

critical care reviews

Physiology of Vasopressin Relevant to Management of Septic Shock*

Cheryl L. Holmes, MD; Bhavesh M. Patel, MD; James A. Russell, MD; and Keith R. Walley, MD

Vasopressin is emerging as a rational therapy for the hemodynamic support of septic shock and vasodilatory shock due to systemic inflammatory response syndrome. The goal of this review is to understand the physiology of vasopressin relevant to septic shock in order to maximize its safety and efficacy in clinical trials and in subsequent therapeutic use. Vasopressin is both a vasopressor and an antidiuretic hormone. It also has hemostatic, GI, and thermoregulatory effects, and is an adrenocorticotrophic hormone secretagogue. Vasopressin is released from the axonal terminals of magnocellular neurons in the hypothalamus. Vasopressin mediates vasoconstriction via V1-receptor activation on vascular smooth muscle and mediates its antidiuretic effect via V2-receptor activation in the renal collecting duct system. In addition, vasopressin, at low plasma concentrations, mediates vasodilation in coronary, cerebral, and pulmonary arterial circulations. Septic shock causes first a transient early increase in blood vasopressin concentrations that decrease later in septic shock to very low levels compared to other causes of hypotension. Vasopressin infusion of 0.01 to 0.04 U/min in patients with septic shock increases plasma vasopressin levels to those observed in patients with hypotension from other causes, such as cardiogenic shock. Increased vasopressin levels are associated with a lesser need for other vasopressors. Urinary output may increase, and pulmonary vascular resistance may decrease. Infusions of > 0.04 U/min may lead to adverse, likely vasoconstriction-mediated events. Because clinical studies have been relatively small, focused on physiologic end points, and because of potential adverse effects of vasopressin, clinical use of vasopressin should await a randomized controlled trial of its effects on clinical outcomes such as organ failure and mortality.

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Key words: adrenergic agents; antidiuretic hormone; hypotension; septic shock; systemic inflammatory response syndrome; vasoconstrictor agents; vasodilation; vasopressins

Abbreviations: ACTH = adrenocorticotrophic hormone; ADH = antidiuretic hormone; cAMP = cyclic adenosine monophosphate; CI = cardiac index; K-ATP = K⁺-sensitive adenosine triphosphate; LVAD = left ventricular-assist device; NO = nitric oxide; OTR = oxytocin receptor; SIRS = systemic inflammatory response syndrome; VIR = V1 vascular receptor; V2R = V2 renal receptor

Vasopressin, also known as antidiuretic hormone (ADH), is essential for cardiovascular homeostasis. Vasopressin is one of the first described and structurally characterized peptide hormones and, as a result, has been very extensively studied and used clinically over the past 5 decades, mainly to treat variceal hemorrhage and diabetes insipidus. Vaso-

pressin is now emerging as a rational therapy in the management of septic shock and vasodilatory shock (systemic inflammatory response syndrome [SIRS] with hypotension) from other causes.^{1,2}

A key lesson learned from the unsuccessful cytokine-modulating clinical trials is that greater physiologic understanding of potential new therapies of septic

*From the University of British Columbia Program of Critical Care Medicine and the McDonald Research Laboratories (Drs. Holmes, Russell, and Walley), St. Paul's Hospital, Vancouver, British Columbia, Canada; and Department of Critical Care Medicine (Dr. Patel), Mayo Clinic, Scottsdale, AZ. Dr. Walley is a BC Lung Association/St. Paul's Hospital Foundation Scientist.

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Correspondence to: Keith R. Walley, MD, University of British Columbia McDonald Research Laboratories, St. Paul's Hospital, 1081 Burrard St, Vancouver, British Columbia, Canada V6Z 1Y6; e-mail: kwalley@mrl.ubc.ca

shock is essential to develop successful therapeutic strategies.³ Thus, the goal of this review is to understand the physiology of vasopressin relevant to septic shock in order to maximize its safety and efficacy in clinical trials and in subsequent therapeutic use in patients with septic shock or SIRS and hypotension from other causes.

HISTORY

Vasopressin is essential for survival as attested to by its teleologic persistence. The oxytocin-vasopressin superfamily is found in both vertebrates and invertebrates with a conserved nonapeptide structure. Therefore, the ancestral gene encoding the precursor protein predates the divergence of the two groups about 700 million years ago.⁴

Oliver and Schafer⁵ in 1895 first observed the vasopressor effect of pituitary extract, attributed to the posterior lobe.⁶ More than 10 years later, the antidiuretic effect was described. Two physicians, Farini⁷ (in 1913) in Italy and von den Velden⁸ (also in 1913), in Germany successfully treated patients with diabetes insipidus by injection of neurohypophyseal extracts. The extract decreased urinary output, increased the density of the urine, and reduced thirst.⁹ In the late 1920s, Krogh established that topical application of the posterior pituitary hormone to the capillaries induced vasoconstriction in the web feet of the frog and the ears of the dog.¹⁰ After isolation and synthesis of vasopressin by Turner et al¹¹ in 1951 and du Vigneaud et al¹² in 1954, it was proven that the same hormone in the posterior pituitary is responsible for both antidiuretic and vasopressor effects.

PHYSIOLOGY

Structure and Synthesis

Vasopressin is a nonapeptide with a disulfide bridge between two cysteine amino acids.¹³ Vasopressin is synthesized as a large prohormone in magnocellular neurons located in the paraventricular and supraoptic nuclei of the hypothalamus.¹⁴ The hormone and neurohypophysin, an axonal carrier protein, then migrate via the supraoptic-hypophyseal tract to the axonal terminals of the magnocellular neurons, located in the pars nervosa of the posterior pituitary, where vasopressin is stored in granules. Vasopressin is released from the axonal terminals of magnocellular neurons in the hypothalamus, and the rate of release increases as the frequency of action potentials stimulating these neurons increases.^{15,16} Only 10 to 20% of the total hormonal pool within the

posterior pituitary can be readily released. Once this amount is discharged into the circulation, vasopressin continues to be secreted in response to appropriate stimuli but at a greatly reduced rate. This is likely relevant to understanding of the biphasic response of vasopressin to septic shock, with high levels early and low levels later. The entire process of vasopressin synthesis, transport, and neurohypophyseal storage takes from 1 to 2 h (Fig 1).¹⁷

Regulation of Vasopressin Release

The regulation of vasopressin release is complex and can be classified into osmotic and nonosmotic stimuli. As a result, vasopressin release is influenced by CNS input, by direct hypothalamic input, and by other circulating hormones and mediators. Increased plasma osmolality (osmotic regulation) and severe hypovolemia and hypotension (hypovolemic regula-

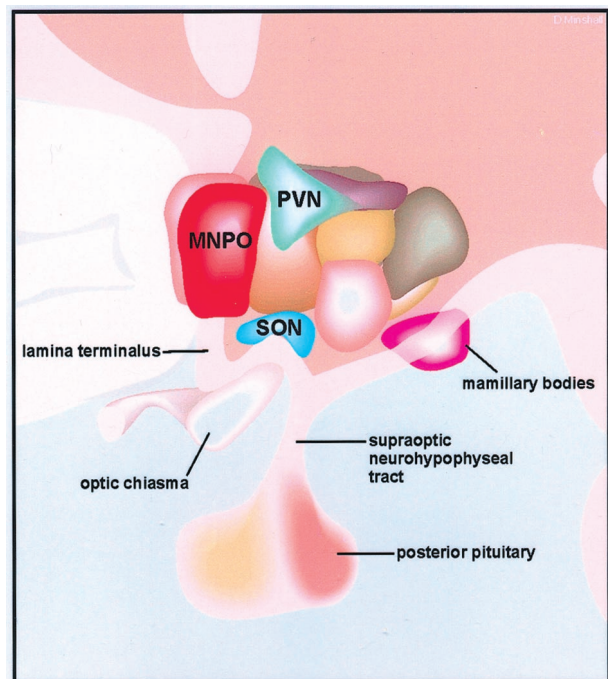


FIGURE 1. Hypothalamic nuclei involved in vasopressin control. The hypothalamus surrounds the third ventricle ventral to the hypothalamic sulci. The main hypothalamic nuclei subserving vasopressin control are the lamina terminalis (containing the organum vasculosum), the median preoptic nucleus (MNPO), the paraventricular nuclei (PVN), and the supraoptic nuclei (SON), which project to the posterior pituitary along the supraoptic-hypophyseal tract. Vasopressin is synthesized in the cell bodies of the magnocellular neurons located in the paraventricular nuclei and supraoptic nuclei. The magnocellular neurons of the supraoptic nucleus are directly depolarized by hypertonic conditions (hence releasing more vasopressin) and hyperpolarized by hypotonic conditions (hence releasing less vasopressin).¹⁸ Finally, vasopressin migrates (in its prohormone state) along the supraoptic-hypophyseal tract to the posterior pituitary where it is released into the circulation.

tion) are the most potent stimuli to vasopressin release. Pain, nausea, hypoxia, pharyngeal stimuli, and endogenous and exogenous chemicals also increase release of vasopressin (Table 1¹⁹⁻²¹). These latter stimuli often result in relatively inappropriate release of vasopressin resulting in excess water retention and thus hyponatremia; this syndrome is better known as the syndrome of inappropriate ADH release.¹⁹

Osmotic Regulation: Hyperosmolality is a potent osmotic stimulus to vasopressin release. Sophisticated behavioral (appetite and thirst) and physiologic responses (vasopressin and natriuretic hormones) have developed in mammals to defend osmolality of extracellular fluid. Osmotic regulation of vasopressin production and release is controlled by osmoreceptors located peripherally and centrally. Peripheral osmoreceptors are located in the region of the hepatic portal vein, which allow early detection of the osmotic impact of ingested foods and fluids. Afferents ascend via the vagus nerve to nuclei in the brain, which project to the magnocellular neurons of the hypothalamus. Changes in systemic osmolality are also detected centrally in regions of the brain excluded from the blood brain barrier. Finally, magnocellular neurons of the hypothalamus are directly depolarized by hypertonic conditions (hence releasing more vasopressin) and are hyperpolarized by hypotonic conditions (hence releasing less vasopressin; Fig 2).¹⁸

Hypovolemic Regulation: Hypotension and decreased intravascular volume are potent nonosmotic stimuli that exponentially increase vasopressin levels. Interestingly, this rise in vasopressin level does not disrupt normal osmoregulation, because hypotension increases the plasma osmolality-vasopressin relationship so that higher plasma vasopressin levels are required to maintain normal osmolality.^{20,22,23} That is, hypovolemia shifts the osmolality-vasopressin relationship up and to the left by changing the threshold for vasopressin release without changing the sensitivity (slope) of the relationship (Fig 3).²⁰

Volume and pressure stimuli modify vasopressin release. Nonspecifically, afferent impulses from stretch receptors in the left atrium, aortic arch, and

carotid sinus carried by the vagus nerve tonically inhibit vasopressin secretion; conversely, a reduction in discharge rate increases vasopressin release.²⁵ Whereas baroreceptors in the atrium and ventricles signal changes in blood volume, the receptors of the aortic arch and carotid sinuses signal changes in arterial BP. Unloading arterial baroreceptors, not cardiac receptors, predominantly drives increased vasopressin during hypotensive hemorrhage.²⁶⁻³⁰ In contrast, atrial stretch receptors influence control of blood volume primarily through atrial natriuretic peptide, sympathetic stimulation, and renin release. Accordingly, a fall in central venous pressure evokes an increase in norepinephrine and renin, while vasopressin does not increase until mean arterial pressure falls.³¹⁻³⁵ Conversely, volume expansion and large increases in BP transiently inhibit vasopressin release, due more to atrial stretch receptors than to arterial baroreceptors.³⁶

Hormonal Regulation: Other nonosmotic stimuli that are relevant in critical illness and septic shock include hormones and mediators that directly stimulate vasopressin release, such as acetylcholine (via nicotinic receptors), histamine, nicotine, dopamine, prostaglandins, angiotensin II, and other catecholamines.¹⁷ Of these various hormonal and mediator effects, adrenergic regulation plays a particularly important role. Of relevance to critical illness, high PaCO₂ or low PaO₂ stimulate carotid body chemoreceptors and thus increase vasopressin levels.¹⁶ Inhibitors of vasopressin release include opioids, γ -aminobutyric acid, and atrial natriuretic peptide. Neurohumoral inhibition of vasopressin release is mediated by nitric oxide (NO) via cyclic guanosine monophosphate,³⁷ which may be important during sepsis.

Norepinephrine has complex effects on vasopressin release. The hypothalamic projections are predominantly noradrenergic.¹⁶ Injection of norepinephrine or phenylephrine into the cerebral ventricles or directly into the magnocellular nuclei stimulates vasopressin release,³⁸ an effect mediated by α_1 -adrenoreceptors.³⁹ Noradrenaline also inhibits vasopressin and oxytocin release via α_2 -adrenoreceptors or possibly β -adrenoreceptors. α -Adrenergic and β -adrenergic receptors may be distributed differentially on the surface of magnocellular neurons allowing different noradrenergic inputs to be excitatory or inhibitory.¹⁶

Vasopressin Levels and Metabolism

Plasma vasopressin levels are normally < 4 pg/mL in overnight fasted, hydrated humans.⁴⁰ The osmoreceptor-vasopressin renal mechanism has exquisite

Table 1—Stimuli of Vasopressin Release in Shock

Stimulus	Source
Pain	Kovacs and Robertson ¹⁹
Hypoxia	Schrier et al ²⁰
Acidosis	Wood and Chen ²¹
Hypotension	Schrier et al ²⁰

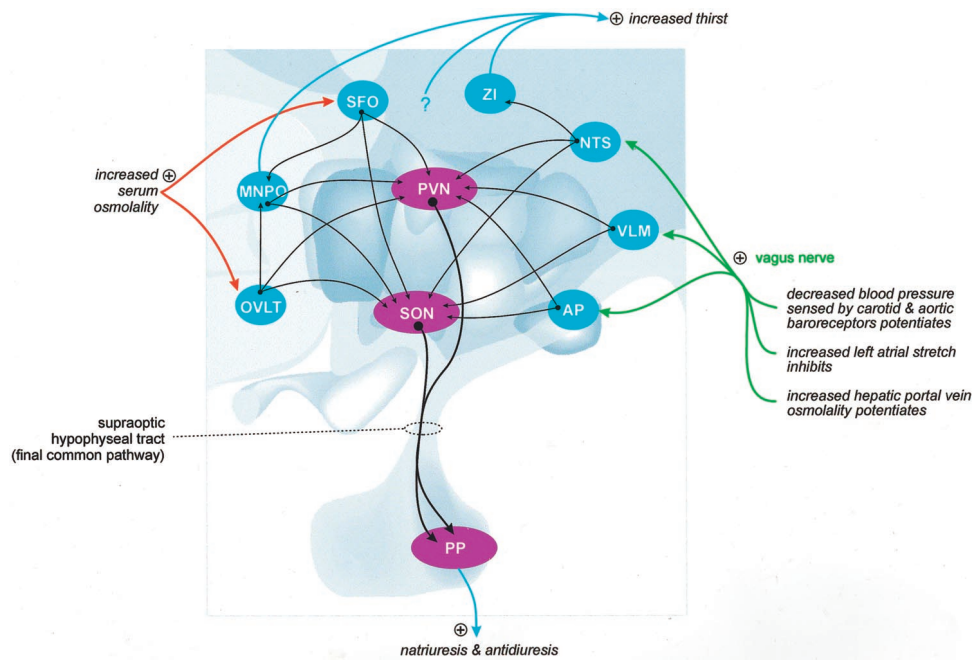


FIGURE 2. The vascular and neural pathways involved in vasopressin release. Afferent nerve impulses from stretch receptors in the left atrium (inhibitory), aortic arch, and carotid sinuses (excitatory) travel via the vagus nerve and terminate in the nucleus tractus solitarius (NTS), area postrema (AP), and ventrolateral medulla (VLM). Cells in these areas project to the paraventricular nuclei and supraoptic nuclei. Osmotic stimuli reach the paraventricular nuclei and supraoptic nuclei (inside the blood-brain barrier) both by projections from the nucleus tractus solitarius and the ventrolateral medulla (receiving vagal input) and by projections from the organum vasculosum lamina terminalis (OVLT) and subfornical organ (SFO). The organum vasculosum lamina terminalis and subfornical organ nuclei are excluded from the blood-brain barrier and thus are influenced by systemic osmolality. The median preoptic nucleus has reciprocal connections with both the organum vasculosum lamina terminalis and the subfornical organ and is the origin of dense projection to the paraventricular and supraoptic nuclei.¹⁶ The final common pathway of vasopressin release is synthesis in the cell bodies of the magnocellular neurons located in the paraventricular nuclei, and migration via the supraoptic-hypophyseal tract to the pars nervosa. The zona incerta (ZI) is involved in initiation of drinking behavior. PP = posterior pituitary; see Figure 1 legend for definition of abbreviations.

sensitivity and gain. As a result, small increases in plasma osmolality are quickly sensed, vasopressin is released, and urine osmolality increases, thereby correcting increased plasma osmolality. Water deprivation increases plasma osmolality and raises vasopressin levels to 10 pg/mL.⁴¹ Maximal increase in urine osmolality requires vasopressin levels ≥ 20 pg/mL. Vasopressin is rapidly metabolized by liver and kidney vasopressinases, making the hormone half-life 10 to 35 min.⁴² A 75% reduction in glomerular filtration rate reduces vasopressin clearance to 30% in dogs, and the liver and the intestines share the splanchnic clearance of vasopressin equally.⁴³

Vasopressin Levels in Shock

Both hemorrhagic and septic shock are associated with a biphasic response in vasopressin levels (Table 2). In early shock, appropriately high levels of vasopressin are produced to defend organ perfusion. As the shock state progresses, plasma vasopressin levels

fall for reasons that are not entirely clear. Hypotensive hemorrhage in dogs and monkeys can acutely increase plasma levels to 100 to 1,000 pg/mL.^{29,44,53} However, during prolonged hemorrhagic shock in dogs, an initial increase in plasma vasopressin levels to 319 pg/mL was followed by a decrease to 29 pg/mL.^{45,46} Similarly, acute endotoxin-induced shock results in extremely high levels of vasopressin (> 500 pg/mL in dogs and > 300 pg/mL in baboons).⁵⁴

Importantly, vasopressin levels in established septic shock and vasodilatory shock are low (Table 2). The reason for this relative deficiency is uncertain,⁵⁵ and several mechanisms have been proposed (Table 3). First, depletion of neurohypophyseal stores of vasopressin in advanced shock due to excessive baroreceptor firing has been postulated. Second, others^{56,57} have postulated autonomic insufficiency, citing lack of baroreflex-mediated bradycardia after vasopressin infusion as evidence.¹ Third, low concentrations of norepinephrine excite central vasopressin-

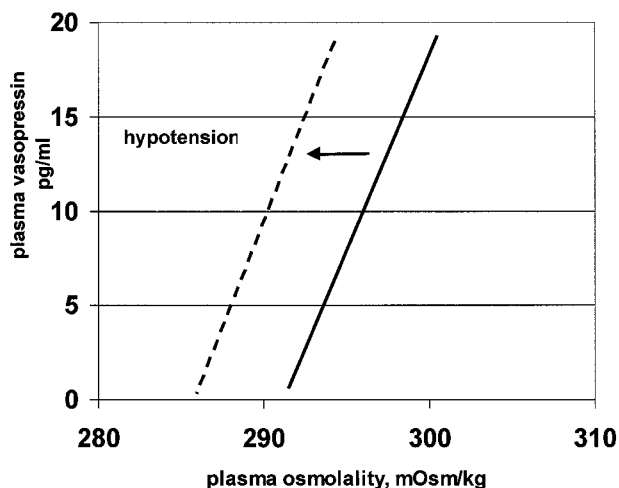


FIGURE 3. Influence of hypotension on threshold and sensitivity of vasopressin release induced by osmotic stimuli. Adapted from Robertson et al²⁴ with permission.

ergic neurons, whereas elevated norepinephrine levels (endogenous or exogenous) have a central inhibitory effect on vasopressin release.³⁸ Finally, increased NO production by vascular endothelium within the posterior pituitary during sepsis may inhibit vasopressin production.

Vasopressin Receptors

It is important to understand the various vasopressin receptors in septic shock to fully understand the

effects of vasopressin. Vasopressin-receptor subtypes are of the G protein-coupled receptor superfamily with seven transmembrane-spanning domains. Similar to adrenoreceptors and muscarinic receptors, ligand binding to vasopressin receptors occurs in a pocket formed by the ring-like arrangement of the seven transmembrane domains.^{13,58} It is relevant to emphasize that the location, density, and distribution of vasopressin receptors account for many of the potentially beneficial effects of vasopressin in patients with sepsis and SIRS (Table 4).

V1 vascular receptors (V1R; formerly known as V1a receptors) are located on vascular smooth muscle and mediate vasoconstriction. Additionally, V1 receptors are found in the kidney, myometrium, bladder, adipocytes, hepatocytes, platelets, spleen, and testis. V1-receptor activation mediates vasoconstriction by receptor-coupled activation of phospholipase C and release of Ca^{++} from intracellular stores via the phosphoinositide cascade.^{59,60}

V2 renal receptors (V2R), which cause the antidiuretic effects of vasopressin, are present in the renal collecting duct system and endothelial cells. Kidney V2 receptors interact with adenylyl cyclase to increase intracellular cyclic adenosine monophosphate (cAMP) and cause retention of water.⁶¹ This interaction occurs through the coupling of the receptor with the s subunit of the G protein complex.¹³ V3 pituitary receptors (formerly known as V1b) have central effects, such as

Table 2—Vasopressin Response in Shock States*

Shock States	Vasopressin Levels, pg/mL	Source
Early shock		
Hemorrhagic		
Dogs	319–991	Wang et al ⁴⁴ ; Morales et al ⁴⁵ ; Errington and Rocha e Silva ⁴⁶
Monkeys	180	Arnauld et al ²⁹
Endotoxic		
Rats	Up to 144	Brackett et al ⁴⁷
Dogs	500–1,200	Wilson et al ⁴⁸
Baboons	300–1,800	Wilson et al ⁴⁸
Cardiogenic		
Humans	Appropriate levels, 22.7 ± 2.2	Landry et al ¹
Late shock		
Hemorrhagic		
Dogs	Decreased to 29	Morales et al ⁴⁵ ; Errington and Rocha e Silva ⁴⁶
Septic		
Humans	3.1 ± 1.0	Landry et al ¹
Vasodilatory		
Humans after LVAD insertion	Five of eight patients had levels < 10	Argenziano et al ⁴⁹
Humans after CPB	12.0 ± 6.6	Argenziano et al ⁵⁰
Children after CPB	Median, 3.3	Rosenzweig et al ⁵¹
Human organ donors	2.9 ± 0.8	Chen et al ⁵²

* CPB = cardiopulmonary bypass.

Table 3—Proposed Mechanisms of Vasopressin Deficiency in Shock

Proposed Mechanism	Rationale
Depletion of neurohypophyseal stores due to excessive stimulation/baroreceptor firing	Hypoxia, acidosis, and hypotension are powerful stimuli of vasopressin release (Table 2) Only 10 to 20% of the total neurohypophyseal pool of vasopressin can be readily released ¹⁷
Decreased stimulation of vasopressin release due to: Impaired autonomic reflexes Tonic inhibition by atrial stretch receptor (volume loading, mechanical ventilation)	The autonomic nervous system is impaired in sepsis ^{56,57} Atrial stretch receptors tonically inhibit vasopressin ¹⁶
Inhibition of vasopressin release due to: NO release in sepsis High circulating norepinephrine levels	NO inhibits vasopressin release ³⁷ High levels of norepinephrine inhibit vasopressin release ³⁸

increasing adrenocorticotrophic hormone (ACTH) production, activating different G proteins, and increasing intracellular cAMP.⁶²

Oxytocin receptors (OTRs) have been found in the uterus and mammary gland and, more recently, in endothelial cells of human umbilical vein, aorta, and pulmonary artery.⁶³ OTRs activate phospholipase C and induce an increase in cytosolic calcium (responsible for the strong contractions of the uterus at term¹³). One important action when considering the beneficial effects of vasopressin infusion in septic patients is that OTRs also mediate a calcium-dependent vasodilatory response via stimulation of the NO pathway on endothelial cells.⁶³

EFFECTS OF VASOPRESSIN

Vasopressin has multiple physiologic effects. Its most well-known effects are suggested by its two names. Vasopressin is a direct vasoconstrictor of the systemic vasculature mediated by V1 receptors. Also known as ADH, one of the primary functions of vasopressin is osmoregulation and maintenance of normovolemia mediated by V2 receptors in the kidney. However, vasopressin has many other physiologic functions. Importantly, vasopressin also vasodilates some vascular beds at certain concentrations, probably by stimulation of OTR. Vasopressin also acts as an ACTH secretagogue, functions in maintaining hemostasis, has GI effects, and plays a role in temperature regulation, memory, and sleep cycles.

Vasoconstrictor Effects

Vasopressin has little effect on BP under normal conditions and at normal concentrations.^{64,65} Supraphysiologic plasma vasopressin levels of about 50 pg/mL must be attained before a significant increase in mean arterial BP is achieved in normal dogs and humans.^{53,66} However during hypovolemia, vaso-

pressin helps maintain arterial BP. V1-receptor antagonists administered to animals subjected to hemorrhage cause hypotension,^{10,67} and vasopressin levels rise during hypotension^{22,68}; therefore, vasopressin is an important hormone in preserving perfusion pressure during hemorrhage. The vasoconstrictive effect of high-dose vasopressin treatment has been utilized with some success in cardiac arrest states.⁶⁹

Vasopressin differs from catecholamines in several respects. Vasopressin is a weak vasopressor in animals with an intact autonomic nervous system because it causes leftward shift of the heart rate-arterial pressure baroreflex curve by acting on V1 receptors in the brain.^{70–72} As a result, the hypertensive effects of vasopressin are diminished because vasopressin causes a reduction in heart rate greater than that observed with other vasoconstrictors, thus decreasing BP. This is one of several unique differences of vasopressin compared to vasopressors used in sepsis, such as norepinephrine, epinephrine, and dopamine.

Vasopressin is a potent vasoconstrictor in skin, skeletal muscle, fat, pancreas, and thyroid gland.¹⁰ In contrast, vasopressin causes less vasoconstriction in mesenteric, coronary, and cerebral circulations.⁷³ Less vasoconstriction in coronary and cerebral circulations may be due to the additional NO-mediated vasodilating effect of vasopressin on these circulations.^{74,75} The effects of vasopressin on the heart (reduced cardiac output and heart rate) are mainly due to increased vagal tone and decreased sympathetic tone as well as a decrease in coronary blood flow at high circulating levels of vasopressin.¹⁰

Of relevance to septic shock, vasopressin enhances the sensitivity of the vasculature to other pressor agents.⁷⁶ Vasopressin potentiates the contractile effect of norepinephrine, electrical stimulation, and KCl in rat and human arteries.^{77,78} This augmentation effect can be inhibited by cortisol and lithium, suggesting that it is prostaglandin mediated.

Table 4—Vasopressin Receptors*

Receptors	Tissues	Principal Effects	Intracellular Signaling
V1R	Vascular smooth muscle Kidney (bladder, adipocytes, platelets, spleen, testis)	Direct and indirect vasodilation	Phosphoinositide pathway (activate phospholipase C) Increased intracellular Ca ⁺⁺
V2R	Renal collecting duct	Increased permeability to water	Increased cAMP
V3R	Endothelium Pituitary	Vasodilation Neurotransmitter ACTH release	NO mediated Increased cAMP
OTR	Uterus, mammary gland Endothelium	Vasoconstriction Vasodilation	Phospholipase C NO mediated

* V3R = V3 pituitary receptors.

Vasopressin blocks K⁺-sensitive adenosine triphosphate (K-ATP) channels in a dose-dependent manner,⁷⁹ an effect that may restore vascular tone in patients with septic shock. The membrane potential of arterial smooth-muscle cells, which is regulated by K⁺ channels, is an important regulator of arterial tone. The opening of K⁺ channels closes voltage-dependent Ca⁺⁺ channels, decreasing Ca⁺⁺ entry, which leads to dilatation.⁸⁰ Endotoxic shock is associated with excessive activation of K-ATP channels.⁸¹

Vasopressin could cause mesenteric vasoconstriction, which could be an adverse effect in septic shock. Vasopressin vasoconstricts the mesenteric circulation in physiologic concentrations (as low as 10 pg/mL).⁸² This mesenteric vasoconstrictor effect is mediated via the V1R¹⁰ and has been demonstrated *in vitro* and *in vivo* in several animal models,^{83–85} and it is dose dependent.⁸⁶ These mesenteric vascular effects of vasopressin are, of course, utilized in the treatment of variceal bleeding secondary to portal hypertension.⁸⁷

Vasodilator Effects

Another difference between vasopressin and catecholamines in septic shock is that vasopressin may cause vasodilation in selected organs. Vasopressin-induced vasodilation is likely mediated ultimately by NO. Although the main effect of vasopressin in mammals is vasoconstriction, studies^{88,89} using selective V1R-antagonists unmask a vasodilatory effect of vasopressin. The vasorelaxation produced by vasopressin appears at low concentrations,⁹⁰ unlike the vasoconstrictor effect, which is dose dependent. Vasodilation also appears to be endothelium dependent and NO mediated.^{63,91} There are significant differences in the ability of different arteries to vasodilate in response to vasopressin; for instance, arteries of the circle of Willis are more sensitive to the vasodilatory effects of vasopressin than are other intracranial and extracranial arteries.⁹²

The receptor subtype responsible for vasodilation is uncertain. The V2 receptor agonist 1-desamino-8-D-arginine vasopressin causes a decrease in BP and facial flushing in humans⁹³ and peripheral vasodilation in dogs.⁸⁸ V2R-antagonist administration also inhibits the vasodilatory response of the renal afferent arteriole to vasopressin.⁹⁴ Thibonnier and coworkers⁶³ have identified endothelial OTRs that mediate vasopressin-induced vasodilation through reverse transcriptase-polymerase chain reaction techniques. Stimulation of endothelial cells by oxytocin produced mobilization of intracellular calcium and the release of NO.⁶³ Thus, despite implicating different receptors, all of these studies suggest that vasopressin-induced vasodilation is mediated ultimately through NO release.⁹¹

Pulmonary Vascular Effects

Vasopressin may cause pulmonary vasodilation, which is of relevance to septic shock because pulmonary vascular tone and resistance are usually increased in patients with septic shock. Vasopressin decreases pulmonary artery pressure when infused in normal or hypoxic conditions.^{95–97} Pulmonary vascular resistance does not increase until very high levels of plasma vasopressin are achieved (300 to 500 µg/mL).⁹⁸ Pulmonary vasodilation by vasopressin is mediated by V1 receptors that cause release of endothelium-derived NO,⁹⁹ a finding confirmed by others.^{100,101}

Renal Effects of Vasopressin

The renal effects of vasopressin also differ from the effects of catecholamines and have potentially great relevance in septic shock. However, the renal effects of vasopressin are complex and require understanding of the interplay of osmoregulatory and renovascular balance for interpretation of effects of vasopressin on renal function and urine output in

septic shock (Table 5). Vasopressin regulates urine osmolality by increasing cortical and medullary collecting duct luminal membrane permeability to water by activation of V2 receptors. V2 receptors are located on the basolateral membrane of the principal cells of the tubular epithelium. This adenylate cyclase-dependent process increases intracellular cAMP, which, through protein kinase activation, results in water channels (aquaporins) containing vesicles to fuse with the luminal membrane (an effect inhibited by V1 receptor-mediated production of prostaglandin E₂). The increased intracellular water then osmotically equilibrates with the interstitial fluid, and the urine becomes more concentrated. Vasopressin contributes to further concentration of urine by increasing the medullary concentration gradient by activating a distinct urea transporter.¹⁰⁸ Vasopressin also induces a selective decrease in inner medullary blood flow without altering cortical blood flow, which also contributes to the maximum concentrating ability of the kidney.¹⁰⁹

Paradoxically, low-dose vasopressin induces diuresis in humans with hepatorenal syndrome and congestive heart failure,¹¹⁰ in patients with septic shock,² and in patients with milrinone-induced hypotension.¹¹¹ The mechanisms of the diuretic effect of vasopressin have not been fully explained. Possible mechanisms include downregulation of the V2R,¹⁰² NO-mediated afferent arteriolar vasodilation, selective efferent arteriolar vasoconstriction,¹⁰³ and OTR-activated natriuresis.¹⁰⁵ Higher levels of vasopressin (pressor doses), however, cause a dose-dependent fall in renal blood flow (afferent arteriole and medulla most sensitive), glomerular filtration rate, and

sodium excretion.^{107,112} A VIR antagonist can block the vasoconstrictor action of vasopressin on the afferent arteriole. Interestingly, even norepinephrine-induced vasoconstriction of the afferent arteriole can be abolished by treatment with vasopressin if the VIR is blocked.⁹⁴

Other Organ System Effects

Vasopressin increases cortisol, which could be very relevant in patients with septic shock, because cortisol levels may not be adequate. Pharmacologic doses of vasopressin in animals and man induce a prompt rise in plasma cortisol levels.¹¹³ In man, adrenocortical activation occurs directly via vasopressin stimulation of ACTH release.¹¹⁴ This effect is likely mediated through NO and cyclic guanosine monophosphate via the V3 receptor.¹¹⁵ Subsets of patients in septic shock have “relative adrenal insufficiency” that independently predicts mortality.¹¹⁶ This raises the interesting speculation that low blood levels of vasopressin in humans may play a role in the adrenal insufficiency of the critically ill.

Vasopressin causes aggregation of human blood platelets,^{93,117} a potential adverse effect in septic shock. The V2-selective agonist 1-desamino-8-D-arginine vasopressin causes release of factor VIIIc and von Willebrand factor,¹¹⁸ and has been used extensively in treating bleeding due to dysfunctional platelets. However, low doses of vasopressin are less likely to stimulate platelet aggregation in most individuals.

The brain has a rich innervation by vasopressin-containing fibers.¹¹⁹ Vasopressin appears to act as a

Table 5—Renal Effects of Vasopressin*

Effects	Receptors	Mechanisms	Models	Vasopressin Levels
Antidiuresis	V2R	Increased collecting duct permeability (inhibited by V1 via prostaglandin)	Animal and human	10–20 pg/mL (higher levels downregulate V2R ¹⁰²)
Diuresis	V1R	Efferent arteriolar vasoconstriction ¹⁰³	Isolated rabbit cortical arterioles	1–1,000 pg/mL
Diuresis/natriuresis	??	Inhibits Na reabsorption distal to the proximal tubule ¹⁰⁴	Bicarbonate and glucose-loaded dogs	Suppressor doses (0.06–3.5 U/min equivalent in 70-kg man)
Diuresis	OTR	Natriuresis ¹⁰⁵	Anesthetized rat	Suppressor doses (up to 0.04 U/min equivalent in 70-kg man)
Increased renal blood flow	NO mediated (blocked by L-NAME)	Decreased renovascular resistance ¹⁰⁶	Anesthetized rat	
Decreased renal blood flow	V1R	Vasoconstriction ¹⁰⁷	Rat (inulin/para-amino hippurate method)	Doses > 0.5 U/min equivalent in 70-kg man

*L-NAME = nitro-L-arginine methyl ester.

neurotransmitter involved in the central control of circadian rhythmicity,^{120,121} water intake, cardiovascular regulation, thermoregulation,¹²² regulation of ACTH release, and nociception.¹²³ Thus, vasopressin acts centrally, coordinating autonomic and endocrine responses to homeostatic perturbations.

VASOPRESSIN IN SEPTIC SHOCK AND SIRS

We have reviewed the human trials of low-dose vasopressin in septic shock and other forms of vasodilatory shock (Table 6). There is evidence for both a deficiency and an exquisite sensitivity to vasopressin, which has mechanistic and therapeutic implications.

Most forms of hypotension are associated with appropriately high levels of vasopressin.^{29,54,125,126} Landry et al¹ observed that some patients with advanced vasodilatory septic shock had inappropriately low plasma levels of vasopressin. Plasma levels of vasopressin were 3.1 ± 0.4 pg/mL in the septic shock patients (n = 19) and 22.7 ± 2.2 pg/mL in cardiogenic shock patients (n = 12). Exogenous infusion of 0.01 U/min of vasopressin in two patients increased vasopressin levels to 27 pg/mL and 34 pg/mL, respectively, indicating that the low vasopressin levels in patients with septic shock were due to impaired vasopressin secretion, not increased vasopressin metabolism or clearance. These results implicated a relative deficiency of vasopressin in patients with late septic shock.

Additionally, septic shock patients are exquisitely sensitive to low-dose vasopressin.^{1,2} Ten patients

received vasopressin at 0.04 U/min, which increased plasma concentrations to 100 pg/mL, increased systolic BP from 92 to 146 mm Hg (p < 0.001), increased systemic vascular resistance by 79% (p < 0.001), and decreased cardiac output by 12% (p < 0.01). Reduction of the infusion to 0.01 U/min resulted in plasma levels of 30 pg/mL. Six patients were able to receive vasopressin as their sole pressor agent. Discontinuation of vasopressin treatment in these patients resulted in a sudden decrease in arterial pressure.

To our knowledge, there has been only one small randomized controlled trial of vasopressin in patients with septic shock. Malay and colleagues¹²⁷ studied 10 patients admitted to the trauma ICU with vasodilatory septic shock (need for pressor agents to maintain mean arterial pressure > 70 mm Hg, cardiac index [CI] > 2.5 L/min/m², and pulmonary wedge pressure > 12 mm Hg), who were randomized to receive either vasopressin at 0.04 U/min (n = 5) or placebo (n = 5). Patients receiving vasopressin had an increase in systolic BP from 98 to 125 mm Hg (p < 0.05) and were able to have treatment with all other catecholamines withdrawn. All patients in the treatment group survived the 24-h study period. The control patients had no statistically significant change in BP, none were able to have vasopressor therapy withdrawn, and two died of refractory hypotension within 24 h. Vasopressin administration had no effect on heart rate, CI, and/or pulmonary artery pressure. The results of this small study further highlight the increased pressor sensitivity to vasopressin in patients with vasodilatory

Table 6—Trials of Low-Dose Vasopressin in Human Septic and Vasodilatory Shock*

Source	Date	Trial	Patients, No./Conditions	End Points
Landry et al ²	1997	Case series	5/septic shock	A, B, C
Landry et al ¹	1997	Matched cohort	19/septic shock 12/cardiogenic shock	A, B, D in septic group
Malay et al ¹²⁷	1999	RCT Placebo: NS	10/septic shock, trauma	A, B in treatment arm
Argenziano et al ⁵⁰	1998	Retrospective case series	40/after bypass vasodilatory shock	A, B, D
Argenziano et al ⁴⁹	1997	RCT Placebo: NS	10/vasodilatory shock after LVAD implant	A, B in treatment arm D in all
Argenziano et al ¹²⁴	1999	Case series	20/vasodilatory shock after cardiac transplant	A, B
Rosenzweig et al ⁵¹	1999	Case series	11/Pediatric, vasodilatory shock after bypass	A, B, D
Morales et al ¹²⁵	2000	Retrospective case series	50/vasodilatory shock after LVAD implantation	A, B
Chen et al ⁵²	1999	Case series	10/organ donors with vasodilatory shock	A, D
Gold et al ¹¹¹	2000	Case series	7/milrinone, hypotension	A, B, C

*A = increase in BP; B = decrease or discontinuance of catecholamines; C = increase in urine output; D = low plasma vasopressin levels in subjects; RCT = randomized controlled trial; NS = not significant.

shock and again raises speculation as to how this may occur. The authors noted lack of baroreflex-mediated decrease in heart rate in these patients, supporting the theory of autonomic insufficiency in septic shock.

Subsequently, Argenziano and colleagues⁴⁹ investigated the role of vasopressin in other forms of vasodilatory shock (SIRS of noninfectious origin) following placement of a left ventricular-assist device (LVAD) for end-stage heart failure. On weaning from cardiopulmonary bypass, selected subjects had mean arterial pressure < 70 mm Hg despite norepinephrine infusion of 8 µg/min and LVAD-assisted CI > 2.5 L/min/m². Consecutive eligible subjects were blindly randomized 5 min after bypass to receive vasopressin at 0.10 U/min or placebo. Ten of 23 LVAD recipients met inclusion criteria. Vasopressin infusion rapidly and significantly increased mean arterial pressure (57 to 84 mm Hg), and norepinephrine infusion rate was decreased by > 50% and then was gradually discontinued. Baseline plasma vasopressin levels were inappropriately low for patients in shock; 7 of 10 patients had levels < 20 pg/mL. The dose of 0.10 U/min produced plasma levels of 150 pg/mL. Argenziano and colleagues⁴⁹ concluded that vasopressin is an effective pressor for LVAD recipients with vasodilatory shock after cardiopulmonary bypass, significantly increasing mean arterial pressure while rapidly reducing catecholamine requirements.

Argenziano and coworkers⁵⁰ prospectively studied 145 patients undergoing cardiopulmonary bypass for elective cardiac surgery and retrospectively analyzed 40 patients who had postbypass vasodilatory shock and who received vasopressin. In the prospective study,⁵⁰ they found that vasodilatory shock after cardiopulmonary bypass is associated with vasopressin deficiency and that this syndrome is more common among patients with low ejection fraction and those receiving angiotensin-converting enzyme inhibitors. In the retrospective group, they observed that in patients undergoing LVAD implantation, administration of vasopressin significantly increased mean arterial pressure while reducing the requirements for catecholamine pressor agents. These investigators⁵⁰ were able to rapidly taper the initial infusion of 0.10 U/min to 0.01 U/min. Morales and coworkers¹²⁸ also reported a retrospective series of 50 patients who received vasopressin after LVAD implantation, again showing an increase in mean arterial pressure and a reduction in pressor requirements.

In another small trial in septic shock, Rosenzweig and coworkers⁵¹ evaluated vasopressin administration in 11 profoundly ill infants and children with hypotension refractory to treatment with multiple

pressor agents after cardiac surgery. The mean baseline plasma vasopressin level was 4.4 pg/mL. Vasopressin administration increased mean arterial pressure in all patients and decreased pressor agents in five of eight patients. All nine children with vasodilatory shock survived their ICU stay, and two patients who received vasopressin in the setting of poor cardiac function died despite transient improvement in their BP.

Chen et al⁵² evaluated vasopressin in hypotension in 10 hemodynamically unstable solid-organ donors. Again, baseline vasopressin levels were inappropriately low (2.9 ± 0.8 pg/mL) for the degree of hypotension. Mean arterial pressure increased allowing discontinuation of catecholamine therapy in four subjects and reduction in requirements in four subjects.

These authors¹¹¹ have also reported the use of low-dose vasopressin as an effective vasopressor for seven patients with milrinone-induced hypotension and found that vasopressin infusion at 0.03 to 0.07 U/min increased systolic arterial pressure from 90 to 127 mm Hg ($p < 0.01$). This pressor response allowed a decrease in the dose and incidence of administration of norepinephrine. Vasopressin did not change pulmonary artery diastolic pressure. Urinary output averaged 42 ± 10 mL/h at baseline, 44 ± 19 mL/h with milrinone (not significant), and 81 ± 20 mL/h ($p < 0.05$) after the addition of vasopressin. There was no decrease in CI with vasopressin administration.

MECHANISMS OF VASOPRESSIN DEFICIENCY IN SEPTIC SHOCK AND SIRS

The mechanisms of vasopressin deficiency in patients with vasodilatory shock are not known. Landry and coworkers¹ showed that increased metabolism or clearance of vasopressin is not a mechanism of the low vasopressin levels in patients with septic shock. The potential mechanisms of vasopressin deficiency include (1) depletion of pituitary stores of vasopressin after exhaustive release of vasopressin in early septic shock, (2) autonomic dysfunction in patients with septic shock,^{56,57} and (3) increased vascular endothelial release of NO within the posterior pituitary, which may downregulate vasopressin production (Table 3).³⁷

The mechanisms of the exquisite sensitivity of vasodilatory shock patients to vasopressin may also be multifactorial. Autonomic insufficiency in vasodilatory shock may “unmask” the pressor effects of vasopressin. Pressor sensitivity to physiologic doses of vasopressin is greatly enhanced following baroreceptor denervation in dogs.⁷² Threshold sensitivity was increased 11-fold, and sensitivity at higher doses

was increased 60-fold to 100-fold. Humans with idiopathic orthostatic hypotension also exhibit a pressor response (1,000-fold sensitivity) to physiologic doses of vasopressin.⁶⁴ Synergy of action with adrenergic agents at the G protein-coupled receptors may occur. Low-dose norepinephrine infusion increased sensitivity to vasopressin at physiologic doses by nearly 8,000-fold.⁷² Finally, blockade of K-ATP channels may be a mechanism of restoration of vascular tone by vasopressin in patients with septic shock.

CONCLUSIONS AND RECOMMENDATIONS

Vasopressin deficiency may contribute to the refractory hypotension of late, refractory septic shock. Infusion of vasopressin increases plasma levels to values found during comparable degrees of hypotension from other causes, such as cardiogenic shock. Vasopressin infusion causes a pressor response and a sparing of conventional exogenous catecholamines.

In “physiologic” doses (*ie*, 0.01 to 0.04 U/min yielding plasma levels of 20 to 30 pg/mL), vasopressin is synergistic with exogenous catecholamines yielding a pressor response without evidence of organ hypoperfusion, and low-dose vasopressin may vasodilate some vital vascular beds. In “pharmacologic” doses (*ie*, > 0.04 U/min, giving plasma levels of > 100 pg/mL), the pressor effect of vasopressin is associated with potentially deleterious vasoconstriction of renal, mesenteric, pulmonary, and coronary vasculature.

Clinical use of vasopressin should await a randomized controlled trial of the effect of vasopressin on clinical outcomes such as organ failure and mortality because it is not yet known whether vasopressin improves organ dysfunction or increases survival. A reasonable rationale for using vasopressin in a randomized controlled trial in patients with established septic shock (refractory to conventional catecholamines) would be to use vasopressin in a low dose, as an additional therapy, with the goal of restoring vasopressin levels to an “appropriate” level, *ie*, 20 to 30 pg/mL. Use of low-dose vasopressin in patients with severe septic shock potentially avoids renal, mesenteric, pulmonary, and coronary ischemia, as well as the hypercoagulable effects of high-dose vasopressin. The potential benefits of low-dose vasopressin include restoration of vasomotor tone and preservation of renal blood flow and urine output. Whether this will translate to improved long-term outcomes is not known.

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REFERENCES

- 1 Landry DW, Levin HR, Gallant EM, et al. Vasopressin deficiency contributes to the vasodilation of septic shock. *Circulation* 1997; 95:1122–1125
- 2 Landry DW, Levin HR, Gallant EM, et al. Vasopressin pressor hypersensitivity in vasodilatory septic shock. *Crit Care Med* 1997; 25:1279–1282
- 3 Natanson C, Hoffman WD, Suffredini AF et al. Selected treatment strategies for septic shock based on proposed mechanisms of pathogenesis. *Ann Intern Med* 1994; 120: 771–783
- 4 Acher R, Chauvet J, Chauvet MT. Man and the chimaera: selective versus neutral oxytocin evolution. *Adv Exp Med Biol* 1995; 395:615–627
- 5 Oliver H, Schafer E. On the physiological action of extracts of the pituitary body and certain other glandular organs. *J Physiol (Lond)* 1895; 18:277–279
- 6 Howell W. The physiological effects of the hypophysis cerebri and infundibular body. *J Exp Med* 1898; 3:245–258
- 7 Farini F. Diabete insipido ed opoterapia. *Gazz Osped Clin* 1913; 34:1135–1139
- 8 von den Velden R. Die nierenwirkung von hypophysenextrakten beim menschen. *Berl Klin Wochenschr* 1913; 50: 2083–2086
- 9 Starling EH, Verney EB. The secretion of urine as studied on the isolated kidney. *Proc R Soc London (Biol)* 1924; 1924:321–363
- 10 Laszlo FA, Laszlo F Jr, De Wied D. Pharmacology and clinical perspectives of vasopressin antagonists. *Pharmacol Rev* 1991; 43:73–108
- 11 Turner RA, Pierce JG, Du Vigneaud V. The purification and the amino acid content of vasopressin preparation. *J Biol Chem* 1951; 191:21–28
- 12 du Vigneaud V, Gash DT, Katsoyannis PG. A synthetic preparation possessing biological properties associated with arginine-vasopressin. *J Am Chem Soc* 1954; 76:4751–4752
- 13 Barberis C, Mouillac B, Durroux T. Structural bases of vasopressin/oxytocin receptor function. *J Endocrinol* 1998; 156:223–229
- 14 Swaab DF, Nijveldt F, Pool CW. Distribution of oxytocin and vasopressin in the rat supraoptic and paraventricular nucleus. *J Endocrinol* 1975; 67:461–462
- 15 Bourque CW. Osmoregulation of vasopressin neurons: a synergy of intrinsic and synaptic processes. *Prog Brain Res* 1998; 119:59–76
- 16 Leng G, Brown CH, Russell JA. Physiological pathways regulating the activity of magnocellular neurosecretory cells. *Prog Neurobiol* 1999; 57:625–655
- 17 Sklar AH, Schrier RW. Central nervous system mediators of vasopressin release. *Physiol Rev* 1983; 63:1243–1280
- 18 Bourque CW, Oliet SH, Richard D. Osmoreceptors, osmoreception, and osmoregulation. *Front Neuroendocrinol* 1994; 15:231–274
- 19 Kovacs L, Robertson GL. Syndrome of inappropriate antidiuresis. *Endocrinol Metab Clin North Am* 1992; 21:859–875
- 20 Schrier RW, Berl T, Anderson RJ. Osmotic and nonosmotic control of vasopressin release. *Am J Physiol* 1979; 236:F321–F332
- 21 Wood CE, Chen HG. Acidemia stimulates ACTH, vasopressin, and heart rate responses in fetal sheep. *Am J Physiol* 1989; 257:R344–R349
- 22 Robertson GL, Shelton RL, Athar S. The osmoregulation of vasopressin. *Kidney Int* 1976; 10:25–37
- 23 Quillen EW Jr, Cowley AW Jr. Influence of volume changes on osmolality-vasopressin relationships in conscious dogs. *Am J Physiol* 1983; 244:H73–H79

- 24 Robertson G, Athar S, Shelton R. Osmotic control of vasopressin function. In: Andreoli TE, Grantham JJ, Rector FC Jr, ed. Disturbances in body fluid osmolality. Bethesda, MD: American Physiological Society, 1977; 125–148
- 25 Bissett GW, Chowdrey HS. Control of release of vasopressin by neuroendocrine reflexes. *Q J Exp Physiol* 1988; 73:811–872
- 26 Thrasher TN. Baroreceptor regulation of vasopressin and renin secretion: low-pressure versus high-pressure receptors. *Front Neuroendocrinol* 1994; 15:157–196
- 27 O'Donnell CP, Thompson CJ, Keil LC, et al. Renin and vasopressin responses to graded reductions in atrial pressure in conscious dogs. *Am J Physiol* 1994; 266:R714–R721
- 28 Johnson JA, Zehr JE, Moore WW. Effects of separate and concurrent osmotic and volume stimuli on plasma ADH in sheep. *Am J Physiol* 1970; 218:1273–1280
- 29 Arnauld E, Czernichow P, Fumoux F, et al. The effects of hypotension and hypovolaemia on the liberation of vasopressin during hemorrhage in the unanaesthetized monkey (*Macaca mulatta*). *Pflügers Arch Eur J Physiol* 1977; 371:193–200
- 30 Quail AW, Woods RL, Komer PI. Cardiac and arterial baroreceptor influences in release of vasopressin and renin during hemorrhage. *Am J Physiol* 1987; 252:H1120–H1126
- 31 Goldsmith SR, Francis GS, Cowley AW, et al. Response of vasopressin and norepinephrine to lower body negative pressure in humans. *Am J Physiol* 1982; 243:H970–H973
- 32 Norsk P, Ellegaard P, Videbaek R, et al. Arterial pulse pressure and vasopressin release in humans during lower body negative pressure. *Am J Physiol* 1993; 264:R1024–R1030
- 33 Bie P, Secher NH, Astrup A, et al. Cardiovascular and endocrine responses to head-up tilt and vasopressin infusion in humans. *Am J Physiol* 1986; 251:R735–R741
- 34 Kiowski W, Julius S. Renin response to stimulation of cardiopulmonary mechanoreceptors in man. *J Clin Invest* 1978; 62:656–663
- 35 Goetz KL, Bond GC, Smith WE. Effect of moderate hemorrhage in humans on plasma ADH and renin. *Proc Soc Exp Biol Med* 1974; 145:277–280
- 36 Leng G, Dyball RE, Russell JA. Neurophysiology of body fluid homeostasis. *Comp Biochem Physiol A* 1988; 90:781–788
- 37 Reid IA. Role of nitric oxide in the regulation of renin and vasopressin secretion. *Front Neuroendocrinol* 1994; 15:351–383
- 38 Day TA, Randle JC, Renaud LP. Opposing α - and β -adrenergic mechanisms mediate dose-dependent actions of norepinephrine on supraoptic vasopressin neurones *in vivo*. *Brain Res* 1985; 358:171–179
- 39 Randle JC, Bourque CW, Renaud LP. α_1 -Adrenergic receptor activation depolarizes rat supraoptic neurosecretory neurons *in vitro*. *Am J Physiol* 1986; 251:R569–R574
- 40 Cowley AW Jr, Cushman WC, Quillen EW Jr, et al. Vasopressin elevation in essential hypertension and increased responsiveness to sodium intake. *Hypertension* 1981; 3:193–1100
- 41 Morton JJ, Padfield PL, Forsling ML. A radioimmunoassay for plasma arginine-vasopressin in man and dog: application to physiological and pathological states. *J Endocrinol* 1975; 65:411–424
- 42 Czaczkes JW. Physiologic studies of antidiuretic hormone by its direct measurement in human plasma. *J Clin Invest* 1964; 43:1625–1640
- 43 Share L, Kimura T, Matsui K, et al. Metabolism of vasopressin. *Fed Proc* 1985; 44:59–61
- 44 Wang BC, Flora-Ginter G, Leadley RJ Jr, et al. Ventricular receptors stimulate vasopressin release during hemorrhage. *Am J Physiol* 1988; 254:R204–R211
- 45 Morales D, Madigan J, Cullinane S, et al. Reversal by vasopressin of intractable hypotension in the late phase of hemorrhagic shock. *Circulation* 1999; 100:226–229
- 46 Errington ML, Rocha e Silva M Jr. The secretion and clearance of vasopressin during the development of irreversible hemorrhagic shock. *J Physiol (Lond)* 1971; 217:43P–45P
- 47 Brackett DJ, Schaefer CF, Tompkins P, et al. Evaluation of cardiac output, total peripheral vascular resistance, and plasma concentrations of vasopressin in the conscious, unrestrained rat during endotoxemia. *Circ Shock* 1985; 17:273–284
- 48 Wilson MF, Brackett DJ, Hinshaw LB, et al. Vasopressin release during sepsis and septic shock in baboons and dogs. *Surg Gynecol Obstet* 1981; 153:869–872
- 49 Argenziano M, Choudhri AF, Oz MC, et al. Prospective randomized trial of arginine vasopressin in the treatment of vasodilatory shock after left ventricular assist device placement. *Circulation* 1997; 96:II-286–290
- 50 Argenziano M, Chen JM, Choudhri AF, et al. Management of vasodilatory shock after cardiac surgery: identification of predisposing factors and use of a novel pressor agent. *Thorac Cardiovasc Surg* 1998; 116:973–980
- 51 Rosenzweig EB, Starc TJ, Chen JM, et al. Intravenous arginine-vasopressin in children with vasodilatory shock after cardiac surgery. *Circulation* 1999; 100:II182–II186
- 52 Chen JM, Cullinane S, Spanier TB, et al. Vasopressin deficiency and pressor hypersensitivity in hemodynamically unstable organ donors. *Circulation* 1999; 100:II244–II246
- 53 Cowley AW Jr, Switzer SJ, Guinn MM. Evidence and quantification of the vasopressin arterial pressure control system in the dog. *Circ Res* 1980; 46:58–67
- 54 Wilson MF, Brackett DJ, Tompkins P, et al. Elevated plasma vasopressin concentrations during endotoxin and *E coli* shock. *Adv Shock Res* 1981; 6:15–26
- 55 Reid IA. Role of vasopressin deficiency in the vasodilation of septic shock. *Circulation* 1997; 95:1108–1110
- 56 Garrard CS, Kontoyannis DA, Piepoli M. Spectral analysis of heart rate variability in the sepsis syndrome. *Clin Auton Res* 1993; 3:5–13
- 57 Zerbe RL, Henry DP, Robertson GL. Vasopressin response to orthostatic hypotension: etiologic and clinical implications. *Am J Med* 1983; 74:265–271
- 58 Mouillac B, Chini B, Balestre MN, et al. The binding site of neuropeptide vasopressin V1a receptor: evidence for a major localization within transmembrane regions. *J Biol Chem* 1995; 270:25771–25777
- 59 Thibonnier M. Signal transduction of V1-vascular vasopressin receptors. *Regul Pept* 1992; 38:1–11
- 60 Briley EM, Lolait SJ, Axelrod J, et al. The cloned vasopressin V1a receptor stimulates phospholipase A2, phospholipase C, and phospholipase D through activation of receptor-operated calcium channels. *Neuropeptides* 1994; 27:63–74
- 61 Orloff J, Handler J. The role of adenosine 3',5'-phosphate in the action of antidiuretic hormone. *Am J Med* 1967; 42:757–768
- 62 Thibonnier M, Preston JA, Dulin N, et al. The human V3 pituitary vasopressin receptor: ligand binding profile and density-dependent signaling pathways. *Endocrinology* 1997; 138:4109–4122
- 63 Thibonnier M, Conarty DM, Preston JA, et al. Human vascular endothelial cells express oxytocin receptors. *Endocrinology* 1999; 140:1301–1309
- 64 Schwartz J, Reid IA. Role of vasopressin in blood pressure

- regulation in conscious water-deprived dogs. *Am J Physiol* 1983; 244:R74–R77
- 65 Abboud FM, Floras JS, Aylward PE, et al. Role of vasopressin in cardiovascular and blood pressure regulation. *Blood Vessels* 1990; 27:106–115
 - 66 Mohring J, Glanzer K, Maciel JA Jr, et al. Greatly enhanced pressor response to antidiuretic hormone in patients with impaired cardiovascular reflexes due to idiopathic orthostatic hypotension. *J Cardiovasc Pharmacol* 1980; 2:367–376
 - 67 Schwartz J, Reid IA. Effect of vasopressin blockade on blood pressure regulation during hemorrhage in conscious dogs. *Endocrinology* 1981; 109:1778–1780
 - 68 Minaker KL, Meneilly GS, Youn GJ, et al. Blood pressure, pulse, and neurohumoral responses to nitroprusside-induced hypotension in normotensive aging men. *J Gerontol* 1991; 46:M151–M154
 - 69 Kelly CM, Ponzillo JJ. Vasopressin use in cardiopulmonary resuscitation. *Ann Pharmacother* 1997; 31:1523–1525
 - 70 Undesser KP, Hasser EM, Haywood JR, et al. Interactions of vasopressin with the area postrema in arterial baroreflex function in conscious rabbits. *Circ Res* 1985; 56:410–417
 - 71 Luk J, Ajaelo I, Wong V, et al. Role of V1 receptors in the action of vasopressin on the baroreflex control of heart rate. *Am J Physiol* 1993; 265:R524–R529
 - 72 Cowley AW Jr, Monos E, Guyton AC. Interaction of vasopressin and the baroreceptor reflex system in the regulation of arterial blood pressure in the dog. *Circ Res* 1974; 34:505–514
 - 73 Liard JF, Deriaz O, Schelling P, et al. Cardiac output distribution during vasopressin infusion or dehydration in conscious dogs. *Am J Physiol* 1982; 243:H663–H669
 - 74 Oyama H, Suzuki Y, Satoh S, et al. Role of nitric oxide in the cerebral vasodilatory responses to vasopressin and oxytocin in dogs. *J Cereb Blood Flow Metab* 1993; 13:285–290
 - 75 Vanhoutte PM, Katusic ZS, Shepherd JT. Vasopressin induces endothelium-dependent relaxations of cerebral and coronary, but not of systemic arteries. *J Hypertens* 1984; (suppl 2):S421–S422
 - 76 Karmazyn M, Manku MS, Horrobin DF. Changes of vascular reactivity induced by low vasopressin concentrations: interactions with cortisol and lithium and possible involvement of prostaglandins. *Endocrinology* 1978; 102:1230–1236
 - 77 Noguera I, Medina P, Segarra G, et al. Potentiation by vasopressin of adrenergic vasoconstriction in the rat isolated mesenteric artery. *Br J Pharmacol* 1997; 122:431–438
 - 78 Segarra G, Medina P, Domenech C, et al. Role of vasopressin on adrenergic neurotransmission in human penile blood vessels. *J Pharmacol Exp Ther* 1998; 286:1315–1320
 - 79 Wakatsuki T, Nakaya Y, Inoue I. Vasopressin modulates K(+) channel activities of cultured smooth muscle cells from porcine coronary artery. *Am J Physiol* 1992; 263:H491–H496
 - 80 Nelson MT, Quayle JM. Physiological roles and properties of potassium channels in arterial smooth muscle. *Am J Physiol* 1995; 268:C799–C822
 - 81 Landry DW, Oliver JA. The ATP-sensitive K⁺ channel mediates hypotension in endotoxemia and hypoxic lactic acidosis in dog. *J Clin Invest* 1992; 89:2071–2074
 - 82 Altura BM. Dose-response relationships for arginine vasopressin and synthetic analogs on three types of rat blood vessels: possible evidence for regional differences in vasopressin receptor sites within a mammal. *J Pharmacol Exp Ther* 1975; 193:413–423
 - 83 Leung FW, Jensen DM, Guth PH. Endoscopic demonstration that vasopressin but not propranolol produces gastric mucosal ischemia in dogs with portal hypertension. *Gastrointest Endosc* 1988; 34:310–313
 - 84 Erwald R, Wiechel KL, Strandell T. Effect of vasopressin on regional splanchnic blood flows in conscious man. *Acta Chir Scand* 1976; 142:36–42
 - 85 Schrauwen E, Houvenaghel A. Vascular effects of vasopressin an oxytocin in the pig mesenteric bed. *Pflugers Arch* 1982; 392:301–303
 - 86 Kerr JC, Jain KM, Swan KG, et al. Effects of vasopressin on cardiac output and its distribution in the subhuman primate. *J Vasc Surg* 1985; 2:443–449
 - 87 Ohnishi K, Saito M, Nakayama T, et al. Effects of vasopressin on portal hemodynamics in patients with portal hypertension. *Am J Gastroenterol* 1987; 82:135–138
 - 88 Liard JF. cAMP and extrarenal vasopressin V2 receptors in dogs. *Am J Physiol* 1992; 263:H1888–H1891
 - 89 Walker BR. Role of vasopressin in the cardiovascular response to hypoxia in the conscious rat. *Am J Physiol* 1986; 251:H1316–H1323
 - 90 Okamura T, Toda M, Ayajiki K, et al. Receptor subtypes involved in relaxation and contraction by arginine vasopressin in canine isolated short posterior ciliary arteries. *J Vasc Res* 1997; 34:464–472
 - 91 Okamura T, Ayajiki K, Fujioka H, et al. Mechanisms underlying arginine vasopressin-induced relaxation in monkey isolated coronary arteries. *J Hypertens* 1999; 17:673–678
 - 92 Suzuki Y, Satoh S, Oyama H, et al. Regional differences in the vasodilator response to vasopressin in canine cerebral arteries *in vivo*. *Stroke* 1993; 24:1049–1054
 - 93 Bichet DG, Razi M, Lonergan M, et al. Hemodynamic and coagulation responses to 1-desamino[8-D-arginine] vasopressin in patients with congenital nephrogenic diabetes insipidus. *N Engl J Med* 1988; 318:881–887
 - 94 Tamaki T, Kiyomoto K, He H, et al. Vasodilation induced by vasopressin V2 receptor stimulation in afferent arterioles. *Kidney Int* 1996; 49:722–729
 - 95 Jin HK, Chen YF, Yang RH, et al. Vasopressin lowers pulmonary artery pressure in hypoxic rats by releasing atrial natriuretic peptide. *Am J Med Sci* 1989; 298:227–236
 - 96 Walker BR, Haynes J Jr, Wang HL, et al. Vasopressin-induced pulmonary vasodilation in rats. *Am J Physiol* 1989; 257:H415–H422
 - 97 Eichinger MR, Walker BR. Enhanced pulmonary arterial dilation to arginine vasopressin in chronically hypoxic rats. *Am J Physiol* 1994; 267:H2413–H2419
 - 98 Wallace AW, Tunin CM, Shoukas AA. Effects of vasopressin on pulmonary and systemic vascular mechanics. *Am J Physiol* 1989; 257:H1228–H1234
 - 99 Russ RD, Walker BR. Role of nitric oxide in vasopressinergic pulmonary vasodilatation. *Am J Physiol* 1992; 262:H743–H747
 - 100 Sai Y, Okamura T, Amakata Y, et al. Comparison of responses of canine pulmonary artery and vein to angiotensin II, bradykinin and vasopressin. *Eur J Pharmacol* 1995; 282:235–241
 - 101 Evora PR, Pearson PJ, Schaff HV. Arginine vasopressin induces endothelium-dependent vasodilatation of the pulmonary artery: V1-receptor-mediated production of nitric oxide. *Chest* 1993; 103:1241–1245
 - 102 Aiyar N, Nambi P, Crooke ST. Desensitization of vasopressin sensitive adenylate cyclase by vasopressin and phorbol esters. *Cell Signal* 1990; 2:153–160
 - 103 Edwards RM, Trizna W, Kinter LB. Renal microvascular effects of vasopressin and vasopressin antagonists. *Am J Physiol* 1989; 256:F274–F278
 - 104 Kurtzman NA, Rogers PW, Boonjareern S, et al. Effect of infusion of pharmacologic amounts of vasopressin on renal electrolyte excretion. *Am J Physiol* 1975; 228:890–894

- 105 Walter R SC, Mehta PK, Boonjarern S, et al. Conformation considerations of vasopressin as a guide to development of biological probes and therapeutic agents. In: Andreoli TE, Grantham JJ, Rector FC, eds. *Disturbances in body fluid osmolality*. Bethesda, MD: American Physiologic Society, 1977; 1–36
- 106 Rudichenko VM, Beierwaltes WH. Arginine vasopressin-induced renal vasodilation mediated by nitric oxide. *J Vasc Res* 1995; 32:100–105
- 107 McVicar AJ. Dose-response effects of pressor doses of arginine vasopressin on renal hemodynamics in the rat. *J Physiol* 1988; 404:535–546
- 108 Nielsen S, Knepper MA. Vasopressin activates collecting duct urea transporters and water channels by distinct physical processes. *Am J Physiol* 1993; 265:F204–F213
- 109 Franchini KG, Cowley AW Jr. Renal cortical and medullary blood flow responses during water restriction: role of vasopressin. *Am J Physiol* 1996; 270:R1257–R1264
- 110 Eisenman A, Armali Z, Enat R, et al. Low-dose vasopressin restores diuresis both in patients with hepatorenal syndrome and in anuric patients with end-stage heart failure. *J Intern Med* 1999; 246:183–190
- 111 Gold J, Cullinane S, Chen J, et al. Vasopressin in the treatment of milrinone-induced hypotension in severe heart failure. *Am J Cardiol* 2000; 85:506–588, A11
- 112 Harrison-Bernard LM, Carmines PK. Juxtamedullary microvascular responses to arginine vasopressin in rat kidney. *Am J Physiol* 1994; 267:F249–F256
- 113 Tucci JR, Espiner EA, Jagger PI, et al. Vasopressin in the evaluation of pituitary-adrenal function. *Ann Intern Med* 1968; 69:191–202
- 114 Antoni FA. Vasopressinergic control of pituitary adrenocorticotropin secretion comes of age. *Front Neuroendocrinol* 1993; 14:76–122
- 115 Bugajski J, Gadek-Michalska A, Ołowska A, et al. Role of nitric oxide in the vasopressin-induced corticosterone secretion in rats. *J Physiol Pharmacol* 1997; 48:805–812
- 116 Annane D, Sebille V, Troche G, et al. A 3-level prognostic classification in septic shock based on cortisol levels and cortisol response to corticotropin. *JAMA* 2000; 283:1038–1045
- 117 Haslam RJ, Rosson GM. Aggregation of human blood platelets by vasopressin. *Am J Physiol* 1972; 223:958–967
- 118 Mannucci PM, Canciani MT, Rota L, et al. Response of factor VIII/von Willebrand factor to DDAVP in healthy subjects and patients with hemophilia A and von Willebrand's disease. *Br J Haematol* 1981; 47:283–293
- 119 Riphagen CL, Pittman QJ. Arginine vasopressin as a central neurotransmitter. *Fed Proc* 1986; 45:2318–2322
- 120 Aikawa T, Kasahara T, Uchiyama M. Circadian variation of plasma arginine vasopressin concentration, or arginine vasopressin in enuresis. *Scand J Urol Nephrol Suppl* 1999; 202:47–49
- 121 Perras B, Pannenberg H, Marshall L, et al. Beneficial treatment of age-related sleep disturbances with prolonged intranasal vasopressin. *J Clin Psychopharmacol* 1999; 19: 28–36
- 122 Pittman QJ, Wilkinson MF. Central arginine vasopressin and endogenous antipyresis. *Can J Physiol Pharmacol* 1992; 70:786–790
- 123 Doris PA. Vasopressin and central integrative processes. *Neuroendocrinology* 1984; 38:75–85
- 124 Argenziano M, Chen JM, Cullinane S, et al. Arginine vasopressin in the management of vasodilatory hypotension after cardiac transplantation. *J Heart Lung Transplant* 1999; 18:814–817
- 125 Brackett DJ, Schaefer CF, Wilson MF. The role of vasopressin in the maintenance of cardiovascular function during early endotoxin shock. *Adv Shock Res* 1983; 9:147–156
- 126 Rurak DW. Plasma vasopressin levels during hemorrhage in mature and immature fetal sheep. *J Dev Physiol* 1979; 1:91–101
- 127 Malay MB, Ashton RC Jr, Landry DW, et al. Low-dose vasopressin in the treatment of vasodilatory septic shock. *J Trauma* 1999; 47:699–703
- 128 Morales DL, Gregg D, Helman DN, et al. Arginine vasopressin in the treatment of 50 patients with postcardiotomy vasodilatory shock. *Ann Thorac Surg* 2000; 69:102–106