The Physiological Regulation of Thirst and Fluid Intake

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Thirst is important for maintaining body fluid homeostasis and may arise from deficits in either intracellular or extracellular fluid volume. Neural signals arising from osmotic and hormonal influences on the lamina terminalis may be integrated within the brain, with afferent information relayed from intrathoracic baroreceptors via the hindbrain to generate thirst.

Thirst is a subjective perception that provides the urge for humans and animals to drink fluids. It is a component of the regulatory mechanisms that maintain body fluid homeostasis and ultimately is essential for survival. This urge to ingest fluids may arise for several reasons that include habitual, cultural, and psychogenic drives as well as the regulatory response to reductions in the fluid content of various bodily compartments, hypertonicity of the extracellular fluid, or increases in the circulating concentration of some dipsogenic hormones. Such regulatory thirst, and the cerebral mechanisms generating it, are the subjects of this review.

When the body loses water, it is usually depleted from both the extracellular and intracellular compartments, but it may not necessarily be lost equally from each of the fluid spaces. Loss of NaCl (the major solute of the extracellular fluid) together with water results in proportionately more extracellular fluid being depleted than if water alone is lost. This may occur, for example, with fluid loss from the alimentary tract that occurs in conditions of vomiting or diarrhea, and when this fluid loss takes the form of an isotonic fluid, then the depletion will be entirely from the extracellular fluid. However, if hypertonic fluid is added to the extracellular compartment, there will be an osmotic depletion of water from the intracellular compartment into the extracellular fluid, and this latter compartment will be expanded.

A range of compensatory responses are engaged when depletion of either the intra- or extracellular compartment occurs. These responses (e.g., vasopressin secretion, stimulation of the renin-angiotensin-aldosterone system, sympathetic activation, and reduced renal solute and water excretion) have the effect of minimizing changes in body fluid volume and composition. However, such mechanisms, although of undoubted benefit to the animal, do not restore body fluids to the original state. For this to occur, fluid losses must be replenished. Therefore, thirst, which provides the motivation to drink, is an important component of the coordinated sequence of physiological responses that maintain the volume and composition of body fluids.

In the following paragraphs, we outline the cerebral mechanisms that subserve the water-drinking responses that are associated with *1*) hypertonicity, cellular dehydration, and osmoreceptor stimulation; *2*) hypovolemia and extracellular dehydration, including the role of circulating angiotensin (ANG) II as a dipsogenic hormone and the afferent neural inflow that also provides stimuli to the thirst mechanism; and *3*) other hormonal signals that may stimulate (e.g., relaxin) or inhibit [e.g., atrial natriuretic peptide (ANP)] thirst.

Osmoregulatory thirst associated with deficits of intracellular fluid volume

Small increases of 1–2% in the effective osmotic pressure of plasma result in stimulation of thirst in mammals. It has been shown in both human subjects and other mammals that when the plasma osmolality (usually in the range of 280–295 mosmol/kgH$_2$O) is increased experimentally as a result of increasing the concentration of solutes such as NaCl or sucrose that do not readily pass across cell membranes, thirst is stimulated. By contrast, increasing plasma osmolality by systemic infusion of concentrated solutes such as urea or D-glucose that more readily cross nerve cell membranes is relatively ineffective at stimulating thirst (8, 12, 18). In the former case, a transmembrane osmotic gradient is established and cellular dehydration results from movement of water out of cells by osmosis. Cellular dehydration does not occur with the permeating solutes in the latter case, and it is considered that specific sensor cells in the brain, termed osmoreceptors (initially in relation to vasopressin secretion), respond to cellular dehydration to initiate neural mechanisms that result in the generation of thirst (8, 18). Although there is evidence that some osmoreceptors may be situated in the liver, much evidence has accrued that localizes an important population of osmoreceptive neurons to the preoptic/hypothalamic region of the brain. The hypothalamus was implicated in the genera-

tion of thirst in the early 1950s when Bengt Andersson was able to stimulate water drinking in goats by electrical or chemical stimulation of the hypothalamus. Although he observed that drinking was induced by injection of hypertonic saline into the hypothalamus in a region between the columns of the fornix and the mamillothalamic tract, the solutions injected were grossly hypertonic, making it difficult to come to a firm conclusion that physiologically relevant osmoreceptors for thirst existed in this region. Andersson and colleagues (1) later found evidence that more rostral tissue in the anterior wall of the third ventricle was more likely to be the site of sensors mediating osmotic thirst and proposed a role for the ambient Na$^+$ concentration in this region of the brain in the initiation of thirst.

Neural mechanisms subserving osmotically stimulated thirst

More than 25 years ago, clues emerged as to the crucial role of a region in the anterior wall of the third ventricle in thirst mechanisms when it was shown that ablation of tissue in the anteroventral third ventricle wall (AV3V region) of goats and rats caused either temporary or permanent adipsia (1, 10). In those animals with lesions that did recover spontaneous water drinking, loss of dipsogenic responsiveness to osmotic and ANG stimuli was evident. Another clue to the location of cerebral osmoreceptors subserving thirst came from studies in sheep suggesting that the cerebral osmoreceptors subserving thirst and vasopressin secretion were, at least in part, located in brain regions lacking a blood-brain barrier (12). In subsequent years, evidence (reviewed in Ref. 14) from the study of lesions, electrophysiological recordings, and the expression of the immediate early gene c-*fos* in rats have confirmed that neurons in both the organum vasculosum of the lamina terminalis (OVLT) and the subfornical organ (SFO) are most likely

the sites of very sensitive osmoreceptors (Fig. 1). The SFO and OVLT are two circumventricular organs that lack a blood-brain barrier and that are situated in the anterior wall of the third ventricle (the lamina terminalis). In particular, the dorsal part of the OVLT and the periphery of the SFO are osmosensitive in the rat. However, the median preoptic nucleus (MnPO), which is situated in the lamina terminalis longitudinally between the two circumventricular organs and is an integral part of the AV3V region, is also strongly activated by osmotic stimuli. Lesion studies in rats have shown that the MnPO may play a crucial role in the generation of thirst in response to both osmotic and hormonal signals being relayed to this nucleus by neural inputs from the SFO and possibly the OVLT (10). Another aspect of osmoregulatory drinking is that it may be blocked pharmacologically by intracerebroventricularly injected ANG antagonists, suggesting that a central angiotensinergic pathway is involved in most mammals. The MnPO, which is rich in ANG type 1 receptors but is not amenable to circulating ANG II, is a likely site of this angiotensinergic synapse (10).

The MnPO receives afferent neural input from neurons in both the SFO and the OVLT and may integrate neural signals coming from osmoreceptive neurons in these circumventricular organs with visceral sensory inflow from the hindbrain (Fig. 2). However, combined ablation of both the SFO and OVLT leaving a considerable part of the MnPO intact reduces but does not totally abolish osmotically induced drinking (13). This suggests that neurons within the MnPO may be osmoreceptive also or that they receive osmotically related input from other parts of the brain [e.g., the area postrema (AP)] or body (e.g., hepatic portal system).

It is clear that the lamina terminalis is a region of the brain where stimuli from the circulation, such as plasma hypertonicity or hormones (e.g., ANG II, relaxin), exert their dipsogenic action. In regard to the subsequent efferent neural path-
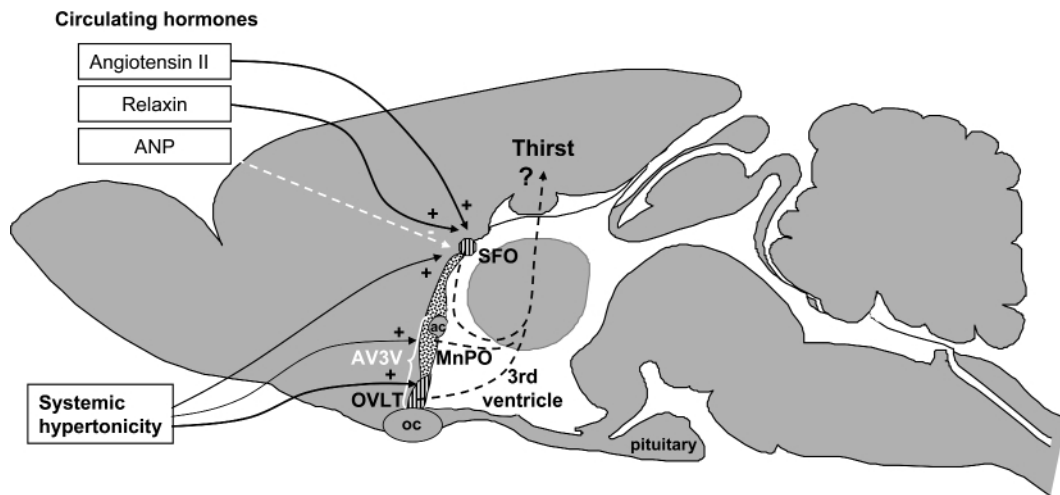

FIGURE 1. Diagram of the sagittal midline of the rat brain showing circulating factors that act on the various components of the lamina terminalis to influence thirst. The two parts of the lamina terminalis that lack a normal blood-brain barrier, the subfornical organ (SFO) and organum vasculosum of the lamina terminalis (OVLT), are shaded with vertical lines, whereas the other component of the lamina terminalis, the median preoptic nucleus (MnPO) is indicated by the spotted area. The part of the lamina terminalis that is included in the anteroventral third ventricle region (AV3V) is indicated by the white bracket. The interrupted white line indicates an inhibitory influence of atrial natriuretic peptide (ANP), whereas angiotensin II, relaxin, and hypertonicity have excitatory actions on the lamina terminalis. The question mark indicates that the efferent pathways from the lamina terminalis that mediate thirst are not yet known. oc, Optic chiasm; ac, anterior commissure.
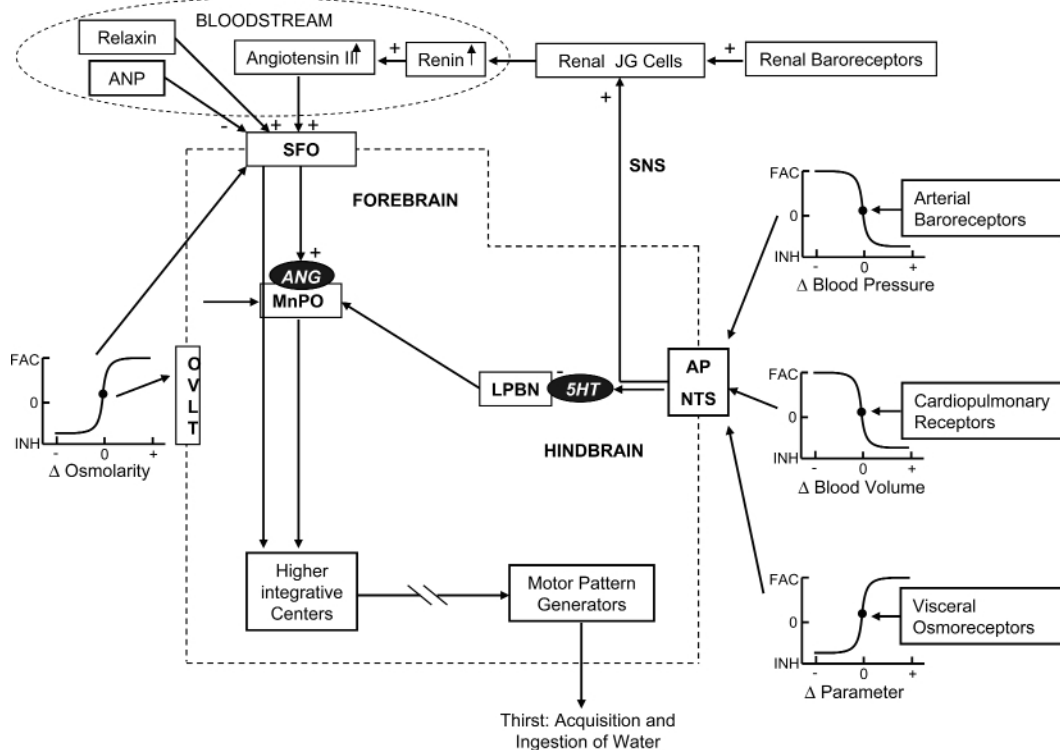
FIGURE 2. Diagram depicting neural and hormonal inputs into the brain and the central neural pathways that mediate sensory integration of signals for the generation of drinking (thirst). Both inhibitory and excitatory inputs from the periphery are derived from arterial and cardiopulmonary baroreceptors as well as other visceral receptors (e.g., gastric, hepatic/portal, renal). Information carried in afferent nerves projects mainly to the nucleus of the solitary tract (NTS). Angiotensin (ANG) acts in the form of ANG II on ANG type 1 (AT_1) receptors in the SFO. Osmoreception takes place in structures along the OVLT (MnPO). Hormonal information to the SFO is subsequently carried in descending pathways, some of which are likely to use ANG in the mode of a neurotransmitter, to forebrain structures such as those in the AV3V. Ascending information to the forebrain is carried in projections from noradrenergic cell groups in the hindbrain, which are activated by arterial and cardiopulmonary receptor input under conditions of hypotension and/or hypovolemia. ANG and noradrenergic inputs act synergistically in forebrain nuclei. A hindbrain inhibitory pathway originating in the area postrema (AP) and medial NTS ascends to the lateral parabrachial nucleus (LPBN). This projection uses serotonin (5-HT) as a neurotransmitter and prevents against excessive sodium and water intake to limit excess expansion of blood volume. Inhibitory input is likely to ascend the neuraxis either directly or indirectly to interact with forebrain structures. FAC, facilitation; INH, inhibition; SNS, sympathetic nervous system.

ways that may project from the lamina terminalis to other brain regions (including the cerebral cortex) to generate thirst, little is known at present. The lateral hypothalamic area, the hypothalamic paraventricular nucleus, and the periaqueductal gray are all regions that receive a strong neural input from the lamina terminalis and have been proposed as regions that may participate in the generation of thirst. However, evidence in support of such proposals is scarce. Recent studies using positron emission tomography in human volunteers identified several brain regions that became activated during an intravenous infusion of hypertonic saline that produced a strong thirst sensation in these subjects. In particular, the anterior and posterior parts of the cingulate cortex were activated (Fig. 3), and on satiation of the thirst, these areas rapidly declined in activity (4). This cingulate region has been implicated in other goal-directed behaviors and probably plays a yet-to-be-specified role in the generation of human thirst.

Thirst in response to deficits in extracellular fluid volume

Extracellular fluid volume can be depleted selectively without producing a reduction in the size of the intracellular fluid compartment. Hemorrhage, sodium loss, or localized sequestration of extracellular fluid (edema) decreases blood and interstitial fluid volume. The immediate response to hypovolemia is activation of components of the endocrine and autonomic nervous systems in a manner that mitigates the consequences of reduced cardiac output and falling blood pressure. Activation of the sympathetic nervous system contributes to increased vascular tone, venous return, heart rate and contractility, and renal sodium and water reabsorption. Elevated plasma vasopressin, renin-angiotensin, aldosterone, epinephrine/norepinephrine, adrenocorticotrophic hormone, and glucocorticoids act directly or indirectly to retain sodium and water or to redistribute blood and interstitial fluids in an attempt to maintain critical regional blood flows. However, eventually it is necessary to correct the absolute deficits in both water and extracellular solutes. This involves the generation of behaviors associated with the acquisition and ingestion of sodium (i.e., salt appetite) in addition to thirst. The generation of behaviors that correct extracellular deficits is similar to the sympathetic and endocrine responses to hypovolemia, in that all of these effector systems require that the central nervous system receive information reflecting the condition of blood and/or interstitial fluid volumes. Body-to-brain signaling

Maximum thirst

3 min after drinking

z scores

1.96 ▇▇▇ 4

-1.96 ▇▇▇ -4

FIGURE 3. Pseudocolor images of positron emission tomography of subjects made thirsty by an intravenous infusion of hypertonic saline (*top*) and then 3 min after thirst had been satiated by the drinking of water (*bottom*). Sagittal images of the left side of the brain 8 mm lateral to the midline show activations (yellow and red regions) proceeding along the cingulate cortex from anterior to posterior parts in the thirsty subjects that were extinguished on slaking the thirst. Reproduced with permission from Ref. 4.

of the status of extracellular fluids entails both hormonal and visceral afferent pathways.

Angiotensin and thirst

Classic studies by Fitzsimons and associates (see Ref. 8 for review) were the first to clearly demonstrate that renin and its effector peptide, ANG II, were highly effective as dipsogenic stimuli in the rat. Systemically administered renin or ANG II generates water intake in sated rats. As is true for osmotically stimulated drinking, ANG-induced thirst requires the structures of the lamina terminalis (i.e., SFO, MnPO, and OVLT) for sensing circulating peptides (particularly the SFO) and for initial central nervous system processing and integration of this peripherally derived information (10).

The dipsogenic action of ANG is even more impressive when it is injected directly into the brain, and this has been

demonstrated in several mammals (rat, goat, dog, sheep) and also in birds (duck, pigeon). This route of administration is believed to mimic the action of this peptide at one or more periventricular brain sites. The presence of a brain renin-angiotensin system with all the components of the metabolic cascade as well as receptors being synthesized de novo in the brain has been demonstrated. It has been hypothesized that circulating ANG II acts on forebrain circumventricular organs (SFO, OVLT) in the mode of a hormone and that, either directly or indirectly, it activates angiotensinergic pathways projecting to central integrative sites when the peptide acts as a neurotransmitter (11). The systemic (renal/circulating) and the brain renin-angiotensin systems, although distinct, are functionally coupled with one another and play complementary roles in the maintenance of body fluid homeostasis.

Inhibition and facilitation of thirst through hindbrain actions

In addition to humoral factors acting through forebrain targets and networks to facilitate drinking, there is evidence of both stimulatory and inhibitory signals acting on or through the hindbrain. When the hypertension induced by intravenous ANG II in rats is reduced or normalized by coadministration of a systemically acting hypotensive drug, drinking responses to infusions of ANG II are enhanced (7). In rats with actions of the systemic renin-angiotensin system blocked, reducing blood pressure to below normal resting levels enhances the drinking response to intracerebroventricular ANG II infusions (11).

Inhibition of thirst arises not only from arterial baroreceptors but also from volume receptors on the low-pressure side of the circulation. Distention of the region of the junction of the right atrium and vena cava or of the pulmonary vein at the entry to the left atrium by inflating balloons inhibits experimentally induced drinking. In contrast, when, in dogs, both low-pressure cardiopulmonary and high-pressure arterial baroreceptors are unloaded by reducing venous return to the heart, drinking is stimulated (9, 17). Under such conditions, Quillen and colleagues (15) found that denervation of either the cardiopulmonary or sinoaortic baroreceptors significantly attenuated thirst in the dog and that denervation of both sets of receptors completely abolished drinking even though circulating levels of ANG were high.

Afferent input from the cardiopulmonary and arterial baroreceptors is carried to the brain by the IXth and Xth cranial nerves, with most of these nerves terminating in the nucleus of the solitary tract (NTS). Lesions centered on the AP, but also encroaching on the medial portions of the medial NTS (i.e., an AP/mNTS lesion), as well as bilateral lesions centering on the medial subnucleus of the NTS proper, produce rats that overrespond to thirst-inducing treatments associated with hypovolemia (5). These effects are likely to be due to removal of inhibitory baroreceptor-derived input. However, it is possible that the AP also plays a role in the inhibitory control of thirst derived from systemic blood volume expansion or acute hypertension. As demonstrated by Antunes-Rodrigues and colleagues (2), a peptide made and released from the car-

diac atria, ANP, inhibits drinking. Release of ANP in response to hypervolemia and hypertension may inhibit drinking. Its action is discussed below.

Interestingly, the AP/NTS region contains cells with axons that project to the lateral parabrachial nucleus (LPBN). Electrolytic, anesthetic, and neurotoxic lesions of the LPBN produce overdrinking to mediators of extracellular dehydration in the rat (11). This is similar to the effects of AP/mNTS lesions. A significant portion of the cells that project from the AP/mNTS to the LPBN contain serotonin (5-HT), and bilateral injections of the nonselective 5-HT receptor antagonist methysergide enhance drinking as well as NaCl solution intake in response to several dipsogenic stimuli in rats (see Ref. 11 for review). The model that has been proposed is that there is a hindbrain inhibitory circuit involving the AP, NTS, and LPBN that receives and processes neural and humoral input derived from activation of cardiopulmonary and arterial baroreceptors. Ascending pathways from this inhibitory complex project to many forebrain structures, such as the structures along the lamina terminalis, the central nucleus of the amygdala, and various hypothalamic nuclei that have been implicated in thirst. In turn, many of these forebrain structures have reciprocal connections with the LPBN and NTS. It is within this visceral neural network where the input from both excitatory and inhibitory humoral and visceral afferent nerves is likely to be processed to give rise to drinking behaviors or the perception of thirst.

Other humoral influences on thirst

Several hormones (peptides and steroids) have been shown to be able to influence thirst in rats. Some peptides (e.g., relaxin, orexin) stimulate water drinking, whereas others (e.g., ANP, glucagon-like peptide-1) may inhibit water intake. The sites of action of relaxin and ANP in the brain to influence water intake have been studied in recent years, and the SFO is crucial in this regard.

Relaxin. Secreted by the corpus luteum of the ovary during pregnancy, relaxin has been shown to influence body fluid homeostasis by stimulating vasopressin secretion and water drinking in rats when it is administered either centrally or systemically. Relaxin receptors occur at high concentrations in both the SFO and OVLT, and therefore these circumventricular organs are likely sites at which relaxin exerts its dipsogenic action. Indeed, relaxin directly stimulates neurons within the SFO, and ablation of the SFO but not the OVLT abolishes water drinking in rats in response to intravenously infused relaxin (16), showing that the SFO is the likely site for the dipsogenic action of circulating relaxin on the brain. ANG II and relaxin may act in synergy to promote thirst during pregnancy because circulating ANG II potentiates the dipsogenic action of intravenously infused relaxin.

During pregnancy, plasma osmolality levels fall in some species, including humans. This should exert an inhibitory influence on thirst mechanisms; however, water intake is maintained or even increased despite this plasma hypotonicity. Relaxin secreted during pregnancy may be one of the factors that promote fluid intake during this period, and it has been suggested that there is a resetting of the central osmostat controlling thirst and vasopressin secretion as a result of the actions of relaxin on the brain.

ANP. ANP, released by cardiac myocytes when the volume of extracellular fluid is expanded, has been shown to have potent inhibitory influences on water intake in rats (2) and on thirst mechanisms in human subjects (3), as well as to inhibit vasopressin secretion. An interesting aspect of this inhibitory influence is that it appears to be directed mainly against ANG-stimulated drinking, although ANP also inhibits osmotically stimulated thirst (3). When ANP was injected into the SFO of the rat, it inhibited ANG-induced drinking (6), and it seems likely that it has its antidipsogenic action via its receptors in the circumventricular organs of the lamina terminalis.

Concluding comments

The homeostatic regulation of fluid intake by the brain is multifactorial. Osmotic, ionic, hormonal, and nervous signals converge on, and are integrated within, the central nervous system. Consequentially, neural circuitry (yet to be identified) that subserves the conscious perception of thirst may become activated. The satiation or extinction of thirst following the intake of water involves the participation of other sensory and integrative neural pathways that also interact with this circuitry but that are beyond the scope of this article. So too are the pathophysiological influences that alter the thirst mechanism so that it becomes either overactive or insensitive to fluid loss. For example, a significant proportion of the elderly have a reduced thirst responsiveness that may result in them becoming severely dehydrated. Conversely, psychogenic polydipsia that is observed in some psychological disorders may cause life-threatening water intoxication. The elucidation of the neural circuitry subserving the conscious perception of thirst will be a step in the path to understanding such disorders.

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