

## EXPANDING THE GEOGRAPHY OF EPILEPSY: IMAGING EVIDENCE FOR BASAL GANGLIA INVOLVEMENT

### Involvement of the Basal Ganglia in Refractory Epilepsy: An $^{18}\text{F}$ -fluoro-L-DOPA PET Study Using 2 Methods of Analysis

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**PURPOSE:** Studies in animal models and epileptic patients have led to the suggestion that the basal ganglia (BG) are involved in seizures. PET with 6- $^{18}\text{F}$ -L-3,4-fluorodihydroxyphenylalanine ( $^{18}\text{F}$ -fluoro-L-DOPA) has recently demonstrated a reduction of striatal dopamine uptake in drug-resistant epileptic patients with ring chromosome 20 (r20) using a multiple-time graphical analysis. The aim of the present study was to evaluate the involvement of dopamine in other epileptic syndromes using a multiple-time graphical analysis and the all-brain statistical parametric mapping (SPM) analysis.

**METHODS:** Patients with drug-resistant epilepsy were divided into three groups: Group 1, with r20 epilepsy ( $n = 16$ ; mean age  $\pm$  SD,  $21.5 \pm 5.4$  y); Group 2, with resistant generalized “absence-like” epilepsy ( $n = 10$ ; mean age,  $32.3 \pm 11.4$  y); and Group 3, with drug-resistant temporal lobe epilepsy with hippocampal sclerosis ( $n = 9$ ; mean age,  $35.2 \pm 10.3$  y). We compared two strategies of analysis of the  $^{18}\text{F}$ -fluoro-L-DOPA uptake constant ( $K_i$ ,  $\text{min}^{-1}$ ) in BG using a multiple-time graphical analysis using regions of interest (the gold-standard method) and an SPM

analysis using a voxel-by-voxel statistical  $t$  test to avoid a priori hypotheses in the analysis. Each epileptic group was compared with a group of healthy volunteers ( $n = 10$ ; mean age,  $45.1 \pm 16.5$  year).

**RESULTS:** A decrease of the mean  $K_i$  value was observed in the striatum in all groups of patients with both types of analysis. With multiple-time graphical analysis, the reduction was evident using the averaged  $K_i$  values over both hemispheres in each BG. Unilateral decreases in each BG were detected in SPM analysis. A ratio of decrease of  $^{18}\text{F}$ -fluoro-L-DOPA uptake was observed in the three groups of patients. Only the SPM analysis showed a decrease of  $^{18}\text{F}$ -fluoro-L-DOPA uptake ipsilateral to the seizure side in patients with temporal lobe epilepsy. Moreover, the all-brain SPM analysis showed a decrease of  $^{18}\text{F}$ -fluoro-L-DOPA uptake in the substantia nigra bilaterally ( $P < 0.001$ ).

**CONCLUSION:** This result confirms the involvement of dopamine neurotransmission in seizure control related to the type of epileptic syndrome. The difference in epileptic types may depend in part on the seizure frequency.

### COMMENTARY

One of the major advantages of positron emission tomography (PET) is its ability to help bridge the chasm between preclinical studies in epilepsy models and clinical investigation. The study of Bouilleret et al. is an excellent example of this application. In a previous study, the same group found that [ $^{18}\text{F}$ ]fluoro-L-dihydroxyphenylalanine ([ $^{18}\text{F}$ ]fluoro-L-DOPA) PET uptake was significantly decreased bilaterally in putamen and caudate nucleus of patients with ring chromosome 20 epilepsy, compared with controls (1). They suggested that dysfunction of striatal dopaminergic neurotransmission might impair mechanisms that interrupt seizures. Here the investi-

gators examined chromosome 20 epilepsy patients (Group 1) plus two additional groups of drug-resistant patients: one with generalized seizures and epileptiform discharges, who were not responsive to antiepileptic drugs (AEDs) [Group 2], and the other with temporal lobe epilepsy (TLE) and hippocampal sclerosis (Group 3). In addition, they compared two competing approaches to PET analysis, addressing an issue that may have particular importance for epileptic syndromes that are associated with structural atrophy.

One analytic approach used 10 millimeter circular regions (drawn on the head of the caudate nucleus and on the putamen in each hemisphere) that were imaged on MRI and coregistered to PET. The mean activity concentration in the circular regions was used to generate regional time–activity curves for calculating [ $^{18}\text{F}$ ]fluoro-L-DOPA uptake in each striatal structure (referred to as the regions of interest uptake analysis), with activity in a defined circular occipital area used as input function.

Values for each patient group were compared with those of the healthy volunteers. The second approach to PET analysis used statistical parametric mapping (SPM)99, with images normalized onto Talairach space and smoothed to 6-mm resolution for group comparison between patients and normal controls.

No side–side differences in uptake were found for the patients as a whole, for any of the individual groups, or the controls. The patients as a whole as well as the ring chromosome 20 and generalized epilepsy groups, individually, had significantly reduced caudate and putamen uptake on the regions of interest uptake analysis; however, the TLE with hippocampal sclerosis group showed no reductions. The SPM approach showed decreases in substantia nigra and putamen but not caudate for the patients as a whole and for all three groups individually. Uptake also was decreased in the putamen, bilaterally, in patient Groups 1 and 2 and ipsilateral to the hippocampal sclerosis in the TLE with hippocampal sclerosis group—a change detected by the greater sensitivity of the SPM approach.

This study showed basal ganglia and substantia nigra dysfunction in several unrelated epilepsy syndromes. The results could be due to reduced receptor number, increased occupancy by endogenous ligand, or an alternative mechanism, such as receptor internalization. Although they did not study the effect of AEDs directly, the authors suggest that the reductions in [<sup>18</sup>F]fluoro-L-DOPA uptake they found were not due to AEDs, at least in the TLE with hippocampal sclerosis group with unilateral substantia nigra findings, while noting that some AEDs have been shown to increase dopamine release in animal models. It is interesting that patients in Groups 1 and 2 were more likely to be on valproic acid than those in Group 3. However, it might be difficult to detect an effect of AEDs on exogenous ligand binding, since baseline dopamine receptor occupancy is probably low (2).

Several previous PET studies have observed decreased thalamic glucose metabolism in patients with localization-related epilepsy, and some investigators have suggested that this finding might be valuable for lateralizing epileptogenic zones (3–6). Benedek et al. found that in patients with intractable frontal and temporal lobe epilepsy, duration of epilepsy was a significant predictor of ipsilateral thalamic glucose metabolism; secondary generalized seizures also were associated with lower metabolism in ipsilateral thalamus (as well as hippocampus) (7). In a subsequent study, the same investigators found that the dorsomedial thalamic nucleus showed significantly lower glucose metabolism as well as binding of the benzodiazepine receptor ligand [<sup>11</sup>C]flumazenil on the side of the epileptic focus (8). In contrast, the lateral nucleus showed bilateral hypermetabolism and increased benzodiazepine receptor binding. The authors thought this increase might represent an upregulation of inhibitory circuits.

Neither Benedek et al. nor Bouilleret et al. performed a partial volume correction in order to assess the effect of struc-

tural atrophy on their results; it is true that this procedure can be particularly difficult to carry out in subcortical nuclei. Mean ipsilateral thalamic, caudate, and bilateral lenticular volumes are significantly smaller in patients with TLE than in control subjects (9). Thalamic signal change has been reported occasionally as well (10). However, structural atrophy alone would be unlikely to account for the PET results.

PET demonstration of reduced dopaminergic neurotransmission in three different epilepsy syndromes suggests that the basal ganglia may be playing a modulatory role in seizure expression in humans, confirming and extending preclinical investigations. If confirmed by additional studies, these data may help to design new therapeutic approaches to epilepsy. Adjunctive use of drugs designed to modulate basal ganglia function might be a promising strategy. Moreover, the PET imaging results may have important implications for the deep brain stimulation trials currently underway, helping to select appropriate targets for intervention.

by William H. Theodore, MD

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