Regional Dynamics of N-Isopropyl-(^{123}I)*p*-iodo-Amphetamine in Human Brain

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Regional cerebral dynamics of N-isopropyl-(^{123}I)*p*-iodoamphetamine (IMP) in the human brain were studied using a multi-detector single photon emission computed tomography (SPECT) scanner in 35 subjects both normal and with a variety of neurological conditions. Distribution of IMP in the brain was also compared with regional cerebral blood flow (CBF) measured by positron emission tomography (PET) in 15 of these 35 cases. A significant regional difference in temporal changes of radioactivity was observed among normal brain structures. A rapid increase with early washout of the tracer was shown in the cerebellum and the occipital cortex, while the basal ganglia revealed a relatively slow increase and prolonged retention, indicating the regional difference in extraction and/or retention of IMP among the cerebral tissues. In cases with unilateral hypoperfusion, the percentage of the activity in the lesion to that in the contralateral normal cortex on the early SPECT was correlated well with that on CBF measured by PET ($r = 0.870$, $p < 0.001$). However, the contrast on the SPECT image decreased with time after injection; 84.0 ± 7.4% on the SPECT at 5–20 min scan, 87.6 ± 7.6% at 35–50 min scan and 96.2 ± 6.3% at 5 hr scan. In a case with a brain tumor having high blood flow documented by PET, increased accumulation of IMP was observed in the tumor on the early images obtained within 20 min followed by a rapid washout. These findings suggested altered extraction and/or retention of IMP in normal and diseased tissues, and these factors should be considered for the assessment of distribution and redistribution of IMP.

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N-isopropyl-(^{123}I)*p*-iodoamphetamine (IMP) has been proved to be a valuable means for the assessment of regional cerebral blood flow (CBF) with single photon emission computed tomography (SPECT) in various brain diseases (*1–4*). Because of high extraction and long-lasting retention of IMP in the brain, the initial uptake of IMP is considered to be flow-dependent and does not change significantly during the SPECT scan. It has been also demonstrated that the distribution of IMP changes with time not only in diseased tissues, but also in normal brain structures (*5,6*). Although the first-pass extraction of IMP is high in animals and healthy human brains (*5–8*), it might be altered in diseased conditions and the pathological tissues may have different retention mechanism from the normal brain tissues (*9*).

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We employed a high resolution and fast-scanning SPECT scanner (*10*) to evaluate regional changes of IMP in the human brain. This paper describes the regional dynamics of IMP in normal and diseased brain tissues in comparison with CBF measured by positron emission tomography (PET).

MATERIALS AND METHODS

Subjects

A total of 35 patients were studied. Seventeen of them had cerebrovascular diseases (CVD) including seven cases with an occlusion of unilateral internal carotid or middle cerebral artery, six cases with cerebral infarction, three with intracerebral hemorrhage, and one case with sagittal sinus thrombosis. Eleven cases were degenerative neurological disorders including eight parkinsonism and three Alzheimer's disease and these cases showed normal x-ray CT and magnetic resonance imaging (MRI). Four cases had brain tumors confirmed by histology and three of them were diagnosed as low-grade

astrocytoma and one as oligodendrocytoma. An additional three cases were studied because of headache or transient abnormal sensation in the upper limb, but their final diagnosis was normal radiologically and clinically.

These three normal subjects and eight cases with parkinsonism who had normal x-ray CT without any clinical symptoms caused by cortical dysfunction were selected to study side-to-side asymmetry in the IMP SPECT images. In addition to these 11 cases, nine cases with unilateral lesion whose contralateral nonaffected hemisphere was considered as normal because of no abnormality on x-ray CT and/or MRI and no symptom caused by the neuronal dysfunction of this hemisphere were selected to study the temporal changes on the IMP SPECT.

Scanning

We used IMP labeled with 3 mCi of iodine-123 obtained by (p,5n) reaction (Nihon Mediphysics, Takarazuka, Japan). In 28 patients out of the 35 cases, twenty 2.5 min SPECT scans (dynamic scan) were performed immediately after an intravenous administration of IMP and one 15 min SPECT scan at 5 hr (late scan). CBF was measured by PET in eight cases of these 28 patients. In the other seven cases, two 15-min SPECT scans were performed at 5 min and 5 hr after the administration of IMP. CBF was also measured by PET in seven of these cases.

All SPECT scans were performed using a multidetector whole-body SPECT scanner (Shimadzu Corporation, Kyoto, Japan), which had three fixed detector rings at 30-mm intervals. Each detector ring was equipped with circular arrangement of 128 sodium iodide crystals and fast rotating collimator (four 180-degree rotation per 2.5 min) to determine the direction of gamma rays (*10*). Therefore, three SPECT images at 30-mm intervals were obtained with a minimum sampling time of 2.5 min. Three types of collimators, high resolution and high sensitivity for whole-body scan, and high resolution for head scan, were available. The use of head dedicated high resolution collimator provided a spatial resolution of 11.0 mm in terms of full width at half maximum (FWHM) at the center of the field-of-view. The axial resolution was 23.5 mm at the center. The sensitivity measured by a 20-cm-diameter cylindrical phantom filled with ^{99m}Tc solution was 6.6 kcps/μCi/ml.

CBF was measured by steady state inhalation method of oxygen-15-(^{15}O) labeled carbon dioxide (*11*) using a whole-body PET scanner, Positologica III (*12*). Steady state condition was achieved after 10 min inhalation of ^{15}O-labeled carbon dioxide (10 mCi/min) and 5 min data acquisition was done with arterial blood sampling for quantitative measurement. The scanner had four rotating detector rings, each containing 192 bismuth germanate crystal, which allowed simultaneous acquisition of seven tomographic images at 16 mm slice intervals. Spatial resolution was 7.6 mm FWHM in the center of the field-of-view with the axial resolution of 12 mm.

Reconstruction

All SPECT scans were reconstructed using the filtered backprojection algorithm with Shepp & Logan filter convoluted with a Butter-Worth filter. We also reconstructed three sequential 15-min SPECT images using the data of the dynamic scan obtained from 5 to 20 min (first scan), those from 20 to 35 min (second scan) and from 35 to 50 min (third scan), in order to obtain better quality SPECT images by reducing the statistical noise. The attenuation correction was performed with the corrected geometric mean approach (*13*) using the attenuation coefficient of 0.05/cm, which was determined experimentally by the 20-cm-diameter cylindrical phantom filled with iodine-123 (^{123}I) solution. The correction for physical decay of ^{123}I was also done.

Analysis

Our SPECT scanner provides three transverse slices simultaneously with a slice interval of 30 mm. The patient's head was positioned parallel to the orbitomeatal line (OM line) and the center of the lower slice was adjusted to 2 cm above the OM line so that the cerebellum, basal ganglia, and centrum semiovale were scanned in the lower, middle, and upper slice, respectively. Corresponding slices were obtained on the PET scan. Irregular shaped regions of interest (ROIs) were defined (>4 cm^2) on cerebellum, pons, basal ganglia, thalamus, white matter and cerebral cortices. In cases with brain tumor, additional ROI was placed over the tumor. All ROIs were carefully set on the anatomic regions comparing to the x-ray CT and CSF space was avoided as much as possible.

Temporal changes of the distribution of IMP were investigated in normal structures. For this purpose, we selected 20 cases with symptoms caused by unilateral cerebral hemisphere and without any abnormality in nonaffected cerebral hemisphere on x-ray CT and MRI. The time-activity curve of each region was generated from dynamic scan for assessing the regional pattern of temporal changes. For the precise analysis, we also calculated the percentage ratio of the activity in each region of the first, second, and late scan compared to that of the third scan.

The variation of the side-to-side asymmetry of IMP SPECT between the normal cerebral cortices was determined in 11 cases. Mean and standard deviation of the activity ratio in the bilateral cerebral cortices (percentage to the higher value) were calculated in these cases, and normal lower limit of the asymmetry was considered as two standard deviations below the average value. We chose those cases with unilateral hypoperfused lesions which showed more profound decrease of the activity than the normal lower limit of the asymmetry. Temporal changes of the activity ratio of the lesion to the nonaffected cortex were investigated among three sequential early SPECTs and late SPECT. The similar ratio was also calculated for CBF and we compared the ratio of IMP uptake in the first scan (5 to 20 min) with that of CBF.

In cases with brain tumor, the temporal changes of the activity in the tumor were assessed visually and compared with the pattern of the CBF images measured by PET.

The statistical analysis was performed with Student's paired t-test. All SPECT and PET images were displayed with patient's right on the left side of the images.

RESULTS

Temporal Changes of IMP in Normal Structures

Figure 1 shows typical time-activity curves in the normal brain, suggesting different dynamics of IMP in the normal structures. Cerebellum showed relatively

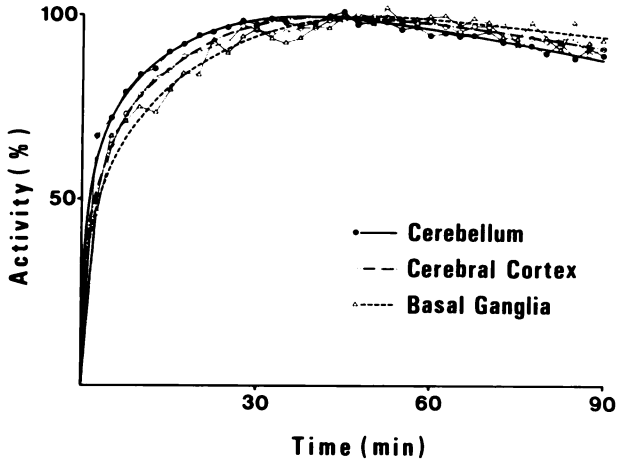

FIGURE 1
Time-activity curves in cerebellum, cerebral cortex, and basal ganglia for 90 min after injection of IMP. Cerebellum showed faster increase and washout compared with the cerebral cortex, while the basal ganglia showed slower increase and more prolonged retention of the tracer than the cerebral cortex.

rapid increase of IMP uptake with fast decrease, while basal ganglia, which also have high blood flow as the cerebellum, demonstrated slower increase and longer retention of the tracer. The regional differences in the temporal changes of the activity are summarized in Table 1. The cerebellum demonstrated significantly different dynamics from the cerebral cortices except for the occipital cortex ($p < 0.001$ on the first scan and the late scan, and $p < 0.01$ on the second scan). The basal ganglia also showed different dynamics from the cerebellum and the occipital cortex ($p < 0.001$ on the first and the late scans, and $p < 0.01$ on the second scan). The occipital cortex had similar tendency as the cerebellum. The activity in the white matter increased slowly over 5 hr, which also had different dynamics from the other structures. Typical changes on the serial SPECT scans are shown in Figure 2.

TABLE 1
Temporal Changes of IMP in Normal Structures*

	5–20 min (%)	20–35 min (%)	35–50 min	5 hr (%)
Frontal	79.5 ± 5.3‡	95.3 ± 2.9†	—	88.9 ± 8.3‡
Temporal	80.2 ± 5.4‡	95.1 ± 2.3†	—	87.0 ± 7.7‡
Parietal	77.8 ± 5.1‡	94.6 ± 3.3‡	—	89.2 ± 10.5‡
Occipital	81.3 ± 4.8†	96.9 ± 2.3	—	83.6 ± 8.1†
WM	77.0 ± 5.1‡	92.2 ± 3.8‡	—	108.2 ± 11.1‡
BG	77.5 ± 5.3‡	94.0 ± 3.7†	—	95.5 ± 8.4‡
Thalamus	79.6 ± 4.7‡	94.5 ± 3.7†	—	91.4 ± 9.0‡
Pons	82.4 ± 3.1	96.5 ± 2.5	—	96.5 ± 8.2‡
Cerebellum	83.7 ± 3.8	96.9 ± 1.9	—	81.1 ± 7.9

*Values are expressed as mean ± standard deviation of the percentage ratio to the third scan (35 to 50 min) in 20 cases. WM: white matter. BG: basal ganglia. Significance of difference between cerebellum and other tissues are indicated by †$p < 0.01$, and ‡$p < 0.001$.

Temporal Changes of IMP in Hypoperfused Lesion

The average asymmetry of normal IMP SPECT was 2.9 ± 1.9% (mean ± s.d.) for 55 cerebral cortical regions. Therefore the normal lower limit of the asymmetry was considered as 93.3% (decrease of mean ± 2 s.d.) of the contralateral cortex, and the cases which showed a >7% decrease of the activity were considered unilateral hypoperfusion. Using this criteria, we defined 49 hypoperfused lesions in 13 cases. Table 2 summarizes the temporal changes in the activity ratio of the hypoperfused lesion to the contralateral normal cortex. The contrast of the hypoperfused lesion gradually diminished with time. Figure 3 demonstrates a typical case, showing apparent temporal changes in visualization of the ischemic lesion. Figure 4 shows a comparison of CBF measured by PET and the first scan (5 to 20 min) of IMP SPECT in the ratio of the lesion to the contralateral nonaffected cortex. An excellent correlation was observed between these two measurements. The average contrast ratio of the hypoperfused lesion was 85.0 ± 5.5% for the first SPECT scan and 83.6 ± 5.5% for the CBF images, respectively.

Temporal Changes of IMP in Brain Tumor

One case with brain tumor had high blood flow in the tumor observed by PET (Fig. 5). The dynamic scan demonstrated increased accumulation of the tracer in the tumor only in the initial several images followed by a rapid washout of the tracer in the later images. Among the sequential 15-min SPECT scans, only the first scan showed the increased uptake of the tracer in the tumor and the other two scans failed to visualize the tumor. Moreover, even in the first scan, the ratio of the tumor to the contralateral nonaffected cortex showed less contrast than the CBF pattern. The other three cases with brain tumor had less accumulation of IMP throughout the SPECT scans.

DISCUSSION

The present study demonstrated regional differences in uptake and retention of the tracer in normal structure. We examined the temporal changes of IMP in the brain using the relative values compared to a certain time or the relative values of side-to-side difference. Absolute values of IMP uptake represented by cts/pixel/mCi/min differ among individuals because of their different body size, the different size of lung reservoir, and the different cardiac output (*14*). We also observed the time-activity curves of the brain and lung simultaneously in a small number of cases, and found large variation. Figure 6 shows the time-activity curves of the brain and the lung in three cases. The absolute activity in the brain differed apparently among the

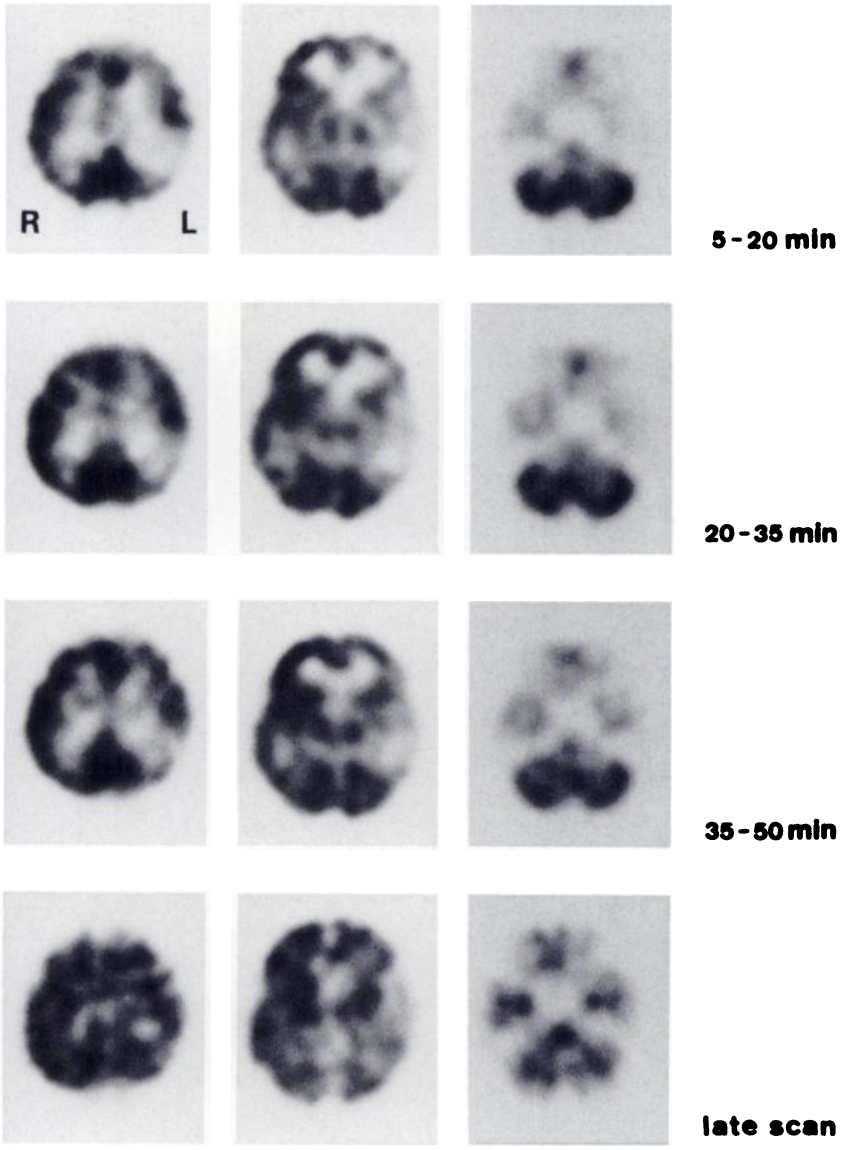

FIGURE 2
Temporal changes in IMP distribution in a case with Alzheimer's disease, showing unilateral temporoparietal hypoperfusion. A relative decrease of the activity in the cerebellum is noticed. A gradual decrease of the contrast between cortex and white matter, and between cortex and hypoperfused lesion are easily detected.

patients, which may be related to the washout of the tracer from the lung.

Slow increase and long retention of IMP was observed in the basal ganglia and the white matter, while the cerebellum and the occipital cortex showed relatively rapid increase and early washout of the tracer. The variation of the regional kinetics of IMP was previously described in animals (*15*) and in humans (*16*), but has not been elucidated in details. In general, IMP has high first-pass extraction through the brain due to its lipophilicity with subsequent retention to the nonspecific binding sites (*17*). Washout of the tracer may concern with the retention especially in the high blood flow area because of backdiffusion occurring in such lipophilic agent as IMP. But the difference in the retention among the different regions with a similar high

TABLE 2
Contrast Ratio of Hypoperfused Lesion to Contralateral Normal Cortex*

5–20 min		20–35 min		35–50 min		5 hr
(%)		(%)		(%)		(%)
84.0 ± 7.4		86.5 ± 8.3		87.6 ± 7.6		96.2 ± 6.3
	$p < 0.001$		$p < 0.05$		$p < 0.001$	

* Mean ± standard deviation of the 49 regions are shown as percentage of the lesion to the contralateral normal cortex.

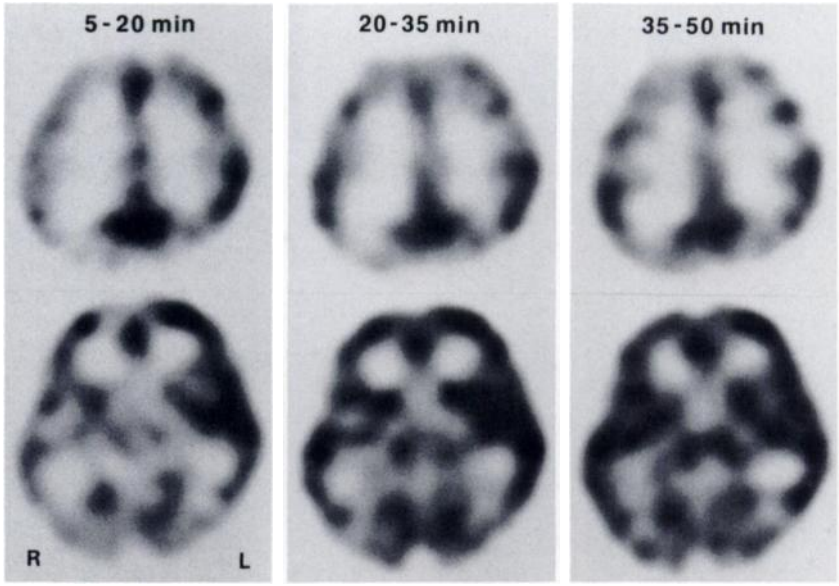

FIGURE 3
Serial IMP SPECT images in a case (11-yr-old boy) with occlusion of the right internal carotid artery. He had several attacks of sensory disturbance in left upper extremity but was asymptomatic at the time of the study. Fifteen percent reduction of the activity was found in the right cerebral hemisphere compared to the contralateral cortex in the 1st scan obtained from 5 to 20 min, but the difference between the hemispheres decreased with time to be only 5% difference in the third scan from 35 to 50 min.

blood flow suggests another mechanism. The basal ganglia, having high blood flow, showed continuous increase of the tracer and prolonged retention, which might indicate relatively quick trapping on the binding sites, resulting in the minimal washout of the tracer. The cerebellum and the occipital cortex, having as high blood flow as the basal ganglia, revealed the early washout of the tracer, indicating slower trapping on the binding sites. These findings suggest the difference in the characteristics of the binding sites among these structures, and these regional characteristics may indicate the relation to specific amine binding sites. But the difference observed in this study is not prominent compared to that of the density in the amine receptor sites, which may take only a little part in the IMP binding. As described in the previous reports, IMP binding is supposed to be mainly associated with high capacity, relatively nonspecific binding sites in the brain synaptosomes (*7,18*). The mechanism of slow increase and prolonged retention of the tracer in the white matter may be different from those in the basal ganglia and could be explained by less washout because of lower blood flow with the slow trapping on the binding sites.

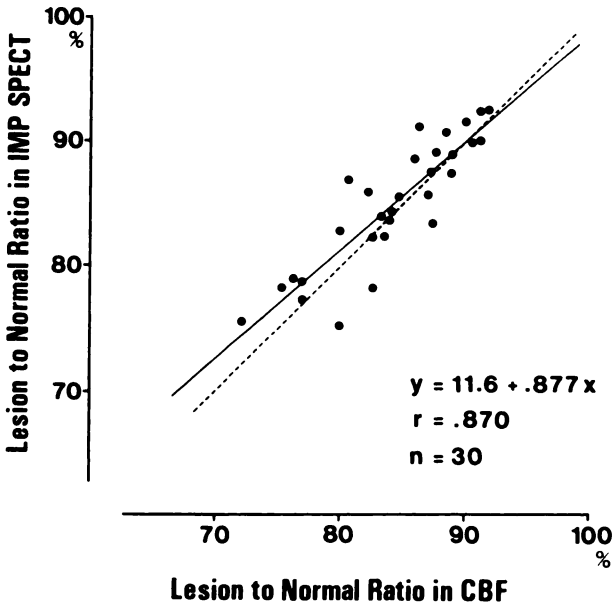

FIGURE 4
Comparison of IMP SPECT and CBF measured by PET as the activity ratio of hypoperfused lesion to the contralateral normal cortex. A good correlation was observed between IMP SPECT and CBF. A dotted line represents the line of identity and a solid line represents the regression line.

The gradual decrease of side-to-side asymmetry between the hypoperfused lesion and the contralateral nonaffected cortex was demonstrated. Previous reports found only the initial distribution of IMP to be in accordance with the CBF (*6,19*). In the present study, we observed the similar tendency in the temporal changes of IMP. In some cases with unilateral mild hypoperfusion, these temporal changes of IMP made the diagnosis difficult in the later SPECT performed within an hour after the administration of IMP. In the late SPECT, side-to-side asymmetry disappeared or reduced if the lesion did not show any abnormality on x-ray CT or MRI. This redistribution phenomenon was thought to be an indicator for tissue viability or oxygen metabolism in some reports and discussed in relation to the correlation with clinical outcome or the selection of candidate for bypass surgery. These observations are of great interest and attractive for clinical use of IMP, however, we cannot define the significance of the redistribution phenomenon in this study because of the limited number of the cases and the lack of uniformity of the diseases. The redistribution of IMP in the brain

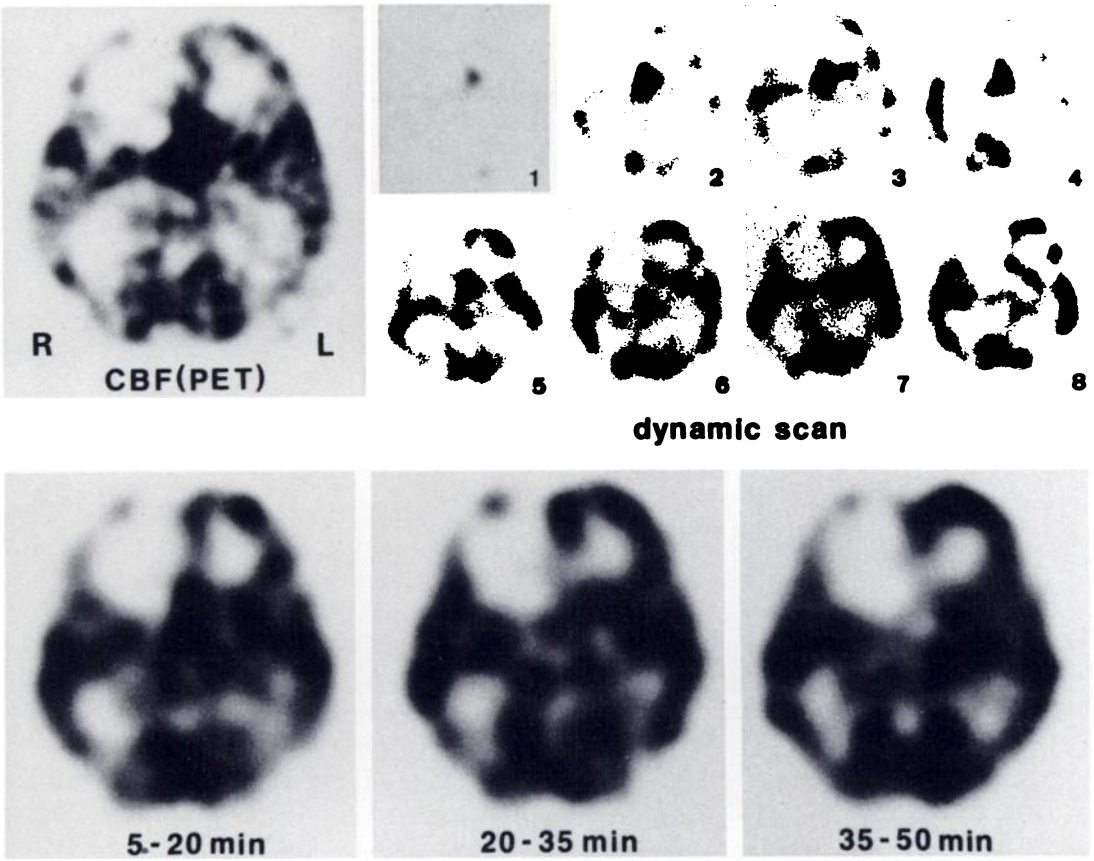

FIGURE 5
IMP SPECT images and CBF measured by PET in a case with oligodendroglioma. PET showed high blood flow in the tumor. IMP SPECT demonstrated high uptake of IMP in the tumor on the initial several images of the dynamic scan. High accumulation in the tumor is also shown on the first scan obtained from 5 to 20 min, but cannot be detected on the later scan.

may be affected by various factors such as lung reservoir, cardiac output and absolute value of CBF, etc., and may differ among individuals. Further investigation is needed to elucide the significance of the redistribution on the late SPECT.

The contrast of the hypoperfused lesion to the contralateral nonaffected cortex on the IMP SPECT was compared with that on the CBF and an excellent correlation was found between them with nearly the same degree of asymmetry. Generally in SPECT study, undesirable scatter radiation and poor spatial resolution degrade the contrast of the lesion compared to the CBF measured by PET. Since we did not perform scatter correction or background subtraction on the SPECT images, the asymmetry observed in the early SPECT images may be enhanced by the reduced extraction and/or the impaired retention of the tracer in the diseased tissues. The reduced accumulation of IMP in the diseased tissues could be explained not only by the reduction of blood flow but also by the severity of cell damages. This factor should also be examined for detail analysis of kinetics of IMP to elucidate the meaning of the redistribution phenomenon.

Hypervascular tumor showed a high accumulation of the tracer in the initial several SPECT images of the dynamic scan, but the activity in the tumor decreased rapidly, which resulted in the low uptake on the later SPECT. This observation suggests that IMP is extracted in the tumor to some extent, but the retention mechanism is impaired, which may be due to the lack or reduction of the binding sites. In the previous study, we observed that seven cases out of 24 with brain tumor had high IMP uptake in the tumor on the dynamic scan but the activity disappeared rapidly with a different time course in each tumor (*20*).

The distribution of IMP in diseased tissues might be modified due to the alteration of extraction and retention mechanism. Therefore, it may not reflect the blood flow accurately. Hypoperfused lesions may be enhanced and be detected more easily. Brain tumors with high blood flow may be overlooked on usual SPECT using a rotating gamma camera. Although IMP SPECT is a useful means for the assessment of various cerebral diseases, the variation of temporal changes in normal and diseased tissues should be considered for the accurate diagnosis, and more details should be investigated in the human brain for delineating the aspects of perfusion and function in different conditions.

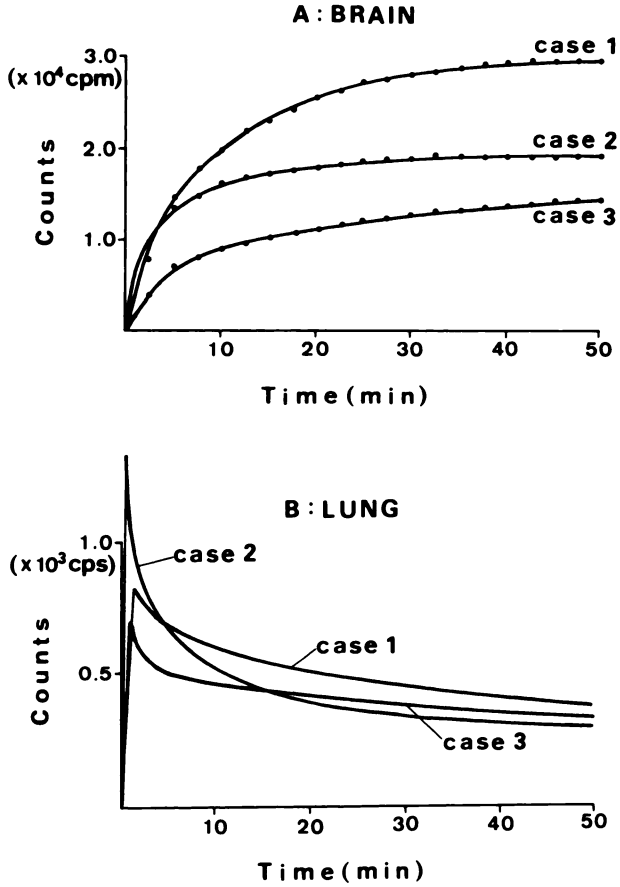

FIGURE 6
Time-activity curves of the brain (A) and lung (B) in three cases. Note the different patterns of the brain activity curves in three cases. These different patterns seem to be related to the lung clearance. A: Total brain activities in the middle slice were obtained by dynamic SPECT scan (cts/min/image). B: Lung activities were simultaneously recorded by a single NaI detector placed over the right lung (cts/sec).

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