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Metabolic disruption in context: Clinical avenues for synergistic perturbations in energy homeostasis by endocrine disrupting chemicals

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Abstract

The global epidemic of metabolic disease is a clear and present danger to both individual and societal health. Understanding the myriad factors contributing to obesity and diabetes is essential for curbing their decades-long expansion. Emerging data implicate environmental endocrine disrupting chemicals (EDCs) in the pathogenesis of metabolic diseases such as obesity and diabetes. The phenylsulfamide fungicide and anti-fouling agent tolylfluanid (TF) was recently added to the list of EDCs promoting metabolic dysfunction. Dietary exposure to this novel metabolic disruptor promoted weight gain, increased adiposity, and glucose intolerance as well as systemic and cellular insulin resistance. Interestingly, the increase in body weight and adipose mass was not a consequence of increased food consumption; rather, it may have resulted from disruptions in diurnal patterns of energy intake, raising the possibility that EDCs may promote metabolic dysfunction through alterations in circadian rhythms. While these studies provide further evidence that EDCs may promote the development of obesity and diabetes, many questions remain regarding the clinical factors that modulate patient-specific consequences of EDC exposure, including the impact of genetics, diet, lifestyle, underlying disease, pharmacological treatments, and clinical states of fat redistribution. Currently, little is known regarding the impact of these factors on an individual's susceptibility to environmentally-mediated metabolic disruption. Advances in these areas will be critical for translating EDC science into the clinic to enable physicians to stratify an individual's risk of developing EDC-induced metabolic disease and to provide direction for treating exposed patients.

Keywords

adipose; circadian rhythm; diabetes; EDCs; endocrine disruptor; glucose intolerance; insulin resistance; metabolic disease; obesity; tolylfluanid

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Introduction

Rates of diabetes mellitus are rising dramatically across the globe, threatening both individual health as well as the stability of national health systems. In the United States, diabetes is the leading cause of adult blindness, kidney failure, and non-traumatic amputations while also playing a central role in the development of cardiovascular disease, the leading killer of those with the disease.[1] With estimates that diabetes currently affects nearly 24 million people in the US and that this number will rise to over 44 million individuals by 2034,[2] the staggering $245 billion spent annually on diabetes-related healthcare costs is sure to rise dramatically.[3] While these costs are unsustainable in the US where the healthcare infrastructure is robust and relatively well-funded, the burden of diabetes in the developing world may be catastrophic. Current projections estimate that 592 million individuals worldwide will have diabetes by 2035, with 77% of those individuals living in middle- or low-income countries with significantly less developed health systems.[4] To prevent this threat from overwhelming health budgets across the globe, identification and elimination of the factors promoting the development of diabetes are essential.

The last decade has witnessed a proliferation of exciting epidemiological and basic science data suggesting that environmental contaminants play a pathogenic role in the development of metabolic disease (reviewed in refs.[5–7]). Indeed, while initially implicated in perturbations of sex steroid and thyroid hormone signaling, environmental endocrine disrupting chemicals (EDCs) have now been shown to be associated with or to directly alter body weight and glucose homeostasis after either adult or developmental exposure (reviewed in refs.[5–7]). Such metabolic disruptors include a diverse array of compounds such as bisphenol A, persistent organic pollutants (POPs), phthalates, antifouling agents, and pesticides. Our own recent work has added to this list a novel class of metabolism-perturbing agents, namely phenylsulfamide fungicides, as exemplified by tolylfluanid (TF).[8] In this work, we've shown that dietary exposure to TF has the capacity to promote weight gain and increase adiposity despite not altering total food intake; rather, these changes appear to occur through altered circadian rhythms of food intake. Moreover, adult mice exposed to TF exhibited glucose intolerance as well as systemic and adipose-specific insulin resistance, phenotypic features commonly seen in the pathogenesis of type 2 diabetes. This new evidence provides further support to the contention that environmental change may play a critical role in the emergence of chronic diseases; however, many questions remain regarding the clinical scenarios in which EDCs exert their deleterious metabolic effects.

Under most circumstances, homeostatic mechanisms maintain normal energy metabolism and resist the development of cardiometabolic disease; however, several factors operating alone or in concert can lower this resistance to metabolic disease (R_{MD}) and accelerate the progression of obesity, diabetes, hypertension, dyslipidemia, and cardiovascular disease (Fig. 1). While accidental or intentional ingestions of a single chemical may be sufficient to cause diabetes in select circumstances (e.g. the rodenticide Vacor[9] and the fungicide chlorothalonil[10]), it is unlikely that a single chemical will be sufficient to explain the dramatic explosion in global diabetes rates. However, as there are tens of thousands of unique chemicals to which humans are potentially exposed, coordinate exposure to multiple EDCs that additively antagonize critical pathways regulating energy metabolism through

complimentary mechanisms may be sufficient to promote cardiometabolic dysfunction, whereas a single signaling disruptor in isolation may be insufficient to drive significant disease.[11] These EDC × EDC interactions may be critical for generating metabolic phenotypes from the chronic, low-dose exposures that characterize human contact with environmental toxicants. Unfortunately, the experimental complexities of analyzing mixtures of metabolic disruptors are immense; however, some recent data demonstrate that such mixtures, at environmentally relevant doses, can disrupt energy handling,[12,13] suggesting that further studies into common co-exposures are warranted. Alternatively, the potency of a metabolic disruptor might be enhanced by permissive conditions in specific patients that may predispose those individuals to environmentally-mediated metabolic disease. Such factors may include underlying genetics, diet, lifestyle, preexisting diseases, pharmacological treatments, and states of fat redistribution that alter the patient's baseline physiology in such a way as to increase their sensitivity to metabolic disruption.

Genetic Sensitivity to Metabolic Disruption

Our recent work demonstrates that dietary exposure to TF increases adiposity, promotes glucose intolerance, and decreases insulin sensitivity both globally and at the level of the adipocyte.[8] Like many metabolic investigations, these studies employed the C57BL/6 strain. While we had previously shown that *ex vivo* exposure to TF induced adipocytic insulin resistance in outbred CD1 mice, inbred C57BL/6 mice, 2 strains of rats, and even human adipose tissue,[14] whether the observed effects on global energy homeostasis are influenced (either positively or negatively) by the background genetics of the animal model is not known. In the field of endocrine disruption, this may be particularly relevant as the C57BL/6 strain is known to harbor a polymorphism in the aryl hydrocarbon receptor gene, a molecular target for many putative EDCs, including dioxins and dioxin-like polychlorinated biphenyls (PCBs).[15] Intriguingly, since a predominant phenotype of exposure to metabolic disruptors is an increase in adiposity, whether mice with a genetic predilection to accrete adipose tissue exhibit divergent metabolic consequences of EDC exposure may suggest that underlying genetics modulate the metabolic risk posed by EDCs. Importantly, because many EDCs are hydrophobic, ascertaining whether sequestration in fat is potentially protective may shed new light on the mechanisms and metabolic consequences of adipose expansion under EDC exposure. Finally, animal models that are resistant to EDC-induced metabolic disruption may provide novel insights into detoxification or resistance pathways that may be exploited pharmacologically to treat or prevent EDC-induced obesity and diabetes.

Built upon and supporting the Developmental Origins of Health and Disease Hypothesis (DOHaD),[16] recent evidence demonstrates that exposure to various EDCs during critical developmental windows can promote metabolic dysfunction in adulthood.[17,18] The mechanisms by which remote exposures to EDCs disrupt energy homeostasis and how these effects can be inherited in a multigenerational or transgenerational manner are not fully understood. Although epigenetic alterations are implicated, the molecular targets of these epigenetic modifications are imprecisely known.[19] While genome-wide association studies have been generally disappointing with regard to identifying genetic polymorphisms that may explain type 2 diabetes, genes for which the data are strongest, e.g., TCF7L2,[20,21] should be considered as potential epigenetic targets of EDCs that induce metabolic

disruption after developmental exposure. More intriguing may be genes implicated in the pathogenesis of neonatal diabetes and maturity onset diabetes of the young (MODY).[22,23] Mutations in genes implicated in these conditions are often inherited in an autosomal dominant fashion and elicit robust metabolic phenotypes, suggesting that EDC-induced alterations in these genes or regions that regulate their expression may be sufficient to drive the onset of diabetes. Intriguingly, the link between MODY genes and type 2 diabetes in larger cohorts has recently been established.[24] Identifying such potential causes of developmentally-derived diabetes is particularly important since some patients with MODY mutations who have historically been treated with insulin can be managed with oral agents (e.g., sulfonylureas), potentially resulting in both better control and reduced morbidity.[25] Determining whether EDCs may promote metabolic dysfunction through these pathways is vital as it may provide vital insights into the best approaches to treat patients with environmentally-mediated diabetes.

The Impact of Diet on EDC-Induced Metabolic Disruption

It is clear that the deteriorating quality of our diet plays an important role in promoting the development of obesity and diabetes; moreover, the exportation of the American diet may be a significant contributor to the global plague of metabolic disease.[26,27] Despite the importance of diet in modulating energy handling, the impact of these global shifts in diet composition on EDC action has only recently been interrogated. To date, the interactions between EDCs and dietary stressors in the disruption of energy homeostasis has largely been interrogated in the context of high fat feeding. Indeed, potentiation of metabolic disruption by a high fat diet has been demonstrated for bisphenol A,[28,29] perfluorooctane sulfonate,[30] POPs,[31] and chemical mixtures.[12] Interestingly, our metabolic cage analyses suggest that mice exposed to TF have a preference for fat over carbohydrate utilization during the fed state.[8] This suggests that diets rich in carbohydrates, or the simple sugars enriched in a "Western Diet," may be particularly deleterious in the context of exposure to TF and potentially other EDCs. This may be significant as the transformation of the American diet over the last 30 years has been one of increased carbohydrate content, particularly the refined grains and simple sugars found in processed foods.[26,32] As increased fructose intake has been implicated in the explosion in diabetes rates,[33,34] understanding how EDCs interact with secular trends in dietary carbohydrate content and composition will be important for contextualizing the importance of EDCs in the current metabolic disease epidemic. Furthermore, as the burden of diabetes spreads to low- and middle-income countries,[4] understanding how EDCs interact with specific dietary factors in these countries will be essential for estimating the risk posed by environmental toxicants as drivers of the metabolic disease epidemic in the developing world.

Lifestyle and the Susceptibility to Metabolic Disruption

An intriguing finding of our work on TF was that adiposity (fat mass as a fraction of total body mass) and weight gain were increased in the presence of this EDC despite no change in total food intake.[8] We were, however, able to discern an intriguing change in the circadian pattern of food intake, with TF-exposed mice consuming more food during the normally fasting light-phase. This evidence provides some of the first experimental support for EDC-

induced disruptions in energy homeostasis arising through perturbations in circadian rhythms. In humans, experimental disruptions in circadian rhythms are associated with deleterious changes in energy handling.[35–37] Clinically, the timing of food intake has been shown to contribute to weight gain.[35,38] Moreover, individuals who consume more calories at night may have a harder time losing weight.[39] This raises several intriguing questions. First, does EDC exposure itself increase food consumption during normal fasting periods? Second, do EDCs augment the deleterious metabolic effects of disruptions in circadian patterns of food intake that are driven by lifestyle factors that are intentional (e.g., night eating) or forced (e.g., shift work)? And finally, if alterations in circadian rhythms are wholly or partially responsible for EDC-induced obesity and diabetes, will restriction of food intake to the normal feeding period be an appropriate treatment approach? Studies examining the lifestyle factors that exacerbate or antagonize the deleterious effects of EDCs on energy homeostasis may provide vital insights into both the mechanisms of EDC-induced metabolic dysfunction as well as potential avenues to treat toxicant-mediated metabolic disease. Beyond influences of feeding behavior, understanding how EDCs modulate central processes such as motivation may help explain difficulties patients have self-regulating food intake and sustaining exercise, as will studies of EDC effects on skeletal muscle, which remains an understudied area of metabolic toxicity.

Disease-Induced Sensitivity to EDC-Mediated Metabolic Perturbations

Some of the early evidence suggesting EDCs have the capacity to alter energy metabolism came from studies examining their ability to promote adipocyte differentiation from preadipocytes or mesenchymal stem cells.[40] In many of these studies the 3T3-L1 cell line is used as a model of adipogenesis, with preadipoctye-to-adipocyte differentiation classically induced by exposure to insulin, a glucocorticoid, and an agent to raise cAMP levels.[41] The capacity of various EDCs to amplify adipose development can be studied by triggering adipogenesis with this differentiation cocktail in the presence or absence of the EDC of interest. By this approach, many environmental contaminants have been shown to promote adipocyte differentiation (reviewed in ref.[42]). As we have recently dissected for the prototypical obesogen tributyltin,[43] most EDCs appear to require one or more components of the differentiation cocktail to induce adipogenesis. As such, it is possible that clinical states that modulate those specific pathways could augment the adipogenic capacity of EDCs. For example, hyperinsulinemic states, as observed in prediabetes or early type 2 diabetes, may sensitize mesenchymal stem cells and preadipocytes to EDC-induced adipocyte differentiation for chemicals requiring co-exposure to insulin to induce adipogenesis. Similarly, clinical states of high adrenergic tone that are predicted to raise intracellular cAMP levels may potentiate the action of some adipogenic EDCs that require pre-activation of cAMP signaling. One example of this is obstructive sleep apnea (OSA), a common disease linked to metabolic dysfunction.[44] Likewise, EDCs that require glucocorticoids to promote adipocyte development may exhibit enhanced adipogenic capacity in individuals with hyperactivation of the hypothalamic-pituitary-adrenal (HPA) axis who exhibit high glucocorticoid levels or enhanced glucocorticoid receptor (GR) signaling. Such clinical states include Cushing’s syndrome, pseudo-Cushing’s syndrome, OSA, or even endogenous obesity.[45–47] We demonstrated that TF activates adipocytic GR

signaling both *ex vivo* and *in vivo*,[8,48] suggesting one mechanism by which this novel endocrine disruptor promotes metabolic dysfunction. It remains to be determined whether clinical states of heightened GR signaling potentiate TF action. It is interesting, however, to speculate that other EDCs that inhibit the enzymes responsible for glucocorticoid inactivation, 11β-hydroxysteroid dehydrogenases, might exhibit enhanced metabolism-disrupting potency in clinical states of glucocorticoid excess (e.g., dithiocarbamates and organotins).[49–51] Whether an individual's underlying disease state renders them more susceptible to EDC-mediated metabolic disruption has not been studied, but knowledge of the mechanisms by which these environmental toxicants disrupt nutrient handling and the development of metabolic tissues may suggest that, under certain clinical scenarios, some individuals may be primed for environmentally-mediated alterations in energy metabolism.

Pharmaceutical-Enhanced Susceptibility to Metabolic Disruptors

Reciprocal to the concept that underlying diseases might augment an individual's sensitivity to the deleterious metabolic effects of an EDC, disease treatments themselves may generate a permissive environment under which EDCs induce metabolic dysfunction. As argued for states of endogenous corticosteroid overproduction, pharmacological treatment with glucocorticoids, as employed in the care of individuals with inflammatory diseases, may potentiate the action of EDCs working through or in conjunction with GR signaling. Similarly, treatment with adrenergic agonists that raise cAMP levels may prime preadipocytes for differentiation upon exposure to some EDCs. For example, standard treatment approaches to asthma, a highly prevalent lung disease, with β_2-adrenergic agonists such as albuterol, may generate a permissive environment for EDC-induced adipogenesis. As our knowledge of the mechanisms by which EDCs exert deleterious metabolic effects expands, we will be better equipped to predict how various disease states and their treatments may render a subset of patients particularly sensitive to environmental contaminants modulating those pathways. Conversely, knowledge of the mechanisms by which EDCs induce metabolic disease may suggest therapeutic avenues to treat environmentally-mediated obesity and diabetes or identify individuals whose exposure to certain EDCs should be aggressively limited. Finally, future studies may take advantage of the known mechanisms by which anti-diabetic medications lower blood sugar (e.g., sulfonylurea receptor, peroxisome proliferator-activated receptor-γ, AMP-activated protein kinase, sodium-glucose co-transporter-2, incretin receptors, etc.) to: a.) unravel the molecular mechanisms of metabolic disruption; b.) identify potential EDC-drug antagonism that limit therapeutic efficacy; and c.) develop molecularly-based approaches to treat EDC-mediated diabetes in a new era of precision environmental medicine.

Clinical States of EDC Repartitioning and Metabolic Dysfunction

A core therapy for myriad metabolic diseases is weight loss. Whether achieved through dietary interventions, exercise, anti-obesity drugs, or surgery, reductions in body weight have multiple salutary effects on energy metabolism and overall health, effectively raising R_{MD} in the disease progression model (Fig. 1). However, because adipose tissue serves as a reservoir for lipophilic EDCs, mobilization of fat with weight loss is accompanied by a repartitioning of these chemicals from adipose tissue into the circulating plasma

compartment. This has been shown in several human studies examining caloric restriction with or without a weight loss drug,[52–55] as well as for patients undergoing bariatric surgery.[53,56] The precise impact of this release on global energy homeostasis is poorly characterized, but evidence suggests that the subsequent rise in serum organochlorine levels is associated with changes in muscle metabolism that suggest an impairment in energy handling.[55] A similar study also showed an inverse association between the extent of pollutant liberation and insulin levels.[54] It is interesting to speculate that this reduction in insulin levels could be compensation for EDC-induced impairments in hepatic gluconeogenesis as we have shown for dioxin-like PCBs.[57] Importantly, reductions in total fat mass have also been shown to concentrate pollutant levels in adipose tissue,[52] suggesting that adipocyte physiology may also be deleteriously affected by effective increases in EDC concentrations in this important metabolic tissue induced through weight loss. Whether this repartitioning of putative metabolic disruptors partially antagonizes further weight loss or its metabolic benefits requires further investigation, as does the hypothesis that adipose expansion itself protects against EDC-induced metabolic dysfunction through fat sequestration that limits EDC action on non-adipose tissues. Finally, the impact of clinical states of altered adipose development, e.g., congenital and acquired lipodystrophies, on an individual's sensitivity to environmental contaminants necessitates interrogation as individuals with these diseases may be especially vulnerable to EDC-induced metabolic dysfunction due to a reduced capacity to safely sequester lipophilic pollutants.

An analogous clinical state of EDC repartitioning that results from energy shifts and promotes systemic pollutant release is lactation. Many studies from diverse geographical regions have demonstrated the presence of various environmental contaminants in breast milk, including POPs such as PCBs and organochlorine pesticides.[58–60] Importantly, while EDC elimination through lactation may be an important mode by which the total body burden of pollutants is reduced in the mother, the subsequent exposure of the developing newborn to these EDCs during this critical developmental period may be especially deleterious for the long-term metabolic health of the child as suggested by the DOHaD hypothesis.[16] Interestingly, while the metabolism-disrupting potency of EDCs to which an individual is exposed in adulthood is likely enhanced by that individual's clinical status (e.g. lifestyle factors, underlying diseases, and medications), it is also possible that early life EDC exposures potentiate the adverse metabolic consequences of those same clinical factors later in life. Improved understanding of the impact of exposure to EDCs through breast milk on later life energy homeostasis is of critical importance for both predicting risk and developing novel treatment strategies to address pollutant-induced metabolic dysfunction.

Conclusions

Our recent work demonstrating that dietary exposure to the phenylsulfamide fungicide TF promotes weight gain, adipose accretion, and glucose intolerance as well as systemic and cellular insulin resistance provides further support to the theory that environmental toxicants likely contribute to the current global epidemic of metabolic disease. While exposure to certain EDCs has been shown to be sufficient to initiate the development of diabetes, this occurs rarely. It is more likely that the contribution of EDCs to the current epidemic of obesity and diabetes results from coordinate exposures to multiple EDCs, each affecting the

same or complimentary signaling pathways that regulate energy handling.[11] Alternatively, EDC-mediated metabolic dysfunction may be enhanced or accelerated by patient-specific parameters that alter an individual's sensitivity to metabolic disruption, including underlying genetics, diet, lifestyle factors, preexisting diseases, pharmaceuticals, and clinical states of fat redistribution. More comprehensive understanding of the complex interplay between these patient-specific variables and EDC action will be essential for determining the contribution of environmental pollutants to the current epidemic of metabolic disease and for devising strategies to address the threat of environmental degradation on human metabolic health.

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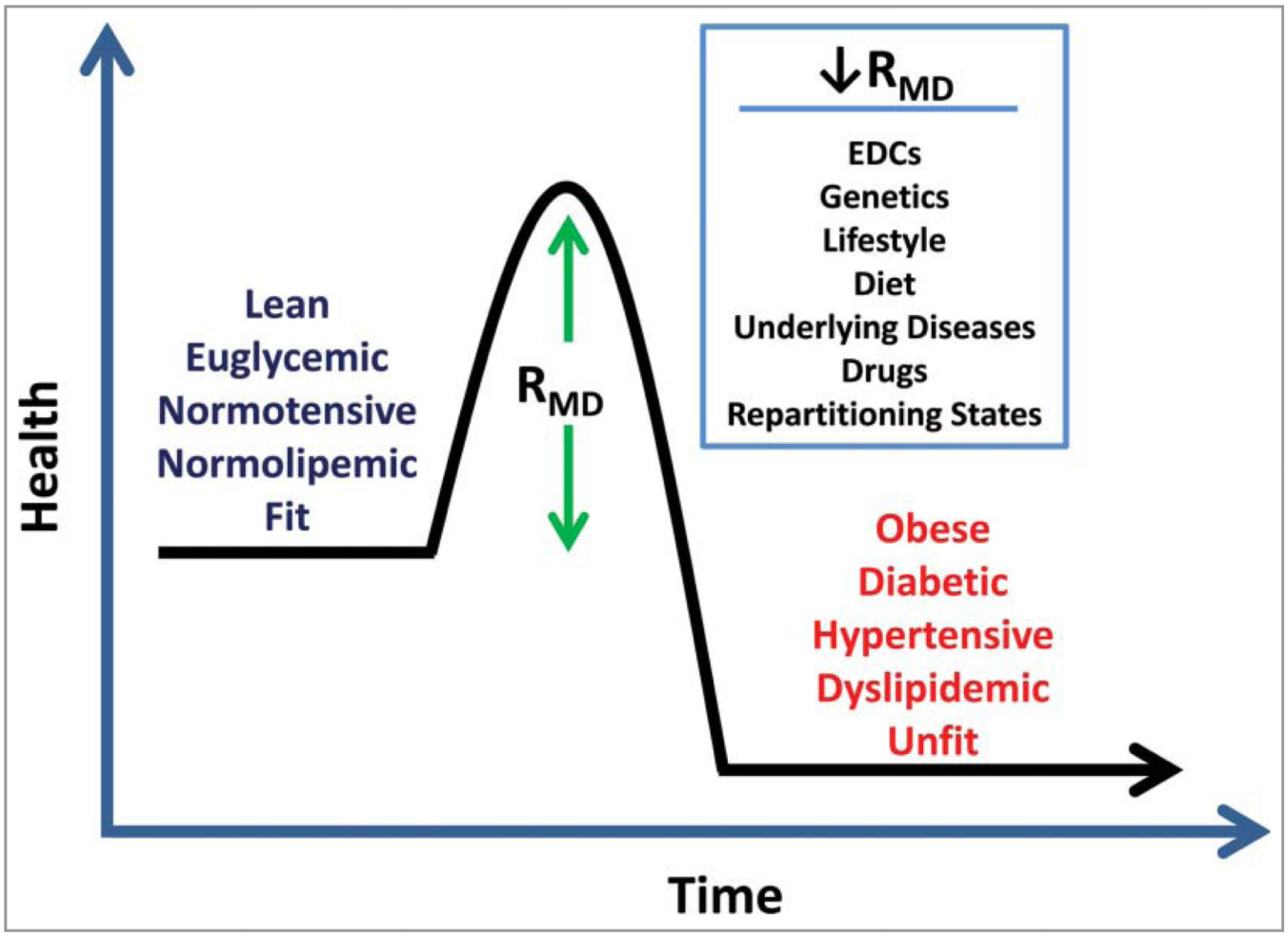

Figure 1.

Conceptual framework for the transition from normal energy homeostasis to metabolic disease. Normally, homeostatic processes resist the development of metabolic and cardiovascular diseases from states of good health. This resistance to metabolic disease (R_{MD}) can be overcome in a number of ways. Rarely, the R_{MD} can be overcome by single toxicant exposures or individual gene defects. More commonly, the development of metabolic diseases results from the summation of multiple hits that, in total, effectively lower R_{MD} and facilitate disease development. These hits may include the coordinate effects of multiple EDCs effectively antagonizing signaling cascades, or multiple complementary signaling pathways, that are critical for maintaining energy homeostasis. Alternatively, EDCs may facilitate disease development when exposure occurs in concert with other cardiometabolic stressors such as the individual's genetics, diet, lifestyle, underlying disease states, pharmacological treatments, and clinical states that promote fat repartitioning. Understanding how EDCs function in the context of these additional stressors is critical for identifying patients at high risk for EDC-induced cardiometabolic disease as well as for devising effective treatment strategies to limit the impact of EDCs on human health.