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Scientific Program & Abstracts



Role of calcium/calmodulin-dependent protein kinase II activation in beta-adrenergic stimulation of potassium currents in canine ventricular cardiomyocytes under action potential clamp conditions

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Introduction and purpose: Acute β -adrenergic receptor (β -AR) stimulation shortens the ventricular action potential (AP). This effect is mainly regulated by the β -adrenergic stimulation of the cardiac potassium currents. Our aim was to investigate the extent of calcium/calmodulin-dependent protein kinase (CaMKII) involvement in mediating the effect of β -AR activation on the most important potassium currents.

Methods: We carried out our experiments on isolated cardiomyocytes originating from canine left ventricles. 4 potassium currents (rapid and slow delayed rectifier potassium current – I_{Kr} , I_{Ks} ; transient outward current – I_{to} and inward rectifier potassium current – I_{K1}) were measured under a “canonical” AP under action potential voltage clamp conditions. Data were collected in four study groups: [1] Tyrode solution (CTRL), [2] after beta-adrenergic stimulation with 10 nM isoproterenol (ISO), [3] inhibition of CaMKII with 1 μ M KN-93 (KN-93), [4] after beta-adrenergic stimulation with inhibited CaMKII (KN-93+ISO).

Results: Neither I_{to} nor I_{Kr} differed significantly in the four groups studied. I_{Ks} was prominently larger in ISO than under CTRL or KN-93 conditions having an about 6-fold larger current amplitude and carrying about 8 times as much total charge. In the KN-93+ISO group, I_{Ks} showed an about 2.5 times smaller amplitude and carried roughly half as much total charge compared to the ISO group.

I_{K1} current amplitude did not differ among the studied groups, the total carried charge however was significantly, about 25 % larger in the ISO group compared to CTRL, and about 15 % larger compared to KN-93+ISO. Under beta-adrenergic stimulation, I_{K1} starts to activate earlier during the AP plateau. I_{K1} density was about 3 times greater both at +20 mV and at 0 mV membrane potential under the command “canonical” AP in ISO compared to CTRL. Similarly, I_{K1} density was about 60 % and 90 % larger at +20 mV and at 0 mV, respectively, in KN-93+ISO compared to KN-93.

Conclusion: Based on the results of our researches the CaMKII activation plays an important role in β -adrenergic stimulation of I_{Ks} and I_{K1} potassium currents.

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Contribution of late sodium current to the electrophysiological characteristics of canine left ventricular cardiomyocytes

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Background: The late sodium current $I(\text{Na,L})$ plays pathophysiological role in several heart diseases. Despite this fact, the contribution of $I(\text{Na,L})$ to the cardiac ventricular action potential (AP) has not yet been characterized under physiological circumstances. We wanted to visualize $I(\text{Na,L})$ during a canine ventricular AP and to determine the effect of $I(\text{Na,L})$ blockade on the AP shape and on the short term variability of the AP duration (APD).

Methods: Experiments were performed in isolated canine left ventricular myocytes. We used the AP voltage clamp technique to visualize $I(\text{Na,L})$ during the AP by 1 μM GS-458967 (GS). Conventional microelectrode technique was used to determine the effects of $I(\text{Na,L})$ blockade on AP morphology.

Results: Under the AP, the GS sensitive current showed a peak at the AP upstroke (likely because of early sodium current ($I(\text{Na,E})$) inhibition), and then showed a sustained, gradually decreasing current due to $I(\text{Na,L})$.

At 1 s pacing cycle length (PCL) GS reduced the maximal rate of depolarization (v_{max}) by 35% and AP amplitude (APA) by 15%. These effects are likely due to the small $I(\text{Na,E})$ blocking effect of GS. GS shortened the APD by 14% measured at 90% of repolarization and depressed the mid-plateau membrane potential by 6 mV. GS decreased short term APD variability by 18%. At shorter PCL, effects of GS on APA and v_{max} were more pronounced, indicating a stronger $I(\text{Na,E})$ blockade under these conditions. Effects of GS on APD, mid-plateau potential and short term APD variability were less prominent with shorter PCL.

Conclusion: In our experiments the profile of $I(\text{Na,L})$ was successfully recorded under physiological conditions. The blockade of $I(\text{Na,L})$ has been shown to affect AP morphology and APD short term variability. Based on these results, $I(\text{Na,L})$ significantly contributes to the electrophysiological characteristics of cardiac ventricular myocytes.

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TRPM4 inhibitor 9-phenanthrol blocks Na^+ and K^+ but not Ca^{2+} currents in canine ventricular myocytes

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Background: 9-phenanthrol has been used for suppression of TRPM4 channels in various cardiac preparations, however, the selectivity of the compound to these channels is uncertain. Therefore, the present study was designed to investigate the concentration-dependent effects of 9-phenanthrol on the action potential morphology and on the major cardiac ionic currents in enzymatically dispersed canine ventricular cells.

Methods and results: Ionic current measurements were carried out in the whole cell configuration of the patch-clamp technique, where the pipette solution contained 10 mM BAPTA in order to prevent the Ca^{2+} -dependent activation of TRPM4 channels during the measurements. 9-phenanthrol (10 and 30 μM) significantly suppressed the transient outward K^+ current, the rapid delayed rectifier K^+ current and the inward rectifier K^+ current with the blocking potency for $I_{\text{Kr}} < I_{\text{K1}} < I_{\text{to1}}$. These effects of 9-phenanthrol were partially reversible. L-type Ca^{2+} current was not affected by 9-phenanthrol up to the concentration of 30 μM . In addition to these effects, 9-phenanthrol induced a steady outward current at potentials positive to -40 mV. The amplitude of this current was larger at more positive voltages and increased with the concentration of 9-phenanthrol.

Action potentials were recorded using sharp microelectrodes. The maximal rate of depolarization, phase-1 repolarization and terminal repolarization were significantly decreased and the plateau potential was depressed by 9-phenanthrol (3-30 μM) without alteration in the resting membrane alterations of ionic currents.

Summary: In conclusion, 9-phenanthrol is not selective to TRPM4 channels in canine ventricular myocardium, therefore its application as a TRPM4 blocker can be appropriate only in expression systems but not in native cardiac cells.

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Johann Wojta, Zoltán Papp

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