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ORIGINAL ARTICLE

ADENOSINE-INDUCED DILATION OF CORONARY RESISTANCE VESSELS IS IMPAIRED IN RATS WITH TYPE 2 DIABETES MELLITUS: POSSIBLE ROLE OF ATP-SENSITIVE POTASSIUM CHANNELS AND NITRIC OXIDE

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Abstract ***Objectives*** The purpose of this study was to test the hypothesis that adenosine-induced coronary microvascular dilation is blunted in the animals with diabetes mellitus (DM) through the impairment of K_{ATP} channel function.

Background Adenosine-induced coronary vasodilation is demonstrated to be mediated by activation of ATP-sensitive potassium (K_{ATP}) channels and nitric oxide (NO).

Methods The hearts of Otsuka Long-Evans Tokushima fatty rats (OLETF, type 2 DM rats), and control Long-Evans Tokushima fatty rats (LETO) at the ages of 32 and 8 weeks were perfused using a Langendorff system with constant perfusion pressure (80 mmHg). Changes in coronary flow to adenosine, pinacidil and sodium nitroprusside (SNP) were examined before and after administration of glibenclamide (10^{-7} M), or N^G-nitro-L-arginine methyl ester (L-NAME, 10^{-4} M).

Results At the age of 32 weeks, adenosine- and pinacidil-induced increases in coronary flow were blunted in OLETF as compared with those in LETO (both $p<0.05$). Glibenclamide attenuated adenosine-induced increase in coronary flow in LETO ($p<0.05$), but not in OLETF. In contrast, L-NAME attenuated adenosine-induced increase in coronary flow in OLETF ($p<0.05$), but not in LETO. SNP-induced increases in coronary flow in LETO and OLETF were comparable and were not affected by glibenclamide. In 8-week-old OLETF and LETO, no difference was observed in adenosine-, pinacidil- and SNP-induced increases in coronary flow between OLETF and LETO.

Conclusions In this type 2 DM model, K_{ATP} channel function in coronary microcirculation is impaired. Adenosine-induced increase in coronary flow is mediated mainly by NO mechanism.

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Key words: adenosine; diabetes mellitus; microcirculation; nitric oxide.

原　著

アデノシン誘発性冠抵抗血管の拡張は2型糖尿病ラットで障害されている：ATP感受性Kチャネルと一酸化窒素の役割

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抄録　アデノシン誘発性冠抵抗血管の拡張はATP感受性Kチャネルと一酸化窒素(NO)を介することが報告されている．本研究ではアデノシン誘発性冠抵抗血管の拡張がATP感受性Kチャネルの障害を介して2型糖尿病動物で抑制されているかどうかを検討した．8，32週齢の2型糖尿病ラット(OLETF)とコントロールラット(LETO)のランゲンドルフ心を用いてアデノシン，ピナシジル，ニトロプルシドによる冠灌流の変化をグリベンクラミドとN^G-nitro-L-arginine methyl ester (L-NAME)投与前後で測定した．32週齢では，アデノシン並びにピナシジル誘発性冠灌流の増加はOLETFがLETOに比して小であった．グリベンクラミドはLETOではアデノシン誘発性冠灌流の増加を抑制したが，OLETFでは抑制しなかった．一方，L-NAMEは，OLETFではアデノシン誘発性冠灌流の増加を抑制したが，LETOでは抑制しなかった．ニトロプルシド誘発性冠灌流の増加はLETOとOLETFで差はなく，グリベンクラミドの影響を受けなかった．8週齢のOLETFとLETOでは，アデノシン，ピナシジル，ニトロプルシド誘発性冠灌流の増加に差は認められなかった．以上より，2型糖尿病モデルでは，冠抵抗血管におけるATP感受性Kチャネルは障害されている．また，アデノシン誘発性冠灌流の増加は主にNOの機序を介する．

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キーワード：アデノシン；糖尿病；微小循環；一酸化炭素．

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Abbreviations and Acronyms

ATP = adenosine triphosphate
CF = coronary flow
DM = diabetes mellitus
K_{ATP} = ATP-sensitive potassium
LETO = Long-Evans Tokushima Otsuka
L-NAME = N^G-nitro-L-arginine methyl ester
LVP = left ventricular pressure
NO = nitric oxide
OLETF = Otsuka Long-Evans Tokushima fatty rats
SNP = sodium nitroprusside

Introduction

Diabetes mellitus (DM) is a devastating disease with a 2- to 4-fold increase in the risk of coronary heart disease, cerebrovascular disease, congestive heart failure, and other cardiovascular complications[1]. Impairment of vasodilator responses has been demonstrated in experimental DM models. It was shown that the coronary dilator response to adenosine is reduced in rats with alloxan-induced type 1 DM.[2] Recent observations have indicated that vasodilator response through nitric oxide (NO)[3,4] or ATP-sensitive potassium (K_{ATP}) channels[5] are impaired in animals with DM.

Coronary blood flow is primarily determined by coronary microvascular resistance[6] and is closely matched to the metabolic demand of the heart[7]. Recent studies in the coronary circulation indicate that K_{ATP} channels play an important role in the metabolic vasodilation. It has been demonstrated that glibenclamide, a selective inhibitor of K_{ATP} channels[8], attenuates vasodilation to metabolic factors including hypoxia[9], acidosis[10] and hyperosmolarity[11]. Adenosine is known to be a potent dilator of coronary arterioles and has been proposed as a factor responsible for the metabolic regulation of coronary blood flow[12,13]. Adenosine causes glibenclamide-sensitive hyperpolarization of coronary arteries[14]. Glibenclamide attenuates adenosine-induced vasodilation of large[15] and small coronary vessels[9,16], indicating that adenosine regulates coronary resistance via the activation of K_{ATP} channels. Recently Hein and Kuo[17] demonstrated that adenosine-induced coronary arteriolar dilation is partially mediated by NO released from the endothelium via the opening of endothelial K_{ATP} channels.

Although K_{ATP} channels are involved in the regulation of coronary blood flow[17], the effect of chronic hyperglycemia on K_{ATP} channel function in coronary circulation is poorly understood. The first goal of the present study was to examine the K_{ATP} channel function in an animal model with type 2 DM. The second goal was to explore the role of the NO pathway in adenosine-induced dilation of coronary resistance vessels in animals with type II DM.

Methods

Preparation of DM and Control rats

Thirty-five male Otsuka Long-Evans Tokushima fatty (OLETF) rats aged 30 to 32 weeks (6-8 weeks after the onset of DM) and five male OLETF rats aged 8 to 10 weeks were used as the experimental animals. OLETF rats have been established as long-term hyperglycemic rats with type 2 DM[18]. Thirty-three male Long-Evans Tokushima Otsuka (LETO) rats aged 30 to 32 weeks and four LETO rats aged 8 to 10 weeks, which were developed from the same colony by selective mating but did not develop DM, were used as control animals. All rats were kept at the specific pathogen-free facility under controlled temperature (23±1°C) and humidity (60%) with a 12-hour artificial light and dark cycle in the Institute for Animal Experiments of our institution. Animals were given free access to standard laboratory rat chow and tap water. All procedures were carried out in accordance with the Guidelines for Animal Experiment in Hirosaki University.

Experimental protocols

The occurrence of DM in OLETF rats was confirmed by an oral glucose tolerance test at 24 weeks in age. Blood glucose level in tail capillary blood was measured after 16 hours of fasting with a glucose test meter (MediSense Precision Plus, Bedford, MA). Oral glucose tolerance test was performed by administering 2 g/kg body weight of glucose. Blood was drawn from a tail vein at baseline, 30, 60, and 120 minutes after glucose administration. The rats which showed the peak plasma glucose level > 300 mg/dl and plasma glucose level at 120 min > 200 mg/dl were diagnosed as DM. OLETF and LETO were anaesthetized with sodium pentobarbital (50 mg/kg, IP) and heparinized (2000 IU, IP). The hearts of OLETF and LETO were excised and promptly bathed in 4℃ saline. The ascending aorta was cannulated for perfusion of the coronary arteries. The hearts were then perfused using a Langendorff system with Krebs-Henseleit solution containing (in mM) NaCl 118, KCl 4.7, $CaCl_2$ 1.2, $MgSO_4$ 1.2, $NaHCO_3$ 25, KH_2PO_4 1.2 and D(+)-glucose 11.5. Coronary perfusion pressure was maintained at 80 mmHg. Heart rate was kept constant (330 beats/min) by atrial pacing during the experiment. A thin fluid-filled high-density polyethylene balloon connected to a 1 mm caliber polyethylene tube was inserted in the left ventricle via the left atrium to monitor isovolumetric left ventricular pressure (LVP) and its first derivative (dP/dt). Balloon volume was adjusted to set the left ventricular diastolic pressure at 10 mmHg at the beginning of the experiment[19]. Once a stable LVP level was attained, no further volume change was made. Aortic pressure and coronary flow (CF) were continuously monitored. After the instrumentation, at least 20 minutes were allowed for stabilization of the monitored variables. All drugs were dissolved in the perfusate and were infused into the coronary arteries through the aortic perfusion cannula. Glibenclamide and N^G-nitro-L-arginine methyl ester (L-NAME, 100 μM) were perfused for 20 minutes and their effects on vasodilators were examined. In the preliminary study, we confirmed that CF responses to the vasodilators used were reproducible in the absence of inhibitors.

Effects of adenosine and pinacidil on CF: Adenosine (10^{-8} to 10^{-6} M in coronary perfusate) or pinacidil (10^{-8} to 10^{-6} M), a specific K_{ATP} channel opener[8], was infused into the coronary arteries and the peak changes in CF were observed. Glibenclamide (0.1 μM) was then administered to the perfusate and adenosine- and pinacidil-induced increases in CF were reexamined. To study the involvement of NO pathway in adenosine- and pinacidil-induced vasodilation, the change in CF in response to adenosine (10^{-8} to 10^{-6} M) or pinacidil (10^{-8} to 10^{-6} M) was examined before and after L-NAME (100 μM).

Effect of sodium nitroprusside: Sodium nitroprusside (10^{-8} to 10^{-6} M) was perfused and its effect on CF was studied in LETO and OLETF rats. To verify the specificity of glibenclamide as a K_{ATP} channel blocker, sodium nitroprusside-induced change in CF was again examined after administration of glibenclamide (0.1 μM). This concentration of glibenclamide is enough to block K_{ATP} channel without affecting cardiac function (3).

To determine the influence of the genetic factors of this animal model to adenosine-, pinacidil- and sodium nitroprusside-induced vasodilation, the changes in CF by adenosine (10^{-8} to 10^{-6} M), pinacidil (10^{-8} to 10^{-6} M) and sodium nitroprusside (10^{-8} to 10^{-6} M) were examined in LETO and OLETF rats at the age of 8-10 weeks.

Drug preparation

Drugs and chemicals were obtained from Sigma Chemical (St. Louis, MO), except for pinacidil which was purchased from Research Biochemicals International (Natick, MA). Glibenclamide and pinacidil were dissolved in

dimethyl sulfoxide. The final concentration of dimethyl sulfoxide in the perfusate was 0.05% or less and had no effect on hemodynamic parameters. Adenosine and sodium nitroprusside were dissolved in Krebs-Henseleit solution. pH of the solution was maintained at 7.4 by bubbling with a mixture of 95% oxygen and 5% carbon dioxide. The perfusate was maintained at 37 °C by a circulating water bath with an external heat exchanger.

Measurements

At the beginning of the experiment, body weight was measured in the conscious state. An electromagnetic flow probe (FF-O45F, Nihon Kohden, Tokyo, Japan) was attached to the middle portion of the tube connected to the aorta and CF was continuously measured with a flowmeter (Model MFV-3100, Nihon Kohden, Tokyo, Japan). Coronary perfusion pressure was measured with a pressure transducer connected to a side arm of the aortic perfusion cannula. All data including LVP and dP/dt were recorded continuously on a polygraph system (Model RMP-6008M, Nihon Kohden, Tokyo, Japan). At the end of the experiment, the left ventricle was separated from the right ventricular free wall, the atria and the great vessels, and wet weights were then measured.

Statistics

All data are shown as mean ± SEM. Body weight, blood glucose level and baseline hemodynamic parameters were compared between LETO and OLETF rats with an unpaired t-test. The changes in CF were quantified by computing percent changes from the baseline. Comparison of the changes in CF in response to various drugs between LETO and OLETF rats, and those in response to various drugs before and after glibenclamide or L-NAME were analyzed with two-way ANOVA. Significance was accepted at $P<0.05$.

Results

At the age of 30-32 weeks, the body weight in OLETF (665 ± 9 g) was greater than that in LETO (513 ± 4 g) ($p<0.01$). The heart weight in OLETF (1.66 ± 0.02 g) was greater than that in LETO (1.47 ± 0.02 g) ($p<0.01$). Blood glucose level measured in the conscious state before the experiment was higher in OLETF (208 ± 10 g/dl) than in LETO (108 ± 3 g/dl) ($p<0.01$). Under the constant perfusion pressure (80 mmHg) and heart rate (330 beats/minute), no hemodynamic parameter differed significantly between LETO and OLETF rats at baseline. The hemodynamic parameters before and after glibenclamide and L-NAME are summarized for LETO and OLETF in Table 1.

Adenosine-induced vasodilation in LETO and OLETF rats

A representative trace of the effects of adenosine on CF, LVP and dP/dt in LETO and OLETF is shown in Figure 1. Adenosine produced dose-dependent increases in CF in LETO (n=7) and OLETF (n=15) (Figure 2). The adenosine-induced increase in CF in OLETF was smaller than that in LETO ($p<0.05$). Glibenclamide attenuated adenosine-induced increase in CF in LETO, but did not attenuate it in OLETF (Figure 2). Adenosine did not affect either LVP or dP/dt in both LETO and OLETF rats.

Pinacidil-induced vasodilation in LETO and OLETF rats

Pinacidil produced dose-dependent increases in CF in LETO and OLETF rats. The pinacidil-induced change in CF in OLETF (n=7) was significantly smaller than that in LETO (n=6) ($p<0.05$) (Figure 3). Glibenclamide (0.1 μM) attenuated pinacidil-induced change in CF both in LETO (n=6) and OLETF (n=7) rats.

Table 1 Comparison of hemodynamic parameters between LETO and OLETF at the age of 30-32 weeks

	LETO (n=21)	OLETF (n=29)		LETO (n=12)	OLETF (n=6)
Baseline			Baseline		
+dP/dt (mmHg/sec)	912 ± 55	983 ± 66	+dP/dt (mmHg/sec)	981 ± 76	982 ± 99
-dP/dt (mmHg/sec)	-611 ± 34	-597 ± 33	-dP/dt (mmHg/sec)	-565 ± 29	-607 ± 28
CF (ml/min)	13.7 ± 0.6	13.6 ± 0.5	CF (ml/min)	13.4 ± 0.3	14.2 ± 1.0
CR (mmHg/ml/min)	6.1 ± 0.3	6.0 ± 0.2	CR (mmHg/ml/min)	6.0 ± 0.2	5.7 ± 0.5
After glibenclamide			After L-NAME		
+dP/dt (mmHg/sec)	799 ± 82	746 ± 49*	+dP/dt (mmHg/sec)	869 ± 96	645 ± 75*
-dP/dt (mmHg/sec)	-457 ± 31*	-426 ± 29*	-dP/dt (mmHg/sec)	-374 ± 35*	-328 ± 17*
CF (ml/min)	10 ± 0.4*	9.9 ± 0.3*	CF (ml/min)	8.8 ± 0.4*	9.0 ± 0.7*
CR (mmHg/ml/min)	8.3 ± 0.3*	8.2 ± 0.2*	CR (mmHg/ml/min)	9.3 ± 0.5*	9.0 ± 0.8*

Values are mean ± SEM. *$p<0.05$ vs Baseline
sLVP; systolic left ventricular pressure, +dP/dt; maximum dP/dt, -dP/dt; minimum dP/dt, CF; coronary flow, CR; coronary resistance

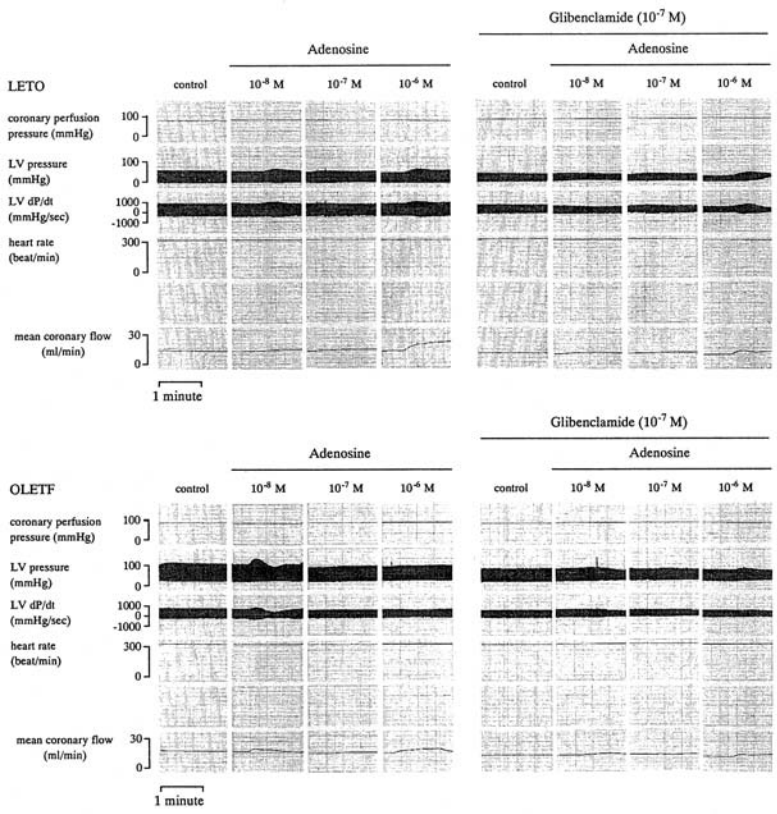

Fig. 1 A representative trace of the effect of adenosine on coronary flow, LV pressure and LV dP/dt in the presence and absence of glibenclamide in LETO (top panel) and OLETF (bottom panel).

Role of NO pathway in adenosine-and pinacidil-induced vasodilation

L-NAME attenuated adenosine-induced increase in CF in OLETF, but did not attenuate in LETO (Figure 4). L-NAME did not affect pinacidil-induced increase in CF in LETO (n=3, data not shown)

Sodium nitroprusside-induced vasodilation in LETO and OLETF rats

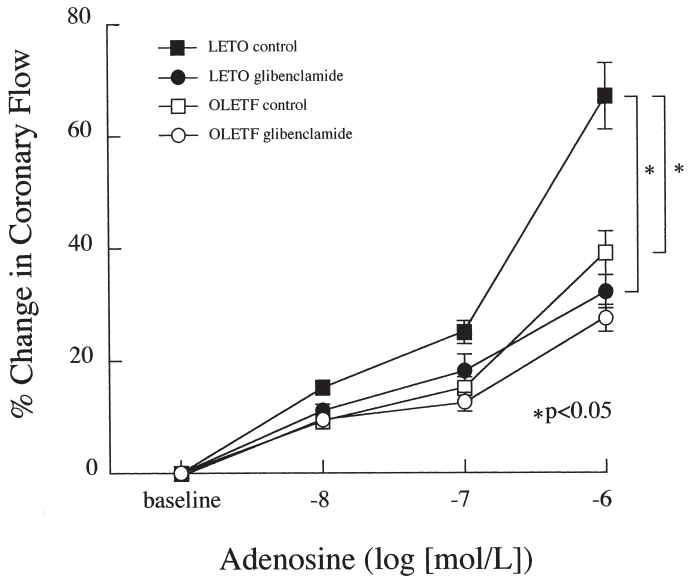

Fig. 2 Graph showing the effect of adenosine (10^{-8} to 10^{-6} M) on coronary flow and the effect of glibenclamide (0.1 μM) on adenosine-induced increase in coronary flow in LETO (n=7) and OLETF (n=15) rats.

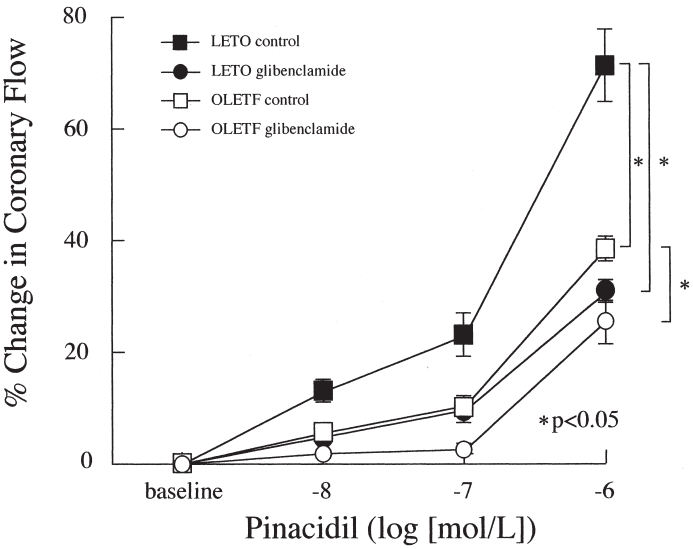

Fig. 3 Graph showing the effect of pinacidil (10^{-8} to 10^{-6} M) on coronary flow in and the effect of glibenclamide (0.1 μM) on pinacidil-induced increase in coronary flow LETO (n=7) and OLETF (n=8) rats.

Sodium nitroprusside produced dose-dependent increases in CF in LETO (n=7) and OLETF (n=6). The change in CF in OLETF was similar to that in LETO (p=NS) (Figure 5). Glibenclamide (0.1 μM) showed no effect on sodium nitroprusside-induced vasodilation in LETO and OLETF rats (Figure 5). Similarly, L-NAME showed no effect on sodium nitroprusside-induced change in CF (n=3, data not shown).

Vasodilation in LETO and OLETF rats before the onset of DM

The effects of adenosine, pinacidil and sodium nitroprusside on CF in LETO and OLETF rats before the onset of DM (at the age of 8-10 weeks) were examined. Blood glucose level was 108±

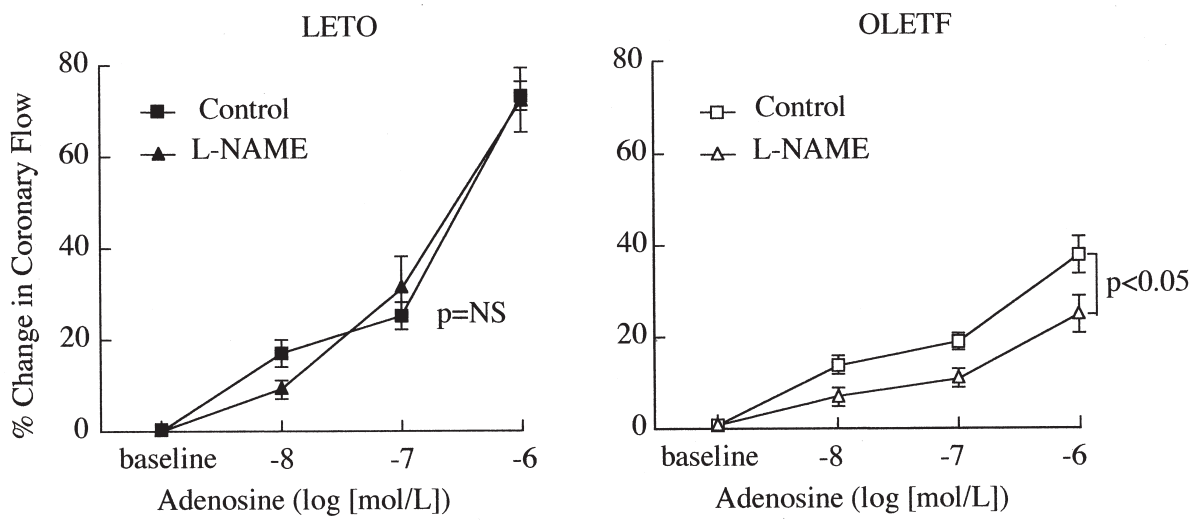

Fig. 4 Graphs showing the effect of L-NAME (100 μM) on adenosine-induced increase in coronary flow in LETO (left panel, n=6) and OLETF (right panel, n=6) rats.

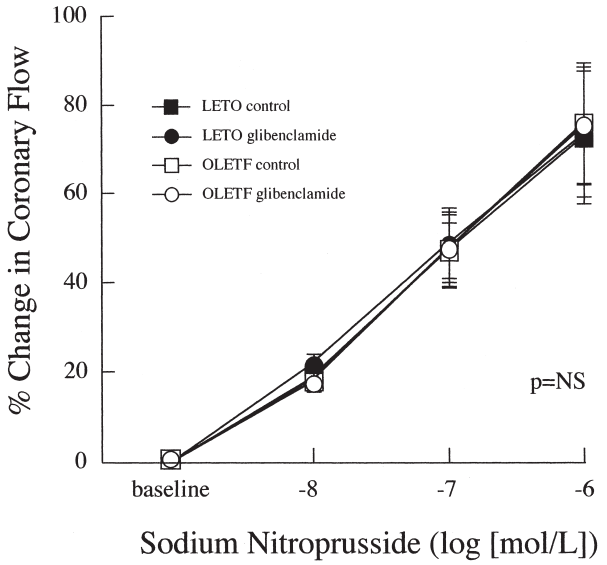

Fig. 5 Graph showing the effect of sodium nitroprusside (10^{-8} to 10^{-6} M) on coronary flow and the effect of glibenclamide (0.1 μM) on sodium nitroprusside-induced increase in coronary flow in LETO (n=7) and OLETF (n=6) rats.

5 mg/dl in LETO and 125±3 mg/dl in OLETF ($p<0.05$). There was no significant difference between LETO and OLETF rats in the changes in CF in response to adenosine, pinacidil or sodium nitroprusside (Figure 6).

Discussion

The major findings of the present study were as follows. 1) Adenosine- and pinacidil-induced increases in CF were blunted in OLETF. 2) Glibenclamide attenuated adenosine-induced increase in CF in LETO but not in OLETF. 3)

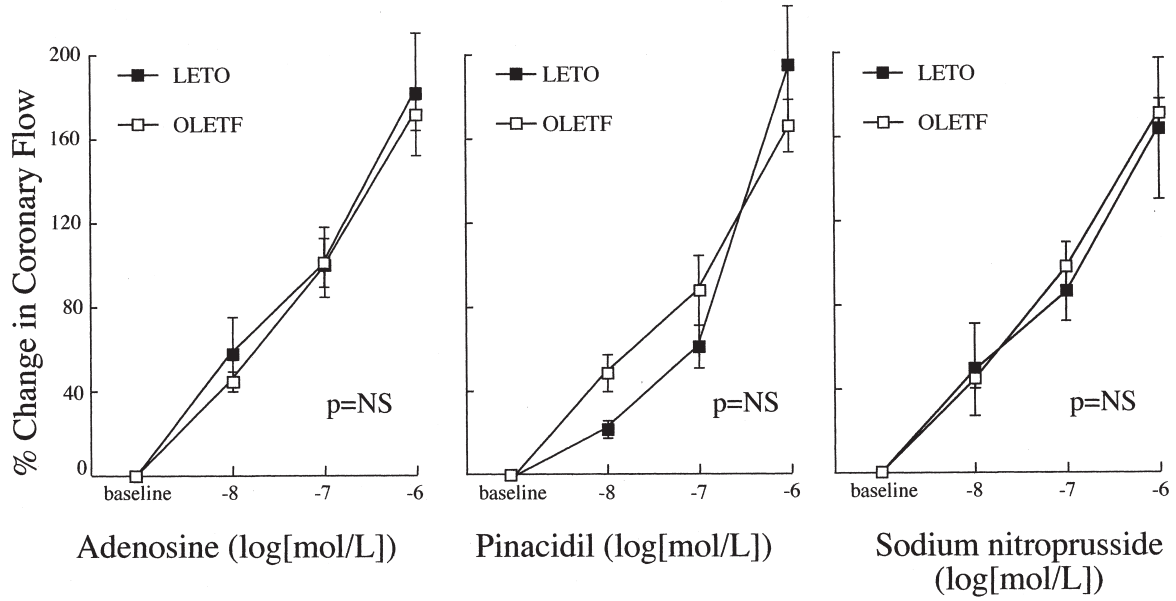

Fig. 6 Graphs showing the effect of adenosine (left panel), pinacidil (center panel) and sodium nitroprusside (right panel) on coronary flow in LETO (n=4) and OLETF (n=5) rats before the onset of DM (at the age of 8-10 weeks).

L-NAME attenuated adenosine-induced increase in CF in OLETF but not in LETO. These findings indicate that adenosine-induced dilation of coronary resistance vessels is blunted through the impairment of K_{ATP} channels in the rats with type II DM, and that adenosine-induced increase in CF in this DM model is mediated by a NO mechanism. To our best knowledge, this is the first report that evaluated the changes in the coronary microcirculation responses to vasodilators in genetically defined type 2 DM model.

Methodological considerations

Previous studies have shown that the coronary dilator effect of adenosine is reduced in animals with alloxan-induced DM, i.e., type I DM[2,20]. Since little research on endothelial dysfunction has been conducted in animal models of type 2 diabetes, it is unknown whether hyperglycemia, in the presence of hyperinsulinemia and insulin resistance, has the same deleterious effects on endothelial cell metabolism as in type 1 diabetes. In the present study, we used OLETF as a type 2 DM model. The characteristic features of OLETF rats include 1) late onset of hyperglycemia (after the age of 18 weeks), 2) a chronic course of disease, 3) mild obesity, 4) hyperinsulinemia, 5) inheritance by males, 6) hyperplastic foci of pancreatic islets, and 7) renal complication[18]. Histologically, the changes of pancreatic islets can be classified into three stages: 1) an early stage (6-20 weeks in age) of cellular infiltration and degeneration: 2) a hyperplastic stage (20-40 weeks); and 3) an end stage (at > 40 weeks). These clinical and pathological features of disease in OLETF rats are genetically defined and resemble those of human type 2 DM. It was shown that the elevation of blood glucose at oral glucose tolerance test became marked after 24 weeks in age. In the present study, the occurrence of DM was confirmed by oral glucose tolerance test at 24 weeks, and the study was performed at 30-32 weeks. Thus, the animals were exposed to hyperglycemia for 6-8 weeks after the onset of DM. Compared with the experiments using isolated vessels, studies on isolated perfused organs yield additional information, since vascular resistance and reactivity were determined by the whole circulation, including the smallest arterioles.

The period of experimental hyperglycemia

appears to be an important determinant of the observed effects of diabetes on vascular K_{ATP} channel function[21] because responses to K_{ATP} channel activation were reported to be enhanced in the early diabetic state[22,23]. On the other hand, Bouchard et al.[24] reported that vasorelaxant responses to lemakalim are impaired in coronary resistance vessels after 2 months of hyperglycemia. Therefore, the present study was performed 6 to 8 weeks after the diagnosis of DM.

Impairment of adenosine-induced dilation and the role of K_{ATP} channels in OLETF

Adenosine is known to depress cardiac contractility via the activation of cardiac A_1 receptor[12]. In the present study, adenosine depressed neither LVP nor dP/dt in both OLETF and LETO, indicating that the effect of adenosine on cardiac contractility was absent or minimum in the concentrations used. At these concentrations, adenosine produced a dose-dependent increase in CF in both OLETF and LETO. However, the increase in CF in OLETF was significantly blunted as compared with that in LETO. On the other hand, sodium nitroprusside-induced coronary dilation in OLETF did not differ from that in LETO. These results suggest that attenuation of adenosine-induced dilation in OLETF is not caused by the impairment of vascular smooth muscle cells due to long-term state of type 2 DM. Since adenosine-induced dilation has been demonstrated to be mediated by K_{ATP} channels[9-11,15-17,25,26], we examined the function of K_{ATP} channels in OLETF and LETO. As shown in Figure 3, the vasodilator effect of pinacidil in OLETF was smaller than that in LETO, suggesting that K_{ATP} channel-mediated coronary dilation is impaired in OLETF. Glibenclamide attenuated the vasodilator response of coronary resistance vessels to pinacidil but not to sodium nitroprusside, indicating that the present dose of glibenclamide selectively inhibited vasodilation via K_{ATP} channels in our preparation. This concentration of glibenclamide attenuated adenosine-induced increase in CF in LETO but not in OLETF. These results suggest that adenosine-induced dilation mediated by K_{ATP} channels is impaired in OLETF. After inhibition of K_{ATP} channel by glibenclamide, adenosine produced a comparable increase in CF in LETO and OLETF rats.

The adenosine- and pinacidil-induced increases in CF in OLETF were similar to thoes in LETO before the onset of type 2 DM. In contrast, they were decreased in OLETF compared with LETO after the onset of type 2 DM, indicating that K_{ATP} channels are impaired under the long-term state of type 2 DM. Although the precise mechanism that results in the impairment of K_{ATP} channels under the state of type 2 DM is unclear, it is possible that K_{ATP} channel density or function in coronary endothelial cells is reduced after long-term state of type 2 DM.

The role of NO pathway in OLETF

Most studies examining the impairment of endothelial vasodilator function associated with diabetes have focused on the role of NO[27]. Recent observations indicate that NO production is reduced and NO-dependent coronary vasodilation is impaired in animals with DM[3,4,28]. Hein and Kuo[17] recently reported that porcine coronary arteriolar dilation to adenosine is mediated by the opening of endothelial K_{ATP} channels followed by NO production/secretion (NO-dependent) and the opening of smooth muscle K_{ATP} channels (NO-independent). In the present study, L-NAME attenuated the adenosine-induced increase in CF in OLETF, suggesting that the adenosine-induced increase in CF is partially mediated by a NO mechanism in the animals with DM. In contrast, L-NAME did not attenuate the adenosine-induced increase in CF in LETO, suggesting that NO mechanism is absent or minimum in the adenosine-induced increase in CF in healthy animals. In the mesenteric arteries, L-NAME

showed greater reduction of both maximum relaxation and maximum hyperpolarization in diabetic rats compared with those in control rats[28]. This suggests that NO has a greater contribution to vasodilation in diabetic rats or that adenosine can activate both NO-dependent and –independent pathways in LETO. Inhibition of the NO-dependent pathway by L-NAME may be compensated by the NO-independent pathway when K_{ATP} channels are intact. In OLETF, the impairment of the NO-dependent mechanism is unmasked since the NO-independent mechanism is diminished as a result of K_{ATP} channel dysfunction. This interpretation appears to be supported by the previous evidence that there is a cross-talk between NO and K_{ATP} channels[29].

It has been shown that endogenous adenosine is involved in the coronary vasodilation during reactive[30] and functional[31] hyperemia, hypoxia[25], and ischemia[26]. In these conditions, the activation of K_{ATP} channels is important for vasodilation since adenosine causes vasodilation via the activation of K_{ATP} channels[9-11,15-17,25,26]. In addition, K_{ATP} channels play an important role in coronary microvascular autoregulation[32] and coronary microvascular dilation to hypoxia[25], acidosis[10] and hyperosmolarity[11]. Since these play crucial roles in the regulation of coronary blood flow[13], the dysfunction of K_{ATP} channels in DM would result in an inadequate oxygen supply during ischemia, hypoxia and intense metabolic demand of the heart. Thus, it is conceivable that myocardial ischemia is produced during exercise or emotional changes through the impairment of metabolic regulation in DM. In light of the current findings, it appears that K_{ATP} channel opener may be beneficial to patients with DM even though they do not show any significant stenotic lesion in the large epicardial coronary arteries.

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