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Oxidative Stress and Psychological Disorders

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Abstract: Oxidative stress is an imbalance between cellular production of reactive oxygen species and the counteracting antioxidant mechanisms. The brain with its high oxygen consumption and a lipid-rich environment is considered highly susceptible to oxidative stress or redox imbalances. Therefore, the fact that oxidative stress is implicated in several mental disorders including depression, anxiety disorders, schizophrenia and bipolar disorder, is not surprising. Although several elegant studies have established a link between oxidative stress and psychiatric disorders, the causal relationship between oxidative stress and psychiatric diseases is not fully determined. Another critical aspect that needs much attention and effort is our understanding of the association between cellular oxidative stress and emotional stress. This review examines some of the recent discoveries that link oxidative status with anxiety, depression, schizophrenia and bipolar disorder. A discussion of published results and questions that currently exist in the field regarding a causal relationship between oxidative and emotional stress is also provided.

Keywords: Psychological stress, oxidative stress, anxiety, depression.

INTRODUCTION

A widely accepted theory is that chronic, persistent stress triggers numerous illnesses. However, exactly how that occurs is a complex process that is not fully understood. The term "stress" is used rather vaguely and often defined in a somewhat confusing manner. Actually, "everybody knows what stress is, and nobody knows what it is", once noted by Hans Selye [1] conveys the vagueness of the word "stress". Well, based upon current knowledge, it is safe to define stress as "a physical, chemical, or an emotional factor that causes bodily harm often causing disease". If we focus on stress as an "emotional factor", the association between stress, anxiety, depression and cognitive dysfunction comes to mind. If we focus on stress as a physiological stressor, one is reminded of hypertension and other cardiovascular conditions. Stress, physiological or emotional is reported to trigger co-occurrence of these conditions. Several attractive theories have been postulated to address the biochemical basis of these observations, one of which is the oxidative stress theory. In 2005, Gingrich [2] proposed that "oxidative stress is the new stress". This seems reasonable considering the reported association of psychological stress with higher levels of oxidative damage [3-6]. Present discussion focusses on this concept proposing that oxidative stress mechanisms mediate cognitive, emotional and physiological health.

Oxidative Stress

Oxidative phosphorylation takes place in the mitochondria and is a major source of ATP in aerobic organisms. As a by-product, it produces free radicals, including reactive oxygen species [ROS], reactive nitrogen species [RNS], carbon-centered and sulfur-centered radicals [7]. Free radicals are atoms or groups of atoms with an unpaired number of electrons, which are highly reactive substances that can result in chain reactions, with each step forming a free radical [8]. The process of oxygen reduction to water generates ROS as intermediates that can cause damage [9]. The primary ROS generated in humans are hydrogen peroxide [H_2O_2], superoxide radical [O_2^-] and hydroxyl radical [OH^-]. The superoxide radical is generated during auto-oxidation of hemoglobin, and photolysis. Superoxide is not particularly reactive by itself, but can be catalytically converted by superoxidase dismutases [SOD] to H_2O_2, which decomposes to yield the highly reactive hydroxyl radical in the presence of iron. RNS mainly include nitric oxide [NO] and nitrogen dioxide. Nitric oxide is a free radical by its unpaired electron, which can also produce hydroxyl radicals and nitrogen dioxide radicals.

In general, any abnormal increase in an oxidative stress promoting substance, often called pro-oxidants, is mitigated by an antioxidant response. The pro-oxidant/antioxidant balance is critical. When this balance is disturbed, oxidative and nitrosative stress is initiated as a result of overproduction of ROS and/or insufficiency of the antioxidant defense mechanisms [10, 11]. In the balanced redox status, ROS are beneficial for normal physiological functions and protect the cell from infections by destroying invading pathogens [12, 13], function as second messengers in the regulation of cardiac and vascular cell functioning [13, 14] and are involved in intracellular regulation of calcium concentration, in protein phosphorylation and/or dephosphorylation. Excessive ROS, however, may have detrimental effects [11] and can disturb the maintenance of normal adenine and pyridine nucleotide status, which can affect the viability of DNA, introduce mutation, and modify gene expression [15]. Protein oxidation by ROS can lead to loss of sulfhydryl

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groups and modifications of amino acids that render proteins nonfunctional [16, 17], and cause peroxidative damage to lipids eventually damaging cell membranes [18]. Hence it is generally believed that, at low concentrations, ROS and RNS are involved in response to injury or infection [13]. When ROS/RNS ratio is increased, the cellular detoxification and repair capacity is diminished leading to an oxidative stress build-up. Hence, oxidative stress can be considered as a state where the level of oxidants [hydrogen peroxide, superoxide, nitric oxide, etc.] produced by biological reactions exceeds the oxidants scavenging capacity of the cells. These oxidants modify cellular macromolecules [proteins, DNA, lipids] and alter cellular functions [19] resulting in apoptosis or necrosis [20-22].

The brain with its extensive capacity to consume large amounts of oxygen and production of free radicals, is considered especially sensitive to oxidative damage [12, 23]. Therefore, it is not surprising that oxidative stress is implicated in several disorders of the brain including neurodegenerative disorders [23-26], psychiatric ailments [27], and anxiety [28]. This association is largely due to the high vulnerability of brain to oxidative load [27]. Several theories have been proposed over the years to conceptualize the pathophysiology of these disorders. While most classical theories suggest involvement of traditional signal transduction mechanisms including abnormalities in the gamma amino butyric acid [GABA] and serotonin receptor systems in the etiology of anxiety, depression and other stress-related illnesses [29], oxidative stress theory also seems quite plausible.

This seems particularly appealing considering that psychological stress is reported to result in the production of ROS, like superoxide anion radical [O_2], hydroxyl radical [HO], and H_2O_2, especially in the brain. When ROS production exceeds the antioxidant capacity, lipid peroxidation often occurs. Several antioxidant enzymes have been reported to be responsible for inhibiting formation of ROS or removal of free radicals. These antioxidant enzymes include catalase [CAT], superoxide dismutase [SOD], glutathione peroxidase [GPx], and glutathione reductase [GSR] [30]. SOD is considered as the first line of defense against ROS and catalyzes dismutation of superoxide anion radical [O_2] into H_2O_2 [30]. H_2O_2 can be reduced to water and molecular oxygen by either CAT or GPx [31]. Besides detoxifying H_2O_2, GPx can also reduce lipid and non-lipid hydroperoxides at the expense of reduced glutathione [GSH], which is in turn oxidized, forming glutathione disulfide [GSSG]. GSH is the most important non-enzymatic endogenous antioxidant and can be regenerated by GSR with the consumption of nicotinamide adenosine dinucleotide phosphate [NADPH] [32]. Thus it can be concluded that oxidative stress reflects a state of cellular imbalance, in which ROS production exceeds antioxidant response mechanisms which help to neutralize ROS-mediated oxidative damage to DNA, RNA and lipids resulting in a variety of different pathophysiological consequences [33, 34].

Anxiety and Oxidative Stress

A brief episode of anxiety caused by a stressful event such as that of public speaking is a normal reaction to immediate stress and in fact is a motivation to do better. But when anxiety becomes irrational, persistent and excessive, it is pathological and often manifests into anxiety disorders. There are several types of anxiety disorders including panic disorder, post-traumatic stress disorder, obsessive-compulsive disorder and generalized anxiety disorders [35]. It is widely accepted that an interplay of genetic, developmental and environmental factors contribute to the pathogenesis of anxiety. As far as the treatment for anxiety disorders are concerned, benzodiazepines and selective serotonin reuptake inhibitors [SSRIs] are considered the "gold standard". Although clinically useful, chronic use of benzodiazepines leads to tolerance, dependence and sedation. SSRIs require weeks to work and are not without side effects either. Better alternatives over existing anxiety treatments are needed but poor understanding of the pathophysiological mechanisms of anxiety has impeded discovery of novel interventions for a long time. A provocative concept away from the traditional GABA and serotonin theories is the involvement of oxidative stress in anxiety [28, 36-49].

Several investigators have suggested a link between oxidative stress and certain anxiety disorders [obsessive-compulsive disorder and panic disorder], demonstrating that oxidative metabolism, can affect the regulation of anxiety. Several reports [28, 36-40] including our own published findings [41-49], have produced interesting results, suggesting relevance of oxidative stress to mental disorders. The causality of oxidative stress in these disorders still seems far from determined. Most studies suggest associative links but not causal roles. Animal studies on the other hand have been quite useful in clarifying role of oxidative stress in anxiety-like behaviors in rodents. Several studies have suggested causal a role of oxidative stress in anxiety-like-behaviors in rats [36, 37, 40, 41], where genetic alterations or pharmacologically induced oxidative stress was reported to cause anxiety-like behavior and treatment with antioxidants or genetic manipulation seemed to prevent drug-induced anxiety-like behavior, all suggesting causal role of oxidative stress. The question whether behavioral outcome of artificial induction of oxidative stress can be mimicked in situations where oxidative stress occurs as a consequence of psychological stress is an interesting one. Relevant to this, Vollert *et al*. [2011] [44] demonstrated that sleep-deprivation causes anxiety-like behavior and induces oxidative stress in the brains of rats. In a recent study Patki *et al*. [2013] [46] using a social defeat model of psychological stress reported that social defeat stress induces oxidative stress and causes anxiety-like behavior in rats.

Current studies seem to suggest an important role for some specific antioxidant enzymes in anxiety-like behaviors. In recent studies from our lab, we observed that the expression of two antioxidant enzymes involved in the oxidative stress pathway and implicated in anxiety-like behaviors [42, 44, 45], glyoxalase [GLO]-1 and glutathione reductase [GSR]-1, were reduced in the hippocampus, amygdala and the cortex of pro-oxidant buthionine-[S,R]-sulfoximine [BSO] treated rats, which was prevented with antioxidant grape powder treatment. Perhaps, failing antioxidant defense contributed by reduced expression of GLO1 and GSR1 leads to anxiety-like behavior in these

animals. Earlier, GlO1 and GSR1 in correlation with oxidative stress metabolism were reported to be involved in anxiety-like behavioral phenotypes. Overexpression of GLO1 and GSR1 in the mouse brain resulted in increased anxiety-like behaviors. However, inhibition of GLO1 expression by siRNA decreased anxiety-like behaviors [36]. Moreover, BSO-induced increased expression of the mitogen activated protein kinase [ERK1/2] in the amygdala, cortex and hippocampus was prevented with antioxidant grape powder treatment. ERK1/2 has been reported to be upregulated in response to induction of oxidative stress [50, 51] and role of ERK1/2 in anxiety, stress, memory, plasticity and depression [52-55] is also known. These observations of increased ERK1/2 activation upon induction of oxidative stress and its prevention with grape powder is particularly interesting considering a previous report where resveratrol was reported to reduce ERK1/2 activation and suppress expression of pro-inflammatory molecules, interleukin [IL]-1β and tumor necrosis factor [TNF]-α [56]. Perhaps, grape powder attenuates ERK1/2 mediated increase in inflammatory markers and in this manner confers neuroprotection.

It is likely that multiple signaling pathways involving antioxidant [42, 44], anti-inflammatory [45], and/or anti-apoptotic [57] mechanisms may regulate anxiety-like behavior. Additional evidence supporting the hypothesis that NOX-derived ROS are involved in the pathophysiology of anxiety and bipolar disorders has also been presented [58-64]. In fact, it is proposed that anxiety and mood disorders are closely linked to NOX-mediated oxidative stress [28, 36, 37, 65, 66]. BSO-induced anxiety-like behaviors were reported to be antagonized by the NOX inhibitor apocynin and PDE_2 inhibitor [37]. Moreover, NOX2-derived oxidative stress is reported to be involved in the development of anxiety disorder after application of social isolation in mice. A marker of oxidative stress 8-hydroxy-2'-deoxy-guanosine was reported to be increased following social isolation [66]. This is in agreement with the report of Patki *et al*. [2013b] [49] in which social defeat stress induced oxidative stress markers in rats. It is speculated that increase in oxidative stress could be in part due to NOX2 activation in microglia, because the pretreatment with apocynin prevented both behavioral and pathological alterations induced by social isolation [66]. Patki *et al*. [2013b] [49] attributed rise in oxidative stress in response to social defeat to a failing antioxidant system arising from an inflammation build up. The question of causality still persists.

Depression and Oxidative Stress

Depression is a complex and heterogeneous disorder that has a negative impact on quality of life, morbidity/mortality, and cognitive function [67, 68]. Over the years, several mechanisms including genetic predisposition, monoamine deficiency, abnormalities in circadian rhythm, hyper-cortisolemia, and increased levels of inflammatory cytokines have been proposed to be involved in its pathogenesis [69]. In the last several years, oxidative stress has received much attention with regards to psychiatric illnesses including depression and oxidative stress and has been proposed as a contributing factor in the pathogenesis of depression [27]. Several lines of evidence indicate involvement of oxidative and nitrosative stress in the pathophysiology of major depression [MDD] [70, 71]. Increased levels of ROS and RNS in MDD, including peroxide [70] and NO [72, 73] and altered levels of antioxidant defenses, such as glutathione [GSH] in the postmortem MDD brain have been demonstrated [74]. Accordingly, oxidative and nitrosative [O&NS] mechanisms have been proposed as targets for novel antidepressants [75]. This is not surprising considering that depression is known to be accompanied by inflammation, oxidative and nitrosative stress. In fact, significantly lower plasma concentrations of several key antioxidants, such as vitamin E, zinc and coenzyme Q10, as well as lower antioxidant enzyme activity, have been reported in major depression [70]. Association between depression and poly-morphisms in genes involved in oxidative pathways, including manganese superoxide dismutase [SOD] and catalase [CAT] is also known [70]. Recent studies suggest that oxidative and nitrosative stress pathways may contribute to the patho-genesis of depression by interacting with neurogenesis/ neuroplasticity, neuroinflammation and monoamine reuptake process [76, 77]. The current thought is that the antidepressants exert their therapeutic effect by suppressing proinflammatory cytokines and ROS/RNS production or enhancing anti-oxidant defense [75]. Molecular targets involved in the oxidative/nitrosative stress including nicotinamide adenine dinucleotide, niacin, brain-derived neurotrophic factor, glycogen synthase kinase 3, heme oxygenase, nuclear factor E2-related factor 2 and telomerase are believed to be connected to the pathophysiology of depression [75].

It was reported that individuals who suffer from depression displayed lower serum/plasma antioxidant potentials and reduced brain GSH levels. Also, F2-isoprostanes circulatory levels are increased in depressed subjects and are correlated with the severity of depressive symptoms. Urinary excretion of 8-hydroxydeoxyguanosine [8-OHdG] seems to be higher in depressed patients when compared to healthy controls. Thus substantial data support the concept that depression is accompanied with heightened oxidative stress and that antidepressant treatments may reduce oxidative stress, suggesting that perhaps augmentation of antioxidant defenses is one of the mechanisms underlying the neuroprotective effects of antidepressants [78]. Although oxidative stress was found to be elevated in patients with depression but may not be causal since treatment with either bupropion or sertraline significantly reduced the symptoms of depression but increased F2 isoprostane excretion [79]. Thus animal research examining causality of oxidative stress in depression-like behaviors has been limited.

Schizophrenia and Oxidative Stress

Schizophrenia is a complex and debilitating psychiatric illness, with the least understood etiology. Several theories including abnormal neuronal development, impaired neuro-transmission, viral infections, and autoimmune dysfunctions have been proposed [67, 68]. Oxidative stress is one such theory. Although role of oxidative stress in schizophrenia is not entirely new, as generation of toxic radicals in the etiology of schizophrenia was proposed back in the 1950s [80], oxidative stress theory is gaining momentum and seems quite pertinent considering the evidenced increased production of ROS and decreased occurrence of antioxidant protection in schizophrenic patients. Genetic studies also

have linked polymorphisms in genes of oxidative pathway to schizophrenia.

Several studies have demonstrated symptom severity with antioxidant status, linking defects in antioxidant defense system with schizophrenia. Reports of normalization of oxidative stress parameters with antipsychotic treatment and the therapeutic benefit of some antioxidants such as vitamin E and EGb, have provided indirect evidence for involvement of oxidative in the pathophysiology of the disease. Supplementation of vitamin C, vitamin E, the combination of vitamin C and vitamin E, or the mixture of fish oil has been shown to reduce oxidative stress and improve clinical symptoms in patients with schizophrenia [81]. A recent study indicated that ginkgo may also help ameliorate schizophrenia symptoms [82] perhaps *via* its antioxidant properties. A number of studies have shown that the N-acetyl-cysteine [NAC], a precursor of antioxidant glutathione [GSH] and known to restore endogenous GSH and maintain the oxidative balance in the cell, is relevant for treatment of schizophrenia [83, 84]. Several studies have reported elevated SOD activity in chronic schizophrenic patients [85-92], while decreased SOD activity has also been reported [93, 94]. Significantly increased plasma SOD activities were reported in chronic schizophrenic patients that were put on antipsychotic medication and SOD activities negatively correlated with positive symptoms of schizophrenics [89], suggesting involvement of endogenous antioxidative mechanisms. Furthermore, the GSH-Px levels were reported to be lower in schizophrenia patients as compared to controls, in schizophrenic patients on neuroleptics [74, 94-97] and psychotic children [98] with the exception of one report where markedly increased GSH-Px activity was observed [86] which may indicate the differences in antioxidants between various subtypes of schizophrenia [99]. Although no association was detected between a GPX1 polymorphism and susceptibility to schizophrenia [100], later studies reported a strong negative correlation between the activity of GSH-Px and brain atrophy in chronic schizophrenic patients, revealing that low GSH-Px is a contributing factor to structural brain abnormalities [101-103].

In addition, a link between an increased NOX activity and resultant superoxide production in interneurons of the ketamine-induced schizophrenic model, also have been reported [104]. NOX expression and activity were upregulated in the temporal region of mild cognitive impairment patients [105]. Finally, it seems that oxidative stress affects several critical cellular processes including mitochondrial signaling and neuronal excitability, both of which adversely affect neuronal phenotypes and contribute to the pathology of schizophrenia and mood disorders [106]. Therefore, interneuron deficits observed in the brains of patients with schizophrenia and mood disorders when mimicked or reproduced in animal models by exposure to oxidative stress will be extremely valuable. These studies can clarify role of oxidative stress in the neuropathology of major mental illnesses [107, 108].

Bipolar Disorder and Oxidative Stress

Bipolar disorder, characterized by intermittent episodes of mania or hypomania, usually interlaced with depressive episodes. It is also a serious mood disorder clinically presented as unusual shifts in mood, energy and cognitive levels, with or without depressive episodes. Symptoms are different from the normal ups and downs, and may seriously damage relationships, job or school performance, and even cause suicide [35].

Several studies have reported that patients with bipolar disorder have significant alterations in antioxidant enzymes, lipid peroxidation, and nitric oxide levels, such as increased lipid peroxidation and increased NO levels [109]. Interestingly, increased oxidative stress parameters and activated antioxidant defenses may be associated with the psychiatric phase of the disease: euthymic, depressed or manic [110], or the number of the manic episodes [111]. However, there are conflicting results, such as alterations in antioxidant enzymes or the association between psychiatric phase of the disease and oxidative stress parameters [109]. Together, the above findings suggest a role of free radicals and antioxidants in the pathophysiology of bipolar disorder and major depression, although further investigations are needed. Similarly, add-on treatment of NAC was also found to be beneficial in patients with bipolar disorder [112, 113] or with moderate depression [114]. The level of tyrosine nitration that reflects the levels of endogenous ROS ONOO- was significantly higher in bipolar patients than in healthy controls [92].

CONCLUSION

In summary, accumulating evidence implicates free radical-mediated pathology, altered antioxidant capacity, neurotoxicity and inflammation in neuropsychiatric disorders. To what extent oxidative stress contributes to specific clinical symptomatology of these complex and debilitating psychiatric ailments remains to be seen. A major question remains regarding the causal role of oxidative stress in these illnesses, which is highly critical for early and preventive intervention.

AUTHOR CONTRIBUTIONS

SS wrote and approved the final review article.

COMPETING INTEREST

We have no conflicts of interest in presenting this article.

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REFERENCES

[1] Selye, H. The Evolution of the Stress Concept. **1973**, *61*(6), 692-699. http://dx.doi.org/10.5254/1.3547211

[2] Gingrich, J.A. Oxidative stress is the new stress. In: *Nat Med*: United States; **2005**; Vol. *11*, pp. 1281-1282. http://dx.doi.org/10.1038/nm1205-1281

[3] Irie, M.; Asami, S.; Ikeda, M.; Kasai, H. Depressive state relates to female oxidative DNA damage *via* neutrophil activation. *Biochem. Biophys. Res. Commun.*, **2003**, *311*(4), 1014-1018. http://dx.doi.org/10.1016/j.bbrc.2003.10.105

[4] Epel, E.S.; Blackburn, E.H.; Lin, J.; Dhabhar, F.S.; Adler, N.E.; Morrow, J.D.; Cawthon, R.M. Accelerated telomere shortening in response to life stress. *Proc. Natl. Acad. Sci. U. S. A.*, **2004**, *101*(49), 17312-17315. http://dx.doi.org/10.1073/pnas.0407162101

[5] Forlenza, M.J.; Miller, G.E. Increased serum levels of 8-hydroxy-2'-deoxyguanosine in clinical depression. *Psychosom. Med.*, **2006**, *68*(1), 1-7. PMID: 16449405

[6] Gidron, Y.; Russ, K.; Tissarchondou, H.; Warner, J. The relation between psychological factors and DNA-damage: a critical review. *Biol. Psychol.*, **2006**, *72*(3), 291-304. http://dx.doi.org/10.1016/j.biopsycho.2005.11.011

[7] Pero, R.W.; Roush, G.C.; Markowitz, M.M.; Miller, D.G. Oxidative stress, DNA repair, and cancer susceptibility. *Cancer Detect. Prev.*, **1990**, *14*(5), 555-561. PMID:2121341

[8] Halliwell, B. Biochemistry of oxidative stress. *Biochem. Soc. Trans.*, **2007**, *35*(Pt 5), 1147-1150. http://dx.doi.org/10.1042/BST0351147

[9] Davies, K.J. Oxidative stress: the paradox of aerobic life. *Biochem. Soc. Symp.*, **1995**, *61*, 1-31. PMID: 8660387

[10] Berg, D.; Youdim, M.B.; Riederer, P. Redox imbalance. *Cell Tissue Res.*, **2004**, *318*(1), 201-213. PMID: 15365815

[11] Kohen, R.; Nyska, A. Oxidation of biological systems: oxidative stress phenomena, antioxidants, redox reactions, and methods for their quantification. *Toxicol. Pathol.*, **2002**, *30*(6), 620-650. http://dx.doi.org/10.1080/01926230290166724

[12] Halliwell, B. Phagocyte-derived reactive species: salvation or suicide? *Trends Biochem. Sci*, **2006**, *31*(9), 509-515. http://dx.doi.org/10.1016/j.tibs.2006.07.005

[13] Valko, M.; Leibfritz, D.; Moncol, J.; Cronin, M.T.; Mazur, M.; Telser, J. Free radicals and antioxidants in normal physiological functions and human disease. *Int. J. Biochem. Cell Biol.*, **2007**, *39*(1), 44-84. http://dx.doi.org/10.1016/j.biocel.2006.07.001

[14] Griendling, K.K.; Sorescu, D.; Lassegue, B.; Ushio-Fukai, M. Modulation of protein kinase activity and gene expression by reactive oxygen species and their role in vascular physiology and pathophysiology. *Arterioscler. Thromb. Vasc. Biol.*, **2000**, *20*(10), 2175-2183. http://dx.doi.org/10.1161/01.ATV.20.10.2175

[15] Konat, G.W. H2O2-induced higher order chromatin degradation: a novel mechanism of oxidative genotoxicity. *J. Biosci.*, **2003**, *28*(1), 57-60. http://dx.doi.org/10.1007/BF02970132

[16] Lockwood, T.D. Redox control of protein degradation. *Antioxid. Redox Signal*, **2000**, *2*(4), 851-878. http://dx.doi.org/10.1089/ars.2000.2.4-851

[17] Stadtman, E.R.; Levine, R.L. Free radical-mediated oxidation of free amino acids and amino acid residues in proteins. *Amino Acids*, **2003**, *25*(3-4), 207-218. http://dx.doi.org/10.1007/s00726-003-0011-2

[18] Horton, A.A.; Fairhurst, S. Lipid peroxidation and mechanisms of toxicity. *Crit. Rev. Toxicol.*, **1987**, *18*(1), 27-79. http://dx.doi.org/10.3109/10408448709089856

[19] Raha, S.; Robinson, B.H. Mitochondria, oxygen free radicals, and apoptosis. *Am. J. Med. Genet.*, **2001**, *106*(1), 62-70. http://dx.doi.org/10.1002/ajmg.1398

[20] Aksenova, M.V.; Aksenov, M.Y.; Mactutus, C.F.; Booze, R.M. Cell culture models of oxidative stress and injury in the central nervous system. *Curr. Neurovasc. Res.*, **2005**, *2*(1), 73-89. http://dx.doi.org/10.2174/1567202052773463

[21] Berk, M.; Ng, F.; Dean, O.; Dodd, S.; Bush, A.I. Glutathione: a novel treatment target in psychiatry. *Trends Pharmacol Sci*, **2008**, *29*(7), 346-351. http://dx.doi.org/10.1016/j.tips.2008.05.001

[22] Filomeni, G.; Ciriolo, M.R. Redox control of apoptosis: an update. *Antioxid. Redox Signal*, **2006**, *8*(11-12), 2187-2192. http://dx.doi.org/10.1089/ars.2006.8.2187

[23] Halliwell, B. Reactive species and antioxidants. Redox biology is a fundamental theme of aerobic life. *Plant Physiol.*, **2006**, *141*(2), 312-322. http://dx.doi.org/10.1104/pp.106.077073

[24] Greco, T.; Fiskum, G. Neuroprotection through stimulation of mitochondrial antioxidant protein expression. *J. Alzheimers Dis.*, **2010**, *20 Suppl 2*, S427-437. doi: 10.3233/JAD-2010-100519

[25] Lassmann, H.; Bruck, W.; Lucchinetti, C. Heterogeneity of multiple sclerosis pathogenesis: implications for diagnosis and therapy. *Trends Mol. Med.*, **2001**, *7*(3), 115-121. http://dx.doi.org/10.1016/S1471-4914(00)01909-2

[26] Reynolds, A.; Laurie, C.; Mosley, R.L.; Gendelman, H.E. Oxidative stress and the pathogenesis of neurodegenerative disorders. *Int. Rev. Neurobiol.*, **2007**, *82*, 297-325. http://dx.doi.org/10.1016/S0074-7742(07)82016-2

[27] Ng, F.; Berk, M.; Dean, O.; Bush, A.I. Oxidative stress in psychiatric disorders: evidence base and therapeutic implications. *Int. J. Neuropsychopharmacol.*, **2008**, *11*(6), 851-876. http://dx.doi.org/10.1017/S1461145707008401

[28] Bouayed, J.; Rammal, H.; Soulimani, R. Oxidative stress and anxiety: relationship and cellular pathways. *Oxid. Med. Cell Longev.*, **2009**, *2*(2), 63-67. http://dx.doi.org/10.4161/oxim.2.2.7944

[29] Kessler, R.C.; Chiu, W.T.; Demler, O.; Merikangas, K.R.; Walters, E.E. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Arch. Gen. Psychiatry*, **2005**, *62*(6), 617-627. http://dx.doi.org/10.1001/archpsyc.62.6.617

[30] McCord, J.M.; Fridovich, I. Superoxide dismutase: the first twenty years (1968-1988). *Free Radic. Biol. Med.*, **1988**, *5*(5-6), 363-369. http://dx.doi.org/10.1016/0891-5849(88)90109-8

[31] Chelikani, P.; Fita, I.; Loewen, P.C. Diversity of structures and properties among catalases. *Cell Mol. Life Sci.*, **2004**, *61*(2), 192-208. http://dx.doi.org/10.1007/s00018-003-3206-5

[32] Krohne-Ehrich, G.; Schirmer, R.H.; Untucht-Grau, R. Glutathione reductase from human erythrocytes. Isolation of the enzyme and sequence analysis of the redox-active peptide. *Eur. J. Biochem.*, **1977**, *80*(1), 65-71. DOI: http://dx.doi.org/10.1111/j.1432-1033.1977.tb11856.x

[33] Furukawa, S.; Fujita, T.; Shimabukuro, M.; Iwaki, M.; Yamada, Y.; Nakajima, Y.; Nakayama, O.; Makishima, M.; Matsuda, M.; Shimomura, I. Increased oxidative stress in obesity and its impact on metabolic syndrome. *J. Clin. Invest.*, **2004**, *114*(12), 1752-1761. DOI: http://dx.doi.org/10.1172/JCI200421625

[34] Poulsen, H.E.; Specht, E.; Broedbaek, K.; Henriksen, T.; Ellervik, C.; Mandrup-Poulsen, T.; Tonnesen, M.; Nielsen, P.E.; Andersen, H.U.; Weimann, A. RNA modifications by oxidation: a novel disease mechanism? *Free Radic Biol Med*, **2012**, *52*(8), 1353-1361. DOI: http://dx.doi.org/10.1016/j.freeradbiomed.2012.01.009

[35] American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders* **2000.** http://dx.doi.org/10.1007/SpringerReference_179660

[36] Hovatta, I.; Tennant, R.S.; Helton, R.; Marr, R.A.; Singer, O.; Redwine, J.M.; Ellison, J.A.; Schadt, E.E.; Verma, I.M.; Lockhart, D.J.; Barlow, C. Glyoxalase 1 and glutathione reductase 1 regulate anxiety in mice. *Nature*, **2005**, *438*(7068), 662-666. DOI: http://dx.doi.org/10.1038/nature04250

[37] Masood, A.; Nadeem, A.; Mustafa, S.J.; O'Donnell, J.M. Reversal of oxidative stress-induced anxiety by inhibition of phosphodiesterase-2 in mice. *J. Pharmacol. Exp. Ther.*, **2008**, *326*(2), 369-379. http://dx.doi.org/10.1124/jpet.108.137208

[38] Souza, C.G.; Moreira, J.D.; Siqueira, I.R.; Pereira, A.G.; Rieger, D.K.; Souza, D.O.; Souza, T.M.; Portela, L.V.; Perry, M.L. Highly palatable diet consumption increases protein oxidation in rat frontal cortex and anxiety-like behavior. *Life Sci*, **2007**, *81*(3), 198-203. DOI: http://dx.doi.org/10.1016/j.lfs.2007.05.001

[39] Bouayed, J.; Rammal, H.; Younos, C.; Soulimani, R. Positive correlation between peripheral blood granulocyte oxidative status and level of anxiety in mice. *Eur. J. Pharmacol.*, **2007**, *564*(1-3), 146-149. DOI: http://dx.doi.org/10.1212/01.WNL.0000134657.25904.0B

[40] de Oliveira, M.R.; Silvestrin, R.B.; Mello, E.S.T.; Moreira, J.C. Oxidative stress in the hippocampus, anxiety-like behavior and decreased locomotory and exploratory activity of adult rats: effects of sub acute vitamin A supplementation at therapeutic doses. *Neurotoxicology*, **2007**, *28*(6), 1191-1199. DOI: http://dx.doi.org/10.1016/j.neuro.2007.07.008

[41] Salim, S.; Asghar, M.; Chugh, G.; Taneja, M.; Xia, Z.; Saha, K. Oxidative stress: a potential recipe for anxiety, hypertension and insulin resistance. *Brain Res.*, **2010**, *1359*, 178-185. http://dx.doi.org/10.1016/j.brainres.2010.08.093

[42] Salim, S.; Sarraj, N.; Taneja, M.; Saha, K.; Tejada-Simon, M.V.; Chugh, G. Moderate treadmill exercise prevents oxidative stress-

induced anxiety-like behavior in rats. *Behav. Brain Res.*, **2010**, *208*(2), 545-552. http://dx.doi.org/10.1016/j.bbr.2009.12.039

[43] Salim, S.; Asghar, M.; Taneja, M.; Hovatta, I.; Wu, Y.L.; Saha, K.; Sarraj, N.; Hite, B. Novel role of RGS2 in regulation of antioxidant homeostasis in neuronal cells. *FEBS Lett.*, **2011**, *585*(9), 1375-1381. DOI: http://dx.doi.org/10.1212/01.wnl.0000338144.10967.2b

[44] Vollert, C.; Zagaar, M.; Hovatta, I.; Taneja, M.; Vu, A.; Dao, A.; Levine, A.; Alkadhi, K.; Salim, S. Exercise prevents sleep deprivation-associated anxiety-like behavior in rats: potential role of oxidative stress mechanisms. *Behav Brain Res*, **2011**, *224*(2), 233-240. DOI: http://dx.doi.org/10.1016/j.bbr.2011.05.010

[45] Salim, S.; Asghar, M.; Taneja, M.; Hovatta, I.; Chugh, G.; Vollert, C.; Vu, A. Potential contribution of oxidative stress and inflammation to anxiety and hypertension. *Brain Res.*, **2011**, *1404*, 63-71. DOI: http://dx.doi.org/10.1016/j.brainres.2011.06.024

[46] Patki, G.; Allam, F.H.; Atrooz, F.; Dao, A.T.; Solanki, N.; Chugh, G.; Asghar, M.; Jafri, F.; Bohat, R.; Alkadhi, K.A.; Salim, S. Grape powder intake prevents ovariectomy-induced anxiety-like behavior, memory impairment and high blood pressure in female wistar rats. *PLoS One*, **2013**, *8*(9), e74522. DOI: http://dx.doi.org/10.1371/journal.pone.0074522

[47] Chugh, G.; Asghar, M.; Patki, G.; Bohat, R.; Jafri, F.; Allam, F.; Dao, A.T.; Mowrey, C.; Alkadhi, K.; Salim, S. A high-salt diet further impairs age-associated declines in cognitive, behavioral, and cardiovascular functions in male Fischer brown norway rats. *J. Nutr.*, **2013**, *143*(9), 1406-1413. http://dx.doi.org/10.3945/jn.113.177980

[48] Allam, F.; Dao, A.T.; Chugh, G.; Bohat, R.; Jafri, F.; Patki, G.; Mowrey, C.; Asghar, M.; Alkadhi, K.A.; Salim, S. Grape powder supplementation prevents oxidative stress-induced anxiety-like behavior, memory impairment, and high blood pressure in rats. *J. Nutr.*, **2013**, *143*(6), 835-842. http://dx.doi.org/10.3945/jn.113.174649

[49] Patki, G.; Solanki, N.; Atrooz, F.; Allam, F.; Salim, S. Depression, anxiety-like behavior and memory impairment are associated with increased oxidative stress and inflammation in a rat model of social stress. *Brain Res*, **2013**. http://dx.doi.org/10.1111/j.1600-0404.2008.01019.x

[50] Klann, E.; Thiels, E. Modulation of protein kinases and protein phosphatases by reactive oxygen species: implications for hippocampal synaptic plasticity. *Prog. Neuropsychopharmacol. Biol. Psychiatry*, **1999**, *23*(3), 359-376. http://dx.doi.org/10.1016/S0278-5846(99)00002-0

[51] Serrano, F.; Klann, E. Reactive oxygen species and synaptic plasticity in the aging hippocampus. *Ageing Res. Rev.*, **2004**, *3*(4), 431-443. http://dx.doi.org/10.1016/j.arr.2004.05.002

[52] Ailing, F.; Fan, L.; Li, S.; Manji, S. Role of extracellular signal-regulated kinase signal transduction pathway in anxiety. *J Psychiatr. Res.*, **2008**, *43*(1), 55-63. http://dx.doi.org/10.1016/j.jpsychires.2008.01.018

[53] Mazzucchelli, C.; Brambilla, R. Ras-related and MAPK signalling in neuronal plasticity and memory formation. *Cell Mol. Life Sci.*, **2000**, *57*(4), 604-611. http://dx.doi.org/10.1007/PL00000722

[54] Qi, X.; Lin, W.; Li, J.; Pan, Y.; Wang, W. The depressive-like behaviors are correlated with decreased phosphorylation of mitogen-activated protein kinases in rat brain following chronic forced swim stress. *Behav. Brain Res.*, **2006**, *175*(2), 233-240. http://dx.doi.org/10.1016/j.bbr.2006.08.035

[55] Reul, J.M.; Chandramohan, Y. Epigenetic mechanisms in stress-related memory formation. *Psychoneuroendocrinology*, **2007**, *32 Suppl 1*, S21-25. http://dx.doi.org/10.1016/j.psyneuen.2007.03.016

[56] Shin, J.A.; Lee, K.E.; Kim, H.S.; Park, E.M. Acute Resveratrol Treatment Modulates Multiple Signaling Pathways in the Ischemic Brain. *Neurochem. Res.*, **2012**. http://dx.doi.org/10.1007/s11064-012-0858-2

[57] Yousuf, S.; Atif, F.; Ahmad, M.; Hoda, N.; Ishrat, T.; Khan, B.; Islam, F. Resveratrol exerts its neuroprotective effect by modulating mitochondrial dysfunctions and associated cell death during cerebral ischemia. *Brain Res*, **2009**, *1250*, 242-253. http://dx.doi.org/10.1016/j.brainres.2008.10.068

[58] Gard, P.R. Angiotensin as a target for the treatment of Alzheimer's disease, anxiety and depression. *Expert Opin. Ther. Targets*, **2004**, *8*(1), 7-14. http://dx.doi.org/10.1517/eott.8.1.7.26409

[59] Sorce, S.; Krause, K.H. NOX enzymes in the central nervous system: from signaling to disease. *Antioxid. Redox Signal*, **2009**, *11*(10), 2481-2504. PMID: 19309263

[60] Inaba, S.; Iwai, M.; Furuno, M.; Tomono, Y.; Kanno, H.; Senba, I.; Okayama, H.; Mogi, M.; Higaki, J.; Horiuchi, M. Continuous activation of renin-angiotensin system impairs cognitive function in renin/angiotensinogen transgenic mice. *Hypertension*, **2009**, *53*(2), 356-362. http://dx.doi.org/10.1161/HYPERTENSIONAHA.108.123612

[61] Andreazza, A.C.; Kapczinski, F.; Kauer-Sant'Anna, M.; Walz, J.C.; Bond, D.J.; Goncalves, C.A.; Young, L.T.; Yatham, L.N. 3-Nitrotyrosine and glutathione antioxidant system in patients in the early and late stages of bipolar disorder. *J Psychiatry Neurosci.*, **2009**, *34*(4), 263-271. http://dx.doi.org/10.1007/s00406-008-0862-3

[62] Tsaluchidu, S.; Cocchi, M.; Tonello, L.; Puri, B.K. Fatty acids and oxidative stress in psychiatric disorders. *BMC Psychiatry*, **2008**, *8 Suppl 1*, S5. http://dx.doi.org/10.1186/1471-244X-8-S1-S5

[63] Yumru, M.; Savas, H.A.; Kalenderoglu, A.; Bulut, M.; Celik, H.; Erel, O. Oxidative imbalance in bipolar disorder subtypes: a comparative study. *Prog. Neuropsychopharmacol. Biol. Psychiatry*, **2009**, *33*(6), 1070-1074. DOI: http://dx.doi.org/10.1016/j.pnpbp.2009.06.005

[64] Steckert, A.V.; Valvassori, S.S.; Moretti, M.; Dal-Pizzol, F.; Quevedo, J. Role of oxidative stress in the pathophysiology of bipolar disorder. *Neurochem. Res.*, **2010**, *35*(9), 1295-1301. DOI: http://dx.doi.org/10.1007/s11064-010-0195-2

[65] Nair, D.; Dayyat, E.A.; Zhang, S.X.; Wang, Y.; Gozal, D. Intermittent hypoxia-induced cognitive deficits are mediated by NADPH oxidase activity in a murine model of sleep apnea. *PLoS One*, **2011**, *6*(5), e19847. DOI: http://dx.doi.org/10.1371/journal.pone.0019847

[66] Schiavone, S.; Sorce, S.; Dubois-Dauphin, M.; Jaquet, V.; Colaianna, M.; Zotti, M.; Cuomo, V.; Trabace, L.; Krause, K.H. Involvement of NOX2 in the development of behavioral and pathologic alterations in isolated rats. *Biol Psychiatry*, **2009**, *66*(4), 384-392. http://dx.doi.org/10.1016/j.biopsych.2009.04.033

[67] Kessler, R.C. The effects of stressful life events on depression. *Annu. Rev. Psychol.*, **1997**, *48*, 191-214. DOI: http://dx.doi.org/10.1146/annurev.psych.48.1.191

[68] Post, R.M. Transduction of psychosocial stress into the neurobiology of recurrent affective disorder. *Am. J. Psychiatry*, **1992**, *149*(8), 999-1010.PMID: 1353322

[69] Belmaker, R.H.; Agam, G. Major depressive disorder. *N. Engl. J. Med.*, **2008**, *358*(1), 55-68. http://dx.doi.org/10.1056/NEJMra073096

[70] Maes, M.; Galecki, P.; Chang, Y.S.; Berk, M. A review on the oxidative and nitrosative stress (O&NS) pathways in major depression and their possible contribution to the (neuro) degenerative processes in that illness. *Prog. Neuropsychopharmacol. Biol. Psychiatry*, **2011**, *35*(3), 676-692. http://dx.doi.org/10.1016/j.pnpbp.2010.05.004

[71] Maes, M. An intriguing and hitherto unexplained co-occurrence: Depression and chronic fatigue syndrome are manifestations of shared inflammatory, oxidative and nitrosative (IO&NS) pathways. *Prog. Neuropsychopharmacol. Biol. Psychiatry*, **2011**, *35*(3), 784-794. http://dx.doi.org/10.1016/j.pnpbp.2010.06.023

[72] Suzuki, H.; Colasanti, M. NO: a molecule with two masks of 'NO' theatre. *Biofactors*, **2001**, *15*(2-4), 123-125. DOI: http://dx.doi.org/10.1002/biof.5520150216

[73] Dhir, A.; Kulkarni, S.K. Nitric oxide and major depression. *Nitric Oxide*, **2011**, *24*(3), 125-131. http://dx.doi.org/10.1016/j.niox.2011.02.002

[74] Gawryluk, J.W.; Wang, J.F.; Andreazza, A.C.; Shao, L.; Young, L.T. Decreased levels of glutathione, the major brain antioxidant, in post-mortem prefrontal cortex from patients with psychiatric disorders. *Int. J. Neuropsychopharmacol.*, **2011**, *14*(1), 123-130. DOI: http://dx.doi.org/10.1017/S1461145710000805

[75] Lee, S.Y.; Lee, S.J.; Han, C.; Patkar, A.A.; Masand, P.S.; Pae, C.U. Oxidative/nitrosative stress and antidepressants: Targets for novel antidepressants. *Prog. Neuropsychopharmacol. Biol. Psychiatry*, **2013**, *46*, 224-235. DOI: http://dx.doi.org/10.1016/j.pnpbp.2012.09.008

[76] Pae, C.U.; Yu, H.S.; Kim, T.S.; Lee, C.U.; Lee, S.J.; Jun, T.Y.; Lee, C.; Serretti, A.; Paik, I.H. Monocyte chemoattractant protein-1 (MCP1) promoter -2518 polymorphism may confer a susceptibility to major depressive disorder in the Korean population. *Psychiatry Res.*, **2004**, *127*(3), 279-281. http://dx.doi.org/10.1016/j.psychres.2004.04.004

[77] Pae, C.U.; Marks, D.M.; Han, C.; Patkar, A.A.; Steffens, D. Does neurotropin-3 have a therapeutic implication in major depression? *Int. J .Neurosci.*, **2008**, *118*(11), 1515-1522. http://dx.doi.org/10.1080/00207450802174589

[78] Behr, G.A.; Moreira, J.C.; Frey, B.N. Preclinical and clinical evidence of antioxidant effects of antidepressant agents: implications for the pathophysiology of major depressive disorder. *Oxid. Med. Cell Longev.*, **2012**, *2012*, 609421. http://dx.doi.org/10.1155/2012/609421

[79] Chung, C.P.; Schmidt, D.; Stein, C.M.; Morrow, J.D.; Salomon, R.M. Increased oxidative stress in patients with depression and its relationship to treatment. *Psychiatry Res.*, **2013**, *206*(2-3), 213-216. http://dx.doi.org/10.1016/j.psychres.2012.10.018

[80] Hoffer, A.; Osmond, H.; Smythies, J. Schizophrenia; a new approach. II. Result of a year's research. *J. Ment. Sci.*, **1954**, *100*(418), 29-45. DOI: http://dx.doi.org/10.1192/bjp.100.418.29

[81] Pandya, C.D.; Howell, K.R.; Pillai, A. Antioxidants as potential therapeutics for neuropsychiatric disorders. *Prog. Neuropsychopharmacol. Biol. Psychiatry*, **2013**, *46*, 214-223. http://dx.doi.org/10.1016/j.pnpbp.2012.10.017

[82] Singh, V.; Singh, S.P.; Chan, K. Review and meta-analysis of usage of ginkgo as an adjunct therapy in chronic schizophrenia. *Int. J. Neuropsychopharmacol.*, **2010**, *13*(2), 257-271. http://dx.doi.org/10.1017/S1461145709990654

[83] Boskovic, M.; Vovk, T.; Kores Plesnicar, B.; Grabnar, I. Oxidative stress in schizophrenia. *Curr. Neuropharmacol.*, **2011**, *9*(2), 301-312. DOI: http://dx.doi.org/10.2174/157015911795596595

[84] Dean, O.M.; van den Buuse, M.; Berk, M.; Copolov, D.L.; Mavros, C.; Bush, A.I. N-acetyl cysteine restores brain glutathione loss in combined 2-cyclohexene-1-one and d-amphetamine-treated rats: relevance to schizophrenia and bipolar disorder. *Neurosci. Lett.*, **2011**, *499*(3), 149-153. http://dx.doi.org/10.1016/j.neulet.2011.05.027

[85] Gama, C.S.; Salvador, M.; Andreazza, A.C.; Kapczinski, F.; Silva Belmonte-de-Abreu, P. Elevated serum superoxide dismutase and thiobarbituric acid reactive substances in schizophrenia: a study of patients treated with haloperidol or clozapine. *Prog Neuropsychopharmacol Biol Psychiatry*, **2006**, *30*(3), 512-515. http://dx.doi.org/10.1016/j.pnpbp.2005.11.009

[86] Herken, H.; Uz, E.; Ozyurt, H.; Akyol, O. Red blood cell nitric oxide levels in patients with schizophrenia. In: *Schizophr. Res*. Netherlands; **2001**; Vol. *52*, pp. 289-290. http://dx.doi.org/10.1016/S0920-9964(00)00169-9

[87] Reddy, R.; Sahebarao, M.P.; Mukherjee, S.; Murthy, J.N. Enzymes of the antioxidant defense system in chronic schizophrenic patients. *Biol. Psychiatry*, **1991**, *30*(4), 409-412. http://dx.doi.org/10.1016/0006-3223(91)90298-Z

[88] Sarandol, A.; Sarandol, E.; Eker, S.S.; Erdinc, S.; Vatansever, E.; Kirli, S. Major depressive disorder is accompanied with oxidative stress: short-term antidepressant treatment does not alter oxidative-antioxidative systems. *Hum. Psychopharmacol.*, **2007**, *22*(2), 67-73. DOI: http://dx.doi.org/10.1002/hup.829

[89] Wu, J.Q.; Kosten, T.R.; Zhang, X.Y. Free radicals, antioxidant defense systems, and schizophrenia. *Prog. Neuropsychopharmacol. Biol. Psychiatry*, **2013**, *46*, 200-206. http://dx.doi.org/10.1016/j.pnpbp.2013.02.015

[90] Yao, J.K.; Reddy, R.; McElhinny, L.G.; van Kammen, D.P. Effects of haloperidol on antioxidant defense system enzymes in schizophrenia. *J. Psychiatr. Res.*, **1998**, *32*(6), 385-391. DOI: http://dx.doi.org/10.1016/S0022-3956(98)00028-4

[91] Zhang, X.Y.; Tan, Y.L.; Zhou, D.F.; Cao, L.Y.; Wu, G.Y.; Haile, C.N.; Kosten, T.A.; Kosten, T.R. Disrupted antioxidant enzyme activity and elevated lipid peroxidation products in schizophrenic patients with tardive dyskinesia. *J. Clin. Psychiatry*, **2007**, *68*(5), 754-760. http://dx.doi.org/10.4088/JCP.v68n0513

[92] Kunz, M.; Gama, C.S.; Andreazza, A.C.; Salvador, M.; Cereser, K.M.; Gomes, F.A.; Belmonte-de-Abreu, P.S.; Berk, M.; Kapczinski, F. Elevated serum superoxide dismutase and thiobarbituric acid reactive substances in different phases of bipolar disorder and in schizophrenia. *Prog. Neuropsychopharmacol. Biol. Psychiatry*, **2008**, *32*(7), 1677-1681. http://dx.doi.org/10.1016/j.pnpbp.2008.07.001

[93] Mukerjee, S.; Mahadik, S.P.; Scheffer, R.; Correnti, E.E.; Kelkar, H. Impaired antioxidant defense at the onset of psychosis. *Schizophr. Res.*, **1996**, *19*(1), 19-26. http://dx.doi.org/10.1016/0920-9964(95)00048-8

[94] Ranjekar, P.K.; Hinge, A.; Hegde, M.V.; Ghate, M.; Kale, A.; Sitasawad, S.; Wagh, U.V.; Debsikdar, V.B.; Mahadik, S.P. Decreased antioxidant enzymes and membrane essential poly-unsaturated fatty acids in schizophrenic and bipolar mood disorder patients. *Psychiatry Res.*, **2003**, *121*(2), 109-122. DOI: http://dx.doi.org/10.1016/S0165-1781(03)00220-8

[95] Altuntas, I.; Aksoy, H.; Coskun, I.; Caykoylu, A.; Akcay, F. Erythrocyte superoxide dismutase and glutathione peroxidase activities, and malondialdehyde and reduced glutathione levels in schizophrenic patients. *Clin. Chem. Lab Med.*, **2000**, *38*(12), 1277-1281. http://dx.doi.org/10.1515/CCLM.2000.201

[96] Stoklasova, A.; Zapletalek, M.; Kudrnova, K.; Randova, Z. Glutathione peroxidase activity in the blood in chronic schizophrenia. *Sb Ved Pr Lek Fak Karlovy Univerzity Hradci Kralove Suppl*, **1986**, *29*(1-2), 103-108.PMID: 3499658

[97] Abdalla, D.S.; Monteiro, H.P.; Oliveira, J.A.; Bechara, E.J. Activities of superoxide dismutase and glutathione peroxidase in schizophrenic and manic-depressive patients. *Clin. Chem.*, **1986**, *32*(5), 805-807. PMID: 2870827

[98] Golse, B.; Debray-Ritzen, P.; Puget, K.; Michelson, A.M. Analysis of platelet superoxide dismutase 1 in the development of childhood psychoses. *Nouv Presse Med.*, **1977**, *6*(27), 2449.PMID: 896430

[99] Yao, J.K.; Reddy, R.D.; van Kammen, D.P. Human plasma glutathione peroxidase and symptom severity in schizophrenia. *Biol. Psychiatry*, **1999**, *45*(11), 1512-1515. http://dx.doi.org/10.1016/S0006-3223(98)00184-X

[100] Shinkai, T.; De Luca, V.; Zai, G.; Shaikh, S.; Matsumoto, C.; Arnold, P.D.; Hwang, R.; King, N.; Trakalo, J.; Potapova, N.; Wong, G.; Hori, H.; Wong, A.H.; Ohmori, O.; Nakamura, J.; Kennedy, J.L. No association between the Pro197Leu polymorphism in the glutathione peroxidase (GPX1) gene and schizophrenia. *Psychiatr. Genet.*, **2004**, *14*(3), 177-180. DOI: http://dx.doi.org/10.1097/00041444-200409000-00012

[101] Buckman, T.D.; Kling, A.S.; Eiduson, S.; Sutphin, M.S.; Steinberg, A. Glutathione peroxidase and CT scan abnormalities in schizophrenia. *Biol. Psychiatry*, **1987**, *22*(11), 1349-1356. http://dx.doi.org/10.1016/0006-3223(87)90069-2

[102] Buckman, T.D.; Kling, A.; Sutphin, M.S.; Steinberg, A.; Eiduson, S. Platelet glutathione peroxidase and monoamine oxidase activity in schizophrenics with CT scan abnormalities: relation to psychosocial variables. *Psychiatry Res.*, **1990**, *31*(1), 1-14. http://dx.doi.org/10.1016/0165-1781(90)90103-C

[103] Yao, J.K.; Reddy, R. Oxidative stress in schizophrenia: pathogenetic and therapeutic implications. *Antioxid. Redox Signal*, **2011**, *15*(7), 1999-2002. http://dx.doi.org/10.1089/ars.2010.3646

[104] Behrens, M.M.; Ali, S.S.; Dugan, L.L. Interleukin-6 mediates the increase in NADPH-oxidase in the ketamine model of schizophrenia. *J. Neurosci.*, **2008**, *28*(51), 13957-13966. DOI: http://dx.doi.org/10.1523/JNEUROSCI.4457-08.2008

[105] Bruce-Keller, A.J.; Gupta, S.; Parrino, T.E.; Knight, A.G.; Ebenezer, P.J.; Weidner, A.M.; LeVine, H., 3rd; Keller, J.N.; Markesbery, W.R. NOX activity is increased in mild cognitive impairment. *Antioxid. Redox Signal.*, **2010**, *12*(12), 1371-1382. http://dx.doi.org/10.1089/ars.2009.2823

[106] Do, K.Q.; Cabungcal, J.H.; Frank, A.; Steullet, P.; Cuenod, M. Redox dysregulation, neurodevelopment, and schizophrenia. *Curr. Opin. Neurobiol.*, **2009**, *19*(2), 220-230. DOI: http://dx.doi.org/10.1016/j.conb.2009.05.001

[107] Hikida, T.; Jaaro-Peled, H.; Seshadri, S.; Oishi, K.; Hookway, C.; Kong, S.; Wu, D.; Xue, R.; Andrade, M.; Tankou, S.; Mori, S.; Gallagher, M.; Ishizuka, K.; Pletnikov, M.; Kida, S.; Sawa, A. Dominant-negative DISC1 transgenic mice display schizophrenia-associated phenotypes detected by measures translatable to humans. *Proc. Natl. Acad. Sci. U. S. A.*, **2007**, *104*(36), 14501-14506. DOI: http://dx.doi.org/10.1073/pnas.0704774104

[108] Johnson, A.W.; Jaaro-Peled, H.; Shahani, N.; Sedlak, T.W.; Zoubovsky, S.; Burruss, D.; Emiliani, F.; Sawa, A.; Gallagher, M. Cognitive and motivational deficits together with prefrontal oxidative stress in a mouse model for neuropsychiatric illness. *Proc. Natl. Acad. Sci. U. S. A.*, **2013**, *110*(30), 12462-12467. http://dx.doi.org/10.1073/pnas.1307925110

[109] Andreazza, A.C.; Kauer-Sant'anna, M.; Frey, B.N.; Bond, D.J.; Kapczinski, F.; Young, L.T.; Yatham, L.N. Oxidative stress markers in bipolar disorder: a meta-analysis. *J. Affect. Disord.*, **2008**, *111*(2-3), 135-144. http://dx.doi.org/10.1016/j.jad.2008.04.013

[110] Machado-Vieira, R.; Andreazza, A.C.; Viale, C.I.; Zanatto, V.; Cereser, V., Jr.; da Silva Vargas, R.; Kapczinski, F.; Portela, L.V.; Souza, D.O.; Salvador, M.; Gentil, V. Oxidative stress parameters in unmedicated and treated bipolar subjects during initial manic episode: a possible role for lithium antioxidant effects. *Neurosci. Lett.*, **2007**, *421*(1), 33-36. http://dx.doi.org/10.1016/j.neulet.2007.05.016

[111] Savas, H.A.; Gergerlioglu, H.S.; Armutcu, F.; Herken, H.; Yilmaz, H.R.; Kocoglu, E.; Selek, S.; Tutkun, H.; Zoroglu, S.S.; Akyol, O. Elevated serum nitric oxide and superoxide dismutase in euthymic bipolar patients: impact of past episodes. *World J. Biol. Psychiatry*, **2006**, *7*(1), 51-55. http://dx.doi.org/10.1080/15622970510029993

[112] Magalhaes, P.V.; Dean, O.M.; Bush, A.I.; Copolov, D.L.; Malhi, G.S.; Kohlmann, K.; Jeavons, S.; Schapkaitz, I.; Anderson-Hunt, M.; Berk, M. N-acetylcysteine for major depressive episodes in bipolar disorder. *Rev. Bras. Psiquiatr.*, **2011**, *33*(4), 374-378. DOI: http://dx.doi.org/10.1590/S1516-44462011000400011

[113] Sarris, J.; Mischoulon, D.; Schweitzer, I. Adjunctive nutraceuticals with standard pharmacotherapies in bipolar disorder: a systematic review of clinical trials. *Bipolar Disord.*, **2011**, *13*(5-6), 454-465. http://dx.doi.org/10.1111/j.1399-5618.2011.00945.x

[114] Berk, M.; Dean, O.; Cotton, S.M.; Gama, C.S.; Kapczinski, F.; Fernandes, B.S.; Kohlmann, K.; Jeavons, S.; Hewitt, K.; Allwang, C.; Cobb, H.; Bush, A.I.; Schapkaitz, I.; Dodd, S.; Malhi, G.S. The efficacy of N-acetylcysteine as an adjunctive treatment in bipolar depression: an open label trial. *J. Affect. Disord.*, **2011**, *135*(1-3), 389-394. http://dx.doi.org/10.1016/j.jad.2011.06.005

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