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Pavlovic, Davor

DOI:
10.1159/000363301

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Document Version
Publisher's PDF, also known as Version of record

Citation for published version (Harvard):

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Download date: 13. Nov. 2018
The Role of Cardiotonic Steroids in the Pathogenesis of Cardiomyopathy in Chronic Kidney Disease

Davor Pavlovic
Cardiovascular Division, King's College London, Rayne Institute, St. Thomas' Hospital, London, UK

Introduction

There is a complex relationship between the kidneys and the heart, with the activity of kidneys strongly influencing the activity of the heart and vice versa. In particular, it has been evident for many years that patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD) are at an increased risk of developing cardiovascular disease. The data from the HOPE trial demonstrate that mild CKD is associated with a 40% increase in the risk of major adverse cardiovascular events [1]. Furthermore, approximately 50% of ESRD patients die prematurely of cardiovascular causes [2, 3], and this percentage is not falling [2]. There is convincing clinical evidence that renal failure results in cardiomyopathy (the ‘uraemic cardiomyopathy’) often characterised by left ventricular hypertrophy, reduced ejection fraction, myocardial fibrosis and arrhythmias [2, 3]. In addition, hypertension, coronary artery stenosis, diabetes and microvascular diseases presumably all contribute to the high risk of cardiovascular events observed in CKD/ESRD patients. Over the last 20 years, a number of studies in animals and humans have shown that, during CKD/ESRD, endogenous circulating cardiotonic steroid (CTS) concentrations are increased. All CTS bind and inhibit the activity of the sodium potassium pump (NKA) whose function is to maintain resting intracellular Na+ concentration in every living cell. Although digoxin has been prescribed to heart failure patients for at least 200 years, the realization that CTS are endogenously produced has intensified research into their physiological and pathophysiological roles. Over the last two decades, substantial evidence has accumulated demonstrating the effects of endogenously synthesised CTS on the kidneys, vasculature and the heart. In this review, the current state of art and the controversies surrounding the manner in which CTS mediate their pathophysiological effects are discussed. Several potential therapeutic strategies have emerged as a result of our increased understanding of the role CTS play in health and disease.
membrane potential by establishing Na\(^+\) and K\(^+\) gradients across the plasma membrane. In this review article, the role that endogenous CTS play in the development of cardiovascular disease during CKD/ESRD is discussed.

**Structure and Function of the NKA**

Our understanding of the structure-function relationship of the NKA has greatly expanded with the discovery [4] and refinement [5–7] of NKA crystal structures. The NKA is composed of 2 subunits, α and β, and an accessory FXYD protein [8, 9]. The minimum functional unit is made up of a α- and β-subunit macromolecular complex with 4 α- (α\(_1\), α\(_2\), α\(_3\) and α\(_4\)) and 3 β-isoforms (β\(_1\), β\(_2\) and β\(_3\)) [10, 11]. The α-subunit, with 10 transmembrane segments, contains the binding sites for Na\(^+\), K\(^+\), ATP and CTS. The catalytic function of the NKA for transport of Na\(^+\) and K\(^+\) relies on the α-subunit, whereas the association with the β-subunit is required for the complex to move through the secretory pathway to the plasma membrane [12, 13]. Each of the α- and β-isoforms is encoded by its own gene and can potentially form 12 different NKA isozymes with distinct transport and pharmacological properties [14]. In the heart and kidneys the NKA α\(_1\)-isoform is the dominant, ubiquitous isoform, regulating bulk Na\(^+\) whereas α\(_2\) plays a more prominent role in smooth muscle contraction and to some extent contributes to inotropy in the heart (see Pavlovic et al. [9], fig. 1).

NKA uses the free energy of hydrolysis of ATP to exchange 3 intracellular Na\(^+\) ions for 2 extracellular K\(^+\) ions, thus setting the electrochemical gradient for both Na\(^+\) and K\(^+\) across the cell membrane. The NKA is therefore vital for maintaining the resting potential and Na\(^+\) and K\(^+\) gradients in almost every eukaryotic cell. These gradients ensure basic cellular homeostasis such as regulation of cell volume, essential ionic and amino acid transport processes. In excitable cells NKA activity restores the Na\(^+\) and K\(^+\) gradients following depolarisation and in the kidney its activity provides the driving force for Na\(^+\) reabsorption essential to control extracellular volume and blood pressure. Among the many Na\(^+\)-dependent transmembrane transport processes in muscle cells, the activity of the NKA drives the Na\(^+\)/Ca\(^{2+}\) exchanger (NCX) and thus regulates the concentration of Ca\(^{2+}\) in both the cytosol and the sarcoplasmic reticulum. An increase in Na\(^+\) would limit ‘forward mode’ Na\(^+\)/Ca\(^{2+}\) exchange (Na\(^+\) in, Ca\(^{2+}\) out) and possibly even favour more Ca\(^{2+}\) influx and less Ca\(^{2+}\) efflux, resulting in a larger Ca\(^{2+}\) transient and therefore increased contractility [15]. This is the accepted mechanism of action for the inotropic effect of herbal remedies such as extract from foxglove (Digitalis purpurea), used to increase cardiac output in patients with congestive heart failure. The British physician William Withering first described these effects in his 1785 publication An Account of the Foxglove and Some of Its Medical Uses: With Practical Remarks on Dropsy and Other Diseases. Some 100 years later, Oswald Schmiedeberg isolated and identified the compound responsible for the inotropic effects of foxglove as digoxin, a member of the CTS family.

**Cardiotonic Steroids**

Nanomolar concentrations of CTS, such as ouabain, digoxin, marinobufagenin, bufalin and telocinobufagin, are detected in serum of experimental animals and humans [16–28]. CTS can be divided into two structurally distinct groups, cardenolides and bufadienolides. Cardenolides, such as ouabain and digoxin, have a 5-membered unsaturated lactone ring attached to the steroid nucleus at position 17, whereas the bufadienolides, such as marinobufagenin and telocinobufagin, have a doubly unsaturated 6-membered lactone ring (fig. 1). All cardenolides have a hydroxyl at position 14, whereas some bufadienolides have a 14–15 epoxide. The steroid nucleus is sometimes glycosylated in position 3. The steroid substitutions of some of the most commonly isolated CTS are summarised in figure 1.

**Cardenolides**

There is substantial evidence that endogenous ouabain is present in the circulation. Hamlyn et al. [21] were the first to identify a substance indistinguishable from ouabain in human serum. Subsequently, endogenous ouabain was detected in the blood of patients with essential hypertension [27, 29], congestive heart failure [30] and end-stage renal failure [31]. Some evidence exists for the presence of digoxin in human urine [32] and of digitoxose sugars in mammals [33, 34]; however, this requires further characterisation.

**Bufadienolides**

Marinobufagenin was originally discovered in amphibians and subsequently isolated and identified in the urine of patients with myocardial infarction [16] and the serum of patients with terminal renal failure [25]. Structurally related telocinobufagin, the reduced form of marinobufagenin, was identified, by high-resolution mass spectrometry and nuclear magnetic resonance, as a con-
Biosynthesis of CTS

Evidence is accumulating that most CTS are synthesised from cholesterol in the adrenal glands [37, 38] and possibly hypothalamus [39] but the biosynthetic pathways for cardenolides and bufadienolides seem to differ. The trigger for biosynthesis initiation is complex, with serum concentrations of ouabain and marinobufagenin increasing in response to volume expansion [40], salt accumulation in the brain, adrenocorticotropic hormone, angiotensin II, vasopressin and phenylephrine [37, 41].

CTS Receptor Function: Ion Transport versus Signalling Pathway

The classic model explaining the effects of CTS are based on the observations that enzymatic and transport functions of the NKA are reduced, thereby raising intracellular Na\(^+\) and Ca\(^{2+}\) (via NCX). The effects of high Ca\(^{2+}\) on contractility [42] and induction of hypertrophic signalling cascades in the heart are well known [43]. However, when concentrations of CTS detected in serum of experimental animals and patients were shown to be in the range of 0.5–20 nM [16–28], these were considered too low to modulate the activity of the NKA and thus were not expected to affect intracellular Na\(^+\) and Ca\(^{2+}\) concentrations [44]. Therefore, in addition to its transport function, a hypothesis that the NKA also acts as a receptor for the CTS has been presented. Indeed, evidence is accumulating that the NKA also plays a signalling role [45], regulating early response genes associated with cell growth (see the review by Lie and Xie [46]). This model proposes that a fraction of NKA subunits are localised in the caveolae and are not involved in the transport of Na\(^+\) and K\(^+\) ions but instead act as receptors for CTS. These ‘inactive’ pumps are physically associated with other key signalling proteins such as epidermal growth factor (EGFR) and Src [47, 48], and binding of the CTS leads to activation of hypertrophic and fibrotic signalling cascades via NKA-Src-ERK [46]. The groups of Shapiro and Xie have shown that other signalling proteins are recruited, including phospholipase C, TRP proteins, phosphoinositide 3-kinase (PI3K) and protein kinase C [44, 48–52], and...
that the CTS induce the endocytosis of the CTS-NKA-Src-EGFR complex [49–51]. Increased reactive oxygen species production that is Ca\(^{2+}\) sensitive has also been observed following CTS binding; however, the mechanisms by which CTS initiate reactive oxygen species production are unclear [24, 44, 52]. Whereas this alternative signaling pathway explains some of the effects of CTS, it does not account for the reported NKA inhibition that can be reversed by antidigalsis antibodies in patients with diabetes [53] or ESRD [28]. Furthermore, there is disagreement whether the activation of signalling cascades via CTS indeed occurs independently of NKA inhibition and the accompanying increases in intracellular Na\(^{+}\) and Ca\(^{2+}\) [54, 55]. Altamirano et al. [42] showed that acute inotropic effects of digoxin, acylstrophantidin and ouabain depend on the presence of intracellular Na\(^{+}\) and a functional NCX. Reuter et al. [56] have also reported that the NCX is required for CTS to induce increased intracellular Ca\(^{2+}\). Furthermore, a recent study by Andrikopoulos et al. [57] reported that elevation of Ca\(^{2+}\) via ouabain-mediated NKA inhibition was sufficient to activate NKA-Src-ERK signalling cascades and lead to angiogenesis in human endothelial cells. Whether CTS induce hypertrophic growth in the heart via the ionic pathway or the signalling one remains to be resolved; however, the weight of evidence in support of both pathways makes it likely that they act in conjunction with each other. For details of the two pathways, please see figure 2.

**CTS and Disease Pathogenesis**

**Hypertension**

Over the last 20 years, search for an endogenous ligand for the ouabain-binding site has intensified, and up to date 5 different CTS [25, 58–60] have been detected in circulation in humans and animals with varying NKA inhibitory properties (for a review, see Bagrov et al. [61]). Increases in endogenous CTS are particularly prominent in states of volume expansion and volume expansion-mediated hypertensive syndromes that are related to water and salt accumulation [18, 62, 63]. In healthy individuals, 3 days of salt loading led to a transient 13-fold elevation in plasma ouabain and an increase in urine Na\(^{+}\) excretion [40]. In another study of normotensive human subjects, 6 days of high salt intake resulted in a similar transient increase in plasma ouabain and an increase in urine Na\(^{+}\) excretion [64]. The hypothesis that CTS play a role in volume and blood pressure control is...
also supported by the facts that: (1) infusion of ouabain or marinobufagenin, at concentrations comparable with in vivo plasma levels, leads to an increase in blood pressure [24, 65–67]; (2) hypertension induced by either salt loading, ouabain infusion or pre-eclampsia was reduced by immunoneutralisation with anti-CTS antibodies [60, 68] or the CTS antagonists rostafuroxin [69] and resibusfagenin [70]. While the effects of individual CTS on changes in blood pressure are complex and require further characterisation, taken together, these studies strongly implicate CTS in the pathogenesis of hypertension.

The mechanisms that govern hypertension development have not yet been fully elucidated; however, evidence is accumulating that in response to high salt intake, CTS are secreted by the brain [39] as well as the adrenal glands [37, 38] and that this leads to both central and peripheral blood pressure elevation and consequent salt excretion. Specifically, high salt intake elevates both plasma and cerebrospinal fluid Na⁺ [71, 72], and this induces the secretion of CTS by the adrenals and the hypothalamus. Intracerebroventricular infusion of Na⁺-rich cerebrospinal fluid [73] or ouabain [71] increased sympathetic nerve activity, heart rate and blood pressure in rodents, and these effects were partially reversed by Digibind®. There is reasonable evidence that this signalling cascade in the brain includes aldosterone, epithelial Na⁺ channels, endogenous ouabain, α₂-sodium pumps and angiotensin II (for a review, see Blaustein et al. [74]). Whereas the effects of brain-derived endogenous ouabain require further characterisation, plasma ouabain produced by the adrenal glands can contribute to acute vasoconstriction and increased myocardial contractility via inhibition of the α₂-sodium pumps in the smooth and cardiac muscle. Furthermore, CTS-mediated activation of the NKA-Src-EGFR complex (as discussed above in CTS Receptor Function: Ion Transport versus Signalling Pathway) is likely to contribute to functional remodelling of the affected tissue leading to hypertrophy and hypertension (fig. 3). Although reduction in endogenous CTS via anti-CTS antibodies lowered urine sodium excretion, no changes in blood pressure were observed in healthy animals [75], suggesting that this pathway is inactive in the absence of salt-loading, volume-expanding conditions. This makes it particularly attractive to therapeutic exploitation. Disappointingly, in a recent Ouabain and Adducin for Specific Intervention on Sodium in Hypertension (OASIS-HT) phase 2 dose-finding trial, rostafuroxin (ouabain antagonist) did not reduce blood pressure at any dose [76]. However, more encouraging data are observed in patients with pre-eclampsia. Pregnancy is associated with plasma volume expansion as a result of renal Na⁺ and fluid retention, thus not surprisingly, levels of endogenous ouabain, α₂-sodium pumps and angiotensin II
ouabain and marinobufagenin were increased 4-fold and 8-fold, respectively, in patients with severe pre-eclampsia [77]. In vivo immunoneutralisation of CTS was presented as an unusual but therapeutically attractive option for the treatment of pre-eclampsia. In particular, 51 severely pre-eclamptic patients were treated with Digibind or placebo for 48 h [78]. Digibind was well tolerated, and results showed a reduction in decline in renal function and significantly improved NKA inhibition. Another exciting multi-centre, double-blind, placebo-controlled efficacy study of Digibind in pre-eclampsia (DEEP) has recently been concluded [79]. In women with severe pre-eclampsia who were remote from term and who were positive for CTS, the use of Digibind was associated with improved maternal and neonatal outcome. A large multi-centre trial that would evaluate the benefits of Digibind in the treatment of women with severe pre-eclampsia who are remote from term and with positive CTS status is required in order to confirm the results of the DEEP trial.

Natriuresis
The basis of natriuresis due to CTS is thought to be dependent on the direct inhibition of the NKA α1-isofrom in renal tubular cells [63]. There is some evidence that marinobufagenin is the dominant CTS as marinobufagenin antibodies given to salt-loaded rats lowered urinary excretion and increased NKA activity [80]. However, due to the similar chemical structures of CTS, antibodies raised against individual CTS tend to have poor specificity [81]. Indeed, administration of ouabain or marinobufagenin resulted in inhibition and internalisation of the NKA by endocytosis in LLCPK1 cells, a model of proximal tubule cells, but no depletion was observed in MDCK cells, a cell line resembling distal tubular cells [51]. Ouabain was reported to stimulate a clathrin-dependent endocytosis pathway that translocates the NKA to intracellular compartments. This translocation required PI3K activation, the plasmalemmal pump to be in the context of caveola, and signalling through the Src-EGFR pathway [50]. It is therefore suggested that salt-loading leads to increases in ouabain and marinobufagenin in the proximal tubules, both of which act to decrease Na+ reabsorption through NKA inhibition and/or activation of a signalling mechanism mediated by NKA-Src-EGFR cascades. This decrease in renal Na+ reabsorption is expected to lead to an increase in urinary Na+ excretion and thus eventually to abrogation of hypertension. Indeed, 3 days of salt-loading in healthy individuals did not result in a change in blood pressure [40] suggesting that acute salt-loading in a healthy individual has no pathological consequences. However, it is clear that during chronic salt-loading or chronic CTS infusion, hypertension persists. It is likely that this is mediated via a combination of chronic elevation of brain Na+, leading to increased sympathetic nerve activity, and the direct effects of endogenous CTS on the smooth and cardiac muscle, potentially resulting in increases in cardiac output, increased total peripheral resistance and thus elevation in blood pressure (as discussed in the previous section). Furthermore, adaptation changes induced via activation of the NKA-Src-EGFR complex may also participate in the arterial remodelling that is often associated with established hypertension [82].

Renal Failure and Uraemic Cardiomyopathy
Serum levels of ouabain, telocinobufagin and marino bufagenin are substantially elevated in patients with ESRD [25, 31]. Similar increases (albeit slightly lower than in ESRD) in ouabain and marinobufagenin were reported in animals with CKD [24, 83]. In fact, plasma endogenous ouabain levels were shown to be powerful biomarkers of acute kidney injury and postoperative complications in cardiac surgery patients [84]. Plasma marinobufagenin levels were also increased in patients with renal artery stenosis, whereas reversal of renal ischaemia by stenting treatment reduced marinobufagenin concentrations, thus implying that renal artery stenosis-induced renal ischaemia may be a major cause of endogenous marinobufagenin synthesis [85]. There is clear evidence that chronic exposure to CTS can contribute to cardiovascular disease development. Sustained ouabain infusion in rats induces left ventricular hypertrophy [66], whereas the presence of left ventricular hypertrophy and reduction in ejection fraction are positively correlated with increased CTS concentrations in the serum of patients with essential hypertension [27, 29], congestive heart failure [30] and ESRD [31]. As discussed earlier, CTS inhibit NKA activity and as a consequence raise intracellular Na+ and Ca2+ via the NCX [86]. A potentially lethal side effect of chronically raised Ca2+ is Ca2+ leakage through the ryanodine receptor from the sarcoplasmic reticulum, giving rise to arrhythmias [87], a common cause of death in ESRD patients.

Shapiro’s laboratory has examined whether CKD alone can lead to cardiovascular dysfunction. CKD was induced by partial nephrectomy in rats and mice, and increases in serum concentrations of ouabain and marinobufagenin were observed in CKD animals. This was accompanied with increases in blood pressure, diastolic dysfunction, ventricular hypertrophy and cardiac fibrosis.
as well as evidence of signalling through the NKA-Src-ERK signalling cascade [24, 83, 88]. Furthermore, infusion of marinobufagenin resulted in similar biochemical, physiological and morphological changes as observed in animals subjected to partial nephrectomy, whereas active and passive immunisation against marinobufagenin reversed most of these alterations [24, 89]. In a separate series of studies, the authors examined the effects of marinobufagenin on cardiac fibrosis. Nanomolar concentrations of marinobufagenin (and of other CTS) stimulated the production of collagen in primary cultures of cardiac fibroblasts isolated from mice and rats [83, 88]. This effect was suggested to be mediated via the NKA-Src-ERK signalling cascade, and collagen synthesis was associated with increased transcription and translation of procollagen [83]. Based on these data it is tempting to conclude that marinobufagenin is solely responsible for the uremic cardiomyopathy development during CKD. However, it is important to note that the protective effects of immunisation are likely not to be simply mediated by removal of marinobufagenin, as antibodies raised to CTS tend to have poor specificity, as discussed previously. Lack of accurate assays, specific for individual CTS that can detect and quantify nanomolar concentrations of individual CTS, has certainly hindered our progress. Currently, there is a commercially available assay for ouabain but not for measurements of marinobufagenin, telocinobufagin and bufalin. Whether the animal experiments performed thus far have any application to human disease remains to be confirmed. Although the CTS binding site is highly conserved across the evolutionary spectrum [90], rats and mice possess an Asn122His substitution in their NKA α1-isozymes, making it less sensitive to CTS [91]. Considering that a large proportion of scientific research is conducted in the rat and mouse, a question of relevance of some of the data to human physiology cannot be disregarded. It should be noted however that α2- and α3-isozymes in rats and mice are sensitive to ouabain.

Recent studies suggest that reduction of NKA content (often manifested in heart failure) in conjunction with nanomolar levels of marinobufagenin potentiates marinobufagenin-induced myocyte apoptosis by activation of the caspase 9-regulated pro-apoptotic pathway and contributes to diastolic dysfunction [92]. Interestingly, in a separate study of 140 patients with idiopathic dilated cardiomyopathy, endogenous ouabain was shown to be an independent and incremental marker that predicts the progression of heart failure [93]. Therefore, therapy aimed at antagonising the effects of ouabain or marinobufagenin should reduce the progression of heart failure by pathological remodelling and should reduce arterial hypertension in renal failure patients. The latest advances in our understanding of how CTS contribute to cardiovascular dysfunction during CKD/ESRD represent a fertile environment for the development of novel therapeutics for a human condition that affects a significant proportion of the population.

**Overlapping Effects of CTS**

Considering a relatively large number of endogenous CTS that have been identified, the question of biological relevance of this diversity is inevitably posed. The α1-subunit is the dominant subunit in the kidneys and the heart, regulating bulk Na+ and therefore presumably involved in long-term adaptive changes to the local milieu. The α2-isozyme is considered to have regulatory functions in vasoconstriction [65, 94] and cardiac inotropy [95]. It is therefore tempting to assume that each CTS has a particular function, i.e. a tissue-specific NKA receptor. Marinobufagenin was initially reported to demonstrate a high affinity for the NKA, with higher selectivity for the α1-subunit [63]. However, Katz et al. [96] and Wang et al. [97] showed that marinobufagenin possesses a very low binding affinity to the NKA, compared to ouabain, and furthermore they showed that marinobufagenin is not selective for either of the 3 NKA isoforms. Digoxin was reported to have a higher affinity for the α1-subunit, ouabain a higher affinity for α1, whereas marinobufagenin and bufalin cannot discriminate between the isoforms [96]. It is difficult to explain the discrepancies in these studies but it is becoming evident that, rather than marinobufagenin alone mediating specific cardiovascular pathophysiological changes as previously suggested [24, 83], CTS show overlapping specificities for various tasks in the body.

While the functional overlaps are becoming apparent for most CTS, perhaps the most surprising observation is that digoxin was shown to oppose ouabain-induced hypertension in rats [98, 99] and possibly even in humans [100]. A study by Song et al. [101] suggests that low doses of digoxin can antagonise the effects of ouabain, possibly explaining the recently reported beneficial effects of low doses of digoxin therapy in heart failure patients [102]. In this context, it is possible that ouabain antagonism represents another beneficial effect of digoxin, on top of already reported effects on improved baroreceptor function and increased vagal tone [103]. The use of digoxin for the treatment of heart failure and possibly even hypertension should therefore be reconsidered; however, toxic effects of higher doses of digoxin, as shown by Rathore et
al. [104], must not be overlooked. Clearly, if digoxin is to be used more extensively in the clinical setting, closer monitoring of patient serum levels will be required and for this more specific (reduced antibody cross-reactivity) digoxin tests must be developed.

Conclusion

Our understanding of the role of CTS in cardiovascular physiology and pathophysiology has rapidly increased over the last 20 years. Discovery of marinobufagenin and telocinobufagin have allowed us to scratch the surface and perhaps observe, no more than a glimpse of, a plethora of complex signalling networks that are regulated by this new class of hormones. Ouabain, marinobufagenin and most likely others, as of yet undiscovered CTS, are involved in the regulation of cardiac contraction, vasocostriction, natriuresis and remodelling of the heart, kidneys and arterial walls. Their secretion seems to be driven by kidney dysfunction or chronic high salt load and is likely to be involved in the pathogenesis of a number of diseases such as uraemic cardiomyopathy, pre-ecclampsia, hypertension, congestive heart failure, myocardial ischaemia-induced arrhythmias and diabetes mellitus. Already we have started making use of the limited knowledge accumulated to develop several therapeutic tools for the treatment of hypertension, and some of these are currently undergoing clinical trials. A clear barrier to further expansion of our knowledge is the lack of tools to accurately detect and measure the CTS present in circulation. Furthermore, as our understanding of the structure-function relationship expands, the development of novel CTS with a greater therapeutic spectrum and better antihypertensive properties will soon become a reality.

Disclosure Statement

None.

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Cardiotoxic Steroids and Cardiomyopathy


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Nephron Clin Pract 2014;128:11–21
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