Pathophysiology: Regulation of Water Intake and Excretion, Ghent 03/2013

Outline: Regulation of water intake and excretion

- Cellular dehydration to perceive thirst and release arginine-vasopressin (AVP), the antidiuretic hormone
- Volume regulation including Angiotensin II osmoregulatory gain
- Unregulated AVP release by tumors or infections
- Concentration and dilution of the urine

Daniel G. Bichet, M.D. Université de Montréal Groupe des Protéines Membranaires; Service de néphrologie, Hôpital du Sacré-Cœur de Montréal
Increased blood-oxygen-level-dependent (BOLD) signal under conditions in which thirst was stimulated in a healthy human by infusion of hypertonic saline anterior cingulate cortex (ACC; left-hand arrow) and in the area of the lamina terminalis (right-hand arrow).

Mammals are Osmoregulators: They have Evolved Mechanisms that Maintain Extracellular fluid Osmolality near a Stable Value

- sagittal section of midline of ventral brain around the 3rd ventricle in mice
- subfornical organ (SFO)
- median preoptic nucleus (MnPO)
- lamina terminalis (OVLT)

Cellular dehydration, that is, cell shrinking, is required for thirst and Vasopressin release
Deconstruction of a neural circuits for thirst and vasopressin secretion...Osmoregulatory circuits in the mammalian brain and the periphery


Anterior Cingulate Cortex: involved in rational decision making

Virginia Hughes; Stress: The roots of resilience Nature 490, 165-167, 11 October 2012
The act of drinking by the thirsty person is pleasurable, Chapter 35 *Thirst* MICHAEL J. MCKINLEY

---

**Mammals Strive to Maintain a constant Osmolality, yet Values Fluctuate around a Set Point:**

- 40 minutes of strenuous exercise in the heat, or 24 hours of water deprivation, causes plasma osmolality to rise by more than 10 mosmol kg\(^{-1}\).
- In a dehydrated individual, drinking the equivalent of two large glasses of water (~850 ml) lowers osmolality by approximately 6 mosmol kg\(^{-1}\) within 30 minutes.
- Ingestion of 13 g of salt increases plasma osmolality by approximately 5 mosmol kg\(^{-1}\) within 30 minutes.
Cationic channels inactivated by stretch, TRPVs (Transient Receptor Potential Vanilloid channels), are the osmoreceptors of the anterior hypothalamus: thirst and magnocellular neurons.


Angiotensin II is inducing an osmoregulatory gain.

This helps restoration of volume and blood pressure maintenance.
Set-points and slopes of vasopressin secretion are changed by effective arterial blood volume perceptions.
Determinants of Vasopressin Secretion

Plasma Arginine-Vasopressin (pg/mL) vs. Plasma Sodium (mEq/L)

Increase in Plasma Arginine-Vasopressin (pg/mL) vs. % Fall in Mean Arterial Blood Pressure

Hypertonicity sensing requires cell shrinking

A, Time course of normalized volume changes (nVol, relative to baseline) observed in three isolated mouse OVLT neurons exposed to a 60 min hyperosmotic stimulus (+40 mosmol/kg; excess mannitol)

B, Steady-state values of nVol observed in different isolated OVLT neurons exposed to various external osmolalities (n = 19).

Sorana Ciura¹, Wolfgang Liedtke², and Charles W. Bourque¹The Journal of Neuroscience, 12 October 2011, 31(41): 14669-14676;
Hepatic Osmoreceptors Require TRPV4 for Normal Function


Defective Osmoregulation of Trpv1-/- and Trpv4-/- mice.

Neuron: 69; 332-344, 2011.
Taste receptors in the mouth, more than just the basic five but no taste for water


Model of urine concentration
Separation of salt and water in the thick ascending loop of Henle
Vasopressin makes the cortical and medullary collecting ducts permeable to water


**Molar mass of urea** $\text{CO(NH}_2\text{)}_2 = 60 \text{ g/mol}$

**Molecular weight calculation** : $12.0107 + 15.9994 + (14.0067 + 1.00794 \times 2)^2$

- 60g of urea = 1000 mmol
- 30g of urea = 500 mmol

“Medicinal urea” 30 g $\times$ 1 month will be less than $\$1.00:
- urea 10, NaHCO$_3$ 2g
- Citric Acid 1.5g, sucrose 200 mg
60g of urea = 1000 mmol: forcing water excretion, however, bitter taste and necessity to absorb with additional fluid

<table>
<thead>
<tr>
<th></th>
<th>Daily Intake (Solute + Water)</th>
<th>Urinary Osmolality (mOsm/kg)</th>
<th>Urine Volume (Liter/day)</th>
<th>Water Balance (Liter/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>500 mmol of solute + 2 liters of water</td>
<td>250</td>
<td>2 liters</td>
<td>0</td>
</tr>
<tr>
<td>SIADH 1</td>
<td>500 mmol of solute + 2 liters of water</td>
<td>500</td>
<td>1 liter (500/500)</td>
<td>+ 1</td>
</tr>
<tr>
<td>2.</td>
<td>500 mmol of solute + 500 mmol of urea + 2 liters of water</td>
<td>500</td>
<td>2 liters (1000/500)</td>
<td>0</td>
</tr>
</tbody>
</table>

Editorial, 

What did we learn?

- Thirst and cellular dehydration
- Vasopressin secretion and cellular dehydration
- TRPV1 channels centrally and TRPV4 in the periphery mediating the effects of cellular dehydration
- Diluting segment of the nephron: thick ascending loop of Henle
- Action of vasopressin on principal cells of the collecting duct.