What Is in a Number? The FDG Lumped Constant in the Rat Brain

PET with ^{18}F-FDG is being used in humans to study regional brain metabolism in normal and disease states. The underpinning of this approach is that FDG, like glucose, is transported across the blood–brain barrier and phosphorylated by hexokinase to FDG-6-phosphate, which accumulates in the tissue at a rate proportional to the rate of glucose use. However, because FDG and glucose differ in their rates of transport and phosphorylation and respective volumes of distribution (VDs) in brain tissue, rigorous calculation of the glucose metabolic rate (MRGlc) in units of μmol/100 g/min from PET with FDG requires a proportionality constant,

the lumped constant (LC_{FDG}), in the operational equation (1). The LC_{FDG} represents the ratio of the metabolic rate of FDG (MRFDG) to the MRGlc and, as such, is a complex constant that contains the K_m and V_{max} for FDG and glucose in the rate-limiting hexokinase reaction, the ratios of the VDs of FDG and glucose (λ), and a ϕ term, assumed to be 1, for the proportion of glucose that, once phosphorylated, is further metabolized. Mathematically,

$$LC_{FDG} = \frac{\lambda}{\phi}\left(\frac{K_{m_{glc}}}{V_{max_{glc}}} \Big/ \frac{K_{m_{FDG}}}{V_{max_{FDG}}}\right). \quad \text{Eq. 1}$$

In the operational equation, the MRGlc equals the MRFDG divided by the LC_{FDG}, that is,

$$MRGlc = MRFDG/LC_{FDG}, \quad \text{Eq. 2}$$

and

$$LC_{FDG} = MRFDG/MRGlc\ (2). \quad \text{Eq. 3}$$

This relationship shows that the MRGlc and the LC_{FDG} are inversely proportional to each other. The accuracy of the measurement of the MRGlc from PET with FDG depends on the accuracy of the LC_{FDG}; erroneous underestimation of the LC_{FDG} yields a correspondingly erroneous overestimation of the MRGlc and vice versa.

The field of imaging of glucose metabolism in humans with PET and animals with quantitative autoradiography can largely be credited to Sokoloff et al. who, in 1977, reported their pioneering studies of regional glucose metabolism in the normal rat brain (1). Their use of the tracer 2-deoxy-D-^{14}C-glucose (^{14}C-DG) and compartmental modeling with quantitative autoradiography allowed them to calculate the regional metabolic rates in numerous brain structures. They determined that the lumped constant for ^{14}C-DG in 15 normal conscious rats was 0.464 (SD, ±0.099). Other estimates of the value of the lumped constant for ^{14}C-DG have been close to this figure, providing support for its accuracy and validity (3–5). Now, 29 y later, Tokugawa et al. are reporting the value of the lumped constant for ^{14}C-FDG to be 0.71 (SD, ±0.12) on pages 94–99 of this issue of *The Journal of Nuclear Medicine* (6). This value is important because it will be used in calculations of the regional MRGlc in

the rat brain with ^{18}F-FDG and small-animal PET scanners.

The work of Tokugawa et al. (6) involved a standard quantitative autoradiographic method with ^{14}C-DG in 1 set of rats and ^{14}C-FDG in another set. The underlying assumption was that the MRGlc values should be the same in both sets; therefore, the lumped constant for FDG is taken as the value that infers the same MRGlc as that obtained with deoxyglucose by use of the previously measured lumped constant (0.48) for that tracer. Another issue is that Tokugawa et al. used the combined deoxyglucose lumped constant of 0.48, which encompasses both anesthetized ($n = 9$) and awake ($n = 14$) animals; however, Tokugawa et al. used awake animals, so that the value 0.464 might have been more appropriate. The experiments were well done, although the methodologic detail was not as rigorous as in the 1977 study of Sokoloff et al. (1). In the earlier work, animals were studied at 5 time points, whereas in the present work, just 1 time point was studied. Also, in the earlier study, the lumped constant was determined directly by measuring the uptake of glucose and the analog and did not involve calculations with human and animal kinetic constants from historical studies.

There are some potential methodologic limitations in the report by Tokugawa et al. (6). To establish the relationship between the kinetic parameters of ^{14}C-DG and ^{14}C-FDG, they used ratios of the constants derived for humans from the work of Reivich et al., which were determined at a time when the methods for synthesizing FDG led to partial contamination with fluorodeoxymannose (7,8). This methodology certainly invites skepticism because of the use of values derived from a different

species and the application of values that cannot be totally representative of FDG uncontaminated by fluorodeoxymannose. Moreover, for the sake of accuracy, the propagation of systematic error from these parameter ratios should have been included in the final estimate of the SD of ± 0.12 around the value 0.71. Also, the uncertainty in the estimate of the lumped constant for FDG should have included propagation of the additional error from the uncertainty in the lumped constant for deoxyglucose. No doubt, the end result (0.71) is a reasonable approximation of the "true" lumped constant, but the SD of 0.12 implies a level of certainty that the data as presented do not justify. Rigor would call for measurements of ^{14}C-FDG versus ^{14}C-DG parameters in the same species with pure tracers and with propagation-of-error estimates included in the final lumped constant result. These measurements could be obtained in rats biochemically, independently of modeling, by the methods described by Kapoor et al. (4). In addition, a model-independent estimate of the rat LC_{FDG} was reported in 1983 by Crane et al. (9). Using anesthetized rats, they determined the phosphorylation ratio for FDG versus glucose to be 0.55 ± 0.16 (mean $\pm$ SD) and predicted the lumped constant for FDG to be 0.89.

There are additional reasons to believe that the error limits are not as good as the report by Tokugawa et al. (6) implies. There are wide variations in the data in Table 1 in their report. Even if one takes the perspective that some ratios should be more robust $[K_1/k_2, k_2/k_3, \text{ or } (K_1 \times k_3)/(k_2 + k_3)]$, the values are quite disparate and make it difficult to believe the 17% coefficient of variance that is reported.

To exemplify further the limitations associated with the propagation of error, we calculated the LC_{FDG} for the rat brain by using the phosphorylation ratio for FDG derived from bovine hexokinase (0.62 ± 0.10) (10) along with the VD data generated from Crane et al. for glucose and FDG in the rat brain (VD for glucose, 0.232 ± 0.163; VD for FDG, 0.303 ± 0.123; and λ, 1.306 ± 1.060) (9,11). This calculation yields an LC_{FDG} of 0.81, not that much different from 0.71, but with a disturbingly large SD of 0.84. When the VD data of Crane et al. are combined with an estimation of the FDG phosphorylation ratio from humans, the lumped constant estimate is 0.85, but again, with a disturbingly large SD of 0.95 (12).

A larger concern regarding the value of 0.71 is, as the title states, the "FDG lumped constant in the rat brain." In reality, it is the lumped constant for the normal adult awake rat brain, specifically, for male Sprague–Dawley rats measured at 45 min. We emphasize all of these qualifiers because human nature is such that once a value for a lumped constant is reported in literature, it tends to be used without consideration for its limitations. The use of this value justifies some caution in that the lumped constant is anything but a constant. There are plausible data in the literature indicating that the lumped constant changes with the length of time between the injection of the tracer and measurement. It surely changes with any disease that has an enzymatic component, such as neoplasia (13). It probably varies with regional glucose concentrations and conditions of ischemia or hypoglycemia (3). The method of anesthesia is another possible variable.

The absence of any discussion of k_4 is another concern. This term, whatever its mechanistic basis, does influence the lumped constant and the metabolic rate, and leaving out k_4 underestimates the lumped constant. Hence, the value reported by Tokugawa et al. (6) should not be applied to measurements that include k_4 in the analysis (12).

In summary, how much does the value of the lumped constant matter? The tracer FDG can be used to estimate the metabolic rates for FDG in humans and in rats. If one is interested in measurements of changes in metabolism over time (e.g., the response of a disease to a drug or other therapy or changes with aging), between a disease state (e.g., neoplasia or ischemia) and normal tissue, or between one physiologic state and another (seizure vs. normal), one could simply determine the metabolic rate for FDG, not that for glucose, quantitatively and skip the nonproductive discussion of the lumped constant. On the other hand, if one uses FDG to study metabolic changes in diseases or treatments that could affect hexose transport or phosphorylation and if one wants to claim precision in estimating the metabolism of the true physiologic hexose substrate, glucose, from FDG results, then one must take the trouble to measure the LC_{FDG} for the condition(s) under study. Otherwise, one should not claim that the result represents an accurate quantitative measure of glucose metabolism. The lumped constant of 0.71 should be used to calculate the MRGlc from FDG data only in studies of the normal awake male rat brain, and one should be careful to realize that the error around this estimate may well be greater than ± 0.12.

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Errata

In the article "Empiric Radioactive Iodine Dosing Regimens Frequently Exceed Maximum Tolerated Activity Levels in Elderly Patients with Thyroid Cancer," by Tuttle et al. (*J Nucl Med.* 2006;47:1587–1591), the percentage of patients having a maximum tolerated activity lower than 7.4 GBq was incorrectly reported to be 8% instead of the correct value, 11%. The authors regret the error.

In the article "^{131}I Ablation Treatment in Young Females After the Chernobyl Accident," by Travis and Stabin (*J Nucl Med.* 2006;47:1723–1727), Table 2 contained several errors. The corrected table appears below. The authors regret the errors.

TABLE 2
Dose Estimates for ^{131}I Ablation Treatment in Female Patients

Age group	0.50-d half-time		0.70-d half-time		1.3-d half-time	
	mGy/MBq	rad/mCi	mGy/MBq	rad/mCi	mGy/MBq	rad/mCi
Adult						
Breasts	4.17E−02	1.54E−01	6.20E−02	2.29E−01	1.26E−01	4.66E−01
Red marrow	4.56E−02	1.69E−01	6.48E−02	2.40E−01	1.25E−01	4.64E−01
Total body	5.83E−02	2.16E−01	8.06E−02	2.98E−01	1.51E−01	5.58E−01
15-y-old child						
Breasts	4.18E−02	1.55E−01	6.21E−02	2.30E−01	1.26E−01	4.66E−01
Red marrow	4.69E−02	1.74E−01	6.68E−02	2.47E−01	1.29E−01	4.79E−01
Total body	5.83E−02	2.16E−01	8.05E−02	2.98E−01	1.51E−01	5.57E−01
10-y-old child						
Breasts	6.64E−02	2.46E−01	9.82E−02	3.63E−01	1.99E−01	7.35E−01
Red marrow	7.30E−02	2.70E−01	1.05E−01	3.88E−01	2.06E−01	7.60E−01
Total body	9.38E−02	3.47E−01	1.30E−01	4.80E−01	2.44E−01	9.02E+00