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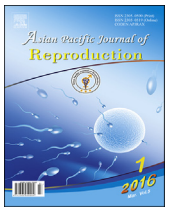

Review http://dx.doi.org/10.1016/j.apjr.2015.12.001

Relationship of oxidative stress with male infertility in sulfur mustard-exposed injuries

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ARTICLE INFO

Article history:
Received 29 Aug 2015
Received in revised form 10 Oct 2015
Accepted 1 Nov 2015
Available online 19 Dec 2015

Keywords:
Sulfur mustard (SM)
Oxidative stress
Reproductive system
Sperm
Male infertility

ABSTRACT

Sulfur mustard (SM) is a cytotoxic and chemical agent that targets different tissues such as reproductive system. SM causes a wide variety of pathological effects on reproductive system such as disturbance in reproductive hormones, testis atrophy, spermatogenesis deficiency, low quality of sperm and fertility problem. However, molecular and cellular mechanisms of its adverse effects are still not well known. General events such as tissue damage, inflammation, DNA alkylation, cell membrane defects, apoptosis and cell death are observed frequently in SM-exposed subjects. Oxidative stress (OS) and antioxidants depletion induced by SM seem to be one of the main factors that lead to low sperm quality and male infertility among exposed patients. It is believed that SM can trigger several molecular and cellular pathways linked to OS and inflammation in reproductive system that can cause impaired spermatogenesis, sperm apoptosis and poor sperm quality as well as loss of tissue structure and function. Identification of these signaling pathways and molecules gives us valuable information regarding the mechanisms of SM effect on reproductive dysfunction and the way for developing a better clinical treatment. Therefore, in this review we aimed to discuss the proposed cellular and molecular mechanisms of SM effect on reproductive system, the significance of oxidative stress and the mechanisms by which SM induces OS and antioxidants depletion in SM exposed men.

1. Introduction

2,2′-Dichlorodiethyl sulfide, commonly known as sulfur mustard (SM), is an oily lipophilic liquid which has been used as a chemical warfare agent. It is one of the major chemical warfare agents developed and used during World War I (1914–1919) [1]. But the highest unconventional application of SM occurred in Iran–Iraq war (1980–1988). During that period, it injured more than one hundred thousand Iranians, one-third of whom are still suffering from late effects [2,3]. This gas has several pathological consequences on various organs and systems of the victims which has previously been reported [4]. Eyes, skin and respiratory system are the main target organs of SM toxicity [5–7]. Other major acute pathological findings of SM exposure in humans include immunological and neuropsychiatric changes, gastrointestinal (GI) effects, hematological effects, sleep disorders and cancer [2,8–11]. Finally, it can induce a wide variety of genetic mutations, genetic damage and particularly lead to increased rates of cancer [12–15].

Reproductive system is one of the main targets of SM toxicity following exposure. Prevalence of infertility among SM exposed men has been reported from 2.5% to 35% [16–18]. Increased follicle stimulating hormone (FSH) levels along with decreased levels of testosterone and reduced semen quality were reported as the major effects after SM exposure [19–22]. An increased rate of fetal death and altered sex ratio were also reported in progenies of Iranian survivors of chemical attacks that included SM [16,19]. Although several studies have shown the negative effects of SM on reproductive function and male infertility, cellular and molecular mechanisms by which SM affects spermatozoa and induces poor sperm quality are still not well known. Therefore, there is a need for further detailed studies with focus on underlying mechanisms by which SM induces reproductive dysfunction and male infertility. One of these mechanisms is likely related to increased seminal plasma oxidative stress (OS) induced by reactive oxidative species (ROS). Recent studies have shown that pathological effects of SM are primarily due to its ability to form adducts with a variety of macromolecules such as DNA, lipids and proteins [23]. This can lead to inhibition of nucleic acid and protein biosynthesis, as well as ATP production which disruption of

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Peer review under responsibility of Hainan Medical College.

intracellular energy metabolism. It is well documented that SM accelerates oxidative stress through either an increase ROS generation from endogenous or a decrease in antioxidant capabilities and oxidative DNA repair [24]. This oxidative stress then, in turn, may damage DNA resulting in chromosome instability, modify gene expression, genetic mutation or modulation of cell growth that may result in cell death [25,26]. Therefore, toxicity from SM on cells may be the result of the direct damage induced by alkylating cellular components or SM-induced ROS production and oxidative stress.

In contrast with other cells, human spermatozoa are particularly susceptible to oxidative stress induced ROS. So, they are the major candidates for pathological and cytotoxic effects of SM [27]. In the following sections, we will discuss general reproductive effects of SM as well as significance of oxidative stress and mechanisms by which SM induces oxidative stress and antioxidants depletion in reproductive organs.

2. Reproductive effects

Although a small number of studies have considered the adverse effects of SM on reproductive function over the past few years, data addressing the negative effects of SM on sperm quality and male infertility are increasing. Several clinical investigations and animal experiments suggest that SM causes a wide variety of structural and functional defects in reproductive system including disturbances in the levels of reproductive hormones, testicular damages, sexual dysfunction, genital lesions, impaired spermatogenesis, poor sperm quality, and reduced fertility [19]. Some evidences addressing toxic effects of SM on reproductive function are summarized in Table 1.

Several studies have shown that SM exposure causes poor sperm quality, suggesting spermatozoa are particularly susceptible to toxic effects of SM. Azoospermia and severe oligospermia have been reported in 42.5% and 57.5% of patients with a history of exposure to SM, respectively [32]. Abnormal morphology of sperm (53.8%), decreased sperm motility (48.4%), reduced sperm count (23.1%) as well as abnormal semen viscosity (17.6%) and decreased semen volume (16.5%) have been reported as the most common semen abnormalities in patients exposed to SM [18]. In a study, semen analysis was considered among patients who had been exposed to SM during the Iran–Iraq war. The results of this analysis indicated the sperm abnormalities in 38% of the SM victims [18]. In another study, long-term toxic effects of SM on the testis and male fertility were investigated two decades after exposure. Male factor infertility was diagnosed in 23% of exposed patients and all semen indices were significantly decreased in the SM exposed men [21].

Several studies have revealed that SM can also disturb levels of reproductive hormones, which are essential for the regulation and initiation of spermatogenesis. Moreover, it has been found to interfere with the hypothalamus-hypophysis-testis axis, which is associated with impaired spermatogenesis and low quality of sperm. Gonadotropins (FSH, LH) and testosterone are the main regulators of germ cell development and spermatogenesis. Therefore, abnormal spermatogenesis is often associated with altered levels of serum gonadotropins and testosterone. Recent studies have revealed significant changes in plasma gonadotropins and testosterone concentrations among SM exposed

Table 1
Toxic effects of SM on male reproductive system.

Study model	Dose	Duration	Effects	References
SM victims	–	Several years	↓ Infertility (23.3%); ↓ Sperm quality (38.7%); ↑ Abortion (13.6%); ↑ Sexual dysfunction (9%); ↓ Libido (30%); ↑ Premature ejaculation (23.6%); ↑ FSH (57.6%); ↑ LH (66.3%)	[28,29]
SM victims	–	1st week after exposure	↓ Free serum testosterone; ↓ Dehydroepiandrosterone (DHES)	[30,31]
SM victims	–	5th week after exposure	↓ Free serum testosterone; ↓ Dehydroepiandrosterone (DHES)	[20]
SM victims	–	3rd and 5th week after exposure	↑ Serum FSH; ↑ Serum LH	[20]
SM victims	–	3 years after exposure	↓ Free serum Testosterone; ↑ Testicular atrophy; ↓ Spermatogenesis; ↑ Sertoli cell only pattern	[20,32,33]
SM victims	–	20 years after exposure	Normal LH, FSH and Testosterone	[21]
SM victims	–	3 months after exposure	↑ Oligozoospermia (33.3%)	[20]
SM victims	–	4 years after exposure	↑ Sperm counts (172×10^6)	[21]
SM victims	–	10 years after exposure	↑ Abnormal sperm (38%); ↑ Abnormal morphology of sperm (54%); ↓ Sperm motility (48%)	[18]
SM victims	–	15 years after exposure	↑ Oligozoospermia (10%)	[16]
SM victims	–	20 years after exposure	↓ Semen volume; ↓ Sperm counts; ↓ Sperm motility; ↓ Normal morphology of sperm	[21,28,34]
SM victims	–	20 years after exposure	↑ Sperm DNA damages	[35]
SM victims	–	8 years after exposure	↓ Libido (33.3%); ↑ Erectile dysfunction (9%); ↑ Premature ejaculation (23.6%)	[29]
SM victims	–	Few hours or few days after exposure	↑ Genital lesions; ↑ Hypopigmentation	[3,36]
Male rats	0.5 mg/kg	10 days	↑ Abnormal sperm; ↓ Sperm counts; ↓ Sperm motility	[37]
Male rats	5 mg/kg 10 mg/kg	10 days	↑ Abnormal sperm; ↓ Sperm counts; ↓ Sperm motility; ↓ Free serum testosterone; ↓ Testis weight	[38]