No Change in Serotonin Type 1A Receptor Binding in Patients With Posttraumatic Stress Disorder

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Objective: Serotonin type 1A receptors (5HT1ARs) have been shown to be affected by stress in experimental animals and related to anxiety and depression in humans. In the present study, the authors sought an association between 5HT1AR binding and posttraumatic stress disorder (PTSD).

Method: Using positron emission tomography and the radioligand [^{18}F]FCWAY, the authors compared 5HT1AR binding between patients with PTSD and healthy subjects.

Results: No significant differences in 5HT1AR distribution volume, binding potential, or tracer delivery were found.

Conclusions: 5HT1AR expression may not be altered in patients with PTSD.

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Serotonin type 1A receptors (5HT1ARs) have been proposed to play a major role in mood and anxiety modulation (1, 2). Chronic stress down-regulates 5HT1ARs in the hippocampus of experimental animals, and 5HT1AR knockout mice have displayed increased stress responsiveness (3). Human pharmacological trials have indicated that partial 5HT1AR agonists are effective in the treatment of generalized anxiety disorder and depression (1).

Several studies have examined 5HT1AR binding in mood and anxiety disorders. A preliminary neuroimaging study reported a significant negative correlation between 5HT1AR binding potential and indirect measures of anxiety in the dorsolateral prefrontal, anterior cingulate, parietal, and occipital cortices of healthy volunteers (4). Neumeister et al. (5) found a robust reduction in 5HT1AR binding potential in the anterior and posterior cingulate cortices and the raphe nucleus of patients with panic disorder relative to healthy comparison subjects. Similarly, mean 5HT1AR binding potential was reduced in frontal, temporal, and limbic cortices as well as the raphe nucleus in unmedicated depressed patients (6, 7).

Posttraumatic stress disorder (PTSD) is an enduring maladaptive response to stress. It is frequently comorbid with other mood and anxiety disorders. Similar to these other disorders, PTSD responds to treatment with selective serotonin reuptake inhibitors. In light of the aforementioned preclinical stress research and the apparent similarity to anxiety and affective disorders, we hypothesized that 5HT1AR density in patients with chronic PTSD would be lower than that seen in healthy comparison subjects.

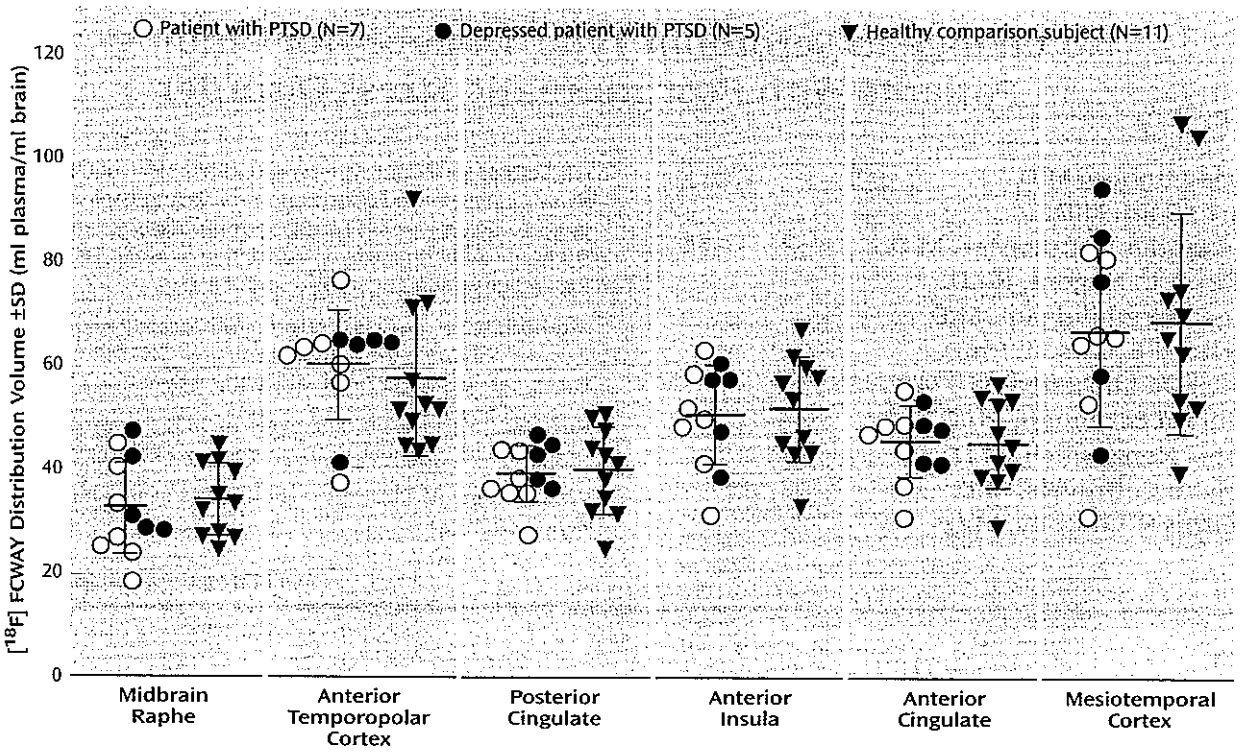
Method

Twelve unmedicated outpatients with PTSD (10 women and two men; mean age=44 years, SD=9) and a matched group of 11 never traumatized, healthy comparison subjects (10 women and one man; mean age=43, SD=8) participated in the study. PTSD status and severity were determined with the Clinician-Administered PTSD Scale. A minimal Clinician-Administered PTSD Scale score of 50 was required for inclusion (mean score=79, SD=19.4). Five PTSD subjects had suffered prepubertal sexual abuse, three had suffered childhood physical/emotional abuse, two had suffered sexual assault as adults, and two had experienced other severe traumatic events as adults. The Structured Clinical Interview for DSM-IV (8) evaluated the presence of concurrent and lifetime DSM-IV axis I disorders. Patients with current or past comorbid diagnoses of anxiety or major depressive disorder were included, provided that diagnosis of PTSD preceded the comorbid condition. Other DSM-IV axis I disorders precluded participation. Two patients suffered from concurrent major depressive disorder, one had generalized anxiety, and another had specific phobia. Three patients previously suffered from major depressive disorder. Two had been previously treated with antidepressants, and four had received benzodiazepines. Depression and anxiety symptoms were assessed with the Montgomery-Åsberg Depression Rating Scale (9) (mean=16.2, SD=8.3) and the Hamilton Anxiety Rating Scale (10) (mean=10.3, SD=3.7).

All participants were free of medical illness or major head trauma and had not been treated with psychotropic drugs in the 3 weeks preceding scanning. Subjects provided written informed consent, as approved by the NIMH Institutional Review Board.

A 120-minute PET study of 5HT1AR binding was acquired by using a GE Advance PET scanner in three-dimensional mode (35 contiguous slices, 4.25 mm plane separation; reconstructed resolution=7 mm full width at half maximum in all planes), bolus intravenous injection of 8 mCi of high specific activity [^{18}F]FCWAY, and arterial blood sampling. Magnetic resonance images, obtained for each subject using a 3.0-T GE Signa Scanner and a three-dimensional MPRAGE sequence (TE=2.982 msec, TR=7.5 msec, inversion time=725 msec, voxel size=0.9×0.9×1.2 mm), were coregistered to the PET images to provide an anatomical

FIGURE 1. Regional 5HT1AR Distribution Volume in Patients With PTSD and Healthy Comparison Subjects[a]



[a] No significant differences between groups were found for any brain region (unpaired t tests, two-tailed).

framework for analysis and to perform partial volume correction of the PET images. Regional 5HT1AR binding was measured in regions of interest defined a priori and transferred to the coregistered PET images using MEDx software (Sensor Systems, Sterling, Va.). The regions of interest were localized to brain structures that contain abundant 5HT1AR concentrations: anterior cingulate cortex, posterior cingulate cortex, anterior insula, mesiotemporal cortex (hippocampus plus amygdala), anterior temporopolar cortex, and midbrain raphe. To correct data for free and nonspecifically bound radiotracer, a reference tissue region of interest was defined in the cerebellum, which is devoid of 5HT1AR (for details of region of interest placement see Neumeister et al. [5]). The regional [^{18}F]FCWAY distribution volume (ml plasma/ml brain), corrected for plasma protein binding, and K_1, the delivery rate of [^{18}F]FCWAY from plasma to tissue (ml/min/min), were obtained by using quantitative tracer kinetic modeling. The mean distribution volume values were compared between groups by using unpaired t tests. The specificity for receptor-specific binding was assessed post hoc by comparing regional binding potentials as ($DV_{ROI}/DV_{cerebellum} - 1$) to factor out the influence of free and nonspecifically bound radiotracer.

Results

As seen in Figure 1, no significant differences in 5HT1AR distribution volume (ml plasma/ml brain, corrected for protein binding) were observed between patients and healthy subjects in any region of interest (midbrain raphe: mean=32.7 [SD=9.2] and 34.2 [SD=7.0], respectively; anterior temporopolar cortex: mean=60.2 [SD=10.8] and 57.6 [SD=15.1]; posterior cingulate: mean=39.4 [SD=5.5] and 40.6 [SD=8.2]; anterior insula: mean=50.7 [SD=9.7] and 51.9 [SD=10.2]; anterior cingulate: mean=45.6 [SD=6.9] and 45.4 [SD=8.6]; mesiotemporal cortex: mean=67.1 [SD=18.4] and 68.7 [SD=21.4]). Mean binding potential and tracer delivery (K_1) did not differ between groups in any region. No difference in 5HT1AR distribution volume was observed between PTSD patients with or without current or past diagnosis of major depression.

Discussion

The results of this investigation suggest that in PTSD, which frequently co-occurs with depression and panic disorder, 5HT1AR binding potential is unchanged. Preclinical investigations have shown changes in 5HT1AR binding after exposure to stress. However, the presence and valence of change vary, depending on the duration and nature of stress and brain region (1). Therefore, the diversity in type and duration of trauma in our patient cohort may obscure potential alterations in 5HT1AR binding in PTSD. Still, state-related changes in 5HT1AR binding in humans have not been shown. Reduced 5HT1AR binding in depressed patients was not affected by clinical state or treatment (7). Acute and chronic corticosteroid administration to mentally healthy subjects, and acute administration of corticosteroids to subjects remitted from depression, likewise had no effect on 5HT1AR binding (11, 12). 5HT1AR binding in PTSD in our cohort was not related to comorbidity with depression or anxiety. Future studies with patient groups homogenous for trauma char-

acteristics and comorbidity are needed to determine whether an interaction between genetic vulnerability and environment affects 5HT1AR expression in PTSD.

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References

1. Millan MJ: The neurobiology and control of anxious states. Prog Neurobiol 2003; 70:83–244
2. Gross C, Zhuang X, Stark K, Ramboz S, Oosting R, Kirby L, Santarelli L, Beck S, Hen R: Serotonin1A receptor acts during development to establish normal anxiety-like behaviour in the adult. Nature 2002; 416:396–400
3. Toth M: 5-HT1A receptor knockout mouse as a genetic model of anxiety. Eur J Pharmacol 2003; 463:177–184
4. Tauscher J, Bagby RM, Javanmard M, Christensen BK, Kasper S, Kapur S: Inverse relationship between serotonin 5-HT^{1A} receptor binding and anxiety: a [^{11}C]WAY-100635 PET investigation in healthy volunteers. Am J Psychiatry 2001; 158:1326–1328
5. Neumeister A, Bain E, Nugent AC, Carson RE, Bonne O, Luckenbaugh DA, Eckelman W, Herscovitch P, Charney DS, Drevets WC: Reduced serotonin type 1A receptor binding in panic disorder. J Neurosci 2004; 24:589–591
6. Drevets WC, Frank E, Price JC, Kupfer DJ, Holt D, Greer PJ, Huang Y, Gautier C, Mathis C: PET imaging of serotonin 1A receptor binding in depression. Biol Psychiatry 1999; 46:1375–1387
7. Sargent PA, Kjaer KH, Bench CJ, Rabiner EA, Messa C, Meyer J, Gunn RN, Grasby PM, Cowen PJ: Brain serotonin1A receptor binding measured by positron emission tomography with [^{11}C]WAY-100635: effects of depression and antidepressant treatment. Arch Gen Psychiatry 2000; 57:174–180
8. Spitzer RL, Williams JBW, Gibbon M, First MB: Structured Clinical Interview for DSM-IV (SCID). New York, New York State Psychiatric Institute, Biometrics Research, 1995
9. Montgomery SA, Åsberg M: A new depression scale designed to be sensitive to change. Br J Psychiatry 1979; 134:382–389
10. Hamilton M: The assessment of anxiety states by rating. Br J Med Psychol 1959; 32:50–55
11. Montgomery AJ, Bench CJ, Young AH, Hammers A, Gunn RN, Bhagwagar Z, Grasby PM: PET measurement of the influence of corticosteroids on serotonin-1A receptor number. Biol Psychiatry 2001; 50:668–676
12. Bhagwagar Z, Montgomery AJ, Grasby PM, Cowen PJ: Lack of effect of a single dose of hydrocortisone on serotonin(1A) receptors in recovered depressed patients measured by positron emission tomography with [^{11}C]WAY-100635. Biol Psychiatry 2003; 54:890–895