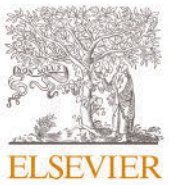
Neuropharmacology 256 (2024) 110009



Contents lists available at ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm

Fluid transitions

Jessica Santollo [a,*], Derek Daniels [b,c]

[a] Department of Biology, University of Kentucky, Lexington, KY 40506, USA
[b] Department of Biology, University at Buffalo, State University of New York, Buffalo, NY 14260, USA
[c] Center for Ingestive Behavior Research, University at Buffalo, State University of New York, Buffalo, NY 14260, USA

ARTICLE INFO

Keywords:
Thirst
Angiotensin II
GLP-1
Estradiol
Satiation

ABSTRACT

Water is critical for survival and thirst is a powerful way of ensuring that fluid levels remain in balance. Overconsumption, however, can have deleterious effects, therefore optimization requires a need to balance the drive for water with the satiation of that water drive. This review will highlight our current understanding of how thirst is both generated and quenched, with particular focus on the roles of angiotensin II, glucagon like-peptide 1, and estradiol in turning on and off the thirst drive. Our understanding of the roles these bioregulators play has benefited from modern behavioral analyses, which have improved the time resolution of intake measures, allowing for attention to the details of the patterns within a bout of intake. This has led to behavioral interpretation in ways that are helpful in understanding the many controls of water intake and has expanded our understanding beyond the dichotomy that something which increases water intake is simply a "stimulator" while something that decreases water intake is simply a "satiety" factor. Synthesizing the available information, we describe a framework in which thirst is driven directly by perturbations in fluid intake and indirectly modified by several bioregulators. This allows us to better highlight areas that are in need of additional attention to form a more comprehensive understanding of how the system transitions between states of thirst and satiety.

This article is part of the Special Issue on "Food intake and feeding states".

1. Introduction

The transition from thirsty to quenched is a common experience, but the importance of it for survival is underappreciated. Of course, we recognize that thirst and hunger are formidable motivated states. Water is critical for survival and thirst is a powerful way of ensuring that fluid levels remain in balance, much in the same way that energy is critical, and hunger is a powerful way of ensuring that sufficient nutrients are consumed to support survival. Indeed, food or water deprivation are used to create these states to drive behavior experimentally, often simply to reward a behavior or performance on a task that has nothing to do with the study of ingestive behavior. But these motivated states can also bring harm. Water or food seeking can drive risky behavior. For instance, spending too much time at an open water or food source can provide opportunities for predators. Moreover, overconsumption of food or of water can have deleterious consequences. Thus, an optimal system requires a need to balance the drive with the satiation of that drive.

2. Why do we transition to drinking?

Most research on the neural control of thirst and on the signals that stimulate drinking have been informed by the double-depletion hypothesis that was originally proposed by Fitzsimons (Fitzsimons, 1973) and Epstein (Epstein, 1973). According to this framework, depletion of water occurs in either the extracellular or the intracellular compartment (see Table 1 for terminology that is frequently used in the literature and in this review). When fluid is lost from the extracellular space (aka extracellular dehydration, hypovolemic dehydration, hypovolemia), it triggers mechanisms that are primarily pressure-sensing in the cardiovascular system. Key components of this detection include baroreceptors that inform the brain of the volume loss through vagal afferents, and the kidney, which detects low pressure and starts the process of synthesizing angiotensin II (Ang II; described in detail below). Because fluid lost from the extracellular compartment often carries both water and solutes in the water, a complete restoration of the lost fluid includes both thirst and sodium appetite (Daniels and Fluharty, 2004; Daniels and Fluharty, 2009; Santollo et al., 2023). Unlike the loss that occurs with depletion of the extracellular space, a loss of fluid from the intracellular space (aka

* Corresponding author. Department of Biology, University of Kentucky, 675 Rose Street, Lexington, KY. 40406, USA.
E-mail address: j.santollo@uky.edu (J. Santollo).

https://doi.org/10.1016/j.neuropharm.2024.110009
Received 15 February 2024; Received in revised form 21 May 2024; Accepted 23 May 2024
Available online 31 May 2024

Table 1
Definitions and usage common in the thirst field.

Fluid State & Synonyms	Definition	Response
•Intracellular Dehydration •Osmotic Dehydration •Intracellular Depletion	Loss of fluids from within the cell (intracellular space/compartment), generally caused by increased tonicity of the extracellular space and the resultant osmosis	Osmotic Thirst
•Extracellular Dehydration •Hypovolemic Dehydration •Hypovolemia •Extracellular Depletion	Loss of fluids and electrolytes from the plasma & interstitial fluids (extracellular compartment)	Hypovolemic Thirst Volumetric Thirst
•Endogenous Intake •Unstimulated Intake •Need-free Intake •Circadian Intake •Overnight Intake •Daily Intake	Intake across a period of time (often daily) that is not stimulated by an injury or experimental manipulation, but that occurs more normally	

intracellular dehydration, osmotic dehydration) is not a true dehydration but is instead a shift of fluid from the intracellular to the extracellular space. This shift is generally caused by an increase in the osmolality of the extracellular space that draws water from the inside to the outside of the cell. Under these conditions, the physical change in shape and membrane properties of the cell, caused by the water loss, triggers a response in osmoreceptive cells that generates thirst and drives water intake. In this case, however, consumption of sodium would exacerbate the osmotic imbalance. Sodium appetite is, therefore, not present, even though it may be stimulated, but is simultaneously suppressed by oxytocin (Blackburn, Samson et al., 1993). In addition to drinking in response to immediate and rapid fluid loss, mammals are constantly losing fluids from breathing, sweating, and excretion. This is in addition to any intracellular dehydration produced by ingesting food. Animals, therefore, are constantly replacing these lost fluids in a non-emergency setting throughout the day to maintain fluid balance. We will refer to this continuous consumption, in the laboratory often measured in 24-h periods, as endogenous water intake.[1]

When conceptualizing the controls of fluid intake we draw inspiration from the direct and indirect controls of food intake described in Smith's classic review on the controls of meal size (Smith, 1996). Our usage of direct and indirect differs somewhat from how Smith used these terms, but the framework described here clearly borrows from Smith's ideas. For an understanding of the controls of fluid intake, we find it helpful to define a direct control of fluid intake as one that causes the animal to transition from a state of not drinking to a state of drinking. In this framework, AngII, osmoreceptors, and baroreceptors fall into the category of direct controls. Indirect control differs from direct control in that indirect control affects the likelihood an animal will continue to drink or will stop drinking, but bioregulators that fall into the indirect category do not directly stimulate intake on their own. In Section 5, we further describe the roles of AngII, which provides direct control of fluid intake, and glucagon like-peptide 1 (GLP-1) and estradiol, both of which provide indirect control of fluid intake. In addition to directly or indirectly influencing fluid intake, there exist tertiary controls of intake that form an extended neural circuit in the control of thirst and drinking. These include signals such as dopamine (Mietlicki-Baase, Santollo et al., 2021), which is released both in response to drinking but also in response to learned cues associated with fluid intake (Fortin and Roitman, 2018; Hsu, Bazzino et al., 2020). We believe that this framework helps clarify the various roles that substances can play in the control of fluid intake and provides an important mechanistic perspective for classifying any newly discovered influences on thirst and fluid intake.

3. Why do we transition to not drinking?

Although the systems that detect fluid perturbations and respond by initiating thirst have been well studied, the process by which thirst is quenched is poorly understood. Limiting intake is very important. From a clinical standpoint, excess body fluid can lead to hypertension, a risk factor for cardiovascular disease and in extreme cases, polydipsia can result in death due to hyponatremia (colloquially known as water intoxication). As mentioned above, from an ecological standpoint, spending too much time at an open water source puts an animal at risk of predation. Thus, it is important to understand how thirst is quenched and drinking bouts are terminated. An obvious and simple (although flawed) explanation of how thirst is quenched is that as the animal drinks, in response to the thirst, the water that is consumed restores the fluid that was lost, thereby removing the stimulus (the deficit) that triggered the thirst response. The flaw in this idea is clear based on studies showing that drinking, and release of vasopressin, stop well before the consumed fluid can circulate and correct the fluid imbalance. This is true in laboratory animals and in human subjects (Rolls, Wood et al., 1980; Thrasher, Nistal-Herrera et al., 1981; Arnauld and du Pont, 1982; Geelen, Keil et al., 1984; Blair-West, Gibson et al., 1985; Takamata, Mack et al., 1995; Stricker and Hoffmann, 2005; McKinley, Weissenborn et al., 2009). Studies using more recently developed approaches have demonstrated that some parts of the circuit respond in an anticipatory manner, with activity that corrects when the anticipated fluid intake does not occur. For instance, vasopressin-expressing cells become active when mice are not allowed to drink for a period of time, and this activity rapidly decreases when drinking begins (Mandelblat-Cerf, Kim et al., 2017), well before the water consumed would have time to reach these brain areas and decrease the osmotic imbalance caused by the water restriction. If, however, the mice are presented with an empty water vessel, the rapid decrease in activity in the vasopressin neurons is still observed, but only transiently with a similarly rapid return to the active state associated with water deprivation. Thus, the feedback from the act of drinking appears to have a learned component as well as a means to correct what is expected, and this feedback reaches the same cells that are involved in stimulating drinking. Because this is clearly more than a simple removal of the deficit that stimulated the drinking (occurring before the deficit is removed), an active process appears to be involved. How this feedback occurs is a source of current study.

Feedback from ingestion seems likely to flow through hindbrain structures. Indeed, gastric distention elicits signals that are relayed through prodynorphin (pdyn) cells in the parabrachial nucleus and the activation of these signaling cells suppresses water intake (Kim, Heo et al., 2020). It is not clear the role these cells play in overall fluid intake, however, because some reports show that the pdyn neurons are activated upon sodium deprivation and activation of these neurons increases sodium intake (Lee, Augustine et al., 2019; Gasparini et al., 2021). Other studies on gut-brain feedback related to drinking suggest that gastric osmolality is an important signal in thirst satiation

[1] Various terms have been used in the literature to describe intake that is generated by an experimental manipulation or intake that occurs more normally. In some instances, the intake occurring more naturally has been referred to as "need-free' or "unstimulated' intake. Although we find these terms useful in that they draw a contrast between intake that occurs without manipulating the animal and intake that occurs after a manipulation, we cannot escape the inaccuracy. Indeed, the intake is not "need-free' because the animal needs water to survive. Likewise, it is not "unstimulated' because something is stimulating the intake (e.g., the change in lights or the change in osmolality induced by eating). Accordingly, we feel that "endogenous" or "exogenous" are better ways to describe, respectively, the intake that occurs as part of the normal daily activity of the animal in contrast with the intake that occurs as the result of an experimental manipulation.

(Zimmerman et al., 2019; Corpuz et al., 2019). But signals from the gut are not the only means by which intake is suppressed. Indeed, gastric bypass in rats failed to have any observed impact on fluid intake after a variety of challenges (Marshall, Santollo et al., 2014) and it has been known since the 1950s that water consumed by mouth is more satiating than water infused into the gut (Miller, Sampliner et al., 1957). The sensing of water in the mouth is detected at least in part via acid-sensing taste receptor cells (Zocchi, Wennemuth et al., 2017) and signals arising from these cells appear to be important for thirst-related forebrain activation (Augustine et al., 2018). Selective activation of these cells alone is not, however, satiating (Zocchi, Wennemuth et al., 2017), suggesting that there is an additional oropharyngeal signal required for the satiation caused by drinking. Nevertheless, there appear to be signals for fluid intake termination that arise from various levels of the orogastric tract and it seems plausible to hypothesize that some of the same neural circuits that carry satiety signals from the gut are overlapping with those that carry signals from the mouth. This is an area that is ripe for exploration.

4. Measuring intake

A full consideration of our current understanding of the systems that govern hunger and thirst is informed by ways that scientists have studied these motivated states and the intake they drive. The amount (vol/wt) of water or food consumed is fairly simple to measure by providing a known quantity to a laboratory animal and measuring what remains after some period of time. Modern refinements have used a variety of ways to improve the time resolution of these measures (e.g., contact lickometers, beam break detection, and load cells that allow for frequent weighing of food hoppers without disturbing the animal), allowing for attention to the details of the patterns within a bout of intake. This has allowed scientists to interpret the behavior in ways that clarify the physiological controls of the behavior. Differences in eating or licking patterns, for example, have provided ways to test hypotheses about the impact of a manipulation on different properties of the substance being ingested. For example, measures of licking patterns can be used to test hypotheses about the effect of a drug on satiation. Indeed, decades of research and fine analyses of lick patterns show that a manipulation that affects the hedonic value (orosensory) of a substance will have a primary effect on the number of licks in a licking burst (Davis, 1989, Davis, Smith et al., 1999). In contrast, a manipulation that impacts satiation during a bout of drinking will have a primary effect on the number of licking bursts within a bout of drinking (Davis, 1989, Davis, Smith et al., 1999). Other measures, such as latency to consume food or water after the experimental manipulation, can provide additional information about the onset or decline of the drive state. These kinds of analyses have been critical in developing an understanding of the systems that govern intake, however, the utility of drinking microstructure analysis is most informative when focusing on the indirect controls of intake. This is because, in the framework presented earlier, a direct control of intake (e.g. AngII) causes the animal to transition from a state of not drinking to drinking. In that scenario both burst number and burst size will obviously differ from when the animal is not drinking because there are no licks to form bursts in the absence of drinking. These analyses are, nonetheless, very helpful in understanding the nature of indirect controls of intake and whether they have a primary effect on the hedonics or satiation.

5. Bioregulators

A variety of chemical signals form or act upon the circuits that drive thirst and thirst satiation. Some of these have been identified as controlling both eating and drinking (Taylor, Bagley et al., 2005; Samson, White et al., 2007; Mietlicki, Nowak et al., 2009; McKay, Kanoski et al., 2011; Yosten, Redlinger et al., 2012; Santollo and Daniels, 2015; Mietlicki-Baase, McGrath et al., 2017; Kurt, Woodworth et al., 2019; Kurt, Kodur et al., 2022; Santollo and Daniels, 2015), while others are more selectively relevant for control of fluid (e.g. atrial naturietic peptide (McCann, Gutkowska et al., 1994) or food (e.g., CCK (Kraly, Carty et al., 1978)) intake. Although the bioregulators that affect thirst with or without effects on hunger, are numerous, several key bioregulators have emerged (AngII, glucagon-like peptide-1, and estradiol). This is not to say that these are the most important bioregulators, but they are arguably the best studied. We have, therefore, selected them for review here. Indeed, learning how these bioregulators control intake reveals important aspects of the system. In this respect, directionality is important to consider, but the direction of the observed response may reflect different mechanisms. For instance, upon discovering that a particular bioregulator stimulates intake, we should not jump to the conclusion that termination of intake involves removal of that bioregulator. In colloquial terms, it is important to think of the control of intake like we would the accelerator and brake functions in an automobile. The automobile can slow down by removing the accelerator or by applying the brake (or by both actions), but it would be irresponsible to observe a slowing automobile and assume that one or the other was responsible for the slowing without more information. Likewise, as we learn more about the bioregulators that are involved in the control of fluid intake, we are repeatedly finding separate roles of complicated signals in increasing and decreasing intake (Fig. 1).

5.1. Angiotensin II

It is arguable that AngII is the most recognized and well characterized bioregulator of water intake. Stimulation of drinking by AngII has been well documented in the literature and is a key signaling peptide in response to a deficit in extracellular volume (Fitzsimons and Simons, 1969; Epstein, Fitzsimons et al., 1970; Hsiao, Epstein et al., 1977). The loss of extracellular fluids is detected by both aortic and carotid baroreceptors along with juxtaglomerular and macula densa cells of the kidney. The kidney releases the enzyme renin, which cleaves the prohormone angiotensinogen to angiotensin I, which is then converted to the active hormone AngII by angiotensin converting enzyme (ACE). AngII has myriad physiological effects to restore blood volume, including activating central angiotensin type 1 receptors (AT1R) in circumventricular organs, specifically the subfornical organ (SFO) and organum vasculosum laminae terminalis (OVLT), which stimulate water intake. The brain also locally synthesizes AngII in response to AngII binding, and this centrally produced AngII then acts in a transmitter-like manner to stimulate water intake (Sigmund, 2012, Coble, Grobe et al., 2015); however, whether this centrally produced AngII is necessary for the stimulation of intake remains unclear. Various transgenic models that overexpress brain renin-angiotensin system (RAS) signaling demonstrate that AngII neurotransmission increases endogenous water intake. Overexpression of SFO AngII or selective production of SFO AngII doubles daily endogenous water intake in mice, but this intake can be prevented by an AngII receptor antagonist (Sakai, Agassandian et al., 2007; Coble, Cassell et al., 2014). Furthermore, transgenic mice with brain RAS hyperactivity have increased daily endogenous water intake, which is mediated by an increase in aldosterone production. Adrenalectomy in these mice restores daily water intake to the levels observed in wild-type mice (Grobe, Grobe et al., 2010). Additional studies are necessary to understand the interactions between peripheral and central AngII signaling in controlling water intake and if central AngII signaling is necessary for drinking.

Pharmacological, optogenetic, and knockout studies all support the role of AngII in stimulating water intake. Ventricular, SFO, or OVLT injection of AngII drive water intake in a dose dependent manner in rodents (Epstein, Fitzsimons et al., 1969; Epstein, Fitzsimons et al., 1970; Fitzsimons, 1971; Simpson and Routtenberg, 1973; Xu and Xinghong, 1999; Vento and Daniels, 2014; Santollo, Torregrossa et al., 2017) and blockade of the type 1 AngII receptor (AT1R) with the antagonist losartan inhibits AngII-induced water intake (Rowland,

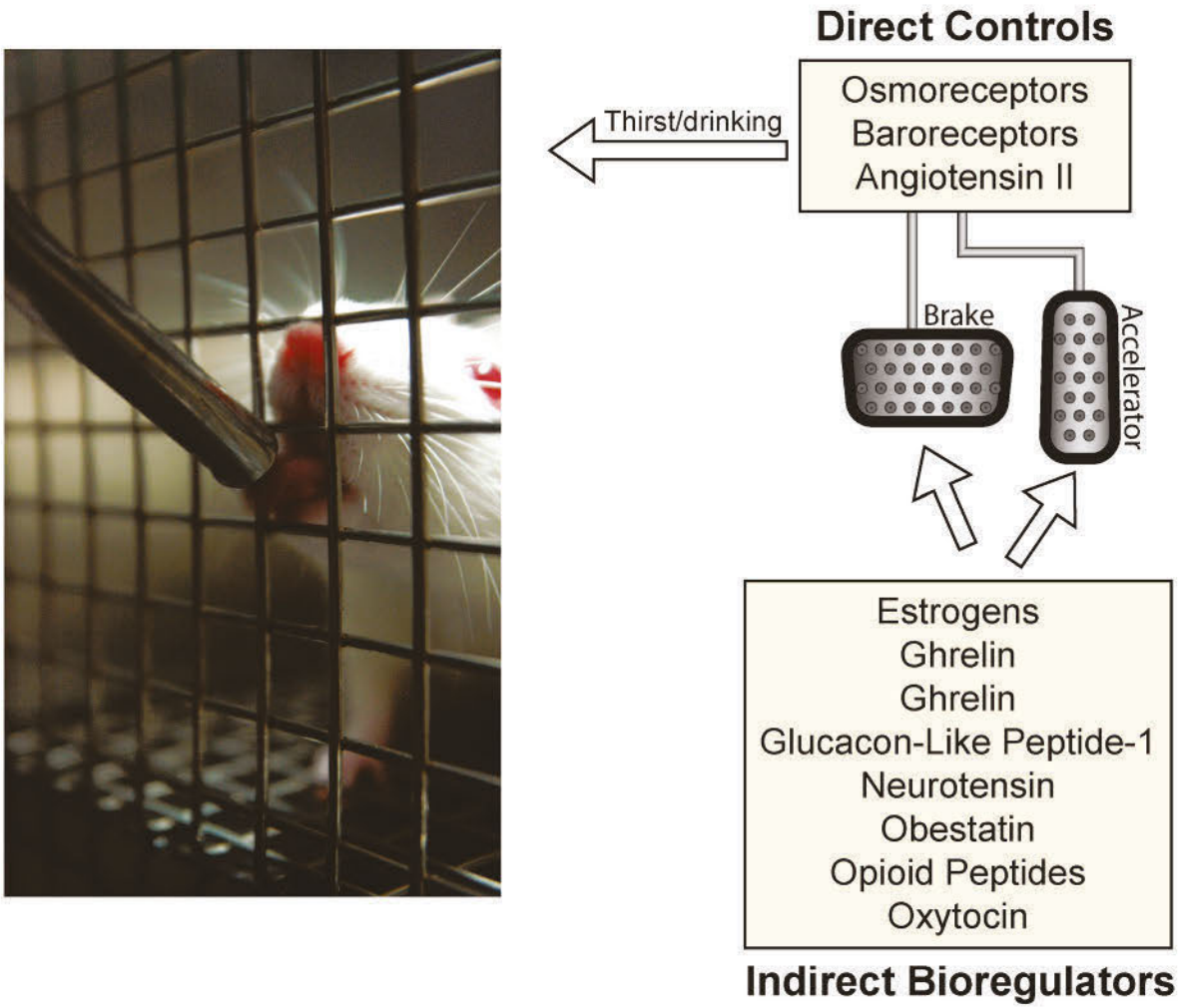


Fig. 1. Direct and indirect controls of thirst and fluid intake. Thirst and the resulting fluid intake are initiated by direct controls that are responsible for signaling a fluid deficit in the intracellular or extracellular space. Indirect controls modify the intake that occurs in response to the direct controls by potentiating or attenuating the impact of the direct controls.

Morien et al., 1996; Grippo, Kirby et al., 2002; Crews and Rowland, 2005; Daniels and Marshall, 2012), especially when forebrain AT1R is targeted (Daniels and Marshall, 2012). Optogenetic and chemogenetic activation of AT1R expressing cells in the SFO and OVLT also increases water intake in sated rodents (Oka, Ye et al., 2015; Matsuda, Hiyama et al., 2017; Kinsman, Simmonds et al., 2020). This apparent role of AngII as a bioregulator that triggers drinking is experimentally supported by myriad studies showing drinking in response to AngII as well as more nuanced studies showing that AngII dose-dependently decreases the latency to drink (Anke, Van Eekelen et al., 1988). Furthermore, studies from mice lacking the angiotensinogen gene demonstrate the involvement of AngII in hypovolemic thirst. While drinking in response to intracellular dehydration is intact in angiotensinogen knockout mice, there is inhibited drinking in response to an injection of a colloid, which induces extracellular fluid loss. A corresponding decrease in Fos expression in the SFO and OVLT is observed under these conditions. Surprisingly, endogenous water intake in mice lacking angiotensinogen is approximately three times larger than in wild-type controls (McKinley, Walker et al., 2008). The increased water intake appears to be mediated by impaired kidney function resulting in the inability to concentrate urine. Interestingly, restoring brain, cardiac, or adipose, but not renal, angiotensinogen corrects the renal defect, and in brain- and cardiac-replaced mice there is a reduced daily water intake, but not to wild type levels (Lochard, Silversides et al., 2003). Angiotensinogen rescue in multiple tissues may be necessary to return endogenous water intake to wild-type levels, however, if endogenous intake requires peripheral AngII, lack of the angiotensinogen would predictably lower water intake beyond that observed in wild-type mice. Therefore, based on the available knockout models, peripheral AngII likely does not play a role in endogenous water intake in mice. This is consistent with the double-depletion framework in which AngII is primarily involved in the response to extracellular depletion (more likely emergency-related), whereas osmoreceptors underly responses to intracellular depletion (more likely caused by routine daily events).

5.2. *Glucagon-like peptide 1*

Glucagon-like peptide-1 (GLP-1) has emerged as a candidate satiety signal for both eating and drinking. Determining which GLP-1 responsive cells are important for thirst has been confounded by the overlap between eating and drinking. Initial evidence for a role for GLP-1 in the control of drinking by pharmacological manipulation of the GLP-1 receptor (GLP-1R) was compelling, but did not rule out the possibility that the decrease in drinking was secondary to a decrease in food intake (Navarro, Rodriquez de Fonseca et al., 1996; Tang-Christensen, Larsen et al., 1996; Wang, Edwards et al., 1998; Larsen, Fledelius et al., 2001). Subsequent studies performed this test by measuring the effect of GLP-1R agonists on drinking in rats that were not allowed to eat, showing that the fluid intake suppression by GLP-1R agonist treatment persisted, even if there was no decrease in food intake (McKay, Kanoski

et al., 2011). Importantly, drinking microstructure analysis demonstrates that the inhibitory effect of GLP-1 is due to changes in post-ingestive feedback. For example, GLP-1R agonist treatment reduces water and saline intake via reductions in burst number, with no change in burst size (McKay and Daniels, 2013). Furthermore, blocking endogenous GLP-1 signaling with the antagonist exendin-9 increases water intake via an increase in burst number, again with no change in burst size (McKay, Galante et al., 2014). Analysis of overnight intake after central injection of a GLP-1R agonist found a treatment-associated difference in both burst number and burst size, but the length of the test leaves open the possibility that one preceded the other (Brakey et al., 2023). Nevertheless, the available data provide strong licking microstructure-based evidence to support the role of GLP-1 as a satiety signal.

Additional experiments provide evidence for clear differences between the effect of GLP-1 on eating and on drinking. For instance, levels of circulating GLP-1 do not increase after water-deprived rats are allowed to drink, but do increase after eating in food-deprived rats (McKay, Galante et al., 2014). Measures of brain GLP-1 expression were, however, affected by either eating or drinking (McKay, Galante et al., 2014). Other findings indirectly support the idea that eating involves both central and peripheral GLP-1 whereas drinking more selectively involves the central GLP-1 system. For instance, maintenance on a high-fat diet attenuates the food intake suppression by GLP-1R agonist treatment, but only when the drug is delivered centrally (Williams, Hyvarinen et al., 2011). In contrast, maintenance on high-fat diet had no effect on the water intake suppression by a GLP-1R agonist (Volcko, Carroll et al., 2020). Whether or not the central GLP-1 system has elements that are selective for food or for water intake control is in need of additional study.

More recently the Brattleboro rat, a rodent model of diabetes insipidus, has emerged as a potential way to tease apart GLP-1 circuits involved in eating and drinking. Brattleboro rats are severely polydipsic because of marked polyuria. The high level of drinking occurs without any differences in the size of licking bursts, but is entirely because Brattleboro rats have more bursts of licking throughout the day (Brakey et al., 2023), suggesting that Brattleboro rats lack the satiating feedback from drinking that occurs in wildtype rats. This difference in satiety, and previous work suggesting that GLP-1 is important for intake satiation, support the hypothesis that GLP-1 function is different in Brattleboro rats. Indeed, Brattleboro rats are hypersensitive to the fluid intake suppression caused by treatment with a GLP-1R agonist (Brakey et al., 2023). This alone makes them an interesting model for the study of GLP-1, but the finding that they are comparable to wildtype rats in the suppression of food intake after GLP-1R treatment opens the exciting possibility that whatever aspect of GLP-1 that is different in Brattleboro rats will reveal drinking-specific parts of the GLP-1 system. Additional research using this model is underway.

5.3. Estradiol

Historically, the role of estrogens in controlling water intake was thought to be inhibitory, like its well characterized anorexigenic effect. Across the estrous cycle, endogenous 24-h water intake is reduced on the day of estrus (Antunes Rodrigues and Covian, 1963; Tarttelin and Gorski, 1971; Findlay et al., 1979; Danielsen and Buggy, 1980; Eckel, Houpt et al., 2000; Santollo et al., 2021). Ovariectomy increases endogenous 24-h water intake (Tarttelin and Gorski, 1971; Santollo, Edwards et al., 2021), and estradiol (the most potent circulating estrogen) replacement decreases intake (Spiteri, Drewett et al., 1980; Santollo, Edwards et al., 2021). Because rats are prandial drinkers, it is important to ask if the effect on fluid intake is direct or if it occurs secondary to a decrease in food intake. Two key findings answer this question. First, in rats, the estrus-related decrease in 24-h water persists when rats are not allowed to eat (Santollo, Edwards et al., 2021). Second, in ovariectomized (OVX) guinea pigs, restricting food intake to 30% less than ad libitum levels abolished the anorexigenic effect of exogenous estradiol treatment but the *anti*-dipsogenic effect remained intact (Czaja, Butera et al., 1983). Thus, even when food and water intakes are uncoupled, the effect of estrogens on water intake remains. Drinking in response to dehydration is also inhibited by estrogens. Although estradiol does not appear to be involved in osmotic thirst (Findlay et al., 1979; Jonklaas and Buggy, 1984; Krause, Curtis et al., 2003; Mecawi, Lepletier et al., 2008), multiple reports demonstrate estradiol's impact on hypovolemic thirst. Multiple laboratories have reported that estradiol decreases water intake in response to 24-h water deprivation in ovariectomized rats (Krause, Curtis et al., 2003; Mecawi, Lepletier et al., 2008; Vilhena-Franco, Mecawi et al., 2016; Howell, Edwards et al., 2024). Although water deprivation clearly causes dehydration, estradiol also inhibits water intake in response to treatments that model portions of dehydration and its relevant signals. For instance, AngII is a powerful dipsogen and part of the response to extracellular dehydration. Although drinking occurs after AngII injection throughout the estrous cycle, drinking after AngII is lowest on the day of estrus than it is on other days of the estrous cycle (Findlay, Fitzsimons et al., 1979; Danielsen and Buggy, 1980). Furthermore, in OVX rats, estradiol treatment reduces AngII-induced drinking, demonstrating that estradiol and not other ovarian hormones mediates the change in intake (Fregly, 1978; Fregly and Thrasher, 1978; Jonklaas and Buggy, 1984; Kisley, Sakai et al., 1999; Santollo and Daniels, 2015; Santollo, Marshall et al., 2016; Santollo, Collett et al., 2021). Estradiol also reduces water intake that is caused by other treatments that stimulate the renin-angiotensin system. For example, estradiol decreases drinking in OVX rats treated with isoproterenol (Thrasher and Fregly, 1978; Krause et al., 2003; Graves, Hayes et al., 2011), renin (Thrasher and Fregly, 1977), furosemide + captopril (Mecawi, Lepletier et al., 2008), or 24-h sodium deprivation (Mecawi, Lepletier et al., 2008), each of which stimulates the release of endogenous AngII. The drinking effects of estradiol occur through activation of estrogen receptor alpha (Santollo, Marshall et al., 2016), similar to its anorexigenic effect (Santollo, Wiley et al., 2007; Thammacharoen, Geary et al., 2009), via both nuclear and membrane-associated receptors (Santollo, Marshall et al., 2013). Of note, the drinking stimulated by these various dipsogens occurs in the absence of food intake, providing additional support for a primary inhibitory role of estradiol in the controls of water intake.

The estrogenic inhibition of water intake is consistent with the general sense that estrogens promote satiety or otherwise serve as a satiety signal. Indeed, this notion is supported by findings related to drinking microstructure patterns. Both estradiol and the ERα agonist PPT reduce endogenous 24-h water intake in OVX rats via reductions in both burst number and burst size (Santollo, Marshall et al., 2013; Santollo, Marshall et al., 2016). As previously discussed, changes in burst number are associated with post-ingestive feedback signals, implicating estradiol in reducing water intake via increasing satiety-specific or satiety-related (i.e. gastric stretch) signals. In addition, estradiol and PPT-treatment in OVX rats reduce AngII-stimulated water intake through changes in burst number, providing additional support for the notion that estradiol increases satiety or satiety-related signaling to enhance water intake termination. The critical satiety signals that estradiol augments are unknown, which may not be surprising given that the critical satiety signals for thirst are overall poorly understood. Past research focused heavily on the hypothesis that direct interactions between estradiol and AngII were responsible for the attenuated drinking responses. These efforts, however, failed to find the hypothesized interactions. For example, estradiol does not influence plasma renin activity in response to isoproterenol treatment (Krause, Curtis et al., 2006), suggesting estradiol does not influence endogenous AngII production. Estradiol also fails to influence AT1R expression when changes in body weight are considered (Krause, Curtis et al., 2006; Santollo, Marshall et al., 2016). Although studying estradiol-AngII interactions was a reasonable approach, it is now unsurprising that estradiol-AngII interactions do not underlie the estrogenic inhibition of

water intake because of the newer appreciation that estradiol is more related to satiation and AngII is more involved in stimulation of water intake. That does not mean that estradiol acts alone. Indeed, recent data suggest that estradiol enhances the sensitivity of the *anti*-dipsogenic effect of GLP-1 (Howell, Edwards et al., 2024). This is a promising step in identifying the bioregulators that estradiol augments and presents an important opportunity for future research investment.

Recent data from our group has drastically expanded our understanding of the estrogenic control of water intake. Despite decades of research describing the estrogenic inhibition of water intake, in 2021 we demonstrated that under certain testing conditions, estradiol can increase water intake in OVX rats (Santollo, Edwards et al., 2021). In the absence of food, estradiol increases endogenous 24-h water intake, through activation of ERβ (Santollo, Edwards et al., 2021; Santollo and Edwards, 2023). Exogenous estradiol also increases rebound drinking, in response to an acute pharmacological suppression of intake, in OVX rats (Santollo, Edwards et al., 2021). In both of these experiments, the drive to drink was experimentally reduced. In the first experiment, removal of food caused an approximate 60% reduction in 24 h water intake and in the second experiment our drug manipulation abolished water intake for a minimum of 4 h. This has led us to hypothesize, that in contexts where the motivation to drink is low, or suppressed, E2 acts to enhance water intake. Although not measured, the differences in intake that were observed, may be a function of latency to drink. In support of this idea, experiments using OVX rats found that estradiol reduces the latency to drink in response to hypertonic saline treatment, despite no hormone-mediated change in total volumetric consumption (Jones and Curtis, 2009). More work is needed to explore the role estradiol may have in changing drinking latency. Consistent with estradiol's inhibitory role in water intake, the increase in endogenous 24-h water intake is also associated with a change in burst number. This change, of course, is in the opposite direction of the *anti*-dipsogenic effect, suggesting that estradiol is weakening the satiety signals that would normally terminate intake. Whether or not estradiol augments the same satiety signals, just in different directions, to both increase and decrease water intake or if different satiety signals are involved in increasing vs decreasing water intake, is an open question.

6. Circadian and seasonal control of water intake

A discussion of transitions between hydration and dehydration need also to consider circadian and seasonal influences. Nocturnal rodents consume most of their water intake during the dark (active phase), similar to their patterns of food intake; however, the nocturnal nature of water intake is not strictly the result of prandial drinking. When food access is restricted to the light phase, the majority of water intake still occurs during the dark phase (Spiteri, 1982). In support for the circadian control of water intake, lesions of the suprachiasmatic nucleus (SCN), the master circadian clock, result in an equal distribution of water intake across the active and inactive phase in Siberian Hamsters (Bittman, Bartness et al., 1991). But how the clock controls water intake is unclear and an open area of research. Interestingly, it has been noted that both rats and mice show an increase in water intake just before the inactive phase (Spiteri, 1982; Johnson, Beltz et al., 2003; Gizowski, Zaelzer et al., 2016). In an eloquent series of experiments, Bourque and colleagues demonstrated that this anticipatory water intake is mediated by the central clock SCN neurons and not physiological need. This anticipatory water intake maintains hydromineral balance throughout the inactive phase (Gizowski, Zaelzer et al., 2016). Specifically, SCN vasopressin neurons excite OVLT neurons via V1a receptors during the 2 h period prior to lights on, which drives water intake. Expanding upon the 24-h control of water intake, seasonal changes in water influx have been reported in a variety of desert dwelling rodents (Stallone, 1979; Degen, 1991; Nagy, 1994). These changes, however, are secondary to changes in dietary content. In these environments, the winter vegetation has a significantly greater water content resulting in greater water influx in the winter, compared to summer months. Whether seasonal cycles influence water intake independent of the water content of the diet in animals living outside of desert climates is unclear and an interesting area of future research.

7. Concepts and future thoughts

Although significant progress has been made in our understanding of the control of thirst and thirst satiation, there are some seemingly important unanswered questions. Despite decades of research on the role of AngII in drinking, it is still not clear if centrally generated AngII is necessary for drinking and if so, is it specific to propagating the signal generated by circulating AngII acting on the brain? It seems likely that central AngII is important, given its position in the circuit and the clear importance of AngII in general, but a specific role has yet to be demonstrated.

The demonstration of numerous bioregulators in the control of thirst is clear progress in our understanding of how thirst is controlled. With the knowledge that these bioregulators play some role in thirst, we now must try to better understand which of the dipsogenic indirect controls act by stimulating drinking or by removing an inhibition of drinking. Conversely, we need to determine if substances with *anti*-dipsogenic properties act by inhibiting stimulation or by terminating drinking (Fig. 1). Studies of estradiol could be especially promising in this respect because it either increases or decreases drinking depending on the context.

Layered upon the complexity of understanding the transition from thirsty to quenched, we must also recognize the intertwined role that food intake plays. In addition to being another drive state that transitions from on to off (or off to on), the frequent co-occurrence of hunger and thirst and the overlapping circuits and bioregulators involved in both create additional complications in studying each in isolation. This is clear in the attempts to understand the roles of estrogens and of GLP-1 in the control of intake. Recent work with the Brattleboro rat suggests one approach to disentangling these drive states, at least with respect to GLP-1, but this approach lacks the ease of genetic manipulation that is abundant in studies using mice, and these types of approaches in rats are still well behind those that are common in mice. A mouse model of the Brattleboro rat could be useful, but to the best of our knowledge, attempts to generate that model have largely been unsuccessful and we are unaware of any tests of GLP-1 effects in other models of diabetes insipidus.

From a broader perspective, the study of drinking has been a critical part of how we understand motivated behaviors. Studies of drinking have helped form ideas about consummatory vs appetitive phases of behavior and have provided a useful and reliable model for the study of peptide and traditional transmitters in the control of behavior. Although we have a strong understanding of the stimuli that trigger drinking, our understanding of the termination of drinking remains somewhat murkier. A better understanding of this, along with a better understanding of how food intake satiation occurs, will allow for a potentially important comparison that will likely reveal overlapping and non-overlapping substrates. This is critical for a full understanding of how the brain functions. We are also in a state of imbalance in our understanding of how experience shapes eating and drinking, with much more attention being paid to the impact of experience on food choice and reactions to energy imbalance. This may be largely because drinking has been considered more innate and less flexible. Studies of sensitization and desensitization of both water and sodium intake (Pereira et al., 2010; Vento and Daniels, 2010; Vento and Daniels, 2012; Vento et al., 2012; Hurley and Johnson, 2013; Hurley et al., 2014; Hurley et al., 2014; Santollo et al., 2014; Vento and Daniels, 2014; Pereira-Derderian et al., 2016; Postolache et al., 2017) show that this is perhaps an unfair characterization. Likewise, early life experience shapes drinking behavior. This is clear from studies of preweanling rats (Myers, Arnold et al., 1997) and from rats only allowed to drink saline or sucrose

solutions from weaning until adulthood (Volcko, Brakey et al., 2020). But these studies barely scratch the surface of how learning and experience may shape water intake. Accordingly, the role of learning is ripe for study. Related to this, understanding differences in reward processes that drive water and that drive food intake could be productive avenues to a better understanding of both intake control and reward. Food intake appears related to both positive and negative reinforcement. Water, however, seems to be more related to negative reinforcement. In more colloquial terms, we often eat for pleasure even when we are not eating to ease the pang of hunger, but deriving pleasure from water intake seems far more limited to times when that water is quenching a thirst. Of course, this may be an apples to oranges (or chocolate to dry toast) comparison. The foods most often consumed as positive reinforcers are a select subset of those eaten for negative reinforcement, but water is always just water. Without more work in this area, the answers to these questions and a better understanding of the system will remain a mystery.

CRediT authorship contribution statement

Jessica Santollo: Writing – review & editing, Writing – original draft, Conceptualization. **Derek Daniels:** Writing – review & editing, Writing – original draft, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

Acknowledgements

We thank Kevin Myers and Reviewer 1 for helping us conceptualize the framework of direct and indirect controls of fluid intake. This work was supported by the National Science Foundation [grant 2019346] to JS and the National Institutes of Health [grant DK133818] to DD.

References

Anke, J., Van Eekelen, M., Phillips, M.I., 1988. Plasma angiotensin II levels at moment of drinking during angiotensin II intravenous infusion. Am. J. Physiol. 255 (3 Pt 2), R500–R506.
Antunes Rodrigues, J., Covian, M.R., 1963. Hypothalamic control of sodium chloride and water intake. Acta Physiol Lat Am 13, 94–100.
Arnauld, E., du Pont, J., 1982. Vasopressin release and firing of supraoptic neurosecretory neurones during drinking in the dehydrated monkey. Pflügers Archiv 394 (3), 195–201.
Augustine, V., Gokce, S.K., Lee, S., Wang, B., Davidson, T.J., Reimann, F., Gribble, F., Deisseroth, K., Lois, C., Oka, Y., 2018. Hierarchical neural architecture underlying thirst regulation. Nature 555 (7695), 204–209.
Bittman, E.L., Bartness, T.J., Goldman, B.D., DeVries, G.J., 1991. Suprachiasmatic and paraventricular control of photoperiodism in Siberian hamsters. Am. J. Physiol. 260 (1 Pt 2), R90–R101.
Blackburn, R.E., Samson, W.K., Fulton, R.J., Stricker, E.M., Verbalis, J.G., 1993. Central oxytocin inhibition of salt appetite in rats: evidence for differential sensing of plasma sodium and osmolality. Proc. Natl. Acad. Sci. U. S. A. 90 (21), 10380–10384.
Blair-West, J.R., Gibson, A.P., Woods, R.L., Brook, A.H., 1985. Acute reduction of plasma vasopressin levels by rehydration in sheep. Am. J. Physiol. 248 (1 Pt 2), R68–R71.
Brakey, D.J., Schatz, K.C., Paul, M.J., Daniels, D., 2023. The role of glucagon-like peptide- 1 (GLP-1) in fluid and food intakes in vasopressin-deficient Brattleboro rats. Physiol. Behav. 262, 114093.
Coble, J.P., Cassell, M.D., Davis, D.R., Grobe, J.L., Sigmund, C.D., 2014. Activation of the renin-angiotensin system, specifically in the subfornical organ is sufficient to induce fluid intake. Am. J. Physiol. Regul. Integr. Comp. Physiol. 307 (4), R376–R386.
Coble, J.P., Grobe, J.L., Johnson, A.K., Sigmund, C.D., 2015. Mechanisms of brain renin angiotensin system-induced drinking and blood pressure: importance of the subfornical organ. Am. J. Physiol. Regul. Integr. Comp. Physiol. 308 (4), R238–R249.
Corpuz, L. Madisen, Zeng, H., Knight, Z.A., 2019. A gut-to-brain signal of fluid osmolarity controls thirst satiation. Nature 568 (7750), 98–102.
Crews, E.C., Rowland, N.E., 2005. Role of angiotensin in body fluid homeostasis of mice: effect of losartan on water and NaCl intakes. Am. J. Physiol. Regul. Integr. Comp. Physiol. 288 (3), R638–R644.
Czaja, J.A., Butera, P.C., McCaffrey, T.A., 1983. Independent effects of estradiol on water and food intake. Behav. Neurosci. 97 (2), 210–220.
Daniels, D., Fluharty, S.J., 2004. Salt appetite: a neurohormonal viewpoint. Physiol. Behav. 81 (2), 319–337.
Daniels, D., Fluharty, S.J., 2009. Neuroendocrinology of body fluid homeostasis. In: Pfaff, D.W., Arnold, A.P., Fahrbach, S.E., Etgen, A.M., Rubin, R.T. (Eds.), *Hormones Brain and Behavior. Neuroendocrinology of Body Fluid Homeostasis*, Second edition. Academic Press, San Diego, pp. 259–288.
Daniels, D., Marshall, A., 2012. Evaluating the potential for rostral diffusion in the cerebral ventricles using angiotensin II-induced drinking in rats. Brain Res. 1486, 62–67.
Danielsen, J., Buggy, J., 1980. Depression of ad lib and angiotensin-induced sodium intake at oestrus. Brain Res. Bull. 5 (5), 501–504.
Davis, J.D., 1989. The microstructure of ingestive behavior. Ann. N. Y. Acad. Sci. 575, 106–119.
Davis, J.D., Smith, G.P., Singh, B., 1999. A microstructural analysis of the control of water and isotonic saline ingestion by postingestional stimulation. Physiol. Behav. 66 (3), 543–548.
Degen, A.A., Hazan, A., Kam, M., Nagy, K.A., 1991. Seasonal water influx and energy expenditure of free-living fat sand rats. J. Mammal. 72 (4), 652–657.
Eckel, L.A., Houpt, T.A., Geary, N., 2000. Spontaneous meal patterns in female rats with and without access to running wheels. Physiol. Behav. 70 (3–4), 397–405.
Epstein, A.N., 1973. Epilogue: retrospect and prognosis. The Neuropsychology of Thirst: New Findings and Advances in Concepts, pp. 315–332.
Epstein, A.N., Fitzsimons, J.T., Simons, B.J., 1969. Drinking caused by the intracranial injection of angiotensin into the rat. J. Physiol. 200 (2), 98P–100P.
Epstein, A.N., Fitzsimons, J.T., Rolls, B.J., 1970. Drinking induced by injection of angiotensin into the rain of the rat. J. Physiol. 210 (2), 457–474.
Findlay, A.L., Fitzsimons, J.T., Kucharczyk, J., 1979. Dependence of spontaneous and angiotensin-induced drinking in the rat upon the oestrous cycle and ovarian hormones. J. Endocrinol. 82 (2), 215–225.
Fitzsimons, J.T., 1971. The effect on drinking of peptide precursors and of shorter chain peptide fragments of angiotensin II injected into the rat's diencephalon. J. Physiol. 214 (2), 295–303.
Fitzsimons, J.T., 1973. Some historical perspectives in the physiology of thirst. The Neuropsychology of Thirst: New Findings and Advances in Concepts, pp. 3–33.
Fitzsimons, J.T., Simons, B.J., 1969. The effect on drinking in the rat of intravenous infusion of angiotensin, given alone or in combination with other stimuli of thirst. J. Physiol. 203 (1), 45–57.
Fortin, S.M., Roitman, M.F., 2018. Challenges to body fluid homeostasis differentially recruit phasic dopamine signaling in a taste-selective manner. J. Neurosci. 38 (31), 6841–6853.
Fregly, M.J., 1978. Attenuation of thirst in estrogen-treated rats. Fed. Proc. 37 (13), 2694–2698.
Fregly, M.J., Thrasher, T.N., 1978. Attenuation of angiotensin-induced water intake in estrogen-treated rats. Pharmacol. Biochem. Behav. 9 (4), 509–514.
Gasparini, S., Resch, J.M., Gore, A.M., Peltekian, L., Geerling, J.C., 2021. Pre-locus coeruleus neurons in rat and mouse. Am. J. Physiol. Regul. Integr. Comp. Physiol. 320 (3), R342–R361.
Geelen, G., Keil, L.C., Kravik, S.E., Wade, C.E., Thrasher, T.N., Barnes, P.R., Pyka, G., Nesvig, C., Greenleaf, J.E., 1984. Inhibition of plasma vasopressin after drinking in dehydrated humans. Am. J. Physiol. 247 (6 Pt 2), R968–R971.
Gizowski, C., Zaelzer, C., Bourque, C.W., 2016. Clock-driven vasopressin neurotransmission mediates anticipatory thirst prior to sleep. Nature 537 (7622), 685–688.
Graves, N.S., Hayes, H., Fan, L., Curtis, K.S., 2011. Time course of behavioral physiological, and morphological changes after estradiol treatment of ovariectomized rats. Physiol. Behav. 103 (3–4), 261–267.
Grippo, A.J., Kirby, R.F., Beltz, T.G., Johnson, A.K., 2002. Angiotensin II-induced drinking and pressor responses to central or systemic irbesartan and losartan. Pharmacol. Biochem. Behav. 71 (1–2), 139–146.
Grobe, J.L., Grobe, C.L., Beltz, T.G., Westphal, S.G., Morgan, D.A., Xu, D., de Lange, W.J., Li, H., Sakai, K., Thedens, D.R., Cassis, L.A., Rahmouni, K., Mark, A.L., Johnson, A. K., Sigmund, C.D., 2010. The brain Renin-angiotensin system controls divergent efferent mechanisms to regulate fluid and energy balance. Cell Metabol. 12 (5), 431–442.
Howell, J.A., Edwards, A.A., Santollo, J., 2024. The estrogenic reduction in water intake stimulated by dehydration involves estrogen receptor alpha and a potential role for GLP-1. Physiol. Behav., 114484
Hsiao, S., Epstein, A.N., Camardo, J.S., 1977. The dipsogenic potency of peripheral angiotensin II. Horm. Behav. 8 (2), 129–140.
Hsu, T.M., Bazzino, P., Hurh, S.J., Konanur, V.R., Roitman, J.D., Roitman, M.F., 2020. Thirst recruits phasic dopamine signaling through subfornical organ neurons. Proc. Natl. Acad. Sci. U. S. A. 117 (48), 30744–30754.
Hurley, S.W., Johnson, A.K., 2013. Dissociation of thirst and sodium appetite in the furo/cap model of extracellular dehydration and a role for N-methyl-D-aspartate receptors in the sensitization of sodium appetite. Behav. Neurosci. 127 (6), 890–898.
Hurley, S.W., Thunhorst, R.L., Johnson, A.K., 2014. Sodium Appetite Sensitization.
Hurley, S.W., Zhang, Z., Beltz, T.G., Xue, B., Johnson, A.K., 2014. Sensitization of sodium appetite: evidence for sustained molecular changes in the lamina terminalis. Am. J. Physiol. Regul. Integr. Comp. Physiol. 307 (12), R1405–R1412.

Johnson, R.F., Beltz, T.G., Thunhorst, R.L., Johnson, A.K., 2003. Investigations on the physiological controls of water and saline intake in C57BL/6 mice. Am. J. Physiol. Regul. Integr. Comp. Physiol. 285 (2), R394–R403.
Jones, A.B., Curtis, K.S., 2009. Differential effects of estradiol on drinking by ovariectomized rats in response to hypertonic NaCl or isoproterenol: implications for hyper- vs. hypo-osmotic stimuli for water intake. Physiol. Behav. 98 (4), 421–426.
Jonklaas, J., Buggy, J., 1984. Angiotensin-estrogen interaction in female brain reduces drinking and pressor responses. Am. J. Physiol. 247 (1 Pt 2), R167–R172.
Kim, D.Y., Heo, G., Kim, M., Kim, H., Jin, J.A., Kim, H.K., Jung, S., An, M., Ahn, B.H., Park, J.H., Park, H.E., Lee, M., Lee, J.W., Schwartz, G.J., Kim, S.Y., 2020. A neural circuit mechanism for mechanosensory feedback control of ingestion. Nature 580 (7803), 376–380.
Kinsman, B.J., Simmonds, S.S., Browning, K.N., Wenner, M.M., Farquhar, W.B., Stocker, S.D., 2020. Integration of hypernatremia and angiotensin II by the organum vasculosum of the lamina terminalis regulates thirst. J. Neurosci. 40 (10), 2069–2079.
Kisley, L.R., Sakai, R.R., Ma, L.Y., Fluharty, S.J., 1999. Ovarian steroid regulation of angiotensin II-induced water intake in the rat. Am. J. Physiol. 276 (1 Pt 2), R90–R96.
Kraly, F.S., Carty, W.J., Resnick, S., Smith, G.P., 1978. Effect of cholecystokinin on meal size and intermeal interval in the sham-feeding rat. J. Comp. Physiol. Psychol. 92 (4), 697–707.
Krause, E.G., Curtis, K.S., Davis, L.M., Stowe, J.R., Contreras, R.J., 2003. Estrogen influences stimulated water intake by ovariectomized female rats. Physiol. Behav. 79 (2), 267–274.
Krause, E.G., Curtis, K.S., Stincic, T.L., Markle, J.P., Contreras, R.J., 2006. Oestrogen and weight loss decrease isoproterenol-induced Fos immunoreactivity and angiotensin type 1 mRNA in the subfornical organ of female rats. J. Physiol. 573 (Pt 1), 251–262.
Kurt, G., Woodworth, H.L., Fowler, S., Bugescu, R., Leinninger, G.M., 2019. Activation of lateral hypothalamic area neurotensin-expressing neurons promotes drinking. Neuropharmacology 154, 13–21.
Kurt, G., Kodur, N., Quiles, C.R., Reynolds, C., Eagle, A., Mayer, T., Brown, J., Makela, A., Bugescu, R., Seo, H.D., Carroll, Q.E., Daniels, D., Robison, A.J., Mazei, M., Leinninger, G., 2022. Time to drink: activating lateral hypothalamic area neurotensin neurons promotes intake of fluid over food in a time-dependent manner. Physiol. Behav. 247, 113707.
Larsen, P.J., Fledelius, C., Knudsen, L.B., Tang-Christensen, M., 2001. Systemic administration of the long-acting GLP-1 derivative NN2211 induces lasting and reversible weight loss in both normal and obese rats. Diabetes 50 (11), 2530–2539.
Lee, S., Augustine, V., Zhao, Y., Ebisu, H., Ho, B., Kong, D., Oka, Y., 2019. Chemosensory modulation of neural circuits for sodium appetite. Nature 568 (7750), 93–97.
Lochard, N., Silversides, D.W., van Kats, J.P., Mercure, C., Reudelhuber, T.L., 2003. Brain-specific restoration of angiotensin II corrects renal defects seen in angiotensinogen-deficient mice. J. Biol. Chem. 278 (4), 2184–2189.
Mandelblat-Cerf, Y., Kim, A., Burgess, C.R., Subramanian, S., Tannous, B.A., Lowell, B.B., Andermann, M.L., 2017. Bidirectional anticipation of future osmotic challenges by vasopressin neurons. Neuron 93 (1), 57–65.
Marshall, A., Santollo, J., Corteville, C., Lutz, T.A., Daniels, D., 2014. Roux-en-Y gastric bypass does not affect daily water intake or the drinking response to dipsogenic stimuli in rats. Am. J. Physiol. Regul. Integr. Comp. Physiol. 307 (2), R114–R120.
Matsuda, T., Hiyama, T.Y., Niimura, F., Matsusaka, T., Fukamizu, A., Kobayashi, K., Noda, M., 2017. Distinct neural mechanisms for the control of thirst and salt appetite in the subfornical organ. Nat. Neurosci. 20 (2), 230–241.
McCann, S.M., Gutkowska, J., Franci, C.R., Favaretto, A.L., Antunes-Rodrigues, J., 1994. Hypothalamic control of water and salt intake and excretion. Braz. J. Med. Biol. Res. 27 (4), 865–884.
McKay, N.J., Daniels, D., 2013. Glucagon-like peptide-1 receptor agonist administration suppresses both water and saline intake in rats. J. Neuroendocrinol. 25 (10), 929–938.
McKay, N.J., Kanoski, S.E., Hayes, M.R., Daniels, D., 2011. Glucagon-like peptide-1 receptor agonists suppress water intake independent of effects on food intake. Am. J. Physiol. Regul. Integr. Comp. Physiol. 301 (6), R1755–R1764.
McKay, N.J., Galante, D.L., Daniels, D., 2014. Endogenous glucagon-like peptide-1 reduces drinking behavior and is differentially engaged by water and food intakes in rats. J. Neurosci. 34 (49), 16417–16423.
McKinley, M.J., Walker, L.L., Alexiou, T., Allen, A.M., Campbell, D.J., Di Nicolantonio, R., Oldfield, B.J., Denton, D.A., 2008. Osmoregulatory fluid intake but not hypovolemic thirst is intact in mice lacking angiotensin. Am. J. Physiol. Regul. Integr. Comp. Physiol. 294 (5), R1533–R1543.
McKinley, M.J., Weissenborn, F., Mathai, M.L., 2009. Drinking-induced thermoregulatory panting in rehydrated sheep: influences of oropharyngeal/esophageal signals, core temperature, and thirst satiety. Am. J. Physiol. Regul. Integr. Comp. Physiol. 296 (6), R1881–R1888.
Mecawi, A.S., Lepletier, A., Araujo, I.G., Fonseca, F.V., Reis, L.C., 2008. Oestrogenic influence on brain AT1 receptor signalling on the thirst and sodium appetite in osmotically stimulated and sodium-depleted female rats. Exp. Physiol. 93 (8), 1002–1010.
Mietlicki, E.G., Nowak, E.L., Daniels, D., 2009. The effect of ghrelin on water intake during dipsogenic conditions. Physiol. Behav. 96 (1), 37–43.
Mietlicki-Baase, E.G., McGrath, L.E., Koch-Laskowski, K., Krawczyk, J., Reiner, D.J., Pham, T., Nguyen, C.T.N., Turner, C.A., Olivos, D.R., Wimmer, M.E., Schmidt, H.D., Hayes, M.R., 2017. Amylin receptor activation in the ventral tegmental area reduces motivated ingestive behavior. Neuropharmacology 123, 67–79.
Mietlicki-Baase, E.G., Santollo, J., Daniels, D., 2021. Fluid intake, what's dopamine got to do with it? Physiol. Behav. 236, 113418.
Miller, N.E., Sampliner, R.I., Woodrow, P., 1957. Thirst-reducing effects of water by stomach fistula vs. water by mouth measured by both a consummatory and an instrumental response. J. Comp. Physiol. Psychol. 50 (1), 1–5.
Myers, K.P., Arnold, H.M., Hall, W.G., 1997. Sensitization of ingestive responding in preweanling rats: time course and specificity. Behav. Neurosci. 111 (2), 413–423.
Nagy, K.A., 1994. Seasonal water, energy and food use by free-living, arid-habitat mammals. Aust. J. Zool. 42, 55–63.
Navarro, M., Rodriquez de Fonseca, F., Alvarez, E., Chowen, J.A., Zueco, J.A., Gomez, R., Eng, J., Blazquez, E., 1996. Colocalization of glucagon-like peptide-1 (GLP-1) receptors, glucose transporter GLUT-2, and glucokinase mRNAs in rat hypothalamic cells: evidence for a role of GLP-1 receptor agonists as an inhibitory signal for food and water intake. J. Neurochem. 67 (5), 1982–1991.
Oka, Y., Ye, M., Zuker, C.S., 2015. Thirst driving and suppressing signals encoded by distinct neural populations in the brain. Nature 520 (7547), 349–352.
Pereira, D.T., Menani, J.V., De Luca Jr., L.A., 2010. FURO/CAP: a protocol for sodium intake sensitization. Physiol. Behav. 99 (4), 472–481.
Pereira-Derderian, D.T., Vendramini, R.C., Menani, J.V., Chiavegatto, S., De Luca, L.A., 2016. Water deprivation-partial rehydration induces sensitization of sodium appetite and alteration of hypothalamic transcripts. Am. J. Physiol. Regul. Integr. Comp. Physiol. 310 (1), R15–R23.
Postolache, M., Santollo, J., Daniels, D., 2017. Associative learning contributes to the increased water intake observed after daily injections of angiotensin II. Physiol. Behav. 179, 340–345.
Rolls, B.J., Wood, R.J., Rolls, E.T., Lind, H., Lind, W., Ledingham, J.G., 1980. Thirst following water deprivation in humans. Am. J. Physiol. 239 (5), R476–R482.
Rowland, N.E., Morien, A., Fregly, M.J., 1996. Losartan inhibition of angiotensin-related drinking and Fos immunoreactivity in hypertensive and hypotensive contexts. Brain Res. 742 (1–2), 253–259.
Sakai, K., Agassandian, K., Morimoto, S., Sinnayah, P., Cassell, M.D., Davisson, R.L., Sigmund, C.D., 2007. Local production of angiotensin II in the subfornical organ causes elevated drinking. J. Clin. Invest. 117 (4), 1088–1095.
Samson, W.K., White, M.M., Price, C., Ferguson, A.V., 2007. Obestatin acts in brain to inhibit thirst. Am. J. Physiol. Regul. Integr. Comp. Physiol. 292 (1), R637–R643.
Santollo, J., Daniels, D., 2015. Activation of G protein-coupled estrogen receptor 1 (GPER- 1) decreases fluid intake in female rats. Horm. Behav. 73, 39–46.
Santollo, J., Daniels, D., 2015. Multiple estrogen receptor subtypes influence ingestive behavior in female rodents. Physiol. Behav. 152 (Pt B), 431–437.
Santollo, J., Edwards, A.A., 2023. Estrogen receptor beta mediates the dipsogenic effect of estradiol in ovariectomized female rats. Neuroendocrinology 113 (9), 930–942.
Santollo, J., Wiley, M.D., Eckel, L.A., 2007. Acute activation of ER alpha decreases food intake, meal size, and body weight in ovariectomized rats. Am. J. Physiol. Regul. Integr. Comp. Physiol. 293 (6), R2194–R2201.
Santollo, J., Marshall, A., Daniels, D., 2013. Activation of membrane-associated estrogen receptors decreases food and water intake in ovariectomized rats. Endocrinology 154 (1), 320–329.
Santollo, J., Whalen, P.E., Speth, R.C., Clark, S.D., Daniels, D., 2014. Properly timed exposure to central ANG II prevents behavioral sensitization and changes in angiotensin receptor expression. Am. J. Physiol. Regul. Integr. Comp. Physiol. 307 (12), R1396–R1404.
Santollo, J., Marshall, A., Curtis, K.S., Speth, R.C., Clark, S.D., Daniels, D., 2016. Divergent effects of ERalpha and ERbeta on fluid intake by female rats are not dependent on concomitant changes in AT1R expression or body weight. Am. J. Physiol. Regul. Integr. Comp. Physiol. 311 (1), R14–R23.
Santollo, J., Torregrossa, A.M., Daniels, D., 2017. Sex differences in the drinking response to angiotensin II (AngII): effect of body weight. Horm. Behav. 93, 128–136.
Santollo, J., Collett, J.A., Edwards, A.A., 2021. The anti-dipsogenic and anti-natriorexigenic effects of estradiol, but not the anti-pressor effect, are lost in aged female rats. Phys. Rep. 9 (14), e14948.
Santollo, J., Edwards, A.A., Howell, J.A., Myers, K.E., 2021. Bidirectional effects of estradiol on the control of water intake in female rats. Horm. Behav. 133, 104996.
Santollo, J., Daniels, D., Leshem, M., Schulkin, J., 2023. Sex differences in salt appetite: perspectives from animal models and human studies. Nutrients 15 (1).
Sigmund, C.D., 2012. Divergent mechanism regulating fluid intake and metabolism by the brain renin-angiotensin system. Am. J. Physiol. Regul. Integr. Comp. Physiol. 302 (3), R313–R320.
Simpson, J.B., Routtenberg, A., 1973. Subfornical organ: site of drinking elicitation by angiotensin II. Science 181 (4105), 1172–1175.
Smith, G.P., 1996. The direct and indirect controls of meal size. Neurosci. Biobehav. Rev. 20 (1), 41–46.
Spiteri, N.J., 1982. Circadian patterning of feeding, drinking and activity during diurnal food access in rats. Physiol. Behav. 28 (1), 139–147.
Spiteri, N.J., Drewett, R.F., Padel, U., 1980. Behavioral effects of ethynyl estrogens in the female rat. Physiol. Behav. 25 (3), 409–415.
Stallone, J.N., 1979. Seasonal changes in the water metabolism of woodrats. Oecologia 38 (2), 203–216.
Stricker, E.M., Hoffmann, M.L., 2005. Inhibition of vasopressin secretion when dehydrated rats drink water. Am. J. Physiol. Regul. Integr. Comp. Physiol. 289 (5), R1238–R1243.
Takamata, A., Mack, G.W., Gillen, C.M., Jozsi, A.C., Nadel, E.R., 1995. Osmoregulatory modulation of thermal sweating in humans: reflex effects of drinking. Am. J. Physiol. 268, R414–R422.
Tang-Christensen, M., Larsen, P.J., Goke, R., Fink-Jensen, A., Jessop, D.S., Moller, M., Sheikh, S.P., 1996. Central administration of GLP-1-(7-36) amide inhibits food and water intake in rats. Am. J. Physiol. 271 (4 Pt 2), R848–R856.
Tarttelin, M.F., Gorski, R.A., 1971. Variations in food and water intake in the normal and acyclic female rat. Physiol. Behav. 7 (6), 847–852.

Taylor, M.M., Bagley, S.L., Samson, W.K., 2005. Intermedin/adrenomedullin-2 acts within central nervous system to elevate blood pressure and inhibit food and water intake. Am. J. Physiol. Regul. Integr. Comp. Physiol. 288 (4), R919–R927.

Thammacharoen, S., Geary, N., Lutz, T.A., Ogawa, S., Asarian, L., 2009. Divergent effects of estradiol and the estrogen receptor-alpha agonist PPT on eating and activation of PVN CRH neurons in ovariectomized rats and mice. Brain Res. 1268, 88–96.

Thrasher, T.N., Fregly, M.J., 1977. Responsiveness to various dipsogenic stimuli in rats treated chronically with norethynodrel, ethinyl estradiol and both combined. J. Pharmacol. Exp. Therapeut. 201 (1), 84–91.

Thrasher, T.N., Fregly, M.J., 1978. Effect of chronic treatment with an estrogen-progestogen combination on beta adrenergic-induced thirst. Pharmacol. Biochem. Behav. 8 (2), 177–183.

Thrasher, T.N., Nistal-Herrera, J.F., Keil, L.C., Ramsay, D.J., 1981. Satiety and inhibition of vasopressin secretion after drinking in dehydrated dogs. Am. J. Physiol. 240 (4), E394–E401.

Vento, P.J., Daniels, D., 2010. Repeated administration of angiotensin II reduces its dipsogenic effect without affecting saline intake. Exp. Physiol. 95 (6), 736–745.

Vento, P.J., Daniels, D., 2012. Mitogen-activated protein kinase is required for the behavioural desensitization that occurs after repeated injections of angiotensin II. Exp. Physiol. 97 (12), 1305–1314.

Vento, P.J., Daniels, D., 2014. The anteroventral third ventricle region is critical for the behavioral desensitization caused by repeated injections of angiotensin II. Behav. Brain Res. 258, 27–33.

Vento, P.J., Myers, K.P., Daniels, D., 2012. Investigation into the specificity of angiotensin II-induced behavioral desensitization. Physiol. Behav. 105 (4), 1076–1081.

Vilhena-Franco, T., Mecawi, A.S., Elias, L.L., Antunes-Rodrigues, J., 2016. Oestradiol effects on neuroendocrine responses induced by water deprivation in rats. J. Endocrinol. 231 (2), 167–180.

Volcko, K.L., Brakey, D.J., Przybysz, J.T., Daniels, D., 2020. Exclusively drinking sucrose or saline early in life alters adult drinking behavior by laboratory rats. Appetite 149, 104616.

Volcko, K.L., Carroll, Q.E., Brakey, D.J., Daniels, D., 2020. High-fat diet alters fluid intake without reducing sensitivity to glucagon-like peptide-1 receptor agonist effects. Physiol. Behav. 221, 112910.

Wang, T., Edwards, G.L., Baile, C.A., 1998. Glucagon-like peptide-1 (7-36) amide administered into the third cerebroventricle inhibits water intake in rats. Proc Soc Exp Biol Med 219 (1), 85–91.

Williams, D.L., Hyvarinen, N., Lilly, N., Kay, K., Dossat, A., Parise, E., Torregrossa, A.M., 2011. Maintenance on a high-fat diet impairs the anorexic response to glucagon-like-peptide-1 receptor activation. Physiol. Behav. 103 (5), 557–564.

Xu, Z., Xinghong, J., 1999. Drinking and Fos-immunoreactivity in rat brain induced by local injection of angiotensin I into the subfornical organ. Brain Res. 817 (1–2), 67–74.

Yosten, G.L., Redlinger, L., Samson, W.K., 2012. Evidence for a role of endogenous nesfatin-1 in the control of water drinking. J. Neuroendocrinol. 24 (7), 1078–1084.

Zocchi, D., Wennemuth, G., Oka, Y., 2017. The cellular mechanism for water detection in the mammalian taste system. Nat. Neurosci. 20 (7), 927–933.

Zimmerman, C.A., Huey, E.L., Ahn, J.S., Beutler, L.R., Tan, C.L., Kosar, S., Bai, L., Chen, Y., Corpuz, T.V., Madisen, L., Zeng, H., Knight, Z.A., 2019. A gut-to-brain signal of fluid osmolarity controls thirst satiation. Nature 568 (7750), 98–102.