MUNISI: Military Mathematics and Natural Sciences
e-ISSN: 3026-2968
Vol. 1, No. 2, December 2023, pp. 65-72
Available online at https://jurnal.idu.ac.id/index.php/munisi

Reactive Oxygen Species in Human Biological Systems and Their Reactivity to Oxidative Stress

Muhammad Naufal Aflah[1], Decintya Jaya Maysha[1], Savitri Setyaningrum[1], Alexander Yabansabra[1], Uzwathul Fathiha Azzahra[1], Miftahul Huda Fendiyanto[1], Mentari Putri Pratami[1]*

[1] Department of Biology, Faculty of Military Mathematics and Natural Sciences, Republic of Indonesia Defense University, Bogor, Indonesia
* Corresponding Author: mentari.pratami@idu.ac.id

Abstract

Aerobic organisms in carrying out their metabolism can result in biological oxidation which produces 2.5% reactive oxygen species (ROS) based on the amount of oxygen supply. Several types of stressors or factors that trigger increased oxidative stress can be caused by physical agents such as the impact of UV radiation and x-rays, non-physiological oxygen levels, drugs, chemical compounds, aging, and pollutants that can cause homeostatic disturbances in cells, survival and processes. cell signaling. In order to maintain life, cells also have a response to oxidative stress through antioxidant-forming tools in the body such as catalase (CAT), hydroperosidase (HPx), and super oxide dismutase (SOD). If the reactive oxygen species (ROS) produced by the body exceeds the limit of the amount of antioxidants produced by the body, it will cause cells in the body to experience oxidative stress. If the amount of reactive oxygen species (ROS) produced is equivalent to the amount of antioxidants, it will direct cells to growth. This reactive oxygen species (ROS) originates from biological oxidation reactions that occur in the mitochondrial matrix. Thus, neutralizing reactive oxygen species (ROS) in the body can only be suppressed by the reaction of two ROS simultaneously, so that two electrons which were initially unpaired will become paired through both enzymatic and non-enzymatic antioxidants and additional antioxidants needed by the body.

Keywords: *Aerobic Organisms; Oxidative Stress; ROS.*

Introduction

The oxygen paradox is a situation experienced by aerobic eukaryotic organisms where all living things cannot survive without oxygen. Oxygen, which has a number of benefits for earth's creatures, is also indirectly dangerous due to its electronic distribution for the lives of each organism itself. Oxygen has one unpaired atom with an electron in its outer valence shell, while molecular oxygen has as many as two unpaired electrons. This causes atomic oxygen to become free radicals. Mitochondria, which act as an electron transport chain, provide security for the reduction of tetravalent oxygen to produce water. However, univalent reduction of oxygen produces reactive intermediates. In the reductive environment of the cell, abundant opportunities for oxygen to undergo univalent reduction are suddenly present. Thus, superoxide anion

radicals, hydrogen peroxide (H_2O_2), and highly reactive hydroxyl radicals are regular products of aerobic respiration and oxidation processes in aerobic environments.

As aerobic eukaryotic organisms, all living creatures, especially humans and higher animals, really need the availability of oxygen to carry out the basal metabolic processes that occur in their bodies (Guyton & Hall, 1996). Living creatures in 24 hours require an oxygen supply of 352.81 lt. The need for oxygen must be met by breathing approximately 23 thousand times (Guyton & Hall, 1996). The product produced through this metabolic process, the biochemical system (biological oxidation) in the human body is capable of producing 2.5% of free radicals from the amount of oxygen needed in the body or as much as 3.4 kg/24 hours.

Even though biological oxidation can take place without the presence of oxygen, all higher living creatures absolutely need a supply of oxygen through respiration. Respiration is a process of forming adenosine triphosphate (ATP) as energy. This energy is obtained from the reaction between hydrogen and oxygen which then forms water. The formation of energy involving this reaction is called oxidative phosphorylation which takes place in the mitochondrial matrix. Mitochondria act as the cell's energy factory. The respiration that takes place in the mitochondrial matrix is what is referred to as the respiratory chain.

According to Botham (2009), the respiratory chain that occurs is structured based on its redox potential, which starts from a negatively charged substrate (H+/H2) and ends on a positively charged substrate (O2/H2O). The reaction that takes place in the bodies of higher living creatures is oxidation-reduction (Turan, 2010). Chemically, oxidation reactions are expressed as reactions that release electrons, while reduction reactions are reactions that receive or accept electrons. Therefore, every oxidation process will be followed by a reduction reaction. Thus, this principle is used in biochemical systems and is the basis for understanding the biological oxidation processes that occur in the bodies of higher living creatures (Rocha et al., 2010). When respiration occurs, oxygen molecules are incorporated into various compounds by the oxygenase enzyme. Apart from that, several other enzymes that also play a role in the biological oxidation process are dehydrogenase, hydroperoxidase, and oxidase which work according to the body's needs (Turan, 2010; Botham, 2009).

Several types of stressors caused by physical agents such as the impact of UV radiation and x-rays, non-physiological oxygen levels, drugs, chemical compounds, aging, and pollutants can cause disruption of cell homeostasis, survival, and cell signaling processes (Rocha et al. al., 2010).

This stimulation of growth, cell survival and cell signaling processes is mediated by reactive oxygen species (ROS) produced by cells in response to oxidative stress. Various types of stressors are markers of oxidative stress, besides triggering the production of reactive oxygen species (ROS) in the body, they also encourage the formation of enzymatic antioxidants such as catalase (CAT), hydroperosidase (HPx), and super oxide dismutase (SOD).

The reactive oxygen species (ROS) produced will disrupt the homeostasis of growth, survival and cell signaling that occur in the bodies of higher living creatures,

depending on how high the level of reactive oxygen species (ROS) produced. If the production of reactive oxygen species (ROS) exceeds the amount of antioxidants present, it will lead cells to oxidative stress, apoptosis or necrosis. In addition, if the production of reactive oxygen species (ROS) is equivalent to total antioxidants, it will direct the cells to growth, survival and the cell singnaling process. The production of reactive oxygen species (ROS) is produced through reactions catalyzed by oxidase enzymes or cytochrome p450 enzymes (Turan, 2010). Apart from that, in order to maintain life, cells also have a response to oxidative stress through tools that form antioxidants in the body such as catalase (CAT), hydroperosidase (HPx), and super oxide dismutase (SOD). However, catalase (CAT), hydroperosidase (HPx), and super oxide dismutase (SOD). However, the production of reactive oxygen species (ROS) is even in small amounts, therefore other additional antioxidants are needed such as vitamin E, vitamin C, flavonoids, uric acid, etc. which function as antioxidants in the body. This is because the reactive oxygen species (ROS) chain can only be suppressed by the reaction of two ROS simultaneously, so that two electrons that were initially unpaired will become paired (Varh, 2010).

Result and Discussion

ROS Formation

There are two categories of molecules in ROS, namely radical and nonradical oxygen derivatives. Radical oxygen derivatives include OH ions, superoxide, nitric oxide, and peroxyl, while non-radical oxygen derivatives include ozone, singlet oxygen, lipid peroxide, and hydrogen peroxide. Roof radiation and ultraviolet light are sources of ROS formation, because these rays can lyse water into H2O, apart from these rays, there are also ions such as Fe2+, CO2+, and Cu2+ which can react with oxygen or hydrogen peroxide to produce OH radicals (Ling Tan et al., 2018).

ROS consist of superoxide (*O2), hydroxyl (*OH), peroxyl (ROO*), hydrogen peroxide (H2O2), singlet oxygen (1O2), nitric oxide (NO*), peroxynitrite (ONOO*), hypochlorous acid (HOCl), and the results of fat oxidation in food. The most common free radical formed in the body is superoxide. Superoxide will be converted into hydrogen peroxide (H2O2). Hydrogen will be converted into hydroxyl radicals (*OH). Hydrosyl radicals are what cause fat peroxidation in cell membranes so that cells are damaged. If left to continue, it will cause an imbalance between free radicals and endogenous antioxidants or what can be called oxidative stress (Parwata, 2015).

The stages of free radical formation are as follows (Winarsih, 2007):

1. The Initiation Stage is the initial phase of free radical formation, for example:
2. The Propagation Stage is the radical chain elongation phase, for example:
3. The termination stage is the stage where a reaction occurs between one radical compound and another radical compound or with a radical catcher, for example:

Free radicals play a role in biological processes involving prooxidant ROS and reactive nitrogen species (RNS). The process of forming free radicals begins with molecules that do not have paired electrons trying to take other electrons around them.

This process is called oxidation which will then form a new free radical molecule. If this process continues continuously, it will form a chain reaction that can destroy thousands of other molecules. Free radicals can be formed as a result of metabolism or deliberately formed to neutralize viruses and bacteria in the body's immune system. Free radicals are formed by many mechanisms, especially by the glucose oxidation mechanism. Glucose will be oxidized through a reaction involving metals to become enediol anions, then converted into ketoaldehyde and O2 -. O2 - undergoes dismutase to become H2O2 which cannot be degraded by catalase or gluthathione peroxidase, thus producing OH• which is very reactive. Superoxide anion can react with NO to form the reactive molecule peroxynitrite (ONOO –). 9 (Berawi and Agverianti. 2017).

ROS are subcellular locations where certain metabolites are generated, because the microenvironment can determine what targets these ROS molecules potentially encounter spatially and temporally. It is a classic example of an organelle with ROS generation whose localization for physiology includes phagosomes in specialized cells of the immune system that used to kill pathogens 14, and peroxisomes 15, intermediate catabolic oxidation reactions for energy metabolism. In addition to these canonical ROS sources, we highlight three other major locations for ROS production in cells under physiological conditions (mitochondria, endoplasmic reticulum (ER) and cell membranes (Bryan & Christopher, 2011).

ROS Cause Cancer

In biological systems, reactive oxygen species (ROS) are continuously produced and eliminated, and they play important roles in a variety of normal biochemical functions as well as abnormal pathological processes. Oncogenic stimuli, increased metabolic activity, and mitochondrial dysfunction have all been associated with increased intrinsic ROS stress in cancer cells.

Since mitochondrial DNA was discovered, the respiratory chain (electron transport complex) is the main source of ROS generation in cells, and the mitochondrial respiratory chain is particularly vulnerable. Exposure of DNA to ROS-mediated damage appears to be a mechanism for cancer cells to increase their sensitivity to ROS stress. In cancer, the production of reactive oxygen species (ROS) has increased dramatically. Endogenous DNA-damaging agents are produced by cells, promoting genetic instability and the growth of drug resistance.

Based on the results of several recent studies, in general cancer cells are under increased oxidative stress compared to normal cells. Increased generation of ROS in cancer cells often causes accumulation of oxidative products from DNA, proteins, and lipids in tissues because the reactive nature of ROS in cancer cells often causes accumulation of oxidative products from DNA, proteins, and urinary secretion and release into the blood. Escalation of levels of DNA oxidative products (8-oxo-G, 8-oxo-dG) and lipid peroxidation products has been detected in various cancer tissues, namely renal cell carcinoma, breast ductal carcinoma, adenocarcinoma (Kondo et al., 2009).

Interestingly, a recent study showed that both 8-oxo-dG accumulation and hMTH1 (DNA repair molecule) expression were increased in most alyzed and brain tumors, and

most prominently in high-grade gliomas. These observations suggest that oxidative stress plays a role in tumor development.

Mechanism of Increasing ROS Stress in Cancer Cells

Several potential mechanisms are thought to contribute to the increase in ROS in cancer cells. First, oncogenic signals have been shown to cause an increase in ROS. For example the c-myc oncogene. This compound can increase ROS generation, induce DNA damage, and reduce DNA damage and p53 function. This is considered to be a mechanism for oncogene-induced genetic instability (Huang, 2005).

Mitochondrial respiratory chain failure may be another mechanism by which cancer cells produce increased amounts of ROS. Because mitochondrial DNA (mtDNA) encodes 13 different components of the respiratory system, mutations in mtDNA are likely to affect the function of the encoded proteins and result in failure of the mitochondrial respiratory chain because it is complex and lacks introns. It is also well known that mtDNA is more susceptible to damage than nuclear DNA, and mtDNA mutations are common in cancer cells (Huang, 2005).

In general, cancer cells are metabolically active and require a lot of ATP to compensate for their active biochemical functions, which include uncontrolled cell growth and proliferation. This increased energy requirement will place additional strain on the mitochondrial respiratory chain likely leading to more ROS production. However, oncogenic signals can lock mitochondrial respiration to a non-phosphorylated mode that is more likely to generate ROS. (Haghdoost, 2005)

Elevated ROS stress can cause a variety of biological responses, including cessation and adaptation of biological responses, including temporary growth cessation and adaptation, increased cell proliferation, permanent growth arrest or senescence, apoptosis, necrosis, and others. More accurate research results suggest that it will likely be influenced by cellular genetic history, the particular type of ROS involved, and the level and duration of ROS stress.

ROS and Infertility

A person's inability to give birth is called infertility. One of the causes of this inability is male factors, including sperm quality, motility and the amount of ROS in them. Almost half of the male population is infertile, namely around 30-40% of their sperm contains high levels of ROS. The presence of ROS in semen can come from immature leukocytes and spermatozoa. The influence of high ROS in sperm cells is also triggered by excessive use of alcohol and smoking (Gharagozloo, 2011). Infection and inflammation can stimulate peroxidase positive leukocytes to produce ROS levels up to 100 times higher (Agarwal, 2003). Very high levels of ROS in seminal plasma can cause damage to sperm. Decreased sperm function is influenced by levels of ROS, IL-6, IL-8, and tumor necrosis (Agarwal, 2005). Another factor that can cause a decrease in sperm function is the fluidity of the sperm membrane (Agarwal, 2005). When ROS levels exceed antioxidants, OS occurs and causes several effects. First, the spermatozoa plasma membrane is very susceptible to oxidation and causes binding by free radicals (Makker,

2009). DNA in sperm becomes susceptible to oxidation and mutation (Agarwal, 2005). Infertility can also occur in women who have high levels of ROS.

ROS and Brain Nerve Damage (Alzheimer's)

Alzheimer's is a symptom that causes the nervous system in the brain to experience damage and disruption of motor and chemical activity in the brain, resulting in errors in translating stimuli properly. This damage is caused by excessive oxygen activity resulting in damage to the brain's nervous system. One of the causes of increased ROS is smoking. Smoking can cause a person to suffer from Alzheimer's disease. And almost everyone in the world is a smoker, especially those aged 24 and over. Smoking can cause other diseases, cigarette smoke contains carbon monoxide which causes oxygen stress and this creates Reactive Oxygen Species (ROS) and Reactive Nitrogen Species, as well as causing the brain to experience problems with the nervous system. ROS causes amyloidogenicity in the process of creating Aβ oligomers and extravecellular fibrillar blunting. Which will create problems with the collection of nutrients and some endothelium and nitregenic nerves and cause the production of Aβ and inhibit blood flow (Tremellen, 2018).

Conclusion

Aerobic organisms or higher living creatures will produce reactive oxygen species (ROS) compounds or free radicals as waste or by-products of the body's metabolism. The source of the emergence of reactive oxygen species (ROS) comes from oxidative phosphorylation in the mitochondrial matrix. If the production of reactive oxygen species (ROS) increases in the body and the antioxidants produced by the body are relatively low, this will result in the balance leading to pro-oxidants which causes oxidative stress in the cells concerned. Thus, neutralizing reactive oxygen species (ROS) in the body can only be suppressed by the reaction of two ROS simultaneously, so that two electrons which were initially unpaired will become paired through both enzymatic and non-enzymatic antioxidants and additional antioxidants needed by the body.

References

[1] Agarwal A, Saleh RA, Bedaiwy MA. 2003. Role of reactive oxygen species in the pathophysiology of human reproduction. Fertil Steril. 79: 829-843.

[2] Agarwal A. 2005. Role of oxidative stress in male infertility and antioxidant supplementation. US Kidney & Urological Disease. 8:122-5.

[3] Arthur, Guyton, MD. 1996. Buku Ajar Fisiologi Kesehatan. Philadelphia: W.B. Saunders Company.

[4] Botham, Kathleen M & Mayes, Peter A. 2009. Cholesterol Syntesis, Transport & Excretion. In: Harper's illustrated Biochemistry.28th Ed. USA: LANGE Mc Graw Hill. chapter 26. p 224-233.

[5] Bryan c dickinson 1 & Christopher J chang 1,2 *.2011. Chemistry and biology of reactive oxygen species in signaling or stress responses.
[6] Dewanto H. N., Lisdiana, Isnaeni W. (2017). Pengaruh Ekstrak Kulit Buah Rambutan terhadap Kualitas Sperma Tikus yang Terpapar Asap Rokok. Life Science 6 (2). Universitas Negeri Semarang.
[7] Gharagozloo M, Ghaderi A. Immunomodulatory effect of concentrated limejuice extract on activated human mononuclear cells. J Ethnopharmacol. 2001; 77(1): 85-90.
[8] Huang, D., Ou, B., Prior, R.L., 2005, Reviews: The Chemistry Behind Antioxidant Capacity Assays, J.Agric. Food Chem, 53, hal. 1841-1856.
[9] Khairun Nisa Berawi, Thedora Agverianti. 2017. Efek Aktivitas Fisik pada Proses Pembentukan Radikal Bebas sebagai Faktor Risiko Aterosklerosis.
[10] Kondo Miwako, zhang liliang, Ji HP, Kou Yan OB. Bioavailability and Antioxidant effect of a xantone-Rich Mangosten (garcinia mangostana) product in humans. brunswick Lab Am Chem Soc. 2009;57–19.
[11] Ling Tan, Bee, Mohd Esa Norhaizan, Winnie Pui Pui Liew. Nutrients and Oxidative Stress: Friend or Foe?. Review Article: Oxidative Medicine and Cellular Longevity. 2018; 9719584.
[12] Makker K, Agarwal A, Sharma R (2009). Oxidative stress & male infertility. Indian J Med Res, 129: 357-367.
[13] Parwata, I Made Oka Adi, 2017, Obat Tradisional, Bukit Jimbaran: Fakultas Matematika Dan Ilmu Pengetahuan Alam Universitas Udayana.
[14] Rocha M, Mijares AH, MalpartidaKG, et al. Mitochondria--Targeted Antioxidant Peptides Current Pharmaceutical Design 2010; 16, 3124--3131.
[15] Turan B. Role of Antioxidants in Redox Regulation of Diabetic CardiovascularComplications.Current Pharmaceutical Biotechnology 2010; 11 , 819-836.
[16] Varh liou G, Storz P. Reactive oxygen species in cancer. Free Radical Research 2010; 44(5): 479–496.
[17] Winarsi H, 2007. Antioksidan alami dan radikal bebas potensi dan aplikasinya dalam kesehatan. Yogyakarta. Kanisius.