Only nutrigenomic anti-oxidant support beneficial for recovery in pro-athletes

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Abstract- Redox cell and mitochondrial signaling can have both physiological (beneficial and important) and pathogenic role in our body. Intense exercise and environmental influences can create imbalances in the redox signaling leading to the expression of pathological pathways, and/or compromise important physiological pathways related to recovery. Intelligent nutrigenomic support can support and maintain proper redox balance. Standard anti-oxidant supplements, like vitamin C, can further imbalance the system. Contrary, correct nutrigenomic supplements upregulate the body's own mechanisms to balance free radicals, and thus yield important beneficial support for physiological signaling, which can boost our recovery and training adaptation systems, and even resulting in increased or enhanced super-compensation.

Index Terms- Nutrigenomics, redox signaling, anti-oxidants, free radicals

I. Introduction

Oxygen is an element indispensable for life. When cells use oxygen to generate energy, oxidants are created as a consequence of ATP (adenosine triphosphate) production by the mitochondria. These by-products are generally reactive oxygen species (ROS) as well as reactive nitrogen species (RNS) that result from the cellular redox process. These species play a dual role as both toxic and beneficial compounds. The delicate balance between their two antagonistic effects is an important aspect of our functioning and of even greater importance in pro-athletes and their ability to get stronger after every workout or training session. Basically one can state that the role of the endogenous and exogenous antioxidant system is to keep the oxidants in check in order to keep them at moderate levels were to exert important and beneficial effects on cellular responses and immune function.
At high concentrations, ROS and RNS generate oxidative stress, a deleterious process that can damage all cell structures (1-10). Oxidative stress plays a major part in the development of chronic and degenerative ailments such as cancer, arthritis, aging, autoimmune disorders, cardiovascular and neurodegenerative diseases. The beneficial role of ROS and RNS on cell responses are the important signaling agents responsible for training adaptation and supercompensation in athletes.

II. THE ANTIOXIDANT CLASSIFICION

Endogenous antioxidant compounds in cells can be classified as enzymatic antioxidants and non-enzymatic antioxidants. The major antioxidant enzymes directly involved in the neutralization of ROS and RNS are: superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) and glutathione reductase (GRx) (6-12). SOD, the first line of defense against free radicals, catalyzes the dismutation of superoxide anion radical ($O2^{\bullet -}$) into hydrogen peroxide (H2O2) by reduction. The oxidant formed (H2O2) is transformed into water and oxygen (O2) by catalase (CAT) or glutathione peroxidase (GPx). The selenoprotein GPx enzyme removes H2O2 by using it to oxidize reduced glutathione (GSH) into oxidized glutathione (GSSG). Glutathione reductase, a flavoprotein enzyme, regenerates GSH from GSSG, with NADPH as a source of reducing power. Besides hydrogen peroxide, GPx also reduces lipid or nonlipid hydroperoxides while oxidizing glutathione (GSH) (2, 5-10). The non-enzymatic antioxidants are also divided into metabolic antioxidants and nutrient antioxidants. Metabolic antioxidants belonging to endogenous antioxidants, are produced by metabolism in the body, such as lipoid acid, glutathione, L-arginine, coenzyme Q10, melatonin, uric acid, bilirubin, metal-chelating proteins, transferrin, etc (5, 6). While nutrient antioxidants belonging to exogenous antioxidants, are compounds which cannot be produced in the body and must be provided through foods or supplements. Some exert direct antioxidant abilities, like vitamin E, vitamin C. Other influence the expression of antioxidant pathways, like PUFA's, carotenoids, alkaloids, isothiocyanates or polyphenols, or are cofactors for the endogenous enzymatic antioxidants like the trace metals selenium, manganese and zinc.

A. Anti-oxidant process

When an antioxidant destroys a free radical, this antioxidant itself becomes oxidized. Therefore, the antioxidant resources must be constantly restored in the body. Thus, while in one particular system an antioxidant is effective against free radicals, in other systems the same antioxidant could become ineffective. Also, in certain circumstances, an antioxidant may even act as a pro-oxidant e.g. it can generate toxic ROS/RNS (10). The antioxidant process can function in one of two ways: chain-breaking or prevention. For the chain-breaking, when a radical releases or steals an electron, a second radical is formed. The last one exerts the same action on another molecule and continues until either the

free radical formed is stabilized by a chain-breaking antioxidant (vitamin C, E, carotenoids, etc), or it simply disintegrates into an inoffensive product. The classic example of such a chain reaction is lipid peroxidation. For the preventive way, an antioxidant enzyme like superoxide dismutase, catalase and glutathione peroxidase can prevent oxidation by reducing the rate of chain initiation, e.g., either by scavenging initiating free radicals or by stabilizing transition metal radicals such as copper and iron (10).

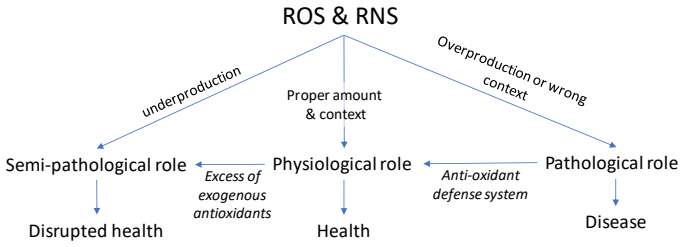
III. THE IMPORTANCE OF PROPER PHYSIOLOGICAL REDOX SIGNALING FOR MAXIMUM RECOVERY AND SUPERCOMPENSATION IN ATHLETES

A. Free radical formation

Formation of ROS and RNS can occur in the cells by two ways: enzymatic and non-enzymatic reactions. Enzymatic reactions generating free radicals include those involved in the respiratory chain, the phagocytosis, the prostaglandin synthesis and the cytochrome P450 system. from non-enzymatic reactions of oxygen with organic compounds as well as those initiated by ionizing radiations. The non-enzymatic process can also occur during oxidative phosphorylation (i.e. aerobic respiration) in the mitochondria (4, 5, 8). ROS and RNS are generated from either endogenous or exogenous sources. Endogenous free radicals are generated from immune cell activation, inflammation, mental stress, excessive exercise, ischemia, infection, cancer, aging. Exogenous ROS/RNS result from air and water pollution, cigarette smoke, alcohol, heavy or transition metals (Cd, Hg, Pb, Fe, As), certain drugs, industrial solvents, cooking (smoked meat, used oil, fat), radiation. (4-14). After penetration into the body by different routes, these exogenous compounds are decomposed or metabolized into free radicals.

At low or moderate concentrations, ROS and RNS are necessary for the maturation process of cellular structures and can act as weapons for the host defense system. Indeed, phagocytes (neutrophils, macrophages, monocytes) release free radicals to destroy invading pathogenic microbes as part of the body's defense mechanism against disease (5, 10). Other beneficial effects of ROS and RNS involve their physiological roles in the function of a number of cellular signaling systems (7-9). In brief, ROS/RNS at the correct levels are vital to human health.

B. Redox signaling and exercise



Physical stressors such as acute aerobic, anaerobic and intense exhaustive exercise can result in excessive reactive oxygen production.12–14 In this regard, the superoxide radical (O2•-), resulting from monoelectronic reduction of oxygen, is considered to be the precursor of ROS including OH-, RO-, ROO- and H2O2. For instance, the superoxide radical (O2•-) can react with nitric oxide (-NO), a nitrogen-centered radical, generating a highly reactive molecule, the peroxynitrite anion (ONOO-), also termed a reactive oxygen and nitrogen species (RONS), able to cause DNA fragmentation and lipid oxidation.(7-8,10). The effects of redox imbalances can have also a profound effect on energy production, such that an oxidative burden can impair energy production in the form of the energy storage molecule, ATP.
It must be clear that proper antioxidant activity is needed in the presence of strong physical stressors to ensure no excessive ROS are produced and redox balance is kept in check.

At the same time, those physical stressors and following reactive oxygen production act as important signaling molecules, that promotes a large amount of physical adaptions in order for our bodies to be able to cope with another similar burst of physical stressors. These oxidants acting as signaling molecules are the most important cellular communication mechanism and thus vital for any adaption of the body to these kind of stressors.
To achieve maximum physiological adaption through proper signaling, and to avoid any improper signaling and damage created by the ROS so that recuperation time minimized, and to avoid any disruption to the energy storage and productions systems, just the wright amount of antioxidant activity is needed. This is underlines the importance of redox balancing.

Antioxidant support by means of nutritional- or supplementation of exogenous antioxidants, is nearly impossible to dose correctly, in order to achieve the maximum physiological effect, as this kind of antioxidant support is disruptive by nature. Only when being consumed in their natural food matrices, doses are most likely to be in the beneficial range.

On the contrary, intelligent nutrigenomic antioxidant support will provide a boost to the endogenous antioxidant system, which is more or less self-balancing and even aid in cell signaling, in such a way that a homeostatic redox balance is attainable. Nutrigenomic antioxidant support can be seen as giving the proper those of certain redox signaling molecules with known and beneficial physiological adaptions.

IV. TRANSCRIPTION FACTORS AND REDOX BALANCE

Expression of antioxidant enzymes and pro-inflammatory cytokines, that produce free radicals, are regulated by transcription factors. Two important transcription factors involved in the delicate redox balance are NRF2 and NF-κB.

C. Nuclear factor (erythroid-derived 2)-like 2

NRF2 or Nuclear factor (erythroid-derived 2)-like 2, also known as NFE2L2, is a transcription factor that in humans is encoded by the NFE2L2 gene. Nrf2 is a basic leucine zipper (bZIP) protein that regulates the expression of antioxidant proteins that protect against oxidative damage triggered by injury and inflammation. Under normal or unstressed conditions, Nrf2 is kept in the cytoplasm by a cluster of proteins that degrade it quickly. Under oxidative stress, Nrf2 is not degraded, but instead travels to the nucleus where it binds to a DNA promoter and initiates transcription of antioxidative genes and their proteins. Nrf2 is kept in the cytoplasm by Kelch like-ECH-associated protein 1 (KEAP1) and Cullin 3 which degrade Nrf2 by ubiquitination. Oxidative stress or electrophilic stress disrupts critical cysteine residues in Keap1, disrupting the Keap1-Cul3 ubiquitination system. When Nrf2 is not ubiquitinated, it builds up in the cytoplasm, and translocates into the nucleus. In the nucleus, it combines (forms a heterodimer) with one of small Maf proteins (MAFF, MAFG, MAFK) and binds to the antioxidant response element (ARE) in the upstream promoter region of many antioxidative genes, and initiates their transcription.

D. Nuclear factor kappa-light-chain-enhancer

Transcription factor NF-κB or nuclear factor kappa-light-chain-enhancer of activated B cells, is a protein complex that controls transcription of DNA, cytokine production and cell survival. NF-κB is found in almost all animal cell types and is involved in cellular responses to stimuli such as stress, cytokines, free radicals, heavy metals, ultraviolet irradiation, oxidized LDL, and bacterial or viral antigens. NF-κB plays a key role in regulating the immune response to infection. Incorrect regulation of NF-κB has been linked to cancer, inflammatory and autoimmune diseases, septic shock, viral infection, and improper immune development. NF-κB has also been implicated in processes of synaptic plasticity and memory.

NF-κB is important in regulating cellular responses because it belongs to the category of "rapid-acting" primary transcription factors, i.e., transcription factors that are present in cells in an inactive state and do not require new protein synthesis in order to become activated (other members of this family include transcription factors such as c-Jun, STATs, and nuclear hormone receptors). This allows NF-κB to be a first responder to harmful cellular stimuli. Known inducers of NF-κB activity are highly variable and include reactive oxygen species (ROS), tumor necrosis factor alpha (TNFα), interleukin 1-beta (IL-1β), bacterial lipopolysaccharides (LPS), isoproterenol, cocaine, and ionizing radiation. The nuclear factor NF-κB pathway has long been considered a prototypical proinflammatory signaling pathway, largely based on the role of NF-κB in the expression of proinflammatory genes including cytokines, chemokines, and adhesion molecules.

Pharmacological and genetic studies suggest that there is functional cross-talk between these two important pathways. The absence of Nrf2 can exacerbate NF-κB activity leading to increased cytokine production, whereas NF-κB can modulate Nrf2 transcription and activity, having both positive and negative effects on the target gene expression. (15) These two pathways are expressed by oxidative stress and proposed to inhibit each other at their transcription level via protein–protein interactions or through secondary messenger effects. Nrf2 pathway inhibits the activation of NF-κB pathway by increasing antioxidant defences and HO-1 expression, which efficiently neutralizes ROS and detoxify toxic chemicals and hence, reduces ROS mediated NF-κB activation. Nrf2 pathway also inhibits NF-κB mediated transcription by preventing the degradation of IκB-α. Similarly, NF-κB mediated transcription reduces the Nrf2 activation by reducing the ARE gene transcription, decreases free CREB binding protein (CBP) by competing with Nrf2 for CH1-KIX domain of CBP. NF-κB also enhances the recruitment of histone deacetylase3 (HDAC3) to the ARE region by binding to Mafk and hence interferes with the transcriptional facilitation of Nrf2.

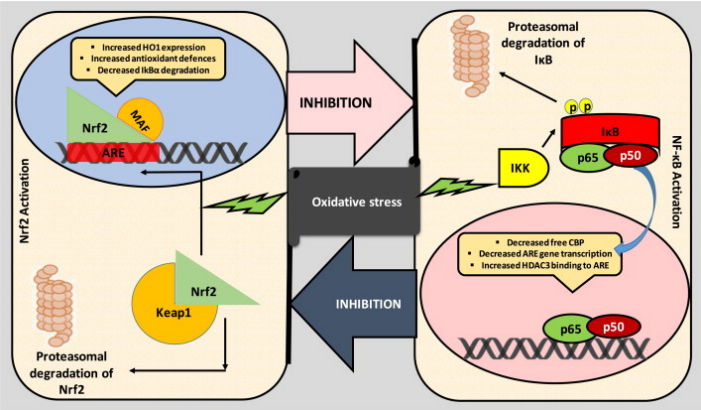


Figure 1 mutual inhibtion - Yerra, Veera Ganesh & Negi, Geeta & Sharma, Shyam & Kumar, Ashutosh. (2013). Potential therapeutic effects of the simultaneous targeting of the Nrf2 and NF-κB pathways in diabetic neuropathy. Redox biology. 1. 394-397. 10.1016/j.

Having the same initiator, but showing mutual inhibition, translates to a very delicate balance. Too much stressors on the body, as result of physical activity in combination with other external factors, can shift the balance towards NF- κB and pro inflammatory pathways. Which lead to more production of free radicals and therefore disrupt the delicate balance in redox signaling, resulting in the improper physiological adaptions, often leading to inflammatory manifestation instead of supercompensation. In those unwanted inflammatory manifestations, providing support for the NRF2 pathway can shift the balance towards NRF2 or equilibrium and thus provide better physiological adaptation. Expression of the NRF2 pathway can be increased by specific nutrigenomic substances found in some plant

matrices. This supports the global statement of this whitepaper, that nutrigenomic antioxidant support is beneficial for recovery and proper physiological adaptation in athletes.

V. CONCLUSION

The balance between oxidation and antioxidation (redox balance) is critical in maintaining a healthy biological system. In cellular redox state, the double-edged effect does not only concern ROS, but also antioxidants. Physiologic doses of exogenous antioxidants are required to maintain or re-establish redox homeostasis. However, high doses of exogenous antioxidants may disrupt redox balance. Considering epidemiological studies and trials on humans taking antioxidant compounds, it is evident that the health benefits of phytochemicals and nutrients were observed predominantly when being consumed within their natural food matrices (fruits, vegetables, grain, etc.). Compounds within plant foods may therefore be considered as being more safe and healthy compared to isolated, high doses, such as present in supplements. Two main factors seem to be predisposing for the beneficial activities of plant foods: (1) the general low concentration of nutrients and non-nutrients in these natural food matrices and (2) the additive or synergistic actions of complex mixture profiles of phytochemicals and nutrients. Supplementation approaches do generally not take into account both aspects, which could explain the controversial results observed in supplementation studies.

Intelligent nutrigenomic supplements upregulate the body's own mechanisms to balance free radicals, and thus yield important beneficial support for physiological signaling, which can boost our recovery and training adaptation systems, and even resulting in increased or enhanced super-compensation.

NRF2 and NF-κB are two important transcription factors involved in maintaining redox balance. Therefor they are excellent starting points in a nutrigenomic supplementation strategy for athletes.

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