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Basal cAMP/Pka/Ca2+ Signaling is Linked to Action Potential (AP) Rhythmicity of Sinoatrial Nodal Cells (SANC) as well as to their Firing Rate

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Compared to freshly isolated SANC (f-SANC), the spontaneous AP firing rate at 34 ± 0.5°C of cultured adult rabbit SANC (c-SANC) is reduced by 50% (from 2.79 Hz to 1.55 Hz), due to G_i protein suppression of basal CAMP/PKA/Ca2+-dependent signaling. Here we demonstrate that altered PKA-dependent modulation of basal intracellular Ca2+ cycling also reduces AP rhythmicity of c-SANC. The AP rhythmicity index (RI, fig.1A), i.e. the offset of the 3rd peak from the autocorrelation function of AP records, or from power spectrum analysis is reduced in c- vs. f-SANC, and is associated with prolongation of spontaneous Local Ca2+ Release (LCR) period during diastolic depolarization and an increase in its coefficient of variation (0.199 ± 0.014 (n=41) for c-SANC vs. 0.122 ± 0.009 (n=32) for f-SANC, p<0.001). Acute β-adrenergic receptor stimulation by isoproterenol (ISO), phosphodiesterase inhibition by 3-isobutyl-1-methylxanthine (IBMX), or prolonged G_i suppression by pertussis toxin (PTX), which rescues impaired cAMP/PKA signaling in c-SANC, not only rescues the reduced AP firing rate, but also restores normal variability of LCR period and restores the rhythmicity of AP firing to the f-SANC level (fig.1B).

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Regional Variations of the Effects of Acetycholine in the Canine Heart

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Acetylcholine (ACH) release slows heart rate and atrioventricular conduction by stimulation of an inward rectifying current (IK,ACh) in atrial tissue. The effect of ACH on ventricular function is still debated. We compared the effect of ACH on APs in canine atria, Purkinje and ventricular tissue as well as on ionic currents in isolated cells. Action potentials were recorded from endo- or epicardial slices, Purkinje fibers, or atrial preparations. Whole-cell currents were recorded under voltage clamp conditions and unloaded cell shortening determined by video edge detection. The effects of ACH (1-10 μM) on IK,ACh and I_{Ca} in the 4 cell types were measured. In atrial tissue, application of ACH hyperpolarized the membrane potential and shortened action potential duration (APD). In Purkinje and ventricular tissues, no significant effect of ACH on APD, membrane potential or dV/dt was observed at 1 Hz pacing. Under voltage clamp, addition of ACH to atrial cells activated a large inward rectifying current (from +140 mV to -23.7 mV at 100 pA in amplitude at 1 Hz). A small inhibition of PAH.

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Changes of Axial Resistance following Mechanical Strain Prevail Over Stretch-Activated Currents in the Modulation of Conduction Velocity in Cardiac Cell Strands

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Tissue deformation and stretch-activated currents (I_{SAC}) exert a feedback on cardiac electrical function (mechano-electrical feedback). The effects of stretch on conduction velocity (CV) and their modulation by ISAC are still debated. We investigated the dependence of CV on passive tissue deformation and its modulation by I_{SAC} in cultured cardiomyocyte strands and simulation studies. Strands of neonatal rat ventricular myocytes were cultured on deformable substrates. CV was measured optically under control conditions, upon 10% shortening and subsequent lengthening, respectively, in agreement with the experiments. When ISAC was incorporated at previously reported levels, it caused a slight resting membrane depolarization by ~1 mV in undeformed fibers, but no major alteration of the CV behavior. These data suggest that functional SK channels are present in the mouse atrium. However, the effects of apamin were different under voltage- or current-clamp conditions, while the effects of UCL1684 were similar. This difference might arise from atrial myocytes expressing more than one population of SK channels, with one being apamin-sensitive and contributing to action potential repolarization. The effect of UCL1684 on APD is consistent with the recruitment of more SK channel activity at higher firing frequencies. Block of these SK channels increases BVR, a marker of drug induced repolarization-related proarrhythmias, raising the possibility that SK inhibition could be proarrhythmic.