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Review

Effects of environmental pollutants on gut microbiota☆

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ABSTRACT

Environmental pollutants have become an increasingly common health hazard in the last several decades. Recently, a number of studies have demonstrated the profound relationship between gut microbiota and our health. Gut microbiota are very sensitive to drugs, diet, and even environmental pollutants. In this review, we discuss the possible effects of environmental pollutants including antibiotics, heavy metals, persistent organic pollutants, pesticides, nanomaterials, and food additives on gut microbiota and their subsequent effects on health. We emphasize that gut microbiota are also essential for the toxicity evaluation of environmental pollution. In the future, more studies should focus on the relationship between environmental pollution, gut microbiota, and human health.

1. Introduction

Recently, we have come to appreciate the tremendous volume and variety of microbiota harbored in the human gut and how critical microbiota is to our health. Collectively, gut microbiota genomes encode more than 3.3 million genes, making the microbiome genome approximately 150 times larger than human genome (Qin et al., 2010). Thousands of species are found in the gut microbiome, and the majority of these species belong to six bacterial phyla: Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, Fusobacteria, and Verrucomicrobia (Eckburg et al., 2005). Gut microbiota are highly dynamic and have substantial interindividual and intraindividual variation. People with different genotypes, geographic locations, lifestyles, and ages have distinct gut microbiota, and microbiomic differences even exist between monozygotic twins (Yatsunenko et al., 2012; Goodrich et al., 2014). Microbiomic differences begin to emerge after we are born. An infant is inoculated with microbiota immediately after delivery, the microbiome changes dramatically during the first year of life, then becomes adult-like at age 2.5 years, and subsequently remains relatively stable until old age (Clemente et al., 2012).

The gut microbiota are very essential for host health. They participate in the regulation of many physiological functions. The gut microbiota reside in our intestinal mucus layer and even participate in shaping the mucus layer (Jakobsson et al., 2015). They help us to digest food (such as fiber); synthesize vitamins and amino acids (Spanogiannopoulos et al., 2016); play very important roles in energy metabolism and storage, immune system modulation, growth, and neurodevelopment; and can even regulate our behavior (Round and Mazmanian, 2010; Diaz Heijtz et al., 2011; Clemente et al., 2012; Hsiao et al., 2013; Yano et al., 2015; Charbonneau et al., 2016). The occurrence of many diseases is correlated with altered gut microbiome composition (Lange et al., 2016). Gut microbiota dysbiosis is considered to be a potential cause of obesity (Cani et al., 2007; Fei and Zhao, 2013). However, gut microbiota are very sensitive to drugs, diet, and environmental pollutants.

Health concerns regarding the effects of environmental pollutants on animals have increased in recent years (Jin et al., 2010, 2016f; Ye et al., 2010; Liu et al., 2016b; Tu et al., 2016). Although most environmental pollutants do not directly target gut microbiota, some pollutants can enter the body and interact with the gut microbiota through different pathways. A number of previous studies have shown that exposure to environmental pollutants can alter the composition of the gut microbiome, leading to disorders of energy metabolism, nutrient absorption, and immune system function or the production of other toxic symptoms (Jin et al., 2015c; Zhang et al., 2015b). In the present review, we conclude that different kinds of environmental pollutants can induce gut microbiota dysbiosis and have multiple potential adverse effects on animal health. We analyze pollutant-induced changes in gut

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microbiota composition and their effects on health to provide a new perspective on the investigation of pollutant toxicity.

2. Antibiotics

During the last 50 years, a large number of antibiotics have been developed for use in human and veterinary medicine throughout the world (Brussow, 2015). Due to their incomplete adsorption in humans and animals, a large portion of the ingested antibiotics are excreted into the environment through feces or urine (Sarmah et al., 2006). An increasing number of studies have discovered that high concentrations of various antibiotics are found in the natural environment, including river and lake sediments, surface water, agricultural soil, and wastewater in China and other countries (Dong et al., 2016; Ferro et al., 2016; Qian et al., 2016; Xu et al., 2016). We now know that humans and animals can passively ingest antibiotics through multiple routes in addition to deliberate pharmaceutical administration. Generally, antibiotics directly target the microorganisms that make up the microbiome; therefore, the composition of animals' gut microbiomes could be changed even by very low concentrations of some antibiotics. Thus, it is believed that environmental antibiotic-induced gut microbiota dysbiosis is tightly linked to human health.

There is no doubt that potent antibiotics could have complex consequences on gut microbiota. Previous studies found that antibiotic treatment did not reduce the total number of gut microbiota but altered the relative numbers of certain species in humans and animals (Cho et al., 2012; Buffie et al., 2015; Russell et al., 2015). In addition, antibiotic exposure typically altered the diversity of the microbiome, either by increasing or decreasing diversity (Vrieze et al., 2014).

More importantly, the effects of antibiotics on human gut microbiota can persist for several years. As Jakobsson et al. (2010) reported, treatment with clarithromycin and metronidazole persistently changed the gut microbiota composition for up to 4 years. After infants finished antibiotic treatment, although some aspects of microbiota composition recovered to pretreatment levels, the abundance of some bacterial species was permanently altered (Fouhy et al., 2012). This kind of change is detrimental for babies because it could perturb their early development. Moreover, a slight difference can be identified in an individual's microbiota composition between two ciprofloxacin treatments (Dethlefsen and Relman, 2011).

Exposure to some antibiotics could increase the severity of certain disease. For example, *Clostridium difficile*, a major cause of antibiotic-induced diarrhea, could greatly increase the morbidity and mortality of hospitalized patients. Treatment with the two most widely prescribed antibiotics, clindamycin and ampicillin, increased the susceptibility of patients to *C. difficile* infection by decreasing *Clostridium scindens*, which is a secondary modulator of bile acid metabolism (Buffie et al., 2015). Streptomycin treatment can increase the levels of the two Bacteroidetes families Porphyromonadaceae and Bacteroidaceae, whose presence is positively correlated with susceptibility or hypersensitivity to pneumonitis (Russell et al., 2015) and colitis (Ferreira et al., 2011) in mice. Treatment with metronidazole decreased the inner mucus layer in the colon of mice and thus increased susceptibility to *Citrobacter rodentium*-induced colitis by decreasing the composition of anaerobic Bacteroidales and increasing the composition of aerotolerant bacteria, including *Lactobacilli* (Wlodarska et al., 2011). Antibiotic treatment also increased the invasion of pathogenic bacteria such as *Escherichia coli* (Sekirov et al., 2008; Looft and Allen, 2012), and antibiotic resistance genes were enriched in the gut microbiota after antibiotic treatment (Jernberg et al., 2007; Jakobsson et al., 2010; Looft et al., 2012; Yang et al., 2016).

In addition, some nonmicrobial-driven diseases would occur more frequently because of antibiotic treatment. Administration of vancomycin to mice in early life enhances allergic asthma by increasing the abundance of Lactobacillaceae and Verrucomicrobiaceae, and these microbiota changes were associated with decreased T_{reg} cells (Russell et al., 2012). More recently, a study reported that oral administration of the combination of streptomycin, colistin, and ampicillin or treatment with vancomycin alone increased the morbidity of type I diabetes after pancreatic β-cell death in mice. Vancomycin treatment of mice increased the levels of *Escherichia*, *Lactobacillus,* and *Sutterella* at the genera level and decreased bacteria belonging to the order Clostridiales and families Lachnospiraceae, Prevotellaceae, and Rikenellaceae. Combination antibiotic treatment resulted in nearly complete ablation of gut microbiota (Candon et al., 2015). These microbiome structural changes were tightly related to the appearance of interleukin (IL)-17-producing cells in the lamina propria of the ileum and colon, indicating that gut microbiota play a very important role in immune homeostasis (Candon et al., 2015).

However, antibiotic-induced alterations in gut microbiota sometimes have beneficial effects on diseases. Cystic fibrosis is an autosomal recessive disease that can cause intestinal bacterial overgrowth (Lisowska et al., 2009). Streptomycin treatment (200 mg/L in drinking water) of mice for 9 weeks modified this disease by reducing gut bacterial overgrowth, modulating T cell profiles by decreasing *Lactobacillus* abundance, and increasing the level of immune cells in the pulmonary and mesenteric lymph nodes (Bazett et al., 2016). Administration of rifaximin to cirrhosis patients can reduce the abundance of Veillonellaceae and increase the abundance of Eubacteriaceae. These microbial composition changes altered the patients' metabolic profiles and reduced the severity of the disease (Bajaj et al., 2013, 2014). Norfloxacin can reduce bacterial translocation and improve intestinal barrier function for cirrhosis patients, which could reduce the risk of spontaneous bacterial peritonitis (Gomez-Hurtado et al., 2014).

Early in the 1950s, antibiotics were used by farmers to promote livestock growth. Recently, mounting evidence shows that antibiotics can influence energy metabolism by affecting the gut microbiome. For example, administration of low doses of penicillin to mice early in life enhances metabolic phenotypes and promotes lipid accumulation by decreasing the levels of *Lactobacillus*, *Candidatus, Arthromitus,* and *Allobaculum* (Cox et al., 2014). Another report shows that administration of Penicillin G, erythromycin, or both to mice (60/10 μg/mL in drinking water for 6/14 weeks, total concentration) could increase lipid accumulation and induce inflammatory response. All these treatments decreased the ratio of Bacteroidetes/Firmicutes (Jin et al., 2016d). This altered metabolic phenotype can be transferred to germ-free hosts (Cox et al., 2014). Vancomycin treatment of obese men with metabolic syndrome decreases secondary bile acid production and peripheral insulin sensitivity and causes decreases in gram-positive bacteria (mainly *Firmicutes*) and compensatory increases in gram-negative bacteria (mainly *Proteobacteria*) (Vrieze et al., 2014). Subtherapeutic antibiotic administration in early life increased adipose mass in young mice and increases body weight in young female mice. In addition, this treatment significantly increases the abundance of Firmicutes and causes a related increase of short chain fatty acid (SCFA) levels in the colon (Cho et al., 2012). It's possible that residual antibiotics in the environment contribute to the high rates of obesity in developed countries. However, the observed increased weight gain could frequently not be reproduced with animals in controlled experimental conditions (Dumonceaux et al., 2006; Lin et al., 2013).

We conclude that antibiotics can easily induce gut microbiota dysbiosis and result in adverse effects on health. Because of their widespread use, relative high concentrations of antibiotics were