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REGULATION OF WATER INTAKE

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INTRODUCTION

Supplied with unlimited fresh water, humans and apparently most mammals satisfy their need for water by anticipatory, habitual, or prandial drinking not motivated by true thirst (23). Nevertheless, an efficient thirst mechanism and appropriate regulation of the liberation of water-retaining antidiuretic hormone (ADH, vasopressin) are indispensable for optimal water balance, the maintenance of which has high homeostatic priority.

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Thus during severe dehydration the craving for water becomes tormenting and constitutes one of the most urgent of human needs (79). Normally, all derangements of fluid
of ADH from the neurohypophysis (although the reverse is sometimes not the case). This implies that water intake and ADH secretion are predominantly regulated by similarly functioning enteroreceptors, which have a lower stimulus threshold for initiating ADH liberation than for eliciting the urge to drink. Hence, research on the regulation of ADH secretion is relevant to the etiology of thirst, and studies on thirst may contribute to our understanding of ADH release. Here we review the regulation of both water intake and ADH secretion, citing current evidence for (*a*) the contribution of cerebral sensory mechanisms to the control of water balance, and (*b*) the role played by the brain as coordinator of relevant afferent signals. We discuss controversies in the area and briefly
festations of disturbed cerebral regulation of water intake.

DEVIATIONS FROM FLUID BALANCE ELICITING THIRST AND ADH RELEASE

Osmotic Regulation

The deviations from fluid balance that most efficaciously elicit thirst and hypersecretion of ADH are (*a*) deficit of water without corresponding loss of Na (hypovolemic hypernatremia, Figure 1 D), and (*b*) osmotic shift of water from the cells to the extracellular fluid
Na intake (hypervolemic hypernatremia, Figure 1 A). The latter condition does not involve any net loss of water, but characteristics common to both conditions are cellular dehydration, hyperosmolality of the body fluids, and elevated extracellular Na concentration. Of these three factors, cellular dehydration is generally considered to constitute the crucial thirst and ADH stimulus. Such regulation is designated osmotic in the light of Verney's (75) fundamental investigations, which imply that ADH release is negatively correlated to the cell volume of hypothalamic osmoreceptors. Whether the sensory mechanism disclosed by Verney in fact consists of osmoreceptors, or elements more specifically sensitive to Na (5), has recently been debated (see the section below on Sensors of Osmotic Regulation). Be that as it may, more than 90% of the osmolality of the interstitial fluid and the blood plasma is created by Na and its associated anions. These particles also exert the effective (cell-dehydrating) tonicity of the ECF since Na is continuously extruded from the cells in exchange for K by active, enzymatic cation transport. In reality, therefore, the osmotic regulation of water intake and ADH release serves as a protector of normal plasma Na concentration; and in conscious individuals having free access to water,

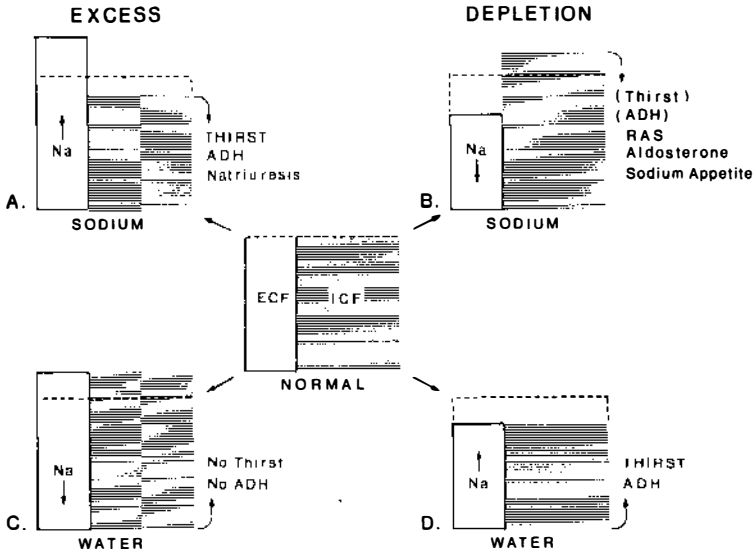

Figure 1 Outline of changes in body fluid distribution and extracellular Na concentration during positive and negative sodium and water balance. Compensatory factors indicated to the right of each diagram. *ADH* = antidiuretic hormone; *ECF* = extracellular fluid compartment; *ICF* = intracellular fluid compartment; *RAS* = the reninangiotensin system. Reprinted with permission from (9).

significant hypernatremia is encountered only if the thirst mechanism is impaired.

By using a sensitive radioimmunological method to determine plasma ADH (arginine vasopressin) and by accurately measuring plasma osmolality, Robertson and associates (58, 60) have disclosed the amazing sensitivity of the enteroceptors responsible for the osmotic control of water balance in man. Performed during various states of hydration, these investigations revealed a close correlation between plasma ADH level and osmolality in healthy adults. Individual variations were seen, but the plasma osmolality during euhydration averaged 287 mOsm/kg with an average plasma vasopressin concentration slightly above 2 pg/ml. ADH secretion of that order involved roughly 50% engagement of the renal capacity to concentrate the urine. A 2% increase in total body water was sufficient to suppress the ADH secretion below the detectable level and, hence, to induce maximal urine dilution. In the opposite direction, the thirst threshold was reached at about 2% deficit of body water (average plasma osmolality 294 mOsm/kg), and this moderate hypovolemic hypernatremia elevated plasma vasopressin to about 5 pg/ml, which was sufficient to induce maximal urine concentration. As pointed out by Robertson et al (60), this implies that the thirst threshold as normally set provides an effective compensation for ADH when the renal action of the hormone can no longer prevent an undue

elevation of plasma Na concentration and tonicity. Thus osmoregulatory thirst in man may be regarded as an emergency mechanism that intervenes only when the water in food and anticipatory or habitual drinking, in combination with fully utilized effect of ADH, are insufficient to maintain extracellular Na concentration below a certain level.

Volume Regulation

It is well known that hemorrhagic shock or persistent profuse diarrhea may induce intense thirst in spite of the fact that plasma Na concentration and osmolality remain normal or are even decreased. Furthermore, animals extensively depleted of sodium, having reduced extracellular Na concentration and osmolality, may increase their water intake and continue to secrete ADH (2). What characterizes these conditions is a pronounced diminution of the ECF volume, which makes it obvious that a volume regulation of water intake and ADH release parallels and complements the osmotic regulation. The dimension of the ECF regulated is evidently the effective circulating blood volume, and both cardiovascular reflexes and the renal renin-angiotensin system (RAS) are apparently involved (see the section below on Mediators of Volume Regulation). However, volume regulation is evidently of negligible importance in normal day-to-day control of water balance and remains subordinate to its osmotic counterpart during moderate fluctuations

sodium depletion the osmotic regulation initially maintains plasma Na concentration and tonicity at or near normal levels. First at the stage when the osmoregulatory preservation of plasma Na concentration has induced critical hypovolemia, the volume regulation takes precedence at the price of hyponatremia (74). The relative insensibility of the volume regulation is also evident from the facts that thirst is no consistent effect of rather substantial blood loss in man (22), and that more than one fifth of the blood volume needs to be drawn in water-replete mammals before the thirst mechanism becomes activated (33, 38, 64). As regards ADH secretion, studies in man (27, 58) and animals (11, 18, 38) have revealed that about a 10% reduction of the blood volume is required before an increase in plasma ADH can be detected with available radioimmunological methods. However, hypovolemia of this order has been found to lower the osmotic threshold for ADH liberation, and to augment the hormone release at super-threshold levels of plasma osmolality, whereas expansion of the blood volume has been shown to have the opposite effect (18, 58). That this subtle interaction between volume and osmotic regulations also embraces thirst is indicated by the observations that hypovolemia lowers (37), and ECF volume expansion elevates (35) the threshold for drinking in response to intravenous infusions of hypertonic NaCl in the dog.

SENSORS OF OSMOTIC REGULATION

Although afferent impulses may modulate the osmotic regulation of water intake and ADH secretion, clinical observations in man and experimental studies in other mammals have gradually made it evident that this regulation is exerted predominantly by cerebral sensors. One hundred years ago Nothnagel (45) postulated that water intake was regulated by a thirst center in the brain. Nothnagel's report concerned the sudden onset of severe thirst without preceding polyuria (primary polydipsia) in a man subjected to head trauma. Other clinical reports on primary polydipsia of apparently cerebral origin followed (79), but the first definite proof of the brain's involvement in the osmotic control of water balance was provided by Verney (75) in the middle of the present century.

The Osmoreceptor Concept

In conscious hyperhydrated dogs Verney conclusively showed that cerebral sensors participate in the regulation of ADH secretion and are stimulated when the carotid blood osmolality is raised with sodium salts and other cell-dehydrating substances (for instance fructose and sucrose). Since no obvious ADH release was obtained in response to carotid blood hyperosmolality induced with substances that more easily equilibrate with the intracellular fluid

question are primarily excited by a diminution of their own volume, and that a certain degree of sensor activity is maintained in euhydrated individuals by the prevailing plasma tonicity. The latter would explain the presence of a basic ADH secretion during euhydration, and the fact that this secretion subsides in response to excessive water intake. The osmoreceptor concept has exerted a far-reaching influence

and when injections of small amounts of hypertonic NaCl into the medial hypothalamus were found to induce polydipsia in water-replete goats (4), it was regarded as evidence that osmoreceptors are also involved in the regulation of water intake. Later replications of Verney's experiments in the same or other mammalian species have confirmed in every respect the results of his pioneering research on the osmotic regulation of ADH secretion (20, 43) and have revealed a positive correlation between the ADH-releasing and thirst-eliciting effects of various substances used to induce plasma hyperosmolality (43, 47, 71, 81). Suggestive evidence for the osmoreceptor concept is also provided by the elucidative radioimmunological investigations on osmotic regulation of ADH secretion in man briefly

cussed above (58, 60). However, the evidence for cerebral osmoreceptors becomes obscured when discussed in relation to presently available knowledge about solute transfer between the blood plasma and the interstitial fluid

of the brain. As mentioned, carotid blood hyperosmolality induced with urea, and also with glycerol (20, 47) is ineffective as a stimulus for ADH release and thirst. Yet a blood-brain barrier for these substances considerably delays their passage into the cerebral interstitial fluid
quently, intravascular administration of hypertonic urea and glycerol solutions dehydrates the brain as a whole. This seems to limit conceivable osmoreceptor locations to sites outside the blood-brain barrier, or to cerebral regions devoid of this barrier. Apparently only the latter possibility needs to be considered, since the sensors involved in the control of water balance are highly susceptible to humoral stimuli and inhibitors administered into the cerebrospinal fluid

The Sodium Sensor Concept

Two observations made in the goat—(*a*) that hypertonic sucrose (in contrast to hypertonic NaCl) does not elicit ADH release and thirst when infused into the third ventricle (46), and (*b*) that the antidiuretic and dipsogenic responses to similar infusions of angiotensin II are positively correlated to the Na concentration of the CSF (7) —— originally gave rise to the suggestions that juxtacerebroventricular sodium sensors might be an alternative to osmoreceptors, and that the CSF may function as an indirect route by which alterations in blood plasma composition influence
ity of cerebral sensors controlling water balance (5). Continued investigations in the goat (6) have substantiated the evidence for this sodium sensor concept, as have recent studies in the sheep (42, 43) and rhesus monkey (70). Strongly supporting this idea are the results of experiments in which the CSF Na concentration has been lowered by intracerebroventricular infusions of hypertonic solutions of substances (fructose, sucrose, and mannitol) that elevate the effective (cell-dehydrating) osmolality of the CSF. Such infusions have been found to extinguish the dipsogenic (48) and antidiuretic (49) effects of hypernatremia and plasma hypertonicity, and to inhibit the basic ADH secretion in euhydrated animals (44). These observations appear hard to reconcile with the osmoreceptor theory. They also seem to eliminate the possibility that intracranial sensors regulating water intake and ADH secretion are situated outside the blood-brain barrier. However, the sensors in question may well be located in areas lacking that barrier, or have a position making them accessible both to blood-borne and CSF-borne influences. Such a state of affairs could explain why the intravascular administration of hypertonic urea, although elevating CSF Na concentration by cerebral dehydration (43), does not elicit ADH release and thirst. This fact has recently been considered a near fatal blow to the sodium sensor concept (66). However, cation transporting enzymatic activity seems to be essential for the excitation of cerebral sensors controlling water balance (6). Like

deuterium (39) and some other inhibitors of active cation transport, urea effectively blocks hyperosmotic thirst and ADH release when administered into the CSF (62). Provided the substance has that action also from the vascular side of the blood-brain barrier, it could explain the lack of dipsogenic and ADH releasing responses to elevated CSF Na concentration induced by the intravascular administration of hypertonic urea. It must be concluded, however, that the nature of the cerebral sensors regulating water intake and ADH secretion in many respects remains to be elucidated.

Tentative Sensor Location

The mere fact that thirst and ADH secretion are easily affected by changes in the composition of the CSF suggests that sensors governing these functions are located somewhere in the surroundings of the cerebroventricular system. More direct evidence for a close juxtaventricular location is provided by the observation that intracerebroventricular infusions of deuterium (with NaCl added to isotonicity) effectively inhibited dehydrative thirst and the basic ADH secretion of euhydrated goats (39). When administered into the CSF, deuterium and other liquids with almost unlimited passage over the blood-brain barrier attain an exceedingly steep CSF/brain-tissue concentration profile (52). Consequently, if the observed effects of deuterium are due to inhibition of sensor activity, these elements must be located in or very near the ventricular wall. The brain area that deserves particular attention is the anterior wall of the third ventricle (Figure 2). Results of both stimulation and ablation experiments suggest that most sensors regulating ADH release and water intake are located in that area (6). Destruction of it by narrow, medially placed radiofrequency lesions was found to have drastic effects on the water balance of goats (8, 63). These lesions caused complete and persistent absence of thirst even during severe dehydration and hypernatremia (permanent adipsia) and lack of apparent ADH release in response to pronounced dehydration and to the intracarotid infusion of hypertonic NaCl and angiotensin II. An uncompensated, temporary water diuresis, which rapidly induced hypernatremia and hypovolemia, was observed as an acute effect of such lesions. The evidence favoring the idea that most sensors subserving water economy are present in or near the anterior wall of the third ventricle has stimulated speculations concerning the particular structures involved, and the morphological characteristics of the tentative sensors. The circumventricular organs present in this area (the subfornical organ and the organum vasculosum of the lamina terminalis) have received particular attention (23), mainly because they are devoid of a blood-brain barrier. This would make sensors confined to these organs accessible both to blood-borne and CSF-borne stimuli and inhibitors. Cell types in the wall of the third ventricle that also have been dis-

cussed as sensor candidates are CSF-contacting neurons (76) and tanocytes (77). The tanocytes, especially, seem structurally well adapted to function as sensors governing water intake and ADH release because these cells provide a morphological connection of CSF, nerve cells, and blood vessels. However, ablation experiments demonstrating that structures in front of the third ventricle are essential for the maintenance of water balance do not prove that the cerebral sensors regulating water intake and ADH secretion are exclusively confined to that part of the brain. An additonal function of the lesioned region may be integration or relaying of relevant impulses from sensors in other parts of the brain or from peripheral receptors. Furthermore, from a phylogenetic point of view it appears rather unlikely that the entire population of cerebral sensory elements governing functions of so vital importance as thirst and ADH secretion should be confined to one periventricular area. Indications exist that sensors having these functions are also present at more posterior levels of the cerebroventricular system (6).

MEDIATORS OF VOLUME REGULATION

Changes in the effective circulating blood volume modulate the activity of cardiovascular mechano-receptors and the renal renin release. Consequently, reduction or increase in the effective amount of circulating blood may induce appropriate volume regulatory changes in water intake and ADH secretion both via cardiovascular reflexes and the RAS.

Cardiovascular Reflexes, ADH Secretion and Thirst

Ambiguities remain concerning the relative importance of differently located cardiovascular mechano-receptors in the volume control of water balance. However, the evidence is convincing that both arterial baroreceptors and left atrial distention receptors exert a tonic inhibition on the neurohypophyseal ADH release (66) and that at least the latter kind of receptors affect the thirst mechanism in a similar manner (23). On the basis of experiments in the dog showing that balloon-inflation of the left atrium induced a diuresis, Henry et al (32) originally proposed that stimulation of distention receptors in this part of the heart inhibits ADH release. This proposal has been verified in similar studies involving determinations of plasma ADH (14, 73). The primary physiological importance of this inhibitory effect of cardiac receptor activity may be to counteract an undue expansion of the blood volume, whereas its importance in the defense against hypovolemia appears to be secondary. Thus underfilling of the heart induced by graded hemorrhage in conscious monkeys (11) and goats (38) did not cause significant ADH release until the hypovolemia had progressed

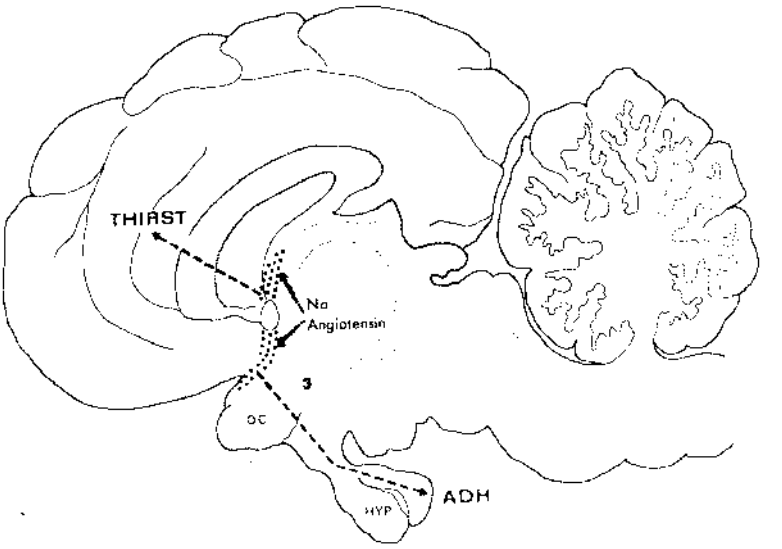

Figure 2 Midsagittal section through a mammalian brain (goat). Juxtacerebroventricular sensors responsible for the osmotic regulation of water intake and antidiuretic hormone (ADH) release are apparently located mainly in the dotted area in front of the third ventricle (3). However, such sensors may also be present at more posterior levels of the cerebroventricular system. *Hyp* = anterior lobe of the pituitary gland; *OC* = optic chiasm. Reprinted with permission from (6).

to a stage when the arterial blood pressure began to fall. This suggests reduced baroreceptor activity as the main cause of the ADH release. Evidence that atrial receptors also exert a tonic inhibition on the cerebral thirst mechanism includes observations that underfilling of the low pressure thoracic circulation elicited angiotensin II independent drinking in the dog (24), and that left thoracic vagosympathectomy lowered the osmotic thirst threshold in that species (69). However, a recent study in the sheep (82) suggests that hypovolemic thirst of cardiac origin may not be solely a release phenomenon. Denervation of the left atrium had no apparent effect on basic and hyperosmotic water intakes but completely abolished hypovolemic drinking. Thus underfilling of the left atrium may act dipsogenically not only by reducing inhibitory input from distention receptors but also by eliciting in some manner afferent nerve activity that stimulates the thirst mechanism.

The RAS, Thirst, and ADH Secretion

To what extent the renal RAS participates in the volume regulation of water intake and ADH secretion is somewhat controversial (31). That the kidney may participate in thirst regulation was originally proposed by Linazasoro

et al (40) on the basis of the observation that parenteral administration of renal extract elicited drinking in nephrectomized rats. In the light of the substantial evidence subsequently presented by Fitzsimons and associates (22, 23) it now appears fully established that hypersecretion of renin induced by pronounced hypovolemia can increase the plasma concentration of angiotensin II in rats and dogs to a level at which this octapeptide stimulates the cerebral thirst mechanism. It is less obvious that the same may happen during volume depletion in some other mammalian species and has so far not been demonstrated in man. In the sheep, for instance, even severe Na depletion did not elevate plasma angiotensin II to a level compatible with the carotid blood concentration of exogenous angiotensin II needed to elicit drinking (1). Furthermore, the use of a competitive angiotensin II antagonist (saralasin) showed that the RAS did not to any measurable extent contribute to the drinking of dogs (54), goats (50), and sheep (3) preexposed to water deprivation for two days. However, extreme hyperactivity of the RAS has apparently contributed to intense thirst experienced by some patients suffering from renal failure (61), and abnormally high plasma levels of angiotensin II seem to have acted dipsogenically in patients with renin-secreting Wilm's tumor (67). Studies in animals have shown that ADH release is another centrally mediated effect of angiotensin II (7, 13), but it remains uncertain also whether that effect of the octapeptide has any physiological significance. Intravascular administration of angiotensin II did not cause increased ADH release in man until highly supraphysiological plasma levels were reached, and no correlation was found between plasma ADH and angiotensin II during acute changes of fluid balance in healthy volunteers, or in hyperreninemic patients (51). However, when discussing a conceivable physiological and/or pathophysiological importance of the RAS in the control of water balance, the possibility must be considered that angiotensin II might lower the osmotic stimulus threshold for thirst and ADH release (see below).

A definite answer has so far not been given to the question of whether blood-borne angiotensin stimulates the cerebral thirst and ADH-releasing mechanism(s) directly or indirectly via the CSF. Speaking in favor of the latter possibility are (*a*) the fact that in these respects angiotensin I and II act as efficient stimuli when administered into the lateral and third ventricles (6), and (*b*) the observation made in the sheep that intracerebroventricular administration of saralasin completely extinguished the dipsogenic response to the intracarotid infusion of angiotensin II but did not affect drinking in dehydrated animals (3). The latter finding implies that systemic angiotensin II either elicits thirst via the CSF or acts on cerebral sensors that are affected simultaneously by the CSF and the blood plasma composition. The latter appears more likely since it was recently shown in the rat

and the dog that angiotensin I and II did not penetrate from the blood into the CSF unless large amounts of these peptides were administered intravenously (65). However, of interest in this connection is that the choroid plexa (19), and apparently also the ependyma (53), are rich in angiotensin I converting enzyme. It may be that conversion of blood-borne angiotensin I at these sites facilitates the exposure of juxtacerebroventricular sensors to angiotensin II during activation of the RAS. Another intricate question is whether "osmotic" and angiotensin II stimulation of thirst and ADH release is exerted via the same or different cerebral sensors. It has been claimed that the octapeptide and hypernatremia induce drinking via separate cerebral mechanisms (22). Evidence includes the observation that the dipsogenic effects of systemic angiotensin II and hypernatremia simply added to each other in the rat (25). However, speaking in favor of a unitary sensory target is the striking cerebral Na/angiotensin interaction demonstrated in the goat (6). Here intracerebroventricular administration of small amounts of angiotensin II caused a pronounced augumentation of thirst and ADH release in response to elevated CSF Na concentration. This led to the suggestion that the RAS may contribute to the control of water balance by lowering the stimulus threshold of cerebral receptors that are primarily sodium sensitive (5). Later support for that idea includes a study involving radioimmunological determination of urinary ADH excretion in response to intracerebroventricular infusions of angiotensin II and hypertonic NaCl, where a potentiated effect was obtained when both stimuli were applied together (41). Also favoring a unitary sensory target is the observation in the dog that intravenous infusions of ineffective amounts of angiotensin II lowered the thirst threshold to elevated blood plasma Na concentration (36).

In conclusion, to judge from presently available evidence, it appears that angiotensin should be regarded as a reserve expedient in the control of water balance that is used only in conditions associated with large ECF deficits. Perhaps it will be necessary to take a different view when we better understand the importance of the isorenin-angiotensin system that may exist in the brain (21, 26). As yet, however, the very existence of that system remains uncertain (53, 56).

PREABSORPTIVE APPEASEMENT OF THIRST

Thirst is not "permanently" slaked until absorbed water brings the activity of cerebral sensors regulating water intake back to a level below that needed to stimulate drinking. This "permanent" satisfaction of thirst occurs at a somewhat higher degree of body hydration than that present at the thirst threshold, and thereby provides a reserve of water that can be lost without

an immediate revival of the urge to drink (23). It is far from obvious that the activity of cerebral sensors regulating water intake also subsides during the reflex temporary appeasement of thirst that takes place in the course of drinking, since the adequate stimulus of the sensors has not yet become reduced by postabsorptive alterations in body fluid composition and volume. It appears more likely that the reflex inhibition from the alimentary canal acts at some synaptic level, and there temporarily prevents sensory information of cerebral origin from reaching other parts of the brain where this information is converted into a conscious urge to drink. Studies in man and experimental animals made relatively long ago revealed that the drinking-induced temporary depression of the thirst drive is mainly exerted from the oropharyngeal region but also from the gastric part of the alimentary canal, implying that a constellation of mechanical, thermal, and chemical factors is involved (22, 79). More recent studies in monkeys indicate that receptors in the duodenum or portal circulation also contribute to the temporary satisfaction of thirst (80). Although no direct evidence exists, it is tempting to speculate that taste receptors, responding specifically to pure water, may contribute to the preabsorptive alleviation of thirst. Such gustatory receptors were originally discovered by Zotterman (83) in the frog and were later demonstrated by recordings of chorda tympani activity in several mammalian species, including the monkey (28). A subsequent study (17) showed that water taste fibers are not present in the human chorda tympani; however, man may have receptors responding to water in other parts of the oropharyngeal region, since afferents conveying impulses from such receptors were recently demonstrated in the superior laryngeal nerve of the rat (68). The temporary appeasement of thirst elicited during drinking obviously fulfills an important physiological mission. Deprived of this inhibitory mechanism man and mammals would yield to excessive drinking each time they became thirsty and would then have to endure the consequence—a profuse water diuresis. A recent study (72) implies that oropharyngeal short-term factors also affect the regulation of ADH secretion. It was shown that the drinking by dehydrated dogs caused an immediate reduction of plasma ADH, which occurred in the absence of diminished plasma osmolality and regardless of whether the imbibed fluid was drained via a gastric fistula or not.

THIRST DISORDERS OF CEREBRAL ORIGIN

Primary Polydipsia

An irresistible craving for water that persists in the absence of known osmotic and nonosmotic thirst stimuli is called primary polydipsia. It has occasionally been reported as a consequence of cerebral (mainly hypothalamic) damage in humans (22, 79), and then seems to have been due to

nonspecific, irritative stimulation of neurons or sensors involved in the regulation of water intake. Speaking in favor of that explanation is the observation that electrical stimulation within the hypothalamus may elicit copious, stimulus-bound drinking in animals (10). However, a more common cause of primary polydipsia in humans is psychic disturbance. Psychogenic polydipsia occurs mainly in middle-aged women suffering from acute or chronic psychosis (12) and is sometimes associated with considerably lowered osmotic threshold for ADH release (30, 55, 57). The condition is then potentially life-threatening since the excessive water intake may rapidly induce hyponatremia of such a degree that fatal cerebral and/or pulmonary edemas develop. Although a somatic cause has not been ruled out, it appears likely that this kind of compulsive water drinking is a manifestation of dysfunctioning interaction between superior parts of the limbic system and the hypothalamus.

Adipsia—Hypodipsia, "Essential" Hypernatremia

The term "essential hypernatremia" was introduced twenty years ago by Welt (78) for a marked elevation of plasma Na concentration sometimes observed as the cardinal sign in fully conscious patients with water available *ad lib.* As explanation for the condition Welt suggested an elevation of the stimulus threshold of cerebral osmoreceptors regulating water intake and ADH release. However, subsequent clinical (31) and experimental (8, 63) studies imply that "essential" hypernatremia in man is rather the consequence of cerebral damage that more or less involves the area shown in Figure 2, and to a varying extent affects the mechanism(s) responsible for the osmotic regulation of water intake and ADH release. Hypothalamic damage that severely impairs the osmotic control of water balance may leave the volume regulation of ADH secretion intact (8, 16, 29, 63). It suggests that cardiovascular afferent influence on ADH liberation reaches its final neuronal link (the cells of the supraoptic or paraventricular nuclei) via intracerebral pathways running at some distance from the sensors and neurons that mediate the osmotic regulation of water intake and ADH release.

SUMMARY AND CONCLUSIONS

Here we have reviewed mainly the cerebral regulation of water intake and its relationship with the regulation of the water-retaining antidiuretic hormone (ADH). Much new information of obvious interest has been gained by experiments in conscious animals, by studies in healthy humans, and by clinical investigations. Of particularly great value has been the development of a sensitive radioimmunoassay for determination of plasma ADH (59).

The sketchy picture that emerges in light of this new information is as follows.

The osmotic regulation of water intake and ADH secretion is exerted by juxtacerebroventricular sensors apparently mainly located on the anterior border of the third ventricle. These sensors may be accessible both to CSF-borne and blood-borne stimuli and inhibitors, and their activity seems to be correlated to the Na concentration of the ECF rather than to its tonicity. A less sensitive volume regulation of water intake and ADH secretion is effectuated by cardiovascular distention and pressure receptors monitoring the effective circulating blood volume, and in severe volume depletion states also by the renin-angiotensin system (RAS). Afferent impulses from the cardiovascular receptors exert a tonic inhibition of the ADH release by acting upon its final neuronal link (the cells of the supraoptic and paraventricular nuclei). Afferent inflow from these receptors also inhibits thirst to some extent, perhaps by preventing at some synaptic level information from cerebral "thirst" sensors from reaching other parts of the brain where the information is converted into a conscious urge to drink. Therefore, increased cardiovascular receptor activity becomes manifested as elevated osmotic thresholds for ADH liberation and thirst. Severe volume depletion may induce RAS hyperactivity to such an extent that generated angiotensin II stimulates the ADH release and water intake. Demonstrated cerebral Na/angiotensin interaction suggests that this may occur via an angiotensin-induced lowering of the stimulus threshold for the sensors involved in the osmotic control of water balance. Cerebral damage affecting the sensors responsible for the osmotic regulation of water intake and ADH release may result in hypo- or adipsia associated with latent diabetes insipidus, and is apparently the ultimate cause of "essential" hypernatremia.

This fragmentary outline of the cerebral control of water intake is based to a considerable extent upon circumstantial evidence, and is for that reason speculative on many points.

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