Environment International 108 (2017) 170–175

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

A role of low dose chemical mixtures in adipose tissue in carcinogenesis

Duk-Hee Lee[a,b,*], David R. Jacobs Jr[c], Ho Yong Park[d], David O. Carpenter[e,f]

[a] Department of Preventative Medicine, School of Medicine, Kyungpook National University, Daegu, Republic of Korea
[b] BK21 Plus KNU Biomedical Convergence Program, Department of Biomedical Science, Kyungpook National University, Republic of Korea
[c] Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, MN, United States
[d] Department of Breast and Thyroid Surgery, School of Medicine, Kyungpook National University, Daegu, Republic of Korea
[e] Center for the Elimination of Minority Health Disparities, University at Albany, Albany, NY, United States
[f] Institute for Health and the Environment, University at Albany, Rensselaer, NY, United States

ARTICLE INFO

Keywords:
Adipose tissue
Chemical mixtures
Halifax project
Obesity paradox
Persistent organic pollutants
Weight loss

ABSTRACT

The Halifax project recently hypothesized a composite carcinogenic potential of the mixture of low dose chemicals which are commonly encountered environmentally, yet which are not classified as human carcinogens. A long neglected but important fact is that adipose tissue is an important exposure source for chemical mixtures. In fact, findings from human studies based on several persistent organic pollutants in general populations with only background exposure should be interpreted from the viewpoint of chemical mixtures because serum concentrations of these chemicals can be seen as surrogates for chemical mixtures in adipose tissue. Furthermore, in conditions such as obesity with dysfunctional adipocytes or weight loss in which lipolysis is increased, the amount of the chemical mixture released from adipose tissue to circulation is increased. Thus, both obesity and weight loss can enhance the chance of chemical mixtures reaching critical organs, however paradoxical this idea may be when fat mass is the only factor considered. The complicated, interrelated dynamics of adipocytes and chemical mixtures can explain puzzling findings related to body weight among cancer patients, including the obesity paradox. The contamination of fat in human diet with chemical mixtures, occurring for reasons similar to contamination of human adipose tissue, may be a missing factor which affects the association between dietary fat intake and cancer. The presence of chemical mixtures in adipose tissue should be considered in future cancer research, including clinical trials on weight management among cancer survivors.

1. Introduction

Traditionally, the carcinogenic potential of chemicals has been evaluated based on a paradigm of risk assessment of single chemicals, without regard to possible joint exposure to any other chemical. In the modern world everyone is exposed to mixtures of many chemicals, some of which are known to be carcinogenic and others not so identified. Little has been done to determine whether or not low dose chronic exposure to chemical mixtures has the potential to increase risk of cancer.

The Halifax project recently analyzed the carcinogenic potential of low dose chemical mixtures (Goodson et al., 2015). In the literature-based review on 85 chemicals which are not currently considered to be known human carcinogens based on single chemical risk assessment, they found that each of these chemicals met some of the "hallmarks of cancer" criteria (Hanahan and Weinberg, 2000; Hanahan and Weinberg, 2011), and concluded that the cumulative effects of individual chemicals acting on different pathways could plausibly result in carcinogenic synergies (Goodson et al., 2015).

Risk factors for cancer in humans are commonly classified into personal lifestyle factors and occupational/environmental pollutants. Compared to lifestyle factors such as cigarette smoking, overweight, diet, and physical inactivity, the role of pollutants is generally considered to be minor (Doll and Peto, 1981; Peto, 2001). Notably, all these lifestyle factors are directly or indirectly related to the exposure to low dose chemical mixtures. Cigarette smoking clearly consists of exposure to chemical mixtures. However, it is largely unrecognized how other lifestyle factors are related to the exposure to low dose chemical mixtures. In particular, human adipose tissue plays a role as an endogenous reservoir of chemical mixtures (Lee et al., 2017). Obesity research without consideration of chemical mixtures in adipose tissue was recently criticized; reevaluation of obesity-related diseases from the viewpoint of chemical mixtures is an important research gap (Lee et al., 2017).

The purpose of this article is to discuss the role of adipose tissue as a storage site for low dose chemical mixtures and the importance of

* Corresponding author at: Department of Preventive Medicine, School of Medicine, Kyungpook National University, 680 Gukchaebosang-ro, Jung-gu, Daegu 41944, Republic of Korea.
E-mail address: lee_dh@knu.ac.kr (D.-H. Lee).

http://dx.doi.org/10.1016/j.envint.2017.08.015
Received 19 June 2017; Received in revised form 7 August 2017; Accepted 23 August 2017

chronic release of chemical mixtures from adipocytes to the circulation in carcinogenesis and prognosis of cancer patients. In fact, human evidence on the carcinogenic potential of low dose chemical mixtures may be illuminated through investigations of the interrelationship between obesity and low dose chemical mixtures. However, traditional epidemiological studies based on the direct measurement of many chemicals in bio-specimens and their associations with cancer outcomes have several critical methodological issues which will be discussed below. We also discuss how diet and physical inactivity are related to low dose chemical mixtures.

2. Low dose chemical mixtures act as a potential carcinogen

2.1. The Halifax project

In the Halifax project, 174 scientists from 28 countries evaluated the carcinogenic potential of 85 non-carcinogenic chemicals, using 11 well-known cancer hallmarks which govern the transformation of normal cells to cancer cells (Hanahan and Weinberg, 2000; Hanahan and Weinberg, 2011). These hallmarks included genetic instability, tumor-promoting inflammation, sustained proliferative signaling, insensitivity to antigrowth signals, resistance to cell death, angiogenesis, tissue invasion and metastasis, the tumor microenvironment and avoiding immune destruction. The chemicals include some persistent chemicals, other organic chemicals having varying lipophilicity that are not so persistent, and some heavy metals.

In the final report, they concluded that each of the individual chemicals affected one or more crucial cancer hallmarks and therefore the mixture of 85 chemicals affected all cancer hallmarks (Goodson et al., 2015). These environmental chemicals are thought to contribute to carcinogenesis through epigenetic and non-genotoxic effects, which would commonly be missed in a mutation-based risk assessment process (Miller et al., 2017).

These 85 chemicals were selected as prototypical in the environment rather than for a specific carcinogenic suspicion of each chemical. Thus, the findings from the Halifax project are not confined to these 85 chemicals, but apply to general chemical mixtures which are commonly encountered from the environment. Also, as the doses of chemicals are mostly within the range of typical human exposures, the Halifax Project conclusion suggests that chronic exposure to low dose chemical mixtures might act as a carcinogen in humans (Goodson et al., 2015).

Under the current paradigm of chemical carcinogenesis, mutagenicity of chemicals is considered the most important feature of carcinogens. However, replicative spontaneous mutations, unavoidable errors which arise from DNA replication, are responsible for two-thirds of the mutations in human cancers (Tomasetti and Vogelstein, 2015). If this is the case, chronic exposure to chemical mixtures which affect processes of proliferation or progression through epigenetic modulation may play a more important role in the development of cancers in humans than the exposure to individual carcinogens which can induce DNA mutations.

2.2. Is there direct human evidence about the carcinogenic potential of low dose chemical mixtures?

Inspired by the result of the Halifax Project, some epidemiologists may consider human studies with direct measurement of the 85 chemicals included in the Halifax project in bio-specimens such as blood or urine and with comparison of cancer risk among different exposure patterns of these 85 chemicals. Sophisticated statistical tools are often suggested to approach complex chemical mixtures in human studies (Taylor et al., 2016). However, there are critical methodological reasons why such an approach may not provide conclusive results.

First, the exposure assessment of many chemicals in humans is often unreliable due to the short half-lives and ubiquitous exposure sources of many chemicals. Bisphenol A (BPA), which is related to many cancer hallmarks, was one of the 85 chemicals included in the Halifax Project. However, human studies of BPA demonstrate a high day-to-day variation within-person, due to variable exposure and fast clearance (Ye et al., 2011). Therefore BPA has low reproducibility among repeated urine collections from the same person. Even 24-hour urine samples would not accurately estimate the usual exposure status of BPA because of huge day to day variability of BPA exposure (Ye et al., 2011). Human studies without reliable exposure assessment have little meaning.

Second, a substantial number of chemicals in the Halifax Project demonstrated non-linear dose-response patterns. Non-linearity often leads to inconsistent results in human studies because the exposure ranges of specific chemicals vary among populations. For example, let us assume an inverted U-shaped risk association from dose 0 to 100 with the peak risk around dose 50. If population A has exposure range from dose 10 to 40, samples from that population would show an increasing dose-response relation. On the other hand, little association would be observed when sampling from population B, which has exposure range from dose 40 to 60. An inverse association would even be possible in samples from a population C with exposure range from dose 50 to 100. This example is a hypothetical case with only one chemical. When there are many chemicals with non-linear dose–response relationships, it would be impossible to reliably predict net effects of chemical mixture in humans.

Third, the possibility of effects of in-utero and early life exposures and transgenerational effects means that we may not be able to solve these puzzles in humans. As biological effects of chemicals during these critical periods may differ depending on the timing of organ development, the precise assessment of chemical mixtures considering the critical stages of organ development may be more important than the exposure during adulthood. Although birth cohort studies with several snapshot measurements are now underway in many countries, we may not reliably assess the carcinogenic effects of chemical mixtures either during the critical period or over the whole lifetime. Thus the combination of low reliability of exposure assessment, non-linear dose response relationships and critical windows of development pose significant limitations.

Because of these limitations, a traditional epidemiological approach based on direct measurement of concentrations of chemicals is not likely to provide reliable evidence concerning the low dose chemical mixtures hypothesis, regardless of study design and sample sizes. More detailed discussion on methodological limitations on human studies on chemical exposure can be found elsewhere (Lee and Jacobs, 2015).

Besides these methodological limitations, there is a more fundamental issue concerning the carcinogenic potential of chemical mixtures in humans because mixtures can lead to antagonistic effects in addition to additive and synergic effects. For example, when one chemical with proliferative effects is mixed with another chemical with apoptotic effects, the net effect may be null. Therefore, unlike the conclusion of the Halifax project based on individual chemical-based experiments, there is a substantial uncertainty about the carcinogenic potential of chemical mixtures in humans.

Considering the complexity of these issues, we may need an indirect alternative approach to test and understand the low dose chemical mixtures hypothesis. Epidemiological study using the dynamics of chemical mixtures in adipose tissue is a plausible study design to address this hypothesis in humans.

2.3. Adipose tissue as a source of chemical mixtures

Adipose tissue plays an important but neglected role as a source of exposure to chemical mixtures. Adipose tissue of all living organisms is widely contaminated with various man-made chemicals (Geens et al., 2012; Kim et al., 2014; Moon et al., 2012a; Moon et al., 2011; Moon et al., 2012b). The most well-known class of chemicals in adipose tissue is persistent organic pollutants (POPs). POPs include several hundred halogenated compounds with common features such as strong