

# Vasopressin – Emerging Importance in Sepsis

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## Introduction

A hormone with two equally descriptive names, Vasopressin and Antidiuretic Hormone, Vasopressin as I'll call it, has been with us, and most of the rest of life of earth, for several hundred millions years. This may well explain its multitude of uses in the body, from the obvious osmotic control effects, past the slightly less well known pressor effects, to the obscure and uncertain central involvements in memory, mood and pain perception.

In the following paragraphs I will cover four main areas. An introduction to Vasopressin and its history will be followed by a review of the molecular biology regarding receptors and other modes of action. Its broad actions in the physiology of cardiovascular control will lead on to the discussion on its potential roles in the management of sepsis and hypotension.

## Vasopressin fact list

It has been with us for ages, ever since our long distant ancestors left the osmotically benign oceans, and set up camp on land. In all mammals except pigs, it is in the form Arginine Vasopressin, with our porcine cousins using lysine Vasopressin. This is not completely trivial information as porcine models of haemorrhagic, septic and cardiac arrest scenarios have been extensively used, particularly in the field of CPR research.

It is a nonapeptide, synthesized in the hypothalamus, and other sites in the brain, and is extremely potent, active in the 1-3pg/ml range of concentrations. Compared to adrenaline and noradrenaline, its action is relatively long, with a T1/2 of 24 minutes, and is renally and hepatically metabolised, with a contribution by blood based vasopressinase.

Central to understanding Vasopressin's effects in sepsis are the specific receptors present for it, as well as the other channels and second messengers it can modulate. These are all the tools it can use to effect changes throughout the body. It is the differential distribution of these receptors in different tissues, which give rise to its special effects.

## Vasopressin Receptors and Other mechanisms

The V1 receptor is present in the vasculature of most organ systems, and, via Gq mediated signalling, causes a rise in Ca<sup>++</sup> leading to vasoconstriction.

V1 receptor activation also inhibits IL-1 $\beta$  formation, reducing NO production.

The V2 receptor is predominantly found in the Renal Collecting duct, where it stimulates the inclusion of Aquaporin channels in the apical membrane of the cells, allowing movement of water into the hyperosmolar renal medulla. This creates concentrated urine, and conserves free water. There is evidence that V2 receptors are present in vessels and, via production of cAMP, produce vasodilation in certain tissues.

V3 receptors, somewhat less well characterized, are found in the brain, particularly the pituitary and hypothalamus. Vasopressinergic projections are found in many parts in the brain, and play a role in memory, social behaviour and other processes.

Oxytocin receptors (OTR) are a possible point of action for Vasopressin, and produce a vasodilatory response via Nitric Oxide release.

## Other Sites of Action

The K-ATP channel, activated particularly in sepsis, is inhibited by Vasopressin. This may prevent the smooth muscle hyperpolarization and subsequent vasodilation and relative unresponsiveness of the circulation to catecholamine vasopressors.

## V1 Receptor-Effector Coupling

Vasopressin binds to the V1 receptor and stimulates Phospholipase C, increasing Inositol Triphosphate levels, which in turn increase intracellular Ca<sup>++</sup> levels. This rise in Ca<sup>++</sup> levels leads to Vasoconstriction, and additional effects depending on the cell, such as ACTH release, platelet aggregation and Glycogenolysis. Long term effects of V1 stimulation may include modulation of cell growth.

V1 receptors may also affect the arachidonic acid pathway, via alterations in Phospholipase A2's activity.

## V2 Receptor Effector Coupling

V2 receptors act by Gs mediated increases in cyclic AMP, which in renal collecting duct cells lead to Aquaporin channel insertion, and in vascular smooth muscle, to vasodilation.

## Baroregulation

Now that we've covered a bit of the receptor pharmacology, let us turn to some of the physiological roles of vasopressin.

Left Atrial, Carotid and Aortic Arch baroreceptors sense arterial pressure, and a reduction in MAP triggers the release of Vasopressin. The release is exponential in nature, and AVP levels, normally 3pg/ml can rise to 50-100pg/ml during severe hypotension.

Of particular importance is Vasopressin's modulatory effect on the arterial baroreflex itself. If given to healthy volunteers, it doesn't cause hypertension, since the raised SVR is countered by a lower HR and Cardiac output. However, in sepsis, autonomic dysfunction blunts this alteration, leading to increased blood pressure.

In addition, Vasopressin markedly enhances the sensitivity of vascular smooth muscle to traditional catecholamine vasopressors.

### Osmoregulation

Vasopressin's V2 receptor mediated modification of renal collecting duct permeability is implicit in its other name; Anti Diuretic Hormone. Osmoreceptors in the subfornical organ, the organum vasculosum of the lamina terminalis and the median preoptic nucleus signal the Supraoptic nucleus and the Paraventricular nucleus to release stored Vasopressin. This release occurs at the axons endings in the posterior pituitary gland.

The slope of the response curve is linear, and maximal urine concentrating occurs at levels of 15-20pg/ml, below those levels is associated with significant hypotension.

### Cardiovascular action

The cardiovascular actions of Vasopressin are complex and still incompletely understood. Its peripheral actions are relatively well defined, but its central effects on cardiovascular regulation, and the influences on its production and secretion remain to be clearly delineated.

In normal subjects given Vasopressin, a hypertensive response is only seen at high doses, due to its stimulation of the baroreceptor reflex.

The regional variations in blood flow secondary to low dose Vasopressin infusion cause a decrease in skin, muscle and possibly bowel bloodflow, although this is still debated. Increases in cerebral, renal and myocardial bloodflow occur, secondary to increased blood pressure, and possible local vasodilation through V2 and OTR activation.

Vasopressin, unlike Noradrenaline and Adrenaline, causes renal efferent arteriolar vasoconstriction, whilst sparing the afferent arteriole. This maintains or increases transglomerular pressure and GFR. Other renovascular alterations secondary to V2, OTR and prostaglandin synthesis occur, but are poorly understood.

As mentioned, Vasopressin increases baroreceptor reflex sensitivity in normal patients, and inhibits KATP channels in smooth muscle. This last point may be important, in that KATP channel modulation has been implicated in the myocardial protection afforded by volatile anaesthetics.

In addition Vasopressin tends to reduce nitric oxide production via inhibition of IL-1 $\beta$  and enhances smooth muscle sensitivity to catecholamines.

### Other Actions

Vasopressin has been used in the therapy of diabetes insipidus, von Willebrand's disease and appears to be involved in

many central nervous system processes, including learning, memory and mood modulation

### Possible Areas of Use

With regard to its action as a vasoconstrictor, Vasopressin is currently being used in CPR, Septic shock, Post CPB shock and in other areas requiring a vasopressor.

### Vasopressin and Sepsis

Vasopressin's use in sepsis stemmed originally from Landry's observation in 1994 that patients in vasodilatory septic shock were very sensitive to the vasopressor action of infused Vasopressin. Since then increasing interest in its unique actions in sepsis has stimulated research.

Several studies have looked at its use in advanced sepsis, in the situation of hypotension unresponsive to the traditional therapies of fluid resuscitation and catecholamine vasopressors.

In 1997 Landry showed, in a matched cohort, that patients with septic shock had low levels of Vasopressin, compared with patients in cardiogenic shock with similar levels of hypotension. Infusion of Vasopressin at 0.04iu/min in the septic patients significantly increased their SVR and blood pressure.

Malay et al, in the only randomised control trial thus far, showed that Vasopressin at 0.04iu/min compared to placebo significantly increased systolic arterial pressure. No alterations in Na levels, creatinine levels were noted, and a worse base deficit in the placebo group was seen.

Holmes et al, in 2001 in a retrospective case series, showed that Vasopressin at 0.04iu/min significantly increased both MAP and urine output compared to pre-infusion levels, and decreased the pressor dosage required significantly.

Patel's group in 2002 demonstrated improvements in MAP, a decrease in the total pressor dosage required, together with an increased urine output and creatinine clearance.

The literature contains several case reports describing the use of Vasopressin as a therapy of last resort in sepsis, with evidence of improvement in haemodynamic variables.

Unfortunately no large enough RCT has been done to demonstrate any change in mortality amongst patient groups.

### Sepsis – Why the low levels?

Any point on the chain, from the signal to produce Vasopressin, to its metabolism, could theoretically lead to decreased levels.

Sharshar et al demonstrated reduced pituitary levels of Vasopressin, combined with low blood levels in 3 patients, using MRI imaging. Guisti-Paiva showed that, in rats, central blockade of inducible Nitric Oxide synthetase cause a marked rise in Vasopressin concentration and blood pressure in a sepsis model.

Current evidence point toward a defect in the production of Vasopressin, possibly due to Nitric Oxide mediated signalling

### Sepsis – Why the sensitivity?

As already mentioned, Vasopressin appears to modulate baroreflexes. This may explain some of the sensitivity to infused Vasopressin in septic patients. In addition, Vasopressin markedly enhances the noradrenaline induced contraction of smooth muscle, perhaps since they utilize similar pathways within the cell.

### Potential Problems with its use

Vasoconstriction of mesenteric and other circulations could cause ischaemic damage and worsen outcomes. However, evidence for these deleterious effects is generally only in high dose infusions used for the treatment of variceal haemorrhage, a situation where one wants to decrease the mesenteric blood flow in any case.

The potential for hyponatraemia, seen fairly regularly in ICU patients, is there, but can be managed by appropriate free water restriction.

Lastly, vasopressin's patent expired sometime ago, lessening pharmaceutical interest in the drug. However, the use of synthetic analogues, specific to receptors, or blocking Vasopressin receptors is being actively investigated, and may stimulate further research.

### Discussion

The body's reaction to any major cardiovascular insult causing hypotension is complex, and not merely a surge of catecholamines. Several interlinked systems are present and act together to maintain cardiovascular stability. The vasopressinergic system is one of those, and is particularly affected in septic shock.

Vasopressin is a dual, or perhaps multi functional molecule, with differing dose ranges for those functions. The potential side effects are very much dependent on the concentration in plasma.

In current practice we manage to keep patients alive much longer than they would have survived without treatment. Thus the argument that physiology seen in these advanced stages of sepsis is somehow adaptive is less appealing.

Just as we routinely replace electrolytes, fluids and all manner of other things, perhaps we should be looking to replace Vasopressin in patients in advanced sepsis.

The many functions of vasopressin make it a target for pharmacological manipulation. We may, along the way, end up with depressed patients who go to the toilet incessantly, whilst trying to remember where they are, or hyponatraemic hypertensives, wondering why their fingers are blue, but hopefully we'll soon be able to use vasopressin or various analogues

for some of the more difficult conditions such as severe sepsis.

Even if, ultimately we do not, we will have learned much from the journey, and will hopefully be closer to truly understanding the pathogenesis of the sepsis syndrome.

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