Exercise Ameliorates Disruption of the Dystrophin-Associated Glycoprotein Complex and Fibrosis in the Aging Rat Heart

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ABSTRACT

The dystrophin-glycoprotein complex (DGC) is localized and integrated into the cell membrane. The DGC provides a mechanical link between the cellular cytoskeleton and the extracellular matrix (ECM). In cardiac muscle, disruption of DGC might be involved in mediating cardiac remodeling that occurs with aging, cardiomyopathy, and heart failure through transforming growth factor-beta (TGF-ß). Decorin is a small leucine-rich proteoglycan closely related to the DGC component that binds to collagen. Decorin reduces fibrosis via inhibition of TGF-ß and myofibroblast formation. PURPOSE: To test the hypothesis that exercise training (ET) would alleviate age-related disruption of localization in DGC proteins (dystrophin, α-syntrophin, and β-sarcoglycan), and ET will upregulate decorin. METHODS: Young (3 mo.) and old (31 mo.) FBNF1 rats were assigned into sedentary (YS, OS) and exercise (YE, OE) groups (n=10/group), with ET rats training on a treadmill 45 min/d, 5 d/wk for 12 wk. Hearts were extracted, weighted, and dissected into the left ventricle (LV), septum, and right ventricle. LV and septa samples were homogenized, and protein expression was detected using western immunoblotting. Histology (H&E staining) and immunofluorescence were conducted to examine morphological changes and localization of DGC proteins, decorin, α-SMA, and TGF-ß. Aging and exercise comparisons were made using two-way ANOVA for repeated measure with Fisher's LSD *post hoc* test ($p<.05$). RESULTS: Dystrophin, α-syntrophin, and β-sarcoglycan in LV were delocalized from the membrane with aging, particularly in fibrotic areas, which was normalized by ET. LVs from old rats displayed higher TGF-β-positive staining and protein abundance (+94.5%,$p<.05$), while TGF-β localization and protein levels were suppressed in OE vs. OS, (-27.5%, $p<.05$). α-SMA localization was significantly elevated with age (+77.3%, $p<.05$), but reduced in old hearts with ET (-27.5%, $p<.05$). Furthermore, collagen type 1 signal intensity was higher in OS (+43.7%, $p<.05$), and was significantly ameliorated with ET (-27.6%, $p<.05$). CONCLUSIONS: Our findings indicate that exercise training provides significant protection against fibrosis, myofibroblast activation, and elevation of TGF-ß associated with upregulation of decorin and protection of DGC structure.