Obesogens and nuclear receptors

Abstract

Obesity is so common within the world’s population and prevalence has increased markedly over. And we know that toxic chemical substance exposure increased that both of obesity prevalence and formation of health problems related with obesity. Nuclear receptors that are sensors of exposure to xenobiotics. In addition 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 pacific helath problem that is obesity and its relationship also evaluated that nuclear receptor signaling pathways of obesogens.

Keywords: public health, obesity, obesogens, nuclear receptors

Abbreviations: ADR3, 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-ethyl-hexyl-phthalate; BPA, bisphenol-A; PPRE, peroxisome proliferator response element; BBP, benzyl butyl phthalate; DPP, dipropyl phthalate; 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-activated receptor-c coactivator-1 (PGC-1), and adiponectin (APM1). Although mutations in these genes may play a modest role in influencing obesity susceptibility in any given individual, they may play more important roles through interaction with 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 (diethyldibisler, bisphenol A, phthalates and organotins among others) that target nuclear hormone receptor signaling pathways (sex steroid, RXR-PPAR 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' 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 share 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. A 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 a few molecules with high affinity. This is the case for the thyroid hormone, gluocorticoid, 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 pregne 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.
PGR (α, δ, γ) receptors and obesity

The peroxisome proliferator-activated receptors (PGR α, δ, γ) are members of the nuclear receptor superfamily of ligand-activated transcription factors that have central roles in the storage and catalysis of fatty acids.13 PGR isotypes (α, β/δ or FAAR, and γ, respectively) were identified in the early 1990s in Xenopus laevis and in mice.13,14 Since then, PGR α, β/δ and γ have also been identified in humans.13,15 The first PGR identified that PGR α.9 PGRα is activated by a broad range of compounds among which several are qualified as endocrine disruptors. Many synthetic compounds to which humans are exposed have peroxisome proliferative properties in rodents. These include plasticizers such as di (2-ethylhexyl) phthalate (DEHP), surfactants such as perfluorocarboxylic acids, herbicides such as 2,4,5-trichlorophenoxyacetic acid, chlorinated solvents such as trichloroethylene, and hypolipidemic drugs such as fenofibrate and gemfibrozil.9 PGRα is much less known about the biology of PGRβ than either of the other two PGR subtypes.12 PGRγ is crucial for white adipose tissue development and adipogenesis in general.5,17 Its ability to bind some endocrine disruptors might contribute to fat accumulation in mature adipocytes upon exposure to the compounds.9 In vitro and in vivo studies show that induced PGRγ lead to differentiation of adipose tissue.18–20 Obesogens activate PGR γ thus leading to obesity.17

RXR receptors and obesity

In 1987 retinoic acid receptors was discovered that are knowns vitamine A metabolite and was found in nuclear receptor superfamily.21–22 RXR has got three receptor types (α, β, γ).23

Molecular basis of the obesogen response

Differantion of the fat cells in obesity occurs in two ways. One of them hiperatrophy that means increase in the volume of fat cell or the other hyperplasia that means increase number of fat cell.24 Adipogenesis became mesenchymal stem cells differentiant.25 Adipose tissue responsible from metabolism regulation like an endocrine tissue.26,27 Obesity relation with adipose tissue endocrine and secretion functions (adipokines, adiponectin, tumor necrosis factor-α, IL-1β, IL-6, monocyte chemotactic protein-1 (MCP-1), macrophage migration inhibitory factor, nerve growth factor, vascular endothelial growth factor, plasminogen activator inhibitor 1 and haptoglobin). Leptin is a hormone that produced adipocyte and its structure protein. Leptin is a hormone that produced adipocyte and its structure protein. Leptin regulates energy balance by influencing hypothalamus.28 Generally each of the individual has a ‘personal threshold of leptin’. Sense of energy sufficient goes to brain when leptin exceeds level of the threshold and fat storage prevented. When PGR γ activate, leptin expression increased and leptin make decreased PGRγ expression in adipocytes.18,20,30 Especially PGRγ has an important role in shaping adipose tissue and formation of fat cells.15 According to Bruce Blumberg if you activate PGRγ in a preadipocyte, it becomes a fat cell. if it already is a fat cell, it puts more fat in the cell.7

Organotins

Organotins are very common pollutants in environment.31,32 Studies Show that prenatal exposure to TBT effect of preadipocytes and it conversion adipocytes.33,34 The persistent TBT represents, the first example of an environmental endocrine disrupter that promotes adipogenesis through RXR and PGRγ activation. 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 (PGRγ). 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’.33

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 polystyrene chloride products.35 Results demonstrate that DEHP exerts species-specific metabolic actions that rely to a large extent on PGRα signaling and highlight the metabolic importance of the species-specific activation of PGRα by xenobiotic compounds.

Concentrations of mono-benzyl ve mono-ethyl-hexyl phthalate metabolites showed statistically significant correlations with abdominal obesity and insulin resistance in men.39,40

Bisphenol-A

Bisphenol-A (BPA) is a monomer in the structure of composite resins and polycarbonate plastics. Bisphenol-A is a xenobiotic and an endocrine disrupters. BPA used to make polycarbonate polymers and epoxy resins, along with other materials used to make plastics.41 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.42 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.42 The continuous exposure of mice to BPA during the perinatal and postnatal periods caused the development of obesity and hyperlipidemia.43 A recombinant Huh7-PPRE-Luc cell line use for analyzing the peroxisome proliferator response element (PPRE). Among five environmental chemicals (troglitazone, benzyl butyl phthalate (BBP), dipropyl phthalate (DPP), bisphenol A (BPA) tested, benzyl 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 PGRγ 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 potential environmental obesogens with PPAR activity.46

Perfluorooctanoic acid, PAH's, organochlorine compounds

PFOA (Perfluorooctanoic Acid),47 DES (Diethylstilbestrol),73,48,49 PAH's and smoking,30-35 organochlorine compounds3-35 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 good balanced diet are important for a healthy lifestyle. Researchers finding support the idea 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.

References


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