Editorial

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Oxidant Stress Amplification by Cardiotonic Steroids as Therapeutic Target in Chronic Kidney Disease and Heart Failure

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Editorial

The cardiotonic steroids are a group of structurally-related hormones that inhibit the Na/K-ATPase pump. They are found in two groups related by structure; the cardenolides, such as ouabain and digoxin, and the bufadienolides, such as marinobufagenin and telocinobufagin [1]. Digoxin has long been used as an inotropic drug to treat heart failure. The cardiotonic steroids bind to the Na/K-ATPase catalytic α subunit in the E2 phosphorylated position, but bind with different structural changes to the enzyme. While marinobufagenin and ouabain bind to the same site with the same K_i, ouabain binding is sensitive to the enzyme's conformation, but IC_{50} for cell death is higher for marinobufagenin [2]. Endogenous cardiotonic steroids play a variety of roles. The search for natriuretic hormones led to the discovery of endogenous cardiotonic steroids and their role in modulating renal sodium retention and blood pressure [3-5]. They have also been implicated in organogenesis [1]. Marinobufagenin appears to play a central role in salt handling in experimental animals [6], and defective signaling is an important component of Dahl salt sensitive hypertension [7].

Extensive work from our laboratories has shown that in addition to its ion transport function, the Na/K-ATPase serves as a scaffolding protein for intracellular signal transduction [8,9]. At high doses, cardiotonic steroids inhibit the exchange of Na and K ions. However, lower concentrations bind to the Na/K-ATPase α_1 isoform and stimulate the translocation of the Na/K-ATPase to the renal tubule basolateral membrane, increase ion exchange, activate signaling via the EGFR/Src/Erk pathway, and promote cell proliferation [9]. In the renal proximal tubule, cardiotonic steroid binding to Na/K-ATPase stimulates a feed-forward production of reactive oxygen species via the direct carbonylation of the actuator domain in the α_1 Na/K-ATPase prior to Src binding [10]. The activation of c-Src and ERK1/2, and transactivation of EGFR, as happens in the handling of high-salt situations, appear necessary for the redistribution of the Na/K-ATPase and NHE3 from the renal tubule plasma membranes for natriuresis and pressure control [7] and is both caveolin and clathrin-dependent [11,12]. The interaction of the Na/K-ATPase with Src is necessary because it lacks inherent tyrosine kinase activity. Low-dose ouabain also reduces NHE3 expression at the genetic level via Na/K-ATPase, c-Src, and PI3K by activating Sp1 and thyroid receptor binding at the NHE3 promoter [13] and inhibits its endocytic recycling [14]. Association with the insulin receptor carcinoembryonic antigen-related cell adhesion molecule is necessary for the endocytosis of insulin receptor-β and the epidermal growth factor receptor [15].

Cardiotonic steroids appear to play a role in the pathology of chronic kidney disease and heart failure. Chronic kidney disease precipitates left ventricular hypertrophy and heart failure through increases pressure (afterload) and volume (preload) of the vasculature, hyperphosphatemia, chronic stimulation of the renin-angiotensin-aldosterone system, and sympathetic over-activity [16]. These signals stimulate the production of endogenous cardiotonic steroids in the adrenals and brainstem which stimulate reactive oxygen species production and fibrosis of the vasculature and heart [9]. These cardiotonic steroids cause proximal tubular cell Na/K-ATPase internalization and sodium retention [17]. Marinobufagenin is found to be increased three-fold in patients with chronic kidney disease and hypothesized to be responsible for a feed-forward pathway which worsens renal fibrosis and damage [18]. In cardiac myocytes, the ouabain-induced increase in intracellular calcium and Src-mediated production of reactive oxygen species at the mitochondrion occur through parallel signaling pathways [19]. At the genetic level, cardiotonic steroids stimulate the expression of skeletal α-actin, atrial natriuretic factor, mitogen-activated protein kinases, ras-dependent proteins, and NF-κB, and inhibit α_3 Na/K-ATPase expression [20]. Marinobufagenin, in turn, causes increased fibrosis and nitrative stress with right ventricular dysfunction and worsened clinical outcomes in human chronic kidney disease patients and marinobufagenin-infused mice [21]. Green tea antioxidants are effective in blocking the development of cardiac hypertrophy in the rat partial nephrectomy model of chronic kidney disease [22].

Other pathologies of cardiotonic steroid-induced reactive oxygen species have therapeutic potential. Marinobufagenin-induced collagen-1 fibrosis is reversed by spironolactone and

its major metabolite, canrenone, in both cardiac and vascular tissues [23,24]. An immune connection with the kidney proximal tubule cell is seen in obesity and hyperlipidemia. These hyperlipidemic, proatherogenic states have increased cardiotonic steroids and oxidized LDL, the ligand for CD36. Indeed, $CD36^{-/-}$ mice had better kidney function and less glomerular and tubulointerstitial macrophage accumulation [25]. Our laboratory recently studied the role of the Na/K-ATPase/oxidative stress pathway in the generation and maintenance of the obesity phenotype [26]. A peptide to block the pathway to reactive oxygen species, pNaKtide, was created based on the Src binding domain of the α_1 subunit of the Na/K-ATPase [27,28]. In mouse preadipocytes, this peptide attenuated lipid accumulation and reduced superoxide levels, a marker of oxidative stress. It inhibited adipocyte dysfunction, evident in increased adiponectin levels, a marker of healthy, insulin-sensitive adipocytes, and reduction of the adipogenic markers fatty acid synthase, mesoderm specific transcript, and peroxisome proliferator–activated receptor γ in mouse preadipocytes and mouse fed a high-fat diet. It improved their insulin sensitivity, and glucose tolerance, and attenuated protein carbonylation, c-Src, and ERK1/2 levels. Unlike cardiotonic steroid antagonists, pNaKtide inhibits the amplification of oxidative stress through the Na/K-ATPase interaction with Src rather than potentially altering the conformation of the Na/K-ATPase itself as presumed for so called antagonists of cardiotonic steroids such as rostafuroxin [29,30], spironolactone, and canrenone [23]. However, we would propose the use of either strategy as a novel approach towards addressing chronic kidney disease, and heart failure.

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