Chaos Synchronization in the Genesis of Cardiac Arrhythmias

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Multiple experimental studies have shown post-pubescent males have shorter QT intervals than females. Clinical studies have revealed that sex differences in QT interval become apparent from puberty, suggesting sex steroid hormones play a role in shortening QT intervals. Testosterone has acute non-transcriptional effects mediated by increased nitric oxide (NO) production, which results in increased slow delayed rectifier K+ currents (I_{Kr}) and reduced L-type Ca2+ currents (I_{Ca,L}). Like testosterone, progesterone modifies I_{ks} and ICa,L currents via E2S production of NO. On the other hand, 17β-estradiol inhibits I_{Kr} current according to very recent experimental results. To investigate effects of sex
hormones on QT interval in males versus females, we constructed “male” and “female” cell models using Faber-Rudy model of the guinea pig myocyte. The female model incorporated physiological concentrations of 37°C epinephrine and progesterone measured in the follicular and luteal phases of the menstrual cycle, and predicts changes in APD at different stages of the menstrual cycle that are consistent with clinically observed QT interval fluctuations. The male model was developed to reflect changes induced by physiology concentrations of Testosterone. The models suggest protective effects of testosterone and progesterone to prevent APD prolongation and reduce QT interval, while estrogen significantly increase QT and susceptibility to drug-induced arrhythmias.

3442-Pos Board B499 Regression Analysis for Constraining Free Parameters in Electrophysiological Models of Ventricular Cells

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One of the challenges of building mathematical models is constraining free parameters. Parameter adjustments that have desirable effects on a given model output sometimes cause unexpected changes to other aspects of model behavior. Here, we extend a novel method for parameter sensitivity analysis and show that this procedure can uniquely define ionic conductances in a simple model of the human ventricular action potential(AP). We random-generated conductances in this model, ran repeated simulations, then collected the randomized parameters and simulation results as “input” and “output” matrices, respectively. Outputs included measures to characterize AP morphology as well as more abstract quantities such as the minimum pacing rate to induce AP alternans. We subjected the results to partial least squares regression, thereby deriving a regression matrix B. The elements of B indicate how changes in ionic conductances affect the model outputs. We show here that the matrix B can be inverted when 1) the number of inputs equals the number of outputs, and 2) outputs are linearly independent. The inverted matrix B\(^{-1}\) can then be used to specify the ionic conductances that would be required to generate particular combinations of model outputs. When we applied this procedure to our simulation results, we found that most ionic conductances could be specified with fairly high precision (R\(^2\) > 0.70 for six out of eight conductances). This procedure therefore shows tremendous promise as a tool for constructing new models. The success of our approach suggests that if several physiological characteristics of cell are known, this information can be used to constrain the model parameters.

Ion Channels, Other

3444-Pos Board B491 VSOP Protein Lacking the C-terminal Half of S4-like Segment Retains Proliferation

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VSOP/Hv1 is a protein that contains a voltage sensor domain but not pore domain [1, 2]. It exhibits properties of native voltage-gated proton channels reported in phagocytes and microglia. Addressing how proton permeates and how voltage-dependent gating is achieved in VSOP/Hv1 will lead to critical clues to understand mechanisms of voltage sensor operation and ion permeation. The putative fourth transmembrane segment (S4) of mouse VSOP (mVSOP) has three positively charged residues in a pattern similar to those conserved in other voltage-gated channels. We have previously shown that VSOP/Hv1 forms dimer and a version lacking the cytoplasmic region (V216X) expressing mainly as monomer exhibits robust voltage-dependent proton currents, suggesting that monomer constitutes proton permeation pathway [3]. However, V216X still contains some cytoplasmic stretch and it remained unknown whether a remaining stretch downstream of S4 segment is essential for proton channel activities. To address this, a series of deletion constructs of mVSOP were expressed in tsA201 cells and whole cell patch recordings were performed, with western blot analysis confirming that appropriately voltage-gated outward currents were elicited in constructs with stop codon at sites upstream to the third transmembrane segment. Proton permeation was verified by measuring intracellular pH using the pH-sensitive fluorescent dye, simultaneously with whole-cell patch clamp recording. Therefore, mVSOP retains functions of voltage-gated proton channel only with a truncated S4 segment, neglecting some possible mechanisms of proton permeation. To gain more insights, we are currently trying to biochemically map the topology of S4 using the cysteine-targeting reagent. [References]

3445-Pos Board B492 Mammalian Spermatozoa Possess A Voltage-Gated Proton Channel

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Mature mammalian spermatozoa are stored in quiescent state in the male reproductive tract. Upon ejaculation and during their transit through the female reproductive tract, they acquire progressive motility and undergo other important functional changes that enable them to reach and fertilize the egg. Sperm intracellular pH controls intracellular Ca\(^{2+}\) concentration, membrane potential and motility of the axoneme, and appears to be a key regulator of the sperm functional changes in the female reproductive tract. Unfortunately, the mechanisms controlling sperm intracellular pH remain poorly understood. Here we applied the whole-cell configuration of the patch-clamp technique to identify and characterize these mechanisms. In human sperm, when pH of the pipette and bath solutions was 6.0 and 7.4 correspondingly, we observed a robust voltage-gated proton current with a half-activation voltage ~13 mV. Similar to voltage-gated proton channels found in other cell types, the sperm proton channel (sHv) was strongly up-regulated by unsaturated fatty acids and potently blocked by Zn\(^{2+}\) with IC\(_{50}\) = 340 nM. Millimolar concentrations of Ca\(^{2+}\) and Mg\(^{2+}\) slowed down sHv activation kinetic but did not significantly reduced its amplitude. The amplitude of the voltage-gated proton current observed in human sperm was one of the highest among different cell types, with average current density ~ 50 pA/pF at +100 mV; however in mouse sperm the amplitude of the voltage-gated proton current at the same conditions was only about 5 pA/pF. Intracellular alkalization induced by sHv can lead to activation of pH-sensitive CatSper calcium channel resulting in well-known phenomenon of voltage-gated Ca\(^{2+}\) entry into the sperm cell. Here we present a model of how sHv may regulate sperm motility and discuss its role in male fertility and contraception.

3446-Pos Board B493 Electron Current and Proton Current in Activated Human Monocytes - Strong Glucose Dependence of the Electron Current

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Monocytes play multiple roles in the immune system, among other things, linking innate to adaptive immunity. Despite their biological importance, monocytes alone among all other phagocytes have not been investigated during...