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Sodium arsenite-induced cardiovascular and renal dysfunction in rat via oxidative stress and protein kinase B (Akt/PKB) signaling pathway

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ABSTRACT

Objectives: Arsenic is a ubiquitous element that is widely distributed in the environment to which man and animals are exposed. Cardiovascular disease is one of the aftermaths of chronic arsenic exposure-related morbidity and mortality. This study sought to investigate the possibility of reversal from arsenic-induced cardio-renal toxicity following exposure and subsequent withdrawal. The study also seeks to understand the mechanism of action of this reversal.

Methods: Rats were orally exposed to sodium arsenite at 10, 20 and 40 mg/kg daily for 4 weeks followed by 4 weeks of withdrawal.

Results: Exposure to arsenic caused a significant increase in malondialdehyde, H_2O_2 generation but decrease total thiol and reduced glutathione levels in both cardiac and renal tissues. Furthermore, increases in superoxide dismutase, glutathione-S-transferase and catalase with significant increases in glutathione peroxidase activities were observed in the cardiac tissues. On the contrary, a significant reduction in the renal antioxidant enzyme activity was recorded following exposure. Also, antioxidant defense system did not return to apparent values after arsenic withdrawal. Immunohistochemistry revealed a reduction in the expression of the pro-survival protein–protein kinase B (Akt/PKB) following exposure to arsenic and this was not reversed by withdrawal

Discussion: Exposure to arsenic caused cardio-renal toxicity via induction of oxidative stress and down-regulation of Akt/PKB expressions.

KEYWORDS
Arsenic acid; oxidative stress; nephrotoxicity; cardiotoxicity; protein kinase B

Introduction

Arsenic is a toxic heavy metal and its toxicity is of global health concern. Toxic levels of arsenic in the blood interfere with many metabolic processes. Toxic arsenic induces oxidative stress through the generation of reactive oxygen species (ROS), leading to multi-system organ failure, chronic diseases and death [1]. Arsenic is ubiquitous and exists in multiple forms such as organic and inorganic compounds widely distributed in the environment to which man and animals are exposed. Arsenic exposure occurs mainly through contaminated food and water sources leading to human and ground water exposures [2]. Arsenic toxicity is largely dependent on its form; trivalent or pentavalent with trivalent salt more potent to cause cancers, and other pathologies.

Oxides of arsenic such as sodium arsenite are components of some underground rocks, thus, present in some water sources as contaminants [3]. Poisoning can also be linked to occupations such as mining and smelting of ore as well as higher concentrations have been found in water containing leached arsenics from rocks in an area endemic with high deposit of arsenic in the environment [3]. Sodium arsenite is primarily used as a pesticide and has also been utilized as antiseptic, hide preservative, and in dye and soap production. Its persistent ingestion has been associated with various cardiovascular, neurologic and carcinogenic effects such as ischemic heart disease, and peripheral neuropathy [4]. Once absorbed, arsenic accumulates in the liver, kidneys, heart and lungs while lower levels are found in muscles and neuronal tissues [5].

Various reports indicate that the generation of ROS, oxidative stress and cellular damage through lipid peroxidation is the major pathway for the pathogenesis of sodium arsenite [6,7]. It has been reported that intracellular ROS levels produced is dependent on the concentration of sodium arsenite which further determine the type and severity of biological/pathological effects [8]. However, sodium arsenite effect has been associated with hormetic properties in which low dose stimulation and high dose inhibition is expected. Chronic exposure to arsenic is expected to lead to accumulation in tissues and cause cellular dysfunction, however, human activities such as relocation or removal of the source of arsenic might reduce or eliminate its toxic effects. This study therefore sought to investigate the probable reversal of arsenic-induced cardio-renal toxicity following exposure and subsequent withdrawal from exposed subjects and its molecular mechanism of action. We therefore test the hypothesis that exposure of animals to arsenic acid as well as subsequent withdrawal does not have public health importance.

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