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Enhanced Detection of Brain Tumors by [^{18}F]Fluorodeoxyglucose PET with Glucose Loading

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Objective: We applied glucose loading during PET studies with [^{18}F]2-fluoro-2-deoxy-D-glucose (FDG) to enhance detection of brain tumors by diminution of FDG uptake in normal gray matter.

Materials and Methods: This study involved three patients with glioblastomas. Two PET scans were performed in all cases within 1 week in control and with glucose loading state.

Results: In all patients, tumor was depicted more clearly with glucose loading than in the control study. The FDG uptake ratio of tumor to normal cortical gray matter showed a mean increase of 27% with glucose loading.

Conclusion: This technique might be useful for detection of recurrent or residual tumors.

Index Terms: Emission computed tomography—Brain, neoplasms—Glucose, metabolism.

The use of [^{18}F]2-fluoro-2-deoxy-D-glucose (FDG) with PET allows the noninvasive study of specific aspects of metabolism in normal (1–3) and malignant (4) tissue. This method is now widely applied in brain tumor patients for grading and for detection of recurrent or residual tumors (5–7). In fact, FDG-PET study has been demonstrated to be the most reliable method to differentiate recurrent tumors from radiation necrosis (8,9). Because of their high glycolytic rate, malignant brain tumors have shown high accumulation of FDG (10).

In clinical situations, however, high glucose metabolism in normal gray matter may obscure FDG uptake of brain tumors. This drawback may lessen the value of this technique particularly when the lesion is small and adjacent to the cortex.

Increased serum glucose levels diminish the uptake of deoxyglucose in the healthy brain (11,12). On the basis of this observation, we have used glucose loading during FDG-PET studies to enhance detection of human brain tumors through a reduction of FDG uptake in normal brain.

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MATERIALS AND METHODS

Three patients with glioblastomas, one man and two women with a mean age of 48 years, were included in this study. The diagnosis was established histologically in all cases (Table 1). Two patients had recurrent tumors after previous surgery, irradiation, and chemotherapy. One patient had not received any treatment prior to the study. All cases showed clear evidence of solid mass on MR and/or CT scans. No patient had an episode of diabetes mellitus, which was diagnosed by normal levels of serum glucose in the fasting state. Informed consent was obtained from each patient under the guidance of the ethical committee of the Kyoto University Faculty of Medicine.

The PCT-3600W system (Hitachi Medical Co., Japan) was employed in this study for PET scans (13). This system simultaneously acquires 15 slices with a center-to-center distance of 7 mm. All scans were performed at a resolution of 7.5 mm full width as half-maximum in the transaxial direction and 6.5 mm in the axial direction using the wobbling mode.

TABLE 1. *Patient data*

Case no./age/sex	Histology	Site	Previous therapy
1/70/F	Glioblastoma	Lt. parasagittal	None
2/42/F	Glioblastoma	Lt. temporoparietal	Surgery, radiation, chemotherapy
3/31/M	Glioblastoma	Lt. temporoparietal	Surgery, radiation, chemotherapy

Two FDG-PET scans were performed in all cases within 1 week in control and under glucose loading conditions. Control study was done first in one patient and second in the other two cases. In each study, patients received 4.6–7.5 mCi of FDG injected intravenously for 15 s. The PET scan was started ~40 min after FDG injection, obtaining a static image of 20 min duration.

In the glucose loading studies, intravenous infusion of 10% glucose solution was started 10–15 min before FDG injection and continued until the end of the study. Total infused volume of glucose solution was ~500 ml, and infusion speed (5–7 ml/min) was kept constant throughout the scan. Plasma glucose levels were measured six times during the glucose loading study, i.e., before glucose loading, just before FDG injection, and 6, 15, 30, and 60 min after FDG injection. Plasma glucose levels were monitored with a dextrometer several times during the study to avoid excessive hyperglycemia.

The control study was performed with at least 2 h fasting condition prior to the examination. Plasma glucose levels were measured three times, just before FDG injection and 30 and 60 min after injection, during the control study.

Tissue activity images of FDG were used for the region of interest (ROI)–based analysis. On the reconstructed FDG images, high uptake areas corresponding to the solid tumor mass on a representative slice in CT and/or MR were outlined, excluding areas of presumed edema or necrosis. Irregular ROIs (10–15 cm^2) were also placed on the representative area of the contralateral gray matter. Similar sizes of ROIs were placed for control and glucose loading PET images. Tissue FDG uptake of the injected dose (% uptake) was calculated both for tumors and for cortices according to the following equation:

$$\%\ \text{uptake} = \frac{\text{tissue activity (nCi/ml)}}{\text{injected dose (mCi)} \times 10^6} \times 100$$

The tumor-to-cortex ratio of FDG uptake was also calculated in both states.

RESULTS

The mean ± SD serum glucose level was 110.3 ± 13.3 mg/dl in the control state and 238.7 ± 51.3 mg/dl in the glucose loading state (Table 2). In all patients, the tumor was visually recognized more clearly with glucose loading than in the control state, although it was visualized in both conditions. Figure 1 shows FDG-PET images of two cases (Cases 1 and 2) studied in the control state and with glucose loading, demonstrating clearer visualization of FDG uptake in the tumor.

Table 2 summarizes quantitative values of FDG uptake between the control and glucose loading studies. Glucose loading apparently decreased FDG uptake in cortex (58.4% on average). On the other hand, tumor showed less decrease (30.6% on average) of FDG uptake, resulting in the increased tumor-to-cortex ratio of FDG uptake (26.8% on average). No patient had any symptom caused by hyperglycemia.

DISCUSSION

The technique of FDG-PET has made it possible in vivo to measure brain glucose utilization (1–3). Because of the high glycolytic rate of many malignant tumors, FDG-PET study has been shown to be valuable in grading brain tumors, monitoring disease progression and response to therapy (6,7), and differential diagnosis of recurrent tumor and radiation necrosis (8,9). In clinical situations, however, high uptake of FDG in normal gray matter is sometimes problematic when differentiating between the lesion and normal tissue. Previous FDG-PET studies have shown that human gliomas may have a wide range of glucose metabolism compared with

TABLE 2. *Changes of % uptake of FDG and tumor-to-cortex ratio with glucose loading*

Case no.	Plasma glucose[a] (mg/dl)	% uptake of FDG[b]		Tumor-to-cortex ratio of FDG uptake
		Cortex	Tumor	
1				
Control	128	0.0078	0.0064	0.82
Loading	295	0.0031	0.0031	1.01
2				
Control	96	0.0102	0.0071	0.70
Loading	250	0.0036	0.0033	0.92
3				
Control	107	0.0072	0.0079	1.10
Loading	171	0.0039	0.0054	1.39
Average				
Control	110	0.0084	0.0071	0.87
Loading	239	0.0035	0.0049	1.11

[a] Mean values for multiple measurements.
[b] % uptake/ml tissue/injected dose.

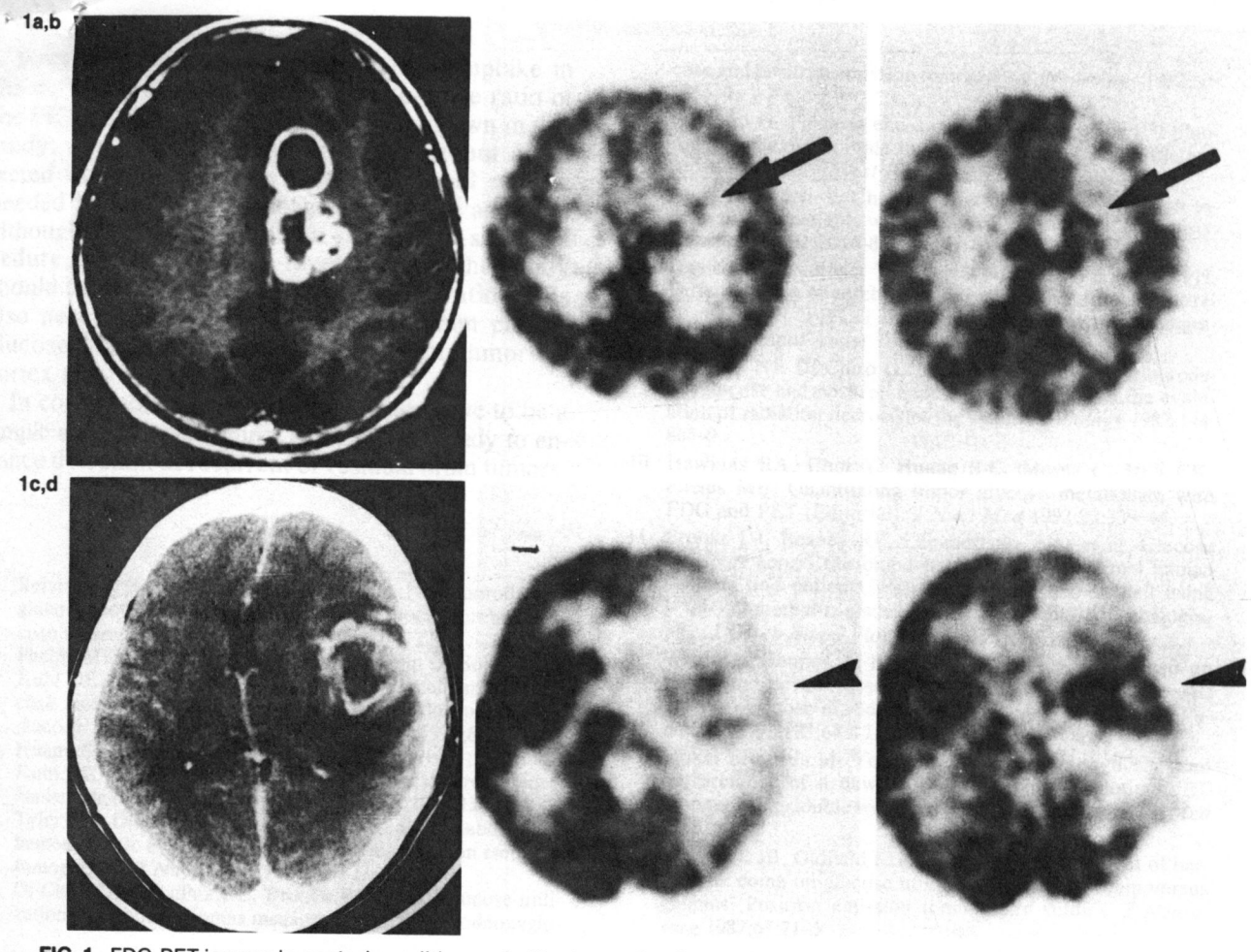

FIG. 1. FDG-PET images in control condition and with glucose loading. **a:** Gd-enhanced MR image of Case 1. **b:** FDG-PET images of Case 1. The tumor (arrows) was visualized more clearly in the glucose loading study. **c:** Postcontrast CT image of Case 2. **d:** FDG-PET images of Case 2. The tumor (arrowheads)-to-cortex ratio of FDG uptake was increased by glucose loading.

the surrounding brain (6). Therefore, reduction of FDG uptake in normal brain tissues would improve the detection of brain tumors as demonstrated by Blacklock et al. (14) who applied barbiturates to suppress glucose utilization in the brain. In our present study, glucose loading also increased the tumor-to-cortex ratio of FDG uptake in three cases of gliomas.

It was shown that increased plasma glucose concentration diminishes the glucose transport in the human brain, presumably due to direct competition (11). Animal study with implanted mammary carcinoma demonstrated that the tumor revealed less reduction of FDG uptake than the normal brain structures by increased plasma glucose level, resulting in elevation of the ratio of tumor to normal brain uptake (12). Although the effects of serum glucose level on FDG uptake in human glioma cells are not clearly understood, the present study also demonstrated less reduction of FDG uptake in human gliomas than in normal brain tissues.

[^{18}F]Fluorodeoxyglucose PET study with glucose loading may play a role in increasing the detectability of recurrent or residual brain tumors after surgical treatment and/or radiation therapy. To confirm this, obviously, further studies should be performed with a larger number of subjects with gliomas and other brain tumors, including metastatic tumors.

In addition, the underlying mechanism of the different kinetics of FDG in tumors and normal brain tissues has to be clarified for clinical application of this technique. Marked reduction of FDG uptake in the normal brain in the hyperglycemic state may be primarily due to the direct competition of FDG uptake with glucose, although it is partly because of decreased arterial input due to the faster blood clearance of FDG. On the other hand, FDG uptake in tumor seems to be more complicated. In addition to the similar direct competitive process and decreased arterial input, increased serum insulin level and breakdown of blood–brain barrier might also have some effects on FDG uptake, which could lessen its reduction.