contraction in tense patients is correct. Oral diazepam appears to offer a simple solution to the diagnostic confusion that can arise between enhanced physiological muscle uptake of FDG and malignant uptake. It is conceivable that patients presenting for restudy are less anxious about the scan procedure and might show reduced muscle uptake for this reason. The potential risk of rescanning without diazepam is that muscle uptake might persist, and a further scan would be required, incurring additional radiation (effective dose equivalent 9.5 mSv per study). We did not consider it justified to rescan the young patients included in the present study without diazepam.

Interestingly, two of the patients who demonstrated enhanced muscle uptake had done so only on their second visit to the PET center. The patients were aware on this occasion that the scan findings would directly influence whether future chemotherapy was required, and it may be that this anxiety was manifested by the increased muscle uptake rather than anxiety about the procedure itself. In these patients, rescanning without the use of diazepam would have been unlikely to help.

CONCLUSION

It is important to recognize that this characteristic pattern of muscle uptake is physiological and, if necessary, to repeat scanning where sites of potential pathology may be obscured. The interpretation of scan results may be significantly altered if the reporting clinician is not aware that this pattern of uptake represents a normal variant, and in one case in our series this might have led to the erroneous diagnosis of malignant disease. For whole-body studies, we have now adopted the policy of administering all injections with the patient in a supine position, with the neck supported by a pillow in an attempt to reduce muscle tension. Scans are repeated, if warranted, after the simple procedure of oral administration of 5–10 mg of diazepam.

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SPECT Imaging of Dopamine Transporters in Human Brain with Iodine-123-Fluoroalkyl Analogs of β-CIT

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Iodine-123-2β-carbomethoxy-3β-(4-iodophenyl)tropane (β-CIT) is a useful SPECT tracer for imaging the dopamine transporter. Its slow kinetics, however, necessitate imaging on the day after the injection. Two N-ω-fluoroalkyl analogs of β-CIT, the fluoropropyl and fluoroethyl compounds (β-CIT-FP and β-CIT-FE, respectively), characterized by faster kinetics in baboons, were tested in humans as potential tracers for the dopamine transporter. Four healthy volunteers were injected with [^{123}I]-β-CIT-FP and another four were injected with [^{123}I]β-CIT-FE. SPECT data were acquired for 1149 ± 590 min and 240 ± 30 min, respectively. Both tracers demonstrated high brain uptake (6.37% ± 0.37% and 7.8% ± 1.5% of the injected dose, respectively). Activity concentrated with time in the striatal area, reaching a peak within 30 min, with little or no washout for [^{123}I]β-CIT-FP and a faster washout for [^{123}I]β-CIT-FE (14.7% ± 6.9%). Occipital and midbrain activity showed similar patterns, displaying a peak within 15 min and rapid washout, followed by stable levels at approximately 100 min for both tracers. The ratio of peak specific striatal-to-peak specific midbrain activity was 9.1 ± 1.8 for [^{123}I]β-CIT-FP and 7.7 ± 0.7 for [^{123}I]β-CIT-FE, showing high in vivo selectivity for the dopamine transporter. These preliminary results suggest that both compounds could be used as SPECT (labeled with ^{123}I) or PET (labeled with ^{18}F) radiotracers to image the dopamine transporters in the living human brain.

Key Words: SPECT; dopamine transporters; iodine-123-β-CIT

J Nucl Med 1996; 37:1129–1133

Received Mar. 1, 1995; revision accepted Oct. 18, 1995.

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2β-Carbomethoxy-3β-(4-iodophenyl)tropane (β-CIT) is a potent cocaine analog with high affinity for the dopamine and serotonin (5-HT) transporters (*1,2*). When labeled with ^{123}I, β-CIT is a useful SPECT radiotracer for visualization of the dopamine and 5-HT transporters in baboons (*3–5*) and humans (*6–8*). SPECT studies in patients with idiopathic Parkinson's disease demonstrated a significant reduction of striatal uptake of [^{123}I]β-CIT (*6*). Thus, SPECT imaging with [^{123}I]β-CIT is a promising new technique for diagnostic evaluation of Parkinson's disease.

The uptake of [^{123}I]β-CIT in human striatum is characterized by slow kinetics. The striatal activity increases for 15–20 hr after bolus injection of the tracer. Thereafter, the striatal activity stabilizes at a constant value, and no significant washout is observable up to 30 hr after injection. The stable level of activity between 20 and 30 hr satisfies conditions of prolonged equilibrium (*7*). Consequently, one acquisition performed on the day after the injection provides all the information needed to

derive the specific-to-nonspecific equilibrium ratio. This simple quantitation procedure, combined with the widespread availability of SPECT cameras and the development of an iodination kit (*9*), allows routine clinical use of this measurement in nuclear medicine. However, the need to acquire images on the day after the injection is not convenient for outpatient evaluations nor optimal from the point of view of the ratio between injected activity and counting statistics in the image.

In an effort to circumvent these difficulties, N-ω-fluoroalkyl analogs of β-CIT have been recently synthesized and tested in baboons and humans as potential tracers for the dopamine transporter (*8–11*). Two compounds, the fluoropropyl and fluoroethyl nortropanes (β-CIT-FP and β-CIT-FE, respectively), have been selected for development in humans because:

1. The affinity of the compounds for the dopamine transporter (β-CIT-FP K_i = 3.5 n*M*; β-CIT-FP K_i = 4.0 n*M*) is lower than β-CIT (K_i = 1.4 n*M*) (*10*), which should allow for faster kinetics.
2. In nonhuman primates, both fluoroalkyl analogs showed high brain uptake (%ID at peak uptake, β-CIT-FP = 12%; β-CIT-FE = 4%), early peak in striatal specific activity (β-CIT-FP = 90–160 min; β-CIT-FE = 30 min), high striatal-to-occipital ratios (3:4 at peak specific binding; 6:10 at 5 hr), and faster striatal washout rate (β-CIT-FP = 4%–6% of peak uptake per hour; β-CIT-FE = 10%–14%/hr) than β-CIT (0.5%/hr), (Table 1) (*11*). Thus, both compounds, but especially β-CIT-FE, are potential rapidly reversible probes for measuring dopamine transporters in the living human brain. In addition, these compounds can be labeled with ^{18}F and are potential radiotracers for PET as well as SPECT.

Another disadvantage of [^{123}I]β-CIT is the lack of selectivity for the dopamine transporters. The affinities of β-CIT for dopamine and 5-HT transporters are equivalent (*2*). Pharmacological characterization of [^{123}I]β-CIT uptake in the primates revealed that striatal activity is associated with dopamine transporters, while midbrain activity is associated with 5-HT transporters (*5*). In primates, the midbrain uptake of [^{123}I]β-CIT-FP and [^{123}I]β-CIT-FE was about 50% smaller as compared to [^{123}I]β-CIT midbrain uptake (with specific-to-nonspecific ratio at peak specific binding in the midbrain of 0.95 and 0.8 for [^{123}I]β-CIT-FP and [^{123}I]β-CIT-FE, respectively, versus 1.57 for [^{123}I]β-CIT). This observation suggested a better dopamine to 5-HT selectivity for the fluoroalkyl analogs. However, in vitro affinity of these compounds for the 5-HT transporters has not been previously reported.

In this article, we describe brain regional uptake of [^{123}I]β-CIT-FP and [^{123}I]β-CIT-FE in healthy human volunteers. Four healthy subjects were studied after injection of [^{123}I]β-CIT-FP and another four were studied after injection of [^{123}I]β-CIT-FE.

TABLE 1
Brain Activity Uptake Characteristics in Baboons

Compound	Brain uptake (% ID)	Time of peak striatal specific binding (min)	Striatal/ Occipital ratio at peak specific binding	Striatal washout rate (% peak uptake)
β-CIT*	5	150	5–7	0.5
β-CIT-FP†	12	90–160	3–4	4–6
β-CIT-FE†	4	30	3–4	10–14

*Values from Laruelle et al. (*5*).
†Values from Baldwin et al. (*11*).

We also report the in vitro affinity of the two fluoroalkyl analogs for the 5-HT transporters to further document the selectivity of these compounds.

METHODS

Subjects

Eight healthy subjects participated in these studies. Inclusion criteria were absence of any current medical condition and absence of present or past neuropsychiatric illnesses, alcohol or substance abuse. Physical examination, EKG and routine blood and urine tests were performed in the screening procedure. All subjects gave written informed consent to the research protocol approved by the local human investigational committee. Subjects received 0.6 g potassium iodide (SSKI solution) in the 24 hr prior to the scan. Four subjects were injected with [^{123}I]β-CIT-FP (3 men, 1 woman; age 35 ± 10 yr) and four subjects were injected with [^{123}I]β-CIT-FE (1 man, 3 women; age 36 ± 12 yr).

Radiolabeling

Iodine-123-β-CIT-FP and [^{123}I]β-CIT-FE were prepared from the corresponding trimethylstannyl precursor as previously described (*10,11*). Iodine-123-β-CIT-FP was obtained with an average radiochemical yield of 57.0% ± 14.9% (n = 4, with this and subsequent values expressed as mean ± s.d.) and radiochemical purity of 98.2% ± 0.9%. Iodine-123-β-CIT-FE was obtained with an average radiochemical yield of 38.7% ± 23.1% (n = 4) and radiochemical purity of 98.1% ± 1.9%. Specific activity was estimated to be >1,850,000 MBq/mmol.

Data Acquisition

SPECT data were acquired with the multislice brain dedicated CERASPECT camera (Digital Scintigraphics, Waltham, MA) equipped with a high-sensitivity collimator which has a resolution of 11 mm full width in three axes. Because of technical problems, one subject (Subject 3 of the [^{123}I]β-CIT-FP study) could not be scanned on the CERASPECT camera and was scanned on the PRISM 3000 (Picker, Columbus, OH) equipped with low-energy, high-resolution, fan-beam collimators, with a resolution of 10 mm full width in three axis). Injected dose was 304.1 ± 28.9 MBq for [^{123}I]β-CIT-FP and 230.9 ± 121.0 for [^{123}I]β-CIT-FE. Acquisition protocols were as follows: [^{123}I]β-CIT-FP; Subjects 1 to 3: four 4-min scans followed by four 6-min scans, followed by two 10-min scans every 30 min up to 500 min on the day of the injection, and up to 1440 min on the day after the injection. The protocol was modified for Subject 4 after review of the first three studies as follows: continuous 4-min scans during the following intervals: 0–150 min, 180–220 min, 250–300 min; [^{123}I]β-CIT-FE: Subject 1: continuous 8-min scans from 0 to 150 min, 180–220 min, 250–300 min; Subjects 2 and 3: continuous 4-min scans from 0 to 150 min and 180–220 min.

Data Analysis

Images were reconstructed, filtered, attenuation-corrected and reoriented as previously described (*7*). The four transaxial slices corresponding to the highest striatal activity were summed. Three regions of interest were positioned on this summed image at the level of right and left striatum (1070 mm^2 each) and occipital pole (2746 mm^2). Activities from the right and left striatum were averaged. The midbrain region was better visualized on the sagittal slices than transaxial slices. Three sagittal slices corresponding to the highest midbrain activity were summed and a region of interest (ROI) (544 mm^2) was placed on the midbrain area. Average regional activities (cpm/cm^3) were decay-corrected for the time of injection and expressed in KBq/cm^3 using a calibration factor of 0.063 KBq/cpm for all studies on the CERASPECT camera and 0.059 KBq/cpm for the one study on the PRISM. This factor was

calculated from an ^{123}I distributed source (13 cm diameter, filled with 845 ml of 7.5 KBq/ml solution) acquired during the period of the study using the same protocol. No attempts were made to correct for partial volume effects or for the scatter fraction of the photopeak window.

Total brain uptake was measured as the total counts within the field of view and expressed as a percentage of the injected dose. Specific binding was operationally defined as the difference between the activity in a ROI (striatum or midbrain) and the occipital pole (a region devoid of detectable dopamine transporters) (*12*). The specific-to-nonspecific equilibrium partition coefficient, V_3'', was calculated as:

$$V_3'' = \frac{(\text{ROI} - \text{occipital})}{\text{occipital}}$$

at the time of peak specific uptake, i.e. when the association and dissociation to and from the transporter are equal (*7*). Washout rates were defined by linear regression and expressed as the percentage of the peak value.

In Vitro Assay

The Ki of β-CIT-FP and β-CIT-FE for the 5-HT transporter was measured in rat occipital membranes using [^{3}H]paroxetine as the radiolabeled ligand (28.8 Ci/mmole) as previously described (*13*).

RESULTS

Iodine-123-β-CIT-FP

The highest camera count rate for the entire field of view of the head was recorded at 14 ± 5 min and corresponded to 6.4% ± 0.4% of the injected dose. Reconstructed images showed that the activity concentrated with time in the striatal area. Striatal activity reached a plateau phase rapidly (striatal activity reached 90% of its highest value at 36 ± 27 min) with little or no washout in three of the four subjects (Fig. 1). In one subject, striatal activity exhibited a more pronounced peak at 80 min, then washed out at a rate of 4.9%/hr. Washout between the day of injection and Day 2 and washout during Day 2 were both negligible (1.4 ± 0.4%/hr and 1.7 ± 0.5%/hr, respectively). Occipital activity was highest within the first 15 min, showed a rapid washout (71%/hr) and then stabilized at constant levels at approximately 100 min. The activity in the midbrain followed a similar pattern to that in the occipital region, with a peak at 18 ± 4 min, a rapid washout in the first 50 min postinjection (43.4 ± 15.4) and stabilized at approximately 100 min. The striatal specific binding reached its peak value later than the midbrain at 281 ± 119 min, or 90% of that value at 148 ± 71 min. At that time, striatal V_3'' was measured as 4.6 ± 1.6. The peak specific binding in the midbrain occured at 72 ± 37 min, at which time the midbrain V_3'' was 0.44 ± 0.15. The ratio of peak specific striatal-to-peak specific midbrain V_3'' was 9.1 ± 1.8.

Iodine-123-β-CIT-FE

The highest camera count rate for the entire field of view of the head was recorded at 11.1 ± 1.4 min and corresponded to 7.8% ± 1.5% of the injected dose. Activity concentrated rapidly in the striatum. In contrast to [^{123}I]β-CIT-FP, [^{123}I]β-CIT-FE striatal activity reached a clearly defined peak at 33 ± 22 min, then washed out at a rapid rate (14.7 ± 6.9%/hr, Fig. 1). The occipital activity displayed a temporal pattern similar to [^{123}I]β-CIT-FP: an early peak within the first 14 min, a rapid washout (67.6 ± 37.1%/hr) and a stabilization phase at approximately 100 min. The activity in the lower midbrain followed a similar pattern to that in the occipital region, with a peak at 16.2 ± 6.3 min, a rapid washout in the first 50 min postinjection (59.9 ± 38) and stabilization at approximately 100 min. The peak striatal specific binding occured significantly earlier for [^{123}I]β-CIT-FE (37.5 ± 20.5 min) than for [^{123}I]β-CIT-FP (148 ± 71 min to reach 90% of the peak value). The peak specific binding in the midbrain occured at 30 ± 9.5 min, at which time the midbrain V_3'' was 0.4 ± 0.17. This peak was earlier than in the striatum for [^{123}I]β-CIT-FE and earlier than the midbrain for [^{123}I]β-CIT-FP (71.7 ± 36.5). Striatal V_3'' was measured at peak specific striatal uptake as 2.7 ± 1.3. The ratio of peak specific striatal-to-peak specific midbrain for all three experiments was 7.7 ± 0.7.

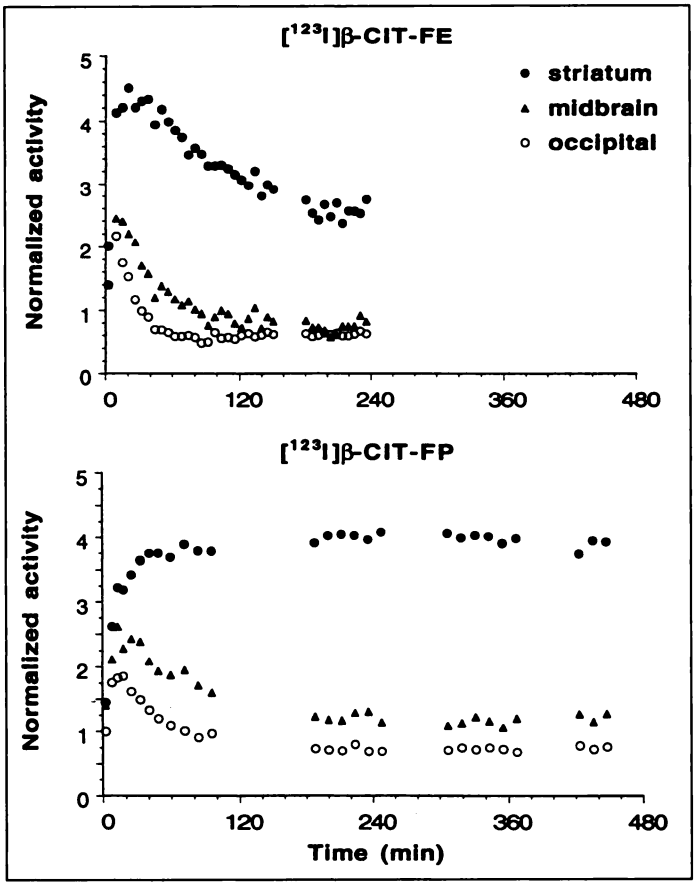

FIGURE 1. Brain regional activities in the striatum (closed circle), midbrain (closed triangle) and occipital (open circle) over time after injection of 214.6 MBq [^{123}I]β-CIT-FE in a 42-yr-old subject (A) and 329.3 MBq [^{123}I]β-CIT-FP in a 27-yr-old subject (B). Brain activities are expressed in normalized activity, calculated as the ROI activity concentration (kBq/ml) divided by the injected dose per kilogram body weight (kBq/kg).

In Vitro Selectivity

The Ki of β-CIT-FP and β-CIT-FE for [^{3}H]paroxetine binding was 9.73 ± 0.58 and 14.43 ± 3.52 n*M*, respectively (Table 2). When affinities to dopamine and 5-HT transporters

TABLE 2
Dopamine (DA) versus 5HT Selectivity

Compound	DA transporters* Ki (n*M*)	5-HT transporters† Ki (n*M*)	DA selectivity 5-HT Ki/DA Ki
β-CIT	1.40 ± 0.20	2.35 ± 0.42	1.68
β-CIT-FP	3.50 ± 0.39	9.73 ± 0.58	2.78
β-CIT-FE	4.00 ± 0.73	14.43 ± 3.52	3.60

*Values taken from Neumeyer et al. (*10*).
†Values are mean ± s.e.m. of 3–4 independent assays.

were compared, the dopamine to 5-HT selectivity of the fluoroalkyl analogs was almost twice that of β-CIT (Table 2).

DISCUSSION

These initial experiments in humans demonstrated that both [^{123}I]β-CIT-FP and [^{123}I]β-CIT-FE provide high brain uptake and preferential uptake in the striatum. Thus, both compounds could be used as SPECT (labeled with ^{123}I) or PET (labeled with ^{18}F) radiotracers to image dopamine transporters in human brain. Iodine-123-β-CIT-FE displayed rapid uptake and washout, whereas [^{123}I]β-CIT-FP showed a protracted plateau phase. Therefore, different strategies may have to be used for these tracers to obtain quantitative measures of dopamine transporter density.

To better understand the place of [^{123}I]β-CIT-FE and [^{123}I]β-CIT-FP in the arsenal of probes available to measure the dopamine transporter with PET or SPECT, it is important to discuss the conflicting requirements that a tracer has to fulfill to allow quantification. A high specific-to-nonspecific ratio is desirable for image quality, and this is usually achieved with high affinity/low lipophilicity tracers. On the other hand, a rapid course of association and dissociation is important to allow equilibrium to occur rapidly. A tracer with fast kinetics of uptake and washout (i.e., a highly reversible radiotracer) will display peak specific binding within the time frame of a typical imaging session. This property simplifies the determination of V_3'' considerably. Short of these qualities, kinetic analysis using the arterial time-activity curve as the input function is needed to calculate the k_3/k_4 ratio (equal to V_3''), which is not practical for routine clinical applications. High reversibility is usually associated with modest affinity and high lipophilicity because both properties increase the rates of association and dissociation of the tracer-receptor complex (*14*).

Clearly, neither [^{11}C]β-CIT (*15*) nor [^{11}C]CFT (also known as [^{11}C]WIN 35,428) (*16*) reach equilibrium within the time frame of a PET experiment. Due to the longer half-life of the SPECT radiotracer ^{123}I, equilibrium data can be acquired with [^{123}I]β-CIT at about 24 hr after injection (*7*). However, as mentioned earlier, this method is inconvenient.

Iodine-123-β-CIT-FE and [^{123}I]β-CIT-FP appear to fulfill the expectations that prompted their development and both tracers might be appropriate for some type of equilibrium analysis on the day of the injection. Iodine-123-β-CIT-FE shows a kinetic profile compatible with a peak equilibrium analysis. The situation is less clear with [^{123}I]β-CIT-FP, but this tracer might display a kinetic profile compatible with a sustained equilibrium analysis.

Iodine-123-β-CIT-FE displays a clearly identifiable peak of specific binding, well within 90 min for each subject. This property would allow a peak equilibrium analysis, such as that developed by Farde et al. (*17*) for [^{11}C]raclopride. Stability of the metabolites-corrected plasma input function at the time of peak is not required for peak equilibrium analysis. Thus, a 90-min scanning session will provide all the data needed for peak equilibrium analysis and β-CIT-FE should be appropriate for both PET and SPECT investigations.

On the other hand, [^{123}I]β-CIT-FP displays a kinetic profile intermediate between the highly reversible [^{123}I]β-CIT-FE and the slowly reversible [^{123}I]β-CIT. The plateau phase is protracted, and the specific binding is stable in most but not all subjects. A larger patient sample is needed to investigate this property in a wider portion of the population. Stability of the specific binding, together with stability of the metabolites-corrected plasma input function, would allow a sustained equilibrium analysis, such as used in constant infusion experiments (*18*) and proposed for [^{123}I]β-CIT (*7*). Thus, if stability of the specific binding and of the tracer plasma concentration are demonstrated in a larger sample, a sustained equilibrium analysis would be applicable on day of injection. Imaging on the day of injection is convenient for outpatient studies and allows the use of lower injected doses of both compounds, thus reducing radiation exposure to the subjects and costs in radioisotopes.

Both tracers appear to be selective in vivo for the dopamine transporter over the 5-HT transporter, as indicated by striatal-to-midbrain V_3'' ratios of 7:9. In vitro measurement of Ki of β-CIT-FE and β-CIT-FP confirmed the higher dopamine to 5-HT selectivity suggested by the studies in nonhuman and human primates.

CONCLUSION

Initial experiments in humans indicate that [^{123}I]β-CIT-FE is a highly reversible and selective probe to quantify the dopamine transporters in the living human brain with SPECT. Iodine-123-β-CIT-FP may be useful in SPECT as an alternative to [^{123}I]β-CIT, as it may allow for use of an equilibrium analysis on the day of injection. Thus, each of these tracers may have a specific use: [^{123}I]β-CIT-FE would be preferable for kinetic modeling with arterial sampling and would allow comparing SPECT and PET when labeled with ^{18}F, while [^{123}I]β-CIT-FP would be preferable for "bloodless" equilibrium analysis.

Additional experiments comparing kinetic modeling and equilibrium analysis are warranted in a larger number of subjects to develop and validate a simple quantitation procedure for measuring binding to dopamine transporters with these new tracers.

ACKNOWLEDGMENTS

We thank Research Biochemicals Intl. (Natick, MA) for supplying the trimethylstannyl precursors of [^{123}I]β-CIT-FE and [^{123}I]β-CIT-FP; Nordion International Ltd. (Vancouver, B.C. Canada) for their generous gifts of [^{123}I]NaI; M.D. Stratton for preparation of the radiotracers, E.O. Smith, G. Wisniewski, M. Early for nuclear medicine technologist support; and Q. Ramsby for image analysis. This work was supported by funds from the Department of Veterans Affairs (Merit Review Award to R. Innis) and a generous gift from Research Biochemicals Intl.

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Abnormal Cerebral Glucose Metabolism in HIV-1 Seropositive Subjects with and without Dementia

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This study was undertaken in order to extend our previous finding of relative basal ganglia hypermetabolism in AIDS dementia complex (ADC) and to develop clinically useful metabolic indices of CNS involvement in HIV-seropositive (HIV+) subjects. **Methods:** Twenty-one HIV+ subjects (11 with AIDS) underwent FDG-PET scanning; 12 had a follow-up scan at 6 mo and 4 had a third scan at 12 mo. Forty-three age-matched heterosexual volunteers served as controls. FDG-PET scanning was performed with arterial blood sampling, and scan data were analyzed using the Scaled Subprofile Model (SSM) with principal component analysis. **Results:** SSM/principal component analysis of the combined (HIV+ and controls) FDG-PET dataset extracted two major disease-related metabolic components: (a) a nonspecific indicator of cerebral dysfunction, which was significantly correlated with age, cerebral atrophy and ADC Stage and (b) the striatum, which was heavily weighted (relatively hypermetabolic) and appeared to provide a disease-specific measure of early CNS involvement. **Conclusion:** FDG-PET scans provide quantitative measures of abnormal functional connectivity in HIV-seropositives—with or without AIDS or ADC. These measures, which are robust across centers with respect to instrumentation, scanning technique and disease severity, appear to track the progression of CNS involvement in patients with subclinical neurologic or neuropsychologic dysfunction.

Key Words: human immunodeficiency virus; fluorine-18-fluorodeoxyglucose; PET; scaled subprofile model

J Nucl Med 1996; 37:1133–1141

The clinical features of the AIDS dementia complex (ADC) are included within the definition of subcortical dementia proposed by Albert et al. (*1*) and elaborated by Cummings and Benson (*2*). Inattentiveness, loss of spontaneity, psychomotor retardation, reduced motor performance and incoordination are the clinical hallmarks of ADC (*3–5*). Focal collections of macrophages and multinucleated giant cells in subcortical white matter and deep gray nuclei, particularly in the putamen, constitute ADC's neuropathological substrate (*4,6–8*).

In an earlier FDG-PET study, we described a metabolic covariance pattern in ADC patients, in which the basal ganglia and thalamus were relatively hypermetabolic and for which individual subject weights were highly correlated with neuropsychological test scores (*9*). We hypothesized that this covariance pattern represents a network or system of functionally interconnected brain regions involved in the production and/or expression of subcortical dementia. Our finding of relative hypermetabolism in the basal ganglia and thalamus was subsequently confirmed by van Gorp et al. (*10*) in an FDG-PET study of 17 subjects with AIDS. The current study was undertaken in an effort to extend our previous findings in a larger population of HIV-seropositives, both symptomatic and asymptomatic, and to develop clinically useful metabolic indices of CNS involvement in seropositive subjects.

MATERIALS AND METHODS

Subjects

HIV-1 seropositive (HIV+) outpatients were recruited from neuroAIDS clinics at the Minneapolis VA Medical Center and the University of Minnesota Hospital. Twenty-one HIV+ subjects (20 men, 1 woman; aged 23–63 yr; mean age 43 ± 10 yr) were scanned at the Minneapolis VA Medical Center; 12 had a follow-up scan at 6 mo and 4 had a third scan at 12 mo. At the time of their initial scan, 11 subjects had AIDS. Four subjects were ADC Stage 0, twelve were Stage 0.5, four were Stage 1 and one was Stage 2 (11); one Stage 1 subject progressed to Stage 2, and two Stage 0.5 subjects "improved" to Stage 0. Of the 37 HIV+ scans, 11 were Stage 0, 18 were Stage 0.5 and 8 were Stage >0.5; there were no significant differences in age (42 ± 6, 43 ± 11, 50 ± 9 yr, respectively) or education (14 ± 2, 13 ± 2 and 15 ± 3 yr, respectively) across these groups.

All but 1 of the 21 subjects were male homosexuals or bisexuals. All but six of the HIV+ scans were performed while the subjects were taking zidovudine (AZT) and/or other antiviral drugs; eight subjects were taking tricyclic antidepressants. Subjects with a history of substance abuse, serious head injury, developmental disorder, or significant medical or psychiatric illness were specifically excluded. Prior to the study and at six-monthly follow-up visits, all subjects underwent a standardized neurologic and neuropsychological examination (*12*). Studies involving human sub-

Received Apr. 4, 1995; revision accepted Jul. 30, 1995.
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