A potential mechanism for the impairment of nitric oxide formation caused by prolonged oral exposure to arsenate in rabbits

Jingbo Pi[1,2], Yoshito Kumagai[3], Hiroshi Yamauchi[4], Guifan Sun[5], Michael P. Waalkes[2], and Nobuhiro Shimojo[3]

[1]Graduate School Doctoral Program in Medical Sciences, University of Tsukuba, Japan; [2]Inorganic Carcinogenesis Section, Laboratory of Comparative Carcinogenesis, NCI at NIEHS, Mail Drop F0-09, 111 Alexander Drive, Research Triangle Park, NC 27709; [3]Department of Environmental Medicine, Institute of Community Medicine, University of Tsukuba, 1-1-1 Tennodai, Tsukuba, Ibaraki, Japan; [4]Department of Preventive Medicine, St. Marianna University School of Medicine, Japan; [5]Department of Labor Hygiene and Occupational Health, School of Public Health, China Medical University, Shenyang, China.

We have recently found evidence for impairment of nitric oxide (NO) formation and induction of oxidative stress in residents of an endemic area of chronic arsenic poisoning in Inner Mongolia, China [1,2]. To investigate the underlying mechanisms responsible for the phenomena observed in humans, a chronic animal experiment was conducted using male New Zealand White rabbits. After 18-weeks of continuous exposure of rabbits to 5 mg/L of arsenate in drinking water, a significant decrease in systemic NO production in vivo occurred, as shown by reduced plasma NO metabolites levels (76% of control, $p < 0.05$) and increased oxidative stress, as shown by increased urinary hydrogen peroxide (H2O2) (120% of control, $p<0.05$). Hepatic levels of (6R, S)-5,6,7,8-tetrahydro-L-biopterin (BH4), a cofactor for NO synthase (NOS) were markedly reduced in arsenate-exposed rabbits to 62% of control ($p < 0.01$), while no significant change occurred in cardiac L-arginine levels, suggesting that arsenate-mediated reduction of systemic NO may be associated with the enzymatic uncoupling reaction of NOS with a subsequent enhancement of reactive oxygen species such as superoxide ($*O_2$-), an endothelium derived vasoconstricting factor. Additional experiments measured aortic tension, the addition of either calcium ionophore A23187 or ACh induced a transient vasocontraction of aortic rings prepared from arsenate-exposed rabbits, but not in those prepared from control animals. This calcium-dependent contractility action observed in aorta rings from arsenate-exposed rabbits was markedly attenuated by the $*O_2$- scavenging enzyme Cu, Zn-SOD, as well as diphenyleneiodonium (DPI) or Nù-nitro-L-arginine methyl ester (L-NAME) which are inhibitors for NOS. However, the cyclooxygenase inhibitor, indomethacin, or the xanthine oxidase blocker, alloprinol, had no effect on this vasocontraction. These results suggest that prolonged exposure of rabbits to oral arsenate may impair the bio-availability of BH4 in endothelial cells and as a consequence, the balance between NO and $*O_2$-, produced from endothelial NOS, could be altered.

[1] Jingbo Pi, et al. Free Rad Biol Med. 28:1137-1142, 2002
[2] Jingbo Pi, et al. Environ Health Perspect. 110:331-336, 2002