Cardiac Sympathetic Denervation from the Early Stage of Parkinson's Disease: Clinical and Experimental Studies with Radiolabeled MIBG

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Autonomic disorder is not infrequent in patients with akinetic–rigid syndromes, including idiopathic Parkinson's disease. In the advanced stage of Parkinson's disease, abnormal blood pressure responses, such as orthostatic hypotension and abnormal circadian blood pressure rhythm, may occur. Few cases of reduced ^{123}I-metaiodobenzylguanidine (MIBG) accumulation in the heart or limbs of Parkinson's disease patients have been reported. However, whether reduced accumulation is caused by damage to the postganglionic sympathetic nervous system or by central autonomic failure corresponding to abnormalities in blood pressure regulation is unknown. **Methods:** We evaluated sympathetic denervation in 32 Parkinson's disease patients using ^{123}I-MIBG cardiac scintigraphy and compared the findings with those for autonomic dysfunction detected by orthostatic hypotension and diurnal blood pressure variation. Cardiac ^{125}I-MIBG accumulation was also determined in an experimental model of Parkinson's disease using mice pretreated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). **Results:** Cardiac ^{123}I-MIBG accumulation 15 min after injection and 4 h after injection was markedly reduced in the Parkinson's disease patients (heart-to-mediastinum ratio: 1.58 ± 0.37 and 1.33 ± 0.28, respectively) compared with 7 healthy volunteers (2.42 ± 0.27 and 2.60 ± 0.15, respectively). This reduction was observed even at the earlier stages of physical activity or disease duration and also in patients with normal blood pressure response and variation, indicating that the marked decrease in cardiac ^{123}I-MIBG accumulation may be a special feature of Parkinson's disease. Pretreatment with a total dose of 100 mg/kg MPTP, which is the standard dose used to destroy the dopaminergic neurons in models of Parkinson's disease, significantly reduced cardiac ^{125}I-MIBG accumulation in C57BL/6 mice. Interestingly, the reduction of ^{125}I-MIBG accumulation was still significant when MPTP was reduced to 5 mg/kg. These findings indicated that the postganglionic sympathetic nerves may be damaged by MPTP or unknown toxic substrates in experimental or human Parkinson's disease during the early stage, because dopaminergic neurons and sympathetic nerves are substantially similar in their plasma membrane transporters. **Conclusion:** Cardiac scintigraphy with ^{123}I-MIBG may be used as a new imaging approach in the diagnosis and characterization of akinetic–rigid syndromes, especially Parkinson's disease.

Key Words: ^{123}I-MIBG; Parkinson's disease; orthostatic hypotension; autonomic disorder

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Parkinson's disease is an idiopathic disorder in adults who are more than 40 y old. It is usually recognized by the 4 cardinal clinical features: bradykinesia, rigidity, tremor, and a characteristic disorder of posture and gait (*1,2*). This disease is frequently associated with autonomic dysfunction, which is usually identified clinically by the presence of orthostatic, postprandial hypotension and an abnormal circadian blood pressure rhythm (*3–8*). Reports show that loss of cardiac accumulation or washout of radiolabeled metaiodobenzylguanidine (MIBG), an analog of norepinephrine, can be used as an index of sympathetic denervation or dysfunction in a variety of cardiac diseases (*9–13*). Reduced accumulation of ^{123}I-MIBG was also recently reported in diseases that predominantly affect the autonomic centers or peripheral nerves (*14–20*). Since Sisson et al. (*14*) reported marked reduction of cardiac ^{123}I-MIBG accumulation in generalized autonomic neuropathies such as Shy-Drager syndrome, the speculation has been that impaired ^{123}I-MIBG uptake is caused by damage to preganglionic components of the sympathetic nervous system. If, however, reduced accumulation of cardiac ^{123}I-MIBG occurs in a similar manner in Parkinson's disease, the severity of the reduction may correspond to the severity of the autonomic disorder, which is caused by impaired autonomic centers. Accumulation of cardiac ^{123}I-MIBG may therefore be a semiquantitative index of autonomic disorders in early-to-advanced stages of Parkinson's disease. In this study, we evaluated cardiac sympathetic impairment in Parkinson's disease using ^{123}I-MIBG scintigraphy in correlation with conventional tests for sympathetic function, i.e., the presence of orthostatic hypotension or a fall in diurnal blood pressure shown by ambulatory blood pressure monitoring. We also determined

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^{125}I-MIBG accumulation in an experimental murine model of Parkinson's disease to study the reduction in ^{125}I-MIBG uptake.

MATERIALS AND METHODS

Clinical Study

Patient Series. Thirty-two parkinsonian patients (15 women, 17 men; mean age [±SD], 67 ± 7.4 y) were studied. All patients with Parkinson's disease who were admitted to or attended our section between January 1996 and August 1998 were imaged as often as they agreed to be part of the MIBG study. The diagnosis of Parkinson's disease was made by at least 2 neurologists on the basis of clinical symptoms, signs, history, and neurologic examination. Patients with secondary (cerebrovascular or toxic) parkinsonism were identified on the basis of clinical history, brain CT findings, and MRI findings and were excluded. Using the clinical activity scale of Hoehn and Yahr (*21*), we classified parkinsonian patients into 5 stages. Two patients had stage I disease; 9, stage II; 14, stage III; 6, stage IV; and 1, stage V. They had been treated with amantadine, L-dopa, or trihexyphenidyl hydrochloride. This medication was continued during the study for obvious ethical reasons. In addition, 5 patients with multiple-system atrophy, including 3 with olivopontocerebellar atrophy and 2 with striatonigral degeneration, were included to compare with Parkinson's disease patients (*22*). The average age of patients with multiple-system atrophy was 69 ± 4.1 y. Patients were excluded if they had been taking any medicine (such as an antidepressant) previously reported to influence MIBG uptake (*23*). In no patient was a history or signs of cardiac disease revealed by an interview with a cardiologist and routine chest radiography, electrocardiography, and echocardiography, and no patient was taking antihypertensive or antihypotensive medication. All patients gave informed consent.

Cardiac ^{123}I-MIBG Imaging. Cardiac ^{123}I-MIBG imaging was performed to detect cardiac sympathetic denervation or dysfunction. Patients, at rest, were intravenously injected with 111 MBq ^{123}I-MIBG. Planar imaging was performed for 3 min in anterior, 45° left anterior oblique, and 70° left anterior oblique views using a γ camera (PRIZM 2000 or 3000; Shimazu, Tokyo, Japan) equipped with a high-resolution parallel-hole collimator. SPECT was not performed because of the poor uptake for reconstruction. Planar imaging was performed 15 min after (early image) and 4 h after (delayed image) the ^{123}I-MIBG injection. ^{123}I-MIBG accumulation was visually graded as none, very low, low, or normal by 2 masked independent observers. With the heart-to-mediastinum (H/M) ratio of Merlet et al. (*24*), cardiac ^{123}I-MIBG accumulation on anterior images was also semiquantitatively evaluated. Briefly, the 7 × 7 pixel region of interest was set over both the upper mediastinum and the heart. The H/M was then computed. This ratio is frequently used in semiquantitative analyses of ^{123}I-MIBG studies and, in healthy volunteers, has been reported to be uninfluenced by age or sex (*25*). An H/M was acquired from the 7 healthy volunteers (1 woman, 6 men; age range, 27–60 y).

Orthostatic Blood Pressure Measurement and Ambulatory Blood Pressure Monitoring. Orthostatic blood pressure changes were measured by sphygmomanometry for all patients, who stood for 20 min after resting supine for at least 10 min. Blood pressure was measured while the patients were supine, immediately after they stood, and every 3 min thereafter. A drop of more than 20 mm Hg in systolic blood pressure at any time after standing was considered to indicate orthostatic hypotension. In 31 patients, 24-h ambulatory blood pressure monitoring was performed. Two of the patients had stage I disease; 7, stage II; 12, stage III; 4, stage IV; 1, stage V; and 5, multiple-system atrophy. Ambulatory blood pressure monitoring was performed using a noninvasive, automatic, portable device (FB 240; Fukuda Denshi, Tokyo, Japan). During the procedure, all patients recorded their sleeping time in a diary. Measurements were collected every 30 min from 6:00 AM to 10:00 PM (diurnal) and every 60 min from 10:00 PM to 6:00 AM (nocturnal). The data were edited for artifacts, and diurnal and nocturnal systolic and diastolic blood pressure values were obtained. The nocturnal fall in systolic blood pressure was calculated as (diurnal systolic blood pressure − nocturnal systolic blood pressure)/diurnal systolic blood pressure. On the basis of these data, patients were considered normal dippers if the nocturnal blood pressure fall exceeded 10% of the diurnal mean systolic blood pressure. When patients had a blunted nocturnal blood pressure fall (<10% of the mean diurnal systolic blood pressure), they were judged as having abnormal circadian patterns of variation in blood pressure (*26*).

Experimental Study

C57BL/6 mice pretreated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) were used for the experimental model of Parkinson's disease. MPTP is known to induce a syndrome in humans and monkeys very much resembling Parkinson's disease (*27*). This agent can also produce an almost complete, permanent, and relatively selective degeneration of nigrostriatal dopaminergic neurons in this strain of mice (*28,29*). C57BL/6 male mice weighing 20–25 g were purchased from a breeder (Nihon Shizuoka Laboratory Animal Center, Hamamatsu, Japan). They were fed normal laboratory chow and given free access to water. Different doses and dosing intervals for MPTP were applied to 33 mice in the following 4 groups. One week before the ^{125}I-MIBG study, MPTP (Sigma, St. Louis, MO) was dissolved in 0.9% saline and administered subcutaneously in 0.5 ml saline to 3 groups of mice, using the following regimens: 5 mg/kg once, 5 mg/kg twice with a 16-h interval, and 50 mg/kg twice with a 16-h interval. Seven mice served as the control group, receiving saline pretreatment. Three mice in the groups twice receiving 50 mg/kg died before the ^{123}I MIBG experiment. Seven days after the last MPTP administration, 74 kBq ^{125}I-MIBG (Daiichi Radioisotope Laboratories, Tokyo, Japan) with a specific activity of 7400 MBq (200 mCi)/mg were injected through the tail vein into all mice. The mice were killed by cervical dislocation 4 h after MIBG administration. The hearts were dissected and weighed quickly. Radioactivity was determined with an automated γ counter (Autogamma 5650; Packard Instrument Co., Downers Grove, IL). Aliquots of the injected doses were counted in parallel with the samples as standards for the calculation of MIBG uptake (percentage injected dose per gram of tissue).

Results are expressed as mean ± SD. ANOVA was used to determine the significance of differences in data in both the experimental and the clinical studies. Differences were considered significant at $P < 0.05$

RESULTS

Clinical Study

As the patient in Figure 1 exemplifies, most Parkinson's disease patients had a marked reduction in cardiac ^{123}I-MIBG accumulation. Visually, no or very low accumulation was seen on delayed images for 26 patients, low accumula-

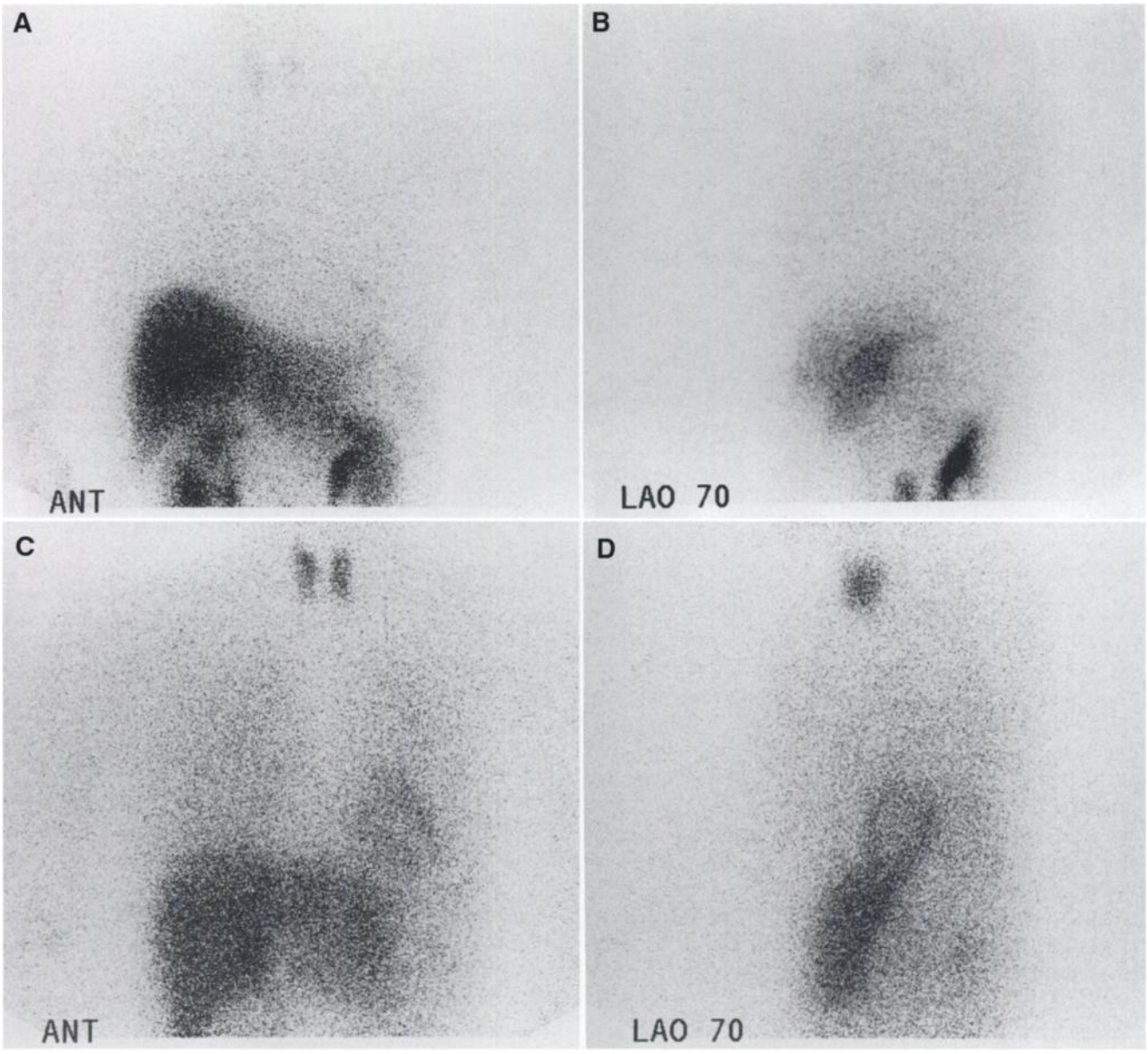

FIGURE 1. (A and B) Representative cardiac ^{123}I-MIBG planar scintigraphic images obtained 4 h after ^{123}I-MIBG injection in 64-y-old woman with Hoehn-Yahr stage IV Parkinson's disease. Cardiac ^{123}I-MIBG accumulation was null in both anterior (ANT) view (A) and 70° left anterior oblique (LAO) view (B). H/M was 1.15. (C and D) For comparison, anterior (C) and 70° left anterior oblique (D) cardiac ^{123}I-MIBG delayed images of healthy 40 y-old female volunteer. H/M was 2.57.

tion was seen for 5, and normal accumulation was seen for only 1 of the total of 32. On the early images, no or very low accumulation was seen for 20 patients, low accumulation was seen for 9, and normal accumulation was seen for 3. The mean H/M for all patients was 1.58 ± 0.37 and 1.33 ± 0.28 on early and delayed images, respectively, whereas for the healthy volunteers the respective ratios were 2.42 ± 0.27 and 2.60 ± 0.15. The reduction of ^{123}I-MIBG accumulation was more prominent on delayed images than on early images. Additionally, no patient showed stronger accumulation on delayed images than on early images. Therefore, we focused on the delayed images. On these images, accumulation was judged normal for only 1 patient (3%); the other 31 patients showed no, very low, or low accumulation. From semiquantitative assessment with H/M, all 32 patients showed an H/M lower than the lower limit in healthy volunteers (mean minus 2 SDs).

Because the severity of Parkinson's disease is usually evaluated on the basis of the patient's physical activity, H/Ms were compared with stage of disease (Fig. 2). A marked reduction in cardiac ^{123}I-MIBG accumulation was seen in patients with stage I or II disease, although the reduction was most significant in patients with stage III or IV disease. Cardiac ^{123}I-MIBG accumulation was also compared with disease duration (Fig. 3), and no significant correlation was found. Figure 4 compares the H/Ms of

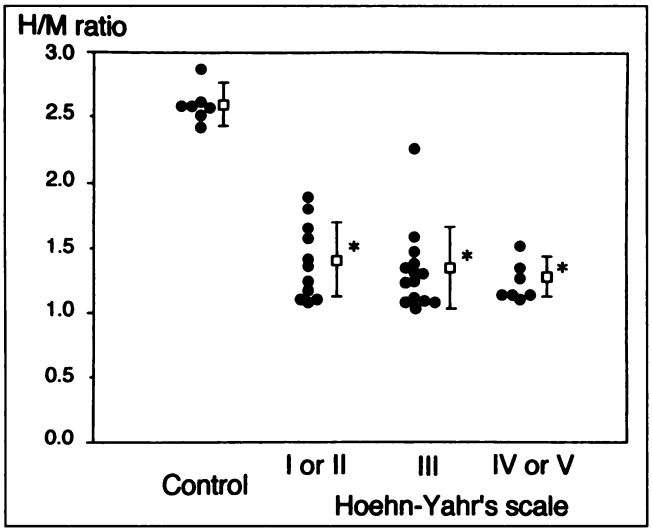

FIGURE 2. Cardiac ^{123}I-MIBG accumulation in 7 healthy volunteers and 32 Parkinson's disease patients. H/Ms were calculated for planar images obtained 4 h after injection. Accumulation was significantly reduced in all patient groups ($P < 0.05$ versus healthy volunteers). Data are means ± SDs.

patients and healthy volunteers with blood pressure monitoring data. Among the 26 patients who underwent both orthostatic testing and ambulatory blood pressure monitoring, ^{123}I-MIBG accumulation was compared between the group negative for orthostatic hypotension and positive for a nocturnal blood pressure fall (i.e., a normal blood pressure response) and the group positive for orthostatic hypotension and negative for a nocturnal blood pressure fall (i.e., an abnormal blood pressure response). Interestingly, cardiac ^{123}I-MIBG accumulation was significantly low even in the group of patients who did not have an abnormal blood pressure response to the orthostatic challenge or abnormal circadian patterns of variation in blood pressure.

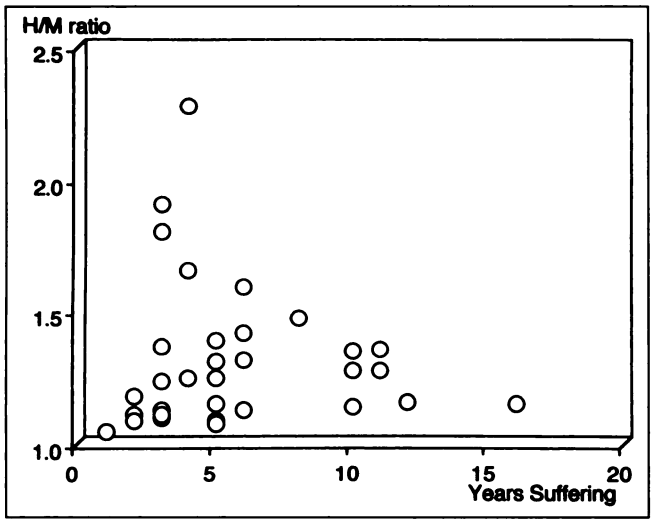

FIGURE 3. Cardiac ^{123}I-MIBG accumulation in 32 patients with Parkinson's disease. No significant correlation was found between H/Ms and disease duration. Data are means ± SDs.

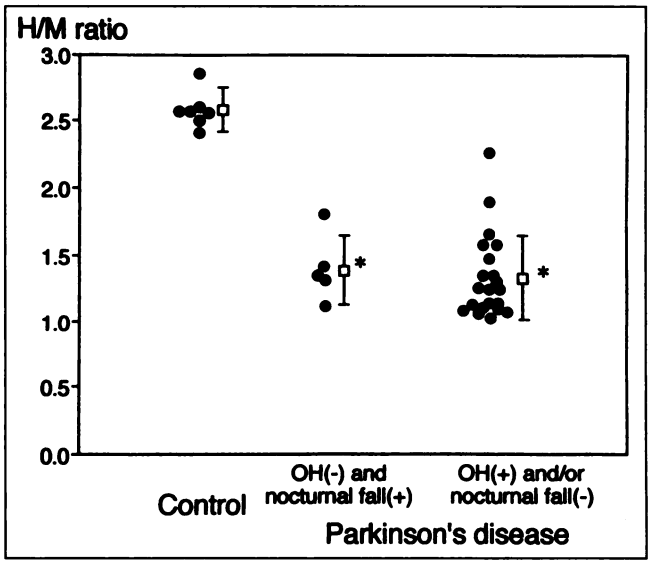

FIGURE 4. Cardiac ^{123}I-MIBG accumulation in 7 healthy volunteers and 26 patients with Parkinson's disease. H/Ms were compared according to existence of autonomic failure, which was detected by orthostatic hypotension (OH) and nocturnal fall in blood pressure variation. Even in patients with normal sympathetic function (n = 5), cardiac ^{123}I-MIBG accumulation was significantly reduced ($P < 0.05$ versus healthy volunteers). Data are means ± SDs.

Next, cardiac accumulation of ^{123}I-MIBG was examined in the 5 patients with multiple-system atrophy. Because all these patients showed no significant orthostatic hypotension but did not have the nocturnal blood pressure fall, we compared 12 parkinsonian patients who similarly did not have either orthostatic hypotension or a nocturnal blood pressure fall. Significant differences in ^{123}I-MIBG accumulation were seen not only between healthy volunteers and Parkinson's disease patients but also between Parkinson's disease patients and patients with multiple-system atrophy, as shown in Figure 5.

Experimental Study

Figure 6 shows cardiac ^{125}I-MIBG accumulation in the mouse model of Parkinson's disease. Four groups of mice were subjected to MPTP pretreatment at various doses and schedules. First, we administered 50 mg/kg MPTP twice, because this dose and schedule were confirmed to cause nearly complete dopaminergic cell depletion in a histologic study (*28,29*). In this group, the reduction in ^{125}I-MIBG accumulation 4 h after MIBG administration was almost complete, considering the previously reported proportion of non-neuronal uptake in the mouse heart (*12*). We also administered a lower dose of MPTP. Although the reduction in ^{125}I-MIBG accumulation was smaller in mice receiving the lower dose than in mice receiving 50 mg/kg twice, the difference was significant in both mice receiving 5 mg/kg once and mice receiving 5 mg/kg twice, compared with the control group.

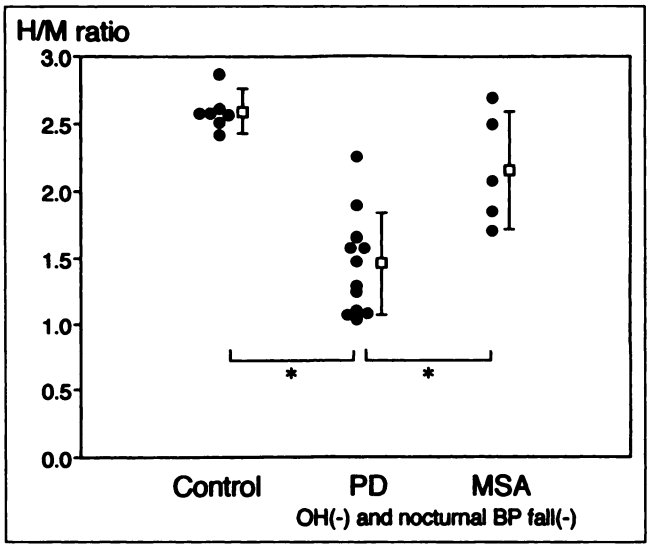

FIGURE 5. Cardiac ^{123}I-MIBG accumulation in 7 healthy volunteers, 12 patients with Parkinson's disease (PD), and 5 patients with multiple system atrophy (MSA). Patients with negative orthostatic hypotension and without nocturnal blood pressure fall were compared. Although they showed same blood pressure response and variation, cardiac ^{123}I-MIBG accumulation in H/M was significantly reduced in patients with Parkinson's disease ($P < 0.05$). Data are means ± SDs.

DISCUSSION

Most of the parkinsonian patients we studied, and the mouse model of Parkinson's disease, showed a marked reduction in cardiac ^{123}I-MIBG accumulation, indicating severe impairment of the cardiac sympathetic nervous system. This reduction was independent of sympathetic dysfunction as evaluated by postural changes or diurnal deviations in blood pressure.

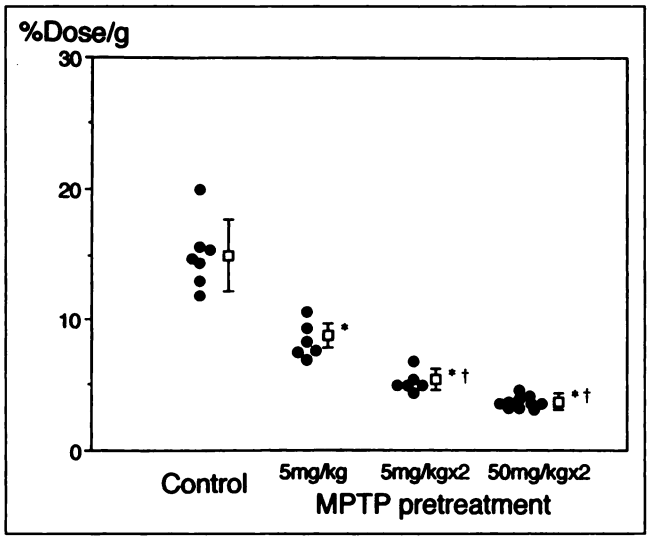

FIGURE 6. Cardiac ^{123}I-MIBG accumulation in control mice and in mice modeling Parkinson's disease (MPTP-pretreated C57BL/6 mice). Even in mice pretreated with small dose of MPTP, ^{123}I-MIBG accumulation was significantly reduced in heart. Control and 5 mg/kg groups had 7 animals each, 5 mg/kg × 2 group had 6; and 50 mg/kg × 2 group had 10. Data are means ± SDs. *$P < 0.05$ versus control; †$P < 0.05$ versus 5 mg/kg group.

Parkinson's disease is common in the elderly population, with a prevalence approaching 900 per 100,000 people more than 65 y old (*2*). Nigral neurons are the principal site of abnormality. The large, pigmented cells of the midbrain degenerate, and the intraneuronal inclusion bodies (Lewy bodies) commonly found in nigral neurons constitute a biologic marker for the disease (*2*). The precise mechanism underlying Parkinson's disease is still unknown, although endogeneous toxic substances and oxidative stress have been proposed as causes (*30,31*). Diagnosis is based mostly on clinical features such as bradykinesia, rigidity, tremor, and a characteristic disorder of posture and gait. No laboratory tests are routine (*2*). A few recent studies reported that ^{123}I-MIBG accumulation in the heart or limbs is reduced in patients with Parkinson's disease (*16–18*). Braune et al. (*32*) reported impaired uptake only in a subset of patients with autonomic failure. Autonomic dysfunction, such as orthostatic hypotension, occurs in Parkinson's disease although not as severely as in Shy-Drager syndrome (*4*). Clarification of whether decreased ^{123}I-MIBG accumulation in Parkinson's disease correlates with systemic autonomic dysfunction is therefore needed.

Several clinical tests can evaluate autonomic function. These tests—of heart rate variability at rest, during hyperventilation, or during the Valsalva maneuver—rely on parasympathetic rather than sympathetic function, whereas MIBG accumulation reflects postganglionic innervation or function. Therefore, we examined orthostatic hypotension and diurnal blood pressure variability in Parkinson's disease patients to evaluate sympathetic dysfunction. A significant blood pressure fall after standing is widely accepted as a sign of a sympathetic disorder. A loss of nocturnal blood pressure decrease shown by ambulatory blood pressure monitoring was recently reported in approximately 60% of patients with Parkinson's disease (*7*). We examined diurnal blood pressure variations in our parkinsonian patients because diurnal variations in the autonomic nervous system are reported to be an important determinant of diurnal blood pressure patterns (*33*).

Interestingly, ^{123}I-MIBG accumulation was markedly reduced even in patients with stage I or II disease and patients whose symptoms had been present less than 5 y, although the reduction was also significant in patients with advanced disease. The reduction appeared to be independent of clinical stage and disease duration. Furthermore, sympathetic dysfunction was evaluated by 2 methods. Five parkinsonian patients showed a normal blood pressure response and variation. Cardiac ^{123}I-MIBG accumulation was significantly less in these 5 patients than in healthy volunteers. Consequently, the marked reduction in cardiac ^{123}I-MIBG accumulation from earlier stages could be a special feature of Parkinson's disease, although the reduction may worsen as sympathetic dysfunction progresses. To test this hypoth-

esis, we examined cardiac ^{123}I-MIBG accumulation in multiple-system atrophy, which belongs to parkinsonism but is classified into a different disease category from Parkinson's disease. ^{123}I-MIBG accumulation was significantly less in Parkinson's disease patients than in healthy volunteers and multiple-system atrophy patients, although all these subjects were selected on the basis of their lack of orthostatic blood pressure change and diurnal blood pressure variation. These findings indicate that cardiac sympathetic denervation in early stages of disease may be specific for Parkinson's disease among the akinetic–rigid syndromes.

We therefore studied MPTP-induced parkinsonism in mice—an established animal model of Parkinson's disease. MPTP selectively destroys dopaminergic neurons of the substantia nigra, with typical clinical manifestations closely resembling those of Parkinson's disease (*27,34*). With the administration of 50 mg/kg MPTP twice in this study, cardiac neuronal ^{125}I-MIBG accumulation was almost completely eliminated, considering that non-neuronal ^{125}I-MIBG accumulation is approximately 30% of total accumulation in the mouse heart. Reports show that more than 70% of cells in the substantia nigra are lost with this dose of MPTP (*29*). We pretreated other cohorts of mice with a tenth or twentieth of that MPTP dose to mimic earlier stages of Parkinson's disease; at these doses, no significant reduction in neostriatal dopamine was expected, because of previous findings (*28*). However, reductions in cardiac ^{125}I-MIBG accumulation were still significant with these small doses of MPTP, showing that this parameter is sensitive for the detection of sympathetic impairment.

Parkinson's disease is caused by degeneration of the substantia nigra. Speculations that the reduction in MIBG accumulation is caused by central autonomic failure are thus reasonable. However, if these speculations are correct, the reduction in MIBG accumulation could be expected to be proportional to clinical stage, disease duration, and degree of systemic sympathetic disorder. In addition, patients with multiple-system atrophy, which similarly affects the autonomic centers and, like Parkinson's disease, is frequently accompanied by autonomic disorders, should show reduced cardiac MIBG accumulation during early stages. One possible explanation for the characteristic impairment of MIBG accumulation in Parkinson's disease is that postganglionic components in the sympathetic nervous system are primarily affected in Parkinson's disease and not in multiple-system atrophy.

Studies of MPTP toxicity have suggested a mechanism for the selective vulnerability of monoamine cell populations. As a hydrophobic molecule, MPTP penetrates the blood–brain barrier relatively easily and undergoes conversion to the active metabolite *N*-methyl-4-phenylpyridinium (MPP^+), which blocks the mitochondrial function of dopaminergic neurons. The susceptible cells must take up exogenous MPP^+ through the plasma membrane transporter that normally serves to terminate the action of monoamine transmitters by removing them from the synapse. All monoamine cell populations express such a transporter, accounting for their selective degeneration in response to MPTP, whereas other central neuronal and glial populations do not and are therefore spared by the toxin. In addition, the members of the family of this plasma membrane transporter show substantial sequence similarity, despite considerable differences between the ligands, such as γ-aminobutyric acid, dopamine, serotonin, and norepinephrine (*34*). Therefore, MPP^+ may quite possibly be taken up into the postganglionic sympathetic nerves through this transporter and destroy these nerves as well as dopaminergic neurons. Moreover, much pathologic evidence exists that MPTP injures several monoamine cell populations in addition to the dopaminergic neurons of the substantia nigra. Similar to the reduction of monoamine cell populations in Parkinson's disease, MPTP also spares chromaffin cells of the adrenal medulla (*34*). Possibly, therefore, an unknown toxic agent primarily may damage not only the substantia nigra but also cardiac sympathetic nerves in Parkinson's disease patients. Thus, the ^{123}I MIBG defect in Parkinson's disease patients may relate to the pathophysiology of Parkinson's disease.

Despite the extraordinary similarity between the MPTP model and idiopathic Parkinson's disease, no exogenous toxin has been identified in idiopathic Parkinson's disease. However, the toxicity of endogenous monoamine transmitters suggests that they may be involved (*31,34,35*). Thus, another possibility is that the cardiac sympathetic nerves in Parkinson's disease, like the dopaminergic neurons, are impaired by the intracellular disposition of a toxin and are unable to take up MIBG from its earlier stage.

A limitation of this clinical study is that we did not discontinue the medication of the Parkinson's disease patients. An ability to induce orthostatic hypotension has been reported for antiparkinsonian drugs (*36*). However, this factor does not result in underestimation of the sympathetic function assessed by the postural blood pressure change, although sympathetic dysfunction may be overestimated because of the treatment for Parkinson's disease. These antiparkinsonian drugs are also not on the lists of drugs that may affect cardiac MIBG accumulation (*23*). Therefore, we believe that our finding of reduced ^{123}I-MIBG accumulation in patients with normal sympathetic function was not influenced by the medication.

CONCLUSION

Cardiac ^{123}I-MIBG accumulation was found to be markedly reduced in patients with Parkinson's disease. The reduction was observed even at earlier stages of physical activity or disease duration and also in patients without autonomic disorders detected using conventional methods. In comparison with patients with multiple-system atrophy, this marked decrease in cardiac ^{123}I-MIBG accumulation may be a special feature of Parkinson's disease. Although data on ^{123}I-MIBG in related diseases are needed, cardiac ^{123}I-MIBG imaging may have the potential to differentiate akinetic–rigid syndromes, especially during early stages.

Moreover, the experimental study with MPTP-pretreated mice showed a similar marked reduction in cardiac ^{125}I-MIBG accumulation, suggesting that this reduction is primarily caused by damage to the postganglionic nervous system.

Cardiac scintigraphy with ^{123}I-MIBG may afford a new imaging approach to the diagnosis and characterization of akinetic–rigid syndromes, especially Parkinson's disease.

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