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Invited Review Article

Toxicological and pharmacological concerns on oxidative stress and related diseases

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ABSTRACT

Although reactive oxygen species (ROS) such as superoxide, hydrogen peroxide and hydroxyl radical are generated as the natural byproduct of normal oxygen metabolism, they can create oxidative damage *via* interaction with bio-molecules. The role of oxidative stress as a remarkable upstream part is frequently reported in the signaling cascade of inflammation as well as chemo attractant production. Even though hydrogen peroxide can control cell signaling and stimulate cell proliferation at low levels, in higher concentrations it can initiate apoptosis and in very high levels may create necrosis. So far, the role of ROS in cellular damage and death is well documented with implicating in a broad range of degenerative alterations *e.g.* carcinogenesis, aging and other oxidative stress related diseases (OSRDs). Reversely, it is cleared that antioxidants are potentially able to suppress (at least in part) the immune system and to enhance the normal cellular protective responses to tissue damage. In this review, we aimed to provide insights on diverse OSRDs, which are correlated with the concept of oxidative stress as well as its cellular effects that can be inhibited by antioxidants. Resveratrol, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, statins, nebivolol and carvedilol, pentaerythritol tetranitrate, mitochondria-targeted antioxidants, and plant-derived drugs (alone or combined) are the potential medicines that can be used to control OSRD.

Contents

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Introduction

Reactive oxygen species (ROS) such as superoxide, hydrogen peroxide and hydroxyl radical are naturally formed because of normal oxygen metabolism. However these free radicals are potentially able to create oxidative damage *via* interaction with bio-molecules. When there is a pathogen attack, oxidative damage might be beneficial. Obviously, ROS are not only always bad for normal physiology of the cells but sometimes useful. For instance, lower amounts of ROS are produced during mitochondrial activity in normal cells to act as the signaling molecules. The point is that level of oxidants and normal biological antioxidants must be in a balance. If the mentioned balance is interrupted, then toxic oxidative stress may happen (Fig. 1). This imbalance usually happens during aging (as an example) or it can involve in the pathology of some diseases and also appears as a consequence of the diseases. Normal body contains enzymatic or non-enzymatic antioxidants such as tocopherols or vitamin E, glutathione and ascorbic acid or vitamin C that are involved in above-mentioned process. Among internal antioxidants, the ascorbic acid (AA) and the reduced form of glutathione (GSH) play the main roles in fighting against ROS as well as in maintenance of normal oxidative balance. It seems that AA and GSH are working closely through the ascorbate–glutathione cycle and have sort of cross-talk, although both have their own mechanisms and pathways (Potters et al., 2004). As mentioned above, mitochondrial respiration generates a proton gradient and $O_2^{\bullet-}$ perhaps as a signaling element that might be involved in oxidative stress and alkaline-induced cell death (Mates et al., 2012). The creation of $O_2^{\bullet-}$ following irradiation seems to be a main character of cell injury (Tominaga et al., 2012). Since manganese superoxide dismutase (Mn-SOD) removes extra $O_2^{\bullet-}$ in the mitochondria to conserve it from oxidative damage, thus over-expression of Mn-SOD reduces the levels of intracellular ROS and protects against cell death (Mates et al., 2012).

The role of oxidative stress as a remarkable upstream part is frequently reported in the signaling cascade of inflammation as well as chemo attractant production. Actually in the presence of transition metals, hydrogen peroxide can be converted to the highly reactive hydroxyl radical, which is responsible for most of the oxidative damages to proteins, lipids, sugars, and nucleic acids. Hydroxyl radical is also a hallmark signaling molecule that is able to activate NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells), an important transcription factor involved in inflammatory responses. Even though hydrogen peroxide can control cell signaling and stimulates cell proliferation at low levels, in higher concentrations it can initiate apoptosis and in very high levels it may create necrosis (Abdollahi and Shetab-Boushehri, 2012; Saeidnia and Abdollahi, 2013). So far, the role of ROS in cellular damage and death is well documented with implication in a broad range of degenerative alterations (*e.g.* tissue degradation, carcinogenesis, aging and other oxidative stress related diseases (OSRDs)).

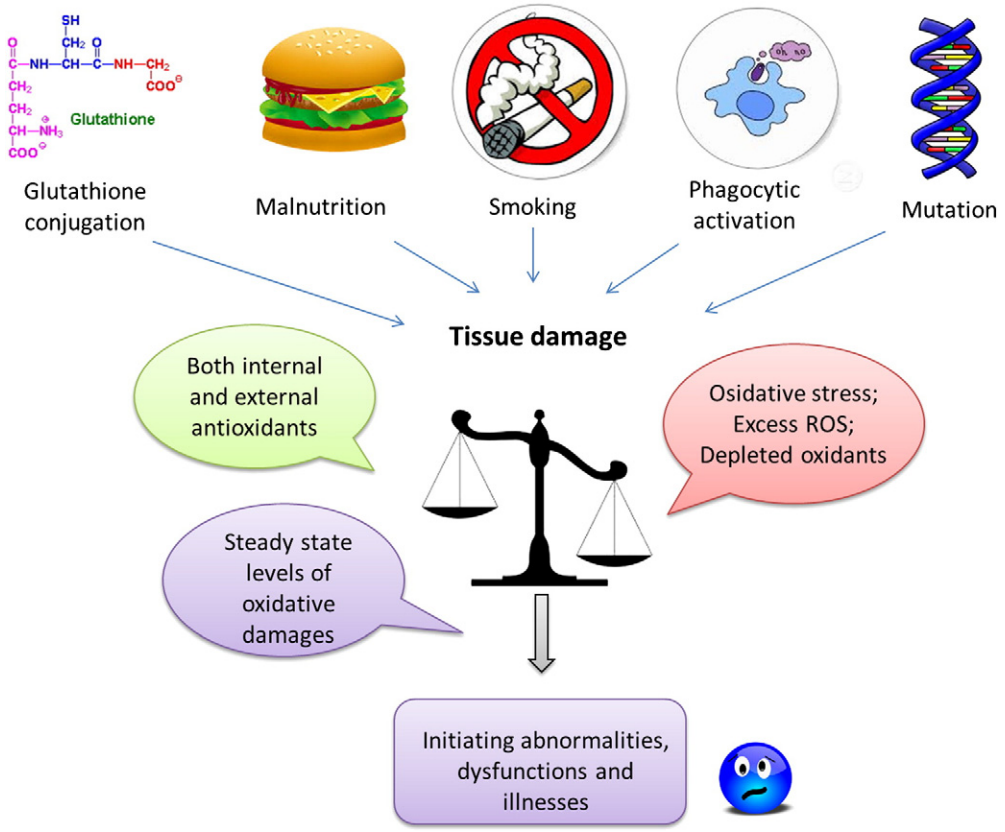

Fig. 1. Induction of oxidative stress and consequent damages leading to OSRD; ROS: reactive oxygen species; AOX: antioxidants.