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Inappropriately sweet: Environmental endocrine-disrupting chemicals and the diabetes pandemic

Margaret C. Schulz[a,b], **Robert M. Sargis**[a,b,c,*]

[a]School of Public Health, University of Illinois at Chicago, Chicago, IL, United States

[b]Department of Medicine, Division of Endocrinology, Diabetes, and Metabolism, University of Illinois at Chicago, Chicago, IL, United States

[c]Jesse Brown Veterans Affairs Medical Center, Chicago, IL, United States

Abstract

Afflicting hundreds of millions of individuals globally, diabetes mellitus is a chronic disorder of energy metabolism characterized by hyperglycemia and other metabolic derangements that result in significant individual morbidity and mortality as well as substantial healthcare costs. Importantly, the impact of diabetes in the United States is not uniform across the population; rather, communities of color and those with low income are disproportionately affected. While excessive caloric intake, physical inactivity, and genetic susceptibility are undoubted contributors to diabetes risk, these factors alone fail to fully explain the rapid global rise in diabetes rates. Recently, environmental contaminants acting as endocrine-disrupting chemicals (EDCs) have been implicated in the pathogenesis of diabetes. Indeed, burgeoning data from cell-based, animal, population, and even clinical studies now indicate that a variety of structurally distinct EDCs of both natural and synthetic origin have the capacity to alter insulin secretion and action as well as global glucose homeostasis. This chapter reviews the evidence linking EDCs to diabetes risk across this spectrum of evidence. It is hoped that improving our understanding of the environmental drivers of diabetes development will illuminate novel individual-level and policy interventions to mitigate the impact of this devastating condition on vulnerable communities and the population at large.

1. Introduction

Diabetes mellitus is a common, chronic disease that is defined phenotypically by elevations in blood glucose levels (i.e., hyperglycemia). Diabetes is estimated to afflict over 463 million individuals worldwide, including over 34 million people in the United States; significantly, disease rates continue to increase across the globe (CDC, 2020; Saeedi et al., 2019). Importantly, diabetes is associated with significant burdens on individuals and society at large. Indeed, diabetes is associated with various micro- and macrovascular complications,

*Corresponding author: rsargis@uic.edu.

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and is a leading cause of kidney failure, blindness, and non-traumatic amputations. Diabetes can quadruple a person's risk of heart disease, which is the leading cause of death in individuals with diabetes (Agarwal et al., 2009). In addition to the toll of the disease on the individual, diabetes imposes a significant economic burden. In the United States alone, the total economic costs of diabetes, including lost productivity, is estimated to be $327 billion annually (American Diabetes Association, 2018).

Unfortunately, the impact of diabetes across the population is not uniform, and diabetes is a source of significant health disparities. Certain racial and ethnic groups are more likely to suffer from the disease as well as its complications. People of Hispanic/Latino ancestry have 80% higher rates of diabetes compared to non-Hispanic Whites (Aguayo-Mazzucato et al., 2019), while non-Hispanic Blacks are almost twice as likely to be diagnosed with diabetes compared to non-Hispanic Whites (CDC, 2020). Importantly, these same communities of color are also disproportionately afflicted by the complications of diabetes, including diabetes-associated death (Aguayo-Mazzucato et al., 2019; Marshall, 2005). Additionally, indigenous populations, including Native American and American Indian peoples, are almost three times more likely to be diagnosed with diabetes and have a 2.5-fold greater likelihood of diabetes-related complications and associated death (Kochanek, Murphy, Xu, & Arias, 2019). While many factors have been posited to account for these health disparities, their origins remain incompletely understood, and the potential contribution of environmental injustice is likely underappreciated.

There are many underlying risk factors for diabetes that contribute to the development and progression of disease. These include lifestyle factors such as excess energy intake via poor diets, physical inactivity, and insufficient or disrupted sleep as well as genetic predisposition. While these risk factors for diabetes are unquestioned, they fail to fully account for the dramatic rise and spread of diabetes over the last decades, raising the likelihood that other factors are at play. This includes the possibility that exposures to endocrine-disrupting chemicals (EDCs) may be an underappreciated risk factor for diabetes and many other chronic metabolic disorders (Heindel et al., 2017). This chapter will review the current literature linking environmental exposures with the pathogenesis of hyperglycemia and the development of diabetes, with a specific focus on type 2 diabetes mellitus (T2DM), the most common form of the disease.

2. Pathogenesis of type 2 diabetes mellitus

Type 2 diabetes mellitus (T2DM) is defined clinically by elevations in blood glucose levels that can arise from various disruptions in the molecular physiology that regulates glucose homeostasis. Specifically, T2DM is diagnosed with evidence of hyperglycemia defined by a hemoglobin A_{1c} (HbA_{1c}) ≥6.5%; fasting plasma glucose ≥126mg/dL; a 2-h plasma glucose of ≥200 mg/dL after a 75-g oral glucose load; or a random plasma glucose of ≥200mg/dL with associated symptoms of hyperglycemia (American Diabetes Association, 2021). Importantly, the pathophysiology of hyperglycemia underlying T2DM development stems from various disruptions in molecular physiology across the multiple metabolic tissues regulating energy homeostasis; however, the common physiological characteristics of diabetes development are impairments in insulin secretion, insulin action, or both.

Pancreatic islets of Langerhans are composed of a variety of cell types, including α-cells that secrete glucagon, β-cells that secrete insulin, and δ-cells that secrete somatostatin, among others. The majority of the islet is composed of α-cells and β-cells, the latter of which couple insulin secretion to glucose metabolism. Whole-body glucose homeostasis is a dynamic process that ensures the economic use of energy; it is dependent upon β-cell insulin secretion and insulin signaling in peripheral tissues (e.g., liver, muscle, and adipose tissue). Insulin secretion from pancreatic β-cells is primarily induced by rising plasma glucose concentrations. Glucose is taken up by glucose transporters 1 and 3 (GLUT1 and GLUT3) on the surface of human β-cells (GLUT2 in rodent β-cells), which subsequently undergoes glycolytic metabolism resulting in the production of adenosine triphosphate (ATP) and an increase in the ATP-to-ADP ratio. Increases in the ATP-to-ADP ratio result in the closure of ATP-dependent potassium (K_{ATP}) channels and cellular depolarization. This results in the activation of voltage-sensitive calcium channels that increase cytosolic calcium, which in turn triggers release of insulin secretory granules (Fu, Gilbert, & Liu, 2013). Although glucose is the primary trigger for insulin secretion, pancreatic β-cells also respond to amino acids, other monosaccharides, and fatty acids. Furthermore, various endocrine hormones can influence β-cell function and insulin secretion. For example, stimulation of estrogen receptors by 17-β-estradiol augments insulin secretion (Sutter-Dub, 2002), while gut-derived incretin hormones such as glucagon-like peptide-1 (GLP-1) augment glucose-dependent insulin secretion via G-protein coupled receptors (GPCRs) (Orskov, 1992). Conversely, leptin and growth hormone (acting via insulin-like growth factor-1) can inhibit insulin secretion (Fu et al., 2013; Sonksen, 2001). Finally, β-cell development and physiology are influenced by other hormonal signaling pathways, including those responsible for glucocorticoid receptor and prolactin signaling (Arumugam et al., 2008). Thus, multiple signaling pathways modulate insulin secretion, some of which may be targets of metabolic toxicants.

Upon secretion from pancreatic β-cells, insulin enters the circulation where it acts on insulin-responsive tissues that express the insulin receptor, a tyrosine kinase receptor; these include liver, muscle, and adipose tissue. Through a complex intracellular signaling cascade, insulin stimulation of the insulin receptor leads to glucose uptake in insulin-responsive tissues. Specifically, insulin receptor autophosphorylation results in kinase activation and the phosphorylation of insulin receptor substrate (IRS) proteins. A subsequent cascade of phosphorylation events and protein activation follows that ultimately results in activation of Akt and mTORC, inhibition of FoxO signaling, and GLUT4 translocation to the cell membrane. The sum of these effects is the promotion of glucose uptake and a shift toward anabolic metabolism. In skeletal muscle, insulin receptor activation stimulates the expression and membrane translocation of GLUT4 glucose transporters to the myocyte cell membrane to facilitate glucose uptake and clearance, with glucose storage in muscle principally as glycogen (Stump, Short, Bigelow, Schimke, & Nair, 2003). In adipose tissue, insulin stimulation triggers increased expression and membrane translocation of GLUT4 for glucose uptake and storage as triglycerides, as well as increased lipoprotein lipase (LPL) expression for clearance of plasma triglycerides and storage in fat. In the liver, insulin promotes de novo lipogenesis and glucose storage through incorporation into glycogen while suppressing gluconeogenesis and hepatic glucose output. Thus, insulin signaling in insulin-responsive

tissues results in clearance of plasma glucose for storage and later energy mobilization during periods of fasting or exercise. Critically, impairments in insulin signaling (i.e., insulin resistance) result in a reduced ability for insulin to clear glucose and triglycerides from the circulation, resulting in higher insulin requirements to maintain euglycemia. As insulin secretion becomes insufficient to overcome insulin resistance, hyperglycemia develops.

Thus, T2DM is a disruption in normal glucose homeostasis that arises from insulin resistance and β-cell dysfunction. Together they result in chronically elevated plasma glucose levels that wreak havoc through the induction of multiple stress pathways, including oxidative stress, inflammation, osmotic stress, and non-enzymatic glycosylation. Activation of these pathways in various tissues leads to the micro- and macrovascular complications of diabetes (i.e., nephropathy, neuropathy, and retinopathy) as well as accelerated atherosclerosis and other derangements. A main driver of insulin resistance is obesity, with excess accumulation of lipids and lipid metabolites being an important mechanism driving impaired insulin action (Samuel & Shulman, 2012). Chronic insulin resistance necessitates increased demand for insulin secretion, resulting in β-cell exhaustion and ultimate failure (Esser, Utzschneider, & Kahn, 2020). Additionally, chronic exposure to elevated glucose and fatty acids is toxic to β-cells (Chang-Chen, Mullur, & Bernal-Mizrachi, 2008). As discussed, when glucose enters β-cells it enters the glycolytic pathway to produce ATP. Excess oxidative phosphorylation can disrupt β-cell mitochondrial function while increasing production of reactive oxygen species (ROS) (Robertson, Harmon, Tran, Tanaka, & Takahashi, 2003). It is suggested that pancreatic β-cells are ill-equipped to handle oxidative stress due to a dearth of antioxidant capacity. In order to compensate, the cells reduce the efficiency of oxidative phosphorylation, thus throttling down ATP generation and ultimately reducing insulin production and cell mass (Prentki & Nolan, 2006). Reductions in insulin secretory capacity arising from β-cell dysfunction results in insufficient insulin delivery to peripheral tissues to effectively clear glucose from the circulation resulting in hyperglycemia and ultimately frank T2DM. Importantly, factors that promote insulin resistance and/or β-cell dysfunction can amplify metabolic deterioration and increase the risk of T2DM. While many such factors have been implicated in this metabolic deterioration, burgeoning evidence now implicates various environmental contaminants acting as endocrine-disrupting chemicals (EDCs) as novel, underappreciated diabetes risk factors.

3. Endocrine-disrupting chemicals (EDCs)

The Endocrine Society defines EDCs as “endogenous chemicals, or mixture of chemicals, that interfere with any aspect of hormone action” (Gore et al., 2015). EDCs have classically been implicated in the disruption of sex steroid and thyroid hormone signaling; however, increasing data across the spectrum of evidence from cells to populations now indicate that various EDCs can disrupt other signaling cascades and may play a role in many chronic diseases, including metabolic disorders such as obesity, diabetes, and non-alcoholic fatty liver disease (Heindel et al., 2017). To date, hundreds of chemicals have been identified as having hormone-disrupting properties, and this list continues to grow with new chemicals and pathways of disruption emerging (Diamanti-Kandarakis et al., 2009; La Merrill et al., 2020). Critically, but often poorly recognized, the nature of endocrine

signaling as well as the organizational effects of hormones on development help explain how EDCs can exert adverse effects at both low concentrations and with non-linear dose-response relationships (Vandenberg et al., 2012). The ultimate impact is adverse effects on health at the time of exposure as well as later in life. Notable EDCs that have been extensively studied and will be reviewed herein, including arsenic, bisphenol A (BPA), the organochlorine pesticide dichlorodiphenyltrichloroethane (DDT) and its metabolite dichlorodiphenyldichlorethylene (DDE), tolylfluanid, polychlorinated biphenyls (PCBs), and multiple air pollutants. Importantly, other EDCs associated with diabetes, its pathological origins, and its clinical manifestations continue to emerge, increasingly supporting the contention that environmental health contributes to metabolic wellness.

Potential exposure to EDCs can occur through various routes and sources (Fig. 1). Arsenic is a common naturally occurring element that has also been used in pesticides, preservatives, and for other industrial purposes (Chung, Yu, & Hong, 2014). BPA exposure can occur through water contamination, soil absorption, paper receipts, and food contamination due to incorporation into plastics as well as the BPA coating on the surfaces of metals and other storage containers (Kang, Kondo, & Katayama, 2006; La Merrill et al., 2020). DDT/DDE are among the organochlorine (OC) pesticides and their metabolites that bioaccumulate and are persistent in the environment. OC pesticides have been implicated in the harming of wildlife, and many have been banned; however, humans continue to be exposed through contaminated foods due to the chemicals' persistence and bioaccumulation in the food chain as well the continued direct handling of some of these agents (Jaga & Dharmani, 2003). Tolylfluanid is a phenylsulfamide fungicide that can contaminate groundwater, and humans can be exposed occupationally in the agriculture industry (Regnier et al., 2015). Finally, PCBs were historically used industrially in electrical and building equipment. They have long half-lives in soil and in the fatty tissue of animals, which results in persistence in the environment and continued human exposure primarily via consumption of contaminated food (Faroon & Ruiz, 2016).

In addition to exposures occurring via contaminated food and water, inhalational exposure to air pollutants has also been implicated in endocrine disruption (Darbre, 2018). Exposure to air pollutants can occur in both indoor and outdoor environments, with specific pollutants being of either natural or synthetic origin. Non-gaseous EDCs can be vaporized into gaseous forms through aerosols, combustion, exhaust, and other routes that can then be absorbed through the respiratory tract (Annamalai & Namasivayam, 2015). Intriguingly, additional sources of EDC exposures include personal and home care products as well as even some medications and medical devices (Encarnacao, Pais, Campos, & Burrows, 2019; Genco, Anderson-Shaw, & Sargis, 2020). While many exposures are inadvertent and need to be addressed through policy, the latter suggest that some EDCs may be avoided through education and improved practice as well as via regulatory policies.

4. EDCs and pathways to environmentally-mediated diabetes

As T2DM can be viewed as arising from a combination of insulin resistance and insulin insufficiency, exposure to EDCs from various sources that affect insulin physiology may play a role in diabetes development. Herein we review evidence linking various EDCs to

disruptions in insulin secretion and action across the spectrum of evidence from cellular assays to population-based and even clinical studies. These data are summarized in Table 1, and taken together, indicate that EDCs represent an underappreciated threat to metabolic health.

4.1 Evidence linking EDCs to alterations in insulin secretion

4.1.1 Evidence from cell-based studies—A plethora of in vitro studies have demonstrated the capacity for EDCs to disrupt endocrine pancreatic function while illuminating mechanisms of toxicity that result in insulin secretory defects (Fig. 2). For example, in murine and human β-cells, short-term BPA exposure increased insulin secretion via an estrogen receptor α (ERα) mechanism (Alonso-Magdalena et al., 2008); however, longer term exposure resulted in reduced glucose-induced insulin secretion (GIIS) and downregulated expression of insulin-related genes with impaired β-cell capacity for compensation (Wei et al., 2017). In earlier studies, PCBs have also been shown to augment insulin release while depleting insulin content (Fischer et al., 1996). Cellular DDT exposure has been shown to impair GIIS (Park et al., 2020; Yau & Mennear, 1977). Human pancreatic β-cells exposed to high concentrations of DDT showed reduced expression of proteins involved in endoplasmic reticulum stress responses, mitochondrial function, and cell morphology (Pavlikova et al., 2020). Also, lower, non-lethal concentrations of DDT have been shown to reduce expression of insulin and proinsulin in the NES2Y human pancreatic β-cell model (Pavlikova et al., 2015). In addition to organic pollutants, inorganic chemicals have also been shown to impair β-cell function as well. For example, arsenic in both its organic and inorganic sub-species has been shown to disrupt β-cell function (Carmean et al., 2019; Dover et al., 2018; Huang, Douillet, & Styblo, 2019; Li, Douillet, et al., 2020). Other EDCs linked to disruptions in insulin secretion and β-cell function in cellular assays include alloxan, cadmium, mercury, phthalates, PBDEs, TCDD, triphenyltin, and other bisphenols such as BPS and BPF. In addition to β-cell disruptions, data also suggest that EDCs, such as BPA, may also disrupt the function of glucagon-secreting pancreatic islet α-cells that function to raise glucose levels (Alonso-Magdalena et al., 2005). Because α-cells make up a larger fraction of cell distribution in human islets, the metabolic impacts of α-cell-disrupting EDCs on human physiology may be more significant than suggested by rodent models.

Intriguingly, EDCs linked to disrupted β-cell function and insulin secretion include structurally diverse compounds of diverse origins. While all result in alterations in β-cell physiology, the mechanisms responsible for these effects vary across EDCs, with multiple mechanisms implicated. For example, arsenic has been shown to disrupt β-cell function through multiple mechanisms, including the induction of mitochondrial dysfunction and oxidative stress, as well as through alterations in serotonin metabolism (Carmean et al., 2019; Dover et al., 2018; Huang et al., 2019; Li et al., 2020). Similar mechanisms have been proposed for other EDCs. In addition, EDCs have been shown to alter other key signaling pathways that regulate β-cell function, including oxidative and endoplasmic reticulum (ER) stress; cellular apoptosis, necrosis, and decreased cellular proliferation; mitochondrial dysfunction and reduced ATP synthesis; disruptions of the cytoskeleton and insulin granule exocytosis; altered insulin gene expression and DNA damage; disturbed incretin signaling

and calcium flux; disruptions in estrogen receptor signaling; altered epigenetics; disruption in ion channel expression and electrical membrane potential; and increased inflammation among others. Importantly, the cellular disruptions induced by EDCs are consistent with known pathways linked to the pathogenesis of diabetes, providing molecular linkage between EDCs and disease development. Furthermore, the fact that human exposure to environmental toxicants is best characterized as being that of polychemical mixtures, real-world scenarios likely reflect multiple pathways altered simultaneously.

4.1.2 Evidence from animal studies—Because in vivo glucose homeostasis and metabolic physiology require the coordinated interplay of various tissues, our understanding of the impact of EDCs on metabolic disease risk is markedly augmented by physiological studies conducted using intact animal models. Indeed, extensive in vivo studies using rodent models have demonstrated the impact of EDCs on insulin secretion, insulin sensitivity, and global glucose homeostasis. Evidence linking environmental toxicants to disruptions in pancreatic islets dates to the early 1940s when alloxan was shown to induce islet necrosis (Dunn, Duffy, Gilmour, Kirkpatrick, & McLetchie, 1944). Since that time, an increasing body of evidence has implicated environmental toxicants with disruptions in insulin secretion. Adult rats exposed to arsenic displayed altered DNA methylation of the GLUT2 transporter gene in pancreatic islets, which impairs glucose sensing and subsequent insulin release (Khan et al., 2020). Consistent with these findings, another study found that arsenic exposure induces glucose intolerance after 8 weeks of exposure in adult male mice with concordant reductions in early insulin release after a glucose load (Kirkley et al., 2018). Furthermore, arsenic exposure in adult male rats promoted iron-dependent oxidation of pancreatic β-cells in mice resulting in membrane lipid peroxidation and cell death (Wei, Qiu, et al., 2020). Adult male mice exposed to a dioxin-like and non-dioxin-like PCB mixture suffered acinar cell atrophy, steatosis, and fibrosis of pancreatic tissue, in addition to reduced expression of insulin and insulin-regulating genes (Shi et al., 2019). Consistent with in vitro models, in vivo exposure to BPA initially augmented insulin release and increased cellular insulin content in an estrogen receptor-β-dependent manner in adult mice, but ultimately induced β-cell apoptosis due to mitochondrial dysfunction in pregnant mouse offspring (Alonso-Magdalena, Morimoto, Ripoll, Fuentes, & Nadal, 2006; Lin et al., 2013; Manukyan, Dunder, Lind, Bergsten, & Lejonklou, 2019). Lastly, developmental BPA exposure resulted in β-cell dysfunction with hyperglycemia in mouse offspring during adulthood (Garcia-Arevalo et al., 2014; Mao et al., 2015). In addition to these models, in vivo exposure to other EDCs has been shown to disrupt insulin secretion, including cadmium, mercury, Vacor, and alloxan as well as DDT and its metabolite DDE (El Muayed et al., 2012; Iavicoli, Fontana, & Bergamaschi, 2009; Lenzen, 2008; Taniguchi et al., 1989). Collectively, these animal models reinforce cellular data indicating that EDC exposure has the capacity to disrupt insulin secretion, with attendant threats to glucose homeostasis and metabolic physiology more broadly.

4.2 Evidence linking EDCs to alterations in insulin action

Central to the pathophysiology of T2DM are impairments in insulin action, often arising from obesity-induced disruptions in lipid metabolism, enhanced inflammation, and other molecular disruptions. This induction of insulin resistance increases secretory demands

on pancreatic β-cells, ultimately leading to their failure. Importantly, while genetic predisposition, excess energy intake, physical inactivity, and sleep disturbances among other factors can promote insulin resistance, data now indicate that exposure to EDCs may also promote insulin resistance and subsequent diabetes risk.

4.2.1 Evidence from cell-based studies—Evidence from cell-based studies demonstrate how EDCs can disrupt insulin action and induce cellular insulin resistance (Fig. 2). Arsenic has been shown to specifically impair insulin signaling and response in cultured 3T3-L1 adipocytes (Paul, Harmon, Devesa, Thomas, & Styblo, 2007). Arsenite also reduces insulin-mediated glucose uptake and induces chronic inflammation in these same cells (Xue et al., 2011). Lastly, arsenic exposure both induces myocyte apoptosis and inhibits myoblast proliferation, resulting in reduced muscle mass that can contribute to insulin resistance (Liu et al., 2015; Yen et al., 2012). In cultured rat L6 myoblast-derived myotubes, DDT exposure resulted in oxidative stress that impaired insulin action (Singh et al., 2019). BPA impairs adipocyte functioning and differentiation, ultimately resulting in inhibition of glucose uptake following insulin stimulation as well as increased expression of inflammatory mediators (Ariemma et al., 2016; Valentino et al., 2013). The phenylsulfamide fungicide tolylfluanid has also been shown to impair cellular insulin signaling. In primary murine and human adipocytes, tolylfluanid disrupts insulin signaling through a specific reduction in the expression of insulin receptor substrate-1 (IRS-1) (Sargis et al., 2012). In C2C12 skeletal myocytes, tolylfluanid reduced insulin-dependent downstream protein phosphorylation and reduced mitochondrial oxygen consumption and membrane potential (Davis, Thomas, Shorter, Brown, & Baumgarner, 2018; Sargis et al., 2012). In studies of primary adipose tissue, tolylfluanid-mediated induction of insulin resistance via reduced IRS-1 expression appears to result from the activation of glucocorticoid receptor signaling (Neel, Brady, & Sargis, 2013). Also, in adipocytes, exposure to PCBs promoted differentiation, increased lipid droplet size, and induced insulin resistance (Kim et al., 2017). The prototypical obesogen, tributyltin (TBT), has been shown to promote adipocyte differentiation via activation of signaling through the retinoid X receptor (RXR) and the peroxisome proliferator-activated receptor-γ (PPARγ) (Shoucri, Hung, Chamorro-Garcia, Shioda, & Blumberg, 2018). Importantly, these adipocytes appear to be physiologically distinct, with characteristics predicted to promote metabolic dysfunction (Regnier et al., 2015).

Other EDCs linked to disruptions in insulin action in cell-based studies include: 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), phthalates, cadmium, and perfluoroalkyl substances (PFASs) among others. In addition to inappropriate activation of nuclear hormone signaling, reductions in the expression of insulin signaling intermediates, and mitochondrial dysfunction, multiple other cellular pathways have been implicated in the pathophysiology of EDC-induced insulin resistance. These include: increased expression of inflammatory mediators, altered lipid metabolism, disrupted adipokine expression, oxidative stress, enhanced cellular senescence, impaired glucose transport, and disruptions in gluconeogenesis and glycogen handling. In summary, the increase in evidence linking EDCs with altered cellular function in tissues regulating metabolic physiology clearly delineate

potential connections between diverse toxicant exposures and molecular pathways linked to the development of diabetes.

4.2.2 Evidence from animal studies—Animal models remain essential tools for assessing the impact of EDCs on metabolic physiology, including insulin action. This is because insulin exerts biological effects on multiple tissues that communicate with one another. Thus, in vivo studies remain necessary tools for assessing the impacts of EDCs on energy metabolism, and they have provided intriguing insights regarding the capacity of these pollutants to promote metabolic dysfunction. For example, adult male mice exposed to tolylfluanid exhibited increased body weight that was characterized by increased fat mass, and these changes were accompanied by impaired glucose tolerance resulting from global insulin resistance (Regnier, Kirkley, et al., 2015). Importantly, adipose from these mice also showed increased glucocorticoid receptor signaling, consistent with cell-based assays and the predicted effects of inappropriate signaling through this important nuclear hormone receptor (Neel et al., 2013). Interestingly, the precise effects of tolylfluanid on global energy metabolism appear to be influenced by dietary macronutrient composition (Regnier et al., 2018). In addition to its effects on insulin secretion, BPA has also been linked to impairments in insulin action through alterations in hepatic glucose sensing as well as impairments in glucokinase activity and the glycolytic pathway when administered to adult male mice (Perreault et al., 2013). In agreement with cellular studies, animal models of arsenic exposure have demonstrated hepatic inflammation that may play a role in arsenic-induced insulin resistance (Jia et al., 2020). Exposure to DDE and other organochlorine pesticides in 6-week-old mice resulted in macrophage recruitment and inflammation of adipocytes, which may contribute to impaired insulin action and resistance (Mangum et al., 2016). Lastly, adult mice exposed to PCBs exhibited insulin resistance in conjunction with adipocyte inflammation (Baker et al., 2015). Other EDCs linked to alterations in insulin sensitivity include: TCDD, phthalates, particulate matter air pollution, cadmium, PFASs, malathion, atrazine, polybrominated diphenyl ethers (PBDEs), mercury, and other persistent organic pollutants (POPs).

In addition to adult exposure paradigms, developmental exposure to EDCs has also been linked to metabolic perturbations in the offspring. For example, perinatal DDT exposure during development resulted in glucose intolerance and hyperinsulinemia in adult female offspring (La Merrill et al., 2014). Mice exposed to tolylfluanid throughout gestation and lactation demonstrated sex-dependent effects on glucose tolerance and insulin sensitivity during adulthood (Ruiz et al., 2019). In adult exposure models, tributyltin exposure has been shown to induce insulin resistance (Xu et al., 2019). Intriguingly, developmental exposure to tributyltin has been shown to induce transgenerational disruptions in metabolic regulation (Chamorro-Garcia et al., 2017). Mechanisms responsible for these heritable changes include epigenetic alterations and changes in chromatin modeling (Rattan & Flaws, 2019; Skinner, 2016). These findings are in line with the Developmental Origins of Health and Disease Hypothesis (Dover, 2009) and raise the intriguing possibility that EDC-induced disruptions in metabolic homeostasis may not only reflect current exposure but may result from historical exposure during sensitive windows of development or even from prior generations.

4.3 Evidence from epidemiological and population-based studies

While cell- and animal-based studies facilitate assessment of the mechanisms of toxicant induced β-cell dysfunction and impaired insulin action, human epidemiological and population-based studies are vital in determining the consequence of EDC exposure on diabetes risk, measures of glycemic control, and diabetes-related outcomes. Unfortunately, many population studies that examine the associations between EDC exposure and diabetes-related traits do not inform the pathophysiological origins of those links, i.e. whether associations are mediated by impaired insulin secretion, insulin resistance, or both. Nevertheless, these studies are critical to link real-life exposures to human disease. Importantly, the potential for environmental toxicants to promote diabetes development has been known for decades. In 1978, a case report described a patient who ingested large amounts of the rodenticide Vacor and subsequently developed diabetic ketoacidosis, a metabolic condition characterized by hyperglycemia resulting from marked insulin deficiency (Miller et al., 1978). While this poisoning event is not characteristic of most environmental exposures, it provides proof-of-principle that agents disseminated into the environment may be linked to diabetes pathogenesis.

Arsenic exposure is associated with an increased risk for diabetes, and the metabolism of the metalloid into its dimethylated sub-species is associated with a further increase in risk (Zhang et al., 2020). In recent studies, even low levels of blood arsenic have been associated with a higher prevalence of diabetes (Dai et al., 2020). Furthermore, arsenic exposure, evaluated by hair and nail samples, was positively associated with increased fasting blood glucose, serum insulin, and increased homeostatic model assessment of insulin resistance (HOMA-IR). Arsenic was also associated with reduced lean body mass, which could be a mechanism for the insulin resistance (Mondal et al., 2020). BPA has been heavily studied in human populations, and the results support the in vitro and in vivo evidence. BPA is associated with increased overall risk for diabetes in a dose-dependent manner (Lee et al., 2020). Furthermore, other studies have established a dose-response relationship between urinary BPA levels and increased diabetes prevalence (Shankar & Teppala, 2011), and BPA exposure was found to be associated with an increased odds ratio for insulin resistance (Wang et al., 2012). Serum BPA levels were higher in patients with T2DM compared to healthy controls and were associated with poorer glycemic control, increased insulin resistance, and overall worse clinical outcomes (Soundararajan, Prabu, Mohan, Gibert, & Balasubramanyam, 2019). Large case-control and cohort studies found that exposure to organochlorine pesticides was associated with increased incidence of diabetes, and patients with diabetes had higher DDT and DDE serum concentrations than healthy individuals (Mansouri & Reggabi, 2020; Rignell-Hydbom et al., 2009; Salihovic et al., 2016; Turyk, Anderson, Knobeloch, Imm, & Persky, 2009). PCB exposure in a Taiwanese population was linked to increased diabetes risk in women (Wang, Tsai, Yang, & Guo, 2008). Both PCB and organochlorine pesticide exposure are associated with increased HOMA-IR, HbA1c, and reduced insulin sensitivity (Lind & Lind, 2018).

The primary route for studying the relationship between air pollution and diabetes is through epidemiological cohort and ecological studies. Recent studies have found very compelling and interesting impacts of air pollution on metabolic health, with most studies focusing on

particulate matter, nitrogen dioxide, and ozone. Particulate matter is a mixture of particles in the air that vary in size and can penetrate the lungs (Brunekreef & Holgate, 2002). $PM_{2.5}$ is particulate matter that is less than 2.5 μm in diameter. Firstly, overall air pollution was found to be associated with reduced insulin sensitivity and β-cell function (Zhang, Mwiberi, et al., 2021). Ozone exposure was positively associated with increased diabetes risk, elevated fasting plasma glucose, fasting insulin, insulin resistance, and β-cell function in non-diabetic adults in China (Li, Mei, et al., 2021; Lin et al., 2020). Additionally, individuals exposed to ambient nitrogen dioxide had an increased risk for diabetes, increased HbA1c, and increased fasting plasma glucose (Zhang, Liu, et al., 2021). Furthermore, $PM_{2.5}$ is associated with increased incidence and prevalence of diabetes and worsened glycemic control among those previously diagnosed with diabetes (Elbarbary et al., 2020; Hwang, Kim, Koo, Yun, & Cheong, 2020). Importantly, the impact of air pollution, particularly particulate matter, appears to be enhanced by warm, humid weather, which raises important concerns about the amplifying impact of climate change on diabetes risk (Jabbari et al., 2020; Lin et al., 2020).

In addition to these EDCs, population-based studies have also linked other EDCs to diabetes and diabetes-related traits, including: TCDD, phthalates, cadmium, PFASs, malathion, PBDEs, polychlorinated dibenzo-*p*-dioxins and furans, and mercury. In addition to these data from epidemiological studies, data from clinical studies have also emerged. In a cross-over study of male and female subjects intentionally given a single low dose of BPA, exposure to this EDC altered insulin secretion during an oral glucose tolerance test and a hyperglycemic clamp (Stahlhut et al., 2018). While further randomized clinical trials have been proposed to illuminate the effects of BPA on metabolic physiology have been proposed, evidence of toxicity in cells, animal models, and epidemiological studies raise significant ethical concerns regarding the justification of such proposed studies (Hagobian et al., 2020). While the failure of regulatory agencies to address the threats posed by BPA is deeply problematic, deliberately exposing research subjects to EDCs with substantial evidentiary support for adverse health effects is ethically dubious and raises significant concerns not just of subject harm, but also of creating an evidence threshold that cannot be met for more toxic EDCs. Despite this, it is important to note that for BPA, we have evidence of adverse metabolic effects across an incredibly wide spectrum of scientific proof. For other EDCs, the strength of evidence varies; however, the totality of the data suggests that environmental exposures are an important-yet-underappreciated contributor to diabetes rates.

5. EDCs and type 1 diabetes

While T2DM is characterized by insulin resistance and relative insulin insufficiency, type 1 diabetes mellitus (T1DM) is a hyperglycemic disorder arising from absolute insulin insufficiency, often arising from autoimmune destruction of pancreatic β-cells. Importantly, data indicate that rates of T1DM are also increasing, with notable geographic variation in rates (Liu et al., 2020). Because of its distinct pathophysiology, understanding the linkage between environmental toxicant exposures and T1DM is important for better understanding how environments modulate the pathogenesis of this devastating autoimmune disease. Unfortunately, this realm of environmental diabetes has been relatively understudied compared to studies examining linkage between EDCs and T2DM. Despite this, there is

some evidence to suggest that EDCs may be linked to increasing rates of T1DM (Howard, 2018). Certainly, EDCs have been shown to promote β-cell apoptosis or necrosis consistent with T1DM development, and exposure to pollutants can induce hypersensitivity reactions, suggesting immune system disruption (Ritz, 2010). Indeed, the early data from Vacor poisoning and alloxan exposure are consistent with these findings (Lenzen, 2008; Miller et al., 1978). Other experimental studies have shown that arsenic and other EDCs directly target pancreatic β-cells resulting in insulin deficient diabetes (Ramdas, Sharma, Kaul, & Bhatia, 2018). Additionally, DDT exposure in rats during development not only resulted in pancreatic dysfunction later in life but in two subsequent generations as well (Song & Yang, 2017). Animal studies have found that exposure to both BPA and its replacement chemical bisphenol S worsens inflammation and glycemia in a non-obese diabetic (NOD) mouse model, which is frequently used to evaluate type 1 diabetes development (Xu, Huang, & Guo, 2019; Xu, Huang, Nagy, & Guo, 2019). Some epidemiological studies have also been consistent with these findings, showing EDCs may be implicated in T1DM pathogenesis. For example, exposure to air pollution during pregnancy is associated with increased risk for T1DM in children (Elten et al., 2020; Malmqvist et al., 2015). Overall, current evidence linking EDCs to T1DM and its pathogenesis is intriguing; however, more work is needed to better understand how environmental exposures contribute to T1DM risk.

6. EDCs and gestational diabetes

Gestational diabetes (GDM) is a physiological condition characterized by hyperglycemia during pregnancy that is associated with adverse maternal and fetal outcomes (American Diabetes Association, 2004). In addition, a prior history of GDM is associated with a greater risk of T2DM in both mother and child (Ben-Haroush, Yogev, & Hod, 2004). Somewhat akin to T2DM, the hyperglycemia of GDM results from insufficient insulin production to meet the demands imposed by gestational insulin resistance. As such, EDCs that augment insulin resistance or impair β-cell compensation, essential for maintaining euglycemia during pregnancy, are likely to augment GDM risk. This area, however, remains relatively understudied. Studies have found that phthalate and BPA exposure are associated with increased plasma glucose and reduced glucose tolerance in pregnant women (Filardi, Panimolle, Lenzi, & Morano, 2020). Other epidemiological studies have found associations between arsenic and cadmium exposure and increased risk for GDM (Farzan et al., 2016; Salmeri et al., 2020; Xing et al., 2018). Other EDCs, including PFASs and POPs have also been implicated in increased GDM risk (Xu et al., 2020). Animal studies have corroborated this epidemiological evidence. Rats, mice, and sheep exposed to gestational BPA exhibited elevated free fatty acid levels, deleterious adipose distribution, and disruption of glucose homeostasis (Veiga-Lopez et al., 2015). Other experimental studies have shown that EDCs mediate GDM through gene disruption in trophoblastic tissue (Ehrlich et al., 2016). Lastly, studies have shown that glycemic control during pregnancy is worsened by climate change and warming temperatures (Preston, Eberle, Brown, & James-Todd, 2020). Altogether, there is some evidence for the role of EDCs in GDM, but further study is needed to better quantify this risk and to illuminate its underlying mechanisms.

7. EDCs, diabetes disparities, and health justice

A particularly disturbing aspect of the diabetes pandemic is its disproportionate impact on communities of color and those with low income. In the U.S., diabetes rates are higher among Blacks, Hispanics/Latinos, and Native Americans than among non-Hispanic Whites (Aguayo-Mazzucato et al., 2019). Furthermore, these same populations are more likely to suffer the consequences of diabetes, including the microvascular complications of nephropathy, neuropathy, and retinopathy and even diabetes-associated death (Clements et al., 2020). In addition to the greater impact of diabetes on these population groups, communities of color are also more likely to have undiagnosed and untreated diabetes (Hsueh et al., 2020). While many factors have been proposed to account for these disparities, too often neglected in this discussion is the contribution of environmental injustice (Ruiz, Becerra, Jagai, Ard, & Sargis, 2018). Indeed, there is evidence that persons of color are disproportionately exposed to EDCs compared to the general population. Importantly, various social and structural determinants of health contribute to EDC exposure and toxicity, including diet, consumer products, neighborhood characteristics, and geographical area (Hicken et al., 2012; James-Todd, Chiu, & Zota, 2016). People of non-white ethnicity are also more likely to work in occupational settings that increase their risk for EDC exposure. Furthermore, EDC exposure in non-white populations tend to be chronic rather than acute, with the health consequences of these exposures disproportionately impacting non-white populations financially (Attina, Malits, Naidu, & Trasande, 2019). These health disparities are deeply concerning. Understanding the contribution of environmental health to diabetes risk is essential for illuminating the sources of health injustice and identifying opportunities to develop and implement countermeasures. Importantly, because environments are modifiable, addressing the disproportionate burden of diabetogenic exposures on vulnerable communities likely represents an underutilized tool for addressing diabetes-associated health injustice.

8. Crosstalk between clinical care and EDC exposure

While clinical management of diabetes rests upon a foundation of dietary changes and increased physical activity, most individuals with diabetes will ultimately require the use of medications and medical devices (e.g. insulin pumps and continuous glucose monitoring systems) to improve glycemic control. Furthermore, the clinical management of diabetes includes pharmacological and lifestyle interventions to address common diabetes-associated comorbidities and factors that accelerate the development of diabetes-associated complications such as atherosclerosis (e.g., dyslipidemia, hypertension). As such, patients with diabetes have significant contact with the healthcare system, which helps explain the significant and rising health costs associated with diabetes (American Diabetes, 2018). Importantly, however, this engagement may lead to treatments that themselves expose patients with diabetes to EDCs (Genco et al., 2020). This creates a unique ethical challenge as health care providers become purveyors of exposure largely unbeknownst to the patient or the clinician. As such, addressing healthcare-associated EDC exposure and its ethical implications on non-maleficence, informed consent, and patient autonomy is a significant concern that warrants interventions at the levels of the patient and provider, pharmaceutical and device manufactures, and government policy makers. Finally, we must begin efforts to

instruct patients on ways that they can reduce their exposures to metabolically deleterious EDCs. Some evidence-based advice exists on this topic (Sargis, Heindel, & Padmanabhan, 2019; Trasande, 2019), and new data continue to emerge (Mengozzi et al., 2021). Despite this, more work is needed to demonstrate which interventions are most useful for addressing environmental drivers of diabetes risk.

9. Bridging the gap to address ecosystems of diabetes risk

Based on the proliferation of data indicating that environmental exposures represent underappreciated risks to metabolic health that disproportionately affect already vulnerable populations, it is incumbent upon society to use all available tools to reduce exposures to diabetogenic chemicals in order to promote public metabolic health and to address environmental contributors to health injustice. This includes policy- and individual-level action. Unfortunately, while some chemicals linked to diabetes have been regulated, a recent analysis of federal environmental policy showed that diabetes and metabolic disease risk have not been considered in public policy (Shaikh, Jagai, Ashley, Zhou, & Sargis, 2018). Closing this gap through improved environmental policies as well as improved urban planning and development offer novel tools to address the devastating rise of diabetes rates and its disproportionate impact on vulnerable communities.

10. Data gaps and the need for further studies

Despite the proliferation of data linking various EDCs with diabetes risk across cell, animal, and human studies, there remain important gaps in our knowledge. Significant among these include the lack of data on the vast majority of the tens of thousands of chemicals used in consumer products as well as a dearth of studies examining the effects of chemical mixtures on health outcomes. Indeed, evaluating mixture exposure is vital for understanding real-world EDC exposures and their consequences. With regard to diabetes-related outcomes, there have been a few studies that have begun to examine the effects of chemical mixtures on metabolic outcomes. For example, in one study a mixture of persistent organic pollutants (POPs) found in fish oil was shown to promote insulin resistance in rats (Ruzzin et al., 2010). Indeed, many studies examining PCB effects on metabolic outcomes have used PCB mixtures (Liu et al., 2021). Additionally, epidemiological advancements have allowed for the study of metal and metalloid mixtures in relation to diabetes risk, status, and control. Specifically, one study evaluated diabetes risk and β-cell function for a mixture of 15 urinary metals and found an increased incidence of diabetes, higher HOMA-IR, and reduced HOMA-B (Wang et al., 2020; Wang, Karvonen-Gutierrez, et al., 2020). Another human population study found metal mixtures to be associated with elevated oxidative stress biomarkers (Domingo-Relloso et al., 2019). Advancements in statistical techniques to evaluate these complex exposures continues to evolve, and these advancements will help better illuminate the impact of complex exposures on metabolic health. Given the plethora of chemicals to which humans are exposed, as well as the possibility that these mixtures might simultaneously impact both insulin secretion and action, the threat of mixtures of diabetogenic chemicals to metabolic health is real and needs to be better understood.

In addition to EDC mixtures, understanding how EDCs interact with traditional diabetes risk factors is essential. Some studies have begun to examine how EDCs modulate the effects of metabolically deleterious diets (Carmean et al., 2020; Ishikawa, Graham, Stanhope, Havel, & La Merrill, 2015; Regnier et al., 2018); however, more work is required in this area, especially studies examining the dual impact of EDCs and the high sucrose and fructose intake that characterizes the secular dietary trends of the last several decades that have coincided with exploding rates of diabetes. Similarly, much more work is needed to understand the impact of physical inactivity on the metabolic toxicity of EDCs; moreover, there is a significant need for additional studies examining effects of EDCs on muscle physiology that may amplify the effect of or contribute to physical inactivity.

Fascinating studies have begun to elucidate the impact of underlying genetics on the impact of EDCs. For example, polymorphisms in the arsenic methyltransferase gene modulate the biological effects of arsenic (Douillet et al., 2017; Valenzuela et al., 2009). Such knowledge has the potential to help us identify those with increased EDC susceptibility. In addition, improved understanding of genetic risk has important implications for the translation of animal models into human risk. For example, mouse versus human PPARs may behave differently regarding responses to EDCs (Casals-Casas, Feige, & Desvergne, 2008). In epidemiological studies, some work has begun to investigate the differential impact of EDCs on diabetes risk and diabetes-related traits in relation to underlying polygenic risk scores that are associated with disease development (McCarthy, 2010; Qi et al., 2017). Ultimately, this knowledge of gene-by-environment interactions may become an essential component of personalized medicine in which clinical care can be tailored to provide individualized advice regarding environmental health threats.

In addition to diet, activity, and genetics, other individual level conditions may influence the risk of diabetes related to EDC exposures. These include factors such as underlying medical conditions and therapies that may influence the metabolism and toxicity of EDCs. This also includes diseases that modulate detoxification and clearance pathways such as liver and kidney dysfunction. Similarly, underlying lung disease may predispose to the toxicity of air pollution, which evidence has shown is associated with diabetes risk. Moreover, medications may themselves disrupt endocrine function or may serve as an addition source of EDC exposure, as discussed. Furthermore, various medications influence hepatic and renal function; thus, they may augment or inhibit the adverse effects of EDCs on metabolic health. Indeed, incorporating environmental health into clinical care has the capacity to empower personalized medicine (Sargis, 2015). The identification of individuals with a heightened risk of pollutant exposure requires clinicians and researchers to consider these various factors, and in doing so empowers us to provide better care for our patients.

11. Conclusion

The consequences of diabetes are enormous for both individuals and society at large. While genetics and lifestyle factors clearly promote risk, burgeoning evidence over the last three decades has emerged to suggest that exposure to EDCs represent a novel yet underappreciated diabetes risk factor. Indeed, evidence from cells to human populations shows that various EDCs have the capacity to disrupt the production and release of

insulin and/or interfere with insulin's action in insulin-responsive tissues, promoting the development of hyperglycemia and diabetes risk. Furthermore, studies suggest that differential exposure to EDCs may underlie diabetes disparities. While further work is needed to clarify the risk posed by EDCs to metabolic health, the current state of the evidence suggests that individualized clinical care as well as public policy must include environmental health as critical tools for understanding and addressing the global diabetes pandemic.

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Abbreviations

ATP	adenosine triphosphate
BPA	bisphenol A
DDE	dichlorodiphenyldichlorethylene
DDT	dichlorodiphenyltrichloroethane
GDM	gestational diabetes mellitus
GIIS	glucose-induced insulin secretion
GLP-1	glucagon-like peptide-1
GPCR	G-protein coupled receptor
HbA1c	hemoglobin A1c
HOMA-β	homeostatic model assessment for β-cell function
HOMA-IR	homeostatic model assessment for insulin resistance
LPL	lipoprotein lipase
OC	organochlorine
PAH	polycyclic aromatic hydrocarbon
PBDE	polybrominated diphenyl ethers
PCB	polychlorinated biphenyl
PFAS	perfluoroalkyl substances
PPARγ	peroxisome proliferator-activated receptor-γ
POP	persistent organic pollutants

ROS	reactive oxygen species
RXR	retinoid X receptor
TBT	tributyltin
TCDD	2,3,7,8-tetrachlorodibenzo-*p*-dioxin
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus

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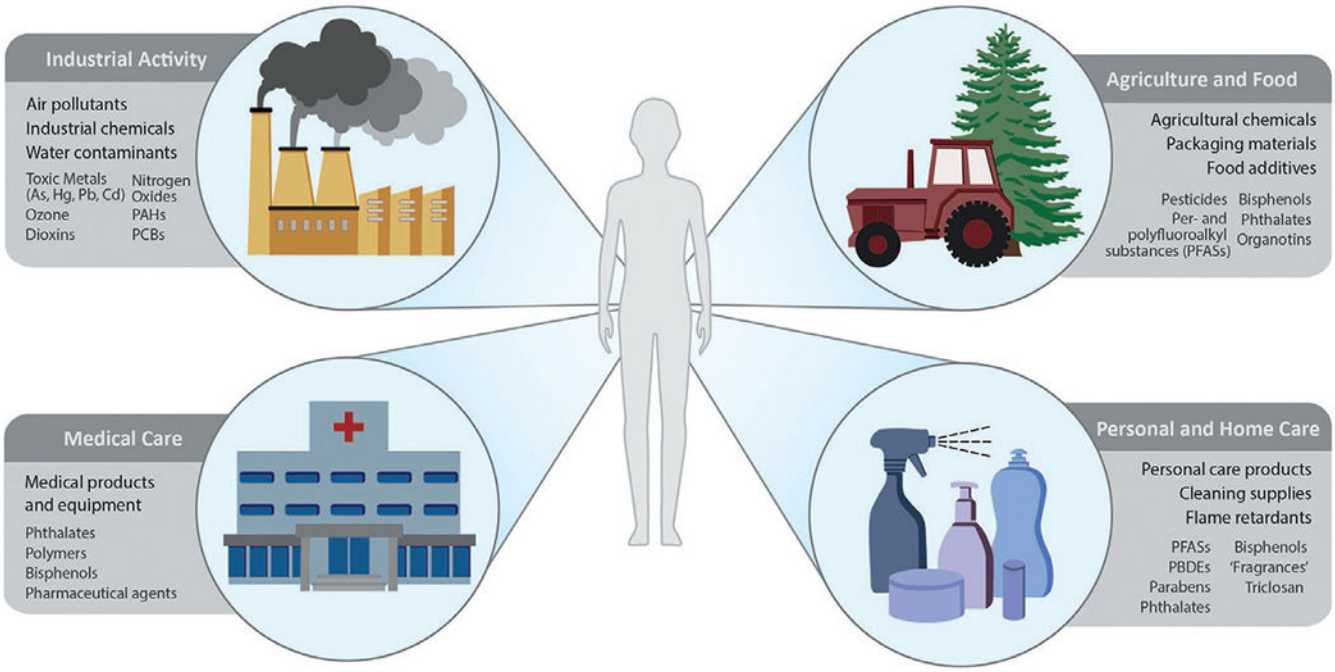

Fig. 1.

Sources of environmental endocrine-disrupting chemicals. PAH: polycyclic aromatic hydrocarbon, PCB: polychlorinated biphenyl, PBDE: polybrominated diphenyl ethers.

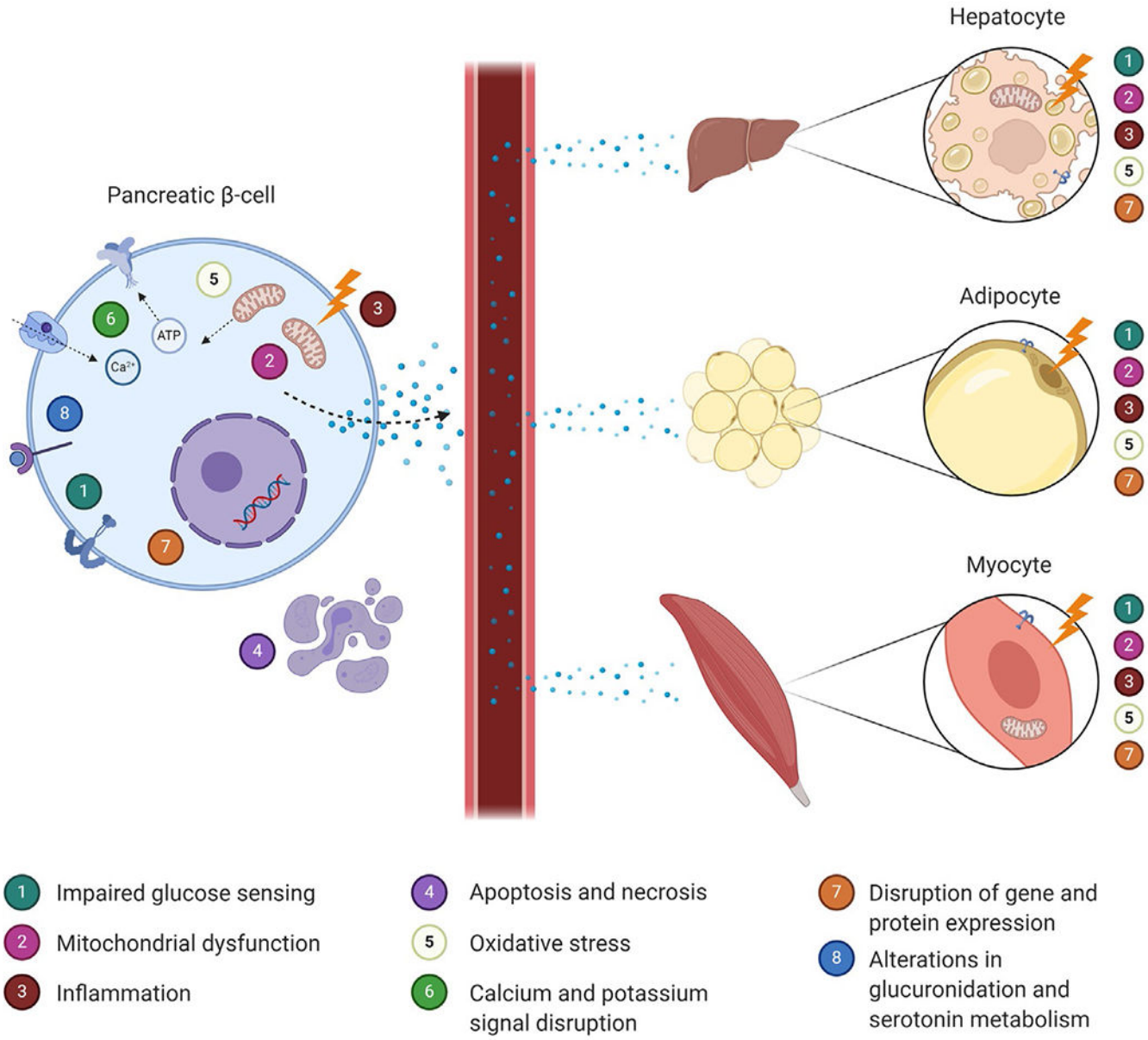

Fig. 2.

Mechanisms by which environmental endocrine-disrupting chemicals have been linked to dysfunction in metabolic tissues. Environmental EDCs may disrupt insulin signaling by damaging both insulin-releasing pancreatic beta cells (left) and insulin-responsive target tissues such as liver, adipose, and skeletal muscle (right). Created with BioRender.com.

Table 1

Example endocrine disruptors and implications in diabetes pathogenesis.

EDC	Insulin secretion	Insulin action	References
Arsenic	• Impaired glucose sensing • Beta cell mitochondrial dysfunction and oxidative stress	• Increased HOMA-IR and reduced skeletal muscle mass • Adipocyte, hepatic, and skeletal inflammation • Impairment of insulin signaling	Zhang et al. (2020) Mondal et al. (2020) Jia et al. (2020); S. Wei et al. (2020) Dover, Patel, and Styblo (2018)
Air pollution		• Increased HOMA-IR • Inflammation and increased expression of inflammatory markers in adipose	Li et al. (2021) Lin et al. (2020) Kim and Lee (2014)
Bisphenol A	• Reduced GIIS and downregulation of insulin related genes • Mitochondrial dysfunction and apoptosis of beta cells	• Increased HOMA-IR • Hepatic DNA methylation and reduction of hepatic glucokinase and overall glucose sensing	Wang et al. (2012) Cimmino et al. (2020) Wei, Ding, Wang, Liu, and Lin (2017) Ma et al. (2013)
DDT/DDE	• Altered beta cell protein expression and toxicity • Impaired GIIS • Reduced insulin mRNA, proinsulin, an insulin content	• Oxidative stress with reduced insulin signaling in skeletal muscle • Adipocyte inflammation	Pavlikova, Sramek, Jelinek, Halada, and Kovar (2020) Singh, Sarkar, Saxena, and Koner (2019) Park, Kim, and Rhyu (2020) Pavlikova, Smetana, Halada, and Kovar (2015) Mangum et al. (2016)
Polychlorinated biphenyls	• Increased insulin release and reduced cellular insulin • Pancreatic atrophy, steatosis, and fibrosis	• Increased adipocyte droplet size and reduced insulin response • Adipocyte inflammation	Fischer, Zhou, and Wagner (1996) Shi et al. (2019) Kim et al. (2017) Baker et al. (2015)
Per/polyfluoroalkyl compounds		• Increased HOMA-IR • Activation of PPAR-α and hepatic steatosis	Cardenas et al. (2017) Shipley et al. (2004) Lv et al. (2013)
Organophosphates	• Pancreatitis and pancreatic necrosis • Oxidative stress • Mitochondrial dysfunction	• Reduced expression of glucose transporters and insulin induced proteins	Farkhondeh et al. (2020) Leonel Javeres et al. (2020) Karami-Mohajeri and Abdollahi (2013), Nurulain, Szegi, Tekes, and Naqvi (2013) Hou et al. (2019) Wang et al. (2018)
Polycyclic aromatic hydrocarbons (PAHs)	• β-cell oxidative stress and toxicity	• Suppression of insulin signaling pathway • Inhibition of beta-adrenergic receptors • Oxidative stress	Fang et al. (2020) Irigaray et al. (2006), Smiljevska-Ristovska et al. (2020) Hu, Kan, Kearney, and Xu (2015)
Neonicotinoid insecticides	• DNA damage • Glutathione reduction	• Increased weight gain, adiposity, and insulin resistance thorough inhibition of downstream signaling molecules and phosphorylation	Kara, Ozta, and Ozhan (2020) Sun et al. (2017)

EDC	Insulin secretion	Insulin action	References
Phthalates	• Reduced β-cell mass and insulin content • Altered expression of genes involved insulin production and pancreatic development • Induce apoptosis	• Epigenetic modifications in skeletal muscle with increased oxidative stress	Lin et al. (2011) Li et al. (2021) Wei et al. (2020)
Heavy metals (cadmium, mercury, etc.)	• Cytotoxicity due to decreased ATP • Inhibit GIIS • Mitochondrial swelling and permeation of membranes • Oxidative stress	• Increased HOMA-IR • Mitochondrial dysfunction	Elmorsy, Al-Ghafari, Al Doghaither, and Ghulam (2021) Buha et al. (2020) Wang et al. (2020) Dover et al. (2018) Kim and Lee (2014)
2,3,7,8-Tetrachlorodibenzodioxin	• Disruption in calcium signaling	• Inflammatory cytokine activation	Ruiz, Perlina, Mumtaz, and Fowler (2016) Rasinger, Carroll, Lundebye, and Hogstrand (2014)
Vacor	• Inhibition of mitochondrial oxidative phosphorylation • Islet necrosis and inflammation		Miller, Stokes, and Silpipat (1978), Taniguchi et al. (1989)
Triphenyltin	• Induces β-cell apoptosis • Reduced ATP production • Reduced calcium signaling	• Reduced insulin signaling in adipose, skeletal, and hepatic tissue	Li et al. (2017), Miura et al. (2012), Zuo et al. (2014)
Alloxan	• Inhibits glucose sensing, glucokinase, and GIIS • Oxidative stress • β-cell necrosis	• Inhibition of insulin signaling	Lenzen (2008) Ader, Richey, and Bergman (1998)