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Can the Electrophysiological Action of Rosiglitazone Explain its Cardiac Side Effects?

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Abstract

Recent large clinical trials found an association between the antidiabetic drug rosiglitazone therapy and increased risk of cardiovascular adverse events. The aim of this report is to elucidate the cardiac electrophysiological properties of rosiglitazone (R) on isolated rat and murine ventricular papillary muscle cells and canine ventricular myocytes using conventional microelectrode, whole cell voltage clamp, and action potential (AP) voltage clamp techniques.

In histidine-decarboxylase knockout mice as well as in their wild types R (1–30 μM) shortened AP duration at 90% level of repolarization (APD_{90}) and increased the AP amplitude (APA) in a concentration-dependent manner. In rat ventricular papillary muscle cells R (1–30 μM) caused a significant reduction of APA and maximum velocity of depolarization (V_{max}) which was accompanied by lengthening of APD_{90} .

In single canine ventricular myocytes at concentrations 10 μM R decreased the amplitude of phase-1 repolarization, the plateau potential and reduced V_{max} . R suppressed several ion currents in a concentration-dependent manner under voltage clamp conditions. The EC_{50} value for this inhibition was 25.2 ± 2.7 μM for the transient outward K^+ current (I_{to}), 72.3 ± 9.3 μM for the rapid delayed rectifier K^+ current (I_{Kr}), and 82.5 ± 9.4 μM for the L-type Ca^{2+} current (I_{Ca}) with Hill coefficients close to unity. The inward rectifier K^+ current (I_{K1}) was not affected by R up to concentrations of 100 μM . Suppression of I_{to} , I_{Kr} , and I_{Ca} has been confirmed under action potential voltage clamp conditions as well.

The observed alterations in the AP morphology and densities of ion currents may predict serious proarrhythmic risk in case of intoxication with R as a consequence of overdose or decreased elimination of the drug, particularly in patients having multiple cardiovascular risk factors, such as elderly diabetic patients.

Keywords

Antidiabetic agents; rosiglitazone; action potential; ion currents

INTRODUCTION

Diabetes mellitus is associated with increased risk of cardiovascular disease sometimes resulting in sudden cardiac death. Patients with diabetes mellitus exhibit a high incidence of diabetic cardiomyopathy, characterized by complex changes in the electrical and mechanical properties of the heart [1, 2]. The most prominent electrical alteration is the prolongation of the QTc interval and increased QTc dispersion. In the isolated cardiomyocytes of diabetic rats, significant prolongation of APD and reduction of K⁺ currents were reported [3, 4]. Cardiac K⁺ currents (I_{to}, I_{Ks}, and the steady-state outward current, I_{ss}) are regulated in a complex manner and its amplitude or density depends on several factors such as cell type, age, species, pathological state of the heart, and various neurohormonal factors. Reduction of these currents has been associated with altered action potential profiles in diabetic heart models [4–6].

As the incidence of type 2 diabetes mellitus (T2DM) continues to increase, the World Health Organization predicts approximately 300 million cases worldwide by the year 2010. During the selection of the most appropriate antidiabetic drug for the T2DM patients, the benefit/risk ratio (benefits *versus* side effects) of the chosen compounds beyond the individual state of the patient should be considered. Recently two widely used thiazolidinediones (TZDs) - rosiglitazone and pioglitazone - became well-established elements of treatment algorithm of T2DM [7]. These drugs, by increasing insulin sensitization, result in a strong and long lasting improvement of glycemic control which may be related to their potential β -cell preserving properties [8–10]. In spite of multiple beneficial effects of these drugs several large scale clinical trials associated thiazolidinedione therapy with adverse cardiovascular (CV) consequences (weight gain, edema, heart failure) [11–14]; and in the case of rosiglitazone an increased risk of acute myocardial infarction was also observed [15]. This latter risk of rosiglitazone therapy resulted in the suspension or restricted access to rosiglitazone in some countries [16, 17].

We hypothesized that rosiglitazone may adversely affect electrophysiological properties of the heart, thus we aimed to study the effects of the drug on action potential morphology in three different mammalian (mouse, rat, and canine) cardiac preparations.

1. GENERAL OVERVIEW OF THIAZOLIDINEDIONES

TZDs, including pioglitazone and rosiglitazone, are oral antidiabetic drugs for the treatment of T2DM. Their chemical structure is presented in Fig. (1). TZDs are high affinity ligands for the nuclear receptor peroxisome-proliferator-activated receptor γ (PPAR γ) [18, 19] which regulates genes involved in the metabolism of glucose and fat. PPAR γ regulates a diverse array of physiological processes including adipogenesis, lipid metabolism, and insulin sensitivity, as well as an important player in the pathogenesis of diseases such as obesity, diabetes, and atherosclerosis [20, 21, 22, 23]. Among TZDs the full PPAR γ agonist rosiglitazone and pioglitazone have been widely used in clinical practice, while others (e.g. troglitazone) were discontinued due to their hepatotoxicity [19, 24]. To separate the desirable, beneficial and adverse negative side effects of the currently available PPAR γ agonists, several drug-discovery programs have attempted to identify PPAR γ partial agonists having appropriate antidiabetic efficacy with less adverse actions [25–27]. Chemical structures of some representative partial PPAR γ agonists are shown in Fig. (2). Balaglitazone is a novel thiazolidinedione under clinical development for the treatment of T2DM. Balaglitazone is a selective partial agonist of PPAR γ , with similar antihyperglycemic efficacy to that of rosiglitazone, but less pronounced body fluid retention properties than rosiglitazone [25]. Compound 50 and MK-0533 are partial PPAR γ agonists

being in preclinical phase of development, both exerting marked antidiabetic activity with less adverse effects [26, 27].

2. CARDIOVASCULAR EFFECTS OF THE MOST COMMONLY USED TZDs

These drugs improving the insulin-sensitivity in adipose tissue and skeletal muscle stimulate the expression and function of glucose transporters in the myocardium, resulting in improved glucose metabolism by the heart [28–33].

Beyond improving glycemic control, TZDs may provide some other therapeutic benefits including vasorelaxant, antihypertensive, anti-inflammatory effects [34–38].

Both rosiglitazone and pioglitazone are known to modify the lipid profile as well. Rosiglitazone increases low-density lipoprotein cholesterol (LDL-C) concentration, increases the number of atherogenic (i.e. apo B100-containing) particles and tends to raise triglycerides, whereas pioglitazone is neutral with respect to LDL-C levels, tends to lower apo B100, and reduces plasma triglyceride levels [39, 40].

Among these, TZDs improve markers of inflammation (e.g. C-reactive protein, CRP), influence components of the coagulation cascade (e.g. plasminogen activator inhibitor-1, PAI-1), and increase levels of the anti-atherosclerotic adipokine and adiponectin [41–44]. They also modulate macrophage foam cell formation, plaque stability, the response to vascular injury, and improve endothelial function and microalbuminuria [45, 46]. Studies in animal models also demonstrate their ability to improve outcomes after experimentally induced myocardial infarction (MI) or stroke [47–49]. In human studies, they also improve cardiac performance, and pioglitazone has been shown to reduce the progression of carotid intima-media thickness, which is a well-established surrogate for atherosclerosis [50, 51]. Indeed, pioglitazone was shown to reduce the progression of atherosclerosis, as measured using intravascular ultrasound, and to improve CV risk factors over 18 months, whereas there was a progression of coronary atherosclerosis with glimepiride [52].

3. CLINICAL EVIDENCES

Based on multiple effects (on glycemia, lipid profile, blood pressure, biomarkers) of TZDs it is assumed that these drugs reduce micro- and macrovascular complications of T2DM. Unfortunately, several large scale clinical studies reported that thiazolidinedione therapy was associated with cardiovascular complications [11, 12], including their propensity to cause edema (and subsequently symptoms of heart failure), weight gain, and increased risk of myocardial infarction [13–15, 53, 54]. It is not easy to confirm the effects of TZDs which are responsible for heart failure (HF). Patients with T2DM are already at increased risk for HF and other adverse CV events and it would be a cause for concern if this risk was increased further by glucose-lowering therapy.

TZDs have a number of effects that are of potential benefit to patients with HF, including blood pressure lowering, angiotensin II reduction, endothelial function and lipid profile improvement, and slowing of atherosclerosis progression [50, 55, 56]. However, TZDs also increase sodium reabsorption in the distal nephron [57, 58] leading to fluid retention and peripheral oedema, which may be of particular concern in patients with HF [59]. Several meta-analyses have indicated that pioglitazone and rosiglitazone use in T2DM increases the risk of HF [60, 61] recommending caution in prescribing TZDs to patients with NYHA class I–II HF and completely avoiding TZDs in patients with NYHA class III–IV HF [62].

While a number of randomised controlled trials have indicated that both rosiglitazone and pioglitazone enhance the risk of HF, the increased risk of acute myocardial infarction and

mortality appeared to be limited to rosiglitazone [15, 63] but not to pioglitazone [64, 65]. In spite of the fact that these latter risks of rosiglitazone therapy were not confirmed by other clinical studies [66, 67] restricted access to rosiglitazone was introduced in some countries [16, 17].

It remains to be elucidated, however, what is the explanation for the differences found between the effects of rosiglitazone and pioglitazone on CV outcomes despite their similar effects on glycemic control.

4. CELLULAR ELECTROPHYSIOLOGICAL EFFECTS OF TZDs

The very limited data concerning the direct cardiac effects of rosiglitazone in experimental conditions may explain its cardiac side effects. Rosiglitazone was shown to attenuate porcine action potential shortening induced both during ischemia and by the K_{ATP} channels opener levocromocalim [68]. Moreover, rosiglitazone increased the propensity of ventricular fibrillation in pigs, which effect was attributed to inhibition of the cardiac ATP-sensitive K^+ channels [68]. This presumed rosiglitazone-resulted reduction of the protective role of ischemia-induced K_{ATP} channels activation might explain its property for inducing higher incidence of myocardial ischemia. Furthermore, rosiglitazone was shown to block a wide variety of non cardiac ion channels, including neuronal Ca^{2+} channels, epithelial Na^+ channels, ATP-sensitive K^+ channels, delayed rectifier K^+ channels, and L-type Ca^{2+} channels in aortic smooth muscle cells [69–72]. In contrast to the lack of data on cardiac cells with rosiglitazone, another thiazolidinedione derivative, troglitazone was shown to effectively block L-type Ca^{2+} current in ventricular myocytes of guinea pigs [73, 74] and rats [75, 76], while in rabbit ventricular cells Na^+ , Ca^{2+} , and K^+ currents were suppressed by the drug [77].

4.1. Effect of Rosiglitazone on Action Potential Configuration

In this study we demonstrate that rosiglitazone exerts complex, very diverse (sometimes similar, sometimes different) electrophysiological actions in small rodent ventricular papillary muscles and canine ventricular cardiomyocytes. Nearly in all of the preparations studied - except for histidine decarboxylase knockout (HDC-KO) mice (Fig. 4C) - rosiglitazone caused a significant concentration dependent reduction of V_{max} (Fig. 3C, 4C, 5C), an indirect indicator of Na^+ current (I_{Na}) density [78]. Rosiglitazone exerted a concentration dependent depression of APA in rats (Fig. 3A), but an increase in APA was observed in wild type as well as in HDC-KO mice (Fig. 4A). In case of canine myocytes, in spite of the reduction of V_{max} , APA was not decreased; in contrast, it was significantly increased by 100 μM rosiglitazone (Fig. 5E).

Action potential duration, especially during the most terminal phase of repolarization was also affected. APD_{90} was shortened in mice (Fig. 4B), while it was prolonged in rat (Fig. 3B) in a concentration-dependent manner. In canine myocytes APD_{90} was significantly shortened by 30 μM rosiglitazone, while it was lengthened by high concentrations (Fig. 5B).

Concerning our results obtained in rats, our V_{max} data are similar to data of Kavak *et al.* [79], while the effects of rosiglitazone on APD_{90} and APA show apparently interspecies differences. These differences can probably be explained by differences in AP morphology and in the kinetic properties of the rat, murine and canine K^+ currents active during ventricular repolarization (over-exposed I_{to} , absence of plateau phase in rats and mice) [80]. Another possible explanation for the differences seen with the HDC-KO group might be the fact that these animals are more susceptible to auto-immune diabetes development. Histidine decarboxylase knockout mice lack endogenous histamine, and they are characterized by impaired glucose tolerance. Furthermore, they have autoantibodies reactive to glutamic acid

decarboxylase (GAD), a possible target-antigen of the diabetogenic autoimmune process [81]. Our previous data showed that electrophysiological changes relevant to diabetes (i.e. prolongation of repolarization and depression of $V_{\max}$) developed in these animals without any diabetes induction [82]. These characteristics can be observed in the present study on Fig. (4), where in HDC-KO control group APD_{90} was lengthened (Fig. 4B) and $V_{\max}$ was depressed (Fig. 4C) comparing to the control values of the wild type animals (Fig. 4B, 4C). Whereas direct ionic current measurements in the case of rats and mice were not performed, the results suggest that rosiglitazone can alter the activity of some cardiac ion channels. This suggestion was supported by data from murine diabetic model showing that chronic treatment of rosiglitazone could modify expression of genes for K^+ channel/channel interacting proteins [83].

4.2. Effect of Rosiglitazone on the Density of Cardiac Ion Currents Measured by Conventional Voltage Clamp

The effects of rosiglitazone on native cardiac ion currents were analysed in canine cardiac myocytes. In these experiments, performed under conventional voltage clamp conditions, cumulative concentration-dependent drug-effects were monitored between 1 and 300 μM , increasing the concentration of rosiglitazone usually in steps of 0.5 log units. Kinetic properties of the channel gating were studied at concentrations which were close to the half effective blocking concentration of rosiglitazone on the given ion current. The results revealed that rosiglitazone suppressed several ion currents in a concentration-dependent manner with the concomitant alterations in action potential configuration. For instance, the rosiglitazone-induced decrease canine phase-1 repolarization is explained by the reduction of I_{to} with an EC_{50} value of $25.2 \pm 2.7 \mu\text{M}$ (Fig. 6A). Similarly, the plateau-depression, observed in the presence of rosiglitazone in Fig. (5), may be a consequence of inhibition of Ca^{2+} and Na^+ currents. Concentration-dependent blockade of I_{Ca} , characterized by an EC_{50} of $82.5 \pm 9.4 \mu\text{M}$, was demonstrated in voltage clamp experiments (Fig. 6C), while the observed suppression of $V_{\max}$ is believed to be a good indicator of I_{Na} blockade [78]. As shown in Fig. (6B), the amplitudes of the I_{Kr} current tails were also progressively decreased by increasing concentrations of rosiglitazone, having an EC_{50} value of $72.3 \pm 9.3 \mu\text{M}$. While the blocking actions of rosiglitazone on I_{to} and I_{Kr} developed rapidly and were fully reversible, suppression of I_{Ca} was only partially reversible upon washout. I_{K1} was not significantly modified by rosiglitazone up to the concentration of 100 μM . At a concentration of 300 μM a small but fully reversible suppression of I_{K1} was observed. Our data on potency of inhibition of I_{to} was supported by recent results of Jeong and coworkers [84] who found that rosiglitazone inhibits recombinant $K_v 4.3$ channels current with an IC_{50} of 25 μM which is in strong agreement with our finding.

In spite of the multiple actions of rosiglitazone on canine cardiac ion channels, its effect on action potential configuration is relatively well compensated. For instance, action potential duration was little affected by rosiglitazone (except for the moderate shortening of APD_{50} at 30 μM and lengthening of APD_{90} at 100 μM). This is the consequence of simultaneous blockade of inward (window I_{Na} and I_{Ca}) and outward (I_{Kr} and I_{to}) currents during the plateau. Suppression of $V_{\max}$ is usually accompanied with reduction of APA. This effect was not observed in canine myocytes with rosiglitazone – in contrast – APA was significantly increased by 100 μM rosiglitazone. This is likely due to the simultaneous blockade of I_{Na} and I_{to} , from which the earlier tends to decrease, while the latter tends to increase the amplitude of action potentials. Finally, the lack of depolarization is in line with the inability of rosiglitazone to alter I_{K1} at concentrations not higher than 100 μM .

The present results allow some comparison between the cellular cardiac electrophysiological effects of rosiglitazone and troglitazone. Troglitazone blocked I_{Ca} with IC_{50} values close to 10 μM in rat [75, 76], rabbit [77] and guinea pig myocytes [73]. This value is significantly

smaller than the IC_{50} of 92 μM obtained with rosiglitazone in canine ventricular cells (present study). The inhibitory effect of troglitazone on I_{Na} is also much stronger than that of rosiglitazone. In contrast to our results, where 100 μM rosiglitazone caused less than 50 % reduction of V_{max} , 1 μM of troglitazone induced 50% V_{max} -blockade, while 10 μM of the compound fully eliminated action potentials in rabbit ventricular myocytes [77]. Thus the difference between the inhibiting potency of rosiglitazone and troglitazone seems to be at least one order of magnitude.

4.3. Effect of Rosiglitazone on Ion Currents Under Action Potential Clamp Conditions

The profile of an ion current may be markedly different when comparing under conventional voltage clamp and action potential clamp conditions [85]. An advantage of the action potential clamp technique is that the effect of any drug on the net membrane current can be recorded allowing thus to monitor drug-effects simultaneously on more than one ion current. Furthermore, this technique enables us to record true current profiles flowing during an actual cardiac action potential. Of course, in the case of a drug acting on more than one ion current, such as rosiglitazone is, a series of peaks can be detected on the current trace, each of them corresponding to the fingerprint of an individual ion current [86]. Accordingly, the early outward current peak, shown in Fig. (7), arises when I_{to} is suppressed, while the inward deflection indicates a blockade of I_{Ca} . The late outward current peak, coincident with terminal repolarization of the canine action potential, is a mixture of I_{Kr} plus I_{K1} [84]. In our case, however, it is likely caused by pure I_{Kr} blockade, since – as we have previously shown – I_{K1} was not affected by 100 μM rosiglitazone. As demonstrated in Fig. (7), rosiglitazone suppressed I_{to} , I_{Kr} , and I_{Ca} under action potential voltage clamp conditions in a concentration-dependent and relatively reversible manner – in line with results of conventional voltage clamp experiments. The amplitudes of the three current peaks (early outward, inward, and late outward) are presented in Fig. (7) H–I.

5. CLINICAL IMPLICATIONS

The lowest concentration of rosiglitazone that caused statistically significant changes in our study was higher than those peak plasma levels obtained in patients. Peak plasma concentration of 0.8 $\mu g/ml$ (corresponding to 2 μM) is typical in patients after receiving a single dose of 8 mg rosiglitazone [87, 88]. Therefore, it is not likely that normally dosed rosiglitazone can alter cardiac electrogenesis in healthy individuals. However, the probable proarrhythmic side effects of rosiglitazone could be not fully excluded in patients (elderly and/or diabetic) having cumulated cardiovascular risk factors (ischemic heart disease +hypertonia+hyperlipidaemia) and/or decreased elimination of the drug. Indeed, rosiglitazone was shown to increase propensity for ventricular fibrillation in ischemic pigs [36]. The ambiguous and contradictory clinical results [11, 12, 15, 66, 67] lead to restriction rather than market removal [16, 17, 89]. The cardiovascular safety profile of rosiglitazone is still an open question, because of the conflicting data on its risk/benefit ratio. The future of the drug probably will be determined by additional multicenter studies.

It is also very important to emphasize that the present results with rosiglitazone were obtained in healthy mammalian hearts, while rosiglitazone is usually used in diabetic patients. Considering that diabetes is known to induce marked remodelling in the set of cardiac ion currents in all studied mammalian species [4–6, 90] further studies in diabetic animal models should be performed.

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ABBREVIATIONS

AP	action potential
APA	action potential amplitude
APD	action potential duration
APD₉₀	action potential duration at 90% level of repolarization
PPARγ	peroxisome-proliferator-activated receptor γ
HF	heart failure
HDC-KO mice	histidine decarboxylase knockout mice
I_{ss}	steady-state outward current
I_{to}	transient outward K ⁺ current
I_{Kr}	rapid delayed rectifier K ⁺ current
I_{Ca}	L-type Ca ²⁺ current
I_{K1}	inward rectifier K ⁺ current
TZD	thiazolidinedione
T2DM	type 2 diabetes mellitus
V_{max}	maximum velocity of depolarization

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Fig. 1.
Chemical structure of thiazolidinediones.

Fig. 2. Chemical structures of some partial PPAR γ receptor agonists, like balaglitazone, MK-0533 and Compound **50**.

Fig. 3.

Electrophysiological parameters of isolated right ventricular papillary muscles in rat under control (Ctrl) conditions and following rosiglitazone treatment (1, 3, and 30 μM). Columns and bars represent mean $\pm$ SEM values of APA (**A**, $n=15$), APD₉₀ (**B**, $n=15$) and V_{max} (**C**, $n=15$) measurements, n =number of animals. ANOVA and Student's t test were used for statistical comparisons (* $p<0.05$ significant difference from control).

Fig. 4.

Comparison of electrophysiological parameters of isolated right ventricular papillary muscles from wild-type (WT) and histidine decarboxylase knockout (HDC-KO) mice under control (Ctrl) conditions and following rosiglitazone treatment (1, 3, and 30 μM). Columns and bars represent mean $\pm$ SEM values of APA (**A**, n=15), APD₉₀ (**B**, n=15) and V_{max} (**C**, n=15) measurements. ANOVA and Student's t test were used for statistical comparisons (*p<0.05 significant difference from control, #p<0.05 significant difference between control WT and HDC-KO group).

Fig. 5.

A: Representative set of superimposed action potentials showing the cumulative concentration-dependent effects of rosiglitazone on action potential configuration. Early events of the action potential are enlarged in the inset, the first time-derivatives of action potential upstrokes are depicted on the right. The action potentials were superimposed so as to match their upstrokes. **B, C, D, E:** Cumulative concentration-dependent effects of rosiglitazone on action potential duration measured at 50% (APD₅₀) and 90% (APD₉₀) level of repolarization, the maximum rate of depolarization (V_{max}), amplitude of phase-1 repolarization, and the action potential amplitude, respectively. Phase-1 amplitude was determined as a difference of overshoot potential and the deepest point of the incisura. Each concentration of rosiglitazone was superfused for 3 min, the washout (Wo) lasted for 10 min. Symbols and bars represent mean ± SEM values obtained in 8 myocytes, asterisks denote significant (P<0.05) changes from pre-drug control values, which are also indicated by dotted lines.

Fig. 6. Cumulative concentration-dependent effects of rosiglitazone on I_{to} (A, n=5), I_{Kr} (B, n=5), I_{Ca} (C, n=6), and I_{K1} (D, n=4) measured using conventional voltage clamp. Left panels show superimposed current traces recorded before and after superfusion with increasing concentrations of rosiglitazone, followed by a washout. I_{Ca} and I_{to} were recorded as current peaks arising during the test pulse (difference between the peak and pedestal value), I_{K1} was determined as absolute values measured at the end of each test pulse, while I_{Kr} was evaluated as a tail current, obtained upon repolarization to the holding potential. Average data showing concentration-dependent blocking effects of rosiglitazone are presented on the right panels as Hill plots. I_{Ca} and I_{Ks} were blocked by 5 μM nifedipine and 1 μM HMR-1556, respectively, when measuring I_{to} and I_{Kr} . During the measurement of I_{Ca} 3 mM 4-aminopyridine and 1 μM E4031 were applied in order to block K^+ currents. Symbols and bars indicate mean values $\pm$ SEM, asterisks indicates significant ($P < 0.05$) changes from control.

Fig. 7. Effects of 1, 10, and 100 μ M rosiglitazone on ion currents under action potential voltage clamp conditions. Representative records of a command signal (**A**), and the underlying current traces obtained before (**B**), in the presence (**C–E**), and after washout of rosiglitazone (**F**). Since ion currents were obtained from the same cell that provided the command action potential, the pre-drug current record was a horizontal line at the zero level. The post-drug difference currents have been inverted in order to present the currents with their conventional polarity. Dotted lines indicate zero current level for each trace. **G–I:** Average results obtained with rosiglitazone on the early outward current peak (indicator of I_{to} , **G**), inward current peak (indicator of I_{Ca} , **H**), and the late out-ward current peak (indicator of I_{Kr} dominantly, **I**) in 5 myocytes. Columns and bars are means $\pm$ SEM, asterisks denote significant ($P < 0.05$) changes from control.