MedCrave
Step into the World of Research
Journal of Applied Biotechnology & Bioengineering

Review Article

Open Access

CrossMark

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 puclic helath problem that is obesity and its relationship also evaluated that nuclear receptor signaling pathways of obesogens.

Keywords: public health, obesity, obesogens, nuclear receptors

Volume 4 Issue 2 - 2017

Gülşen Göney,[1] Arzu Didem Yalçin[2]
[1]Department of Toxicology, Gazi University, Turkey
[2]Department of Internal Medicine, Allergy and Clinical Immunology, Taiwan and University of Medical Science, Turkey

Correspondence: Gülşen Göney, Gazi University, Faculty of Pharmacy, Department of Toxicology, 06330, Hipodrom-Etiler, Ankara, Turkey, Fax +90 312 222 2326, Tel +90 0537 250 22 07, Email gulsengoney@gmail.com

Received: April 13, 2017 | **Published:** November 16, 2017

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-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.[1–4] 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.[5,6] 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).[7,8] Exposure to obesogens initiates or exacerbates obesity through mis-regulation of critical pathways involved in adipogenesis, lipid metabolism, or energy balance.[8]

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 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.[9,10] 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.[9]

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 ofmolecules 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 proliferatoractivated receptors (PPARs), can bind molecules that belong to metabolic pathways as substrates, intermediates or end-products.[9,11]

PPAR (α, δ, γ) receptors and obesity

The peroxisome proliferator-activated receptors (PPAR α, δ, γ) are members of the nuclear receptor superfamily of ligand-activated transcription factors that have central roles in the storage and catabolism of fatty acids.[12] PPAR 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, PPAR α, β/δ and γ have also been identified in humans.[15,16] The first PPAR identified that PPAR α.[9] PPARα is activated by a broad range of compounds among which several are qualified as endocrine disrupters. 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] PPARδ is much less known about the biology of PPARδ than either of the other two PPAR subtypes.[12] PPARγ is crucial for white adipose tissue development and adipogenesis in general.[9,17] Its ability to bind some endocrine disrupters might contribute to fat accumulation in mature adipocytes upon exposure to the compounds.[9] *In vitro* and *in vivo* studies show that induced PPARγ lead to differentiation of adipose tissue.[18–20] Obesogens activate PPAR 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 hipertrophy 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 differantion.[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 regulate 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 PPAR γ activate, leptin expression increased and leptin make decreased PPARγ expression in adipocytes.[18,29,30] Especially PPARγ has an important role in shaping adipose tissue and formation of fat cells.[18] According to Bruce Blumberg if you activate PPARγ 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 PPARγ 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 (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 identifie as the first "obesogen.[35]"

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.[36] 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 PPARα 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.[37] 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 exogenous 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, β, 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.[9] MEHP directly activates PPARγ and promotes adipogenesis MEHP induces a selective activation of different PPARγ target genes. MEHP induces selective transcriptional regulations during adipocyte differentiation.[38] 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 xenoestrogen 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.[43] The continuous exposure of mice to BPA during the perinatal and postnatal periods caused the development of obesity and hyperlipidemia.[44,45] 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 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 potential environmental obesogens with PPAR activity.[46]

Perfluorooctanoic acid, PAH's, organochlorine compounds

PFOA (Perfluorooctanoic Acid),[47] DES (Diethylstilbestrol),[30,48,49] PAH's and smoking,[50–52] organochlorine compounds[53–55] 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 obesed 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 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 receptorsare 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.

Acknowledgements

None. No funding to declare.

Conflict of ınterest

No potential conflict of interest was reported by the authors.

References

1. Zahorska-Markiewicz B, Janowska J, Olszanecka-Glinianowicz M, et al. Serum concentrations of TNF-[alpha] and soluble TNF-[alpha] receptors in obesity. *Int J Obes Relat Metab Disord*. 2000;24(11):1392–1395.
2. Hotamisligil GS. The role of TNFα and TNF receptors in obesity and insulin resistance. *J Intern Med*. 1999;245(6):621–625.
3. Kersten S. Peroxisome proliferator activated receptors and obesity. *Eur J Pharmacol*. 2002;440(2-3):223–234.
4. Girardet C, Butler AA. Neural melanocortin receptors in obesity and related metabolic disorders. *Biochim Biophys Acta*. 2014;1842(3):482–494.
5. Damcott CM, Sack P, Shuldiner AR. The genetics of obesity. *Endocrinol Metab Clin North Am*. 2003;32(4):761–786.
6. Altshuler-Keylin S, Kajimura S. Mitochondrial homeostasis in adipose tissue remodeling. *Sci Signal*. 2017;10(468):9248.
7. Grün F, Blumberg B. Environmental obesogens: organotins and endocrine disruption via nuclear receptor signaling. *Endocrinology*. 2006;147(6 Suppl):S50–S55.
8. Grün F, Blumberg B. Perturbed nuclear receptor signaling by environmental obesogens as emerging factors in the obesity crisis. *Rev Endocr Metab Disord*. 2007;8(2):161–171.
9. Desvergne B, Feige JN, Casals-Casas C. PPAR-mediated activity of phthalates: A link to the obesity epidemic? *Mol Cell Endocrinol*. 2009;304(1-2):43–48.
10. Pawlak M, Lefebvre P, Staels B. General molecular biology and architecture of nuclear receptors. *Curr Top Med Chem*. 2012;12(6):486–504.
11. Mangelsdorf DJ, Thummel C, Beato M, et al. The nuclear receptor superfamily: the second decade. *Cell*. 1995;83(6):835–839.
12. Kliewer SA, Xu HE, Lambert MH, et al. Peroxisome proliferator-activated receptors: from genes to physiology. *Recent Prog Horm Res*. 2000;56:239–263.
13. Dreyer C, Krey G, Keller H, et al. Control of the peroxisomal β-oxidation pathway by a novel family of nuclear hormone receptors. *Cell*. 1992;68(5):879–887.
14. Issemann I, Prince R, Tugwood J, et al. A role for fatty acids and liver fatty acid binding protein in peroxisome proliferation? *Biochem Soc Trans*. 1992;20(4):824–827.
15. Desvergne B, Wahli W. Peroxisome proliferator-activated receptors: nuclear control of metabolism 1. *Endocr Rev*. 1999;20(5):649–688.
16. Feige JN, Gelman L, Michalik L, et al. From molecular action to physiological outputs: peroxisome proliferator-activated receptors are nuclear receptors at the crossroads of key cellular functions. *Prog Lipid Res*. 2006;45(2):120–159.
17. Janesick A, Blumberg B. Endocrine disrupting chemicals and the developmental programming of adipogenesis and obesity. *Birth Defects Res C Embryo Today*. 2011;93(1):34–50.
18. Rosen ED, Sarraf P, Troy AE, et al. PPAR gamma is required for the differentiation of adipose tissue in vivo and in vitro. *Mol Cell*. 1999;4(4):611–617.
19. Razquin C, Marti A, Martinez JA. Evidences on three relevant obesogenes: MC4R, FTO and PPARγ. Approaches for personalized nutrition. *Mol Nutr Food Res*. 2011;55(1):136–149.
20. Li X, Ycaza J, Blumberg B. The environmental obesogen tributyltin chloride acts via peroxisome proliferator activated receptor gamma to induce adipogenesis in murine 3T3-L1 preadipocytes. *J Steroid Biochem Mol Biol*. 2011;127(1-2):9–15.
21. Giguere V, Ong ES, Segui P, et al. Identification of a receptor for the morphogen retinoic acid. *Nature*. 1987;330(6149):624–629.
22. Petkovich M, Brand NJ, Krust A, et al. A human retinoic acid receptor which belongs to the family of nuclear receptors. *Nature*. 1987;330(6147):444–450.
23. Allenby G, Bocquel MT, Saunders M, et al. Retinoic acid receptors and retinoid X receptors: interactions with endogenous retinoic acids. *Proc Natl Acad Sci USA*. 1993;90(1):30–34.
24. Sternberg S. Adipose Tissue. *Histology for Pathologists*. 2nd ed. USA: HPB; 1997. p. 167–196.
25. Rosen ED, MacDougald OA. Adipocyte differentiation from the inside out. *Nat Rev Mol Cell Biol*. 2006;7(12):885–896.
26. Mohamed-Ali V, Pinkney JH, Coppack SW. Adipose tissue as an endocrine and paracrine organ. *Int J Obes Relat Metab Disord*. 1998;22(12):1145–1158.
27. Greenberg AS, Obin MS. Obesity and the role of adipose tissue in inflammation and metabolism. *Am J Clin Nutr*. 2006;83(2):461S–465S.
28. Ahima RS, Flier JS. Adipose tissue as an endocrine organ. *Trends Endocrinol Metab*. 2000;11(8):327–332.
29. Spiegelman BM, Flier JS. Obesity and the regulation review of energy balance. *Cell*. 2001;104(4):531–543.
30. Newbold RR, Padilla-Banks E, Snyder RJ, et al. Perinatal exposure to environmental estrogens and the development of obesity. *Mol Nutr Food Res*. 2007;51(7):912–917.

31. Oberdörster E, Rittschof D, LeBlanc GA. Alteration of [14 C]-testosterone metabolism after chronic exposure of Daphnia magna to tributyltin. *Archives of Environmental Contamination and Toxicology*. 1998;34(1):21–25.

32. McAllister BG, Kime DE. Early life exposure to environmental levels of the aromatase inhibitor tributyltin causes masculinisation and irreversible sperm damage in zebrafish (Danio rerio). *Aquat Toxicol*. 2003;65(3):309–316.

33. Iguchi T, Watanabe H, Ohta Y, et al. Developmental effects: oestrogen-induced vaginal changes and organotin-induced adipogenesis. *Int J Androl*. 2008;31(2):263–268.

34. Kirchner S, Kieu T, Chow C, et al. Prenatal exposure to the environmental obesogen tributyltin predisposes multipotent stem cells to become adipocytes. *Mol Endocrinol*. 2010;24(3):526–539.

35. Grün F, Watanabe H, Zamanian Z, et al. Endocrine-disrupting organotin compounds are potent inducers of adipogenesis in vertebrates. *Mol Endocrinol*. 2006;20(9):2141–2155.

36. NTP-CERHR Monograph on the potential human reproductive and developmental effects of Di(2-Ethylhexyl) Phthalate (DEHP). *National Toxicology Program Center for the Evaluation of Risks to Human Reproduction*. USA: US Department of health and humn services; 2006. p. 1–308.

37. Feige JN, Gerber A, Casals-Casas C, et al. The pollutant diethylhexyl phthalate regulates hepatic energy metabolism via species-specific ppar [alpha]-dependent mechanisms. *Environ Health Perspect*. 2010;118(2):234–241.

38. Feige JN, Gelman L, Rossi D, et al. The endocrine disruptor mono-ethyl-hexyl-phthalate is a selective PPARgamma modulator which promotes adipogenesis. *J Biol Chem*. 2007;282(26):19152–19166.

39. Stahlhut RW, Van Wijngaarden E, Dye TD, et al. Concentrations of urinary phthalate metabolites are associated with increased waist circumference and insulin resistance in adult US males. *Environ Health Perspect*. 2007;115(6):876–882.

40. Hatch EE, Nelson JW, Qureshi MM, et al. Association of urinary phthalate metabolite concentrations with body mass index and waist circumference: a cross-sectional study of NHANES data, 1999-2002. *Environ Health*. 2008;7:27.

41. Mori C. *Fetal exposure to endocrine disrupting chemicals (EDCs) and possible effects of EDCs on the male reproductive system in Japan*. Japan: International Symposium on Environmental Endocrine Disruptors; 1998. p. 11–13.

42. Sendón García R, Paseiro Losada P. Determination of bisphenol A diglycidyl ether and its hydrolysis and chlorohydroxy derivatives by liquid chromatography-mass spectrometry. *J Chromatogr A*. 2004;1032(1-2):37–43.

43. Vandenberg LN, Hauser R, Marcus M, et al. Human exposure to bisphenol A (BPA). *Reprod Toxicol*. 2007;24(2):139–177.

44. Rubin BS, Murray MK, Damassa DA, et al. Perinatal exposure to low doses of bisphenol A affects body weight, patterns of estrous cyclicity, and plasma LH levels. *Environ Health Perspect*. 2001;109(7):675–680.

45. Miyawaki J, Sakayama K, Kato H, et al. Perinatal and postnatal exposure to bisphenol a increases adipose tissue mass and serum cholesterol level in mice. *J Atheroscler Thromb*. 2007;14(5):245–252.

46. Wang YF, Chao HR, Wu CH, et al. A recombinant peroxisome proliferator response element-driven luciferase assay for evaluation of potential environmental obesogens. *Biotechnol Lett*. 2010;32(12):1789–1796.

47. Hines EP, White SS, Stanko JP, et al. Phenotypic dichotomy following developmental exposure to perfluorooctanoic acid (PFOA) in female CD-1 mice: low doses induce elevated serum leptin and insulin, and overweight in mid-life. *Mol Cell Endocrinol*. 2009;304(1-2):97–105.

48. Newbold RR, Padilla-Banks E, Snyder RJ, et al. Developmental exposure to endocrine disruptors and the obesity epidemic. *Reprod Toxicol*. 2007;23(3):290–296.

49. Newbold RR, Jefferson WN, Grissom SF, et al. Developmental exposure to diethylstilbestrol alters uterine gene expression that may be associated with uterine neoplasia later in life. *Mol Carcinog*. 2007;46(9):783–796.

50. Power C, Jefferis BJ. Fetal environment and subsequent obesity: a study of maternal smoking. *Int J Epidemiol*. 2002;31(2):413–419.

51. Oken E, Huh SY, Taveras EM, et al. Associations of maternal prenatal smoking with child adiposity and blood pressure. *Obes Res*. 2005;13(11):2021–2028.

52. Hill SY, Shen S, Locke Wellman J, et al. Offspring from families at high risk for alcohol dependence: increased body mass index in association with prenatal exposure to cigarettes but not alcohol. *Psychiatry Res*. 2005;135(3):203–216.

53. Smink A, Ribas-Fito N, Garcia R, et al. Exposure to hexachlorobenzene during pregnancy increases the risk of overweight in children aged 6 years. *Acta Paediatr*. 2008;97(10):1465–1469.

54. Karmaus W, Osuch JR, Eneli I, et al. Maternal levels of dichlorodiphenyl-dichloroethylene (DDE) may increase weight and body mass index in adult female offspring. *Occup Environ Med*. 2009;66(3):143–149.

55. Valvi D, Mendez MA, Martinez D, et al. Prenatal concentrations of polychlorinated biphenyls, DDE, and DDT and overweight in children: a prospective birth cohort study. *Environ Health Perspect*. 2012;120(3):451–457.