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Relationship Between Oxidative Stress and Anxiety: Emerging Role of Antioxidants Within Therapeutic or Preventive Approaches

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1. Introduction

Oxidative stress (OS) represents a loss of balance in oxidation-reduction reactions (redox state). It is characterized by the reduced ability of the antioxidant defense system to efficiently eliminate the excess of the oxygen-derived species production, eliciting the toxicity of oxygen and its detrimental effects.

OS state is related to probably more than 100 human diseases including male infertility, autoimmune diseases, atherosclerosis, cardiovascular troubles, diabetes and cancer. Interestingly, certain diseases associated with OS disturbances such as neurodegenerative diseases and neuropsychiatric diseases including schizophrenia and some forms of behaviour, such as aggressiveness, depression and anxiety are more specific for the nervous system impairments. In particular, recent research observed a close relationship between OS and anxiety in both human patients suffering from anxiety disorder (obsessive–compulsive disorder and panic disorder), and humans and animals displaying high trait anxiety (Bouayed & Bohn, 2010; Bouayed, 2010; Bouayed et al., 2009). It has been debated that brain OS disturbances might be a plausible pathogenesis and risk factor for several specific diseases of the nervous system including behavioural troubles and disorders (Ng et al., 2008; Bouayed, 2010; Bouayed et al., 2009).

Brain controls several activities and functions including emotion; a correct function of the nervous system, that is mediated by neurotransmitters and its adequate interaction with other regulatory systems including the endocrine system (involving hormones) and the immune system (involving cytokines) is crucial for health. Oxygen is very essential for brain activity and in this respect mammal brain is highly sensitive to oxygen deprivation and even short duration of hypoxia can cause irreversible damage or even death. Albeit oxygen is vital, high oxygen-derived species production (through respiration and metabolism) produces toxicity in brain, owing to its intrinsic oxidative vulnerability (Mariani et al., 2005;

Halliwell, 2006; Ng et al., 2008; Bouayed et al., 2009). Interestingly, human brain uses about 20% of oxygen consumed by the body even though this organ constitutes only about 2% of the body weight (Halliwell, 2006; Bouayed et al., 2009). The high energy needed by the brain may explain its high oxygen uptake. However, the antioxidative defense system of the brain is not well equipped (due to relatively low levels of certain antioxidant enzymes, particularly catalase) to deal with the high rate of reactive oxygen species (ROS) resulting from the brain's high oxygen consumption (Mariani et al., 2005; Halliwell, 2006). Catalase and glutathione peroxidase play a key role in the catabolism of hydrogen peroxide (H_2O_2) into water and oxygen, avoiding the formation of the highly reactive hydroxyl radicals ($OH^{\bullet}$) following the Fenton reaction

$$(H_2O_2 + Fe^{2+} \text{ or } (Cu^{+}) \longrightarrow {}^{\bullet}OH + {}^{-}OH + Fe^{3+} \text{ or } (Cu^{2+})) \text{ or}$$

Haber–Weiss reaction ($O_2^{\bullet -} + H_2O_2 \longrightarrow {}^{\bullet}OH + {}^{-}OH + O_2$) (Valko et al., 2007). Brain metabolism produces a lot of H_2O_2, while low levels of catalase have been reported in the most brain regions (Halliwell, 2006). In addition, the abundant presence of iron and copper ions in neuronal cells (Hovatta et al., 2010) may catalyze the production of $OH^{\bullet}$ and $RO^{\bullet}$ generated via peroxides (H_2O_2 and ROOH, respectively). Neuronal membrane lipids, which are rich in highly polyunsaturated fatty acids, may undergo rapid lipid peroxidation following the occurrence of OS (Mariani et al., 2005; Halliwell, 2006; Bouayed et al., 2009). The sensitivity of brain to oxygen increases with increasing age following the natural consequence of brain aging, which is characterized among others by the declining ability of the antioxidant system to prevent against oxidative damages resulting from non-detoxified ROS (Mariani et al., 2005; Pandey & Rizvi, 2010).

The present chapter focuses on the link between OS and anxiety, discussing and reviewing different findings obtained from humans and rodents in this field. The emerging role of antioxidants as a potential new strategy for the prevention and treatment of anxiety is also debated.

2. Anxiety disorder and OS

GABAergic and serotoninergic systems are considered among the principal regulatory systems of anxiety. However, following to recent findings of Kuloglu et al. (2002a and 2002b)— emphasizing that patients with anxiety disorders (obsessive–compulsive disorder and panic disorder), compared to healthy controls, have higher activity levels of the antioxidant enzymes superoxide dismutase and glutathione peroxidase as well as higher lipid peroxidation activity — oxidative metabolism is being also regarded as a plausible pathway that can affect the regulation of anxiety. This hypothesis has gained interest due to the intrinsic oxidative vulnerability of the brain (see above). When the production of ROS prevails over the brain defense systems, the lipid-rich constitution of brain may favour lipid peroxidation, constituting a free radical chain reaction that may result in decrease in membrane fluidity and damage in membrane proteins inactivating receptors, enzymes and ion channels, even disrupting membrane integrity resulting eventually in cell death. In addition to oxidative damage of neuronal membrane lipids and proteins, oxidation of other sensitive components such as nucleic acids and neurotransmitters can occur. As a result, OS can alter neurotransmission, neuronal function and overall brain activity (Bouayed et al., 2009). Therefore, brain oxidative damage might be also a plausible pathogenic factor for

certain multifactorial neurological diseases including neuropsychiatric troubles. Interestingly, OS state was recently linked to other behavioural disorders, such as aggressive behaviour and depression, and also to deterioration of short-term spatial memory (Bouayed et al., 2009, 2010; Dean et al., 2009; Bouayed, 2010), highlighting that OS disturbances could be implicated in the pathophysiology of conditions that are more specific for the nervous system impairment. In this respect, we have reported a statistically significant positive correlation between aggressive behaviour in the resident/intruder test and cell oxidative status in adult male mice (Rammal et al., 2010b). Moreover, patients suffering from major depression have presented OS in both their peripheral as well as their central systems (Bilici et al., 2001, Michel et al., 2007). Curiously, some of these conditions (e.g. aggressiveness and depressed mood) could also be associated with anxiety. For instance, Bayani et al. (2007) demonstrated that in teachers, the high level of anxiety is associated with a high level of hostility. In animals, it has been shown that dominant rodents had high levels of anxiety and they often exhibited aggressive behaviour toward subaltern subjects (Ferrari et al., 1998; Blanchard et al., 1993).

Anxiety may also coexist with depression and for defining these states the term comorbidity is usually used. Such mixed states of anxiety and depression make coping of the disease more difficult. It concerns both general prognosis, as well as treatment response in this cohort of patients. For example, in the Finnish population-wide Health 2000 Survey, it has been estimated that 35.9% of the anxiety disorder patients had a comorbid depressive disorder (major depressive disorder and/or dysthymia) (Pirkola et al., 2005).

In their studies, Kuloglu et al. (2002a and 2002b) have used the activity of antioxidant enzymes (e.g. superoxide dismutase and glutathione peroxidase) in erythrocytes and the level of malondialdehyde in plasma as markers of oxidative status of human subjects (healthy volunteers versus patients suffering from obsessive–compulsive disorder and panic disorder). Other human studies have shown the validity of these biomarkers to assess OS state. For example, several studies have demonstrated that peripheral oxidative status markers in human erythrocytes and plasma significantly correlated with human age, and as a result they have been proposed as biomarkers of the aging process, which is characterized by an increase of oxidative stress with age (Pandey & Rizvi, 2010).

3. High anxiety level and OS

In the light of results from Kuloglu et al (2002a and 2002b) establishing a relationship between OS and anxiety disorder, other recent studies have focused on the link between redox status and normal anxiety, and also on a possible causal relationship between cellular oxidative stress and emotional stress using rodents as animal model. Mice and rats are often used as translational models for studying anxiety in humans due to the similarity in the extremely complex mechanisms involved in anxiety in these species. Indeed, the principal brain areas (e.g. the amygdala) implicated in the processing (or the suppression) of fear and anxiety, the comparable brain circuits involved with anxiety, and the similar neurochemical substrates (e.g. GABA, serotonin) among others, make rodents a good model to study anxiety in humans (Mathew et al., 2008). Anxiety of rodents is detected from specific behavioural model tests, among which the elevated plus maze, the light/dark choice test, open field test and hold board test are most employed. These behavioural tests are also sensitive to pharmacological agents with anxiolytic or anxiogenic properties, causing a decrease or an increase in the anxiety-related behaviour of animals, respectively.

Based on their anxiety-like behaviour assessed in both the dark/light choice test and the open field test, Hovatta et al., (2005) ranked six inbred mouse strains from the less anxious to the more anxious. Afterwards, they have demonstrated a close correlation between brain expression of genes of the antioxidative defense system (*glutathione reductase 1* and *glyoxalase 1*) and anxiety-related phenotypes across all mouse strains. They further found that the activity of the antioxidative enzymes of glutathione reductase 1 and glyoxalase 1 is highest in the most anxious strain and lowest in the least anxious strains. A link between OS and emotional stress is not surprising per se; since it is well accepted that oxidative damage in the brain may cause an impairment of the nervous system. For example, abnormalities in the regulatory systems of anxiety in rodents (e.g. GABAergic and serotoninergic systems) can result in anxious behaviour. Furthermore, alteration of the function of the hypothalamic-pituitary-adrenal (HPA) axis, which is implicated in stress responses and anxiety disorders, could also impact the emotional response. However, the second part of results of Hovatta et al. (2005) obtained from a genetic manipulation using lentivirus-mediated gene transfer was surprising because the role of oxidation or reactive oxygen species is not clear in the genesis of anxiety, despite the role of *glyoxalase 1* and *glutathione reductase 1* in the regulation of anxiety in transgenic mice was established. Indeed, they found that local overexpression of *glutathione reductase 1* and *glyoxalase 1* in the cingulated cortex of the murine brain results in an increase of anxiety-like behaviour, while inhibition of *glyoxalase 1* expression produces low-anxiety. Thus, Hovatta et al. (2005) were able to make a causal link between the antioxidative status of the brain and anxiety-related behaviour supposing that *glyoxalase 1* and *glutathione reductase 1* regulate anxiety in mice. However, *in vivo*, antioxidant genes (e.g. *superoxide dismutase, glutathione peroxidase* and *glutathione reductase*) are normally overexpressed in response to an uncontrolled production of ROS. In certain cases, OS leads to silencing of genes encoding antioxidant defensive enzymes. In the lentivirus experiments of Hovatta et al., (2005) however, the overexpression of the transgenes (*glyoxalase 1* and *glutathione reductase 1*) was induced *in vivo* with a lentiviral vector and not an excessive production of toxic oxygen metabolites. Clearly, the mechanism by which these antioxidant defensive enzymes regulate anxiety is of great interest. Additionally, Hovatta et al., (2005) used *glyoxalase 1*, which is an enzyme of the glyoxalase system, as a marker of oxidative stress, however the link is indirect. Enzymatic activity of glyoxalase 1 aims to protect against carbonyl stress (resulting from excessive accumulation of reactive dicarbonyl compounds). Carbonyl stress leads to protein and nucleotide damages by dicarbonyl glycation, which is associated with several pathologies including diabetes (Thornalley, 2006a, 2006b and 2006c). Glutathione (GSH), which is a major antioxidant in the brain, constitutes a determinant cofactor for the enzymatic reaction that is catalyzed by glyoxalase 1. However, a close relation between oxidative stress and carbonyl stress was established.

Curiously, other findings from another laboratory (Krömer et al., 2005; Ditzen et al., 2006) have complicated the understanding the role of glyoxalase 1 in trait anxiety because they are discordant with those of Hovatta et al. (2005). Contradictory, they have proposed that the level of expression of glyoxalase 1 could be used as a physiological marker of trait anxiety level, with high protein expression indicating low trait anxiety level and low expression for high trait anxiety. Indeed, comparing two Swiss CD1 mouse lines with extremes in trait anxiety, these authors found that glyoxalase 1 was more expressed in the line with low-anxiety-related behavioural phenotype than in the line with high-anxiety-related behavioural phenotype. The expression of glyoxalase 1 has been assessed in several brain areas

and also in red blood cells of mice. The lines of mice with contrasting anxiety-like behavioural phenotypes were generated from wild type mice after > 15 generations of selection. Differences in the genotype of this strain and those used by Hovatta et al. (2005) could play a role in the differences of observed results. Thus, it would be interesting to compare in the same strain, anxiety-related behaviour of mice with their oxidative status rather than compare the redox status of strains differing in their anxiety-related phenotypes. This approach takes into account the intra-variability between individuals of the same strain.

Because of the large heterogeneity in their anxiety levels, Swiss albino male mice (OF1) constitute an interesting behavioural model to study the link between oxidative status and anxiety-related behaviour. Correlation analyses indicated a linear and significant relationship between the intracellular redox status of peripheral blood granulocytes and different parameters of anxiety-related behaviour, assessed in the behavioural light/dark choice test, including latency time (R^2=0.74, P<0.001), cumulative time spent in the lit box (R^2=0.61, P<0.01) and number of entries into the lit box (R^2=0.66, P<0.01) (Bouayed et al., 2007, 2009). Our results suggested a positive relationship between peripheral oxidative status and level of anxiety in mice. To confirm the relationship between OS and emotional stress, we comparatively evaluated the peripheral oxidative status of mice with contrasting levels of anxiety (anxious and non-anxious). Following strict selection criteria from a general population of 100 mice (Rammal et al., 2008a, 2008b, 2010), only 10% of mice were considered as anxious (n = 10) and 10% as non-anxious (n = 10). Thus, mice with intermediate behaviours were eliminated (n=80). We found that high anxiety level was associated with a significant generation of ROS in the peripheral blood lymphocytes, granulocytes and monocytes in mice compared to low anxiety level (Rammal et al., 2008a). Our results confirm that there is a relationship between the level of intracellular ROS in peripheral blood cells and anxiety-related behaviour in mice. These results prompted us to study the oxidative status of the brain in mice with distinct levels of anxiety. Using the same behavioural approach to distinguish between anxious and non-anxious mice, we found that anxiety levels were associated with the oxidative status in both neuronal and glial cells in the cerebellum and hippocampus, in neurons of the cerebral cortex and in peripheral leucocytes (monocytes, granulocytes and lymphocytes) (Rammal et al., 2008b). Our results clearly indicated the presence of OS in the central and peripheral systems of anxious mice. OS in the brain and blood immune cells could predispose anxious mice to neuroinflammation and neurodegeneration as well as recurrent infections. In another study, we have found that high levels of anxiety inhibited part of the cellular and humoral immune systems by significantly decreasing total lymphocytes numbers (including TCD_4^+ and TCD_8^+) and immunoglobulin (A and E) concentrations, emphasising the vulnerability of anxious mice to infections (Rammal et al., 2010a). We considered that type of anxiety evaluated in mice with contrasting levels of anxiety is a trait-anxiety, for two reasons. First, we have verified that the level of anxiety of anxious and non-anxious mice was stable during time (a period of 15 days). In fact, they did not change their status of anxiety in the light/dark choice test. Secondly, we have also verified that in a general population of mice, the anxious (or non-anxious) mice in the light/dark choice test are usually the anxious (or non-anxious) in the elevated plus maze. We have also found that the general activity, both horizontal (locomotion) and vertical (rears), of anxious mice was significantly lower than of non-anxious mice (unpublished results), which was in keeping with the findings of do-Rego et al. (2007) comparing anxious with non anxious male Swiss albinos CD1 mice. These authors also found that these groups of mice did not significantly differ with regard to their immobility

time, marker of depressive behaviour, in the forced swimming test. In agreement with these results, we have also found that the behaviour of anxious and non-anxious mice did not significantly vary in the tail suspension and forced swimming tests, the well-known predictive tests of depression-related behaviour (unpublished results). From the above, it could be suggested that high trait anxiety level in anxious mice from Swiss albino male mice (OF1) was not associated with depressive symptoms.

The results of our studies are in good concordance with the initial findings of Hovatta et al. (2005) associating OS to high trait anxiety level, but our findings do not permit us to declare a causal relationship between these stresses. In keeping with the animal experiments, the link between OS and human trait anxiety was also determined. Indeed, Yasunari et al. (2006) found a significant relationship between trait anxiety and ROS formation in monocytes of hypertensive individuals.

To study the causal relation between OS and anxiety, Masood et al. (2008) provoked OS by depleting glutathione (GSH) in mice using buthionine-S,R-sulfoximine (BSO), and afterwards they assessed the impact of BSO treatment on the level of anxiety. Surprisingly, BSO-treated mice developed anxious behaviour in several mouse models of anxiety including elevated plus maze, hole-board and open field tests. The NADPH oxidase was suggested to be the principal oxidative pathway responsible for the anxiogenic behaviour following BSO treatment. Depletion of GSH was also reported to cause cognitive impairment (short-term spatial memory disturbances) in rodents as assessed in the Y-maze test (Dean et al., 2009). It is also suggested that GSH might play a role in psychiatric illnesses including schizophrenia and bipolar disorder (Dean et al., 2009). However, despite that GSH is considered as a major antioxidant in aerobic cells functioning as an important cellular redox buffer, GSH depletion can cause other cellular stresses, including nitrosative and carbonyl stresses, as GSH is also an important determinant of the nitrogen and dicarbonyl metabolism. Excessive production of ROS induces oxidative damage of cellular structures; production of reactive nitrogen species triggers nitrosylation reactions, which can alter the structure of proteins to inhibit their normal function; excessive accumulation of reactive dicarbonyl compounds leads to damage of protein and nucleotides by dicarbonyl glycation. Additionally, GSH may also have an additional double role in the central nervous system by acting as a neurotransmitter and neuromodulator, e.g. by regulating the release of other neurotransmitters such as dopamine and gamma-aminobutyric acid (GABA), which is an important regulator of anxiety (Oja et al., 2000). Therefore, the anxiogenic behaviour resulting from depletion of GSH in mice could be independent from oxidative metabolism disturbances generated by BSO treatment. Thus, it is difficult to deduce, from this study, a direct causal relationship between oxidative stress and anxiety.

Other studies have mentioned that OS state could cause anxiogenic behaviour, however the link is indirect. Desrumaux et al. (2005) showed that vitamin E deficiency in the mouse brain significantly causes brain OS, resulting in anxiogenic behaviour without abnormalities in the locomotor performance of the mice. Souza et al. (2007) demonstrated in rats that the consumption of a highly palatable diet enriched with sucrose leads to an obese phenotype, increases protein oxidation in the frontal cortex and induces anxiety-like behaviour in the dark/light choice test without altering locomotion in an open field test. Berry et al. (2007) showed that mice developed anxious behaviour during aging, likely due to the accumulation of oxidative damage, which is a characteristic of the aging process in animals. In addition, Berry et al. (2007) showed that a deletion of the $p66^{Shc}$ longevity gene in mice, which results in lower levels of OS and an extended life span, decreased anxiety-related behaviour.

4. Antioxidants as therapeutic or preventive approaches

At physiologic conditions, antioxidants play a crucial role in maintaining redox homeostasis by maintaining the level of ROS at physiological doses necessary for optimal cellular functioning. Thus, the excess of ROS is neutralized by antioxidants avoiding the oxidation of cellular components and consequently their damage. Exogenous antioxidants complete the antioxidative action of endogenous antioxidants by acting together, e.g. additively or synergistically. The principal source of exogenous antioxidants is our diet. However, diets relatively deficient in antioxidants may favour oxidative stress. Vitamin E, vitamin C, carotenoids, zinc, selenium, and polyphenols (e.g. phenolic acids and flavonoids) constitute the principal dietary antioxidants existing in food. Of course, these antioxidants can be found naturally (e.g. in plant foods or animal products such as eggs and honey), however, other sources can also exist (e.g. supplementation and fortification). Currently, there is increasing evidence that the advantageous effects of antioxidants on health are not only attributed to their antioxidant properties. This is due to the fact that antioxidants can also act e.g. as signalling molecules or as chemopreventive agents by displaying other activities such as anti-inflammatory activity (Bouayed & Bohn, 2010). The effect of dietary antioxidants on the central nervous system has gained interest in the last decades. In this sense, it has been demonstrated that dietary antioxidants can also exhibit cognitive enhancing effect, psychostimulant activity, and antidepressant and anti-anxiety properties. For example, it has been shown that antioxidants (e.g. vitamin C, rutin, caffeic acid and rosmarinic acid) possess antidepressant activity with relatively lower doses (0.1-2 mg/kg) than commonly used antidepressants such as imipramine or fluoxetine, which are active at higher doses (≥ 10 mg/kg) in rodents. The mechanism of action of antioxidants on the central nervous system is not well elucidated, however, it has been demonstrated that rutin exerts its antidepressant activity similarly to conventional antidepressants by increasing the availability of serotonin and noradrenalin in the synaptic cleft (reviewed by Bouayed , 2010). Interestingly, antioxidant effects of conventional antidepressants have been reported in several studies (Atmaca et al., 2004; Réus et al., 2010). The antioxidant effects of anxiolytic treatments with citalopram (also used as an antidepressant) have been emphasized by Atmaca et al. (2004) on patients with social phobia. Polyphenols have also shown their ability to reverse anxiety-related behaviour of rodents. Some polyphenols have a pharmacological profile that suggests a partial agonistic action that may produce the anxiolytic-like effects, but without the side effects such as dependency, which are a feature of full agonists such as benzodiazepines. For example, at 3 mg/kg, apigenin exerts its anxiolytic effect in mice without sedation or myorelaxant effects. However, a 10-fold increase in dosage of this flavonoid produced slight sedative effects. Polyphenols may present a dose-effect response on the central nervous system. Rosmarinic acid at a dose of 2-4 mg/kg exhibited anti-anxiety effects, however, in the same animal model this polyphenol exerted psychostimulant effects at the dose 8 mg/kg. Contrarily to conventional anxiolytics, which only have anti-anxiety effects at relatively low doses (1-5 mg/kg), polyphenols can display anxiolytic effects at a spectrum of doses ranging from 2 to 30mg/kg. For example, chlorogenic acid and (−)-epigallocatechinn gallate (EGCG) are active at 25 mg/kg and 30 mg/kg, respectively. The ability of polyphenols to cross the blood-brain barrier might explain the difference in their active concentration. The intranasal administration of polyphenols in the form of liposomes could be an effective strategy both to facilitate the movement of these substances across the blood-brain barrier and to effectively reduce the

active dose. For example, it has been shown that quercetin, which is a flavonoid having difficulty crossing the blood-brain barrier, that its single intrasanal administration (20 µg) to rats reduced the active oral dose (300 mg/kg) by around 6000 times. Noteworthy, the reduction of anxiety was obtained by the oral administration of quercetin (300 mg/kg) but only after one-week of daily treatment. Therefore, the use of liposomes is a potentially novel strategy which can facilitate the delivery of polyphenols across the blood-brain barrier and also can effectively reduce the active dose (reviewed by Bouayed, 2010).

Although psychopharmacological studies present antioxidants as a potential new strategy for the treatment of anxiety and depression, the use of these substances has to be with caution. Several studies are required to investigate the toxicity of antioxidants at non-nutritional doses. At high doses, it has been discussed that antioxidants could enact deleterious effects on health, acting e.g. as prooxidants. As an example, it has been demonstrated that EGCG at pharmacological doses (30 and 60 mg/kg) abolishes anxiety in mice; at 150 mg/kg however this tea polyphenol caused death to mice (100% mortality) in less than 24 h, presumably due to its high hepatotoxicity noticed above 100 mg/kg. Despite that antioxidants, once outside in their natural matrix or at higher doses could be toxic, they, generally, are safe in plant foods due to their presence at physiological doses and also to their resulting combined effect (reviewed by Bouayed & Bohn, 2010). Therefore, antioxidants from a normal diet could prevent from anxiety development. In this respect, it has been demonstrated that some specific foods prevent aging-accompanying anxiety. Viggiano et al. (2006) demonstrated that anxiety of aged rats fed for 10 weeks with a standard diet supplemented with fresh apple fruits was significantly lower than aged rats fed with the standard diet. The decrease of anxiety was not associated with a change in general activity, however a reduction of OS was also found. Indeed, these authors found that brain superoxide dismutase (SOD) activity of aged rats fed with an apples enriched diet was not different from young animals feed with the standard diet with or without apples, while SOD activity of aged rats fed with the standard diet was significantly elevated. Pitozzi et al. (2010) found that aged rats fed, for one year, with a diet containing olive oil naturally rich in antioxidants have displayed a low anxiety than aged rats fed either with a diet containing olive oil naturally low in antioxidants or with maize oil. Interestingly, the reduction of anxiety was associated with significant decreased glutathione reductase activity and expression in the brain. Chepulis et al. (2009) conducted a study on rats fed *ad libitum* for 52 weeks with a diet that was either sugar-free or contained 7.9% sucrose or 10% honey (which is the equivalent amount of sugar). They found that anxiety of rats fed with the diet supplemented with honey was significantly lower than in the other groups. No information was given on the oxidative status of different groups; however, the antioxidant power of honey has already been stressed in other reports. It has been suggested that the anti-anxiety effect of long intake of apples, olive oil and honey may be attributed to the whole food matrix containing complex mixtures of nutrients and non-nutrients including vitamins, flavonoids, phenolic acids, several carotenoids, and many more acting on a synergistic or additive manner, rather than to specific compounds.

5. Conclusion

Anxiety has a multifactorial origin and can result e.g. from pharmacological treatment with some drugs (e.g. methyl-β-carboline-3-carboxylate), stressful situations (e.g. immobilization stress) or natural conditions (e.g. aging process). Although the link between OS disturbances

and anxiety is not disputed, whether oxidative stress is a side effect resulting from emotional stress, or inversely itself is the pathogenesis factor for this condition remains unclear. Nevertheless, results of Masood et al. (2008) showing that the well known anxiolytic diazepam does not fully reverse the anxiety generated by BSO treatment, can suggest that OS could be one of factors causing anxiety. Nevertheless, diazepam can abolish e.g. restraint stress-induced anxiety, although immobilization stress being a prooxidant. Interestingly, Masood et al. (2008) showed that OS-related anxiety could be reversed in mice after inhibition of NADPH oxidase or phosphodiesterase-2, enzyme that is indirectly implicated in OS mechanisms. Salim et al. (2010) demonstrated that anxiety generated by BSO treatment of rats was reversed either by preventive treatment by antioxidant using tempol, or by moderate treadmill exercise. It has been discussed that moderate physic activity reduces the vulnerability of brain to oxidative stress by increasing the resistance of brain antioxidant system following an adaptation, while acute or intense exercise are prooxidants. The vulnerability of brain to oxidative damages is in line with the theory that anxiety could be generated directly by OS. Antioxidants may constitute a potential treatment when OS is the causal factor in anxiety. In addition, a mixture of antioxidants and anxiolytics could be also a useful treatment in patients with anxiety, since OS is associated with anxiety disorders. It has been demonstrated that vitamin C caused a synergistic antidepressant-like effect with conventional antidepressants administered at subeffective doses. However, the use of antioxidants as a pharmacological approach to treat anxiety or as a co-adjuvant treatment with conventional anxiolytics should be employed with precaution. Indeed, antioxidants at high doses could become toxic by behaving e.g. as prooxidants. In this sense, supplementation of the human diet with high doses of antioxidants, e.g. vitamin C or carotenoids resulted in several adverse effects (reviewed by Bouayed & Bohn, 2010). Therefore, several studies are necessary to determine the safety of antioxidants at high doses, and the duration of the treatment, when the pharmacological approach is envisaged. However, antioxidants from natural foods rich in antioxidants could constitute a preventive therapy against anxiety, owing to their presence at physiological doses. Several animal studies have shown that long-term consumption of honey, apple or olive oil can prevent aging-accompanying anxiety. Nevertheless, the efficiency of antioxidants from fruits and vegetables has been prospectively verified against human diseases related to oxidative stress including coronary heart disease and stroke but has shown to be effective in preventing diseases predominantly when consumed at least at 5 portions per day.

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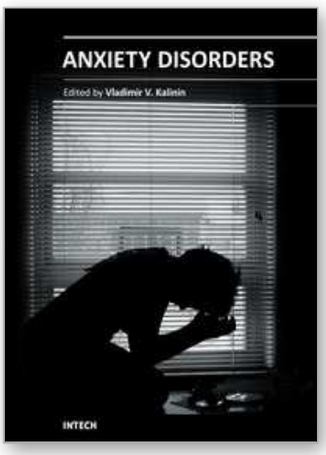
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During the last 2-3 decades drastic research progress in anxiety issues has been achieved. It concerns mostly the study of different subtypes of anxiety and their treatment. Nevertheless, the data on anxiety pathogenesis is less elaborated, although here a multidimensional approach exists. It includes neurochemistry, pathophysiology, endocrinology and psychopharmacology. Again, we are able to recognize the multifarious sense of anxiety, and the present collective monograph composed of 16 separate chapters depicting the different aspects of anxiety. Moreover, a great part of book includes chapters on neurochemistry, physiology and pharmacology of anxiety. The novel data on psychopathology and clinical signs of anxiety and its relationship with other psychopathological phenomena is also presented. The current monograph may represent an interest and be of practical use not only for clinicians but for a broad range of specialists, including biochemists, physiologists, pharmacologists and specialists in veterinary.

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