ROLE OF SODIUM/POTASSIUM ATPase INHIBITORS IN HYPERTENSIVE AND CARDIOVASCULAR DISORDERS AND IN KIDNEY DISEASE PROGRESSION

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Endogenous Cardiac Glycosides.

Cardenolides (left column) Bufodienolides (right column).  H Kost, 2001
CARDIAC GLYCOSIDES

Characteristics

- Act as inhibitors of $\text{Na}^+$/K$^+$ ATPase
- Transport enzyme inhibition results in natriuresis
- Are vasoconstrictive, often causing hypertension
- Act as cardiac intropes
CARDIAC GLYCOSIDES

Differences

1. Structural
   a. Cardenolides: unsaturated 5-membered lactone ring
   b. Bufodienolides: doubly unsaturated 6-membered lactone ring

2. Activity
   a. Cardenolides: predilection for the α-2 and α-3 isoforms of Na⁺/K⁺ ATPase
   b. Bufodienolides: act primarily on the α-1 isoform (predominant form in the kidney)

3. The bufodienolides may be more important in the pathogenesis of disease states (e.g., preeclampsia, kidney fibrosis)
# Blood Levels of Marinobufagenin

<table>
<thead>
<tr>
<th>Group</th>
<th>Marinobufagenin (nMol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy individuals (n = 38)</td>
<td>0.225 ± 0.045</td>
</tr>
<tr>
<td>Chronic renal failure (n = 24)</td>
<td>16.6&lt;sup&gt;a&lt;/sup&gt; ± 5.3</td>
</tr>
<tr>
<td>Primary aldosteronism (n = 5)</td>
<td>13.5&lt;sup&gt;a&lt;/sup&gt; ± 12.9</td>
</tr>
<tr>
<td>Congestive heart failure (n = 7)</td>
<td>1.69&lt;sup&gt;a&lt;/sup&gt; ± 1.29</td>
</tr>
<tr>
<td>Essential hypertension (n = 27)</td>
<td>1.74&lt;sup&gt;a&lt;/sup&gt; ± 0.67</td>
</tr>
</tbody>
</table>


<sup>a</sup>p < 0.05 versus healthy controls.
Circulating Vasoactive Substances in the Pathogenesis of Essential Hypertension

- Dahl
- deWardener and Clarkson
- Blaustein and Hamlyn
Essential Hypertension

Major Etiologic Factors

• Expanded extracellular fluid volume

• Increased peripheral vascular resistance
PREECLAMPSIA

- New onset hypertension (>140/90 mmHg)
- Proteinuria (>300 mg/24 hr)
- Onset after 20 weeks of gestation
- Excessive edema often present
- Intrauterine growth restriction (IUGR) common
- Second leading cause of fetal wastage and maternal morbidity and mortality
- Syndrome remits by 12 weeks postpartum
Alterations in blood and plasma volume and red cell mass during pregnancy
Blood Pressure Modification during Pregnancy (all groups)
Weight Gain after 2 Weeks of Pregnancy

![Bar graph showing weight gain in grams for different groups: Control, Pregnant, and Pregnant+DOCA. The graph compares the weight gain between these groups, with Pregnant+DOCA showing the highest gain.]
The difference between the two groups was significant (NP = 14.28 +/- 2.56 vs. DOCA = 9.43 +/- 3.2, p=0.002).
Marinobufagenin Excretion (pmol/24h)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>NP</th>
<th>Preg + DOCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average</td>
<td>160</td>
<td>262</td>
<td>314</td>
</tr>
<tr>
<td>St. Dev.</td>
<td>14</td>
<td>16</td>
<td>17</td>
</tr>
<tr>
<td>p vs Control</td>
<td>&lt;0.01</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>p vs Normal pregnant</td>
<td>&lt;0.05</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
MBG pmol/24h

- t0
- t1
- t2
- t3

- Control
- Pregnant
- Pregnant+DOCA
Hematocrit Change In Preeclampsia Indicates Hemoconcentration
HEMATOCRIT VALUES IN NONPREGNANT, NORMAL PREGNANT, AND “PREECLAMPTIC” RATS

<table>
<thead>
<tr>
<th>Animal Group</th>
<th>Number of Rats</th>
<th>Hematocrit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control, nonpregnant (C)</td>
<td>9</td>
<td>0.44 +/- 0.01†</td>
</tr>
<tr>
<td>Normal pregnant (NP)</td>
<td>10</td>
<td>0.34 +/- 0.02‡</td>
</tr>
<tr>
<td>“Preeclamptic” (PDS)*</td>
<td>8</td>
<td>0.38 +/- 0.02</td>
</tr>
</tbody>
</table>

* “Preeclamptic” (PDS) rats = animals given saline as drinking water and weekly DOCA injections.

† Control rats differ from all other groups (p < 0.001).
‡ NP differs from PDS (p < 0.05).
VASCULAR LEAKAGE IN NON-PREGNANT, NORMAL PREGNANT AND "PREECLAMPTIC" RATS
MBG CAUSES VASCULAR LEAK IN A MESENTERIC POST-CAPILLARY VENULE
### Table: PDS + RBG

<table>
<thead>
<tr>
<th></th>
<th>T - 0</th>
<th>T - 1</th>
<th>T - 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ave BP</td>
<td>106.3</td>
<td>132.5</td>
<td>108.8</td>
</tr>
<tr>
<td>St. Error</td>
<td>3.8</td>
<td>3.2</td>
<td>5.5</td>
</tr>
</tbody>
</table>

For T - 0 and T - 2, the difference is significant at p < 0.05.
MBG + RBG

Ave BP 108.3 121.7 109.6
St. Error 4.2 4.2 3.2

p < 0.01  p < 0.01
## BLOOD PRESSURE, 24 HOUR PROTEIN EXCRETION, PUP NUMBER, PERCENT ABNORMAL PUPS AND HEMATOCRIT VALUES

<table>
<thead>
<tr>
<th>Groups</th>
<th>Number of Rats</th>
<th>Baseline BP</th>
<th>Final BP</th>
<th>Protein (mg/24hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>9</td>
<td>104 ± 5</td>
<td>102 ± 4 †</td>
<td>1.1 ± 0.9 †</td>
</tr>
<tr>
<td>NP</td>
<td>10</td>
<td>105 ± 4</td>
<td>90 ± 6 ‡</td>
<td>2.4 ± 1.2</td>
</tr>
<tr>
<td>PDS</td>
<td>8</td>
<td>103 ± 7</td>
<td>140 ± 8 * ‡</td>
<td>5.6 ± 1.8 *</td>
</tr>
<tr>
<td>PDSR</td>
<td>8</td>
<td>106 ± 6</td>
<td>87 ± 5 ‡</td>
<td>2.5 ± 1.1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Groups</th>
<th>Number of Rats</th>
<th>Pups</th>
<th>% Malformed</th>
<th>Hematocrit</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>9</td>
<td>15.0 ± 1.9</td>
<td>0</td>
<td>0.44 †</td>
</tr>
<tr>
<td>NP</td>
<td>10</td>
<td>11.1 ± 1.4 *</td>
<td>18</td>
<td>0.34</td>
</tr>
<tr>
<td>PDS</td>
<td>8</td>
<td>14.7 ± 1.3</td>
<td>0</td>
<td>0.38 *</td>
</tr>
<tr>
<td>PDSR</td>
<td>8</td>
<td></td>
<td>0</td>
<td>0.33</td>
</tr>
</tbody>
</table>

*Abbreviations: C = Control, Non-pregnant; NP = Normal pregnant; PDS = Pregnant+DOCA+Saline
C = "Preeclamptic" rats; PDSR = "Preeclamptic" rats given resibufagenin from early pregnancy;
BP = Blood pressure

* p<0.05 PDS vs Control, NP and PDSR
† p<0.05 C vs NP, PDS and PDSR
‡ p<0.05 Baseline vs Final
URINARY MBG IN NORMAL PREGNANT AND PREECLAMPTIC PATIENTS

* p < 0.001

- Normal pregnant
- Preeclamptic patients

Urinary MBG (pg/mg Creatinine)
PREECLAMPSIA OUTCOMES

Subjects:
22 Formerly preeclamptic patients
20 Parous controls (matched for age, BMI, date of birth)

Results:
1) Hypertension was present in 55% of the formerly hypertensive patients, 7% of controls.

2) Mean arterial pressure was higher in the formerly preeclamptic women compared to the controls (100 vs. 88 mm Hg).

3) Renal blood flow was 15% lower in the formerly preeclamptic patients, unaffected in the controls.

The Induction of Cardiac Fibrosis by Marinobufagenin


* p<0.05, ** p<0.01 vs. sham, # p<0.05, ## p<0.01 vs. PNx.
The Induction of Cardiac Fibrosis by Marinobufagenin

Accumulation of collagen in the interstitium (B) and development of fibrosis in the peritubular and periglomerular areas of the cortex (D-F). Actin deposition in the tubulointerstitium (H).

MBG Causes Enhanced Procollagen Deposition

Western blots and densitometry measurements in kidney interstitium. *P< 0.05.

SUMMARY

1. MBG is involved in the pathogenesis of volume expansion-mediated hypertension.

2. MBG plays an important role in the cardiomyopathy of experimental uremia.

3. MBG is a factor in the generation of kidney fibrosis and in the epithelial-to-mesenchymal transition that is characteristic of this process.

4. Further study in human subjects and CKD patients will be required to verify these findings, perhaps leading to new therapeutic measures to prevent or minimize these disorders.