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Oxidative Stress-Associated Pathology: A Review

(Patologi berkaitan Tekanan Oksidatif: Suatu Kajian)

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ABSTRACT

Currently, oxidative stress (OS) has become a major interest in point of basic science and clinical research. The imbalance between generations and clearances of oxidants leads to OS. Oxidants are mainly composed of reactive oxygen species (ROS) and reactive nitrogen species (RNS) which are manifested as oxidized macromolecules causing deleterious effects in several organs. Lipid, protein and DNA oxidation products can provide extensively approach of potential oxidative stress biomarkers. OS leads to the fundamental cellular and tissue damages and consequence effect to various organs or systems. This review emphasizes the systemic pathology induced by OS that particularly affect to specialized organs or systems including the nervous system, the cardiovascular system, the lung, the liver and the kidney.

Keywords: Oxidative stress; reactive nitrogen species; reactive oxygen species

ABSTRAK

Dewasa ini, tekanan oksidatif (OS) telah menjadi salah satu kajian yang menarik perhatian dalam sains asas dan penyelidikan klinikal. Ketidakseimbangan antara generasi dan kelegaan oksida membawa kepada OS. Oksidan terutamanya terdiri daripada spesies reaktif oksigen (ROS) dan spesies nitrogen reaktif (RNS) yang dimanifestasikan sebagai makromolekul teroksida menyebabkan kesan yang merosakkan ke dalam beberapa organ-organ. Lipid, protein dan produk pengoksidaan DNA boleh memberikan pendekatan menyeluruh potensi penanda biologi tekanan oksidatif. OS boleh membawa kepada kerosakan sel dan tisu dan memberi kesan kepada pelbagai organ atau sistem. Kajian ini menekankan patologi sistemik yang disebabkan oleh OS terutamanya memberi kesan kepada organ atau sistem khusus termasuk sistem saraf, sistem kardiovaskular, paru-paru, hati dan buah pinggang.

Kata kunci: Spesies nitrogen reaktif; spesies oksigen reaktif; tekanan oksidatif

INTRODUCTION

Oxidative stress (OS) has increasingly become a major interested point of basic science and clinical research. OS is conceptually defined as the imbalance between generations and clearances of oxidants (Figure 1). As shown in Table 1, oxidants are composed of reactive free-radical and radical including reactive oxygen species (ROS) and reactive nitrogen species (RNS) which are manifested by several macromolecules especially lipid, protein and DNA causing deleterious effects in several organs (Arnouk et al. 2011; Bhimaraj & Tang 2012; Brzóska et al. 2011; Matsubara et al. 2015; Rác et al. 2015). ROS are composed of superoxide radical ($O_2^{\bullet -}$), hydroxyl radical ($^{\bullet}OH$), hydrogen peroxide (H_2O_2), peroxyl radical ($RO_2^{\bullet}$), alkoxyl radical ($RO^{\bullet}$), hydroperoxyl radical ($HO_2^{\bullet}$), singlet oxygen and ozone. RNS include nitric oxide ($^{\bullet}NO$), nitrogen dioxide ($^{\bullet}NO_2$), nitrous acid (HNO_2), dinitrogen tetroxide (N_2O_4), dinitrogen trioxide (N_2O_3), peroxynitrite ($ONOO^{\bullet}$), peroxynitrous acid (ONOOH), alkyl peroxynitrites (ROONO) and nitryl chloride (NO_2Cl). Oxidizing agents can be produced by both endogenous source (inflammatory cells, fibroblast, epithelial cells, endothelial cells, respiratory chain, xanthine and NADPH oxidase) and exogenous source (cigarette smoke, exogenous toxins, pollution, radiation, carcinogens and drugs) (Bargagli et al. 2009; Choi et al. 2014; Nomura et al. 2014; Nourazarian et al. 2014). Under normal physiological condition, oxidants are removed through antioxidant defense mechanism. If incompletely cleared by antioxidants, oxidants will caused accumulation of OS. Inefficiency and insufficiency of antioxidant defense system are concerned in some pathological conditions induced by OS (Gao et al. 2009; Luchese et al. 2009; Mathy-Hartert et al. 2008; Palipoch 2013; Palipoch & Punsawad 2013).

As shown in Figure 2, risk factors which are related to OS-induced pathologies include alcohol consumption, cigarette smoking, diet, gender, geographic location specifically at high altitude and occupation. Alcohol metabolism is linked to ROS/RNS generations leading increased oxidative stress biomarkers such as malondialdehyde (MDA) and 4-hydroxynonenal (HNE) and decreased antioxidative defense systems (Das & Vasudevan 2007; Kim et al. 2015). Cigarette smoking causes injury to the cardiovascular, pulmonary and other OS related diseases including infertility in men (Elshal et al. 2009; Kim et al. 2014; Lee et al. 2015; Saleh et al. 2002). Consumption of high fat diet causes OS through overproduction of ROS resulting in hepatic oxidative

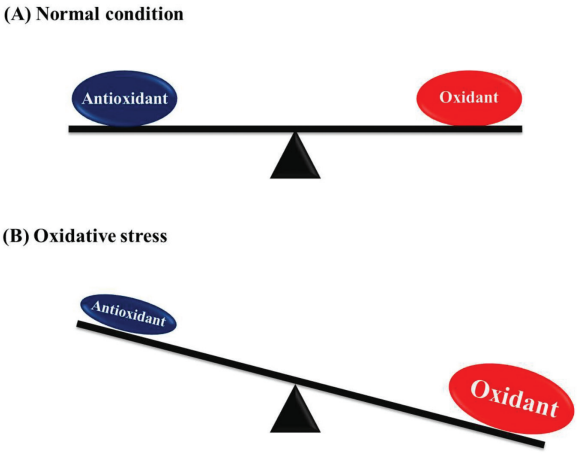

FIGURE 1. General concept of oxidative stress (a) Normal condition is indicated the balance between oxidant production and antioxidant defense system and (b) OS is demonstrated the imbalance between generation and clearance of oxidant

TABLE 1. Main reactive oxygen species and reactive nitrogen species (Bargagli et al. 2009)

Reactive oxygen species (ROS)	Reactive nitrogen species (RNS)
Superoxide radical ($O_2^{\bullet -}$)	Nitric oxide ($^{\bullet}NO$)
Hydroxyl radical ($^{\bullet}OH$)	Nitrogen dioxide ($^{\bullet}NO_2$)
Hydrogen peroxide (H_2O_2)	Nitrous acid (HNO_2)
Peroxyl radical ($RO_2^{\bullet}$)	Dinitrogen tetroxide (N_2O_4)
Alkoxyl radical ($RO^{\bullet}$)	Dinitrogen trioxide (N_2O_3)
Hydroperoxyl radical ($HO_2^{\bullet}$)	Peroxynitrite ($ONOO^{\bullet}$)
Singlet oxygen	Peroxynitrous acid (ONOOH)
	Alkyl peroxynitrites (ROONO)
	Nitryl chloride (NO_2Cl)

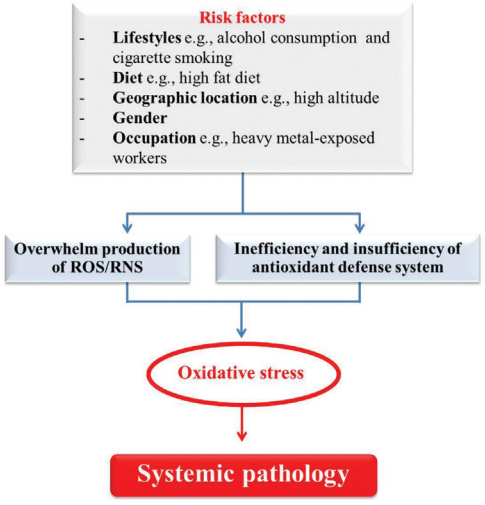

FIGURE 2. Risk factors related with OS-induced pathologies

damage, thus antioxidant supplementations are good beneficial choices (Feillet-Coudray et al. 2009; Yang et al. 2008). Gender differences in OS are shown in several diseases such as coronary artery disease (Vassalle et al. 2008) and hypertension (Ward et al. 2004). Exposure to high altitude causes hypoxia which is associated with OS and resembles ischemia/reperfusion injury by either increased ROS/RNS production or weak antioxidant defense

system (Dosek et al. 2007; Lundby et al. 2003). In addition, workers who are exposed to heavy metals demonstrated increased OS in their system (Gurer-Orhan et al. 2004).

Oxidative Stress Biomarkers

Oxidative stress biomarkers are the measurable biologically produced change in the body connected with pathology induced by OS (Table 2). Lipid, protein and DNA oxidation products provide extensively approach of potential biomarkers (Blumberg 2004; Kurutas et al. 2015; Zhong & Yin 2014). Currently, lots of methods exist that potentially allow the measurement of oxidative stress status in the blood, plasma and urine (Blumberg 2004; Kadiiska et al. 2011, 2005; Kurutas et al. 2015; Parker et al. 2001). Lipid peroxidation (LPO) is demonstrated to induce disturbance of membrane function and integrity and modification of proteins and DNA bases which has been implicated in the pathogenesis of various diseases (Dzięgielewska-Gęsiak et al. 2014; Etsuo 2009). Polyunsaturated fatty acids are especially susceptible to oxidation and readily form lipid hydroperoxides which ultimately give rise to α, β unsaturated aldehydes and other LPO products. These aldehyde species exhibit toxicity by covalently modifying nucleophilic moieties of proteins and DNA. MDA and HNE are the most potential biomarkers of LPO (Ayala et al. 2014; Sowell et al. 2005). MDA is the stable end product from the oxidative degradation of polyunsaturated fatty acids (Ayala et al. 2014; Horton & Fairhurst 1987) which are usually correlated with the pathogenesis of various diseases such as atherosclerosis, stroke and Graves' disease (Cherubini et al. 2005; Duryee et al. 2010; Guerra et al. 2005; Kirisattayakul et al. 2013; Wang et al. 2014). A second toxic messenger of oxygen free radicals, HNE is the major aldehyde formed as consequence of the oxidation of *n*-6 unsaturated fatty acids (Esterbauer et al. 1991) that is related to various pathological conditions including age-related macular degeneration (Kaarniranta et al. 2005), stroke (Cherubini et al. 2005) and liver diseases (Poli et al. 2008). Other LPO potential biomarker is a complex family of compounds produced from arachidonic acid, F2-isoprostanes which provide a strong link to diseases associated with ischemia-reperfusion, atherosclerosis and inflammation (Cracowski et al. 2002; Ishii et al. 2010). Urinary excretions of 8-isoprostane-F2α were significantly higher in children with oxidative stress-related autism (Ming et al. 2005). Oxidative damage to proteins especially susceptible amino acid such as lysine, proline and threonine may results in protein-bound carbonyl structures which are often associated with protein denaturation, reduced solubility and loss of biological function (Mehlhase & Grune 2002; Stadtman & Levine 2003, 2000). These protein carbonyls can be used as a representative biomarker of the protein oxidation. During LPO, carbonyl groups may be introduced into proteins by secondary reaction of aldehydes such as MDA and HNE with nucleophilic side chains of amino acids including cysteine, histidine and lysine (Dalle-Donne et al. 2003). In addition, reactive carbonyl derivatives such as ketoamines and deoxyosones can be affected by amino residues with consequence of glycoxidation and lipoxidation products (Stadtman & Berlett 1997). Protein oxidation products are related with various OS-induced pathologies including chronic periodontitis (Baltacıoğlu et al. 2008), familial hypercholesterolemia (Pirinccioglu et al. 2010), acute pancreatitis (Winterbourn et al. 2003), Alzheimer's disease (Korolainen et al. 2006), multiple sclerosis (Miller et al. 2012) and myocardial infarction (Paton et al. 2010). The level of oxidized DNA damage has

TABLE 2. Oxidative stress biomarkers and OS-related diseases

Biomarkers	Targets of oxidation	Examples of OS-related diseases	References
8-hydroxy-2'-deoxyguanosine (8-OHdG)	DNA	Parkinson's disease, rheumatoid arthritis, cancer, atherosclerosis and diabetics	(Dong et al. 2015; Kuo et al. 2007; Rall et al. 2000; Wu et al. 2004; Yasuhara et al. 2007)
8-oxo-7,8-dihydroguanine (8-oxoGua)	DNA	Cancer, Alzheimer's disease, aging and neurodegenerative diseases	(Eiberger et al. 2008; Moreira et al. 2008; Protano et al. 2014; Radak et al. 2011)
Malondialdehyde (MDA)	Polyunsaturated fatty acids	Atherosclerosis, stroke and Graves' disease	(Cherubini et al. 2005; Duryee et al. 2010; Guerra et al. 2005; Yoon et al. 2015)
4-hydroxynonenal (HNE)	*n*-6 unsaturated fatty acids	Age-related macular degeneration, stroke and liver diseases	(Cherubini et al. 2005; Kaarniranta et al. 2005; Poli et al. 2008; Yang et al. 2014)
F2-isoprostanes	Arachidonic acid	Ischemia-reperfusion, atherosclerosis and inflammation	(Cracowski et al. 2002; Ishii et al. 2010; Wan Ahmad et al. 2015)
Protein carbonyls	Lysine, proline and threonine	Chronic periodontitis, familial hypercholesterolemia, acute pancreatitis, Alzheimer's disease, multiple sclerosis and myocardial infarction	(Baltacıoğlu et al. 2008; Korolainen et al. 2006; Miller et al. 2012; Paton et al. 2010; Pirinccioglu et al. 2010; Winterbourn et al. 2003)

been extensively used as an indicator of the occurrence of OS. The most commonly biomarkers of oxidative DNA damage are 8-oxo-7, 8-dihydroguanine (8-oxoGua) and 2,6-diamino-4-hydroxy-5-formamidopyrimidine. LPO-derived DNA adducts have been suggested as potential biomarkers for oxidative stress to generate etheno-purinone, propano-purinone and pyrimido-purinone DNA base adducts (Blair 2008). Surprisingly, base excision repair of oxidative purine modifications is vulnerable to OS, while the nucleotide excision repair of pyrimidine dimers is not (Eiberger et al. 2008). Oxidized DNA damage induced by oxidative stress play a key role in human carcinogenesis (Kryston et al. 2011) and has often been linked to other pathological conditions such as Alzheimer's disease (Moreira et al. 2008), aging and neurodegenerative diseases (Radak et al. 2011). Currently, several approaches are applied for investigation as indicator of oxidative stress-induced tissue damage such as microRNAs, cytokinesis block-micronucleus (CBMN-cytome) assay and telomere integrity assay (Prasad et al. 2015; Ren et al. 2015; Wang et al. 2010).

Oxidative Stress-Related Systemic Pathology

Overwhelm production of oxidants and or inefficiency and insufficiency of antioxidant defense system cause OS leading to the fundamental cellular and tissue damages and consequently affecting specialized organs or systems. This review focused on the nervous system, the cardiovascular system, the lung, the liver and the kidney.

Pathology of The Nervous System

OS has been implicated in the pathogenesis of both ischemic brain and neurodegenerative diseases including Alzheimer's disease (AD), Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS) (Uttara et al. 2009). Due to high oxidative phosphorylation and low level of endogenous antioxidants, the nervous system is more susceptible to oxidative damage than any other organs (Warner et al. 2004). As in ischemia, neuronal cells can be damaged through many mechanisms that are glutamate excitotoxicity, inflammation and OS. Both excitotoxicity and inflammation also cause OS in common (Dong et al. 2009). Glutamate excitotoxicity activates NMDA receptor or even Ca^{2+}-permeable AMPA receptor resulting in toxic increase of Ca^{2+} in cells (Nakka et al. 2008). Ca^{2+}-dependent enzymes such as neuronal NOS (nNOS) and Phospholipase A2 (PLA2) produce peroxynitrite and superoxide anion damaging macromolecules and mitochondria (Godínez-Rubí et al. 2013; Sun et al. 2007). Mitochondrial dysfunction in brain even causes ROS/RNS production. Additionally, brains contain a high percentage of polyunsaturated fatty acids which are vulnerably susceptible to interaction with ROS/RNS leading to LPO (Sun et al. 2007). Inflammation which is the complex response to harmful stimuli particularly cell damage recruits white blood cells such as neutrophil releasing oxygen-free radicals and proteolytic enzymes (Wang et al. 2006). Matrix metalloproteinase destroys blood-brain barrier leading to vasogenic brain edema which worsens cerebral blood flow (Kahle et al. 2009). OS causes the oxidation of macromolecules including lipid, protein, RNA, and DNA which consequence elicits various pathologies in nervous system. Not only severe reduction of cerebral blood flow in focal cerebral ischemia or ischemic reperfusion causes reactive oxygen species but also mild reduction of cerebral blood flow which is virtually no reperfusion like chronic cerebral hypoperfusion can also generate reactive oxygen species leading to neuronal death and impairments of learning and memory (Dong et al. 2011; Koomhin et al. 2012; Xu et al. 2009). Extracellular amyloid plaques, intracellular neurofibrillary tangles, amyloid-β peptide (Aβ) accumulation and synapse loss can be found in AD brains. The excessive release of Aβ in AD patients causes OS via NMDA receptor-dependent mechanism (De Felice et al. 2007). Aβ generates ROS in a metal-catalyzed reaction which damages neuronal membrane lipid, protein and DNA ultimately, triggers neurodegeneration (Pimentel et al. 2012). It induces OS-mediated neuronal apoptosis by eliciting a SAPK-dependent multiple regulation of pro-apoptotic mitochondrial pathways involving both p53, bcl-2 and pro-death BNIP3 genes (Tamagno et al. 2003; Zhang et al. 2007). Inflammatory response also occurred as the consequence of NOD-like receptor family pyrin domain containing 1 (NLRP1) inflammasome-induced caspase1 activation (Tan et al. 2014). In addition, OS induced by Aβ may result in the impairment of astrocytic glutamate uptake which also result in the increase of extracellular glutamate supporting glutamate excitotoxicity-induced OS (Matos et al. 2012). PD is defined by death of dopaminergic neurons in the substantia nigra pars compacta and is associated with the deficiency of the neurotransmitter dopamine in the corpus striatum. Etiology of the disease is still obscured. α -synuclein aggregation is the typical feature in extracellular space of substantia nigra (Pimentel et al. 2012). The aggregation may activate microglia respiratory burst resulting in ROS production and causing dopaminergic neuron degeneration (Zhang et al. 2005). Striatal OS was increased in PD patients which is related with disease severity, particularly in the contralateral striatum (Ikawa et al. 2011). Postmortem brain tissues have suggested that ROS/RNS are involved in neurodegeneration of PD patients (Danielson & Andersen 2008). Depletion of GSH levels and high levels of HNE and 8-hydroxyguanosine are common in brain tissues of PD patients (Danielson & Andersen 2008). NMDA receptor-dependent mechanism may be involve in pathological mechanisms suggested by alleviation of symptoms in PD animal model after NMDA receptor antagonist applications (Dauer & Przedborski 2003). ALS is characterized by progressive injury and death of lower motor neurons in the spinal cord and brainstem and upper motor neurons in the motor cortex which leads to muscle weakness, wasting and spasticity (Barber et al. 2006). Approximately 90% of all ALS cases are sporadic disease, while 10% of individuals ALS are familial disease

(Menzies et al. 2002). Base on dying back hypothesis, the pathology firstly occurs at presynaptic terminals and OS takes a major contribution in pathogenesis (Pollari et al. 2014). OS contributes to motor neuron injury and death by either increased ROS/RNS production or reduced activity and levels of antioxidant defense system (Babu et al. 2008). Alterations of copper and iron metabolism undergo redox cycling and generate ROS and contribute to the induction of cell death pathways (Carrı` et al. 2003). Mitochondrial oxidative damage contributes to the pathogenesis of sporadic ALS (Murata et al. 2008). Additionally, mitochondrial dysfunction has been linked to the ALS variants of SOD1 (Shi et al. 2010). Mutations in the copper and zinc-superoxide dismutase (SOD1) gene implicate OS in the pathogenesis of familial ALS (Catherine 1995). Moreover, aberrant accumulation of Aβ42 in ALS spinal cord motor neurons is associated with OS which may play a role in the pathogenesis of neurodegeneration in ALS (Calingasan et al. 2005). Increased LPO and protein glycoxidation in the spinal cord motor neurons and glial cells of sporadic ALS patients is implicated in motor neuron degeneration (Shibata et al. 2001). Oxidative stress biomarkers are demonstrated in high levels including LPO product, HNE, protein carbonyl in spinal cord and motor cortex and oxidized DNA adduct, 8-hydroxy-2'-deoxyguanosine in whole cervical spinal cord of sporadic ALS patients (Barber 2006). Glutamate transporter dysfunction was shown in animal study of ALS (Le Verche et al. 2011). In 2005, Rothstein found that upregulation of glutamate transporter especially by β-lactam antibiotics delayed neuronal death and muscle strength in animal model of the fatal disease ALS (Rothstein et al. 2005). It suggests that the contribution of glutamate excitotoxicity also take a crucial role in pathogenesis. The excitotoxicity observed in the model may be a cause of reactive oxygen species production in the disease. Taken together, the development of treatments focusing on OS in both direct and indirect ways through other mechanisms such as glutamate excitotoxicity and inflammation have a promising future on both cerebral ischemia and other neurodegenerative diseases.

Pathology of The Cardiovascular System

Several cardiovascular diseases are resulted from complications of atherosclerosis. Atherosclerosis is a multifactorial disease which refers to the buildup of plaques (fats and cholesterol) in arterial walls. It can affect any artery in the body such as arteries in the heart, brain and kidneys which eventually restricts blood flow. Several risk factors including hypertension, hyperlipidemia, diabetes and cigarette smoking are involved in the development of atherosclerosis. Underlying mechanisms contributing to the disease process are not completely understood. Previous studies believed that OS plays a crucial role in the pathogenesis of atherosclerotic disease. The generation of ROS and oxidation of low density lipoprotein (LDL) play the key roles in the oxidative signaling pathway to vascular inflammation from the initiation of fatty streak development to plaque rupture (Cipollone et al. 2007). Oxidative DNA damage biomarker, 8-Hydroxy-2'-deoxyguanosine (8-OHdG) were found to be at high level in aorta fragments taken from patients suffering from severe atherosclerotic lesions (De Flora et al. 1997). In type 2 diabetic patients, the accumulation of OS-associated gene polymorphisms of several enzymes including myeloperoxidase, human paraoxonase and NAD(P)H oxidase is likely associated with the progression of carotid atherosclerosis (Katakami et al. 2009). Lipid peroxidation marker, 8-iso-prostaglandin F2 is possible linked with alterations of arterial elastic properties which are the sign of early vascular damage in atherosclerosis (Kals et al. 2006).

Pathology of The Lung

OS is one of the most important causes of various lung diseases including chronic obstructive pulmonary disease (COPD), bronchopulmonary dysplasia, pulmonary sarcoidosis, asthma, idiopathic pulmonary fibrosis (IPF) and lung cancer. COPD is one of the leading causes of morbidity and mortality worldwide which is primarily associated with cigarette smoking. Excessive OS contributes to pathophysiology of COPD. OS-triggered apoptosis of alveolar structural cells, including epithelial cells and thus may be an underlying mechanism in the development of COPD (MacNee 2001). High oxygen level, lower antioxidant defense, infection and inflammation susceptibility and excess free iron are the risk factors contributing to OS. A lower antioxidant is more susceptible to OS because of uncontrolled formation of free radicals. Exposure to infection and inflammation activated phagocytic cells and eventually release large amounts of ROS. Iron is the transitional metal which is found abundant in human body. It is the important metal to produce toxic hydroxyl radical by participating in the Fenton reaction ($H_2O_2 + Fe^{2+} \rightarrow OH^{\cdot} + OH^{-} + Fe^{3+}$). In preterm infants, these factors contributed to OS which triggers permanently molecular and cellular changes of lung leading to chronic lung disease or bronchopulmonary dysplasia (Pitkänen & Hallman 1998; Saugstad 2003). Idiopathic pulmonary fibrosis is a fatal fibrotic disorder characterized by an abnormal accumulation of fibroblast/myofibroblast resulting in severe dyspnea and impairment of pulmonary function. Serum levels of OS are increased in IPF patients suggested that OS plays a possible role in the pathogenesis of IPF (Daniil et al. 2008). A potent stimulator of myofibroblast differentiation and proliferation, TGF-β1 is believed to play a substantial role for OS in IPF. Treatment with enzymatic antioxidant such as extracellular superoxide dismutase can inhibit activated TGF-β1 and the development of persistent pulmonary fibrosis in animal model (Cui et al. 2011).

Pathology of The Liver

The important cause of alcoholic liver disease is OS by which ethanol induces increased mitochondrial ROS

production in the liver. Patients with alcoholic liver disease exhibit the high levels of serum oxidative stress biomarker, MDA associated with the increase in severity of the disease and demonstrated low levels of serum vitamins E and C (Masalkar & Abhang 2005). The exact mechanism is unknown. Bailey and Cunningham (2002) believed that increased oxidant levels are linked with mitochondrial metabolism through oxidative process and/or alteration of mitochondrial electron transport chain. Moreover, ROS might have the effect on inactivation of mitochondrial proteins which would diminish mitochondrial function and ultimately cause some deleterious effects to hepatocytes in alcohol abusers (Bailey & Cunningham 2002). The generation of ROS and RNS is stimulated by cytokine-induced oxidative stress signals in hepatic parenchymal cells and via the induction of Kupffer cells and inflammatory cells. The shift in the balance of cytokines in hepatocytes including tumor necrotic factor (TNF)-α, interleukin (IL)-1β and IL-6 also contributes to hepatic damage in alcoholic hepatitis (Hoek & Pastorino 2002). Fatty liver disease associated with chronic alcohol consumption or obesity/type 2 diabetes is linked to mitochondrial defect. The alterations of mitochondrial genome and proteome cause loss of mitochondrial respiration, the inability to maintain sufficient ATP concentrations and a further increased ROS and RNS generation ultimately resulting in OS (Mantena et al. 2008). Non-alcoholic liver disease includes a spectrum of hepatic steatosis, steatohepatitis and fibrosis which is also linked with OS. Previous study demonstrated that the transgenic Ren2 rats, harboring the mouse rennin gene with elevated tissue Angiotensin II, developed significant hepatic steatosis by 9 weeks of age and developed to marked steatohepatitis and fibrosis by 12 weeks which are associated with the increased levels of hepatic ROS and LPO. After treatment with an angiotensin type 1 receptor blocker or superoxide dismutase/catalase mimetic, hepatic indices of steatosis, fibrosis and OS are attenuated (Wei et al. 2008). Moreover, the development of hyperdynamic circulation in portal hypertension is also associated with OS by impact on function of vascular smooth muscle. Normally, ROS and RNS are recognized as the regulatory molecules in signaling pathways of normal vascular smooth muscle cells depending on concentration, cellular compartment of generation and access, nature of action and target site of molecular species. However, their action depends on cellular antioxidant status (Bomzon & Ljubuncic 2001). The toxicity of chemotherapeutic agent such as cisplatin also caused the liver damage which OS was implicated in the pathogenesis (Palipoch & Punsawad 2013; Palipoch et al. 2014). Heavy metals such as lead nitrate can induce OS in liver by increased LPO, decreased concentrations of hepatic glutathione and decreased activities of enzymatic antioxidants including catalase, glutathione reductase and glutathione peroxidase in fish. Medicinal plant-derived antioxidants are able to reduce hepatic pathology induced by OS in $Pb(NO_3)_2$-exposed fish (Palipoch et al. 2011a, 2011b).

Pathology of The Kidney

In fish model, OS can cause various kidneys alterations via increased oxidant production and decreased antioxidant defense system (Palipoch et al. 2011a, 2011b). According to Robbins et al. (2002), generation of ROS induced by irradiation leads to nephropathy in rats via OS induction. Detection of specific DNA oxidative stress marker, 8-OHdG and localized kidney irradiation illustrates a marked, dose-independent increase in glomerular and tubular cell nuclear DNA oxidation which is associated with persistent and chronic oxidative stress. Moreover, a relation between chronic oxidative stress and tubulointerstitial fibrosis in irradiated kidney remains to be established. Antioxidant such as superoxide dismutase is demonstrated as an effective approach in the treatment of kidney fibrosis induced by irradiation (Robbins et al. 2002). Aykanat et al. (2011) believed that chronic kidney disease especially in the uremic state and dialysis treatment is believed to cause the imbalanced antioxidant defense system and the increased ROS production consequently leading to OS. Pediatric patients with chronic kidney disease including pre-dialysis, regular hemodialysis and received kidney transplantation exhibit increased oxidative DNA damage using comet assay (Aykanat et al. 2011). Pawlak et al. (2007) indicated that uremic patients illustrated with impaired renal function and duration of dialysis treatment are associated with increased of OS. Compared to healthy control, the increased Cu/Zn superoxide dismutase is found in peritoneal dialysis and maintenance hemodialysis patients. Antioxidant therapy might be a new method to reduce intradialytic OS (Pawlak et al. 2007).

Conclusion

OS has been implicated in various pathologies via underlying mechanism of increased ROS/RNS production and/or decreased scavenging ability of antioxidant defense system. Oxidants play the key role to oxidize several macromolecules especially lipid, protein and DNA and ultimately lead to injury of various organs or systems. Detections of biomarkers including lipid, protein and DNA oxidation products from blood and urine are the important methods to measure oxidative stress status. Future investigation will provided the effective approach to prevent and or treat OS-associated diseases. Currently, exogenous antioxidant supplementations from various sources especially medicinal plants are believed to ameliorate pathologies induced by OS.

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