Low levels of arsenic may cause kidney disease, but existing drug could become key treatment

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A study in which researchers exposed human kidney epithelial cells to different concentrations of arsenic suggests that long-term exposure — even at the low levels currently allowed by the Environmental Protection Agency — can increase the risk of kidney fibrosis; but the same study also revealed a potential treatment for overexposure.

While arsenic exposure has been linked to chronic kidney disease in a number of studies, a similar relationship between arsenic exposure and kidney fibrosis is not yet understood, according to co-authors Kamaleshwar P. Singh, PhD, associate professor in the department of environmental toxicology at the Texas Tech University's Institute of Environmental and Human Health, and Yu-Wei Chang, a PhD candidate and research assistant.

"Because the process of fibrosis is not an immediate outcome of renal injury, we treated human kidney cells for 2 months to evaluate the arsenic effects related to renal fibrosis," Singh and Chang said in a joint email response.

Singh and Chang exposed human renal cortex/proximal tubule cells (HK-2) to 100 pg/mL and 10 ng/mL arsenic — the latter based on EPA guidelines, which allow 10 ppb of arsenic in drinking water, and the former a lower than allowable amount. To determine the results of acute exposure, cells were treated for 72 hours. For long-term treatment effects, cells were treated until they reached the confluency of about 80%, they were placed in a new flask and treated again. The process was repeated for 2 months.

The results showed HK-2 cells exposed to arsenic underwent phenotypic, biochemical and molecular changes indicative of epithelial-mesenchymal transition (EMT) and acquired the pathogenic features of fibrosis. The cells showed increased expression of markers for fibrosis including collagen I, fibronectin, transforming growth factor-beta (TGF-β) and alpha-smooth muscle actin (α-SMA).

The researchers noted further study with an animal model is needed to confirm the initial results before they could provide a safe recommendation to arsenic exposure, "but our research does provide an evidence that chronic toxicity of low-dose arsenic exposure should be an important aspect for the assessment of arsenic toxicity," they added.

Another impact of long-term, low-dose arsenic exposure the study revealed was the increased expression of epigenetic genes (DNA methyltransferases 3a and 3b; methyl-CpG binding domain 4).

"Multiple published studies have indicated that arsenic exposure can alter DNA without causing mutations ... and that [DNA methylation] can contribute in initiation of disease development," the researchers said. "We believed that long-term exposure to arsenic can cause alteration of DNA methylation, which further leads to the fibrotic changes observed in arsenic-exposed cells."

To evaluate the role of DNA methylation in arsenic-induced EMT and profibrotic changes, the researchers exposed both groups of cells — those treated with 100 pg/mL arsenic and with 10 ng/mL arsenic — to DNA methylation inhibitor 5-Aza-2'-deoxycytidine.

This treatment, using a drug approved by the FDA for treatment of blood cancer, reversed the EMT properties and restored the level of phospho-AKT. This essentially returned the cells to their pre-exposure-to-arsenic condition.

"In principle, our study suggests the potential of epigenetic therapeutics to inhibit arsenic-induced kidney fibrosis," the researchers said. More research is needed to confirm the results produced in a laboratory, and the review process for further study is still ongoing. – by Amanda Alexander

Reference:

Disclosures: Chang and Singh report no relevant financial disclosures.