Lithium-induced Tubular Dysfunction

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11/30/10
Use of Lithium

• Mid 19th century: treatment of gout
• Late 19th century: used for psychiatric disorders
• Early 20th century: sodium substitute to improve taste
• 1949: successful use of lithium for manic-depressive disorders, first reported by Australian psychiatrist John Gade.
• Approximately 0.1% of the US population is undergoing lithium treatment for psychiatric problems.

• Known to cause urinary-concentrating defects in as many as 40% of pts during and after lithium treatment.

• Most common cause of nephrogenic diabetes insipidus.

• Up to 12% develop frank DI, and some continue to have this problem for years after discontinuing lithium.
<table>
<thead>
<tr>
<th>Period</th>
<th>Group</th>
<th>Element</th>
<th>Properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>H</td>
<td>High ionization potential and water solubility, greater distribution through body water than Na or K</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>Li</td>
<td>Li is freely filtered through the glomeruli and up to 80% of the filtered load is reabsorbed, mostly in the proximal tubule</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>Na</td>
<td>Small fraction reabsorbed in distal parts of the nephron through ENaC</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>K</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>4</td>
<td>Ca</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>Sr</td>
<td></td>
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Water Diuresis

• In rat kidney medulla, lithium for 25 days induced a severe water diuresis with marked (70%) down regulation for AQP2 water channel expression. Marples et al. 1995

• Only partly reversed by stopping lithium, by thirsting or by DDAVP administration.

• Subsequent studies showed that the severity of lithium toxicity was time-dependent, leading to morphological changes in the collecting duct after 2 weeks of treatment.
Lithium induced AQP2 Downregulation

Decreased whole kidney AQP2 expression after 4wks lithium diet in Wistar rats

Christensen et al. AJP 2003
Li-induced Change of Cellular Composition

Proportion of intercalated cells increased at the expense of principal cells

<table>
<thead>
<tr>
<th></th>
<th>Control, %</th>
<th>Lithium Treatment, %</th>
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<tbody>
<tr>
<td><strong>Cortex/CCD</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AQP-2</td>
<td>62±1.8</td>
<td>40±3.4*</td>
</tr>
<tr>
<td>[H⁺]ATPase</td>
<td>38±1.7</td>
<td>50±2.0*</td>
</tr>
<tr>
<td>Negative</td>
<td>0.1±0.07</td>
<td>10±2.1*</td>
</tr>
<tr>
<td><strong>ISOM</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AQP-2</td>
<td>61±4.1</td>
<td>59±4.9</td>
</tr>
<tr>
<td>[H⁺]ATPase</td>
<td>36±4.2</td>
<td>39±4.6</td>
</tr>
<tr>
<td>Negative</td>
<td>2.3±1.9</td>
<td>1.6±0.7</td>
</tr>
<tr>
<td><strong>IM-1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AQP-2</td>
<td>81±1.3</td>
<td>58±1.6*</td>
</tr>
<tr>
<td>[H⁺]ATPase</td>
<td>18±1.3</td>
<td>42±1.6*</td>
</tr>
<tr>
<td>Negative</td>
<td>0.2±0.1</td>
<td>0.06±0.03</td>
</tr>
</tbody>
</table>

Christensen et al. AJP 2003
• It was hypothesized that lithium interferes with the AC-cAMP-PKA-dependent recruitment of AQP2 to the apical membrane of collecting duct cells.

• However, a 2006 study (Li et al. JASN 2006) showed that the development of lithium-induced NDI was dissociated from adenyl cyclase activity.
Effects of lithium on DDAVP-stimulated cAMP production in MpkCCD cells

Effects of lithium on AQP2 expression and DDAVP-stimulated cAMP production in Wistar rat inner medulla

Li et al. JASN 2006
Lithium effects on GSK-3β and COX2

• Recent studies indicate that lithium acts as an inhibitor of GSK-3.

• GSK-3 can be inhibited by phosphorylation of Ser9 residue.

• Constitutive GSK-3 activity has recently been shown to tonically suppress COX-2 expression in cultured renal interstitial cells.

• Lithium is shown to inhibit GSK-3 activity and to promote COX-2 dependent polyuria.

• In vitro, activity of GSK-3 is inhibited by 50% in the presence of a Li concentration of 1-2mmol/l
Lithium inhibits GSK-3β

Effects of lithium on GSK-3/pGSK-3 in C57BL/6J mice (Li 4mmol/kg/day) (left) and on cultured renal medullary interstitial cells (30mM Li x 8h) (right)

Rao et al. AJP 2006
Effect of LiCl on COX2 expression.

A: *C57BL/6J mice were injected with LiCl (4 mmol/kg/day) for the indicated length of time. Whole kidney microsomal COX2 expression was determined by immunoblotting.*

B: *confluent cultures of renal medullary interstitial cells (RMICs) were treated with 30 mM LiCl for 8 h. Cell lysate COX2 was analyzed by immunoblotting.*

*P < 0.01. **P < 0.0001.
Role of ENaC

- Apical entry of Na into cells of the collecting duct is mediated by ENaC, permeable only to Na and Li. Permeability to Li is 1.5-2 fold higher than to Na.
- Li poor substrate for Na-K-ATPase at basolateral membrane
- Toxic intracellular levels of lithium could therefore build up quickly in cells of the collecting duct that are exposed to therapeutic concentrations of Li (0.6-1.2mmol/l)
• Transgenic mice lacking alpha ENaC expression and littermate controls with normal ENaC function were fed with lithium 40mmol/kg of dry food for 25 days. Christensen et al. JASN 2006

• Fourfold increase in water intake/polyuria in control mice.

• It supports that ENaC-mediated lithium entry into the Principal cells is a crucial step in the pathogenesis of Li-induced DI.
Segment Specific ENaC Downregulation

Nielsen et al. AJP 2003
Semiquantitative immunoblots using protein prepared from homogenates from the cortex (A), inner stripe of OM (B), and inner medulla (C)
Questions to Be Explored

• Which mechanisms lead to selective and segment-specific downregulation of β-ENaC and γ-ENaC in Li-NDI?

• Is there a difference in the luminal Li concentrations along the connecting and collecting duct subsegments?

• Exit pathway for Li across the basolateral membrane may be important to determine intracellular Li concentration / transepithelial reabsorption.
• Lithium has more widespread chronic renal effects:

• Microarray screening of gene expression in the renal medulla of lithium-treated rats demonstrated altered transcription and mRNA expression of a number of genes involved in cellular proliferation and regulation of the actin cytoskeleton.

• Li also a/w activation of several signaling pathways incl. protein kinase B (Akt) and mitogen-activated protein kinases.
Treatment of Li-NDI

- Decreased dietary solute; Low salt (<100meq/day), low protein (<1g/kg) diet
- Thiazide diuretics (hypovolemia-induced increase in proximal Na and water reabsorption > diminishing water delivery to the ADH-sensitive sites in the collecting tubules and reducing the urine output)
- NSAIDs
- DDAVP
- Amiloride
Amiloride in Li-NDI

Amiloride reduces Li-induced AQP2 down regulation in mCCD cells

Marleen et al. KI 2009
Amiloride in Li-NDI

Marleen et al. KI 2009
Amiloride in Li-NDI

(a) Immunofluorescence images showing the expression of AQP2 (red) and H-ATPase (green) under different conditions: control (−), lithium (Li), and lithium plus amiloride (Li + Am).

(b) Bar graph showing the ratio of principal to intercalated cells under control (Con), lithium (Li), and lithium plus amiloride (Li + Am) conditions. The graphs indicate significant differences (*) between conditions.
THANK YOU!