Glucose Analogs as Potential Diagnostic Tracers for Brain Tumors

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SUMMARY

No tumor-specific tracer has yet been found for the detection of brain tumors by external scintiscanning. Glucose is a substrate in high demand by almost all tumors, and therefore an investigation was undertaken into the potential value of glucose and its analogs as tracers for brain tumors. The compounds studied were D-[l-3H]glucose, D-[l-14C]glucose, [3H]-O-methyl-D-glucose and L-[l-14C]glucose. The tracers were injected i.v. into C57BL/6J mice carrying a transplantable s.c. ependymoblastoma. At specific time intervals after injection, mice were sacrificed and the radioactivity of 6 tissues including tumor and brain were assayed by means of an automated combustion technique and liquid scintillation counting.

Tumor uptake, expressed as percentage mean body concentration, was 60% for 2 of the tracers, and 92 and 143%, respectively, for 2 others. Brain uptake was over 130% mean body concentration, with 3 of the 4 tracers studied. With L-glucose, brain uptake was only 15.4% mean body concentration, and a maximum tumor-to-brain ratio of 9.5 was achieved. The very high tumor uptake achieved with two of these carbohydrates demonstrates that a carbohydrate analog may be found that shows high tumor specificity and uptake, and that may be useful for external scintiscanning.

INTRODUCTION

All diagnostic tracers in clinical use for γ encephalography depend upon exclusion from normal brain by an intact blood brain barrier for their success in localizing brain tumors. These agents are not specific for tumors and are successful in locating cerebral infarcts, abscesses, diffuse inflammatory diseases, and hematomas (20). There is no diagnostic tracer available at present that enters brain tumors in high concentration such as might occur if the tracer were essential for tumor growth or energy production. Glucose is required by tumors in large amounts for energy and growth. Therefore, the study of glucose analogs as potential diagnostic tracers might be fruitful. This is the first systematic study of labeled carbohydrates as potential diagnostic tracers for brain tumors. The initial phase of this study is an examination of the uptake and distribution of D-[l-3H]glucose, D-[l-14C]glucose, [3H]-O-methyl-D-glucose and L-[l-14C]glucose in mice bearing a transplanted ependymoblastoma.

MATERIALS AND METHODS

Animals. C57BL/6J female mice, 4 to 6 weeks of age weighing 16 to 18 g were obtained from The Jackson Laboratory, Bar Harbor, Maine.

Tumors. A mouse ependymoblastoma was used that has been maintained in our laboratory for the past 9 years by serial s.c. transplantation of tumor fragments every 2 weeks into the lower abdominal wall. The tumor was originally induced by Zimmerman and Arnold (27) in mouse brain with intracerebrally implanted methylcholanthrene.

Tracers. D-[l-3H]Glucose and D-[l-14C]glucose were obtained from New England Nuclear, Boston, Mass. The former was supplied at a specific activity of 3.46 Ci/mM and the latter at 0.055 Ci/mM. [3H]-O-Methyl-D-glucose was obtained from International Chemical and Nuclear Corp., Irvine, Calif., at a specific activity of 2.47 Ci/mM; and L-[l-14C]glucose was obtained from Amersham/Searle Corp., Arlington, Heights, Ill. at a specific activity of 0.003 Ci/mM.

Tritiated materials were prepared by first evacuating off the solvents in which they were shipped and then dissolving the residue in 0.90% NaCl solution so that a concentration of 100 μC/m was obtained. Each mouse received 1 μCi in 0.01 ml solution i.v. per g body weight. D-[l-14C]Glucose and L-[l-14C]glucose were similarly prepared, except that the injected solution contained 50 μCi/mM, and each mouse received 0.5 μC/m in 0.01 ml solution i.v. per g body weight.

Experimental Protocol. Mice bearing 14- to 18-day-old s.c. tumors were prepared for study by depriving them of food but not water for 4 hr prior to the administration of the tracers so that blood glucose values would tend to be uniform in all mice. After i.v. administration of each of the above-mentioned compounds to separate groups, the mice were sacrificed at selected time intervals, from 2 min to 24 hr. At each time interval, at least 6 animals were studied. Mice receiving D-[l-3H]glucose or [3H]-O-methyl-D-glucose were anesthetized with diethyl ether and then killed by exsanguination. Blood samples were obtained by cardiac puncture. Mice receiving D-[l-14C]glucose or L-[l-14C]glucose were sacrificed by decapitation, and terminal

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arterial blood was collected. With all 4 tracers, samples of brain, s.c. tumor, muscle, blood, liver, and kidney were taken for radio-isotopic assay. D-[1-3H]Glucose uptake was studied at 2 min, 10 min, 30 min, 1 hr, and 2 hr after injection, whereas D-[1-14C]glucose and [3H]3-O-methyl-D-glucose were studied at 2 min, 10 min, 30 min, 1 hr, 2 hr, and 24 hr. L-[1-14C]Glucose was studied at 2 min, 10 min, and 2 hr.

**Sample Preparation.** Tritium containing tissue samples ranging in weight from 50 to 200 mg were placed in ashless filter-paper baskets made from 2.1 cm in diameter Whatman No. 541 filter-paper circles. The baskets were in preweighed vials which were then reweighed. The samples were kept in the vials until just before combustion, at which time they were removed from the vials, rolled in a 9.0-cm circle Whatman No. 42 ashless filter paper and compressed into pellets (Parr Instrument Co., Moline, Ill.) to ensure maximum recovery and uniformity of burning. At the time of sacrifice, blood samples were placed directly on filter-paper pellets in preweighed vials which were then reweighed. The 14C-containing tissue samples were prepared in a similar fashion except that only one-half of a 9-cm circle of filter paper was used for pelletization because 1 circle weighs about 650 mg and the oxidizer’s CO2-trapping column can only accommodate dry weight specimens up to 500 mg. To prevent tissue from being squeezed out of this much smaller piece of filter paper during pelletization, the tissue and basket were dipped in liquid nitrogen, rapidly rolled in filter paper, and pelletized.

**Sample Combustion and Counting.** The samples were oxidized in a Packard-Kinaarten Model 305 sample oxidizer (14). Tritiated water was collected in a vial of scintillation fluid made up of naphthalene, 100.0 g; PPO, 5.0 g; dimethyl POPOP, 0.3 g; dioxane, 720 ml; toluene, 135 ml; and absolute methanol, 45 ml. This cocktail gave a counting efficiency of 24 to 28%. The 14C as 14CO2 was collected in a solution of ethanolamine, methanol, and scintillation fluid in the proportion of 5:9:5, with the scintillation fluid containing PPO, 15 g; p-bis-(O-methyl-tyryl)benzene, 1 g, and toluene, 1 liter. The counting efficiency of this solution was 26 to 31%.

The recovery efficiency of the automated combustion technique was determined at regular intervals. A standard solution was made by putting 20 μCi of 3H tracer or 10 μCi of 14C tracer in 100 ml of water from which 0.1 ml aliquots were pipetted into each of 3 vials filled with scintillation fluid and onto each of 5 filter-paper pellets. The filter-paper pellets were then oxidized and the radioactive products were collected in the usual manner. The radioactivity recovered in the oxidized pellets was then compared with that placed directly in the scintillation fluid, and the recovery was found to be about 92 to 96% for both 3H and 14C. There was a carryover of radioactivity from one oxidized sample to the next of approximately 2%. To prevent this, a blank filter-paper pellet was oxidized between each radioactive tissue sample. The 3H or 14C standard solutions were counted together with the tissue samples at 4° in a Nuclear-Chicago Unilux I I liquid scintillation counter, using the channels ratio method. A minimum of 10,000 counts were recorded for each sample.

**Calculations.** The radioactivity in the tissues is expressed as the percentage mean body concentration, this value is a ratio of the dps/g tissue to the dps injected per g animal.

\[
\text{dps/g tissue} \times 100 = \% \text{ mean body concentration} \\
\text{dps injected/g animal}
\]

Expressed this way, the percentage mean body concentration of a radiochemical that is uniformly distributed and not excreted is 100% in all tissues. To determine the dps injected per g animal, an aliquot of injected tracer was placed on filter-paper pellets, combusted, and counted. All calculations were done on a Sigma-5 computer by the Medical Computing Department, Medical Sciences Building, University of Toronto.

**RESULTS**

Chart 1 shows the distribution of radioactivity in the various tissues of mice after injection of D-[1-3H]glucose. The initial activity of tumor was low at 73 ± 14% mean body concentration but, over the next 8 min, this value doubled to 143 ± 12% mean body concentration. Brain radioactivity started off high at 163 ± 25% mean body concentration and dropped only slightly over the next 28 min. Liver and kidney started off very high at 249 ± 29 and 171 ± 13% mean body concentration, respectively. After 10 min, the uptake values in all tissues converged towards 100% mean body concentration.

D-[1-14C]Glucose distribution is outlined in Chart 2. Although radioactivity in the tumor was low initially, the concentration almost doubled by 30 min (Chart 2). Thirty min after injection, the uptake values in all tissues began to decline. Except for brain at 10 min, the percentage mean body concentration values for all tissues were considerably less for D-[1-14C]glucose than for D-[1-3H]glucose.

The distribution of [3H]3-O-methyl-D-glucose is pre-

![Diagram](chart1.png)

Chart 1. The distribution of the 3H label at various time intervals following i.v. administration of D-[1-3H]glucose is shown. Each point is an average of 6 tissues. The molecular structure is depicted in the left-hand corner. This is a log-log plot with the uptake in percentage mean body concentration of 3H in the tissues along the ordinate and the time in hr along the abscissa.
Uptake of Glucose and Its Analogs in Ependymoblastoma

Chart 2. The distribution of the 14C label in tissues at various time intervals following i.v. administration of D-[1-14C]glucose is depicted. Each point is an average of 6 tissues. The molecular structure is shown in the left-hand corner of the graph. This is a log-log plot with the uptake in percentage mean body concentration of 14C in the tissues along the ordinate and the time in hr along the abscissa.

sented in Chart 3. At 2 min, the tumor value was 48 ± 12% mean body concentration, and at 10 min it had reached its maximum, 92 ± 20%. By 1 hr it had fallen to 49.4 ± 4.7% mean body concentration. Brain started off at its maximum value of 138 ± 12% mean body concentration, declined gradually over the next 8 min, and then dropped off steeply. Kidney, liver, muscle, and blood were at their maximum values at the initial assay time. Ten min after injection, all tissues showed a very steep decline in radioactivity and, by 24 hr, less than 2% mean body concentration remained in each tissue.

L-[1-14C]Glucose (Chart 4) has a unique distribution pattern, compared to the previous 3 tracers. Brain reached a maximum of only 15.4 ± 4.3% mean body concentration at 2 min, and rapidly declined to 3.1 ± 0.6% mean body concentration by 2 hr. Tumor showed only a small increment in uptake from 2 min to 10 min, compared with the increases seen in tumor with the tritiated tracers. Kidney uptake with L-[1-14C]glucose reached 780 ± 220% mean body concentration, and this was the highest uptake recorded with all 4 tracers. Ten min following injection, the uptake values in all tissues began to decline rapidly.

With 2 of the 4 tracers studied, there was a very significant (p < 0.05) rise in tumor radioactivity during the 1st 10 min after injection, but with the other 2 tracers, tumor radioactivity remained almost constant during that time. This is shown in Charts 1 to 4 and in Table 1, where it is seen that with D-[1-3H]glucose and [3H]3-O-methyl-D-glucose, tumor radioactivity rose steeply during the 1st 10 min, but with D-[1-14C]glucose and L-[1-14C]glucose, tumor radioactivity was near its maximum at 2 min, and did not show a steep accumulation during the 10 min. In contrast to tumor, with all 4 tracers all the other tissues were at or near their maximum values at 2 min (Charts 1 to 4).

The initial brain uptake values were very high, with D-[1-3H]glucose, D-[1-14C]glucose, and [3H]3-O-methyl-D-glucose ranging from 109 to 163% mean body concentration (Table 2). However, with L-[1-14C]glucose, brain uptake at 2 min was very low at 15.4 ± 3.4% mean body concentration.

L-[1-14C]Glucose and [3H]3-O-methyl-D-glucose both showed a very rapid decline in all the tissues studied after the 10-min interval. In both cases, kidney showed by far the highest uptake values as compared with the other tissues (Charts 3 and 4).

DISCUSSION

The detection of brain tumors by external scintiscanning has become one of the most valuable diagnostic tests in clinical neurology and neurosurgery. However, there are definite shortcomings to the test. For example, only 80% of
Table 1

Tumor uptake percentage of mean body concentration

Uptake of radioactivity in mouse ependymoblastoma 2, 10, and 30 min after i.v. administration of tracers. Each value is the mean of 6 mice. D-[1-14C]glucose and [3H]3-O-methyl-D-glucose show a significant (p < 0.05) increase in tumor uptake during the 1st 10 min.

<table>
<thead>
<tr>
<th>Tracer</th>
<th>2 min</th>
<th>10 min</th>
<th>30 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-[1-1H]Glucose</td>
<td>73 ± 14*</td>
<td>143 ± 12</td>
<td>120 ± 7.2</td>
</tr>
<tr>
<td>D-[1-14C]Glucose</td>
<td>38 ± 19</td>
<td>51 ± 24</td>
<td>60 ± 28</td>
</tr>
<tr>
<td>[3H]-3-O-Methyl-d-glucose</td>
<td>48 ± 12</td>
<td>92 ± 20</td>
<td>58.6 ± 8.4</td>
</tr>
<tr>
<td>L-[1-14C]Glucose</td>
<td>63 ± 26</td>
<td>70 ± 18</td>
<td></td>
</tr>
</tbody>
</table>

* Mean ± S.E.

Table 2

Summary of maximum uptake values and ratios in tumor and brain

Maximum uptake values in tumor and brain, and maximum tumor-to-brain and brain-to-tumor ratios after i.v. administration of tracers to mice bearing the s.c. ependymoblastoma. Each value represents the mean of 6 mice.

<table>
<thead>
<tr>
<th>Maximum tumor uptake</th>
<th>Maximum brain uptake</th>
<th>Maximum tumor-to-brain ratio</th>
<th>Maximum brain-to-tumor ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>% MBC *</td>
<td>Time (min)</td>
<td>% MBC</td>
<td>Time (min)</td>
</tr>
<tr>
<td>D-[1-1H]Glucose</td>
<td>143 ± 12*</td>
<td>163 ± 25</td>
<td>2.06</td>
</tr>
<tr>
<td>D-[1-14C]Glucose</td>
<td>60 ± 28</td>
<td>148 ± 15</td>
<td>0.62</td>
</tr>
<tr>
<td>[3H]-3-O-Methyl-d-glucose</td>
<td>92 ± 20</td>
<td>138 ± 12</td>
<td>2.1</td>
</tr>
<tr>
<td>L-[1-14C]Glucose</td>
<td>70 ± 18</td>
<td>15.4 ± 3.4</td>
<td>9.5</td>
</tr>
<tr>
<td>[99mTc]Pertechnetate (14)</td>
<td>83.8 ± 10</td>
<td>8.1</td>
<td>15.2</td>
</tr>
</tbody>
</table>

* MBC, mean body concentration.
* Mean ± S.E.

brain tumors are detected (13, 20), and certain tumors, including benign gliomas and those lying inferiorly in the cranium, are especially difficult to detect. During the last decade, new tracers and equipment have come into use, but the overall detection rate for brain tumors has not improved. Detection rates would be greatly enhanced if tumor-specific tracers were found. All tracers now in use for brain tumor detection are nonspecific and depend mainly upon an intact blood-brain barrier for the differences in lesion-to-brain uptake. Ideally, the tracer should have an extremely high tumor-to-brain concentration ratio, and the absolute concentration in tumors should also be very high. The concentration of the tracer in blood, bone, and muscle should be low, since elevated activity levels in these "background" tissues interfere with the detection of tumors in areas covered by muscle, and in those areas lying near large venous channels.

In the past there have been attempts to find tumor-specific tracers by using labeled substances required by tumors as substrates for tumor metabolism (22, 23), but there have been no previous attempts to use labeled carbohydrates as diagnostic tracers for tumors. Over 50 years ago, Warburg (24) observed that tumors had a high rate of aerobic and anaerobic glycolysis. He went on to suggest that the central lesion in cancer was an irreversible injury to the cells' respiratory mechanism. The discovery that tumor cells could utilize oxygen and that they contained a full complement of respiratory enzymes (1) quickly dispelled this belief. However, it has been shown repeatedly that tumors do have a high glucose uptake (11, 17). Thus, it was felt that glucose analogs might be avidly accumulated by neoplastic cells. It was also considered possible that a glucose analog might be found which would show tumor specificity. For example, Weinhouse (25) recently reported that the high rates of aerobic glucose metabolism in experimental hepatomas were due to a change in their glycolytic isoenzyme patterns, and similar changes have been confirmed in human hepatomas (2). For these reasons it was felt that an analog of glucose might be tumor specific.

It is recognized that brain also has a high glucose demand (6, 11), but it is postulated that a glucose analog avidly accumulated by brain tumors might be sufficiently different from glucose that the analog would be impeded from entering normal brain by the blood-brain barrier. For example, studies of the transport of D- and L-tyrosine in brain demonstrate the feasibility of such a scheme. L-Tyrosine is rapidly accumulated by brain in the intact animal, but D-tyrosine does not enter brain to any significant degree (4, 19). However, during in vitro incubation, where the effect of the blood brain barrier is eliminated, both D- and L-tyrosine are actively accumulated in the brain slices to the same degree (12). By analogy we hope to find a carbohydrate analog that is excluded from brain by the blood-brain barrier but is actively accumulated by tumor. Such an analog might yield a high tumor-to-brain ratio and produce a conventional type of brain scan in which tumor appeared...
as a radioactive focus on a “cold” background of brain.

Another possible advantage of a glucose analog as a tracer for brain tumor detection is that the analog might be rapidly metabolized. This would produce a high rate of blood clearance, and consequently the “background” tissues including the dural venous sinuses, temporalis muscles, and scalp would have lower levels of radioactivity. It is acknowledged that, in this investigation, only 3H and 14C-labeled analogs have been used, and that an analog showing an ideal tissue distribution would subsequently have to be tagged with a γ-emitting isotope of suitable energy and half-life to be of clinical value.

The initial uptake of D-[1-3H]glucose and D-[1-14C]glucose by brain was more than twice that taken up by tumor (Charts 1 and 2). However, with D-[1-3H]glucose, the uptake in tumor doubled to 143% mean body concentration during the first 10 min. Although certain conventional brain tumor diagnostic tracers show an accumulation in tumor with time, none of them increases its uptake as quickly or reaches as high a value as that seen here with D-[1-3H]glucose (16). D-[1-14C]glucose did not show the same degree of accumulation in tumor, probably due to the difference in metabolic fate of the 2 labels. For example, D-[1-14C]glucose and D-[1-3H]glucose metabolic studies in ependymal fat pad slices indicate that, after 3 hr, 62% of 3H is recoverable as tritiated water and 37% of 14C is recoverable in CO2 (15). Tritiated water resulting from the metabolism of D-[1-3H]glucose would be retained in the tumors because of their large water content (10) and because the biological half-life of water in the body is about 10 days (21). In contrast, the half-lives of 14CO2 and 14C-lactate, the principal metabolic products of D-[1-14C]glucose metabolism (3), are short, and therefore these radioactive products would not be retained in the tumors. Hence the level of radioactivity found in the tissues of mice given D-[1-14C]glucose is less than that found with D-[1-3H]glucose.

The [3H]3-O-methyl-D-glucose molecule provides a method for studying glucose distribution and uptake, with glucose metabolism eliminated. [3H]3-O-Methyl-D-glucose competes with glucose for transport into the cell (5, 18), but it is not metabolized and is excreted unchanged in the urine (7, 8). Chart 3 shows that its early distribution pattern in tumor-bearing mice was almost the same as that of D-[1-14C]glucose (Chart 2), except for brain. With [3H]3-O-methyl-D-glucose, brain at 2 min was 18% mean body concentration, which then declined to 97.6 at 10 min whereas, with D-[1-14C]glucose, brain was 109% mean body concentration at 2 min, which then increased to 148% mean body concentration at 10 min. This difference is explained by the accumulation of the products of D-[1-14C]glucose metabolism as compared with the rapid removal of the nonmetabolized [3H]3-O-methyl-D-glucose molecule. Kidney also showed an early high accumulation with [3H]3-O-methyl-D-glucose which reflects the route of excretion. Tumor slowly accumulated [3H]3-O-methyl-D-glucose over the first 10 min, in contrast to the other 5 tissues, which had their maximum uptake value at 2 min. After the 10 min-time interval, [3H]3-O-methyl-D-glucose is rapidly lost from all tissues except muscle. The [3H]3-O-methyl-D-glucose content of muscle drops off slowly over the first 2 hr but, from 2 to 24 hr, is lost from muscle at the same rate as that seen in other tissues.

L-[1-14C]Glucose was handled in an entirely different fashion than the other sugars presented here. Very little entered the brain, which had a value of 15.4% mean body concentration at 2 min, and then showed a rapid decline to 3.1% mean body concentration over the next 2 hr (Chart 4). Tumor uptake was also low, starting off at 63% mean body concentration and declining to 29.2% mean body concentration at 2 hr. The probable route of L-glucose excretion was renal, in view of the high amounts of radioactivity found in this organ at 2 and 10 min.

D-[1-3H]Glucose, D-[1-14C]glucose, and [3H]3-O-methyl-D-glucose accumulated in tumor during the early time intervals. This may be explained on the basis of the vascularity of the tumor, since this experimental ependymoblastoma, and indeed most transplantable tumors, have been shown to be poorly vascularized (9, 17, 26). The delayed uptake may be due to slow diffusion of the tracer into poorly vascularized areas of the tumor via the interstitial fluid. However, L-[1-14C]glucose did not show this rapid rise during the early time intervals and, therefore, slow diffusion into poorly vascularized areas may not account for the initial rise seen with the other 3 tracers. An alternate explanation for the differences observed between the 3 “D” configuration tracers and the “L” tracer may be on the basis of membrane transport of the D tracers into the tumor cells while the L configuration tracer remained extracellular.

Glucose analogs were chosen as potential tracers because it was felt that they might be highly accumulated by brain tumors, yield high tumor-to-brain ratios, and low uptake in background tissues. However, only the 1st goal has been achieved with the molecules described here. High concentrations of radioactivity in the tumor were obtained, and in some instances these were higher than have been obtained in the same tumor system with tracers such as 99mTc pertechnetate which is the tracer most commonly used clinically for brain tumor detection. This is shown by comparing the uptake values obtained with 99mTc pertechnetate in the mouse ependymoblastoma in a previous study in our laboratory (14) with those obtained here (Table 2).

Unfortunately, high tumor-to-brain ratios were not achieved in the present study, the highest obtained being 9.5 with L-[1-14C]glucose (Table 2). This substance is not metabolized by normal mammalian tissue, and presumably the same is true for mammalian neoplasms. Furthermore, the tumor-to-brain ratio of 9.5 is due mainly to its exclusion from the brain and not to high accumulation by the tumor (Table 2). This ratio is still considerably lower than the tumor-to-brain ratio found with 99mTc pertechnetate (Table 2). Although L-glucose accumulation in tumor is too low for isotopic encephalography, some features of its distribution in background tissues are favorable for brain tumor detection. For example, at 2 hr with 99mTc pertechnetate, the tumor-to-muscle ratio was 4, but with L-glucose this ratio was 7. At the same time interval with 99mTc pertechnetate, the tumor-to-blood ratio was 0.5 and with L-glucose it was 1. These higher ratios would be helpful for localizing tumors situated inferiorly in the cranium.
[\textsuperscript{3}H]-3-O-methyl-D-glucose was so high in normal brain and that these molecules gave higher percentage mean body concentrations in brain than in the tumor. The maxima in brain were reached within the 1st 2 to 10 min after injection (Table 2). The maximum brain-to-tumor ratio was 2.9, which is insufficient for clinical use.

The results of this preliminary investigation have been encouraging, and other glucose analogs are under investigation as potential tracers for isotopic encephalography.

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REFERENCES


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