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Accumulation of L-[2-(F-18)]fluorophenylalanine in peri-infarct area in a patient with acute cerebral infarction

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We studied the brain uptake of amino acid in a patient with acute cerebral infarction with L-[2-(F-18)]fluorophenylalanine and positron emission tomography. The increased accumulation of the ligand was specifically found in the peri-infarct area where oxygen metabolism was still maintained but decreased later in the 72-day follow-up period. The kinetic analysis revealed that increased accumulation was not due to increased transport from the blood to the brain but to delayed washout from the brain to the blood. Although the mechanism is still unknown, abnormally high accumulation of L-[F-18]fluorophenylalanine may predict delayed neuronal changes after ischemic insults of the brain.

Key words: PET, cerebral infarction, amino acid transport, phenylalanine

INTRODUCTION

AMINO ACID TRANSPORT at the blood brain barrier and cerebral amino acid metabolism after brain ischemia have not yet been precisely studied in humans although a number of studies suggested that they play an important role in ischemic tissue damage.[1,2] In addition to the suppression of protein synthesis, rapid proteolysis has been implicated in the process of hypoxic/ischemic neuronal death.[3]

We previously developed a ligand of L-[2-(F-18)]fluorophenylalanine (^{18}FPhe) to evaluate the transport of a large neutral amino acid across the blood-brain barrier in humans by means of positron emission tomography.[4] Large neutral amino acids such as phenylalanine, tryptophan, leucine, isoleucine, histidine, valine, threonine, methionine, tyrosine and the ligand, ^{18}FPhe are transported into the brain by the same carrier system at the blood-brain barrier in a competitive fashion. As shown in previous rat experiments,[5,6] this ligand was metabolized slowly because of its low affinity with phenylalanine transfer ribonucleic acid synthetase. Only a small amount of ^{18}F activity of the macromolecule was detected in the brain and plasma. The ligand therefore traces the transport of large neutral amino acids from the blood to the brain and from the brain to the blood.

Shishido et al. investigated the clinical application of ^{18}FPhe for brain tumor imaging.[7] They demonstrated the feasibility of detecting a brain tumor and its extension. In the present study, we evaluated the uptake of this ligand into ischemic brain lesions in a patient with acute cerebral infarction. In relation to the cerebral perfusion and oxygen metabolism, the increased accumulation of the ligand to the peri-infarct area was analyzed.

CASE REPORT

A 73-year-old female who complained of sudden onset of left visual field deficit was transferred to our hospital for closer examinations. The CT scan revealed a low density area in the right occipital lobe (Fig. 1-left). After administering contrast medium, no abnormally enhanced lesion was found. Cerebral angiography demonstrated complete occlusion of the right posterior cerebral artery as shown in Figure 2 and severe stenosis of the right internal carotid artery.

The patient underwent a positron emission tomographic study by administering 370 MBq of ^{18}FPhe on the 5th

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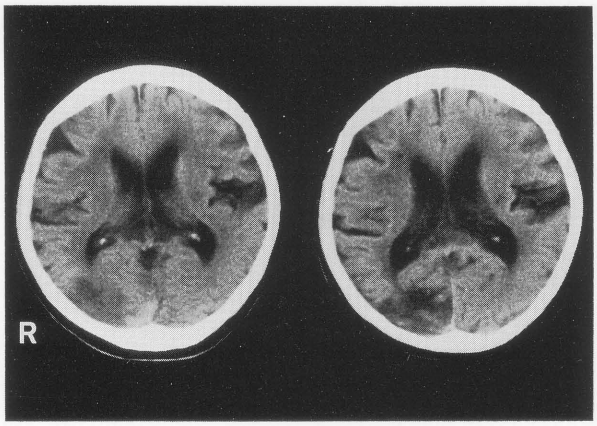


Fig. 1 A 73-year-old female patient with left visual field deficit. Cranial X-ray CT images obtained 2 days after onset showed a low density area in the right occipital lobe surrounded by slightly swelling normodensity brain (left image). After administering contrast medium, abnormally enhanced lesion was not found (image not shown). The follow-up CT scan revealed a complete infarction extending to medial occipital lobe previously showing normodensity in acute phase (right image). CT images were obtained at 45 mm above and parallel to the orbito-meatal line.

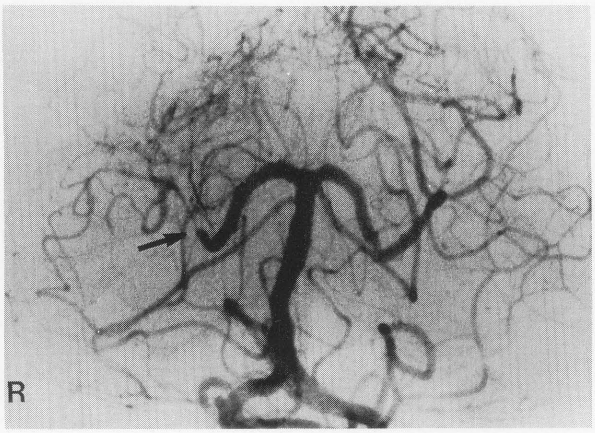


Fig. 2 Vertebral angiography demonstrated complete occlusion of right posterior cerebral artery at its ambeint segment (arrow). The distal territory was poorly perfused through the collateral circulation.

day after onset. Sequential scanning of 10 three-minute and 6 five-minute data acquisition was performed with a HEADTOME IV PET scanner (Shimadzu, Kyoto). Arterial blood was taken periodically to measure the input function of the ligand. The influx rate constant k_1 (from blood to brain) and the efflux rate constant k_2 (from brain to blood) was estimated by employing a 2 compartment analysis.[8] Prior to the ^{18}FPhe study, regional cerebral blood flow (rCBF), regional extraction fraction for oxygen (rOEF), regional metabolic rate for oxygen ($rCMRO_2$) and regional cerebral blood volume (rCBV) were measured by administering oxygen-15 labeled water, and by inhaling oxygen-15 labeled molecular oxygen and oxygen-15 labeled carbon monoxide, respectively.[9] The patient underwent a follow-up PET measurement of rCBF, rOEF, $rCMRO_2$, and rCBV 72 days after the onset. All the PET images were obtained parallel to the anterior commissure-posterior commissure (AC-PC) line. The AC-PC line was first identified in a mid-sagittal image of T_1 weighted MRI. Each patient was lying on a bed for the PET study. A lateral cranial X-ray photograph was taken with a metal line landmark placed parallel to the scanning slices. By fitting the cranial X-ray photograph to the MR-mid sagittal image and by measuring the angle produced by a metal line landmark and the AC-PC line of the MRI, the tilting angle of the PET gantry was determined.

Figure 3 shows the ^{18}FPhe image obtained 55 minutes after the administration at a level of 45 mm above and parallel to the AC-PC line. The round region of interest with a 16 mm diameter was placed on the increased accumulation of ^{18}FPhe in the right medial occipital lobe (see Fig. 5). This region corresponded to the normodensity area surrounding the low attenuation in CT and defined as the peri-infarct area. The radioactivity of the peri-infarct area was 1.6 times higher than that of the left frontal reference region. Regional CBF, rOEF, $rCMRO_2$, and rCBV for the peri-infarct area were 9.2 m*l*/100 m*l*/min, 0.70, 1.11 m*l*/100 m*l*/min (Fig. 4-upper row), and 5.3 m*l*/100 m*l*, respectively. In the follow-up measurements, regional CBF recovered to 15 m*l*/100 m*l*/min but oxygen metabolism decreased to 0.40 m*l*/100 m*l*/min (Fig. 4-lower row) associated with shrinkage of the lesion in the CT image (Fig. 1-right).

In Figure 5, the images obtained at 9.5 min (left), 19.5 min (middle), and 38 min (right) after ^{18}FPhe administration are demonstrated with the region of interest for the peri-infarct area and reference frontal region. The kinetic analysis revealed that the influx rate constant in the peri-infarct area (0.036) was not different from that in the left frontal reference region (0.035) but the efflux rate constant (0.060) was decreased compared with that in the left frontal reference region (0.087). The time-radioactivity curves for the peri-infarct area and left frontal reference region are shown in Figure 6.

DISCUSSION

In the ischemia-recirculation model of rat brain, the accumulation of neutral amino acid labeled with ^{14}C to post-ischemic brain was found to be 1.7 times higher than the control level.[1] The present results for the peri-infarct area are consistent with this experimental observation. Several mechanisms of abnormally high accumulation of ^{18}FPhe in the peri-infarct area are considered. The blood-brain barrier might be damaged after the ischemia. The accumulation may simply indicate leakage of the ligand to brain tissue. However, ^{18}FPhe was not accumulated in the ischemic center where brain matter was more profoundly

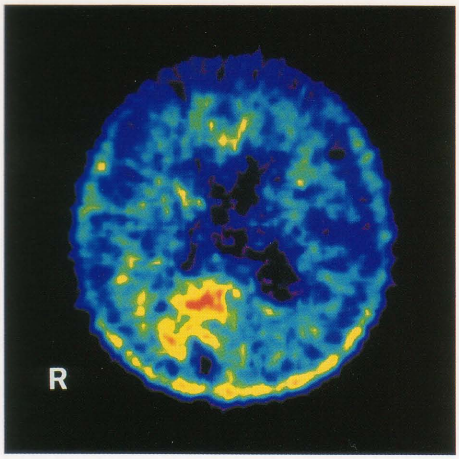


Fig. 3

Fig. 3 The image obtained 55 minutes after intravenous administration of L-[2-(F-18)]fluorophenylalanine. The ligand was specifically accumulated into the peri-infarct area with normal CT density. The radioactivity measured using 1 cm-circular region of interest for peri-infarct area was 1.6 times higher than that for reference cortical region (left frontal lobe). In the ischemic core, no accumulation was found.

Fig. 4 Regional CBF (left column), rOEF (center column), and $rCMRO_2$ (right column) measured on the 5th day (upper row) and the 70th day after onset. The right medial occipital lobe showed a maintained oxygen metabolism with decreased CBF in the first study. The oxygen metabolism of this area deteriorated in the follow-up measurement. The peak value of rCBF, rOEF, and $rCMRO_2$ image was 50.0 ml/100 ml/min, 1.00, 3.5 ml/100 ml/min, respectively, in both PET studies.

Fig. 5 Dynamic ^{18}FPhe images obtained at 9.5 min (scan midtime, left), 19.5 min (middle), 38 min (right) after injection. In the initial phase, ^{18}FPhe accumulation was not different between peri-infarct area and normal cortices. In the later images, ^{18}FPhe activity was gradually decreased in normal cortices whereas ^{18}FPhe in the peri-infarct area was residual.

Fig. 4

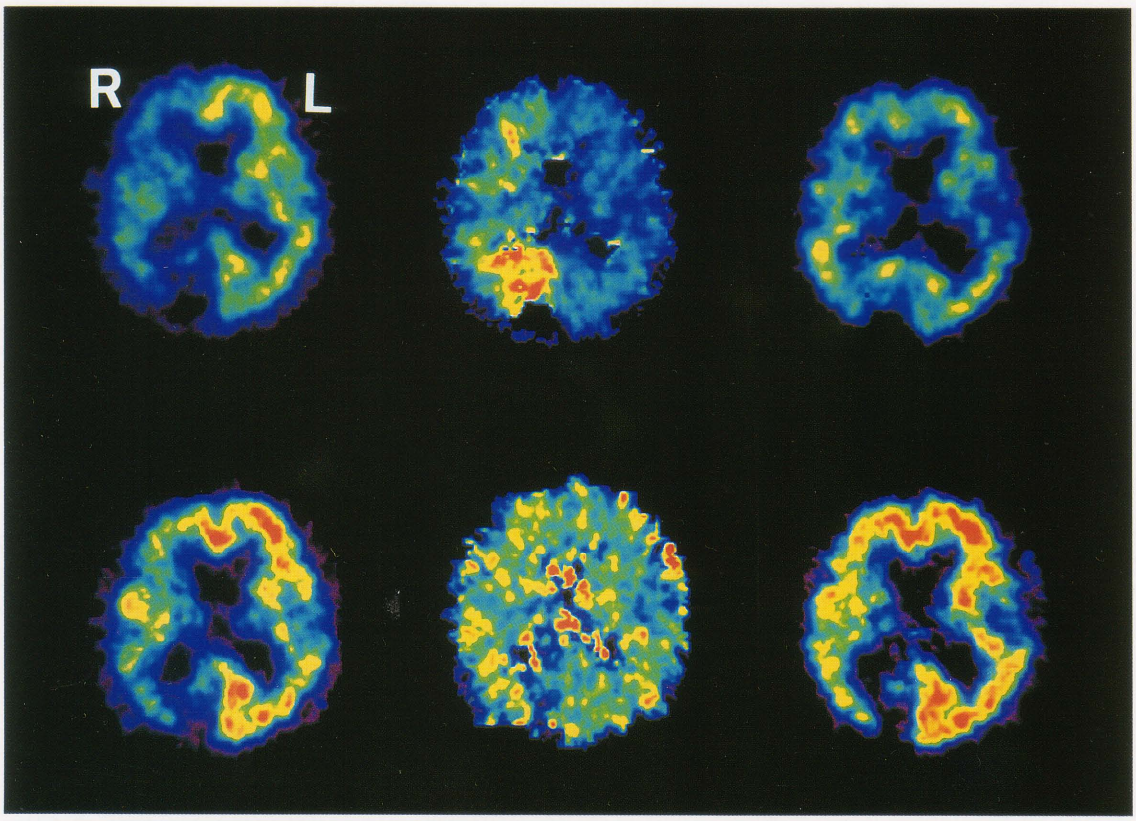
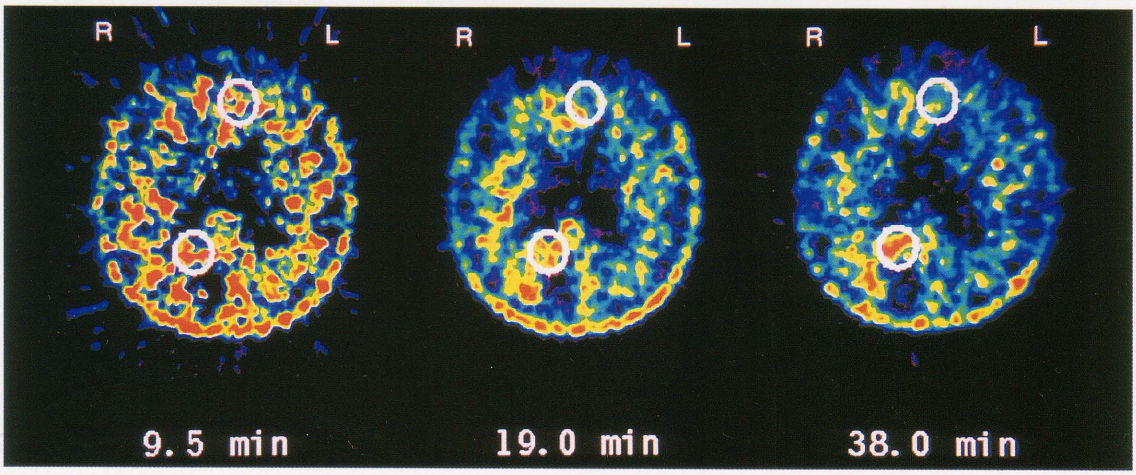


Fig. 5



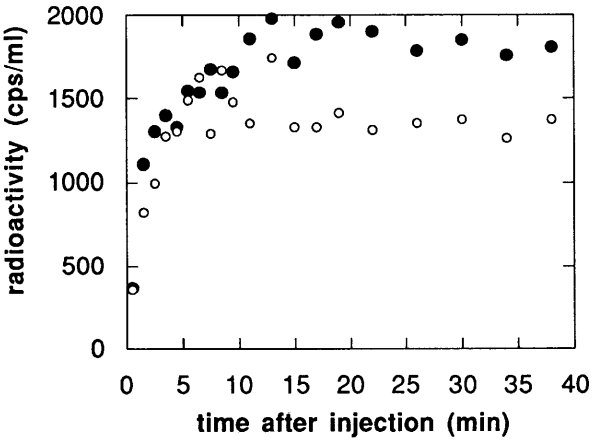


Fig. 6 Time-radioactivity curves for the peri-infarct area (○) and reference frontal cortex (●). Regions of interest (ROI) for these data were shown in Figure 5. The round ROI with diameter of 16 mm and 14 mm was employed for peri-infarct area and reference frontal region, respectively.

impaired. When the leakage occurred, the ligand may have accumulated in the early phase after iv administration because of the high level of plasma ^{18}FPhe in that phase. However, the time-radioactivity curve for the peri-infarct area did not differ from that for non-ischemic cortical regions in the early phase. In addition, CT examination with contrast medium did not show abnormal enhancement in the peri-infarct area. It is unlikely that the leakage of the ligand played a major role in the increased accumulation.

The kinetic analysis revealed that the efflux of the ligand was decreased in the peri-infarct area. This indicated that the washout, but not the uptake of the ligand in the peri-infarct area, was mainly affected. The images in Figure 5 and time-radioactivity curves for the peri-infarct area and reference region in Figure 6 may intuitively confirm the result. The efflux rate constant k_2 is positively correlated with the maximal capacity of the transport system, and inversely correlated with the cerebral concentration of free amino acids sharing the same transport system as ^{18}FPhe.[10] Theoretically, when the amino acid concentration increases in the peri-infarct brain, this may prolong the washout of ^{18}FPhe because of the higher competition for the transport system. Previous rat experiments proved the cerebral amino acid concentration to be increased to 1.5 times the control level during recirculation after complete ischemia.[2] In addition, rapid proteolysis of cytoskeletal proteins activated by elevated intracellular calcium has been demonstrated following cerebral ischemic events.[11] These studies suggested that an increased amino acid concentration in the peri-infarct brain region is one of the mechanisms involved in the increased accumulation of ^{18}FPhe.

In acute cerebral infarction, variation in the magnitude and duration of ischemia may induce different conditions in the ischemic regions to complete the infarction. Higano et al.[12] demonstrated that the regions with a residual flow as low as 10–17 m*l*/100 m*l*/min could maintain $rCMRO_2$ for at least 7 hours after onset, and that these ischemic lesions demonstrate normodensity on CT in the acute phase but subsequently develop irreversible morphological changes. Heiss et al.[13] found that in some parts of the peri-infarct tissue a progressive decrease in $CMRO_2$ occurred even if CBF was improved after ischemic stroke. Powers et al.[14] reported that $rCMRO_2$ was a good indicator for predicting viable tissue escaping complete infarction. Regional $CMRO_2$ less than 1.3 m*l*/100 m*l*/min was inadequate to maintain tissue viability for a long period. These studies indicated that there are two distinguishable types of tissue derangement after brain ischemia: in the ischemic core where blood flow and metabolism are profoundly impaired from the acute to chronic stage of ischemia; and in the peri-infarct area where oxygen metabolism is preserved in the early phase but may deteriorate some time later. The area with a high accumulation of ^{18}FPhe may be classified as the latter type of cerebral infarction. The increased accumulation of ^{18}FPhe was a more sensitive indicator to use in detecting such ischemic damage than the oxygen metabolism in the acute stage.

In this preliminary study, the increased accumulation of ^{18}FPhe was an indicator of the delayed neuronal deterioration after ischemic brain insult. Further studies of a larger population should be performed to confirm these observations and conclusions.

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