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Altered Delayed Rectifier K^+ Current of Rabbit Coronary Arterial Myocytes in Isoproterenol-Induced Hypertrophy

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The aim of present study was to define the cellular mechanisms underlying changes in delayed rectifier K^+ (K_{DR}) channel function in isoproterenol-induced hypertrophy. It has been proposed that K_{DR} channels play a role in regulation of vascular tone by limiting membrane depolarization in arterial smooth muscle cells. The alterations of the properties of coronary K_{DR} channels have not been studied as a possible mechanism for impaired coronary reserve in cardiac hypertrophy. The present study was carried out to compare the properties of coronary K_{DR} channels in normal and hypertrophied hearts. These channels were measured from rabbit coronary smooth muscle cells using a patch clamp technique. The main findings of the study are as follows: (1) the K_{DR} current density was decreased without changes of the channel kinetics in isoproterenol-induced hypertrophy; (2) the sensitivity of coronary K_{DR} channels to 4-AP was increased in isoproterenol-induced hypertrophy. From the above results, we suggest for the first time that the alteration of K_{DR} channels may limit vasodilating responses to several stimuli and may be involved in impaired coronary reserve in isoproterenol-induced hypertrophy.

Key Words: Potassium channels, Isoproterenol, Hypertrophy, Coronary, Patch clamp technic

INTRODUCTION

Reduced coronary reserve in response to various factors (Vrobel et al, 1980; Bache et al, 1981; 1988; Murray & Vatner, 1981; Hittinger et al, 1989; 1990) is a recognized feature of cardiac hypertrophy and is often accompanied by a high incidence of sudden cardiac death (Kohya et al, 1988; Pye & Cobbe, 1992; Hart, 1994). It is generally assumed that alterations in the coronary circulation play a major role in the enhanced susceptibility of the myocardium in cardiac hypertrophy to ischemic injury (Dunn & Pringle, 1987; Marcus et al, 1987; Bounhoure & Galinier, 1991). While a number of studies have addressed the role of coronary vascular anatomy in this redistribution of blood flow in hypertrophied heart, varied results have been reported in different models. Structural variables previously proposed to explain this phenomenon include: (1) an inadequate growth of the capillary vascular bed while ventricular mass is increasing (Breisch et al, 1980, 1984), (2) a reduction in the luminal radii of major resistance vessels (Marcus, 1987; Tomanek, 1990), (3) an increase in the medial area of resistance vessels (Anderson et al, 1989; Brilla et al, 1991) and (4) failure of the large epicardial conductance arteries and cross sectional area of the vascular bed to enlarge in proportion to the degree of hypertrophy (Stack et al, 1983). In contrast, other studies have demonstrated a return toward normal in vascular density in both the capillary bed and the intramyocardial vessels in chronic models of cardiac hypertrophy in the rat and the dog (Wangler et al, 1982; Peters et al, 1984; Tomanek et al, 1989) and no transmural differences in vascular morphology in chronic moderately severe left ventricular hypertrophy in the dog (Bishop et al, 1996). These controversial explanations for structural alterations of coronary

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artery suggest that other possible factors would appear to be involved in the reduced coronary reserve in cardiac hypertrophy.

The maintenance of coronary blood flow is dependent upon a certain level of tone maintained by coronary arterial smooth muscle cells. Several channels in the plasma membrane of vascular smooth muscle cell are known to play a major role in the regulation of smooth muscle excitability (Nelson & Quayle, 1995). Among the channels, activation of K^+ channels in arterial smooth muscle cells can increase blood flow and lower blood pressure through vasodilation. Inhibition of K^+ channels in arterial smooth muscle leads to vasoconstriction. Delayed rectifier K^+ (K_{DR}) channels are one of dominant K^+ channels found in vascular smooth muscle cells. The properties of K_{DR} channels have been described at the whole cell and single-channel levels in rabbit coronary myocytes (Volk et al, 1991; Volk & Shibata, 1993). Especially, K_{DR} channels probably act mainly to limit membrane depolarization in arterial smooth muscle cells (Hille, 1992; Ishikawa et al, 1993; Leblanc et al, 1994). Nevertheless, the cellular mechanisms by which coronary K_{DR} channels are altered in cardiac hypertrophy are unknown.

We have carried out this study to elucidate whether coronary K_{DR} channels are altered in a hypertrophied heart compared to a normal heart.

METHODS

Induction of cardiac hypertrophy

Cardiac hypertrophy was induced in New Zealand white rabbits by injection of isoproterenol (300 μg/kg) once daily for 10 days as described previously (Benjamin et al, 1989; Gillis et al, 1996). Age-matched control rabbits received the same amount of 0.9% NaCl solution only. The animals were used for experiments 24 hr after the last injection. The degree of hypertrophy was estimated by measuring the blotted wet heart weight and the body weight and calculating the heart weight-to-body weight ratio.

Cell-isolation procedure

Single vascular myocyte was isolated from rabbit coronary artery by enzymatic dissociation. Rabbits of either sex were anaesthetized with sodium pentobarbital (10 mg/kg I.V.). The heart was quickly removed and placed in a cold oxygenated Tyrodes solution composed of (in mM): 143 NaCl, 5.4 KCl, 5 N-[2-Hydroxyethyl]piperazine-N'-[2-ethanesulfonic acid] (HEPES), 0.33 NaH_2PO_4, 1 $MgCl_2$, 16.6 glucose, and 1.8 $CaCl_2$ (pH 7.4 with NaOH). The left anterior descending coronary artery was carefully removed with a portion of myocardium attached to it and was then pinned down to silicone elastomer layered in a dissecting Petri dish. The adhering ventricular myocardium and connective tissue were carefully removed under binocular examination. The arteries were then incubated for 30 min at room temperature in the same medium, except that calcium was omitted. Enzymatic dispersion was then initiated by incubating the artery for 30~40 min with collagenase (2.5 mg/ml, Wako Pure Chemical), bovine albumin (1 mg/ml, Sigma Chemical), and dithioerythritol (0.5 mg/ml). After 30~40 min of incubation with the enzymes, arteries were retrieved and rinsed several times with fresh Ca-free solution. Single smooth muscle cells were mechanically dispersed by triturating of the tissue pieces by using a Pasteur pipette in Kraft-Brühe (KB) solution composed of (in mM): 70 KOH, 50 *L*-glutamic acid, 50 KCl, 20 taurine, 20 KH_2PO_4, 3 $MgCl_2$, 20 glucose, 10 HEPES, and 0.5 ethylene glycol-bis (β-aminoethyl ether) *N, N, N', N'*-tetraacetic acid (EGTA) (pH 7.3 with KOH). When a sufficient number of relaxed spindle-shaped smooth muscle cells became apparent under microscopic examination, the isolated cells were stored cold (4°C) until use.

Experimental procedure and electrophysiological techniques

All experiments were performed at room temperature. The recording chamber was mounted on a movable stage of an inverted microscope. The volume of the recording chamber was ~1 ml. Before each experiment, a sample of the stored supernatant containing single cells was deposited in the experimental chamber, and the cells were allowed to settle for 20~30 min. They were then superfused for 5 min with normal Tyrodes solution before the patch-clamp experiment was started. Some of the cells contracted irreversibly during the initial perfusion. Patch-clamp experiments were only carried out on cells that remained in a relaxed state. Gigaohmseals were obtained using pipettes of 5~10 MΩ resistance pulled from borosilicate glass capillaries (Clark Electroche-

mical, Pangbourne, England) with a vertical puller (Narishige PP-83, Japan). Their tips were coated with Sylgard and fire polished. After a whole-cell mode was obtained, an equilibration period of ~5 min was allowed. Whole-cell currents were filtered at 5 kHz and stored in digitized format on digital audiotapes using a Biologic DTR-1200 recorder (Grenoble, France). For the analysis, the data were transferred to a computer (IBM-PC, 80486 DX2-66) with pCLAMP v 6.03 software (Axon Instruments, Burlingame, CA, USA) through an analogue-to-digital converter interface (Digidata-1200, Axon Instruments Inc.).

Solutions and drugs

The solutions facing the inside of the cell membrane contained (in mM) 133 K-Aspartic acid, 7 KCl, 2.5 Mg-ATP, 2.5 Na-ATP, 2.5 tris-creatine phosphate, 2.5 Na-creatine phosphate, 5 HEPES and 10 ethylene glycol-bis (β-aminoethyl ether) *N, N, N', N'*-tetra-acetic acid (EGTA); pH was adjusted to 7.3 with KOH. The solutions facing the outside of the cell membrane contained (in mM) 143 NaCl, 5.4 KCl, 5 HEPES, 0.33 NaH_2PO_4, 1 $MgCl_2$, 16.6 glucose, 0 or 1.8 $CaCl_2$; pH was adjusted to 7.4 with NaOH. All chemicals and drugs were obtained from Sigma Chemical (St. Louis, MO, USA).

Statistical analysis

Data are presented as mean±S.E. when appropriate. Unpaired Student's *t* test was used to assess the

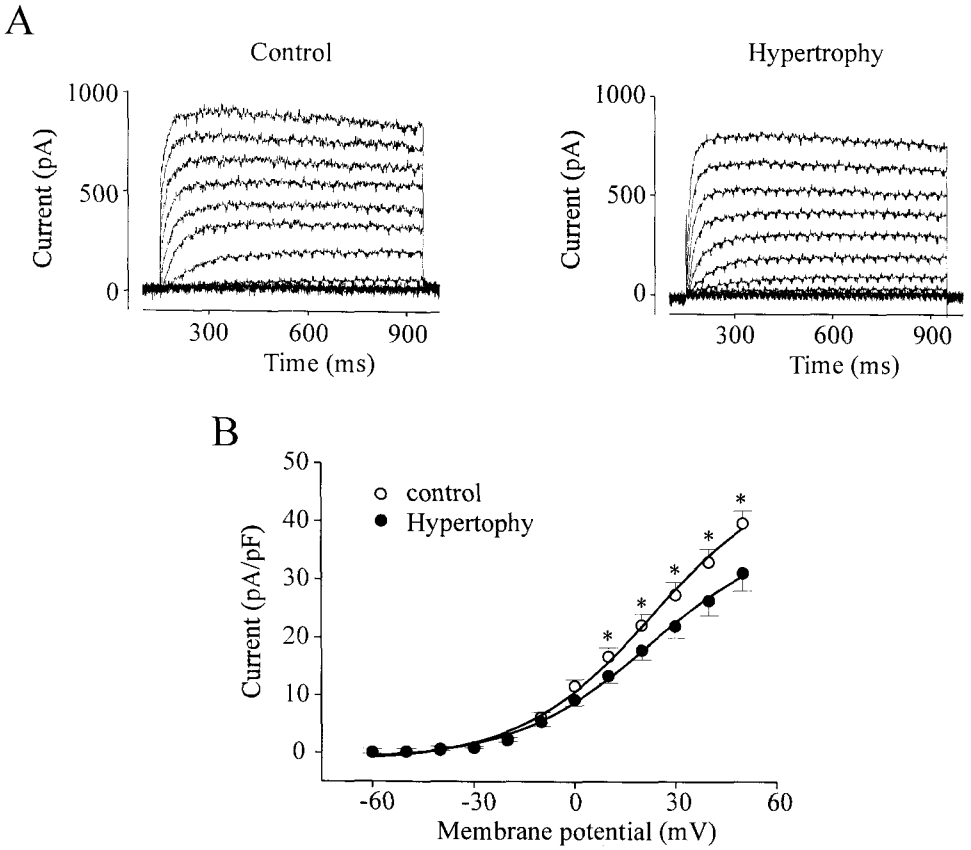

Fig. 1. Reduced delayed rectifier K (K_{DR}) current density of the coronary arterial myocytes from hypertrophy hearts. A: Superimposed currents recorded test potentials from −60 to +50 mV for a control coronary arterial myocyte (C_m=13.6 pF) and coronary arterial myocyte isolated from hypertrophy heart (C_m=16.7 pF). B: Mean current-voltage (*I-V*) relationships of K_{DR} current density in coronary arterial myocytes from control and hypertrophy hearts. Mean data at test potentials positive to +10 mV for myocytes from hypertrophy hearts are significantly less than control (control, n=7 and hypertrophy, n=10, $P<0.05$). Each values are means±S.E. *$P<0.05$ compared with control (unpaired *t*-test).

statistical significance of differences observed between control and hypertrophy. $P \leq 0.05$ was accepted as the level of significance.

RESULTS

Characteristics of hypertrophy

The body weight of the animals was unchanged by isoproterenol injections: 1.29±0.06 and 1.36±0.05 kg in control (n=14) and hypertrophy (n=26), respectively ($P > 0.05$). The wet heart weight was increased from 7.93±0.41 g in control to 9.66±0.33 g in hypertrophy ($P < 0.05$). The heart weight-to-body weight ratio was increased by 13%: 0.62±0.01 and 0.70±0.01 g/kg in control and hypertrophy, respectively ($P < 0.05$). No serous cavity effusions or increases in lung or liver weights were observed. From these data, this model can be considered to demonstrate mild hypertrophy (Hart, 1994). With this in cardiac structure, the mean cell capacitance (C_m) was 24% greater for isolated coronary arterial myocytes from isoproterenol-induced hypertrophy than for control coronary arterial myocytes (control, 14.12±0.01 pF, n=26; hypertrophy, 17.46±0.69 pF, n=40, $P < 0.05$).

Changes in delayed rectifier K^+ current density

To determine whether isoproterenol-induced hypertrophy altered delayed rectifier K^+ (K_{DR}) channel properties, we first recorded whole-cell current of K_{DR} channel. The bath contained the Ca^{2+}-free Tyrode solution +1 mM TEA/10 μM nicardipine and the pipette contained the 10 mM EGTA solution. Fig. 1A compares raw currents recorded at the test potentials from −60 to +50 mV in a control coronary arterial myocyte (C_m=13.6 pF) and in a coronary arterial myocyte isolated from isoproterenol-induced hypertrophic heart (C_m=16.7 pF). In this example, maximum K_{DR} current amplitude (+50 mV) in the control cell was ~11.3 % greater than in the coronary arterial smooth muscle cell from hypertrophied heart (884.30 vs. 794.21 pA), whereas maximum K_{DR} current was 34.7 % greater (65.02 vs. 47.56 pA/pF). Fig. 1B plots the mean current-voltage (*I-V*) relationships for each group of myocytes and demonstrates that K_{DR} current density was markedly less in coronary arterial myocytes from hypertrophic hearts than in coronary arterial myocytes from control hearts. Specifically, when compared at the test potential of +50 mV, mean K_{DR} current density in myocytes from the hypertrophy group (31.14±3.04 pA/pF, n=10, $P < 0.05$) was less than that from the control (39.76±2.16 pA/pF, n=7).

Comparing the kinetic properties of coronary K_{DR} channels

To examine the kinetic properties of K_{DR} channels,

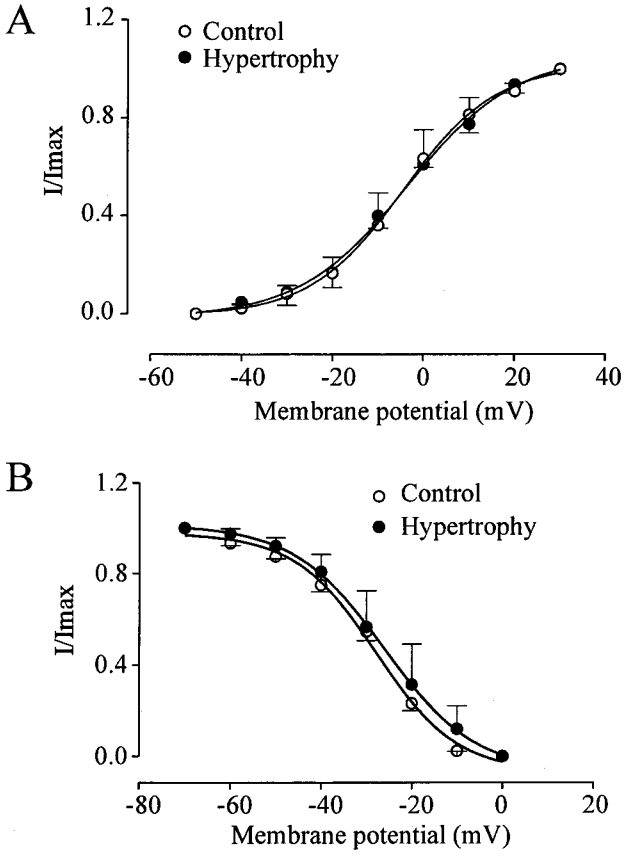

Fig. 2. Effect of hypertrophy on steady-state activation and inactivation kinetics of K_{DR} currents. A: The activation points are means±S.E. (control, n=3 and hypertrophy, n=4) and were determined by fitting deactivation tail at −35 mV after voltage steps to various potentials. The voltage steps that preceded deactivation varied in length so as to return to −35 mV at the peak of the current. The amplitude of each tail normalized using the largest tail. These points were fitted with Boltzmann distribution equation. B: The inactivation points are means±S.E. (control, n=3 and hypertrophy, n=4) and represent normalized peak outward current at +40 mV after holding at various potentials until this current stabilized. The smooth curve through these points is the best fit to the Boltzmann distribution equation.

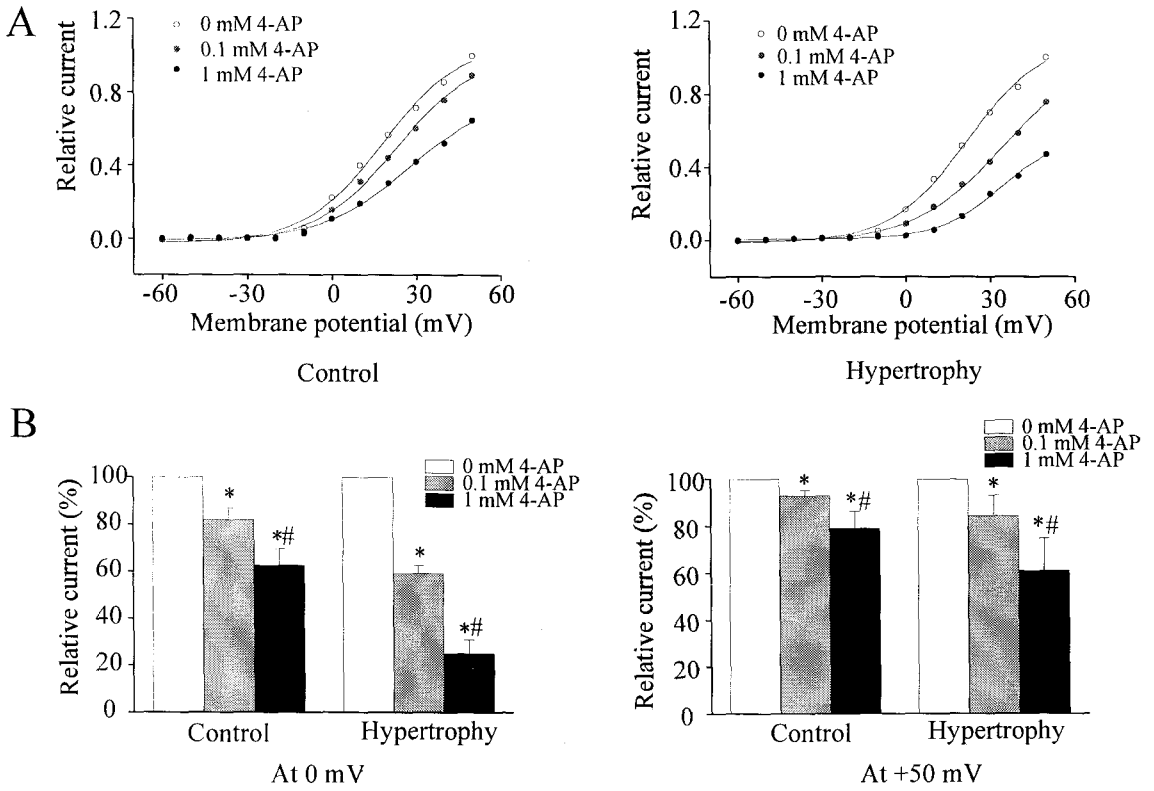

Fig. 3. Comparing of the inhibitory effect of 4-AP on K_{DR} channels in hypertrophy and control. A: Whole-cell current-voltage relationships in hypertrophy (right panel) and control (left panel). B: Summary of results for each 4 cells. Percent inhibition of 0.1 and 1 mM 4-AP at 2 different voltages (0 and +50 mV) is shown. TEA (1 mM) and nicardipine (10 μM) are present. Bath (external) and pipette (internal) K^+ were 5 and 140 mM, respectively. Each values are means±S.E. *$P<0.05$ compared with control (unpaired t-test) #$P<0.05$ compared with 0.1 mM 4-AP (unpaired t-test).

the activation and inactivation kinetics of the channels were analyzed in coronary arterial smooth muscle cells from hypertrophied and normal hearts. The activation and inactivation curves were well fitted by Boltzmann distribution equation. In activation curve (Fig. 2A), half-maximal activation voltage and slope factor were −3.58±1.09 mV and 11.76±1.12 for control (n=3) and −4.46±0.71 mV and 10.18±0.71 for hypertrophy (n=4). In inactivation curve (Fig. 2B), half-maximal inactivation voltage and slope factor were −27.82±1.36 mV and 8.97±1.31 for control (n=3) and −26.02±0.44 mV and 10.10±0.42 for hypertrophy (n=4). There is no significant difference between the two groups of cells ($P>0.05$).

Comparing the effect of 4-aminopyridine on coronary K_{DR} channels

4-aminopyridine (4-AP) inhibits K_{DR} channels in coronary arterial smooth muscle (Beech & Bolton, 1989; Volk et al, 1991; Robertson & Nelson, 1994). In the present study, 4-AP reduced K_{DR} currents evoked by depolarizing test pulses in concentration-dependent manner. Fig. 3A shows the relationship between external 4-AP concentration and inhibition of K_{DR} currents. The inhibition of 4-AP on K_{DR} currents was more effective in coronary arterial smooth muscle cells from hypertrophied hearts than from the normal hearts. Fig. 3B summarizes the K_{DR} current inhibition by 0.1 and 1 mM of 4-AP at 2 different voltages (0 and +50 mV).

DISCUSSION

This paper is the first report, which clearly shows that the density of K_{DR} current is significantly affected without change in the kinetic properties of K_{DR} current in coronary arterial smooth muscle cells from a model of isoproterenol-induced cardiac hypertrophy.

The principal findings of this study are that K_{DR} current density is significantly reduced with no half-maximal voltage and the slope factor for its activation and inactivation and that the sensitivity of K_{DR} current on 4-AP is significantly increased.

Isoproterenol-induced cardiac hypertrophy is a simple well-established model and provides useful information that may have a relevant application to clinically observed disease (Meszaros et al, 1996). We have demonstrated in the present study that the cardiac hypertrophy was induced by daily administration of 300 μg/kg isoproterenol for 10 days in the rabbits. In this model, there is a 13% increase in the heart to body weight ratio. No change was seen in the lung to body weight and the liver to body weight ratio, suggesting that heart failure does not occur in this model. Therefore, this model can be classified as mild cardiac hypertrophy (Hart, 1994).

The significant decrease in coronary K_{DR} current density observed in this model could be partly explained by a possibility that hypertrophy would not induce an over-expression of functional K_{DR} channels. Although there are no studies available to show alteration of protein synthesis in coronary arteries, we suggest this possibility out of some studies in hypertrophied ventricles (Potreau et al, 1995; Meszaros et al, 1996). The present results show the hypertrophy-induced increase in membrane capacitance of coronary arterial smooth muscle cell is approximately 24% whereas the K_{DR} current density is decreased by about 34.7% for potential positive to +50 mV (Fig. 1). The absence of an over-expression could not therefore be responsible for the total decrease of K_{DR} current. We have also shown that isoproterenol-induced hypertrophy induced a decrease in the unitary current amplitude of coronary Ca^{2+}-activated K^+ channel (in press). Therefore, at least in part, repeated administration of isoproterenol may induce the alteration of channel synthesis of coronary arterial smooth muscle cells. Our data also demonstrated that the steady-state kinetics of K_{DR} current were not altered in the coronary arterial smooth muscle cells from hypertrophied hearts. In our model, neither half-maximal activation voltage nor half-maximal inactivation voltage was altered, and thus it seems unlikely that the decrease in K_{DR} current density can be explained by a change in the open probability of the channels. Possible explanations for this decrease are altered single-channel conductance or, perhaps more likely, fewer K_{DR} channels in the sarcolemma.

K_{DR} channels provide an important K^+ conductance in the physiological membrane potential range in arteries (Smirnov & Aaronson, 1992; Volk & Shibata, 1993; Leblanc et al, 1994). The membrane potential of smooth muscle cells in the arterial wall appears to be an important regulator of vascular tone. The relationship between smooth muscle membrane potential and arterial tone is very steep, so even membrane potential changes of a few millivolts cause significant changes in blood vessel diameter (Nelson et al, 1988, 1990). Membrane potential changes would then act in concern with other mechanisms to alter blood vessel diameter. Activation of K_{DR} channels by membrane depolarization in response to several stimuli may limit membrane depolarization (Nelson & Quayle, 1995). Indeed, inhibition of K_{DR} channels by 4-AP depolarizes and constricts many arteries (Hara et al, 1980; Knot & Nelson, 1995). Thus, reduced K_{DR} current density, shown in present study, may affect the regulation function of K_{DR} channels to limit membrane depolarization. Therefore, the alteration of K_{DR} channels may relate to the impaired coronary reserve in isoproterenol-induced hypertrophy.

K_{DR} channels were relatively insensitive to block by external TEA and can be blocked by 4-AP. In our experiments, 4-AP inhibited the outward current a by 17.93 (0.1 mM) and 37.28 (1 mM) % at 0 mV, and 7.06 (0.1 mM) and 20.8 (1 mM) % at 50 mV. In present study, the inhibitory effect of 4-AP on K_{DR} channels was markedly in coronary arterial smooth muscle cells from isoproterenol-induced hypertrophy comparing the control. It is possible that coronary arterial smooth muscle cells from isoproterenol-induced hypertrophy, at least, may be more sensitive some vasoconstrictor, which are associated with 4-AP binding site, than control.

From the above results, we hypothesize that the alteration of K_{DR} channels may limit vasodilating responses to several stimuli and may be involved in impaired coronary reserve in isoproterenol-induced hypertrophy.

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