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REVIEW

ADIPOSE TISSUE ACCUMULATION OF ENDOCRINE DISRUPTING COMPOUNDS: VARIANT OF A COMMON THEME IN EXPOSOME RESEARCH

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Abstract

Today, a wide variety of exogenous agents (xenobiotics) collectively termed endocrine disrupting compounds (EDC) includes almost 1000 synthetic chemicals. The group of EDC is highly heterogeneous and embodies chemicals used as industrial solvents and their by-products (persistent organic pollutants and dioxins), plastics (bisphenol A) and various pesticides, herbicides and industrial pollutions. The concept of endocrine disruption refers to exogenous chemicals present in the environment, including the food and drugs, that affect human's hormonal systems. Both epidemiological and experimental evidence suggest an association between exposure to EDC and diabetes and related cardiometabolic disorders. These compounds are not just accumulate in the white adipose tissue, but also release into the blood circulation and exhibit their pathogenic effects on various organs. The present review is focused on the factors influencing the accumulation, metabolism and release of EDC in the white adipose tissue.

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Key words: white adipose tissue, xenobiotics, environmental chemicals, chronic exposure, exposome, target organs, toxic effects

Introduction

The exposome encompasses the totality of human environmental exposures from conception onwards. It was first proposed by Christopher Wild in 2005 article entitled "Complementing the genome with an "exposome" (1).

Xenobiotics as a part of human exposome are chemical compounds foreign to a given biological system. With respect to animals and humans, xenobiotics include drugs, drug metabolites, and environmental chemicals such as synthetic pesticides, herbicides, and industrial pollutants. Originally articulated in the early 1990s the theory of *endocrine disruption* refers to exogenous chemicals present in the environment and/or diet that interfere and disrupt physiological hormonal systems, inducing adverse effects on human and wildlife health (2). Today, the EU definition of endocrine disrupting compounds (EDC) refers to: "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"(3).

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Endocrine disrupting compounds interfere and disrupt physiological hormonal balance inducing adverse effects on human health through different mechanisms, such as direct interaction with hormone receptors, competition on binding and transport proteins or interference with hormone metabolism, thus blocking or inducing the synthesis of the hormones. A wide variety of chemicals act as EDC. The Endocrine Disruption Exchange List to date includes almost 1000 endocrine disruptors (4). The group of EDC is highly heterogeneous and includes synthetic chemicals used as industrial solvents/lubricants and their by-products (persistent organic pollutants - POP), dioxins such as 2,3,7,8-tetrachlorodibenzo-p-dioxin - TCDD), plastics (bisphenol A - BPA), pesticides (dichlorodiphenyltrichloroethane - DDT), plasticizers (phthalates such as diethylhexyl phthalate - DEHP), heavy metals (arsenic, cadmium), tributyl tin (TBT), triphenyltin (TPT), fungicides (vinclozolin) and pharmaceutical agents (diethylstilbestrol - DES). Persistent organic pollutants comprise a broad class of organohalides, including polychlorinated biphenyls (PCB), polybrominated biphenyls (PBB) and organochlorine pesticides.

Endocrine disrupting compounds are widely dispersed in the environment, therefore environmental human exposure occurs through a variety of routes and varies widely around the world. Food ingestion represents the major route by which people are exposed to EDC. For example, diet is thought to account for up to 90% of a person's POP body burden (5). Taking into account that these pollutants are accumulated particularly in highly rank predators, like fish, in Sweden, consumption of fatty fish from the Baltic Sea is the major source of POP (6).

White adipose tissue (WAT) is classically considered the main reservoir of lipids and energy (7). When stimulated by insulin, adipocytes store glucose as triglycerides in lipid droplets. In addition to the energy-storing, adipocytes, also other adipose tissue cells, secrete - *via* endocrine and paracrine pathway - a large number of signalling proteins, collectively named adipokines (8, 9). Moreover, as discussed herein, WAT represents the major storage compartment for lipophilic contaminants, due to rapid penetration through the cell membranes, followed by their metabolism and discharge.

Endocrine disrupting compounds, including POP, PCB and numerous other environmental chemicals, are highly attracted to lipids and accumulate in the WAT (10). Therefore, their adipose storage can be considered as an internal source of chronic exposure to EDC. The adipose tissues can be also the target of EDC that alters its functions, by increasing adipose tissue inflammation or modulating the differentiation of adipose precursor cells. For instance, TBT which acts on nuclear receptors involved in fat metabolism and regulation of glucose uptake, induces in animals hepatic steatosis, hyperinsulinemia, hyperleptinemia and a reduction in hepatic adiponectin levels, in a dose-dependent fashion (11). Similar results, meaning the developed insulin resistance syndrome, abdominal obesity and hepatosteatosis were obtained in adult Sprague-Dawley rats exposed for 28 days to crude salmon oil containing POP (12).

Factors that influence adipose accumulation and release of endocrine disrupting compounds

Physiological factors

The kinetics of accumulation by the adipose tissues depends on various physiological factors, but also on physicochemical properties of the EDC. The physiological factors that may influence the accumulation and also the release from the adipose tissues are: (*i*) alteration or change in the mass or composition of the adipose tissue or change in their perfusion rates, (*ii*) protein and lipid binding, (*iii*) change in the rate of EDC biotransformation, and (*iv*) change in the absorption rate.

It is obvious that POP storage in the adipose tissue could be considered a protective effect in respect to the general toxic effect induced by POP. Moderate or severe weight loss elicited by dietary changes either alone or coupled with bariatric surgery was associated with increased plasma concentrations of POP such as PCB and organochlorine pesticides (13-15), suggesting that the systemic presence of POP could be the result of an increased lipolysis. In all studies, serum POP levels were positively correlated with liver toxicity markers and lipid parameters. Released POP in blood can be taken up readily by the remaining fat, which is essentially an infinite sink, but generally the total POP body burden tends to decrease by 15% after weight loss, excreted via feces, but also via lactation or placental transfer (16).

Adipose tissues perfusion rates could influence the differential accumulation of EDC in different anatomical locations. For instance, organochloride insecticides are accumulated in subcutaneous and renal adipose tissue, while POP are accumulated in the subcutaneous and visceral adipose tissue (17). Other researchers (15) observed that the patterns of POP congeners distributions in these adipose tissues are extremely similar, therefore subcutaneous adipose tissue could be used to estimate total POP body burden.

Recent studies have suggested a selective distribution of PCB in visceral and subcutaneous adipose tissue (18, 19). The low chlorinated polychlorinated PCB (as PCB74, 99, 105 and 118), and the pesticide dichloro-diphenyl dichloroethylene were distributed to both visceral and subcutaneous adipose tissues, whereas the more highly chlorinated PCB, like PCB 153, 156, 157, 169, 180, 206, and 209, were inversely distributed to the same tissues. Taking into account that visceral and subcutane-

ous adipose tissues have different contributions to the PCB serum concentrations, the selective distribution may explain the different profiles of PCB in serum and adipose tissue.

Also the protein binding influences, at least partially, the EDC accumulation. As an example, PCB and organochlorine pesticides in blood are associated with the protein fraction, but also with lipoproteins (20). Although their binding with lipoproteins is considered as the major mechanism responsible for their accumulation, it may also be partially responsible for their lipotoxicity (21).

It is well known that biotransformation has a critical impact on EDC accumulation but also on their toxicity. The adipose tissues biotransformation contributes considerably to body detoxification taking into account that it contains a complete set of enzymes such as paraoxonases, carboxylesterases and some isozymes of UDP-glucuronosyltransferases, several cytochrome P450 (CYP) isozymes such as aromatase (CYP19) being also expressed in adipocytes and their activity may play a crucial role in EDC-induced diabetogenic and obesogenic effects (reviewed in 22).

Sometimes even the hepatic biotransformation can induce the formation of metabolites with high affinity to adipose tissues. As an example, in the case of POP, hepatic biotransformation that involves glutathione-*S*-transferase induces the formation of more lipophilic metabolites, *via* mercapturic acid pathway. These metabolites accumulate in lipid-rich tissues such as liver and WAT (23, 24).

Physiochemical properties

There are several physiochemical properties that could influence the distribution and accumulation of EDC, such as pKa or molecular weight, but the most relevant characteristics are the lipid solubility and EDC biological-life.

Regarding the lipid solubility, expressed by octanol/water partition coefficient (K_{ow}) and its influence on accumulation, some researchers used PBPK model to predict the correlation between K_{ow} value and adipose-blood diffusion for highly fat soluble POP that have a slow and incomplete diffusion. The adipose-blood diffusion becomes rate limiting if log K_{ow} is greater than 5.6, and is reduced by a factor of 30 for a POP with a log K_{ow} of 7.36. At steady state, the value of log K_{ow} predicts the capacity of the EDC to accumulate into the adipose tissue (25).

The biological life is directly related to EDC pathways of biotransformation and the rate of excretion. Based on this property, some EDC as PCB are considered persistent, having long half-lives (26). It is important to underline that this parameter is partially influencing EDC total toxicity, taking into account that some EDC, that are rapidly degraded in the human body, may be present for only short periods of time but at critical periods of development. Of special concern are EDC such as phthalates (27), PBB (28) and BPA (29), detectable in pregnant women, foetuses and newborns, taking into account that exposures that occur early in pregnancy can have influence on short-term health effects, while exposures later or during early childhood may induce cognitive and developmental deficiencies.

Adipose tissue: the source and target of endocrine disrupting compounds

Lipophilic EDC are stored primarily in WAT, therefore alteration or change in the mass or composition of this tissue release EDC into blood circulation, a process designated "toxocrine secretion" (22). As mentioned before, moderate or severe weight loss was associated with increased plasma levels of POP, like PCB and organochlorine pesticides (13-15). The increased plasma levels of POP induced by weight loss are also correlated to changes in adipose POP. Some researchers investigated POP concentrations in blood and adipose tissues and also assessed the total amount of fat mass (30). Their results indicated that the POP concentration in the adipose tissue increased with weight loss, this being correlated with the significantly decrease of the total amount of fat mass. This isleading to the increased concentration of POP in remained tissue. The same study revealed that weight loss had improved blood lipid and liver toxicity parameters, but the individuals who had the highest serum POP levels showed a delay in improvement of these parameters (30). This suggests that POP presence in blood may counteract the positive effects of weight loss on hepatic and serum lipids.

In the same time, POP release in the blood is correlated with toxic outcomes in other organs and tissues. There is enough evidence that increased serum POP levels is correlated with alterations in resting metabolic rates, thermogenesis, and oxidative capacity of skeletal muscle (31, 32). Experimental evidence suggested that fasting is accompanied by an increase in the serum concentration of PCB (33), but also to the redistribution of PCB from adipose tissue toward other lipid-rich tissues. For example, in rodents pretreated with hexachlorobenzene, weight loss led to a time-dependent increase in the brain content of hexachlorobenzene (34), while in mice pretreated with DDT, weight loss led to increased DDT level in all tissues examined (including brain, lung, heart, spleen, kidney, liver, adipose tissue, blood), except for muscle (35). The new localization of DDT in the brain was associated with toxic effects on central nervous system, once again suggesting that the release from adipose tissue potentially is correlated with toxic outcomes in other organs and tissues.

Also the presence of lipophylic POP in breast milk is the result of the equilibrium between lipid, blood and milk, meaning

that it originates from the adipose tissue storage compartment, as well as from newly absorbed contaminants. It is important to underline that breastfeeding provides a significant source of exposure to POP early in human life and may have significant consequences on sensitive groups (infants), based on their susceptibility to hormonal effects (31). Disruptions induced during this time-frame can lead to subtle functional changes that may not emerge until later in life or even later, to the next generation. Despite the potential negative impact of POP presence in breast milk, breastfeeding is still recommended based on its nutritional and immune benefits.

The disrupting effects exhibited by EDC can be observed indifferent tissues and organs including adipose tissue. At least three important effects are promoted at this level: disruption of adipose tissue function and cell differentiation, induction of inflammation, lipotoxicity and obesogen effect.

Disruption of adipose tissue function

The mechanisms through which EDC could induce the disruption of adipose tissue function and cell differentiation are diverse. Some EDC are acting on other nuclear receptors involved in fat metabolism and regulation of glucose uptake, such as peroxisome proliferator-activated receptors (PPAR), especially on PPARγ, which are involved in the regulation of adipocyte differentiation, production of adipokines or insulin responsiveness (36). By antagonizing PPARγ, EDC significantly inhibit the release of adiponectin that has insulin-sensitizing effects, as it enhances inhibition of hepatic glucose output as well as glucose uptake and utilization in fat and muscle. For example, BPA at 0.1 and 1 nM doses is a potent antagonist of PPARγ that suppresses adiponectin release in human adipose tissue explants (37). In the same time, BPA influences adiponectin level via another mechanism, that implies binding to protein disulfide isomerase, a critical player in the retention of adiponectin in cells (38).

Interestingly, it has been observed *in vitro* that the estrogen receptor β can act as a negative regulator of PPARγ, decreasing ligand-induced PPARγ and PPARγ induced adipogenesis (39), therefore is obvious that PPARγ function is affected by EDC directly interaction with the receptor, but also by EDC that modulate the estrogen receptor β activity. Also, TCDD inhibits adipogenesis through a suppression of PPARγ (40).

Other EDC, such as phtalates (DEHP) act as potent agonists of PPARα or PPARγ. In rodent models, PPARα appears to mediate high-dose DEHP-induced body weight loss (41), but these effects cannot be extrapolated to humans, taking into account that the levels required to activate human PPARα are almost three times higher than the concentrations required to activate mouse PPARα, and the maximum-fold induction is less for human PPARα than for mouse PPARα (42).

Induction of inflammation

Several animal studies have shown that low doses of POP, such as co-planar PCB77 or TCDD, increase the expression of inflammatory genes in adipose cells (43, 44). Another study, on the impact of POP on human adipose cells, showed that in preadipocytes and adipocytes the inflammatory pathway is activated *via* the AhR (45).

Other researchers analyzed the influence of POP concentrations on inflammation and insulin resistance, showing the association between exposure and increased levels of C-reactive protein (46). It was demonstrated that serum levels of interleukin (IL)-17, IL-1β, IL-23, and tumor necrosis factor-α (TNF-α) were higher in individuals who were exposed to POPs, including PCBs, through consumption of contaminated rice (47).

Taking into account that in obese individuals,circulating inflammatory biomarkers such as C-reactive protein, IL-6, TNF-α, monocyte chemotactic protein 1, intercellular adhesion molecule 1 and E-selectin have been associated with a variety of metabolic disorders, is obvious that increased inflammatory mediators may contribute to total EDC metabolic disruption.

Lipotoxicity

There are experimental findings that suggested that some EDCs are associate with disruption of lipids homeostasis. Lipotoxicity and dyslipidemia induced by TCDD and low chlorinated PCB occur even in the absence of an obese phenotype. As an example, PCB-77 has been shown to elevate serum very low density lipoprotein (LDL) in $ApoE^{-/-}$ mice (43), while TCDD caused an AhR-dependent elevated cholesterol and serum LDL in $ApoE^{-/-}$ mice (43, 48, 49). Oral exposure to DDT increased cholesterol and triglycerides in serum and adipose tissue and increased hepatic triglyceride synthesis (50). Similar findings regarding increased triglyceride synthesis were observed in dieldrin-exposed rats (51).

Lipotoxicity, assessed based on elevated cholesterol level, has been observed in humans after exposure to brominated flame retardants and perfluorinated chemicals(52). Similarly, exposure to perfluorinated chemicals in PPARα knockout mice induced changes in gene expression and alteration of fatty acid metabolism (53-55).

National Health and Nutrition Examination Survey (NHANES) data demonstrated a positive association of perfluorooctane sulfonate (PFOS), perfluorooctanoic acid (PFOA) and perfluorononanoic acid (PFNA) concentrations with total colesterol and low density lipoprotein fraction (LDL). Linear regression analysis of serum lipids and cholesterol in children with

high PFOA exposure, revealed that PFOA was positively associated with total cholesterol and LDL cholesterol, and that PFOS was positively associated with total, LDL and HDL cholesterols (56).

Obesogen effect

Several experimental studies suggested that organotins such as TBT and TPT have a role in obesity taking into account that both are activating PPARγ and consequently increase the number of differentiated adipocytes and disrupt normal adipogenesis (57).

Phthalates, which are also known to act as PPAR activators, are also suspected obesogens. Published cohort studies done on representative sampling of the US population, using data from NHANES, focused on correlation between phtalate exposure and obesity. For example, Stahlhut *et al.* (58) investigated adult male participants in the NHANES 1999–2002 and revealed that urinary concentrations of three phthalate metabolites (mono-n-butyl phthalate, mono-benzyl phthalate and mono-ethylphtalate) were associated with increased waist circumference but also insulin resistance, assessed by HOMA-IR. A similar association between urinary phthalate metabolite concentrations and body mass index and waist circumference was found in another cross-sectional study of NHANES data (59).

Polybrominated diethyl ethers are potential obesogens as well. Prenatal exposure to low doses of BDE-99 (2,2´,4,4´,5-penta-BDE) increased mouse birth weight (60), while perinatal exposure to BDE-47 (2,2´,4,4´-tetra-BDE) increased rat body weights from birth to puberty (61).

Another widespread obesogen is PFOA, a known PPARγ agonist (62). Alterations in lipid metabolism and the obesogenic effects observed in epidemiological studies were presented before. Experimental studies in mature CD-1 mice exposed to low levels of PFOA (0.01-0.3mg/kg) *in utero* revealed an increased body mass, with an inverted U-shaped dose–response curve, indicating that PFOA acts *via* a non-monotonic dose response curve (63). It is interesting to underline that authors observed a positive relationship between *in utero* PFOA exposure levels and abdominal brown adipose tissue weight, but a negative relationship with the mass of WAT. Consistent with experimental findings, a prospective human study demonstrated that prenatal exposure to PFOA is associated with obesity in the daughters twenty years later (64).

Neuronal effects

Nonylphenol (NP), one of the most prevalent and best-studied EDC, arises as a degradation product of the alkylphenol polyethoxylates, which are widely used as nonionic surfactants in commercial production, affects neuronal growth (65), and NP is also accumulated in adipose tissue (66). As with the majority of EDC, NP is not itself a steroid but nonetheless acts as an agonist at nuclear estrogen receptors and thus can be defined as an environmental estrogen (estrogen mimetic).

Conclusion

All currently collected information indicates that adipose tissue, particularly WAT, appears to play a complex role in EDC exposure, both in terms of adaptation and toxic effects. There is enough evidence to suggest that adipose EDC accumulation and metabolism has a dual life: protective, as a reservoir at least in the case of acute exposure, and harmful, as an internal, "toxocrine" source of chronic exposure. In effect, adipose tissue can be considered one of the major target organs of EDC, resulting in obesity and related cardiometabolic diseases. Indeed, the diabesity (67) epidemic has become global health burden. Although the genetic and epigenetic background, in particular, our thrifty genes, also take part in this epidemia, mounting epidemiological and exprimental evidence links it with increases in intrauterine influences, viruses, microbiota, climate changes, and xenobiotics including EDC, all these „exposure" factors being embodied in Christopher Wild's concept of exposome (as indicated in the Introduction, also see 68). Hence, biomonitoring adipose EDC, also milk, could be an important marker of such an exposure. The standardization of such procedures at clincolaboratory level is required. Altogether, further studies are needed to enrich our knowledge in human exposure to EDC and to investigate its consequences as well as prediction and prevention.

Conflict of interest

The authors declare no conflict of interest.

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