REGULATION OF TOTAL BODY and CELL WATER

AntiDiuretic Hormone (**ADH**, Vasopressin)

1. Sensors of changes in body water content and osmolarity

A. Role of the Hypothalamic Osmoreceptors

Osmoreceptors are cells in hypothalamic Organus Vasculosus Lamina Terminales (OVLT). They sense increases in effective osmolarity capable of inducing decreases in cell volume (not like urea) when the osmolar concentration rises above a threshold of 280 mOsm/Kg,.

Increases in effective osmolarity enhance the electrical activity of the osmoreceptor cells, which in turn increase the synthesis of antidiuretic hormone (ADH) by **supraoptic** and **paraventricular hypothalamic neurons** and release of stored **ADH** into the blood from the terminals of these **neurosecretory cells** in the posterior pituitary gland.

With a 1% (3 mOsm/Kg) increase in effective osmolarity, **ADH** levels increase in plasma by 2 pg/ml, reducing the urine flow to 1/3 and increasing urine concentration 3-fold, from 200 to 600 mOsm/Kg.

Inability to produce ADH in hypothalamus or release it from the posterior pituitary leads to central **diabetes insipidus**, a disease characterized by large urinary water loss and thirst.

B. Role of the Atrial Stretch Receptors

Left atrial stretch receptors sense changes (10%) in central blood volume and small changes in ECFV due, for example, to dietary sodium changes or to redistribution of blood between legs and central blood reservoirs (changes in position, water immersion, absence of gravity) that need not alter mean arterial pressure.

These **mechano-receptors,** when stretched by increased volume, send impulses via the Xth nerve to inhibit hypothalamic synthesis and posterior pituitary release of ADH, leading to an increased flow of dilute urine (water diuresis).

With continuos stretch (as in congestive heart failure) these receptors adapt and cease to inhibit synthesis and release of ADH.

Decreased stretch promotes ADH synthesis and release.

C. Role of Systemic Arterial baroreceptors

Arterial (aortic and carotid) baroreceptors sense decreases in mean arterial pressure (MAP), reducing neural impulses via the IXth and Xth nerves to the hypothalamus, and allowing unrestrained massive release of vasopressin (ADH). This emergency response leads to water

retention and general vasoconstriction that defend perfusion of the heart and brain against hypotension and /or low cardiac output.

D. Other Influences

Release of ADH is increased by **pain, nausea, hypoxia, smoking**, and **morphine**. ADH release is inhibited in the **cold, by opiates, alcohol**, and **glucocorticoids**.

2. Metabolism of ADH

ADH is rapidly metabolized after endocytosis by liver and kidney cells. Its half life in blood is only 20 minutes. DAVP, an analogue of ADH, persists several hours.

3. Effects of ADH

ADH binds to **V2 receptors** in **CD principal cells**. These receptors, through a **Gs protein**, activate **adenyl cyclase**, an enzyme that promotes synthesis of **cyclic AMP**. cAMP activates **protein kinase A**, an enzyme that **phosphorylates several proteins**, altering the cytoskeleton and allowing subapical vesicles containing **aquaporin water channel** proteins to fuse with the apical plasma membrane of the principal cells, increasing their permeability to water.

In the absence of ADH aquaporins are retrieved from the membrane and stored in subapical vesicles (aggrofores).

Defects in V2 receptors or in ADH-dependent aquaporin (Type II) leads to lack of response to ADH and development of nephrogenic (of renal origin) diabetes insipidus.

ADH at high concentrations binds also to V1 receptors in vascular smooth muscle, mesangial cells, and platelets, which through a G protein cause activation of phospholipase C. This enzyme induces release of IP3 and DAG, which in turn raise cytosolic calcium and activate protein kinase C. These activate myosin light chain kinase and produce cell contraction. As a consequence, high levels of ADH result in vasoconstriction, reductions in RPF, GFR, and renal medullary blood flow. Low levels of ADH favor increases in RPF and renal medullary washout.

The effect of ADH on urine flow is measured through changes in free water clearance.

4. Free water clearance

A dilute urine excreted in the absence of ADH can be thought of as being made up of two fluid volumes:1) a volume which contains the urine solutes at the same concentration as in plasma and called the Osmolar clearance (= Uosm x V/Posm) and 2) pure water excreted with no solutes, called positive free water clearance (CH2O = V - Cosm).

A concentrated urine produced in the presence of ADH can be thought of as the difference between two volumes: 1) the volume of plasma from which the urinary solutes derive (Cosm) and the (smaller) volume of urine actually excreted (V). The difference Cosm - V represents water free of solutes retained in the body due to the action of ADH. This is called the negative free water clearance or tubular free water reabsorption