Validation of an Analytic Method of Calculating Cerebral Glucose Metabolism Using PET

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Quantitative modeling of cerebral metabolic rate for glucose (CMRglc) using PET with the FDG method requires calculation of the integral of the time course of radioactivity in arterial plasma. Numeric integration has typically been used but requires 30 or more blood samples taken between 15 s and 100 min after injection of the radiotracer. Our laboratory has developed an alternative integration method that fits the values of the plasma samples to an analytically integrable function using only 4–6 samples taken between 40 and 110 min after radiotracer injection. **Methods:** The plasma integrals were calculated by both the analytic and the numeric methods with data from FDG PET studies that were not used in the development of the analytic method. In 39 PET studies from 22 healthy volunteers, 30 plasma samples were taken over 110 min. **Results:** The plasma integrals determined by the analytic and numeric methods yielded a within-subject correlation coefficient of >0.95 and differences of <10%. **Conclusion:** Because the analytic method requires less blood sampling and does not require sampling immediately after radiotracer injection, the experimental procedure is simplified without loss of accuracy in CMRglc computation, and the effect of missing or incorrect samples is reduced.

Key Words: plasma integral; FDG PET; analytic method

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Quantitative modeling of cerebral metabolic rate for glucose (CMRglc) using PET with the FDG method is based on an equation that requires 3 measurements. The first is the concentration of FDG in the brain at steady state (typically 45 min or more after injection of radiotracer). The second is the concentration of FDG in the plasma (Cp), integrated over time (t) from the injection of radiotracer until the end of FDG measurement in the brain. The third is the concentration of glucose in the arterial plasma (*1,2*).

Two methods of calculating the integral of the time course of radioactivity in arterial plasma have been established. Numeric integration of the plasma curve has been used historically, but this method requires 30 or more blood samples taken between 15 s and 110 min after injection of the radiotracer, with rapid sampling during the first 15 min. Experimentally, this method can be cumbersome, and difficulties in drawing blood samples in quick succession can introduce a variety of errors, including missed or diluted samples or the inability to collect sufficient quantities of blood per sample. Although certain techniques, such as fitting a function that can be integrated analytically to the measured values of $Cp_n(t)$, have been attempted to correct for these sampling errors (*2,3*), a full blood curve reflecting the entire time course of Cp is still required. Thus, these correction efforts do not substantially improve the experimental protocol.

An alternative method of calculating the integral for arterial plasma radioactivity was developed at our laboratory (*4*). This method uses 4–6 plasma samples taken 40–110 min after radiotracer injection and fits the values of these plasma samples with a function suitable for analytic integration. The analytically derived integral estimates CMRglc with accuracy that matches that of the numeric method while reducing sensitivity to sampling errors and simplifying the experimental procedure.

We sought to validate the accuracy of the analytic method of calculating the integral for arterial plasma radioactivity and to compare it with the numeric method. For this validation, we used an independent set of data that were not used in the development of the analytic method.

MATERIALS AND METHODS

Data were derived from a clinical study of 22 healthy volunteers (2 women, 20 men; age range, 24–42 y). Every volunteer gave written informed consent to participate in the study, which was approved by our institutional review boards. Before participation, the volunteers underwent physical examination to exclude disease in any major organ, a history of head trauma, or a psychiatric diagnosis other than substance abuse.

Thirty-nine PET studies representing data from the 22 volunteers were used in the analysis. The experimental protocol investigated the neural basis of cocaine craving by exposing the volunteers to video presentations containing either cocaine-related cues or neutral cues during the FDG uptake period and then measuring brain activation with PET (*5*). Before injection of FDG, the participants fasted for 3–7 h and abstained from cigarette smoking for the same interval. Seventeen underwent PET 2 times, corre-

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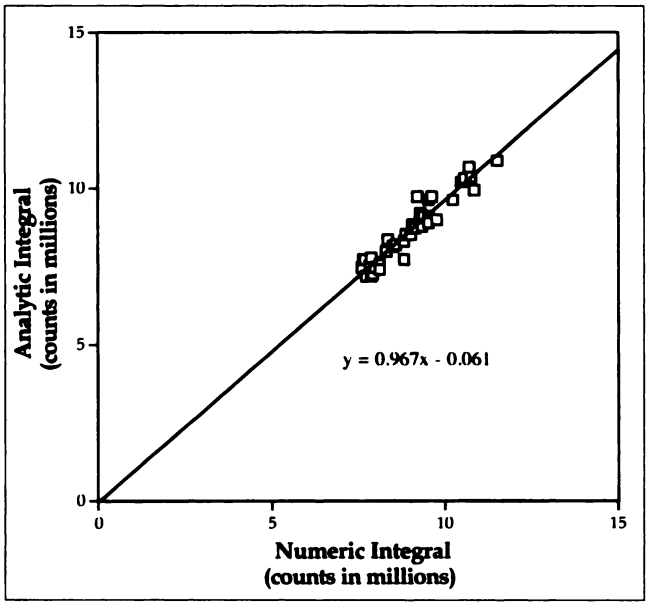

FIGURE 1. Comparison of plasma integral values (counts in millions) as determined by analytic and numeric methods.

sponding to each of the 2 cue-related conditions, whereas 5 underwent PET only once. All data were included in the analysis.

FDG was obtained from the National Institutes of Health in Bethesda, MD. Each batch of FDG was supplied as sterile, pure, and nontoxic. FDG (185 MBq in 5.0 mL saline) was infused manually for 30 s through a catheter in the antecubital vein and was followed by a saline flush.

Blood was sampled manually through an indwelling catheter in the radial artery. Between 30 and 35 samples were drawn during the PET session. Samples were drawn on a fixed schedule after injection of FDG: samples 1–8 were drawn every 15 s; samples 9–12, every 30 s; samples 13–14, once every minute; samples 15–18, once every 2 min; and samples 19–20, once every 5 min. The remaining samples were drawn once every 10 min until completion of the final PET scan. After the samples were centrifuged, aliquots of plasma from each were counted in a γ counter. Approximately 45 min after FDG injection, PET began.

The plasma integrals for each volunteer were calculated using both the numeric and the analytic methods. The equation for the numeric method of integration is found in Sokoloff et al. (*1*). The equation for the analytic method is $C_p(t) = b_1te^{(-\alpha 1t)} + b_2e^{(-\alpha 2t)}$ (*4*).

RESULTS

The plasma integral for arterial radioactivity, a requirement of the operational equation for determining CMRglc, was calculated in 2 ways: numerically and analytically. Figure 1 compares the integrals analyzed by these 2 methods. Regression of the calculated values for the integrals yielded a correlation coefficient > 0.95. The percentage difference between integrals calculated by numeric or analytic methods was <10%, with the analytically derived integrals being consistently lower than the numerically derived integrals.

These data replicate the results from our previous study, which had a correlation coefficient of 0.99 between the analytic and numeric integrals and a difference of <10% between the methods of data analysis (*3*). In that study, we showed that when the difference in integral calculation between the analytic and the numeric methods was <10%, the effect on CMRglc was negligible. Thus, the high correlation observed between the 2 methods suggests that either is valid for the operational equation.

Figure 2 shows the fit of the plasma samples to the plasma curve as predicted by the analytic method. This graph represents the mean ± SD of the data for each time point from 20 to 110 min for 39 studies. On average, each time point after 20 min shows less than a 2% difference between the actual radioactivity in plasma compared with that predicted by the analytic method. For time points between 45 and 110 min (the time points used in determining the analytic integral), the difference between the predicted and the actual plasma curves is 0.2% ± 0.4%. This difference is comparable with the results of our previous study, in which the percentage residuals were 0.03% ± 2.0%.

DISCUSSION

The results from this study validate the analytic method for calculating the plasma integral required for the operation

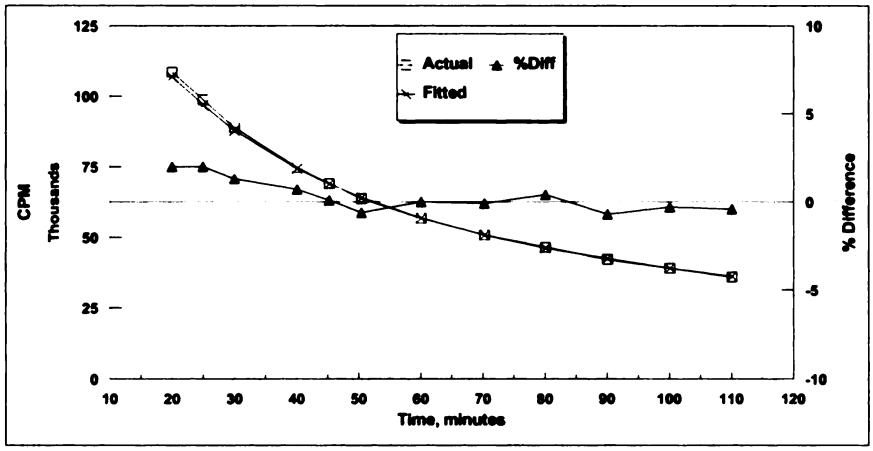

FIGURE 2. Average curve fit of plasma samples (n = 39) to predicted plasma curve for radioactivity, based on calculation of plasma integral using analytic method.

equation that determines CMRglc. Because the analytic method uses plasma samples drawn only every 10 min, and the samples are drawn later after injection of FDG, the experimental procedure is greatly simplified by elimination of the rapid blood sampling that the numeric method requires. This advance reduces the chance of error from poorly drawn or missed blood samples and provides a way to correct for any aberrant samples. Up to 2 samples may be eliminated from the total used in the fitting process, leaving 4–6 samples, a quantity that reduces the potential influence of sampling error in determining CMRglc.

CONCLUSION

The use of the analytic method for calculating the plasma integral greatly expands the ability to study individuals from whom repeated early blood sampling may be difficult. These include individuals who are elderly, have a history of intravenous drug abuse, or have physiologic dysfunction (from disease or drug administration) that reduces blood flow.

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