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Studies on the effect of sodium arsenate on the enzymes of carbohydrate metabolism, brush border membrane, and oxidative stress in the rat kidney

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ABSTRACT

Arsenic is an environmental pollutant and its contamination in drinking water poses serious world wide environmental health threats. It produces multiple adverse effects in various tissues, including the kidney. However, biochemical mechanism and renal response to its toxic insult are not completely elucidated. We hypothesized that sodium arsenate (ARS) induces oxidative stress and alters the structure and metabolic functions of kidney. Male Wistar rats were administered ARS (10 mg/kg body weight/day), intraperitoneally daily for 10 days. ARS administration increased blood urea nitrogen, serum creatinine, cholesterol, glucose, and phospholipids but decreased inorganic phosphate, indicating kidney toxicity. The activity of brush border membrane (BBM) enzymes significantly lowered in both cortex and medulla. Activity of hexokinase, lactate dehydrogenase, glucose-6-phosphate dehydrogenases, and NADP-malic enzyme significantly increased whereas malate dehydrogenase, glucose-6-phosphatase, and fructose 1,6 bis phosphatase decreased by ARS exposure. The activity of superoxide dismutase, GSH-peroxidase, and catalase were selectively altered in renal tissues along with an increase in lipid peroxidation. The present results indicated that ARS induced oxidative stress caused severe renal damage that resulted in altered levels of carbohydrate metabolism and BBM enzymes.

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Abbreviations: ACPase, acid phosphatase; ALP, alkaline phosphatase; ANOVA, analysis of variance; ARS, arsenate; ATP, adenosine 5′-triphosphate; BBM, brush border membrane; BBMV, brush border membrane vesicles; BUN, blood urea nitrogen; GGTase, γ-glutamyl transferase; G6Pase, glucose-6-phosphatase; G6PDH, glucose-6-phosphate dehydrogenase; HK, hexokinase; HMP, hexose monophosphate; LAP, leucine aminopeptidase; LDH, lactate dehydrogenase; LPO, lipid peroxidation; MDH, malate dehydrogenase; ME, malic enzyme; NADPH, nicotinamide adenine dinucleotide phosphate (reduced); $NADP^+$, nicotinamide adenine dinucleotide phosphate; NADH, nicotinamide adenine dinucleotide reduced; Pi, inorganic phosphate; ROS, reactive oxygen species; SOD, superoxide dismutase; SH, sulphydryl groups; TCA cycle, tricarboxylic acid cycle.

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1. Introduction

Arsenic is one of the most dangerous elements due to its wide range of human health effects and extensive distribution in the environment from both natural and human sources (ATSDR, 1991; U.S. NRC, 1999; Meliker and Nriagu, 2008). Exposure to arsenic contaminated water is the main source of global health problems and millions of people are suffering from toxic effects of arsenicals in many countries all over the world by arsenic contaminated water (Bagla and Kaiser, 1996; Kumar, 1997; Chen et al., 1999; Nordstrom, 2002). Arsenic toxicity depends on its chemical form and oxidation state. Inorganic arsenic tends to be more toxic than organic arsenic and trivalent arsenite is more toxic than pentavalent arsenate (Upreti et al., 2007).

Long-term exposure to arsenic is associated with cancer of skin, bladder, lung, liver and kidney (Chen et al., 1988; Kitchin, 2001; Rossman, 2003). Arsenic is known to cause severe toxic effects in almost all of the major target organs (Abernathy et al., 1999; Singh et al., 2011; Jomova et al., 2011). It causes a variety of health effects after acute and/or chronic exposure such as dermal changes, cardiovascular abnormalities, hypertension, diabetes, neurotoxicity, nephrotoxicity, hepatotoxicity and problems of the digestive system etc. (Chen et al., 1995, 1996; Wang et al., 2002; Mandal and Suzuki, 2002; Tseng, 2004; Meliker and Nriagu, 2008; Balakumar and Kaur, 2009; Singh et al., 2011).

Several studies have reported that acute/chronic exposure to inorganic arsenic caused renal damage in humans and experimental animals (Brown et al., 1976; Ratnaike, 2003; Sinha et al., 2008). Histopathological studies have shown that arsenic caused a significant damage to the kidney resulting in marked tubular damage, loss of brush border, tubular dilatations, and tubular necrosis, nephritis along with mitochondrial swelling and acute renal failure (Brown et al., 1976; Sinha et al., 2008; Das et al., 2010; Singh et al., 2011; Zheng et al., 2013). Arsenic accumulates in the kidney during its urinary elimination and increases oxidative stress that affects the structure and functions of renal proximal tubule (Sinha et al., 2008; Singh et al., 2011). However, the effect of arsenic on the enzymes of carbohydrate metabolism, brush border membrane (BBM) and oxidative stress in different renal tissues has not been studied in detail. To understand the mechanism of arsenic-induced nephrotoxicity and other deleterious effects, we now hypothesized that ARS exposure induces oxidative stress, causes damage to renal proximal tubule, its BBM, and alters metabolic functions of the kidney.

To address the above hypothesis, the effect of ARS was examined on nephrotoxicity parameters and biomarkers of carbohydrate metabolism, brush border membrane (BBM) and oxidative stress in the renal cortex and medulla. The results demonstrate that ARS administration caused ultra structural changes in the kidney and significantly increased nephrotoxicity parameters and lipid peroxidation (LPO). Various enzymes of carbohydrate metabolism, BBM and antioxidant defense mechanism were selectively altered. We conclude that ARS caused severe damage to the kidney most likely by suppressing the antioxidant defense system.

2. Materials and methods

Sodium arsenate was purchased from Loba Chemical Company, India. All other chemicals used were of analytical grade and were purchased either from Sigma Chemical Co. (St Louis, MO, USA) or Sisco Research Laboratory, Mumbai, India.

2.1. *Experimental design*

The animal experiments were conducted according to the guidelines of the committee for Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Ministry of Environment and Forests, Government of India. Adult male Wistar rats (8 rats/group), weighing 150–200 g were acclimatized to the animal facility for one week on a standard rat diet (Aashirwad Industries, Chandigarh, India) and water ad libitum. Sodium arsenate (ARS) treated rats were given ARS (10 mg/kg body weight/day), in 0.9% saline intraperitoneally daily for 10 days. The Control rats received an equivalent amount of normal saline in the same manner. The rats were sacrificed under light ether anesthesia. Blood samples were collected and the kidneys were harvested and processed for the preparation of homogenate and BBM vesicles as described below. All the preparations and analyses of various parameters were carried out simultaneously under similar experimental conditions to avoid any day-to-day variations. Body weights of the rats were recorded at the start and at the completion of the experimental procedure.

2.2. *Preparation of homogenates*

After the completion of the experiment, the kidneys were removed, decapsulated and kept in ice-cold buffered saline (154 mM NaCl, 5 mM Tris–HEPES, pH 7.5). The cortex was carefully separated from medulla as described earlier (Khundmiri et al., 2004). A 15% (w/v) homogenate was prepared in 0.1 M Tris–HCl buffer pH 7.5 using Potter-Elvehejem homogenizer (Remi motors, Mumbai, India) with five complete strokes. The homogenate was centrifuged at $3000 \times g$ at 4 °C for 15 min to remove cell debris and the supernatant was saved in aliquots and stored at −20 °C for assaying the enzymes of carbohydrate metabolism, free-radical scavenging enzymes and for estimation of total-SH and lipid peroxidation.

2.3. *Preparation of brush border membrane vesicles (BBMV)*

BBMV were prepared from whole cortex using the $MgCl_2$ precipitation method as previously described (Yusufi et al., 1994). Briefly, freshly minced cortical slices were homogenized in 50 mM mannitol and 5 mM Tris–HEPES buffer pH 7.0 (20 ml/g), in a glass Teflon homogenizer with 4 complete strokes. The homogenate was then subjected to high speed homogenization in an Ultra Turex homogenizer (Type T-25, Janke & Kunkel GMBH & Co. KG. Staufen) for three strokes of 15 s each with an interval of 15 s. $MgCl_2$ was added to the homogenate to a final concentration of 10 mM and the mixture stirred for 20 min on ice. The homogenate was centrifuged at $2000 \times g$ for 10 min in a Beckman centrifuge (J2 MI, Beckman instruments

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