Regional Cerebral Blood Flow and Glucose Utilization in Spontaneously Epileptic EL Mice

Chisa Hosokawa, Hironobu Ochi, Sakae Yamagami and Ryusaku Yamada
Departments of Radiology and Neuropsychiatry, Division of Nuclear Medicine, Osaka City University Medical School, Osaka, Japan

The dynamics of the relative regional cerebral blood flow (rCBF) and regional glucose utilization (rGU) were examined in spontaneously epileptic EL mice in the interictal, ictal and postictal states, using autoradiography with ^{125}I-N-isopropyl-p-iodoamphetamine (IMP) and ^{14}C-2-deoxyglucose (DG), respectively. **Methods:** EL mice were used in the study, which have previously been used as a model of the idiopathic human epilepsy. EL mice develop secondary generalized tonic-clonic convulsions, and ddY and EL(o) mice, which do not experience seizures, were used as controls. IMP and DG, respectively, were injected in EL mice in the interictal, ictal and postictal states. We examined the relative rCBF and rGU from the obtained autoradiograms of mouse brain sections. **Results:** No significant changes in the relative rCBF were obtained in the hippocampus in the course of epileptic seizures. In contrast, significant increases in the relative rGU were observed in the hippocampus in the ictal and early postictal states. The dissociation between the dynamics of the rCBF and rGU were found in the event of epileptic seizures of EL mice. **Conclusion:** The flow metabolism dissociation in the ictal and early postictal states is of both conceptual and practical interest, while the reason for the dissociation of rCBF from the rGU in epileptic seizures remains to be established. Our results emphasize the importance of estimating both cerebral perfusion and glucose metabolism in epilepsy.

Key Words: epilepsy; EL mouse; interictal; ictal and postictal states; flow metabolism dissociation

J Nucl Med 1997; 38:613–616

Various studies of animal seizure models (*1–3*) and epilepsy in humans (*4–7*) have been done on cerebral perfusion or metabolism, but it has been suggested that the animal data and human data cannot be compared because each animal seizure model produces a unique, model-specific perfusion and metabolic pattern. This probably reflects true differences between the mechanisms mediating different types of animal seizures and those mediating human epilepsy (*8*). Contrast to electrically and chemically induced convulsions (*1–3*), the genuine or hereditary epilepsy in animals could be expected to be comparable with that observed in humans.

The EL mouse is an inbred mutant strain with a convulsive disposition discovered by Imaizumi et al. (*9*). The seizures originate in the hippocampus and then spread to the other brain regions electroencephalographically (*10,11*). They are, therefore, considered as complex partial seizures with secondary generalization (*12*). EL mouse appears to be a suitable model of a human genuine or hereditary epilepsy due to the apparent similarities between the convulsive seizures in this mouse and in human epileptic patients (*12*). The much available data regarding EL mice have been obtained by different physiological and biochemical methods (*12*), but no information is available on the changes in cerebral blood flow and glucose metabolism.

This study was attempted to reveal the dynamic changes of relative regional cerebral blood flow (rCBF) and regional glucose utilization (rGU) in EL mice in the interictal, ictal and postictal states using autoradiography with ^{125}I-N-isopropyl-p-iodoamphetamine (IMP) (*13–15*) and ^{14}C-2-deoxyglucose (DG) (*16*), respectively. The EL mouse offers the opportunity to explore the cerebral perfusion and metabolic correlates of convulsive predisposition to provide us with important data for understanding the mechanism of idiopathic human epilepsy.

MATERIALS AND METHODS

Experimental Animals

Thirteen-week-old EL mice of both sexes weighing between 25 and 33 g were supplied from our laboratory conditioned with a 12-hr light-dark cycle. The room temperature and the relative humidity were regulated at 22–26°C and 50%–60%, respectively. Commercial pellet food and drinking water were provided ad libitum.

The EL mouse was internationally registered as a spontaneously epileptic mouse strain in 1964, and its heredity has been classified (*9*). The hippocampus is identified as the epileptic focus by electroencephalography (*10,11*) and EL mouse exhibits secondary generalized tonic-clonic convulsions by tossed-up stimulations. It is considered a good model of the idiopathic human epilepsy (*12*).

Convulsions in adult EL mice were produced by tossed-up stimulations once a week from 4 wk after birth. The EL mice exhibiting tonic-clonic convulsions were designated EL(+). The others that have not been stimulated, and have not convulsed, were designated EL(o) and used as control. Nonseizure-susceptible, age-matched ddY mice of strain, which are progenitors of EL mice, were used as additional control.

Radiopharmaceuticals

Iodine-125-N-isopropyl-p-iodoamphetamine (IMP = specific activity; 13.7Bq/mmole) and ^{14}C-2-deoxyglucose (DG = specific activity; 8.5–12.2 GBq/mmole) were used as indicators of the rCBF and rGU, respectively. 5.18kBq of each radiopharmaceutical/g body weight was injected in mouse.

We examined the relative rCBF and rGU of EL(+), EL(o) and ddY mice using autoradiography. As concerns EL(+), studies were performed in the interictal, ictal and postictal (10, 30, 60 and 120 min after seizures, respectively; expressed as P-10, P-30, P-60 and P-120) states. Six mice were examined in each group and state. The brain regions analyzed included the right and left striatum, cortex, thalamus, hippocampus, amygdala, entorhinal cortex and cerebellum.

In a pilot study for the measurements of the rCBF, we examined the time-course IMP uptakes in the mouse brains after intraperitoneal administration (Fig. 1). According to Figure 1, no detectable uptake was found after 3 min, 0.42% uptake was found after 5 min and a steep increase in uptake was found 10 min after IMP administration. Thereafter, radioisotope uptake became slow and

Received Apr. 12, 1996; revision accepted Jul. 8, 1996.
For correspondence or reprints contact: Chisa Hosokawa, MD, Dept. of Radiology, Osaka City University Medical School, 1-5-7 Asahi-machi, Abeno-ku, Osaka, 545, Japan.

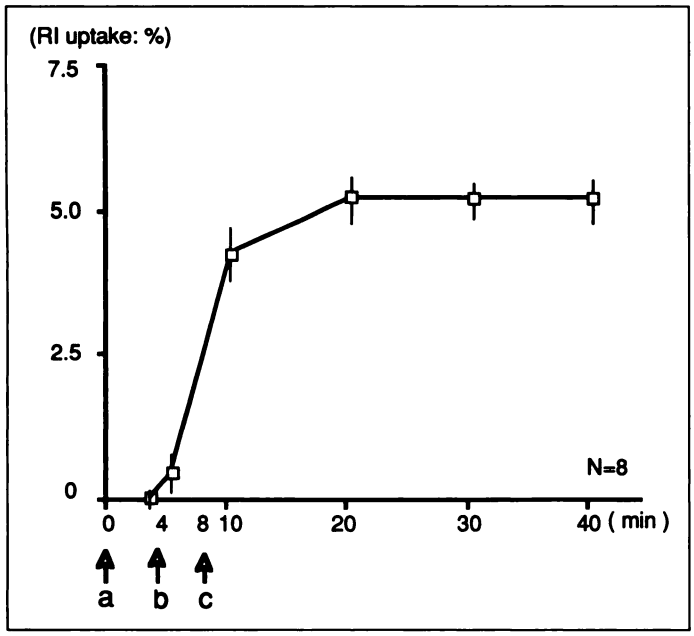

FIGURE 1. The time-course radioisotope uptake in the EL mouse brains shown after intraperitoneal administration of IMP. Arrowhead a = intraperitoneal administration; arrowhead b = tossed-up stimulation to EL (+) mice in the ictal state; and arrowhead c = killed mice.

reached a plateau 20 min later. Based on this result, mice were killed 8 min after the injection of IMP, taking the time required for distribution to the brain, the effects of the clearance in the blood and the duration of seizures (the mean time = 1 min) into consideration. To examine the ictal state of EL (+) mice the tossed-up stimulations were given to EL (+) mice 4 min (Fig. 1, arrowhead b) after intraperitoneal administration and EL (+) mice exhibiting tonic-clonic convulsions were used.

For the measurements of rGU, the time-course DG uptakes in the mouse brains were previously demonstrated by Nonaka et al. (*17*). As in their methods (*18*), mice were killed 40 min after the intraperitoneal administration. In the ictal state of EL (+) mice, tossed-up stimulations were given 4 min after injection as a method for the measurements of the rCBF.

Tissue Slice and Autoradiogram Preparation

Immediately after the mice were killed, brain was placed on powdered dry ice for several minutes, embedded in tissue compound and transferred to a criostat. Serial coronal sections (20 μm) were cut at −20°C. The sections were placed on glass cover slips and rapidly dried by 60°C steam. The cover slips with labeled tissue sections were exposed to x-ray film in an x-ray cassette for 2 wk at 4°C along with microscales for ^{125}I (46Bq-23.7kBq/mg) or ^{14}C (1.15–32.7kBq/g) as standards. Autoradiograms were prepared by developing the films.

Densitometry

Densitometric analyses of the autoradiograms were performed with the NIH image software for a Macintosh computer. The resolution of the system involved a matrix size of 1024 × 1024 and a density level of 8 bit. First, degrees of blackening with each microscale were digitalized and a density-radioactivity curve was prepared. From autoradiograms, digitalized values for brain regions were obtained, and radioactivities/g of tissue were calculated using the calibration curve.

Assessment

We examined relative rCBF and rGU, respectively, which were the ratios of the regional radioactivity of IMP or DG to the average

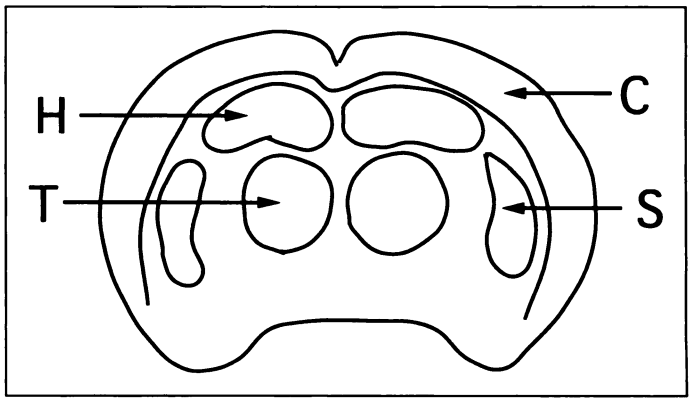

FIGURE 2. The schematic of the autoradiogram on coronal section of the mouse brain. The amygdala, entorhinal cortex and cerebellum are not shown. S = striatum; T = thalamus; C = cortex; H = hippocampus.

of the whole brain. Relative rCBF and rGU values rather than absolute values were generated for the following reasons:

1. To eliminate the effects of the arterial input function to the brain and the systemic circulation.
2. To estimate cerebral glucose metabolism during or soon after seizures. Previous studies used this qualitative approach (i.e., regional distribution pattern) instead of (semi-) quantitative assessment (for example, percent injected dose/g) because of nonsteady states and the poor temporal resolution (*7,19–21*). We also examined the relative (qualitative) rGU in all of the groups and states.

Statistical Analysis

The results were given as mean ± s.d. for six mice. Comparisons between different groups or states were performed using ANOVA and significance was set at $p < 0.001$. The regional activities were measured on both the right and left sides, and side-to-side differences were determined. Since no significance of side-to-side differences were found in either EL or ddY mice, bilateral regional data were averaged in subsequent analyses.

RESULTS

A schematic illustration is shown in Figure 2. Regarding autoradiograms for IMP, radioactivities in the cortex and thalamus are higher than that in the hippocampus in the control. This finding is the same in EL mice. No clear different distribution patterns of regional radioactivities were observed between different autoradiograms. Figure 3 shows the autoradiograms obtained after injection of IMP or DG in each mouse.

Regarding autoradiograms for DG, similar relative regional distribution of radioactivities was observed in the interictal state of EL(+) mice and the controls. Namely, higher radioactivities were in the cortex and thalamus than in the hippocampus. In the ictal and early postictal states of EL(+) mice, much higher radioactivities were observed in the hippocampus than in the cortex and thalamus. In the late postictal state, the relative distribution of radioactivities returned to that of the interictal state.

As shown in Figure 3, the distribution patterns of regional radioactivities between IMP and DG were similar in the control groups of ddY and EL(o) and EL(+) mice in the interictal state. They did not match in the ictal and early postictal states of EL(+) mice. In late postictal state, they matched again.

The relative rCBF and rGU of all brain regions in each group and state are summarized in Table 1. The significant changes in the relative rCBF in the whole brain including the hippocampus were not obtained in the course of the epileptic seizures. The significant increases (23.3%, $p < 0.001$) in the relative rGU of

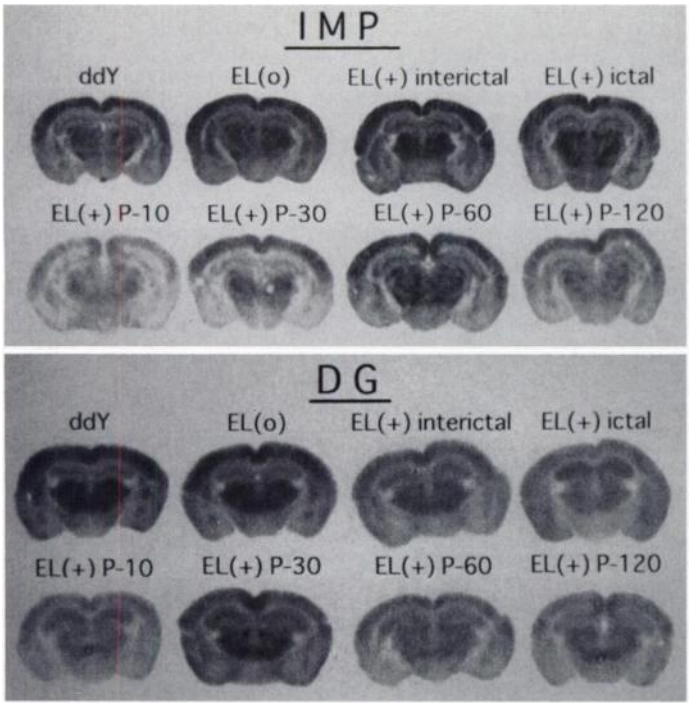

FIGURE 3. The autoradiograms for IMP (A) and DG (B) are shown. Upper row from left to right: ddY, EL(o), interictal EL(+) and ictal EL(+). Lower row from left to right: P-10 EL(+), P-30 EL(+), P-60 EL(+) and P-120 EL(+).

the hippocampus in the ictal and early postictal states of EL (+) mice compared with those in the interictal state. In the late postictal state, the relative rGU of each brain region returned to that of the interictal state of EL (+) mice.

DISCUSSION

Several studies examining both cerebral perfusion and glucose metabolism in epileptic seizures of human (*22–27*) and experimental animals (*28–31*) were reported. It has already been established that the increased neural metabolism associated with seizure activity is accompanied by a rise in rCBF during active seizures (*32–35*). While many studies reported similar changes indicating flow metabolism coupling (*22–24*), others showed different dynamics reflecting flow metabolism uncoupling (*25–31*). In this study, we examined both the relative rCBF and rGU of EL mice in the interictal, ictal and postictal states using autoradiography. The results showed different dynamics of rCBF and rGU in the course of the epileptic seizures.

Methodological Considerations

We assessed the radioisotope uptakes in the mouse brain regions after intraperitoneal administration of radiopharmaceuticals in the interictal, ictal and postictal states of the EL (+) mice. These studies raise two major methodological questions: one is the methodological validity, and the other is the possibility of the comparison between the dynamics of the rCBF and rGU.

Methodological Validity. Since the ictal and postictal states are not strictly steady states, there has been no practicable way to visualize changes in metabolism during or soon after seizures in humans. The absolute values of the rCBF and rGU in these states are difficult to obtain, and they may be underestimated due to the changes of the systemic circulation and the postictal suppression of the neuronal activities (*3,19–21*). But this is a qualitative and anatomical study, that is, a relative regional dynamic study in the course of the epileptic seizures. In this respect, we can estimate the dynamics of the relative rCBF and rGU by eliminating the effects of the changing arterial input function and systemic circulation.

Possibility of Comparison Between rCBF and rGU. The time of death after administration between IMP and DG was different. But the time-course uptake of both tracers are similar (Fig. 1), and DG uptake at 40 min after injection is considered to reflect the early phase despite poor temporal resolution (*17*). In

TABLE 1
Relative rCBF and rGU of ddY, EL(o) and EL(+) Mouse Brains

			IMP					
			EL(+)					
Region	ddY	EL(o)	Interictal	Ictal	P-10	P-30	P-60	P-120
Striatum	1.16 ± 0.03	1.09 ± 0.03	1.10 ± 0.02	1.13 ± 0.04	1.07 ± 0.03	1.08 ± 0.00	1.12 ± 0.05	1.10 ± 0.03
Cortex	1.25 ± 0.04	1.27 ± 0.03	1.29 ± 0.04	1.20 ± 0.04	1.10 ± 0.00	1.22 ± 0.09	1.19 ± 0.05	1.21 ± 0.07
Thalamus	1.23 ± 0.03	1.23 ± 0.03	1.20 ± 0.06	1.35 ± 0.06	1.26 ± 0.02	1.24 ± 0.04	1.23 ± 0.09	1.29 ± 0.11
Hippocampus	0.91 ± 0.02	0.95 ± 0.02	0.97 ± 0.02	0.97 ± 0.04	0.95 ± 0.01	0.94 ± 0.03	1.01 ± 0.03	1.00 ± 0.02
Amygdala	0.75 ± 0.02	0.75 ± 0.04	0.75 ± 0.04	0.80 ± 0.04	0.88 ± 0.02	0.84 ± 0.03	0.81 ± 0.05	0.81 ± 0.06
Entorhinal	0.72 ± 0.03	0.75 ± 0.05	0.74 ± 0.33	0.77 ± 0.06	0.87 ± 0.02	0.84 ± 0.04	0.82 ± 0.06	0.79 ± 0.06
Cerebellum	0.98 ± 0.03	0.96 ± 0.05	0.95 ± 0.02	0.78 ± 0.04	0.86 ± 0.02	0.84 ± 0.04	0.82 ± 0.06	0.80 ± 0.06
			DG					
			EL(+)					
Region	ddY	EL(o)	Interictal	Ictal	P-10	P-30	P-60	P-120
Striatum	1.40 ± 0.08	1.39 ± 0.14	1.16 ± 0.04	1.11 ± 0.11	1.13 ± 0.11	1.21 ± 0.07	1.21 ± 0.10	1.26 ± 0.07
Cortex	1.28 ± 0.03	1.33 ± 0.04	1.09 ± 0.05	0.98 ± 0.06	1.01 ± 0.09	1.08 ± 0.05	1.07 ± 0.05	1.08 ± 0.07
Thalamus	1.48 ± 0.01	1.28 ± 0.05	1.33 ± 0.02	1.07 ± 0.05	1.29 ± 0.07	1.31 ± 0.06	1.35 ± 0.02	1.39 ± 0.07
Hippocampus	0.83 ± 0.03	0.86 ± 0.10	1.03 ± 0.03	1.27 ± 0.04*	1.27 ± 0.07*	1.09 ± 0.06	1.04 ± 0.04	1.00 ± 0.04
Amygdala	0.60 ± 0.08	0.60 ± 0.09	0.69 ± 0.02	0.95 ± 0.06	0.61 ± 0.03	0.72 ± 0.10	0.62 ± 0.06	0.71 ± 0.07
Entorhinal	0.47 ± 0.04	0.58 ± 0.07	0.76 ± 0.02	0.87 ± 0.05	0.65 ± 0.09	0.69 ± 0.07	0.64 ± 0.10	0.63 ± 0.05
Cerebellum	0.94 ± 0.05	0.95 ± 0.07	0.93 ± 0.03	0.75 ± 0.04	1.05 ± 2.16	0.90 ± 0.20	1.07 ± 0.04	0.94 ± 0.03

*$p < 0.001$ as compared to the interictal state of EL(+) mice.
Values are the ratios of the rGU to the average of the whole brain (mean ± s.d.) obtained for six mice.

fact, comparative studies of blood flow and metabolism permit this different temporal resolution (*22,23,26,27*). Therefore, it may be possible to compare rCBF with rGU.

Flow Metabolism Dissociation

The most striking finding in this study was the dissociation of the dynamics of rCBF and rGU in the hippocampus, the epileptic focus, in the event of epileptic seizures of the EL (+) mice. The type of mismatch between rCBF and rGU was the difference, that is, no significant change in rCBF and increases in rGU, in the epileptic foci in the ictal and early postictal states of epileptic seizures. In the investigations presenting the flow metabolism uncoupling, during the seizures, a rise in cerebral perfusion induced by increased metabolism appeared to become less by repeated or prolonged seizures (*28,29*). A similar pathophysiology may be possible in EL mice because EL mice suffer from chronic or repeated epileptic seizures. This flow metabolism dissociation is difficult to reflect the true pathophysiological mechanism. But EL mice are spontaneously epileptic mice and a good model of the idiopathic human epilepsy (*12*). Therefore, it may reflect the pathophysiology of some types of clinical epilepsies and be useful in understanding them. Our present observation of the dissociation between the rCBF and rGU is not only of conceptual interest, why does it occur, but also of practical interest. It is considered that since cerebral perfusion and glucose metabolism may dissociate in epileptic seizures, it is important to assess both cerebral perfusion and glucose metabolism in epilepsy.

CONCLUSION

We studied rCBF and rGU using autoradiography with IMP and DG, respectively, in spontaneously epileptic EL mice in the interictal, ictal and postictal states of epileptic seizures. The flow metabolism dissociation of mouse brain was observed in the ictal and early postictal states, namely no significant changes in rCBF in contrast to increases in rGU in the epileptic foci were observed, which finding has never been described before. The pathophysiological mechanism is difficult to explain, but it is important to examine both cerebral perfusion and glucose metabolism in epilepsy because they may dissociate.

ACKNOWLEDGMENT

We thank Hidero Saji, PhD, and Yoshiharu Yonekura, MD, for conducting the experiments, and Masako Hosono, MD, and Reinhaldt Grzanna, PhD, for critical reading and discussion of the manuscript. We also thank Nihon Medi-Physics for the generous supply of ^{125}I-N-isopropyl-p-iodoamphetamine.

REFERENCES

1. Ben-Ari Y, Tremblay E, Riche D, Ghilini G, Naquet R. Electrographic, clinical and pathological alterations following systemic administration of kainic acid, bicuculline or pentetrazole: metabolic mapping using the deoxyglucose method with special reference to the pathology of epilepsy. *Neuroscience* 1981;6:1361–1391.
2. Evans MC, Meldrum BS. Regional brain glucose metabolism in chemically-induced seizures in the rat. *Brain Res* 1984;297:235–245.
3. VanLandingham KE, Lothman EW. Self-sustaining limbic status epilepticus. I. Acute and chronic cerebral metabolic studies: limbic hypermetabolism and neocortical hypometabolism. *Neurology* 1991;41:1942–1949.
4. Engel J Jr, Kuhl DE, Phelps ME, Mazziotta JC. Interictal cerebral glucose metabolism in partial epilepsy and its relation to EEG changes. *Ann Neurol* 1982;12:510–517.
5. Duncan R, Patterson J, Hadley DM. Bone ICT, MR and SPECT imaging in temporal lobe epilepsy. *J Neurol Neurosurg Psychiat* 1990;53:11–15.
6. Theodore WH, Newmark ME, Sato S, et al. Fluorine-18 fluorodeoxyglucose PET in refractory complex partial seizures. *Ann Neurol* 1983;14:429–437.
7. Engel J Jr, Kuhl DE, Phelps ME. Patterns of human local cerebral glucose metabolism during epileptic seizures. *Science* 1982;218:64–66.
8. Ackermann RF, Engel J Jr, Phelps ME. Identification of seizure mediating brain structures with the deoxyglucose methods: studies of human epilepsy with PET and animal seizure models with contact autoradiography. In: Delgado Escueta AV, Ward AA Jr, Woodbury DM, Porter RJ, eds. *Advances in Neurology*. New York: Raven Press; 1986:44:921–934.
9. Imaizumi K, Nakano T. Mutant stocks strain El mouse. *News Letter* 1964;3:157.
10. Suzuki J. Paroxysmal discharges in the electroencephalogram of the El mouse. *Experientia* 1976;32:336–338.
11. Suzuki J, Nakamoto Y. Seizure patterns and electroencephalograms of El mouse. *Electroenceph Clin Neurophysiol* 1977;43:299–311.
12. Seyfried TN, Glaser GH. A review of mouse mutants as genetic models of epilepsy. *Epilepsia* 1985;26:143–150.
13. Kuhl DE, Barrio JR, Huang SC, et al. Quantifying local cerebral blood flow by N-isopropyl-p-[^{123}I]niodoamphetamine (IMP) tomography. *J Nucl Med* 1982;23:196–203.
14. Lear JL, Ackermann RF, Kameyama M, Kuhl DE. Evaluation of [^{123}I]isopropyliodoamphetamine as a tracer for local cerebral blood flow using direct autoradiographic comparison. *J Cereb Blood Flow Metab* 1982;2:179–185.
15. Hoshi H, Jinnouchi S, Watanabe K, Ueda T, Kinoshita K, Yamaguchi T. Biodistribution of N-isopropyl-p-iodoamphetamine in the rat brain. *Nuklearmedizin* 1987;26:131–134.
16. Sokoloff L, Reivich M, Kennedy D, et al. The ^{14}C deoxyglucose method for the measurement of local cerebral glucose utilization: theory, procedure and normal values in the conscious and anesthetized albino rat. *J Neurochem* 1977;28:897–916.
17. Nonaka R, Nakamoto Y, Suzuki J. Distribution of 2-deoxy-D-[1-^{14}C]-glucose (2DG) in normal and epileptic mice brains. *Jpn J Neuropsychopharmacol* 1980;2:419–423.
18. Suzuki J, Nakamoto Y, Shinkawa Y. Local cerebral glucose utilization in epileptic seizures of the mutant El mouse. *Brain Res* 1983;266:359–363.
19. Engel J Jr. The use of PET scanning in epilepsy. *Ann Neurol* 1984;15:(suppl):S180–S191.
20. Engel J Jr, Kuhl DE, Phelps ME, Rausch R, Newer M. Local cerebral metabolism during partial seizures. *Neurology* 1983;33:400–413.
21. Shen W, Lee BI, Park HM, et al. HIPDM-SPECT brain imaging in the presurgical evaluation of patients with intractable seizures. *J Nucl Med* 1990;31:1280–1284.
22. Kuhl DE, Engel J, Phelps ME, Silin C. Epileptic patterns of local cerebral metabolism and perfusion in humans determined by emission computed tomography of ^{18}FDG and ^{13}NH3. *Ann Neurol* 1980;8:348–360.
23. Frank G, Sadzot B, Salmon E, et al. Regional cerebral blood flow and metabolic rates in human focal epilepsy and status epilepticus. In: Delgado-Escueta AV, Ward AA, Woodbury DM, Porter RJ, eds. *Advances in neurology*, 44th ed. New York: Raven Press; 1986:935–948.
24. Bernardi S, Trimble MR, Frackowiak RSJ, Wise RJS, Jones T. An interictal study of partial epilepsy using positron emission tomography and the ^{15}O inhalation technique. *J Neurol Neurosurg Psychiat* 1983;46:473–477.
25. Ryvlin P, Philippon B, Cinotti L, Froment JC, Le Bars D, Mauguiere F. Functional neuroimaging strategy in temporal lobe epilepsy: a comparative study of ^{18}FDG-PET and ^{99m}Tc-HMPAO SPECT. *Ann Neurol* 1992;3:650–656.
26. Leiderman DB, Balish M, Sato S, et al. Comparison of PET measurements of cerebral blood flow and glucose metabolism for the localization of human epileptic foci. *Epilepsy Res* 1992;13:153–157.
27. Stefan H, Pawlik G, Bocher-Schwarz HG, et al. Functional and morphological abnormalities temporal lobe epilepsy: a comparison of interictal and ictal EEG, CT, MRI, SPECT and PET. *J Neurol* 1987;234:377–384.
28. Meldrum BS, Nilsson B. Cerebral blood flow and metabolic rate early and late in prolonged epileptic seizures induced in rats by bicuculline. *Brain* 1976;99:523–542.
29. Ingvar M, Siesjo BK. Local blood flow and glucose consumption in the rat brain during sustained bicuculline-induced seizures. *Acta Neurol Scand* 1983;68:129–144.
30. Ingvar M. Cerebral blood flow and metabolic rate during seizures, relationship to epileptic brain damage. *Ann NY Acad Sci* 1986;462:207–223.
31. Tanaka S, Sako K, Nishihara I, Yonemasu Y. Uncoupling of local blood flow and metabolism in the hippocampal CA3 in kainic acid-induced limbic seizure status. *Neuroscience* 1990;36:339–348.
32. Meyer JS, Gotoh F, Favele E. Cerebral metabolism during epileptic seizures in man. *Electroencephalogr Clin Neurophysiol* 1966;21:10–22.
33. Posner JB, Plum F, Van Poznak A. Cerebral metabolism during electrically induced seizures in man. *Arch Neurol* 1969;20:388–395.
34. Broderson P, Paulson OB, Bolwig TG, et al. Cerebral hyperemia in electrically induced seizures in man. *Arch Neurol* 1973;20:334–338.
35. Penfield W, Von Santha K, Cipriani A. Cerebral blood flow during induced epileptiform seizures in animals and man. *J Neurophysiol* 1939;2:257–267.