ENDOCRINE DISRUPTORS

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INTRODUCTION

The term *endocrine disruptor* was coined at the Wingspread Conference Centre in Wisconsin, in 1991. An endocrine-disrupting compound was defined by the U.S. Environmental Protection Agency (EPA) as "an exogenous agent that interferes with synthesis, secretion, transport, metabolism, binding action, or elimination of natural blood-borne hormones that are present in the body and are responsible for homeostasis, reproduction and developmental process."

Endocrine disruptors act via nuclear receptors, nonnuclear steroid hormone receptors, non-steroid receptors (*e.g.* neurotransmitter receptors such as the serotonin receptor, dopamine receptor, norepinephrine receptor), orphan receptors [*e.g.*, aryl hydrocarbon receptor (AhR)—an orphan receptor], enzymatic pathways involved in steroid biosynthesis and/or metabolism, and numerous other mechanisms that eventually converge upon endocrine and reproductive systems. Endocrine disruptors may turn on, shut off, or modify signals that hormones carry, which may affect the normal functions of tissues and organs.

The past two decades have seen a lot of new information and research done on the hazards of endocrine disruptors and their impact on wildlife and also in humans[1]. The Endocrine Society has in a scientific statement noted that it is difficult to show that endocrine disruptors cause human diseases, however, it has recommended that the precautionary principle should be followed.[2] Another concurrent statement expresses policy concerns.[3]

TYPES OF ENDOCRINE DISRUPTORS

A wide variety of chemicals act as endocrine disruptors. The Endocrine Disruption Exchange List (TEDX) to date has almost 870 endocrine disruptors listed. Chemicals commonly detected in people include Dichloro-diphenyl-trichloroethane (DDT), polychlorinated biphenyls (PCB's), bisphenol A (BPA), polybrominated diphenyl ethers (PBDE's), and a variety of phthalates.[4] DDT is still used as anti-malarial insecticide in Africa and parts of Southeast Asia in limited quantities DDT interfered with reproductive development.[4,5] Recent studies suggest DDT may inhibit the proper development of female reproductive organs that adversely affects reproduction into maturity.[6] Additional studies suggest that a marked decrease in fertility in adult males may be due to DDT exposure.[7] Most recently, it has been suggested that exposure to DDT in utero can increase a child's risk of childhood obesity.[8] DDT is still used as anti-malarial insecticide in Africa and parts of Southeast Asia in limited quantities. Recent studies have also shown the historical record of DDT deposition on remote glaciers in the Himalayas.[9]

Polychlorinated biphenyls (PCBs) are a class of chlorinated compounds used as industrial coolants and lubricants. Recent studies show the endocrine interference of certain PCB congeners is toxic to the liver and thyroid,[10] increases childhood obesity in children exposed prenatally,[11] and may increase the risk of developing diabetes.[12,13] Bisphenol A is commonly found in plastic bottles (including many baby bottles), plastic food containers, dental materials, and the linings of metal food and infant formula cans. Another exposure comes from receipt paper commonly used at grocery stores and restaurants, because today the paper is commonly coated with a BPA containing clay for printing purposes.[13]

Laboratory animals exposed to low levels of it have elevated rates diabetes, mammary and prostate cancers, decreased sperm count, reproductive problems, early puberty, obesity.

Polybrominated diphenyl ethers or PBDE, are organobromine compounds that are used as flame retardants. Like other brominated flame retardants, PBDEs have been used in a wide array of products, including building materials, electronics, furnishings, motor vehicles, airplanes, plastics, polyurethane foams, and textiles. It exposure interferes with proper thyroid hormone regulation.[14] Phthalates are found in some soft toys, flooring, medical equipment, cosmetics and air fresheners. They are of potential health concern because they are known to disrupt the endocrine system of animals, and some research has implicated them in the rise of birth defects of the male reproductive system.[15,16] Certain alkylphenols are degradation products from nonionic detergents. Nonylphenol is considered to be a low-level endocrine disruptor owing to its tendency to mimic estrogen.[17] Perfluorooctanoic acid (PFOA) exerts hormonal effects including alteration of thyroid hormone levels. Blood serum levels of PFOA were associated with an increased time to pregnancy — or "infertility" — in a 2009 study. PFOA exposure is associated with decreased semen quality. PFOA appeared to act as an endocrine disruptor by a potential mechanism on breast maturation in young girls. One study has reported an association between exposure in girls and a later onset of puberty.

Some other examples of putative EDCs are polychlorinated dibenzo-dioxins (PCDDs) and -furans (PCDFs), polycyclic aromatic hydrocarbons (PAHs), phenol derivatives and a number of pesticides (most prominent being organochlorine insecticides like endosulfan and DDT and its derivatives, the herbicide atrazine, and the fungicide vinclozolin), the contraceptive 17-alpha ethinylestradiol, as well as naturally occurring phytoestrogens such as genistein and mycoestrogens such as zearalenone.

ROUTES OF EXPOSURE

Food is a major mechanism by which people are exposed to pollutants. Diet is thought to account for up to 90% of a person's PCB and DDT body burden.[18]

A recent study reported that urinary concentrations of the phytoestrogens genistein and daidzein were about 500-fold higher in infants fed soy formula compared with those fed cow's milk formula.[19] With the increase in household products containing pollutants and the decrease in the quality of building ventilation, indoor air has become a significant source of pollutant exposure.[20]

Recent studies suggest that contaminated house dust, not food, may be the major source of PBDE in our bodies.[21] One study estimated that ingestion of house dust accounts for up to 82% of our PBDE body burden.[22]

Research conducted by the Environmental Working Group found that 19 out of 20 children tested had levels of PBDE in their blood 3.5 times higher than the amount in their mothers' blood.[22] It may be that babies and toddlers ingest more contaminated housedust than the adults they live with, and therefore have much higher levels of pollutants in their systems.

DOSE-RESPONSE CONTROVERSY

One major objection to the theory of endocrine disruptors is the dosage effect. There is a large gap between high exposures seen in a laboratory experiment versus the relatively low levels found in the environment.[23,24] Critics argue that dose-response relationship data suggest that the amounts of the chemicals actually in the environment are too low to cause an effect. A consensus statement by the Learning and Development Disabilities Initiative rebuts this criticism arguing that "The very low-dose effects of endocrine disruptors cannot be predicted from high-dose studies, which contradicts the standard 'dose makes the poison' rule of toxicology.

ENVIRONMENTAL AND HUMAN BODY CLEANUP

Through the efforts of several large-scale monitoring programs the most prevalent pollutants in the human population are fairly well known. The first step in reducing the body burden of these pollutants is enacting policies that eliminate or phase out their production.

The second step toward lowering human body burden is awareness of and potentially labeling foods that are likely to contain high amounts of pollutants. This strategy has worked in the past - pregnant and nursing women are cautioned against eating seafood that is known to accumulate high levels of mercury. Ideally, a certification process should be in place to routinely test animal products for POP concentrations. This would help the consumer identify which foods have the highest levels of pollutants.

The most challenging aspect of this problem is discovering how to eliminate these compounds from the environment and where to focus remediation efforts. Even pollutants no longer in production persist in the environment, and bio-accumulate in the food chain. An understanding of how these chemicals, once in the environment, move through ecosystems, is essential to designing ways to isolate and remove them. Working backwards through the food chain may help to identify areas to prioritize for remediation efforts. This may be extremely challenging for contaminated fish and marine mammals that have a large habitat and who consume fish from many different areas throughout their lives.

Many persistent organic compounds, PCB, DDT and PBDE included, accumulate in river and marine sediments. Several processes are currently being used by the EPA to clean up

heavily polluted areas, as outlined in their Green Remediation program.

One of the most interesting ways is the utilization of naturally occurring microbes that degrade PCB congeners to remediate contaminated areas.[25] There are many success stories of cleanup efforts of large heavily contaminated Superfund sites. A 10-acre (40,000 m^2) landfill in Austin, Texas contaminated with illegally dumped VOCs was restored in a year to a wetland and educational park.

A US uranium enrichment site that was contaminated with uranium and PCBs was cleaned up with high tech equipment used to find the pollutants within the soil. The soil and water at a polluted wetlands site were cleaned of VOCs, PCBs and lead, native plants were installed as biological filters, and a community program was implemented to ensure ongoing monitoring of pollutant concentrations in the area. These case studies are encouraging due to the short amount of time needed to remediate the site and the high level of success achieved.

ENDOCRINE DISRUPTORS, DIABETES, AND GLUCOSE HOMEOSTASIS

It is speculated that by the year 2030 the prevalence of diabetes will increase to 4.4% worldwide (from 2.8% in 2000) with more than 300 million diabetic adults.[26] Widespread EDCs, such as dioxins, pesticides and bisphenol A, cause insulin resistance and alter β-cell function in animal models. These EDCs are present in human blood and can accumulate in and be released from adipocytes. After binding to cellular receptors and other targets, EDCs either imitate or block hormonal responses. Many of them act as estrogens in insulin-sensitive tissues and in β cells, generating a pregnancy-like metabolic state characterized by insulin resistance and hyperinsulinemia. Adult exposure in mice produces insulin resistance and other metabolic alterations; in addition, during pregnancy, EDCs alter glucose metabolism in female mice, as well as glucose homeostasis and endocrine pancreatic function in offspring.

Several epidemiological studies have linked high dioxin levels with increased risk for diabetes or altered glucose metabolism[27]. Alonso-Magdalena *et al.*[28] undertook an *in vivo* experiment to evaluate the impact of BPA on pancreatic beta cell function. Its biological action was compared with 17 beta estradiol. The results showed that acute treatments with either estradiol or BPA caused a temporary hyperinsulinemia, whereas longterm exposure provoked insulin resistance with chronic increased insulin levels, an aggravating factor for the development of diabetes mellitus[29]. Recently, in conditioned media from human breast, sc and visceral adipose explants, it was demonstrated that BPA at environmentally relevant doses (0.1 and 1 nM) inhibits the release of adiponectin, an adipocyte-specific hormone that increases insulin sensitivity. Therefore, factors that suppress adiponectin release could aggravate insulin resistance and susceptibility to obesity-related syndromes like metabolic syndrome and type 2 diabetes mellitus.

Low doses of BPA and DES were shown to impair the molecular signaling that leads to secretion of glucagon by suppressing intracellular calcium ion oscillations in beta cells in response to low blood glucose levels through a nongenomic mechanism[30]. Importantly, whereas current evidence represents experimental data from laboratory animals or *in vitro* studies, no direct association with humans has yet been established, with the exception of the epidemiological studies discussed above.

IMPACTS OF EDCS ON FEMALE REPRODUCTION:

Endocrine disruption by environmental chemicals may indeed contribute to the pathogenesis of PCOS. It is plausible that *in utero* exposure of human female fetuses to androgen-like EDCs could result in PCOS in adulthood, along with associated metabolic disorders.

Very recent evidence for androgenic properties of personal-care products such as triclocarban[31] add to the possibility of environmental androgens, although a connection to PCOS has not yet been drawn. Women with PCOS have higher levels of the EDCBPA,[32] and increased testosterone in these women is consistent with decreased clearance of BPA.[33]

Although a cause and effect of BPA and PCOS have not been demonstrated definitively, the biological plausibility is interesting and worthy of further consideration.

In utero exposure to DES increased the risk of abnormal cervical, uterine, and oviduct anatomy[34], vaginal adenocarcinoma,[35] subfertility and infertility, ectopic pregnancy.

High levels of the DDT metabolite p,p_-DDE, in plasma from foreign immigrant girls with precocious puberty in Belgium.[36]

Breastfed girls exposed to high levels of PBB *in utero* (_7 ppm) is associated with earlier age at menarche.[37]

Premature thelarche Higher levels of phthalates and its major metabolite mono-(2-ethylhexyl) phthalate in serum of girls from Puerto Rico with premature breast development.[38]

Increased levels of serum AGEs in women with PCOS and positive correlation between AGE proteins and testosterone levels.[39]

In polycystic ovaries, increased immunostaining of colocalized AGEs, RAGEs, and activated nuclear factor-κB.[40,41] Isolation of persistent organochlorine chemicals from ovarian follicular fluid of women undergoing IVF[42] Indications that exposure to pesticides may contribute to female infertility in some occupationally exposed groups.[43]

MALE REPRODUCTIVE AND DEVELOPMENTAL HEALTH: THE HUMAN EVIDENCE

Anway and Skinner[44] showed direct as well as transgenerational effects of EDCs on semen quality after intrauterine exposure.

A large study on male partners of subfertile couples from an infertility clinic in Massachusetts[45,46] found associations between monobutyl phthalate and low sperm count and motility. There was also a dose-response relationship between monobenzyl phthalate and sperm counts. In contrast to the U.S. study, in a Swedish study there were no relationships of MBP or MBzP with any of the semen parameters[47]. Potential reasons explaining why the two studies found differing results include differences in age and fertility of the study populations.

Men presenting to an infertility clinic may be more "susceptible" to reproductive toxicants, including phthalates, than men from the general population. Furthermore, it is also unclear whether middle-aged men, compared with young men, are more susceptible to reproductive toxicants because of an age-related response to the toxicant.

2. PCBs and semen quality

   The epidemiological evidence on the relationship between PCBs and semen quality support an inverse association of PCBs with reduced semen quality, specifically reduced sperm motility. Such relationships have been consistently reported across studies performed in different countries (India, The Netherlands, Taiwan, Sweden, and the United States). The associations were found across a range of PCB levels, suggesting that there was not a threshold.

Dioxins and semen quality

A recently published study of dioxin exposure and semen quality suggested that timing of exposure may have an impact upon the response.[48]

Interestingly, the men exposed prepubertally (1 to 9 yr) had an inverse association between serum TCDD concentrations and semen quality, specifically sperm count and motility, whereas the men exposed at ages 10–17 yr had a positive association with semen quality, referred to as stimulatory by the authors. The men exposed at 18–26 yr of age had no associations of TCDD with semen quality. Men exposed at both 1–9 and 10–17 yr of age had lower estradiol and higher FSH concentrations compared with unexposed men. These results suggest that the timing of exposure, *i.e.*, life stage, may have importance.

THYROID, METABOLISM, AND GROWTH

Many natural substances are known to affect thyroid function, including low iodine as well as goitrogens in various foods[49]. There are a number of chemicals that can interfere with iodide uptake by the NIS[50], including chlorate, thiocyanate, and nitrates that are particularly prevalent.

Perchlorate is used as an oxidant in solid rocket propellants, in ordnance, fireworks, airbag deployment systems, and others. Because of the environmental stability of perchlorate, it has become a widespread contaminant in drinking and irrigation waters and in food,[51] such that perchlorate contamination is nearly ubiquitous in the U.S. population.[52] Experimental studies in humans indicate that the serum half-life of perchlorate is about 8 h and that a dose of about 5.2 _g/kg_d is sufficient to begin to reduce iodide uptake into the thyroid gland.[53]

Because infants are particularly vulnerable to thyroid hormone insufficiency[54] and because perchlorate levels are particularly high in breast milk,[55] it is of concern that perchlorate may be affecting thyroid hormone signaling in early infant development in some proportion of the U.S. population.[56] Cigarettes contain thiocyanates that also inhibit iodine uptake.

A number of compounds are known to block TPO. TPO inhibitors include the isoflavones, especially those found in soy protein (*e.g.*, genistein, coumesterol). In humans, goiter has been reported in infants fed soy formula.[57,58] In addition, teenage children diagnosed with autoimmune thyroid disease were found to have twice the rate of occurrence if they had consumed soy formula as infants.

Boker *et al*[59] recently reviewed the dietary sources of a variety of isoflavones, showing that these are common dietary components. These isoflavones are also so-called "phytoestrogens," which are highly enriched in some commercial preparations.

ENVIRONMENTAL CHEMICALS IMPACTING THYROID HORMONE TRANSPORT, METABOLISM, AND CLEARANCE

Many chemicals are known to decrease the serum half-life of T4 by inducing liver enzymes that glucuronidate T4.[60,61] These enzymes uridine diphosphate glucuronyl transferase can be induced by dioxin-like compounds acting on the AhR or through the pregnane X-receptor or constitutive androstane receptor nuclear receptors[62].

These chemicals fall into many industrial categories including pesticides of many types.[63] A number of environmental chemicals affect deiodinase activity including PCBs[64] and others.[65] Environmental chemicals that affect deiodinase activity may have effects that are not entirely consistent with the appearance of "hypothyroidism" and, therefore, may be difficult to recognize in the absence of mechanistic studies.

ENVIRONMENTAL CHEMICALS IMPACTING THE THYROID HORMONE RECEPTOR

1. PCBs

   PCBs alter motor behavior associated with cerebellar

function, as well as cerebellar anatomy[66]. Interestingly, PCB exposure is associated with an increase in expression of glial fibrillary acidic protein[67], which is also increased by thyroid hormone insufficiency.[68] Finally, in young children, the association between PCB body burden and behavioral measures of response inhibition is stronger in those children that have a smaller corpus callosum,[69] an area of the brain affected by thyroid hormone.[70]

2. PBDEs

PBDEs may also bind to the thyroid hormone receptor.[71] Marsh et al[72] demonstrated that two hydroxylated PBDEs can bind to both TR alfa and TR beta, but with a significant preference for TR beta.

ENVIRONMENTAL CHEMICALS, OBESITY, AND METABOLISM

A. Introduction to EDCs and the obesity epidemic

The rise in the incidence in obesity matches the rise in the use and distribution of industrial chemicals that may be playing a role in generation of obesity,[73] suggesting that EDCs may be linked to this epidemic. Gru¨n and Blumberg[74,75] have coined the terminology "obesogens" in reference to molecules that inappropriately regulate lipid metabolism and adipogenesis to promote obesity.

B. Environmental estrogens and obesity

The impact of environmental estrogens on adipose tissue may be through direct modulation of lipogenesis, lipolysis, and adipogenesis, or indirect by affecting food consumption and leptin secretion targeting the central nervous system or lipid homeostasis in liver.[76]

The estrogenic pharmaceutical chemical DES illuminates the relationship between perinatal exposures and latent development of high body weight and obesity.

C. Peroxisome proliferator-activated receptor (PPAR) gamma **and organotins:**

PPAR gamma is molecular targets for endocrine disruptors, in particular organotin compounds such as tributyltin (TBT) and triphenyltin, which have been widely used in agriculture and industry. In addition, at high doses, TBT can inhibit aromatase enzyme activity in adipose tissue directly, leading to decreased estradiol levels and down-regulation of ER target genes. TBT at moderate to high doses inhibits the activity of 11β-hydroxysteroid dehydrogenase 2, resulting in decreased inactivation of cortisol. It has been hypothesized that the increased local glucocorticoid levels could influence late stages in adipocyte differentiation and thus, metabolic regulation.[77,78]

D. Phytoestrogens

In recent years, efforts to implement healthier eating habits have resulted in an increased consumption of soy products and supplements and hence, increased exposure to phytoestrogens. Genistein is the principal phytoestrogen in soy and has a wide range of biological actions. It binds to ER, but also displays antiestrogenic action[78]. At low concentrations, genistein was found to act as estrogen and exert an inhibitory effect on lipogenesis. At higher concentrations, genistein promotes lipogenesis.[79]

CONCLUSIONS

Although direct causal links between exposures to EDCs and disease states in humans are difficult to draw, results from basic research and epidemiological studies make it clear that greater screening for exposures and targeting at-risk groups is a high priority. In addition to enhancing research in these areas, an important and effective approach is prevention of disease. Our chemical policies at local, state, and national levels, as well as globally, need to be formulated, financed, and implemented to ensure the best public health.

Further, by communicating these priorities to basic and clinical researchers, physicians, community advocates, and the public at large, we are hopeful that early identification and intervention will be facilitated.

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