

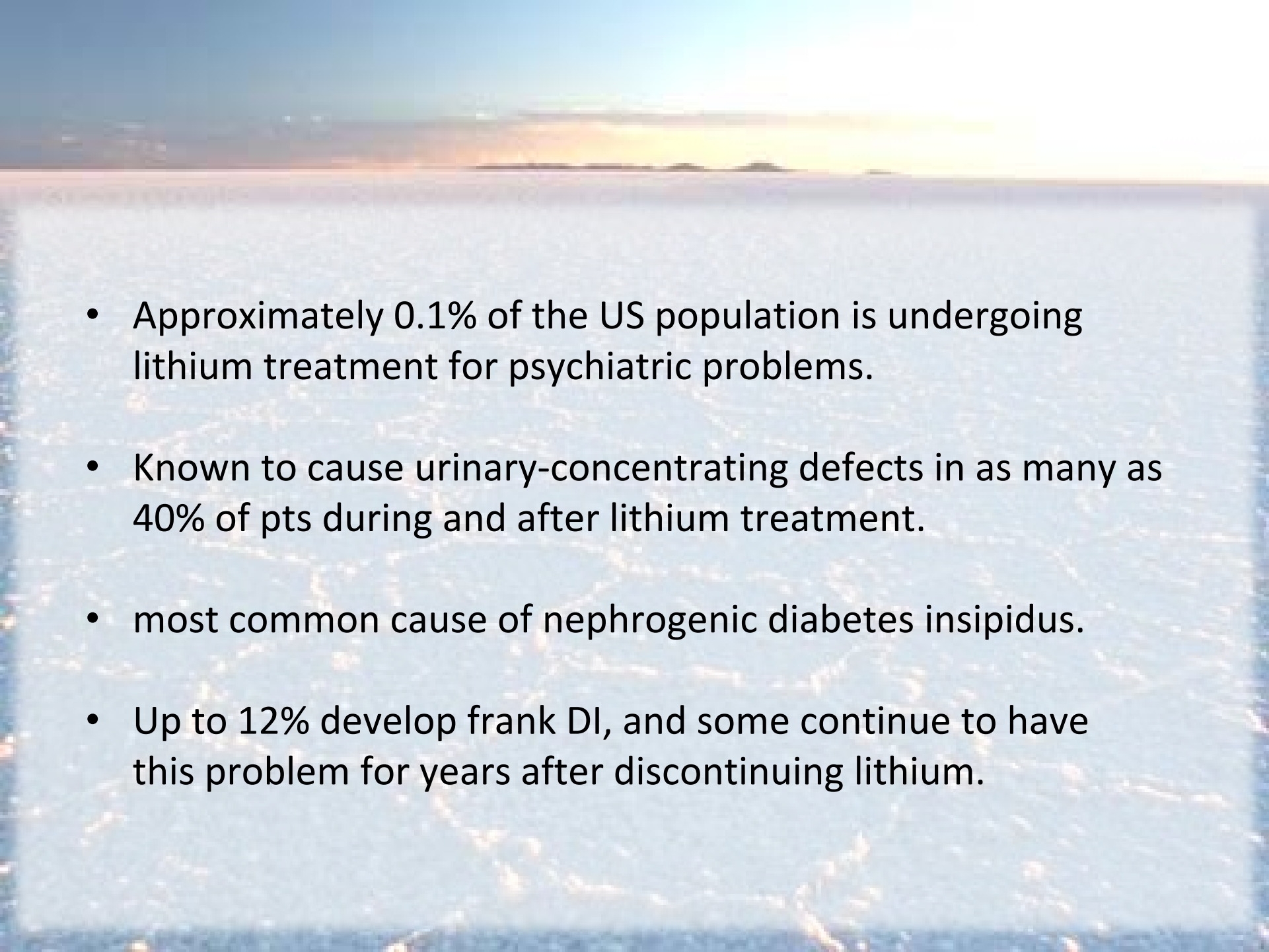
# Lithium-induced Tubular Dysfunction

Jun-Ki Park

11/30/10

# Use of Lithium

- Mid 19<sup>th</sup> century: treatment of gout
- Late 19<sup>th</sup> century: used for psychiatric disorders
- Early 20<sup>th</sup> century: sodium substitute to improve taste
- 1949: successful use of lithium for manic-depressive disorders, first reported by Australian psychiatrist John Gade.

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- 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.

PERIOD	GROUP IA	GROUP IIA	GROUP IIIA
1	1 1.008 <b>H</b> Hydrogen Alkali Metal Boiling Point: -252.87°C		
2	3 6.941 <b>Li</b> Lithium Alkali Metal Boiling Point: 1347°C	4 9.012 <b>Be</b> Beryllium Alkaline Earth Metal Boiling Point: 2970°C	
3	11 22.990 <b>Na</b> Sodium Alkali Metal Boiling Point: 883°C	12 24.305 <b>Mg</b> Magnesium Alkaline Earth Metal Boiling Point: 2472°C	
4	19 39.098 <b>K</b> Potassium Alkali Metal Boiling Point: 774°C	20 40.078 <b>Ca</b> Calcium Alkaline Earth Metal Boiling Point: 1484°C	21 88.906 <b>Sc</b> Scandium Transition Metal Boiling Point: 2835°C
5	37 85.468 <b>Rb</b> Rubidium Alkali Metal Boiling Point: 394°C	38 87.62 <b>Sr</b> Strontium Alkaline Earth Metal Boiling Point: 1382°C	39 88.906 <b>Y</b> Yttrium Transition Metal Boiling Point: 3370°C

High ionization potential and water solubility, greater distribution through body water than Na or K

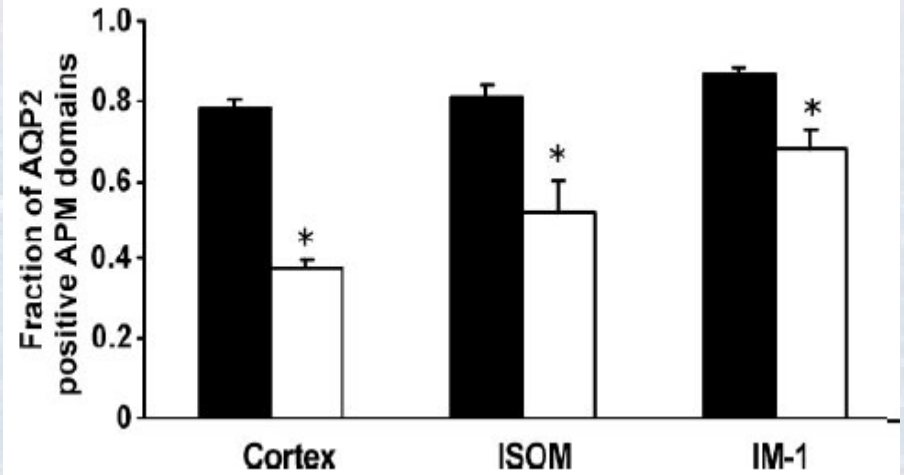
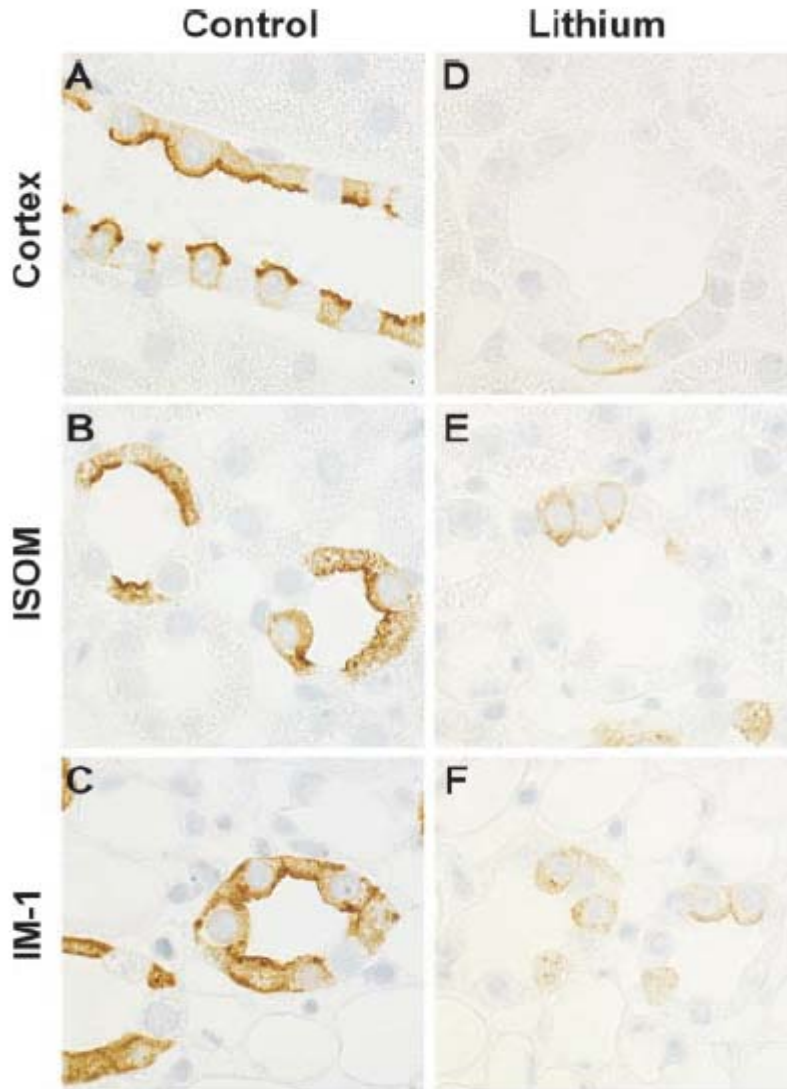
Li is freely filtered through the glomeruli and up to 80% of the filtered load is reabsorbed, mostly in the proximal tubule

Small fraction reabsorbed in distal parts of the nephron through ENaC

# 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

# Li-induced Change of Cellular Composition

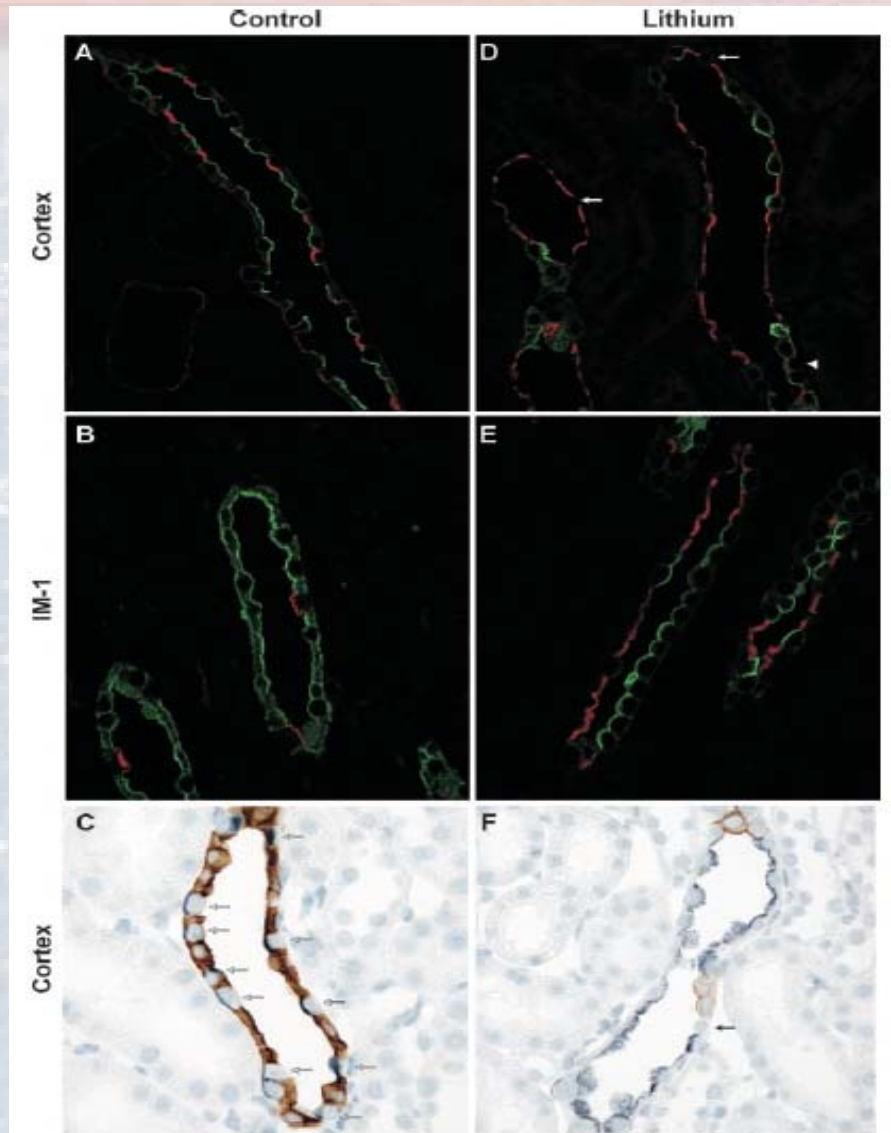
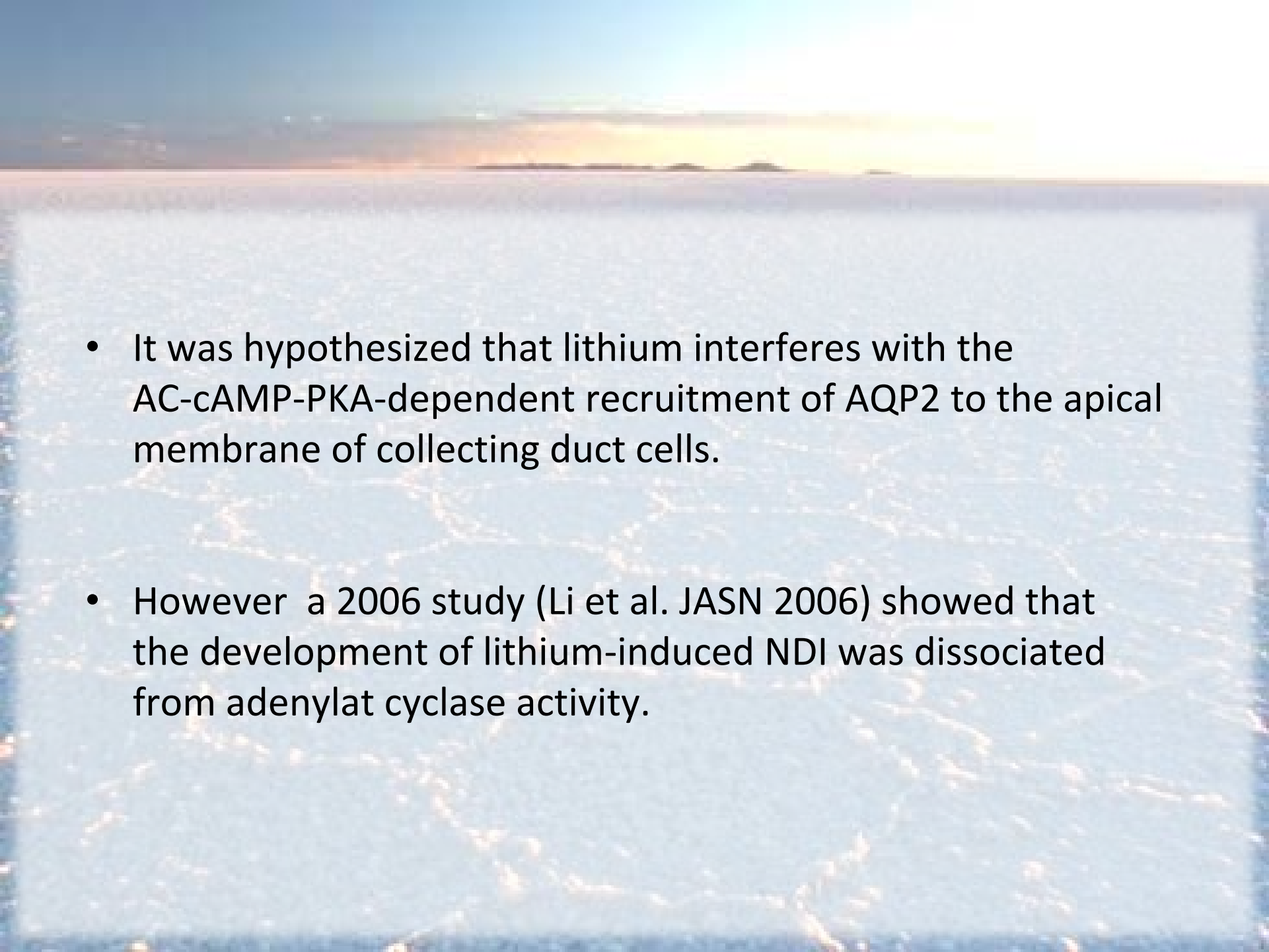
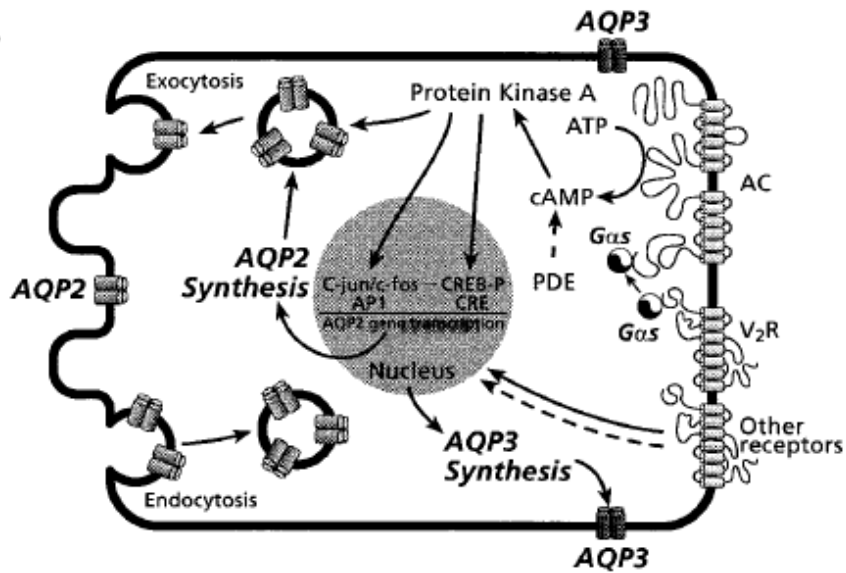
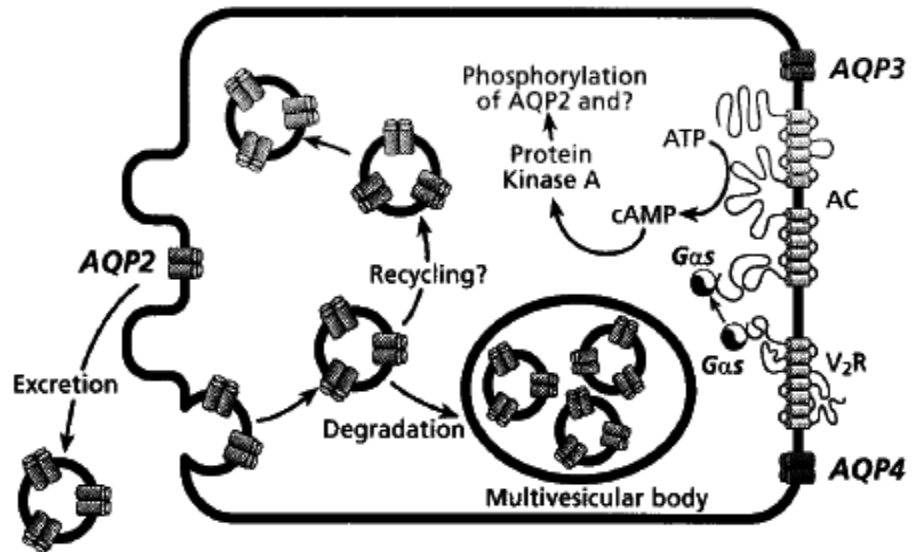


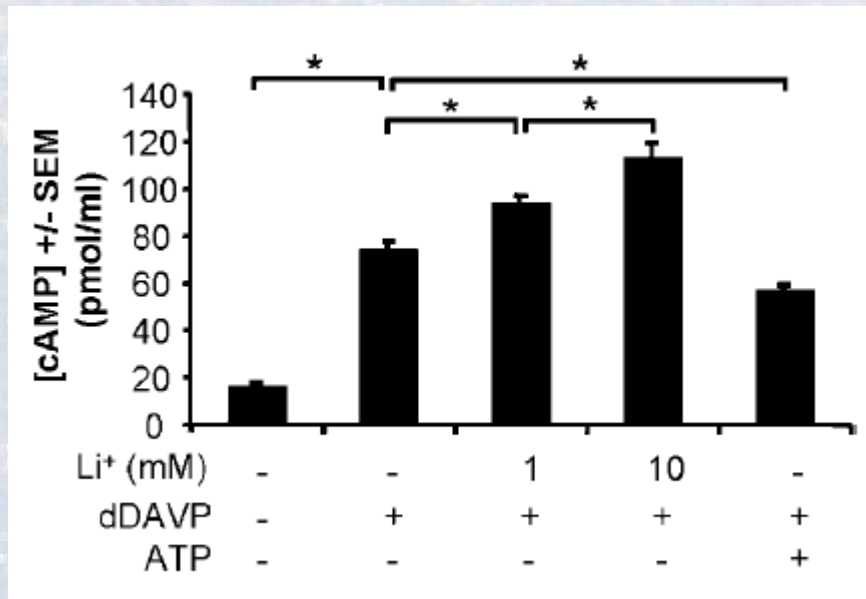
Table 2. Fraction of AQP-2 and  $[H^+]ATPase$ -labeled cells in control and lithium-treated animals

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

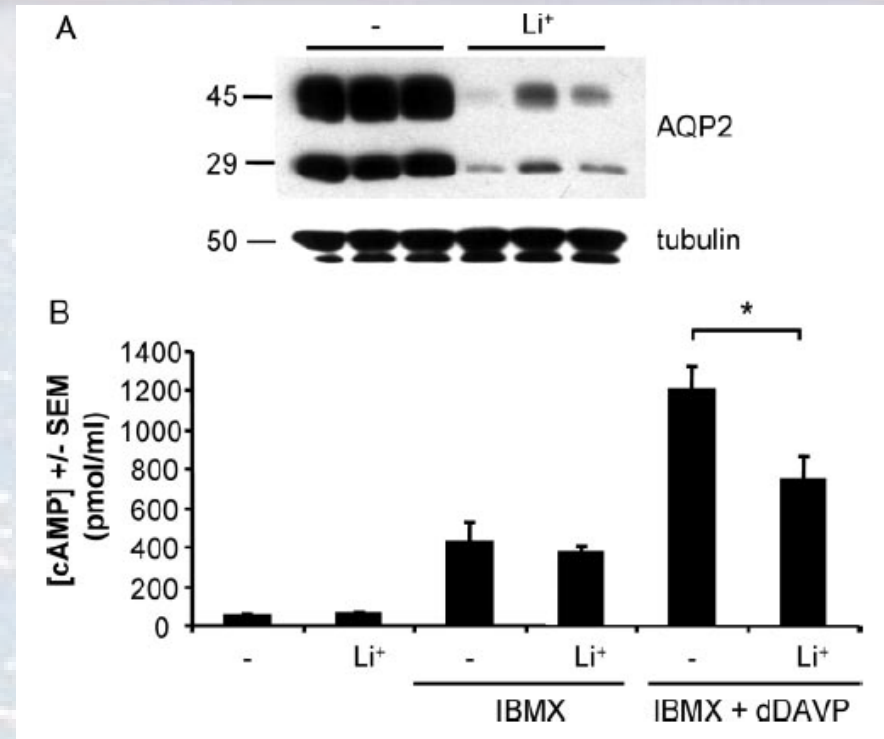
Proportion of intercalated cells increased at the expense of principal cells

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- 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 adenylat cyclase activity.

**A****B**



Effects of lithium on DDAVP-stimulated cAMP production in MpkCCD cells

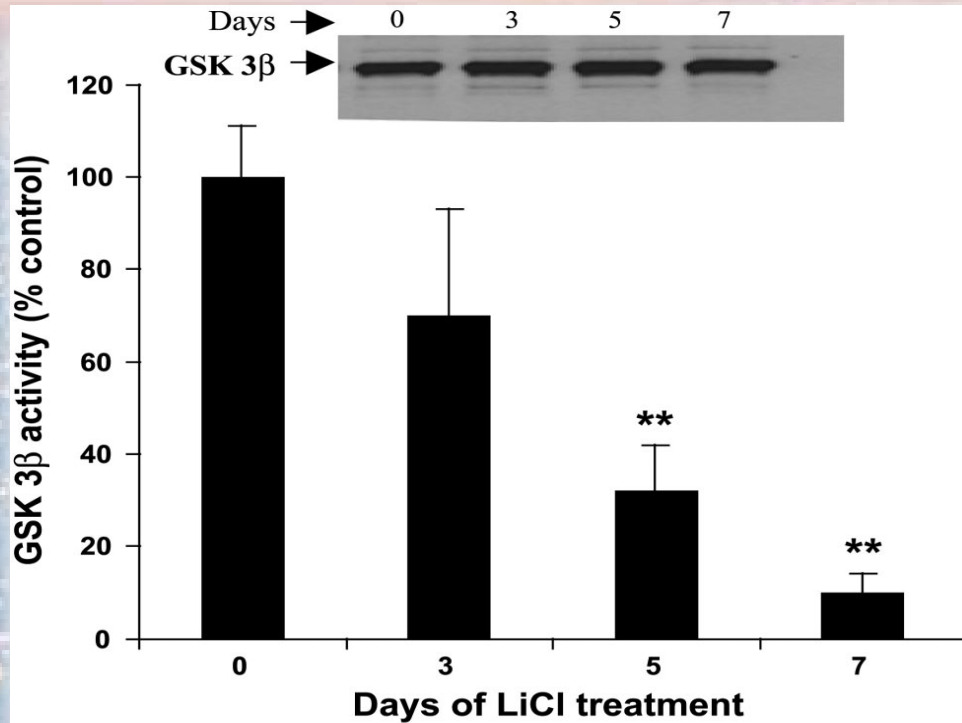


Effects of lithium on AQP2 expression and DDAVP-stimulated cAMP production in Wistar rat inner medulla

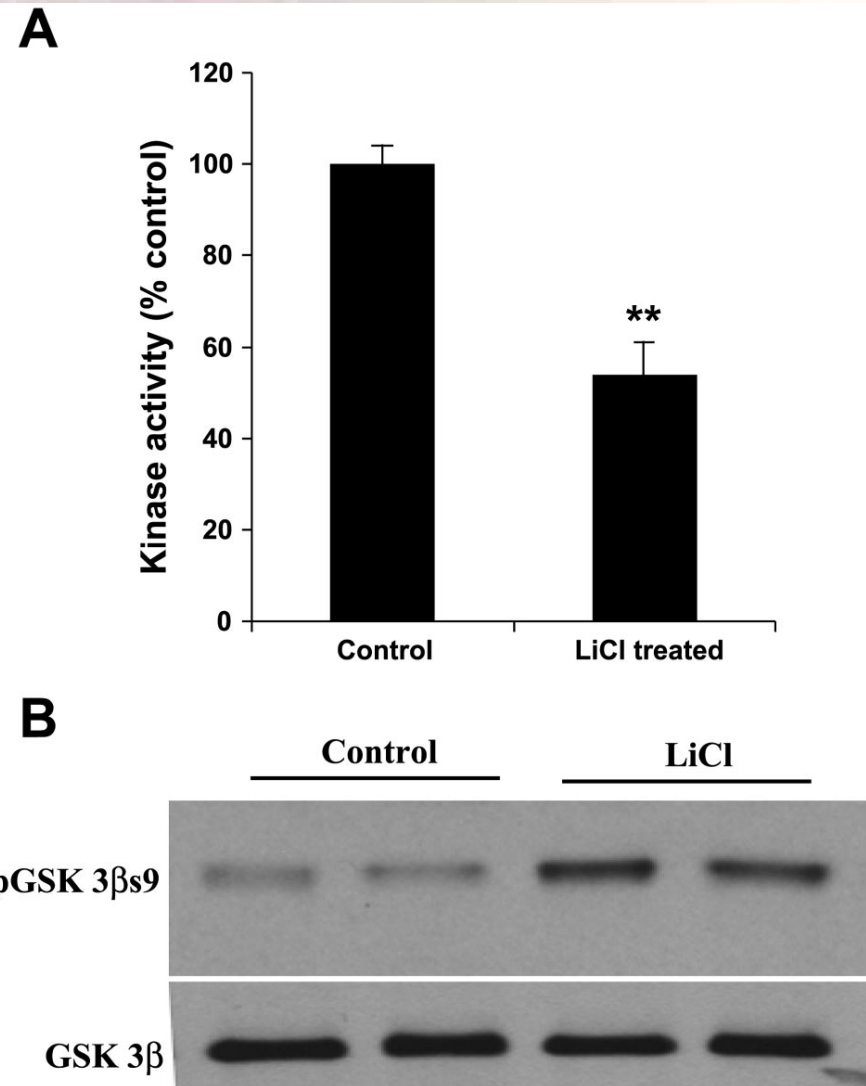
# Lithium effects on GSK-3 $\beta$ and COX2

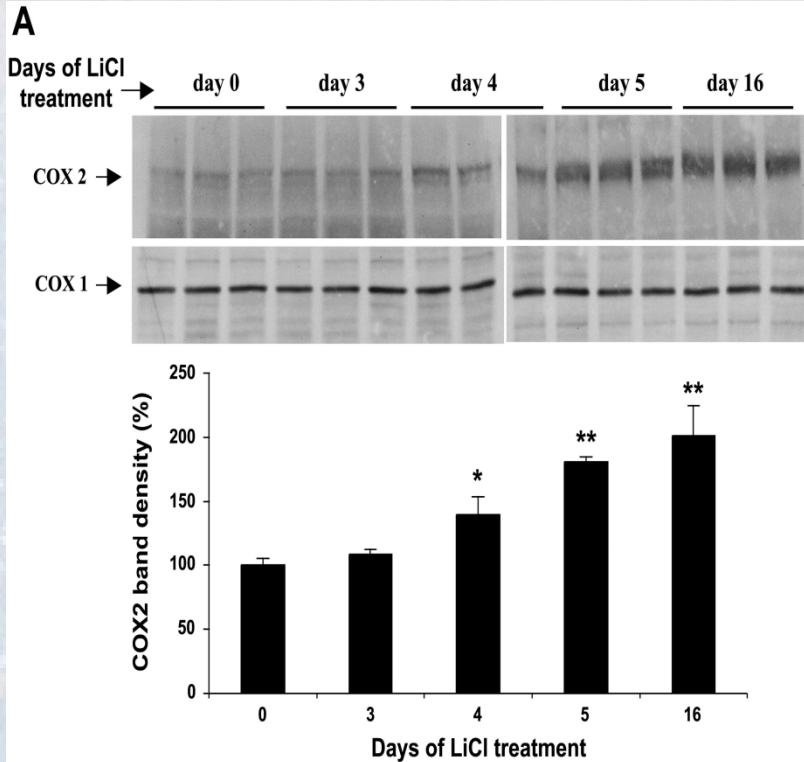
- Recent studies indicate that lithium acts as an inhibitor of GSK-3.
- GSK-3 can be inhibited by phosphorylation of Ser9 residue.
- Constitutive GSK-3 activity has recently been shown to tonically suppress COX-2 expression in cultured renal interstitial cells.
- Lithium is shown to inhibit GSK-3 activity 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-3 $\beta$



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)



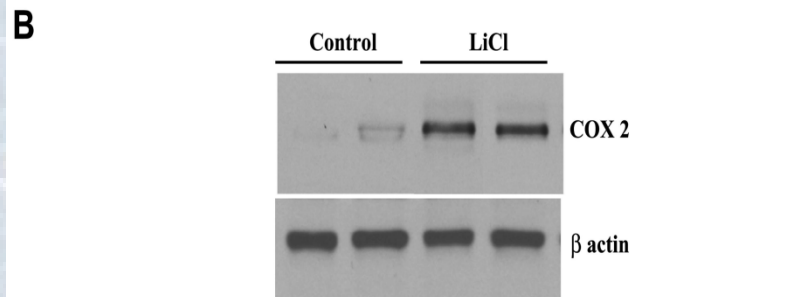


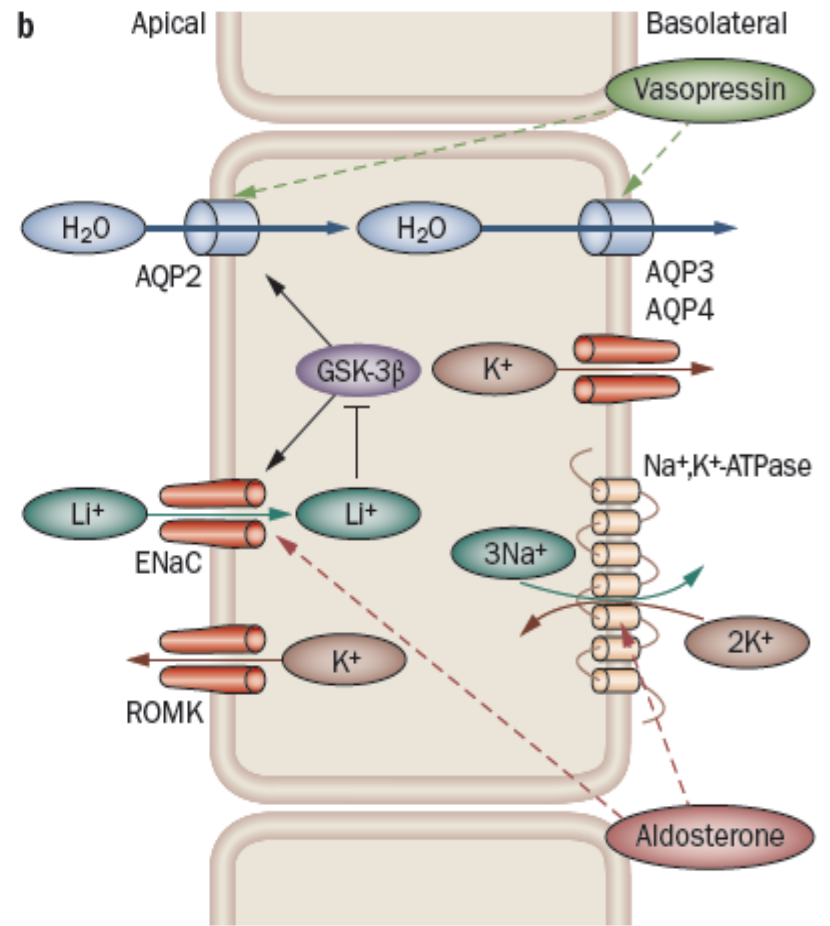
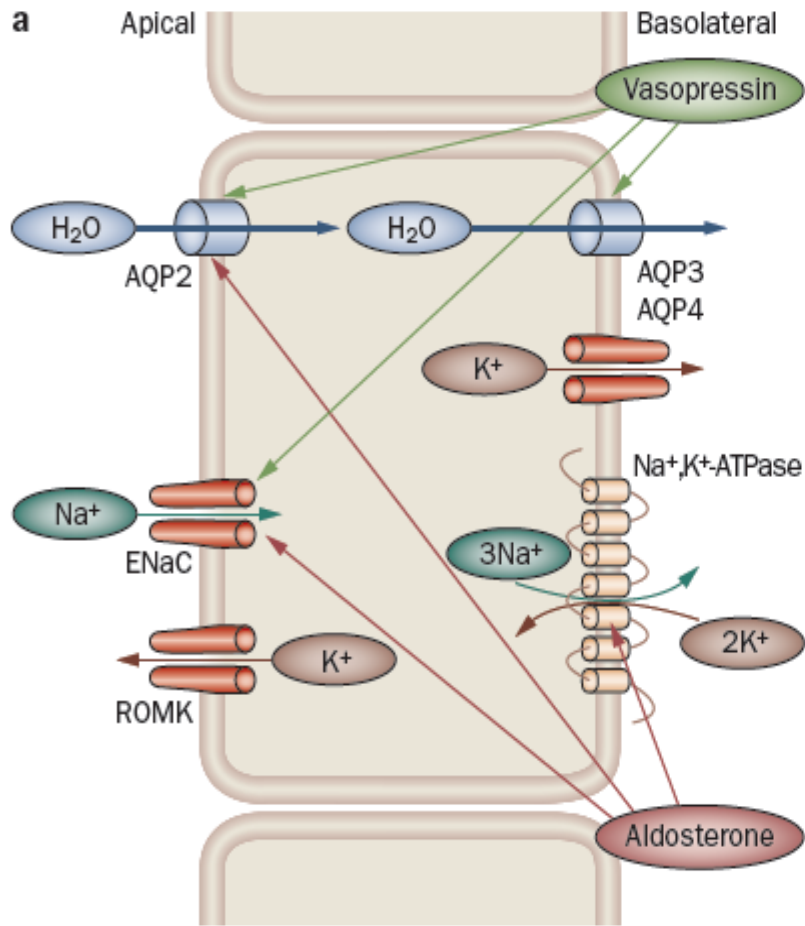
Effect of LiCl on COX2 expression.

*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.*

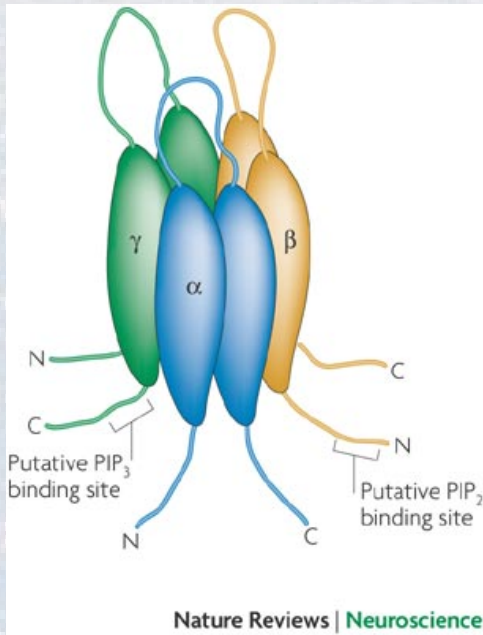
*B: confluent cultures of renal medullary interstitial cells (RMICs) were treated with 30 mM LiCl for 8 h. Cell lysate COX2 was analyzed by immunoblotting.*

*\*P 0.01. \*\*P 0.0001.*

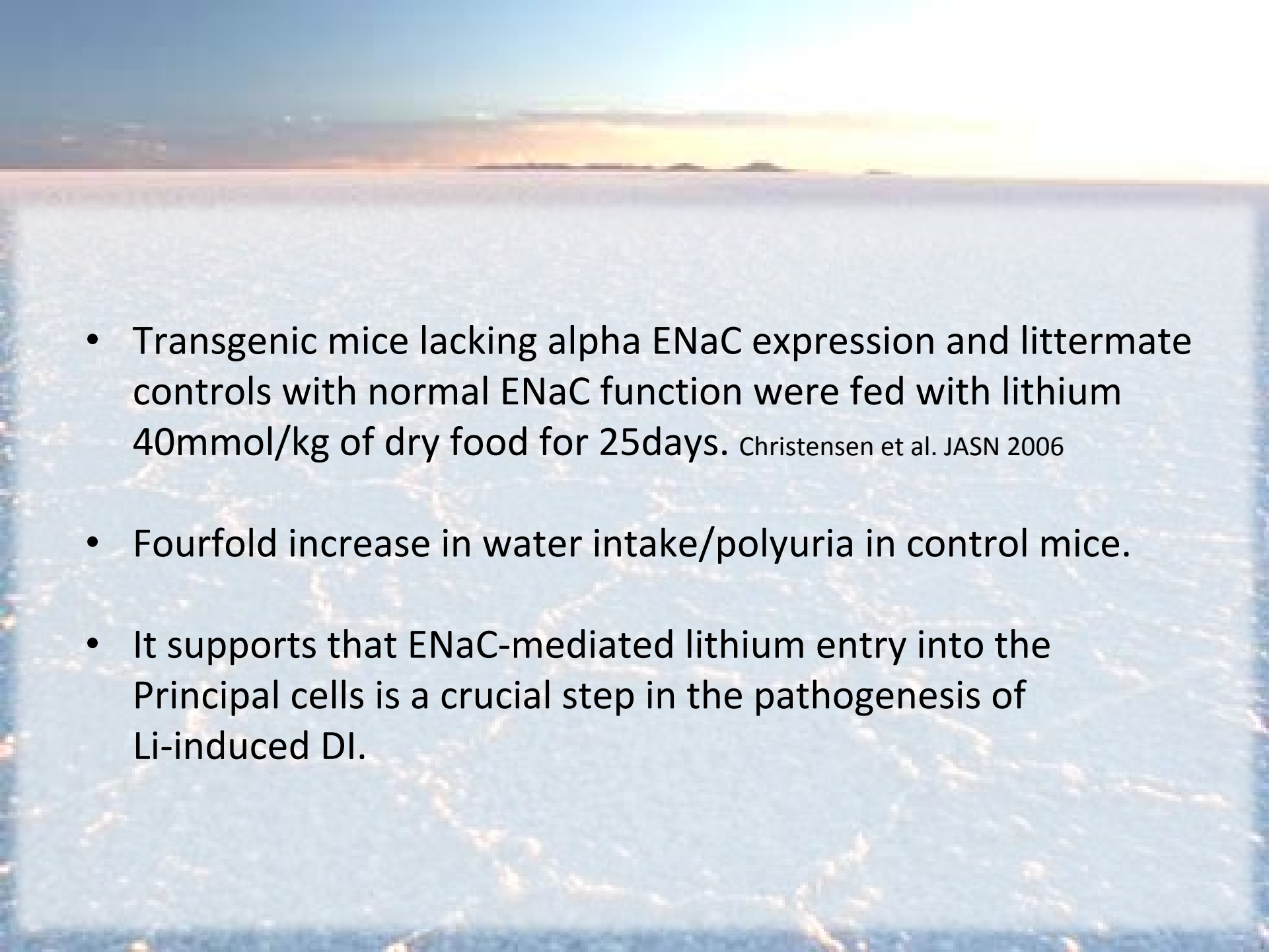




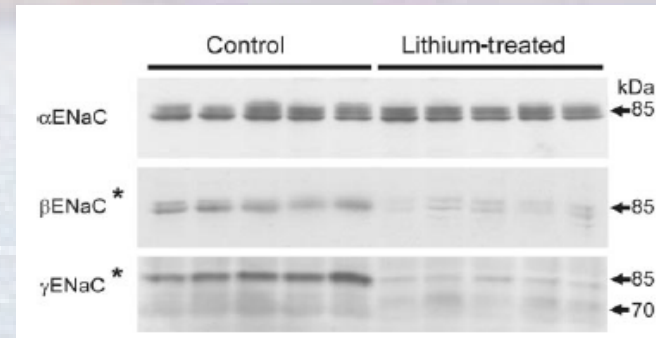
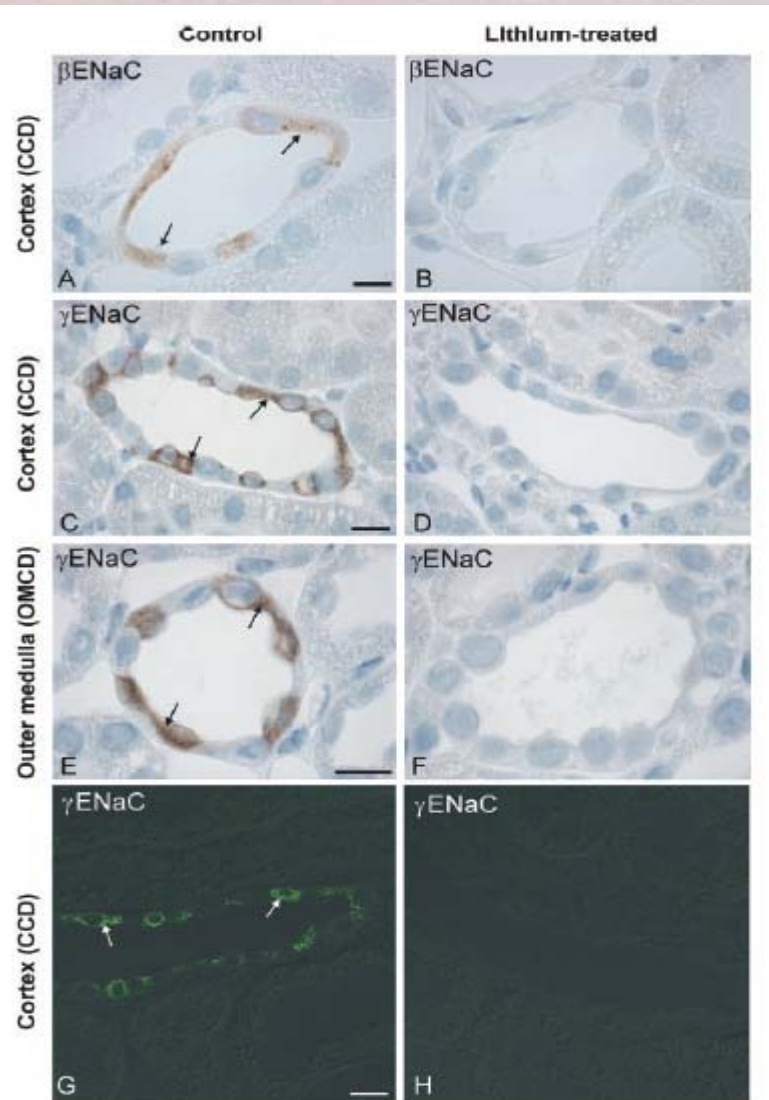
# Role of ENaC



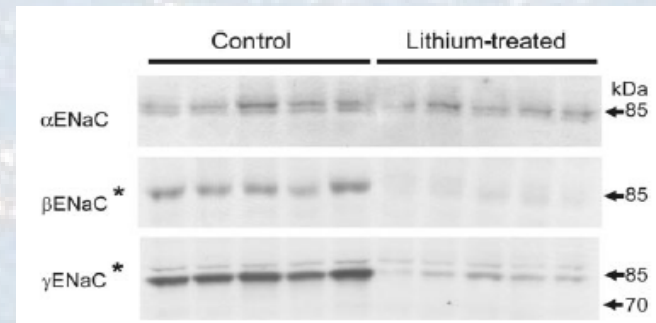
- Apical entry of Na into cells of the collecting duct is mediated by ENaC, permeable only to Na and Li. Permeability to Li is 1.5-2 fold higher than to Na.
- Li poor substrate for Na-K-ATPase at basolateral membrane
- Toxic intracellular levels of lithium could therefore build up quickly in cells of the collecting duct that are exposed to therapeutic concentrations of Li (0.6-1.2mmol/l)

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- Transgenic mice lacking alpha ENaC expression and littermate controls with normal ENaC function were fed with lithium 40mmol/kg of dry food for 25days. 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.

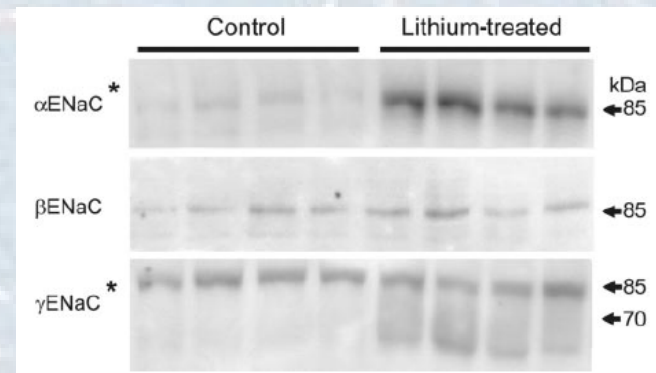
# Segment Specific ENaC Downregulation



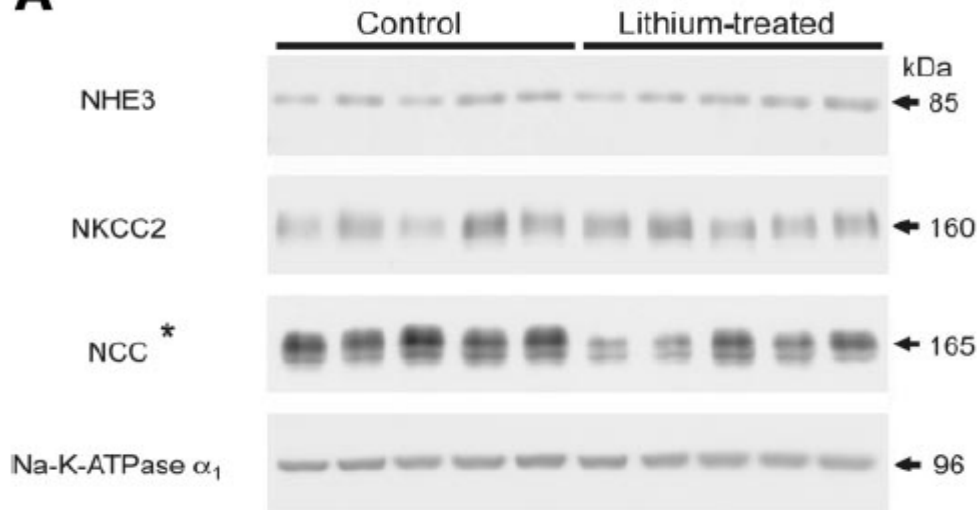
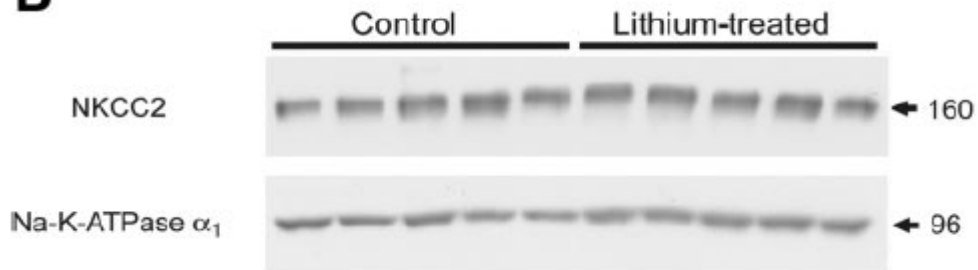
cortical homogenate



Inner stripe of OM homogenate



Inner medulla homogenate

**A****B****C**

Semiquantitative immunoblots using protein prepared from homogenates from the cortex (A), inner stripe of OM (B), and inner medulla (C)

# Questions to Be Explored

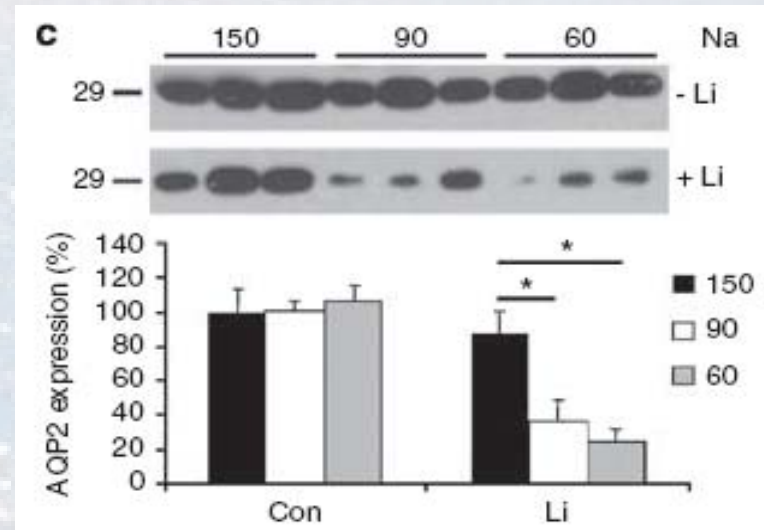
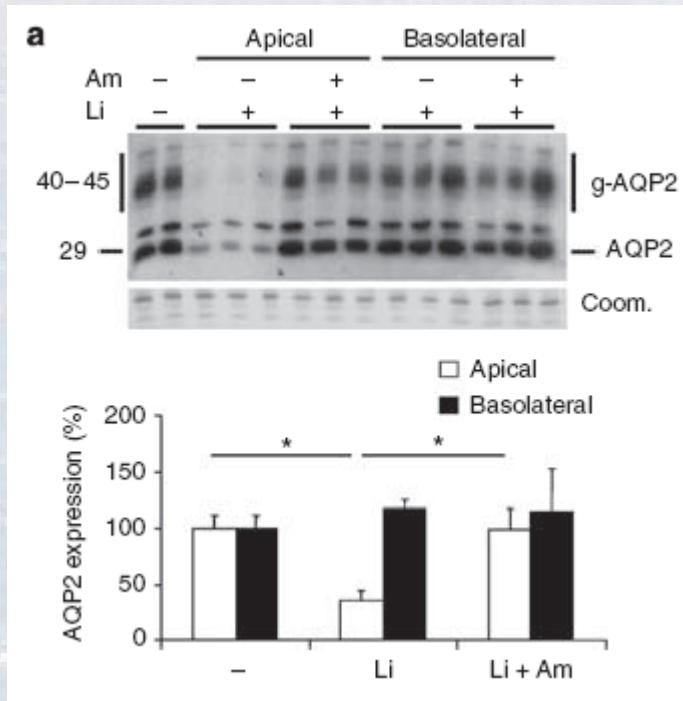
- Which mechanisms lead to selective and segment-specific downregulation of  $\beta$ -ENaC and  $\gamma$ -ENaC in Li-NDI?
- Is there a difference in the luminal Li concentrations along the connecting and collecting duct subsegments?
- Exit pathway for Li across the basolateral membrane may be important to determine intracellular Li concentration / transepithelial reabsorption.

- Li shown to reduce the abundance of the urea transporters UT-A1 and UT-B in the renal medulla of rats ; also inhibits vasopressin-mediated phosphorylation of UT-A1, thus potentially contributing to the loss or reduction of the medullary osmotic gradient. Bedford et al. AJP 2008
- 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

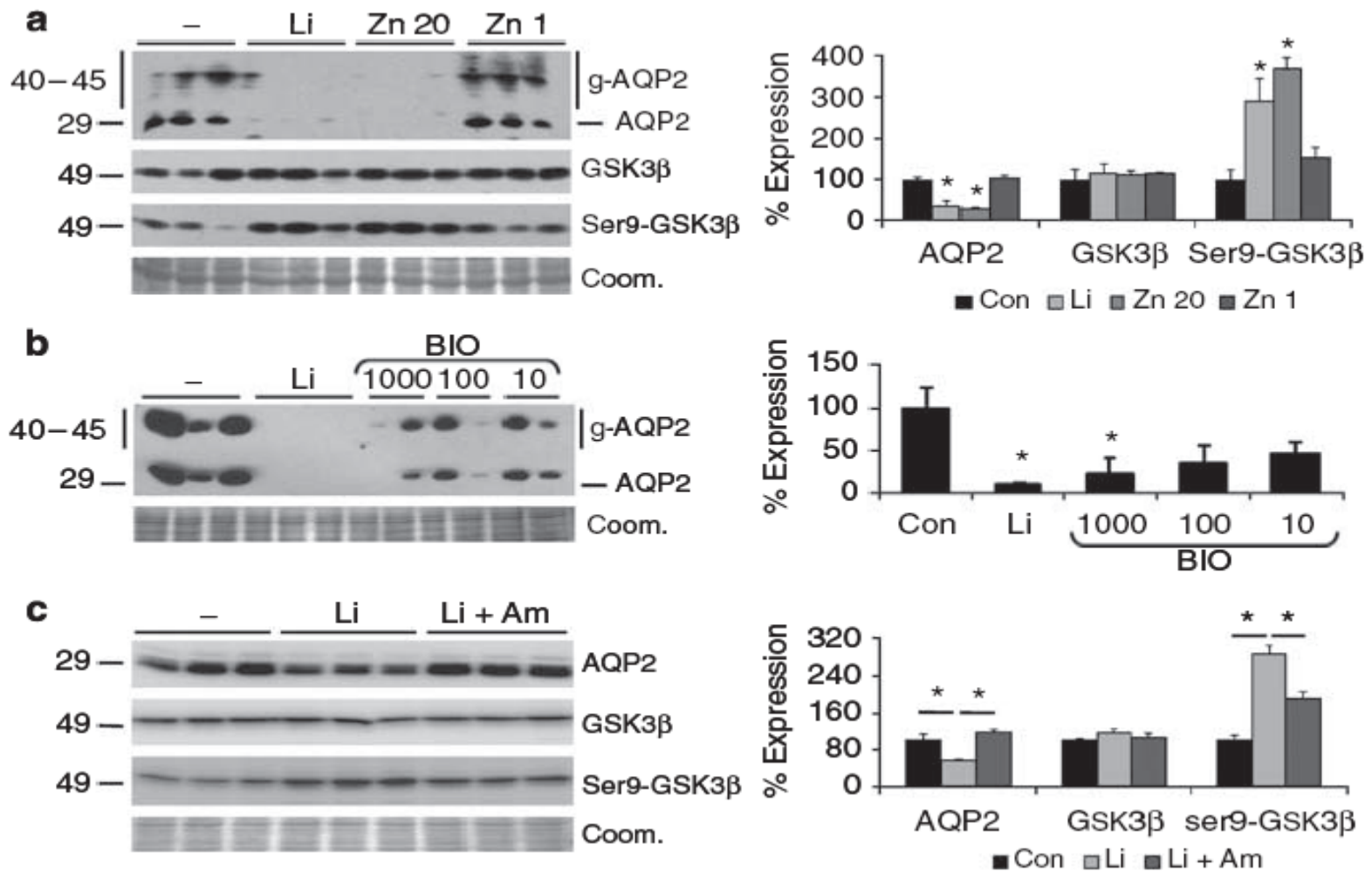
- Decreased dietary solute; Low salt (<100meq/day), low protein (<1g/kg) diet
- Thiazide diuretics (hypovolemia-induced increase in proximal Na and water reabsorption > diminishing water delivery to the ADH-sensitive sites in the collecting tubules and reducing the urine output)
- NSAIDs
- DDAVP
- **Amiloride**

# Amiloride in Li-NDI

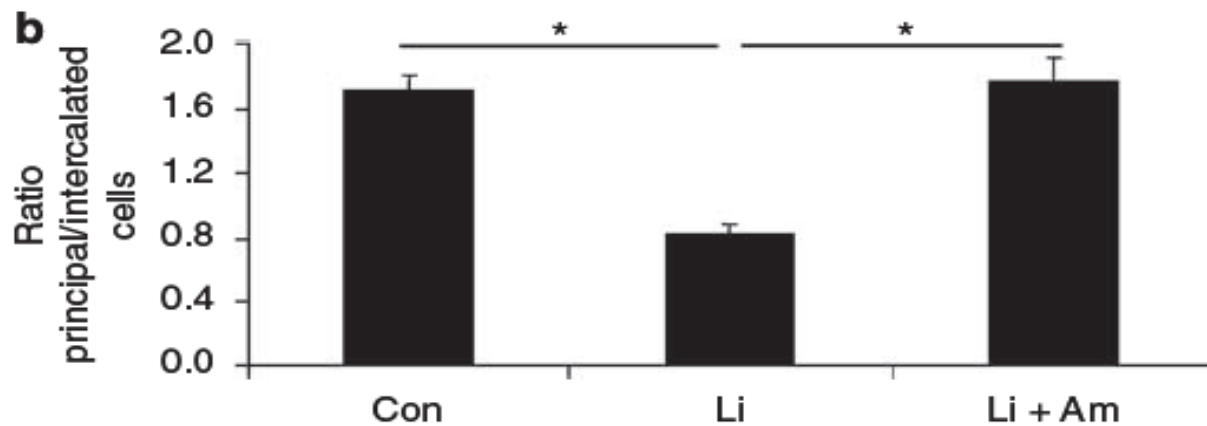
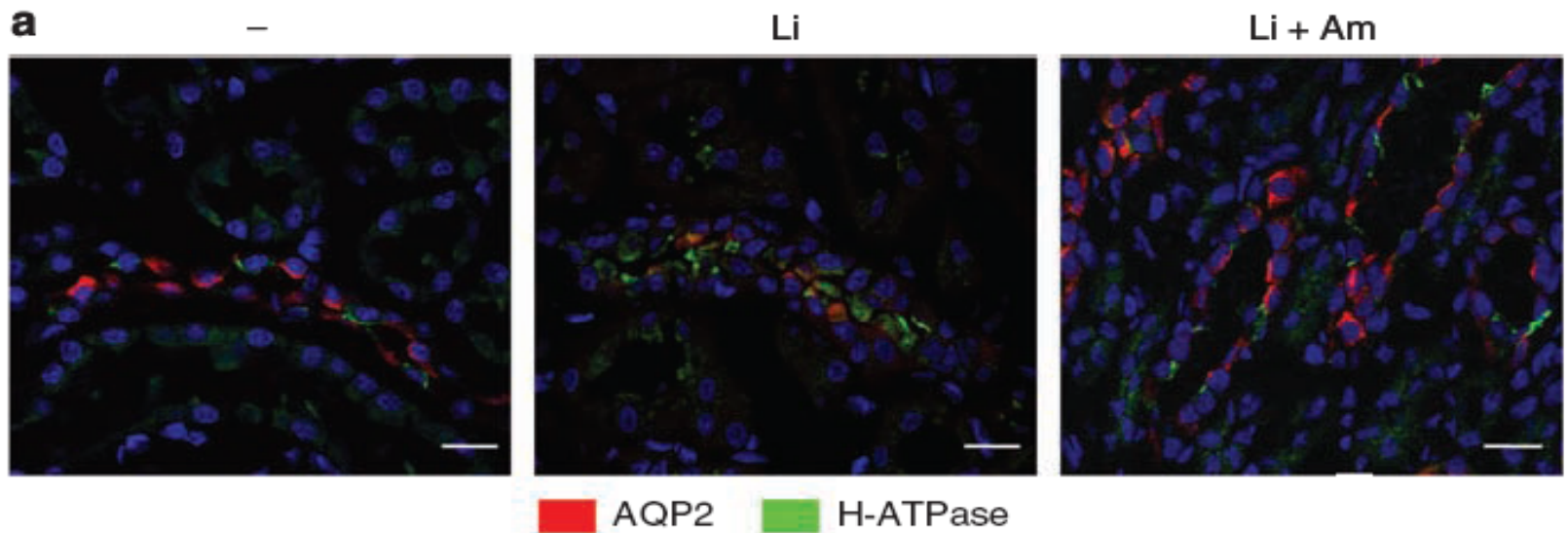


Amiloride reduces Li-induced AQP2 down regulation in mCCD cells

# Amiloride in Li-NDI



# Amiloride in Li-NDI



An aerial photograph of a vast, flat, blue landscape, possibly a salt flat or a large body of water, under a clear sky. The horizon is visible in the distance, and the text "THANK YOU!" is centered in the middle of the image.

**THANK YOU!**