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Environmental Endocrine Disruption of Energy Metabolism and Cardiovascular Risk

Andrew G. Kirkley · Robert M. Sargis

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Abstract Rates of metabolic diseases have increased at an astounding rate in recent decades. Even though poor diet and physical inactivity are central drivers, these lifestyle changes alone fail to fully account for the magnitude and rapidity of the epidemic. Thus, attention has turned to identifying novel risk factors, including the contribution of environmental endocrine disrupting chemicals. Epidemiologic and preclinical data support a role for various contaminants in the pathogenesis of diabetes. In addition to the vascular risk associated with dysglycemia, emerging evidence implicates multiple pollutants in the pathogenesis of atherosclerosis and cardiovascular disease. Reviewed herein are studies linking endocrine disruptors to these key diseases that drive significant individual and societal morbidity and mortality. Identifying chemicals associated with metabolic and cardiovascular disease as well as their mechanisms of action is critical for developing novel treatment strategies and public policy to mitigate the impact of these diseases on human health.

Keywords Atherosclerosis · Cardiovascular disease · Endocrine disruptors · Diabetes · Pollution · Environment · Energy metabolism · Cardiovascular risk

Topical Collection on *Macrovascular Complications in Diabetes*

A. G. Kirkley
Committee on Molecular Pathogenesis and Molecular Medicine, University of Chicago, Chicago, IL, USA

R. M. Sargis (✉)
Committee on Molecular Metabolism and Nutrition, Kovler Diabetes Center, Section of Endocrinology, Diabetes and Metabolism, University of Chicago, 900 E. 57th Street, MC 1027, Chicago, IL 60637, USA
e-mail: rsargis@medicine.bsd.uchicago.edu

Introduction

Type 2 diabetes (T2DM) exerts a tremendous individual and societal toll. Patients with diabetes have a risk of death approximately double that of their healthy peers, and T2DM remains the leading cause of kidney failure, blindness, and nontraumatic amputations [1]. Consequently, recent estimates suggest that total costs associated with diagnosed diabetes amount to a staggering $245 billion annually in the United States alone [2]. This massive economic and societal burden has increased at an alarming rate, with both disease incidence and associated costs exceeding that of even the most recent projections. As many as one-third of U.S. adults are expected to have T2DM by the year 2050 [3], and even optimal intervention strategies are projected to achieve only moderate success at reversing these trends at their current rates of growth [4]. Finally, these estimates do not account for the global burden of the disease, which is expected to rise from 382 million to 592 million individuals worldwide by the year 2035 [5].

In addition to the clear association with microvascular complications such as retinopathy, neuropathy, and nephropathy; T2DM, type 1 diabetes, and other prediabetic conditions (eg, impaired fasting glucose and glucose intolerance) are major risk factors for the development of macrovascular complications, including atherosclerosis, stroke, coronary artery disease, and peripheral vascular disease [6–8]. In fact, diabetes is considered an independent risk factor for cardiovascular disease (CVD) and mortality [9, 10]. T2DM is associated with several common CVD risk factors, including obesity, diabetic dyslipidemia, hyperglycemia, and insulin resistance. Importantly, the clustering of these metabolic risk factors in T2DM works in an additive fashion to promote vascular disease.

Although the genetic contributions to T2DM and cardiovascular disease are substantial, environmental factors are often cited as the major drivers of risk for these chronic

disease states. Increased energy intake, particularly consumption of calorically-dense foods common to the Western diet, combined with an increasingly sedentary lifestyle clearly contribute to the current metabolic disease epidemic [11]. However, these factors alone fail to fully account for the magnitude of the metabolic disease epidemic. As such, attention has turned to the increasing body of evidence linking the risk for diabetes and CVD to additional exogenous factors, including environmental contaminants [12]. Voluntary and involuntary exposures to myriad synthetic chemicals are a common feature of modern society, and these exposures form the basis for many recent studies examining the links between environmental chemicals and the etiology of multiple chronic diseases [13•, 14, 15].

Endocrine disrupting chemicals (EDCs) are a broad class of structurally diverse compounds that have the capacity to modulate endogenous hormonal signaling pathways. These chemicals include industrial pollutants, waste products, pharmaceuticals, phytochemicals, pesticides, consumer products, and plastics; and they vary widely in both structure and mode of action. A wide variety of EDCs have been previously associated with an increased risk of T2DM and other metabolic disorders in both epidemiologic studies and experimental animal models [16–18]. Furthermore, these findings are supported by an increasing body of cell-based and biochemical studies demonstrating the capacity of these compounds to modulate insulin production in pancreatic β cells as well as insulin action in target tissues, which would be predicted to drive systemic metabolic dysfunction [19–21].

The growing body of evidence suggesting that EDCs have the capacity to augment the development of metabolic diseases such as obesity and diabetes is compelling; however, less well studied is the role of these toxins in the pathogenesis of atherosclerosis and CVD. Only more recently have studies begun to examine links between environmental pollutants and macrovascular disease [22•]. This data implicates several compounds that may accelerate the development of atherosclerosis through their effects on established risk factors common to both diabetes and CVD (eg, obesity, dyslipidemia). Given the terrible burden of T2DM and macrovascular disease in modern society, understanding the links between environmental pollutants and these disease states is critical for formulating effective prevention strategies and identifying novel therapeutic interventions.

Epidemiologic Studies Linking EDCs with Diabetes and Cardiovascular Disease

Epidemiologic studies have provided intriguing links between environmental contaminants and the development of diabetes and other metabolic diseases [13•, 16, 18, 22•]. To date, the majority of studies connecting environmental exposures to diabetes and metabolic dysfunction have focused on a narrow group of compounds for which exposure data is most complete. A recent meta-analysis by the National Toxicology Program (NTP) determined that there is sufficient evidence to support a positive association between T2DM and persistent organic pollutants (POPs) [23••]. These diabetogenic POPs include the pesticide dichlorodiphenyltrichloroethane (DDT) and its metabolite dichlorodiphenyldichloroethylene (DDE), as well as pollutants from the dioxin and polychlorinated biphenyl (PCB) families [23••]. A similar NTP analysis concluded that there was a potential connection between arsenic, a common groundwater contaminant, and diabetes [24•]. Although was somewhat inconclusive, especially at lower levels of exposure, the data showed a relatively robust association at high levels of exposure. Urinary levels of bisphenol A (BPA), a monomer used in polycarbonate plastics that results in widespread exposure [25], has also been shown to be significantly associated with diabetes in the 2003-4 NHANES data set [26].

In addition to links between EDCs and diabetes per se, other studies have identified associations between various toxins and risk factors for diabetes such as obesity, the metabolic syndrome, and insulin resistance. Several POPs, including organochlorine pesticides and their metabolites (eg, DDE) as well as various PCB congeners, positively associate with obesity, abdominal adiposity, and components of the metabolic syndrome [15, 27–29]. Phthalates are used in the plastics industry as well as in various consumer goods and medical devices [30], and phthalate metabolites have been associated with insulin resistance and abdominal obesity [31, 32]. Insulin resistance has also been shown to correlate with urinary concentrations of BPA [33] and serum dioxin levels [34]. Finally, air pollution has been implicated in metabolic derangements with exposure to particulate matter (PM) of either the 2.5 μm ($PM_{2.5}$) [35, 36] or 10 μm (PM_{10}) [37] size correlating with either reduced insulin sensitivity or the incidence of diabetes. Collectively, these studies suggest that a diverse array of environmental contaminants may play a central role in the pathophysiology of diabetes and its antecedent states in some individuals.

Similar to studies in diabetes, research evaluating the associations between cardiovascular risk factors and exposure to environmental toxins has provided intriguing preliminary evidence to suggest a potential contribution of EDCs to the pathogenesis of CVD. Atherosclerosis is a progressive metabolic and inflammatory disease of the vasculature that plays a central role in CVD, the leading cause of death in the United States [38]. In epidemiologic studies, circulating levels of phthalates [39], BPA [26], and multiple PCB congeners [40] have all been linked to atherosclerosis or CVD in different populations. In addition, inorganic arsenic (iAs), the primary arsenic species in groundwater contamination, has been

positively associated with carotid intimal medial thickness (cIMT), a clinical measure of atherosclerosis [41, 41], as well as increased levels of serum matrix metalloproteinase-9, a biomarker for CVD [42, 43]. Interestingly, a recent analysis suggested that the relationship between arsenic exposure and cIMT may be potentiated by incomplete arsenic methylation [44], emphasizing the need to consider specific arsenic species in the analysis of EDC associations with CVD. Importantly, a number of risk factors associated with obesity, including diabetes and insulin resistance as well as dyslipidemia and hypertension, are associated with the development of atherosclerosis [45]. As such, EDCs that promote these conditions would be predicted to enhance the development of CVD. In addition to those environmental toxins that promote metabolic dysregulation discussed above, other studies have shown positive associations between serum levels of 7 different PCB congeners and hypertension, suggesting that elevated PCB levels may play a role in raising blood pressure [46]. Furthermore, serum organochlorine pesticide levels have been associated with increased triglyceride levels, an independent risk factor for CVD [15, 47]. In a study of endemic arsenic exposure in Bangladesh, arsenic levels were associated with lower levels of high-density lipoprotein cholesterol (HDL-C) and increases in atherogenic oxidized low-density lipoprotein (LDL) despite lower total levels of LDL-C and total cholesterol [48].

In addition to metabolic parameters, tobacco smoke has long been appreciated as a prominent risk factor for atherosclerosis and CVD [49] and is also a prominent source of local hazardous air pollution [50]. Tobacco smoke is comprised of a multitude of chemicals, many of which are toxic or carcinogenic and may also play a pathophysiological role in the development of atherosclerosis [51]. One component of interest in tobacco smoke is particulate matter [52]. In the context of ambient air pollution, exposure to particulate matter has been linked to long-term cardiovascular effects, including hypertension [36], markers of oxidative stress [53], and CVD-related mortality [54]. Cadmium, another pollutant metal found in tobacco, has also been associated with an increased prevalence of atherosclerotic plaque formation [55, 56]. Taken as a whole, these population-based data support the hypothesis that various environmental contaminants have the potential capacity to promote the development of diabetes and other risk factors associated with atherosclerosis, ultimately leading to the development of clinical CVD.

Diabetes and Cardiovascular Disease in Animal Models of EDC Action

This epidemiologic data provides important evidence of potential deleterious effects of EDCs; however, many of these studies are cross-sectional, making it difficult to draw conclusions regarding causality. The suggestions drawn from these studies are, however, supported by animal models of exposure that have examined the pathogenesis of diabetes and vascular disease. A number of compounds have been shown to promote glucose intolerance and frank hyperglycemia in animal models. These include organic toxins, such as the plasticizer diethylhexylphthalate (DEHP) [57], PCBs [58], and triphenyltin [59] as well as the inorganic contaminant arsenic [60]. In addition to overt disruption of glucose handling, several EDCs have been shown to promote hyperinsulinism and insulin resistance. Chronic exposure of mice to the PCB mixture Aroclor 1254 promoted insulin resistance and hyperinsulinemia [61]. In addition, BPA [62•, 63], the polybrominated diphenyl ether flame retardants [64], POPs [65], atrazine [66], particulate air pollution [67], and arsenic [68] have all been shown to cause impairments in insulin action and glucose homeostasis. Interestingly, in 1 study, insulin resistance induced by exposure to $PM_{2.5}$ air pollution was only observed in the presence of a high fat diet, suggesting potential synergy between EDCs and dietary risk factors for metabolic disease [67].

Of particular interest in the field of endocrine disruption is the possibility that susceptibility to adverse effects varies across the lifespan. The Developmental Origins of Health and Disease hypothesis postulates that organisms have periods of unique sensitivity to environmental insults during development and that exposure during these sensitive windows predisposes to the development of disease later in life [69]. Furthermore, exposure during these periods may also result in heritable changes through epigenetic modifications that can promote development of disease in generations remote from the initial chemical exposure [70, 71]. In a recent study, the effects of perinatal BPA exposure were found to be dose-, sex- and time-dependent, further suggesting that the perinatal period is a critical window of EDC susceptibility [63]. Multiple studies have shown that exposure to BPA during pregnancy can alter metabolic homeostasis in both the mother and in her adult offspring [62•, 72, 73]. Similarly, gestational and lactational exposure to perfluorooctane sulfonate (PFOS), a worldwide industrial pollutant once commonly used in stain and water repellents [74], was shown to impair glucose and lipid homeostasis in adult rats [75, 76]. Thus, consideration of not only the chemical but the timing of exposure across the lifespan is critical for assessing the effects of EDCs on energy metabolism.

In addition to studies demonstrating connections between EDCs and pro-atherogenic disruptions in glucose metabolism and insulin action, several studies have specifically interrogated the role of environmental toxicants in the development of atherosclerosis and other atherosclerosis-associated risk factors (Table 1). Apolipoprotein-E-deficient (ApoE-/-) mice are commonly used as a model of macrovascular disease because these mice are susceptible to the development of diet-induced atherosclerotic plaques [77]. Subchronic treatment of ApoE-/-

Table 1 In vivo models of EDC-mediated disruption of vascular and metabolic function

Pollutant	Animal model	Dose	Physiological alterations	Ref.
Arsenic	FvB mice	100 ppb, drinking water (6 mo)	- Increased CRP in liver and kidneys	[134]
	Wistar Kyoto rats	133 μg/mL, drinking water (20 wk)	- Decrease ratio of HDL-C/LDL-C	[85]
Atrazine	Sprague-Dawley rats	30 or 300 μg/kg/d (5 mo)	- Increased obesity - Insulin resistance	[66]
Benzo[a]pyrene	ApoE-/- mice	5 mg/kg, once/wk, orally (24 wk)	- Increased atherosclerotic plaque area	[80]
BPA	Wistar rats (gestational/lactational exposure)	50 μg/kg/d, offspring fed on HFD	- Increased obesity - Elevated triglycerides - Elevated LDL-C	[73]
	Wistar rats (gestational/lactational exposure)	50 μg/kg/d, oral gavage	- Abnormal DNA methylation in hepatic tissues - Insulin resistance	[162]
	OF-1 mice (gestational exposure)	10 or 100 μg/kg/d	- Insulin resistance in adulthood	[62•]
	CD-1 mice (gestational exposure)	$5–5\times10^4$ μg/kg/d	- Increased body weight and adiposity - Increased serum insulin levels (adult males)	[72]
	ICR mice (gestational/lactational exposure)	1 or 10 μg/mL, in drinking water	- Increased adiposity - Increased total serum cholesterol	[86]
Cadmium	ApoE-/- mice	100 mg/L, in drinking water	- Increased atherosclerotic plaque area	[56]
	Male Sprague-Dawley rats	2 mg/kg/d (4 d)	- Impaired glucose tolerance	[163]
	Male Wistar rats	5 or 50 mg/L, in drinking water (6 mo)	- Increased free fatty acids and LDL-C - Decreased HDL-C	[83]
	Male Albino rats	1 mg/kg/d, ip, (4 wk)	- Increased plasma triglycerides and LDL - Decreased HDL	[84]
	Male Slc:ICR mice	0, 5, 10, 20 μM/kg, subcutaneously (2 wk)	- Reduced adipocyte size - Reduced adiponectin expression in adipose tissue	[117]
Combustion emissions	Male ApoE-/- mice	6 h/d inhalation exposure (50 d)	- Increased expression of CVD-related genes	[164]
Diazinon	Sprague-Dawley rats	0.5 or 2 mg/kg/d, subcutaneously (4 d)	- Upregulation of adenylate cyclase activity	[142]
Dioxins / TCDD	C57BL/6 and ApoE-/- mice	5 μg/kg, ip, (3 d)	- Increased blood pressure - Elevated triglycerides	[165]
	C57BL/6 mice	10 μg/kg, ip	- Impaired glucose-stimulated insulin secretion	[93]
	C57BL/6 mice	300 ng/kg, oral gavage, 3× wk (60 d)	- Increased superoxide production - Cardiac hypertrophy	[166]
	ApoE-/- mice	15 μg/kg, ip, (once)	- Increased atherosclerosis - Inflammatory gene induction	[79]
Malathion	Male Wistar rats	100–400 ppm, orally (4 wk)	- Increased blood glucose and insulin levels	[167]
Nicotine	Wistar rats (transgenerational exposure)	1 mg/kg/d, subcutaneous injection	- Increased total cholesterol - Increased blood pressure	[90]
	Sprague-Dawley rats (gestational exposure)	4 μg/kg/min. via osmotic mini-pump	- Increased vascular oxidative stress - Increased blood pressure	[139]
PCBs	ApoE-/- mice	49 mg/kg, ip	- Increased atherosclerosis	[132]
	C57BL/6 mice	50 mg/kg, oral gavage	- Impaired glucose homeostasis	[58]
	C57BL/6 mice	36 mg/kg/wk (20 wk)	- Hyperinsulinemia	[61]
	AhR+/+ (mixed) mice	170 μmol/kg, ip	- Increased VCAM-1 expression	[130]
	ApoE-/- mice	49 mg/kg, ip	- Adipocyte hypertrophy - Elevated serum cholesterol, VLDL levels - Increased atherosclerosis	[128]
	Sprague-Dawley rats	224 μg/kg, ip, (total dosage)	- Elevated total serum cholesterol	[168]
PFOS	Wistar rats (gestational/lactational exposure)	0.5 or 1.5 mg/kg/d	- Increased fasting serum insulin - Impaired glucose tolerance - Hepatic steatosis	[75]
$PM_{2.5}$	C57BL/6 mice	10 wk, whole-body exposure (inhalation)	- Activation of inflammatory response - Glucose intolerance	[109]

Table 1 (continued)

Pollutant	Animal model	Dose	Physiological alterations	Ref.
			- Insulin resistance	
	Various mouse strains	6 h/d, 5 d/wk (20 wk)	- Systemic inflammatory response (via TLR4) - Increased superoxide production in monocytes	[169]
	Male ApoE-/- mice	6 h/d, 5 d/wk (2 mo)	- Increased ROS and oxidative stress in brown adipose tissue	[119]
	Male Sprague-Dawley rats	Once per wk, intratracheal installation (3 wk)	- Enhanced insulin resistance in HFD-fed rats	[67]
	C57BL/6 mice	6 h/d, 5 d/wk (128 d)	- Systemic inflammation - Insulin resistance - Increased adipose tissue-associated macrophages	[111]
Tributyltin	C57BL/6 mice (gestational exposure)	0.05 or 0.5 mg/kg/d	- Increased adiposity	[170]
	Male KM mice	0.5, 5, 50 μg/kg, once/3 d (45 d total)	- Increased body weight - Hepatic steatosis - Reduced hepatic adiponectin	[171]
Triflumizole	CD-1 mice (gestational exposure)	0.1, 1, 10 μM, in drinking water	- Increased adiposity	[172]

mice with 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) demonstrated a trend toward earlier onset and greater severity of atherosclerotic lesions in one model of exposure [78], whereas a second study revealed that TCDD aggravated atherosclerosis progression, an effect enhanced by high fat diet feeding [79]. Polycyclic aromatic hydrocarbons (PAHs) (eg, benzo[a]pyrene [BaP]) have also been shown to increase the size of atherosclerotic plaques in ApoE-/- mice [80], and in a more recent study, exposure to ambient particulate matter air pollution from Beijing increased aortic arch atherosclerotic plaque growth in ApoE-/- mice [81].

Disruptions in lipid metabolism can lead to the development of an atherogenic dyslipidemia, including an increase in small, dense LDL, elevated triglycerides, and reduced anti-atherogenic HDL. High concentrations of circulating atherogenic lipoproteins enhance lipid accumulation in the subendothelial space where oxidized-LDL (oxLDL) is taken up by macrophages, generating "foam cells" and triggering an inflammatory cascade resulting in formation and progression of atherosclerotic plaques [82]. Environmental pollutants that promote the dysregulation of lipid metabolism, therefore, are predicted to enhance the risk of macrovascular disease. In male rats, cadmium exposure was found to increase plasma free fatty acids and LDL-C in addition to also decreasing HDL-C [83]. Similar effects of cadmium on LDL-C and HDL-C were observed in a second model of rat exposure that also demonstrated an increase in serum triglycerides [84]. Coupled with a high cholesterol diet, arsenic was shown to promote a pro-atherogenic reduction in the HDL-to-LDL cholesterol ratio without altering total cholesterol or triglyceride levels [85]. In ApoE-/- mice, TCDD exposure was shown to increase LDL-C levels [78]. The increased atherogenesis observed in ApoE-/- mice exposed to ambient particular matter was associated with an increase in serum total cholesterol and LDL-C [81]. Similar to models of diabetes, developmental exposure to BPA has been shown to increase total serum cholesterol levels [86], whereas in utero TCDD attenuated HDL-C increases in high-fat diet-fed ApoE-/- mice [87].

Hypertension is a key risk factor in the development of CVD. Highly prevalent in human populations mainly as a result of voluntary exposure, nicotine is a hazardous compound that may result in high levels of in utero exposure in smoking mothers [88, 89]. Offspring of exposed mothers had elevated blood pressure, demonstrating cardiovascular abnormalities resulting from nicotine exposure [90]. A separate study found that nicotine exposure promoted atherosclerotic lesion growth in a mouse model of the disease [91]. This diverse set of data suggests that various environmental contaminants in a variety of experimental contexts have the capacity to promote dysregulation of energy metabolism while facilitating the development of atherosclerosis and its associated risk factors.

Mechanisms of EDC-Induced Metabolic Dysregulation and Cardiovascular Risk Factors

Studies at the population and animal levels have provided intriguing insights into the potential role of environmental toxicants in the pathogenesis of diabetes and macrovascular disease; however, they fail to fully characterize the molecular mechanisms by which EDCs exert their deleterious effects. In order to identify pathophysiological pathways, predict novel EDCs, and develop novel therapeutic targets, several studies

have aimed to identify the molecular mechanisms responsible for prodiabetic and proatherogenic environmental toxicants. These studies show that environmental pollutants implicated in the pathogenesis of T2DM and CVD in vivo can modulate important cellular events involved in insulin production and glucose homeostasis, and also disrupt processes crucial for regulating vascular health (Fig. 1).

In healthy individuals, glucose levels are maintained within a very tight range through an augmentation of insulin secretion from pancreatic β cells in response to increases in insulin resistance [92]. Under conditions of significant and sustained insulin resistance, however, β cells begin to lose their ability to adequately compensate at times of peak demand, and the individual transitions to a state of impaired glucose tolerance. Ultimately, the persistent β-cell stress results in insufficient insulin secretion even during periods of fasting, and the patient enters a state of frank T2DM. Thus, EDCs that impair β-cell insulin secretion or interfere with peripheral insulin action can promote the development of T2DM. The effects of various environmental contaminants on β-cell physiology and insulin action have been examined [21]. Several compounds have been shown to disrupt β-cell function, promote β-cell death, or disrupt signal transduction pathways in β cells. These include organic compounds such as TCDD [93–95], PCBs [96], BPA [97, 98], and triphenyltin [99]. Inorganic compounds have also been shown to modulate β-cell function as well, including cadmium [100] and mercury [101]. Furthermore, arsenic in both its inorganic and methylated forms has been shown to disrupt β-cell function [102, 103]. Interestingly, BPA [97] and PCBs [104] have been shown to augment insulin secretion; however, this may still reflect a deleterious disruption in energy homeostasis, possibly through insulin-induced insulin resistance.

In addition to those chemicals affecting insulin secretion, a number of compounds have been shown to antagonize cellular insulin action in a variety of experimental systems. TCDD [105], BPA [106], and DEHP [107] have all been shown to reduce insulin receptor levels in some studies, whereas the phenylsulfamide fungicide tolylfluanid [108], particulate matter [109], TCDD [105], and DEHP [107] have been shown to reduce levels of insulin receptor substrate-1 (IRS-1), a key intermediate in the insulin signaling cascade. Downstream of IRS-1, the insulin-stimulated activating phosphorylation of Akt (protein kinase B) has been shown to be attenuated by a host of environmental toxicants, including arsenic [110], particular matter [111], PCB-77 [112], tolylfluanid [108], and BPA [62•], whereas arsenic has also been shown to antagonize insulin action distal to Akt phosphorylation [113]. Finally, antagonism of cellular insulin action at the level of the facilitative glucose transporter, type 4 has been shown for DEHP [107], TCDD [105], and cadmium [114]. Thus, a host of environmental pollutants have the capacity to alter energy homeostasis through a variety of cellular mechanisms that are predicted to promote the development of diabetes and its associated complications, including vascular injury.

In addition to direct effects on insulin production or insulin action, EDCs may augment the risk of T2DM indirectly by altering the expression of the various secreted factors that modulate global insulin sensitivity. For example, adipose tissue plays a critical role in energy metabolism through the secretion of a number of adipokines. Adiponectin is one such secretory product that promotes insulin sensitivity while also exerting anti-inflammatory effects and promoting β-cell function [115]. Environmentally relevant doses of BPA suppress adiponectin release from adipose tissue ex vivo [116]. In addition, cadmium [117], tributyltin [118], and particulate matter [119] have also been shown to reduce adiponectin expression and/or release. In addition to promoting dysglycemia, EDC-induced reductions in adiponectin may also accelerate atherosclerosis, as this adipokine appears to play an important protective role in the vasculature by suppressing foam cell formation and promoting macrophage cholesterol efflux [120]. In contrast, tumor necrosis factor-α (TNFα) and IL-6 induce insulin resistance and are increased by TCDD [105], PCB-77 [58, 112], and particulate matter [111]. EDC-induced changes in these pro-inflammatory mediators may also play a role in enhancing the development of atherosclerosis [121].

Atherosclerosis is a multifaceted disease resulting from multiple metabolic and inflammatory derangements. Atherogenic, apolipoprotein-B-containing lipoproteins infiltrate the subendothelial space where they can undergo oxidative modification. Oxidized lipoproteins cause alterations in endothelial function and protein expression that lead to the recruitment of monocytes to the subendothelial space. These infiltrating monocytes are activated, accumulate lipid, and transform into macrophage "foam cells." This results in a cascade of inflammatory responses that recruits other cell types, including smooth muscle cells and other immune cells. As the atherosclerotic plaque enlarges and becomes necrotic, a fibrous cap forms, rupture of which promotes platelet adherence and initiates the coagulation cascade resulting in acute occlusion of the vessel lumen. EDCs that modulate any of these events or that alter risk factors associated with these processes are predicted to promote the development of macrovascular disease.

Several EDCs have been examined for their effects on mechanisms specific to the development of CVD (Table 2). Vascular inflammation, a hallmark of atherosclerosis, has been studied extensively in cellular models of exposure, including exposure to PCBs [122] and particulate matter [123]. PCB-77 [124, 125] and the PAH benzo[a]pyrene [126] have been shown to up-regulate expression of monocyte chemoattractant protein-1 (MCP-1), an inducible cytokine responsible for attracting circulating monocytes to sites of inflammation (eg, early atherosclerotic lesion). TCDD and other PCB congeners

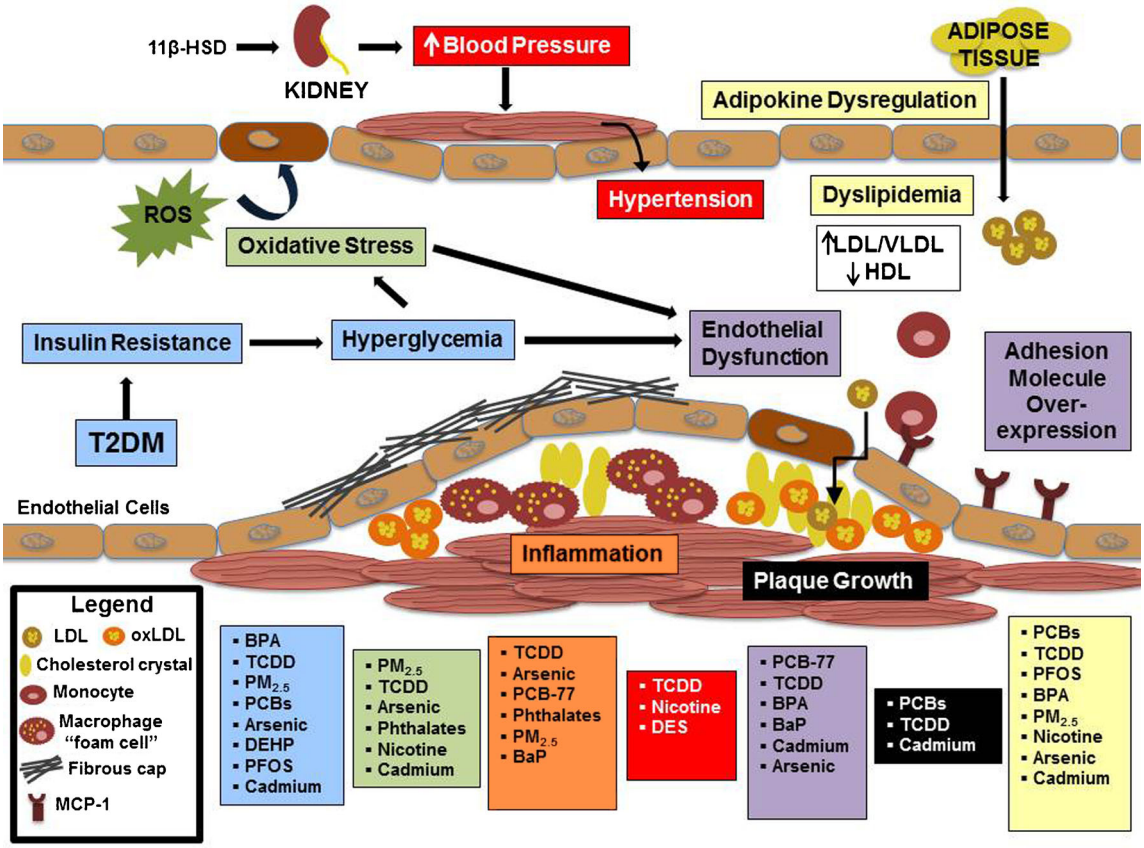

Fig. 1 Contributions of environmental pollutants to cardiovascular disease pathology. This figure presents compounds and mechanisms related to the development of vascular disease observed in either *in vivo* exposure studies or *in vitro* cellular models

have also been shown to upregulate MCP-1 expression in other tissues; however, whether these effects are also observed in vascular tissue is incompletely known [127, 128]. Similarly, endothelial dysfunction and inflammation have been shown in animal models of exposure to cadmium [129] and PCBs [125, 130]. Endothelial dysfunction, in turn, is known to promote the progression of inflammatory vascular diseases, including atherosclerosis [131]. Activation of the aryl hydrocarbon receptor (AhR) induces vascular inflammation and promotes atherosclerosis in apoE-/- mice, and the AhR is also a common target for a number of diverse EDCs including TCDD [93], dioxin-like PCBs [132], and the fungicide cyprodinil [133]. Systemic inflammation has also been shown to be increased in mice exposed to aerosolized particulate matter [109] and arsenite [134], and TCDD exposure was associated with the induction of global inflammatory gene responses [79].

Oxidative stress is an important pathway in the initiation and progression of the atherosclerotic lesion through the oxidative modification of lipoproteins and the induction of cellular dysfunction [135, 136]. Persistent hyperglycemia, as seen in uncontrolled diabetes, induces endothelial dysfunction, likely through increased oxidative stress [137]. Thus, EDCs that promote the development of diabetes may also aggravate the development of atherosclerosis. A recent epidemiologic study showed that urinary phthalate (eg, DEHP) levels correlated with levels of the oxidative stress marker malondialdehyde [32], further suggesting this mechanism as relevant for EDC-mediated atherosclerotic disease. Uptake of oxidized LDL by endothelial cells has been shown to be upregulated by arsenic [138]; whether arsenic has similar effects in promoting macrophage foam cell formation, however, requires further study. In utero exposure to nicotine has been shown to promote vascular dysfunction mediated by oxidative stress [89, 139]. Acute cadmium exposure in isolated rat aortic rings induced vascular injury by increasing endothelial cell oxidative stress [129], and co-planar PCBs have been shown to induce oxidative stress in vascular endothelial cells through the NF-κB pathway [130].

In addition to their effects on oxidative stress, selected PCB congeners were also found to decrease the angiogenic capacity of human umbilical vein endothelial cells (HUVEC) [140]. A follow-up study showed that the endothelial toxicity of co-planar PCBs could be inhibited by metabolites produced from the oxidation of omega-3 fatty acids, providing a possible mechanism to explain the anti-inflammatory properties of these lipid species [122]. A recent study also showed that BPA at environmentally relevant doses interferes with

Table 2 Mechanisms linking environmental pollutants to disruption of vascular biology

Pollutant	Mechanism of disruption	Model system	Ref.
2,4-D	Impaired glucose uptake and metabolism	Rat Sertoli cells	[173]
Arsenic / iAS	Activation of NFκB through increased C-reactive protein expression	HepG2 cells	[134]
	Augmented uptake of ox-LDL	Mouse aortic endothelial cells	[138]
	Impaired glucose-stimulated insulin secretion by β cells	INS-1(832/13) cells	[103]
	Impaired insulin-stimulated glucose uptake, induction of inflammatory response genes	3T3-L1 adipocytes	[110]
Atrazine	Potentiated cAMP activity	Rat pituitary and testicular Leydig cells	[143]
Benzo[a]pyrene	Increased MCP-1 expression	HUVEC	[126]
BPA	Disrupted endothelial cell proliferation with mitotic abnormalities	HUVEC	[141]
	Suppressed adiponectin release	Primary human adipose tissue	[116]
	Modulated metabolic and inflammatory gene expression	Human PBMCs	[174]
Cadmium	Impaired glucose tolerance	Primary rat adipose tissue	[163]
	Increased ROS production, increased oxidative stress	Isolated rat aortas	[129]
	Increased vascular endothelial permeability, inhibited cell proliferation	HUVE cells	[56]
Cyprodinil	Induced nuclear translocation and transcriptional activity of the AhR	HO-23 cells	[133]
DEHP	Increased H_2O_2 and OH^- radicals, decreased glucose uptake	Primary rat adipose tissue	[107]
Nonylphenol	Enhanced ischemia/reperfusion injury	Guinea pig heart	[175]
$PM_{2.5}$	Pro-inflammatory cytokine induction, C-reactive protein induction	U937 cells	[123]
PCB-77	Increased MCP-1 expression	Primary mouse endothelial cells	[125]
	Pro-inflammatory cytokine expression and release	3T3-L1 adipocytes	[128]
PCB-126	Altered metabolic gene expression	Human PBMCs	[174]
TCDD (dioxin)	Decreased nuclear ER levels through aryl hydrocarbon receptor (AhR)	MCF-7 cells	[176]
	Impaired insulin-stimulated glucose uptake, induction of inflammatory response genes	3T3-L1 adipocytes	[105]
	Impaired glucose-stimulated insulin secretion by β cells	Primary mouse pancreatic islets	[93]
	Impaired glucose-stimulated insulin secretion by β cells	INS-1E β-cell line	[94]
	Altered gene expression associated with cell growth and cell death	Mouse VSMCs	[177]

AhR aryl hydrocarbon receptor, *iAS* inorganic arsenic species, *2,4-D* 2,4-dichlorophenoxyacetic acid, *HUVEC* human umbilical vein endothelial cells, *PBMCs* peripheral blood mononuclear cells, *ROS* reactive oxygen species

endothelial cell proliferation and mitotic division [141]. Together, these studies suggest that some EDCs may drive atherosclerotic lesion progression by inducing endothelial cell dysfunction while also antagonizing reparative mechanisms critical for restoring blood flow.

Hypertension is a clear risk factor for micro- and macrovascular disease, and promotes atherosclerosis by enhancing sheer stresses and endothelial inflammation mediated by oxidative stress. Blood pressure is regulated by a host of local and systemic signaling molecules, some of which have been shown to be modulated by EDCs. Developmental exposure of rats to nicotine resulted in an enhanced blood pressure response to angiotensin II in adulthood [89]. Catecholamines play a critical role in regulating blood pressure through their action on adrenergic G-protein coupled receptors, some of which signal through adenylate cyclase. Organophosphorus pesticides, including diazinon and parathion, have been shown to upregulate adenylate cyclase activity in a model of neonatal rat exposure [142]. Additionally, exposure to the herbicide atrazine has been shown to potentiate cAMP signaling in cultured rat pituitary cells [143]. Thus, EDC-induced sensitization of the cAMP pathway to catecholamines may potentiate their effects on blood pressure. In the kidneys, aldosterone acting on mineralocorticoid receptors plays a critical role in regulating blood pressure. Because cortisol circulates at much higher concentrations than aldosterone and has affinity for mineralocorticoid receptors, cortisol-induced activation of these receptors is prevented physiologically through the local inactivation of glucocorticoids by 11β-hydroxysteroid dehydrogenase, type 2 (11β-HSD-2). Several studies have examined the capacity for EDCs to inhibit this enzyme. The dithiocarbamate pesticide Thiram [144], organotin compounds [145], and cadmium [146] all exhibit the capacity to inhibit this enzyme. Because antagonism of 11β-HSD-2 would be predicted to elevate blood pressure, determining whether these or other EDCs enhance the development of macrovascular disease through the promotion of hypertension is worthy of further investigation.

Finally, because insulin exerts vasodilatory effects on the vasculature, compounds discussed that induce insulin resistance may also raise blood pressure through antagonism of insulin action on vascular smooth muscle.

Disruption of nuclear hormone signaling may play an important role in mediating the negative vascular effects of EDCs. Sex steroids play a critical role in lipoprotein metabolism, and disruption of sex steroid signaling has been a central area of interest in the field of endocrine disruption. A variety of compounds have been shown to modulate estrogenic and/or androgenic signaling (reviewed in refs. [19, 147, 148]), and some of these compounds may promote the development of an atherogenic lipid profile. Similarly, thyroid hormone is known to play a critical role in lipoprotein metabolism [149]. Disruption of thyroid hormone action has also been described for a number of different EDCs, including hydroxylated PCBs [150, 151]. Whether these or other compounds have the capacity to augment cardiovascular risk through the modulation of lipoprotein metabolism requires further study. Finally, states of glucocorticoid excess (ie, Cushing's Syndrome) are characterized by hypertension, dyslipidemia, and hyperglycemia, in addition to other abnormalities. Agents that promote glucocorticoid receptor signaling may therefore contribute to elevated CVD risk through multiple mechanisms. Tolylfluanid was shown to stimulate glucocorticoid action in adipose tissue [152], whereas studies in rat EDR3 cells showed that low doses of arsenic stimulated GR-mediated gene transcription [153]. These studies suggest a potential role for EDC disruption of glucocorticoid receptor signaling as a potential mediator of metabolic and vascular disease. Finally, other nuclear hormone receptors that play a role in pathways regulating energy and lipid metabolism (eg, liver X receptor and steroid and xenobiotic receptor [SXR]) may also be important sites of endocrine disruption of vascular health [154].

In addition to further clarification of these mechanisms, a greater understanding is required of how EDCs modulate lipoprotein metabolism, including lipid synthesis, transport, enzymatic and nonenzymatic modification, and receptor-mediated uptake. Because many EDCs are highly lipophilic, they are transported in the circulation incorporated into lipoproteins. As such, they are enriched at sites of lipid metabolism and may have uniquely potent effects on cellular processes governing lipid handling. For example, it has been shown that the fatty acid and phospholipid composition of lipid membranes and lipoproteins as well as membrane fluidity modulate lipid oxidation, a key step in atherogenesis [155, 156]. Likewise, the physical properties of membranes govern cholesterol efflux [157], and intercalation of lipophilic EDCs into membranes may modulate this process. Enzymatic action on lipoproteins is also governed by lipid composition, which may influence delivery of critical fatty acids to tissues such as the brain [158]. Furthermore, it will be important to determine whether EDCs modulate activity of proteins mediating lipid uptake and efflux in order to fully appreciate their role in contributing to vascular disease. Whether lipid soluble environmental contaminants alter metabolic function by interfering with lipid handling remains largely unresolved. Studies correlating EDC exposure with alterations in circulating levels of the CVD biomarker serum matrix metalloproteinase-9 levels [42, 43], suggest that specific investigations examining EDC effects on the extracellular matrix of the atherosclerotic plaque as well as plaque stability are warranted. Finally, as effects are often concentration-dependent and nonmonotonic [72, 159, 160], better assessment of human exposure to EDCs is required to inform these mechanistic studies as well as to improve risk assessment.

Potential Clinical Implications and Conclusions

The current state of scientific evidence supports a potential role for EDCs in the pathogenesis of metabolic diseases and atherosclerotic disease. Whether any specific individual can tie their disease to a particular exposure, however, is much more complex given the immense heterogeneity of chemicals, concentrations, combinations, timing, and durations of exposure. However, as improvements are made in identifying risk to specific individuals, current data may suggest how an individual's EDC exposure can influence both their metabolic disease development and response to specific therapies. For example, SXR regulates expression of cytochrome P450 enzymes [161], and this nuclear receptor is disrupted by multiple EDCs, including DDT and nonylphenol [154]. This suggests that individuals with exposure to these EDCs may experience differential efficacy or enhanced side effects from drugs metabolized by these enzymes, including key CVD drugs such as statins. Evidence that atrazine and organophosphate pesticides can potentiate the action of adenylate cyclase [142, 143] may suggest enhanced efficacy for adrenergic blockers in the treatment of hypertension or the use of agents with anti-glucagon effects in the treatment of diabetes in patients exposed to these agents. Patients with known ongoing exposure to EDCs that inhibit 11β-HSD-2 may experience enhanced benefit with agents targeting the mineralocorticoid receptor (eg, spironolactone). Similarly, those with exposures contributing to the development of their diabetes may receive preferential benefit with either insulin replacement or an insulin-sensitizing agent depending on the mechanisms of action of the EDCs to which they are exposed. Given the fact that there are over 150,000 chemicals registered with the European Chemicals Agency [22•], most exposure is polychemical, many chemicals have multiple mechanisms of action, dose-effect relationships are sometimes characterized as nonmonotonic, and phenotypes are influenced by the timing of exposure; it may be impossible to achieve the level of granularity necessary to draw specific conclusions regarding the efficacy of any particular treatment. However, in instances of known, well-characterized exposures (eg, occupational,

recreational, or accidental), our expanding knowledge base may ultimately provide us with the tools necessary to improve the care of specific patient groups.

The last 2 decades have witnessed an important transformation in our knowledge of toxicity with the recognition that environmental pollutants have the capacity to modulate endocrine and metabolic signaling pathways, opening the door to a greater appreciation of the myriad factors contributing to the burgeoning global metabolic disease epidemic. Epidemiologic studies support a role for a variety of organic and inorganic pollutants in the development of insulin resistance, obesity, diabetes, and cardiovascular disease; and these studies are supported by preclinical studies associating individual exposures with specific mechanisms of disease development. Although many challenges remain, the current level of evidence supports the hypothesis that deleterious health consequences, at least in part, arise from our exposure to environmental toxicants. It is hoped that scientific advances at the population and basic science levels will permit us to better address this important issue through environmental remediation, targeted therapies, and sound public policy.

Acknowledgments Due to reference constraints, the authors were unable to include all the important work performed in the field of endocrine disruption of metabolism and cardiovascular disease. The current manuscript was meant to emphasize important aspects of environmental disruption of energy homeostasis and cardiovascular risk; any omissions were not meant to exclude important work contributing to the hypothesis that environmental contaminants play an important pathogenic role in the global epidemic of metabolic and cardiovascular disease. This work was supported by grants from the National Institutes of Health (K08-ES019176, R21-ES021354, and the Diabetes Research and Training Center [P60-DK020595]).

Compliance with Ethics Guidelines

Conflict of Interest Andrew G. Kirkley declares that he has no conflict of interest. Robert M. Sargis has received honoraria from the Korean Diabetes Association.

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