Transforming growth factor-β1 decreases cardiac muscle L-type Ca$^{2+}$ current and charge movement by acting on the Ca$v_1.2$ mRNA

Guillermo Avila, Irma M. Medina, Esperanza Jiménez, Guillermo Elizondo, and Citlalli I. Aguilar

1Department of Biochemistry and 2External Section of Toxicology, Cinvestav, México

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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$v_1.2$ 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$v_1.2$ 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

G. Avila, Dept. of Biochemistry, Cinvestav, Mexico DF 007000, Mexico (e-mail: gavila@cinvestav.mx)