

PERIICTAL DYNAMIC CHANGES IN BENZODIAZEPINE RECEPTORS

Seizure-related Short-term Plasticity of Benzodiazepine Receptors in Partial Epilepsy: An [¹¹C]Flumazenil-PET Study

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We have undertaken a test–retest [¹¹C]flumazenil (FMZ) positron emission tomography (PET) study in 10 drug-resistant epilepsy patients, including six with a mesiotemporal epilepsy (MTE), and 10 normal controls, to investigate seizure-related short-term plasticity of benzodiazepine (BZD) receptors. All subjects underwent two FMZ-PET scans at a 1-week interval. Patients benefited from a concurrent video-EEG monitoring, which allowed determination of the duration of the interictal period (IP) preceding each PET study. Test–retest whole-brain B'_{\max} variations, evaluated with a partial-saturation injection protocol, were similarly observed in patients and controls, suggesting a physiologic modulation of BZD receptors. Five (50%) pa-

tients, but no controls, also demonstrated clinically significant test–retest FMZ-PET variations in the mesial temporal region. This was observed in all three patients with MTE and no hippocampal atrophy, in whom only the PET study associated with the shortest IP correctly identified the epileptogenic zone. Statistical analysis revealed a significant effect of IP duration on BZD receptor B'_{\max} in MTE patients, suggesting that the shorter the IP, the lower the B'_{\max} in the epileptogenic hippocampus. FMZ-PET appears to be an interesting tool for investigating both normal and abnormal short-term modulations of the BZD receptor system and should ideally be performed within a few days after a seizure in patients with MTE and a normal MRI.

COMMENTARY

Functional neuroimaging with positron emission tomography (PET) has been used in the diagnostic evaluation of patients with partial epilepsy (1,2). 18-Fluoro-2-deoxyglucose PET (FDG-PET) is the most commonly performed study and may reveal interictal temporal lobe glucose hypometabolism in patients with temporal lobe epilepsy (1,2). PET is a reliable indicator of the temporal lobe of seizure origin, and the findings are of prognostic importance in patients who undergo epilepsy surgery (1,2). Temporal lobe epilepsy is the most common indication for surgical treatment of intractable epilepsy (1,2). Patients with unilateral FDG-PET temporal lobe hypometabolism may be highly favorable candidates to experience a significant reduction in seizure tendency after focal cortical resection for intractable epilepsy (1–3). The FDG-PET findings are often lobar or regional in individuals with medial temporal lobe epilepsy and focal hippocampal neuronal loss (1–3).

[¹¹C]Flumazenil (FMZ) PET studies (FMZ-PET) have been performed for patients with localization-related epilepsy to evaluate benzodiazepine (BZD) receptors. FMZ-PET images most subtypes of GABA_A receptors (3–5), and GABA is the

most important inhibitory neurotransmitter in the brain (3). A decrease or increase in the neocortical or hippocampal BZD allosteric site of the GABA_A receptor has been demonstrated in patients with partial epilepsy (3–5). A localized alteration in BZD binding may be a reliable indicator of the epileptogenic zone (6,7). A reduction in FMZ binding has been demonstrated in patients with medial temporal lobe epilepsy associated with hippocampal sclerosis (4,5). Compared with FDG-PET, an FMZ-PET study on intractable partial epilepsy may reveal a more well-localized imaging alteration, which is concordant with the epileptogenic zone. FMZ-PET is significantly more sensitive than FDG-PET for patients with partial epilepsy in identifying the epileptic brain tissue (7). The potential mechanisms for the alteration in central BZD receptors in these patients include structural pathology (i.e., hippocampal neuronal loss) or a functional abnormality related to seizure activity (3–7). The frequency of seizures may affect and correlate with FMZ-PET BZD binding. An increase in FMZ binding in patients with an unremarkable MRI study may represent a malformation of cortical development (6). Impaired BZD-receptor binding may be identified in patients with dysembryoplastic neuroepithelial tumors, suggesting increased focal epileptogenesis (5). The FMZ-PET alteration in nonresected cerebral cortex may be reversible in patients undergoing a successful surgical procedure for temporal lobe epilepsy. Resection of a focal FMZ-PET abnormality in individuals with a neocortical epilepsy indicates a favorable

operative outcome (7). The presence of a BZD-receptor binding abnormality remote from the epileptogenic zone in patients with neocortical epilepsy may indicate an unfavorable operative outcome (7).

The study of Bouvard et al. indicates that FMZ-PET studies may reveal variable findings in patients with medial temporal lobe epilepsy. The test–retest variation in the FMZ-PET occurred in all three patients with medial temporal lobe epilepsy without MRI-identified hippocampal atrophy. The duration of the interictal period before the FMZ-PET study correlated with the decrease in BZD binding, suggesting that a potential mechanism for this alteration may be partial-seizure activity. In patients with a normal MRI, the FMZ-PET study should be performed in proximity to a clinical seizure to reveal a localized imaging alteration reflecting a BZD-receptor-binding abnormality. The functional neuroimaging may lateralize reliably the epileptic temporal lobe in these patients.

In approximately one third of potential candidates with intractable epilepsy, the preoperative MRI study does not reveal a pathologic substrate underlying the epileptogenic zone (3,5,6). In patients with a normal MRI, the FMZ-PET may indicate the site of seizure onset and alter the surgical management of the individual's seizure disorder. The potential applications of these studies in patients with nonlocalizing, scalp-recorded ictal EEG findings and no obvious pathologic substrate include the placement of intracranial EEG electrodes and tailoring of the focal cortical resection. Excision of the principal FMZ-PET abnormality may correlate with a seizure-free outcome. Patients with multilobar FMZ-PET abnormalities may represent unfavorable operative candidates, either because of widely distributed multifocal epileptogenic zones or of possible secondary epileptoge-

nesis. The study of Bouvard et al. indicates that abnormalities of BZD-receptor binding may reflect “short-term plasticity” and are intimately associated with seizure activity. Potentially, a transient decrease in BZD receptors may have occurred after seizures.

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References

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