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Review article

Review on molecular and biochemical insights of arsenic-mediated male reproductive toxicity

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ABSTRACT

Arsenic is a natural metalloid found in abundance, in the environment. Exposure to arsenic can cause health issues due to its carcinogenic nature. The primary source of arsenic contact is drinking water. Exposure to arsenic in drinking water can cause reproductive dysfunction in males through a reduction in testes weight, accessory sex organ weight, viability, and motility of sperm, epididymal sperm count, decreased gonadotrophins level, decreased testosterone, and steroidogenesis disruption. This review focuses on the mechanisms by which arsenic impairs the quality of semen, based on epidemiological observations in humans, and experimental studies in different biological research models. Arsenic-mediated male reproductive toxicity can be induced by various mechanisms such as inhibition of spermatogenesis, testosterone pathway hinderance, oxidative stress, inflammation, genotoxic effects, activation of heat shock proteins, and activation of a signaling pathway in testes (ERK/AKT/NF-kB signaling pathway), among others. The interplay between the principal mechanisms involved needs to be elucidated further in future since an overall examination of arsenic-mediated male reproductive toxicity is still a deficit.

1. Introduction

Arsenic is a naturally occurring geochemical metalloid element, found in abundance in nature and humans. It occupies the 20th rank as the most abundant element in the earth crust, 14th in seawater and 12th in humans [1]. It is grey, tasteless, odorless, and commonly occurs in combination with carbon element [2]. Arsenic can be found in either organic or inorganic states, depending on binding with oxygen, chloride, sulfur, or hydrogen [3]. Arsenic compounds are separated into three types- organic, inorganic, and arsine gas. Based on the valence state, arsenic is divided into different classes such as As(o)-arsenic in metalloid condition, o oxidation state; As(III)-trivalent form of arsenic with 3rd oxidation state are (As^{III}) arsenates, (CH_3As^{III}) monomethylarsonous acid, ($(CH_3)_2As^{III}$) dimethylarsinous acid, ($(CH_3)_3As^{III}$) trimethylarsine, (NaAsO(2)) sodium arsenite; As(V) - pentavalent form of arsenic with 5th oxidation state such as (As^{V}) arsenates, (CH_3As^{V}) monomethyl arsonic acid, ($(CH_3)_2As^{V}$) dimethyl arsenic acid, ($(CH3)_3As^{V}$) trimethylarsine oxide, (Na(2)HAs(O4)) sodium arsenate, ($C_6H_8AsNO_3$) arsanillic acid, and ($C_5H_{11}AsO_2$) arsenobetaine. The solubility of arsenites and arsenates are high in water [2]. Contamination of water with arsenic was discovered in many countries such as India, Bangladesh, Taiwan, China, Chile, Argentina, Mongolia, Mexico and few regions of United States [4,5]. The major problem of hydroarsenicism is established worldwide, in millions of people [6]. Arsenic was used as a homicidal agent in the long history, but the documented history of arsenic began in the 18th century [7]. In 1976, potassium arsenite (1%) also called as flower solution which was utilized as a treatment for many diseases such as syphilis, asthma, malaria, psoriasis. Also, it has a long history of utilizing as a chemotherapeutic agent [7]. Arsenic and its compounds are utilized productively in pharmaceuticals, agricultural industries as pesticides, herbicides and insecticides, wood preservatives, mining applications such as metallurgical, semiconductor industries and glass making industries for the past 100 years [7,8]. Arsenic has a possible twin role such as both buddy and enemy based on the nutritional and health condition of a human. A low dosage of arsenic is desired for the safeguarding of dietary and health condition of human beings. Water contamination with arsenic causes various diseases such as skin cancer [9], cardiovascular diseases, bladder cancer, lung disorders, diabetic pathophysiology [10], and reproductive toxicity [3]. Arsenic toxicity pivot on either inorganic or organic,

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valences, solubility, physical state, purity, and its absorption and exclusion rate. This article focuses on inorganic trivalent arsenic since it is more toxic than organic arsenic. The possible chemical structure for inorganic arsenic methylation is as follows: $As^{V} + 2e^{-} \rightarrow As^{III} + CH_3 \rightarrow CH_3As^{V} + 2e^{-} \rightarrow CH_3As^{III} + CH_3 \rightarrow (CH_3)_2As^{V} + 2e^{-} \rightarrow (CH_3)_2As^{III} + CH_3 \rightarrow (CH3)_3As^{V} + 2e^{-} \rightarrow (CH_3)_3As^{III}$ [7].

Arsenic metabolism is catalyzed by 3^{+} oxidation state of arsenic metyltransferase, which is a performed in a sequence of reduction of pentavalent to trivalent, followed by oxidation in which trivalent converts to pentavalent. Therefore, trivalent arsenic is more toxic than pentavalent arsenic. Trivalent oxidation state has high toxicity. Biological trivalent arsenite has approximately 2–10 folds more toxic and active than pentavalent arsenate. This trivalent arsenic reacts with the compound containing sulfur and products ROS [3,7]. Exposure of arsenic in male mice with different concentration of both sodium arsenite and arsenate with the concentration ranging from 0.01 to 10 mg/L for 56 days in drinking water. Sodium arsenite caused more toxic than arsenates such as sodium arsenite reduced the seminiferous epithelium percentage, its volume, and proportion of Leydig cells. Apart from this, it increased the tunica propria percentage, lymphatic space, lumen, macrophages, and blood vessels. It caused more seminiferous epithelium vacuolization. Also, it decreased the activity of antioxidant defense in a testicular milieu [11]. So in this review we mainly concerned on the male reproductive toxicity of trivalent arsenic, however, pentavalent arsenic also mentioned. Arsenic-mediated toxicity in male reproduction is connected with spermatotoxicity, which leads to a reduction in testicular androgenesis and a decrease in the weight of testis and accessory sex organs. Arsenic exposure reduces the sperm count, motility of sperm, and augmentation of sperm abnormality. Even a low dosage of arsenic exposure causes testicular cytotoxicity [12–14]. Some studies report accumulation of arsenic in testes, seminal vesicle, epididymis and prostate glands [12,15]. Epidemiological studies reveal that arsenic exposure affects the quality of semen in men [16]. The toxic effect of arsenic is due to oxidative stress and disruption of sex hormones, as indicated by biomarkers present in urine [17], or binding with thiol groups in sperm nuclear chromatins [3]. The main purpose of this review is, although many kinds of literature are available on the general toxicity of different metabolites of arsenic. However, detailed information on male reproductive toxicity is much obligatory to explore the degree of arsenic poisoning. Hence this review is required to provide an updated molecular and biochemical insights of arsenic-mediated male reproductive toxicity.

2. Arsenic impairs male reproductive system

2.1. Arsenic impairs quality of semen: epidemiological observations in humans

Epidemiological observation studies in humans expose an association between arsenic exposure and reproduction activities in males. Semen evaluation based on motility, viability, functional membrane integrity and DNA integrity of sperm were considered an important key in male reproductive function [18]. Exposure of males (177 in number, age ≥50 years) to arsenic > 50 ppb in drinking water increased the risk of erectile dysfunction with reduced circulating testosterone level in Taiwan [19]. Male reproductive toxicity by arsenic is not completely investigated in the human population [20]. However, an earlier report suggests that exposure of humans to arsenic deregulated the quality of semen and helped for the determination of urinary biomarkers in a Chinese population. Totally 160 fresh semen from infertile male and 66 controls were collected in a Chinese group and divided based on the *Ureaplasma urealyticum* (Uu) infection. A high concentration of arsenic was found in Uu patients who had high abnormal sperm quality than patients without Uu [21]. Totally 74 blood and semen samples from infertile and 76 blood and semen samples from fertile men aged 38 years were collected and analyzed for arsenic concentration [20]. Further, it was divided based on fertile, exposure of environment and occupation such as fertile, environment and occupation exposed (F-EO), fertile and environment (F-E), infertile, environment and occupation exposed (IF-EO), infertile and environment (IF-E). The concentration of arsenic in blood was lower in F-EO, IF-EO than F-E and IF-E. Oligospermia, azoospermia, and asthenospermia had a low concentration of arsenic in whole blood than normal sperm counts. Oligoasthenospermia had a slightly higher concentration of arsenic but not significantly higher than average sperm counts [20]. Environmental exposure of arsenic for 96 males (between 32 and 36 years of age) decreased the quality of semen by decreasing the concentration of sperm; it was positively associated with the arsenic concentration according to a Chinese cohort study [22]. In Han Chinese population study comprising of 268 males, poor semen quality with arsenic exposed cases has revealed a correlation between urine biomarkers and infertility cases with arsenic. The urinary biomarkers were metabolites which are involved in different pathways such as amino acid, lipid, nucleotide, and hormonal pathways. Some of the urinary biomarkers were found to be negatively correlated with arsenic exposure, such as aspartic acid, acylcarnitines, and hydroxyestrone. Arsenic changed some of the urinary biomarkers such as methylxanthine and uridine via oxidative stress, and hormonal imbalance was positively correlated with the poor semen quality [17]. Exposure of arsenic in 127 males in a Chinese cohort (19 to 43 years of age) deregulated metabolites such as guanine (involved in purine metabolism), testosterone (involved in androgen metabolism), hippurate (involved in glycine metabolism), serine (involved in glycine and serine metabolism), and acetyl-*N*-formyl-5-methoxykynurenamine (involved in tryptophan metabolism) in urine. The perturbation of metabolites in urine might act as a biomarker for arsenic exposure. The biomarkers suggested that the disturbed arsenic in urine had been due to the endocrine disruption and oxidative stress [23] (represented in Table 1). Though the metabolic biomarkers were determined through metabolomics studies, the mechanism of toxicity and its mode of actions need to be elucidated in humans with different populations exposed to arsenic.

2.2. Arsenic impairs male reproductive system: experimental studies in different biological research models

Exposure of adult mice to sodium metaarsenite (30 or 40 mg/L) in drinking water for 30, 45 and 60 days impaired the process of spermatogenesis at meiosis and post-meiotic stages, including interruption of spermatogenesis in mice in a dose-dependent manner via seminiferous tubular diameter reduction, cell populations (gametogenic) such as resting spermatocyte, pachytene, step 1–7 spermatid reductions except for spermatogonia and elevated degree of atrophy in Leydig cells in a dose-dependent manner [24]. Exposure of male mice to sodium arsenite (53.39, 133.47, 266.95 or 533.90 pmol/L amounting to 4, 10, 20, or 40 ppm respectively) for 35 days altered the enzymes at testicular level, sperm count, motility of sperm, and morphological abnormalities in sperm [12]. Exposure of male mice to arsenic trioxide with the concentration 0.3 mg/kg/day to 3 mg/kg/day administrated subcutaneously for 5 days/week with interruption 2 days for 5 weeks showed that there is a reduced number of spermatozoa, seminiferous epithelium degeneration production, germ cell tubule lumen exfoliation, there is an adjustment of nuclear/cytoplasm percentage in Leydig cells and decreased immunoreactivity of AR [25]. Exposure of rabbit bucks to 10 mg/kg/day sodium arsenite for 58 days reduced the weight of the testes, luteinizing hormone (LH), testosterone and follicle-stimulating hormone (FSH) [26]. Sodium arsenite 5 mg/kg for 12 weeks reduced sperm count, sperm motility, LH and FSH in the serum of teddy goat bucks [27]. Sodium arsenite (8 mg/kg/day for 8 weeks) reduced the sperm count, sperm motility, viability of sperm, and sperm morphology of rats [28,29]. Exposure to arsenic trioxide at a concentration of 3 mg/kg body weight in a single dose for 28 days, diminished the