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Assessment of Regional Glucose Metabolism in Aging Brain and Dementia with Positron-Emission Tomography

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Introduction

The first measurements of cerebral blood flow and metabolism in patients with dementia were performed by Freyhan, et al. (5) in 1951 utilizing the newly developed nitrous oxide technique for the measurement of cerebral blood flow (13). These measurements of flow and oxygen metabolism were average measurements for the whole brain. Since then additional studies of cerebral oxygen metabolism and studies of cerebral glucose metabolism in aging and dementia have been performed (12,16,19,30,31). However, it was not until the introduction of the ^{18}F-fluorodeoxyglucose method (27) has it been possible to make regional measurements of metabolism in the human brain. Investigators from our group and elsewhere have used this technique for the determination of alterations of regional cerebral glucose metabolism in response to a variety of sensory stimuli (7,26), seizure disorders (14), psychoses (2), and cerebrovascular accidents (15). The purpose of this paper is to explore the alterations in regional glucose metabolism that occur in elderly subjects and those with senile dementia compared to normal young volunteers.

Methods

The measurement of regional glucose metabolism in humans (27) is based upon the ^{14}C-deoxyglucose autoradiographic technique for the determination of LCMRgl in animals (32). In this method ^{18}F-2-fluoro-2-deoxy-D-glucose (^{18}F-FDG) is used as a tracer for glucose metabolism. Based upon the model shown in Figure 1 and several assumptions

ennumerated below, an operational equation can be developed which enables one to determine LCMRgl in terms of measurable parameters. This model considers that glucose and ^{18}F-FDG share and compete for a common transport carrier between plasma and brain tissue. Once transported into a common homogeneous precursor pool, glucose and ^{18}F-FDG either compete for a common carrier for transport back from brain to plasma or for hexokinase for phosphorylation to their respective hexose-6-phosphates. It is assumed that ^{18}F-fluoro-deoxyglucose-6-phosphate (^{18}F-FDG-6-P), once formed, is not further metabolized and is trapped in the tissues. This assumption, however, is not necessary and, as shown by Phelps, et al., (25), the model can be extended to include the presence of phosphatase activity in the brain. This, however, is in very low concentrations in the brain and for studies performed over a period of 50 minutes this term can be omitted.

In order to use this model to quantify the rate of local cerebral glucose utilization, the following assumptions, in addition to those above, are required: (1) the local region is homogeneous with respect to blood flow, rates of transport of glucose and ^{18}F-FDG between plasma and tissue, and rates of phosphorylation of glucose and ^{18}F-FDG, (2) these rates and the plasma glucose concentration are constant during the period of measurement, (3) the ^{18}F-FDG and glucose are present in a single compartment in each homogeneous local region, (4) the ^{18}F-FDG and ^{18}F-FDG-6-P are present in trace amounts and (5) the arterial plasma concentrations of glucose and ^{18}F-FDG are approximately equal to their capillary plasma concentrations. Since the cerebral extraction ratios of glucose and ^{18}F-FDG are normally very low,

approximately 10%, the mean capillary plasma concentrations are fairly well approximated by the arterial plasma concentrations. On the basis of this model and these assumptions, the following operational equation can be derived.

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

where R = the calculated rate of glucose consumption per gram of tissue; C_T^* = the concentration of ^{18}F-FDG + ^{18}F-FDG-6-P in the tissue; C_p^* and C_p = the arterial plasma concentrations of ^{18}F-FDG and glucose, respectively; k_1^*, k_2^*, k_3^* are the rate constants for the transport from plasma to the tissue precursor pool, for the transport back from tissue to plasma, and for the phosphorylation of ^{18}FDG in the tissue, respectively; λ = the ratio of the distribution volume of ^{18}F-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 ^{18}F-FDG and glucose, respectively. The latter six constants can be combined into one constant, which has been designated the lumped constant $(\lambda \cdot V_{max}^* \cdot K_m / \phi \cdot V_{max} \cdot K_m^*)$.

Thus, by quantitating the total ^{18}F activity regionally by means of positron emission tomography, measuring the time course of arterial ^{18}F-FDG specific activity and knowing the values of k^*_1, k^*_2, k^*_3, and the lumped constant for ^{18}F-FDG in man it is possible to calculate the LCMRgl in various structures of the brain.

In these studies the regional ^{18}F activities were determined with the PETT III scanner at Brookhaven National Laboratory. This scanner

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 detectors in the opposite bank. With translation of the banks and rotation of the gantry 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 in the plane of the section is 1.7 cm full-width-half-maximum.

In addition the 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-FDG is required. In order to minimize the amount of free ^{18}F-FDG in the precursor pool, 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. Thus, most of the ^{18}F activity in the section scan is in the form of ^{18}F-FDG-6-P. 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.

Nine normal young male volunteers of mean age 22 years (range 19-26) were studied. Four elderly normal subjects of mean age 72 years (range 60-86) were also examined as were eight patients with a

diagnosis of senile dementia of mean age 72 (range 64-78). The elderly control subjects and the patients with senile dementia were evaluated by a battery of psychometric tests. The Guild Memory Scale and WAIS vocabulary sub-tests were used. Individuals with a previous history of neuropsychiatric conditions or severe cardiopulmonary disorders were excluded. On the basis of the psychometric testing each subject was assigned a Global Deterioration Scale (GDS) rating of 1-7 as follows: 1 = normal, 2 = very mild, 3 = mild, 4 = moderate, 5 = moderately severe, 6 = severe, and 7 = very severe.

The measurement of local cerebral glucose metabolism was performed as previously described (27). Briefly, this consisted of the insertion of a radial artery catheter under local anesthesia following which the subject was made comfortable in the scanner and the head positioned in a restraining device. The orbital medial line was positioned perpendicular to the horizontal plane of the scanner. An intravenous bolus of 70-140 μCi/Kg body weight of ^{18}F-FDG was then administered. The arterial ^{18}F-FDG specific activity time course was measured by withdrawing blood samples from the radial artery. These samples were withdrawn every 15 seconds for the first minute, every minute for the next 9 minutes, then every 5 minutes for 30 minutes, and finally, every 15 minutes until the end of the study. With this information plus the tissue ^{18}F activity determined from the section scan and knowledge of the rate constants and lumped constant for ^{18}F-FDG in man (28) LCMRgl was calculated for various regions of the brain in the normal subjects and patients with senile dementia.

Results

The mean metabolic rates for various gray matter areas of the brain were determined in all three groups (Table 1). In the young subjects the metabolic rates ranged from 4.1 mg/100 g/min (frontal cortex) to 14.2 mg/100 g/min (visual cortex). The metabolic rates ranged from 3.1 mg/100 g/min (frontal cortex) to 6.9 mg/100 g/min (visual cortex) in elderly controls and from 2.1 mg/100 g/min (frontal cortex) to 6.3 mg/100 g/min (visual cortex) in patients with senile dementia. The mean cortical value (average metabolic rates from frontal, auditory, and visual cortices) was 6.5 ± 2.9 mg/100 g/min for the young controls, 4.8 ± 1.0 mg/100 g/min in the elderly controls and 3.7 ± 0.9 mg/100 g/min in the demented patients. There was a signficant difference between the mean cortical values obtained in young controls and patients with dementia ($p < .05$). However, no significant difference in metabolic rates was found between the latter group and the elderly controls or the elderly controls and the young control subjects. In general, the metabolic rates were relatively lower in the frontal areas of patients with dementia. The metabolic activity was symmetric in all three groups (Table 2). There was no correlation between the mean cortical metabolic rates and the Global Deterioration Scale rating as determined by psychometric studies in either elderly controls or patients with dementia (Table 3). No attempt was made to correlate the regional metabolic rates with a specific psychometric measurement.

Discussion

Freyhan, et al. (5), in 1951 made the first measurements of cerebral blood flow and metabolism in patients with senile dementia. They found that there was a significant reduction in cerebral blood flow from a normal value of 54 to 41 ml/100g/min and in cerebral oxygen consumption from a normal value of 3.3 to a mean of 2.8 ml/100gm/min. Lassen et al. (19) studied cerebral oxygen consumption in a group of patients with dementia. The average cerebral blood flow in the group of demented patients was significantly lower than that of normal subjects of comparable age. They also found a significant correlation between the cerebral metabolic rate of oxygen and the degree of dementia that was present. In a further study by Lassen et al. (16) aged normal subjects with an average age of 72 years were compared with young normal adults. Their cerebral metabolic rate for oxygen was found to be significantly lower (9%) than that of the young normal subjects. In addition, nine subjects with organic dementia (average age 74 years) were examined and found to have a cerebral oxygen consumption significantly below that of both the young normal and aged normal subjects, being on the average 20% below the level found in young normal adults.

The relationship between age and cerebral blood flow and cerebral oxygen consumption was examined by Kety (12). During the first decade of life, values for both cerebral blood flow and oxygen consumption are relatively high, almost twice the value found in the early 20's. There is a rapid decline in both of these parameters in the second decade. From the third decade on there is a more gradual decline

through middle and old age to a value of approximately 75% of that in the early 20's. Sokoloff (30) studied a selected group of healthy elderly subjects. The subjects were free of any evidence of disease including vascular disease. There was no significant difference in their cerebral blood flow or oxygen consumption compared to normal young subjects. There was, however, a significant decrease in cerebral glucose metabolism. This consisted of approximately a 25% decline compared to the young normal subjects. In a similar group of elderly men, differing only in that they had clear evidence of minimal asymptomatic disease, chiefly vascular, there was a significant decrease in cerebral blood flow of approximately 15%. The cerebral oxygen consumption was not significantly different, but again, cerebral glucose metabolism was approximately 20% below the value for young normal subjects. On the basis of these data it was suggested that the decreases in cerebral blood flow and oxygen consumption reported in elderly subjects are not the consequences of chronological age per se but rather of concomittant disorders, primarily atherosclerosis, which causes a relative cerebral circulatory insufficiency and hypoxia and then after a protracted period of the latter, cerebral tissue damage with consequent reduction in cerebral metabolic rate.

In patients with senile dementia both oxygen and glucose metabolism are depressed compared to elderly control subjects with the depression in glucose metabolism being greater than oxygen metabolism (31). The disassociation between oxygen uptake and glucose consumption by the brain in elderly subjects and patients with dementia may be due in part to the utilization by the brain of substrates other than glucose.

Gottstein et al. (6) have shown in normal subjects fasting for 12 to 18 hours that there is a significant uptake of acetoacetate and hydroxybutrate by the brain. This had been shown previously by Owen et al. (24) in three obesse subjects who had fasted for 40 days. The findings of Gottstein et al. (6) revealed that even in normal subjects with minimal fasting the brain utilizes ketone bodies. They found that about 10% of the oxygen consumed by the brain is required for the oxidation of these ketone bodies. It may be that in normal aging and senile dementia the observed disassociation between oxygen and glucose metabolism is due to an even greater percent of the oxygen being utilized for the oxidation of ketone bodies.

Following the introduction of the intracarotid ^{85}Kr and ^{133}Xe techniques, it became possible to measure regional cerebral blood flow (17,18). Obrist et al. (21) using the ^{133}Xe intracarotid injection technique, measured regional cerebral blood flow in a group of patients with senile dementia and presenile dementia and compared the results to normal healthy control subjects. Significant overall reductions in cerebral blood flow and relative gray matter weight were found in both the senile and presenile groups which correlated well with the degree of dementia. In the senile patients blood flow reductions occurred primarily in the gray matter while in the presenile patients, both the gray and white matter flows were reduced. Focal reductions in flow were consistently found in the frontal-temporal region in the patients with senile dementia but had a more variable localization in the presenile patients. Similar studies by Ingvar and Gustafsen (10), Simard et al. (29), and Lavy et al. (20) have confirmed these findings.

Hagenberg and Ingvar (9), in addition to the generalized decrease in flow in patients with presenile dementia, were able to demonstrate focal flow abnormalities correlated with specific cognitive defects. Patients who showed only memory disturbances demonstrated a focal flow reduction in the temporal region. More severely affected patients with reduction of verbal abilities and signs of agnosia showed very low flows in occipital-temporal-parietal regions of the hemisphere. Gustafsen et al. (8) found that in patients with presenile dementia and expressive aphasias flow was focally decreased in Wernicke's and Broca's areas.

The effects of activation with various forms of psychological tests on regional blood flow was examined by Ingvar et al. (11). They found that during activation the flow augmentation in the association areas in the demented patients was not as marked as in normal control subjects. Thus, organic dementia appears to be accompanied, not only by a low level of functional activity in the association cortex, but also by a reduced ability to activate these regions during mental effort.

The intracarotid ^{133}Xe technique is an invasive procedure and requires administration of this radionuclide into the internal carotid artery for each study. This has prevented its use as a routine test for the evaluation of neuropsychiatric disorders. Furthermore, usually only one hemisphere is studied by this technique excluding comparison of the two hemispheres.

The use of noninvasive cerebral blood flow techniques (22,23) either by inhalation or intravenous administration of ^{133}Xe has permitted the

measurement of regional flow in both hemispheres on a routine basis. With this technique, Obrist et al. (23) and Wang and Busse (33) have shown a significant difference between aged normal subjects and young normal subjects. They also demonstrated significant flow reductions in demented patients compared to a normal age-matched group. They concluded that blood flow declines significantly in the average (unselected) old individual and this reduction is noted earlier and is of greater magnitude when accompanied by intellectual deterioration. They found a good correlation between the cerebral blood flow findings in the aged group and the performance on standard psychological testing. Using Obrist's technique, Baer et al. (1) and Lavy et al. (20) have shown a decline in cerebral blood flow with aging and further reduction with both presenile and senile dementia.

Although measurements of regional blood flow have been conducted, until now, it has not been possible to measure changes in regional glucose consumption in patients with dementia. Our data have revealed decreased regional metabolic rates for glucose in normal elderly subjects compared to young normal subjects and a further decline in patients with dementia. However, only the change in metabolic rates from normal young subjects to patients with dementia was statistically significant. With larger numbers of subjects, the differences in LCMRgl between the elderly normal subjects and young normal subjects and between demented patients and elderly normal subjects may become significant. With the introduction of higher resolution scanners, significant regional differences among these groups may become apparent. In this study there was a tendency for the frontal regions

to have a lower metabolic rate in patients with dementia although this did not reach the level of significance when compared to the elderly control subjects. The changes in glucose metabolism were symmetrical in both the left and right hemispheres.

These results are consistent with similar findings with regional blood flow determinations and with the only other measurements of LCMRgl in dementia which were performed by Ferris et al. (3). The latter investigators found a 33-37% decline in LCMRgl in patients with dementia compared to elderly control subjects. In addition, they found a correlation between the LCMRgl and the cognitive deficit in their patients. In the present study there was a lack of correlation between the mean cortical metabolic rates for glucose and the global mental function in the patients with senile dementia. This is at variance with most of the regional cerebral blood flow data that has been collected. This may be partly related to the use of substrates other than glucose by the brain in elderly and demented subjects. This could be further evaluated by the measurement of local cerebral oxygen consumption which would enable an estimate to be made of the proportion of oxygen being utilized for the oxidation of substrates other than glucose. It is now possible to make such measurements of regional cerebral oxygen consumption using oxygen-15 and positron emission tomography (4).

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Table 1

LCMRgl mg/100 g/min *

Area	Young Controls n = 4	Old Controls n = 4	Senile Dementia n = 8
Frontal	6.3 ± 2.4	3.8 ± 1.0	2.9 ± 0.8
Auditory	6.2 ± 2.5	4.4 ± 0.8	3.7 ± 1.1
Visual	6.9 ± 2.6	5.6 ± 1.3	3.3 ± 1.1

Table 2

LCMRgl (L/R ratio)

	Young Controls n = 9	Elderly Controls n = 4	Senile Dementia n = 8
Frontal Cortex	.98 ± .02	1.01 ± .06	.96 ± .03
Auditory Cortex	1.00 ± .05	1.02 ± .07	1.02 ± .15
Visual Cortex	.99 ± .02	.98 ± .03	.96 ± .03

Table 3

LCMRgl mg/100 g/min

	Global Rating	n	Mean *	Range
Old Controls	1	4	4.6 ± 1.0	3.5 - 5.7
Senile Dementia	3-5	8	3.7 ± 0.9	2.5 - 5.2
Group 1	3		4.0 ± 1.2	2.8 - 5.2
Group 2	4		3.4 ± 1.2	2.5 - 4.2
Group 3	5		3.5 ± 0.7	3.0 - 4.3

* Mean ± stand deviation.

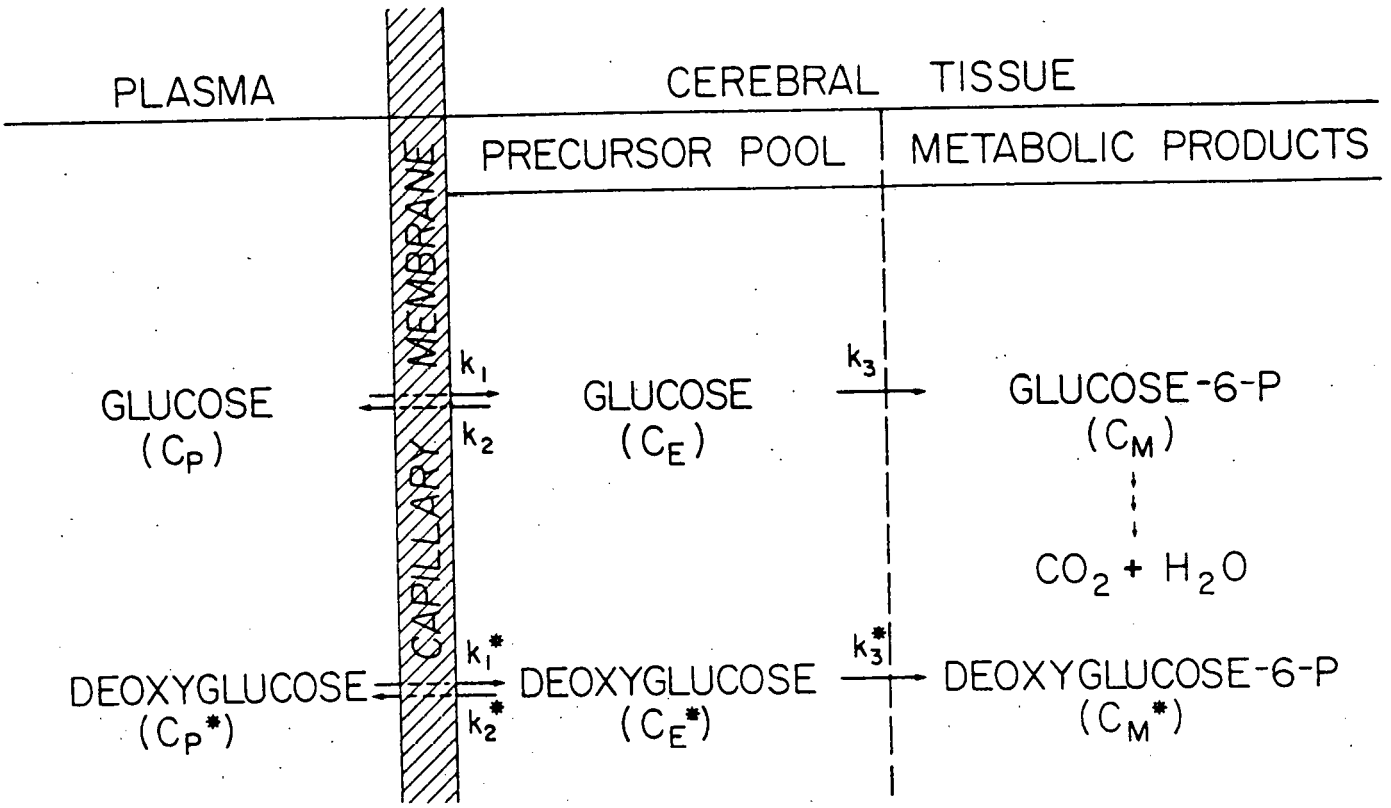
PLASMA
CEREBRAL TISSUE
PRECURSOR POOL
METABOLIC PRODUCTS
CAPILLARY MEMBRANE
GLUCOSE
(Cp)
k1
k2
GLUCOSE
(CE)
k3
GLUCOSE-6-P
(CM)
CO2 + H2O
DEOXYGLUCOSE
(Cp*)
k1*
k2*
DEOXYGLUCOSE
(CE*)
k3*
DEOXYGLUCOSE-6-P
(CM*)

Figure Legend:

Fig. 1. Theoretical model for transport and metabolsim of glucose and deoxyglucose in the brain. Cp and Cp* represent the concentrations of glucose and ^{11}C-deoxyglucose in the arterial plasma, respectively; C_E and C_E* represent their respective concentrations in the tissue pools that serve as substrates for hexokinase; and C_M and C_M* represent the concentrations of glucose-6-phosphate and ^{11}C-deoxyglucose-6-phosphate in the tissue. The constants k_1^*, k_2^* and k_3^*, represent the rate constants for carrier mediated transport of ^{11}C-deoxyglucose from plasma to tissue, from tissue back to plasma, and for phosphorylation by hexokinase, respectively. The constants k_1, k_2, k_3, are the equivalent rate constants for glucose.