Selective enhancement of intratumoral blood flow in malignant gliomas using intra-arterial adenosine triphosphate

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The effect of intravenous and intracarotid administration of adenosine triphosphate (ATP) on the regional blood flow of glioma patients has been examined by means of positron emission tomography. Intracarotid administration of ATP at a dose of 0.52 to 1.3 μg/kg/min selectively increased the blood flow in the tumor by 26.2% ± 10.5% (mean ± standard deviation). The side effects observed were tolerable. In contrast, intravenous administration of ATP failed to increase tumor blood flow. It is suggested that intracarotid administration of ATP may serve to selectively enhance the delivery of anticancer agents to malignant brain tumors.

KEY WORDS □ drug delivery □ adenosine triphosphate □ glioma □ regional blood flow □ positron emission tomography

To enhance the effect of chemotherapy on malignant brain tumors, several attempts to increase drug delivery to the tumor have been undertaken. Neuwell, et al., proposed osmotic opening of the blood-brain barrier (BBB) with anticancer agents to enhance drug delivery to malignant brain tumors. This method did not effectively open the BBB in the brain tumors of experimental animals, but it did involve the risk of delivering a greater amount of neurotoxic drugs into the normal brain tissue than without BBB opening.

Alternative methods for enhancing drug delivery to brain tumors with so-called “vasoactive” agents have recently been reported. Tomura, et al., conducted a clinical study using positron emission tomography (PET) and reported that a selective increase of intratumoral blood flow was obtained by inducing hypertension with angiotensin II. Panther, et al., reported that intravenous administration of adenosine selectively increased regional cerebral blood flow (rCBF) within experimental brain tumors.

We studied the effects of intravenous and intracarotid infusion of adenosine and adenosine triphosphate (ATP) in 20 glioma patients. After administration into the body, ATP is partially degraded to adenosine and has a similar vasodilating action on cerebral vessels. Prior to the clinical study, the rCBF of intracerebrally transplanted RG-C6 tumor in rats was examined using the hydrogen clearance method. Details of the animal experiment are given elsewhere and are not repeated here. The results showed that intravenous administration of both adenosine and ATP failed to increase tumor blood flow. However, intracarotid adenosine (1.4 μg/kg/min) or ATP (10 μg/kg/min) selectively increased blood flow in the tumor by a mean percentage of 23.9% and 51.5%, respectively, without producing a significant change in the rCBF of the extratumoral ipsilateral hemisphere or in normal brain. Based on these results, a clinical study using PET was designed to examine the effects of intracarotid and intravenous administration of ATP on the blood flow of tumor tissue in patients with malignant glioma. This investigation and its results are described here.

Clinical Material and Methods

This series included 20 patients with glioma. There were 14 men and six women, aged from 20 to 75 years. Contrast-enhanced computerized tomography (CT) was performed and the pathology of the tumor was confirmed by surgery in all cases. The tumors included four glioblastomas, six anaplastic astrocytomas, five astrocytomas, two oligodendrogliomas, one oligodendro-astrocytoma, one gliosarcoma, and one neurocytoma. A PET study was performed with the informed consent of the patient either before or after surgery in all cases. Postoperative PET was carried out when a considerable amount of tumor was left behind (Cases 7, 13, and 16). The postoperative study was usually...
performed 1 month after surgery but in one patient (Case 7) it was conducted on the 18th postoperative day. Four patients were examined twice (Cases 9, 15, 16, and 17).

Prior to PET, atropine sulfate (0.5 mg) and hydroxyzine pamoate (50 mg) were given intramuscularly. In Cases 8 and 12, betamethasone (8 mg) was administered intravenously 30 minutes before the PET study. For intracarotid administration of ATP in Cases 6 to 20, a catheter was introduced transfemorally into the internal carotid artery on the tumor side (on the dominant tumor side when tumor involvement was bilateral), using the Seldinger method.

Both the heart rate and arterial blood pressure were monitored throughout the PET examination. The PET device* had a spatial resolution of 8.2 mm FWHM (full width at half-maximum height). The rCBF was measured by $^{15}$O steady-state method using a continuous infusion of $H_2^{15}O$ at a speed of 4 mCi/min through a vein in the forearm. When a steady state was achieved on the radioactivity monitor for the head, five cross-sectional planes were scanned simultaneously for 6 minutes at 20, 35, 50, 65, and 80 mm above the orbitomeatal line. During each emission scan, samples of arterial blood were obtained every 2 minutes through the sheath of the catheter and their radioactivity was measured. Blood gas levels were also measured with a pH/blood gas analyzer.†

After the first PET study, the radioactivity was permitted to decay for 10 minutes. Thereafter, intravenous or intracarotid ATP was administered by continuous infusion. Intravenous ATP was given to five patients (Cases 1 to 5) at a dose of 29 to 51 µg/kg/min (about 10 to 20 mg in total). For the intracarotid administration, ATP (30 µg/kg/min) was given to the first patient treated (Case 20), but the patient suffered a severe pulsating headache on the side of the ATP injection. For the remaining patients (Cases 6 to 19), intracarotid ATP was given at a dose of 0.52 to 1.3 µg/kg/min (about 0.4 to 0.8 mg in total). About 2 to 5 minutes after the start of ATP administration, a second PET study was begun in the same manner as before.

Regions of interest were selected, including the tumor, a plane representing the extratumoral ipsilateral hemisphere (on the dominant tumor side when tumor involvement was bilateral), and a cross section of the contralateral hemisphere. The percent change of rCBF was calculated and statistically analyzed using the unpaired Student t-test. A probability of 0.05 or less was considered significant.

**Results**

Before administration of ATP in the 20 patients studied, the mean arterial blood pressure (MABP) ranged from 72 to 95 mm Hg, the heart rate from 55 to 88 beats/min, and the PaCO$_2$ from 33.5 to 52.7 mm Hg. Neither intracarotid nor intravenous administration of ATP at the doses used produced any significant change in the blood pressure (preinfusion pressure 84.9 ± 9.1 mm Hg, postinfusion pressure 86.0 ± 8.9 mm Hg) or heart rate (preinfusion rate 75.7 ± 12.3 beats/min, postinfusion rate 82.1 ± 16.8 beats/min). Severe hemicranial headache occurred in the first patient treated with intracarotid ATP infusion (Case 20) to whom an ATP dose similar to the intravenous dose was given. Hyperventilation followed, and the PaCO$_2$ decreased from 38.5 to 28.9 mm Hg. The PaCO$_2$ in the other patients did not change from baseline values (preinfusion pressure 41.3 ± 4.7 mm Hg, postinfusion pressure 43.9 ± 3.9 mm Hg).

The regional blood flow in the tumor ranged from 10.8 to 111 ml/100 gm/min (32.9 ± 24.8 ml/100 gm/min; mean ± standard deviation). The rCBF for extratumoral ipsilateral hemisphere ranged from 14.0 to 50.7 ml/100 gm/min (29.9 ± 9.0 ml/100 gm/min), and the rCBF for contralateral hemisphere ranged from 19.0 to 50.2 ml/100 gm/min (32.1 ± 6.8 ml/100 gm/min).

**Intravenous ATP**

Intravenous administration of ATP in five patients did not produce a significant change in blood flow. The mean change in blood flow was -2.2% ± 17.4% in the tumor, +2.8% ± 14.9% in the extratumoral ipsilateral hemisphere, and +2.6% ± 14.2% in the contralateral hemisphere (Table 1).

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* Headtome III PET machine manufactured by Shimadzu Corp., Akita Noken, Japan.
† Blood gas analyzer manufactured by Corning Glass Works, Corning, New York.
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**TABLE 1**

Values and percent changes in blood flow during intravenous ATP delivery*

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Intravenous ATP (µg/kg/min)</th>
<th>Regional Blood Flow in Tumor</th>
<th>rCBF Ipsilateral Hemisphere</th>
<th>rCBF Contralateral Hemisphere</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>48</td>
<td>38.7 (+22%)</td>
<td>21.9 (+32%)</td>
<td>29.0 (+30%)</td>
</tr>
<tr>
<td>2</td>
<td>41</td>
<td>15.0 (+4%)</td>
<td>24.1 (−1%)</td>
<td>27.9 (0%)</td>
</tr>
<tr>
<td>3</td>
<td>29</td>
<td>10.8 (−2%)</td>
<td>27.7 (−2%)</td>
<td>29.3 (0%)</td>
</tr>
<tr>
<td>4</td>
<td>42</td>
<td>111.0 (−32%)</td>
<td>41.8 (−8%)</td>
<td>50.2 (−9%)</td>
</tr>
<tr>
<td>5</td>
<td>51</td>
<td>99.9 (−3%)</td>
<td>39.8 (−7%)</td>
<td>38.9 (−8%)</td>
</tr>
<tr>
<td>mean</td>
<td></td>
<td>55.1 ± 42.4</td>
<td>31.1 ± 8.2</td>
<td>35.1 ± 8.5</td>
</tr>
<tr>
<td>mean % change</td>
<td></td>
<td>−2.2% ± 17.4%</td>
<td>+2.8% ± 14.9%</td>
<td>+2.6% ± 14.2%</td>
</tr>
</tbody>
</table>

*Regional blood flow (ml/100 gm/min) in the tumor, extratumoral ipsilateral hemisphere, and contralateral hemisphere, and the percent change of those values (% within parenthesis) during intravenous administration of adenosine triphosphate (ATP). rCBF = regional cerebral blood flow. Means are given ± standard deviation.

Intra-Arterial ATP

In Case 20, intracarotid ATP was given at a dose of 30 µg/kg/min, but the infusion was stopped after 2 minutes because the patient complained of severe headache. The second PET scan started just after the cessation of ATP infusion. Because of hyperventilation, the PaCO2 decreased from 38.5 to 28.9 mm Hg, and the percent change of regional blood flow in the tumor was only +7%. In the 14 other patients studied, intracarotid ATP at a dose between 0.52 and 1.3 µg/kg/min produced a significant increase in rCBF in the tumor (+26.2% ± 10.5%; range +7% to +49%) (Fig. 1). In two patients (Cases 8 and 12) to whom betamethasone was given prior to PET, the percent changes of rCBF in the tumor were only +12% and +7%, respectively.

In the extratumoral ipsilateral areas supplied by the anterior cerebral artery (ACA), middle cerebral artery (MCA), and posterior cerebral artery (PCA), the mean percent change of rCBF during intracarotid administration of ATP at a dose between 0.52 and 1.3 µg/kg/min was +11.8% ± 10.3%, +10.6% ± 9.9%, and +5.2% ± 10.4%, respectively (Fig. 1). In the areas adjacent to the tumor, the percent change of rCBF ranged from +4% to +24%. In Case 7, examined on the 18th postoperative day, intracarotid ATP increased the rCBF in the extratumoral ipsilateral areas supplied by the ACA and MCA (+23% and +34%, respectively).

Intracarotid administration of ATP at a dose between 0.52 and 1.3 µg/kg/min did not produce any significant percent change of rCBF in the areas supplied by the contralateral ACA, MCA, and PCA (mean +3.5% ± 9.0%, +1.4% ± 8.8%, and +0.7% ± 10.3%, respectively; Fig. 1). The percent change of the regional blood flow in the tumor was significantly higher than the rCBF of the extratumoral ipsilateral areas supplied by the ACA, MCA, and PCA (unpaired t-test, p < 0.001), and also significantly higher than that of the areas in the contralateral hemisphere (unpaired t-test, p < 0.001) (Fig. 1).

Outcome of Studies

Side effects related to the examination included skin eruption in Case 8, mild headache in Case 10, generalized convulsions after examination in Case 14, and severe headache and hyperventilation in Case 20. These complications were all transient.

Contrast-enhanced CT scans and PET scans before and during intracarotid ATP administration are shown in Fig. 2 for Case 6 and Fig. 3 for Case 17.

Discussion

In the clinical study presented here, intracarotid administration of ATP selectively increased blood flow in malignant gliomas, but intravenous ATP administration did not. These results were consistent with those of previous animal experiments. The mechanism of this phenomenon is difficult to explain, but the following observations might be suggestive.

In two cases (Cases 8 and 12), betamethasone was given before the PET examination and the percent change of the tumoral blood flow was relatively small in both cases. This result might indicate that a selective increase in the blood flow of the tumor induced with ATP is possibly related to disruption of the BBB in the tumor tissue. It is known that ATP does not penetrate the BBB of normal brain tissue and that adrenocortical steroids protect the BBB in tumor tissue.

In Case 7, examined on the 18th postoperative day, the rCBF of the extratumoral ipsilateral areas supplied by the ACA and MCA increased 23% and 34%, respectively. In the ipsilateral hemisphere, intracarotid administration of ATP increased not only the regional blood flow in the tumor, but also the rCBF in extratumoral areas adjacent to the tumor, although to a smaller degree. This phenomenon may be favorable for the...
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FIG. 2. Case 6. Recurrent astrocytoma in the right frontal lobe. *Left:* Contrast-enhanced computerized tomography scan showing an enhanced tumor. *Right:* Positron emission tomography scans before and during intracarotid administration of adenosine triphosphate (ATP) at a dose of 0.91 µg/kg/ml. Regional blood flow in the tumor increased 44% during ATP administration (arrows).

FIG. 3. Case 17. Recurrent astrocytoma in the corpus callosum with extension to the left frontoparietal lobe. *Left:* Contrast-enhanced computerized tomography scan showing an enhanced tumor. *Right:* Positron emission tomography scans before and during intracarotid administration of adenosine triphosphate (ATP) at a dose of 0.89 µg/kg/min. Regional blood flow in the tumor increased 33% during ATP administration (arrows).

Concomitant chemotherapy of malignant gliomas, because increased drug delivery to the peritumoral tissue is considered necessary for improving the results of chemotherapy.

In Case 20, hypocapnia due to hyperventilation occurred during ATP infusion. In this case, the percent change of the regional blood flow in the tumor was +7%, while the percent changes of rCBF in the extratumoral ipsilateral hemisphere and the contralateral hemisphere were −2% to +2% and −12% to −14%, respectively. Although the rCBF in the contralateral hemisphere decreased in response to hypocapnia, the regional blood flow in the tumor increased. The effect of ATP was probably negligible in the second PET study, which was performed immediately after the cessation of ATP, because ATP is rapidly broken down in the body. Therefore, this result may indicate that the tumor vessels are less responsive to the PaCO₂. This view is shared by Panther, et al., who reported that tumor vessels in rats with experimental brain tumors
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were less responsive to hypercapnia. The difference in the responsiveness of vessels between the tumor and normal brain might be related to the selective enhancement of the blood flow in malignant gliomas. However, this mechanism is still unclear at present.

Intracarotid ATP administration at a dose between 0.52 and 1.3 μg/kg/min produced an average, selective 26.1% increase in the tumoral blood flow and the side effects were tolerable. As the delivery of lipid-soluble anticancer agents, such as nitrosourea, to brain tumors has been reported to depend on regional blood flow to the tumor, intracarotid administration of ATP might be a useful adjunct for malignant glioma chemotherapy.

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References


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