Drug Toxicity on Cardiac Pacemaking: a Multi-scale Modelling Study

Xiangyun Bai[1], Henggui Zhang[1,2], Kuanquan Wang[1],Yongfeng Yuan[1], Qince Li[1], Na Zhao[1]

[1]School of Computer Science and Technology, Harbin Institute of Technology, Harbin, Heilongjiang, China
[2]School of Physics and Astronomy, The University of Manchester, Manchester, UK

Abstract

Drugs, such as cisapride, have to be withdrawn from clinical uses due to their side effects, i.e., cardiotoxicity. As an agonist, it can activate 5-Hydroxytryptamine 4 (5-HT$_4$) receptors which are localized in sinoatrial node (SAN) and atrium. Our goal was to investigate the actions of cisapride alone and its combined effects with 5-HT$_4$ receptors that impair cardiac pacemaking action potentials (APs) and their conduction using multi-scale models (the Zhang et al. models of APs of rabbit SAN cells and an anatomically detailed 2-D model of the intact SAN-atrium tissue models). At single cell level, the action of cisapride on I_{Kr} had positive chronotropic effect in the central SAN cell, but had virtually no effect on the peripheral cell. When its activation to 5-HT$_4$ receptors was also considered, cisapride increased the pacing rate (PR) in centre SAN cell; but decreased it substantially in the periphery SAN cell. At the tissue level of the intact SAN-atrium, cisapride increased the PR and amplified the tachycardia effect of 5-HT$_4$ receptor activation. It altered the activation sequence of cardiac excitation waves and reduced the maximum up-stroke velocity of the atrium. Moreover, early afterdepolarization was observed in the atrium. Our study shed light on the mechanisms of cisapride-induced arrhythmogenesis, suggesting that 5-HT$_4$ receptors activation should be avoided in designing new anti-arrhythmic drugs.

1. Introduction

Drugs, such as cisapride, have to be withdrawn from clinical uses due to their severe side effects, i.e., cardiotoxicity. Previous studies suggest that cisapride treatment is associated with the genesis of tachycardia [1,2]. As a class III anti-arrhythmic agent, it is used to prolong the QT interval of the electrocardiogram by partially blocking the rapid rectifier potassium channel current (I_{Kr}) [3]. However, the mechanism of cisapride-induced tachycardia remains unclear. As an agonist, cisapride activates 5-Hydroxytryptamine 4 (5-HT$_4$) receptors which are expressed in sinoatrial node (SAN) and atrial cells [4,5], potentially contributing to the genesis of tachycardia [6]. It has been shown that 5-HT$_4$ receptor activation stimulated cyclic Adenosine monophosphate (cAMP) synthesis and therefore induced activation of L-type Ca^{2+} channels (I_{CaL}) via cAMP-dependent protein kinase (PKA) in the atria [7a]. In addition to I_{CaL} activation, 5-HT$_4$ receptor activation also mediated the so-called pacemaker current I_f in human atrial myocytes [8].

The direct effect of cisapride alone and its indirect effect associated with 5-HT$_4$ receptors activation on cardiac pacemaking impairment are still unclear. Although a research has been manually expressed 5-HT$_4$ receptor splice variants in mouse cardiomyocytes [9], it remains difficult to experimentally investigate the effect of 5-HT$_4$ receptor on cardiac arrhythmogenesis due to the absence of 5-HT$_4$ receptor expression in the hearts of small laboratory animals, such as rat, guinea pig and rabbit [9]. In this study, the effects of cisapride and 5-HT$_4$ receptors were mathematically simulated and incorporated into previous rabbit SAN and atrial mathematical models developed by Zhang et al [10]. The aim of this study was to theoretically investigate the impacts of cisapride on cardiac pacemaking action potentials and the AP conduction toward atrium. This study shed light on the mechanisms of cisapride-induced arrhythmogenesis, suggesting that 5-HT$_4$ receptors activation should be avoided in designing new anti-arrhythmic drugs.

2. Methods

2.1. Sinoatrial node cell models and modeling methods

The Zhang et al. models [10] of action potentials of rabbit central and peripheral SAN cells were modified to incorporate the effects of cisapride. Its impact on the I_{Kr} was simulated by simple pore blocking of I_{Kr} based on experimental data [11]. Due to the lack of experimental data, the impact of cisapride on the activation of 5-HT$_4$

receptors was mimicked based on the experiment data of serotonin-induced 5-HT_4 activation [8], not only as cisapride and serotonin have similar affinity to 5-HT_4 receptor, but also as both of them have similar effect on 5-HT_4 activation-induced cAMP production in unit time [4]. In detail, the effect of cisapride on the activation of 5-HT_4 receptors was modelled by increasing the maximal conductance of I_{CaL} and shifting the activation curve of the I_f toward more positive potentials [8]. Three conditions including mild, moderate and severe 5-HT_4 activation were defined to represent different doses of cisapride on cardiac cell according to experimental data [8,11] summarized as follows (Table 1):

Table 1. Currents remodeling with cisapride action on central and peripheral SAN cells.

Cisapride (mol/L)	↓g_{Kr} (%)	5-HT_4 receptor activation	↑g_{CaL} (%)	I_f shift (mV)
$4.7 \cdot 10^{-8}$	30	Mild	205.9	+2.7
$7.4 \cdot 10^{-8}$	50	Moderate	270.6	+3.6
$9.8 \cdot 10^{-8}$	70	Severe	332.4	+4.4

2.2. Tissue model and numerical approach

Single cell models were then incorporated into an anatomically detailed 2-D model of the intact SAN-atrium, in which effects of cisapride and 5HT_4 receptors activation on atrial cellular electrophysiology and AP conduction were simulated. Using the multi-scale models, we quantified the effects of cisapride and its activation of 5-HT_4 receptors on cardiac pacemaking action potentials and AP conduction.

The 2D model of the intact SAN-atrium was solved using the explicit Euler method with a 5-node approximation of the Laplacian operator. In numerical simulations, the time step and space step were 0.005 ms and 0.04 mm respectively, producing accurate numerical solutions compared to experimental data.

3. Results

3.1. Cisapride effect on SAN cells

Figure 1 represents the effect of cisapride with and without activating 5-HT_4 receptors on the APs in central and peripheral SAN cells. Simulation results show that blocking I_{Kr} by cisapride alone had a positive chronotropic effect on the central SAN cell, which was manifested by an increased pacing rate (PR) by 48.3% (Figure 1, Ai). Whereas it had an insignificant effect on the AP of peripheral cell (Figure 1, Aii). When 5-HT_4 receptors was activated by cisapride together with I_{Kr} blocking, the PR was increased by 78.4% in central SAN cells(Figure 1Bi), but substantially decreased by 21% in peripheral SAN cells (Figure 1, Bii). It was demonstrated that the combined effects with 5-HT_4 receptors on APs were significantly severer than that of cisapride-induce I_{Kr} inhibition alone.

The effect of low dose and high dose of cisapride in the central and periphery cells was demonstrated in Figure 2, showing that the effect of tachycardia was amplified with high dose of cisapride, especially with additional activation of 5-HT_4 receptors in central SAN cells (Figure 2, A). It is notable that in peripheral SAN cells, the dosage of cisapride had an insignificant effect on pacing rate (Figure 2, B).

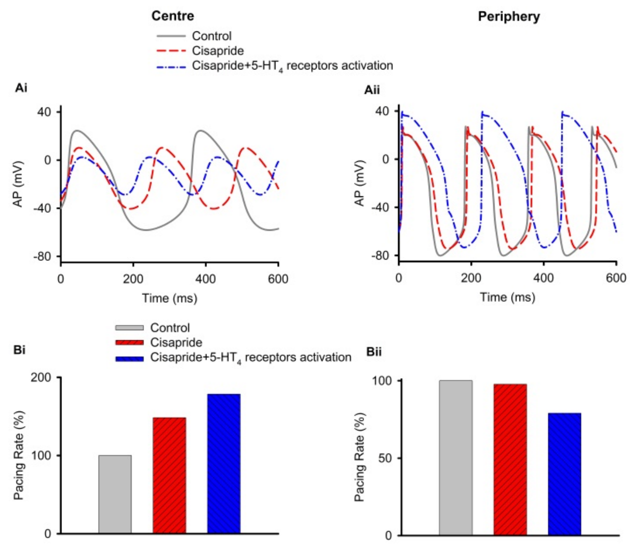

Fig1. Effects of cisapride with/without 5-HT_4 receptors activation on pacing rate. (Cisapride $=7.4 \cdot 10^{-8}$ mol/L)

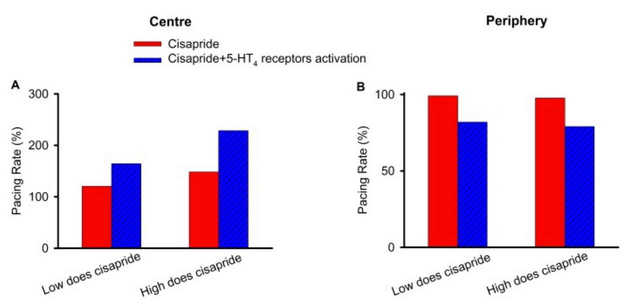

Fig2. Effects of low and high dose of cisapride with/without 5-HT_4 receptors activation on pacing rate. (Low does: Cisapride $=4.7 \cdot 10^{-8}$mol/L, high does: Cisapride $=7.4 \cdot 10^{-8}$ mol/L)

3.2. Cisapride effect on SAN-atrium tissue

The effects of increasing activation of 5-HT_4 receptors by cisaprid on AP initiation and conduction were studied in the 2D SAN-atrium tissue slice model. Figure 3 presents the spatial (running vertically) and temporal

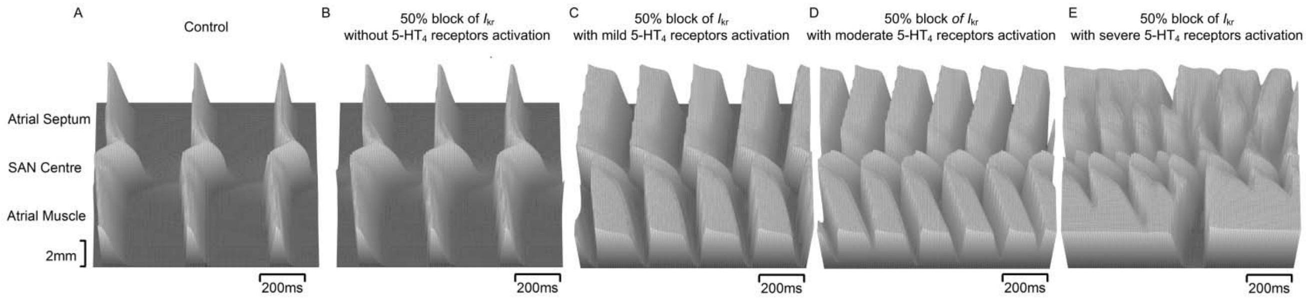

Figure 3. Effects of various degree of 5-HT$_4$ receptors activation by cisaprid on AP conduction across SAN-atrium tissue.

(running horizontally) profiles of APs during conduction through the 2D slice. At tissue level, blocking I_{Kr} alone by cisapride without activation of 5-HT$_4$ receptors caused a slight increase of the PR in the intact SAN-atrium (Figure 3B). With increasing activation of 5-HT$_4$ receptors by cisaprid, the tachycardia effect was amplified (Figure 3, C, D and E), resulting in the excitation propagation sequence shift (Fig 3C and D). It also lead to pacemaking site shift (data were not shown). The relative PRs in figure 3 also summarized in Figure 4A.

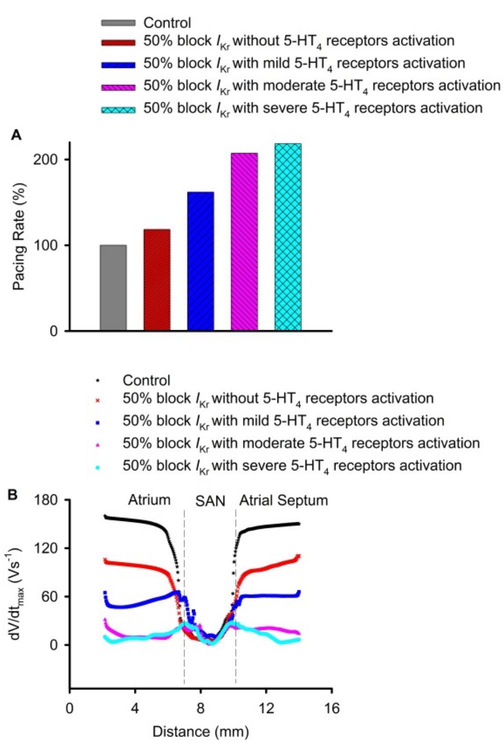

Fig 4. Summarized effects of various degree of 5-HT$_4$ receptors activation by cisaprid on pacing rate and conduction velocity.

The effect of cisaprid with various degree of activation of 5-HT$_4$ receptors on the relative conduction characteristic (maximal upstroke velocity [dV/dt$_{max}$]) was shown in Figure 4B. Both I_{Kr} blockade and 5-HT$_4$ receptors activation reduced dV/dt$_{max}$ in the atrium, implicating the reduction of the conduction velocity across the SAN-atrium.

With gradually increasing activation of 5-HT$_4$ receptors by cisaprid, abnormal APs analogue to early-afterdepolarizations (EADs) were induced (Fig 5, green and blue curves) in atrial septum cells, which may contribute the genesis of atrial arrhythmia. The induction of abnormal AP profiles may be partially attributed to the combined effect of the prolongation of AP plateau due to the increases of I_{CaL} and the accelerated excitation from central SAN.

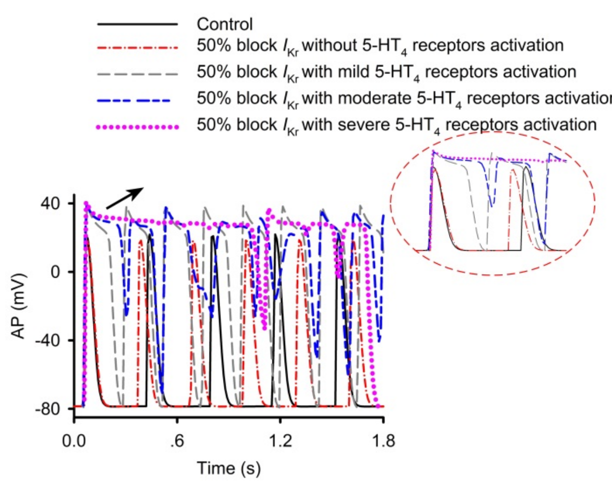

Figure 5. Abnormal APs induced by increasing 5-HT$_4$ receptors activation. (50% block I_{Kr} with various degree 5-HT$_4$ receptors activation.)

4. Discussion and conclusion

In this study, we investigated the actions of cisapride alone and its combined effects with 5-HT_4 receptors impair cardiac pacemaking APs and their conduction using multi-scale models.

At single cell level, the action of cisapride on I_{Kr} alone had positive chronotropic effect in the central SAN cell (increasing the pacemaking rate by 48.3%), but had virtually no effect on the peripheral cell. When its activation to 5-HT_4 receptors was considered together with I_{Kr} blocking, cisapride increased the pacing rate (PR) (by 78.4%) in centre SAN cell, which dominates the heart rhythm; but decreased the PR substantially in the periphery SAN cell (by 21%). At the tissue level, cisapride increased the PR in the intact SAN-atrium, and amplified the tachycardia effect of 5-HT_4 receptor activation, leading to pacemaking site shift. It altered the activation sequence of cardiac excitation waves and reduced dv/dt_{max} of the atrium. In addition, EADs were observed in the atrium. In this study, the accelerated excitation from SAN and increasing I_{CaL} in atrium may the main causes of abnormal APs analogue to EADs in atrial cells.

Our simulation study substantiates the causative link between cisapride and cardiac pacemaking dysfunctions. It suggests that activation of 5-HT_4 receptors by cisapride may account for atrial arrhythmogenesis, which should be taken into consideration for new anti-arrhythmic drug design.

Acknowledgements

Give any acknowledgements here. This study was supported by the National Natural Science Foundation of China (NSFC) under Grant No.61173086 and No.61179009.

References

[1] Olsson S, Edwards IR. Tachycardia during cisapride treatment. *Bmj*. 1992;305:748-749

[2] Inman W, Kubota K. Tachycardia during cisapride treatment. *Bmj*. 1992;305:1019-1019

[3] Wilhelms M, Rombach C, Scholz EP, Dossel O, Seemann G. Impact of amiodarone and cisapride on simulated human ventricular electrophysiology and electrocardiograms. *Europace*. 2012;14 Suppl 5:v90-v96

[4] Bach T, Syversveen T, Kvingedal AM, Krobert KA, Brattelid T, Kaumann AJ, Levy FO. 5ht4(a) and 5-ht4(b) receptors have nearly identical pharmacology and are both expressed in human atrium and ventricle. *Naunyn-Schmiedeberg's archives of pharmacology*. 2001;363:146-160

[5] Pau D, Workman AJ, Kane KA, Rankin AC. Electrophysiological and arrhythmogenic effects of 5-hydroxytryptamine on human atrial cells are reduced in atrial fibrillation. *Journal of molecular and cellular cardiology*. 2007;42:54-62

[6] Bateman DN. The action of cisapride on gastric emptying and the pharmacodynamics and pharmacokinetics of oral diazepam. *European journal of clinical pharmacology*. 1986;30:205-208

[7] Langlois M, Fischmeister R. 5-ht4 receptor ligands: Applications and new prospects. *Journal of medicinal chemistry*. 2003;46:319-344
Bach T, Syversveen T, Kvingedal AM, Krobert KA, Brattelid T, Kaumann AJ, Levy FO. 5ht4(a) and 5-ht4(b) receptors have nearly identical pharmacology and are both expressed in human atrium and ventricle. *Naunyn-Schmiedeberg's archives of pharmacology*. 2001;363:146-160

[8] Pino R, Cerbai E, Calamai G, Alajmo F, Borgioli A, Braconi L, Cassai M, Montesi GF, Mugelli A. Effect of 5-ht4 receptor stimulation on the pacemaker current i(f) in human isolated atrial myocytes. *Cardiovascular research*. 1998;40:516-522

[9] Castro L, Mialet-Perez J, Guillemeau A, Stillitano F, Zolk O, Eschenhagen T, Lezoualc'h F, Bochet P, Fischmeister R. Differential functional effects of two 5-ht4 receptor isoforms in adult cardiomyocytes. *Journal of molecular and cellular cardiology*. 2005;39:335-344

[10] Zhang H, Holden AV, Kodama I, Honjo H, Lei M, Varghese T, Boyett MR. Mathematical models of action potentials in the periphery and center of the rabbit sinoatrial node. *American journal of physiology. Heart and circulatory physiology*. 2000;279:H397-H421

[11] Rampe D, Roy ML, Dennis A, Brown AM. A mechanism for the proarrhythmic effects of cisapride (propulsid): High affinity blockade of the human cardiac potassium channel herg. *FEBS letters*. 1997;417:28-32

Address for correspondence.
Henggui Zhang
Mailbox 332, Harbin Institute of Technology
Harbin 150001, China
H.Zhang-3@manchester.ac.uk