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Beneficial and side effects of arginine vasopressin and terlipressin for septic shock

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ARTICLE INFO

Article history:
Received 6 November 2014
Received in revised form
22 January 2015
Accepted 12 February 2015
Available online 18 February 2015

Keywords:
Septic shock
Terlipressin
Arginine vasopressin
Vascular hyporeactivity
Side effect

ABSTRACT

Arginine vasopressin (AVP) and its analog, terlipressin (TP), were all demonstrated beneficial for septic shock. What advantages and disadvantages that AVP and TP have for septic shock as well as the mechanism, however, are not completely known. With cecal ligation and puncture-induced septic shock rats and lipopolysaccharide-induced septic shock rabbits, we systematically compared the beneficial and side effects of AVP and TP, in septic shock and the sex difference, and investigated their relationship to Rho kinase and calcium sensitivity. The results indicated that low dose of TP (2.6 μg/kg/h) in combination with norepinephrine (NE) improving vascular reactivity and animal survival were superior to a small dose of AVP (0.03 U/kg/h) in septic shock rats and rabbits. This improving effect of AVP and TP on vascular reactivity was closely related to the activation of Rho-kinase and Rho-kinase–mediating vascular calcium sensitization. A small dose of TP did not result in hyponatremia, did not increase blood bilirubin and decrease platelet count, whereas AVP did. Animal survival and vascular reactivity in female rats after TP or AVP administration were slightly better than male rats, while there were no significant differences. It was suggested that a small dose of TP has better beneficial effect and less side effects on septic shock than AVP. AVP and TP improving vascular reactivity is closely related to Rho-kinase activation and calcium sensitivity improvement. TP or plus NE may be more appropriate for early emergency care for severe septic shock than AVP.

1. Introduction

Severe sepsis and septic shock are very severe problems in the intensive care unit with its fast onset, high mortality, and difficulty for treatment. The mortality of severe sepsis and septic shock among intensive care unit patients is as high as 32.2% and 54.1%, respectively [1]. The most important goal of early resuscitation for septic shock is raising the mean arterial pressure (MAP) to enhance the tissue perfusion of vital organs and elevating the oxygen supply [2,3]. The major obstacle preventing from achieving the early resuscitation goal for severe sepsis and septic shock is the resistance to vasoactive agents (insensitivity or no response to vasoactive agents), which is called “vascular hyporeactivity”, and it is the major reason causing refractory hypotension in these patients [4]. Arginine vasopressin (AVP) has been demonstrated effective and recommended as the first-line vasopressor in vasodilatory and refractory shock after sepsis [5,6]. However, AVP

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0022-4804/$ – see front matter
http://dx.doi.org/10.1016/j.jss.2015.02.022

has no specificity for V1 and V2 receptors (1:1). Hence, AVP, except for having a modulatory effect on vascular reactivity via V1 receptor, can often induce the decrease of cardiac output and platelet count (PLT), increase the blood direct and indirect bilirubin (DBIL and IBIL) level, and induce hyponatremia and water retention via V2 receptors [7–10]. Terlipressin (TP) is an analog of AVP. It has stronger binding specificity for the V_1 receptor (2.2:1 for the V1 receptor: V2 receptor). TP has also been demonstrated beneficial for septic shock [11–13]. Some scattered studies compared the beneficial effect of AVP and TP in septic animal and patients [14,15], but there were no systemic comparison for the beneficial effect and side effects of AVP and TP in septic shock. In addition, the mechanism of AVP and TP improving vascular reactivity in sepsis is not clear. Although our previous study showed that AVP could improve the vascular reactivity in hemorrhagic shock rats, and it is related to vascular calcium sensitization and Rho kinase [16], whether AVP and TP can improve the vascular reactivity and calcium sensitivity and its relationship to Rho kinase including Rho kinase α (ROCK I) and β (ROCK II) are not clear. Research showed many diseases including trauma and sepsis have sex-based differences in clinical representation and treatment response [17,18]. Whether AVP as well as TP improving vascular reactivity and animal survival in sepsis has sex difference is not clear.

To elucidate these issues, with two species animal sepsis and endotoxemia model (cecal ligation and puncture [CLP]-induced septic shock rats and lipopolysaccharide [LPS]-induced septic shock rabbits), we systematically compared the beneficial and side effects of AVP and TP in septic shock and the sex differences and investigated the relationship of AVP and TP improving vascular reactivity to calcium sensitivity and ROCK I and ROCK II in the present study.

2. Materials and methods

2.1. Ethical approval of the study protocol

The study protocol was approved by the Ethics Committee of Research Institute of Surgery at Daping Hospital of the Third Military Medical University (Chongqing, China). None of the authors of this article are the members of the Ethics Committee. Animal experiments were conducted in accordance with the Laboratory Animal Use and Care Guide published by the US National Institutes of Health (NIH Publication, Eighth Edition, 2011). The approval number of this protocol is 20120815.

2.2. Animal management

Male and female Sprague–Dawley rats and rabbits were obtained from the Animal Center in Research Institute of Surgery at the Third Military Medical University. They were maintained in a room at constant humidity (60 ± 5%), temperature (24 ± 1°C), and light cycle (6 AM–6 PM), and fed standard pellet diets *ad libitum*.

2.2.1. Model of septic shock in rats

Six hundred Sprague–Dawley male and female rats weighing 220–250 g were used in present study. On the day of the experiment, rats were anesthetized with 3% sodium pentobarbital (45 mg/kg, intraperitoneal) and fixed on the experiment platform. After disinfection, left femoral arterial catheterizations were made to measure the baseline MAP, then the laparotomy was undertaken, and the cecum was exposed, ligated, and punctured at 1 cm from its end with a triangular needle (the needle size is about 1.5 mm). The cecum was then put back in the abdominal cavity. After the abdominal incision was closed, the rats were returned to their cages with free access to water and food. Ten hours later, rats were anesthetized with 3% sodium pentobarbital (15 mg/kg, intraperitoneal), the left femoral vein was catheterized for infusion of lactated Ringer solution (LR) with a micro-pump at 4 mL/kg/h and sodium pentobarbital at 5 mg/kg/h [19]. The MAP was monitored with a mercury pressure detector. When the MAP decreased to <70 mm Hg or by >30% of the baseline level, the septic shock model was considered achieved and was used for the following experiments. In the present study, about 80% of CLP rats achieved septic shock, about 10% rats died after CLP, and about 10% rats did not achieve septic shock, which were abandoned after 14 h from CLP.

2.2.2. Model of septic shock in rabbits

To further compare the effects of AVP and TP in another species' animal suffering from sepsis, three hundred sixty rabbits were used in the present study. As the rabbit is not suitable for performance of the CLP, LPS-induced endotoxemia in the rabbit was used. Male and female rabbits (2–2.5 kg) were anesthetized (sodium pentobarbital, 40 mg/kg, intravenous). Right femoral arteries and veins were catheterized with a polyethylene catheter used for monitoring MAP and drug administration, respectively. LPS (1 mg/kg) was injected intravenously [8]. When MAP decreased to <70 mm Hg or decreased by >30% from the normal level, septic shock was considered achieved. The success rate of septic shock with this method is about 90%.

2.3. Experimental protocol

2.3.1. Dose response of AVP or TP on MAP and animal survival in CLP rats

One hundred forty-four septic shock rats were divided into the LR control group, AVP (0.01, 0.03, 0.1, and 0.3 U/kg/h), and TP (1.3, 2.6, 5, and 10 μg/kg/h) groups ($n = 16$ per group). Rats in the LR control group received 40 mL/kg of LR infusion within 30 min first and then received LR 4 mL/kg/h infusion for 6 h. Except for receiving LR as the LR control group, rats in AVP or TP groups received different doses of AVP or TP for 6 h. AVP and TP were infused in 4 mL/kg/h of LR. MAP was measured at 1, 2, 4, and 6 h from the beginning of administration, and the animal survival was recorded.

2.3.2. Effects of small doses of TP or AVP in combination with NE on survival of septic shock rats and rabbits

One hundred ninety-two septic shock male and female rats and ninety-six male and female septic shock rabbits were divided into six groups as follows: LR, NE, TP, TP + NE, AVP, and AVP + NE ($n = 16$ per group per sex for the rat experiment and $n = 8$ per group per sex for the rabbit experiment). Rats or rabbits in the LR control group received 40 mL/kg of LR infusion