Serotonergic PET in temporal lobe epilepsy

Biomarking or etiologic mapping?

PET and selected ligands offer brain mapping for a panoply of neuronal receptors and other important brain molecules. Neurochemically specific PET studies have yielded numerous biomarkers of hippocampal and extrahippocampal dysfunction, which often have been used to study groups with temporal lobe epilepsy (TLE). Etiologies and the development of epilepsy are poorly understood in TLE, however. Further, causative pathophysiology is largely unelucidated with regard to the variations in neuronal function that induce seizure onset at a particular point in time, or the persistence of the interictal state; the mechanisms underlying interictal disorders of cognition and mood in TLE are equally obscure. Perhaps as a result, neurochemically specific PET biomarkers have been less helpful in helping us understand epilepsy progression or other manifestations in individual patients with TLE, than in simply contrasting differences in interictal biomarkers between groups with and without TLE. An ever more elusive goal has been development of etiology-specific PET maps that might guide precise diagnosis and effective therapy of the individual patient with TLE.

Serotonergic systems are best known to clinicians as underlying affective disorders, evidenced by the efficacy of selective serotonin reuptake inhibitors (SSRIs) in treating depression. Serotonin also has major roles in arousal, feeding, and satiety, and in migrainous disorders. A lesser-known role of serotonin in endogenous antiseizure mechanisms is apparent in several experimental epilepsy models, in which increased regional serotonin levels antagonize seizures. Serotonergic signaling also appears to be mechanistically involved in brain development, including malformations of cortical development that predispose to epilepsy. Enhanced serotonin availability in the temporal lobe has antidepressant effects in rodent epilepsies. Major depression adds further discomfort and disability to the burden of TLE, and at least one-half of those with the most refractory temporal lobe seizures appear to have severe depression. Clinical neurologists may naively assume that the limitations of TLE commonly engender a reactive depression that might be adequately addressed with a kindly bedside manner and a supportive family, but evidence of altered brain serotonergic function should suggest that pharmacotherapy is indicated.

Brain serotonin metabolism and signaling involves precursors and enzymes for synthesis, synaptic release, and termination of effect by reuptake, and binding to various receptors that mainly mediate intracellular second messenger systems but also gate ion channels. PET has been used to map cerebral serotonin synthesis capacity in human mesial TLE and neocortical epilepsy, using carbon-11-labeled α-methyl tryptophan (AMT), which is a substrate of tryptophan hydroxylase, the enzyme that catalyzes the rate-limiting step in serotonin synthesis; findings include increased AMT activity at epileptogenic sites. The density of certain serotonin receptor subtypes also has been mapped with various PET ligands. The latter have shown specific reductions in serotonin 1A (5-HT1A) receptors, a receptor subtype implicated in both affective disorders and endogenous antiseizure effects of serotonin. Human brain maps in TLE now also include the serotonin transporter (5-HTT), the main terminator of synaptic serotonin effect, as reported in this issue of Neurology®.

Martinez et al. found evidence that 5-HTT activity is lower in the insula and fusiform gyrus on the epileptogenic side, more so in depressed patients with TLE than in nondepressed patients with TLE. This suggests that depressed patients with TLE may have a beneficial endogenous mechanism to locally reduce serotonin reuptake, perhaps in an attempt to increase serotonin levels in insular and temporal lobe synapses. This study also found reduced 5-HT1A receptor binding in the hippocampus and other limbic sites on the epileptogenic side, in agreement with earlier reports in TLE. Interestingly, in insular cortex there was a correlation between 5-HTT asymmetry and 5-HT1A asymmetry for patients with TLE but not for healthy controls. This observation suggests that greater loss of 5-HT1A receptors may in some way drive the compensatory mechanism of reduced transport, such that higher synaptic serotonin levels will be maintained at the sites that have fewer 5-HT1A receptors.

Glucose metabolic mapping and central benzodiazepine receptor mapping with brain PET have revealed...
regional abnormalities that are related to sites of ictal onset and propagation in TLE. Focal glucose hypometabolism of the orbitofrontal cortex ipsilateral to the epileptogenic temporal lobe was greater in patients with TLE with depression than in nondepressed patients with TLE. In the future, more specific mechanisms of depression-associated limbic dysfunction in TLE may be defined with additional PET imaging. Perhaps different clinical syndromes of affective disorders in epilepsy will be associated with distinct brain map signatures. Severity of clinical depression may be related to the extent and severity of various neurotransmitter, receptor, or transporter abnormalities detectable by molecular neuroimaging. Such associations may serve as biomarkers to define treatment groups in future clinical trials. Will we be able to identify those patients with TLE who will improve in mood with SSRIs? Could we find similar imaging markers in extratemporal lobe epilepsies? Might SSRIs serve as antiseizure adjuncts in selected epilepsy patients? In addressing these and other questions, a combination of translational studies and clinical trials may move us from biomarking to etiologically specific PET mapping.

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REFERENCES