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Mini Review

Transgenerational Inheritance of Obesity Caused by Endocrine-Disrupting Chemicals

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Abstract

The transgenerational epigenetic inheritance of diseases is an emerging area of research. Multiple environmental factors including toxicants are involved. Endocrine-disrupting chemicals (EDCs) are a heterogeneous group of exogenous chemicals or chemical mixtures that interfere with the action of hormones. The obesity pandemic cannot be explained solely by alterations in food intake and/or decrease in exercise. It coincides with the exponential increase in the number of EDCs present in the air, water, and food. Some EDCs called obesogens can promote weight gain despite normal diet and exercise. At least 50 obesogens have been identified. Exposure to obesogens (e.g., bisphenol A, phthalates, and tributyltin) during critical windows of embryonic/fetal development (e.g., Weeks 4-8) can induce transgenerational inheritance of increased obesity risk. By inducing epigenetic changes in germ cells (egg or sperm), the EDCs directly influence genetic variation, inheritance, phenotypic variation, and adaptation. The changes propagate and the transgenerational phenotype can persist through multiple generations without any new exposure to the initiating factor. The proposed mechanisms implicated in transgenerational inheritance caused by EDCs include deoxyribonucleic acid (DNA) methylation (the most studied mechanism), histone methylation, histone retention, chromatin structure alteration, and non-coding ribonucleic acids (RNAs) expression. A better understanding of the mechanisms of the transgenerational inheritance is critical for the implementation of preventive strategies in the fight against obesity pandemic. Every effort should be made to minimize or avoid the exposure to obesogens, especially during the windows of sensitivity of the embryo/fetus.

Keywords: Epigenetics; Endocrine-disrupting chemicals; In utero life; Obesogens; Obesity; Transgenerational inheritance

Abbreviations

AZ: Arizona

DNA: Deoxyribonucleic Acid

EDC: Endocrine-Disrupting Chemical

e.g.: Exempli Gratia

LLC: Limited Liability Company

MD: Medical Doctor

RNA: Ribonucleic Acid

USA: United States of America

Introduction

The transgenerational epigenetic inheritance of diseases is an emerging area of research where multiple environmental factors including toxicants, nutrition imbalance, and stress are involved [1-3].

Pregnancy is a very sensitive window for EDCs exposure. Exposure of pregnant women to EDCs can cause prenatal damage with heritable phenotypes propagating and persisting through multiple generations without any new exposure to the initiating factor (transgenerational inheritance) [1-11].

The obesity pandemic cannot be explained solely by alterations in food intake and/or decrease in exercise. It coincides with the exponential increase in the number of EDCs present in the air, water, and food. Some EDCs can promote weight gain leading to obesity [1-4, 6-9, 11-20].

This mini review presents an update on transgenerational inheritance of obesity caused by EDCs.

Epigenetics

Epigenetics is defined as heritable changes in gene expression without changes in the DNA sequence. It provides an additional molecular mechanism known to be essential for gene expression. The proposed mechanisms include DNA methylation, histone methylation, histone retention, chromatin structure alteration, and non-coding RNAs expression [1-5,11]. Although DNA methylation is the most studied mechanism, other epigenetic processes are equally important.

EDCs

In 2002, the International Programme on Chemical Safety belonging to the World Health Organization proposed the following definition for EDCs: "An endocrine disruptor is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations." The first scientific statement of the Endocrine Society in 2009 provided a wake-up call to the scientific community on the risks of EDCs for human health. The second statement of the Endocrine Society in 2015 provided a global update on EDCs based on the available data in the literature [4].

EDCs are mainly man-made chemicals but can also be found in plants or fungi. The number of man-made chemicals is over 140,000. According to the Endocrine Disruption Exchange, there are approximately 1,000 chemicals considered as EDCs. The sources of EDCs include industrial (e.g., bisphenol A and phthalates), agricultural (e.g., organochlorines and organophosphates), and pharmaceutical (e.g., diethylstilbestrol and parabens) (non-exhaustive list) [1-4, 7-11, 13, 14, 16-22].

Modern life is associated with the daily use of multiple chemicals. Over the past 60 years, the number of EDCs has markedly increased. The EDCs are present in a variety of products including dust, soil, water, food, cosmetics, soaps, shampoos, toothpastes, plastic containers, toys, nicotine, and fertilizers (non-exhaustive list), and humans are regularly exposed to them (Figure 1). Exposure to EDCs begins before birth, even before conception. Air, water, food, skin, vein, breast milk, and placenta represent different routes of exposure to EDCs [4,6,7,9,11,13,14,17,21].

Figure 1: Several cosmetics contain EDCs. Copyright svl861 (Svetlana Lukienko)/Depositphotos Inc.

The majority of EDCs are highly lipophilic and stored in adipose tissue. Non-lipophilic EDCs are bound to albumin. Some EDCs have long half-lives (months or years, e.g., organochlorines) while others have short half-lives (minutes, hours, or days, e.g., bisphenol A) [4,9,14,16]. The liver metabolizes EDCs and may store lipophilic EDCs. Lipophilic EDCs are more resistant to degradation.

EDCs may interact with or activate hormone receptors (membrane and nuclear receptors), antagonize hormone receptors, alter hormone receptor expression, alter signal transduction in hormone-responsive cells, induce epigenetic modifications in hormone-producing or hormone-responsive cells (e.g., DNA methylation and histone modifications), alter hormone synthesis, alter hormone transport across cell membranes, alter hormone distribution or circulating hormone levels, alter hormone metabolism or clearance, and alter fate of hormone-producing or hormone-responsive cells [2, 4-6, 8-11, 13-18, 21-23].

The exposure to EDCs can be a significant component of the environmental origin of several medical conditions including obesity, nonalcoholic fatty liver disease, diabetes, infertility, and cancers (non-exhaustive list) [1-4, 6-11, 13-22, 24-27].

In Utero Life

The developing embryo/fetus is more sensitive than adults to the actions of EDCs (Figure 2) [4, 8-10, 17, 21, 28-31]. Pregnant women can be exposed to multiple EDCs that are able to cross the placenta and affect the embryo/fetus. This EDC exposure

is associated with inflammatory cytokine levels in maternal circulation [31]. The Week 4 to Week 8 of the embryonic/fetal period is a vulnerable window of organogenesis and any exposure to EDCs during that period can cause major congenital anomalies and may lead to several adverse health outcomes later in life (developmental origins of adult disease) [5,10,25]. The oxidative stress caused by EDCs can be the mediator of these adverse consequences [29].

Figure 2: The developing embryo/fetus is more sensitive than adults to the actions of EDCs. Copyright lelik759 (Alexey Belous)/ Depositphotos Inc.

Obesogens

Some EDCs can promote weight gain leading to obesity [1-4,6-9,11-20]. In humans, these EDCs can cause obesity despite normal diet and exercise. They can also cause resistance to weight loss in subjects on anti-obesity diet and/or drug. These EDCs are called obesogens. At least 50 obesogens have been identified (Table 1). Bisphenol A is one of the most widespread obesogens affecting humans.

Obesogens	Sources
Bisphenol A	Industrial chemicals
Phthalates	Industrial chemicals
Tributyltin	Biocides
Diethylstilbestrol	Pharmaceuticals
Nicotine	Smoking
Monosodium glutamate	Food

Table 1: Examples of obesogens, a subset of EDCs promoting obesity (non-exhaustive list).

Obesogens impair the regulation of adipose tissue and food intake and reduce basal metabolic rate. They impact several tissues and organs including adipose tissue, brain, liver, stomach, and pancreas. At the level of adipose tissue, obesogens increase the number of adipocytes by activating the nuclear receptor signaling pathways critical for adipogenesis and increase storage of fat, leading to obesity [2,6-9,11,15,16,18,19].

Obesity

Obesity is a major pandemic responsible for increased morbidity and mortality and high cost for the society [32-36]. Its prevalence has doubled in more than 70 countries since 1980. The number of adult subjects with obesity is more than 650 million worldwide.

The pathogenesis of obesity is complex. Several factors are contributing (e.g., genetic, sociocultural, behavioral, environmental, and medical factors) (non-exhaustive list) [34]. EDCs may have significantly contributed to the obesity pandemic since the obesity pandemic coincides with the exponential increase in the number of EDCs.

Multiple organs and systems are impacted by obesity resulting in different comorbidities and high mortality (Figure 3) [32, 33]. Nearly 4.7 million subjects die each year from the consequences of obesity. The annual worldwide cost of obesity is more than $2 trillion [36].

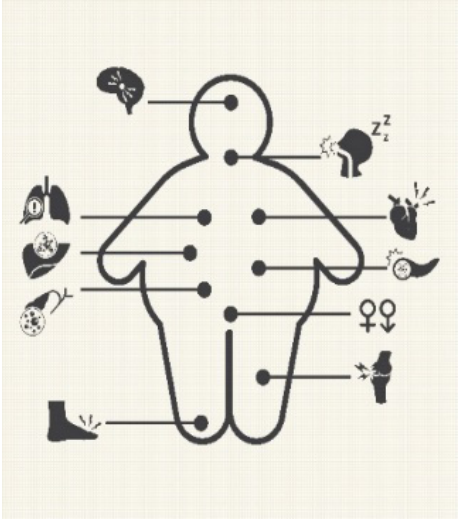

Figure 3: Multiple organs and systems can be impacted by obesity. Copyright Kittichai (Kittichai Songprakob)/Depositphotos Inc.

Management of obesity requires multidisciplinary approaches including lifestyle (e.g., diet, exercise, and behavioral change), food supplements, drugs, medical devices, gut microbiome modulation, body contouring, and bariatric surgery [34,37].

Transgenerational Inheritance of Obesity

The transgenerational epigenetic inheritance of diseases is an emerging area of research for multiple medical disorders including obesity and diabetes. Transgenerational inheritance is the occurrence of heritable phenotypes that are propagated and persistent through multiple generations without any new exposure to the initiating factor [1-11]. By inducing epigenetic changes (e.g., DNA methylation) in germ cells (egg or sperm), the EDCs directly

influence genetic variation, inheritance, phenotypic variation, and adaptation.

An adverse maternal exposure (F0 generation) can affect the fetus (F1 generation) and the germ cells of the fetus which form the F2 generation. With a direct exposure of the parents (F0 generation) and the fetus (F1 generation), the true transgenerational transmission is the F3 generation and beyond for the exposure of a pregnant female and the F2 generation and beyond for the exposure of a non-pregnant female or a male [1-3].

Animal studies have shown the link between alterations in the early-life environment, during critical windows of embryonic/fetal development, and increased susceptibility to obesity. Exposure to obesogens (e.g., bisphenol A, phthalates, and tributyltin) can induce transgenerational inheritance of increased obesity risk via both maternal and paternal lineages [1-4,6-8,11]. Evidence for epigenetic transgenerational inheritance of obesity from human studies is limited. Most reported studies on transgenerational epigenetic inheritance are up to the F2 generation.

Preventive Strategies

EDCs, and particularly obesogens, represent a threat for human health and a financial burden for the society. According to a relatively recent report, the cost of EDCs-related medical disorders in the United States of America was $340 billion (2.33% of the gross domestic product), higher than in the European Union where it was $217 billion (1.28% of the gross domestic product) [38]. The promotion of public knowledge and the initiation of preventive measures can minimize the deleterious consequences of EDCs, especially obesity, for future generations.

Regulatory actions allowing the limitation of the most prevalent and hazardous EDCs could have significant economic benefits. Several agencies are regulating the EDCs. However, there are differences in regulations between countries. Countries with significant heavy chemicals industry are less open to promote greener chemicals production [21,39,40].

Although exposure to EDCs/obesogens and the resulting transgenerational inheritance of obesity cannot be entirely avoided in many situations, every effort should be made to minimize them [11,17,21]. It is particularly important to identify windows of sensitivity (e.g., embryo/fetal period) to reduce or avoid the exposure to EDCs/obesogens.

Conclusion

Epigenetic alterations or "epimutations" can explain transgenerational inheritance of parentally acquired traits.

The obesity pandemic coincides with the exponential increase in the number of EDCs. The metabolic programming of obesity risk and its transgenerational inheritance can be linked to parental exposure to a subset of EDCs called obesogens.

A better understanding of the mechanisms of the transgenerational inheritance is critical for the implementation of preventive strategies in the fight against obesity pandemic. Every effort should be made to minimize or avoid the exposure to obesogens, especially during the windows of sensitivity of the embryo/fetus.

References

1. Nilsson EE, Sadler-Riggleman I, Skinner MK (2018) Environmentally induced epigenetic transgenerational inheritance of disease. Environ Epigenetics 4: 1-13.
2. Mohajer N, Joloya EM, Seo J, Shioda T, Blumberg B (2021) Epigenetic transgenerational inheritance of the effects of obesogen exposure. Front Endocrinol 12: 787580.
3. Beck D, Nilsson EE, Ben Maamar M, Skinner MK (2022) Environmental induced transgenerational inheritance impacts systems epigenetics in disease etiology. Sci Rep 12: 5452.
4. Gore AC, Chappell VA, Fenton SE, Flaws JA, Nadal A, et al. (2015) EDC-2: The Endocrine Society's second scientific statement on endocrine-disrupting chemicals. Endocr Rev 36: E1-150.
5. Alavian-Ghavanini A, Rüegg J (2018) Understanding epigenetic effects of endocrine disrupting chemicals: From mechanisms to novel test methods. Basic Clin Pharmacol Toxicol 122: 38-45.
6. Chamorro-Garcia R, Blumberg B (2019) Current research approaches and challenges in the obesogen field. Front Endocrinol 10: 167.
7. Heindel JJ (2019) History of the obesogen field: Looking back to look forward. Front Endocrinol 10: 14.
8. Lee MK, Blumberg B (2019) Transgenerational effects of obesogens. Basic Clin Pharmacol Toxicol 125(Suppl 3): 44-57.
9. Papalou O, Kandaraki EA, Papadakis G, Diamanti-Kandarakis E (2019) Endocrine disrupting chemicals: An occult mediator of metabolic disease. Front Endocrinol 10: 112.
10. Sargis RM, Simmons RA (2019) Environmental neglect: Endocrine disruptors as underappreciated but potentially modifiable diabetes risk factors. Diabetologia 62: 1811-1822.
11. Egusquiza RJ, Blumberg B (2020) Environmental obesogens and their impact on susceptibility to obesity: New mechanisms and chemicals. Endocrinology 161: 1-14.
12. Agay-Shay K, Martinez D, Valvi D, Garcia-Esteban R, Basagaña X, et al. (2015) Exposure to endocrine-disrupting chemicals during pregnancy and weight at 7 years of age: A multi-pollutant approach. Environ Health Perspect 123: 1030-1037.
13. Le Magueresse-Battistoni B, Labaronne E, Vidal H, Naville D (2017) Endocrine disrupting chemicals in mixture and obesity, diabetes and related metabolic disorders. World J Biol Chem 8: 108-119.
14. Yang C, Lee HK, Kong APS, Lim LL, Cai Z, et al. (2018) Early-life exposure to endocrine disrupting chemicals associates with childhood obesity. Ann Pediatr Endocrinol Metab 23: 182-195.
15. Marraudino M, Bonaldo B, Farinetti A, Panzica GC, Ponti G, et al. (2019) Metabolism disrupting chemicals and alteration of neuroendocrine circuits controlling food intake and energy metabolism. Front Endocrinol 9: 766.

16. Griffin MD, Pereira SR, DeBari MK, Abbott RD (2020) Mechanisms of action, chemical characteristics, and model systems of obesogens. BMC Biomed Eng 2: 6.

17. Hall JM, Greco CW (2020) Perturbation of nuclear hormone receptors by endocrine disrupting chemicals: Mechanisms and pathological consequences of exposure. Cells 9: 13.

18. Le Magueresse-Battistoni B (2020) Adipose tissue and endocrine-disrupting chemicals: Does sex matter? Int J Environ Res Public Health 17: 9403.

19. Ribeiro CM, Beserra BTS, Silva NG, Lima CL, Rocha PRS, et al. (2020) Exposure to endocrine-disrupting chemicals and anthropometric measures of obesity: A systematic review and meta-analysis. BMJ Open 10: e033509.

20. van der Meer TP, van Faassen M, van Beek AP, Snieder H, Kema IP, et al. (2020) Exposure to endocrine disrupting chemicals in the Dutch general population is associated with adiposity-related traits. Sci Rep 10: 9311.

21. Encarnacão T, Pais AACC, Campos MG, Burrows HD (2019) Endocrine disrupting chemicals: Impact on human health, wildlife and the environment. Sci Prog 102: 3-42.

22. La Merrill MA, Vandenberg LN, Smith MT, Goodson W, Browne P, et al. (2020) Consensus on the key characteristics of endocrine-disrupting chemicals as a basis for hazard identification. Nat Rev Endocrinol 16: 45-57.

23. Kassotis CD, Stapleton HM (2019) Endocrine-mediated mechanisms of metabolic disruption and new approaches to examine the public health threat. Front Endocrinol 10: 39.

24. Mimoto MS, Nadal A, Sargis RM (2017) Polluted pathways: Mechanisms of metabolic disruption by endocrine disrupting chemicals. Curr Environ Health Rep 4: 208-222.

25. Howard SG (2018) Developmental exposure to endocrine disrupting chemicals and type 1 diabetes mellitus. Front Endocrinol 9: 513.

26. Lauretta R, Sansone A, Sansone M, Romanelli F, Appetecchia M (2019) Endocrine disrupting chemicals: Effects on endocrine glands. Front Endocrinol 10: 178.

27. Heshmati HM (2022) Endocrine-disrupting chemicals and related medical disorders. Rep Glob Health Res 5: 140.

28. Reed CE, Fenton SE (2013) Exposure to diethylstilbestrol during sensitive life stages: A legacy of heritable health effects. Birth Defects Res C Embryo Today 99: 134-146.

29. Neier K, Marchlewicz EH, Dolinoy DC, Padmanabhan V (2015) Assessing human health risk to endocrine disrupting chemicals: A focus on prenatal exposures and oxidative stress. Endocr Disruptors 3: e1069916.

30. Rich AL, Phipps LM, Tiwari S, Rudraraju H, Dokpesi PO (2016) The increasing prevalence in intersex variation from toxicological dysregulation in fetal reproductive tissue differentiation and development by endocrine-disrupting chemicals. Environ Health Insights 10: 163-171.

31. Kelley AS, Banker M, Goodrich JM, Dolinoy DC, Burant C, et al. (2019) Early pregnancy exposure to endocrine disrupting chemical mixtures are associated with inflammatory changes in maternal and neonatal circulation. Sci Rep 9: 5422.

32. Di Angelantonio E, Bhupathiraju SN, Wormser D, Gao P, Kaptoge S, et al. (2016) Body-mass index and all-cause mortality: Individual-participant-data meta-analysis of 239 prospective studies in four continents. Lancet 388: 776-786.

33. Afshin A, Forouzanfar MH, Reitsma MB, Sur P, Estep K, et al. (2017) Health effects of overweight and obesity in 195 countries over 25 years. N Engl J Med 377: 13-27.

34. Gadde KM, Martin CK, Berthoud HR, Heymsfield SB (2018) Obesity. Pathophysiology and management. J Am Coll Cardiol 71: 69-84.

35. Malenfant JH, Batsis JA (2019) Obesity in the geriatric population – A global health perspective. JoGHR 3: e2019045.

36. Shephard RJ (2019) On determining how much obesity is costing society. HFJC (2019) 12: 80-116.

37. Heshmati HM (2022) Management of excess adiposity. Rep Glob Health Res 5: 144.

38. Attina TM, Hauser R, Sathyanarayana S, Hunt PA, Bourguignon JP, et al. (2016) Exposure to endocrine-disrupting chemicals in the USA: A population-based disease burden and cost analysis. Lancet Diabetes Endocrinol 4: 996-1003.

39. Slama R, Bourguignon JP, Demeneix B, Ivell R, Panzica G, et al. (2016) Scientific issues relevant to setting regulatory criteria to identify endocrine-disrupting substances in the European Union. Environ Health Perspect 124: 1497-1503.

40. Michel C (2019) How to regulate endocrine disrupting chemicals? Feedback and future development. Curr Opin Endocr Metab Res 7: 21-25.