Mechanisms of lead-induced hypertension and cardiovascular disease

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Lead is a common environmental toxin that is capable of causing numerous acute and chronic illnesses. Historically, the main sources of lead exposure in the United States and many other countries were lead-based paint, leaded gasoline, lead-soldered plumbing fixtures, pipes, and canned foods, contaminated alcoholic beverages, lead-glazed kitchen/dining utensils, and mining and industrial contaminations, as well as occupational exposure. Since the banning of lead-based gasoline, paint, and solder, as well as passage and enforcement of industrial and environmental regulations, exposure to lead has declined significantly in the United States (53). However, heavy ground contamination is a persistent source of lead exposure in the industrial societies. In addition, heavy exposure continues in countries where effective environmental and industrial regulations are nonexistent or not strictly enforced. Recently, reclamation-recycling of discarded computers has emerged as a source of heavy lead exposure among workers involved in this process.

Lead is absorbed via the respiratory and gastrointestinal tracts and, occasionally, through the skin. Lead absorption via the respiratory tract is highly efficient, resulting in an average uptake of 40% of the inhaled lead (22). The dominant route of exposure through the lung in adults is associated with smelting and burning processes, as well as inhalation of lead-containing dust from scraping, burning, or sanding lead paint from surfaces, a well as exhaust from vehicles and planes powered by lead-containing gasoline. The gastrointestinal tract is less efficient, with ~10–15% of the ingested lead being absorbed. In addition, tetraethyl lead, a previously common gasoline additive, is absorbed via the cutaneous route.

After absorption, lead is distributed in the blood, bone, and soft tissues. Approximately 99% of blood lead content is bound to red blood cells; only 1% is present in the plasma and is available for exchange with lead contained in the other tissues. The half-life of lead in the blood is ~30 days in individuals with normal renal function and longer in those with renal insufficiency (35, 62).

Over 95% of the total body lead content resides in the bone, where the half-life of lead is decades long. Consequently, bone serves as the principal repository of this element in the body. Gradual release of lead from the bone serves as a persistent source of toxicity long after cessation of external exposure. The rate of release of lead from the skeleton is increased in conditions associated with heightened bone reabsorption/turn-
over, such as pregnancy, lactation, menopause, osteoporosis, immobilization, and hyperthyroidism. The kidney is the principal route of lead excretion.

It is impossible to accurately measure total body lead burden. For instance, measurement of blood lead concentration primarily reflects recent/current lead exposure. X-ray fluorescent imaging provides a semiquantitative tool for measurement of lead content in individual bones. In addition, measurement of urinary lead excretion after EDTA administration provides a rough estimation of lead burden.

**CARDIOVASCULAR EFFECTS OF LEAD EXPOSURE**

As recently described in an elegant systematic review by Navas-Acien et al. (54), numerous population studies have demonstrated a link between long-term lead exposure and elevated arterial pressure (33, 54, 56, 69, 73, 77). In addition, a limited number of studies have identified a positive association between lead exposure and cardiovascular disorders, including coronary artery disease, stroke, and peripheral arterial disease, in the general populations (47, 51, 54, 55, 68, 78). The causal link between chronic lead exposure and hypertension (HTN) in adult individuals has been irrefutably confirmed by numerous studies in experimental animals (83, 92). In addition, a few in vivo and in vitro studies have examined the effects of lead on the heart and vascular function. This article is intended to provide an in-depth review of the underlying mechanisms by which lead can cause HTN and cardiovascular disease.

**LEAD-INDUCED HTN**

Numerous population studies have demonstrated a link between long-term exposure to lead and increased arterial pressure (33, 54, 56, 69, 73, 77). Several factors have hampered the ability of epidemiological studies to discern the contribution of environmental lead exposure to the overall prevalence of HTN in the general population. In contrast to acute intoxication, environmental exposure to a low level of lead is obscure, insidious, and asymptomatic. Moreover, arterial HTN manifests decades after initial exposure, at which time blood lead level is no longer elevated. The task of isolating the contribution of lead exposure to the pathogenesis of HTN in the general population is further complicated by confounding factors, such as genetic traits, smoking, obesity, alcohol consumption, dietary habits, and the level of physical activity, menopause, and the presence of renal disease. Surveys of the effects of chronic lead exposure in children have been primarily focused on neuropsychological development. Consequently, little is known about the effect of lead exposure in children on the pathogenesis of childhood HTN or future development of HTN.

**Mechanisms of Lead-Induced HTN**

Long-term exposure to low levels of lead causes persistent HTN in genetically normal animals (83, 92). Using experimental animals, cultured endothelial cells, and vascular smooth muscle cells (VSMC), as well as isolated tissues, numerous studies have explored the mechanisms of lead-induced HTN. These studies have identified several candidates, including oxidative stress, impaired nitric oxide (NO) system, inflammation, dysregulation of vasoactive hormones, and alteration of cellular Ca\(^{2+}\) transport and intracellular Ca\(^{2+}\) distribution.

**Effects of lead on production of reactive oxygen species and the NO pathway.** Significant amounts of reactive oxygen species (ROS), such as superoxide (O\(_2^−\)) and H\(_2\)O\(_2\), are normally produced in the course of oxygen metabolism and are safely contained by the antioxidant defense system. However, a variety of pathophysiological conditions result in heightened production of ROS and/or impaired antioxidant capacity, which culminate in oxidative stress. In the presence of oxidative stress, uncontained ROS cause tissue damage and dysfunction by directly attacking and denaturing functional/structural molecules and by activating redox-sensitive transcription factors and signal transduction pathways. Oxidative stress plays a critical part in the pathogenesis of many acute and chronic illnesses, including HTN and cardiovascular disease (3, 32, 46, 71, 91). Lead can promote ROS production and oxidative stress by participating in Fenton- and Haber-Weiss-type reactions. As described below, lead exposure causes oxidative stress in the kidney and cardiovascular tissues in vivo and in endothelial cells and VSMC in vitro. Moreover, animal studies have shown that lead-induced oxidative stress is, at least in part, responsible for the associated HTN.

Khalil-Manesh et al. (43) found that chelation therapy with dimercaptosuccinic acid (DMSA) resulted in rapid amelioration of HTN and increased cGMP in rats with lead-induced HTN before significantly affecting body lead burden. Since DMSA possesses strong antioxidant properties, they proposed that lead exposure must raise arterial pressure by promoting ROS production and ROS-mediated inactivation of endothelium-derived relaxing factor. Accordingly, they attributed the rapid reduction of arterial pressure to attenuation of lead-induced oxidative stress and consequent restoration of endothelium-derived relaxing factor by DMSA.

Subsequently, Gonick et al. (29) showed a significant accumulation of the lipid peroxidation product malondialdehyde, along with a marked increase in the abundance of inducible NO synthase (NOS), in the kidneys of rats with lead-induced HTN. These observations substantiated the presence of oxidative stress in the kidneys of lead-exposed animals.

Ding et al. (17) showed that l-arginine infusion lowers arterial pressure to a much greater extent in lead-exposed rats than in either control animals or DMSA-treated lead-exposed rats. These observations provided indirect evidence for the role of depressed NO availability in lead-induced HTN. The study also suggested that oxidative stress might play a role in the reduced NO availability in this model. Oral administration of DMSA for 2 wk significantly lowered blood pressure and reduced blood lead concentration in rats with lead-induced HTN. To determine whether amelioration of HTN is caused by the reduction of lead burden or attenuation of oxidative stress by DMSA, we conducted a study in which rats with lead-induced HTN were treated with a potent, nonchelating antioxidant agent, lazaroid (88). We showed significant HTN and oxidative stress (increased lipid peroxidation) and depressed NO availability (low urinary NO\(_2^+\) + NO\(_3^−\) excretion) in the untreated lead-exposed rats. Antioxidant therapy with lazaroid significantly improved oxidative stress, NO availability, and HTN without changing blood lead level. Together, these observations provided compelling evidence for the role of oxidative stress in the pathogenesis of HTN and the associated reduction of NO availability in lead-exposed animals. In confirmation of these findings, Dursun et al. (19) found a signifi-
cantly reduced NO availability (urinary NO_2 + NO_3 excretion) in rats treated daily with lead acetate (8 mg/kg ip) for 2 wk. The authors further showed that the rise in arterial pressure in this model was accompanied by a significant reduction of renal blood flow, denoting a rise in renal vascular resistance similar to that seen in a subgroup of rats treated with the NOS inhibitor nitro-L-arginine methyl ester. In an attempt to further explore the underlying mechanism of lead-induced reduction of NO availability, we examined expression of NOS isoforms in this model (85). We found that depressed NO availability is paradoxically associated with a marked increase in endothelial NOS (eNOS) and inducible NOS abundance in the kidney and cardiovascular tissues in lead-treated animals. To determine whether reduced NO production, despite increased NO abundance, is due to inhibition of the enzyme by lead, using normal tissue lysate, we examined NOS activity in the presence and absence of lead in vitro. These experiments showed no significant change in NOS activity in the presence of lead. It is of note that antioxidant therapy with high doses of vitamins E and C lowered NOS abundance and, paradoxically, increased NO availability in rats with lead-induced HTN (85). These findings were confirmed by a subsequent study (86) that demonstrated reduced NO availability, despite marked upregulation of NOS isoforms, in the kidney, brain, aorta, and heart of lead-exposed rats and their restoration to normal levels after treatment with the cell-permeable SOD mimic tempol (15 mg·kg⁻¹·day⁻¹ ip for 2 wk). These observations suggest that depressed NO availability (ROS-mediated NO inactivation) promotes compensatory upregulation of NOS isoforms in this model. This supposition has been confirmed by several other studies that demonstrated the presence of negative-feedback regulation of eNOS by NO in cultured endothelial cells (87, 93, 97). The ability of lead to provoke oxidative stress and compensatory upregulation of NOS in intact animals (85, 86) was replicated in cultured human endothelial cells that were incubated in medium containing lead acetate compared with cells incubated in control medium containing sodium acetate (84). As seen in intact animals, coincubation with tempol abrogated compensatory upregulation of eNOS by lead in cultured endothelial cells. These in vitro experiments illustrated the direct negative impact of lead on the endothelium, independently of the humoral, hemodynamic, and other factors that are operative in intact animals or humans.

Together, the findings cited above indicate that the lead-induced reduction in availability of biologically active NO is due to oxidative stress, rather than diminished NO production capacity. Oxidative stress can limit NO availability by several mechanisms, including avid inactivation/sequestration of NO by ROS, depletion of the NOS cofactor tetrahydrobiopterin, and uncoupling of eNOS (23). In an attempt to explore NO interaction with ROS in lead-exposed animals, using tissues harvested from untreated and antioxidant-treated (vitamin E + vitamin C) rats with lead-induced HTN and normal control animals, we probed kidney, brain, and cardiovascular tissues for the presence of immunodetectable nitrotyrosine (89). Nitrotyrosine was used as a marker of NO oxidation by ROS (NO + O_2•⁻ → ONOO⁻; ONOO⁻ + tyrosine → nitrotyrosine). We found an overabundance of nitrotyrosine in all tested tissues, as well as in the plasma of the untreated lead-exposed rats. Antioxidant therapy lowered nitrotyrosine accumulation, reduced arterial pressure, and raised NO availability in the lead-exposed animals. In contrast, antioxidant therapy had no effect in the normal control rats. These findings provided convincing evidence that, by provoking oxidative stress, lead causes functional NO deficiency, which is, in part, due to NO inactivation by ROS. NO deficiency, in turn, contributes to development and maintenance of HTN and cardiovascular disease. In addition to NO deficiency, formation of peroxynitrite (ONOO⁻), a highly cytotoxic reactive nitrogen species, can contribute to the adverse cardiovascular, renal, and neurological consequences of lead exposure. In an attempt to identify the source of ROS in lead-exposed animals, in a subsequent study, we (90) examined expression of NAD(P)H oxidase (a well-known source of ROS in immune cells and renal, cardiovascular, neuronal, and other tissues), as well as those of the main antioxidant enzymes, namely, Cu-Zn SOD, Mn SOD, catalase, and glutathione peroxidase, in rats with lead-induced HTN. The study revealed significant upregulation of the gp91phox subunit of NAD(P)H oxidase in the brain and, to a lesser extent, in the left ventricle and renal cortex of lead-exposed rats. In addition, rats with lead-induced HTN showed significant compensatory upregulation of Cu-Zn SOD in the kidney and brain and of Mn SOD in the heart but no change in catalase or glutathione peroxidase. Similar findings were subsequently reported by Farmand et al. (20), who showed a significant increase in Cu-Zn SOD activity, with no change in catalase or glutathione peroxidase activity, in the aorta of rats with lead-induced HTN. Since catalase and glutathione peroxidase are responsible for the reduction of H_2O_2 and liperoxides, the absence of an appropriate rise in their tissue levels can contribute to the severity of lead-induced oxidative stress.

Further evidence for participation of oxidative stress in the pathogenesis of HTN in this model comes from the experiments that demonstrated normalization of arterial pressure with infusion of the superoxide scavenger drug tempol in lead-exposed animals (90). As mentioned earlier, despite severe oxidative stress, which should raise catalase and glutathione peroxidase expression, tissue abundance of these enzymes is unchanged in the lead-exposed animals. Relative deficiency of these enzymes, which are responsible for conversion of H_2O_2 to water (H_2O_2 → H_2O + O_2), can result in accumulation of H_2O_2, which serves as a cellular growth signal and a potent nuclear factor-κB (NF-κB) activator, events that can contribute to inflammation and cardiovascular remodeling. In addition, H_2O_2 is the substrate for production of the hydroxyl radical (·OH), which is a highly reactive free radical and, as such, can cause oxidative injury. In an in vitro study, Ni et al. (57) showed that addition of lead acetate to the culture medium results in a transient rise in O_2•⁻ production followed by a sustained increase in H_2O_2 generation by cultured human coronary endothelial cells and VSMC. This was accompanied by upregulation of NAD(P)H oxidase and SOD. However, catalase and glutathione peroxidase levels were reduced or unchanged in the lead-treated cells. Thus the findings of these in vitro experiments confirmed those of the in vivo studies in lead-exposed rats (20, 90) and validated the anticipated accumulation of H_2O_2.

H_2O_2 is the substrate for the Fenton and Haber-Weiss reactions, which result in formation of the highly toxic ·OH (H_2O_2 + e⁻ → ·OH + H_2O). Thus accumulation of H_2O_2 in animals with lead-induced HTN can facilitate ·OH production...
and, thereby, promote oxidative stress and tissue damage. This supposition was confirmed in a series of studies by Ding et al. (16) that showed increased ·OH production in rats with lead-induced HTN. Intravenous infusion of dimethylthiourea (DMTU), a reputed ·OH scavenger, reversed oxidative stress, lowered arterial pressure, and reduced ·OH production in the lead-exposed animals. Increased ·OH generation in lead-treated animals was confirmed in lead-treated cultured endothelial cells (15).

A number of other investigations have demonstrated the critical role of oxidative stress in the pathogenesis of lead-induced endothelial dysfunction and HTN in experimental animals. Attri et al. (1) showed that Wistar-Kyoto rats treated with lead for up to 12 wk exhibit significant HTN, which is accompanied by oxidative stress (elevated plasma lipid peroxidation and DNA oxidation and diminished ferric-reducing antioxidant power) and depressed NO availability (low plasma NO2 + NO3), as well as electrophoretic evidence of DNA damage. These abnormalities were ameliorated by concomitant antioxidant therapy with a high dose of ascorbic acid. Malvezzi et al. (48) found partial amelioration of HTN with administration of DMSA or L-arginine alone and a much greater response with DMSA + L-arginine in lead-exposed rats.

As described above, lead-induced HTN is, at least in part, due to oxidative stress-mediated limitation of NO availability. Most biological actions of NO are mediated by activation of soluble guanylate cyclase (sGC), which results in production of the second messenger cGMP from GTP. cGMP, in turn, promotes vasorelaxation by lowering cytosolic Ca2⁺ concentration ([Ca2⁺]i) in VSMC via sequestration of Ca2⁺ in sarcoplasmic reticulum and inhibition of Ca2⁺ entry. In an earlier study, Khalil-Manesh et al. (42) reported a significant reduction in plasma concentration and urinary excretion of cGMP in rats with lead-induced HTN. These observations prompted a number of studies to evaluate the effect of lead on sGC expression and cGMP production in vascular tissues obtained from rats with lead-induced HTN or in normal vascular tissues incubated in lead-containing medium. Marques et al. (50) showed that, despite upregulation of eNOS, the vasorelaxation response to acetylcholine was markedly reduced in the aorta of rats with lead-induced HTN. They further found significant attenuation of vasodilatory response to the NO donor sodium nitroprusside, diminished sGC abundance, and reduced cGMP production in the aorta of lead-exposed animals. These abnormalities were not seen in a subgroup of rats treated with lead + ascorbic acid. Thus the study identified diminished sGC as an additional mechanism by which lead-induced oxidative stress causes endothelial dysfunction and HTN. Downregulation of the sGC in the aorta by lead exposure shown in the above-mentioned study was recently confirmed by Farmand et al. (20) in Sprague-Dawley rats. In an in vitro study, Courtois et al. (14) showed that a 24-h incubation of normal rat aorta in lead-containing medium causes a concentration-dependent downregulation of sGC (ß-subunit) expression, elevation of O2⁻ production, and upregulation of cyclooxygenase-2 (COX-2) expression. Addition of ascorbic acid lowered O2⁻ production and COX-2 expression and partially restored sGC expression. Similarly, cotreatment with the COX-2 inhibitor rofecoxib or the protein kinase A inhibitor H-89 partially mitigated the effect of lead on sGC expression but failed to lower O2⁻ production in the aorta. They concluded that lead-induced downregulation of vascular sGC is mediated by oxidative stress and upregulation of COX-2.

These above-described studies provide compelling evidence that lead exposure causes oxidative stress and profound alterations of the NO pathway (Fig. 1). As illustrated in Fig. 2, oxidative stress and altered NO metabolism can trigger a cascade of events that culminate in development and progression of HTN and cardiovascular disease in the lead-exposed animals and humans.

### Lead and protein kinase C activation.

Protein kinase C (PKC) isoforms are members of a serine-threonine kinase family that are involved in many cellular functions, such as cell growth, vascular contraction, blood flow, and permeability. Several studies have shown that lead exposure raises PKC activity. Hwang et al. (36) found elevated erythrocyte PKC activity in a group of lead-exposed Korean workers, and Markovac and Goldstein (49) reported increased PKC activity in the microvessels of rat brain after exposure to lead at micromolar concentrations. In an in vitro study, Watts et al. (94) demonstrated that lead acetate (10⁻¹⁰⁻¹⁰⁻³ M) causes contraction in intact and endothelium-denuded rabbit mesenteric artery preparations. They found that lead-induced vasoconstriction was augmented by a PKC agonist, reduced by a PKC inhibitor, and attenuated, but not fully abolished, by the Ca²⁺ channel blocker verapamil. They concluded that lead-induced vasoconstriction is, in part, mediated by PKC activation. However, in contrast to rabbit mesenteric artery, lead-induced contraction in the rat aortic rings is not attenuated by PKC inhibition (81). Therefore, the role of PKC activation in lead-induced vasoconstriction seems to be vessel and species specific. Although lead can raise PKC activity in VSMC in some vascular beds, at high concentrations lead can lower PKC activity in a number of other cells and tissues such as mouse macrophages and rat brain cortex (49). On the basis of the observations cited above, PKC activation in VSMC may play a part in the pathogenesis of HTN caused by lead exposure.

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**Fig. 1.** By promoting oxidative stress, lead exposure lowers nitric oxide (NO) production, causes NO inactivation, downregulates soluble guanylate cyclase, and, hence, reduces cGMP production. The latter, in turn, increases cytosolic Ca²⁺ concentration ([Ca2⁺]i) in vascular smooth muscle cells and, thereby, heightens systemic vascular resistance and raises arterial pressure.
Lead and NF-κB activation, inflammation, and apoptosis.

As mentioned above, lead causes oxidative stress in animals and in cultured endothelial cells and VSMC. Oxidative stress can promote inflammation, fibrosis, and apoptosis by activating NF-κB, which is the general transcription factor for numerous proinflammatory cytokines, chemokines, and adhesion molecules. Numerous studies have demonstrated the presence of tubulointerstitial infiltration of T cells and macrophages in the kidneys of experimental animals with various forms of hereditary and acquired HTN. The associated renal tubulointerstitial inflammation plays a major role in the pathogenesis of HTN and is linked to NF-κB activation (67, 91). Pharmacological inhibition of NF-κB activation has been shown to attenuate renal interstitial inflammation and lower arterial pressure in hypertensive animals. Several studies have demonstrated that lead exposure results in NF-κB activation. For instance, Ramesh et al. (63) found activations of NF-κB and capsases in the brain of rats exposed to low levels of lead (50 ppm in drinking water) for 90 days. More recently, Rodriguez-Iturbe et al. (66) reported marked 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 lead-induced HTN. In an attempt to determine the contribution of renal tubulointerstitial inflammation to lead-induced HTN, Bravo et al. (2) treated subgroups of lead-exposed rats with the immunosuppressive drug mycophenolate mofetil (MMF) or placebo. MMF prevented HTN, oxidative stress, and NF-κB activation, attenuated tubulointerstitial lymphocyte and macrophage infiltration, and reduced the number of angiotensin II-expressing cells in the lead-exposed animals. These observations provide compelling evidence for the role of renal interstitial inflammation in lead-induced HTN.

Effect of Lead Exposure on Vasoactive and Volume Regulatory Hormones

Lead exposure has been shown to alter production and action of many hormones involved in regulation of vascular tone, body fluid volume, arterial pressure, and renal-cardiovascular function and structure (Table 1).

Impact of lead on the adrenergic system. The adrenergic system plays a major part in regulation of arterial pressure by direct and indirect modulation of renal and cardiac functions and systemic vascular resistance. The adrenergic system has been the focus of several investigations into the pathogenesis of lead-induced HTN and cardiovascular disease. In a study of lead-exposed workers, Chang et al. (10) found high plasma norepinephrine but normal plasma dopamine and epinephrine levels, pointing to heightened sympathetic nervous system activity. In another study, Chang et al. (11) showed that exposure to lead (0.5% lead acetate in drinking water) for 2 mo significantly increased arterial pressure and plasma norepinephrine without changing plasma epinephrine concentration in Wistar rats. They further found significant reductions of β-adrenergic receptor density and isoproterenol (β-agonist)-stimulated cAMP production in the aorta of lead-exposed animals. The findings of the latter study were subsequently confirmed by Tsao et al. (79), who reported significant elevation of plasma norepinephrine, marked reduction of β-receptor density, and diminished basal and isoproterenol-stimulated cAMP production in the aorta and heart of lead-exposed Wistar rats. On the contrary, β-adrenergic receptor density, as well as basal and β-agonist-stimulated cAMP generation, was significantly elevated in the kidney of lead-exposed animals. In a study of rats with lead-induced HTN, Carmignani et al. (7) observed significant elevations of plasma catecholamines and cardiac contractility (dP/dt), along with diminished carotid blood flow. In an attempt to explore the effect of lead on the sympathetic nervous system activity, Lai et al. (45) evaluated the rapid response to injection of lead chloride in vivo and addition of lead chloride to the thoracic spinal cord slices in vitro in the rat. Intrathecal injection of lead chloride resulted in a significant increase in heart rate and arterial pressure, which could be prevented by ganglionic blockade using hexamethonium. The in vitro experiments showed a significant increase in excitatory and a significant decrease in inhibitory postsynaptic potentials on addition of lead to the bathing medium and their reversal with saline washout. In a study of rats with lead-

![Fig. 2. Lead exposure results in oxidative stress and inflammation, which in turn, lower bioavailability of NO and promote hypertension, endothelial injury/dysfunction, hypertension, and cardiovascular disease. ROS, reactive oxygen species; NF-κB, nuclear factor-κB.](http://ajpheart.physiology.org/)
induced HTN, Chang et al. (12) found a gradual reduction of lead contents of the kidney, heart, aorta, and blood toward control levels within 7 mo after cessation of exposure. The reduction of the lead contents of these tissues during the observation period was associated with parallel declines in plasma norepinephrine, renal tissue β-receptor density, and arterial pressure, as well as parallel increases in the aorta and heart β-receptor densities. However, although HTN and β-receptor abnormalities significantly improved with the decline in blood and soft tissue lead contents, they were not completely normalized. This is most likely due to persistent elevation of bone lead, which had not been measured in the study animals. Taken together, the studies cited above provide convincing evidence that lead exposure results in profound dysregulation of the sympathetic nervous system activity, which supports development and maintenance of HTN and cardiovascular disease. The changes in the sympathetic system are inextricably linked to the maintenance of HTN. The reason for this linkage is that the reduction of vascular tissue β-adrenergic receptor, despite elevated plasma norepinephrine, intensifies α-receptor-mediated vasoconstriction, while elevation of kidney tissue β-receptor expression activates the renin-angiotensin-aldosterone system (RAAS) by promoting renin release, events that support development and maintenance of HTN. Central sympathetic outflow is inhibited by NO and stimulated by NO deficiency (4). As noted above, by promoting oxidative stress, lead exposure limits availability of NO in the kidney, cardiovascular tissues, and brain. The reduction of NO bioavailability can, in turn, contribute to heightened sympathetic activity in lead-exposed animals employed in the above-described studies.

Impact of lead exposure on endothelin. Endothelins are powerful vasoconstrictor peptides that are primarily synthesized and secreted by endothelial cells but are also produced by several other cell types. Increased production or enhanced sensitivity to the biological actions of endothelin can raise arterial pressure. In a study of rats exposed to a low level of lead (lead acetate, 100 ppm in drinking water) for 1–12 mo, Khalil-Manesh et al. (42) found a significant rise in arterial pressure and a marked increase in plasma endothelin-3 concentration. In contrast, rats exposed to a high dose of lead (5,000 ppm in the drinking water) for the same period exhibited nephropathy but no rise in arterial pressure or plasma endothelin. Elevation of plasma concentration and urinary excretion of endothelin in rats with lead-induced HTN was confirmed in a separate study by Khalil-Manesh et al. (43) and Gonick et al. (29). In an in vitro study, Molero et al. (52) found indirect evidence that lead can heighten endothelin activity in the vascular tissue. They showed that incubation in the lead-containing medium results in downregulation of sGC and cGMP production in the isolated normal rat arteries. They further found that coincubation with an endothelin type A receptor antagonist partially reverses lead-induced downregulation of sGC and cGMP production. These observations suggest that the negative effect of lead on cGMP production is, in part, mediated by its ability to raise endothelin activity in the vascular tissue.

Thus exposure to low levels of lead appears to raise endothelin production and/or activity, which may directly or indirectly participate in the pathogenesis of lead-induced HTN and cardiovascular disease. Further studies are needed to explore the effects of lead on production of endothelin isotypes and expression of endothelin receptor types and their signaling pathways in the kidney and cardiovascular tissues. In addition, it would be of interest to explore the effect of endothelin receptor blockers in animal models of lead-induced HTN.

Impact of lead on the RAAS. The effects of lead exposure on the circulating RAAS in experimental animals appears to vary depending on the dose and duration of lead exposure and the age at which exposure is initiated, as well as the presence or absence of nephropathy. In a meta-analysis of the studies published between the late 1970s and 1990s, Vander (82) found elevated plasma renin activity and kidney tissue renin content in young rats after several weeks of lead exposure sufficient to achieve blood lead concentrations in the range 30–40 μg/dl. Similar phenomena were observed in rats exposed to lead in utero and for 1 mo after birth. However, plasma renin activity and renal renin contents were unchanged or even depressed in older rats in which lead exposure had begun in the prenatal period.

In a study of rats exposed to lead (60 ppm lead acetate in water) for 10 mo beginning at an early age (weanling rats), Carmignani et al. (6) found a significant increase in plasma angiotensin-converting enzyme (ACE) activity, as well as plasma kininase I, kininase II, and kallikrein activities. In a subsequent study of young adult rats (200 g body wt) exposed to lead (100 ppm lead acetate) for 2–8 wk, Sharifi et al. (72) found a steady rise in ACE activity in the plasma, aorta, kidney, and heart, peaking at 2–4 wk. 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. They concluded that the rise in ACE activity is involved in the induction of HTN but may not be required for maintenance of lead-associated HTN. Recent studies by Rodriguez-Itrurbe et al. (66) and Bravo et al. (2) revealed large numbers of angiotensin II-positive cells in the tubulo-interstitial region of the kidney in adult rats exposed to lead-acetate (100 ppm in water) for 3 mo. Many of the angiotensin II-positive cells were infiltrating macrophages in this region of the kidney. This phenomenon points to the link between inflammation, intrarenal angiotensin system activation, and HTN in lead-exposed animals. A similar linkage has been found in other forms of HTN (67, 91). This supposition is supported by the effectiveness of the immunosuppressive drug MMF in alleviating the tubulointerstitial inflammation, reducing the number of angiotensin II-positive cells, and attenuating HTN in the lead-exposed rats (2).

Thus lead exposure results in heightened intrarenal angiotensin II and early activation of circulating RAAS, events that participate in the pathogenesis of the associated HTN. These findings may be of relevance in selection of antihypertensive agents used in treatment of HTN in lead-exposed individuals. As noted above, lead-induced HTN is associated with upregulation of the endothelin system. Since endothelin and angiotensin II share many overlapping actions, they can individualize or collectively participate in the cardiovascular effects of chronic lead exposure.

Impact of lead on prostaglandins. Lead has been shown to lower production of vasodilatory and raise production of vasoconstrictive prostaglandins in humans. Cardenas et al. (5) found increased urinary excretion of the thromboxane metabolite TXB2 and reduced excretion of the vasodilatory prosta-
glandin metabolite 6-keto-PGF$_1$ in a group of lead workers with elevated blood lead concentration compared with control workers. These observations were subsequently confirmed by Hotter et al. (34), who found increased urinary TXB$_2$ excretion in a separate group of lead-exposed workers. In contrast, Gonick et al. (30) failed to find a difference in urinary excretion of these metabolites in rats with lead-induced HTN.

Release of arachidonic acid is a crucial step in the biosynthesis of prostaglandins. In this context, Dorman and Freeman (18) demonstrated that addition of lead results in activation of phospholipase A$_2$ and consequent release of arachidonic acid by VSMC in vitro. In addition, they found that, at low concentrations, lead augments angiotensin II-induced VSMC proliferation. However, at high concentrations, lead diminished the viability of the quiescent cells and reduced DNA syntheses.

Thus, via activation of phospholipase A$_2$, lead promotes release of arachidonic acid, which is required for prostaglandin synthesis. In addition, lead seems to alter the balance between vasoconstrictive and vasodilatory prostaglandins in a manner that supports development and progression of cardiovascular disease and HTN in humans.

Impact of lead on atrial natriuretic peptide. Atrial natriuretic peptide (ANP) is synthesized and secreted by the cardiac myocytes in response to distension of cardiac chambers. Thus plasma ANP rises with volume expansion and falls with volume contraction. ANP serves as a vasodilator and a natriuretic agent and, as such, plays a role in regulation of arterial pressure by modulating systemic vascular resistance and blood volume. The available data on the effect of lead on production, action, and metabolism of ANP are limited. Giridhar and Isom (27) studied the effect of lead exposure on plasma ANP in rats treated with lead acetate (0.0–1.0 mg/kg ip twice weekly) for 30 days. The lead-exposed animals exhibited fluid retention, which was paradoxically accompanied by a dose-dependent decline in plasma ANP level. On the basis of these observations, the authors speculated that lead may alter hormonal regulation of the cardiovascular system, which may reflect its cardiovascular toxicity.

Effects of Lead on Vascular Tone and Reactivity and Ca$^{2+}$ Signaling

Several studies have addressed the effects of lead on vascular tone, vascular response to vasoactive compounds, and its interaction with Ca$^{2+}$.

Direct effect of lead on vascular tone. Several studies have explored the direct and indirect effects of lead on vascular contractility in vitro. The results appear to vary depending on the type of the vessel, as well as the animal species, used in the experiments. For instance, lead acetate was shown by Watts et al. (94) to cause a concentration-dependent vasoconstriction in isolated rabbit mesenteric artery in vitro. The lead-induced vasoconstriction shown in their study was, in part, mediated by PKC activation. Similarly, Valencia et al. (81) found a concentration-dependent contraction in response to lead acetate (0.1–3.1 mM) in intact and endothelium-denuded rings prepared from Wistar rat thoracic aorta. The lead-induced contraction in the latter study was preserved in Ca$^{2+}$-free medium and was unaffected by $\alpha_1$-blockade (prazosin), PKC inhibition (calphostin), or L-type Ca$^{2+}$ channel blockade (verapamil). In contrast, lead-induced contraction could be inhibited by lanthanum, which is a general Ca$^{2+}$ channel blocker. The findings of this study suggest that 1) lead can cause a direct endothelium-independent vascular smooth muscle contraction and 2) the effect of lead is independent of Ca$^{2+}$ and, instead, may depend on lead entry into the cell via a lanthanum-blockable channel. In contrast to the latter studies, Shkolnikov and Gonick (74) found no contraction in response to lead acetate in the rat aorta rings. Thus the rapid action of lead on vascular reactivity in vitro seems to vary depending on the type of the vessel, the lead concentration, and the animal species.

Effect of lead exposure on vascular response to vasoactive agonists. A number of studies have attempted to discern whether lead exposure can modify vascular reactivity to various agonists. In a study of Sprague-Dawley rats treated with lead acetate (100 ppm) for 12 wk, Purdy et al. (61) found no significant difference in vasoconstrictive response to nor epinephrine and phenylephrine or vasodilatory response to acetylcholine or nitroprusside in the aorta rings obtained from lead-treated and normal control rats. In contrast, Marques et al. (50), using Wistar rats treated with lead acetate (5 ppm in the drinking water) for 4 wk, showed a significant reduction of vasodilatory response to acetylcholine and nitroprusside. The Wistar rats used in the latter study (50) were treated with a lower dose of lead for a shorter period, whereas the Sprague-Dawley rats used in the former study (61) were treated with a higher dose of lead for a much longer period. These differences may account for the apparent discrepancy in the results of the two studies. In addition, the effect of lead exposure on vascular reactivity to different agonists may vary among different vessels. In a study of rats exposed to lead acetate for 3 mo, Oishi et al. (58) found a significant reduction of endothelium-dependent vasorelaxation of the mesenteric artery response to acetylcholine in the presence of the NOS inhibitor nitro-L-arginine methyl ester, suggesting that chronic lead exposure may impair endothelium-dependent hyperpolarization in this tissue. In contrast, this effect was not seen in the aorta of the same rats.

It thus appears that the effect of lead exposure on vascular reactivity to different agonists may vary depending on the extent and duration of exposure, the nature of the vessel, and, perhaps, the animal species.

Interaction of lead with Ca$^{2+}$ in vascular tissue. Basal [Ca$^{2+}$], its rise in response to vasoconstrictor agonists, and its fall in response to vasodilator agonists are intimately involved in regulation of vascular tone and arterial pressure. For this reason, several studies have focused on the interaction of lead with cellular Ca$^{2+}$ and Ca$^{2+}$-dependent signaling pathways (21, 28, 59, 94, 95). These investigations revealed that lead can potentially compete with Ca$^{2+}$ for the transport systems, such as channels and pumps involved in physiological movements of ions, particularly Ca$^{2+}$, into and out of the cell (75, 76). In addition, lead has been shown to modify intracellular distribution of Ca$^{2+}$ between endoplasmic reticulum, mitochondria, and cytoplasm, which normally regulates [Ca$^{2+}$] (75, 76). Moreover, by interacting with calmodulin, PKC, and Ca$^{2+}$- dependent potassium channels, lead can serve as a substitute for Ca$^{2+}$ in Ca$^{2+}$-dependent signaling pathways (9, 31, 65, 75, 76, 94). Consequently, interference of lead with these and other Ca$^{2+}$-dependent mechanisms may contribute to HTN and vascular remodeling by altering vascular resistance and cellular growth. In a study of lead-exposed rats, Piccinini et al. (59) and
Favalli et al. (21) found increased tail artery Ca\(^{2+}\) content, which they attributed to potential interference by lead with cellular Ca\(^{2+}\) extrusion mechanisms. Watts et al. (94) showed that lead-induced vasoconstriction in intact and endothelium-denuded rabbit mesenteric artery preparations can be substantially attenuated by blockade of PKC or voltage-gated Ca\(^{2+}\) channels. They suggested that, in the rabbit, lead causes mesenteric artery vasoconstriction via Ca\(^{2+}\)-dependent activation of PKC. However, using rat aorta rings, Valencia et al. (81) observed a vasoconstrictive response to lead acetate in Ca\(^{2+}\)-free and Ca\(^{2+}\)-containing media, as well as in the absence or presence of the PKC inhibitor calphostin or the L-type Ca\(^{2+}\) channel blocker verapamil. Furthermore, they showed that preincubation of rings in EGTA, which depleted intracellular Ca\(^{2+}\) stores, diminished, but did not abolish, lead-induced vasoconstriction in rat aortic rings. Instead, lead-induced vasoconstriction was prevented by lanthanum (a general blocker of Ca\(^{2+}\) channels) in Ca\(^{2+}\)-replete and Ca\(^{2+}\)-free media. The authors concluded that lead can enter VSMC via a non-voltage-gated Ca\(^{2+}\) channel and elicit a PKC-independent contractile response in the rat aorta by mimicking the action of Ca\(^{2+}\).

Thus lead seems to adversely affect major Ca\(^{2+}\) and Ca\(^{2+}\)-dependent mechanisms in the vascular tissue. Lead’s interference with normal Ca\(^{2+}\)-dependent pathways appears to be species and vessel specific.

**Effect of Lead on Vascular Cell and Structure**

Lead exposure has been found to adversely affect endothelial cells and VSMC. These adverse effects of lead can compound the impact of the associated HTN in promoting cardiovascular disease (Table 2).

**Effects of lead on endothelial lining.** The endothelium plays a central role in regulation of vascular function, macromolecular permeability, tissue perfusion, blood fluidity, and numerous other vital functions. Endothelial damage or dysfunction results in atherosclerosis, thrombosis, and tissue injury. Long-term exposure to lead causes HTN and accelerates atherosclerosis in experimental animals. In view of the critical role of endothelial injury/dysfunction in the pathogenesis of atherosclerosis and cardiovascular disease, numerous studies have examined the effect of lead on cultured endothelial cells. Kaji et al. (39) showed that incubation of cultured bovine aortic endothelial cells in medium containing lead nitrate (≤50 μM) for 24 h causes mild deendothelialization of the established endothelial monolayer. In addition, they demonstrated that, at 10 μM, lead significantly intensified cadmium-induced endothelial injury. These observations illustrate lead’s ability to damage the endothelium.

**Effects of lead on endothelial growth and repair process.** Endothelial cell proliferation is an essential step for restoration of injured endothelium and prevention of vascular thrombosis, smooth muscle cell migration/proliferation, and plaque formation. Kaji et al. (39) showed that lead (0.5–5 μM lead nitrate) can significantly inhibit DNA synthesis and proliferation in cultured bovine aortic endothelial cells. In addition, they found that lead can significantly inhibit basic fibroblast growth factor (bFGF)- and acidic fibroblast growth factor-stimulated endothelial cell proliferation (37). If this is true, lead-induced inhibition of endothelial cell proliferation can impede the repair process following endothelial injury. Fujiwara et al. (26) showed that repair of the wounded endothelial monolayer is inhibited by 5–10 μM lead. They further found that lead can severely retard zinc-stimulated cell proliferation and repopulation of the denuded sections of the endothelial monolayer. These findings illustrate lead’s ability to interfere with the endothelial repair processes.

**Effects of lead on angiogenesis.** Angiogenesis is essential for many vital physiological functions, including growth, development, wound repair, and the menstrual cycle. In addition, angiogenesis is involved in numerous pathological processes, such as diabetic retinopathy and tumor growth. Endothelial cell proliferation is an essential step in the angiogenic process. Given its demonstrated ability to inhibit endothelial cell growth, it is reasonable to assume that lead may impair angiogenesis. A number of studies have confirmed this assumption by testing the effect of lead on the in vitro angiogenesis assay. This assay involves endothelial cell culture on a Matrigel matrix (containing a laminin-rich basement membrane product) on which endothelial cells form tubular structures, mimicking in vivo angiogenesis. Using this assay system, Ueda et al. (80) and Kishimoto et al. (44) demonstrated that lead acetate (1–100 μM) inhibits tube formation by cultured human umbilical vein endothelial cells in a concentration- and time-dependent manner. These findings reveal inhibitory effects of lead on angiogenesis.

**Mechanism of lead-induced inhibition of endothelial cell growth and angiogenesis.** Angiogenesis and repair of the damaged endothelium depend on migration and proliferation of endothelial cells. bFGF serves as a potent mitogen for endothelial cells and several other cell types. It is synthesized and stored by endothelial cells and released after cell injury or death. Once released, bFGF initiates the repair process by promoting migration and proliferation of the adjacent endothelial cell. Binding of bFGF to its receptor on the endothelial cell is facilitated by heparan sulfate proteoglycans (HSPGs). HSPGs are normally produced by endothelial cells and secreted for attachment to the cell surface and incorporation into the extracellular matrix. Lead has been shown to reduce binding of bFGF to HSPG on the endothelial cell surface without altering the biosynthesis or intracellular content of this growth factor (24). In addition, lead has been shown to lower production of glycosaminoglycans (GAGs) in the growing endothelial cells (40). These findings indicate that lead-induced inhibition of bFGF-mediated endothelial cell proliferation reported by

**Table 2. Effects of lead exposure on EC and VSMC in vitro**

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<th>Effects of Lead Exposure</th>
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<tr>
<td><strong>EC</strong></td>
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<tr>
<td>Mild deendothelialization of cultured EC monolayer</td>
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<tr>
<td>Intensification of cadmium-induced endothelial injury</td>
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<tr>
<td>Inhibition of cultured EC DNA synthesis, growth, and proliferation</td>
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<tr>
<td>Inhibition of zinc-stimulated EC proliferation</td>
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<td>Inhibition of cultured EC monolayer wound repair</td>
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<tr>
<td>Inhibition of in vitro angiogenic activity in cultured EC and aorta ring</td>
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<tr>
<td>Suppression of HSPG synthesis</td>
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<tr>
<td><strong>VSMC</strong></td>
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<tr>
<td>Stimulation of VSMC growth and proliferation at low lead concentrations</td>
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<td>VSMC transformation from spindle-shaped to cobblestone phenotype</td>
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<td>VSMC growth arrest at high lead concentrations</td>
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EC, endothelial cell; VSMC, vascular smooth muscle cell; HSPG, heparan sulfate proteoglycan.
Kaji et al. (37) is largely due to impaired production of HSPG. This supposition is further supported by the observation that addition of heparin can restore bFGF-mediated DNA synthesis in lead-treated endothelial cells (40). Lead significantly lowers GAG production, not only in the growing endothelial cells (40), but also in the confluent (quiescent) endothelial cells (38). These studies showed that lead reduced production of heparan sulfate more than other GAGs and lowered cell surface-associated GAGs more than newly synthesized GAG found in the incubation medium. GAGs combine with a series of specific core proteins to form anionic macromolecular complexes, which are known as proteoglycans and are widely distributed in the extracellular matrix. Endothelial cells produce two classes of HSPGs, the high- and low-molecular-weight HSPGs. Perlecan, a high-molecular-weight HSPG, is a component of basement membrane. Syndecan, glypicans, ruddocan, and fibroglycan, low-molecular-weight HSPGs, are primarily associated with the cell surface. Proteoglycans play a vital role in vascular function and structure. By expressing a negative electrostatic charge, these molecules deter extravasations of negatively charged plasma proteins. By interacting with anti-thrombin III and tissue plasminogen activator (t-PA), they serve as major endogenous anticoagulants. By facilitating bFGF binding to its receptor on the endothelial cells, perlecan contributes to endothelial growth and repair processes. In addition, these molecules tend to inhibit VSMC migration and proliferation and, hence, plaque formation. HSPGs serve as the anchor for binding lipoprotein lipase and VLDL receptor to the endothelial surface. This process is essential for clearance of VLDL and chylomicrons and, as such, has major implications for energy metabolism and protection against cardiovascular disease.

In the in vitro studies, confluent (quiescent) endothelial cells are used as a model of intact endothelium, whereas growing cells are used to mimic the endothelium’s response to injury in vivo. Kaji et al. (38) showed that addition of 10 μM lead chloride significantly lowers HSPG production in confluent (quiescent) bovine aorta endothelial cells by inhibiting incorporation of glycosamine and sulfate into HSPG. The inhibitory effect of lead was more severe on low- than on high-molecular-weight HSPGs. Although lead did not change the length of heparan sulfate chains, it slightly increased the HSPG core proteins, thus excluding reduced core protein synthesis as a cause of diminished HSPGs in the lead-treated confluent endothelial cells. Fujiwara and Kaji (24) subsequently examined the effect of lead nitrate on production of high- and low-molecular-weight HSPGs in growing bovine aortic endothelial cells. They found that, in contrast to quiescent cells, lead exposure caused a significant reduction of high-molecular-weight HSPGs, but no change in production of low-molecular-weight (~50,000) HSPGs, in growing endothelial cells. This was accompanied by a marked reduction of the core protein of perlecan, which is a high-molecular-weight (400,000) HSPG.

It thus appears that production of subclasses of HSPGs is affected differently by lead, depending on the endothelial cell growth cycle. Given the importance of perlecan for bFGF-mediated migration and proliferation of endothelial cells and inhibition of migration and proliferation of VSMC, its down-regulation by lead may adversely affect endothelial repair and promote athero- and arteriosclerosis. Simultaneously, reduction of the cell surface-associated low-molecular-weight HSPGs (which are involved in lipolytic, anticoagulant, and other functions of the endothelium) in the confluent endothelial cells may contribute to hyperlipidemia, thrombosis, and other disorders.

Effect of lead on VSMC. The effect of lead on VSMC growth is the opposite of its effect on endothelial cells. Lead has been shown to stimulate proliferation of bovine aortic smooth muscle cells in a concentration-dependent manner (25). Moreover, lead exerts an additive effect on bFGF-stimulated VSMC proliferation (25). Similarly, a low concentration of lead citrate (100 μg/l) causes hyperplasia in cultured rat aorta smooth muscle cells. Hyperplasia in these cells is accompanied by transformation from the spindle- or ribbon- to the cobblestone-shaped phenotype, resembling the neointimal cell morphology, and significant reduction of angiotensin II receptor but no change in α- and β-adrenergic receptor or ANP receptor densities (8). In contrast, at high concentration (500 μM), lead causes growth arrest in cultured rat aorta smooth muscle cells.

Thus exposure to low levels of lead seems to stimulate proliferation and induce phenotypic transformation in VSMC, simulating events involved in the evolution of arteriosclerosis.

Effects of Lead on Blood Coagulation

Prevention of intravascular coagulation and preservation of blood fluidity are among the most important functions of the endothelium. Normal endothelial lining prevents thrombosis by several mechanisms: 1) coating of the endothelial surface by HSPG, which possesses heparin-like anticoagulant properties, 2) endothelium-derived NO, which is a potent inhibitor of platelet adhesion and activation, 3) t-PA, which promotes fibrinolysis, and 4) prostacyclin, among others. As described above, lead exposure damages the endothelium, deters endothelial repair, lowers HSPG production, and reduces NO availability via ROS-mediated NO inactivation (89). In addition, as shown by Kaji et al. (41), 0.01–1.0 μM lead nitrate significantly lowers basal and thrombin-stimulated t-PA release in confluent human umbilical vein endothelial cells. It therefore appears that lead exposure may increase the risk of thrombotic complications.

Intact endothelium lining normally shields fibroblasts and smooth muscle cells residing in the subendothelial region from direct contact with the blood. However, loss of this barrier when the endothelium is injured can lead to platelet adhesion and aggregation, as well as fibrin thrombus formation. In such circumstances, unlimited propagation of a fibrin clot is prevented by simultaneous activation of the fibrinolytic system, which depends on the balance between t-PA and plasminogen activator inhibitor-1 (PAI-1). Endothelial cells, VSMC, and fibroblasts express t-PA and PAI-1. Using cultured human aorta smooth muscle cells and fetal lung fibroblasts, Yamamoto et al. (96) showed that lead chloride causes a significant inhibition of t-PA release and a significant increase in PAI-1 release in cultured

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<th>Table 3. Effects of lead on blood coagulation</th>
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<td><strong>Effect of Lead</strong></td>
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<tr>
<td>Endothelial injury</td>
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<td>Reduced NO availability</td>
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<td>Reduced t-PA and increased PAI-1 production</td>
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NO, nitric oxide; t-PA, tissue plasminogen activator; PAI-1, plasminogen activator inhibitor-1.
fibroblasts in a dose-dependent manner. In addition, lead-treated smooth muscle cells exhibited a significant dose-dependent decline of t-PA release and, to a lesser extent, PAI-1 release.

Thus exposure of the cellular constituents of the subendothelial tissue to lead appears to shift the balance of fibrinolytic and antifibrinolytic forces in favor of the latter, thereby raising the risk of thrombosis (Table 3).

Role of Lead in Cardiac Toxicity and Atherogenesis

Acute lead poisoning has been reported to affect cardiac function, and chronic lead exposure has been linked to atherosclerosis and heightened cardiovascular mortality in some, but not all, epidemiological studies (13, 47, 70). In an earlier study aimed at assessing potential cardiac toxicity of lead, using solutions containing 0.3 and 30 μM lead acetate, Prentice and Kopp (60) conducted ex vivo isolated rat heart perfusion experiments for up to 60 min. Perfusion with the solution containing 30 μM lead acetate altered cardiac energy metabolism, prolonged the atrioventricular node and His bundle conduction times, lowered coronary blood flow, and reduced heart rate. The response to perfusion with solution containing 0.3 μM lead was milder and did not reach statistical insignificance. These findings illustrate the direct toxic effects of lead on the heart independent of the indirect cardiovascular effects, which are caused by the associated systemic and neuroendocrine disturbances in subjects with acute lead poisoning. Revis et al. (64) exposed male white pigeons to lead (0.8 ppm in drinking water) for extended periods to determine whether chronic exposure to lead or cadmium can cause atherosclerosis. Long-term exposure to low-level lead resulted in a marked elevation of arterial pressure and a nearly twofold increase in the number of atherosclerotic plaques in the aorta. The findings of this study clearly illustrate the proatherogenic effects of chronic low-level exposure to lead in this model. Further studies using apolipoprotein E-deficient and LDL receptor-deficient mice will be useful in elucidating the potential atherogenic effects of lead exposure.

SUMMARY/CONCLUSION

In vivo and in vitro studies have shown that chronic lead exposure causes oxidative stress, limits NO availability, impairs NO signaling, promotes inflammation, heightens sympathetic activity, increases endothelin production, alters the renin-angiotensin system, raises production of vasconstrictor prostaglandins, lowers production of vasodilator prostaglandins, disturbs vascular smooth muscle Ca2+ signaling, and diminishes endothelium-dependent vasorelaxation. In addition, lead can cause endothelial injury, impede endothelial repair, inhibit angiogenesis, reduce endothelial cell growth, suppress proteoglycan production, stimulate VSMC proliferation, induce phenotypic transformation of VSMC, reduce t-PA production, and raise PAI-1 production. Via these actions, lead exposure can promote HTN, arteriosclerosis, atherosclerosis, thrombosis, and cardiovascular disease.

REFERENCES


24. Fujiwara Y, Kaji T. Possible mechanism for lead inhibition of vascular endothelial cell proliferation: a lower response to basic fibroblast growth factor.


