THE ACTIONS OF ANTIDIURETIC hormone or vasopressin (AVP) to promote water retention and to acutely increase arterial pressure are well established. Oxytocin (OT) has well known effects on uterine contraction and milk ejection. In addition to these widely recognized hormonal actions, these peptides have additional behavioral, autonomic, renal, and cardiovascular effects, the physiological significance of which has been a topic of considerable interest to the authors contributing to this journal.

AVP is a potent vasoconstrictor, but it is also capable of producing vasodilation. The vasoconstrictor effects of AVP are mediated via activation of V1 receptors; V2 receptors mediate the vasodilatory effects of the hormone, as well as its antidiuretic actions. Usually, the vasoconstrictor effects of AVP predominate, which is the basis for its role in the acute regulation of arterial pressure. For example, infant rats respond to moderate cold exposure with increased heat production by brown adipose tissue (5). However, at greater thermal challenges, thermogenesis can no longer compensate for heat loss, leading to substantial bodily cooling and bradycardia. In response to the resultant decrease in cardiac output, maintenance of arterial pressure is dependent on an increase in peripheral resistance, which is due, in part, to the vasoconstrictor effects of AVP (5). An impaired vasoconstrictor response to AVP appears to contribute to systemic vasodilation and hypotension in septic shock (6). In septic shock, the diminished vasoconstrictor response to AVP is due to downregulation of V1 receptors, a response that is likely mediated by proinflammatory cytokines. The vasodilatory effects of AVP are most readily exposed after V1 receptor antagonist administration, particularly when sympathetic reflexes are impaired. After V1 receptor blockade, incremental infusions of AVP caused progressive and comparable reductions in peripheral resistance in normal and quadriplegic subjects (9). However, arterial pressure decreased only in the latter, despite much larger compensatory increases in PRA, because of deficient reflex-mediated increments in cardiac output. At least in rats, hypotension stimulates the secretion of OT, as well as AVP. During hypotension, OT contributes to the maintenance of arterial pressure by stimulating renin release (15).

Both AVP and OT have actions at the central nervous system that impact cardiovascular function. These actions are a result of the secretion of these peptides from oxytocinergic and vasopressinergic projections within the nervous system, as well as the secretion of these neurohypophysial hormones from magnocellular neurons, which, via the circulation, activate receptors at circumventricular organs. OT projections from paraventricular neurons of the paraventricular nucleus (PVN) to the solitary vagal complex are involved in the restraint of exercise-induced tachycardia and facilitate baroreflex-mediated bradycardia in response to increased arterial pressure (14). OT released at the lumbosacral spinal cord by descending projections from the paravascular PVN activates proerectile neurons and, therefore, plays a role in reproductive function (12). The central actions of AVP (V1 receptor response) account for postexercise reductions in arterial pressure and heart rate, possibly by enhancing baroreflex function by activating receptors in the area postrema that project to the nucleus of the solitary tract (8). AVP is also released during stress and contributes, along with corticotropin-releasing hormone (CRH), to increased ACTH secretion (17). This presumably occurs in two ways. First, the AVP that is coreleased with CRH into the primary capillaries of the portal circulation in the stalk-median eminence region directly stimulates ACTH producing anterior pituitary cells. Second, the circulating AVP secreted from magnocellular neurons acts at the hypothalamus to increase the synthesis and release of CRH.

There has been considerable interest in the neurohormonal mechanisms that influence salt appetite (1, 10, 24, 25, 29). The diversity of experimental models (e.g., adrenalectomy, dietary sodium deprivation, hypovolemia, fluid deprivation) used to evoke salt appetite undoubtedly results in different alterations in body fluid volumes, blood pressure, and neurohormonal responses, all of which must be carefully considered in the interpretation of experimental findings. In rats purportedly sodium depleted by administration of furosemide and DOCA, central administration of an antagonist to the AVP-V1 (but not the AVP-V2) receptor suppressed salt appetite, implicating a central role for this peptide in stimulating salt intake (10). In contrast, Schoorlemmer et al. (25) concluded that circulating ANG II, but not circulating AVP, accounts for most of the sodium appetite in adrenalectomized rats. In another study, mice in which the gene for OT had been deleted were given the choice between hypertonic saline and tap water after overnight fluid deprivation (1). Compared with wild-type, OT-deficient mice ingested considerably greater amounts of saline, supporting an inhibitory role for OT in the control of sodium appetite in this model. Further support for an inhibitory role of OT in salt appetite was provided by Roesch et al. (24), who were cognizant of the fact that OT limits the

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central actions of ANG II to increase sodium intake. Their findings indicate that the synergistic effects of mineralocorticoids on ANG II-induced salt intake are a result of the former attenuating the stimulatory effects of ANG II on the activation of inhibitory OT neurons.

The antidiuretic effects of AVP and the role of AVP in osmoregulation continue to be important topics relating to neurohypophysial hormone function (2, 3, 11, 23, 26). To determine if the neuroendocrine link between volume sensing and renal function is preserved in compensated heart failure, Gabrielsen et al. (11) determined the renal excretory response to intravascular and central blood volume expansion by water immersion. Compared with control subjects, patients with compensated heart failure and an activated renin-angiotensin system had a diminished natriuretic and diuretic response to water immersion. A less predictable finding, however, was that free water clearance was impaired in patients with heart failure, despite normal values for plasma AVP concentration. The transition from the seated to the head-down tilted position increases central blood volume and reflexly promotes salt and water excretion. Therefore, investigators from these same laboratories determined whether prolonged head-down bed rest leads to hypovolemia, activation of antinatriuretic mechanisms, and attenuation of the natriuretic response to acute saline loading (3). The impetus for this study was to determine whether this change in posture would serve as a model to study fluid regulation to weightlessness in space. Unfortunately, this did not prove to be the case. Although prolonged head-down bed rest did lead to a sustained reduction in body fluid volume and activation of the renin-angiotensin system, for reasons that were unclear it did not result in an attenuated natriuretic response to an acute saline load. Another unexpected finding was that chronic bed rest resulted in a reduction, not an increase, in plasma AVP concentration. Because central blood volume was chronically reduced and plasma osmolality increased, responses expected to increase AVP secretion, the authors speculated that suppression of AVP secretion was a result of either increased carotid sinus pressure or increased arterial pulse pressure. As activation of arterial baroreceptors inhibits AVP secretion, this contention is consistent with recent findings indicating that arterial baroreflexes do not completely reset when arterial pressure is chronically elevated (19). In northern elephant seal pups, the secretion of AVP is regulated by both volume (pressure) and osmolality (23). Furthermore, AVP appears to play an important role in promoting antidiuresis during their postweaning fasts of up to 12 wk in duration.

Recent studies have provided a more complete understanding of the multiple factors and central mechanisms that influence AVP and OT secretion. Whereas cerebral osmoreceptors located in the forebrain are known to mediate osmotically induced changes in AVP and OT secretion, studies in rats given gastric salt loads are consistent with the notion that hepatic portal osmoreceptors as well stimulate neurohypophysial hormone secretion (28). Activation of this feedforward mechanism for hormone secretion precedes significant salt absorption into the general circulation and its detection by cerebral osmoreceptors. AVP secretion and nausea are induced by high doses of the gut hormone CCK after activation of gastrointestinal vagal afferent inputs to the nucleus of the solitary tract (4). ANG II also stimulates AVP secretion, and receptors for ANG II are present in the PVN and supraoptic nucleus (SON), as well as in brain regions that are osmosensitive (20). That the link between ANG II and AVP secretion may be physiologically relevant is supported by the observation that AVP secretion is impaired in dehydrated mice lacking the ANG AT1a receptor (20). Although there is a lower osmotic threshold for AVP secretion when plasma estrogen and progesterone are elevated, such as during the luteal phase of the menstrual cycle, progesterone does not affect osmotic AVP regulation through a mechanism independent of estrogen (7).

The central nervous system pathways and the neurotransmitters responsible for regulating AVP secretion in response to various stimuli are incompletely resolved. The perinuclear zone surrounds the SON and is a major source of the inhibitory neurotransmitter GABA, which is present in many synaptic contacts in this nucleus. As lesions of the perinuclear zone attenuate the inhibition of SON AVP neurons induced by activation of both arterial and cardiopulmonary baroreceptors, it would appear that this region is an essential component of the pathway mediating nonosmotic secretion of AVP (13). Nitric oxide also inhibits AVP and OT secretion, and neural nitric oxide is expressed in both the SON and PVN, where it is colocalized with AVP and OT synthesizing neurons. Electrophysiological recordings from the SON indicate that nitric oxide inhibits AVP and OT neurons by potentiating GABAergic synaptic activity at this nucleus (27). The secretion of AVP and OT is stimulated by a number of different excitatory neurotransmitters with synaptic inputs into the SON (16, 18, 21, 22). One of the most important neurotransmitters that increases the excitability of the neurons in the SON is glutamate. The glutamate receptor subtypes that elicit AVP and OT secretion and mediate the hormonal response to an osmotic stimulus have been characterized by Sladek and coworkers (21, 22) using an explant of the hypothalamo-neurohypophysial system.

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