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Cardiotonic Steroids and Cardiac Fibrosis

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1. Introduction

It is well known and has been shown that patients who have chronic renal failure tend to develop and die of cardiac causes. These patients are known to develop a cardiomyopathy that is characterized by left ventricular hypertrophy and significant diastolic dysfunction. It has also been shown that the chronic renal failure condition is characterized by significant sodium pump inhibition due to increases in the circulating levels of cardiotonic steroids (CTS) such as marinobufagenin (MBG). In this review we will try to elucidate the mechanisms involved in the pathogenesis of uremic cardiomyopathy and the role of CTS in the pathogenesis as well as the possible areas of therapeutic interventions.

2. Renal failure and cardiotonic steroids

The current treatment of patients with end stage renal failure is complicated by the tremendous cardiovascular mortality associated with it. Such patients tend to develop a cardiomyopathy characterized by marked diastolic dysfunction and left ventricular hypertrophy (LVH). These patients also have substantial increases in the circulating levels of CTS (Mohmand, Malhotra et al. 2005). Perhaps of greater importance, it has more recently been shown that patients with more modest degrees of chronic renal insufficiency have markedly worse outcomes in high cardiovascular risk settings as well as a substantial worsening of cardiovascular risk (Alsheikh-Ali, Trikalinos et al. 2011; Kreuz, Horlbeck et al. 2011)

It was proposed nearly 4 decades ago that there is accumulation of CTS in chronic renal failure that causes the inhibition of the Na/K ATPase. The patients with chronic renal failure developed some antibodies to digoxin and had false positive digoxin levels even though these patients had not been treated with digitalis (Graves 1986; Graves and Williams 1987). More recently using more definitive analytical techniques several of these CTS have been characterized. These include ouabain (Hamlyn, Blaustein et al. 1991) which is a cardenolide and marinobufagenin (MBG) and telocinobufagin (TBG) (Bagrov and Fedorova 1998; Komiyama, Dong et al. 2005) which are bufadienolides. These CTS have been considered only as drugs until recently as studies now indicate that these compounds are secreted in the body and regulated by multiple physiological stimuli such as ACTH and angiotensin II (Fedorova, Agalakova et al. 2005; Bagrov, Shapiro et al. 2009). They have also been found to play an important role in renal salt handling as well as the regulation of cardiac contractility and vascular tone (Hamlyn, Blaustein et al. 1991; Fedorova, Doris et al.

1998). Recently, many other functions of these endogenous ligands of the Na/K-ATPase have been proposed.

The mechanism of elevation of these CTS possibly includes a combination of decreased elimination and increased production, but one would anticipate an elevation as it was initially thought that these hormones functioned as natriuretic hormones since the Na/K ATPase comprises a major sodium transporting mechanism in the kidney (de Wardener, Clarkson et al. 1971). Increases in sodium levels would be caused by decreased renal elimination due to loss of renal function. It has also been thought that the increases in the CTS effect vasoconstriction by inhibition of Na/K ATPase causing coupled activation of the Na/Ca exchanger in the vascular smooth muscles (Jaitovich and Bertorello 2010). Bricker and colleagues postulated that in order to maintain sodium homeostasis in renal failure, increases in circulating CTS were necessary, but the effects of CTS on other tissues other than the kidneys explained many of the clinical features seen in renal failure. This was termed as the trade off hypothesis for the pathogenesis of the 'uremic syndrome' (Bricker and Fine 1978) and is illustrated in figure 1. Now it is well known that the reduced pump activity has been seen in red cells, white blood cells, transporting epithelia, muscle cells, adipocytes and the cardiomyocytes (Stokes, Willcocks et al. 1986; Okamoto 1988; Takahashi, Nishimura et al. 1989; Mimura, Makino et al. 1992; Periyasamy, Chen et al. 2001).

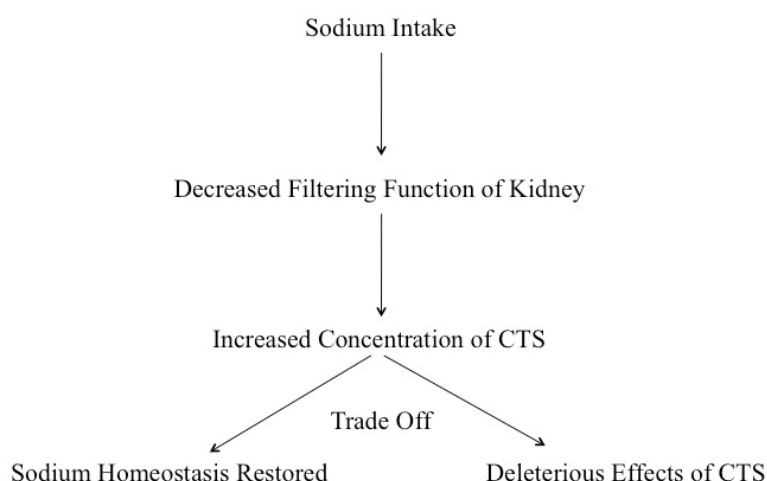


Fig. 1. Illustration of the role of cardiotonic steroids (CTS) in "trade off." With decreased filtering function, CTS concentrations increase to maintain sodium homeostasis, but these elevated hormone levels have adverse effects on different tissues.

Ouabain the prototypical CTS described in 1991 by Hamlyn and colleagues (Hamlyn, Blaustein et al. 1991) was initially thought to function as the natriuretic peptide responsible for the effects seen. However it is well known now that ouabain has high affinity to the alpha 2 and 3 isoforms of Na/K ATPase where as rat tubular cells mainly express the alpha 1 isoform which is relatively insensitive to ouabain (Sweadner 1989). However in humans the sensitivity of the different isoforms to ouabain seems to be not that significant (Croyle, Woo et al. 1997; Lingrel 2010). It is now known that ouabain probably has a more neuro-hormonal function and has been isolated from the hypothalamus and the hippocampus (Kawamura, Guo et al. 1999; Fedorova, Zhuravin et al. 2007). A new body of evidence is emerging that brain ouabain may play important role in pathogenesis of salt sensitive hypertension (Fedorova, Zhuravin et al. 2007).

More recently other CTS have been described such as MBG and TBG, which has a structure very similar to that of MBG (Bagrov, Roukoyatkina et al. 1993; Komiyama, Dong et al. 2005). They were seen to be elevated significantly in plasma of ESRD patients. The bufadienolides were first described from the skin of amphibians such as the marine toad (*Bufo marinus*) (Bagrov, Shapiro et al. 2009) and MBG emerged as the most important contender since it has the affinity towards the alpha 1 isoform which is the isoform present almost exclusively in the mammalian tubules. MBG at low doses also causes vasoconstriction in isolated human blood vessels (Bagrov, Roukoyatkina et al. 1995). Bagrov and colleagues have demonstrated that the levels of MBG are elevated in response to both salt loading and in the presence of experimental renal failure (Fedorova, Agalakova et al. 2005). They have also demonstrated the role of ouabain as a neuro-hormone by intra-hippocampal administration of ouabain and demonstrating an increase in the plasma and urine concentration of MBG as well as increased natriuresis from this (Fedorova, Agalakova et al. 2005). Also it has been shown that the synthesis of these CTS occurs in the mammalian adrenal cells; however the specific metabolic steps in this biosynthesis are still unknown (Dmitrieva, Bagrov et al. 2000).

3. Signaling through the sodium pump

Signaling through the sodium pump has been studied extensively in the recent years and our knowledge about the process has considerably increased. It is well known that there is more than just the 'classical enzymatic inhibition' causing increases in cytosolic sodium (Jaitovich and Bertorello 2010). One concern is that the circulating levels of CTS seen in pathological conditions do not appear to cause extensive inhibition of the pump in vitro and in vivo (Bagrov, Shapiro et al. 2009). In fact, the growth regulatory effects of CTS are seen even at nano and sub-nano molar concentrations, which do not cause any demonstrable inhibition of the pump activity (Aydemir-Koksoy, Abramowitz et al. 2001; Aydemir-Koksoy and Allen 2001; Saunders and Scheiner-Bobis 2004; Khundmiri, Metzler et al. 2006; Qiu, Gao et al. 2007). Another concern is that it has been difficult if not impossible to demonstrate changes in cytosolic sodium caused by physiological and even pharmacological concentrations of CTS. Perhaps more troubling, small increases in the cytosolic sodium levels caused by pump inhibition would be expected to minimize effects on net Na/K-ATPase activity by mass action as cytosolic Na is generally maintained at concentrations where it can actually regulate pump activity. Last but most significantly, sodium ionophores do not cause the biological effects of CTS (Liu, Tian et al. 2000; Oweis, Wu et al. 2006).

While the classical pathway of pump inhibition may still explain some of the effects of CTS, a novel signal cascade involving the Na/K-ATPase residing in specific membrane environments has been proposed and documented by Xie and others (Li and Xie 2009). This research performed on neonatal rat cardiac myocytes showed that ouabain caused the Na/K ATPase to interact with neighboring membrane proteins and caused cytosolic cascades of signaling. The administration of ouabain to the cardiomyocytes caused an increase in reactive oxygen species (ROS) (Liu, Tian et al. 2000). It was seen from the experiments that first there was phosphorylation of Src and leading to the activation of Ras. This trans-activated the EGFR and triggered a signaling cascade that led to the production of ROS (Haas, Askari et al. 2000; Liu, Tian et al. 2000; Kometiani, Askari et al. 2001; Haas, Wang et al. 2002; Wang, Haas et al. 2004; Tian, Cai et al. 2006). Also it has been shown that these ROS were key in the signaling function of Na/K ATPase. The administration of N Acetyl Cysteine (NAC) or green tea extract which act as ROS quenchers blocked the gene

transcription effects of CTS (Xie, Kometiani et al. 1999; Liu, Tian et al. 2000; Priyadarshi, Valentine et al. 2003; Elkareh, Kennedy et al. 2007). At present it is unclear as to how ROS effect downstream signaling. One possibility albeit unproven is that the Na/K ATPase itself may serve as a receptor for the ROS enhancing its sensitivity by conformational change. Further work in this exciting area is currently underway. Development of ROS in response to sodium pump signaling is shown in figure 2.

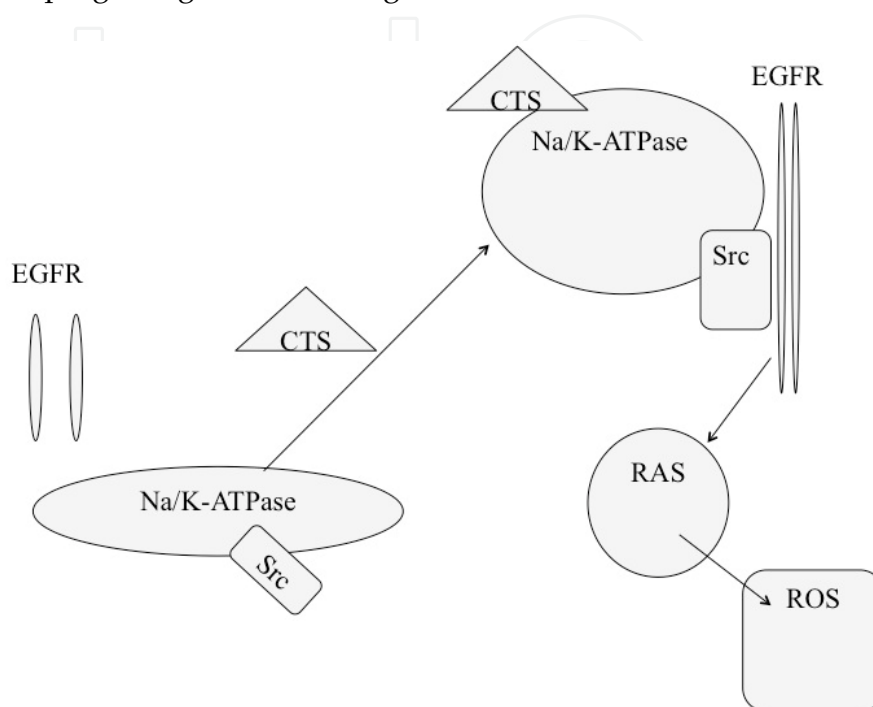


Fig. 2. Schematic showing how cardiostonic steroids (CTS) change the conformation of the Na/K-ATPase residing in caveolae or lipid rafts, allowing Src to transactivate the EGFR and cause signal transduction through RAS resulting in the generation of reactive oxygen species (ROS).

Several studies have shown that low concentrations of ouabain have stimulated tyrosine phosphorylation of several proteins in a variety of cells including cardiac myocytes, HeLa and LLC-PK1 cells (Kometiani, Li et al. 1998; Contreras, Shoshani et al. 1999; Haas, Askari et al. 2000; Aydemir-Koksoy, Abramowitz et al. 2001; Kometiani, Liu et al. 2005; Kotova, Al-Khalili et al. 2006; Kotova, Galuska et al. 2006). Importantly the addition of tyrosine kinase inhibitors like herbimycin A and genistein, blocked ouabain induced tyrosine phosphorylation and subsequently the downstream effects in these cultured cells (Haas, Askari et al. 2000; Aydemir-Koksoy, Abramowitz et al. 2001). Tyrosine phosphorylation can occur in one of two ways, either by activation of tyrosine kinases or by inhibition of tyrosine phosphatases or a combination of both. The Na/K ATPase does not have intrinsic tyrosine kinase activity. It is interesting that even though the alpha subunit has a phosphatase activity, preliminary studies suggest that it does not have significant tyrosine phosphatase activity (Li and Xie 2009). However, it has clearly been shown that ligands extrinsic to the Na/K-ATPase signal cascade can stimulate tyrosine kinase activity by employing receptors without any intrinsic tyrosine kinase activity (Ihle and Kerr 1995; McGarrigle and Huang 2007). One such demonstrated pathway is the G protein coupled receptors (GPCRs) that employ the Src family of kinases (McGarrigle and Huang 2007). It was hence postulated that

the Src family of kinases could play a role in the ouabain induced tyrosine phosphorylation (McGarrigle and Huang 2007).

Studies done by Haas et al. have indeed shown that Src is involved in the phosphorylation of proteins in CTS signaling. These studies showed that ouabain caused stimulation of Src in cardiac myocytes as well as LLC-PK1 cells. Inhibition of Src blocked the ouabain-induced phosphorylation and abolished the downstream signaling including the activation of ERK (Haas, Askari et al. 2000; Haas, Wang et al. 2002). Furthermore there is sufficient evidence for the fact the Na/K ATPase interacts with Src and forms a functional receptor complex. These workers observed that the pump and Src could be co-localized in the caveolar fractions in several different types of cells. Also immunofluorescence showed the co-localization of these two in the plasma membrane. Both the proteins could also be co-immunoprecipitated by using antibodies to either alpha 1 and to Src. Fluorescence resonance energy transfer (FRET) has also shown these two proteins to be in close proximity (Liu, Mohammadi et al. 2003; Wang, Haas et al. 2004; Liang, Cai et al. 2006; Tian, Cai et al. 2006). They have also showed that the interaction between the Na/K ATPase and Src keeps Src in an inactive state. It was seen that when ouabain binds to the sodium pump it reduced the binding of the Src Kinase domain. This freeing of the Src kinase domain possibly results in the activation of the Na/K ATPase associated Src kinase (Tian, Cai et al. 2006). Additionally experiments were done to see if the loss or knockdown of Na/K ATPase would release the interacting Src and increase in tyrosine kinase activity. Graded knockdown of LLC-PK1 cells with alpha 1 specific siRNA was achieved and Src activity was studied. It was seen that the knockdown of the pump resulted in an increase in basal Src activity in an alpha 1 amount dependent manner. Tyrosine phosphorylation of several protein molecules was also increased secondary to this. Moreover stimulation of these cells with ouabain failed to stimulate Src and ERK 1 and 2 any further. When these knockdown cells were rescued with rat alpha 1, it restored Src to its basal levels and allowed for stimulation of the complex at higher levels of Ouabain as would be expected with the differences in sensitivity of rat versus pig alpha 1 (Liang, Cai et al. 2006).

It is also known that the binding of ouabain to the receptor complex leads to the recruitment and transactivation of the EGFR. This was due to the Src dependent phosphorylation of the EGFR at sites other than the major auto-phosphorylation site Y1173. The transactivated EGFR in turn recruited Shc to the complex and resulted in the activation of the Ras/Raf/MEK/ERK cascade (Haas, Askari et al. 2000; Aydemir-Koksoy, Abramowitz et al. 2001; Haas, Wang et al. 2002; Kotova, Al-Khalili et al. 2006). Further studies have shown that once the Src Na/K ATPase complex has been activated it leads to the synthesis of ROS, which has been thought of as a second messenger. It has been demonstrated by Xie and coworkers that exposure of myocytes to ouabain causes a rapid increase in the generation of ROS. These ROS were demonstrated with the help of a fluorescence dye CMDCF. The generation of the ROS was prevented by pre-treatment of the cells to anti-oxidants such as N Acetyl Cysteine (NAC) and Vitamin E. By studying the blockade of the downstream signaling it was seen that ROS is involved with the signaling causing stimulation of Ras, activation of p42/44 mitogen-activated protein kinases, induction of genes for skeletal muscle actin and atrial natriuretic peptide and the activation and translocation of the transcription factor NF- κ B among several other effects (Xie, Kometiani et al. 1999). Since a lot of these are calcium dependent steps further experiments were done to see if the ROS production was calcium dependent as well. Ouabain caused the production of ROS in

myocytes that were stimulated in culture media that were calcium deficient. This indicated that the production of ROs was calcium independent and possibly the increases in calcium was due to a parallel mechanism from the inhibition of the sodium pump activity (Liu, Tian et al. 2000)

Sites of generation and targets of ROS are currently being worked out, with clues in favor of Ras activation induced mitochondrial production (Liu, Tian et al. 2000) however other components of the downstream signaling including the involvement of PLC, PI3K and PKC have been established. Src activation led to the stimulation of PLC gamma and subsequently the activation of PKC and PI3 mediated calcium signaling. Moreover it was seen that ouabain also stimulates PI3K which works with PKC to cause endocytosis of this sodium pump complex. This probably is the explanation for how the signal transduction is eventually terminated. (Tian, Liu et al. 2003; Liu, Liang et al. 2005; Yuan, Cai et al. 2005; Pierre, Yang et al. 2007; Chen, Cai et al. 2008; Elkareh, Periyasamy et al. 2009).

This signaling pathway may link to Bricker's concept of CTS as a natriuretic hormone. Specifically, our group has noted that CTS induce endocytosis of the Na/K-ATPase in kidney tissues. In chronically salt loaded Sprague-Dawley rats, renal MBG excretion was significantly elevated and anti-MBG antibody reduced natriuresis and restored sodium pump activity in the renal cortex (Periyasamy, Liu et al. 2005). The same study demonstrated that in addition to the direct inhibition of the Na/K-ATPase, MBG is capable to exhibit its natriuretic via internalization of the sodium pump in the proximal tubule (Periyasamy, Liu et al. 2005). The endocytosis of the proximal tubular Na/K-ATPase induced by CTS has been shown to proceed through clathrin coated pits and require PI3K activation as well as the plasmalemmal pump being in the context of caveolae as well as signaling through the Src-EGFR pathway (Liu, Kesiry et al. 2004; Liu, Liang et al. 2005). Further work demonstrated that CTS could induce decreases in the apical expression of one of the plasma membrane Na^+/H^+ exchanger, NHE3 (Oweis, Wu et al. 2006; Liu and Shapiro 2007). Taken together, these data suggest that increases in the circulating levels of MBG accompany salt loading, which, in turn, may induce decreases in both basolateral and apical sodium transport in the proximal tubule.

4. Uremic cardiomyopathy

It is a well-known fact that cardiovascular mortality accounts for more than 50% of all deaths in patients with renal failure. It is seen that this mortality is more attributed to cardiac failure and sudden cardiac death than coronary events (Sarnak, Levey et al. 2003; Weiner, Tighiouart et al. 2004). Available data also suggests that pre end stage renal disease (ESRD) patients have cardiac mortality rates very similar to that of ESRD patients (Stack and Bloembergen 2001; Paparello, Kshirsagar et al. 2002; Sarnak 2003; Sarnak, Levey et al. 2003). Echocardiography has shown that diastolic dysfunction and LVH are both very common in ESRD patients on dialysis and other patients with chronic kidney disease (Harnett, Parfrey et al. 1988; Mitsnefes, Daniels et al. 2001; Stack and Saran 2002). Systolic dysfunction in these patients is less uniformly demonstrable (Raj, D'Mello et al. 1997) and it has been shown that development of LVH may be a predictor of higher mortality in dialysis patients (Nakazato, Kawada et al. 2002; Tyralla and Amann 2003) as this correlates with the development of cardiac arrhythmias.

Of late myocardial fibrosis that was described in uremia as early as 1943 by Rossle and then described again by Ritz et al. seems to play a very important role in the pathogenesis (Mall, Huther et al. 1990). It has been shown by the same group that the fibrosis occurred early after subtotal nephrectomy without myocardial necrosis suggesting a reactive fibrosis rather than a reparative fibrosis. It was seen that the interstitial volume density increased at the expense of capillary volume and this caused the swelling of the cytoplasm and nuclei of the interstitial cells where as the endothelial cells remained unchanged (Mall, Rambauser et al. 1988). The cardiac fibrosis can explain the abnormalities in the left ventricular compliance causing diastolic dysfunction as well as inhomogeneity in the electrical conduction causing arrhythmias. The factors thought to be involved in the genesis of myocardial fibrosis and LVH include anemia, hypertension, hyperparathyroidism, cardiotonic steroids, oxidative stress and the activation of the RAS aldosterone system.

Of the above-mentioned factors anemia seems to be the weakest to be implicated in uremic cardiomyopathy. Only a very modest improvement in LVH to the tune of 10-20% has been seen with sustained increases in hematocrit (Foley, Parfrey et al. 2000). Also the LVH seen is concentric in nature which is not what would be expected with anemia (Harnett, Parfrey et al. 1988). Interestingly erythropoietin therapy worsened LVH possibly because of worsening BP control (Minagawa, Hirano et al. 1994).

Among the several implicated factors hypertension seems to be the factor in chronic renal failure that is best linked to LVH (Huting and Alpert 1992; Morduchowicz, Zabudowski et al. 1993; Harnett and Parfrey 1994). Although there is sufficient evidence to prove that hypertension causes LVH, it does not account for the frequency and severity of LVH seen in ESRD patients (Huting and Alpert 1992; Foley and Parfrey 1998; Nishikimi, Minami et al. 2001). Hence this points to the presence of other factors in the pathogenesis. However hypertension must be aggressively pursued in patients with renal failure as treatment has resulted in a modest amelioration of LVH (Dyadyk, Bagriy et al. 1997).

It also seems that the activation of the renin angiotensin aldosterone axis seems to be a factor independent of hypertension. Experimental studies by Diez et al. and Ritz et al. have shown that the activation of this system is involved in the genesis of cardiac fibrosis (Amann, Simonaviciene et al. 2001; Diez, Lopez et al. 2001; Diez 2004; Gonzalez, Lopez et al. 2004). In conjunction with this Pirola et al. have also shown that angiotensin II also stimulated the release of PTH (Pirola, Wang et al. 1993; Okano, Wu et al. 1994) and in the next section we will discuss how PTH seems to be an important factor in causing fibrosis and LVH. It has been shown that treatment with ACE inhibitors causes regression of LVH independent of hypotensive effects (Cannella, Paoletti et al. 1997; Dyadyk, Bagriy et al. 1997; Vlahakos, Hahalis et al. 1997). This lends more credibility to the idea that cardiac fibrosis may be an important factor in the pathogenesis of uremic cardiomyopathy.

Hyperparathyroidism has been proposed to be a factor as it causes abnormalities in cardiac energy metabolism and growth. Calcium ions are very important for the myocardial excitation contraction coupling and the cardiac contraction and relaxation. The release of calcium from the sarcoplasmic reticulum is the key step in the initiation of the coupling. Dissociation and sequestration of the calcium by an energy dependent pump like SERCA produces relaxation. The intracellular calcium homeostasis seems to be maintained by the membrane bound Na/Ca exchanger and SERCA which in turn is dependent on Na/K ATPase and Na/H exchanger (Morgan 1991). Both parathyroid hormone (PTH) and Parathyroid hormone related peptide (PTHrP) have been shown to acutely increase the force

of contraction in isolated beating rat cardiac myocytes (Wang, Wu et al. 1993; Smogorzewski 1995). PTH excess in uremic patients has also been shown to increase cytosolic calcium levels that were correlated with the plasma PTH concentrations. These were also shown to be corrected with parathyroidectomy (PTX) (Raine, Bedford et al. 1993). Even though increased calcium entry has been thought to be the most important step in sustaining high intra myocyte calcium concentrations reductions in the Na/K ATPase and Na/H exchange rates suggesting impaired calcium extrusion may contribute to altered cellular calcium homeostasis (Smogorzewski 1995). Parathyroid hormone (PTH) now is known to cause increased endocytosis of Na/K ATPase and this may amplify CTS mediated signaling through the sodium pump (Khundmiri, Bertorello et al. 2004). Baczynski et al. have also reported that there is uncoupling of the oxidative phosphorylation and inhibited myocardial energy production in isolated myocardial mitochondria which may further this problem (Baczynski, Massry et al. 1985).

In humans with ESRD the presence of secondary hyperparathyroidism has been shown to be associated with increased myocardial calcium content and impaired systolic and diastolic functions. However these changes have not consistently been seen to improve with PTX suggesting that in the long term these changes induced by PTH become irreversible or there are other factors contributing to the myocardial dysfunction that are more important than just PTH excess (Drueke, Fauchet et al. 1980; Rostand, Sanders et al. 1988; Coratelli, Buongiorno et al. 1989; Ohara, Hiramatsu et al. 1995; Rostand and Drueke 1999). In reference to this the presence of 1,25 (OH)₂ D₃ receptors have been confirmed on the myocardial cells and the administration of Vitamin D in ESRD patients seems to correct the cardiac dysfunction either by correcting the excessive secretion of PTH or by a Vitamin D dependent process in the cardiac cells (Coratelli, Petrarulo et al. 1984; Shane, Mancini et al. 1997).

Our group has focused attention on CTS in the pathogenesis of uremic cardiomyopathy. Along with acute impairment of relaxation in normal adult rat cardiomyocytes when exposed to MBG (Periyasamy, Chen et al. 2001) experimental chronic renal failure induced in rats by 5/6th nephrectomy (Kennedy, Elkareh et al. 2008) causes a cardiomyopathy that is very similar to clinical chronic renal failure. It has been observed that LVH develops quite early and this is accompanied by impaired myocyte relaxation causing diastolic dysfunction. It seems that this impaired relaxation is associated with a significant down regulation of SERCA2a mRNA (Kennedy, Omran et al. 2003; Kennedy, Vetteth et al. 2006), which is known to be responsible for the rapid reduction of cytosolic calcium after systole (Bassani, Bassani et al. 1995; Bers, Bassani et al. 1996; Kennedy, Vetteth et al. 2006). Left ventricular catheterization in 5/6th nephrectomized rats at 4 weeks and calculation of dP/dT for relaxation indicated the presence of significant diastolic dysfunction (Kennedy, Vetteth et al. 2006). LVH was also demonstrated in these hearts by echocardiography as well as increases in heart weights and left ventricular end systolic volumes. There were also increases in the posterior wall thickness. Interestingly the LVH and diastolic dysfunction were also present in rats that were just infused MBG using an intra-peritoneal pump, and tended to resolve in animals immunized with an MBG-BSA conjugate that resulted in high titer specific response to MBG (Kennedy, Vetteth et al. 2006).

The animal studies done to reproduce the phenotype of cardiomyopathy by infusing with MBG so as to achieve plasma levels of MBG consistent with renal failure as well as induction of experimental renal failure by 5/6th nephrectomy, both interestingly revealed a significant amount of cardiac fibrosis in both the rat and the mouse. Also active immunization against the

MBG as discussed above as well as reduction of MBG levels by adrenalectomy prevented the onset of cardiac fibrosis seen in these animals. The heart tissue from these animals also showed evidence of activation of Na/K ATPase signaling as seen by increases in Src and MAPK phosphorylation. It was also demonstrated that there was significant increases in oxidant stress in the heart and other tissues (Kennedy, Vetteth et al. 2006). This noted fibrosis seems to play a significant role in the pathogenesis of uremic cardiomyopathy.

The above studies prompted in-vitro studies on fibroblast in order to see the effects of MBG and other CTS such as ouabain. It was seen that in fibroblast cultures grown to confluence there was increased proline incorporation as well as increased collagen production. There was also evidence of activation of Na/K ATPase signaling as there was increased Src and MAPK activation. Interestingly there was evidence of increases in oxidant stress and the scavenging of these ROS resulted in the inhibition of the Src pathway as well as prevented the increases in proline incorporation and collagen synthesis (Elkareh, Kennedy et al. 2007).

It has been further established that this fibrosis is dependent on the down regulation of Fli-1, which is a negative regulator of collagen synthesis (Czuwara-Ladykowska, Shirasaki et al. 2001). MBG was seen to induce decreases in Fli-1 expression in cardiac and renal fibroblasts, which was dependent on the nuclear translocation of PKC delta from the cytoplasm. This translocation seems to be necessary for the phosphorylation and degradation of the Fli-1 (Elkareh, Periyasamy et al. 2009). This is illustrated in figure 3.

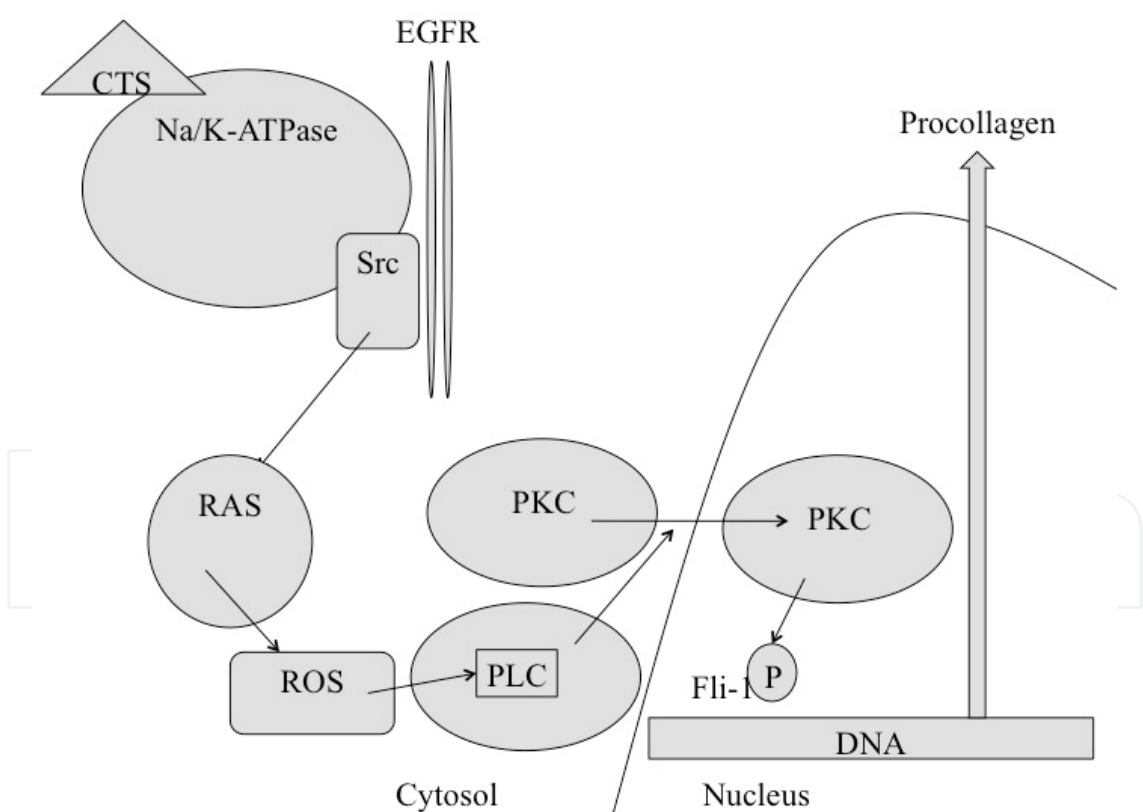


Fig. 3. Schematic showing how the signal cascade caused by cardiotonic steroids (CTS) causes the activation of phospholipase C (PLC) which then causes the translocation of protein kinase C (PKC, delta isoform) to the nucleus where it phosphorylates Fli-1. The phosphorylated Fli-1 is then rapidly degraded allowing for the disinhibition of procollagen synthesis and tissue fibrosis.

Since mineralocorticoid antagonists have been shown to ameliorate cardiac fibrosis, studies using spironolactone and canrenone have shown that both cause significant attenuation of fibrosis in-vivo as caused by experimental renal failure. Both these compounds also seemed to act as competitive inhibitors of CTS binding to Na/K ATPase and hence prevent MBG signaling (Tian, Shidyak et al. 2009). The role of CTS is thus clear in the pathogenesis of cardiac dysfunction with respect to calcium handling and the genesis of fibrosis.

The presence of oxidative stress in the ESRD patients has been well documented (Fiorillo, Oliviero et al. 1998; Tetta, Biasioli et al. 1999). Most of the reactive oxygen species are produced by the mitochondria and a dysfunction in the mitochondria has been discussed above. Oxidative stress has been well known to affect cardiovascular function, cause endothelial dysfunction and hence promote atherosclerosis as well as cause increases in sympathetic activity (Miyazaki, Matsuoka et al. 2000; Wolf 2000; Zanzinger and Czachurski 2000; Himmelfarb, Stenvinkel et al. 2002). Reactive aldehydes measured as carbonyl compounds can be formed as the end product of various oxidative reactions and have been shown to be elevated in uremia. These result in the formation of advanced glycation end products (AGE). These reactive aldehydes and AGE have been demonstrated in the pathogenesis of vascular dysfunction as well as fibrosis (Uchida 2000; Amann, Tornig et al. 2002). The interaction of the AGE with specific receptors have also shown to increase the production of IL-6 and thus increasing the production of CRP in the liver and thereby propagating inflammation (Himmelfarb, Stenvinkel et al. 2002). Increases in CRP have a strong negative correlation with the levels of plasma tocopherol as shown by Thevenin et al. (Nguyen-Khoa, Massy et al. 2001) further showing that antioxidants are decreased in inflammation. Importantly it has been shown that tocopherol decreased fibrosis in the hearts of nephrectomized rats (Amann, Tornig et al. 2002). Hence chronic oxidative stress and damage seems to be an important mechanism in the pathogenesis of chronic inflammation and uremic cardiomyopathy.

5. Conclusion

Chronic renal failure is complicated by a cardiomyopathy that is characterized by LVH and diastolic dysfunction. CTS such as MBG are found in higher concentrations in the plasma of such patients. It is clear from several studies that these CTS are involved via signaling through Na/K ATPase in causing cardiomyocyte hypertrophy, impairing relaxation and inducing fibrosis by increased collagen synthesis, which seems to be dependent on increased oxidant stress. Other major factors possibly involved in the pathogenesis of this cardiomyopathy include hyperparathyroidism, chronic oxidant stress and the activation of the RAS aldosterone system.

However mechanisms involving CTS and PTH and the interaction of the two systems seem to be emerging as the foremost candidate involved in the pathogenesis of uremic cardiomyopathy and may present prime targets for therapeutic interventions in the future.

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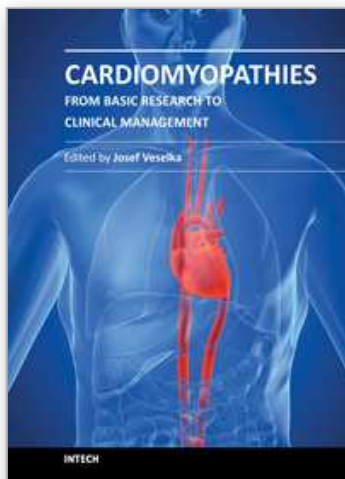
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Cardiomyopathy means "heart (cardio) muscle (myo) disease (pathy)". Currently, cardiomyopathies are defined as myocardial disorders in which the heart muscle is structurally and/or functionally abnormal in the absence of a coronary artery disease, hypertension, valvular heart disease or congenital heart disease sufficient to cause the observed myocardial abnormalities. This book provides a comprehensive, state-of-the-art review of the current knowledge of cardiomyopathies. Instead of following the classic interdisciplinary division, the entire cardiovascular system is presented as a functional unity, and the contributors explore pathophysiological mechanisms from different perspectives, including genetics, molecular biology, electrophysiology, invasive and non-invasive cardiology, imaging methods and surgery. In order to provide a balanced medical view, this book was edited by a clinical cardiologist.

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