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International Immunopharmacology 6 (2006) 454–464

International Immunopharmacology

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Synergism in immunotoxicological effects due to repeated combined administration of arsenic and lead in mice

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Received 5 May 2003; received in revised form 28 April 2004; accepted 15 September 2005

Abstract

Arsenic and lead are considered potent human hazards because of their neoplastic outcomes; increasing epidemiologic evidence indicates a link between heavy metal exposure and health risk. Since health risks of singly administered metals are well-established, in the present study we determined whether simultaneous repeated multimetal (arsenic + lead) exposure influences the development of immunotoxicity in mice exposed (in vivo) to lead acetate (10 mg/kg b.w.) and sodium arsenite (0.5 mg/kg b.w.) simultaneously. We report that in vivo multimetal exposure alters cell morphology, inhibits cell adhesion, nitric oxide release, intracellular killing ability, chemotactic migration, myeloperoxidase release, bacterial clearance from blood and spleen and increases DNA fragmentation. On measuring bacterial density in blood and spleen after 0, 24, 48 and 72 h post infection (with *Staphylococcus aureus* MC524) in control and multimetal treated groups, bacterial load showed delayed clearance from blood and spleen in the multimetal exposed group. We also found that in vivo exposure to the multimetal caused a decrease in cell adhesion, indicated by a fall in absorbance at 570 nm with respect to control. Exposure to multimetal led to morphological changes in macrophages, since more deformed cells were obtained in repeated combined exposure to arsenic and lead compared to control. Nitric oxide, which has a potent microbicidal activity in macrophages, was found to be released in fewer amounts in the multimetal exposed group from that of control group. It was observed that the viability of bacteria gradually decreased in control macrophage with time, whereas, in macrophages of multimetal exposed mice, the viability of *S. aureus* gradually increased. Chemotactic migration of splenic macrophages significantly decreased in the multimetal exposed group from that of control. Lysosomal enzyme release from splenic macrophages decreased upon simultaneous exposure to arsenic and lead, as is evident from the decrease in myeloperoxidase release in multimetal group from that in control. That the structural integrity of splenic macrophages is decreased in the multimetal exposed group is also evident from the enhanced percentage of DNA fragmentation after multimetal exposure, suggesting apoptotic death of splenic macrophage. Intracellular viable bacteria in the splenic macrophage from multimetal exposed group was $89.16 \pm 3.54\%$ while that from control group was $49.19 \pm 1.16\%$, whereas single metal exposed groups showed a bacterial viability of $69.6 \pm 2.45\%$ and $71.71 \pm 1.89\%$ in arsenic and lead treated groups respectively. What is essentially noteworthy from the observed results is that lead and arsenic causes a greater immunotoxic effect when administered together as multimetal than when singly administered.

Simultaneous exposure to lead and arsenic appears to be additive as is further established from the isobologram constructed by plotting the concentration of arsenic against the concentration of lead at which effect (in this case myeloperoxidase release) remained constant, a convex line showing synergism was demonstrated. The present study reports a definite synergistic trend of

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doi:10.1016/j.intimp.2005.09.011

immunotoxicity during simultaneous exposure to arsenic and lead, that is, a multimetal challenge, as compared to the effects of independent exposure to them.
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Keywords: Arsenic; Lead; Interactivity; Synergism; Myeloperoxidase; Isobologram

1. Introduction

Heavy metals including cadmium (Cd), mercury (Hg) and lead (Pb) are essential for certain biological functions and enzymatic reactions but when present at high level can induce dysregulation of the physiological system for promoting an immune response [1]. In exposed population, the effects of heavy metal or multimetal exposure on the immune system are of concern, since they are associated with various tumors of lung, skin, liver, altered hematological parameters indicating an immunocompromised status of the occupational exposure [2]. Results of an intermediate duration dietary study of toxicity and interactions for lead, arsenic and cadmium indicated that the effects of the trinary mixture generally reflected those for the binary mixtures, suggesting that components-based approaches that focus on interactions for the binary mixture may be useful in predicting the toxicity of the mixture [3]. In exposed population, arsenic is associated with melanosis, leukomelanosis, keratosis, hyperkeratosis, nonpitting edema, gangrene and skin cancer [4]. Increased mortality from ischemic heart disease was first reported in copper smelter workers exposed to arsenic [5] and induction of oxidative stress caused by chronic exposure has also been reported [6]. Although historically arsenic is considered a potent human hazard because of its neoplastic outcomes, increasing epidemiological evidence indicates a link between arsenic exposure and risk to vascular diseases related to atherosclerosis [7]. The primary biochemical mechanism of arsenic toxicity is binding of the metal to cellular sulfhydryl groups resulting in inhibition of numerous cellular enzyme systems [8]. All protein tyrosine phosphatases contain such –SH groups and it was recently shown that arsenite inhibits a JNK phosphatase presumably via this mechanism [9]. Although arsenic is not a transition metal, it has been demonstrated to have oxidative potential including induction of reactive oxygen species in porcine aortic endothelial cells [10]. Arsenic is a potent activator of AP-1 and NF-KB DNA binding activity. Furthermore, AP1 and NF-KB can regulate interleukin-8 (IL-8) expression because the IL-8 gene contains multiple biding sites for these transcription factors and both are subject to redox-dependent regulation [11].

Chronic low-level exposure to inorganic lead constitutes the more serious occupational hazards and health risk [12]. Lead interferes with the synthesis of heme and its inhibitory effects on the enzymes of this pathway were detected in human beings [13]. Lead has been shown to alter various parameters of immune function such as host resistance and antibody formation. Blood serves as a good medium for bringing in contact the immune cells with lead or arsenic present in blood itself and also those immune cells present in different lymphoid organs of our body. However, lead and arsenic as environmental pollutants remain an enigma, because although they are definitely active in human, combined toxic effects of lead and arsenic simultaneously on the rodent model have never been convincingly demonstrated. Low levels of lead exposure cause inhibition of nitric oxide release, inhibit neutrophil chemotaxis, phagocytosis, superoxide formation and interleukin-2 production [14]. Reports are also available on the effect of lead on in vitro antigen presentation and killing of pathogens by the cells is also described [15]. The lack of knowledge on the mechanism of action, together with the apparent sensitivity of human populations creates even more concern about the diverse potential of these environmental pollutants. The objective of the present study was to examine the functions of murine splenic macrophages following simultaneous exposure to arsenic and lead, in order to determine whether the combined exposure to these heavy metals alters their immunotoxicity. In the present study, we have reported that in vivo combined exposure to arsenic and lead inhibits normal functional activities of murine splenic macrophages leading to enhanced intracellular survival of microorganism.

2. Experimental procedures

2.1. Materials

Adult Swiss male Albino mice were obtained from local animal supplier to the department. Fetal Bovine Serum (FBS), Histopaque-1077, Bovine Serum Albumin (BSA), *N*-2-hydroxyethyl piperazine *N*-2-ethane sulphonic acid (HEPES) and *o*-Phenylenediamine (OPD) from Sigma Chemical Co.,St Louis, MO 63178, USA. Gentamycin sulfate was purchased from

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