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COMMENTARY

Cellular Protection During Oxidative Stress: A Potential Role for D-ribose and Antioxidants

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ABSTRACT. A healthy cellular system involves the maintenance of an intracellular metabolic balance. Reactive oxygen species (ROS) are constantly produced as a normal product of cellular metabolism; however, during situations of cellular stress, these levels can increase dramatically with the potential to cause deleterious cellular structural and/or functional consequences. There is a significant elevation in these ROS following stressful situations, such as ischemia, hypoxia, high-intensity exercise, and in many diseases. To combat these ROS, neutralizing endogenous enzymes, as well as exogenous antioxidants, can aid in minimizing their potential untoward cellular effects. Exogenous reducing antioxidant agents, such as vitamin C and/or E, play a role in addressing these formed species; however, recent research has suggested that fruit seed extracts may provide additional cellular benefits beyond their antioxidant features. Furthermore, supplemental D-ribose enhances the recovery of high-energy phosphates following stress and appears to potentially offer additional benefits by reducing radical formation. Specifically, during periods of hypoxia/ischemia, supplemental D-ribose may play an inhibitory role in the breakdown of adenine nucleotides, influencing the subsequent formation of xanthine and uric acid compounds; and thereby affecting the release of superoxide anion radicals. The combination of D-ribose with reducing antioxidants may provide a more optimal state of cellular protection during and following times of oxidative stress.

KEYWORDS. antioxidants, D-ribose, oxidative stress, oxygen free radicals, reactive oxygen species

OVERVIEW

The maintenance of a healthy cellular system involves perpetual regulation of its metabolic balance, including during and following states of oxidative stress (Bouayed & Bohn, 2010). A reactive oxygen specie (ROS) may be either a radical that has at least one unpaired electron in its outer valence shell and is produced as a natural byproduct from oxygen metabolism, including superoxide anion radical, hydroxyl radical, and peroxyl radical or non-radical species, such as hydrogen

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peroxide and hypochlorous acid. ROS are constantly produced; however, during times of stress, a biologically significant elevation in ROS can occur (Valko et al., 2007). This significant increase in ROS can affect a cell's structure and/or function by altering cellular metabolism, such as the oxidation of polyunsaturated fatty acids in lipids, oxidation of amino acids in proteins, potentially damaging deoxyribonucleic acid (DNA), inactivating specific enzymes by oxidation of co-factors, and in extremely high concentrations, a cell's survival (Seifried, Anderson, Fisher, & Milner, 2007). These potential damaging effects of ROS involving DNA, ribonucleic acid, and proteins could in theory contribute to our aging process.

Elevated levels of ROS have been mentioned as a potential factor in the development of atherosclerosis, neurodegenerative diseases, dementia, heart failure, myocardial infarction, chronic fatigue syndrome, fibromyalgia, and carcinogenesis (Valko et al., 2007). Lipid oxidation products, including aldehydes and cholesterol oxides, either formed in vivo or consumed from exogenous food sources, participate in the development of atherosclerotic lesions (Addis & Warner, 1991). The elevation in ROS levels plays not only a profound role in the development of specific diseases, but also in their effect on the progression of a disease. For example, in congestive heart failure, a study has reported an increase in ROS levels with higher levels corresponding with the severity of the disease (Belch, Bridges, Scott, & Chapra, 1991). Besides the potential causative role in these diseases, measured ROS markers may act as a tool in the therapeutic management of a disease, as a way to increase the availability of antioxidants to combat ROS and to develop methods to limit the ultimate production of ROS. Research has shown that a diet high in fruits and vegetables, as well as the daily consumption of antioxidants can aid oxidative stress by minimizing the production of ROS and potentially providing therapeutic ROS scavengers (Kelly, 1998).

Besides the profound negative cellular effects of ROS, there are also positive physiological benefits of ROS, such as cell signaling and aiding our immune system. For example, the presence of ROS can interact with pathogens, aid in the mobilization of ion transport systems, recruit leukocytes, enhance cellular signaling within and between cells, aid in the response to growth factors, and can play a significant role in cellular apoptosis by eliminating damaged cells (Bouayed & Bohn, 2010; Hancock, Desikan, & Neill, 2001; Simon, Haj-Yehia, & Schaffer, 2004; Berg, Trofast, & Bengtsson, 2003). Further, during bleeding conditions in which hemostasis is critical and for subsequent wound healing/repair, platelets play a key function, for which there is a release of ROS to recruit platelets to aid at the site and degree of injury (Berg et al., 2003).

The production of ROS can also play a significant indirect role in cellular metabolism. Normally, glycolytic and oxidative pathways are essential for this production of cellular energy, but under stressful conditions, the pentose phosphate pathway (PPP) can play a key role. The PPP, generating reduced nicotinamide adenine dinucleotide phosphate for biosynthetic reactions and the synthesis of pentose sugars, and the glycolytic pathway are interrelated by transketolase and transaldolase enzymes. These enzymes are involved in the nonoxidative steps of the PPP (Zimmer, 1992). D-ribose, a natural occurring reducing carbohydrate and an intermediate in the PPP, plays an important role in the production of energy [adenosine triphosphate (ATP)], our genetic material, and in many of our cellular metabolic

reactions. Adequate levels of ATP are necessary for the preservation of cellular integrity and function. Under normal oxygenated situations, the cellular demand for ATP is satisfied. However, during stressful states, such as myocardial ischemia and/or hypoxia, the production of these energy compounds is insufficient, where demand outstrips supply. Kriett et al. have reported that the post-stress, ischemic recovery of these necessary energy levels is prolonged with an associated impairment in function (Kriett et al., 1983). A common dietary carbohydrate intake may not be the answer to supplement this cellular-deficient energy-dysfunctional problem. Recently, reports indicated that a high-carbohydrate diet can negatively affect cardiac function by decreasing the utilization of fatty acid and glucose. This reduction in myocardial contractile function is probably due to altered fatty acid and glucose metabolism, resulting in a low availability of ATP (Porto et al., 2011).

Preclinical studies have reported that D-ribose can enhance the regeneration of ATP following ischemia. Tveter et al. showed that supplemental D-ribose improved myocardial ATP levels and function following reversible ischemia (Tveter, St.Cyr, Schneider, Bianco, Foker, 1989). In addition, clinical benefits have also been reported in patients with cardiovascular diseases. Pliml et al. published that oral supplementation of D-ribose allowed stable coronary artery patients to endure longer treadmill exercise sessions before developing angina or electrographic changes (Pliml et al., 1992). Perkowski et al. found its functional benefits in patients undergoing "off pump" coronary artery bypass procedures (Perkowski, Wagner, & St.Cyr, 2007). Other researchers have found that in congestive heart failure patients, D-ribose improved diastolic dysfunction, quality of life, and physical function in class II–III patients (Omran, Illien, MacCarter, St. Cyr, & Luderitz, 2003). Vijay et al. reported that during submaximal cardiopulmonary exercise testing in patients with heart failure, ventilatory efficiency was enhanced with D-ribose with a noted 44% Weber functional class improvement (Vijay, MacCarter, Shecterle, & St.Cyr, 2008).

Benefits of ingesting D-ribose have also been found in the field of sports medicine. The availability of D-ribose to our skeletal muscle is a limiting factor in the resynthesis rate of ATP following high-intensity exercise. Hellsten et al. found that supplementation with D-ribose influenced the rate of muscular ATP resynthesis during intense intermittent exercise (Hellsten, Skadhauge, & Bangsbo, 2004). Furthermore, in a pilot study, Seifert et al. reported in healthy, adult subjects that D-ribose supplementation maintained lower levels of ROS following hypoxic, high-intensity exercise, unlike the significant increase found without D-ribose. D-ribose significantly minimized the excretion of urinary malondialdehyde levels, a marker of ROS, as well as demonstrating a positive effect in measured plasma-reduced glutathione levels (Seifert et al., 2009). Ideally, the use of D-ribose with antioxidants as additives during times of oxidative stress may offer a benefit.

Physiologically, the body's defense towards the production of ROS centers on the production and the interaction of neutralizing enzymes, such as superoxide dismutases, catalase, glutathione peroxidase and glutathione reductase. However, the endogenous antioxidant defense system is not always adequate; therefore, over decades there has been a campaign for the daily consumption of supplemental antioxidant reducing compounds, such as vitamins C and E, carotenoids, and polyphenols due to their potential anti-ROS reactivity (Bouayed & Bohn, 2010). It is

perhaps significant to note that certain combinations of antioxidants often exhibit marked synergistic effects (Loliger, 1991). Antioxidants aid in interacting with ROS; and thereby, potentially minimizing the potential damaging cellular effects caused by these radicals. Furthermore, antioxidants also aid in cellular signal transduction, regulation of proliferation, and influence both the recognition and subsequent immune response our body generates (Seifried et al., 2007).

The biochemical activities of D-ribose, combined with endogenously produced and exogenous supplementation of antioxidants, could potentially offer a synergistic cellular benefit during and following states of oxidative stress. Besides the known antioxidants of vitamin C and E, food scientists have proposed that the combination of antioxidants found in a variety of fruits, such as blueberry, cranberry, grape, pomegranate, red and black raspberry, black cumin, and milk thistle, may offer a more complete, ideal solution to this problem (Davis, 2011; Botanic Oil Innovations, Inc., 2011). Biochemical analyses have shown that these natural fruit seed ingredients provide substantial antioxidant levels with high oxygen radical absorbance capacity. These seed extracts have the potential to enhance our immune function, increase the levels of omega 3 fatty acid levels, proanthocyanin, and resveratrol, and provide anti-inflammatory properties. The combination of fruit seed extract antioxidants along with D-ribose could provide a healthy focus in addressing the production and neutralization of ROS. Additional nutritional benefits may also be found for our cardiovascular, immune, neurologic systems, which are stressed every day; and thus, potentially reducing the impact of oxidative stress in a potential solution to some of these complicated issues.

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