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Review article

Mechanisms of arsenic disruption on gonadal, adrenal and thyroid endocrine systems in humans: A review

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ABSTRACT

Due to its toxicity as a carcinogen and wide distribution in the environment, arsenic (As) exposure in humans is of public concern globally. Many studies have manifested that As exposure induces cancers besides pathological effects in humans. Animal studies showed that chronic As exposure induces serious neurological effects. Based on recent studies, researchers proposed that As, including arsenate (AsV) and arsenite (AsIII), is also an endocrine disruptor. This review discusses the mechanisms of As toxicity on three endocrine systems including gonadal, adrenal and thyroid endocrine systems. Arsenic methylation and oxidative stress are responsible for As-induced disorders of endocrine systems, however, strong binding of AsIII to thiols also play an important role. Some studies showed AsV toxicity on endocrine systems, but mechanistic investigation is lacking. Research is needed to look into their toxicity mechanisms to help cure the illnesses caused by As-induced endocrine system disorders.

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1. Introduction

Arsenic (As) is a toxic metalloid widely distributed in the environment. Its presence in soil, food, and water leads to unavoidable As exposure in humans. Furthermore, increasing anthropogenic activities have increased As concentrations in the environment, resulting in greater As exposure. With As concentration increasing in the environment, As pollution is considered an worldwide issue, posing a threat to public health (Halder et al., 2012; Sun et al., 2014). Chronic exposure to As results in a series of health problems, including cancers such as kidney, bladder, skin, and lung cancers, and non-cancerous diseases including cardiovascular, peripheral neuropathy, and obstructive pulmonary disease (Table 1). These diseases may be attributed to As-induced immune disorders in humans. Investigators showed that As can damage immune system, rendering them susceptible to pathogenic challenge (Ahmed et al., 2014; Raqib et al., 2009; Soto-Peña et al., 2006). It is known that

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Table 1
Various health problems associated with As exposure.

Target organ	Health problems	References
Cardiovascular	Hypertension Carotid atherosclerosis Ischemic heart disease Vascular disease mortality	Srivastava et al., 2009
Nervous system	Neurobehavioral alterations Encephalopathy Peripheral neuropathy Delirium	Vahidnia et al., 2007
Lung	Lung cancer Obstructive pulmonary disease Interstitial lung disease Bronchiectasis	Guo et al., 2004; Mazumder, 2007
Liver	Liver damage Affect liver enzyme Portal tract fibrosis Cirrhosis	Guha, 2001
Gstrointestinal	Gastrointestinal irritation Haemorrhagic gastrointestinal lesions	Jomova et al., 2011
Kidney	Kidney cancer	Hopenhayn-Rich et al., 1998
Bladder	Bladder cancer	Moore et al., 2002
Skin	Skin cancer Hyperpigmentation Hyperkeratosis	Maloney, 1996

endocrine system modulates the external toxic effects on the immune system (Davis, 1998). Based on recent research, some proposed that As is a potential endocrine disrupting compound (EDC), which has attracted much attention (Davey et al., 2008; Watson and Yager, 2007).

Endocrine system consists of various glands that produce and secrete hormones, which are transported to distant target organs, thereby regulating the metabolism, growth and development in humans (Witorsch, 2002). EDC is defined as an exogenous agent that interferes with the production, transport and metabolism of natural hormones in human body that are responsible for maintaining homeostasis and regulating reproductive and developmental processes (USEPA, 1996). EDC exerts adverse impacts on humans via either mimicking or antagonizing the effect of hormones and/or disrupting the synthesis of hormones and/or hormone receptors (Amaral Mendes, 2002; Mantovani, 2006).

Arsenic is mainly present as inorganic form in terrestrial environment, including arsenate (AsIII) and arsenite (AsV), both are toxic to humans and animals. It is known that AsIII and AsV induce different toxicity, with AsIII having higher toxicity than AsV. AsIII exerts toxicity via three pathways: 1) binding to sulfhydryls thereby impairing proteins and enzymes, 2) causing oxidative stress via production of reactive oxygen species (ROS), and 3) inducing nucleophilicity via depletion of *S*-adenosylmethionine (Kitchin et al., 2003; Sun et al., 2014). With respect to AsV, due to its structure similarity with phosphate, besides its weak interaction with proteins, it can interfere with oxidative phosphorylation by forming an unstable arsenate ester, impacting ATP production. Furthermore, AsV toxicity also results from the oxidative stress caused by AsV reduction to AsIII (Hughes, 2002; Jomova et al., 2011). The effect of As on endocrine system has been investigated for many years, research shows that As disrupts the gonadal, adrenal, and thyroid endocrine systems (Tables 2-1, 2-2 and 2-3) (Bodwell et al., 2006; Ciarrocca et al., 2012; Jana et al., 2006).

These endocrine systems are controlled primarily by three axes, i.e., the hypothalamic-pituitary-gonad (HPG), hypothalamic-pituitary-adrenal (HPA), and hypothalamic-pituitary-thyroid (HPT) axes (Fig. 1; Liu et al., 2010). This review will primarily focus on the toxicity mechanisms of As-induced disruption of these endocrine systems. Such information helps to understand the pathways of As disruption on the endocrine systems and provides important information for therapy-based strategies to cure As-induced endocrine illness. This review discusses various pathways of As-induced toxicity on the three endocrine systems.

2. Arsenic toxicity on gonadal endocrine systems

Gonadal endocrine system plays a crucial role in regulating human reproductive behavior via controlling gonadal hormones from HPG axis (Figs. 1 and 2) (Hoffmann and Kloas, 2010). The HPG axis consists of hypothalamic-pituitary-ovarian (HPO) in females and hypothalamic-pituitary-testicular (HPTT) axis in males, which control the gonadal hormone production (estrogen and androgen) by the ovaries/testicular through a double-level hormonal hierarchy, i.e., gonadotropin-releasing hormone, and the gonadotropins (follicle-stimulating hormone; FSH, and luteinizing hormone; LH). Gonadotropin-releasing hormone is secreted in the hypothalamus, which then circulates to the pituitary gland and stimulates the production and release of gonadotropins (FSH and LH). These gonadotropins, in turn, stimulate estrogen/androgen production by the ovaries and testicular, regulating gonadal gametogenesis in the initiation of gametogenesis, gonadal maturation and spermiation/ovulation (Stafford, 2005).

Earlier investigators examined As toxic effect on gonadal glands via an animal model, and found that As can be accumulated in the gonadal glands and induce inhibitory effect on the gonadal development (Andersen and Depledge, 1994; Shukla and Pandey, 1985; Zaroogian and Hoffman, 1982). In subsequent studies, investigators discovered that As influences one or more sex hormones, and induces inhibition of ovarian steroidogenesis, reproductive disturbance, testicular steroidogenic function and spermatogenesis (Chattopadhyay et al., 1999; Chattopadhyay et al., 2003; Zadorozhnaja et al., 2000).

Table 2-1
The effects of As on gonadal endocrine system.

As species	Exposure time	Experimental material	Toxic effect	Reference
10 mg L^{-1} AsIII	7 days	Female rats	AsIII stimulates progesterone production	Yuan et al., 2012
20–225 μg L^{-1} AsIII	24 h	MCF-7 cell	AsIII disrupts many ER related genes	Davey et al., 2007
0.4–80 μg mL^{-1} AsIII	7–56 days	Female albino rat	AsIII decreases estradiol, LH and FSH levels	Chatterjee and Chatterji, 2010
0.4 mg kg^{-1} AsIII	28 days	Female albino rat	AsIII decreases ovarian Δ5-3β-HSD, 17β-HSD, and activity of peroxidase	Chattopadhyay et al., 2001
0.5 mg kg^{-1} AsV	20 weeks	Female mice	AsV induces mice lesion, and upregulation of ER immunoreactive protein	Waalkes et al., 2000
Drinking water containing As		Women	Chronic As exposure may increase the risk of fetal and infant death	Milton et al., 2005
Drinking water containing As		Girls	As exposure has a negative effect on menarcheal age	Sen and Chaudhuri, 2007
5 mg kg ∗ day^{-1} AsIII	4 weeks	Male rats	AsIII decreases sperm counts, and LH, FSH, testosterone, and testicular levels and inhibits testicular enzymes	Jana et al., 2006
2, 5 μM AsIII	48 h	Human prostate cancer cell line and PC-3 cell	AsIII represses androgen receptor transcriptional level	Rosenblatt and Burnstein, 2009
0–3 mg kg^{-1}	3 weeks	Male mice	AsIII decreases some key enzymes expression	Chiou et al., 2008
<3590 μg L^{-1} AsVexposure	>50 years	Male	AsV impacts the erectile function	Hsieh et al., 2008
As exposure		Male	AsV exposure is associated with infertility	Shen et al., 2013

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