Evaluation of Kinetic Constants In The Brain Glucose Metabolism by The Weighted Integration Method: Studied with the TOF PET

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Ono S., Yamada K., Yoshioka S., Miyazawa H., Kinomura S., and Fukuda H.

Dept of Radiol and Nucl Med,The Research Inst for Tbc and Cancer, Tohoku University

Introduction

The functional mapping of the brain is an important tool for understanding the brain activity. One of good examples for this purpose is the measurement of the brain glucose metabolism. The utilization of glucose is believed to be parallel to the brain activity. To date, however, mechanism for increase of brain glucose metabolism in the activated state or decrease of that in the various pathological state is not elucidated enough. On the horizon of the Sokoloff's 3 compartment model for the glucose metabolism, its rate constants are to be investigated for elucidation of changes in the glucose metabolism.

The common method for calculation, the kinetic method, employs the fitting method to obtain these rate constants from the tissue and plasma time-activity curves after injection of [^{18}F]-2-fluoro-2-deoxy-D-glucose (FDG). This fitting method requires enormous iterative procedures, and thus long calculation time even on a computer of large capacity. Recently, an improved method was developed for calculation, which uses the weighted integration method (Ono et al., 1992). This method does not require iterative procedure and thus can be realized in much shorter time.

In the usual PET images, structures of relatively low RI concentration are affected by the surrounding high activity structures. Those activities are usually underestimated. Because of this count recovery problem, the rate constants of white matter which is close to gray matter that has much higher activity have not been calculated accurately. On the contrary, the time-of-flight (TOF) PET is believed to produce more accurate PET values in such cases (Ishii et al., 1989). Therefore we tried to investigate the more accurate rate constant of white matter by using this TOF PET and the weighted integration method along with those and glucose utilization of the gray matter calculated by the constrained FDG PET method.

Materials and methods

3 normal volunteers were injected with 3.3 to 4.8 mCi (122.1 to 177.6 MBq) of ^{18}F-FDG in a extended bolus fashion of 1 minute into their radial subcutaneous veins. Before the

PET studies, written informed consents were obtained from all of those subjects. Also they were studied with MRI for image reference previously. We started the data acquisition at the start of the injection. Simultaneously arterial blood samples were derived from previously inserted radial artery catheter every 15 seconds at the beginning of the studies followed by gradually increasing intervals. Those blood samples were centrifuged immediately and separated. We weighed and counted those obtained plasma samples to get accurate plasma time-activity curves. We obtained 10 of 1 minute scans followed by 5 of 2 minutes scans, and 2 of 5 minutes scans with the PT711 which is the TOF type advanced PET unit in the cyclotron RI center of Tohoku university (Ishii et al., 1989). During the studies, their eyes were closed, not patched under relatively dark light and ears were not plugged. We chose the slice of approximately 80 mm above the OM line which contains large components of white matter, centrum semiovale.

On those images, we put circular regions of interest (ROIs) of approximately 14 mm in diameter (17 voxels) on the cortical gray matter and the centrum semiovale with the aid of the MRIs carefully not to contain the other component. Those data were cross-calibrated to correlate with the plasma time-activity curves.

Then we analyzed these time-activity curves on a personal computer of usual ability. The operational equation for the analysis was the linear equation derived by Blomqvist (1984). This equation concerning the influence of tissue blood volume is shown in equation (1) where $A^*(t)$ is the tissue RI concentration as a function of time, $Ca^*(t)$ the plasma RI concentration, and V_0 the tissue blood volume. This influence of blood volume was eliminated by using particular weighting functions to make plasma time weighted integrals and double integrals into 0 as shown in equation (2) (Ono et al., 1992) where w(t) is the weighting function. Using this equation, we first obtained the value of K^* which is the net clearance of FDG from plasma, in both gray and white matter (equation (3)). Thereafter the values of K_1^* and the lumped constant were calculated using the constrained FDG PET method (Kuwabara et al., 1990) only in gray matter, because application of this constrained method is not validated for white matter. In this method, the lumped constant is expressed as equation (4), where LC is the lumped constant, phi the ratio between phosphorylation coefficient of FDG (K_3^*) and that of native glucose (Gjedde, 1981), and tau the ratio between unidirectional transport rate of FDG (K_1^*) and that of native glucose (Gjedde and Christensen, 1984). Finally we obtained regional glucose utilization (CMRglc) from those data as shown in equation (5) where Ca is the plasma glucose concentration. Those obtained data were compared with other published data.

Results

Figure 1 shows an example of tissue time-activity curves taken from a ROI of 17 voxels in gray matter. Generally, good agreement with usual time-activity curves was obtained. In these cases, the activity was high enough to be analyzed. As can be seen on this figure,

however, there was some influence of noise even though time-activity curves in voxels were averaged. In the first part of the curves, the instability was the largest. The coefficients of variation of voxel values in a ROI were 20 to 60%, sometimes over 100%.

Figure 2 is a tissue time-activity curve in white matter. As expected, activity was generally lower than in gray matter. And the curves were more unstable. The coefficients of variation were larger than those in gray matter, sometimes up to 300%. Even in the later part of the curves, this tendency was observed.

Table 1 shows the results of ROI analysis. In gray matter, those values were in the reasonable range. This method gives the most reliable values of K^*. In the case of K_1^*, the values were in the range of the previously published data. The lumped constant was a little higher than the usual values. Finally, we observed the values of CMRglc in a reasonable range. As expected, we obtained the lower values of K^* in white matter than those in gray matter. Although the standard deviation was larger, this value was in a reasonable range. In this calculation, however, we experienced a few cases of a quite unreliable output value i. e. negative values, extremely high values etc. which were out of the physiological range. As mentioned earlier, application of the constrained method is not validated for white matter. Even though knowing that fact, we tried to calculate the values of CMRglc in white matter and obtained the average value of 4.44mg hg^{-1} min^{-1} which was quite similar to the previously published data that were derived using the usual method.

Discussion

In this study, we used PT711, the TOF type PET unit. This machine has not only excellent time resolution but the strong advantage that it is devoid of statistical errors from the count recovery problem. We attempted to make the most of this point to elucidate glucose metabolism of white matter. The value of K^* in white matter was 0.0158 from data by Phelps et al. (1979) and 0.0223 from data by Reivich et al. (1985) (ml hg^{-1} min^{-1}). These previously published data cannot be free from this problem and thus are of limited accuracy. In contrast, our data of the rate constant, K^*, is calculated from tissue time-activity curves that were not influenced by the high activity of gray matter. Therefore we believe that our data is the most reliable in the rate constants in white matter.

In the case of gray matter, we could obtain reasonable values of rate constants. K^* was 0.0363 in our study which was almost comparable to those from data by Phelps et al. (0.0329) or by Reivich et al. (0.0338) (ml hg^{-1} min^{-1}). K_1^* was 0.102 ml hg^{-1} min^{-1} in our study which was strikingly the same as that by Phelps et al. These rate constants by the weighted integration method have been proved as reliable as those by the fitting method (Ono et al., 1992). Thus we might say that we are able to evaluate these rate constants precisely under this condition.

Although we used the TOF PET unit which theoretically has a good signal to noise ratio, we could not avoid the influence of noise. It is fact that there were a few cases, especially in

white matter, that we could not obtain parameters in the physiological range even though we used averaged tissue time-activity curves of 17 voxels in a ROI. As a speculation, analysis of voxel-by-voxel basis is not realistic in this condition. When evaluating gray matter, however, those problems were rare. In this context, this combination of the weighted integration method and the TOF PET is, as it is, a good tool for evaluation of glucose metabolism in gray matter. And we believe that this combination is able to produce the most accurate kinetic constant in white matter when used for ROI analysis or when used for voxel-by-voxel estimation after the problem of noise is overcome.

Reference

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Appendix:

Equation (1);

$$A^*(t) = V_oCa(t) + [K_1^* + (k_2^* + k_3^*)V_o] \int Ca(t) + K_1^*k_3^* \iint Ca(t) - (k_2^* + k_3^*)\int A(t)$$

Equation (2);

$$\int w(t)A^*(t) = K_1^*k_3^*\int w(t)\iint Ca^*(t) - (k_2^* + k_3^*)\int w(t)\int A^*(t)$$

Equation (3);

$$K^* = K_1^*k_3^*/(k_2^* + k_3^*)$$

Equation (4);

$$LC = \varphi + (\tau - \varphi)K^*/K_1^*$$

Equation (5);

$$CMRglc = K^*Ca/LC.$$

Table 1. The result of ROI analysis.

		K^*	K_1^*	LC	CMRglc
Gray matter	mean	0.0363	0.102	0.599	6.19
	SD	0.0121	0.0221	0.0821	1.17
	n		18		
White matter	mean	0.0214	-	-	-
	SD	0.0106	-	-	-
	n	10			

K^*, K_1^*: ml hg^{-1} min^{-1}
CMRglc: mg hg^{-1} min^{-1}

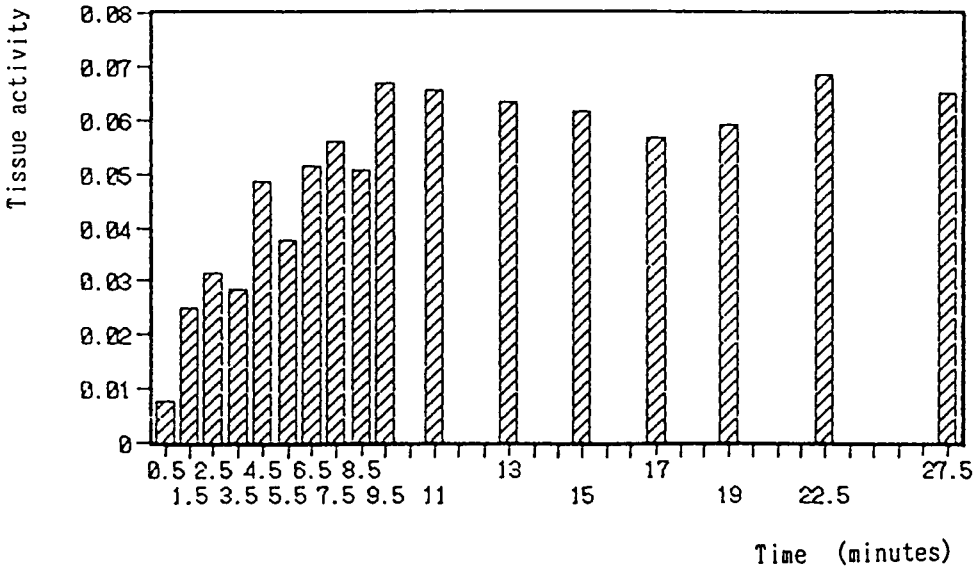

Fig. 1. Tissue time activity curve in gray matter.

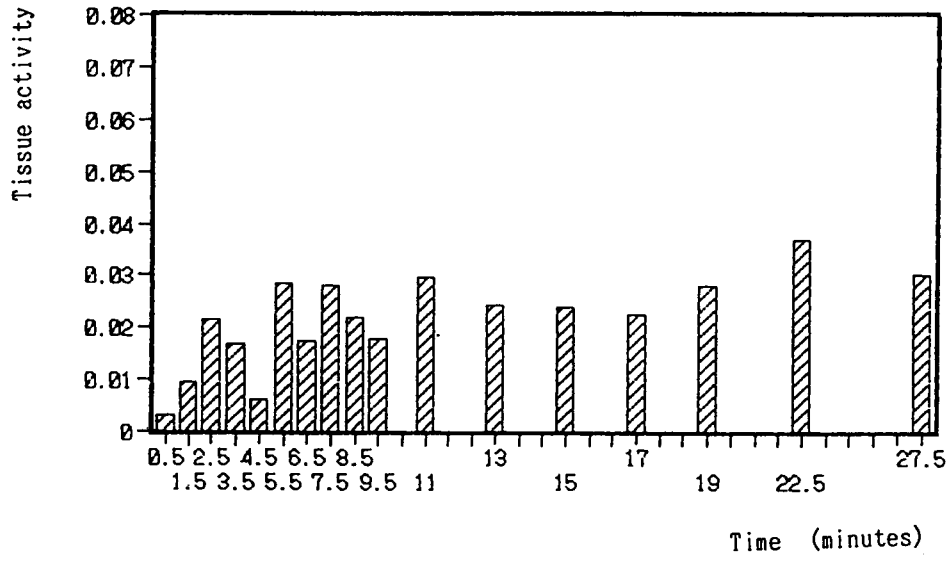

Fig. 2. Tissue time activity curve in white matter