Is Oxytocin a Player in Antidiuresis?

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The nonpeptide hormone oxytocin does not receive much thought from the renal community compared with its colleague, vasopressin. These two hormones display close similarities in chemical structure (differing by only two amino acids), their genes cluster at the same locus (20p13), and they are transcribed from opposite DNA strands and exhibit similar intron–exon structures. Both are synthesized in the hypothalamus of humans and transported through the neurohypophysial tract to the posterior pituitary for storage or secretion into the bloodstream. Furthermore, receptors for both hormones belong to the G-protein–coupled receptor family and share high sequence homology, varying 40 to 85% and forming a subfamily. Oxytocin has one receptor, whereas vasopressin has three types (V1aR, V1bR, and V2R). Despite these many similarities, the main biologic functions of oxytocin and vasopressin differ substantially. Oxytocin modulates contraction of uterine smooth muscle at parturition, ejection of milk from lactating breasts, and sperm transport and ejaculation in men, whereas vasopressin regulates water permeability of the collecting ducts to alter urine-concentrating ability.

The understanding of water permeability along the collecting ducts at a molecular level has substantially advanced since the discoveries of the vasopressin type 2 receptor (V2R) and aquaporin-2 water channel (AQP2). Binding of vasopressin to V2R located at the basolateral membrane of collecting duct cells activates adenylyl cyclase, which in turn increases cAMP levels and stimulates protein kinase A. Subsequent protein kinase A–mediated phosphorylation of AQP2 itself triggers trafficking of AQP2 from storage vesicles to the apical membrane (short-term regulation). Increased intracellular cAMP also enhances the transcription of AQP2 through a pathway mediated by a cAMP-responsive element, increasing the abundance of AQP2 (long-term regulation).

Oxytocin as well increases the expression of AQP3 on the basolateral membrane of collecting ducts. This evidence clearly tells us that circulating vasopressin and V2R and AQP2/AQP3 in collecting duct cells are key players in urine concentration.

What about oxytocin? Does it contribute to urine-concentrating ability? Recognition of the antiuretic effect of oxytocin goes back to the early 1960s with clinical observations showing that systemic infusion of high-dosage oxytocin in obstetric patients causes antiurexia, indicating vasopressin-like effects. Later studies in Brattleboro rats (congenital vasopressin-deficient rats) clearly show that exogenously administered oxytocin also has an antiuretic effect. Oxytocin at low physiologic dosages increases the water permeability of medullary collecting ducts in Brattleboro rats through the V2 receptor but not the oxytocin receptor.

In patients with SIADH, plasma vasopressin levels are usually increased, whereas vasopressin-deficient rats) clearly show that exogenously administered oxytocin also has an antiuretic effect. Oxytocin at low physiologic dosages increases the water permeability of medullary collecting ducts in Brattleboro rats through the V2 receptor but not the oxytocin receptor. Oxytocin binds to V2R, regulates AQP2 and AQP3 in short- and long-term settings, and ultimately facilitates water permeability of the collecting duct.

What are the implications of this antiuretic effect by oxytocin? Two issues of clinical relevance are immediately apparent. First, oxytocin infusions are not infrequently used to induce labor toward the end of pregnancy; however, because rates of infusion are low and transient, antiurexia is mild and water intoxication unlikely. In relatively rare clinical situations, such as when evacuating the products of conception in cases of missed or incomplete abortion or stimulating myometrial conceptions in instances of uterine atony during the early puerperium, larger infusions of oxytocin can be administered for a longer period and may cause antiurexia, resulting in water intoxication. In these settings, harmful events can be prevented if physicians are aware of the antiuretic action of oxytocin and restrict infusions of water. Limiting the volume of electrolyte-free fluid is essential. In this regard, the recent clinical availability of nonpeptide V2R antagonists is good news.

Second, oxytocin may be a good candidate to explain the presence of unknown antidiuretic substances in syndrome of inappropriate secretion of antidiuretic hormone (SIADH). In patients with SIADH, plasma vasopressin levels are usually...
inappropriately high compared with plasma osmolality, but vasopressin levels are below the limits of RIA detection in a certain portion of the patients (as much as 10 to 20%).

The existence of other antidiuretic substances in plasma has been postulated. Oxytocin may fit this profile nicely. A few studies have shown elevated levels of plasma oxytocin in patients with small-cell lung cancer; however, these increments were usually accompanied by concomitant increases in vasopressin.

At present, no report has suggested that oxytocin alone produces SIADH in clinical cases, but this may be attributable to the lack of a reliable RIA for oxytocin in clinical settings. Related to this topic, the nephrogenic syndrome of inappropriate antidiuresis (NSIAD) is caused by a gain-of-function mutation of V2R. In this disease, endogenous vasopressin is completely suppressed while antiuresis persists.

The symptoms of disease start from childhood, but similar mutations seem to explain some sporadic episodes of SIADH in adults.

How should we differentiate oxytocin-induced SIADH from NSIAD? Oxytocin-induced SIADH will respond to V2R antagonists as illustrated by Li et al., whereas patients with NSIAD are unable to respond to V2R antagonists. Clinicians would thus be well advised to note that oxytocin has antidiuretic activity and contributes to hyponatremia in certain clinical settings and that V2R antagonists may be useful in the differential diagnosis and treatment of inappropriate antiuresis.

REFERENCES


DISCLOSURES

None.

Podocyte-Specific Gene Mutations Are Coming of Age

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Major leaps have been made recently in the understanding of the cause of proteinuria and hence in the regulation of glomerular permeability in health. Progress has been fueled by the description of single-gene mutations, the majority of which affect genes expressed selectively in the podocyte, resulting in nephrotic syndrome in human and mouse.

This has placed the podocyte center stage as a key regulator of normal selective permeability to albumin in the glomerular capillary wall, although we should not forget that single-gene mutations affecting components of the glomerular basement membrane can also result in heavy proteinuria, or that the third component of the glomerular capillary wall, the glomerular endothelial cell, can also play an important role in regulating glomerular permeability in health and disease.

The first podocyte-specific gene identified by studying disease-associated mutations was NPHS1, encoding nephrin; this was swiftly followed by identification of NPHS2, encoding podocin, also a novel protein important in the structure and function of