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Dietary selenate attenuates adiposity and improves insulin sensitivity in high-fat diet-induced obese mice

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ABSTRACT

Selenium is an essential micronutrient required for maintaining cellular redox homeostasis. Despite its potential beneficial role in lowering the risk of type 2 diabetes in humans with lower selenium status and diabetic mice, its role in preventing the development of obesity and metabolic syndrome is unknown. Here, we report that chronic selenate supplementation to high fat (HF) diet-fed mice resulted in resistance to diet-induced adiposity and insulin resistance. The body weight and adipose tissue mass gain associated with HF diet-induced obesity in mice was abrogated by selenate supplementation at 0.72 mg/kg body weight. This was accompanied by alteration of HF diet-induced expression of genes involved in adipokines, inflammation, transforming growth factor-β (TGF-β) signalling, mitochondria function, and beige adipocyte differentiation in adipose tissue. Selenate supplementation also resulted in an increase in faecal calorie content and improved glucose tolerance in HF diet-induced obese mice. Collectively this study elucidated a novel role of selenate as a dietary micromineral in the prevention of obesity and its related energy dysfunction.

1. Introduction

Obesity and its associated insulin resistance are important risk factors for the development of metabolic syndrome (Rosen & Spiegelman, 2006; Shulman, 2000). Obesity largely results from prolonged positive energy balance between energy intake and energy expenditure with the resultant increase in adipocyte number and size due to excess storage of lipid surplus (Kopelman, 2000). Given the high prevalence of obesity and

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Abbreviations: BAT, brown adipose tissue; C/EBP, CCAAT/enhancer binding protein; DGAT2, diacylglycerol acyltransferase 2; FAS, fatty acid synthase; H&E, haematoxylin and eosin; HF, high fat; HOMA-IR, homeostasis model assessment-insulin resistance; IL-6, interleukin-6; IPGTT, intraperitoneal glucose tolerance test; LD50, median lethal dose; MCP-1, monocyte chemoattractant protein-1; NEFA, non-esterified fatty acid; PPARγ, peroxisome proliferator-activated receptor γ; PGC-1α, PPARγ coactivator-1α; PRDM16, PR domain containing 16; RPL27, ribosomal protein L27; SAA3, serum amyloid A3; TBX1, T-box transcription factor1; TFAM, mitochondrial transcription factor A; TGF-β1, transforming growth factor-β1; TGF-βR, TGF-β receptor; TMEM26, transmembrane protein 26; TG, triacylglycerol; TNF-α, tumour necrosis factor-α; UCP-1, uncoupling protein-1; WAT, white adipose tissue

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its associated threat to public health, it is critical to develop effective methods to prevent the development of obesity and/or reverse obesity-related metabolic disorders. There is growing evidence that various dietary bioactive compounds confer protection from diet-induced obesity and insulin resistance in animals through attenuation of adipose tissue development and lipid metabolism (Baboota et al., 2013; Kim & Park, 2011; Patel, 2015; Yu, Cai, Zhang, Feng, & Huang, 2015). However, poor water solubility, instability in the gastrointestinal tract, and low bioavailability of many of these compounds limit their application to dietary control of human obesity. Selenium is a water-soluble essential micronutrient required for maintaining redox homeostasis, thyroid hormone metabolism and immune function mainly through cotranslational incorporation of selenocysteine into selenium-containing selenoproteins (Kryukov et al., 2003; Reeves & Hoffmann, 2009; Stoytcheva & Berry, 2009). Selenium is found in both plant and animal foods, and the concentration of foods varies depending on cultivation location (Rayman, Infante, & Sargent, 2008). Although animal sources such as organ meat, seafood, muscle meat contain more selenium content than agricultural crops (Rayman, 2008), plants of the *Brassica* (*e.g.*, cabbage, cauliflower, and broccoli) and *Allium* (*e.g.*, onion, garlic and chives) families, brazil nuts and whole wheat bread are known to be selenium-enriched foods (Rayman et al., 2008). Both selenium deficiency and suboptimal intake of selenium (*i.e.*, over 350–400 μg/day) are known to result in Keshan disease (Chen, Yang, Chen, Wen, & Ge, 1980), cardiomyopathy, and an increase in the risk of various cancers such as gastrointestinal and prostate cancers (Whanger, 2004). On the other hand, several prospective studies indicate beneficial effects of selenium on prevention of colorectal, esophageal and other cancers in humans (Duffield-Lillico et al., 2002; Letavayova, Vlckova, & Brozmanova, 2006; Patrick, 2004; Qiao et al., 2009), whereas epidemiological studies have provided a positive correlation between selenium and the risk of various cancers (Goyal, Terry, & Siegel, 2013; Lippman et al., 2009). In addition, recent studies implicated a potential beneficial role of selenium supplementation in metabolic syndrome such as type 2 diabetes. Selenium, particularly selenate, has been shown to improve insulin sensitivity in diabetic animal models, potentially through its insulinomimetic effect on hepatic energy metabolism (Iizuka, Ueda, Yagi, & Sakurai, 2010; Mueller & Pallauf, 2006; Muller, Most, & Pallauf, 2005; Wang et al., 2014). Intriguingly, recent human studies have shown that high intake of selenium is positively associated with the prevalence of diabetes (Bleys, Navas-Acien, & Guallar, 2007; Stranges et al., 2007), potentially due to its effect on modulation of selenoprotein expression (Zeng et al., 2012) and production of reactive oxygen species (Wang et al., 2014). Nevertheless, we recently reported an anti-adipogenic function of selenate *in vitro* through its anti-oxidant property and activation of TGF-β1 signalling pathway in the early phase of adipogenesis (Kim, Kim, Wiacek, Chen, & Kim, 2012). We further demonstrated that the anti-adipogenic function of selenate is attributed to selenate as other forms of selenium (*e.g.*, selenite and methylseleninic acid) exhibited toxic effect on preadipocytes. However, the direct role of selenate in the generation of adipose tissue and the development of obesity remains elusive.

In the present study we attempt to elucidate the physiological function of selenate in the development of obesity and its associated insulin resistance in diet-induced obese mice.

2. Materials and methods

2.1. Animals and treatments

Five-week-old male C57BL/6J mice were purchased from The Jackson Laboratory (Bar Harbor, ME, USA) and kept on a 12/12 h light/dark cycle at 22–25 °C. Food and water were provided *ad libitum*. The mice were acclimated for 2 weeks after receipt in the facility and then randomly assigned to three groups, such as a standard chow diet (15% of calories from fat), HF diet (60% of calories from fat; cat. no. D12492, Research Diet, New Brunswick, NJ, USA), and HF with selenate supplementation (HF+Se) in the drinking water for an 8-week feeding. The HF+Se group received water containing sodium selenate at a concentration of 0.72 mg/kg body weight [*i.e.*, 20% of the medium lethal dose (LD_{50})]. Food and water consumption and body weight were monitored twice per week. Experimental procedures were approved by the Purdue University Institutional Animal Care and Use Committee (approved protocol no. 1112000347).

2.2. Faecal calorie and lipid composition

At the end of the study, faecal samples were collected from individual cages and pooled for further analysis. Faecal calories were determined by Bomb calorimeter (Parr 1261 bomb calorimeter, Parr Instruments Co., Moline, IL, USA) using benzoic acid as a calibration standard (Murphy et al., 2010). The faeces were freeze-dried for 4 h and faecal lipids were extracted by the Folch method. The extracted lipids were dried and measured to calculate lipid content (lipid weight/faeces weight × 100%).

2.3. Histological analysis

At the end of the feeding, various fat pads, brown adipose tissue (BAT), liver, kidney and spleen were dissected from the mice. Epididymal fat pads were fixed with 10% formalin and were subjected to paraffin embedding. All slides were stained with haematoxylin and eosin (H&E) and digitalized by a scanning system (Aperio Technologies, Vista, CA, USA) in the Purdue Histology & Phenotyping Laboratory. Adipocyte size and number in H&E stained epididymal fat pad sections were quantified by ImageScope analysis software (ver.9, Aperio Technologies).

2.4. Measurement of serum glucose concentration and intraperitoneal glucose tolerance test (IPGTT)

At 13 weeks of age, mice were fasted for 12 h and a blood sample was taken in order to measure the basal glucose level. Glucose concentration was determined using a glucometer (Bayer Healthcare LLC, Mishawaka, IN, USA). Mice were subjected to IPGTT by administration of a 50% glucose solution via intraperitoneal injection at 2 g/kg body weight. After injection, blood was drawn from the tail vein at 0, 15, 30, 45, 60,