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ECOLOGICAL OXIDATIVE BALANCE AND ANTIOXIDANTS – A REVIEW

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Summary

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High amounts of reactive oxygen species (ROS) or inadequate removal of ROS result in oxidative stress. In a state of oxidative stress that is accompanied by disrupted ecological oxidative balance (EOB), biological systems are not at optimal ecological protection against toxic oxidative assaults. An impaired EOB leads to failure in ecological protection from assaults by oxidative radicals that cause a number of toxic effects. The presence of oxidative stress in the organism, and therefore violation of the EOB, has been shown to occur via level products arising from lipid peroxidation and damages of antioxidant enzymes. EOB, like any other system balance phenomenon, is dynamic and is possible to restore to homeostatic reset with the help of proper ways and means like antioxidants as SH7 and SH8 (analogues of isoniazid) synthesized in our laboratory.

Key words: antioxidants, ecological oxidative balance (EOB), isoniazid, oxidative stress, reactive oxygen species (ROS)

INTRODUCTION

According to a hypothesis of ours (Georgieva & Gadjeva, 2005) the state of equilibrium between the generation of reactive oxygen species (ROS) and the detoxicating capacity of the endogenic antioxidant systemic defense could lead to a sate of ecological oxidative balance (EOB) in the endogenic biological systems. In a state of EOB, biological systems are at maximum protected against the toxic oxidative damage of ROS (Georgieva & Gadjeva, 2005). All endogenous and exogenous sources of uncontrolled ROS production – superoxide anion-radical ($O_2^{\cdot -}$), nitric oxide (NO), hydrogen peroxide (H_2O_2), hydroxyl radical ($^{\cdot}OH$) etc., produce oxidative stress related to considerably violated EOB. The disrupted EOB in aerobes could be evidenced through assaying of some oxidative stress parameters – lipid peroxidation products and antioxidant enzymatic activities. In a state of oxidative stress and greatly violated EOB, biological systems are vulnerable to the toxic impact of ROS (Georgieva & Gadjeva, 2005) resulting in cellular damage and pathological states.

The consequences of violated EOB are dependent on systemic resources to restore it, either independently or with suitable antioxidant preparations.

ANTIOXIDANTS (SPIN TRAPS)

From chemical point of view, antioxidant is every substance that in a concentration lower than that of the oxidizable substrate, reduces considerably or inhibits the oxidation of substrate. Generally speaking, all factors that slow down or prevent the oxidative damage of biological molecules are accepted as antioxidants (Halliwell & Gutteridge, 1985). In living beings, there are complex and precise antioxidant defense mechanisms that prevent ROS formation or restrict their toxic effects. According to Dormandy (1978), these mechanisms are directly dependent on cell integrity and the impairement of this structural integrity results in cellular damage. The systemic antioxidant defense is the compilation of all antioxidants interconnected with multiple functional bonds, so that the damage, reduced concentration or the depletion of any antioxidant has an important effect on the influence of other ones (Oberley *et al.*, 1996). The relative significance of a given antioxidant in systemic oxidative balance is determined not only by its concentration and reactivity, but also by its ability to interact with other antixidants that regenerate or potentiate it (Tsvetkov & Bochev, 1996). Many literature sources report the ability of antioxidants to inhibit ROS formation (Hermes-Lima *et al.*, 1998, 1999; Santos *et al.*, 2001; Gitto *et al.*, 2001) and thus, to decrease oxidative stress (Hermes-Lima *et al.*, 2001; Domenech *et al.*, 2001; Himmelfarb & Hakim, 2003).

Spin traps are natural and synthetic antioxidants with various chemical structure (Mankovskaya *et al.*, 2000; Christensen *et al.*, 2003; Stolze *et al.*, 2003), that protect biological systems against the toxic oxidative damages of ROS. Some of the natural plant spin traps are medications, containing substances as silymarin recognized in practice as Carsil (Legalon) (Wagner *et al.*, 1974). Carsil is a powerful hepatoprotector used very successfully in liver damage due to chronic alhocol abuse and intoxications with chloroform, carbon tetrachloride and fungal toxins (Baraboy, 1976). Anthocyanin flavonoids are the biologically active substances of *Aronia melanocarpa* (AM) that possess antioxidant activity (Kähkönen, 2001). The natural AM juice is rich in phenolic compounds and decreases the tetrachlormethane-induced necrotic and degenerative changes in liver (Valcheva-Kuzmanova *et al.*, 2002).

Enzymatic antioxidants

Enzymatic antioxidants are absolutely necessary for aerobic life and appeared first in the course of the evolution. They decrease the unbalanced ROS production that cause oxidative damage in biological systems. The most important antioxidant enzymes are the three types superoxide dismutase (SOD) – extracellular Cu/Zn-SOD, cytoplasmic Cu/Zn-SOD and mitochondrial Mn-SOD, catalase (CAT) and the enzymes of the glutathione system – glutathione peroxidase (GSH-Px), glutathione reductase and glutathione-S-transferase (GST) (Marks *et al.*, 1996).

The number of facts evidencing the altered expression of the main antioxidant enzymes in various diseases is increasing. A considerable reduction of the total antioxidant mechanism of defense is reported in patients with different pathology (Coursin *et al.*, 1996; Oberley *et al.*, 1996; Baker *et al.*, 1997; Davydova & Sabirova, 2002). Other authors communicate a compensatory increase in the activity of antioxidant enzymes following activation of lipid peroxidation (Inozemtseva & Chetverikova, 1991).

Superoxide dismutase (SOD) is an antioxidant enzyme that catalyzes the dismutation of the highly toxic superoxide anion-radical ($O_2^{\cdot-}$), and is a chain reaction initiator to less reactive species (McCord & Fridovich, 1969; Wang *et al.*, 1993). SOD pulls $O_2^{\cdot-}$ via oxidation and reduction of the transient metal ion in the active site (Fee *et al.*, 1981). SOD activity increases under the influence of chemical agents or conditions that increase the production of $O_2^{\cdot-}$ (Meier *et al.*, 1998). According to some authors (McCord & Fridovich, 1969; Fridovich, 1975; Bannister *et al.*, 1987) the rate of catalyzed dismutation is much bigger than that of spontaneous one, that forms a singlet oxygen. Thus, the formed $O_2^{\cdot-}$ that could react with H_2O_2 and form $^{\cdot}OH$ and singlet oxygen is rapidly removed. This is the first step of antioxidant defense against systemic oxidative stress. The amount and the activity of SOD vary in the different organs and tissues, the highest SOD activity being detected in human hepatocytes (Yu, 1994).

The role of SOD in ageing is also investigated and its favourable effect for life longetivity is proved (Nohl *et al.*, 1979; Magnes & Li, 1980; Fee *et al.*, 1981; Turrens *et al.*, 1984).

The antioxidant enzyme *catalase (CAT)* preserves cells from the formed reactive H_2O_2, converting it to water and molecular oxygen (Cheng *et al.*, 1981). This function of CAT is performed together with glutathione peroxidases. The low concentrations of H_2O_2 or organic peroxides are transformed by peroxidases to water and alcohols. When the concentrations of H_2O_2 are high, they are metabolized by catalase (Yu, 1994). CAT is considered as not so important for cells under normal conditions, but it plays an essential role in cell adaptation to oxidative stress (Turrens *et al.*, 1984). It protects the cell against drug-induced consumption of oxygen either by H_2O_2 conversion or by direct interaction with the drug (Speranza *et al.*, 1993). The treatment with CAT inhibitors (Davydova & Sabirova, 2002) results in increased systemic oxidative damage consequently to ROS production and thus, to increased lipid peroxidation (Kazuya *et al.*, 2003).

Other enzymes participating in ROS conversion, are *glutathione-S-transferases (GST)*, whose most important role is cell detoxication (O'Brien & Tew, 1996). Apart the metabolism of xenobiotics, these enzymes are also involved in the synthesis of some endogenous biologically active compounds (Osmak *et al.*, 1997).

The equilibrium between antioxidant enzyme activities and the intracellular levels of these enzymes is essential for the survival and the health of living beings (Aleryani *et al.*, 1998; Brouwer & Brouwer, 1998).

Nonenzymatic antioxidants

Nonenzymatic antioxidant systems of defense against ROS include low-molecular hydrophobic and hydrophilic compounds. In general, they protect the polyunsaturated fatty acids in cellular membranes from damage (Rouser *et al.*, 1976). As the most antioxidants are initially generated in the aqueous compartments, water-soluble antioxidants are the first line of defense. With regard to the lipid peroxidation protection however, liposoluble antioxidants acting in the lipid phase of cell membranes are more effective. Having studied the interactions of $O_2^{\cdot-}$ and the altered cell membrane potential under the effect of $O_2^{\cdot-}$, the protective effect of nonenzymatic antioxidants tocopherol and ascorbic acid

against systemic radical-induced damage in cells is established (Jones *et al.*, 1981). The group of nonenzymatic antioxidants includes natural poducts and synthetic antioxidants.

Natural products. They include: the ascorbic acid, tocopherol, carotenoids, thiol compounds, reduced glutathione, uric acid, glucose, liposoluble bilirubin, ubiquinone-10 (the reduced form of coenzyme Q10), some chelators of iron, that binding to it, prevent the formation of ·OH radicals and other thiols that apart from interacting with radicals, function also as cofactors in glutathione peroxidase system, some hormones etc. (Prior, 1979).

The ascorbic acid (*vitamin C*) and reduced glutathione are spin traps in an aqueous medium. Vitamin C is the most effective water-soluble antioxidant in plasma (Sies *et al.*, 1992). It interacts with hydrogen peroxide, hydroxyl and superoxide radicals, peroxyl and other ROS, converting them to nonradical substances owing to its reduction properties (Frei, 1991). Ascorbic acid protects cell membranes by recycling tocopherol through scavenging of peroxyl radicals in aqueous compartments before they could induce a lipid peroxidation (Sies *et al.*, 1992). According to some authors, the main function of ascorbic acid as an antioxidant is to restore vitamin ,E that is probably responsible for the higher tissue vitamin C concentrations vs those of vitamin E (Bendich, 1986; Leung *et al.*, 1981). In liver cells, vitamin C concentration is 2.10^{-3} mol.L^{-1}, and that of vitamin E – 2.10^{-5} mol.L^{-1} (Yu, 1994). The synergism between vitamin C and vitamin E is also manifested with their detoxicating effect against nitrates through blocking of the formations of cancerogenic N-containing compounds such as nitrosamines and nitrosamides (Mirvish, 1986). Sies *et al.* (1992) showed that ascorbate protected human semen against oxidative damage that could augment the risk of genetical defects. Ascorbic acid could also act as a prooxidant because it is able to reduce Fe^{+3} to Fe^{+2} and in the presence of H_2O_2 to stimulate the formation of ·OH radicals (Gitto *et al.*, 2001). Whether the final effect would be prooxidant or antioxidant, depends on the ratio between ascorbic acid concentration and the available Fe^{+3} ions. When large amounts of vitamin C are available, the molecules that did not react with Fe^{+3} reduce and destroy the formed ·OH (Aust *et al.*, 1985; Halliwel, 1991).

The monitoring of plasma antioxidants in oxidative stress shows that ascorbic acid levels decreased the first and after its depletion, lipid peroxidation occurs even if plasma tocopherol concentrations are normal (Frei *et al.*, 1988; Saygili *et al.*, 2003). These observations explain the hypoascorbinaemia in smokers, where increased plasma lipid peroxidation products are present (Pre, 1989).

Tocopherol (*vitamin E*) inhibits lipid peroxidation through breaking the chain reaction of this process (Ross & Moldeus, 1991; Sies, 1992; Ahmad & Suhail, 2002). It is the most prevalent nonenzymatic lipophilic antioxidant in nature. Accoring to Burdon *et al.* (1982) vitamin E exists in four principal tocopherol isomers (α-tocopherol, β-tocopherol, γ-tocopherol and δ-tocopherol). Numerous studies confirmed that the most effective antioxidant is α-tocopherol that reduces significantly the lipid peroxidation (Skakun & Slivka, 1992; Yamamoto *et al.*, 1995; Shumaev *et al.*, 1997). Vitamin E is said to be the major antioxidant in the lipid phase of biological membranes and lipoproteins, but the human organism could not synthesize it. A protective

action of vitamin E against drug-induced cardiotoxicity is established (Kalender *et al.*, 2002). Vitamins C and E protect the organism from ROS-induced oxidative damage (Gitto *et al.*, 2001; Ahmad & Suhail, 2002; Saygili *et al.*, 2003).

Retinol (vitamin A) and *β-carotene* increase the systemic antioxidant status, reduce lipid peroxidation (Nagler *et al.*, 2003) and probably have a cardioprotective effect (Nicolle *et al.*, 2003). The vitamins C and E assist in the conversion of β-carotene to retinol (Gomboeva *et al.*, 1998).

Glutathione and other thiols, are also in the groups of water-soluble antioxidants. Besides from reacting with free radicals, they act as cofactors in glutathione peroxidase system. It is established that the increased GST activity plays an important role in the protectiox against ROS toxic effect (Choi *et al.*, 2000).

Uric acid is a water-soluble antioxidant and singlet oxygen and hydroxyl scavenger. It is a physiological antioxidant and traps efficiently the plasma free radicals (Martinez-Cayuela, 1995).

The group of nonenzymatic radical scavengers comprises also cholesterol, the amino acid histidine, proteins, lipids, unsaturated fatty acids etc.

Synthetic antioxidants. As a result of studies performed, we established a superoxide scavenging activity (SSA), antituberculosis activity and low toxicity (Georgieva & Gadjeva, 2002) of isonicotinoylhydrazones synthesized by us (Varbanova & Georgieva, 1993) (Fig. 1) that are structural analogues of isoniazid (isonicotinic acid hydrazide, rimifon, INH) (Fig. 2), approved in tuberculosis chemotherapy.

Our data evidence that isonicotinoylhydrazones (Fig. 1) trap $O_2^{\cdot-}$ i.e. they exhibit a SSA similarly to SOD. The anti-

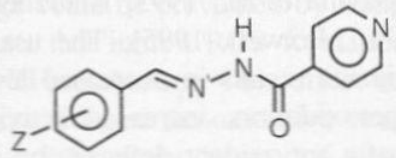

Fig. 1. Isonicotinoylhydrazones. Z= halogen or alkoxy radical

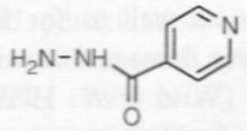

Fig. 2. Isoniazid

oxidant activity of studied compounds was compared to that of already known reference antioxidants – ascorbic acid (vitamin C), tocopherol (vitamin E, Trolox), 2,2,6,6-tetramethyl-4-oxo-piperidine-1-oxyl (TEMPO), 4-amino-2,2,6,6-tetramethyl-4-oxo-piperidine-1-oxyl (A-TEMPO), 4-oxo-2,2,6,6-tetramethyl-4-oxo-piperidine-1-oxyl (O-TEMPO). Out of studied isonicotinoylhydrazones, the highest SSA activity was that of: N-isonicotinoyl-N´-(3,5-dichloro-2-hydroxybenzal)hydrazone (SH7) and N-isonicotinoyl-N´-(3-etoxy-2-hydroxybenzal)hydrazone (SH8). The SSA of SH7 was found to be higher than that of O-TEMPO, vitamins A and C and was similar to that of the stable free radical TEMPO. The antioxidant activty of SH8 was comparable to that of vitamin C and A-TEMPO and higher than the SSA of Trolox and O-TEMPO. The structural analogue of SH7 and SH8 – isoniazid, does not possess SSA activity (Georgieva & Gadjeva, 2002).

ANTIOXIDANTS AND EOB

It is found out that antioxidants reduce the oxidative stress due to treatment with various drugs and improve the chemothe-

rapy (Savula *et al.*, 1993; Andrzheiuk *et al.*,1994; Maxwell, 1995). The usage of antioxidants results in decreased level of lipid peroxidation, increased activity of enzymatic antioxidant defense and is determined as a promising field of contemporary chemotherapy for controlling many diseases as lung inflammations, cancer, AIDS, arthritis, aterosclerosis, diabetes etc, as well as for lessening of toxic oxidative damage following medication therapy (Wiid *et al.*, 1999; Meral *et al.*, 2001; Saraswathy *et al.*, 1998; Himmelfarb & Hakim, 2003; Mantovani *et al.*, 2003; Yoshida *et al.*, 2003).

The data of our investigations revealed statistically significantly increased levels of malondialdehyde (MDA) – a biomarker of radical-induced damage and oxidative stress respectively and decreased activities of antioxidant enzymes SOD and CAT after treatment of albino mice with INH (Georgieva *et al.*, 2004a). The increased MDA levels and the lower enzymatic activity could be related to the produced oxidative stress (Buss *et al.*, 2002, Popova & Popov, 2002), accompaneid by a disruption of EOB in biological systems (Georgieva & Gadjeva, 2005). The lower activities of antioxidant enzymes SOD and CAT observed by us in liver homogenates of INH-treated mice proved that the impaired EOB exposes at a maximum biological systems to the toxic oxidative ROS effects, that in this case are manifested by reduced antioxidant defense. This damage is also probably due to enhanced ROS generation in isoniazid metabolism (Albano & Tomasi, 1987). It could be that produced ROS are only partly quenched by the complex and accurate antioxidant defense that results in inhibition of SOD and CAT activity, production of oxidative stress and impaired EOB under conditions of acute and chronic isoniazid toxicity (Georgieva & Gadjeva, 2005).

ANTIOXIDANTS AND CHEMOTHERAPY

An effective means for preventing the abnormal ROS production is antioxidant prophylaxis and therapy. On the basis of available experimental data, the possibility of decreasing the negative impact of ROS for better life longetivity and for slowing down of ageing processes with the aid of antioxidants is elucidated (Harman, 1981; Fridovich, 1976).

During the last years, the studies about the effect of combinations of drugs applied in the treatment of various diseases and different spin traps upon the systemic antioxidant status became more numerous. Many investigators (Skakun, 1991; Sies *et al.*, 1992; Shumaev, 1997; Mankovskaya *et al.*, 2000; Christensen *et al.*, 2003; Ahmad & Suhail, 2002; Stolze *et al.*, 2003) proved the positive influence of chemotherapy including various chemotherapeutics combined with natural and synthetic antioxidants. The presence of improved biological activity and lower toxic effect of combinations is evidenced (Skakun & Shman'ko, 1986; Kalender *et al.*, 2002). The improved anticancer effect and low toxicity of spin-labeled 1-ethyl-1-nitroso-3-(4-) 2,2,6,6-tetramethylpiperidyl-1-oxyl))-urea (SLENU) is said to be due to its high antioxidant activity (Gadjeva *et al.*, 1994). The use of suitable antioxidants results in decreased lipid peroxidation products and improved systemic antioxidant defense of aerobes (Skakun, 1991; Savula *et al.*, 1993; Shumaev *et al.*, 1997; Saraswathy *et al.*, 1998; Wiid *et al.*, 1999; Meral *et al.*, 2001; Mantovani *et al.*, 2003; Yoshida *et al.*, 2003).

These and many other examples are supporting the hypothesis that the studies about the effect of drug and spin trap combinations applied in the treatment of various diseases in order to decrease the toxicity of used chemotherapeutics and to increase the systemic antioxidant statius are extremely important nowadays.

Isoniazid and natural antioxidants

The tuberculostatic activity of one of the most active antituberculosis drugs – isoniazid (Fig. 3) is discovered by the German scientisit Gerhardt Domagk in 1953. Despite the strong antibacterial effect, INH is sometimes ineffective because of the rapid development of drug resistance of tuberculosis bacteria (Selkon, *et al.*, 1964; Zhang *et al.*, 1992; Jagannath *et al.*, 2000; Mishin & Chukanov, 2000; Campos-Outcalt, 2003) and its side toxic effects (cytotoxicity, hepatotoxicity, cardiotoxicity) (Byrd & Nelson, 1972; Farrer *et al.*, 1977; Sokolova *et al.*, 1989; Vidal Pla *et al.*, 1991; Sodhi *et al.*, 1998). Recently, the ROS levels formed in the course of INH treatment, the activity of antioxidant enzymes and their role in drug resistance are studied (Benchekroun, *et al.*, 1993; Andrzheiuk, *et al.*, 1994; Hyang-Suk Kim *et al.*, 2001). It is established that patients with tuberculosis are subject to oxidative stress during and following chemotherapy with INH that produces free radicals. It is considered that oxidative stress is involved in the activation of resistance to chemotherapy (Toyokuni *et al.*, 1995).

The INH-induced oxidative stress (Sodhi *et al.*, 1998) according to data of ours is accompanied by violated EOB in biological systems that leads to oxidative damage, including hepatotoxicity (Georgieva *et al.*, 2004a). Reported data (Attry *et al.*, 2001; Edmonds, 2001; Buss *et al.*, 2002) show that INH-induced oxidative damage could be prevented by using antioxidants that inhibit ROS formation during INH metabolism. This effect of antioxidants reduced the oxidative stress and improved the chemotherapy of tuberculosis (Savula *et al.*, 1993; Andrzheiuk *et al.*, 1994). The simultaneous treatment with INH and melatonin, that possesses antioxidant properties, demonstrates decreased lipid peroxidation products and about 3 times increased tuberculostatic activity of INH (Wiid *et al.*, 1999). The co-adminsitration of INH and tocopherol in albino rats suppresses the lipid peroxidation and was found to have a hepatoprotective effect (Skakun & Slivka, 1991; Shumaev *et al.*, 1997). Vitamin C protects the cell membranes by scavenging of peroxyls in aqeuous phases before they could cause lipid peroxidation (Sies *et al.*, 1992) and improves INH activity when co-administered with it. There are also reports about the protective activity of antioxidants Liv. 100 (Saraswathy *et al.*, 1998) and N-acetylcysteine (Attri *et al.*, 2001) against the hepatotoxicity of isoniazid.

Isoniazid and synthetic antioxidants

In our studies we observed that the newly synthesized antioxidants SH7 and SH8 co-administered with INH, decreased its hepatotoxicity probably by scavenging of $O_2^{\cdot-}$ (Georgieva *et al.*, 2004a). The observed normalization in MDA, SOD and CAT levels after treatment of mice with INH combined either with SH7 or SH8 (Georgieva *et al.*, 2004 a, b; Georgieva *et al.*, 2005) could be related to the ability of these antioxidants to increase the engoneous antioxidant enzymatic defense, to restore the EOB and to reduce the oxidative stress due to INH. Thus, SH7 and SH8 protect the cellular structures against the toxic oxidative damage of ROS

(including hepatotoxicity) that occur in INH metabolism. Our results are similar to those of other authors that have used various hepatoprotectors with antioxidant properties (Skakun, 1991; Reiter *et al.*, 1997; 2002; Wiid, 1999). It could be assumed that combinations of antioxidants SH7 and SH8 with INH, would have also a synergistic effect against *Mycobacterium tuberculosis*. Similar results for the presence of synergistic anticancer effect of combinations between antioxidant and anticancer antibiotics are reported by Gadjeva & Koldamova (2001).

Future studies could be directed to the determination of the effect of combinations of INH with SH7 or SH8 on antituberculosis activity. Taking into account the cited data and our own results (Georgieva *et al.*, 2004a; 2004b) we suppose that the efficacy of the contemporary chemotherapy could be improved by coadministration of antituberculosis drugs (at lower doses) and antioxidants in order to decrease systemic oxidative damage.

In conclusion, the free radical processes are constantly occurring in living organisms and antioxidant defense could not always eliminate ROS formation. Under normal conditions, there is a dynamic equilibrium between ROS production and their elimination. When, however, ROS formation is bigger that the quenching capacity of cell defense mechanisms, oxidative stress is produced (Czene *et al.*, 1997; Chopra & Wallace, 1998; Patterson & Leake, 1998; Popova & Popov, 1999; Hristozov *et al.*, 2001). It is accompanied by impaired EOB between pro- and antioxidants that results in toxic damages, diseases, ageing or death of the aerobic organisms. Antioxidants could assist a given biological system to restore the EOB and thus to ensure at maximum its protection against the oxidative assault of ROS (Georgieva & Gadjeva, 2005).

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