Several epidemiological studies have suggested that exposure to arsenic is strongly correlated with the development of cardiovascular diseases such as hypertension. To determine whether arsenic affects vasomotor tone in blood vessels, we investigated the effect of arsenic on vasorelaxation using isolated rat aortic rings in an organ-bath system. Treatment with arsenite inhibited acetylcholine-induced relaxation of the aortic rings in a concentration-dependent manner, whereas several other arsenic species did not have any effect. Consistent with these findings, the levels of guanosine 3′,5′-cyclic monophosphate (cGMP) in the aortic rings were significantly reduced by arsenite treatment. In cultured human aortic endothelial cells, treatment with arsenite resulted in a concentration-dependent inhibition of endothelial nitric oxide synthase (eNOS). In addition, higher concentrations of arsenite decreased the relaxation induced by sodium nitroprusside (an NO donor) and 8-Br-cGMP (a cGMP analog) in aortic rings without endothelium. These in vitro results indicate that arsenite is capable of suppressing relaxation in blood vessels by inhibiting eNOS activity in endothelial cells and by impairing the relaxation machinery in smooth muscle cells. In vivo studies revealed that the reduction of blood pressure by acetylcholine infusion was significantly suppressed after arsenite was administered intravenously to rats. These data suggest that an impairment of vasomotor tone due to arsenite exposure may be a contributing factor in the development of cardiovascular disease.

Key words: arsenic, arsenite, blood vessels, cardiovascular disease, endothelial nitric oxide synthase, nitric oxide, vasorelaxation. Environ Health Perspect 111:513–517 (2003). doi:10.1289/ehp.5916 available via http://dx.doi.org/ (Online 16 December 2002)
MEM with 100 U/mL penicillin and 100 µg/mL streptomycin at 37°C in a 95% air/5% CO2 incubator for 14 hr. The rings were then mounted in four-channel organ baths filled with Krebs-Ringer solution (pH 7.4): 115.5 mM NaCl, 4.6 mM KCl, 1.2 mM KH2PO4, 1.2 mM MgSO4, 2.5 mM CaCl2, 25.0 mM NaHCO3, and 11.1 mM glucose. The organ baths were continuously gassed with 95% O2/5% CO2 and maintained at 37°C. The rings were stretched gradually to an optimal resting tension of 2 g and equilibrated for 30 min. We measured the change in tension isometrically with Grass FT03 force transducers (Grass Instrument Co., Quincy, MA, USA) and recorded the change using the AcqKnowledge III computer program (BIOPAC Systems Inc., Goleta, CA, USA).

To investigate the effects of As3+ on endothelium-dependent relaxation, acetylcholine was used as an agonist. The aortic rings were precontracted submaximally by adding phenylephrine, and acetylcholine was then cumulatively added to the organ bath to obtain concentration-relaxation curves. To examine the effects of As3+ on the NO donor-induced relaxation and on direct cGMP-dependent relaxation, sodium nitroprusside was used as the NO donor and 8-bromoguanosine 3',5'-cyclic monophosphate (8-BrcGMP) was used as the cGMP analog. Relaxation was expressed as the percent decrease in contractile tone elicited by phenylephrine.

Determination of eNOS activity. We determined eNOS activity by measuring the conversion of [3H]-l-arginine to [3H]-l-citrulline. These amino acids were separated by anion exchange chromatography using a modification of the method of Bredt and Snyder (1990). We maintained HAEC (six to eight passages) in the EGM kit at 37°C in a 95% air/5% CO2 incubator. We determined eNOS activity by measuring the conversion of [3H]-l-arginine to [3H]-l-citrulline. Aortic rings were then added to each tube, and chemiluminescence was measured for 60 min using a luminometer (Berthold, Germany).

Measurement of basal NO release. We treated rat aortic rings with As3+ or saline for 14 hr as described previously (Lee et al. 2001). For the experiments in which we examined cGMP levels stimulated by an agonist, 10–7 M acetylcholine was added to the organ bath for 1 min. The reactions were immediately stopped with liquid nitrogen, and the tissue was homogenized in 1 mL ice-cold 6% trichloroacetic acid. The homogenate was centrifuged at 13,600 × g for 15 min at 4°C. The supernatant was extracted with water-saturated ether. We assayed extracts for cGMP levels by radioimmunoassay (RIA) using a [125I]-cGMP RIA kit (Amersham) according to the procedure described by the manufacturer. We determined protein content from the pellet according to the method of Lowry et al. (1951).

Measurement of blood pressure change induced by acetylcholine. Rats were anesthetized with phenobarbital (50 mg/kg, intraperitoneal). A catheter of polyethylene PE-50 tubing (Clay Adams, Sparks, MD, USA) filled with heparinized saline (100 U/mL) was placed in the carotid artery for the measurement of blood pressure, and a catheter was tunneled subcutaneously and exteriorized at the back of the neck. Wounds were sutured and cleaned with alcohol. We began experiments after a 1-day recovery period. On the day of the experiment, the arterial catheter was connected to a pressure transducer (BIOPAC Systems Inc.), and blood pressure was measured using the AcqKnowledge III computer program. Blood pressure was allowed to stabilize for a minimum of 30 min before treatment began. To determine the effects of As3+ on blood pressure reduction induced by acetylcholine, we administered As3+ solution (1 mg/kg) by an intravenous bolus injection into the jugular vein. In the controls, equivalent amounts of saline were injected. After 2 hr, the rats were infused with 10 µg/kg/min acetylcholine for 2 min via the jugular vein, and the change in blood pressure in response to acetylcholine was monitored simultaneously. Infusions were performed with a Harvard syringe pump (Southinstall, MA, USA) at a rate of 0.1 mL/min.

Statistical analysis. We calculated the means and standard errors of means for all treatment groups. The data were subjected to one-way analysis of variance followed by Duncan’s multiple range test to determine which means were significantly different from the control. In all cases, a p value of < 0.05 was used to determine significance.

Results

To determine whether arsenic affects relaxation of blood vessels, we treated intact aortic rings with various concentrations of As3+ for 14 hr. Phenylephrine was applied to precontract the rings, followed by cumulative addition of acetylcholine to obtain concentration–relaxation curves (Figure 1A). As3+ suppressed the relaxation induced by acetylcholine in a concentration-dependent manner. We also investigated the effects of the pentavalent inorganic species (As5+) and two major metabolites, MMA and DMA, on the inhibition of acetylcholine-induced vasorelaxation (Figure 1B). However, As5+, MMA, and...
DMA failed to inhibit the acetylcholine-induced relaxation.

Acetylcholine stimulates eNOS to produce NO in endothelium, which results in the relaxation of smooth muscle (Wanstall et al. 2001). To examine whether As\(^{3+}\) inhibits NO synthesis by endothelial cells, we investigated the effect of As\(^{3+}\) on eNOS activity in cultured HAEC. As\(^{3+}\) reduced eNOS activity in a concentration-dependent manner (Figure 2A), suggesting that As\(^{3+}\) can suppress vascular NO production in endothelial cells. Others have reported that As\(^{3+}\) can generate superoxide anions in cultured endothelial cells and smooth muscle cells (Lynn et al. 2000; Smith et al. 2001). Superoxide anions interact with NO to form peroxynitrite, resulting in suppression of vascular relaxation by blocking the NO pathway (Pryor and Squadrito 1995). To determine if superoxide anions generated by As\(^{3+}\) may play a role in the suppression of vascular relaxation, we treated aortic rings with intact endothelium with As\(^{3+}\), and superoxide production was evaluated by measuring lucigenin-induced chemiluminescence. Increased chemiluminescence was not observed at any concentration of As\(^{3+}\) tested (Figure 2B).

NO released from endothelium elicits vascular relaxation by increasing the levels of cGMP in smooth muscle (Robertson et al. 1993). To determine the effects of As\(^{3+}\) on the NO-dependent pathway, we measured the accumulation of cGMP in aortic rings. The basal cGMP levels in the aortic rings were significantly decreased by As\(^{3+}\) treatment in a concentration-dependent manner (Figure 3A). After stimulation with 10\(^{-7}\) M acetylcholine, As\(^{3+}\) again significantly reduced cGMP levels, even though the cGMP levels were 30 times greater due to the acetylcholine stimulation (Figure 3B). However, unlike the results for acetylcholine-induced relaxation (Figure 1A), no difference in cGMP level was found between the 25- and 50-\(\mu\)M As\(^{3+}\) treatments, suggesting that arsenic may interfere with some relaxation mechanism in addition to inhibiting endothelium-dependent NO production.

Therefore, using aortic rings without endothelium, we examined the effect of As\(^{3+}\) on relaxation induced by SNP, a direct NO-releasing agent. Treatment with As\(^{3+}\) inhibited vasorelaxation induced by SNP to a lesser extent (Figure 4A) than the vasorelaxation induced by acetylcholine. As\(^{3+}\) at a concentration of 25 \(\mu\)M did not suppress SNP-induced relaxation, but 50 \(\mu\)M As\(^{3+}\) showed significant inhibition. Consistent with this finding, when we investigated the effect of As\(^{3+}\) on relaxation induced by the cGMP analog, 8-Br-cGMP in aortic rings without endothelium, only 50 \(\mu\)M As\(^{3+}\) resulted in significant reduction of cGMP analog-induced relaxation (Figure 4B). These results suggested that 50 \(\mu\)M As\(^{3+}\) could interfere with the cGMP-dependent relaxation machinery of smooth muscle in blood vessels.

To verify the effects of As\(^{3+}\) on blood vessels in vivo, we monitored the change in blood pressure after intravenous infusion of acetylcholine into conscious rats (Figure 5). An intravenous bolus of As\(^{3+}\) had no effect on basal blood pressure (Figure 5A). When rats were infused with 10 \(\mu\)g/kg/min acetylcholine 2 hr after As\(^{3+}\) treatment (Figure 5C), the reduction of blood pressure induced by acetylcholine was significantly suppressed compared to the control group (10.8 ± 3.5 vs. 31.3 ± 4.7 mmHg) (Figure 5B). These results suggest that As\(^{3+}\) caused suppression of vasorelaxation induced by acetylcholine in vivo. This confirms the previous in vitro results shown in Figure 1A.

Discussion

This is the first study to evaluate the effects of As\(^{3+}\) on vasomotor function in vitro and in vivo. We have shown that As\(^{3+}\) inhibits the vascular relaxation induced by acetylcholine in a concentration-dependent manner and that possible mechanisms are the inhibition of NO production in endothelial cells and the suppression of cGMP-dependent relaxation mechanisms in smooth muscles. These in vitro results were consistent with in vivo results (Figure 5) in which As\(^{3+}\) suppressed the reduction of blood pressure by acetylcholine in conscious rats. Our findings correlate well with a previous study reporting that serum concentrations of NO metabolites were decreased in a population exposed to arsenic in drinking water (Pi et al. 2000). In addition, this As\(^{3+}\)-induced suppression in vitro was still observed after the removal of residual As\(^{3+}\) by changing the incubation medium, suggesting that the As\(^{3+}\)-induced effect was irreversible and that damaged blood vessels might not recover even after As\(^{3+}\) has disappeared from the bloodstream.
Several epidemiologic studies have reported that arsenic-contaminated drinking water causes various types of cardiovascular disease such as blackfoot disease, atherosclerosis, cerebrovascular disorders, and hypertension (Chen et al. 1988; Chiou et al. 1997; Rahman et al. 1999; Rubanyi 1993; Vanhoutte 1997). Because blood vessels, however, are another tissue important in the development of cardiovascular diseases. Dysfunction in blood vessels disrupts the balance in vasomotor tone between relaxation and contraction, with vasoconstriction predominating and ultimately leading to possible increased risk for development of vascular diseases such as hypertension and atherosclerosis (Lefer et al. 1991; Luscher et al. 1993; Rahman et al. 1999; Rubanyi 1993; Vanhoutte 1997). Because our data showed that As$^{3+}$ could suppress endothelium-dependent vasorelaxation with subsequent changes in vasomotor tone in blood vessels, we propose arsenic-induced dysfunction in blood vessels as an alternative mechanism for arsenic-associated cardiovascular disease observed in human populations.

Treatment with As$^{3+}$ did not result in concentration-dependent inhibition of vasorelaxation induced by SNP (Figure 4A) compared to the results obtained by acetylcholine (Figure 1A). As$^{3+}$ at a concentration of 25 µM did not inhibit SNP-induced relaxation but did inhibit acetylcholine-induced relaxation, suggesting that 25 µM As$^{3+}$ may interfere with NO production in endothelial tissue. This conclusion is supported by our finding that As$^{3+}$ can significantly inhibit eNOS activity in cultured human aortic endothelial cells (Figure 2A). In addition to interfering with NO generation in aortic endothelium, higher concentrations of As$^{3+}$ may also disrupt the relaxation mechanisms in smooth muscles.

First, only 50 µM concentrations of As$^{3+}$ showed an inhibitory effect on SNP-induced relaxation in aortic rings without endothelium (Figure 4A). Second, unlike acetylcholine-induced vasorelaxation (Figure 1A), levels of acetylcholine-stimulated cGMP in aortic rings showed no difference between treatments with 25 or 50 µM As$^{3+}$ (Figure 3B). Third, treatment with 50 µM As$^{3+}$ resulted in significant reduction of cGMP analog-induced vasorelaxation in aortic rings without endothelium (Figure 4B). These results suggest that impairment of NO generation in endothelium and impairment of cGMP-dependent relaxation mechanisms in smooth muscles depended on the concentrations of As$^{3+}$ that blood vessels were exposed to.

As$^{3+}$ is reported to stimulate the formation of reactive oxygen species (ROS) in vascular endothelial and smooth muscle cells, mainly via NADH/NADPH oxidase (Lynn et al. 2000; Smith et al. 2001); thus, the generation of superoxide could elicit the reduced relaxation due to elimination of NO. Therefore, we considered the possibility that superoxide production is involved in suppression of vasorelaxation by As$^{3+}$. However, we detected no significant increase in ROS generation in intact aortic rings when measuring superoxide anions with the chemiluminescent probe lucigenin (Figure 2B). These contradictory results might be explained by the differences in experimental systems (we used aortic rings in an organ-bath system and the previous studies used a cell culture system), but the exact reason for this discrepancy is currently unknown. In any case, our results suggest that superoxide generation does not play an important role in the suppression of vasorelaxation by As$^{3+}$.

Our study revealed that higher concentrations of As$^{3+}$ inhibited cGMP-dependent relaxation of smooth muscle in aortic rings isolated from rats. Arsenic is well known to induce heat-shock proteins (Del Razo et al. 2001), a large family of proteins whose expression is usually induced by cellular stress. Knoepp et al. (2000) reported that smooth muscle relaxation induced by SNP and forskolin, an adenylyl cyclase activator, was inhibited by cellular stresses such as heat shock and As$^{3+}$ via inhibition of the phosphorylation of heat shock protein 20, which is a regulatory component of the actin-associated cytoskeleton. However, those effects were observed in bovine carotid artery, whereas our aortic rings were isolated from rats. Furthermore, 0.5 mM As$^{3+}$ was used in those experiments, which was 10 times higher than the concentrations used in our experiment. In fact, treatment with 0.5 mM As$^{3+}$ resulted in complete impairment of phenylephrine-induced precontraction in rat artery (data not shown), and thus the relaxation experiment by acetylcholine was not feasible. Therefore, it appears inappropriate to apply the explanation of Knoepp’s group to our observation that 50 µM As$^{3+}$ could suppress the relaxation.

**Figure 4.** Effects of As$^{3+}$ on relaxation induced by sodium nitroprusside and 8-Br-cGMP in aortic rings without endothelium. After aortic rings without endothelium were treated with As$^{3+}$ for 14 hr, 1 µM phenylephrine was added to precontract the aortic rings and then relaxation was elicited by (A) cumulative addition of SNP, NO donor and (B) 30 µM 8-Br-cGMP, a cGMP analog. Relaxation is expressed as percentage of decrease in contractile tone elicited by phenylephrine. Values are means ± SEM of four independent experiments.

*Significant difference from control (p < 0.05).
machinery in smooth muscles. The exact mechanism remains to be identified.

Previous study reported that the normal concentration of arsenic in human plasma is 2.4 ± 1.9 µg/L and that this level may be increased up to 38 µg/L with chronic arsenic exposure (Heydorn 1970). Our in vivo arsenic experiment showed significant suppression of acetylcholine-induced vasorelaxation after only a 2-hr exposure (Figure 5), at which time arsenic reached its plasma level of less than 100 µg/L (data not shown). This experimental arsenic exposure was therefore not more than a factor of 3 greater than arsenic levels to which human blood vessels are exposed after chronic intake of arsenic-contaminated drinking water. Considering the facts that humans are more sensitive to arsenic toxicity than are several other species (Chan and Huff 1997), the concentration of arsenic used in the current investigation could be well within the range to induce cardiovascular disease when humans drink arsenic-contaminated water for weeks or even years.

From this study, we determined that As+3 caused altered vascular tone by decreasing vasorelaxation. The inhibitory effects may be due to suppression of NO production mediated by eNOS inhibition in endothelial cells and interference of cGMP-dependent relaxation machinery in smooth muscles (Figure 6). In our in vivo study, As+3 treatment of rats blocked the acetylcholine-induced hypotensive effect. These results confirm our in vitro observations and suggest that reduced vasorelaxation may be a contributing factor in development of cardiovascular diseases in populations exposed to arsenic.

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