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Arsenite in drinking water produces glucose intolerance in pregnant rats and their female offspring

María Marta Bonaventura [a, b], Nadia Soledad Bourguignon [a], Marianne Bizzozzero [a], Diego Rodriguez [a], Clara Ventura [c], Claudia Cocca [c], Carlos Libertun [a, d], Victoria Adela Lux-Lantos [a, *]

[a] Instituto de Biología y Medicina Experimental (IBYME-CONICET), Vuelta de Obligado 2490, C1428ADN, CABA, Argentina
[b] Escuela de Ciencia y Técnica, Universidad Nacional de San Martín, Av 25 de mayo 1650, Partido de San Martín, Bs As, Argentina
[c] Laboratorio de Radioisótopos, Facultad de Farmacia y Bioquímica, Universidad de Buenos Aires, Viamonte 444, CABA, Argentina
[d] Departamento de Fisiología, Facultad de Medicina, Universidad de Buenos Aires, CABA, Argentina

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ABSTRACT

Drinking water is the main source of arsenic exposure. Chronic exposure has been associated with metabolic disorders. Here we studied the effects of arsenic on glucose metabolism, in pregnant and postpartum of dams and their offspring.

We administered 5 (A5) or 50 (A50) mg/L of sodium arsenite in drinking water to rats from gestational day 1 (GD1) until two months postpartum (2MPP), and to their offspring from weaning until 8 weeks old.

Liver arsenic dose-dependently increased in arsenite-treated rats to levels similar to exposed population. Pregnant A50 rats gained less weight than controls and recovered normal weight at 2MPP. Arsenite-treated pregnant animals showed glucose intolerance on GD16-17, with impaired insulin secretion but normal insulin sensitivity; they showed dose-dependent increased pancreas insulin on GD18. All alterations reverted at 2MPP. Offspring from A50-treated mothers showed lower body weight at birth, 4 and 8 weeks of age, and glucose intolerance in adult females, probably due to insulin secretion and sensitivity alterations.

Arsenic alters glucose homeostasis during pregnancy by altering beta-cell function, increasing risk of developing gestational diabetes. In pups, it induces low body weight from birth to 8 weeks of age, and glucose intolerance in females, demonstrating a sex specific response.

1. Introduction

The effects of exposure to chemicals that act as endocrine disruptors on the general population are a growing worldwide concern. Endocrine disruptors are synthetic or natural compounds that have the ability to interfere with, mimic or antagonize the function and/or production of hormones. These compounds are widely distributed in our environment and include pesticides, pharmaceutical drugs and several chemicals, including metals. Metals that possess endocrine disrupting effects are varied, affecting one or more targets. For example Cadmium can induce endometriosis (Smarr et al., 2016), alterations in gonadotropin levels and in testicular or ovarian structure and activity (Lafuente, 2013), breast cancer (De Coster and van Larebeke, 2012) and also cardiovascular disease by increasing atherosclerotic plaque formation (Kirkley and Sargis, 2014). Metals, such as iron, arsenic, mercury, lead, cadmium and nickel, can also have effects of glycemic control (Gonzalez-Villalva et al., 2016). Among them, arsenic has been described as an endocrine disruptor and is currently being studied from this new perspective (Davey et al., 2008).

Arsenic is a naturally occurring metalloid released into the environment by natural events and human activities. The largest sources of exposure to inorganic arsenic are drinking water, crops such as rice and meals (Charnley, 2014; Nacano et al., 2014; Turra et al., 2010). Millions of people worldwide are exposed to

* Corresponding author. V. de Obligado 2490, C1428ADN, Buenos Aires, Argentina.
E-mail addresses: mmbonaventura@gmail.com (M.M. Bonaventura), nsbourguignon@yahoo.com.ar (N.S. Bourguignon), m.bizzozzero@hotmail.com (M. Bizzozzero), keruvino@hotmail.com (D. Rodriguez), cmcocca@ffyb.uba.ar (C. Cocca), libertun@dna.uba.ar (C. Libertun), vlux@ibyme.conicet.gov.ar, vlux@dna.uba.ar, vlux@lantos.com.ar (V.A. Lux-Lantos).

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contaminated water, mostly from natural mineral deposits. High levels of arsenic in water, up to 200 mg/L, have been reported around the world (Concha et al., 1998; Akter et al., 2005; National Research Council, 2001; Gonzalez-Villalva et al., 2016). The WHO's recommended safety limits for arsenic in drinking water is 10 μg/L, and it is calculated based on the effects of arsenic on cancer incidence. According to these standards, there is a huge concern in India, Bangladesh, Chile, Mexico, Taiwan and Argentina, among other parts of the world. An extended zone in Argentina contains ground water with relatively high levels of arsenic, with an estimated population exposed of approximately 7% of country population. (Ministerio de Educación de la Nación-Argentina, 2009) Although the effects of arsenic exposure increasing cancer incidence in the Argentine population have been described (Bardach et al., 2015), little is known on the effects of this metal on glucose metabolism in our country.

Inorganic arsenic is highly toxic and carcinogenic to humans; numerous studies have associated chronic exposure to inorganic arsenic in drinking water with increased prevalence of several cancers (Steinmaus et al., 2014; Cheng et al., 2016; Yang et al., 2008). Regarding the non-cancer health effects, chronic exposure to inorganic arsenic has been associated with loss of body weight (Nandi et al., 2005), metabolic disorders such as diabetes (Brauner et al., 2014; Longnecker and Daniels, 2001; Gonzalez-Villalva et al., 2016), cardiovascular disease (Moon et al., 2013; Li et al., 2013), chronic respiratory symptoms (Smith et al., 2013), and reproductive system alterations (Singh et al., 2007).

Epidemiological and experimental data indicate a diabetogenic role of arsenic. *In vitro* and *in vivo* experiments sustain this hypothesis (Paul et al., 2007a, 2007b; Brauner et al., 2014; James et al., 2013; Islam et al., 2012; Wang et al., 2014), but the biological mechanism for an association between chronic arsenic exposure and increased diabetes risk is not completely understood. Several studies suggest that arsenic might increase the risk for type 2 diabetes via multiple mechanisms, affecting a cluster of regulated events, which in conjunction trigger the disease (Diaz-Villasenor et al., 2007). Furthermore, gestational diabetes is similar to type 2 diabetes regarding its pathogenesis and clinical symptoms; however, it occurs in women during pregnancy and usually improves or disappears after childbirth. Epidemiological data suggest that arsenic may also increase the risk of developing gestational diabetes (Shapiro et al., 2015).

During the gestational period, exposure to As may cause alterations to the host and fetus in rats and humans at fairly low exposure levels (Chattopadhyay et al., 2001; DeSesso, 2001; Holson et al., 2000; Ahmad et al., 2001; Hopenhayn-Rich et al., 2000; Hopenhayn et al., 2003; Kile et al., 2014). Arsenic crosses the placental barrier in both animals and humans, and experimental studies support a role for arsenic as a developmental toxicant, e.g. exposure from drinking water has been related with increased rates of fetal loss, congenital malformation, pre-term births, and neonatal and young adult mortality, as well as decreased birth weight (Hopenhayn et al., 2003; Nandi et al., 2005; Concha et al., 1998; Devesa et al., 2006; Smith et al., 2012).

The goal of this study was to elucidate the deleterious effects of arsenic exposure through drinking water on rat glucose metabolism in particular physiological conditions that have not been thoroughly addressed such as during pregnancy and postpartum in dams, as well as on their offspring.

2. Materials and methods

2.1. Animals

We used young, virgin female Sprague-Dawley rats from the IBYME colony. Animals were housed in air-conditioned rooms, with lights on from 0700 to 1900, and given free access to laboratory chow and water. Studies were performed according to protocols approved by the Institutional Animal Care and Use Committee of the IBYME-CONICET (in accordance with the Division of Animal Welfare, Office for Protection from Research Risks, National Institutes of Health, Animal Welfare Assurance for the Institute of Biology and Experimental Medicine A#5072-01). Animals were treated humanely and with regard for alleviation of suffering.

Rats were given sodium arsenite in drinking water at doses previously described (Paul et al., 2007b): A5: 5 mg/L or A50: 50 mg/L dissolved in distilled water, or distilled water as Control. Beverages were given ad libitum and changed every 2–3 days to avoid oxidation of As (III); standard chow was given ad libitum. Rats were exposed to sodium arsenite from gestation day 1 (GD1), confirmed by presence of vaginal sperm plug, until sacrifice. The offspring received the same treatments as their mother from weaning until sacrifice.

Water consumption did not show statistical differences among groups and the mean consumption per day was 53 ± 4 ml/animal; mean body weight (BW) of adult Sprague Dawley rats at GD1 was 229 ± 4 g. Thus, exposure levels expressed as mg/kg BW/day were 1.15 mg/kg BW/day and 11.5 mg/kg BW/day for A5 and A50 animals respectively.

Pregnant dams were housed singly until weaning; litter size was determined at birth and then reduced to eight pups when necessary; at weaning, offspring were separated by sex. Additionally, duration of pregnancy and male/female pup proportion was recorded.

We evaluated the effects of arsenic exposure in three experimental groups: pregnant dams, postpartum dams and their offspring.

2.1.1. Pregnant dams

Body weight was determined along pregnancy. Glucose metabolism (glucose tolerance test, insulin secretion test and HOMA of insulin resistance) was evaluated on GD16-17 and litter parameters at birth. One group of pregnant rats was sacrificed on GD18 and insulin content was determined in their pancreases.

2.1.2. Postpartum dams

Body weight was determined on the day after parturition (0 month) and at 1 and 2 months postpartum. Glucose metabolism, liver arsenic content and liver oxidative stress parameters were evaluated at 2 months postpartum.

2.1.3. Offspring

Body weight was determined on postnatal day 1 and at 4 and 8 weeks of age. At 8 weeks of age glucose metabolism was evaluated. Animals were sacrificed at two months of age and liver arsenic content and liver oxidative stress parameters were determined.

2.2. Arsenic tissue levels

We determined arsenic content in liver samples from dams sacrificed at two months postpartum (2MPP), and from offspring at two months of age. After a wet-digested mineralization, total As was determined by the silver diethyldithiocarbamate (AgDDTC) method that follows ISO 2590 guidelines. (ISO TC 47 SC1, 1973).

2.3. Glucose tolerance test (GTT) and insulin secretion test (IST)

We performed GTT/IST on GD16-17 and 2MPP in the same dams; GD16-17 was chosen to ensure that the animals were in a condition equivalent to the human third trimester for the first GTT (Petry