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Serotonin 1A Receptors, Depression, and Memory in Temporal Lobe Epilepsy

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Abstract

Purpose—Memory deficits and depression are common in patients with temporal lobe epilepsy (TLE). Previous PET studies have shown reduced mesial temporal 5HT1A receptor binding in these patients. We examined the relationships among verbal memory performance, depression, and 5HT1A receptor binding binding measured with 18FCWAY positron emission tomography (PET) in a cross sectional study.

Methods—We studied 40 patients (24 male; mean age 34.5 ±10.7) with TLE. Seizure diagnosis and focus localization were based on ictal Video-Electoencephalographic recording. Patients had neuropsychological testing with Weschler Adult Intelligence Score III (WAIS III) and Weschler Memory Score III (WMS III) on stable AED regimens at least 24 hours since the last seizure. Beck Depression Inventory (BDI) scores were obtained. We performed interictal PET with [18F]FCWAY, a fluorinated derivative of WAY100635, a highly specific 5HT1A ligand, and structural magnetic resonance imaging (MRI) scans to estimate partial volume and plasma free fraction corrected [18F]FCWAY volume of distribution (V/f1).

Key Findings—Hippocampal V/f1 was significantly lower ipsilateral than contralateral to the epileptic focus (73.7 ± 27.3 versus 95.4 ± 28.4; p<.001). We found a significant relation between both left hippocampal FCWAY V/f1 (r= 0.41; p < 0.02) and left hippocampal volume (r=0.36; p < 0.03) and delayed auditory memory score. On multiple regression there was a significant effect of the interaction of left hippocampal FCWAY V/f1 and left hippocampal volume on delayed auditory memory, but not of either alone. High collinearity was present. In an analysis of variance including the side of the seizure focus, the effect of left hippocampal FCWAY V/f1 but not focus laterality retained significance.

Mean BDI was 8.3 ±7.0. There was a significant inverse relation between BDI and FCWAY V/f1 ipsilateral to the patient's epileptic focus (r= 0.38 p<0.02) There was no difference between patients with a right or left temporal focus. There was no relation between BDI and immediate or delayed auditory memory.

Significance—Our study suggests that reduced left hippocampal 5-HT1A receptor binding may play a role in memory impairment in patients with TLE.

Keywords

Serotonin Receptors; Temporal Lobe Epilepsy; Memory; Depression; PET Scanning

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Introduction

Studies using several ligands have shown reduced serotonin (5-HT) 1A receptor binding in mesial temporal structures of patients with temporal lobe epilepsy (TLE) (Toczek et al 2003, Savic et al 2004, Merlet et al 2004, Giovacchini et al 2005, Ito et al 2007, Didelot et al 2008, Liew et al 2009). Investigators using WAY-100635 labeled with either ^{11}C or ^{18}F found that the degree and distribution of reduced binding was correlated with scores on depression scales (Savic et al 2004, Theodore et al 2007) or a diagnosis of depression on the Standardized Clinical Interview for Depression (SCID) (Hasler et al 2007). One study using ^{18}F-MPPF reported a positive correlation between 5-HT1A receptor binding potential (BP) and Beck Depression Inventory (BDI) score in several regions, including midbrain raphe, contralateral insula and ipsilateral hippocampus (Lothe et al 2008). The contrast in results with studies that found a relation between reduced binding and depression may be due to greater sensitivity of ^{18}F-MPPF than WAY-100635 to extracellular serotonin concentration. Nevertheless, these studies parallel findings in primary major depressive disorders showing alterations in 5-HT1A receptor binding (Parsey et al 2006, Drevets et al 2007).

Imaging studies suggest a role for 5-HT1A in cognitive function as well. 5-HT1A binding is reduced in most PET studies of Alzheimer's disease (SDAT) compared to controls, but correlations between memory and binding in healthy volunteers have been limited (Borg 2008). 5-HT1A receptor binding measured in post-mortem temporal cortex from patients with dementia was positively correlated with cognition (Elliott and Ballard 2009).

Cognitive impairment in epilepsy may be related to a variety of factors, including antiepileptic drug therapy, focal cortical atrophy or dysfunction, the effect of repeated seizures themselves, or underlying pathological processes (Hermann et al 2010). However, the role of specific neurotransmitters has not been investigated. In this study, we tested whether left hippocampal 5-HT1A binding and a clinical depression index were related to auditory memory performance in patients with TLE.

Methods

We studied 40 patients (24 male; mean age 34.5 ±10.7) with temporal lobe epilepsy who had been referred to the NINDS Clinical Epilepsy Section for evaluation of intractable seizures. Seizure diagnosis and focus localization were based on ictal Video-Electroencephalographic recording.

Patients had neuropsychological testing with Weschler Adult Intelligence Score III (WAIS III) and Weschler Memory Score III (WMS III) on stable AED regimens at least 24 hours since the last seizure. The WAIS III is a multidimensional assessment of both verbal and nonverbal tasks that generate a Verbal IQ, Performance IQ and a Full Scale IQ. The WMS III was used to assess memory and learning for verbal and visual material in immediate and delayed conditions. We used the Wechsler Memory Scale-III "Prose" memory (LM I&II) with immediate and 30 minute delayed trials (Shamim et al 2009). Subjects self-administered the Beck depression Inventory (BDI).

Imaging studies

No patient experienced seizures for at least 2 days before positron emission tomography (PET) scanning.

We obtained whole brain structural magnetic resonance imaging (MRI) scans on either a 1.5-T Horizon or a 3T Signa scanner (GE Medical Systems, Waukesha, Wisconsin) with standard T-2, Fluid attenuated inversion recovery and T1-weighted pulse sequences. We performed MRI segmentation and measured hippocampal volumes using published methods (Giovacchini et al 2005, Shamim et al 2009).

Dynamic PET scans were acquired for 120 min after bolus injection of approximately 10 mCi of Fluoro-N-(2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl)-N-(2-pyridyl)cyclohexanecarboxamide ([18 F]FCWAY), a fluorinated derivative of WAY100635, on an Advance scanner (GE Medical Systems), with a 68Ga transmission scan for attenuation correction. The scanner provides 35 slices with 4.25-mm separation in three-dimensional mode with septa retracted. Spatial resolution is 6 to 7 mm full-width half-maximum. Tissue radioactivity concentration was corrected for blood volume and acid metabolite uptake. Estimation of distribution volume (V) was performed with data fitted to a 2 compartment 3 parameter model using metabolite-corrected input arterial function. To correct for structural atrophy, we used an MRI-based partial volume correction (PVC) algorithm (Giovacchini et al 2005). To correct for potential antiepileptic drug (AED) effects on ligand protein binding, we used free fraction corrected V (V/f1) as our binding measure. We did not perform correction for nonspecific binding using cerebellum or another region in order to avoid introducing inaccuracies from structural atrophy, or binding heterogeneity (Parsey et al 2005, Theodore et al 2006, Giovacchini et al 2009). Previous studies have shown close agreement between FCWAY v/f1 and binding potential (Bmax/Kd) measurements, and lack of effects of AEDs after free fraction correction (Theodore et al 2006).

Statistical analysis was performed with SPSS Version 19 (IBM Inc Armonk N.Y). Student's t-Tests were used to compare the effects of dichotomous variables, including side of focus on hippocampal FCWAY V/f1, BDI, and memory indices. Linear regression with colinearity diagnostics was used to assess the relation of continuous variables, and analysis of variance for comparing fixed and continuous variables.

Written informed consent was obtained. The study was approved by the National Institute of Neurological Disorders and Stroke Combined Neuroscience Institutional Review Board and NIH Radiation Safety Committee.

Results

Twenty-two patients had a left, and 18 a right temporal focus. Hippocampal V/f1 was significantly lower ipsilateral than contralateral to the epileptic focus (73.7 ± 27.3 versus 95.4 ± 28.4; $p<.001$).

We found no difference between males and females in age at scan, seizure onset, or BDI.

We found a significant relation between left hippocampal FCWAY V/f1 and delayed auditory memory score ($r= 0.41$; $p < 0.02$) (figure 1). Patients with a left temporal focus had lower verbal IQ (92.7 ± 12.8 versus 104.5 ± 16.0; $P<0.02$) and non-significant trends toward lower immediate (89.8 ± 16.4 versus 100.3 ± 16.2) and delayed auditory memory (89.7 ± 13.3 vs 97.3 ± 13.9). However, in an analysis of variance including the side of the seizure focus, the effect of left hippocampal FCWAY V/f1 was still present, while the seizure focus lateralization was not significant. The relation between left hippocampal FCWAY V/f1 and immediate auditory memory was not significant ($p<0.07$). Right hippocampal FCWAY V/f1 was not related to either memory measure.

The presence of a structural abnormality on MRI did not affect delayed auditory memory score. There was a significant relation of left hippocampal volume to delayed auditory memory ($r=0.36$; $p < 0.03$). In a multiple regression, neither left hippcampal volume ($p=0.11$) nor left hippocampal FCWAY V/f1 ($p=0.11$) was significant, although the regression itself was ($r=0.43$; $p < 0.03$). However, there was significant multi-collinearity between the two variables. There was a trend toward a relationship between left hippocampal volume and left hippocampal FCWAY V/f1 ($r=2.7$; $0.05<p<0.10$). Mean BDI was 8.3 ±7.0. There was a significant inverse relation between BDI and FCWAY V/f1 ipsilateral to the patient's epileptic focus $r= 0.38$ $p<0.02$ (figure 2). There was no difference between patients with a right or left temporal focus, or a relation between BDI and immediate or delayed auditory memory.

Discussion

Our study suggests that reduced left hippocampal 5-HT1A receptor binding may play a role in memory impairment in patients with TLE. This effect remained after the side of the epileptic focus, based on ictal video-EEG monitoring, was included in the analysis. We also found that there was a significant relation between BDI score and hippocampal 5-HT1A receptor binding on the side of the focus, irrespective of side, confirming previous results. In this study the relation was weaker, perhaps because the patients had lower mean BDI. We found no relation between left hippocampal volume and BDI, or between BDI and memory performance. The relation between left hippocampal FCWAY V/f1 and immediate auditory memory was not significant. Moreover, the multicollinearity found between left hippocampal volume and FCWAY binding complicates interpretation of the multiple regression analysis.

Previous studies suggested that intractable TLE hippocampal volume predicts delayed verbal memory functioning in TLE (Stewart et al 2009). Hippocampal and parahippocampal volumes, but not glucose metabolism measured by 18FDG-PET were correlated with memory measures (Griffith et al 2004).

In our study, hippocampal volume and 5HT1A binding were both significant predictors of delayed auditory memory. On multiple regression, neither variable alone was significant but the interaction was. These results, as well as our use of a stringent partial volume correction procedure, suggest that the reduced 5HT1A binding has an independent effect on delayed auditory memory that interacts with hippocampal volume loss. Moreover, results were independent of the side of the epileptic focus, suggesting that structural atrophy alone cannot explain the finding. The presence of significant collinearity between the two variables is consistent not only with an effect of volume loss on receptor density, but also with data showing that 5-HT1A innervation itself may be important for maintenance of hippocampal neoneurogenesis and functional integrity (Chugani and Chugani 2003, Ogren et al 2008).

5-HT1A receptors play a role in learning and memory as well as mood (Nagai et al 2009). Cell bodies in the midbrain raphe have dense projections to hippocampus (King et al 2008). Chronically tryptophan-depleted rats with 40–50% reduced hippocampal 5HT had impaired object-recognition memory (Jenkins et al 2009). Knockout rats (SERT −/−) for the serotonin transporter (5-HTT) gene, with lower intracellular basal serotonin levels than controls in several brain regions showed impaired performance compared with wild-type controls on a delayed object recognition task (Olivier et al 2009). Several studies have suggested an association between 5-HTT polymorphisms and epilepsy (Kauffman et al 2009, Hecimovic et al 2010).

5-HT1A receptor PET studies in patients with SDAT show decreased binding in hippocampus and parahippocampal gyrus, while studies in patients with minimal cognitive impairment have shown both increases and decreases, suggesting the possibility of compensatory receptor upregulation early in the pathophyiologic process, followed by progressive loss of serotoninergic innervation (Kepe et al 2006, Truchot et al 2008). In patients with large vessel cerebrovascular disease, 5-HT1A binding in temporal cortex correlated positively with performance on several cognitive scales (Elliott et al 2009).

Acute tryptophan depletion in normal volunteers caused impaired verbal learning, delayed recall and delayed object relocation in a spatial task (Sambeth et al 2008). Although tryptophan depletion is not receptor subtype-specific, some data suggesting that acute tryptophan depletion impairs consolidation of episodic memory are consistent with 1A receptor effects on neurogenesis (Grabiec et al 2009, Mendelsohn et al 2009). Treatment with partial 5-HT1A agonists has been shown to improve some cognitive parameters in patients with schizophrenia (Meltzer and Sumiyoshi 2008, Piskulić et al 2009). 1A effects on cognitive function could be related to baseline 5-HT levels and receptor availability, and relative effects on postsynaptic versus presynaptic autoreceptors, modulated by dose and timing.

Patients with depression may have impairment on a variety of memory measures, even if hippocampal volume loss is not present (MacQueen et al 2003, Vythilingam et al 2004, O'Brien et al 2004, Douglas et al 2011). Some studies have shown reduced mesial temporal 5-HT1A binding in depression, paralleling TLE (Drevets et al, 2007). Successful treatment with antidepressants improved memory but did not affect hippocampal volume in patients with depression, implicating serotoninergic mechanisms rather than diffuse hippocampal dysfunction (Vythilingam et al 2004). A 5-HT1A receptor agonist impaired memory function in normal volunteers, but improved it in depressed patients (Ogren et al 2008). In patients with chronic stress, performance in attention, odor discrimination, and semantic memory tasks was impaired, correlating with 5-HT(1A) receptor binding potential (BP) measured with [(11)C]WAY100635 PET (Jovanovic et al 2011). Unfortunately, there have been no specific PET studies of 1A binding in relation to cognitive function in depression (Borg, 2008).

Reduced 5HT innervation may be related to other epilepsy comorbidities in addition to depression and cognitive impairment. Patients taking selective serotonin reuptake inhibitors had significantly fewer episodes of ictal oxygen desaturation during complex partial seizures (Bateman et al 2010). Our study supports previous work suggesting that serotoninergic pathways are potential therapeutic targets for the treatment of seizures and co-morbidities in TLE.

We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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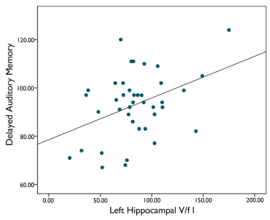

Figure 1.
Delayed auditory memory scores showed a significant relationship with 5HT1A receptor plasma free-fraction corrected volume of distribution (V/f1) in left hippocampus, independent of the side of the epileptic focus.

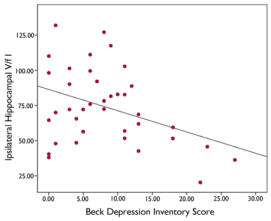

Figure 2.

Beck Depression Inventory Score showed a significant inverse relation with HT1A receptor plasma free-fraction corrected volume of distribution (V/f1) in the hippocampus on the side of the seizure focus.