Mechanism for Arsenic-Induced Alteration of Contractility in Blood Vessels

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Several epidemiological studies suggested that arsenic exposure was strongly correlated with the development of cardiovascular disease such as hypertension. In order to examine whether arsenic affects vasomotor tone in blood vessels, we investigated the effect of arsenic on agonist-induced vasorelaxation using the isolated rat aortic rings in *in vitro* organ bath system. Treatment with arsenite inhibited acetylcholine-induced relaxation of aortic rings in a concentration-dependent manner. The inhibitory effects by arsenic were also observed in the relaxation induced by sodium nitroprusside, a NO-donor. Consistent with these findings, the cGMP levels stimulated by acetylcholine in blood vessels were reduced significantly by arsenite treatment. In addition, higher concentration of arsenite decreased the relaxation by 8-Br-cGMP, a cGMP analog, in aortic rings without endothelium. These *in vitro* results indicated that arsenite was capable of suppressing acetylcholine-induced relaxation in blood vessels by inhibiting production of nitric oxide in endothelial cells and by impairing the relaxation machinary 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 vasomotor tone impaired by arsenite exposure may be one of the contributing factors in development of cardiovascular disease.

Chronic exposure of arsenic is well known to be the cause of cardiovascular disease such as hypertension. In order to investigate the effect of arsenic on blood vessels, we examined whether arsenic affected agonist-induced contraction of aortic rings in isolated organ bath system. Treatment with arsenite increased vasoconstriction induced by phenylephrine or serotonin in a concentration-dependent manner. Similar effects were also shown in the aortic rings without endothelium, suggesting that vascular smooth muscle played a key role in enhanced vasoconstriction induced by arsenite. Arsenite is the most potent form among arsenic species tested. These alterations were well correlated with myosin light chain (MLC) phosphorylation induced by arsenite in smooth muscles. Direct calcium measurement using fura-2 dye in aortic rings revealed that arsenite enhanced contraction by high K^+ without further increase in intracellular calcium levels. Calcium-sensitization of contractile machinery, therefore, may contribute to the enhanced vasoconstriction by arsenite. Consistent with these *in vitro* results, intravenous administration of 1.0 mg/kg arsenite augmented blood pressure increase induced by phenylephrine in conscious rats. These results suggest that arsenite increases agonist-induced vasoconstriction mediated by MLC phosphorylation and calcium-sensitization in smooth muscles was one of the key mechanisms for the arsenite-induced hypercontraction in blood vessels.