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Polluted Pathways: Mechanisms of Metabolic Disruption by Endocrine Disrupting Chemicals

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Abstract

Purpose of review—Environmental toxicants are increasingly implicated in the global decline in metabolic health. Focusing on diabetes, herein the molecular and cellular mechanisms by which metabolism disrupting chemicals (MDCs) impair energy homeostasis are discussed.

Recent findings—Emerging data implicate MDC perturbations in a variety of pathways as contributors to metabolic disease pathogenesis, with effects in diverse tissues regulating fuel utilization. Potentiation of traditional metabolic risk factors, such as caloric excess, and emerging threats to metabolism, such as disruptions in circadian rhythms, are important areas of current and future MDC research. Increasing evidence also implicates deleterious effects of MDCs on metabolic programming that occur during vulnerable developmental windows, such as *in utero* and early post-natal life as well as pregnancy.

Summary—Recent insights into the mechanisms by which MDCs alter energy homeostasis will advance the field's ability to predict interactions with classical metabolic disease risk factors and empower studies utilizing targeted therapeutics to treat MDC-mediated diabetes.

Keywords

EDCs; MDCs; diabetes; obesity; metabolism; endocrine disruptor; glucose intolerance; insulin resistance; metabolic syndrome

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Compliance with Ethics Guidelines

Conflict of Interest

Mizuho S. Mimoto and Angel Nadal declare that they have no conflict of interest. Robert M. Sargis reports honoraria from CVS Health.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Introduction

Diabetes and obesity rates have risen exponentially over the last several decades, and the impact of this on individual morbidity and societal costs are significant. In addition to the burden of disease in adults, metabolic disease in children has risen dramatically [1], and the impact of diabetes across the lifespan has been further compounded by increased rates of gestational diabetes mellitus (GDM) in pregnant women [2]. Indeed, GDM has tripled in the past 20 years, affecting 9% of pregnancies in the United States [2], which is critical because GDM is linked to adverse pregnancy outcomes for both mother and child [3]. While traditional metabolic risk factors such as reduced physical activity, increased caloric intake, aging, and sleep deficits are undoubted contributors to this phenomenon, they insufficiently account for this upsurge. Indeed, for a given level of activity and caloric intake, individuals in today's society weigh more than they did 20–30 years ago [4••]. Consequently, other factors are implicated in the global deterioration of metabolic health, including exposure to environmental factors that drive or facilitate metabolic dysfunction [5••. Over the last decade, abundant epidemiologic evidence has emerged linking an increasing number of endocrine disrupting chemicals (EDCs) to the development of metabolic disease; however, our understanding of the mechanisms by which these exposures promote metabolic dysregulation remains relatively rudimentary. This report will integrate the current molecular and cellular evidence by which EDCs act as metabolism disrupting chemicals (MDCs) to dysregulate glucose homeostasis and increase diabetes risk (Table 1, Supplemental Table 1) in order to provide direction for future research aimed at mitigating the deleterious impact of environmental exposures on human metabolic health.

Afflicting 415 million individuals globally with 642 million projected to suffer from the disease by 2040 [6], diabetes is a common, heterogeneous disorder defined by hyperglycemia arising from inadequate insulin production, impaired insulin action, or a combination of the two. Traditionally, type 2 diabetes (T2DM), the most common form of the disease, is thought to originate from the development of insulin resistance, which increases synthetic demand for insulin that eventually becomes unsustainable as pancreatic β-cells begin to decompensate, ultimately leading to overt T2DM [7]. In contrast, type 1 diabetes (T1DM) classically arises from the primary destruction of β-cells. Thus, factors that potentiate insulin resistance or promote β-cell failure augment diabetes risk. Importantly, mounting evidence demonstrates that MDCs affect multiple levels of glucose regulation from β-cell insulin secretion to insulin signaling in metabolically active tissues such as the liver, muscle, adipose, brain, and gastrointestinal (GI) tract (Figure 1).

MDC Disruption of β-Cell Function

Classically, increased extracellular glucose concentrations increase glucose uptake into β-cells via glucose transporter 2 (GLUT2), followed by entry into glycolysis, oxidative phosphorylation, and ATP generation. Increases in the ATP/ADP ratio promote ATP-sensitive K^+-channel (K_{ATP}) closure, membrane depolarization, and calcium influx. Increased intracellular calcium induces cytoskeletal rearrangements that result in transport and release of insulin-containing vesicles [8]. Defects in insulin secretion are central to diabetes pathogenesis [9]. Insulin secretion is also regulated by incretin hormones, such as

glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP), as well as estrogens, which modulate intracellular calcium flux and potentiate insulin secretion via a cAMP-mediated pathway (reviewed in [10]). Post-prandial incretin release from the GI tract augments insulin response, an effect that is attenuated in diabetes [10]. Importantly, multiple EDCs have been shown to disrupt β-cell function at various points in these pathways.

Triphenyltin (TPT) is a persistent organotin compound historically used as an antifouling agent. Islets from TPT-exposed hamsters exhibited impaired intracellular calcium flux and insulin secretion in response to known β-cell stimuli, including acetylcholine, GIP, and glucose [11]; and TPT exposure of primary islets in culture reduced NAD(P)H and ATP production [12]. These findings are consistent with TPT interference in β-cell function upstream of K_{ATP} channel closure, possibly via impaired mitochondrial ATP production [12]. Additionally, TPT reduced GIP and GLP-1 induced insulin release in a protein kinase A (PKA)-dependent manner [13], a pathway central to β-cell function.

A number of studies demonstrated that arsenic also impairs insulin secretion [14–17]. Arsenic is a ubiquitous environmental pollutant that contaminates drinking water above the current WHO safety standard of 10 μg/L for over 150 million individuals globally [18]. In a rat β-cell line, while high levels of arsenic reduced insulin gene expression [17], low micromolar concentrations impaired calpain-10 mediated proteolysis and activation of SNAP-25, a key step in insulin granule exocytosis [16]. The insulin exocytic machinery is similarly disrupted by phenolic compounds, widely used in adhesives and detergents. Exposure to low levels of phenolic estrogens reduced mRNA expression of Snap25 and Rab27a in rodent islets [19]. In contrast, polychlorinated biphenyl (PCB) treatment *increased* calcium influx and insulin secretion in a calcium/calmodulin-dependent protein kinase II (CaMKII)-dependent fashion [20]. Thus, MDCs can affect β-cell function both directly through altering calcium flux, and via modulation of downstream signaling.

Sex steroids play an important role in glucose homeostasis, regulating β-cell insulin secretion in both cGMP-dependent and -independent ways [21,22]. Physiologic fluctuations in estrogen balance are associated with increased vulnerability to metabolic stress [23]. Importantly, multiple EDCs have been shown to alter estrogen signaling, including PCBs, bisphenol A (BPA), phthalates, phytoestrogens, and polycyclic aromatic hydrocarbons (PAHs) [5], making this pathway a likely target of metabolic disruption by exogenous chemicals (discussed in [24,25]).

Endoplasmic Reticulum and Oxidative Stress in MDC Action

Under conditions of hyperglycemia, insulin biosynthesis accelerates and can account for half of all β-cell protein synthesis [26]. This high synthetic demand coupled with their relatively small size renders β-cells uniquely vulnerable to both endoplasmic reticulum (ER) and oxidative stress, and thus to chemicals that induce these reactions. Indeed, recent studies have implicated oxidative and ER stress as significant contributors to diabetes pathogenesis (reviewed in [27,28]). Mitochondria are critical regulators of the cellular redox balance, responsible for both ROS and antioxidant production; thus perturbations to mitochondrial integrity leads to increased cellular stress. Several MDCs promote oxidative stress in β-cells,

including BPA [19,29], arsenic [30,31], and diethylhexylphthalate (DEHP) [32]. For example, rat islets exposed to the phenolic compounds octylphenol, nonylphenol, and BPA exhibited disruptions in islet mitochondrial architecture with alterations in mitochondrial gene expression [19]. Micromolar concentrations of BPA also induced reactive oxygen species (ROS) in INS-1 cells, causing glutathione depletion, DNA damage, and p53 induction, which was partially rescued by pretreatment with the antioxidant N-acetylcysteine (NAC) [29]. In INS-1 cells treatment with 0.25-1 μM sodium arsenite for 96 hours reduced thioredoxin reductase activity, increased pro-apoptotic gene expression, and reduced viability, possibly via a c-Jun-N-terminal kinase (JNK)-mediated pathway [31]. Importantly, arsenic toxicity was also attenuated by pretreatment with NAC [30], suggesting oxidative stress as a mechanism of toxicity and supporting trials of NAC as a potential treatment for arsenic-induced diabetes. Exposure to other heavy metals such as cadmium [33,34] and mercury [35,36] also impair insulin secretion and induce β-cell toxicity, although the epidemiologic evidence on a role for those metals in diabetes is inconsistent [37]. These effects have been presumed to occur via oxidative stress; however, the precise mechanisms by which these toxicants induce β-cell dysfunction require further study.

The role of ROS in β-cell function is complex as ROS also regulate insulin release [38]. Although arsenic has a well-documented ability to induce oxidative damage in multiple contexts, arsenic exposure has also been shown to *reduce* glucose-stimulated ROS generation [15]. This decrease in ROS coincides with a robust induction of an endogenous Nrf2-mediated antioxidant pathway, raising the hypothesis that chronic exposure to low levels of arsenic leads to an adaptive antioxidant response that indirectly dampens GSIS [15]. Taken together, these data indicate that MDCs may perturb insulin secretion through bidirectional alterations in β-cell ROS handling.

Increased cellular stress and resultant inflammation in β-cells have been implicated in the pathogenesis of T1DM as well [9], and are hallmarks of EDC toxicity. Chronic exposure to BPA accelerated spontaneous insulinitis in non-obese diabetic (NOD) mice, a model of immune-mediated diabetes [39]. In addition, NOD mice exposed to BPA *in utero* exhibited more severe insulinitis at 11 weeks of age and increased diabetes prevalence at 20 weeks [40•], suggesting that BPA may also play a role in accelerating the decline of β-cell reserve by promoting immune disruption of pancreatic islets, implicating MDCs as possible contributors to increasing T1DM prevalence.

MDC Disruption of Insulin Action

Insulin functions primarily in myocytes and adipocytes to promote glucose uptake, and in hepatocytes to promote glucose storage as glycogen. On a molecular level, insulin binds to its receptor triggering autophosphorylation and recruitment of the insulin receptor substrate (IRS) scaffolding proteins. This is followed by a series of iterative phosphorylation events that recruit and activate phosphatidylinositol-3-kinase (PI3-K), generate phosphatidylinositol triphosphate (PIP_3), and activate phosphoinositide- dependent kinase 1 (PDK1), ultimately resulting in phosphorylation and activation of Akt/protein kinase B. Akt mediates many of the metabolic actions of insulin, including glucose uptake by promoting GLUT4 translocation to the plasma membrane, lipid biogenesis, hepatic glycogen synthesis, and

suppression of gluconeogenesis [41]. Impairments in insulin action promote diabetes pathogenesis when insulin resistance outstrips the β-cell's capacity for insulin secretion [7]. Global insulin resistance associated with MDC exposure is supported by epidemiologic, animal, and molecular studies [5]. Human exposures to a wide variety of chemicals have been associated with insulin resistance, including BPA [42,43], particulate matter (PM) [44], 2,3,7,8-tetrachlorodibenzo dioxin (TCDD) [45], and phthalates [46,47]. The precise mechanisms by which these chemicals promote insulin resistance are discussed below.

Multiple MDCs can disrupt insulin action in target tissues by altering the expression or activity of insulin signaling intermediates including the insulin receptor [48], IRS-1 [49], PDK-1 [50], and Akt [48–53]. For example, rodents exposed to BPA exhibit global insulin resistance associated with defects in phosphorylation of both the insulin receptor [48] and Akt [48,52]. The phenylsulfamide fungicide tolylfluanid (TF) impaired insulin-stimulated Akt phosphorylation in primary rodent and human adipocytes, likely via down-regulation of IRS-1 expression and protein destabilization [49]. Similarly, insulin-stimulated Akt phosphorylation was attenuated and glucose uptake reduced following arsenite exposure in 3T3-L1 adipocytes [53]. Independent studies in this model showed that 4 hour exposure to either 50 μM arsenite or 2 μM methylarsonous acid also reduces Akt phosphorylation, inhibits PDK-1 activity, and prevents membrane GLUT4 translocation [50], the primary glucose transporter in adipocytes and myocytes. Dysregulation of GLUT proteins has been observed following exposure to multiple MDCs, including TCDD [54,55], DEHP [56-58], cadmium [59], and arsenic [53]. For example, mice injected with a single high dose of TCDD exhibited reduced GLUT4 and GLUT1 expression in adipose and neuronal tissue, respectively [55]. Similarly, DEHP exposure in L6 myotubes downregulated GLUT4 with concomitant impaired glucose utilization [56]. Importantly, while skeletal muscle is responsible for the majority of glucose disposal following nutrient intake [60], few studies have directly addressed MDC effects on muscle; further work on MDC-mediated alterations in skeletal muscle metabolism may illuminate the potential for exercise to antagonize MDC-associated diabetes risk.

In addition to skeletal muscle disruptions, understanding MDC effects on hepatic function is critical for predicting metabolic risk, a fact underscored by the liver's dual role in energy and xenobiotic metabolism as well as the recent rise in non-alcoholic fatty liver disease (NAFLD) [61••]. Multiple MDCs can disrupt hepatic function, leading to toxicity, altered gluconeogenesis, and impaired glycogen storage, including POPs [62], BPA [63,64], PCBs [65], perfluorooctanoic acid (PFOA) [66], atrazine [67], arsenic [68], and DEHP [69]. For example, rats exposed to lipophilic POPs contained in dietary fish oil exhibited insulin resistance, abdominal obesity, and hepatosteatosis [62]. Exposure of rodents to BPA led to impaired glucose oxidation and significantly reduced glycogen stores in primary hepatocytes [64]. Similarly, PCB 126 inhibited hepatic glycogen metabolism, cAMP-mediated gluconeogenesis, and expression of a key enzyme in this pathway, phosphoenolpyruvate carboxykinase (PEPCK), in an aryl hydrocarbon receptor (AhR)-dependent fashion [65]. AhR is an orphan receptor that regulates hepatic detoxification of xenobiotic substances via controlling the activity of cytochrome P450 enzymes [70]. It has several known exogenous ligands including PAH, dioxin-like compounds (e.g. TCDD), and polyphenols [70]; thus, it is a likely mediator of MDC toxicity. Interestingly, RNA-Seq analysis of human hepatocytes

exposed to PFOA and PFOS demonstrate altered expression of lipid metabolism genes, possibly by direct interference with and downregulation of hepatocyte nuclear factor 4α (HNF4α), a master regulator of hepatocyte development and metabolism [66]. Mutations in HNF4α also cause a form of familial diabetes, maturity onset diabetes of the young type 1 (MODY1), which is uniquely responsive to the insulin augmenting class of sulfonylurea drugs. Thus, MDC disruption of HNF4α may have effects on both β-cell and hepatocyte physiology. Integrating understanding of the genetic and environmental causes of metabolic disease may thus inform future therapy decisions. Collectively, these data demonstrate that disruption in hepatic energy metabolism is emerging as an important consequence of MDC exposure [61••].

Context-Dependent MDC Action

The impact of MDCs may be context-dependent. For example, TCDD [71–74], organotins [75,76], and BPA [48,51,64,77,78] differentially affect insulin levels and action depending on the experimental model. Acute TCDD exposure induces a wasting syndrome characterized by weight loss, adipose derangements, hyperlipidemia, ectopic lipid deposition, and hypoinsulinemia [79]. Conversely, multiple epidemiologic studies link TCDD to diabetes and *hyper*insulinemia [80,81]. In β-cell models, TCDD effects are similarly conflicting. TCDD impaired GSIS in primary rodent islets [71] and INS-1 cells [72], and caused AhR-dependent reductions in second-phase insulin secretion in intact animals [74]; however, other studies using INS-1 cells exhibited persistently *increased* intracellular calcium levels and basal insulin secretion, an effect antagonized by calcium channel blockade [73]. Similarly, hamsters exposed to the organotin tributyltin (TBT) for 45 days exhibited hyperinsulinemia and insulin resistance [76]; however, continuing exposure to 60 days promoted β-cell apoptosis with concomitant reduction in insulin levels [75]. These findings suggest a model whereby acute MDC exposure may augment insulin secretion at the expense of subsequent β-cell exhaustion and diminished metabolic reserve later in life; however, this hypothesis requires further interrogation.

Adipose Disruption and Global Metabolic Dysfunction

Adipose tissue is an important regulator of metabolic health, as increased adiposity is a well-recognized risk factor for insulin resistance and diabetes, and impairments in adipose development and function are also associated with metabolic disease [82]. Adipose tissue performs several important functions for metabolic homeostasis, including controlling the storage and redistribution of lipids as well as secreting adipokines (e.g. leptin and adiponectin) that regulate food intake, insulin sensitivity, and β-cell health. Due to the lipophilic nature of many MDCs, adipose tissue is a toxicant depot and may determine their chemical persistence *in vivo*. MDCs that affect adipose function, termed obesogens, have been tied to alterations in adipocyte differentiation, insulin action, and nutrient handling (reviewed in [83]). The transcription factor peroxisome proliferator activated receptor-γ (PPARγ) is a key regulator of normal adipocyte development (reviewed in [82]). PPARγ null mice lack adipose tissue, and PPARγ ablation leads to adipocyte death within days. PPARγ also influences glucose homeostasis by controlling expression of GLUT4, adiponectin, leptin, TNFα, and resistin [82]. Humans with heterozygous loss of function

PPARγ mutations have lipodystrophy and insulin resistance [84]. Thus, disruption of PPARγ activity has multiple negative consequences on adipocyte development and function. Several MDCs disrupt PPARγ signaling, including organotins and phthalates [85]. Importantly, the classical obesogen TBT, has been shown to promote adipogenesis in multiple model systems via PPARγ activation [86], while generating a dysfunctional adipocyte with reduced expression of the beneficial adipokine adiponectin [87]. In addition to MDCs that modulate PPARγ activity, several MDCs alter adipogenesis through other key regulatory pathways such as the glucocorticoid receptor (GR) and sex steroid nuclear receptor pathways. For example, TF promotes adipogenesis in 3T3-L1 cells [88], likely by activating GR signaling, as treatment of primary mouse adipocytes with TF led to GR activation, nuclear translocation, and enrichment at GR response elements in target genes [89]. Moreover, rodents exposed to TF developed increased visceral adiposity, impaired glucose tolerance, and reduced adiponectin levels [90•], mimicking the pathologic features of glucocorticoid excess in humans [91]. Disruptions in the balance of estrogens and androgens also impair adipocyte differentiation. Human adipocyte stem cells exposed to BPA demonstrated increased adipogenesis in an ER-dependent fashion [92]. Interestingly, prolonged exposure of 3T3-L1 preadipocytes to BPA led to development of a compromised adipocyte with increased lipid accumulation, impaired glucose utilization, and increased expression of inflammatory cytokines [93•]. Importantly, while many studies have emphasized the adipogenesis-promoting capacity of MDCs, more attention is required to understand the potential dysfunctional state of MDC-generated adipocytes. Moreover, MDCs that inhibit adipogenesis are likely to promote metabolic dysfunction since impaired adipose expansion shifts lipid storage to muscle and liver, resulting in metabolic dysregulation in these vital tissues, as seen in lipodystrophies [82].

Inflammation in MDC Action

In the obese state, adipocytes enlarge owing to increased triglyceride accumulation; this is accompanied by an increase in inflammatory markers, macrophage infiltration, and release of cytokines such as TNFα and IL-1β that further recruit immune cells and propagate the inflammatory cascade. Multiple molecular signaling pathways have been implicated in the pathogenesis of obesity-induced inflammation, including nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB), mitogen-activated protein kinase (MAPK), and JNK; conversely, targeted loss-of-function mutations in key pathway members is protective [82]. Increased inflammation shifts adipocytes away from lipogenesis and toward lipolysis, increasing circulating free fatty acids and promoting deleterious ectopic lipid deposition in muscle, liver, and β-cells [94]. Furthermore, inflammatory cytokines directly impair insulin action by exerting inhibitory effects on IRS proteins [95], and downregulating insulin receptor, IRS-1, and GLUT4 expression [96]. Many MDCs induce inflammation. For example, BPA treatment of 3T3-L1 cells increased IL-6 and IFNγ release in association with reduced glucose uptake [51]. Exposure of mice to particulate matter (PM) increased systemic inflammation with concomitant insulin resistance, impaired hepatic glycogen storage, and increased visceral adiposity [97•,98]. Thus, inflammation may mechanistically link poor air quality with diabetes and obesity [99]. TCDD also increased TNFα expression with an associated downregulation of insulin signaling intermediates, an effect partially

rescued by disruption of key inflammatory mediators, including AhR, ERK, and JNK [54], highlighting their role in the negative metabolic effects of TCDD. Interestingly, microarray analysis of human adipose-derived stem cells treated with TCDD or PCB-126 identified genes regulating inflammation as the principal molecular alterations induced by these chemicals [100]. Collectively, these studies demonstrate that inflammation is a likely inducer of MDC-associated metabolic disease, and therapies directed at inflammatory responses should be investigated as potential interventions.

Developmental Origins of Metabolic Disease

Increasing evidence suggests that environmental exposures during key developmental windows program metabolic disease risk later in life; this includes the *in utero* and early post-natal period. For example, six-month old male offspring of dams exposed to BPA exhibited impairments in glucose tolerance, insulin sensitivity, and insulin secretion [101]. Earlier interrogation showed that these mice exhibited increased β-cell mass and hyperinsulinemia that preceded a subsequent decline in both parameters. This suggests that *in utero* BPA exposure may promote insulin-induced insulin resistance that is detrimental to long-term β-cell function [102••]. Additionally, the consequences of BPA exposure may synergize with traditional metabolic risk factors such as a high fat diet [63]. The metabolic disruptions in these offspring were associated with altered expression of genes regulating fatty acid metabolism, including the sterol regulatory element-binding protein 1, PPARα, and carnitine palmitoyltransferase [63], suggesting potential molecular disruptions in lipid handling. *In utero* exposures to several EDCs disrupts glucose homeostasis, including TCDD [103], arsenic [104], DEHP [58,105], PFOA [106], and PFOS [107]; however, the precise molecular defects remain largely undefined. In one study, however, *in utero* DEHP exposure induced inhibitory chromatin modifications at the GLUT4 promoter with reduced GLUT4 expression [58], suggesting that site-specific epigenetic alterations may mechanistically define links between early life stressors and later life metabolic disease; however, significant additional work is required to define the relevant mechanisms in this area.

In addition to being a sensitive period of development for the fetus, pregnancy is also a window of susceptibility for mothers. For example, pregnant mice exposed to BPA exhibit hyperinsulinemia [101] similar to women with GDM before the onset of overt diabetes [3]. Pregnant dams exposed to BPA exhibited increased weight, impaired glucose tolerance, and insulin resistance [108••], effects likely arising from defects in adipocyte and β-cell function as these mice exhibited increased periuterine fat mass as well as reduced β-cell mass resulting from both decreased proliferation and increased apoptosis [108••]. Importantly, β-cells from BPA-exposed dams exhibited persistent reductions in the expression of proliferative genes [cyclin D2 and cyclin-dependent kinase-4 (CDK4)] and increased expression of cell cycle inhibitors [p16 and p53] months after delivery [108••]. Collectively, these data suggest that MDC exposures during pregnancy may increase the risk of GDM while also predisposing to later life metabolic insults that augment diabetes risk (reviewed in [109]). To understand the impact of MDCs on metabolic risk in mothers and their offspring, further work into the underlying mechanisms responsible for these alterations are required, including efforts to precisely define causal epigenetic changes (e.g. DNA methylation and histone modifications) linked to energy physiology.

MDCs and Classical Metabolic Risk

Central to understanding how MDCs threaten metabolic health is a need to appreciate how this emerging metabolic risk intersects with traditional diabetes and obesity risk factors (e.g. caloric excess, physical inactivity, sleep disruption, and aging). Current evidence indicates that MDCs potentiate these risks. For example, in C57BL/6 mice, high fat diet-induced glucose intolerance and insulin resistance were exacerbated by BPA exposure [52]. Similarly, perinatal BPA exposure impaired glucose tolerance and promoted hyperinsulinemia, effects amplified with high fat feeding [110]. Particulate matter [111] and the herbicide atrazine [112] also promoted insulin resistance in rodents on high fat but not a standard chow diet. However, this potentiation of metabolic risk is not uniform. Offspring of CD-1 mice exposed to BPA did not exhibit glucose intolerance or increased adiposity when fed either normal chow or a high fat diet [113]. Furthermore, while high fat feeding worsened glucose tolerance in arsenic-exposed C57BL/6 mice, these animals also exhibited reduced fat mass, *improved* fasting blood glucose, and may have had enhanced insulin sensitivity [114]. Thus, there are likely toxicant- and strain-specific differences that impact metabolic outcomes. Importantly, exploring these differences as well as interactions with specific dietary components may illuminate the underlying biological mechanisms by which MDCs promote disease risk.

Recently, disruptions in circadian rhythms have emerged as novel metabolic risk factors. In human and mouse models, impaired sleep and disruptions in normal circadian patterns of food intake impair metabolic health [115], and MDCs are emerging as novel contributors to disease risk in this area. For example, TF was shown to deleteriously alter normal circadian feeding patterns in mice [90•]. Additionally, population studies have associated higher urinary BPA levels with shorter sleep duration [116]; a finding supported by studies in male zebrafish demonstrating BPA-induced alterations in circadian activity [117]. Exposure to estradiol, tamoxifen, BPA, and 4-tert-octylphenol in mangrove killifish also altered expression of circadian clock genes [118•]. A mechanistic basis for these associations is supported by genetic analysis of these circadian genes demonstrating conserved promoter binding sites for estrogen, the AhR, and the xenobiotic response element [118•], factors implicated in various MDC responses.

Conclusions: From Mechanisms to Interventions

As our mechanistic understanding of MDC action improves, a central challenge moving forward is translating this knowledge into interventions to improve human health. Clearly, preventing exposures and rapid remediation of environmental contaminants is critical to address MDC-induced metabolic dysfunction. Indeed, there may be promise in this as one study demonstrated that arsenic's β-cell toxicity in cultured islets could be reversed by incubation in arsenic-free media, providing evidence for islet recovery [14]. Where exposure reduction is not possible or the effects of exposures are irreversible, employing mechanism-based therapeutics will be essential for improving human metabolic health. For those MDCs that interfere with β-cell insulin production, studies from neonatal diabetes may illuminate therapeutic approaches. The most common form of neonatal diabetes results from a heterozygous activating mutation in *KCNJ11* that prevents closure of the K_{ATP} channel

[119]. In these patients, sulfonylureas are highly effective. Several MDCs affect β-cell K_{ATP} channel function, suggesting that sulfonylureas may be beneficial in these contexts as suggested by one study of TPT's metabolic effects [12]. Conversely, several MDCs promote insulin resistance that impairs insulin action in peripheral tissues and stresses β-cells by increasing synthetic demand for insulin. While insulin is a mainstay of diabetes treatment, newer therapies that reduce the glycemic burden such as the sodium-glucose cotransporter-2 (SGLT-2) inhibitors, or that promote a more physiologic insulin release from the pancreas, such as dipeptidyl peptidase-4 (DPP4) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists may be beneficial in treating MDC-mediated diabetes. Because of the central role of adipose tissue in regulating global energy metabolism and evidence that many MDCs target adipocyte function, another class of anti-diabetic therapies of interest are the thiazolidinediones (TZDs), which target PPARγ and inhibit hepatic gluconeogenesis, improve adipose function, reduce inflammation, and increase insulin sensitivity [120–123]. Where oxidative stress is implicated in MDC action, investigations into the utility of antioxidants are warranted. This approach is supported by studies showing that pre-treatment with NAC mitigates some of the β-cell toxicity induced by arsenic [30,124] and BPA [29]. As our appreciation of MDCs as metabolic risk factors increases, future work mandates investigations into the specific disease-promoting mechanisms by which these toxicants work in order to devise targeted interventions to stem the global tide of metabolic deterioration.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

EDCs	endocrine disrupting chemicals
GDM	gestational diabetes mellitus
MDCs	metabolism disrupting chemicals
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
GI	gastrointestinal
ATP	adenosine triphosphate
ADP	adenosine diphosphate
K_{ATP}	potassium sensitive ATP channel

TPT	triphenyltin
GLP- 1	glucagon-like peptide-1
GIP	gastric inhibitory polypeptide/glucose-dependent insulinotropic polypeptide
cAMP	cyclic AMP, NAD(P)H, Nicotinamide adenine dinucleotide phosphate
SNAP-25	Synaptosome Associated Protein 25kDa
GPCR	G-protein coupled receptor
TBT	tributyltin
PKA	protein kinase A
PCB	polychlorinated biphenyl
CamKII	calcium/calmodulin-dependent protein kinase II
BPA	bisphenol A
GSIS	glucose-stimulated insulin secretion
PAH	polycyclic aromatic hydrocarbon
ncmER	non-classical membrane estrogen receptor
ER-β	estrogen receptor beta
CREB	cAMP-response element binding
ERα	estrogen receptor alpha
ERK	extracellular signal–regulated kinase
ER	endoplasmic reticulum
DEHP	diethylhexylphthalate
ROS	reactive oxygen species
DNA	deoxyribonucleic acid
NAC	N-acetyl cysteine
JNK	c-Jun-N-terminal kinase
NOD	non-obese diabetic
IRS	insulin receptor substrate
PI3-K	phosphatidylinositol 3 kinase
PIP_3	phosphatidylinositol triphosphate
PDK1	phosphoinositide-dependent kinase 1

PKB	Protein Kinase B
PM	particulate matter
TCDD	2,3,7,8-tetrachlorodibenzo dioxin
TF	tolylfluanid
POP	persistent organic pollutant
PFOA	perfluorooctanoic acid
PEPCK	phosphoenolpyruvate carboxykinase
AhR	aryl hydrocarbon receptor
PFOS	perfluorooctanesulfonic acid
HNF4-α	hepatocyte nuclear factor 4 alpha
PPARγ	peroxisome proliferator activated receptor gamma
TNFα	tumor necrosis factor alpha
AMPK	5' adenosine monophosphate-activated protein kinase
IL-1β	interleukin 1 beta
NFκB	nuclear factor kappa-light-chain-enhancer of activated B cells
MAPK	mitogen-activated protein kinases
IL-6	interleukin 6
NEFA	non-esterified fatty acids
Srebpc1	sterol regulatory element-binding proteins 1
PPARα	peroxisome proliferator activated receptor alpha
Cpt1b	carnitine palmitoyltransferase 1B
CDK4	cyclin-dependent kinase-4
SGLT-1	sodium-glucose cotransporter-2
DPP4	dipeptidyl peptidase 4
GLP-1	glucagon-like peptide-1

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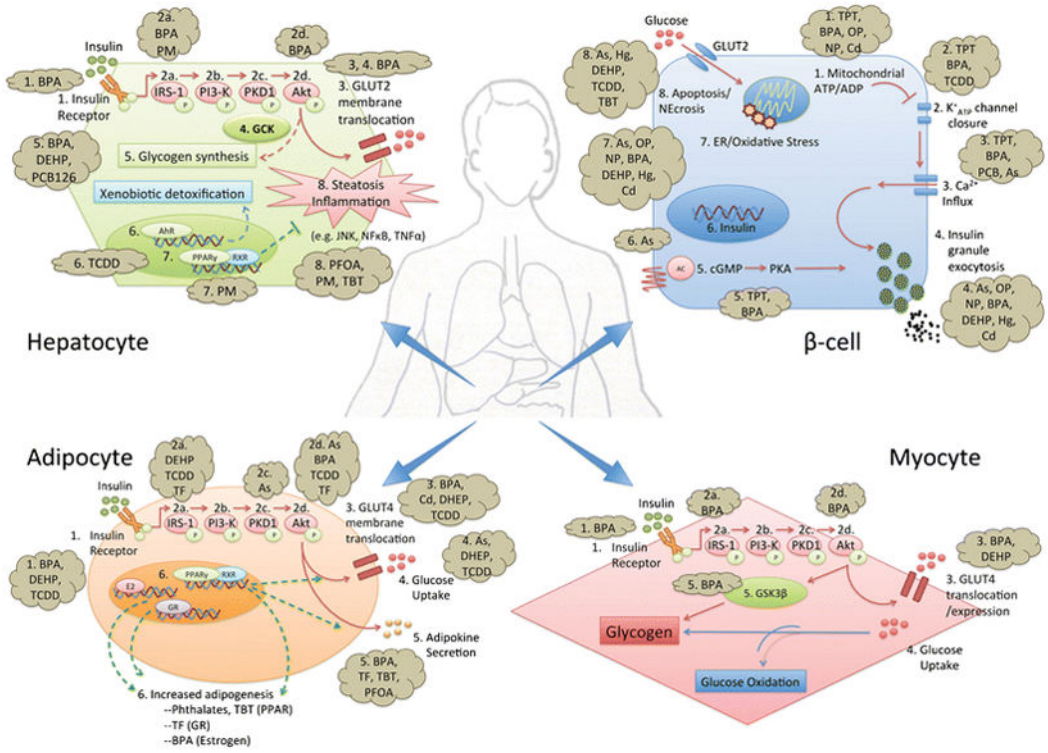

Figure 1.

Overview of the molecular mechanisms by which MDCs disrupt energy homeostasis in the β-cell, myocyte, hepatocyte, and adipocyte.

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Table 1

Summary of cellular and molecular effects of MDCs with common routes of exposure, nationally recommended safe exposure levels, and estimated elimination half-lives in humans

Compound	Uses and Common Routes of Exposure	Recommended Safe Exposure Level in Humans	Cellular/Molecular Metabolic Effects	Elimination Half-life in Humans	References
Organotins (TPT, TBT)	*Biocide in marine paints, fungicide, wood preservative, PVC stabilizer *Drinking water, seafood, PVC products	0.1 mg/m^3 air (OSHA/NIOSH)	General mechanisms: Activates PPARγ and RXR Whole animals: Increased weight, increased/reduced insulin levels, leptin, hepatic steatosis β-cells: Reduced GSIS, impaired Ca2+ signaling, reduced NAD(P)H and ATP, and PKA levels Insulin target cells: Increased adipogenesis	Serum half-life 3 days (POP)	[11–13,75, 76,87,103, 125]
Arsenic	*Pesticides, smelting, industrial waste *Drinking water, soil, seafood, rice, mushrooms, poultry	10 ppb (water; EPA)	General mechanisms: Oxidative stress/Unknown Whole animals: Glucose intolerance Gestational exposure: Glucose intolerance, obesity in dams β-cells: Reduced GSIS, increased ROS, impaired Ca^{2+} signaling, insulin granule exocytosis, insulin gene expression. Induced autophagy, apoptosis. Insulin target cells: Reduced insulin signaling, ROS, reduced hepatic glycogen	4–6 hours; 20–30 hours (methyl ated)	[14–17,30, 31,50,53, 68,104,126]
Cadmium	*Byproduct of mining, combustion, waste incineration *Soil, water, air; leafy vegetables, peanuts, soybeans, sunflower seeds; inhalation	0.005 mg/L (water; EPA); 5 μg/m^3 per day (air; OSHA)	General mechanisms: Oxidative stress/Unknown Whole animals: Insulin resistance, increased insulin levels β-cells: Reduced GSIS, increased ROS, mitochondrial dysfunction, apoptosis, mediated by JNK Insulin target cells: Reduced GLUT4	4–38 years	[33,34,59,1–27]
Mercury	*Mining, waste incineration, manufacturing *Fish, shellfish, medical/dental procedures	2 ppb (water; EPA); 1 ppm (food; FDA); 0.1 mg/m^3 (air; OSHA)	General mechanisms: Oxidative stress/Unknown β-cells: Reduced GSIS, increased ROS, PI3 kinase and Akt, induced apoptosis and necrosis.	1–3 weeks to 1–3 months (depend s on route of exposur e, chronicit y)	[35,36]
Alkylphenoli c Compounds (e.g. Octylphenol, Nonylphenol)	*Surfactants, detergents, emulsifiers *Fish, drinking water, personal care products	Undetermi ned	General mechanisms: Modulates estrogen signaling β-cells: Reduced GSIS, impaired mitochondrial structure and function. Insulin target cells: Impaired FA metabolism, reduced lipogenesis	2–3 hours (POP)	[19,128]
BPA	*Food packaging, toys, canned food liners *Ubiquitous exposure	50 mcg/kg/da y (FDA) 4 mcg/kg/da y (European Food Safety Authority)	General mechanisms: Modulates estrogen signaling Whole animals: Glucose intolerance Gestational exposure: Glucose intolerance, increased weight in both dams and offspring. β-cells: Reduced GSIS, disrupted mitochondrial structure and function, increased ROS Insulin target cells: Reduced insulin action and signaling intermediates, increased adipose inflammation (JNK, NFκB)	4–5 hours	[19,29,40,4–8, 51,52,77,7–8, 92,93,101, 102, 108]

Compound	Uses and Common Routes of Exposure	Recommended Safe Exposure Level in Humans	Cellular/Molecular Metabolic Effects	Elimination Half-life in Humans	References
Phthalates/P hthalate esters (e.g. DEHP, MEHP)	*Liquid plasticizers; Lend flexibility to plastics (e.g. PVC); lubricants, perfumes, cosmetics, medical tubing, wood finishes, adhesives, paints, toys, emulsifiers in food. *Ubiquitous exposure	DEHP: 6ppb (water; EPA); 5mg/m^3/8 hour day (OSHA)	General mechanisms: Activates PPARγ signaling Whole animals: Insulin resistance, reduced hepatic glycogen, increased ROS. Gestational exposure: increased systemic inflammation and altered adipose development in offspring β–cells: Reduced GSIS, insulin content, increased ROS Insulin target cells: Reduced insulin signaling, glucose oxidation, increased ROS in muscle	12 hours	[32,56,57,6–9, 105]
PCBs (mix of >200 congeners)	*Plasticizers, in resins, carbonless copy paper, adhesives, paints, inks (banned 1979) *High fat food (dairy, meat, fish)	0.0005 ppm (water; EPA) 0.2–3.0 ppm (food; FDA); 0.5– 1.0 mg/m^3 (air; OSHA); 6.0 ug/kg/d (total)	General mechanisms: Unknown/Varied Whole animals: Glucose intolerance β-cells: increased insulin secretion and Ca^{2+} signaling	6 months - >100 years (varies by exposur e; POP)	[20,129,130]
Dioxins (e.g. TCDD, PCB126)	*Byproducts of smelting, paper manufacture, herbicides and pesticides, hospital waste. *Soil, dairy, meat, seafood.	0.01- 1ng/L/day pg/kg/d (water; EPA)	General mechanisms: Activates AhR signaling, induces inflammation Whole animals: Glucose intolerance β-cells: Reduced GSIS, insulin content; increased basal insulin secretion, $[Ca^{2+}]_{IC}$ Insulin target cells: Reduced insulin signaling, increased inflammation (JNK, ERK1/2), reduced hepatic glycogen	7–11years (POP)	[54,55,65, 71–74]
Perfluoroalk yl substances (e.g. PFOA, PFOS)	*Stain resistant coating in clothing, cookware, upholstery; food packaging *Food, drinking water	70 ppt (water; EPA)	General mechanisms: Modulates estrogen signaling, activates PPARα signaling Whole animals: Altered lipid metabolism, steatosis Gestational exposure: increased weight, leptin, insulin levels, glucose intolerance Insulin target cells: Increased insulin signaling/sensitivity, reduced hepatic glycogen synthesis	3–5 years	[66,106,107,131]
Tolylfluanid	*Agricultural fungicide, biocide on ships, paints *Food, water; occupational exposures in shipping and agriculture	0.1 mg/kg/day (FDA)	General mechanism: Activates GR signaling Whole animals: increased weight, adiposity, insulin resistance, glucose intolerance, altered circadian feeding patterns. Insulin target cells: reduced insulin signaling	hours - days	[49,88,90]
Atrazine	*Most widely used herbicide in the U.S.; used on corn, sorghum, sugar cane, Christmas trees, golf courses *Food, drinking water	3 μg/L (water; EPA), 5 mg/m^3/shif t (OSHA)	General mechanisms: Unknown Whole animals: Increased weight, insulin resistance Insulin target cells: Reduced insulin signaling, mitochondrial toxicity, impaired FA oxidation in liver	10–11 hours	[67,112]
Particulate Matter	*Aerosol particles with diameter less than 2.5 μm; combustion associated with traffic,	35 μg/m3 air daily average; 15 μg/m3 annual average.	General mechanisms: Inflammation/Unknown Whole animals: Increased visceral adiposity, insulin resistance	Unknow n	[97,98,111]

Compound	Uses and Common Routes of Exposure	Recommended Safe Exposure Level in Humans	Cellular/Molecular Metabolic Effects	Elimination Half-life in Humans	References
	mining, burning coal, oil, wood *Ubiquitous; Inhalation		Insulin target cells: Reduced insulin signaling, PKC activity, increased inflammation, ROS, NASH, reduced glycogen.		