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Elevated dopa decarboxylase activity in living brain of patients with psychosis

(dopamine/epilepsy/6-fluoro-L-dopa/positron emission tomography/schizophrenia)

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ABSTRACT **The hypofrontality theory of the pathogenesis of schizophrenia predicts that cortical lesions cause psychosis. During a search for abnormalities of catecholaminergic neurotransmission in patients with complex partial seizures of the mesial temporal lobe, we discovered an increase of the rate of metabolism of an exogenous dopa tracer (6-[^{18}F]fluoro-L-dopa) in the neostriatum of a subgroup of patients with a history of psychosis. When specifically assayed for this abnormality, patients with schizophrenia revealed the same significant increase of the rate of metabolism in the striatum. The finding is consistent with the theory that a state of psychosis arises when episodic dopamine excess is superimposed on a trait of basic dopamine deficiency in the striatum. The finding is explained by the hypothesis that cortical insufficiency, a proposed pathogenetic mechanism of both disorders, causes an up-regulation of the enzymes responsible for dopa turnover in the neostriatum as well as the receptors mediating dopaminergic neurotransmission.**

A substantial current theory of the pathogenesis of psychosis claims that psychosis is the result of denervation supersensitivity after insufficient cortical (glutamatergic) stimulation of nigrostriatal terminals (1). The theory predicts that the lack of stimulation leaves a baseline of a low concentration of extracellular dopamine in the striatum. One logical consequence of functional corticostriatal denervation is therefore an increase of dopamine receptor density, confirmed by Wong *et al.* (2, 3) and Seeman *et al.* (4) for the spiperone-labeled receptors, which include the D_2, D_3, and D_4 subtypes, in drug-naive patients with schizophrenia and psychotic patients with bipolar disease. If the increased receptor density is a reaction to low extracellular dopamine, the dopamine-synthesizing enzymes would be expected to increase their activity in response to denervation. This would be true also of diseases other than schizophrenia that are characterized by cortical lesions that prevent excitation of the striatum. Psychotic symptoms frequently arise in complex partial seizures of temporal lobe origin in which cortical lesions develop.

To test the hypothesis that the state of psychosis in temporal lobe epilepsy is associated with the same striatal supersensitivity that may cause psychosis in schizophrenia, we measured the rate of metabolism of an exogenous analog of dopa in both disorders, using positron emission tomography (PET) of the tracer 6-[^{18}F]fluoro-L-dopa (^{18}F-dopa) (5, 6). We have previously shown that the rate of metabolism of externally administered ^{18}F-dopa is an index of the activity of the enzyme responsible for the decarboxylation of dopa to dopamine (EC 4.1.1.28) (7, 8). We determined the brain metabolism of ^{18}F-dopa in 31 subjects, including 10 patients with psychotic disorders, of whom 5 had schizophrenia and 5 had a history of complex partial seizures (CPS) with schizophreniform psychosis, and 21 control subjects, of whom 8 had CPS without psychosis and 13 were healthy volunteers.

SUBJECTS, MATERIALS, AND METHODS

All procedures were performed in accordance with an experimental protocol approved by the Research and Ethics Committee of the Montreal Neurological Institute and Hospital. Written informed consent was obtained from each subject after full explanation of the nature, possible consequences, and risk of the studies. According to the protocol, we recruited 31 subjects to four groups.

Group I, the control group of *healthy volunteers*, consisted of nine men and four women with a mean (±SD) age of 36 ± 13 years. They completed a health questionnaire prior to the scan and had no history, signs, or symptoms of neurological or psychiatric disorders.

Groups II and III, the *patients with CPS*, consisted of patients admitted to the Montreal Neurological Institute for evaluation of surgical intervention. The epileptic foci were defined by interictal and ictal electroencephalogram (EEG) recording, using scalp and sphenoidal electrodes. All studies were performed while the patients were in the interictal state, at least 48 h after the last clinical seizure. Anticonvulsant medications were gradually withdrawn during the work-up for surgery. At the time of the study all patients were on reduced-dose monotherapy with carbamezapine or phenytoin. The EEG was monitored during the study and revealed no seizures during scanning. Localization of speech was determined by the carotid amytal test.

Group II, the control group of *patients with CPS without psychosis*, consisted of three men and five women with a mean age of 28 ± 5 years. Six were right-handed and two were left-handed. Four patients had a seizure focus in the left temporal lobe, two in the right temporal lobe, and two in both temporal lobes. The onset of seizures occurred 19 ± 12 years before the last admission.

Group III, the *patients with CPS with psychotic episodes*, included a man and four women with a mean age of 39 ± 5 years, all right-handed. A psychiatrist (G.S.) evaluated the patients by the Present State Examination (9). Two patients

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Abbreviations: PET, positron emission tomography; ^{18}F-dopa, 6-[^{18}F]fluoro-L-dopa; CPS, complex partial seizures.

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had chronic organic delusional syndromes with schizophreniform features, one had an acute postictal delusional syndrome with schizophreniform features, one had an acute postictal delusional syndrome with paranoid features, and one had an organic personality disorder with psychotic affective symptoms. Three patients never received neuroleptics, and two had not received oral neuroleptics for more than a year prior to the scan. All patients had a right-sided seizure focus, two patients also a left-sided focus. Three patients had atrophy of the frontal cortex. The onset of seizures occurred 10 ± 9 years before last admission.

Group IV, the *patients with schizophrenia*, consisted of five men with a mean age of 38 ± 4 years and a mean duration of illness of 14 ± 9 years. Four patients were neuroleptic-naive, and one had not received oral neuroleptics for more than 3 years before the study. They were evaluated independently by two psychiatrists with a semistructured clinical interview (SCID-P) (10), standard assessment of positive and negative symptoms by using the PANSS inventory (11), and evaluation of extrapyramidal symptoms (12). The patients met the *Diagnostic and Statistical Manual* (DSM-IIIR) criteria for the diagnosis of chronic schizophrenia (13). The subclassification of the schizophrenia was residual (three subjects), undifferentiated (one subject), and paranoid (one subject). The scores (±SD) on the total Brief Psychiatric Rating Scale (14) were 24 ± 4 (minimal score 0 for 18 items), PANSS P 14 ± 3, PANSS N 12 ± 2, and PANSS H 32 ± 7. Four patients were right-handed and one was left-handed, according to Annet's test (15). There was no evidence of abnormal involuntary movements or parkinsonism. Of potential concern is the relatively long duration of illness without neuroleptic treatment. Most of these patients expressed long-standing reluctance to accept either psychotropic medication or psychiatric diagnosis and may be atypical. However, their symptoms and Present State Examination were typical of schizophreniform illness.

The subjects received venous and radial arterial catheters. After placement in the tomograph, the subjects were injected with 130–200 MBq of ^{18}F-dopa, which circulated for 90 min. During this time, 15 planes of dynamic images were obtained with the Scanditronix PC-2048B tomograph (16). Radioactivity maps were reconstructed from the last frame with correction for tissue attenuation, dead time, scatter, and randomly coincident disintegrations. After the PET sessions had been completed, each subject underwent a high-resolution T_1-weighted magnetic resonance scan of the head, consisting of 64 slices, 2 mm each, obtained from a Philips 1.5-T Gyroscan and coregistered with the PET data (17).

We identified the head of the caudate nucleus and the putamen in at least four consecutive resectioned magnetic resonance images and used the two midsections to draw regions of interest (ROI). The radioactivity associated with a given structure was calculated as the weighted average, based on area, of the activity in corresponding ROIs of both slices. When expressed as fraction of whole brain area, caudate and putamen sizes were not significantly different.

At least three processes affect the accumulation of ^{18}F-dopa-derived radioactivity in the tissue: transport of ^{18}F-dopa from blood to brain, described by the clearance K_1; transport of ^{18}F-dopa from brain to blood, described by the fractional clearance k_2; and metabolism of ^{18}F-dopa, described by the decarboxylation rate constant k_3 (8), defined (5) as

$$k_3 = \frac{V_{max}}{K_m V_d}, \quad [1]$$

where k_3 is equal to the enzyme activity relative to the Michaelis half-saturation constant, V_{max} is the maximal velocity of the decarboxylation reaction, K_m is the half-saturation constant for ^{18}F-dopa, and V_d is the ^{18}F-dopa distribution volume in brain.

We determined the rate constant for conversion of ^{18}F-dopa to fluorodopamine in the manner described by Kuwabara *et al.* (5). The method includes separation of ^{18}F-dopa and ^{18}F-dopa metabolites in blood, and ^{18}F-dopa and ^{18}F-dopa metabolites in brain, by deconvolution using the differential equations established for the exchange of ^{18}F-dopa and ^{18}F-dopa metabolites between blood and brain. Leakage of fluorodopamine metabolites from brain was separately accounted for. Under these circumstances, the model parameter k_3 is directly proportional to the maximal velocity of the enzyme reaction in a brain region, assuming negligible variation of K_m.

To obtain regional estimates of the rate constant k_3 in striatum, the ^{18}F-dopa distribution volume was fixed globally to the value obtained in the cerebral cortex of individual subjects. In principle, the estimates of the blood–brain barrier permeability coefficients (K_1, k_2) were independent of the estimates of k_3 (5).

The partial volume effect causes an underestimation of the radioactivity associated with "hot spots" and hence of the estimated decarboxylation rate constant (k_3). The effect is nonlinearly proportional to the radioactivity gradient between surrounding tissue and striatum and hence tends to attenuate the estimated increase when the regions of interest are of similar size.

RESULTS

The accumulation of radioactivity in the striatum of patients with psychosis was visibly elevated in the averaged positron emission tomograms, merged with the magnetic resonance maps, shown in Fig. 1. In the patients with CPS, maximum elevation was recorded in the plane placed 6 mm above, and parallel to, the anterior-commissure–posterior-commissure (AC-PC) plane. In the schizophrenic patients, maximum elevation was noted in a plane 1.5 mm below the AC-PC plane, as shown in Fig. 1, corresponding approximately to the level of the ventral striatum just above the nucleus accumbens.

The kinetic analysis of ^{18}F-dopa turnover is summarized in Table 1. One-way analysis of variance with three planned orthogonal contrasts for each region revealed highly significant increases of the ^{18}F-dopa decarboxylation rate constant (k_3) in the four subdivisions of the striatum in all patients with psychotic episodes (patients with schizophrenia or CPS), compared with healthy volunteers and patients without psychotic episodes. The analysis revealed no differences between the healthy volunteers and patients without psychotic episodes, or between the patients with schizophrenia and the patients with complex partial seizures and psychotic episodes.

When the schizophrenic patients were compared separately with the control population, simple two-tailed t tests revealed significant increases of the ^{18}F-dopa decarboxylation rate constant in the left ($P < 0.01$) and right ($P < 0.02$) caudate heads.

DISCUSSION

The finding of elevated tracer ^{18}F-dopa metabolism in the present study is evidence of increased enzyme activity. It does not *per se* signify increased dopamine synthesis. The effect of the increased enzyme activity on the synthesis of dopamine depends on the concentration of the native substrate (dopa) for this product.

We have previously shown that the rate constant of metabolic trapping of ^{18}F-dopa in brain is an index of the activity of dopa decarboxylase (5, 8) rather than of other processes,

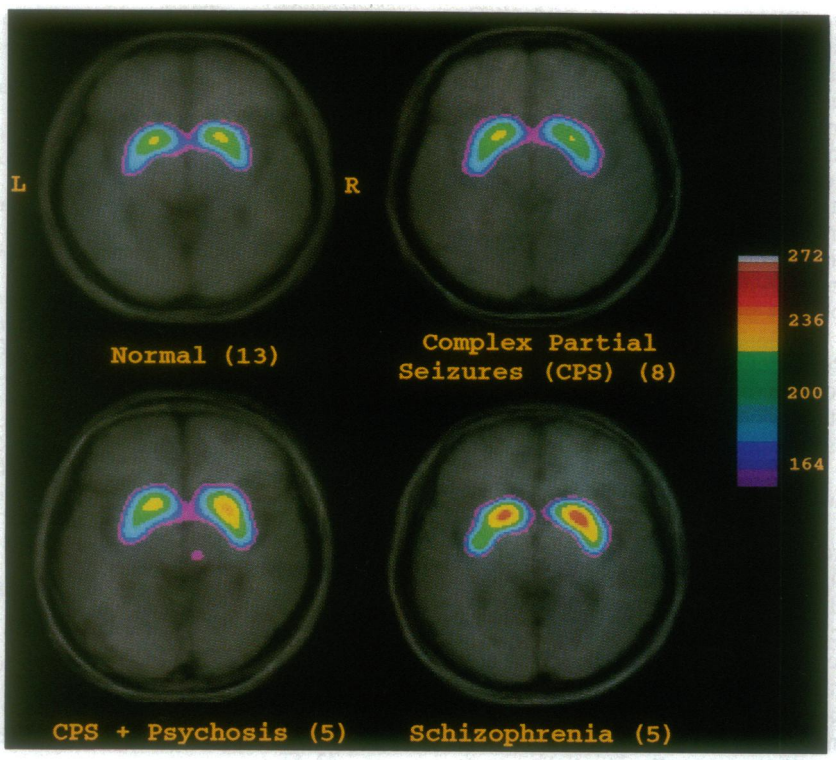

FIG. 1. Averaged, merged radioactivity and magnetic resonance maps in 13 healthy volunteers, 8 patients with CPS, 5 patients with CPS and psychosis, and 5 patients with schizophrenia. Individual PET and magnetic resonance maps were transformed in a common stereotaxic coordinate system to enable averaging (18). The pseudocolor code indicates radioactivity concentration in percentage of the average radioactivity concentration of the entire brain volume, in a plane 1.5 mm below the anterior-commissure–posterior-commissure (AC-PC) plane. Left (L) and right (R) are indicated for the normal volunteers.

such as vesicular storage of dopamine, breakdown of dopamine, or removal of dopamine metabolites. The activity of dopa decarboxylase is generally believed to have a passive role in dopamine synthesis from endogenous dopa. However, we recently argued that the facilitated diffusion of dopa from the striatum to the blood makes dopa decarboxylase the catalyst of the first committed step in the dopamine synthetic pathway, and as such makes it a factor in dopamine homeostasis (19). This situation is not unlike the relationship between hexokinase and phosphofructokinase in glycolysis, in which hexokinase is the saturated enzyme (like tyrosine hydroxylase) but phosphofructokinase catalyzes the first irreversibly committed step (like dopa decarboxylase) due to the alternate paths available to glucose 6-phosphate.

Dopa decarboxylase has been shown to be subject to regulation in some cases: a promoter specific for the neuronal enzyme has been cloned from the human genome (20). In rat striatal homogenates, the enzyme is increased after 2-week treatment with tranylcypromine, a monoamine oxidase (MAO) inhibitor (21). Gene expression of the enzyme is stimulated in PC12 cells exposed to deprenyl, another MAO inhibitor (22). In rat retina, *ex vivo* activity of the enzyme is stimulated by light (23). In striatum, *ex vivo* activity of the enzyme is regulated by dopamine receptors in rat (24) and mouse (25). The regulation seems to be mediated by a cAMP-dependent protein kinase within dopamine terminals (26).

We base our interpretation of the increased enzyme activity on the observations suggesting (*i*) that dopa decarboxylase is regulated, possibly by the extracellular dopamine concentration (20–27), and (*ii*) that tonic dopamine release is stimulated by the corticostriatal glutamatergic projection from the prefrontal cortex and by afferent fibers from the amygdala and hippocampus (28–30). These observations show that glutamate and dopamine are mutually interactive: Stimulation of frontal cortex increases tonic dopamine release in the caudate nuclei by an *N*-methyl-D-aspartate-mediated rise of membrane calcium conductance (29), and the primary action of dopamine in the neostriatum is the attenuation of excitatory responses mediated by glutamate (30).

We claim that an up-regulation of dopa decarboxylase follows the lowering of extracellular dopamine after the decline of tonic dopamine release. An up-regulation of the decarboxylation step is consistent with the reported up-regulation of dopamine D_2-like receptors (particularly the

Table 1. Regional estimates of the ^{18}F-dopa decarboxylation rate constant, k_3

Region	k_3, h^{-1}: Group I, healthy volunteers (n = 13)	Group II, CPS without psychosis (n = 8)	Group III, CPS with psychosis (n = 5)	Group IV, schizophrenia (n = 5)	Contrast F values (F_1, df 27) by one-way analysis of variance: I vs. II	III vs. IV	I + II vs. III + IV
Left caudate	4.5 ± 0.3	4.2 ± 0.4	5.4 ± 0.3	6.3 ± 0.5	0.03	1.98	13.2**
Right caudate	4.5 ± 0.3	4.3 ± 0.3	5.9 ± 0.5	5.9 ± 0.3	0.00	0.00	17.5**
Left putamen	4.3 ± 0.3	3.9 ± 0.2	4.9 ± 0.2	5.1 ± 0.3	0.61	0.12	8.8*
Right putamen	4.3 ± 0.2	4.1 ± 0.2	5.0 ± 0.2	5.0 ± 0.4	0.11	0.00	11.2**

Values are means ± SEM. **, $P < 0.005$; *, $P < 0.01$.

subtype D_4) in at least two disorders with episodes ("bursts") of psychosis, including schizophrenia and bipolar disease (2–4). In the present study also, the up-regulation was evident in two separate disorders in which episodes of psychosis may occur—i.e., schizophrenia and complex partial seizures. In the patients suffering from these disorders, increased extracellular dopamine is not easily reconciled with up-regulation.

The speculation that the essence of these diseases is low extracellular dopamine in the striatum is not new (31–33). The concentration of dopamine metabolites is significantly lower in complex partial seizures with schizophreniform symptoms, compared with complex partial seizures without such symptoms (34).

Consistent with a state of deficient tonic release of dopamine in striatum, numerous studies have revealed a dysfunction of the prefrontal cortex in schizophrenia (reviewed in ref. 35). In the patients with schizophrenia, we noted the greatest trapping of ^{18}F-dopa in the ventral portions of the caudate nuclei to which the association areas of the frontal cortex project. In the patients with complex partial seizures, the greatest trapping occurred higher in the neostriatum.

How do episodes ("bursts") of psychosis occur in fundamentally different disorders that have only cortical lesions in common? Dopaminergic neurotransmission is characterized by burst firing and phasic release of dopamine, superimposed on the tonic release. Grace (1) speculated that the compensatory up-regulation of key enzymes and receptors with time would cause the dopamine surge associated with phasic release to have an abnormally intense effect in the form of a psychotic episode. This speculation explains the observation that lesions of the corticostriatal pathways augment the effect of amphetamine-induced dopamine release (36). According to this concept, psychosis (the state) is a sign of striatal denervation supersensitivity, generated by low tonic dopamine release (the trait).

In conclusion, the findings of the present study suggest an increase of the dopa decarboxylation rate in the striatum in two disorders believed to involve lesions of cerebral cortex and episodes of psychosis. This increase is consistent with the theory of suppressed tonic release of dopamine in striatum of patients with schizophrenia or temporal lobe epilepsy with episodic psychosis.

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