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Enzymatic and nonenzymatic antioxidants in kidney diseases

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Abstract

Reactive species and oxidative stress have become increasingly known during the last decade as significant factors that influence different cellular functions of the body. Normally, reactive species (reactive oxygen species and reactive nitrogen species) are produced by natural cellular reactions. The sufficient level of reactive species is vital for cellular pathway like signaling, cellular proliferation and also cellular growth. Although the high concentrations of oxidants are produced by an imbalance between oxidant and antioxidant defense system, they have pathogenetic effects on living organisms and also cause tissue damage. This phenomenon is called oxidative stress. Oxidative stress contributes to several pathological situations, including hypertension, diabetes, cancer, chronic diseases like chronic kidney disease and some acute health problems. In this paper, we summarized the formation of main oxidants originating from a variety of important sources, consisting of cellular metabolism and ecological factors and also enzymatic and nonenzymatic antioxidant systems that have a major role in the regulation of reducing and oxidizing state in the body.

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Oxidative stress

Oxidative stress has an important role in the pathogenesis of different ailments like heart and vessels disease, atherosclerosis, high blood pressure, malignancy and diabetes and also various neurodegenerative diseases (Alzheimer's and Parkinson's diseases). The imbalance of producing of reactive species (reactive oxygen species or reactive nitrogen species) and the normal antioxidant capacity of the cells is termed "oxidative stress." Reactive oxygen species and reactive nitrogen species often act together to generate a condition of oxidative stress (1). It results in inflammation, cell death, tissue injury and disease development. However, sufficient levels of both reactive species are essential for natural cell functions such as the pathways connected to pro-survival signaling, cellular proliferation and also cellular growth (2). Oxidative stress is commonly related to the process of aging. However, it has also been observed to be grown in people with chronic kidney disease (CKD) as well as other chronic diseases. Oxidative stress both directly and indirectly influences all functions of the kidney. It increases vascular reactivity and disturbs renal hemodynamics.

Core tip

Oxidative stress has an important role in the pathogenesis of the different disease. Many intracellular and extracellular antioxidant systems undergo advancement to inactivate free radicals and reduce tissue damage. This review intended to discuss on a group of important oxidants and also several antioxidant compounds that inhibit the oxidative damage.

Moreover, it diminishes glomerular filtration and perturbs tubular reabsorption. These are various pathologies that lead to renal failure, that aggravate by oxidative stress mechanisms (3). This review intended to elaborate on a group of important oxidants and also several antioxidant compounds that inhibit the oxidative damage.

Materials and Methods

For this review, we used a variety of sources including PubMed, Embase, Scopus and directory of open access journals (DOAJ). The search was conducted by using combinations of the following key words and or their equivalents; nonenzymatic antioxidant, oxidative stress, hypertension, diabetes, cancer, reactive oxygen species, reactive nitrogen species, kidney diseases,

tissue injury, inflammation, cell death, chronic kidney disease, mitochondrial reactive oxygen species, free radicals, diabetic nephropathy, superoxide dismutase and glutathione.

Reactive species

Free radicals are extremely unstable molecules that have one or more unpaired electrons in an outer orbitals of atoms or molecules. Reactive oxygen species are possibly the most important free radicals in living systems. The major reactive oxygen species are superoxide (O^{-2}), the hydroxyl radical (OH^{-}) and also hydrogen peroxide (H_2O_2). Superoxide anion (O^{-2}) is the main free radical produced in vivo as the result of molecular oxygen reduction. Furthermore, it undergoes dismutation of O^{-2} or by direct reduction of O_2 to produce another reactive oxygen species, the non-radical species—hydrogen peroxide (H_2O_2). Hydrogen peroxide that generates in the cells is unstable. It has the ability to react with different kinds of compounds (proteins, lipids, carbohydrates and DNA) in order to induce injury, especially in the presence of transmission metals like Fe^{2+}. Peroxides react with different forms of Fe, connected to proteins (like heme) or molecules with low-molecular weight to produce another powerful reactive oxidant species (OH^{-}) (4). Like peroxides, hydroxyl radicals can also react with approximately all cellular components and produce extra reactive free radicals. Hence, the production of one free radical can lead to the formation of more free radicals through consequent chain reactions. Reactive nitrogen species (including nitrogen dioxide [.NO2], non-radical peroxynitrite [ONOO-], and other reactive nitrogen species) are the other free radicals that originate from nitric oxide and play the main role in renal pathophysiology. Free radical nitric oxide is produced by several isoforms of nitric oxide synthase and can make other reactive nitrogen species, including peroxynitrite, which is formed by reaction of nitric oxide with superoxide (5). Overgeneration of reactive nitrogen species through nitrosylation reactions can also damage the specific macromolecules including proteins, lipids, and DNA. For example, it can modify the structure of proteins and lead to loss or change of protein function. Numerous mechanisms and pathways are related to the production of reactive species, including mitochondria respiration, nicotinamide adenine dinucleotide phosphate (NADPH) oxidases, xanthine oxidase, and uncoupled nitric oxide (NO) synthases. However, the main sources of oxidative stress in the kidney are produced by NADPH oxidase and mitochondrial respiratory chain (6). The kidney is a very active organ and therefore depend on aerobic pathway for producing ATP that occurs in the mitochondrial inner membrane. The reduction of molecular O_2 along the electron transport chain (ETC) within mitochondria is essential for renal cells to do their functions. The mitochondrial electron-transport chain is the major source of producing reactive oxygen species not only in normal metabolism but also under pathological states. Normally, electrons are transferred within mitochondrial electron transport chain in order to reduce oxygen to a water molecule. However, almost 1 to 3 percent of all electrons escape from the system and make superoxides. The electron transport chain involves five multiprotein complexes that are responsible for keeping mitochondrial membrane potential and producing ATP. In the electron transport system, the transferring of electrons from complex I to IV is connected to transposition of protons to the intermembrane space, creating a membrane potential that is used by the ATP-synthase to produce ATP .Complex I and also complex III of the electron-transport chain are the most important sites for the generation of reactive oxygen species. Normally, these oxidants remain completely inside the mitochondria, but a changed redox state of mitochondria can enhance the permeability of mitochondria membrane and lead to more reactive oxygen species production and development of tissue destruction. Moreover, some factors of the mitochondrial outer membrane, like monoamine oxidases, generate NO or H_2O_2 which results to raised free radical stress (7). Overproduction of mitochondrial reactive oxygen species has been linked to a variety of pathologic conditions including hypoxia, ischemia, aging and early atherosclerosis. Furthermore, mitochondrial reactive oxygen species cause kidney damage in diabetes. In 2000, Nishikawa et al, asserted that mitochondrial superoxide was the source of oxidative stress in diabetes. NADH/NADPH oxidase is another major source of producing reactive oxidant species in the kidneys. NADH/NADPH oxidases are membrane-associated enzymes. They catalyze the transfer of electrons from NADPH to molecular oxygen that forms superoxide, which is usually altered to hydrogen peroxide promptly. Seven isoforms of NADPH oxidase have been recognized in different organs. The most important form of this enzyme in the kidney is Nox4. However, there are some evidences that show Nox2 is also expressed and may act in kidneys. It is clear that Nox and reactive species which are formed by its activity, participate in the regulation of kidney hemostasis and kidney ion transport. Hence, any disorder in Nox expression and function can play a significant role in renal oxidative stress and kidney diseases like diabetic nephropathy and other chronic kidney diseases (8). On the other hand, NADPH is extremely important in the making of reactive oxygen species in phagocyte system that are produced in response to the attendance of foreign organisms in a series of modifications known as "respiratory burst".

Antioxidant system

In normal states, the cells increase the activities of antioxidant enzymes and also other antioxidant guards to counteract the formation of oxidative stress. Therefore, many intracellular and extracellular antioxidant systems undergo advancement to inactivate free radicals and reduce tissue damage. There are various antioxidant systems, enzymatic and non-enzymatic, that can be

endogenous or gained exogenously. These enzymatic and non-enzymatic antioxidant systems are required for survival by preserving a sensitive intracellular redox balance and reducing unpleasant cellular damage which is caused by reactive oxygen species (9). In addition, they consist of several high molecular weight and also a few low-molecular weight compounds that work together to protect the body against the harmful effects of reactive species. Endogenous antioxidant defense contains a network of enzymatic antioxidant and non-enzymatic molecules that usually spread in the cytoplasm and different cell organelles. Endogenous enzymatic antioxidants are including superoxide dismutase, catalase, and glutathione peroxidase including selenium (GSH-Px). There are also several antioxidant systems in the kidney that effort to protect renal tissue and related cells against harmful effects of oxidative stress.

Enzymatic antioxidant

The first enzymes of an antioxidant defense system that work against oxidative stress are some isoforms of the superoxide dismutase (SOD). Three isoforms of superoxide dismutase have been identified to be widely found in the human kidney. These isoforms, namely, CuZn-SOD, Mn-SOD, and also EC-SOD, are located in the mitochondria, cytoplasm, and extracellular space, respectively. Superoxide dismutase enhances the speed of dismutase from superoxide ($\bullet O^{2-}$) to hydrogen peroxide (H_2O_2), and then peroxidases and catalase reduce hydrogen peroxide into more stable molecules, water and O_2 (10). Catalase, which is found in all cells with aerobic activities, has high expression in renal cells. It is a tetrameric peroxidase enzyme that is formed by four identical monomers. Each of its monomers includes a hem group at the active site. It is very effective in the stimulation of reducing reactive oxygen species against water and molecular oxygen and stopping lipid peroxidation (11). Another enzyme that plays an important role in cellular antioxidant defense systems is glutathione peroxidase (GPx). Several types of glutathione peroxidase are known in mammals which are distributed all over the cells in the mitochondria, cytoplasm, and nucleus. It is a tetrameric enzyme that consists of selenocysteine in the active site. The presence of selenocysteine at the catalytic site of GPx regulates its enzyme activity. It catalyzes the reduction of H_2O_2 and lipid peroxides to water and lipid alcohols via the oxidation of reduced GSH into its disulfide form. In the deficiency of sufficient GPx activity or glutathione amounts, hydrogen peroxide and lipid peroxides are not converted to non-reactive compound and may be altered to OH-radicals and lipid peroxyl radicals, respectively.

Non-enzymatic antioxidant

Non-enzymatic antioxidants consist of low-molecular-weight substances that can be endogenous or gained exogenously. Endogenous antioxidants have a significant role in maintaining optimum cellular functions. Nevertheless, under some conditions which stimulate oxidative stress, these antioxidants may not be adequate and exogenous antioxidants may be essential to keep the best cellular functions. Exogenous antioxidants are a type of non-enzymatic antioxidants that are provided as the result of daily food intake or dietary supplements. They include low-molecular-weight compounds that are classified into hydrophilic (ascorbic acid/vitamin C and flavonoids) and lipophilic (α-tocopherol/vitamin E, ubiquinol, and carotenoids) (12). Vitamin E is a lipid-soluble antioxidant that has eight different forms. In humans, α-tocopherol is the most active form, and is the most efficient membrane bound antioxidant in cells. Vitamin E joins the cell membrane and regulates the formation of free radicals. Moreover, it has stopped lipid peroxidation through the donation of an electron to peroxyl radical, which is produced through lipid peroxidation (13). A number of antioxidants can collaborate with other antioxidants in order to regenerate their original properties. This process is often referred to as the "antioxidant network". This network plays the main role in vitamin E regeneration. Following the oxidization of vitamin E by the elimination of reactive oxygen species (especially peroxyl radicals), vitamin C reduces and efficiently reconditions the antioxidant capacities of vitamin E. Vitamin C is another compound that has antioxidant effects. It is an effective water-soluble antioxidant in humans. Hence, it works in hydrophilic environments of the body to protect cells against death caused by oxidative stress. Vitamin C has been referred to as a potent antioxidant because of its ability to donate electrons. This characteristic is related to all its known functions, while vitamin C interacts directly with free radicals (superoxide, hydroxyl, and lipid hydroperoxide radicals) and combats with them. Consequently, it changes free radicals of vitamin E back to vitamin E indirectly. Glutathione (GSH) is another important non-enzymatic antioxidant which is abundantly found in all cell compounds. GSH is the reduced form of glutathione that detoxifies hydrogen peroxide and lipid peroxides to non-reaction species via the action of GSH-Px. The antioxidant ability of thiol compounds is caused by the sulphur atom, which can easily donate a single electron to other molecules. GSH displays its antioxidant activity in several ways. As a co-factor for some detoxifying enzymes, GSH takes part in amino acid transportation along plasma membrane (14). Subsequently, it scavenges hydroxyl radicals and singlet oxygen directly. These protective activities result in the protection of cells against apoptosis and recycle vitamins C and E back to their active forms.

Oxidative stress and kidney diseases

As notated above, oxidative stress is described as a situation that happens due to an imbalance between cellular production of reactive species and reduced antioxidant defenses that guard against them. Oxidative stress is now getting attention as a significant pathogenetic mechanism that causes tissue damage. There are some documents indicating the uncommon productions of free radicals that

make more stress, which can affect cellular and molecular structures and might bring about serious human diseases such as cardiac diseases, neurological abnormalities, malignant disorders and also the physiological process of ageing. Oxidative stress and inflammation boost kidney and vascular injury by damaging the molecular components of a nephron. The reactions of reactive species with the molecular components of a renal cell lead to harmful effects on kidney functions. They consist of the oxidation of amino acids that result in the loss of significant structural properties, lipid peroxidation of cell membranes causing the lessened viability of cell membrane, and split and crosslinking of DNA in a renal cell that makes destructive mutations (15). Uric acid is the final product of purine metabolism in human's hepatic cells which may also be a source of oxidative stress in chronic kidney disease patients and increases its development and also promotes inflammation. A familiar connection between all types of acute and chronic kidney damages is related to the overproduction of reactive oxygen species and reactive nitrogen species throughout the damage and disease development. Oxidative stress is extremely common in patients with chronic renal failure. Chronic kidney disease is an international health problem with a high level of occurrence, which is defined by a developing loss of kidney reserve, chronic inflammation, oxidative stress, vascular remodeling, tubulointerstitial scarring and also glomerular damage. In patients with chronic kidney disease, the equilibrium among pro-oxidant and antioxidant volumes is changed towards a condition of strengthened oxidative stress. Moreover, patients who are suffering from diabetes or hypertension are at a high risk of chronic kidney disease. In renal failure state, the perturbations in cellular oxidant handling influence the downstream cell signaling. This condition will promote renal tubular cell apoptosis and cellular aging. Furthermore, it decreases the regenerative ability of cells with leads to fibrosis and irreversible renal function.

Conclusion

Oxidative stress happens due to an imbalance between the production of reactive species and antioxidant defense systems. Reactive species are produced not only by cellular metabolic pathways but also by environmental elements, such as air pollutions, heavy metal ions and cigarette smoking. Reactive oxygen species and reactive nitrogen species are two types of significant reactive species. They often work together to generate a condition of oxidative stress. At high concentration, reactive species can react with approximately all cellular components including proteins, lipids and DNA. They can also severely damage cell structures. They bring about inflammation, cell death, tissue injury and disease development. There are various antioxidant systems, enzymatic and non-enzymatic, that can be endogenous or gained exogenously. The antioxidant compounds reduce free radicals and decrease the harmful effects of oxidative stress.

Author's contribution

Both authors contributed equally to the study.

Conflicts of interest

The authors declared no competing interests.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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