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Mirror, mirror on the wall: Which is the best vasopressin receptor of them all?*

Arginine vasopressin (AVP) is a potent vasoconstrictor hormone that can stabilize hemodynamic function in septic shock even when high doses of catecholamines fail to do so (1). In a European-wide survey, 43% of responding intensivists stated use of AVP as a supplementary vasopressor in septic shock (2). Although no beneficial outcome effect of an AVP infusion was observed in an unselected septic shock population in a multicenter study (3), AVP lowered mortality when administered to patients with less severe septic shock. A post hoc analysis of the latter trial suggested a potential survival benefit of the concomitant use of AVP and corticosteroids in septic shock (4). AVP exerts its biological effects via stimulation of three vasopressin receptors. In addition, oxytocin and purinergic are stimulated by AVP (5). Characteristics and physiologic actions of each receptor are summarized in Table 1.

Apart from inducing vasoconstriction, V1 receptors appear to convey several effects that may be advantageous in patients suffering from septic shock. These actions specifically include reduction of vascular leakage (6), augmentation of vasoconstrictive effects of other vasopressor hormones (7), increased secretion of vascular endothelial growth factor (8), and reversal of platelet-aggregating factor-induced hemodynamic alterations (9). Considering potentially disadvantageous effects related to V2 receptor stimulation such as vasodilatation (10), coagulation activation with possible induction of microthromboses (10), induction of P-selectin expression and leukocyte rolling (11), or tubular dysfunction (12), selective stimulation of V1 receptors (optionally combined with V2 antagonists) appears attractive in septic shock. So far, three experimental studies, two of them published in abstract form only, have evaluated the effects of selective V1 agonists (F-180 and FE-202158) in sepsis-like models and found optimistic results (6, 9, 13). Additional experimental and clinical evidence suggests that the synthetic vasopressin analog terlipressin, which has a higher affinity for the V1 receptor than AVP (V1/V2 ratio, 2.2:1 vs. 1:1), may carry some benefits in septic shock (14, 15).

In this issue of *Critical Care Medicine*, Dr. Rehberg and colleagues (16) present an innovative animal experiment, in which they compared the effects of three different vasopressor protocols (norepinephrine [maximum 1 μg/kg/min] plus normal saline vs. norepinephrine plus AVP [0.5 μg/kg/hr equivalent to 0.035 IU/min in a 70-kg patient] vs. norepinephrine plus the selective V1 agonist Phe2-Orn8-vasotocin [POV] [0.05 μg/kg/hr]). The experienced and productive working group used a well-established, clinically relevant fecal peritonitis model that resulted in septic shock with corresponding metabolic derangements. Compared with norepinephrine or AVP, the selective V1 agonist POV maintained a higher mean arterial blood pressure throughout the shock period despite lower norepinephrine requirements. Systemic oxygen delivery and urine flow were better preserved with POV and lead to both improved metabolic function and even slightly longer survival times compared with the other vasopressor protocols. These results support the authors' conclusion that selective V1 receptor stimulation appeared superior over AVP or norepinephrine in ovine septic shock. Based on these data, it is impossible to conclude whether beneficial effects have primarily resulted from selective V1 agonism, avoidance of V2 receptor stimulation or both.

Particularly interesting results that go beyond the major hemodynamic effects of POV deserve in-depth discussion. First, a lower net fluid balance (estimated by subtracting diuresis from the amount of fluids infused) was observed in this experiment. Although reduced fluid requirements have been associated with V1 receptor stimulation or terlipressin use before (6, 14), an increased diuresis during the first 4 hrs after randomization may explain this result in the present experiment. However, considering somewhat different plasma protein levels together with comparable hematocrit values between groups, it is tempting to speculate that V1 receptor stimulation resulted in reduced vascular leakage in this model. Yet, future studies applying more reliable methods to assess vascular permeability (e.g., labeled albumin) are needed before definite conclusions can be made. A lower net fluid balance may also explain why POV-treated animals exhibited better oxygenation during shock compared with the other groups. Increased admixture of less deoxygenated venous blood or reduced

*See also p. 119.

KEY WORDS: vasopressin; receptors; V1 receptor stimulation; septic shock; Phe2-Orn8-vasotocin

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Table 1. Characteristics and physiologic actions of receptors stimulated by arginine vasopressin and its analogs

Receptor Type	Location	Second Messenger[a]: Intracellular Effect	Physiologic Actions
V1 (formerly V1a)	Vascular smooth muscle cells, kidney (medulla), liver, brain, heart, endothelium, platelets, immune cells, spleen, bladder, testes, superior cervical ganglion	Phosphatidyl-inositol-bisphosphonate cascade, phospholipase C, A2, and D: Increase in cytosolic calcium, inhibition of adenosine triphosphate-sensitive potassium channels, inhibition of nitric oxide, sensitization of contractile apparatus to calcium, and increase of nitric oxide production (via endothelial V1 receptors)	Vasoconstriction, augmentation of catecholamine pressor effects, reduction of vascular permeability, potentiation of baroreflexes, vasodilatation (via endothelial V1 receptors), increased production of vascular endothelial growth factor, increase in diuresis, platelet aggregation, activation of T cells, increase in immunoglobulin type M production, liver glycogen breakdown, gluconeogensis, inhibition of fatty acid oxidation, increased metabolism of certain amino acids, reduction of bile flow, modulation of hepatocyte tight junctions, antipyresis, various neurologic and behavioral effects
V2	Kidney (collecting ducts), endothelium	Activation of cyclic aminomonophosphate	Antidiuresis, vasodilation, increase in von Willebrand factor, factor VIIIc and tissue type plasminogen activator, anti-inflammatory effects, increase in P-selectin expression and postcapillary leukocyte rolling, tubular dysfunction, and stimulation of alveolar sodium pumps
V3 (formerly V1b)	Anterior hypophysis, pancreatic isle cells	Activation of cyclic aminomonophosphate	Secretion of corticotropin releasing hormone and adrenocorticortropin, prolactin, and insulin
Oxytocin[b]	Uterus, breast, umbilical vein, heart, hypothalamus, endothelium	Phosphatidyl-inositol-bisphosphonate cascade, phospholipase C: Increase in cytosolic calcium, formation of calcium-calmodulin complexes, and increase in nitric oxide production	Vasodilation, contraction of myometral and mammary myoepithelial cells, and release of atrial natriuretic factor
Purinergic receptor (subclass 2)	Endothelium, heart	Phospholipase C: Increase in cytosolic calcium, prostacyclin, and nitric oxide production	Controversial results published for vasopressin; purinergic receptor sublcass 2 stimulation results in vasodilation, positive inotropy without positive chronotropy

[a]All receptors are G-protein coupled; [b]oxytocin receptors have a ten-fold higher affinity for oxytocin than for arginine vasopressin. Arginine vasopressin acts as a partial agonist on the oxytocin receptor. To produce the same effects as induced by oxytocin, 100-fold higher concentrations of arginine vasopressin are necessary. Vasopressin effects on gastrointestinal motility are independent of vasopressin receptors and vary among different parts of the gastrointestinal tract. V1/V2 receptor selectivity for different vasopressin analogs are as follows: Arginine vasopressin, 1:1; terlipressin, 2.2:1; lysine vasopressin, 0.8:1; ornithine vasopressin, 4:1; 1-desamino-8-D-arginine vasopressin, 0.003:1.

oxidative stress as evidenced by immunohistochemical analysis may serve as additional or alternative explanations.

The study carries several strengths, of which the clinical relevance of the sepsis model and the fact that investigators were blinded to the study drugs are most important. On the other hand, certain limitations need to be acknowledged when interpreting its results. First, it is astonishing that AVP exerted only minor hemodynamic effects in this experiment. This is in striking contrast to earlier animal studies but may be due to the severity of septic shock combined with absence of causative sepsis treatment. Additionally, it is conceivable that the AVP dose chosen was too low in relation to the severity of cardiovascular failure (17). Nonetheless, it is noteworthy that POV could stabilize hemodynamic function in a shock state in which even AVP remained ineffective. Furthermore, it is unclear whether the AVP and POV dosages applied are indeed comparable. Based on theoretical considerations, including receptor selectivity and potency, they are, but comparison of dose-response curves between the two drugs in healthy animals would have rendered more-reliable information. Finally, when attempting to draw clinical conclusions from the presented data, possible interspecies variations in the homology of the V1 receptor, as observed between rats and men (18), need to be taken into account.

With this well-conceived and nicely performed study, the authors have definitely lifted the curtain and opened the stage for future experimental and clinical studies on selective V1 agonists in septic shock. Which steps are to be taken next? Paying tribute to the exceptionally pronounced vasoconstrictive effects of POV and its lack of V2-mediated vasodilation in selected vascular beds, it seems prudent to investigate further the regional organ and tissue perfusion during selective V1 stimulation in the experimental setting. Particular attention should thereby be paid to both the mesenteric and coronary circulation, since mesenteric artery blood flow was remarkably reduced during POV infusion in this study, and myocardial tissue is known to be at high risk for damage due to multiple mechanisms in septic shock (19). If POV then still proves beneficial and safe, one of the first studies in the clinical setting needs to define the optimum dosage of POV in septic shock. Based on these results, clinical cohort studies and randomized controlled trials in-

cluding selected septic shock patients may ensue.

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The present is pregnant with the future*

Pregnancy is a unique immunologic period. The progression of pregnancy requires immunologic tolerance to paternal immunogenic components to allow survival of the fetus, but at the same time the mother should not suppress her own immune system and expose herself and the fetus to infection. During pregnancy, a switch to a predominantly T-helper-2-type pattern of cytokines plays some part in the maintenance of transient tolerance to paternal antigens in pregnancy (1). Furthermore, the generation of specific regulatory T cells is key to this maintenance (2). Additionally, the abundant release of pregnancy hormones is implicated in the immune suppressive phenotype during pregnancy. The importance of pregnancy-induced immune suppression is stressed by the marked improvement of several immune-mediated inflammatory diseases during pregnancy. This phenomenon has drawn attention to pregnancy hormones as potential therapeutics for autoimmune disease as well as hyperinflammatory disorders such as sepsis. Recently, fractions derived from the pregnancy hormone human chorionic gonadotrophin have been shown to excerpt immunosuppressive effects in models of sepsis and hemorrhagic shock (3–5). Especially, the peptide LQGV has anti-inflammatory activities in models of autoimmune diabetes, hemorrhagic shock, and lipopolysaccharide-induced shock (6, 7). In this issue of *Critical Care Medicine*, Dr. van den Bergh and colleagues (8) describe the anti-inflammatory effects of LQGV in a murine model of cecal ligation and puncture.

In this study, the tetrapeptide LQGV significantly improves survival during the early hyperinflammatory phase of cecal ligation and puncture-induced polymicrobial sepsis, which is associated with a reduction in inflammatory mediators in the peritoneal cavity and the lung but not in plasma. The authors show that although the number of inflammatory cells recruited to the peritoneal cavity is comparable, the induction of cytokine release by these cells is diminished by treatment with LQGV. It is counterintuitive and puzzling however that the release of the anti-inflammatory cytokine interleukin 10 is diminished. In the pulmonary compartment, LQGV treatment results in reduced pulmonary nuclear factor-κB activation in combination with a significant reduction of levels of relevant cytokines and a reduction in histologic pulmonary damage. Taken together, treatment with LQGV decreases peritoneal and pulmonary inflammation during polymicrobial sepsis and results in a survival benefit.

*See also p. 126.

Key Words: β-human chorionic gonadotrophin; innate immunity; peptide LQGV; sepsis; cecal ligation and puncture; murine model

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