Neuroendocrine Control of Body Fluid Metabolism

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physrev.00017.2003.—Mammals control the volume and osmolality of their body fluids from stimuli that arise from
both the intracellular and extracellular fluid compartments. These stimuli are sensed by two kinds of receptors:
osmoreceptor-Na$^+$ receptors and volume or pressure receptors. This information is conveyed to specific areas of the
central nervous system responsible for an integrated response, which depends on the integrity of the anteroventral
region of the third ventricle, e.g., organum vasculosum of the lamina terminalis, median preoptic nucleus, and
subfornical organ. The hypothalamo-neurohypophysial system plays a fundamental role in the maintenance of body
fluid homeostasis by secreting vasopressin and oxytocin in response to osmotic and nonosmotic stimuli. Since the
discovery of the atrial natriuretic peptide (ANP), a large number of publications have demonstrated that this peptide
provides a potent defense mechanism against volume overload in mammals, including humans. ANP is mostly
localized in the heart, but ANP and its receptor are also found in hypothalamic and brain stem areas involved in body

fluid volume and blood pressure regulation. Blood volume expansion acts not only directly on the heart, by stretch of atrial myocytes to increase the release of ANP, but also on the brain ANPergic neurons through afferent inputs from baroreceptors. Angiotensin II also plays an important role in the regulation of body fluids, being a potent inducer of thirst and, in general, antagonizes the actions of ANP. This review emphasizes the role played by brain ANP and its interaction with neurohypophysial hormones in the control of body fluid homeostasis.

I. INTRODUCTION

The precise regulation of the volume and osmolality of body fluids is fundamental to survival. Sodium chloride (NaCl) represents an important constituent of the extracellular compartment and is the major determinant of the plasma osmolality as well as extracellular fluid volume. All vertebrates maintain plasma osmolality and extracellular volume primarily by regulating the ingestion and urinary excretion of water and electrolytes. For example, such animals develop a special behavioral sensation, thirst, that is defined as a need or desire to drink that leads the animal to increase water intake. An elevation in the plasma osmolality, and consequent cellular dehydration, is the most potent stimulus of thirst. In mammals, a minimal increase in the plasma osmolality of 1–2% induces thirst. A decrease in the extracellular fluid volume, although less effective, is also capable of generating thirst. A 10% reduction in blood volume or in arterial pressure both will induce an animal to drink water. Sodium intake occurs later, but initially the animal looks for water. Several other conditions can induce thirst, independent of changes in volume or plasma osmolality, e.g., dry mouth and breathing dry air. However, oral ingestion of water produces only a transient satiation of thirst. Because animals with esophageal or gastric fistulae are not satiated by peroral water ingestion but only by replacing the deficit through the fistula, it is apparent that absorption of water into the bloodstream also is required for satiation (for review, see Refs. 17, 18, 110, 111, 153, 254, 257, 335, 344, 371, 547, 549).

The classic studies of Verney (537) introduced the concept of effective osmolality (i.e., increased extracellular osmolality induced by solutes that do not cross the cell membrane) and the presence of osmoreceptors involved in arginine vasopressin (AVP) release in response to increased osmolality. Andersson, McCann, and co-workers (9–13) postulated that an osmoreceptor was a sodium sensor located in brain regions within the blood-brain barrier, and it could be involved in the control of sodium appetite as well as in the control of sodium excretion in response to changes in brain extracellular fluid sodium concentration.

It is accepted that in the genesis of thirst there is an important role for osmoreceptor-Na^+ receptor cells located in the circumventricular organs (CVO) of the anterior aspect of the third ventricle. These structures contain sensory cells that respond to variations in the plasma osmotic pressure or the sodium concentration of plasma and cerebral spinal fluid (CSF). It should be pointed out that equiosmolar NaCl hypertonic solution is a more effective stimulus than nonsaline hypertonic solutions (345). Lesions in the region of the anteroventral portion of the third ventricle (AV3V), involving the ventral part of the median preoptic nuclei (MnPO), induce permanent or temporary adipsia (13, 65, 305). Sodium receptors have been demonstrated also in afferent neural terminals adjacent to the hepatic, renal, and intestinal vessels. Liver receptors are activated by an increase in $[Na^+]$ in the portal vein, augmenting hepatic afferent vagal inputs to the nucleus of the solitary tract (NTS) that generate efferent signals increasing renal sodium excretion, and concomitantly decreasing intestinal sodium absorption (230).

In some species, such as the rat, increased production and release of angiotensin II (ANG II) into the systemic circulation mediates thirst in response to a reduction in the extracellular volume. Central nervous system (CNS)-generated ANG II is also an important thirst inducer, acting as a neurotransmitter on ANG II-sensitive neurons in brain structures such as the subfornical organ (SFO) or organum vasculosum of the lamina terminalis (OVLT), both of which are CVO of the lamina terminalis. ANG II may be the mediator of the thirst induced by hypertonic saline (2% NaCl) microinjected into the cerebral ventricle (in rat, mouse, sheep, and rabbit), since the dipsogenic effects can be decreased by the previous administration of losartan, an AT_1 ANG II receptor antagonist (337, 340–344). In addition, Franci et al. (171) demonstrated that dehydration-induced drinking could be blocked by injection of ANG II antiserum in the third ventricle of male rats.

It is known that when water is offered to a water-deprived animal, it will begin drinking within 3–10 min and continue until the thirst is satiated. Interestingly, the process of thirst satiation commences even before plasma osmolality is normalized; thus, even while plasma osmolality has not been corrected, the volume of water drunk usually is the amount needed to return osmolality to normal. This may occur through stimuli originating in the mouth, pharynx, or stomach and conveyed by afferent impulses to CNS structures involved in the integrative response.

During the last four decades a number of studies have attempted to identify brain areas specifically involved in satiety, regulation of plasma osmolality, water/electrolyte ingestion, and excretion. The first studies to

determine the synaptic transmitters in the CNS circuits that control body fluid homeostasis were published in the 1960s by Grossman (197, 198). He demonstrated that hypothalamic cholinergic or noradrenergic stimulation induced an increase in water or food intake. Cholinergic and angiotensinergic stimulation of the AV3V region caused a rapid increase in water intake in normal hydrated animals, as well as increased natriuresis (21, 152, 155, 197). Intracerebroventricular (icv) injection of carbachol (a cholinergic agonist) also evoked dramatic natriuretic, kaliuretic, and antidiuretic responses similar to the effects observed with central (icv) injection of hypertonic saline (121). Thus it became clear that both α-adrenergic and cholinergic synapses are involved in the control of both natriuresis and kaliuresis. Microinjection of agonists and antagonists of these neurotransmitters into the septal area, AV3V, or the third ventricle altered the natriuretic, kaliuretic, and carbachol-induced antidiuretic responses (72, 73, 120, 170, 172, 351, 365, 431, 432, 443, 444). Phentolamine, an α-adrenergic antagonist, abolished the natriuretic response to third ventricle injection of hypertonic saline, norepinephrine, or carbachol. Meanwhile, isoproterenol, a β-adrenergic agonist, exhibited an antinatriuretic and antikaliuretic effect. In contrast, propranolol, a β-receptor blocker, induced natriuresis and kaliuresis when injected alone and also potentiated the natriuretic response to carbachol. Cholinergic blockade with atropine decreased the response to norepinephrine and blocked the natriuretic response to hypertonic saline (365, 366, 399).

The lamina terminalis is a forebrain structure that contains the SFO, the MnPO, and the OVLT. The AV3V includes the ventral part of the MnPO and the OVLT. The AV3V and SFO region contains neurons that are sensitive to changes in plasma or CSF osmolality (50, 207, 340, 384, 385, 386), and these cells have direct connections with the paraventricular nucleus (PVN) (204, 356, 480, 550). Also, a direct connection from the region of the lamina terminalis to the raphé nuclei and locus ceruleus (LC) has been described (483). These connections appear to be important to induce the hormonal, sympathetic nervous system, and behavioral changes that restore the body fluid balance as described below. Sly et al. (482) demonstrated a polysynaptic pathway connecting neurons in the brain areas controlling body fluid balance to the kidney, by injecting the Bartha strain of pseudorabies virus into the kidney of rats. The application of this neurotropic virus resulted in retrograde infections, which permitted the identification of higher order neurons (putative third and fourth order) in regions of the forebrain including the OVLT, MnPO, SFO, bed nucleus of the stria terminalis, anteroventral periventricular nucleus, medial and lateral preoptic area, supraoptic nucleus (SON), retrochiasmatic nucleus, primary motor cortex, and the visceral area of the insular cortex. Renal innervation (considered to be

entirely sympathetic) participates in the control of three aspects of renal function: renal blood flow, tubular reabsorption of electrolytes, and renin secretion. Thus renal sympathetic nerves regulate the function of the vasculature, the tubules, and the juxtaglomerular granular cells that, following activation of β-adrenergic receptors, cause an increase in renin secretion rate and renal blood flow and a reduction in urinary sodium excretion (115, 116).

In summary, mammals control the volume and osmolality of their body fluids in response to stimuli that arise from both the intracellular and extracellular fluid compartments. These stimuli are sensed by two kinds of receptors: osmoreceptor-Na^+ receptors (plasma osmolality or sodium concentration) and volume or pressure receptors. This information is conveyed to specific areas of the CNS responsible for an integrated response, which is dependent on the integrity of the AV3V (OVLT and MnPO) and SFO. In addition, the PVN, SON, LC, dorsal raphé nuclei (DRN), and the lateral parabrachial nuclei, among others, also represent important structures involved in hydromineral balance. Such structures, once stimulated, can determine responses that involve 1) the induction of thirst, salt appetite, or both; 2) changes in sympathetic activity; 3) activation of the renin-angiotensin-aldosterone system; or 4) secretion of AVP and oxytocin (OT) from the neurohypophysis and natriuretic peptides from the heart.

II. VASOPRESSIN AND OXYTOCIN EFFECTS ON WATER METABOLISM

A. The Hypothalamo-Neurohypophysial System

The hypothalamo-neurohypophysial system is located in the medial part of the anterior hypothalamus and comprises the paired PVN on each side of the dorsolateral wall of the third ventricle and the paired SON. The perikarya of the magnocellular neurons responsible for the synthesis and release of OT and AVP are located in both the PVN and SON (292). The PVN contains a preponderance of OT neurons and the SON a preponderance of AVP neurons. The axons of these neurons form the hypothalamo-hypophysial tract, which terminates in the neurohypophysis. Some of these axons terminate in the median eminence in juxtaposition to the capillaries of the hypophysial portal veins, whereas most terminate in the neural lobe (32, 66, 214, 424). The AVP and OT released in the median eminence are transported by the hypophysial portal vessels to the anterior lobe of the pituitary gland where they act to stimulate the release of ACTH and prolactin, respectively (333, 334, 336). The AVP and OT released from the neural lobe are in part transported by the short portal vessels to the anterior lobe, and the blood from both lobes empties into the hypophysial veins to return to the heart (409).

OT and AVP are synthesized and released by magnocellular neurosecretory neurons classified into AVP- and OT-producing subtypes. Recent evidence from qualitative RT-PCR experiments on single cells confirms the fact that the majority of magnocellular neurons coexpress both peptide mRNAs. Furthermore, there is some OT and AVP mRNA coexpression in virtually all of the magnocellular neurons in the SON of the hypothalamus (559). However, because PCR grossly magnifies the mRNA content, it is clear that most of these neurons express only one of these peptides at a functionally significant level.

Changes in the firing pattern and frequency of magnocellular neurons in response to relevant physiological stimuli regulate the circulating levels of their secreted hormones (196, 424). The electrophysiological profiles of OT and AVP neurons can be distinguished from each other, and from that of neurons in the immediately adjacent perinuclear zone (33). Oxytocinergic neurons possess properties that favor the production of short spike trains, which are enhanced during lactation (289, 492). In contrast, vasopressinergic magnocellular neurons in the hypothalamus exhibit phasic electrical activity that depends on intrinsic membrane properties and is influenced by extrinsic factors such as plasma osmolality, blood volume, and pressure (for review, see Ref. 32). OT and AVP, released from the soma and dendrites of neurons, bind to specific autoreceptors and induce an increase in intracellular $[Ca^{2+}]$. In OT cells, the increase in $[Ca^{2+}]$ results from a mobilization of Ca^{2+} from intracellular stores, whereas in AVP cells, it results mainly from an influx of Ca^{2+} through voltage-dependent channels (99, 191).

A selective afferent neural input to the vasopressinergic neurons provides a mechanism for the release of AVP independently of OT in response to appropriate physiological stimuli. Two alternative models of the neural pathways and transmitters involved in the activation of the supraoptic hypophysial tract have been suggested. Some authors have suggested the existence of an excitatory relay through a cholinoceptive area on the ventral surface of the brain stem that has been termed the nicotine-sensitive area because topical application of nicotine to this area in the cat causes the release of AVP without OT (51). Afferent input from a noradrenergic projection from the NTS to the SON has also been demonstrated (102, 553). With the use of combined retrograde tracer-immunofluorescence methods, OT and AVP neurons in the SON and PVN were shown to receive noradrenergic innervation that arises mainly from A1 neurons in the ventrolateral medulla (457). Furthermore, an inhibitory relay was demonstrated through the A1 group of noradrenergic neurons on the ventral surface, which selectively innervate the AVP-secreting neurons in the SON. This model implies an inhibitory role for norepinephrine acting on β- or α_2-receptors and explains the antinatriuretic

effect of β-adrenergic receptor activation (72, 73, 365, 443). However, most investigations suggest an excitatory, rather than inhibitory, function of the A1 noradrenergic neurons involving α_1-receptors, consistent with the previously described stimulatory role of α_1-receptors in natriuresis (72, 73, 365, 443). The posterior magnocellular division of the PVN and SON is mainly innervated by the A1 noradrenergic cell group (93), and noradrenergic afferents have been shown to have a facilitatory role in the regulation of the activity of neurohypophysial AVP neurons (101, 102). The PVN receives a dense noradrenergic innervation from the A1 cell bodies of the caudal ventrolateral medulla, A2 cell bodies of the NTS, and A6 cell bodies of the LC. Noradrenergic neurons in the LC participate in the baroreflex activation of the diagonal band of Broca (195), which has been shown to be an integral component of the pathway regulating the baroreceptor-induced inhibition of AVP release and, possibly, the stimulation of OT release (94, 251). In addition, an inhibitory GABAergic pathway from the diagonal band of Broca preferentially innervates AVP-secreting SON neurons, supporting the view that the baroreflex-induced depression of SON firing may be mediated by GABA (252).

B. Osmotic Control of Vasopressin Release

The hypothalamo-neurohypophysial system plays a fundamental role in the maintenance of body fluid homeostasis by secreting AVP and OT in response to osmotic and nonosmotic stimuli (461). Microinjections of hypertonic saline into the AV3V area, the major central site for the regulation of body fluid composition, cardiovascular, and renal function, were first shown to induce an increase in water intake in goats by Andersson, McCann, and co-workers (9–13). These results were confirmed in rats by Antunes-Rodrigues and McCann (21). Electrical stimulation of this structure also induced water intake together with natriuresis (12). In addition, lesions of the AV3V had several important effects, including adipsia and hypernatremia (10, 13), impaired drinking responses and AVP secretion in response to hypertonic saline and ANG II (280), impaired recovery of arterial pressure in response to hypertonic saline in rats submitted to hemorrhagic shock (41), decreased osmotic- and volume-induced atrial natriuretic peptide (ANP) release (25, 417), a decrease in the number of Fos-like immunoreactive neurons in the MnPO, PVN, and SON in response to intravenous infusion of hypertonic saline (223, 561), and an interruption of neuronal inputs that trigger AVP secretion from the posterior pituitary as well as AVP release into the extracellular compartment of the SON (315).

Other evidence indicates that, besides the AV3V, other structures such as the MnPO, SFO, medial septal

area, anterior lateral hypothalamus, SON, PVN, medial habenula, and stria medullaris are organized into a neural circuit involved in the regulation of water/sodium intake and excretion (90, 170, 172, 432). Neurons in the PVN, MnPO, preoptic and hypothalamic periventricular nuclei, median eminence, and OVLT also contain α-ANP as determined by immunocytochemistry (245, 267, 268, 363, 401, 573), which suggests that ANP neurons may be one of the effectors involved in control of water and salt intake. It was also shown that the SFO and OVLT send ANP immunoreactive fibers to the PVN and SON (318). Therefore, osmoresponsive neurons located in the OVLT project to magnocellular and parvicellular neurosecretory neurons and are likely candidates for cerebral osmoreceptors (8, 339, 340, 384). There is evidence for the involvement of other brain areas, such as the area postrema (AP) and NTS in the osmotic response (75).

The most important physiological osmotic regulation of AVP release takes place in the CNS within the regions listed above, although it has been suggested that peripheral osmoreceptors in the liver, mouth, and stomach detect the early osmotic impact of foods and fluid intake (51, 230, 429). Indeed, intragastric hypertonic saline infusion increases portal venous but not systemic plasma osmolality and increases Fos-like immunoreactivity in the AP, NTS, lateral parabrachial nuclei, the SON, and PVN (391). Osmoreceptors are highly specialized neurons capable of transducing changes in external osmotic pressure into electrical signals that activate CNS areas involved in the control of water and salt intake and excretion by the release of acetylcholine or angiotensin at synapses in the SON (51). Patch-clamp studies using isolated rat SON magnocellular neurosecretory cells demonstrated that these neurons are, respectively, depolarized and hyperpolarized by increases and decreases in extracellular osmolality and that these responses result from changes in the activity of mechanosensitive cation channels (59).

Osmoreceptors are located in the OVLT and SFO, structures that lie outside the blood-brain barrier and, therefore, are in contact with plasma ionic concentrations and hormones, such as ANP and ANG II (256, 346). Small changes in plasma osmolality within the physiological range can rapidly stimulate AVP transcription in the SON and PVN, suggesting that stored AVP released into the blood circulation is rapidly replaced by de novo synthesis, processing, and transport of AVP (29).

Fos protein expression, a marker of neuronal activity, has been used to investigate the hypothalamic activation following systemic osmotic stimulation (207). Water deprivation for 24 h resulted in the expression of the c-Fos protein in the PVN and SON (448). Transient expression of c-Fos protein was also detected in magnocellular neurons of the SON and PVN of the rat hypothalamus after injection of hypertonic saline. This activation of the SON and PVN was maintained by a chronic osmotic stimulus induced by the drinking of hypertonic NaCl solution or by water deprivation, and was reversed by water intake for 24 h after the chronic osmotic stimulation. Chronic stimulation provides sustained activation of these neurons, presumably accompanied by increased synthesis and release of AVP and, possibly, OT (358). Fos immunoreactivity was also observed in many neurons of the MnPO, OVLT, and, to a lesser extent, in the SFO of rats submitted to water deprivation for 24 or 48 h, confirming that these structures play a role in homeostatic responses to dehydration (187, 347). It was also demonstrated that lesions within the AV3V region (including the MnPO) suppressed water intake after 24 h of water deprivation, as well as c-Fos expression in the SON and, less completely, in the PVN nuclei, indicating that the cellular response of supraoptic neurons to osmotic stimuli requires inputs from the AV3V region, while the PVN is less dependent on this (561).

As expected, chronic osmotic stimulation also increases AVP mRNA expression in the SON and PVN (69, 303). Hyperosmolality causes a 1.5- to 2-fold increase in AVP mRNA expression (474). On the other hand, long-term hyposmolality reduces AVP mRNA expression in the hypothalamus to only 10–15% of the control level (430, 534). Recently, using in situ hybridization histochemistry techniques, Glasgow et al. (188) confirmed earlier studies reporting an increase in the AVP, OT, and AVP-binding protein (neurophysin) mRNAs during hypernatremia, as well as a decrease in these mRNAs during hyponatremia. In addition, these authors demonstrated that the magnocellular neurons of the SON responded to hypernatremia with an increase in the expression of a variety of genes including cytochrome oxidase, tubulin, Na^+-K^+-ATPase, spectrin, PEP-19, calmodulin, GTPase, DnaJ-like, clathrin-associated protein, and synaptic glycoprotein, a regulator of GTPase activation. This analysis suggests that adaptation to chronic osmotic stress results in global changes in gene expression in the magnocellular neurons of the SON.

The brain stem has also been implicated in the control of body fluid homeostasis. For example, ascending projections from the caudal region of the ventrolateral medulla have been implicated based on the expression of Fos protein and AVP mRNA in the SON after electrical stimulation of this region (475). Furthermore, intravenous infusions of hypertonic saline increase c-fos gene activity in neurons of the caudal ventrolateral medulla (224).

Nitric oxide (NO) has been proposed as a local modulator of magnocellular neuron activity. NO is a neuronal messenger produced from L-arginine by neuronal NO synthase (nNOS). The presence of nNOS in the PVN and SON vasopressinergic and oxytocinergic neurons and its increase in these cells after osmotic stimulation or dehydration suggest a role for NO in the regulation of AVP and OT (61, 213, 263, 528, 538, 564). In addition, nNOS has been detected by immunocytochemistry in other neural

structures involved in AVP secretion, such as the SFO, OVLT, and MnPO (539). However, the role of NO in OT and AVP release is still not clearly defined. Ota et al. (392) showed that the intracerebroventricular injection of *S*-nitroso-*N*-acetylpenicillamine (SNAP), which spontaneously breaks down to form NO, caused a transient, dose-related increase in plasma AVP concentration. In addition, when D-arginine, which cannot be used as a substrate by NO synthase, was injected intracerebroventricularly, there was only a slight, delayed increase in the plasma AVP concentration. Thus NO can act centrally to stimulate AVP release and may serve as a neuromodulator controlling its release. However, intracerebroventricular injection of N^G-nitro-L-arginine methyl ester (L-NAME), an inhibitor of NOS, increased plasma OT and AVP above basal levels, suggesting that NO tonically inhibits both hormones. On the other hand, L-NAME did not change the AVP response to an osmotic stimulus (260). Furthermore, studies using rat hypothalamic explants showed that L-arginine reduced the KCl-evoked AVP release, and this effect was reversed by the inhibition of NOS (571); thus NO appears to directly and specifically inhibit the stimulated release of AVP from rat hypothalamic explants in vitro. In another study, discharges of SON neurons from slices of rat hypothalamus were inhibited by sodium nitroprusside, a spontaneous releaser of NO; furthermore, preincubation of the slices with hemoglobin, an inactivator of NO, prevented this inhibition (261, 310). These data demonstrate that NO exerts a predominantly inhibitory effect on SON neurons.

Endogenous NO may be involved in the regulation of magnocellular functions, especially when the internal environment is disturbed. Chronic salt loading upregulates the expression of nNOS mRNA in the SON and PVN of the hypothalamus, and this is accompanied by an increase in NOS activity in the posterior pituitary. The effects of NO on AVP and OT regulation were summarized in a recent review, as follows: NO tonically inhibits the basal release of AVP and OT into plasma, but the NO inhibition of AVP secretion is removed during water deprivation, hypovolemia, moderate osmotic stimulation, and after injection of ANG II, while the inhibition of OT is enhanced. NO facilitates drinking behavior stimulated by water deprivation, osmotic stimulation, hemorrhage, and ANG II (261).

C. Volume Control of Vasopressin Release

The maintenance of body fluid homeostasis requires autonomic and endocrine responses and activation of specific behaviors. Changes in blood volume or pressure lead to appropriate changes in renal fluid and electrolyte excretion through neural and endocrine adaptive responses. Hypovolemia induces AVP release from magnocellular neurons, which acts by increasing reabsorption of water in the distal nephron by opening aquaporin-2. The threshold for stimulation of AVP release in hypovolemia is generally reported to be between 10 and 20% of the blood volume in several different species (471). In normal, standing human subjects, a reduction in blood volume of 6% or a reduction in plasma volume of 10% induced by furosemide injection was sufficient to increase the plasma AVP concentration (272). On the other hand, isotonic expansion of blood volume results in a reduction in plasma AVP concentration (206, 258, 295, 298, 470, 471).

The release of AVP from the neurohypophysial terminals of hypothalamic magnocellular neurosecretory neurons is regulated by peripheral baroreceptors, cardiopulmonary volume receptors, and the circulating ANG II concentration (522). Information from these sources is transmitted through afferent pathways with differential effects on the excitability of the AVP-secreting cells (423). A brief increase in arterial pressure, sufficient to activate baroreceptors, is associated with a transient and selective GABAergic inhibition of these neurosecretory neurons, achieved through a multisynaptic pathway that involves ascending catecholaminergic projections from neurons in the diagonal band of Broca (DBB). Baroreceptor activation induces a consistent increase in firing of DBB neurons, which project to the hypothalamic supraoptic neurosecretory neurons, indicating that baroreceptor-induced inhibition of hypothalamic vasopressinergic neurons may be mediated through DBB neurons (81, 251, 252, 271, 393).

Afferent nerve impulses from stretch receptors in the left atrium, aortic arch, and carotid sinus tonically inhibit AVP secretion, and a reduction in their discharge leads to AVP release (51). Baroreceptors in the atrium and ventricles signal changes in blood volume, and the receptors in the aortic arch and carotid sinuses signal changes in arterial blood pressure. These data are relayed through, respectively, the vagal and glossopharyngeal nerves to the NTS in the brain stem, from which postsynaptic pathways connect with the magnocellular neurons of the SON and PVN (125, 471). Indeed, stimulation of the cervical vagus induces Fos expression in noradrenergic A1 neurons of the caudal ventrolateral medulla and excites AVP cells (103). Low-pressure receptors in the atrium tonically inhibit AVP release via a pathway involving the NTS, and AVP release induced by hypovolemia occurs through a reduction in the activity of this inhibitory input (51, 471).

Although there is abundant evidence to support the role of the AV3V and the low-pressure receptors in the regulation of AVP release, the afferent pathways controlling AVP release appear to be more complex, and it has been suggested that other mechanisms might also be involved in this regulation. A decrease in arterial pressure activates peripheral low-volume receptors in the great veins, atria, and lungs, which give rise to neural inputs that result in an increase in the excitability of AVP-secret-

ing neurons, achieved via pathways that include direct projections from caudal ventrolateral medulla A1 neurons. The AVP response to an acute reduction in central blood volume, such as that produced by hemorrhage, depends on the A1 projection only if the stimulus is of moderate intensity. Severe stimuli appear to involve activation of both the A1 projection and an additional AVP-stimulatory pathway that bypasses the A1 region (483). There is evidence that the area postrema, the most caudal circumventricular organ located on the dorsal surface of the medulla, is also involved in several physiological control mechanisms, including the regulation of AVP synthesis and release. Lesions of the AP decreased AVP mRNA levels in the PVN and SON as well as plasma AVP levels in the basal state and after hyperosmolality or hypovolemic stimulation (30).

The neurosecretory system contains an elaborate array of neural inputs, including a catecholaminergic innervation that is predominantly noradrenergic, but which also has a dopaminergic component (105, 562, 563). The precise role of hypothalamic norepinephrine in the control of AVP release remains unclear, due to reports of both inhibitory and excitatory effects of norepinephrine (NE) and only a few studies with direct hypothalamic manipulation (298). The excitatory effect of central noradrenergic stimulation on serum AVP is highly site-specific and localized to the PVN and SON (297, 367, 373, 413). Activation of the locus ceruleus-PVN ascending noradrenergic pathway accounts for the increase in NE release in rat PVN induced by systemic hemorrhage (367). However, NE has also been reported to inhibit AVP and OT release from cells in the PVN of lactating rats (228). Adrenergic receptors may be differentially distributed in vasopressinergic neurons allowing excitatory or inhibitory impulses (298) or, alternatively, the results may be accounted for by a bell-shaped response of AVP to NE.

Vasopressin release under conditions of hypovolemia involves stimulation by ANG II/III. Hypotension causes renal renin release and leads to the formation of ANG II; binding of this hormone to AT_1 receptors in the SFO neurons promotes activation of a central angiotensinergic input that, in turn, has a predominantly excitatory effect on AVP neurons. In support of this role for ANG II, injection of ANG II or III into the SON or PVN increases magnocellular activity and AVP release into the bloodstream (28, 476, 578).

The SFO exhibits functional segregation, which may be observed through the distinct patterns of c-Fos expression in this area induced by hypovolemic or osmotic stimuli. Hypertonic saline induces c-Fos expression in the peripheral SFO only, while hypovolemia induced by subcutaneously administered polyethylene glycol (PEG) induces c-Fos in the central region of the SFO (484). In addition, c-Fos protein is rapidly induced in hypothalamic magnocellular nuclei following hemorrhage. AVP and OT

neurons express c-Fos in a graded response to hypovolemic stimuli, which was correlated with stimulus intensity and also with the amount of hormone released into the peripheral blood. A differential pattern of activation of AVP neurons occurs in response to hemorrhagic stimuli. AVP neurons in the SON had a lower response threshold than those in the PVN (472). OT neuron activation requires a greater hypovolemic stimulus than that for AVP, revealing functional heterogeneity among magnocellular neurons (428). Lesions of the hypothalamic SON blunted the increase in plasma AVP to below levels attained in normal rats submitted to hemorrhage, indicating that these nuclei are primary regulatory sites for AVP release in response to hemorrhage and that lack of adequate AVP release significantly retards blood pressure recovery after bleeding (146). In addition to AVP release, AVP gene transcription in the SON and PVN is increased in the hypothalamus of conscious rats submitted to hemorrhage or normovolemic hypotension, as determined by intronic in situ hybridization (264).

D. Vasopressin and Oxytocin Receptors

1. Vasopressin receptors

The actions of AVP are mediated by plasma membrane receptors, which belong to the G protein-coupled receptor family characterized by the presence of seven transmembrane helices connected by three extracellular and three intracellular loops. Three different subtypes of AVP receptors, V_{1a}, V_{1b}, and V_2, have been cloned (312, 360, 507). V_{1a} receptor expression has been described in smooth muscle and liver, with the V_{1b} receptor in the anterior pituitary and the V_2 receptor in the kidney (270, 311, 517). V_{1a} receptors are involved in blood pressure control and in all other known functions of AVP, except for the stimulation of corticotropin secretion by the adenohypophysis, which is mediated via the V_{1b} receptor. The presence of V_{1a} receptors has been described in structures of the limbic system (septum, amygdala, bed nucleus of the stria terminalis, accumbens nucleus), in the suprachiasmatic and dorsal tuberal region of the hypothalamus, and in the area of the nucleus of the solitary tract, suggesting that V_{1a} is the main receptor responsible for the central effects of AVP (525). Recently, V_{1b} receptors have been detected by RT-PCR and in situ hybridization not only in pituitary corticotrophs but also in the hypothalamus, amygdala, cerebellum, and in those areas close to the CVO (medial habenula, SFO, OVLT, median eminence, and nuclei lining the third and fourth ventricles), as well as in the external zone of the median eminence. These data suggest that V_{1b} receptors may also mediate different functions of AVP in the brain (220).

V_2 AVP receptors are responsible for the antidiuretic effect of AVP. The expression of V_2 receptors has been

described in some of the thick ascending limbs and all of the principal and inner medullary collecting duct cells, not only in the basolateral membrane but also in the luminal membrane (382, 378). Vasopressin regulates transcription of the aquaporin-2 gene through a cAMP regulatory element located in the 5′-flanking region (232, 327, 330).

X-linked nephrogenic diabetes insipidus is a disease that results from mutations in the V_2 receptor gene (46) that map to chromosome region Xq28 (48, 434). Functional characterization of V_2 AVP receptor gene mutations identified in patients has brought insight into the residues that are critical for V_2 receptor expression and function (552). Natural mutation of Arg113Trp in the V_2 receptor significantly reduced receptor expression in transfected cells, receptor-ligand binding affinity, and G_s coupling (47). A similar reduction in binding affinity and the inability to concentrate the urine after the administration of the antidiuretic hormone AVP was found in association with the deletion of Arg-202, which is located in the second extracellular loop of the human V_2 receptor (2), suggesting that this domain is also important for ligand binding.

Vasopressin receptor subtypes are coupled to different G proteins (136). V_{1a} and V_{1b} receptors are coupled to G proteins of the $G_{q/11}$ family, which mediate the breakdown of phosphatidylinositol (64, 517), whereas V_2 receptors are coupled to the G_s protein, which activates adenylate cyclase (48). Different single intracellular domains determine the G protein-coupling selectivity profile of the different AVP receptor subtypes.

Liu and Wess (309) created and analyzed a series of V_{1a} and V_2 hybrid receptors in which distinct intracellular domains were systematically exchanged between the two wild-type receptors. cAMP assays showed that all mutant receptors that contained the V_2 receptor sequence in the third intracellular loop were able to stimulate adenylate cyclase activity with high efficacy, whereas all mutant receptors in which the third intracellular loop was derived from the V_{1a} receptor had little or no effect on intracellular cAMP levels. These data strongly suggest that the third intracellular loop of the V_2 receptor plays a key role in the proper recognition and activation of G_s. On the other hand, all hybrid constructs in which the second intracellular loop consisted of the V_{1a} receptor sequence were able to activate the phosphoinositide (PI) cascade in a fashion very similar to the wild-type V_{1a} receptor, whereas all mutant receptors that contained the V_2 sequence in this receptor region displayed only residual PI activity, similar to that of the wild-type V_2 receptor, indicating that the second intracellular loop of the V_{1a} receptor is critically involved in the selective activation of $G_{q/11}$.

2. Oxytocin receptors

In a recent paper, Gimpl and Fahrenholz (186) comprehensively reviewed the current knowledge of the physiological effects of OT and the distribution of OT receptors throughout the body, focusing mainly on the research of the past decade.

The OT receptor has been cloned from human (273), rat (440), and other species (43, 190, 284, 427, 451). The OT receptor is highly conserved across species and has been found in a variety of tissues, particularly in uterus but also in mammary gland, pituitary, brain, kidney, thymus, ovary, testis, heart, and blood vessels. The OT receptor density in the uterus increases through pregnancy (477, 535). In the brain, Tribollet et al. (525) showed that the anatomical localization of OT receptors in the olfactory tubercle, the ventromedial hypothalamic nucleus, the central amygdaloid nucleus, and the ventral hippocampus was markedly different from that of the binding sites for AVP.

The OT receptor is a member of the class I protein-coupled receptor superfamily that activate G_q and G_i, which in turn stimulate phospholipase C-mediated hydrolysis of PI. The cleavage of PI generates inositol 1,4,5-trisphosphate, which mobilizes calcium from the sarcoplasmic reticulum, and 1,2- diacylglycerol, which activates protein kinase C, resulting in the phosphorylation of several target proteins. Oxytocin causes a rapid increase in intracellular free calcium, activates mitogen-activated protein (MAP) kinase, and stimulates prostaglandin E_2 synthesis by activating cyclooxygenase (157, 362). In addition, an increase in Ca^{2+}-bound calmodulin leads to the activation of a kinase primarily responsible for the phosphorylation of myosin light chain, which regulates myometrial contractility (487).

The existence of OT receptor subtypes remains to be established (186, 477, 535). The presence of such subtypes has been suggested in the rat uterus, kidney, and brain, to explain differential pharmacological profiles or immunoreactivity patterns. Oxytocin-binding sites in the macula densa and thin Henle's loop, detected in the rat kidney, may represent two subtypes of OT receptors that could mediate distinct effects of OT on kidney function (34). On the other hand, it should be pointed out that high concentrations of OT can interact with V_1 and V_2 AVP receptors, since these are closely related to the OT receptor (518). PCR and Southern analysis in several tissues known to have OT binding activity failed to identify a gene encoding a second OT receptor, making the existence of OT receptor subtypes unlikely (274).

E. Actions of Vasopressin and Oxytocin

The AVP and OT amino acid sequences differ only in the 3 and 8 positions. However, in both hormones disulfide bond formation between cysteine residues at the 1 and 6 positions results in a peptide, consisting of a 6-amino acid cyclic part and a 3-amino acid COOH-terminal part, which exerts various hormonal effects.

The antidiuretic action of AVP is the main physiological effect of this hormone, involving increased permeability to water of the renal collecting duct cells, allowing more water to be reabsorbed from urine to blood. Circulating AVP activates the AVP V_2 receptor on the luminal tubular membrane, leading to an increase in intracellular cAMP and phosphorylation of the COOH-terminal of the water channel protein aquaporin-2 in the tubular cells of the distal nephron (568). The number and distribution of aquaporin channels in the collecting duct cells are regulated by AVP V_2 receptors as shown by the decreased urine osmolality and increased aquaporin-2 expression in apical membranes and subapical cytoplasm of collecting duct cells of the inner medulla in dehydrated rats treated with a V_2 receptor antagonist (216). AVP appears to stimulate the synthesis of aquaporin-2 mRNA and also to regulate the insertion of aquaporin-2 into the luminal membrane of the collecting tubules through fast exocytosis to the plasma membrane (281, 378, 449, 455). The presence of aquaporin-2 in the apical membrane causes an increase in water permeability allowing the movement of free water from the collecting duct into the tubular cell and, thereafter, the transport of water across the basolateral membrane is facilitated by the constitutively expressed aquaporins-3 and -4 (127, 279, 516).

Oxytocin is also involved in vascular and cardiac relaxation and hydromineral homeostasis (88, 200, 202, 206, 233, 249, 486). It has long been recognized that OT increases renal electrolyte excretion in various species and that its natriuretic and kaliuretic effects are AVP independent. OT and AVP are secreted simultaneously in response to hyperosmolality and hypovolemia (38, 39, 206, 496, 498) and when systemically administered (iv or ip), they induce natriuresis (173, 458). OT is a more potent natriuretic hormone than AVP. These effects can be explained by a direct action of both peptides on specific receptors already shown to be present in the tubular cells of the kidney (494, 525). The different potencies of these hormones can be attributed to a relative affinity of OT for its own receptor or to its lower affinity for V_2 and V1 AVP receptors.

Studies have suggested a synergistic effect of AVP and OT in the inner medullary collecting duct, where both peptides induce an increase in cAMP accumulation and natriuresis (38, 160). Oxytocin binds to the AVP V_2 receptor because of its structural similarity to AVP. The urinary sodium excretion induced by OT is completely blocked by pretreatment with an OT receptor antagonist, but not affected by an AVP V_1 antagonist. However, this effect was partially blocked by the combination of AVP V_1 and V_2 antagonist treatment (536). To clarify the effect of OT as an agonist of the V_2 receptor, Terashima et al. (515) investigated the influence of acute elevation of plasma OT levels on the expression of V_2 and aquaporin-2 mRNAs in the rat. They found that OT can downregulate the former and upregulate the latter in the collecting duct, by acting as an agonist of the V_2 receptor in the same manner as AVP. However, other studies employing an inner medullary collecting duct cell line showed that both AVP and OT elicited dose-dependent increases in cAMP generation, although OT was less potent than AVP ($EC_{50} = 1.6 \times 10^{-8}$ M vs. 7.4×10^{-10} M) (544). AVP-induced cAMP accumulation was blocked in the presence of a V_2 receptor antagonist but not by an OT receptor antagonist. On the other hand, OT-induced cAMP accumulation was reduced by the addition of an OT antagonist, while coincubation with the V_2 receptor antagonist had no effect. These results indicate that AVP and OT induce cAMP accumulation from a common ATP pool in inner medullary collecting duct cells and that separate AVP V_2 and OT receptor systems are involved, perhaps coupled to a common adenylate cyclase system (544). In addition to their peripheral effects, these peptides may also produce other effects that could complement their physiological action. Indeed, when injected into the CNS, AVP increases water intake (511). In contrast, the central administration of OT decreases salt intake (496, 500). The inhibitory role of OT in the control of sodium appetite has been supported by studies in OT knock-out mice showing that OT $-/-$ mice display an enhanced salt appetite compared with OT $+/+$ mice after water deprivation (7, 411).

III. THE RENIN-ANGIOTENSIN SYSTEM IN THE BRAIN

A. General Aspects of the Brain Angiotensin System

Brain ANG II increases blood pressure, thirst, sodium appetite, AVP, and ACTH release. It causes sympathetic activation and decreases the baroreceptor sensitivity. Circulating ANG II has its access to the brain limited to the blood-brain barrier-free circumventricular organs. Thus the brain angiotensin system is separate and independent of blood-borne ANG II (445). The brain renin-angiotensin system acts on blood pressure regulation independently of the systemic renin-angiotensin system (RAS) by influencing the secretion of AVP and ACTH and by modulating the baroreceptor reflex and the sympathetic output. Indeed, all components of the RAS, including the precursor and enzymes required for the production and degradation of angiotensins, as well as the specific angiotensin receptors type 1 and type 2 have been identified in the brain (299, 445).

Ganten et al. (181) reported the first evidence for the presence of renin in the CNS of dogs, in tissue from the caudate nucleus. They examined renin activity and showed that aldosterone administration decreased the conversion of angiotensinogen to ANG II in the caudate

nucleus; the authors further demonstrated that brain renin is not altered by bilateral nephrectomy (181, 182). Thereafter, the presence of renin in the brain was confirmed by radioimmunoassay (185) and by immunocytochemistry (70, 177). The very low levels of renin in the brain have made localization of its mRNA very difficult (126, 509); however, Lippoldt et al. (307) recently succeeded in demonstrating this in rat brain by in situ hybridization.

Other components of the RAS have also been localized to the brain. Thus ANG II has been demonstrated by immunocytochemistry and measured directly by radioimmunoassay, while angiotensinogen has been detected by Northern blotting (126, 180, 317, 406). Angiotensinogen is a critical component of the RAS, since it is the only known precursor of ANG II (361). Angiotensinogen is widely distributed in the brain, with a marked presence in the hypothalamus and midbrain (302, 316, 495), and its presence correlates with the distribution of angiotensin receptors (184, 488) and ANG II (403, 468).

There is disagreement over the cell types that express angiotensinogen (469). Angiotensinogen gene expression in astroglia has been reported in several studies (67, 240, 355, 495). Colocalization of angiotensinogen and glial fibrillary acidic protein, a glial-specific protein, further indicated the presence of angiotensinogen in the astrocytes (112, 495). However, other studies have shown that the angiotensinogen gene is expressed in both astrocytes and neurons, a finding consistent with multiple functions for brain angiotensinogen, including as a precursor for neuronal ANG II (238, 469, 570). For example, both astrocytes and neurons express angiotensinogen mRNA and secrete angiotensinogen in primary cell culture (286, 468, 519). It is not completely clear whether ANG II is formed intracellularly in neurons from endogenous angiotensinogen or if ANG II is synthesized outside the cell by angiotensin converting enzyme (ACE, an exoenzyme) and then taken up by neurons, thus forming a paracrine RAS (112, 405, 446, 469, 502). Brain levels of ANG II determined by radioimmunoassay and high-pressure liquid chromatography were found to be increased in rats submitted to bilateral nephrectomy, mainly in the hypothalamus and brain stem, suggesting that brain RAS has paracrine and autocrine functions independent of the endocrine function of circulating plasma angiotensin (526).

As in the periphery, brain ANG II is generated by sequential cleavage of the precursor angiotensinogen by renin, producing the inactive decapeptide ANG I, which is then converted to ANG II by ACE. Thereafter, ANG II is metabolized into ANG III, which is converted to ANG IV by aminopeptidases (445). In addition to its other functions, brain ANG II may possibly influence cognitive functions by acting on the specific angiotensin receptor type 1. ANG II and ANG III have the same affinity for type 1 (AT_1)

and type 2 (AT_2) angiotensin receptors (401, 445). The distribution of ANG II-containing fibers has been demonstrated by immunohistochemical studies in the hypothalamus, SFO, limbic system, the medulla oblongata, sympathetic lateral column, caudate nucleus and putamen, as well as the spinal cord (176, 179, 217, 259, 306).

It has been suggested that ANG III may have an important role in the brain RAS (419), and it may be the case that ANG III is the effector of the biological actions of ANG II (28, 210, 558). Using a selective aminopeptidase A inhibitor that blocks the metabolism of ANG II, Zini et al. (577) showed that ANG III may exert a tonic control on the basal firing level of vasopressinergic neurons. ANG III has also been shown to have a positive influence over blood pressure as seen by the reduced pressor response to ANG II in rats pretreated with microinjections into the right lateral ventricle of a selective aminopeptidase A inhibitor (418). The dipsogenic response to ANG II is decreased by immunoneutralization of aminopeptidase A, suggesting that drinking behavior is also dependent on the action of ANG III (489, 557). Angiotensin IV has been shown to be involved in memory retention and neuronal development (359, 556). ANG IV binding sites in the human brain are similar to those found in guinea pig and monkey, and their distribution supports a role for ANG IV in the facilitation of memory retention and retrieval (76). Interestingly, in contrast to ANG II, ANG IV acts as a vasodilator and increases cerebral blood flow through an ANG IV (AT_4) receptor (283, 375). Angiotensin-(1–7), an endogenous bioactive peptide constituent of the RAS, is nondipsogenic in rats even in large doses and has an inhibitory effect on angiogenesis (322). It has been demonstrated that angiotensin-(1–7) has an excitatory action on some glial cells, increasing prostaglandin synthesis in astrocytes and glioma cells (145).

B. Functions of Brain Angiotensin in Thirst

A decrease in circulating blood volume due to hemorrhage or dehydration stimulates renin release from the kidney, which results in increased circulating levels of ANG II that acts on ANG II receptors in the SFO (497). Access of circulating ANG II to the brain is limited to those CVO structures, which lack the blood-brain barrier and interact with other nuclei in the maintenance of several homeostatic processes by neural and humoral mechanisms. Neuronal structures sensitive to ANG II were identified electrophysiologically and are present in the lamina terminalis, CVOs, and limbic areas. Furthermore, these regions contain immunoreactive neurons and binding sites for ANG II (153), and studies have shown that the area postrema, SFO, and OVLT are the sites of action for angiotensin within the brain. The area postrema is involved in the pressor action of angiotensin, whereas the

SFO is concerned with drinking behavior, the pressor effect, and AVP secretion (325). The OVLT and adjacent tissue have also been suggested as a site for these three central effects of angiotensin (481). Lesions of the SFO and AV3V regions (OVLT, ventral median preoptic nucleus, periventricular preoptic nuclei, and periventricular nuclei) decrease the angiotensin-induced drinking and AVP release (133, 357, 481). Access of ANG II to the anterior ventral third ventricle appears to be essential for drinking (107, 225). Circulating ANG II derived from renal renin contributes to hypovolemic thirst and sodium appetite, acting with the mineralocorticoids and other hormones. Autoradiographic studies have identified ANG II receptors within the SFO (352, 353, 447), suggesting a role for circulating ANG II in regulating activity of the SFO. Dipsogenic responses to systemic administration of ANG II are observed in normovolemic rats (257); however, blood pressure affects the dipsogenic potency of ANG II (138, 493). There is a relationship between blood pressure control and drinking behavior, as shown by the inhibition of drinking stimulated by ANG II, hyperosmolality, or hypovolemia, in the presence of increased arterial pressure (139, 493). It is likely that pressure-induced inhibition of drinking in response to ANG II is mediated by cardiopulmonary and arterial baroreceptors (278, 285, 425).

The SFO is not the only site for the dipsogenic action of ANG II in the brain. Several other structures involved in thirst and sodium appetite are located inside the blood-brain barrier and cannot be stimulated directly by circulating ANG II, including the MnPO nucleus in the lamina terminalis, the PVN (250), preoptic area (134, 154), and the central gray of the midbrain (510) which receives projections from the preoptic area (153).

The role of ANG II formed locally in the brain in thirst and salt appetite was well described by Fitzsimons (153). In the presence of a hypovolemic stimulus there is an increase in circulating ANG II due to the low pressure in the renal artery, which stimulates renin secretion. Concomitantly, changes in blood volume influence inputs to the brain through the NTS, which causes ANG II release in the brain leading to the stimulation of thirst. However, chronic lesions of the NTS do not prevent the stimulation of thirst and salt appetite during plasma volume deficits induced by polyethylene glycol (PEG) treatment in rats (459). The authors suggested that hypovolemia-induced thirst may involve pathways that bypass the NTS or, alternatively, these afferent neural signals from the heart and circulating ANG II may together stimulate hypovolemic thirst in rats. Indeed, rats submitted to a chronic NTS lesion present an increased dipsogenic response to systemic ANG II compared with control rats (460).

Angiotensin II plays a critical role in dehydration-induced drinking in male rats, since microinjection of ANG II antiserum, but not normal rabbit serum, completely blocked this drinking. A lesser, delayed effect on dehydration-induced drinking was obtained with antisera against ANP, AVP, and OT. On the other hand, ANG II antiserum had no effect on the so-called prandial drinking that occurs with feeding (171).

C. Functions of Brain Angiotensin in Salt Intake

Several hormones (ANG II, AVP, OT, ANP, and mineralocorticoids) applied to the anterior hypothalamus of the rat modify neuronal activity and appear to be involved in the regulation of fluid and electrolyte balance (23, 381, 520, 521).

Angiotensin II-induced sodium appetite presents a longer latency than water intake, and this does not result from ANG II-induced natriuresis (71). It has been suggested that an active inhibitory system may exist that restrains NaCl intake until water has been replenished. Peptides or hormones with the opposite effect to that of ANG II on fluid and electrolyte balance, such as ANP, may attenuate the response to ANG II (23). It has also been demonstrated that intracerebroventricular injection of ANG II, preceded by an OT receptor antagonist, increases NaCl intake without significant changes in water intake, suggesting an inhibitory action of OT (53).

Lesions of the SFO have been shown to reduce sodium depletion-induced salt appetite, which is largely dependent on ANG II (368, 442, 523, 548). On the other hand, infusions of ANG II in the OVLT increase salt appetite without significant changes in the blood pressure. Disconnection of afferent and efferent fibers of the rostroventral region of the SFO abolished water intake during the infusion of ANG II into the femoral vein but failed to reduce salt appetite during an infusion of ANG II into the OVLT. These data suggest that the role of the OVLT in salt appetite induced by ANG II is independent of the SFO (151).

Mechanisms of action of ANG II on sodium intake involve not only neuron depolarization but also protein synthesis, cell growth, and long-term potentiation (153). There is an interaction between central ANG II and desoxycorticosterone acetate in sodium intake as revealed by the greater sodium appetite and shorter latency than with separate applications of each hormone (14, 71, 158, 231).

Circulating ANG II also contributes to the sodium appetite in rats as demonstrated by the decrease in sodium appetite after bilateral nephrectomy (155, 156). In addition, it has been found that there is an increase in plasma renin activity and c-Fos expression in the SFO of rats submitted to a water deprivation-induced sodium appetite even after rehydration, although before sodium intake (108). These results are consistent with a role for circulating ANG II in the control of sodium appetite. The effect of circulating ANG II on sodium appetite may occur

by a direct action on CNS structures outside the blood-brain barrier (for review, see Ref. 153) or through stimulation of mineralocorticoid secretion, which could act on the basolateral or medial region of the amygdala to induce sodium appetite (148, 574). It should be pointed out that the effect of systemic ANG II on sodium intake shows species differences (153).

D. Angiotensin Receptors

Angiotensin II acts through specific cell membrane receptors termed AT_1 and AT_2 receptors (106). These are seven transmembrane domain G protein-coupled receptors that belong to the rhodopsin subclass. Angiotensin receptors have been cloned from several species, including humans (45, 372, 456, 512, 513). Most, if not all, of the central and peripheral actions of ANG II, such as vasoconstriction, stimulation of aldosterone secretion, facilitation of sympathetic transmission, and promotion of cell growth are mediated by the AT_1 receptor (142, 144). The function of the AT_2 receptor has not been well established, but it may play a role in cellular differentiation, apoptosis, and vasodilatation (92). Two other receptors, AT_3 and AT_4, have been proposed that may recognize other angiotensin peptide fragments, but their transduction mechanisms are unknown (63).

In humans, rabbits, and dogs, AT_1 appears to be a single receptor with no subtypes (106). However, in rat and mouse two highly homologous AT_1 receptor subtypes have been identified, termed AT_{1A} and AT_{1B}, which are 95% identical in their amino acid sequences and possess similar binding characteristics and mRNA tissue expression (244). Both AT_{1A} and AT_{1B} mRNAs have been reported to be widely expressed in rat tissues including the adrenal gland, kidney, heart, aorta, lung, liver, testis, pituitary gland, cerebrum, and cerebellum with a predominance of AT_{1A} mRNA expression, except in the adrenal and pituitary glands where AT_{1B} mRNA predominates (277). It appears that the increase in blood pressure induced by centrally administered ANG II occurs via the AT_{1A} receptor, whereas the drinking response requires the presence of AT_{1B} receptors (98). There is a high correlation between the distribution of AT_1 receptors and that of ANG II immunoreactive nerve terminals, suggesting that ANG II may be released from nearby synapses to activate AT_1 receptors (5).

In the adult human CNS, the distribution of AT_1 receptors has been determined using quantitative in vitro autoradiography. AT_1 receptors were found in the forebrain, midbrain, pons, medulla, and spinal cord as well as in the small and large arteries in the adjacent meninges and in the choroid plexus. Both AT_1 and AT_2 receptors are present in the molecular layer of the cerebellum (321). This distribution pattern of AT_1 receptors suggests that

angiotensin may act as a neuromodulator or neurotransmitter in the human CNS to influence fluid and electrolyte homeostasis, pituitary hormone release, and autonomic control of cardiovascular function (3). A dense population of AT_1 receptors is present in the circumventricular organs allowing neural inputs from these organs to inform the brain of circulating levels of ANG II (338, 404, 488). ANG II binding sites also occur in the NTS, which has connections with vagal afferent terminals in the dorsal motor nucleus of the vagus, the rostral and caudal ventrolateral medulla, and intermediolateral cell column of the spinal cord. The presence of ANG II receptors in the NTS supports the involvement of this peptide in the modulation of cardiovascular control and autonomic function (5, 329).

Expression of AT_2 receptor mRNA has been detected by in situ hybridization in the lateral septum, several thalamic nuclei, the subthalamic nucleus, the medial geniculate nuclei, the nucleus of the optic tract, the interposed nucleus of the cerebellum, and the inferior olive in adult rat brain (259, 299). The distribution of AT_2 receptors is very restricted in the human brain, but they are present in the molecular layer of the cerebellum. Although the physiological role of this receptor in the adult CNS is unclear, some of the AT_1-mediated effects may be enhanced by blockade of AT_2 receptors in the brain, suggesting that the central AT_2 receptor can exert an inhibitory control on AT_1 receptor-mediated actions in the brain (227). Deletion of the mouse gene for the AT_2 receptor subtype led to hypersensitivity to pressor and antinatriuretic effects of ANG II in vivo, reinforcing the suggestion that the AT_2 receptor subtype may counteract some of the biological effects of AT_1 receptor signaling (60).

E. Interactions With Other Hormones

The interaction between the central ANG II and AVP systems is well established (269, 369). ANG II activates AVP neurons, as demonstrated by in vivo studies using c-Fos and AVP mRNA expression and AVP secretion (100, 226, 314, 402). Moreover, disturbances of hydromineral balance, such as dehydration or osmotic stimuli, have been shown to increase ANG II receptor density, ANG II AT_{1A} receptor mRNA, and AVP mRNA in the central nervous system (377, 454).

Intracerebroventricular injection of ANG II has been shown to elicit an increase in plasma AVP (323). The results obtained by Antunes et al. (16) demonstrated that both AT_1 and V_1 receptors within the SON might be involved in water and sodium intake induced by the activation of ANG II receptors within the medial septal area. Intracerebroventricular injection of ANG II also induces OT secretion, and it appears to depend on the activation of cyclooxygenase and production of prostaglandins (262).

As stated above, the actions of ANG II on water and salt intake and excretion are antagonized by ANP and OT. Within the brain ANP inhibits ANG II- and dehydration-induced drinking (22). α-Adrenergic agonists block ANG II-induced drinking by stimulating the release of ANP from ANP-secreting (ANPergic) neurons within the brain (42). Previous injection of phenylephrine (an α_1-adrenergic agonist) or clonidine (an α_2-adrenergic agonist) into the anterior portion of the third ventricle significantly reduced ANG II-induced water intake (96). Injection of adrenergic agonists into the AV3V region also induces a significant increase in plasma ANP concentration and in ANP content of the olfactory bulb, AV3V, medial basal hypothalamus, and median eminence (42). These results suggest that the inhibitory effect of both α-adrenergic agonists on ANG II-induced water intake can be explained, at least in part, by the increase in ANP content and its presumed release from these neural structures.

It has been shown that central OT administration decreases ANG II-induced NaCl intake (53). In addition, systemic and central administration of ANG II stimulates pituitary release of OT (143, 291). On the other hand, intracerebroventricular injections of an OT receptor antagonist enhance ANG II-induced NaCl intake without modifying ANG II-induced water intake, suggesting that OT inhibits NaCl intake in this experimental condition (53, 501, 499). Thus, within the brain, ANP and OT act together to inhibit drinking and sodium intake. They also act in concert on the heart and vasculature to produce a rapid decrease in circulating blood volume. Finally, blood volume is returned to normal by the combined natriuretic action of circulating OT on the kidney, via activation of NO production with consequent cGMP release, and by circulating ANP acting on its receptors to also release cGMP. cGMP, in turn, closes sodium channels, thereby having a natriuretic effect and finally returning blood volume to normal. At least with regard to water and salt intake, but possibly also with regard to the other actions of OT and ANP, these effects may be opposed by ANG II (486).

IV. AUTONOMIC NERVOUS SYSTEM AND BODY FLUID METABOLISM

A. Role of the Sympathetic Nervous System Innervation of the Kidney in Sodium Excretion

The kidney regulates cardiovascular homeostasis and hydrosaline equilibrium through three principal mechanisms: *1*) sodium excretion, *2*) water excretion, and *3*) renin secretion. Renal functions are controlled mainly by humoral factors and by the sympathetic nervous system. Renal sympathetic nerves innervate the tubules, the vessels, and the juxtaglomerular granular cells, modulating multiple renal functions such as renal blood flow and urinary sodium excretion. Sympathetic nervous system innervation of the kidney has been shown to exert an important control over renal function. Information from various peripheral and central structures brings about changes in efferent renal sympathetic nerve activity (RSNA) modulating kidney function, including renal blood flow, glomerular filtration rate, solute and water transport, and hormonal production and secretion (115, 118, 211, 212, 266).

Electrical stimulation of the renal nerves has several effects, including norepinephrine release, vasoconstriction, antinatriuresis, and renin secretion (565). The decreased urinary sodium and water excretion obtained by an increase in renal sympathetic nerve activity is due to an increase in the renal tubular water and sodium reabsorption throughout the nephron, decreased renal blood flow and glomerular filtration rate caused by constricting the renal vasculature, and increased activity of the RAS after stimulation of renin release from juxtaglomerular granular cells. The ANG II formed acts on AT_1 receptors in tubular and vascular segments to enhance renal tubular sodium, chloride, and water reabsorption as well as constricting the renal vasculature (116).

The antinatriuretic response observed after stimulation of the RAS by a low dietary sodium intake was blocked by an ANG II converting enzyme inhibitor, captopril, which prevents the formation of ANG II, thus confirming a role for ANG II in antinatriuresis (253). On the other hand, suppression of renin-angiotensin system activity can be obtained by a high dietary sodium intake. It has been suggested that an important action of ANG II in the kidney occurs through a presynaptic mechanism, stimulating renal sympathetic nerve terminals to release norepinephrine in both renal tubular epithelial cells and vessels (56). On the other hand, administration of captopril or an ANG II receptor antagonist attenuates the antinatriuretic response obtained by either low-frequency electrical or reflex renal sympathetic nerve stimulation in rats (208, 209). These data suggest a close interaction between the renin-angiotensin system and the renal sympathetic system. Secretion of renin is obtained through stimulation of β_1-adrenoceptors on juxtaglomerular granular cells by the norepinephrine released from renal nerve terminals (115–117).

After renal denervation ANG II is able to increase proximal tubular chloride and water reabsorption by only 25%, a result believed to be caused by a direct action on ANG II receptors located on proximal tubules. The remaining putative antinatriuretic effect (75%) of ANG II under normal conditions would depend on an intact renal innervation (308). In accordance with this finding losartan, an ANG II AT_1-receptor antagonist, or prazosin, an α_1-adrenoceptor antagonist decreased proximal tubular chloride and water reabsorption (555).

The proximal tubule synthesizes and secretes high

levels of ANG II into the lumen, which modulates proximal tubule transport independently of systemic ANG II (394). These authors performed in vivo microperfusion studies to evaluate the role of the renal nerves in the modulation of the action of intraluminal ANG II on proximal tubule transport. They described a 50% decrease in volume reabsorption after addition to the lumen of enalaprilat, an ACE inhibitor, indicating the participation of luminal ANG II in sodium and water transport mechanisms. Furthermore, the authors showed that the renal nerves play a role in the modulation of the intraluminal ANG II-mediated component of proximal tubule transport.

ANP causes potent natriuresis and suppresses the renal nerve stimulation-induced renin secretion and renal vasoconstriction without affecting the norepinephrine release in dogs (222). These findings are consistent with the view that ANP activates its receptors on the juxtaglomerular apparatus and renal vessels to release cGMP, which opposes the renin-releasing action of cAMP synthesized in response to norepinephrine.

Leonard et al. (300) stated that oscillations observed in the RSNA and renal blood flow (RBF) are still not well understood, and their functional significance remains unknown. They performed experiments in animals that underwent surgery to implant an electrode for recording renal nerve activity and a flow probe for recording RBF. Volume expansion resulted in a decrease in mean RSNA, associated with an increase in RBF from resting levels. Renal denervated rabbits did not show an increase in RBF in response to volume expansion in the presence of arterial baroreflexes. Thus natriuresis and diuresis observed after blood volume expansion (BVE) may be the result of both cardiac ANP release and decreased RSNA, which thereby increase RBF, increasing glomerular filtration rate (GFR) and filtered load, and also decreasing tubular reabsorption of sodium. Colombari et al. (87) presented evidence that the renal vasodilatation in response to volume expansion was blocked by sinoaortic denervation, indicating the essential role of the baroreceptors in the control of RBF.

B. CNS Regulation of the Renal Sympathetic Nerve Activity

Discrete areas of the forebrain and the brain stem may participate in the regulation of the RSNA, which could occur through direct projections from the brain to sympathetic preganglionic neurons in the intermediolateral column of the spinal cord. In addition, these areas may participate in major reflexes that modulate RSNA, such as those arising from peripheral arterial and cardiac baroreceptors, chemoreceptors, and somatic receptors.

ANG II may regulate those brain areas either as a neurotransmitter released from neurons or as ANG II circulating in the blood. Circulating ANG II modulates peripheral sympathetic nerve activity by acting on the area postrema, since ablation of this brain area prevents hypertension caused by chronic intravenous administration of ANG II. The area postrema establishes efferent connections with the NTS and the lateral parabrachial nucleus (PBLN), both of which provide substantial input to sympathetic preganglionic neurons in the intermediolateral column of the spinal cord. Lesions of the PBLN also impair chronic ANG II-induced hypertension (149). Activation of the area postrema by circulating ANG II may increase peripheral sympathetic nerve activity through a direct excitatory connection with the rostral ventrolateral medulla (RVLM), a central vasomotor region (532). Mayorov and Head (332) demonstrated in rabbits that the RVLM has an important influence on renal sympathetic nerve activity at rest and during baroreflex responses. Neuronal excitation and inhibition in the region of the RVLM increase and decrease arterial pressure and RSNA, respectively.

Other endogenous stimuli also contribute to the regulation of the RSNA. The stimulation of different purinergic receptor subtypes located in the NTS evokes changes in regional hemodynamic and efferent sympathetic responses. Stimulation of adenosine 2a receptors (A_{2a}), a purinergic receptor subtype, decreased RSNA and postganglionic adrenal sympathetic nerve activity. On the other hand, stimulation of A_1 receptors evoked sympathoactivation (464). The different patterns of regional sympathetic responses strongly suggest that purinergic receptor subtypes may be specifically located and differentially expressed on NTS neurons/neural terminals that control different sympathetic outputs and may contribute to autonomic responses observed in specific physiological or pathological situations.

C. Role of α-Adrenergic and Cholinergic Receptors in Control of Natriuresis

In a recollection micropuncture experiment along proximal and distal renal tubules, it was found that carbachol stimulation of the lateral hypothalamic area (LHA) led to diuresis and natriuresis with only transient changes in GFR and renal plasma flow. These effects are only partially due to the release of neurohypophysial hormones, since the administration of OT and AVP promoted a further effect of LHA stimulation (479). Silva-Netto et al. (478) have also shown the natriuretic effect of carbachol stimulation of the LHA in rats with intact or denervated kidneys. The control values for Na^+ excretion were significantly higher in rats with denervated kidneys, consistent with the previously described "denervation diuresis" (114, 115, 119). Injection of carbachol into the LHA led to

a highly significant increase in urine volume and sodium excretion, without changes in GFR or renal plasma flow in rats with innervated and denervated kidneys. Micropuncture studies in denervated kidneys showed that after carbachol injection into the LHA, tubular fluid-to-plasma inulin concentration ratio [(F/P)In] at the end of the proximal tubule decreased significantly without changes in single-nephron GFR. Therefore, these results clearly show that the natriuresis induced by intrahypothalamic injection of carbachol is independent of the alterations in renal efferent nerve activity. It is likely that other factors, including OT and/or ANP effects, are involved in the efferent renal nerve activity (324, 478).

V. THE NEUROENDOCRINE REGULATION OF ATRIAL NATRIURETIC PEPTIDE SECRETION

A. Control of Hydromineral Balance by a Brain Neural Circuit

In 1935, Fisher et al. (150) drew attention to the role of the hypothalamus in the regulation of water metabolism. Many other groups have since studied the effects of chemical or electrical stimulation of different areas of the CNS involved in the control of hydromineral balance. From the work of Andersson and McCann (11–13) and Andersson et al. (10) it became clear that the hypothalamus was very important in the control of water and electrolyte metabolism.

In the early 1960s, Covian and Antunes-Rodrigues (89) and their associates (Brazil) and McCann (United States) published their results on the role played by the CNS in the control of salt intake. Systematic studies were undertaken to determine the effects of bilateral localized lesions of the rat hypothalamus on the free choice ingestion of tap water or 2% NaCl solution. After several experiments it was possible to demonstrate the existence of a neural circuit that controls the sodium intake and/or excretion. This circuit involves the septal area, AV3V, amygdaloid complex, hypothalamus, and olfactory bulbs. The existence and the role played by this neural circuit in sodium intake were investigated by electrolytic lesions and by electrical and chemical stimulation. Bilateral lesions of the anterior hypothalamus, destroying the PVN and part of the SON, caused a decrease in the intake of saline solution, while lesions in the anterior lateral hypothalamus caused an increase in saline intake (89). Lesions of the septal area, olfactory bulbs, and of the corticomedial region of the amygdala increased specifically Na^+ intake, while this was decreased by lesions of the basolateral region. Conversely, electrical stimulation of the septal area or amygdala decreased Na^+ but not water intake. When a lesion was placed in the anterior hypothalamic area of animals bearing olfactory bulb, septal area, or corticomedial amygdala lesions, the increased salt intake was abolished. These data suggested that the neuronal pathway involved in increased salt intake after initial lesions converges on the hypothalamus. Neural impulses stimulating salt appetite may pass from there to the corticomedial amygdala and thence to the hippocampus, sensory, and motor cortex to initiate drinking. Therefore, the hypothalamus is the principal structure in the circuit involved in the control of saline ingestion/excretion, and the septal area, olfactory bulb, and amygdala have modulating influences on its activity (79, 90). Several other laboratories have also made important contributions to understanding of the role played by the CNS in the control of body fluid homeostasis (for review, see Refs. 9, 65, 121, 135, 153, 170, 172, 255, 257, 478, 479).

There has been increased interest in identifying the neural pathway involved in hydromineral balance. A serotonergic pathway with cell bodies in the area postrema and in the raphé nuclei seems to exert an inhibitory control to limit sodium intake (168, 169, 290, 350).

More recently, new technologies, such as immunocytochemistry, radioimmunoassay, and radioreceptor techniques, have enabled the demonstration of the presence of ANP-secreting neurons and ANP receptors in structures of the CNS related to the control of water and electrolyte homeostasis, and in the cardiovascular system (396, 414–416, 573). Because ANP is a major natriuretic hormone, it became of interest to determine the effect of central administration of hypertonic saline on the plasma ANP levels. Indeed, intravenous injection of hypertonic saline was already known to increase plasma ANP with concomitant natriuresis. Antunes-Rodrigues et al. (25) found in water-loaded rats that microinjection of hypertonic saline into the AV3V caused an elevation in plasma ANP levels after 20 min. However, Morris and Alexander (364) had presented conflicting evidence showing that intracerebroventricularly injected hypertonic saline increased blood pressure, heart rate, and OT secretion, with no change in plasma ANP levels. Probably, the concentration of hypertonic NaCl in the latter experiments did not reach the threshold for ANP release.

The effects of ANP on electrical activity in neurons of the SON were demonstrated by a decrease in the firing rate and hyperpolarized cell membrane in phasically firing AVP neurons after application of ANP or brain natriuretic peptide (BNP) in rat hypothalamic slices (1). These effects were mimicked by a cGMP analog as well as by the specific inhibitor of cGMP phosphodiesterase. This suggests that the inhibitory effects of natriuretic peptides on putative vasopressin neurons are mediated through cGMP (1). Interestingly, applications of ANP over the SON did not affect depolarizing responses to local hypertonicity, but they reversibly abolished the synaptic excitation of magnocellular neurons after hypertonic stimulation of the OVLT (426). In addition, these cells receive afferents from

osmoreceptor neurons located in the OVLT that appear to be glutamatergic. Richard and Bourque (426) obtained results indicating that centrally released ANP may inhibit osmotically evoked neurohypophysial hormone release through presynaptic inhibition of glutamate release by these osmoreceptor neurons.

ANP released from the heart may reach the brain centers in sufficient concentrations to regulate its own secretion through a putative negative-feedback mechanism. It has been reported that ANP or C-type natriuretic peptide (CNP) injected into the AV3V region decreases the plasma ANP concentration in blood volume expanded rats, with no change in mean arterial pressure and heart rate (412). Moreover, intracerebroventricular ANP injection induces a decreased natriuresis and also blocks cholinergic-induced natriuresis (130). The mechanism of these effects remains to be determined. Because ANP penetrates poorly into the brain, it is unlikely that systemic levels of the peptide would increase brain ANP sufficiently to have a feedback effect; however, local increases of ANP from ANP neurons excited by volume expansion might provide sufficient concentrations to inhibit ANP neuronal activity. Further experiments are needed to determine the physiological significance of these findings.

B. CNS Neurotransmitters/Neuromodulators and Modulation of Hydromineral Homeostasis

1. Dopamine

Among the catecholamines, dopamine has the unique ability to improve RBF, GFR, sodium excretion, and creatinine clearance, independent of its cardiac effects. Low doses of dopamine can decrease renal and systemic vascular resistance, suppress aldosterone secretion, and interact with ANP in the kidney (74). Endogenous dopamine, by activation of D_1 receptors, enhances the diuretic and natriuretic effect of ANP (218). Because of these clinically significant properties, dopamine has been used successfully to improve and treat acute oliguric renal failure in a variety of clinical situations.

Dopamine is a neurotransmitter that interacts with different receptor subtypes to evoke dual antagonist effects. The interaction with D_1 and D_5 receptor subtypes leads to stimulation of many biological systems; on the other hand, when dopamine activates D_2, D_3, and D_4 receptor subtypes it inhibits the specific cell function controlled by this catecholamine. In this context, D_1, D_2, and D_5 receptors have been detected on ANP neurons located in the rat hypothalamus (296). Thus dopamine may regulate the synthesis and release of brain ANP by either inhibiting or stimulating, depending on the receptor subtype activated, as demonstrated in neonatal rat hypothalamic cultures (296). In addition, Samson and Bianchi

(452) and Samson et al. (453) have shown that intracerebroventricular injection of ANP can modify the hypothalamic control of lactotroph function. Because prolactin secretion is under inhibitory influence from the hypothalamus, these data support an interaction between ANP and dopaminergic neuron systems (452).

However, Shenker et al. (473) have shown that intravenously infused dopamine in humans induces natriuresis and diuresis without changing plasma ANP levels. It appears that ANP is not involved in dopamine-induced natriuresis (296). In addition to these effects, dopamine injected into the zona incerta of rats submitted to overnight water deprivation inhibits drinking behavior via activation of D_2 receptors (524).

The possible involvement of brain dopaminergic systems in the diuresis and natriuresis induced by AV3V-injected ANP was investigated by Israel et al. (241). The diuretic and natriuretic actions of injection of ANP in the third ventricle were inhibited in animals with central sympathectomy. Similar effects were observed when ANP was intracerebroventricularly administered to rats pretreated with a dopamine antagonist (haloperidol icv or domperidone intragastric). These results suggest an interaction of ANP with dopaminergic systems.

2. Hypothalamic GABAergic neurons

The role played by hypothalamic GABAergic neurons in AVP secretion and in the modulation of blood pressure is still not well established. Administration of GABA in the third ventricle did not alter AVP and pressor responses to central ANG II or carbachol injections, although changes in blood pressure modulate GABA release in an area adjacent to the PVN, which increases plasma AVP levels (271). Microinjections of ANP into the preoptic/anterior hypothalamic area resulted in a reduction of local GABA release. ANG II, on the other hand, stimulated the release of GABA (433).

3. Endothelin

The endothelins (ET) are a family of isopeptides (ET-1, ET-2, and ET-3) synthesized mainly by endothelial cells and involved in the regulation of the cardiovascular system (132, 183, 221, 441, 529, 569). Their physiological actions at the target cells (heart, lungs, kidney, adrenal, pituitary, and CNS) occur via ET_A and ET_B receptors (27, 282, 376, 450). In view of their wide distribution in several structures of the CNS (SFO, OVLT, PVN, SON, median eminence, and choroid plexus) and in the anterior and posterior pituitary gland, a physiological function is expected for these peptides in the control of blood pressure, body fluid, and electrolyte metabolism (175, 282, 572). Evidence suggests that ETs act within the CNS to increase arterial pressure and AVP secretion (178, 437). For example, third ventricle injections of ET-1 increase systemic

arterial pressure in rats (379, 380, 438, 439, 566, 567). This peptide also increases AVP secretion both in vivo (326, 435, 438, 439, 566) and in vitro (435, 436). However, it seems that the pressor response is independent of AVP, since similar responses were obtained in Brattleboro rats, which lack AVP. Furthermore, electrolytic lesions of the AV3V, that interrupt projections from the SFO to the SON, block AVP secretion but not the increase in arterial pressure observed with central ET-1 administration (438, 439). The pressor response to ET-1 intracerebroventricular administration seems to be mediated by increased sympathetic outflow (199, 287, 304, 437–439).

The effect of ET on CNS structures related to the control of hydromineral balance and blood pressure has been investigated by AV3V injection of ET-3 in water-loaded rats (26). This treatment evoked a dose-related natriuresis correlated with a rapid increase in plasma ANP levels. In contrast, intravenous injection of the same dose of ET-3 did not induce any significant change in plasma ANP levels. On the other hand, Yamamoto et al. (566) demonstrated a central effect of ET-1, increasing the mean arterial pressure and the release of AVP but not ANP. These data suggest that ET-1 acts centrally and may activate the sympathetic nervous system and AVP release to cause an increase in blood pressure and ANP-induced natriuresis.

In cultured rat diencephalic neurons, ET-3 has been shown to increase the release of ANP (301). An identical effect was observed in cardiac atria after in vitro incubation (554). This latter effect has also been observed with ET-1, which was shown to stimulate ANP release in neonatal ventricular cardiomyocytes via an ET_A receptor-mediated pathway involving cAMP formation and activation of a nifedipine-sensitive calcium channel (420). It seems that ET is released as a neurotransmitter in the brain in response to afferent input from baroreceptors stimulated by BVE and, in turn, causes ANP release.

4. Neurotensin

Several gut peptides, including neurotensin, have been found within the kidney. Neurotensin plasma levels rise promptly in response to feeding. In conscious rabbits, neurotensin produces a dose-related fall in renal sodium excretion (54). It has also been shown that neurotensin and vasoactive intestinal polypeptide (VIP) reduce blood pressure and natriuresis, followed by a dose-related fall in plasma ANP (6).

5. Substance P

Substance P (SP) is a neuropeptide found principally in the CNS and peripheral afferent nerve fibers. SP injected into the medial preoptic area of conscious, unrestrained, water-loaded male rats induces a significant decrease in urinary sodium, potassium, and water excretion.

As expected, a significant natriuretic effect is observed after injection of a specific competitive SP antagonist. SP partially blocks carbachol-induced natriuresis in a time-dependent manner. These data indicate a tonic inhibitory action of SP on sodium excretion and suggest a putative inhibitory action of SP on the cholinergic system (407). SP (10^{-10} M) caused a 50% reduction in the rate of fluid absorption by rabbit proximal tubules in vitro (147). Interestingly, SP induces ANP secretion from neonatal ventricular cardiomyocytes through a protein kinase C and prostaglandin-dependent signaling pathway (83).

6. Melanocyte-stimulating hormone

There is considerable evidence to suggest the participation of the pars intermedia peptides in the control of hydromineral balance. Melanocyte-stimulating hormone (MSH) content and histological changes in the pars intermedia are correlated with hyperosmolality induced by dehydration or intake of hypertonic saline solution (331, 398). The amino acid sequences of β-endorphin, ACTH, α-, β-, and γ-MSH are contained within the precursor proopiomelanocortin. All of these MSH peptides are present in plasma, and all exhibit natriuretic activity. Orias and McCann (387–390) established the natriuretic effect of α- and β-MSH in rats. The natriuretic effect of both α- and β-MSH is correlated with changes in plasma ANP levels, indicating that these natriuretic actions of MSH peptides could be explained by their ability to release ANP from the heart (530). Valentin et al. (530) and Picanço-Diniz et al. (408) reported that the natriuretic activity of γ-MSH occurs without a change in systemic blood pressure and renal hemodynamics, suggesting a possible direct tubular inhibition of sodium reabsorption. In rats, γ-MSH is involved in the reflex increase of sodium excretion after acute unilateral nephrectomy and after unilateral carotid artery baroreceptor traction. In addition to these effects, γ-MSH induces an increase in plasma ANP concentrations. Because no specific MSH receptors have been demonstrated in renal tissue, it is possible that the natriuretic activity of this peptide could be explained through its direct atrial ANP-releasing action and by modulation of the renal autonomic innervation on tubular cells (530). On the other hand, it has been reported that in frogs, ANP stimulates α-MSH release from the neurointermediate lobe (288).

7. Neuropeptide Y

Neuropeptide Y (NPY) and polypeptide YY (PYY) are members of a family of 36-amino acid peptides with a wide distribution in the central and peripheral nervous systems. NPY modulates renal function by reducing RBF, enhancing diuresis and natriuresis without changing the GFR (6). Recently, it has been shown that NPY may also induce kaliuresis. However, NPY-induced kaliuresis is

much less pronounced than natriuresis and is mediated by distinct mechanisms (49). Indeed, the L-type Ca^{2+} channel blocker nifedipine abolished natriuresis but did not inhibit kaliuresis. Systemically injected NPY increases plasma ANP, in a dose-dependent manner, in normally hydrated as well as in water-loaded rats. An opposite effect was reported with PYY. These data suggest that both peptides may participate in the control of ANP secretion by acting mainly at the atrial level (40).

8. Opioid peptides

A number of studies have examined the mechanism by which opioid peptides regulate water-electrolyte balance and blood pressure. Stimulation of μ-opiate receptors by agonists, such as morphine, enkephalins, and β-endorphin, has an antidiuretic effect (235). In 1944, Bodo (55) was the first to suggest that the antidiuretic effect of morphine was a consequence of AVP release, confirmed by several other investigators (235, 531). Plasma AVP levels were elevated by intravenous injections of β-endorphin and enkephalins in rabbits and rats (52, 551). In addition to the antidiuretic effect, opioids also exhibit an inhibitory effect on thirst and renal electrolyte excretion, suggesting a central site of action (508, 531).

The SFO contains a large population of enkephalinergic cell bodies and fibers (36, 542). Fregoneze and Antunes-Rodrigues (174) confirmed a central inhibitory effect of morphine, β-endorphin, and other opioid peptides on water, sodium, and potassium excretion. The Met-enkephalin analog FK-33824, injected into the SFO in water-loaded rats, reduced urine output as well as sodium and potassium excretion with no change in blood pressure. These effects were independent of the pituitary gland or median eminence area, raising the possibility that AVP is not the most important determinant of the urinary response to central administration of opioids.

On the other hand, systemic injection of morphine has a potent diuretic effect in both humans and experimental animals (541). Intracerebroventricular injection of β-endorphin in rats and enkephalins in humans decreases plasma AVP (205). Thus the administration of κ-opioid agonists increases diuresis (294, 400), an effect mediated at least in part by inhibition of AVP release (293). A κ-opioid receptor agonist injected into the lateral ventricle also induced a decrease in OT plasma levels in water-deprived rats (194). Naloxone increases OT secretion when administered during late pregnancy in rats. This effect was accompanied by an increase in the number of SON neurons expressing c-Fos (122). These data suggest an inhibitory action of endogenous opioid peptides on neurohypophysial hormone secretion.

Crum and Brown (91) reported that morphine induces ANP release through a central mechanism, since the dose required to obtain this effect was much lower with intracerebroventricular injection compared with systemic administration (203, 229). This effect can be reversed by naloxone pretreatment, which demonstrates the specificity of the morphine action. Dynorphin, an endogenous opioid peptide that acts on kappa receptors, has also been shown to stimulate the release of ANP in vivo (560) as well as in isolated rat atria (490). Because the morphine-induced release of ANP is much lower in Brattleboro than in Long-Evans rats, the mechanism of ANP release must be much more complex, inferring an AVP involvement in the potentiation of the opioid peptide action. In summary, the above results indicate that opioid peptides and analogs have opposite effects on diuresis and natriuresis. Natriuretic and diuretic responses are probably caused by ANP release and occur at low doses of these peptides, whereas higher doses release AVP, which induces the antidiuresis.

9. Other transmitters

Other CNS neurotransmitters such as adenosine, excitatory amino acids, nitric oxide, corticotrophin releasing hormone, urocortin, sauvagine, and urotensin may also participate in the regulation of body fluid homeostasis (200, 397, 533, 575). The amino acid taurine is present at high concentrations in the brain, retina, and heart. Taurine lowers the mean arterial pressure, induces diuresis, and causes vasodilatation, as well as being involved in the transmission of osmotic information to the osmosensitive neurons of the SON (237). Taurine depletion caused by guanidinoethylsulfonate, an inhibitor of taurine transport that decreases myocardial (50%) and plasma (43%) concentrations of the amino acid, is accompanied by a decrease in plasma ANP concentration and hypernatremia, suggesting that taurine is essential for ANP secretion (85).

C. Natriuretic Hormones and Hydromineral Balance

The Romans described the diuretic effect of immersion in their divers (*Caesarea urinatores*) that also follows immersion in thermal baths as pointed out in the historical description of water immersion diuresis in the mid 19th century. The diuresis evoked by immersion may be due to the increased pressure on the extremities, abdomen, and thorax, which increases venous return to the heart resulting in dilation of the atria. The existence of a natriuretic hormone was hypothesized during the 1950s, and the first evidence for the participation of the atria in the control of urine excretion was published by Henry et al. (219), who observed a diuresis elicited by expansion of a balloon in the left atrium. Later, Davis and Freeman (97) obtained evidence for the existence of a circulating natriuretic factor in volume-expanded dogs by cross-circula-

tion experiments. Based on these findings it was predicted that distension of the atria generated impulses, which travel up through the vagus to inhibit the release of AVP. De Wardener and Clarkson (543) presented evidence showing that natriuresis could occur following blood volume expansion, even in the absence of increased GFR or changes in aldosterone secretion.

Kisch (276) reported the detection by electron microscopy of secretory granules in guinea pig atrial myocytes. Subsequently, several other laboratories confirmed the presence of endocrine-like cells in the heart atria, possibly involved in the control of hydromineral homeostasis (44, 57, 164, 167, 246, 348, 395).

de Bold et al. (104) made a landmark discovery when they demonstrated that atrial extracts had a natriuretic effect. This led rapidly to the determination of the structure of ANP by this same group (159). The myorelaxing action of the atrial extracts on vascular muscle was determined subsequently by several groups (95, 113, 161, 165). ANP released from atrial myocytes circulates to the kidneys and causes diuresis and natriuresis. These initial findings led to the identification and characterization of other hormones of the natriuretic peptide family that are involved in the control of body fluid homeostasis (62, 159, 163, 165, 265, 503–506).

The prototype of the natriuretic hormone is the circulating peptide containing 28 amino acids (ANP 99–126 amino acids) (159), which is processed from the atrial prohormone (1–126 amino acids). The mRNAs of several members of the natriuretic peptide family (35, 383, 467) and the gene structure of human ANP have been described (193, 466). Other members of the natriuretic peptide family are BNP, CNP (503, 505, 506), and urodilatin.

Urodilatin, a natriuretic peptide of kidney origin described by Forssmann's group (463), is synthesized in the distal tubules and has diuretic and natriuretic paracrine actions on the tubular cells of the kidney (141, 162, 166, 275, 354). Urodilatin contains a four-amino acid extension of the NH_2-terminal end of ANP (192, 319), a characteristic that ensures its greater resistance to enzymatic degradation (265). Thus exogenously administered urodilatin succeeds in reaching the distal tubule and the collecting duct without being degraded. Urodilatin plays an important role in kidney function, especially in the control of sodium and water excretion. Studies by other investigators have shown that acute volume loading (123, 124) or dilatation of the left atrium (189) is followed by an increase in the excretion of sodium and urodilatin. Although in humans urodilatin is not normally detected in the systemic circulation or in the lung, this peptide also produces a significant relaxation of the tracheobronchial tree so that it is now prescribed for the treatment of asthma (161, 165).

The natriuretic peptides act at the cell membrane through three types of receptors (NPR-A, NPR-B, and NPR-C). NPR-A and NPR-B, but not NPR-C, have an intracellular guanylate cyclase domain that generates cGMP from GTP, with cGMP, in turn, activating protein kinase G. In contrast, NPR-C performs a clearance receptor function by binding the peptides (319, 320). All three receptors have been cloned by several groups (77, 80, 313, 462). The distribution of NPR-A, analyzed by RT-PCR, indicates the presence of receptors through all layers of the kidney.

D. The Brain ANPergic Neurons in Water and Salt Intake

The presence of a natriuretic factor in the CNS, mediating the natriuresis induced by brain manipulation in different experimental models, was postulated by Sedlakova et al. (465) who reported the purification of a hypothalamic natriuretic factor that they believed was an OT analog. Independently, Orias and McCann (387–390) were able to demonstrate that AVP, OT, and α-MSH had natriuretic activities in water-loaded rats. Diuresis induced by the distension of the atria could be due to a reflex activation of the neuroendocrine system, resulting in the release of a natriuretic peptide from the neurohypophysis (365).

The role of the natriuretic peptide in the control of hydromineral balance was investigated in rats by studying the effect of median eminence lesions on the natriuretic responses to hypertonic saline, carbachol, or norepinephrine injected into the third ventricle. The median eminence lesions induced diabetes insipidus through the interruption of the supraopticohypophysial tract, and blocked the natriuresis, kaliuresis, and antidiuresis that follow the injection of hypertonic saline or norepinephrine into the third ventricle (365, 366). Hypophysectomy did not block these responses, which ruled out the participation of anterior pituitary hormones (120). In addition, the natriuresis was maintained in rats with hereditary diabetes insipidus, which lacked AVP (390), suggesting that AVP was not an essential component of the natriuretic responses induced by the injection of hypertonic saline into the third ventricle. Therefore, the median eminence lesions interrupted the secretion of a natriuretic hormone, other than AVP, possibly OT, involved in the natriuresis induced by central nervous system stimulation.

Neural structures involved in the control of natriuresis also contain the cell bodies of the ANP neurons (396). Injection of ANP into the AV3V region induces a dose-related inhibition of both water intake following overnight dehydration and ANG II-induced drinking in rats (22). Similar results were described by Masotto and Negro-Vilar (328), Tarjan et al. (514), Itoh et al. (243), Nakamura et al. (374), Imura et al. (239), and Zhu and Herbert (576). The inhibition of drinking by ANP was also re-

ported in sheep by Weisinger et al. (546). In addition, even smaller doses of ANP than those required to inhibit water intake, when injected into the AV3V, dramatically reduced the intake of 1.5% sodium chloride in conscious salt-depleted rats (23). Therefore, ANP suppresses salt intake as well as water intake induced by dehydration and ANG II.

ANP exerts its antidipsogenic effect by acting directly in the SFO, since this circumventricular organ is also a critical site for ANG II-induced drinking. Indeed, pretreatment with various doses of ANP microinjected into the SFO of rats reduced drinking induced by subsequent ANG II injection into this site, and also blocked ANG II-induced neuronal excitation in the SFO (68, 128, 215).

E. The Brain ANP System in the Control of Cardiovascular and Renal Functions

Stimulation of the AV3V region by a cholinergic drug, carbachol, and lesions of the AV3V have been shown to either increase or decrease sodium excretion, respectively. The natriuresis induced by cholinergic stimulation is accompanied by a dramatic rise in the plasma ANP concentration and a rise in ANP content in the medial basal hypothalamus, the neurohypophysis and, particularly, the anterior hypophysis, but with no change in the ANP content of the lungs or the right or left atrium (37). The marked rise in ANP content of the basal hypothalamus and neuro- and adenohypophysis suggested that the natriuresis resulting from this stimulation is brought about at least in part by release of ANP from the brain (37). Because the quantity of ANP in the hypothalamus is 1,000-fold less than in the heart, it is likely that ANP released from the neurohypophysis makes little contribution to the circulating plasma ANP after BVE.

The importance of the brain ANP system to plasma ANP levels has been demonstrated by the decrease in plasma ANP and natriuresis induced by BVE after central ANP immunoneutralization (24). These data confirmed results obtained from similar experiments in sheep by Charles et al. (78) and indicate that ANP released from hypothalamic ANP neurons is crucial for the increased secretion of ANP from the heart, which mediates the ensuing natriuresis.

The muscarinic cholinergic receptor blocker atropine sulfate microinjected into the AV3V region had no effect on resting plasma ANP levels, but significantly decreased BVE-induced ANP release. Similar results were observed after microinjection of the α-receptor blocker phentolamine into the AV3V region (20). These results are consistent with a pathway for physiological control of ANP release, which involves distension of baroreceptors within the right atrium, carotid and aortic sinuses, and

kidney which alters afferent input to brain stem noradrenergic neurons with axons projecting to the AV3V region (200).

As described above, ANG II and ANP have opposing actions on water and salt intake and excretion. Previous injection of phenylephrine (an α_1-adrenergic agonist) or clonidine (an α_2-adrenergic agonist) into the AV3V region significantly reduces ANG II-induced water intake. α-Adrenergic agonist injection induces a significant increase in plasma ANP concentration and in ANP content of the olfactory bulb, AV3V, medial basal hypothalamus, and median eminence. These findings show that the inhibitory effect of α-adrenergic agonists on ANG II-induced water intake can be explained, at least in part, by the increase in ANP content and release from these neural structures. The increased release of ANP by neurons terminating on the effector neurons of the drinking behavior would inhibit the stimulatory response to ANG II (42).

F. Afferent Inputs to the Brain ANPergic System

The crucial participation of the CNS and the brain ANP neurons in the response of plasma ANP to volume expansion is well established. An increase in blood volume causes distension of baroreceptors in the right atrium, carotid and aortic sinuses, and in the kidney, which alters their afferent input to the NTS. Impulses from there might be relayed to and activate the locus ceruleus and raphé nuclei (Fig. 1). The role of the locus ceruleus has been demonstrated by experiments with electrolytic lesions of different regions of this structure, which decreased blood pressure and increased plasma ANP in animals submitted to BVE. The axons of noradrenergic neurons located in the locus ceruleus project to the AV3V region where they activate its cholinergic interneurons, which in turn stimulate the hypothalamic ANPergic neurons (15). These neurons may activate an efferent neurohumoral or neuronal pathway to bring about the concomitant release of ANP from the brain and the atria.

An afferent pathway to the AV3V region via serotonergic neurons with cell bodies in the raphé nuclei has been identified (58), suggesting that 5-HT might play a role in the control of ANP neurons in the region of the AV3V. Indeed, early studies had shown that injection of 5-HT agonists into the third or lateral ventricles could increase electrolyte excretion (491) and plasma ANP, and these responses were prevented by 5-HT$_2$ receptor blockers (421). Furthermore, bilateral lesions of the dorsal raphé nuclei (DRN), a major source of 5-HT neurons that project to the AV3V region, induced a highly significant increase in water intake and urine volume, as well as a decrease in basal and BVE-stimulated plasma ANP levels (421, 422). These data suggest that the serotonergic sys-
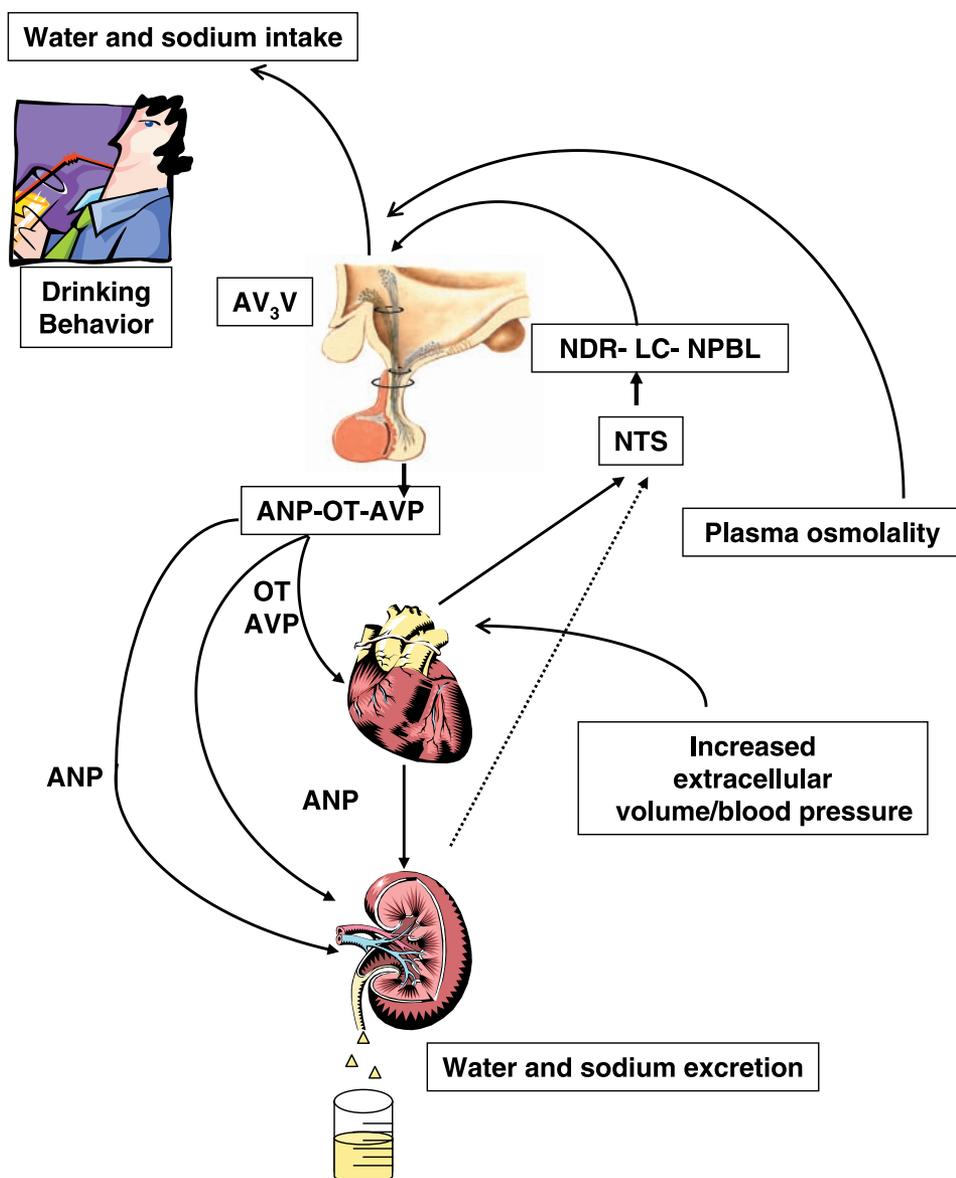
FIG. 1. Schematic diagram of the atrial natriuretic peptide (ANP) neuroendocrine control of ANP release. For explanation, see text. OT, oxytocin; AVP, arginine vasopressin; NTS, nucleus tractus solitarius.

tem has a tonic stimulatory drive on the release of ANP. The raphé nuclei may be stimulated by afferent input from the baroreceptors via the NTS and may contribute to the stimulation of ANP release following BVE (422).

G. Role of the Brain in ANP Release in Response to Increased Extracellular [Na$^+$] and Acute Blood Volume Expansion

An increase in extracellular [Na$^+$] in the vicinity of Na$^+$ receptors in the OVLT or SFO can be achieved by microinjection of hypertonic NaCl into the AV3V region. Such injections cause a rapid elevation in plasma ANP followed by natriuresis. Lesions of the AV3V, median eminence, neurohypophysis, or hypophysectomy cause a decrease in both basal and BVE-induced plasma ANP concentrations compared with those seen in sham-operated rats (25), indicating that brain ANP plays an important role in mediating the release of ANP after volume expansion.

Plasma ANP levels after volume expansion are decreased in rats submitted to deafferentation of the carotid-aortic baroreceptors or renal deafferentation (19, 364). The evidence from these experiments, together with our previous stimulation and lesion studies, indicates that ANP release in response to volume expansion is mediated by afferent baroreceptor input to the AV3V region, which mediates the increased ANP release via activation of the hypothalamic ANP neuronal system. Furthermore, we demonstrated that volume expansion could induce the release of AVP, OT, or ET, which may cause the release of ANP from atrial myocytes (19, 25).

Eskay et al. (137) carried out important experiments that also pointed to the neural control of ANP release. In conscious rats with chronic indwelling catheters, they showed that volume loading with isotonic saline or glucose increased the amount of circulating ANP by a factor of 4–5. Results obtained with the denervated heart preparation indicated that neuronal influences are important in the release of ANP induced by volume loading (137).

H. Efferent Pathways of the CNS and the Cardiac Release of ANP

Some of the ANP neurons from AV3V and PVN regions terminate in the median eminence and neural lobe of the hypophysis. Activation of these neurons leads to release of the peptide into the vasculature that drains the median eminence and the neural lobe, dilating the long and short portal vessels and thereby increasing portal blood flow. The ANPergic neurons may activate descending pathways, which then activate efferent pathways to the heart with consequent release of ANP from the cardiac myocytes. The efferent pathway to the heart may be completely neural; however, it cannot be cholinergic since bilateral section of the vagi does not block the ANP response to BVE. It is also unlikely that it is a sympathetic efferent pathway, since BVE elevates blood pressure and, therefore, diminishes sympathetic outflow. Alternatively, ANP neurons may stimulate release of other brain peptides from the neurohypophysis, such as endothelin (26), α-MSH, AVP, or OT, which in turn could stimulate ANP release from the atria. We have previously shown that median eminence lesions (25) or removal of the neural lobe of the pituitary decrease basal ANP release and block the ANP release induced by BVE. These results prompted us to investigate the role of neurohypophysial hormones in the secretion of ANP. Oxytocin was favored, since it is a more potent natriuretic peptide than AVP. Also, although median eminence lesions blocked the natriuretic response to third ventricle injections of hypertonic saline, this was not impaired in Brattleboro rats, which lack AVP but not OT (365). Furthermore, decreased blood volume secondary to hemorrhage stimulates AVP release via decreased baroreceptor input to the brain stem. For this reason, one would predict that BVE would not elevate, and perhaps would suppress, AVP release. Thus we hypothesized that hypothalamic ANP neurons would release OT, which triggers the release of ANP from the atria. Indeed, we found that isotonic BVE induced a concurrent OT and ANP release that was followed by natriuresis, providing evidence that BVE-induced ANP release was caused by release of OT, which stimulates ANP release that, in turn, induces natriuresis (206).

The role of OT in the natriuresis and ANP release induced by volume expansion was further investigated (206). In water-loaded rats undergoing diuresis, OT induced a significant, dose-related increase in sodium and potassium excretion, as well as in urine osmolality, and a decrease in urine volume. Plasma ANP concentration increased significantly after intraperitoneal or intravenous injection of OT, which induced the greatest natriuretic response. BVE by intra-atrial injections of isotonic saline induced a rapid increase in plasma OT and ANP and a concomitant decrease in plasma AVP concentration (206). When hypertonic volume expansion was performed by injection of 0.3 M NaCl, which should stimulate putative osmo- or sodium receptors, in addition to baroreceptors that were stimulated by isotonic BVE, there was an increase in both plasma ANP and OT similar to that produced by isotonic BVE. However, in contrast to isotonic volume expansion, the hypertonic volume expansion induced a significant, transient (5 min) increase in plasma AVP levels. The magnitude of the OT release after BVE was even greater than that which followed suckling in lactating rats, the classical stimulus for OT release. Moreover, the OT release by suckling was also associated with an increase in plasma ANP that was prevented by prior intravenous injection of an OT antagonist, which supports the hypothesis that the ANP-releasing action of OT is physiologically significant. On the other hand, AV3V injections of ANP antiserum did not change the basal OT levels but blocked the OT secretion induced by an osmotic stimulus. Thus we demonstrated that endogenous hypothalamic ANP is necessary to stimulate OT release in the hyperosmolality condition (82). Taken together, these results support the hypothesis that isotonic volume expansion by baroreceptor input to the brain stem stimulates intrahypothalamic ANP release, which causes release of OT from the neurohypophysis; this OT circulates to the heart to induce ANP release.

VI. INTERACTION BETWEEN NEUROHYPOPHYSIAL HORMONES AND ATRIAL NATRIURETIC PEPTIDE

A. Effects of Oxytocin on the Release of ANP From the Heart

The direct effect of OT on the heart was demonstrated in vitro showing a dose-related release of ANP from the right atrium, but not from the left atrium or ventricles (140). Indeed, OT was detected in the right atrium by radioimmunoassay (140). Further studies showed that OT not only is present but is also synthesized in the heart (247). OT, similar to ANP, also has inotropic and chronotropic effects on the heart, decreasing heart rate and force of contraction (Fig. 2). These effects can be mimicked by cGMP, the principal mediator of the actions of ANP, and cardiac effects of OT are mediated by ANP
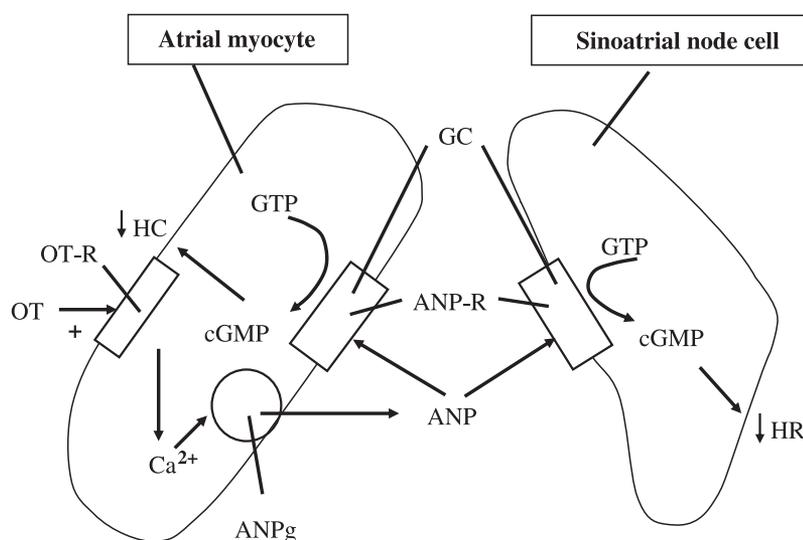
FIG. 2. Schematic diagram of the proposed mechanism of oxytocin-induced ANP release in the right atrium. For detailed description, see text. OT, oxytocin; OT-R, oxytocin receptor; ANPg, ANP secretory granule; ANP-R, ANP receptor; GC, guanylyl cyclase; HC, heart contraction; HR, heart rate; ↑, increase; ↓, decrease.

release (140). In the Langendorf perfused heart preparation, Gutkowska et al. (201) showed that OT had negative inotropic and chronotropic effects and that it released ANP from the rat heart; this action was blocked by an OT antagonist, resulting in positive inotropic and chronotropic effects.

Reinforcing the direct action of OT in the heart, OT receptors have been characterized in the rat heart, which appear to be identical to those in other organs. Binding affinity and the number of OT receptors were similar in atria and ventricles. In addition, the presence of specific transcripts for the OT receptor was demonstrated using PCR amplification of cDNA obtained from mRNA of both rat atria and ventricles. The presence of OT receptor transcripts was also shown by in situ hybridization in atrial and ventricular tissues (247, 249).

Because OT is produced and released by the heart and acts on its cardiac receptors to decrease heart rate and force of contraction, Jankowski et al. (248) hypothesized that OT might be generated in the vasculature and dilate vessels. Indeed, studies have shown that an intrinsic OT system sensitive to estrogenic regulation exists in the vasculature. OT binding density has been shown to be regulated by ovarian steroids, since estrogen at concentrations found in pregnancy increased the number of cardiac OT receptors (84, 370). Therefore, not only would OT reach the heart via the circulation to induce ANP release, but also OT produced in the heart may play a role in stimulating ANP release. It should be pointed out that other neuropeptides (ANG II, bradykinin, calcitonin gene-related peptide, enkephalin, NPY, SP, and VIP) have been reported to be involved in the regulation of cardiac function by intrinsic cardiac neurons (31).

All of the studies described so far have been conducted in animals, such as the rat and guinea pig. In the only study in humans, Weis et al. (545) reported that a bolus injection of OT (5–10 U) in young, healthy women undergoing elective termination of pregnancy decreased arterial blood pressure by 30% and total peripheral resistance by 50%. This was accompanied by increases in heart rate and stroke volume of 30 and 25%, respectively, which increased cardiac output by >50%. Thus, in pregnant women with elevated estrogen and progesterone levels and, possibly, increased OT receptors, OT appears to have a physiologically significant vasodilatatory effect. The increased heart rate and stroke volume presumably were reflexively induced by baroreceptors. It would be very interesting to perform similar studies in normal men and women to investigate the effect of OT on the cardiovascular and renal systems.

B. Effects of Vasopressin on Cardiac Function

A stimulatory role for AVP in ANP release at the atrial level has been demonstrated by the dose-related increases of plasma ANP levels induced by intravenous (242) or intracerebroventricular injections (131) of AVP in rats. In addition, pretreatment with an AVP V_1 receptor blocker significantly reduced the ANP secretion induced by isotonic blood volume expansion (0.5 ml/100 g body wt, 1 min) (131). AVP is known to be synthesized not only in the CNS but also in other, extraneural tissues, such as the heart and blood vessels (236). Evidence for a possible local influence of AVP on heart function has been provided by the dose-related coronary vasoconstriction and a positive inotropic effect of AVP in isolated hearts with retrograde perfusion of coronary arteries (540). Vasopressin mRNA has been detected in the endothelial cells and vascular smooth muscle cells of arterioles, and in perivascular tissue that could induce coronary vasoconstriction and impaired relaxation in the pressure-overloaded heart

(236). In addition, these authors also detected the induction of cardiac AVP mRNA in pressure-overloaded rat hearts, an effect that was markedly depressed by NOS blockade with L-NAME. These data suggest that in the heart stressed by acute pressure overload AVP is expressed at concentrations sufficient to cause local effects, and this expression is mediated by NO.

On the other hand, in isolated, spontaneously beating heart, intracoronary perfusion of AVP, acetylcholine, ANG II, and L-arginine significantly reduced ANP secretion with no concomitant changes in coronary flow and heart rate. AVP alone or in combination with L-arginine does not further affect ANP secretion. These results indicate that AVP inhibits ANP secretion in the isolated heart indirectly by increasing NO and suggest a role for NO as a negative modulator of ANP secretion (349). Thus the final effects of intravenously administered AVP, increasing ANP release (242, 131), probably occur indirectly, via an action on baroreceptors that counteracts the systemic pressor effect of AVP.

Finally, in humans, it is likely that AVP influences ANP secretion. Cogan et al. (86) have shown high plasma ANP levels in patients with the syndrome of inappropriate secretion of AVP, which is associated with persistent natriuresis. Furthermore, we have shown that patients with central diabetes insipidus present lower plasma ANP levels in basal and stimulated conditions compared with controls (129). These data strongly support the hypothesis of a neuroendocrine modulation of ANP secretion by AVP.

C. Actions of Oxytocin and Vasopressin in the Kidney

In response to plasma hyperosmolality, AVP and OT are secreted simultaneously (38, 498–500), resulting in natriuresis (173, 458). These effects can be explained by a direct action of both peptides on specific receptors already shown to be present in the kidney tubular cells (494, 525). In fact, some studies have suggested a synergistic effect of AVP and OT on natriuresis in rats (39, 494).

Oxytocin causes natriuresis by activation of renal NOS, which releases NO, followed by cGMP production that mediates the natriuresis. Indeed, although a decrease in NO production caused by L-NAME, an inhibitor of NOS, had no effect on the natriuresis induced by intravenous injection of ANP it almost completely inhibited OT-induced natriuresis, NO^{2-} and NO^{3-} excretion. However, at a high dose of OT that markedly increased plasma ANP concentrations, L-NAME only partly inhibited the natriuresis. These data suggest that the natriuretic effect of OT occurs through a dual mechanism: generation of NO leading to increased cGMP and, at higher doses, the release of ANP that, in turn, also increases cGMP. Oxytocin-induced

natriuresis occurs mainly through a cGMP-mediated decrease in tubular Na^+ reabsorption. In contrast to ANP, which increases cGMP in the renal vessels as well as in the tubules, OT acts through its receptors located in NOergic cells identified in the macula densa and proximal tubules, increasing cGMP production and closing Na^+ channels. Thus both ANP- and OT-induced natriuresis and kaliuresis appear to be mediated by cGMP (486) as shown in Figure 3.

Recently, the relative importance of neuronal NOS and inducible NOS in mediating the natriuresis elicited by low doses of OT was investigated. NO activates cyclooxygenase as well as guanylate cyclase leading to the production of prostaglandins, which appear to have an antinatriuretic effect, since blockade of cyclooxygenase by indomethacin increases basal natriuresis and also the natriuresis induced by OT.

Finally, OT given in doses to produce plasma OT levels similar to those that occur in response to hypotension or hypovolemia caused a significant increase in plasma renin activity that was not secondary to the natriuretic action of OT. This finding raises the possibility that OT secretion during hypotension or hypovolemia in rats may serve to support blood pressure by enhancing activation of the RAS via a β-adrenergic receptor-dependent mechanism (234).

VII. CONCLUSIONS AND PERSPECTIVES

During the last two decades, since the discovery of ANP by de Bold et al. (104), a large number of publications have demonstrated that natriuretic peptides play an important homeostatic role in preserving cardiovascular function and body fluid balance. ANP is one of a family of natriuretic peptides that contains at least three other members, brain natriuretic peptide, C-type natriuretic peptide, and urodilatin, encoded by different independent genes. These peptides provide all mammals with a potent defense mechanism against volume overload. ANP is mostly localized in the heart, but ANP and its type A receptor are also localized in hypothalamic and brain stem areas involved in body fluid volume and blood pressure regulation. Most, if not all, of the actions of ANP are mediated by activation of a specific guanylate cyclase that generates cGMP from GTP; cGMP acts in the brain, as in the periphery, through activation of PKG (35, 44, 57, 164, 167, 193, 246, 319, 348, 383, 395, 466, 467, 505, 506).

The earlier hypothesis was that volume expansion acts directly on the heart by stretch of atrial myocytes to increase the release of ANP leading to a reduction in the effective circulating blood volume. However, there is compelling evidence that hypothalamic ANP is also released during volume expansion through afferent inputs from baroreceptors to the brain. This review emphasizes
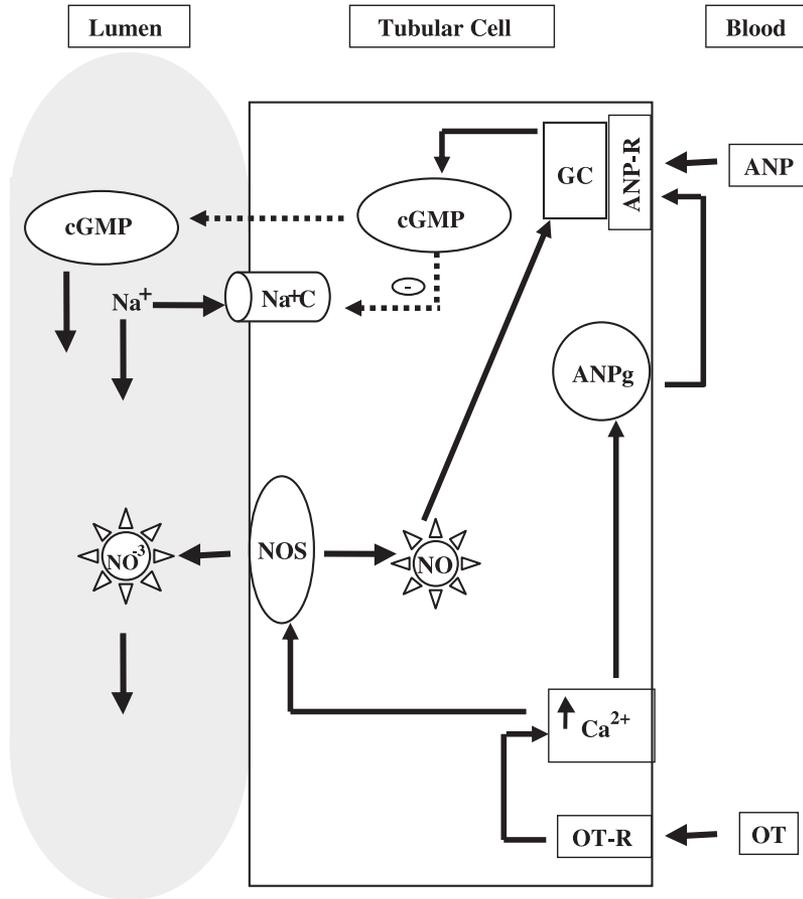
FIG. 3. Schematic diagram indicating the mechanism for action of atrial natriuretic peptide (ANP), oxytocin (OT), and nitric oxide (NO) in induction of natriuresis. After volume expansion, ANP is secreted by the heart and probably the vascular system. It acts on its membrane receptor coupled to guanylyl cyclase (GC) on the renal tubular cell to produce cGMP. OT is also released in response to volume expansion, circulates to the kidney, and acts upon OT receptors in the tubular cell to increase intracellular free calcium that activates release of ANP from putative storage granules in the tubular cell. This ANP acts in a positive auto-feedback loop to further stimulate GC and augment cGMP production. The OT also acts on its receptors to increase intracellular calcium that combines with calmodulin to activate nitric oxide synthase (NOS). The NO released intracellularly activates guanylyl cyclase causing further production of cGMP. The cGMP acts to close sodium channels reducing the reabsorption of sodium, thereby producing natriuresis. NO diffuses into the lumen and is metabolized to NO^{2-} and NO^{3-}. NO^{3-} and cGMP are excreted in the urine together with sodium. Potassium excretion is reduced by a similar mechanism in response to ANP and OT.

the role played by the brain ANP and its interaction with neurohypophysial hormones, particularly OT, in the control of body fluid homeostasis. ANP released from the neurohypophysis would play only a minor role, if any, in mediating natriuresis after volume expansion, since the quantity of ANP stored in the hypothalamus and neurohypophysis is 1,000-fold lower than that stored in the heart. Indeed, the ANP in the heart plays a major role in reducing the increase in effective circulating blood volume in response to volume expansion by a direct action in the heart. ANP decreases the force and frequency of heart contraction and dilates the peripheral vessels, as well as inducing a natriuresis that, coupled with reduced intake of water and salt, provides the final adjustment of body fluid volume.

Extensive studies have demonstrated that volume expansion distends the baroreceptors in the right atrium, carotid and aortic sinuses, and in the kidney, thereby increasing their afferent input to the NTS (410). Neurons in the NTS project to the locus ceruleus and, probably, to other noradrenergic neuronal nuclei in the brain stem whose axons project to cholinergic interneurons in the

hypothalamus and activate these via α-adrenergic receptors. These cholinergic interneurons, in turn, activate the hypothalamic ANPergic neurons through muscarinic receptors. The ANPergic neurons act on the perikarya of oxytocinergic neurons of the SON and PVN to stimulate the release of OT from the neurohypophysis. In support of this hypothesis, isotonic volume expansion was accompanied by increased plasma OT and ANP concentrations, but with a decrease in plasma AVP. Therefore, natriuresis following isotonic volume expansion is mediated by OT and ANP, but not by AVP (19, 364).

Oxytocin evokes ANP release through specific OT receptors present in all chambers of the heart as well as in the great vessels. It is important to point out that OT is also synthesized and released from the heart and great vessels, suggesting a possible role of locally produced OT. Consequently, the accumulated data strongly support the hypothesis that OT released by volume expansion not only circulates to the heart to release ANP, but also OT produced in the heart and in the vessels may also play a role in stimulating ANP release. The activation of guanylate cyclase and generation of cGMP mediate the action of

OT and ANP in the brain, cardiovascular system, and kidney. Therefore, cGMP is the common mediator of vascular relaxation, negative inotropic and chronotropic effects in the heart, as well as natriuresis and inhibition of water and salt intake (140, 247–249, 486).

NO activates soluble guanylate cyclase that synthesizes cGMP, which mediates many of the physiological actions of NO. NO produced within the central nervous system maintains resting arterial blood pressure partially by attenuating the pressor actions of ANG II and prostaglandins. The central production of NO is enhanced during osmotic stimulation to counterbalance the salt-induced pressor response. NO has been proposed as a local modulator of magnocellular neuron activity, and the presence of nNOS in the PVN and SON vasopressinergic and oxytocinergic neurons, together with its increase in these neurons by osmotic stimulation or dehydration, suggests a role for NO in the regulation of AVP and OT (61, 263, 527, 538). Although such a role is still not clearly defined, recent data have shown that NO tonically inhibits the basal release of AVP and OT and that the NO inhibition of AVP secretion is removed during water deprivation, hypovolemia, moderate osmotic stimulation, and after injection of ANG II, while its inhibition of OT secretion is enhanced (260–262, 310). The natriuretic effect of OT occurs through a dual mechanism: generation of NO leading to increased cGMP and, at higher doses, the release of ANP that, in turn, also increases cGMP (486).

Vasopressin also has a modulatory role in ANP release probably through an indirect action on baroreceptors to counteract the systemic pressor effect of AVP. In conditions that lead to a decrease in effective circulating blood volume, such as dehydration or hemorrhage, there is an increase in AVP and a decrease in ANP release that induce an increase in sodium and water intake, peripheral vasoconstriction, antidiuresis, and antinatriuresis, which would lead to a return of body fluid volume to normal (131, 242).

Angiotensin II also plays an important role in the regulation of body fluids. ANG II is a potent inducer of thirst and, in general, it antagonizes the actions of ANP. ANG II is also a powerful vasoconstrictor and has actions on the kidney that oppose those of OT and ANP. In dehydration or decreased blood volume conditions, renin is released from the juxtaglomerular apparatus leading to the formation of ANG II by ACE. Conversely, volume expansion inhibits ANG II release, which removes the dipsogenic stimulus and decreases salt intake (111, 126, 153, 180–182, 254, 257, 317, 335, 338, 340, 344, 346, 547, 549).

Because the quantity of ANP stored in the hypothalamus and pituitary is small, we hypothesize that the activation of hypothalamic ANP neurons might stimulate the release of another peptide with natriuretic activity from the neurohypophysis. The evidence indicates that this peptide is OT, which circulates to the heart and activates ANP release through binding to its receptors in the atria and other cardiac chambers and also in the vessels. Consequently, ANP released by OT would, in turn, circulate to the kidneys inducing natriuresis. In support of the hypothesis that ANP released intrahypothalamically causes the release of OT, microinjection of antiserum against ANP into the AV3V region decreased the natriuresis in response to volume expansion (19, 24, 25, 78, 137, 206, 365, 366) (Fig. 1).

In addition to the well-known natriuretic peptides, hormones, and neurotransmitters, new evidence has emerged for the participation of many other peptides, including bradykinin, other natriuretic peptides, and other brain polypeptides in the control of salt and water metabolism. In addition to the preceding considerations, brain activation studies using positron emission tomography blood-flow procedures have identified those regions sensitive to changes in plasma osmolality and involved in the sensation of thirst (109). Thus the important work of the future is to further define the physiological and molecular mechanisms that contribute to the regulation of hydromineral homeostasis.

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