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Review

Mechanosensing in hypothalamic osmosensory neurons

Masha Prager-Khoutorsky*

Department of Physiology, McGill University, Montreal, QC, Canada

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ABSTRACT

Osmosensory neurons are specialized cells activated by increases in blood osmolality to trigger thirst, secretion of the antidiuretic hormone vasopressin, and elevated sympathetic tone during dehydration. In addition to multiple extrinsic factors modulating their activity, osmosensory neurons are intrinsically osmosensitive, as they are activated by increased osmolality in the absence of neighboring cells or synaptic contacts. This intrinsic osmosensitivity is a mechanical process associated with osmolality-induced changes in cell volume. This review summarises recent findings revealing molecular mechanisms underlying the mechanical activation of osmosensory neurons and highlighting important roles of microtubules, actin, and mechanosensitive ion channels in this process.

Contents

1. Introduction

Mammals have developed sophisticated regulatory mechanisms that work together to maintain stable plasma osmolality [1–3]. Plasma osmolality is a measure of total solute concentration in the blood plasma. As a class, all mammals strive to maintain this parameter around the set points of ~300 mosmol/kg (288 mosmol/kg in humans) [2]. Changes in the plasma osmolality occur when the solute to water ratio is altered, for example following evaporative water loss during breathing, by the production of sweat, and the ingestion of dry solutes and hypertonic solutions (e.g. salt and soy sauce), or as a result of drinking of hypotonic fluids (e.g. water). These changes in the plasma osmolality are corrected by modulating salt and water consumption (promoting salt appetite and thirst sensation, respectively), as well as by altering salt and water excretion by regulating sympathetic tone and renal function, leading to the stabilization of the blood tonicity [1,2,4]. This regulation is vital to the organism, as changes in the extracellular fluid osmolality promote swelling or shrinkage of cells and tissues, and therefore, large deviations in the plasma osmolality can lead to irreversible organ injury and cause lethal neurological trauma [5–9]. Changes in the plasma osmolality larger than 1% (~3 mosmol/kg) above or below the set point modulate the rate of salt and water intake and secretion of vasopressin (VP, antidiuretic hormone) to restore plasma osmolality to the set point level [2]. An increase in the plasma osmolality above the set point induces VP secretion into the circulation, leading to water reabsorption by the

Abbreviations: VP, vasopressin; MTs, microtubules; SON, supraoptic nucleus; OVLT, *organum vasculosum lamina terminalis*; ΔN-TRPV1, a variant of the transient receptor potential vanilloid receptor 1.

* Correspondence to: McIntyre Medical Sciences Building, Rm#1229, 3655 Promenade Sir William Osler, Montreal, QC, Canada.
E-mail address: masha.prager-khoutorsky@mcgill.ca

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kidney, and thereby decreasing the plasma osmolality toward the set point [2,10] (Fig. 1).

VP is synthesized in the somata of magnocellular neurosecretory cells located in the hypothalamic supraoptic (SON) and paraventricular nuclei. These neurons project their axons to the posterior pituitary, where VP is secreted into the circulation [2,10] (Fig. 1). Both extrinsic and intrinsic factors modulate the firing activity and VP secretion [2,11]. The *organum vasculosum laminae terminalis* (OVLT) is a primary osmosensory area within the brain, critical for body fluid homeostasis [12,13]. OVLT harbors a population of intrinsically-osmosensitive neurons [14,15], which send direct axonal projections into the SON to regulate the firing activity of VP neurons [16–19]. The activity of VP neurons can be also affected by osmosensory neurons found in other parts of the nervous system [2,11]; such as subfornical organ, the median preoptic nucleus, and peripheral osmosensory neurons *via* vagal and spinal pathways [20–24]. Futhermore, glia cells play a functional role in controlling the activity of SON neurons [25–27]. In addition to these extrinsic mechanisms, both OVLT and SON VP neurons are intrinsically osmosensitive [14,15,28–30]. Activity of isolated SON and OVLT neurons is increased by hypertonicity and inhibited by hypotonicity in the absence of neighbouring glial cells and synaptic contacts (Fig. 1).

Modulation of the activity of osmosensory OVLT and SON VP neurons by osmolality is a mechanical process associated with osmotically-triggered changes in cell volume. Hypertonicity-induced cell shrinkage causes an excitation and increases the firing rate of these neurons, whereas hypotonicity-induced cell swelling inhibits their basal activity and firing rate (Fig. 1). Recent studies have provided insights into the molecular mechanisms underlying the mechanical regulation of the osmosensory neuron activity. The objective of this review is to summarize our current understanding of mechanosensing in osmosensory neurons and to highlight new findings of the distinct molecular machinery involved in this process.

2. Osmosensory neurons are mechanosensitive

The activation of osmosensory OVLT and SON VP neurons by hypertonicity is associated with a decrease in cell volume as a result of water flowing out of the cell to balance the elevated concentration of solutes in the extracellular fluid. Other cell types display compensatory adaptive responses to restore their volume when exposed to environments with altered extracellular fluid osmolality [31,32]. In contrast, osmosensory neurons display stable changes in volume that are inversely proportional to the osmolality, and these changes can be maintained for many minutes up to hours [33,34]. This feature is crucial, as osmosensory neurons should remain active for as long as the plasma osmolality is elevated above the set point in order to secrete VP to minimize water loss by the organism by promoting water retention in the kidney. Importantly, the changes in the volume of osmosensory cells are directly coupled to their activity. Accordingly, inducing cell shrinkage or swelling without changing the osmolality of the extracellular solution cause activation or inhibition of the cell which is equivalent to changes provoked by alterations in the osmolality (Fig. 2). Likewise, the osmolality-induced modulation of neuronal activity can be reversed by restoring the cell volume by applying increasing or decreasing pressure through a whole-cell patch pipette [14,35]. These findings demonstrate that osmolality-induced modulation of neuronal activity does not depend on changes in solute concentration or ionic strength, but is a mechanical process linking changes in cell volume to the excitation or inhibition of the osmosensory neurons.

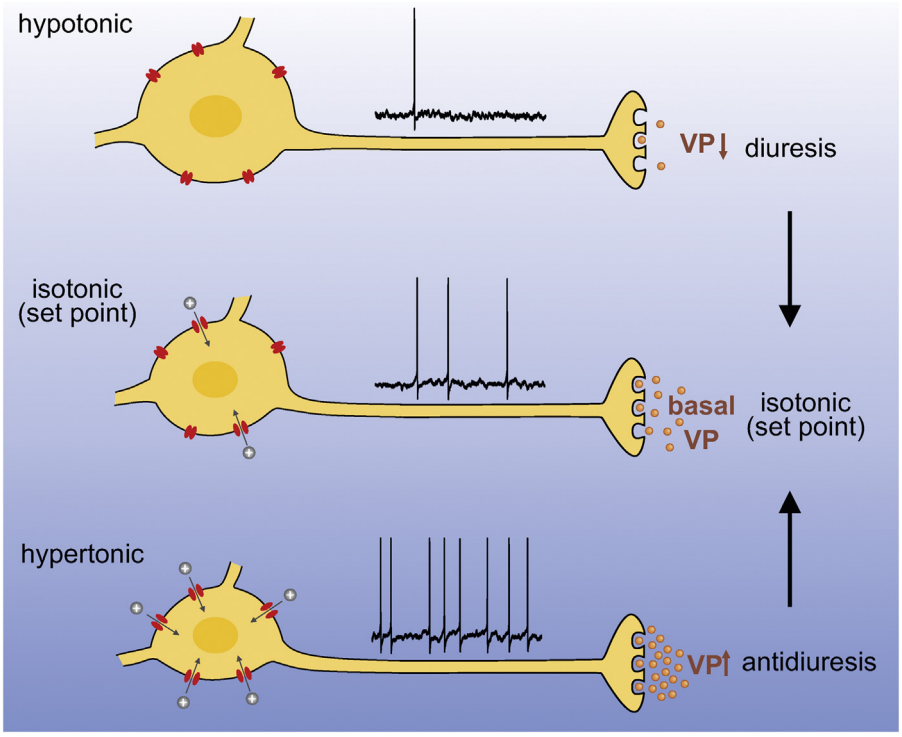

Fig. 1. Vasopressin-releasing neurons in SON are intrinsically osmosensitive. Changes in osmolality cause inversely proportional changes in cell volume. Hypertonicity-evoked shrinkage activates transduction ion channels (a variant of the transient receptor potential vanilloid receptor 1, ΔN-TRPV1), leading to depolarization and an increase in the action-potential firing rate and vasopressin (VP) release from axon terminals in the neurohypophysis. Increased VP levels in blood enhance water reabsorption by the kidney (antidiuresis) to restore extracellular fluid osmolality toward the set point. Hypotonic stimulus inhibits the transduction channels that are open under the basal isotonic condition (set point), leading to hyperpolarization and a decrease in the firing rate of osmosensory neurons. This causes a reduction in the VP release and promotes diuresis.

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