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Decreased Dopamine D2/D3-Receptor Binding in Temporal Lobe Epilepsy: An [^{18}F]Fallypride PET Study

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Summary: *Purpose:* Although animal data are suggestive, evidence for an alteration of the extrastriatal dopaminergic system in human focal epilepsy is missing.

Methods: To quantify D2/D3-receptor density, we studied seven patients with temporal lobe epilepsy (TLE) and nine age-matched controls with positron emission tomography (PET) by using the high-affinity dopamine D2/D3-receptor ligand [^{18}F]Fallypride ([^{18}F]FP) suitable for imaging extrastriatal binding. TLE was defined by interictal and ictal video-EEG, magnetic resonance imaging (MRI), and [^{18}F]fluorodeoxyglucose ([^{18}F]FDG)-PET and was due to hippocampal sclerosis (HS), based on histology in all patients. Primary analysis was based on regions of interest (ROIs) defined on individual MRIs. For each patient, binding potential (BP) was calculated by using the simplified reference tissue model, and the epileptogenic was compared with the unaffected hemisphere in each ROI. To confirm the results, an additional voxel-based group analysis was performed by using statistical parametric mapping.

Results: Compared with controls, [^{18}F]FP BP was significantly decreased in the epileptogenic temporal lobe in all patients. On ROI analysis, this reduction was evident in areas surrounding the seizure-onset zone at the pole (–34.2%) and lateral aspects (–32.9%) of the temporal lobe. Although the hippocampus [^{18}F]FDG uptake (–8.1%) and hippocampal MR volume (–35.1%) were significantly reduced, no significant decrease of [^{18}F]FP BP was found. Reduction of [^{18}F]FP BP did not correlate with hippocampal atrophy.

Conclusions: D2/D3-receptor binding is reduced at the pole and in lateral aspects of the epileptogenic temporal lobe in patients with mesial TLE and HS. This area might correspond to "the irritative zone," indicating that D2/D3 receptors might play a specific role in the pathophysiology of mesial TLE.

The role of dopamine in the pathophysiology of focal epilepsy is controversial (1). In extrastriatal areas, the limbic system receives particularly rich dopaminergic innervation (2) and expresses different types of dopamine receptors (3). The dopaminergic influence on epileptic seizures arising from mesial temporal structures (4) might be inhibitory (i.e., via dopaminergic hippocampal projections enhancing a Ca^{2+}-dependent K^+ conductance) (5). Animal data suggest that activation of D1 and D2 receptors has diverging effects on the regulation of seizure threshold, D2 being anticonvulsant and D1 activation, more proconvulsant (4,6,7). In this positron emission tomography (PET) study, the high-affinity D2/3-receptor antagonist [^{18}F] Fallypride (FP) was used to characterize D2/D3-receptor binding in patients with mesial temporal lobe epilepsy (mTLE), with emphasis on changes in extrastriatal binding.

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MATERIALS AND METHODS

Patients and controls

With ethical and radiation-protection authority approval and after written, informed consent, we studied seven mTLE patients [five men; mean (±SD) age, 31.6 ± 5.5 years; clinical details in Table 1].

Controls were nine healthy men (age, 32.3 ± 8.4 years; for ethical reasons, no women could be included as controls). Mesial TLE with hippocampal sclerosis (HS) was defined by interictal and ictal EEG, magnetic resonance imaging (MRI), interictal fluorodeoxyglucose–positron emission tomography (FDG-PET), histology, and the postsurgical seizure-free outcome [mean (±SD) follow-up, 16.3 ± 6.6 months; Table 1]. Patients had been seizure free for ≥2 days and free of generalized tonic–clonic seizures for ≥2 weeks before [^{18}F]FP-PET studies. Surface EEG recordings were performed during all PET

TABLE 1. *Clinical characteristics of patients*

Patient no.	Age (yr)	Sex	Duration (yr)	Side affected	Interictal EEG	Ictal EEG	MRI	HV (cc)	AED therapy	Postoperative follow-up
1	27	M	19	L	L temp 100%	L temp (n = 3)	Left HS	L 0.93 R 2.47	LTG LEV	28 mo
2	26	M	1	L	L temp 100%	L temp (n = 5)	Left HS	L 2.79 R 3.61	LTG	12 mo
3	34	M	12	L	L temp 100%	L temp (n = 2)	Left HS	L 2.55 R 3.04	OXC LEV	9 mo
4	33	F	27	L	L temp 100%	L temp (n = 4)	Left HS	L 1.17 R 1.97	VPA LEV	9 mo
5	39	M	32	R	R temp 73% L temp 34%	R temp (n = 8)	Right HS	L 2.72 R 1.93	LTG LEV	14 mo
6	24	M	20	L	L temp 100%	L temp (n = 5)	Left HS	L 2.16 R 3.80	LTG TPM	18 mo
7	38	F	34	R	R temp 70% L temp 30%	R temp (n = 2)	Right HS	L 2.68 R 1.83	LTG LEV	22 mo

L, left; R, right (dominant hemisphere); temp, temporal; %, spike distribution; HS, hippocampal sclerosis; HV, hippocampal volume; LTG, lamotrigine; LEV, levetiracetam; OXC, oxcarbazepine; VPA, sodium valproate; TPM, topiramate.

studies. [^{18}F]FDG and [^{18}F]FP-PET studies were acquired on separate days. Images were acquired on a Siemens ECAT EXACT (Siemens/CTI, Knoxville, TN, U.S.A.) whole-body PET scanner. After a 20-min transmission scan, a 180-min dynamic emission recording was initiated after a mean (±SD) intravenous bolus injection of 220 ± 22 MBq and 213 ± 38 MBq [^{18}F]FP for patients and controls, respectively (for more detail, see ref. 8). For assessment of regional glucose metabolism, 351 ± 43 MBq (mean ± SD) [^{18}F]FDG was injected in the patients and 355 ± 38 in controls under standard resting conditions (9), followed after 30 min by a 20-min emission scan. Binding potentials (BPs) of [^{18}F]FP were calculated on a voxel-wise basis by using the Simplified Reference Tissue Model (10). The reference input was derived from cerebellar time–activity curves (8). The cerebellum was chosen as a reference region because it is generally considered free of dopamine receptor. Images were realigned by using MPItool (ATV Erftstadt, Germany). An individual region of interest (ROI) template was defined on transaxial MRI images. We drew ROIs for the hippocampus, temporal pole, anterior lateral temporal lobe (ant.-lat. temp.), posterior-temporal, parahippocampal gyrus, parietal, occipital cortex, central and frontal cortical areas, as well as the thalamus (anterior nuclei), caudatum, and putamen. The relative variation of BP between hemispheres was calculated by using the formula:

$$\Delta \text{ change} = [\text{BP epileptogenic} - \text{BP unaffected}/\text{BP unaffected side}] \times 100$$

For hippocampal volumetry (using Voxel Q on coronal slices) and ROI analysis, MRI acquisition consisted of three-dimensional (3D) anatomic scans of the entire brain in a sagittal plane (TR/TE, 1,900/3.93 ms; slice thickness, 1 mm; 512 × 512 matrix) by using a 1.5-T system (Siemens Magnetom Vision). Voxelwise statistical analysis and transformation into Talairach coordinates was performed by using SPM 99 (Wellcome Department of Cognitive Neurology, London, U.K.). For group comparisons, *t*-statistical parametric maps were calculated by using a threshold of $p < 0.05$ (corrected at cluster level; minimal cluster size, >20 voxels).

RESULTS

The BP of [^{18}F]FP was significantly reduced in all patients in the epileptogenic temporal lobe compared with controls and with the unaffected side. As shown in one typical case (Fig. 1A), a reduction of [^{18}F]FP BP was found in lateral and anterior but not in mesial aspects of the left temporal lobe.

The categoric group comparison of [^{18}F]FP BP in controls versus patients with SPM revealed a significantly decreased regional [^{18}F]FP BP restricted to the pole and in anterior lateral areas of the temporal lobe of the epileptogenic hemisphere (Fig. 1B; x, y, z = [–34, 4, –37] with Z = 4.23 (lateral temporal) and anterior temporal pole (x, y, z = [–46, 10, –31]; Z = 3.84). In contrast, mesial temporal areas were not significantly affected. No significant difference of [^{18}F]FP BP was noted with the reverse contrast (patients – controls) (reflecting relative BP increases in patients). [^{18}F]FP BP of the unaffected temporal lobe and in extratemporal areas did not significantly differ from that of the control population.

ROI-based quantification confirmed this result, with [^{18}F]FP BP significantly reduced (by 39.9%) on the epileptogenic side compared with controls in the temporal pole (0.5 ± 0.05 vs. 0.84 ± 0.12; $p = 0.012$, $p < 0.05$ if corrected for multiple comparisons) and in the ant.-lateral temporal cortex (–37.5%; 0.37 ± 0.06 vs. 0.6 ± 0.10; $p = 0.036$, $p > 0.05$ if corrected for multiple comparisons) (Fig. 2).

Interestingly, despite considerable hippocampal atrophy on MR volumetry, no significant [^{18}F]FP BP changes were seen in the hippocampus (0.92 ± 0.14 vs. 0.83 ± 0.10; NS). Differences of [^{18}F]FP BP in other ROIs between patients and controls were not significant, except for a borderline difference in putamen (20.45 ± 0.5 vs. 21.8 ± 0.5; $p = 0.03$).

[^{18}F]FDG uptake was significantly ($p < 0.0001$) reduced in lateral and mesial aspects of the temporal lobe on the epileptogenic side (–24, 2, –35, mesial temporal/hippocampus; –50, –9, –30, anterior temporal; and –53, –25, –26, lateral temporal inferior; with Z = 5.55,

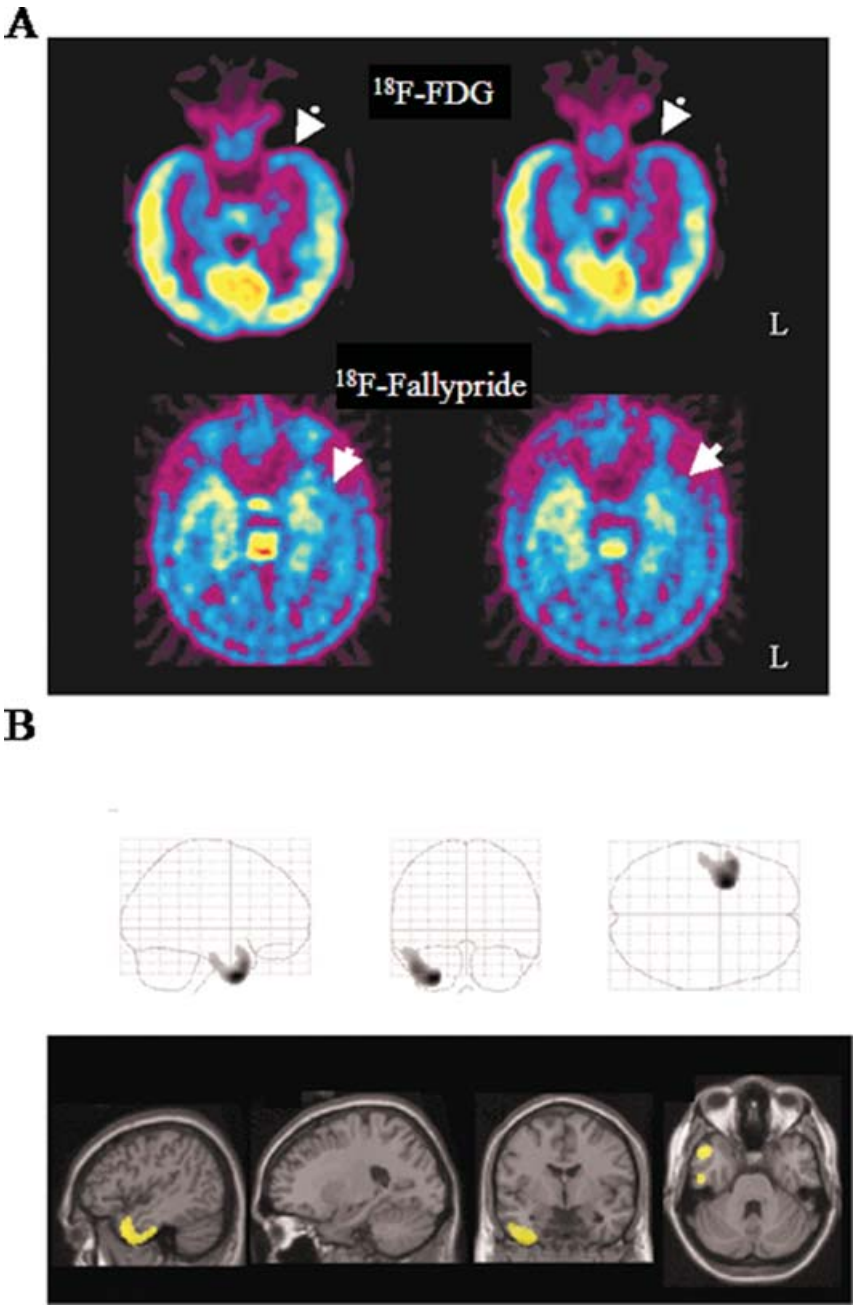

FIG. 1. A: Static [^{18}F]FP (bottom) and [^{18}F]FDG-PET (top) data in patient with left mesial temporal epilepsy and hippocampus sclerosis on histology (no. 1 of Table 1) as an illustrative example. L, left. *Arrows*, Areas of decreased [^{18}F]FDG uptake or [^{18}F]FP BP in the mesial and lateral left temporal lobe ipsilateral to the side of seizure onset. **B:** Statistical parametric mapping results (contrast controls – patients) for all patients of [^{18}F]FP BP. Glass brain of the statistical map (top) and superposition of statistical maps onto an averaged MRI (bottom). The statistical threshold for illustrative purposes is $p < 0.001$ (uncorrected).

4.74, and 4.57, respectively). In ROI analysis of [^{18}F]FDG uptake, the most robust decreases of [^{18}F]FDG uptake was found in the hippocampus [standardized uptake value (SUV) of FDG uptake: –8.4%; $p = 0.003$] and the temporal pole (–11.9%; $p = 0.047$). Decreases of [^{18}F]FDG uptake extended laterally into the lateral temporal lobe, but this was less evident. No statistically significant difference of [^{18}F]FDG uptake was found for the other ROIs. Hippocampal volume (HV) on MR volumetry was significantly reduced (mean, –35.1% ± 5.3%; range, –4.1% to –16.1%; $p = 0.0009$) on the epileptogenic side in all patients. Findings comparing relative changes of [^{18}F]FDG uptake, [^{18}F]FP BP, and hippocampus volumetry between hemispheres are illustrated in Fig. 2. The mean decrease of [^{18}F]FP BP was significantly greater than the mean decrease of [^{18}F]FDG uptake at the temporal pole (–34.2% ± 7.2% vs. –11.3% ± 3.7%; $p = 0.013$) and the anterior–lateral temporal cortex (–32.9% ±8.7% vs. –12.4% ± 5.3%; $p = 0.022$). Differences were not significant and less evident (–17.7% ±9.3% vs. –4.3% ± 5.0%; $p = 0.2$) in the parahippocampal gyrus. In contrast, the most obvious finding in the hippocampus was a significant reduction of HV compared with both PET techniques (HV, –35.1% ± 5.3% vs. [^{18}F]FP BP, +10.1% ±10.1% vs. [^{18}F]FDG,

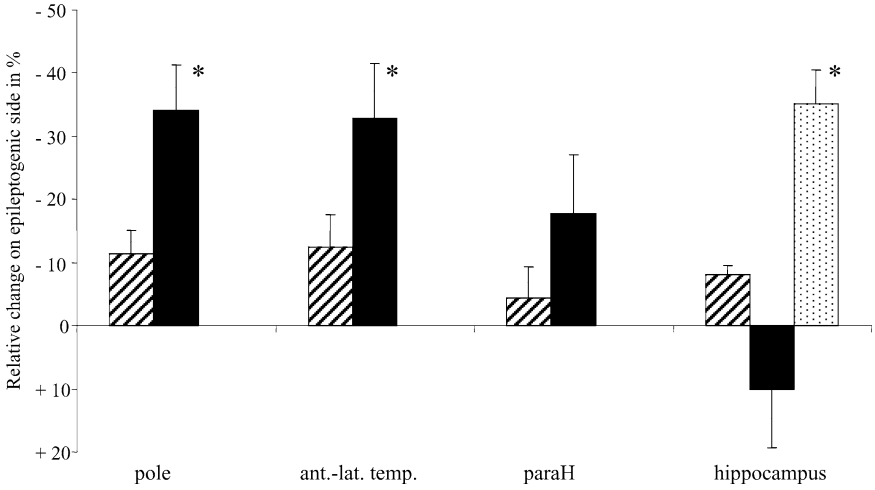

FIG. 2. Mean (±SEM) relative changes of [^{18}F]FP BP (*black*), [^{18}F]FDG uptake (*dashed*), and hippocampus volume (*dotted bar*) comparing regions of interests in the epileptogenic versus unaffected hemisphere in patients with hippocampal sclerosis (n = 7). Pole, temporal pole; ant-lat, anterior–lateral temporal lobe; paraH, parahippocampal gyrus. *p < 0.05 in two-sided paired *t* test.

–8.1% ± 1.4%; p = 0.0012 and 0.005, respectively). No significant correlations were found between [^{18}F]FP BP and [^{18}F]FDG uptake in all ROIs. The reduction of the HV was not correlated with [^{18}F]FP BP but with [^{18}F]FDG uptake in the hippocampus ($R = 0.89$, p = 0.007).

DISCUSSION

This study showed that the binding to D2-like receptors is reduced in patients with mTLE and HS. This preliminary study is not so much of importance for the lateralization of the epileptic focus and is not meant for any clinical application at this time. For the first time, however, it provides evidence of an involvement of the dopaminergic system in the pathophysiology of TLE with HS in humans, revealing a distinct monomorphic pattern of reduced binding in all patients studied. These findings may be in line with evidence from animal studies suggesting a neuroprotective role of dopamine through the inhibitory control of glutamate neurotransmission and excitotoxicity in epilepsy (11). Dopamine agonists can be protective in photosensitive epilepsy (12), and experiments using glutamate-induced seizures suggest that the absence of D2 receptors lowers the threshold for kainic acid–induced limbic seizures in dopamine D2-receptor knockout mice (11). Although [^{18}F]FP exhibits the highest affinity for D2 receptors, it is not clear which of the D2-like receptor subtypes precisely is responsible for the changes observed, because [^{18}F]FP also binds to D3 and (albeit weakly) to D4 receptors. It is remarkable that although all of our patients had a significant reduction of the size of the hippocampus (range, –16 to –62%) and a significant hypometabolism on [^{18}F]FDG PET in this area, no relevant decrease of [^{18}F]FP BP was seen in the hippocampus. Moreover, we did not find any correlation between [^{18}F]FP BP and HV in the whole group, whereas HV was strongly related to [^{18}F]FDG uptake. Potential explanations for a lack a decreased D2/D3-receptor binding in a considerably sclerotic hippocampus might be a relative upregulation of D2/D3 receptors balancing the neuronal loss or that HCS involves different neuronal elements than those expressing D2/D3 synapses. The fact that [^{18}F]FP BP was unchanged in the hippocampus despite significant hippocampal atrophy, however, makes it unlikely that [^{18}F]FP BP changes can be explained by anatomic changes. We cannot rule out that differences in dopamine D(2)-like receptors between the sexes may have confounded the comparison between patients and controls, because controls were only males. However, for several reasons, we think that this is unlikely: (a) sex differences are relevant only for frontal areas; (b) differences in temporal areas are well below those found in our study, and data suggest that differences between sexes in temporal areas are not significant (13); (c) the availability of D(2)-like receptors in the frontal cortex is higher in women than in men, so sex differences would have biased our results in favor of a reduced overall FP uptake in our male control group, making it even harder to show a reduction of FP uptake in the patients; and (d) sex differences do not explain the interhemispheric differences found in our patients. Our findings therefore are compatible with the view that reduction of [^{18}F]FP BP in mTLE is more prominent in functionally related areas of the seizure-onset zone rather than in the seizure-onset zone itself. We are not able to determine whether the decreased specific binding of dopamine reflects reduced receptor concentration, lower affinity, or an increased occupancy of the D2/D3 receptors by dopamine based on the present data. Autoradiographic studies of resected tissue could better characterize changes of receptor concentration. It is also unclear whether the BP decrease is cause or consequence of seizures or the epilepsy. Additional studies with larger series of patients with different epilepsy syndromes could aid in better understanding of this aspect.

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