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Review

The roles of cellular reactive oxygen species, oxidative stress and antioxidants in pregnancy outcomes

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ABSTRACT

Reactive oxygen species (ROS) are generated as by-products of aerobic respiration and metabolism. Mammalian cells have evolved a variety of enzymatic mechanisms to control ROS production, one of the central elements in signal transduction pathways involved in cell proliferation, differentiation and apoptosis. Antioxidants also ensure defenses against ROS-induced damage to lipids, proteins and DNA. ROS and antioxidants have been implicated in the regulation of reproductive processes in both animal and human, such as cyclic luteal and endometrial changes, follicular development, ovulation, fertilization, embryogenesis, embryonic implantation, and placental differentiation and growth. In contrast, imbalances between ROS production and antioxidant systems induce oxidative stress that negatively impacts reproductive processes. High levels of ROS during embryonic, fetal and placental development are a feature of pregnancy. Consequently, oxidative stress has emerged as a likely promoter of several pregnancy-related disorders, such as spontaneous abortions, embryopathies, preeclampsia, fetal growth restriction, preterm labor and low birth weight. Nutritional and environmental factors may contribute to such adverse pregnancy outcomes and increase the susceptibility of offspring to disease. This occurs, at least in part, via impairment of the antioxidant defense systems and enhancement of ROS generation which alters cellular signalling and/or damage cellular macromolecules. The links between oxidative stress, the female reproductive system and development of adverse pregnancy outcomes, constitute important issues in human and animal reproductive medicine. This review summarizes the role of ROS in female reproductive processes and the state of knowledge on the association between ROS, oxidative stress, antioxidants and pregnancy outcomes in different mammalian species.

Contents

Abbreviations: ROS, reactive oxygen species; O_2, molecular oxygen; $^1O_2$, singlet oxygen; $^{\bullet}O_2^-$, superoxide anion; H_2O_2, hydrogen peroxide; H_2O, water; $^{\bullet}OH$, hydroxyl radical; $ONOO^-$, peroxynitrite; NO, nitric oxide; NOS, nitric oxide synthase; ROOH, peroxy radical; ROH, alcohol, reduced flavin adenine dinucleotide ($FADH_2$); ATP, adenosine triphosphate; G6P, glucose-6-phosphate; HMP, hexose monophosphate; G6PD, glucose-6-phosphate dehydrogenase; ICDH, isocitrate dehydrogenase; NADPH/NADP, reduced/oxidized nicotinamide adenine dinucleotide phosphate; OXPHOS, oxidative phosphorylation; MtDNA, mitochondrial DNA; PUFA, polyunsaturated fatty acids; LPO, lipid peroxides; Cu,Zn-SOD or SOD1, copper–zinc superoxide dismutase; Mn-SOD or SOD2, manganese superoxide dismutase; GPX, glutathione peroxidase; CAT, catalase; GSR, glutathione reductase; GST, glutathione S-transferases; GSH/GSSG, reduced/oxidized glutathione; Zn, zinc; Cu, copper; Mn, manganese; Se, selenium; IUGR, intra-uterine growth restriction; HIFs, Hypoxia-inducible factors; (PGC)-1α, Peroxisome proliferator-activated receptor-γ coactivator; VHL, Von Hipple-Lindau protein; NRF-1, nuclear respiratory factor 1; NF-κB, Nuclear factor kappa B; AP1, activator protein-1; Apaf-1, apoptosis protease-activating factor-1; TNF, tumor necrosis factor; FasL, Fas ligand; Bcl-2, B-cell lymphoma 2; BAX, BCL-2-associated X protein.

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1. Introduction

Cellular reactive oxygen species (ROS) and their control by antioxidants are involved in the physiology of the female reproductive system. Physiological levels of ROS play an important regulatory role through various signalling transduction pathways in folliculogenesis, oocyte maturation, corpus luteum and uterine function, embryogenesis, embryonic implantation and feto-placental development (Agarwal et al., 2008). Imbalances between antioxidants and ROS production (oxidative stress) is considered to be responsible for the initiation or development of pathological processes affecting female reproductive processes (Agarwal and Allamaneni, 2004; Agarwal et al., 2006). Oxidative stress has been suggested as a causative agent in human pregnancy-related disorders, such as embryonic resorption, recurrent pregnancy loss, preeclampsia, intra-uterine growth restriction (IUGR) and fetal death (Gupta et al., 2007). Nevertheless, the relationship between ROS-induced oxidative stress and such disorders is not clear and cannot be adequately investigated in human pregnancies for self-evident ethical reasons. Furtheremore, there is a lack of fundamental insights regarding cellular, biochemical and molecular adaptive responses to an oxidant environment under both physiological and disease states. Therefore, animal models of both normal and disturbed pregnancies are essential to fill in these important gaps in our knowledge. A thorough understanding of the developmental changes in antioxidant expression, as well as the cellular and molecular mechanisms of antioxidant regulation, in the female reproductive tract is needed. Such studies will provide insights about ROS-mediated antioxidant adaptive responses in normal and disturbed pregnancies and will eventually facilitate treatment of pregnancy-related disorders.

ROS are generated as by-products of aerobic respiration and metabolism. Since the purification of superoxide dismutase (SOD) from bovine erythrocytes by McCord and Fridovich (1969), evidence indicates that living organisms have adapted to a coexistence with ROS through the development of highly complex and integrated enzymatic antioxidant mechanisms (Fig. 1). ROS have been linked to numerous biological processes when they are produced at the right levels and they may exert damaging effects when they are over-abundant. Tightly controlled ROS generation is an important constitutive process and is one of the central elements in cell signalling (Khan, 1995; Finkel, 1998), gene expression (Allen and Tresini, 2000) and maintenance of redox homeostasis and signal transduction pathways involved in cell function, growth, differentiation and death (Valko et al., 2007).

Dietary antioxidants play important roles in protecting cells from ROS damage. Both dietary and enzymatic antioxidants are components of interrelated and systems that interact with each other to control ROS production, thereby ensuring adequate defences against oxidative stress (Machlin and Bendich, 1987). Nutritional deficiencies in protein and/or micronutrient antioxidant vitamins and trace minerals may impair cellular antioxidant capacities because proteins provide the amino acids needed for the synthesis of antioxidant enzymes. In addition, many micronutrients form part of the active site necessary for the antioxidant enzyme function or act as cofactors in the regulation of antioxidant enzymes. Exposure to environmental chemicals is inevitable as it occurs through the consumption of contaminated food, water and beverage. Nutritional and environmental factors play a major role in programming the susceptibility of offspring to disease (Luo et al., 2006). Commonly known or suspected causes of preterm birth or low birth weight, such as nutritional and environmental factors, are sources of oxidative stress (Luo et al., 2006). Oxidative stress programming may operate either directly through the modulation of gene expression or indirectly through the adverse effects of oxidized molecules, such as lipids and proteins, at critical developmental windows (Luo et al., 2006). Preconception nutrition plays a major role in programming the offspring susceptibility to disease, which may be mediated by macro- and micronutrient deficiencies and oxidative stress (Chavatte-Palmer et al., 2008). Research is essential to determine the maternal antioxidant micronutrient requirements needed to improve fetal survival in undernourished populations or in populations at high risk of micronutrient deficiency and low birth weight.

This review summarizes the role of ROS and antioxidants in female reproductive processes and pregnancy outcomes among different mammalian species. A discussion is devoted to the importance of cellular enzymatic antioxidants and dietary antioxidants in female reproductive functions and pregnancy outcomes. The review also examines the available evidence for the involvement of cellular ROS-induced oxidative stress in pregnancy-related disorders. Antioxidant and prooxidant biochemical markers have becoming increasingly important for the design of a strategy for prevention or management of oxidative diseases and could be used as useful tools in estimating the risk of oxidative damage and