

MEASUREMENT AND SIGNIFICANCE OF CHANGES IN BENZODIAZEPINE RECEPTORS IN TEMPORAL LOBE EPILEPSY

Quantitative Analysis of Benzodiazepine Receptor in Temporal Lobe Epilepsy: [¹²⁵I]Iomazenil Autoradiographic Study of Surgically Resected Specimens

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PURPOSE: To evaluate the changes of the inhibitory neurotransmitter receptor system related to epileptogenesis by measuring central benzodiazepine receptors (BZDRs) in surgically resected specimens of temporal lobe epilepsy by using [¹²⁵I]iomazenil autoradiography.

METHODS: Surgically resected specimens were obtained from 66 temporal lobe epilepsy patients [51 with mesial temporal lobe epilepsy (MTLE) and 15 with non-MTLE] receiving no BZDs and seven MTLE patients receiving BZDs. BZDR densities in brain sections were measured by using [¹²⁵I]iomazenil autoradiography. Cell densities were measured from cresyl violet–stained sections.

RESULTS: Compared with non-MTLE patients, non-BZD-treated MTLE patients showed remarkable reduction of BZDR density in the pyramidal cell region of cornu ammonis (CA) 1, CA3, and CA4, and a smaller but significant reduction in CA2 and the molecular and granule cell layers of dentate gyrus (mDG). In the MTLE group, the BZDR density in the mDG correlated with that in lateral cortex. Significant correlations between BZDR density and cell density were found in all hippocampal regions. A significant difference in BZDR density/cell-density ratio was observed in CA1 region between MTLE and non-MTLE. BZD-treated patients tended to have lower BZDR densities than did non-BZD-treated patients, although the differences did not reach significance. In all MTLE cases, [¹²³I]iomazenil single-photon emission computed tomography (SPECT) showed decreased BZDR binding in MTL.

CONCLUSIONS: In MTLE, BZDR densities decreased

parallel to reduction in cell density in most hippocampal subfields, but BZDR density appeared to decrease in excess of neuron loss in CA1. [¹²⁵I]iomazenil SPECT might be useful for detecting in vivo changes of BZDR density.

COMMENTARY

Medial temporal lobe epilepsy is the most common surgically remediable epileptic syndrome. The pathologic findings underlying the epileptogenic zone include hippocampal neuronal loss with gliosis. Selected subfields of the hippocampal formation (CA1, CA2, CA3, and hilus) show the maximal cell loss. The hippocampal pathologic abnormalities may be intimately associated with both epileptogenesis and the development of co-morbidity. Abnormalities in excitatory and inhibitory neurotransmitter systems have been implicated in medial temporal lobe epilepsy. There are conflicting findings regarding the relative importance of excitatory and inhibitory (γ -aminobutyric acid subtype A; GABA_A) neurotransmitters in mesial temporal sclerosis. Measuring the central benzodiazepine receptor (BZDR) would provide an assessment of GABA_A receptors. There may be a reduction in GABA_A-inhibitory synapses and BZDR at the site of seizure onset. [¹¹C]Flumazenil (BZD antagonist) positron emission tomography (PET) has been used to image the GABA_A receptors in patients with medial temporal lobe epilepsy. [¹²⁵I]Iomazenil is a partial BZDR agonist that may be used in single-photon emission computed tomography (SPECT) studies. The clinical utility of [¹²⁵I]iomazenil SPECT in patients with medial temporal lobe epilepsy is unknown.

The present study by Sata et al. used [¹²⁵I]iomazenil autoradiography to provide in vitro measurements of BZDR density in brain sections in 73 patients with temporal lobe epilepsy who underwent epilepsy surgery. Sixty-six patients were not receiving BZD drugs: 51 patients had medial temporal lobe epilepsy, and 15 patients had non-medial temporal lobe epilepsy (extrahippocampal seizures). Seven patients were evaluated with medial temporal lobe epilepsy while receiving BZD drugs. The 51 patients with medial temporal lobe epilepsy

showed a significant reduction in BZDR density in the pyramidal cell region of CA1, CA3, and CA4 compared with that in patients with non-medial temporal lobe epilepsy. There also was a correlation between BZDR density and cell density. Patients treated with BZD drugs "tended to have lower BZDR densities," although the differences were not significant. Finally, in seven of seven patients with medial temporal lobe epilepsy and mesial temporal sclerosis, the preoperative in vivo [¹²⁵I]iomazenil SPECT scans showed a decrease in BZDR binding in the ipsilateral mesial temporal lobe. There was not a similar mesial temporal lobe reduced accumulation of BZDR binding in three patients with extrahippocampal seizures.

The present study provides additional evidence that abnormalities of BZDR occur in patients with medial temporal lobe epilepsy related to mesial temporal sclerosis. This would

correlate with the previous observations indicating a reduction in GABA_A inhibitory synapses in the epileptogenic focus. The lower BZDR densities in the current study likely are related to underlying cell loss in the pyramidal cell region. The use of [¹²⁵I]iomazenil SPECT scans in patients with medial temporal lobe epilepsy by Sata et al. may be an important innovation in the evaluation of patients with intractable seizure disorders being considered for surgical treatment. It remains to be seen if [¹²⁵I]iomazenil SPECT scans will be sensitive and specific in a larger patient group. The diagnostic yield of this neuroimaging technique in patients without MRI-identified hippocampal formation atrophy or a mesial temporal lobe signal-intensity alteration also must be critically evaluated.

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