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Evolutionarily adapted hormesis-inducing stressors can be a practical solution to mitigate harmful effects of chronic exposure to low dose chemical mixtures☆

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ABSTRACT

Although the toxicity of synthetic chemicals at high doses is well known, chronic exposure to low-dose chemical mixtures has only recently been linked to many age-related diseases. However, it is nearly impossible to avoid the exposure to these low-dose chemical mixtures as humans are exposed to a myriad of synthetic chemicals as a part of their daily lives. Therefore, coping with possible harms due to low dose chemical mixtures is challenging. Interestingly, within the range of environmental exposure, disease risk does not increase linearly with increasing dose of chemicals, but often tends to plateau or even decrease with increasing dose. Hormesis, the over-compensation of various adaptive responses through cellular stresses, is one possible mechanism for this non-linearity. Although the hormetic effects of synthetic chemicals or radiation have long been debated in the field of toxicology, the hormesis concept has recently been generalized in the field of molecular biology; similar to responses to synthetic chemicals, mild to moderate intermittent stressors from any source can induce hormetic responses. Examples of stressors are exercise, calorie restriction, intermittent fasting, cognitive stimulation, and phytochemicals. Mitohormesis is hormesis induced by such stressors through mitochondrial retrograde signalling including the increased production of mild reactive oxygen species. Xenohormesis is phytochemical-induced hormesis, reflective of a mutualistic relationship between plant and animals. As humans had repeated exposure to all of these stressors during their evolution, the hormetic effects of these health behaviours may be considered to be evolutionarily adapted. Although hormesis induced by synthetic chemicals occurs in humans, such hormesis may not be recommended to the public due to unresolved issues on safety including the impossibility of control exposure. However, the use of personal health behaviors which enhance mitohormetic- or xenohormetic-stress can be readily incorporated into everyone's daily lives as a practical way to counteract harmful effects of unavoidable low-dose chemical mixtures.

1. Introduction

The general population is currently exposed to a myriad of man-made synthetic chemicals in daily life. In the past 100 years, the number of synthetic chemicals to which humans are exposed has dramatically increased. Today, more than 85,000 synthetic chemicals are included in the U.S. Toxic Substances Control Act (TSCA) inventory; this number does not include common synthetic chemicals such as pesticides, foods and food additives or cosmetics, which are regulated by other U.S. statutes (US Environmental Protection Agency).

Recently, chronic exposure to low-dose chemical mixtures has

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gained scientific attention because evidence shows that they may play an important role in the development of many age-related diseases including diabetes, cancer, cardiovascular diseases and dementia (Lee et al., 2014a, 2014b, 2016; Lim et al., 2010; Miller et al., 2017). There is a particular need to re-evaluate obesity-related diseases from the viewpoint of lipophilic chemical mixtures which are stored in adipose tissue because they are released to circulation in an uncontrolled way among obese persons with dysfunctional adipocytes (Lee et al., 2017a, 2017b).

Current risk assessment and chemical regulations target individual chemical compounds. However, this approach misses the cumulative effects of exposure to low-dose chemical mixtures (Miller et al., 2017). Although cumulative risk assessment has been attempted for several groups of chemicals with common modes of action or common adverse outcomes (Monosson, 2005), chemicals can contribute to the development of diseases through dissimilar mechanisms and different target organs, and this real life situation is difficult to model experimentally (Miller et al., 2017). The complexity of cumulative risk assessment on chemical mixtures is exacerbated by the possibly non-monotonic dose-response relationships within the current levels of chemical exposure in the environment (Vandenberg et al., 2012). Reliable cumulative risk assessment of the mixtures of several hundreds or thousands of individual compounds with non-monotonic dose-response relationships might not be possible, even using state-of-the-art technology. Therefore, if the chronic exposure to low-dose chemical mixtures is truly harmful to humans, an alternative approach should be explored.

This article was written to (1) present recent human evidence on the possible harmful effects due to chronic exposure to low-dose chemical mixtures and (2) discuss how the concept of hormesis can be used practically in humans to mitigate the harmful effects of chronic exposure to low-dose chemical mixtures. Neither detailed descriptions of the underlying molecular mechanisms nor discussion of individual chemicals or hormesis-inducing stressors were within the scope of this article.

2. Persistent organic pollutants as chemical mixtures

2.1. Practical restrictions on epidemiological studies on low dose chemical mixtures

Many articles linking a specific chemical to one disease have been published across research fields, including epidemiology. As the population lives with exposure to chemical mixtures, epidemiological study focusing on individual chemicals is only sensible for study of high exposure to one specific chemical, such as occurs in an occupational or accidental exposure. When environmental low dose exposure is the main concern, mixtures should always be considered. In fact, even though several hundred environmental chemicals are measured in human studies, this number is still only part of the picture.

In addition, many chemicals, especially common endocrine-disrupting chemicals (EDCs) such as bisphenol A or phthalate, have short half-lives of several hours to days, and intra-individual variation in repeated measures during 1 week is larger than inter-individual variation (Li et al., 2010; Preau et al., 2010; Ye et al., 2011). Even 24-h urine collection is insufficient to reliably estimate the usual exposure levels of short half-life chemicals due to a large day-to-day variation (Kissel et al., 2005; Scher et al., 2007; Ye et al., 2011). In this situation, most epidemiological studies of these chemicals might not be credible, regardless of the study design. This issue was thoughtfully discussed in a recent review article on methodological issues in human studies of EDCs (Lee and Jacobs, 2015b).

On the other hand, there is a group of chemicals with very long half-lives whose usual exposure levels in humans can be reliably estimated in a blood sample. Typical examples are persistent organic pollutants (POPs), which have half-lives of several years to decades. POPs include several hundred halogenated compounds with common features including strong lipophilicity, poor biodegradation, bioaccumulation in the food chain, and storage in the adipose tissue of living organisms (Lee et al., 2014a). Typical examples of chemicals classified as POPs are polychlorinated compounds such as organochlorine pesticides (OCPs), polychlorinated biphenyls (PCBs), and dioxins (Lee et al., 2014a). Another characteristic of these chemicals is that they exist as a mixture in living organisms and their concentrations are highly correlated in most cases. Thus, one or several compounds of POPs can represent POP mixtures. These features make POPs unique in human studies.

2.2. Harmful effects of chronic exposure to low dose POPs

Chronic exposure to low-dose POPs has recently been linked to many diseases of the endocrine, immune, nervous and reproductive systems (Carpenter, 2013). In particular, a substantial body of evidence has shown that low-level POP exposure, especially to chlorinated POPs, may be important in the development of obesity-related metabolic dysfunctions such as type 2 diabetes and metabolic syndrome (Lee et al., 2014a; Ruzzin et al., 2012).

These findings about POPs seem surprising because the burden of chlorinated POPs on the human body is now very low due to the banning of these chemicals since the 1970s and 1980s. Direct toxicity due to high-dose exposure to individual compounds belonging to these chemicals has long been well known. However, harmful effects due to chronic exposure to low-dose POP mixtures have recently become an issue, and their molecular mechanisms would differ from the traditional toxicities of high-dose individual compounds. Interestingly, epidemiological studies have suggested that harmful effects due to chronic exposure to POP mixtures may not increase linearly with increasing doses of POPs (Lee and Jacobs, 2015a; Lee et al., 2014a).

2.3. Possible mechanisms

Even though human studies have measured several or dozens of specific POP compounds, their findings may not be attributed to those specific compounds. The reason is that they may act as surrogate markers of various lipophilic chemical mixtures, including both measured and unmeasured chemicals.

Thus far, few experimental studies have investigated an exposure pattern that resembles actual human exposure to POPs in terms of number of chemicals, exposure dose and exposure duration. Considering this large research gap, we suggest two possible mechanisms underlying harmful effects of chronic exposure to low-dose POPs, mainly based on basic knowledge of physiology and toxicology. It is important to note that these mechanisms are consistent with the observed non-monotonic dose-response relationships.

2.3.1. Endocrine disruption

POP compounds are well-known EDCs (Carpenter, 2013). EDCs can be defined as exogenous substances or mixtures that alter the function of the endocrine system, causing adverse effects on the health of an organism or its progeny (Zoeller et al., 2012). Chemicals acting as EDCs are known to show non-monotonic dose-response relationships with disease and disease markers; a common shape is an inverted U-shaped association (Vandenberg et al., 2012).

As the endocrine system is the fundament for diverse hormonal