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ENVIRONMENTAL CHEMICALS INCREASING RISK OF OBESITY THROUGH EPIGENETIC MECHANISMS

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Abstract:

The obesity epidemic in the United States is often blamed on individuals for living sedentary, high-caloric lifestyles. However, people today who exercise and eat the same amount as those twenty years ago are still heavier. Furthermore, the epidemic has spread to pets, wild animals, and laboratory animals living near humans. These trends suggest that environmental factors may be contributing to the epidemic, and evidence has emerged that environmental pollutants can epigenetically reprogram metabolic processes and contribute to the development of obesity. Thus, this essay will first suggest that external factors are driving the obesity epidemic and provide emerging epidemiological and experimental evidence linking environmental pollution to obesity via epigenetic mechanisms. It will then analyze the socioeconomic and political implications of these findings. Due to the cumulative evidence presented in this paper, I argue that a One Health approach is needed to address obesity in the United States.

Keywords:

Epigenetics| One Health | Obesity epidemic | Environmental chemicals | Pollution Socioeconomics | Metabolic disease | Chronic disease

Introduction

From 1962-2010, the prevalence of obesity in adults over the age of 20 years has more than doubled in the United States, rising from 13.4% of the population to 35.7% of the population (NIDDK 2012). Furthermore, the prevalence of obesity in children between 2-19 years rose to 17% in the 1980s, and children are becoming obese at earlier ages (Ogden et al. 2012). The rise in obesity is concerning, because it is correlated with excess morbidity and mortality (NCHS 2016). To illustrate, obesity increases the risk of developing cardiovascular disease and cancer, which are both the leading causes of death in the United States (NHLBI 2012; Xu et al. 2016). Furthermore, the increase in childhood obesity corresponds with the increased prevalence of Type 2 diabetes, previously unheard of in children (Hurt et al. 2010; Kaufman et al. 2007). Although the obesity epidemic was previously confined to the United States and Europe, it has more recently become a global epidemic, and data shows that obesity is rising at the highest rate in developing countries (Caballero 2007).

Although obesity was previously blamed on individual lifestyle factors, such as increased caloric intake and decreased exercise, emerging evidence suggests that environmental factors are contributing to the epidemic through epigenetic mechanisms. Epigenetics refers to the alteration of DNA methylation patterns, the alteration of histone proteins around which DNA is packaged, and changes in the expression of non-coding RNA, all of which affect gene function and

expression, without modifying the DNA sequence. Previous studies have shown that environmental factors can modify the epigenome, especially during critical stages of development, and that these changes are heritable in future generations (Herrera et al. 2011). For example, evidence suggests that prenatal exposure to environmental chemicals such as polycyclic aromatic hydrocarbons (PAHs), bisphenol-A (BPA), and tobacco smoke, promote the development of obesity through epigenetic mechanisms (Perara and Herbstman 2011; CCCEH 2016). These chemicals are examples of what are becoming known as obesogens, since they act on the body at the cellular and molecular level to induce lipid accumulation and obesity in humans and animals (Chamorro-Garcia and Blumberg 2014).

This essay first introduces evidence suggesting that external factors are contributing to the obesity epidemic. It then discusses emerging evidence that prenatal exposure to environmental chemicals is contributing to the obesity epidemic through epigenetic mechanisms, focusing on tributyltin (TBT), PAHs, and dichlorodiphenyltrichloroethane (DDT) as examples of emerging obesogens. Finally, the socioeconomic and political implications of these findings are analyzed. The role of epigenetics in the obesity epidemic, combined with the political and socioeconomic implications of epigenetic research, provide evidence for the necessity of a One Health approach in addressing both the obesity epidemic as well as other chronic diseases in which epigenetic alterations are involved.

Results

Evidence that external factors are contributing to the obesity epidemic

A growing body of evidence in both humans and animals suggests that external factors, independent of individual lifestyle choices, are contributing to the obesity epidemic. For example, a statistical analysis, involving over 20,000 animals from 24 populations and 8 species, was conducted to track the percent weight gain per decade and changes in the odds of the animals being overweight over time. The analysis included animals in highly controlled settings, such as those used in studies conducted by the National Toxicology Program (NTP), as well as domestic and feral animals in less controlled settings living near humans. In all 24 populations, both body weight and the odds of being obese increased with time. The results were statistically significant in over half of the individual populations and highly significant when all the data was pooled together. For example, among control mice in the NTP, there was an 11.8% and 10.3% increase in body weight per decade in females and males respectively between 1982-2003 (Klimentidis et al. 2010). Similarly, among control rats, there was a 0.2% and 6% increase in body weight per decade in females and males respectively (Klimentidis et al. 2010). Although the surge in human obesity is attributed to increased calorie consumption and decreased physical activity, these factors were constant per decade in the animals involved in the analysis and cannot explain the rise of animal obesity, especially in controlled laboratory settings. The consistent rise in body weight among different species' in different environments suggests that its etiology involves other external causes such as epigenetic factors (Klimentidis et al. 2010).

Furthermore, another analysis in humans examined whether the relationship between caloric and macronutrient intake, physical activity, and obesity has changed over time between 1971-2008. The study found that people who ate and exercised a given amount twenty years ago had a lower BMI compared to people today who eat and exercise the same amount, and that this was the case for people on both a low and high calorie diet. Therefore, the study is consistent with the hypothesis that factors unrelated to lifestyle choices are contributing to the obesity epidemic, and

perhaps these factors are more prevalent today than they were twenty years ago (Brown et al. 2015). Due to consistent findings in both humans and animals that external factors are contributing to the obesity epidemic, research is being conducted regarding the role of environmental chemicals in promoting obesity, leading to the discovery that chemicals can epigenetically disrupt metabolic function in humans and animals.

Epigenetic and experimental evidence linking environmental pollution to obesity via epigenetic mechanisms

Emerging evidence has suggested that environmental chemicals can alter gene expression through epigenetic mechanisms by altering DNA methylation patterns, altering histone proteins around which DNA is packaged (Joss-Moore and Lane 2010), and by changing the expression of non-coding RNA (Svoboda and Flemr 2010). These mechanisms are processes in which chemicals interact with genes to alter the magnitude of their expression. Epigenetic modifications are common during the early stages of development, in which a variety of cell types are generated through the activation and deactivation of genes, and these expression profiles persist in each cell type throughout life. Thus, chemicals or other external stresses that modify the epigenome during critical stages of development can induce permanent changes in the expression profile of genes, and the epigenetic dysregulation that results is associated with adult disease later in life (Perara and Herbstman 2011). Furthermore, epigenetic changes appear to be heritable, and pollutants can interfere with the epigenetic programming process and increase disease risk in F1, F2, and F3 generations (Perara and Herbstman 2011). To demonstrate that environmental chemicals can disrupt epigenetic processes during development and promote obesity later in life, three endocrine disrupting chemicals (EDCs), TBT, PAHs, and DDT will be discussed as case studies.

Epigenetic mechanisms by which TBT promotes obesity

TBT is a highly toxic chemical used in industrial paints, toilet and carpet cleaners, as a pesticide additive, and as a wood preservative (CCCSD 2009). A recent study found that prenatal exposure to TBT is associated with increased rodent body weights (Kirchener et al. 2010), and another study showed that the effect was transgenerational (Chamorro-García et al. 2013). TBT is a ligand for the nuclear receptor PPAR-γ, and thus it can bind with the receptor and recruit cellular complexes that directly modify the methylation patterns of PPAR-γ and other genes in its signaling pathway. By modifying the methylation patterns of genes involved in the PPAR-γ pathway, TBT can change their relative expression. During development, the relative expression of PPAR-γ- induced genes determines whether mesenchymal stem cells will differentiate into bone cells or fat cells. Thus, depending on the extent to which PPAR-γ is expressed, the body could be predisposed to favor fat accumulation (Stel et al. 2015). The hypothesis that TBT modifies the methylation patterns of genes involved in the PPAR-γ pathway was examined in a separate, in vitro study, which found that TBT exposure to pre-fat mouse cells resulted in increased fat cell accumulation and decreased global DNA methylation. (Sales et al. 2013). Another study found that TBT exposure was associated with decreased methylation in the promoter region of the PPAR-γ target gene, *Fapb4,* and an increase in PPAR-γ mRNA levels (Stel et al. 2015). Despite the experimental evidence that the obesogenic effects of TBT are at least in part mediated by changes in methylation of PPAR-γ and its target genes, the exact mechanism has not been determined, and the association between TBT exposure and obesity has not been tested in humans.

Epigenetic mechanisms by which PAHs promote obesity

Another class of chemicals shown to induce similar epigenetic modifications are PAHs. PAHs make up a group of over 100 chemicals formed during the incomplete combustion of coal, oil, tobacco, charbroiled meat, and other organic substances. They are typically present as a mixture, and people are exposed by breathing contaminated air or eating grilled foods (ATSDR 2016). A recent epidemiological study followed a group of African-American and Hispanic pregnant mothers living in the Bronx or Northern Manhattan, New York. The cohort of women underwent personal air monitoring during their day to day lives to measure the extent to which they were exposed to PAHs during pregnancy. Their children were then measured for obesity-related endpoints. After the confounding factors were adjusted, including socioeconomic status, prenatal exposure to ambient PAHs predicted higher BMI score and obesity in the children at age 5 years. Furthermore, increased PAH exposure led to a higher fat mass, BMI score, and obesity in the same children at age 7 years (Rundle et al. 2012).

Studies have proposed that prenatal PAH exposure increases the risk of developing obesity by altering DNA methylation patterns and activating PPAR-γ (Herbstman et al. 2012; Yan et al. 2014). A study examining the effect of prenatal PAH exposure in pregnant rats found that greater prenatal PAH exposure was associated with increased weight, fat mass, adipose gene expression, and epigenetic changes in their progeny. For instance, prenatal PAH exposure was associated with decreased methylation of the PPAR-γ promoter, and greater expression of PPAR-γ and other genes that regulate adiposity. Thus, the methylation levels of the PPAR-γ promoter were negatively correlated with gene expression in this study, which was consistent with other studies that have found that the PPAR-γ promoter region is demethylated during adipogenesis of 3T3L1 cells (Yan et al. 2014). These findings were consistent with another study looking at the epigenetic mechanism of PAH induced obesity in humans, which found that PAH exposure was sufficient to decrease global DNA methylation in the study population (Herbstman et al. 2012).

Epigenetic mechanisms by which DDT promotes obesity

DDT was developed as the first modern synthetic insecticide in the 1940s and widely used for malaria control and crop production. It was banned in the United States in 1972 due to its environmental persistence and adverse reproductive effects in humans and animals (EPA 2015). However, the breakdown product of DDT, DDE, is highly persistent in the environment and thus is still present in the environment, animals, and humans worldwide, especially in heavy agricultural areas where DDT was extensively sprayed (Cox et al. 2007). Furthermore, the World Health Organization still recommends DDT for malaria control in developing countries (La Merrill et al. 2014).

The role of prenatal exposure to DDT in the development of obesity has been examined in multiple studies. Several longitude birth cohort studies in Europe found a positive association between prenatal DDT and DDE exposure and BMI in children ages 1-7 years. However, this association was not seen in the United States or Mexico. A recent report used data from the CHAMACOS study, a longitudinal birth cohort of pregnant mothers living in the agricultural Salinas Valley (Warner et al. 2014). The mothers involved in this cohort were measured for exposure to pesticides and other environmental chemicals, and their children were evaluated for associated adverse health effects (CERCH 2012). Although no association was found between DDT exposure and obesity in the children ages 2-7 years, the results trended toward a positive association as the children aged. A significant association was observed in boys by the age of 9 years, in which higher

prenatal DDT and DDE exposure was associated with greater BMI, waist circumference, and overweight and obesity status. In contrast, there was no association in girls (Warner et al. 2014). A separate meta-analysis, conducted to estimate the probability of causation of EDC exposures in the European Union on obesity and diabetes, concluded that the toxicological evidence for DDE-attributable childhood obesity was moderate, and that the probability of causation was between 40%-60% (Legler et al. 2015). In addition, DDT has been shown to increase adiposity in female mice. To illustrate, a study found that perinatal DDT exposure resulted in impaired energy expenditure and metabolism in female mice. Furthermore, genes involved in these processes were expressed at different levels than the controls, suggesting the involvement of epigenetic mechanisms. The concentration of DDT used in this study was the same as the concentration of DDT found in maternal blood samples of people living in the United States (La Merrill et al. 2014).

Finally, epigenetic changes have been associated with DDT exposure. For instance, a study was conducted on the relationship between plasma persistent organic pollutant (POP) concentration and global DNA methylation. The study was conducted in the Greenlandic Inuit population, who are heavily exposed to POPs. The results showed that plasma levels of DDE and DDT were inversely associated with global DNA methylation levels (Rusiecki et al. 2008). A similar study was conducted in a Korean population, to examine whether these results would extend to populations with lower POP plasma levels. The results were consistent and demonstrated that low-level POP exposure, including DDT, was associated with global DNA hypomethylation (Kim et al. 2010).

This essay focuses on the epigenetic mechanisms by which prenatal exposure to TBT, PAHs, and DDT promote the development of obesity later in life. However, it should be noted that prenatal exposure to other persistent environmental chemicals, including tobacco smoke (Perara and Herbstman 2011), BPA (Hoepner et al. 2016 and Rubin et al. 2001), and other ubiquitous chemicals found in the environment are associated with the development of obesity, and the epigenetic mechanisms by which this occurs are under investigation.

Discussion

The socioeconomic and political implications of epigenetic research

Over the past few years, the field of epigenetics has rapidly expanded. For instance, North American and European funding agencies have launched epigenomic projects, universities have developed departments and research groups devoted to epigenetic research, journals have been created, and thousands of publications have resulted (Landecker and Panofsky 2013). However, the focus of the research has thus far been confined to the biomedical world, in which the goal is to develop therapeutics that could reverse epigenetic changes from prenatal exposure to environmental chemicals or other external factors that may perturb the epigenome and lead to disease (Dupras et al. 2014). However, the therapeutic approach primarily benefits businesses who can now utilize epigenetics as a market niche, which is already seen on the labels of nutritional supplements that claim to enhance the epigenome. In contrast, it does little to address the core problem regarding the environmental chemicals at fault for inducing the epigenetic changes (Meloni and Giuseppe 2014).

The evidence that environmental chemicals are contributing to the obesity epidemic through epigenetic mechanisms brings salience to the question of where the responsibility of health should lie: whether it be the individual, the community, or both. At present, the responsibility of avoiding exposures that may induce epigenetic alterations is placed on

individuals; an unfair burden for pregnant mothers who are told that their actions and exposures are altering the epigenome to promote disease in their children (Landecker 2013). There is too little discussion in epigenetic research regarding the limits of individual responsibility and the need for community and societal responsibility to take precedence.

To illustrate, pollution is disproportionately distributed in the United States. Among other factors, poor neighborhoods suffer from a disproportionate number of polluting factories, food deserts and lack of housing infrastructure. Thus, environmental chemicals that are inducing epigenetic changes are disproportionately concentrated in underserved populations (Dupras et al. 2014). For instance, the mothers in the CHAMACOS cohort were primarily Mexican-borne, low-income, farmworkers. Thus, they are disproportionately burdened by pesticides and their children bear the legacy of persistent pollutants, such as DDT, that were sprayed decades earlier. The number of obese Mexican-American children in the United States is significantly greater than the number of obese non-Hispanic white and black children (CERCH 2012). Furthermore, a survey found that 53.3% of Mexican-American children living in California are obese, while only 14.9% of children living in Mexico are obese (CERCH 2012). The fact that prenatal exposure to DDT leads to epigenetic changes that promote obesity, combined with the high rate of obesity in this population, raises environmental justice concerns. It also raises ethical concerns as future generations are harmed by companies that emit large scale pollutants into disadvantaged communities.

The necessity of a one-health approach in epigenetic research

The One-Health model for addressing disease was first introduced as an interdisciplinary approach for addressing zoonotic diseases. It called for collaboration among professionals from numerous disciplines, such as medical doctors, veterinarians, and environmental scientists, to work together in preventing zoonosis. The initiative has since expanded to address other pressing health issues, such as food insecurity and antimicrobial resistance (Paul and Gibbs 2014). This interdisciplinary approach ensures that all angles of a public health threat are examined. The findings that prenatal exposure to environmental chemicals is inducing epigenetic changes that predispose infants to developing obesity later in life necessitates a one-health approach in epigenetic research. While life scientists currently dominate the field of research, their goal is centered on therapeutic intervention, and there is little being done to address the political and social implications of their research. Thus, sociologists are slowly finding a niche within the epigenetic conversation, as epigenetics research presents a unique situation in which molecular changes result from behavior manifested from social, cultural, and political decisions (Landecker 2013). Furthermore, the field of bioethics is entering the conversation and trying to shift responsibility away from the individual and toward society and industry. A review of the bioethics of epigenetics suggests that epigenetics has veered the rationale away from looking at the environment as an external factor, to recognizing the dynamic relationship between humans and the environment (Dupras et al. 2014). One Health approaches that acknowledge the role in which environmental chemicals are contributing to the obesity epidemic could integrate the epigenetic findings from biomedical research with their social and political implications. This multidisciplinary approach would shift intervention strategies away from individual responsibility, and toward a conversation that centers on the societal responsibility to reduce chemical exposures and take responsibility for the health of future generations.

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