Neuro-endocrinology

BRIEFINGS

43

Apelin and Vasopressin: Two Work Better Than One

SUMMARY

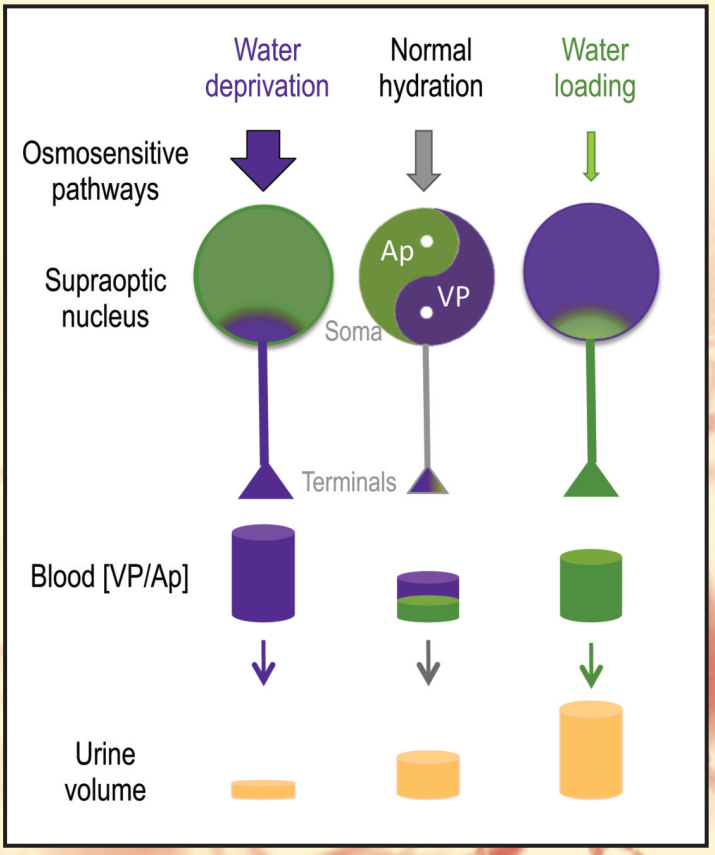
Water retention in the kidney is known to be an active phenomenon, controlled by a neuropeptide, vasopressin. Instead, water excretion was believed to be a passive phenomenon, due to vasopressin release blockade. This simplistic view is incorrect because water excretion is also controlled by a diuretic neuropeptide, apelin, produced not only by several peripheral tissues, but also by hypothalamic neurons, in particular the vasopressin ones projecting to the posterior pituitary.

Retaining or Losing

In healthy adults and animal models, the osmotic pressure of body fluids is maintained within a remarkably narrow range. Body fluid homeostasis is centrally controlled, and it depends upon neuronal pathways bearing very sensitive osmoreceptors located in several areas of the brain, including the endocrine neurons in the supraoptic nuclei. These neuronal pathways convert small changes in plasma solute concentration (osmolality) into a voltage signal to neurons. These signals influence the release into the blood of two neuropeptides, vasopressin and apelin, that control renal water excretion in opposing ways.

Targets

Both neuropeptides act at central and peripheral levels to exert their opposite biological actions. Centrally, vasopressin released locally in rodent hypothalamus, exerts an autocrine feedback control on vasopressin neurons. In particular, it facilitates the expression of a phasic electrical pattern that is the most efficient to release vasopressin by axon terminals. This effect is crucial during dehydration when the hormonal demand for vasopressin is high and must be sustained for hours, until osmolality recovers basal values. On its hand, apelin, injected centrally in lactating rodents, inhibits the phasic electrical activity of these same



Yin-Yan type function of dual Vasopressin (VP, purple) and Apelin (Ap, green) neurons

vasopressin neurons, thus reducing vasopressin release in the blood circulation and increasing aqueous diuresis.

"...vasopressin and apelin control renal water excretion in opposing ways..."

At the kidney, vasopressin, by acting on its receptors (V2), activates water channels, the aquaporin-2 (AQP2) facilitating their insertion in the apical membrane. This allows water reabsorption from the pro-urine, and results in urine concentration and volume reduction. Apelin receptors have also been detected in collecting ducts that express V2 receptors. Because, in rodents, intravenous injections of apelin increase diuresis, we hypothesise that apelin, by acting on its renal receptors, counteracts the stimulatory effects of vasopressin on AQP2 activation. By adjusting the output of water to counteract changes in solute concentration, vasopressin and apelin thus prevent plasma osmolality from deviating by more than a few percent from the average basal level.

A Balancing Act

Because vasopressin and apelin coexist in the same neurons, one can ask how vasopressin and apelin can be differentially regulated in order to maintain body fluid homeostasis. In fact, vasopressin and apelin are not only synthesized from different genes in the same neurons but are segregated within distinct sub-cellular compartments inside these neurons, suggesting that the two peptides might be differentially released from two distinct vesicular pools within the same cells. Indeed, following water deprivation, neurons are strongly activated and vasopressin is released in the blood circulation faster than it is synthesized, resulting in a depletion of vasopressin stores in the soma, whereas apelin accumulates within neurons rather than being released. By contrast, after water loading, neurons are inhibited, which stops vasopressin release and results in accumulation of vasopressin in the soma. Apelin release in the bloodstream rapidly increased, faster than its synthesis, resulting in a depletion of neuronal apelin content. Thus, both neuronal and plasma apelin levels are regulated by osmotic stimuli in opposite direction to vasopressin.

Yin-Yang

Together, this suggests a new physiological concept of dual potentiality for endocrine neurons that, according to the degree of their activation/inhibition, will dynamically ensure opposite physiological functions in accordance with the hormonal demand, owing to the selective release of one of their co-expressed neuropeptides. During changes in plasma osmolality, neurons in the supraoptic nuclei have a dual and opposite functional potentiality of Yin-Yang type. Both functions are interconnected and interdependent, and only exist in relation to each other. While vasopressin plays a major role in the retention of water to prevent a deleterious hyperosmolality, generally as a consequence of high concentration of sodium in plasma (hypernatremia), apelin may play a crucial role in the case of hyponatremic disorders resulting from hypoosmolar states.

Because changes in plasma vasopressin and apelin concentration reflect changes in osmolality, analysing the relationship between these parameters may reveal new classifications of the multiple etiologies of hypoosmolar states of impaired urinary dilution or concentration in patients. Clinically, the development of non-peptide apelin receptor agonists may constitute alternative or complementary therapeutic tools to V2 receptor antagonists, for the treatment of water retention and/or hyponatremic disorders. In addition, given that activation of apelin receptors induces aqueous diuresis, vasodilatation and positive inotropic effects in the heart, the apelin receptor could constitute a potential therapeutic target in heart failure treatment.

Authors:
Catherine Llorens-Cortes
Laboratory of Central Neuropeptides and Regulations of Water Balance and Cardiovascular Functions, Inserm U1050, Collège de France, Paris, France

Francoise Moos
Institute of Integrative and Cellular Neuroscience, University of Strasbourg, Strasbourg, France

Editor:
Professor Mike Ludwig
Centre for Integrative Physiology, University of Edinburgh, Edinburgh UK
mike.ludwig@ed.ac.uk

The full Briefings series can be viewed at website http://www.neuroendo.org.uk