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Role of environmental toxicants in the development of hypertensive and cardiovascular diseases

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Abstract

The incidence of hypertension with diabetes mellitus (DM) as a co-morbid condition is on the rise worldwide. In 2000, an estimated 972 million adults had hypertension, which is predicted to grow to 1.56 billion by 2025. Hypertension often leads to diabetes mellitus that strongly puts the patients at an increased risk of cardiovascular, kidney, and/or atherosclerotic diseases. Hypertension has been identified as a major risk factor for the development of diabetes; patients with hypertension are at two-to-three-fold higher risk of developing diabetes than patients with normal blood pressure (BP). Causes for the increase in hypertension and diabetes are not well understood, environmental factors (e.g., exposure to environmental toxicants like heavy metals, organic solvents, pesticides, alcohol, and urban lifestyle) have been postulated as one of the reasons contributing to hypertension and cardiovascular diseases (CVD). The mechanism of action(s) of these toxicants in developing hypertension and CVDs is not well defined. Research studies have linked hypertension with the chronic consumption of alcohol and exposure to metals like lead, mercury, and arsenic have also been linked to hypertension and CVD. Workers chronically exposed to styrene have a higher incidence of CVD. Recent studies have demonstrated that exposure to particulate m (PM) in diesel exhaust and urban air contributes to increased CVD and mortality. In this re we have imparted the role of environmental toxicants such as heavy metals, organic pollutants, PM, alcohol, and some drugs in hypertension and CVD along with possible mechanisms and limitations in extrapolating animal data to humans.

Keywords: Hypertension, Cardiovascular diseases, Diabetes mellitus, Atherosclerotic diseases, Environmental toxicants, Chronic exposure

Highlights

- Rising incidence of hypertension may be linked to chronic exposure with environmental toxicants.
- Urban lifestyle and alcohol intake may be responsible for increased incidence of hypertension among urbanites.
- Exposure with organic solvent, heavy metals and pesticides could also be contributing to the rise in blood pressure.

1. Introduction

The incidence of hypertension and diabetes is on the rise worldwide [135]. A detailed analysis of hypertension indicates that median systolic blood pressure (BP) in men and women has decreased slightly among the rich industrialized nations in Europe, Central Asia, Middle East, Caribbean, and Latin America between 1975 and 2015. However, an increase in median systolic and diastolic BP is observed among Sub-Saharan Africa, South Asia, and Southeast Asia [135]. The causes for the increase in populations with hypertension are not well understood. It is believed that due to industrial activity and exposure to environmental toxicants such as diesel exhaust particles (DEP), polycyclic aromatic hydrocarbons (PAH), residues of organochlorine insecticides (OCI), polychlorinated biphenyls (PCBs), particulate matters (PM), and heavy metals (Pb, Hg, Cd, and As) may be playing a role (Table 1). Studies have demonstrated that exposure of workers to styrene, an industrial chemical, causes an increased incidence of cardiovascular diseases (CVD) [100]. Recent studies have demonstrated that exposure to DEP and urban PM increases CVD and mortality. In addition, consumption of alcohol may also contribute to hepatotoxicity and an increase in BP [12]. The role of OCI, PCBs, and heavy metals (Pb, Hg, As, and Cd) in increasing BP is not addressed systematically. These xenobiotics cause immune disruption and create inflammation, which might play a role in CVD as in increased incidences of cancer [80], [191]. These xenobiotics increase levels of interleukin (IL-1β, IL-6, and IL-8), tumor necrosis factor-α (TNFα), and C-reactive protein (CRP). The IL-1β, TNFα, and IL-6 are cytokines responsible for acute phase response (APR) from liver. The increase in CRP has been suggested to arise from APR by IL-6 [93], [208]. These cytokines can modulate APR in liver and modify secretion of proteins, like CRP and angiotensinogen (AGT), which play significant role in inflammation and BP regulation.

Table 1

Examples of Environmental Pollutants and their Mechanism of Causing Hypertension-Related Diseases.

Class of the Compound	Examples	Risk of Hypertension-Related Diseases	Potential Mechanisms	Reference
Heavy metals	Arsenic	Hypertension, Atherosclerosis/Coronary Heart Disease, Stroke	Increased Peroxynitrite (RNS) and inflammatory mediator; cyclooxygenase (Cox-2) formation	[22]
	Cadmium	Hypertension, Stroke	Oxidative stress, impaired nitric oxide (NO) signaling, modified vascular response to neurotransmitters, disturbed vascular muscle Ca^{2+} signaling, and interference with the renin-angiotensin system	[43], [148]
	Mercury	Hypertension, Cardiovascular, Mortality	Mitochondrial dysfunction, energy production process impaired, mechanism obscure	[43]
	Chromium	Cardiovascular disease	Promoting oxidative stress, limiting nitric oxide availability, impairing nitric oxide signaling, increasing adrenergic activity, and endothelin production, altering the renin-angiotensin system	[213]
	Lead	Hypertension	Increasing	[196]

The BP is the force of blood that is pushed against the walls of different arteries as the heart pumps blood. As per the NIH guideline for blood pressure (European guideline discussed later in comparison to revised guideline in the USA), a normal BP is defined as < 120 mm Hg systolic and < 80 mmHg diastolic BP. The BP is considered elevated when systolic BP is ≥ 120 mm Hg and diastolic is > 80 mm Hg. Prehypertension is defined when systolic BP is > 120 and < 140 while diastolic BP is > 80 but < 89 mm Hg. A stage 1 hypertension is defined when systolic BP is between 140 and 159 mm Hg and diastolic is between 90 and 99 mm Hg. It is stage 2 hypertension when systolic and diastolic BPs are ≥ 160 and ≥ 100 mm Hg, respectively (Table 2) [134].

Table 2

Blood pressure parameters and stages of hypertension.

BP Category	Systolic mm Hg (upper #)		Diastolic mm Hg (lower #)
Normal	less than 120	and	less than 80
Prehypertension	120 – 139	or	80 – 89
High BP (Hypertension) Stage 1	140 – 159	or	90 – 99
High BP (Hypertension) Stage 2	160 or higher	or	100 or higher
Hypertensive Crisis (Emergency care needed)	Higher than 180	or	Higher than 110

Hypertension is amenable with a low-salt diet and antihypertensive agents (e.g., blockers of various steps in the AGT derived peptides, receptors, calcium channel, beta-adrenergic receptor, diuretics, and aldosterone synthase inhibitor). High BP for an extended period can cause cardiac dysfunction, kidney damage, and damage to other vital body organs [125]. Hypertension is classified as primary (essential) and secondary hypertension. The causes or mechanisms of primary hypertension are not well defined. It is believed that primary hypertension involves interaction between genetic loci and environmental factors. Primary hypertension is responsible for affecting more than 90% of hypertensive patients, and therefore is the most common type of hypertension; the prevalence of which increases with age [30], [140]. On the other hand, secondary hypertension is mainly due to known causes or genetic diseases [34], [90]. For example, the secondary hypertension may be due to malfunction of kidneys, lungs, arteries, endocrine system, or the heart. When lungs are involved, it is referred to as pulmonary hypertension [183]. Hepatotoxicants cause liver injury that may lead to portal hypertension from the repair of tissues around the portal vein causing constriction and increasing resistance to blood flow into the liver consequently increasing the BP. An increase in BP during pregnancy (or preeclampsia) is defined as pregnancy-induced hypertension leading to proteinuria at later stages of pregnancy [19]. Simplistically, cause(s) of secondary hypertensions (e.g., Liddle's syndrome, glucocorticoid remediable hyper-al-

dosteronism, and G-protein-beta subunit mutant) is known and treatment is easier than primary hypertension, the causes of which are mostly not well defined [161]. One of the concerns of the treatment of hypertension is making it a resistant hypertension refractory to treatments [1].

American College of Cardiology and American Heart Association in November 2017 replaced the Joint National Committee hypertension guidelines [106], [88]. Similarly, the European Society of Cardiology and the European Society of Hypertension brought their recommendation in June 2018 for diagnosing, and management of hypertension [206]. The European guidelines remained the same while American guidelines changed. Previously, both Americans and Europeans defined hypertension when BP readings were ≥ 140/90. Earlier American guideline defined PB > 120/80 mmHg but less than 140/90 mmHg as prehypertension which now has become the first stage of hypertension as per the new guidelines. Now, as per American guidelines, BP ≥ 130/80 mmHg is a hypertension stage 1. This new guideline certainly increased the number of patients who required treatments. The European guidelines continue to define hypertension at BP > 140/90 mmHg. The systolic and diastolic blood pressure readings of the American and the European guidelines are presented in the Table 3.

Table 3

Classification of Blood Pressure [44].

Category	**SBP**		**DBP**
American College of Cardiology/American Heart Association			
Normal	< 120	and	< 80
Elevated	120–129	and	< 80
Stage-1 hypertension	130–139	or	80–89
Stage-2 hypertension	≥ 140	or	≥ 90
European Society of Cardiology and European Society of Hypertension			
Category	SBP		DBP
Optimal	< 120	and	< 80
Normal	120–129	and/or	80–84
High-normal	130–139	and/or	85–89
Stage-1 Hypertension	140–159	and/or	90–99
Stage-2 hypertension	160–179	and/or	100–109
Stage-3 hypertension	≥ 180	And/or	≥ 110
Isolated systolic hypertension	≥ 140	and	< 90

SBP, systolic PB; DBP, diastolic BP.

Hypertension is a complex disease that causes many morbidities and mortalities worldwide. Hypertension is considered the major risk factor for CVD. Statistically, high BP affects almost one-third of adults worldwide and contributes to 13.5 million deaths annually [135]. Even with recent advances in science and understanding the pathophysiology of diseases and treatments, the prevalence of hypertension is still on the rise in certain parts of the world [81], [114], [135]. Ethnicity plays an important role in the development and maintenance of high BP which is the reason that one ethnic population respond better to one specific treatment whereas the other ethnic group respond better to another class of antihypertensive drugs [70], [107]. As an example, African Americans always respond better to diuretics and calcium channel blockers (CCB) than Caucasian and selected Asians who respond better to beta-blockers (BB) and angiotensin-converting enzyme I inhibitors (ACEI) [70], [71].

2. Role of aging in hypertension (elderly hypertension)

Studies on monitoring blood pressure in an urban population of developed countries demonstrate a rise in systolic blood pressure and pulse pressure with increasing age [181]. In developed countries, 35–50% of individuals over age 65 are thought to be hypertensive [181]. With increasing age, there is a generalized reduction in organ function [21]. Among older individuals, increased inflammation, arteriolar stiffening, and increased peripheral resistance are common [181]. Inflammation and oxidative stress contribute to endothelial dysfunction, the cells which line the internal walls of circulating blood vessels [20], [147], [158]. The decrease in elasticity of connective tissues increased in oxidative stress (superoxide and hydrogen peroxide) due to increased inflammation with decreased levels of antioxidants in endothelial cells which incapacitates the nitric oxide-mediated smooth muscle relaxation and vascular dysfunction are assumed to be the cause of elderly hypertension [21]. Moreover, decreased sensitivity to beta-2-adrenergic receptors may also be a contributing factor towards the reduced relaxation of smooth muscles [53]. Thus, endothelial dysfunction remains one of the contributing factors in the development of elderly hypertension.

Environmental chemicals and drugs are metabolized by CYP P450 based enzymatic system. It has been difficult to interpret the effects of aging on the levels and activities of P450 isozymes [204]. CYPs produce reactive oxygen species (ROS), which are removed by antioxidants [65], [198]. In addition to CYP450-mediated ROS production, many other biomolecules such as Ang II, endothelin-1, and urotensin II also produce ROS in endothelial cells. Decreasing levels of antioxidants among the elderly and increased ROS can cause vasoconstriction and exacerbate elderly hypertension [171].

2.1. Pulmonary hypertension

Pulmonary hypertension (PH) develops when resistance to blood flow in the lungs is increased. PH is defined when mean pulmonary artery pressure (mPAP) is ≥ 25 mm Hg with pulmonary wedge pressure of ≤ 15 mm Hg [79]. Due to increased resistance of blood flow to blood vessels by narrowing or blockage, increases the resistance to blood flow into lung leading to a rise in the BP in the arteries of lung. To pump enough oxygenated blood to meet the demand, heart puts extra effort which may lead to heart muscle failure. The diagnosis of PH cannot be performed by regu-

lar *arm-cuff cut* measurement. The PAH develops slowly and when developed, symptoms include dyspnea during exercise initially but later even at rest, fatigue, syncope, swelling in the ankles, legs and ascites, and palpitation; cyanosis may also be present in the patients.

Pulmonary arterial hypertension can be differentiated from pulmonary venous hypertension which occurs due to left side of heart disease. The PH due to diseased left-side of the heart can occur from defects in the mitral or aortic valves. It can also occur due to the failure of the left ventricle. The PH due to lung disease can occur when individuals are suffering from chronic obstructive pulmonary disease (COPD), fibrosis of the lung air sacs, obstructive sleep apnea. Individuals with long term exposure with high altitude climbing are also at a risk of pulmonary hypertension (https://www.mayoclinic.org/diseases-conditions/pulmonary-hypertension/symptoms-causes/syc-20350697). A thorough detail on PH definition and its causes is available online for readers to access by simple Google search.

In addition to reasons for PH described above, drugs and exposure with environmental toxicants also cause PH. Use of drugs such as anorexigenics, aminorex fumarate (e.g. amphetamine for suppressing appetite), and fenfluramine can cause increased incidence of PAH and PH [129], [176]. A whole host of other agents, like interferons used to treat viral hepatitis, tyrosine kinase inhibitors to treat various malignancies (e.g., dasatinib, mitomycin C) have also been reported to cause PH [141].

Tobacco smoke inhalation is a risk factor for pulmonary arterial hypertension [170], [96]. Recently, chronic inhalation of the component of tobacco, i.e., nicotine, has been found to cause PH and systemic hypertension (https://www.sciencedaily.com/releases/2020/05/200501125832.htm; [138]. Occupational exposure to trichloroethylene also causes PH [25]. The biochemical mechanisms of the development of PH from these agents in humans are not known; however, shown to be significantly different in humans and animals and therefore, animal models have far less application in studying the pulmonary hypertension by environmental chemicals and drugs [120].

3. Involvement of genes in hypertension: the monogenic hypertension

Liddle's syndrome (LS) is a genetic hypertensive disorder from the malfunction of Na^+/K^+ ATPase (SCNN1B and SCNN1G genes) due to gain of function mutation in SCNN1B and SCNN1G genes. SCNN1B and SCNN1G encode the beta and gamma subunit of Na^+/K^+ ATPase; often referred to as epithelial sodium channel [104]. It involves abnormal kidney function with loss of potassium and excess reabsorption of sodium from the renal tubule. In 1963, a new clinical syndrome that looked like primary aldosteronism (pseudoaldosteronism, subsequently named Liddle syndrome) was reported by Liddle and Coppage [113], which affected a 16-year-old Caucasian girl who presented severe resistant hypertension with low renin, metabolic alkalosis, and severe hypokalemia [17], [143]. Biochemical analyses to characterize decreased urinary sodium excretion rate with the absence of effects on aldosterone secretion after low sodium intake led to establish LS [17]. When comparing LS patients with Addison's disease patients (a disorder of adrenal glands not producing enough hormones), it was found that patients with LS have lower urinary sodium indicative of higher renal reabsorption of sodium due to a mechanism independent of mineralocor-

ticoids activity [160]. Thus, LS is a genetic dominant form of low renin arterial hypertension that is caused by a mutation in the SCN genes encoding the non-voltage-gated sodium channel (SCNN1A, SCNN1B, and SCNN1G). The mutation results in an epithelial sodium channel (ENaC) to increase sodium and water reabsorption leading to increased blood volume and hypertension. The genetic disorder is characterized by not only the high BP but also the low plasma level of renin activity, metabolic alkalosis, hypokalemia, and normal to low levels of aldosterone. As a result, it is called pseudoaldosteronism/pseudohyperaldosteronism. In LS, kidney function is characterized by abnormally high sodium reabsorption with potassium loss due to the high activity of ENaC. So, treatment may be initiated with potassium sparing diuretics like amiloride after the confirmation of LS [187], [197].

Glucocorticoid remediable aldosteronism (GRA) is a rare familial autosomal dominant form of primary aldosteronism (PA, also referred to as Familial Hyperaldosteronism (FH) Type I), which comes with increased aldosterone secretion under the feedback control of adrenocorticotropic hormone (ACTH). GRA has a unique clinical response of aldosterone production and hypertension to the administration of glucocorticoids. GRA was first described by Sutherland and colleagues in 1996 in a father and son [173]. It is also characterized by being low renin hypertension with a high aldosterone/renin ratio [92]. GRA is caused by unequal crossing over of the genes encoding steroid 11 β-hydroxylase (CYP11B1) and aldosterone synthase (CYP11B2), which results in chimeric gene CYP11B1/CYP11B2 that has aldosterone synthase activity with CYP11B1 promoter under the regulation of ACTH rather than angiotensin II [109], [115], [145]. GRA patients are represented by mild hypokalemia, low plasma renin, and metabolic alkalosis [40]. As the name suggests, GRA is treatable by glucocorticoids, which inhibit ACTH production that is the activator of aldosterone production [73]. There are other forms of FH, i.e., FH type-II, type-III, and Type-IV, which are very rare and occur due to the gain of functions in channel proteins [110].

The FH type-II occurs due to adenomas or adrenal hyperplasia which is unresponsive to glucocorticoids. Blunting the aldosterone action by unilateral adrenalectomy or mineralocorticoid receptor antagonists are the recommended treatments [110]. The mutation in the chloride channel (ClC-2) is of the gain of function causing increased chloride efflux, resulting in the increased CYP11B2 expression and aldosterone production [110]. In type-III FH, a gain of function mutation in KCNJ5 causes increased calcium entry into adrenal glomerulosa cells due to membrane depolarization causing increased CYP11B2 expression and subsequent aldosterone synthesis. Gene KCNJ5 encodes the Kir 3.4 K^+ channel which is an inward rectifier potassium channel [110]. The type-IV FH occurs due to gain of function in the CACNA1H gene [110]. In another form of hypertension referred to as Gordon's hypertension syndrome, the mutation is observed in WNK1 (with no K (lysine) protein kinase-1) and WNK4 where sodium-chloride cotransporter activity in the kidney is increased [52].

Non-chimeric CYP11B2 has also been shown to cause hypertension and cardiac fibrosis via Angiotensin II type I receptor (AT1R) increasing absorption of Na^+ from the kidney, thus increasing blood volume and hypertension. Absorptions of Na^+ occurs via aldosterone, which is synthesized by aldosterone synthase (Cytochrome P450 [CYP] 11B2) which is released from the adrenal cortex. Activation of CYP11B2 occurs via K^+ resulting in Ca^{++} release and activation of T and L-type calcium channel and increased CYP11B2 expression in the adrenal cortex [137]. The increased ex-

pression of CYPIIB2 is through the upregulation of cyclic-AMP response element (CRE) mediated protein kinase; however, transcriptional regulation of CYP11B2 is not well defined. The CRE and ATF-1 have been shown to bind CRE-element after phosphorylation [137]. Recently, ubiquitin-proteasome inhibitor, bortezomib, is found to suppress the expression of CYP11B2 raising the prospect of the development of antihypertensive drugs [85]. To develop H295R cells as an in vitro cell-based model for screening chemicals for endocrine disruption properties, octyl methoxycinnamate, and acetyl tributyl citrate were found to increase the expression of CYP11B2 [182]. In a study evaluating the endocrine disruption activity of persistent organic pollutants using H295R as in vitro cell-based model, TCCD, PCB, PFOS, HBCD, and BDE-47 were found to increase the secretion of steroid hormone indicating steroid synthesis interference by these compounds. The study did not evaluate effects on the CYP11B2 expression levels [193]. Th use of H295R to study the gene regulation and transcriptional activation of CYP11B2 after xenobiotics exposure and establish a linkage between the environmental toxicants and the regulation of CYP11B2 is insufficient, and thus, the association to hypertension.

4. Alcohol and hypertension

A divergent view on the beneficial and harmful effects of the use of ethanol exists among scientists and researchers. Current and past research suggest that moderate alcohol intake is beneficial to the cardiovascular system lowering BP while excessive use is harmful causing an elevation in BP. Low to moderate alcohol use has been linked to decreased incidence of coronary heart disease and an increase in longevity [48], [94]. However, alcohol is also known to increase BP, especially with the chronic intake. Continued consumption of more than 2 servings of ethanol (30–50 g) per day results in a dose-dependent rise in BP [56]. Heavy alcohol usage (>2 drinks/day) has also been associated with hypertension [56], [69], [101], [188]. The biochemical mechanism of alcohol-mediated hypertension is not unequivocally defined. The alcohol-mediated increase in BP involves several mechanisms including impairment of baroreceptors, increase in sympathetic activity, stimulation of the endothelium to release endothelin, inhibition of endothelium-dependent nitric-oxide production, and stimulation of the renin-angiotensin-aldosterone system (RAAS) [152]. Lowering of alcohol-induced hypertension in rats has been obtained by dexamethasone treatment blocking the activation of the sympathetic nervous system responsible for releasing corticotrophin-releasing hormone [152]. In another study, ethanol exposure increased circulating levels of vasopressin in rats resulting in hypertension [153]. Antihypertensive drugs, e.g., ACEI (zofenoprilat), beta-blocker (carvedilol) and calcium channel blocker (lacidipine) have shown to protect cultured human endothelial cells against alcohol-induced oxidative-stress and endothelial dysfunction [175]. Blunting of oxidative-stress and endothelial dysfunction by zofenoprilat (ACEI) indicates involvement of RAAS. Inhibition of RAAS in experimental animals and clinical studies has proven to effectively lower BP in hypertensive animal models and human subjects [8]. Like alcohol that is responsible for hepatosteatosis and steatohepatitis, OCI and PCBs exposure can produce such effects pointing to (i) a common mechanism of hepatotoxicity and regulation of genes, and (ii) possibly an APR activation after injury to the liver resulting in the production and secretion of proteins from liver into blood. There are two types of APR, (i) APR I that is induced by TNF-α and IL-1β which activate NF-κB, and (ii) APR II that is activated by glucocorticoids and IL-6 via STAT3 activation. Human AGT is an APR II protein, which is triggered by glucocorticoids and IL-6 / STAT3 activation [131]. Metabolism of alcohol in the liver produces oxidative stress from increased ROS

levels [51]. In addition, xenobiotics' metabolism (e.g., OCI and PCBs) in the liver also produces oxidative stress [119]. Liver is the source of many secretory proteins like clotting factors and AGT. The ROS and metabolic products (acetaldehyde in case of ethanol) mediated effects on transcription factors in the liver after xenobiotic exposure likely target the synthesis and secretion of liver-specific genes including AGT, the precursor of vasopressor peptide, angiotensin II. The angiotensin II is released sequentially by proteolytic cleavage of AGT in the kidney by renin and angiotensin-I converting enzyme (ACE) in the lung while it serves as a precursor to other peptide hormones (Fig. 1).

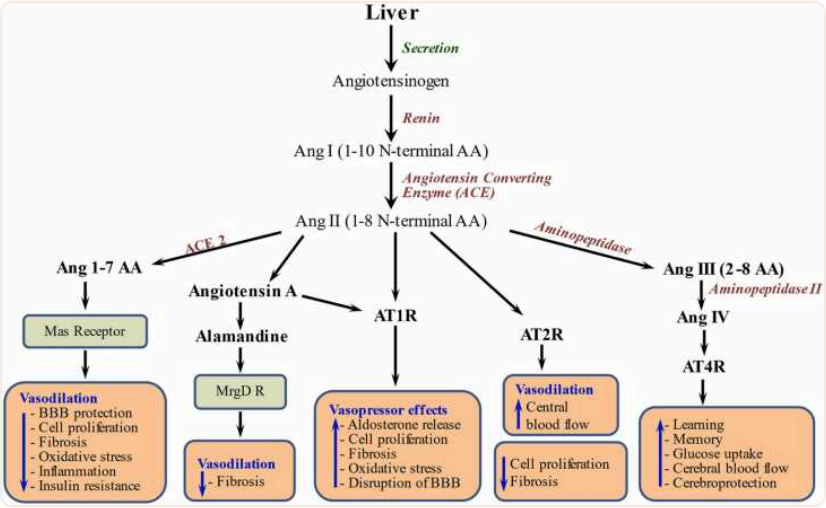

Fig. 1

Peptides of Angiotensinogen.

The circulating plasma concentrations of AGT is closed to saturating concentration of aspartyl protease, renin [66]. Therefore, alterations in the circulating AGT levels can cause corresponding changes in the blood angiotensin II levels. Thereby, a rise in blood AGT level can lead to a parallel increase in the formation of angiotensin II causing hypertension [49].

Higher blood AGT levels have been demonstrated more frequently in hypertensive subjects and their children than healthy individuals with normal BP [202]. Expression of the renin-AGT in body organs such as kidneys, heart, placenta, brain, and adrenals are examples of organ-specific BP regulation [26]. The overexpression of human AGT (hAGT) in a humanized mice model was shown to increase BP while the effect was not observed in the AGT gene-knockout mice [99], [185]. Administration of antisense RNA of AGT causes a profound reduction in BP in hypertensive rats [184]. These studies demonstrate that changes in blood AGT levels can measurably alter BP. Similar studies duplicating the ACE gene in mice led to an increase in blood ACE level but no change in BP [105]. The inhibition of RAAS in hypertensive experimental animals and humans has shown to lower BP. Individuals with insulin-dependent diabetes secrete increased levels of AGT in urine from increased RAAS activity in the kidney that is a biomarker of poor glycemic control [133]. Regulation of synthesis and secretion of AGT-related oxidative stress in individuals with dia-

betes is considered a key step towards reducing AGT synthesis, better glycemic control, and reducing hypertension. The link between environmental toxicants and AGT synthesis and secretion from the liver has not been established. However, results of studies conducted in our laboratory indicate that alcohol can enhance IL-6 mediated AGT secretion from human hepatocytes (unpublished data).

Human AGT possesses several single nucleotide polymorphisms (SNP) in the coding region. Polymorphism resulting from the conversion of methionine into threonine (M235T) causes higher blood AGT levels and hypertension [91]. Similarly, the T174M allele in hAGT is also associated with hypertension [111]. It is known that hAGT SNPs, especially − 6A (−6A/G), − 217A (−271 A/G), and 235 M are associated with hypertension [150]. Due to the association of hAGT with primary hypertension, the role of SNPs in hAGT proximal promoter activity was determined in transgenic mouse models; however, these studies did not provide an unequivocal answer to the role of several proximal promoter SNPs. In one of the studies, Grobe et al. [68] observed no difference in the level of circulating hAGT with either − 6 A or − 6 G nucleotide in context with − 6A/235 T or − 6 G/235 M variant. In another study, Jain et al. [86] found that − 6 A and − 6 G SNP caused an increase in the blood hAGT; − 6 G SNP was less effective than − 6A SNP. Previously, [87] investigated the role of − 217A and − 217 G SNP which is the site of glucocorticoid receptor binding and observed that − 217A increases AGT levels in blood more than − 217 G does. Currently, data on the regulation of hAGT and hepatotoxicants are apparently lacking. However, our laboratory has demonstrated that treatment of human hepatocytes with alcohol results in increased secretion of AGT [7].

5. Role of environmental toxicants in hypertension

We are continuously exposed to environmental pollutants and scientists have shown a strong relationship between exposure to environmental pollutants such as persistent organic pollutants (POP), PM, and chemicals from diesel exhaust and the risk of developing several diseases. Evidence suggests that humans living close to hazardous waste sites and exposure to hazardous waste are more susceptible to developing high BP [61], [76], [172]. However, the biochemical mechanism of these toxicants affecting BP is not completely understood. The major environmental toxicants present in most of these studies were organic pollutants, such as OCI, and PCB. In a cross-sectional epidemiological study conducted in Spain, the POP was found to induce opposite actions on the BP of individuals. The organochlorine cyclodiene insecticide, Aldrin, was negatively associated with hypertension, while dichlorodiphenyltrichloroethane (DDT) metabolite, dichlorodiphenyldichloroethane (DDE), is well known to elevate the BP [55]. These opposing effects were suggested to be from the difference in chemical structures and concentrations. Most POPs play a role in the endocrine function altering hormonal homeostasis that may result in elevating BP [61], [76]. For example, postmenopausal women who take supplement estrogen to control the effects of menopause are at a higher risk of developing hypertension from the hormone, estradiol [179], [180]. Similarly, some of the POPs such as DDE, a known xenoestrogen can modify estrogen homeostasis and impair the regulation of BP [46], [144]. Additionally, POPs can generate free radicals that can lead to triggering proinflammatory cytokine signaling pathways and associated inflammatory diseases including hypertension [146]. In another study, PCBs exposure was associated with hypertension in healthy individuals [29]. The increase in both systolic and diastolic

BP was observed, even though the exact reason(s) of PCBs-mediated elevation in BP could not be determined [180]. It has been demonstrated, however, that the dysfunction in the endothelium contributed to the increase in BP [61], [76], [139]. The POPs are not the only environmental pollutants causing hypertension but other air pollutants like those from the exhaust of diesel fuel can also be as bad. A recent study indicated that increased exposure to air pollutants make human more vulnerable to hypertension. When diesel fuel burns, the resulting exhaust, made up of soot consisting of very small particles, and a variety of other harmful chemicals (i.e., carbon dioxide, carbon monoxide, nitrogen dioxide, and nitric oxide) can deposit in the lungs [199]. These air pollutants and the byproducts of burning some organic materials, like tetrachlorodibenzo-p-dioxin (TCDD), are known to induce high BP as they may be an agonist of the aryl hydrocarbon receptor (AhR) [77], [212]. The AhR is a heterodimer of HIF-1α, transcriptionally regulates phase I/II genes in the endothelium [103]. These air pollutants and smoking are further risk factors for CVD. The AhR plays a major role in regulating the level of Angiotensin II from AGT, endothelial nitric oxide synthase (eNOS), and endothelin-1 [212], [214]. In addition to activating AhR, the pollutants may activate the expression of genes involved in the inflammatory response and endothelial dysfunction, thus contributing even further to the development of atherosclerosis, hypertension, and CVD [214], [216].

Other studies have demonstrated a correlation between particulate air pollutants, especially diesel exhaust, and hypertension [59], [166]. Studies conducted on human subjects, who inhaled PM present in the urban and industrial environment, in which the results revealed a correlation between the exposure to PM and the increased BP and CVD [23], [166]. In another study, macrophage U937 cells were used to determine urban dust particles (UDP) and diesel exhaust particulates (DEP) effects on proinflammatory cytokines induction [199]. Both UPD and DEP along with their organic extracts (OE) and stripped particles (sUDP and sDEP) caused induction of proinflammatory cytokines and CRP in macrophage U937 cells [199]. An increase in IL-8, TNF-α, and cyclooxygenase-2 mRNA expressions was noticed after the exposure to OE-UDP, OE-DEP, UDP, and DEP. On the other hand, an increase in the production of CRP and IL-6 mRNA was noticed after the exposure to sUDP, sDEP, UDP and DEP [199]. This inflammatory response is known to play a major role in the pathological process of CVD [112]. A positive association between CRP and coronary artery diseases due to chronic inflammation is well known [9], [47]. Other harmful effects of proinflammatory cytokines include triggering acute vasoconstriction which may lead to hypertension and atherosclerosis [178].

A study conducted by Olea et al. [139] of the University of Chicago, investigating the link between environmental toxicants and the occurrence of elevated BP through a completely different mechanism. They studied different classes of environmental chemicals, i.e., industrial pollutants, phytochemicals, pesticides, waste products, and consumer products - chemicals with different structures, for the mode of action of inducing hypertension. Chemicals they studied could modulate endogenous hormonal signaling pathways (i.e., endocrine-disrupting chemicals [EDCs]). Both, epidemiological and animal data have shown the association between EDCs and metabolic disorders, particularly type 2 diabetes, and CVD. The effect of these EDCs on the cardiovascular system starts with an increase in the prevalence of atherosclerosis plaque and their ability to promote dysregulation of energy metabolism. Unfortunately, many humans and animal studies have failed to fully describe the molecular mechanism by which EDCs exert their effects and only provided some in-

sights into the potential role of EDCs in pathogeneses of macrovascular diseases. High BP is one of the major risk factors that can promote atherosclerosis by enhancing stress and endothelial inflammation mediated by oxidative stress. The regulation of BP is by a host of local and systemic signaling molecules, some of which are modulated by the EDCs. For example, nicotine-exposed rats have shown elevated levels of angiotensin II leading to higher BP. In addition, some chemicals, e.g., organophosphorus pesticides upregulate the activity of adenylate cyclase in neonatal rats. Adenylate cyclase directly signals adrenergic G-protein coupling, which plays a major role in regulating BP through catecholamines [139].

6. Roles of heavy metals in hypertension

The mechanisms of action through which heavy metals, like arsenic (As), mercury (Hg), cadmium (Cd), and lead (Pb) instigate hypertension are still not completely understood; further investigations are needed to enhance the understanding of the relationship between them and CVD including hypertension.

6.1. Arsenic and hypertension

As, as one of the omnipresent metalloids, is found in nature and causes hypertension by several mechanisms including an increase in subclinical atherosclerosis, electrocardiographic abnormalities, oxidative stress, and inflammation [42], [210]. Many cross-sectional epidemiological studies on As exposure and subclinical atherosclerosis are available in the literature. Wang et al. [201] studied 199 adult males and 264 adult females, who were exposed to As, in the southwestern area of Taiwan. Their study examined the duration of consumption of artesian well water, average As concentration in the water consumed, and cumulative As exposure adjusted for factors like age, sex, cholesterol, body mass index (BMI) ratio, diabetes, and hypertension. They found a dose-response relationship between long-term exposure to As and carotid atherosclerosis. Later, Wang et al. [200] studied 280 men and 355 women in the same area of Taiwan. They found a dose-response relationship between the cumulative As exposure and carotid intima-media thickness (cIMT) and prevalence of carotid plaque after adjustment for age, sex, hypertension, diabetes, cholesterol, and triglyceride, BMI, smoking, and alcohol consumption [200]. In addition to Wang et al. [201], [200] studies, Hsieh et al. [83] concluded that the formation of atherosclerosis is increased in people with exposure to high levels of As in drinking well water (>50 μg/l) when they have As metabolic genes, including purine nucleoside phosphorylase (PNP), As (+3) methyltransferase (As3MT), glutathione S-transferase omega 1 (GSTO1), and omega 2 (GSTO2). In a study conducted in Bangladesh, 66 young adults, who consumed well water containing 0.5–439 μg/L As were analyzed. The results showed that the levels of As in their urine ranged 6–209 μg/L, and subjects with higher urinary As levels had higher cIMT (> 0.75 mm) [210]. Another cross-sectional study in Bangladesh of 959 subjects found an effect of long-term As exposure on cIMT which was assessed ~7 years later with a dose-response relationship of urinary As and urinary monomethylarsonic acid with cIMT [36], [38], [39]. Osorio-Yanez et al. [142] found that the concentrations of total speciated As (tAs) were positively associated with cIMT increase. The estimated cIMT diameter was higher in groups with urinary As of 35- to 70-ng/mL and > 70-ng/mL (0.035 mm and 0.058 mm per 1-ng/mL increase in urinary tAs, respectively).

The As-exposed and non-exposed individuals of Bangladesh were assessed for their cardiac status by Ahmad et al. [3]. The subjects of this study were divided into As-exposed individuals with arsenicosis (arsenicosis group), As-exposed persons without arsenicosis (non-arsenicosis group), and individuals not exposed to As (non-exposed group), each group was composed of 50 subjects. The Arsenicosis group had abnormal electrocardiograms findings (58% of total subjects) [3]. In another study conducted in Turkey on 40 men exposed to As with mean As levels in village water of 659 μg/L (ranged 422–1066 μg/L), the study found that exposed individuals had a slight QT prolongation and a higher prevalence of subtle repolarization abnormalities [215]. Mumford et al. [132] found that prolong exposure of As from well-water is associated with the prevalence of QT prolongation in men from Bangladesh and hypothesized that QT prolongation is due to the functional alterations in cardiac cell surface channels in a dose-dependent manner. Mordukhovich et al. [130] conducted a study to assess the relationship between As in toenail and QT, heart rate-corrected QTc, and the effect of modification by calcium channel blocker used by elderly men. They observed a positive association between As in toenail and QT duration; QT and QTc duration was increased by 3.8-millisecond and 2.5-millisecond, respectively in subjects exposed to As [130]. Chen et al. [39] found a prolonged QT in As exposure group assessed on average 6 years after exposure, the association appeared to be present in women but not in men. A positive association between long-term well-water As exposure and plasma levels of soluble ICAM-1 and soluble VCAM-1 (biomarkers to predict future CVD), biomarkers of endothelial dysfunction, and vascular inflammation is observed in an As-exposed population of Araihazar, Bangladesh [15], [37], [155]. Wu et al. [209] found a positive association between As exposure and plasma levels of soluble VCAM-1. They also found an interaction between As exposure and higher BMI in addition to increased plasminogen activator inhibitor-1 (PAI-1) and VCAM levels [209]. In addition, increased concentrations of PAI-1 were associated with acute myocardial infarction in individuals with a high prevalence of coronary heart disease [189]. Karim et al. [95] found significantly higher levels of oxidized LDL (ox-LDL), CRP, ICAM-1, and VCAM-1 in As-endemic subjects than those in nonendemic subjects. They also showed dose-response relationships with As exposure and HDL, ox-LDL, and CRP [95]. A study of 50 subjects in West Bengal, India, who were exposed to As through well water and 41 subjects not exposed to As found that the exposed group had higher catalase (CAT) and myeloperoxidase (MPO) with a higher incidence of chromosomal aberrations (CA) [10]. MPO is linked to atherosclerosis and CVD [169]. Another study found an increase in catalase activity in patients suffering from oxidative stress, CVD, diabetes, tumor, inflammation, dermatological diseases, anemia, and Wilson's disease [4]. Osorio-Yanez et al. [142] found that tAs was positively associated with plasma asymmetric dimethylarginine (ADMA) levels and cIMT, an indicator of subclinical atherosclerotic. Thus, all observed associations, between As exposure and atherosclerosis leading to CVD, are considered major factors [95]. In a study in Southwest Taiwan of 533 subjects, Tseng et al. [192] suggested that the chronic As exposure, i.e., duration of drinking well water, could positively associate with the serum levels of TC and LDL, which are the risk factors for atherosclerosis and CVDs such as hypertension.

6.2. Mercury and hypertension

The inhalation exposure of metallic mercury causes elevation of heart rate and BP (ATSDR, 1999). Occupational mercury exposure also causes an increase in blood pressure and heart rate. However, a low level of chronic mercury exposure (0–0.27 mg/m^3 in one and 0.075 mg/m^3 in an-

other study) for 0.5–7 years did not increase the blood pressure or caused abnormal electrocardiograph [2]. Furthermore, estimated exposure with 0.03 mg/m^3 of mercury vapors for 5 years caused a reduction in cardiovascular reflexes and increased palpitations [2]. Workers in the thermometer plant were found with hypertension [2]. An increase in the systolic and diastolic pressure has been observed among individuals carrying dental amalgam of mercury, however, the increases in systolic and diastolic pressure were not markedly different from the normal or non-amalgam group [2].

The mechanisms by which Hg causes hypertension are still not completely understood. Hg induces hydrogen peroxide production and mitochondrial dysfunction at the ubiquinone-cytochrome-b site of the mitochondrial respiratory chain [116]. It causes mitochondrial reduced glutathione (GSH) content depletion by more than 50% and increases thiobarbiturate reactive substances (TBARS), an indication of increased mitochondrial lipid peroxidation, by 68% [117]. Following the addition of Hg to mitochondria isolated from kidneys of untreated rats, an increased depolarization of the inner mitochondrial membrane was observed [118], [154]. Oxidation of pyridine nucleotides (NADPH) was also observed in mitochondria incubated with Hg along with significantly increased Ca^{2+}, H_2O_2, and TBARS due to its effect on the ubiquinone-cytochrome b site of the mitochondrial electron transport chain [117]. These events cause increased oxidative stress and decreased oxidant defense [117]. Increased risk of myocardial infarction and coronary issues resulting from mercury exposure from dietary fish has been recorded in Finnish men [165]. Hg promotes lipid peroxidation by three main sources: Fenton reaction, affinity for sulfhydryl groups, and selenium deficiency [57]. It acts as a catalyst in Fenton-type reactions resulting in the formation of free radicals [57]. In another study, Hg(II) ions in micromolar concentrations increased the production of superoxide anions in human neutrophils [89]. In a relatively newer study, mercuric ions (1–6 μmol/L) caused a concentration-dependent increase (up to 5-fold) in mitochondrial H_2O_2 production. Hg has been found to enhance iron-stimulated lipid peroxidation in vitro [72]. Mercury's high affinity for sulfhydryl groups is responsible for most of the antioxidant capacity of plasma such as glutathione, n-acetyl cysteine, and alpha-lipoic acid, which could reduce both membrane and plasma antioxidant defense [58]. Insoluble complexes of Hg with selenium (Hg selenides) reduce selenium availability, a necessary cofactor for glutathione peroxidase (GPx), which is an important scavenger of H_2O_2 and lipid peroxides. Depletion of selenium increases the risk of CVD and cerebrovascular accidents (CVA) [13], [177]. Hg increases hypertension risk by increasing carotid atherosclerosis. A population-based 4-year prospective study in men in eastern Finland found an increase in mean carotid IMT which was directly related to hair Hg content ($P = 0.0007$) [164]. An increase in hair Hg by 1 μg equaled a 0.008-mm increase in carotid IMT; a 7.3% increase over the mean value. In addition, Hg hair content was proportional to BP, fibrinogen levels, BMI, and low HDL cholesterol [164]. Hg can interfere with the normal catabolic processing of catecholamines via the cytosolic enzyme catecholamine-O-methyltransferase by inactivating coenzyme S-adenosylmethionine (SAM) which donates the methyl group to catecholamine-O-methyltransferase. As a result, norepinephrine, dopamine, and epinephrine accumulate in blood elevating BP [78]. This catecholamine excess is responsible for the pheochromocytoma-like syndrome [124]. Studies have shown that Hg concentrates in the renal tubules and glomerulus resulting in proteinuria, fibrosis, chronic renal dysfunction, and renal insufficiency [16], [102], [205]. Finally,

Hg stimulates proliferation of vascular smooth muscle cells and inactivates paraoxonase, an extracellular antioxidative enzyme related to HDL, and increases the risk of coronary heart disease (CHD), and myocardial infarction (MI) [64], [163].

6.3. Lead and hypertension

The mechanisms of action by which Pb causes hypertension are still not completely understood. Several mechanisms have been suggested for Pb-induced hypertension including oxidative stress, impaired nitric oxide system, inflammation, dysregulation of vasoactive hormones, and alteration of cellular Ca^{2+} transport and intracellular Ca^{2+} regulation. Pb can facilitate the production of ROS (e.g., O_2^- and H_2O_2) and can produce oxidative stress by acting as the catalyst in Fenton- and Haber-Weiss-type reactions [98]. Khalil-Manesh et al. [98] found dimercaptosuccinic acid (DMSA)-mediated Pb chelation increased cyclic guanosine monophosphate (cGMP) and rapid reduction of BP in rats with Pb-induced hypertension. They proposed that Pb exposure raises arterial BP by promoting ROS production and ROS-mediated inactivation of endothelium-derived relaxing factors. They also proposed that amelioration of high BP is due to attenuation of Pb-induced oxidative stress caused by the strong antioxidant activity of DMSA [97]. Gonick et al. [63] found significant accumulation of the lipid peroxidation product; malondialdehyde and inducible nitric oxide synthase (NOS), in the kidneys of Pb-treated rats. These observations support the presence of oxidative stress in the kidneys of Pb-exposed animals increasing the risk of hypertension [63]. Another study by Ding et al. [45] found a much greater reduction in arterial pressure in Pb-exposed rats than in either control or DMSA-treated Pb-exposed rats after the infusion of L-arginine. The study suggested the reduced nitric oxide production may be due to the oxidative stress. Administration of DMSA for 2 weeks lowered BP and reduced blood Pb concentration in Pb-induced hypertensive rats [45]. Another mechanism of hypertension involves Pb-mediated protein kinase C (PKC) isoforms activation, which is involved in many cellular functions including blood flow, vascular contraction, and cell growth [84]. Hwang et al. [84] assessed blood Pb levels, neurobehavioral effects, and PKC activity in 212 current Pb workers in the Republic of Korea and found elevated erythrocyte PKC activity among them. Increased PKC activity was also found in the microvessels of the rat brain after exposure to Pb at micromolar concentrations [122]. In another study, Watts et al. [203] found PKC in intact and endothelium-denuded rabbit mesenteric artery preparations following exposure of rabbits to Pb acetate at 10^{-10} to 10^{-3} M concentrations. They found that Pb-induced vasoconstriction was augmented by a PKC agonist, reduced by a PKC inhibitor, and attenuated by the Ca^{2+} channel blocker verapamil. In another proposed mechanism, Pb promoted inflammation, fibrosis, and apoptosis by Nuclear Factor-kappa B (NF-κB), which is a transcription factor for numerous proinflammatory cytokines, chemokines, and adhesion molecules. Two studies observed that NF-κB activation is linked to renal tubulointerstitial inflammation and the development of hypertension [157], [195]. Ramesh et al. [151] found activations of NF-κB in the brain of rats exposed to low levels of Pb (50 ppm in drinking water) for 90 days. Recently, Rodriguez-Iturbe et al. [157] reported NF-κB activation, tubulointerstitial accumulation of T cells, macrophages, and angiotensin II-expressing cells, increased number of apoptotic cells, and heavy tyrosine nitration in kidneys of rats with Pb-induced hypertension. Pb exposure also elevates plasma catecholamines and cardiac contractility [32]. Chang et al. [32] found high plasma norepinephrine but normal plasma dopamine and epinephrine levels, pointing to heightened sympathetic nervous system activity. In another study, Chang et al. [33] found increased arterial pressure

and plasma norepinephrine without changing plasma epinephrine concentration in Pb-induced hypertensive rats. Another mechanism may be by increased production of endothelins, which are powerful vasoconstrictor peptides, primarily synthesized and secreted by endothelial cells. For instance, Khalil-Manesh et al. [98] found significantly increased arterial pressure, a marked increase in plasma endothelin-3, and decreased endothelin derived relaxing factor (cGMP) levels in rats exposed to the low levels of Pb (0.01% via drinking water) which increased nephropathy without a rise in arterial pressure or plasma endothelin. In another in vitro study, Molero et al. [128] suggested that Pb can increase endothelin activity in the vascular tissue; incubation of isolated rat arteries in the Pb-containing medium led to decreased soluble guanylate cyclase (sGC) and cGMP production. They also found that coincubation with an endothelin type A receptor antagonist partially reverses Pb-induced downregulation of sGC and cGMP production. Another possible mechanism is due to an increase in circulating renin level that eventually elevates BP [194]. In a meta-analysis of the studies published between the late 1970 s and 1990 s, Vander [194] concluded that Pb exposure in young rats for several weeks is sufficient to achieve blood Pb levels in the range of 30–40 µg/dL and elevate plasma and kidney renin activity. Another study by Carmignani et al. [28] found that Pb exposure (60 ppm Pb acetate in water) to young rats for 10 months increased plasma angiotensin-converting enzyme activity as well as plasma kininase-I, kininase-II, and kallikrein activities. A subsequent study by Sharifi et al. [174] reported a steady rise in ACE activity in the plasma, aorta, kidney, and heart in young adult rats exposed to 100 ppm Pb acetate for 2–8 weeks. The initial rise in plasma and tissue ACE activity was followed by a decline to subnormal values by 8 wk., coinciding with a marked elevation of arterial pressure. Another way BP can be increased is by lowering the production of vasodilatory and increasing the production of vasoconstrictive prostaglandins in humans [27]. Cardenas et al. [27] studied a group of Pb workers with elevated blood Pb concentration and compared with control workers, they found increased urinary excretion of the thromboxane metabolite TXB2 and reduced excretion of the vasodilatory prostaglandin metabolite; 6-keto-PGF1. Later in another study by Hotter et al. [82] confirmed the results in a separate group of Pb-exposed workers. However, Gonick et al. [62] failed to find a difference in urinary excretion of these metabolites in rats with Pb-induced hypertension. Another mechanism may involve reduced plasma atrial natriuretic peptide (ANP), which is synthesized and secreted by the cardiac myocytes in response to the distension of cardiac chambers. ANP is also considered a vasodilator and plays a role in regulation of arterial pressure by modulating systemic vascular resistance and blood volume [60]. Giridhar and Isom [60] concluded that Pb-exposed animals exhibited fluid retention, which was paradoxically accompanied by a dose-dependent decline in plasma ANP level.

6.4. Cadmium and Hypertension

Cadmium is a food chain toxicant with a greater rate of soil to plant transfer. Cadmium is also an environmentally persistent toxic metal, which is present in cigarette smoke and polluted air causing human exposure [167]. Cadmium occupational exposure is linked to hypertension; however, the data remains inconsistent [24]. Occupationally exposed individuals with Cd were found to have increased systolic and diastolic pressure [24]. In a study of the Korean National Health and Nutrition Examination Survey, Lee et al. [108] observed increased Cd blood level positively associated with increased blood pressure, indicating risk of hypertension. In a Strong Heart Study (SHS), Franceschini et al. [54] observed that Cd exposure resulted in increased blood pressure. The

blood Cd levels but not urine levels are linked to a modest rise in blood pressure. This effect is even more prominent in non-smokers [186]. In this study, it was observed that the effects of Cd exposure to former smokers were intermediate and current smokers were null [186]. In a marked contrast, the 1999–2004 National Health and Nutrition Examination Survey (NHANES) of the USA did not find the link between either blood or urine Cd level with an increase in blood pressure [43]. To decipher Cd-mediated hypertension, Al-Naemi and Das [6] demonstrated abnormal endothelial function in animals as the cause of hypertension. While exposure leads to increased eNOS expression, yet Cd produced oxidative stress by stimulating NOX expression by reducing the bioavailability of nitric oxide (NO) [5]. Satarug and coworkers (2017) have summed up the mechanism of Cd exposure and hypertension. Cadmium, which is absorbed from the GI tract, is transported to the liver by portal vein where Cd binds with metallothionein. After secretion of metallothionein bound Cd in bile and blood it reaches to kidney especially the proximal tubular cells. The Cd-metallothionein complex is broken down in proximal tubular cells. The released Cd causes oxidative stress and inflammation. Thereby, the activity of Na^+/K^+-ATPase is decreased, in large part due to the oxidation of Na^+/K^+-ATPase and the changes in the production of 20-hydroxyeicosatetraenoic acid (2-HETE) in proximal tubule causing salt and water retention and hence plasma expansion. Such effects can impose pressure-natriuresis and persistent increased blood pressure and hypertension [168].

7. Role of particulate matter in hypertension

Particulate matter is a complex mixture of extremely small particles and liquid droplets. PM vary extensively in physical (diameter, morphology, surface area, and hygroscopicity) and chemical (organic, inorganic, metallic) characteristics. The diameter ranges from tens of micrometers (μm) to tens of nanometers (nm). Because of this large range, PM of health concern is typically categorized in three size fractions, i.e., ≤ 10 μm in diameter (PM_{10} or coarse PM), ≤ 2.5 μm in diameter ($PM_{2.5}$ or fine PM), ≤ 0.1 μm ($PM_{0.1}$ or ultrafine PM). Two main characteristics of airborne particles dictate the toxicity of exposure – size and chemical composition. Size dictates the fate of airborne particles entering the human respiratory system. Depending on their size, airborne particles can get filtered early on by the respiratory cilia or move past them and get deposited in various regions of the respiratory tract. Larger PM are deposited in the extra thoracic region of the respiratory tract, PM_{10} in the tracheobronchial region, $PM_{2.5}$ in the pulmonary region, and $PM_{0.1}$ in the alveolar region and may exchange with blood [207]. While the deposition fractions may vary as a function of the breathing patterns of a person (i.e., cilia in the head airways are bypassed during mouth breathing; deposition fractions may differ during resting, conversation, or exercise), generally, the smallest fractions reach deeper into the lungs.

Laboratory studies have suggested that exposure to $PM_{2.5}$ can trigger a combination of pathophysiological responses inducing hypertension. The risk of hypertension associated with long-term exposure to $PM_{2.5}$ is still sparse and unclear from studies conducted in North America and Europe; however, in epidemiological studies conducted in developing countries with typically higher ambient concentrations of $PM_{2.5}$ have provided evidence of an association between $PM_{2.5}$ and hypertension. Huang et al. [75] found an association between long-term exposure to $PM_{2.5}$ and hypertension in a large-scale prospective study in China comprising of cohorts of 59,456 participants aged ≥ 18 years without hypertension and followed from 2004 to 2015 for ambient

$PM_{2.5}$ and hypertension. Similarly, Prabhakaran et al. [149] found a temporal association between high levels of $PM_{2.5}$, higher systolic BP, and incident hypertension in Indian. A population-based cohort study (comprising of 35,303 participants) was conducted in Ontario, Canada by Chen et al. [35] to determine whether exposure to ambient $PM_{2.5}$ is associated with incident hypertension. Results of the study supported an association between $PM_{2.5}$ and the incidence of hypertension.

8. Conclusions

In today's life, humans are exposed to various environmental pollutants, which might influence blood pressure in a meaningful way. Several pollutants such as heavy metals, diesel exhausts, and PM have been linked to increased blood pressure. A number of studies have been carried out reporting the linkage between the exposure to environmental pollutants and the increased blood pressure, while no substantial data provided unequivocally unraveling the possible mechanisms involved in such phenomena. However, increased incidence of hypertension worldwide points to the role of environmental pollutants as one of the factors and understanding the mechanisms by which pollutants affect blood pressure is required for meaningful interventions.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Notes

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