ACUTE ARSENIC ADMINISTRATION INDUCES IMPAIRED GLUCOSE TOLERANCE IN MICE

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ABSTRACT

Background. Arsenic contamination of ground water is a serious health threat to people in many countries of the world including Bangladesh and West Bengal, India. A number of previous reports suggest that chronic exposure to arsenic may lead to diabetes in humans. It was of interest to determine whether acute exposure to arsenic can lead to impaired glucose tolerance and consequently elevated blood glucose levels (hyperglycemia). Methods. Impairment of glucose tolerance was determined through oral glucose tolerance tests (OGTT) in mice. Results. Oral administration of arsenic to mice at dose levels of 100, 200 and 400 µg per 20g body weight led to dose-dependent and statistically significant elevations in blood glucose levels compared to control animals (without arsenic). At the aforementioned three doses, the elevations in blood glucose in glucose-challenged mice were, respectively, 114.0, 123.5, and 160.9% compared to control mice (100.0%). Conclusion. Acute administration of arsenic can cause impaired glucose tolerance, which can serve as a model to explore various mitigating factors to alleviate the problem.

KEYWORDS: Arsenic, Bangladesh, glucose, OGTT.

BACKGROUND

In the last two decades, ground water has formed the major source of water for drinking, cooking and irrigation in practically every district of Bangladesh. In most districts of
Bangladesh as well as districts of West Bengal, India, the ground water has been found to be contaminated with arsenic, sometimes even to levels 30-40 fold more than the World Health Organization advised safe limit of 10 μg per liter.\[1\] Irrigation with arsenic contaminated ground water, in turn, has led to arsenic accumulation in soil, from which arsenic is accumulated by various plants including crops, leading to presence of arsenic in a variety of foodstuffs.\[2\]

From a population-based study, association of low to moderate levels of chronic exposure to arsenic has been postulated to lead to greater risk of Type 2 diabetes in Bangladesh.\[3\] It has been observed in Denmark that long-term exposure to low-level arsenic in drinking water may contribute to the development of diabetes.\[4\] Similar report of linkage between chronic arsenic exposure and diabetes as well as a host of other diseases has been seen in South Korea, Taiwan and Canada.\[5-7\] It was therefore of interest to study the effect of acute arsenic exposure at a high dose on glucose tolerance in mice. Any impairment of glucose tolerance at a single high dose of arsenic intake in mice can serve as a quick reference model for further studies on possible measures for alleviation of arsenic induced impaired glucose tolerance.

**METHODS**

*Chemicals and Drugs*

Sodium arsenite was obtained from Sigma Chemical Co., USA and glucose was obtained from Square Pharmaceuticals Ltd., Bangladesh. All other chemicals were of analytical grade. Sodium arsenite was dissolved in double distilled water and filtered prior to oral gavaging in mice.

*Animals*

Swiss albino mice, which weighed between 19-21g were used in the present study. The animals were obtained from International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR, B). The animals were acclimatized for three days prior to actual experiments. The study was conducted following approval by the Institutional Animal Ethical Committee of University of Development Alternative, Dhaka, Bangladesh.

*Oral glucose tolerance tests*

Oral glucose tolerance tests were carried out as per the procedure previously described by Joy and Kuttan (1999)\[8\] with minor modifications. Briefly, mice were grouped into four groups of eight mice each. The various groups received different treatments like Group 1 received
vehicle (double distilled water) and served as control, Groups 2-4 received sodium arsenite solution at concentrations such that each mice received inorganic arsenic at doses of 100, 200 and 400 μg per 20g body weight, respectively. All substances were orally administered. Following a period of two hours, all mice were fasted overnight for 14 hours. After 14 hours fasting, mice were orally administered 2g glucose/kg of body weight. Blood samples were collected 120 minutes after the glucose administration through puncturing heart. Blood glucose levels were measured by glucose oxidase method.[9]

Statistical analysis
Experimental values are expressed as mean ± SEM. Independent Sample t-test was carried out for statistical comparison. Statistical significance was considered to be indicated by a p value < 0.05 in all cases.[10]

RESULTS
Administration of high acute doses of inorganic arsenic, even at a single dose showed pronounced impairment of glucose homeostasis in mice as demonstrated through oral glucose tolerance tests in glucose-loaded mice. At the experimental doses of 100, 200 and 400 μg inorganic arsenic per 20 kg body weight, the percent elevations of blood glucose were, respectively 14.0, 23.5 and 60.9 more when compared to control (without arsenic administered mice). Thus the results suggest that since a single acute high dose of arsenic can cause glucose impairment, chronic doses of arsenic, even at relatively low concentrations, may be able to induce diabetes in rodents or human subjects. The results are shown in Table 1.

Table 1. Effect of single acute high dose of inorganic arsenic administration on blood glucose level in mice in oral glucose tolerance tests.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose (μg arsenic/20g body weight)</th>
<th>Blood glucose level (mmol/l)</th>
<th>% elevation in blood glucose level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>-</td>
<td>5.71 ± 0.25</td>
<td>-</td>
</tr>
<tr>
<td>Inorganic arsenic</td>
<td>100 μg</td>
<td>6.51 ± 0.22</td>
<td>14.0*</td>
</tr>
<tr>
<td>Inorganic arsenic</td>
<td>200 μg</td>
<td>7.05 ± 0.27</td>
<td>23.5*</td>
</tr>
<tr>
<td>Inorganic arsenic</td>
<td>400 μg</td>
<td>9.19 ± 0.50</td>
<td>60.9*</td>
</tr>
</tbody>
</table>

All administrations were made orally. Values represented as mean ± SEM, (n=8); *P < 0.05; significant compared to hyperglycemic control animals.
DISCUSSION

Hyperglycemic conditions have been observed in male albino Wistar rats following high dose of sodium arsenite oral administration (5 mg per kg body weight) for 4 weeks.[11] Our results indicate that high doses of sodium arsenite can impair glucose homeostasis even after a single oral dose. The underlying causes behind arsenic induced glucose impairment leading to hyperglycemia and eventually diabetes are yet to be studied in detail. However, it has been postulated that arsenic induces diabetic effects through pancreatic β-cell dysfunction and increased gluconeogenesis in mice.[12] It has also been suggested that Sirt3/FOXO3a/MnSOD signaling plays a significant role in the inhibition of insulin-stimulated glucose uptake (ISGU) induced by chronic arsenic exposure.[13] The exact mechanism lying behind the observed arsenic-induced impaired glucose tolerance in the present study needs to be investigated.

Our results indicate that a single acute high dose of arsenic can probably be used as an experimental model to test various agents for alleviating such glucose impairment effect and so ultimately can prove beneficial in finding suitable antidotes against such arsenic induced disease(s) and particularly diabetes. We had been experimenting with various antihyperglycemic or antidiabetic plants and formulations for a number of years.[14-34] These plants and formulations will now be examined in our laboratory to determine whether they can counteract the diabetic effects including hyperglycemia induced by chronic and acute intake of arsenic. That can prove extremely beneficial to the people of many countries suffering from arsenic-induced diabetes.

CONCLUSION

The results suggest that a single acute high dose of inorganic arsenic can induce glucose intolerance in mice.

Conflicts of interest

The author(s) declare that they have no competing interests.

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