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Oxidative stress in reproductive toxicology

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Abstract

Oxidative stress (OS) has been implicated in the causation of environmentally-induced diseases. However, the role of toxicants in the pathophysiology of disorders and diseases affecting the reproductive system are less understood. This review focuses on some of the mechanisms that underlie OS-induced reproductive toxicity at the cellular- and organ levels (germ cell damage and perturbed organ responses to endocrine stimuli). While most of the reproductive and developmental studies conducted in adult animals and transgenerational adult animals point to the involvement of genotoxicity, the part played by epigenetic alterations is accorded a recent recognition, thus warranting more studies in this area. Additionally, metabolomic, proteomic and transcriptomic approaches need to be employed to advance our understanding of key metabolites formed and the expression of anti-OS genes at the molecular level that are necessary for combating reactive oxygen species formation. The resulting data could be analyzed using bioinformatics tools to identify the pathways linked to disease causation and as a consequence, the adoption of therapeutic strategies, including but not limited to administering phytochemicals (many of which possess antioxidant properties) to improve disease outcomes.

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1. Introduction

Procreation is a naturally endowed right of every couple. Regretfully, infertility among women of reproductive age in the USA was estimated as 4.5–4.9 million annually between 1982 and 1988. By 1995 this estimate increased to 6.2 million and is predicted to increase to about 7.7 million by 2025 [1,2]. Diagnosis of infertility in women is complicated by the fact that only about 400 of the ~2 million oocytes in primordial follicles at birth are ovulated during their reproductive life [3]. Incidentally, infertility does not affect females only. Roughly 50% of infertility cases in USA is of male partner origin when deviations from World Health Organization (W.H.O.) standards for normal semen are present in at least one of two semen analyses (SA; [4]). This problem is further compounded when no identifiable reason can be found for abnormal SA hence the diagnosis of idiopathic infertility. As a consequence, affected couples seek medical advice and interventions for improving their chances for successfully effecting fertilization and pregnancy. Currently, oxidative stress (OS) is believed to be an important and plausible cause for idiopathic male and female infertility [5,6].

OS is a condition that reflects an imbalance between the systemic generation of reactive oxygen species (ROS) and the ability of the body to readily detoxify (antioxidant defenses) the reactive intermediates or to repair the resulting damage. OS has become an area of great concern for clinicians and scientists due to the fact that this pathway of programmed health deterioration has also resulted in poor fertilization, poor embryonic development, pregnancy loss, birth defects (including autism), and childhood cancer (for review see Agarawal [5].

In this review, we will provide a comprehensive overview of the latest evidence regarding the mechanism of ROS production, the physiological roles of ROS, the pathophysiology of ROS, as well as the impact of OS on reproductive function. Furthermore, we will elaborate on different treatment strategies for reducing OS levels in the vicinity of gametes and embryos in infertile patients, with the ultimate intention of increasing the probability for normal natural fertilization and conception.

2. Production of free radicals in the body

Free radicals and other ROS are derived either from normal essential metabolic processes in the body or from external sources such as exposures to X-rays, ozone, cigarette smoking, air pollutants, and industrial chemicals. Free radical formation occurs continuously in the cells as a consequence of both enzymatic and non-enzymatic reactions. Enzymatic reactions, which serve as sources of free radicals, include those involved in the respiratory chain, phagocytosis, prostaglandin synthesis

and the cytochrome P-450 system (for review, see Lobo et al. [7]). Free radicals can also be formed in non-enzymatic reactions of oxygen with organic compounds as well as those initiated by ionizing reactions.

Some internally generated sources of free radicals are [7]:

- Mitochondria
- Xanthine oxidase
- Peroxisomes
- Inflammation
- Phagocytosis
- Arachidonate pathways
- Exercise
- Ischemia/reperfusion injury

Some externally generated sources of free radicals are:

- Cigarette smoke
- Environmental pollutants
- Radiation
- Certain drugs, pesticides
- Industrial solvents
- Ozone

3. Need for antioxidants

Antioxidants are low molecular weight molecules that are stable enough to each donate an electron to a rampaging free radical and neutralize it, thus reducing its capacity to cause damage. These antioxidants delay or inhibit cellular damage mainly through their free radical scavenging property [8]. Some of these antioxidants, including glutathione, ubiquinol, and uric acid, are produced during normal metabolism in the body [9]. Other lighter antioxidants are found in the diet. Although there are several enzymes system within the body that scavenge free radicals, the principal micronutrient (vitamins) antioxidants are vitamin E (α-tocopherol), vitamin C (ascorbic acid), and B-carotene [10]. The body cannot manufacture these micronutrients, so they must be supplied in the diet.

4. Sources of antioxidants

Various antioxidants are supplied to the human body through vegetarian as well as non-vegetarian diets. Vitamins C and E, β-carotene and coenzyme Q are the most famous antioxidants of diet sources (for review see Akbarirad et al [11]. Plants (fruits, vegetables, medicinal herbs) may contain a wide variety of free radical scavenging molecules such as phenolic compounds (Phenolic acids, flavonoids, quinones, coumarins, lignans, stilbenes, tannins etc.), nitrogen compounds (alkaloids, amines, betalains etc.), vitamins, terpenoids (including carotenoids) and some other endogenous metabolites which are rich in antioxidant activity [11].

5. Mechanism of action of antioxidants

Two principle mechanisms of action have been proposed for antioxidants [12]. The first is a chain-breaking mechanism by which the primary antioxidant donates an electron to the free radical present in the systems. The second mechanism involves removal of ROS/reactive nitrogen species initiators (secondary antioxidants) by quenching chain-initiating catalyst. Antioxidants may exert their effect on biological systems by different mechanisms including electron donation, metal ion chelation, co-antioxidants, or by gene expression regulation [13].

6. Potential agent of oxidative stress to reproductive function

Any oxidizing radical is a potential agent of oxidative stress. Some are highly reactive with short half-lives, such as hydroxyl radicals, whereas others are less reactive but with longer half-lives, such as hydrogen peroxide (though ROS but not a free radical). A consequence of a longer half-life is the potential for a greater diffusion distance, which can allow the reactive species to do damage more remotely from its source. Oxidative damage can occur in many classes of molecules, including lipids, proteins, nucleic acids, and sugars, implying that cell, nuclear, and mitochondrial membranes, structural and cytoplasmic proteins, complex carbohydrates, RNA, and DNA are all susceptible to OS [14]. In gonads (testis and ovaries) with their high rates of metabolism and cell replication, OS can be very damaging, thus making the antioxidant capacity of gonadal tissues very important.

Excessive nitrosylated oxygen radicals (NO), play a role in amplifying testicular/ovarian injury. NO can form another potent oxidizing agent (peroxynitrite; $ONOO_2$) by interacting with superoxide radicals [14,15]. Furthermore, NO can also react with CO_2 to form nitrogen dioxide, a radical of less activity than peroxynitrite but of longer diffusion distance [14]. Peroxynitrite can modify proteins with thiol groups to generate nitrosothiols, which can trigger the generation of other metal-derived free radicals by disrupting metal-protein interactions [14,15].

NO is synthesized by nitric oxide synthase (NOS), which exists in the following 3 known forms: endothelial NOS (eNOS), inducible NOS (iNOS) and neuronal NOS. The latter appears to exist only in a truncated form in the gonads. NOS and/or NO have been found to be up-regulated in a number of experimental conditions known to induce gonadal OS, such as cryptorchidism, testicular torsion, obstructive azoospermia, and varicocele and during ischemia-reperfusion injury sustained during the treatment for ovarian torsion (for review see Turner and Lysiak [16]).