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Functional Imaging of the Brain with ^{18}F-Fluorodeoxyglucose

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DISCLAIMER

There is a large body of evidence in the literature demonstrating a close link between the functional activity of a region of the brain and its metabolic activity (16). This forms the basis for using metabolic studies to map the regions of the brain which are functionally activated in response to a given stimulus.

Roy and Sherrington in 1890 (19) were the first to postulate such a relationship between changes in functional activity in the brain and alterations in cerebral metabolism which then secondarily produce changes in local cerebral blood flow. Since then numerous studies have lent support to this hypothesis (1,4,13,14,20,22).

The development of the Kety-Schmidt technique (10) for the determination of average cerebral blood flow and metabolism in 1945 made it possible to measure these parameters directly in man for the first time. These studies in man confirmed the earlier animal experiments demonstrating metabolic and hemodynamic changes in the brain in association with functional changes. For example, it was found that depression of cerebral functional activity due to coma of varied etiologies was associated with a decrease in cerebral oxygen metabolism and that the reduced level of consciousness correlated roughly with the decrease in cerebral oxygen utilization (11). In patients with organic dementia, cerebral blood flow and metabolism are reduced and a definite correlation between the degree of depressed cerebral oxygen consumption and the degree of dementia has been reported (6,12).

Drug induced depression of cerebral functional activity as for example with anesthetic agents also results in a reduction of cerebral oxygen consumption (23). On the other hand, convulsant

agents have been shown in animal experiments to produce an increase in cerebral oxygen uptake during the induced seizure (5 ,21). Similar changes have been found during seizures induced in man. Brodersen et al.(2) found during electrically induced seizures in man a doubling of $CMRO_2$ and CMROglucose followed by a depression of metabolism during the postictal period.

The development of an autoradiographic technique for the measurement of local CMRgl in animals (24) has enabled studies of the relationship between functional activity and metabolism to be performed on a regional basis. For example, electrical stimulation of the sciatic nerve in the rat produces an increase in glucose consumption in the ipsilateral dorsal horn of the lumbar spinal cord (8). The production of focal seizure activity by the local injection of penicillin into the hand-face area of the motor cortex of the rhesus monkey results in a selective increase in glucose utilization in the motor cortex and in small discrete regions of the putamen, globus pallidus, caudate nucleus and thalamus of the same side; regions believed to be selectively activated during the seizure (3,8). Metabolic mapping of the primary visual system of the monkey in response to different conditions of visual input has been carried out (9). Following bilateral retinal stimulation different rates of glucose consumption were observed in at least four cytoarchitectural layers of the striate cortex. The most intense metabolic activity appeared to be in Layer IV, the locus of the termination of the geniculocortical pathway. Bilateral visual occlusion lowered the rates of glucose consumption in the striate cortex and markedly reduced the metabolic differentiation of the various layers. Unilateral visual

deprivation delineated the laminae of the lateral geniculate body and the ocular dominance columns of the striate cortex as well as the regions with normally monocular input in the striate cortex.

The exquisite specificity of the metabolic response to functional activation is demonstrated by a study of the rat vibrissal-cortical barrel system (7). Stimulation of one vibrissa produced an increase in glucose consumption in the corresponding cortical barrel column in the S1 barrel field. The increase in glucose utilization in the single column extended from lamina I through VI, with the greatest increase occurring in lamina IV. The diameter of the column of increased glucose uptake was 375-425 μm which corresponds very closely to the anatomic dimensions of the cortical barrel column.

With the development of a method for the determination of LCMRgl in man (17) it became possible to see whether changes in functional activity in the human brain could be detected by observing the concomitant metabolic alterations. The method for the determination of LCMRgl utilizes ^{18}F-2-fluoro-2-deoxyglucose ([^{18}F]-FDG). In this method [^{18}F]-FDG is used as a tracer for the exchange of glucose between plasma and brain and its phosphorylation by hexokinase in the tissues. The labeled product of metabolism, [^{18}F]-FDG phosphate, is essentially trapped in the tissue over the time course of the measurement. A model based on the assumptions of a steady state for glucose consumption, a first-order equilibration of the free [^{18}F]-FDG pool in the tissue with the plasma level, and relative rates of phosphorylation of [^{18}F]-FDG and glucose determined by their relative concentration in the precursor pool and their

respective kinetic constants for the hexokinase reaction has been developed (24). The following operational equation based on this model has been derived in terms of measurable variables:

$$R = \frac{C_T^*(T) - k_1^* e^{-(k_2^*+k_3^*)T} \int_0^T C_p^* e^{(k_2^*+k_3^*)t} dt}{\left[\frac{\lambda \cdot V_{max}^* \cdot K_m}{\phi \cdot V_{max} \cdot K_m^*}\right]\left[\int_0^T (C_p^*/C_p)dt - e^{-(k_2^*+k_3^*)T} \int_0^T (C_p^*/C_p) e^{(k_2^*+k_3^*)t} dt\right]}$$

where R = the calculated rate of glucose consumption per gram of tissue;

C_T^* = the concentration of FDG + FDG-6-phosphate in the tissue;

C_p^* = the arterial plasma concentration of FDG;

C_p = the arterial plasma concentration of glucose;

k_1^* = the rate constant for the transport from plasma to the tissue precursor pool of FDG;

k_2^* = the rate constant for the transport back from the tissue precursor pool to plasma for FDG;

k_3^* = the rate constant for the phosphorylation of FDG in the tissue;

λ = the ratio of the distribution volumes of FDG in the tissue to that of glucose;

ϕ = the fraction of glucose that once phosphorylated continues down the glycolytic pathway;

and K_m^* and V_{max}^* and K_m and V_{max} are the kinetic constants of hexokinase for FDG and glucose respectively.

The latter six constants can be combined into one constant which has been designated the lumped constant ($\lambda \cdot V_{max}^* \cdot K_m / \phi \cdot V_{max} \cdot K_m^*$).

The three-dimensional distribution of ^{18}F activity in the brain (C_T^*) is quantified by positron emission tomography. In the work reported here the PETT III Scanner at Brookhaven National Laboratory was used. This instrument consists of 48 NaI (Tl) scintillation detectors in a hexagonal array. Each side of the hexagon has 8 detectors mounted on a platform capable of rectilinear motion and the entire hexagon is mounted on a gantry capable of rotating. Collimation is achieved by measuring only positron annihilation radiation by having each detector in coincidence with all the detectors in the opposite bank. With translation of the banks (1 cm) and rotation of the gantry (60 degrees in 3 degree increments) the radioactivity in the brain tissue is measured from a number of angles. A reconstruction algorithm similar to that used in CAT scanning allows local tissue isotope concentration to be calculated. The intrinsic spatial resolution of the PETT III is 1.7 cm fullwidth-half maximum (15).

In addition to the determination of the distribution of brain ^{18}F-activity knowledge of both the arterial blood plasma glucose and [^{18}F]-FDG concentrations as a function of time following the intravenous administration of [^{18}F] is required. The [^{18}F]-FDG is administered as a bolus and then 30 minutes are allowed to elapse before the brain distribution of ^{18}F activity is determined in order to minimize the amount of free ^{18}F-FDG in the precursor pool. Thus most of the ^{18}F activity in the section scan is in the form of ^{18}F-FDG-PO_4. Correction is made for the small amount of free ^{18}F-FDG present from knowledge of the arterial plasma ^{18}F-FDG time course and the turnover rate of the precursor pool.

With this information plus knowledge of the values for k_1^*, k_2^*, k_3^* and the lumped constant for fluorodeoxyglucose in man,

which have been determined in a series of normal subjects (18), it is possible to calculate the value of local cerebral glucose metabolism for any region of the brain with a resolution of 1.7 cm.

In addition to using this technique to make quantitative measurements of LCMRgl in man, we investigated its usefulness in mapping functionally active systems of the brain in response to a physiologic stimulus.

We examined three different stimuli; a visual, a tactile and an auditory stimulus in a series of seventeen normal subjects. Each of the stimuli was started 2 to 3 minutes prior to the intravenous administration of [^{18}F]-FDG and was continued for 60 minutes following injection. The section scans were started 30 minutes after the FDG injection. Each scan took 10 to 14 minutes and 6 to 8 scans were obtained at 1 cm levels through the region of interest of the brain. Figure 1 is a drawing of a lateral and medial view of the human brain with the plane of the scans indicated and their relationship to the striate cortex, somatosensory cortex, and primary auditory cortex illustrated.

In the visual study the subject was asked to look into an 18" diameter plexiglas hemisphere positioned 28" from his eyes. He was asked to fixate on a small light located at the center of the hemisphere which was dimmed at random so slightly as to be detectable only by foveal vision. The subjects reported the dimming events with greater than 95% accuracy indicating good visual fixation. One-half of the plexiglas hemisphere was painted black and the other half remained clear. In the latter hemifield a well-illuminated, slowly moving high-contrast black and white pattern of small lines at various orientations was placed. The visual studies were per-

formed in six subjects, three of whom had their left visual field stimulated and three their right. In all six subjects in whom one visual field was stimulated, the glucose consumption in the contralateral striate cortex was greater than that in the ipsilateral striate cortex. Normal control subjects not receiving a visual stimulus exhibited symmetry in glucose metabolism in the striate cortex. The striate cortex is located in section scan planes OM+4 and OM+5 (Fig. 1). In the subject shown in Figure 2 the metabolic rate in the right striate cortex, contralateral to the stimulated visual field, was 25% to 30% greater than that of the ipsilateral striate cortex.

In the tactile study the stimulus consisted of light stroking of the volar and dorsal surface of the fingers and hand of one arm with a brush. Five subjects were studied, two of which received a stimulus to the left hand and three to the right hand. Scans from unstimulated control subjects at levels OM+8 and OM+9 through the hand area of the somatosensory cortex showed bilateral symmetry while a scan at the same level from a subject in whom the left hand and fingers were stimulated exhibited increased glucose utilization in the hand area of the right postcentral gyrus (Figure 3). The metabolic rate for glucose of the right postcentral gyrus is 15% greater than the homologous area in the left hemisphere. It should be noted that the region of increased glucose consumption extends well beyond the somatosensory cortex. In 4 out of 5 of the subjects glucose utilization was greater in the postcentral gyrus contralateral to the stimulated hand.

In the auditory study, subjects with normal hearing defined as 15 dB hearing threshold level or better at frequencies of 250 Hz through 8000 Hz were used. The stimulus consisted of a tape recorded

story presented monaurally by means of earphones. Both ears of the subject were covered with earphones housed in Maico auditory enclosures providing 30 to 35 dB attenuation. The auditory stimulus was presented at 75 dB sound pressure level. The subject's task was to recount as much detail of the story as possible at the end of the study and they were told that they would be paid in proportion to the details remembered. Auditory studies were performed in six right-handed subjects. Three received the auditory stimulus via the right ear and three via the left.

The primary auditory cortex is located in section scan plane OM+4. In the six subjects receiving the auditory stimulus an increase in glucose metabolism was present in the right temporal cortex independent of the ear into which the stimulus was introduced. Figure 4 is a section scan at OM+4 at the level of the auditory cortex in a subject receiving the auditory stimulus in the left ear. The right temporal cortex has a metabolic rate for glucose 30% greater than the homologous region of the left hemisphere. This area of increased glucose metabolism extends well beyond the primary auditory cortex. Subjects receiving the stimulus in the right ear showed quantitatively similar results with the right temporal cortex always more metabolically active than the left.

In eight control subjects not receiving any stimulation the mean side to side difference in cerebral metabolic rate for glucose in any region of the brain did not exceed 6%.

These studies demonstrate that by mapping the local changes in cerebral glucose metabolism it is possible to determine which regions of the human brain become functionally active in response to a specific stimulus. This technique should be useful not only in studying physiologic changes in normal subjects but in pathologic

conditions in which an area may be normal structurally but be disconnected from other areas of the brain or be unable to function because of metabolic derangements. Such changes would not be detected by angiography or x-ray tomography (CAT scan) whereas methods that measure functionally related parameters may demonstrate the changes that are present.

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