TECHNICAL NOTES

Alternative Formula for Glucose Utilization using Labeled Deoxyglucose

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The measurement of glucose utilization using labeled deoxyglucose (C-14 or F-18), a glucose analog that becomes metabolically trapped, is a well-accepted technique. A new formula is presented for calculating the metabolic rate of glucose from tissue concentration of tracer. This formula is both simpler and more accurate than those previously published.

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Several years ago an autoradiographic method for measuring metabolic rate in experimental animals using [^{14}C]deoxyglucose was introduced (*1*). With the advent of positron emission tomography (PET), this method has been extended to in vivo studies on patients, using [^{18}F]deoxyglucose (FDG) (*2*). The PET procedure is closely modeled after the autoradiographic animal method. In a typical study, FDG is injected as a bolus, arterial blood is sampled frequently thereafter, and after about 45 min a series of PET scans are made. Tissue concentrations can be determined from the PET image, just as from an autoradiogram. The glucose utilization rate R is then calculated from the relationship between the tissue concentration and the integrated plasma levels of FDG, using either Sokoloff's original equation (*1*) or a later modification (*3,4*) that includes a correction for dephosphorylation of the metabolically trapped FDG.

Both equations are based on the three-compartment model illustrated in Fig. 1. The Sokoloff equation is

$$R = \frac{c_g}{LC} \cdot \frac{c_i(t) - k_1 x}{\int_0^t c_p(t')dt' - x}, \quad (1)$$

where

$$x = \int_0^t c_p(t') \exp[-(k_2 + k_3)(t - t')]dt',$$

c_i is the concentration of tracer in the tissue, c_p the concentration of tracer in the plasma, c_g the concentration of glucose in the plasma. LC is Sokoloff's lumped constant, t is the time interval from injection to scan, t′ is the variable of integration, ranging from 0 to t, and k_1, k_2, k_3, are the rate constants for FDG, as shown in Fig. 1.

The extended equation incorporating k_4 is (*3,4*)

$$R = \left(\frac{c_g}{LC}\right) \frac{c_i(t) - [k_1/(\alpha_2 - \alpha_1)] \int_0^t [(k_4 - \alpha_1)\, e^{-\alpha_1(t-t')} + (\alpha_2 - k_4)\, e^{-\alpha_2(t-t')}]c_p(t')dt'}{[(k_2 + k_3)/(\alpha_2 - \alpha_1)] \int_0^t [e^{-\alpha_1(t-t')} - e^{-\alpha_2(t-t')}]c_p(t')dt'}, \quad (2)$$

where

$$\alpha_{1,2} = \frac{1}{2}[k_2 + k_3 + k_4 \mp \sqrt{(k_2 + k_3 + k_4)^2 - 4k_2k_4}]. \quad (3)$$

Eq. (2) is identical to Eq. (1) if $k_4 = 0$.

The purpose of the present note is to present an alternative equation for metabolic rate that, while incorporating the k_4 correction, is simpler than both of the above equations. Our starting point is an intermediate equation (Eq. A13 of Ref. 4) for the total tissue concentration of tracer:

$$c_i(t) = A \int_0^t e^{-\alpha_1(t-t')}c_p(t')dt' + B \int_0^t e^{-\alpha_2(t-t')}c_p(t')dt', \quad (4)$$

where

$$A = k_1(k_3 + k_4 - \alpha_1)/(\alpha_2 - \alpha_1) \cong k_1k_3/(k_2 + k_3) \quad (5)$$

and

$$B = k_1(\alpha_2 - k_3 - k_4)/(\alpha_2 - \alpha_1) \cong k_1k_2/(k_2 + k_3). \quad (6)$$

(The above approximations, which are valid for $k_4 \ll k_2 + k_3$, are not used in the analysis, and are presented only to elucidate the meaning of the constants.)

Equation (4) expresses the tissue concentration as proportional to the integral of the plasma concentration multiplied by two exponential factors, reflecting the k_2 and k_4 backflow terms.

The key to the simplification is that the constant A is proportional to metabolic rate, which, following Eq. A27 of Ref. 4, may be expressed as

$$R = \frac{c_g}{LC} \frac{k_1k_3}{k_2 + k_3}. \quad (7)$$

But, by rearranging Eq. (5), we obtain

$$A = \frac{\beta k_1k_3}{k_2 + k_3} \quad (8)$$

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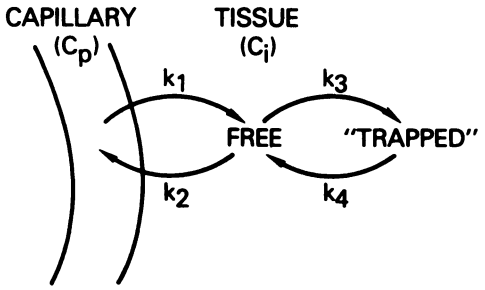

FIG. 1. Three-compartment model for FDG uptake, showing plasma concentration c_p and concentration of FDG in tissue c_i, which is subdivided into "free" and metabolically "trapped" (i.e., phosphorylated) components. Rate constants $k_1 - k_4$ are those that determine flow rates between compartments.

where

$$\beta = \left(1 + \frac{k_4 - \alpha_1}{k_3}\right)\left[\left(1 + \frac{k_4}{k_2 + k_3}\right)^2 - \frac{4k_2k_4}{(k_2 + k_3)^2}\right]^{-1/2}. \quad (9)$$

If $k_4 \ll k_2, k_3$, then $\beta \cong 1$.

Thus, solving Eq. (4) for A and using Eqs. (7) and (8), we have

$$R = \frac{c_g}{LC} \frac{c_i(t) - B\int_0^t e^{-\alpha_2(t-t')}c_p(t')dt'}{\int_0^t \beta e^{-\alpha_1(t-t')}c_p(t')dt'}. \quad (10)$$

If, following Sokoloff, we set $k_4 = 0$, the simplified equation becomes

$$R = \frac{c_g}{LC} \frac{c_i(t) - [k_1k_2/(k_2 + k_3)]\int_0^t e^{-(k_2+k_3)(t-t')}c_p(t')dt'}{\int_0^t c_p(t')dt'}. \quad (11)$$

The light-face terms in Eqs. (10) and (11) are corrections for backflow. Specifically, the light-face term in the numerator corrects for the fact that some of the tissue activity at time t is free FDG, which will flow back to the blood vessel (k_2) without being metabolized, and the light-face factor in the denominator of Eq. (10) corrects for the fact that some activity has been "untrapped" by the k_4 reaction. By omitting these terms we would have a zeroth-order approximation (bold face) expressing metabolic rate as the ratio of tissue concentration to blood integral multiplied by c_g/LC to convert from FDG to glucose. The important feature of these equations, as with Eqs. (1) and (2), is that the rate constants occur only in the correction terms, so that accurate knowledge of them is not required. This is important, since nominal or tabulated rate constants are usually used to calculate R.

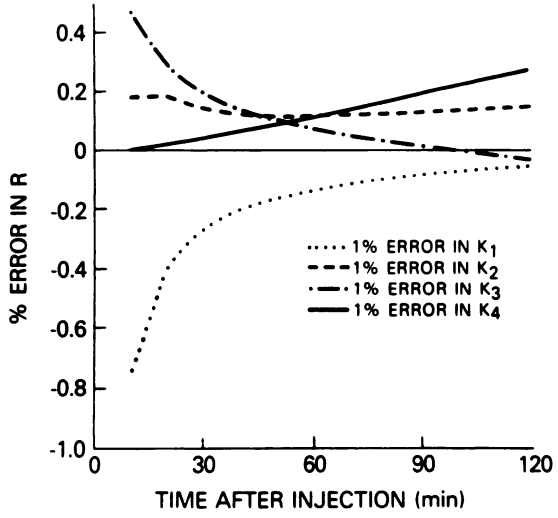

FIG. 2. Percent error in R as obtained with Eq. (10) arising from 1% error in rate constants. These errors are approximately half those shown in a similar plot in Ref. 4.

Equations (10) and (11) are not mere algebraic rearrangements of Eqs. (2) and (1), but have basically different correction terms. They are equivalent to the earlier equations only if Eq. (7) is valid, i.e., if proper rate constants are used. However, if the rate constants are not accurate for the tissue being studied, as is usually the case, the new equations will give different results. Both results will be erroneous, but the error will be different for each equation.

The error sensitivity of Eq. (2) was determined by Huang et al. (4) by taking partial derivatives with respect to the four rate constants, and multiplying each partial derivative by a 1% change in the corresponding constant. We evaluated the error sensitivity of Eq. (10) using the equivalent (and for us, easier) method of calculating R twice: first with nominal rate constants (4), and then with each rate constant altered, in turn, by 1%. (This method required, as an intermediate step, the determination of tissue concentration from Eq. (4).) The difference between the two R values, expressed in %, is plotted in Fig. 2 for the four rate constants, as a function of time. A comparison of this plot with that of Huang et al. (Fig. 6A, Ref. 4) shows that the present errors are in most cases about 50% lower.

To check this result in a more realistic setting, we calculated metabolic rates for gray and white matter for the population of 13 patients scanned with the PET Scanner* with scan times ranging from 45 min to 2 hr after injection, using nominal rate constants (4). We found that Eqs. (2) and (10) gave similar metabolic rates, to within ±0.5%, as expected. However, if the wrong rate constants were deliberately used—i.e., white-matter constants when calculating gray-matter values and vice versa—the average absolute error with Eq. (2) was 10%, whereas with Eq. (10) it was only 4%.

FOOTNOTE

* EG&G/ORTEC ECAT-II.

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