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

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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Drugs, such as cisapride, have to be withdrawn from clinical uses due to their side effects, i.e., cardiotoxicity.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-HT₄) 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-HT₄ 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 IKr had positive chronotropic effect in the central SAN cell, but had virtually no effect on the peripheral cell. When its activation to 5-HT₄ receptors was also considered, cisapride increased the pacing rate (PR) in centre SAN cell; but decreased it substantially in the periphery SAN cell. When its activation to 5-HT₄ receptors was also considered, cisapride increased the pacing rate (PR) in centre SAN cell; but decreased it substantially in the periphery SAN cell. When its activation to 5-HT₄ receptors was also considered, cisapride increased the pacing rate (PR) in centre SAN cell; but decreased it substantially in the periphery SAN cell. When its activation to 5-HT₄ receptors was also considered, cisapride increased the pacing rate (PR) in centre SAN cell; but decreased it substantially in the periphery SAN cell. When its activation to 5-HT₄ receptors was also considered, cisapride increased the pacing rate (PR) in centre SAN cell; but decreased it substantially in the periphery SAN cell. When its activation to 5-HT₄ receptors was also considered, cisapride increased the pacing rate (PR) in centre SAN cell; but decreased it substantially in the periphery SAN cell.

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Drugs, such as cisapride, have to be withdrawn from clinical uses due to their severe side effects, i.e., cardiotoxicity.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 (IKr) [3]. However, the mechanism of cisapride-induced tachycardia remains unclear. As an agonist, cisapride activates 5-Hydroxytryptamine 4 (5-HT₄) 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-HT₄ receptor activation stimulated cyclic Adenosine monophosphate (cAMP) synthesis and therefore induced activation of L-type Ca²⁺ channels (ICaL) via cAMP-dependent protein kinase (PKA) in the atria [7a]. In addition to ICaL activation, 5-HT₄ receptor activation also mediated the so-called pacemaker current IF in human atrial myocytes [8].

The direct effect of cisapride alone and its indirect effect associated with 5-HT₄ receptors activation on cardiac pacemaking impairment are still unclear. Although a research has been manually expressed 5-HT₄ receptor splice variants in mouse cardiomyocytes [9], it remains difficult to experimentally investigate the effect of 5-HT₄ receptor on cardiac arrhythmogenesis due to the absence of 5-HT₄ 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-HT₄ 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-HT₄ 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 IKr was simulated by simple pore blocking of IKr based on experimental data [11]. Due to the lack of experimental data, the impact of cisapride on the activation of 5-HT₄
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.

<table>
<thead>
<tr>
<th>Cisapride (mol/L)</th>
<th>↓$g_{Kr}$ (%)</th>
<th>5-HT$_4$ receptor activation</th>
<th>↑$g_{CaL}$ (%)</th>
<th>$I_f$ shift (mV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.7·10$^{-8}$</td>
<td>30</td>
<td>Mild</td>
<td>205.9</td>
<td>+2.7</td>
</tr>
<tr>
<td>7.4·10$^{-8}$</td>
<td>50</td>
<td>Moderate</td>
<td>270.6</td>
<td>+3.6</td>
</tr>
<tr>
<td>9.8·10$^{-8}$</td>
<td>70</td>
<td>Severe</td>
<td>332.4</td>
<td>+4.4</td>
</tr>
</tbody>
</table>

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 =7.4·10$^{-8}$ mol/L)

Fig2. Effects of low and high dose of cisapride with/without 5-HT$_4$ receptors activation on pacing rate. (Low does: Cisapride =4.7·10$^{-8}$ mol/L, high does: Cisapride =7.4·10$^{-8}$ 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 (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.

![Figure 3](image)

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

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 4](image)

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

![Figure 5](image)

**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-HT4 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-HT4 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-HT4 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 $I_{CaT}$ in atrium may be 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-HT4 receptors by cisapride may account for atrial arrhythmogenesis, which should be taken into consideration for new anti-arrhythmic drug design.

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References

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