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Neurohypophyseal Hormones and Atrial Natriuretic Peptide in the Control of Body Fluid Homeostasis

Contents

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Abstract

Mammals control the volume and osmolality of their body fluids by 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 central nervous system responsible for an integrative 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. In addition, the paraventricular, supraoptic and suprachiasmatic nuclei are also important structures involved in hydromineral balance. The hypothalamo-neurohypophyseal system plays a fundamental role in the maintenance of body fluid homeostasis by secreting vasopressin and oxytocin in response to osmotic and non-osmotic stimuli. The natriuretic factor in the heart, which is released by the distension of the atria, leading to natriuresis and a myorelaxing action on vascular smooth muscle, also contributes to the hydromineral balance. In addition to the natriuretic factor in the heart, the identification of a natriuretic factor in the central nervous system mediating natriuresis was also demonstrated by purification of hypothalamic extracts. Therefore, the presence of the natriuretic factor in the heart and in the central nervous system allowed the characterization of a neuroendocrine system controlling body fluid homeostasis.

Key words: body fluid homeostasis, vasopressin, oxytocin, atrial natriuretic peptide, central nervous system, heart, and natriuresis.

Introduction

The maintenance of plasma osmolality and extracellular volume is regulated by water and electrolyte ingestion and their urinary excretion. Vertebrates have developed a special sensation, thirst, which is mostly stimulated by an increase in plasma osmolality. In mammals, an increase in plasma osmolality up to 1% or 2% is able to induce thirst. In addition, a 10% reduction in blood volume or in arterial pressure is also capable to generate thirst. The presence of sodium sensors located in the brain regions within the blood-brain barrier has been postulated to be involved in the control of sodium appetite in response to changes in brain extracellular fluid sodium concentration (Andersson & McCann, 1955, 1956; Andersson et al., 1966; Andersson, 1972, 1977).

The participation of osmoreceptor-Na^+-receptor cells located in the circumventricular organs of the anteroventral portion of the third ventricle (AV3V) and the subfornical organ (SFO) are important structures for the genesis of thirst (Andersson & McCann, 1956; Brody & Johnson, 1980). The presence of sodium receptors has been also demonstrated in the hepato-renal and hepato-intestinal regions. These receptors are activated by a sodium increase in the portal vein, augmenting the hepatic afferent nerve activity. These afferent inputs are conveyed to

the nucleus tractus solitarii (NTS) and efferent signals increase renal sodium excretion and concomitantly decrease intestinal sodium absorption (Hosomi & Morita, 1996). The information from the osmoreceptors is conveyed to specific areas of the central nervous system (CNS) responsible for an integrative response, which depends on the integrity of the AV3V, organum vasculosum of the lamina terminalis (OVLT), median preoptic nucleus (MnPO), and SFO. In addition, the paraventricular (PVN), supraoptic (SON) and suprachiasmatic nuclei are also 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 arginine vasopressin (AVP) and oxytocin (OT) from the neurohypophysis and natriuretic peptides from the heart. In addition, a decrease in extracellular volume induces thirst, which is mediated by angiotensin-II (ANG II), acting as a neurotransmitter on ANG II-sensitive brain regions, also involving the SFO and AV3V. Activation of baroreceptors located on the walls of large vessels and in the cardiac atrium also participates in the control of thirst mechanisms (Fig. 1).

The amount of water ingested should be enough to correct plasma osmolality; however, satiation of thirst occurs within the first 3-10 minutes after water ingestion, even before plasma osmolality normalization. This may be due to stimuli originating from the mouth and pharynx, or to neural inputs from the gastric

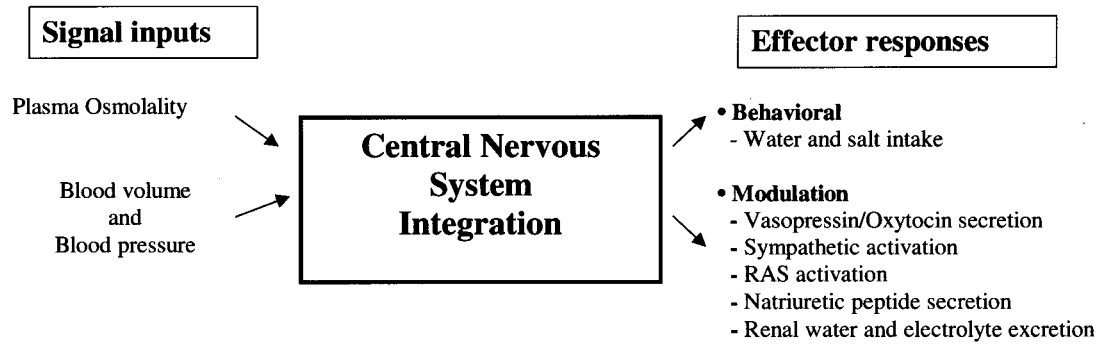

Figure 1. Schematic representation of the afferent and efferent pathways involved in the neuroendocrine control of body fluid homeostasis. RAS: renin-angiotensin-system.

region conveyed through afferent impulses to CNS structures involved in the integrative response. During the last four decades a series of experiments were designed to identify brain areas specifically involved in satiety, regulation of plasma osmolality, and water/electrolyte ingestion or excretion. The first studies using CNS manipulations to understand the synaptic transmitters involved in the control of body fluid homeostasis were performed in the sixties by several authors (Grossman, 1960; Grossman, 1969; Antunes-Rodrigues & McCann, 1970; Fitzsimons & Stricker, 1971). These studies demonstrated that cholinergic, noradrenergic or angiotensinergic stimulation of the hypothalamus induces an increase in water or food intake, as well

as changes in natriuresis, kaliuresis and antidiuresis in normally hydrated animals (Dorn & Porter, 1970; Dorn et al., 1970; Morris et al., 1976, 1977; Saad et al., 1976; Camargo et al., 1976, 1979; Franci et al., 1980, 1983; Rocha et al., 1985, 1999).

In the control of body fluid metabolism the kidney also plays a crucial role through water and electrolyte excretion. The kidney innervation, predominantly sympathetic, plays a major role in the control of renal blood flow, tubular reabsorption of electrolytes, and renin secretion rate (DiBona, 2000). The presence of a polysynaptic pathway connecting neurons from the brain areas involved in the body fluid control to the kidney has also been suggested (Sly et al., 1999). In 1981, De Bold and his group (De Bold et al., 1981) characterized the presence of atrial natriuretic peptide (ANP), which is released by the distension of the atria leading to natriuresis. The objective of this review is to describe the role of the brain neural circuit and the involvement of the ANP and the neurohypophyseal hormones (OT and AVP) in hydromineral balance.

The Brain Neural Circuit and the Hydromineral Balance

In 1935, Fisher et al. called attention to the role of the hypothalamus in the regulation of water metabolism. Many other groups have studied the effects induced by chemical or electrical stimulation of different areas in the CNS involved in the control of hydromineral balance. From the work of Andersson and McCann (1955, 1956) and Andersson et al. (1966) it became clear that the hypothalamus is very important in the control of water and electrolyte metabolism. Thus, in the early fifties, Andersson and McCann (1955) showed that microinjection of hypertonic saline into the hypothalamus of goats could induce drinking. Electrical stimulation of the hypothalamus also induced drinking, in addition to antidiuresis and milk ejection (Andersson, 1977).

In the early sixties, Covian and his associates in Brazil and McCann in USA independently published their data on the role of the CNS in the control of salt intake. Systematic studies were undertaken to determine the effects of bilateral 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 seems to involve the septal area, particularly the AV3V, amygdaloid complex, hypothalamus, and olfactory bulbs. Lesions of the anterior hypothalamus, involving both PVN, caused a decrease in the intake of saline solution, while lesions in the anterior lateral hypothalamus caused an increase in saline intake (Covian & Antunes-Rodrigues, 1963). Lesions of the septal area, olfactory bulbs, and the corticomedial region of the amygdala increased sodium intake while lesions of the basolateral region decreased it. Electrical stimulation of the septal area and amygdala induced an opposite effect

on sodium intake. Interaction studies provided evidence that the hypothalamus is the principal structure in the circuit regulating saline ingestion/excretion and the septal area, olfactory bulb and amygdala have modulatory influences on its activity (Chiaraviglio, 1969; Covian et al., 1975). Several other laboratories have also made important contributions to the elucidation of role played by the CNS in the control of body fluid homeostasis (Andersson, 1977; Brody & Johnson, 1980; Dorn & Porter, 1970; Franci et al., 1980, 1983; Malnic et al., 1979; Silva-Netto et al., 1980, 1986; Johnson & Epstein, 1975; Epstein & Sakai, 1986; Johnson & Thunhorst, 1997; Fitzsimons, 1998).

Regulation of ANP Secretion

Natriuretic Peptides and Hydromineral Balance

Henry et al. (1956) described the first evidence for the participation of the atria in the control of urine excretion. Independently, Kisch (1956) reported the detection of secretory granules in the guinea pig heart atrium by electron microscopy, which was confirmed by other laboratories (Bompiani et al., 1959; Palade, 1961; Jamieson & Palade, 1964; McNutt & Fawcett, 1969; Forssmann & Girardier, 1970; Berger et al., 1972; Forssmann et al., 1998). Gauer and Henry, in 1963, showed that dilation of the atria induced diuresis, and later Davis and Freeman (1976) obtained evidence for the existence of a circulating natriuretic factor in volume-expanded dogs by cross-circulation experiments. Thereafter, in 1981, De Bold and his group (De Bold et al., 1981) characterized the presence of ANP, which is released by the distension of the atria, leading to natriuresis. In addition to the effect on natriuresis, the atrial extracts have also been demonstrated to have a myorelaxing action on vascular smooth muscle (Deth et al., 1982; Currie et al., 1983; Forssmann et al., 1983; Forssmann, 1986).

In addition to the natriuretic factor in the heart, the presence of a natriuretic factor in the CNS mediating natriuresis was also demonstrated by purification of hypothalamic extracts by Cort and co-workers (1969). Simultaneously, Orias and McCann (1970; 1972) demonstrated that AVP, OT, alpha-MSH and median eminence extracts also have natriuretic effects. The pretreatment of the median eminence extract with thioglycollate, an agent which opens the disulfide bridge of the neurohypophyseal hormones, did not inactivate the natriuretic activity, suggesting that neither AVP nor OT alone was the hypothalamic factor with natriuretic activity. Therefore, the diuresis induced by the distension of the atria could be due to a reflex activation of the neuroendocrine system, resulting in ANP release from myocardial cells (De Bold et al., 1981). These findings permitted the identification and characterization of hormones of the natriuretic peptide family, which are involved in

the control of body fluid homeostasis (Flynn et al., 1983; Forssmannn et al., 1983, 1984; Kangawa & Matsuo, 1984; Sudoh et al., 1988[a,b], 1989, 1990; Brenner et al., 1990).

The prototype of the natriuretic hormone is the circulating peptide containing 28 amino acids (ANP 99-126 aa) (Flynn et al., 1983), which is processed from the atrial prohormone (1-126 aa). The mRNA expression of a family of natriuretic peptides (Atlas et al., 1984; Oikawa et al., 1984; Seidman et al., 1984[a]) and the gene structure of human ANP were later described (Greenberg et al., 1984; Seidman et al., 1984[b]). Other members of the natriuretic peptide family are brain natriuretic peptide (BNP), C-type natriuretic peptide (CNP) (Sudoh et al., 1988[a,b]; 1990) and urodilatin. The latter, a natriuretic peptide of kidney origin described by Forssmann's group (Schulz-Knappe et al., 1988), is synthesized in the distal tubules to exert a diuretic and natriuretic paracrine action on the tubular cells of the kidney (Forssmann et al., 1994; Feller et al., 1991; Forssmann, 1995; Meyer et al., 1996). Studies have shown that acute volume load (Drummer et al., 1991, 1993), dilatation of the left atrium (Goetz, 1990), or increase of the blood sodium in the carotid artery (Emmeluth et al., 1992) induced an increase in the concomitant excretion of sodium and urodilatin (Feller et al., 1991).

The natriuretic peptides act on the cell membrane through three types of receptors (NPR-A, NPR-B and NPR-C). NPR-A and NPR-B, different from NPR-C, have an intracellular guanylyl cyclase domain. On the other hand, NPR-C has a clearance receptor function (Maack et al., 1987; Maack, 1992). All these receptors have been cloned by several authors (Chinkers et al., 1989; Lowe et al., 1989; Chang et al., 1989; Schulz et al., 1989). The distribution of NPR-A, analyzed by RT-PCR, indicates the presence of receptors through all layers of the kidney. Since ANP activates these receptors, it induces an increase in the intracellular 3', 5'-cyclic guanosine monophosphate (cGMP) concentrations in the kidney as well as in other target cells, inducing natriuresis and kaliuresis.

The Brain ANPergic Neurons in Water and Salt Intake

Fundamental sensory information received by the CNS, its organization, and its chemical pathways have been demonstrated by techniques such as ablation, electric stimulation, metabolic activation and expression of immediate early genes (e.g. c-fos), which have provided extensive information related to intra- and extracellular volume and arterial blood pressure control. The CNS neurons related to the hydromineral balance are activated or inhibited mainly by osmotic and blood volume/pressure stimuli which are regulated by several neurotransmitters. Studies using immunocytochemistry, radioimmunoassay and radioreceptor techniques have demonstrated the presence of ANP-secreting neurons and ANP receptors in structures

of the CNS related to the control of water, electrolytes and blood pressure (Quirion et al., 1984, 1986, 1988; Zamir et al., 1986; Palkovits et al., 1987).

Injection of ANP into the AV3V region induces a dose-related blockade of water ingestion after overnight dehydration and ANG II-induced drinking (Antunes-Rodrigues et al., 1985; Masoto & Negro-Vilar, 1985; Tarjan et al., 1988; Imura et al., 1992; Itoh et al., 1988). In addition, ANP injected into the AV3V also inhibits saline intake in conscious salt-depleted rats (Antunes-Rodrigues et al., 1986). Therefore, it appears that ANP can definitely suppress salt intake as well as water intake provoked by dehydration or ANG II. Angiotensin II plays an important role in dehydration-induced drinking, either reaching the brain from the systemic circulation via circumventricular organs, or more likely being released from neurons containing ANG II within the hypothalamus, in close association with ANP neurons. (Franci et al., 1989, 1990, 1992). ANP might exert its antidipsogenic effect by acting directly on 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 (Hattori et al., 1988; Buranarugsa & Hubbard, 1988; Ehrlich & Fitts, 1990; McKinley et al., 1998).

The opposite actions of ANG II and ANP on water and salt intake and excretion may be mediated by alpha-adrenergic agonists known to release ANP and to antagonize ANG II-induced drinking. Previous injection of phenylephrine [an alpha(1)-adrenergic agonist] or clonidine [an alpha(2)-adrenergic agonist] into the AV3V region significantly reduced ANG II-induced water intake and also significantly increased plasma ANP concentration and ANP content in several brain structures, such as olfactory bulb, AV3V, medial basal hypothalamus and median eminence (Bastos et al., 2001). The inhibitory effect of alpha-adrenergic agonists on ANG II-induced water intake can be partially explained by the increase in ANP content and presumed release from those neural structures.

The muscarinic cholinergic receptor blocker, atropine sulfate, microinjected into the AV3V region has no effect on resting plasma ANP levels, but significantly decreases the ANP release induced by extracellular volume expansion (EVE). Similar results were observed after microinjection of the alpha adrenergic receptor blocker, phentolamine, into the AV3V region (Antunes-Rodrigues et al., 1993[a]). These results are consistent with a hypothetical pathway for physiological control of ANP release involving distension of baroreceptors within the right atria, carotid, aortic sinuses, and kidney. The baroreceptor distension alters afferent input to the brain stem noradrenergic neurons whose axons project to the AV3V region.

Recently, Puyó et al. (2000) presented data suggesting the existence of a negative feedback mechanism that regulates cardiac ANP release mediated by cen-

tral ANP and CNP localized in brain areas related to the control of body fluid metabolism and cardiovascular function. CNP applied into the AV3V region decreased EVE-induced ANP release. In contrast, centrally applied ANP did not induce changes in circulating basal and blood volume expanded ANP release. However, injection of an antiserum against ANP into the third ventricle prior to EVE has no effect on resting levels of ANP but partially blocks the increase in plasma ANP and natriuresis induced by EVE (Charles et al., 1991; Antunes-Rodrigues et al., 1993[b]). According to this putative negative feedback mechanism that regulates cardiac ANP release, we have demonstrated that intracerebroventricular (icv) ANP injection induces decreased natriuresis in water-loaded rats and also blocks the cholinergic-induced natriuresis (Elias et al., 2001).

Akamatsu et al. (1993) evaluated the effects of ANP on electrical activity and cellular cGMP levels in neurons of the SON of rat hypothalamic slices. The application of ANP or BNP into the SON decreased the firing rate and hyperpolarized the membrane potential in phasically firing AVP neurons. These data indicated that the osmotic stimulus induced ANP/BNP secretion in the hypothalamus, which interacted with AVP/OT neurons, modulating their hormonal secretion. In rats, ANP inhibited the release of both hormones in response to hypovolemia, dehydration (Samson, 1985) and hypertonicity (Poole et al., 1987). Interestingly, applications of ANP over the SON did not affect depolarizing responses to local hypertonicity, but abolished the synaptic excitation of magnocellular neurons after hypertonic stimulation of the OVLT. It has been described that the magnocellular cells of the SON have an intrinsic osmosensitivity. In addition, these cells receive afferents from the OVLT where the osmoreceptor neurons are located. Richard and Bourque (1996) showed that centrally released ANP might inhibit osmotically evoked neurohypophyseal hormone release. This effect occurs by presynaptic inhibition of glutamate release due to osmoreceptor afferent activation in the OVLT.

The Role of the Brain in ANP Release in Response to Acute Extracelular Volume Expansion

EVE causes the release of ANP that is important to induce subsequent natriuresis and diuresis, which, in turn, reduce the increase in blood volume. Cholinergic and osmotic stimulation of the AV3V region induced a rapid elevation of plasma ANP with concomitant natriuresis. Lesions of the AV3V, median eminence and neural lobe markedly decrease the basal plasma ANP concentration and natriuresis. In addition, EVE induced by intra-atrial injection of hypertonic saline (0.3M NaCl), isotonic saline or 5% glucose determined a rapid increase in plasma ANP concentration which was blocked by lesions of the AV3V, median eminence, neurohypophysis or by hypophysectomy (Antunes-Rodrigues et al., 1991). These results strongly support the idea that brain ANP (or another peptide) plays an

important role in the mediation of the systemic release of ANP under basal conditions as well as after volume expansion.

The mechanisms involving brain structures in EVE-induced ANP release could be mediated by baroreceptor activation, triggered by stretch, may activate the brain ANP neurons, releasing ANP into the circulation with consequent natriuresis. Deafferentation of the carotid-aortic baroreceptors decreases basal and EVE-induced plasma ANP concentrations, confirming the baroreceptor participation in the ANP release induced by volume expansion (Antunes-Rodrigues et al., 1992). Results obtained with the denervated heart preparation indicate that neuronal influences are important in the release of ANP induced by volume loading (Eskay et al., 1986). Rats submitted to unilateral right vagotomy show reduced resting levels of plasma ANP, but a preserved response to EVE. On the other hand, bilateral vagotomy did not change resting ANP concentration or its response to EVE. These data indicate that the afferent impulses via right vagus nerve may be important under basal conditions, but are not required for the ANP release induced by EVE. However, baroreceptor impulses from the carotid-aortic sinus regions and the kidney are important pathways involved in the neuroendocrine control of ANP release (Morris & Alexander, 1988; Antunes-Rodrigues et al., 1992). The evidences from these experiments, in addition to our previous studies, indicate that the 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. Thereafter, volume expansion has been shown to induce the release of other neurohypophyseal hormones such as AVP, OT or endothelins, which in turn induce release of ANP from the atrial myocytes (Antunes-Rodrigues et al., 1991, 1992).

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 has been well established. Changes in blood volume provoke distension of baroreceptors in the right atriun, carotid and aortic sinuses and in the kidney, which alters their afferent input to the NTS. Impulses from this structure may be relayed and activate the locus coeruleus (LC) and raphe nuclei, as demonstrated by studies showing that lesions of both structures lowered resting and EVE-induced plasma ANP levels (Reis et al., 1991, 1994). The anterior region of the LC may be part of an inhibitory pathway, which modulates the circuits controlling the depressor reflex response and ANP secretion after EVE (Anselmo-Franci et al., 1999). The axons of noradrenergic neurons located in the LC project to the AV3V region activating the cholinergic interneurons, which in turn stimulate the hypothalamic ANPergic neurons. These neurons may activate efferent neurohumoral or neuronal pathways, inducing the release of ANP from the brain and the atria.

An afferent pathway to the AV3V region via serotonergic neurons with

cell bodies in the raphe nuclei has been demonstrated (Bosler & Descarries, 1987). Early studies had shown that injection of serotonin (5-HT) agonists into the third or lateral ventricles could increase plasma ANP, an event that was prevented by 5-HT2 receptor blockers (Stein et al., 1987; Reis et al., 1991). Bilateral lesions placed in the dorsal raphe nuclei (DRN), a major source of 5-HT neurons that project to the AV3V region, induced an increase of water intake and urine output with a concomitant sodium retention and reduction of basal as well as EVE-induced plasma ANP levels (Reis et al., 1991, 1994). These results suggested that ascending stimulatory serotoninergic input into the ANP neuronal system in the AV3V region produces a tonic stimulation of ANP release, which augments sodium excretion and inhibits water intake. Therefore, the raphe nuclei may be stimulated by afferent input from the baroreceptors via NTS and may contribute to the stimulation of ANP release following EVE (Reis et al., 1994; for review see Gutkowska et al., 1997[a]).

Efferent Pathways of the CNS and the Cardiac Release of ANP

Some of the ANP neurons in the CNS terminate in the median eminence and neural lobe of the hypophysis and their activation may lead to the release of ANP into the vasculature draining these regions. Since the quantity of the peptide is much smaller in these brain structures than in the atria (Baldissera et al., 1989), ANP released from the brain plays a minor role compared to the circulating ANP. These 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 might be completely neural; however, it cannot be cholinergic since bilateral section of both vagi does not block the response to EVE. It is also unlikely that it is a sympathetic efferent pathway, since EVE elevates blood pressure and, therefore, diminishes sympathetic outflow. Alternatively, ANP neurons may stimulate release of other brain peptides from the neurohypophysis such as AVP, OT, endothelin, or alpha-MSH (Antunes-Rodrigues et al.,1993[c]) which could stimulate ANP release from the atria. Both AVP and OT are stored in large amounts in the neural lobe of the pituitary and they are the prime candidates to be released into the venous drainage of the neurohypophysis by EVE.

Decrease in blood volume secondary to hemorrhage stimulates AVP release via baroreceptor input to the brainstem. Thus, one may predict that EVE would not elevate, and perhaps would suppress, AVP release. Therefore, it is possible that hypothalamic ANP neurons cause release of OT, which triggers the release of ANP from the atria. In accordance with this possibility, it has been recently shown that ANP immunoneutralization did not change the basal OT levels, but blocked the OT secretion induced by an osmotic stimulus, indicating that the endogenous hypothalamic ANP seems to be necessary to stimulate OT release in the hyperosmolality condition (Chriguer et al., 2001).

It has been found that EVE induced concurrent OT and ANP release, which was followed by natriuresis. The magnitude of the OT release following EVE was even greater than that induced by 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 injection of an OT antagonist, supporting the hypothesis that the ANP-releasing action of the OT is physiologically relevant. Hence, EVE-induced ANP release and natriuresis might be modulated by release of OT, which stimulates ANP release that, in turn, induces natriuresis. On this basis, injection of OT significantly increased plasma ANP concentration, indicating the role of OT on ANP secretion (Haanwinckel et al., 1995).

Neurohypophyseal Hormones and Water Metabolism

The Hypothalamo-neurohypophyseal System

The neurohypophysis receives axons from a set of hypothalamic nuclei, namely the SON and the PVN which house the perikarya of the magnocellular neurons responsible for synthesis of OT and AVP which form the hypothalamo-hypophyseal tract that terminate in the posterior lobe of the pituitary. OT and AVP are synthesized and released by magnocellular neurosecretory neurons classified into vasopressin- and oxytocin- producing subtypes. The axons of these neurons pass caudally through the internal layer of the median eminence to terminate in the neural lobe of the posterior pituitary where the polypeptides are secreted into the capillaries (Brownstein et al., 1980; Renaud & Bourque, 1991; Armstrong, 1995; Hatton, 1997). AVP is also produced in parvocellular neurons of the PVN and secreted into pituitary portal capillaries from axon terminals in the external layer of the median eminence (Antoni, 1993). AVP of parvocellular origin is involved in the regulation of the pituitary adrenocorticotropic hormone secretion. Recent evidence using qualitative RT-PCR experiments on single cells has confirmed the fact that the majority of magnocellular neurons co-express both peptide mRNAs.

The release of AVP from the neurohypophysis is regulated by perypheral baroreceptors and cardiopulmonary volume receptors (Share, 1988; Renauld, 1996). Magnocellular AVP neurons in the hypothalamus exhibit phasic electrical activity that depends on intrinsic membrane properties and is controlled by extrinsic factors such as plasma osmolarity, blood volume and pressure (Armstrong, 1995), and also by AVP itself. A selective afferent neural input to magnocellular neurons provides a mechanism for the release of AVP independently of OT in response to appropriate physiological stimuli. Release of AVP is controlled by changes in plasma osmolality (osmotic control) and in blood volume or pressure (volume control) while OT release is predominantly regulated by afferent impulses generated by uterine contraction in the case of parturition and suckling during lactation.

Osmotic Control of Vasopressin Release

The hypothalamo-neurohypophyseal system plays a fundamental role in the maintenance of body fluid homeostasis by secreting AVP and OT in response to osmotic and nonosmotic stimuli (Schrier et al., 1979). The first description that microinjections of hypertonic saline into AV3V area, the major central site in the regulation of body fluid, cardiovascular and renal function, induced increased water intake was reported by Andersson and McCann (1955, 1956), Andersson (1977), and Andersson et al. (1966) in goats. Antunes-Rodrigues and McCann (1970) and Dorn and Porter (1970) confirmed these results in rats. In addition, lesions of the AV3V cause: 1) adipsia and hypernatremia (Andersson & McCann, 1956; Andersson et al., 1966), 2) impaired drinking responses and AVP secretion in response to hypertonic saline and ANG II (Knepel et al., 1982), 3) impaired recovery of arterial pressure with hypertonic saline in rats submitted to hemorrhagic shock (Barbosa et al., 1992), 4) decreased osmotic- and volume-induced ANP release (Rauch et al., 1990; Antunes-Rodrigues et al.,1991), 5) decrease of the number of Fos-like immunoreactive neurons in the MnPO, PVN and SON in response to intravenous infusion of hypertonic saline (Hochstenbach & Ciriello, 1995), and 6) interruption of neuronal inputs that trigger AVP secretion from the posterior pituitary as well as AVP release into the extracellular compartment of the SON (Ludwig et al., 1996).

Other lines of evidence have indicated that, besides AV3V, other structures such as SFO, medial septal area, anterior lateral hypothalamus, SON, PVN, medial habenula and stria medullaris are organized in a neural circuit involved in the regulation of water/sodium intake and excretion (Covian et al., 1975; Franci et al., 1980, 1983; Rocha et al., 1985). Immunoreactive ANP-positive cell bodies were observed in the OVLT, in hypothalamic nuclei including the PVN, periventricular, arcuate, and ventral premammillary nuclei, in the dorsolateral tegmental nuclei of the pons, and median preoptic nucleus (Jacobowitz et al., 1985; Kawata et al., 1985[a]; 1985[b], Morii et al., 1985; Zamir et al., 1986), 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 (Ma et al., 1991). C-fos expression after osmotic stimulation has been observed in most magnocellular cells, within the SFO, dorsal portion of the MnPO and in the OVLT (Oldfield et al., 1994; Luckman, 1997). In addition, lesions of the SFO, the AV3V or both resulted in a decreased number of Fos-like immunoreactive neurons in the MnPO, PVN and SON in response to an osmotic stimulus (Hochstenbach & Ciriello, 1996). Therefore, the osmoresponsive neurons in OVLT, by virtue of their response to infusions of hypertonic saline and their axonal connections to regions of the hypothalamus responsible for AVP production, are likely candidates for cerebral osmoreceptors (Anderson et al., 1990; McKinley et al., 1992; Oldfiled et al., 1994).

The most important physiological osmotic regulation of AVP release takes place in the CNS, within regions that include the MnPO, OVLT, SFO, and SON, although peripheral osmoreceptors in the liver, mouth and stomach have been suggested to detect the early osmotic impact of foods and fluid intake (Hosomi & Morita, 1996; Bisset & Chowdrey, 1988). Osmoreceptors are highly specialized neurons capable of transducing changes in external osmotic pressure into electrical signals activated by the release of synaptic transmitters in CNS areas involved in control of water and salt intake and output. Patch-clamp studies demonstrated that SON neurons are respectively depolarized and hyperpolarized by increases and decreases in extracellular osmolality (Bourque et al., 1994). The brainstem has also been implicated in the control of body fluid homeostasis. Projections ascending from the caudal region of the ventrolateral medulla also play a role in body fluid homeostasis based on the expression of c-Fos protein and AVP mRNA in the SON induced by electrical stimulation of this region (Shioda et al., 1998). Furthermore, intravenous infusions of hypertonic saline increase c-fos activity in the caudal ventrolateral medulla neurons (Hochstenbach & Ciriello, 1995).

The release of AVP into the blood is stimulated by the activation of osmoreceptors able to detect small increases (1%) in osmolality of extracellular fluid (Verney, 1947; Robertson et al., 1976). These osmoreceptors are located in the AV3V, which is made of a thin membrane, the lamina terminalis, comprising the MePO, the SFO and OVLT. These organs lie outside the blood-brain barrier and therefore are in contact with plasma ionic concentrations and hormones such as ANP and ANG II (Johnson & Gross, 1993; McKinley et al., 1999). Small changes in plasma osmolality in the physiological range can rapidly stimulate AVP transcription in the SON and PVN, suggesting that stored AVP release into the blood circulation is replaced in time by increased synthesis, processing, and transport of AVP (Arima et al., 1999). The threshold to activate osmoreceptor neurons to stimulate AVP release is approximately 275 mOsm/kg (Bourque et al., 1994). Chronic osmotic stimulation has been shown to increase AVP mRNA expression in the SON and PVN (Lightman & Young, 1987). AVP mRNA expression induced by hyperosmolality increases by 1.5-2-fold (Sherman et al., 1988); on the other hand, long-term hyposmolality reduces AVP mRNA levels in the hypothalamus to only 10-15% of the control levels (Robinson et al., 1990; Verbalis, 1993). More recently, using *in situ* hybridization histochemistry studies, Glasgow et al. (2000) confirmed earlier studies describing an increase in AVP, OT, and the AVP-binding protein (neurophysin) mRNAs during hypernatremia and a decrease in these mRNAs during hyponatremia.

Nitric oxide (NO) has been proposed as a local modulator of magnocellular neuron activity. NO is a neuronal messenger produced from L-arginine by NO synthase (NOS). The presence of NOS in the PVN and SON AVP neurons and its increase in these neurons by an osmotic stimulus or dehydration reinforced the role of NO in

AVP regulation (Bredt et al., 1990; Kadowaki et al., 1994; Villar et al., 1994; Ueta et al., 1998). In addition, NOS has also been shown to be present in structures involved in AVP secretion such as SFO, OVLT and MnPO (Vincent & Kimura, 1992). The role of NO in OT and AVP release is still not clearly defined. In a recent review, Kadekaro and Summy-Long (2000) summarized the effects of NO on AVP and OT regulation. NO tonically inhibits the basal AVP and OT plasma levels. However, the NO inhibition of AVP secretion is abolished during water deprivation, hypovolemia, moderate osmotic stimulation and also by the actions of ANG II. NO facilitates drinking behavior stimulated by water deprivation, osmotic stimulation, hemorrhage or ANG II. These results promote a positive water balance during reductions in intracellular and intravascular volumes. NO produced within the CNS 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. Paradoxically, central production of NO is also enhanced during hemorrhage, presumably to maintain peripheral vasodilatation and blood flow to vital organs. NO preferentially potentiates the inhibitory synaptic inputs into SON neurons by acting on GABA terminals in the SON, possibly via a cGMP-independent mechanism. This potentiation may, at least in part, account for the inhibitory action of NO on the neural activity of supraoptic neurons (Ozaki et al., 2000).

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. Extracellular hypovolemia induces AVP release from magnocellular neurons, which acts by increasing reabsorption of water in distal nephrons 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 (Share, 1988). In normal standing human subjects, a reduction in blood volume of 6% (reduction in plasma volume of 10%) induced by furosemide injection was sufficient to increase the plasma AVP concentration (Kimura et al., 1976). On the other hand, isotonic expansion of blood volume results in a reduction of plasma AVP concentration (Johnson et al., 1970; Shade & Share, 1975; Ledsome et al., 1985; Share, 1988; Leng et al., 1999).

The release of AVP from the neurohypophyseal terminals of hypothalamic magnocellular neurosecretory neurons is also regulated by peripheral baroreceptors, cardiopulmonary volume receptors and circulating ANG II concentration. Information from these sources is transmitted through different pathways to exert different

influences on the excitability of the vasopressin-secreting cells (Renaud, 1996). 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 fibers and 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 (Jhamandas & Renaud, 1986[a]; 1986[b]).

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 (Bisset & Chowdrey, 1988). 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 signals send afferent inputs through the vagal and glossopharyngeal nerves to the NTS in the brain stem, from which postsynaptic pathways project to the magnocellular neurons in the SON and PVN (Share, 1988). Indeed, stimulation of the cervical vagus induces Fos expression in A1 neurons and excites AVP cells (Day et al., 1992). Low-pressure receptors in the atrium tonically inhibit AVP release via a pathway involving the NTS, and AVP release induced by hypovolemia occurs through the reduction in activity of this inhibitory input (Bisset & Chowdrey, 1988; Share, 1988).

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, initiating neural inputs that result in an increase in the excitability of vasopressin-secreting 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 vasopressin-stimulatory pathway that bypasses the A1 region (Smith & Day, 1995).

AVP release under conditions of hypovolemia involves stimulation by ANG-II/III. Hypotension releases renal renin and leads to the formation of ANG II; binding to angiotensin II receptors type I (AT1) on SFO neurons promotes activation of a central angiotensinergic input that evokes a predominantly excitatory effect on AVP neurons. Functional segregation is demonstrated within the SFO, 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 polyethyleneglycol/water induces c-fos in the central core of SFO and also induces c-fos in both the central and peripheral regions (Smith & Day, 1995). Injection of ANG II or III into the SON or PVN increases magnocellular activity and AVP release into the blood (Shoji et al., 1986; Zini et al., 1996; Ardaillou, 1997).

AVP release and AVP gene transcription increase rapidly after both hypotensive hemorrhage and normovolemic hypotension (Kakiya et al., 2000). 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 regulations, including the regulation of AVP synthesis and release. Lesions of area postrema reduce AVP mRNA levels in PVN and SON and plasma AVP levels in the basal state and after hyperosmolality or hypovolemia stimulation (Arima et al., 1998).

The neurosecretory system contains an elaborate array of neural inputs, including a catecholaminergic innervation, predominantly noradrenergic, and a dopaminergic component (Decavel et al., 1987). The precise role of hypothalamic norepinephrine in the control of AVP release has remained unclear, due to reports of both inhibitory and excitatory effects of norepinephrine (NE) and only a few studies with direct hypothalamic manipulations (Leng et al., 1999). The excitatory effect of central noradrenergic stimulation on serum AVP is highly site specific, localized to the PVN and SON (Morris et al., 1994; Nakamura et al., 1992; Qualy & Westfall, 1998; Leibowitz et al., 1990). Activation of the locus coeruleus-PVN ascending noradrenergic pathways accounts for the increase in NE release in rat PVN induced by systemic hemorrhage (Morris et al., 1994). However, NE has also been reported to inhibit AVP and OT release from cells in the PVN of lactating rats (Honda et al., 1985). Adrenergic receptors may be distributed differentially in vasopressinergic neurons allowing excitatory or inhibitory impulses (Leng et al., 1999). In relation to dopaminergic inputs regulating AVP secretion, most of the evidence supports a stimulatory action (Forsling & Williams, 1984; Kimura et al., 1981; Moos & Richard, 1982; Yamaguchi et al., 1996), but data showing no change or inhibition also exist (Passo et al., 1981; Reid et al., 1986). Dopamine provokes antidiuresis and increases plasma AVP levels in euvolemic or water-loaded rats (Lookingland et al., 1985; Leibowitz et al., 1990) that is inhibited by a nonselective dopamine receptor antagonist (Forsling & Williams, 1984). Dopamine on its own increases AVP release via dopamine type I (D_1) receptor activation and also potentiates the stimulatory effect of a subthreshold dose of ANG II-induced AVP secretion within the hypothalamo-neurohypophyseal system (Rossi, 1998). On the other hand, periventricular dopaminergic mechanisms have been shown to inhibit hemorrhage-induced AVP secretion, as verified by marked enhancement of plasma AVP response to hemorrhage in rats receiving icv injection of haloperidol, a dopamine antagonist (Yamaguchi et al., 1990).

Vasopressin and Oxytocin Receptors

Vasopressin receptors

The actions of AVP are mediated by plasma membrane receptors, which belong to the guanyl nucleotide binding (G-protein) coupled receptor (GPCR) family characterized by the presence of seven transmembrane helices connected by three extracellular and three intracellular loops. Three different subtypes of AVP receptors, V1a, V1b and V2, have been cloned (Morel et al., 1992; Lolait et al., 1992; Sugimoto et al., 1994). V1a receptor expression was described in smooth muscle and liver, whereas V1b receptor expression has been reported in anterior pituitary and V2 receptor expression in kidney (de Keyzer et al., 1994; Thibonnier et al., 1994; Lolait et al.,1995). V1a receptors are involved in blood pressure control and the V1b receptor subtype mediates corticotropin secretion by the adenohypophysis. The presence of V1a receptors was 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 NTS, suggesting that V1a is the main receptor responsible for the central effects of AVP (Tribollet et al., 1988). Recently, using RT-PCR and *in situ* hybridization, V1b receptors have been detected not only in pituitary corticotrophs but also in the hypothalamus, amygdala, cerebellum, and in those areas close to the circumventricular organs (medial habenula, SFO, organum vasculosum laminae terminalis, 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 V1b may also mediate different physiological functions of AVP in the brain (Hernando, 2001).

V2 receptors are responsible for the antidiuretic effect of AVP. The expression of V2 receptor was described in some cells of the thick ascending limbs and all of principal and inner medullary collecting duct cells not only in the basolateral membrane but also in the luminal membrane (Nonoguchi et al., 1995; Nielsen et al., 1995). AVP regulates transcriptional activity of the aquaporin-2 gene through a cAMP regulatory element located in the 5' flanking region (Hozawa et al., 1996; Matsumura et al., 1997).

The three AVP receptors and the OT receptor share a high sequence identity, but they have distinct functional activity. As a hallmark of GPCR, they have a glycosylation site on the asparagine (Asn) residues in the extracellular domain, a disulfide bridge between two cysteine residues in the second and third extracellular domain, and two other cysteine residues in the C-terminal domain (Barberis et al., 1998). Ligand binding to AVP receptors is predicted to occur in a pocket formed by the ring-like arrangement of the seven trasnmembrane domains (Barberis et al., 1998). All residues supposed to have a key role in agonist binding (glutamines 214, 218, 311, 413, and 620, lysine 308) are highly conserved in all the AVP and OT

receptors cloned. Therefore, the agonist-binding pocket is common to all the different subtypes of this receptor family. However, it was also demonstrated that part of the agonist selectivity of the AVP/OT receptor family is not localized in the transmembrane regions of these receptors but in the first extracellular loop (Chini et al., 1995). In addition to glycosylation sites, most GPCR have conserved cysteine residues in their C-terminal cytoplasmic domain that appear to be generally palmitoylated. Site-directed mutagenesis of the putative palmitoylation site and functional studies were used to examine the significance of palmitoylation for the V2 receptor. The replacement of the conserved cysteine residues Cys-341 and Cys-342 by serine residues showed that palmitoylation of the V2 receptor is important for intracellular trafficking and/or sequestration/internalization, but not for agonist binding or activation of the Gs/adenylate cyclase system (Schuelein et al., 1996).

X-linked nephrogenic diabetes insipidus is a disease due to mutations in the V2 receptor gene (Bichet et al., 1993) that maps to chromosome region Xq28 (Rosenthal et al., 1992, Birnbaumer et al., 1992). Functional characterization of V2 AVP receptor gene mutations identified in these subjects brought insight into residues critical for V2 receptor expression and function (Wenkert et al., 1996). The natural mutation Arg113Trp in the V2 receptor significantly reduces receptor expression in transfected cells, receptor-ligand binding affinity and Gs coupling (Birnbaumer et al., 1994). A similar reduction in binding affinity and the inability to concentrate the urine after the administration of the antidiuretic hormone arginine-vasopressin was found in association with deletion of Arg 202, which is located in the second extracellular loop of the human V2 receptor (Ala et al., 1998), suggesting that this domain is also important for the ligand binding.

The three AVP receptor subtypes are coupled to different G proteins (Erlenbach & Wess, 1998). V1a and V1b receptors are coupled to G proteins of the $G_{q/11}$ family, which mediate the breakdown of phosphatidylinositol lipids (Briley et al., 1994; Thibonnier et al., 1994), whereas V2 receptors are coupled to G_s protein, resulting in the activation of adenylate cyclase (Birnbaumer et al., 1992). Different single intracellular domains determine the G protein-coupling selectivity profile of the different AVP receptor subtypes. Liu and Wess (1996) created and analyzed a series of V1a and V2 hybrid receptors in which distinct intracellular domains were systematically exchanged between the two wild type receptors. They suggested that the third intracellular loop of the V2 receptor plays a key role in proper recognition and activation of Gs and the second intracellular loop of the V1a receptor is critically involved in selective activation of $G_{q/11}$.

Oxytocin Receptors

In a recently published review, Gimpl and Fahrenholz (2001) described the present knowledge of the physiological effects of OT and OT receptor system in

the different fields of research, focusing mainly on the work over the past decade. The OT receptor has been cloned from humans (Kimura et al., 1992), rats (Rozen et al., 1995), and from other species (Gorbulev et al., 1993; Riley et al., 1995; Bathgate et al., 1995; Kubota et al., 1996; Salvatore et al., 1998). The OT receptor presents high homology across species and has been found in a variety of tissues, mostly in the uterus but also in mammary gland, pituitary, brain, kidney, thymus, ovaries, testis and heart. The OT receptor density in the uterus increases with the progress of pregnancy (Verbalis, 1999; Shojo & Kaneko, 2000). Earlier studies have indicated that rat hypothalamic OT mRNA accumulation rises gradually during pregnancy and remains elevated throughout the lactation period (Zingg & Lefebvre, 1989). In the brain, Tribollet et al. (1988) showed the anatomical localization of OT receptors, markedly different from that of binding sites for AVP, in the olfactory tubercle, the ventromedial hypothalamic nucleus, the central amygdaloid nucleus and the ventral hippocampus. The human OT receptor mRNAs were found to be of two sizes, 3.6 kb in breast and 4.4 kb in ovary, endometrium, and myometrium. The regulation of uterine oxytocin binding involves at least two different mechanisms: estradiol-induced up-regulation is accompanied by an increase in OT receptor mRNA accumulation, implying that the estradiol effect is mediated via increased OT receptor gene transcription and/or OT receptor mRNA stabilization. In contrast, progesterone-induced OT receptor down-regulation may occur via a novel non-genomic mechanism involving a direct interaction of progesterone with the OT receptor at the level of the cell membrane (Zingg et al., 1995, 1998). In addition to estradiol and progesterone, glucocorticoids, which also act through a specific nuclear receptor, have been shown to regulate OT receptor gene transcription. Adrenalectomized rats showed a significant decrease in OT receptor binding in the hippocampus, which was prevented by corticosterone replacement, suggesting that OT receptor expression may be also regulated by glucocorticoids (Liberzon et al., 1994).

OT acts through a specific OT receptor, which is also a member of the class I GPCR superfamily, which via Gq and Gi stimulates phospholipase C-mediated hydrolysis of phosphatidyl inositol. The generation of inositol 1,4,5- triphosphate mobilizes calcium from the sarcoplasmic reticulum and 1,2- diacylglycerol which activates protein kinase C, resulting in the phosphorylation of several target proteins. OT stimulates a rapid increase in intracellular free calcium, activation of mitogen-activated protein (MAP) kinase through an islet-activating protein-sensitive G-protein and prostaglandin E_2 synthesis (Ohmichi et al., 1995; Guinn et al., 2000). On the other hand, in cardiac tissue, the OT receptor mediates the action of OT to release a potent cardiac hormone, ANP (Gutkowska et al., 1997[b], 2000), which has a vasodilating action through cGMP generation.

The OT receptor presents conserved residues involved in a common mechanism for activation and signal transduction to the G protein. The Asp in the

second transmembrane (TM2) domain (Asp-85 in human OT receptor) and a tripeptide (E/D RY) at the interface of TM 2 and the first intracellular loop are believed to be important for receptor activation (Bockaert & Pin, 1999; Fanelli et al., 1999; Wheatley et al., 1998). The different molecular masses for the myometrial versus the mammary gland and amnion OT receptor are probably due to differential glycosylation patterns. However, the full glycosylation of the OT receptor observed *in vivo* is not essential for its activity (Kimura et al., 1997).

The sequence homologies of the OT receptor with the AVP V1 and V2 receptors are nearly 50% and 40%, respectively. The highest homology between the AVP/OT receptor types is found in the extracellular loops and the transmembrane helices. Common structural features of the OT/AVP receptor family could play an important role in ligand/receptor recognition. The highly conserved Gln and Lys residues in the TM 2, 3, 4 and 6 in V1a and OT receptors suggest that the agonist-binding pocket is common to all the different subtypes of this receptor family (Mouillac et al., 1995; Barberis et al., 1998). In the first extracellular loop, the homologous residues F103, Y115, and D115 in the human OT, V1a/V1b, and V2 receptors were found to be crucial for the determination of the ligand selectivity (Chini, 1995; Ufer et al., 1995).

The possible existence of OT receptor subtypes remains to be established (Verbalis, 1999; Shojo & Kaneko, 2000; Gimpl & Fahrenholz, 2001). Such subtypes have been suggested to be present in the rat uterus, kidney, or brain to explain differential pharmacological profiles or immunoreactivity patterns. OT-binding sites of the macula densa and thin Henle's loop, detected in the rat kidney, may represent two subtypes of OT receptors which could mediate distinct effects of OT on kidney function (Arpin-Bott et al., 1997). On the other hand, it should pointed out that OT can interact with V1 and V2 AVP receptors as they are closely related (Thibonnier et al., 1999). Polymerase chain reaction and Southern analysis in several tissues known to have OT binding activity failed to identify a gene encoding a further OT receptor subtype, suggesting that there is little possibility for the presence of OT receptor subtypes (Kimura & Saji, 1995).

Actions of Vasopressin and Oxytocin: Interactions with ANP

The antidiuretic action of AVP is the main physiological effect of this hormone, which increases water permeability of the renal collecting duct cells, allowing more water to be reabsorbed from urine to blood. Circulating AVP activates specific membrane receptors, leading to an increase of intracellular cAMP and phosphorylation of the C-terminus of the water channel aquaporin-2 protein in the tubular cells of the distal nephron (Yamamoto et al., 1995). The distribution and amount of aquaporin in the collecting duct cells are regulated by AVP V2 receptors as shown by the

decreased urine osmolality and aquaporin-2 expression in apical membrane and subapical cytoplasm of collecting duct cells of the inner medulla in dehydrated rats treated with a V2 receptor antagonist (Hayashi et al., 1994). The insertion of aquaporin-2 into the luminal surface of the collecting tubules appears to be regulated by AVP through fast exocytosis to the plasma membrane and also stimulates the synthesis of aquaporin-2 mRNA (Nielsen et al., 1995; Knepper, 1997; Saito et al., 1997; Sasaki et al., 1998). 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 water transport across the basolateral membrane is facilitated by the constitutively expressed aquaporins 3 and 4 (Ecelbarger et al., 1995; Terris et al., 1995; Klussmann et al., 2000).

Vasopressin of magnocellular origin is stored in the neural pituitary lobe and secreted into the peripheral circulation, whereas AVP produced in the parvocellular neurons of the PVN reaches the anterior pituitary through portal capillaries in the external zone of the median eminence. Parvocellular AVP participates in the regulation of ACTH release at the pituitary level (Antoni, 1993) through interaction with the V1b AVP receptor (Sugimoto et al., 1994). AVP is a weak secretagogue of ACTH secretion itself, however it has a synergistic action potentiating the effect of corticotrophin releasing hormone (CRH) on ACTH secretion (Gilles et al., 1982; Rivier et al., 1983, 1984). The mechanism of the synergism between CRH and AVP includes protein kinase C-mediated potentiation of CRH-stimulated cAMP production and also a post cAMP-dependent mechanism (Bilezikjian et al., 1987; Liu et al., 1990; Oki et al., 1990). AVP has been involved in the regulation of the corticotroph during chronic stress (Aguilera, 1994) and it is critical for sustaining corticotroph responsiveness in the presence of high circulating glucocorticoid levels during chronic stress (Ma & Lightman, 1998; Aguilera & Rabadan-Diehl, 2000). In addition, transcripts of the V1b AVP receptor have been detected throughout the rat brain by RT-PCR and *in situ* hybridization besides pituitary corticotrophs, including the hypothalamus, amygdala, cerebellum, and particularly in those areas with a leaky blood brain barrier or close to the circumventricular organs. The widespread distribution of the V1b receptor protein in the rat brain suggests that the V1b receptor mediates different physiological functions of AVP in the brain (Hernando et al., 2001).

Besides the antidiuretic and natriuretic effects previously described, the neurohypophyseal hormones can also induce ANP release. AVP is known to be synthesized not only in the CNS but also in other extraneural tissues, such as the heart. Cogan et al. (1986) have shown that high plasma ANP levels in patients with the syndrome of inappropriate secretion of AVP are associated with persistent natriuresis. On the contrary, we have shown that patients with central diabetes insipidus present lower plasma ANP levels in comparison with controls (Elias et al.,

1997). These data strongly support the hypothesis of a neuroendocrine modulation of ANP secretion. Intravenous and icv injections of AVP induce a dose-related increase in plasma ANP levels, suggesting a modulatory role of AVP on ANP release at the atrial level (Itoh et al., 1987; Elias et al., 2001). In addition, pretreatment with an AVP V1-receptor blocker significantly reduces the ANP secretion induced by blood volume expansion with no difference in plasma ANP levels after higher volume expansion. These data support the idea that ANP secretion induced by AVP stimulation involves both peripheral and CNS mechanisms. ANP secretion is proportional to the degree of atrial stretch induced by blood volume expansion and may involve an AVP action through its V1-receptor activation.

Circulating OT is mostly known to elicit the contraction of uterine smooth muscle at term pregnancy and of myoepithelial cells that surround the alveoli of the mammary gland during lactation (Soloff et al., 1979; Russell & Leng, 1998). In addition to the well-known effects on the uterus and mammary gland, OT given as a bolus injection, also decreases mean arterial blood pressure by approximately 30% and total peripheral resistance by 50% (Weis et al., 1975). There is also evidence that OT produces natriuresis in rats at physiological plasma levels and the elevated OT plasma levels correlate with increased sodium excretion (Verbalis et al., 1991). OT is also involved in vascular and cardiac relaxation and hydromineral homeostasis (Gutkowska et al., 1997[a,b], 2000; Soares et al., 1999; Jankowski et al., 2000; Conrad et al., 1986; Huang et al., 1995; Haanwinckel et al., 1995). It has long been recognized that OT increases renal electrolyte excretion in various species, and that its natriuretic and kaliuretic effects are independent of AVP (Balment et al., 1980; Stricker et al., 1987; Stricker & Verbalis, 1988; Fraser, 1942; Sawyer, 1952). These effects can be explained by a direct action of both peptides on specific receptors already demonstrated to be present in the kidney tubular cells (Stoeckel et al., 1987; Tribollet et al., 1988). Studies have suggested a synergistic effect of AVP and OT on the inner medullary collecting duct where both peptides induce an increase in cAMP accumulation and natriuresis (Balment et al., 1980; Forsling et al., 1982). OT binds to the AVP V2 receptor (V2R) because of its structural similarity to AVP. 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. The urinary sodium excretion induced by OT was not affected by an AVP V1 antagonist and was only partially blocked by a combined AVP V1 and V2 antagonist. These data suggested that the natriuretic effect of OT might be partially mediated by AVP receptors at the kidney level (Haanwinckel et al., 1995). In addition to their peripheral effects, these peptides may also produce other effects that could complement their physiological action. Indeed, AVP when injected into the CNS increases water intake. In contrast, the central administration of OT decreases salt intake (Stricker & Verbalis, 1988; Stricker et al. 1987; Verbalis et al., 1991).

Besides the antidiuretic and natriuretic effects described above, the neurohypophyseal hormones can also induce ANP release. Experimental models using OT and AVP administered either intravenously or intraperitoneally at nanomolar doses to normally hydrated or water-loaded rats also demonstrated an increase in ANP concentration in the circulation (Haanwinckel et al., 1995). This evidence supports the concept that, following volume expansion, OT is released and circulates to the right atrium, both inducing ANP release and mediating the ensuing natriuresis (Haanwinckel et al., 1995). Moreover, suckling of dams by their litter evoked OT and ANP release, which was blocked by prior injection of an OT antagonist. Therefore, the accumulated data strongly support the hypothesis of a neuroendocrine modulation of OT and AVP on ANP secretion.

Recently, Jankowski et al. (2000) reported in rats that the heart is also a site of OT synthesis and release. OT was detected in all four chambers of the heart, with the highest concentration in the right atrium. OT-receptors as well as the gene expression of specific OT mRNA were also found in the rat left ventricle and in human right atrium cardiomyocytes (Gutkowska et al., 2000). These findings support the idea that OT has an important role in ANP release from the atria. In addition, OT receptor mRNA was also found in the vena cava, pulmonary vein, and pulmonary artery, with lower levels in the aorta, suggesting vessel-specific OT receptor distribution. The abundance of OT receptor mRNA in the vena cava and pulmonary vein was associated with high ANP mRNA. Therefore, locally produced OT may have important regulatory functions within the heart and vascular beds. These data suggest that the vasculature contains an intrinsic OT system, which may be involved in the regulation of vascular tone as well as vascular regrowth and remodeling (Gutkowska et al., 2000; Jankowski et al., 2000).

ANP concentration in the atria is much higher than in the vascular system, suggesting that ANP may also act directly on the heart, exerting a negative chrono- and inotropic effect in the atrium (Favaretto et al., 1997). These effects were similar to those obtained with 8-monobutyryl cGMP, indicating that ANP acts on the heart through the stimulation of its membrane-bound guanylate cyclase receptors. Since OT stimulates ANP release from the right atrium (Haanwinkel et al., 1995), we postulated that OT acting on its putative receptor in the right atrium stimulates ANP release, which then exerts its effects (Favaretto et al., 1997). These effects of OT on the heart are independent of cholinergic vagal inhibition since they were not blocked by previously administration of atropine (Favaretto et al., 1997). Since the function of OT in males is largely unknown, OT might be involved in the control of sodium and potassium excretion and body fluid homeostasis in both genders. Finally, a number of other neuropeptides (ANG II, bradykinin, calcitonin gene-related peptide, enkephalin, NPY, substance P, and VIP) have been described to be involved in regulation of cardiac function by intrinsic cardiac neurons (Armour et al., 1993) and might interact with AVP, OT and ANP.

Concluding Remarks

During the last two decades, since the discovery of the natriuretic peptides by de Bold (1981), a large number of publications have demonstrated that these peptides play an important role in cardiovascular function and body fluid homeostasis. ANP is a member of the family of natriuretic peptides comprising three other members, brain natriuretic peptide (BNP), c-type natriuretic peptide (CNP) and urodilatin, which have potent effects on mechanisms against volume overload. ANP is mostly localized in the heart, but ANP and its receptor are also localized in hypothalamic and brain stem areas involved in body fluid volume and blood pressure regulation. ANP fibers originating from the AV3V area project to PVN, the median eminence and neural lobe of the pituitary.

This review emphasized the role played by brain ANP and its interaction with neurohypophyseal hormones, mainly OT, in the control of body fluid homeostasis. ANP secretion involves distension of the baroreceptors in the right atria, carotid and aortic sinuses and in the kidney, which alters their afferent input to the brain stem in the NTS, which in turn induces OT release from the neural lobe through ANPergic neurons. OT circulates in the heart leading to ANP release and ensuing vasorelaxation and natriuresis. The presence of OT and OT receptor in all chambers of the heart atria and also in the vessels supports the hypothesis that circulating and intracardiac OT released by volume expansion induces ANP secretion through endocrine and paracrine mechanisms. Within the brain ANP interacts with OT to inhibit water and sodium intake in order to normalize blood volume, leading to natriuresis, kaliuresis and water excretion after blood volume expansion. On the other hand, in conditions leading to a decrease of effective circulating blood volume, such as dehydration or hemorrhage, there is an increase of plasma AVP and a decrease of plasma ANP leading to an increase in sodium and water intake, peripheral vasoconstriction, antidiuresis and antinatriuresis.

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