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COMMENTARY

Cardiac ion channel modulation by the hypoglycaemic agent rosiglitazone

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The hypoglycaemic thiazolidinedione rosiglitazone is used clinically in the treatment of type 2 diabetes. However, in 2010, information relating to rosiglitazone-associated increased cardiovascular risk led the European Medicines Agency to recommend suspension of marketing authorizations for rosiglitazone-containing anti-diabetes drugs, while the US Food and Drug Administration recommended significant restriction on the agent's use. Two timely studies in this issue of the *British Journal of Phrarmacology* provide new information regarding modification of cardiac cellular electrophysiology by rosiglitazone. Szentandrássy *et al.* demonstrate canine ventricular action potential modification and concentration-dependent suppression of L-type Ca current and of transient outward and rapid delayed rectifier K currents. Jeong *et al.* demonstrate concentration-dependent inhibition of recombinant $K_v4.3$ channels, providing mechanistic insight into the likely molecular basis of transient outward K current inhibition by the compound. Further studies using diabetic models would be of value to determine whether, in a diabetic setting, rosiglitazone modification of these channels could affect the risk of arrhythmia at clinically relevant drug concentrations.

LINKED ARTICLES

This article is a commentary on Szentandrássy *et al.*, pp. 499–509 of this issue and Jeong *et al.*, pp. 510–520 of this issue. To view these papers visit http://dx.doi.org/10.1111/j.1476-5381.2011.01215.x and http://dx.doi.org/10.1111/j.1476-5381.2011.01210.x

Abbreviations

AP, action potential; APD, action potential duration; $I_{Ca,L}$, L-type calcium channel current; I_{K1}, inwardly rectifying potassium channel current; I_{KATP}, ATP-activated potassium channel current; I_{Kr}, rapid delayed rectifier potassium channel current; I_{Na}, fast inward Na current; I_{TO}, transient outward potassium channel current; MAP, monophasic action potential; MI, myocardial infarction; PPAR γ, peroxisome proliferator-activated receptor γ

Rosiglitazone and pioglitazone, which are thiazolidinediones and high-affinity ligands for the peroxisome proliferator-activated receptor γ, have been used widely as hypoglycaemic agents in the treatment of type 2 diabetes (McGuire and Inzucchi, 2008; Doshi *et al.*, 2010). Due to a propensity to increase peripheral oedema and the risk of heart failure, the use of these agents in patients with heart failure is to be avoided (McGuire and Inzucchi, 2008; Doshi *et al.*, 2010; European Medicines Agency, 2010), while rosiglitazone has been the subject of specific attention in recent years, due to debated evidence for increased cardiovascular event risk.

In 2007, two meta-analyses concluded that sustained rosglitazone use was associated with a significantly increased risk of myocardial infarction (MI) (Nissen and Wolski, 2007; Singh *et al.*, 2007). The subsequent multi-centre open-label 'RECORD' study confirmed an increased risk of heart failure with rosiglitazone, but did not show a conclusive effect regarding MI risk, and suggested that rosiglitazone does not increase cardiovascular mortality/morbidity compared with other glucose-lowering drugs (Home *et al.*, 2009). A recent study of rosiglitazone-receiving patients showed no adverse effects on markers of cardiac function examined using cardiac magnetic resonance imaging (McGuire *et al.*, 2010). However, in 2010, two further risk analyses raised significant questions regarding the continued use of rosiglitazone-containing medications in type 2 diabetes. One, focusing on elderly diabetic patients receiving either rosiglitazone or pioglitazone who had undergone 3 years follow-up after thiazolidinedione

initiation, reported increased risk for rosiglitazone compared with pioglitazone of stroke, heart failure, all-cause mortality and of the composite of acute MI, stroke, heart failure or all-cause mortality (Graham *et al.*, 2010). The second was an updated meta-analysis of randomized controlled trials up to February of 2010 of at least 24 weeks duration reporting adverse cardiovascular events; this study confirmed increased risk with the rosiglitazone treatment of MI, though not of increased cardiovascular or all-cause mortality (Nissen and Wolski, 2010). Following a review of rosiglitazone by the Committee for Medicinal Products for Human Use concluding that the benefits of rosiglitazone no longer outweighed its risks, in September 2010 the European Medicines Agency recommended suspension of marking authorization for rosiglitazone-containing medicines (European Medicines Agency, 2010). In the same month, the US Food and Drugs Administration recommended restricting rosiglitazone to those patients who are unable to control their type 2 diabetes with other medicines (FDA, 2010).

Against such a background, it is perhaps timely that two studies published in the present volume of this journal provide new information regarding cardiac actions of rosiglitazone, specifically on the ability of the drug to inhibit ion channels that are important in the generation of normal cardiac activity. Szentandrássy *et al.* (2011) have focused on establishing the effects of the drug on ventricular action potentials and major ventricular ionic currents from a large (canine) animal model; Jeong *et al.* (2011) have focused on studying recombinant $K_v4.3$ channels, as this K_v channel subtype is involved in mediating transient outward potassium current (I_{TO}) that contributes significantly to the early phase of repolarization of ventricular action potentials (see Dixon *et al.*, 1996).

In studying dog ventricular myocytes, Szentandrássy *et al.* (2011) have chosen a species that exhibits closer similarities to human in ventricular action potential configuration and repolarizing potassium channel currents than small rodents do (mice or rats). They report a concentration-dependent reduction in action potential (AP) maximum upstroke velocity (V_{max}; significant at drug concentrations of 10 μM or greater), which represents indirect, though likely reliable, evidence for an inhibitory effect of rosiglitazone on fast Na current (I_{Na}). A similar concentration-dependent suppression of phase 1 repolarization was observed (Szentandrássy *et al.*, 2011). By contrast, AP duration (APD) was comparatively little affected by rosiglitazone, except for a small (though significant) shortening of APD at 50% repolarization by 30 μM of the drug, and a lengthening of APD at 90% repolarization with 100 μM rosiglitazone (Szentandrássy *et al.*, 2011). Whole-cell recordings of I_{TO}, of rapid delayed rectifier K current (I_{Kr}) and of L-type Ca current ($I_{Ca,L}$) revealed concentration-dependent inhibition of each of these currents with half-maximal effective concentrations (EC_{50}s), respectively, of ~25 μM, ~72 μM and ~83 μM (Szentandrássy *et al.*, 2011). The inwardly rectifying K current, I_{K1}, was not significantly altered by the drug at concentrations below 300 μM. The multi-channel blocking effects of the drug, with differing concentration-dependences for effects on the different channels, are likely to underlie the comparative lack of effect of the drug on APD, a supposition borne out by the results of AP voltage clamp experiments in the study (Szentandrássy *et al.*, 2011).

The second rosiglitazone study in this issue by Jeong *et al.* (2011) is complementary to that by Szentandrássy *et al.* (2011), in that it provides increased insight into the likely basis of I_{TO} inhibition by rosiglitazone. Recombinant $K_v4.3$ channel current was inhibited with an IC_{50} (half maximal inhibitory concentration) of ~25 μM (Jeong *et al.*, 2011), which is in strong agreement with the observed potency of inhibition of native I_{TO} (Szentandrássy *et al.*, 2011). Voltage-dependent activation of $K_v4.3$ channels was little-affected by the drug, but voltage-dependent inactivation was negatively voltage-shifted in a concentration-dependent manner, from which an apparent dissociation constant (K_i) for inactivated channels of ~1.5 μM was estimated (Jeong *et al.*, 2011). Closed state inactivation of $K_v4.3$ channels was also accelerated by the drug (Jeong *et al.*, 2011).

A key question that arises is whether or not the results of these two studies may provide insight into increased cardiovascular risk with rosiglitazone. In comparing their findings with earlier studies, Szentandrássy *et al.* (2011) note that rosiglitazone appears to be a weaker inhibitor of cardiac ion channels than troglitazone (e.g. see Ikeda and Watanabe, 1998). Moreover, in healthy individuals, maximal plasma rosiglitazone concentrations following a single 8 mg oral dose of the drug reach approximately ~370–700 $ng \cdot mL^{-1}$ (equivalent to ~1–2 μM; Thompson-Culkin *et al.*, 2002; Park *et al.*, 2004). Thus, the majority of acute ion channel inhibitory effects seen in the two studies reported here (Jeong *et al.*, 2011; Szentandrássy *et al.*, 2011) occur at higher drug concentrations than are likely to occur *in vivo*, except – as noted by Szentandrássy *et al.* (2011) – potentially in overdose. An exception to this is inactivation state-dependent inhibition of $K_v4.3$ /I_{TO}, as the K_i for this action of the drug occurs at clinically relevant concentrations (Jeong *et al.*, 2011). It is feasible, therefore, that some modulation of I_{TO} and thereby of early AP repolarization could occur at low μM rosiglitazone concentrations, although it is not possible on the basis of the available information to reach firm conclusions as to whether or not this could be sufficient to affect the risk of arrhythmias.

These observations do not preclude the occurrence of greater cardiac ion channel inhibitory effects of rosiglitazone under different conditions such as ischaemia. Nor do they preclude acute inhibitory effects of the drug on ionic currents other than those investigated in either of the present studies. Indeed, the authors of both reports note earlier work reporting thiazolidinedione inhibition of various ion channels in other tissues (Jeong *et al.*, 2011; Szentandrássy *et al.*, 2011). It is worth noting that thiazolidinedione drugs have been shown to attenuate porcine ventricular monophasic action potential (MAP) shortening induced during ischaemia, with a greater effect of rosiglitazone than of troglitazone (Lu *et al.*, 2008). In the same study, thiazolidinediones attenuated porcine MAP shortening induced by the K_{ATP} channel opener levcromakalim, which is strongly indicative that this class of drugs can block cardiac K_{ATP} channels (Lu *et al.*, 2008). Moreover, during coronary occlusion, the median time to ventricular fibrillation was greatly reduced by rosiglitazone (Lu *et al.*, 2008), which is consistent with a reduction by the drug of the protective role of ischaemia-induced K_{ATP} channel activation. In this regard, data on acute rosiglitazone inhibition of native ventricular K_{ATP} channel current (I_{KATP}) would con-

stitute a valuable comparator for the native current data provided here by Szentandrássy *et al*. (2011).

Whereas diabetic patients receive drug treatment on an ongoing basis, chronic effects of rosiglitazone exposure on ion channel currents have not been investigated in the two studies that are the subject of this commentary (Jeong *et al*., 2011; Szentandrássy *et al*., 2011). It is possible that effects of chronic and acute rosiglitazone exposure on cardiac ionic currents could differ and this possibility warrants experimental investigation. Moreover, recent data from a murine diabetic model indicate that rosiglitazone treatment can influence expression of a number of genes, including some for potassium channel/channel interacting proteins (Wilson *et al*., 2008). Considering this together with the potential for electrophysiological remodelling in diabetic hearts, it may be valuable now to use diabetic animal models in order to conduct additional studies of both acute and chronic effects of rosiglitazone on cardiac ion channels and electrogenic transporters.

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Conflicts of interest

None.

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