Endogenous Cardiotonic Steroids in Kidney Failure: A Review and an Hypothesis

John M. Hamlyn and Paolo Manunta

In response to progressive nephron loss, volume and humoral signals in the circulation have increasing relevance. These signals, including plasma sodium, angiotensin II, and those related to volume status, activate a slow neuromodulatory pathway within the central nervous system (CNS). The slow CNS pathway includes specific receptors for angiotensin II, mineralocorticoids, and endogenous ouabain (EO). Stimulation of the pathway leads to elevated sympathetic nervous system activity (SNA) and increased circulating EO. The sustained elevation of circulating EO (or ouabain) stimulates central and peripheral mechanisms that amplify the impact of SNA on vascular tone. These include changes in synaptic plasticity in the brain and sympathetic ganglia that increase preganglionic tone and amplify ganglionic transmission, amplification of the impact of SNA on arterial tone in the vascular wall, and the reprogramming of calcium signaling proteins in arterial myocytes. These increase SNA, raise basal and evoked arterial tone, and elevate blood pressure (BP). In the setting of CKD, we suggest that sustained activation/elevation of the slow CNS pathway, plasma EO, and the cardiotonic steroid marinobufagenin, comprises a feed-forward system that raises BP and accelerates kidney and cardiac damage. Block of the slow CNS pathway and/or circulating EO and marinobufagenin may reduce BP and slow the progression to ESRD.

Key Words: Ouabain, Marinobufagenin, Brain, Hypertension, Dialysis

VOLUME EXPANSION, NATRIURETIC HORMONES, AND SODIUM PUMP INHIBITORS IN KIDNEY DISEASE

The kidney is critical to long-term salt and water balance. In addition to kidney perfusion pressure and an adequate glomerular filtration rate (GFR), salt balance involves well-recognized hormones including aldosterone, the atrial peptides, and angiotensin II (Ang II). Moreover, as the number of functional nephrons progressively declines, the behavior of volume-regulating hormones and extracellular fluid volume (ECFV) status in general becomes of increasing significance.

A progressive increase in ECFV becomes apparent as the number of filtering nephrons declines to a critically low number, and profound adjustments in sodium-regulating mechanisms have been suggested. In response to acute or chronic expansion of ECFV, a "third" factor other than aldosterone or GFR (or kidney perfusion pressure) is required to explain sodium balance.[1] Numerous studies showed that the third factor was humoral and it induced natriuresis.[2] This so-called natriuretic hormone (NH) has long been associated with the efferent natriuretic response to elevated plasma and intracerebroventricular sodium and intravascular volume expansion.[3] Hence, a significant portion of the pioneering work in the search for NHs employed human or experimental animals with CKD in whom ECFV is expanded. Some examples are presented in Table 1. The working assumption was that, in the progression to CKD, circulating factors that inhibit the tubular sodium pump were a compensatory mechanism that might help offset the decline in GFR.[29-32] Furthermore, elevated levels of an NH might, as a side effect, augment vascular tone and raise blood pressure (BP). Indeed, increased circulating levels of a sodium pump inhibitor were readily detected in low renin (ie, volume expanded) hypertension,[33] and subsequent work demonstrated multiple natriuretic materials in the circulation and urine.[3] Moreover, in the last decade, several natriuretic materials have been isolated and identified. Some inhibit sodium transport and, like the classic cardiotonic steroids (CTS) ouabain and digoxin, inhibit sodium pumps. Yet other identified materials are natriuretic through secondary transport mechanisms.[3] Here, we focus on two endogenous CTS implicated in the pathogenesis of CKD and propose a feed-forward mechanism including specific elements by which one or both CTS become elevated in the circulation, raise BP, and promote kidney and cardiac damage.

ENDOGENOUS CARDIOTONIC STEROIDS IMPLICATED IN KIDNEY FAILURE

Three endogenous CTS (eCTS) of relevance to ECFV balance and long-term BP control have been isolated and identified by analytical means in human plasma and/or urine.[24,34-36] The identified eCTS are ouabain, marinobufagenin (MBG), and telocinobufagin. In addition, there are strong indications that small amounts of digoxin, in addition to one or more digoxin-immunoreactive materials, are present in the circulation, urine, and peritoneal dialysate of humans.[18,22,25,28,37] The presence of these multiple eCTS in mammals implies different signaling systems and functional effects.[38-45] The general evidence supporting the biosynthesis of eCTS is clear[46-51] although the specific details of the various pathways remain to be elucidated. Nevertheless, as noted subsequently, elevated circulating and or urinary levels of several eCTS are present in conditions associated with acute or chronic increases in ECFV. Furthermore, these eCTS appear to contribute significantly to the underlying

From Department of Physiology, University of Maryland Baltimore, Baltimore, MD; and Nephrology, Dialysis and Hypertension Division, Scientific Institute San Raffaele, Università "Vita-Salute" San Raffaele, Milan, Italy.

Financial Disclosure: See Acknowledgment on page 240.

Address correspondence to John M. Hamlyn, PhD, Department of Physiology, University of Maryland Baltimore, 655 West Baltimore Street, Baltimore, MD 21201. E-mail: jhamlyn@umaryland.edu

1548-5595/$36.00

http://dx.doi.org/10.1053/j.ackd.2014.12.005

kidney and cardiac pathology in kidney failure, and recent animal studies show that methods to control the negative effects of the eCTS are valuable. Indeed, one or more of these methods may warrant investigation as possible new therapeutic modalities in humans to delay dialysis and/or transplantation.

ENDOGENOUS CTS, KIDNEY DAMAGE, AND CARDIAC FIBROSIS

Kidney Damage

The circulating levels of endogenous ouabain (EO), MBG, and telocinobufagin are increased dramatically in virtually all patients who underwent dialysis for kidney disease.[15,23,24] Furthermore, in the rat, partial nephrectomy raises MBG[52] and EO.[53] There is kidney fibrosis associated with elevated MBG,[54] whereas the sustained elevation of circulating EO or ouabain causes podocyte damage and proteinuria, and these effects can be blocked by the ouabain receptor antagonist, rostafuroxin,[55,56] that blocks ouabain binding to the Na^+ pump without causing inhibition of ion transport. Thus far, there appears to be no large differences in circulating EO in patients with CKD with or without HTN, which may be explained by differences in the types and dosages of therapeutic agents. Furthermore, as noted subsequently, the relationship between EO and BP is complicated by lag phases, and there are no studies that address these issues.

The mineralocorticoid receptor (MR) antagonists, long recognized for their beneficial effect in heart failure[57] have, together with inhibitors of aldosterone biosynthesis, been suggested as a way to minimize kidney fibrosis.[58,59] Indeed, spironolactone attenuates experimental uremic cardiomyopathy where MBG and EO are elevated.[60] It has been suggested that the basis for the beneficial effect of spironolactone is not solely related to MR blockade but may also involve their ability to compete with MBG and EO and possibly other CTS for binding to the sodium pump.[61,62] Yet other mechanisms have been suggested for the beneficial actions of spironolactone.[63] Furthermore, when given into the central nervous system (CNS) in tiny amounts that have no effect when given peripherally, MR antagonists reduce sympathetic outflow, are antihypertensive,[64] and have a dramatic beneficial impact on cardiac function in heart failure.[65] Furthermore, as an MR-dependent pathway in the brain controls circulating EO,[66] the CNS, not ordinarily recognized as a key factor in chronic kidney failure (CKF), is likely to play an important role in the progression to ESRD. In the latter context, nothing is known about the potential benefits of CNS MR blockade in experimental models of CKF. However, spironolactone is beneficial for the long-term treatment of resistant hypertension (rHT) in patients with CKF and may improve kidney function.[67,68] The improved outcomes are reminiscent of the unanticipated beneficial effect of MR blockers in severe heart failure[57], ie, a condition where ECFV is often expanded, and there are also elevated levels of circulating EO and other CTS.[69-71]

CLINICAL SUMMARY

- The failing kidney enhances signals that activate a slow neurohumoral pathway in the brain that, in turn, controls the long-term level (ie, nonreflexive) of sympathetic nerve activity and the circulating level of endogenous ouabain (EO).
- Inappropriate activation of the brain pathway raises sympathetic activity, circulating EO, and blood pressure, and all these effects are prevented by agents that block the binding of angiotensin II, mineralocorticoids, and EO with their respective receptors in the brain and periphery.
- In patients with end-stage kidney failure, 2 endogenous cardiotonic steroids (EO and marinobufagenin) circulate in elevated and clinically significant amounts and exacerbate cardiac hypertrophy and kidney fibrosis. It may be possible to specifically remove these materials during dialysis.
- The "lag phenomenon," ie, the delayed return of blood pressure after dialysis to dry weight, may be related to plasticity changes in the brain and periphery, ie, the slow rewiring of synaptic connections in the central nervous system and/or sympathetic ganglia that reduce sympathetic outflow to the vasculature.
- Research directed to improving therapy for chronic kidney failure should consider the role of the central nervous system, humoral cardiotonic steroid mediators, and test methods that chronically reduce or neutralize these steroids.

Cardiac Fibrosis

Patients with CKF progressively lose cardiac diastolic function and develop ventricular hypertrophy with various geometric manifestations.[72] Systolic dysfunction affects 10% to 20% of patients with ESRD. It appears that the diastolic dysfunction and ventricular hypertrophy are not simply secondary to the hypertension and anemia observed in CKF.[73] Partially nephrectomized rats also develop diastolic dysfunction, ventricular hypertrophy, and cardiac fibrosis.[41,74,75] Furthermore, in rats, the prolonged infusion of MBG reproduces many features of uremic cardiomyopathy, and MBG per se stimulates collagen formation in cardiac fibroblasts in cell culture.[41] More significantly, in partially nephrectomized rats, both active and passive immunization against MBG attenuates most of the cardiomyopathy.[75,76]

RECENT INSIGHTS INTO HOW EO RAISES VASCULAR TONE AND BLOOD PRESSURE

Hypertension is a frequent and early component in CKF. Expansion of ECFV is associated with hypertension in approximately 75% of patients with CKF and typically can be controlled with hemodialysis, ie, benefit reflects removal of fluid and not dialyzable vasopressor agents. Another significant cause of hypertension in uremic patients is hyper-reninemia. The hypertension tends to be more severe, unresponsive to volume manipulation, and likely will require bilateral nephrectomy and/or transplant. There is a clear need for better control of hyperten-