (±SEM) age of the patients with PTSD was 46.7±0.54 years; in the controls, it was 44.1±2.5 years. All of the patients with PTSD were white; 7 of 10 controls were white and 3 of 10 were black (this difference was not statistically significant). All patients and controls were male and right-handed.

Patients were evaluated with the SCID for comorbid psychiatric diagnoses. The SCID data were available for 9 of 10 patients. In the patients for whom SCID data were available, 1 patient met criteria for a lifetime history of major depression and 3 for a current history of major depression. One patient met criteria for a lifetime history of dysthymia and 1 for a current history of dysthymia. None of the patients met criteria for a lifetime or current history of bipolar disorder. One patient met criteria for a lifetime history of hypomania, and none for a current history of hypomania. Three patients met criteria for a lifetime and current history of panic disorder with agoraphobia; 1 for a lifetime and current history of panic disorder without agoraphobia. One patient met criteria for a lifetime and current history of agoraphobia without panic disorder, 2 for a lifetime and current history of social phobia, 2 for a lifetime and current history of OCD, 1 for a lifetime and current history of simple phobia, and none for a lifetime or current history of GAD. No patients met criteria for a lifetime or current history of schizophrenia; 2 patients met criteria for a lifetime history and 1 for a current history of psychotic disorder not otherwise specified. Seven patients met criteria for a lifetime history of alcohol dependence and 1 for alcohol abuse; 1 for sedative, hypnotic, or anxiolytic dependence and none for abuse; 5 for cannabis dependence and none for cannabis abuse; 1 for stimulant dependence and 1 for stimulant abuse; none for opiate dependence or abuse, 1 for cocaine dependence and 2 for cocaine abuse; 2 for hallucinogen or phencyclidine hydrochloride dependence and 1 for abuse; and 1 for polydrug dependence and none for abuse.

BEHAVIORAL ASSESSMENTS

Mean (±SEM) score on the Mississippi Scale for Combat-Related PTSD in the patients with PTSD was 140.4±15.1, which indicates high levels of PTSD symptoms. Mean (±SEM) score on the Combat Exposure Scale in the patient group was 32.4±7.8 (a high level of combat exposure).

Patients also were evaluated at baseline and 20 minutes after yohimbine administration or placebo injection for anxiety symptoms with the Hamilton Anxiety Scale; panic attack symptoms with the Panic Attack Symptom Scale (PASS), clinician and patient versions; and PTSD symptoms with the PTSD Symptom Scale, clinician and patient versions. Panic attacks and flashbacks were defined using previously described criteria.[56] In 2 situations, subjects did not meet criteria for panic attacks using the full criteria but were judged clinically by 2 investigators (S.M.S. and D.S.C.) blinded to study conditions as having experienced a panic attack.

POSITRON EMISSION TOMOGRAPHY (PET) SCANNING METHODS

All subjects underwent 2 days of testing in a randomized, double-blind design with administration of yohimbine or placebo. Subjects were scanned at the Yale/Veterans Affairs Positron Emission Tomography Center, West Haven, Conn, with a 21-slice camera (Posicam 6.5, Positron Corp, Houston, Tex), with 5.125-mm interslice distance. The resolution of the camera in-plane is 5.8 mm and 11.9 mm in the z-axis.[68] The sensitivity of the camera measured in a 20-cm-diameter cylinder phantom can be expressed as the system sensitivity (165 000 kcounts/s per

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microcurie per cubic centimeter); slice sensitivity (9.5 kcounts/s per microcurie per cubic centimeter); or the sensitivity/axial cm (8.0 kcounts/μCi per cubic centimeter per axial centimeter). An intravenous line was inserted in the hand and warmed with heating pads for measurement of arterialized venous blood samples. Subjects received yohimbine (0.4 mg/kg) or placebo intravenously for 10 minutes immediately followed by injection of 5 mCi of FDG in a single intravenous bolus and scanning with eyes open in a dimly lit room. A PET image was reconstructed 30 to 50 minutes after injection to determine brain tissue activity. Brain and tissue time-activity curves were then combined for measurement of cerebral glucose metabolic rate in milligrams per minute per 100 mL using the fixed rate constant approach of Sokoloff et al.[69] Separate kinetic rate constants were used for gray and white matter.[70] Images were attenuation-corrected based on a transmission scan performed with a $^{67}Ga/^{68}Ge$ rotating rod source and reconstructed using a spatially varying convolution scatter subtraction technique and a Butterworth filter. A 20-cm cylindrical fluid-filled phantom was scanned on the same day as each study to obtain a calibration factor for each of the 21 slices.

PET-MRI COREGISTRATION

Magnetic resonance imaging scans were obtained in all subjects for coregistration with PET (**Figure 1**). Magnetic resonance imaging scans of 3-mm contiguous slices were obtained with a 1.5-T scanner (Signa, General Electric, Milwaukee, Wis). Axial images were acquired with a spoiled gradient recall acquisition in the steady state sequence with repetition time=25 ms, echo time=5 ms, number of excitations=2, flip angle=30°, matrix=256×256, field of view=24 cm. The PET and MRI scans were transferred using a computer network to a SUN Sparc10 Workstation (SUN Microsystems, Mountain View, Calif). Analyze[71] was used for coregistration of PET and MRI scans using a surface-matching algorithm.[72] The MRI was then resliced to obtain 21 MRI slices, each of which corresponded to 1 of the 21 PET slices.

MEASUREMENT OF REGIONS OF INTEREST

Regions of interest measurements on resliced MRI were performed by a blinded investigator using specific criteria developed in conjunction with a neuroradiologist (R.A.B.). These criteria were developed for reproducibility of measurements between observers and to have criteria based on an anatomical atlas that allows for the use of a common terminology and that is available to general access.[73] We have shown high levels of agreement between 2 raters using these criteria (J.D.B., Gabriel De Erasquin, MD, Eric Vermetten, MD, et al, unpublished data, March 15, 1996) (available on request). Templates for regions of interest drawn on the MRI were transferred to the PET by the Analyze computer program. These included the neocortical regions and the caudate nucleus (**Table 1**), which were hypothesized to change based on the aforementioned preclinical studies. Pons, midbrain, and white matter were not anticipated to change with yohimbine administration and were selected as comparison regions to assess the specificity of the effect of yohimbine. The other regions were examined on an exploratory basis because they have noradrenergic innervation (Table 1). Global brain metabolism was calculated by obtaining the mean of bilateral posterior white matter measurements and the mean of all gray matter measurements, with a 50% weighting to gray matter and a 50% weighting to white matter.

DATA ANALYSIS

Three-way repeated measures analysis of variance (ANOVA) with drug (yohimbine vs placebo) as the repeated measure and diagnosis and laterality (left vs right) as factors was used to examine the effects of yohimbine on metabolism in patients vs controls for specific regions of interest. Hypothesized regions of interest (Table 1), based on animal studies of areas that have been shown to decrease in metabolism with yohimbine administration, were initially combined in a single model and compared with all nonhypothesized regions for the effects of yohimbine on metabolism in patients and controls. We also compared metabolic response to yohimbine in patients vs controls in individual brain regions, including hypothesized and nonhypothesized regions. Possible asymmetries were assessed by including left and right sides for each region and conducting a 3-way ANOVA for each of the regions given in Table 1 with hemisphere (left vs right) as a factor in the ANOVA.

Exploratory analyses included univariate analyses to compare patients who had PTSD with controls at baseline (placebo day), and to compare placebo and yohimbine days within the control subjects. The Bonferroni correction (dividing the α value of .05 by the number of comparisons [18], or $P=.05/18=.003$) was used to adjust the level of significance for the potential confounder of multiple comparisons for all exploratory analyses.

Behavioral data (Hamilton Anxiety Scale and PASS clinician scores) were analyzed using nonpaired 2-tailed t tests to compare scores at baseline with scores 20 minutes after infusion of yohimbine or placebo (**Table 2**). The relation between behavioral data (the difference between baseline-subtracted anxiety scores (measured with the PASS clinician, PASS patient, and Hamilton Anxiety Scale) with yohimbine and baseline-subtracted anxiety scores with placebo and placebo-subtracted metabolism with yohimbine (a subtraction of brain metabolism on the placebo day from brain metabolism on the yohimbine day) was analyzed using Pearson product correlations. Results are reported as mean (±SEM).

locus caeruleus resulted in a decrease in brain metabolism[37] and blood flow[38-40] in several cortical and subcortical regions, but lesions of the locus caeruleus had the opposite effect.[41-43] In summary, high levels of norepinephrine release cause a decrease in blood flow and metabolism in brain areas that receive noradrenergic innervation, but low levels of norepinephrine release increase blood flow and metabolism.

Evidence for alterations in noradrenergic brain system function in patients with PTSD[44] includes (1) increased resting heart rate and blood pressure,[3,45] and increases in heart rate and systolic blood pressure with reminders of combat trauma,[46-49] (2) increased urinary norepinephrine and epinephrine in some studies[50,51] but not others,[52] (3) increased plasma epinephrine[48] and norepinephrine[53] following exposure to traumatic remind-

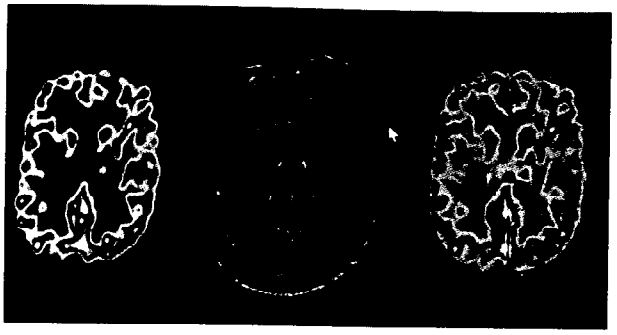

Figure 1. *Positron emission tomography (PET) and magnetic resonance imaging (MRI) coregistration using the Chamfer surface-matching technique. The images represented include a PET fludeoxyglucose F18 scan of a patient with PTSD at baseline (left), an MRI resliced to correspond to the PET (center), and a fused PET and MRI image (right). A fiducial marker, filled with fludeoxyglucose F 18, is also visualized (arrow), which was used to check for head movement during the scan.*

ers but not baseline plasma norepinephrine,[53,54] (4) decreased adrenergic receptors on platelets,[55] and (5) increased methoxyhexene phenylglycol after yohimbine administration and flashbacks in 40% and panic attacks in 70% of patients.[56] Yohimbine administration also resulted in an increase in panic attacks and plasma methoxyhexene phenylglycol in patients with another anxiety disorder, panic disorder,[57,58] but not in patients with generalized anxiety disorder (GAD),[59] depression,[60] obsessive-compulsive disorder (OCD),[61] or schizophrenia.[62] We hypothesized[5,6,56] that PTSD is associated with an increase in responsiveness to the noradrenergic agent yohimbine, which results in patients with PTSD "seeing" higher levels of yohimbine than the controls. One would predict that yohimbine causes high levels of norepinephrine release in the brain of subjects with PTSD, which results in decreased metabolism, and lower levels of norepinephrine release in controls, with increased metabolism.

Little is known about central brain function in patients with PTSD. We previously reported a decrease in right hippocampal volume as measured with magnetic resonance imaging (MRI) with associated deficits in short-term verbal memory[63,64] in Vietnam combat veterans with PTSD compared with controls. The purpose of this study was to use PET fludeoxyglucose F 18 (FDG) in the measurement of cerebral metabolism following administration of yohimbine and placebo in Vietnam combat veterans with PTSD and in healthy subjects. We hypothesized that yohimbine administration in patients with PTSD would be associated with a decrease in brain metabolism compared with controls in brain regions that have been shown to decrease in metabolism with yohimbine in preclinical studies, namely neocortical areas and the caudate nucleus.

RESULTS

BEHAVIORAL EFFECTS OF YOHIMBINE

Six of 10 patients with PTSD had a panic attack with yohimbine administration, compared with none of the controls, and 3 of 10 patients with PTSD had a flashback with yohimbine administration compared with none of the controls. Patients with PTSD had a significant increase from baseline to 20 minutes after yohimbine administration in anxiety as measured by the Ham-D (9.3±1.9 vs 20.3±2.4) (t=3.6, df=18; P<.01) and panic attack symptoms as measured by the PASS-clinician (30.7±1.4 vs 39.5±1.9) (t=3.7, df=18; P<.01) and PASS patient (31.9±1.8 vs 41.2±2.4) (t=3.1, df=18; P<.01). Controls did not have an increase in anxiety or panic symptoms with yohimbine. Neither patients nor controls had an increase in anxiety or panic symptoms on the placebo day (Table 2). These findings are similar to our previous reports.[56]

EFFECTS OF YOHIMBINE ON REGIONAL CEREBRAL METABOLISM

Two-way analysis of variance (ANOVA) with repeated measures for drug administration (placebo vs yohimbine) showed a significant difference in yohimbine response between the patients with PTSD and the controls when all regions that were hypothesized to change based on preclinical studies (neocortical regions and the caudate nucleus) were combined in a single model (main effect for drug, F[1,438]=90.65, P<.001; drug by diagnosis interaction, F[1,438]=29.05, P<.001). As predicted, patients with PTSD had a decrease in metabolism with yohimbine administration compared with placebo (t=2.09, df=238; P=.02), while controls had an increase in metabolism with yohimbine administration compared with placebo (t=5.27, df=238; P<.001). When hypothesized regions were examined individually, significant differences between patients and controls were observed for orbitofrontal cortex (main effect for drug, F[1,78]=5.18, P<.05; main effect for diagnosis, F[1,78]=13.10, P<.001; drug by diagnosis interaction, F[1,78]=12.71, P≤.006) (**Figure 2**), temporal cortex (main effect for diagnosis, F[1,78]=37.94, P<.001; drug by diagnosis interaction, F[1,78]=5.30, P<.05), prefrontal cortex (main effect for drug, F[1,78]=5.98, P<.05; main effect for diagnosis, F[1,78]=25.1, P<.001; drug by diagnosis interaction, F=5.69, P<.05), and parietal cortex (main effect for diagnosis, F[1,78]=16.07, P<.001; drug by diagnosis interaction, F[1,78]=4.29, P<.05), but not occipital cortex or postcentral gyrus (sensory cortex) (Table 1). Healthy subjects had an increase in metabolism with yohimbine administration compared with placebo in orbitofrontal cortex (t=3.79, df=39; P≤.005) and prefrontal cortex (t=3.18, df=39; P≤.003).

Repeated measures ANOVA showed a significant difference between patients and controls when all nonhypothesized regions (Table 1) were combined in a single model (main effect for diagnosis, F[1,438]=34.5, P<.001; drug by diagnosis interaction, F[1,438]=25.32, P<.001). In the patients with PTSD, metabolism decreased with yohimbine administration compared with placebo (t=3.91, df=238; P<.001), but in the controls, metabolism increased with yohimbine administration compared with placebo (t=3.29, df=238; P=.001). When these regions were examined individually, however, a difference in yohimbine response between patients and controls was observed in only 1 region, globus pallidus (main effect for diagnosis, F[1,38]=7.96, P<.01; drug by diagnosis interaction, F[1,38]=7.36, P<.05), which was not significant after correction for multiple comparisons. When patients

Table 1. Metabolic Rates With Yohimbine Administration in Patients With Posttraumatic Stress Disorder and Controls*

Brain Region	Controls (n=10)		Patients With PTSD (n=10)		3-Way Analysis of Variance Drug by Diagnosis Interaction	
	Placebo	Yohimbine	Placebo	Yohimbine	F	P
			Hypothesized Region†			
Orbitofrontal cortex	7.60 (0.25)	10.20 (0.46)	7.40 (0.21)	6.80 (0.31)	12.71	<.001§
Parietal cortex	10.00 (0.34)	11.20 (0.41)	9.00 (0.23)	8.40 (0.21)	4.29	.04
Prefrontal cortex	11.30 (0.43)	11.90 (0.44)	9.50 (0.26)	8.60 (0.30)	5.69	.02‖¶
Temporal cortex	10.80 (0.31)	11.90 (0.32)	9.20 (0.20)	8.60 (0.24)	5.30	.02#
Postcentral gyrus	9.70 (0.37)	10.60 (0.35)	8.20 (0.22)	7.60 (0.22)	1.29	.26
Occipital cortex	9.70 (0.31)	9.80 (0.29)	8.60 (0.23)	8.20 (0.25)	0.26	.61
Caudate nucleus	11.10 (0.41)	11.50 (0.41)	9.70 (0.26)	8.60 (0.31)	2.28	.14
			Nonhypothesized Region‡			
Putamen	11.50 (0.45)	12.90 (0.38)	10.20 (0.31)	9.40 (0.34)	2.59	.12
Globus pallidus	6.70 (0.27)	8.30 (0.38)	6.20 (0.27)	5.20 (0.18)	7.36	.01
Thalamus	8.00 (0.27)	9.10 (0.35)	7.20 (0.30)	6.50 (0.30)	2.09	.15
Cingulate	10.90 (0.33)	11.90 (0.41)	9.10 (0.33)	8.80 (0.25)	1.10	.30
Parahippocampal	7.60 (0.32)	8.40 (0.41)	6.20 (0.26)	5.40 (0.24)	3.53	<.07
Hippocampus	7.00 (0.27)	6.90 (0.39)	6.60 (0.18)	5.00 (0.24)	2.15	.15**
Amygdala	6.30 (0.23)	6.40 (0.33)	5.60 (0.17)	5.00 (0.23)	0.54	.47
Cerebellum	8.80 (0.31)	10.90 (0.33)	8.10 (0.26)	8.10 (0.27)	2.71	.10††
Midbrain	5.40 (0.29)	5.90 (0.27)	4.80 (0.22)	4.30 (0.21)	1.28	.26
Pons	5.80 (0.24)	5.20 (0.29)	4.90 (0.23)	3.80 (0.23)	0.46	.50
Global metabolism	7.00 (0.31)	8.20 (0.33)	7.00 (0.22)	6.10 (0.18)	2.60	.12

*Regional metabolic rates are given as mean (SEM) milligrams per minute per 100 mL of glucose. PTSD indicates post-traumatic stress disorder.

†Hypothesized regions include those found to change with yohimbine administration in unconflicted animal studies; significant main effects for diagnosis were found in all hypothesized regions.

‡Nonhypothesized regions include those not found to change with yohimbine in animal studies; significant main effects for diagnosis (P<.05) were found in all nonhypothesized regions except hippocampus and global metabolism.

§Increase in metabolism within the control group with yohimbine vs placebo administration (P<.001).

‖Decrease in metabolism for PTSD group vs control group on placebo day (P=.02).

¶Increase in metabolism within the control group with yohimbine vs placebo administration (P<.003).

#Decrease in metabolism in PTSD group vs control group on placebo day (P<.003).

**Decrease in metabolism within PTSD group with yohimbine vs placebo administration (P=.006).

††Increase in metabolism within control group with yohimbine vs placebo administration (adjusted P=.003).

with PTSD were considered alone, there was a significant decrease on the yohimbine administration day compared with the placebo day in the hippocampus (t=3.08, df=19; P=.006) (Table 1). Global metabolism with yohimbine administration did not differ between patients and controls. When an additional analysis was performed for each region (Table 1) using 3-way repeated measures ANOVA with hemisphere (right vs left) entered as a factor (in addition to drug [yohimbine vs placebo] and diagnosis [PTSD vs controls]), there was no significant main effect for hemisphere for any of the individual regions.

Exploratory univariate analyses also were performed to examine differences in metabolism at baseline between patients and controls. Patients with PTSD had a significant decrease in metabolism at baseline (placebo day) compared with controls, which was significant after correction for multiple comparison (18) (ie, P=.05/18=.0029) for temporal cortex ($F[1,78]$=9.63; $P \leq .003$), but not prefrontal cortex ($F[1,78]$=6.05; $P \leq .02$).

RELATION BETWEEN BEHAVIORAL MEASURES OF ANXIETY AND REGIONAL CEREBRAL METABOLISM

A relation did not exist between the difference between baseline-subtracted anxiety scores on the yohimbine and placebo days and placebo-subtracted metabolism with the yohimbine day in patients or controls for any brain region in this study. Of the patients who met criteria for panic disorder without agoraphobia, 2 of 3 had a panic attack with yohimbine administration, but the patient who met criteria for panic disorder with agoraphobia did not have a panic attack with yohimbine administration, and 3 of 5 patients without panic disorder had a panic attack with yohimbine administration. The single patient for whom the SCID was unavailable had a panic attack with yohimbine administration. No statistically significant differences were observed in placebo-subtracted metabolism with yohimbine administration in patients with PTSD who had a panic attack with yohimbine administration (n=6) compared with patients with PTSD who did not have a panic attack with yohimbine (n=4). A pattern of a decrease in placebo-subtracted metabolism with yohimbine administration was observed in the patients who had a panic attack compared with those who did not have a panic attack, with the magnitude of the difference being greatest for orbitofrontal cortex ($-1,73 \pm 0.89$ vs 0.03 ± 0.94) and hippocampus (-2.14 ± 1.02 vs -0.74 ± 0.47). The lack of a statistically significant difference may be due to the small number of subjects in each subgroup.

Table 2. Scores on Behavioral Ratings Following Administration of Yohimbine and Placebo*

Behavioral Rating	Patients With PTSD (n=10)		Controls (n=10)	
	Baseline	+20 Minutes	Baseline	+20 Minutes
Placebo				
Hamilton Anxiety Scale	11.3 (1.4)	12.4 (2.2)	1.3 (0.4)	0.8 (0.5)
Panic Attack Symptom Scale				
Clinician	32.9 (1.0)	32.8 (1.9)	27.5 (0.2)	27.8 (0.4)
Patient	33.9 (2.2)	34.9 (3.0)	27.5 (0.3)	28.0 (0.4)
PTSD Symptom Scale				
Clinician	22.1 (1.5)	19.1 (1.6)	...	...
Patient	22.1 (2.0)	20.6 (1.8)	...	...
Yohimbine				
Hamilton Anxiety Scale	9.3 (1.9)	20.3 (2.4)†	2.0 (0.7)	5.0 (1.6)
Panic Attack Symptom Scale				
Clinician	30.7 (1.4)	39.5 (1.9)†	27.3 (0.2)	28.8 (0.8)
Patient	31.9 (1.8)	41.2 (2.4)†	27.3 (0.2)	30.3 (1.5)
PTSD Symptom Scale				
Clinician	20.6 (2.2)	19.7 (0.9)	...	...
Patient	21.3 (1.9)	22.0 (1.8)	...	...

*Values are given as mean (SEM). PTSD indicates posttraumatic stress disorder.
†P<.01.

COMMENT

Administration of the α_2-antagonist yohimbine, which results in an increase in anxiety in patients with PTSD but not in healthy subjects, was associated with a significantly different metabolic response pattern in patients with PTSD compared with healthy subjects in neocortical brain regions that were hypothesized to change based on preclinical studies, including temporal, prefrontal, parietal, and orbitofrontal cortex. There was a tendency for yohimbine to be associated with a decrease in metabolism in the patients with PTSD and an increase in metabolism in the healthy subjects, with significant decreases in the hippocampus in patients with PTSD and significant increases in prefrontal and orbitofrontal cortex in the controls. These findings may be explained by a dose-dependent effect of norepinephrine on brain metabolism. Pharmacological studies[33,34] showed that high levels of norepinephrine release in the brain are associated with a decrease in brain metabolism, and lower levels result in an increase in brain metabolism. Yohimbine administration in normal controls may be associated with lower levels of norepinephrine release in central brain regions than in patients with PTSD, which results in increased metabolism. Consistent with this, a study with another α_2-antagonist, idazoxan, has shown an increase in prefrontal and occipital metabolism measured with PET FDG in healthy human subjects.[74] A large increase in norepinephrine in patients with PTSD, on the other hand, may lead to decreased metabolism. We are positing that patients with PTSD are in effect "seeing" higher doses of yohimbine than the controls, due to an increased sensitivity to yohimbine in PTSD.

Alterations in specific noradrenergic receptors (α_1, α_2, and β) in the brain[55,75,76] in patients with PTSD compared with controls also may account for our findings. One might speculate that in patients with PTSD, the primary effect of yohimbine on α_2-receptors is presynaptically at the level of the locus caeruleus, with a greater release of norepinephrine centrally in the brain compared with controls, which is associated with decreased neuronal function (and therefore metabolism). Conversely, in healthy subjects, the effects might be primarily on postsynaptic α_2-receptors, with blockade resulting in a release of postsynaptic α_2-receptor–mediated inhibition of cortical neuronal function. Consistent with the idea of a dose-dependent effect of norepinephrine on metabolism, PET studies in healthy subjects showed that mild degrees of stress increased cerebral blood flow, but severe stress decreased blood flow,[77] with an inverse correlation between metabolism in frontal and temporal cortex shown.[78,79]

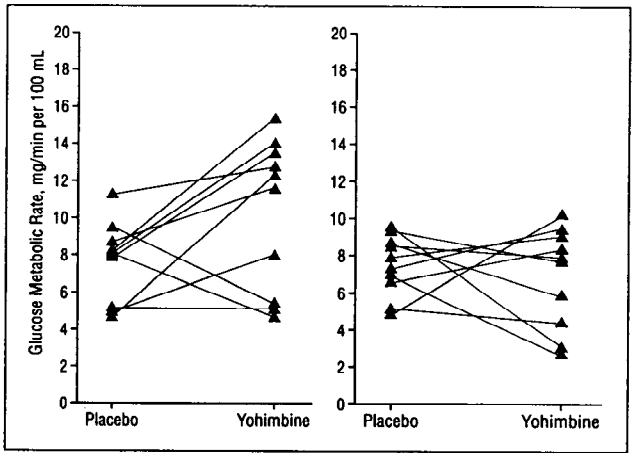

Figure 2. *Regional glucose metabolism in orbitofrontal cortex with placebo and yohimbine administration in controls (left) and patients with posttraumatic stress disorder (right). Symbols represent metabolism in individual subjects on the days of placebo and yohimbine administration. Analysis of variance with repeated measures for drug showed a significant interaction between drug and diagnosis in orbitofrontal cortex.*

We considered the possibility that yohimbine affects brain metabolism through effects on the cerebral

vasculature.[80] Studies of intracarotid injection of norepinephrine in dogs[81] and humans[82] have not shown an effect of norepinephrine on brain blood flow. We have conducted preliminary studies using the Patlak Plot method,[83] in which the rate constant parameter K_1, which reflects FDG uptake from the blood into the brain and is hence influenced by blood flow, is not fixed as it is in the Sokoloff method. Preliminary results from these analyses suggest that similar results are obtained from the Patlak Plot and Sokoloff methods.

One might question whether our results are secondary to comorbid disorders in the Vietnam veterans with PTSD. Vietnam combat veterans with PTSD have high rates of comorbidity with other psychiatric disorders, ranging from 62% to 88%, most commonly depression, anxiety disorders, and alcohol and substance abuse and dependence.[84] Exclusion of patients with PTSD with comorbidity, however, would represent a highly atypical and potentially biased sample. The question of comorbidity with OCD, GAD, panic disorder, depression, and other disorders has been carefully assessed in the biological studies that have been performed in patients with PTSD.[85] These studies, using psychophysiological responsivity,[86] startle response,[49] dexamethasone suppression test,[87] and hippocampal volume,[64] did not show a difference between patients with PTSD with and without comorbid disorders that included OCD, GAD, panic disorder, depression, and alcohol and substance abuse disorders. Our previous studies have shown an exaggerated behavioral and biochemical responsiveness to yohimbine in patients with PTSD[56] and panic disorder,[57,58] but not patients with GAD,[59] depression,[60] OCD,[61] or schizophrenia.[62]

These studies did not resolve, however, whether our findings might be due to the presence of comorbid panic disorder. Previous PET and single photon emission computed tomography studies in patients with anxiety disorders, including panic disorder,[88-98] showed alterations in similar brain regions to the current study, including a blunting of cortical blood flow to lactate[92] and yohimbine[93] in panic disorder. Patients with PTSD, with and without comorbid diagnoses of panic disorder, often experience panic anxiety, often in the context of flashbacks,[99] and symptoms of panic disorder and PTSD have been linked temporally with exposure to the trauma of war in Vietnam combat veterans.[100] In our experience, patients with primary diagnoses of combat-related PTSD and comorbid panic disorder are not clinically equivalent to our patients with primary panic disorder. Findings suggest, however, that PTSD and panic disorder share alterations in noradrenergic system function. Our previous studies showed high rates of yohimbine-induced panic attacks in PTSD, and an increase in plasma levels of the metabolite of norepinephrine, methoxyhexene phenylglycol, following administration of yohimbine, in patients with PTSD with a yohimbine-induced panic attack compared with patients with PTSD without a yohimbine-induced panic attack.[56] We attempted to examine the relation between panic anxiety and brain metabolic response to yohimbine in the current study by comparing patients with PTSD with and without a yohimbine-induced panic attack. Patients with a yohimbine-induced panic attack (which occurred in 60% of patients) had a pattern of a greater reduction in metabolism with yohimbine administration than did patients without a yohimbine-induced panic attack, a difference that did not reach statistical significance, possibly due to the small sample size. In summary, questions remain about the relation between the neurobiological characteristics of PTSD and panic disorder that are not answered by our findings. Future studies are required to investigate the relation between the neurobiological characteristics of PTSD and the neurobiological characteristics of panic disorder.

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