A skeptical view on the use of antioxidant supplementation in sport

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Oxidative stress induction by exercise

The first assumption that physical exercises can lead to generation of reactive oxygen species (ROS) that cause oxidative modifications of biomolecules occurred in 1978. At this time Dillard et al. demonstrated a 1.8-fold increase in exhaled pentane as a lipid peroxidation marker after 60 minutes of cycling at 25-75% of the maximum oxygen consumption (VO_2max). Since then, a number of studies have shown excess generation of ROS and oxidative stress (OS) induction in physical exercise. It is widely accepted that the primary tissue of ROS generation during physical activity is skeletal and heart muscle. At subcellular level numerous sites for ROS production exist: electron transport chains in mitochondria, NAD(P)H oxidase enzymes, xanthine oxidase, phospholipase A_2, lipoxygenases, catecholamines and prostanoid metabolism. As well as several secondary sources, such as macrophages (Jackson, 2000) and neutrophils by γ-interferon (IFN-γ), interleukin-1 (IL-1) and tumor necrosis factor (TNF) (Peake and Suzuki, 2004) exist.

ROS are a natural byproduct of the normal metabolism of oxygen. They result from partial reduction of oxygen and include superoxide anion radicals ($\bullet O^-_2$), hydrogen peroxide (H_2O_2) and hydroxyl radicals (•OH). The term ROS includes also other oxygen-containing radicals and molecules such as peroxyl, alkoxyl, and hydroperoxyl radicals, hypochlorous acid, singlet oxygen. Because of their high reactivity ROS are able to modify oxidatively all biological macromolecules impairing the functions of structures they make up.

Increased lipid oxidation, DNA oxidation, and protein oxidation have been reported during, or immediately following exercise (Fisher-Wellman and Bloomer, 2009). The negative consequences of ROS's action in muscles are related to altered contractile function (Reardon and Allen, 2009), decreased maximal force and enhanced fatigue (Baclay and Hansel, 1991), and muscle atrophy (Gumucio and Mendias, 2013). The molecular mechanisms for detrimental effect of ROS could be associated not only with the direct action on muscle structural proteins (Prochniewicz et al., 2008), but also with impairment of mitochondrial enzymes, responsible for energy supply such as succinate dehydrogenase and cytochrome oxidase (Haycock et al., 1996), ATPase pumps for calcium uptake by sarcoplasmic reticulum (Xu et al., 1997; Scherer and Deamer, 1986), ATPase pumps for potassium transport involved in development of action potentials (Sen et al., 1995). In addition the muscle damage could be mediated by ROS-induced gene expression. The activation of NF-κB and FoxO by ROS lead to expression of two specific muscle E3 ubiquitin ligases: atrogin-1 or MAFbx (muscle atrophy F-box) and MuRF-1 (muscle RING-finger protein-1) that participate in degradation of titin, nebulin, troponin, myosin-binding

protein C, myosin light chains 1 and 2 and myosin heavy chain (Gumucio and Mendias, 2013). Sriram et al. (2014) demonstrated that OS is able to activate CHOP transcription factor (CCAAT/enhancer-binding protein homologous protein) leading to increase of MuRF1expression and subsequent protein degradation.

The aerobic organisms have developed defense mechanisms against ROS. Cells, including muscle fibers, as well as the extracellular and vascular spaces are equipped with enzymatic and non-enzymatic antioxidants. The enzymatic antioxidant system includes superoxide dismutase, catalase and glutathione peroxidase, and the non-enzymatic antioxidants include glutathione, ascorbic acid, tocopherol, coenzyme Q10 and other low-molecular substances.

However, when ROS generation exceeds the antioxidant defense capacity or antioxidant defense is unable to counteract ROS, oxidative stress occurs.

Thus in front of the athletes and their coaches arise the question whether antioxidant supplementation will improve athletic performance and whether antioxidant supplements should be a part of the nutritional plane. Surveys have indicated that most elite athletes take vitamin supplements (Bojanic et al., 2011) and the most often supplemented antioxidants in sports practice are vitamin C and vitamin E. However the athletes are not very aware with the effect of these vitamins and recommended doses. Some athletes take vitamins in dosages greater than 50-100 times the Recommended Dietary Allowances (Williams, 1989). For instance it has been reported consumption of 10 000 mg of vitamin C daily (Williams, 1984).

Vitamin C

There is a huge amount of data about the protective effect of vitamin C on markers of oxidative stress, induced by exercise (Evans, 2000; Goldfarb et al., 2005; Popovic et al., 2015). Studies on the effect of vitamin C on athletes' health and performance started in 1952, when Staton reported decreased muscle soreness after 30 days of 100 mg vitamin C supplementation. In regards to exercise-induced muscle damage vitamin C supplementation appears to reduce muscle soreness (Kaminski and Boal, 1992; Bryer and Goldfarb, 2006). In regards to effect of vitamin C supplementation on performance, there was no beneficial effect on either endurance (Gey et al., 1970) or strength (Paulsen et al., 2014) performance. Even in case of vitamin C deficiency it supplementation does not appear to improve the performance (Van de Beek et al., 1990).

Vitamin E

Similar to vitamin C, vitamin E administration has shown protective effect against oxidative stress, induced by exercise leading to muscle cell damage. Decrease in exercise-induced lipid peroxidation was demonstrated in many researches (Dillard et al. 1978; Sumida et al., 1989; Rokitzki et al., 1994a; Takanami et al., 2000; Evans, 2000) in different doses and period of administration. Indeed a relatively recent critical review (Viitala and Newhouse, 2004) aimed to analyze the strength of evidences about the effect of vitamin E on exercise-induced lipid peroxidation, concludes that vitamin E supplementation does not appear to decrease exercise-

induced lipid peroxidation in humans. The vitamin E supplementation results in decreased leakage of muscle enzymes in plasma as an indirect marker of muscle damage in response to exercise. Itoh et al. (2000) demonstrated that the intake of 1200 IU vitamin E/day 4 weeks prior to and during 6 successive days of endurance running training (48.3 ±5.7 km/day) reduce the leakage of creatine kinase (CK) and lactate dehydrogenase (LDH) following the days of running. A significant diminution of serum CK increase induced by strenuous exercise, as well as a trend toward decrease in GOT, GPT, and LDH was observed in top-class cyclists after 5 months of vitamin E supplementation (Rokitzki et al., 1994). However, some studies indicated that vitamin E supplementation did not significantly change lipid and protein oxidation and CK values at rest, after exercise to exhaustion, and cycling (Gaeini et al., 2006). Reduction of plasma cytokines (IL-1β and IL-6) after a single session of eccentric exercise (downhill running on an inclined treadmill) preceded by 48-days intake of 800 IU/day vitamin E was reported by Cannon et al., (1991). However the researches do not establish enhancement in exercise performance (Sharman et al., 1971; Talbot and Jamieson, 1977; Shephard, 1983; Tiidus and Houston, 1995; Gerster, 1991; Rokitzki et al., 1994b; Takanami et al., 2000; Gaeini et al., 2006).

Other antioxidants

Other antioxidants as Coenzyme Q 10 (CoQ10), N-acetylcysteine (NAC), beta-carotenes also were tested about their effect on athletes. Several researches demonstrated that administration of CoQ10 has no measurable effect on exercise performance. Braun et al. (1991) examined the effect of CoQ10 intake at dose of 100 mg/day for 8 weeks on bicycle racers. The performance of graded exercise test using cycling ergometer was not affected by the prolonged antioxidant administration and there were no differences in all tested physiological and biochemical parameters between the placebo group and CoQ10 group. Similar results were obtained by Bonetti et al. (2000) after CoQ10 (ubidecarenone) oral treatment for same period (8 weeks). N-acetylcysteine, although inhibits fatigue, did not enhance the performance of sustained maximal efforts in handgrip exercise (Matuszczak et al., 2005). Corn and Barstow (2011) also demonstrated that acute oral dose of NAC extended time to fatigue at 80% P_{max} but did not enhance work rates. Only the data about beta-carotene application indicated that it can provide a beneficial influence on race performance. The ingestion of 25000 IU beta-carotene daily of well-trained runners led to significant improvement in 5000 meter race performance (Leblanc, 1998). However, there is not an adequate explanation of the mechanism by which this occurs (Leblanc, 1998).

Combination of antioxidants

There are some investigations about the effect of combined intake of vitamin C and E on endurance (Rokitzki et al., 1994b) and strenuous exercise (Petersen et al., 2001). It has been supposed this combination will be better than either vitamin alone, since vitamin C regenerates vitamin E by reducing vitamin E radicals formed when vitamin E scavenges the oxygen radicals. However, there were no data about enhancement of exercise performance (Paulsen et al., 2014; Morrison et al., 2015). There are also data about application of triple combinations: vitamin C,

vitamin E and beta-carotene (Kanter et al., 1993; Scroder et al., 2000); vitamin C, vitamin E and CoQ10 (Nielson et al., 1999), as the response to exercise was not affected by the applied antioxidants.

Why antioxidants do not improve exercise performance?

With development of molecular biology it was discovered that ROS, generated in exercise, are powerful cellular signals, promoting expression of multiple genes involved in training adaptation (Niess and Simon, 2007; Powers et al., 2010). Nowadays is widely accepted that basal and physiological increase of ROS is required for muscle force production, whereas higher levels lead to oxidative damage and decline in performance (Reid, 2001). This is in accordance with hormesis concept whereby a beneficial adaptive effect results from exposure to low continuous or higher intermitted doses of a stressor that is otherwise harmful at large or chronic doses (Ristow, 2014; Yun and Finkel, 2014). Therefore antioxidant supplementation in exercise training, leading to reduction of ROS generation, may hamper the favorable adaptations.

It has been demonstrated that ROS take part in regulation of following processes: mitochondrial biogenesis, angiogenesis, vasodilatation, insulin sensitivity, immune response, antioxidant enzyme expression and growth factor signaling (Grodstein et al., 2013; Ristow, 2014; Yun and Finkel, 2014; Webb et al., 2017).

Gomez-Cabrera et al. (2008) demonstrated that supplementation with vitamin C affected adaptation to endurance exercise training. They found a reduction in the exercise-induced expression of key transcription factors involved in mitochondrial biogenesis (peroxisome proliferator–activated receptor co-activator 1 alpha (PGC-1α), nuclear respiratory factor 1 (NRF1), and mitochondrial transcription factor A (mTFA)) after administration of vitamin C. This reduction resulted in hampered endurance capacity in rats. In addition vitamin C supplementation did not improve $\dot{V}O_2max$ associated with training in rats and in humans. The suppression of PGC-1α led also to antioxidant enzymes decrease, since PGC-1 activates NRF2, which induce the antioxidant enzyme expression (St. Pierre et al., 2006). Gomez-Cabrera et al. (2008) found decrease in gene (mRNA) expression of manganese-superoxide dismutase (Mn-SOD) and glutathione peroxidase (GPx) after treatment of rats with high dose of vitamin C (500 mg/kg body wt). Similar results were obtained in humans after 4 weeks of vitamin C (1000 mg/day) and E (400 IU/day) supplementation: the training-induced expression of antioxidant enzyme mRNAs was blocked (Ristow et al., 2009). In the same study was demonstrated that the training-induced expression of ROS-sensitive transcriptional regulators of insulin sensitivity increased only in absence of antioxidants.

Paulsen et al. (2014) reported that vitamin C and E supplementation led to a reduction of phosphorylation of p70S6 kinase and mitogen-activated protein kinases p38 and ERK1/2 that interrupt the cellular and physiological adaptations to strength training in humans.

It should be mentioned that some research did not find effect of high dose antioxidants administration and reported normal adaptations to exercise training in rats (Higashida et al.,

2011) and human (Yfanti et al., 2010). The contradictory results and conclusions provoked discussion on the topic (Gomez-Cabrera et al., 2008; Holloszy et al., 2012).

In conclusion, although there is some discrepancy about the effect of antioxidant supplementation on sport performance, more consistently it has been reported that the antioxidants blunt the favorable adaptation to training load (Merry and Ristow, 2016). Therefore athletes, couches and nutritionists involved in compiling sports diets should re-evaluated the antioxidant supplements intake.

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