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The Natural Protective Elements of the Central Nervous System and Therapeutic Approaches For Oxidative Stress

EDITORIAL
EDİTORYAL

Merkezi Sinir Sisteminin Doğal Koruyucu Elemanları ve Oksidatif Strese Karşı Tedavi Yaklaşımları

Ömer Akyol

The readers of Erciyes Medical Journal will find a well-designed and -planned original article in this issue (1). This study assessed the effects of regular physical exercise and coenzyme Q_{10} (CoQ_{10}) supplementation on brain superoxide dismutase (SOD) activity and glutathione (GSH) levels, which are the enzymatic and non-enzymatic key elements of the antioxidant defense system of the central nervous system (CNS) (1). The authors randomly assigned eight groups of rats as follows: untrained, trained, untrained exhausted, trained exhausted, untrained plus CoQ_{10}, trained plus CoQ_{10}, untrained exhausted plus CoQ_{10} and trained exhausted plus CoQ_{10}. What they found was that exhaustive exercise causes the GSH level to decrease in the control group whereas it increases in the untrained and trained exhausted plus CoQ_{10} groups. Swimming training led to increase in SOD activity in the brain but in the exhausted group the SOD activity did not change. On the other hand, CoQ_{10} supplementation increased SOD activity in the control group whereas decreased in the trained group. The authors concluded that regular exercise alone might trigger the natural antioxidant defense system individually in the brain (1).

In brief, free radicals are called special atoms or molecules that have one or more unpaired electrons. In the case of an unpaired electron, it becomes unstable and very reactive and, to gain stability, it reacts with another stable compound and steals an electron. They are formed after a couple of chemical reactions such as hemolytic cleavage of covalent bonds, by electron loss from a molecule or one electron transfer to a non-radical molecule forming a new radical (2). The most well-known reactive oxygen species (ROS) are superoxide, hydroxyl radical, hydroperoxyl, NO, peroxinitrite, alkoxyl, peroxyl, singlet oxygen, and hydrogen peroxide. The endogenous sources of ROS are microsomal oxidation, flavoproteins and cytochrome enzymes in the endoplasmic reticulum, oxidases and flavoproteins in peroxisomes, lipoxygenases, prostaglandin synthase and NADPH oxidase of plasma membrane, electron transport in mitochondria, transition metals, xanthine oxidase and NOS isoforms in cytoplasm, and myeloperoxidase in lysosomes (2). Exogenous sources of ROS are UV light, x-rays, gamma rays; chemicals that react to form peroxides such as ozone and singlet oxygen; chemicals that promote superoxide formation such as quinones, nitroaromatics; chemicals that are metabolized to radical species such as phenols, aminophenols and chemicals that release iron.

The antioxidant defense system of the body can be classified as enzymatic and non-enzymatic defense systems. The most well known antioxidant enzymes are SOD, glutathione peroxidase (GPx), catalase and glutathione reductase (GR) (3). Superoxide dismutase catalyzes the conversion reaction of superoxide into hydrogen peroxide. There are 4 forms of enzyme, three of which are found in mammals, the other is found in prokaryotes: intracellular SOD (Cu,Zn-SOD), extracellular SOD (EC-SOD), mitochondrial SOD (Mn-SOD), and Fe-SOD (in bacteria). Glutathione peroxidase (GPx) catalyzes the reduction of hydrogen peroxide and organic peroxides into water by using GSH. In mammalian tissues, 4 major selenium dependent GPx are identified; classical GPx (GPx1 in red cells, liver, lung, and kidney), gastrointestinal GPx (GPx2), plasma GPx (GPx3 in kidney, lung, epididymis, vas deferens, placenta, seminal vesicle, heart, and muscle), and phospholipid GPx (GPx4, broadly distributed in various tissues). Catalase is an enzyme that catalyzes the reduction of hydrogen peroxide into water without using any extra molecular electron donor. It is localized in microsomes and found in erythrocytes as an unique property. Glutathione reductase (GR) catalyzes the conversion of oxidized GSH to reduced GSH, which in turn is used by GPx as a reducing equivalent. Some examples of antioxidant molecules are GSH, ferritin, transferrin, lactoferrin, ceruloplasmin, metallothioneines, histidine, uric acid, haptoglobin, hemopexin, albumin, ascorbic acid, bilirubin, tocopherols, ubiquinones, and catatenoids.

Neurons and other cells located in the CNS are more vulnerable to the toxic and damaging effects of ROS compared to other parts of the body. The reason for this vulnerability is the high rate of oxidative metabolic activity

[1]Department of Biochemistry, Medical School, Hacettepe University, Ankara, Turkey

[2]Division of Chemistry, Ankara Branch of Council of Forensic Medicine, Ankara, Turkey

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Correspondance/Yazışma
Dr. Ömer Akyol,
Hacettepe Üniversitesi Tıp Fakültesi, Biyokimya Anabilim Dalı, Dekanlık Binası 3. Kat, 06100 Sıhhıye, Ankara, Turkey
Phone: +90 312 305 16 52-123
e.mail: oakyol@hacettepe.edu.tr

such as catecholamine degradation, high oxygen uptake, low level of protective antioxidant enzymes, high ratio of membrane surface to cytoplasmic volume, anatomical network of the neurons vulnerable to disruption, and a high proportion of membrane polyunsaturated fatty acids (PUFAs) that are readily oxidizable in case of ROS overproduction (4). In addition to this, endogenous ROS generation by neurochemical reactions is very high in the brain. Enzymatic degradation of neurotransmitter dopamine results in the generation of hydrogen peroxide, while the non-enzymatic auto oxidation of dopamine results in the formation of a couple of quinones that easily generate ROS such as hydrogen peroxide, superoxide, and hydroxyl radicals (5). Furthermore, the CNS is selectively susceptible to oxidative injury because the major function of the CNS is transmission and the elements of transmission in the membrane can easily be damaged upon ROS attack. (6).

ROS-mediated neuronal injury in the brain occurs when oxidative stress exists. Therefore, oxidative stress is a state in which there is an imbalance between the oxidant and the antioxidant defense system and generally occurs as a consequence of increased production of ROS, or when the antioxidant defense system is inefficient, or a combination of both events. Lipid peroxidation results in structural changes in membranes (altered fluidity and channel function, membrane-bound signaling proteins, and increased ion permeability), forming crosslinks of lipid peroxidation products with non lipids (e.g. proteins and DNA), direct toxic effects of lipid peroxidation end-products such as 4-hydroxynonenal, disruptions of membrane-localized signaling, DNA damage and mutagenesis (7). Protein thiol oxidation results in oxidation of catalytic sites on proteins, leading to loss of functions, formation of mixed sulfide bonds (between proteins and protein and GSH, leading to alteration in second and third structure of proteins), and increased susceptibility to proteolysis. DNA oxidation results in DNA adducts and strand breaks which in turn lead to mutation and initiation of cancer, stimulation of DNA repair leading to depletion in energy reserves, imbalance in DNA repair enzymes, induction of error prone polymerases, and activation of other pathological signaling pathways (8). Because of the relatively large size of the CNS compared to other compartments of the human body, the changes in the amount of the enzymes in the neuronal cells can easily affect the serum levels of the activities of the enzymes (4). ROS attacks can cause extensive damage. They especially damage PUFAs in lipoproteins and in cell membranes. They also damage cell proteins (altering functions) and DNA (creating mutations). If ROS damage becomes extensive, health problems can develop (9-11).

The mechanism of CNS injury by ROS under pathological conditions is quite clear. Both trauma and occlusion of the artery due to several factors in the brain may lead to some extent of additional injuries where the occlusion occurs. The posttraumatic period has several factors that can lead to the release of ROS and accumulation of neutrophils (12, 13). Oxygen radicals that accumulate during trauma and ischemia can damage proteins, carbohydrates, lipids, nucleic acids and some other cellular elements. To cope with this potential damage, enzymatic defense systems such as SOD, GPx and catalase as well as non-enzymatic antioxidants such as GSH, vitamin C, carotenes and tocopherols in both intracellular and extracellular compartments work together. During ischemia, ATP is degraded to AMP. In the last phase of purine catabolism, hypoxanthine is metabolized to xanthine and then uric acid by XO enzyme in the presence of oxygen. XO is one of the major sources of ROS in the body. Non-enzymatic lipid peroxidation is a good example of the free radical-associated process through which oxidative stress promotes cellular damage. MDA is the end product of lipid peroxidation *in vivo* that serves as a reliable marker of oxidative stress per se (14).

One of the most interesting molecules having radical properties in the CNS is nitric oxide (NO). Current data have shown that there is a strong link between NO neurotoxicity and some neuropsychiatric disorders (7). Since NO is a lipid soluble molecule involved in the signaling system of membranes, it can easily affect cellular communication. On the other hand, NO and other products linked to NO (NOx) can react with PUFAs in the cellular and subcellular membranes through a series of complicated mechanisms which lead to initiation of oxidation and formation of lipid hydroperoxides. At the end of this lipid peroxidation reaction series, NOx and ROS can alter the quantity and quality of membrane phospholipids that contribute to the pathophysiology of neuropsychiatric disorders (15, 16). Generally, ROS has been implicated in several psychiatric diseases including especially schizophrenia, depression and autism (17). It has been suggested that supplementation of some antioxidant vitamins such as vitamin E, C, and A in addition to classical schizophrenia treatment with antipsychotics may protect membranes from lipid peroxidation by ROS and NOx, leading to faster and better results (18). In our previous experimental studies, we have suggested that, adding fish omega-3 essential fatty acids to the diet together with standard neuroleptic treatment in schizophrenia may be necessary for prevention of oxidation in cellular membranes and subcellular structures of the CNS, which consists of highly oxidizable fatty structures and components under physiological conditions (19).

Oxidative stress also plays a central role in Alzheimer's disease, which has a neuroinflammatory loop contributing to neurodegeneration and dementia. Amyotrophic lateral sclerosis, a progressive degenerative disease affecting motor neurons, is another disease in which ROS also play a central role (20). These are under extensive investigation by several groups.

In conclusion, recent data in the last decades have approved the role of ROS in health and disease situations of CNS. The developed strategies aimed to limit ROS production and prevent tissue damage may slow the progression of some neurodegenerative and psychiatric diseases. Glutathione and the other synergistic partner antioxidants for maintaining the defense system might help in preventing or delaying the progression of ROS-related CNS damage.

Conflict of Interest
No conflict of interest was declared by the author.

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