Asymmetries of benzodiazepine receptor binding potential in the inferior medial temporal lobe and cerebellum detected with $^{123}$I-iomazenil SPECT in comparison with $^{99m}$Tc-HMPAO SPECT in patients with partial epilepsy

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We examined the relation between regional $^{123}$I-iomazenil (IMZ) parameters and cerebral blood flow (CBF) to evaluate the difference between the quantitative parameters of IMZ and the CBF in detecting epileptic abnormality. Seventeen patients with unilateral partial epilepsy were subjected to $^{99m}$Tc-hexamethylpropylene amine oxime (HMPAO) SPECT, and early and delayed IMZ SPECT. Then we quantitatively obtained the blood-to-brain transfer constants ($K_i$) and binding potentials (BP) for nine regions of interest, and the regional CBF was also by using the simple angiographic method. From our data, significant asymmetries of BP in the inferior medial temporal lobe and cerebellum were shown and may be related to a remote effect such as crossed cerebellar diaschisis. In conclusion, the asymmetry of BP with iomazenil SPECT was demonstrated in patients with unilateral epilepsy that was not detectable by HMPAO SPECT.

Key words: partial epilepsy, benzodiazepine receptor, cerebral blood flow, binding potential, brain receptor imaging

INTRODUCTION

$^{123}$I-iomazenil (IMZ) is a partial inverse agonist of radiolabeled ligand for the central type of benzodiazepine receptor which cooperates with the gamma-aminobutyric acid A (GABA$_A$) receptor. IMZ is especially expected to detect the epileptic foci in patients with partial epilepsy uncontrollable by medication. In temporal lobe epilepsy, the decrease in benzodiazepine receptor binding in the ipsilateral anterior medial temporal lesion was seen with $[^1]C$lumazenil PET and also IMZ, but the changes in IMZ uptake in other partial epilepsies are unclear. There have been few reports about quantitative SPECT analysis of patients with partial epilepsy based on kinetic models. In addition, the effect of CBF on IMZ uptake in partial epilepsy has not been sufficiently clarified. In this study, we quantitatively compared the binding potentials (BP) and blood-to-brain transfer constant ($K_i$) with early and delayed SPECT of IMZ and the cerebral blood flow (CBF) with $^{99m}$Tc-hexamethylpropylene amine oxime (HMPAO) SPECT, to evaluate the difference between quantitative benzodiazepine binding imaging and CBF imaging at the interictal phase in patients with partial epilepsy.

MATERIALS AND METHODS

Patients
Sixteen patients with partial epilepsy (9 male and 7 female; average age ± s.d., 31.6 ± 11.9 years; range 19–56 years) who had not undergone any operative procedure. All patients were part of phases 2 and 3 of a clinical preliminary test conducted by Nihon Medi-Physics Co. Ltd. (Nishinomiya, Japan) in Japan, and each gave informed consent to participate in this study. These patients were suspected of having unilateral epileptic foci based on their clinical background including neuropsychological symptoms, seizure patterns, magnetic resonance imagings and superficial electroencephalogram (EEG) (Table 1), and were administered neither benzodiazepine analog nor antagonist. An epileptic side in this article means a side of
| Patient | Age (year-old) | Sex | Onset (year) | Seizure frequency | Seizure pattern | Medication | MRI finding | Ictal EEG burst | Intercital EEG burst | Suspected focus |
|---------|----------------|-----|--------------|-------------------|----------------|------------|------------|---------------|-------------------|------------------|------------------|
| 1       | 22             | F   | 11           | 1–2/mo            | SPS, CPS       | CBZ, ZSM   | L-TL atrophy | B-TL           | L-TL              | L-TL             |
| 2       | 42             | F   | 17           | 2–3/w             | SPS, CPS+SGS   | PHT, PRM   | R-TL ecopic | Not done       | R-TL              | R-TL             |
| 3       | 29             | M   | 19           | 3–4/mo            | SPS, CPS       | VPA        | gray matter | Not done       | R-TL              | R-TL             |
| 4       | 19             | M   | 8            | 3/d              | SPS            | CBZ        | WNL        | Not done       | L-FL              | L-FL             |
| 5       | 31             | M   | 14           | 20/mo            | SPS, CPS       | CBZ, PB, PHT | L-FL atrophy | Not done       | L-TL              | L-TL             |
| 6       | 40             | M   | 12           | 4–5/mo            | SPS, CPS+S     | CBZ, PHT, PB | WNL        | Not done       | B-FL              | R-FL             |
| 7       | 23             | F   | 3            | 2–3/d            | SPS            | CBZ, PHT, ZSM | WNL        | Not done       | R-TL              | R-TL             |
| 8       | 44             | F   | 28           | 2–3/mo            | CPS+SGS        | CBZ, VPA   | WNL        | Not done       | B-TL              | L-TL             |
| 9       | 21             | M   | 19           | 1/mo              | SPS, CPS+S     | PHT, VPA   | WNL        | Not done       | L-FL              | L-FL             |
| 10      | 30             | M   | 15           | 2–3/w            | SPS            | CBZ, PHT, PB | R-TL arachnoid | Not done       | L-TL              | L-TL             |
| 11      | 56             | F   | 25           | 3–4/mo            | CPS, SGS       | CBZ, PHT, VPA | Lacunae    | Not done       | R-TL              | R-TL             |
| 12      | 24             | M   | 20           | 2–3/d            | SPS            | CBZ, PHT   | L-PL atrophy | Not done       | L-FL-PL           | L-FL-PL          |
| 13      | 19             | M   | 18           | 2–3/w            | CPS            | CBZ        | WNL        | Not done       | R-TL              | R-TL             |
| 14      | 53             | F   | 20           | 5–6/y            | CPS+SGS        | CBZ        | Not done   | B-TL           | B-TL              | L-TL             |
| 15      | 22             | F   | 22           | 1/mo             | CPS            | No medication | WNL        | L-PL           | L-PL              | L-PL             |
| 16      | 31             | M   | 29           | 6/y              | CPS+SGS        | CBZ, VPA   | WNL        | Not done       | L-FL              | L-FL             |

The focus was suspected by superficial electroencephalogram and clinical symptoms. EEG: electroencephalogram; M: Male; F: Female; SPS: Simple partial seizure; CPS: complex partial seizure; SGS: secondary generalized seizure; CBZ: carbamazepine; PB: phenobarbital; PHT: phenytoin; PRM: primidone; VPA: sodium valproate; ZSM: zonisamide; WNL: within normal limit; R: Right; L: Left; B: Bilateral; FL: frontal lobe; TL: temporal lobe; PL: parietal lobe

the epileptic focus. Neither intracranial EEG nor operative procedures were performed for further diagnosis of the epileptic foci. None of the patients had any evidence of anxiety disorders. The anxiety level was not measured.

**HMPAO data acquisition**

First, the passage through the heart to the brain was monitored with a rectangular large-field gamma-camera (Toshiba GCA-901A/SB) after a bolus injection of $^{99m}$Tc-HMPAO (740 MBq) via the right brachial vein. Data acquisition was a sequence of 110 frames at 1st interval with a 128 × 128 matrix. Second, after angiography, a SPECT acquisitions of 128 × 128 matrix over 360 degrees with 6 degrees steps in a continuous rotating mode were conducted with a triple-head gamma-camera (Toshiba GCA-9300A/HG) with high-resolution fanbeam collimators. The data were reconstructed into images 3.4 mm thick with a back-projection method with a Butterworth preprocessing filter (order 8, cutoff 0.65 cycle/cm) and a Shepp and Logan postprocessing filter. The scatter correction was made by the triple energy window method, but no attenuation correction was made. A venous blood sample was obtained 30 min after the administration of IMZ, and whole blood counts were measured in a gamma well-counter.

**ROI setting**

The SPECT images of early and delayed IMZ were visually adjusted to the same orientation as HMPAO images. On each of five SPECT images of HMPAO, the regions of interest (ROI) of 5 cortical regions (high frontal, parietal, frontal, temporal and occipital cortex), basal ganglia, thalamus, inferior medial temporal lobe and cerebellar cortex were set bilaterally to obtain each count (Fig. 1). Then the same ROI settings were copied on the same level of the early and delayed IMZ SPECT images.

**CBF calculation**

With HMPAO data, the mean CBF was estimated by the brain perfusion index obtained with the angiography, and regional blood flow in each ROI was calculated from each count with the mean CBF according to the method reported by Matsuda et al.56

**K1 and BP of IMZ calculation**

The blood-to-brain transfer constants (K1) and binding potentials (BP) of IMZ based on the three-compartment model (Fig. 2) were obtained from IMZ SPECT data and

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Fig. 1 Setting of regions of interest (ROI) on early $^{123}$I-iodomazenil (IMZ) images. Each ROI was set on $^{99m}$Tc-HMPAO (HMPAO) images and was moved on IMZ images. Displayed images were early IMZ images and ROI settings copied from HMPAO images. HFC, high frontal cortex; PC, parietal cortex; FC, frontal cortex; TC, temporal cortex; OC, occipital cortex; BG, basal ganglia; Th, thalamus; Hi, inferior medial temporal lobe; Ce, cerebellum.

Fig. 2 Three-compartment model. $K_i$, $k_2$-$k_4$ were rate constants. $K_i/k_2$ ratio was fixed to be 3.00 and $k_4$ was fixed to be 0.026, according on Onishi et al.

venous blood counts with the previously reported table look-up method of Onishi. In this method, $K_i/k_2$ ratio was fixed at 3.00 in the three-parameter configuration, and $k_4$ was fixed at 0.026 in the two-parameter configuration, and also the free fraction of IMZ in the plasma was 0.24. If the $K_i$ or $k_2$ is outside the 0.0–1.0 range, $K_i$ and $BP$ are not given because they are not in the look-up table.

Analysis

Patients were divided into two groups: temporal lobe epilepsy and others. Each individual group and all the groups together were analyzed, respectively. Ratios of CBF, $K_i$, and $BP$ on the epileptic side compared to those on the contralateral side were calculated. A significant difference in asymmetry was considered to exist when $p < 0.05$ in the Wilcoxon signed rank test.

### Table 2: Ratios of regional CBF using $^{99m}$Tc-HMPAO, $K_i$, and $BP$ of I-123 iomazenil in the epileptic side to the contralateral side in patients with partial epilepsy ($n=16$) and $K_i$ (ratio of $K_i$)

<table>
<thead>
<tr>
<th>Region</th>
<th>TLE (n=10)</th>
<th>Others (n=6)</th>
<th>All (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High frontal cortex</td>
<td>100.5 ± 8.6</td>
<td>92.1 ± 7.8</td>
<td>97.7 ± 8.9</td>
</tr>
<tr>
<td>Parietal cortex</td>
<td>97.0 ± 11.0</td>
<td>92.0 ± 10.0</td>
<td>92.0 ± 9.0</td>
</tr>
<tr>
<td>Frontal cortex</td>
<td>96.6 ± 8.2</td>
<td>94.6 ± 10.5</td>
<td>95.2 ± 10.0</td>
</tr>
<tr>
<td>Temporal cortex</td>
<td>98.7 ± 8.3</td>
<td>97.4 ± 8.8</td>
<td>97.8 ± 8.5</td>
</tr>
<tr>
<td>Occipital cortex</td>
<td>98.7 ± 7.1</td>
<td>102.5 ± 7.3</td>
<td>104.9 ± 7.3</td>
</tr>
<tr>
<td>Basal ganglia</td>
<td>101.2 ± 6.7</td>
<td>96.2 ± 8.7</td>
<td>98.3 ± 8.7</td>
</tr>
<tr>
<td>Thalamus</td>
<td>102.0 ± 6.2</td>
<td>101.5 ± 8.8</td>
<td>101.8 ± 8.4</td>
</tr>
<tr>
<td>Inferior temporal lobe</td>
<td>100.5 ± 5.5</td>
<td>105.5 ± 10.2</td>
<td>102.8 ± 10.6</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>99.0 ± 9.1</td>
<td>101.2 ± 10.2</td>
<td>100.5 ± 9.4</td>
</tr>
</tbody>
</table>

*Indicates percentage of the ipsilateral (at the side of epileptic focus) value to the contralateral value.

Values were displayed as mean ± SD.

CBF, cerebral blood flow; $K_i$, blood-to-brain constant; $BP$, binding potential; TLE, temporal lobe epilepsy.

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Fig. 3 Relationship of the ipsilateral-to-contralateral ratios between BP and CBF in the inferior temporal lobe (upper) and in the cerebellum (lower). Note the high ipsilateral-to-contralateral ratios of BP in the inferior medial temporal lobe, but the low ipsilateral-to-contralateral ratios of BP in the cerebellum, although the ratios of CBF are around 1.0.

RESULTS

Ratios of CBF, \( K_1 \) and BP on the epileptic side compared to those on the contralateral side in each region are shown in Table 2. There were no significant differences in any regional CBF and \( K_1 \) between the ipsilateral and contralateral sides. In the groups with temporal lobe epilepsy and all groups together, the BP in the ipsilateral inferior medial temporal lobe was significantly greater than that on the contralateral side, although the CBF on the two sides did not differ significantly (Table 2, Fig. 3). In contrast, in the groups of others and all groups together, the BP in the cerebellum on the epileptic side was significantly lower than that on the contralateral side, although the CBF did not differ significantly (Table 2, Fig. 3). On the other hand, the BP were not significantly different in other regions.

Significant differences in the inferior medial temporal lobe and cerebellum were observed in all groups together temporal lobe epilepsy and others. Differences were not statistically significant in the BP in the inferior medial temporal lobe in the group of no temporal lobe epilepsy and the BP in the cerebellum in the group of temporal lobe epilepsy, the BP trends in those regions in the two groups were similar.

A patient with unilateral temporal lobe epilepsy is shown in Fig. 4. Asymmetry of the activity in the inferior medial temporal lobe was demonstrated on the early and delayed IMZ images despite the symmetric HMPAO activity. Asymmetry of the cerebellar IMZ activity was unclear on the images visually.

DISCUSSION

In this study we evaluated the asymmetry of BP compared to \( K_1 \) and CBF at the interictal phase in patients with partial epilepsy.

We measured the CBF distribution with HMPAO, but Koyama reported that the HMPAO accumulation in the cerebellum and the basal ganglia is higher than the CBF with O-15 butanol, and also reported that the HMPAO SPECT resulted in the underestimation of high regional CBF and overestimation of lower regional CBF.\(^3\) We emphasize the clinical usefulness of the regional CBF with HMPAO in a routine study, although it has limitations.

The hemispherical distribution of IMZ was shown to be symmetrical in volunteers.\(^9\) A decrease in radiolabeled IMZ in epileptic lesions was reported,\(^1\) and this decrease in IMZ was normalized after 2 months' successful treatment with carbamazepine,\(^11\) but a decrease was not always observed in epilepsy.\(^10\) In contrast, the CBF in the epilep-
tic lesion in the interictal phase has been shown to vary from decrease to increase, although the CBF in the lesion increases at the ictal phase.

From our quantitative data, the asymmetries of BP in the inferior medial temporal lobe and cerebellum were confirmed to patients with unilateral partial epilepsy. If the BP in the contralateral inferior medial temporal lobe were normal, there was assumed to be a relative increase in BP in the inferior medial temporal lobe and a relative increase in BP in the cerebellum on the contralateral side to the epileptic side. Nagata et al. reported a postictal increase in IMZ binding in the hippocampus of spontaneously epileptic rats compared to controls in an ex vivo quantitative autoradiographic study. The relative increase in BP in the ipsilateral inferior medial temporal lobe also resembled this, but Kurokawa et al. showed that benzodiazepine receptor imaging is much more sensitive in the detection of epileptic foci than CBF imaging in experimental hippocampal kindled rabbits. Tanaka et al. also reported a decrease of Kᵢ and BP in the mesial temporal lobe when using the same quantitative method. The relative increase in BP on the epileptic side inferior medial temporal lobe at the interictal phase in our results did not agree with the report that the IMZ binding decreased in the inferior medial temporal lobe on the epileptic side in patients with temporal epilepsy. The reason is that our subjects had other kinds of partial epilepsy in addition to temporal lobe epilepsy, and the epileptic lesions in our subjects were not detectable by MRI, whereas the lesions in the patients reported by Tanaka et al. were detectable. Asymmetry of rCBF was also significant in our patients, but asymmetry of rCBF was apparent in the study by Tanaka et al. Therefore, the inferior medial temporal lobe in our study did not always include the epileptogenic lesion, and the changes may be regionally different even in the inferior medial temporal lobe. It is suggested that the benzodiazepine receptor binding in the ipsilateral inferior medial temporal lobe on the epileptic side may be rather increased due to suppression of neuronal activity around the inferior medial temporal lobe.

On the IMZ early images, asymmetry of BP in the inferior medial temporal lobe was revealed, although the activity of HMPAO was symmetrical. The asymmetry on the IMZ early image was greater than that on the IMZ delayed image. If CBF is symmetrical, we have two ways to explain the mechanism. A decrease in the extraction fraction and an increase in the washout in the inferior medial temporal lobe were taken into consideration. When changes in the mechanism of diffusion of IMZ through the blood-brain barrier occurred in the inferior medial temporal lobe on the epileptic side, if the binding capacity of IMZ were preserved, the activity on the delayed IMZ image in the inferior medial temporal lobe is relatively symmetrical. Because the extraction fraction depends mainly on the lipophilicity of the blood-brain barrier, we think that the major factor in altering the mechanism of the IMZ uptake on the early image is the increase in efflux from the blood-brain barrier to the blood in the inferior medial temporal lobe. On the other hand, an increase in HMPAO in the inferior medial temporal lobe on the epileptic side was also possible, because of the phenomenon called hyperfixation of HMPAO. If the tissue were intact in the inferior medial temporal lobe, the neuronal regulation may act on the transport of IMZ in the blood-brain barrier.

The asymmetry of benzodiazepine receptor binding in the contralateral cerebellar hemisphere in patients with unilateral epilepsy, which was confirmed for the first time in our study to our knowledge, may be a remote neurotransnal effect like crossed cerebellar diaschisis for suppression of the contralateral cerebellar hemispheric neuronal activity. Asymmetry of CBF in the cerebellum of children was reported in a previous study, but no significant asymmetry was observed in our study. Therefore the benzodiazepine receptor binding was thought to be a more sensitive parameter for cerebellar neurological and functional changes in partial epilepsy than the CBF.

Drugs such as phentoin and barbiturates involved the probability of change in the BP of benzodiazepine receptor. After chronic toxic doses of phentoin administration, in rats a significant decrease in [H]flunitrazepam receptor density was observed because of the cerebellar Purkinje cell degeneration that was experimentally induced. Barbiturates have the same effect as IMZ on the GABAₓ receptor and chloride ion channel complex. Several patients were given these drugs, but these changes did not have an effect on the ratio of the BP on the epileptic side to that on the contralateral side.

On the other hand, there was the possibility that anxiety levels alter the benzodiazepine receptor binding. Tokunaga et al. stated that anxiety and somatoform disorders were significantly decreased in the superior frontal, temporal and parietal cortices, in comparison with those of epileptic patients. There was a slight low possibility of an effect on the ratio of the BP on the epileptic side to that on the contralateral side, but there are no data on anxiety in the IMZ SPECT acquisition in our patients.

A limitation of our study is the ambiguity of the true epileptic lesions in the epileptic patients. If a more definite diagnosis had been made, more valuable information would have been obtained, but our results were able to demonstrate the advantage of BP with IMZ over CBF with HMPAO in partial epilepsy. BP distribution image may be of great value for the evaluation of epilepsy.

In conclusion, the asymmetry of BP in iomazenil SPECT was demonstrated in patients with unilateral partial epilepsy that was not detectable by HMPAO SPECT.

REFERENCES


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