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Protective effect of astaxanthin against multiple organ injury in a rat model of sepsis

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ABSTRACT

Background: Astaxanthin, a xanthophyll carotenoid, holds exceptional promise as an antioxidant, anti-inflammatory, and anticancer agent. No evidence has been published whether it has protective effects on sepsis. The study aimed to investigate the potential effects of astaxanthin on sepsis and multiple organ dysfunctions.

Materials and methods: Sepsis was induced by cecal ligation and puncture (CLP) in Sprague–Dawley rats. Animals subjected to CLP and sham-operated control rats were given vehicle or astaxanthin 100 mg/kg/d by oral gavage for 7 d before the operation. The rats were killed at the indicated time points, and the specimen was collected. Cytokines and multiorgan injury-associated enzymatic and oxidative stress indicators were investigated. Multiorgan tissues were assessed histologically, the peritoneal bacterial load and the 72-h survival was observed too.

Results: Sepsis resulted in a significant increase in serum tumor necrosis factor-α, interleukin-1β, and interleukin-6 levels showing systemic inflammatory response; it also caused a remarkable decrease in the superoxide dismutase activity and a significant increase in the malondialdehyde content showing oxidative damage; sepsis caused a great increase in organ injury-associated indicators, including blood urea nitrogen, creatinine, lactate dehydrogenase, creatine kinase isoenzyme-MB isotype, alanine aminotransferase, and aspartate aminotransferase, which was confirmed by histologic examination. And there was a dramatical increase of colony-forming units in the peritoneal cavity in septic rats. Astaxanthin reversed these inflammatory and oxidant response, alleviated the organ injury, reduced the peritoneal bacterial load, and improved the survival of septic rats induced by CLP.

Conclusions: Astaxanthin exerts impressively protective effects on CLP-induced multiple organ injury. It might be used as a potential treatment for clinical sepsis.

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1. Introduction

Sepsis is a devastating and complex syndrome with a high mortality rate and limited therapeutic options. Despite recent advances in surgical techniques and critical care medicine, overall case mortality from septic events is still high, ranging between 30% and 50% [1]. Septic causes are responsible for 200,000 deaths per year in the United States [2], making it a leading cause of death in hospitals of the 21st century. In words, the burden of morbidity, mortality, reduced quality of life, and excessive cost of sepsis on the healthcare system ($14–16 billion/year) [3] are obvious indicators of how much of an unmet medical challenge this condition truly represents [4]. Because of increase in the aging population, immunosuppressive therapies and invasive procedures, the incidence and mortality of sepsis are likely to increase despite the recent medical advances. Thus, new therapeutic perspectives are highly warranted.

Sepsis is a complex clinical syndrome that is caused by a harmful host response to infection. Over the past decades, our collective knowledge regarding the pathophysiology of sepsis has grown exponentially. During the development of sepsis, bacterial components, such as lipopolysaccharide (LPS), may activate an inflammatory cascade, which results in the release of inflammatory mediators, including tumor necrosis factor-α (TNF-α), interleukin-1β (IL)-1β, IL-6, and so on [5]. The overproduction of inflammatory mediators induces endothelial and epithelial injury, vascular leakage, edema, and vasodilatation, subsequently causing the development of multiple organ dysfunction syndrome (MODS). Marked oxidative stress as a result of the inflammatory responses inherent with sepsis also initiates changes in mitochondrial function, which may result in organ damage and MODS [6]. Thus, the development of new drugs with an effective anti-inflammatory and antioxidant profile to reduce the incidence and mortality associated with this devastating condition would be valuable.

Astaxanthin is a xanthophyll carotenoid, which is found in various microorganisms and marine animals [7]. It plays biological roles and possesses a number of desired features for food applications, such as natural origin, nil toxicity, high versatility, and both hydro and liposolubility [8,9]. The United States Food and Drug Administration has approved the use of astaxanthin as a food colorant in animal and fish feed [10]. The European Commission considers natural astaxanthin as a food dye [11]. In addition to its pigmentation function, astaxanthin has shown a variety of physiologic and pharmacologic important properties such as antioxidant, anti-inflammatory, and anticancer activity [12,13]. It has been reported that astaxanthin is effective for the prevention or treatment of diabetes [14], cardiovascular diseases [15], and neurodegenerative disorders [16], and also stimulates immunization [17]. Moreover, research has so far reported no significant side effects of astaxanthin consumption in animals and humans. Previous studies have shown that astaxanthin can decrease inflammation by inhibiting reactive oxygen species (ROS)-induced nuclear factor kappa-B (NF-κB) activation [18], it also has therapeutic properties protecting U937 cells from LPS-induced inflammatory and oxidative stress [19]. Astaxanthin inhibited LPS-stimulated IL-6 messenger RNA and protein in BV-2 microglial cells by suppressing extracellular signal-regulated kinase (ERK-), mitogen- and stress-activated protein kinase (MSK-), and NF-κB–mediated signals [20]. No evidence has been published, however, whether it has protective effects on sepsis mortality and associated organ dysfunction. Therefore, the present study was designed to investigate the potential effect of astaxanthin on sepsis and sepsis-induced MODS.

2. Materials and methods

2.1. Animal preparation

All experimental protocols used for animals were approved by the Animal Care and Use Committee of Xiangya School of Medicine, Central South University and conformed to the Guide for the Care and Use of Laboratory Animals published by the National Institutes of Health. Male 8-wk-old specific pathogen-free Sprague–Dawley rats, each weighing 220–250 g, were purchased from the Laboratory Animals Center of Central South University (Changsha, China). They were acclimated in a humidified room and maintained on a standard pellet diet before the experiment. The temperature in both the feeding room and the operation room was maintained at about 25°C.

2.2. Experimental design

2.2.1. Animal groups

Rats were randomly divided into three groups as follows: rats undergoing sham cecal ligation and puncture (CLP) operation (sham group); rats undergoing CLP and treated with vehicle (CLP + V group), and rats undergoing CLP and treated with astaxanthin (CLP + Asta group). Astaxanthin was purchased from Sigma–Aldrich, St. Louis, MO. It was diluted in olive oil (100 mg/mL) immediately before use. Either astaxanthin (100 mg/kg) or an equal volume of olive oil was administered by oral gavage for 7 d before the operation. Rats in the sham group received olive oil in a volume equivalent to that used to dissolve astaxanthin. The dose of astaxanthin used in this study was based on previous experiments [21].

2.2.2. Sepsis model: CLP

Animals were anesthetized with ketamine (60 mg/kg, intramuscular) plus xylazine (10 mg/kg, intramuscular). And then a 2-cm midline abdominal incision was performed. The cecum was then exposed, ligated just distal to the ileocecal valve to avoid intestinal obstruction, punctured twice with an 18-gauge needle, and returned to the abdominal cavity. The incision was then closed in layers. In sham group rats, the cecum was exposed and the bowel was massaged as described previously, but it was not ligated or punctured. The rats were resuscitated with 30 mL/kg body weight normal saline subcutaneously immediately after surgery. The animals were then returned to their cages.

2.2.3. Specimen collection

Under anesthesia, blood samples were collected from the external carotid vein at 1, 3, 6, 12, 24, and 48 h after CLP. The