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Invited Review

An update on oxidative stress-mediated organ pathophysiology

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ABSTRACT

Exposure to environmental pollutants and drugs can result in pathophysiological situations in the body. Research in this area is essential as the knowledge on cellular survival and death would help in designing effective therapeutic strategies that are needed for the maintenance of the normal physiological functions of the body. In this regard, naturally occurring bio-molecules can be considered as potential therapeutic targets as they are normally available in commonly consumed foodstuffs and are thought to have minimum side effects. This review article describes the detailed mechanisms of oxidative stress-mediated organ pathophysiology and the ultimate fate of the cells either to survive or to undergo necrotic or apoptotic death. The mechanisms underlying the beneficial role of a number of naturally occurring bioactive molecules in oxidative stress-mediated organ pathophysiology have also been included in the review. The review provides useful information about the recent progress in understanding the mechanism(s) of various types of organ pathophysiology, the complex cross-talk between these pathways, as well as their modulation in stressed conditions. Additionally, it suggests possible therapeutic applications of a number of naturally occurring bioactive molecules in conditions involving oxidative stress.

1. Introduction

Existence of aerobic organisms on the earth is possible because of the presence of oxygen (Farrugia and Balzan, 2012). However, an adverse role is also played by this molecule in biological systems by facilitation of oxidative stress. In living systems, even at the steady state, oxygen always undergoes metabolism to produce oxygen-derived free radicals (superoxide O_2^-, hydroxyl OH·, alkoxyl RO· and peroxyl RO_2^-) as well as non-radicals (hydrogen peroxide H_2O_2, peroxynitrite ONOO–, hypochlorous acid HOCl and hypobromous acid HOBr). These two groups are collectively termed reactive oxygen species (ROS) and are considered as important factors for oxidative stress mediated cellular damages (Valko et al., 2004). Normally, an appropriate balance between the production and neutralization of ROS determines the physiological state in a living system and does not lead to any oxidative damage (Turrens and Boveris, 1980). A group of researchers characterized oxidative stress as an imbalance between the production of ROS (prooxidants) and antioxidants defense system in an organ or the organism as a whole, in favor of the former and brings about cellular disruption (Sies, 1997). This imbalance occurs due to two reasons; either by the overproduction of ROS such as the superoxide radical (O_2^-) or hydroxyl radical (OH·), or by the diminution in the elimination of ROS by oxidant defense mechanisms. The most important sources of ROS generation include the mitochondrial electron transport chain (one of the important sites involves in the production of significant amounts of H_2O_2) (Narayanan et al., 2010), peroxisomes and the cytochrome P450 system. Moreover, production of ROS can be accelerated by the action of various enzymes such as cyclooxygenases (Didion et al., 2001; Niwa et al., 2001), xanthine oxidase (Kinugawa et al., 2005), uncoupled NOS (Vasquez-Vivar et al., 1997, 1998; Landmesser et al., 2003; Dikalova et al., 2010; Santhanam et al., 2012) and NADPH oxidases (Drummond et al., 2011). Different drugs, such as doxorubicin (Das et al., 2012a, 2011a,b; Ghosh et al., 2011a,b,c; Pal et al., 2012a,b), cisplatin, acetaminophen (Ghosh et al., 2010; Sarkar and Sil, 2011, 2007; Das et al., 2010a,b; Ghosh and Sil, 2009, 2007; Bhattacharjee and Sil, 2006), and nimesulide, (Chatterjee and Sil, 2007, 2006; Chatterjee et al., 2006), toxicants such as heavy metals (As, Pb, Cd, Hg, etc.) (Bhattacharyya et al., 2012; Pal et al., 2013, 2012, 2011; Das et al., 2009a,b), acrolein, chloroform, and carbon tetrachloride (Jia et al., 2007); and tertiary butyl hydroperoxide (Roy and Sil, 2012a,b; Bhattacharya et al., 2011a,b; Ghosh et

Abbreviations: SOD, superoxide dismutase; GPx, glutathione peroxidases; CAT, catalase; GSH, reduced glutathione; GSSG, oxidized glutathione; GST, glutathione S-transferase; GR, glutathione reductase; mtDNA, mitochondrial DNA; DOX, doxorubicin; APAP, acetaminophen; NAPQI, *N*-acetyl-parabenzoquinone imine; AZT, azidothymidine; HIV, human immunodeficiency virus; As, arsenic; Pb, lead; Hg, mercury; Cd, cadmium; F^-, fluoride; TBHP, tertiary butyl hydroperoxide; CCl_4, carbon tetrachloride; DN, diabetic nephropathy; CRF, chronic renal failure; DM, diabetes mellitus; IR, insulin receptor; ALX, alloxan; STZ, streptozotocin; AA, arjunolic acid; KT, kombucha tea; DSL, D-saccharic acid-1,4-lactone; ADG, advanced glycation end product; GABA, gamma amino butyric acid.

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al., 2011a,b,c; Sarkar and Sil, 2010), xenobiotics, ultraviolet (UV) irradiation, environmental pollutants (oxides of nitrogen, SO_2, CO_2, etc.), and other factors enhance the process of ROS production. A number of metabolic disorders, such as insulin resistance, familial amyotrophic lateral sclerosis, obesity, and diabetes mellitus all assist the formation of ROS in the biological system (Bhattacharya et al., 2013a,b; Rashid et al., 2012, 2013; Manna et al., 2010a,b, 2009a,b; Das et al., 2012b). Three important ROS in organisms are hydrogen peroxide (H_2O_2), the hydroxyl radical ($OH^{\cdot}$) and the superoxide radical (O_2^-) (Matés et al., 2012). Among these three, O_2^- acts as a parent ROS molecule formed due to one electron reduction of molecular oxygen by various enzymes (e.g. NADPH oxidase, cyclooxygenase, enzymes in the mitochondrial electron transport chain, and cytochrome P450 enzymes). Superoxide dismutase converts O_2^- into H_2O_2 by the dismutase reaction. Various enzymatic and non-enzymatic reactions further convert this ROS molecule into a reactive and harmful hydroxyl radical ($OH^{\cdot}$), hyperchlorous acid (HOCl) and peroxynitrite ion (ONOO–) (Chrissobolis and Faraci, 2008; Miller et al., 2010). An enhanced level of ROS molecules has deleterious cellular impact and results in the damage of vital cellular macromolecules such as lipids (Bilinski et al., 1989), proteins (Cabiscol et al., 2000) and nucleic acids (Yakes and VanHouten, 1997). In order to combat oxidative stress, cells possess their own antioxidant defense machinery (Halliwell and Gutteridge, 1999) that includes three major antioxidant enzymes, SOD, glutathione peroxidases (GPx), and catalase (CAT), and a number of other non-enzyme molecules, such as reduced and oxidized glutathione. Among these three enzymes, SOD catalyzes the conversion of O_2^- to H_2O_2, while CAT converts H_2O_2 into H_2O and O_2. Using reduced glutathione (GSH), GPx, catalyzes the reduction of two molecules of peroxide to produce oxidized glutathione (GSSG) and water (Savaskan et al., 2007). Besides these enzymes, glutathione S-transferase (GST), glutathione reductase (GR), as well as non-enzymatic glutathione (GSH) and glutathione disulfide (GSSG), in combination play various important roles in the series of antioxidant defense activities.

Several lines of earlier evidence suggested that oxidative stress is implicated in the pathogenesis of various diseases such as cardiovascular diseases, diabetes (Rashid et al., 2013, 2012; Das et al., 2012b, 2012c; Manna et al., 2012a; 2012b), aging in human (Orr and Sohal, 1994), Alzheimer's disease (Behl, 1999), Parkinson's disease (Hirsch, 1993), progression of cancer (Ames et al., 1993; Farrugia and Balzan, 2012), and epilepsy (Cardenas-Rodriguez et al., 2013).

The objective of this review is to present a combined research report of various studies on the detrimental effects of oxidative stress on different organs, especially emphasizing the mechanism of its associated pathophysiology. Beneficial role of some important antioxidants will also be discussed.

2. Oxidative stress, its associated lesions and pathophysiology

In eukaryotic cells ROS are produced as a consequence of regular metabolism (Cossarizza et al., 2009). In the normal physiological conditions, these prooxidants are counter-balanced by cellular antioxidant mechanisms. Oxidative stress occurs when the balance between the prooxidants and antioxidants becomes disturbed in favor of the former leading to potential injury. A number of cellular sources generate considerable amounts of ROS which in turn contribute to cellular oxidative stress among which the mitochondrion is the major intracellular source of ROS which has at least 10 different sites competent to generate ROS (Circu et al., 2010; Cossarizza et al., 2009; Turrens, 2003). Besides the major contribution of the electron transport chain, an intermembrane space enzyme (p66Shc), an outer membrane enzyme monoamine oxidase (MAO) (Migliaccio et al., 2006; Circu et al., 2010), α-ketoglutarate dehydrogenase (α-KGDH) and pyruvate dehydrogenase enzyme complexes of the Krebs cycle (Sinha et al., 2013), altered mitochondrial matrix pH and membrane potential (Pal et al., 2013; Bhattacharyya et al., 2012) also impart considerable effects on total cellular ROS generation. Manganese superoxide dismutase-mediated dismutation of O_2^- generates H_2O_2 (Cossarizza et al., 2009) which in turn is converted to extremely reactive $HO^{\cdot}$ through Fenton and/or Haber–Weiss reactions and cause considerable cellular lesions (Sinha et al., 2013).

As mentioned above, oxidative stress induces severe lesions to cells in many forms. As the major site of ROS production, mitochondria are mostly prone to oxidative stress-related lesions with lethal consequences, such as mitochondrial DNA (mtDNA) damage (Rachek et al., 2009). Not only the elevated levels of $HO^{\cdot}$ and O_2^- are associated with mtDNA lesions (Circu and Aw, 2010), but oxidative impairment of iron–sulfur (Fe–S) proteins like aconitases can also induce mitochondrial toxicity (Orrenius et al., 2007). The structure and function of mitochondrial membrane lipids are drastically changed and damaged by the H_2O_2 (Sinha et al., 2013). Mitochondrial oxidative stress can also lead to severe genomic DNA lesions, which may have further serious consequences such as apoptosis (Das et al., 2010a).

3. Mechanism of oxidative stress-mediated organ pathophysiology

3.1. Mechanism of drug-induced organ pathophysiology

Lately, use of many drugs (drugs for cancer treatment, non-steroidal anti-inflammatory drugs, antipsychotics, antiretroviral agents, analgesics, etc.) has been made limited as most of them are responsible for oxidative stress-mediated toxicity in various tissues and organs including heart, kidney, liver and brain. Exposure to these drugs results in the generation of ROS by utilizing different pathways to induce toxicity, though the exact mechanisms are still not clearly known. These ROS then react with different macromolecules of the cell to exert adverse effects. In this part of the review, we discuss the role of various commonly used drugs in the generation of ROS and induction of toxicity taking the examples of doxorubicin (DOX), cisplatin, acetaminophen, azidothymidine and nimesulide. An outline of the mechanism of action of these drugs in inducing toxicity is presented in Fig. 1.

3.1.1. Doxorubicin induced toxicity

Doxorubicin (DOX) is an anthracycline drug and is well known for its unmatched efficacy and broad spectrum use in cancer therapy (Hortobagyi, 1997; Lown, 1993). It shows antineoplastic effects by intercalating DNA, preventing replication and inhibiting topoisomerase-II (Gewirtz, 1999; Fortune and Osheroff, 2000). Like all other chemotherapeutic drugs, the effective dose of DOX can also cause injury to non-targeted and non-cancerous tissues (mainly cardiac tissue and testis) by the direct or indirect promotion of oxidative stress. DOX impairs the health of the patients during the course of treatment and even after that. As a result, the application of DOX has been restricted to some extent now (Yeh et al., 2007). The mechanism of DOX-mediated cardiotoxicity should, therefore, be known clearly in order to develop strategies that can prevent this drug-induced cardiotoxicity without affecting its effectiveness.

A number of reports suggest that DOX can generate ROS by using more than one mechanism (Simunek et al., 2009; Menna et al., 2007). The quinone moiety of DOX first undergoes reduction by one electron via NADH dehydrogenase to generate anthracyclin semiquinone free radical (Davies and Doroshow, 1986). In the

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