Symposium

The Measurement of the Local Cerebral Metabolic Rate for Glucose in Man with Positron CT in the Resting, Stimulated and Pathological States

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The capability of positron computed tomography (PCT) to delineate the substructures of the brain and its facility for accurately measuring the local tissue radioactivity concentration allow the application of tracer kinetic models for the study of local cerebral function in man. This principle and an adaption of the $^{13}$C-deoxy-glucose (FDG) has been used to determine the local cerebral glucose metabolic rate (LCMRGlc) in normal man at rest (2, 4, 9) and during sensory activation (8, 10) and the changes that occur in patients with a variety of cerebral disorders (1–3).

The in vivo measurement of the LCMRGlc in man requires the integration of three major components:

1. A tomography capable of providing analytical measurements of tissue radioactivity concentration,
2. A labeled compound that traces glucose utilization in a known and predictable manner, and
3. A tracer kinetic model that properly describes the kinetics of the labeled compound and of glucose and allows the calculation of LCMRGlc from PCT data.

The first requirement is met in our studies by the ECAT positron CT (5, 6). A PCT system designed to perform analytical measurements rather than to simply provide images, is the in vivo analogy of autoradiography. The autoradiograph provides quantitative tissue radioactivity measurements of excised brain slices (11) while PCT provides the equivalent measurement in vivo. The image reconstruction process (algorithm) used in PCT is the same as used in x-ray CT (6). The difference is that PCT collects the emission of radiation from labeled compounds administered to the subject. The final image in PCT thus represent the cross-sectional distribution of the labeled compound as opposed to x-ray attenuation of tissue with x-ray CT. Another way to view the distinction between these two modalities is that PCT provides physiologic information while x-ray CT provides morphology.

The requirements of the second component of this technique are met by deoxyglucose (DG). DG is a competitive substrate with glucose for the facilitated transport sites and for hexokinase (11). However, the end product DG-6-PO$_4$ is not a substrate for glycolysis or glycogen synthesis and is therefore trapped in the cell due to its low membrane permeability. Thus, intuitively the rate of...
accumulation or the net amount DG-6-PO₄ accumulated over a given period of time after an intravenous injection of DG is proportional to the rate of glucose utilization.

The third component is met by a tracer kinetic model which describes membrane transport and phosphorylation of glucose and DG. This concept is rigorously derived in the form of a compartmental tracer kinetic model by Sokoloff et al (11) for autoradiographic studies with ¹⁴C-DG. The same approach holds for DG labeled with ¹⁸F, FDG (7, 9), a positron emitting radionuclide that can be detected externally with PCT. Because PCT has a number of special requirements and a longer study time than autoradiography, we (7) have derived a new form of the tracer kinetic model. This model is an extension of Sokoloff et al’s model and takes into account the dephosphorylation of FDG-6-PO₄ that occurs at the late times after injection when PCT imaging is performed. The operational equation of this model is incorporated into the computer programs of the tomograph so that images are converted to units of LCMRGlc, e.g. mg/min/gm (7). This technique, PCT imaging of FDG and extraction of LCMRGlc values, is set up in such a manner at UCLA that the studies are now routinely carried out by nuclear medicine technicians (7). Kinetic studies with PCT have been employed to measure the rate constants of the model in different gray and white matter structures of the brain in both normal and ischemic states. The precision of the method in normals has been shown to be about ±5% for 1.5 to 2.0 cm² regions of the brain (7).

Studies in normals have yielded values for hemispheric CMRGlc that are in agreement with measurements using the Kety-Schmidt technique and LCMRGlc values in agreement with values in monkeys using DG autoradiography (2, 4). LCMRGlc was highest in the primary visual cortex, temporal cortex and basal ganglia and lowest in white matter structures such as the centrum semiovale and the corpus callosum (2, 4). Comparison between homologous regions in the right and left hemispheres performed at rest, failed to reveal any statistically significant difference in LCMRGlc (4).

Stimulation studies of the visual system have been performed and demonstrate a graded increase in LCMRGlc in the visual cortex to stimuli of increasing complexity (i.e. white light, checkerboard pattern, outdoor scene) (8). Studies of patients with lesions of the visual pathway (i.e. retinal thalamic, optic radiations) reveal decreases in visual cortical metabolism appropriate to the lesion’s location and extent (8). Studies in volunteers subjected to visual and more recently, auditory stimulation demonstrate the potential of this technique for investigating the human brain’s response to different stimuli.

Studies in patients with stroke show excellent correlation between the degree, extent and particular structures involved and the clinical symptoms (2). The method consistently detected hypometabolism in cortical, thalamic and striatal tissues which were dysfunctional due to deactivation or damage but which appeared normal on x-ray CT. Studies in patients with partial epilepsy have shown hypometabolic zones which correlated anatomically with interictal EEG spike foci and were associated with normal x-ray CT studies in 77% of the patients examined (3). The studies on epilepsy at UCLA have resulted in the integration of the LCMRGlc study into the clinical workup of patients with partial epilepsy that are candidates for surgical resection of their epileptogenic focus.

Studies on Huntington’s chorea, aphasia, dementia (1), schizophrenia, and tumors are in early stages of investigation but are also providing exciting new results and examples of these will be
presented. Further studies are needed to determine the role of the local functional information obtained with the PCT FDG method in elucidating basic cerebral mechanisms and the potential to aid in improving the approach to medical therapy.

REFERENCES