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Case Report

Antioxidants in Immunity, Neoplastic, and Neurodegenerative Disorders

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Abstract: Neurodegenerative diseases are ailments that disturb the brain, precisely the neurons. The utmost mutual indicators include failures in stability, inhalation, movement, reflexes, motor skills or heartbeat activity. These can be prevented using ordinary antioxidants, like vitamins E and C, flavonoids, and polyphenols compounds. Antioxidants show a substantial effect in human's health since they can ameliorate aging by fighting free radicals. Precisely Vitamin C can serve as a commanding antioxidant in reducing the consequence of oxidative injury triggered by pollutants, anxiety and poor diets amongst others. Hence it reduces the long-term risk of neurodegenerative diseases. Currently, neurodegenerative diseases have no cure, but they can be managed. This diseases management reduces the symptoms so as to sustain the value of life. Management with natural antioxidants such as polyphenols through diet or dietary supplements with lots of benefits have become an attractive alternative. The present knowledge on antioxidant in the treatment of neurodegenerative disorders and future bearings will be discussed and also assess the value for antioxidants as neuroprotective.

Keywords: Neurodegenerative diseases; vitamins; antioxidants; Neuroprotectives; Alzheimer's disease; Parkinson's disease.

INTRODUCTION

The term "free radicals" designates a family of compounds characterized by great reactivity due to the impaired electron in the outer orbital. To this group belong reactive oxygen species (ROS), such as superoxide anion, hydroxyl radical and hydrogen peroxide, as well as reactive nitrogen species (RNS) which include nitric oxide and peroxynitrite. Although structurally different, free radicals share similar mechanisms to harm body's cells and tissues through damage on proteins, DNA and lipids (Pauwels, E. K. *et al.,* 2007). The alterations of membrane functions occurring as a consequence of phospholipid modifications represent a relevant, radical species-dependent injury, either when considering the organism as a whole, or a specific integrated function, such as the immune response (Valko, M. *et al.,* 2007). The potential therapeutic applications of antioxidants in free radical-related diseases led to the hypothesis of their use to slow down or reverse, for example, symptoms associated with neurodegenerative disorders, such as Alzheimer's disease (AD), Parkinson's disease (PD), or spongiform encephalopathies. Such effect could occur through a block of proinflammatory cytokines action and the resulting oxidative damage (Mancuso, C. et a 2007; Whitton, P. S. 2007; Ramassamy, C. 2006; Pham, D. Q., & Plakogiannis, R. 2005; & Drisko, J. A. 2002). However, several clinical studies demonstrated that not only malnutrition, but also the excess of certain nutrients (e.g. iron, alpha-tocopherol, beta-carotene, ascorbic acid) may set into motion oxidation phenomena and, therefore, cell injury (Fang, Y. Z. *et al.*, 2002; & Alpha-Tocopherol Beta Carotene Cancer Prevention Study Group. 1994). Thus, it is of relevance that prior to considering introducing antioxidant therapy into mainstream medicine, significant advances in basic cell biology, pharmacology and clinical bioanalysis will be required.

OXIDATIVE STRESS

The body is normally under a dynamic equilibrium between free radical generation and quenching. The physiological defense systems to counteract free radicals encompass endogenous enzyme systems, such as catalase, glutathione reductase and superoxide dismutase, as well as glutathione, urate and coenzyme Q, or exogenous factors (β-carotene, vitamin C, vitamin E and selenium) (Valko, M. *et al.*, 2006). All these molecules have an antioxidant effect due to their ability to transform ROS into stable and harmless compounds or by scavenging both ROS and RNS with a redox-based mechanism (Valko, M. *et al.*, 2006). Very

recently, a main role in the fight against oxidative stress has been assumed by enzymes such as heme oxygenase (HO) and biliverdin reductase (BVR). Heme oxygenase is a microsomal enzyme which metabolizes heme into ferrous iron, carbon monoxide and biliverdin (BV); the latter is then reduced by BVR into bilirubin (BR), a molecule endowed with strong antioxidant and antinitrosative activities (Mancuso, C. *et al.,* 2007; Mancuso, C. *et al.,* 2006a; Mancuso, C. *et al.,* 2006b; & Mancuso, C. *et al.,* 2003). Interestingly, all these protective factors act in a concerted way, enhancing the antioxidant defense system of the cell. When the balance between ROS/RNS and antioxidants turns in favor of the former, oxidative/nitrosative stress occurs. Although oxidative stress is associated with most diseases, routine assay methods are not nowadays available in the clinical practice. A strategy widely used to determine oxidative stress is measurement of malonyldialdehyde, F2-isoprostanes, or 8-hydroxydesoxyguanosine. Actually, these molecules are regarded as the most reliable markers available (Ramassamy, C. 2006). A classic example of an oxidation product apparently leading to disease, is oxidized cholesterol in low-density lipoprotein (LDL), which displays a higher atherogenic potential than native LDL, and mainly involved in the pathogenesis of atherosclerosis and coronary heart disease (CHD) (Ramassamy, C. 2006).At the cellular level, a large body of data clearly demonstrated that ROS, when produced in low amounts and in a controlled manner, are physiological components of the signalling generated by cytokines, growth factors and neurotrophic peptides (Mancuso, C. *et al.,* 2006a; & Mancuso, C. *et al.,* 2006b), although they may also activate apoptotic cell death (Pauwels, E. K. *et al.,* 2007; & Valko, M. *et al.,* 2007). Extracellularly generated ROS can diffuse through anion channels into the cytoplasm; the resulting variation in the cell redox state leads to modulation of an array of transcription factors (e.g NF-kB, AP-1), protein kinases (e.g. AKT, JNK, p38), and receptor activated MAP kinases involved in apoptosis (Valko, M. *et al.,* 2007; Mancuso, C. *et al.,* 2007; & Ramassamy, C. 2006). Moreover, the proapoptotic molecules Fas and Fas ligand (FasL) undergo positive transcriptional regulation after exposure to oxidants (Drisko, J. A. 2002). Interestingly, Krammer and Colleagues demonstrated that in vitro administration of vitamin E suppresses FasL mRNA expression and protects T cells of HIV-1 infected individuals from Fas mediated apoptosis (Valko, M. *et al.,* 2007). Moreover, it was demonstrated that administration of combinations of vitamin E and C to cultures of human umbilical vein endothelial cells (HUVEC) treated with lipopolysaccharide could prevent apoptosis by upregulation of *Bcl-2* (Alpha-Tocopherol Beta Carotene Cancer Prevention Study Group. 1994).

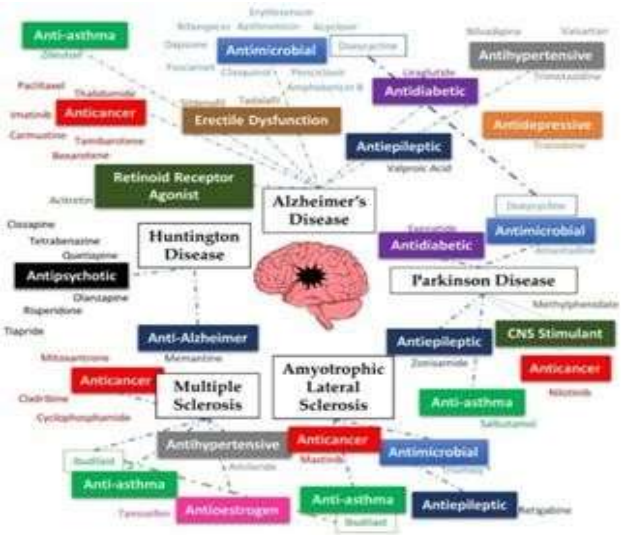

Fig.1 Neurodegenerative Disorders

Antioxidants, the Immune System and Related Disorders

The protective function against external pathogens carried out by the immune system is by itself a source of ROS, since activated neutrophils, produce free radicals to a significant extent (Mancuso, C. *et al.,* 2007). Moreover, during the inflammatory process, activation of phagocytes through the interaction of proinflammatory mediators, or bacterial products with specific receptors results in the assembly of the multicomponent flavoprotein NADPH oxidase which catalyzes the production of large quantities of the superoxide anion radical ($O_2^{\cdot}$) (Mancuso, C. *et al.,* 2007;& Whitton, P. S. 2007). In addition to classical reactive oxygen metabolites, activated neutrophils and monocytes release the hemoprotein myeloperoxidase (MPO) into the extracellular space, where it catalyzes the oxidation of Cl^{-} by H_2O_2 to yield hypochlorous acid (HClO) (Mancuso, C. *et al.,* 2007;& Whitton, P. S. 2007). HClO is a non-specific oxidizing and chlorinating agent that reacts rapidly with a variety of biological compounds, such as sulphydryls, polyunsatured fatty acids, DNA, pyridine nucleotides, aliphatic and aromatic aminoacids and nitrogen-containing compounds (Pham, D. Q., & Plakogiannis, R. 2005; & Drisko, J. A. 2002). Moreover, apart from their direct toxic effects, neutrophil-derived oxidants may promote tissue injury indirectly by altering the protease/antiprotease equilibrium that normally exists within the intestinal interstitium. The oxidative inactivation of important protease inhibitors, coupled to the oxidant-mediated activation of latent proteases, creates a favorable environment for neutrophils that allows degradation of the interstitial matrix through elastases, collagenases and gelatinases, as well as injury to epithelial cells (Mancuso, C. *et al.,* 2007; & Whitton, P. S. 2007). However, not only immune cell produce ROS necessary for the microbicidal activity, but they are also sensitive to external ROS, due to their high polyunsaturated fatty acids (PUFA) content. Immune cells are atypical, as compared with other somatic cells,

in that they contain high levels of antioxidant vitamins, presumably providing protection against lipid peroxidation and immunosuppression, both of which are well known risks posed by high PUFA content (Fang, Y. Z. *et al.,* 2002; & Alpha-Tocopherol Beta Carotene Cancer Prevention Study Group. 1994). The reactivity of immune cells to exogenous ROS has been shown to be age-dependent. In fact, lymphocytes from elderly individuals appear to be more sensitive to exposure to hydrogen peroxide than those from young adults.

AUTOIMMUNITY

Autoimmunity has been for decades considered the result of a breakdown in self-tolerance. At the present, it is known that autoimmunity is a physiological process (Ramassamy, C. 2006). This phenomenon becomes pathological when the number of autoreactive cells, and particularly the avidity of their receptors for autoantigens, increases (Whitton, P. S. 2007). Triggering of the disease usually depends both on the increase in immunogenicity of the target cell, which may be secondary to a viral infection (Chediak-Higashi syndrome and Griscelli syndrome by EBV), and on the individual's own capacity to recognize the autoantigens (HLA, or T cell repertoire in Familial hemophagocytic lymphohistiocytosis [FHL]) (Whitton, P. S. 2007; & Ramassamy, C. 2006). Moreover, apart from the genetic defects that may predispose to autoimmune diseases, one must take into account the environmental factors that are implicated in the development of such pathologies. Among them, an important role is played by xenobiotics such as chemicals, drugs and metals (Ramassamy, C. 2006; & Pham, D. Q., & Plakogiannis, R. 2005). Iron, aluminum, and manganese readily cross the blood brain barrier via specific or non-specific carriers, and contribute to the nervous tissue damage (Valko, M. *et al.,* 2007; & Mancuso, C. *et al.,* 2007). The toxic effects of metals are mediated through free radical formation, or enzyme inhibition (Whitton, P. S. 2007).

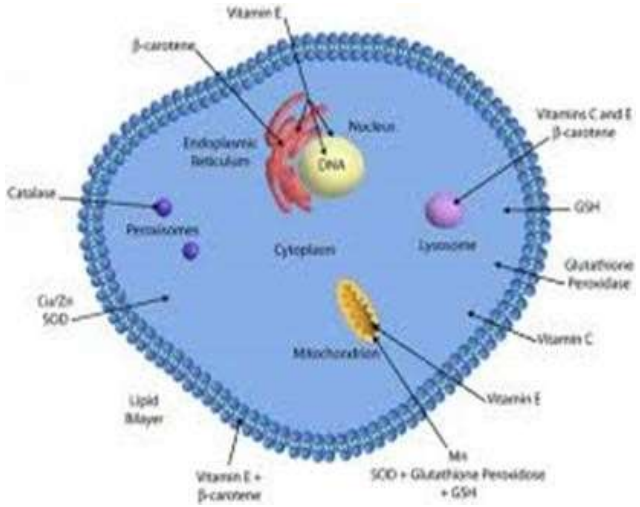

Fig.2 Members of Antioxidant Machinery

Antioxidants, Cancer and Neurodegenerative Disorders

It is well known that the dietary consumption of fruits, vegetables, herbs, or their phytochemical constituents aid in cancer prevention (Drisko, J. A. 2002; & Fang, Y. Z. *et al.,* 2002). It is believed that the antioxidant properties of such foods protect cells from ROS-mediated DNA damage that can result in mutation and subsequent carcinogenesis. ROS-induced DNA damage can take many forms, ranging from specifically oxidized purine and pyrimidine bases, to DNA lesions such as strand breaks, sister chromatid exchanges (SCEs), and the formation of micronuclei (Fang, Y. Z. *et al.,* 2002; & Alpha-Tocopherol Beta Carotene Cancer Prevention Study Group. 1994). However, the equation "antioxidant = benefit" is not always true. In vivo experiments demonstrated that retinol increases both the humoral and the cell-mediated immune response and could enhance immune surveillance against tumorigenesis (Fang, Y. Z. *et al.,* 2002). Retinol may influence the immune response by quenching free radicals, which could lower the level of immunosuppressing lipid peroxides. These studies, initially, have shown that a high consumption of fruit and vegetables decreases risks of lung cancer in healthy individuals and a combination of β-carotene, vitamin E and selenium reduced stomach cancer mortality in China (Ramassamy, C. 2006;& Alpha-Tocopherol Beta Carotene Cancer Prevention Study Group. 1994). Conversely, supplemental β-carotene alone or in combination with retinol or vitamin E did not have any effect on cancer risk, or increased the development of lung cancer in smokers (Fang, Y. Z. *et al.,* 2002; & Alpha-Tocopherol Beta Carotene Cancer Prevention Study Group. 1994). In the light of these first contrasting results, and also as a consequence of the wide antioxidant consumption in the general population, various systematic reviews to estimate the association between antioxidant use and disease prevention, in particular for primary cancer incidence and mortality, have been issued. Vitamin E treatment also appears to be associated with a slightly increased incidence of lung cancer (Ramassamy, C. 2006). Other studies report that combination of vitamin A and other antioxidants, significantly increases mortality related to neoplastic diseases (Drisko, J. A. 2002). According to these studies, selenium would be the only element displaying beneficial effects, as it has been shown that it reduces total cancer incidence, an apparently sex-related effect, as it is predominant among males, rather than in females (Fang, Y. Z. *et al.,* 2002). The reason why β-carotene may exert dual activity, namely antioxidant or pro-carcinogenic has been debated for quite a long time. The first hypothesis is that at high concentrations, β-carotene stimulates free radical production, whereas at lower concentrations β-carotene exerts antioxidant activity (Alpha-Tocopherol Beta Carotene Cancer Prevention Study Group. 1994). Furthermore, in the presence of cigarette smoke-derived free radicals β-carotene is cleaved into many derivatives

which are very unstable and may trigger further oxidation. An oxidative stress response and compensatory defense reactions can be seen in the affected neural cells; further, disturbances of the mitochondrial metabolism are observed, which may account for an increased leakage of ROS originating from the respiratory chain (Drisko, J. A. 2002; & Fang, Y. Z. *et al.,* 2002). However, in addition to the direct induction of oxidative stress, metabolic disorders underlying every single disease can also indirectly generate an oxidative microenvironment, for example via the induction of a local immune response (Mancuso, C. *et al.,* 2003). On this basis, antioxidant and antinflammatory drugs, such as polyphenols and non-steroidal antinflammatory drugs (NSAIDs), have been proposed in the treatment of different neurodegenerative diseases (Mancuso, C. *et al.,* 2007). Unfortunately, although the role played by free radical to the pathogenesis of ALS has been demonstrated, antioxidants did not have any effect to prevent or slow down its progression.

CONCLUSION

The field of antioxidants is moving rapidly. About 20 years ago the hypothesis that diet might have a substantial influence on the development of some pathologies, such as cancer, has been raised by many scientists. In this light, during the last decade, efforts have been made to analyze the effects of plant food and synthetic antioxidants on the development and prevention of chronic diseases. Nowadays, antioxidants are used on a large scale to try to obtain and preserve optimal health. While there is no doubt that the correct balance between endogenous and exogenous antioxidant capacity is essential to life, the curative power of antioxidants has often been overestimated. In fact, according to the popular idea "if one is good two is better", antioxidants are taken in excess too often and the risk to originate diseases instead of preventing them is quite high. It is noteworthy to underlie that as for all drugs, antioxidants may give important side effects if not correctly used or in combination with other drugs. Vitamin A, E and β-carotene for instance, have been shown to have pro-oxidant effects at higher doses or under certain conditions (Alpha-Tocopherol Beta Carotene Cancer Prevention Study Group. 1994). Another point of criticism is the possibility to take experimental results "from the bench to the bedside". In fact, although the promising results obtained by in vitro experiments, the use of antioxidants in the treatment of human disease states has not been as successful as might have been envisaged due to intrinsic pharmacokinetic or pharmacodynamic limitations.In addition, conclusions on beneficial effect of antioxidant are often drawn from studies conducted with synthetic antioxidant supplement, whereas fruits and vegetable are a complex mixture of antioxidant, as well as other potentially beneficial micronutrients and macronutrients, which may, thus, work with different kinetics and dynamics (Fang, Y. Z. *et al.,* 2002). In conclusion, the correct use of antioxidants may be useful to prevent free radical-related disorders. However, the repair of existing critical structural damage may be beyond the possibilities of antioxidants and therefore they may not be considered to be useful in therapeutic clinical applications, where their limits and eventual side effects must be better understood.

REFERENCES

1. Alpha-Tocopherol Beta Carotene Cancer Prevention Study Group. (1994). The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. *New England Journal of Medicine*, *330*(15), 1029-1035. doi: 10.1056/NEJM199404143301501
2. Drisko, J. A. (2002). The use of antioxidants in transmissible spongiform encephalopathies: a case report. *Journal of the American College of Nutrition*, *21*(1), 22-25.
3. Fang, Y. Z., Yang, S., & Wu, G. (2002). Free radicals, antioxidants, and nutrition. *Nutrition*, *18*(10), 872-879. doi: 10.1016/S0899-9007(02)00916-4
4. Mancuso, C., Bates, T. E., Butterfield, D. A., Calafato, S., Cornelius, C., Lorenzo, A. D., ... & Calabrese, V. (2007). Natural antioxidants in Alzheimer's disease. *Expert opinion on investigational drugs*, *16*(12), 1921-1931. doi: 10.1517/13543784.16.12.1921.
5. Mancuso, C., Bonsignore, A., Capone, C., Stasio, E. D., & Pani, G. (2006). Albumin-bound bilirubin interacts with nitric oxide by a redox mechanism. *Antioxidants & redox signaling*, *8*(3-4), 487-494. doi: 10.1089/ars.2006.8.487.
6. Mancuso, C., Bonsignore, A., Di Stasio, E., Mordente, A., & Motterlini, R. (2003). Bilirubin and S-nitrosothiols interaction: evidence for a possible role of bilirubin as a scavenger of nitric oxide. *Biochemical pharmacology*, *66*(12), 2355-2363. doi: 10.1016/j.bcp.2003.08.022.
7. Mancuso, C., Pani, G., & Calabrese, V. (2006). Bilirubin: an endogenous scavenger of nitric oxide and reactive nitrogen species. *Redox Report*, *11*(5), 207-213. doi: 10.1179/135100006X154978.
8. Mancuso, C., Scapagini, G., Curro, D., Giuffrida Stella, A. M., De Marco, C., Butterfield, D. A., & Calabrese, V. (2007). Mitochondrial dysfunction, free radical generation and cellular stress response in neurodegenerative disorders. *Front Biosci*, *12*(1), 1107-1123. doi: 10.2741/2130.
9. Pauwels, E. K., Erba, P. A., & Kostkiewicz, M. (2007). Antioxidants: a tale of two stories. *Drug news & perspectives*, *20*(9), 579-585.
10. Pham, D. Q., & Plakogiannis, R. (2005). Vitamin E supplementation in Alzheimer's disease, Parkinson's disease, tardive dyskinesia, and cataract: Part 2. *Annals of Pharmacotherapy*, *39*(12), 2065-2072. doi: 10.1345/aph.1G271.

11. Ramassamy, C. (2006). Emerging role of polyphenolic compounds in the treatment of neurodegenerative diseases: a review of their intracellular targets. *European journal of pharmacology*, *545*(1), 51-64. doi: 10.1016/j.ejphar.2006.06.025
12. Valko, M., Leibfritz, D., Moncol, J., Cronin, M. T., Mazur, M., & Telser, J. (2007). Free radicals and antioxidants in normal physiological functions and human disease. *The international journal of biochemistry & cell biology*, *39*(1), 44-84. doi: 10.1016/j.biocel.2006.07.001
13. Valko, M., Rhodes, C., Moncol, J., Izakovic, M. M., & Mazur, M. (2006). Free radicals, metals and antioxidants in oxidative stress-induced cancer. *Chemico-biological interactions*, *160*(1), 1- 40. doi: 10.1016/j.cbi.2005.12.009.
14. Whitton, P. S. (2007). Inflammation as a causative factor in the aetiology of Parkinson's disease. *British journal of pharmacology*, *150*(8), 963-976. doi: 10.1038/sj.bjp.0707167.