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Water Intake and the Neural Correlates of the Consciousness of Thirst

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Thirst and resultant water drinking can arise in response to deficits in both the intracellular and extracellular fluid compartments. Inhibitory influences mediating the satiation of thirst also are necessary to prevent overhydration. The brain regions that underpin the generation or inhibition of thirst in these circumstances can be categorized as sensory, integrative, or cortical effector sites. The anterior cingulate cortex and insula are activated in thirsty human beings as shown by functional brain-imaging techniques. It is postulated that these sites may be cortical effector regions for thirst. A major sensory site for generating thirst is the lamina terminalis in the forebrain. Osmoreceptors within the organum vasculosum of the lamina terminalis and subfornical organ detect systemic hypertonicity. The subfornical organ mediates the dipsogenic actions of circulating angiotensin II and relaxin. Major integrative sites are the nucleus of the tractus solitarius, the lateral parabrachial nucleus, the midbrain raphé nuclei, the median preoptic nucleus, and the septum. Despite these advances, most of the neural pathways and neurochemical mechanisms subserving the genesis of thirst remain to be elucidated.
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The intake of fluids is an essential behavior for nearly all mammals, including human beings. If fluid intake does not occur regularly, dehydration will ensue regardless of the powerful urinary concentrating effect that vasopressin exerts on the kidney to reduce further fluid loss to a minimum. Much of our normal intake of fluid is of either a social or habitual nature, and often is associated with the ingestion of food, yet the brain mechanisms that initiate habitual drinking or that associated with meals still largely are unknown.[1]

Thirst and fluid intake as a response to body fluid deficit, however, has been investigated in some detail. Considerable knowledge has accrued during the past half century in regard to some of the brain regions and neural circuits that participate in the physiologic regulation of fluid intake when animals become depleted of body fluids. This fluid depletion may occur from either or both of the intracellular and extracellular compartments. Such homeostatic regulation of fluid intake is controlled by the thirst drive that can arise when the body becomes depleted of water, when the effective osmotic pressure of body fluids increases as a result of excess solute intake, or when the concentration of certain humoral factors in the circulation increases.[2-4] Conversely, after adequate or excess ingestion of water, inhibitory influences on thirst and fluid intake arise that are also of a regulatory nature. In this article we consider the brain regions and neural mechanisms that participate in the stimulation and inhibition of thirst.

Traditionally, textbooks of physiology refer to the hypothalamus as the site of a thirst center. The concept of a center is somewhat outmoded these days, and consideration of neural circuitry regulating fluid intake is probably a more realistic approach. The hypothalamus achieved such status as a thirst center mainly as a result of the pioneering work of the Swedish physiologist Andersson and McCann,[5] who were able to obtain stimulus-bound drinking of water in animals (goats) with electrical stimulation of electrodes that had been implanted surgically into the hypothalamus. Earlier, Anders-

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son[6] had shown that chemically stimulating the hypothalamus with injections of hypertonic saline also could stimulate drinking. Although some interpreted these results as evidence that the thirst osmoreceptor was located in the hypothalamus, Andersson[6] himself was particularly careful in the interpretation of these data because he was aware that the concentration of NaCl in the solutions injected was supraphysiologic and the spread of the stimulus was not controlled. In addition, early studies of hypothalamic lesions, particularly in the lateral hypothalamic area, that resulted in adipsia and aphagia, also influenced the idea of a thirst center in the hypothalamus.[7,8] Besides the hypothalamus, several other brain regions that include the medulla oblongata, midbrain, and cerebral cortex participate in the homeostatic regulation of water intake and thirst. These brain regions are considered in the context of sensors or receptor sites for circulating hormones, integrative regions that relay thirst signals within the brain, or as cortical effector sites.

Effector Sites in the Cerebral Cortex

Thirst has been described as one of the primal or homeostatic emotions. Similar to the experience of hunger, full bladder, lack of breath, or fatigue, thirst is a subjective state of the conscious brain that demands a response—in the case of thirst, the ingestion of water is the response. Because thirst is a function of the conscious brain, it has been assumed that regions of the cerebral cortex have a role in the generation of this homeostatic emotion. Supporting this assumption is evidence that decorticate rats, in which the forebrain has been separated from the brainstem, are unable to regulate water intake in response to osmotic stimuli.[9]

The most extensive electrophysiologic survey of the cortical regions that may participate in the generation of thirst was made by Robinson and Mishkin.[10] They stimulated numerous cortical sites in conscious monkeys and observed stimulus-bound water drinking at several loci. The anterior cingulate cortex was the site at which electrical stimulation most reliably resulted in water drinking, although drinking responses also were obtained less frequently by stimulation of the putamen and substantia nigra, the substantia innominata and diagonal band, the preoptic region, lateral hypothalamus, and ventral tegmentum.

In recent years, we have performed neuroimaging studies of thirsty human beings using positron emission tomography or functional magnetic resonance imaging (fMRI). Hypertonic saline was infused intravenously to stimulate thirst in the patients being imaged and regional cerebral blood flow was correlated with their thirst scores.[11,12] These studies have revealed several cortical regions that became activated in human patients with the onset of thirst (Fig 1), this activation being extinguished with satiation of thirst by the drinking of water. The cortical sites that consistently showed a correlation between activity and thirst score (ie, they became activated as patients became thirsty and inactive as thirst decreased) in both positron emission tomography and fMRI

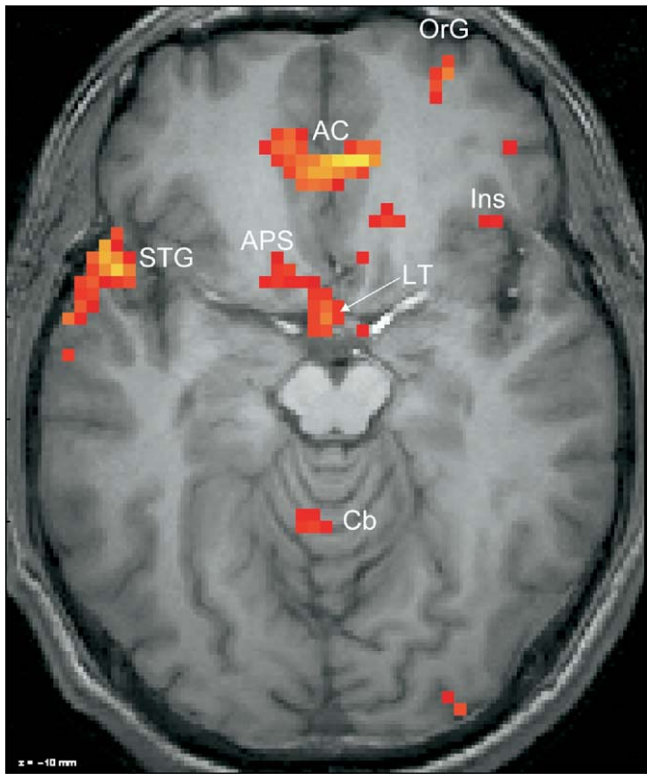

Figure 1 fMRI highlighting areas of significant increase in blood oxygen dependent (BOLD) signal in a human patient experiencing strong thirst in response to an intravenous infusion of hypertonic saline. A horizontal plane ($z = -10$) 10 mm below the level of the anterior commissure is shown. Pseudocolor images are shown with yellow and red areas indicating regions of increased activity. Areas implicated in the generation of thirst are the anterior cingulate cortex (AC), cerebellum (Cb); insula (Ins), and lamina terminalis (Lt). Other regions of activation indicated are the anterior perforated substance (APS), orbital gyrus (OrG), and the superior temporal gyrus (STG). Reproduced with permission from Egan et al.[12]

studies were the anterior and posterior cingulate cortex, parahippocampal gyrus, insular cortex, precentral gyrus, and parts of the cerebellum.[11,12]

Such correlations unfortunately do not allow us to define the role of the particular cortical regions mentioned earlier in the generation of thirst, however, some general comments can be made regarding the anterior cingulate, insular, and parahipppocampal regions of the cortex. Several homeostatic emotions such as deep pain, air hunger, or thirst cause both the anterior cingulate and insular cortices to be activated. Craig[13,14] proposed that homeostatic emotions such as thirst, hunger, or deep pain reflect an adverse condition within the body that requires a behavioral response and suggested that a specific sensation may be engendered in the interoceptive anterior insular cortex, whereas an affective motivation may be generated in the anterior cingulate region. For the evocation of thirst in this scenario, specificity for the interoceptive modality of thirst might be a function of a particular part of the insula. It is not surprising that activation of the parahippocampal gyri, which are implicated in memory, may be associated with thirst stimuli, because memory of water

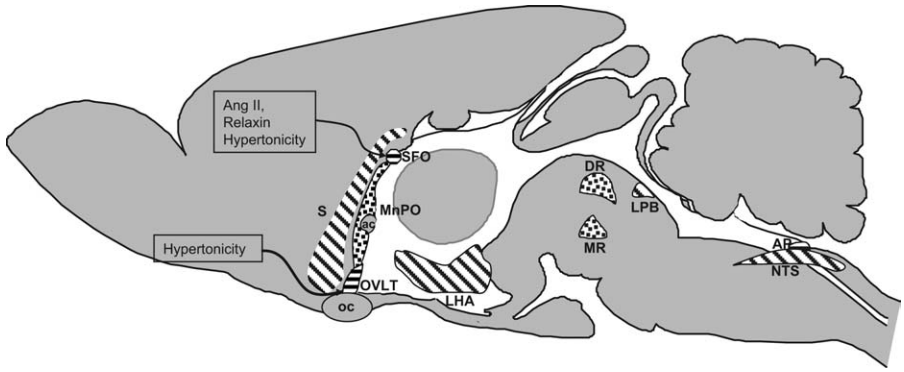

Figure 2 A midsagittal diagram of rat brain showing subcortical regions implicated in the generation or inhibition of thirst. The midline sensory circumventricular organs (shown by vertical stripes) in the lamina terminalis that are responsive to hypertonicity or the hormones angiotensin II and relaxin are the OVLT and subfornical organ (SFO). The area postrema (AP) also is indicated. Medially located integrative regions implicated in thirst (shown by stippling) are the dorsal raphé nucleus (DR), median raphé nucleus (MR), and median preoptic nucleus (MNPO). Laterally situated integrative regions (indicated by diagonal stripes) projected onto the midsagittal diagram are the NTS, LPB, LHA, and septum (S).

sources would be advantageous in the search for and ingestion of fluids.

Sensory Inflow

The lamina terminalis situated in the forebrain in the anterior wall of the third ventricle, contains 2 circumventricular organs (Fig 2): the subfornical organ and the organum vasculosum of the lamina terminalis (OVLT, from Latin *organum vasculosum laminae terminalis*). Both of these circumventricular organs are lacking in a blood-brain barrier because of the presence of fenestrated capillary endothelium. Such fenestrated endothelium is not present in the remainder of the brain, where tight junctions connecting adjacent endothelial cells form a blood-brain barrier.[15] Unlike the rest of the brain, the circumventricular organs are exposed directly to the chemical environment of the systemic circulation, and appear to detect changes in the osmotic and hormonal composition of blood. Thus, together with the area postrema in the medulla oblongata, they have been designated as sensory circumventricular organs.[15]

Osmoreceptors in the Circumventricular Organs

The lack of a blood-brain barrier in the OVLT and subfornical organ was an important factor that led to the proposal that osmoreceptors for thirst may have been located in 1 or more of these brain regions.[16] The reason behind this suggestion lay in the observations that increasing the osmolality of plasma by systemic infusion of sodium salts or saccharides stimulated thirst in human patients and water drinking in animals, whereas the systemic infusion of an equivalent concentration of hyperosmolar urea solution was far less effective in stimulating thirst. Although evidence suggested that the thirst osmoreceptors resided in the brain, measurement of the NaCl concentration on the brain side of the blood-brain barrier showed that the infusion of hyperosmolar urea caused a similar increase in the NaCl concentration of cerebrospinal fluid as an infusion of hypertonic saline or sucrose, yet was a far less effective dipsogen.[16] Systemic infusion of hyperosmolar urea increased the NaCl concentration of cerebrospinal fluid because urea (ie, NaCl and sucrose) does not cross the blood-brain barrier readily,[17] therefore creating an osmotic gradient across this barrier that results in the movement of water by osmosis out of the brain and into the circulation. Because NaCl is the most abundant solute molecule contributing to the tonicity of extracellular fluid, the question arose as to how the brain could distinguish between infusions of hyperosmolar NaCl and sucrose on the one hand and hyperosmolar urea on the other, when similar increases in the NaCl concentration and therefore the tonicity of fluid behind the blood-brain barrier occurred with all 3 solutes. The only places in the brain where sensors of tonicity (osmoreceptors) could have differentiated between hypertonic NaCl and sucrose on the one hand, and hyperosmolar urea on the other, was within a brain region (or regions) lacking the blood-brain barrier, thus the proposal that the OVLT and/or subfornical organ were sites of osmoreceptors.[16]

Subsequent experiments in several mammals have generated evidence to support the view that these 2 circumventricular organs are indeed the site of some (but probably not all) osmoreceptors for thirst. Ablation of the OVLT and immediately adjacent tissue, or combined ablation of the OVLT and the subfornical organ reduces, but does not abolish, water drinking in response to acute intravenous infusion of hypertonic saline.[18-20] Electrophysiologic studies show that neurons are activated within the OVLT and also the subfornical organ by systemic hypertonicity or increased NaCl concentration.[21,22] Consistent with these observations is an increase in *c-fos* expression, a marker of neuronal activity, in neurons within these 2 circumventricular organs in response to intravenous infusion of hypertonic saline.[23] However, hypertonicity also activates neurons in the median preoptic nu-

cleus, which separates the subfornical organ from the OVLT but is behind the blood-brain barrier.[23,24] In addition, ablation of the median preoptic nucleus causes depressed drinking responses to systemic hypertonicity, raising the possibility that it may contain osmoreceptors too.[25,26] Thus, a continuum of tissue in the lamina terminalis stretching ventrally from the subfornical organ to the OVLT is activated by systemic hypertonicity. When the lamina terminalis is ablated totally, drinking in response to acute systemic hypertonicity is abolished.[20] Although it seems likely that osmoreceptors are situated throughout the lamina terminalis, there also is evidence that osmosensitive neurons within the OVLT and subfornical organ may be driving neurons in the median preoptic nucleus.[27] Reciprocal neural connections run between neurons in the median preoptic nucleus, OVLT, and subfornical organ,[15,28] and cutting these connections reduces the osmotic activation of neurons within the median preoptic nucleus.[27] Regardless of the mode by which hypertonicity activates the median preoptic nucleus, it is clear from several lines of evidence in a variety of mammals that the lamina terminalis is a crucial brain region for the detection of acute increases in plasma tonicity.

Although the evidence from studies of human patients regarding the role of the lamina terminalis is relatively meager, lack of thirst has been shown to be associated with damage to the anterior wall of the third ventricle (ie, the lamina terminalis).[29] In addition, recent results of fMRI of thirsty human patients has shown that systemic hypertonicity increases regional cerebral blood flow in the lamina terminalis, which is indicative of neuronal activation within this region.[12]

The third sensory circumventricular organ, the area postrema (Fig 2), also contains neurons that in the rat are responsive to hypertonicity in that they show increased expression of *c-fos* in response to hypertonicity.[29] However, cutting nerve fibers caudal to the lamina terminalis reduced this *c-fos* expression in the area postrema, leading to the suggestion that osmoreceptors in the subfornical organ were responsible for the activation by hypertonic saline loads of neurons within the area postrema. There is little evidence from lesion studies to suggest that the area postrema has a role in the generation of osmotically stimulated thirst. In studying the effects of ablating the area postrema on water intake, it often has been difficult to avoid damage to the adjacent nucleus of the solitary tract (NTS). In rats with lesions that were restricted largely to the area postrema, water intake ad libitum was not altered by this procedure,[30-33] but when the lesion also encroached on the adjacent caudal medial NTS, rats developed a permanent polydipsia that appeared to be secondary to a primary polyuria.[34] Such rats show a moderately greater drinking response to systemic hypertonicity than sham-lesioned animals, suggesting a role for the NTS in thirst mechanisms, and this will be considered in this article in the section on brain regions that have an integrative role in thirst.

Hormonal Influences on Thirst

Site of Action of Angiotensin II to Stimulate Thirst

Angiotensin II was the first hormone to be shown to exert potent dipsogenic actions in animals.[3] Being a hydrophilic peptide, it does not cross the blood-brain barrier readily, thus the question again arises as to how such a molecule could act directly on the brain to stimulate thirst. The answer was provided by Simpson and Routtenberg,[35] who showed that in the rat the subfornical organ was exquisitely sensitive to angiotensin II injected directly into this circumventricular organ. They also showed that ablation of the subfornical organ abolished the dipsogenic response to systemically infused (but not intracerebroventricularly injected) angiotensin II.[36] These data, together with evidence of high concentrations of the angiotensin AT_1 receptor in the subfornical organ[37] and stimulation of neurons in this circumventricular organ (CVO) by circulating angiotensin II,[38] makes it very likely that the neurons within the subfornical organ mediate the dipsogenic action of circulating angiotensin II in rats.

Whether circulating angiotensin II stimulates thirst in human patients still is unresolved. Although there are specific high-affinity binding sites for angiotensin II in the human subfornical organ,[39] intravenous infusions of physiologic levels of angiotensin II did not make human patients thirsty.[40] However, there are reports that angiotensin may have a role as a dipsogenic stimulus in certain pathophysiologic conditions such as renal failure.[41] Some patients undergoing hemodialysis experience intense thirst that is reduced by administration of an angiotensin-converting enzyme inhibitor, suggesting an angiotensin-mediated thirst.[42,43]

Angiotensin II also may stimulate strong dipsogenic responses when injected directly into the lateral or third cerebral ventricles. This response is not mediated by neurons within the subfornical organ because it is not abolished by ablation of this circumventricular organ.[36,44] However, ablation of the anteroventral wall of the third ventricle region, and, more specifically, the median preoptic nucleus, which largely is contained within the anteroventral wall of the third ventricle region, does abolish drinking in response to intracerebroventricular (ICV) administration of angiotensin II.[44,45] The median preoptic nucleus (Fig 2) contains a high density of angiotensin AT_1 receptors[37] and ICV injection of angiotensin II activates many neurons within this nucleus.[46] Because microinjection of angiotensin II directly into this brain site also elicits a drinking response,[47] it seems likely that the median preoptic nucleus is the principal site of the dipsogenic action of angiotensin II injected into the cerebral ventricles.

Site of action of relaxin to stimulate drinking

Relaxin, a hormone secreted by the corpus luteum during pregnancy, also will stimulate animals to drink water when administered systemically or centrally.[48,49] Systemically administered angiotensin II potentiates the drinking response to intravenously infused relaxin[49] and administration of neu-

tralizing antibodies to relaxin reduces the fluid intake of pregnant rats.[50] Being a peptide hormone, relaxin in the bloodstream is unlikely to cross the blood-brain barrier. The presence of specific high-affinity relaxin-receptor binding sites in both the subfornical organ and OVLT[51] led us to investigate the possibility that neurons within either or both of these circumventricular organs are the sites of the dipsogenic action of systemically infused relaxin. Ablation of the subfornical organ in rats abolished the dipsogenic response to intravenously infused relaxin in the rat, whereas ablation of the OVLT had little effect on this response.[52] In addition, intravenously infused relaxin stimulated neurons within the subfornical organ (as shown by the increased expression of c-fos) and locally applied relaxin increased the electrical firing of single units in slices of rat subfornical organ.[52] Most relaxin-sensitive neurons in the subfornical organ also increased firing in response to angiotensin II.[52] These data indicate that neurons within the subfornical organ are the likely site at which circulating relaxin stimulates drinking in the rat. The remaining neural circuitry that subserves relaxin-stimulated drinking remains to be determined.

Integrative Sites

The Nucleus of the Solitary Tract

In regard to the role of the nucleus of the solitary tract (Fig 2) in nonosmotic thirst as mentioned earlier, ablation of the area postrema together with some adjacent tissue in the NTS increased water intake induced by several different experimental procedures. These were hypovolemia resulting from subcutaneous injection of the hyperoncotic colloid polyethylene glycol, subcutaneous injection of isoproterenol, and systemic or central administration of angiotensin II.[30-32] Interestingly, Wang and Edwards[33] showed that when the lesion was more restricted to the area postrema, the animal did not increase water intake induced by isoproterenol but, with more involvement of the NTS in the lesion, there was a greater water intake in response to this stimulus. Thus, the evidence to date suggests that inhibitory signals that may affect the generation of thirst and water intake are relayed via the NTS. However, this suggestion requires qualification because there also is evidence that chronic ablation of the NTS in the rat does not affect ad libitum water intake or drinking resulting from acute hypovolemia induced by subcutaneous injection of polyethylene glycol over a 5-hour test period.[53]

The NTS is a primary site of termination in the brain of vagal and glossopharyngeal afferent nerve fibers.[54,55] As such, it receives neural input from baroreceptors, the gastrointestinal tract, and taste receptors, which all may influence thirst and fluid intake. In regard to baroreceptors, increased arterial pressure has an inhibitory influence on water drinking,[56] and it is likely that neural signals from arterial baroreceptors reach the NTS when arterial pressure increases, and then are relayed to other brain regions to inhibit thirst.

Midbrain Raphé

Several investigators have reported that the midline dorsal and median raphé nuclei (Fig 2), midbrain sites that are endowed richly with serotonin-containing neurons, probably exert an inhibitory influence on water intake in rats. The initial findings that led to this suggestion were observations that chronic ablation of these sites caused increases in water intake in rats, although the polydipsia was of a temporary nature.[57-59] Recently, it was shown that the drinking response to water deprivation or subcutaneous isoproterenol treatment (that produces an angiotensin II–dependent thirst in rats) were increased in rats with dorsal raphé lesions. In addition, such lesions of the dorsal raphé nucleus changed the sodium preference of rats so that a large increase of NaCl intake and water ensued when the dorsal raphé was ablated.[60]

In regard to the median raphé nucleus, a microinjection of 5,7-dihydroxytryptamine to destroy serotonin-containing neurons caused a gradual increase of water drinking in rats over a period of 6 days. This result suggested an inhibitory median raphé serotonergic involvement in thirst mechanisms.[61] Consistent with this idea are observations that acute inhibition of neurons within the median raphé nucleus by microinjection of the GABA agonist, muscimol, caused a rapid large drinking response in water-replete rats.[62,63] The midbrain raphé nuclei are connected directly and reciprocally to several brain regions known to play important roles in the genesis of thirst, such as the subfornical organ and median preoptic nucleus in the lamina terminalis, and the lateral hypothalamic area (LHA).[28,64,65] Stratford and Wirtshafter[62] investigated the effects of ablating these regions on the fluid intake caused by injection of muscimol into the median raphé nucleus, and showed that lesions in the subfornical organ or the LHA severely disrupted this response, whereas lesions in the median preoptic or lateral preoptic nuclei significantly enhanced the response. They suggested that neural inputs from the median raphé nucleus, to either or both the subfornical organ and LHA, may have a tonic inhibitory influence on angiotensin-induced thirst responses; however, they suggested that these inhibitory influences probably were nonserotonergic.

Lateral Parabrachial Nucleus

The lateral parabrachial nucleus (LPB), located dorsolateral to the superior cerebellar penducle in the midbrain (Fig 2), is connected neurally to many regions that participate in the regulation of fluid intake.[64,66] It is likely that the LPB has an inhibitory role in thirst pathways. Although disruption of neurons within the LPB does not alter daily water intake, it does enhance angiotensin-stimulated water intake. Electrolytic ablation of the ventrolateral part of the LPB increased the dipsogenic effect of angiotensin II administered systemically or centrally, and also the fluid intake in response to subcutaneous injection of isoproterenol. However, such a lesion did not affect water intake induced by ICV injection of carbachol, systemic hypertonicity, or by hypovolemia caused by subcutaneous injection of polyethylene glycol.[67,68] Edwards and Johnson[69] showed that injections of the excitoneurotoxin ibotenic acid, which destroyed neuron cell bodies but not fibers within the LPB, also increased the dipsogenic effects of angiotensin II and subcutaneous isoproterenol, without affecting osmotically stimulated drinking. These data suggest

that the activity of neurones in the LPB, not fibers of passage, is important in determining water intake. In addition, it seems that although the LPB does not influence water intake ad libitum, it may participate in the prevention of excessive drinking after specific thirst mechanisms have been stimulated.

How the LPB inhibits water intake is unclear. It could disrupt an excitatory system or facilitate an inhibitory pathway. One possibility is that the LPB restricts water intake through activation of mechanisms involved in satiety. Consistent with this proposal is the observation that microinjection of muscimol into the LPB to activate its $GABA_A$ receptors and thereby inhibit its neuronal activity induces a small but significant increase in water intake of satiated rats.[70]

The LHA

As mentioned in the introductory section of this article, the LHA (Fig 2) has long been considered as having a role in the generation of thirst, yet the true nature of this role remains obscure. Early studies of the hypothalamus showed that electrical stimulation of the part of the hypothalamus between the fornix and mammillothalamic tract reliably initiated water drinking behavior in goats and rats.[5,71,72] Many researchers have shown that electrolytic ablation of the LHA caused adipsia and aphagia, the lateral hypothalamic syndrome,[7,8] and, on recovery from the adipsia, drinking responses to hypertonicity or angiotensin II were disrupted severely.[73] For a period, this disruption of mechanisms of fluid intake generally was attributed to the destruction of nerve fibers within the median forebrain bundle that passes through the LHA. In particular, the disruption of ascending catecholaminergic fibers in the median forebrain bundle was considered crucial for the production of the lateral hypothalamic syndrome.[74] The subsequent advent of excitotoxic neurotoxins (eg, kainic acid, ibotenic acid) that ablated neuronal cell bodies but spared fibers of passage led to a re-evaluation of the lateral hypothalamic syndrome. Lesions of the LHA made with injections of kainic acid or N-methyl D-aspartate into the LHA that left the catecholaminergic fibers passing through this region undamaged still elicited a period of adipsia and permanently disrupted water drinking in rats in response to several acute dipsogenic stimuli.[75-77] These stimuli included acute hypertonicity, systemically administered angiotensin II, and hypovolemia resulting from the subcutaneous injection of hyperoncotic polyethylene glycol that caused subcutaneous sequestration of extracellular fluid.[75-77] Interestingly, although the drinking responses to a number of acute dipsogenic stimuli were disrupted by excitotoxic lesions of the LHA, drinking after a period of water deprivation in these rats with LHA lesions was not inhibited. Paradoxically, injections of clonidine (α2-adrenoreceptor agonist) into the LHA inhibits water intake in response to a period of water deprivation.[78] Of relevance also to the interpretation of these data, is evidence that osmosensing and sensorimotor function remained intact, and the dopamine content of the hypothalamus was not reduced.

In explanation of these results, it has been proposed that LHA lesions destroy neurons in this region that are projecting to the cerebral cortex to relay information related to acute changes in body fluid homeostasis.[77] In regard to the neural input to the LHA, there are afferent neural connections from regions that influence thirst mechanisms such as the lamina terminalis (subfornical organ and median preoptic nucleus), lateral parabrachial nucleus, and median raphé.[15,28,79,80] There also are efferent neural projections of neurons within the LHA to the insular cortex,[81] showing the neuroanatomic feasibility of such thirst relays in the LHA. However, because drinking responses to more slowly developing fluid deficits such as that which occurs with water deprivation are not disrupted by ablation of the LHA, there also must be alternative neural pathways from the sensory inputs coming from the lamina terminalis, midbrain, and hindbrain to the cerebral cortex to generate thirst.

Preoptic Region

Two parts of the preoptic region have been implicated in thirst mechanisms, the median preoptic nucleus—already mentioned as the principal site of action of ICV angiotensin II to stimulate drinking, and the lateral preoptic region. Although it is possible that the median preoptic nucleus may have a sensory function related to osmoregulation, its neural connectivity has led several investigators to the conclusion that it is an important integrative site for the regulation of thirst.[2,4,28,64] The median preoptic nucleus (Fig 2) receives afferent neural input from central sites known to relay sensory information related to blood volume, blood pressure, blood tonicity, and circulating hormone levels. These are sites such as the subfornical organ, OVLT, hypothalamic paraventricular nucleus, midbrain raphé, LPB, and NTS.[28,64,65] Therefore, it is ideally placed to integrate sensory information and relay signals to cortical effectors for the initiation of appropriate levels of thirst.

Ablation of the median preoptic nucleus severely disrupts the drinking responses to both osmotic and hormonally stimulated drinking,[20,25,26,45] consistent with the notion that it is an important integrative region for thirst. The high concentration of angiotensin AT_1 receptors in the median preoptic nucleus[37] suggests angiotensinergic afferent neural inputs influence its function, especially because it is inside the blood-brain barrier and not directly influenced by circulating angiotensin II. It has been proposed that such angiotensinergic inputs to the median preoptic nucleus drive neural circuits that initiate thirst.[82]

The other preoptic site that has been implicated in thirst mechanisms is the lateral preoptic area. Although attention has focused on the lamina terminalis as a site of thirst osmoreceptors in recent years, earlier studies suggested that the lateral preoptic area may contain osmoreceptors. Ablation of the lateral preoptic area disrupts osmotically stimulated drinking, and microinjections of hypertonic solutions into this region stimulates drinking, suggesting the presence of

osmoreceptors.[83,84] The results of later microinjection studies showed that drinking responses to hypertonic sucrose solution injected into the lateral preoptic area were more variable than the initial results.[85] In addition, the elicitation of these drinking responses could be obtained from a wider spread of sites in the preoptic region.[85] However, there is evidence that osmoreceptors may be located both outside and within the blood-brain barrier,[16] thus it is feasible that lateral preoptic osmoreceptors may jointly detect hypertonicity in combination with those in the lamina terminalis. Otherwise, it is possible that the lateral preoptic region also integrates neural signals related to thirst.

Septal Region

The septal region of the brain (Fig 2) has attracted attention for many years as a region that may relay both inhibitory and excitatory signals related to thirst.[86,87] In regard to inhibitory relays, Harvey and Hunt[86] were the first to show that bilateral electrolytic ablation of tissue in the septum of the rat resulted in increased ad libitum water intake that persisted for months. Since then, many other researchers also have observed this effect in several different species.[88,89] Although Harvey and Hunt[86] speculated that the polydipsia associated with septal lesions was a primary hyperdipsia, they also considered the possibility that it could have been secondary to increased renal fluid losses. In regard to this point, there are direct neural connections from the medial septal region to the vasopressin-containing neurons of the supraoptic and paraventricular nuclei, and ablation of the medioventral septal area in rats has been associated with lower basal or osmotically stimulated plasma vasopressin levels.[90] Lubar et al[91] observed that rats with posterior septal lesions had high water intake, high urine output, and low urine osmolality. They also showed that in addition to reducing urine output, exogenous administration of vasopressin reduced the daily water intake of septal-lesioned rats to prelesion levels, suggesting the polydipsia was secondary to excessive urinary losses. However, in a telling experiment, Blass and Hanson[92] reached the opposite conclusion because they observed that polydipsia persisted in septal-lesioned rats when the ureter was ligated to prevent loss of urine. We have observed chronic septal polydipsia in sheep over several months when medial septal tissue was ablated by radiofrequency current (Smardencas and McKinley, unpublished observations). These animals developed hyponatremia and continued to drink despite low rates of urine output when vasopressin was infused intravenously, which is also an indication of a primary polydipsia caused by ablation of the septum in these animals.

Blass et al[93] observed in rats that drinking associated with hypovolemia and increased blood angiotensin levels was potentiated specifically by septal lesions, whereas such brain damage did not affect the water intake in response to acute hypertonicity.[93] They proposed that specific potentiation of angiotensin-induced drinking had an important role in septal hyperdipsia, but they also considered that other factors, not identified, also may contribute to this phenomenon. This later point is shown by the fact that the daily water intake of unchallenged rats increases after septal ablation, but it is unlikely that angiotensin-induced thirst has a significant role in normal day-to-day water intake of unchallenged animals. Our observations in hyperdipsic sheep with septal lesions was that they do not show any specific enhancement of angiotensin-induced, feeding associated, or osmotically stimulated drinking, but that they continue to drink during the day when the plasma osmolality has decreased below the normal set-point (Smardencas and McKinley, unpublished observations). It seems likely that the normal inhibitory influences of hypotonicity or hypervolemia on thirst are disrupted in these animals when the medial septal region is ablated.

Conclusions

Several brain regions that participate in the regulation of water intake, and presumably thirst, now have been identified. These sites encompass all the major divisions of the brain, from the NTS in the medulla and lateral parabrachial and raphé nuclei in the midbrain, to regions of the forebrain such as the lateral hypothalamus, preoptic region, septum, lamina terminalis, and cortical sites. Yet much of the neural circuitry subserving thirst still remains obscure. This contrasts with the considerably better understanding that we have of the neural circuitry that drives vasopressin secretion,[94] the other major centrally regulated component of body fluid homeostasis. In the case of vasopressin secretion, there is a clear understanding of the final motor output of the neural circuitry—the magnocellular neurons of the hypothalamic supraoptic and paraventricular nuclei projecting to the posterior pituitary gland. This knowledge has been instrumental in the elucidation of such neural circuitry. Similarly, unequivocal identification of the ultimate cortical sites responsible for the genesis of thirst will considerably aid the elucidation of the neural pathways that underpin thirst.

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