Effects of Taurine-Magnesium Coordination Compound on Type 2 Short QT Syndrome: A Simulation Study

Cunjin Luo[1,2], Dominic G Whittaker[3], Ying He[4], Tong Liu[5], Yacong Li[6], Kuanquan Wang[6], Na Zhao[6], Henggui Zhang[1,6,7]

[1]Southwest Medical University, Luzhou, China
[2]Northeastern University, Shenyang, China
[3]The University of Nottingham, Nottingham, UK
[4]De Montfort University, Leicester, UK
[5]Tianjin Medical University, Tianjin, China
[6]Harbin Institute of Technology, Harbin, China
[7]The University of Manchester, Manchester, UK

Abstract

Short QT Syndrome (SQTS) is an identified genetic arrhythmogenic disease associated with abnormally abbreviated QT intervals and an increased susceptibility to malignant arrhythmia and sudden cardiac death (SCD). SQT2 variant (linked to slow delayed rectifier, I_{Ks}) of SQTS, results from a gain-of-function (V307L) in the KCNQ1 subunit of the I_{Ks} channel. Pro-arrhythmogenic effects of SQT2 have been well characterized, but less is known about the pharmacological treatment of SQT2. We find that taurine-magnesium coordination compound (TMCC) exerted anti-arrhythmic effects with low toxicity. Therefore, this study aimed to assess the potential effects of TMCC on SQT2. The channel-blocking effect of TMCC on I_{Ks} in healthy and SQT2 cells were incorporated into computer models of human ventricular action potential (AP) and into one dimensional transmural tissue simulations. In the single-cell model, TMCC prolonged cell AP duration at 90% repolarization (APD_{90}). In the one dimensional intact model, TMCC prolonged the QT interval on the pseudo-ECGs. Thus, the present study provides evidence that TMCC can extend the repolarization period and APD_{90} and QT interval, thereby representing a therapeutic candidate for arrhythmia in SQT2.

1. Introduction

SQTS was first discovered by Gussak *et al* in 2000 as a new clinical syndrome related to sudden cardiac death (SCD) [1]. SQTS is characterized by an abnormally short QT interval, paroxysmal atrial fibrillation (AF), and life-threatening ventricular fibrillation (VF) due to accelerated cellular repolarization. Researchers have focused on the pathogenesis and therapy of SQTS.

To date, mutations in seven genes (*KCNH2, KCNQ1*, *KCNJ2*, *CACN1Ac*, *CACNB2b*, *CACNA2D1*, and *SCN5A*) have been identified as responsible for types 1 to 7 of SQTS (SQT1-SQT7) [2-4]. Therapies for SQTS include implantation of an implantable cardioverter defibrillator (ICD) and anti-arrhythmic drugs (quinidine, carvedilol, and disopyramide) [5-10]. However, ICD is not suitable for children. Furthermore, few reports have been published on effective pharmacological treatments for SQT2 and its mechanism.

Current research on SQTS is focused on the discovery of new therapeutic factors (new mutations, susceptibility to disease and drugs, *etc*) and effective therapeutic drugs. SQTS models are often used in the development of new drugs. Current models include gene-mutant experimental and computer models of SQTS. The gene-mutant model is more widely used in experimental studies. However, gene mutations in experiments can only be studied at the cellular level. Therefore, in this study, we chose mathematical technique to establish computer models of SQT2 to study the potential pharmacological effects at both cellular and tissue levels.

Previous studies have demonstrated that taurine magnesium coordination compound (TMCC) had protective effects against arrhythmias, and had very low toxicity [11]. However, little is known about the mechanisms of actions of TMCC on SQT2. Furthermore, several recent studies have highlighted the power of computer models to investigate mechanisms of arrhythmias and predict pharmacological effects of drugs. Therefore, this study was undertaken to assess the effects of TMCC on SQT2 by using computational human ventricular cell and tissue models, and pharmacological

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effects on action potential (AP) duration at 90% repolarization (APD_{90}) and QT interval in this variant of SQTS.

2. Materials and methods

The ten Tusscher *et al* biophysically detailed computer model for human endocardial (ENDO), mid-myocardial (MIDDLE) and epicardial (EPI) ventricular AP was used in this study [12].

Parameters in the equations for I_{Ks} in the model were modified to incorporate experimental data of Bellocq *et al* on KCNQ1 V307L mutation-induced changes in I_{Ks} channel kinetics that include half-activation voltage $V_{0.5}$, slope factor *s* and activation rate [13]. Following ten Tusscher *et al*, I_{Ks} was described as

$$I_{Ks}=g_{Ks}x_s^2(V_m-E_{Ks}) \quad (1)$$

$$\frac{dx_s}{dt}=\frac{(x_{s,\infty}-x_s)}{\tau_{x_s}} \quad (2)$$

$$x_{s,\infty}=\frac{1}{1+e^{(V_{0.5}-V_m)/s}} \quad (3)$$

where g_{Ks} is the channel maximal conductance, x_s is the activation variable, V_m is the cell membrane, E_{Ks} is the channel equilibrium potential. For details of other equations please see ten Tusscher *et al*.

KCNQ1 V307L mutation-induced changes in I_{Ks} channel kinetics were described as

a: Control/wild-type (WT):

$$x_{s,\infty}=\frac{1}{1+e^{(-5.9-V_m)/17.4}} \quad (4)$$

$$\tau_{x_s}=\tau_{x_s}(original) \quad (5)$$

b: Heterozygous (Het):

$$x_{s,\infty}=\frac{1}{1+e^{(-20.6-V_m)/10.9}} \quad (6)$$

$$\tau_{x_s}=0.7*\tau_{x_s}(original) \quad (7)$$

c: Homozygous (Hom):

$$x_{s,\infty}=\frac{1}{1+e^{(-24.0-V_m)/16.0}} \quad (8)$$

$$\tau_{x_s}=0.52*\tau_{x_s}(original) \quad (9)$$

d: Homozygous with reduced KCNE1 (HomKCNE1red):

$$x_{s,\infty}=\frac{1}{1+e^{(-24.0-V_m)/16.0}} \quad (10)$$

$$\tau_{x_s}=0.32*\tau_{x_s}(original) \quad (11)$$

A model of transmural ventricular tissue was constructed using the equation

$$\frac{\partial V_m}{\partial t}=I_{tot}+\nabla\cdot(D\nabla V_m) \quad (12)$$

where *D* is the diffusion parameter modelling the intercellular electrical coupling via gap junctions. I_{tot} is the total ionic current flowing across the cell membrane and is modelled by ten Tusscher *et al*. In simulations, *D* was set to a constant value of 0.4. In the model, *D* was set to be homogeneous throughout the one dimensional strand, except for a 5-fold decrease at the EPI-MIDDLE border, as previously suggested by Gima and Rudy [14].

A one-dimensional transmural strand was simulated to have a total length of 15.0 mm, of which 3.75 mm was ENDO, 5.25 mm was MIDDLE and 6mm was EPI. The simulated strand employed a spatial resolution of 0.15 mm, which generated 25 nodes for ENDO, 35 nodes for MIDDLE and 40 nodes for EPI. Differential equation was numerically solved by the Euler method with a time step of 0.02 ms.

A computed pseudo-ECG was calculated as an integral of the transmural gradient of the cell AP at all positions on the strand using [15-17]

$$\phi_e(x')=\frac{\alpha^2}{4}\int(-\nabla V_m)\cdot[\nabla\frac{1}{r}]dx \quad (13)$$

where *a* is the radius of the strand, *dx* is the spatial resolution, *r* is the Euclidean distance. In this study, the virtual electrode was placed at a position 2.0 cm away from the EPI end of the strand.

A simple pore block theory was used to model drug-ion channel binding interactions. The maximum conductance of cardiac ion channels was reduced according to the Hill equation. The reduction of ion currents in the presence of TMCC was determined by using half maximal inhibitory concentration (IC_{50}) and Hill coefficient (nH) values taken from literatures. The blocking potency of the compound on ionic currents is shown in Table 1.

Table 1. Cardiac ion currents and conductivities (% of original value) in the presence of TMCC [11].

Current	TMCC Dose	Conductivities
I_{Ks}	0.01 mm	16.95%
I_{Ks}	0.1 mm	28.33%
I_{Ks}	1 mm	36.94%

3. Results

Figure 1, Figure 2 and Figure 3 exhibit the time course of action potential (AP) with the action-in-action of different doses of TMCC under SQT2 Het, Hom and HomKCNE1red conditions. These results indicate: (i) the KCNQ1 V307L mutation I_{Ks} increased more rapidly following the AP upstroke, and led to the APD abbreviation; (ii) different doses of TMCC prolonged the APD, and did not affect the resting potential (RP).

Figure 4, Figure 5 and Figure 6 show the effects of

TMCC on the pseudo-ECG under SQT2 Het, Hom and HomKCNE1red conditions. These results indicate: (i) the KCNQ1 V307L mutation I_{Ks} caused abnormally abbreviated QT intervals on the ECG, and decreased the height of the T waves; (ii) different doses of TMCC prolonged the QT intervals, and increased the height of the T waves.

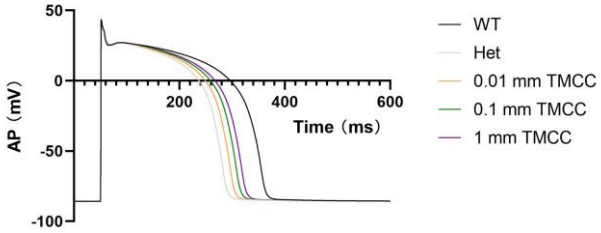

Figure 1. Effects of different doses of TMCC on human ventricular ENDO cells under the SQT2 Het condition.

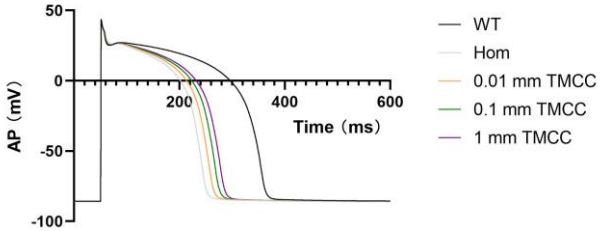

Figure 2. Effects of different doses of TMCC on human ventricular ENDO cells under the SQT2 Hom condition.

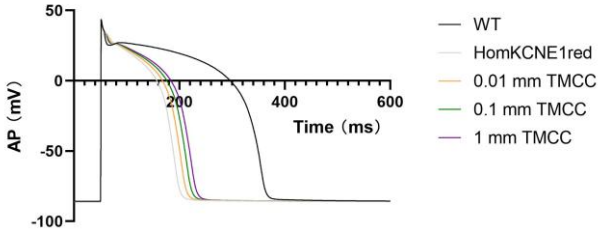

Figure 3. Effects of different doses of TMCC on human ventricular ENDO cells under the SQT2 HomKCNE1red condition.

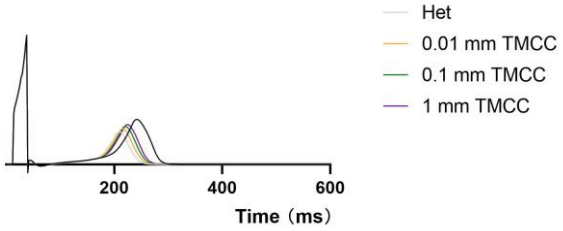

Figure 4. Effects of different doses of TMCC on computed pseudo-ECGs under the SQT2 Het condition.

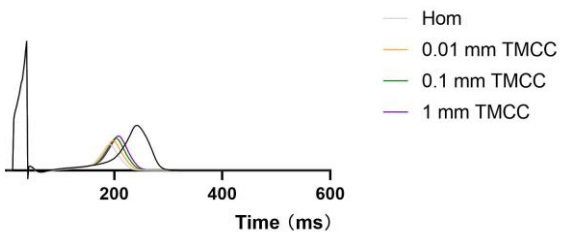

Figure 4. Effects of different doses of TMCC on computed pseudo-ECGs under the SQT2 Hom condition.

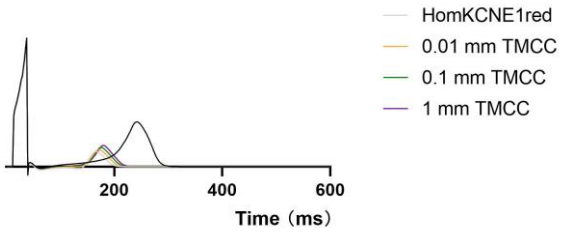

Figure 4. Effects of different doses of TMCC on computed pseudo-ECGs under the SQT2 HomKCNE1red condition.

4. Discussion and Conclusion

In this study, the simulation data indicate that TMCC (i) caused the prolongation of APD; (ii) prolonged the QT interval on the ECG. These findings represent a therapeutic candidate for arrhythmia in SQT2. In future, we will consider the factors of inhibiting delayed L-type calcium currents and sodium currents, in order to produce more accurate data.

Acknowledgments

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Address for correspondence:

My Name.
Cunjin Luo

My Full postal address.
Key Laboratory of Medical Electrophysiology, Ministry of Education, Institute of Cardiovascular Research, Southwest Medical University, Luzhou 646000, China

My E-mail address.
cunjin.luo@yahoo.co.uk