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Effect of Arsenic on Platelet Aggregation: Strong Association to Cardiovascular Disease

Moo-Yeol Lee, Ok-Nam Bae and Jin-Ho Chung

College of Pharmacy, Seoul National University, Seoul, 151-742, Korea

Arsenic (As) is a ubiquitous element found in several forms in foods and environmental media, such as soil, air, and water. All humans are exposed to low levels of this element. Although arsenic is a micronutrient, it is known to be highly toxic and the intended or daily use of arsenic-containing compounds is strictly regulated by food and environmental agencies. The primary route of human exposure is through ingestion of arsenic-contaminated food and drinking water. Foods contain substantial levels, but arsenic in foods is primarily organic and relatively low in toxicity compared to inorganic forms. In contrast, the predominant form of arsenic in drinking water is inorganic arsenic, which is both highly toxic and readily bioavailable. Chronic ingestion of arsenic-contaminated drinking water is therefore considered the major pathway that drives risk to human health.

Chronic arsenic exposure has been associated with diverse health effects including cancer, hyperkeratosis, hyperpigmentation, reproductive toxicity, diabetes, and cardiovascular disease. Cardiovascular effects associated with high arsenic levels in drinking water include Blackfoot disease (BFD), peripheral vascular disease, atherosclerosis, hypertension and ischemic heart disease. BFD is known to be a peripheral occlusive vascular disease that exhibits arteriosclerosis obliterans and thromboangitis. This suggests the possibility that long term ingestion of inorganic arsenic may alter hemostasis and normal blood vessel function.

Blood platelets play a major role in hemostasis, thrombosis and initiation of various vascular diseases. Under normal physiological conditions,

hemostatic balance by platelets is strictly regulated between proaggregatory and antiaggregatory activity. Platelet aggregation is activated by collagen (contained in the blood vessel wall), thrombin (generated by plasma from prothrombin), thromboxane A_2 (secreted from platelets) and hemodynamic factors, such as shear stress. Antiaggregatory activity (inhibition of platelet aggregation) is mainly controlled by nitric oxide (NO) and prostaglandin I_2 (PGI_2), which are produced by endothelium. Certain chronic diseases such as diabetes or exposure to exogenous chemicals and drugs can alter the normal proaggregatory/anitaggregatory balance, thereby causing excessive platelet aggregation and ultimately lead to various cardiovascular diseases (CVD), such as thrombosis.

The present study investigated the effects of arsenic on platelet aggregation to determine if arsenic-induced alteration of hemostasis could be a causative factor in the cardiovascular disease observed following chronic ingestion of arsenic-contaminated drinking water. Sodium arsenite (iAsⅢ) enhanced *in vitro* platelet aggregation induced by several agonists (thrombin, collagen, ADP and arachidonic acid) in a concentration- and time-dependent manner, but was not directly toxic to platelets and did not directly induce platelet aggregation. The relative potency of various forms of arsenic to enhance thrombin-induced platelet aggregation was iAsIII > iAs V>MMA>>DMA. Treatment of iAsⅢ with thrombin also resulted in a concentration-dependent significant increase of serotonin secretion from platelets. Formation of thromboxane B_2 (TXB_2) from platelets followed the same general trend, but was not statistically significant. *In vivo,* iv infusion of iAsⅢ increased thrombus formation by thromboplastin. Ingestion of iAs Ⅲ-contaminated drinking water elevated the plasma serotonin levels, which was consistent with the *in vitro* serotonin secretion from platelets. These results suggest that arsenic exposure renders platelets more susceptible to aggregatory stimulus and readily enhances serotonin secretion from platelets, two effects which may contribute to arsenic-associated cardiovascular diseases.