We present a method to obtain the resting membrane potential ($\Delta\Psi$) from the dielectric behavior of a suspension of living cells by the use of dielectric spectroscopy. Since cells behave as conducting particles surrounded by low-conducting shells with surface charge densities, we can apply this technique to record the dielectric permittivity ϵ and conductivity σ of the suspension as a function of frequency. A previous theoretical model has correlated the relative dielectric permittivity ϵ of the suspension with resting membrane potential in the very low radio frequency regime (alpha). We use this model with our experimental results to obtain $\Delta\Psi$ for bacteria (E.Coli K12) and mammalian cell suspensions from HEK293-hERG line. We compare our value for $\Delta\Psi$ and its changes with the traditional methods-voltage sensitive dyes and patch clamping. For E. Coli measurements, resting membrane potential is changed by KCl addition to the suspension bath. As for mammalian cells, $\Delta\Psi$ changes are triggered by the use of various pharmaceutical compounds that act as HERG K^+ channel blockers and IC_{50} values are computed for each compound. Precise measurements of the dielectric permittivity ϵ and conductivity σ of live cells suspensions in the alpha frequency regime require prior elimination of the polarization errors. Polarization errors are caused by the ionic content of a buffer, and they affect the total impedance in the low frequency interval. We hereby present our approach of measure the polarization impedance then remove it by fitting both real and imaginary experimental curves with an ideal impedance $Z=d/i\omega\epsilon^*S$, where $\epsilon^*=\epsilon+1/i\omega\sigma$.

3423-Pos Board B470

Continuum Multi-dielectric Treatment Of Fluctuations And Breakdown In Membranes With Embedded Charges

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Stabilization of protein charges due to their interaction with membrane fluctuations is a subject of growing interest, especially because of its possible implications for voltage gating. Two complementary mechanisms governing charge-fluctuation interactions are considered: (1) the *electroelastic mechanism (EM)* [Partenskii, et al., *Israel J. Chem.* **47**, 385 (2007)], where the membrane is treated as an elastic slab (smectic bilayer model); (2) the *hydrophobic mechanism* (*HM*), which accounts for water penetration into the membrane's hydrophobic core with a corresponding interfacial tension contribution. In both cases the linear Poisson-Boltzmann equation is solved using a multi-dielectric continuum model with arbitrarily shaped membrane-water interfaces and a point charge surrounded by a ''Born sphere'' of low dielectric constant. The *EM* often leads to large membrane thickness perturbations, far larger than are consistent with elastic model descriptions. We demonstrate that switching from *EM* to *HM* becomes energetically advantageous at intermediate perturbation amplitudes. We apply kinetic Monte Carlo Reaction Path Following [Miloshevsky & Jordan. *J. Chem. Phys.* **122**, 214901 (2005)] using the water dimple's amplitude or the z-coordinate of the charge as the reaction coordinate for determining the shape of the solvation cavity. The resulting picture confirms that of recent MD studies.

3424-Pos Board B471

Phosphatidylserines Transduce Cell-Penetrating Peptides

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Certain short polycations, such as TAT and polyarginine, rapidly pass through cell membranes and pervade all intracellular compartments by an unknown mechanism called transduction. These cell-penetrating peptides (CPPs) when fused to biologically active peptides promise to be medically useful. I offer a simple model in which phosphatidylserine (and possibly other anions) transduce CPPs. The model also involves surface tension and the electrostatic field across the membrane of the cell. The model is consistent with the empirical upper limit on the cargo peptide of about 35 amino acids. More importantly, it also fits experimental data on how the transduction of a polyarginine-fluorophore into mouse C2C12 myoblasts depends on the number of arginines in the CPP and on the CPP concentration.

3425-Pos Board B472

Electrical Relaxation Experiments With Bilayer Lipid Membranes In The Presence Of Cationic Quinones

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Mitochondria-targeted antioxidants consisting of a quinone part conjugated with a lipophilic cation via a hydrocarbon linker were previously shown to prevent oxidative damage to mitochondria *in vitro* and *in vivo*. In the present work, we studied the permeation of a series of compounds of this type across a planar bilayer phospholipid membrane. For this purpose, relaxation of the electrical current after a voltage jump was measured. All compounds studied exhibited slow relaxation kinetics in the time range from seconds to minutes. With respect to the characteristic time of the relaxation, hydrophobic cations can be ranked in the following series: 10(plastoquinonyl) decylrhodamine 19 (SkQR1) > 10-(6′-plastoquinonyl) decyltriphenylphosphonium (SkQ1) > 10-(6′-methylplastoquinonyl) decyltriphenylphosphonium (SkQ3) > 10-(6′-ubiquinonyl) decyltriphenylphosphonium (MitoQ). The relaxation was strongly dependent on the redox state of the quinone part of the molecule being substantially suppressed in the reduced form. Surprisingly, the kinetics of relaxation of several compounds depended not only on the phospholipid composition of the bilayer but also on the pH of the bathing solution.

3426-Pos Board B473

Impact Of $Na_V1.7$-PEPD Missense Mutations That Slow The Rate Of Inactivation On Sensory Neuronal Resurgent Sodium Currents

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Voltage-gated sodium ($Na_v1.1$-9) channels are dynamic transmembrane proteins that, in response to changes in the potential across the lipophilic cell membrane, undergo specific conformational (gating) modifications, between ion-conducting (open) and non-conducting (closed and inactivated) states, to selectively conduct sodium ions through their aqueous pore. Importantly, changes in these voltage-dependent gating properties can impact action potential (AP) characteristics. TTX-sensitive sodium channels in cerebellar neurons can produce resurgent currents (Raman & Bean, 1997), intriguing currents that are reactivated during intermediate repolarizations following strong, but short, depolarizations. We observe resurgent currents in some DRG neurons and found that wild-type $Na_v1.6$ but not wild-type $Na_v1.7$ channels can generate resurgent currents in DRG neurons (Cummins *et al.*, 2005). It has been demonstrated that, in cerebellar neurons from $Na_v1.6$-null mice, slowing inactivation of the remaining Na_v current can induce resurgent currents (Grieco & Raman, 2004). Interestingly, single-point missense mutations in the SCN9A gene that encode for $Na_v1.7$, implicated in paroxysmal extreme pain disorder (PEPD), slow the rate of $Na_v1.7$ inactivation (Jarecki *et al.*, 2008). Therefore, we hypothesized that slowing of $Na_v1.7$ by PEPD mutations might induce abnormal resurgent currents, thus altering AP properties. To explore this hypothesis, we transiently transfected adult rat DRG neurons with a TTX-resistant form of human $Na_v1.7$-wild-type or PEPD mutant cDNA and rat $Na_v1.8$-targeted shRNA. Voltage-dependent properties were observed using whole-cell voltage-clamp electrophysiology and AP generation was tested using current-clamp electrophysiology. Recordings were made in the presence and absence of extracellular TTX. These experiments should yield insight into (1) the mechanism of resurgent sodium current generation in DRG neurons, (2) a potential additive effect in channel dysfunction observed in PEPD, and (3) how these mutant channels contribute to alterations in AP characteristics.

Cardiac Electrophysiology II

3427-Pos Board B474

Effects Of Mitochondrial Depolarization On Cardiac Electrical Activity In An Integrated Multiscale Model Of The Myocardium

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Metabolic or oxidative stress can trigger the abrupt collapse or oscillation of mitochondrial membrane potential, which activates KATP current and alters the cardiac action potential. This mechanism can introduce both temporal and spatial dispersion of electrical excitability in the form of a ''metabolic sink'', leading to heterogeneous conduction in the tissue, reentrant tachyarrhythmias, or fibrillation. To quantitatively study this mechanism, a 2D monodomain model of the myocardium (5×5cm2; 200 micron resolution) was developed, comprised of 63,000 nodes, each representing an integrated cellular model of cardiac excitation-contraction coupling, mitochondrial energetics, and ROS-induced ROS release (ECME-RIRR). Oxidative stress was initiated in a central circular zone of the tissue by increasing the fractional mitochondrial ROS production (shunt) during oxidative phosphorylation from 2% to 10%. Model simulations show that mitochondrial dynamics bifurcate during stimulation at 1 Hz and complete depolarization of $\alpha\Psi m$ ensues in the sink zone. Within the metabolic sink, sarcolemmal KATP currents increase, action potentials dramatically shorten, and the refractory period is abbreviated. These effects are enhanced by increasing the KATP density. In addition, fast and irregular electric activity (ventricular fibrillation) in the electrically paced tissue is observed when an S2 stimulus is introduced within or near the border of the