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Metaiodobenzylguanidine (MIBG) uptake in Parkinson's disease also decreases at thyroid

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Background: Decreased cardiac metaiodobenzylguanidine (MIBG) uptake was reported in Parkinson's disease and this contributes to the differential diagnosis between Parkinson's disease and other forms of parkinsonism such as multiple system atrophy. However, decreased MIBG uptake of the thyroid has not been demonstrated. ***Objective:*** To compare MIBG uptake of the thyroid among Parkinson's disease, multiple system atrophy and controls. ***Methods:*** Twenty-six patients with Parkinson's disease, 11 patients with multiple system atrophy and 14 controls were examined in this study. Planar images were taken 15 minutes (early images) and 3 hours (late images) after intravenous injection of 111 MBq ^{123}I-MIBG. ***Results:*** MIBG uptake of the thyroid on early images decreased significantly in Parkinson's disease compared to controls ($p < 0.0001$) and multiple system atrophy ($p = 0.018$). MIBG uptake of the thyroid on early images decreased significantly also in multiple system atrophy compared to controls ($p = 0.027$). On late images, thyroid uptake differed significantly only between Parkinson's disease and controls ($p = 0.010$). ***Conclusions:*** Our study is the first to demonstrate decreased MIBG uptake of the thyroid in Parkinson's disease. Sympathetic nervous denervation of Parkinson's disease occurred not only in the heart but also in the thyroid.

Key words: Parkinson's disease, thyroid, ^{123}I-labeled metaiodobenzylguanidine (MIBG), autonomic nervous system

INTRODUCTION

Iodine-123 labeled metaiodobenzylguanidine (MIBG) scintigraphy has been used for the evaluation of various cardiac diseases. The movement of MIBG in the human body has been reported to be similar to that of norepinephrine, thus allowing evaluation of cardiac sympathetic nerve activity by MIBG scintigraphy. MIBG uptake was reported to indicate presynaptic distribution of sympathetic nerves.

In patients with autonomic failure associated with various neurological diseases of the central and peripheral nervous system, MIBG scintigraphy has demonstrated reduced myocardial uptake of tracer, suggesting cardiac sympathetic dysfunction or denervation.[1] Recently, decreased cardiac MIBG uptake was reported in Parkinson's disease and this contributed to the differential diagnosis between Parkinson's disease and other forms of parkinsonism such as multiple system atrophy.[2–6] Although the sympathetic nervous system exists in organs other than the cardiac system, MIBG scintigraphy of other parts of the body had seldom been evaluated. Goldstein et al. reported that 6-[^{18}F]fluorodopamine-derived radioactivity was less not only in the myocardium but also in the thyroid and renal cortex of patients with Parkinson's disease,[7] although decreased MIBG uptake of the thyroid has not been demonstrated.

This study investigated MIBG uptake of the thyroid in Parkinson's disease and evaluated whether differences in the thyroid uptake were seen between Parkinson's disease, multiple system atrophy and controls.

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Table 1 Summary of clinical findings

	Control	MSA	PD	p values
n	14	11	26	
Age	68.2 ± 14.3	64.3 ± 9.8	68.5 ± 7.2	NS
Sex (male/female)	5/9	6/5	11/15	NS
Disease duration (year)	not applicable	3.8 ± 1.6	7.4 ± 7.3	NS
Hoeh-Yahr stage	not applicable	3.5 ± 0.5	3.5 ± 0.9	NS
Orthostatic hypotension	not applicable	6	11	NS
Constipation	not applicable	8	21	NS
Urinary symptom	not applicable	6	9	NS
TSH (μU/m*l*)	1.61 ± 0.23	1.49 ± 0.26	1.55 ± 0.17	NS
fT3 (pg/m*l*)	2.64 ± 0.14	2.42 ± 0.15	2.28 ± 0.10	NS
fT4 (ng/d*l*)	1.01 ± 0.05	0.99 ± 0.06	0.99 ± 0.04	NS

NS: not significant. Data of age, disease duration and Hoehn-Yahr stage are expressed as the mean value ± SD.

Table 2 Summary of ANOVA between controls, multiple system atrophy (MSA) and Parkinson's disease (PD)

	Control	NSA	PD	p values
Thyroid uptake on early images (T/M)	1.56 ± 0.23	1.34 ± 0.22	1.18 ± 0.20	<0.0001
Thyroid uptake on late images (T/M)	2.23 ± 0.64	1.97 ± 0.60	1.70 ± 0.58	0.034
Cardiac uptake on early images (H/M)	2.68 ± 0.48	2.45 ± 0.22	1.64 ± 0.32	<0.0001
Cardiac uptake on late images (H/M)	2.63 ± 0.61	2.61 ± 0.39	1.44 ± 0.35	<0.0001

Data are expressed as the mean value ± SD.

MATERIALS AND METHODS

Subjects

MIBG scintigraphy was performed in patients diagnosed as having Parkinson's disease or multiple system atrophy who were admitted to our hospital. All patients with Parkinson's disease fulfilled the UK Parkinson's Disease Society Brain Bank criteria for idiopathic Parkinson's disease,[8] and dopaminergic treatment was effective for parkinsonian symptoms in all patients. The clinical diagnosis of multiple system atrophy was based on the probable multiple system atrophy diagnostic criteria proposed by Gilman et al.[9] Twenty-six patients with Parkinson's disease and 11 patients with multiple system atrophy (7 striatonigral degeneration and 4 olivopontocerebellar atrophy) were examined in this study. Fully informed consent was obtained, and all patients agreed to undergo MIBG scintigraphy and participate in this study. Electrocardiography, chest roentgenography, ultrasonic cardiography and blood examinations including thyroid function were also performed, and none of the patients showed any abnormality on these examinations. Brain MRI including T2 and T2* sequence and ^{123}I-IMP-SPECT were obtained and used for differential diagnosis. Fourteen controls were also included in this study. None of the controls subjects had abnormalities on general and neurological examinations including autonomic dysfunction. Case profiles are presented in Table 1. The severity of Parkinson's disease was classified on the basis of the criteria established by Hoehn-Yahr[10] and that of multiple system atrophy was also classified by the same criteria. To compare the three groups, we used ANOVA. If a variable was not applicable to the control, we used unpaired t-test for disease duration and Hoehn-Yahr stage and Mann-Whitney U test for the presence of autonomic symptoms for comparisons of the two patient groups. Significance was set at $p < 0.05$. Gender and age distributions did not differ between the three groups. Hoehn-Yahr stage and frequencies of orthostatic hypotension, urinary symptoms (urinary retention or incontinence) and constipation did not differ between Parkinson's disease and multiple system atrophy. In this study, we simply defined orthostatic hypotension as a reduction in systolic blood pressure by more than 20 mmHg after standing up.[11]

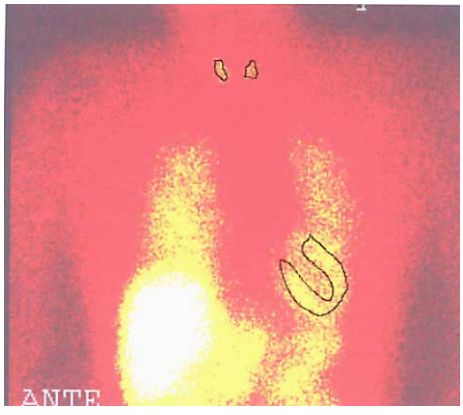

Fig. 1 Establishment of ROIs.

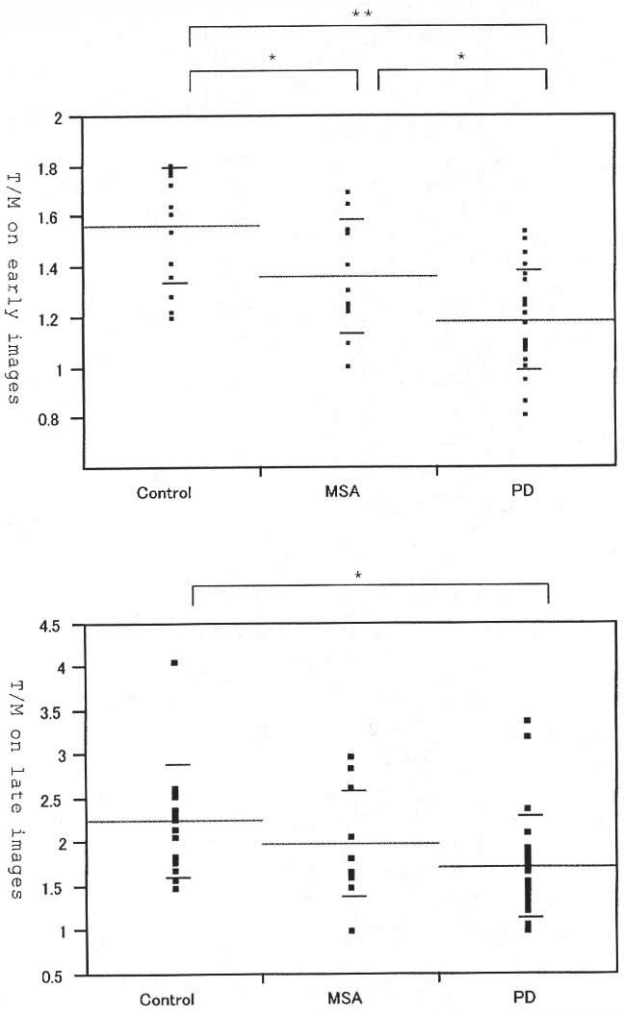

Fig. 2 Distribution of thyroid MIBG uptake in controls, multiple system atrophy (MSA) and Parkinson's disease (PD). *: $p < 0.05$, **: $p < 0.01$

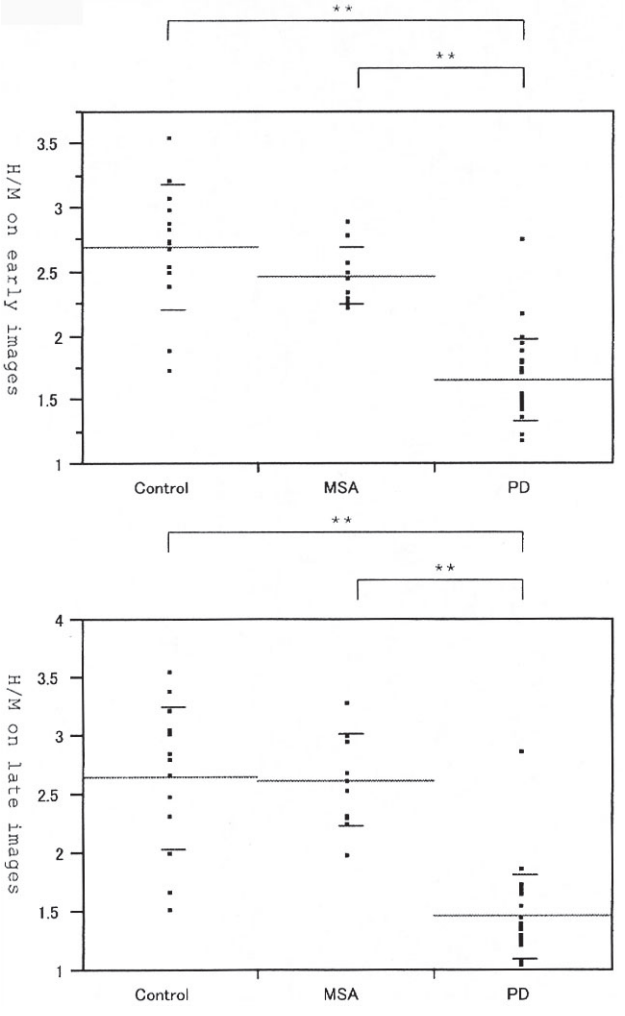

Fig. 3 Distribution of cardiac MIBG uptake in controls, multiple system atrophy (MSA) and Parkinson's disease (PD). *: $p < 0.05$, **: $p < 0.01$

MIBG scintigraphy

MIBG scintigraphy was performed in a fasted and drug-free state. None of the patients had ingested any medications that were reported to influence MIBG metabolism. Planar images were taken 15 minutes (early images) and 3 hours (late images) after intravenous injection of 111 MBq ^{123}I-MIBG. We analyzed these images and created regions of interest (ROI) as shown in Figure 1. M refers to average counts of the mediastinum, H refers to those of the heart, T those of the thyroid. It is common practice in scintigraphic analysis to normalize a data set to a reference region. We measured the ratios of H/M and T/M on both early and late images.

RESULTS

The results are shown in Table 2 and Figures 2, 3. We performed ANOVA and Post-hoc analysis using JMP version 5.1 (SAS Institute Inc.). Post-hoc analysis was performed by Fisher's PLSD (Protected Least Significant Difference). All data were expressed as the mean value ± SD. Significance of differences was recognized at $p < 0.05$. As a result, T/M on early images decreased significantly in Parkinson's disease compared to controls ($p < 0.0001$) and multiple system atrophy ($p = 0.018$). T/M on early images decreased significantly also in multiple system atrophy compared to controls ($p = 0.027$). On late images, T/M differed significantly only between Parkinson's disease and controls ($p = 0.010$). H/M decreased significantly in Parkinson's disease compared to controls and multiple system atrophy on both early and late images ($p < 0.0001$).

DISCUSSION

In Parkinson's disease the entire autonomic nervous system is affected, including the hypothalamus, parasympathetic system (Edinger-Westphal nucleus, salivary nuclei,

dorsal vagal nucleus and parasympathetic ganglia) and sympathetic system (intermediolateral nucleus of the thoracic cord and sympathetic ganglia).[12] Lewy bodies are found in the enteric nervous system of the alimentary tract, the heart, the pelvic plexus and the adrenal medulla.[12]

MIBG is a substance similar to norepinephrine and has been studied mainly with regard to its cardiac uptake. There are various mechanisms of MIBG uptake. Uptake 1 is specific to sympathetic nerves, while uptake 2 is a non-specific, non-neuronal uptake such as that by cardiac cells other than sympathetic nerve. Other mechanisms of uptake include passive diffusion.[12]

In globally denervated canine hearts, non-neuronal MIBG uptake is observed in early images followed by complete washout. However, patients receiving heart transplants showed an absence of MIBG uptake in early and delayed images, implying that the non-neuronal uptake mechanism (uptake 2) is not significant in humans.[13–15] In rat heart, yohimbine induced an almost identical increase in the rates of loss of hydrogen-3 noradrenaline and ^{125}I-MIBG, while clonidine induced decreases in the rates of loss for both tracers. Similar findings were observed in dogs and humans, suggesting that the rate of loss on MIBG reflects sympathetic tone in heart.[16,17] In the lung however, MIBG uptake does not seem to represent pulmonary sympathetic nervous activity because reserpine-treated rats showed increased lung MIBG uptake while heart MIBG uptake decreased.[18]

MIBG is stored mainly in norepinephrine vesicles. MIBG is quickly washed out in non-neuronal uptake and almost disappears after 4 hours. In contrast, MIBG clearance in neuronal uptake is low. Therefore, late images of cardiac MIBG are more significant for the evaluation of the sympathetic nervous system.[19,20]

In Parkinson's disease compared with control and multiple system atrophy, the H/M ratio was significantly decreased on both early and late images as previously reported.[2–6] A possible mechanism contributing to the changes in MIBG uptake is thought to be (a) loss of cardiac sympathetic nerve endings or (b) sympathetic dysfunction such as a decline in MIBG reuptake or a reduction in uptake or increased release by storage vesicles. Pathological studies indicated that Lewy bodies are often present in the hypothalamus, nucleus intermediolateralis and sympathetic ganglion.[21–23] However, in multiple system atrophy, preganglionic sympathetic nervous fibers are often involved.[24] Differences in lesions cause a decrease in MIBG uptake in Parkinson's disease compared with that in multiple system atrophy. Although sympathetic nerves are distributed not only in the heart, but also the lung, thyroid, extremities, liver and other organs, there were no significant differences reported in MIBG uptake in organs other than the heart.

Taki et al. studied the MIBG uptake in lung, parotid glands, thyroid, liver, thigh and legs in Parkinson's disease and multiple system atrophy and reported that there were no significant differences among the control, Parkinson's disease and multiple system atrophy except for decreased uptake in the legs in patients with multiple system atrophy compared with that in the controls.[2] In this study we set the mediastinum MIBG uptake as a reference, because there are few sympathetic nerves. However, Taki et al. set the head MIBG uptake as a reference for the thyroid uptake evaluation. This may have caused the differences between Taki's study and our study. Furthermore, the patients in our study were in a more advanced stage than those in Taki's study, which also may explain the differences.

Goldstein et al. reported that 6-[^{18}F]fluorodopamine-derived radioactivity was less not in the myocardium but also in the thyroid and renal cortex of patients with Parkinson's disease.[7] Since 6-[^{18}F]fluorodopamine is a catecholamine handled in the heart in a manner similar to the way in which norepinephrine is handled,[25] positron emission tomography (PET) scanning may allow functional and anatomic assessment of sympathetic cardiac innervation.[26] Our study was the first to demonstrate decreased MIBG uptake of the thyroid in Parkinson's disease. In this point, our study matched the PET study of Goldstein et al. These results demonstrated that sympathetic nervous denervation occurred not only in the heart but also in the thyroid. We also demonstrated decreased MIBG uptake of the thyroid only on early image in multiple system atrophy and this may also due to sympathetic denervation. On late image there was no significant difference of the thyroid uptake between controls and multiple system atrophy, but this might be due to the relatively small sample size.

Unfortunately, ^{123}I-MIBG movement in the thyroid is still not understood. A little free ^{123}I does not combine with MIBG. The rate of free ^{123}I is about 3.7% and that of ^{123}I-MIBG is 96.3% at injection, and at 37°C the free ^{123}I increses up to 4.5% after 5 hours *in vitro*. There are no *in vivo* data. Such free ^{123}I can not be ignored. However, because there is probably no difference in the uptake of free ^{123}I and the non-neuronal MIBG uptake including passive diffusion between the three groups, we believe differences in the thyroid uptake are due to the sympathetic denervation in Parkinson's disease and multiple system atrophy. Because there was some overlap in the thyroid uptake between the three groups in this study, the clinical implication may less important than the cardiac uptake. Furthermore, because the participants did not manifest any cardiac symptoms, thyroid symptoms or thyroid dysfunction, MIBG uptake in the thyroid may have no direct connection with clinical symptoms. However, this study is important because MIBG uptake decrease in Parkinson's disease was thought to be cardioselective to date. We believe that cardiac MIBG uptake is most sensitive to the sympathetic denervation in Parkinson's disease but other organs may also disclose

sympathetic denervation by MIBG scintigraphy to a lesser degree than the heart. There may be regions other than the heart and thyroid that disclosed decreased MIBG uptake or 6-[^{18}F]fluorodopamin uptake. Further studies are needed.

Limitations of the study

The diagnosis was carefully determined based on clinical findings but not pathological findings. We did not perform myocardial perfusion imaging such as thallium scintigraphy because none of the patients had either cardiac disease or risk factors for cardiac disease, and our main aim was not demonstration of the difference in cardiac uptake but examination of MIBG uptake in the thyroid.

REFERENCES

1. Hakusui S, Yasuda T, Yanagi T, Tohyama J, Hasegawa Y, Koike Y, et al. A radiological analysis of heart sympathetic functions with meta-[^{123}I]iodobenzylguanidine in neurological patients with autonomic failure. *J Auton Nerv Syst* 1994; 49: 81–84.
2. Taki J, Nakajima K, Hwang EH, Matsunari I, Komai K, Yoshita M, et al. Peripheral sympathetic dysfunction in patients with Parkinson's disease without autonomic failure is heart selective and disease specific. *Eur J Nucl Med* 2000; 27: 566–573.
3. Druschky A, Hilz MJ, Platsch G, Radespiel-Troger M, Druschky K, Kuwert T, et al. Differentiation of Parkinson's disease and multiple system atrophy in early disease stages by means of I-123-MIBG-SPECT. *J Neurol Sci* 2000; 175: 3–12.
4. Reinhardt MJ, Jungling FD, Krause TM, Braune S. Scintigraphic differentiation between two forms of primary dysautonomia early after onset of autonomic dysfunction: value of cardiac and pulmonary iodine-123 MIBG uptake. *Eur J Nucl Med* 2000; 27: 595–600.
5. Orimo S. Usefulness of MIBG myocardial scintigraphy to differentiate parkinsonism and dementia with Lewy bodies. *Neurol Med* 2003; 58: 544–554. (in Japanese)
6. Taki J, Yoshita M, Yamada M, Tonami N. Significance of ^{123}I-MIBG scintigraphy as a pathophysiological indicator in the assessment of Parkinson's disease and related disorders: it can be a specific marker for Lewy body disease. *Ann Nucl Med* 2004; 18: 453–461.
7. Goldstein DS, Holmes CS, Dendi R, Bruce SR, Li ST. Orthostatic hypotension from sympathetic denervation in parkinson's disease. *Neurology* 2002; 58: 1247–1255.
8. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: A clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry* 1992; 55: 181–184.
9. Gilman S, Low PA, Quinn N, Albanese A, Ben-Shlomo Y, Fowler CJ, et al. Consensus statement on the diagnosis of multiple system atrophy. *J Neurol Sci* 1999; 163: 94–98.
10. Hoehn MM, Yahr MD. Parkinsonism: onset, progression, and mortality. *Neurology* 1967; 17: 427–442.
11. Goldstein DS, Holmes CS, Dendi R, Bruce SR, Li ST. Orthostatic hypotension from sympathetic denervation in Parkinson's disease. *Neurology* 2002; 58: 1247–1255.
12. Yamamoto M. *Parkinson's disease: Advances in pathology and autonomic nervous system*. Tokyo; Chugai Igakusha 2004. (in Japanese)
13. Dae MW, De Marco T, Botvinick EH, O'Connell JW, Hattner RS, Huberty JP, et al. Scintigraphic assessment of MIBG uptake in globally denervated human and canine hearts—implications for clinical studies. *J Nucl Med* 1992; 33: 1444–1450.
14. Fagret D, Wolf JE, Vanzetto G, Borrel E. Myocardial uptake of metaiodobenzylguanidine in patients with left ventricular hypertrophy secondary to valvular aortic stenosis. *J Nucl Med* 1993; 34: 57–60.
15. Glowniak JV, Turner FE, Gray LL, Palac RT, Lagunas-Solar MC, Woodward WR. Iodine-123 metaiodobenzylguanidine imaging of the heart in idiopathic congestive cardiomyopathy and cardiac transplants. *J Nucl Med* 1989; 30: 1182–1191.
16. Sisson JC, Bolgos G, Johnson J. Measuring acute changes in adrenergic nerve activity of the heart in the living animal. *Am Heart J* 1991; 121: 1119–1123.
17. Jager WADH, Bethlem J. The distribution of Lewy bodies in the central and autonomic nervous system in idiopathic paralysis agitans. *J Neurol Neurosurg Psychiatry* 1960; 23: 283–290.
18. Nakajo M, Shimabukuro K, Yoshimura H, Yonekura R, Nakabeppu Y, Tanoue P, et al. Iodine-131 metaiodobenzylguanidine intra- and extravesicular accumulation in the rat heart. *J Nucl Med* 1986; 27: 84–89.
19. Hirayama M, Kato R. The clinical assessment of peripheral sympathetic function using ^{123}I-metaiodobenzylguanidine. *Neurol Med* 1997; 47: 158–163.
20. Takahashi N, Inoue T, Oka T. Quantitative evaluation of cardiac disease using ^{201}Tl, ^{99m}Tc-MIBI, ^{123}I-MIBG and ^{123}I-BMIPP single photon emission computed tomography. *Jpn J Diag Imag* 2002; 22: 749–759.
21. Sisson JC, Shapiro B, Meyers L, Mallette S, Mangner TJ, Wieland DM, et al. Metaiodobenzylguanidine to map scintigraphically the adrenergic nervous system in man. *J Nucl Med* 1987; 28: 1625–1636.
22. Langston JW, Forno LS. The hypothalamus in Parkinson's disease. *Ann Neurol* 1978; 3: 129–133.
23. Rajput AH, Rozdilsky B. Dysautonomia in parkinsonism. A clinicopathological study. *J Neurol Neurosurg Psychiatry* 1976; 39: 1092–1100.
24. Matthews MR. Autonomic ganglia in multiple system atrophy and pure autonomic failure. In: Bannister R, Mathias CJ (eds), *Autonomic failure, 3rd ed*. Oxford; Oxford University Press, 1992: 593–621.
25. Chiueh CC, Zukowska-Grojec Z, Kirk KL, Kopin IJ. 6-Fluorocatecholamines as false adrenergic neurotransmitters. *J Parmacol Exp Ther* 1983; 225: 529–533.
26. Goldstein DS, Holmes C, Stuhlmuller JE, Lenders JW, Kopin IJ. 6-[^{18}F]fluorodopamine positron emission tomographic scanning in the assessment of cardiac sympathoneural function-studies in normal humans. *Clin Auton Res* 1997; 7: 17–29.