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Impact of Nutrition on Pollutant Toxicity: An Update with New Insights Into Epigenetic Regulation

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Review

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Abstract: Exposure to environmental pollutants is a global health problem and is associated with the development of many chronic diseases, including cardiovascular disease, diabetes and metabolic syndrome. There is a growing body of evidence that nutrition can both positively and negatively modulate the toxic effects of pollutant exposure. Diets high in proinflammatory fats, such as linoleic acid, can exacerbate pollutant toxicity, whereas diets rich in bioactive and anti-inflammatory food components, including omega-3 fatty acids and polyphenols, can attenuate toxicant-associated inflammation. Previously, researchers have elucidated direct mechanisms of nutritional modulation, including alteration of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling, but recently, increased focus has been given to the ways in which nutrition and pollutants affect epigenetics. Nutrition has been demonstrated to modulate epigenetic markers that have been linked either to increased disease risks or to protection against diseases. Overnutrition (i.e. obesity) and undernutrition (i.e. famine) have been observed to alter prenatal epigenetic tags that may increase the risk of offspring developing disease later in life. Conversely, bioactive food components, including curcumin, have been shown to alter epigenetic markers that suppress the activation of NF-κB, thus reducing inflammatory responses. Exposure to pollutants also alters epigenetic markers and may contribute to inflammation and disease. It has been demonstrated that pollutants, via epigenetic modulations, can increase the activation of NF-κB and upregulate microRNAs associated with inflammation, cardiac injury and oxidative damage. Importantly, recent evidence suggests that nutritional components, including epigallocatechin gallate (EGCG), can protect against pollutant-induced inflammation through epigenetic regulation of proinflammatory target genes of NF-κB. Further research is needed to better understand how nutrition can modulate pollutant toxicity through epigenetic regulation. Therefore, the objective of this review is to elucidate the current evidence linking epigenetic changes to pollutant-induced diseases and how this regulation may be modulated by nutrients allowing for the development of future personalized lifestyle interventions.

Keywords: anti-inflammatory nutrients; antioxidant response; environmental pollutants; epigenetics; nutrition.

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Introduction

The levels of environmental pollutants continue to rise worldwide, despite our increasing knowledge base of the negative health effects of pollutant exposure. There is increasing evidence that exposure to pollutants, including persistent organic pollutants (POPs), heavy metals and air pollution, can contribute to the progression of chronic diseases such as cardiovascular disease (CVD), diabetes and cancer. Currently, the strongest evidence linking POPs with inflammatory diseases is related to pollutant-induced diabetes (1, 2). Multiple meta-analyses show positive associations of exposures to POPs such as polychlorinated biphenyls (PCBs) and pesticides with increased risk of developing type 2 diabetes (1, 2). The health effects of pollutant exposure not only pose a problem for the individual but also contribute to the global burden of disease.

The mechanisms by which many of these pollutants contribute to disease involve an increase in cellular oxidative stress and subsequent inflammatory responses. For example, coplanar PCBs, a class of POPs, increase downstream inflammatory responses by binding to the aryl hydrocarbon receptor,

which can upregulate the transcription of cytochrome p450 (Cyp1a1) (3, 4). Cyp1a1 is primarily involved in xenobiotic detoxification; however, in the presence of certain PCBs, it results in the production of reactive oxygen species (ROS) via an uncoupling mechanism (5). This production of ROS yields an increase in oxidative stress because of the imbalance in the cellular redox status (4). This pro-oxidative cellular status contributes to a state of chronic inflammation, which is a hallmark of many diseases, including atherosclerosis, diabetes and other metabolic disorders (6).

The most common routes of exposure to these environmental pollutants are through inhalation of airborne pollutants as well as ingestion of contaminated foods (7). POPs, including PCBs and organochloride pesticides, are lipophilic and therefore readily accumulate in the tissue of living animals (8). Although the production of many of these pollutants has been banned, their resistance to degradation and stability in the environment have allowed for their bioaccumulation throughout the ecosystem (8). Additionally, in humans, the accumulation of these lipophilic pollutants over the course of many years can lead to the activation of inflammatory pathways contributing to the development of numerous chronic inflammatory diseases (9, 10). Obesity is linked to higher pollutant body burden, but there is no consensus if obesity makes a person more or less susceptible to pollutant-induced disease. Interestingly, there is some experimental evidence that points to the sequestration of pollutants in large adipose depots as actually being protective (11–13). Lipophilic pollutants may accumulate within adipocytes and lipid droplets, which limits their availability to other target cell types. Importantly, it appears that obese individuals undergoing weight loss through either bariatric surgery or lifestyle intervention may be a highly susceptible population to pollutant-induced inflammation (11–13). Because overweight and obese individuals are not only capable of accumulating greater levels of pollutants but also already at an increased risk for developing chronic inflammatory diseases, dietary interventions that provide a means of combatting pollutant toxicity and chronic disease risk factors are of great importance. (8, 14, 15).

Nutrition as a modulator of pollutant toxicity

Poor nutrition can exacerbate the toxicity of pollutants

It is well established that exposure to environmental pollutants can increase risk of developing chronic inflammatory diseases, including CVD, diabetes, and metabolic syndrome (6–9). Additionally, evidence implicates that individuals with a less nutritious or healthful diet (i.e. rich in processed foods and low in fruits and vegetables) are also at a greater risk of developing these same chronic diseases (16). Common to both pollutant exposure and poor nutrition is the activation of proinflammatory molecular proteins, including NF-κB, a key player in the development of inflammatory responses (17). Because of the overlap between pathways that mediate the negative effects of poor nutrition and environmental pollutants, there is an increasing body of experimental evidence demonstrating that certain nutritional components or overall nutritional status can exacerbate the negative health effects of environmental pollutant exposure.

Obesity is a global health problem and is a risk factor for the development of numerous inflammatory diseases (18). The rise in obesity is often attributed to overconsumption of processed, nutritionally poor foods (i.e. high energy density and low nutrient density) and foods high in proinflammatory fats (18). It has been consistently demonstrated that high fat diets, particularly those with greater proportions of fatty acids coming from saturated, trans, and linoleic fatty acids can increase inflammation and risk of CVD as well as other metabolic complications (19, 20). In addition to overconsumption of nutritionally poor foods, emerging evidence now links exposure to environmental pollutants with increased adiposity and weight gain (21). Pollutants that elicit this physiological effect are termed “obesogens” and are believed to contribute to obesity and metabolic disorder through promotion of chronic imbalances in lipid storage mechanisms and adipocyte hyperplasia (21). Current evidence suggests that pollutant exposure can intensify the detrimental effects of a proinflammatory high-fat diet (22). For example, non-alcoholic fatty liver disease (NAFLD), commonly seen in developed countries as a hepatic indicator of obesity and metabolic syndrome, may be worsened by pollutant exposure. It has been demonstrated that the pollutant PCB153 exacerbates diet-induced obesity and NAFLD in mice through alterations in adipokines and disruptions in hepatic lipid metabolism (23). Additionally, high-fat diets appear to worsen arsenic-induced liver fibrosis and inflammation (24), whereas diets high in saturated fat appear to increase the toxicity and carcinogenic effects of POPs (25). Furthermore, the flame retardant hexobromocyclododecane, was observed to enhance high-fat diet-induced obesity and hepatic steatosis and to impair glucose and lipid homeostasis in mice (26).

Cardiovascular diseases (CVDs) are the leading cause of death worldwide, and it is estimated that approximately 90% of CVDs can be prevented (27). The primary modifiable risk factors contributing to the development of CVDs include poor dietary habits, physical inactivity, and smoking (27). Similarly, to the development of obesity, diets containing certain fatty acid profiles may promote the development of CVDs. For example, consumption of proinflammatory fatty acids such as linoleic and trans-fatty acids can contribute to endothelial cell dysfunction, a beginning stage of atherosclerosis (19, 20). Additionally, it has been demonstrated, primarily in experimental models, that exposure to environmental pollutants can cause endothelial cell dysfunction and chronic inflammation and may contribute to the development of CVDs (3, 28, 29). Furthermore, there is increasing experimental evidence that poor nutrition and pollutant exposure can interact and synergistically increase CVD risk (30). For example, it has recently been shown that trimethylamine N-oxide (TMAO), produced from the metabolism of dietary carnitine or phosphatidyl choline, is a strong clinical biomarker of CVD (31–35). Interestingly, a recent preclinical paper from our group found that dioxin-like pollutant exposure increases the hepatic expression of the enzyme flavin-containing monooxygenase (*FMO3*), which is critical for the production of TMAO. As such, this increase in the hepatic expression of *FMO3* resulted in increases in circulating TMAO (36). Although this study was conducted in mice and the transcriptional regulation of *FMO3* could differ in humans, this finding is important in that it provides new evidence on how certain nutritional components and pollutants may interact to contribute to a greater risk of CVD.

It is not surprising that pollutant exposure exhibits detrimental combinatory effects with suboptimal nutrition as pollutants and nutritional components can target the same molecular pathways, for example, the proinflammatory NF-κB pathway (4). However, this same idea can be used from the perspective of nutrition as a protective modulator of pollutant toxicity and may be more meaningful for those already exposed to high levels of pollutants and exhibiting signs of chronic inflammatory diseases.

Healthful nutrition can protect against the health effects of pollutant exposure

It is well understood that a nutritious diet, rich in foods containing bioactive food components such as polyphenols and anti-inflammatory fatty acids, can be protective against chronic inflammation, diabetes, metabolic syndrome, and CVD (16). Diets rich in these bioactive food components often contain greater levels of antioxidant and anti-inflammatory compounds and thus have the capacity to attenuate the inflammatory and oxidative properties of pollutant exposure. This paradigm has been demonstrated consistently throughout the literature (37–43). For example, we have shown that consumption of polyphenol-rich green tea can decrease oxidative stress in response to PCB 126 exposure and does so via upregulation of antioxidant enzymatic pathways (38). Additionally, it has been observed that epigallocatechin gallate (EGCG), a major polyphenol in green tea, can attenuate arsenic-induced cardiovascular inflammation and toxicity (42). Resveratrol, a polyphenol found abundantly in fruits and other plants, has been demonstrated to protect against PCB-induced neuronal cell death as well as impairment in adipocyte glucose homeostasis (44, 45).

Omega-3 polyunsaturated fatty acids, including eicosapentaenoic acid and docosahexaenoic acid, found abundantly in fatty fish and fish oil, exhibit potent anti-inflammatory properties (46, 47). Indeed, individuals consuming a diet abundant in omega-3 fatty acids, such as the well-studied Mediterranean diet, are documented as having lower incidences of CVD, diabetes, and metabolic syndrome (48). It is not surprising then, that experimental evidence shows that omega-3 fatty acids can be protective against pollutant-induced inflammation and toxicity. As such, we have demonstrated that omega-3 fatty acids can protect against PCB-induced vascular endothelial cell dysfunction (37), and others have shown that these fatty acids can protect against pollutant-associated atherosclerotic plaque formation (49). Additionally, omega-3 fatty acids appear to be protective against air pollutant-associated oxidative stress and cardiovascular complications by increasing the activity of endogenous antioxidants and decreasing lipoperoxidation (40, 43).

In addition to consuming a diet rich in polyphenols and anti-inflammatory components, choosing to live an active lifestyle may also protect against pollutant toxicity. For example, a recent study by our laboratory observed that exercise is capable of reducing inflammation and CVD risk associated with PCB exposure (50). Furthermore, other groups have demonstrated that exercise can attenuate PCB-associated alterations in the mouse gut microbiome (51). This is an important finding because the gut microbiome has recently been observed to regulate numerous health conditions, including obesity, CVD, immune function, and neurological disorders (52–54). Importantly, the gut microbiome is incredibly plastic and can change rapidly in response to nutrition, exercise,

and even pollutant exposure (52–54). Using nutrition and exercise to combat pollutant-induced alterations in the gut microbiome that may contribute to disease may allow for important advances in therapeutic interventions and is a critical area of research that needs to be further explored.

Because many of these environmental pollutants are lipophilic and accumulate within the adipose tissue of exposed individuals, examining nutritional means to promote the excretion and reduction of body burden is an important facet as well. It has been noted that individuals consuming a vegetarian or vegan diet trended towards lower amounts of organochloride body burden (55). However, it remains unclear whether this observation was due to less exposure to contaminated foods (e.g. contaminated meats, fish, or dairy) or whether a plant-based diets contain nutritional components that can promote excretion of these pollutants. Although further research is still warranted to examine nutritional means by which to reduce pollutant body burden, some studies have indicated promising opportunities for therapeutic interventions in exposed individuals (56–58). Specifically, it has been observed that consumption of olestra, a dietary fat substitute, is effective at enhancing the excretion rate in individuals exposed to high concentrations of PCBs and is believed to do so through interference with the enterohepatic circulation of these pollutants (58–62). Because olestra is no longer in production due to decreased popularity associated with adverse gastrointestinal side effects, there is a need for research examining other dietary components that may alter enterohepatic circulation and/or enhance pollutant excretion. As discussed, it is well documented that nutrition and lifestyle choices can both positively and negatively regulate pollutant toxicity. Recently, the field of epigenetics has become important in furthering our understanding how environment and lifestyle choices differentially influence gene expression and may alter susceptibility to disease on an individual level.

Epigenetics as an emerging area of pollutant toxicity research and avenue for future intervention

Epigenetics overview

Epigenetics is a term given to describe all heritable changes in gene expression that do not involve changes within the genetic code (63). One of the most commonly studied means of epigenetic modifications is DNA methylation, which involves the addition of a methyl group to the five position of a cytosine. This modification most often occurs on a cytosine-guanine dinucleotide (CpG). CpG dinucleotides tend to be clustered in certain regions, termed CpG islands, and are often located in the promoter regions of protein-coding genes (63, 64). DNA methylation is involved in the regulation of numerous cellular processes, ranging from chromosome stability, to X-chromosome inactivation, to gene transcription. Generally, the hypermethylation of CpG islands within the promoter regions results in gene silencing. Another common type of epigenetic alteration includes histone modifications. Histones are nuclear proteins that aid in the condensation of DNA into structural units called nucleosomes. Histones can undergo posttranslational modifications such as acetylation, methylation, and phosphorylation, which affect the interactions of histones with the DNA and associated nuclear proteins (63). Through these histone modifications, alterations in chromatin structure and subsequently gene expression are often observed (63, 64). A third major type of epigenetic modification involves microRNAs (miRNAs). miRNAs are small single-stranded noncoding RNA molecules that when fully mature lead to the degradation of target mRNA by direct binding. This downregulation of target mRNAs can ultimately lead to decreased protein production. miRNAs regulate numerous biological processes, and it has been observed that alterations in miRNA expression are associated with the development of diseases such as CVD, metabolic disorders and cancer (63–65).

Environment and lifestyle play critical roles in contributing to the epigenetic alterations discussed above (65). Studies on monozygotic twin pairs have demonstrated that throughout the aging process, identical twins develop differences in their epigenetic status despite their common genetic makeup (63). These observations and the knowledge that differences in epigenetic modifications can play a role in disease contributed to increasing interest in examining the ways and extent to which our environment influences our epigenetic code.

Epigenetics, environmental exposures and nutrition

It has been consistently demonstrated that exposure to environmental pollutants can influence epigenetic modifications (65–69). Specifically, exposure to POPs can alter the epigenetic code through several mechanisms. For example, we have demonstrated that exposure to coplanar

PCBs, including PCB 77 and PCB126, can induce vascular endothelial cell dysfunction and inflammation through alterations in histone modifications of the p65 subunit of NF-κB that result in its increased activation (66). Additionally, we have shown that the commercial PCB mixture Aroclor 1260 can upregulate miRNAs associated with cardiac injury and inflammatory pathways in primary human endothelial cells (69). In humans, it has been observed that exposure to polyaromatic hydrocarbons (PAH) results in alterations in specific miRNAs associated with oxidative DNA damage and lipid peroxidation in coke oven workers (67). Moreover, it was noted that exposure to air pollution was associated with expression of miRNAs that may mediate detrimental biological responses and health effects (68).

One common theme with many pollutant-associated epigenetic alterations is that they induce modifications that contribute to proinflammatory and oxidative pathways (65, 70). Interestingly, nutrition and positive lifestyle choices can also contribute to epigenetic modifications that may combat these detrimental effects by increasing antioxidant and anti-inflammatory responses (71, 72). Polyphenolic compounds found in many fruits and vegetables exhibit significant antioxidant and anti-inflammatory capacities and thus are good candidates for studies examining epigenetic means of protection against pollutant toxicity. For example, curcumin, a component found in turmeric that exhibits anti-inflammatory properties, has been observed to reduce histone acetylation of the *NF-κB* coactivator p300 histone acetyltransferase and thus suppress the activation of NF-κB (73). Similar results were observed by our group with the tea catechin EGCG (74). Furthermore, it has been reported that numerous polyphenols can activate SIRT1, a member of the sirtuin family of histone deacetylases. When activated, SIRT1 can participate in the deacetylation of transcription factors such as NF-κB, forkhead box class O (FoxO) and p53, in turn modulating cellular pathways involved in inflammation, metabolism, aging, and several other conditions (71).

In addition to healthful nutrition, physical exercise also contributes to epigenetic modifications that may provide protection against metabolic, cardiovascular, and other diseases. For example, one study found that acute exercise resulted in changes in the methylation of the promoter region of genes involved in energy and glucose homeostasis, including pyruvate dehydrogenase kinase isoenzyme 4 (*PDK4*), peroxisome proliferator-activated receptor gamma coactivator 1-alpha (*PCG1α*), and peroxisome proliferator-activated receptor delta (*PPARδ*) within skeletal muscle (75). Furthermore, physical exercise was observed to inhibit the miRNA miR-33 (76, 77). Cellular effects of miR-33 inhibition involve the upregulation of *AMPK* and subsequent increases in β-oxidation, which may aid in balancing factors related to metabolic syndrome by increasing the breakdown of fatty acids from adipose stores (77). The role of β-oxidation in metabolic syndrome is complex and is influenced by both dietary components and exercise, leading to an increase in fatty acid oxidation and ultimately decreased obesity and metabolic syndrome (78–80). Understanding the role of miRNAs in lipid homeostasis may provide potential therapeutic strategies for reducing metabolic syndrome.

Although epigenetics can be modulated by healthful nutrition and positive lifestyle choices, there is also evidence that epigenetics can be modified by poor nutrition. Epidemiological data are very helpful at examining epigenetic alterations, as there appears to be inheritance to specific DNA methylation patterns over generations. For example, it has been shown that individuals who were prenatally exposed to famine during the Dutch famine (1940s) had reduced DNA methylation of the insulin-like growth factor II (*IGF2*) gene six decades later, compared to their siblings who were unexposed to the famine (81). Also, it has been demonstrated that parental obesity can alter DNA methylation patterns in imprinted genes of their offspring, compared to offspring of nonobese parents, and this is believed to increase the risk for the development of obesity and metabolic diseases later in life (82). Although there is still much to be studied about the effects of these alterations related to epigenetic modifications, it is hypothesized that in both cases of undernutrition and over-nutrition, the acquired epigenetic alterations may be passed down to the subsequent generation and may increase susceptibility to development of chronic diseases throughout life (81–83).

The epigenetic alterations in response to nutrition and lifestyle choices have been well documented; however, studies examining the epigenetic effects of nutritional components on the modulation of pollutant toxicity are limited. A recent study conducted by our group showed that EGCG, the most abundant polyphenol found in green tea, can prevent against PCB126-induced endothelial cell inflammation through epigenetic alterations of proinflammatory target genes of NF-κB (74). This study was important in that it was one of the first studies to indicate the epigenetic role of healthful nutrition in the modulation of pollutant toxicity. Because of the gaps in the literature regarding epigenetic regulation of pollutant toxicity via nutritional and lifestyle interventions, there is a great need for further research to formulate a better understanding of this topic.

Conclusion and future directions

Environmental pollutant exposure is associated with numerous health complications ranging from cardiovascular disease, diabetes, and metabolic syndrome. There is evidence that pollutant toxicity can be modulated by nutrition and lifestyle choices. Western diets, abundant in processed foods, excess caloric content and proinflammatory fatty acids, may contribute to the development of obesity and, cardiovascular diseases and can enhance pollutant toxicity. Conversely, diets rich in bioactive food components, such as polyphenols and omega-3 fatty acids (i.e. the Mediterranean diet), are associated with reduced risk of inflammatory diseases and can attenuate the negative health effects of pollutant exposure. Recently, epigenetics has become a focus of both nutrition and pollutant research and may provide a deeper mechanistic insight into how these two environmental factors can interact. It has been shown that both over- and undernutrition can contribute to epigenetic modifications that are associated with an increased risk of disease. Additionally, exposure to pollutants can alter epigenetic markers that may also contribute to the development of health complications. Importantly, we have shown that bioactive food components (e.g. EGCG) can induce epigenetic alterations that attenuate inflammatory responses associated with PCB exposure and thus may protect against the development atherosclerosis. Epigenetic marks differ for every individual, and therefore future studies may allow us to understand how certain foods may be used to alter specific epigenetic tags to reduce the risk of pollutant-associated disease. Future studies also need to focus on metabolites of both pollutants and nutrients and the complex interplay of epigenetic regulation of chronic diseases. Fostering an understanding at this detailed level could help in developing personalized nutritional interventions that could epigenetically favor good health and thus reduce the risk of disease.

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