Endogenous Cardiotonic Steroids Levels and their Significance in Children with Chronic Kidney Disease

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Abstract

Previous reports demonstrated that digitalis-like cardiotonic steroids (CTS) may contribute to the pathogenesis of end-stage renal disease and its complications. The role of CTS in nature of CKD in pediatric patients is not fully studied. The goal of the present study was to define the levels of CTS in pediatric patients with chronic kidney disease (CKD). In 22 patients with CKD plasma marinobufagenin (MBG) but not endogenous ouabain (EO) was increased as compared to that in 17 healthy individuals. Thus, we speculate that in chronic renal failure elevated levels of bufadienolide CTS MBG may cause the Na/K-ATPase inhibition and may represent a potential target for therapy.

Keywords: Children; Chronic Kidney Disease; Hemodialysis; Marinobufagenin; Ouabain; Na/K-ATPase

Introduction

Endogenous cardiotonic steroids (CTS), also called digitalis-like factors, have been postulated to play important roles in health and disease for nearly half a century [1].

For more than 200 years, digitalis, a cardiotonic steroid, has been used to treat congestive heart failure. The endogenous cardiotonic steroids ouabain and marinobufagenin have been identified in humans. Cardiotonic steroids are considered to be important in the regulation of renal sodium transport and arterial pressure, control of cell growth, apoptosis and fibrosis, among other processes [2].

Almost all of the newly detected mammalian steroid hormones were previously isolated as cardiotonic constituents and toxins from plants and amphibians. Cardiotonic steroids or cardiac glycosides are specific ligands of the sodium pump (Na+/K+-ATPase). Endogenous cardiotonic steroids (Figure 1) have been extracted from mammalian tissues such as hypothalamus [3], heart [4] and adrenal gland [5]. Ouabain (g-Strophanthin) was identified in human blood plasma [6].
CTs act as physiological regulators of sodium pump activity and are implicated in regulation of natriuresis and vascular tone [7]. It has been shown that they are increased in end-stage renal disease in adults [8]. However, this remains unclear in pediatric patients.

In this study, we determined the level of CTs in children with different stages of kidney function reduction due to glomerular and tubular diseases. Values of CTs were related to serum creatinine levels.

Methods

Twenty-two patients with CKD of different stages were included in this study. Of the patients, 5 were on hemodialysis (HD). The cause of CKD was chronic glomerulonephritis (11 patients), pyelonephritis (2 patients), congenital renal dysplasia (9 patients). None of the subjects studied had ever been administered digitalis drugs. All patients were divided into 4 experimental groups based on the glomerular filtration rate (GFR) determined based on serum creatinine levels (Table 1) [9].

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>eGFR (mL/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kidney damage with normal or ↑ GFR</td>
<td>≥ 90</td>
</tr>
<tr>
<td>2</td>
<td>Kidney damage with mild ↓ GFR</td>
<td>60 - 89</td>
</tr>
<tr>
<td>3</td>
<td>Moderate ↓ GFR</td>
<td>30 - 59</td>
</tr>
<tr>
<td>4</td>
<td>Severe ↓ GFR</td>
<td>15 - 29</td>
</tr>
<tr>
<td>5</td>
<td>Kidney failure</td>
<td>&lt; 15 or dialysis</td>
</tr>
</tbody>
</table>

Table 1: Stages of chronic kidney disease.

For measurement of CTs, plasma samples were extracted using C18 SepPak cartridges (Waters Inc., Cambridge, MA). This assay is based on competition between immobilized antigen (MBG-glycoside-thyroglobulin) and MBG. EO assays were based on a similar principle.

The results are presented as box-plots. To determine whether the differences among the groups were significant, two-way ANOVA followed by Fisher-LSD post-hoc test was used. If the distribution of the variables was not parametric, the data were analyzed using the non-parametric Mann-Whitney test. The comparisons between groups were made using Kruskal-Wallis one-way ANOVA on ranks with pair-wise multiple comparisons made by Dunn’s method. The statistical significance level was defined as P < 0.05.

Results

All patients from experimental and control groups were analyzed for age, sex, body weight. Patients with CKD did not differ significantly from the control group with respect to all mentioned above parameters.

We measured levels of both CTs in plasma of CKD patients and controls. As presented in Figure 2, patients with CKD had 3.5-fold greater plasma levels of MBG as compared to those in the control group. Moreover, the gradual increase of plasma MG levels was found between the progressive stages of CKD. Whereas the EO concentrations of this hormone in patients with CKD were not different from control values.

Figure 2: CTs levels in patients with CKD and controls.
We analyzed CTS levels in CKD patients with arterial hypertension. The results show that both CTS documented at higher levels in hypertensive patients. Patients with arterial hypertension identified in CKD 3 group and hemodialysis patients (Figure 3).

![Figure 3](image)

**Figure 3:** CTS levels in children with CKD in relation arterial hypertension presence.

**Discussion and Conclusion**

The major findings of the present study are that levels of CTS in patients with chronic renal failure exhibit a pattern where MBG rather than EO becomes elevated in pediatric patients with CKD. Since in chronic renal failure CTS represent potentially important therapeutic targets, the importance of this finding in pathogenesis of CKD is obvious.

Previously, three endogenous CTS (ouabain, marinobufagenin, digoxin) were shown to balance blood pressure in experimental animals [10]. Here we found the direct relation of CTS levels in CKD patients and arterial hypertension. Previously shown that the circulating levels of EO, MBG and telocinobufagin are increased dramatically in rat with partial nephrectomy. There is renal fibrosis associated with elevated MBG 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 which blocks ouabain binding to the Na⁺ pump without causing inhibition of ion transport [11]. We found no differences in circulating EO in CKD patients. This might be explained by un-known compensative mechanisms preserving progression of ouabain-induced damages in CKD patients with late CKD stages and uremia. In contrast, MBG levels gradually increased in patients with progressive CKD. The highest levels documented in HD patients meaning. This may have an evidence that endogenous MBG is dealing with renal fibrosis and increased blood pressure in this cohort of patients.

Overall understanding the functions of CTS in CKD is still quite incomplete. However, the importance of this class of hormones seems to be considerable. Taking to the account that endogenous CTS exhibit physiological functions that go far beyond regulation of sodium transport, natriuresis, and blood pressure and include regulation of cell growth and differentiation, apoptosis and proliferation [12-14] makes this area dramatically important from the clinical point of view. Dysregulation of these hormones seems to play an important role in a number of diseases including progressive CKD. We propose that expanding our understanding of this class of hormones will lead to novel and effective therapeutic strategies of great relevance to optimizing CKD.

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Bibliography

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