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The role of vasopressin and the vasopressin type V1a receptor agonist selepressin in septic shock

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ABSTRACT

Septic shock remains one of the major causes of morbidity and mortality in the critically ill. Despite early goal therapy and administration of cathecholaminergic agents, up to 30% of patients succumb to the disease. In this manuscript, we first summarize the standard of care of patients with septic shock and current guidelines. We review the physiologic role of vasopressin and its role in septic shock management. We then review the most up-to-date evidence on the potential role of V1a receptor agonists such as Selepressin, in septic shock. Exciting new trials are being completed in order to elucidate the role of V1a receptor agonists as potential first-line vasopressor alternatives in the therapy of circulatory shock in septic patients.

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1. Introduction

In the United States, septic shock remains a serious condition associated with high morbidity and high mortality [1,2]. Mortality from circulatory shock has gone down from 80% to 30% in the past three decades [2,3], especially by contribution of the early goal directed fluid therapy as described by Rivers and colleagues [4]. The first line therapy of patients with septic shock is fluid resuscitation with the goal to achieve hemodynamic stability and adequate perfusion to vital organs [5]. The sepsis survival campaign guidelines have been recently updated [6,7] and the committee recommends crystalloids to be used first, followed by albumin administration (if large volumes for resuscitation are required). If the initial management strategy fails to achieve a mean arterial pressure (MAP) of 65 mm Hg, vasopressors should be administered. The first choice of vasopressors recommended by the campaign is norepinephrine (NE) followed by epinephrine. Vasopressin at doses of 0.03 units/min may be used in addition to NE with the aim of increasing the MAP or weaning down NE dosage. In addition, the consensus recommends against either using low dose vasopressin (AVP) as the single

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initial vasopressor or doses >0.03–0.04 units/min. The latter should be used only as a salvage therapy for catecholamine-resistant septic shock patients. Dopamine should only be reserved in patients with low risk to tachyarrythmias and bradycardia. Evidence from the Vasopressin in Septic Shock Trial (VASST) [8] regarding the role of AVP in circulatory shock, reignited the interest on alternative vasopressors other than the catecholaminergic agents, such as AVP and vasopressin-like agents [9]. Since the publication of these guidelines, interest on V1a receptor agonists and their role in the management of septic shock have emerged in the field of critical care medicine. In this review, we describe the current evidence about the potential use of AVP and V1a receptor agonists such as selepressin in the treatment of septic shock [10].

1.1. Catecholamines in septic shock

Catecholamines are the main stay of management in patients presenting to the hospital with circulatory shock due to sepsis [6]. However, one should be aware that these drugs may have serious adverse effects including immune suppression, hypermetabolic state, and myocardial cell death [11-14]. In addition, the present guidelines for use of catecholamines in septic shock is based on circumstantial evidence. Annane et al. [15] performed a randomized control trial comparing NE plus dobutamine versus epinephrine alone in 330 patients with septic shock. The NE plus dobutamine group had a lower 28-day mortality than the epinephrine only group. Another study by Myburgh et al. [16] compared NE to epinephrine in 280 critical ill patients with hypotension. The patients that received NE had a 28-day mortality of 27% versus those that received epinephrine (23%). The trials' pitfalls not being adequately powered for mortality and not accounting for confounding variables such as lactate levels, which were higher in the epinephrine group. A third study of 1679 septic shock patients found that the 28-day mortality was lower in the NE group versus dopamine group, despite being underpowered. The authors also noted that the dopamine group had higher adverse events of dysrhythmias [17]. These observations led for experts in the field of critical care medicine to consider other alternatives such as AVP or vasopressin-like agents.

1.2. Decatecholaminization

In light of possible adverse events of catecholamines at various levels (hemodynamic, metabolic, immune and coagulative), interest towards the reduction of sympathetic drive during sepsis has rose among intensivists. The role of beta-blockers in sepsis remains controversial [18,19]. Morelli et al. recently showed that reducing heart rate in septic shock patients with esmolol lead to improved arterial elastance [20]. In contrast, a meta-analysis by Huang SJ. et al. [21] reported no difference in left ventricular ejection fraction, right ventricular ejection fraction and right ventricular dimensions among severe sepsis or septic shock survivors and non-survivors. Whereas, others have described an association between diastolic dysfunction and mortality in this target population [22].

1.3. Physiology of vasopressin

Before we elaborate on the relationship of AVP and pathologic states such as septic shock, one should understand its physiologic function in the human body. AVP is produced in the hypothalamic supraoptic nuclei and paraventricular nuclei (known as osmoreceptors). It is stored in the posterior pituitary. Important triggers for its release and synthesis include hyperosmolar plasma/urine, hypotension, and hypovolemia [23, 24]. AVP is a non-specific V1a, V1b (V3) and V2 receptors agonist [25-29]. Its vasoconstriction effect is mainly through V1a receptor stimulation in the smooth muscles of the vasculature [24]. When V1a receptors are activated, phosphatidylinositol bisphosphate is hydrolyzed to inositol triphosphate and diacylglycerol, by phospholipase C, leading to increase in intracellular concentrations of calcium, ultimately potentiating the interaction of actin-myosin chains and leading to vasoconstriction (Fig. 1). Other proposed effects from V1a receptor activation include vasodilator effects in the pulmonary and coronary vasculature. The proposed mechanism is through release of nitric oxide (NO) from the endothelium [30,31]. V1b receptors are found in the hippocampus and anterior pituitary gland. Activation of these receptors lead to adrenocorticotropic hormone (ACTH) release from the anterior pituitary. This pathway is responsible for the potential role of AVP in stress

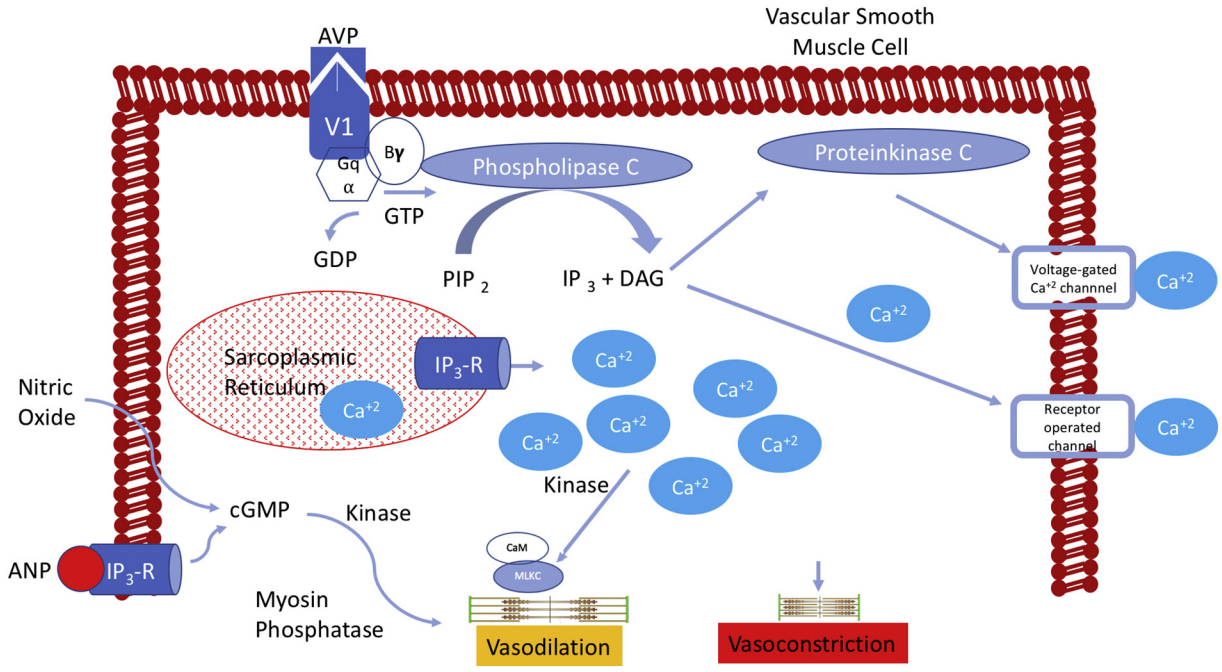

Fig. 1. Action of vasopressin analogues on V1 receptor and involved cellular signaling. In vascular smooth muscle. *CaM*, calcium-calmodulin complex; *GDP*, guanosyl diphophate; Gq a ß g, G-protein subunits; *GTP*, guanosyl triphosphate; *MLCK*, myosin light chain kinase; *ANP*, atria natriuretic peptide.