

## Initial clinical experiences with dopamine D<sub>2</sub> receptor imaging by means of 2'-iodospiperone and single-photon emission computed tomography

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Dopamine D<sub>2</sub> receptor imaging was performed with <sup>123</sup>I labeled 2'-iodospiperone (2'-ISP) and single-photon emission computed tomography (SPECT) in 9 patients: 4 with idiopathic Parkinson's disease, 2 with parkinsonism, 1 with Wilson's disease and 2 with pituitary tumor, and the results were compared with the data for 9 normal subjects. Following an intravenous injection of <sup>123</sup>I-2'-ISP, early (within 30 min) and late (between 2 and 4 hr) SPECT images were obtained by means of a multi-detector SPECT scanner or a rotating gamma camera. In normal subjects, early SPECT images demonstrated uniform distribution of radioactivity in the cerebral gray matter and cerebellum reflecting regional cerebral blood flow, whereas late SPECT images showed high radioactivity only in the basal ganglia. All the patients with Parkinson's disease also demonstrated symmetrical basal ganglia uptake in the late SPECT images, but it was diminished in parkinsonism and Wilson's disease. One patient with a growth hormone-producing pituitary tumor had a positive uptake in the tumor. These preliminary clinical data demonstrated that 2'-ISP can be used for SPECT imaging of D<sub>2</sub> dopamine receptors and may be of clinical value for the diagnosis and planning of the treatment of neurological diseases.

**Key words:** SPECT, dopamine D<sub>2</sub> receptor, <sup>123</sup>I-2'-iodospiperone (2'-ISP), movement disorder, pituitary tumor

### INTRODUCTION

OVER THE PAST DECADE there has been considerable interest in the development of radiopharmaceuticals for receptor imaging with single-photon emission computed tomography (SPECT).<sup>1</sup> Although positron emission tomography (PET) still plays an important role in neuroscience research for understanding the biochemical mechanism of the neurotransmission function of the living human brain, SPECT is now expected to become a valuable tool in clinical nuclear medicine.

Iodine-123 labeled 2'-iodospiperone (2'-ISP) is one of the butyrophenone derivatives developed for SPECT imaging of dopamine D<sub>2</sub> receptors.<sup>2</sup> Previous *in vitro* and *in vivo* animal experiments demonstrated specific binding of 2'-ISP to D<sub>2</sub> receptors with high affinity.<sup>2,3</sup> Consequently the validity of *in vivo* SPECT imaging in human brain was confirmed in normal subjects.<sup>4</sup> Compared with *N*-methylnspiperone, which is another butyrophenone derivative used for PET imaging,<sup>5</sup> 2'-ISP showed slightly less affinity with D<sub>2</sub> receptors and negligible binding to serotonin receptors. In addition, the relatively long half-life of iodine-123 (T<sub>1/2</sub> = 13 hr) compared with the 20 min half life of carbon-11 makes it possible to measure the radioactivity over several hours. These characteristics allowed the evaluation of the specific receptor binding in basal ganglia with a simple equilibrium approach with the cerebral cortex as a reference region.<sup>4,6</sup>

In this article we report the first clinical experiences

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with 2'-ISP in cases of movement disorders and pituitary tumor.

## MATERIALS AND METHODS

### Radiolabeled compound

Iodine-123 labeled 2'-ISP (Figure 1) was synthesized by bromine-radioiodine exchange reaction as reported previously.<sup>4,7</sup> The specific activity was approximately 13 TBq/mmol, and the radiochemical purity determined by TLC and analytical HPLC was greater than 98%.

### SPECT imaging

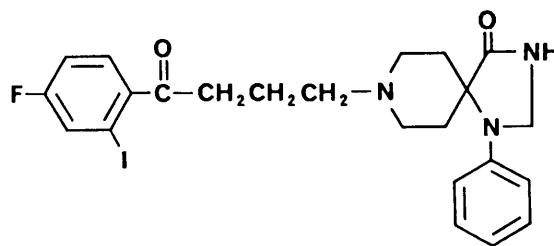
Nine patients were involved in this study: 4 with Parkinson's disease, 2 with parkinsonism due to other causes, one with Wilson's disease, and 2 with pituitary adenoma. These patients were under medical treatment. Nine normal subjects who volunteered to participate in this study were also included for comparison. In order to prevent the thyroid from being subjected to unnecessary radiation, all subjects received potassium iodide (60 mg/day) for 4 days starting two days prior to the administration of I-123 labeled 2'-ISP. The study was approved by the Ethical Committee of Kyoto University School of Medicine.

The subjects received 111 to 222 MBq of I-123 labeled 2'-ISP via the cubital vein as a bolus, and SPECT scan was performed with a multi-detector SPECT scanner (SET-030W; Shimadzu Co., Kyoto, Japan) or a single head rotating gamma camera (RC-150E; Hitachi Medical Co., Tokyo). The former had 3 fixed detector rings at 30 mm intervals, and the spatial resolution measured by measure of a <sup>99m</sup>Tc line source was 10.6 mm in terms of full width at half maximum (FWHM) at the center of the field, and the axial resolution was 23.5 mm at the center.<sup>8</sup> The subject's head was positioned parallel to the canthomeatal line (CM-line) and the plane of the lowest slice was adjusted to 2 cm above the OM-line, providing 3 tomographic slices at 2, 5 and 8 cm above the CM-line. SPECT images with the rotating gamma camera were obtained by rotating the detector with a low energy general purpose collimator over 360° (64 views with 40 sec acquisition for each view). The data for the limited field of the camera (25.6 × 25.6 cm) were stored as 64 × 64 matrix images (4 mm pixel size), and SPECT images of every 3 slices (12 mm thickness) were reconstructed.

For both SPECT systems used in this study, attenuation correction was performed by a simple post-correction method assuming the head to have an ellipsoid shape with uniform attenuation.

### Data analysis

In addition to the visual interpretation of the SPECT images, semi-quantitative analysis was performed by placing the region of interest (ROI) on the late SPECT images. A square shaped ROI (8 × 8 mm) was placed to cover the basal ganglia in each hemisphere including the



### 2'-iodospiperone (2'-ISP)

Fig. 1 Chemical structure of 2'-iodospiperone (2'-ISP).

area of highest activity in the late SPECT image. Same sized ROIs were placed to cover the cortical rim of the bilateral frontal cortex in the early SPECT image (6 ROIs in total for each subject). The basal ganglia to frontal cortex (BG/FCx) activity ratio was used for the semi-quantitative evaluation of receptor binding.

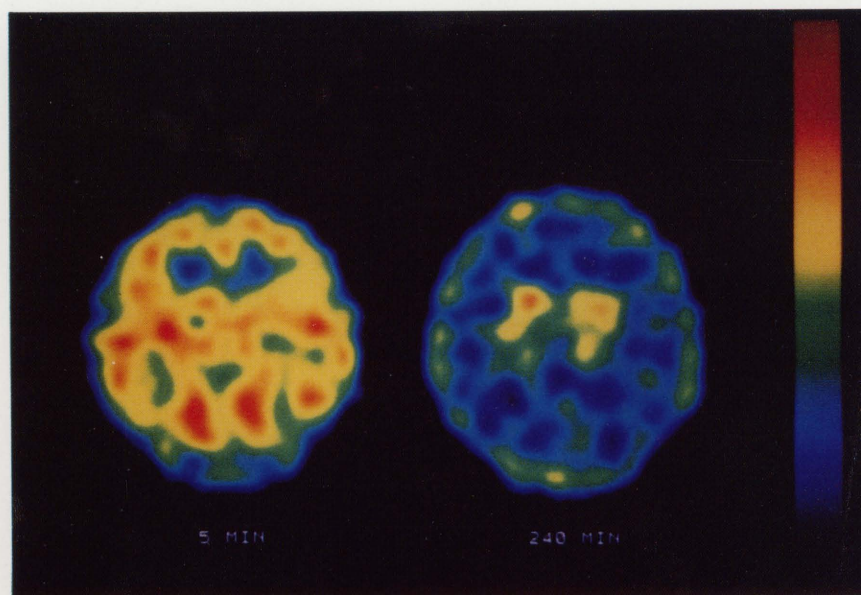
## RESULTS

Figure 2 demonstrates a typical example of early and late SPECT images obtained in a normal subject. The early SPECT images showed rapid initial uptake in the whole brain according to cerebral blood flow. On the other hand, the late SPECT images revealed high radioactivity only in the basal ganglia.

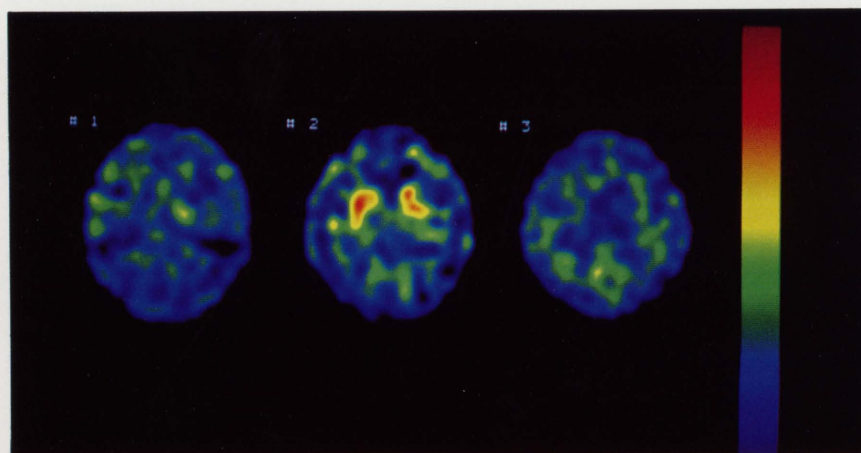
Four patients with Parkinson's disease showed symmetrical accumulation in the basal ganglia on visual analysis of the SPECT images, similar to the normal subjects. On the other hand, the uptake was decreased in Wilson's disease and in one of the two cases of parkinsonism. Figures 3 and 4 show the SPECT images in two patients manifesting similar parkinsonian symptoms. Figure 3 shows a case of idiopathic Parkinson's disease with good response to L-DOPA treatment. The SPECT images showed a normal pattern of post-synaptic receptors in the bilateral basal ganglia. In the case shown in Figure 4, however, although the clinical symptoms were similar to those of the previous case, L-DOPA did not have any therapeutic effect and the patient was clinically thought to have striatonigral degeneration. The SPECT images showed decreased uptake of 2'-ISP in the bilateral basal ganglia, indicating decreased post-synaptic receptors.

One of the two cases of pituitary adenoma demonstrated positive uptake of 2'-ISP in the tumor. Figure 5 shows a coronal section of the SPECT images obtained in this patient, who had growth hormone-producing pituitary adenoma. This patient received pituitary surgery followed by medical treatment with bromocriptine, which had a remarkable effect. The other case of pituitary adenoma did not show a sign of positive uptake, probably because the tumor was necrotic.

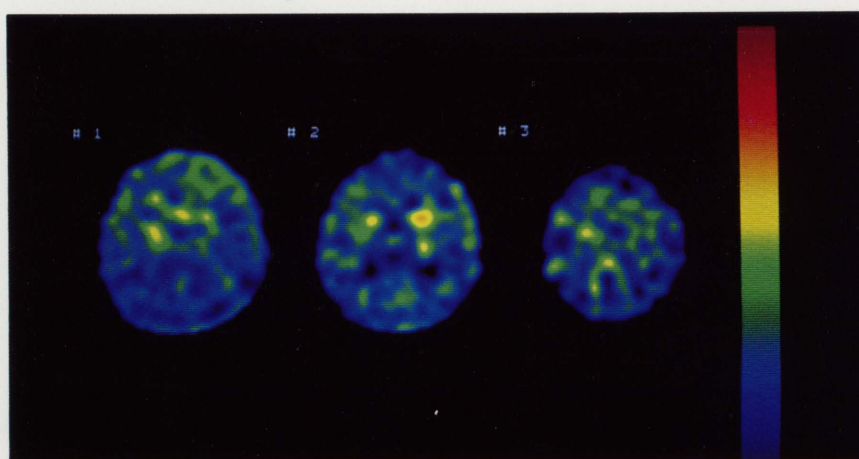
Figure 6 shows the BG/FCx ratio obtained from all



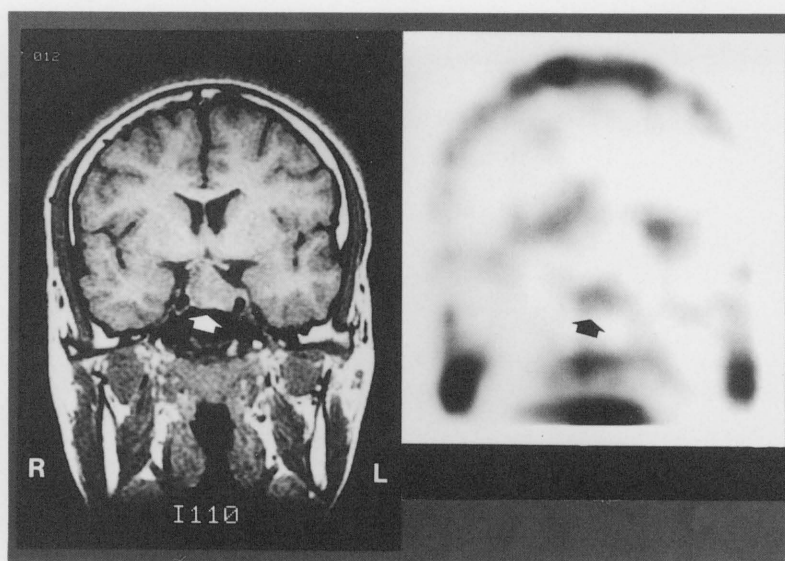
**Fig. 2** Early and late SPECT images of 2'-ISP obtained from a normal subject. The initial distribution was essentially similar to blood flow, but late distribution showed specific binding to dopamine D<sub>2</sub> receptors.



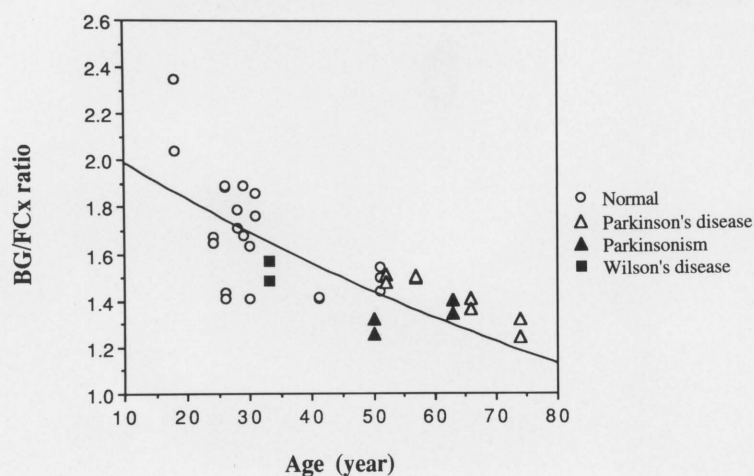
**Fig. 3** Typical late SPECT images of 2'-ISP in Parkinson's disease, showing normal uptake pattern in the basal ganglia. Three tomographic slices corresponding to cerebellum, basal ganglia, and centrum semiovale are shown from left to right.



**Fig. 4** Late SPECT images in a case of parkinsonism possibly due to striatonigral degeneration in which L-DOPA was ineffective. The radioactivity in the basal ganglia was reduced compared with normal subjects and Parkinson's disease.



**Fig. 5** MRI and SPECT image of 2'-ISP in a case with growth hormone-producing pituitary adenoma. Note the intense accumulation of 2'-ISP in the tumor (arrow).



**Fig. 6** Basal ganglia to frontal cortex ratio (BG/FCx) plotted against age. Values of the right and left side are shown for each subject. The regression curve obtained from the 9 normal subjects and 2 cases of pituitary tumor (open circles) demonstrated an age dependent decrease of 2'-ISP binding in basal ganglia ( $y = 2.16 \cdot 10^{-0.035x}$ ).

subjects. The BG/FCx ratio showed an age dependent decrease, similar to previous reports. Although the values tended to be lower in one case of parkinsonism, no clear distinction was possible due to variation among the normal subjects.

## DISCUSSION

The present study demonstrated the clinical feasibility of  $^{123}\text{I}$  labeled 2'-ISP for SPECT imaging of  $\text{D}_2$  dopamine receptors. Although the results obtained in this study were limited to a relatively small number of patients, they were consistent with the clinical data obtained previously with different radioligands. Reduced striatal binding of the  $\text{D}_2$  radioligand was reported in a few neurological movement disorders including Huntington's disease<sup>9</sup> and supranuclear palsy.<sup>10,11</sup> On the other hand, no definitive conclusion was obtained in idiopathic Parkinson's disease, and SPECT imaging of  $\text{D}_2$  receptor may have potential clinical value

for differentiation of the diseases, elucidation of the pathophysiology, and selection of the treatment. The present study demonstrated that the patient with parkinsonism, in which L-DOPA treatment had been ineffective, had diminished uptake of 2'-ISP, suggesting a reduced number of post-synaptic receptors. The method may therefore be valuable for differentiating various neurodegenerative diseases involving movement disorders.

Dopamine receptors in pituitary adenomas were first visualized by PET and carbon-11 labeled *N*-methylspiperone (NMSP) in prolactinoma.<sup>12</sup> As both 2'-ISP and NMSP are butyrophenone derivatives with similar pharmacological characteristics, it is not surprising to observe the accumulation of 2'-ISP in pituitary adenoma. It is well known that some pituitary adenomas have rich dopamine receptors, and the number of receptors may be important in determining the effectiveness of medical treatment.<sup>12-14</sup> SPECT imaging of dopamine receptors



may therefore also be of clinical value for predicting the therapeutic effect of a dopamine agonist such as bromocriptine on pituitary adenoma. Obviously more extensive studies will be needed to confirm the clinical role of receptor imaging with SPECT.

For the quantitative analysis of receptor binding, we measured the simple target to non-target ratio, with the frontal cortex as a reference region. This ratio method was applicable to 2'-ISP because the kinetic analysis in normal subjects demonstrated a gradual decrease in radioactivity in basal ganglia after 1 hour, and the basal ganglia to frontal cortex ratio (BG/FCx) was stable at between 2 and 4 hours.<sup>9</sup> This pseudo-equilibrium condition allows to use the simple BG/FCx ratio as a semiquantitative parameter of receptor binding. The cerebellum has been frequently used as a reference region for the analysis of D<sub>2</sub> receptor binding in PET studies,<sup>15</sup> but it is not suitable for SPECT studies because SPECT values in the cerebellum may not be accurate due to significant attenuation of the head holder. In contrast to NMSP, the binding of 2'-ISP in serotonin receptors is negligible and the cerebral cortex can be used as a non-specific binding site.<sup>2,9</sup> In addition to the two classical subtypes of dopamine receptors, recent studies with a molecular genetic technique have revealed more subtypes, such as D<sub>3</sub>, D<sub>4</sub> and D<sub>5</sub> receptors. The affinity of 2'-ISP for these subtypes has not been investigated.

The BG/FCx ratio of 2'-ISP demonstrated an age dependent decrease. The target to non-target ratios were similar to those obtained with other SPECT ligands,<sup>9,11</sup> but obviously lower than the PET results.<sup>15</sup> This was partly due to the physical limitations of the SPECT measurement such as lower spatial resolution and greater fraction of scattered radiation, but the characteristics of 2'-ISP itself may also be responsible for this. The instability of 2'-ISP causes the accumulation of a fairly large amount of radioactivity in the extracranial soft tissues and salivary glands as demonstrated in the coronal section of the SPECT images (Fig. 5). Even normal subjects sometimes showed a side-to-side difference in the uptake and distribution pattern in the basal ganglia, probably due to the poor image quality of the SPECT images. Moreover, very little radioactivity in the reference region results in a large variation among the normal subjects. These limitations results in a large variation in the BG/FCx ratio, and the reduced binding of 2'-ISP could not be clearly separated from the normal values in the present study. More careful kinetic analysis may be necessary to obtain better quantification.<sup>16</sup>

In summary, the preliminary clinical data demonstrated the feasibility of dopamine D<sub>2</sub> receptor imaging with SPECT, but more extensive efforts, including both the development of tracers with better characteristics and technical improvement in the quantitative analysis, are needed for clinical use of this method.

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