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Review

The neurobiology of thirst and salt appetite

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SUMMARY

The first act of life was the capture of water within a cell membrane,[1] and maintaining fluid homeostasis is critical for the survival of most organisms. In this review, we discuss the neural mechanisms that drive animals to seek out and consume water and salt. We discuss the cellular and molecular mechanisms for sensing imbalances in blood osmolality, volume, and sodium content; how this information is integrated in the brain to produce thirst and salt appetite; and how these motivational drives are rapidly quenched by the ingestion of water and salt. We also highlight some of the gaps in our current understanding of the fluid homeostasis system, including the molecular identity of the key sensors that detect many fluid imbalances, as well as the mechanisms that control drinking in the absence of physiologic deficit, such as during meals.

INTRODUCTION

All biological processes take place in a solution of water and salt,[2] and maintaining the appropriate balance of these substances is essential for most forms of life. One reason is that many cells are more permeable to water than salt and, as a result, swell or shrink when the extracellular salt concentration changes, disrupting their structural integrity. A second reason is that many biological processes, such as the excitability of neurons, are finely tuned to specific concentrations of ions inside or outside of the cell. For these and other reasons, animals must regulate their internal water and salt content through a combination of autonomic and behavioral mechanisms.

In this review, we focus on the neural mechanisms that motivate animals to find and consume water (thirst) and sodium (salt appetite). Aside from their physiologic importance, these two appetites are unique in that they are nutrient-specific, innate, and reliably elicited following deprivation. We provide first an overview of basic concepts that describe the fluid homeostasis system in mammals. We then discuss the neural mechanisms that govern thirst, describing how the nervous system detects dehydration and generates thirst, and then how it monitors water ingestion to quench thirst. We next discuss the analogous mechanisms that regulate salt appetite. Finally, we summarize some of the outstanding questions in this field.

INTRODUCTION TO FLUID HOMEOSTASIS

Autonomic and behavioral control of fluid homeostasis

There are two basic responses that defend against fluid imbalance (Figure 1). The first is the regulation of the rate of water and salt loss by the kidney. Water loss by the kidney is controlled primarily by the hormone vasopressin (AVP), which is released from neuroendocrine cells in the hypothalamus in response to dehydration and acts on the kidney to concentrate the urine, thereby conserving water. Salt retention by the kidney, on the other hand, is controlled by a collection of hormones that include AVP, aldosterone, and angiotensin.

While the kidney can help conserve water and salt, there are inevitable losses that result from respiration, excretion, and sweating. Therefore, animals must ingest water and salt at regular intervals to maintain fluid balance over the long term. For the remainder of the review, we focus on these ingestive processes, but there is a considerable overlap in the mechanisms that trigger the autonomic and behavioral responses to dehydration.

Intracellular and extracellular dehydration

There are two types of dehydration that trigger drinking (Figure 2A). Intracellular dehydration occurs when there is an increase in the osmolality of extracellular fluids, resulting in osmotic pressure that draws water out of cells.[3,4,5] In most animals, the blood and interstitial fluids are thought to be in rapid equilibrium, and so intracellular dehydration can be estimated by measuring the osmolality of the blood. Experimentally, blood osmolality can be increased by injecting animals with a concentrated solute, such as sodium chloride or mannitol. In everyday life, humans experience thirst in response to increases in blood osmolality as small as 1%–3%.[6,7]

Extracellular dehydration occurs when there is a decrease in the volume of extracellular fluids (hypovolemia). Pure hypovolemia can be triggered by blood loss, such as during a hemorrhage. Experimentally, hypovolemia is usually produced by subcutaneous injection of a colloid, such as polyethylene glycol (PEG), which produces an edema at the injection site and draws water out of the extracellular fluid.[20] This hypovolemia is detected in peripheral tissues as a decrease in blood pressure, which is then relayed to the brain by a combination of hormonal and neural signals. Of note, whereas intracellular dehydration

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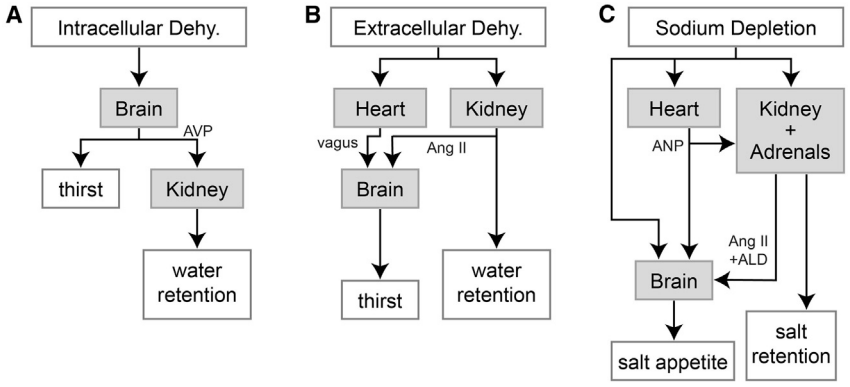

Figure 1. Major systems involved in fluid balance

(A) Intracellular dehydration (dehy.) is sensed by circumventricular organs in the brain, which generates thirst and increases kidney water retention via release of AVP.

(B) Extracellular dehydration is sensed by mechanosensors in the cardiovascular system (primarily heart and aortic baroreceptors) and the kidney. Kidney mechanosensation leads to increased levels of angiotensin II (Ang II), which increases water retention by acting on the kidney and increases thirst by acting on the brain. Mechanosensation in the cardiovascular system is primarily relayed to the brain via the vagus nerve to generate thirst.

(C) Sodium depletion can be sensed by cells in the brain, heart, kidney, and adrenal glands. Osmosensation by the kidney and adrenal glands leads to increased Ang II and aldosterone (ALD), which increase kidney salt retention and the activity of salt appetite circuits in the brain. Mechanosensation by heart myocytes leads to the release of atrial natriuretic peptide (ANP), which acts on both the brain and adrenal glands to generate salt appetite.

can be corrected by consuming water alone, extracellular dehydration requires ingestion of both water and salt to restore blood volume at the appropriate osmolality and sodium concentration.

Water deprivation normally produces both intracellular and extracellular dehydration. For example, there is a 4% increase in blood osmolality and a 13% decrease in blood volume after 24-h water deprivation in the dog.[21] By selectively blocking one of these two stimuli, it has been shown that about 70% of dehydration-induced drinking is driven by the increase in blood osmolality, whereas the remaining 30% is attributable to the decrease in blood volume.[22–24]

Hypovolemia stimulates both thirst and salt appetite. However, salt appetite can also be triggered by a deficiency in sodium (hyponatremia), independent of any deficit in blood volume. Experimentally, this can be produced by combining a sodium-deficient diet with drugs that prevent sodium retention by the kidney, such as furosemide. Of note, the salt appetite triggered by this regimen drives animals to consume concentrations of salt that would otherwise be aversive (e.g., seawater) and is distinct from the everyday experience that low concentrations of dietary sodium are appetitive.

Fluid homeostasis involves both pre-systemic and systemic signals

There are two classes of signals that regulate fluid homeostasis. Systemic signals are those associated with the current state of the blood and interstitial fluids, such as blood osmolality and volume. Pre-systemic signals are those that arise prior to fluid absorption into the blood and include orosensory and gastrointestinal feedback. The distinction between these two types of signals is important because, while thirst and salt appetite are often triggered by changes in the blood, they are quenched (satiated) during ingestion primarily by pre-systemic signals from the mouth and gut.

In some cases, pre-systemic signals can also drive thirst. One example is drinking during meals (i.e., prandial drinking), which is important for facilitating the digestion of solid food and preventing later dehydration by ingested solutes. This anticipatory drinking often occurs before there is any change in blood osmolality and is thought to anticipate future deficits. Another example of anticipatory drinking is circadian drinking, which refers to the fact that animals drink more during the subjective day and also may drink in anticipation of fluid needs during sleep.[25–27]

Balancing fluid needs

Fluid balance is tightly connected to other bodily needs, and drinking behavior can be modulated by competing homeostatic demands. A prominent example is thermoregulation, since many mechanisms for heat defense cause either the loss of water (e.g., panting, sweating, or saliva spreading) or changes in local blood pressure (e.g., vasodilation). For this reason, heat exposure promotes drinking and, conversely, dehydration impairs the defense of body temperature.[28] Another example is seen in pregnancy and lactation, which result in a decrease in the defended blood osmolality and are associated with increased thirst and water retention.[29,30]

The evolution and diversity of fluid homeostasis mechanisms

Most vertebrates maintain an internal osmolality around 300–350 mOsm. This fluid composition is thought to replicate the intertidal brackish water environment in which vertebrates first evolved.[9,31,32] For these early vertebrate fish, fluid balance was likely controlled by purely autonomic mechanisms involving brainstem circuits, and they continuously drank the saltwater in which they lived and excreted or captured extra osmolytes via their gills and kidneys.[9–11] Once bony fish evolved and began to inhabit freshwater, neural circuitry evolved to start and stop drinking based on internal signals.[14,33–35] Amphibians were the first vertebrates to move onto land, but they are able to absorb most of their water through the skin and do not drink in response to deprivation.[36] It was not until early terrestrial vertebrates (e.g., reptiles) moved entirely onto land that they had to locate sources of water, and it is in these animals that forebrain circuits specialized for water seeking and consumption are observed (Figure 2C).[12,13]

Mammals have evolved to occupy almost every environment on earth, and this was accompanied by the development of diverse strategies for maintaining fluid balance. For example, desert-living mammals such as the kangaroo rat can survive indefinitely without drinking due to a greatly increased ability to concentrate their urine and efficiently excrete salt[37] as well as

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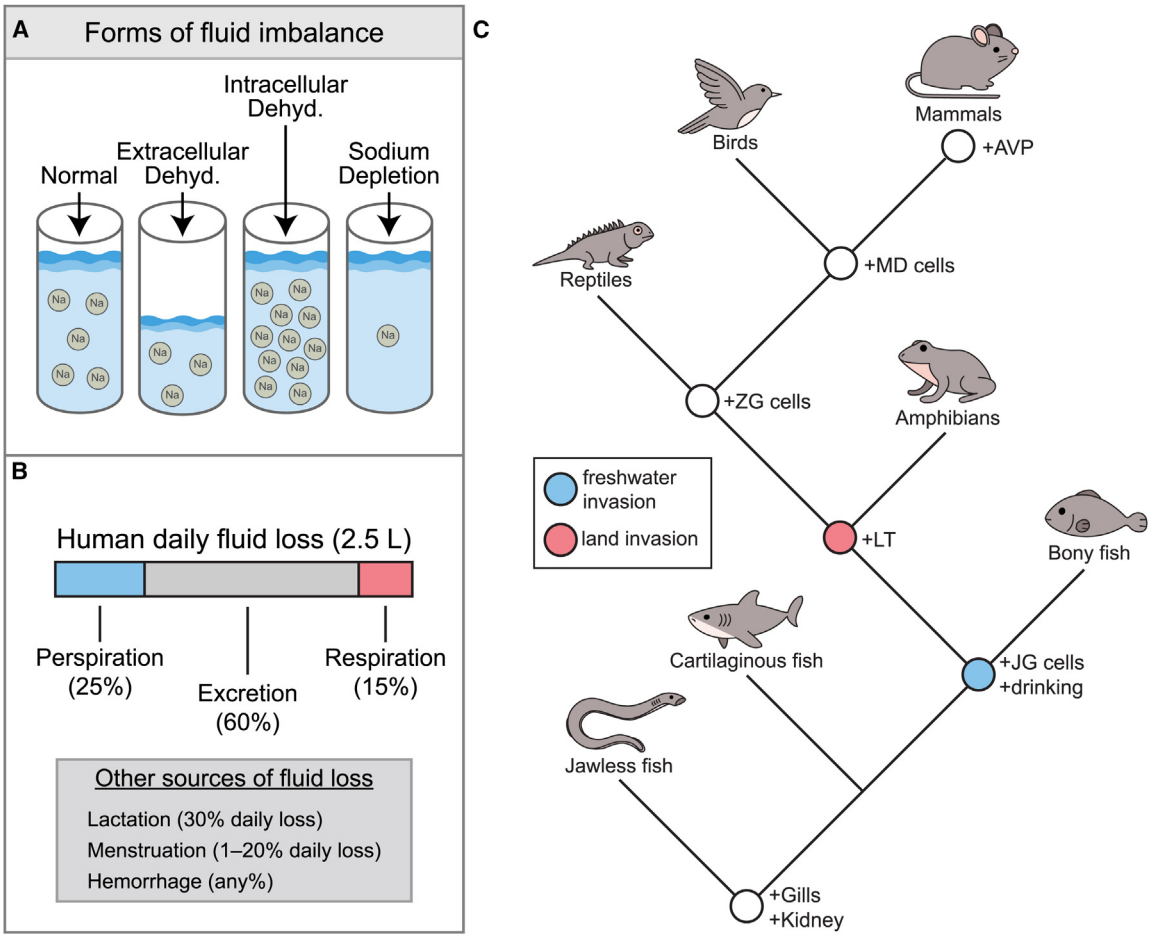

Figure 2. Foundation of mammalian fluid balance

(A) The main forms of fluid imbalances occur when fluid storage deviates in volume or sodium content. Extracellular dehydration (or hypovolemia) occurs when fluid volume decreases. Intracellular dehydration (or hypernatremia) occurs when sodium content rises. Sodium depletion (or hyponatremia) occurs when sodium content falls.

(B) Humans lose ~18% of their extracellular volume daily, largely through urination but also through defecation, perspiration, and respiration.[3,8] These sources of daily loss largely lead to both intracellular and extracellular dehydration.

(C) Simplified vertebrate phylogenetic tree showing timeline for major adaptations impacting thirst and salt appetite in mammals. The first controls over fluid balance were the kidney and gills, which evolved early in basal vertebrates.[9–13] Later, bony fish developed juxtaglomerular (JG) cells and with them a basic renin-angiotensin system (RAS), as well as basic hindbrain circuitry to control drinking.[12,14,15] The lamina terminalis (LT) thirst circuit evolved in amphibians.[16] The system controlling salt appetite evolved first in reptiles with the development of aldosterone-releasing zona glomerulosa (ZG) cells.[17] The kidney develops further in warm-blooded animals and now includes salt-sensitive macula densa (MD) cells.[18] Finally, in mammals, we see the development of the potent antidiuretic hormone AVP.[19]

the ability to recognize and consume foods rich in water.[38] On the opposite end of the spectrum, marine mammals such as seals get most of their water from food, as they cannot drink salt water without becoming dehydrated.[39] Of note, while all land mammals are capable of drinking water, many rely on food for most of their water in the wild. For example, rabbits will avoid drinking when foods rich in water are readily available, and as a result, rabbits in the wild consume little or no water up to 9 months of the year. [40]

THIRST

The core neural circuit driving thirst consists of three interconnected nuclei located in the vicinity of the third ventricle (Figure 3). These structures are collectively known as the lamina terminalis (LT) and consist of the subfornical organ (SFO), the organum vasculosom of the lamina terminalis (OVLT), and the median preoptic nucleus (MnPO). The SFO and OVLT are situated outside the blood-brain barrier and contain primary sensory neurons that are directly activated by increases in blood osmolality or the hormone angiotensin II (AngII), which signals decreases in blood volume (discussed below). These SFO and OVLT interoceptors project to second-order neurons in the MnPO, which functions as an integratory site and relays this information to downstream structures that drive behavioral and neuroendocrine responses, including cells in the paraventricular nucleus of the hypothalamus (PVH) and the supraoptic nucleus (SON) that produce AVP.

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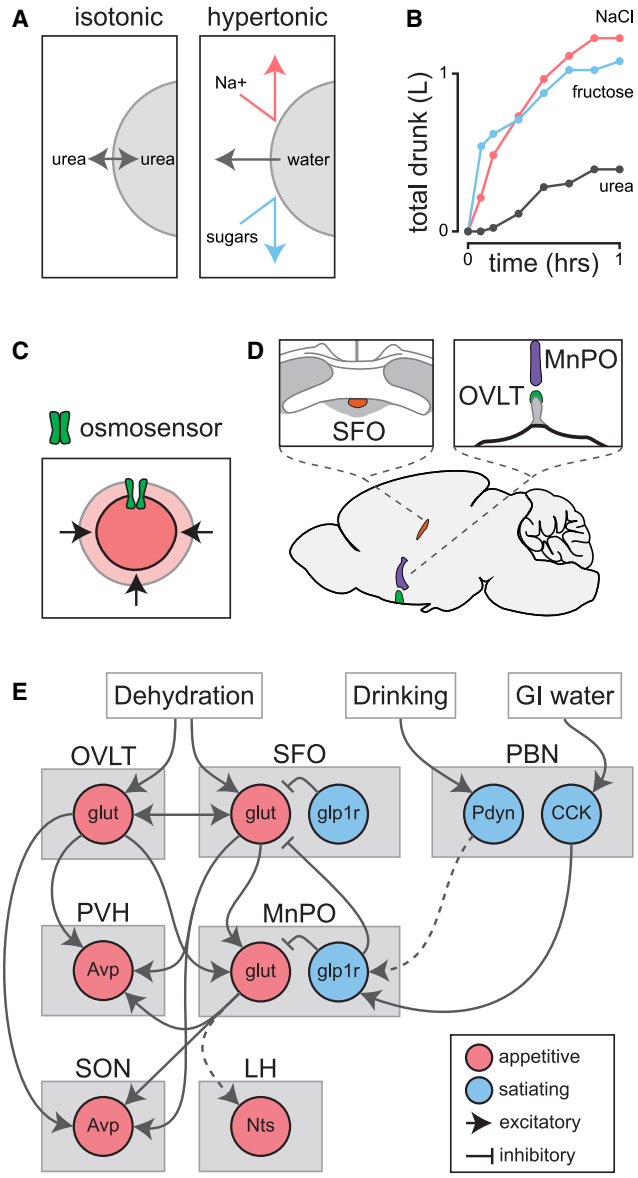

Figure 3. Central thirst circuit

(A) Membrane-permeable urea can increase osmolality without affecting tonicity (left), whereas other osmolytes increase tonicity, leading to cellular dehydration (right).

(B) Figure of cumulative water drunk by goats following intra-carotid injection of equiosmolal solutions (from Olsson[36]), demonstrating that hypertonicity drives thirst.

(C) Central SFO/OVLT osmosensors respond to cell shrinkage caused by hypertonicity.

(D) Location of SFO, OVLT, and their major output nucleus, the MnPO, in the mouse brain.

(E) Simplified diagram of circuitry that generates (red) and satiates (blue) thirst. Dehydration signals (Ang II and Na+) converge on glutamatergic neurons in SFO and OVLT to drive thirst. Drinking or gastrointestinal (GI) sensation of water is relayed to this circuit via the PBN to quench thirst.

In the sections that follow, we discuss first how thirst is generated, describing the cellular and molecular mechanisms for sensing increases blood osmolality and decreases in blood volume, and the detailed circuitry within and beyond the LT that drives water seeking and consumption. We then discuss how thirst is satiated by drinking by pre-systemic signals from the mouth and gut.

Discovery of the role of osmosensing in thirst

In 1937, Alfred Gilman showed that intravenous infusion of NaCl stimulates drinking in dogs, demonstrating for the first time that thirst can be driven by increases in blood osmolality.[41] Later studies localized this effect to the brain by showing that NaCl infusions into the carotid artery, which supplies blood to the brain, were sufficient to stimulate drinking[42] and inhibit urine production,[43] even when delivered at concentrations that do not increase systemic osmolality. Conversely, preventing central dehydration by infusing water into the carotid artery blocked drinking induced by peripheral NaCl, even if peripheral osmolality remained elevated.[44] Thus, the key osmosensors that drive thirst are located in the brain.

The critical role of the hypothalamus in mediating these effects was first demonstrated by Bengt Andersson in the 1950s, who showed that small infusions of hypertonic saline into the medial hypothalamus of goats caused profound drinking (one animal consumed nine liters of water in 1 h[45]). These effects were localized to the LT, and electrical stimulation of this structure caused dramatic drinking and suppression of urine production.[46] Conversely, lesioning of this region resulted in near-complete adipsia and unresponsiveness to carotid salt infusion.[47] This indicated that the key neurons that sense and respond to dehydration are located in the LT. Later work would establish that the key osmosensors reside within two LT subregions: the SFO and OVLT.

Brain regions involved in osmosensing

The OVLT is a primary site that directly senses blood osmolality. In brain slices, 50%–75% of OVLT neurons are activated by increases in extracellular sodium or mannitol,[48–52] and these responses are absent in cells recorded from other brain regions such as hippocampus.[48] These OVLT osmosensors are located within 55 μm of the third ventricle surface[50] and respond to physiologic changes in systemic osmolality (e.g., +2.5 to 10 mM NaCl) with stepwise increases in firing rate.[49,51,52] These *in vitro* findings have been supported by *in vivo* recordings showing that OVLT neurons are strongly activated by intracarotid or intracerebroventricular salt.[51] Moreover, lesioning or silencing of the OVLT reduces drinking and AVP release in response to blood hypertonicity.[53,54]

The SFO also contains many neurons that are activated by increases in extracellular osmolality *in vitro*[55–58] and *in vivo*.[59,60] Compared with the OVLT, the cellular mechanisms involved in SFO osmosensing are less well characterized, and it remains unclear to what extent the SFO activation in response to blood hyperosmolality is mediated by direct sensing in the SFO versus synaptic input from the OVLT. Some studies have found that SFO lesions do not affect drinking in response to blood hyperosmolality,[61] whereas others report deficits after SFO silencing,[62] and these differences may be species-specific.

The MnPO, SON, and PVH all contain neurons that can be activated by hyperosmolality *in vitro*.[63–68] However, the activation of these cells *in vivo* is due primarily to excitatory input from the

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OVLT and SFO rather than direct osmosensing. This is based on the fact that lesioning or silencing of the SFO/OVLT can block the activation of these downstream circuits[69] and also by the fact that some features of thirst are most readily explained if the key osmosensors are outside the blood-brain barrier,[70] which is the case for the SFO and OVLT but not the MnPO, SON, and PVH.

Molecular mechanisms of osmosensing

OVLT and SFO neurons are thought to directly sense changes in blood tonicity via a cation-selective mechanoreceptor activated by cell shrinkage (Figures 3A–3C). The evidence for this includes: (1) hypertonic solutions induce a cation current in OVLT neurons that is not prevented by blocking synaptic inputs and therefore is cell intrinsic[51,52,71]; (2) the activity of OVLT neurons can be bidirectionally modulated *in vitro* by changes in cell size caused by pressure application, independent of any changes in the extracellular solution, indicating that cell shrinkage is a sufficient stimulus[71]; and (3) OVLT neurons undergo a sustained reduction in cell size in response to a hypertonic extracellular solution.[71] This last observation is important because many cells resist shrinkage via a "volume regulatory increase" in solute content,[72] which prevents these cells from sensing changes in blood tonicity by monitoring their size.

The identity of the ion channel(s) that mediate this effect is unresolved, but several candidates have been proposed. Early studies focused on TRPV1 and TRPV4. [52,71,73,74] This was based on the fact that some TRP channels are mechanosensitive and that a homologous channel, Osm9, is required for osmosensation in *C. elegans*.[75] Although initial reports indicated that knockouts of *Trpv1* or *Trpv4* have defects in thirst, AVP release, and LT neuron activation,[52,67,71,74] later studies failed to observe changes in fluid balance when these genes were knocked out alone or combination.[76–78] Some studies have also failed to detect TRPV1 and TRPV4 expression in the LT.[79,80] It is important to note that these channels may modulate fluid balance by mechanisms other than acting as osmosensors in LT neurons. For example, TRPV4 has been proposed to sense hypotonicity[81,82] in spinal afferents that innervate the liver[83] and in glia.[84]

A third channel proposed to be involved in fluid homeostasis is the "NaX channel" (Scn7a). This protein has sequence similarity to traditional voltage-gated sodium channels but is not voltage-gated and instead is activated by increases in extracellular sodium concentration (EC_{50} ~160 mM).[85] Expression of the NaX channel in the brain is restricted to circumventricular organs including the SFO and OVLT and *Scn7a* knockout mice have a distinctive phenotype in which the animals consume excessive salt after fluid deprivation.[86,87] However, responses to dipsogenic stimuli in *Scn7a* knockout mice are generally normal, and there is no evidence that this channel functions as an osmosensor.

Recently, two studies have proposed that TMEM63b functions the LT osmosensor responsible for thirst.[57,58] A role for this gene in osmosensing was first suggested when the calcium channel OSCA1 emerged from an Aradopsis screen for genes required for responses to osmotic stress.[88] OSCA1 is homologous to the TMEM63 family of cation channels in animals, some of which function as mechanosensors.[89] Several observations indicate that TMEM63b specifically is important for osmosensing in SFO neurons, including (1) genetic deletion of *Tmem63b*, either globally or specifically in the SFO, decreases both SFO activation and drinking in response to dipsogenic stimuli, and (2) expression of TMEM63b in heterologous systems, including reconstitution of purified TMEM63b protein in liposomes, results in hyperosmolality-gated currents.[57,58]

The available data support a role for TMEM63b in thirst, but several questions remain. (1) TMEM63b is not expressed in the OVLT in mice,[58] and thus, at least one additional osmosensory mechanism must exist. (2) TMEM63b is expressed in many brain regions that have no apparent role in fluid balance,[90] and so it is unclear how TMEM63b expression confers osmosensitivity to some neurons but not others. Possible explanations include the co-expression of accessory subunits that alter channel properties[91] or specializations in SFO neurons that alter their volume response to hypertonicity. (3) TMEM63b is also activated by hypotonicity[58] and has been proposed to function as a hypoosmolality sensor in the inner ear.[92] It is unclear how the same channel can be a sensor for both hypo- and hyperosmolality. (4) Knockout of *Tmem63b* reduces SFO neuron activity at baseline[57,58] (i.e., in a isotonic solution). Thus, some of the behavioral effects of *Tmem63b* knockout could be due to a general reduction in excitability as opposed to a specific impairment in osmosensing. Despite these open questions, TMEM63b appears to be a promising candidate to represent one of the sensors involved in thirst.

Mechanisms of sensing blood volume

Drops in blood volume, as caused by hemorrhage or fluid deprivation, are a strong stimulus for thirst independent from changes in osmolality.[93] The SFO is thought to be the main site where changes in blood volume are integrated to drive thirst. This is mediated by two kinds of afferent signals of hypovolemia, one mediated by the hormone AngII and the other mediated by neural signals from peripheral pressure sensors (baroreceptors).

AngII. During hypovolemia, the kidney releases renin, which processes circulating angiotensinogen to generate angiotensin I. This is further processed by angiotensin-converting enzyme to Ang II, which has three effects on fluid balance[94]: (1) it induces a rapid increase in blood pressure; (2) it promotes thirst and, in some contexts, salt appetite; and (3) it stimulates the release of aldosterone from the adrenal cortex, which promotes sodium retention by the kidney. Of note, unlike thirst caused by hyperosmolality,[44] drinking evoked by Ang II cannot be blocked by intracerebral water injection,[95] indicating that these are separable responses. Consistently, genetic deletion of the *Angiotensinogen* gene blocks drinking in response to hypovolemia but not hyperosmolality.[96]

The SFO is the major site where AngII drives drinking.[61,97,98] The SFO expresses a high concentration of AngII receptors (*Agtr1a*), and small amounts of AngII delivered directly to the SFO drive voracious drinking.[97] Moreover, ablation of the SFO blocks drinking in response to AngII and attenuates drinking in response to hypovolemia or hypotension.[61,62,98] The OVLT also contains neurons that are directly activated by AngII and promote thirst,[99–101] but lesions of the OVLT do not usually block drinking in response to hypovolemia,[54,62] suggesting that the SFO is sufficient for this function.

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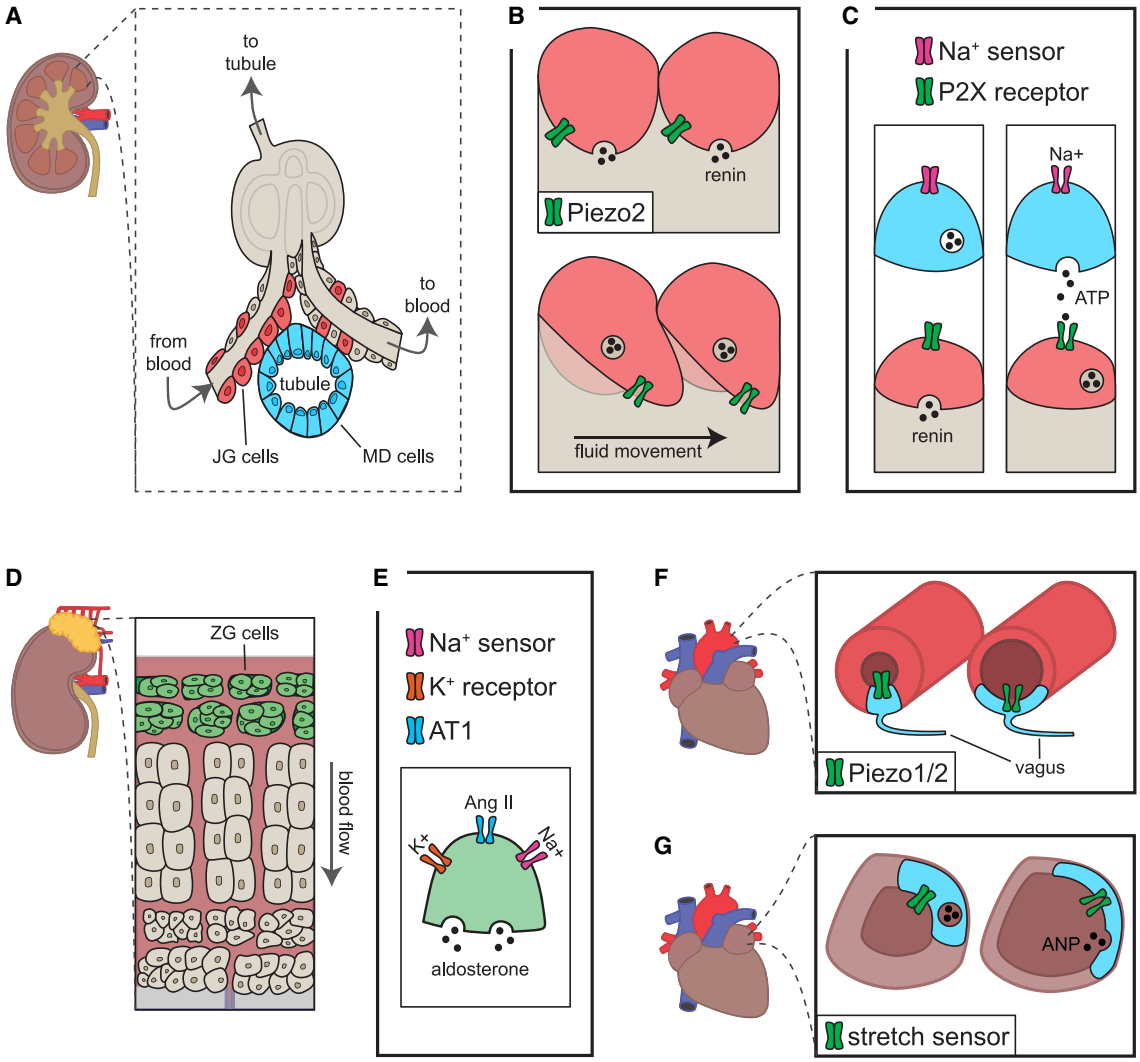

Figure 4. Peripheral sensors that drive thirst and salt appetite

(A) Cross-section of kidney with expanded view showing juxtaglomerular (JG) apparatus. Arrows show afferent and efferent arteriole blood flow past JG cells (in red). Collected filtrate then flows into the convoluted tubule and eventually past macula densa (MD) cells (in blue).
(B) (Top) JG cells release renin at baseline. (Bottom) Arteriole fluid movement causing shear stress opens Piezo2 channels to inhibit renin release.
(C) Baseline JG renin release (left) can also be inhibited by adenosine triphosphate (ATP), which is released by MD cells in response to sodium sensor activity.
(D) Cross-section of adrenal glands, showing location of zona glomerulosa (ZG) cells in outer adrenal cortex.
(E) ZG cells release aldosterone in response to Ang II, low Na+, and high K+ sensors.
(F) Cross-section of aortic arch showing high-pressure baroreceptor Piezo1/2 opening with arterial stretch, activating vagal afferents.
(G) Cross-section of heart atrium showing a myocyte releasing atrial natriuretic peptide (ANP) in response to stretch sensor activity.

Ang II production is dependent on renin release. The kidney releases renin from juxtaglomerular (JG) cells[102] in response to decreasing blood flow[103–105] (Figures 4A and 4B). These cells are intrinsically mechanosensitive, and renin release is inhibited by membrane stretch.[106] Since these JG cells flank blood vessels, it is proposed that they sense blood flow via changes in shear stress on their membrane. A recent preprint[107] found that the mechanosensor Piezo2 is expressed in JG cells and modulates renin release. However, Piezo2 knockout did not abolish renin responses to hypovolemia, implying the existence of a second sensor on JG cells. Similarly, the channel TRPV4 is expressed on JG cells and modulates renin release, but its knockout does not abolish the pressure sensitivity of renin release.[108] While these two channels are in part responsible for JG mechanosensitivity, the existence of other sensors has not been ruled out. Furthermore, it is unclear how TRPV4 and Piezo2, which quickly inactivate in response to membrane stretch, continuously inhibit renin release under prolonged stretch.

Baroreception. Since blood volume loss leads to a drop in blood pressure, hypovolemia can also be indirectly sensed by baroreceptors in peripheral tissues. One set of sensors, known as low-pressure or cardiopulmonary baroreceptors, are found in the atrium and ventricles of the heart and in systemic veins.

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These are stretch receptors that are unloaded when there is a decrease in blood volume, and their activity is thought to tonically inhibit thirst.[109] For example, surgically disrupting venous blood return to the heart, thereby creating hypovolemia in the vicinity of these receptors, is sufficient to stimulate drinking,[110] whereas engaging these receptors by inflating a balloon near the right or left atrium inhibits drinking.[24,111]

A second set of pressure sensors are found at specific sites within large arteries, such as the aortic arch and carotid sinus (Figure 4F). These are known as high-pressure or arterial baroreceptors, and they are primarily involved in reflexes that regulate short-term blood pressure through changes in heart rate. An example is the baroreflex, which is mediated by Piezo1 and Piezo2.[112,113] These arterial baroreceptors can also inhibit thirst when there is a rapid increase in blood pressure. For example, peripherally injected AngII triggers a pressor response that is detected by arterial baroreceptors and counteracts the effect of central AngII on thirst.[114–116] For this reason, peripherally injected AngII does not drive robust drinking in some species, including the mouse. Many of these peripheral blood pressure signals are conveyed to the nucleus of the solitary tract (NTS) by the vagus nerve,[116] but how this is then relayed to the forebrain thirst circuitry has not been described.

Efferent circuits that drive thirst

The SFO, OVLT, and MnPO each contain glutamatergic neurons that are activated by dehydration and promote thirst, and GABAergic neurons that are activated by water ingestion and inhibit thirst. Within these broad classes, RNA sequencing has revealed a diversity of neurochemically distinct cell types,[80,117] but the functional significance of these cell populations is not well understood. Thirst-promoting glutamatergic neurons are labeled by several partially overlapping marker genes, including *Slc17a6*, *Etv1*, *Nos1*, *Adcyap1*, *Rxfp1*, *Agtr1a*, *Pdyn*, and *Nxph4*,[80,100,117–120] whereas thirst-inhibiting GABAergic neurons have been targeted based on expression of *Glp1r* and *Cckbr*.[118,121] In a few cases, stimulation of specific glutamatergic subsets has been shown to differentially drive consumption of pure water versus saline.[80,120] For example, one study found that stimulation of RXFP1 neurons in the SFO/OVLT drives pure water consumption, whereas stimulation of PDYN neurons in the SFO/OVLT neurons drives balanced water and salt intake, suggesting these cell types define distinct nodes for hyperosmotic and hypovolemic thirst in the LT.[80] However, other studies found considerable overlap between the neurons that respond to AngII and those that respond to blood osmolality.[100,101] To understand how these different kinds of thirst are represented in the LT, it will be important to record the *in vivo* dynamics of these SFO and OVLT subtypes in response to different kinds of dipsogenic stimuli.

The SFO and OVLT are bidirectionally connected to each other,[59] suggesting that signals of blood osmolality and volume—which are likely sensed independently in each nucleus—are then shared with each other. The SFO and OVLT relay this information via excitatory projections to the SON and PVH, which drive AVP release, and to the MnPO, which promotes both thirst and AVP release through its own projections to the SON and PVH.[59,100,117,118,122] These dehydration-activated, glutamatergic pathways are counteracted by GABAergic interneurons in the LT that respond to signals of water ingestion from the mouth and gut and drive satiation (discussed in the following section).

The MnPO is the major output nucleus of the LT. Stimulation of MnPO^{Vglut2} axons that innervate either the lateral hypothalamus (LH), paraventricular thalamus (PVT), or PVH is sufficient to drive drinking.[100,117] Among these structures, the LH is strongly implicated in the control of drinking behavior based on the fact that (1) LH lesions cause profound adipsia,[123–125] (2) many LH neurons are activated by water ingestion or changes in fluid balance,[126–129] and (3) stimulation of LH^{Vgat} neurons promotes ingestive behaviors, including water consumption.[130–133] The specific cell types in the LH that are postsynaptic to MnPO^{Vglut2} neurons are unknown, but LH neurons expressing neurotensin are activated by dehydration[128] and promote drinking when stimulated.[132] Like the LH, the PVH contains neurons that are activated during dehydration,[69] but no PVH neurons have been shown to promote thirst. Finally, tracing studies suggest the PVT may be responsible for relaying fluid balance information to the cortex[134,135] (discussed below).

Water seeking is a motivated behavior, and water is a reinforcer that drives learning. Stimulation of thirst-promoting neurons in the SFO, OVLT, or MnPO is aversive, and animals will perform work (e.g., lever-press) to stop stimulation of these cells.[100,117,136] This suggests that an important mechanism by which the LT drives motivation and learning is by linking bodily dehydration to an aversive state, which is then relieved by water ingestion (i.e., negative reinforcement). Human imaging studies have shown that water deprivation causes strong activation of parts of cingulate, insular, and prefrontal cortices, including regions linked to the perception of pain, and this cortical activation is thought to give rise to the conscious sensation of thirst and its quenching.[137–139] These brain regions are also important for making "interoceptive predictions" that anticipate how water ingestion will alter fluid balance in the future,[140] and their manipulation can alter fluid ingestion.[141–143]

In addition to providing an aversive drive, thirst increases the incentive salience of water cues. This effect likely involves the midbrain dopamine system, since either dehydration or virtual thirst caused by SFO stimulation is sufficient to increase phasic dopamine release in the nucleus accumbens in response to water cues.[144] Midbrain dopamine neurons are also activated, on a slower scale, by bodily rehydration, and this delayed activation is important for learning about flavors associated with foods and fluids that are rehydrating.[127] Finally, thirst also enhances the hedonic pleasure of water ingestion, a phenomenon known as allesthesia.[145,146] One site involved in allesthesia for water may be the peri-locus coeruleus (periLC), which contains neurons that are modulated by water ingestion and influence fluid preference.[147] It is important to note, however, that high-density neural recordings have revealed widely distributed changes in neural activity in response to dehydration and drinking,[148] suggesting that many brain regions contribute to the motivational effects of water deprivation.

Quenching thirst

There is a significant delay between the ingestion of water and its full absorption into the blood (e.g., 30–60 min in humans[149]). For this reason, animals must anticipate how drinking will alter the blood in the future and meter their ingestion accordingly. This

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is achieved by two classes of anticipatory signals: those arising from the oropharynx, which report primarily on fluid volume, and those arising from the GI tract, which also contain information about fluid osmolality.

Oropharyngeal signals of volume

Early experiments revealed that thirsty dogs would drink all the water necessary to replace their fluid deficit in as little as 2 min.[150,151] Moreover, when this ingested water was allowed to drain out of the esophagus (and therefore never absorbed), this rapid metering of ingestion remained intact, except that the animals would reinitiate drinking after a variable delay of several minutes. On the basis of these observations, Roland Bellows hypothesized in 1938 that there are "two factors" involved in the satiation of thirst[151]: a rapid but temporary signal arising from the oropharynx and a delayed, more durable signal arising from elsewhere in the body.

Many subsequent studies have confirmed that the detection of water ingestion in the mouth and throat rapidly quenches thirst and reduces AVP release prior to any change in blood osmolality.[149,152–157] Importantly, this oropharyngeal signal is transmitted to and inhibits the same neural circuits in the forebrain that are directly activated by systemic dehydration.[59,117,158] For example, SFO^{Vglut2} neurons are progressively inhibited during drinking in a manner that tracks the volume of water that passes through the oral cavity.[59] Similar dynamics are observed in downstream $MnPO^{Vglut2}$ neurons[117] and SON^{AVP} neurons.[158,159] Drinking stops at approximately the point when the activity of SFO^{Vglut2} and $MnPO^{Vglut2}$ neurons returns to their pre-deprivation baseline,[59,117] and satiation is delayed if this inhibition is prevented by artificial stimulation. This suggests that animals meter their fluid ingestion by comparing two signals that converge on the LT: an excitatory signal of systemic dehydration that arises from the blood and an inhibitory signal of fluid ingestion that arises from the oropharynx.

The detection of water in the oropharynx involves multiple sensory modalities. One component is temperature, which is supported by the fact that cold fluids are more satiating,[146,160–163] and indeed oral cooling alone (without water ingestion) is rewarding for thirsty rodents[164] and reduces AVP levels in humans.[165] Oral cooling also rapidly inhibits thirst-promoting SFO^{Vglut2} neurons.[59] This phenomenon has been attributed to the fact that water, even at room temperature, tends to cool the oral cavity when drunk, and therefore, oral cooling provides a signal of water ingestion. In addition, temperature-independent responses to water can be observed throughout the taste pathway,[166] but many of these responses are conditional on context (i.e., water is sensed as the removal of other tastants), and it has been argued that this is poorly suited to track the volume of water consumed.[109] While one study found that thirsty animals would perform optogenetic self-stimulation of acid-sensing taste cells[167] and suggested this pathway could be involved in oral detection of water, this finding was not replicated in a subsequent study.[168] Aside from taste and temperature, it is plausible that a mechanosensory signal related to water volume or even a motor signal related to swallowing contributes to thirst satiation. Clarifying the precise nature of the orosensory stimuli and afferent pathways that drive thirst quenching would be an important advance in this field.

Sensory afferents innervating the mouth and throat converge on small number of nuclei in the hindbrain. Among these, the parabrachial nucleus (PBN) contains three cell types—one expressing oxytocin receptor (OXTR),[169–171] one expressing prodynorphin (PDYN),[172] and a third expressing cholecystokinin (CCK)[173]—that may receive oropharyngeal signals involved in quenching thirst. The first two cell types are both rapidly activated by water ingestion, and their artificial stimulation inhibits further drinking.[169–172] The activation of OXTR neurons is specific to water,[169] whereas PDYN neurons respond more generally to fluid ingestion and signals of mechanical stretch.[172] Importantly, both of these glutamatergic cell types project to the MnPO, where they may activate GABAergic $MnPO^{GLP1R}$ neurons that are critical for thirst satiation.[118] These $MnPO^{GLP1R}$ neurons directly inhibit neighboring $MnPO^{Vglut2}$ and SFO^{Vglut2} neurons, and their stimulation inhibits drinking, whereas their silencing delays thirst satiation.[118] Moreover, a subset of these $MnPO^{GLP1R}$ neurons are activated by water ingestion in a manner time-locked to its passage through the mouth.[118,173,174] This suggests that the oropharynx → PBN → MnPO pathway is a core circuit involved in thirst quenching, although many details remain to be elucidated.

Gastrointestinal signals of osmolality

The role of oropharyngeal signals in quenching thirst is primarily to track the volume of ingested fluids, whereas the osmolality of these fluids is first measured in the GI tract. Osmosensing in the gut is important because ingestion of hypertonic solutions can activate the same thirst-quenching pathways in the oropharynx that respond to water. Since the ultimate effect of hypertonic solutions is to increase dehydration, a second post-ingestive signal is needed.

The existence of an osmosensory signal from the gut is supported by the fact that infusion of water into the stomach or duodenum can quench thirst and inhibit AVP release before there is any change in blood osmolality.[175,176] Infusion of hypertonic saline has the opposite effect, stimulating AVP release and increasing water consumption.[156,175,177–179] This gastrointestinal (GI) osmosensory signal is transmitted to thirst circuits in the LT with a delay of 20–60 s from the onset of drinking or infusion of fluids into the stomach.[59,174,180] For example, when thirsty mice drink hypertonic saline, SFO^{Vglut2} neurons are initially inhibited but then show a characteristic rebound in activity after ~60 s.[59,174] This two-stage response is attributed to a rapid, inhibitory signal from the oropharynx, which reflects the volume of fluid ingested, followed by a delayed, excitatory signal from gut, which reflects its hypertonicity. When the ingested solution is water, these oropharygneal and GI signals are aligned, and thirst neurons are durably inhibited.

Osmosensing in the gut could occur pre-absorptively in the lumen of the intestine or post-absorptively in the portal circulation. The most is known about osmosensing in the hepatic portal area. Infusion of hypertonic saline into the portal vein, in small amounts that do not affect systemic osmolality, stimulates AVP release and activates neuroendocrine cells in the SON, whereas infusion of small amounts of water has the opposite effect.[181,182] This portal osmosensing is mediated, in part, by the hepatic branch of vagus nerve.[176,179,183] In the mouse, the activation of hypotonic-sensitive vagal afferents has been proposed to

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involve local vasoactive intestinal peptide (VIP) release,[183] but this mechanism cannot explain all portal osmosensation. There is also evidence that hepatic spinal afferents contribute to gut osmosensing, but little is known about the nature of these cells or their functional relationship to vagal pathways.

Vagal and spinal signals from the gut are relayed to several brainstem nuclei involved in ingestive behavior, including the NTS, area postrema (AP), and the PBN. Among these, PBN^{CCK} neurons are activated with dynamics consistent with GI feedback and project to the MnPO.[173] Stimulation of this PBN^{CCK} projection inhibits water intake and selectively activates the subset of $MnPO^{VGAT}$ neurons that are naturally activated by GI signals of water ingestion,[173] indicating that PBN^{CCK} neurons can convey GI fluid signals to $MnPO^{VGAT}$ neurons. There are also GABAergic neurons in the SFO that are activated by intragastric water and inhibit drinking.[180]

SALT APPETITE

Mammals have developed autonomic and behavioral mechanisms to defend blood sodium levels. The two major hormones involved in salt appetite are aldosterone and angiotensin, which increase in response to sodium deficiency and have two functions: to promote sodium retention by the kidney and stimulate salt appetite by acting on neurons in the brain.

History of salt appetite

The kidney efficiently retains sodium, such that sodium deficiency is rare under normal conditions. For example, rats can go over a month without dietary sodium before experiencing significant deficiency.[184] However, when sodium depleted, animals exhibit a remarkable salt appetite in which they will voraciously consume high salt solutions that would otherwise be aversive.[185] This response is completely innate and does not require prior experience with salt deficiency or the effects of subsequent sodium consumption.

The first demonstration of salt appetite was achieved by removing the adrenal glands, which results in loss of aldosterone and thereby prevents sodium retention by the kidneys.[186] The resultant salt deficiency causes increased production of AngII, which in turn acts on the brain to stimulate consumption of both water and saline. It was later revealed, paradoxically, that salt appetite could also be evoked by injection of aldosterone.[187] This is not an AngII-dependent process because it is not prevented by inhibiting AngII signaling.[188] Instead, aldosterone acts directly on the brain and, unlike AngII, generates salt appetite without thirst. During natural sodium deprivation, AngII and aldosterone levels increase in unison to promote fluid balance.

Mechanisms of sensing salt depletion

Salt appetite is triggered by two different physiologic states, hypovolemia and hyponatremia. Hypovolemia is associated with a decrease in blood pressure, which is detected by sensors located in the heart, arteries and veins, and kidney (see above). By contrast, hyponatremia can be sensed by chemosensors specific for individual ions, which are located in the kidney, adrenal gland, and brain.

AngII

Decreases in blood pressure are detected by the kidney, which releases renin to increase AngII levels, as described above (Figures 4A and 4B). Renin release is also stimulated by hyponatremia without any change in blood volume. This is mediated by macula densa (MD) cells in the kidney, which are intrinsically sensitive to sodium[189] and release adenosine triphosphate (ATP) to inhibit renin release from JG cells[190,191] (Figure 4C). The sensors responsible for MD cell activation in response to NaCl are unknown. Of note, although the Na-K-Cl cotransporter (NKCC) has been proposed to be the sodium sensor in MD cells,[192] it is an electroneutral cotransporter and therefore cannot result in cell activation alone.

Aldosterone

The hormone aldosterone is released by the adrenal glands both in response to Ang II and other signals. The specific source of aldosterone is adrenal cells in the zona glomerulosa[193] (ZG), which are activated by Ang II[194] as well as increases in serum K[195] (Figures 4D and 4E), which inversely correlates with sodium levels,[196] likely due to decreased kidney NKCC output. Despite strongly evoking salt appetite, ZG cells only respond to changes in NaCl levels if these cells are already excited by either Ang II or high K.[197,198] The specific sensors for Na and K in this system have not been identified.

Cardiac mechanisms

Blood pressure changes can also be sensed by the heart to affect salt appetite via two pathways, one driven by atrial stretch and one by aortic stretch (these two pathways also modulate thirst, see above; Figures 4F and 4G). In the first pathway, atrial stretch results in the release of atrial natriuretic peptide (ANP)[199,200] which, in addition to decreasing blood pressure via its actions on the kidney and spleen,[201,202] also strongly inhibits salt appetite caused by aldosterone and sodium depletion.[203,204] Although ANP release is blocked by inhibitors of mechanosensation,[205] the identity of the sensor is unknown.

In the second pathway, aortic stretch also impacts salt appetite. Decreasing aortic pressure results in the release of adrenocorticotrophic hormone (ACTH) via a pathway involving the NTS.[206] Release of ACTH likely then increases salt appetite by acting on the adrenal gland,[207] where it can stimulate ZG cells to release aldosterone.[194] In the context of the baroreflex, aortic stretch is detected by Piezo channels, which may also be involved in release of ACTH (see above).

Brain sensing

Increasing the sodium concentration in the cerebrospinal fluid (CSF) immediately decreases salt consumption,[208] indicating that there is a sodium sensor in the brain that can regulate salt appetite. Moreover, the SFO contains glial cells that directly sense sodium via Nax channels[209] (Figure 5A), as discussed above, and these channels can inhibit excessive sodium intake during salt appetite.[86] The generation of salt appetite, however, appears to be primarily driven by peripheral hormonal signals reaching the brain.

Salt appetite circuit

Key nodes in the salt appetite circuit include the NTS and periLC in the hindbrain and the SFO and ventral portion of the bed nucleus of the solitary tract (vBNST) in the forebrain (Figure 5). In the NTS,

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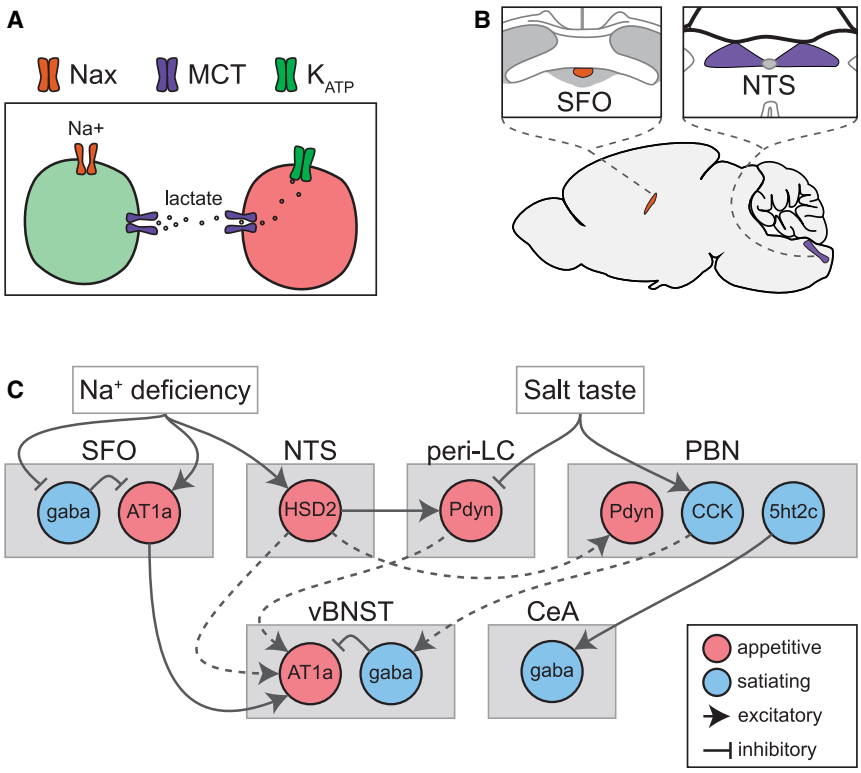

Figure 5. Central salt appetite circuit

(A) High sodium levels activate Nax sensors on microglia, triggering lactate release, which enters SFO^{VGAT} neurons via monocarboxylate transporters (MCT) to close ATP-sensitive K channels (KATP) channels and activate the cell.

(B) Location of SFO and NTS neurons that sense Ang II and aldosterone to generate salt appetite

(C) Simplified diagram of circuitry that generates (red) and satiates (blue) salt appetite. Separate signals for sodium deficiency are first conveyed to SFO and NTS neurons (via Ang II and aldosterone, respectively) to drive salt appetite. This drive is sated when salt taste signals converge on the major target of these neurons, the vBNST.

neurons expressing the enzyme 11-β-hydroxysteroid dehydrogenase type II (HSD2) are specifically sensitive to aldosterone[210–212] and drive salt appetite. These cells are sensitive to aldosterone because the enzyme HSD2 degrades cortisol, which is a competing (and more abundant) ligand for the mineralocorticoid receptor (MR), thereby allowing only aldosterone to bind to the MR in NTS^{HSD2} cells.[213] Chemogenetic activation of NTS^{HSD2} neurons is sufficient to drive salt appetite, whereas inhibition or ablation of these cells significantly decreases salt appetite caused by sodium depletion.[214,215]

The three major targets of NTS^{HSD2} neurons are the vBNST, the lateral PBN, and periLC.[214–216] While activation of NTS^{HSD2} terminals in the PBN does not evoke salt intake, activation of vBNST projections does.[215] The contribution of the NTS^{HSD2} projection to periLC has not been directly tested, but the periLC contains neurons important for salt appetite.[217] Activation of these periLC neurons, which express PDYN, immediately increases salt intake, whereas their inhibition decreases but does not entirely abolish salt appetite.[217]

Sodium depletion is also communicated to the brain by Ang II, which increases salt intake when injected specifically nearby forebrain circumventricular organs, which includes the SFO.[218] The SFO expresses Ang II receptor 1a (AT1a), and deletion of these receptors[120] or lesion of the SFO[219] significantly decreases but does not eliminate salt appetite caused by sodium depletion. SFO^{AT1a} neurons specifically project to vBNST, and activation of this projection selectively increases sodium intake.[120] Interestingly, NTS^{HSD2} neurons also project to this area, suggesting that the vBNST could be responsible for integrating aldosterone and Ang II signals of sodium need.

Satiation of salt appetite

Although the onset of salt appetite is slow, it is quickly inhibited by sodium consumption.[220] Importantly, this fast inhibition of intake is not seen if sodium is infused into the stomach instead,[217,221] suggesting that taste is the primary signal that satiates salt appetite during normal ingestion. The majority of salt taste is mediated by taste cells expressing calcium homeostasis modulators 1 and 3[222,223] (CALHM1/3). These CALHM1/3 cells express epithelial sodium channels (ENaC), which are activated by Na concentrations above 60 mM. However, in the absence of ENaC, these and other taste cells still respond to NaCl concentrations above 240 mM.[222,224] This high concentration NaCl sensing depends on a chloride sensor,[225] and activation of either pathway is sufficient to satiate salt appetite.[214,223]

Taste is conveyed from the tongue to the brain primarily by the facial nerves, which consist of cells that have cell bodies in geniculate ganglion and include cells that are tuned to NaCl taste at both high and low concentrations.[226–229] The facial nerve terminates in the brain at the rNTS, where there are neurons that preferentially respond to NaCl over other tastants.[230] Signals from the rNTS are transmitted to forebrain circuits that mediate taste perception, such as insular cortex, but how taste information is routed to areas that track salt need is not well defined. Nevertheless, taste responses are observed in periLC^{PDYN} neurons, which are activated by sodium deficiency and inhibited by the taste of salt.[217] Similar taste responses are seen in PBN^{CCK} neurons, which are activated by salt taste and inhibit salt appetite.[173]

While salt appetite is rapidly satiated by taste under normal conditions, it can be alleviated by post-ingestive feedback when taste signals are bypassed, albeit on a much slower timescale. For example, there is a delay of up 8 h between the infusion of salt into the stomach and the full suppression of salt appetite.[221] This is not due to a delay in absorption, as plasma sodium rises within 15 min after intragastric salt delivery.[231] This delay may be related to the amount of time required for degradation and clearance of hormones that promote salt appetite or for their target neurons to return to baseline activity. This delay also raises the interesting question of how transient taste

signals are able to suppress salt appetite circuits for hours before systemic signals come online.

Although systemic feedback signals take hours to completely suppress salt appetite, post-ingestive changes in sodium level are mildly satiating in the short term.[221] These increases in sodium level can be sensed after ingestion by several brain areas to decrease salt intake quickly, but never completely. In the SFO, high circulating sodium activates SFO^{VGAT} neurons indirectly via Nax-mediated glial activity,[232] which reduces salt intake in sodium-depleted mice.[120] Likewise, PBN neurons expressing serotonin receptor 5HT2c are also activated by high sodium, and activation of these neurons immediately decreases salt intake.[233] Sodium level can also be sensed indirectly by the brain via circulating ANP, which increases with sodium load. Neurons in the SFO and OVLT express receptors for this peptide,[234] and local ANP infusion inhibits salt intake,[235] yet the dynamics and function of this signaling pathway are unclear.

Conclusions

In this review, we have described how animals detect imbalances in the salt and water content of the blood and then generate appropriate behavioral responses. This reflects the focus of the vast majority of studies in this field, which have investigated thirst and salt appetite as responses to physiologic deficits. However, it is important to note that most water and salt consumption by humans occurs in the absence of any immediate physiologic need.[109,236] An example is prandial thirst, which is triggered by eating and is a major stimulus for water intake in humans and rodents but occurs in the absence of any systemic deficit. It is hypothesized that this is an anticipatory response to impending dehydration,[158,159,237] but the mechanisms that govern this and other spontaneous ingestive behaviors are not well understood. This is an important area for future investigation.

In assembling this review, we have noticed several other areas where our knowledge is clearly limited. For example, the molecular identity of most of the sensors involved in fluid balance remains unresolved. It is also unknown how the circuits for thirst and salt appetite create motivation that is selective for water and sodium, or how they connect to and modulate the downstream motor structures that generate behavior. Lastly, we have integrated in this review findings from a wide range of species—such as dogs, sheep, rats, mice, and humans—but it is clear that there are species-specific differences in the mechanisms that govern fluid balance. For example, our understanding of the role of oropharyngeal signals in thirst satiation originates from early studies of dogs,[150,151] which drink rapidly and then have slow gastric emptying. Oral cues may be less important in species that drink more slowly, such as rats.[238] This emphasizes the need for caution in extrapolating mechanisms described in one species to others, including humans.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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