Vasopressin and its role in critical care

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Key points

Vasopressin is an endogenous hormone responsible primarily for osmoregulation and blood volume control.

Vasopressin use in cranial diabetes insipidus and variceal bleeding is well established.

In asystolic cardiac arrest, there is increasing evidence that vasopressin may be more effective than epinephrine in restoring cardiac output.

Vasopressin depletion in septic shock may contribute to catecholamine-resistant hypotension.

Vasopressin replacement in septic shock may correct some of the haemodynamic disturbance but has yet to be shown to reduce mortality.

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Vasopressin or antidiuretic hormone is a potent endogenous hormone which is responsible for regulating plasma osmolality and volume. It acts as a neurotransmitter in the brain to control circadian rhythm, thermoregulation, and adrenocorticotrophic hormone release (ACTH). The therapeutic use of vasopressin has become increasingly important in the critical care environment in the management of cranial diabetes insipidus, bleeding abnormalities, oesophageal variceal haemorrhage, asystolic cardiac arrest, and septic shock.

Physiology

Vasopressin is a nonapeptide, synthesized as a pro-hormone in magnocellular neurone cell bodies of the paraventricular and supraoptic nuclei of the posterior hypothalamus. It is bound to a carrier protein, neurohypophysin, and transported along the supraoptic hypophyseal tract to the axonal terminals of magnocellular neurones located in the posterior pituitary. Synthesis, transport, and storage takes 1–2 h. Normal plasma concentrations are <4 pg ml^{-1}. It has a half-life of 10–35 min, being metabolized by vasopressinases which are found in the liver and kidney. Vasopressin acts on V1, V2, V3, and oxytocin-type receptors (OTR).

V1 receptors are found on vascular smooth muscle of the systemic, splanchnic, renal, and coronary circulations. They are also located on myometrium and platelets. These G-protein-coupled receptors activate phospholipase C via Gq G-protein, which ultimately leads to an increase in intracellular calcium. The major effect is to induce vasoconstriction, the magnitude of which is dependent on the vascular bed. In the pulmonary circulation, vasodilation is produced via nitric oxide release.

V2 receptors are predominantly located in the distal tubule and collecting ducts of the kidney. These G-protein-coupled receptors stimulate Gs G-protein to activate adenylate cyclase, increasing CAMP, causing the mobilization of aquaporin channels. These channels insert into the apical membrane of the distal tubules and collecting duct cells. V2 receptors are essential for plasma volume and osmolality control. Their presence on endothelial cells induces the release of Von Willebrand Factor (VWF) and Factor VIII:coagulant (FVIII:c). VWF protects FVIII from breakdown in plasma and is important in binding platelets to the site of bleeding.

V3 receptors are found mainly in the pituitary. They are Gq-coupled G-protein receptors which increase intracellular calcium when activated. They are thought to be involved in ACTH release and may act as a neurotransmitter or mediator involved with memory consolidation or retrieval and body temperature regulation.[1, 2]

Vasopressin has equal affinity for OTR as oxytocin. Activation of these receptors raises intracellular calcium via the phospholipase C and phosphoinositide pathway. They are found predominantly on myometrium and vascular smooth muscle. In addition, they are located on vascular endothelial cells where they increase constitutive endothelial nitric oxide synthase activity, increasing nitric oxide, which is a potent vasodilator. It is postulated that OTR placement on vascular endothelium and their subsequent activation may account for vasopressin's selective response on different vascular beds. V1 and V2 receptors located on the vascular endothelium may also have a role by increasing NO production.[3]

Control of release

Table 1 illustrates the factors which affect the release of vasopressin. Most factors (physical or chemical) cause direct stimulation of vasopressin release. Hypoxaemia and acidosis stimulate the carotid body chemoreceptors causing vasopressin release. Catecholamine stimulation of central adrenergic receptors has a variety of effects on vasopressin release. At low concentration, catecholamines activate α1 receptors inducing vasopressin release. At

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Table 1 The major factors involved in the release of vasopressin from the posterior pituitary. *Norepinephrine can stimulate release by α1 receptors and inhibit release by stimulation of α2 and β receptors

Stimulate release	Inhibit release
Increasing plasma osmolality	Decreasing plasma osmolality
Reduced plasma volume	Increased plasma volume
Chemical mediators	Chemical mediators
Norepinephrine*, dopamine, acetylcholine, histamine, prostaglandins, angiotensin II, endotoxin, cytokines	Opioids, GABA, ANP, norepinephrine*
Nausea, vomiting	
Pain, Stress	
Hypoxia, $\uparrow Paco_2$, acidosis	
Exercise, IPPV	

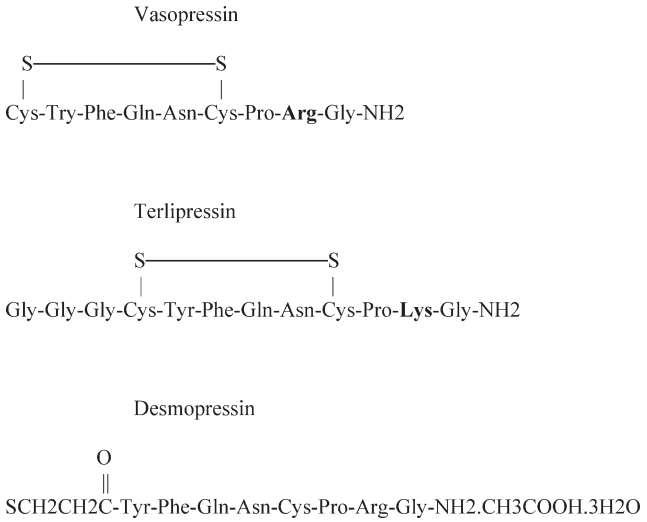

Fig. 1 The structure of vasopressin (8-arginine-vasopressin) which is the exact synthetic protein of human endogenous vasopressin is shown. Terlipressin (triglycyl-lysine-vasopressin) is a prodrug requiring the enzymic cleavage of the three glycyl residues to form the active lysine vasopressin found naturally in pigs. Desmopressin, DDAVP, is an arginine vasopressin analogue.

higher concentration, their actions on α2 and β receptors inhibit vasopressin release.[3]

The most potent stimulus for vasopressin release is an increased plasma osmolality. Central osmoreceptors in the subfornical organ nuclei, located outside the blood–brain barrier, monitor systemic plasma osmolality. Peripheral osmoreceptors are found in the portal veins and give early warning of ingested food and fluid osmolality. Signals are transmitted via the vagus to the nucleus tractus solitarius, area postrema, and ventrolateral medulla, and finally to the paraventricular nuclei and supraoptic nuclei, where vasopressin is manufactured in the magnocellular neurone cell bodies. Osmolality is finely controlled in the range of 275–290 mOsm kg^{-1}. A 2% decrease in total body water results in a doubling of the vasopressin plasma concentration. This acts on V2 receptors increasing the collecting duct permeability to water. Conversely, a 2% increase in total body water will result in maximal suppression of vasopressin release and maximally dilute urine of 100 mOsm kg^{-1}.

Plasma volume and the resultant change in arterial pressure are less sensitive controllers of vasopressin release, but the potential response far exceeds that induced by changes in plasma osmolality. A 20–30% reduction in mean arterial pressure (MAP) is needed to induce a response. This results in a reduced arterial baroreceptor output causing an exponential increase in vasopressin release. The response to a reduction in plasma volume and its effect on vasopressin release is not well defined but is probably qualitatively and quantitatively similar. An 8–10% reduction in plasma volume, detected by atrial stretch receptors, is required to induce an exponential increase in vasopressin release. A reduction in plasma volume increases the sensitivity of the osmoreceptors and vice versa. However, as the plasma volume decreases, it becomes increasingly difficult to maintain a normal plasma osmolality. The defence of plasma volume always takes precedence over plasma osmolality. Less is known about acute elevations in arterial pressure and volume, but both appear to suppress vasopressin release.[4]

Pharmacology

In most mammals, 8-arginine vasopressin is the native antidiuretic hormone. Original preparations were extracted from posterior pituitary cells (Fig. 1). It is now made as a synthetic peptide, argipressin. It is metabolized in a way similar to endogenous vasopressin and has a half-life of 24 min.

Tri-glycyl-lysine-vasopressin is terlipressin or glypressin. Arginine is replaced with lysine at position 8 and has three glycine residues at the beginning of the peptide. The lysine substitution makes it identical to pig vasopressin. The three glycine residues make terlipressin a prodrug. In the body, these are enzymatically cleaved by endothelial peptidases to produce lysine vasopressin. It has an elimination half-life of 50 min, but an effect half-life of 6 h.

Desmopressin (1-deamino-8-*O*-arginine-vasopressin, DDAVP) is a synthetic analogue of arginine vasopressin. It has 10 times the antidiuretic action of vasopressin, but 1500 times less vasoconstrictor action. These modifications make metabolism slower (half-life of 158 min).

Therapeutic uses

Cranial diabetes insipidus

The causes of diabetes insipidus are listed in Table 2. In cranial diabetes insipidus, there is a lack of vasopressin due to destruction of part or all of the hypothalamus or pituitary gland. This is in contrast to nephrogenic diabetes insipidus where there is a resistance of the kidney to vasopressin's action. Clinically, the patient produces vast quantities of dilute urine. The key feature is that

Table 2 The causes of diabetes insipidus

Cranial	Nephrogenic
Familial	Familial
Idiopathic	Idiopathic
Neurosurgery	
Tumours	
Craniopharyngioma; hypothalamic gliomas; metastases, e.g. breast; lymphoma/leukaemia	Renal tubular acidosis; hypokalaemia; hypercalcaemia
Infections	Drugs
Tuberculosis; meningitis; cerebral abscess	Lithuim; glibenclamide; demeclocycline
Infiltrations	
Sarcoidosis	
Vascular	
Haemorrhage; aneurysms; thrombosis	
Trauma	
Head injury	

urine osmolality is inappropriately low compared with the plasma osmolality. Desmopressin (DDAVP) can reduce the polyuria, nocturia, and polydypsia. It is given nasally, sublingually, i.m., or if in critical care setting, i.v..

Syndrome of inappropriate antidiuretic hormone

The syndrome of inappropriate antidiuretic hormone is a form of hyponatraemia where the level of antidiuretic hormone is inappropriate to the osmotic or volume stimuli, almost a reverse of cranial diabetes insipidus. The causes can be grouped into ectopic secretion by tumours, particularly small cell carcinoma of the lung, central nervous system disorders, including tumours, infection, and trauma, and pulmonary lesions, mainly infections and drugs, for example, carbamazepine. There are strict diagnostic criteria which include the need for normovolaemia, normal endocrine, cardiac, and liver function, in the presence of urinary osmolality greater than plasma osmolality. Treatment is the correction of hyponatraemia appropriate to the speed of onset and eradication of the underlying cause.

Bleeding abnormalities

Vasopressin acts via extra-renal V2 receptors to increase predominantly FVIII:c and VWF. These actions are very useful in certain types of Von Willebrand disease and in mild forms of haemophilia A, where there is a relative deficiency of FVIII:c. Likewise, in patients with impaired platelet function due to drugs such as aspirin or renal failure, DDAVP (0.3 μg kg^{-1} i.v. over 15–30 min) may be useful before minor surgical procedures. The exact mechanism of its effect in these situations is not fully understood, but the increase in FVIII levels which allows activation of FX and the more efficient activation of platelets are all important.[5]

Oesophageal variceal haemorrhage

In chronic liver disease, fibrosis of the liver results in an increase in portal venous pressure as the mesenteric blood requires increasing pressure to flow through the scarred liver. Eventually, collateral circulation opens up to allow the return of blood to the systemic circulation through shunts. One of these is the intrinsic and extrinsic gastro-oesophageal veins. These veins become increasing dilated, forming varices. Vasopressin, acting via V1 receptors, reduces portal blood flow, portal systemic collateral blood flow, and variceal pressure. Its side-effects include increased peripheral vascular resistance, reduced cardiac output, and decreased coronary blood flow. The combined use of glyceryl trinitrate with vasopressin has been shown to reduce these side-effects. Terlipressin, a prodrug of vasopressin, is more commonly used. A Cochrane review[6] found that terlipressin produced a relative risk reduction in mortality from variceal haemorrhage of 34% compared with placebo. The i.v. dose is typically 2 mg 4 hourly.

Asystolic cardiac arrest

Epinephrine has been considered the main drug for resuscitation for over 100 years. Recently, some doubt has been cast over its use. Patients who were sucessfully resuscitated with epinephrine showed increased myocardial oxygen consumption and ventricular arrhythmias, ventilation–perfusion mismatch, and myocardial dysfunction post-resuscitation. In survivors of cardiac arrest, vasopressin levels have been shown to be higher than in those who died. Wenzel and colleagues[7] performed a multicentre randomized double-blinded trial in 1186 patients who had an out-of-hospital cardiac arrest. They were randomly assigned to receive either 40 IU of vasopressin or 1 mg of epinephrine during resuscitation. In the asystolic group, significantly more patients reached hospital who received vasopressin, compared with those who received epinephrine (29% vs 20%, $P=0.02$). In the vasopressin group, 4.7% were discharged from hospital compared with 1.5% in the epinephrine group. Of the 732 patients where spontaneous circulation was not achieved initially, in those who received vasopressin then epinephrine, 25.6% reached hospital and 6.7% were discharged compared with 16.4% and 1.7% of those who received epinephrine alone. There was no difference between the groups in those patients who suffered pulseless electrical activity or ventricular fibrillation cardiac arrests. There is a suggestion that vasopressin may work better than epinephrine in hypoxaemic, acidotic conditions. Other trials have shown a varying response to vasopressin in all forms of cardiac arrest. These differences may be related to poor initial cardiopulmonary resuscitation and prolonged time to advanced life support. The trend suggests a better outcome in the vasopressin groups, if there was delayed or prolonged resuscitation. The use of epinephrine in resuscitation is universal, yet there is a paucity of evidence to show it improves survival in humans. The European resuscitation guidelines state there is insufficient evidence for the use of vasopressin with or instead of epinephrine in any type of cardiac arrest and that further evidence is required.

Septic shock

The cause of hypotension in septic shock is multifactorial. Inappropriate vasodilation compromises organ perfusion. Fluid,

vasoconstrictors, and inotropes are usually used to maintain arterial pressure. Norepinephrine is the most commonly used vasoconstrictor. Unfortunately, cardiac and vascular smooth muscle can become resistant, requiring increasing doses of norepinephrine. This produces adverse effects which include increasing tissue oxygen demand, reducing renal and mesenteric blood flow, pulmonary hypertension, and arrhythmias. Vasopressin's role in maintaining arterial pressure has been investigated in septic shock. Landry and colleagues[8] were the first to show vasopressin was inappropriately low in vasodilatory septic shock. In 19 patients with vasodilatory septic shock, vasopressin levels were 3.1 pg ml^{-1} with systolic arterial pressure (SAP) of 92 mm Hg and cardiac output of 8 litre min^{-1} (all data are given as mean values). In patients who had cardiogenic shock, vasopressin levels were 22.7 pg ml^{-1}. If an infusion of 0.04 IU min^{-1} of vasopressin was started, SAP increased from 92 to 146 mm Hg and then decreased when vasopressin was withdrawn. An infusion of 0.01 IU min^{-1} was shown to increase vasopressin levels into the normal range in these patients suggesting that reduced secretion, not increased metabolism, was the cause of vasopressin deficiency.

Why vasopressin is low in septic shock is open to conjecture. There appears to be a biphasic response. Initially, vasopressin levels are elevated but 6 h after the onset of hypotension levels may be inappropriately low for the degree of hypotension. Possible explanations include exhaustion of stores and autonomic nervous system dysfunction. Large doses of norepinephrine are inhibitory to vasopressin release. Nitric oxide, an inflammatory mediator, may also act on the pituitary to prevent release.[4]

Numerous case studies and small trials show vasopressin increases arterial pressure in septic shock. The largest randomized prospective controlled study was published in 2003 by Dunser and colleagues.[9] In this study, 48 patients with catecholamine-resistant vasodilatory shock were prospectively randomized to receive a combined infusion of vasopressin, 4 IU h^{-1} (0.066 IU min^{-1}) and norepinephrine or norepinephrine alone to maintain a MAP above 70 mm Hg. The vasopressin group showed a significant increase in MAP, cardiac index, systemic vascular resistance index, and left-ventricular stroke work index as well as reduced norepinephrine requirements and heart rates. Compared with the norepinephrine group, there was better preservation of gut mucosal blood flow and a significantly lower incidence of tachyarrhythmias.

In sepsis, there is an increased sensitivity to vasopressin. The theories suggested include increased receptor density as endogenous vasopressin levels are reduced and alteration in receptor expression on different vascular beds with possible changes in signal transduction. Vasopressin and norepinephrine are believed to have a synergistic action when used together. Vasopressin increases intracellular calcium, maintaining vascular tone when norepinephrine receptor sensitivity is reduced. In endotoxic shock, excessive activation of potassium-sensitive ATP channels causes increased potassium conductance leading to the closure of voltage-gated calcium channels and the reduction in vascular tone. Vasopressin blocks these potassium-sensitive ATP channels, restoring vascular tone. The additional action on other hormone systems like cortisol and endothelin1 may also play a role in the maintenance of arterial pressure.

The use of vasopressin is not without side-effects. Myocardial ischaemia may occur, but this effect is limited by avoiding high doses. A varied effect on splanchnic blood flow has been found. At lower doses, a minimal response occurs provided the patients are adequately intravascularly filled. Both the dosage and timing of the use of vasopressin in sepsis are currently under investigation. However, in the literature, a dose range of 0.01–0.04 IU min^{-1} is commonly used to replace falling vasopressin levels. It is usually started when increasing norepinephrine doses are being used to maintain arterial pressure. It is best administered through central access as extravasations can cause skin necrosis.

The vasopressin and septic shock trial (VASST)[10] was the first multicentre, blinded randomized trial comparing low dose vasopressin with norepinephrine in 778 patients with septic shock. The use of vasopressin did not reduce mortality but was shown to be as safe as norepinephrine. Vasopressin is acknowledged as an adjunct vasopressor in the *Surviving Sepsis Guidelines* and certainly its use is increasing, but further investigations are needed to define its exact role in sepsis related hypotension.

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Please see multiple choice questions 16–18