Obesogens and nuclear receptors

Abstract
Obesity is so common within the world’s population and prevalence has increased markedly over decades. Obesity is associated with obesity prevalence and formation of health problems related with obesity. Nuclear receptors are sensors of exposure to xenobiotics. In recent studies have proposed a first set of obesogens that target nuclear hormone receptor signaling pathways with relevance to adipocyte biology and the developmental origins of health and disease. In this paper assesses the information about a huge public health problem that is obesity and its relationship also evaluated that nuclear receptor signaling pathways of obesogens.

Keywords: public health, obesity, obesogens, nuclear receptors

Abbreviations: ADRB3, B3-adrenergic receptor; DOHD, developmental origins of health and disease; ED, endocrine disrupters; PXR, pregnane X receptor; CAR, constitutive androstane receptor; LXR, liver X receptor; FXR, farnesoid X receptor; PPARs, peroxisome proliferator activated receptors; MCP-1, monocyte chemotactic protein-1; RXR, retinoid x receptor; MEHP, mono-ethylhexyl-phthlate; BPA, bisphenol-A; PPRE, peroxisome proliferator response element; BBP, benzyl butyl phthlate; DPP, dipropyl phthlate; DES, diethyl stilbestrol; PFOA, perfluoro octanoic acid

Introduction
Obesity prevalence has increased markedly over the past few decades. The obesity pandemic has huge implications for public health. Recently several approaches have been used to understand the genetic receptors that control the function of obesity. The candidate gene approach focuses the search for specific obesity susceptibility mutations in genes that are chosen based on their presumed relevance to energy homeostasis. Although several genes have been examined, most candidate gene studies in humans have been negative, or alternatively, the gene variant has shown to play a modest role in influencing obesity susceptibility. Four of the many genes that have drawn the attention of researchers in this capacity include the b3-adrenergic receptor (ADRB3), peroxisome proliferator activated receptor-c (PPAR-c), peroxisome proliferator activator activated receptor-c (PPAR-c), and adiponectin (APM1). Although mutations in these genes may play a modest role in influencing obesity susceptibility in any individual, these genes may play more important roles through interaction at other gene variants. Furthermore, some of these gene variants are common in the population, and, thus, despite their modest effects, may be responsible for substantial population attributable risk for obesity. Research that obesogens come out past decade toxic chemical substance exposure increased that both of obesity prevalence and formation of health problems related with obesity. The environmental obesogen hypothesis purpose that examine the relationship between toxic chemicals and obesity. Recent studies have proposed a first set of candidate obesogens (diethylstilbestrol, bisphenol A, phthalates and organotins among others) that target nuclear hormone receptor signaling pathways (sex steroid, RXR-PPARγ and GR) with relevance to adipocyte biology and the developmental origins of health and disease (DOHD). Exposure to obesogens initiates or exacerbates obesity through mis-regulation of critical pathways involved in adipogenesis, lipid metabolism, or energy balance.

Nuclear receptors, sensors of exposure to xenobiotics
A privileged mechanism for endocrine disrupters (ED) interference with metabolic pathways is their direct or indirect activity on nuclear receptors. Nuclear receptors are transcription factors characterised by three important properties. First one is a common modular organization, with a DNA binding domain and ligand binding domain second one activated by the binding of specific ligands third one the activated receptors bind to specific response elements located in the vicinity of the promoter of their target genes. Nuclear receptors bind to DNA as dimers, either homodimers, or more often heterodimers with the receptor for 9-cis retinoic acid, known as RXR transactivation via nuclear receptors occurs in at least two steps. One them in the absence of a ligand, the nuclear receptor dimer binds to a co-repressor protein that inhibits its transactivation properties. Other one is in the presence of a ligand, or due to an alternative pathway of activation such as phosphorylation, the co-repressor is released and a co-activator is recruited, allowing further contacts to bemade with the transcription machinery, eventually resulting in transcription enhancement. It is important to note that the general properties of the ligands for nuclear receptors, i.e. small size and lipophilicity, are commonly found in Eds.

Classification of nuclear receptors
Nuclear receptors can be ordered into three classes according to their ligand binding properties. Class one are the classic hormone receptors that recognise only one or a few molecules with high affinity. This is the case for the thyroid hormone, glucocorticoid, retinoic acid, oestrogen, vitamin D, as well as progesterone, mineralocorticoid, and androgen receptors. Class two are orphan receptors, which possess the structural characteristics of nuclear receptors, including a ligand binding domain, but for which no ligand has so far been identified. Class 3 are bind a broad range of molecules with, as a corollary, relatively poor affinity. Rather than responding to hormones secreted by endocrine glands with tight feedback controls, these receptors, namely pregnane X receptor (PXR), constitutive androstane receptor (CAR), farnesoid X receptor (FXR), liver X receptor (LXR) and peroxisome proliferator-activated receptors (PPARs), can bind molecules that belong to metabolic pathways as substrates, intermediates or end-products.
Peroxisome proliferator-activated receptors (PPAR α, δ, and γ) play a crucial role in adipogenesis and obesity. They are members of the nuclear receptor superfamily of ligand-activated transcription factors that have central roles in the storage and catabolism of fatty acids. PPAR isotypes (α, δ/β, and γ) work together to activate transcription factors that have central roles in the storage and catabolism of fatty acids. The persistent and ubiquitous environmental contaminant, tributyltin chloride (TBT), induces the differentiation of adipocytes in vitro and increases adipose mass in vivo. TBT is a dual, nanomolar affinity ligand for both the retinoid X receptor (RXR) and the peroxisome proliferator-activated receptor γ (PPARγ). TBT promotes adipogenesis in the murine 3T3-L1 cell model and perturbs key regulators of adipogenesis and lipogenic pathways in vivo. Also TBT was thus identified as the first “obesogen.”

**Phthalates**

DEHP (di-ethyl-hexyl-phthalate) is the most widely used industrial plasticizer, and human exposure to this pollutant is high through the daily use of polyvinyl chloride products. Results demonstrate that DEHP exerts species-specific metabolic actions that rely to a large extent on PPARα signaling and highlight the metabolic importance of the species-specific activation of PPARs by xenobiotic compounds. Results demonstrate that exposure to the environmental pollutant DEHP has far-reaching metabolic consequences that rely on hepatic oxidative metabolism via PPARα activation. Furthermore, a species-specific relationship between exposure to DEHP and diet-induced obesity. Many of these chemicals may interact with members of the nuclear receptor superfamily. Peroxisome proliferator-activated receptors (PPARs) are such candidate members, which interact with many different endogenous and xenogenous lipophilic compounds. Mono-ethyl-hexyl-phthalate (MEHP), a metabolite of the widespread plasticizer DEHP, has been found in exposed organisms and interacts with all three PPARs (α, δ/β, and γ). A thorough analysis of its interactions with PPAR γ identified MEHP as a selective PPAR γ modulator, and thus a possible contributor to the obesity epidemic. MEHP directly activates PPARγ and promotes adipogenesis MEHP induces a selective activation of different PPARγ targets. MEHP induces selective transcriptional regulations during adipocyte differentiation. Concentrations of mono-benzyl vs mono-ethyl-hexyl phthalate metabolites showed statistically significant correlations with abdominal obesity and insulin resistance in men.

**Bisphenol-A**

Bisphenol-A (BPA) is a monomer in the structure of composite resins and polycarbonate plastics. Bisphenol-A is a xenoestrogen and an endocrine disruptor. BPA used to make polycarbonate polymers and epoxy resins, along with other materials used to make plastics. Epoxy resins are used to make internal surface coatings for food cans (sea products, vegetables, beer, soft drinks, powder milk), big storage vessels (wine, water) and various types of food containers. Bisphenol-A (BPA) is one of the highest volume chemicals produced worldwide, with over 6 billion pounds produced each year and over 100 tons released into the atmosphere by yearly production. Humans are exposed to BPA inadvertently through their food and beverages, but they are also likely to be exposed via air, drinking and bathing water, dust, and soil. The continuous exposure of mice to BPA during the perinatal and postnatal periods caused the development of obesity and hyperlipidemia. A recombinant HuH7-PPRE-Luc cell line used for analyzing the peroxisome proliferator response element (PPRE). Among five environmental chemicals (troglitazone, benzy butyl phthalate (BBP), dipropyl phthalate (DPP), bisphenol A (BPA) tested, benzy butyl phthalate and bisphenol induced PPRE-driven luciferase activation in HuH7-PPRE-Luc cells and caused adipogenic differentiation of 3T3-L1 cells. BBP and BPA, like the PPARγ agonist troglitazone, induced marked formation of oil droplets, whereas DPP did not. The results show that a recombinant HuH7-PPRE-Luc cell line would be useful for screening potent environmental obesogens with PPAR activity.

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Perfluorooctanoic acid, PAH's, organochlorine compounds

PFOA (Perfluorooctanoic Acid),\textsuperscript{47} DES (Diethylstilbestrol),\textsuperscript{70,48,49} PAH's and smoking,\textsuperscript{30-35} organochlorine compounds\textsuperscript{3-55} are associated with an increase of BMI and overweight also studies show that have been implicated in altering adipocyte distribution and function.

Conclusion

Now that most of the world has adopted an increasingly “obesogenic” lifestyle of excess caloric intake and decreased physical activity and same genes contribute to obesity and poor health. In the entire world obesity is well known and USA has the highest ratio of obese people while else where in the world the ratio is gradually increasing. Due to the need to fight obesity many nations have come up with healthy ideas towards a healthy living. For instance there is need to reduce caloric intake, increase physical activities and balanced diet are important for a healthy lifestyle. Researchers finding support the ides that environmental estrogens may play role in regulating the expression of obesity related genes in development but additional studies are needed. Also research with endocrine disrupter chemicals only studied in laboratory animals but the genetic receptors that control the function of fat cells has not been identified yet. It is importantly that nuclear receptors are sensors of exposure to xenobiotics. Because of that reasons the next step for researchers begin to investigate the action mechanism of obesogens and learn how it affects peoples.

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Conflict of interest

No potential conflict of interest was reported by the authors.

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