Endocrine disruptors: link with obesity?

Overweight and obesity are defined as a disease in which abnormal excessive body fat accumulation causes adverse effects on health. This disease has reached epidemic proportions, with, in Europe alone, half of the population suffering from overweight and one third being obese. Whereas nutrition (caloric intake) and lifestyle choices (physical activity) are universally considered the most important, other environmental influences can also play a role in the development of obesity. A proposed contributor to the rise in obesity is exposure to endocrine disrupting chemicals (EDC's). EDC's are chemicals that alter the normal functioning of hormones or signaling molecules in the body. While much early work on endocrine disruption focused on reproductive effects (cfr the disruption of the normal activity of our sex hormones, the estrogens and androgens, …), the hypothesis that chemicals may affect weight homeostasis (called obesogens or metabolic disruptors) emerged more recently from different lines of research.

Plausible mechanisms

Hormones function mainly through interaction with their receptors, which can be classified in two large groups: membrane bound receptors (primarily respond to peptide hormones) and nuclear receptors (NRs) which are activated by interaction with small lipophilic hormones such as sex steroids. EDCs may possess multiple mechanisms of action, however, because many EDCs are small lipophilic compounds, one privileged route is through their direct interaction with a given NR leading to perturbation or modulation of downstream gene expression.

Several NRs are linked to metabolism and obesity. Firstly, regarding the estrogen receptor, periods of low estrogen levels can lead to an increase in adipose tissue and this seems to be mediated by ERα (an isotype of the estrogen receptor or ER). During development however, estrogens contribute to an increase in adipocyte or fat cell numbers. Androgen levels on the other hand are related to lower body mass index in men. EDCs known as estrogens are bisphenol A (BPA), diethylstilbestrol, alkylphenols, some pesticides … Several EDCs block the normal function of the androgen receptor, they are called antagonists or antiandrogens. Examples are some phthalates, alkylphenols and some pesticides (Casals-casas & Desvergne, 2011; Grün & Blumberg, 2009).

Also, thyroid hormones (THs) and their receptors (TRα en β) are tightly associated with basal metabolism. Besides the receptors, thyroid disruptors can target or interfere with the synthesis of thyrotropin releasing hormone, the TH synthesis and metabolism, iodine uptake, TH transport, … which can lead to a change in TH serum levels. Elevated TH levels accelerate metabolism, increase lipolysis and provoke weight loss, the opposite effect is seen with low TH levels. A number of EDCs, including phthalates, BPA, flame retardants, … are suspected thyroid disruptors and may reduce circulating thyroid level (Zoeller et al., 2010; Grün & Blumberg, 2009).

In addition, glucocorticoids acting through glucocorticoid receptors (GR1 and 2) allow an organism to adequately respond to physical or emotional stresses by promoting gluconeogenesis, increasing blood glucose levels, and mobilizing the oxidation of fatty acids. Besides BPA and dicyclohexylphthalate, many pharmaceutical compounds interact with these receptors (Sargis et al., 2010).
Most importantly, PPARs (peroxisome proliferator activated receptors, the main isotypes being PPARα and PPARγ) play critical roles in adipogenesis and lipid metabolism. PPARα’s primary purpose is the regulation of energy homeostasis, PPARα activates fatty acid catabolism and increases gluconeogenesis. PPARα stimulation during development might lead to obesity in later stages. PPARγ is described as the master regulator of fat cell development, with activation required for adipocyte differentiation and fat storage, it also improves insulin sensitivity. A variety of chemicals have been shown to bind and activate with for example perfluoroalkyl compounds that mostly bind PPARα; and organotins, and some phthalates or their metabolites like MEHP (monoethylhexylphthalate) that mostly bind PPARγ (Hatch et al., 2010; Feige et al., 2007; OECD draft, 2011).

Recently, AhR (aryl hydrocarbon receptor), well known as the receptor for dioxin like compounds, has been implicated as another regulator of metabolism. The mechanisms are not yet well described, but cross-talk with ER and PPARγ may be involved through influencing their expression (Casals-casas & Desvergne, 2011).

Figure 1: Endocrine disrupting chemicals or EDCs interact with diverse members of the nuclear receptor family and with aryl hydrocarbon receptor (AhR). PFCs: perfluoroalkyl compounds, ER: estrogen receptor, GR: glucocorticoid receptor, TR: thyroid receptor, PPARα/γ: peroxisome proliferator activated receptors, RXR: retinoid x receptor.
In vivo and epidemiological evidence: some examples

A number of epidemiological studies have linked pesticide exposure with obesity and metabolic syndrome. For example in utero (or foetal) exposure of dichlorodiphenyldichloroethylene (DDE) and hexachlorobenzene are associated with an increased BMI in women and children. A similar result was seen for diethylstilbestrol in an animal model. A positive correlation with BMI was also seen for nonylphenol measured in adipose tissue of women and BPA blood levels. Several phthalate metabolites, measured in urine, are also linked with abdominal obesity in adult males. (Casals-casas & Desvergne, 2011; Diamanti-Kandarakis et al., 2009)

The most well known pharmaceuticals that are obesogens are thiazolidinediones, used to treat type 2 diabetes. These compounds are linked to weight gain in humans through activation of PPARy. (Casals-casas & Desvergne, 2011). The organotin tributyltin induces adipogenesis in cell culture models and increases adipose mass in vivo in two vertebrate model organisms, frogs and mice (Grun et al., 2006). However, for tributyltin, no epidemiological data are available concerning human exposure.

Screening for obesogen candidates

Since PPARy is the most important regulator of adipogenesis and fat metabolism, screening for activity through this receptor is a good way to start. Classically, a transactivation reporter assay can screen for possible binders to PPARy (both agonists or antagonists). It consists of a cell line in which the human PPARy receptor and a PPARy responsive reporter gene (mostly luciferase) are expressed. For possible interactions with the other NRs mentioned similar assays exist (OECD draft, 2011).

However, an effect in a transactivation test does not prove that the particular compound is an obesogen. Additionally, the mouse preadipose cell line, 3T3-L1 cells can be used. This cell line can be induced to differentiate and accumulate fat. For several compounds like 4-nonylphenol, BPA, organotins, ... lipid accumulation and adipocyte differentiation was indeed observed in these cells (Li et al., 2011). However, this does not necessarily mean that the changes in differentiation are due to PPARy activation, since this can be induced by several pathways, for example these cells also contain ER and GR receptors (OECD draft, 2011).

Alternatively, recently the zebrafish obesogenic test was designed; adiposity is measured using a fluorescent probe that stains lipid droplets. Zebrafish is one of the most important models in environmental toxicology and is rapidly becoming a major model for studies on human health and disease. For both BPA and tributyltin an increase in adiposity was seen in this model (Tingaud-Sequeira et al., 2011).

Although all previous tests can also be used to test mixtures or extracts, they can only hint for possible obesogenicity. Even though there is evidence that EDCs can play a role in obesity and some mechanisms are available, it still remains hard to predict the outcome for human health. Many EDCs can interact with different hormone receptors (for example BPA and phthalates, see Figure 1) and cross-talks between receptors exist. Experiments in mammalian models are therefore still needed preferably in combination with human biomonitoring.

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Interesting lecture