Applications of SPECT imaging of dopaminergic neurotransmission in neuropsychiatric disorders

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Single photon emission computed tomography (SPECT) tracers selective for pre- and post-synaptic targets have allowed measurements of several aspects of dopaminergic (DA) neurotransmission. In this article, we will first review our DA transporter imaging in Parkinson's disease. We have developed the in vivo dopamine transporter (DAT) imaging with [123I]β-CIT ((1R)-2β-Carbomethoxy-3β-(4-iodophenyl)tropane). This method showed that patients with Parkinson's disease have markedly reduced DAT levels in striatum, which correlated with disease severity and disease progression. Second, we applied DA imaging techniques in patients with schizophrenia. Using amphetamine as a releaser of DA, we observed the enhanced DA release, which was measured by imaging D2 receptors with [123I]IBZM (iodobenzamide), in schizophrenics. Further we developed the measurement of basal synaptic DA levels by AMPT (alpha-methyl-paratyrosine)-induced unmasking of D2 receptors. Finally, we expanded our techniques to the measurement of extrastriatal DA receptors using [123I]epidepride.

The findings suggest that SPECT is a useful technique to measure DA transmission in human brain and may further our understanding of the pathophysiology of neuropsychiatric disorders.

**Key words:** single photon emission computed tomography (SPECT), dopamine, Parkinson's disease, schizophrenia

**INTRODUCTION**

Recent brain imaging methods afford unprecedented opportunities for the in vivo study of central nervous system (CNS) function. To understand the pathophysiology of neuropsychiatric disorders such as Parkinson's disease, schizophrenia, substance abuse and mood disorders, the methods have played an important role and highlighted abnormalities in CNS neurotransmission. Single photon emission computed tomography (SPECT) tracers selective pre- and post-synaptic targets have allowed measurements of several aspects of neurotransmission including dopaminergic (DA) transmission.

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Focusing on the abnormalities in DA transmission, to apply SPECT methods to Parkinson's disease or schizophrenia will be interesting and in fact the methods has been contributing to recent significant findings about the DA abnormalities in these disorders. In this review, we will review our progress in DA imaging by SPECT in Parkinson's disease and schizophrenia.

**DOPAMINE TRANSPORTER IMAGING IN PARKINSON’S DISEASE**

1) In vivo brain imaging in Parkinson's disease
Parkinson's disease is a progressive neurodegenerative disorder, characterized clinically by bradykinesia, tremor, rigidity and postural instability, and characterized pathologically by loss of pigmented neurons in the brainstem, particularly DA neurons in the substantia nigra pars compacta.1-4 However, the pathological processes underlying the continued clinical progression in Parkinson's disease remain unknown.

Specific markers for the DA system have been widely
used to evaluate patients with Parkinson’s disease. Several investigators have used positron emission tomography (PET) imaging with $[^{18}F]$FDOPA (6-fluoro-L-3,4-dihydroxyphenylalanine) and shown 50–60% decrease in putamenal activity and 20–25% decrease in caudate activity in patients with early Parkinson’s disease.5–9 Dopamine transporter (DAT) imaging using both PET and SPECT have demonstrated a similar reduction in striatal uptake in early Parkinson’s disease patients.7,9,10 In addition, the reduction in DAT striatal uptake correlated with severity of Parkinson’s disease in a larger patient cohort.10,11

Three in vivo imaging studies have been reported evaluating the reduction of $[^{18}F]$FDOPA activity in sequential PET scan in Parkinson’s disease patients. The rate of reduction in the $[^{18}F]$FDOPA uptake varied from 1.7%–12.5%/annum in the three studies.12–14 In these studies, the reduction in $[^{18}F]$FDOPA activity was significantly greater in PD patients than in healthy subjects. The work of Morrish (1996) suggests that early patients have an increased rate of progression compared to more severely affected patients.14 Extrapolation of results from these progression studies have suggested to the authors that the pre-clinical phase of Parkinson’s disease may range from between 3 and 40 years.12–14 These studies clearly do not provide definitive evidence to establish the rate of DA neuronal degeneration and of clinical progression in Parkinson’s disease.

2) DAT imaging using $[^{123}]$β-CIT
   A. Kinetics of $[^{123}]$β-CIT uptake in humans

We have developed the in vivo DAT imaging with $[^{123}]$β-CIT ((1R)-2β-Carboxethoxy-3β-(4-iodophenyl)tropane). A typical time-activity curve for $[^{123}]$β-CIT is shown in Figure 1. Striatal activity reached a plateau 20 h after injection, changing less than 1%/h thereafter. Occipital and cerebellar activity peaked at about 30 to 45 min, then stabilized 100 to 200 min after injection. The midbrain activity reached a plateau after 4 h. The slow striatal uptake of $[^{123}]$β-CIT was caused in part by the exceptionally slow clearance of tracer from the plasma. The terminal half-life of plasma clearance is greater than 48 h, which caused a state of near equilibrium binding conditions on the day after injection. Our group has performed kinetic modeling of arterial input function and brain activity for the first 8 h after injection of $[^{123}]$β-CIT in 8 healthy subjects.15 The compartmentally modeled results of equilibrium distribution volumes from day 1 data closely matched the results obtained from day 2 imaging in these same individuals. These results provide strong support for the simple calculation of striatal uptake as the ratio of specific to nonspecific uptake (termed $V_s$) and calculated as (striatal – occipital)/occipital activity. As shown in earlier works,16,17 the value of $V_s$ = ($B_{max}$/Kp)$/$V₂, where $B_{max}$ is transporter density, 1/Kp is affinity, and V2 is the nonspecific volume of distribution (e.g., occipital). Thus, this relatively simple outcome measure is linearly related to DAT density and is now used as the primary outcome measure for all groups using this radiotracer.

This simple method for $V_s$ measurement was supported by the following two findings: 1. Striatal, midbrain, and occipital activities were very stable during the interval 18–24 h post injection and decreased by less than 1%/h, as observed in over 33 subjects to date18; and 2. Compartmental analyses of the day 1 kinetic data provided the same $V_s$ values as that obtained from a simple ratio of SPECT brain activities measured on day 2.15

B. Effects of aging on DAT

In vitro studies of human tissue demonstrate a decline in DAT with age of approximately 8% per decade.19,20 To explore the sensitivity of $[^{123}]$β-CIT to detect DAT changes with normal aging, we studied 28 healthy controls at 18–24 h after single bolus injection of $[^{123}]$β-CIT.18 Both outcome measures, striatal $V_s$ and percent striatal uptake, demonstrated linear age-related decreases of 0.07 ± 0.01 $V_s$ units per year. Expressed relative to the average 18 year extrapolated baseline, this linear decline corresponded to ~8% per decade. This study has been extended to a total of 103 healthy subjects and has shown a similar decline of about 8% per decade. These data demonstrate that studies require either an age-correction of the outcome measure or the use of age-matched controls.

3) DAT imaging with $[^{123}]$β-CIT in Parkinson’s disease
   A. Decreased $[^{123}]$β-CIT uptake in Parkinson’s disease

To determine the sensitivity of $[^{123}]$β-CIT to distinguish patients with Parkinson’s disease and healthy subjects,
we evaluated 55 (28 patients and 27 healthy) subjects with SPECT acquisitions at 18, 21, and 24 h after injection of [123I]β-CIT. PD patients met standard criteria for diagnosis and were responsive to l-dopa and were of varying severity (Hoehn & Yahr 1–4) and age (43–78 years). Striatal [123I]β-CIT uptake was measured in the putamen and caudate; and the side contralateral and ipsilateral to initial symptoms was identified. Results demonstrated that a dramatic reduction in putaminal and caudate [123I]β-CIT uptake. The age-corrected uptake in the patients with Parkinson’s disease (expressed as a % of values in healthy subjects) was 30% in contralateral putamen, 38% in ipsilateral putamen, 47% in contralateral caudate, 56% in ipsilateral caudate. Linear discriminant analysis showed that [123I]β-CIT uptake in the four striatal regions correctly predicted the category of the 55 subjects in this study with 100% accuracy.11

B. [123I]β-CIT SPECT in hemiparkinson patients
To further assess whether [123I]β-CIT SPECT striatal uptake to distinguish the most mildly affected patients from healthy subjects, we examined eight Hoehn & Yahr I patients with Parkinson’s disease (hemiparkinsonian).9 Patients were imaged at 18, 21, and 24 h following bolus injection of [123I]β-CIT. V3 in the putamen was reduced both contralateral (47 ± 11% of control) and ipsilateral (63 ± 14% of control) to the symptomatic side compared with age and gender-matched healthy controls (Fig. 2). The reduction in V3 was greater in the putamen than that in the caudate. An asymmetry index (A.I.) was calculated as the absolute value of (left-right)/(mean left and right) expressed as a percent. The A.I. value was 30.0% ± 11.1% for the patients with Parkinson’s disease and 3.2% ± 3.9% for controls. These data demonstrate that [123I]β-CIT SPECT can identify patients at the threshold of their disease and possibly prior to the development of motor symptoms.

C. Disease severity and DAT
After establishing the sensitivity of [123I]β-CIT uptake as a diagnostic marker of Parkinson’s disease, further analyses were completed to assess the correlation between Parkinson’s disease severity and DAT loss. As previously described 28 l-dopa-responsive patients with Parkinson’s disease (Hoehn & Yahr stages I–V) underwent SPECT brain scans at 18, 21, and 24 h after bolus injection of 9.6 ± 1.1 mCi [123I]β-CIT. Data were analyzed relative to the two measures; V3 and specific striatal activity expressed as a percent of injected radiotracer and corrected for patient age. Both V3 and percent uptake were correlated with disease severity as measured by the “defined off” medication total Uni-fied Parkinson’s disease Rating Scale (UPDRS) score ($r^2 = 0.41, p = 0.0004, r^2 = 0.46, p = 0.001$, respectively (Fig. 3)).11 Patients with Parkinson’s disease demonstrated greater reductions of uptake in putamen compared to caudate with average caudate/putamen ratios of 2.1 ± 0.42 in patients and 1.3 ± 0.17 for control values determined in 27 healthy subjects.

D. Anti-parkinson medication
Since patients with Parkinson’s disease require dopaminergic medications for symptomatic treatment, we examined the effect of l-dopa on [123I]β-CIT uptake. Eight patients who had not previously been treated with l-dopa were evaluated with [123I]β-CIT SPECT at baseline, after treatment with l-dopa for six weeks up to a daily dose of 750 mg, and again after 2 day withdrawal.21 All patients responded clinically to l-dopa therapy. However, there was no significant change in [123I]β-CIT striatal uptake. The V3 values (mean ± SD) were: baseline (3.1 ± 0.8), on medication with 6 weeks treatment (3.0 ± 0.9), and after withdrawal (3.2 ± 0.5).

Another group of 8 patients were examined for the effects of l-selegiline on [123I]β-CIT imaging.21 Subjects were scanned at baseline, after 6 weeks treatment with l-selegiline (10 mg/day), and after 2 days withdrawal. The striatal V3 values showed no significant changes: baseline (3.0 ± 0.6), on medication with 6 weeks treatment (2.8 ± 0.7), and after withdrawal (2.8 ± 0.6).

These studies suggest that concurrent treatment with either l-dopa or l-selegiline does not significantly interfere with [123I]β-CIT imaging.

E. Sequential imaging to monitor disease progression
To investigate the rate of reduction of [123I]β-CIT uptake and therefore the rate of degeneration of DA terminals, patients with Parkinson’s disease have been imaged sequentially with scan intervals from 6 to 48 months. Preliminary analysis of the data suggest that the annualized rate of loss in patients is more than 10 times faster than that in healthy, age-matched subjects imaged over.
similar time intervals. These data suggest that DA terminal degeneration can be measured by $[^{125}]$IBZM SPECT, and this method is useful to assess Parkinson's disease progression and to assess the efficacy of neuroprotective therapies.

DA IMAGING IN SCHIZOPHRENIA

The "classical" DA hypothesis of schizophrenia proposed that hyperactivity of DA transmission is responsible for the symptoms of the disorder$^{22}$ and was supported by two observations: 1) the correlation between the antipsychotic potency of neuroleptics and their potency to block D2 receptors$^{23,24}$ and 2) the psychotogenic effect of amphetamine and other DA enhancing drugs such as methylphenidate and L-DOPA (for review see).$^{25}$ The DA hypothesis of schizophrenia, formulated more than 30 years ago, still lacks definitive experimental validation (for reviews see)$^{26-28}$.

Increased density of striatal D2 receptors in patients with schizophrenia has been a relatively consistent finding in postmortem studies, although patient values show significant overlap with those of control subjects.$^{26,30,31}$ Studies with limited samples of subjects with no prior neuroleptic exposure or who have been drug free for more than 1 year have also shown upregulation of striatal D2 receptors.$^{32-35}$ Studies of D2 density in drug naive schizophrenic patients with PET have generated conflicting results. Elevated D2 density in drug free schizophrenics compared to controls has been observed using the tracer $[^{11}]$C]N-methylspiperone$^{36,37}$ but not with $[^{11}]$C]raclopride.$^{38,39}$ Negative results were also reported with the SPECT tracer $[^{123}]$IBZM (iodobenzamide)$^{40}$.

Considering these results, two reasonable conclusions are that striatal D2 receptors are elevated in some (but not all) schizophrenics and that additional pathophysiological processes must underlie the disorder.

Recently, competition between neurotransmitters and radioligands for neuroreceptor binding allows measuring changes in synaptic neurotransmitter levels with in vivo binding techniques.$^{41,42}$ We have developed and validated a SPECT method both to quantify striatal D2 receptors with $[^{125}]$IBZM and to monitor stimulant-induced release of DA.

1) Imaging amphetamine-induced DA release

A. Measurement of DA release

Striatal D2 receptor availability is measured before and after treatment with intravenous amphetamine. This stimulant releases DA into the synapse, which then displaces the tracer from the D2 receptor. This paradigm was first developed in monkeys and validated with concurrent in vivo microdialysis measurements.$^{33,44}$ $[^{125}]$IBZM is administered as a bolus plus constant infusion to establish in about 4 h stable levels of both brain activity and parent tracer in plasma. At this point, the body as a whole is in a steady state condition, with equal rates of administration (i.e., constant infusion) and clearance of the tracer. The stable free levels of tracer in the brain create conditions equivalent to those of equilibrium receptor binding in tissue homogenate studies. These steady state/equilibrium binding conditions provide stable values against which to assess the effects of displacing agents. Within a single experiment, the baseline scan prior to amphetamine administration provides the standard measurement of D2 receptor availability, and the decrease in signal induced by amphetamine provides a measure of stimulant induced release of DA. The decrease in D2 receptor Binding Potential (BP = Bmax/KD) and D2 V3 are equivalent, assuming that the nonspecific volume of distribution is unaffected by amphetamine injection. Thus, we can express the outcome measure by the term ΔV3 ($\delta$e., the
Table 1  Measurement of D2 receptor availability at baseline and after amphetamine (modified from ref 47)

<table>
<thead>
<tr>
<th>Measure</th>
<th>Control</th>
<th>Schizophrenia</th>
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<tbody>
<tr>
<td>Baseline $[^{125}]$IBZM binding potential, mU/g</td>
<td>178 ± 12 (14)</td>
<td>204 ± 15 (14)</td>
</tr>
<tr>
<td>Amphetamine effect of $[^{125}]$IBZM binding potential, % decrease</td>
<td>-7.6 ± 2.1% (15)</td>
<td>-19.5 ± 4.1% (15)*</td>
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Values are mean ± SEM. Number of subjects are in parentheses.
*Unpaired two-tailed t-test; p = 0.014.

percent reduction in $V_s$ calculated as 100 × (1 - $V_s$' / $V_s$); where the subscript “a” denotes after amphetamine; “b” denotes before amphetamine). Because measurements are taken at equilibrium, these ratios are independent of any potential effects which amphetamine might have on regional cerebral blood flow and/or peripheral radiotracer clearance.

Amphetamine (0.3–1.0 mg/kg i.v.) caused a dose-dependent displacement of striatal activity in monkeys, with no effects in background regions such as occipital lobe and cerebellum. The displacement induced by amphetamine (but not by raclopride) could be blocked by prior treatment of the animal with AMPT (alpha-methyl-paratyrosine), an inhibitor of DA synthesis. Thus, AMPT treatment distinguished an indirectly acting agent such as amphetamine (which requires tissue levels of DA) from a direct acting agent such as raclopride (which itself binds to the D2 receptor). Concurrent in vivo microdialysis studies showed that the displacement of $[^{125}]$IBZM induced by amphetamine was correlated in a dose-dependent manner with the peak increase in extracellular DA.

The bolus plus constant infusion paradigm with $[^{125}]$IBZM was extended to human subjects and combined with a d-amphetamine challenge. In human subjects, stable levels of brain and plasma activity were achieved in 2–3 h and were maintained for the duration of the infusion (up to 7–8 h). Baseline D2 receptor scans were typically acquired at 3–4 h; d-amphetamine sulfate (0.3 mg/kg i.v.) was administered at 4 h; the subject removed from the camera for an hour for behavioral measurements; and a second scanning session of 1 hour obtained from 5–6 h. Subjects had two scanning session each—one with injection of placebo (to assess stability of the measurement) and a second time with injection of amphetamine. The specific to non-specific ratio ($V_s$') was stable from 150 to 420 min. In the same subjects, under identical experimental conditions, amphetamine 0.3 mg/kg i.v. induced a 15 ± 4% decrease in this ratio. The magnitude of this decrease was comparable to the decrease in $[^{125}]$IBZM $V_s$' observed in baboons after the same dose of amphetamine (20 ± 4%) and to previously published values from PET studies using $[^{11}C]$raclopride: 10 ± 5%, n = 3 and 23 ± 15%, n = 6. Furthermore, the magnitude of the decrease in D2 receptor availability was correlated with behavioral activation reported by the subjects on self-rating scales.

B. Increased DA release in schizophrenic patients

We have measured amphetamine-induced DA release in fifteen drug-free schizophrenic patients and fifteen healthy controls. The baseline D2 receptor binding and DAT levels were not significantly different between the patient and control groups. In contrast, the amphetamine-induced decrease in $[^{125}]$IBZM BP was significantly larger in schizophrenic patients (−19.5 ± 4.1%) than in controls (−7.6 ± 2.1%; t-test: p = 0.014; Mann Whitney U test: p = 0.034) (Table 1). No significant between-group differences were observed in amphetamine plasma levels (35 ± 9 vs. 32 ± 3 ng/mL), and no correlation was observed between amphetamine plasma levels and amphetamine-induced decreases in $[^{125}]$IBZM BP (r = 0.08). Thus, between-group differences in amphetamine-induced $[^{125}]$IBZM BP could not be attributed to differences in amphetamine's peripheral disposition. Finally, the percent displacement of striatal activity in the patients was positively correlated with the transient increase in positive symptoms.

This study has been replicated at Yale in a new cohort of 15 drug-free patients and 15 matched healthy subjects. When the results of the two cohorts were pooled, the amphetamine-induced displacement of $[^{125}]$IBZM in schizophrenics was 2.3 fold greater than that in the healthy subjects (p < 0.001) and was significantly correlated with transient increase in positive symptoms (r² = 0.31; p < 0.001). Similar results in schizophrenic patients have been obtained with PET imaging using $[^{11}C]$raclopride by groups at NIMH and Johns Hopkins. Taken together, these studies strongly support both an abnormal DA responsiveness in schizophrenia and the involvement of DA in positive psychotic symptomatology.

2) Measurement of basal DA level using AMPT

To measure the basal DA level in human brain will be interesting. Synaptic DA levels were assessed by unmasking of D2 receptors induced by AMPT, which inhibits tyrosine hydroxylase, the rate-limiting enzyme in DA synthesis.

A. Non-human study

We conducted a study on DA depletion and D2 receptor imaging in monkeys. Using in vivo microdialysis, an infusion of AMPT (275 mg/kg given over 4 h) depleted baseline extracellular DA by 80%. In a separate group of primates, two baboons underwent one SPECT imaging
session after pretreatment with a dose of AMPT identical to that used in the in vivo microdialysis studies (i.e., 275 mg/kg i.v. over 4 h). Results of these experiments were compared to those from experiments performed under control conditions (i.e., non-AMPT pretreated). In both animals, baseline $\Delta V_y$ was increased (−29%) compared to control experiments (0.85 vs. 0.66 for baboon A and 1.07 vs. 0.82 for baboon B). This increase was far in excess of our test/retest reproducibility for measurements of D2 BP in baboons (coefficient of variation of 6%, n = 12). Thus, these results indicate that baseline levels of DA compete with radiotracer binding and suggest the feasibility of D2 receptor imaging to provide an indirect index of basal DA levels.

B. Human study

To assess a similar paradigm in human subjects, we compared $^{[123]}$IBZM $V_y$ before and after 2 days (48 h) of oral AMPT administration (1 g PO q 6 h or a total of 4 g per day) in 9 healthy human subjects. Clinical and preclinical evidence have previously shown that this regimen induces a near complete depletion of brain DA.53 Over the course of AMPT treatment, subjects demonstrated increases in sleepiness, restlessness, and Parkinsonism (akinesia and tremor) and decreases in mood consistent with a clinically meaningful depletion of DA.

A comparison of baseline $^{[123]}$IBZM $V_y$ to that following AMPT depletion indicated a statistically robust (p < 0.0003) increase (mean ± SD $\Delta$ = 28 ± 16%; range 4–54%) in D2 receptor availability. These values agree closely both with previously published rodent data using reserpine54 and our own data using AMPT in nonhuman primates (vide supra). In addition, AMPT significantly decreased plasma HVA by 70 ± 12% (p < 0.0001; range 54% to 84%).

Since D2 receptor upregulation requires at least one week of DA depletion, this increase is likely not due to receptor upregulation.55 To confirm these findings, rats were treated with 7 times the human dose of AMPT and sacrificed after two days treatment. The two days treatment caused no significant increase in D2 receptor binding.

Taken together, these data suggest that AMPT-induced increase in $^{[123]}$IBZM binding was due to a decrease in D2 receptor occupancy by DA and that roughly one third of D2 receptors are occupied by DA at baseline.

3) Imaging the extrastriatal DA system

Pycock et al. (1980) examined the interaction of cortical and subcortical DA activity in rats. The destruction of frontal cortical DA afferents with local injection of 6-hydroxydopamine caused an upregulation of subcortical DA transmission.56 The measurements of DA transmission included increased turnover (i.e., homovanillic acid concentration), increased densities of D2 receptors, and increased responsiveness to d-amphetamine. The reformation of the DA hypothesis of schizophrenia have built upon these findings and emphasized an imbalance between cortical and subcortical systems.29,57

However, almost all D2 receptor imaging studies to date have measured only the neostriatum, because of the low densities of these sites in extrastriatal regions. Our studies with $^{[123]}$IBZM exemplify the problem; since this tracer can reliably detect uptake higher than background (e.g., cerebellum) only in the striatal region. $^{[123]}$IBZM presumably binds to D2 receptors in extrastriatal regions, but the relatively small signal can not be detected above high nonspecific binding. Even in the striatum, the ratio of target to background activity (i.e., striatum/occipital) is only 1.8 for $^{[123]}$IBZM (which corresponds to a specific to nonspecific ratio of 0.8). High affinity ligands have recently been developed to study extrastriatal D2 receptors with SPECT ([$^{[123]}$I]epidepride)58 and PET ([$^{[18]}$F]fallypride)59,60 and [11C] or [18F] (S)-N-(1-ethyl-2-pyrroldinyl)methyl)-5-bromo-2,3-dimethoxybenzamide (FLB 457)),51,61,62 [$^{[123]}$I]Epidepride (EPID) and other related analogs have very high affinity for the D2 receptor (approximately 20 pM). We conducted extrastriatal D2 receptor imaging with $^{[123]}$I[EPID].

A. Kinetic and equilibrium imaging with $^{[123]}$I[EPID]

Quantitative SPECT measures with $^{[123]}$I[EPID] is complicated by its high affinity and lipophilic metabolites. The method for quantification has been established by comparing bolus/kinetic and bolus plus constant infusion (B/I) equilibrium paradigms in healthy subjects.53,64 To fully characterize the kinetics of this high affinity tracer, data were acquired for long duration. To take into account the influence of the metabolites, a model with two input functions (parent (P) and lipophilic metabolites (M)) were applied in kinetic paradigm in addition to the conventional model with one input function (P). Data were acquired for 14 h in kinetic (n = 11) and for 32 h in equilibrium studies (n = 7: all seven subjects participated in the kinetic studies) (B/I = 10 h). High (striatum) and low (temporal cortex) density regions were studied. In receptor-rich regions, the distribution volumes in nondisplaceable compartments were fixed to those in cerebellum. In addition, in the two input function model, $K'_P/K'_M$ was fixed to the values in the cerebellum. The one input function model provided $V_y$ values ($= f_1 \cdot B_{max}/K_D$) which were consistent with those obtained in equilibrium studies in both receptor-rich regions, while the two input function model provided consistent values only in striatum. Poor identifiability of the rate constants of metabolites seemed to be the source of errors in the two input function model. These results suggest that correct $V_y$ values can be obtained with the one input function model both in high and low density regions.

In equilibrium paradigm, $V_y$ can be obtained without arterial blood sampling. However, to achieve equilibrium in all brain regions including striatum, about 20 h infusion
is required and count rates in temporal cortex become very low. To overcome this drawback, we have developed an alternative method to measure V₅ only in extrastriatal regions in equilibrium paradigm with a lower B/I ratio of 6 h and a shorter infusion for 9 h.⁶⁵ A test-retest study performed on ten healthy subjects showed good reproducibility in V₅ measurement with variability of 13.3 and 13.4% in thalamus and temporal cortex respectively.

B. Effect of AMPT on extrastriatal D₂ receptor imaging

The effect of endogenous DA on D₂ receptors in extrastriatal regions was evaluated with SPECT and [¹²³I]EPID by comparing the binding potential before and after acute DA depletion.⁶⁶ DA depletion was achieved by per-oral administration of 5.5 g/70 kg body weight AMPT given in 37 h. [¹²³I]EPID was administered with a total dose of 314 ± 13 MBq (bolus: 142 ± 6.5 MBq and constant infusion: 172 ± 6.7 MBq), bolus to infusion ratio of 6.00 ± 0.03 h, and duration of 8.82 ± 0.08 (baseline studies) and 8.78 ± 0.08 h (during AMPT administration). AMPT treatment increased the binding potential significantly in the temporal cortex (13 ± 15%, p = 0.036) but not in the thalamus (2 ± 9%). These results suggested that V₅ at equilibrium in the temporal cortex was affected by endogenous DA levels while V₅ in the thalamus was not. Although none of the five clinical dimensions of the Positive and Negative Symptom Scale (PANSS)⁶⁶ showed a significant change by the AMPT administration after correction for multiple comparison, the increase of the binding potential in the temporal cortex correlated strongly with the increase of dysphoric mood evaluated by the PANSS (Spearman's r = 0.88, p = 0.004). These results imply that [¹²³I]EPID, coupled with acute DA depletion might provide estimates of synaptic DA concentration and DA dysfunction in the temporal cortex might be related to dysphoric mood.

4) Discussion

The result of the increased DA release in patients with schizophrenia has been replicated at Yale in a new cohort of 15 drug free patients and 15 matched healthy subjects.⁶⁸ When the results of the two cohorts were pooled, the amphetamine-induced displacement of [¹²³I]IBZM in schizophrenics was 2.3 fold greater than that in the healthy subjects (p < 0.001) and was significantly correlated with transient increase in positive symptoms (r² = 0.31; p < 0.001). Taken together with the other institutes' results, this finding is very reliable and well reflecting the abnormalities in DA transmission in schizophrenics. Further, the additional data from our group suggested that the increased DA release is present in schizophrenia during the initial episode and subsequent relapses, but not in periods of remission.⁶⁹ These findings strongly suggest that a hyperdopaminergic state exists in schizophrenics during a certain period. The mechanisms responsible for increased DA release in the disorder are unclear but could involve pre- or postsynaptic adaptations.⁷⁰

Imagings of basal DA level or extrastriatal DA receptor will be important methods to examine the reformulated DA hypothesis of schizophrenia, that is, an imbalance between cortical and subcortical systems in the disorder.

CONCLUSION

SPECT imaging or neurochemical brain imaging has great potential to elucidate pathophysiological mechanisms in neuropsychiatric disorders. Significant understanding is likely to occur with the development of new probes and enhanced instrument technology. These techniques will provide not only better understanding of pathophysiology but also more precise evaluation of clinical status or more specific treatment in the disorders.

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