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Determination of Regional Cerebral Glucose Transport and Utilization Rates in Man with ^{11}C-Glucose: Preliminary Results[1]

J.C. Depresseux, A. Feron, J.M. Peters, G. Del Fiore, L. Quaglia

Cyclotron Research Center, University of Liège, Belgium

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Abstract. This paper describes the methodology and the first results of a method of measurement of the cerebral metabolic rate of glucose, using ^{11}C-glucose and regional detection by probes. The present method has the advantages of being rapidly repeatable and of yielding a determination of the rates of transfer of glucose across the blood-brain barrier.

Introduction

The measurement of the regional cerebral blood flow with diffusible inert gases or non-diffusible tracers brought the hope of many potentials of progress in the understanding of cerebral circulation and function in man. Theses approaches nevertheless encounter several limitations, particularly in the interpretation of physiopathological phenomena – such as the luxury perfusion syndrome – and in the implementation of useful clinical applications.

The difficulty results mainly from the lack of non-invasive and reliable methods for the study of the cerebral metabolism in man.

The nervous and glial cells are restricted almost exclusively to glucose as the substrate for their energy metabolism. The measurement of the rate of cerebral uptake of glucose appears therefore as a valuable approach to the study of the energy supply and utilization in the various regions of the brain.

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Method

Glucose randomly labeled with carbon-11 is prepared in our laboratory by photosynthesis, using Chlorella algae rather than green leaves [1]. This original method of labeling has the advantage of yielding very high and reliable levels of activity of ^{11}C-*d*-glucose.

After radiochemical and radiopharmaceutical controls, 7 mCi of ^{11}C-*d*-glucose are injected intravenously. The regional transfer functions in the brain are detected and registered during the 3 min following the injection, by means of a multiprobe device with shields and collimators allowing the simultaneous study of up to 26 distinct cerebral area.

Table I. The main parameters ruling the transport and utilization of glucose in the brain computed with the ^{11}C-glucose method

Φ_{43}	cerebral metabolic rate of glucose	26.2	μmol glucose [100 g tissue]$^{-1}$ min^{-1}
Φ_{32}	forward flux of glucose through the BBB	87.2	μmol glucose [100 g tissue]$^{-1}$ min^{-1}
Φ_{23}	reverse flux of glucose through the BBB	61.0	μmol glucose [100 g tissue]$^{-1}$ min^{-1}
$Q_v W^{-1}$	intravascular free glucose mass	21.2	μmol glucose [100 g tissue]$^{-1}$
$Q_3 W^{-1}$	extravascular free glucose mass	132.0	μmol glucose [100 g tissue]$^{-1}$
C_3/C_v	brain-to-blood concentration ratio	0.529	

Values obtained in a normal subject are displayed. BBB = Blood-brain barrier.

The model of interpretation of the data and their numerical analysis are based on the previous experiments performed on monkeys by *Raichle* et al. [2, 3].

The unlabeled and labeled glucose are considered to be distributed through four subsystems, in each detected area of head: subsystem 1, the intravascular inexchangeable glucose in the arteries and veins; subsystem 2, the intravascular exchangeable glucose in the capillaries; subsystem 3, the extravascular unmetabolized glucose; subsystem 4, the metabolites of glucose.

Three main assumptions are at the basis of the mathematical formulation of the model.

(1) The transport and metabolism of labeled glucose are assumed to be ruled by the same dynamic constants as the substrate under study. In the present method, this assumption is valid, because of the biochemical identity between the tracer and the traced compound.

(2) The flow rate and concentrations of glucose through the system are assumed to be in a steady state during the time interval (3 min) of measurements.

(3) The outflow of ^{11}C-labeled metabolites of glucose is assumed to be negligeable between the injection time and the end of detection of the transfer function of glucose in the head. This point has been controlled and validated by *Raichle* et al. [2, 3].

The mathematical development of the model yields an equation with three parameters and two variables:

$$\chi = \frac{r_{hg}(T) - r_{vg}(T)}{\frac{\alpha}{\alpha - 1}\int_0^T r_{vg}(t)dt - \frac{\kappa}{\alpha - 1}\int_0^T e^{-\kappa t} r_{vg}(t)dt}.$$

The three parameters are as follows: χ is the ratio between the net flux of glucose to the tissues and the intravascular mass of glucose; α is the ratio between forward and reverse fluxes of glucose through the blood-brain barrier, and κ is the sum of the transport constants of glucose out of compartment 3.

The formula contains also two time-dependent variables: r_{hg} is the value of the transfer function of labeled glucose through the detection field, and r_{vg} is the corresponding value in the intravascular compartment.

The values of the variable r_{vg} are not measured directly but are computed from a second set of data, obtained after intravenous injection of ^{11}CO-tagged red blood cells.

The detection data obtained with the head probes and with an additional probe detecting the activity in an arterial catheter, after injection of ^{11}C-glucose and of ^{11}CO-erythrocytes, allow us to compute the function r_{vg}, with the aid of a convolution-deconvolution procedure.

Results

The results are displayed in two ways: (1) as an analytical display of the transfer functions of ^{11}C through the intravascular glucose, extravascular glucose and glucose metabolites compartments, and (2) as a table of derived parameters, particularly, the cerebral metabolic rate of glucose, and the parameters ruling the transport of glucose

through the blood-brain barrier, namely the glucose tissular concentration and space of diffusion and, also, the forward and reverse fluxes of glucose through the barrier (table I).

The results, obtained in the normal human at rest, are consistent with the values computed for the whole normal brain from the data obtained by *Reivich* et al. [4] using ^{18}F-fluorodeoxyglucose as a tracer.

Conclusion

These results are preliminary, but even now the attractiveness of the present method lies in its applicability to human studies, in its repeatability, in its potentiality for regional studies and, finally, in the possibility of assessing not only the uptake rate of glucose, but also the transport of this substrate through the blood-brain barrier. It appears to us that the possible alterations of this transport are not to be overlooked, especially in pathological cases and in pharmacological studies, and that the present method brings a valuable tool for research in the metabolism of the brain.

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J.C. Depresseux, Cyclotron Research Center, University of Liège, Liège (Belgium)