The neural basis of homeostatic and anticipatory thirst

Claire Gizowski and Charles W. Bourque

Abstract | Water intake is one of the most basic physiological responses and is essential to sustain life. The perception of thirst has a critical role in controlling body fluid homeostasis and if neglected or dysregulated can lead to life-threatening pathologies. Clear evidence suggests that the perception of thirst occurs in higher-order centres, such as the anterior cingulate cortex (ACC) and insular cortex (IC), which receive information from midline thalamic relay nuclei. Multiple brain regions, notably circumventricular organs such as the organum vasculosum lamina terminalis (OVLT) and subfornical organ (SFO), monitor changes in blood osmolality, solute load and hormone circulation and are thought to orchestrate appropriate responses to maintain extracellular fluid near ideal set points by engaging the medial thalamic–ACC/IC network. Thirst has long been thought of as a negative homeostatic feedback response to increases in blood solute concentration or decreases in blood volume. However, emerging evidence suggests a clear role for thirst as a feedforward adaptive anticipatory response that precedes physiological challenges. These anticipatory responses are promoted by rises in core body temperature, food intake (prandial) and signals from the circadian clock. Feedforward signals are also important mediators of satiety, inhibiting thirst well before the physiological state is restored by fluid ingestion. In this Review, we discuss the importance of thirst for body fluid balance and outline our current understanding of the neural mechanisms that underlie the various types of homeostatic and anticipatory thirst.

Adipsia
Lack of thirst even under conditions that normally stimulate thirst, such as dehydration.

Vasomotor tone
The degree of tension in the smooth muscles that surround blood vessels.

Centre for Research in Neuroscience, Research Institute of the McGill University Health Centre and Montreal General Hospital, 1650 Cedar Avenue, Montreal H3G1A4, Canada.

Correspondence to C.W.B.
charles.bourque@mcgill.ca

doi:10.1038/nrneph.2017.149
Published online 13 Nov 2017

Mammals experience continual water losses through the production of urine and the evaporation of hypotonic fluid during breathing or sweating[1–3]. Consequently, the intermittent ingestion of water is essential to sustain life[4], and individuals with chronic adipsia must follow a disciplined regimen of voluntary fluid intake to remain healthy[5–10]. Although often overlooked as an instinctive process, the perception of thirst is critical to the control of body fluid homeostasis[11–15], and its dysregulation can result in life-threatening pathologies[6,10,16–18]. Although clear evidence demonstrates that the perception of thirst is primarily orchestrated by central neural networks, adaptive changes in thirst can be induced by systemic processes, for instance, in response to alterations in kidney function or pharmacological treatment with agents such as the vasopressin V2 receptor antagonist tolvaptan[19]. Here, we review the importance of thirst as a regulated system and outline our current understanding of the neural mechanisms that underlie its control by homeostatic and anticipatory signals. Since our focus is on the control of hydration, we employ herein the term 'thirst' to designate specifically a drive to ingest water and do not consider factors involved in the choice or motivation to drink other types of fluid[20]. Moreover, for simplicity, we define thirst as any drive that can motivate water intake, regardless of cause.

Fluid balance in health and disease

Disturbances in the balance of body fluid encompass a spectrum of changes that can occur in the composition or volume of extracellular fluid (ECF)[16,21] and are frequently encountered in emergency medicine because they can be triggered by drugs[22–26] or by the ingestion of inappropriate amounts of water[27–29] or salt[30,31]. Disorders of fluid balance also occur secondary to acute conditions such as cerebral trauma[32], heart failure[33] and sepsis[34] as well as in chronic ailments that affect the kidneys[35] or liver[36]. Indeed, perturbations in fluid balance feature among the top 10 causes for patient admission at hospital emergency departments in the United States[37].

Small changes in ECF volume are well tolerated owing to dynamic compensatory changes in vasomotor tone that modulate the compliance and capacity of the

Key points

- Thirst has a key role in the maintenance of body fluid homeostasis by driving water intake to compensate for losses incurred as a result of breathing, sweating and the production of urine
- Thirst is associated with the activation of neurons in the anterior cingulate cortex and insular cortex; activation of these neurons might be induced via relay midline thalamic neurons
- Two distinct types of thirst emerge under different circumstances: homeostatic thirst is evoked in response to an existing water deficit, whereas anticipatory thirst occurs before an impending deficit
- Homeostatic thirst is induced in response to hypernatraemia, hyperosmolality and hypovolaemia, whereas anticipatory thirst occurs in response to food intake or hyperthermia or before sleep
- Thirst is rapidly inhibited by oropharyngeal afferents in response to water intake; inputs from gastric distension sensors can also provide feedback signals that suppress thirst

Tonicity
A measure of a solution's potential to attract or repel water across a semipermeable membrane and thus generate osmotic pressure. Solutions with a higher total concentration of solutes will attract water and vice versa.

Anterior cingulate cortex
ACC. The anterior part of the cingulate cortex, which is a midline structure that lies dorsal to the corpus callosum. The ACC has a role in regulating body homeostasis and higher-order functions such as reward anticipation and decision making.

Affective motivation
Motivation to complete a task driven by a particular emotion.

Primordial emotions
Instinctive processes that drive behaviour to maintain optimal body homeostasis (for example, thirst, hunger and pain).

Insular cortex
(IC). The portion of the cerebral cortex within the lateral sulcus. It is believed to have roles in consciousness, emotions and regulating body homeostasis.

Interoceptive sensory modalities
Sensory signals related to the internal state of the body and viscera (for example, stomach distension, temperature and acidity).

Cortex
The outermost portion of the brain, thought to mediate consciousness, memory, attention, awareness, language and thought.

vascular system[38]. For example, decreases in blood volume of up to 15% can be experienced without significant changes in mean arterial pressure in humans[39]; however, progressively greater reductions in blood volume induce a reflex increase in cardiac output[38]. Therefore, very large increases or decreases in ECF volume will ultimately cause arterial pressure to rise or fall, respectively; thus, under physiological conditions, a series of volume-regulated homeostatic mechanisms maintains ECF volume near a desired set point (FIG. 1a).

Pathological symptoms can also be induced by changes in the solute concentration (that is, osmolality) of ECF. Sodium is the dominant ion in ECF, and in healthy animals, its concentration varies in direct proportion to osmolality[40]. Therefore, changes in either osmolality or sodium (Na^+) concentration can serve as indicators of tonicity in otherwise healthy individuals. Acute changes in extracellular tonicity are poorly tolerated because they cause swelling or shrinking of cells and organs due to osmosis[41]. Notably, acute decreases in ECF Na^+ concentration (hyponatraemia) or osmolality (hypoosmolality) cause significant increases in brain volume[42], whereas acute hypernatraemia or hyperosmolality causes shrinking[43]. The brain is particularly sensitive to such insults, and changes in ECF tonicity can result in the development of neurological symptoms. In otherwise healthy individuals, acute changes in tonicity of ±7% are asymptomatic[44], whereas changes greater than ±10% will cause weakness and lethargy, followed by nausea. More severe insults will lead to mental confusion and ultimately to convulsions and coma[25,44,45]. In healthy organisms, ECF osmolality is normally maintained near an optimal set point by osmotic or sodium-dependent mechanisms (FIG. 1b).

Thirst as a central homeostatic mechanism

As mentioned above, the overall control of fluid balance is achieved by the regulation of several behavioural and physiological responses that are orchestrated to maintain the volume and osmolality of ECF near ideal set points (FIG. 1). Thirst, as a behavioural regulator of water intake, is a central player in this regulation. As discussed later, the control of thirst is not mediated exclusively by negative feedback signals. Rather, the intensity of its perception can also be enhanced or suppressed through feedforward mechanisms that anticipate an impending gain or deficit in hydration status[46].

In 1821, Rullier described thirst as "le sentiment le plus vif et le plus impérieux de la vie" (the strongest sense and the most imperative of life)[47]. It is a physiological urge to oppose the continual fluid loss that occurs through daily activities and if neglected for long periods becomes one of the most painful and difficult sensations to ignore[11]. Most humans have experienced thirst at some point in their lives, and it has been a subject of study for centuries. In 1867, Schiff hypothesized that thirst was a general sensation that arose from a deficiency of water content in the body[48]; however, whether thirst was a general or a localized sensation was much debated. The involvement of the central nervous system in the sensation of thirst was proposed as early as the 19th century, and in 1901, Wettendorff hypothesized that the brain was the "seat of the conscious perception of the sensation" (REFS 11,49).

A putative thalamocortical thirst module

The anterior cingulate and insular cortices. Experiments in rhesus monkeys provided the first evidence that activation of prefrontal cortical neurons might be responsible for the conscious perception of thirst in mammals. In a classic study, Robinson and Mishkin[50] showed that water intake could be evoked by delivering current pulses through a stimulating electrode placed in the anterior cingulate cortex (ACC) of awake animals. Unlike responses sometimes evoked by stimulation in other regions, which were often delayed and outlasted the stimulus, responses evoked by ACC stimulation were 'stimulus bound' in that they occurred with short latency (2–8 s) and promptly ceased when stimulation was stopped. Moreover, water intake occurred much more reliably when induced by ACC stimulation than by stimulation of other regions. The ACC is thought to be associated with affective motivation, whereby basic homeostatic modalities such as hunger or thirst can prompt reflexive autonomic adjustments similar to those induced by pain or an itch[51,52]. Indeed, thirst is considered one of the primordial emotions[53].

The involvement of the prefrontal cortex in the perception of thirst has also received considerable support from human studies of brain activation using PET and functional MRI (fMRI). These studies have shown that intense thirst caused by systemic infusion of hypertonic saline[54–56] or exercise-induced dehydration[57,58] is consistently linked to activation of the ACC and other regions such as the insular cortex (IC). The observation that ACC activation occurs when thirst is driven by multiple interoceptive sensory modalities (such as increases in osmolality or decreases in blood volume), which flow in distinct neuroanatomical pathways, suggests that this site is critical for the genesis of thirst perception at the level of the cortex. Further support for this hypothesis is provided by the observation that in humans, the ACC and IC are immediately deactivated when thirst is satiated by the ingestion of water, well before water absorption from the digestive tract corrects the affected physiological parameter[57–61].

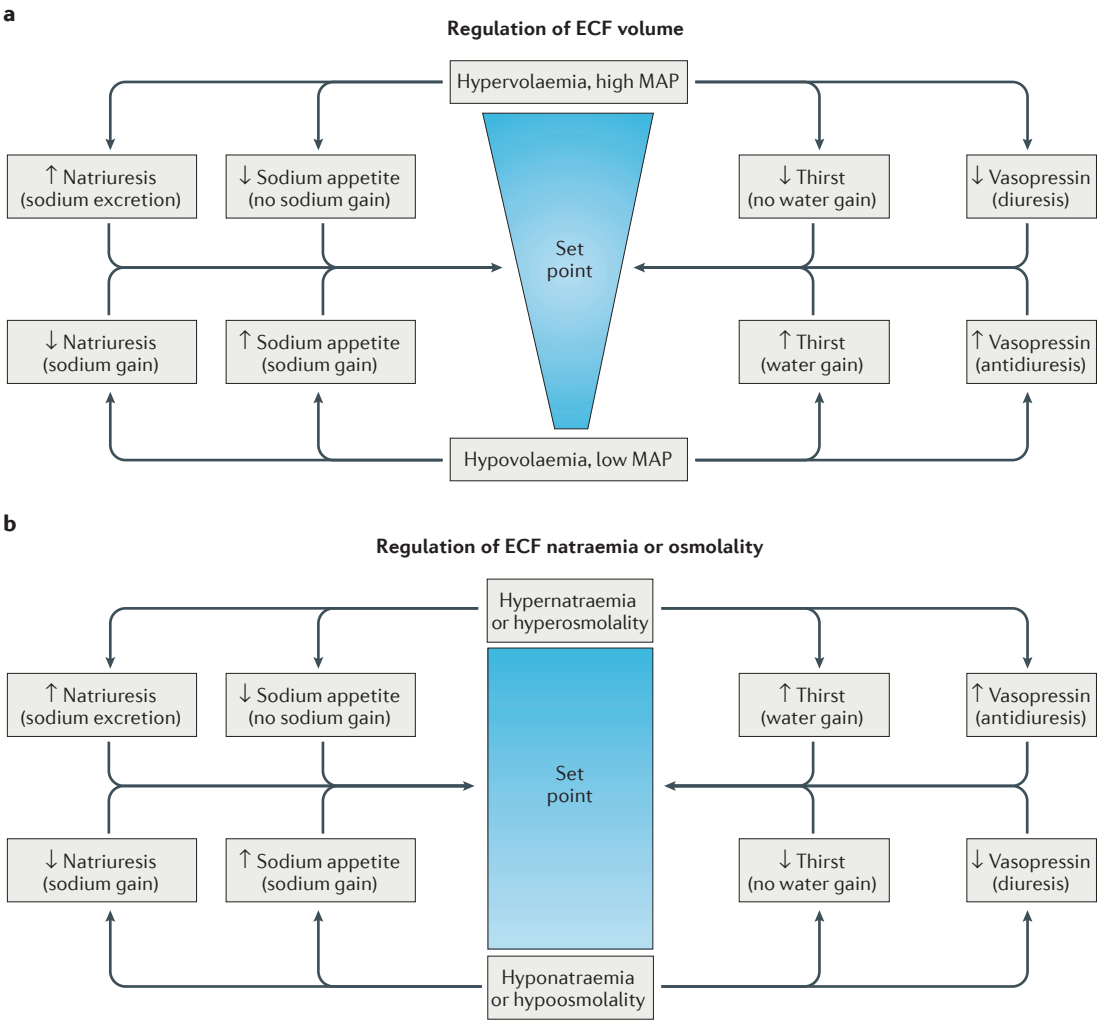

Figure 1 | **Feedback mechanisms to maintain body fluid balance.** Perturbations in body fluid balance can involve changes in the osmolality and volume of the extracellular fluid (ECF), and their correction often requires the coordinated regulation of both parameters. Maintenance of volume and osmotic set points requires the intake and excretion of sodium and water to be controlled through feedback mechanisms involving volume receptors, osmoreceptors and sodium (Na^+) detectors. **a** | When hypovolaemia occurs in the absence of a change in osmolality, for example, as a result of blood loss, maintenance of fluid homeostasis requires a net accumulation of both salt and water to achieve a net gain of isotonic fluid. This effect is achieved through the stimulation of both sodium appetite and thirst, together with an increase in the reabsorption of sodium and water by the kidney. Sodium reabsorption is promoted by the renin–angiotensin–aldosterone system (RAAS), whereas water reabsorption is stimulated by an increase in circulating levels of the antidiuretic hormone vasopressin, which is released from the neurohypophysis. The stimulation of salt appetite and thirst during hypovolaemia is mediated in part by ascending neural inputs from blood volume sensors in the periphery and by the central effects of angiotensin II and aldosterone. By contrast, correction of isotonic hypervolaemia requires a net loss of isotonic fluid, which is achieved in part by suppression of thirst and salt appetite and by stimulation of renal diuresis and natriuresis. Diuresis is provoked mainly by suppressing basal vasopressin release, which reduces water reabsorption[248]. Natriuresis, on the other hand, is enhanced by suppression of basal RAAS activity; by the release of natriuretic peptides, namely, atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP), from cardiac myocytes; and through regulation of the kidney via renal nerves. **b** | Increases in ECF osmolality (or natraemia) can be readily induced in the absence of an altered ECF volume by the ingestion of salt or food. Appropriate homeostatic responses to hypernatraemia include the suppression of sodium appetite and an increase in natriuresis, combined with an increase and water intake and antidiuresis to promote dilution of the ECF. Conversely, a hypoosmotic status is corrected by suppressing thirst and antidiuresis while promoting sodium intake and its reabsorption by the kidney. MAP, mean arterial pressure.

Prefrontal regions
The anterior portions of the brain.

Autoradiographic metabolic trapping
A method of visualizing glucose utilization in the brain. It is used as a surrogate to indicate that neurons have been electrically activated.

Immediate early gene *c-Fos*
A gene that is transcribed and translated transiently and rapidly in response to increased cellular calcium. Expression of an immediate early gene often indicates that neurons have been electrically activated.

Studies in rodents have also provided support for the involvement of the prefrontal regions in thirst. For example, autoradiographic metabolic trapping studies have shown that [^{14}C]glucose accumulates in the ACC of water-deprived rats[62], suggesting metabolic activation of that region. Moreover, hypovolaemic thirst induced by injection of the diuretic furosemide induces expression of the immediate early gene *c-Fos* in the rat IC, indicating neuronal activation[63]. Whether the activation of ACC and IC neurons is necessary and sufficient to mediate the

sensation of thirst remains to be determined; however, taken together, these studies suggest that the ACC and IC are putative primary sites for the perception of thirst in mammals.

Thalamic nuclei. The flow of somatosensory information to ACC and IC neurons in the cortex occurs through thalamic nuclei. Interoceptive signals that ascend from the viscera are relayed to cortical sites via the nucleus tractus solitarius (NTS), the parabrachial nucleus (PBN) and midline nuclei of the thalamus[51,64]. Similar to studies of the ACC and IC in laboratory animals, functional imaging studies in humans have shown that medial thalamic nuclei become activated following stimulation of thirst by infusion of hypertonic saline[54] or exercise-induced dehydration[58]. Moreover, rat medial thalamic neurons that project to the ACC and IC express *c-Fos* in response to systemic hypertonicity, indicating their activation[65]. During the wake period, the thalamus transmits accurate real-time sensory information to the cortex by generating single action potentials; however, during the sleep period, thalamic neurons generate rhythmic oscillations that are thought to prevent the relay of coherent sensory information to the cortex[66]. Therefore, the delivery of interoceptive information to the ACC and IC via thalamic relay cells could potentially provide an opportunity for these inputs to be gated according to the sleep–wake cycle[66] and thus prevent thirst from interfering with sleep — a hypothesis that remains to be proven. However, the activation of these regions in response to thirst suggests that a neuronal network linking the medial thalamus with the ACC and IC might represent the core thirst-promoting module of the brain. It is therefore reasonable to speculate that the feedback and feedforward mechanisms that drive thirst might do so via distinct anatomical pathways that engage the thalamo–ACC/IC circuit.

Homeostatic mechanisms

As mentioned above, thirst is perceived whenever water intake is required to counteract an increase in ECF sodium concentration or osmolality or to correct a deficit in ECF volume (FIG. 1). Thus, specialized molecular and cellular systems have evolved to enable sodium-sensitive, osmosensitive and volume-sensitive neurons to encode quantitative changes in these parameters by altering the rate of action potential firing, thereby regulating the electrical activity of thirst-promoting neurons via negative feedback. The sections below outline our understanding of these homeostatic mechanisms.

Natraemic thirst

Increases in ECF Na^+ concentration can stimulate thirst (FIG. 1b), implying that sodium-specific detectors can initiate neural signals that are capable of activating thirst-encoding neurons. Early studies showed that afferent fibres in the hepatic branch of the vagus nerve can detect changes in extracellular Na^+ concentration[67]; however, whether these axons carry information from sodium-specific detectors or osmoreceptors to the brain remains unclear[68–70]. Moreover, sensory fibres that innervate the liver[69,70], local mesentery[71,72], and hepatic portal vein[73–75] are presumably exposed to high concentrations of substances that are absorbed from the digestive tract before their dilution into the general circulation. Thus, sensory afferents from these areas are ideally poised to contribute to anticipatory responses related to the ingestion of water or food (see below) and might be better suited to such a purpose than to the dynamic monitoring of steady-state values of ECF Na^+ concentration.

A series of classic experiments in the 1960s and 1970s (REF. 76–80) showed that thirst can be specifically regulated by sodium receptors expressed within the brain[78,81]. The molecular mechanisms responsible for sodium detection are not fully understood, but they presumably involve proteins that can mediate an increase in the rate of action potential firing of specialized neurons that are exposed to small increases in extracellular Na^+ concentration[82–85]. At least four subtypes of ion channels could mediate such effects. These include epithelial-like Na^+ channels (ENaCs)[86–89], slowly inactivating voltage-gated Na^+ channels, such as Nav1.6 (REF. 90), the persistent and weakly voltage-sensitive Na^+ channel Na_X (REFS 91–95) and nonselective cation channels[83,85,96]. In most cases, these channels contribute small amounts of inward (depolarizing) Na^+ current under resting conditions. Changes in the driving force resulting from changes in external Na^+ concentration could modulate the amplitude of this current, causing proportional and Na^+-specific changes in membrane potential and the rate of action potential firing[83].

Nonselective cation channels[97–99], ENacs[86,87,100] and Na_X channels[101] are expressed in the organum vasculosum lamina terminalis (OVLT) and subfornical organ (SFO) — a pair of midline circumventricular organs that have key roles in the control of fluid balance[14,102–105]. Electrophysiological recordings have shown that neurons in the OVLT[82,106,107] and SFO[93,108] can be depolarized or excited by increases in extracellular Na^+ concentration. Interestingly, Na_X is also expressed in the median preoptic nucleus (MnPO)[109], a structure that is interposed between the SFO and OVLT and whose neurons also display intrinsic sensitivity to changes in extracellular Na^+ concentration[109,110]. Although these observations support the hypothesis that detection of changes in Na^+ concentration could occur in any or all of these nuclei, the specificity of responses observed in the OVLT and SFO remains to be formally established because most of these experiments were performed under conditions in which osmolality was also affected by changes in extracellular Na^+ concentration. Additionally, whereas Na_X channels directly mediate the excitation of MnPO neurons[110], Na_X-dependent excitation of SFO neurons has been shown to be mediated indirectly by the release of lactate from adjacent glial cells[84,111]. Thus, Na_X might mediate detection of Na^+ concentration through distinct cell-autonomous and non-cell-autonomous mechanisms in different areas.

Anatomical studies have shown that neurons in the MnPO, OVLT and SFO are extensively and reciprocally interconnected[104,105,112–117] (FIG. 2), and functional studies have shown that activation of neurons in any of these areas by optogenetic (FIG. 3) or chemogenetic approaches can stimulate thirst[113,114,118–120]. Since neurons in the MnPO, OVLT

Somatosensory information
Signals that encode information relating to sensory modalities such as hearing, touch and vision.

Action potentials
All-or-none electrical impulses generated at the soma of a neuron. An action potential is rapidly conducted to the axon terminal, where it can activate voltage-gated calcium channels and stimulate transmitter release onto a distinct target neuron.

Membrane potential
The electrical potential of a cell.

Organum vasculosum lamina terminalis
(OVLT). A midline brain structure located in the ventral part of the lamina terminalis and contained within the preoptic area of the hypothalamus.

Subfornical organ
(SFO). A midline brain structure that is located at the dorsal aspect of the lamina terminalis and attached to the hippocampal commissure.

Circumventricular organs
Regions of the brain that lack a blood–brain barrier, such as the organum vasculosum lamina terminalis, subfornical organ and area postrema. Neurons in these regions are directly exposed to circulating substances in the blood.

Depolarized
A term used to designate that the membrane potential of a cell has become relatively more positive. In neurons, depolarization commonly causes an increase in electrical excitability.

Median preoptic nucleus
(MnPO). A midline region of the hypothalamus that is part of the lamina terminalis and lies directly above the organum vasculosum lamina terminalis. The MnPO is thought to be an integrative nucleus involved in regulating blood pressure, fluid balance and body temperature.

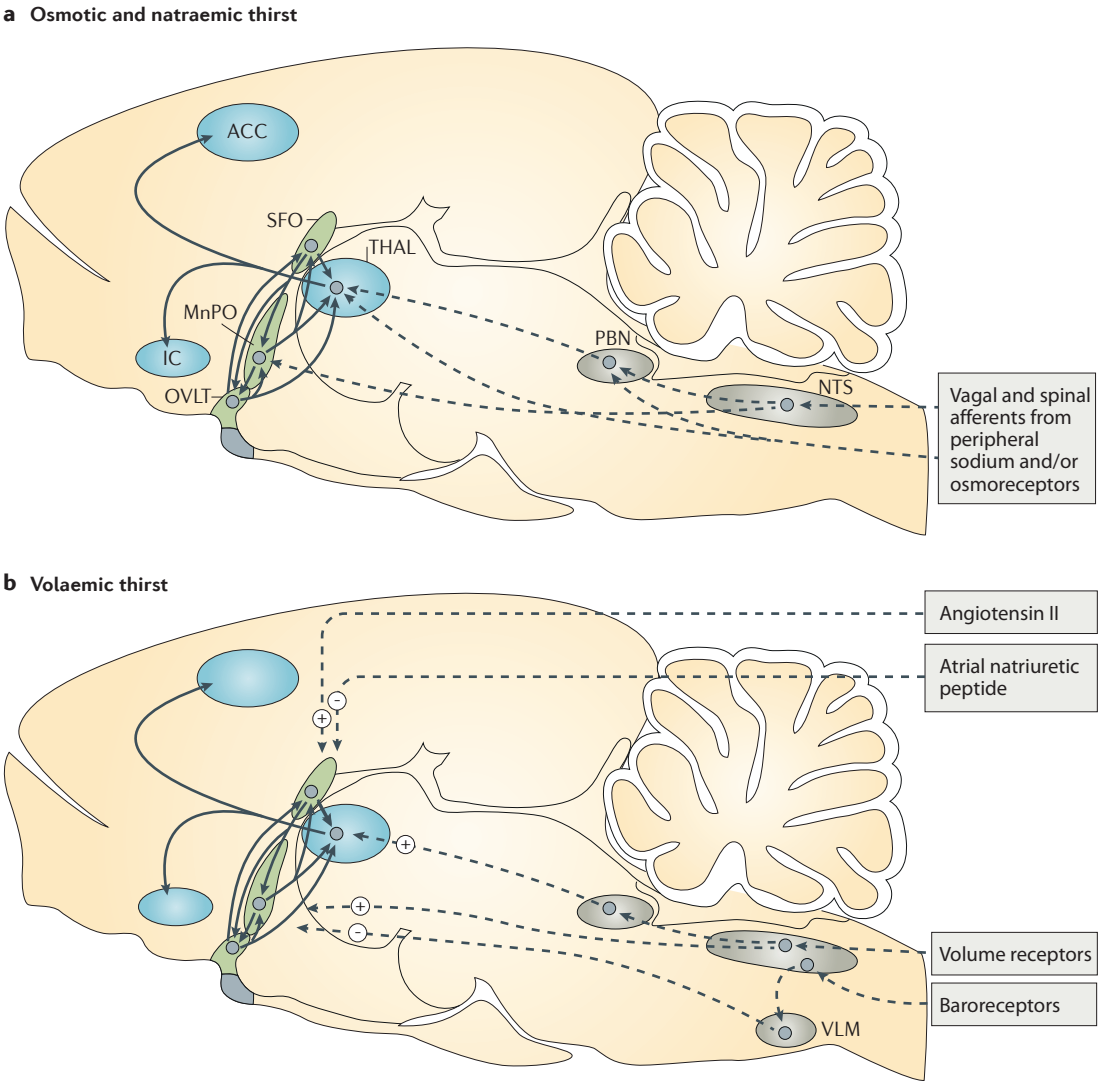

Figure 2 | **Neural pathways that control thirst homeostasis.** Sagittal representation of anatomical pathways that contribute to the regulation of thirst during changes in extracellular fluid (ECF) osmolality and/or Na^+ concentration (part **a**) or volume (part **b**). The various signals that affect thirst integrate mainly within the region of the lamina terminalis, which includes the median preoptic nucleus (MnPO), organum vasculosum lamina terminalis (OVLT) and subfornical organ (SFO). Optogenetic or chemogenetic activation of thirst-promoting neurons in any of these structures can stimulate water intake. The perception of thirst seems to involve activation of the anterior cingulate cortex (ACC) and insular cortex (IC), which might be mediated by relay neurons in the medial parts of the thalamus (THAL). Signals from peripheral sodium and osmoreceptors (part **a**), as well as baroreceptors and volume receptors (part **b**), reach thirst-promoting regions via visceral afferents that course through spinal or vagal pathways. These afferents may converge onto neurons within brainstem nuclei such as the nucleus tractus solitarius (NTS), the ventrolateral medulla (VLM) and/or the parabrachial nucleus (PBN), which then project to thirst-promoting regions. Alternatively, peripheral signals may be directly or indirectly relayed to the THAL, from which thalamic relay neurons transmit sensory information directly to the ACC and/or IC to promote thirst. Humoral signals, such as angiotensin II and atrial natriuretic peptide, can influence the network by affecting the activity of neurons located in the SFO.

Optogenetic
A technique that uses light to activate a rhodopsin channel for the purpose of causing depolarization or hyperpolarization. The rhodopsin expression is directed by genetic approaches that enable the control of specific subsets of neurons.

Chemogenetic
A technique that uses a modified G-protein receptor that is specifically activated by a unique and otherwise biologically inactive drug. Because receptor expression can be targeted to specific cells, the drug can be used to control the activity of specific subsets of neurons.

and SFO project to the medial paraventricular and mediodorsal nuclei of the thalamus[65], it is tempting to speculate that changes in ECF Na^+ concentration might modulate thirst through these nuclei via proportional feedback regulation of the thalamocortical thirst circuit (FIG. 2). Further studies are required to explore this hypothesis and to fully define the network, cellular and molecular mechanisms that specifically mediate the sodium-dependent negative feedback control of thirst.

Osmotic thirst

The specific involvement of ECF osmolality as a factor that regulates thirst (FIG. 1) was first established in pioneering studies by Gilman[121] and Wolf[122], who showed that cellular dehydration (that is, shrinking) at an unidentified locus was required to induce thirst during ECF hypertonicity in dogs and humans. Conversely, dilution of the ECF (hypotonicity) was recognized as an inhibitory factor for thirst[123]. Classic work in goats and sheep

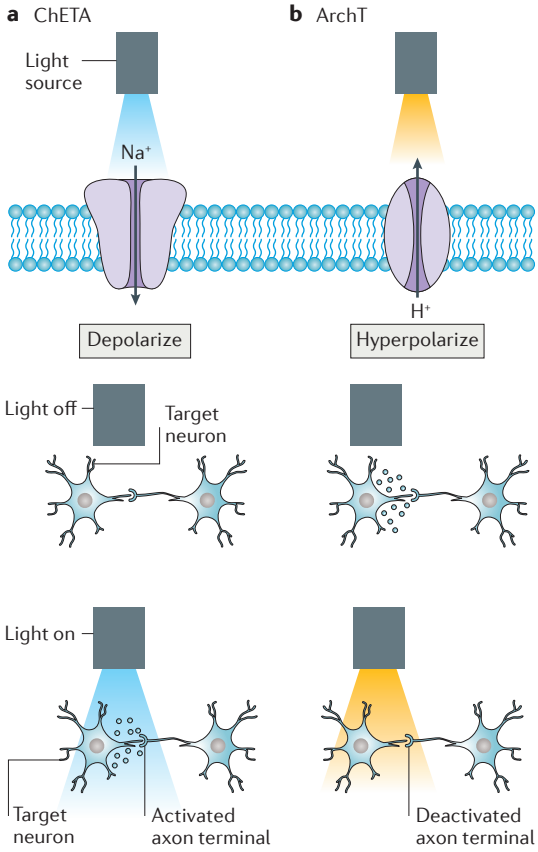

Figure 3 | **Optogenetic manipulation of neuronal activity.** Specialized light-sensitive ion channels or pumps genetically expressed in neurons can be activated by different wavelengths of light to cause membrane depolarization or hyperpolarization. When this process is induced in neuronal somata or dendrites, these effects regulate the rate at which action potentials are discharged (not shown). However, in this case, light is used to depolarize or hyperpolarize the axon terminals of the neuron and to stimulate or inhibit the release of neurotransmitters or neuropeptides, such as vasopressin. **a** | Channelrhodopsins (such as ChETA, illustrated here) are blue-light (~470 nm)-sensitive ion channels that, when photoactivated, enable the influx of sodium ions into the axon terminals of the neuron, down their electrochemical gradient. The influx of positive ions depolarizes the terminals, thereby activating voltage-gated calcium channels and stimulating calcium-dependent release of neurotransmitters and neuropeptides. **b** | Archaerhodopsin T (ArchT) is a yellow-light (~589 nm)-sensitive proton pump that, when photoactivated, moves positively charged ions from the intracellular compartment to the extracellular space, resulting in a net hyperpolarization of the axon terminals. In this example, photoactivation of ArchT hyperpolarizes the axon terminals and prevents the opening of voltage-gated calcium channels, thereby inhibiting the release of neurochemicals.

revealed that hypertonic solutions could induce water intake when injected directly into the third ventricle[76,77], thus identifying the brain as a key site for osmosensory detection. Subsequent work demonstrated that a central osmosensitive system could stimulate water intake in a manner that was independent of changes in extracellular Na^+ concentration[77] and further indicated that the osmosensory sites were present in a brain region that lacks a blood–brain barrier[78]. Although SFO neurons display intrinsic osmosensitivity[98,124] and are activated by systemic hypertonicity as detected by increased *c-Fos* expression[65] and *in vivo* fibre photometry[104], lesions of the SFO fail to prevent water intake induced by systemic hypertonicity[125,126]. Thus, activation of SFO neurons under such conditions might not be essential for the induction of osmotic thirst. By contrast, lesions encompassing the OVLT and MnPO were found to cause adipsia[127] and prevented water intake induced by a hyperosmotic stimulus[128–130]. Since the OVLT is a circumventricular organ (whereas the MnPO is not), the OVLT was identified as the putative osmoreceptor region responsible for the control of thirst[131,132]. Indeed, fMRI studies in humans have shown that the ventral portion of the lamina terminalis, which encloses the OVLT, is activated in response to systemic hyperosmotic stimuli[59,133].

In agreement with a role in the regulation of osmotic thirst, neurons in the rodent OVLT are excited by hypertonic solutions infused into the internal carotid artery *in vivo*[107] or bath applied *in vitro*[82,97,106]. The mechanisms that mediate this effect are not completely understood. Neurons freshly isolated from the OVLT of adult mice are intrinsically sensitive to hypertonic solutions containing excess mannitol. Exposure to such solutions induces OVLT neurons to undergo membrane depolarization and increase the rate of action potential firing through the mechanical activation of DN-Trpv1 (REFS 97,134–137), an N-terminal variant of the transient receptor potential vanilloid type 1 (Trpv1) channel. However, systemic administration of hyperosmotic stimuli *in vivo* induces equivalent water intake and expression of *c-Fos* in the OVLT of wild-type and $Trpv1^{-/-}$ mice[138,139]. Thus, additional network and non-cell-autonomous mechanisms are likely to participate in the detection of osmotic stimuli by OVLT neurons *in situ*. For example, studies of osmosensitive neurons in the supraoptic nucleus (SON) have shown that locally applied hypotonic stimuli can inhibit electrical activity through the activation of glycine receptors in response to taurine release by surrounding glial cells[140–142] and that hypertonic stimuli can cause excitation by suppressing taurine release[143]. Although OVLT neurons are densely wrapped by glial processes[144], whether neuroglial interactions contribute to the osmotic control of OVLT neurons is unknown. Additionally, afferent signals from peripheral sodium receptors or osmoreceptors that rely on channels other than DN-Trpv1 are likely to contribute to the regulation of OVLT neurons and thirst. Indeed, systemic hypertonicity can induce *c-Fos* expression in brainstem regions that relay interoceptive sensory signals, such as the PBN, NTS and ventrolateral medulla (VLM), in animals that have full lesions of the lamina terminalis (that is, the region encompassing the MnPO, OVLT and SFO)[145]. This observation indicates that the lamina terminalis is not the only source of systemic osmosensory information and that the thirst-promoting ACC/IC network might also receive such signals via vagal[69] or spinal[146] afferents that project via the brainstem.

Third ventricle
One of four interconnected cavities in the brain that are filled with cerebrospinal fluid. It is a midline ventricle surrounded by the hypothalamus and thalamus.

Fibre photometry
A technique used to detect changes in fluorescence *in vivo* by use of an implanted fibre-optic microprobe. When targeted to neurons expressing a calcium-sensitive fluorophore, the technique can be used as a surrogate indicator of neuronal activity.

Supraoptic nucleus
(SON). A nucleus within the hypothalamus that contains magnocellular neurosecretory cells. These cells project to the posterior pituitary (neurohypophysis) and release vasopressin and oxytocin into the circulating peripheral blood.

As mentioned earlier, studies in rats have shown that systemic hyperosmotic stimuli increase the expression of *c-Fos* in MnPO and OVLT neurons that project to midline thalamic nuclei and in midline thalamic neurons that project to the ACC and IC[65]. Human studies using fMRI have also indicated that the ventral part of the lamina terminalis (encompassing the OVLT and MnPO) is functionally connected to the medial thalamus and that functional connectivity within this network is enhanced during thirst perception stimulated by systemic hypertonicity[58]. Thus, the activation of thirst by systemic hyperosmotic stimuli might involve the osmotic excitation of OVLT neurons and interconnected neurons in the MnPO and SFO, as well as neurons in brainstem nuclei, which together engage the medial thalamic–ACC/IC network (FIG. 2).

Volaemic thirst

Perhaps the most intuitive form of hydration deficit is hypovolaemia, a term that designates a net loss of ECF volume regardless of its composition. In its simplest form, hypovolaemia can be caused by haemorrhage, a condition that leads to a loss of isotonic ECF. Experiments in rats have shown that haemorrhage is a potent stimulus for thirst[11,147,148]. As mentioned previously, mammals incur an incessant fluid loss through the evaporation of lung exudate and the production of sweat. Since these fluids are hypotonic in comparison to ECF[1–3,149], the impact of restricting water intake for a significant amount of time is typically dehydration that combines hypovolaemia with ECF hyperosmolality. Regardless of cause, it is now well established that mammals have evolved sensitive systems that monitor ECF volume independently of osmolality or natraemia and that these systems can either promote or inhibit thirst via negative feedback (FIG. 1).

Changes in ECF volume are monitored indirectly by pressure receptors that detect stretch forces within the walls of the vasculature. Specifically, low-pressure cardiopulmonary receptors located in the atria, pulmonary artery and vena cava[150,151] detect blood volume, whereas high-pressure baroreceptors in the walls of the aortic arch and carotid sinus detect arterial pressure. The contribution of these two receptor systems to volume homeostasis varies under different pathological conditions[11,151]. Detailed discussion of the mechanism of action of these two systems is beyond the scope of this Review; however, their global contribution to the control of thirst in healthy individuals can be simplified as follows. Decreases in vascular stretch forces associated with an ECF volume deficit (that is, hypovolaemia or hypotension) induce a number of compensatory responses that maintain blood pressure and ECF volume, including an increase in the perception of thirst (FIG. 1). Conversely, an increase in stretch forces associated with overfilling (hypervolaemia or hypertension) induces opposite responses, including a suppression of thirst[152,153]. While hypotension or hypovolaemia may stimulate thirst via both sets of receptors, a study has demonstrated that baroreceptors play a greater role than volume receptors in the suppression of thirst during hypervolaemia or hypertension[154].

The neural circuitry through which thirst is stimulated by volume receptors and baroreceptors is unknown, but it likely involves neurons in the NTS, PBN and VLM[13,150,155–157]. Neurons in these areas receive afferents from low-pressure and high-pressure receptors and project axons to the medial thalamus[51,64] and MnPO[115,116,150]. The possible involvement of the lamina terminalis in mediating the effects of hypovolaemia is supported by the observation that neurons in the MnPO, OVLT and SFO all express *c-Fos* in response to volume depletion[157,158]. Moreover, optogenetic activation of glutamatergic neurons in these areas can promote thirst[104,113,119,120]. Efferent signals from the lamina terminalis target the paraventricular nuclei of the thalamus[65,115] and could therefore activate thirst via the thalamic–ACC/IC circuit (FIG. 2). Interestingly, a new study has shown that optogenetic inhibition of glutamatergic thirst-promoting MnPO neurons is sufficient to suppress water intake in mice that have been water deprived for 48 h[120]. The output of these neurons might therefore provide an excitatory drive that is required to activate the thalamocortical circuitry either directly or indirectly (for example, via the OVLT or SFO) under conditions of water deprivation. In that case, brainstem cardiopulmonary afferent signals are likely to be relayed via the MnPO rather than the medial thalamus.

The networks responsible for the inhibition of thirst during hypervolaemia remain obscure. Isoosmotic volume expansion in rats induces *c-Fos* expression in a number of brainstem areas, including the NTS, PBN and VLM[159–161]. In principle, neurons in these areas could inhibit thirst by reducing the activity of thirst-promoting neurons throughout the lamina terminalis (that is, in the MnPO, OVLT or SFO)[104,113,114,119,162] or through activation of thirst-inhibiting neurons in the MnPO or SFO[113,119] (FIG. 2). Further work is required to resolve the specific networks that modulate thirst in response to changes in ECF volume.

Hypovolaemia can also stimulate thirst through the release of renin from the kidney[11,151]. Specifically, when renal arterial perfusion is reduced as a consequence of hypovolaemia, renin is released into the circulation by the juxtaglomerular apparatus. Renin is a protease that cleaves angiotensinogen, a precursor protein produced by the liver, to yield angiotensin I, which is then catalysed into angiotensin II (Ang II) by angiotensin-converting enzyme. Circulating Ang II promotes a wide spectrum of responses that enhance vasomotor tone; moreover, classic studies from the 1970s showed that circulating Ang II can also serve as a powerful stimulator of thirst[151] through actions mediated via the SFO[163,164].

Hypervolaemia associated with excess ECF volume can also inhibit thirst through humoral mechanisms, whereby stretching of specialized cardiac myocytes causes the release of atrial natriuretic peptide (ANP) into the bloodstream. ANP is well known to promote a decrease in ECF volume by stimulating renal natriuresis[165,166] but is also recognized for its potent inhibition of thirst[165]. Although the location at which ANP acts to inhibit thirst is not completely clear, studies have shown that ANP can oppose the dipsogenic effect of

Ang II when injected into the SFO of rats[167]. Additional work is required to define the mechanisms by which ANP inhibits thirst, but it seems likely that this peptide hormone mediates this effect through actions at a circumventricular organ, such as the SFO (FIG. 2).

Thirst-promoting anticipatory mechanisms

The above sections examined the primary feedback mechanisms through which thirst is bidirectionally regulated in response to changes in the volume or composition of the ECF. Although these mechanisms are important to maintain ECF volume, natraemia and osmolality near desired set points (FIG. 1), they are by definition delayed consequences of ongoing physiological perturbations. A host of feedforward responses are now understood to drive water intake in anticipation of impending systemic solute loads or water deficits associated with various behavioural and environmental conditions[11–13,168,169]. These types of mechanisms are important because they can blunt the impact of physiological perturbations before they occur.

Prandial thirst

Rats consume approximately 70% of their daily water intake immediately before (preprandial), during (prandial) and following a meal (postprandial)[170]. This behaviour is appropriate because food absorption creates a solute load that must be complemented with water intake to preserve ECF isotonicity. Indeed, food ingestion without water causes plasma to become hypertonic within minutes following a meal[171,172]. Postprandial water intake therefore reflects in part the osmotic thirst triggered by solute absorption. However, water intake before and during the early part of a meal occurs well before ECF osmolality is increased by solute ingestion[104,171] and is therefore stimulated by mechanisms other than osmotic thirst. The existence of preprandial thirst implies the influence of a learned behaviour, or perhaps of a subconscious learned anticipatory benefit. The basis for preprandial thirst will not be further considered here. Prandial water intake, however, is directly proportional to the salt content of a meal[173], suggesting the presence of solute sensors in the upper gastrointestinal tract, the liver or the interposed hepatoportal system, which can provide ascending feedforward information to stimulate prandial thirst in accordance with prevailing water requirements. Indeed, intragastric solute loads delivered by cannula can stimulate drinking in a dose-dependent manner[174–176], and removal of water ingested during a meal through a gastric fistula enhances water intake[177].

The cellular and network mechanisms that drive prandial thirst remain to be established, but studies have shown that Na^+ receptors and osmoreceptors are present within the mesenteric hepatic portal area[71,178–180], which is innervated by side branches of the major splanchnic nerves[71] and vagal afferent nerves[180]. The involvement of this system in the regulation of prandial thirst is illustrated by the fact that water intake stimulated by intragastric NaCl can be inhibited by vagotomy[174]. Activation of hepatic portal receptors with hypertonic NaCl in rats also affects the firing of NTS neurons *in vivo*[178,179] and induces *c-Fos* expression in the NTS as well as other brain regions involved in the control of thirst (such as the lamina terminalis)[181]. Moreover, a 2011 study identified hepatic osmoreceptors that send ascending signals to the brainstem via dorsal root ganglia, indicating a possible contribution of spinal pathways to the control of prandial thirst[146]. Additional work is needed to identify the cellular location and molecular mechanisms responsible for the detection of ingested solutes and the networks that control prandial thirst.

Although projections that ascend from the NTS could mediate prandial thirst by activating the ACC or IC via projections to the OVLT, MnPO or medial thalamus (FIG. 4), additional pathways might also be involved. Specifically, lesions of the SFO reduce prandial thirst in rats[182], whereas thirst-promoting SFO neurons are activated at the onset of feeding in mice[14,104]. Remarkably, optogenetic inhibition of these neurons reduces prandial water intake[104], suggesting that the firing of these SFO neurons is necessary to stimulate this behaviour. How thirst neurons in the SFO receive and integrate these signals to mediate prandial thirst remains to be established. Although a 2016 study observed only a few direct projections from the PBN to thirst-promoting SFO neurons[104], these neurons might receive signals from PBN inputs to other local non-thirst-promoting SFO neurons[183–185]. Taken together, these findings indicate that hepatoportal sensors that monitor the solute load associated with food intake can adaptively mediate an anticipatory feedforward stimulation of water intake to mitigate the increase in ECF osmolality that would otherwise occur as a result of eating.

Thermal thirst

Hyperthermia caused by exercise or heat exposure in homeotherms leads to a loss of ECF solutes and water due to the evaporation of fluids during cooling responses such as sweating, panting or the spreading of saliva[186]. These responses can cause dehydration (resulting in ECF hypertonicity and hypovolaemia) since the fluids that are secreted and evaporated are hypotonic relative to the osmolality of ECF[1–3,187]. Several studies have shown that rodents exposed to high ambient temperatures drink considerable quantities of water before ECF osmolality or volume is increased[188–191] and that the magnitude of the observed water intake is proportionate to the change in core body temperature[190]. Together, these observations suggest that hyperthermia can provoke a feedforward anticipatory stimulation of water intake that could mitigate the dehydrating effect of thermoregulatory cooling.

Although the specific mechanisms by which increases in temperature can induce thirst remain unknown, a considerable amount of information is available concerning cellular thermosensation and neural pathways that carry thermosensory information to the brain[192]. Thermosensitive neurons located in the brain and periphery can detect changes in temperature owing to the expression of various heat-sensitive and cold-sensitive ion channels[137,193,194]. Cutaneous thermoreceptors, for example, can detect a wide range of ambient temperatures to which skin can be exposed and relay this sensory

Vagotomy
A procedure that involves removing part of the vagus nerve.

Homeotherms
Organisms that maintain their core body temperature at a stable temperature.

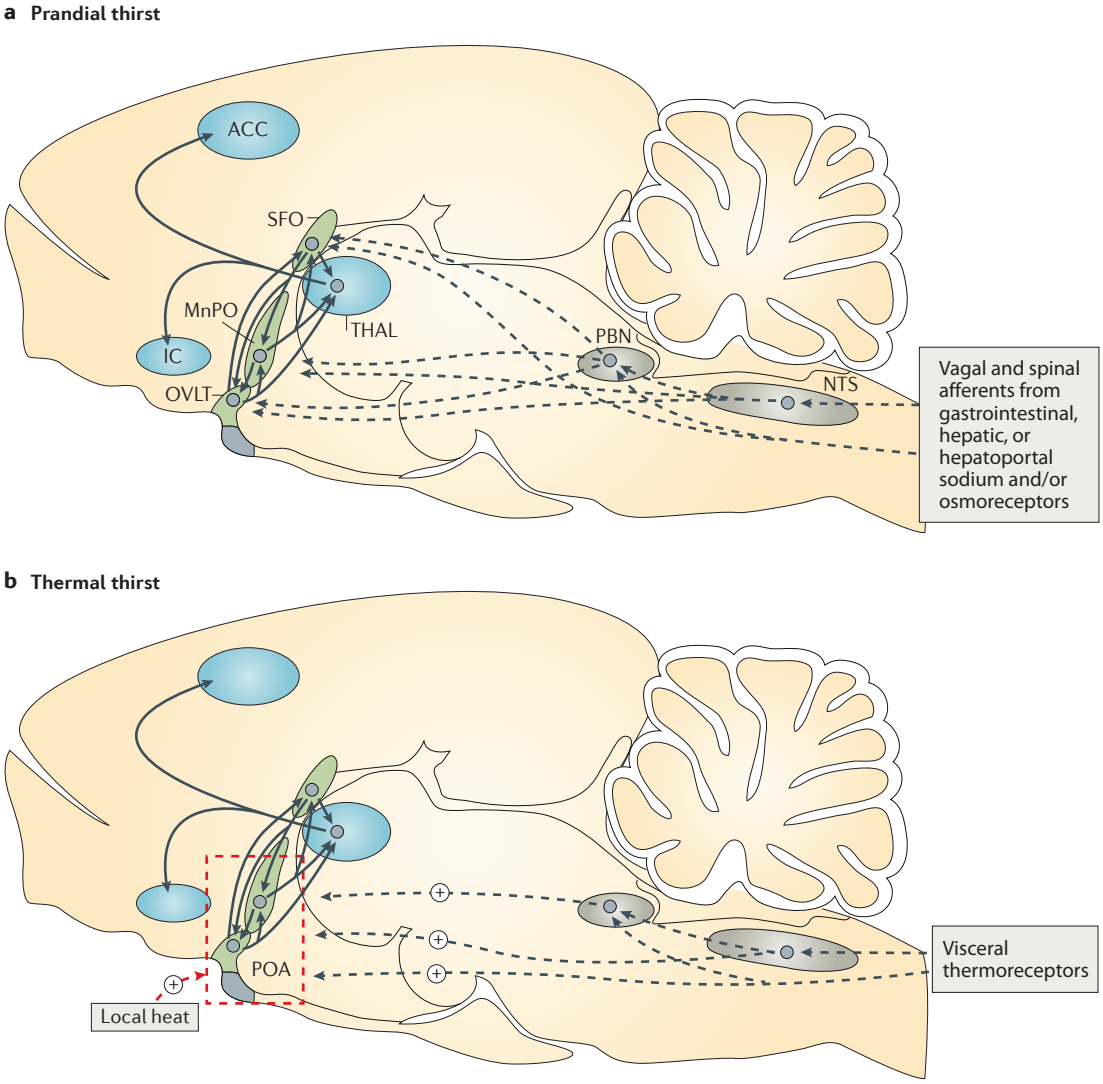

Figure 4 | **Neural pathways involved in the anticipatory stimulation of thirst during food intake and hyperthermia.** **a** | Ingestion of solutes (such as salt or solid food) during a meal can provoke a marked increase in extracellular fluid (ECF) osmolality within minutes. Sensors that detect solutes within the stomach or duodenum can activate thirst-promoting brain regions, such as the median preoptic nucleus (MnPO), organum vasculosum lamina terminalis (OVLT) and subfornical organ (SFO) of the lamina terminalis, with subsequent activation of the anterior cingulate cortex (ACC) and insular cortex (IC) via relay neurons in the medial parts of the thalamus (THAL) to stimulate prandial water intake and blunt this effect. **b** | Sustained increases in body temperature can lead to dehydration caused by evaporative water loss. Sensors of core body temperature in the viscera project to the preoptic area (POA) via the nucleus tractus solitarius (NTS) and/or the parabrachial nucleus (PBN). Alternatively, the POA, which encloses the OVLT and MnPO, could potentially receive direct sensory inputs from visceral thermoreceptors. Neurons in the POA are also temperature sensitive; thus, local activation of POA neurons due to intrinsic and synaptic responses could drive thirst via the activation of projections to the THAL–ACC/IC network.

information to the brain via projections that ascend in the lamina I spinothalamocortical pathway[51,64,195] or via thermal somatosensory afferent collaterals that transmit signals to the PBN via dense projections from the dorsal horn[192,196]. Thermoreceptor afferents are also located in various organs (for example, skeletal muscle[197]) and especially the viscera[198–201], where they presumably detect changes in local or core body temperature. Visceral afferents of this type, including those that innervate the splanchnic mesentery[201], probably project to the NTS and/or PBN via spinal or vagal pathways[51]. Neurons in the PBN project directly to the preoptic area (POA)[196] — a large region of the hypothalamus that encompasses several structures involved in the control of fluid balance, including the OVLT and MnPO (FIG. 4). *In vivo* electrophysiological recordings in cats have shown that a subset of POA neurons can be activated by heating cutaneous thermoreceptors in the absence of changes in core body temperature[202], indicating that information regarding ambient temperature can potentially access the thirst-promoting regions of the brain via neurons in this area. However, it remains to be determined whether increases in cutaneous temperature can stimulate thirst via such a pathway (FIG. 4).

Although a role for cutaneous receptors in the stimulation of thirst cannot be fully excluded, experiments have shown that humans report significantly greater subjective thirst following injections of hypertonic saline in the presence of elevated core body temperature and that this effect is not observed when skin temperature is elevated[203]. Sensors responsible for the detection of core body temperature might therefore be particularly relevant to the control of thermal thirst. Although thirst-promoting neurons within the POA may receive information concerning core temperature via visceral afferents, the hypothalamus is also recognized as a key site for detection and regulation of core body temperature[204–207]. Indeed, studies performed over a century ago established the hypothalamus as the only brain region that is capable of responding to local thermal stimulation by promoting peripheral thermoregulatory responses (such as panting, sweating on footpads or shivering)[208]. Since these pioneering observations, ample evidence has established the POA as the main locus of the central thermostat[208–210]. Specifically, POA warming activates heat-dissipating mechanisms, whereas cooling drives thermogenesis[196,209,211–214]. Moreover, structures within the POA and other areas of the hypothalamus orchestrate the thermoregulatory responses induced by heating or cooling of the periphery[192,196,206,214,215].

Interestingly, local heating of the ventral medial part of the POA (vmPOA) by use of a thermode can elicit intense thirst in euhydrated goats, whereas cooling inhibits water intake[216], suggesting that heat-sensitive neurons within this area can drive thermal thirst. A 2016 study showed that vmPOA neurons that express the neuropeptides brain-derived neurotrophic factor and pituitary adenylyl cyclase-activating polypeptide are activated by heat exposure and that optogenetic stimulation of these neurons induces heat-dissipating behaviours[214]. In addition, we showed that thirst can be induced by optogenetic activation of OVLT neurons that express the heat-sensitive channel DN-Trpv1 (REF. 114). Whether the vmPOA and/or the OVLT are functionally activated during hyperthermia to drive thermal thirst remains to be established.

Circadian thirst

Prolonged sleep is a potential cause of dehydration because fluid losses caused by breathing and urine production at this time are not opposed by regular water intake. However, mammals, including rodents and humans, can mitigate this effect through circadian responses that optimize osmoregulation during sleep[217–219]. For example, studies in humans and rodents have shown that renal water reabsorption is progressively enhanced during the sleep period[218–222]. This effect is caused by an increase in vasopressin release from the neurohypophysis[219,223], which might result in part from enhanced synaptic excitation of magnocellular neurosecretory neurons[224]. This topic has been reviewed elsewhere[217] and is not further considered here. Another important adaptation observed in rodents is a substantial increase in water intake that occurs just before sleep (that is, circadian thirst), which creates a fluid reserve that compensates for the absence of water intake during sleep.

In agreement with previous reports in rats[225] and mice[226,227], we have shown that mice drink significantly more water during the last 2 h of their active period than in the 2 h period preceding it (that is, the basal period)[114]. Mice that were denied this enhanced intake were significantly dehydrated on waking, indicating that this behaviour is physiologically adaptive. Moreover, control experiments showed that increased water intake during the active period was not driven by osmotic, prandial, volaemic or thermal thirst, supporting the hypothesis that water intake at this time is an anticipatory behaviour driven by the circadian clock (that is, the suprachiasmatic nucleus (SCN)).

The SCNs are a pair of midline nuclei that each comprise thousands of neurons that mainly contain the inhibitory neurotransmitter GABA; the neurons can also express or co-express a number of different neuropeptides, such as vasopressin, vasoactive intestinal peptide and gastrin-releasing peptide[228,229]. Findings from anatomical tracing studies have prompted the suggestion that vasopressin-containing neurons located in the outer shell of the SCN serve as the main output neurons that mediate a variety of circadian rhythms[229–231]. Vasopressin-expressing neurons of the SCN communicate with many parts of the brain, but notably, they send direct projections to the paraventricular nucleus of the thalamus, SFO and OVLT[229]. In principle, projections to any of these areas might be involved in the control of circadian thirst. However, results from our group have shown that projections from SCN vasopressin-expressing neurons to the OVLT are necessary and sufficient to mediate circadian thirst[114] (FIG. 5).

In *in vitro* studies of brain slices, we showed that the electrical activity of OVLT neurons is significantly increased during the active period compared with the basal period and, specifically, that the firing rate of vasopressin-expressing SCN neurons was significantly increased during the active period. Analysis of whole-cell currents revealed that OVLT neurons are depolarized (that is, excited) by electrical stimulation of the SCN. Surprisingly, these effects did not involve fast neurotransmission by GABA or glutamate but were mediated by the vasopressin V1a receptor (V1aR) and activation of downstream nonselective cation channels. *In vivo* experiments subsequently showed that optogenetic stimulation of vasopressin release from the axon terminals of SCN neurons within the OVLT during the basal period could increase water intake to a level equivalent to that observed during the active period. Conversely, optogenetic inhibition of vasopressin release from these terminals abolished water intake during the active period. These results indicate that circadian thirst during the active period is driven by an excitatory effect of vasopressin released by SCN neurons on thirst-promoting neurons in the OVLT (FIG. 5).

Satiation of thirst

The above sections describe how homeostatic (feedback) and anticipatory (feedforward) mechanisms can promote water intake in response to existing or impending fluid deficits. However, dehydrated animals that are given free

Euhydrated
Having a normal level of body water at rest. This condition implies an absence of absolute or relative excess hydration or dehydration.

Neurohypophysis
The posterior part of the pituitary gland that contains axon terminals originating from magnocellular neurosecretory neurons in the supraoptic nucleus and paraventricular nucleus.

Magnocellular neurosecretory neurons
Neuroendocrine neurons that synthesize either vasopressin or oxytocin within the supraoptic nucleus and paraventricular nucleus.

Active period
The last 2 h of the wake period. Animals ingest significantly more water at this time compared to the basal period.

Basal period
The 2 h period preceding the active period. During the basal period, animals ingest small volumes of water.

Whole-cell currents
Electrical currents generated by the entire cell membrane and recorded by patch clamp electrophysiology.

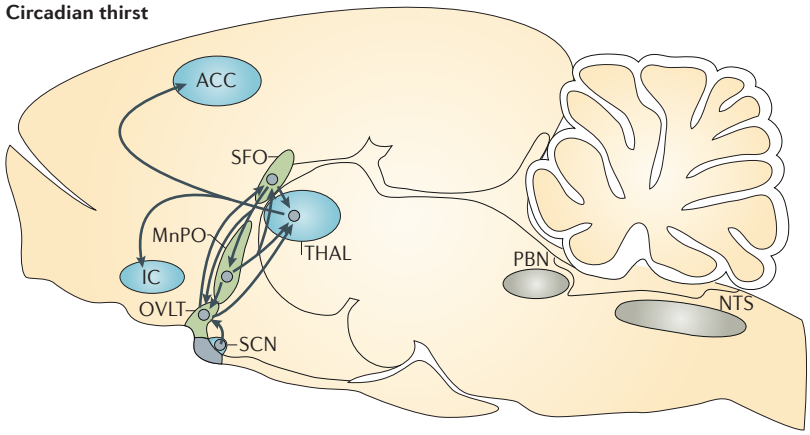

Figure 5 | **Circadian regulation of thirst.** The circadian clock drives water intake before sleep to protect animals against overnight dehydration, which would otherwise occur owing to the absence of water intake during sleep. Vasopressin-expressing neurons in the suprachiasmatic nucleus (SCN; the region of the brain that controls circadian rhythms) project to the organum vasculosum lamina terminalis (OVLT). In mice, these neurons are suppressed during the active period but increase their firing rate towards the end of the active period. Vasopressin release at this time excites OVLT neurons to promote water intake ahead of a period of sleep during which no water intake occurs. ACC, anterior cingulate cortex; IC, insular cortex; MnPO, median preoptic nucleus; NTS, nucleus tractus solitarius; PBN, parabrachial nucleus; SFO, subfornical organ; THAL, thalamus.

access to water will stop drinking well before ECF volume and osmolality are restored[46,169,180,232]. Indeed, the negative valence associated with thirst and the motivation to drink declines rapidly upon water intake to terminate fluid ingestion and avoid overhydration[60,61,120,162,233]. In agreement with these observations, imaging studies in humans have shown that the ACC and IC are rapidly deactivated upon water ingestion[54,55,57,59,61]. Remarkably, however, the OVLT remains activated even after the ACC and IC are deactivated upon satiation prompted by water intake in hyperosmotic humans[59], suggesting that osmosensory OVLT neurons that monitor systemic tonicity continue to signal the hyperosmotic state until it is fully corrected by water absorption and that satiety must occur at another level. Interestingly, use of fibre photometry to monitor cellular calcium levels *in vivo* has shown that the activity of thirst-promoting neurons in the MnPO and SFO of thirsty mice can be rapidly suppressed by water intake[14,104,120], suggesting that these sites may mediate satiety signals under some conditions. Notably, glutamatergic MnPO neurons seem to proportionally encode the aversive quality (negative valence) of thirst, and inhibition of these neurons is sufficient to quench thirst in water-deprived mice[120,162]. Signals that mediate early satiety probably originate from oropharyngeal afferents, perhaps via the trigeminal nerve[234], since cold metal placed within the oral cavity can alone transiently reduce SFO neuron activity[104]. Moreover, gustatory receptors can also modulate water intake[235].

Although oropharyngeal signals can mediate the rapid inhibition of thirst neurons in the SFO and MnPO following water intake, animals with open gastric fistulas ingest excessive amounts of water over the long term[177,236–238]. This finding suggests that the immediate inhibitory effect of oropharyngeal signals might be temporary and that thirst will reemerge owing to the persistent drive of feedback signals from homeostatic inputs; it also indicates that gastric and postgastric signals have a key role in limiting the degree of water ingestion and can produce a long-lasting inhibition of water intake. The gastric signal that mediates satiety seems to specifically reflect the volume of the ingested fluid[169]; this process might be mediated by afferent signals from stretch receptors in the vagus nerve that innervate the stomach and duodenum[239–241]. In agreement with this hypothesis, gastric distension increases the rate of action potential firing[242] and expression of *c-Fos*[243] in NTS neurons. Moreover, this pathway can mediate an inhibitory effect on thirst because water intake induced by hypertonicity or hypovolaemia is enhanced by lesions of the area postrema (AP) and NTS[244,245] or by blunting the function of the vagal NTS afferents by systemic administration of capsaicin[246]. In addition, gastric or hepatoportal osmoreceptors might be able to detect hypotonicity[68,69] and could also contribute to the osmotic inhibition of thirst via pathways that ascend through the NTS. Importantly, water intake in thirsty rats with AP and NTS lesions or in animals with gastric fistulas[177] eventually declines 15–30 min after the onset of drinking; thus, gastric distension or dilution signals provide the immediate inhibitory signal to cease drinking once sufficient fluid has been ingested. However, in the absence of this feedforward effect, postingestive homeostatic signals (for example, ECF hypoosmolality or hypervolaemia) can act to suppress thirst should the ECF become hypoosmotic (FIG. 1).

Conclusions

Thirst is a complex behavioural response governed by multiple mechanisms that serve to correct ongoing and imminent homeostatic fluid perturbations. Maladaptive changes in the perception of thirst can lead to severe acute pathologies; thus, understanding the neural basis underlying this physiological response is crucial for the development of treatments and therapeutic strategies for these disorders. For example, hyperglycaemic patients experience polydipsia (excessive thirst) as a result of concurrent hyperosmolality. Although this pathology is fairly well understood, other pathologies that affect thirst perception are not. For example, psychogenic polydipsia in patients with schizophrenia or obsessive–compulsive disorder can lead to severe states of hyponatraemia and hypoosmolality, which can result in seizures and even death. By contrast, adipsia — a condition that is particularly common in elderly individuals — leads to dehydration. This condition can be life threatening during hot weather and could contribute to the predicted 257% increase in the annual number of heat-related deaths by 2050 as a result of climate change[247]. Although thirst has been a subject of study for decades, a lack of tools to enable the analysis of specific cell types has prevented the study of detailed neural circuits that underlie defined thirst behaviours. The development of tools, such as optogenetics and chemogenetics, to analyse neural networks has provided new insights into the mechanisms that govern thirst and will likely facilitate further advances in this field in the future.

Negative valence
Aversive or unpleasant emotion associated with an event or condition.

Oropharyngeal afferents
Nerve fibres carrying sensory signals that originate from different tissues in the mouth or pharynx.

Trigeminal nerve
The fifth cranial nerve; it is a sensory and motor nerve that transmits information responsible for much of orofacial sensation and mediates motor functions associated with biting and chewing.

Area postrema
(AP). A midline circumventricular organ in the brain stem that is involved in the detection of circulating substances, the relay of autonomic signals and the control of emesis.

1. Morgan, R. M., Patterson, M. J. & Nimmo, M. A. Acute effects of dehydration on sweat composition in men during prolonged exercise in the heat. *Acta Physiol. Scand.* **182**, 37–43 (2004).
2. Effros, R. M. *et al.* Epithelial lining fluid solute concentrations in chronic obstructive lung disease patients and normal subjects. *J. Appl. Physiol.* **99**, 1286–1292 (2005).
3. Griese, M., Noss, J. & Schramel, P. Elemental and ion composition of exhaled air condensate in cystic fibrosis. *J. Cyst. Fibros.* **2**, 136–142 (2003).
4. Bolt, E. E., Hagens, M., Willems, D. & Onwuteaka-Philipsen, B. D. Primary care patients hastening death by voluntarily stopping eating and drinking. *Ann. Family Med.* **13**, 421–428 (2015).
5. Arima, H., Azuma, Y., Morishita, Y. & Hagiwara, D. Central diabetes insipidus. *Nagoya J. Med. Sci.* **78**, 349–358 (2016).
6. Cuesta, M., Hannon, M. J. & Thompson, C. J. Adipsic diabetes insipidus in adult patients. *Pituitary* **20**, 372–380 (2017).
7. Eisenberg, Y. & Frohman, L. A. Adipsic diabetes insipidus: a review. *Endocr. Pract.* **22**, 76–83 (2016).
8. Manning, S., Shaffie, R. & Arora, S. Case Report: Severe hypernatremia from psychogenic adipsia. *F1000Res.* **6**, 34 (2017).
9. Pereira, M. C., Vieira, M. M., Pereira, J. S. & Salgado, D. Adipsia in a diabetes insipidus patient. *Case Rep. Oncol.* **8**, 385–388 (2015).
10. Koch, C. A. & Fulop, T. Clinical aspects of changes in water and sodium homeostasis in the elderly. *Rev. Endocr. Metab. Disord.* **18**, 49–66 (2017).
11. Fitzsimons, J. T. The physiology of thirst and sodium appetite. *Monogr. Physiol. Soc.* **35**, 1–572 (1979).
12. Johnson, A. K. The sensory psychobiology of thirst and salt appetite. *Med. Sci. Sports Exerc.* **39**, 1388–1400 (2007).
13. McKinley, M. J. & Johnson, A. K. The physiological regulation of thirst and fluid intake. *News Physiol. Sci.* **19**, 1–6 (2004).
14. Zimmerman, C. A., Leib, D. E. & Knight, Z. A. Neural circuits underlying thirst and fluid homeostasis. *Nat. Rev. Neurosci.* **18**, 459–469 (2017).
This paper reviews recent studies dissecting the neural circuits underlying thirst.
15. Bourque, C. W. Central mechanisms of osmosensation and systemic osmoregulation. *Nat. Rev. Neurosci.* **9**, 519–531 (2008).
16. Verbalis, J. G. Disorders of body water homeostasis. *Best Pract. Res. Clin. Endocrinol. Metab.* **17**, 471–503 (2003).
17. Lafontan, M., Visscher, T. L., Farpour-Lambert, N. & Yumuk, V. Opportunities for intervention strategies for weight management: global actions on fluid intake patterns. *Obes. Facts* **8**, 54–76 (2015).
18. Popkin, B. M., D'Anci, K. E. & Rosenberg, I. H. Water, hydration, and health. *Nutr. Rev.* **68**, 439–458 (2010).
19. Orlandi, C., Zimmer, C. A. & Gheorghiade, M. Tolvaptan for the treatment of hyponatremia and congestive heart failure. *Future Cardiol.* **2**, 627–634 (2006).
20. Redondo, N., Gomez-Martinez, S. & Marcos, A. Sensory attributes of soft drinks and their influence on consumers' preferences. *Food Function* **5**, 1686–1694 (2014).
21. Adler, S. M. & Verbalis, J. G. Disorders of body water homeostasis in critical illness. *Endocrinol. Metab. Clin. North Am.* **35**, 873–894 (2006).
22. Brvar, M. *et al.* Polydipsia as another mechanism of hyponatremia after 'ecstasy' (3,4 methyldioxymethamphetamine) ingestion. *Eur. J. Emerg. Med.* **11**, 302–304 (2004).
23. Kalantar-Zadeh, K., Nguyen, M. K., Chang, R. & Kurtz, I. Fatal hyponatremia in a young woman after ecstasy ingestion. *Nat. Clin. Pract. Nephrol.* **2**, 283–288 (2006).
24. Traub, S. J., Hoffman, R. S. & Nelson, L. S. The "ecstasy" hangover: hyponatremia due to 3,4-methylenedioxymethamphetamine. *J. Urban Health* **79**, 549–555 (2002).
25. Sandifer, M. G. Hyponatremia due to psychotropic drugs. *J. Clin. Psychiatry* **44**, 301–303 (1983).
26. Lu, X. & Wang, X. Hyponatremia induced by antiepileptic drugs in patients with epilepsy. *Expert Opin. Drug Safety* **16**, 77–87 (2017).
27. Furth, S. & Oski, F. A. Hyponatremia and water intoxication. *Am. J. Dis. Child.* **147**, 932–933 (1993).
28. Kushnir, M., Schattner, A., Ezri, T. & Konichezky, S. Schizophrenia and fatal self-induced water intoxication with appropriately-diluted urine. *Am. J. Med. Sci.* **300**, 385–387 (1990).
29. Patel, J. K. Polydipsia, hyponatremia, and water intoxication among psychiatric patients. *Hospital Commun. Psychiatry* **45**, 1073–1074 (1994).
30. Ofran, Y., Lavi, D., Opher, D., Weiss, T. A. & Elinav, E. Fatal voluntary salt intake resulting in the highest ever documented sodium plasma level in adults (255 mmol L^{-1}): a disorder linked to female gender and psychiatric disorders. *J. Intern. Med.* **256**, 525–528 (2004).
31. Turk, E. E., Schulz, F., Koops, E., Gehl, A. & Tsokos, M. Fatal hypernatremia after using salt as an emetic — report of three autopsy cases. *Leg. Med.* **7**, 47–50 (2005).
32. Kirkman, M. A., Albert, A. F., Ibrahim, A. & Doberenz, D. Hyponatremia and brain injury: historical and contemporary perspectives. *Neurocrit. Care* **18**, 406–416 (2013).
33. De Smet, H. R., Menadue, M. F., Oliver, J. R. & Phillips, P. A. Increased thirst and vasopressin secretion after myocardial infarction in rats. *Am. J. Physiol.* **285**, R1203–R1211 (2003).
34. Sonneville, R. *et al.* Understanding brain dysfunction in sepsis. *Ann. Intensive Care* **3**, 15 (2013).
35. Lyons, O. D., Bradley, T. D. & Chan, C. T. Hypervolemia and sleep apnea in kidney disease. *Semin. Nephrol.* **35**, 373–382 (2015).
36. Iwasa, M. & Takei, Y. Pathophysiology and management of hepatic encephalopathy 2014 update: ammonia toxicity and hyponatremia. *Hepatol. Res.* **45**, 1155–1162 (2015).
37. Wier, L. M. *et al. HCUP Facts and Figures: Statistics on Hospital-Based Care in the United States, 2009* (Agency for Healthcare and Research and Quality, 2011).
38. Magder, S. Volume and its relationship to cardiac output and venous return. *Crit. Care* **20**, 271 (2016).
39. Moranville, M. P., Mieure, K. D. & Santayana, E. M. Evaluation and management of shock states: hypovolemic, distributive, and cardiogenic shock. *J. Pharm. Pract.* **24**, 44–60 (2011).
40. Senay Jr., L. C. & Christensen, M. L. Changes in blood plasma during progressive dehydration. *J. Appl. Physiol.* **20**, 1136–1140 (1965).
41. Bedford, J. J. & Leader, J. P. Response of tissues of the rat to anisosmolality *in vivo*. *Am. J. Physiol.* **264**, R1164–R1179 (1993).
42. Ayus, J. C., Varon, J. & Arieff, A. I. Hyponatremia, cerebral edema, and noncardiogenic pulmonary edema in marathon runners. *Ann. Intern. Med.* **132**, 711–714 (2000).
43. Machino, T. & Yoshizawa, T. Brain shrinkage due to acute hypernatremia. *Neurology* **67**, 880 (2006).
44. Spigset, O. & Hedenmalm, K. Hyponatraemia and the syndrome of inappropriate antidiuretic hormone secretion (SIADH) induced by psychotropic drugs. *Drug Safety* **12**, 209–225 (1995).
45. Sterns, R. H. Disorders of plasma sodium—causes, consequences, and correction. *N. Engl. J. Med.* **372**, 55–65 (2015).
46. Stricker, E. M. & Sved, A. F. Thirst. *Nutr.* **16**, 821–826 (2000).
47. Rullier, S. Soif [French]. *Dictionaire des Sciences Medicales* **51**, 448–490 (1821).
48. Cannon, W. B. Croonian Lecture: The physiological basis of thirst. *Proc. R. Soc. Lond. B Biol. Sci.* **90**, 283–301 (1918).
49. Wettendorff, H. Modifications de sang sous l'influence de la privation d'eau: contribution a l'étude de la soif [French]. *Travaux du Laboratoire de Physiologie, Institut de Physiologie, Instituts, Solvay* **4**, 353–384. (1901).
50. Robinson, B. W. & Mishkin, M. Alimentary responses to forebrain stimulation in monkeys. *Exp. Brain Res.* **4**, 330–366 (1968).
51. Craig, A. D. How do you feel? Interoception: the sense of the physiological condition of the body. *Nat. Rev. Neurosci.* **3**, 655–666 (2002).
52. Craig, A. D. A new view of pain as a homeostatic emotion. *Trends Neurosci.* **26**, 303–307 (2003).
53. Denton, D. A., McKinley, M. J., Farrell, M. & Egan, G. F. The role of primordial emotions in the evolutionary origin of consciousness. *Conscious. Cogn.* **18**, 500–514 (2009).
54. Denton, D. *et al.* Correlation of regional cerebral blood flow and change of plasma sodium concentration during genesis and satiation of thirst. *Proc. Natl Acad. Sci. USA* **96**, 2532–2537 (1999).
55. Denton, D. *et al.* Neuroimaging of genesis and satiation of thirst and an interoceptor-driven theory of origins of primary consciousness. *Proc. Natl Acad. Sci. USA* **96**, 5304–5309 (1999).
56. Farrell, M. J. *et al.* Unique, common, and interacting cortical correlates of thirst and pain. *Proc. Natl Acad. Sci. USA* **103**, 2416–2421 (2006).
57. Saker, P. *et al.* Regional brain responses associated with drinking water during thirst and after its satiation. *Proc. Natl Acad. Sci. USA* **111**, 5379–5384 (2014).
58. Farrell, M. J. *et al.* Cortical activation and lamina terminalis functional connectivity during thirst and drinking in humans. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **301**, R623–R631 (2011).
This human fMRI study reveals the brain regions involved in generating thirst.
59. Egan, G. *et al.* Neural correlates of the emergence of consciousness of thirst. *Proc. Natl Acad. Sci. USA* **100**, 15241–15246 (2003).
60. Saker, P., Farrell, M. J., Egan, G. F., McKinley, M. J. & Denton, D. A. Overdrinking, swallowing inhibition, and regional brain responses prior to swallowing. *Proc. Natl Acad. Sci. USA* **113**, 12274–12279 (2016).
61. Becker, C. A., Flaisch, T., Renner, B. & Schupp, H. T. From thirst to satiety: the anterior mid-cingulate cortex and right posterior insula indicate dynamic changes in incentive value. *Front. Hum. Neurosci.* **11**, 234 (2017).
62. Duncan, G. E. *et al.* Metabolic mapping of functional activity in rat brain and pituitary after water deprivation. *Neuroendocrinology* **49**, 489–495 (1989).
63. Pastuskovas, C. V., Cassell, M. D., Johnson, A. K. & Thunhorst, R. L. Increased cellular activity in rat insular cortex after water and salt ingestion induced by fluid depletion. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **284**, R1119–R1125 (2003).
64. Craig, A. D. Interoception: the sense of the physiological condition of the body. *Curr. Opin. Neurobiol.* **13**, 500–505 (2003).
65. Hollis, J. H., McKinley, M. J., D'Souza, M., Kampe, J. & Oldfield, B. J. The trajectory of sensory pathways from the lamina terminalis to the insular and cingulate cortex; a neuroanatomical framework for the generation of thirst. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **294**, R1390–R1401 (2008).
This anatomical study demonstrates brain regions and circuits involved in generating thirst in rats.
66. McCormick, D. A. & Bal, T. Sensory gating mechanisms of the thalamus. *Curr. Opin. Neurobiol.* **4**, 550–556 (1994).
67. Andrews, W. H. & Orbach, J. Sodium receptors activating some nerves of perfused rabbit livers. *Am. J. Physiol.* **227**, 1273–1275 (1974).
68. Adachi, A. Thermosensitive and osmoreceptive afferent fibers in the hepatic branch of the vagus nerve. *J. Auton. Nerv. Syst.* **10**, 269–273 (1984).
69. Adachi, A., Niijima, A. & Jacobs, H. L. An hepatic osmoreceptor mechanism in the rat: electrophysiological and behavioral studies. *Am. J. Physiol.* **231**, 1043–1049 (1976).
70. Andrews, W. H. & Orbach, J. Effect of osmotic pressure on spontaneous afferent discharge in the nerves of the perfused rabbit liver. *Pflugers Arch.* **361**, 89–94 (1975).
71. Choi-Kwon, S. & Baertschi, A. J. Splanchnic osmosensation and vasopressin: mechanisms and neural pathways. *Am. J. Physiol.* **261**, E18–E25 (1991).
72. King, M. S. & Baertschi, A. J. Central neural pathway mediating splanchnic osmosensation. *Brain Res.* **550**, 268–278 (1991).
73. Haberich, F. J. Osmoreception in the portal circulation. *Fed. Proc.* **27**, 1137–1141 (1968).
74. Chwalbinska-Moneta, J. Role of hepatic portal osmoreception in the control of ADH release. *Am. J. Physiol.* **236**, E603–E609 (1979).
75. Baertschi, A. J. & Vallet, P. G. Osmosensitivity of the hepatic portal vein area and vasopressin release in rats. *J. Physiol.* **315**, 217–230 (1981).
76. Andersson, B., Jobin, M. & Olsson, K. A study of thirst and other effects of an increased sodium concentration in the 3rd brain ventricle. *Acta Physiol. Scand.* **69**, 29–36 (1967).
77. McKinley, M. J., Blaine, E. H. & Denton, D. A. Brain osmoreceptors, cerebrospinal fluid electrolyte composition and thirst. *Brain Res.* **70**, 532–537 (1974).
78. McKinley, M. J., Denton, D. A. & Weisinger, R. S. Sensors for antidiuresis and thirst — osmoreceptors or CSF sodium detectors? *Brain Res.* **141**, 89–103 (1978).
79. Olsson, K. Further evidence for the importance of CSF Na^+ concentration in central control of fluid balance. *Acta Physiol. Scand.* **88**, 183–188 (1973).

80. Olsson, K. Attenuation of dehydrative thirst by lowering of the CSF [Na^+]. *Acta Physiol. Scand.* **94**, 536–538 (1975).
81. Weisinger, R. S., Considine, P., Denton, D. A. & McKinley, M. J. Rapid effect of change in cerebrospinal fluid sodium concentration on salt appetite. *Nature* **280**, 490–491 (1979).
82. Vivas, L., Chiaraviglio, E. & Carrer, H. F. Rat organum vasculosum laminae terminalis *in vitro*: responses to changes in sodium concentration. *Brain Res.* **519**, 294–300 (1990).
83. Voisin, D. L. & Bourque, C. W. Integration of sodium and osmosensory signals in vasopressin neurons. *Trends Neurosci.* **25**, 199–205 (2002).
84. Noda, M. & Hiyama, T. Y. Sodium sensing in the brain. *Pflugers Arch.* **467**, 465–474 (2015).
85. Voisin, D. L., Chakfe, Y. & Bourque, C. W. Coincident detection of CSF Na^+ and osmotic pressure in osmoregulatory neurons of the supraoptic nucleus. *Neuron* **24**, 453–460 (1999).
86. Miller, R. L. & Loewy, A. D. ENaC γ-expressing astrocytes in the circumventricular organs, white matter, and ventral medullary surface: sites for Na^+ regulation by glial cells. *J. Chem. Neuroanat.* **53**, 72–80 (2013).
87. Miller, R. L., Wang, M. H., Gray, P. A., Salkoff, L. B. & Loewy, A. D. ENaC-expressing neurons in the sensory circumventricular organs become c-Fos activated following systemic sodium changes. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **305**, R1141–R1152 (2013).
88. Ruiz, C., Gutknecht, S., Delay, E. & Kinnamon, S. Detection of NaCl and KCl in TRPV1 knockout mice. *Chemical Senses* **31**, 813–820 (2006).
89. Teruyama, R., Sakuraba, M., Wilson, L. L., Wandrey, N. E. & Armstrong, W. E. Epithelial Na^+ sodium channels in magnocellular cells of the rat supraoptic and paraventricular nuclei. *Am. J. Physiol. Endocrinol. Metab.* **302**, E273–E285 (2012).
90. Tanaka, M. *et al.* Molecular and functional remodeling of electrogenic membrane of hypothalamic neurons in response to changes in their input. *Proc. Natl Acad. Sci. USA* **96**, 1088–1093 (1999).
91. Hiyama, T. Y. *et al.* Autoimmunity to the sodium-level sensor in the brain causes essential hypernatremia. *Neuron* **66**, 508–522 (2010).
92. Hiyama, T. Y., Watanabe, E., Okado, H. & Noda, M. The subfornical organ is the primary locus of sodium-level sensing by Na_x sodium channels for the control of salt-intake behavior. *J. Neurosci.* **24**, 9276–9281 (2004).
93. Hiyama, T. Y. *et al.* Na(x) channel involved in CNS sodium-level sensing. *Nat. Neurosci.* **5**, 511–512 (2002).
94. Matsumoto, M. *et al.* Channel properties of Na_x expressed in neurons. *PLoS ONE* **10**, e0126109 (2015).
95. Goldin, A. L. Resurgence of sodium channel research. *Annu. Rev. Physiol.* **63**, 871–894 (2001).
96. Bourque, C. W., Voisin, D. L. & Chakfe, Y. Stretch-inactivated cation channels: cellular targets for modulation of osmosensitivity in supraoptic neurons. *Progress Brain Res.* **139**, 85–94 (2002).
97. Ciura, S. & Bourque, C. W. Transient receptor potential vanilloid 1 is required for intrinsic osmoreception in organum vasculosum lamina terminalis neurons and for normal thirst responses to systemic hyperosmolality. *J. Neurosci.* **26**, 9069–9075 (2006).
98. Bourque, C. W., Oliet, S. H. & Richard, D. Osmoreceptors, osmoreception, and osmoregulation. *Front. Neuroendocrinol.* **15**, 231–274 (1994).
99. Desson, S. E. & Ferguson, A. V. Interleukin 1beta modulates rat subfornical organ neurons as a result of activation of a non-selective cationic conductance. *J. Physiol.* **550**, 113–122 (2003).
100. Amin, M. S. *et al.* Distribution of epithelial sodium channels and mineralocorticoid receptors in cardiovascular regulatory centers in rat brain. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **289**, R1787–R1797 (2005).
101. Watanabe, E. *et al.* Nav2/NaG channel is involved in control of salt-intake behavior in the CNS. *J. Neurosci.* **20**, 7743–7751 (2000).
102. Coble, J. P., Grobe, J. L., Johnson, A. K. & Sigmund, C. D. Mechanisms of brain renin angiotensin system-induced drinking and blood pressure: importance of the subfornical organ. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **308**, R238–R249 (2015).
103. Mimee, A., Smith, P. M. & Ferguson, A. V. Circumventricular organs: targets for integration of circulating fluid and energy balance signals? *Physiol. Behav.* **121**, 96–102 (2013).
104. Zimmerman, C. A. *et al.* Thirst neurons anticipate the homeostatic consequences of eating and drinking. *Nature* **537**, 680–684 (2016).
This study demonstrates that thirst-promoting SFO neurons are required for prandial thirst.
105. Miselis, R. R., Shapiro, R. E. & Hand, P. J. Subfornical organ efferents to neural systems for control of body water. *Science* **205**, 1022–1025 (1979).
106. Nissen, R., Bourque, C. W. & Renaud, L. P. Membrane properties of organum vasculosum lamina terminalis neurons recorded *in vitro*. *Am. J. Physiol.* **264**, R811–R815 (1993).
107. Kinsman, B. J., Simmonds, S. S., Browning, K. N. & Stocker, S. D. Organum vasculosum of the lamina terminalis detects NaCl to elevate sympathetic nerve activity and blood pressure. *Hypertension* **69**, 163–170 (2017).
108. Sibbald, J. R., Hubbard, J. I. & Sirett, N. E. Responses from osmosensitive neurons of the rat subfornical organ *in vitro*. *Brain Res.* **461**, 205–214 (1988).
109. Grob, M., Drolet, G. & Mouginot, D. Specific Na^+ sensors are functionally expressed in a neuronal population of the median preoptic nucleus of the rat. *J. Neurosci.* **24**, 3974–3984 (2004).
110. Tremblay, C. *et al.* Neuronal sodium leak channel is responsible for the detection of sodium in the rat median preoptic nucleus. *J. Neurophysiol.* **105**, 650–660 (2011).
111. Shimizu, H. *et al.* Glial Nax channels control lactate signaling to neurons for brain [Na^+] sensing. *Neuron* **54**, 59–72 (2007).
112. Camacho, A. & Phillips, M. I. Horseradish peroxidase study in rat of the neural connections of the organum vasculosum of the lamina terminalis. *Neurosci. Lett.* **25**, 201–204 (1981).
113. Oka, Y., Ye, M. & Zuker, C. S. Thirst driving and suppressing signals encoded by distinct neural populations in the brain. *Nature* **520**, 349–352 (2015).
This study demonstrates that SFO neurons containing nitric oxide synthase (NOS) promote thirst.
114. Gizowski, C., Zaelzer, C. & Bourque, C. W. Clock-driven vasopressin neurotransmission mediates anticipatory thirst prior to sleep. *Nature* **537**, 685–688 (2016).
This study demonstrates that thirst prior to sleep is driven by the circadian clock.
115. McKinley, M. J. *et al.* The median preoptic nucleus: front and centre for the regulation of body fluid, sodium, temperature, sleep and cardiovascular homeostasis. *Acta Physiol.* **214**, 8–32 (2015).
116. Saper, C. B. & Levisohn, D. Afferent connections of the median preoptic nucleus in the rat: anatomical evidence for a cardiovascular integrative mechanism in the anteroventral third ventricular (AV3V) region. *Brain Res.* **288**, 21–31 (1983).
117. Lind, R. W., Van Hoesen, G. W. & Johnson, A. K. An HRP study of the connections of the subfornical organ of the rat. *J. Comp. Neurol.* **210**, 265–277 (1982).
118. Nation, H. L., Nicoleau, M., Kinsman, B. J., Browning, K. N. & Stocker, S. D. DREADD-induced activation of subfornical organ neurons stimulates thirst and salt appetite. *J. Neurophysiol.* **115**, 3123–3129 (2016).
119. Abbott, S. B., Machado, N. L., Geerling, J. C. & Saper, C. B. Reciprocal control of drinking behavior by median preoptic neurons in mice. *J. Neurosci.* **36**, 8228–8237 (2016).
This study demonstrates that optogenetic activation of glutamatergic MnPO/OVLT neurons drives thirst.
120. Allen, W. E. *et al.* Thirst-associated preoptic neurons encode an aversive motivational drive. *Science* **357**, 1149–1155 (2017).
This study demonstrates that MnPO neurons encode the negative valence associated with thirst.
121. Gilman, A. The relation between blood osmotic pressure, fluid distribution and voluntary water intake. *Am. J. Physiol.* **120**, 323–328 (1937).
122. Wolf, A. V. Osmometric analysis of thirst in man and dog. *Am. J. Physiol.* **161**, 75–86 (1950).
123. Stricker, E. M. Osmoregulation and volume regulation in rats: inhibition of hypovolemic thirst by water. *Am. J. Physiol.* **217**, 98–105 (1969).
124. Anderson, J. W., Washburn, D. L. & Ferguson, A. V. Intrinsic osmosensitivity of subfornical organ neurons. *Neuroscience* **100**, 539–547 (2000).
125. Kucharczyk, J., Assaf, S. Y. & Mogenson, G. J. Differential effects of brain lesions on thirst induced by the administration of angiotensin-II to the preoptic region, subfornical organ and anterior third ventricle. *Brain Res.* **108**, 327–337 (1976).
126. Thrasher, T. N., Simpson, J. B. & Ramsay, D. J. Lesions of the subfornical organ block angiotensin-induced drinking in the dog. *Neuroendocrinology* **35**, 68–72 (1982).
127. Johnson, A. K. & Buggy, J. Periventricular preoptic-hypothalamus is vital for thirst and normal water economy. *Am. J. Physiol.* **234**, R122–R129 (1978).
128. Buggy, J. & Jonhson, A. K. Preoptic-hypothalamic periventricular lesions: thirst deficits and hypernatremia. *Am. J. Physiol.* **233**, R44–R52 (1977).
129. Thrasher, T. N., Keil, L. C. & Ramsay, D. J. Lesions of the organum vasculosum of the lamina terminalis (OVLT) attenuate osmotically-induced drinking and vasopressin secretion in the dog. *Endocrinology* **110**, 1837–1839 (1982).
130. Mangiapane, M. L., Thrasher, T. N., Keil, L. C., Simpson, J. B. & Ganong, W. F. Deficits in drinking and vasopressin secretion after lesions of the nucleus medianus. *Neuroendocrinology* **37**, 73–77 (1983).
131. Johnson, A. K., Cunningham, J. T. & Thunhorst, R. L. Integrative role of the lamina terminalis in the regulation of cardiovascular and body fluid homeostasis. *Clin. Exp. Pharmacol. Physiol.* **23**, 183–191 (1996).
132. McKinley, M. J. *et al.* Efferent neural pathways of the lamina terminalis subserving osmoregulation. *Progress Brain Res.* **91**, 395–402 (1992).
133. McKinley, M. J., Denton, D. A., Oldfield, B. J., De Oliveira, L. B. & Mathai, M. L. Water intake and the neural correlates of the consciousness of thirst. *Semin. Nephrol.* **26**, 249–257 (2006).
134. Ciura, S., Liedtke, W. & Bourque, C. W. Hypertonicity sensing in organum vasculosum lamina terminalis neurons: a mechanical process involving TRPV1 but not TRPV4. *J. Neurosci.* **31**, 14669–14676 (2011).
135. Zaelzer, C. *et al.* ΔN-TRPV1: a molecular co-detector of body temperature and osmotic stress. *Cell Rep.* **13**, 23–30 (2015).
136. Sharif-Naeini, R., Ciura, S., Zhang, Z. & Bourque, C. W. Contribution of TRPV channels to osmosensory transduction, thirst, and vasopressin release. *Kidney Int.* **73**, 811–815 (2008).
137. Sudbury, J. R., Ciura, S., Sharif-Naeini, R. & Bourque, C. W. Osmotic and thermal control of magnocellular neurosecretory neurons — role of an N-terminal variant of *trpv1*. *Eur. J. Neurosci.* **32**, 2022–2030 (2010).
138. Kinsman, B. *et al.* Osmoregulatory thirst in mice lacking the transient receptor potential vanilloid type 1 (TRPV1) and/or type 4 (TRPV4) receptor. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **307**, R1092–R1100 (2014).
139. Taylor, A. C., McCarthy, J. J. & Stocker, S. D. Mice Lacking the transient receptor vanilloid potential 1 (TRPV1) channel display normal thirst responses and central Fos activation to hypernatremia. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **294**, R1285–R1293 (2008).
140. Hussy, N., Deleuze, C., Pantaloni, A., Desarmenien, M. G. & Moos, F. Agonist action of taurine on glycine receptors in rat supraoptic magnocellular neurones: possible role in osmoregulation. *J. Physiol.* **502**, 609–621 (1997).
141. Choe, K. Y., Olson, J. E. & Bourque, C. W. Taurine release by astrocytes modulates osmosensitive glycine receptor tone and excitability in the adult supraoptic nucleus. *J. Neurosci.* **32**, 12518–12527 (2012).
142. Choe, K. Y., Trudel, E. & Bourque, C. W. Effects of salt loading on the regulation of rat hypothalamic magnocellular neurosecretory cells by ionotropic GABA and glycine receptors. *J Neuroendocrinol* **28** (2016).
143. Hussy, N., Deleuze, C., Desarmenien, M. G. & Moos, F. C. Osmotic regulation of neuronal activity: a new role for taurine and glial cells in a hypothalamic neuroendocrine structure. *Prog. Neurobiol.* **62**, 113–134 (2000).
144. Prager-Khoutorsky, M. & Bourque, C. W. Anatomical organization of the rat organum vasculosum laminae terminalis. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **309**, R324–R337 (2015).
145. Hochstenbach, S. L. & Ciriello, J. Effect of lesions of forebrain circumventricular organs on c-fos expression in the central nervous system to plasma hypernatremia. *Brain Res.* **713**, 17–28 (1996).
146. Lechner, S. G. *et al.* The molecular and cellular identity of peripheral osmoreceptors. *Neuron* **69**, 332–344 (2011).

147. Russell, P. J., Abdelaal, A. E. & Mogenson, G. J. Graded levels of hemorrhage, thirst and angiotensin II in the rat. *Physiol. Behav.* **15**, 117–119 (1975).
148. Fitzsimons, J. T. Drinking by rats depleted of body fluid without increase in osmotic pressure. *J. Physiol.* **159**, 297–309 (1961).
149. Joris, L., Dab, I. & Quinton, P. M. Elemental composition of human airway surface fluid in healthy and diseased airways. *Am. Rev. Respir. Dis.* **148**, 1633–1637 (1993).
150. Zardetto-Smith, A. M., Thunhorst, R. L., Cicha, M. Z. & Johnson, A. K. Afferent signaling and forebrain mechanisms in the behavioral control of extracellular fluid volume. *Ann. NY Acad. Sci.* **689**, 161–176 (1993).
151. Fitzsimons, J. T. Angiotensin, thirst, and sodium appetite. *Physiol Rev.* **78**, 583–686 (1998).
152. Stocker, S. D., Stricker, E. M. & Sved, A. F. Arterial baroreceptors mediate the inhibitory effect of acute increases in arterial blood pressure on thirst. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **282**, R1718–R1729 (2002).
153. Stocker, S. D., Stricker, E. M. & Sved, A. F. Acute hypertension inhibits thirst stimulated by ANG II, hyperosmolality, or hypovolemia in rats. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **280**, R214–R224 (2001).
154. Stricker, E. M. & Sved, A. F. Controls of vasopressin secretion and thirst: similarities and dissimilarities in signals. *Physiol. Behav.* **77**, 731–736 (2002).
155. Dampney, R. A., Polson, J. W., Potts, P. D., Hirooka, Y. & Horiuchi, J. Functional organization of brain pathways subserving the baroreceptor reflex: studies in conscious animals using immediate early gene expression. *Cell. Mol. Neurobiol.* **23**, 597–616 (2003).
156. Thunhorst, R. L., Xu, Z., Cicha, M. Z., Zardetto-Smith, A. M. & Johnson, A. K. Fos expression in rat brain during depletion-induced thirst and salt appetite. *Am. J. Physiol.* **274**, R1807–R1814 (1998).
157. Badoer, E., McKinley, M. J., Oldfield, B. J. & McAllen, R. M. Distribution of hypothalamic, medullary and lamina terminalis neurons expressing Fos after hemorrhage in conscious rats. *Brain Res.* **582**, 323–328 (1992).
158. Potts, P. D., Ludbrook, J., Gillman-Gaspari, T. A., Horiuchi, J. & Dampney, R. A. Activation of brain neurons following central hypervolaemia and hypovolaemia: contribution of baroreceptor and non-baroreceptor inputs. *Neuroscience* **95**, 499–511 (2000).
159. Godino, A., Giusti-Paiva, A., Antunes-Rodrigues, J. & Vivas, L. Neurochemical brain groups activated after an isotonic blood volume expansion in rats. *Neuroscience* **133**, 493–505 (2005).
160. Howe, B. M., Bruno, S. B., Higgs, K. A., Stigers, R. L. & Cunningham, J. T. FosB expression in the central nervous system following isotonic volume expansion in unanesthetized rats. *Exp. Neurol.* **187**, 190–198 (2004).
161. Randolph, R. R., Li, Q., Curtis, K. S., Sullivan, M. J. & Cunningham, J. T. Fos expression following isotonic volume expansion of the unanesthetized male rat. *Am. J. Physiol.* **274**, R1345–R1352 (1998).
162. Gizowski, C. & Bourque, C. W. Neurons that drive and quench thirst. *Science* **357**, 1092–1093 (2017).
163. Simpson, J. B. & Routtenberg, A. Subfornical organ: a dipsogenic site of action of angiotensin II. *Science* **201**, 379–381 (1978).
164. Simpson, J. B. & Routtenberg, A. Subfornical organ: site of drinking elicitation by angiotensin II. *Science* **181**, 1172–1175 (1973).
165. Antunes-Rodrigues, J., de Castro, M., Elias, L. L., Valenca, M. M. & McCann, S. M. Neuroendocrine control of body fluid metabolism. *Physiol. Rev.* **84**, 169–208 (2004).
166. Kuwahara, K. & Nakao, K. Regulation and significance of atrial and brain natriuretic peptides as cardiac hormones. *Endocr. J.* **57**, 555–565 (2010).
167. Ehrlich, K. J. & Fitts, D. A. Atrial natriuretic peptide in the subfornical organ reduces drinking induced by angiotensin or in response to water deprivation. *Behav. Neurosci.* **104**, 365–372 (1990).
168. Stanhewicz, A. E. & Kenney, W. L. Determinants of water and sodium intake and output. *Nutr. Rev.* **73** (Suppl. 2), 73–82 (2015).
169. Stricker, E. M. & Stricker, M. L. Pre-systemic controls of fluid intake and vasopressin secretion. *Physiol. Behav.* **103**, 86–88 (2011).
170. Fitzsimons, T. J. & Le Magnen, J. Eating as a regulatory control of drinking in the rat. *J. Comp. Physiol. Psychol.* **67**, 273–283 (1969).
171. Mandelblat-Cerf, Y. *et al.* Bidirectional anticipation of future osmotic challenges by vasopressin neurons. *Neuron* **93**, 57–65 (2017).
172. Hatton, G. I. & Almli, C. R. Plasma osmotic pressure and volume changes as determinants of drinking thresholds. *Physiol. Behav.* **4**, 207–214 (1969).
173. Gamble, J. L., Putnam, M. C. & McKhann, C. F. The optimal water requirement in renal functions: 1. Measurements of water drinking by rats according to increments of urea and of several salts in the food. *Am. J. Physiol.* **88**, 571–580 (1929).
174. Kraly, F. S., Kim, Y. M., Dunham, L. M. & Tribuzio, R. A. Drinking after intragastric NaCl without increase in systemic plasma osmolality in rats. *Am. J. Physiol.* **269**, R1085–R1092 (1995).
175. Stricker, E. M., Huang, W. & Sved, A. F. Early osmoregulatory signals in the control of water intake and neurohypophyseal hormone secretion. *Physiol. Behav.* **76**, 415–421 (2002).
176. Manesh, R., Hoffmann, M. L. & Stricker, E. M. Water ingestion by rats fed a high-salt diet may be mediated, in part, by visceral osmoreceptors. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **290**, R1742–R1749 (2006).
177. Krause, E. G., de Kloet, A. D. & Sakai, R. R. Post-ingestive signals and satiation of water and sodium intake of male rats. *Physiol. Behav.* **99**, 657–662 (2010).
178. Kobashi, M. & Adachi, A. Projection of nucleus tractus solitarius units influenced by hepatoportal afferent signal to parabrachial nucleus. *J. Autonom. Nerv. System* **16**, 153–158 (1986).
179. Kobashi, M. & Adachi, A. Convergence of hepatic osmoreceptive inputs on sodium-responsive units within the nucleus of the solitary tract of the rat. *J. Neurophysiol.* **54**, 212–219 (1985).
180. Stricker, E. M. & Hoffmann, M. L. Presystemic signals in the control of thirst, salt appetite, and vasopressin secretion. *Physiol. Behav.* **91**, 404–412 (2007).
181. Morita, H. *et al.* Fos induction in rat brain neurons after stimulation of the hepatoportal Na-sensitive mechanism. *Am. J. Physiol.* **272**, R913–923 (1997).
182. Starbuck, E. M. & Fitts, D. A. Influence of the subfornical organ on meal-associated drinking in rats. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **280**, R669–R677 (2001).
183. Gu, G. B. & Ju, G. The parabrachio-subfornical organ projection in the rat. *Brain Res. Bull.* **38**, 41–47 (1995).
184. Han, Z. S., Gu, G. B., Sun, C. Q. & Ju, G. Convergence of somatosensory and baroreceptive inputs onto parabrachio-subfornical organ neurons in the rat: an electrophysiological study. *Brain Res.* **566**, 239–247 (1991).
185. McKinley, M. J. *et al.* The sensory circumventricular organs of the mammalian brain. *Adv. Anat. Embryol. Cell Biol.* **172**, III–XII (2003).
186. Sladek, C. D. & Johnson, A. K. Integration of thermal and osmotic regulation of water homeostasis: the role of TRPV channels. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **305**, R669–R678 (2013).
187. Bel'skaya, L. V., Kosenok, V. K. & Sarf, E. A. Chronophysiological features of the normal mineral composition of human saliva. *Arch. Oral Biol.* **82**, 286–292 (2017).
188. Lund, J. P., Barker, J. H., Dellow, P. G. & Stevenson, J. A. Water intake of normal and desalivate rats on exposure to environmental heat. *Can. J. Physiol. Pharmacol.* **47**, 849–852 (1969).
189. Grace, J. E. & Stevenson, J. A. Thermogenic drinking in the rat. *Am. J. Physiol.* **220**, 1009–1015 (1971).
190. Box, B. M., Montis, F., Yeomans, C. & Stevenson, J. A. Thermogenic drinking in cold-acclimated rats. *Am. J. Physiol.* **225**, 162–165 (1973).
191. Barney, C. C. & Folkerts, M. M. Thermal dehydration-induced thirst in rats: role of body temperature. *Am. J. Physiol.* **269**, R557–R564 (1995).
192. Morrison, S. F. & Nakamura, K. Central neural pathways for thermoregulation. *Front. Biosci.* **16**, 74–104 (2011).
193. Palkar, R., Lippoldt, E. K. & McKemy, D. D. The molecular and cellular basis of thermosensation in mammals. *Curr. Opin. Neurobiol.* **34**, 14–19 (2015).
194. Schepers, R. J. & Ringkamp, M. Thermoreceptors and thermosensitive afferents. *Neurosci. Biobehav. Rev.* **34**, 177–184 (2010).
195. Craig, A. D., Bushnell, M. C., Zhang, E. T. & Blomqvist, A. A thalamic nucleus specific for pain and temperature sensation. *Nature* **372**, 770–773 (1994).
196. Nakamura, K. & Morrison, S. F. A thermosensory pathway that controls body temperature. *Nat. Neurosci.* **11**, 62–71 (2008).
197. Jessen, C., Feistkorn, G. & Nagel, A. Temperature sensitivity of skeletal muscle in the conscious goat. *J. Appl. Physiol.* **54**, 880–886 (1983).
198. Fajardo, O., Meseguer, V., Belmonte, C. & Viana, F. TRPA1 channels mediate cold temperature sensing in mammalian vagal sensory neurons: pharmacological and genetic evidence. *J. Neurosci.* **28**, 7863–7875 (2008).
199. Riedel, W. Warm receptors in the dorsal abdominal wall of the rabbit. *Pflugers Arch.* **361**, 205–206 (1976).
200. Rawson, R. O. & Quick, K. P. Localization of intra-abdominal thermoreceptors in the ewe. *J. Physiol.* **222**, 665–667 (1972).
201. Adelson, D. W., Wei, J. Y. & Kruger, L. Warm-sensitive afferent splanchnic C-fiber units *in vitro*. *J. Neurophysiol.* **77**, 2989–3002 (1997).
202. Wit, A. & Wang, S. C. Temperature-sensitive neurons in preoptic-anterior hypothalamic region: effects of increasing ambient temperature. *Am. J. Physiol.* **215**, 1151–1159 (1968).
203. Takamata, A., Mack, G. W., Stachenfeld, N. S. & Nadel, E. R. Body temperature modification of osmotically induced vasopressin secretion and thirst in humans. *Am. J. Physiol.* **269**, R874–880 (1995).
204. Boulant, J. A. Cellular mechanisms of temperature sensitivity in hypothalamic neurons. *Progress Brain Res.* **115**, 3–8 (1998).
205. Fealey, R. D. Interoception and autonomic nervous system reflexes thermoregulation. *Handb. Clin. Neurol.* **117**, 79–88 (2013).
206. Morrison, S. F. Central control of body temperature. *F1000Res.* **5**, 880 (2016).
207. Boulant, J. A. Hypothalamic mechanisms in thermoregulation. *Fed. Proc.* **40**, 2843–2850 (1981).
208. Barbour, H. G. Die wirkung unmittelbarer erwarmung und abkuhlung der warmezentra auf die korpertemperatur [German]. *Arch. Exp. Path. Pharmak.* **70**, 1–15 (1912).
209. Hammouda, M. The central and the reflex mechanism of panting. *J. Physiol.* **77**, 319–336 (1933).
210. Magoun, H. W., Harrison, F., Brobeck J. R., Ranson, S. W. & Paolini, P. Activation of heat loss mechanisms by local heating of the brain. *J. Neurophysiol.* **87**, 885–905 (1986).
211. Jacobson, F. H. & Squires, R. D. Thermoregulatory responses of the cat to preoptic and environmental temperatures. *Am. J. Physiol.* **218**, 1575–1582 (1970).
212. Szczepanska-Sadowska, E. Plasma ADH increase and thirst suppression elicited by preoptic heating in the dog. *Am. J. Physiol.* **226**, 155–161 (1974).
213. Morrison, S. F., Nakamura, K. & Madden, C. J. Central control of thermogenesis in mammals. *Exp. Physiol.* **93**, 773–797 (2008).
214. Tan, C. L. *et al.* Warm-sensitive neurons that control body temperature. *Cell* **167**, 47–59.e15 (2016).
215. Nakamura, K. & Morrison, S. F. A thermosensory pathway mediating heat-defense responses. *Proc. Natl Acad. Sci. USA* **107**, 8848–8853 (2010).
216. Andersson, B. & Larsson, B. Influence of local temperature changes in the preoptic area and rostral hypothalamus on the regulation of food and water intake. *Acta Physiol. Scand.* **52**, 75–89 (1961).
217. Trudel, E. & Bourque, C. W. Circadian modulation of osmoregulated firing in rat supraoptic nucleus neurones. *J. Neuroendocrinol.* **24**, 577–586 (2012).
218. Moon, D. G. *et al.* Antidiuretic hormone in elderly male patients with severe nocturia: a circadian study. *BJU Int.* **94**, 571–575 (2004).
219. Miller, M. Nocturnal polyuria in older people: pathophysiology and clinical implications. *J. Am. Geriatr. Soc.* **48**, 1321–1329 (2000).
220. Tokonami, N. *et al.* Local renal circadian clocks control fluid-electrolyte homeostasis and BP. *J. Am. Soc. Nephrol.* **25**, 1430–1439 (2014).
221. Firsov, D., Tokonami, N. & Bonny, O. Role of the renal circadian timing system in maintaining water and electrolytes homeostasis. *Mol. Cell. Endocrinol.* **349**, 51–55 (2012).
222. Asplund, R. Nocturia, nocturnal polyuria, and sleep quality in the elderly. *J. Psychosom. Res.* **56**, 517–525 (2004).
223. Windle, R. J., Forsling, M. L. & Guzek, J. W. Daily rhythms in the hormone content of the neurohypophysial system and release of oxytocin and vasopressin in the male rat: effect of constant light. *J. Endocrinol.* **133**, 283–290 (1992).

224. Trudel, E. & Bourque, C. W. Central clock excites vasopressin neurons by waking osmosensory afferents during late sleep. *Nat. Neurosci.* **13**, 467–474 (2010).
225. Spiteri, N. J. Circadian patterning of feeding, drinking and activity during diurnal food access in rats. *Physiol. Behav.* **28**, 139–147 (1982).
226. Satinoff, E. & Prosser, R. A. Suprachiasmatic nuclear lesions eliminate circadian rhythms of drinking and activity, but not of body temperature, in male rats. *J. Biol. Rhythms* **3**, 1–22 (1988).
227. Johnson, R. F., Beltz, T. G., Thunhorst, R. L. & Johnson, A. K. Investigations on the physiological controls of water and saline intake in C57BL/6 mice. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **285**, R394–R403 (2003).
228. Lee, J. E. *et al.* Endogenous peptide discovery of the rat circadian clock: a focused study of the suprachiasmatic nucleus by ultrahigh performance tandem mass spectrometry. *Mol. Cell. Proteom.* **9**, 285–297 (2010).
229. Abrahamson, E. E. & Moore, R. Y. Suprachiasmatic nucleus in the mouse: retinal innervation, intrinsic organization and efferent projections. *Brain Res.* **916**, 172–191 (2001).
230. Kalsbeek, A. & Buijs, R. M. Output pathways of the mammalian suprachiasmatic nucleus: coding circadian time by transmitter selection and specific targeting. *Cell Tissue Res.* **309**, 109–118 (2002).
231. Moore, R. Y., Speh, J. C. & Leak, R. K. Suprachiasmatic nucleus organization. *Cell Tissue Res.* **309**, 89–98 (2002).
232. Appelgren, B., Eriksson, S. & Jonasson, H. Oro-gastro-intestinal inhibition of hypernatremia-induced drinking in the goat. *Acta Physiol. Scand.* **115**, 273–280 (1982).
233. Wood, R. J., Rolls, E. T. & Rolls, B. J. Physiological mechanisms for thirst in the nonhuman primate. *Am. J. Physiol.* **242**, R423–R428 (1982).
234. Krashes, M. J. Physiology: Forecast for water balance. *Nature* **537**, 626–627 (2016).
235. Zocchi, D., Wennemuth, G. & Oka, Y. The cellular mechanism for water detection in the mammalian taste system. *Nat. Neurosci.* **20**, 927–933 (2017).
236. Blass, E. M., Jobaris, R. & Hall, W. G. Oropharyngeal control of drinking in rats. *J. Comp. Physiol. Psychol.* **90**, 909–916 (1976).
237. Maddison, S., Wood, R. J., Rolls, E. T., Rolls, B. J. & Gibbs, J. Drinking in the rhesus monkey: peripheral factors. *J. Comp. Physiol. Psychol.* **94**, 365–374 (1980).
238. Davis, J. D., Smith, G. P. & McCann, D. P. The control of water and sodium chloride intake by postingestional and orosensory stimulation in water-deprived rats. *Physiol. Behav.* **75**, 7–14 (2002).
239. Paintal, A. S. Impulses in vagal afferent fibres from stretch receptors in the stomach and their role in the peripheral mechanism of hunger. *Nature* **172**, 1194–1195 (1953).
240. Malbert, C. H. & Leitner, L. M. Mechanoreceptors sensitive to flow at the gastroduodenal junction of the cat. *Am. J. Physiol.* **265**, G310–G313 (1993).
241. Paintal, A. S. A study of gastric stretch receptors; their role in the peripheral mechanism of satiation of hunger and thirst. *J. Physiol.* **126**, 255–270 (1954).
242. Raybould, H. E., Gayton, R. J. & Dockray, G. J. CNS effects of circulating CCK8: involvement of brainstem neurones responding to gastric distension. *Brain Res.* **342**, 187–190 (1985).
243. Olson, B. R. *et al.* c-Fos expression in rat brain and brainstem nuclei in response to treatments that alter food intake and gastric motility. *Mol. Cell. Neurosci.* **4**, 93–106 (1993).
244. Hyde, T. M. & Miselis, R. R. Area postrema and adjacent nucleus of the solitary tract in water and sodium balance. *Am. J. Physiol.* **247**, R173–R182 (1984).
245. Curtis, K. S., Verbalis, J. G. & Stricker, E. M. Area postrema lesions in rats appear to disrupt rapid feedback inhibition of fluid intake. *Brain Res.* **726**, 31–38 (1996).
246. Curtis, K. S. & Stricker, E. M. Enhanced fluid intake by rats after capsaicin treatment. *Am. J. Physiol.* **272**, R704–R709 (1997).
247. Hajat, S., Vardoulakis, S., Heaviside, C. & Eggen, B. Climate change effects on human health: projections of temperature-related mortality for the UK during the 2020s, 2050s and 2080s. *J. Epidemiol. Commun. Health* **68**, 641–648 (2014).
248. Robertson, G. L., Shelton, R. L. & Athar, S. The osmoregulation of vasopressin. *Kidney Int.* **10**, 25–37 (1976).

Acknowledgements
The authors' work is supported by a Foundation Grant from the Canadian Institutes of Health Research (CIHR, FDN 143337), an operating grant from the Heart and Stroke Foundation of Canada (G-16-00014197), a James McGill Chair to C.W.B., and a Frederick Banting and Charles Best Canada Graduate Scholarship Doctoral Award to C.G. The Research Institute of the McGill University Health Centre receives generous funding from the Fonds de Recherche Québec Santé.

Author contributions
Both authors researched the data for the article, discussed its content and contributed to writing and editing the manuscript before submission.

Competing interests statement
The authors declare no competing interests.

Publisher's note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.