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Endocrine Disruptors and Metabolic Dysregulation: Molecular Mechanisms Linking Environmental Toxins to Obesity and Insulin Resistance

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ABSTRACT

Endocrine-disrupting chemicals (EDCs) are pervasive environmental toxins that interfere with hormonal signaling and metabolic homeostasis. Emerging evidence implicates EDCs in the pathogenesis of obesity and insulin resistance, hallmark features of metabolic syndrome. This review provides an in-depth analysis of molecular mechanisms by which EDCs such as bisphenol A (BPA), phthalates, organotins, polychlorinated biphenyls (PCBs), and dioxins promote metabolic dysregulation. We explore how EDCs modulate nuclear receptor signaling, alter adipogenesis, induce oxidative stress, reprogram epigenetic profiles, and disrupt gut microbiota, all contributing to adipocyte dysfunction, hepatic steatosis, and impaired insulin sensitivity. Additionally, we examine transgenerational effects and sex-specific vulnerabilities. Understanding these mechanisms is crucial for mitigating the public health burden of environmentally induced metabolic disorders and guiding regulatory policies on chemical exposure.

Keywords: endocrine-disrupting chemicals, metabolic syndrome, obesity, insulin resistance, environmental toxins, molecular mechanisms

INTRODUCTION

The global escalation of metabolic disorders such as obesity, insulin resistance, type 2 diabetes mellitus (T2DM), and metabolic syndrome has emerged as a significant public health concern [1]. While genetic predisposition and lifestyle factors, including poor diet and physical inactivity, have long been implicated, growing attention is being directed toward environmental contributors. One class of environmental agents that has drawn substantial scrutiny is endocrine-disrupting chemicals (EDCs) [2]. These exogenous compounds are capable of interfering with the endocrine system by mimicking, antagonizing, or modifying the synthesis, transport, and metabolism of endogenous hormones. EDCs are ubiquitous in the modern environment. They are present in food packaging materials, plastic containers, pesticides, flame retardants, cosmetics, industrial solvents, and personal care products [3]. Human exposure occurs through ingestion, inhalation, dermal absorption, and maternal-fetal transfer. Alarmingly, EDCs have been detected in amniotic fluid, placental tissue, and breast milk, indicating early-life and potentially lifelong exposure [4].

Mounting evidence from epidemiological and animal studies indicates that EDCs can reprogram metabolic pathways, leading to increased adiposity, impaired glucose homeostasis, and altered energy balance [5]. These effects often manifest at low-dose exposures and may be more pronounced during critical windows of development, such as prenatal, neonatal, and pubertal stages. The concept of "metabolic programming" suggests that transient exposure to EDCs during early development can have lasting consequences on an individual's metabolic phenotype, a concept supported by both human cohort data and experimental models [6]. This review explores the molecular and cellular mechanisms through which EDCs disrupt endocrine and metabolic functions, ultimately contributing to the pathogenesis of obesity and insulin resistance. Particular emphasis is placed on key signaling pathways, epigenetic modifications, organ-specific effects, and the emerging role of gut microbiota. A comprehensive

understanding of these mechanisms is essential for the development of public health policies and preventive interventions aimed at reducing EDC-related metabolic burden.

Classes and Sources of Endocrine Disruptors

Endocrine-disrupting chemicals encompass a diverse range of structurally unrelated substances that interfere with hormonal signaling [2]. These include both synthetic industrial compounds and naturally occurring substances. The major classes of EDCs relevant to metabolic health include bisphenols, phthalates, organotins, polychlorinated biphenyls (PCBs), dioxins, and perfluoroalkyl substances (PFAS) [7].

Bisphenol A (BPA) is a widely studied synthetic estrogen commonly found in polycarbonate plastics and epoxy resins used in food and beverage containers, dental sealants, and thermal receipts [8]. BPA can leach into consumables, particularly under conditions of heat or acidity, and has been shown to mimic estrogenic activity by binding to estrogen receptors (ERα and ERβ) [9]. It also influences non-classical receptors such as GPR30, thereby modulating cellular signaling beyond traditional genomic pathways [10].

Phthalates, primarily used as plasticizers, are present in soft PVC plastics, cosmetics, medical devices, and household items [11]. These compounds are known to activate peroxisome proliferator-activated receptors (PPARs), particularly PPARα and PPARγ, which are involved in lipid metabolism and adipocyte differentiation [12]. Human exposure to phthalates occurs through ingestion of contaminated food and water, inhalation of dust, and dermal absorption [12].

Organotins, such as tributyltin (TBT), are used as stabilizers in PVC and biocides in antifouling paints [13]. TBT has garnered attention for its role as an obesogen, activating RXR-PPARγ heterodimers to promote adipogenesis even at nanomolar concentrations [14].

Persistent organic pollutants (POPs), including PCBs and dioxins, are by-products of industrial processes and combustion. These lipophilic compounds accumulate in the food chain and in adipose tissue due to their resistance to degradation [15]. PCBs, for instance, interact with the aryl hydrocarbon receptor (AhR) and have been linked to altered glucose and lipid metabolism in both animal models and epidemiological studies [16].

Perfluoroalkyl substances, such as PFOA and PFOS, are found in non-stick cookware, water-resistant fabrics, and food packaging. These chemicals persist in the environment and the human body for extended periods and have been associated with dyslipidemia, impaired glucose tolerance, and thyroid hormone disruption [17].

Thus, the sources of EDCs are widespread, and human exposure is continuous and cumulative. Understanding the various classes and their exposure pathways is crucial for assessing the risk of metabolic disruption and implementing effective regulatory policies to reduce the associated health burden.

Molecular Mechanisms of Metabolic Disruption

The metabolic effects of EDCs are mediated through a range of molecular mechanisms that disrupt hormonal homeostasis and alter energy balance, glucose metabolism, and lipid storage. These mechanisms primarily involve nuclear receptor interactions, disruption of insulin signaling, induction of oxidative stress, and modulation of adipogenesis.

A central mechanism by which EDCs exert metabolic disruption is through their ability to bind and modulate nuclear hormone receptors [18]. Peroxisome proliferator-activated receptor gamma (PPARγ) is a master regulator of adipogenesis, and its activation promotes differentiation of preadipocytes into mature adipocytes, leading to increased fat mass [19]. EDCs such as tributyltin (TBT) and some phthalates act as potent agonists of PPARγ [7]. Moreover, these compounds also activate retinoid X receptors (RXRs), which heterodimerize with PPARγ to regulate adipocyte gene transcription [20]. This inappropriate activation results in ectopic fat accumulation and contributes to obesity.

Estrogen receptors (ERα and ERβ) also play a crucial role in metabolic regulation. BPA and related compounds can mimic endogenous estrogens and disrupt estrogen signaling, leading to alterations in glucose homeostasis, lipid metabolism, and energy expenditure [21]. For example, BPA has been shown to impair insulin signaling in adipose tissue by affecting phosphorylation of insulin receptor substrate-1 (IRS-1) and downstream PI3K/AKT signaling [22].

Insulin resistance is a hallmark of metabolic dysfunction induced by EDCs. Chronic exposure to these compounds reduces insulin sensitivity by interfering with the insulin signaling cascade, particularly at the level of IRS proteins and glucose transporter 4 (GLUT4) translocation [23]. This impairs glucose uptake in skeletal muscle and adipose tissue, resulting in hyperglycemia and compensatory hyperinsulinemia.

Oxidative stress is another major mechanism implicated in EDC-induced metabolic disruption. EDCs can increase the production of reactive oxygen species (ROS), leading to mitochondrial dysfunction, endoplasmic reticulum stress, and activation of stress kinases such as JNK and NF-κB [24]. These events contribute to chronic low-grade

inflammation, which further impairs insulin signaling and promotes adipose tissue dysfunction. Furthermore, EDCs influence adipocyte function and lipid metabolism through dysregulation of transcription factors such as CCAAT/enhancer-binding proteins (C/EBPs), sterol regulatory element-binding protein 1c (SREBP-1c), and others that govern lipid biosynthesis and storage [25].

The integration of these molecular mechanisms ultimately results in a metabolic milieu characterized by increased adiposity, dyslipidemia, insulin resistance, and systemic inflammation. These processes are often initiated at low doses and during critical developmental windows, underscoring the importance of early-life exposure in shaping long-term metabolic outcomes.

Epigenetic Modifications and Transgenerational Effects

Endocrine-disrupting chemicals (EDCs) exert lasting biological effects through epigenetic mechanisms such as DNA methylation, histone modifications, and non-coding RNA regulation [26]. These modifications influence gene expression without altering DNA sequence and can persist across generations, particularly when exposure occurs during critical developmental windows [26]. Prenatal exposure to bisphenol A (BPA), for example, has been shown to alter the methylation of genes involved in adipogenesis and insulin signaling, such as PPARγ and IGF2 [27]. These epigenetic disruptions can impair metabolic regulation, increasing susceptibility to obesity, insulin resistance, and other components of metabolic syndrome in offspring. In animal models, such changes have also been observed in subsequent generations, suggesting transgenerational inheritance mediated by stable alterations in germline epigenetic marks [28].

Crosstalk with the Gut Microbiota

EDCs disrupt the composition and function of the gut microbiota, contributing to dysbiosis and metabolic dysfunction [29]. Exposure to compounds like BPA and phthalates shifts microbial diversity, often increasing the Firmicutes-to-Bacteroidetes ratio, a pattern associated with obesity [30]. Dysbiosis enhances intestinal permeability, allowing microbial products such as lipopolysaccharides (LPS) to enter systemic circulation. This triggers Toll-like receptor 4 (TLR4)-mediated inflammatory responses, promoting low-grade chronic inflammation and insulin resistance [31]. Additionally, reduced levels of beneficial microbial metabolites such as short-chain fatty acids further impair glucose homeostasis and immune regulation [32].

Sex-Specific and Developmental Vulnerabilities

EDCs exhibit sex-specific effects due to differences in hormone signaling and receptor expression [33]. Females may experience greater disruption of estrogenic pathways, while males are more vulnerable to anti-androgenic effects. Exposure during fetal, neonatal, or pubertal periods can induce irreversible metabolic reprogramming. Animal studies have shown that in utero exposure to EDCs such as DEHP or BPA leads to sexually dimorphic metabolic phenotypes in adulthood, underscoring the importance of developmental timing and sex in determining EDC-related risk [34].

Future Directions

Several critical areas demand further investigation to advance our understanding of endocrine-disrupting chemicals (EDCs) and their role in metabolic disorders. One priority is the elucidation of dose-response relationships, particularly the non-monotonic effects observed at low exposure levels, which challenge traditional toxicological models. Longitudinal human cohort studies integrating exposome data, including dietary, environmental, and occupational exposures, are essential to establish causal links between EDC exposure and long-term metabolic outcomes. Another key focus is the identification and validation of sensitive biomarkers that can detect early EDC exposure and predict subsequent metabolic disruption, enabling timely intervention. Additionally, novel therapeutic strategies targeting EDC-induced alterations in epigenetic regulation and gut microbiota composition hold promise. These may include dietary modulation, microbiome-targeted therapies, or epigenetic reprogramming agents. Integrative, multidisciplinary research combining environmental science, systems biology, and precision medicine is crucial for developing effective prevention and mitigation strategies against EDC-driven metabolic diseases.

CONCLUSION

The growing body of evidence implicates endocrine-disrupting chemicals as significant contributors to obesity and insulin resistance through diverse molecular pathways. Their pervasive presence in the environment and their subtle, long-term effects on metabolic programming necessitate urgent regulatory attention and further mechanistic research. A comprehensive understanding of these interactions will be instrumental in developing effective preventive and therapeutic strategies against environmentally induced metabolic disorders.

REFERENCES

1. Swarup S, Ahmed I, Grigorova Y, Zeltser R. Metabolic syndrome. StatPearls – NCBI Bookshelf. 2024. Available from: https://www.ncbi.nlm.nih.gov/books/NBK459248/

2. Ho V, Pelland-St-Pierre L, Gravel S, Bouchard MF, Verner MA, Labrèche F. Endocrine disruptors: Challenges and future directions in epidemiologic research. Environmental Research. 2021;204:111969. doi:10.1016/j.envres.2021.111969
3. Metcalfe CD, Bayen S, Desrosiers M, Muñoz G, Sauvé S, Yargeau V. An introduction to the sources, fate, occurrence and effects of endocrine disrupting chemicals released into the environment. Environmental Research. 2022;207:112658. doi:10.1016/j.envres.2021.112658
4. Di Pietro G, Forcucci F, Chiarelli F. Endocrine disruptor chemicals and children's health. International Journal of Molecular Sciences. 2023;24(3):2671. doi:10.3390/ijms24032671
5. Heindel JJ, Blumberg B, Cave M, Machtinger R, Mantovani A, Mendez MA, et al. Metabolism disrupting chemicals and metabolic disorders. Reproductive Toxicology. 2016;68:3–33. doi:10.1016/j.reprotox.2016.10.001
6. Jacobs MN, Marczylo EL, Guerrero-Bosagna C, Rüegg J. Marked for life: Epigenetic effects of endocrine disrupting chemicals. Annual Review of Environment and Resources. 2017;42(1):105–60. doi:10.1146/annurev-environ-102016-061111
7. Anne B, Raphael R. Endocrine disruptor chemicals. Endotext – NCBI Bookshelf. 2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK569327/
8. Manzoor MF, Tariq T, Fatima B, Sahar A, Tariq F, Munir S, et al. An insight into bisphenol A, food exposure and its adverse effects on health: A review. Frontiers in Nutrition. 2022;9. doi:10.3389/fnut.2022.1047827
9. Ohore OE, Zhang S. Endocrine disrupting effects of bisphenol A exposure and recent advances on its removal by water treatment systems. A review. Scientific African. 2019;5:e00135. doi:10.1016/j.sciaf.2019.e00135
10. Cimmino I, Fiory F, Perruolo G, Miele C, Beguinot F, Formisano P, et al. Potential mechanisms of bisphenol A (BPA) contributing to human disease. International Journal of Molecular Sciences. 2020;21(16):5761. doi:10.3390/ijms21165761
11. Norris DO, Carr JA. Environmental endocrinology of vertebrates. In: Elsevier eBooks. 2020. p. 527–68. doi:10.1016/B978-0-12-820093-3.00015-0
12. Latini G, Scoditti E, Verrotti A, De Felice C, Massaro M. Peroxisome Proliferator-Activated Receptors as mediators of Phthalate-Induced effects in the male and female reproductive Tract: Epidemiological and Experimental evidence. PPAR Research. 2008;2008(1). doi:10.1155/2008/359267
13. Sousa AC. OBSOLETE: Organotins: Sources and impacts on health and environment. In: Elsevier eBooks. 2017. doi:10.1016/B978-0-12-409548-9.09986-3
14. Regnier SM, El-Hashani E, Kamau W, Zhang X, Massad NL, Sargis RM. Tributyltin differentially promotes development of a phenotypically distinct adipocyte. Obesity. 2015;23(9):1864–71. doi:10.1002/oby.21174
15. Guo W, Pan B, Sakkiah S, Yavas G, Ge W, Zou W, et al. Persistent organic pollutants in food: contamination sources, health effects and detection methods. International Journal of Environmental Research and Public Health. 2019;16(22):4361. doi:10.3390/ijerph16224361
16. Eti NA, Flor S, Iqbal K, Scott RL, Klenov VE, Gibson-Corley KN, et al. PCB126 induced toxic actions on liver energy metabolism is mediated by AhR in rats. Toxicology. 2021;466:153054. doi:10.1016/j.tox.2021.153054
17. Pezeshki H, Rajabi S, Hashemi M, Moradalizadeh S, Nasab H. Per- and Poly-fluoroalkyl Substances as Forever Chemicals in Drinking Water: Unraveling the Nexus with Obesity and Endocrine Disruption – A Mini Review. Heliyon. 2025;11(4):e42782. doi:10.1016/j.heliyon.2025.e42782
18. Lee H, Jeung E, Cho M, Kim T, Leung PCK, Choi K. Molecular mechanism(s) of endocrine-disrupting chemicals and their potent oestrogenicity in diverse cells and tissues that express oestrogen receptors. Journal of Cellular and Molecular Medicine. 2012;17(1):1–11. doi:10.1111/j.1582-4934.2012.01649.x
19. Ma X, Wang D, Zhao W, Xu L. Deciphering the roles of PPARγ in adipocytes via dynamic change of transcription complex. Frontiers in Endocrinology. 2018;9. doi:10.3389/fendo.2018.00473
20. Shoucri BM, Hung VT, Chamorro-García R, Shioda T, Blumberg B. Retinoid X receptor activation during adipogenesis of female mesenchymal stem cells programs a dysfunctional adipocyte. Endocrinology. 2018;159(8):2863–83. doi:10.1210/en.2018-00056
21. Tang Y, Qin G, Qian N, Zeng X, Li R, Lai KP. Bisphenol A and its replacement chemicals as endocrine disruptors and obesogens. Environmental Chemistry and Ecotoxicology. 2025. doi:10.1016/j.enceco.2025.04.001

22. Sivashanmugam P, Mullainadhan V, Karundevi B. Dose-dependent effect of Bisphenol-A on insulin signaling molecules in cardiac muscle of adult male rat. Chemico-Biological Interactions. 2017;266:10-6. doi:10.1016/j.cbi.2017.01.022
23. Zhao X, An X, Yang C, Sun W, Ji H, Lian F. The crucial role and mechanism of insulin resistance in metabolic disease. Frontiers in Endocrinology. 2023;14. doi:10.3389/fendo.2023.1149239
24. Bansal A, Henao-Mejia J, Simmons RA. Immune System: an emerging player in mediating effects of endocrine disruptors on metabolic health. Endocrinology. 2017;159(1):32–45. doi:10.1210/en.2017-00882
25. Maradonna F, Carnevali O. Lipid metabolism alteration by endocrine disruptors in animal models: an overview. Frontiers in Endocrinology. 2018;9. doi:10.3389/fendo.2018.00654
26. Akanbi CA, Rotimi DE, Ojo AB, Ojo OA. Endocrine-disrupting chemicals (EDCs) and epigenetic regulation in embryonic development: mechanisms, impacts, and emerging trends. Toxicology Reports. 2024;101885. doi:10.1016/j.toxrep.2024.101885
27. Naomi R, Yazid MD, Bahari H, Keong YY, Rajandram R, Embong H, et al. Bisphenol A (BPA) leading to obesity and cardiovascular complications: A compilation of current in vivo study. International Journal of Molecular Sciences. 2022;23(6):2969. doi:10.3390/ijms23062969
28. Legoff L, D'Cruz SC, Tevosian S, Primig M, Smagulova F. Transgenerational inheritance of environmentally induced epigenetic alterations during mammalian development. Cells. 2019;8(12):1559. doi:10.3390/cells8121559
29. Fabozzi G, Rebuzzini P, Cimadomo D, Allori M, Franzago M, Stuppia L, et al. Endocrine-disrupting chemicals, gut microbiota, and human (in)fertility-It is time to consider the triad. Cells. 2022;11(21):3335. doi:10.3390/cells11213335
30. Chiu K, Warner G, Nowak RA, Flaws JA, Mei W. The impact of environmental chemicals on the gut microbiome. Toxicological Sciences. 2020;176(2):253–84. doi:10.1093/toxsci/kfaa065
31. Di Vincenzo F, Del Gaudio A, Petito V, Lopetuso LR, Scaldaferri F. Gut microbiota, intestinal permeability, and systemic inflammation: a narrative review. Internal and Emergency Medicine. 2023;19(2):275–93. doi:10.1007/s11739-023-03374-w
32. Portincasa P, Bonfrate L, Vacca M, De Angelis M, Farella I, Lanza E, et al. Gut microbiota and short chain fatty acids: Implications in glucose homeostasis. International Journal of Molecular Sciences. 2022;23(3):1105. doi:10.3390/ijms23031105
33. Rebuli ME, Patisaul HB. Assessment of sex specific endocrine disrupting effects in the prenatal and pre-pubertal rodent brain. The Journal of Steroid Biochemistry and Molecular Biology. 2015;160:148–59. doi:10.1016/j.jsbmb.2015.08.021
34. Palanza P, Nagel SC, Parmigiani S, Saal FSV. Perinatal exposure to endocrine disruptors: sex, timing and behavioral endpoints. Current Opinion in Behavioral Sciences. 2015;7:69–75. doi:10.1016/j.cobeha.2015.11.017

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