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Immunomodulating effect of inositol hexaphosphate against *Aeromonas hydrophila*-endotoxin

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Abstract

The present study was carried out to evaluate the effect of inositol hexaphosphate (IP6) administration on endotoxemia as an example of the systemic inflammatory response. Mice were divided into three groups as follows: First group, remained as a naive group injected intraperitoneally (i.p.) with PBS (pH 7.4; 0.2 ml/mice) at intervals parallel to the treated groups. The second group was injected i.p. with the lipopolysaccharide (LPS) of *Aeromonas hydrophila* once a week for four weeks at a dose of LPS suspension: 20 mg/kg mice/week. The third group was injected with the same LPS dose and synergistically intubated with IP6 three times a week for four weeks at a total dose of 40 mg/kg. At different experimental periods (1, 2, 3 and 4 weeks), six animals from each group were sacrificed under mild diethyl ether anesthesia. Blood and sera were taken for the estimation of phagocytic activity, electrophoretic pattern of proteins and immunoglobulin levels. Also, a slice of liver was homogenized to estimate the respiratory burst enzymes activities and nitric acid synthesis. Histopathological changes of hepatic tissues were investigated. In the LPS-treated group, marked increase in the phagocytic activities and nitric oxide synthesis, and a decrease in hepatocyte catalase, total peroxidase and superoxide dismutase activities were observed. The histopathological features revealed a degeneration and highly mitotic division within the hepatic nuclei in addition to some karyomegaly and nuclear pyknosis. During the treatment period, liver sections of the LPS + IP6 group showed somewhat regenerative features. Reduction in the toxicity of free radicals by IP6 was observed and the IP6 effect seemed to be responsible for the observed ameliorative influence.
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Introduction

One of the most frequent and serious problems confronting clinicians is the management of a syndrome termed sepsis. One detrimental consequence of sepsis is the development of multiple organ dysfunction syndrome (MODS) which is the leading cause of morbidity and mortality in intensive care units. When this syndrome results in hypotension and organ dysfunction, it is called septic shock. Despite improvements in the care of critically ill patients, mortality rates from sepsis and MODS remain unchanged. Emphasis has been placed on the fact that sepsis is one example of a systemic inflammatory response that can be triggered not only by infections but also by noninfectious disorders, such as trauma and pancreatitis. Severe sepsis is associated with organ dysfunction, hypoperfusion

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(lactic acidosis, oliguria, or altered mental status), or hypotension (septic shock) (Parrillo, 1993; DePauw and Verweij, 2005).

Aeromonas spp. have been placed in the family Aeromonadaceae which causes both intestinal and non-intestinal infections in adults (Carnahan and Altwegg, 1996), gastroenteritis in young children (Janda and Abbott, 1998; DePauw and Verweij, 2005), infections in immunocompromised patients yielding hematologic malignancies (Tsai et al., 2006) and necrotizing fasciitis disease in immunodeficiency patients, that is characterized by extensive subcutaneous and muscle necrosis (Abuhammour et al., 2006).

Aeromonas spp. produce an array of virulence factors that include endotoxins: lipopolysaccharides (LPS) (Merino et al., 1995; Chopra and Houston, 1999). LPS is a major constituent of the outer membrane of Gram-negative bacteria, and serves as a potent proinflammatory stimulus by interacting with humoral and cellular mediator systems (Morrison and Bucklin, 1996). In addition, LPS harbor binding sites for antibodies and non-immunoglobulin serum factors, and are, therefore, involved in the specific recognition and elimination of bacteria by the host organism's defense system (Rietschel et al., 1990, 1993; Chaby, 1999; Phalipon et al., 2005).

Among recently studied natural products, inositol hexaphosphate (IP6), also known as myo-IP6 and phytic acid, is a naturally occurring polyphosphorylated carbohydrate that is present in substantial amounts in almost all plant and mammalian cells first identified in 1855. Vucenik and Shamsuddin (2003) and Vucenik et al. (2004) demonstrated that phytic acid has multiple biological functions: reducing cell proliferation and increasing differentiation of malignant cells, and reversion to normal phenotype. IP6 also appears to be a natural antioxidant that can reverse the effects of damaging free radicals, fight tumor formation and enhance the body's natural disease resistance (Saied and Shamsuddin, 1998; Lee et al., 2005).

It is well known that during the process of phagocytosis professional phagocytes undergo a vigorous respiratory burst in which they consume oxygen and convert it enzymatically to O_2^-, that interacts with hydrogen ions to form H_2O_2, then form later hypochlorous acid, hydroxyl radical, and other potent oxidants (Roos et al., 1980a, b; Babior, 1999; Seres et al., 2000). Fortunately, the cells in the body possess a wide range of interlinked antioxidant defense mechanisms to protect themselves from damage by reactive oxygen species (ROS). Among these mechanisms, several antioxidant enzymes including catalase (EC 1.11.1.6), superoxide dismutase (SOD, EC 1.15.1.1), glutathione peroxidase (GPx, EC 1.11.1.9) and glutathione S-transferase (GST, EC 2.5.1.18), play an important role in scavenging ROS produced in cells.

The link between the production of ROSs and the pathogenesis of endotoxin septic shock has been highlighted in several studies (Parrillo, 1993; Chaby, 1999; Morikawa et al., 1999). These investigations have indicated that ROS such as the superoxide anion (O_2^-); hydroxyl radical ($OH\cdot$), and reactive nitrogen species (RNS) like nitric oxide ($NO\cdot$) and peroxynitrite ($\cdot ONOO$) are involved in LPS-induced toxicity. Released hydrogen peroxide during respiratory burst of phagocytosis causes chemical alteration of thymidine residues and oxidation of critical respiratory chain components causing cell death (Khanduja et al., 1998). So, the killing activity by phagocytic cells is dependent on the ability of the organism to respond to increased levels of H_2O_2. In addition, increased expression of MnSOD, one form of SOD present in cells and tissues (Fridovich, 1999), can diminish oxygen radical-mediated injuries and the cytotoxic effects of TNF-α (Liochev and Fridovich, 1997; Majima et al., 1998).

The present study was aimed to study the effect of IP6 on repeated challenge of the innate immune system as one of the natural products that may have a profound deleterious effect on sepsis.

Materials and methods

Animals

Seventy-two (25–30 g) adult male Swiss mice (Biological Supply Center, Theodore Bilharz Research Institute, Cairo, Egypt) were used. Mice were housed in stainless-steel cages under strict hygienic conditions at 25–28 °C, 8–20 h light and free access to feed and water. Animals were divided into three groups as follows: first group remained as a control group injected intraperitoneally (i.p.) with PBS (pH 7.4; 0.2 ml/mice) at intervals parallel to the treated groups. The second group was injected i.p. with the LPS extracted from *Aeromonas hydrophila* (as shown later) once a week for four weeks at a dose of 0.2 ml of LPS suspension (20 mg/kg mice/week). The third group was injected with LPS suspension as second group and synergistically injected with IP6 three times/week for four weeks at a total dose of 40 mg/kg mice. At different experimental periods (1, 2, 3 and 4 weeks), six animals from each group were sacrificed under mild diethyl ether anesthesia. Blood samples were drawn and divided into two portions, one portion was added into heparinized tubes for WBCs counting and NBT estimation, while the other portion was centrifuged at 3000 r.p.m. for 20 min. The clear, non-hemolyzed supernatant sera were quickly removed and kept at −20 °C for estimating different electrophoretic protein bands and IgG and IgM antibodies. Liver slices were homogenized in PBS solution (pH 7.4) and kept at −20 °C until used for the estimation of the

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