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Cardiac Sympathetic Neuropathy and Effects of Aldose Reductase Inhibitor in Streptozotocin-Induced Diabetic Rats

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Cardiac autonomic neuropathy can be a cause of sudden death in patients with diabetes mellitus. Clinical evaluation methods for diabetic cardiac sympathetic neuropathy have not been established. Using ^{125}I-metaiodobenzylguanidine (MIBG) and streptozotocin (STZ)-induced diabetic rats, we evaluated cardiac sympathetic neuropathy and the effects of aldose reductase inhibitor (ARI). **Methods:** Myocardial MIBG uptake was measured 4 hr after injection in the following groups: control rats, rats treated with insulin or ARI (epalrestat, 100 mg/kg/day) from immediately to 4 wk after STZ injection and rats treated with insulin or ARI from 4–8 wk. Myocardial MIBG distribution and norepinephrine content were evaluated in the control and diabetic rats with or without ARI therapy started immediately after STZ injection. **Results:** Myocardial MIBG uptake was significantly lower in diabetic rats than in control rats; the reduction was marked in the subendocardial myocardium. Myocardial norepinephrine content was increased significantly in diabetic rats compared with control rats. Decreased MIBG uptake and increased norepinephrine content in diabetic myocardium were completely prevented by insulin therapy started immediately after STZ injection and partially, but significantly, by ARI administered from immediately after STZ injection. Heterogeneous MIBG distribution also disappeared with the ARI therapy. In contrast, diabetic rats treated with insulin or ARI therapy started 4 wk after STZ injection showed no improvement in MIBG uptake. **Conclusion:** These results suggest that MIBG abnormalities observed in diabetic rats may reflect diabetic cardiac sympathetic neuropathy independently of cardiomyopathy, nephropathy or coronary heart disease secondary to diabetes and that MIBG imaging may be useful for clinical assessment of cardiac sympathetic neuropathy.

Key Words: diabetic neuropathy; MIBG; cardiac sympathetic nerve system; diabetic cardiomyopathy; aldose reductase inhibitor

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Autonomic neuropathy can be a cause of sudden death in patients with diabetes mellitus (*1*). Compared to diabetic patients without autonomic neuropathy, those with autonomic neuropathy have been reported to exhibit a proportionately greater lengthening of QT interval for a given increase in RR interval (*2*), which implies that diabetic autonomic neuropathy may be a causative factor in arrhythmia and even sudden death (*3*). Moreover, myocardial concentrations of norepinephrine have been reported to be significantly reduced in long-term diabetics (*4*).

Recently, myocardial scintigraphy with radiolabeled metaiodobenzylguanidine (MIBG) has been recognized as useful for

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clinically evaluating cardiac sympathetic nerve system function (*5–7*). Myocardial ^{123}I-MIBG uptake has been demonstrated to be heterogeneously distributed (*3*) or diffusely reduced (*8*) in patients with diabetes mellitus, particularly in those with diabetic autonomic neuropathy.

Polyol accumulation in peripheral nerve tissue has been indicated as one causative factor in diabetic neuropathy (*9*). Animal experiments and clinical trials have shown an aldose reductase inhibitor (ARI), an inhibitor of the key enzyme in polyol synthesis, decreases in polyol accumulation in nerves of diabetic rats (*10*), subjective benefit in patients with diabetic peripheral neuropathy (*11*) and improvement in neural conduction velocity (*12*). In this study, we investigated alterations in myocardial MIBG uptake and distribution of streptozotocin (STZ)-induced diabetic rats and the preventive effects of ARI on myocardial MIBG abnormalities.

MATERIALS AND METHODS

Animals

This study was performed under the guidance of the animal care committee at the Hamamatsu University School of Medicine and conformed to the position of the American Heart Association on research animal use. Sixty-four Sprangue-Dawley male rats at 8 wk of age were divided into six groups: a control group (n = 14); a diabetic group with no treatment (n = 15); a diabetic group with insulin therapy started immediately after STZ injection (n = 10, INS group); a diabetic group with ARI therapy started immediately after STZ injection (n = 7, ARI group); a diabetic group with insulin therapy started 4 wk after STZ injection (n = 11, INS4 group); and a diabetic group with ARI therapy started 4 wk after STZ injection (n = 7, ARI4 group). The diabetic group with no treatment was divided into two subgroups: one (n = 7, DM group) for comparison with the INS and ARI groups; and the other (n = 8, DM4 group) for comparison with the INS4 and ARI4 groups. Similarly, the control group also was divided into two subgroups: one (n = 8, CONT group) for comparison with the DM, INS and ARI groups; and the other (n = 6, CONT4 group) for comparison with the DM4, INS4 and ARI4 groups.

A quantity of 50 mg/kgBW STZ adjusted to a concentration of 50 mg/ml with citrate buffer (pH 4) was administered by injection into the caudal vein to the DM, INS, ARI, DM4, INS4 and ARI4 groups, thereby creating STZ-induced diabetic animals. Citrate buffer (1 ml/kgBW) was intravenously administered to the CONT and CONT4 groups. The rats of the CONT, DM, INS and ARI groups were housed for 4 wk in individual cages and given food and water ad libitum and those of the CONT4, DM4, INS4 and ARI4 groups for 8 wk.

Starting 2 days after STZ injection, maintenance insulin (6–12 units) was administered by subcutaneous injection to the INS group on successive days for 4 wk. Starting 4 wk after STZ injection, it was administered to the INS4 group for 4 wk using the same protocol as in the INS group. In the INS and INS4 groups, the blood glucose level was measured once a week and the amount of insulin was adjusted to maintain the blood glucose value before insulin injection at about 100 mg/dl.

Starting on the next day of STZ injection, epalrestat (100 mg/kgBW suspended in a solution of 0.5% carboxy-methyl-cellulose) was administered through a gastric tube to the ARI group daily for 4 wk. Starting 4 wk after STZ injection, it was administered to the ARI4 group for 4 wk using the same protocol as in the ARI group.

Measurement of Myocardial Iodine-125-MIBG Uptake

Four weeks after STZ injection, ^{125}I-MIBG (3.7 MBq) was injected into the caudal vein under ether anesthetization in the DM, INS and ARI groups, and 8 wk after STZ injection in the DM4, INS4 and ARI4 groups. Similarly, 4 or 8 wk after injection of the citrate buffer, it was injected in the CONT or CONT4 groups, respectively. Four hours after ^{125}I-MIBG injection, the rats were again anesthetized with a large amount of ether, the heart was excised and the ^{125}I radioactivity of the ventricles was measured immediately. Radioactivity per 1 g wet weight of ventricular muscle was divided by a radioactivity of ^{125}I-MIBG administered per 1 kg BW to obtain a value of %kgDose/g (*13*).

Immediately after measurements of radioactivity, the ventricle was frozen with liquid nitrogen and sliced along the long and short axes of the left ventricle with a cryomicrotome to prepare sections of 20 μm thickness. Autoradiograms were obtained by adhesion and exposure on Leica ultrafilms. By digitizing ^{125}I autoradiograms using a videodensitometric system (*14*), the optical density was measured in the endocardial and epicardial sides of the lateral wall and in the left and right ventricular sides of the interventricular septum. Transmural MIBG distribution was assessed with the ratio of the optical density in the endocardial (or left ventricular) side to that in the epicardial (or right ventricular) side.

Measurement of Myocardial Norepinephrine Content

In each of the CONT, DM, INS and ARI groups, four frozen ventricles were selected for measurements of norepinephrine content. The content of norepinephrine was measured using high-performance liquid chromatography.

Statistics

All measures were expressed as mean ± s.d. Statistical differences of means among groups were assessed using one-way analysis of variance, followed by Duncan's multiple-range test. A probability value of less than 0.05 was considered statistically significant.

TABLE 1
Blood Glucose Level and Myocardial Iodine-125-MIBG Uptake and Norepinephrine Content of CONT, DM, INS and ARI Groups

Group	N	Blood glucose (mg/dl)	Myocardial ^{125}I-MIBG (%kgDose/g)	Myocardial norepinephrine (ng/g)
CONT	8	82 ± 5	0.52 ± 0.05	423 ± 230
DM	7	244 ± 38*	0.28 ± 0.03*	803 ± 103*
INS	10	68 ± 11‡	0.51 ± 0.09‡	405 ± 65‡
ARI	7	277 ± 30*	0.43 ± 0.07†‡	616 ± 129§

*$p < 0.01$ versus CONT group, †$p < 0.05$ versus CONT group, ‡$p < 0.01$ versus DM group, §$p < 0.05$ versus DM group.
Data presented are mean ± s.d.

RESULTS

Blood Glucose Levels

Tables 1 and 2 show the blood glucose level measured immediately before ^{125}I-MIBG study in the CONT, DM, INS, ARI, CONT4, DM4, INS4 and ARI4 groups. The blood glucose levels of the INS and INS4 groups were similar to those of the CONT and CONT4 groups, respectively ($p > 0.05$). On the other hand, the blood glucose levels of the DM and ARI groups were significantly higher than those of the CONT group, and those of the DM4 and ARI4 groups were significantly higher than those of the CONT4 group.

Myocardial Iodine-125-MIBG Uptake

Table 1 also shows the comparison of myocardial ^{125}I-MIBG uptake among the CONT, DM, INS and ARI groups. It was significantly lower in the DM group than in the CONT group and significantly higher in the INS group than in the DM group,

TABLE 2
Blood Glucose Level and Myocardial Iodine-125-MIBG Uptake of CONT4, DM4, INS4 and ARI4 Groups

Group	N	Blood glucose (mg/dl)	Myocardial ^{125}I-MIBG uptake (%kgDose/g)
CONT4	6	84 ± 5	0.63 ± 0.04
DM4	8	249 ± 44*	0.26 ± 0.05*
INS4	11	107 ± 15‡	0.29 ± 0.03*
ARI4	7	244 ± 9*	0.29 ± 0.11*

*$p < 0.01$ versus CONT group, ‡$p < 0.01$ versus DM group.
Data presented are mean ± s.d.

but it was similar between the CONT and INS groups ($p > 0.05$). That is, STZ-induced diabetes caused the decrease in myocardial ^{125}I-MIBG uptake, and the insulin therapy started immediately after STZ injection prevented the decrease. On the other hand, myocardial ^{125}I-MIBG uptake was significantly higher in the ARI group than in the DM group. Furthermore, it was not significantly different between the INS and ARI groups ($p > 0.05$), although it was significantly lower in the ARI group than in the CONT group. That is, the ARI therapy that started immediately after STZ injection partly prevented the decrease in myocardial ^{125}I-MIBG uptake of STZ-induced diabetic rats, although the ARI therapy did not improve the high level of blood glucose.

Table 2 shows the comparison of myocardial ^{125}I-MIBG uptake among the CONT4, DM4, INS4 and ARI4 groups. Myocardial ^{125}I-MIBG uptake was significantly lower in the DM4, INS4 and ARI4 groups, compared to the CONT4 group. On the other hand, it was similar among the DM4, INS4 and ARI4 groups ($p > 0.05$). That is, neither the ARI nor insulin therapy started 4 wk after STZ injection could prevent the decrease in myocardial ^{125}I-MIBG uptake of STZ-induced diabetic rats.

Myocardial Norepinephrine Content

The myocardial norepinephrine content of the CONT, DM, INS and ARI groups is shown in Table 1. It was significantly higher in the DM group than in the CONT group and significantly lower in the INS group than in the DM group. The myocardial content of norepinephrine was not significantly different among the CONT, INS and ARI groups ($p > 0.05$), although it was significantly lower in the ARI group than in the DM group.

Transmural Iodine-125-MIBG Distribution

Table 3 shows the ratios of ^{125}I-MIBG uptake in the endocardial to epicardial side among the CONT, DM and ARI groups. In both the interventricular septum and lateral wall, the ratio was significantly lower in the DM group than in the CONT group, but it was similar between the CONT and ARI groups ($p > 0.05$). That is, STZ-induced diabetes caused the transmural heterogeneity of ^{125}I-MIBG uptake, and the ARI therapy could prevent the heterogeneity.

TABLE 3
Ratio of Iodine-125-MIBG Uptake in Endocardial (or Left Ventricular) to Epicardial (or Right Ventricular) Side

Group	N	Interventricular septum	Lateral wall
CONT	5	0.93 ± 0.05	0.94 ± 0.03
DM	6	0.70 ± 0.05*	0.69 ± 0.15*
ARI	6	0.94 ± 0.03‡	0.93 ± 0.03‡

*$p < 0.01$ versus CONT group, ‡$p < 0.01$ versus DM group.
Data presented are mean ± s.d.

DISCUSSION

Our study demonstrated the following findings: (a) myocardial ^{125}I-MIBG uptake significantly decreased in STZ-induced diabetic rats; (b) the reduction was marked in the subendocardial myocardium; (c) it was completely prevented by insulin therapy started immediately after STZ injection; (d) it was partly, but significantly, prevented by ARI therapy started immediately after STZ injection; (e) myocardial norepinephrine content significantly increased in STZ-induced diabetic rats, and the increase was prevented by insulin or ARI therapy started immediately after STZ injection; (f) the heterogeneous ^{125}I-MIBG distribution within the myocardium also disappeared by the ARI therapy; and (g) insulin or ARI therapy started 4 wk after STZ injection did not prevent the decrease in myocardial ^{125}I-MIBG uptake.

Cardiac ^{125}I-MIBG accumulation was not directly inhibited by STZ since the insulin therapy that started immediately after STZ injection could prevent the reduction in myocardial ^{125}I-MIBG uptake. Similarly, the ARI therapy that started immediately after STZ injection could prevent the reduction. Contrary to the insulin therapy, however, the ARI therapy did not restore plasma glucose levels. It is, therefore, highly possible that ARI directly prevented diabetic cardiac sympathetic neuropathy.

Reduction in myocardial MIBG uptake has been reported in patients with diabetes mellitus (*3,8,15–17*). However, the direct association between diabetes mellitus and myocardial MIBG abnormalities may not be easily confirmed in clinical settings since diabetic patients are often complicated with coronary artery disease, myocardial small vessel disease (*18*), renal failure (*19*), myocardial dysfunction (*20*), hypertension and so on. There are few reports that have evaluated myocardial MIBG uptake in diabetic animals such as STZ-induced diabetic rats. Our study demonstrated that myocardial MIBG uptake was markedly reduced in STZ-induced diabetic rats and that ARI therapy started immediately after STZ injection could prevent the reduction. Our study, therefore, suggests that diabetic cardiac sympathetic neuropathy may directly cause myocardial MIBG abnormalities. In other words, MIBG abnormalities may not be due to sympathetic nerve dysfunction secondary to diabetic myocardial injury, but may be due to diabetic sympathetic nerve injury itself.

Myocardial norepinephrine content was significantly increased in our STZ-induced diabetic rats. There are contraversial reports, however, regarding changes in myocardial norepinephrine content induced by diabetes mellitus (*4,21–23*). Neubauer et al. (*4*) and Yoshida et al. (*21*) reported the reduced myocardial content of norepinephrine in diabetic patients and STZ-induced diabetic rats, respectively. On the contrary, Fushimi et al. (*22*) and Ganguly et al. (*23*) reported the increased myocardial content of norepinephrine in STZ-induced diabetic rats. As mentioned above, cardiac sympathetic nerve system activity may be complexly influenced by various diabetic complications. According to the complications, therefore, the myocardial norepinephrine content may be either increased or decreased. Diabetic sympathetic neuropathy in some phase of diabetes mellitus may be associated with the increase in myocardial norepinephrine content since ARI could prevent the increase in our study. On the contrary, myocardial norepinephrine depletion may occur in patients or animals with congestive heart failure, for example, due to diabetic cardiomyopathy.

In our diabetic animals, myocardial MIBG uptake was

decreased despite the increase in myocardial norepinephrine content. Inconsistency between myocardial norepinephrine and MIBG levels may be partly due to increased biosynthesis of norepinephrine associated with impaired neuronal uptake. In our previous study of cardiomyopathic hamsters, a significant positive correlation was found between myocardial norepinephrine content and MIBG uptake in untreated animals, but not in treated animals (*24*). Thus, myocardial MIBG uptake may not necessarily reflect myocardial norepinephrine concentrations (*25*).

Accumulation of polyols in nerve tissue may play an important role in the development of diabetic peripheral nerve dysfunction (*9,10,12*). Dysfunction and/or destruction of distal sympathetic postganglionic neurons induced by polyol accumulation may be one mechanism for MIBG abnormalities. For instance, abnormal energy metabolism with decreased Na^+, K^+-ATPase activity may impair the neuronal uptake of MIBG. Mäntysaari et al. (*8*) suggested that the capacity of MIBG to enter neuronal tissue was weakened in both diabetic patients with and without autonomic neuropathy and that the ability of sympathetic tissue to store MIBG was reduced in those with autonomic neuropathy. On the other hand, decreased myocardial sympathetic innervation is inconsistent with the increase in myocardial norepinephrine content of our diabetic rats. Therefore, cardiac sympathetic denervation cannot explain the decreased MIBG uptake in our animals, although it may be involved in some diabetic models. Other possible mechanisms of decreased MIBG uptake may include hyperglycemia-induced systemic alterations that cause fluctuations in sympathetic nerve activity. Ganguly et al. (*23*) suggested that the presence of hypervolemia in STZ-induced diabetic rats may be of crucial importance for activating the sympathetic system. Moreover, Yoshida et al. (*26*) suggested that the decreased norepinephrine turnover in STZ-induced diabetic rats may be a direct result of weight loss and negative caloric balance although their results are completely opposite. These systemic alterations, however, might not play an important role in the reduction of MIBG uptake because ARI treatment prevented it without correcting hyperglycemia.

Diabetic cardiomyopathy may be associated with sympathetic nervous system dysfunction (*25*). Kahn et al. (*27*) reported that cardiac autonomic neuropathy was associated with left ventricular diastolic dysfunction in patients with diabetes mellitus. Recently, Mustonen et al. (*15*) have demonstrated that decreased myocardial MIBG uptake is associated with impaired left ventricular diastolic filling. In addition, Zola et al. (*28*) observed an inverse correlation between autonomic function and left ventricular ejection fraction and suggested the involvement of cardiac autonomic neuropathy in diabetic cardiomyopathy. On the other hand, congestive heart failure induced by diabetic cardiomyopathy may reduce myocardial MIBG uptake (*7*), although diabetic neuropathy may directly cause myocardial MIBG abnormalities. Diabetic complications such as coronary artery disease and renal failure (*19*), as well as diabetic cardiomyopathy, may cause myocardial MIBG abnormalities, and it remains to be investigated whether diabetic cardiac autonomic neuropathy may be one of causes of diabetic cardiomyopathy (*23,29*).

CONCLUSION

Our study demonstrates that myocardial MIBG uptake was reduced and heterogeneously distributed in STZ-induced diabetic rats and that the MIBG abnormalities could be prevented by ARI therapy started immediately after STZ injection. Thus, MIBG abnormalities may reflect diabetic cardiac sympathetic neuropathy itself independently of cardiomyopathy, nephropathy or coronary heart disease secondary to diabetes mellitus, and MIBG imaging may be useful for assessment of the development and prevention of diabetic cardiac sympathetic neuropathy.

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