Vasopressin and Osmoregulation: Older Than You Thought

The regulation of water balance (“osmoregulation”) is a complex mechanism in which neural and kidney responses adjust urinary concentration in response to changes in plasma water content assessed by osmolality. The capacity to concentrate urine, one of the classical ways to assess renal function, reflects the structural integrity of the kidney and the action of a small neuropeptide (9 amino acids) called arginine vasopressin (AVP)—that is, the antidiuretic hormone.

When plasma osmolality increases, specialized neurons in the supraoptic and paraventricular nuclei of the hypothalamus synthesize AVP, which is then released into the blood from the posterior pituitary gland. In turn, AVP acts on G protein–coupled receptors (the vasopressin V1 and V2 receptors) that mediate cellular responses in the distal nephron to build up the corticomedullary osmotic gradient and thus concentrate urine. In particular, AVP binding to the V2 receptor in the principal cells of the collecting ducts increases the level of 3',5'-cyclic adenosine monophosphate (cAMP), which leads to phosphorylation of the aquaporin-2 water channels and their insertion into the apical membrane, thus facilitating osmotic water reabsorption from urine.

Any defect in the foregoing mechanism impairs the process of urinary concentration, as evidenced by diabetes insipidus. Conversely, excessive activation of this pathway causes inappropriate antidiuresis (1), and excessive production of cAMP downstream of the V2 receptor has been associated with cyst progression in autosomal dominant polycystic kidney disease (2). Although AVP is not primarily involved in the peritoneal membrane, the osmotic transport of water through aquaporins is essential in mediating ultrafiltration in peritoneal dialysis (3).

A recent paper in *Science* demonstrated—in the nematode *Caenorhabditis elegans*, a 1-mm worm whose nervous system contains less than 400 easily tractable neurons—extraordinary conservation of neuropeptides related to AVP that regulate NaCl chemotaxis and thus osmoregulation (4). In that study, Beets *et al.* used the nematode model to characterize a vasopressin- and oxytocin-related neuropeptide named nematocin and its G protein–coupled

receptor NTR-1. Nematocin is structurally conserved and similar to the human neuropeptides AVP and oxytocin. Like AVP, nematocin induces calcium and cAMP messengers in cells expressing NTR-1. Through a series of sophisticated behavioral testing experiments, the authors showed that nematocin plays an essential role in the attraction of the worm for NaCl, a function named “salt chemotaxis.” Furthermore, it does so by controlling the gustatory associative learning mediated by specific neurons expressing NTR-1. Such associative learning is crucial for the ability of animals to monitor the environment and adapt their behavior. The authors conclude that acquisition of this neuropeptide signaling system was probably crucial when animals became mobile and started to make experience-based decisions more than 700 million years ago.

TAKE-HOME MESSAGE

The Beets *et al.* nematode study illustrates how model organisms with simplified, tractable systems can help in reaching an understanding of the complex physiologic mechanisms operating in humans (5). The fact that the nematode *C. elegans* uses a vasopressin-related neuropeptide to regulate attraction to NaCl will probably help us to better understand ancestral functions still crucial in our daily lives.

DISCLOSURES

The author has no financial conflicts of interest to declare.

Olivier Devuyst
Deputy Editor

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