Enhancement of Ischemic Myocardial Metabolic Derangement by Glibenclamide

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ABSTRACT—We examined whether opening of the ATP-sensitive potassium (K_{ATP}) channels in the ischemic myocardium plays an important cardioprotective role during ischemia. Dogs were anesthetized with sodium pentobarbital (30 mg/kg, i.v.). Sixty minutes after treatment of the dog with glibenclamide (0.3 or 3 mg/kg, i.v.), the LAD was ligated. At 3 or 15 min after LAD ligation, left ventricular tissue was taken from the ischemic region to measure tissue metabolite levels. After ischemia, the tissue levels of ATP and creatine phosphate decreased to 49-74% and 26-34%, respectively, and lactate level increased to 380-660%. Ischemia (either 3 or 15 min) increased the levels of G6P and F6P and decreased the FDP level, indicating the inhibition of glycolysis. Glibenclamide at either dose decreased the level of blood glucose by 20-30% and increased the blood insulin level twice. The decrease in ATP and increase in lactate due to ischemia were significantly enhanced by glibenclamide at a dose of 3 mg/kg. The increase in G6P due to 15 min of ischemia were also enhanced significantly by 0.3 and 3 mg/kg of glibenclamide. Glibenclamide worsened the metabolic alterations produced by ischemia. These results suggest that K_{ATP} channels that can be inhibited by glibenclamide may perform some functions in the ischemic myocardium.

Keywords: K_{ATP} channel, Myocardial ischemia, Glibenclamide, Energy metabolism

By the use of a patch clamp method, ATP-sensitive potassium (K_{ATP}) channels were found first in the myocardial cell (1), and then in the pancreatic β cell (2). The cells of other organs also possess K_{ATP} channels (3-5). This channel plays a role in shortening of the action potential in the myocardium (6), insulin secretion in the pancreas (7) and vasodilation in vascular smooth muscle (8). Sulfonylureas, oral hypoglycemic agents, inhibit K_{ATP} channel in the cell membrane of the pancreatic β cells. This effect leads to depolarization of the cell membrane, which in turn increases Ca^{2+} influx through voltage-sensitive Ca^{2+} channels, and thus triggers insulin release (7). Glibenclamide, an antidiabetic sulfonylurea, is a specific K_{ATP} channel antagonist, which is widely used for the experiments on K_{ATP} channels.

In the heart, ischemia opens K_{ATP} channels in the myocardial cells because it reduces the ATP level (9, 10). Opening K_{ATP} channels decreases the cytoplasmic Ca ion concentration because of inhibition of Ca^{2+} influx through voltage-sensitive Ca^{2+} channels (11). This results in a decrease in cardiac contractile force. Although there is no evidence that the ATP level in the coronary arteries decreases during ischemia, in vitro experiments reveal that the increase in blood flow produced by ischemia is possibly mediated by K_{ATP} channels (12). The cardiodepression and coronary dilation caused by opening of the K_{ATP} channels improve oxygen supply-demand imbalance. During ischemia, K_{ATP} channels may be involved in the mechanism by which myocardial ischemic damage is lessened. If this is true, blockade of K_{ATP} channels would enhance the ischemic injury. The present study, therefore, was undertaken to examine the effect of glibenclamide on changes in the myocardial energy and carbohydrate metabolism during ischemia.

MATERIALS AND METHODS

The investigation conforms with the Guiding Principles for the Care and Use of Laboratory Animals approved by The Japanese Pharmacological Society.

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Animal preparation

Healthy mongrel dogs (68 animals) of either sex weighing 7–26 kg were used under pentobarbital (30 mg/kg, i.v.) anesthesia. Animals were endotracheally intubated and ventilated with a respirator. A left thoracotomy was performed between the fourth and fifth ribs to expose the left ventricular wall. After suspending the heart in a pericardial cradle, the main trunk of the left anterior descending coronary artery (LAD) was dissected free from the adjacent tissue and was then loosely encircled with a silk thread for ligation. Ischemia was produced by tightening this thread. Aortic blood pressures were measured via cannula introduced from the left femoral artery to near the aortic arch. Heart rate was counted from the QRS signals from an ECG taken in the standard limb lead II. Double products were calculated from the systolic blood pressure and heart rate. Coronary blood flow was measured by an electromagnetic flow probe positioned just proximally to the ligature.

After control observations had been completed, either the vehicle (dimethyl sulfoxide, DMSO) or 0.3 or 3 mg/kg of glibenclamide dissolved with DMSO was injected i.v. over a period of 30 sec into the left femoral vein. Then 60 min later, the ligature around the LAD was not tied (nonischemia) or tied for 3 or 15 min (ischemia). The animals used were divided into the following groups: vehicle-treated nonischemic group (n=7), 0.3 mg/kg of glibenclamide-treated nonischemic group (n=6), 3 mg/kg of glibenclamide-treated nonischemic group (n=9), vehicle-treated 3-min ischemic group (9), 3 mg/kg of glibenclamide-treated 3-min ischemic group (n=9), vehicle-treated 15-min ischemic group (n=11), 0.3 mg/kg of glibenclamide-treated 15-min ischemic group (n=6), and 3 mg/kg of glibenclamide-treated 15-min ischemic group (n=11). After 3 or 15 min of ischemia, a full thickness sample of the myocardium (about 10 mm) was taken from the center of the ischemic area identified by the cyanotic appearance. A corresponding sample was taken from the animals that had not had the ligature tied around the LAD. The samples were immediately pressed and frozen with clamps previously immersed for more than 10 min in liquid nitrogen. When clamping the samples, the tissue was pressed in such a way that the subendo- and subepicardial portions would be separated from the thin pressed frozen tissue (13). The subendocardial portion of the myocardium was collected and used for analysis. An ischemic myocardial sample was obtained from the subendocardial portion of the myocardium, because the subendocardium is more sensitive to metabolic changes induced by ischemia (13).

Biochemical analyses

The frozen samples of subendocardial tissue were pulverized in liquid nitrogen with a mortar and pestle. A part of the tissue powder was weighed and extracted with 6% perchloric acid. After centrifugation, the supernatant was neutralized and used to determine the levels of adenosine triphosphate (ATP), adenosine diphosphate (ADP), adenosine monophosphate (AMP), creatine phosphate (CrP), glucose-6-phosphate (G6P), fructose-6-phosphate (F6P), fructose-1,6-diphosphate (FDP), pyruvate and lactate according to standard enzymatic procedures (14). The remainder of the tissue powder was weighed and stood in an oven overnight to determine tissue wet weight and tissue water content. The contents of metabolites in the myocardium are expressed in g wet weight, because ischemia did not influence the water content of the myocardium in the present experiment (data not shown).

The energy charge potential (ECP) was calculated from the concentration of ATP, ADP and AMP to estimate the myocardial energy state according to the equation ([ATP]+0.5[ADP])/([ATP]+[ADP]+[AMP]) (15). The ratio of ([G6P]+[F6P])/[FDP] was calculated from the concentration of hexose phosphates to estimate the rate of glycolytic flux through the phosphofructokinase (PFK) reaction (16, 17). The ratio of lactate to pyruvate was also calculated as an index of the cytoplasmic redox state of the myocardial cell.

Serum glucose was determined by the use of Reflolux II (Boehringer Mannheim-Yamanouchi, Co., Ltd., Tokyo), and serum insulin determined by a radioimmunoassay method (18). To avoid some influences of blood sampling, the venous blood was obtained 15 min before coronary ligation and 5 min before termination of the experiments.

Statistics

All values are expressed as a mean±S.E. (n=number of preparations). Hemodynamic data and the levels of blood glucose and insulin were evaluated by a paired Student's *t*-test, and biochemical data were analyzed by one-way analysis of variance followed by the Dunnett's *t*-test. A value of $P<0.05$ was considered statistically significant.

RESULTS

Blood glucose and insulin

Serum glucose and insulin levels are shown in Fig. 1. Serum levels of glucose and insulin were not changed by vehicle injection. Glibenclamide at either 0.3 or 3 mg/kg decreased blood glucose level significantly, whereas it increased insulin level significantly. The increased level of insulin tended to decrease 70 min after glibenclamide injection.

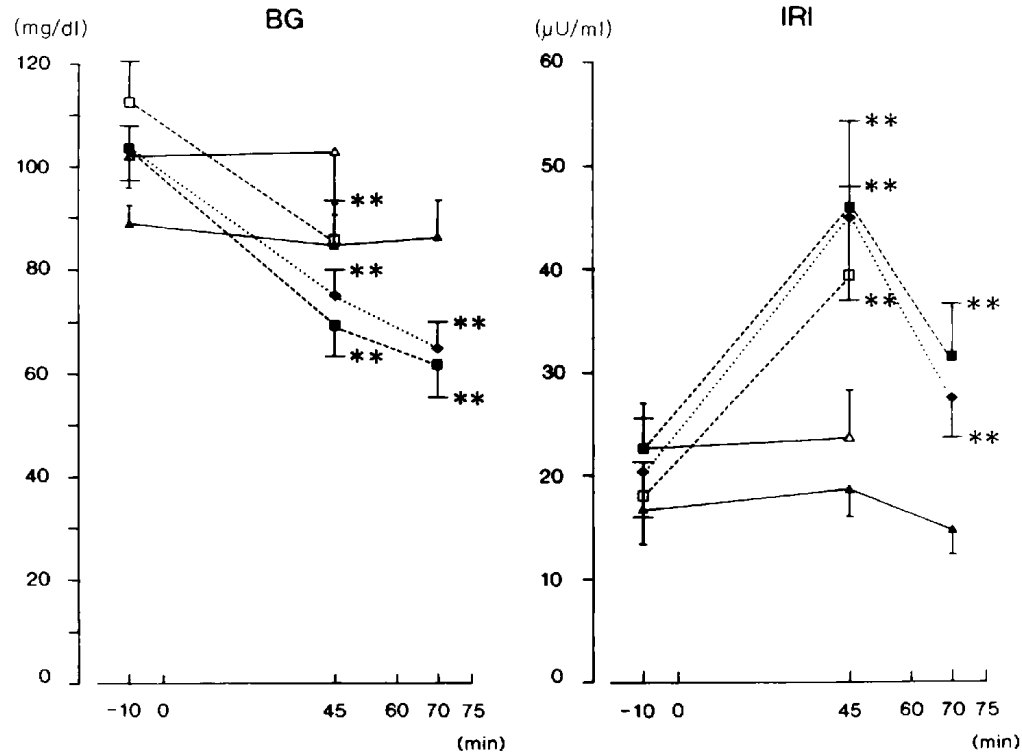

Fig. 1. Blood glucose (BG) and immunoreactive insulin (IRI) levels. Blood samples (serum) were obtained 10 min before and 45 min after vehicle and glibenclamide (0.3 or 3 mg/kg) injection. The BG and IRI values in the nonischemic group were combined with those in the 3-min ischemic group, respectively, because the time at which these levels were obtained in each group corresponded. When the coronary artery was ligated for 15 min, an extra blood sample was taken 10 min after the ligation. △, vehicle-treated nonischemic plus 3-min ischemic groups; □, glibenclamide (3 mg/kg)-treated nonischemic plus 3-min ischemic groups; ▲, vehicle-treated 15-min ischemic group; ◆, glibenclamide (0.3 mg/kg)-treated 15-min ischemic group; and ■, glibenclamide (3 mg/kg)-treated 15-min ischemic group. $^{**}P < 0.01$, compared with the value obtained 10 min before injection.

Hemodynamics (Table 1)

Systolic and diastolic blood pressures increased 30 and 60 min after glibenclamide administration. Changes in the blood pressures were statistically significant in the glibenclamide 0.3 mg/kg-treated ischemic and 3 mg/kg-treated nonischemic and ischemic groups. Heart rate significantly decreased 30 min after the injection, except for the 0.3 mg/kg glibenclamide-treated nonischemic group. Coronary flow did not change after glibenclamide injection, Injection of vehicle did not modify the systolic blood pressure, heart rate and coronary flow appreciably. The diastolic pressure, however, increased slightly but significantly after vehicle injection. Ligation of the LAD, to stop the coronary flow through this artery, slightly decreased the blood pressures. A slight increase in heart rate was observed after coronary ligation in the vehicle-treated animals, but not in the glibenclamide-treated ones. Double products (systolic blood pressure × heart rate) were not significantly changed by either glibenclamide injection or LAD ligation.

Energy metabolism (Figs. 2 and 3)

In the vehicle-treated heart, the level of ATP significantly decreased 3 min after ischemia and was even more decreased at 15 min after ischemia. The levels of ADP and AMP increased significantly 3 min after ischemia, and they returned to the nonischemic level 15 min after ischemia. Glibenclamide at either dose did not modify the ATP level in the nonischemic myocardium. The levels of ADP and AMP were significantly decreased by 0.3 mg/kg glibenclamide, but not 3 mg/kg. Decreases in the levels of ATP caused by ischemia were significantly enhanced by pretreatment with glibenclamide at a dose of 3 mg/kg. The ADP and AMP levels in the 3-min post ischemic myocardium were increased, but the effects of glibenclamide did not reach significance as compared with those in the vehicle-treated hearts. ECP calculated from the adenine nucleotide levels was decreased significantly by ischemia in the vehicle- and glibenclamide-treated heart. The ECP in 0.3 mg/kg of glibenclamide-treated nonischemic group was significantly higher as compared with that in the vehicle-treated group, because of the low levels of ADP and

Table 1. Effects of glibenclamide and LAD ligation on hemodynamic parameters

Time after the onset of experiments (min)	0	60	63	75
		SBP (mmHg)		
Vehicle-treated				
Nonischemia	158.8± 9.4	173.1±10.0		
Ischemia, 3 min	157.2± 7.0	166.7±10.9	160.6±13.5	
Ischemia, 15 min	153.6±12.4	163.1±11.1	—	156.8±12.3
Glibenclamide (0.3 mg/kg)-treated				
Nonischemia	140.5± 7.9	148.7± 7.6		
Ischemia, 15 min	142.5±14.3	159.3±14.9*	—	155.2±15.0*
Glibenclamide (3 mg/kg)-treated				
Nonischemia	141.7± 7.0	170.6± 6.3**		
Ischemia, 3 min	168.3± 8.0	180.6± 8.4**	169.4± 9.2	
Ischemia, 15 min	157.5± 6.5	176.5± 8.3**	—	159.0± 9.7
		DBP (mmHg)		
Vehicle-treated				
Nonischemia	116.3± 4.6	125.6± 5.5**		
Ischemia, 3 min	115.0± 4.9	125.0± 6.6**	116.1± 8.7	
Ischemia, 15 min	108.1± 8.6	119.1± 7.9*	—	112.7± 9.2
Glibenclamide (0.3 mg/kg)-treated				
Nonischemia	94.2± 5.5	103.3± 4.4**		
Ischemia, 15 min	100.0±10.2	116.7±11.1**	—	114.2±10.1**
Glibenclamide (3 mg/kg)-treated				
Nonischemia	96.1± 7.6	113.3± 8.2**		
Ischemia, 3 min	115.6± 7.4	130.0± 7.0**	114.4± 7.6	
Ischemia, 15 min	107.5± 7.0	124.8± 6.9**	—	114.5± 8.6
		HR (beats/min)		
Vehicle-treated				
Nonischemia	169.5±11.2	164.7±13.5		
Ischemia, 3 min	172.1± 8.1	175.1± 7.5	179.7± 7.9	
Ischemia, 15 min	177.2± 7.7	176.5± 6.6	—	187.4± 7.5
Glibenclamide (0.3 mg/kg)-treated				
Nonischemia	172.7± 8.5	173.2± 5.7		
Ischemia, 15 min	168.5± 6.9	162.2± 6.3*	—	163.3± 5.2
Glibenclamide (3 mg/kg)-treated				
Nonischemia	159.6± 8.8	146.7± 7.4		
Ischemia, 3 min	165.4±11.0	154.6±11.3	154.2±10.7*	
Ischemia, 15 min	182.2± 7.5	176.8± 9.2	—	173.7± 7.9
		DP (mmHg/min)		
Vehicle-treated				
Nonischemia	24943±3479	27309±3555		
Ischemia, 3 min	24919±3287	27186±3358	27391±3361	
Ischemia, 15 min	27219±2697	28860±2334	—	29294±2594
Glibenclamide (0.3 mg/kg)-treated				
Nonischemia	26525±2313	27652±1647		
Ischemia, 15 min	22273±2655	25212±3202	—	24269±3056
Glibenclamide (3 mg/kg)-treated				
Nonischemia	24714±1333	27827±2131		
Ischemia, 3 min	29936±2723	29845±2894	27472±2761	
Ischemia, 15 min	27737±2080	31190±3089	—	28277±2680
		CF (ml/min)		
Vehicle-treated				
Nonischemia	19.0± 2.5	20.5± 3.2		
Ischemia, 3 min	24.0± 3.1	30.4± 5.2	0**	
Ischemia, 15 min	18.7± 2.4	17.3± 2.2	—	0**
Glibenclamide (0.3 mg/kg)-treated				
Nonischemia	15.0± 2.0	14.7± 1.5		
Ischemia, 15 min	15.0± 1.6	15.4± 1.6	—	0**
Glibenclamide (3 mg/kg)-treated				
Nonischemia	22.2± 4.4	22.6± 3.3		
Ischemia, 3 min	22.9± 4.5	20.7± 3.4	0**	
Ischemia, 15 min	18.1± 1.7	17.2± 1.6	—	0**

Values are means±S.E. of 6–11 observations. Values at 0 min were obtained immediately before either vehicle (DMSO, 1 ml/kg) or glibenclamide (0.3 or 3 mg/kg) was injected. Ischemia was induced for 3 or 15 min by LAD ligation 60 min after the injection. Values at 60 min were obtained immediately before the LAD ligation. LAD=left anterior descending coronary artery, SBP=systolic blood pressure, DBP=diastolic blood pressure, HR=heart rate, DP=double product (SBP×HR), CF=coronary flow. *$P<0.05$, **$P<0.01$, compared with the value of "before injection" in each group.

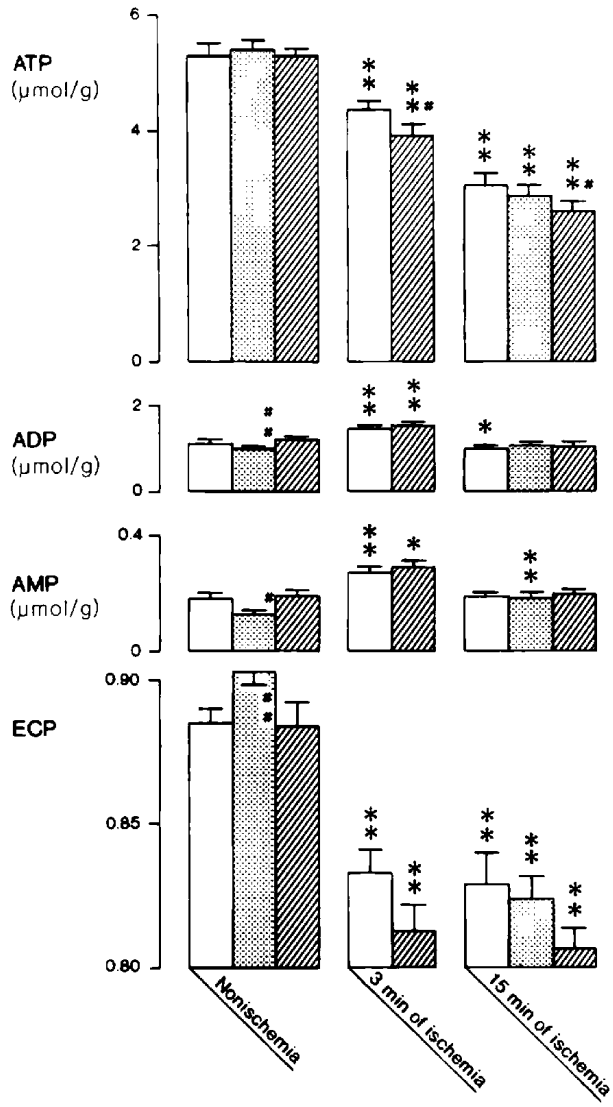

Fig. 2. The levels of adenine nucleotides and ECP in the myocardium. Either vehicle (□) or 0.3 mg/kg (▒) or 3 mg/kg of glibenclamide (▨) was injected 60 min before coronary ligation. The myocardial tissue samples were taken immediately before (nonischemia) or 3 (3 min of ischemia) or 15 min (15 min of ischemia) after the ligation. Values of the metabolites measured are expressed as μmoles/g wet weight (means ± S.E.). ATP = adenosine triphosphate, ADP = adenosine diphosphate, AMP = adenosine monophosphate, ECP = energy charge potential, ([ATP] + 0.5[ADP])/([ATP] + [ADP] + [AMP]). *P < 0.05, **P < 0.01, compared with the respective nonischemic value. #P < 0.05; ##P < 0.01, compared with the vehicle in each group.

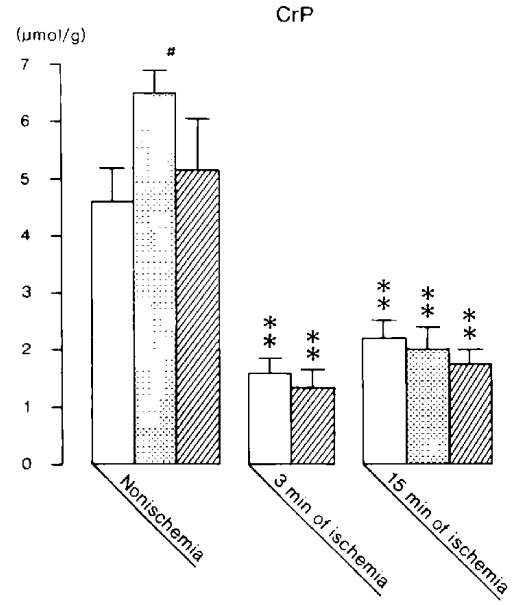

Fig. 3. The myocardial level of CrP. Symbols are the same as those in Fig. 2. CrP = creatine phosphate. **P < 0.01, compared with the respective nonischemic value. #P < 0.05, compared with the vehicle.

AMP in the group. Although glibenclamide potentiated the decrease in ECP value after 15 min of ischemia, there was no significant difference between the vehicle- and glibenclamide-treated groups.

Ischemia decreased similarly the creatine phosphate level significantly in both vehicle- and glibenclamide-treated hearts (Fig. 3). Again, the decrease in creatine phosphate level due to ischemia tended to be enhanced by glibenclamide, but no significant difference was observed.

Carbohydrate metabolism (Figs. 4 and 5)

In the vehicle-treated myocardium, ischemia significantly increased the levels of G6P and F6P, while it significantly decreased the level of FDP. Therefore the ratio of ([G6P] + [F6P])/[FDP] was significantly increased by ischemia, indicating a negative crossover point between F6P and FDP. Pretreatment with glibenclamide at either dose enhanced significantly the increase in G6P level due to 15 min of ischemia, whereas it attenuated the decrease in the FDP level. The increase in the ratio of ([G6P] + [F6P])/[FDP] caused by 15 min of ischemia appeared to be potentiated by glibenclamide. Because the FDP level in the glibenclamide-treated 3-min post ischemic heart was high, the ratio was not changed by glibenclamide.

The level of lactate increased significantly after ischemia, depending on the period of ischemia. Because the level of pyruvate was not altered appreciably, the ratio of [lactate]/[pyruvate] was significantly increased by ischemia. The accumulation of lactate caused by ischemia was significantly enhanced by pretreatment with 0.3 and 3 mg/kg of glibenclamide. The increase in the [lactate]/[pyruvate] ratio caused by ischemia was also potentiated by 3 mg/kg of glibenclamide, and the difference in the ratio between the nonischemic group and the 3-min ischemic group was significant.

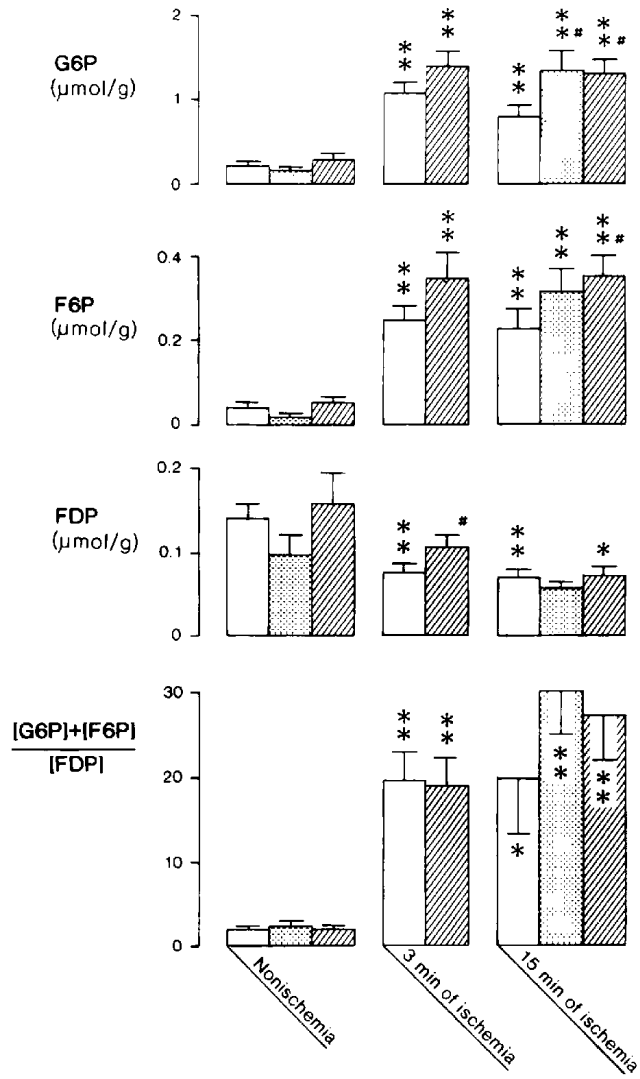

Fig. 4. The levels of hexose phosphates and the ratio of ([G6P]+[F6P])/[FDP] in the myocardium. Symbols are the same as those in Fig. 2. G6P=glucose-6-phosphate, F6P=fructose-6-phosphate, FDP=fructose-1,6-diphosphate. *$P<0.05$, **$P<0.01$, compared with the respective nonischemic value. #$P<0.05$, compared with the vehicle in each group.

DISCUSSION

The present study was undertaken to verify the hypothesis that K_{ATP} channels play an important role in protecting the myocardium against ischemic insults. Cole et al. (9) showed in guinea pig heart that recovery of cardiac function after ischemia and reperfusion is enhanced by a K_{ATP} channel opener and worsened by a K_{ATP} channel blocker. Mitani et al. (19) also reported in isolated perfused rat heart that nicorandil delays the onset of ischemia-induced contracture and glibenclamide accelerates it. Recently, Auchampach et al. (20) have reported that glibenclamide resulted in a worsening of the segment shortening function after reperfusion following ischemia. They suggest that K_{ATP} channels serve an endogenous function, which is to provide protection from ischemic insults (20). In the present study, the decreased level of ATP and increased level of lactate induced by either 3 or 15 min of ischemia were significantly enhanced by glibenclamide. Similarly, the hexose monophosphate levels (G6P and F6P) increased during ischemia, and glibenclamide enhanced significantly their increases caused by 15 min of ischemia. This finding shows that glibenclamide worsens myocardial metabolic derangement during ischemia. This means that K_{ATP} channels were opened by ischemia, and the blockade of the opening by glibenclamide can worsen the metabolic derangement produced by ischemia. Auchampach et al. (20) have demonstrated that aprikalin, a potassium channel opener, improves segment shortening in the ischemic/reperfused myocardium only when given before the coronary occlusion, but not when given immediately before reperfusion. The opening of the K_{ATP} channels during ischemic period but not during reperfusion period is necessary for protecting the myocardium from ischemic injury.

There is a discrepancy in the concentration of ATP at which K_{ATP} channels open between in vitro and in vivo experiments. According to the in vitro experiments, the K_{ATP} channel will open when the concentration of ATP is under a μM concentration (1). Although the level of ATP decreases during ischemia, the level in the ischemic myocardium is still at a mM concentration. Nichols and Lederer (21) have demonstrated that the ATP/ADP ratio, even within their physiological concentration rages, may influence cellular function in the heart via a direct action on the K_{ATP} channel. Compartmentalization of ATP in the cell (22) may be another explanation for this problem. During ischemia, the ATP concentration in the pool near the K_{ATP} channel may decrease to the level at which the K_{ATP} channel can open. A total reduction of ATP is not necessary to open the K_{ATP} channel. Kirsch et al. (23) have demonstrated that a guanosine triphosphate-dependent protein (G protein), especially G_i, reduces the channel sensitivity to ATP in cultured neonatal rat heart cells. Ischemia stimulates the release of adenosine from the myocardium (24). It is possible to consider that the released adenosine activates the G protein through adenosine receptors. Reduction of K_{ATP} channel sensitivity to ATP due to activation of G protein may open the channels although the concentration of ATP is still high.

Ischemia inhibits the glycolytic pathway at the level of PFK (25, 26). In the present study, a negative crossover point between F6P and FDP was observed in the ischemic myocardium, suggesting an inhibition of glycolytic flux through the PFK reaction (Fig. 4). In the ischemic myocardium where there is no coronary flow, glycolysis may

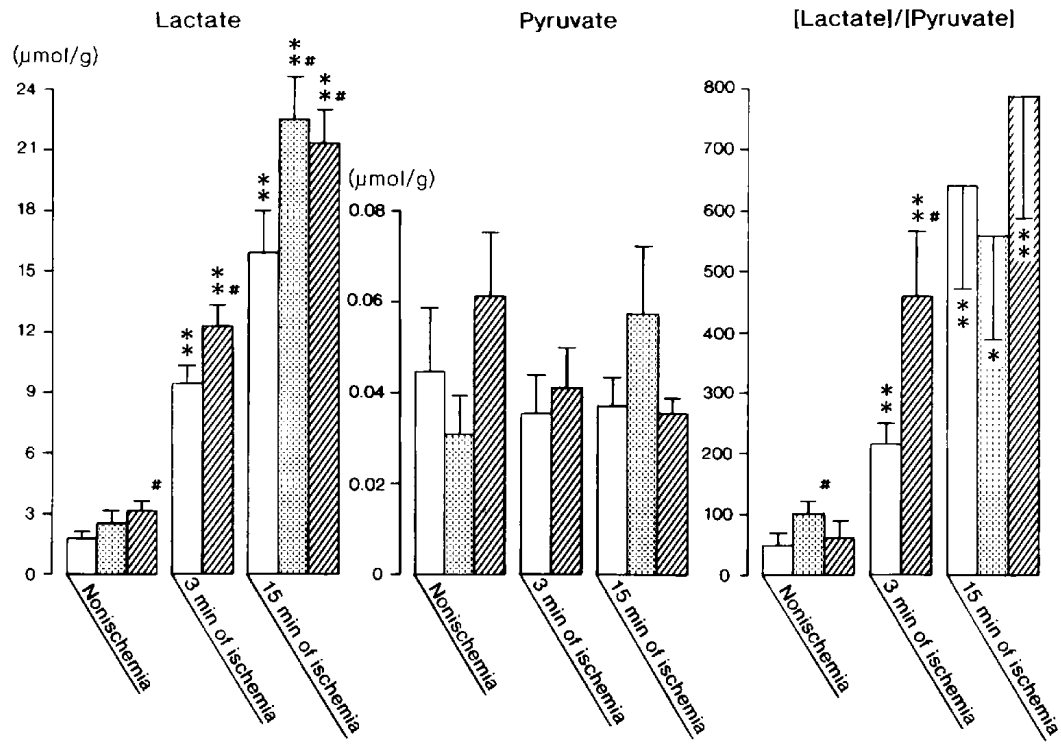

Fig. 5. The levels of myocardial lactate and pyruvate. Symbols are the same as those in Fig. 2. *$P<0.05$, **$P<0.01$, compared with the respective nonischemic value. #$P<0.05$, compared with the vehicle in each group.

be inhibited to prevent an abnormal accumulation of the deleterious metabolic end products such as lactate and hydrogen ions (27). Without a direct measurement of glycolytic flux, static measurements of the substrates and products of a reaction do not quantify the rate of glycolytic flux (28). Opie has stated clearly in his paper that measurement of glycolytic flux in regionally ischemic myocardium is not easy (26). Aside these limitations, the ratio of ([G6P]+[F6P])/[FDP] is useful for estimating the metabolic deterioration in the ischemic myocardium. We have demonstrated that many cardioprotective drugs attenuate the increase in the ratio caused by ischemia (16, 29, 30).

Glibenclamide at a high dose produces a significant increase in blood pressure and a decrease in heart rate (Table 1). Blockade of K_{ATP} channel opening may constrict systemic vascular smooth muscle (31), and then increases peripheral vascular resistance. However, the coronary flow was not modified by glibenclamide in spite of its vasoconstrictive action. Imamura et al. (32) reported that intracoronary infusion of glibenclamide decreases coronary blood flow without any change in mean aortic pressure. In the present study, the coronary blood flow was probably maintained by elevation of the aortic pressure that increased perfusion pressure to propel the coronary flow. The decrease in heart rate may be due to a compensatory response to the hypertension. The elevation of the arterial blood pressures may be involved partly in the mechanism by which glibenclamide make the metabolic derangement worse because of increasing energy requirement of the heart. Double products did not change significantly, however. Auchampach et al. (20) reported that a low dose of glibenclamide (1 mg/kg) results in significant worsening of segment shortening during reperfusion without systemic hemodynamic changes. Glibenclamide at 0.3 mg/kg in the present study also showed some enhancements of ischemic metabolic derangements under the less hemodynamic changes. Another possibility by which glibenclamide enhanced the myocardial metabolic derangements during ischemia is via alterations in blood glucose and/or insulin levels. The lower dose of glibenclamide (0.3 mg/kg) also decreased the blood glucose level and increased insulin level to the same extent as the higher dose of glibenclamide (3 mg/kg) did (Fig. 1). To avoid the hypoglycemic effect of the drug, glucose solution was infused in our preliminary experiments. The infusion of glucose, however, increased the insulin level further (data not shown). It is very difficult to cancel both the effects of low glucose and high insulin levels on the ischemic myocardium. Schaffer et al. (33) demonstrated that glibenclamide increases glucose utilization and lactate production and potentiates insulin effects in the isolated perfused rat heart. Because glibenclamide affects the pancreas and releases insulin, it accelerates glycogen break-

down and glycolysis, leading to high levels of hexose phosphates and lactate. This is one of the possibilities that glibenclamide enhances the myocardial metabolic changes during ischemia. If this is true, some metabolic changes should have been observed even in the nonischemic myocardium treated with glibenclamide.

Opening of the K_{ATP} channels hyperpolarizes the membrane potential and as a result reduces the calcium influx through the voltage-dependent calcium channels. This cases the coronary vasodilation in the smooth muscle cells and reduction of myocardial contraction in the cardiac cells, resulting in an increase in blood supply and a decrease in energy demand, respectively. Because the K_{ATP} channels cannot open in the presence of glibenclamide even during ischemia, these compensatory mechanisms do not work in the ischemic myocardium. This is partly responsible for worsening the metabolic alterations produced by ischemia in the present study.

In conclusion, myocardial K_{ATP} channels may play an important role in the compensatory mechanism to protect the myocardium from ischemic insults.

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