REACTIVE OXYGEN SPECIES (ROS)

Free Oxygen Radicals

Group of highly reactive oxygen compounds that play an important role in cellular signalling and cellular damage.

⚠️ Risk factor ☀️ Male & Female

About Reactive oxygen species (ROS)

Reactive oxygen species (ROS) are generally very small molecules which are highly reactive, and include oxygen ions, free radicals and peroxides (Pic. 1) both inorganic and organic. ROS form as a natural byproduct of the normal metabolism of oxygen and have important roles in cell signaling. However, during times of environmental stress ROS levels can increase dramatically, which can result in significant damage to cell structures. This cumulates into a situation known as oxidative stress (OS).

Oxidative stress is a disturbance in the balance between the production of reactive oxygen species (free radicals) and antioxidant defenses. Cells are normally able to defend themselves against ROS damage through the use of enzymes such as superoxide dismutases and catalases. Small molecule antioxidants such as ascorbic acid (vitamin C), uric acid, and glutathione also play important roles as cellular antioxidants. Antioxidants neutralize free radicals by donating one of their own electrons. The antioxidant nutrients themselves don’t become free radicals by donating an electron because they are stable in either form. When this capacity of neutralizing ROS is overloaded, oxidative stress results.

The effects of ROS on cell metabolism have been well documented in a variety of species. These include not only roles in programmed cell death (apoptosis), but also positive effects such as the induction of host defence genes and mobilisation of ion transport systems. This is implicating them more frequently with roles in redox signaling or oxidative signaling. In particular, platelets involved in wound repair and blood homeostasis (the balance of the blood flow) release ROS to recruit additional platelets to sites of injury. These also provide a link to the immune system via the recruitment of leukocytes.

Reactive oxygen species are implicated in cellular activity to a variety of inflammatory responses including cardiovascular disease. Generally, harmful effects of reactive oxygen species on the cell are most often:

- damage of DNA
- oxidations of polydesaturated fatty acids in lipids
- oxidations of amino acids in proteins

The structural modifications in the molecules of nucleic acids, proteins and lipids caused by increased concentration of reactive oxygen species may lead to various metabolic changes that may contribute to the development of neurological diseases, cardiovascular diseases, cancer, and irreversible post-inflammatory damage to various organs, among others.

Free radicals are also produced inside organelles, such as the mitochondrion. According to the Free Radical Theory of Aging, aging occurs (via a loss of energy producing cells) either when mitochondria begin to die out because of free radical damage or when fewer functional mitochondria remain within these cells.

Symptoms

The symptoms of an excessive amount of ROS in the organism are intertwined with symptoms of conditions of oxidative stress. These include:

- fatigue
- memory loss and/or brain fog
- muscle and joint pain
• decreased eyesight
• elevated body temperature, or fever
• headaches
• sensitivity to noise
• susceptibility to infections

**Associated diseases**

ROS have been discovered to play a role in a great variety of diseases and conditions. They play a key role in virtually all inflammatory conditions, and in addition, are currently known to contribute to such conditions as atherosclerosis (Pic. 2), neurodegenerative diseases, tumour development and certain complications of pregnancy.

Some diseases associated with a state of excess of ROS and oxidative stress include:

- Alzheimer’s disease
- Parkinson’s disease
- other neurodegenerative diseases
- cardiovascular diseases
- diabetes
- cancer
- asthma
- arthritis
- preeclampsia (a disorder of pregnancy characterized by the onset of high blood pressure and often a significant amount of protein in the urine)

**Complications**

**Pre-eclampsia**

Preeclampsia is a multisystem, pregnancy-specific disorder (affects 5–8% of all pregnancies) that is characterised by the development of hypertension (high blood pressure) and proteinuria (elevated levels of protein in the urine) after 20 weeks of gestation. Also, PE is associated with an increased risk of placental abruption, preterm birth, foetal intrauterine growth restriction (IUGR), acute renal failure, cerebrovascular and cardiovascular complications, disseminated intravascular coagulation, and maternal death.

The pathogenesis of preeclampsia is still not fully understood. In normal pregnancies, there is an increase of free radical production and oxidative deterioration of lipids towards the end of pregnancy when compared with non-pregnant women. In a parallel fashion, total antioxidant capacity (Uric acid, Vitamins C and E) gradually increases during pregnancy, leading to an oxidative balance maintained throughout pregnancy. Evidence in recent years has shown that a biochemical imbalance in pre-eclampsia occurs with an increase of oxidative stress and lipoperoxidation and, at the same time, a deficient antioxidant protection.

**Neurodegenerative diseases**

Different tissues have different oxygen demands depending on their metabolic needs. The brain is particularly vulnerable to the effects of reactive oxygen species due to its high demand for oxygen, and its abundance of highly peroxidisable substrates. Neurons and astrocytes, the two major types of brain cells, are largely responsible for the brain’s massive consumption of O2 and glucose; indeed, the brain represents only 2% of the total body weight and yet accounts for more than 20% of the total consumption of oxygen.

Oxidative stress has been detected in a range of neurodegenerative disease, and evidence suggests that oxidative stress may play a role in disease pathogenesis. Aging has been established as the most important risk factor for the common neurodegenerative diseases, Alzheimer’s disease (AD), and Parkinson’s disease (PD). Most theories of aging centre are on the idea that cumulative oxidative stress leads to mitochondrial mutations, mitochondrial dysfunction, and oxidative damage.

**Risk factors**

- hyperoxia (occurs when cells, tissues and organs are exposed to an excess supply of oxygen or higher than normal partial pressure of oxygen)
- tissue injury
- cigarette smoke
- stress
- hypertension
- inflammation
- environmental pollutants
- UV radiation
- pesticides
- low intake of antioxidant-rich food
Antioxidants from our diet play an important role in helping endogenous antioxidants for the neutralization of oxidative stress. The nutrient antioxidant deficiency is one of the causes of numerous chronic and degenerative pathologies. Eating foods that are high in antioxidants like beets, kale, berries can help. To promote the production of antioxidants it is necessary to eat foods that help body make more glutathione such as asparagus, walnuts, spinach, tomatoes.

### How it can affect fertility

#### Female fertility

ROS affect multiple physiological processes from oocyte maturation (Fig. 3) to fertilization, embryo development and pregnancy. It has been suggested that OS modulates the age-related decline in fertility.

Each month, a cohort of oocytes begin to grow and develop in the ovary, but meiosis I (a specialized type of cell division that reduces the chromosome number by half, creating an egg cell or sperm cell) resumes in only one of them, the dominant oocyte.

This process is targeted by an increase in ROS and inhibited by antioxidants.

In contrast, the progression of meiosis II (a specialized type of cell division that reduces the chromosome number by half, creating sperms and eggs) is promoted by antioxidants, suggesting that there is a complex relationship between ROS and antioxidants in the ovary. The increase in steroid production in the growing follicle resulting in ROS formation. Reactive oxygen species produced by the pre-ovulatory follicle are considered important inducers for ovulation (the release of egg from the ovaries).

Oxygen deprivation stimulates follicular formation of new blood vessels, which is important for adequate growth and development of the ovarian follicle.

Any disruption in these processes can lead to irregular ovulation, which can decrease the possibility of natural conception. Because without ovulation, there is no egg to be fertilized.

ROS play an important role during pregnancy and normal parturition and in initiation of preterm labor. There is growing literature on the effects of OS in female reproduction with involvement in the pathophysiology of preeclampsia, free radical-induced birth defects and other situations such as abortions.

Numerous studies have shown that OS plays a role in the pathophysiology of infertility and assisted fertility. There is some evidence of its role in endometriosis (a condition in which the layer of tissue that normally covers the inside of the uterus, grows outside it) tubal and peritoneal factor infertility and unexplained infertility.

#### Male fertility

During reproduction, ROS are involved in many important mechanisms of sperm physiology. ROS are involved in the sperm nucleus condensation, and in regulating the number of germ cells by induction of apoptosis (programmed cell death) or the growth of spermatogonia (the male precursor of germ cells, capable of infinite cell division).

In the mature sperm, ROS play an important role in the capacitation (the change undergone by sperm in the female reproductive tract that enables them to penetrate and fertilize an egg), acrosome reaction (a sperm must first fuse with the plasma membrane and then penetrate the female egg in order to fertilize it) and sperm motility, and they can also function as signaling molecules.

ROS must be maintained at appropriate levels to ensure appropriate physiological function while preventing pathological damage to the sperms. In order to ensure appropriate fertilization, high levels of ROS cause sperm pathologies such as loss of sperm motility and viability. ROS is thought to affect sperm membranes and sperm DNA.
There are many agents that cause an increase in testicular oxidative stress, such as environmental toxins, or conditions such as varicocele (an abnormal enlargement of the venous plexus in the scrotum), orchitis (an inflammation of testicles), cryptorchidism (undescended testes), and aging, all of which leads to an increase in germ cell apoptosis and hypospermatogenesis (abnormally decreased production of sperms). ROS-induced DNA damage may also potentiate germ cell apoptosis, leading to a decrease in sperm count and thus to the decline of semen quality, both of which are associated with male infertility.

Prognosis

In males, the role of ROS in pathologies has long been recognized as a significant contributor to infertility. Men with high ROS levels or DNA damaged sperm are likely to be infertile. The contribution of oxidative stress to male infertility has been well documented and extensively studied.

On the other hand, the role of ROS in female infertility continues to emerge as a topic of interest, and thus, the majority of conducted studies provide indirect and inconclusive evidence regarding the oxidative effects on female reproduction.

Excessive ROS production and resulting oxidative stress may contribute to aging and several diseased states affecting female reproduction. Endothelial dysfunction secondary to oxidative stress contributes to the development of obstetric complications. ROS and oxidative stress can negatively affect embryo implantation and may influence the development of reproductive disorders such as endometriosis and preeclampsia. These effects have been reported to improve with the aid of antioxidants, and thus could minimize the associated risk for infertility.

Find more about related issues

Diagnoses

Testicular failure
The inability of the testicles to produce sperm or testosterone.
Learn more at: www.fertilitypedia.org/therapy/diag/testicular-failure

Gallery

Pic
A schema showing the main compounds representing ROS, and their metabolic paths of neutralization.

Pic
An illustration of the basic process in atherosclerosis, the plaque formation in the wall of arteries. Atherosclerosis is the dominant cause of cardiovascular diseases.
An illustration of the stages of oocyte maturation, from the initiation of follicle growth to ovulation and the corpus luteum formation.

**Sources**

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