

SEROTONIN RECEPTORS: A NEW EPILEPSY IMAGING MODALITY?

Limbic Reductions of 5-HT_{1A} Receptor Binding in Human Temporal Lobe Epilepsy

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OBJECTIVE: To test the hypothesis that in mesial temporal lobe epilepsy (MTLE) there is involvement outside of mesial structures and that this involvement affects serotonin systems, thus suggesting a mechanism for affective symptoms in this population.

METHODS: Serotonin 5-HT_{1A} receptor binding was studied with positron emission tomography (PET) and [carbonyl-¹¹C]WAY-100 635 in 14 patients (six with left-, eight with right-sided mesial temporal lobe focus) and 14 controls. The 5-HT_{1A} receptor-binding potential was calculated for hippocampus, amygdala, orbitofrontal, insular, lateral temporal, and anterior cingulate cortex, in raphe nuclei, and in two regions presumably uninvolved in the epileptogenic process (parietal and dorsolateral frontal neocortex).

RESULTS: The binding potential was reduced in the epileptogenic hippocampus ($p = 0.0001$) and amygdala

($P = 0.0001$) in all patients, including the six with normal [¹⁸F]fluorodeoxyglucose (FDG)-PET and magnetic resonance imaging (MRI). It also was reduced in the anterior cingulate ($P = 0.002$), insular ($P = 0.015$), and lateral temporal cortex ($P = 0.029$) ipsilateral to the focus, in contralateral hippocampus ($P = 0.025$), and in the raphe nuclei ($P = 0.016$).

CONCLUSIONS: Patients with severe MTLE show reduced 5-HT_{1A} receptor-binding potential in the EEG focus and its limbic connections. [¹¹C]WAY-100 635 PET may provide additional information to EEG, [¹⁸F]FDG-PET, and MRI when evaluating patients with intractable seizures. Reductions in 5-HT_{1A} binding in the insula and cingulate suggest a mechanism by which affective symptoms in MTLE may result.

Several recent positron emission tomography (PET) studies have shown that 5-hydroxytryptamine_{1A} (5-HT_{1A}) receptors are decreased in temporal lobe epileptic foci. Savic and associates used WAY-100 635, a potent, highly selective, silent 5-HT_{1A} antagonist, labeled with carbonyl-¹¹C, to compare 14 patients with mesial temporal lobe epilepsy (confirmed on ictal video EEG) with 14 controls. Seven patients had relative hippocampal volume reduction ipsilateral to the focus. They found reduced 5-HT_{1A} binding ipsilateral to the epileptogenic zone in the hippocampus, amygdala, lateral temporal cortex, anterior cingulate, and insula as well as in the midbrain raphe and contralateral hippocampus. The investigators used a region-of-interest approach, in which individual magnetic resonance images (MRIs) were transformed to fit within a normalized, computerized human brain atlas, and then individual PET images were reformatted to the same brain atlas, to coregister PET and MRI images with a common anatomic space. By using the Montgomery-Asberg Depression Rating Scale (MADRS), they found a significant inverse association between scores on the psychiatric rating scale and anterior cingulate [¹¹C]-FCWAY binding.

This study adds to PET results, using [¹⁸F]*trans*-4-fluoro-*N*-2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl-*N*-(2-pyridyl)

cyclohexanecarboxamide ([¹⁸F]FCWAY), demonstrating reduced 5-HT_{1A} binding volume of distribution ipsilateral to the epileptic focus in mesial temporal regions (1). Reduced activity was found in patients both with and without hippocampal atrophy on MRI. Reduced volume of distribution and binding remained significant after partial volume correction, showing that receptor binding was reduced in excess of volume loss. Lateral temporal neocortex reductions were not present after partial volume correction. Preliminary autoradiographic data from the patients' temporal lobectomy specimens showed 5-HT_{1A} loss in excess of neuronal loss (2). Merlet and associates, with a slightly different tracer, 4,2-(methoxyphenyl)-1-[2-(*N*-2-pyridinyl)-*p*-fluorobenzamido]ethylpiperazine ([¹⁸F]MPPF), reported that binding decrease was significantly greater in seizure-onset and propagation regions and was present even when quantitative and qualitative MRI were normal (3). With another analytic approach, statistical parametric mapping, in a study of seven patients, the 5-HT_{1A}-binding decrease was restricted to the temporal pole. In patients with normal hippocampal volumes, increased contralateral binding was found in some regions as well (4).

Taken together, these studies suggest a role for 5-HT_{1A} imaging in epilepsy. Receptor loss clearly exceeds structural

atrophy, at least in hippocampus and other mesial temporal regions. Additional lateral temporal data are needed. In the work by Savic and associates as well as in other studies, FCWAY and MPPF binding were decreased to a greater extent than was FDG (1) and were found in patients with normal MRIs (1,3). Could receptor loss be an early sign of neuronal dysfunction, followed by hypometabolism and, finally, structural atrophy? Does reduced 5-HT_{1A} binding help explain the high incidence of depression in epilepsy? Patients with endogenous depression have similar mesial temporal patterns on FCWAY scans, although without the asymmetry present in the epileptic focus (5,6). Will 5-HT_{1A}-receptor imaging prove to be of clinical value for patients with uncontrolled epilepsy being considered for surgery, particularly when MRI is normal?

To answer these questions, several methodologic issues must be addressed in subsequent studies. The influence of antiepileptic drugs on 5-HT_{1A} binding has not been studied extensively; although preliminary data show little significant effect, and selective serotonin reuptake inhibitors do not alter FCWAY binding (5–7). Several methods have been used to analyze data, and the best approach is uncertain. Only the statistical parametric mapping approach found increased binding (4). It will be interesting to see if this result is replicated in a larger patient sample. Statistical parametric mapping also entails some reduction in spatial resolution. The approach used by Savic et al. (i.e., registration to a normalized atlas) may reduce the subjectivity and error involved in drawing brain regions on MRIs but lead to some individual reformatting that might introduce error—particularly in patients with epilepsy who may have subtle anatomic anomalies. Partial-volume correction will be important to ensure that reduced receptor binding is not due to neuronal loss alone, particularly in extramesial temporal regions for which data, to some extent, are conflicting. However,

the results of the preliminary PET studies suggest a promising new approach for epilepsy imaging.

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