Vasopressin: Mechanisms of action on the vasculature in health and in septic shock

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LEARNING OBJECTIVES

On completion of this article, the reader should be able to:

1. Explain the effects of vasopressin on healthy patients.
2. Describe the effects of vasopressin in patients with septic shock.
3. Use this information in the clinical setting.

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Background: **Vasopressin is essential for cardiovascular homeostasis, acting via the kidney to regulate water resorption, on the vasculature to regulate smooth muscle tone, and as a central neurotransmitter, modulating brainstem autonomic function. Although it is released in response to stress or shock states, a relative deficiency of vasopressin has been found in prolonged vasodilatory shock, such as is seen in severe sepsis. In this circumstance, exogenous vasopressin has marked vasopressor effects, even at doses that would not affect blood pressure in healthy individuals. These two findings provide the rationale for the use of vasopressin in the treatment of septic shock. However, despite considerable research attention, the mechanisms for vasopressin deficiency and hypersensitivity in vasodilatory shock remain unclear.**

Objective: **To summarize vasopressin's synthesis, physiologic roles, and regulation and then review the literature describing its vascular receptors and downstream signaling pathways. A discussion of potential mechanisms underlying vasopressin hypersensitivity in septic shock follows, with reference to relevant clinical, *in vivo*, and *in vitro* experimental evidence.**

Data Source: **Search of the PubMed database (keywords: *vasopressin and receptors and/or sepsis or septic shock*) for articles published in English before May 2006 and manual review of article bibliographies.**

Data Synthesis and Conclusions: **The pathophysiologic mechanism underlying vasopressin hypersensitivity in septic shock is probably multifactorial. It is doubtful that this phenomenon is merely the consequence of replacing a deficiency. Changes in vascular receptors or their signaling and/or interactions between vasopressin, nitric oxide, and adenosine triphosphate-dependent potassium channels are likely to be relevant. Further translational research is required to improve our understanding and direct appropriate educated clinical use of vasopressin. (Crit Care Med 2007; 35:33–40)**

Key Words: vasopressin; septic shock; vasopressor agents; receptors; nitric oxide; potassium channels

Vasopressin (antidiuretic hormone) is a nonapeptide hormone synthesized in the magnocellular neurons of the paraventricular and supraoptic nuclei of the hypothalamus. Hormone precursors migrate via the supraoptic-hypophyseal tract to the posterior pituitary gland, where they are stored in neurosecretory vesicles (1). Under normal conditions, circulating levels are maintained at around 2 pg/mL (10^{-12} M) (1, 2). Only 10–20% of the hormone within the posterior pituitary can be rapidly released, and with sustained stimulation this occurs at a greatly reduced rate (1). Vasopressin is rapidly metabolized by liver and kidney vasopressinases and has a half-life of 10–35 mins (1).

Regulation of vasopressin release is complex. In health, secretion is primarily governed by changes in serum osmolarity (osmoregulation). This system is highly sensitive, such that a small (2%) increase in osmolarity is reversed by the antidiuretic effect of a small (~5 pg/mL) increase in vasopressin (2). In contrast, baroregulation of vasopressin secretion only plays a significant role in the context of a >10% decrease in blood pressure. Hormone levels can then increase more than ten-fold to help restore normotension, largely via vasoconstriction (2).

Vasopressin release is affected by other hormones. At low concentrations, catecholamines tend to exert stimulatory ef-

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fects via central α_1 receptors but at higher levels may inhibit vasopressin release via α_2 and β receptors (3, 4). Secretion of vasopressin also stimulates release of adrenocorticotropic hormone from the anterior pituitary, with consequent negative feedback of glucocorticoids on the posterior pituitary (2). Additional factors are important in critical illness. Hypoxia and acidosis stimulate carotid body chemoreceptors to increase vasopressin release (1). Furthermore, both endotoxin and cytokines enhance vasopressin production (2), whereas nitric oxide (NO) plays a mainly inhibitory neuromodulating role on its secretion (5).

The actions of vasopressin are mediated via G protein-coupled receptors, classified by virtue of their location and second messenger pathways into V_1 (or V_{1a}), V_2, and V_3 (formerly V_{1b}) receptors (6). In addition, vasopressin has equal affinity with oxytocin for oxytocin receptors (OTRs) and may exert some of its actions via this route (7).

V_1 Receptors (V_1Rs). V_1Rs are found mainly on vascular smooth muscle in the systemic, splanchnic, renal, and coronary circulations. They are coupled through $G_{q/11}$ to phospholipase C (PLC), and their activation produces vasoconstriction via the elevation of intracellular calcium (Ca^{2+}) (Figs. 1 and 2). The emptying of stores within the sarcoplasmic reticulum transiently increases cytoplasmic Ca^{2+}, whereas a sustained increase is produced by influx of extracellular Ca^{2+} (8, 9). The pathways leading to vasopressin-induced extracellular calcium entry are complex (Fig. 1). Store-operated channels probably play a minor role compared with voltage-gated calcium channels and receptor-operated channels (10, 11). Voltage-gated calcium channels are activated indirectly by cell membrane depolarization or directly by protein kinase C (PKC) (12) (Fig. 1). The opening of receptor-operated channels is G protein-dependent via PLC and its downstream second messengers, diacylglycerol and arachidonic acid (10, 13). Receptor-operated channels permit nonselective cation influx, promoting membrane depolarization, and a significant Ca^{2+} entry, which contributes directly to contraction (13). In addition to its effects on calcium influx, V_1R stimulation may sensitize the contractile apparatus to the effect of calcium via the inhibition of myosin light chain phosphatase by PKC (14) (Fig. 2).

V_1Rs are also found on platelets, on renal collecting duct cells, and in the brainstem (7). The latter mediate vasopressinergic modulation of the autonomic nervous system (15) and are responsible for a baroreflex-mediated decrease in heart rate, which precludes a pressor effect when vasopressin acts on vascular smooth muscle in healthy people (16).

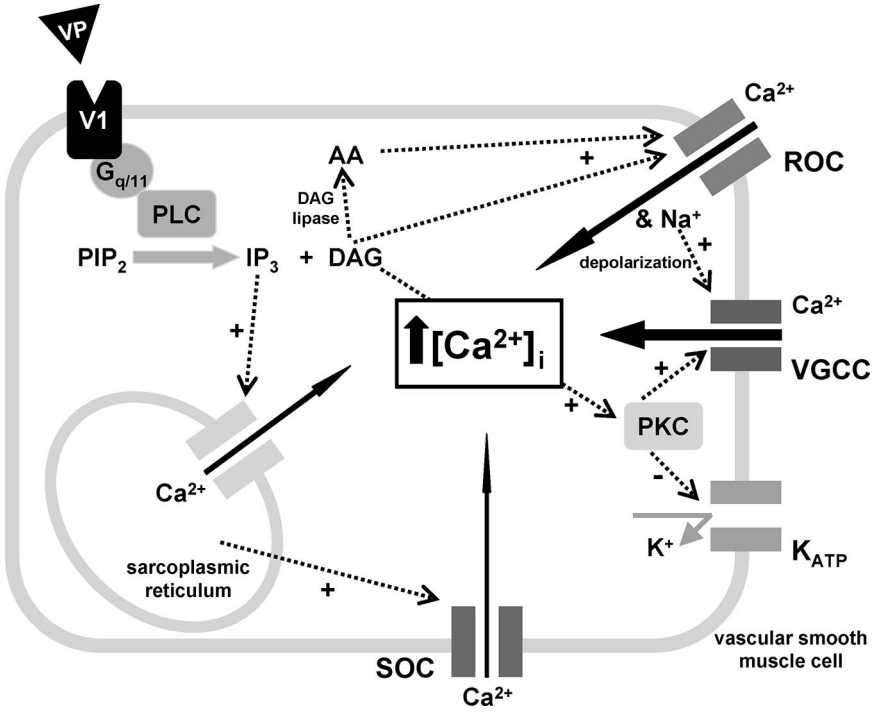

Figure 1. A schematic showing the pathways of intracellular calcium (*Ca^{2+}*) elevation following the binding of vasopressin (*VP*) to the V_1 receptor (*V_1R*) on a vascular smooth muscle cell. The weighting of the black solid arrows demonstrates the relative importance of the different pathways. V_1Rs are coupled through $G_{q/11}$ to phospholipase C (*PLC*), which hydrolyzes phosphatidyl inositol bisphosphonate (*PIP_2*) to produce inositol triphosphate (*IP_3*) and diacylglycerol (*DAG*). The latter, in turn, stimulates the activity of protein kinase C (*PKC*). A transient increase in intracellular Ca^{2+} is produced by the action of IP_3 on the sarcoplasmic reticulum, whereas a sustained increase is triggered by influx of extracellular Ca^{2+}. Store-operated channels (*SOCs*), activated by intracellular store depletion, appear to play a minor role in comparison to voltage-gated calcium channels (*VGCCs*) and receptor-operated channels (*ROCs*). VGCCs are opened by cell membrane depolarization, secondary to cation influx via ROCs and the PKC-mediated closure of adenosine triphosphate-sensitive potassium (*K_{ATP}*) channels. PKC can also open VGCCs directly. The opening of ROCs is G protein-dependent via PLC, with a downstream mechanism involving DAG and arachidonic acid (*AA*). They have significant permeability to Ca^{2+}, which is likely to contribute directly to contraction.

V_2 Receptors (V_2Rs). V_2Rs mediate the antidiuretic actions of vasopressin within the kidney and are coupled through G_s to adenylyl cyclase. Receptor stimulation produces an increase in intracellular cyclic adenosine monophosphate (cAMP), activation of protein kinase A, and the insertion of water channels (aquaporins) into the luminal membranes of renal collecting duct cells (2, 7). As discussed in a later paragraph, there is ongoing debate regarding the expression of V_2Rs in the vasculature.

V_3 Receptors (V_3Rs). V_3Rs are found in the anterior pituitary and are coupled to various second messenger systems. To date, the best characterized role of the V_3R is in the secretion of adrenocorticotropic hormone, which appears to be mediated via the activation of PKC (7).

Oxytocin Receptors (OTRs). Like V_1Rs, OTRs are coupled to PLC, the metabolism of phosphoinositides, and the consequent elevation of intracellular calcium (7). In myometrial and mammary myoepithelial cells, OTR stimulation produces smooth muscle contraction (7), and this may also occur in vascular smooth muscle (17, 18) (Fig. 2). In addition, OTRs are highly expressed in the vascular endothelium (19), where an increase in intracellular Ca^{2+} activates constitutive endothelial NO synthase to release NO and produce vasorelaxation (7) (Fig. 2). The lack of pressor response observed with oxytocin infusions in obstetrical practice may be consequent to the opposing effects of OTR stimulation on endothelial and smooth muscle cells.

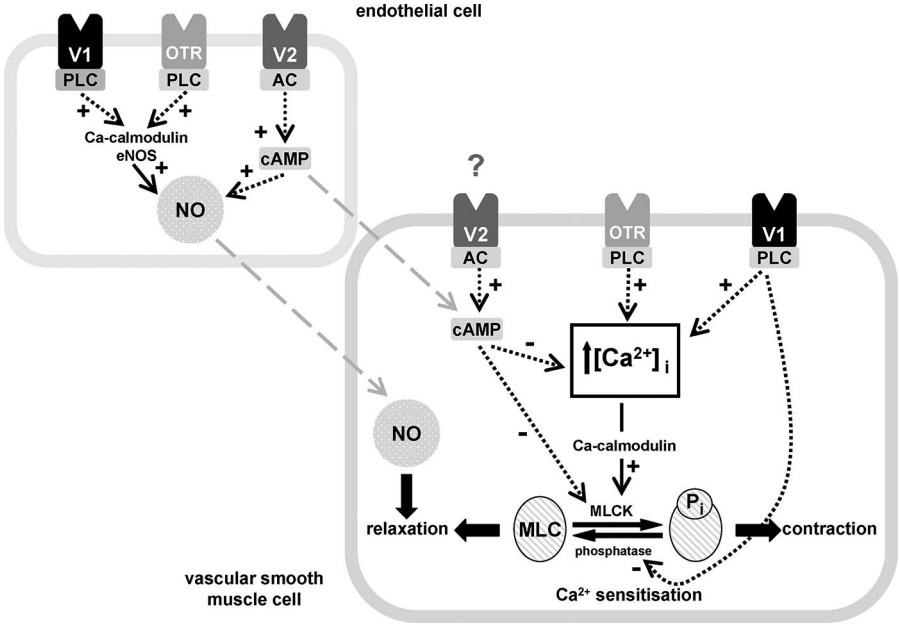

Figure 2. Interplay between an endothelial and a vascular smooth muscle cell showing the mechanisms by which vasopressin may produce vasoconstriction and/or vasodilation. Vascular smooth muscle V_1 receptor (*V_1R*) stimulation produces an elevation of intracellular calcium (Ca^{2+}). Smooth muscle oxytocin receptors (*OTRs*) are similarly coupled to phospholipase C (*PLC*) and its downstream second messenger pathways. Ca^{2+} binds to calmodulin and activates myosin light chain kinase (*MLCK*). This enzyme catalyzes the phosphorylation (*P_i*) of myosin light chains (*MLC*), facilitating the interaction between myosin and actin, which produces muscle contraction. V_2 receptor (*V_2R*) actions are mediated via adenylate cyclase (*AC*) and, if present on vascular smooth muscle, could produce vasorelaxation via a cyclic adenosine monophosphate (*cAMP*)-mediated decrease in intracellular Ca^{2+}. V_1R activation may also enhance the response of the contractile apparatus to the effect of Ca^{2+} via the inhibition of myosin light chain phosphatase (Ca^{2+} sensitization). OTRs are highly expressed in the vascular endothelium, where an increase in intracellular Ca^{2+} activates constitutive endothelial nitric oxide synthase (*eNOS*) to release nitric oxide (*NO*). There is experimental evidence to suggest the existence of endothelial V_1Rs and V_2Rs. Stimulation of either subtype would activate eNOS, the former via calcium-calmodulin and the latter via an elevation in cAMP. Endothelial-derived NO causes vascular smooth muscle relaxation by a number of different pathways that are not detailed here.

Vasopressin produces vasodilation in some vascular beds, but the receptor subtype responsible is uncertain, may vary between blood vessels, and may depend on hormone concentration. The receptors mediating this effect may be situated on endothelial or smooth muscle cells or both. V_2Rs on vascular smooth muscle could produce vasorelaxation via a cAMP-mediated drop in intracellular calcium; alternatively, generation of cAMP in the endothelium would trigger NO liberation via endothelial NO synthase (Fig. 2). Infusion of the V_2 agonist, DDAVP, in anephric dogs elevated levels of plasma cAMP coincident with a decrease in peripheral vascular tone, supporting the existence of extrarenal V_2Rs (20). In healthy humans, high-dose vasopressin decreased forearm vascular resistance in a V_2R- and NO-dependent manner (21, 22). This vasodilation was not seen in patients with nephrogenic diabetes insipidus secondary to a V_2R defect (23). Real-time polymerase chain reaction has demonstrated V_2R expression on cultured human lung endothelial cells and in heart, spleen, and lung whole tissue specimens (24). Use of a selective V_2R radioligand to demonstrate binding to either vascular smooth muscle or endothelium in the rat, however, has been unsuccessful (25). *Ex vivo* studies support an endothelium-dependent mechanism for vasopressin-induced vasodilation, but the effect of selective V_2 agonists on relaxed arterial preparations has been variable (26–30). Furthermore, endothelial V_1Rs (28, 29) or OTRs (19) coupled to endothelial NO synthase activation could also account for vasopressin-mediated vasorelaxation (Fig. 2).

Vasopressin in Septic Shock

Septic shock describes organ dysfunction and hypotension unresponsive to fluid resuscitation following a systemic inflammatory response syndrome to infection (31). Shock states generally trigger sympathetic and renin-angiotensin system activation and hence profound peripheral vasoconstriction. In septic shock, however, vascular smooth muscle shows a decreased ability to contract, and the concomitant hypotension may be refractory to standard catecholamine vasopressor therapy. Although sepsis is the most common cause of so-called vasodilatory shock, it is also the final common pathway for long-lasting and severe shock of any cause (32).

The pathogenesis of vasodilatory shock is multifactorial. Increased NO, consequent to the activation of inducible NO synthase (iNOS), is a major contributor to vasodilation, acting both directly and via cyclic guanosine monophosphate to lower intracellular calcium levels, decrease myosin light chain phosphorylation, and activate calcium-sensitive (K_{Ca}) and adenosine triphosphate-sensitive (K_{ATP}) K^+ channels (32). Under physiologic conditions, K_{ATP} channels have low-level activity and play a minor role in blood pressure control (33, 34). In vasodilatory shock, however, these channels are persistently open with consequent vascular smooth muscle hyperpolarization and decreased Ca^{2+} entry via voltage-gated calcium channels. This contributes to both hypotension and hyporesponsiveness to catecholamines (35–37). In addition to the effect of elevated NO, persistent K_{ATP} activation may result from tissue hypoxia, acidosis, reduced ATP, and changes in calcitonin gene-related peptide, adenosine, and atrial natriuretic factor levels (34). A third factor is adrenoceptor desensitization and down-regulation due to high circulating levels of catecholamines (38, 39).

The finding that patients with severe, refractory septic shock were exquisitely sensitive to the pressor effects of exogenous vasopressin led to the investigation of its endogenous profile (40). In acute septic shock, an early increase (approximately ten-fold) in plasma vasopressin occurs in both patients (41) and animal models (42, 43). When prolonged (≥24 hrs), however, levels fall back toward baseline (40, 41), a pattern mimicking that observed for other hormones in advanced critical illness (44). Hence, a relative deficiency of vasopressin may also be crucial to the altered functional status of vascular smooth muscle. Indeed, in endotoxic models, V_1R blockade worsened hypotension (45), whereas survival was decreased in vasopressin-deficient Brattleboro rats (46).

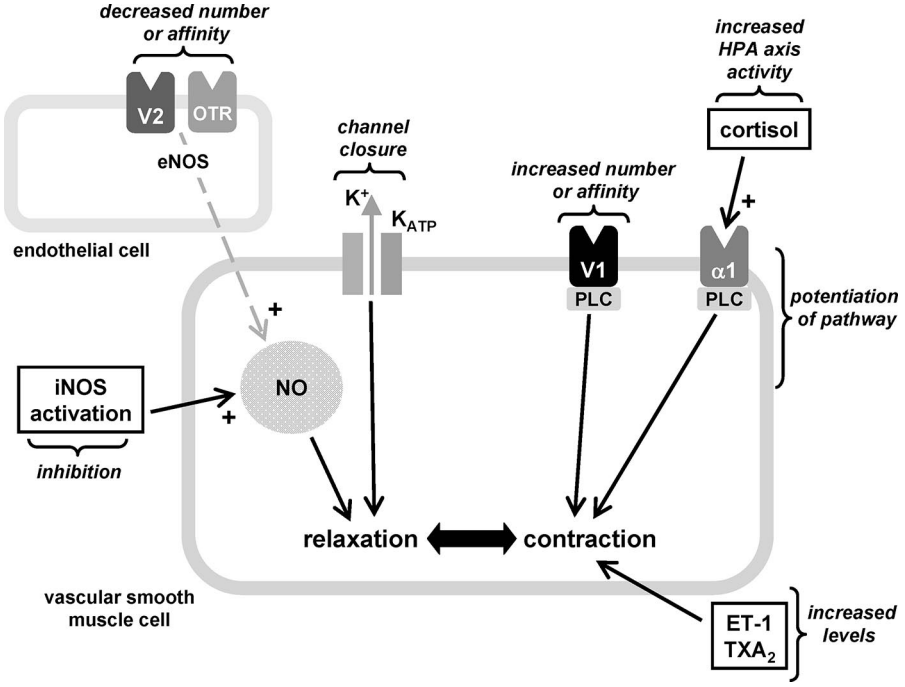

Figure 3. A schematic showing the potential mechanisms of hypersensitivity to vasopressin in septic shock at the level of a vascular smooth muscle cell. A further possibility not shown here is altered baroreflex sensitivity consequent to autonomic dysfunction. *OTR*, oxytocin receptor; *PLC*, phospholipase C; *eNOS*, endothelial nitric oxide synthase; *iNOS*, inducible nitric oxide synthase; *NO*, nitric oxide; K_{ATP}, adenosine triphosphate-sensitive potassium channel; *HPA*, hypothalamic-pituitary-adrenal; *ET-1*, endothelin-1; TXA_2, thromboxane A_2; *V1*, V_1 vasopressin receptor; *V2*, V_2 vasopressin receptor; $\alpha 1$, α_1 adrenoceptor.

Inappropriately low hormone levels are not explained by increased vasopressin breakdown but may be caused by depletion of neurohypophyseal stores or inhibition of synthesis or release (47). Either osmoregulation or baroregulation may be abnormal, and baroreflex dysfunction could underlie the apparent loss of correlation between blood pressure and vasopressin levels in septic shock (48). Impaired vasopressin release has been documented in patients with autonomic insufficiency (49, 50), a phenomenon well recognized in sepsis (51). Elevated levels of NO may contribute to autonomic dysfunction (52) and have direct inhibitory effects on vasopressin secretion (5). Sustained elevation of hormone levels following endotoxin challenge in mice was seen in iNOS knockouts or after pharmacologic NO inhibition (53–55).

EVIDENCE FOR HYPERSENSITIVITY TO VASOPRESSIN IN SEPTIC SHOCK

Exogenous administration of vasopressin in health does not elevate blood pressure, and hypertension is not characteristic of the syndrome of inappropriate antidiuretic hormone. Landry and colleagues (56) reported marked pressor sensitivity to a low dose of vasopressin in five patients with sepsis-related refractory hypotension. The pressor effect occurred within minutes and enabled catecholamines to be discontinued. Our group has published comparable results in a cohort of eight similar patients in whom terlipressin, a long-acting synthetic vasopressin analogue, was administered (57). Despite an increasing number of related studies, most have only included small numbers of patients and have been retrospective or nonrandomized (58). Ongoing is a large, multiple-center Canadian trial of vasopressin vs. norepinephrine in septic shock (VASST), which will examine 28-day mortality as the primary end point. Current consensus opinion is that low-rate constant infusion (0.01–0.04 units/min) of vasopressin is preferable to a higher, blood pressure-titrated dose if coronary, mesenteric, and skin ischemias are to be avoided (59, 60). There is increasing evidence to suggest neutral or beneficial effects on renal blood flow and urine output at these low doses (58, 61).

Several animal models of septic shock have demonstrated hypersensitivity to vasopressin. In anesthetized endotoxic rats, a heightened contractile response of cremaster muscle microvessels to topical vasopressin was coincident to hyporeactivity to norepinephrine (62, 63). In our laboratory's conscious, fluid-resuscitated model of rat fecal peritonitis (64), septic animals show a marked pressor response to terlipressin 24 hrs postinsult that is not seen in paired sham controls (65). Hypersensitivity to terlipressin was also seen in conscious ewes after 16 hrs of endotoxemia (66). Other *in vivo* setups have, however, produced discordant results (67–69), most likely related to the wide experimental variation in terms of duration, insult, severity, and fluid resuscitation.

Although *ex vivo* reproduction of the vascular hyporeactivity to catecholamines is well described in septic models (70–72), there has been relatively little work examining vascular reactivity to vasopressin. One study showed increased potency of vasopressin to constrict isolated mesenteric vessels from endotoxemic compared with control rats (73). In contrast, attenuated responses to vasopressin were observed in human gastroepiploic arteries after endotoxin treatment, but vasopressin significantly enhanced norepinephrine-induced contractions in the same tissue (74). Decreased sensitivity to both vasopressin and norepinephrine was found in isolated rat mesenteric arteries pretreated with an NO donor to simulate septic shock (75).

MECHANISMS UNDERLYING VASOPRESSIN HYPERSENSITIVITY

These are summarized in Figure 3.

Interaction With Other Factors Contributing to Vasodilatory Shock

Nitric Oxide. As discussed previously, elevated levels of NO in septic shock may contribute to relative vasopressin deficiency. Another consideration is a possible reciprocal negative effect of vasopressin on the NO cascade. Vasopressin inhibited interleukin-1 stimulated iNOS messenger RNA expression and nitrite and cyclic guanosine monophosphate production in cultured rat vascular smooth muscle cells (76). Basal NO production was unaltered, suggesting an effect specific to iNOS and hence states of

inflammatory activation. The hypothesis that heightened sensitivity to exogenous vasopressin in septic shock may be consequent to iNOS inhibition is further supported by the findings of an *in vivo* study where administration of terlipressin to endotoxic rats resulted in recovery of arterial blood pressure associated with decreased iNOS expression in isolated aortic tissue (77). However, no decrease in serum nitrite/nitrate concentrations was demonstrated in patients with vasodilatory shock after vasopressin infusion (78).

K_{ATP} Channels. In septic shock K_{ATP} channels are persistently open, resulting in a sustained hyperpolarized state and vasorelaxation. Inhibition of these channels could therefore help to restore normal vascular reactivity (37, 79). *In vitro* work in cultured porcine vascular smooth muscle cells and isolated cardiac myocytes has demonstrated the ability of vasopressin to close K_{ATP} channels (80, 81). This effect was blocked by selective inhibition of PKC (81), which may act by direct phosphorylation of the channel (82) or by increasing sarcolemmal ATP (81). Other non-PKC-mediated mechanisms are also possible. An increase in intracellular calcium evoked by V_1R stimulation could activate the calcium-dependent phosphatase, calcineurin, to promote channel inhibition (79, 83). In addition, calcineurin regulates gene transcription via the nuclear transcription factor nuclear factor of activated T cells; this in turn may down-regulate genes encoding K_{ATP} channel subunits, as has been shown for delayed rectifier potassium channels (84).

Catecholamine Sensitivity. Clinical experience with vasopressin and terlipressin in patients with refractory septic shock suggests that vasopressin and terlipressin restore vascular reactivity to both endogenous and exogenous catecholamines (56, 57, 85). *In vivo* potentiation of the vasoconstrictor actions of endogenous norepinephrine by physiologic doses of exogenous vasopressin was first reported >40 yrs ago (86). Parallel *ex vivo* studies with rat aortic strips suggested a direct vascular rather than central mechanism of vasopressin action (86). This potentiation has been confirmed in rat and human resistance arteries, seen in both normal vessels (87, 88) and those exposed to experimental sepsis (74, 75). Similarly, constriction evoked by stimulation of periarterial nerves is also enhanced and observed at concentrations of vasopressin that do not appreciably constrict blood vessels alone (87).

Several possible explanations may underlie this interaction. Norepinephrine produces its vasoconstrictive effect via α_1 adrenoceptors which, like V_1Rs, are coupled via $G_{q/11}$ proteins to PLC. Norepinephrine-induced contractions appear more dependent on release of intracellular calcium stores than influx of extracellular calcium, whereas the opposite applies for vasopressin (89). Thus, the utilization of different calcium pathways may in part explain the synergism between the two agonists. Indeed, vasopressin potentiation of adrenergic contraction in isolated rat mesenteric arteries was blocked by both a V_1R antagonist (74, 87) and the voltage-gated calcium channel blocker nifedipine (87). Alternatively, vasopressin may act via PKC and/or Rho-associated kinase to inhibit myosin light chain phosphatase, thereby sensitizing the contractile apparatus to the calcium increase produced by α_1 adrenoceptor stimulation (14). Cross-regulation may also occur at the level of the receptors. In a cell line, V_2R activation nonreciprocally inhibited adrenoceptor internalization (90). The proposed mechanism is via altered β-arrestin function; this protein normally acts by binding to activated G protein-coupled receptors and effecting their removal from the cell membrane.

Changes in Vasopressin Receptor Behavior

The opposing effects of vasopressin on vascular tissue are consequent to the stimulation of different vasopressin receptor subtypes located on smooth muscle and/or endothelial cells. Differential changes in the regulation of these subtypes could therefore explain the hypersensitivity seen in septic shock.

V_1 Receptors. In contrast to high norepinephrine levels and the resultant α_1 receptor changes, relatively low circulating concentrations of vasopressin in prolonged septic shock would leave V_1Rs available for occupancy by exogenous hormone and decrease the endogenous stimulus for receptor desensitization (6, 32). Sepsis may also induce specific changes in receptor populations. Endotoxin can alter receptor function directly (91) or indirectly via cytokines, NO, and PKC. No change in either the number or affinity of V_1Rs was seen in cultured aortic smooth muscle cells exposed to lipopolysaccharide for 24 hrs, however (92). Another group reported a cytokine-mediated decrease in V_1Rs in liver, lung, kidney, and heart tissue isolated from endotoxic rats exposed for a similar period (93). This model was not fluid resuscitated and did not demonstrate hypersensitivity to *in vivo* administration of a vasopressin agonist. Comparable results were seen in nonshocked rats who received continuous endotoxin infusion for 30 hrs (94). Further studies are required to examine changes in receptor binding in tissues from models more representative of human septic shock.

V_2 and Oxytocin Receptors. Whereas vasorelaxation can be mediated via both V_2Rs and OTRs, changes in the expression or function of these receptors in sepsis remain unknown. Increasing availability of specific agonists and antagonists now makes this a realistic proposition. V_2R recycling and resensitization are slow compared with V_1Rs (6, 7). This may well be of relevance in the context of exogenous vasopressin administration and could be one explanation for the observation that rebound hypotension on cessation of vasopressin treatment in septic shock is often prevented with the use of terlipressin (57, 95), an analogue with greater selectivity for V_1Rs over V_2Rs (2.2 vs. 1) (57, 96).

Autonomic Nervous System Dysfunction

Vasopressin release is under the control of the autonomic nervous system, with baro- and chemoreceptor afferents projecting to the brainstem and efferents from the brainstem to the paraventricular and supraoptic (3). By virtue of its neurotransmitter role, autonomic nervous system output is also modulated by vasopressin (15). Therefore, the autonomic and vasopressinergic system abnormalities seen in sepsis may well be related. Further complexity is added by the apparent negative correlation between NO levels and sympathetic cardiovascular output (52, 97) and the known interactions between vasopressin and NO described previously. In patients who died from septic shock, iNOS expression was linked to apoptosis in the paraventricular and supraoptic nuclei (52). Primary autonomic failure is associated with hypersensitivity to vasopressin's pressor effects (98) as well as with abnormalities of its release (49). The former has also been reported in dogs with baroreceptor denervation (99). Moreover, cirrhotic pa-

tients show an abnormally prolonged blood pressure response to vasopressin, and this has been ascribed to abnormal autonomic cardiovascular regulation (100). Vasopressin administration in septic shock does not produce the degree of bradycardia seen in normal individuals (40), suggesting impairment of normal baroreflexes.

Interaction With Other Vasoconstrictors

Elevated levels of endothelin-1 and thromboxane A_2 are found in septic shock and contribute to the heterogeneity in tone observed across different vascular beds (101). Vasopressin administration may increase the synthesis of these vasoconstrictors. *In vitro* work with human platelets showed that V_1R stimulation activates not only PLC but also phospholipase A_2, resulting in arachidonic acid metabolism and thromboxane production (102). In cultured endothelial cells, vasopressin enhanced both preproendothelin-1 messenger RNA expression and release of mature peptide (103, 104). *In vivo* findings support the potential role of endothelin-1 in vasopressin hypersensitivity: An exaggerated pressor response to exogenous vasopressin in spontaneously hypertensive rats was abolished by pretreatment with the endothelin antagonist bosentan (105).

Interactions With the Hypothalamic-Pituitary-Adrenal Axis

Vasopressin stimulates adrenocorticotropic hormone and hence cortisol secretion (2). Relative adrenal insufficiency is recognized in severe sepsis (106), and "low-dose" steroid replacement may provide outcome benefit in such patients (107). Steroid administration is thought to restore vascular sensitivity to catecholamines via an increase in adrenoceptor gene expression (39). Although a similar effect on vasopressin receptor expression is feasible (108), vasopressin replacement may increase cortisol levels, thus acting synergistically to restore reactivity. However, septic patients with relative adrenal insufficiency were less likely to have a relative deficiency of vasopressin than those with normal adrenal function (41). Furthermore, hypersensitivity to vasopressin may still occur despite no hemodynamic response to corticosteroids (57).

CONCLUSIONS

Understanding the pathogenesis and pathophysiology of septic shock is challenging. Reviewing the literature relevant to vasopressin hypersensitivity shows that this particular area is no exception. The relationship between relative deficiency of endogenous vasopressin and heightened sensitivity to its exogenous administration is not straightforward. Recent work has found the circulating hormone concentrations achieved with vasopressin treatment to be supraphysiologic (>100 pg/mL), despite "low-dose" regimens, and that pressor response is independent of baseline hormone levels (109). The explanation behind this complex vasopressinergic system dysfunction is likely to be multifactorial, and hence many possibilities exist for further investigation. Ideally, an *in vivo* model truly representative of prolonged, severe septic shock is required to evaluate temporal changes in vascular reactivity and endocrine and autonomic function. If observed changes in vascular reactivity could be reproduced *ex vivo*, suitable tissue would be available for assessment of the NO pathway, potassium channel activity, receptor characteristics, and intracellular calcium. Increased insight into these mechanisms will direct educated clinical use of this intriguing new intervention.

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