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Pioglitazone Improves Potassium Channel Remodeling Induced by Angiotensin II in Atrial Myocytes

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Background: It has been demonstrated that atrial electrical remodeling contributes toward atrial fibrillation (AF) maintenance, and that angiotensin II (AngII) is involved in the pathogenesis of atrial electrical remodeling. Peroxisome proliferator activated receptor-γ (PPAR-γ) agonists have been shown to inhibit atrial electrical remodeling, but the underlying mechanisms are poorly understood. In the present study we investigated the regulating effects of PPAR-γ agonist on AngII-induced potassium channel remodeling in atrial myocytes.

Material/Methods: Whole-cell patch-clamp technique was used to record transient outward potassium current (Ito), ultra-rapid delayed rectifier potassium (Ikur), and inward rectifier potassium current (Ik1). Real-time PCR was used to assess potassium channel subunit mRNA expression.

Results: Compared with the control group, AngII reduced Ito and Ikur current density as well as amplified Ik1 current density, which were partially prevented by pioglitazone. Furthermore, pioglitazone alleviated the downregulation of Ito subunit (Kv 4.2) and Ikur subunit (Kv 1.5), as well as the upregulation of Ik1 subunit (Kir 2.1 and Kir 2.2) mRNA expression stimulated by AngII.

Conclusions: These results suggest that pioglitazone exhibits a beneficial effect on AngII-induced potassium channel remodeling. PPAR-γ agonists may be potentially effective up-stream therapies for AF.

MeSH Keywords: Angiotensin II • Atrial Fibrillation • Atrial Remodeling • Potassium Channels • PPAR gamma

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Background

Atrial fibrillation (AF) remains the most common arrhythmia in humans and causes substantial morbidity and mortality [1]. The prevalence of AF is growing in aging populations and the complications of AF are become increasingly burdensome [1]. The mechanisms underlying AF remain elusive, and atrial electrical remodeling has emerged as crucial in the onset or persistence of AF. Electrical remodeling, such as changes in major repolarized ion channels, leads to the shortening of the action potential duration (APD) and the effective refractory period (ERP), and results in an increase in atrial conduction slowing, re-entry, and, thereby, inducible AF [1]. There is considerable interest in the role of the renin-angiotensin-aldosterone system (RAAS) in the development of atrial remodeling and AF. It has been shown that atrial electrical remodeling in part is due to the activation of the RAAS. Angiotensin II (AngII) has been implicated in the process of atrial electrical remodeling characterized by ion channels remodeling as well as shortening of the APD and ERP [1–3].

Thiazolidinediones (TZDs), agonists of peroxisome proliferator-activated receptor-γ (PPAR-γ), have been proven to have anti-inflammatory and anti-proliferative effects induced by AngII in addition to their anti-diabetic activities [4–8]. Recent studies have shown that PPAR-γ agonist pioglitazone inhibited age-related [8] or congestive heart failure-induced [7] atrial electrical remodeling as well as AF promotion. Our previous study indicated that pioglitazone is capable of alleviating AngII-induced L-type calcium channel (ICa-L) remodeling in atrial myocytes [9].The present study was designed to investigate the effects of pioglitazone on AngII-induced potassium channels remodeling, including transient outward potassium current (Ito), ultra-rapid delayed rectifier potassium (Ikur), and inward rectifier potassium current (Ik1) of atrial myocytes.

Material and Methods

Culture of atrial myocytes (HL-1)

HL-1 cells (mouse atrial myocytes) were obtained from the laboratory of Dr. William Claycomb (Louisiana State University Health Science Center, New Orleans, LA). Cells were cultured in Claycomb medium (JRH Biosciences, USA) supplemented with 10% fetal bovine serum (JRH Biosciences, USA), 2 mM L-glutamine (Gibco, USA), 100 μM norepinephrine (Sigma, USA), 100 U/ml penicillin, and 100 μg/ml streptomycin (Gibco, USA) on flasks pre-coated with fibronectin and gelatin (Sigma, USA), then incubated at 37°C, 5% CO_2/95% air. The medium was changed every 24–48 h. HL-1 cells were placed in serum-free medium for 24 h before AngII (1 μM, Sigma, USA) stimulation.

Whole cell patch clamp in HL-1 cells

HL-1 cells were isolated from the culture dishes after treatment with AngII and/or pioglitazone for 24 h using enzymatic dissociation for 2 min with 0.05% trypsin-EDTA (Gibco, USA). Digestion was arrested with 0.025% trypsin inhibitor and medium, and the sediment cells were used for experimentation within 6 h. Cells were observed using an inverted microscope (Nikon, JAPAN) and allowed to adhere to the bottom of the dish.

For Ito and Ikur current recording [10,11], the internal PIPette solution contained (in mM) KCl 45, K-aspartate 85, Na-pyruvate 5, MgATP 5.0, EGTA 10, HEPES 10, and glucose 11 (pH 7.4), while the bath solution contained (in mM) N-methyl-D-glucamine (NMG) 149, $MgCl_2$ 5, $CaCl_2$ 0.65, and HEPES 5. To block Ik1 and Ica, $BaCl_2$ (200 μM) and $CdCl_2$ (200 μM) were added to the superfusion. For Ik1 recording[12], the internal PIPette solution contained (in mM) NaCl 5, KCl 40, KF 100, EGTA 5, EDTA 3, glucose 5, K4P2O7 10, $NaVO_3$ 0.1, and HEPES 10 (pH7.4), while the bath solution contained (in mM) NaCl 132, $CaCl_2$ 1.8, KCl 20, $MgCl_2$ 10, glucose 10, and HEPES 10 (pH 7.4). Dof (5 nM), TTX (100 μM), and $CdCl_2$ (200 μM) were added to the superfusion to block Ikr, Ina, and ICa. Tip potentials were compensated before the pipette touched the cell. After a gigaseal was obtained, the cell membrane was ruptured by gentle suction to establish the whole-cell configuration. Current signals were recorded with an EPC-10 amplifier using the pulse+pulsefit 8.53 data-acquisition system (HEKA Instruments). Signals were filtered at 5 kHz and stored on a computer. Series resistances (Rs) were 3–5 MΩ and were electrically compensated by 70–80% to minimize the capacitive surge on the current recording and voltage drop across the clamped membrane, and were maintained at a constant value during the current recording. The holding potential was kept at –80 mV. Ito was elicited by 300-ms test pulses between –40 and +50 in 10 mV increments, and verapamil (10 μM) was added to inhibit Ikur [13]. IKur stimulus consisted of 300 ms of incremental 10-mV voltage steps from –50 mV to +70 mV, preceded by a 200-ms prepulse to +30 mv to inactivate Ito. Ik1 was recorded by 300-ms test pulses between –150 and +10 mV in 20-mV increments. Peak current levels were plotted as a function of the command potential. To account for differences in cell size, all mean data are expressed as current density. The action of AngII in the presence and absence of pioglitazone was analyzed for its effects on the current-to-voltage (I–V) relationship. All experiments were performed at 25°C.

Quantitative real-time PCR

Total RNA was extracted from HL-1 cells with TRIzol (Invitrogen, USA) and used to synthesize single-stranded complementary DNA with a high-capacity complementary DNA reverse transcription kit (Toyobo, JAPAN). Quantitative real-time RT-PCR

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Table 1. Real-time PCR primer sequences.

Target (bp)	Forward primer	Reverse primer
GAPDH (124)	AACTTTGGCATTGTGGAAGG	GGATGATGTTCTGGGCAGC
Kv4.2 (126)	GCAAGCGGAATGGGCTAC	TGGTTTTCTCCAGGCAGTG
Kv1.5 (123)	TCAAGGAAGAGGAGAAGCCC	GAATGACCAAGACCGACACG
Kir2.1 (186)	TGAAGTTGCCCTAACAAGCA	AAAGTAAGTATGACAAAGACGGAA
Kir2.2 (167)	CGCCAACTCTTTCTGCTATG	ATCTCCGACTCCCGTCTGT

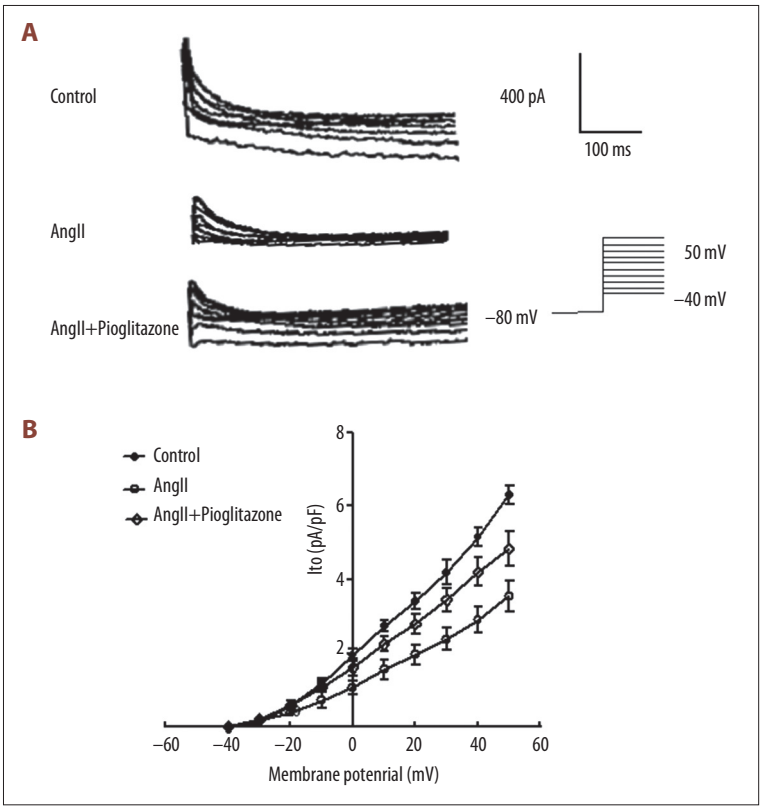

Figure 1. Effect of pioglitazone on AngII inducing current-voltage (I–V) curve change of Ito in HL-1 cells. Quiescent HL-1 cells were pretreated with pioglitazone (10 μM) or vehicle for 60 min then stimulated with 1 μM AngII for 24 h. (**A**) Representative recordings of whole-cell Ito are shown for the control, AngII, and AngII+pioglitazone. (**B**) Ito current density-voltage (I–V) curve in control, AngII, and AngII+pioglitazone. Data represent means ±SD of 5 independent experiments.

involved the use of gene-specific primers [14] (see Table 1 for details) and SYBR kit (Takara, JAPAN). GAPDH was used as an internal control. Results are expressed as fold difference for each gene against GAPDH by the use of the $2^{-\Delta\Delta}$CT method. A melting-point dissociation curve generated by the instrument was used to confirm that only a single product was present.

Statistical analysis

Statistical analysis was performed using SPSS 16.0 software. All data are expressed as mean ±SD. The differences between all measured values were assessed by one-way ANOVA followed by Dunnett post hoc test. A value of $P < 0.05$ was considered statistically significant.

Results

The effects of AngII and/or Pioglitazone on Ito

Figure 1 shows AngII (1 μM) reduced the peak of Ito current density from 6.3±0.6 pA/pF to 3.6±0.4 pA/pF ($P<0.01$) at 50 mV compared with the control group, but the addition of pioglitazone (10 μM) markedly alleviated this change (4.8±1.0 pA/pF *vs.* 3.6±0.4 pA/pF, $P<0.05$). Furthermore, AngII made the I–V curve shift downward compared with the control group, but preincubation with pioglitazone partially prevented AngII-induced alteration.

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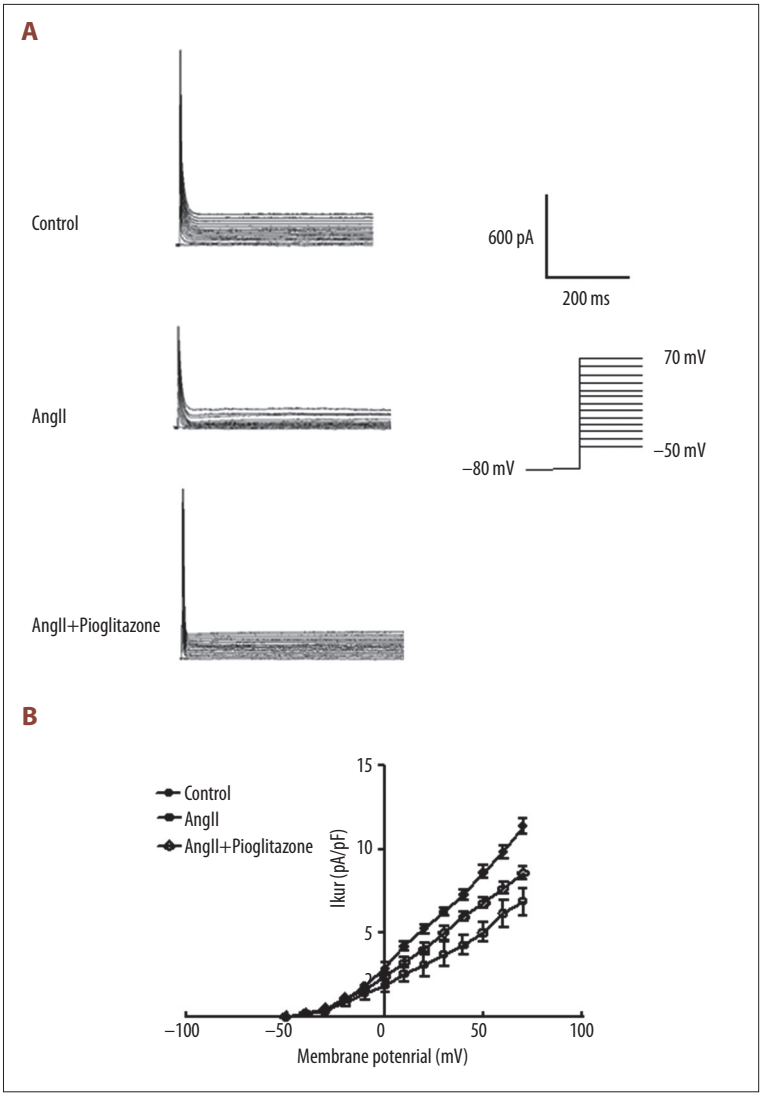

Figure 2. Effect of pioglitazone on AngII inducing current-voltage (I–V) curve change of Ikur in HL-1 cells. Quiescent HL-1 cells were pretreated with pioglitazone (10 μM) or vehicle for 60 min, then stimulated with 1 μM AngII for 24 h. (**A**) Representative recordings of whole-cell Ikur are shown for the control, AngII, and AngII+pioglitazone. (**B**) Ikur current density-voltage (I–V) curve in control, AngII, and AngII+pioglitazone. Data represent means ±SD of 5 independent experiments.

The effects of AngII and/or Pioglitazone on Ikur

AngII (1 μM) inhibited the peak of Ikur current density from 11.4±1.1 pA/pF to 6.9±0.8 pA/pF (P<0.01) at 70 mV compared with the control group, while pretreatment of cells with pioglitazone had an inhibitory effect (8.6±0.8 pA/pF *vs.* 6.9±0.8 pA/pF, P<0.05, Figure 2). Moreover, AngII made the I–V curve shift downward but pioglitazone alleviated the changes (Figure 2).

The effects of AngII and/or Pioglitazone on Ik1

In contrast to the control group, AngII (1 μM) amplified the peak of Ik1 current density from –6.1±0.6p A/pF to -10.1±1.1 pA/pF (P<0.01) at –150 mV. However, pretreatment with pioglitazone (10 μM) markedly suppressed AngII-induced amplification of Ik1 peak current density (–7.9±0.6 pA/pF *vs.* –10.1±1.1 pA/pF, P<0.01, Figure 3). AngII made the I–V curve shift downward, but pioglitazone partially prevented AngII-induced change (Figure 3).

Gene expression of potassium channels in atrial myocytes

Since the above results revealed a functional change in potassium channel activities carrying Ito, Ikur, and Ik1 in atrial myocytes treated with AngII and/or pioglitazone, we analyzed the expression levels of the genes encoding Ito (Kv4.2), IKur (Kv1.5), and IK1 (Kir2.1 and Kir2.2). The mRNA expression of Kv4.2 and Kv1.5 in the AngII group (1 μM) was significantly decreased compared with the control group, but the mRNA expression of Kir2.1 and Kir2.2 in the AngII group (1 μM) was markedly increased compared with the control group. Pretreatment with pioglitazone (10 μM) could in part reverse the aforementioned changes (Figure 4).

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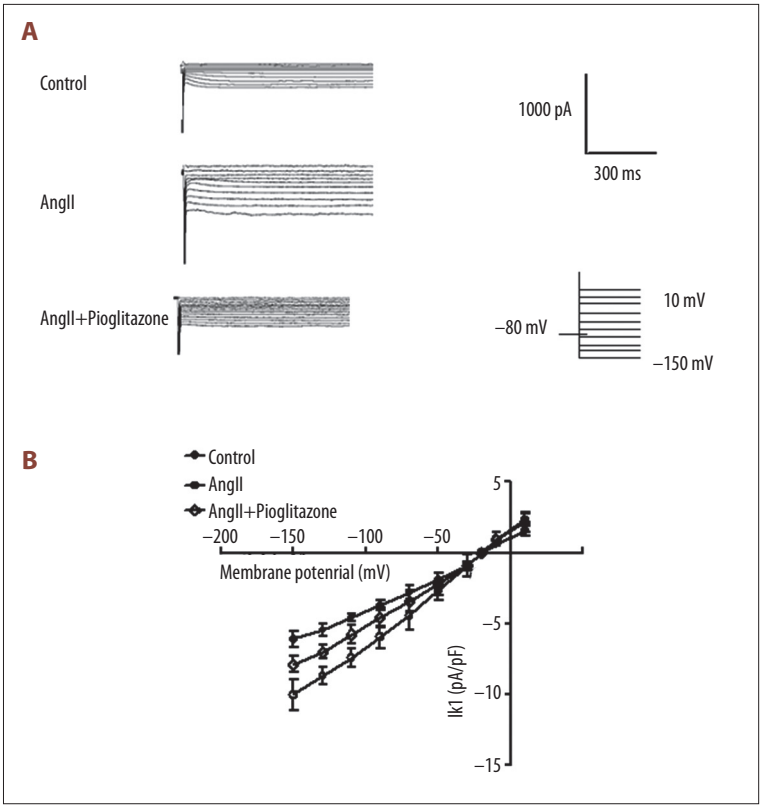

Figure 3. Effect of pioglitazone on AngII inducing current-voltage (I–V) curve change of Ik1 in HL-1 cells. Quiescent HL-1 cells were pretreated with pioglitazone (10 μM) or vehicle for 60 min, then stimulated with 1 μM AngII for 24 h. (**A**) Representative recordings of whole-cell Ik1 are shown for the control, AngII, and AngII+pioglitazone. (**B**) Ik1 current density–voltage (I–V) curve in control, AngII, and AngII+pioglitazone. Data represent means ±SD of 5 independent experiments.

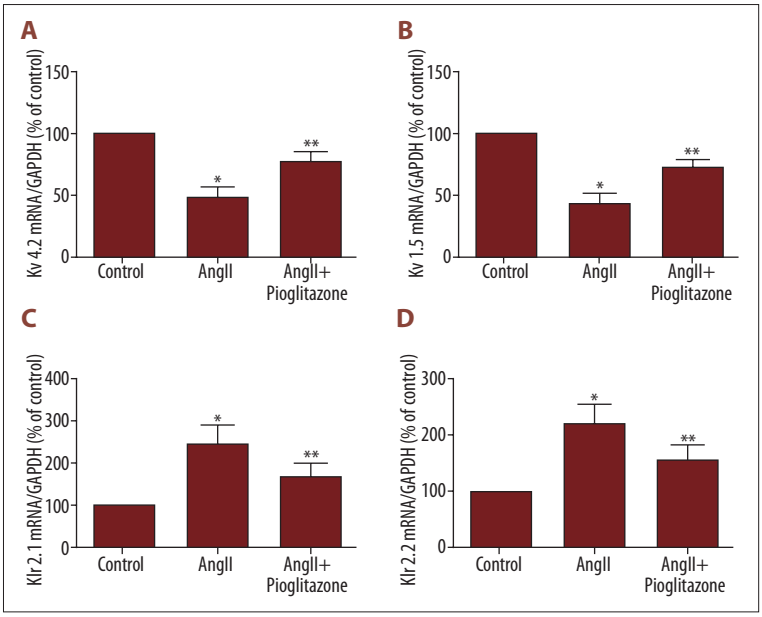

Figure 4. Effect of pioglitazone on AngII inducing mRNA expression change of potassium channel subunit in HL-1 cells. * P<0.01 *vs.* control; ** P<0.01 *vs.* AngII.

Discussion

The major findings of the present study are: (1) AngII significantly inhibited Ito, Ikur, and amplified Ik1 current density in atrial myocytes, which were in part reversed by PPAR-γ agonist pioglitazone (2). Correspondingly, downregulation of Kv4.2 (encoding Ito) and Kv1.5 (encoding Ikur) and upregulation of Kir 2.1, Kir 2.2 (encoding Ik1) were evident in mRNA levels in AngII-treated atrial myocytes, which was also inhibited by pioglitazone.

AF is a highly prevalent condition associated with pronounced morbidity and mortality, which can cause or exacerbate heart failure and is an important risk factor for stroke [1]. AF is

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characterized by atrial electrical remodeling, which favors arrhythmia recurrence and maintenance. A prominent feature of the electrical remodeling associated with AF is abbreviation of APD and ERP [1]. Such alterations in atrial electrical properties are caused by derangements in the ion channel. It is well known that cardiac repolarization and action potential duration are mainly dependent on the balance of Ca^{2+} current and K^+ currents [15].

AngII plays an important role in electrical remodeling. Our previous study found that AngII increased ICa-L α1C subunit expression and current density in atrial myocytes [9]. AngII stimulation shortened APD and augmented calcium transient, thus increasing the electrochemical gradient of forward-mode sodium-calcium exchanger (NCX) current and induced frequent irregular after-depolarizations and fibrillatory-like complex electrogram [16]. It was also demonstrated that blockade of AngII with angiotensin-converting enzyme inhibitor (ACEI) and/or AngII type I receptor (AT1R) antagonist slowed the progression of atrial remodeling and AF in both experimental and human diseases [17–19]. In the present study, we found that AngII significantly inhibited Ito and Ikur current density, amplified Ik1 current, and changed their channel subunit expression.

AngII-induced changes in Ito, Ikur, and Ik1 current densities in atrial myocytes quantitatively parallel changes in mRNA levels for corresponding ionic channel subunits, suggesting that transcriptional modulation is a central mechanism of AngII-induced ionic remodeling. Ik1 contributes to late repolarization and stabilizes the resting membrane potential (RMP). Upregulation of Ik1 induced by AngII may contribute to the shortening of APD and ERP [20]. Ito contributes significantly to the early repolarization phase of the human atrial action potential (AP), which is analogous to its contribution to phase 1 repolarization in ventricular myocytes. Ikur, a sustained outward current that is expressed in atrial but not ventricular myocytes, contributes to both early and late repolarization in the atrial myocytes. The decline of Ito and Ikur may not explain the shortening of APD and ERP, because the reduction of outward K+ flow will lead to extension of APD and ERP. This may be explained by the fact that AngII-induced increase in intracellular calcium may induce calcium overload, which is speculated to modulate various potassium ion channels to protect the cardiomyocytes against further cellular stress and lethal cell damage. One possible hypothesis is that the reduced expression of potassium channel is attributed to the self-adaption of the atrium [21–23]. AngII also leads to structural changes in atrial myocytes, the expression of proteolytic enzymes can be increased in the atrial tissues, and the neutral protease (such as calpains) be activated. These enzymes can lead to degradation of skeleton proteins, membrane proteins, and regulatory protein, and also influence the expression of potassium ion channels [24,25]. The decrease in Ito and Ikur is considered to result in loss of physiological rate adaptation of the action potential.

Other studies indicated that a marked reduction of Ito current density has been reported [1,26–29], while IK1 was found to be increased or unchanged [27,28,30,31] and IKur was decreased or unchanged [26–28,31] in various models of rapid atrial pacing, AF, or AngII stimulation. This may be explained by the fact that different models or species were used in different experiments, such as animal models or *in vitro* cultured cardiomyocytes, and mouse atrial myocytes or human atrial myocytes.

PPAR-γ agonists such as pioglitazone are clinically well-established insulin-sensitizing and hypoglycemic agents. Besides their anti-diabetic action, they exhibit anti-inflammatory and anti-fibrotic effects, and have been shown to prevent left ventricular hypertrophy [7], age-related [8] atrial arrhythmogenic remodeling, and AF perpetuation, as well as to reduce the AF duration and atrial fibrosis in a model of ventricular pacing-induced congestive heart failure (CHF) [6]. Recently, Chao et al. demonstrated that rosiglitazone reduced the risk of new-onset AF by 31% after adjustment for age, underlying diseases, and baseline medications in 12 605 diabetic patients during a follow-up period of 5 years [32]. Furthermore, our previous study indicated that pioglitazone reduced AF recurrence following catheter ablation during a 23-month follow-up period in 150 diabetic patients [33]. Our prior experimental research added further evidence to the benefits of pioglitazone for the prevention of AF substrate development by demonstrating that this PPAR-γ agonist was capable of attenuating characteristic aspects of AngII-induced electrical remodeling. In HL-1 cardiomyocytes, pioglitazone prevented the AngII-dependent induction of the mRNA and protein expression of ICa-L α1c, with similar effects on ICa-L current density [9]. Another PPAR-γ agonist rosiglitazone was also shown to attenuate arrhythmogenic atrial remodeling and AF promotion in alloxan-induced diabetic rabbits [4].

In the present study, we found that AngII-induced alterations of potassium channel currents and subunit expression were alleviated by pioglitazone. These effects may account for significant cardiac protection against atrial electrical remodeling and AF. In line with our results, another study indicated that PPAR-γ activation improved the molecular and functional components of Ito remodeling by AngII [5]. As regards the molecular mechanisms, we found that pioglitazone inhibited AngII-induced CAMP responsive element binding protein (CREB) Ser 133 phosphorylation in HL-1 cells, which might be at least in part related to its inhibitory effect on ICa-L electrical remodeling [9]. Our prior results also showed that the beneficial effects of PPAR-γ agonists on AngII-induced atrial electrical remodeling might be related to AT1R downregulation and PPAR-γ upregulation [9]. It has been reported that PPAR-γ agonist-mediated

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modulation of AT1R is associated with suppression of the activity of the AT1R promoter [34]. Moreover, PPAR-γ agonists seem to alleviate AngII-induced atrial electrical remodeling or AF promotion by virtue of its inhibitory effect on oxidative stress and inflammation [4]. Another study also indicates that the protective effect of PPAR-γ agonists on cardiomyocyte Ito is dependent on preventing NADPH oxidase activation and the ensuing reactive oxygen species (ROS) formation [5].

Study limitations

Our current study had some limitations that should be mentioned. First, the major limitation of the current study is that no *in vivo* model was used to verify the *in vitro* finding. Second, we did not evaluate the effect of pioglitazone on AngII-induced potassium channel remodeling *in vitro* in dose-dependent manners and recommended dosage was adopted according to previous studies [9,35,36]. Third, besides the I–V curve, we did not analyze the voltage dependence of potassium channel inactivation and activation curves or the time course of recovery from inactivation. Fourth, we only analyzed the mRNA level of potassium channel subunit, but the protein level was not determined.

Conclusions

Collectively, we have demonstrated that the PPAR-γ agonist, pioglitazone, significantly inhibits AngII-induced Ito, Ikur, and Ik1 remodeling. Further studies are needed to determine if pioglitazone is effective against AF.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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