Environmental Toxicology and Pharmacology 46 (2016) 337–343

Contents lists available at ScienceDirect

Environmental Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/etap

Review or Mini-review

Pollution by metals: Is there a relationship in glycemic control?

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ARTICLE INFO

Article history:
Received 19 February 2016
Received in revised form 20 June 2016
Accepted 21 June 2016
Available online 10 August 2016

Keywords:
Metals
Pollution
Hyperglycemia
Hypoglycemia
Diabetes
Insulin

ABSTRACT

There are evidences of environmental pollution and health effects. Metals are pollutants implicated in systemic toxicity. One of the least studied effects, but which is currently becoming more important, is the effect of metals on glycemic control. Metals have been implicated as causes of chronic inflammation and oxidative stress and are associated to obesity, hyperglycemia and even diabetes. Arsenic, iron, mercury, lead, cadmium and nickel have been studied as a risk factor for hyperglycemia and diabetes. There is another group of metals that causes hypoglycemia such as vanadium, chromium, zinc and magnesium by different mechanisms. Zinc, magnesium and chromium deficiency is associated with increased risk of diabetes. This review summarizes some metals involved in glycemic control and pretends to alert health professionals about considering environmental metals as an important factor that could explain the poor glycemic control in patients. Further studies are needed to understand this poorly assessed problem.

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http://dx.doi.org/10.1016/j.etap.2016.06.023
1382-6689/

1. Introduction

Environmental pollution is an important problem in big cities. Recently, air pollution has been associated as a risk factor for Diabetes Mellitus and obesity, mainly because their ability to cause oxidative stress and inflammation that leads to lipogenesis, adipose tissue inflammation and insulin resistance (Rao et al., 2015; Janghorbani et al., 2014). Air pollution is an important source of metals attached to particulate matter. Metals are pollutants with historical relevance because of the effects reported on population's health. There is extensive evidence showing their toxic effects on many systems, but there is scarce information about their role in carbohydrate metabolism and glycemic regulation. The relevance of studying these effects is that the exposure to some metals has been involved in hyperglycemia and increased risk of Diabetes (*i.e.* arsenic and iron) (Forte et al., 2013), but some other metals have shown a hypoglycemic effect and have been studied as a potential treatment for Diabetes, as vanadium and chromium (Fortoul et al., 2015). Further studies about the hypoglycemic effect on exposed individuals are needed.

A significant proportion of world population is obese with insulin resistance or diabetes already diagnosed; in these conditions there are problems with blood sugar control. Environmental pollution by metals may be a hidden factor that could be playing a role in the difficulty of controlling glycemia and may be also implicated in the complications arising from it.

It is important to remember that there are many organs and tissues involved in glycemia regulation. It is relevant that there are many mechanisms to prevent hypoglycemia because the brain must have enough glucose to do its functions and severe hypoglycemia could lead people to coma or even death. Some of the organs involved in glycemia regulation are: endocrine pancreas, liver, adipose tissue and autonomous nervous system. Endocrine pancreas produces insulin and glucagon, the liver is the main organ producing glucose. It responds to different hormones to do many metabolic pathways, as glucolisis, glycogenolisis, neoglucogenesis. Adipose tissue contributes to metabolism of carbohydrates doing lipogenesis or lipolysis to have elements for neoglucogenesis. Autonomous nervous system also contributes to glucose production. And there are different glucose transporters that also play and important role in glycemic control (Tirone, 2001). Metals are known to affect mitochondrial mechanisms and increase the production of free radicals leading to oxidative stress and inflammation, both of these conditions, could play a role in metabolic disorders as diabetes or obesity. These effects are clearly studied for cardiopathies and neurodegenerative diseases, but further studies are needed to understand this mechanism in metabolic disorders (Grubman et al., 2014; Rines and Ardehali, 2013).

This review focuses on analyzing the available information of the effects on carbohydrate metabolism, insulin secretion or pancreatic beta cell damage of several pollutant metals and its possible implications on glycemic regulation.

2. Hyperglycemic metals

Some element imbalances have been associated with diabetes, as altering normal glucose levels or/and insulin metabolism effects. The disturbance in some metals can increase oxidative stress and inflammation, which may contribute to insulin resistance and development of the complications. Possible mechanisms involved in hyperglycemia induced by metals are summarized in Fig. 1.

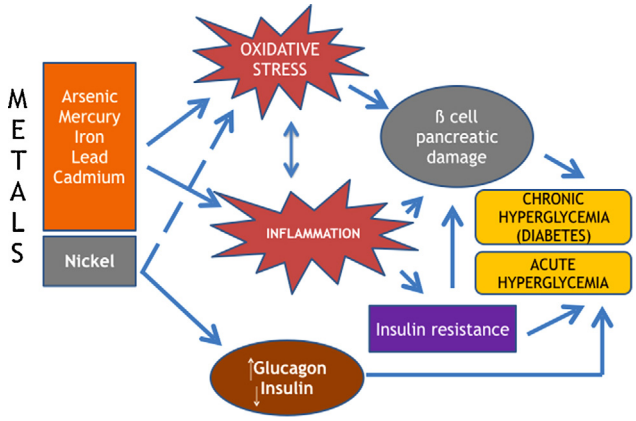

Fig. 1. Some metals cause oxidative stress and inflammation that are associated to insulin resistance and may be the cause for acute hyperglycemia. If these conditions become chronic, beta-pancreatic cell may be damaged or exhausted and it could lead to chronic hyperglycemia and diabetes. Other mechanism involved in acute hyperglycemia might be the abnormal release of glucagon and insulin.

2.1. Arsenic

Arsenic (As) is a pollutant of great interest worldwide because it is found in drinking water and groundwater in many countries. In Latin America it is considered that approximately 14 million people consume arsenic contaminated water at a concentration equal to or greater than 10 g/L. Pollution sources of As are natural, because mineral containing As can dissolve in water and anthropogenic by mining and metallurgical activity or by the use of agricultural chemicals containing arsenic. Epidemiological studies in populations exposed to inorganic As in drinking water show that this element increases the risk of developing diabetes, because fasting hyperglycemia and impaired glucose tolerance are observed (Del Razo et al., 2011). Doses greater than 200 mg/L have been associated with high risk of type 2 diabetes in populations exposed and it is unclear if there is a risk with lower doses (Wang et al., 2014). *In vitro* studies have demonstrated that inorganic arsenic or its metabolites modify pancreatic insulin secretion stimulated by glucose. Reactive oxygen species (ROS) are involved in the regulation of insulin secretion stimulated by glucose, and arsenic induces antioxidative enzymes that decrease ROS, and in consequence alters the synthesis and secretion of insulin from pancreatic β-cells by this mechanism and also by decreasing free intracellular calcium. In contrast, subchronic and chronic *in vivo* studies show that arsenic causes oxidative stress that damage pancreatic beta cells. Both, *in vitro* and *in vivo* studies show the hyperglycemic effect of arsenic (Huang et al., 2011).

2.2. Mercury

Mercury (Hg), a toxic heavy metal, is widespread and persistent in the environment. There is growing evidence of its presence in some components of the human food chain including seafood, seeds, and other foodstuffs, but also it can be present in disinfectant, disk batteries and dental amalgam. Also, a cross-sectional analysis has shown that people in the highest quartile of fish consumption