The environmental obesogen hypothesis for diabesity

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There is abundant evidence that the rising levels of obesity in the Western world are strongly influenced by lifestyle factors, such as diet and exercise, and that these contribute to a number of medical conditions, including type 2 diabetes. It is also becoming clear that a variety of environmental factors play an important role in diabesity, as proposed by the environmental obesogen hypothesis. This overview looks at the role that endocrine-disrupting chemicals (EDCs) – synthetic agents that interfere with natural, blood-borne hormones – may play a role in the development of obesity by altering physiological control mechanisms. A number of possible EDCs are examined, along with their sources and methods of exposure. The author argues that the complexity of the response in humans to different levels of EDC exposure is worthy of further study.

The prevalence of obesity has increased dramatically over the last two to three decades and is, in the Western world, reaching epidemic proportions (Ogden et al, 2006; Go et al, 2013) and contributing to a number of serious medical conditions, such as diabesity and cardiovascular diseases (Daousi et al, 2006).

The obesity axiom

The conventional wisdom holds that obesity is primarily driven by a prolonged positive energy balance (i.e. too many calories are ingested and too few calories burned). Although this axiom explains the fundamental basis of obesity in its simplest terms, a complex set of physiological interactions are necessary to move body weight outside of its normal range. The accumulation of fat or mobilisation of lipids from adipose storage depots is controlled by a variety of factors, including the central control of basal metabolic rate, hormonal regulation of appetite and satiety, regulation of metabolic set points, and the number, size and metabolic activity of adipocytes. Moreover, adipose tissue itself produces key components in the body's feedback systems, such as adipokines that help to fine-tune appetite and satiety.

The role of endocrine-disrupting chemicals in obesity

Interestingly, the production and use of synthetic chemicals have increased dramatically in parallel with growing obesity (Baillie-Hamilton, 2002) and it has been suggested that endocrine-disrupting chemicals (EDCs) may play a key role in obesity development by altering physiological control mechanisms (Baillie-Hamilton, 2002; Elobeid and Allison, 2008; Newbold et al, 2008). An endocrine-disrupting compound was defined by the United States Environmental Protection Agency as "an exogenous agent that interferes with synthesis, secretion, transport, metabolism, binding action, or elimination of natural, blood-borne hormones that are present in the body and are responsible for homeostasis, reproduction and developmental process" (Diamanti-Kandarakis et al, 2009).

There is growing evidence that some EDCs can act as obesogens and interfere with the body's natural weight control mechanisms (Baillie-Hamilton, 2002; Grun and Blumberg, 2006). Biologic mechanisms that could underlie this association include alterations in thyroid and steroid hormone function,

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Article points

1. There is increasing evidence that, as well as a positive energy balance, a complex set of physiological interactions are necessary to lead to obesity.
2. Humans are exposed to a range of synthetic endocrine-disrupting chemicals (EDCs) that may interfere with the actions of natural, blood-borne hormones.
3. The environmental obesogen hypothesis proposes that changes in metabolic signalling, resulting from exposure to EDCs, increase an individual's susceptibility to diabesity.

Key words

- Endocrine-disrupting chemicals
- Hormones
- Obesity

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Page points

1. Humans are exposed to endocrine-disrupting chemicals (EDCs) mainly through the ingestion of contaminated food or water, inhalation of polluted air or from dermal exposure.
2. The responses to EDC exposure are complex, and depend on timing, dose and gender.
3. Exposure to EDCs might produce adverse effects leading to weight gain at levels similar to normal human environmental exposures.

and activation of peroxisome proliferator-activated receptors, which play a major role in adipocyte differentiation and energy storage (Hatch et al, 2008). If exposure takes place in early life stages (foetal and/or childhood) EDCs might interfere with the programming of endocrine-signalling pathways established during vulnerable periods of life (Newbold et al, 2007). In addition, exposure to EDCs has been associated with elevated triglycerides and cholesterol (Goncharov et al, 2008), impaired fasting glucose (Langer et al, 2007) and diabetes (Vasiliu et al, 2006, Codru et al, 2007) in humans, which are all related to obesity.

Sources of EDC exposure

Humans are exposed to EDCs mainly through ingestion of contaminated food or water, inhalation of polluted air or from dermal exposure (Baillie-Hamilton, 2002; Diamanti-Kandarakis et al, 2009). A growing number of animal studies have demonstrated that prenatal exposure to low doses of some EDCs is associated with later development of obesity. The endocrine disruptors that have been linked with obesity in animals are bisphenol A (Masuno et al, 2002; Miyawaki et al, 2007) and phthalates (Boberg, 2008), which are widely used today as plasticisers and stabilisers in the manufacture of consumer products, such as children's toys and food-packaging materials (Hauser and Calafat, 2005). In addition, the organotin compound tributyltin, which until recently has been extensively used as an antifouling agent in ship paint, has been found to possibly alter gene expression to promote fat cell differentiation (Inadera and Shimomura, 2005; Grun et al, 2006). Moreover, the semi-persistent organobromine compound polybrominated diphenyl ether, used as flame retardant in a wide range of products, has been found to exhibit hallmark features of metabolic obesity (Hoppe and Carey, 2007).

Phytoestrogens, contained in various foods and food supplements, in particular soy products, are another class of chemicals that are considered to be endocrine disruptors. Genistein and daidzein, which are two of the most abundant phytoestrogens in the human diet, and genistein, because of its oestrogenic activity, have been proposed to have a role in the maintenance of health by regulating lipid and carbohydrate homeostasis (Park et al, 2005). Genistein at pharmacologically high doses in mice has been shown to inhibit adipose deposition but, at lower doses similar to that found in Western diets containing soy, induced adipose tissue deposition, especially in males (Penza et al, 2006). Further, this increase in adipose tissue deposition by genistein was correlated with mild peripheral insulin resistance.

Response to EDC exposure levels

There is a complexity in the response to exposure to EDCs depending on timing, dose and gender. There is evidence that EDCs can exhibit adverse effects at concentrations far below those currently being tested in toxicological studies, contradicting the assumption that dose–response relationships are monotonic (Welshons et al, 2003; 2006). High-dose exposures might have toxic effects leading to weight loss or growth restriction, whereas lower levels, which may be more similar to the normal human environmental exposures, may lead to weight gain (Grun and Blumberg, 2009).

Conclusion

Although there is abundant evidence that diet and exercise are key factors in the obesity epidemic, it is becoming equally clear that a variety of environmental factors play an important role in this process. The environmental obesogen hypothesis proposes that perturbations in metabolic signalling, resulting from exposure to dietary and environmental chemicals, may further exacerbate the effects of imbalances in diet and exercise, resulting in an increased susceptibility to diabesity and is, therefore, worthy of further study. ■

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