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# Vasopressin Response to Osmotic and Hemodynamic Stress: Neurotransmitter Involvement

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Osmotic and hemodynamic stress are the two primary regulators of vasopressin (VP) release from the posterior pituitary. The pathways providing information about plasma osmolality and blood pressure or blood volume are distinct and utilize different chemical neurotransmitters. Osmotic regulation of VP release is dependent upon afferents from the lamina terminalis region. Glutamate is an important transmitter in this system and angiotensinergic afferents from this region to the VP neurons modulate responses to osmotic challenges. Hemodynamic information is transmitted to the VP neurons via multisynaptic pathways from the brainstem with the A1 catecholamine neurons of the ventrolateral medulla providing the final link for information about decreases in blood pressure and volume. Several neurotransmitters and neuropeptides are expressed in the A1 neurons including norepinephrine (NE), ATP, neuropeptide Y, and substance P. The impact of co-release of these agents on VP release is reviewed and the potential physiological significance is discussed.

*Keywords*: Angiotensin; AV3V region; Neurohypophysis; Organum vasculosum lamina terminalis; Oxytocin; Paraventricular nucleus

Secretion of vasopressin (VP) by the hypothalamo-neurohypophyseal system (HNS) occurs primarily in response to increases in osmolality of the extracellular fluid or decreases in blood pressure or volume. The receptors monitoring these parameters are distinct as are the neuronal pathways carrying this information to the VP neurons. Thus, it is not surprising that the neurotransmitters involved in conveying osmotic and hemodynamic information to the VP neurons are different. Certain physiological and pathophysiological stressors activate both the osmotic and hemodynamic regulatory pathways while other stresses access only one of the regulatory afferents. For example, water deprivation activates both osmotic and hemodynamic afferents, because it results in concentration of extracellular fluid osmolytes (hypertonicity) and constriction of the extracellular fluid volume (thus, causing hypovolemia). In contrast, a salty meal only activates the osmoregulatory pathways while hemorrhage selectively activates the cardiovascular afferents and increases circulating angiotensin II (AII) which can activate additional afferent pathways [for review, see Sladek, (2000)].

Since the VP neurons receive independent information about tonicity and volume of the extracellular fluid and since VP acts on multiple target organs (kidney, vasculature, CNS) via distinct receptors, VP is important for regulating both blood volume and plasma osmolality. Under physiological conditions, VP responses reflect a balance between these two roles, but in certain pathophysiological conditions, this balance is disrupted resulting in abnormalities in either plasma osmolality or blood volume as the system focuses on maintaining homeostasis in one parameter at the expense of the other.

The VP neurons are innervated by an extensive and complex array of afferent pathways arising from diverse regions of the central nervous system ranging from the brainstem to the forebrain. These afferents use a wide variety of chemical neurotransmitters [for review, see Sladek, (2000)]. In addition, the VP neurons are regulated by numerous blood borne signals such as hormones, cytokines, and tonicity. In order to understand how the VP neurons produce responses that are appropriate to these complex physiological signals as well as what is responsible for disruption of these integrated responses under stress conditions, it is necessary to understand the role of each pathway and transmitter, how they interact, and how the VP neurons integrate this complex array of information to achieve secretory

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responses appropriate for maintaining or re-establishing homeostasis.

## OSMOTIC REGULATION OF VP RELEASE

An increase in plasma osmolality is a potent physiological stimulus for VP release. Plasma VP levels sufficient to achieve maximal antidiuresis by the kidneys are achieved with 1–2% increases in plasma osmolality (Robertson *et al.*, 1976). This is achieved by integration of information from a complex of osmoreceptive mechanisms. The VP neurons themselves are osmosensitive (Mason, 1980; Oliet and Bourque, 1993). This renders the neurons more sensitive to excitatory potentials arising from other osmoreceptors located in rostral forebrain structures anterior to the third ventricle including the subfornical organ (SFO) and organum vasculosum of the lamina terminalis (OVLT). Early investigations identified these sensors as osmoreceptors based on their selective responsiveness to agents that do not permeate the cell membrane (Verney, 1947; Sladek and Knigge, 1977; Thrasher *et al.*, 1980). Subsequently, Bourque and his colleagues elucidated at least one of the cellular mechanisms underlying this osmosensitivity as a stretch-inactivated, non-selective, cation channel expressed in the VP neurons as well as in neurons in the OVLT and SFO [see, for review Bourque *et al.* (1994)]. Under hypotonic conditions, water moves into the cell resulting in stretch of the membrane and inactivation of this channel. This hyperpolarizes the neuron resulting in reduced sensitivity to excitatory afferents in the case of the VP neurons and decreased release of excitatory transmitters in the case of the OVLT osmoreceptors. The reverse occurs under hypertonic conditions resulting in stimulation of VP release. There has also been a long-standing debate about the role of sodium receptors in the regulation of VP release and thirst (Andersson, 1971; McKinley *et al.*, 1975; Morris *et al.*, 1976). The recent identification of a sodium-sensitive channel expressed in neurons of the SFO and OVLT (Hiyama *et al.*, 2003) suggests that both sodium and osmolality may be selectively monitored. Furthermore, the demonstration that increases in the extracellular Na concentration cause proportional changes in the relative permeability of the stretch-inactivated (osmosensitive) channels provides a basis for integration of osmotic and sodium-sensing (Voisin *et al.*, 1999). Therefore, both sodium and osmolality participate in regulation of body fluid homeostasis.

Plasma osmolality and sodium are also monitored in the periphery by visceral osmoreceptors and/or sodium receptors (Johnson and Thunhorst, 1997). These receptors provide an early detection system for ingested water and sodium. Water and sodium are more effective in eliciting diuresis and antidiuresis, respectively, when administered into the portal vein than when given intravenously (Haberich, 1968), and hyperosmotic solutions administered intragastrically or into the portal vein increase plasma VP without altering systemic osmolality (Chwalbinska-Moneta, 1979; Baertschi and Vallet, 1981; Carlson *et al.*, 1997; Stricker *et al.*, 2002). Information from these receptors is transmitted to the brain via vagal afferents and then is relayed to the median preoptic nucleus (MnPO) in the ventral lamina terminalis via multisynaptic pathways where it is integrated with information from the osmo- and sodium-receptors in OVLT and SFO (King and Baertschi, 1991). Thus, the forebrain regions anterior and ventral to the third ventricle (e.g. the AV3V region) and the SFO monitor central osmolality and sodium as well as integrating information from the peripheral osmo- and sodium-receptors. The importance of this region for osmotic regulation of VP release has been clearly demonstrated by the loss of osmoregulation of VP release in animals prepared with electrolytic lesions in this region (Johnson and Gross, 1993). Since the AV3V lesion destroys efferent projections from the SFO to the VP neurons, this source of osmotic information is lost even though the osmoreceptive elements in SFO remain intact. Although these animals are still capable of releasing VP in response to hypovolemia (Feuerstein *et al.*, 1984), plasma osmolality increases dramatically (e.g. 80–100 mOsm/kg $H_2O$) when these animals are water restricted (Somponpun *et al.*, 2004).

The primary neurotransmitter involved in conveying information from the osmoreceptors in OVLT to the VP neurons in the SON is probably glutamate or another excitatory amino acid (EAA). VP release from explants of the HNS is stimulated by increases in osmolality of the perifusion or culture medium (Sladek and Knigge, 1977; Yagil and Sladek, 1990). This requires an intact OVLT in the explant (Sladek and Johnson, 1983) indicating that the endogenous osmoreceptive characteristics of the VP neurons are inadequate to mount a response to an osmotic stimulus without the excitatory afferents from osmoreceptors in OVLT. As summarized in Table I, glutamate and selective agonists of all three classes of EAA receptors [n-methyl-D-aspartate (NMDA), non-NMDA, and metabotropic] stimulate VP release from HNS explants (Sladek *et al.*, 1998; Swenson *et al.*, 1998). Furthermore, non-selective EAA receptor antagonists as well as selective antagonists of NMDA and non-NMDA EAA receptors block osmotically-stimulated VP release from HNS explants (Swenson *et al.*, 1998; Sladek *et al.*, 1998; Morsette *et al.*, 2001), but antagonists of the metabotropic EAA receptors do not (Table I). These data indicate that activation of NMDA and AMPA EAA receptors are required for osmotically-stimulated release. They are consistent with the electrophysiological studies of Richard and Bourque (1995) that excitation of SON neurons following osmotic stimulation of the OVLT involves glutamatergic afferents.

*Angiotensin II* AII has also been implicated in osmotic regulation of VP release. The AV3V region and the SFO are important sites for mediating the effects of peripherally generated AII, because both the SFO and

TABLE I Effects of EAA receptor agonists and antagonists on basal and osmotically-stimulated VP release from HNS explants

| EAA compound | Type of EAA receptors | Effect on VP release from HNS explants | |
|---|---|---|---|
| | | Basal release | Osmotically-stimulated release* |
| *Agonists* | | | |
| Glutamate | All types | ++[†] | |
| NMDA | NMDA receptor | ++ | |
| AMPA | Non-NMDA | ++ | |
| t-ACPD | Group I and II mGluRs | ++ | |
| DHPG | Group I mGluR | ++ | |
| L-AP4 | Group III mGluR | No effect | No effect |
| *Antagonists* | | | |
| Kynurenic acid | Non-selective | – | – |
| MK801 | NMDA receptor | | – |
| AP5 | NMDA receptor | | – |
| DNQX | Non-NMDA | No effect | – |
| AIDA | Group I mGluR | No effect | No effect |

NMDA—n-methyl-D-aspartate; AMPA—α-amino-3-hydroxy-5-methyl-4-isooxazole-propionic acid; t-ACPD—(+/−)-1-Aminocyclopentane-*trans*-1,3-dicarboxylic acid, *trans*-ACPD; AP5—2-amino-5-phosphono-pentanoic acid; DNQX—6,7-dinitroquinoxaline-2,3-dione; AIDA—1-aminoindan-1,5-idicarboxylic acid.
From Sladek *et al.* (1998); Swenson *et al.* (1998); Morsette *et al.* (2001).
* A ramp increase in osmolality (40 mOsm over 6 h achieved by increasing [NaCl]).
[†] When AMPA receptor desensitization was blocked with cyclothiazide; ++ stimulated; − inhibited.

OVLT lack a blood brain barrier and express AII receptors (Sunn *et al.*, 2003). In addition, angiotensinergic neurons in the SFO and MnPO innervate both the SON and PVN (Johnson and Thunhorst, 1997). Antagonists of AII receptors block and AII potentiates osmotically-stimulated VP release from HNS explants (Sladek and Joynt, 1980; Sladek *et al.*, 1982). These and other observations indicate that AII can modulate VP responses to osmotic stimuli. One cellular mechanism for this modulation identified by Chakfe and Bourque (2001) is modulation of the stretch-inactivated (osmosensitive) current by AII. Thus, AII may directly modulate responses of osmoreceptive neurons in the SFO and OVLT, and may participate as a neurotransmitter in pathways transmitting osmotic information from the SFO and OVLT to the VP neurons.

## CARDIOVASCULAR REGULATION OF VP RELEASE

Decreases in blood pressure and blood volume are potent stimuli for VP release (Dunn *et al.*, 1973; Sladek, 2000) while increases in blood pressure and volume expansion inhibit the VP neurons (Cunningham *et al*., 2002). Independent afferent pathways mediate excitation and inhibition of VP neurons by decreases or increases in blood volume. Inhibition is mediated by an indirect projection from the nucleus of the diagonal band of Broca through the perinuclear zone (PNZ) adjacent to the SON (Jhamandas *et al.*, 1989). The inhibition is the result of diagonal band afferents exciting GABAergic inhibitory neurons in the PNZ that in turn project to the SON (Jhamandas and Renaud, 1986). Excitation in response to decreases in blood volume or pressure is mediated either by peripherally generated AII stimulation of the SFO afferents to the SON and PVN described above (Knepel *et al.*, 1982) or by direct afferents from the A1 catecholamine neurons in the ventrolateral medulla to the VP neurons in the SON and PVN. Blood pressure is monitored by the baroreceptors in the carotid sinus. This information is relayed to neurons in the nucleus of the tractus solitarius via the ninth cranial nerve, the glossopharyngeal nerve, and then via the A1 neurons to the SON and PVN (Day and Sibbald, 1989; Day *et al.*, 1990; 1992).

Although the A1 neurons were originally identified as catecholaminergic, subsequent studies demonstrated that norepinephrine (NE) is not the primary neurotransmitter in this pathway (Buller *et al.*, 1996). Instead, the A1 catecholamine neurons utilize a mixture of transmitters including ATP, neuropeptide Y, and possibly substance P in addition to NE (Willoughby and Blessing, 1987; Khanna *et al.*, 1993; Buller *et al.*, 1996). Substance P is co-localized in a sub-population of the A1 neurons (Bittencourt *et al.*, 1991). The co-localization of multiple neurotransmitters and neuropeptides in the A1 neurons, and evidence supporting roles for multiple agents in conveying information by this pathway, led us to investigate the interaction between these agents in regulation of VP release (Kapoor & Sladek, 2000; 2001). As summarized in Table II, we found selective

TABLE II Interactions between agents co-localized in A1 neurons: Effect on VP release from HNS explants

| Agent | ATP (100 μM) | PE (100 μM) |
|---|---|---|
| PE (100 μM) | ++peak<br>++duration | |
| NPY(10 μM) | No synergism | ++duration |
| SP (1 μM) | ++peak<br>++duration | No synergism |

For original data see (Kapoor & Sladek, 2000; 2001).
++peak—an increase in the maximal rate of VP release.
++duration—a transient response was converted to an extended response.

synergistic actions between the co-localized agents in stimulation of VP release from perifused HNS explants (Kapoor & Sladek, 2001).

NE is considered a classic neurotransmitter, and ATP has been shown to function as a fast acting neurotransmitter at numerous synapses. In addition, ATP functions as a co-transmitter with NE in a number of tissues innervated by the sympathetic nervous system (Burnstock, 1990). VP release from HNS explants was markedly potentiated by simultaneous exposure to ATP and the α1-adrenergic receptor agonist, phenylephrine (PE). Not only was the peak response to either agent increased, but the responses were transformed from transient to sustained responses that lasted for several hours (Kapoor and Sladek, 2000). Another interesting and important characteristic of the synergism between ATP and PE was that the response was delayed. This suggested the possibility that the synergism required new protein synthesis. In fact, the synergistic response was obliterated by treatment with actinomycin, an inhibitor of gene transcription (Kapoor and Sladek, 2000). Thus, gene transcription is required that presumably leads to either increased synthesis of existing proteins or production of new proteins. A variety of proteins are candidates to support the observed synergistic response. These include the receptors for ATP and PE, e.g. the P2X purinergic receptor and the α-adrenergic receptor; proteins involved in signal transduction from these receptors to cellular effectors; the VP prohormone itself; proteins involved in prohormone processing and packaging; and proteins involved in stimulus-secretion coupling.

In order to ascertain what mechanism might initiate the synergistic response between ATP and PE, we examined the signal transduction cascades for the receptors mediating the effects of ATP and PE. Since both the response to ATP alone and the synergistic response to ATP plus PE is blocked by an antagonist of the P2X-purinergic receptor, PPADS (pyridoxal-phosphate-6-azophenyl-2′,4′-disulphonic acid), we identified the ATP receptor as the P2X receptor. This receptor is a ligand-gated, non-selective, cation channel that allows $Ca^{++}$, $Na^{+}$, and $K^{+}$ to enter the cell (Chen *et al.*, 1995). Thus, it increases influx of extracellular $Ca^{++}$ via entry through the receptor as well as opening voltage sensitive $Ca^{++}$ channels secondary to depolarization of the membrane via $Na^{+}$ entry. PE is a selective agonist for α-adrenergic receptors. These are $G_{q/11}$-coupled receptors that activate phospholipase C that leads to the production of inositol triphosphate (IP3) which in turn stimulates release of $Ca^{++}$ from intracellular stores. Thus, activation of both P2X and α-adrenergic receptors increases intracellular $[Ca^{++}]$, but by different mechanisms. This represents a point of convergence of these signaling cascades that could give rise to synergistic responses when the two receptors are activated simultaneously. Although further work is required to test the hypothesis that convergence of mechanisms to increase intracellular $[Ca^{++}]$ is responsible for the sustained response, it is clear that a sustained response to a decrease in blood volume or blood pressure such as that induced by hemorrhage has physiological benefit to the organism. During hemorrhage, a sustained increase in plasma VP level initiated via the A1 pathway would be beneficial to support blood pressure until the body has the opportunity to replenish the fluid loss and restore blood volume.

The other two agents co-localized in the A1 pathway are the neuropeptides, NPY and substance P. As shown in Table II these agents also selectively synergize with ATP and PE: NPY synergizes with PE, but not with ATP while substance P synergizes with ATP, but not PE. NPY did not increase VP release when applied alone to HNS explants (Kapoor and Sladek, 2001). However, when applied with PE, NPY converted the transient response to PE into a sustained stimulation of VP release (Kapoor and Sladek, 2001). This is consistent with the report that NPY stimulated VP release when injected into the SON *in vivo* (Willoughby and Blessing, 1987), because NE was probably released from endogenous sources in those experiments. In contrast to NPY, Substance P induced a sustained increase in VP release from HNS explants. It did not show any synergism with PE, but did convert the transient effect of ATP into a sustained increase in VP release (Kapoor and Sladek, 2001). Further studies are required to determine the contribution of NPY and substance P to the VP response to decreases in blood pressure or blood volume, but it is possible that these peptides are critical for eliciting a sustained response under conditions of chronic activation of the A1 pathway.

The mechanisms underlying the selective synergism between substance P and ATP and NPY and PE, probably do not rely on gene transcription and new protein synthesis, because, unlike the synergism between ATP and PE, these synergistic responses are not delayed. However, they may involve signaling cascades that converge to increase intracellular $[Ca^{++}]$, because in both instances the synergism is between pairs of receptors that increase intracellular $[Ca^{++}]$ by IP3-dependent (activation of PLCβ1 by $G_{q/11}$ coupled receptors) and IP3- independent pathways (e.g. influx of extracellular $Ca^{++}$ via P2X receptors or $G_{i/o}$-mediated, IP3-independent mobilization of intracellular $Ca^{++}$ by NPY) [See Sladek and Kapoor, 2001].

## CONCLUSION

Osmotic regulation of VP release is solely dependent on afferent information from the AV3V forebrain region, because this region both directly senses osmolality and integrates information from peripheral osmoreceptors. Since this region regulates drinking behavior as well as VP release (Johnson and Gross, 1993), it integrates both afferent (sensory) and efferent (motor/endocrine) responses concerned with osmotic maintenance of fluid homeostasis. Although this same region can transmit hemodynamic information following activation of

the peripheral renin-AII system, hemodynamic regulation of VP release remains essentially intact in AV3V-lesioned animals. Therefore, hemodynamic information is transmitted to the VP neurons over pathways that do not require the AV3V region. Thus, responses to hypovolemia and hypotension activate pathways and transmitters that are independent of those employed to elicit responses to alterations in plasma osmolality. Under normal conditions, the response to these distinct regulatory signals is integrated by the VP neurons or by presynaptic elements near the VP neurons. This is clearly demonstrated by the effect of water deprivation on plasma osmolality and hematocrit in AV3V-lesioned and sham-lesioned rats (Somponpun *et al.*, 2004). When sham-lesioned animals are water restricted, both pOsm and hematocrit increase significantly indicating that the system is working to maintain homeostasis in both tonicity and blood volume. However, when AV3V-lesioned animals are water restricted, pOsm increases dramatically as mentioned previously, but plasma volume is better controlled than in sham-lesioned animals resulting in changes in plasma volume that are too small to detect by measuring hematocrit (Somponpun *et al.*, 2004). Thus, intact animals integrate information from osmotic and hemodynamic afferent pathways to attempt to maintain homeostasis of both plasma osmolality and blood volume.

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