



Interactions of the Mechanosensitive Channels with Extracellular Matrix, Integrins, and Cytoskeletal Network in Osmosensation

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Life is maintained in a sea water-like internal environment. The homeostasis of this environment is dependent on osmosensory system translation of hydromineral information into osmotic regulatory machinery at system, tissue and cell levels. In the osmosensation, hydromineral information can be converted into cellular reactions through osmoreceptors, which changes thirst and drinking, secretion of antidiuretic vasopressin (VP), reabsorption of water and salt in the kidneys at systemic level as well as cellular metabolic activity and survival status at tissue level. The key feature of osmosensation is the activation of mechanoreceptors or mechanosensors, particularly transient receptor potential vallinoid (TRPV) and canonical (TRPC) family channels, which increases cytosolic Ca²⁺ levels, activates osmosensory cells including VP neurons and triggers a series of secondary reactions. TRPV channels are sensitive to both hyperosmotic and hyposmotic stimuli while TRPC channels are more sensitive to hyposmotic challenge in neurons. The activation of TRP channels relies on changes in cell volume, membrane stretch and cytoskeletal reorganization as well as hydration status of extracellular matrix (ECM) and activity of integrins. Different families of TRP channels could be activated differently in response to hyperosmotic and hyposmotic stimuli in different spatiotemporal orders, leading to differential reactions of osmosensory cells. Together, they constitute the osmosensory machinery. The activation of this osmoreceptor complex is also associated with the activity of other osmolarity-regulating organelles, such as water channel protein aquaporins, Na-K-2Cl cotransporters, volume-sensitive anion channels, sodium pump and purinergic receptors in addition to intercellular interactions, typically astrocytic neuronal interactions. In this article, we review our current understandings of the composition of osmoreceptors and the processes of osmosensation.

Keywords: cytoskeleton, extracellular matrix, integrin, transient receptor potential canonical channel, transient receptor potential vallinoid channel, vasopressin

Since the concept of homeostasis of internal environment was introduced by Claude Bernard and Walter B. Cannon about 100 years ago (Modell et al., 2015), the importance of hydromineral balance in life processes has been extensively explored. However, the identity of osmoreceptors that can detect changes in hydromineral balance and initiate osmotic regulation remains elusive. In this article, we review our current understandings of this osmosensory machinery.

OSMOSENSATION

Osmosensation requires functioning of osmoreceptors that detect hydromineral disturbance and initiate osmoregulation (Knepper et al., 2015). In the CNS, hypothalamic magnocellular vasopressin (VP) neurons in the supraoptic (SON), paraventricular (PVN), and their accessory magnocellular nuclei (Rhodes et al., 1981) and neurons in the circumventricular organs are considered as the main components of central osmosensory system (McKinley et al., 2004). The central osmosensation involves local neuronal activity, astrocytic plasticity, blood-borne factors, direct osmotic stimuli and autoregulation (Scott and Brown, 2010; Wang et al., 2011; Pedrino et al., 2014); however, the essential requirements for osmosensation are still the ability of osmosensory cells to sense hydromineral changes.

Noteworthy is that other neurons outside of this central osmosensory system can also sense changes in osmotic pressure, such as oxytocin neurons in the SON and PVN (Kortus et al., 2016) and hippocampal neurons (Arranz et al., 2014). In addition, cognitive activity of the cerebrum can exert anticipatory regulation of VP neuronal activity during drinking (Mandelblat-Cerf et al., 2017). In peripheral sites, many types of tissues and cells have the capacity of osmosensation (Pedrino et al., 2014), typically seen in the digestive tract (Zhu et al., 2001) that could change VP neuronal activity through medulla-mediated viscerosensory inputs (Rinaman, 2007). Thus, osmosensation is likely a universal feature among different tissues/cells.

The activation of osmosensory system can change thirst and drinking, secretion of antidiuretic VP, and reabsorption of water and salt in the kidneys (Wang et al., 2011; Danziger and Zeidel, 2015) as well as VP gene transcription following increase in cAMP (Arima et al., 2001), cellular metabolic activity and survival status (Moeckel et al., 2006; Hollborn et al., 2015), thereby helping the body and its parts to restore hydromineral balance.

MAJOR CELLULAR EVENTS EVOKED BY OSMOTIC STRESS

Osmosensation is closely associated with the following cellular events.

Electrochemical Events

Early studies showed that hyperosmotic stress activates stretch-inactivated cation channels (SICs) and increases the excitability of VP neurons (Voisin and Bourque, 2002). In contrast, short hyposmotic stimulation inactivates the SICs, hyperpolarizes VP neurons and thus reduces VP secretion (Kusano et al., 1999). Further studies showed that the SICs are associated with a class of transient receptor potential (TRP) vallinoid (TRPV) channels since TRPV1- (Sharif Naeini et al., 2006) and TRPV4-null mice (Liedtke and Friedman, 2003) showed reduced hyperosmotic reactions in the organum vasculosum of lamina terminalis.

Further studies reveal that these SICs could also be stretch-activated cation channels because hyposmotic challenges can increase intracellular Ca^{2+} concentration through activation of

TRPV1, TRPV2, TRPV4 in Merkel cells from hamster buccal mucosa (Soya et al., 2014), TRPV4 in acinar cells (Aure et al., 2010) and in nonpigmented epithelial cells (Jo et al., 2016). Consistently, in acute hyponatremic condition, serum VP levels increase significantly following initial inhibition (Yagil and Sladek, 1990), which reflects a reactivation of VP neurons following the initial inhibition (Wang et al., 2013a,b) through the mechanism of “resetting osmosensory threshold at the local neural circuit” (Wang et al., 2011). Clearly, the activation of these TRPV channels could occur under both hyperosmotic and hyposmotic challenges.

In fact, many other ion channels are also involved in osmosensation, such as TMEM63 proteins found in *Arabidopsis* (Zhao et al., 2016), TRP ankyrin-1 and TRP melastatin-8 channels in Merkel cells from hamster buccal mucosa (Soya et al., 2014) and P2X receptors that are membrane ion channels gated by extracellular ATP (Fountain et al., 2007). Among them, TRP canonical (TRPC) 5 channel (Jemal et al., 2014) and TRPC6 (Wilson and Dryer, 2014) were found to sense hyposmotic stretch but not hyperosmotic stimulus. Thus, many TRP channels are involved in and play dual role in osmosensation and thus are not specifically bound to hyperosmotic or hyposmotic stimulus; however, TRPC could be more selective to hyposmotic challenge.

Plasticity of Cytoskeletal Elements

Cytoskeletal elements including actin filament and microtubule have direct molecular association with the C-terminus of TRPV4 revealed in co-immunoprecipitation (Goswami et al., 2010), and thus could be important regulator of TRP channel activity in osmosensation. Blocking actin polymerization (Prager-Khoutorsky and Bourque, 2010) or disrupting microtubule network (Prager-Khoutorsky and Bourque, 2015) can block hyperosmolarity-evoked activation of osmosensory neurons in rat brain slices. Thus, an increased interactions between microtubule network with TRPV1 during cell shrinkage could account for hyperosmotic activation of osmosensory neurons (Prager-Khoutorsky and Bourque, 2015). However, this hypothesis could not explain hyposmotic intracellular Ca^{2+} increase (Aure et al., 2010; Soya et al., 2014; Jo et al., 2016), the recovery of VP neuronal activity from hyposmotic inhibition (Wang et al., 2013a,b) and the increased VP secretion during volemic increase in chronic osmotic stress (Zhang et al., 2001). Here, referring to the hearing mechanism (Sukharev and Corey, 2004; Martinac, 2014), we propose that if hyperosmotic activation of TRP channels is due to a “push” of microtubule network (Prager-Khoutorsky and Bourque, 2015), the hyposmotic activation of TRP channels should be because of a “pull” of the network in coordination with conformational changes in other cellular components (Figure 1A).

CELLULAR VOLUME

Change in cell volume is a common and remarkable phenomenon in response to hydromineral disturbance.

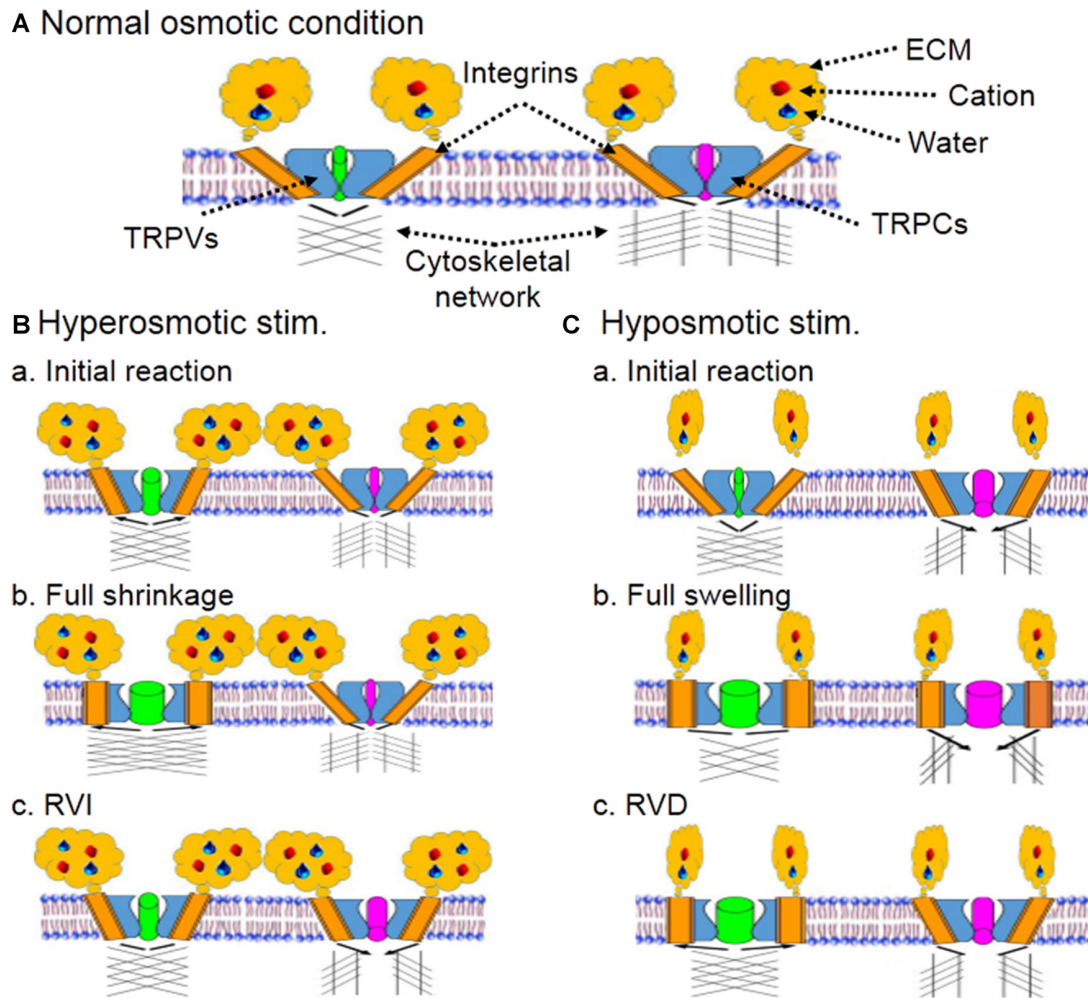


FIGURE 1 | Schematic diagram of hypothetical osmoreceptors and osmosensation. (A) Composition of osmoreceptors and osmosensation at resting condition. Cation along with water binds with extracellular matrix (ECM) that interacts with integrins embedded in plasma membrane and spatially-conjugated with transient receptor potential (TRP) vallinoid (TRPV) and canonical (TRPC) family channels. The ECM-integrin-TRP channel complex could bind to microtubule network directly or through actin filaments. The integrins and cytoskeletal networks connected with TRPVs and TRPCs could be different, which would allow hyperosmotic cell shrinkage and hyposmotic swelling to activate the two families in different manners. **(B)** Hyperosmotic stimulus (stim.). **(Ba)** Initial cellular reactions. The ECM binding with cation and water activates TRPV-associated integrins and the ensuing conformational change of integrins leads to partial opening of TRPVs. However, the integrin subunits binding to TRPCs could be different from that to TRPVs and show no activation during cell shrinkage. **(Bb)** Cellular reactions toward full cell shrinkage. Hyperosmotic environment draws water outflow from intracellular compartment, decreases cell volume and increases the pushing force (black arrows) of cytoskeletal network for the full opening of TRPVs. **(Bc)** Regulatory volume increase (RVI) following full cell shrinkage. Activation of TRPVs triggers oscillatory cytosolic Ca^{2+} increase, activates mitogen-activated kinases, and installs more aquaporins on the membrane, thereby leading to a RVI, which could reduce microtubule-associated TRPV opening but cause partial opening of TRPCs through relative volumic increase that yields a pulling force between TRPCs and cytoskeletal network. As a result, hyperosmotic activation of osmosensory neurons occurs. **(C)** Hyposmotic stimulus. **(Ca)** Initial cellular reactions. Hyposmotic environment decreases the activity of integrins by uncoupling ECM with integrins but initiates cell swelling, leading to complete inhibition of TRPVs. The swelling and mild membrane tension causes partial activation of TRPCs, which could result from a pulling force (black arrows) of cytoskeletal network. At this stage, weakly increased cytosolic Ca^{2+} through TRPCs could activate K^+ current and thus, inhibition of osmosensory neurons occurs. **(Cb)** Cellular reactions toward full cell swelling. As water increasingly gets into the cells and increases intracellular volume, increased interactions between ECM and TRPV-associated integrins cause activation of TRPVs while further activating TRPCs. As a result, reversal of hyposmotic inhibition occurs. **(Cc)** Regulatory volume decrease (RVD) following full cell swelling. As the swelling of cells proceeds, volume-/stretch-sensitive anion channels are also activated, which leads to RVD and volume reduction. Once the RVD occurs, interactions between microtubule networks and TRPVs also increase while opening of TRPCs is partially decreased. As a result, osmosensory neurons could show prolonged excitation or apoptotic alteration.

Hyperosmotic stress evokes cell shrinkage which could be followed by a regulatory volume increase (RVI) while hyposmotic challenge causes cell swelling before a regulatory

volume decrease (RVD) occurs, which have been shown in cultured neurons (Zhang et al., 2001), astrocytes (Eriksson et al., 1992; Evanko et al., 2004) and hepatocytes

(Mundinger et al., 2012). Hence, we further analyze the contribution of these volume changes to osmosensation.

Change in cell volume is an essential driving force of osmosensation. In neurons, progressive decline in cell volume leads to increase in neuronal activity (**Figures 1Ba,Bb**), and effects of shrinking evoked by mechanical aspiration are quantitatively equivalent to that of hyperosmotic stress in mouse organum vasculosum of lamina terminalis neurons (Ciura et al., 2011). Consistently, cell shrinkage evoked with sucrose or sorbitol can also activate Swiss 3T3 cells (Lunn and Rozengurt, 2004). By contrast, cell swelling or membrane stretch following hyposmotic challenge can also activate TRP channels (**Figures 1Ca,Cb**), such as TRPV2 in freshly isolated cells from mouse aorta (Muraki et al., 2003), TRPV1, TRPV2 and TRPV4 in mouse odontoblasts (Sato et al., 2013), etc. Consistently, TRPC5 channels of sensory neurons can also be activated by intracellular application of steps of positive pressure through the patch pipette in the whole-cell configuration (Gomis et al., 2008). Noteworthy is that transient hyposmotic Ca^{2+} increase (Sánchez and Wilkins, 2004) can activate Ca^{2+} -activated K^+ channels and that results in inhibition of cellular activity (Ohbuchi et al., 2010) before the occurrence of RVD. Thus, cell volume change could account for osmosensation; however, their excitation or inhibition should be controlled by factors other than volume change itself.

The volume change, ion channel activity and cellular signaling process can form a feedback loop. For example, RVD depends on cation influx following membrane tension during hyposmotic cell swelling as shown in astrocytes and kidney cells (Hua et al., 2010). The influx of Ca^{2+} in turn triggers a series of cellular signaling events, such as activation mitogen-activated protein kinases (MAPKs) including c-Jun NH2-terminal kinase, p38 MAPK and extracellular signal-regulated protein kinase 1/2 (Horiguchi et al., 2011; Shi et al., 2011). The last kinase is known to activate TRP channels (Ebner et al., 2006; Dine et al., 2014).

Osmosensation also involves some osmotic/volemic rebalance machineries, such as aquaporin (AQP)4 (Benfenati et al., 2011; Mola et al., 2016) that mediates water transport and volume alteration, volume-/stretch-sensitive anion channels that release organic osmolytes and Cl^- from cytosolic compartment to regain volemic and osmotic balance in swollen cells. Additionally, other membrane transport organelles, such as sodium pumps, Na-K-2Cl cotransporters and sodium-hydrogen exchanges, are also involved in the rebalance of osmolytes across cell membrane (Jia et al., 2016). By changing osmotic gradients, these machineries can sensitize or desensitize the osmoreceptors.

In the CNS, astrocytes are the major target of osmotic disturbance and show remarkable volume changes (Evanko et al., 2004) relative to neurons (Aitken et al., 1998). Importantly, astrocytes can influence neuronal activity through multiple approaches (Wang and Zhu, 2014; Hertz and Chen, 2016; Wang and Parpura, 2016). For instance, β -alanine release from astrocytes (Pasantes-Morales et al., 1994) can inhibit astrocyte GABA transporters and thus inhibits VP secretion through increasing extracellular GABA (Wang et al., 2013a); coordinated D-serine metabolism between astrocytes and magnocellular neurons along with exhaustion of β -alanine and taurine in the

SON can increase NMDA receptor activation, and participate in the recovery of VP neurons from hyposmotic inhibition (Wang et al., 2013b). Thus, astrocytes are important osmosensory cells not only by co-expression of TRPV channels and AQP4 (Benfenati et al., 2011; Mola et al., 2016; Iuso and Križaj, 2016) but also by astrocytic plasticity-associated neuronal effects (Hou et al., 2016; Jia et al., 2016).

HYDRATION STATE OF EXTRACELLULAR MATRIX (ECM)

Hydrated gel on plasma membrane is the first cellular component to be influenced by hydromineral disturbance. It has been reported that remodeling of glycocalyx can change membrane rafts and the actin cytoskeleton (Zeng and Tarbell, 2014) that in turn modulates TRP channel activity (Prager-Khoutorsky and Bourque, 2015). This hydrated gel has strong binding capacity with cation and water, and thus contributes to osmotic regulation. On cell surface of the SON, there are also abundant polysaccharide-enriched neural cell adhesion molecule and the glycoprotein, tenascin-C (Pierre et al., 2001). These extracellular matrix (ECM) can decrease inter-membrane adhesion mediated by neural cell adhesion molecule (Loers et al., 2014) and thus should share the common effects of ECM on other tissues in osmosensation, such as endothelial cells (Tarbell et al., 2005), cartilage cells (Likhitpanichkul et al., 2005), hepatocytes (Mundinger et al., 2012), kidney cells (Shestopalova et al., 2008) and neurons (Arranz et al., 2014).

We propose that during hyperosmotic stress, ECM binds with excessive cation, buffers osmotic stress, reduces membrane stretch (**Figure 1Ba**) while accelerating water efflux to reduce intracellular volume (**Figure 1Bb**), and thus increases the interactions between integrin, actin filament and microtubules (Sims et al., 1992; Martinac, 2014). During hyposmotic challenges, ECM binds with fewer cation and water, which allows excessive water to get into the cell and increases intracellular volume, and thus decreases the pushing/opening force of microtubules on TRPV channels (Prager-Khoutorsky and Bourque, 2015), resulting in stretch-inactivation of TRPVs (**Figure 1Ca**). These proposals are supported by the finding that in hyaluronan synthase HAS3^{-/-} slices, spontaneous epileptiform activity in the CA1 hippocampus was blocked by hyperosmotic stress (Arranz et al., 2014). This is likely because excessive cation introduced by the hyperosmotic solution, not bound to ECM in HAS3^{-/-} slices, quickly diffuses into intracellular space through the Na-K-2Cl cotransporter 2 (Konopacka et al., 2015) and other osmolyte transport organelles (Jia et al., 2016), and thus increase cellular volume and interrupt the interactions between TRPV channels and cytoskeletal elements. In the same experiment, hyposmotic solution induced spontaneous epileptiform activity in the CA1 hippocampus, which was blocked upon returning to normosmotic solution (Arranz et al., 2014). The hyposmotic reaction could result from fast water influx and swelling-evoked RVD, while the blocking effect of normosmotic solution could be due to osmotic restoration of cell volume, similar to the effect of hyperosmotic solution (Arranz et al., 2014).

Considering the involvement of other TRP channels in osmosensation, we further propose that hyposmotic volume increase could increase the pulling force of microtubules on TRPC channels that could increasingly open TRPC channels (**Figure 1Cb**) following the increases in membrane stretch (Gomis et al., 2008) and compensate for the reduced excitatory effects of closing TRPV channels, resulting in hyposmotic activation of osmosensory cells.

Hydration state of ECM could also function through altering extracellular space (ECS). Without ECM binding in hyaluronan synthase HAS3^{-/-} slices, hyperosmotic stress increased ECS in brain slices by attracting more water efflux in exchange of ion influx, while hyposmotic challenge reduced ECS by promoting more water influx (Arranz et al., 2014). The increased ECS also decreases cellular apposition and reduces inter-neuronal interactions in the CA1 hippocampus, which is a condition known to reduce VP neuronal activity in the SON; the increased cellular apposition due to reduced ECS can increase junctional coupling and mutually excitatory influence between adjacent cells (Tweedle and Hatton, 1977; Tweedle et al., 1993), thereby increasing neuronal activity and their synchronization (Hatton, 1990; Theodosis et al., 2008).

INTEGRINS

In extracellular to intracellular signal transduction, integrins play a critical role as an ECM receptor in whole body including the hypothalamus (Ablooglu et al., 2007; Gao et al., 2007) and the SON (Seidah et al., 1991). It has been reported that TRPV1 receptor is co-expressed with integrin subunits that bind fibronectin (Jeske et al., 2009); GM1 ganglioside binds to TRPC5 by the mediation of integrin (Wu et al., 2007). Thus, integrins are the mediator of ECM regulation of TRP channel activity in osmosensation.

It is known that active integrin complexes are specifically enriched for proteins associated with microtubule-based functions; active integrins establish an environment to stabilize microtubules at the cell periphery (Byron et al., 2015). Moreover, the activation of membrane integrins elicits actin cytoskeleton reorganization (Jin et al., 2011) via integrin-linked kinase (O'Meara et al., 2013). Thus, osmotic conformational alterations of integrins could change TRP channel activity.

This proposal is supported by the following evidence. Silencing integrin $\beta 1$ expression reduces RVD of the adherent cells (Sørensen et al., 2015). Interrupting an integrin $\beta 3$ /Src/CIC-3 signaling pathway influences the hyposmotic activation of volume-regulated chloride channels (Zeng et al., 2014). Deletion of the integrin $\alpha 1$ subunit inhibited the intracellular Ca^{2+} transients of chondrocytes to hyposmotic stress *ex vivo* and *in vitro* (Jablonski et al., 2014). Thus, integrins are the key components in relaying ECM signals under various osmotic conditions.

Integrin involvement in osmosensation is related to the following approaches (**Figure 1A**). (1) Contacts between ECM and integrin are a prerequisite of osmotic cellular responses, such as hyperosmotic enhancement of spontaneous quantal release of

neurotransmitter (Kashani et al., 2001) and glutamine uptake in response to hyposmotic and hyperosmotic exposure (Low and Taylor, 1998). (2) There are direct interactions between TRPV4, $\alpha 2$ integrin and the Src tyrosine kinase Lyn (Alessandri-Haber et al., 2008) and co-expression of the TRPV1 receptor with integrin subunits that bind fibronectin in sensory neurons (Jeske et al., 2009). (3) Activated integrins could stabilize microtubules at the cell periphery (Byron et al., 2015) to form an integrin-TRPV-microtubule complex (Goswami et al., 2010) through eliciting actin cytoskeleton reorganization (Jin et al., 2011).

Under different osmotic conditions, signaling process modulated by integrin-ECM contacts is either activated or inhibited in a time-dependent manner. For example, upon hyposmotic stimulation, more water retains in the interstitial tissues at the initial stage, which gives rise to a disjoining force and places the integrin-ECM bonds under mechanical tension, thus accelerating their dissociation and inactivating integrins (Halperin and Kröger, 2012). Once cell swelling occurs, the increased cell volume pushes membrane out-bound expansion and leads to increases in integrin/ECM contacts, which causes the activation of integrins as shown in the volume regulation of skeletal muscles (Low and Taylor, 1998) and hepatocytes (Mundinger et al., 2012). Resultantly, cells experience an initial inhibition and subsequent activation.

CONCLUDING REMARKS

Osmosensation is a complex cellular process involving coordinated interactions between extracellular and intracellular processes, particularly involving ECM, integrins, actin filament, microtubule and TRP channels. (1) Increased ECM-integrin interactions during hyperosmotic stress could directly activate TRPV channels by conformational change-associated “gate” opening through actin reorganization (Jin et al., 2011). This external signal could work coordinately with increased interactions between microtubule network and TRP channels during hyperosmotic shrinkage (Prager-Khoutorsky and Bourque, 2015) to push TRP channel opening (**Figure 1B**). (2) Prolonged hyperosmotic stress promotes VP gene transcription and translation and RVI (**Figure 1Bc**) while maintaining ECM-integrin-associated gate opening. (3) Early hyposmotic tension causes mild conformational change in integrin-TRP complex, inhibition of TRPV channels by their uncoupling with microtubule network and the “leakage” of these channels (Muraki et al., 2003; Sato et al., 2013; Jo et al., 2016) including ATP. ATP activation of purine-associated opening of TRPC and other TRP channels (Goel et al., 2007; Soya et al., 2014) can quickly reverse this initial inhibition and lead to cytosolic Ca^{2+} increase. The opening of TRPC channels is likely achieved by a pulling force exerted by actin-microtubule network (**Figure 1C**). (4) Further cellular swelling increases ECM-integrin interaction and activation of TRPVs while triggering RVD which further strengthens the activation of TRPVs even activity of TRPCs could be reduced (**Figure 1Cc**). Certainly, the buffer effects of ion-transporting organelles,

AQPs, and volume-/stretch-sensitive anion channels on osmotic gradients can modulate the osmosensation by changing the osmotic gradients across the membrane. Moreover, hyposmotic effects on cell volume (Lohr and Yohe, 2000) and VP secretion (Yagil and Sladek, 1990) are largely rate-dependent, and thus the large buffering capacity of the body can account for the resistance of brain to osmotic maladaptation (Go, 1997; Verbalis, 2010).

Further studies should address the structural and functional relationship between ECM-integrin bonding and cytoskeletal elements as well as the temporal association between TRP channel activation and cell volume change during osmotic stimuli in osmosensory neurons. Moreover, the relationship between instant VP release from pre-existing VP pool and delayed transcription of VP gene (Arima et al., 1999, 2010) should be clarified. Worth noting is also that the osmotic responses of SON cells (Tweedle and Hatton, 1977) are much faster and stronger than PVN cells (Gregory et al., 1980). It is interesting to further explore potential differences in their

histology and the functioning of the osmoreceptors. Lastly, interactions between local and systemic osmotic factors should be clarified as well. Answering these challenging questions would shed more light on a variety of medical and biological etiologies that are currently not well understood yet.

AUTHOR CONTRIBUTIONS

RJ, DC and SCW wrote different sections of the first draft; DL participated in the revision; Y-FW designed the review and made final revision.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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