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Effects of arsenic on adipocyte metabolism: Is arsenic an obesogen?

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ABSTRACT

The environmental obesogen model proposes that in addition to a high-calorie diet and diminished physical activity, other factors such as environmental pollutants and chemicals are involved in the development of obesity. Although arsenic has been recognized as a risk factor for Type 2 Diabetes with a specific mechanism, it is still uncertain whether arsenic is also an obesogen. The impairment of white adipose tissue (WAT) metabolism is crucial in the onset of obesity, and distinct studies have evaluated the effects of arsenic on it, however only in some of them for obesity-related purposes. Thus, the known effects of arsenic on WAT/adipocytes were integrated based on the diverse metabolic and physiological processes that occur in WAT and are altered in obesity, specifically: adipocyte growth, adipokine secretion, lipid metabolism, and glucose metabolism. The currently available information suggests that arsenic can negatively affect WAT metabolism, resulting in arsenic being a potential obesogen.

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1. Introduction

High body-mass index (BMI) is an important risk factor for type 2 diabetes (T2D), as well as other metabolic diseases and some types of cancers. From 1975 to 2014, the global age-standardized BMI has increased from 21.9 kg/m^2 to 24.2 kg/m^2 (Collaboration, 2016), and between 1980 and 2008, the prevalence of worldwide obesity rose from 4.8% to 9.8% in men and from 7.9% to 13.8% in

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women (Malik et al., 2013), meaning that obesity affects more than half a billion people around the world (Bhurosy and Jeewon, 2014). Over the past 35 years, a four-fold global increase in the prevalence of T2D has also occurred, with an estimated 422 million adults with diabetes in 2014, reflecting an increase in associated risk factors such as overweight or obesity. Furthermore, diabetes prevalence has risen faster over the past decade in low- and middle-income countries than in high-income countries (Collaboration, 2016; WHO, 2016). Thus, diverse economic and health services efforts have been focused on preventing and managing pre-diabetes and T2D (Collaboration, 2016).

Improved access to food intake with high caloric content and decreased physical activity levels have been identified as the prime risk factors for the increasing prevalence of overweight, obesity and chronic metabolic diseases, such as T2D (Bhurosy and Jeewon, 2014), in the last 30 years. However, these factors by themselves do not fully explain this phenomenon, and have failed in the prevention and/or treatment of these metabolic diseases. Thus, other risk factors could be involved in obesity and T2D etiologies.

Environmental pollutants and chemicals, most of them catalogued as endocrine-disrupting chemicals because they interfere with hormone actions, have been proposed to act as obesogens and/or diabetogens (Gore et al., 2015; Grun and Blumberg, 2009; Holtcamp, 2012; Kuo et al., 2013; Neel and Sargis, 2011). Chemicals that promote obesity have been functionally defined as obesogens because they increase the number of adipocytes (hyperplasia) and/or the storage of fat into existing adipocytes (hypertrophia). Obesogens can also act indirectly to promote obesity by changing basal metabolic rates, shifting energy balance to favor calorie intake and storage and altering hormonal or neuronal control of appetite and satiety, among others (Heindel et al., 2015).

The obesogen hypothesis is less than 10 years old, and approximately 20 environmental chemicals are already known to have obesogenic properties (Heindel et al., 2015). In animals, pharmaceutical drugs such as diethylstilbestrol, chemicals used for the polymerization of plastics and resins such as bisphenol A and phthalates, pesticides (particularly DDT) organotins such as fungicides, disinfectants used for marine paints such as tributyltin and the nonstick coating perfluorooctanoic acid are obesogenic (Gore et al., 2015; Heindel et al., 2015; Janesick et al., 2014; Karoutsou and Polymeris, 2012). Diverse compounds have shown to alter adipocyte differentiation, and several endocrine-disrupting chemicals modulate adipocyte physiology (Regnier and Sargis, 2014). However, arsenic has not been defined as an obesogen, even though it is a considerable risk factor for the development of T2D and available data exit in relation to its diverse effects on white adipose tissue (WAT).

Arsenic in drinking water obtained from underground occurs naturally in many countries worldwide, and from 2001 to 2009, it has been estimated that 140 million people were exposed to concentrations above 50 μg/L, which is five-fold higher than the upper limit established by the World Health Organization (WHO) (Pilsner et al., 2009; van Halem et al., 2009; WHO, 2012).

The epidemiologic relationship between high chronic arsenic exposure and obesity development has not been evaluated directly. Based on epidemiological studies from the mid-90s, arsenic has been associated with an increased risk of developing T2D in humans, more evident in areas with high exposure levels (Kile and Christiani, 2008; Maull et al., 2012; Thayer et al., 2012; Wang et al., 2014). In particular, a prospective study in Taiwan carried out in people with and without arsenic exposure through drinking water, shows that the multivariate-adjusted relative risk for T2D was 2.3 (1.2–4.3) for a BMI ≥ 25 *vs* < 25 kg/m^2 (Tseng et al., 2000). Although obesity and T2D are not completely equitable, obesity is one of the major risk factors for T2D development (Boles et al., 2017).

The mechanisms by which arsenic increases the risk for T2D involves the impairment of glucose-stimulated insulin secretion in pancreatic beta-cells, the induction of pancreatic oxidative damage and insulin resistance in skeletal muscle, increment of gluconeogenesis in liver, and modulation of other hepatic insulin signaling (Diaz-Villasenor et al., 2006, 2008; Douillet et al., 2013; Hamann et al., 2014; Izquierdo-Vega et al., 2006; Liu et al., 2014; Padmaja Divya et al., 2015). Interestingly, in an integrated computational systems biology approach that examines possible pathogenetic linkages between environmental chemicals to genes and proteins involved in T2D through genome-wide associations, disease similarities, and published epidemiologic and experimental evidence, arsenic was found in the top 10 potentially environmental chemicals linked to T2D, and moreover arsenic also showed literature-based association with obesity (Audouze et al., 2013). Thus, arsenic has been considered an important risk factor for T2D, though its obesogenic effects are uncertain because the effects of arsenic on WAT have been explored non-specifically and with diverse objectives. Therefore, we believe it is relevant to review the findings from these studies with the purpose of better understanding the mechanism of action and the role arsenic plays as an obesogen, as well as to identify the knowledge gaps in the area.

Adipose tissue is a central metabolic organ in the regulation of whole-body energy homeostasis, thus adipose dysfunction is a critical step in obesity. Particularly, WAT functions as a key energy reservoir for other organs and secretes various hormones, cytokines, and metabolites (termed as adipokines), as well as free fatty acids that control systemic energy balance by regulating appetite signals in the central nervous system and metabolic activity in peripheral tissues (Choe et al., 2016).

Moreover, a number of studies suggest that overnutrition during pregnancy is a major risk factor for obesity in offspring in adulthood, in part, due to epigenetic mechanisms (Elshenawy and Simmons, 2016). Similarly, exposure to various substances during critical periods, such as the embryonic stage, can cause health effects. Thus, prenatal exposure to substances can have lasting and potentially permanent effects on offspring, including changes on adipogenesis, lipid imbalance and obesity (Janesick et al., 2014). In fact, the consequences of ancestral exposure to obesogenic chemicals can result in the transmission of obesity-related phenotypes even through three generations via epigenetic mechanisms (Boekelheide et al., 2012; Chamorro-Garcia and Blumberg, 2014).

Blood concentrations of arsenic and its metabolites in newborns have been found to be similar to those of their mothers because the placenta is not a barrier to arsenic (Hall et al., 2007). Literature about prenatal arsenic exposure on experimental animal models and its changes on adipocyte metabolism are limited. However, some studies have shown evidence that arsenic may act on adipocyte function across generations.

Thus, the aim of this review is to compile the available information about the direct and transgenerational effects of arsenic on adipocytes to understand how arsenic exposure can contribute as a risk factor to obesity and the onset of T2D by specifically focusing on roles that do not lead to pancreas, skeletal muscle and liver impairment. Based on the diverse metabolic and physiological processes that occur in WAT, the review is divided into the following topics: (1) adipocyte growth, (2) adipokine secretion, (3) lipid metabolism (particularly lipogenesis and lipolysis), and (4) glucose metabolism (mainly glucose uptake).

2. Effects of arsenic on adipocyte growth

The increase in adipose mass is the result of an increase in size of adipocytes (hypertrophy) and number of adipocytes (hyperplasia)