contractile reserve decreases with consideration of protein characteristics governing the force-frequency relationship. However, the molecular alterations involved in the beta-adrenergic response lead to an increase in sensitivity. By following contractile function over time, and assessing the impact of physiologically relevant modulators of function, we will obtain a temporal resolution of cardiac function in its transition from the healthy to the diseased state.

3746-Pos

A Novel Pleiotropic Effect of Statins: Enhanced Cardiomyocyte β2-Adrenoceptor Responsiveness

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Pleiotropic effects of statins on endothelial cells, vascular smooth muscle cells and fibroblasts are well-established and contribute to reduced cardiovascular morbidity and mortality. Here we test whether these effects extend to the cardiomyocyte. Adult rat ventricular cells were maintained in culture +/- 10 μM simvastatin (SIMV). After 48h, shortening and $[Ca^{2+}]_i$ responses to β1-adrenoceptor stimulation were identical in SIMV and control cells, but a marked SIMV potentiation of the β2 response was seen (Figure 1). Statins mediate their effects through cholesterol-dependent and -independent pathways. Caveolae are cholesterol-dependent signalosomes that limit the magnitude of β2, but not β1, responses in the adult cardiomyocyte. Therefore we surmised that SIMV's effects could be mediated through caveolar disruption. Indeed, the mean density of caveolae (visualised by electron microscopy) was reduced in SIMV-treated cells (0.63 ± 0.08 vs. 0.86 ± 0.11 μm^{-1}; $P<0.05$; n=9 cells from 3 hearts). This is the first demonstration of effects of statins on the β responsiveness of the adult cardiomyocyte. These data suggest a novel mechanism for the beneficial effects of statins in heart failure - enhancing the contractile reserve of the failing heart, through effects on the caveolar signalosome.

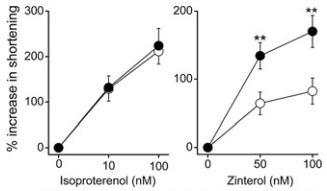

Figure 1. Simvastatin (●) selectively enhances the inotropic response of the cardiac myocyte to β2, but not β1, adrenoceptor stimulation compared with controls (○). Similar effects on $[Ca^{2+}]_i$ responses to β-stimulation were seen. Data are from n=24-28 cells; 7 hearts. ** $P<0.01$ vs control; Student's t-test.

Intracellular Cargo Transport

3747-Pos

Real Time Visualization of Axonal Transport of GTPase Rab7 in Rat Embryonic Dorsal Root Ganglia

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Charcot-Marie-Tooth (CMT) neuropathy, characterized by severe sensory neuron loss, is the most common inherited disorder of the peripheral nervous system. Several GTPase Rab7 protein mutants, mainly targeted to the highly conserved amino acid, have been identified in CMT type 2B. Exact mechanism of how such point mutations cause malfunction of neurons is not well understood. Here, we studied how those Rab7 mutations affect their axonal transport in primary rat dorsal root ganglia neurons. Real time fluorescence imaging revealed that Rab7-containing endosomes engage in bi-directional transport in axons, similar to that of TrkA receptors in the same culture. However, the speed of Rab7 transport is significantly slower than that of TrkA. In addition, there is a clear variation in the speed of axonal transport between wild-type Rab7 and mutated Rab7 proteins. Our work suggested that point mutations of Rab7 proteins could potentially cause or contribute to CMT2B neurodegenerative disease by regulating its axonal transport process.

3748-Pos

Modeling Cytoskeletal Dynamics and Vesicle Movements in Growing Pollen Tubes

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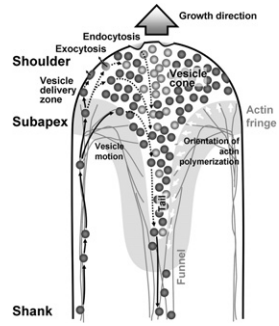
Intracellular cargo transport is a crucial process in growing plant cells. Since cellular expansion in walled cells entails the continuous assembly of new wall material, enormous amounts of polysaccharides need to be delivered to the growth site. In the rapidly elongating pollen tube the spatio-temporal movement pattern of exocytotic vesicles is precisely targeted and controlled by the continuously polymerizing actin cytoskeleton in the subapical region of the cell. Remarkably, the cone-shaped target region at the apical pole of the cylindrical cell does not contain much filamentous actin. We model the vesicular trafficking using as boundary conditions the expanding cell wall and the actin array forming the subapical actin fringe. Dynamic advancement of this actin fringe was obtained by imposing a steady shape and constant polymerization rate of the actin filaments. Letting vesicle flux into and out of the apical region be determined by the orientation of the actin microfilaments was sufficient to generate a flow that corresponds in magnitude and orientation to that observed experimentally. This model explains how the cytoplasmic streaming pattern in the apical region of the pollen tube can be generated without the presence of filamentous actin.



3749-Pos

Velocities of Microtubule-Based Motors in Living *Chlamydomonas*

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Reports in the published literature suggest that the velocities of vesicle transport in living neurons are discrete and quantal (multiples of a fundamental velocity), with the instantaneous velocity being dependent upon the number of molecular motors driving transport (Shtridelman *et al*., *Cell Biochem. Biophys*, 2008). We similarly observed discrete changes in the velocity of microspheres undergoing saltatory transport on the flagella of *Chlamydomonas*, and that these velocities appeared to be dependent upon location along the flagellum. We therefore studied the movements of adherent microspheres on flagella, driven by the intracellular motors kinesin-2 and dynein-2, to determine whether transport is driven at multiple, discrete velocities and whether they are spatially correlated. We measured separately the translational velocities of unconstrained and optically trapped microspheres as a function of position along the flagellum. The velocities of unconstrained microspheres were on average about two-fold higher than those of trapped microspheres. Unconstrained microsphere velocities in the anterograde and retrograde directions were not spatially correlated except at turn-around points near the beginning and end of the flagellum where velocities were consistently lower. Histograms of these data showed a broad distribution of velocities and suggested no strong evidence for quantized velocities. For trapped microspheres, for a given anterograde or retrograde transport event we often saw at least two discrete velocities; however, any two transport events can have different 'slow'and 'fast'velocities. Thus even when velocities are measured from a single microsphere at a specific position on a flagellum, combining multiple velocity histograms results in an apparently non-quantized, broad distribution of velocities. What causes the abrupt change between discrete velocities during movements of a microsphere is yet unknown.

3750-Pos

How the Flagellum Measures Its Length

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The intraflagellar transport (IFT) particle injector controls eukaryotic flagellar length. The injector works by restricting the availability of new material for growth of the organelle, analogous to a fuel injector controlling the speed of a single piston engine by limiting fuel in the piston. Using quantitative TIRF microscopy and computational image processing we measure GFP-tagged IFT proteins KAP and IFT27 in Chlamydomonas reinhardtii flagella over a range of cellular and flagellar states (i.e. regenerating cell vs steady state cell and short flagellum vs long flagellum). From measuring the IFT particles in the flagellum, we then back-calculate the behavior of the IFT particle injector. We then derive mathematical models for the system that controls the IFT particle injector, finding that our data are consistent with a two-state time of flight model and not a diffusing signal or a constant IFT particle number model as previous studies have suggested. These results indicate that the group of proteins responsible for the injector behavior includes a two-state protein, such as a GTPase, that travels the length of the flagellum to measure the flagellar length. A mutant in this putative protein with either a constitutive excited state or a constitutive ground state would then have abnormally long or abnormally short flagella respectively. Our results further indicate that the flagellar length is set by the flagellum rather than the cell, which implies that the organelle can self-regulate, to some extent independent of the cell.

3751-Pos

On the Movement of Cargo Driven by Molecular Motors and the Asymmetric Exclusion Processes

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