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Modification of actin fibers changes the electrical phenotype of cardiac myofibroblasts

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Background

Slow conduction and ectopic activity are major determinants of cardiac arrhythmogenesis. Both of these conditions can be elicited by myofibroblasts (MFBs) following establishment of heterocellular gap junctional coupling with cardiomyocytes. MFBs appear during structural remodeling of the heart and are characterized by the expression of α -smooth muscle actin (α -SMA) containing stress fibers. In this study, we investigated whether pharmacological interference with the actin cytoskeleton affects myofibroblast arrhythmogenicity.

Methods

Experiments were performed with patterned growth strands of neonatal rat ventricular cardiomyocytes coated with cardiac MFBs. Impulse conduction velocity (θ) and maximal upstroke velocities of propagated action potentials (dV/dt_{max}), expressed as % action potential amplitude change (%APA) per ms, were measured optically using voltage sensitive dyes. Actin was destabilized by latrunculin B (LtB) and cytochalasin D and stabilized with jasplakinolide. Data are given as mean \pm S.D. ($n = 5-22$). Single cell electrophysiology was assessed using standard patch-clamp techniques.

Results

As revealed by immunocytochemistry, exposure of MFBs to LtB (0.01–10 μ mol/L) profoundly disrupted stress fibers which led to drastic changes in cell morphology with MFBs assuming an astrocyte-like shape. In control cardiomyocyte strands (no MFB coat), LtB had negligible effects on θ and dV/dt_{max} . In contrast, LtB applied to MFB-coated strands increased θ dose-dependently from 197 ± 35 mm/s to 344 ± 26 mm/s and dV/dt_{max} from 38 ± 5 to 78 ± 3 %APA/ms, i.e., to values virtually identical to those of cardiomyocyte control strands (339 ± 24 mm/s; 77 ± 3 %APA/ms). Highly similar results were obtained when exposing the preparations to cytochalasin D. In contrast, stabilization of actin with increasing concentrations of jasplakinolide exerted no significant effects on impulse conduction characteristics in MFB-coated strands. Whole-cell patch-clamp experiments showed that LtB hyperpolarized MFBs from -25 mV to -50 mV, thus limiting their depolarizing effect on cardiomyocytes which was shown before to cause arrhythmogenic slow conduction and ectopic activity.

Conclusions

Pharmacological interference with the actin cytoskeleton of cardiac MFBs affects their electrophysiological phenotype to such an extent that they lose their detrimental effects on cardiomyocyte electrophysiology. This result might form a basis for the development of therapeutic strategies aimed at limiting the arrhythmogenic potential of MFBs.