ENDOCRINE DISRUPTORS: WHERE DO WE GO FROM HERE?

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INTRODUCTION

The incidence of conditions such as diabetes, obesity, asthma, and neurodevelopmental problems have increased substantially in the past 20 years. The human genome has not changed in that period of time, so the environment is likely the cause of much of this increase. The "environment" is very broad and includes industrial and agricultural chemicals, physical agents such as heat and radiation, food and nutrients, prescription drugs, by-products of combustion and industrial processes (e.g., dioxin), lifestyle choices (including substance abuse), social and economic factors, infectious agents, and the microbiome (i.e., gut flora). We will never understand the full etiology of disease without a more complete understanding of the role of the environment in disease.

The increased incidence of testicular cancer, breast cancer, hypospadias, sperm count, diabetes, autism and attention-deficit hyperactivity disorder points to the role of endocrine disruptors as a potential source. The endocrine system is a highly organized system of glands and hormones that regulates vital functions such as growth, response to stress, sexual development and behavior, production and utilization of insulin, metabolism, intelligence and behavior, and the ability to reproduce. It is now clear that this system can be perturbed by environmental chemicals that were designed for one effect but have been shown to interfere with endocrine signaling.

DISCUSSION

To date, there are over 800 of these so-called endocrine disrupting chemicals (EDCs) which include pharmaceuticals, dioxin and dioxin-like compounds, polychlorinated biphenyls, DDT and other pesticides, and components of plastics such as bisphenol A (BPA), phthalates, flame retardants and solvents. EDCs are found in many everyday products--including plastic bottles, metal food cans, detergents, foam and fabric, food additives, toys, cosmetics, and household products.

EDCs were originally thought to exert their actions solely through nuclear hormone receptors, including receptors for estrogen, androgen, progesterone, thyroid hormones, and retinoids. However, recent evidence shows that the mechanisms by which EDCs, as well as endogenous hormones, act are much broader than originally recognized. Studies have shown that in addition to altering nuclear receptor signaling, EDCs are capable of acting through membrane receptors, nonsteroid receptors, transcriptional coactivators and repressors, that can all converge upon endocrine, reproductive, metabolic, and neurological systems, among others. Many EDCs can perturb multiple endocrine pathways, and effects are context (time and tissue) dependent.

One aspect of endocrine disruptors is their ability to create effects at low doses. Just as tiny amounts of hormones can have large effects on physiological systems, tiny amounts of chemicals that mimic hormones can have similar large effects.

A feature related to low dose effects is the non-monotonic dose-response behavior of EDCs. In the past, basic toxicology focused on the simple dichotomy of toxic versus nontoxic, which implies that all

substances can be harmful at high doses while at some lower dose, no harm is done. However, we now know that EDCs can create physiologically relevent effects at low doses, and these effects can have a substantial impact on our health. These effects may be beneficial at certain doses and deleterious at others. This modern understanding of non-monotonic effects is critical to understanding the behavior of chemical agents and also how resulting health effects may differ based on various exposures. One practical example of this effect is "Tamoxifen flare" in which breast cancer patients treated with the chemotherapeutic agent Tamoxifen experience tumor growth during early treatment with small doses of the drug, then, as the drug dose increases, tumor reduction.

EDCs also produce a wide range of health effects. Since endocrine signals govern every organ and process in the body, interference with these processes are likely to affect multiple organ systems and complex physiological pathways. As such, EDCs can result in alterations in diverse, heterogenous health endpoints. Cancer and birth defects are not the only endpoints to generated by EDCs; decreasing age of pubertal onset, shortened anogenital distance, and obesity are some of the conditions produced by exposure to EDCs.

The effects of EDCs can persist long after exposure, and latent health effects from this exposure can be observed much later in life. This is especially true when exposures occur during growth and development, processes that are very sensitive to endocrine regulation. Chemical exposures during early life stages can disrupt normal patterns of development and thus dramatically alter disease susceptibility later in life. EDC exposures during developmental "windows of susceptibility" have been shown to affect endocrine signaling pathways that can lead to endocrine cancers, obesity, diabetes, infertility, premature puberty, learning disabilities, cognitive and brain development problems, and sexual development problems including feminizing of males or masculine effects on females.

Also of concern are ubiquitous exposures, as chemicals with endocrine disrupting activity are widely dispersed in our environment. EDCs are often dispersed at biologically effective levels and human exposure is common. In addition, exposures do not occur singly – humans are exposed to mixtures of many different chemicals at the same time. Exposures to mixtures can have synergistic effects on various metabolic pathways, and one exposure can alter the body's response and susceptibility to later exposures.

The public health impact of EDC exposures can be significant. Small decreases in physiologic functioning or increases in disease susceptibility at the individual level can result in compounded, aggregate effects at the population level. When viewed from a population standpoint, environmental exposures to EDC scan exact a huge toll.

Finally, given these unique properties of EDCs, toxicity testing and research into EDCs' effects should take into consideration these characteristics. Testing needs to take into consideration low dose effects, varied sensitivity across developmental stages, assessment of a wide range of endpoints, some of which may be novel, later life effects from early exposures, effects of mixtures, exposure assessment, and the public health impact of EDCs.

ACKNOWLEDGEMENTS

This abstract has been reviewed by the National Institute of Environmental Health Sciences, and approved for publication. Approval does not signify that the contents necessarily reflect the views of the Agency, nor does the mention of trade names or commercial products constitute endorsement or recommendation for use. The opinions expressed in this manuscript are those of the authors and do not necessarily reflect the official opinion of the National Institutes of Health.