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Arginine Vasopressin Resistance and Hyperuricemia

Olta Qurku[1*], Alma Idrizi[2]

[1] Nephrologist in Internal Medicine Department, Regional Gjirokaster Hospital, Albania
[2] Nephrologist in Dialysis, Transplantation and Nephrology Department, UHC "Mother Teresa", Tirana, Albania

Address for correspondence: Olta Qurku *, Nephrologist in Internal Medicine Department, Regional Gjirokaster Hospital, Gjirokaster, Albania. E-mail: oltaqurku@yahoo.com

INTRODUCTION

In 1794, Johann Peter Frank of the University of Pavia described the first patients characterized by "long continued abnormally increased secretion of nonsaccharine urine which is not caused by a disease condition of the kidney" and introduced the term "diabetes insipidus" (1). Later in 1901 Magnus and Shaffer discovered the antidiuretic and pressor function of posterior pituitary glandule (2). Fariniand van den Velden, following this track, used posterior pituitary extract to treat diabetes insipidus, in 1913 (3). At the same time, AVP was able to be synthesized by Vigneaud who received Nobel Prize late on 1955 (4). The term "nephrogenic diabetes insipidus" was described by Williams and Henry for the congenital syndrome of polyuria and renal concentrating defect with normal vasopressin production, in 1947 (5).

The role of Arginine vasopressin in water homeostasis.

In the human body, AVP is synthesized as a part of 164 amino-acid precursor protein together with neurophysin-2 protein and copeptin (a glycosylated peptide with a leucine core segment), in magnocellular neurons located in two discrete areas of the hypothalamus, the supraoptic and paraventricular nuclease (6). Both of these nuclei have axonal extensions to the posterior pituitary. After the synthesis, AVP is transported down the axon of these neurons and then it is reserved in pituitary gland waiting to release in circulation due to specific signals. Two major factors determine the release of AVP in circulation, the effective osmotic pressure of the extracellular body

fluid and the decreased extracellular volume (7). So an increase of plasmatic osmolarity causes a change in nerves membrane permeability and an increase of calcium entries. AVP which is stored in the intracellular vesicles of the nerve endings will be released in response to the increased calcium entry. Cardiovascular reflexes such as the arterial baroreceptor reflexes and the cardiopulmonary reflexes are also a stimulus for AVP release. Whenever blood pressure and blood volume are reduced, there is an increase of AVP secretion which will cause an increase of fluid reabsorption by the kidney. Also, high pro-inflammatory cytokines like IL-6 and hypoxic pulmonary vasoconstriction lead to significant stimulation of hypothalamic AVP (8,9). IL-6, which is known to be linked with development of cytokine storm observed during Covid 19 infection, activates the release of AVP due to direct activation of hypothalamus or indirectly through induction of ALI-induced pulmonary vasoconstriction and Angiotensin II-induced hypothalamic activation (10,11). Immediately after the release from pituitary gland, AVP interacts with four subtypes of AVP G-protein coupled receptors (V-receptors and OT-receptors) localized in different cells (12). V1A receptors, expressed in vascular smooth muscle, myocardium, hepatocytes and platelets are responsible respectively for the vasoconstrictions, myocardial hypertrophy, platelet aggregation and glycogenolysis. V1B

receptors expressed in the anterior pituitary glandule are responsible for the release of three types of hormones such as prolactin, adrenocorticotrophic hormone and endorphin. Whereas V2 receptors are localized in renal collecting duct, vascular smooth muscle and vascular endothelium (13,14). Binding of AVP to V2 receptor at the basolateral plasma membrane of the principal cells of the kidney collecting duct is the mainstay of AVP antidiuretic action (15).

The physiology of water reabsorption in the renal tubules.

Normal plasma osmolality is determined by the balance of water/salt intake-excretion and the key role in water homeostasis is known to be the kidney. So proximal tubules and the Henle's loops are responsible for obligatory reabsorption of approximately 90% of the filtered water through the AQP1 (aquaporin 1) localized to the apical cell membrane. In addition to the transcellular route, water reabsorption in the proximal tubules occurs also through tight junctions due to high oncotic pressure and low hydrostatic pressure within the peritubular capillaries. The remaining of water reaching the distal tubules and the collecting ducts are reabsorbed due to AVP signal (16). So once activated by AVP, AVP-V2 receptors initiate a signal transduction cascade that consists of the activation of adenylate cyclase, an increase in intracellular cyclic adenosine monophosphate concentration and the activation of protein kinase A with a final result as it is the phosphorylation of AQP2 and translocation of it from intracellular storage vesicles to the apical plasma membrane of the principal cells (17). APQ2, present at this part of membrane cell, permits water permeability into the cell which then will exit it with the help of AQP3 and AQP4 localized to basolateral membrane. Through this process the water leaves the tubules to enter the bloodstream and so to restore plasma osmolality and volume based on negative feedback (18). All above could explain how a defect in the affinity of receptor V2 to AVP and an altered trafficking of AQP2 induce nephrogenic diabetic insipid.

Arginine vasopressin resistance

Nephrogenic diabetes insipidus, now known as arginine vasopressin resistance is characterized by a decrease in urinary concentrating ability that results from resistance to the action of AVP hormone. In early 1928 De Lange was the first to observe patients diagnosed with diabetes insipidus who did not respond to posterior pituitary extracts as had been proposed before. Also, there was no X-linked (male to male) transmission of the disease (19). It was Forssman who analyzed and came up with the idea of the kidney being the critical part of resistant diabetes insipidus. The term "nephrogenic diabetes insipidus" was described by Williams and Henry for the congenital syndrome of polyuria and renal concentrating defect with normal vasopressin production, in 1947. Meantime in 1971, Sutherland won the Nobel Prize in Medicine for his discovery of the hormones action mechanisms. He offered new concepts of how hormones activate the intracellular adenylyl

cyclase molecule (20). Subsequently Pastan and his team presented the concept of transmembrane receptors with high affinity for the hormones (21). Most adults with AVP-R have an acquired abnormality, with the most common causes being lithium therapy toxicity and other medications, hypercalcemia, hypokalemia, protein malnutrition, aging and release of bilateral ureteral obstruction or unilateral ureteral obstruction in solitary kidney (22). About 40-55% of individuals treated with lithium develop AVP-resistance approximately eight weeks after onset of treatment. Lithium is filtered and reabsorbed by the kidney similarly to sodium into principal cells of collecting ducts. Toxic concentration of lithium into principal cells leads to a decrease in AQP2 expression on the luminal cell membrane (23). Wilting I. et al. suggest that long-term lithium treatment causes reduced kidney ability to concentrate the urine due to direct interference with the vasopressin 2 receptor-cyclic AMP part of the cascade, rather than direct effect to the AQP2 gene (24). Meanwhile, in hypercalcemia induced AVP-R forms, S. Khositseth et al. suggests that hypercalcemia causes AQP2 downregulation due to autophagy. So, the study demonstrated that AQP2 in IMCD cells was sequestered in autophagosomes/autolysosomes in the absence of changes in AQP2 mRNA level (25). The other forms of AVP-resistance are congenital forms, involving AQP2 gene mutations and AVP-receptor 2 gene mutations which will be described below.

Hereditary form of Arginine vasopressin resistance

Hereditary AVP-R, caused by mutation of AVP receptor gene, are X-linked inheritance and presenting by more severe symptoms in males compare to women (26). The AVP-R2 genes that encodes the V2-receptors was cloned in 1992 and then was found the correlation of V2-receptors mutations with familiar nephrogenic diabetes insipidus (20,27). The number of identified AVP-R mutations is constantly increasing. These mutations now are classified in 4 types based on differences in transport to the cell surface and AVP binding and/or stimulation of adenyl cyclase as following: the mutant receptor is not inserted in membrane; the mutant receptor is inserted in to the membrane but does not bind or respond to AVP; the mutant receptor is inserted in the membrane and binds AVP but does not activate adenylyl cyclase; the mutant protein is inserted into the membrane and binds AVP but responds sub normally in terms of adenylyl cyclase activation (28). The other congenital form of AVP-R caused by mutation of AQP-2 gene is mostly autosomal recessive which was identified by van Liegurg in 1994. Then, in 1998 Sabine M. Mulders et al. prescribed for the first time the autosomal dominant form of AVP-R caused by a mutation in the AQP2 gene (29). The AQP-2 gene is located on chromosome 12q13 and codes for the 271 amino acid AQP-2 protein, a type IV-A transmembrane protein characterized by six transmembrane domains connected by five loops and intracellular N- and C-termini (30).

This gene was cloned for the first time in 1993 by scientists of Tokyo University, whom also found that AQP-2 genes to be expressed in the renal collecting duct (31). In 1994 Deen and his team demonstrated that AQP-2 is required for AVP dependent concentration of urine (32). The mutations of AQP-2 affect amino-acids at the carboxyl-terminal which contain regulatory sequences for trafficking and sorting. Aquaporins are homo-tetramers, but the functional unit is the monomer. So, they described that the mutant gene can oligomerize with wild-type-AQP2 and the complex is perturbed in its routing after oligomerization. The hetero-tetramers formed by wild-type and mutated AQP2 monomers are either retained in the Golgi apparatus or are misrouted to late endosomes, lysosomes or basolateral membrane (27). Currently, 65 mutations of APQ-2 gene have been described as causative of autosomal AVP-R, 54 out 65 are recessive inheritance (33,34,35).

Aquaporins and their role in water balance.

AQP2 are part of a transmembrane channels family that mainly transport water across the cell, and some facilitate low-molecular-weight solutes. There are 13 members of AQPs in mammals which are widely distributed in various tissues and organs. In the kidney are localized eight AQPs, including AQP 1, 2 ,3 ,4,5,6,7 and 11, which are responsible to maintain normal urine concentration, tissue development and substance metabolism (32). Aquaporin 2 is the most important channel protein involved in regulating urine concentration, located at the apical membrane of principal cells in the collecting duct. As we described above, the binding of AVP on its transmembrane receptor V2 activates production of intracellular cyclic adenosine monophosphate and further phosphorylation of AQPs at Ser256 and Ser269 to stimulate the intracellular trafficking of AQPs to the lumen membrane (33,34). This pathway of AQPs activation has also other stimulations as erlotinib, an epidermal growth factor receptor inhibitor, AP1, NF-kB and NFAT. So studies have suggested using urinary excretion of AQPs as a marker for diagnosis of renal disease and to evaluate the mutation of AVP-V2 receptors (35).

Diagnosis of Arginine vasopressin resistance

Establishing the diagnosis of diabetes insipidus requires measuring of AVP plasmatic level. But mainly due to technical reasons and its short half-life, it is recommended to measure the plasmatic level of copeptin instead of AVP level. Copeptin is known now as a stable, sensitive surrogate marker that reflects synthesis, level, and biological activity of AVP (36). Even though copeptin was detected in 1972 in the posterior pituitary of pigs, still the physiological function of it is largely unknown (37). In addition to osmotic and arterial pressure, somatic stress seen in serious illness as ischemic stroke, myocardial infarction, lower respiratory tract infections and septic shock has shown to be a major determinant of copeptin regulation (38,39,40). Also it has been observed a positive correlation between psychological stress and copeptin release (41). These findings suggest avoiding emotional and

physical stress level before analyzing the plasmatic copeptin level. In healthy patients this level has been evaluated to be 1.0 to 13.0 pmol/L. Compared to women, median plasma copeptin level is higher in men but no differences have been found relating to age (42). So the suspect diagnosis of diabetes insipidus is made in patients with symptom of polyuria. There are 2 major causes of polyuria, osmotic and water diuresis (37,43,44,45). After ruling out osmotic diuresis the next step in diagnosis is measuring plasma copeptin level as it described above. The level more than 21,4 pmol/L confirms the diagnosis of AVP-R (46). Lower levels of copeptin exclude AVP-R and in this case it is necessary to remeasure this level after water restriction (or hypertonic saline application), once the serum sodium is > 145 mEq/L. AVP-D is diagnosed if the plasma copeptin is </= 4.9 pmol/L and primary polydipsia is diagnosed if a higher value is obtained. In patients whose water restriction could be contraindicated, measuring of plasma copeptin could be done after infusion of arginine (0.5 g/kg over 30 min). Both methods are useful in differential diagnosis of primary polydipsia and AVP-D (47,48,49).

The risk of hyperuricemia during the treatment.

In the case of drug induced AVP-R, the treatment of choice is the withdrawal of the responsible drug. However, in psychiatric patients, the withdrawal of Lithium is not the recommended solution, and, in this case, it is suggested to continue with it and administer at the same time thiazide diuretics. One of proposed mechanisms of thiazide action on the treatment of lithium induced AVP-R is by reduction of sodium reabsorption in the distal tubule, increasing sodium excretion and decreasing extracellular fluid volume. In continuing of this process, there will be a decrease in glomerular filtration rate and an increase in sodium and water reabsorption in the proximal tubule. So, the amount of water and sodium delivered to the collecting tubules will decrease and the result of all this will be less excreted water. A. Megaldi and co. suggest that thiazide-stimulated water transport is not linked to inhibition of the NaCl cotransporter and that thiazides act only when they are applied to the luminal side of the cell (50). Kim. Gheun-Ho & co. has prescribed in his study that chronic HCTZ treatment induces upregulation of AQP2, NCC, and ENaC in Li-induced AVP-R rats. The AQP2 downregulation induced from chronic use of Lithium was found to be partially reversed due to HCTZ treatment (from 20%-40% of normal controls) (51). But the use of hydrochlorothiazide is associated with increase of uric acid plasma level (52). Uric acid is the end-product of purine metabolism and its balance into human body is maintained by the kidney. Its reabsorption is mediated by the apical human urate/anion transporter URAT1/SLC22A12 (53) and by basolateral voltage-driven urate transporter URATv1/SLC1A9/GLUT9 (54,55) in proximal tubular cells. Whereas the secretion is mediated by the OAT1 and OAT3 localized to the basolateral membrane of proximal cells and by apical electrogenic antiporters NPT4 (Human

Na-phosphate cotransporter 4), NPT1 and adenosine triphosphate-efflux pumps as ABCG2, ABCC4. Urate enters the cell from interstitium by exchanging with divalent anions as alpha-ketoglutarate. The use of thiazide diuretics causes an increase in serum urate levels due to inhibition of urate secretion at the level of OAT1 and OAT3 and competition with urate at the level of NPT4. Thiazide drugs inhibit NPT4-mediated urate uptake with IC50 values less than 1.0 mM (56,57). These data suggest that the use of thiazide diuretics in the treatment of AVP-R, especially in the forms induced by medications at a time when these medications cannot be stopped, requires close monitoring of the uric acid level as it is known the positive correlation of hyperuricemia with causing and progression of chronic kidney disease (58,59,60).

CONCLUSION

The etiology of arginine vasopressin resistance is based on the arginine vasopressin action on principal cells of the kidney. Most of them are acquired form as the lithium induced- AVP. Selection of the treatment in this case should be oriented by comorbidity and the risk of hyperuricemia.

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