Journal of Pharmacopuncture

ISSN 2093-6966 [Print], ISSN 2234-6856 [Online]
Journal of Pharmacopuncture 2016;19[3]:195-196
DOI: http://dx.doi.org/10.3831/KPI.2016.19.019

Letter to the editor

Epigenetic Mechanisms: New Targets for Heart Failure Pharmacopuncture

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Key Words

cardiac muscle, epigenetics, histones, protein kinases

Pharmacopuncture treatments are proposed for cardiovascular disease and heart failure [1]. Heart failure results from complex environment-gene interactions. β-adrenergic receptors and protein kinase A (PKA) interact with histones and related segments of deoxyribonucleic acid (DNA) at promoter regions of genes for messenger ribo nucleic acid (mRNA) transcription. This increases cardiac muscle mass and contractility in normal hearts. In heart failure, activation of β-adrenergic receptors and PKA promote pathological hypertrophy and decreased contractility. Experimental models show that prenatal exposure to hypoxia, cocaine, or nicotine increases susceptibility to heart failure when animals reach adulthood. Hypermethylation of DNA is an epigenetic mechanism associated with downregulation of the protein kinase C (PKC) gene in such models of heart failure. Downregulation of PKC is also produced by the stress-related hormone norepinephrine with upregulation of the hypoxia-inducible differentiation regulator Nix in norepinephrine-induced cardiac fibrosis [2]. Norepinephrine is also the main mediator of sympathetic neural activity. Sympathetic neural overactivity, a significant cofactor in human heart failure, is, therefore, implicated as a cofactor in this epigenetic mechanism for heart failure. Other epigenetic mechanism for cardiac hypertrophy and heart failure involve endothelin-1 induced downregulation of the cardiac myocyte differentiation factor RE1-silencing transcription signaler (REST) and GATA zinc-finger domain-containing protein-1 (GATAD1) induced inhibition of histone deacetylase (HDAC-2) in cardiac myocytes harvested from autosomal-recessive dilated cardiac myopathy patients with heart failure [3]. In contrast, both the HDAC-2 in cardiac myocytes and the HDAC-1 in cardiac fibroblasts are upregulated in experimental animal models of congestive heart failure [4]. A prominent role for inflammation in heart failure is suggested by tumor necrosis factor (TNF-α), a proinflammatory cytokine, inducing hypermethylation of the sarcoplasmic reticulum calcium ATPase (SERCA-2A) gene in cardiac myocytes, associated with diastolic dysfunction and heart failure. An important role for epigenetic mechanisms in heart failure is also suggested by HDAC-dependent stimulation of the stress-apoptosis intracellular signaling pathway, which induces hypertrophy of both cardiac and vascular smooth muscle [5].

A treatment involving manipulation of the epigenome is shown to be effective for reversal of pathological hypertrophy of cardiac myocytes, the forerunner of heart failure. This treatment involves downregulating DNA methyltransferase (DNMT) with lithium resulting in hypomethylation of cardiac myocyte DNA, upregulation of the glycogen synthase kinase-3 beta (GS3Kβ) gene, downregulation of the cell adhesion protein β-catenin, and inhibition of the Wnt pathway for signaling of cardiac myocyte differentiation.

Received: Aug 11, 2016 **Reviewed:** Aug 12, 2016 **Accepted:** Aug 12, 2016

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In summary, histone and DNA acetylations/methylations appear to have multiple roles in regulating cardiomyocyte contractility and producing heart failure. Expression of epigenetic signaling molecules should, therefore, be evaluated and considered as novel molecular targets for acupuncture and pharmacopuncture for prevention and treatment of heart failure.

Acknowledgment

This was supported in part by a training fellowship awarded to Yulia A Volkova MD by the American Center for Investigative Cardiology.

Conflict of interest

The authors declare that there are no conflict of interest.

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