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Ozone modifies the metabolic and endocrine response to glucose: Reproduction of effects with the stress hormone corticosterone

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ABSTRACT

Air pollution is associated with increased incidence of metabolic disease (e.g. metabolic syndrome, obesity, diabetes); however, underlying mechanisms are poorly understood. Air pollutants increase the release of stress hormones (human cortisol, rodent corticosterone), which could contribute to metabolic dysregulation. We assessed acute effects of ozone, and stress axis involvement, on glucose tolerance and on the metabolic (triglyceride), endocrine/energy regulation (insulin, glucagon, GLP-1, leptin, ghrelin, corticosterone), and inflammatory/endothelial (TNF, IL-6, VEGF, PAI-1) response to exogenous glucose. Male Fischer-344 rats were exposed to clean air or 0.8 ppm ozone for 4 h in whole body chambers. Hypothalamic-pituitary-adrenal (HPA) axis involvement in ozone effects was tested through subcutaneous administration of the glucocorticoid synthesis inhibitor metyrapone (50 mg/kg body weight), corticosterone (10 mg/kg body weight), or vehicle (40% propylene glycol) prior to exposure. A glucose tolerance test (2 g/kg body weight glucose) was conducted immediately after exposure, with blood samples collected at 0, 30, 60, 90, and 120 min. Ozone exposure impaired glucose tolerance, an effect accompanied by increased plasma triglycerides but no impairment of insulin release. Ozone diminished glucagon, GLP-1, and ghrelin responses to glucose, but did not significantly impact inflammatory/endothelial analytes. Metyrapone reduced corticosterone but increased glucose and triglycerides, complicating evaluation of the impact of glucocorticoid inhibition. However, administration of corticosterone reproduced the profile of ozone effects, supporting a role for the HPA axis. The results show that ozone-dependent changes in glucose tolerance are accompanied by altered metabolic and endocrine responses to glucose challenge that are reproduced by exogenous stress hormone.

1. Introduction

A number of recent epidemiological studies have linked exposure to air pollution with metabolic disorders including insulin resistance, metabolic syndrome, and type 2 diabetes (Chen et al., 2013; Eze et al., 2015; Jiang et al., 2016a; Kramer et al., 2010; Thiering et al., 2013). Because of the ubiquitous exposure of the population, and the increasing global prevalence of metabolic disorders (Engin, 2017), impacts of air pollution on cardiometabolic diseases could represent a significant public health burden. Several plausible mechanisms have been advanced to explain how air pollutants may contribute to the pathogenesis of metabolic diseases (Liu et al., 2013; Rajagopalan and Brook, 2012; Thomson, 2014). Experimental models of acute exposure to ozone or particulate matter (Bass et al., 2013; Thomson et al., 2013; Vella et al., 2015) and chronic exposure to particulate matter (Sun et al., 2009) provide compelling evidence that pollutant exposure can acutely provoke systemic effects including impacts on metabolic homeostasis and in the longer term contribute to the acceleration of disease processes. However, there remains uncertainty regarding the nature and relative importance of underlying biological mechanisms, and how the various biological processes collectively contribute to the pathogenesis of metabolic disease.

Although there is considerable evidence to support a central role for inflammatory processes in metabolic dysfunction (Liu et al., 2013), several recent studies suggest that air pollutants need not necessarily produce proinflammatory effects to provoke insulin resistance or dysregulate glucose metabolism (Brook et al., 2013, 2016; Liu et al., 2017; Ying et al., 2016). We have previously shown that short-term exposure to ozone and particulate matter activates the hypothalamic-pituitary-adrenal (HPA) axis, resulting in increased circulating levels of the

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glucocorticoid corticosterone (Thomson et al., 2013). Pharmacological blockade of glucocorticoid synthesis prevented a subset of transcriptional responses in metabolic pathways across multiple organs, and effects of ozone exposure were reproduced by administration of corticosterone, establishing stress hormone involvement in downstream effects of ozone exposure (Thomson et al., 2016). Glucocorticoids are important regulators of glucose metabolism and insulin sensitivity, and chronic activation and dysregulation of the HPA axis can lead to metabolic dysfunction and disease (Bose et al., 2009; Chrousos and Kino, 2009). Evidence that ozone's ability to cause metabolic perturbations may be secondary to its effects on the HPA axis is therefore of interest in establishing plausible underlying mechanisms.

While there has been considerable interest in determining whether air pollutants contribute to the development and progression of metabolic diseases, little is known about how exposure to air pollutants may modify the response to glucose of biological systems implicated in energy homeostasis and inflammation. Abnormal responses of metabolic, endocrine, and inflammatory factors to exogenous glucose may serve as early indicators of pathogenic processes (Ahren, 2006; Corica et al., 2001; Esposito et al., 2002; Giugliano et al., 2008; Reynolds et al., 2003; Vossen et al., 2011); accordingly, examination of the effect of pollutants on responses of circulating factors to glucose may be useful in identifying effects and mechanisms that contribute to the development and progression of metabolic diseases. We have established an approach to monitor the responses of a variety of plasma factors during a glucose tolerance test (Pilon et al., 2017). In the present study, our objectives were to 1) determine whether exposure to ozone alters glucose tolerance in Fischer-344 rats, a common toxicological model for which we have previously characterised systemic effects of air pollutants (Thomson et al., 2013, 2016); 2) assess whether ozone inhalation modifies the metabolic, endocrine, and inflammatory response to exogenous glucose; and 3) test whether glucocorticoids are involved in observed effects. We found that ozone reduced glucose tolerance in Fischer rats and modified metabolic and endocrine impacts of glucose, with exogenous corticosterone administration reproducing effects of ozone exposure.

2. Methods

2.1. Animals

Specific pathogen-free male Fischer-344 rats (200–250 g) were obtained from Charles River (St. Constant, Québec, Canada). Animals were housed in individual plexiglass cages on wood-chip bedding under HEPA-filtered air and held to a 12 h dark/light cycle. Food and water were provided ad libitum until 2 h prior to inhalation exposures (6 h fast prior to glucose tolerance test). All experimental protocols were reviewed and approved by the Animal Care Committee of Health Canada.

2.2. Inhalation exposures

Rats were trained in whole-body chambers for 2 h/day for 3 days prior to inhalation exposures for acclimatization. One hour prior to ozone exposure, rats were administered vehicle (40% propylene glycol in buffered saline), 50 mg/kg body weight metyrapone, or 10 mg/kg body weight corticosterone by subcutaneous injection as previously described (Thomson et al., 2016). Inhalation exposures were conducted using clean air or 0.8 ppm ozone for 4 h in whole body chambers (n = 8/group with the exception of corticosterone group exposed to air where n = 6; Table 1). A silent arc generator (Erwin Sander, Uetze, Germany) made ozone from medical-grade oxygen. A feedback loop (Guenette et al., 1997) maintained a steady ozone concentration of 0.8 ppm (average 0.791 ppm) by measuring the ozone concentration (TECO model 49; CD Nova-Tech, Markham, Ontario) in the centre of the chamber and adjusting the ozone bypass flow mixing with the main airstream (400 lpm HEPA-filtered air). A slightly negative pressure (~ −0.5 mm water) was maintained by continuously removing air from the chamber.

Table 1
Experimental groups.

	Vehicle (n/group)	Metyrapone (n/group)	Corticosterone (n/group)
Air	8	8	6
Ozone	8	8	N/A

2.3. Glucose tolerance test

Glucose tolerance tests were conducted immediately following exposure. Blood glucose was measured prior to glucose administration (50% dextrose, Vétoquinol N.-A.Inc., Lavaltrie, Québec, Canada, 2 g/kg body weight via intraperitoneal injection), and then 30, 60, 90, and 120 min after administration using a OneTouch®Verio™IQ glucometer (LifeScan Canada Ltd., Burnaby, British Columbia, Canada). At each time point, approximately 200 μL of blood was collected from the tail vein with a heparinized needle and transferred to a BD plasma microtainer with plasma separator (BD, Mississauga, Ontario, Canada, cat# B365985). Tubes were centrifuged immediately and kept on ice until the end of the glucose tolerance test at which point plasma was aliquoted for future analyses and stored at −80C.

2.4. Plasma analyses

Insulin was analyzed using an ultra-sensitive rat enzyme-linked immunosorbent assay (ELISA) kit (Crystal Chem Inc., Downers Grove, IL, USA). Corticosterone was analyzed using the DetectX® ELISA kit (Arbor Assays, Ann Arbor, Michigan, USA). Triglycerides were analyzed using a colorimetric assay kit (Cayman Chemical Company, Ann Arbor, Michigan USA). Cytokine and metabolic hormone levels were analyzed by multiplexing glucagon, glucagon-like peptide (GLP)-1, ghrelin, leptin, plasminogen activator inhibitor (PAI)-1, tumour necrosis factor (TNF), interleukin (IL)-6, and vascular endothelial growth factor (VEGF) assays (Bio-Rad Laboratories (Canada) Ltd., Mississauga, Ontario, Canada) as previously described (Pilon et al., 2017). All analyses were conducted in duplicate.

2.5. Indices of insulin resistance, sensitivity and β-cell function

Surrogate indices of insulin resistance and β-cell function were calculated (Matthews et al., 1985) according to the following equations:

$$\text{HOMA} - \text{IR} = G_0 \times I_0/22.5 \text{ and HOMA\%}\beta = (20 \times I_0)/(G_0 - 3.5)$$

where G_0 and I_0 are fasting glucose (mmol/L) and insulin (μIU/mL) values, respectively.

The Quantitative Insulin Sensitivity Check Index (QUICKI) (Katz et al., 2000) was calculated as follows:

$$\text{QUICKI} = 1/(\log G_0 + \log I_0)$$

where G_0 and I_0 are fasting glucose (mg/dL) and insulin (μIU/mL) values, respectively.

The Matsuda Index (Matsuda and DeFronzo, 1999) was calculated according to:

$$\text{Matsuda} = 10,000/\text{sqrt}(G_0 \times I_0 \times \text{glucose mean (30–120 min)} \times \text{insulin mean (30–120 min)})^{0.5}$$

2.6. Statistical analyses

A generalized estimating equation (GEE) analysis was utilized to analyze the repeated measures data for each endpoint independently.

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