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Review

Arsenic and atherosclerosis ☆

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Abstract

Epidemiological studies have demonstrated a correlation between environmental or occupational arsenic exposure and a risk of vascular diseases related to atherosclerosis. Studies summarized in this review suggest that arsenic induces endothelial dysfunction, including inflammatory and coagulating activity as well as impairs nitric oxide (NO) balance. This may provide the pathophysiological basis for atherogenic potential of arsenic. Consistent with these data, arsenic accelerates atherosclerosis in apolipoprotein E (ApoE) deficient mice, a model of human atherosclerosis.

Keywords: Arsenic toxicity; Cardiovascular toxicity; Inflammation; Environmental factors; Vascular diseases

Epidemiological evidence of arsenic-associated cardiovascular diseases

Arsenic is considered a potent human hazard because of its neoplastic outcomes. However, increasing epidemiological evidence suggests that there is also a link between arsenic exposure and risk of vascular diseases related to atherosclerosis. This is not surprising because many epidemiological studies on occupational mortality as well as cigarette smoking demonstrate concomitant occurrence of chemical-related carcinogenesis and atherogenesis (rev. in Hansen, 1990).

Arsenic is considered a major risk factor for an endemic peripheral artery disease characterized by severe arteriosclerosis and subsequent gangrene of affected extremities, so-called “blackfoot” disease (BFD). The epidemiological evidence for an association between BFD and arsenic is obtained from ecological, case-control studies, and from the co-occurrence of BFD with arsenic-dependent cancers (Tseng, 1989; Tseng et al., 1996). In addition to endemic peripheral vascular effects, arsenic exposure has been related to systemic vascular effects. Increased mortality from ischemic heart disease was first reported in copper smelter workers exposed to arsenic (Lee and Fraumeni, 1969; Welch et al., 1982). Furthermore, exposure of individuals from Taiwan to arsenic in artesian well water has been associated with BFD, and increased mortality from cardiovascular and cerebrovascular diseases (Chen et al., 1988, 1996; Tseng et al., 2003;Wu et al., 1989). Epidemiological studies from the United States have also suggested correlations between standard mortality ratios for cardiovascular diseases and arsenic levels in drinking water (Engel and Smith, 1994; Engel et al., 1994; Lewis et al., 1999). Ischemic heart disease and cerebral infarction are considered late clinical manifestations of generalized atherosclerotic process. Recently, a dose–response relationship between carotid atherosclerosis and long-term exposure to arsenic in drinking water has been reported in a BFD population using ultrasonographic evaluation of the superficial carotid artery (Wang et al., 2002). This strong biological gradient has

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Abbreviations: ApoE, apolipoprotein E; BFD, “blackfoot” disease; HAEC, human aortic endothelial cells; eNOS, endothelial nitric oxide synthase; IL-8, interleukin-8; LDL, low-density lipoprotein; MCP-1, monocyte chemoattractant protein; NO, nitric oxide; ROS, reactive oxygen species; VCAM-1, vascular adhesion molecules.

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been demonstrated after adjustment for major risk factors including hypertension, diabetes mellitus, cigarette smoking, alcohol consumption, serum levels of total cholesterol and LDL, which suggests that arsenic exposure might be an independent risk factor for atherosclerosis.

Atherosclerosis—pathogenic mechanisms

Atherogenesis is a multifactorial pathophysiological process of the arterial vasculature, which is characterized with progression from inflammation and smooth muscle cell proliferation to late stage of thrombotic and fibrotic obliterations of the vessels. The vessel wall is normally composed of an endothelial cell lining on a medial layer of vascular smooth muscle cells and enwrapped by an adventitial layer of connective tissue. The endothelial cells provide the transduction of signals in the microenvironment between the blood and vessel wall, and they orchestrate the homeostatic balance of the vessels by production of mediators regulating vascular tone, coagulation status, cell death, and inflammatory cell trafficking.

The disruption or activation of endothelial cells leads to series of events including vasoconstriction, increased adhesiveness resulting in inflammatory cell infiltration and platelet-thrombus formation (Cai and Harrison, 2000; Gibbons and Dzau, 1996; Libby, 2000). Endothelial cell dysfunction is associated with alteration of the cellular redox state. Oxidative modification of low-density lipoprotein (LDL) particles is a dominant hypothesis of atherogenesis (Daugherty and Roselaar, 1995; Mertens and Holvoet, 2001; Steinberg et al., 1989). Oxidized LDL particles are readily taken by macrophage scavenger receptors, leading to "foam cell" formation (macrophage loading with lipids), an obligatory step in atheroma development. Bioactive lipids derived from LDL oxidation can also modulate intracellular signal transduction and expression of genes coding inflammatory mediators and adhesion molecules (Chen et al., 2003; Harrison et al., 2003; Kita et al., 2001). Furthermore, reactive oxygen species (ROS) can directly function as signaling molecules that help to induce the activity of nuclear transcription factors such as NF-kB and AP-1 (Collins and Cybulsky, 2001; Haddad, 2002; Valen et al., 2001). The increased activity of these transcription factors is associated with up-regulation of vascular adhesion molecules (VCAM)-1 and chemokines including monocyte chemoattractant protein (MCP)-1 and interleukin (IL)-8 in the endothelium (Cushing et al., 1990; Roebuck, 1999; Takei et al., 2001). Chronic inflammation has been demonstrated histopathologically as an accompanying event in atheroma formation and may be an important modifying factor of atherosclerosis progression (Ross, 1999).

Endothelial dysfunction and atherogenesis have also been strongly related to an impaired nitric oxide (NO) homeostasis in the vessel (Gibbons and Dzau, 1996; Rekka and Chrysselis, 2002). NO plays multiple physiological roles in vascular wall including endothelium-mediated vasodilatation, inhibition of platelet activation and smooth muscle cell migration and proliferation, and suppression of the pro-inflammatory mediators through NF-kB inactivation. An attenuation in NO bioavailability may be caused by inhibition of the endothelial NO synthase (eNOS) expression, a lack of substrate or cofactors for eNOS, alterations of cellular signaling such that eNOS is not appropriately activated, and, finally, NO inactivation through interaction with ROS such as superoxide anion (Cai and Harrison, 2000; Napoli, 2002; Thomas et al., 2003). Many risk factors, including cigarette smoking, hypertension, diabetes mellitus, hypercholesterolemia, herpes viruses, and Chlamydia pneumoniae, can induce atherogenesis by modulation of inflammatory potential, oxidative stress, or NO perturbations in the endothelium (d'Uscio et al., 2001; Liuba et al., 2000).

Arsenic-induced molecular and cellular events related to atherogenesis

In vitro studies with endothelial cell cultures suggested that arsenic can cause cellular redox modulation, transcription factor activation, and gene expression relevant to endothelial dysfunction. For example, it has been demonstrated that exposure of endothelial cells to arsenite induces NF-kB activation and DNA synthesis through reactive oxygen species (Barchowsky et al., 1996, 1999) as well as decreases Fas ligand expression through oxidant formation (Tsai et al., 2001). In this connection, it has been shown that arsenic induces an increase of intracellular oxidized glutathione (GSSG) in porcine endothelial cells which may lead to oxidative stress (Yeh et al., 2002). Hirano et al. (2003) have demonstrated an uptake of arsenic into endothelial cells and concomitant induction of antioxidative enzymes, including heme oxygenase-1, thioredoxin perooxidase-2, NADPH dehydrogenase, and glutathione *S*-transferase P subunit, which suggests arsenic-induced oxidative stress. Other investigators have also demonstrated that arsenic disrupts cell proliferation in endothelial cell cultures (Chen et al., 1990). Recently, it has been reported that arsenic increases the expression of cyclooxygenase-2 in bovine aortic endothelial cells as well as human umbilical vein endothelial cells (HUVEC) through peroxynitrite formation and NF-kB activation, respectively (Bunderson et al., 2002; Tsai et al., 2002). We also found that arsenic induces expression of genes coding for inflammatory mediators including IL-8 in human aortic endothelial cells (HAEC) (Simeonova et al., 2003). Atherogenesis requires local chemokine production for regulating migration and activation of leucocytes. Classically, IL-8 is recognized as a major neutrophil chemotactic factor, but consistent observations of increased IL-8 expression without neuthrophil involvement in atherosclerotic lesions suggested alternative roles of IL-8 in atherosclerosis (rev. in Terkeltaub et al., 1998). Consistently, it has been demonstrated that IL-8 is an angiogenic factor (Koch et al., 1992), and chemotactic for vascular smooth muscle cells (Yue et al., 1993), T-cells (Lloyd et al., 1996), and monocytes (Gerszten et al., 1999). The expression of IL-8 by arsenic was accompanied with activation of transcription factors, including NF-kB and AP-1. Previous studies also demonstrated that arsenic is a potent activator of AP-1 and NF-kB DNA binding activity in different type of cells including porcine aortic endothelial cells, keratinocytes, and urinary bladder cells (Barchowsky et al., 1996; Burleson et al., 1996; Simeonova et al., 2000). AP-1 and NF-kB can regulate inflammatory gene expression, for example, the IL-8 gene promoter region contains multiple binding sites for these transcription factors (Ahmad et al., 1998; Simeonova and Luster, 1996) and the transcription factors are subject to redox-dependent regulation (Flohe et al., 1997; Simeonova et al., 1999).

Consistent with the "lipoprotein oxidative-modification hypothesis" of atherosclerosis, free transition metal ions, such as copper, have been shown to stimulate the lipoprotein oxidation by endothelial cells in vitro (Steinbrecher et al., 1984; Witztum and Steinberg, 1991). Although arsenic is not a transition metal, it has been shown to posses an oxidative potential. However, we were unable to demonstrate that arsenic, in contrast to copper or hydrogen peroxide, induces oxidation of LDL in human aortic endothelial cells (Simeonova et al., 2003).

Accumulating evidence demonstrates that arsenic exposure modulates the coagulation status. In this respect, arsenic has been shown to enhance the aggregation activities of platelets (Lee et al., 2002). Exposure of human microvascular endothelial cells to arsenic in vitro resulted in a decrease of tissue-type plasminogen activator (t-PA) and an increase of plasminogen activator inhibitor type-1 (PAI-1) expression as well as reduced fibrinolysis (Jiang et al., 2002; Wu et al., 1993). Increased coagulating and lowered fibrinolytic activities contribute to endothelial dysfunction and atherogenesis through induction of thrombotic events in the circulation.

Arsenite exposure has been recently related to an impaired NO homeostasis. Arsenic inhibited acetylcholine-induced relaxation of aortic rings and reduced the levels of guanosine 3,5-cyclic monophosphate (cGMP), a surrogate for NO (Lee et al., 2003). These effects were consistent with concentration-dependent eNOS inhibition in endothelial cells. Arsenic-mediated impaired vasomotor tone, as a result of reduced NO bioavailability, may contribute to arsenic-related atherosclerosis and hypertension.

All of the atherosclerosis-related effects induced by arsenic, including transcription factor activation, gene expression, or an impaired NO homeostasis, might be mediated indirectly by induction of oxidative stress (as discussed above) or directly through arsenic reactivity to vicinal sulfhydryl groups. Macromolecules involved in cell signaling, such as receptors, integrins, or protein phosphatases contain high numbers of vicinal sulfhydryls and are capable of reacting with arsenic (rev. in Simeonova and Luster, 2002).

Animal models of atherosclerosis and arsenic

The wild-type C57BL/6 mice are resistant to atherosclerosis but atheroma formation can be triggered by long-term (more than 24 weeks) high-fat diet (Plump and Breslow, 1995). Progress in understanding the risk factors leading to atherosclerosis have resulted from development of specific genetic mouse models that make the mouse from very resistant to highly susceptible of atherosclerosis. One of these models is deficiency of the gene coding apolipoprotein

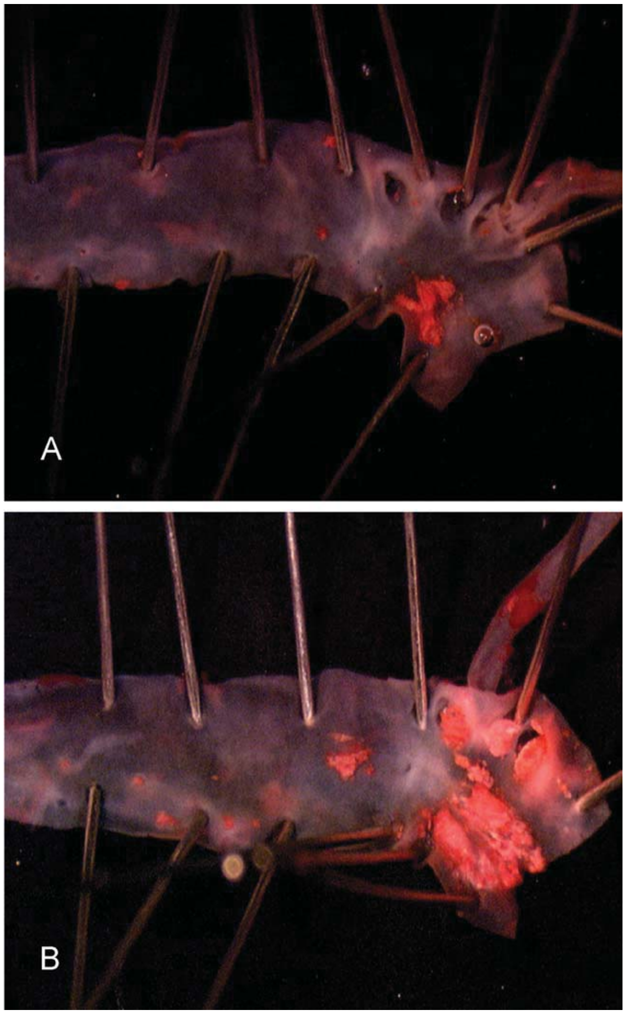

Fig. 1. Photomicrographs of representative Sudan IV-stained aortas from mice administered arsenic for 24 weeks. The mice were fed a mouse chow diet (LM-485, Harlan, Indianapolis, ID) for 22 weeks and a Cocoa butter diet (15.8% fat; TD 88051, Harlan) for the last 2 weeks. (A) ApoE −/− mouse receiving control drinking water. (B) ApoE −/− mouse receiving drinking water containing sodium arsenite (100 μg/ml).

E (ApoE), one of several lipoprotein transfer genes (Nakashima et al., 1994; Palinski et al., 1994). The primary function of ApoE protein is mediation of receptor-dependent lipoprotein removal from the blood. The ApoE-deficient mouse develops massive fibroproliferative atherosclerosis when fed a low-fat and low-cholesterol chow diet (Plump and Breslow, 1995). The lesions are dispersed throughout the arterial tree forming at the base of the aorta, in the proximal coronary arteries, and along the entire length of the aorta, with predisposition at the branch points of major vessels leaving the aorta. In terms of anatomical localization and histopathological characteristics of the plaques, this model more closely resembles human atherosclerosis compared to the high-fat diet-induced mouse (wild type) atherosclerosis model.

Arsenic exposure, through drinking water, was found to increase atheroma formation in ApoE−/− mice in parallel with increasing levels of arsenic in the vessel wall (Simeonova et al., in press). An example of the effect of arsenic exposure on plaque formation in these mice is presented in Fig. 1. Arsenic-related ischemic heart diseases in humans are not associated with serum lipid profiles (Hsueh et al., 1998). Consistently, exposure of ApoE−/− mice to arsenic accelerated the atheroma formation without altering cholesterol levels, except when the higher dose of arsenic was combined with an atherogenic diet. Introduction of an atherogenic diet for 2 weeks induced severe hypercholesterolemia without a significant effect on the lesion size. If the atherogenic diet was continued for longer than 4 weeks, significant increases in cholesterol blood levels and lesion size were observed. However, the effect of arsenic on atherosclerotic lesion size, under these conditions, was diminished probably because it was masked by the diet effects. The atherogenic effect by arsenic was not observed in wild-type mice, although they accumulate arsenic in the cardiovascular tissue. If atherosclerosis is induced in the C57BL/6 mice by a high-fat diet, arsenic exposure might also accelerate the atherogenesis in these mice. It is possible that arsenic, similarly to cigarette smoking, infections and other risk factors, modifies rather than initiates atherosclerotic process. Subsequently, it has been suggested that arsenic accumulates in skin or bladder tissue, major targets of arsenic carcinogenicity, but acts to promote tumorogenesis rather than being a complete carcinogen (Germolec et al., 1998; Rossman et al., 2001).

Conclusions

In conclusion, based on the accumulating epidemiological evidence and experimental data, arsenic exposure should be considered a modifying factor in atherosclerosis and related cardiovascular diseases, at least under certain circumstances (including genetic background, diet, co-exposure). Studies summarized in this review suggest that arsenic induces pathophysiological events relevant with atherogenic potential including increased oxidative stress, inflammatory and coagulation activity of endothelium and impaired vascular nitric oxide homeostasis (Fig. 2). Genetically modified atherosclerosis-susceptible mouse models may provide important information on the mechanisms and factors involved in arsenic-induced cardiovascular diseases.

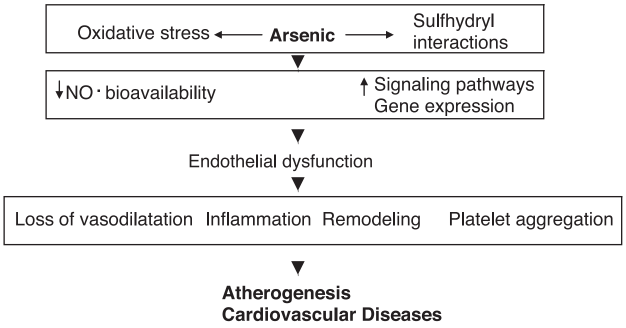

Fig. 2. Schematic representation showing possible mechanisms involved in arsenic-related atherogenesis and cardiovascular diseases.

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