

Chapter 3 / Capítulo 3

*Electrolyte and Internal Environment Imbalances in
Emergencies (English Edition)*

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Key Hormones: ADH and the Renin-Angiotensin-Aldosterone System

Hormonas clave: ADH y el sistema renina-angiotensina-aldosterona

Jorge Márquez Molina¹ , Mauricio Paz del Río² , Isis Scarleth Funes-Galindo³ 

¹Hospital del Norte. Cochabamba, Bolivia

²Hospital Municipal de Cotahuma. La Paz, Bolivia

³Instituto Nacional de Previsión del Magisterio (INPREMA). Tegucigalpa, Honduras

Objectives:

- Understand the role of Antidiuretic Hormone (ADH) and the Renin-Angiotensin-Aldosterone System (RAAS) in regulating water balance and extracellular fluid volume.
- Determine the role of atrial natriuretic peptide.
- Identify the physiological mechanisms of secretion and action of each hormone.
- Apply these concepts to clinical situations such as hyponatremia, hypovolemia, and heart failure.

INTRODUCTION

The human body maintains water and sodium balance through two complementary systems:

Table 3.1. Complementary regulators of hydroelectrolytic balance		
System	Primary function	Key hormone
Osmoregulation	Controls plasma sodium concentration and osmolality	ADH (also known as vasopressin)
Volume regulation	Controls extracellular fluid volume and blood pressure	RAAS + natriuretic peptides

ADH regulates water concentration, while RAAS regulates the amount of water and sodium.

Hormonal regulation of volume balance

Antidiuretic Hormone (ADH or vasopressin)

Origin and synthesis:

- Synthesized in the hypothalamus, in the supraoptic and paraventricular nuclei.
- Stored and released from the neurohypophysis (posterior lobe of the hypophysis).

Stimuli for Its Release:

- Increase in plasma osmolality (>280 mOsm/kg).
- Decrease in volume or arterial pressure (>10-15 %).
- Pain, stress, or nausea (stimulate release).
- Alcohol, volume expansion, and cold exposure (inhibit release).

Receptors and mechanism of action

Table 3.2. Receptors and mechanism of action		
Receptor	Location	Main Effect
V2	Renal collecting tubule	↑ Aquaporin-2 (AQP2) → ↑ free-water reabsorption → concentrated urine
V1a	Blood vessels, liver	Vasoconstriction and ↑ blood pressure
V1b	Adenohypophysis	Stimulates ACTH release
Source: Own elaboration		

Main physiological effect:

- Increases water reabsorption without sodium → decreases plasma osmolality.
- Helps maintain blood pressure during hypovolemia.

Pathophysiological correlation:

- ADH deficiency → Central diabetes insipidus → polyuria, polydipsia, dilute urine.
- ADH resistance → Nephrogenic diabetes insipidus (secondary to lithium, hypercalcemia, etc.).
- Excess ADH → Syndrome of inappropriate ADH secretion (SIADH) → dilutional hyponatremia.

Remember:

- ADH is released in response to osmoreceptors (hypothalamus) and volume receptors (atria, great vessels).
- Acts only on free water, not sodium.
- Alcohol inhibits its secretion (hence post-consumption diuresis).

Renin-Angiotensin-Aldosterone System (RAAS)

Renin

Renin is an enzyme produced by juxtaglomerular cells of the renal afferent arteriole. It converts angiotensinogen (from the liver) into angiotensin I, which is then transformed by angiotensin-converting enzyme (ACE) into angiotensin II. Its secretion responds to certain stimuli.

- ↓ Renal perfusion (intrarenal baroreceptors).
- ↓ Cl^- in the macula densa (reduced tubular delivery).
- ↑ Sympathetic activity (β_1 -adrenergic).

Angiotensin II

Formation

Angiotensin I → (ACE in lungs and endothelium) → Angiotensin II

Main effects:

- Arteriolar vasoconstriction → ↑ resistance and arterial pressure.
- Proximal sodium and water reabsorption (stimulates Sodium-Hydrogen Exchanger type 3, NHE3)
- Stimulates aldosterone secretion (zona glomerulosa).
- Increases thirst and releases ADH → additional water retention.
- Efferent glomerular vasoconstriction → preserves GFR (glomerular filtration rate) during hypovolemia.

Aldosterone

It is a mineralocorticoid hormone produced in the zona glomerulosa of the adrenal cortex. Its main stimulus is the presence of Angiotensin II and increases in plasma K^+ (hyperkalemia).

Effects on the distal tubule and collecting tubule:

- $\uparrow$ ENaC channels (apical membrane).
- $\uparrow$ Na^+/K^+ -ATPase (basolateral membrane).
- $\uparrow$ K^+ and H^+ secretion.

Final result: Na^+ reabsorption, expansion of extracellular volume, and increased blood pressure.

Clinical pearl:

- Aldosterone excess $\rightarrow$ Conn syndrome (hypertension, hypokalemia, alkalosis).
- Aldosterone deficiency $\rightarrow$ hyporeninemic hypoaldosteronism (hyperkalemia, acidosis)

Regulatory mechanisms

No fixed values exist for renin, angiotensin II, or aldosterone. Levels must be interpreted in the context of the patient's volume status.

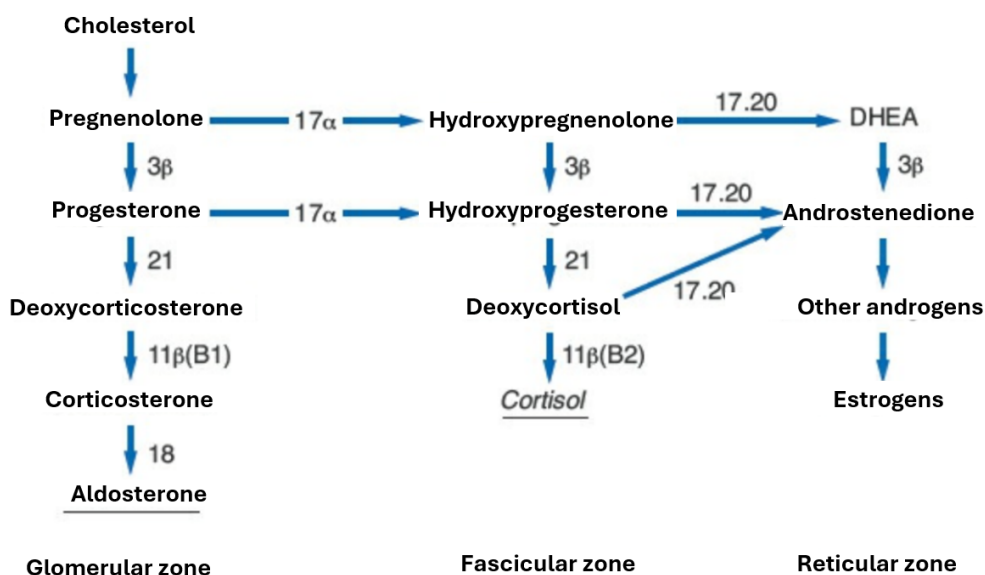


Figure 3.1. Lipid hormone production

Situation	Predominant hormone	Effect
$\downarrow$ Volume / blood pressure	Renin-Ang II-Aldosterone	Sodium and water retention
$\uparrow$ Volume / BP	Decreased RAAS	Natriuresis
$\uparrow$ Atrial stretch	ANP/BNP	Inhibit RAAS and ADH

BP: Blood pressure, Ang II: Angiotensin II, RAAS: Renin-Angiotensin-Aldosterone System, ANP/BNP: Atrial natriuretic peptide / Brain natriuretic peptide.

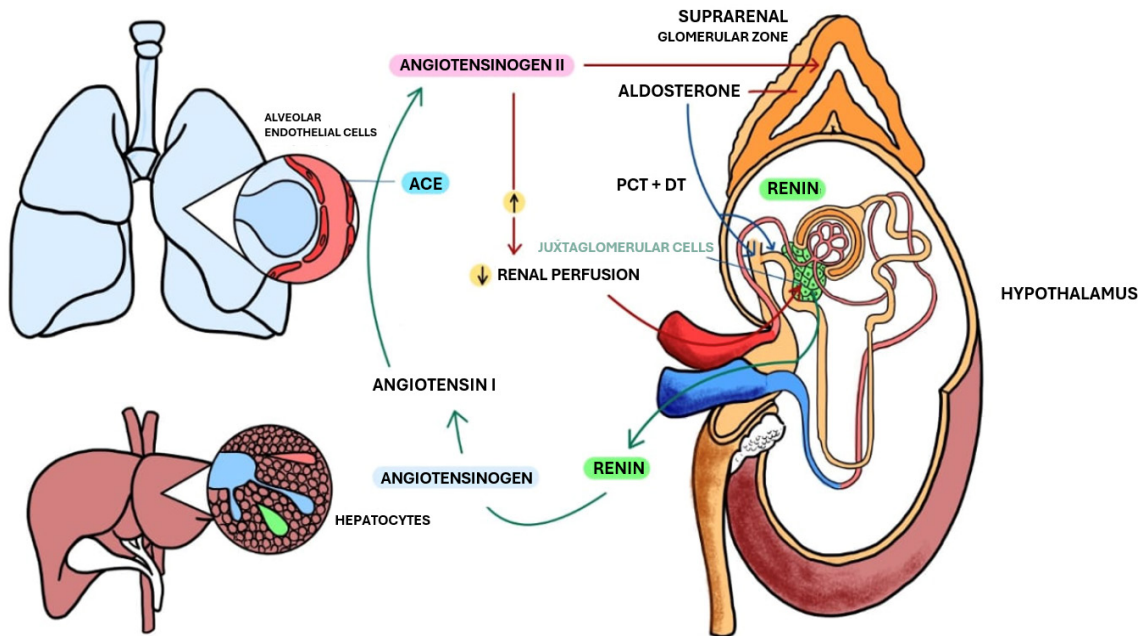


Figure 3.2. Production of Renin-Angiotensin-Aldosterone

Natriuretic Peptides (ANP, BNP, and CNP)

ANP: Atrial Natriuretic Peptide

Produced by myocardial cells (atria, ventricles in Congestive Heart Failure).

Released in response to volume expansion ($\uparrow$ atrial stretch) or increased venous pressure.

Actions:

- Vasodilation $\rightarrow$ $\downarrow$ blood pressure.
- $\uparrow$ Glomerular filtration rate (GFR) (afferent vasodilation and efferent constriction).
- Inhibits renin, aldosterone, and ADH.
- Increases Na^+ and water excretion (natriuresis and diuresis).

Physiological limitations:

- In Congestive Heart Failure, despite $\uparrow$ ANP, sodium retention persists.
- Reduced renal perfusion is thought to limit its effectiveness.

Final result decreases volume and therefore blood pressure. Remember that ANP is released when the heart becomes “stretched” due to volume overload.

BNP: Brain Natriuretic Peptide (or B-type Natriuretic Peptide)

Produced by cardiac ventricular myocytes.

Released in response to ventricular pressure or volume overload (as in heart failure).

Actions similar to ANP (vasodilation, natriuresis, inhibition of RAAS and ADH)

Clinical relevance:

- Diagnostic marker of heart failure: $\text{BNP} > 100 \text{ pg/mL}$ or elevated NT-proBNP.
- Reflects the severity of ventricular overload.

Remember the higher the BNP, the greater the cardiac dysfunction and the higher the risk of hospitalization.

CNP – C-type Natriuretic Peptide

Produced by vascular endothelium and the brain.

Released in response to local factors (parietal stress and cytokines).

Actions:

- Local vasodilation effect predominates.
- Weaker natriuretic effect than ANP/BNP.
- Regulates vascular tone and endothelial growth.

Other related peptides are urodilatin: secreted in the distal tubule, more potent effect than ANP.

Table 3.4. Summary of regulation by natriuretic peptides

Peptide	Source	Stimulus	Physiological Effects
ANP	Cardiac atria	Increased pressure or volume	Vasodilation, ↑ GFR; ↓ renin and aldosterone
BNP	Ventricles	Pressure overload	Similar to ANP; diagnostic marker in heart failure
CNP	Endothelium	Local stimuli	Local vasodilation, autocrine/paracrine regulation

Physiological integration

Table 3.5. Physiological integration of regulation

Condition	ADH	RAAS	ANP/BNP	Outcome
Dehydration	↑	↑	↓	Water and Na ⁺ retention
Volume overload	↓	↓	↑	Natriuresis and diuresis
Hemorrhagic hypovolemia	↑ (water)	↑ (Na ⁺)	↓	Restoration of volume and pressure
SIADH	↑ Inappropriately	Normal	↓	Dilutional hyponatremia

Complementary mechanisms

Pressure natriuresis

- A mild increase in arterial pressure → ↑ sodium excretion.
- Does not require hormonal regulation.
- Explains “aldosterone escape”: sodium balance despite hyperaldosteronism.

Steady state

- Balance is achieved when intake = excretion.
- Hormonal changes allow this adjustment.

Example: high sodium intake

- Initially → retention and volume expansion.
- Later → ↓ renin and aldosterone, ↑ ANP → new matching level of excretion.

Example: high potassium intake

- $\uparrow$ aldosterone and plasma K^+ $\rightarrow$ $\uparrow$ excretion until it matches intake.
- A “potassium adaptation” is established.

Clinical applications

Electrolyte Disorders

- Persistent hyperkalemia: indicates impaired renal excretion (hypoaldosteronism, renal failure).
- Hyponatremia: results from water retention; requires an inability to excrete dilute urine (high ADH, renal failure).
- Metabolic alkalosis: associated with bicarbonate (HCO_3^-) reabsorption in states of volume depletion.

Diuretics

- Maximal natriuretic effect occurs with the first dose.
- Then the RAAS activates and ANP decreases ($\downarrow$) $\rightarrow$ a new steady state is reached within 1-2 weeks.
- Fluid and electrolyte disturbances stabilize within that time.

CONCLUSIONS

ADH regulates plasma osmolality by adjusting free water content. The RAAS regulates extracellular volume through sodium and water retention. ANP/BNP are the physiological brake system of the RAAS. All these systems interact within a feedback network to maintain cardiovascular and renal homeostasis. The final balance depends on the steady state, not on absolute levels.

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