Simulating the effect of anti-diabetic drugs on ATP-sensitive potassium (K_{ATP}) channels inhibition in a human cardiac cell model (ORd)

Mitra Abbasi[1], Sebastian Polak[1,2]
[1]Simcyp Limited (a Certara Company), Sheffield, S2 4SU, UK
[2]Faculty of Pharmacy, Jagiellonian University Medical College, Krakow, Poland
mitra.abbasi@certara.com

Introduction

The contribution of the ATP-sensitive potassium (K_{ATP}) current to the action potential (AP) is an important component of cardiac ischaemia. The purpose of this study was to, investigate how anti-diabetic drugs effect through ATP-sensitive potassium (K_{ATP}) channel inhibition in the O'Hara-Rudy dynamic (ORd) model of human ventricular myocytes. We embedded $I_{K,ATP}$ formulation (Shaw & Rudy 1997) in an AP model (O'Hara et al. 2011) to investigate the effect of $I_{K,ATP}$ activation in cardiac myocytes.

Methods

We used the O'Hara-Rudy dynamic (ORd) model (O'Hara et al. 2011) to represent human cellular electrophysiology. The parameters for epicardial, midmyocardial (M) and endocardial cells were used. Using a formulation of the ATP activated K^+ current $I_{K,ATP}$, we analysed the drug effects on $[ATP]_i$ variation in cardiomyocyte, in a dose-dependent manner. The mathematical model of $I_{K,ATP}$ that Shaw and Rudy (Shaw & Rudy 1997) formulated based on data for guinea-pig ventricular cells was used in this study. $I_{K,ATP}$ activated at $[ATP]_i$ level and $K_{0.5}$ parameter was assigned to highlight the possible role of pH dependence of the K_{ATP} channel (Table 1). Drug concentration data was used from Liu study (Liu et al. 2015), which performed in our simulations as the fraction(x0.5,x3,x5 and x10) of drug concentrations. These concentrations values presented in Table 2.

$$I_{K,ATP} = G_{K,ATP}\frac{1}{1+\left(\frac{[ATP]_i}{K_{0.5}}\right)^H}\left(\frac{[K^+]_o}{5.4}\right)^n (V_m - E_k)$$

Table 2. IC_{50} and concentration values for three anti-diabetic drugs

Glibenclamide (Glb) IC_{50}=0.01 µM (0.01×10^{-3} mM) C= (0.0015-0.03) µM	Gliclazide (Glc) IC_{50}=15.28 µM (15.28×10^{-3} mM) C= (4.59-91.8) µM	Gliquidone (Glq) IC_{50}=119.1 µM (119.1×10^{-3} mM) C= (29.15-583) µM
C1= 0.0015 µM (13% reduction of the max conductance)	C1= 4.59 µM (23% reduction of the max conductance)	C1= 29.15 µM (20% reduction of the max conductance)
C2=0.003 µM (23%)	C2=9.18 µM (37%)	C2=85.30 µM (41%)
C3= 0.009 µM (47%)	C3= 27.54 µM (64%)	C3= 175 µM (59%)
C4= 0.015 µM (60%)	C4= 45.9 µM (75%)	C4= 291.5 µM (71%)
C5= 0.03 µM (75%)	C5= 91.8 µM (99%)	C5= 583 µM (83%)

Table 1. Intracellular *ATP* values accompanied with the half maximal saturation of $I_{K,ATP}$

$[ATP]_i$ (mM)	6.8	6.0	5.0	4.0
KATP (Half-Maximal saturation point of ATP-sensitive K current) mM	0.042	0.117	0.212	0.306

Results and discussion

- Cardiac K_{ATP} channels were activated during ischaemia when $[ATP]_i$ was depleted, thus leads to shortening of the AP (Figure 2.b). $I_{K,ATP}$ was decreased with increasing anti-diabetic drug concentration (Figure 3) in the ischaemic cells and AP duration was increased (Figure 5).
- It was assumed that other channels/currents apart from K_{ATP} channels were not taken into consideration by tested anti-diabetic drugs in this study.
- These simulations are not exhaustive representation of all ischaemic conditions. Other ischaemic conditions (hyperkalaemia and acidosis) will be investigated that their effects require further experimental characterization.

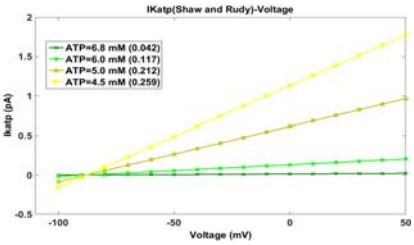

Figure 1. Current-Voltage relationships for the K_{ATP} channels in Shaw and Rudy formulation, using different $[ATP]_i$ values.

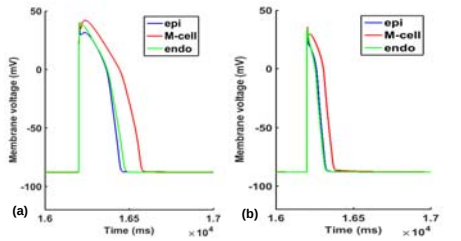

Figure 2. Action potential (epi, endo, M cells), with no drug effects. Action potential under (a) normal physiological and (b) ischaemic conditions.

The effect of anti-diabetic drugs on K_{ATP} channels , under normal and ischaemic conditions

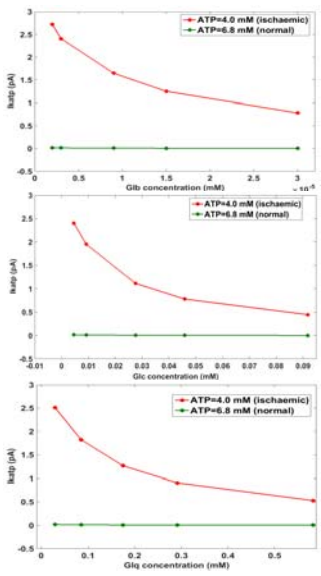

Figure 3. Current-Concentration relationships, with increasing concentration, the $I_{K,ATP}$ decreased (inhibition of K_{ATP} channels in ischaemia), and with negligible effect on K_{ATP} channels for the normal condition.

Drug concentration effects on normal cells

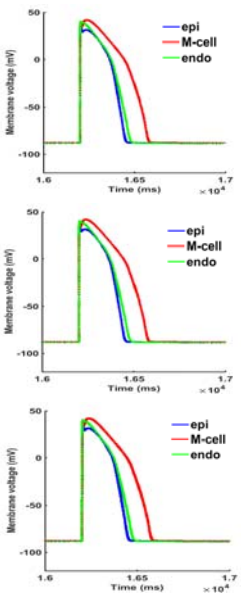

Figure 4. Effects of three different anti-diabetic drugs concentration , no effect on action potential in the healthy heart.

Drug concentration effects on ischaemic cells (epi, endo and M) , action potential ORd cell model

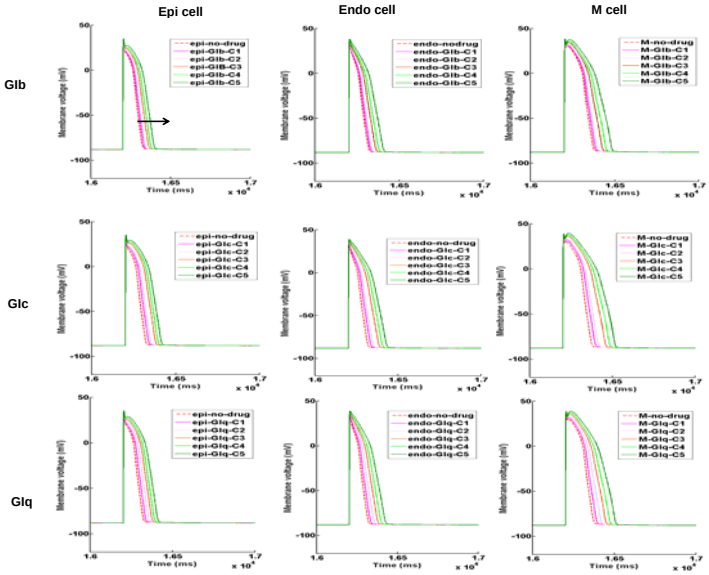

Figure 5. With increasing anti-diabetic drug (Glb, Glc and Glq) concentration in the ischaemic cells (diabetic heart), the action potential duration is increased in all cell (epi, endo and M) types.

Conclusions

1. For diabetes, the similarity of the simulated electrical behavior observed, by using all models presented in this study, supports the hypothesis that K_{ATP} channels cannot function properly and lead to ischaemia.
2. Cardiac K_{ATP} channels are activated during ischaemia (in diabetic heart), and K_{ATP} channels are inhibited by anti-diabetic drugs (Figures 6 and 7).

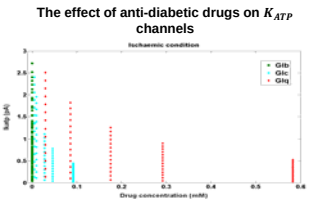

Figure 6. Reduction of $I_{K,ATP}$ (inhibition of K_{ATP} channels) are shown for all anti-diabetic drugs.

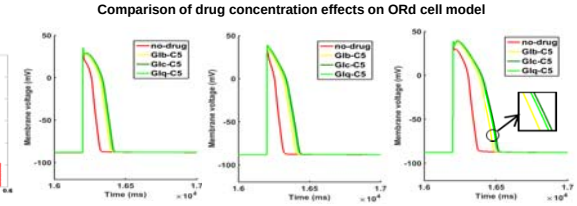

Figure 7. Drug concentration effects was similar for all anti-diabetic drugs, however this effect was lesser for the Glibenclamide compared to the rest of anti-diabetic drugs.

References

1. Liu et al., 2015. The effect of gliquidone on KATP channels in pancreatic β-cells, cardiomyocytes, and vascular smooth muscle cells. *Diabetes Research and Clinical Practice*, 109(2):334-9. doi: 10.1016. 2. O'Hara, T. et al., 2011. Simulation of the undiseased human cardiac ventricular action potential: model formulation and experimental validation. *PLoS computational biology*, 7(5), p.e1002061. 3. Shaw & Rudy, Y., 1997. Electrophysiologic effects of acute myocardial ischemia: a theoretical study of altered cell excitability and action potential duration. *Cardiovascular research*, 35(2), pp.256–72.