Noninvasive determination of local cerebral metabolic rate of glucose in man

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HFANG, SUNG-CHENG, MICHAEL E. PHELPS, EDWARD J. HOFFMAN, KLEAR SIDERIS, CARL J. SELIN, AND DAVID E. KUHL. Noninvasive determination of local cerebral metabolic rate of glucose in man. Am. J. Physiol. 238 (Endocrinol. Metab. 1): E39-E82, 1980.-A method for the determination of local cerebral metabolic rates of glucose (LCMRGlc) in normal man is described. The method employs $[^{18}F]$fluoro-2-deoxy-D-glucose (FDG) and emission-computed tomography (ECT). FDG was injected intravenously as a bolus. Radioactivities in separate brain regions were measured with ECT. Plasma FDG concentration following injection was measured from blood samples. A mathematical model that describes the kinetics of FDG transports was employed to determine the transport rate constants of FDG and to convert the radioactivity measurements to metabolic rates. The model has taken into account the possible dephosphorylation reaction from FDG-6-PO$_4$ to free FDG in brain tissues. Experiments were performed in 13 normal volunteers. The rate constants of FDG in man were found to be comparable to those of deoxyglucose in rat and in rhesus monkey. The average LCMRGlc in gray and white matter were found to be 7.30 ± 1.18 (SD) and 3.41 ± 0.64 mg/min per 100 g brain tissue, respectively. The subject-to-subject variation of LCMRGlc as measured by the present method was comparable to those of other methods that measure whole-brain CMRGlc.

physiologic tomography; gray matter; white matter; compartmental model; deoxyglucose; transport rate constants; error sensitivity; extraction fraction; gamma emitter

WITH THE RECENT DEVELOPMENT OF emission-computed tomography (ECT), in vivo quantification of local tissue radioactivity becomes feasible (19, 21). This capability of ECT, when coupled with appropriate labeled pharmaceuticals and mathematical models, provides a practical methodology that can give quantitative information on local physiological processes that were previously unattainable. This methodology will be referred to as physiologic tomography (PT) (22).

In PT, the ECT scanner must be well characterized with respect to its resolution, linearity, noise level, and the effects of variations in object size. The labeled pharmaceuticals must trace physiological processes in a known and predictable manner. The mathematical model must be able to adequately describe the labeled tracer’s behavior in tissue under both normal and pathological conditions, and it must be compatible with the data measured by ECT. These requirements on labeled tracers and on mathematical models are very similar to those for quantitative autoradiography, which is an in vitro analogue of PT for measuring regional physiology (39).

In autoradiography, $[^{14}C]$deoxyglucose (DG), an analogue of glucose has been successfully used to measure the regional utilization of glucose in brain of rat (33) and monkey (14). DG has the unique property of mimicking glucose in its transport across the blood-brain barrier (1, 4, 11, 18) and in the phosphorylation reaction catalyzed by hexokinase (2, 34). However, the phosphorylated DG is not a substrate for further metabolic reactions (3, 11, 34): the permeability of cell membranes to the phosphorylated DG is low (36), and the reverse reaction of dephosphorylation is very slow (4, 7). In other words, DG follows glucose at the beginning of its metabolism, but stops and accumulates in tissue in the form of deoxyglucose-6-PO$_4$ (DG-6-P). Sokoloff et al. (33) have developed a compartmental model to mathematically describe the behavior of DG in brain tissue. Applying their model to autoradiographic measurements, Sokoloff et al. (33) and Kennedy et al. (14) were able to calculate quantitatively the local cerebral metabolic rate of glucose (LCMRGlc) in rate and monkeys. One essential requirement of the mathematical model employed by Sokoloff et al. is the complete trapping of DG-6-P in tissue. Their model assumes DG crosses the blood-brain barrier bidirectionally, but once it is converted to DG-6-P, it is assumed to remain in tissue during the entire period of the measurement. Recently, it was discovered by Sokoloff (personal communication) and Hawkins and Miller (9) that the hydrolysis from DG-6-P, although slow, may not be negligible for long experiments.

The technique employed by Sokoloff et al. for LCMRGlc measurements approximated the plasma concentration of DG in capillaries by the arterial plasma concentration of DG. Phelps et al. (20, 24) have shown in man that venous plasma concentrations from a hand heated in a hot water bath give equivalent results with a noninvasive procedure.

Because $[^{14}C]$-labeled DG is not a gamma-emitting tracer, it cannot be measured externally with emission-computed tomography. In 1977, Ido et al. (13) developed a method to synthesize $[^{18}F]$fluoro-2-deoxy-D-glucose (FDG). FDG, also an analogue of glucose, has chemical and physiological properties very similar to those of DG (2, 7, 29). In addition, because $[^{18}F]$ is a gamma emitter, FDG is suitable for ECT measurements. Reivich et al.
(29), Phelps et al. (20), and Kuhl et al. (15) have used FDG with ECT and Sokoloff et al.'s model to provide in vivo measurements of LCMRGlc in man. In these studies, the calculation of metabolic rate was based on the model parameters originally determined for DG in brain tissues of rats.

Global CMRGlc in rhesus monkeys has also been measured with another method by Raichle et al. (26). [14C]glucose was used as the tracer, and collimated scintillation probes were used for radioactivity detection. The conversion to metabolic rate was based on a model that required continuous measurement of the time course of the total radioactivity in tissue. Although the technique has been modified for ECT measurements (27), the relatively short retention time of the [14C]glucose in tissue poses some potential difficulties for ECT. From the modeling point of view, it is a more difficult and potentially less accurate method of measuring LCMRGlc.

In this paper, a method of measuring LCMRGlc is presented that utilizes the characteristics of FDG as a glucose analogue and the unique three-dimensional imaging capability of ECT. Complete trapping of FDG in tissue is not assumed in the present method since we have modified Sokoloff et al.'s model to include the reversed reaction of hydrolysis of FDG-6-P to FDG. The basic assumptions of the model are first discussed, and the equations for the calculation of metabolic rates as well as model parameters are presented. The sensitivity of the calculated metabolic rate to errors in the model parameters is evaluated. The results of this evaluation allow experiments to be designed to minimize the errors due to uncertainties in the model parameters.

Experiments with FDG and ECT were performed on 13 normal human volunteers to estimate the model parameters and to verify the present method for LCMRGlc measurements in man. Normal values of the model parameters are first obtained from the experimental measurements, and LCMRGlc for both gray and white matter are calculated for the volunteer subjects according to the model. The calculated values of LCMRGlc are found to be very stable and reproducible.

MATHEMATICAL MODEL

The compartmental model used to describe the kinetics of FDG in brain tissue is illustrated in Fig. 1. It consists of three compartments, viz., FDG in plasma, FDG in tissue, and FDG-6-P in tissue. The concentrations of FDG or FDG-6-P in the three compartments are C^p, C^e, and C^m, respectively, as shown in Fig. 1. The glucose or glucose-6-P concentrations in the three compartments are C_p, C_e, and C_m. The asterisk is used to denote quantities of FDG or FDG-6-P, and the symbols without the asterisk denote the quantities of natural substrates.

The boundary between the plasma compartment and the tissue's FDG compartment represents the blood-brain barrier for the transport of FDG. The boundary between the compartments of tissue's FDG and tissue's FDG-6-P is not a physical barrier. It represents the enzyme catalyzed chemical reactions between FDG and FDG-6-P. The enzyme for the forward reaction is hexokinase. At present, the enzyme for the reverse reaction is not exactly known. Glucose-6-phosphatase, which is known to be present in brain tissue (25), although in small amounts, is a possibility. The present model is an extension of Sokoloff et al.'s model (33) by including expressions for the reverse reaction of hydrolysis from FDG-6-P to FDG in tissue. The ability of this model for the measurement of LCMRGlc is based on the characteristics of FDG that it resembles glucose at the beginning reactions of glucose metabolism. Once the difference in terms of transport kinetics between FDG and glucose is known, LCMRGlc can be estimated from the more easily measured kinetics of FDG.

All the basic assumptions of Sokoloff et al.'s model (33), except the complete trapping of FDG-6-P, are required for the present model. The essential assumptions are:

1) Glucose metabolism in tissue is in a steady state. The metabolic rate of glucose and concentrations of all the substrates and intermediates of the glycolytic pathway are constant during time of study.
2) Concentrations of glucose, FDG, and FDG-6-P are homogeneous in the compartments.
3) Concentrations of FDG and FDG-6-P are small relative to their natural counterparts so that the presence of FDG and FDG-6-P does not affect the steady-state environment of glucose metabolism.
4) The transports of FDG and FDG-6-P between compartments have first-order kinetics.
5) Tissue extraction fraction of glucose and FDG from plasma is small. In other words, the transports of glucose and FDG to local brain tissue is not flow limited.

The first three assumptions are fundamental to the application of tracer methods and compartmental analysis.
since the total amount of 18F activity in a local region is related to the rate constants of FDG as first-order reaction if DG or FDG is present in trace amounts. The hydrolysis of FDG-6-P is very likely to be an enzyme catalyzed reaction with FDG-6-P and G-6-P as competitive substrates. The reaction would be very similar to the phosphorylation of FDG, and thus the same reasoning for approximating the phosphorylation of FDG as a first-order reaction is also applicable to the kinetics of the hydrolysis of FDG-6-P. The fifth assumption is made to reduce the complexity of the model allowing the capillary plasma concentration of glucose and FDG to be approximated by the plasma concentrations in arteries or in hand veins. The conditions under which the fifth assumption is valid have been discussed by Sokoloff et al. (33) and by Phelps et al. (20, 24).

For the model shown in Fig. 1, various concentrations in tissue can be solved (see APPENDIX) in terms of the plasma concentration of FDG to be

\[
C^\prime_g(t) = \frac{k^*_g}{\alpha_2 - \alpha_1} (k^*_g - \alpha_1) e^{-\alpha_1 t} + (\alpha_2 - k^*_g) e^{-\alpha_2 t} \otimes C^*_p(t)
\]

\[
C^\prime_m(t) = \frac{k^*_g k^*_s}{\alpha_2 - \alpha_1} (e^{-\alpha_1 t} - e^{-\alpha_2 t}) \otimes C^*_p(t)
\]

\[
C^\prime_s(t) = \frac{k^*_s}{\alpha_2 - \alpha_1} \left[ (k^*_s + k^*_g - \alpha_1) e^{-\alpha_1 t} + (\alpha_2 - k^*_g - k^*_s) e^{-\alpha_2 t}\right] \otimes C^*_p(t)
\]

where \(C^\prime_g(t)\) is the total 18F activity in tissue, \(\otimes\) denotes the operation of convolution, and

\[
\alpha_1 = (k^*_g + k^*_s + k^*_g) - \sqrt{(k^*_g + k^*_s + k^*_g)^2 - 4 k^*_g k^*_s}\]

\[
\alpha_2 = (k^*_g + k^*_s + k^*_g) + \sqrt{(k^*_g + k^*_s + k^*_g)^2 - 4 k^*_g k^*_s}\]

Since the total amount of 18F activity in a local region (\(C^\prime_L\)) can be measured with ECT, and the plasma concentration of FDG (\(C^*_p\)) can be obtained from arterial or venous blood samples, the values of the rate constants (\(k^*_s\)) of FDG can be estimated according to Eq. 3. As shown in the APPENDIX, the metabolic rate of glucose in a local region is related to the rate constants of FDG as

\[
R_i = \frac{1}{(LC) k^*_g + k^*_s} C^*_p
\]

where \(LC\) denotes the lumped constant of Eq. A26 and it has the same form as the lumped constant used by Sokoloff et al. (33). The value of \(LC\) accounts for the differences in transport and phosphorylation of FDG and glucose and has been discussed by Sokoloff et al. (33) to be uniform within a whole brain and insensitive to the physiological state of the brain tissue. Thus, as shown in the APPENDIX, the value of the lumped constant can be determined in advance by the following formula

\[
LC = \frac{C^*_p \left( k^*_g k^*_s \right)}{k^*_g + k^*_s}
\]

where \(R\) is the average metabolic rate of the whole brain, and \(k^*_g k^*_s / (k^*_g + k^*_s)\) is the average value of the factor over the whole brain. With the value of \((LC)\) determined, Eq. 6 in combination with Eq. 3 can be used to calculate LCMRgic. The disadvantage of Eq. 6 for the calculation of metabolic rate is that it requires repeated measurements of the total 18F activity in tissue at different times to estimate the time course of \(C^*_g\) up to some sufficiently long time \(T\) (60 min) to determine the values of the rate constants \(k^*_s\). This disadvantage can be removed by changing the form of the equation to the following (see APPENDIX)

\[
C^*_p(C^\prime_g(t)) = \frac{k^*_g}{\alpha_2 - \alpha_1}
\]

\[
R_i = \frac{\left[ (k^*_g - \alpha_1) e^{-\alpha_1 t} + (\alpha_2 - k^*_g) e^{-\alpha_2 t}\right] \otimes C^*_p(t)}{\alpha_2 - \alpha_1}
\]

Note that if \(k^*_g\) is equal to zero, Eq. 8 is reduced to the operational equation used by Sokoloff et al. (33). Although Eq. 8 still needs the values of the \(k^*_s\)'s, it is expected that, with the directly measured value of \(C^*_g(t)\) in the formula, the accuracy requirements on the \(k^*_s\)'s values will be less demanding. In other words, it is expected that the metabolic rate calculated by Eq. 8 is not very sensitive to small errors in the \(k^*_s\)'s. To evaluate this sensitivity, the effects on the calculated metabolic rate due to errors in the values of the \(k^*_s\)'s are investigated. The sensitivity equations are shown in the APPENDIX from A32 to A41. By accepting a predictable error range for the calculated metabolic rate, a set of average values of the \(k^*_s\)'s can be used in Eqs 8, thus eliminating the need for repeated measurement of the 18F activity in tissue over a long time period for each study.

Equation 8 is the primary equation for the calculation of metabolic rates in this paper. It only requires 1) the measurement of the total 18F activity in local regions of tissue at some appropriate time after the FDG injection, 2) the plasma concentration of glucose, and 3) the plasma FDG concentration from the time of FDG injection to the time of ECT measurements.

METHODS

Preparation of FDG. FDG was prepared by the method developed by Ido et al. (13) as modified by Robinson et al. (30). The chemical purity of FDG was determined by liquid chromatography to be greater than 95%. The specific activity is about 10–20 mCi per mg of FDG.

Human studies. Studies were carried out on 13 normal volunteers. For each volunteer, a bolus of FDG in the amount of 5–10 mCi (about 0.5 mg) was injected intravenously. In nine volunteers, blood samples were taken from the vein of a hand which was heated to 44°C by a temperature-regulated hot water bath. Heating was used to arterialize the venous blood, thereby permitting arterial blood samples to be obtained less invasively (20, 24).
In four volunteers, arterial catheters were placed in the brachial arteries under local anesthesia for blood sampling. No special dietary instructions were given to the volunteers before the studies, and all studies were carried out under approval of the UCLA human use committee.

**Measurement of plasma FDG and glucose concentrations.** Concurrent to the injection of FDG, 2- to 3-ml samples of arterial or venous blood were taken at 15-s intervals for the first 2 min, with sampling intervals gradually increased with time. Samples were immediately placed on ice, and plasma was subsequently separated for the determination of FDG and glucose concentrations. Plasma glucose concentrations were determined by standard enzymatic techniques in duplicates. Plasma FDG concentrations were determined by counting a known volume of the samples in a precalibrated well counter. Precisions of better than 2% were obtained by these measurement techniques (24).

**Measurement of total $^{18}$F activity in tissue.** $^{18}$F activities in regional brain tissues were measured with ECAT (ORTEC, Inc., Oak Ridge, TN) (21), which is a positron-emission tomography scanner originally designed by Phelps and Hoffman. The medium resolution mode with full width at half maximum (FWHM) equal to 1.4 cm was used for scanning. After the injection of FDG, a preselected slice of the brain was scanned repeatedly for 3–12 h. In the early times after FDG injection, 5-min scans were normally used. Later, 10- and 20-min scans were employed when the rate of change of $^{18}$F activity in tissue was slower and the $^{18}$F activity was reduced due to its radioactive decay. Normally, a total of 14–30 scans was obtained in each study.

After scanning, images corresponding to the $^{18}$F distributions in the selected slice of the brain at various times were reconstructed. Activity suppressions due to the higher attenuation coefficients in skull were also compensated (12). The region of interest (ROI) programs of ECAT were used to calculate $^{18}$F activities in different local regions of the scanned slice. Four to five gray matter regions (2–3 cm$^2$ each) were normally selected and their activities averaged to represent the $^{18}$F activity in gray matter. The region selection procedure was repeated to obtain the $^{18}$F activity in white matter.

The calibration between the $^{18}$F measurements by ECAT and by the well counter were performed for each study by scanning a cylinder of uniform $^{18}$F concentration. A known volume of $^{18}$F solution from the cylinder was also counted in the well counter. The two measurements (one from ECAT and the other from well counter) of the same $^{18}$F concentration thus established a calibration between the two instruments (24).

**Estimation of rate constants of FDG.** The estimation of the rate constants of FDG in gray and white matter was based on Eq. 3, which related the $^{18}$F activities in tissue to that in plasma. For a set of rate constants values, the tissue $^{18}$F activity as a function of time could be predicted from the time course of the plasma FDG concentration. The measured values of the tissue $^{18}$F as a function of time in gray and white matter (as obtained according to the procedure described above) were fitted by a least-squares criterion with the predicted curve by iteratively adjusting the values of the rate constants. The least-squares fitting was performed in a PDP-11/55 computer. The iterative fitting algorithm used was the magnified diagonal method (32). The rate constants estimated from all volunteer subjects were then averaged to give two sets of average values for the rate constants, one set for gray matter and one set for white matter.

**Determination of lumped constant.** The determination of the lumped constant was based on Eq. 7. For each subject, the values of the factor $k_1k_2/(k_2^* + k_3^*)$ for gray and white matter were calculated from the rate constants of the subject as described above. The values for gray and white matter were then averaged (with 50% weight to each) to give an estimate of the average value of $k_1k_2/(k_2^* + k_3^*)$ over the whole brain. The average metabolic rate of glucose over the whole brain of each subject could be calculated independently from the cerebral blood flow and the arterial-venous difference of glucose concentrations across the brain. However, the procedure to obtain these measurements is very invasive. In this paper, a first-order estimate of $R$ was sought from the literature for cerebral metabolic rate of glucose in man. A weighted average (weighted by the inverse of the variance) of the values from five sources in the literature (6, 8, 17, 31, 35) gives $R = 5.36$ mg·min$^{-1}$·100 g$^{-1}$ ($SD = \pm 0.77$).

The plasma glucose concentration was determined from blood samples as described earlier. Therefore, according to Eq. 7, the estimated value of the lumped constant could be calculated for each volunteer subject. The average of these estimates from all studies was taken as the value of the lumped constant for FDG in human brain.

**Calculation of LCMRGlc.** LCMRGlc of gray and white matter of the subjects were calculated according to either Eq. 6 or Eq. 8 When Eq. 6 was employed, the rate constants for the region of interest were first estimated according to the least-squares fitting procedure described earlier in this section. When calculated with Eq. 8 the average values of the rate constants were used. Depending on whether the region was in the gray matter or in the white matter, the corresponding set of average values was chosen in the calculation.

**Estimation of error sensitivity of LCMRGlc to rate constants.** The possible errors in the calculated metabolic rates due to the usage of a common set of rate constants in Eq. 8 were estimated according to the sensitivity equations (Eqs. A33-A41). The error range due to each of the four rate constants was first evaluated, and the overall effects was calculated as the square root of the sum of squares of each error term. The correct values of the rate constants were assumed to be in the neighborhood of the average values, with standard deviations equal to the values observed among the 13 studies in this paper. The procedure was repeated for measurements at various times after FDG injection.

**RESULTS**

**Rate constants and lumped constant.** Table 1 shows the values of the rate constants for FDG in gray and in white matter of 13 volunteer subjects. The estimated values of the lumped constant from these subjects are also shown. In four studies, the scanned slices were near
TABLE 1. Rate constants of FDG transports in cerebral tissues of normal human subjects

|                | Subj | k_1 | k_2 | k_3 | k_4 | k_5 | k_6 | Rate Constants
<table>
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</thead>
<tbody>
<tr>
<td>Gray Matter</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>k_1, k_2, k_3,</td>
<td>RS</td>
<td>0.120</td>
<td>0.107</td>
<td>0.044</td>
<td>0.065</td>
<td>0.0348</td>
<td>0.074</td>
<td>0.103</td>
</tr>
<tr>
<td>k_4, k_5, k_6,</td>
<td>PB</td>
<td>0.072</td>
<td>0.087</td>
<td>0.096</td>
<td>0.029</td>
<td>0.067</td>
<td>0.044</td>
<td>0.048</td>
</tr>
<tr>
<td>White Matter</td>
<td>LS</td>
<td>0.123</td>
<td>0.074</td>
<td>0.029</td>
<td>0.0074</td>
<td>0.0346</td>
<td>0.044</td>
<td>0.048</td>
</tr>
<tr>
<td></td>
<td>DM</td>
<td>0.086</td>
<td>0.167</td>
<td>0.086</td>
<td>0.0073</td>
<td>0.0293</td>
<td>0.044</td>
<td>0.048</td>
</tr>
<tr>
<td></td>
<td>TM</td>
<td>0.081</td>
<td>0.089</td>
<td>0.074</td>
<td>0.0073</td>
<td>0.0416</td>
<td>0.044</td>
<td>0.048</td>
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<tr>
<td></td>
<td>GB</td>
<td>0.143</td>
<td>0.184</td>
<td>0.068</td>
<td>0.0082</td>
<td>0.0386</td>
<td>0.047</td>
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<tr>
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<td>DV</td>
<td>0.093</td>
<td>0.099</td>
<td>0.074</td>
<td>0.0069</td>
<td>0.0389</td>
<td>0.046</td>
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<tr>
<td></td>
<td>DO</td>
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<td>0.0347</td>
<td>0.060</td>
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<tr>
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<td>RP</td>
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<td>0.169</td>
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<td>0.0042</td>
<td>0.0250</td>
<td>0.060</td>
<td>0.123</td>
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<tr>
<td></td>
<td>DE</td>
<td>0.109</td>
<td>0.125</td>
<td>0.067</td>
<td>0.0070</td>
<td>0.0382</td>
<td>0.054</td>
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<td></td>
<td>SD 1</td>
<td>0.061</td>
<td>0.058</td>
<td>0.047</td>
<td>0.0079</td>
<td>0.0273</td>
<td>0.042</td>
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<td>SD 2</td>
<td>0.143</td>
<td>0.273</td>
<td>0.096</td>
<td>0.0058</td>
<td>0.0371</td>
<td>0.060</td>
<td>0.164</td>
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<td>TV</td>
<td>0.138</td>
<td>0.207</td>
<td>0.052</td>
<td>0.0048</td>
<td>0.0277</td>
<td>0.072</td>
<td>0.164</td>
</tr>
<tr>
<td></td>
<td>Avg</td>
<td>0.102</td>
<td>0.130</td>
<td>0.062</td>
<td>0.0068</td>
<td>0.0334</td>
<td>0.054</td>
<td>0.109</td>
</tr>
<tr>
<td></td>
<td>±SD</td>
<td>±0.028</td>
<td>±0.066</td>
<td>±0.019</td>
<td>±0.0014</td>
<td>±0.0058</td>
<td>±0.014</td>
<td>±0.044</td>
</tr>
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</table>

Injection, the plasma FDG concentration decreases to about 10-20% of the peak value, depending on the sharpness of the peak, which in turn is dependent on the bolus size and the injection speed. At 3 and 10 h, the FDG concentration decreases to about 50% and 20% of value at 1 h.

FIG. 2. Typical plasma FDG curve following bolus injection intravenously. The curve can be described as sum of 5 exponential components as shown. Times in the exponentials are in minutes. If only early part of curve (3 h) is considered, it can also be adequately represented with 4 exponential components. Depending on bolus size and injection speed, peak of curve is about 5-10 times the curve value at 1 h. FDG concentrations at 3 and 10 h after injection are, respectively, 50% and 20% of value at 1 h.

FIG. 3. Distribution of FDG in cross section (OM + 8 cm) of normal human brain at various times following intravenous injection of FDG bolus. Distributions were measured and reconstructed with ECAT. At early times, distribution reflects both LCMRGlc and cerebral blood flow (CBF), with effects of CBF gradually diminishing with time. After 20 min, distribution becomes stable. Photographic gray scales in these distributions of different times are not normalized to a common reference. Although relative distribution in brain remains stable, absolute amount of FDG does change slowly as shown in Fig. 4. Distributions shown are selected from a total of 14-30 distributions obtained for each study.
concentrations are, respectively, about 50% and 20% of the 1-h value. As shown in Fig. 2, a plasma FDG curve 10 h long can be represented very well by a sum of five exponential components. For the part up to 3 h, four exponentials are quite sufficient to describe the curve.

The $^{18}$F distributions in a cross-sectional slice (8 cm above the orbital meatus) of the brain at various times after FDG injection are shown in Fig. 3. Figure 4A shows the time course of the $^{18}$F activity in a gray matter region of a typical study. The lower curves represent the amount of FDG-6-P and free FDG in tissue as estimated from the plasma FDG curve according to Eqs. 1 and 2. Figure 4B shows the corresponding curves for white matter. Figure 4C shows the clearance rate of total $^{18}$F from the whole brain slice in the interval between 7 and 12 h after FDG injection. The clearance has a half time of 9.6 h during this period.

LCMRGlc in normal brain tissue. Figure 5 shows the calculated LCMRGlc (with Eq. 8) in gray and in white matter at different measurement times after the injection of FDG. Values from four studies are plotted in the figure to show the subject-to-subject variations of the calculated LCMRGlc in both gray and white matter. The figure also shows the stability of the calculated LCMRGlc from 30 to 210 min. The larger variations at the earlier times are due to the high sensitivity of Eq. 8 at these times to the differences between the correct values and the average values of the rate constants. The LCMRGlc for gray and white matter in all the subjects are listed in Table 2. Values in columns 2 and 4 were calculated with

**FIG. 4.** Local $^{18}$F activities (-----), FDG-6-P (-----), and free FDG (-----) in brain tissues following FDG injection. A: gray matter. B: white matter. C: whole brain slice. $^{18}$F activity on vertical axes of A and B is in arbitrary units. Local $^{18}$F activities were measured by ECAT; activities due to free FDG were generated, according to Eq. 1, from plasma FDG curve and with average rate constants. Activities of FDG-6-P were obtained as difference between total $^{18}$F and free FDG activities.
A41.\[\text{Eq. 8 (with average values for the rate constants) at a}\]
in columns I and 3 were from the same regions but were
between gray matter and white matter was found to be
ures 6A shows the time function of the error sensitivity
ation (SD) of error is within 11%. For white matter, the
error sensitivity is similar in characteristics. The SD of
of the calculated LCMRGlc in gray matter to each of the
rate constants appearing in Eq. 8.

The rate constants are estimated by least-squares curve fitting. Reasonable convergence is usually
achieved within 20 iterations. In three of the studies, we
experience slow convergence, depending on the initial
values employed in the fitting. However, the value of the factor \(k^* k_2^* / (k_2^* + k_3^*)\) was found to be very insensitive
to the exact fitting results. In other words, the value of the factor \(k^* k_2^* / (k_2^* + k_3^*)\) converges very fast and is
independent of the initial values chosen for the curve
fitting. Thus, the LCMRGlc calculated according to Eq.
6 is insensitive to the exact fitting results.

The rate constants for DG in rat's brain have been
estimated by Sokoloff et al. (33). The values of \((k_1^* + k_2^*)\)
for DG in awake monkeys were reported by Kennedy et
al. (14). These values were according to a model very
similar to the one used in this paper. Table 3 shows a
comparison of their values with the average values
obtained in the present study. Despite the differences in
species and in the chemical compounds, there are some
similarities among these three sets of values. In general,
the values of \(k_1^*\) and \(k_2^*\) for FDG in man are smaller than
those of DG in rat. The values of \(k_3^*\) are very similar. The
values of \(k_1^*\) of the present results are not equal to zero.
Due to the presence of the \(k_2^*\)-mediated reaction, the
turnover rate of FDG in tissue has two components \((\alpha_1\text{ and } \alpha_3\text{ of Eqs. 1, 2, and 3}).\text{ For small values of } k_1^*, \text{ the fast}\)
component \((\alpha_3)\text{ is approximately equal to } (k_2^* + k_3^*),\text{ which corresponds to the turnover rate of tissue DG in}\)
Sokoloff et al.'s model (33). The slow component is the
apparent clearance rate of FDG-6-P from brain tissue if
plasma concentration of FDG is zero. Both the fast and
the slow components of FDG turnover rates in gray and
white matter of human brain are listed in Table 3 as a
comparison with those of DG in rats and in monkeys.

**TABLE 2. Cerebral metabolic rates of glucose in gray and white matter of normal human subjects**

<table>
<thead>
<tr>
<th>Subj</th>
<th>CMRGlc in Gray Matter, mg·min⁻¹·100 g⁻¹</th>
<th>CMRGlc in White Matter, mg·min⁻¹·100 g⁻¹</th>
<th>Ratio of CMRGlc's for Gray and White Matter</th>
</tr>
</thead>
<tbody>
<tr>
<td>With Eq. 6</td>
<td>With Eq. 8</td>
<td>With Eq. 6</td>
<td>With Eq. 8</td>
</tr>
<tr>
<td>RS</td>
<td>7.66</td>
<td>8.07</td>
<td>3.57</td>
</tr>
<tr>
<td>PB</td>
<td>5.91</td>
<td>6.06</td>
<td>2.56</td>
</tr>
<tr>
<td>LS</td>
<td>7.30</td>
<td>6.60</td>
<td>2.71</td>
</tr>
<tr>
<td>DM</td>
<td>7.85</td>
<td>8.53</td>
<td></td>
</tr>
<tr>
<td>TM</td>
<td>8.06</td>
<td>8.96</td>
<td></td>
</tr>
<tr>
<td>GB</td>
<td>9.12</td>
<td>9.94</td>
<td>3.39</td>
</tr>
<tr>
<td>DV</td>
<td>8.00</td>
<td>7.57</td>
<td></td>
</tr>
<tr>
<td>DO</td>
<td>7.14</td>
<td>8.08</td>
<td>4.51</td>
</tr>
<tr>
<td>RP</td>
<td>4.84</td>
<td>4.83</td>
<td></td>
</tr>
<tr>
<td>DE</td>
<td>8.32</td>
<td>8.05</td>
<td>4.09</td>
</tr>
<tr>
<td>SD 1</td>
<td>5.76</td>
<td>5.28</td>
<td>2.96</td>
</tr>
<tr>
<td>SD 2</td>
<td>7.90</td>
<td>7.61</td>
<td>3.73</td>
</tr>
<tr>
<td>TV</td>
<td>7.09</td>
<td>7.00</td>
<td>3.17</td>
</tr>
<tr>
<td>Avg</td>
<td>7.30</td>
<td>7.35</td>
<td>3.41</td>
</tr>
<tr>
<td>±SD</td>
<td>±1.18</td>
<td>±1.33</td>
<td>±0.64</td>
</tr>
</tbody>
</table>

Eq. 8 (with average values for the rate constants) at a
measurement time of 80 min after FDG injection. Values in
columns 1 and 3 were from the same regions but were
calculated according to Eq. 6. The ratio of LCMRGlc
between gray matter and white matter was found to be about 2.2 for the normal subjects studied.

**Fig. 5.** LCMRGlc in gray and white matter as determined from
ECAT measurements at various times after FDG injection. Equation
8 was used in calculation. Calculated LCMRGlc are seen to be stable
after 30 min. Larger variations at early times are due to high sensitivity
of model equation at those times to errors in rate constants. Results of
4 studies plotted also show range of variations among normal subjects studied.
The values of the fast component are seen to be in the same order of magnitude as those of DG in rats and in monkeys. The values of the slower component correspond to a half time of about 3 h. Sokoloff et al. (33) reported that the clearance of DG-6-\textit{P} from rat's brain has a half time of 7-9 h at 24 h after the injection. Sokoloff et al. (33) assumed plasma and tissue concentrations of DG to be negligibly low at these late times. The results obtained in the present study show that, at 12 h after the injection, the plasma FDG concentration is still about 20\% of its concentration at 1 h, suggesting that the plasma concentration of DG in Sokoloff et al.'s experiments might still be at a significant level at 24 h after injection. Therefore, the difference between our value of 3 h and the 7-9 h reported by Sokoloff et al. (33) probably results from the residual activity in the plasma that was assumed to be negligible by Sokoloff et al. In fact, as shown in Fig. 4C, the present result of 9.6 h half time for the clearance of the total $^{18}$F activity in a brain section at 9-12 h after the injection is quite comparable with the values reported by Sokoloff et al. (33).

The constancy of the lumped constant has been discussed extensively by Sokoloff et al. (33). The composition of the lumped constant that appears in the model of
TABLE 3. Comparison of rate constants for DG and FDG in brain tissue

<table>
<thead>
<tr>
<th></th>
<th>DG in Rat Brain*</th>
<th>DG in Monkey Brain†</th>
<th>FDG in Human Brain‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gray Matter</td>
<td>White Matter</td>
<td>Gray Matter</td>
</tr>
<tr>
<td>$k_i^*$</td>
<td>0.189</td>
<td>0.079</td>
<td>0.102</td>
</tr>
<tr>
<td>$k_2^*$</td>
<td>0.245</td>
<td>0.133</td>
<td>0.130</td>
</tr>
<tr>
<td>$k_3^*$</td>
<td>0.051</td>
<td>0.020</td>
<td>0.062</td>
</tr>
<tr>
<td>$k_i^* + k_2^*$</td>
<td>0.297</td>
<td>0.153</td>
<td>0.347</td>
</tr>
<tr>
<td>$\alpha_1$</td>
<td>0.0046</td>
<td>0.0041</td>
<td>0.0046</td>
</tr>
<tr>
<td>LC</td>
<td>0.483</td>
<td>0.344</td>
<td>0.418</td>
</tr>
</tbody>
</table>

* Sokoloff et al. (33). † Kennedy et al. (14). ‡ This work.

This paper is identical to that of Sokoloff et al. (33). It is composed mainly of two ratios between FDG and glucose. One is the ratio of hexokinase specific activity for FDG and glucose. Due to the similarity between the chemical structures of FDG and glucose (13), it is expected that a change in tissue's chemical environment will affect hexokinase's specific activities for FDG and for glucose in similar ways (1, 2, 4, 11, 18) and that the ratio between their specific activities will not be altered greatly. The other ratio in the lumped constant is between the factor $k_i^*/(k_i^* + k_2^*)$ of FDG and the same factor for glucose. Although the exact physiological mechanism that affects these factors of FDG and glucose is not known, it is not very likely that the effects on FDG and glucose are completely different (i.e., the ratios of these factors between FDG and glucose are insensitive to physiological conditions). Therefore, while its value can vary from species to species, the lumped constant is expected to be uniform within an organ and remains constant within a species. Sokoloff et al. (33) have shown that the value of the lumped constant in rat's brain is not affected by anesthesia or by $\text{PCO}_2$-induced changes in cerebral blood flow. Nevertheless the value of the lumped constant must be investigated further to understand its characteristics in various physiological and pathological conditions.

The basic equation used in this work for the estimation of the lumped constant is different from the one used by Sokoloff et al. (33). Sokoloff et al.'s method requires the plasma FDG concentration to be kept constant by adjusting the FDG injection schedule. The steady-state ratio of the extraction fractions for FDG and glucose is then equal to the lumped constant, provided there is no hydrolysis of FDG-6-P (i.e., $k_i^* = 0$). For $k_i^*$ not equal to zero, the situation is slightly different. The net extraction of FDG at a time $t$ is equal to $k_i^*C_p\ast(t) - k_2^*C_E\ast(t)$, which is the net influx of FDG across the blood-brain barrier at that time. The extraction fraction of FDG at time $t$ is thus equal to $[k_i^*C_p\ast(t) - k_2^*C_E\ast(t)]/(C_p\ast(t)\cdot F)$, where $F$ denotes blood perfusion. For glucose, the steady-state extraction fraction is equal to the rate of glucose utilization $(-\phi k_i^*k_2^*C_p)/((k_2 + \phi k_3))$ divided by the rate of plasma glucose supply (FC$_{p}$). Therefore, the ratio of the extraction fractions for FDG and glucose is

$$\frac{\text{EF}\ast(t)}{\text{EF}} = \frac{k_i^* - k_2^*C_E\ast(t)/C_p\ast(t)}{\phi k_i^*k_2^*/(k_2 + \phi k_3)}$$

where EF and EF* denote the extraction fractions of glucose and FDG, respectively. For a constant level of plasma FDG (i.e., constant C$_p$), the ratio of FDG concentrations across the blood-brain barrier (i.e., C$_E$/C$_p$) is shown in Fig. 7 for both gray and white matter. At an infinite time, the ratio is equal to $k_2^*/k_i^*$, and the extraction fraction of FDG (i.e., EF*) becomes zero. However, for small values of $k_i^*$, the convergence to zero is slow, as shown in Fig. 8. In Figs. 7 and 8, plasma FDG concentration is kept constant after a step increase from zero, and the k* values from Table 1 are assumed. As shown in Fig. 8, at early times between 20 and 40 min, the ratio of the extraction fractions for FDG and glucose is approximately equal to the lumped constant obtained by the method used in the present work. In other words, even though the value of $k_i^*$ is not identically zero, if extraction fraction measurements are taken for the first 40 min after FDG injection, Sokoloff et al.'s method of using the asymptotic equilibrium value for the estimation of the lumped constant should yield the same value as the one used in the present work.

The variations of the lumped constant as estimated from the subjects in the present work has a percent SD of 15%. This variation is due to the method used to estimate the lumped constants. In the estimation based
on Eq. 7 an average value of CMRGlc from the literature was assumed for all volunteers, although the percent SD of the measured CMRGlc in each report were quite large (18–64%). If there were true variations of metabolic rate among these volunteers, the variation would be reflected directly in the estimated values of the lumped constant. A direct estimate of the lumped constant can be attained by actually measuring the total glucose extraction across the whole brain as obtained from the product of the cerebral blood flow and the arterial-venous difference of glucose concentration.

Another possible cause for the variation of the lumped constant is in the calculation of the average value of \( k^*_f k^*_o / (k^*_f + k^*_o) \). It was determined as the average value of the factor in the gray and white matter. The regions selected to represent typical gray and white matter were different in different volunteer studies because of the variations in positioning the scanned slice. Therefore, even if the whole brain CMRGlc were the same, there would be variations in the average value of \( k^*_f k^*_o / (k^*_f + k^*_o) \), resulting in variations in the estimated values of the lumped constant.

The time course of \(^{18}F\) in brain tissue (Figs. 4A and B) shows a steady increase for the first 80 min, becomes saturated between 80 and 120 min, and then begins to decrease slowly. The first part (0–45 min) of this curve is very similar to the curve of DG uptake in rat brain as reported by Sokoloff et al. (33). However, it differs significantly from the results of Hawkins and Miller (9) and from those of Gallagher et al. (7). Their results showed a very rapid rise of DG in brain tissue during the first 5 min after injection, but with a subsequent decrease. The fraction of free FDG to total \(^{18}F\) in tissue as estimated in the present study at various times after injection (Fig. 4) is very similar to the results for DG reported by Sokoloff et al. (33). It is also very comparable with the results by Hawkins and Miller (9), but differs significantly from the results of Gallagher et al. (7), which show a steady increase for the first 80 min, becomes saturated between 80 and 120 min, and then begins to decrease slowly. The first part (0–45 min) of this curve is very similar to the curve of DG uptake in rat brain as reported by Sokoloff et al. (33). However, it differs significantly from the results of Hawkins and Miller (9) and from those of Gallagher et al. (7). Their results showed a very rapid rise of DG in brain tissue during the first 5 min after injection, but with a subsequent decrease. The fraction of free FDG to total \(^{18}F\) in tissue as estimated in the present study at various times after injection (Fig. 4) is very similar to the results for DG reported by Sokoloff et al. (33). It is also very comparable with the results by Hawkins and Miller (9), but differs significantly from the results of Gallagher et al. (7), which show a very small fraction of free DG in tissue after the first 5 min. The factors that account for the large differences among these studies are not clearly known. It could be due to the differences in the animal species and in the experimental procedures. Phelps et al. (24) have provided a comprehensive comparison of the different results of various laboratories.

A direct evaluation of the LCMRGlc results of the present method is difficult due to a lack of direct measurements of LCMRGlc in normal man. Since the average whole brain metabolic rate in the literature is used to estimate the lumped constant, the calculated average CMRGlc certainly, as expected, have values similar to those in the literature. It has been reported that the CMRGlc in the whole brain is rather constant under different physiological conditions. Although the constancy of CMRGlc on a regional basis has not been fully confirmed, it is expected that a valid method for the measurement of LCMRGlc should give comparable results in different normal subjects. The variations (standard deviation) in the calculated metabolic rates of the 13 volunteers are 18% and 21%, respectively, for gray and white matter. This variation is comparable to those reported in the literature for the whole brain—23% in Ref. 31, 64% in Ref. 17, 8% in Ref. 8, 19% in Ref. 5, and 38% in Ref. 35.

The results of Table 2 show a ratio of about 2.2 between the metabolic rates of gray and white matter. This ratio is smaller than the value of 3 commonly reported in the literature for rat (33) and monkey (14). Our value would be expected to be lower due to the resolution limitation of ECT. As the size of the object becomes smaller than the FWHM of the imaging device, the contrast is severely reduced (10).

The stability of the calculated LCMRGlc as shown in Fig. 5 also indicates the adequacy of the present model and the reproducibility of the measurement of LCMRGlc. Figure 9 shows the calculated LCMRGlc for the corresponding subjects at various times following the FDG injection, if \( k^*_f \) is set to zero (i.e., if Sokoloff et al.'s model is used). The dependency of the metabolic rate on the scanned time is undesirable for the ECT technique, which requires sequential scanning of different cross-sectional slices of the brain. Even if sequential scanning were not employed, the value of LCMRGlc calculated at late times would be underestimated if \( k^*_f \) is not taken into account.

In this work, LCMRGlc can be calculated by either of the two formulas—Eq. 6 and Eq. 8. When Eq. 6 is used, the values of the rate constants of FDG need not be presumes. They are estimated from the time courses of the plasma's FDG concentration and of the total \(^{18}F\) activity in the particular region of interest. The rate constants of FDG serve as an information linkage between Eq. 3 and Eq. 6. The formula of Eq. 6 does not explicitly require the value of \( k^*_f \). In fact, the same relationship holds even for \( k^*_f \) equal to zero. However, the value of \( k^*_f \) will influence the values of the other rate constants \( k^*_o \), \( k^*_g \), and \( k^*_r \) when the rate constants are estimated through Eq. 3.

On the other hand, the calculation of LCMRGlc by Eq. 8 requires a predetermined set of rate constants, but it does not need the time course information of the \(^{18}F\) activities in tissues. (Using Eq. 8 with the individually determined rate constants for each region is identical to the usage of Eq. 6). The error sensitivity results show that the error range due to the usage of an average set of
rate constants is smallest between 50 and 120 min after
injection. In other words, if Eq. 8 is used as the equation
to calculate LCMRGlc, the ECT measurements of the
local radioactivity (C\textsubscript{T}) and of the plasma glucose
and FDG concentrations (C\textsubscript{p}, C\textsubscript{*}). Errors in these measure-
ments will be reflected directly in the calculated
LCMRGlc. In the present studies, the measurements on
plasma and FDG concentrations have a precision of
better than 2% (24). The accuracy in the measurement of
local radioactivity depends critically on the ECT scan-
ing and reconstruction procedures, the size of object,
and the area of the region of interest (10, 12, 21, 23). In
the present work, the accuracy in the ECT radioactivity
measurements other than the effect of object size is
expected to be within 10% (21).

The model used in this work assumes that FDG and
FDG-6-P are present in trace amounts (assumption 3).
In the human studies, the injected dose is about 1 mg of
FDG. The highest plasma FDG concentration (at the
peak of the plasma FDG curve) is found to be less than
2 \mu M. As compared to about 5.56 mM (100 mg/100 ml)
for normal plasma glucose concentration, it is less than
4 parts in 10,000. In brain tissues, maximal FDG con-
centration, which can be estimated from the rate constants
and the plasma FDG concentration curve, is less than 1
\mu M. This is a trace amount as compared to about 1.54
mmol glucose in 1 kg of brain tissue (16). For FDG-6-P,
the highest concentration in tissue is reached at about 2
h after injection. At this time, FDG-6-P concentration is
less than seven times the tissue FDG concentration (Fig.
4), which, as estimated from plasma FDG concentration,
is less than 0.05 \mu M at 2 h after injection (Fig. 2). In other
words, with the FDG dose used in the human studies,
the maximal concentration of FDG-6-P in tissue is less
than 0.35 \mu M, which is still a trace amount as compared
to about 80 \mu mol of glucose-6-P in 1 kg of normal brain
tissue (16). Therefore, the assumption that FDG and
FDG-6-P are present in trace amounts is well satisfied
for the human studies reported here.

Although the present mathematical model removes
the requirement of complete trapping of FDG-6-P, there
are still other limitations. In the model, plasma concen-
tration of FDG in capillaries is approximated by its value
in the peripheral arterial or venous vessels. The validity
of using the arterial concentration has been discussed by
Sokoloff et al. (33). The less invasive approach of using
venous concentrations has been verified by Phelps et al.
(24) and is being employed for routine patient studies at
Division of Nuclear Medicine, UCLA. However, the va-
idity of these approximations depend on having small
extractions fractions for glucose and FDG in brain tissues.
In other words, they require the transport of glucose and
FDG to tissues be diffusion limited and not flow limited.

Normally, the extraction fraction of glucose across the
brain is only about 5–10% (5, 8, 17, 31, 33, 35). Thus this
requirement is well satisfied. However, in certain patho-
logical states, in which the blood flow is drastically re-
duced (e.g., stroke) or the glucose extraction fraction
significantly increases (e.g., hypoglycemia), the approxi-
mations may overestimate C\textsubscript{p} and C\textsubscript{*}. Therefore, the
calculated metabolic rates have to be interpreted with
care. Including blood flow in the plasma FDG compart-
ment of the model could remove this limitation, but the
tradeoffs between the complexities added to the model
and the accuracy improvements of the results must be
investigated further.

The model also assumes that the plasma glucose con-
centration is in a steady state. In some instances, glucose
concentration in plasma were not constant during the
entire period of study, which usually took more than 2 h
from the time of injection. In those situations, a question
arises as to which glucose concentration to use. This can
be partially answered through the following reasoning.
Since the lumped constant is insensitive to the plasma
concentration of glucose (Sokoloff, personal communi-
cation), according to Eq. 6, the factor \(k_1^*k_3^*/(k_2^* + k_3^*)\)
must vary inversely proportional to the changes in glu-
cose concentration, if the metabolic rate is to remain
constant. Our results on estimating the rate constants
show that the estimated \(k_1^*, k_3^*,\) and \(k_4^*\) are most sensitive
to the early times (first 25 min) when the \(^{18}F\) uptake in
tissue increases most rapidly. Therefore, it is conjectured
that using the glucose concentration at the early times
will give a better estimate of the metabolic rate. A
complete solution to the problem of nonconstant glucose
concentration will require a better understanding of the
relationship between glucose concentration and the rate
constants. A reformulation of the model may also be
needed.

As in Sokoloff et al.'s (33) model, the present model
only calculates the rate of glucose uptake by tissue. The
calculated values will reflect true metabolic rate of glu-
cose only if the tissue does not have a net glycogen
accumulation or glycogenolysis.

In this paper, results on 13 normal volunteers are
reported. More studies, both on normal volunteers and
on patients, are being carried out in our laboratory to
fully understand the capability and the limitations of the
present method. Also, it is expected that the method
reported here will be applicable to the determination of
regional metabolic rates of other substances in other
organisms. However, in each case, the model assumptions
will need to be verified; error characteristics will need to
be investigated to optimize the experimental design and
to predict the accuracy of the results; and many experi-
ments will be required to estimate the model parameters
and to verify the final results.

APPENDIX

Mathematical Derivation of the Model Equations

In the model shown in Fig. 1, the rates of change of FDG and FDG-
6-P concentrations in tissue (C\textsubscript{T} and C\textsubscript{*}) are equal to the net transpor-
tation of FDG and FDG-6-P into their compartments. That is

\[
\frac{d}{dt} C_T = k_5 C_* - (k_2^* + k_3^*)C_T + k_1^* C_p
\] (A1)
The concentrations of FDG ($C_g$) and FDG-6-P ($C_6$) in tissue can be solved in terms of FDG concentration in plasma ($C_p$) by taking the Laplace transform (28) of Eqs. A1 and A2, which become

$$SC_g(S) = k_1C_g(S) - (k_1 + k_4)C_6(S) + k_7C_6(S)$$  \hspace{1em} (A3)

$$SC_6(S) = k_7C_g(S) - k_4C_6(S)$$  \hspace{1em} (A4)

where initial conditions are assumed to be zero, and $C_g(S)$, $C_6(S)$, and $C_6(S)$ are the Laplace transforms of $C_g$, $C_6$, and $C_6$. From Eqs. A3 and A4, $C_g(S)$ and $C_6(S)$ can be expressed in terms of $C_p(S)$ as

$$C_g(S) = \frac{k_1}{a_2 - a_1 \left( \frac{S}{S + a_1} + \frac{S}{S + a_2} \right)} C_p(S)$$  \hspace{1em} (A5)

$$C_6(S) = \frac{k_4 k_7^*}{a_2 - a_1 \left( \frac{1}{S + a_1} - \frac{1}{S + a_2} \right)} C_p(S)$$  \hspace{1em} (A6)

where

$$a_1 = (k_1 + k_4 + k_1^* - \sqrt{(k_1 + k_4 + k_1^*)^2 - 4k_4 k_1^*})/2$$  \hspace{1em} (A7)

$$a_2 = (k_1 + k_4 + k_1^* + \sqrt{(k_1 + k_4 + k_1^*)^2 - 4k_4 k_1^*})/2$$  \hspace{1em} (A8)

Inverse Laplace transform of Eqs. A5 and A6 gives

$$C_g(t) = \frac{k_1^*}{a_2 - a_1} \left( \frac{a_2 - a_1}{a_2} \right) e^{a_1 t} + \left( \frac{a_2 - a_1}{a_2} \right) C_p(t)$$  \hspace{1em} (A9)

$$C_6(t) = \frac{k_4 k_7^*}{a_2 - a_1} \left( \frac{a_2 - a_1}{a_2} \right) e^{a_1 t} \otimes C_p(t)$$  \hspace{1em} (A10)

where $\otimes$ denotes the operation of convolution. That is

$$a(t) \otimes b(t) = \int_0^t a(\tau) b(t - \tau) d\tau$$  \hspace{1em} (A11)

The total amount of $^{18}$F activity in tissue (denoted as $C^*_t$) is equal to the sum of $^{18}$F activities of free FDG and FGD-6-P in tissue. The $^{18}$F activity due to FDG in the vascular space is negligible (24). Thus

$$C^*_t = C_g + C_6$$  \hspace{1em} (A12)

Substituting $C_g$ and $C_6$ from Eqs. A9 and A10, Eq. A12 becomes

$$C^*_t(t) = \frac{k_1^*}{a_2 - a_1} \left( \frac{(a_2 - a_1)}{a_2} \right) e^{a_1 t} + \left( \frac{(a_2 - a_1)}{a_2} \right) C_p(t)$$  \hspace{1em} (A13)

Since the total amount of $^{18}$F activity in a local region ($C^*_t$) can be measured as a function of time with ECT, and the plasma concentration of FDG ($C^*_p$) can be obtained from arterial or venous blood samples, the values of the rate constants ($k^*$'s) of FDG can be estimated from Eq. A13. The values of the rate constants can then be used to calculate the metabolic rate of glucose as shown in the following derivations.

In a steady state, the metabolic rate of glucose in a local region is equal to the net phosphorylation rate of glucose. This is

$$R_i = k_3 k_4 C_E - k_4 C_M$$  \hspace{1em} (A14)

where $R_i$ denotes LCMRGlc in a local region. Since the rates of $k_3 C_E$ and $k_4 C_M$ are constant during steady state, $k_3 C_M$ can be expressed as a fraction of $k_3 C_E$

$$k_3 C_M = \frac{k_3 C_E}{k_3 C_E - k_4 C_M}$$  \hspace{1em} (A15)

and

$$R_i = (1 - r) k_3 C_E$$  \hspace{1em} (A16)

where $r = (1 - r)$ is the fraction of glucose that is metabolized after it is phosphorylated. As pointed out by Sokoloff et al. (33), the value of $r$ for brain is very nearly equal to 1, due to the low activity level of glucose-6-phosphatase in brain tissue.

In a steady state, there is no net accumulation or net depletion of glucose in tissue. Thus, the rate of transport into and out of the tissue pool of glucose should be equal

$$k_3 C_p + k_3 C_M = k_3 C_E + k_3 C_M$$  \hspace{1em} (A17)

Thus, by substituting $C_i$ from Eq. A18 into Eq. A16, we have

$$R_i = \frac{k_3}{k_3 + k_4} C_p$$  \hspace{1em} (A19)

In the above equation, the metabolic rate is in terms of the rate constants of glucose. These rate constants cannot be easily measured. However, the metabolic rate can also be expressed in terms of the rate constants of FDG by first multiplying both the numerator and the denominator of Eq. A19 by $k^{*1}_1 (k^{*1}_1 + k^{*1}_6)$ as

$$R_i = \frac{k_3}{k_3 + k_4} C_p$$  \hspace{1em} (A20)

The term in the denominator of $\lambda$ is the distribution volume of glucose. For $\phi = 1$, the numerator and denominator have the same form. Thus, $\lambda$ is the ratio between the same factor for FDG and glucose. The value of $\rho$ is the ratio of phosphorylation rate constants between FDG and glucose. Since FDG and glucose are competitive substrates for hexokinase in the phosphorylation process their rate constants can be expressed according to the Michaelis-Menten relationship as

$$k^*_i = \frac{V^*_v/K^*_v}{1 + C_E/K^*_v + C_M/K^*_m}$$  \hspace{1em} (A23)

$$k_3 = \frac{V^*_v/K^*_v}{1 + C^*_E/K^*_E + C^*_M/K^*_M}$$  \hspace{1em} (A24)

where $V_v$ and $V^*_v$ are maximum velocities, and $K_v$ and $K^*_v$ are the apparent Michaelis-Menten constants. Thus

$$\lambda = \frac{V^*_v K^*_v}{V^*_v K^*_v}$$  \hspace{1em} (A25)

and the factor in Eq. A21 can be expressed as

$$\phi = \frac{\lambda V^*_v K^*_v}{\phi V^*_v K^*_v}$$  \hspace{1em} (A26)

This factor is exactly the same as the lumped constant in Sokoloff et al.'s model. The significance of this lumped constant is that its value is expected to be constant over the whole brain and does not vary within a single species (33). Its value is related only to the enzyme hexokinase and to the transport mechanism of FDG and glucose across the blood-brain barrier. It has been shown on a preliminary basis to be independent of the physiological state of the tissue (33). The value of the lumped constant can be determined in advance and then be used as a calibration factor between the behaviors of FDG and glucose. Therefore, Eq. A21 can be expressed as

$$R_i = \frac{1}{(LC)} \frac{k^*_i k^*_i}{k^*_E + k^*_E} C_p$$  \hspace{1em} (A27)

where $(LC)$ denotes the lumped constant of Eq. A26. The rate constants $k^*_i$'s can be estimated from Eq. A13. Thus Eq. A27 in combination with Eq. A13 can be used for the calculation of LCMRGlc.

By averaging the metabolic rate over the whole brain, Eq. A27 becomes

$$R_i = \frac{C_p}{(LC)} \left( \frac{k^*_i k^*_i}{k^*_E + k^*_E} \right)$$  \hspace{1em} (A28)
where \( R \) denotes the average metabolic rate in brain and \( k_i/k_f/(k_s + k_t) \) denotes the average value of the factor over the whole brain. By rearranging terms in Eq. A28, the lumped constant can now be evaluated from the average metabolic rate in brain, \( R \), and the average value of \( k_i/k_f/(k_s + k_t) \) as

\[
(LC) = \frac{C_p}{R} \left( \frac{k_i/k_f}{k_s + k_t} \right) \quad (A29)
\]

This is the equation used in this paper for the estimation of the lumped constant for FDG in human brain.

The disadvantage of using Eq. A27 for the calculation of metabolic rate is that it requires repeated measurements of \( C(T) \) at various times to determine the values of \( k^* \)'s. This disadvantage can be removed by multiplying both the numerator and the denominator of the right side of Eq. A27 by an equal quantity as

\[
R_i = \frac{C_p}{(LC)} \left( \frac{k_i/k_f}{k_s + k_t} \right) \quad (A30)
\]

Substituting \( C_p \) and \( C_* \) from Eqs. A9 and A10, Eq. A30 becomes

\[
R_i = \frac{C_p}{(LC)} \left( \frac{k_i/k_f}{k_s + k_t} \right) \left( \frac{C_*(T)}{C_*} \right) \left( \frac{(k_s + k_t)(e^{-k_t} - e^{-k_s})}{(a_0 - a_1)} \right) \quad (A31)
\]

This formula only requires a single measurement of \( C_* \) at some time \( T \). It does not need the time course information of \( C(T) \). Although the formula of Eq. A31 still needs the values of the \( k^* \)'s, it is expected that, with the directly measured values of \( C(T) \) in the formula, the accuracy requirements on the \( k^* \)'s values are less demanding. In other words, it is expected that the metabolic rates calculated by Eq. A31 is not very sensitive to the errors in the \( k^* \)'s. To evaluate the validity of this conjecture, the effects on the calculated metabolic rate due to errors in the values of the \( k^* \)'s need to be investigated. By taking the differential of \( R_i \) with the \( k^* \)'s as independent variables, we have

\[
dR_i = \sum_1^4 \frac{\partial R_i}{\partial k^*} dk^*_i \quad (A32)
\]

and

\[
dR_i = \sum_1^4 \frac{\partial R_i}{\partial R} \frac{dk^*_i}{k_i} \quad (A33)
\]

where \( \partial / \partial \) denotes the partial derivative. With some mathematical manipulations it can be shown that

\[
k^* R_i = \frac{C_p C_*}{(LC) R C_*} \quad (A34)
\]

\[
k^* R_i = \frac{k_i C_p C_* \otimes f_1 + k_f C_p C_* \otimes f_1}{C_*} \quad (A35)
\]

\[
k^* R_i = \frac{k_i C_p C_* \otimes f_1 + k_f C_p C_* \otimes f_1}{R C_*} \quad (A36)
\]

\[
k^* R_i = \frac{k_i C_p C_* \otimes f_1 + k_f C_p C_* \otimes f_1}{R C_*} \quad (A37)
\]

where

\[
f_1(t) = \frac{1}{a_0 - a_1} \left( (k_f + k_s) e^{-\alpha t} + (a_0 - k_s) e^{-\alpha t} \right) \quad (A38)
\]

\[
f_2(t) = \frac{1}{a_0 - a_1} \left( -a_k e^{-\alpha t} + a_k e^{-\alpha t} \right) \quad (A39)
\]

\[
f_3(t) = \frac{1}{a_0 - a_1} \left( (k_f - a_0) e^{-\alpha t} + (a_0 - k_s) e^{-\alpha t} \right) \quad (A40)
\]

and \( R_i \) is the value actually calculated from Eq. A31. With Eqs. A33-A41 the sensitivity of the calculated metabolic rate can be estimated by accepting a predictable error range for the calculated metabolic rate, a set of average values for \( k^* \)'s can be used in Eq. A31, thus eliminating the need for the measurement of the time course of the total \( ^{18} \text{F} \) activity in tissue for each study.

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