**GENETIC BASIS OF CARDIAC DYSFUNCTION: PROTECTIVE ROLE OF ALL-TRANS RETINOIC ACID AND HISTONE DEACETYLASE INHIBITOR**

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In the present study, we examined the effect of genetically determined differences in the guanylyl cyclase-A/natriuretic peptide receptor-A (GC-A/NPRA) gene (Npr1) copies on the expression levels of proinflammatory mediators, matrix metalloproteinases (MMPs), and cardiac hypertrophic markers in Npr1 gene-targeted mouse models. We also determined whether stimulation of Npr1 by all-trans retinoic acid (RA) and histone deacetylase (HDAC) inhibitor, sodium butyric acid (SB) suppresses the expression of cardiac disease markers. We utilized Npr1 gene-disrupted heterozygous (Npr1+/-, 1-copy), wild-type (Npr1+/+, 2-copy), and gene-duplicated (Npr1++/+, 3-copy) mice, which were treated intraperitoneally with RA, SB, and a combination of RA/SB, hybrid drug (HB) for 2 weeks. Untreated 1-copy haplotype mice showed significantly increased blood pressure, heart weight/body weight (HW/BW) ratio, hypertrophic markers, including beta-myosin heavy chain (beta-MHC) and proto-oncogenes (c-fos and c-jun), proinflammatory mediator nuclear factor kappa B (NF-kB), and MMPs (MMP-2, MMP-9) compared with 2-copy and 3-copy mice. The heterozygous 1-copy mice treated with RA, SB or HB, exhibited significant reduction in the expression of beta-MHC, NF-kB, c-fos, c-jun, MMP-2, and MMP-9. In drug-treated animals, the activity and expression levels of HDACs were significantly reduced and histone acetyltransferase activity and expression levels were increased. The drug treatments markedly increased the fractional shortening and reduced the systolic and diastolic dysfunction of the haplotype Npr1+/- mice hearts. The present findings demonstrate that a decreased Npr1 copy number enhances the expression of hypertrophic markers, proinflammatory mediators, and MMPs; on the contrary an increased Npr1 gene-copies as well as treatments with RA, SB, and HB repressed the cardiac disease markers and protect the heart in a Npr1 gene-dose-dependent manner.