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Vasopressin in Thermoregulation – Competitive Demands: Experimental Evidence and Theoretical Considerations

M. HOROWITZ, Y. EPSTEIN[1], Y. SHAPIRO[1]

Department of Physiology, Hadassah School of Dental Medicine, The Hebrew University, Jerusalem and [1]Heller Institute, Sheba Medical Center, Tel-Hashomer, Israel

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Summary

Previous studies have substantiated the antipyretic role played by extrahypothalamic limbic system (EXHY-LS) AVP during fever. Repeated attempts to elucidate other thermoregulatory functions of this hormone have failed. Circumstantial evidence, however, suggest central role for this hormone in thermoregulation under hypohydration. Hypohydration, hyperosmolarity and hypovolaemia induce upward shifts in temperature thresholds for activation of heat dissipating mechanisms. When hypovolaemia is superimposed on hyperosmolarity these shifts are additive. Analogously, these two stressors when combined, decrease the osmotic threshold for AVP release. In rats, the elevated temperature thresholds for evaporative cooling and peripheral vasodilation occurring with hypohydration are positively correlated with lower Hypothalamic/EXHY-LS AVP ratio. Reciprocal relations between limbic system and blood AVP contents suggest competitive interaction between central and peripheral demands. Hypothesis for the possible mode of action of central AVP in thermoregulation under hypohydration is discussed.

Key words

Thermoregulation – Osmoregulation – Vasopressin – Fever

Introduction

Body temperature regulation and body fluid adjustment during heat stress are intimately related. Temperature regulation under conditions of hypohydration is readjusted to operate on an elevated temperature "set point" and different thermal sensitivity, primarily of the evaporative cooling effectorial loop. It is not surprising, therefore, that repeated attempts have been made to implicate the possible role of arginine vasopressin (AVP) as a modulator of thermoregulation under hypohydration.

In view of various experimental evidence accumulated in our laboratory in this respect, this presentation aims to re-evaluate the role played by AVP in thermoregulation during hypohydration, when peripheral demands are taken into consideration.

Early Evidence on AVP Involvement in Thermoregulation

1. AVP – a component in the physiological process of thermoregulation

Evidence of the involvement of vasopressin in thermoregulation goes back as early as 1931 when Cushing demonstrated that administration of an extract obtained from the posterior pituitary gland into the ventricles caused vasodilation, sweating and hypothermia. In 1965, Okuno *et al.* reported that intracarotid administration of supra-physiological doses of AVP decreased rectal temperature of hyperthermic rats and suggested a peripheral role for AVP in thermoregulation (Okuno *et al.* 1965). Since

then, additional evidence implicates a causal relationship between AVP and thermoregulation. However, the data are rather controversial and show species differences. For example, intraventricular administration of AVP produced a hypothermic response in rodents but induced hyperthermia in rabbits (Kasting *et al.* 1980, Lipton and Glyn 1980). Likewise, while in some species body/hypothalamic heating elevate plasma AVP and hypothalamic cooling reduce or inhibit the release of AVP in the plasma (Forsling *et al.* 1976, Hayward and Baker 1968), in other species cooling may trigger plasma AVP elevation (Zeisberger *et al.* 1988). The role played by AVP under these circumstances has not been elucidated.

2. Fever and central AVP

The direct role of AVP in thermoregulation has been shown only during fever. In that state AVP has been identified as an endogenous antipyretic, operating in the ventral septal area (VSA) of the limbic system. Considerable amounts of the hormone found in this discrete area during fever may reflect central specific dynamics. The inability to decrease body temperature of afebrile animals by direct administration of the hormone to the vicinity of the VSA further supports the specificity of this function.

A large body of evidence derived from neuroanatomical, physio-logical and biochemical studies (Kasting *et al.* 1982) has substantiated our knowledge of this peptidergic antipyretic system. Cell bodies, axons and nerve terminals projecting from paraventricular (PVN) and bed nuclei of the stria terminalis, immunoreactive for vasopressin, terminate in the VSA (Naylor *et al.* 1987). Along with this, specific AVP receptors binding sites (V1 subtype) have been identified. Immunoreactivity of this system increases with fever (Merker *et al.* 1980) and electrical stimulation of the PVN, which enhances immunoreactivity, blocks the rise of temperature associated with fever (Disturnal 1986). In contrast, administration of a specific AVP antagonist enhances fever (Kasting 1980, Wilkinson and Kasting 1986). But while the efferent pathway in fever suppression by AVP is already established, our understanding of the afferent pathway leading to AVP release is less understood. Possibly a thermosensitive area in the septal area (Nakashima *et al* 1989) may play a role.

Convergence of Thermal and other Homeostatic Signals on PO/AH

The thermoregulatory system does not work in isolation and shares its effector organs with other homeostatic regulatory systems. Thus, the net thermoregulatory response is the result of competitive interaction between various homeostatic thermal and non-thermal drives, all "drained" into corresponding control structures in the hypothalamus and extrahypothalamic limbic system (Hori *et al.* 1988). The integrity of the system depends on a well coordinated hierarchy of interconnected hypothalamic and extrahypothalamic thermosensitive/thermo-regulatory structures, with the PO/AH playing the leading role. A number of studies have demonstrated that various AVP neuronal populations, with axonal projections to hypothalamic and extrahypothalamic areas increase their immunoreactivity in a stress-specific manner (Kasting *et al.* 1982). Furthermore, some of these non-thermal stressors may modify thermoregulation. Thus, Kasting (1986) showed that both haemorrhage and hyperosmolarity, leading to increased AVP release into the CSF, suppress the fever response in rats. A similar observation was reported for sheep (Kasting *et al.* 1981) in which intravenous administration did not mimic this effect.

Taking into consideration the findings that electrical stimulation, e.g. in the septal area may increase AVP immunoreactivity of these projections, and in view of our knowledge of the role played by AVP during fever, one may hypothesize that AVP plays a role in other thermoregulatory functions.

Thermoregulation during Hypohydration and the Involvement of AVP

1. Theoretical considerations

Accumulating circumstantial evidence suggests that AVP plays a role in thermoregulation during hypohydration and its consequences, hyperosmolarity and hypovolaemia. Hypohydration as well as hyperosmolarity and hypovolaemia produce an upward shift in thermoregulatory thresholds

(T-Tsh). In the rat, this is exhibited primarily by elevation of the controlled body temperature and the threshold for evaporative cooling (salivation, S-Tsh) (Horowitz and Meiri 1985, Horowitz 1990). Hyperosmolarity superimposed on hypovolaemia produced greater elevation in S-Tsh than each of these stressors alone and severe hypovolaemia alone caused a delayed vasodilation threshold. It was noted that while only small changes in osmolarity were required to elicit thermoregulatory changes, a greater blood volume deficit was required to affect thermoregulation. Analogously, Dunn *et al.* (1973) demonstrated that a lower osmotic threshold and increased sensitivity to osmotic stimulation for AVP release occurs during moderate hypovolaemia. They also showed that the osmotic threshold for AVP release is lower than the hypovolaemic threshold. These two phenomena in parallel (Fig. 1) call our attention to a possible role played by AVP in the interaction between the osmoregulation/body fluid adjustment system and thermoregulation.

This was tested by various investigators, however, direct experiments aimed at elucidating the role played by AVP in thermoregulation under conditions of body water deficit and impaired osmolarity, failed to do so (Doris 1983).

2. AVP content in the brain during fever and osmotic stress and the presence of thermosensitive neurones in the VSA

Push-pull perfusion studies revealed that experimentally induced fever (e.g. PGE1 induced fever) is accompanied by a significant increase in the AVP content of VSA perfusates in both sheep (Cooper *et al.* 1979) and rats (Langraf *et al.* 1990). This increase was considered to be specific, since no AVP elevation was found in other brain areas (Langraf *et al.* 1990). This specificity was also found following stimulation of AVP release by various convulsive drugs (Mens *et al.* 1983). Hyperosmolarity, as well as hypovolaemia can also induce alterations in the brain AVP content. Under such stimulation, the AVP content was elevated in the hypothalamus (e.g. SON, PVN) as well as in various locations in the VA3V and in the ventral septum, the site of action of AVP during fever (Demotes-Mainard 1986). This may explain the resulting antipyretic response to hypovolaemia or hypertonicity in febrile rats.

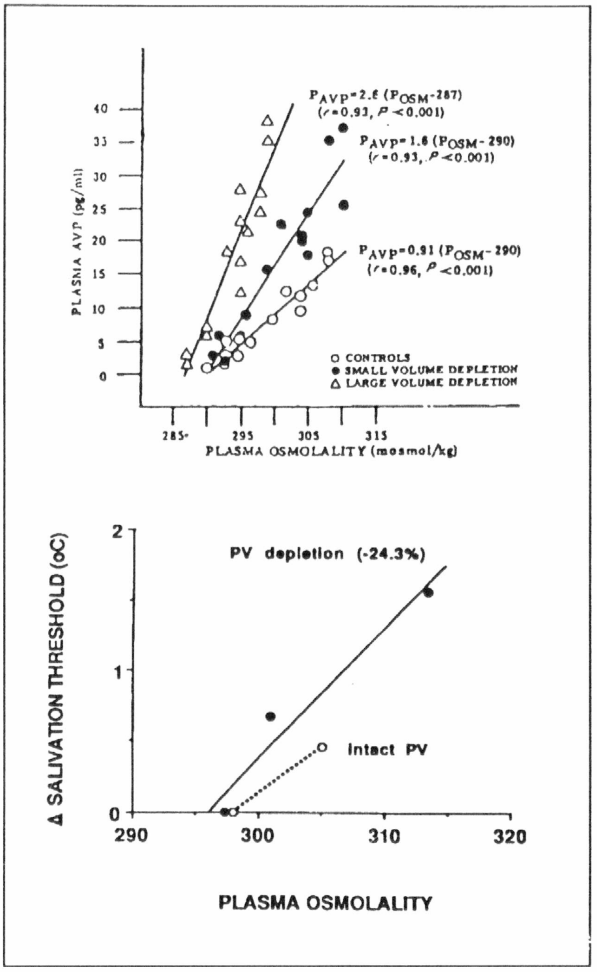

Fig. 1
Upper panel: osmotic threshold for AVP release into the blood in normovolaemic and hypovolaemic rats (from Dunn *et al.* 1973). Bottom panel: the elevation in salivation temperature threshold in heat stressed, hyperosmotic and hyperosmotic-hypovolaemic rats. (Reproduced from Horowitz and Meiri 1985).

The above mentioned observations and the existence of thermosensitive neurones in the VSA may favour the idea that AVP plays a role in thermoregulation during hypohydration. We should bear in mind, however, that while AVP produces antipyresis during fever , thermoregulation during hypohydration is on a hyperthermic level.

Could the same hormone play two opposing roles?
Partial reconciliation of this discrepancy may be found in the findings of Epstein *et al.* (1983), who reported a pronounced decrease

Table 1

Rectal temperature (T_{re})and AVP in the hypothalamic and extrahypothalamic limbic system (M ± S.E.M.) in normothermic and heat stressed rats subjected to osmotic and hypovolaemic stresses

Treatment	T_{re}	HY-AVP	EXHY-LS-AVP
	°C	pg/mg	pg/mg
NORMOTHERMIA			
Control	38.0 ± 0.1	338 ± 14	28.0 ± 2.8
WD (72 h)		135 ± 10	5.9 ± 0.6
Hyosmol		351 ± 17	34.2 ± 2.1
Hypvol		338 ± 24	27.3 ± 4.2
Hyosmol & Hypvol		432 ± 23	31.9 ± 1.7
HYPERTHERMIA			
Control	39.2 ± 0.2	633 ± 12	35.6 ± 3.0
Thermal Deh	40.3 ± 0.1	436 ± 23	62.9 ± 2.0
Hyosmol	39.3 ± 0.2	507 ± 18	39.6 ± 0.4
Hypvol	40.5 ± 0.1	383 ± 11	75.2 ± 3.3
Hyosmol & Hypvol	39.8 ± 0.1	331 ± 9	50.5 ± 2.2

WD-water deprivation; Hyosmol hyperosmolarity; Hypvol-hypovolaemia
Thermal Deh-Thermal dehydration.
Data were reproduced from Epstein *et al.* 1990.

in AVP content in both hypothalamic and extrahypothalamic limbic structures of the rat's brain following long-term water deprivation (3 days). Similar findings were reported by Negro-Vilar and Samson (1979) following 5 days' water deprivation.

Elevated T-Tsh can then be explained by depletion of AVP from the septal area.

Hyperosmolarity, Hypovolaemia and Heat Stress

To further elucidate the involvement of AVP in thermoregulation during hypohydration, we (Epstein *et al.* 1990) conducted experiments in which the AVP content in various brain areas of the limbic system was measured under various combinations of heat stress, hypohydration, hyperosmolarity and hypovolaemia. Progressive levels of chronic hypohydration resulted in a graded depletion in both the hypothalamic (HY) and extrahypothalamic limbic system (EXHY-LS) AVP concentrations. In contrast, continuous exposure to moderate heat during which regulated hyperthermia attained a plateau, signifying normal thermoregulatory activity, brought about progressive elevation in both HY and EXHY-LS AVP concentration. Acute manipulation of body fluid osmolarity and volume showed no significant effect although a tendency for elevation was noticed. This tendency became significant during thermal dehydration or a combined heat and osmotic/hypovolaemic stress. The rise in rectal temperature under these stresses was correlated with an increase in AVP concentration in EXHY-LS and with a concomitant reduction in HY AVP from its peak level attained during heat stress alone (Table 1). In Fig. 2 the correlations between rectal temperature, HY and EXHY-LS are depicted. The data suggest that 1. heat stress specifically elicits elevation in AVP concentration (with a reciprocal relationship between HY and EXHY-LS AVP); 2. The greater the elevation in body temperature the higher is the HY/EXHY-LS AVP ratio. A plot of T-Tsh in intact rats subjected to similar stressor conditions, in respect to HY/EXHY-LS content following exposure to heat stress

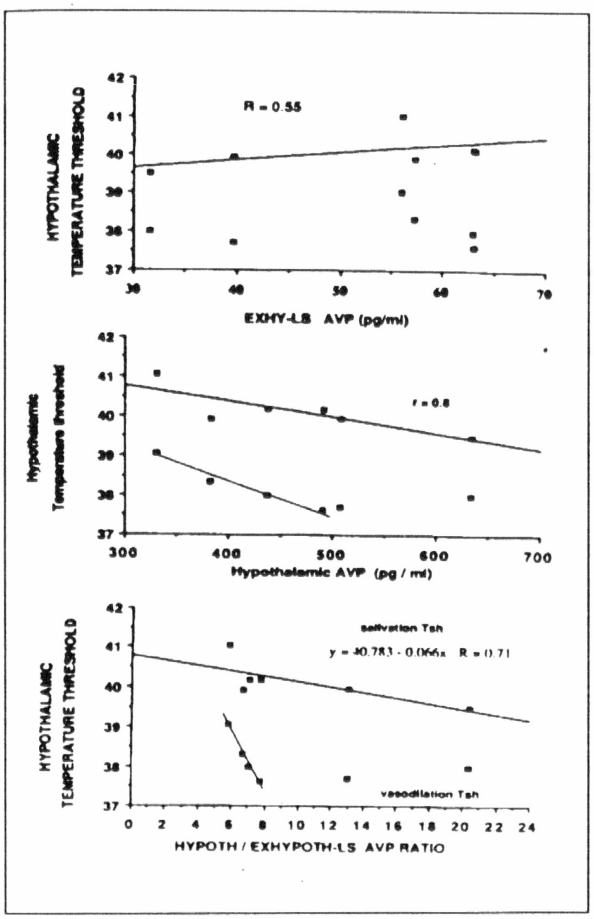

Fig. 2

Hypothalamic vasodilation Tsh and salivation Tsh as a function of limbic system AVP concentration. The individual correlations imply that the hypothalamic AVP content has more weight in this correlation. (From Horowitz 1990).

and hypohydration or hypovolaemia and hypertonicity, demonstrates that elevations in T-Tsh are correlated with a decrease in HY/EXHY-LS ratio of AVP.

In contrast to our findings, Langraf *et al.* (1990) could not show an elevation in septal AVP during artificial heating. Their experimental protocol differed from ours in the short duration of artificial heating (1 h vs 8-10 h) and in the fact that the animals were anaesthetized. Simon and Nolte (1989), studying thermal effects on osmotic control of ADH release have shown that the AVT (arginine vasotocin) producing system is particularly susceptible to brain hyperthermia. Positive temperature coefficients were evident in mammals as well. It is therefore possible that the "build up" of elevated central AVP level in response to environmental heat stress (natural hyperthermia) is a time-dependent process. A time-dependent redistribution of central AVP has been shown under other stimulations. Mens *et al.* (1983) for example, showed time dependent differences in septal AVP accumulation following histamine and pentylenetetrazol administration.

Hypothalamic-extrahypothalamic Limbic System (HY-EXHY-LS) vs Hypothalamic Pituitary Plasma Axes (HY-PT-P)

While several physiological stimulations elicit the activation of both HY-PT-P and HY-EXHY-LS axes other stimuli are specific and activate the HY-EXHY-LS pathway alone.

A linear correlation was found between plasma and CSF AVP elevations in response to osmotic stress. Fever, as well as osmotic stress, induce plasma AVP elevation. Nevertheless, this elevation may be secondary to the fever response and may be associated with the hypovolaemia and increased sweating known to occur during fever. Unfortunately, data are insufficient to draw a correlation between plasma and central AVP elevations.

In the experimental design of Epstein *et al.* (1983, 1990), the peripheral and central AVP response to varying osmotic/hypovolaemic stimuli was compared during normothermia and the following "build-up" of heat stress induced high AVP central content. This allowed us to evaluate the interactions between the two stimuli. Similarly to previous findings, during normothermia, a linear (negative) correlation between plasma and both septal and hypothalamic AVP content was observed. No correlation could be framed, however, between these components during heat stress, thus suggesting competitive (?) demands between peripheral and central AVP dependent drives.

In respect to the involvement of AVP in physiological (in addition to pathophysiological) processes of thermoregulation we can currently provide data suggesting a linear, negative correlation between HY/EXHY-LS and T-Tsh elevations. No correlation, however, has been found between plasma AVP and central thermoregulatory activity. This indicates that AVP plays a central role in thermoregulation.

Our data do not provide conclusive results as to the site of action of AVP in

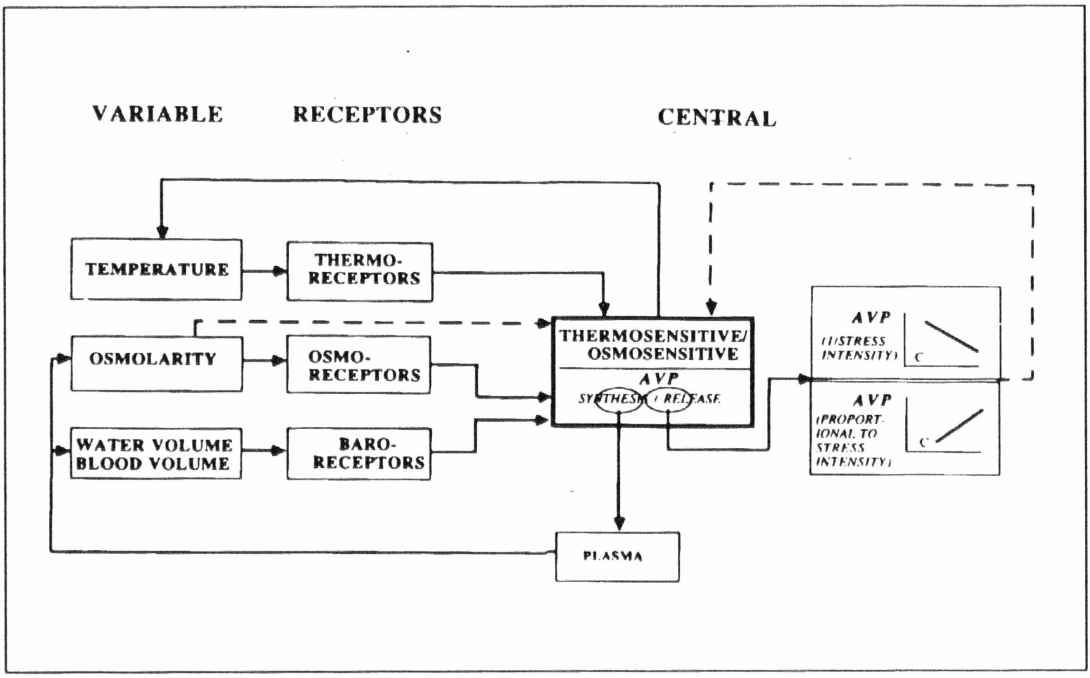

Fig. 3
Peripheral and the possible central roles of AVP during a combined stress induced by heat and dehydration. Broken lines – hypothesized pathways. (Reproduced from Horowitz 1990).

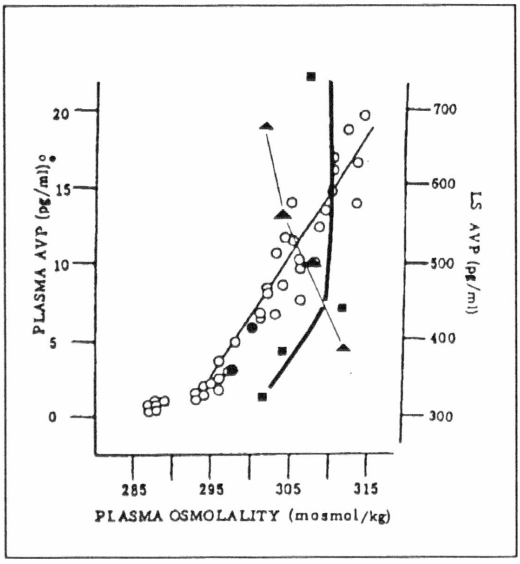

Fig.4
Plasma osmotic threshold for AVP release during normothermic (circles) and hypothermic (squares) conditions. Triangles depict the matched HY plus EXHY-LS AVP content during hypothermia. Data depicted by open circles were derived from Dunn *et al.* 1973. Black triangles and squares were reproduced from Epstein *et al.* 1990.

physiological thermoregulation. Both the hypothalamus alone and hypothalamus and septum simultaneously, could be the candidates. It could be suggested, however, that similarly to the antipyretic role of AVP during fever, AVP can counter the elevation of T-Tsh during conditions of heat stress and dehydration. The cellular effects of AVP, leading to alteration in "set-point" of the temperature regulation system is not fully understood. We do know, however, that its action is receptor mediated, and it may change ionic membrane permeability (e.g. Ca, Na) which inturn will affect thermal sensitivity/stimulus transmission.

Central vs Peripheral AVP – Competitive Demands

It is evident from the experiments of Epstein *et al.* (1990) that increased peripheral demands for AVP (osmotic, hypovolaemic stresses) during heat stress were associated with elevated body temperature and decreased central AVP concentration. This may indicate that central AVP distribution during heat stress is the net result of competitive osmotic (peripheral) and thermoregulatory (central) drives, as depicted in Fig. 3. Our data suggest

that during heat stress, with increased peripheral demands, less AVP is directed to the HY-EXHY-LS axis. This is exhibited primarily in PO/AH AVP content (Fig. 4). Immunocytochemical data, as well as many others, have shown that HY-PT-P and HY-EXHY-LS AVP pathways are furnished from different AVP pools (e.g. Castel and Moris 1988). Thus, the mode of competition suggested is hard to reconcile unless there is a ceiling of the synthesizing capacity. Unfortunately, comparative data are sparse, leaving us with question unanswered.

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M. Horowitz, Department of Physiology, Hadassah Medical School, The Hebrew University, P.O.B. 1172, Jerusalem 91010, Israel.