BNL--30225

DE82 004782

# REGIONAL CEREBRAL GLUCOSE METABOLISM IN AGING AND SENILE DEMENTIA AS DETERMINED BY 18F-DEOXYGLUCOSE AND POSITRON EMISSION TOMOGRAPHY

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Supported in part by USPHS Grant 14867-02.

## Introduction

Studies of the effect of aging and dementia on the cerebral circulation and metabolism started shortly after the introduction of the nitrous oxide technique by Kety and Schmidt in 1948 (1). This technique, however, only measures average cerebral blood flow and metabolism. With the use of positron emission tomography in conjunction with appropriate radiopharmaceuticals, it has become possible to measure regional cerebral function relatively noninvasively in man (2). Investigators from our group and elsewhere have used this approach in the mapping of cerebral metabolism and function in response to a variety of sensory stimuli (3,4), seizure disorders (5), psychoses (6) and cerebrovascular accidents (7). In this communication we discuss the use of positron emission tomography in the evaluation of aging and senile dementia.

## Background

Following the introduction of the $^{14}$C-2-deoxyglucose ($^{14}$C-DG) technique, for the first time it became possible to measure the rates of glucose metabolism in specific discrete regions of the brain in different states of functional activity (8). This substrate is phosphorylated by hexokinase to $^{14}$C-DG-6 phosphate. Because $^{14}$C-DG-6-$PO_4$ is not a substrate for either phosphohexose isomerase or glucose-6-phosphate dehydrogenase, it is essentially trapped in the tissue over the time course of the measurement. A model has been designed based on the assumptions of a steady state for glucose consumption, a first-order

equilibration of the free $^{14}$C-DG pool in the tissue with the plasma level, and relative rates of phosphorylation of $^{14}$C-DG and glucose determined by their kinetic constants for hexokinase reaction. The operational equation based on this model (see Equation 1) has been derived in terms of determinable variables, where R is the calculated rate of glucose consumption per gram of tissue; $C_t^*$ is the concentration of DG + DG-6-$PO_4$ in the tissue; $C_p^*$ and $C_p$ are the arterial plasma concentrations of DG and glucose, respectively; $k_1^*$, $k_2^*$, and $k_3^*$ 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 DG in the tissue, respectively; $\lambda$ is the ratio of the distribution volume of DG in the tissue to that of glucose; $\phi$ is 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 DG and glucose, respectively. The latter six constants can be combined into one constant, which has been designated the lumped constant ($\lambda \cdot V_{max}^* \cdot K_m / \phi \cdot V_{max} \cdot K_m^*$).

$$R = \frac{C_t^*(T) - k_1^* e^{-(k_2^* + k_3^*)T} \int_0^T C_p^* e^{(k_2^* + k_3^*)t}\, dt}{\left[\frac{\lambda \cdot V_{max}^* \cdot K_m}{\phi \cdot V_{max} \cdot K_m^*}\right]\left[\int_0^T (C_p^*/C_p)\, dt - e^{-(k_2^* + k_3^*)T} \int_0^T (C_p^*/C_p) e^{(k_2^* + k_3^*)t}\, dt\right]} \quad \text{Equation 1.}$$

The extension of this method to man requires the use of a tracer (radiopharmaceutical) that satisfies the following criteria: (1) The tracer must be taken up by the brain at a rate proportional to that of glucose, and its metabolic products must remain within the tissue in a known form , as is the case with DG. (2) The tracer must be labeled with a γ-emitting radionuclide that is chemically stable in vivo and can be detected through the skull using emission tomography. (3) The radiation exposure resulting from the use of this tracer must be safe.

With the introduction of $^{18}$F-2-deoxy-2-fluoro-D-glucose ($^{18}$F-DG), all of these requirements have been met for a suitable radiopharmaceutical for the determination of local cerebral metabolism. This agent behaves very similarly to $^{14}$C-DG and therefore, using the above described model and emission tomography, it has become possible to measure regional cerebral metabolism for the first time in man (2,9).

## Methods and Materials

In this study we examined nine young normal male volunteers (mean age, 22; range 19-26) and twelve elderly subjects. The normal young controls were free of mental and physical disorders. The elderly subjects were evaluated by a battery of psychometric tests (Guild Memory Scale and WAIS vocabulary subtest) and were categorized as elderly normal or senile dementia. Individuals with previous history of neuropsychiatric conditions or severe

cardiopulmonary disorders were excluded. Based on the psychological testing, each subject was assigned a Global Deterioration Scale (GDS) rating of 1 to 7 as follows: 1 = normal, 2 = very mild, 3 = mild, 4 = moderate, 5 = moderately severe, 6 = severe, 7 = very severe. There were four elderly normal subjects (mean age, 72; range, 60-86) and eight patients with dementia (mean age, 72; range 64-78) in this group.

Following the insertion of a radial artery catheter under local anesthesia, the subjects were made comfortable in the scanner, and the head was positioned securely in a restraining device. The head was extended or flexed to make the orbital-meatal line perpendicular to the horizontal plane. Each subject received 70-140 μCi/kg of $^{18}$F-DG intravenously as a bolus. Blood samples were drawn from the radial artery to monitor the time course of the $^{18}$F-DG and glucose. Blood was drawn every 15 sec for the first minute, every minute until 10 min, every 5 min until 30 min, and every 15 min until the end of the study. The tissue activity of $^{18}$F-DG was measured using the PETT III tomographic scanner at the Brookhaven National Laboratory (10,11). In each subject multiple tomographic scans were obtained.

The PETT III is a positron emission transaxial tomographic unit consisting of 48 sodium iodide (Tl) scintillation detectors arranged in a hexagonal array. Each side of the hexagon has eight detectors installed on a platform capable of translational motion; the entire hexagon is mounted on a gantry capable of transaxial rotation. This scanner achieves collimation by

measuring only positron annilhilation radiation. Each detector is in coincidence with all the detectors on its opposite bank. By translation of the banks (1 cm) and rotation of the gantry ($60^{o}$ in $3^{o}$ increments), the radioactivity in the brain tissue is measured from a number of angles. Regional concentration of the radioactivity is reconstructed from these measurements using a computer. The spatial resolution of PETT III is 1.7 cm full width half maximum.

## Results and Discussion

The mean metabolic rates for various 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 control and 3.7 ± 0.9 mg/100 g/min in the demented patients. There was a significant 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 this group and old controls or the old controls and the patients with dementia. In general the metabolic rates were relatively lower in the frontal

areas of patients with dementia. The metabolic activity appeared symmetric in all three groups. No significant correlation was noted 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 2). No attempt was made to correlate the regional metabolic rates with a specific psychometric measurement.

Table 1

| | CMRgl mg/100 g/min* | | |
|---|---|---|---|
| Area | Young controls | Old controls | Senile dementia |
| 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 |

* Mean ± standard deviation.

Table 2

| | CMRgl mg/100 g/min | | |
|---|---|---|---|
| | Global Rating | Mean* | Range |
| Old controls | 1 | 4.6 ± 1.0 | 3.5 - 5.7 |
| Senile dementia | 3-5 | 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 ± standard deviation.

Studies of the effect of aging on the cerebral circulation and metabolism started very soon after the introduction of the nitrous oxide technique by Kety and Schmidt in 1948 (12). Shortly thereafter it was shown that patients with senile dementia had markedly reduced cerebral blood flow and $O_2$ consumption compared to young men (1). Later it was found that all types of dementia had reductions in cerebral blood flow and $O_2$ metabolism (13,14). One report states that with advancing age there was diminution in cerebral blood flow and $O_2$ consumption compared to young men (15). Although the subjects in this report were considered to be normal, they included hospitalized patients with a variety of disorders which could have affected cerebral metabolism and function. Also the possibility of early arteriosclerosis in these patients could not be ruled out. In a better controlled study with more careful selection of the subjects, cerebral blood flow, $O_2$ consumption and cerebral glucose utilization were determined (16). No significant difference in cerebral blood flow and $O_2$ consumption was found between the young controls and normal old subjects. However, a significant difference was found between these two groups and patients with Alzheimer's disease. On the other hand, cerebral glucose consumption was significantly lower in normal old subjects than normal young controls, and lower in dementia patients than in the elderly normal subjects. In other words, there occurs a dissociation between $O_2$ consumption and glucose utilization with aging. This dissociation

is even more pronounced in patients with dementia. This dissociation may be partly related to the use of substrates other than glucose (e.g. ketone bodies) in the aging brain (17).

Following the introduction of the intracarotid Krypton 85 and Xenon-133 techniques to measure cerebral blood flow, for the first time it became possible to measure local cerebral function (with very poor resolution) in man (18,19). Obrist et al, 1970, found an overall reduction in cerebral blood flow in senile dementia with greater decline in prefrontal and anterior temporal regions (20). Similar work by Ingvar and Gustafson, 1970, and Simard, 1971, extended this investigation further and confirmed these findings (21,22). The latter investigators found a good correlation between the regional cerebral blood flow pattern and clinical symptomatology, as well as the autopsy findings (21). These researchers were able to show a decrease in mean hemispheric blood flow grossly proportional to the intellectual decline (23). They also noted a relation between the memory disturbance and reduction of flow in the temporal region (24). Agnosia and confusion correlated with a drop in flow to temporo-occipito-parietal regions (21,23). Expressive aphasias showed low flows in regions related to Wernicke's and Broca's areas (25). One very important finding was that in patients with dementia activation stimuli did not result in the expected flow increases as seen in normal subjects (26). While less than normal response was noted in mildly affected cases, significantly deteriorated patients hardly showed any change in flow, if any.

In these patients decreases in frontal activity correlated well with defects in abstract thinking which is noted in demented patients.

The intracarotid Xe-133 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 one hemisphere is studied by this technique which excludes the comparison of two hemispheres simultaneously.

The use of noninvasive cerebral blood flow techniques (27,28), either by inhalation or intravenous administration of Xe-133, has permitted the measurement of regional flow on a routine basis. With this technique, Obrist et al, 1975, and Wang and Busse, 1975, have shown a significant difference between the normal-aged group and young controls (28,29). 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, Lavy and Melamed, 1978, have shown a decline in cerebral blood flow with aging and further

reduction with both pre-senile and senile dementia (30,31). These investigators speculated that similar underlying morphological changes may be responsible for the decrease in cerebral blood flow in both groups with more dramatic alteration in patients with dementia.

Although Obrist's technique allows examination of both hemispheres simultaneously it suffers from poor resolution of the areas of the brain similar to the early work with the intracarotid administration of Xenon-133. Both techniques provide information weighted by the superficial brain tissues.

Our data as described above revealed decreasing metabolic rates for glucose from young to old age and further decline from old age to the demented state. However, only the change in metabolic rates from young controls to patients with dementia was statistically significant. (Normal controls vs. old controls and old controls vs. demented patients, showed no significant difference in their metabolic rates for glucose.) This can be partially explained by the relatively poor resolution of the system used for this study. With the introduction of high resolution instruments and the acquisition of images with considerable detail, it is anticipated that a statistically significant difference may be noted between these groups. Another interesting finding in our study was the lack of correlation between the mean cortical metabolic rates for glucose and the global mental function in either old controls or patients with senile dementia. This may be partly related to the use of substrates other than glucose by the brain with aging and dementia. It is conceivable that the

degree of shift from glucose to other substrates may differ among individuals with the same mental function. Therefore the measurement of the other indicators of cerebral metabolism and function such as $O_2$ consumption and blood flow may be necessary for a more complete study. With the introduction of the positron emission tomographic techniques to measure regional cerebral $O_2$ metabolism and blood flow, all three indicators (CMRgl, $CMRO_2$ and CBF) can be determined noninvasively in the same subject (32). The latter approach may offer a powerful tool in the evaluation of cerebral function in health and diseased state.

Footnote:

The data presented in this communication differs from those discussed in the 10th Salzburg Conference on Cerebral Vascular Disease (September, 1980). Because of an error in the earlier reconstruction algorithms, the metabolic rates originally obtained were considerably lower than the values calculated with the corrected algorithm. The revised rates are probably a more accurate representation of the metabolic activity in the brain. Also the asymmetric metabolic activity (right hemisphere more active than the left) is no longer noted in the revised images.

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