INTRODUCTION

Vasopressin administration has emerged as a rational and promising therapy in the management of vasodilatory shock states due to sepsis or cardiopulmonary bypass ***(Strohmenger et al., 2003).***

Depletion of vasopressin stores in the neurohypophysis or vasopressin release inhibited by centrally inducible nitric oxide production have been presumed to be underlying mechanisms responsible for the low plasma vasopressin concentration ***(Sharshar et al., 2002).***

Profound hypovolemic shock that is unresponsive to volume replacement or catecholamine intervention implicates a poor prognosis. There has been growing evidence suggesting that vasopressin may be helpful in these clinical scenarios, mainly due to its extremely vasoconstrictive effect ***(Strohmenger et al., 2003).***

Epinephrine has been the drug of choice for vasopressor therapy during cardiopulmonary resuscitation, but its use has also linked to ventricular arrhythmias, increased myocardial oxygen consumption and myocardial dysfunction after resuscitation. Laboratory studies correlating vasopressin with increased blood flow and delivery of oxygen to the brain, a better chance of resuscitation, and improved neurological outcome, compared with epinephrine ***(McIntyre, 2004).***

In cardiac arrest, vasopressin is a reasonable alternative to epinephrine, at least initially. Vasopressin in the recommended dose is a potent vasoconstrictor. In out-of-hospital cardiac arrests, vasopressin was found to be comparable to epinephrine when the rhythm was pulseless electrical activity but superior to epinephrine for patients in asystole ***(Wenzel et al., 2004).***

The American Heart Association (AHA) released revised guidelines for cardiopulmonary resuscitation (CPR) and emergency cardiovascular care. The consensus was that, vasopressors should remain a part of pulsless sudden cardiac arrest management, with epinephrine being the recommended adrenergic of choice ***(Cayley, 2010).***

Epinephrine has been the preferred vasopressor according to advanced cardiac life support guidelines, although the lack of definitive evidence regarding effectiveness has created much controversy surrounding its use, vasopressin is a reasonable first-line vaspressor in patients with ventricular fibrillation or pulseless ventricular tachycardia. The guidelines comment that one dose of vaspressin may replace the first or second dose of epinephrine in all pulseless sudden cardiac arrest scenarios ***(Miano and Crouch, 2006).***

Vasopressin and corticosteroids are both commonly used adjunctive therapies in septic shock. Retrospective analyses have suggested that there may be an interaction between these

drugs, with higher circulating vasopressin levels and improved outcomes in patients treated with both vasopressin and corticosteroids ***(Gordan et al., 2014).***

Small doses of arginine vasopressin in combination with norepinephrine buy time for definitive treatment for uncontrolled hemorrhagic shock in some studies. This early treatment strategy significantly improved the effects of subsequently definitive treatments after bleeding controlled ***(Liu et al., 2013).***

Aim of the Work

This essay discusses the physiology pharmacology of vasopressin and showing its role in management of different types of shock and its use during cardiopulmonary resuscitation.

Chapter 1

PHYSIOLOGICAL AND PHARMACOLOGICAL ASPECTS OF VASOPRESSIN

Vasopressin is becoming a widely used pressor in conditions with severe hypotension. Like several other hormones important in cardiovascular and extracellular fluid control, however, vasopressin can activate several receptors that when pharmacologically or pathologically stimulated may result in conflicting effects ***(Landry and Oliver, 2010).***

Physiological role of vasopressin

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 ***(Andrew and James, 2008).***

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. 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) ***(Andrew and James, 2008).***

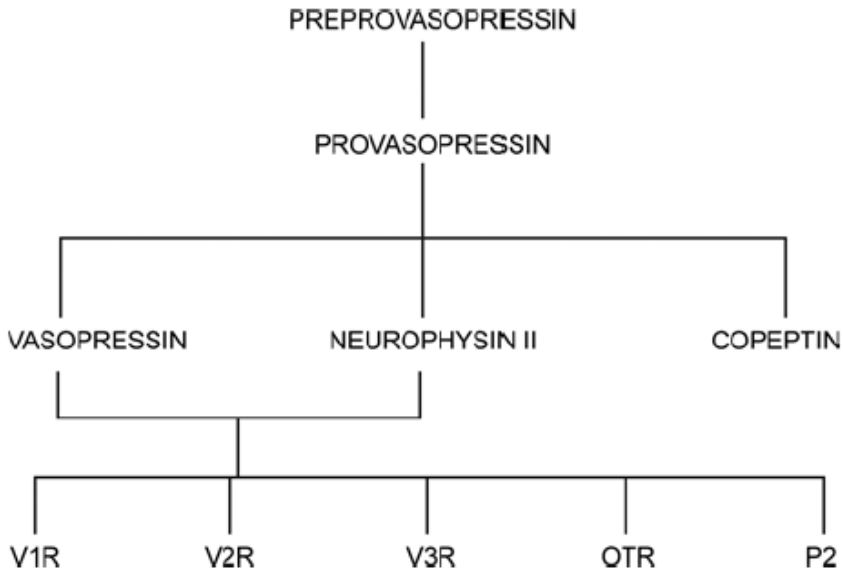
It is now established that activation of two vasopressin receptors located in the circulation, V1-R and V2-R, causes opposite vascular effects; that is, vasoconstriction and vasodilation, respectively. Hence, Rehberg and colleagues examined whether a V2-R blocker may prevent vasodilation and help maintain cardiovascular homeostasis during septic shock. Vasopressin has long been recognized to have very potent vasoconstrictor action in isolated vascular preparations, but when infused *in vivo* under normal conditions vasopressin increases blood pressure only modestly at best. In addition, development of vasopressin's vasoconstriction blockers a few decades ago showed them to be ineffective in lowering the blood pressure of most forms of hypertension. Unsurprisingly, therefore, there was little interest in vasopressin's vascular action until this report that some patients with prolonged

vasodilatory shock had inappropriately low plasma vasopressin levels and that administration of exogenous hormone quickly restored blood pressure ***(Landry and Oliver, 2010).***

Synthesis, release and clearance of vasopressin

Vasopressin is synthesized and released into the systemic circulation from the posterior pituitary gland. Vasopressin, like many hormones, is synthesized as a prohormone and then is cleaved to form the mature active hormone. Serum levels of vasopressin - a nonapeptide - represent the interactions of the synthesis, release, and metabolism of vasopressin. Synthesis of preprovasopressin occurs in neurophypophyseal neurons (also known as magnocellular neurons) of paraventricular and supraoptic nuclei of the hypothalamus. Provasopressin is packaged in neurosecretory granules and transported along the suprahypophyseal tract to the posterior pituitary. Subsequently, there is conversion to provasopressin followed by conversion of provasopressin by subtilisin-like proprotein convertase (SPC3) to vasopressin ***(James, 2011).***

Provasopressin is subsequently released in three fragments: vasopressin, neurophysin-II, and copeptin. Most of the newly synthesized vasopressin is stored intracellularly, and only 10 to 20 percent of the total hormonal pool within the posterior pituitary can be readily released under appropriate stimuli. Once secreted in the circulation, vasopressin is accompanied by its carrier protein, neurophysin-II, which does not have any independent biological activity (figure 1.1) ***(Singh et al., 2009).***



Receptor	Location	Action
VIR	Vascular smooth muscle	Vasoconstriction
	Kidney, platelets, bladder, spleen, testis	Selective renal efferent arteriolar constriction
	Myocardium	? Inotropy
V2R	Renal collecting duct	Antidiuretic
	Endothelium	Coagulation factor release
V3R	Pituitary	Acth release
Oxytocin (OTR)	Reproductive and non reproductive tissue	Uterine contractions
	Vascular endothelium	No mediated vasodilatiom
	Heart	Anp release
Purinergic (P2R)	Myocardium	Increase cardiac contractility
	Cardiac endothelium	Selective coronary vasodilation

Figure (1-1): Flow diagram depicting synthesis, release and mechanism of action of arginine-vasopressin ***(Singh et al., 2009).***

Vasopressin is metabolized by several promiscuous vasopressinases (which are found in the liver and kidney), vasopressinases also clear oxytocin (a vasodilator), GLUT4 (which modulates cellular uptake of glucose) and angiotensin-converting enzyme 4 (which converts angiotensinogen to the potent vasoconstrictor angiotensin), indicating that variations in levels and function of vasopressinases could have complex effects on hemodynamics and blood pressure in sepsis ***(James, 2011).***

There are many factors stimulate the release of vasopressin. Most factors (physical or chemical) cause direct stimulation of vasopressin release. Hypoxaemia, hypercapnia 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 α 1 receptors inducing vasopressin release. At higher concentration, their actions on α2 and β receptors inhibit vasopressin release. The most potent stimulus for vasopressin release is an increased plasma osmolality ***(Andrew and James, 2008)***.

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. 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 ***(Andrew and James, 2008)***.

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 ***(Andrew and James, 2008).***

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 ***(Andrew and James, 2008).***

Other factors that stimulate the release of vasopressin are: Nausea, vomiting, Pain, Stress, Exercise and Chemical mediators: (norepinephrine, dopamine, acetylcholine, histamine, prostaglandins, angiotensin II, endotoxin, cytokines). While factors that inhibit the release of vasopressin are: Decreasing plasma osmolality, Increased plasma volume, Chemical mediators: (Opioids, gama-amino-buteric-acid, atrial natruretic peptide, norepinephrine). Norepinephrine can stimulate release by α 1 receptors and inhibit release by stimulation of α2 and β receptors ***(Andrew and James, 2008).***

Vasopressin receptors (figure 1.2)

Vasopressin stimulates a family of receptors: AVPR1a (also known as V1 receptor, mainly vascular), AVPR1b (V3 receptor, mainly central), AVPR2 (V2 receptor, mainly renal), oxytocin receptors and purinergic P2 receptors (P2X and P2Y) ***(James, 2011).***

Like most hormones involved in blood pressure and extracellular fluid control, however, vasopressin has several receptors that regulate different functions. Vasopressin's vasoconstriction action is mediated by the V1a receptor, V1a-R, located in vascular smooth muscle. The second vasopressin

receptor (V2-R) is abundantly present in the collecting duct, where it mediates the hormone's antidiuretic action. While the role of this receptor outside the kidney is less well understood, it is known to be located in the endothelium and pharmacological studies have shown that its specific activation in the circulation induced vasodilation and hypotension and the release of the coagulation factors VIIIc and von Willebrand factor. These findings suggest that the use of vasopressin as a pressor in clinical medicine could be made safer and perhaps more effective using selective activation of V1a-R or blockade of V2-R ***(Landry and Oliver, 2010).***

V 1 receptors

AVP binds to three types of receptors. The V1 receptors (old name V1a) located in vascular smooth muscles, platelets, and hepatocytes through G protein coupled phosphorylation cause vasoconstriction, myocardial contractility, platelet aggregation, glycogenolysis, and uterine contraction ***(Narayen and Mandal, 2012).***

Stimulation of the AVPR1a receptor causes smooth muscle contraction and also induces production of the potent vasodilator nitric oxide in coronary vessels and pulmonary vessels ***(James, 2011)***.

V 2 receptors

The arginine vasopressin type 2 receptor (V2R) is unique among arginine vasopressin (AVP) receptor subtypes in signaling through cAMP. Its key function is in the kidneys, facilitating the urine concentrating mechanism through the AVP/V2 type receptor/aquaporin 2 system in the medullary and cortical collecting ducts ***(Juul et al., 2014).***

Recent clinical and research observations strongly support the existence of an extrarenal V2R. The clinical importance of the extrarenal V2R spans widely from stimulation of coagulation factor in the endothelium to as yet untested potential therapeutic targets. These include V2R-regulated membranous fluid turnover in the inner ear, V2R-regulated mitogensis and apoptosis in certain tumor tissues, and numerous other cell types where the physiological role of V2Rs still requires further research ***(Juul et al., 2014).***

Here, we review current evidence on the physiological and pathophysiological functions of renal and extrarenal V2Rs. These functions of V2R are important, not only in rare diseases with loss or gain of function of V2R but also in relation to the recent use of nonpeptide V2R antagonists to treat hyponatremia and possibly retard the growth of cysts and development of renal failure in autosomal dominant polycystic kidney disease ***(Juul et al., 2014).***