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From chemical mixtures to antibiotic resistance

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ABSTRACT

In real environment, it is unlikely that contaminants exist singly; environmental contamination with chemical mixtures is a norm. However, the impacts of chemical mixtures on environmental quality and ecosystem health have been overlooked in the past. Among the complex interactions between different contaminants, their relationship with the rise of antibiotic resistance (AR) is an emerging environmental concern. In this paper, we review recent progresses on how chemicals or chemical mixtures promote AR. We propose that, through co-selection, agents causing stress to bacteria may induce AR. The mechanisms for chemical mixtures to promote AR are also discussed. We also propose that, mechanistic understanding of co-selection of chemical mixtures for AR should be a future research priority in environmental health research.

Contents

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Introduction

The environment contains a lot of natural and man-made chemicals and/or their degradation products (Backhaus and Faust, 2012). Environmental contamination with chemical mixtures is ubiquitous. For example, in pig manures and manured soils in China, metals such as copper, zinc, and arsenic, as well as numerous antibiotics, are found present simultaneously (Qiao et al., 2012; Zhu et al., 2013). Although most environmental studies focus on one type of pollutants at a time, understanding the toxicity of a chemical mixture is a major challenge in environmental health research (Braun et al., 2016). To address this challenge, in-depth studies of toxicity and risk assessment of chemical mixtures have been emerging, starting from mixtures of metals (Nys et al., 2017; Traudt et al., 2017).

Antibiotic resistance (AR) has become a worldwide concern for public health. Since the discovery of penicillin and other antibiotics, they have been used to treat infectious diseases and have saved millions of lives. Almost in every case, introduction of a new antibiotic was followed by resistance to the very antibiotic (Lobanovska and Pilla, 2017), leading to huge cost of health care and deaths. The genetic determinants of AR, antibiotic resistance genes (ARGs), are found in almost every ecosystem (Su et al., 2017), even in extreme environments. The spread of ARGs in the environment could potentially increase the opportunity that human pathogens acquire AR from environmental bacteria. Exposure to antibiotics also can lead to amplification of existing ARGs by processes such as gene duplication or increasing the copy number of plasmids carrying ARGs (Paul et al., 2017; Sandegren and Andersson, 2009).

Conventionally the emergence and spread of AR is believed to be the consequence of use and abuse of antibiotics. However, in natural environment, bacteria are exposed to miscellaneous potential hazards such as heavy metals, antibiotics, and solvents. Therefore, bacteria were under selective pressure to evolve and develop mechanisms to better tolerate not only single stressors but actually mixtures of contaminants. Resistance mechanisms for heavy metals, antibiotics, organic solvents and other substances have been described in great detail (Chandrangsu et al., 2017; Hughes and Andersson, 2017; Ramos et al., 2002). In contrast, not much is known on how different resistance determinants evolved together and how much these resistances are simultaneously regulated. The importance of chemicals other than antibiotics causing cross-resistance may be overlooked. It is clear that the presence of metals in the environment co-selects for resistance to antibiotics (Song et al., 2017; Wu et al., 2016; Pal et al., 2017). Here we review recent studies that suggest various chemicals or chemical mixtures promote AR. Research on this front is vastly needed and chemical mixtures' role in AR should be taken into account when the overall strategy to counter AR is considered.

1. Chemicals or chemical mixtures and antibiotic resistance

Among all chemicals, metals are probably the most thoroughly studied in relation to AR. The association of AR with metals has been reviewed extensively (Baker-Austin et al., 2006; Pal et al., 2017). Metal mixtures, along with antibiotics, are often used as feed supplements in animal farms. High throughput analysis of ARGs from pig farms and impacted soils reveals that ARGs can be enriched up to 28,000-fold (Zhu et al., 2013). Despite locations separated by over 1000 km, the diversity and abundance patterns of ARGs show similar profile of the same management types. More importantly, the abundance of ARGs is correlated with the concentrations of antibiotics, and metals such as copper, zinc, and arsenic, suggesting metals provide selection pressure for AR (Zhu et al., 2013).

In pure cultures, individual metals have been found to induce AR. In a bacterium LSJC7, arsenic, copper, and zinc enhanced the resistance towards tetracycline (Chen et al., 2015). This is further demonstrated by the surface-enhanced Raman scattering (SERS) technique (Cui et al., 2016), in which spectral changes representing phenotypic bacterial responses, in combination with multivariate analysis, indicated that arsenic enhanced the resistance to tetracycline.

In addition to the more thoroughly studied metals, other chemicals are increasingly found to be linked to the rise of AR. Halogenated nitrogenous disinfection byproducts (N-DBPs) are a group of unintended byproducts formed during chlorination or chloramination for treatment of drinking water. It has been found that exposure to bromoacetamide, trichloroacetonitrile or tribromonitromethane, three representatives of N-DBPs, increased the resistance of *Pseudomonas aeruginosa* PAO1 to both individual and multiple antibiotics (Lv et al., 2015). The same induction phenomena were also observed in *Escherichia coli*, raising concerns about the rise of AR in drinking water.

Triclosan is an antiseptic present in many health care and consumer products, such as soaps, lotions, toothpaste, and some commonly used household fabrics and plastics. It has been shown that a *P. aeruginosa* mutant, which is susceptible to triclosan due to the deletion of triclosan-resistant MexAB-OprM efflux system, selects multidrug-resistant bacteria at high frequencies when exposed to triclosan (Chuanchuen et al., 2001). The minimum inhibitory concentrations (MICs) of several antibiotics for some of the mutants were increased up to 500-fold.

In wastewater treatment plants, UV/H_2O_2 process is considered an effective method to control spread of antibiotic resistant bacteria. Although UV/H_2O_2 process is effective for bacterial inactivation, it's not effective in ARGs removal from water suspension (Ferro et al., 2016). Actually, an increase of antibiotic resistance gene bla_{TEM} was observed in total DNA after 240 min treatment. Chlorination is commonly used for treatment of wastewater and disinfection of drinking water. It has been shown that after chlorination, a higher proportion of the surviving bacteria is resistant to several antibiotics (Shi et al., 2013). Chlorination results in enrichment of some ARGs. Osmotic stress can also influence microbial susceptibility to antibiotics. For example, when isolates of *Listeria monocytogenes* are exposed to different concentrations of salt, their resistance to antibiotics increases as salt concentration increases (Al-Nabulsi et al., 2015).

Some herbal extracts, such as essentials oils, have been used in various consumer products. Pine oil, a disinfectant used in household products, has been found to select mutants of *E. coli* for resistance to multiple antibiotics (Moken et al.,