Effects of Potassium Channel Openers Nicorandil and Pinacidil on Electrical Activity of Cardiac Cells and Cardiac Tissues: a Simulation Study

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Abstract

Potassium channel openers (KCOs) have been reported to activate ATP-sensitive potassium channels ($K_{(ATP)}$) in cardiac muscle. The activation of this current accelerates the process of repolarisation of the cell and shortens the action potential duration (APD). In this study we analyse whether this effect is proarrhythmic or not. Indeed, there is a big controversy in this sense supported by several studies.

Based on experimental data, we formulated a mathematical description of the effects of two KCOs (pinacidil and nicorandil) on the ATP-sensitive potassium current. These models were introduced in a ventricular myocyte action potential description to carry out unicellular and multicellular simulations.

Our results suggest that pinacidil shortens APD further than nicorandil, as reported in several experimental works. In a cellular tissue, both drugs increase the probability of unidirectional block and thus reentry.

1. Introduction

It is well known that potassium channel openers (KCOs) increase ATP-sensitive potassium current ($I_{K(ATP)}$) in vascular smooth muscle, in pancreatic Beta cells and in heart myocytes [1,2]. The activation of these channels decreases the action potential duration (APD) [3] by accelerating the process of repolarisation of the cell. This effect elicits inhomogeneities of APD in the cardiac tissue, which can lead to serious arrhythmias and reentries. While several investigators support the hypothesis that KCOs are proarrhythmic [4,5], other authors describe KCOs effects as beneficial in specific arrhythmias [6].

The aim of this study is to approach this controversial action of KCOs on heart tissue. In this sense, computer simulations are a very helpful tool. While in experimental works, results are sensible to the uncontrolable variability of some experimental conditions, these variations are under control with computer simulations.

In this work we have analysed the probability of reentry in a ventricular tissue under different conditions, to study the proarrhythmic or antiarrhythmic potential of nicorandil and pinacidil. This study is based on mathematical models. Experimental data extracted from several works [7,8] allowed us to formulate these models.

2. Methods

It is known that KCOs activate $I_{K(ATP)}$ current by increasing the fraction of open channels (f_{ATP}). In a previous study [9] we described the formulation of f_{ATP} under the effects of pinacidil, based on pharmakokinetic equations and on experimental data. Following a similar procedure, we formulated a mathematical model of the effects of nicorandil on f_{ATP}. The pharmacokinetic scheme [9] yields:

$$f_{ATP} = 1 - \frac{[A]^H}{[A]^H + \frac{k_1 k_{11} k_{13}}{k_{d1}} + \frac{[D] k_{11} k_{13}}{k_{d2}} + \frac{k_1 k_{13} [N]}{k_{d3}} + \frac{k_1 [N][D]}{k_{d4}}}$$

where [A] is the intracellular concentration of ATP, [N] is the concentration of nicorandil and [D] is the concentration of intracellular ADP. To evaluate the constants, we carried out a non-linear multiple regression using experimental data from Nakayama et al. [7] and from Weiss et al. [8].

Once we formulated the effect of the drug, we introduced it in the mathematical description of $I_{K(ATP)}$ by Ferrero et al. [10]. This current, added to 12 other ionic currents described in the Luo and Rudy phase II model [11], reproduce the ventricular action potential. Unicellular simulations were carried out to test our model, and to compare the effects of nicorandil and pinacidil. The stimulation protocol consisted on a train of 10 rectangular

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current pulses, 2 ms in duration and amplitude 1.5 times diastolic threshold with a basic cycle length (BCL) of 800 ms. We recorded the data from the fourth AP elicited. APD was defined for 90% repolarization time. The programs were written in ACSL language using Gear's stiff algorithms to solve the non-linear system of differential equations. The maximum time step allowed was 0.01 ms. All simulations were carried out in a SUN SparcStation4.

The arrhythmic potential of both drugs was investigated through simulations on an unidimensional tissue of 300 cells based on the models described above. Metabolic conditions of the group of cells are defined in figure 1.

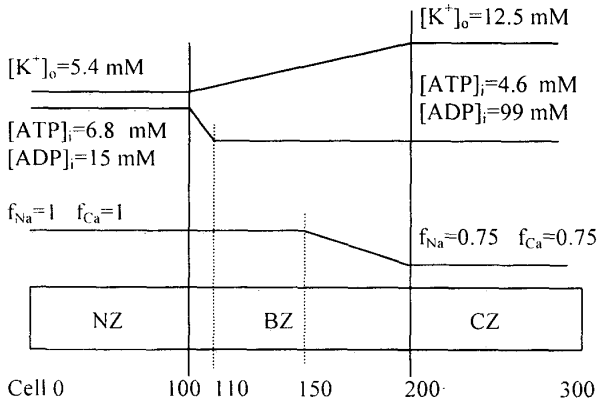

Figure 1. The normal zone (NZ) of the tissue is defined by the first 100 cells. Metabolical conditions are normoxia conditions: extracellular potassium concentration ($[K^+]_o$) of 5.4 mM, intracellular ATP and ADP concentrations ($[ATP]_i$ and $[ADP]_i$) of 6.8 and 15 mM respectively, and sodium and calcium channels unblocked. Along the 100 cells of the border zone (BZ) metabolical conditions change. $[K^+]_o$ increases to 12.5mM in the central ischemic zone (CZ), ($[ATP]_i$ and $[ADP]_i$ reach the ischemic rate earlier, 4.6 and 99 mM respectively. Finally, in the cell number 150 starts the block of sodium and calcium channels, due to a decrease in pH reaching a fraction of open channels in the CZ of 0.75 in both cases .

The first group of simulations consisted on a train of 4 rectangular current pulses, 2 ms in duration and amplitude 1.5 times diastolic threshold with a basic cycle length of 500 ms, applied to the tissue under different doses of the drugs. Then, immediately after these first basic simulations, we introduced one premature stimulus at different instants, to study the propagation of action potential (AP) in the cellular tissue under different drug conditions.

3. Results

The k_i constants resulting from the non-linear multiple regression, leaded us to a mathematical formulation of f_{ATP} for different doses of nicorandil. This model is similar to the one we described for pinacidil [9]. Both equations fit accurately the experimental data [7,8] extracted for their formulation.

The obtained results of APD shortening in one cell under the effects of different doses of the drugs, agreed with experimental studies, proving that pinacidil is a more potent KCO than nicorandil. Indeed, a lower dose of pinacidil (0.01mM) has stronger effects on APD (reduction to 78% of APD in the absence of the drug) than nicorandil (0.1mM) (reduction to 88.8% of APD in the absence of the drug) under the same metabolical conditions. These results were in argreement with experimental studies [12]. In figure 2, we can observe APD shortening under different metabolical conditions and different doses of the drugs.

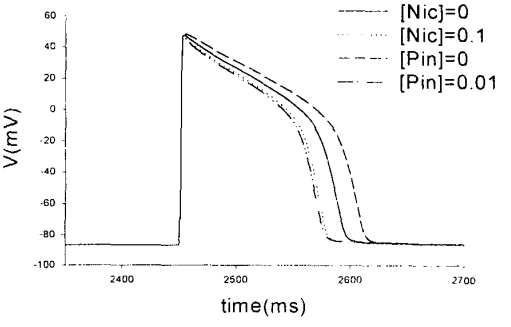

Figure 2. Action potentials for different concentrations of nicorandil ([Nic]) and pinacidil ([Pin]) under the same metabolical conditions: $[ATP]_i$ = 5 mM and $[ADP]_i$ = 30 mM.

On the unidimensional tissue of 100 healthy cells, 100 cells with the border zone properties and 100 ischaemic cells, the effects of a premature stimulation with the presence of different doses of both drugs were analysed, as detailed above in the methods section. The possible unidirectional block window is defined as the time interval of the premature stimulation, in which the action potential is not propagated. When the instant of premature stimulation is too close to the last basic stimulus, the action potential cannot be developed, because the cell is still in refractoriness. The first limit of the window is the instant from which AP propagation starts. This propagation stops in a certain cell, thus causing a block. The second limit of the window responds for the instant

from which there is complete propagation.

An increase in the dose of drug, increases this window; these results are summarized in table 1. Our results prove once more how pinacidil is more efficient than nicorandil, since the window limits do not show an important difference for doses of 0.005 mM pinacidil and 0.1 mM nicorandil, as shown in figure 3.

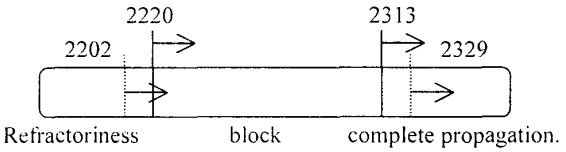

Figure 3. After 5 normal stimulations with a BCL of 500 ms, we stimulated cell 0 prematurely at the instants 2220 and 2200 ms, in tissues with [Pin]=0.005 mM (dashed lines) and [Nic]=0.1 mM (line) respectively. Those are the earliest instants from which action potential propagation starts, blocked at a certain cell of the tissue. When the premature stimulation takes place at the instants 2313 and 2329 respectively for pinacidil and nicorandil, a complete action potential propagation is achieved. These intervals of time [2220-2313] for pinacidil and [2202-2329] for nicorandil, are the possible unidirectional block windows.

Pinacidil dose (mM)	Nicorandil dose (mM)	Block window Time (ms)
0	---	[2229-2272]
0.0025	---	[2224-2300]
0.005	---	[2220-2313]
0.01	---	[2213-2367]
---	0	[2218-2310]
---	0.1	[2202-2329]
---	0.3	[2176-2500]

Table 1. Possible unidirectional block windows for different doses of pinacidil and nicorandil.

In figure 4 we can see the block of AP propagation when the premature stimulus takes place at an instant of time of the window.

4. Discussion

KCO drugs, such as pinacidil, nicorandil and cromakalim, activate K_{ATP} channels present in ventricular myocytes. Several experimental studies [1] have proved their efficacy at cellular level.

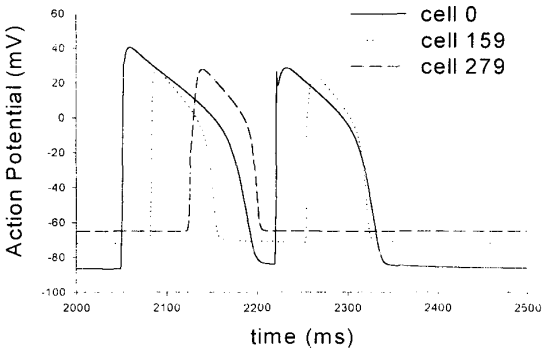

Figure 4. The first 3 action potentials were originated by the fifth basic stimulation in cell 0,159 and 279 with a dose of 0.1 mM nicorandil. A premature stimulation at the instant 2220 ms was propagated as action potential until cell 279, where we can observe a block.

Other in vivo experiments were carried out to describe their proarrhythmic or antiarrhythmic effect. In some cases [3], KCOs enhanced arrhythmias provoked by reentries. However, other authors have proved in their experiments the protective potential of these drugs against triggered arrhythmias and ischemic injury [6]. The ambiguous behavior of this kind of drugs should be further analyzed.

In this study, by means of computer simulations, we have investigated the effects of KCOs drugs on an ischemic tissue. During ischemia, the activation of K_{ATP} channels elicits the shortening of APD. Another effect of ischemia is the high rate of extracellular potassium concentration, responsible for the post-repolarisation-refractoriness. In this sense, the complete refractory period is prolonged in comparison to healthy cells. The addition of KCO, shortens the APD even more, which should shorten as well the complete refractory period of the cell. However, in this study, we have showed how the effect of an increased dose of the drug seams to due a higher probability of block. Indeed, there is an important shortening of APD due to the drug action. This effect could be proarrhythmic if the action potential block was unidirectional, being the nest of a possible reentry.

5. Conclusions

Pinacidil and nicorandil have a similar effect on APD , although pinacidil is more efficient as a KCO. The APD shortening they both elicit creates difficulties in the propagation of the action potential and can lead to an unidirectional block and thus reentry. In this study we have shown that higher doses of pinacidil and nicorandil,

increase the possibility of reentries. However, further studies should be carried out to characterize properly the role of these drugs.

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