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REVIEW

Oxidative Stress and Down Syndrome. Do Antioxidants Play a Role in Therapy?

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Summary

Oxidative stress is a phenomenon associated with imbalance between production of free radicals and reactive metabolites (e.g. superoxide and hydrogen peroxide) and the antioxidant defences. Oxidative stress in individuals with Down syndrome (DS) has been associated with trisomy of the 21st chromosome resulting in DS phenotype as well as with various morphological abnormalities, immune disorders, intellectual disability, premature aging and other biochemical abnormalities. Trisomy 21 in patients with DS results in increased activity of an important antioxidant enzyme Cu/Zn superoxide dismutase (SOD) which gene is located on the 21st chromosome along with other proteins such as transcription factor Ets-2, stress inducing factors (DSCR1) and precursor of beta-amyloid protein responsible for the formation of amyloid plaques in Alzheimer disease. Mentioned proteins are involved in the management of mitochondrial function, thereby promoting mitochondrial theory of aging also in people with DS. In defence against toxic effects of free radicals and their metabolites organism has built antioxidant defence systems. Their lack and reduced function increases oxidative stress resulting in disruption of the structure of important biomolecules, such as proteins, lipids and nucleic acids. This leads to their dysfunctions affecting pathophysiology of organs and the whole organism. This paper examines the impact of antioxidant interventions as well as positive effect of physical exercise on cognitive and learning disabilities of individuals with DS. Potential terapeutic targets on the molecular level (oxidative stress markers, gene for DYRK1A, neutrophic factor BDNF) after intervention of natural polyphenols are also discussed.

Key words

Down syndrome • Cognitive functions • Oxidative stress • Antioxidants • Physical activities • Polyphenols

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Down syndrome (DS) is a genetic disorder associated with trisomy 21. Although pathological mechanisms leading to DS phenotypes are not known yet, it is obvious that the presence of the third chromosome 21 is responsible for altered development during embryogenesis and organogenesis (Šustrová *et al.* 2004). It is still unclear how the additional chromosome 21 interferes with normal developmental processes and which structural changes are formed in fetus.

Oxidative stress is a phenomenon that is often discussed in connection with many diseases, such as atherosclerosis and cardiovascular diseases, neurodegenerative diseases, rheumatoid arthritis, diabetes mellitus, cancer and mental disorders. Oxidative stress is also considered as one of the main causes of aging. Oxidative stress is defined as an imbalance between production of free oxygen and nitrogen radicals (FR) and their reactive metabolites (RM) on the one hand, and on the other hand, by the ability of the organism to eliminate toxic action of these FR and their RM. This imbalance in favor of the RM leads to the oxidative modification of

important biomolecules such as lipids, proteins and nucleic acids, resulting in the damage or change of the function of several organs or the whole organism. Free radicals including superoxide anion radical (abbreviated as superoxide $O_2^{\bullet-}$), trigger formation of a number of new FR or RM such as the most toxic hydroxyl radical ($^{\bullet}OH$), singlet oxygen ($^1O_2$), and hydrogen peroxide (H_2O_2) (Fig. 1).

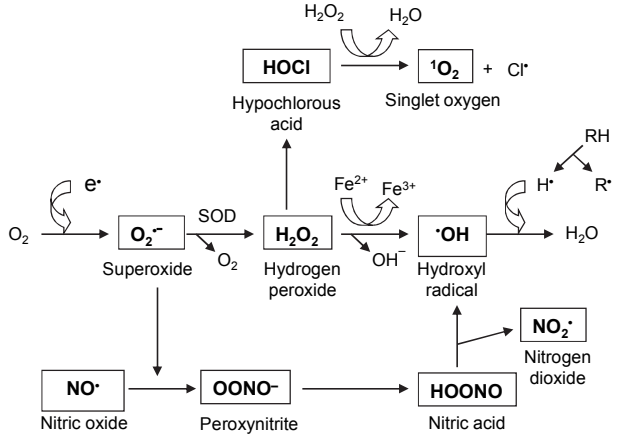

Fig. 1. Mutual conversion of free radicals and their metabolites.

Initially, the FR and RM were assumed to have only negative functions in the organism. However, now it is known that some of them play an important role in certain physiological processes, e.g. $O_2^{\bullet-}$ and H_2O_2 are part of the myeloperoxidase microbicidal system of phagocytic cells during phagocytosis. In addition, FR and RM are involved in several oxidation, hydroxylation and carboxylation reactions during detoxification of the organism, in peroxidase reactions during fertilization of eggs by sperms or in prostaglandin reactions. It is currently accepted that under certain circumstances FR and RM as well as a weak or moderate oxidative stress play an important regulatory role in transduction of information within cells (signaling pathways) and between cells, which affects several biological functions such as apoptosis (cell death), proliferation, differentiation (realization of genetic information), repair systems (repair of damaged molecules) and other processes (Ďuračková 2010).

However, FR and RM can become toxic during uncontrolled formation causing damage to lipids, cell membranes as well as lipoproteins in the periphery. They are also detrimental to proteins, they modify function of hormones and receptors and activity of enzymes. Oxidative damage to nucleic acids results in mutations of DNA bases which might lead to initiation of cancer.

Against FR and RM toxicity organisms have built defence mechanisms operating on three levels:

a) systems preventing formation of FR and RM (e.g. allopurinol is an inhibitor of the enzyme *xanthine oxidase* catalyzing formation of superoxide and uric acid from xanthine and hypoxanthine);
b) antioxidants that scavenge and eliminate already formed FR and convert them into non-radical and non-toxic molecules;
c) if antioxidant protection fails and biomolecules (lipids, proteins and nucleic acids) are damaged, repair systems detect the damaged molecules and restore or degrade them (e.g. DNA with repair endonucleases, damaged lipids with lipases, damaged proteins with proteasomes).

Antioxidants from biological point of view are substances that at low concentrations can prevent oxidation of important biomolecules and thus eliminate toxic effects of FR and RM by generation of non-toxic products. In the organism there are present either high molecular weight antioxidants (enzymatic e.g. *superoxide dismutase* or non-enzymatic e.g. transferrin) or endogenous low molecular weight antioxidants (e.g, glutathione, uric acid). Exogenous antioxidants, e.g. vitamins C and E or natural flavonoids (e.g. catechin, quercetin) and polyphenols (e.g. resveratrol) (Table 1) also significantly contribute to the antioxidant defence of the organism.

The most important antioxidant enzymes include the **enzyme *superoxide dismutase* (SOD)**, which occurs in the body in three isoforms: Cu/Zn SOD - intracellular dimeric enzyme containing Cu and Zn ions in the active centre (also labeled as SOD-1), extracellular Cu/Zn SOD has the same ions in the active centre but different tetrameric apo-enzyme and mitochondrial also tetrameric Mn SOD (SOD-2) containing Mn ion in the active centre. SOD catalyzes dismutation of superoxide to non-radical molecules, oxygen and hydrogen peroxide. Paradox of this reaction is generation of the new harmful oxidant, hydrogen peroxide. Organism is, however, a wise system containing two other enzymes, *glutathione peroxidase* (GPx) and *catalase* (CAT), which can decompose hydrogen peroxide to oxygen and water (Fig. 2). Therefore it is very important to have the right ratio between activities of SOD and (GPx + CAT) together.

Although pathological mechanisms leading to DS phenotypes are not known yet, it is obvious that the presence of the third chromosome 21 is responsible for

altered development during embryogenesis and organogenesis (Šustrová *et al.* 2004). How the additional chromosome 21 influences normal developmental processes in the fetus of trisomic individuals is still unknown.

Table 1. Overview of the most important antioxidants.

Endogenous and exogenous antioxidants	
High molecular weight	**Low molecular weight**
• Superoxide dismutase (SOD) • Glutathione peroxidase (GPx) • Catalase (CAT) • Albumin • Transferrin • Metalothioneins	• Uric acid • Ascorbic acid (vitamin C) • Lipoic acid • Glutathione (GSH) • Tocopherol (vitamin E) • Coenzyme Q (CoQ) • Polyphenols / Flavonoids

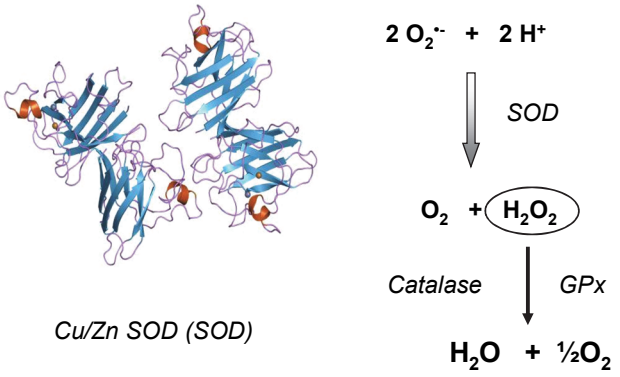

Fig. 2. Cu/Zn superoxide dismutase (SOD) function in the organism.

It has long been assumed that increased activity of the enzyme Cu/Zn SOD contributes to the Down syndrome pathology. The gene for this enzyme is located on the distal part of the chromosome 21 (Tan *et al.* 1973). This gene has been used as a molecular marker for DS (Ďuračková 2004). Patients with DS have 150 % activity of the enzyme Cu/Zn SOD resulting in increased production of H_2O_2 as well as in an imbalance in the superoxide concentrations leading to disorders in microbicidal systems and immunity (Šustrová and Šaríková 1997). Slow degradation of hydrogen peroxide due to the low activity of *catalase* and not sufficiently increased GPx activity leads to disturbed ratio of SOD/(GPx + CAT) (Muchová *et al.* 2001). These changes result in changed redox state of cells (Garaiová *et al.* 2004) and in modulation of signal transduction pathways affecting cell apoptosis (Monti *et al.* 1992), immune processes and activities of repair systems (Subba Rao 2007). Furthermore, increased expression and activity of SOD leads to an imbalance in the concentration of metal ions, especially Cu and Zn. It was found that also antioxidant element selenium is at insufficient concentrations in DS individuals (Kadrabová *et al.* 1996, Meguid *et al.* 2001).

Increased oxidative stress in DS individuals has been confirmed in multiple studies. An increased concentration of uric acid and its non-physiological metabolite allantoin was found in individuals with DS (Žitňanová *et al.* 2004), as well as the marker of oxidative damage to proteins (protein carbonyls), but the marker of oxidative damage to lipids (4-hydroxynonenal) was unchanged (Žitňanová *et al.* 2006). Disorder in the level of reduced glutathione, an important redox marker, was found in individuals with DS, along with increased production of the marker of oxidative damage to lipids, malondialdehyde and marker of aging, lipofuscin in erythrocytes and serum of children with DS (Muchová *et al.* 2007).

Oxidative stress affects the number of processes in DS patients (Kedziora and Bartosz 1988). Especially it affects:

– **Immunity** – increased activity of Cu/Zn SOD traps also superoxide necessary for the proper functioning of microbicidal systems and generates an increased concentration of H_2O_2 affecting mainly the immune response through modification of signaling pathways in activation of phagocytosis. Increased activity of Cu/Zn SOD is involved in impairment of neutrophil

functions, mainly in the decrease of their bactericidal activity, which is the reason of increased tendency of DS individuals to bacterial infections (Šustrová 2007).

- It increases **the risk of cancer** – increased DNA damage was found in urine and reduced ability of the DNA repair in children with DS (Morawiec *et al.* 2008). Zana *et al.* (2006) unlike Morawiec found no difference in repair ability of DNA, probably because of the small number of subjects involved in the study (7 children and 18 adults). Presence of an additional chromosome may contribute to genomic instability, which might be the reason of higher sensitivity of DS patients to cancer disease, particularly leukemia.
- It affects **mental development** – people with DS were found to have a positive correlation between GPx activity and IQ and a negative correlation between GPx and the marker of lipid peroxidation as well as lipofuscin formation (Weiss 1984). On the other hand, disturbed ratio of SOD/GPx is associated with reduced ability to memorize (Strydom *et al.* 2009).
- **Premature aging** – for a long time it has been assumed that the increased production and activity of Cu/Zn SOD is responsible for changing the redox potential of cells and pro-oxidation state of patients with DS as well as for many pathological features. Later on, several disorders in mitochondrial enzyme activities were found as well as the impairment of repair system of oxidatively damaged mitochondrial DNA. As individuals with DS show premature signs of aging, interest has turned to the study and review of mitochondrial theory of aging in relation to DS.

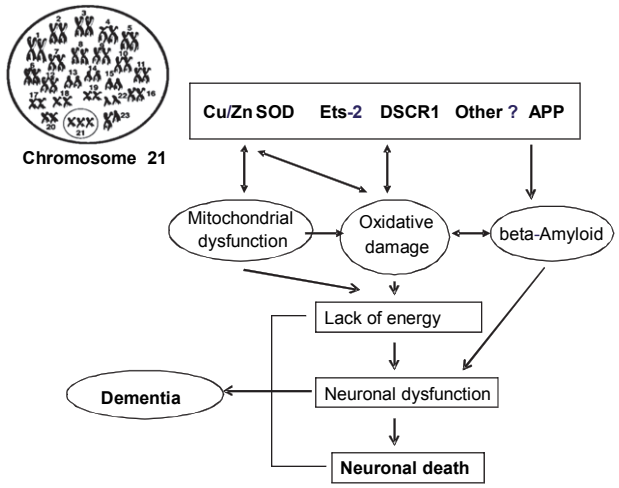

Fig. 3. Down syndrome and aging (adapted according to Lott *et al.* 2006). Ets-2 – transcription factor, DSCR1 – gene for "Down syndrome critical region", APP – precursor for beta amyloid protein

Mitochondria of the aging cells are characterized by increased production of RM and accumulation of products of oxidative damage to mitochondrial DNA in particular (Pallardó *et al.* 2010), as well as by dysfunction of mitochondrial respiration and reduction of energy generation (Fig. 3). Increased activity of Cu/Zn SOD producing an increased concentration of H_2O_2 contributes also to mitochondrial dysfunction which leads to the damage to mitochondrial membrane, damage to mitochondrial pores for passage of Ca^{2+} ions and to the respiratory chain dysfunction and reduction of energy. Triplet gene for Ets-2 transcription factor located on trisomic chromosome 21 modulates signaling pathways increasing apoptosis of nerve cells. Increased gene dosage of another trisomic gene DSCR1 (Down syndrome critical region) produces a protein that inhibits the phosphatase calcineurin participating in several signaling pathways. DSCR1 is increased in the brain of individuals with DS and it is assumed that it affects the DS phenotype and also inhibits the function of mitochondria (Chang and Min 2005). On trisomic chromosome 21 there is also located a gene for APP/A beta – a precursor of β-amyloid protein gives rise to β-amyloid from which β-amyloid sheets and neurofibrillary tangles are formed. These processes are the basis of pathophysiology of Alzheimer disease (AD) that occurs in DS individuals at an earlier age in comparison to healthy people (Lott *et al.* 2006). Since the function of mitochondria is associated with oxygen metabolism and also with the formation of superoxide on the one hand, and on the other hand disorder in mitochondrial functions is reflected in the redox imbalance resulting in the oxidative stress (Pagano and Castello 2012).

Effects of antioxidants on oxidative brain damage have been investigated in several studies on canine animal model of aging. It was found that after 1 and 6 months of administration of D,L-α-tocopherol, carnitine, D,L-α-lipoic acid, ascorbic acid and other dietary antioxidants ability of spatial attention was improved (Cotman *et al.* 2002). In earlier studies examining effects of antioxidant elements on DS pathophysiology, controversial results were obtained. Zinc (25-59 mg/day) administered for 6 months had no effect on lymphocyte functions, but daily cough subsided (Lockitch *et al.* 1989). Selenium (10 μg/kg/day) administered for 6 months increased levels of IgG and decreased infections (Annerén *et al.* 1990) and a dose of 25 μg/kg/day administered for 0.3 to 1.5 years increased activity of GPx and reduced SOD/GPx ratio.

Supplementation with megavitamin mixtures together with minerals had no significant effect, on the contrary, such megavitamins administration is not currently recommended. Lott *et al.* (2011) daily administered α-tocopherol (900 IU), ascorbic acid (200 mg) and α-lipoic acid (600 mg) to 53 individuals with DS and AD (Alzheimer disease) for two years. The authors found no impact of antioxidants on cognitive functions compared to the placebo group (Lott 2012). Similar results were obtained in a study with 156 DS children who were supplemented with antioxidants, including reduced form of folic acid (Ellis *et al.* 2008). At present, reasons of the relative failure of antioxidant interventions is not known, despite undoubted evidence of the presence of oxidative stress in individuals with DS. Whether it is an inappropriate choice of antioxidants, inadequate dose or duration of administration remains under investigation. Promising results were observed when oxidative stress in people with AD was affected by physical exercise as well as in experimental animal model with a positive impact on learning and memory and on reduction of markers of lipid peroxidation (Berchtold *et al.* 2010, Littbrand *et al.* 2011, Zambrano *et al.* 2009). These results confirm an important role of physical exercise in the function of "physical antioxidant" (Ďuračková 2010) with potential widespread use in children and adults with DS (Andriolo *et al.* 2011).

Another promising antioxidant for reduction of oxidative stress in DS individuals seems to be the **coenzyme Q_{10}** (CoQ) (mitochondrial nutrient), even though it showed no significant clinical results when administered alone (beside inhibition of statin-induced myopathy) (Caso *et al.* 2007). Tiano and Busciglio (2011) investigated effects of CoQ on oxidative DNA damage. They supplemented DS children with CoQ (4 mg/kg/day) or placebo for 6 or 20 months and found the effect of age on DNA damage. In the younger age group (5-12 years) CoQ inhibited oxidative damage to DNA pyrimidines and in the age group of 13-17 years oxidized purines were reduced. CoQ might not act as a primary antioxidant, but it interferes with the modulation of repair systems of the damaged DNA.

Furthermore, CoQ regulates permeability of mitochondrial pores, thereby reducing the negative impact of increased calcium transport into mitochondria (Chaturvedi and Beal 2008, Mancuso *et al.* 2010). A study finished just recently, reported improved language skills after CoQ administration (Miles 2013, www.clinicaltrials.gov/ct2/show/NCT00891917). Furthermore, CoQ supplementation reduces energy insufficiency and destabilizes formation of beta-amyloid fibrils (Ono *et al.* 2005). More perspective appears administration of CoQ with other agents, such as creatine and lipoic acid and other substances (mitochondrial cocktail) (Rodriguez *et al.* 2007, Palacka *et al.* 2010, Tarnopolsky 2008).

Recently, there appeared also studies demonstrating the positive effect of **natural polyphenolic compounds** on cognitive functions. It was found that polyphenols present in green tea modulate activity of kinase DYRK1A (dual-specificity tyrosine-phosphorylation regulated kinase 1A). It was found that the most important polyphenol belonging to the catechins group of flavonoids, ***epigallocatechin-3-gallate*** (*EGCG*) is an inhibitor of DYRK1A (Pons-Espinal *et al.* 2013). DYRK1A gene is located on chromosome 21. It is assumed that the increased expression of the gene for DYRK1A and its increased activity is associated with cognitive deficits in people with Alzheimer disease (AD) and might be associated with learning disability characteristic of individuals with DS (de la Torre and Dierssen 2012). One of pharmacological approaches for treating cognitive deficits is based on these facts. Inhibition of DYRK1A function could alleviate several processes such as neurodegeneration in patients with AD, as well as in DS individuals. Pharmacological use of the most effective DYRK1A inhibitor, alkaloid ***harmine 1a***, has been limited for its significant side effects. However, researchers have focused also on other natural and synthetic substances which act on the principle of DYRK1A inhibition (Smith *et al.* 2012).

Another potential therapeutic target is the neurotrophic factor BDNF (Brain Derived Neurotrophic Factor), a protein formed in the brain and involved in promoting the growth of neurons, synaptic plasticity and survival of neurons (Klein *et al.* 2011). Increased gene expression of BDNF protein was achieved after administration of ***curcumin***, lipophilic polyphenol substance able to cross the blood-brain barrier (BBB). Similarly, consumption of green tea containing EGCG increased the levels of BDNF and correlated well with improvement in cognitive functions in several studies in China and Japan (Gomez-Pinilla and Nguyen 2012). ***Melatonin*** is pineal indoleamine, a hormone, also known as *N*-acetyl-5-methoxytryptamine found in humans, animals, microbes and plants. In animals and humans, melatonin levels vary during the daily cycle. It is involved in regulating the sleeping and waking cycles. It exhibits strong antioxidant abilities. Melatonin has been

able to reduce neurodegenerative processes and improve cognitive deficits in various animal models. Corrales *et al.* (2013) have found that melatonin administration might improve the cognitive abilities of Ts65Dn and also control mice by reducing the age-related degeneration of basal forebrain cholinergic neurons. In human study melatonin was analyzed in serum and tryptophan metabolites in urine of 15 children with DS together with 15 controls. Lower levels of melatonin in serum and urinary kynurenine (metabolite of amino acid tryptophan) were determined in patients with DS, although the level of nocturnal secretion of melatonin was higher (Uberos *et al.* 2010).

As stated above („physical antioxidant“) physical activity and regular exercise have a positive impact on cognitive functions. Cotman and Engesser-Cesar (2002) found increased BDNF gene expression in animal experiments depending on increased physical activity during voluntary wheel running. Similarly, in addition to elevated levels of BDNF in animal experiments Cotman and Berchtold (2002) using high-density oligonucleotide microarray analysis found that exercise mobilizes expression of genes predicting improvement of brain plasticity processes. In 15 young volunteers Ferris *et al.* (2007) found increased serum BDNF, as well as improved cognitive functions after physical exercise during graded exercise test by determination of VO_2 max and ventilatory threshold on a cycle ergometer. These results implicate that regular exercise and physical activity should be prescribed to improve neurological health.

In conclusion, oxidative stress is involved in the pathophysiology of Down syndrome, although defence of the organism against its toxicity is amazing. Controlled supplementation with antioxidants, physical activity and regular exercise could be used to improve the cognitive functions and comprehensively benefit people with DS.

Conflict of Interest

There is no conflict of interest.

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