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EDITORIAL COMMENT

Neuregulin-1

A Tonic for Cardiorenal Syndrome? And All Else That Ails Us?*

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The heart and kidneys are interlinked in their responsibility to maintain homeostasis. In a state of health, the 2 organs work in a partnership to maintain—to tone—proper blood volume and electrolyte status and tissue perfusion. Disturbances in either organ's function—whether acute or chronic—adversely effects the other. Globally, 15% to 20% of adults are afflicted with chronic kidney disease (CKD), which increases mortality dramatically. Age-associated declines in kidney function go hand in hand with declines in cardiovascular reserve, and it is widely known that cardiovascular disease (CVD) is the primary driver of mortality in patients with CKD. CKD accelerates aging of the cardiovascular system, and the ensuing cardiorenal syndrome has deleterious effects on other organ systems such as the musculoskeletal and nervous systems, making cardiorenal syndrome a disease with high morbidity and mortality.

We could certainly use a "tonic" for cardiorenal syndrome. Merriam-Webster defines a "tonic" as "an agent (such as a drug) that increases body tone; or: producing or adapted to produce healthier muscular condition and reaction of organs."[1] A growing body of evidence suggests that there are endogenous molecular pathways that regulate the "tone" of many organs, and perhaps can be used pharmacologically as a "tonic," as reported by Sárközy et al[2] in this issue of *JACC: Basic to Translational Science* for the ligand neuregulin-1 beta (NRG1β).

NRG1β is a protein ligand expressed in many tissues and cell types, including the endothelium, that acts through ErbB receptor tyrosine kinases to regulate a wide variety of processes that include tissue morphogenesis and plasticity.[3] A role for NRG1β/ErbB signaling in CVD became relevant clinically when trastuzumab, a humanized monoclonal antibody against ErbB2 developed for the treatment of ErbB2 (aka, HER2, Neu) overexpressing cancers, was found to be associated with myocardial injury and the development of dilated cardiomyopathy. Since that time, numerous studies found NRG1β signaling through ErbB receptors to be protective of cardiomyocytes against a wide range of physiologic stressors, including but not limited to hypoxic-ischemic injury and anthracyclines, leading to investigations of recombinant NRG1β as a potential therapy for heart failure. The mechanisms of cardiac protection are multifaceted including up-regulation of anabolic pathways, metabolic regulation, resistance to stress, as well as regulation of the inflammatory response within the myocardium.[3]

Because NRG1β/ErbB signaling was found to have therapeutic potential in heart failure with reduced ejection fraction (HFrEF), studies have since investigated a role of NRG1β in heart failure with preserved ejection fraction (HFpEF). In a mouse model of diabetes-induced HFpEF, circulating levels of NRG1β are reduced, and this is accompanied by reduced activation of ErbB2 and ErbB4. In cardiomyocyte sarcomeres, NRG1β affects titin elastance, producing increased ventricular compliance and a decrease in the left ventricular end-diastolic pressure. Furthermore, NRG1β acting through ErbB3 and ErbB4 induces apoptosis of inflammatory macrophages and attenuates inflammation. Thus, NRG1β may have a modulatory role in chronic inflammation associated with HFpEF.[3]

There are different phenotypes of cardiorenal syndrome that describe the temporal relationship

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between cardiac and renal dysfunction. In this issue of *JACC: Basic to Translational Science*, Sárközy et al[2] study the effect of recombinant human NRG1β (rhNRG1β) on type 4 cardiorenal syndrome in rats produced by nephrectomy with subsequent development of HFpEF. rhNRG1β suppressed the development of diastolic dysfunction as well as renal dysfunction following nephrectomy. The authors postulated that the therapeutic effects of rhNRG1β were mediated by an antifibrotic mechanism, because rhNRG1β suppressed fibrosis by tissue staining assay and as measured by decreased transcriptional activity of fibrotic genes. Using human ventricular cardiac fibroblasts in vitro, they demonstrated that rhNRG1β attenuates the fibrotic stimulatory effects of transforming growth factor-β via ErbB3. The results of this study are consistent with NRG1β's effect on the immune system's response to inflammation in multiple organs including the CNS, heart, lungs, GI tract and kidneys.[3]

The results fit with a broader theme warranting further investigation—that increasing NRG1β/ErbB signaling appears to "tone" many organs. Because many of the diseases that plague older adults (including HF and CKD) lead to higher mortality manifested through chronic inflammation and fibrosis, it is a reasonable hypothesis augmenting NRG1β/ErbB signaling could lead to a longer life span through effects on multiple organs. It is interesting that NRG1β levels in the brain have been linked to longevity in rodents.[4] Supportive circumstantial evidence implicating NRG1β as a pleotropic "tonic" comes from work showing that exercise—a behavioral "tonic" for all ages—activates NRG1β/ErbB signaling in skeletal muscle, and enhanced exercise performance is associated with higher circulating levels of NRG1β. As self-declared NRG1β/ErbB signaling enthusiasts, we enjoy reflecting on these observations during our sessions at the gym.

One unique and unexplored finding from Sárközy et al[2] is rhNRG1β's effect on uremic toxins (indoxy-sulfate and cresyl-sulfate). Uremic toxins are molecules that accumulate as glomerular filtration decreases and cause harmful effects including cardiovascular injury. Urea is the classic uremic toxin that is dialyzable, whereas there are numerous other uremic toxins that cannot be easily removed. It has been long thought that the higher CVD mortality in CKD comes from similar predisposing risk factor profiles; however, through unique mechanisms, CKD independently increases CVD mortality.[5] Indoxy-sulfate and cresyl-sulfate are molecules produced from gut derived bacteria metabolism of amino acids that are systemically absorbed. In CKD, the gut microbiome is significantly altered leading to higher production of uremic toxins and higher systemic levels. Both indoxyl-sulfate and cresyl-sulfate are 2 of several uremic toxins that have been linked to an increased risk of CVD.[6] rhNRG1β was impressively able to keep indoxy-sulfate and cresyl-sulfate at normal levels despite a decrease in creatinine clearance in the nephrectomy group. In one in vivo model, reducing indoxy-sulfate reduced cardiac fibrosis in a CKD model.[6] This provokes the question of whether NRG1β is acting directly on the myocardium or indirectly through a reduction in uremic toxins? NRG1β has direct effects on gut inflammation demonstrated in an *in vivo* model of colitis.[7] There is little known about what regulates the colonic microbiota, but could NRG1β directly influence the colonic endothelium and attenuate the absorption of uremic toxins? Further studies are needed to investigate the mechanism by which NRG1β reduces uremic toxins as this could be a novel targetable mechanism to attenuate CVD in CKD.

We congratulate Sárközy et al[2] in their contributions to the growing body of literature supporting NRG1β/ErbB signaling as a therapeutic target for CVD and CKD. Because there are no definite therapies that impact mortality in HFpEF or cardiorenal syndrome, there is an urgent need for novel therapies. Recombinant NRG1β has been studied in 2 phase II clinical trials in humans with HFrEF, and both found sustain moderate improvements in left ventricular ejection fraction. A phase III trial of neuregulin in HFrEF is ongoing, and we patiently await the results in hope of an additional therapy for HFrEF. There remains some theoretic concern that NRG1β could be oncogenic via activation of ErbB2 and ErbB3 in malignancy. This has provoked the search for therapeutics with a more targeted agonism for ErbB4. Although this has yet to be born out in clinical studies, this paper and others suggest that NRG1β has a multifaceted effect through ErbB2, ErbB3, and ErbB4 in numerous organs and tissue types. Thus, targeting ErbB4 alone might limit the therapeutic "tonic" effects that NRG1 has to offer.

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