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Diabetogenic effects and pancreatic oxidative damage in rats subchronically exposed to arsenite

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Abstract

Recent epidemiologic studies have associated chronic inorganic arsenic ($_i$As) exposure with an increase in the prevalence of diabetes mellitus. Currently, the diabetogenic mechanism caused by $_i$As exposure is unclear. However, it is recognized that $_i$As contributes to oxidative stress in several organs and systems through generation of reactive oxygen species (ROS). ROS can function as signaling molecules to activate a number of cellular stress-sensitive pathways linked to insulin resistance and decreased insulin secretion. Male Wistar rats were administered sodium arsenite at 1.7 mg/kg (12 h), or water (controls) orally for 90 days. At the end of the 90 days of $_i$As exposure hyperglycemia, hyperinsulinemia and low insulin sensitivity, evaluated by the homeostasis model assessment of insulin resistance, was observed. Arsenicals in pancreas of rats exposed to $_i$As were significantly higher than the control group, being dimethyl and trimethyl metabolites the predominant arsenic species. The activity of pancreatic thioredoxin reductase was lower than the control group. Also, the levels of total glutathione and lipoperoxidation in pancreas increased significantly relative to the control group indicating the presence of stress and oxidative damage, respectively. These results represent an attempt to establish an animal model for in vivo studies of diabetogenic effects of chronic arsenic exposure.
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1. Introduction

Numerous studies have associated chronic exposure to inorganic arsenic ($_i$As) in drinking water with increased prevalence of skin, lung, liver, bladder, prostate and kidney cancers (NRC, 2001). The non-cancer health effects have been examined in a variety of population-based epidemiological studies and clinical reports, including diseases of the peripheral vasculature, cardiovascular system (Wu et al., 2003) nervous system (Rodriguez et al., 2003), and endocrine dysfunctions (Kaltreider et al., 2001; Tseng et al., 2000). The association between arsenic exposure and the risk of non-insulin-dependent diabetes mellitus is a relatively new finding (Tseng, 2004). The potential relationship between mortality from diabetes and chronic arsenic exposure via drinking water has been uncovered (Tsai et al., 1999). Indications of a relationship between arsenic exposure and diabetes mellitus have also been reported in

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studies of copper smelters (Rahman and Axelson, 1995) and art glass workers (Rahman et al., 1995).

Generation of reactive oxygen species (ROS) is the major mechanism by which arsenic exerts its toxicity (Del Razo et al., 2001). Accumulation of ROS causes cytotoxic effects by peroxidation of membrane phospholipids leading to change in permeability and loss of membrane integrity. ROS also produce conformational protein changes and loss of their biological role. In addition, ROS function as signaling molecules to activate several stress-sensitive pathways. In type 2 diabetes, there is growing evidence that activation of stress-sensitive pathways, such as nuclear factor-κB (NF-κB), NH2-terminal Jun kinases/stress activated protein kinases (JNK/SAPK), p38 mitogen-activated protein (MAP) kinase, and hexosamine, is linked to insulin resistance and beta-cell dysfunction (Evans et al., 2003).

In humans, as in many mammals, $_{i}$As is readily absorbed and distributed to a number of organs, such as the liver, where most of its biotransformation takes place. The biomethylation, an enzymatic conversion of $_{i}$As to mono-, di- and tri-methylated metabolites, results in exposure to the parent compound and the methylated arsenicals. Evidence suggest that some of the adverse health effects associated with exposure to $_{i}$As may be mediated by these metabolites (Thomas et al., 2004).

The aim of this study was to analyze the effect of subchronic exposure to $_{i}$As on pancreatic oxidative stress and glucose regulation in rats. Here, we report insulin resistance and the presence of oxidative pancreatic damage after 90 days of $_{i}$As exposure. We also present data on the distribution of arsenic metabolites in pancreatic tissue samples and its relation to pancreatic damage.

2. Methods

2.1. Chemicals

Sodium *m*-arsenite ($NaAs^{III}O_2$), 99% pure, Antifoam B, butylated hydroxytoluene, malondialdehyde bis-dimethylacetal were purchased from Sigma Chemical Co. (St. Louis, MO). Methylarsonic acid, disodium salt (MMA), $CH_3As^{V}O(ONa)_2$, 99% pure, was obtained from Ventron (Danvers, MA), and dimethylarsinic acid (DMA, $(CH_3)_2As^{V}O(OH)$), 98% pure, was obtained from Strem (Newburyport, MA). Trimethylarsenic oxide (TMAO) was a gift from Dr. Hiroshi Yamauchi (St. Marianna University, School of Medicine, Kawasaki City, Japan). Sodium borohydride ($NaBH_4$), sodium hydroxide, di-sodium hydrogen phosphate monohydrate, di-sodium hydrogen phosphate dodecahydrate were obtained from Merck, Mexico. Trichloroacetic acid (TCA), TRIS–hydrochloride and ultrapure phosphoric acid were purchased from J.T. Baker (Phillipsburg, NJ). All other chemicals used were from the highest purity commercially available.

2.2. Animal treatments

Male Wistar rats (200 g) were obtained from Cinvestav animal unit. The animals were housed in polycarbonate cages (60.9 cm × 45.7 cm × 30.5 cm, Quality cage Co., Portland, OR) with hardwood chip bedding in groups of 5 animals per cage and they were provided with food (LabDiet® 5013, PMI Nutrition International, St. Louis, MO) and distilled water ad libitum. Housing conditions were a 12-h light:12-h dark cycle and temperature and humidity of 18–23 °C and 40–70%, respectively.

Rat groups were administered sodium arsenite at 1.7 mg/kg or deionized water (2.5 ml/kg) for the control group, by gavage every 12 h (7:00 a.m. and 7:00 p.m.) during 90 consecutive days. We used a subchronic dose of 1.7 mg/kg (12 h), lower the than no-observed-adverse-effect level concentration (NOAEL = 4.0 mg/kg (day) reported in rats exposed to trivalent $_{i}$As concentration in repeated oral doses (Holson et al., 2000).

After 90 days of treatment, rat groups ($n = 10$) were then euthanized by cardiac puncture under sodium pentobarbital anesthesia (60 mg/kg, i.p.). Blood was collected into EDTA tubes. Pancreas was immediately remove and rinsed in saline solution and homogenized in phosphate buffer (pH 7.4), for determinations of lipid peroxidation, total glutathione (GSH), thioredoxin reductase (TrxR) and arsenic species. Basic inspection of animals was performed daily. Food and water consumption and animal weights were monitored daily.

Rats received humane care and the study complied with the Institution's guidelines and the Mexican Official Norm (NOM-062-ZOO-1999) regarding technical specifications for production, care and use of laboratory animals.

2.3. Blood glucose levels

Blood glucose levels were determined in serum at 340 nm, with an automated clinical spectrophotometer analyzer (Vitalab Eclipse, Merck) using the glucose hexokinase kit (Randox®, San Francisco, CA).

2.4. Insulin resistance

Fasting insulin, fasting insulin-to-glucose ratio (Legro et al., 1998), and a homeostasis model assessment

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