Annals of Nuclear Medicine Vol. 15, No. 1, 69–73, 2001

Evaluation of resting brain conditions measured by two different methods (i.v. and oral administration) with ^{18}F-FDG-PET

Mehedi MASUD,* Keiichiro YAMAGUCHI,* Hisashi RIKIMARU,* Manabu TASHIRO,* Kaoru OZAKI,* Shoichi WATANUKI,* Masayasu MIYAKE,* Tatsuo IDO** and Masatoshi ITOH*

*Division of Nuclear Medicine and **Division of Nuclear Pharmacology, Cyclotron Radioisotope Center, Tohoku University*

Our aim was to evaluate regional differences between brain activity in two resting control conditions measured by 3D PET after administration of FDG through either the intravenous (i.v.) or the oral route. Ten healthy male volunteers engaged in the study as the i.v. group (mean age, 26 ± 9.3 years, ± S.D.) who received FDG intravenously and another 10 volunteers as the oral group (mean age, 27.9 ±11.3 years, ± S.D.) who received FDG per os. A set of 3D-PET scans (emission and transmission scans) were performed in both groups. To explore possible functional differences between the brains of the two groups, the SPM-96 software was used for statistical analysis. The results revealed that glucose metabolism was significantly higher in the superior frontal gyrus, superior parietal lobule, lingual gyrus and left cerebellar hemisphere in the i.v. group than in the oral group. Metabolically active areas were found in the superior, middle and inferior temporal gyrus, parahippocampal gyrus, amygdaloid nucleus, pons and cerebellum in the oral group when compared with the i.v. group. These differences were presumably induced by differences between FDG kinetics and/or time-weighted behavioral effects in the two studies. This study suggests the need for extreme caution when selecting a pooled control population for designated activation studies.

Key words: 3D-PET, FDG, oral intake, resting condition, pooled control

INTRODUCTION

POSITRON EMISSION TOMOGRAPHY (PET) is an imaging tool to visualize brain function by using energy metabolism[1–5] or cerebral blood flow distribution[6–9] as a marker. The FDG-PET method has been widely used to explore regional cerebral glucose metabolism to assess neuronal function. By applying appropriate statistical analysis (SPM in particular) over the brain image data, the task-induced regional activations were detected (Friston et al. 1995).[10] For the time being, FDG was administered by the intravenous route for human studies. An attempt to introduce FDG by the oral route to evaluate glucose absorption by the alimentary system was carried out. This method is also suitable for assessing the regional metabolic rate for glucose (rCMRGlc) in organs other than the digestive tract. Oral-FDG introduction is less intrusive and more suitable in pediatric patients or adults who are nervous about having intravenous injections. And the procedure is more demanding concerning the quality control process for the radiopharmaceuticals than the intravenous procedure. In brain science, fMRI has been replaced by PET due to its short time resolution. To trace human cognitive function, quick time resolution of less than 1 second is required which is out of reach for PET. Nevertheless, the longer time resolution of PET may have an advantage over fMRI in the study of emotion and behavior. The aim of this study is to determine whether the resting brain images obtained by i.v. injection and oral intake of FDG are identical or not.

Received July 24, 2000, revision accepted December 4, 2000.

For reprint contact: Mohammad Mehedi Masud, M.D., Division of Nuclear Medicine, Cyclotron Radioisotope Center, Tohoku University, Aoba, Aramaki, Aoba-ku, Sendai 980–8578, JAPAN.

E-mail: mehedi@cyric.tohoku.ac.jp

Table 1 Brain areas detected as hypermetabolic at the resting condition of i.v. group when compared with that of the oral group

Structure	Bradmann's area	Side	Talairach Co-ordinates of statistical peak			Z score of statistical peak
			x	*y*	*z*	
Superior frontal gyrus	6	Right	6	4	80	3.88
Superior parietal lobule	7	Left	−38	−46	64	3.74
Lingual gyrus	18	Left	−16	−92	−20	3.45
Cerebellum		Left	−20	−82	−20	3.60

The statistical threshold is $p < 0.001$.

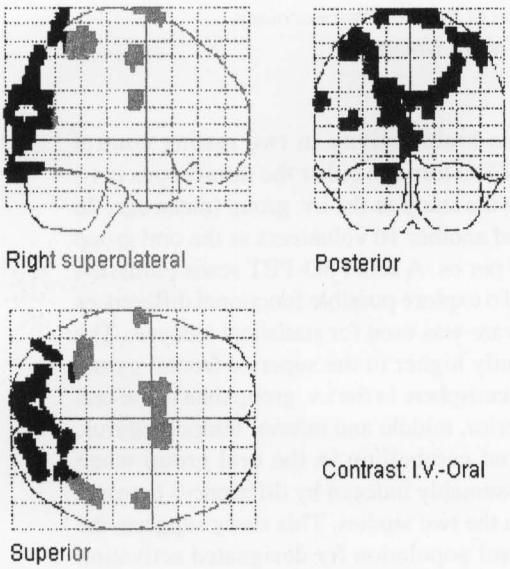

Fig. 1 Hypermetabolic brain areas found in the i.v. group when compared with the oral group are shown on a SPM standard result format. The statistical threshold was set at $p < 0.005$ without correction for the multiple comparisons.

SUBJECTS AND METHODS

Twenty healthy male volunteers participated in this study as the i.v. and oral groups. The i.v. group (mean age, 26.9 ± 9.3 y, ± S.D.) were studied by intravenous FDG administration while resting, whereas the oral group (27.9 ± 11.3 y) received FDG orally. Each group comprised 10 male subjects. They served as resting control subjects for the other studies. Written informed consent was obtained from all the subjects after detailed explanation of the study protocol. This study was approved by the Clinical Committee for Radioisotope Use of Tohoku University School of Medicine. All the subjects abstained from eating and drinking for at least 3 hours before the start of the experiment. In this experiment, the resting condition was defined as remaining in the sitting posture after the intake of FDG in a light quiet room, with eyes open and without ear-plugs. An intravenous blood sample was obtained from all the subjects to measure the plasma glucose level just before the FDG injection.

Study Protocol

I.V. group: The i.v. group subjects rested for 5 minutes on a chair and then were administered FDG manually through an antecubital vein. The FDG infusion time was about 20 seconds and the radioisotope dose averaged 39.7 ± 6.1 (± s.d.) MBq. The subjects remained in the same position for another 45 minutes in the same room before PET measurements were taken. After voiding they lay on a PET examination table and emission scanning started at 60 min after FDG injection. A 3D whole brain emission scan was performed with a PET Scanner (SET-2400W, Shimadzu Co., Japan) with an intrinsic in-plane spatial resolution of 3.9 mm at full width at half maximum (FWHM) and a 200 mm axial field of view.[11] The emission scan lasted for 5 to 7 minutes depending on the subjects' physique. Transmission scan (post-emission transmission) which continued 5 to 7 minutes, was performed with a $^{68}Ge/^{68}Ga$ external rotating line source (370 MBqs at purchase) to correct the tissue attenuation of emission photons.

Oral group: The oral group subjects rested for 5 minutes on a chair before the administration of FDG. They were given FDG (40.4 ± 3.9 MBq) orally and kept in the same sitting posture for another 15 minutes prior to the PET scan. After voiding, the subjects lay on the PET examination table and dynamic whole body emission scan (3 min/scan) was performed in 3 minute segments from the pelvis to the vertex with the PET scanner. The brain images, scanned at 60 min after the oral intake of FDG, were used for the analysis. The post-emission transmission scan, a 3 min/scan, was performed to correct the attenuation of emission photons.

PET image data were reconstructed with a filtered 3D back projection algorithm in a Tohoku University supercomputer (SX-4/128H4).[11,12]

Statistical Analysis

The statistical parametric mapping (SPM-96) software was used for the analysis. First, the brain images were

Table 2 Brain area detected as hypermetabolic at the resting condition of oral group when compared with the i.v. group

Structure	Brodmann's area	Side	Talairach Co-ordinates of statistical peak			Z score of statistical peak
			x	*y*	*z*	
Superior temporal gyrus	38	Left	−42	28	−20	3.91
Middle temporal gyrus	21	Right	46	0	−32	4.12
Middle temporal gyrus	21	Left	−50	−26	−8	3.92
Inferior temporal gyrus	20	Right	52	−14	−16	4.46
Parahippocampal gyrus	35	Left	−22	−22	−16	3.18
Amygdaloid nucleus		Left	−18	−12	−8	3.65
Pons		Right	12	−26	−24	3.83
Cerebellum		Right	20	−56	−44	3.57
Cerebellum		Left	−18	−46	−36	3.88

The statistical threshold is $p < 0.001$.

spatially normalized to minimize anatomical variations between subjects. An SPM blood flow template was used for this normalization. Smoothing was performed with a 14-14-14 mm isotropic Gaussian filter kernel. Voxel based statistical analysis was performed on these smoothed images by choosing "compare-groups: one scan per subject analysis" (Friston et al. 1995 and 1991).[10,13] The locations of relative hypermetabolic brain regions for each group were identified in the *x*, *y* and *z* standard coordinates (Talairach and Tournoux, 1988)[14] with the statistically significant threshold level at $p < 0.001$ without correction for multiple comparisons, but a significantly lower level of $p < 0.005$ was used to threshold result images to minimize possible type II errors in the statistical inference.

RESULTS

Figure 1 and Figure 2 depict the relative hypermetabolic regions in the i.v. and the oral group, respectively. Applying the statistical analysis, the i.v. group showed hypermetabolic brain regions in the right superior frontal gyrus, left superior parietal lobule, left lingual gyrus (Brodmann's area (BA), BA6, BA7, and BA18) and left cerebellar hemisphere (Table 1 and Fig. 1). The oral group showed signs of relative regional hypermetabolism in the left superior temporal gyrus, bilateral middle temporal gyrus, right inferior temporal gyrus and left parahippocampal gyrus (BA38, BA21, BA20 and BA35 respectively). The left amygdaloid nucleus, right pontine nucleus and bilateral cerebellar areas also showed signs of higher metabolism (Table 2 and Fig. 2).

DISCUSSION AND CONCLUSION

We attempted to compare resting brain images obtained through the use of oral or intravenous administration of FDG to the normal resting subjects, although the i.v. and

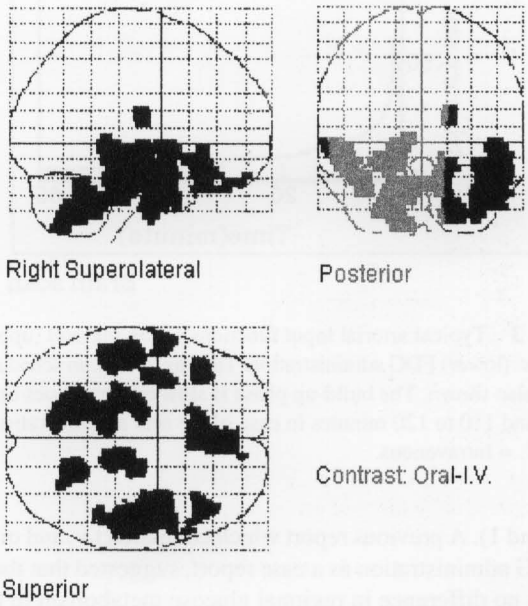

Fig. 2 Hypermetabolic brain areas found in the oral group when compared with the i.v. group are shown on a SPM standard result format. The statistical threshold was set at $p < 0.005$ without correction for the multiple comparisons.

oral subjects were engaged in different study protocols, while endeavoring to keep similar time schedules with regard to FDG administration and brain imaging. Intravenous administration of FDG is one of the most common methods used in clinical PET practice.[15–17] Since glucose is the principal energy source for brain tissue, regional cerebral FDG uptake is a clear indicator of the functional level of the brain in physiological[18,19] and pathological[20,21] conditions. The most remarkable differences between studies with i.v. and oral FDG administration were found in the limbic structures (parahippocampal gyrus and amygdaloid nucleus) in the oral group and visual association cortex (lingual gyrus) in the i.v. group (Figs.

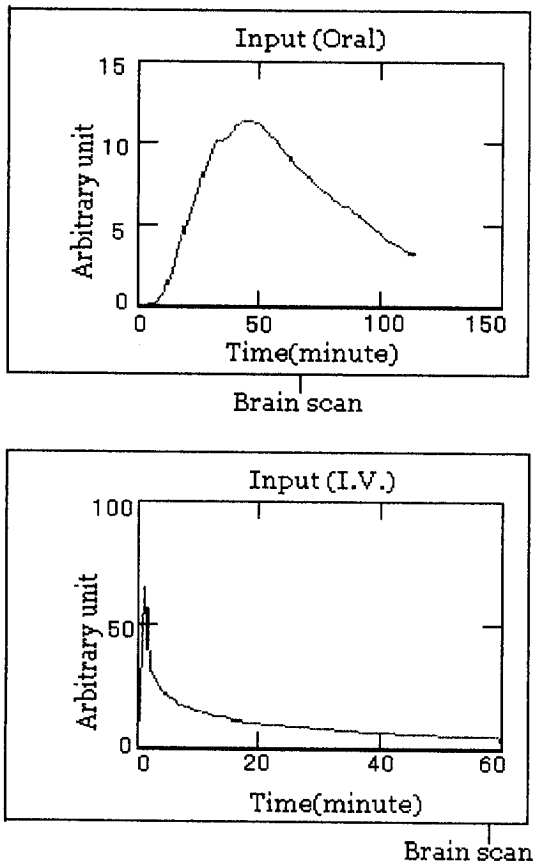

Fig. 3 Typical arterial input functions following oral (upper) or i.v. (lower) FDG administration. The emission scan schedules are also shown. The build-up phase is slow and continues up to around 110 to 120 minutes in case of the oral administration. *I.V. = Intravenous.

2 and 1). A previous report which compared i.v. and oral-FDG administration as a case report, suggested that there was no difference in regional glucose metabolism in the brain.[22] But in the case report a simple subtraction instead of the statistical image comparison was used. We searched regional brain areas with statistical differences by applying the SPM analysis.

We used post-injection transmission for tissue attenuation correction of emission data. The contamination of emission components in these transmission data is known to reduce the accuracy of quantification.[23] Although we did not correct emission contamination, these effects would be less in the 3D emission scans because a smaller dose of radioactivity was used. Selection of the SPM template is another problem in our study. As FDG templates are not available, the blood flow template was used for spatial normalization. The difference between radioactivity distribution for the two tracers, ^{15}O-H_2O and ^{18}F-FDG is substantial in the periphery of the brain as radioactivity exists in the vascular compartment in the ^{15}O-H_2O study only. As these confusing effects do exist in both studies, they do not have to be taken into consideration and can be canceled out in the SPM group comparisons, but the use of an unmatched template for spatial normalization could introduce significant errors in the anatomical locations. Normalized FDG images may differ spatially from the Talairach space, but our study was not concerned with the precise identification of anatomical locations.

The significant differences found in our study between via i.v. and oral FDG administration might emerge from inter-subject variations because there were different subjects in each group. This is a limitation of this study. When FDG is given orally, blood pool radioactivity may not be negligible due to slow FDG absorption, but no trace of large brain vessels was seen on the oral FDG images, and significant areas revealed by SPM analysis were not close to large vessels. We therefore considered that the effects of blood radioactivity in the oral FDG did not affect our results.

Figure 3 shows average input functions of FDG-tracer in normal volunteers for oral and i.v. routes respectively obtained in our other studies. Regional FDG uptake is a function of regional transfer or rate constants. If the regional distributions of these rate constants differ substantially, FDG accumulation is possibly changed regionally. The determinant parameters in FDG tissue uptake are K1 and k3, since k4 is very small and k2 is related to K1 by the distribution volume (Vd). K1 and k2 are responsible for the influx and efflux of glucose between plasma and tissue, and k3 is the rate constant responsible for phosphorylation by hexokinase. Brain image taken 60 minutes after i.v. injection are considered to reflect radioactivity of the metabolized compartment, whereas brain radioactivity at a similar time after oral introduction includes both unmetabolized and metabolized compartments because FDG input remains in the blood. Therefore any regional rate constant changes may affect SPM results in i.v. and oral input comparisons. Nevertheless, we have no report that confirmed the systemic regional rate constant changes in the limbic structures, especially in the parahippocampal gyrus and amygdaloid nucleus which were identified in our study.

Although we tried to have similar resting conditions during PET scans, the scanning set-ups for the two groups were not completely matched due to different study purposes. Sequential blood samplings were taken in the oral group only. Habituation and discomfort should also be taken into account due to slow FDG kinetics in the tissue. Since arterial input reaches a peak at around 60 minutes after oral introduction, FDG brain images by the oral route reflect brain condition in the later phase. Therefore the effect of behavioral distress caused by longer scanning time should have a greater affect on the oral FDG brain images than by the i.v. route. The identification of the limbic structures in the oral study also indicates this possibility. Although the precise mechanism involved in the difference in brain activity for oral and i.v. FDG

introduction is not known, this study indicates the need for substantial caution in FDG PET activation studies especially when normally resting subjects are to be used for a pooled control resting experiment.

ACKNOWLEDGMENTS

The authors would like to convey special thanks to all the staffs of Cyclotron Radioisotope center for their courageous collaborations and technical supports. This study was conducted in collaboration with the multi-center PET activation projects in Japan (Senda M. et al).

REFERENCES

1. Fahey FH, Wood FB, Flowers DL, Eades CG. Evaluation of brain activity in FDG-PET studies. *J Comput Assist Tomogr* 1998; 22 (6): 953–961.
2. Loessner A, Alavi A, Lewandrowski KU, Mozley D, Souder E, Gur RE. Regional cerebral function determined by FDG-PET in healthy volunteers: normal patterns and changes with age. *J Nucl Med* 1995; 36 (7): 1141–1149.
3. Nofzinger EA, Mintun MA, Wiseman M, Kupfer DJ, Moore RY. Forebrain activation in REM sleep: an FDG PET study. *Brain Res* 1997; 770 (1–2): 192–201.
4. Schreckenberger M, Gouzoulis-Mayfrank E, Sabri O, Arning C, Schulz G, Tuttass T, et al. Cerebral interregional correlations of associative language processing: a positron emission tomography activation study using fluorine-18 fluorodeoxyglucose. *Eur J Nucl Med* 1998; 25 (11): 1511–1519.
5. Boivin MJ, Giordani B, Berent S, Amato DA, Lehtinen S, Koeppe RA, et al. Verbal fluency and positron emission tomographic mapping of regional cerebral glucose metabolism. *Cortex* 1992; 28 (2): 231–291.
6. Itoh M, Miyazaki H, Tashiro M, Xu-Zhan X. Functional analysis of the brain at rest studied by PET and EEG. *J Intl Soc Life Info Sci* 1997; 15 (2): 282–287.
7. Schiltz C, Bodart JM, Dubois S, Dejardin S, Michel C, Roucoux A, et al. Neuronal Mechanisms of Perceptual Learning: Changes in Human Brain Activity with Training in Orientation Discrimination. *NeuroImage* 1999; 9: 46–62.
8. Paul TR, Benjamin JZ, Robert DN, Carolyn CM, Mark AM, James TB. Functional Neuroanatomy of Sementic Memory: Recognition of Sementic Associations. *NeuroImage* 1999; 9: 88–96.
9. Gereon RF, Douglas RC, Kevin M, Ichiro K, Christian D, Lewis A, et al. Human cerebral activity with increasing inspiratory force: a study using positron emission tomography. *J Appl Physiol* 1996; 81 (3): 1295–1305.
10. Friston KJ, Holmes AP, Worsley KJ, Poline JP, Frith CD, Frackowiak RS. Statistical parametric maps in functional imaging: A general linear approach. *Hum Brain Mapping* 1995; 2: 189–210.
11. Fujiwara T, Watanuki S, Yamamoto S, Miyake M, Seo S, Itoh M, et al. Performance evaluation of a large field-of-view PET scanner: SET-2400W. *Ann Nucl Med* 1997; 11 (4): 307–313.
12. Defrise M, Townsend D, Geissbuhler A. Implementation of three-dimensional image reconstruction for multi-ring positron tomographs. *Phys Med Biol* 1990; 35 (10): 1361–1372.
13. Friston KJ, Frith CD, Liddle PF. Comparing functional (PET) images: the assessment of significant change. *J Cereb Blood Flow Metab* 1991; 11: 690–699.
14. Talairach J, Tournoux P. *Co-planner Stereo-taxic Atlas of the Human Brain*. Rayport M (translator), Stuttgart: Theim, 1988.
15. Farrell MA, McAdams HP, Herndon JE, Patz EF Jr. Non-small cell lung cancer: FDG PET for nodal staging in patients with stage I disease. *Radiology* 2000; 215 (3): 886–890.
16. Iwata Y, Shiomi S, Sasaki N, Jomura H, Nishiguchi S, Seki S, et al. Clinical usefulness of positron emission tomography with fluorine-18-fluorodeoxyglucose in the diagnosis of liver tumors. *Ann Nucl Med* 2000; 14 (2): 121–126.
17. Sugawara Y, Daniel KB, Paul VK, Joseph ER, Kenneth RZ, Richard LW. Rapid detection of human infections with fluorine-18 fluorodeoxyglucose and positron emission tomography: preliminary results. *Eur J Nucl Med* 1998; 25 (9): 1238–1243.
18. Reivich M, Gur R, Alavi A. Positron emission tomographic studies of sensory stimuli, cognitive processes and anxiety. *Human Neurobiol* 1983; 2 (1): 25–33.
19. Seibner HR, Peller M, Willoch F, Auer C, Bartenstein P, Drzezga A, et al. Imaging functional activation of the auditory cortex during focal repetitive transcranial magnetic stimulation of the primary motor cortex in normal subjects. *Neurosci Lett* 1999; 270 (1): 37–40.
20. Albin RL, Minoshima S, D'Amato CJ, Frey KA, Kuhl DA, Sima AA. Fluorodeoxyglucose positron emission tomography in diffuse Lewy body disease. *Neurology* 1996; 47 (2): 462–466.
21. Imamura T, Ishii K, Sasaki M, Kitagaki H, Yamaji S, Hirono N. Regional cerebral glucose metabolism in dementia with Lewy bodies and Alzheimer's disease: a comparative study using positron emission tomography. *Neurosci Lett* 1997; 235: 49–52.
22. Martinez ZA, Colgan M, Baxter LR Jr, Quintana J, Siegel S, Arion C, et al. Oral ^{18}F-fluoro-2-deoxyglucose for primate PET studies without behavioral restraint: demonstration of principle. *Am J Primatol* 1997; 42 (3): 215–224.
23. Turkington TG, Coleman RE. An evaluation of Post-Injection Transmission Measurement in PET[1]. *IEEE Trans Nucl Sci* 1994; 41 (4): 1538–1544.