Institute of Experimental Morphology, Pathology and Anthropology with Museum
Bulgarian Anatomical Society

Acta morphologica et anthropologica, 28 (1-2)
Sofia ● 2021

Toxic Effects of Heavy Metals (Mercury and Arsenic) on the Male Fertility

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Heavy metals are proving to be an important factor in determining male infertility. The accumulation of lead, cadmium, mercury, arsenic, bismuth and other elements, even in low concentrations, induces strong toxic effects in the reproductive tract. The current review focuses on the naturel toxicants mercury (Hg) and arsenic (As) as the main pollutants of the environment, and their effects on the function of the male gonads and spermatogenesis, as well as the related reproductive consequences as poor sperm quality and male infertility. Massive degeneration of germ cells and alterations in the levels of testosterone are also reported. Generally, it has been accepted that heavy metals affect the oxidative stress.

Key words: arsenic, mercury, heavy metals, testis, male reproductive system, male fertility

Introduction

Most of the heavy metals are able to form toxic diluted compounds in the living organisms, (including humans), but also in the environment. The professional exposition of these elements could be available in many fields of the industry, and it could lead to significantly increased pathogenicity and mortality. It has been suggested that the risk is usually connected with both increased concentrations and exposition duration. Each one of them could be harmful to the organism, if it is applied in a high dose or when the normal mechanisms of its elimination and/or metabolism are disrupted. The intoxications (acute or chronic) with metal ions are usually due to the impossibility for regeneration of the normal functions in the injured tissues of the organism.

It has generally been accepted that the exposure on the influence of heavy metals causes abnormalities in the male reproductive tract [34, 59, 65]. According to many literature data, even low doses of cadmium (Cd), mercury (Hg), arsenic (As) and lead (Pb) could lead to appearance of such effects [11, 53, 62]. For instance, exposure to Cd could lead to decreased semen quality and to damages in the sperm DNA. Pb could reduce male fertility by decreasing sperm count and motility, but also by causing abnormal

morphology and by affecting many functional parameters. Hg could be connected with sperm abnormality in humans. As could impair the development of the reproductive organs and steroidogenesis, but also to reduce the sperm quality. Generally, it has been accepted that heavy metals affect the mechanisms, related to the oxidative stress (OS) [25, 28]. The environmental tools of Hg and As could be natural and/or anthropogenic (by human activities). The application of As and Hg as pesticides, herbicides, fungicides and rodenticides is also an important factor for contamination [27, 41]. Besides the professional exposure, other important sources of heavy metals are harmful food habits and the consumption of contaminated marine organisms/seafood [38].

The main routes of non-occupational Hg exposure include dental amalgams, pharmaceutical applications, cosmetics, but also Hg vapor exposure from flooring in homes and schools [3, 6]. The organic Hg or methylmercury (MeHg) is found in water sediments, where microorganisms methylate inorganic mercury converting it to MeHg. This compound is persistent and it can accumulate in the food chain with predator species, such as fish and raptors, having the highest levels of Hg [33]. The reference intake levels for MeHg exposures range from 0.7 to 2 μg per kilogram (μg/kg) body weight per week. Levels of MeHg in the blood are related to fish consumption. The Hg concentration in approximately 98% of all urine samples from people without known exposure to Hg is less than 5 μg/l. Mild proteinuria may occur in the most sensitive adults at urine values of 50–100 μg/l following chronic occupational exposures. A positive point in Hg vapor poisoning is that most of the toxic effects usually disappear within a few months after cessation of exposure. Mercury blood levels higher than 200 μg/l may be associated with healthy effects in adults, but a concentration of 40-50 μg/l in a pregnant woman could be associated with a toxic risk for the fetus. Total blood Hg includes inorganic and organic forms, while urinary or plasma levels reflect inorganic Hg exposure. Blood levels of mercury higher than 5.8 μg/l are accepted as toxic. Mercury is suspected to have a negative impact on male fertility [61].

Chronic use of As may cause severe health-destructive effects including lung disease, reproductive problems, vascular disease and gangrene [12]. In absorption in the human body (by breath, digestive tract and skin), As passes into the blood, 95-99% of which accumulates in erythrocytes in the form of stable compounds with hemoglobin, and it is thus transported to the tissues and organs in the organism. The body releases through urine about 70% of the absorbed As as reference values of As in urine in humans show 10–30 μg/l and 0.5-1.5 μg/l in the blood, respectively. The average daily human intake of As is about 20 μg, while the lowest fatal dose is estimated to be in the range of 70-180 mg. Arsenic is categorized by the IARC (International Agency for Research on Cancer) as a human carcinogen (group 1), associated with increased risks of various cancers, as well as with numerous other non-cancer illnesses including cardiovascular diseases, diabetes, reproductive and developmental problems, but also neurological and cognitive problems [4, 30].

According to the Panel on Contaminants, the toxic tolerable weekly intake (PTWI) of 15 μg/kg body weight as determined by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) is not applicable due to uncertainty regarding the dose-response relationship and because of the established much lower doses of As to cause lung and urinary tract cancer. The degree of impact of As on the living organisms depends on its form (organic or inorganic), as well as its valency/oxidation degree. About the inorganic As, it is not considered necessary to determine a dose of permissible daily or weekly

intake without having a significant healthy risk [14]. Diagnosis is by testing the urine, blood, or hair [48]. Arsenic acts by changing the functioning of around 200 enzymes [48]. The toxicity of the inorganic compounds of As has been found as higher than that of the organic ones. Furthermore, the tri-valent As ion (As^{3+}) in the chemical compounds is more toxic than the five-valent (As^{5+}) [57]. The high toxicity of the inorganic forms of As induced severe reproductive impairments in both men and women. It could cause miscarriages, stillbirths, or premature births. Also, women who work or live near industrial activity with As or As-compounds have a higher-than-normal miscarriage rate, and newborns are underweight because of the inorganic arsenic ingested, passing through the placenta. Similar teratogenic effects have been demonstrated in rodents (rats and mice) too. In the study of rats exposed to As in an amount of 0.24 mg per day for 28 days, ovarian and uterine compressed and inhibition of enzymes responsible for the normal course of individual stages of reproductive development has been observed. Regarding the organic forms of As, no negative reproductive effects have been identified so far.

The current review focuses on the toxic metals Hg and As as the main pollutants of the environment. In this regard, we discuss their effects on male gonadal function and spermatogenesis, as well as related reproductive effects such as poor sperm quality and male infertility.

Testicular and hormonal effects of heavy metals

Chronic intoxication with Hg and As (and/or their compounds) also affects the endocrine glands, including the testes and spermatogenesis. Similarly to Pb and Cd, the exposure to Hg can develop a pathological affect on the male reproductive organs [42] and to influence negatively the criteria of male reproductive health/fertility [54, 61]. Mercury has also been proved to pass through the blood-testis barrier (BTB) and to accumulate in Sertoli and Leydig cells [17], in the testes of experimental animals. In experimental *in vitro* incubation of rat Sertoli cells with 31 mM (6.22 mg/L) of inorganic Hg, lower levels of cell-produced inhibin B have been established [37]. Treatment of rats with inorganic (50 or 100 mg/kg) or organic Hg (MeHg) (5 or 10 mg/g) for 90 days has induced disintegration of the Leydig cells and inhibited the activity of 3b-hydroxysteroid dehydrogenase (3-b-HSD), an enzyme critical for testosterone (TE) production, and decreased TE levels respectively [58]. The treatment of mice (aged 12 weeks) with inorganic Hg at a dose of 4 mg kg^{-1}/dg body weight for 12 weeks by gavage caused a decrease in the epididymal sperm number and testicular weight [42]. According to another study, also showing a declined number of rat epididymal sperm after incubation with inorganic Hg, a dose-dependent decrease in motility has also been noted [47].

Increased Hg levels in patients with infertility and subfertility than fertile men have been assessed [13], as observed and tubular atrophy or/and Sertoli-cell-only syndrome (SCOS) in infertile patients exposed to mercury [29]. In one case (25-year-old male with infertility), bilateral testicular biopsy has revealed marked interstitial lymphatic infiltration and about 33% of the tubules analyzed showed SCOS) and tubular atrophy. Fewer than 4% of the tubules showed qualitatively intact spermatogenesis. Furthermore, autometallographic (AMG) analysis of the biopsy material yielded silver-enhanced Hg grains, primarily in the interstitial Leydig cells, but sections from a control patient not exposed to this element have devoid of Hg grains [29].

Arsenic, like other toxicogens, has been shown to impair the development of the reproductive organs, to inhibit steroidogenesis and to reduce sperm quality, which can lead to male infertility [23, 61]. However, a general view of As-induced male reproductive toxicity still lacks, and the underlying mechanisms remain largely unclear. Data on the harmful effects of As on the male reproductive health criteria are mainly from studies with experimental animals. The substantial amounts of arsenic detected in testes, epididymus, seminal vesicle, and ventral prostate suggest a possible direct effect on testicular tissue. In an experimental model of mice treated with drinking water containing 533.9 mmol/L arsenite (the form of arsenic that is normally found in drinking water) for 35 days, the As levels increased of about 10-fold in the testes (0.52 to 5.26 mg/kg), approximately twice in the epididymis (2.70 to 4.70 mg/kg) and relatively less in the seminal vesicles, but no signs of toxicity were found [43]. However, mice injected subcutaneously with 3 mg/kg arsenic trioxide accumulated As in the testes and plasma and exhibited inhibition of spermatogenesis. The results of different studies show that most likely adverse effects of arsenic exposure are due to large individual variability in As metabolism affecting both retention and distribution of As metabolites [43].

According to a recent study on the general influence of As exposure on the proteome and metabolome in rat testis, significant changes in all of the identified proteins (total 70, up- and down-regulated) and metabolites (total 13, increased and decreased) have been established, compared with the controls [23]. For instance, elevated expression levels of glutathione peroxidase 4 (GPx4), 11β–hydroxysteroid dehydrogenase (HSD11B1), nuclear autoantigenic sperm protein (NASP), and calcium-binding and spermatid-specific protein 1 (CABS1) have been established, which have suggested impaired spermatogenesis (with damage of germ cells morphology and functions) after As exposure. Overexpression of protein GPx4 has been proposed to cause spermatogenic defects, including primary spermatocyte apoptosis, loss of haploid cells and seminiferous epithelium disorganization [44]. Testicular NASP was demonstrated to be involved in cell cycle progression in male germ cells (probably through an interaction with the Cdc2/cyclin B and Hsp70-2 complex) [51] and its overexpression has been observed during androgen receptor blockade when the process of meiosis of spermatocytes could be inhibited [52]. CABS1 is a calcium-binding protein that is involved in the extremely complex structural rearrangements occurring in haploid germ cells (with specific expression in the elongated spermatids) during spermiogenesis. The depletion of scaffolding factor B1 (SAFB1), transcriptional intermediary factor 1β (TIF1β), retinol-binding protein 1 (RBP1), DnaJ homolog subfamily A member 1 (DNAJA1), Y-box binding protein 3 (YBX3) and allopregnanolone in As-treated rats have been suggested as connected with abnormal spermatogenesis in the testis due to germ cell deficiency and low testosterone levels [23]. SAFB1 contains a transcriptional repression domain and can bind certain hormone receptors and repress their activity. Arsenic-induced inhibition of SAFB1 similar to male SAFB1 null mice may lead to infertility due to increased germ cell apoptosis, Leydig cell hyperplasia, and low TE levels, which may be due to decreased circulating insulin-like growth factor 1 (IGF1), and loss of SAFB1-mediated suppression of hormone receptors [24]. TIF1β is a transcriptional co-repressor known to play key roles in spermatogenesis and early embryonic development. This factor is preferentially associated with heterochromatin structures in the Sertoli cells and round spermatids, as well as with the formation of meiotic chromosomes [60]. Its absence has been observed to lead to a clear defect in spermatogenesis, associated

with failure to spermatids release and testicular degeneration [21]. RBP1 is a specific plasma transport protein (mainly localized in the SCs) that delivers retinol (Vit. A) in the seminiferous tubules required for the maintenance of normal spermatogenesis in the mammalian testis. The continuous deficiency of RBP1 and retinol, respectively, could lead to spermatogenic arrest at preleptotene spermatocytes, followed by extensive loss of germinal epithelium in rats [42]. DNAJA1 works similarly as a co-chaperone of Hsp70 in protein folding and mitochondrial protein import. Its loss could cause severe defects in the SCs, increased androgen receptor (AR) levels and disrupted Sertoli-germ cell contacts, which proves the critical role of this protein in the spermatogenesis through AR-mediated signaling in the Sertoli cells [55]. The necessity of protein YBX3 for the activation of protamine 2 transcription in post-meiotic male germ cells has been suggested, and thus, a relationship between its loss and decreased protamine 2 transcription [64]. It has further been proposed that As mainly impaired spermatogenesis and fertilization via aberrant modulation of the described male reproduction-related proteins and metabolites, which could be mediated by the ERK/AKT/NF-κB-dependent signaling pathway [23]. Also, As levels in the serum and testis of rats in the treated experimental groups were significantly higher than those in the control, and a dose-dependent increase has been assessed. In the serum, As concentration ranged from 0.18 to 0.67μg/mL, while in the testes - from 0.35 to 1.74μg/g, respectively. These results suggest a possibility for passing of As through the BTB, which could lead to its accumulation in the rat testes, and subsequently, to a variety of adverse effects on male reproduction [23]. However, no significant effects of the As exposure on the body weight (BW), testis weight (TW) and testicular coefficient (TW/BW) of rats have been established. The described data are important for clarification in some cases of idiopathic male infertility.

Spermatogenesis-related hormonal disruptions

Androgen hormones play a complex and important role in the regulation of spermatogenesis and maturation of male germ cells. The results of experimental studies in rats show many locations where the effects of heavy metals are involved in the dynamics of male sex hormones, mainly in the hypothalamic-pituitary-testicular axis [63].

In the pituitary gland is also possible to be accumulated Hg following exposure to Hg vapour. However, as a Hg exposure giving rise to a mean urinary Hg level of 37 μg/g of creatinine, there was no association between Hg exposure and serum levels of prolactin, thyroid-stimulating hormone, luthenizing hormone (LH) and foliculle-stimulating hormone (FSH) [16]. Decreased TE levels have also been reported in other experiments with rats. Impaired spermatogenesis and decreased TE levels were observed in 7-week-old rats treated with MeHg-chloride by subcutaneous injection at a daily dose of 10 mg/kg for 8 days [22]. Decreased TE levels were reported in animals with mean blood Hg levels of 30.8 ng/ml [39], and in other cases (among 3-month-old rats) observed OS and significant variations of the TE levels with blood mercury concentrations of 94.3 and 176.5 ng/ml [7].

Human studies on the toxic effects of Hg on male reproductive hormones are few and contradictory. A limitation of most epidemiological studies is the small sample size [1]. However, in one large epidemiological study (529 adult men from Greenland, Poland, and Ukraine) about hazardous effects of environmental Hg exposure on the human semen quality and male reproductive hormones, a significant positive

association between blood Hg levels (average whole blood concentration 9.2 ng/ml) with the serum concentrations of inhibin B among the Greenlandic Inuit men has been proved. The authors found that inhibin B serum levels increased with increasing Hg exposure among the Inuit. Usually, the high serum concentrations of inhibin B reflect high activity of the Sertoli cells and high sperm counts, and thus the direction of the association between blood Hg and inhibin B odds with the alleged toxic effects of Hg [36]. In this regard, an *in vitro* study of immature rat Sertoli cells has shown markedly decreased inhibin B levels after Hg exposure at levels far below those causing cellular toxicity [37]. The diet among Greenlandic Inuit is mainly based on seafood and fish that contain polyunsaturated fatty acids (PUFAs), but also accumulates Hg along the aquatic food chain. Authors have reported that levels of omega-3 PUFAs in human sperm are positively correlated with semen characteristics [2], and their positive association between Hg and inhibin B among Greenlandic Inuit may be due to their higher consumption of PUFAs through diet [36]. However, in this study the influence of low Hg levels on the reproduction-related hormones has been evaluated.

Arsenic is an electrophilic element and can bind to the electron-rich sulfhydril groups in proteins and may thus directly modulate the activities of key enzymes involved in TE production. The activity of 17β-HSD, an enzyme involved in TE metabolism, has been established to be decreased from 3.28 units to 1.50 units [8]. Plasma and testicular TE levels decreased by 38.2% and 59.4%, respectively, and plasma LH level decreased by 51.6%. Decreased expression and activities of 3β-HSD and 17β-HSD have been established in rodents administered to low levels of As (20–40 mg/L drinking water) [8, 10]. Several studies have suggested as major targets of As influence the hypothalamus and brain, which could cause hormone dysregulation and decreased sperm concentrations [26]. According to another report, the increasing arsenic level was associated with increased odds for low LH levels, after adjusting for age, BMI and current smoking [35].

In experiments with rats, As has been found to affect the levels of various proteins in the testicular tissue, which play an important role in the synthesis of TE and, accordingly, for the normal course of spermatogenesis. For example, arsenic-induced inhibition of SAFB1 may defect the activity of certain hormone receptors [24]. Corticosteroid 11β-dehydrogenase isozyme 1 (HSD11B1) is an enzyme (located exclusively in Leydig cells in rat testes), generating cortisol by catalyzation of the conversion of inactive cortisone to biologically-active cortisol and involved in this way in the TE production [51] allopregnanolone is the metabolite of progesterone by the actions of enzymes 5α-reductase and 3α-HSD [50]. The As-induced decrease of allopregnanolone levels is associated with the reduction of progesterone - a key intermediate metabolite in TE biosynthesis pathway levels, which would lead to impaired TE synthesis and spermatogenesis, but also to abnormal functions of other biologically-active proteins, described above. Thus, indirect inhibition on the TE synthesis, which then impaired spermatogenesis and produced low-quality sperm in rats, has been proposed on the influence of As [23].

By taking in consideration the ethical limitations, many of the described studies on the reproductive organs have been performed on experimental animals (mainly rodents), where large doses of Hg and As ions have been applied to reveal their influence on cellular and tissue levels. However, the used experimental animal models substantially differ from human occupational and environmental exposure conditions (including that through smoking).

Influence of heavy metals on sperm quality and male fertility

Similarly to other spermato-toxicants, Hg derivatives are also the cause of oligozoospermia, and chronic poisoning with them causes infertility in men. Some studies have reported that high, even low doses of mercury exposure harm men's reproductive health [1, 11, 54]. In most of these studies, the increased blood Hg levels in men were associated with a diet or consumption of more seafood than in people with lower Hg levels [61]. However, human studies are few and contradictory, probably due to different interpretations of the results, which did not always take into account the possibility of exposure to other substances (contaminants) in the food, environment or lifestyle, as well as the small number of men participating in the study. In most of the cases, seminal fluid Hg concentrations are correlated with abnormal sperm morphology and motility [11, 15]. In *in vitro* studies have been demonstrated changes in many bio-physiological parameters of human sperm after treatment with Hg (concentrations from 10.0 to 160.4 mg/L), inducing membrane lipid peroxidation and DNA breaks, decreased sperm motility, viability and lowered rate of the acrosome reaction leading to sperm dysfunction [1]. A large-scale study with subfertile men (111 men from Hong Kong) has shown a correlation of the seminal fluid Hg concentrations (mean level 22.1 ± 2.0 nmol/L) with abnormal sperm morphology, particularly with defects in the head and midpiece, as well as with abnormal sperm motility [11]. Straightline velocity (VSL), linearity (LIN) of the motion path, and amplitude of lateral head displacement (ALH) were reduced, whereas average path velocity (VAP) was increased, depicting that sperm motion lost forward progression and became violently erratic in the presence of higher semen Hg concentrations. Besides, these authors have shared that the men with significantly higher blood Hg concentrations than those in semen (41.4 ± 1.7 nmol/L versus 22.1 ± 2.0 nmol/L) have shown the presence of a functionally-active blood-testis barrier to Hg, but no correlation of the overall percentage of motile spermatozoa and sperm concentration with blood Hg concentrations [11]. In one case with a young man with unexplained infertility, with assessed chronic Hg intoxication (with high blood and urine levels), semen analysis has been connected with severe oligoasthenoteratospermia (or azoospermia) with elevated serum FSH [29]. Thus, Hg may behave as a spermatotoxicant and to impair fertility potential both *in vivo* and in IVF programs, because fertility potential has been shown to be related to sperm morphology and motion [15]. In other small investigations, performed by Swedish, Michigan (USA) and Singapore scientists, no associations between blood or semen MeHg levels and sperm concentration (or total sperm count), motility, chromatin integrity or on the proportion of Y-chromosome bearing sperm [9, 46, 49], and/or significant alterations in reproductive hormone levels [35], have been found, except a study of infertility patients in Singapore [9]. Other case-patients, characterized with high total blood Hg concentrations (14.4 ng/L), have had lower sperm number, as well as percentages of morphologically normal sperm and motile sperm, compared to men, characterized with lower levels (6.3 ng/L) of the same element [31]. The authors, however, have noted no statistically significant differences in sperm parameters probably due to the small number of participants [31]. Taken together, these findings suggest that probably men with somewhat higher blood Hg concentrations (above 8 mg/L) were more likely to have reduced sperm parameters than men with a lower concentration of the element [36]. Many studies with different animal models (mice, rats, monkeys) have also confirmed the toxic effects of Hg on the reproductive system, with adverse effects on seminal parameters (decreased sperm motility, viability and induced DNA breaks in the

spermatozoa) after Hg exposure [7, 22, 42]. Another experiment has shown a decreased sperm number in the rat epididymis after incubation with inorganic Hg, as well as their decreased motility, in a dose-dependent manner [47]. Adult monkeys treated with MeHg orally at doses 50 or 70 mg/kg/day for 20 weeks had a decreased motility and swimming speed sperm (in a dose-dependent fashion) and increased abnormal sperm tail morphology (probably associated with interference in the dynein/microtubule sliding assembly). The percent total tail defects increased significantly in the MeHg treated groups compared to controls (approximately 16% vs. approximately 33% for both treated groups) [36].

According to most of the epidemiological reports, As exposure has also been associated with genotoxicity, increased risk of prostate carcinogenesis, reduced sperm quality, and lead to adverse birth outcomes [5, 62]. Sperm nuclear chromatin showed large amounts of thiol-rich protamines, but their flagellums are also rich in thiol bonds. These groups provide binding sites for As in the sperm nucleus or flagellum, impairing their structure and function. Just a few experimental animal studies available have found the harmful effects of As on parameters of male reproductive health [10, 23, 30]. Significantly reduced sperm motility, sperm viability, and total epididymal sperm counts, as well as the increased percent of germ cells with morphological abnormalities, have been observed in mice, experimentally treated with As [10, 43]. Elevated levels of GPx4, HSD11B1, NASP, and CABS1 lead to produced low-quality sperm, that sperm number and motility have been reduced in As-treated rats [23]. Furthermore the As-induced repression of other proteins such as VDAC3 (voltage-dependent anion channel protein 3), PRKACA (cAMP-dependent protein kinase catalytic subunit alpha), and GPD2 (glycerol-3-phosphate dehydrogenase 2), as well as the aberrant increase of L-tyrosine, may disrupt the extent of protein tyrosine phosphorylation required for sperm capacitation, which then results in fertilization failure and male infertility. Tyrosine phosphorylation of proteins is one of the most common mechanisms, through which several signal transduction pathways in the spermatozoa are adjusted. This mechanism regulates various sperm functions, such as motility, hyperactivation, capacitation, acrosome reaction, and fertilization [27]. It has also been suggested that As could negatively affect the fertilization process by inhibiting the binding and fusion of spermatozoa with the ovum. In this regard, 6 proteins (down-regulated) and 1 metabolite with an elevated level have been studied, which inhibited the fertilization process in arsenic-exposed rats [23]. Besides, decreased expression levels of SPACA1 (sperm acrosome membrane-associated protein 1), ACE (angiotensin-converting enzyme), and SMCP (sperm mitochondrial-associated cysteine-rich protein) in the testis under the influence of As, hinder sperm fertility, has been assessed in the rat. Disruption of SPACA1 levels has also been found to lead to abnormal formation of the sperm head (or globozoospermia), leading to male infertility in mice [18]. Also, antibodies against recombinant SPACA1 inhibit both the binding and the fusion of sperm to zona-free eggs [20]. A germinal ACE knockout in mice has caused a defect in zona pellucida of the oocyte [19]. Li *et al.* reported that the absence of gACE expression is responsible for fertilization failure [32]. Sperm mitochondrial-associated cysteine-rich protein (SMCP) is a constituent of the keratinous capsule surrounding sperm mitochondria that enhances sperm motility. The deletion of SMCP has been found to impair sperm motility, resulting in male germ cells that fail to migrate in the female reproductive tract and to penetrate the egg membranes during fertilization [40]. On the other hand, a possible mechanism for decreased sperm motility might be associated with the direct binding of arsenic to sperm [56].

The studies investigating the effects of As (in natural or low-level exposure) on human male reproductive outcomes are relatively few. Recently, a few epidemiologic studies showed that As-exposure significantly lower sperm quality and causes infertility, as well as erectile dysfunction in men [35]. Another cross-sectional investigation of men attending infertility clinics in Michigan, USA, has indicated a significantly increased risk for low sperm motility in exposure to environmental levels of As (after adjusting for smoking and age) [35]. The odds ratio for low sperm motility with the highest As quartile was 3.80 (1.38–10.4). Arsenic was also a significant risk factor for low semen volume in a multi-metal model. However, the molecular mechanisms underlying As-induced male reproductive dysfunctions are still poorly understood.

Conclusion

As and Hg injure the reproductive system by mechanisms, associated with hormonal regulation and function, binding to sperm and regulation of steroidogenesis, as well as direct effects of testicular component cells. The toxic effects are influenced by the sources, forms and routes, but also by the doses and periods of exposure of these elements. However, the reproductive and developmental toxicity of Hg and As is poorly understood and the molecular mechanisms of the induced reproductive toxicity remains unclear. As-induced dysregulation of series of differential proteins and metabolites (specifically related to male reproduction) could lead to impaired spermatogenesis and sperm function, and/or to male infertility. Arsenic also influences the hypothalamus and brain, which could cause hormone dysregulation and may thus directly modulate the activities of key enzymes involved in TE production. Mercury also induces massive degeneration of germ cells and alterations in the levels of the testosterone. The wide specter of harmful effects in the different tissues and organs is probably due to the activated production of reactive oxygen species and OS, in result of the exposure on high Hg and As levels, together with the influence of other heavy metals.

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