Effect of barbiturate coma on glucose utilization in normal brain versus gliomas

Positron emission tomography studies

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Glucose utilization by normal and neoplastic cerebral tissue can be measured in humans using positron emission tomography (PET) with fluorine-18-labeled 2-deoxy-D-glucose (FDG). Malignant gliomas are known to exhibit hypermetabolic glucose consumption compared to normal brain. Barbiturate-sensitive cerebral glucose utilization is coupled to neuronal activity, and lesions lacking neuronal activity should be relatively insensitive to barbiturate suppression of glucose utilization. In a study to examine this phenomenon, three patients with cerebral gliomas underwent FDG-PET while awake and during deep barbiturate coma. Cerebral glucose utilization was measured in normal brain, tumor, and a homologous, non-neoplastic control site in the contralateral hemisphere. A glucose utilization ratio for tumor/control tissue was calculated.

The mean reduction of glucose utilization during barbiturate coma was: gray matter 67%, white matter 47%, basal ganglia 66%, thalamus 57%, cerebellar cortex 55%, tumor 32%, and the contralateral control site 64%. The mean tumor glucose utilization ratio was 1.48:1 in the awake state and 2.69:1 during barbiturate coma. The changes in gray matter, basal ganglia, thalamus, cerebellar cortex, and tumor/control tissue ratio were significant (p < 0.05). In one patient, deep tumor invasion not evident on computerized tomography, magnetic resonance imaging, or baseline FDG-PET was apparent during barbiturate-enhanced FDG-PET scanning.

The study findings suggest that gliomas resist suppression of glucose utilization by barbiturates; this supports the hypothesis that barbiturates reduce neuronal metabolism by blocking synaptic activity. This differential effect on normal brain and gliomas enhances the capability to assess the extent of neoplastic tissue in brain and may represent the basis for novel therapeutic strategies.

Key Words: brain neoplasm, glioma, positron emission tomography, barbiturate coma, diagnostic imaging, glucose utilization

Positron emission tomography (PET) with fluorine-18-labeled 2-deoxy-D-glucose (FDG) permits in vivo measurement of glucose utilization by normal cerebral tissue and by pathological tissue. The FDG-PET technique is an extension of the method of quantitative autoradiography that uses carbon-14-labeled 2-deoxy-D-glucose (2DG) as a measure of glucose uptake by tissue. Increased glucose uptake in malignant cerebral gliomas compared to normal brain parenchyma is well established. Additionally, the magnitude of glucose utilization by tumor correlates with the degree of malignancy and with the prognosis for survival. We determined the extent to which human cerebral glucose utilization is suppressed by barbiturates and tested the hypothesis that gliomas, which lack normal inhibitory controls of glucose metabolism, resist suppression of glucose utilization by barbiturates. The magnitude of barbiturate suppression of cerebral glucose consumption in normal and neoplastic parenchyma was determined using paired FDG-PET scans.
TABLE 1

Glucose utilization rate of normal brain while awake and during barbiturate coma*

<table>
<thead>
<tr>
<th>Case No.</th>
<th>White Matter</th>
<th>Gray Matter</th>
<th>Basal Ganglia</th>
<th>Thalamus</th>
<th>Cerebellum</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Awake</td>
<td>Coma</td>
<td>% Drop</td>
<td>Awake</td>
<td>Coma</td>
</tr>
<tr>
<td>1</td>
<td>2.4</td>
<td>2.1</td>
<td>12</td>
<td>6.3</td>
<td>2.4</td>
</tr>
<tr>
<td>2</td>
<td>2.1</td>
<td>0.8</td>
<td>62</td>
<td>7.7</td>
<td>2.7</td>
</tr>
<tr>
<td>3</td>
<td>5.0</td>
<td>1.6</td>
<td>68</td>
<td>8.8</td>
<td>2.2</td>
</tr>
</tbody>
</table>

* Glucose utilization rates are expressed as mg/100 gm/min.

Materials and Methods

Three patients with cerebral gliomas underwent FDG-PET while awake and during barbiturate coma. The patients were aged 28 to 32 years, and all participated in the study after informed consent was obtained as required by a National Institutes of Health Institutional Review Board (Protocol 85N 14). One to 7 days before surgery, each patient underwent baseline PET scanning 30 minutes after receiving a 5-mCi intravenous bolus of FDG. On the day of craniotomy for tumor removal, general anesthesia was induced with intravenous thiopental during continuous 16-lead electroencephalographic (EEG) monitoring. Thiopental was infused to maintain a prolonged burst-suppression EEG pattern throughout the experiment (52 to 53 mg/kg over 1.5 hours). The FDG was injected 15 minutes after obtaining a continuous burst-suppression EEG pattern. Three sets of PET scans were obtained beginning 30 minutes after the isotope infusion.

Glucose utilization in the cerebral gray matter was calculated by a region-of-interest analysis, and was expressed as the mean of frontal, parietal, temporal, and occipital cortex on the side opposite to the tumor. White matter activity was analyzed in the centrum semiovale contralateral to the tumor. The basal ganglia were measured in the caudate head and putamen contralateral to the tumor. Glucose utilization in the cerebellar cortex was measured bilaterally. The change in FDG utilization during barbiturate coma was calculated by comparing the control (awake) scan to the scan performed during anesthesia. In each scan, a glucose utilization ratio for the tumor was calculated by comparing glucose uptake in the tumor to that in the corresponding anatomic location (mirror site) in the contralateral hemisphere (tumor:mirror). Expressing tumor glycolytic activity as a glucose utilization ratio quantifies the degree to which glucose consumption by tumor exceeds background consumption by normal brain. Comparison of the glucose utilization ratio during barbiturate coma to that of the control study indicates the degree to which glucose utilization by the glioma was suppressed by barbiturates compared to levels in normal brain parenchyma.

Results

In all patients there was a marked reduction in glucose uptake in normal brain structures during barbiturate coma (Fig. 1, Table 1). The glucose utilization ratio of the tumor in all patients increased during barbiturate coma (Student's t-test, p < 0.05; Fig. 2, Table 2). Case 1 had a malignant astrocytoma in the posterior left temporal lobe, which had been treated previously with radiotherapy. The FDG-PET obtained while the patient was awake demonstrated reduced glucose utilization in the ipsilateral parietal and occipital cortex compared to the opposite hemisphere (Fig. 2). When metabolic activity of the brain was suppressed during barbiturate coma, the tumor was much better displayed. Examination of the excised tissue by light microscopy revealed a malignant astrocytoma with foci of radiation necrosis. Since the mirror-image site for calculation of the glucose utilization ratio in this patient was in the white matter, and the reduction in FDG uptake in normal white matter of this patient was only 12%, the increase of the FDG utilization ratio during barbiturate coma was less in this patient than in the other two.
TABLE 2

| Glucose utilization rate of tumors and normal brain (mirror site) while awake and during barbiturate coma* |
|---|---|---|---|---|---|
| Patient No. | Awake GU in Brain | GU in Tumor | Tumor GU Ratio | Thiopeptal Anesthesia GU in Brain | GU in Tumor | Tumor GU Ratio |
| 1 | 3.00 | 4.95 | 1.65 | 1.85 | 3.60 | 1.94 |
| 2 | 7.10 | 8.20 | 1.15 | 2.60 | 7.30 | 2.80 |
| 3 | 9.50 | 15.50 | 1.63 | 2.60 | 8.70 | 3.34 |

*GU = glucose utilization (mg/100 gm/min).

Case 2 had a cystic pilocytic astrocytoma in which the tumor nodule was anterior to a cyst in the left temporal lobe. During barbiturate coma there was little change in the uptake of FDG by the tumor, although the accumulation of FDG by the surrounding normal brain was greatly diminished.

Case 3 had a glioblastoma multiforme in the right frontal lobe. In the awake study the tumor was seen as a delimited area of increased FDG uptake in the right frontal area. During barbiturate coma the tumor appeared to be much more extensive than in the control study (Fig. 2). The region that resisted barbiturate suppression extended from the superficial portion of the right frontal lobe deep into the corpus callosum and into the right thalamus. This area of deep tumor invasion was not seen by other radiological studies, including contrast-enhanced computerized tomography (CT) and the awake FDG-PET scan. The presence of malignant glioma was confirmed during surgery by biopsy of the corpus callosum and the deep margin of the tumor.

Discussion

A significant fraction of glucose utilization in the brain is coupled to neuronal activity. Studies in animals indicate that barbiturates suppress cerebral glucose consumption, whereas glucose consumption by non-neuronal brain tissue resists barbiturate suppression. Frey and Agranoff compared 2DG uptake by the normal striatum of rat brain to the contralateral striatum in which the neurons had been destroyed by intracerebral ibotenic acid injection. In awake animals 2DG uptake in the gliotic striatum was less than that of the control side. However, during barbiturate anesthesia the normal striatum had markedly decreased 2DG uptake compared to the awake state, whereas the ibotenic acid lesions demonstrated little change in 2DG uptake.

Barbiturates suppress neuronal synaptic activity, but have less effect on basal metabolic activity required for preserving the structural integrity of tissue. Barbiturates suppress synaptic activity by augmenting and mimicking the action of gamma-aminobutyric acid to increase membrane conductance of chloride ions. In animals, barbiturates progressively reduce the rate of glucose uptake by brain until the EEG is isoelectric, when the normal glucose metabolism diminishes by about 50%. Additional administration of barbiturates does not further reduce metabolism. After an isoelectric EEG is obtained with barbiturate anesthesia, the cerebral glucose utilization can be further reduced by 40% to 50% with lidocaine, which inhibits sodium and potassium leakage, or with ouabain, which blocks sodium and potassium adenosine triphosphatase activity. This suggests that, under barbiturate anesthesia, about 50% of the residual metabolic activity is devoted to maintaining ionic balances against leakage gradients. The role of the remaining basal metabolic activity is not yet well understood. In our study of three patients, FDG uptake by gray matter was decreased by 62% to 75%
during barbiturate coma. Accumulation of FDG in the normal white matter dropped by 62% to 68% during barbiturate coma in two patients, which exceeded the decrease predicted from animal investigations. In the third patient (Case 1) the FDG uptake was decreased only by 12%.

In the present study, barbiturates caused increased uptake of FDG by the tumor compared to the uptake by normal cerebral tissue. The use of barbiturates to increase the relative uptake of cytotoxic analogues of glucose, or other cytotoxic substances that depend on metabolic activity for intracellular accumulation, in tumors versus normal tissues may contribute to the treatment of malignancies.

Two-deoxyglucose (2DG) uses the same facilitated transport system into the cell as glucose, where it undergoes phosphorylation to 2DG-6-phosphate as the first step of glycolysis.2 2DG-6-phosphate is a competitive antagonist of phosphohexoisomerase, the second step in glycolysis, and further metabolism of 2DG-6-phosphate proceeds slowly.27 Accumulated 2DG-6-phosphate blocks further glucose metabolism, which leads to depletion of high-energy phosphate compounds and loss of cell viability.7,19,29 Most tumors are primarily glycolytic (2 moles adenosine triphosphate (ATP)/1 mole glucose), while normal tissues utilize glucose more efficiently through respiration-dependent pathways. These metabolic differences have been exploited experimentally with glucose analogues, which effect a greater inhibition of glycolysis, increased rate of ATP depletion, reduced cell viability, and greater loss of plate adherence in tumors than in nontumorous tissue in vitro.37,60 The glucose analogues 2DG and 5-thio-D-glucose inhibit tumor growth and prolong survival in tumor-bearing experimental animals.5,12,18,26 They also have a synergistic inhibitory effect with ionizing radiation on tumor cell cultures and on tumor growth in experimental animals.15,16,25 Moreover, anesthetic doses of barbiturates may not be required for suppression of brain metabolism. In rats, the major portion of pentobarbital-induced suppression of cerebral glucose utilization can be achieved by 1/3 to 1/2 the normal anesthetic dose, and while the animals are only lightly sedated.8

Many current treatments of malignant brain tumors (such as focused external beam irradiation, interstitial radioactive tumor implants, and intra-arterial chemotherapy) are based on the assumption that tumor involvement is limited to, or near, the limits of the contrast-enhanced region on CT scanning. For pharmacological accentuation of the image produced by an area of abnormality, imaging techniques such as CT depend upon structural differences between normal and diseased tissues or disruption of the normal blood-brain barrier. Since FDG-PET imaging is based on metabolic rather than structural differences, a functional contrast-enhancement technique is achieved by the barbiturate-induced suppression of normal neuronal activity during FDG-PET. The true extent of invasion of adjacent brain by tumor may be apparent with this technique prior to changes in the blood-brain barrier, and when the distribution of involvement by tumor may be underestimated by routine FDG-PET scanning, as was demonstrated in Cases 2 and 3 (Fig. 2). This technique may also prove useful in the study of other diseases of the central nervous system, including degenerative disease, ischemia, infection, epilepsy, and aging.1 Sedative rather than anesthetic doses of barbiturates may be sufficient for image enhancement during PET scanning with FDG.

The findings of this study demonstrate that gliomas resist suppression of glucose utilization by barbiturates, and thus support the hypothesis that barbiturates reduce neural metabolism by blocking synaptic activity. This differential effect of barbiturates on normal brain tissue and gliomas enhances the capability to identify and localize the presence and distribution of the neoplastic tissue in brain. The differential effect may also represent the basis for novel therapeutic strategies.

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