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Adrenergic Modulation of Potassium Currents in Isolated Human Atrial Myocytes

Key Words
Human atrial myocytes
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Abstract
The adrenergic modulation of inwardly rectifying and depolarization-activated outward potassium currents was studied in single cardiac myocytes obtained from the human atrium. Membrane currents were recorded in enzymatically dissociated cells using the whole-cell voltage-clamp technique. It was observed that, in the presence or absence of atenolol (or 1 μ*M* propranolol), 30 μ*M* phenylephrine attenuated inwardly rectifying and depolarization-activated outward potassium currents including both transient and late-activated current. This suppressant effect of phenylephrine could be prevented by pretreatment with an α-adrenoceptor antagonist. Isoproterenol (30 μ*M*) increased the late outward potassium current and net transient outward current. It is concluded that, in human atrial myocytes, α-adrenergic activation reduces depolarization-activated transient and late outward potassium current and inwardly rectifying background potassium current. β-Adrenergic activation resulted in an increase in the depolarization-activated transient and late outward potassium current.

It is well established that catecholamines, by activating α- and β-receptors, modulate a variety of physiological responses in the heart including heart rate and force of cardiac contraction [31, 35, 44]. Stimulation of the β-receptor by catecholamines generates activated $G_{s\alpha}$, which leads to the production of cAMP. cAMP, in turn, activates protein kinase A, which phosphorylates various proteins including sodium, calcium, and potassium channel proteins in the myocytes [9, 18]. In the myocardium, calcium channels are a major site of action of β-adrenergic agonists. However, it is known that stimulation of β-receptors can also lead to enhanced activity of delayed rectifier potassium current [10, 12, 19, 45, 46]. Under normal physiological conditions, cardiac α-adrenergic receptor stimulation may not have important physiological effects; nevertheless, α-adrenergic receptors probably function as a backup inotropic system for conditions in which the β-adrenergic responses are compromised. α-Adrenoceptors will gain greater functional importance when β-adrenoceptor-mediated positive inotropic effects are impaired [15, 35].

β-Adrenergic stimulation of ventricular cells results in the enhancement of the L-type calcium current and delayed outward potassium current that regulate the plateau phase of the action potential. β-Adrenergic stimulation by a low concentration of isoproterenol induces a prolongation of the action potential, whereas a higher concentration of isoproterenol causes a shortening of the action potential. Isoproterenol elicited single or multiple delayed afterdepolarizations (DAD), with a corresponding in-

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crease in the amplitude of the DAD in adult canine ventricular and atrial myocytes [23, 33].

Enhanced α-adrenergic responsiveness occurs during pathological states and appears to be a mediator of malignant dysrhythmias induced by catecholamines during myocardial ischemia and reperfusion [38]. The loss of repolarizing current during the critical stages of action potential repolarization brought about by inhibition of transient outward current (I_{to}) [16] and inwardly rectifying background potassium (I_{K1}) current [14] could allow the development of early afterdepolarizations and triggered arrhythmias [38]. A reduction of background potassium current in Purkinje fiber [37] and rabbit ventricle [14] and the long-lasting depolarization-activated outward current in rat ventricle [34] and atrium [25] have been reported.

A recent report [4] showed that α_1-agonist, in the presence of propranolol, can reduce both I_{K1} and the muscarinic-cholinergic-receptor-mediated potassium current in rabbit atrial myocytes, resulting in action potential prolongation during the final phase of repolarization and a depolarization of the resting membrane potential. The depolarization of resting membrane potential tends to generate an abnormal action potential and leads to arrhythmia.

Most of the above evidence was found in animal models, and there are few studies in a human model. In the present experiments, we used phenylephrine (a mixed α_1- and β-agonist) and isoproterenol (a β-agonist), and a whole-cell voltage-clamp method to study the adrenergic modulation of potassium currents in human atrial cells.

Methods

Human Cardiac Specimens

Specimens of human right atrial tissues were obtained with consent from patients (16 to 59 years old) during the surgical procedure when starting the extracorporeal circulation. Samples were obtained from patients with coronary artery disease, rheumatic heart disease, and congenital heart disease. Immediately after surgical excision, the specimens were placed in a chilled oxygenated HEPES buffer solution containing (m*M*) NaCl 136, KCl 10.8, $MgCl_2$ 1.1, N-2-hydroxyethylpiperazine-N′-2-ethanesulfonic acid (HEPES) 10, dextrose 22, Ca 3 μ*M*, adjusted with NaOH to pH 7.5, and were transported from the operating room to the laboratory.

Cell Isolation

Single cells from human atrial tissue were prepared using an isolation procedure modified from that described by Escande et al. [13]. Briefly, myocardial specimens were chopped into small pieces with scissors, and placed in oxygenated modified HEPES buffer solution. Washout of blood and calcium from the tissue was aided by shaking (at 125 rpm, three times). After 10 min of wash, the chunks were incubated in a similar solution prewarmed to 35 °C, supplemented with 400 IU/ml collagenase type I (Sigma) and 4 IU/ml protease XXVII (Sigma) as an enzymatic solution. The supernatant was removed from the atrial tissue after 45 min digestion and discarded. Another fresh enzymatic solution containing collagenase alone at similar concentration was placed with the minced tissue. Microscopic examination of the enzymatic solution was used to assess the number and quality of isolated cells. The cells were separated from the medium by centrifugation at 2,000 rpm for 5 min. Afterwards, the cells were stored in a modified Kraftbrühe (KB) medium [13] at room temperature (25 ± 2 °C). The composition of the KB medium (in m*M*) was taurine 10, glutamic acid 70, KCl 25, KH_2PO_4 10, dextrose 22, ethylene glycol-bis(β-aminoethyl ether)N-N′-tetraacetic acid (EGTA) 0.5, adjusted with KOH to pH 7.3.

Recording Techniques

The whole-cell voltage-clamp technique was used to measure the ionic currents [20]. The myocytes were placed in an experimental chamber and bathed with an 'external solution' containing (in m*M*) NaCl 137, dextrose 11, $CaCl_2$ 2, KCl 5.6, $MgCl_2$ 1.1, HEPES 10, pH 7.4. The solution used to fill the glass pipettes (internal solution) contained (in m*M*): NaCl 10, KCl 120, $MgCl_2$ 5, MgATP 5, K_2EGTA 5, HEPES 10, adjusted to pH 7.2 by KOH. All experiments were performed at room temperature (25 ± 2 °C). The formation of a high-resistance seal was monitored by applying 1 nA current from a digital pulse generator. A high-resistance seal (5 to 10 GΩ) was obtained before the disruption of the membrane patch. The cells were dialyzed with the electrode solution for 10 min to reach a state of equilibrium after disruption of the membrane patch. In this voltage-clamp experiment, series resistance compensation was used to offset the series resistance due to the pipette tip resistance. Cell capacitance and series resistance were estimated from the capacitative transient produced by a 10-mV hyperpolarizing step from the resting membrane potential. Capacitance was defined as the ratio of the area under the current transient to the magnitude of the hyperpolarizing step. The holding potential was −80 mV. The potassium currents were elicited by 160 ms depolarization to levels between −60 and +60 mV or hyperpolarization to levels between −100 and −140 mV. Membrane currents measured at the start and end of 160-ms depolarization or hyperpolarization pulses were defined as peak and late current, respectively. Net transient outward current was obtained when the value of the late outward current was subtracted from the value of the peak outward current. The contamination of I_{Na} was reduced by 10 μ*M* tetrodotoxin (TTX). I_{Ca} was reduced by nifedipine (1 μ*M*) or $CdCl_2$ (0.2 m*M*).

Evaluation of Results

Recording was made through a Dagan 8900 voltage-clamp amplifier (Dagan Minneapolis, Minn., USA) and displayed on a storage oscilloscope (Model 511A, Tektronix, Beaverton, Oreg., USA) or a digital oscilloscope (TDS520, Tektronix) and photographed for subsequent analysis. Results are expressed as the means ± SE. Student's t test for paired data was performed to determine whether alterations produced by maneuvers on the same cell were statistically significant. Comparison of mean values among groups was done by one-way analysis of variance following a Student-Newman-Keuls test. Probability (p) values less than 0.05 were considered to be significant.

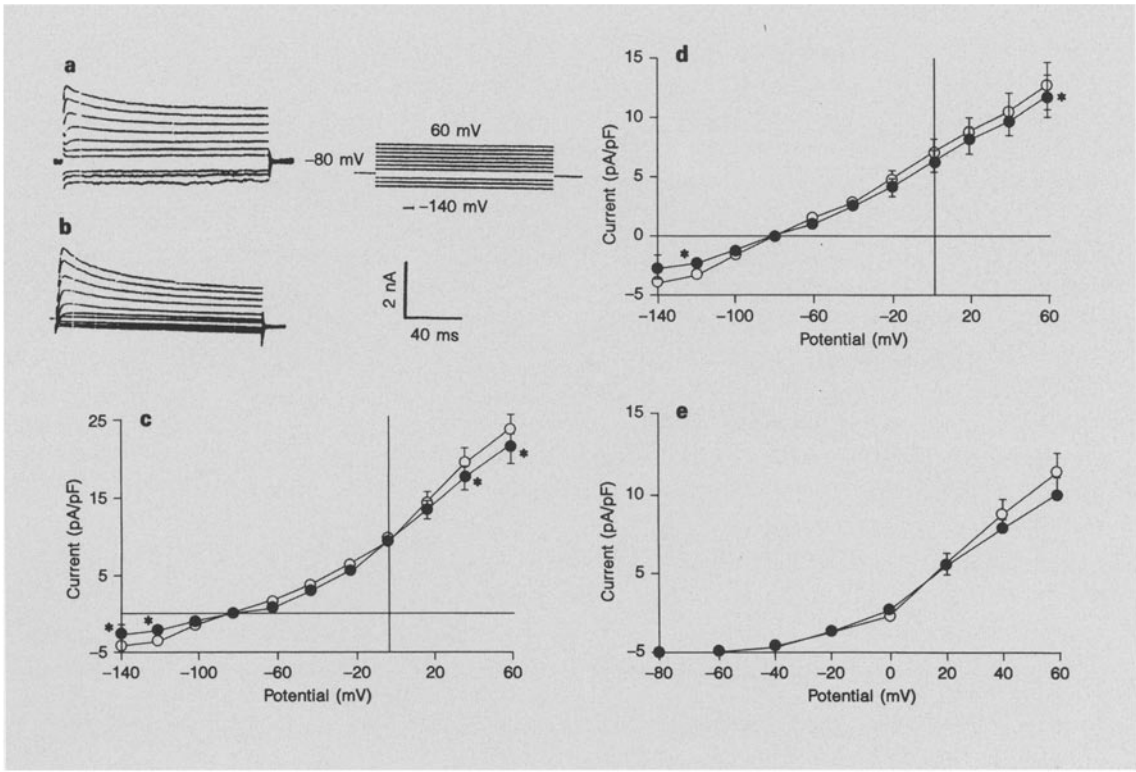


Fig. 1. Effects of phenylephrine on human atrial potassium currents. Family of potassium current traces obtained before (**a**) and after exposure to 30 μ*M* phenylephrine (**b**). Graphs show current-voltage relations between −140 and 60 mV of peak current (**c**), late current (**d**) and net transient outward current (**e**) before (○) and after (●) exposure to phenylephrine (n = 7). Data before and after exposure to phenylephrine were compared by the paired Student t test (* $p < 0.05$). Peak current was defined as the current measured at the start of depolarizations or hyperpolarizations minus the holding current. Late current was the current measured at the end of 160-ms depolarizations minus the holding current. Net transient outward current was defined as the peak outward current minus the late outward current.

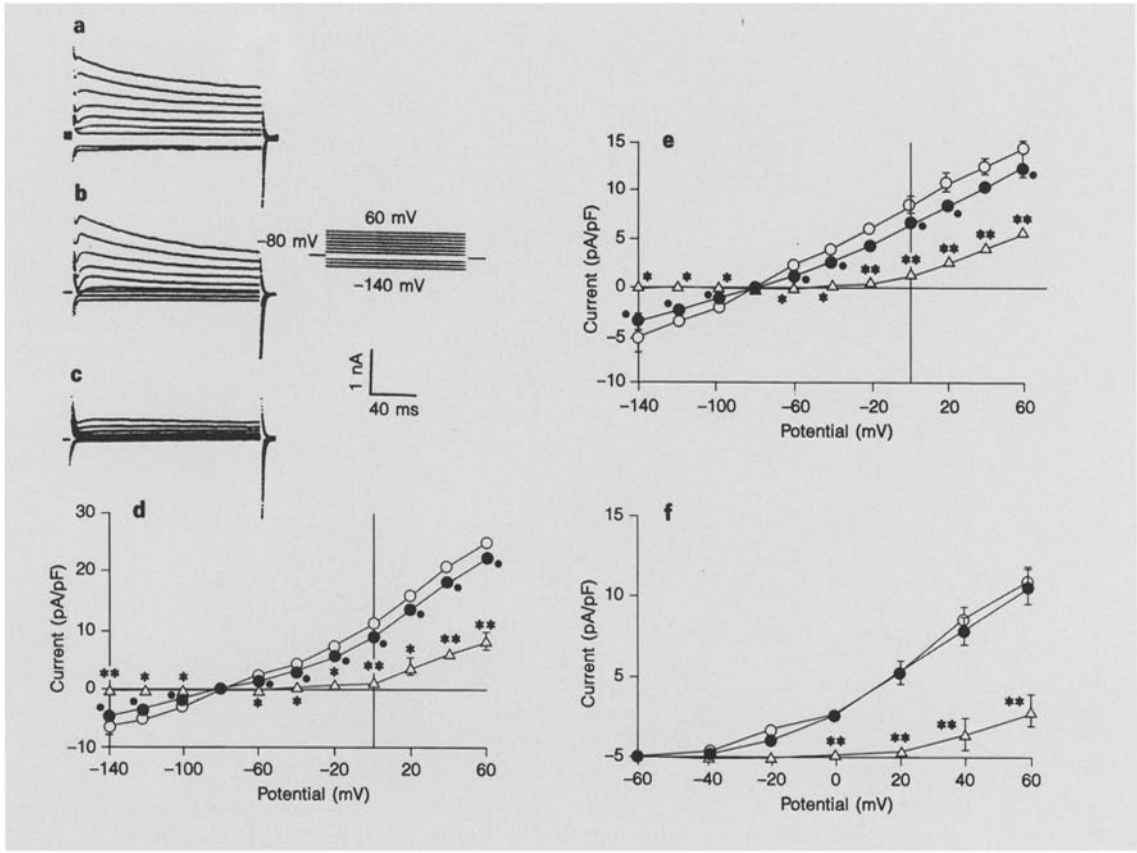
Drugs

L-phenylephrine hydrochloride, prazosin hydrochloride, (−)-isproterenol hydrochloride, atenolol, nifedipine and TTX were purchased from Sigma (St. Louis, Mo., USA). Nifedipine was dissolved in dimethylsulfoxide (DMSO) as a stock solution. The stock solution was diluted by the bathing solution to a given concentration. In control experiments, DMSO (up to 0.1%) alone had no discernible effect on the electrophysiological parameters.

Results

α-Adrenergic Modulation of Potassium Currents

When the cell was depolarized or hyperpolarized to potential levels between −60 and −140 mV, a small current through inwardly rectifying potassium channels (I_{K1}) was observed. In the presence of sodium and calcium channel blockers, a prominent peak transient outward current and late outward current were activated when the membrane potential was depolarized to levels positive to −40 mV. On exposure to 10 μ*M* phenylephrine, the magnitude of transient and late outward currents and I_{K1} was unaffected. On exposure to 30 μ*M* phenylephrine, a slight but significant suppression of all these currents was observed (fig. 1). For peak transient outward current, the average current (measured at 40 mV) in 7 cells was reduced by about 10.9 ± 3.6%. For I_{K1} measured at −120 mV, the average amplitude was reduced by about 31 ± 11.4%. To rule out the possible contamination of a β-adrenergic effect, the inhibitory effect of 30 μ*M* phenylephrine on the potassium current was examined in cells pretreated with 10 μ*M* atenolol, a selective β_1-adrenoceptor blocker. In these cells, 30 μ*M* phenylephrine reduced I_{K1} (measured at −120 mV) by about 24.1 ± 7.4% (n = 8). Depolarization-activated transient and late outward cur-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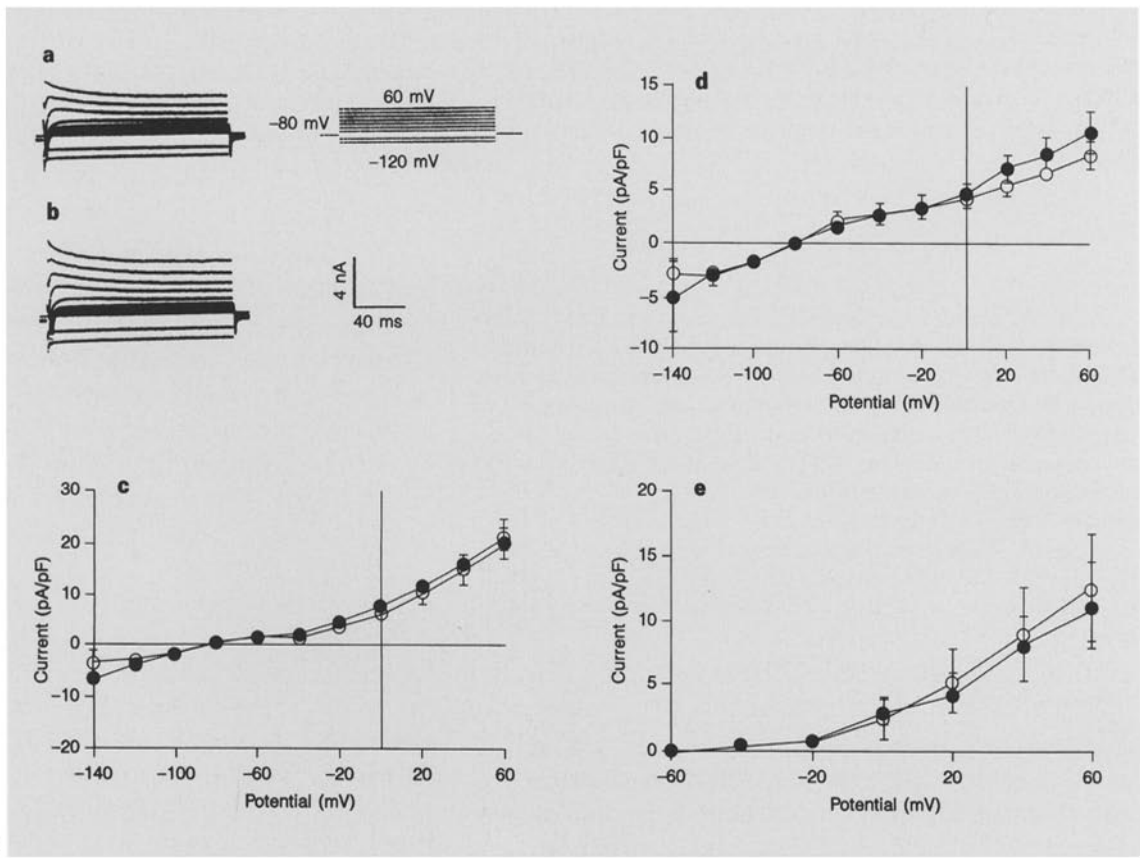
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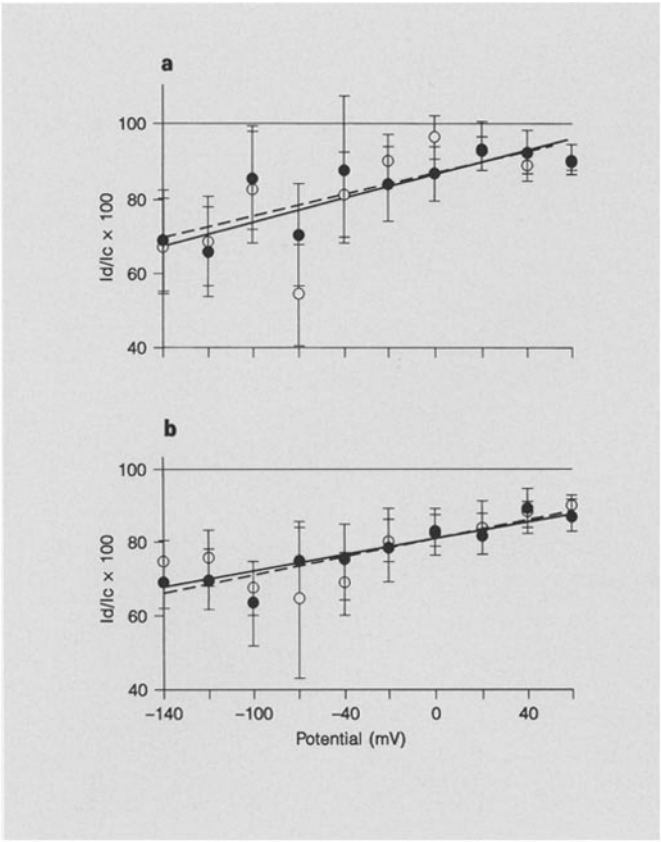

Fig. 4. Comparison of the percentage change of potassium current induced by 30 μ*M* phenylephrine in the absence (**a**) and presence (**b**) of a β-adrenergic blocker (10 μ*M* atenolol). Ic = Control current; Id = currrent obtained after treatment with 30 μ*M* phenylephrine; ○ = peak current; ● = late current.

Fig. 2. Effect of phenylephrine on potassium currents in human atrial cells pretreated with atenolol (10 μ*M*). A family of potassium current tracts obtained before (**a**) and after (**b**) exposure to 30 μ*M* phenylephrine, and final exposure to 1 m*M* $BaCl_2$ (**c**) are shown. Graphs show current-voltage relations between −140 and 60 mV of peak current (**d**), late current (**e**) and net transient outward current (**f**) before (○) and after (●) exposure to phenylephrine and $BaCl_2$ (△). Comparison of mean values among these three groups at each potential was significant by one-way analysis of variance (* $p < 0.05$; ** $p < 0.01$). Data before and after exposure to phenylephrine were compared by the paired Student t test (• $p < 0.05$), n = 7–11.

Fig. 3. Effects of phenylephrine on potassium currents in human cells pretreated with atenolol (10 μ*M*) and prazosin (1 μ*M*). Shown are a family of potassium current traces obtained before (**a**) and after (**b**) exposure to 30 μ*M* phenylephrine. Graphs show current-voltage relations between −140 and 60 mV of peak current (**c**), late current (**d**) and net transient outward current (**e**) before (○) and after (●) exposure to phenylephrine; n = 3.

rents were also reduced by phenylephrine (fig. 2). The potassium current which remained in the cells after treatment with 30 μ*M* phenylephrine could be further reduced by 0.2–1 m*M* $BaCl_2$ (fig. 2c). The remaining I_{K1} (measured at potentials between −60 and −140 mV) was blocked completely by barium. A similar suppression of all these currents by phenylephrine was also observed in cells pretreated with 1 μ*M* propranolol (data not shown). In cells pretreated with 1 μ*M* prazosin and 10 μ*M* atenolol, 30 μ*M* phenylephrine failed to inhibit these potassium currents. On the contrary, a slight increase of late outward current was observed at potentials positive to 0 mV (fig. 3).

β-Adrenergic Modulation of Potassium Currents

Fig. 4 shows the percentage change of potassium current induced by 30 μ*M* phenylephrine in the absence and presence of β-blocker. The extent of inhibition of I_{K1} (measured at potentials between −60 and −140 mV) by phenylephrine was unaffected by the absence and presence of the β-blocker. For the potassium outward current measured at potential levels positive to −60 mV, the extent of inhibition by phenylephrine was greater in the cells pretreated with β-blocker. Therefore, activation of the β-adrenoceptor by phenylephrine may enhance the depolarization-activated potassium outward current which then counterbalances the suppression of potassium outward current mediated by activation of α-adrenoceptors. This indication was further proved by exposure of the cells to 10–30 μ*M* isoproterenol, which led to an increase of the depolarization-activated potassium outward current at potentials positive to −20 mV (fig. 5). The sensitivity to isoproterenol seemed to differ in atrial myocytes from various patients. Isoproterenol could increase the net transient outward current only at potential levels between −40 and 0 mV (fig. 5e inset). Since this increase of the late outward current by isoproterenol was inhibited by 1 m*M* barium (data not shown), it is inferred that the increase of late outward current at positive potentials is not due to the increase of chloride influx (I_{Cl}) through chloride channels but to an increase of potassium outward current.

Discussion

This is the first report of adrenergic modulation on potassium currents in single human atrial cells using whole-cell voltage-clamp methods. Previously, the adrenergic modulation of the potassium current has only been shown in animal models.

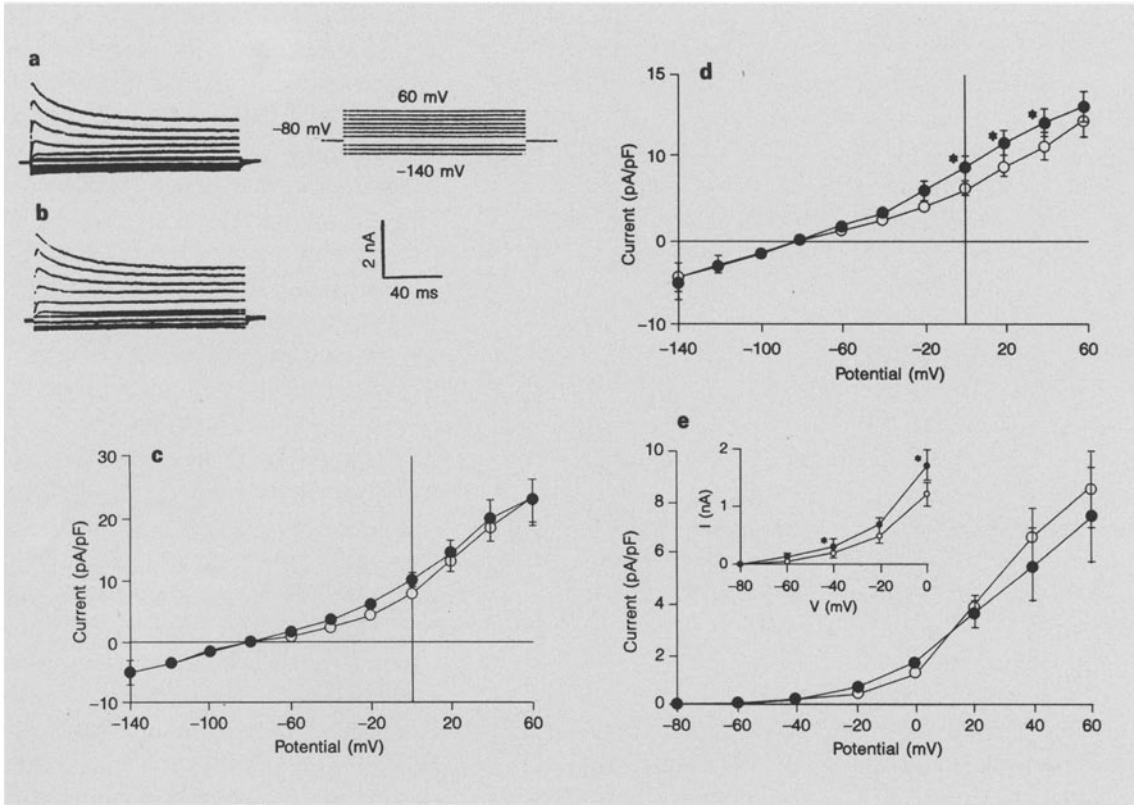

Fig. 5. Effects of isoproterenol on potassium currents in human atrial cells. Shown are a family of potassium current traces obtained before (**a**) and after (**b**) exposure to 30 μ*M* isoproterenol. Graphs show current-voltage relations between −140 and 60 mV of peak current (**c**), late current (**d**) and net transient outward current (**e**). Inset graph (in **e**) is an augmented view of the isoproterenol-elicited increase in net transient outward potassium current induced by a depolarized membrane potential to levels between −60 and 0 mV. Data before and after exposure to isoproterenol were compared by the paired Student t test (* $p < 0.05$); n = 5. ○ = control; ● = isoproterenol.

The existence of β-adrenoceptors in human atrial and ventricular tissues has been reported and confirmed by many groups [6, 26]. Human cardiac cells possess α_1-adrenoceptors [1, 3, 7, 11, 24, 36, 40]. This has been demonstrated by binding studies using selective α_1-adrenoceptor ligands, [^{3}H]prazosin or [^{125}I]IBE 2254. α-Adrenoceptor may serve as a reserve mechanism in the case of an impaired function of β-adrenoceptor.

Recently, evidence has been obtained that activation of α_1-adrenoceptors can affect transmembrane potassium currents in the heart. Four separate potassium currents are reduced by α_1-adrenoceptor activation. First, the voltage-activated transient outward current, which contributes to early repolarization in the heart [2, 15, 16, 42]. Second, a separate component of delayed rectifier current [34]. Third, the inwardly rectifying potassium current, which is responsible for maintaining a stable resting potential [14]. Fourth, $I_{K.Ach}$, the potassium channel activated via muscarinic receptors in the atrium [17, 30]. It seems likely that the physiological effects of α_1-adrenoceptors may be explicable in terms of their actions on potassium currents in many tissues and species. For example, a reduction in depolarization-activated transient and late outward potassium currents in the heart can slow repolarization of the action potential which may contribute to the positive inotropic action and negative chronotropic effect.

It has been reported that transient outward and inwardly rectifying potassium currents exist in human atrial myocytes [13, 21, 39]. According to our results, both the outward and inwardly rectifying potassium current were reduced by 30 μ*M* phenylephrine (fig. 1). Further reduction of potassium currents was observed in human atrial cells pretreated with atenolol (fig. 2). Since the reduction

of the potassium currents was prevented by pretreatment with an α_1-blocker (fig. 3), this effect was mediated by activation of α_1-adrenoceptors. The depression of the outward potassium current will increase the action potential plateau and prolong action potential duration. The depression of inwardly rectifying potassium current will decelerate the late repolarization of the action potential, which will then contribute to the generation of early afterdepolarizations or triggered activities. The suppression of I_{K1} may also contribute to the increase in automaticity [28, 29]. Since the inhibition of depolarization-activated potassium outward current by phenylephrine may prolong action potential duration and be antiarrhythmic, this effect opposes the arrhythmogenic effect induced by its inhibition of I_{K1}. The percentage of inhibition of I_{K1} by phenylephrine was found in our study to be higher than its inhibition of depolarization-activated outward current (fig. 4). Thus, activation of α-adrenergic receptors on human atria may result in arrhythmia rather than antiarrhythmia.

An isoproterenol-induced increase in the delayed rectifier potassium current (I_K) in frog atrium was first reported by Brown and Noble [10]. Results in agreement with their observation have been observed by others in multicellular [43] and single-cell [27, 32] preparations from mammalian heart. In our present study, late outward potassium current in human atrial cells was also significantly increased by 10–30 μ*M* isoproterenol (fig. 5). It has been reported that there are both transient outward [13] and delayed rectifier potassium currents [47] in human atrial cells. Our data suggest that isoproterenol may affect the delayed rectifier potassium current in human atrial myocytes. However, the type(s) of potassium current affected by isoproterenol needs further investigations.

The responsiveness of human cardiac tissues to α_1-adrenoceptor stimulation can be affected by several factors. These include prior condition of the heart (e.g., failing versus nonfailing), types of disease, exposure of cardiac muscle to different drugs, and the procedure of tissue removal during surgery and further manipulations of the specimens. The absolute number of α_1-adrenoceptors does not change or even increase during the development of cardiac failure [8, 40, 41]. Because there is no reduction of cardiac α-adrenoceptors but an increased ratio of α- to β-adrenoceptors, α-adrenoceptors might contribute to the maintenance of cardiac function in which β-adrenoceptor-mediated responses are severely impaired [3, 5].

Because of the differential changes of α- and β-adrenoceptors under pathological conditions, it is impossible to extrapolate the effects of catecholamines on preparations from healthy animals to human hearts with different cardiac diseases. The electrophysiological function of α_1- and β-adrenoceptor in the human heart mediating a decrease and increase of potassium current, respectively, may stimulate further research on the possible role of these receptor systems in cardiac diseases such as dilative and hypertrophic cardiomyopathy. Thus, examinations of the effects of drugs in human heart cells from patients with cardiac disease can provide new insights into the pathophysiology and pathopharmacology. Within the limits of surgical technical difficulties and ethical considerations, further studies to compare the different effects of catecholamines on cardiac cells from normal hearts and hearts from patients with well-defined stages of heart diseases are required.

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