Myotonic dystrophy (DM) is the most prevalent human dystrophy; it results from a *splicingopathy* in which muscleblind-like (MBNL) regulatory proteins are sequenced by expanded CUG repeat tracts. In order to investigate the specific role that MBNL proteins play on the functional expression of chloride (ClC-1) channels, we studied the chloride currents (ICl) in fibers isolated from FDB muscles of adult knockout (KO) mice lacking MBNL1, MBNL3, or both (MBNL1/3 DKO). ICl were recorded in fibers voltage clamped with 2 microelectrodes, internally equilibrated with 70 mM intracellular chloride, and bathed in TEA CI solution. We found that ICl records in fibers from the three knockout strains display kinetic and voltage-dependent properties comparable to those in control fibers (1295V mice). However, the maximal peak ICl (peak-IClmax), and the maximal conductance calculated from them (gClI,max), varied markedly among strains. Both peak-IClmax and gClI,max are significantly smaller (−34%, p<0.005) in fibers of adult MBNL1 KO mice, than in those of the controls. The persistently impaired functional expression of ClC-1 channels contrasts with the transient chloride channelopathy of the HSA15 model of DM. Furthermore, while ICl records in fibers of MBNL3 KO mice are identical to those from their control counterparts, peak-IClmax in fibers of MBNL1/3 DKO mice show more severe reductions (−50%, p<0.005) than those of MBNL1 KO. These interesting results suggest novel synergistic regulatory interactions between MBNL proteins which ultimately affect the functional expression of ClC-1 channels. This work was supported by NIH grants AR047664, AR048102, and AR054816. Precursors of MBNL1 mice were kindly provided by Dr. M. Swanson, University of Florida.

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1516-Pos

To the Molecular Mechanism of Mechanoelectrical Transduction in Cell
Biology

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Biology

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Admittedly, mechanical deformation governs intracellular potential by means of specific stretch-activated channels in cell membrane. At the same time, the key mechanism of the mechanical stimulus (stretch) transduction in electrophysiological response is still not clear. Numerous studies by different authors have convincingly demonstrated the cytoskeleton sub-membrane structures (cortex) critical need for the mechanoelectrical transduction providing. From the physicochemical point of view, the cytoskeleton as a whole, and the cortex in particular resembles a polyelectrolyte hydrogel, i.e., a 3D biopolymer network with the electric charges localized on the macromolecular filaments, and with free counterions dispersed in the liquid phase inside the network. Presented investigation addresses the possible mechanism of stretch on cell electrochemical potential change, based on the physicochemical properties of cytoskeletal network. Synthetic polyelectrolyte gels were used as an experimental model of the cytoskeleton. We have found that axial deformation of polyelectrolyte gel shifts gel potential to depolarization. The decrease of potential with gel is the result of diminishing of counterion concentration inside the gel. The underlying mechanism of it is likely the universal process of counterion adsorption on charged polymer filaments due to the decrease of the distance between polymer filaments owing to gel elongation. Thus, the physicochemical properties of the gel network may affect the balance of ions between the cortex and liquid phase of the cell. Independently of the activity of stretch-activated channels, stretch of the cortex network is able to diminish the absolute value of cell potential. On the other hand, we may suppose also that such depolarization is the main factor that determines stretch-activated channels activity.

1517-Pos

Mathematical Modelling of the Autonomous Activity of Cultured Neonatal Rat Ventricular Myocytes

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Problem statement. The biological pacemaker is a new therapeutic approach that could lead to optimized treatment of bradyarrhythmia. A possibility is the development of a thin sheet of cardiomyocytes, cultured to obtain a target activation rate. Fundamental research, often conducted with neonatal rat ventricular myocytes (NRVMs), partially revealed two basic mechanisms of automaticity termed Voltage Clock (synergy of membrane currents) and Calcium Clock (internal oscillations of calcium concentration). To date, no model is able to reproduce such the complex automaticity found in cultured NRVMs. The present project aims to fill this gap. Methods. A non-autonomous NRVM ionic model (Korhonen-Tavi, 2009) is modified according to documented Voltage and Calcium Clocks mathematical formulations. The myocytes are cultured for 48 hours at low density, allowing cells to remain single on dishes. Autonomic action potentials (APs) are measured with patch clamp method, and calcium transients (CTs) with Fluo-4 AM.