



Do Environmental Chemicals Make Us Fat?

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Obesity is a global pandemic. Nearly 40% of adults and 20% of all children in the United States are classified as obese. There are differences among men and women, race and ethnicity, and regions of the country (1), illustrating in part the complexity of this issue. Because of the relationship between obesity and comorbidities of diabetes, cardiovascular disease, and hypertension—and the attendant human and economic costs (2)—both a *cause* and a *cure* have been urgently sought and hotly debated (3).

But it is as dangerous as it is seductive to frame the question in terms of a single cause (as the title is framed) because it suggests that a single factor is “causing” the obesity pandemic and, by extension, eliminating this factor will eliminate the problem. It is clearly not that simple. Body weight regulation is highly complex and controlled by a variety of hormones, including hormones regulating glucose homeostasis, hunger and satiety, metabolism, energy balance, and adiposity. Such a complex system could be perturbed by many factors, including nutrition, exercise, sleep cycles, genetics (3), and environmental chemicals (4, 5) acting singly and in concert. So a better question might be, “Do environmental chemicals contribute to the obesity epidemic and, if they do, how do they interact with the other regulators of body weight and what is their contribution?”

The article by Shoucri *et al.* (6) in this issue of *Endocrinology* adds an important contribution to understanding both the mechanism by which adipocyte development occurs and the importance of environmental chemicals in the obesity epidemic. This article builds on a series of seminal observations about the ability of an environmental chemical—tributyltin (TBT)—to cause increased body weight and fat in mice and for this effect to be passed on to future generations

that had not been exposed (transgenerational inheritance) (7). Previously, without a basic mechanistic understanding for this effect, many scientists have dismissed these and other findings, concluding that environmental chemicals do not contribute to the obesity epidemic. Shoucri *et al.* (6) make several experimental observations relating to the mechanism by which TBT can cause an increase in adiposity during development that should shake us from complacency about the role of environmental chemicals in the obesity epidemic. They showed that an environmental chemical, TBT, can alter the epigenome of mesenchymal stem cells, leading to both a commitment to and differentiation into adipocytes, which *in vivo* would result in increased numbers of adipose cells and thus to weight gain.

Shoucri *et al.* (6) show convincingly that TBT causes mesenchymal stem cells to commit to the adipocyte lineage in a retinoid X receptor (RXR)–dependent, peroxisome proliferator-activated receptor γ (PPAR- γ)–independent manner. To do this, they first developed a unique “adipocyte commitment assay” that can distinguish between commitment to becoming an adipocyte and actual differentiation into an adipocyte. They used this assay to show that TBT, or the RXR selective agonist IRX4204, induces mesenchymal stem cells to commit to the adipocyte lineage, whereas the PPAR- γ ligand rosiglitazone did not induce commitment but stimulated differentiation. This is strong evidence that signaling through RXR is responsible for adipocyte commitment. Interestingly, TBT can bind to both PPAR- γ and to RXR, so this chemical appears to induce both commitment and differentiation in low nanomolar concentrations.

Using a combination of RNA sequencing and chromatin immunoprecipitation sequencing, Shoucri *et al.* (6) also provide important evidence supporting a mechanism

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Abbreviations: PPAR- γ , peroxisome proliferator-activated receptor γ ; RXR, retinoid X receptor; TBT, tributyltin.

whereby TBT can cause adipocyte commitment. They showed that signaling through RXR decreases genome-wide H3K27me3 histone marks in proximity to genes that regulate adipose commitment. Thus, TBT signaling through the RXR appears to de-repress adipose commitment genes by chromatin remodeling, thereby inducing genes that define the preadipocyte, setting the stage for PPAR- γ stimulation of adipocyte differentiation. Although the role of PPAR- γ in adipocyte formation is well established, these data identify RXR as an important interface between the environment and the epigenome, as measured by histone changes, which can also influence programming of obesity. This ability of rexinoids or dual RXR-PPAR- γ activators such as TBT (but not PPAR- γ activators such as rosiglitazone) to elicit transgenerational effects on fat accumulation underscores the importance of this new finding to our understanding of transgenerational inheritance.

The World Health Organization has defined endocrine disrupting chemicals as “an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse effects in an intact organism, or its progeny, or (sub)populations” (8). But this definition has been interpreted very differently by different groups (9). Thus, it is interesting that a chemical such as TBT, a fungicide and a component of many products from vinyl floor coverings to plastic diapers, would be used by a research group to uncover the fundamental properties of adipocyte commitment and differentiation yet continues to be used in many products. Moreover, despite the fact that many studies focus on the ability of TBT to affect metabolic function broadly, there is a lack of human biomonitoring studies and prospective cohort studies that are needed to prove that TBT is a human obesogen, and the production volume listed on the Environmental Protection Agency’s website is classified as confidential. These data from Shoucri *et al.* (6) and the Blumberg laboratory in general provide important information about the basic biology of adipocyte development and programming and simultaneously provide important insight into the potential role

of environmental chemicals in the obesity pandemic. These mechanistic insights should be incorporated into the analysis of the causes of obesity, recognizing that no single factor will be the magic bullet.

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