Disorders of sodium handling

Detlef Bockenhauer
Objectives

• Physiology of sodium transport
• Clinical consequences of disturbed transport
Overview of renal salt handling

Filtration 100%

Proximal Tubule (Renal Fanconi Syndromes)
- \( \text{H}_2\text{O} \) 70-80%
- \( \text{Na}^+ \) 70-80%

Distal Convoluted Tubule (Gitelman and EAST Syndromes)
- \( \text{Na}^+ \) 5-10%

Thick Ascending Limb (Bartter Syndromes)
- \( \text{Na}^+ \) 10-20%

Collecting Duct (Pseudohypoaldosteronism Type I)
- \( \text{H}_2\text{O} \) 20-30%
- \( \text{Na}^+ \) 2-5%

\( \text{H}_2\text{O} \) 1%
\( \text{Na}^+ \) 1%
Biochemical “Fingerprinting”

• Disorders of tubular sodium handling are associated with specific biochemical profiles
• Identification of these patterns help establish a specific diagnosis
The “Aldosterone fingerprint”
Biochemistry alone is not sufficient

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Bartter</th>
<th>AME</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP (mmHg)</td>
<td>74/46</td>
<td>128/84</td>
</tr>
<tr>
<td>Na (mmol/l)</td>
<td>140</td>
<td>142</td>
</tr>
<tr>
<td>K (mmol/l)</td>
<td>2.2</td>
<td>1.9</td>
</tr>
<tr>
<td>Cl (mmol/l)</td>
<td>98</td>
<td>95</td>
</tr>
<tr>
<td>HCO3 (mmol/l)</td>
<td>27</td>
<td>29</td>
</tr>
</tbody>
</table>
Another case

• 10-day old baby referred by visiting nurse because of weight loss (2.275 kg, birth weight: 2.280)
• Pregnancy complicated by IUGR
• Born at 37+3 weeks
• Family history: Two healthy siblings. Parents are first cousins
• Examination: good peripheral perfusion, BP: ?, no clinical signs of dehydration
# Laboratory Investigations

<table>
<thead>
<tr>
<th>Blood Measure</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na [mmol/l]</td>
<td>133</td>
</tr>
<tr>
<td>K [mmol/l]</td>
<td>7.4</td>
</tr>
<tr>
<td>Cl [mmol/l]</td>
<td></td>
</tr>
<tr>
<td>HCO3 [mmol/l]</td>
<td>16</td>
</tr>
<tr>
<td>Creatinine [mcmol/l]</td>
<td>40</td>
</tr>
<tr>
<td>pH</td>
<td>7.25</td>
</tr>
<tr>
<td>Osmolality [mmol/l]</td>
<td></td>
</tr>
</tbody>
</table>
Diagnosis?

- Congenital Adrenal Hyperplasia
- Pseudohypoaldosteronism
Sodium transport in CD
Treatment

- Na-bicarbonate 13 mmol/kg/d
- Na-Resonium 450 mg three times daily
- NaCl 10 mmol (3 mmol/kg/d) added to iv fluids
- Fludrocortisone 75 mcg
Subsequent course

• Develops significant hypertension (systolic BP >100 mmHg), but persistent hyperkalaemia (>6 mmol/kg)

• What now?
Further investigations

- Normal synacthen test, urinary steroid profile => CAH excluded
- Initial aldosterone level: 3480 pmol/l (normal for neonate: <2000), repeat level (on treatment: 758 pmol/l), renin:<0.3 nmol/l
- Normal renal US, no evidence of UTI
- Diagnosis?
PHA2 (Gordon syndrome)
## Trial of Hydrochlorothiazide

<table>
<thead>
<tr>
<th>Plasma</th>
<th>before</th>
<th>On thiazide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na [mmol/l]</td>
<td>133</td>
<td>134</td>
</tr>
<tr>
<td>K [mmol/l]</td>
<td>6.6</td>
<td>3.2</td>
</tr>
</tbody>
</table>
Blood pressure
Diagnosis?

- PHA type 2 (Gordon syndrome)
- Genetics: homozygous splice site mutation in KLHL3: c.903G>A; p.= (last base exon 8)
# Disorders of renal salt handling

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Gene(s)</th>
<th>Corresponding drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal Fanconi Syndromes</td>
<td>EHHADH, SLC34A1, ....</td>
<td></td>
</tr>
<tr>
<td>Bartter syndromes</td>
<td>SLC12A1, KCNJ1, CLCNKB, BSND</td>
<td>Loop diuretics</td>
</tr>
<tr>
<td>Gitelman</td>
<td>SLC12A3</td>
<td>thiazide</td>
</tr>
<tr>
<td>EAST/SESAME</td>
<td>KCNJ10</td>
<td></td>
</tr>
<tr>
<td>PHA1</td>
<td>SCNN1A,B,G, NR3C2</td>
<td>Amiloride/spironolactone</td>
</tr>
<tr>
<td>Hypoaldosteronism</td>
<td>CYP11B2,</td>
<td></td>
</tr>
<tr>
<td>PHA2/Gordon</td>
<td>WNK1, WNK4, CULL3, KLHL3</td>
<td>tacrolimus</td>
</tr>
<tr>
<td>Liddle</td>
<td>SCNN1B,G</td>
<td></td>
</tr>
<tr>
<td>AME</td>
<td>HSD11B2</td>
<td>licorice</td>
</tr>
<tr>
<td>Hyperaldosteronism</td>
<td>CYP11B1, KCNJ5, CACNA1D,H, CYP11B2</td>
<td>fludrocortisone</td>
</tr>
</tbody>
</table>

**Note:** Gene abbreviations are used for brevity. Full gene names and their functions can be found in genetic databases such as OMIM (Online Mendelian Inheritance in Man). Treatment options include medications that target the specific disorder, or lifestyle changes.
Key message 1

Sodium transport determines blood pressure/volume homeostasis
There is only one organ...

...and it works through salt
Physiology

From: Hoenig & Zeidel, CJASN 2014;9(7):1272-1281
Key aspects of disorders of sodium transport

- Primarily affects volume homeostasis
- Rarely affects plasma sodium concentration
- Molecularly linked to other transport processes
Pathophysiology

- 2-week old neonate transferred to GOSH renal ward
- Born at 32-wk gestation
- Pregnancy complicated by polyhydramnios (2 amniocenteses)
- Postnatal: polyuria (200 ml/kg/d) and severe electrolyte disturbance
- 3rd child of healthy parents, 1st cousins
Examination

- Decreased peripheral perfusion
- Wt: 1.68 kg
- Length: 44 cm
- HC: 29 cm
- BP: 68 mmHg systolic
# Biochemistries

<table>
<thead>
<tr>
<th>Parameter</th>
<th>admission</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na (mmol/l)</td>
<td>116</td>
<td>133-146</td>
</tr>
<tr>
<td>K (mmol/l)</td>
<td>2.1</td>
<td>3.5-5.5</td>
</tr>
<tr>
<td>Cl (mmol/l)</td>
<td>59</td>
<td>100-108</td>
</tr>
<tr>
<td>81*</td>
<td></td>
<td>7.37-7.43</td>
</tr>
<tr>
<td>Ca (mmol/l)</td>
<td>1.99</td>
<td>2.17-2.44</td>
</tr>
<tr>
<td>g ( )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine (mcmol/l)</td>
<td>116</td>
<td>16-33</td>
</tr>
</tbody>
</table>
Diagnosis

• Bartter syndrome
• Also has sensorineural deafness
• Bartter type 4
• Homozygous mutation in Barttin p.Pro151Leufs*27
Pathophysiolog

CLCNKB/A
Barttin
Treatment

- Salt! up to 14 mmol/kg/d
- Potassium up to 13 mmol/kg/d
- NSAID (indomethacin, celecoxib)
Further course

<table>
<thead>
<tr>
<th>parameter</th>
<th>min</th>
<th>max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na (mmol/l)</td>
<td>116</td>
<td>173</td>
</tr>
<tr>
<td>K (mmol/l)</td>
<td>1.4</td>
<td>6.9</td>
</tr>
<tr>
<td>Cl (mmol/l)</td>
<td>56</td>
<td>125</td>
</tr>
<tr>
<td>Creatinine (mcmol/l)</td>
<td>29</td>
<td>182</td>
</tr>
<tr>
<td>pH</td>
<td>7.58</td>
<td>7.90</td>
</tr>
</tbody>
</table>
“Renal Apnoea”

• Recurrent desaturations
• Inability to extubate after GA for central line insertion
Polysomnography
More complications

- Hypophosphataemic rickets

<table>
<thead>
<tr>
<th>test</th>
<th>Value [unit]</th>
</tr>
</thead>
<tbody>
<tr>
<td>PO4</td>
<td>0.3 mmol/l</td>
</tr>
<tr>
<td>PTH</td>
<td>56 pmol/l</td>
</tr>
<tr>
<td>ALP</td>
<td>1226 IU/l</td>
</tr>
<tr>
<td>TmP/GFR</td>
<td>&lt;0.8 mmol/l</td>
</tr>
</tbody>
</table>
....and more complications

- Severe developmental delay
- Failure-to-thrive
- Stuck in hospital
Homer said it all
How to move forward?

- Palliative care
- Titration with HCl
- Nephrectomy(ies)
- amiloride
Amiloride action
Pathophysiology
Bartter syndrome affects tubuloglomerular feedback

- MD cells are TAL cells
- ↓ chloride reabsorption leads to renin/angiotensin activation via Prostaglandins
- COX-2

![Diagram showing tubuloglomerular feedback](image)
Amiloride justification

- JG apparatus is “short circuited”, as no chloride reabsorption
- \( \rightarrow \text{prostaglandin} \rightarrow \text{renin} \rightarrow \text{aldosterone} \)
  independent of volume status
- Volume homeostasis must be maintained by adequate salt supplementation
Course since

- Blood pH <7.6
- Improved mental state
- No further phosphate supplementation
- Discharged home age 12 months (2 months after starting amiloride)

- Severe developmental delay
- CKD stage 3 (eGFR 30 ml/min)
Conclusions

• Renal salt handling regulates volume homeostasis

• Renal sodium transport is molecularly linked to multiple other transport pathways

• Volume homeostasis “rules”!

• Disorders of renal sodium handling clinically manifest with altered BP and secondary electrolyte abnormalities

• They rarely affect plasma sodium concentration