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How do glutathione antioxidant enzymes and total antioxidant status respond to air pollution exposure?

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ABSTRACT

This study aims to investigate how antioxidant enzyme activity and overall antioxidant capacity respond to short-term changes in exposure to air pollution. 201 participants were recruited before- and followed up during- and after- the 2008 Beijing Olympics. Serum levels of antioxidant enzymes including glutathione S-transferases (GST), glutathione peroxidase (GPx), glutathione reductase (GR), and total antioxidant status (TAS) were measured. We used linear mixed-effects models to compare changes in antioxidant enzymes across the three periods after adjusting for potential confounding factors. Among all participants, glutathione peroxidase (GPx) levels decreased by 12.0% when air pollution dropped by 50–60% during the Olympics and increased by 6.5% when air pollution levels rose after the Olympics. The magnitude of increase among males, smokers, and older individuals was relatively smaller compared to females, nonsmokers, and younger individuals. Among all participants, total antioxidant status (TAS) significantly decreased by 6.23% during the games and continued to decrease by 4.41% after the games. However, among females, nonsmokers, and younger participants, there was an increase in TAS response to the elevated air pollution levels. Our study observed strong responses in GPx and TAS levels to the short-term decrease and increase of air pollution levels and responses varied among subgroups.

1. Introduction[2]

The impact of air pollution on human health remains a critical worldwide concern. Epidemiologic studies have consistently identified air pollution to be associated with increased morbidity and mortality (Lodovici and Bigagli, 2011; Seaton et al., 1995). Various air pollutants, including fine and ultrafine particles, ozone, nitrogen oxides, polycyclic aromatic hydrocarbons and transition metals, can act as free radical initiators generating reactive oxygen species (ROS), which directly attack cellular DNA (Lodovici and Bigagli, 2011). Oxidative stress, which results from the imbalance of reactive oxygen species (ROS) generation and antioxidant enzymes, may induce damage of tissue, lipids, proteins, and nucleic acids, and therefore, plays a critical role in environment related diseases in humans including cancer, asthma, respiratory diseases, and arteriosclerosis (Lodovici and Bigagli, 2011).

When a cell sustains oxidative stress, antioxidants present in the cell respond to quench the reactive oxygen species (ROS). Phase I and II metabolic enzymes interact with foreign and toxic compounds in the body (Delfino et al., 2011; Sies, 1997), and therefore, are important for regulating the balance between the overproduction and destruction of ROS within the cell. Glutathione peroxidase (GPx), a key front line defense phase II enzyme, is responsible for breaking down hydrogen peroxide and additional peroxides into less toxic compounds, and reduces the formation of free hydroxyl radicals (Ceballos-Picot et al., 1996). Glutathione peroxidase (GPx) requires glutathione (GSH) as a co-factor producing glutathione disulfide (GSSG) as a product.

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[2] GST, glutathione S-transferases; GPx, glutathione peroxidase; GR, glutathione reductase; TAS, total antioxidant status; ROS, reactive oxygen species; GSSG, glutathione disulfide, PM, particulate matter.

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Glutathione reductase (GR) is responsible for the reduction of GSSG to glutathione (GSH), which is critical for maintaining glutathione levels and minimizing oxidative stress in cells (Carlberg and Mannervik, 1985). Glutathione S-transferases (GST), a large family of Phase II enzymes, use glutathione to detoxify xenobiotic substances to less toxic products that can be removed from the body (Sies, 1997). Among all antioxidant enzymes, GPx has been considered as the most important given its higher affinity to hydrogen peroxide compared to catalase, which also catalyzes hydrogen peroxide into water and oxygen (Baud et al., 2004; Davis and Uthus, 2003; Valko et al., 2006). Moreover, the treatment of using GPx-1 as a therapeutic target might have potential benefits for COPD patients against hydrogen peroxide and the peroxynitrite molecules from cigarette smoke-induced inflammation and emphysema (József and Filep, 2003; Vlahos and Bozinovski, 2013). In addition, it has been shown that deletion of the genes regulating glutathione enzyme activity influences the level of DNA adducts and development of cancer, specifically lung cancer (Nielsen et al., 1996).

Over the years, measures of total antioxidant status (TAS) have been developed to capture the collective effect of antioxidant defense capacity, including enzymatic and nonenzymatic systems (Fraga et al., 2014; Franco et al., 2007). Multiple antioxidant enzymes, as well as antioxidant vitamins and micronutrients, are thought to work in concert and interact with each other to maintain the balance of ROS; therefore, total antioxidant status (TAS) has been found to be a useful indication of antioxidant defense capacity (Emin et al., 2012).

To date, several published literature based on the Beijing Olympics have reported findings on inflammation and oxidative stress related biomarkers. These previous studies found responses in airway inflammation markers (fractional exhaled nitric oxide, FENO), respiratory and systemic stress markers (nitrate and nitrite in exhaled breath condensate), and DNA and lipid oxidative damage markers (8-hydroxy-2′–deoxyguanosine (8-OHdG) and urinary malondialdehyde (MDA)) (Huang et al., 2012; Lin et al., 2015; Rich et al., 2012). However, to our knowledge, none of the studies have measured the response of antioxidant enzymes and total antioxidant status markers.

Human epidemiological studies regarding antioxidant response to air pollution remain limited. In a study among elderly subjects with coronary heart disease, GPx-1 was inversely associated with $PM_{0.25}$ and $PM_{2.5–10}$ (Delfino et al., 2009). Another study in a rural Indian population found women exposed to biomass smoke had higher ROS production and lower total antioxidant status (TAS) compared to liquefied petroleum gas users (Mondal et al., 2010). Given the limited human research so far, additional epidemiologic studies are needed to further understand the role of antioxidants among human populations exposed to environmental pollutants.

Beijing is a heavily polluted city in China. This current analysis was based on a panel study conducted during the 2008 Beijing Olympics when there was a significant decline in air pollution levels and a later increase after the games (Mu et al., 2014). The current study hypothesizes that the antioxidant enzymes will respond to the drastic change of pollution levels during the three exposure periods.

2. Methods

2.1. Study design

This panel study was conducted during the 2008 Beijing Olympics and the details of the study design can be found elsewhere (Mu et al., 2014). Briefly, 201 participants, recruited from a community health service center in the Haidian district of Beijing, China, were interviewed during three visits: pre-Olympics (baseline), during-Olympics (1st follow-up), and post-Olympics (2nd follow-up). The study was approved by the Institutional Review Boards at the University at Buffalo and Peking University, China. Inclusion criteria included female and male participants ages 20 to 65 years old, of Han ethnicity, residing in the Haidian district for the past year, who did not have any prior chronic health conditions (Mu et al., 2014).

2.2. Data collection

During in-person interviews at each visit, participants completed questionnaires that collected information regarding social demographics, medical history, dietary and cooking habits, and occupational history. All the participants resided in the Beihang community of the Haidan district, which is a relatively small and closed community with an area of 0.27 km^2. During the study period, particulate matter concentration was measured with a mass monitor (Met One® 531 AEROCET Particulate Profiler, Met One Instruments, Inc. Grant Pass, Oregon) located in the center of the community of Beihang. The monitor was positioned in an open space close to a main road. The monitor was placed 1.5 m above the ground and recorded PM_1, $PM_{2.5}$, PM_7, PM_{10}, and total suspended particulates (TSP) in duplicate, along with temperature and relative humidity, twice a day at 10:00 a.m. and 4:00 p.m. Air pollutant measures were recorded every four days over the study period. The concentration range was up to 1 mg/m^3. The air pollution measurements were conducted on the dates of the blood sampling or 1–2 days before the blood sampling.

2.3. Blood collection

There were three waves of data collection among participants. The official period for the Olympic and Paralympics was from August 8, 2008 to September 17, 2008. Blood samples were collected 13–14 days before the Olympics (baseline), 29 days after the opening of the Olympics (first follow-up during the game), and 74 days after the last day of the Olympics (2nd follow-up).

The protocols were designed with oxidative stress metabolite analyses in mind to ensure the integrity and utility of the samples. All participants were asked to come for their visit without having breakfast. Participants were instructed to arrive at the center between 8 and 9 a.m. on the day of their interview. Prior to the physical examination, a blood sample was collected by a trained nurse under sterile and standardized conditions. All the samples were allowed to clot for 30 min at room temperature, separated by centrifugation and aliquoted before being stored in the freezer at -80 °C. The samples were kept from light throughout the process.

2.4. Antioxidant enzymes

Glutathione S-transferases (GST), glutathione peroxidase (GPx), and glutathione reductase (GR) enzymes were analyzed using an automated enzyme kinetic methodology adapted to the Cobas Fara II automated, centrifugal analyzer (Pippenger et al., 1998). Total antioxidant status (TAS) was analyzed with the Randox TAS kit adapted to the Cobas Fara II autoanalyzer. Using the TAS kit (Randox Laboratories, Kearneysville, West Virginia), ABTS (2,2′-Azino-di-[3-ethylbenzthiazoline sulphonate]) is incubated with a peroxidase (metmyoglobin) and H_2O_2 to produce the radical cation $ABTS^+$, which has a relatively stable blue-green color, and is measured at 600 nm. Antioxidants in the added sample cause suppression of this color production to a degree, which is proportional to their concentration (Miller et al., 1993).

2.5. Statistical analyses

Univariate analyses were performed to describe participant demographic information by age, sex, BMI, and smoking status among the 199 study participants (2 participants did not donate their blood samples). For continuous variables, means (SD) and their 95% confidence intervals were reported for GPx, GR, GST, and TAS. Categories were created based on their biological relevance and distribution: BMI < 24 kg/m2 and ≥ 24 kg/m^2 were based on the cut point for overweight status among Chinese and nonsmokers consisted of those