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Water and Electrolyte Disturbances in Diabetes Insipidus & Their Biochemical Relationship

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ABSTRACT

Antidiuretic hormone is released by the pituitary gland, and is responsible for regulating water absorption at the distal nephron level, specifically in the renal collecting tubule. This occurs by binding to its type 2 receptor which generates the induction of aqueous channels towards the basolateral membrane of the main cells of the kidney. When diabetes insipidusoccurs, patients have a state of decreased secretion or peripheral resistance of this hormonein its receptor, so that water is not reabsorbed, it is abundantly eliminated and this generateshydroelectrolyte imbalances. This article will review the biology of the antidiuretic hormone,physiology, hydroelectrolytic alterations and based on the understanding of the altered mechanisms, its association with the management of diabetes insipidus.

KEYWORDS: Diabetes insipidus, Antidiuretic hormone, Vasopressin, Aquaporins.

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INTRODUCTION

Diabetes insipidus is a syndrome characterized by elimination of large volumes of dilute urine. This disorder has multiple etiologies, but it is grouped in 2 possible anatomical sites associated with it which are the central nervous system (CNS) and the kidney. (1,2) When we speak of diabetes insipidus in the CNS we refer to the insufficiency of the neurohypophysis to sustain the adequate capacity of secretion of the antidiuretic hormone, also called vasopressin (AVP), which in the literature is called neurogenic or central diabetes insipidus. Likewise, when the kidney is the anatomical site affected by its inability to sustain thewater balance, it is called nephrogenic diabetes insipidus. (1-4) Table 1 shows the different causes dependingon the anatomical site affected. The prevalence of this disease is not very precise due to the lack of epidemiological information since it is established as an uncommon syndrome in some countries. It is estimated that there are 1:25000cases without being able to differentiate between male and female sex. Globally, central diabetes insipidus is more frequent due to genetic manifestations at early ages and the hereditary pattern of AVP gene mutations. (5,6) However, more studies should be carried out to track intrahospital cases in our countries and to find the most frequent etiology in order to create guidelines for anearly approach. Likewise, we have to recognize the degree of complicationsin water disorders in this disease whichis what causes the specific symptomatology of the patients. (5-7) The aim of our article is to identify the hydroelectrolytic disorders of diabetes insipidus and to relate them to their clinical manifestations, diagnosis and treatment.

Table 1. Etiology of diabetes insipidus differentiating between central and nephrogenic origin. Taken from Mejorado, F. J. (2021). Diabetes insipidus. Diagnostic and therapeutic approach. Revista Española De Endocrinología Pediátrica, 12. https://doi.org/10.3266/RevEspEndocrinolPediatr.pre2021.Apr.644

Central diabetes insipidus	Nephrogenic diabetes insipidus
Idiopathic	**Idiopathic**
Genetic • AVP gene mutation (locus 20p13): ADI/ARI pattern • HRLX pattern (locus Xq28): unidentified gene • WFS1 gene mutation (4p16): Wolfram syndrome, ARI • PCSK1 gene mutation (locus 5p15): with morbid obesity, ARI	**Genetic** • AVPR2 gene mutation (locus Xp28): HRLX pattern • AQP2 gene mutation (12p13): ADI/ARI pattern
Acquired • Tumor pathology: - Craniopharyngioma - Germinoma -Lymphomas - Metastasis • Congenital malformations: - Septo-optic dysplasia - Aneurysms • Post-surgery and/or hypothalamic radiotherapy pituitary • Infections: - Viral encephalitis - Meningitis - Congenital toxoplasma or citomegalovirus • Granulomatous diseases: - Langerhans cell histiocytosis - Wegener's granulomatosis - Sarcoidosis - Tuberculosis • Autoimmune: • - Lymphocytic infundíbulo-neurohypophysitis • Head injury	**Acquired** • Electrolyte disturbances: - Hypercalcemia - Hypokalemia • Obstructive uropathy • Changes in the renal parenchyma: - Polycystic disease - Acute tubular necrosis - Pyelonephritis • Drugs: - Lithium - Aminoglycosides - Cisplatina - Colchicine • Systemic diseases - Sarcoidosis - Amyloidosis - Systemic lupus erythematosus

ADI: autosomal dominant inheritance. ARI: autosomal recesivo inheritance

METHODOLOGY

A narrative literature review and search of our target was conducted bysearching for articles in the following databases: PubMed, Science Direct, Google Academic, SciELO, Wiley, Oxford Academic, Dialnet, Scopus and UpTodate. Full-text articles wereincorporated, in English or Spanish,published between 2012 and 2022, related to the hydroelectrolytic disorders of diabetes insipidus and theaction of antidiuretic hormone.

THE ACTION OF ANTIDIURETIC HORMONE AT THE PHYSIOLOGICAL ANDBIOCHEMICAL LEVEL

AVP is a peptide composed of nine amino acids with a ring structure and disulfide bond between its components. This compound is synthesized at the level of the magno cellular neurons located in the supraoptic and paraventricular nuclei of the hypothalamus; and its synthesisis accompanied by the specific bindingprotein (neurophysin II). (7-9) Then, AVP binds to this protein and is transported by the axons of the hypophyseal-hypothalamic fascicle to the neurohypophysis, where subsequently the hormonal complexesare stored in the form of granules untiltheir utilization. (10-13) Additionally, an intracellular calcium entry must occur in order to stimulate the membrane potential and generate theexocytosis process for AVP to go out to perform its functions.

This hormone has 3 important receptors:

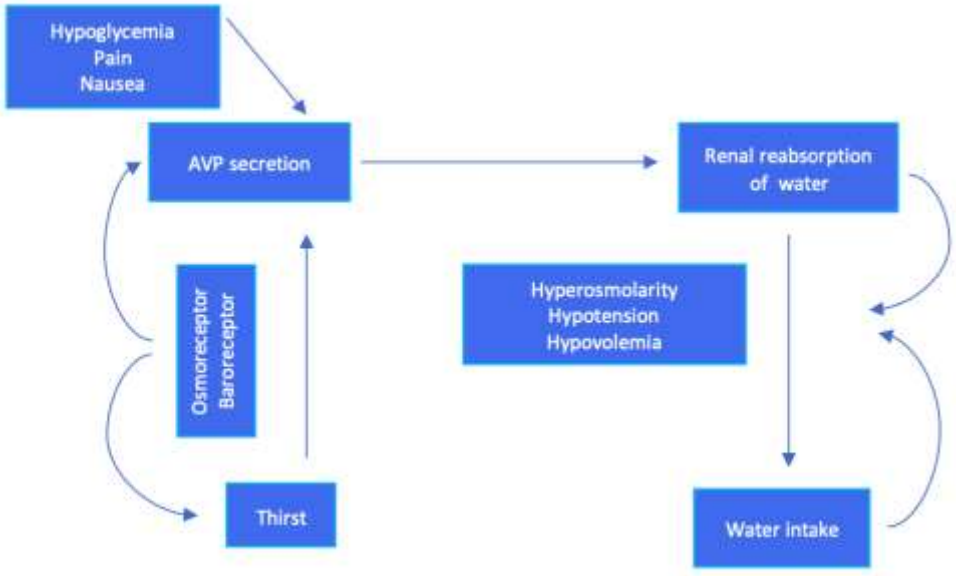
- V1a: This receptor is located invascular smooth muscle, platelets, hepatocytes and myometrium, for which functions such asvasoconstriction (associated with Gq protein increasing the intracellular calcium level), platelet aggregation, glycogenolysis and uterine contraction have beendemonstrated.
- V1b: Found at the corticotropic level, it contributes to increasedACTH secretion.
- V2: found in the distal nephronsof the kidney; its main action is to regulate the effects of AVP inrelation to osmolality, which is why it is called antidiuretic

hormone.

AVP is an important hormone in the conservation of body water throughthe reduction of urine output. Itsantidiuretic effect is given by the reabsorption of water at the level of the collecting tubule of the nephron by means of the V2 receptor of AVP at therenal level; this generates the increaseof water permeability at the level of thecollecting tubule where a water channel called aquaporin-2 (AQ2) is involved, this is found at the level of the apical membranes. (12,13) This effect is initiated by the binding of AVP with the V2 receptor, triggering activation ofthe adenylate cyclase system by means of the GS protein andincreasing cAMP levels. (13,14) The latter, in turn, increases the synthesis of protein kinase A, which is responsible for phosphorylating the AQ2 aqueous channel so that it insertsinto the tubular cell membrane, which is normally impermeable to water, becoming permeable. Thus, under theosmotic gradient of sodium, water moves transcellularly, enters the cell through AQ2 and exits to the interstitium through another type of aquaporins. (8,9) At the end of theAVP effect, endocytosis of the aqueous channel occurs, again restoring water impermeability in the luminal membrane of the nephron.

WATER-ELECTROLYTE DISORDER IN DIABETES INSIPIDUS

The control of osmolality (tonicity) andextracellular volume has a close and fundamental relationship to maintainnormal cell structure and functionality.Therefore, it is fundamental within the physiology of water balance tocomment on the relationship between water and sodium. (15-18) The tonicity of the extracellular fluid is regulated at its maximum expression by excretion and intake of water, while the extracellular volume is regulated bysodium through its intake and excretion. The management of plasma tonicity and intravascular volume is given by the integration of the endocrine, nervous and behavioral systems of the person (Figure 1). (19)



Regulation of antidiuretic hormone secretion and serum osmolality. Taken from:Authors.

AVP, secreted from the posterior pituitary system, is the hormone responsible for regulating tonicity, being stimulated by the increase in plasma tonicity. Likewise, to maintain volume homeostasis it must be regulated mainly by the Renin- Angiotensin-Aldosterone System (RAS) associated with AVP and also receives contributions from natriuretic peptide. (17-19) We must take intoaccount that its half-life in the circulation is around 5 minutes, so its response to osmotic stimuli is fast. Also, it is secreted when we have abrupt decreases in volumes and intravascular pressure, through the baroreceptor pathways of the carotid sinus and the different volume receptors at the level of the pulmonaryveins and the atria. (20,21)

However, these stimuli are notisolated, but act synergistically. One of the situations most related to AVP release is the sensation of thirst, whichis regulated by hypothalamic and cortical neurons (18,19). Thirst has an osmotic threshold above the thresholdfor AVP release. Therefore, elevated AVP levels have been found before theonset of thirst, which allows water intake to be delayed and regulated by homeostatic mechanisms before hyperosmolar situations. Subsequently, vasopressin secretionis decreased prior to water intake to prevent hyponatremia and even the thirst stimulus is decreased prior towater intake to avoid excessive drinking. (1,18)

However, all the regulations of the physiology of the water balance deteriorate in patients with diabetesinsipidus, so there is evidence of decreased secretion, relative deficit or resistance in the renal action of AVP. (22,23) This generates a decrease in urinary concentration (urinary density <1005 in uroanalysis) since there is no water reabsorption mechanism at the level of the collecting tubule and clinically

it is classified with an increase in the amount of urine excreted in 24 hours. Likewise, hyperosmolar states above 300 mosm/kg are evidenced causingactivation of the central thirst system, clinically evidenced as polydipsia (increased thirst). Likewise, patients within the syndrome present a characteristic dysnatremia such as hypernatremia (21-23). This always develops in three situations: When there is a decrease in free water intakein relation to body water losses; secondly, when there is a net gain of sodium and, finally, when there is a loss of free water or with low ion concentrations, which is the case in patients with diabetes insipidus with sodium levels above 150 mEq/L. The clinical and biochemical criteria for diabetes insipidus are listed in Table 2.

Table 2. Clinical and biochemical characteristics of diabetes insipidus in symptomatic patients. Performed by the authors.

CLINICAL AND BIOCHEMICAL CHARACTERISTICS OF DIABETES INSIPIDA	
Plasma volume	Diminished
Hypovolemia/Dehydration	Yes
Serum osmolality (mOsm/kg)	>300
Urinary osmolality/ Plasma Osm	<1,5
Urine density	<1005
Diuresis (ml/kg/h)	>4
Plasma sodium	>150
Urinary Sodium	<40
Plasma antidiuretic hormone	Diminished

TREATMENT

The basis of treatment is based on themain alteration of the affected anatomical site, so it is divided into whether it is diabetes insipidus of central or nephrogenic origin.

Central Diabetes Insipidus (DIC)

In this case, we have a relative deficit or decreased secretion of AVP, so patients present with some degree of dehydration or hemodynamicdecompensation. Water intake shouldalways be established in conscious patients or in the case of unconscious patients, water resuscitation with isotonic solutions and close monitoring of vital signs should be performed. Likewise, AVP supplementation should be performed. (23,24) We have

2 drugs recommended for this pathology:

1. Desmopressin: It is a synthetic analogue of AVP with a longer duration and little effect on the V1a receptor, so that atrecommended doses it does not generate vasoconstriction. However, its use can generate dilutional hyponatremia and aqueous intoxication, due to the potent effect at the V2 receptorlevel. If the patient tolerates thedrug, we can obtain an increasein urinary density, a decrease in urinary volume, sodium returns to physiological levels and plasma osmolality returns to normal (23,24).
2. Vasopressin: It is the direct derivative of AVP with a shorterhalf-life, but with more side effects because it activates all receptors. Another situation that limits its use is its high costand availability, which is why it is only used in intensive care units (23-25).

Nephrogenic Diabetes Insipidus (DIN)

This entity is suspected in patients without central nervous system alterations who present symptoms anddo not respond to DIC management. Inthese patients, sodium restriction and control of dietary protein intake areperformed in order to reduce the osmolar load at the kidney level and water excretion. Likewise, the patient must maintain an optimal hydric intake to maintain his hemodynamic status (17,19) Likewise, the literature recommends the use of NSAIDs because they decrease the glomerularfiltration rate, generate an increase in the osmotic gradient and this leads to a decrease in urine production. However, we must take into account the gastrointestinal side effects of these drugs (23-25).

CONCLUSION

Diabetes insipidus is a disease caused by the relative or insufficient decrease of AVP that generates inability to concentrate urine or AVP is unable to perform its function at the renal level. Hypernatremia is the most characteristic electrolyte alteration of this pathology associated with the hyperosmolar dehydration that is caused, so patients show polydipsia, polyuria and intense thirst. We must take into account the pathophysiology of the disease to perform the excellent hydroelectrolytic correction depending on its etiology and to be able to generate a better quality of life for these patients. Blood biochemistry will always be a good complementary helpto differentiate this syndrome from other etiology of hypernatremia.

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