Multi-focal Metabolic Disturbances in Human Brain at a Chronic Stage of Stroke Studied with 18FDG and Positron Emission Tomography

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Introduction

We have reported that postischemic delayed neuronal damage was observed in the remote areas, i.e., the ipsilateral thalamus and the substantia nigra of the rat brain after occlusion of the middle cerebral artery (MCA)[1]. These exo-focal postischemic neuronal damages in the remote areas might be caused by transsynaptic process associated with the infarcted areas and intracellular and transsynaptic signal transduction systems might play important roles in this mechanism[2-4]. To determine if that phenomenon also occurs in humans, we measured cerebral metabolic rates for glucose (CMRGlc) in the remote brain areas at the chronic stage after cortical infarction using 2[^{18}F]-fluoro-2-deoxy-D-glucose (^{18}FDG) and positron emission tomography (PET).

Subjects and Methods

We studied 7 patients, 5 men and 2 women, ranging in age from 41-72 years (mean ±SD, 61.1±8.8), who were affected by unilateral cerebral infarction in the cortex supplied by the MCA. The patients were diagnosed by a neurological examination, neuropsychological evaluation and using magnetic resonance imaging (MRI) and/or computed tomography (CT) scans of the brain. In all patients, the infarcted areas were limited in the cortex and no ischemic lesions were observed in the remote brain areas, such as the thalamus and the cerebellum, using MRI and/or CT scan. PET study was performed at the chronic stage, more than three months after stroke in all patients.

The control group consisted of 6 normal volunteers, 4 men and 2 women with an age range of 49-74 years (63.5±9.0), without a history of recent medical illness, neurological diseases, developmental disorder, or substance abuse. MRI and/or CT scan of the brain, obtained in the control group, were normal. Control subjects underwent a complete neurological examination and neuropsychological evaluation before PET scanning. The project was approved by the Research Ethics Committee of the Tohoku University, School of

Medicine. All subjects gave their written informed consent after a full explanation of the procedure.

Positron emission tomography

PET study was performed with a scanner, PT-931 (CTI Inc, USA), according to the FDG method[5,6] at the Cyclotron and Radioisotope Center, Tohoku University, Sendai, Japan. Before the study, a short 21-gauge cannula was placed in a brachial or a radial artery under local anesthesia for arterial blood sampling. Each subject was then positioned in the scanner, with the orbitomeatal (OM) line parallel to the detector rings according to the brain slices by MRI and/or CT scan. A cross of light was projected onto marks on the subjects' heads from three dimensions and their heads were set at the standard points of 16, 63, and 110 mm above and parallel to the OM line. All studies were conducted in a quiet, semidarkened room with minimal background noise. The subjects had their eyes opened and ears unplugged.

Before the emission scanning, a 20-min transmission scan using a ^{68}Ge-^{68}Ga external ring source was performed. Thirty min after an intravenous bolus injection of 111-183 MBq ^{18}FDG (3-5 mCi), a series of three emission scans, each of 10 min duration, was commenced by using a PT-931 with an 8 mm axial and transaxial resolution at the center of each standard point. Each emission data was simultaneously collected from seven contiguous axial sections. A total of 21 slices parallel to the OM line with a slice thickness of 6 mm comprising virtually the whole brain including the cerebellum were analyzed. Twenty blood samples were colleccording to the following protocol: from injection to 2 minutes, one sample every 20 seconds, then samples at 2.5, 3, 4, 5, 7.5, 10, 15, 20, 25, 30, 40, 50 and 60 min after the intravenous administration of ^{18}FDG. The blood samples were immediately centrifuged, and the arterial plasma radioactivities of ^{18}FDG was measured with the cross-calibrated well counter. The arterial plasma glucose concentrations were measured every 10 min during the study.

In each case, CT scan or MR was examined in detail at the same head position as the PET study. To ascertain the anatomical position of each brain structure, the positions of regions of interest (ROIs) were manually defined on the PET images using MRI or CT images of the same brain slices. Each ROI was positioned in the relevant region, if some ROIs appeared on several slices that overlapped the entire volume of each structure, using neuroanatomical atlases[7,8]. Cerebral metabolic rates for glucose (CMRGlc) were calculated using the operational equation derived by Phelps et al.[5] and Huang et al.[9] from that of Sokoloff et al.[10] The emission data were corrected for attenuation using transmission data. The average values of CMRGlc within each structure were calculated and data of CMRGlc were analyzed using a paired Student's t-test with $p<0.01$ considered to be statistically significant.

Results

Two different pairs of images of two patients, the PET images and the images obtained by CT scan or MR at the same brain slices, are shown in Figures 1 and 2. The values of CMRGlc (mean±S.D.) in each structure of the control subjects and the patients are represented in Table 1. In the patients, regional CMRGlc in the parietal cortex of the infarcted side was markedly decreased as 3.51±1.21 mg/100g/min. The parietal cortex was defined as infarcted area by CT scan or MRI, which was directly affected by ischemic insult. However, significant decreases of CMRGlc were observed as 3.74±1.86 in the ipsilateral thalamus and 4.54±1.70 mg/100g/min in the contralateral cerebellum compared with the value of each corresponding region of the opposite side and normal control values ($p<0.01$). No ischemic lesions had been detected in the thalamus and the cerebellum of the patients by CT scan or MRI (Figure 1 and 2).

Discussion

In the present study, we selected the patients who had suffered from cortical stroke more than three months. In all patients examined by CT scan or MRI, the infarcted areas were limited to the unilateral cerebral cortex with variable involvement of the adjacent centrum semiovale, in which areas had been supplied by the MCA. Our results indicate that focal cortical stroke produces widespread metabolic disturbances in the ipsilateral thalamus and the contralateral cerebellum, regions which are remote from the infarcted areas. Recent studies using experimental animals with MCA occlusion have revealed the delayed neuronal degeneration in the ipsilateral thalamus which had not directly been affected by the original ischemic insult[1,11]. Kataoka et al. reported that the disturbances of the neuronal network occurred in the remote areas in the MCA occlusion model of the rats using Fink-Heimer silver impregnation and succinate dehydrogenase immunohistochemistry[12]. In their study, massive silver staining of degenerated synaptic terminals and decreases in succinate dehydrogenase activity were observed in the ipsilateral thalamus at a chronic stage after the MCA occlusion and they considered that the absence of succinate dehydrogenase staining reflected early changes in retrograde degeneration of thalamic neurons associated with the thalamocortical pathways from the cortex with ischemic insult[12]. We also reported that regional glucose metabolism was decreased in the ipsilateral thalamus one week after the ischemia using the MCA occlusion model in rats[1]. Delayed neuronal damage and decrease of glucose metabolism in the ipsilateral thalamus are considered to explain by retrograde neuronal degeneration due to thalamocortical fiber damage in ischemic cortical regions. The present data suggest that such phenomenon observed in the animal experiments also occur in the ipsilateral thalamus of the patients with cortical infarction. Reduction of CMRGlc in the thalamus may be explained by retrograde neuronal degeneration due to thalamocortical fiber damage after cortical stroke in humans.

In another opinion, reduction of CMRGlc in the ipsilateral thalamus might reflect a significant functional suppression of neuronal activity caused by loss of corticothalamic fibers from the ischemic cortical regions. This could happen without cell death in the thalamus and consequently would not be detected by CT scan and MRI. Furthermore, such hypometabolism due to corticothalamic fiber damage might not be reversible and this would consequently lead to delayed neuronal death in the thalamus during the chronic stage of stroke.

On the other hand, decrease of glucose metabolism in the contralateral cerebellum is not easily explained. In our study, metabolic disturbance observed in the contralateral cerebellum three months and more after the cortical infarction. As shown in Figure 2, metabolic disturbance still observed in the right cerebellum, though a patient who had suffered from left cortical infarction more than 4 years previously. Such a phenomenon may reflect irreversible change of neuronal function and is quite different from the crossed cerebellar diaschisis reported by Baron et al.[13]. There were few reports about the delayed damage in the contralateral cerebellum after cortical injury using experimental animals[14]. Further detailed study is required to clarify the mechanism of decreased glucose metabolism in the contralateral cerebellum at a chronic stage after the cortical infarction. In conclusion, decreases of regional glucose utilization in the exo-focal remote areas indicate that disturbances in brain function after stroke occur not only in the ischemic areas directly affected by the original ischemic insult, but also in the remote areas due to secondary neuronal degeneration. We suggest that these multi-focal metabolic disturbances observed in the postischemic brain may exacerbate clinical symptoms at a chronic stage of stroke.

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Table 1. Cerebral metabolic rate of glucose in each brain structure of normal control and patients.

Structure	Control (N=6)	Patients (N=7)	
		Infarcted side	Non-infarcted side
Frontal cortex	7.64 ± 1.45	6.37 ± 1.70	7.56 ± 1.81
Parietal cortex	7.87 ± 1.38	3.51 ± 1.21**	7.22 ± 1.46
Occipital cortex	7.74 ± 1.62	7.73 ± 1.76	7.65 ± 1.79
Temporal cortex	7.26 ± 1.64	5.81 ± 1.51	6.92 ± 0.90
Thalamus	7.57 ± 1.97	3.74 ± 1.86**	8.07 ± 1.71
Cerebellum	7.02 ± 1.89	6.77 ± 1.60	4.54 ± 1.70**

Values are given in mean ± S.D. mg/100g/min. N: number of subjects.
**: $p<0.01$, significant difference from the values in the corresponding area of the contralateral side and normal control values.

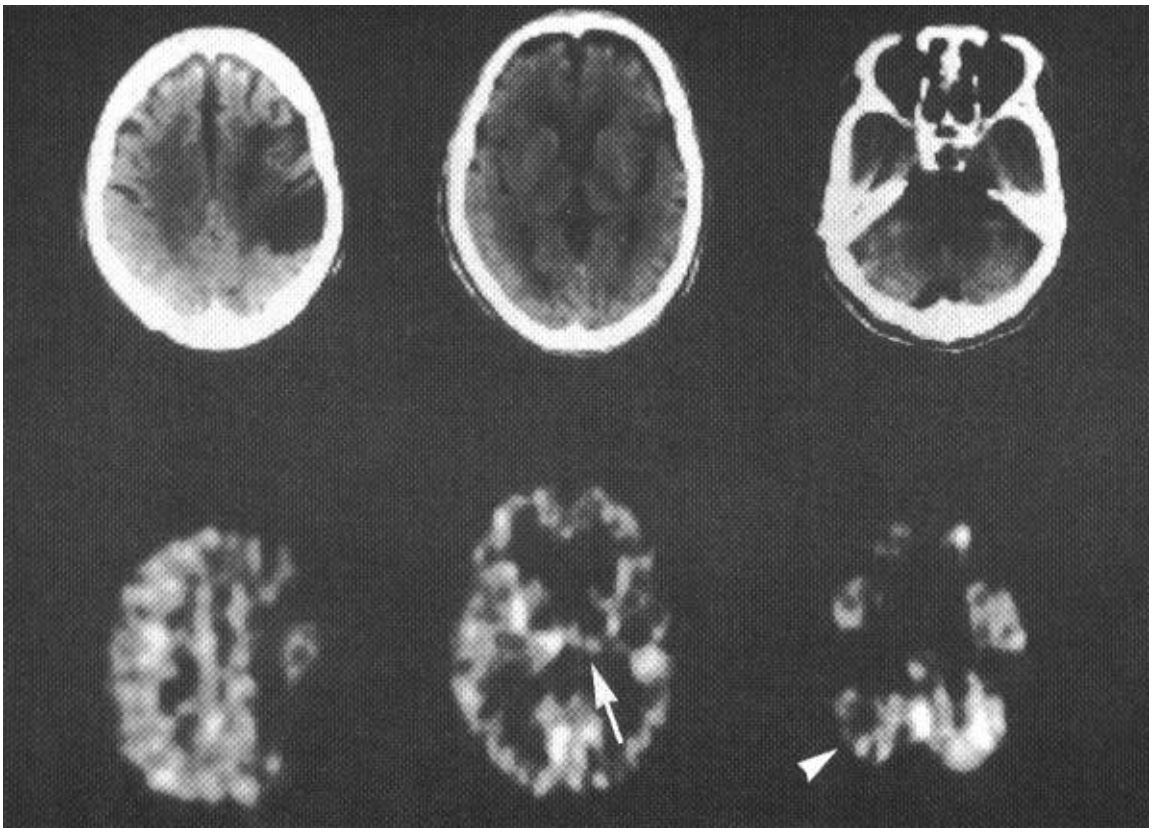

Fig. 1. Representative appearances of CT Scan and PET image data at the same brain slices from a 68-year-old man who had suffered from left cortical infarction 5 months previously. Decreases of CMRGlc were observed in the left thalamus (arrow) and in the right cerebellum (arrowhead).

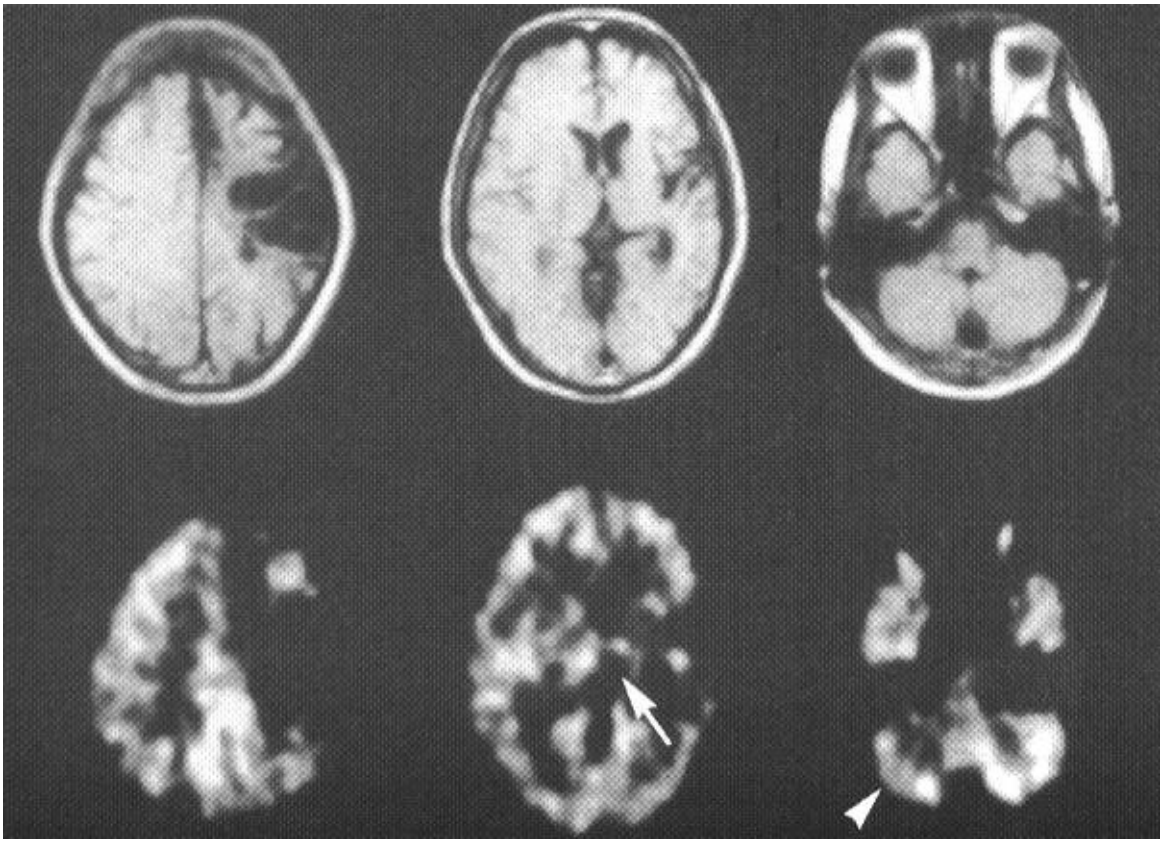

Fig. 2. Representative appearances of MRI and PET image data at the same brain slices from a 41-year-old man who had suffered from left cortical infarction 4 years and 2 months previously. Decreases of CMRGlc were observed in the left thalamus (arrow) and in the right cerebellum (arrowhead).