PET Study of Carbon-11-PK 11195 Binding to Peripheral Type Benzodiazepine Sites in Glioblastoma: A Case Report

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The utility of the peripheral type benzodiazepine site ligand $^{11}$C-PK 11195, for imaging human glioma in conjunction with Positron Emission Tomography, relies on a high specific binding of the tracer to tumoral peripheral type benzodiazepines sites. In a patient with glioblastoma, we found that $^{11}$C-PK 11195 binding was two-fold higher in the tumor than in normal gray matter and that 30% of tumoral binding could be displaced by a large excess of unlabeled drug. These findings suggest that tumoral retention of the ligand is due, in part, to specific binding.


Although computed tomography (CT) and magnetic resonance imaging (MRI) provide accurate detection of brain tumor, for discriminating between edema and neoplastic tissue or between tumor recurrence and radiation, these methods may be inconclusive. Experimental and postmortem human studies have shown a high density of peripheral type benzodiazepine binding sites (PTBS) in brain tumors, suggesting that they could be used as marker of cell density in human brain tumors (1–6). PK 11195, a specific ligand of PTBS, has been labeled with $^{11}$C (7), and the labeled ligand has recently been used in combination with PET for imaging human glioma though, definitive evidence of the specificity of the $^{11}$C-PK 11195 binding to tumoral PTBS was not provided (8). In this case, a patient with glioblastoma, we show $^{11}$C-PK 11195 uptake that is increased two-fold in the tumor with respect to the normal contralateral gray matter. About 30% of tumoral $^{11}$C-PK 11195 was displaced by an excess of unlabeled PK 11195, as a result of the competitive inhibition between the tracer and the excess of unlabeled drug. These data suggest that increased uptake of $^{11}$C-PK 11195 by malignant brain tumor in this patient may represent, in part, increased specific binding of the tracer to PTBS.

CASE REPORT

Patient

The subject was a 69-yr-old, right-handed man with a 1-mo history of progressive altered mental status and right hemiparesis. CT and MRI provided images consistent with a left frontal malignant tumor. The patient was treated by corticosteroids without any benefit and died suddenly 1 mo later. Neuropathologic examination revealed a large tumor in the left frontal lobe, extending into the basal ganglia and through the genu of the corpus callosum to the contralateral cingulate gyrus. Microscopic examination showed a diffusely infiltrating and highly cellular glial tumor with marked pleomorphic features, necrosis, and endothelial proliferation, consistent with a diagnosis of multiform glioblastoma.

PET

Two PET studies were carried out in this patient during consecutive weeks. These studies were approved by the ethics committee of our institution. In the "control" study, 22 mCi of $^{11}$C-PK 11195 labeled at a specific radioactivity (SRA) of 135 mCi/umol (corresponding to 164 nmol) was injected intravenously. In the "displacement" study, a large amount of unlabeled PK 11195 (56.7 umol) was injected intravenously 10 min after $^{11}$C-PK 11195 (26 mCi, SRA:397 mCi/umol).

A 7-slice LETI time-of-flight assisted positron camera (spatial resolution: 12 mm, slice thickness: 13 mm) was used as previously described (9). The subject's head was positioned in the head holder, by means of a crossed laser beam system so that the lowest slice was 10 mm above the orbitomeatal plane. Special care was taken to ensure reproducible positioning in the repeated study. Before radioligand injection, a $^{68}$Ge–$^{68}$Ga transmission scan was done for the correction of attenuation. A dynamic series of 18 ("control" study) and 23 ("displacement" study) scans were acquired over 60 min, the acquisition time being progressively increased from 0.5 to 10 min. Images were automatically corrected for $^{11}$C decay.

Data Analysis

Regions of interest (ROIs) were placed on the tumoral area and the normal contralateral gray matter. We define the tumoral ROI as the area outlined by an isocountour set at 85% of the maximal pixel value in the image of the "control" study at level OM+25mm and at t=60 min. This level was selected because of the small amount of intratumoral necrosis found at neuropathologic examination. The same ROI was copied on the remaining

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FIGURE 1. Carbon-11-PK 11195 distribution in the brain of a patient with a glioblastoma. (the left side of the images corresponds to the right side of the brain). (Left) PET images (OM+25 mm) obtained 60 min after the injection of 11C-PK 11195 at high-specific activity ("control" study), showing relatively increased activity in the tumor. (Right) PET image at the same level obtained 50 min after the injection of the excess (20 mg; 0.3 mg/kg) of unlabeled PK 11195 ("displacement" study). The unlabeled PK 11195 was injected 10 min after the injection of trace amount of 11C-PK 11195. Compared to "control" (left), this image shows a large decrease of 11C-PK 11195 in the tumor. Note, however, the radioactivity in the tumor remained higher than in the normal brain tissue. The color scale is arbitrary with white corresponding to the higher radioactivity. Both images are normalized to the same maximum (2.2% ID/liter).

images of the “control” study and on the whole set of the “displacement” study images. The normal contralateral gray matter was defined on the early images (t=10 min) of each study at two different levels (OM+40 and OM+55 mm) as a hemispheric cortical ribbon (thickness 1.6 cm). The averaged normal gray matter radioactivity was calculated by combining the data from both levels. Regional brain radioactivity values were expressed as percentage of the injected dose per liter of tissue (% I.D./l) and plotted versus time. The tumor to contralateral gray matter radioactivity ratios were subsequently calculated in both “control” and “displacement” studies at different times. Finally, displacement indices were calculated after normalization of the time-activity curves of both “control” and “displacement” studies to a value of 100% at t=10 min (which is the time immediately before the injection of unlabeled PK 11195). These indices were defined as (C-D)/C × 100, where C is the averaged value of the regional radioactivity measured between 40 and 60 min during the “control” study and D is the regional radioactivity measured at the same time during the “displacement” study.

RESULTS

Control Study
Carbon-11-PK 11195 uptake was higher in the tumor than in the remaining brain (Figs. 1 and 2). In the tumor area, the maximal uptake of 11C-PK 11195 (2.46% ID/liter) was reached 10 min after the tracer injection (Fig. 2) and the radioactivity decreased slowly to 1.85% ID/liter at 60 min. In the normal gray matter area, the peak activity (1.16% ID/liter) was reached 7 min after the tracer injection, and was followed by a similar decrease. The tumor/normal gray matter ratio was 2.12 at 10 min and remained quite constant until the end of the study.

Displacement Study
The initial uptake of 11C-PK 11195 was similar to the “control” study. While the tumoral radioactivity was 2.42% ID/liter 10 min after the injection of 11C-PK 11195, it decreased to 1.32% ID/liter 50 min after the injection of 56700 nmol of unlabeled PK 11195. The displacement indices were 28% in the tumor and 6% in the normal gray matter. Tumor to normal gray matter ratios decreased from 2.16 before PK 11195 injection to 1.62 at 20 min after the injection of unlabeled drug, and remained roughly constant until the end of the study.

DISCUSSION
In the present study, 11C-PK 11195, injected at high SRA in a patient with glioblastoma, accumulated more in the tumor than in the normal cerebral cortex. We observed values close to 2 for the tumor to normal gray matter ratio in agreement with previous findings (8). In the previous report, the authors suggested that the retention of 11C-PK 11195 by the tumor represented 11C-PK 11195 specific binding to PTBS, since the tumor/normal gray matter
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REFERENCES


