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Chapter 5

Na/K-ATPase Signaling and the Tradeoff Between Natriuresis and Cardiac Fibrosis

Joe Xie, Larry D. Dial and Joseph I. Shapiro

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1. Introduction

The care of patients with chronic renal insufficiency continues to be complicated by significant cardiovascular dysfunction causing substantial morbidity and mortality. These patients develop cardiovascular disease that is characterized by left ventricular dysfunction and left ventricular hypertrophy (LVH). It has been demonstrated that patients with chronic renal insufficiency develop elevated levels of cardiotonic steroids (CTS) such as marinobufagenin (MBG) in an effort to promote natriuresis and resolve the volume expansion associated with renal insufficiency and cardiac failure. In this review we will try to elucidate the mechanisms involved in the pathogenesis of uremic cardiomyopathy and the role of CTS in cardiac fibrosis.

2. Renal failure and cardiotonic steroids

Patients with renal insufficiency continue to demonstrate significantly high risk of cardiovascular disease with an associated mortality exceeding 50% cardiovascular causes including sudden cardiac death and heart failure [1]. While end stage renal disease confers a high risk of complications those patients with a more modest degree of renal insufficiency (stage 2 and stage 3) continue to have high risk of cardiac events including heart failure, arrhythmia, coronary events and sudden cardiac death all independent of traditional risk factors such as diabetes, hypertension and hyperlipidemia. The cardiac dysfunction most commonly manifest as diastolic dysfunction and left ventricular hypertrophy although systolic dysfunction can occur as a natural progression [2].

In the past there has been substantial interest and research related to digitalis-like substances (DLS) their accumulation in chronic renal failure and pathology associated with elevated

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circulating levels. Patients with chronic renal failure frequently developed antibodies to digoxin despite no administration of the drug [3, 4]. These DLS were later characterized as cardiotonic steroids and are significantly elevated due to decreased glomerular filtration and increased endogenous production. These endogenous ligands have been found to significantly alter renal sodium handling, inotropic activity and vascular tone [5, 6].

Cardiotonic steroids are known to play a key role in sodium excretion in response to volume expansion. Their effect is primarily mediated through binding to the Na/K-ATPase, a ubiquitous membrane ion transporter and a crucial protein in controlling the electrochemical gradient in cells. Recently, our understanding of the interaction between cardiotonic steroids and the Na/K-ATPase has undergone re-evaluation, and it has since been proposed that this binding leads to the generation of a signaling cascade, which not only produces the natriuretic response in dealing with volume expansion, but may also offer an explanation for the profibrotic effects of cardiotonic steroids.

For many years, the understanding of renal physiology and the kidney's role in maintaining volume homeostasis revolved around the renin-angiotensin-aldosterone pathway, its effects on the glomerular filtration rate as well as contributions from the sympathetic nervous system. Standard therapies offered for congestive heart failure are mostly limited to modulation of this neurohumoral axis through drug therapy. However, this has been inadequate in explaining how volume expansion is handled by the body [7, 8]. In 1961, de Wardener introduced an entirely new concept in renal hemodynamics when he discovered that kidneys were still able to increase sodium excretion after saline infusion despite controlling glomerular filtration rate and aldosterone [9]. Thus, it was proposed that a "Third Factor" was also in play, named for its discovery after glomerular filtration rate (Factor-1) and aldosterone (Factor-2). Uncovering this "Third Factor" galvanized great interest over the next two decades, and significant contributions from Schrier, Kramer, Bricker, Gruber, and others resulted in our current understanding that the "Third Factor" was in fact a circulating endogenous digitalis-like substance, now commonly referred to as a cardiotonic steroid (CTS) [10-14]. CTS include plant-derived cardenolides such as ouabain and digoxin, and amphibian-derived bufadenolides such as marinobufagenin and proscillaridin A [15-18]. Ouabain and marinobufagenin were identified as endogenous hormones after they were detected in human plasma and urine [15-19]. Coincidentally, along with the fervent CTS research in renal physiology, many scientists were also interested in the role ouabain played as an ionotropic agent in myocardium. In 1963, Repke was the first to suggest the Na/K-ATPase was a receptor for these drugs [20]. Since then, extensive studies from many laboratories revealed that these compounds were specific ligands for the Na/K-ATPase, and in fact, produced their natriuretic and ionotropic effects through binding to the Na/K-ATPase [21].

2.1. Na/K-ATPase inhibition and CTS-regulated natriuresis

The Na/K-ATPase was discovered in 1957 by Jens Skou through his studies on crab nerves, and is a member of the P-type ATPase family responsible for the exchange of Na and K ions across cell membranes via the hydyolysis of ATP [22]. Its structure and function has since been extensively studied. It consists of a non-covalently linked alpha and beta subunit, of which multiple

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isoforms in various combinations exist [23]. Four alpha isoforms and three beta isoforms have been identified and their expression is tissue-specific, as well as their sensitivity to CTS. The alpha-1 isoform appears to be the main functional receptor for CTS in the kidney [24-28].

When de Wardener first considered the possibility of a "Third Factor," ion pumping was the only function attributed to the Na/K-ATPase. Thus classically, the mechanism of CTS-induced natriuresis was understood as follows: volume expansion or a salt-heavy diet leads to an increase in circulating CTS, which in turn results in the inhibition of the Na/K-ATPase in the nephron, specifically, its ion pumping ability. Consequently, cytosolic Na+ begins to rise, and eventually this disruption in the Na+ gradient across the cell membrane decreases Na reabsorption in the renal proximal tubules (RPT) leading to increased sodium excretion. Systemically, increased levels of CTS also inhibit the Na/K-ATPase in vasculature, thereby altering intracellular Na gradients in vascular smooth muscle cells. This indirectly leads to the inhibition of the Na/Ca exchanger causing intracellular calcium in these smooth muscle cells to rise as well [29-31]. Chronically, this leads to an important trade-off. Despite its pivotal role in renal salt handling, this pathway has substantial consequences in the vasculature and has been implicated in the pathogenesis of hypertension [29-31] (Figure 1).

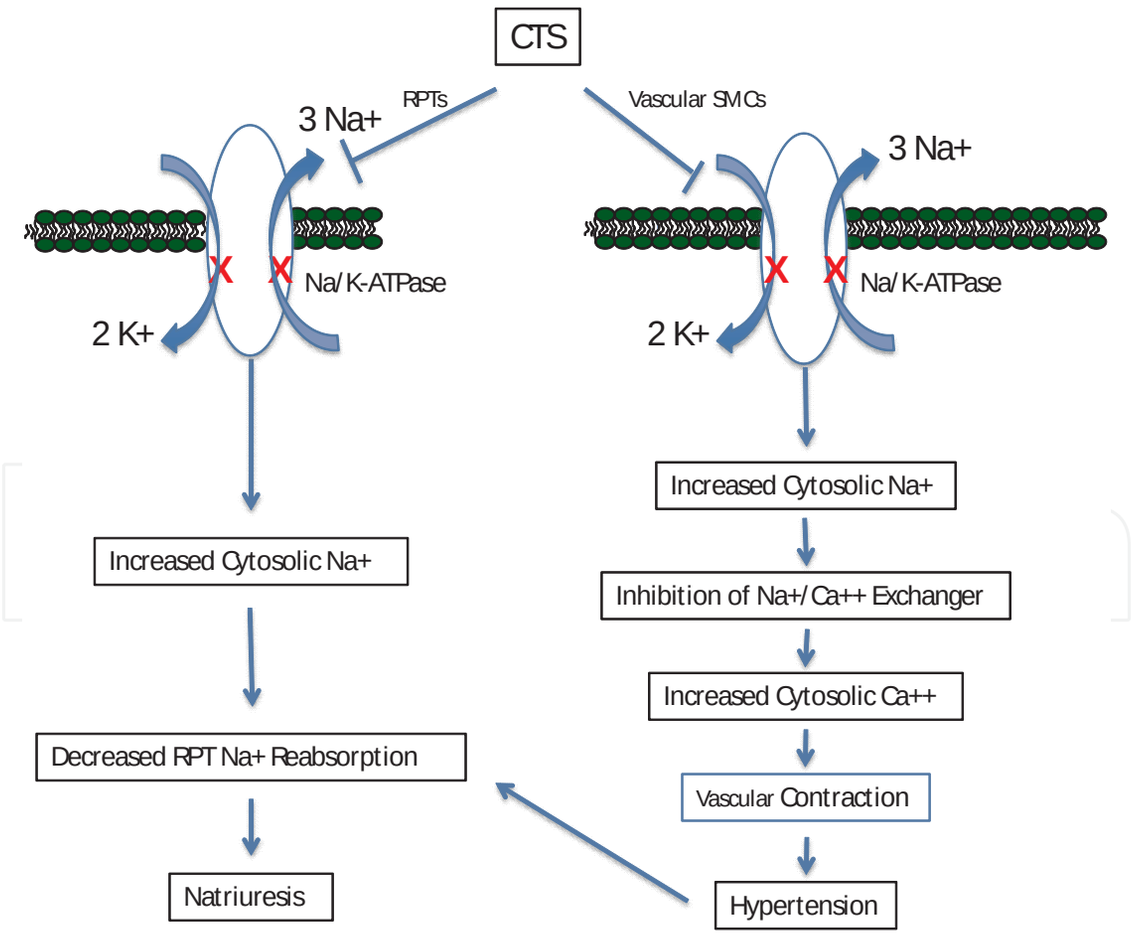


Figure 1. Ionic Mechanism for CTS Induced Hypertension

2.2. CTS and Na/K-ATPase-mediated signal transduction

In the late 1990's, Xie and colleagues suggested that the Na/K-ATPase had an additional signaling function in addition to its transportation of ions. He proposed that instead of only inhibiting the pumping activity of the Na/K-ATPase, CTS also bound to a non-pumping pool of Na/K-ATPase residing in caveolae [32]. This subset of Na/K-ATPase innately held Src, a non-receptor tyrosine kinase, in an inactive state. With the structural change induced by CTS binding, Src was subsequently released and activated. In turn, EGFR became transactivated and a number of additional downstream targets in the signaling cascade such as Ras/Raf/MAPK, PI3 kinase/Akt, phospholipase C/PKC, and the generation of ROS have been identified [33-40].

3. Uremic cardiomyopathy

It is well substantiated that cardiovascular mortality remains the leading cause of death in patients with end stage renal disease with the majority of the cases due to sudden cardiac death and coronary events [1]. While traditional risk factors associated with cardiac dysfunction exist in patients with renal failure the risk conferred can exceed twice that of normal patients [41]. The risk of cardiovascular disease is not limited to those with end stage renal failure but rather confers a gradual risk of increased cardiovascular and all-cause mortality as glomerular filtrate rate declines and albuminuria increases [42]. Systolic dysfunction in these patients have been less consistently demonstrated [43] but rather the development of LVH is more common and may be a predictor of higher mortality related to arrhythmia and sudden death in patients on dialysis [44]. The myocardial fibrosis initially described with uremia as early as 1943 by Rossle and later characterized by Ritz et al has a pivotal role in the development of uremic cardiomyopathy [45]. While traditional thought regarding cardiac fibrosis revolved around a reparative process related to myocardial necrosis; early fibrosis after subtotal nephrectomy without myocardial necrosis has been demonstrated suggesting the potential for a reactive process rather reparative. Mall and colleagues utilizing a uremic cardiomyopathy model in rats demonstrated that interstitial volume density increased with a resultant decrease in the capillary volume. Additionally, cytoplasmic and nuclear swelling occurred whereas the endothelial cells remained unchanged [46]. This reactive cardiac fibrosis can explain the alterations in left ventricular compliance in addition to the electrical conduction abnormalities causing arrythmogenic potential. The risk factors in patients with chronic renal failure believed to be involved in cardiac fibrosis and LVH include anemia, activation of the RAS aldosterone system, oxidative stress, hyperparathyroidism, hypertension and cardiotonic steroids.

4. Natriuresis versus fibrosis—A new trade-off model

The activation of Na/K-ATPase signaling by CTS also appears to be responsible for the coordinated inhibition of Na+ transporters in the nephron resulting in natriuresis. This concept

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is not without precedence. Dopamine, another known natriuretic hormone, increases sodium excretion through signal transduction by mediating the synchronized downregulation of basolateral Na/K-ATPase and apical Na/H antiporter isoform-3 (NHE3) after binding to D1 and D2 receptors in the nephron [47, 48]. Similarly, Liu and Shapiro as well as others noted that CTS at physiological concentrations activated the previously described signaling cascades, resulting in the endocytosis of both the basolateral Na/K-ATPase and apical NHE3 in cultured renal epithelial cells. As a result, this redistribution of membrane Na+ transporters in RPTs leads to a reduction in sodium reabsorption and increased sodium excretion [49-53].

Support for this theory has also been demonstrated in vivo. Lingrel first established that ouabain binding to the Na/K-ATPase is crucial in the natriuretic response of the kidney. His laboratory developed ouabain-sensitive mice by incorporating a mutation in the ouabain receptor domain of the mouse alpha-1 Na/K-ATPase and noted that saline infusion increased the natriuretic response in ouabain-sensitive in comparison to ouabain-resistant mice [54]. More recently, Nascimento showed that bufalin—another derivative of the bufadenolides—required Na/K-ATPase signaling in order to produce natriuretic effects in isolated rat kidneys [55]. Studies from our laboratories also found that high-salt diets cause the endocytosis of Na/K-ATPase in rat proximal tubules, correlating with an increase in Na+ excretion [56]. More recently, we demonstrated that high-salt diets in Dahl salt-resistant mice (R) induced the endocytosis of RPT Na/K-ATPase and NHE3 transporters concurrent with increased Src activity. In contrast, Na/K-ATPase signaling was not activated in Dahl salt-sensitive mice (S) [57].

To re-emphasize, natriuresis due to Na/K-ATPase signaling is a markedly different model from that of the classic pathway. Here, intracellular Na+ is unaffected by the coupling of CTS to the Na/K-ATPase, and instead, signal transduction is responsible for the effects on Na+ transport in RPTs. This alternate pathway also presents distinct tradeoffs from those of the classic pathway (i.e. hypertension). More specifically, natriuresis through CTS-Na/K-ATPase signaling appears to lead to the development of fibrosis in cardiac and renal organs. Of note, previous experiments have already implicated CTS in the hypertrophic growth of cardiac cells [58-65]. Also taking into account the well-established effects of the Src tyrosine kinase in cell growth and differentiation, it is conceivable to suggest a role of CTS in organ remodeling. Remarkably, this phenomenon of fibrosis development has recently been supported by both in vivo and in vitro studies from our laboratory and others.

Using partial (5/6th) nephrectomy models, which have been utilized for many years to simulate renal failure, we noted that the development of cardiac fibrosis in both rats and mice was mediated by an increase in systemic oxidative stress as well as increased levels of circulating MBG [2, 66-68]. Presumably, this suggests that the CTS-induced fibrosis appears to be dependent on Na/K-ATPase signaling leading to the generation of ROS, thus causing oxidative stress to cardiac and renal tissues. This finding in the animal models corresponded to evidence of signaling through the Na/K-ATPase as we detected activation of both Src and MAPK phosphorylation in the fibrotic cardiac tissue [2, 67]. These results were similarly demonstrated in rats subjected to MBG infusion [2, 67]. Remarkably, after adrenalectomy to lower circulating levels of MBG and active immunization against an MBG-albumin conjugate, cardiac fibrosis

was significantly reduced in both partial nephrectomy and MBG-infusion experimental groups [2, 66-68].

In a separate set of experiments, Wansapura subjected genetically altered ouabain-sensitive mice (originally developed by Lingrel) to aortic banding in order to simulate a pressure overload model. After four weeks, the ouabain-sensitive group was noted to have developed substantially greater cardiac hypertrophy and fibrosis compared to ouabain-resistant (wild-type) mice. Furthermore, the administration of Digibind to the ouabain-sensitive mice diminished these cardiac changes [69].

Additional in-vivo data support the potential for a more significant reversal of cardiotonic steroid associated hypertension, cardiac hypertrophy and oxidative stress through utilization of a monoclonal antibody (mAb). Haller subjected partially nephrectomized rats demonstrating elevated levels of MBG to mAb with a high affinity for MBG and Digibind. Both treatments resulted in significant improvement in cardiac hypertrophy, hypertension and measures of oxidative stress. While both therapies demonstrated similar responses there were significantly better results with the MGG directed monoclonal antibody [70].

Furthermore, in cultures of rat cardiac and renal fibroblasts as well as human dermal fibroblasts, we found that both ouabain and MBG were able to directly increase collagen production and proline incorporation [67, 71, 72]. By inducing a translocation of PKC to the nucleus, MBG appears to cause the subsequent phosphorylation and degradation of Friend leukemia integration-1 (Fli-1), which Watson and colleagues have demonstrated is a negative regulator of collagen synthesis in dermal fibroblasts [71, 73]. In fact, we found MBG reduced Fli-1 expression and increased procollagen-1 in all three of our fibroblast cell lines (cardiac, renal, dermal) [71]. Furthermore, MBG infusion stimulates the expression and nuclear translocation of Snail, a transcription factor involved in epithelial-mesenchymal transition, which is implicated in renal fibrosis [74].

Similar to the animal studies, these findings in cell culture have corresponded with increased Na/K-ATPase signaling activity and the generation of ROS, which notably was successfully blocked by both ROS scavengers and Src inhibitors [67]. In addition, we examined the effects of spironolactone—known to be a competitive antagonist of CTS binding to the Na/K-ATPase—as well as its major metabolite, canrenone. Corroborating with our hypothesis, we found that spironolactone significantly attenuated cardiac fibrosis in the renal failure models, and both spironolactone and canrenone reduced collagen production in cardiac fibroblasts. It was further demonstrated that MBG-induced Na/K-ATPase signaling was blocked in these experiments [75].

5. Conclusions

Endogenous circulating CTS such as ouabain and MBG are known to be upregulated in the body's stress response towards volume expansion. Binding to its receptor—the Na/K-ATPase—leads to increased sodium excretion in the proximal tubules of the nephron. Whether this is

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accomplished through the classic ionic pathway, the alternate signaling pathway, or both is still debated; however, its effect on re-establishing volume homeostasis is undeniable. Like many other physiological processes, the fine-tuning of one pathway may result in unintended consequences elsewhere in the body. In the case of CTS-induced natriuresis through Na/K-ATPase signaling, the tradeoff is apparent in the development of cardiac and renal fibrosis as demonstrated both in vivo and in vitro (Figure 2). Because the fibrosis appears to be dependent on Na/K-ATPase signaling, the generation of ROS, and subsequent oxidative stress to cardiac and renal tissues, this creates the potential for both new and old drugs to target and block the signaling cascade. ROS scavengers, Src inhibitors, spironolactone, and canrenone have already demonstrated exciting possibilities in our experiments. Further research in developing more specific CTS antagonists as well as whether this concept can be extrapolated to humans needs to be explored. Interestingly, in the late 1990's and early 2000's, Pitt and colleagues conducted the Randomized Aldactone Evaluation Study (RALES), followed by the Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) and determined that spironolactone and eplerenone, respectively, were cardioprotective in patients with advanced stages of congestive heart failure [76, 77]. More recently, the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) and the Anti-Remodeling Effect of Canrenone in Patients with Mild Chronic Heart Failure (AREA IN-CHF) trials found further therapeutic benefit in patients with mild (NYHA Class II) CHF [78, 79]. These clinical studies proposed that the anti-aldosterone effects were primarily responsible for the reduction in morbidity and mortality; however, it is certainly plausible to speculate whether these drugs as Na/K-ATPase signaling inhibitors may have also played a role. Nonetheless, CTS-induced signaling through the Na/K-ATPase is a significant and novel link in balancing the hemodynamics of salt handling and the development of fibrosis.

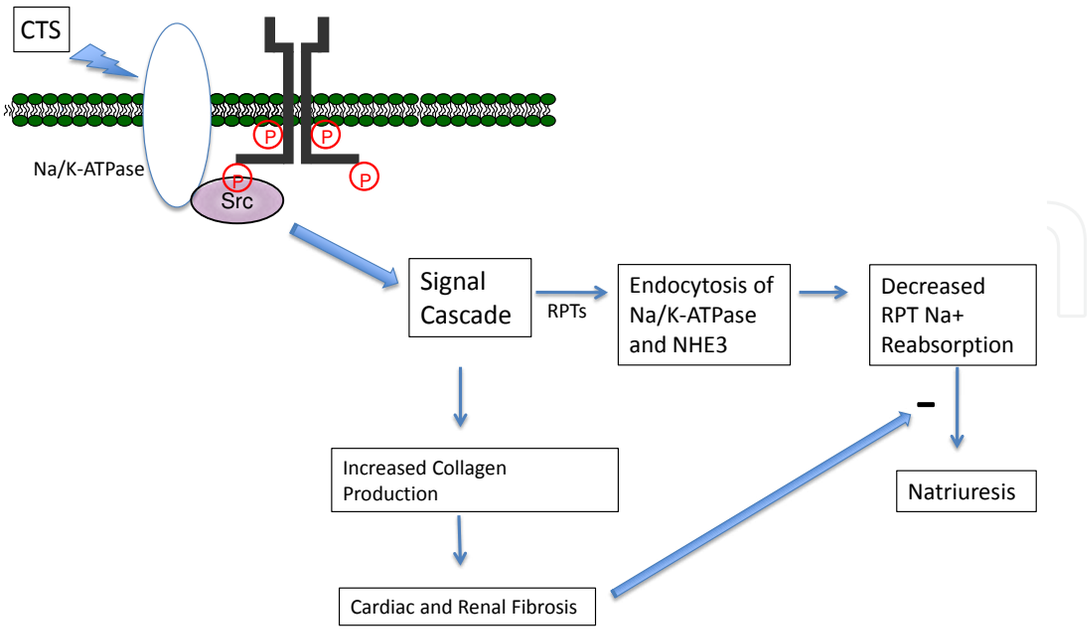


Figure 2. Signaling Pathway: Relationship Between Fibrosis and Natriuresis

Author details

Joe Xie[1], Larry D. Dial[2] and Joseph I. Shapiro[2*]

*Address all correspondence to: shapiroj@marshall.edu

1 The University of Colorado School of Medicine, USA

2 The Joan C. Edwards School of Medicine of Marshall University, USA

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