Transforming growth factor-β1 decreases cardiac muscle L-type Ca^{2+} current and charge movement by acting on the $Ca_V1.2$ mRNA

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Transforming growth factors-β (TGF-βs) are essential to the structural remodeling seen in cardiac disease and development; however, little is known about potential electrophysiological effects. We hypothesized that chronic exposure (6–48 h) of primary cultured neonatal rat cardiomyocytes to the type 1 TGF-β (TGF-β1, 5 ng/ml) may affect voltage-dependent Ca^{2+} channels. Thus we investigated T- (I_{CaT}) and L-type (I_{CaL}) Ca^{2+} currents, as well as dihydropyridine-sensitive charge movement using the whole cell patch-clamp technique and quantified $Ca_V1.2$ mRNA levels by real-time PCR assay. In ventricular myocytes, TGF-β1 did not exert significant electrophysiological effects. However, in atrial myocytes, TGF-β1 reduced both I_{CaL} and charge movement (55% at 24–48 h) without significantly altering I_{CaT}, cell membrane capacitance, or channel kinetics (voltage dependence of activation and inactivation, as well as the activation and inactivation rates). Reductions of I_{CaL} and charge movement were explained by concomitant effects on the maximal values of L-channels conductance (G_{max}) and charge movement (Q_{max}). Thus TGF-β1 selectively reduces the number of functional L-channels on the surface of the plasma membrane in atrial but not ventricular myocytes. The TGF-β1-induced I_{CaL} reduction was unaffected by supplementing intracellular recording solutions with okadaic acid (2 μM) or cAMP (100 μM), two compounds that promote L-channel phosphorylation. This suggests that the decreased number of functional L-channels cannot be explained by a possible regulation in the L-channels phosphorylation state. Instead, we found that TGF-β1 decreases the expression levels of atrial $Ca_V1.2$ mRNA (70%). Thus TGF-β1 downregulates atrial L-channel expression and may be therefore contributing to the in vivo cardiac electrical remodeling.

calcium channel; atrial fibrillation; muscle disease

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