Operational Lumped Constant for FDG in Normal Adult Male Rats

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We determined an operational value for the lumped constant to be used in measurements of the local rate of cerebral glucose use ($lCMR_{glc}$) with FDG in normal adult male rats. **Methods:** The standard quantitative autoradiographic method was used with 2-deoxy-D-^{14}C-glucose (^{14}C-DG) and with ^{14}C-FDG in awake normal adult male rats. Timed arterial blood samples were drawn for 45 min after the bolus and assayed for plasma glucose and ^{14}C concentrations. At the end of the 45-min experimental period, the rats were killed, and their brains were removed and divided in half sagittally. One hemisphere was immediately frozen and assayed for local ^{14}C concentrations by quantitative autoradiography; the other was weighed, homogenized in *t*-octylphenoxypolyethoxyethanol solution, and assayed for ^{14}C concentrations in the whole brain by liquid scintillation counting. Paired rats (3 pairs), one in each pair receiving ^{14}C-DG and the other receiving ^{14}C-FDG, were studied in parallel on the same day. Additional unpaired animals ($n = 8$) were studied with either ^{14}C-DG or ^{14}C-FDG but not in parallel on the same day. To calculate the $lCMR_{glc}$ in rats studied with ^{14}C-FDG, the rate constants for ^{14}C-FDG were estimated from the ^{14}C-DG values determined for rats and the ^{14}C-FDG/^{14}C-DG ratios determined for humans. In all of the rats studied with either ^{14}C-DG or ^{14}C-FDG, the $lCMR_{glc}$ was first calculated in 12 representative brain structures with the lumped constant of 0.48 previously determined for ^{14}C-DG in rats. The ratio of the $lCMR_{glc}$ thus determined with ^{14}C-FDG to that determined with ^{14}C-DG for each structure was then multiplied by the lumped constant for ^{14}C-DG to estimate the lumped constant for ^{14}C-FDG. The $lCMR_{glc}$ and the lumped constant for FDG in the brain as a whole were similarly estimated from the tracer concentrations in the brain homogenates. **Results:** The mean values for the lumped constant for FDG were found to be 0.71 and 0.70 in the autoradiographic assays and the assays with brain homogenates, respectively. **Conclusion:** The appropriate value for the lumped constant to be used in determinations of the $lCMR_{glc}$ in normal adult male rat studies with ^{18}F-FDG and small-animal PET scanners is 0.71.

Key Words: lumped constant; FDG; rats

J Nucl Med 2007; 48:94–99

The 2-deoxy-D-^{14}C-glucose (^{14}C-DG) method was originally developed to measure the local rates of cerebral glucose use ($lCMR_{glc}$) in the brains of animals and used quantitative autoradiography to achieve localization (*1*). Shortly thereafter, it was adapted for use in humans by substituting for ^{14}C-DG the fluorinated, positron-emitting analog of deoxyglucose, ^{18}F-FDG, and replacing the autoradiography first with single-photon emission scanning (*2*) and then with PET (*3*). ^{18}F-FDG was used instead of labeled deoxyglucose because it was shown to have biochemical properties similar to those of deoxyglucose (*2*) and because the 110-min half-life of ^{18}F made ^{18}F-FDG easier to synthesize than deoxyglucose labeled with the other possible but much shorter-lived positron-emitting isotopes, ^{11}C or ^{15}O.

An important component of the operational equation of the deoxyglucose method, the so-called lumped constant, is used to compute the rates of glucose use from the measured variables. This constant is comparable to a correction factor for an isotope effect because it corrects for the differences between the kinetic properties of ^{14}C-DG or ^{18}F-FDG and those of glucose with regard to blood–brain barrier transport and phosphorylation by hexokinase. This correction is needed to compute the rate of glucose use from the measured uptake of the radioactive tracer within brain tissues. The value for the lumped constant for deoxyglucose was first determined by a completely model-independent, steady-state method in rats (*1*) and subsequently determined in several other animal species (*4*). Because ^{14}C-DG was more readily available commercially and its use in the autoradiographic method was thoroughly established, there was little reason to use ^{14}C-FDG or ^{18}F-FDG or to determine the kinetic constants for ^{14}C-FDG or ^{18}F-FDG for use with autoradiography in rats and other animals. There were some attempts to determine the lumped constant for FDG in rats (*5–9*), but these determinations were made indirectly and were vulnerable to the inevitable uncertainties of the kinetic models on which they were based. However, when the deoxyglucose method was adapted for use in humans with ^{18}F-FDG and emission tomography, it became essential to determine the kinetic constants for ^{18}F-FDG in

Received Mar. 31, 2006; revision accepted Jul. 25, 2006.

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humans. These constants for ^{18}F-FDG in humans were first determined by Reivich et al. (*10*), who used the same model-independent method to determine the lumped constant as that which had been used for ^{14}C-DG in rats, and subsequently determined by Hasselbalch et al. (*11*).

The advent of small-animal PET scanners has made it possible to use the ^{18}F-FDG method with PET in rats and mice and thus to exploit its advantage over autoradiography in allowing repeated measurements in the same animal. This advance has made it important to define the kinetic constants for FDG in small animals. The purpose of this study was to determine a value for the lumped constant for FDG that could be used in rats.

MATERIALS AND METHODS

Chemicals and Reagents

Chemicals were obtained from the following sources: ^{14}C-DG (specific activity: 2,257 MBq/mmol) from Amersham Biosciences Corp.; ^{14}C-FDG (specific activity: 11,100 MBq/mmol) from American Radiolabeled Chemicals, Inc.; halothane from Halocarbon; *t*-octylphenoxypolyethoxyethanol (Triton X-100) from Sigma-Aldrich, Inc.; and euthanasia solution (Beuthanasia-D special) from Schering-Plough Animal Health Corp.

Animal Preparation

Normal Sprague–Dawley male rats weighing 380–428 g were purchased from Taconic Farms and maintained in a climate-controlled room on a 12-h light–dark cycle with food and water available ad libitum. They were subjected to fasting but were allowed free access to water for 16–22 h before the initiation of the experimental procedure. All procedures were in strict accordance with the *Guide for the Care and Use of Laboratory Animals* (*12*) and approved by the National Institute of Mental Health Animal Care and Use Committee. Under light halothane anesthesia, polyethylene catheters (PE50; Clay-Adams) were inserted into both femoral arteries and a femoral vein. The animals were then partially restrained by means of a loose-fitting plaster cast applied to the lower torso to prevent their locomotion. At least 3 h were allowed for recovery from the anesthesia before the initiation of the experimental procedure.

A total of 14 animals were studied. Six of these were studied in parallel in matched pairs, 1 animal with ^{14}C-DG and the other with ^{14}C-FDG. Each pair was drawn from the same batch of animals and studied on the same day by the same personnel, and all blood and brain samples were treated under the same conditions in parallel. Studies with paired animals were done to minimize statistical variance attributable to animal age or batch and technical and personnel differences. The other 8 animals were unpaired because of scheduling and other technical difficulties that prevented pairing.

Experimental Procedure

The standard deoxyglucose method was used as previously described (*1*). In brief, the procedure was as follows. Each animal was injected intravenously with a bolus of either ^{14}C-DG or ^{14}C-FDG at 4,625 kBq/kg (125 μCi/kg), after which timed arterial blood samples were drawn during the next 45 min of the experimental procedure. The timing of the sampling was as follows: 6 samples drawn continuously and consecutively, 1 sample after the other, during the first 20 s, beginning with the bolus injection, and then samples drawn at 0.5, 0.75, 1, 2, 3, 5, 7.5, 10, 15, 25, 35, and 45 min. The blood samples were centrifuged immediately to separate the plasma, which was then assayed for glucose concentrations (Beckman Glucose Analyzer 2; Beckman Instruments) and for ^{14}C-DG or ^{14}C-FDG concentrations by liquid scintillation counting with external standardization. At 45 min, the animal was killed by a bolus injection of euthanasia solution, and the brain was quickly removed. The brains were cut in half sagittally along the interhemispheric fissure and frozen in isopentane at about −40°C. The frozen brain samples were stored at −70°C until further processed as follows. One half of each brain was cut into 20-μm-slice sections in a cryostat and autoradiographed along with calibrated ^{14}C-methylmethacrylate standards as previously described (*1*). The other half was weighed, homogenized in *t*-octylphenoxypolyethoxyethanol solution (1:30 [v/v] in water) with an all-glass homogenizer, and assayed for ^{14}C concentrations by liquid scintillation counting with external standardization.

Monitoring of Physiologic Variables

Arterial blood pressure was monitored continuously with a Micro-Med Blood Pressure Analyzer (model 300; Micro-Med). Arterial blood P_{O_2}, P_{CO_2}, and pH were measured with a blood gas analyzer (model 288 Blood Gas System; Ciba-Corning Diagnostics Corp.). Arterial plasma glucose concentrations were measured with the Beckman Glucose Analyzer 2. Body temperature was monitored with a rectal thermistor connected to an indicating controller (YSI model 73A; Yellow Springs Instrument Co.) and maintained at 36°C–37°C by a thermostatically controlled heat lamp.

Data Analyses

The $lCMR_{glc}$ in 12 representative gray and white structures of the brain was determined. For computation of the $lCMR_{glc}$ in rats studied with ^{14}C-DG, the rate constants determined for gray matter or white matter by Sokoloff et al. (*1*) were used. Because the rate constants for FDG in rats have not yet been definitively determined, we adjusted the rate constants for deoxyglucose in rats to values to be used for FDG in rats by multiplying the DG constant values by the respective ratios of the FDG rate constants to the deoxyglucose rate constants that were determined for humans by Reivich et al. (*10,13*). The computation was as follows:

$$k_i^{3x} = (k_{i\,FDG}^{x}/k_{i\,DG}^{x}) \times k_{i\,DG}^{2x}, \qquad \text{Eq. 1}$$

where k_i^x is K_1, k_2, or k_3 determined for ^{14}C-FDG in the present study; $k_{i\,FDG}^{x}$ is K_1, k_2, or k_3 determined for FDG and $k_{i\,DG}^{x}$ is K_1, k_2, or k_3 determined for deoxyglucose in humans by Reivich et al. (*10,13*); and $k_{i\,DG}^{2x}$ is K_1, k_2, or k_3 determined for ^{14}C-DG in rats by Sokoloff et al. (*1*). These adjustments were made for each of the gray matter and white matter rate constants, and the adjusted values used in the present study are shown in Table 1.

The value for the lumped constant previously determined by Sokoloff et al. (*1*) for normal rats was 0.48, and this value was used to calculate the $lCMR_{glc}$ for all of the brain structures in rats receiving ^{14}C-DG or ^{14}C-FDG. The $lCMR_{glc}$ obtained with ^{14}C-FDG differed systematically in all structures from that obtained with ^{14}C-DG. The ratios of the values for the $lCMR_{glc}$ obtained with ^{14}C-FDG to those obtained with ^{14}C-DG were used to adjust the value of 0.48 to the value that would lead to the same values for the $lCMR_{glc}$ in rats receiving ^{14}C-FDG and for the $lCMR_{glc}$ in rats receiving ^{14}C-DG. Therefore,

TABLE 1
Determination of Rate Constants Used in Present Study

Tissue rate constant	Value (reference or source) for: Humans Deoxyglucose (*13*)	Humans FDG (*10*)	Rats Deoxyglucose (*1*)	Rats FDG* (present study)
Gray matter				
K_1	0.090	0.105	0.189	0.221
k_2	0.221	0.148	0.245	0.164
k_3	0.105	0.074	0.052	0.037
White matter				
K_1	0.057	0.069	0.079	0.096
k_2	0.109	0.129	0.133	0.157
k_3	0.078	0.064	0.02	0.016

*Calculated by use of Equation 1.

$$\text{Lumped Constant}_{FDG} = (lCMR_{glcFDG}/lCMR_{glcDG}) \times 0.48, \quad \text{Eq. 2}$$

where Lumped Constant$_{FDG}$ is the correct lumped constant for FDG and $lCMR_{glcFDG}$ and $lCMR_{glcDG}$ are the values for the $lCMR_{glc}$ calculated with the lumped constant of 0.48 in rats receiving ^{14}C-FDG and ^{14}C-DG, respectively.

For the homogenized brain samples, only the rate constants for gray matter were used to compute the rate of glucose use because gray matter comprises about 80%–90% of the tissue in the rat brain. The values for the rate of glucose use thus obtained represented the weighted averages for the brain as a whole, and the lumped constant for FDG was calculated from the values obtained with ^{14}C-DG and ^{14}C-FDG by use of Equation 2.

RESULTS

Physiologic Variables

The body weights of the rats receiving ^{14}C-DG and ^{14}C-FDG (404.1 ± 15.9 and 407.5 ± 13.6 g, respectively; mean ± SD) were not statistically significantly different ($P > 0.5$; Student t test). All of the physiologic variables determined shortly before the initiation of the experimental procedure were within normal physiologic limits and were not statistically significantly different between the groups (Table 2).

Lumped Constant Determined for ^{14}C-FDG by Autoradiography

The lumped constant determined for FDG as described earlier from all of the brain structures in the 3 matched pairs of rats receiving ^{14}C-DG and ^{14}C-FDG was 0.71 ± 0.12 (mean ± SD) (Table 3). The comparable lumped constant determined from the brain structures in all 14 rats, including the paired and unpaired rats (8 receiving ^{14}C-DG and 6 receiving ^{14}C-FDG), was 0.68 ± 0.03, a value that was not statistically significantly different from the value of 0.71 ± 0.12 obtained in the studies with paired rats (Table 3).

TABLE 2
Physiologic Variables

Variable	Mean ± SD for animals receiving: ^{14}C-DG (n = 8)	^{14}C-FDG (n = 6)
Body temperature (°C)	36.9 ± 0.3	36.7 ± 0.3
Mean arterial blood pressure (mm Hg)	125 ± 6	121 ± 11
Hematocrit (%)	52 ± 3	53 ± 4
Plasma glucose concentration (mg/dL)	135 ± 18	135 ± 7
P_{CO_2} (mm Hg)	37 ± 2	36 ± 3
P_{O_2} (mm Hg)	92 ± 4	92 ± 6
pH	7.43 ± 0.02	7.44 ± 0.03

Lumped Constant for ^{14}C-FDG Determined from Homogenized Brain Tissue

The values for the average rates of cerebral glucose use in the brain as a whole, calculated with the lumped constant for deoxyglucose from the homogenized halves of the brains of animals studied with ^{14}C-DG and ^{14}C-FDG, are shown in Table 4. Only values obtained from the homogenized halves of the brains of paired animals, which were processed simultaneously in parallel, are included. The values obtained from the homogenized halves of the brains of unpaired animals, which were processed on different days with different extraction solutions and sometimes by different personnel, were found to be so markedly variable, indicating day-to-day variations in the effectiveness of the brain extractions not seen in paired animals, that it was decided to exclude them. The lumped constant calculated for FDG by use of Equation 2 from paired animals was 0.70 ± 0.03 (mean ± SD) and was in excellent agreement with the value of 0.71 ± 0.12 obtained by quantitative autoradiography of the other half of the same brains.

DISCUSSION

To our knowledge, there have been no determinations of the lumped constant for FDG in rats by the direct model-independent, steady-state method of Sokoloff et al. (*1*). There have been several attempts to estimate the lumped constant by indirect methods. For example, Crane et al. (*6*) used the single-pass carotid injection method (*14*) and estimated the lumped constant for FDG in rats to be about 0.85. Lear and Ackermann (*15*) used a double-tracer autoradiographic technique and estimated the lumped constant to be 0.6. Fuglsang et al. (*7*) reported that the lumped constant was 1.55 and 1.63 times that of 2-deoxyglucose in adult rats and newborn rats, respectively. Hasselbalch et al. (*11*) used the model-independent method to determine the lumped constant in humans but not in rats and, in contrast to the findings of Reivich et al. (*10*), reported that it varies and declines with time. This time dependence has not been found in rats and monkeys. Several studies with the model-independent, steady-state method have uniformly shown that once the steady state for the brain uptake of ^{14}C-DG

TABLE 3
$lCMR_{glc}$ Determined by Autoradiography*

Structure	$lCMR_{glc}$ (mean ± SD μmol/g/min) in:			
	Studies with paired animals receiving:		All studies, with animals receiving:	
	^{14}C-DG (n = 3)	^{14}C-FDG (n = 3)	^{14}C-DG (n = 8)	^{14}C-FDG (n = 6)
Cerebellar cortex	0.55 ± 0.07	0.85 ± 0.08	0.59 ± 0.07	0.89 ± 0.07
Cerebellar white matter	0.32 ± 0.03	0.68 ± 0.05	0.39 ± 0.07	0.68 ± 0.04
Inferior colliculus	1.16 ± 0.13	1.74 ± 0.24	1.24 ± 0.16	1.74 ± 0.18
Superior colliculus	0.80 ± 0.04	1.13 ± 0.13	0.86 ± 0.11	1.24 ± 0.17
Visual cortex	0.95 ± 0.06	1.41 ± 0.20	1.00 ± 0.11	1.51 ± 0.17
Superior olive	1.04 ± 0.18	1.53 ± 0.24	1.15 ± 0.17	1.64 ± 0.21
Lateral lemniscus	0.93 ± 0.08	1.33 ± 0.27	1.07 ± 0.14	1.45 ± 0.24
Auditory cortex	1.12 ± 0.07	1.58 ± 0.29	1.16 ± 0.09	1.71 ± 0.24
Medial geniculate body	1.00 ± 0.06	1.51 ± 0.33	1.07 ± 0.09	1.58 ± 0.26
Lateral geniculate body	0.83 ± 0.014	1.19 ± 0.24	0.86 ± 0.11	1.25 ± 0.17
Internal capsule	0.34 ± 0.04	0.59 ± 0.04	0.39 ± 0.06	0.63 ± 0.05
Caudate putamen	1.02 ± 0.10	1.38 ± 0.26	1.00 ± 0.13	1.46 ± 0.21
Lumped constant for FDG	0.71 ± 0.12		0.68 ± 0.03	

*Rate constants for white matter were used to compute $lCMR_{glc}$ of cerebellar white matter and internal capsule; for all other structures, rate constants for gray matter were used. Lumped constants for FDG of 0.71 ± 0.12 and 0.68 ± 0.03, obtained in paired and unpaired animals, were not statistically significantly different.

and glucose has been established (i.e., the cerebral arteriovenous differences and extractions of ^{14}C-DG and glucose from the blood by the brain become constant)—an absolute requirement of the model-independent method—the calculated lumped constant for deoxyglucose does not change with time between 30 and 45 min (*1,16,17*) or for as long as 120 min (*18*) after the onset of the infusions. There is no reason to doubt that the same is true for the FDG lumped constant in rats and monkeys.

There are reasons to question the validity of the conclusion of Hasselbalch et al. (*11*). First, by definition, the "true" lumped constant cannot change with time because it is composed only of the ratios of the Michaelis-Menten constants, V_{max} and K_m, of hexokinase for the labeled tracer, deoxyglucose or FDG, to those of glucose and the ratio of their distribution spaces in the brain. These are all time-independent constants that cannot change with time and, therefore, neither can the true lumped constant. What can change with time, however, is the estimation of the lumped constant if the requirements for its estimation are not met. One such requirement of the model-independent method is that the exchanges of FDG and glucose between the brain and the blood are in steady states that are reflected in the constancy of their cerebral arteriovenous differences and extractions from the blood by the brain. It is only then that the extractions represent only the net metabolism of the hexoses and not changes in their concentrations in the tissue pools. The model-independent method achieves these steady states by programmed intravenous infusions of FDG or deoxyglucose and, if necessary, of glucose, which are designed to establish and maintain their concentrations in arterial blood and plasma long enough for the tissue concentrations to equilibrate with the blood and reach the levels representative of the tissue distribution spaces. A practical problem is that after the onset of the programmed infusions, their concentrations in the blood and plasma take time to rise from zero to constant levels, and then additional time is needed for the brain to equilibrate with the blood and plasma. Calculation of the lumped constant from the blood and plasma concentrations before this steady state is reached yields erroneously high values, which then progressively decline with time until they become constant when the steady state is reached (*1*). In the study of Hasselbalch et al. (*11*), the cerebral venous blood needed to determine the cerebral arteriovenous differences for FDG and glucose was sampled from the internal jugular vein. In humans, this blood, even when sampled under the best of circumstances from the superior bulb of the internal jugular

TABLE 4
Average Cerebral Glucose Use in Homogenized Brain Hemispheres, Calculated with Lumped Constant for Deoxyglucose, in Paired Rats

Pair	Average cerebral glucose use (μmol/g/min) calculated in studies with:		^{14}C-DG/ ^{14}C-FDG ratio
	^{14}C-DG (n = 3)	^{14}C-FDG (n = 3)	
1	0.55	0.79	0.70
2	0.51	0.71	0.72
3	0.54	0.81	0.67
Mean ± SD	0.53 ± 0.02	0.77 ± 0.05	0.70
Lumped constant for FDG = 0.70 ± 0.03*			

*Calculated by use of Equation 2.

vein, is almost always significantly contaminated with blood from extracerebral tissues (*19*), which have much lower perfusion rates and therefore equilibrate much more slowly with the blood than does the brain. Furthermore, not far below the superior bulb the facial vein joins the internal jugular vein, and if the blood samples are withdrawn too rapidly or if the catheter tip is below the bulb, then the samples may be even more heavily contaminated with blood from the facial vein. The effects of this extracerebral contamination may persist for long times and continue to diminish the arteriovenous differences after the cerebral tissues have reached their steady state, thus leading to the erroneous conclusion that it is the lumped constant for the brain that diminishes with time.

The method used in the present study is not model independent. Instead, it relies mainly on the validity of the established and generally accepted ^{14}C-DG method. It is based on the determination of the value for the lumped constant that provides the same values for cerebral glucose use with ^{14}C-FDG and for cerebral glucose use with ^{14}C-DG. In principle, this approach is very much like that originally used by Phelps et al. (*3*) and others to determine the value for the lumped constant for ^{18}F-FDG in humans, namely, the determination of the value for the lumped constant that leads to rates of glucose use that are the same as those obtained with an established and accepted method. The value obtained for the lumped constant for FDG in rats in the present study is larger than those obtained in humans by Phelps et al. (*3*) and Reivich et al. (*10*). This result should not be surprising. The lumped constant for deoxyglucose has been found to vary with the species of animal, probably because of species differences in the kinetic properties of the hexokinases in the brains of those species (*4*).

Not only the lumped constant but also the rate constants for FDG have been reported to differ from those of deoxyglucose, and these, especially the value for K_1, may influence the calculation of glucose consumption. Redies et al. (*8*) determined the values for K_1, k_2, and k_3 for FDG in rats by external coincidence counting by the method of Lockwood and Kenny (*20*). The values that they reported for K_1, k_2, and k_3 in rats were 0.195, 0.296, and 0.060 min^{-1}, respectively. Crane et al. (*6*) reported that the K_1 for FDG was 1.2 times that of deoxyglucose. Fuglsang et al. (*7*) reported K_1, k_2, and k_3 values for FDG in rats of 0.116, 0.162, and 0.080 min^{-1}, respectively. Our indirect estimation of the rate constants for FDG in rats from the ratios of the rate constants for FDG and deoxyglucose in humans and the rate constants for deoxyglucose in rats (Table 1) differed somewhat from these published values. Inasmuch as these rate constants were used to calculate the $lCMR_{glc}$ on which our estimate of the lumped constant for FDG is based, we cannot claim its complete independence from the rate constants. It is likely, however, that because we used the autoradiographic method in which tissue concentrations are measured only at 45 min after the bolus administration of the tracer—a time when the influence of the rate constants, particularly k_2 and k_3, on the calculated $lCMR_{glc}$ is reduced to very low levels (*21*)—the exact values of the rate constants did not play a very critical role in our estimation of the lumped constant. Nevertheless, it may be sufficient for us to emphasize that this is not a true lumped constant for FDG, only an operational lumped constant to be used to determine the $lCMR_{glc}$ under experimental conditions similar to those that we used in the present study, that is, the measurement of tissue FDG concentrations at 45 min after the bolus administration and calculation of the $lCMR_{glc}$ with the rate constants for FDG that we used in the estimation of the lumped constants.

The lumped constant for deoxyglucose has been shown to vary with the species (*4*) and has been found to rise markedly in rats with hypoglycemia (e.g., at plasma glucose concentrations below 4–5 mM) (*17*), to decline very gradually with increasing degrees of hyperglycemia (e.g., at plasma glucose concentrations of 10–30 mM) (*18*), and to be unaffected by general anesthesia (*1*). It may change with some pathologic conditions in the brain. It is almost certain that the same constraints and limitations that apply to the lumped constant for deoxyglucose also apply to the lumped constant for FDG, and these should be considered when the $lCMR_{glc}$ is determined in rats with FDG and PET.

CONCLUSION

We determined an operational value for the lumped constant for FDG in rats by measuring the $lCMR_{glc}$ obtained by the standard quantitative autoradiographic method with ^{14}C-DG and ^{14}C-FDG in both paired and unpaired rats and then adjusting the value of the lumped constant needed to provide the same values for the $lCMR_{glc}$ with ^{14}C-FDG and for the $lCMR_{glc}$ with ^{14}C-DG. The value for the lumped constant thus obtained was 0.71. We also measured brain isotope concentrations in paired animals by extraction of samples from brain tissue and liquid scintillation counting instead of autoradiography to obtain weighted average concentrations in the brain as a whole; the value of the lumped constant obtained in these experiments was 0.70. Therefore, we recommend that the value of 0.71 be used for the lumped constant in rat studies with small-animal PET scanners and ^{18}F-FDG.

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