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Chemical Stressors and Gonadal Oxidative Stress

Research Article

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Abstract:

With growth in technology and industrializations over the years, there has been a tremendous rise in the amount of chemicals generated. Chemicals such as furans, dioxins, hydrocarbons, flame retardants, perfluorinated compounds, volatiles, phthalates, semi-volatiles, pharmaceuticals, heavy metals and endocrine disrupting chemicals pose a huge threat to human health and reproductive functions. Owing to their salutary role in hormone action, receptors are one of the major targets for the disruptive effects of chemical stressors causing hormone resistance. Many chemical stressors accumulate within the tissue due to their non-biodegradability and modulate p53 expression. They also orchestrate productions of several cytokines from activated kupffer cells including interlukin-1, interlukin-2, and interlukin-8 and gamma interferon and potentiate oxidative stress in various tissues including the gonads. The aim of the review was to discuss the effects of chemical stressors on gonadal oxidative stress inductions.

Keywords: Religion Oxidative stress; Chemical stressors; Reproductive function; Gonad, Chemicals.

INTRODUCTION

The environment is replete with hundreds of chemicals generated through inevitable natural and human processes [1]. Quite a bulk of them is a product of industrial activities. The most appalling aspect is not actually the preponderance of chemicals but their undeniable deleterious effects on human and animal health. Chemical stressors are chemicals produced within and out of organismal confines that poses threats to homeostasis and defense processes. Examples include furans, dioxins, hydrocarbons, heavy metals, flame retardants, perfluorinated compounds, volatiles, phthalates, semi-volatiles, some pharmaceuticals and endocrine disrupting chemicals [2].

Chemical stressors contribute barrage of adversities to the production of many hormones such as sex hormones and the hypothalamic hypophyseal-gonadal axis in the body resulting in subfecundity and fertility problems [3]. Hormone receptors are one of the major targets for chemical stressors due to the importance of receptors in hormone action [4]. Suppression of endocrine receptors within the endocrine system, disruption of endocrine receptor expression, alteration in signal transduction as outcomes of chemical stressor and with attendant change in hormone production, transport, distribution, and degradation.

Owing to their non-biodegradability, many chemical stressors bio-accumulate within the tissues and alter p53 expression [5]. They also induce secretions of several chemical signals from activated kupffer cells including interlukin-1, interlukin-2, and interlukin-8 and gamma interferone [5]. In addition, they orchestrate a cascade of redox reaction culminating in oxidative stress [6]. Oxidative stress is a dishomeostasis in which oxidants are in excess of

antioxidants. It is a consequence of unregulated oxidant generations or reduced antioxidant generation [7]. Generation of free radicals is increased in nutritional deficiencies, mitochondrial dysfunctions, stress, aging and diseases, increased oxygen pressure, light stress [8,9], ultraviolet rays, ionizing radiation and chemical stressors such as heavy metals, water contaminants, sprays, smokes, alcohols and xenobiotics [10].

Although, a level of Reactive Oxygen Species (ROS) is necessary for gene expression [11,12] and signal transduction [13], the maintenance of oxidant/antioxidant balance is important for cellular function within the gonadal tissues. This is majorly supported by the high replicative abilities of germ cells during reproductive life. Several primary studies have examined the deleterious effects of chemical stressors on reproductive system and fertility in males and female and the underlying mechanisms. The aim of the review was to concisely highlight the effects of chemical stressor on gonadal oxidative stress induction.

CHEMICAL STRESSORS

Chemical stressors are noxious stimuli that enter the body through faeco-oral, respiratory and dermal routes. They include carbon-containing substances such as furans, dioxins, hydrocarbons, flame retardants, heavy metals, perfluorinated compounds, volatiles, phthalates, semi-volatiles, endocrine disrupting chemicals, some pharmaceuticals and many more [2]. They are produced naturally and also exist as product of human and industrial processes. They threaten physiological processes and cause derangement of homeostatic mechanisms [14].

The toxicity of chemical stressors is directly attributable to their lipophilicity, non-biodegradability and longer half -life. As lipophilic agents, they are easily able to find their ways through the lipid membrane barrier into vital internal organs in the body. Being non-biodegradable implies resistance to first pass metabolisms and renal degradation and a consequent precipitation in body tissues such as liver, adipose tissues, kidney, brain and gonads [5, 15,16]. Long half avails them the opportunity to maintain their activities within the body without option of decimation. Chemical stressors contribute imperils to the production of many hormones including sex hormones and the hypothalamic hypophyseal-gonadal axis in the body culminating in reproductive and fertility problems [3]. Hormone receptors are important target for chemical stressors owing to the importance of receptors in hormone action [4]. Suppression of endocrine receptors within the endocrine system, disruption of endocrine receptor expression, alteration in signal transduction as outcomes of chemical stressor and with attendant change in hormone production, transport, distribution, and degradation.

Exposure to water contamination for seven days was shown by Azubuike *et al.,* (2013) [17] to result in bio-accumulation of heavy chemicals such as Nickel, Copper, Lead, Zinc and Iron in descending order of their testicular level. High levels of heavy metals may disrupt the regenerative ability of sperm producing cells and cause decline in steroidogenic tendency of the testes. Moreover, oogenesis is another hormonally controlled process. Proliferation of chemical stressors in modern society due to industrialization and technological improvement has left Scientists wondering the possible impact of this trend on gamete development. Björvang and Damdimopoulou, (2020) [2] in their study reported detection of chemical stressors in the ovarian follicular fluid. This astonishing finding indicated that oocytes are not shielded from these disruptive substances. In addition, exposure to chemical stressors has been reported to cause poor *In vitro* Fertilization successes.

OXIDATIVE STRESS

Oxidative stress is a derangement in oxidant/antioxidant balance. It occurs whenever oxidant levels are unregulated or antioxidant scavenging ability falls short of oxidant generation. Oxidants are chemicals generated during normal cellular metabolisms and pathological conditions and are capable of interacting with tissue atoms either to attain stable electronic configuration or as routine processes [7]. Oxidants that interact with tissue atoms for the purpose of achieving stable electronic configuration are called free radicals and they tend to possess unpaired electrons. Examples are superoxide anion, singlet oxygen and hydroxyl radical [13,18]. Hydroxyl radicals are highly reactive free radicals but with low half-life *in vivo*. They are difficult to measure in the blood. Unlike hydrogen peroxide and superoxide anions which possess intrinsic regulatory enzymes, there is none for hydroxyl radical. Reactive nitrogen species such as nitric oxide (NO), nitric dioxide and peroxynitrite formed when nitric oxide reacts with superoxide anion. Those that interact on basis of routine are sluggishly reacting chemical. They lack unpaired electrons and an example is hydrogen peroxide. Malondialdehyde (MDA) is orchestrated as a result of peroxidation of polyunsaturated fatty acid [19].

It is important to note that oxidants are necessary for physiological functions including cell signaling. In fact, free radicals' function as second messengers for some chemical messengers. For example, hydrogen peroxide and p38 Mitogen-activated protein kinase were indicated by Ushio-Fukai *et al.,* (1998) [20] as an important part of the angiotensin II signaling pathways. Bae *et al.,* (1997) [21] also reported that epidermal growth factor induced hydrogen peroxide production in the presence of tyrosine kinase. Neutrophils generate superoxide anion and peroxides to combat invading agents using its Nicotinamide Adenine Dinucleotide phosphate oxidase and myeloperoxidase respectively. Microglia and macrophage generate hydroxyl radical in response to certain antigenic substances most especially bacteria. Nitric oxide is necessary for regulation of vascular tone. Being produced by granulosa cells, macrophages and neutrophils and corpus luteum, normal level of free radicals are necessary for ovarian function and ovulation induction [22].

However, generation of free radicals is increased by situations such as occurs in malnutrition, mitochondrial dysfunctions, stress, aging and diseases, increased oxygen pressure, light stress [8,9,23], ultraviolet rays, ionizing radiation and chemical stressors such as heavy metals, water contaminants, sprays, smokes, alcohols and xenobiotics [10]. Some of these chemicals tend to accumulate within the body organs due to their non-biodegradability while others may activate oxidant generations by cytochrome P-450 systems. However, it is important for them to be kept in check since they are produced even during normal cellular metabolisms; xanthine oxidase pathway, oxidative phosphorylation and many more. Secondly, excess of oxidants can cause deteriorate tissue functions.

Regulation of oxidant and reactive oxygen species level occurs both intrinsically and extrinsically through antioxidants. Intrinsic antioxidants are those that are produced by the cell organelles. It is also possible to acquire antioxidants from external sources such as foods, water, supplements and infusions. Intrinsic antioxidants include enzymatic and non-enzymatic antioxidants [24-27]. Examples of intrinsic enzymatic antioxidants are superoxide dismutase, catalase and glutathione peroxidase. There are plethora of intrinsic non-enzymatic antioxidants in the body and they include glutathione, lipoic acids, thioredoxin, melatonin [8.28,29], binding proteins, cysteine, tocophenols, uric acid. Extrinsic antioxidants include antioxidant vitamins and minerals such as vitamins A, C and E, flavonoids, rutin, lycopene, selenium which are obtainable from plant and animal foods and water.

Oxidant/Antioxidant Balance And Reproduction

Although, a certain quantity of Reactive Oxygen Species (ROS) is necessary for gene expression [11,12] and signal transduction [13], the maintenance of oxidant/antioxidant balance is important for cellular function within the gonadal tissues. This is majorly supported by the high replicative abilities of germ cells during reproductive life. Studies have shown that the equilibrium between free radicals (oxidants) and antioxidants greatly influences endometrial changes in different luteal phases, folliculogenesis, ovulation, fertilization, placental growth, embryogenesis, and implantation [12,22]. However, under deranged oxidant/antioxidant balance, impairment in reproduction and fertility may ensue [12,30].

Catalase plays important role in free radical regulations. Catalase is predominantly registered in peroxisomes. Although the expression of catalase in oocytes is low compared with other cell types in the follicles [31], inhibition of catalase led to chromosomal misalignment in the oocyte nucleus [12]. During meiotic maturation in mouse oocytes, catalase has been shown to protect the genome from oxidative damage [12,31]. The relevance of antioxidants during spermatogenesis is unquestionable owing to the rapidity with which cells divide.

The activity of catalase in granulosa cells from large follicles has been shown to be greatly higher than that in small and medium follicles in pigs [32], goats [33], and rats [34]. In rat ovarian granulosa and theca cells, increased catalase activity occurs during ovarian development and luteinization [12]. During estrous cycle, catalase activity in ovary homogenate was found to be greatest in the metestrus phase but declined in the estrous and pro-estrous stages, and reached the lowest levels in the diestrus phase [12].

Glutathione peroxidase is a selenium requiring enzyme that protects the organisms from oxidative damage. The biochemical function of glutathione peroxidase (Gpx) is to reduce lipid hydroperoxides to their corresponding alcohols and to reduce free hydrogen peroxide to water [35]. Several Studies have documented the correlation between increased dietary selenium intake and glutathione activity level in human and animal models. For example, in old female rats, the minimum dietary selenium requirement of 0.05µg Se/g diet or below maintained red blood cell glutathione peroxidase enzyme Gpx-1 activity [36]. Since the bioavailability

of selenium is directly related to the activity of the GPx system acting as a free radical scavenger and preventing the lipid radicals, selenium concentrations may decrease in those patients at risk of recurrent miscarriage because selenium is incorporated into the active site of GSH-Px [37].

Effect of Chemical Stressors on Testicular Oxidative Stress

The male gonad contains actively dividing cells to produce up to 1500 sperm cells in 1 second courtesy of spermatogenesis provided all necessary conditions are in place. Being metabolically active cells as they produce gametes and gonadal hormones, free radical generation cannot be ruled out. Preponderance of primary studies exists on the impacts of chemical stressors on oxidative stress induction in gonadal tissues. In Nigeria, water contamination by crude oil is one of the principal chemical stressors. Hence, Farombi et al., (2010) [38] in their study exposed male rats to bonny crude oil for 7 days. There was a fall in testicular levels of catalase, superoxide dismutase and glutathione transferase and a rise in malondialdehyde and hydrogen peroxide in the testes. When crabs were administered cadmium ranging from 0 to 116mg/l for a period of 7 days, Wang *et al.*, (2011) [39] showed a transient rise in testicular catalase, glutathione peroxidase and superoxide dismutase levels and a subsequent decline in these antioxidant enzymes in a pattern that was dependent on cadmium dose. There was also a rise in testicular levels of hydrogen peroxide and malondialdehyde based on the dose of cadmium exposure.

A study by Toshiaki and Zhi, (1992) [40] indicated that exposure of rats to 30 nmol/kg of cadmium after 6 and 9 hours caused xanthine oxidase, one of the sources of free radicals to increase in Interstitial Cells of Leydig. There was lipid peroxidation, elevated production of iron level and hydrogen peroxide in Leydig Cells after 12 hours of exposure as well as reduction in glutathione, catalase and glutathione reductase level. Said *et al.,* (2010) [41] assessed the likely outcome of reversing testicular adversity caused by cadmium using the duo of zinc and selenium for a period of 35 days. In the study, cadmium was shown to lead to elevated production of malondialdehyde as well as reduced levels of catalase, superoxide dismutase and glutathione peroxidase in the testes. In a study by Bartolini *et al.,* (2022) [6], cadmium toxicity induced impairment in Sertoli cell viability was characterized by elevated generation of hydrogen peroxide. The authors also showed that administration of 5 and 10 µM of cadmium caused restoration of hydrogen peroxide levels.

TABLE 1- *Effect of chemical stressors on gonadal oxidative stress*

S/N		CHEMICAL STRESSORS	EFFECT ON GONADS	REFERENCES
1		Water contaminant (bonny crude oil)	Decreased testicular catalase, superoxide dismutase and increased malondialdehyde in rats	Farombi *et al.,* (2010) [38]
2		Cadmium	Initial increase in testicular catalase, superoxide dismutase and glutathione and subsequent decrease in the enzymes in crabs	Wang *et al.,* (2011) [39]
3		Cadmium	Testicular hydrogen peroxide rose, catalase, glutathione reductase and glutathione reduced in rats.	Toshiaki and Zhi (1992) [40]
4		Cadmium	hydrogen peroxide and malondialdehyde increased and productions of glutathione peroxidase and catalase reduced in fresh water leech ovaries	Ichrak *et al.,* (2022) [43]
5		Cadmium	Rise in malondialdehyde. Superoxide dismutase, glutathione and catalase reduced.	Rotimi *et al.,* (2021) [44]
6		Cadmium	Rise in ovarian malondialdehyde and reduction in catalase	Ruslee *et al.,* (2020) [47]

Effect of Chemical Stressors on Ovarian Oxidative Stress

Oogenesis and hormone secretions are among the metabolic activities that occur within the ovaries. The processes are associated with free radical generations. Martino et al., (2017) [42] investigated the effect of cadmium, a heavy metal on egg fertilization as a way of underscoring the role of cumulus-oocyte complex oxidative stress in derangement in fertilization orchestrated by cadmium. At nanomolar level of cadmium, cumulus-oocyte oxidative damage occurred culminating in deranged fertilization of oocyte was observed. There was also over-activity of mitochondrial at the same concentration. Since mitochondria are an important epicenter for reactive oxygen species generation, it is possible that the oxidative stress identified in the study emanated from the overactive mitochondria. The aim of the study conducted by Ichrak *et al.,* (2022) [43] was to understand whether cadmium administration at a 50 µg/l concentration for a period of 7 days would affect oxidant/antioxidant balance in freshwater leech ovaries. A significant rise in ovarian hydrogen peroxide and malondialdehyde generations as well as decline in productions of glutathione peroxidase and catalase was reported.

A study by Rotimi *et al.,* (2021) [44] was designed to determine the effect of gallic acid on oxidative toxicity in ovary caused by cadmium. However, they showed that administration of cadmium chloride at 20mg/kg for a period of 14 days orchestrated a rise in malondialdehyde and decreased superoxide dismutase, glutathione and catalase levels in the ovaries. Kechiche *et al.,* (2021) [45] demonstrated the possibility of assuaging ovarian toxicity induced by cadmium using melatonin. In the study cadmium was reported to orchestrate oxidative stress in rats' ovary. A study by Piras *et al.,* (2022) [46] found that a natural polyphenol 'Resveratrol' at 1 µmol/L was able to cause restoration of the diminished oocyte meiotic competence orchestrated by administration of cadmium. In the study cadmium was reported to cause disruption of oocyte cytoplasmic maturation by raising reactive oxygen species. A study by Ruslee *et al.,* (2020) [47] was primarily designed to examine the effect of Tualang honey on cadmium induced ovarian toxicity. After 42 days of exposure, cadmium at 5mg/kg was reported to cause a rise in malondialdehyde levels and decreased in catalase levels in ovarian tissues.

DISCUSSION

The deleterious effects of oxidative stress on tissues cannot be undersized. The review specifically covered the hypothalamic-hypophyseal-gonadal axis from gonadal angle. Beyond doubt several evidences are available from primary studies on the effects of chemical stressors on gonadal oxidative stress induction. In the review, cadmium was the most prominent chemical stressor. Cadmium is a period table element generated industrially and through several environmental sources. The metal exists bound with other period table elements as cadmium sulfate, cadmium chloride or in unbound state.

As a heavy metal, its non-biodegradability and bio-accumulation play important role in oxidative stress induction and organ toxicity. Within the tissue, cadmium modulates the expression of p53 and induces production of chemokines from activated kupffer cells including interlukin-1, interlukin-2, and interlukin-8 and gamma interferon [5,48,49]. Cadmium also orchestrates a cascade of redox reaction culminating in oxidative stress and causing reductions in the levels of superoxide dismutase, catalase, glutathione peroxidase and an increase in malondialdehyde and hydrogen peroxide productions by tissues [6].

Oxidative stress is an antagonist factor to gametogenesis, gonadal endocrinology and reproduction. Free radicals attenuate expression of follicle stimulating hormone receptors [4] and orchestrate gonadotropin resistance. This results into impaired folliculogenesis, and anovulation. One of the possible mechanisms of oxidative stress induced reproductive derangement is activation of nuclear factor kappa-B and activator protein-I [22]. These transcription factors have been implication in several diseases. Furthermore, oxidative stress may promote increased membrane permeability resulting in efflux of calcium from sarcoplasmic reticulum and increase in intracellular calcium concentration with attendant induction of apoptosis. Oxidative stress may likewise target plasma membrane making it more permeable with resultant instability in membrane potential. Oxidation of deoxyribonucleic acid (DNA) by oxidative stress is also not uncommon. Oxidation may lead to increased DNA damage and decrease in DNA repair [12,31] with attendant reduction in gonadal response to gonadotropins, subfecundity and infertility.

As the impacts of environmental factors and chemical stressors in the induction of reproductive derangements cannot be overemphasized, more studies especially organ-specific works are needed to aid in understanding the pathophysiology and pathogenesis of chemical stressor induced reproductive abnormalities more comprehensively.

CONCLUSION

In testes and ovaries, exposure to chemical stressors caused gonadal oxidative stress that was characterized by decreased gonadal levels of superoxide dismutase, catalase and glutathione peroxide and an increase in malondialdehyde and hydrogen peroxidase.

DECLARATION

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Authors' Contributions

All authors contributed equally.

Competing Interest

The authors declared no competing interest.

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