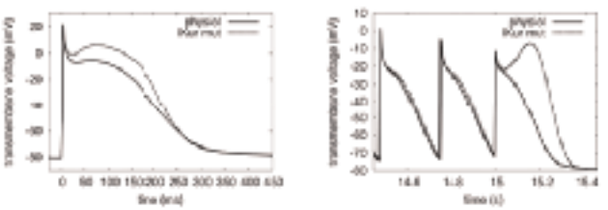
effect. The simulation results demonstrated a complementary way how a loss-of-function mutation can influence electrophysiology of cardiomyocytes and how this might induce AF.



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Smooth & Skeletal Electrophysiology

3027-Pos Familial Hypokalemic Periodic Paralysis - The Catastrophe on the Cusp of Weakness

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Board B330

Familial Hypokalemic Periodic Paralysis is an inherited muscle disease. Patients suffer from episodically occurring attacks of flaccid muscle paralysis, lasting hours to days. These episodes go along with an shift of potassium ions into muscle. Attacks are triggered by stimuli, that increase cellular uptake of potassium, e. g. insulin, adrenaline and rest after exercise. To relieve paralysis therapeutically, a large, overshooting administration of potassium, to increase its extracellular concentration, is needed. This does not result in a gradual increase of force, but a sudden jump from weak to strong, indicative of hysteresis. It is well known, that the paralysis is due to membrane inexcitability, caused by a pathologic depolarization. This has long been puzzling, since the known genetic defects in the genes, coding either for the voltage-gated sodium ($Na_V1.4$) or the voltage-gated calcium channel ($Ca_V1.1$), cause a loss-of-function in the channel proteins. Recently, evidence has been presented, that mutant channels are leaky for sodium, potassium or protons (Sokolov et al, 2007, Struyk et al, 2007). By using methods of systems dynamics, we analysed the effects of such a leak current on the behaviour of a mathematical model of an excitable cell. Bifurcation analysis reveals a cusp catastrophe as the manifold, that describes the dependency of equilibrium states on the extracellular potassium concentration and the size of the leak current. This elementary catastrophe can explain main features of the disease: bistability (strong vs. weak), hysteresis (potassium administration leads to a sudden increase of strength) and the occurrence of permanent weakness with no prior episode of weakness. Unclarities remain on the existence and meaning of compensatory mechanisms, the location of the resting state on the manifold, the quantitative impact of hysteresis and the exact mode of jumping between states.

3028-Pos Voltage-gated Ca^{2+} Currents In Smooth Muscle Cells Of Arterioles From Leg Muscles Of Mouse

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Board B331

Voltage-dependent Ca^{2+} currents are important for the myogenic tone and contractile responses of the smooth muscle cells (SMCs) in the resistance arteries of skeletal muscle. However, they have not been measured directly due to the difficulty of isolation of these SMCs. We succeeded to record voltage-dependent Ca^{2+} currents in single SMC of arterioles (20–40 μm diameter) from semitendinosus and biceps femoris muscles. The SMCs were not separated from the arteriole. Instead the electrical coupling between cells was prevented by various techniques.

With 20 mM Ca^{2+} in the bath, maximal currents (+30 mV) were 12±7 pA/pF (n=4). When 10 μM of nifedipine was added to the solution, currents peaked at +10 mV and their maximal density decreased to 2.3±0.3 pA/pF (n=3). The nifedipine resistant current could be further blocked by 45±13 % (n=3) by addition of 40 μM of Ni^{2+}. The magnitude of the low-voltage Ni^{2+}-sensitive component changed little when Ba^{2+} substituted extracellular Ca^{2+}. Based on these properties, this current is likely to be through the T-type Ca^{2+} channels. Although the presence of dihydropyridine-resistant Ca^{2+} channels in SMCs of resistance arterioles of skeletal muscle had been proposed previously, this is the first report of their significant contribution to Ca^{2+} currents in these cells.

3029-Pos AAV Delivery of the BK Channel Gene to Vascular Smooth Muscle as a Long-lasting Antihypertensive Strategy

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Board B332

Essential hypertension is a polygenetic disease afflicting nearly 1 billion individuals worldwide. Of the individuals offered antihypertensive drugs, only one third achieve blood pressure control due to the high cost, side effects and lack of adherence to the daily, multi-drug therapy that is often required. In this regard, the long-term expression of vasodilator proteins would be extremely advantageous to avoid the high cost and lack of adherence to daily drug regimens, and to minimize blood pressure fluctuations caused by short-acting antihypertensive drugs. Of major interest as a candidate vasodilator protein is the high-conductance, Ca^{2+}-activated K^+ (BK) channel that is expressed in the surface membrane of vascular smooth muscle cells (VSMCs). The BK channel is activated by rises in intravascular pressure, and mediates compensatory vasodi-

lation. We hypothesized that using adeno-associated viral (AAV) delivery to overexpress the pore-forming α subunit of the BK channel in VSMCs will provide a long-term antihypertensive effect. We constructed AAV plasmids using the VSMC-specific SM22α promoter to drive expression of the BKα gene. AAV/SM22α-BKα was administered by tail vein injection to mice with angiotensin II-induced hypertension. Blood pressure decreased to basal levels and this effect was observed for 6 weeks. Overexpressed BKα mRNA was detected only in arteries but not in heart or liver. We are currently assessing the properties of transduced BK channels in VSMCs, and will use isolated, perfused vessels to verify an enhanced dilator influence of BK channels in arteries of mice treated with AAV/SM22α-BKα as antihypertensive therapy.

3030-Pos The Inhibition Of K_V Channels Mediates The 5-HT-induced Mesenteric Artery Constriction In Rat: Role Of 5-HT_{2A} Receptor

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Board B333

Voltage-gated K^+ (K_V) current is the major regulator of resting membrane potential (E_m) in rat mesenteric artery myocytes. Recently, we reported that serotonin (5-hydroxytryptamine, 5-HT) depolarizes the mesenteric artery myocytes by decreasing K_V currents. Although it has been known that the 5-HT-induced mesenteric vasoconstriction is mediated via 5-HT_{2A} receptor in rat, the precise mechanism of the 5-HT-induced mesenteric vasoconstriction is still to be elucidated. Here, using nystatin-perforated patch-clamp technique and isometric tension measurement, we examined the hypothesis that inhibition of K_V current and subsequent membrane depolarization via 5-HT_{2A} receptor plays a role in 5-HT-induced vasoconstriction in rat mesenteric artery.

Nifedipine (1 μM) largely suppressed the 5-HT-induced mesenteric vasoconstriction, indicating that the 5-HT-induced vasoconstriction is primarily contributed by E_m depolarization. 4-aminopyridine (10 mM), a relatively selective K_V channel blocker in artery myocytes, caused marked mesenteric artery constrictions, whereas tetraethylammonium (1 mM) had no effect. These results support the hypothesis that 5-HT-induced inhibition of K_V channels and subsequent E_m depolarization contribute to mesenteric artery constriction. Next, we examined whether 5-HT-induced inhibition of K_V channels is mediated via 5-HT_{2A} receptor. Under control condition, 5-HT decreased the K_V current by ~40%. A 5-HT_2 receptor agonist α-methyl 5-HT similarly inhibited the K_V currents. However, neither anpirtoline, a 5-HT_{1B} receptor subtype agonist, nor BW-723C86, a 5-HT_{2B} receptor agonist, inhibited the K_V current. In addition, pretreatment of ketanserin, a selective 5-HT_{2A} receptor antagonist completely prevented the 5-HT-induced K_V current inhibition. The contractile responses to the 5-HT receptor subtype agonists and antagonists were well corresponded to the K_V channel response. These results suggest that 5-HT-induced inhibition of K_V current is mediated via 5-HT_{2A} receptor and this K_V inhibition plays the major role in 5-HT-induced vasoconstriction in rat mesenteric artery.

TRP Channels

3031-Pos Cation Permeability, Conductance And Block Of TRPV1 Receptors

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Board B334

TRPV1 receptors are polymodal cation permeable ion channels. They are widely expressed in sensory neurons where they stimulate membrane depolarization and act as a conduit for Ca^{2+} entry. These receptors discriminate poorly between monovalent cations and even appear to conduct the passage of relatively large cations, such as NMDG, across the plasma membrane. Further, they exhibit a high relative permeability to divalent cations. In this study, we aimed to further investigate the characteristics of the TRPV1 receptor channel pore. First, using standard reversal potential-based methods, we determined the permeability of the TRPV1 receptors to a spectrum of cations of different sizes. Beginning with the most permeable cation, the permeability sequence was as follows: Ca>Mg>Na~K~Cs>Li>Ethylammonium>Diethylammonium, Triethyl-ammonium>Tetraethylammonium~NMDG. Plotting relative permeability against the size of the permeating cation allowed us to estimate an approximate TRPV1 receptor pore diameter of ~8Å. Next, we recorded single channel conductance from outside-out patches in the presence of different extracellular cations, and determined the following conductance sequence for small monovalent cations: K~Cs~Na>Li>Ca~Mg. Finally, we observed that the chord conductance of single channel currents at −60mV was reduced from −4.1pA to −2.3pA upon addition of 2mM extracellular Ca^{2+}. Taken together, these data concur with previous studies indicating that the pore of TRPV1 receptors can accommodate large monovalent cations. However, the channel's high relative permeability and low relative conductance to divalent cations, together with the observation that Ca^{2+} blocks single channel cation currents, suggests the presence of a divalent cation-selective site of interaction somewhere in or near the channel pore.

3032-Pos The Fractional Calcium Current Of The TRPV1 Receptor Is Attenuated By Neutralization Of Acidic Side Chains Near The Channel Pore

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Board B335

TRPV1 receptors select poorly amongst small monovalent cations, but exhibit a high relative Ca^{2+} permeability (P_{Ca}/P_{Na}) comparable