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Review article

Oxidative stress as an etiological factor and a potential treatment target of psychiatric disorders. Part 2. Depression, anxiety, schizophrenia and autism

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ABSTRACT

The pathophysiology of psychiatric diseases, including depression, anxiety, schizophrenia and autism, is far from being fully elucidated. In recent years, a potential role of the oxidative stress has been highlighted in the pathogenesis of neuropsychiatric disorders. A body of clinical and preclinical evidence indicates that psychiatric diseases are characterized by higher levels of oxidative biomarkers and with lower levels of antioxidant defense biomarkers in the brain and peripheral tissues. In this article, we review current knowledge on the role of the oxidative stress in psychiatric diseases, based on clinical trials and animal studies, in addition, we analyze the effects of drug-induced modulation of oxidative balance and explore pharmacotherapeutic strategies for oxidative stress reduction.

Contents

Abbreviations: CAT, catalase; GABA, γ-aminobutyric acid; GSH, glutathione; GSH-Px, glutathione peroxidase; GSH-R, glutathione reductase; MDA, malondialdehyde; NO, nitrite oxide; OSI, oxidative stress index; ROS, reactive oxygen species; SOD, superoxide dismutase; SSRI, selective serotonin reuptake inhibitors; TAC, total antioxidant capacity; TBARS, thiobarbituric acid reactive substances; TOS, total oxidant status; XO, xanthine oxidase.

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Introduction

Oxidative stress occurs when reactive oxygen species (ROS) generation exceeds the antioxidant capacity of cells (see Part 1). This state provokes different kinds of oxidative damage of cellular components and leads to several disorders, including psychiatric diseases. A body of clinical and preclinical evidence indicates that in psychiatric diseases production of ROS prevails over the brain defense systems. Oxidative damage may play a crucial role in the pathophysiology of certain neuropsychiatric diseases, including depression, anxiety, schizophrenia and autism.

The present review summarizes the current knowledge on the role of oxidative stress in psychiatric diseases, based on clinical trials and animal studies, in addition, we analyze the effects of drug-induced modulation of oxidative balance and explore novel therapeutic strategies for oxidative stress reduction.

Psychiatric disorders

Depression

Depression, as one of the major lifestyle diseases of the twenty-first century, is a serious therapeutic problem in modern pharmacotherapy. According to DSM-V, depressive disorders are characterized by "the presence of sad, empty, or irritable mood, accompanied by somatic and cognitive changes that significantly affect the individual's capacity to function" [1]. Despite many preclinical and clinical studies on this brain disorder, the pathophysiology of depression is far from being fully elucidated. One of the newest attempts to explain the etiology of the disease is the hypothesis of oxidative stress [2].

Clinical studies

Oxidative biomarkers. A body of clinical evidence indicates that depression is characterized by a higher oxidant status. In fact, total oxidant status (TOS) and oxidative stress index (OSI) were increased in depressed patients as compared to normal controls in plasma [3,4] and serum [5,6]. Some studies demonstrated higher levels of plasma peroxides [7] and serum nitric oxide (NO) [5,6,8–10] in depressed patients, while Ozcan and co-workers reported lowered levels of NO in depressed patients in the pre-treatment period [11]. Plasma NO levels were also higher in suicidal depressed patients compared to non-suicidal depressed patients or control subjects [12]. In depression, xanthine oxidase (XO) levels were higher in clinical studies [10] as well as in *postmortem* studies which showed XO level increase in the thalamus and putamen [13].

In depressed patients, markers of lipid peroxidation were increased [5,6,11,14–18], especially during depressive episodes [3], while elevated levels of isoprostanes were present in urine [19,20], serum [21] and plasma [17]. Oxidative DNA damage was detected in serum [5,6,16,22], leukocytes [23] and urine [24], while higher protein peroxidation was seen in plasma [25] of depressed patients.

In *postmortem* analyses, the levels of lipid peroxidation was increased in the anterior cingulate cortex [26], while protein oxidation was higher in the prefrontal cortex of patients diagnosed with bipolar disorder [27]. Oxidative damage of RNA (rather than to DNA) was elevated in several regions (CA1, CA3 and dentate gyrus regions) of the hippocampus among patients with either bipolar disorder or major depressive disorder [28].

Antioxidant defense biomarkers. There are several lines of evidence indicating that antioxidant mechanisms are disturbed during depression, namely total antioxidant capacity (TAC) [3,4,6,29], non-enzymatic antioxidant molecules [glutathione (GSH) [30], coenzyme Q10 [31], alpha-tocopherol [32] and ascorbic acid [14]] fall, while enzymatic antioxidants, like glutathione peroxidase (GSH-Px) [11,30], catalase (CAT) [5,11], and superoxide dismutase (SOD) [5,6,8,10] show a trend to fall in depressed patients. This conclusion appears to be questioned by some reports, which indicated a rise of activities of glutathione reductase (GSH-R) [25,30] and GSH-S-transferase [25] in the late stage of the illness, without alteration in GSH-Px activity [3,25]. Similarly, higher levels of SOD activities were also found in serum and erythrocytes of depressed patients [14–16,18,30].

In *postmortem* studies of depressed patients, the concentration of SOD was found to be increased in the prefrontal cortex, but not in the hippocampus [2]. An increase in antioxidant defense biomarkers can be considered as a compensatory response to oxidative stress.

Modulation of oxidative balance by antidepressant drugs. As mentioned above, oxidative stress is enhanced during depression, while antidepressant treatments are connected with manipulation of biomarkers of oxidative damage. In fact, several studies revealed the normalization of GSH-Px activity after sub-chronic treatment with antidepressants [11], while 3-month antidepressant treatment let to reduction in TOS and OSI, and increases in TAC [29]. NO levels significantly decreased and normalized whereas SOD activity significantly increased but did not reach the control levels on the 30th day of antidepressants treatment [8]. After 8 weeks of antidepressants treatment, decreased SOD activities and increased NO and XO levels were normalized [10]. However, Sarandol and co-workers [15] indicated that oxidant-antioxidant system did not seem to be affected by 6 weeks of antidepressant treatment. After a 3-month treatment with selective serotonin reuptake inhibitors (SSRI), antioxidant enzyme activities and lipid peroxidation level in blood were decreased to normal levels [18]. Treatment with milnacipran, but not with paroxetine, increased the plasma NO levels by 4th and 8th week [9]. After 3 months of fluoxetine treatment, the examined parameters did not change significantly [3], but in the combined therapy with acetylsalicylic acid a decrease in the activity of SOD, CAT, GSH-Px, and malondialdehyde (MDA) concentration was reported [33]. An increase of the serum SOD activity and MDA levels was reversed after treatment with fluoxetine and citalopram [14].

Pharmacotherapeutic strategy to reduce oxidative stress. Human studies provide evidence that some antioxidants show antidepressant effect and potentiate the antidepressant therapy. Several clinical trials supported the usefulness of omega-3 acids (polyunsaturated fatty acids) [34] or N-acetylcysteine (a mucolytic drug) [35–39] in depressed patients.

Conclusions. Oxidative stress seems to be an important factor contributing to the pathogenesis of depression. However, based on the literature data it is still difficult to unequivocally

conclude if the oxidative stress is one of the causes or the effect of this illness.

Animal studies

Oxidative biomarkers. Animal studies indicate a general down-regulation of antioxidant defense leading to tissue damage of different kinds (Table 1). Lipid [40–57] and protein [40,41,43,51, 52,58] peroxidation was raised in several preclinical models of depression, while chronic restraint stress was accompanied by DNA damage [59] (Table 1).

Antioxidant defense biomarkers. In preclinical models of depression, the levels of non-enzymatic antioxidants and antioxidant enzymes were reduced (Table 1). Based on the animal models of depression, it was shown that the concentration of non-enzymatic antioxidants: GSH [44–46,48–57,60], vitamin A, C and E [42,45,58] was reduced. As for the enzymes, the activity of GSH-Px [45,46,54–57], GSH-R [44,52] and GSH-S-transferase [52] was found to be decreased. A reduction of the TAC was seen in the cerebellum and nucleus accumbens in the bulbectomized rats, while an increase of this parameter was observed in the prefrontal cortex [61]. Lowered SOD activity was seen in several animal models [40,41,44,47–49,51,52,54–57,61,62], and its down-regulation seemed to be a general mechanism caused by exposure to chronic stress (see also [58,60]). The CAT activity either decreased following sleep deprivation [41,48,49,51–53,62] or increased [40,58] (Table 1).

Modulation of oxidative balance by antidepressant drugs. There is a compelling evidence that antidepressants possess antioxidant effects in animal models of depression (Table 2). A decrease in raised lipid and protein peroxidation was seen after treatment with imipramine [63,64], desipramine [64], citalopram [64], escitalopram [45], fluoxetine [51,63], venlafaxine [46,63] and tianeptine [62]. Chronic treatment with imipramine also evoked a rise of TAC [61] and lipid hydroperoxide [60]. A recovery of depleted GSH levels was seen after treatment with imipramine [63,64], desipramine [53,64], citalopram [53,64], escitalopram [45], fluoxetine [51,63] and venlafaxine [46,63]. Antidepressants with different mechanisms of actions evoked a recovery in the activities of SOD [51,61–63], CAT [51,53,62–64], GSH-Px [45,46], GSH-S-transferase and GSH-R [51,63] (Table 2). So, antidepressant drugs normalize the oxidant/antioxidant balance in the brain.

Pharmacotherapeutic strategy to reduce oxidative stress. Some antioxidants showed antidepressant activity and normalized altered markers of oxidative stress. Based on preclinical studies, treatment with N-acetylcysteine [43,61], sesamol (an antioxidant) [48], melatonin (a hormone, antioxidant) [54,56,57], and coenzyme Q10 (a vitamin-like substance) [59] resulted in amelioration of oxidant/antioxidant balance.

Conclusions. Based on the preclinical studies it seems that dysregulation in the oxidative balance is implicated in the pathogenesis of depression, but the oxidative status seems to depend on the particular animal model of depression.

Anxiety

Anxiety disorders include disorders that share features of excessive fear (the emotional response to real or perceived imminent threat) and anxiety (anticipation of feature threat) as well as related behavioral disturbances [1]. Anxiety is implicated in several disorders, such as depression, panic, phobias, generalized anxiety disorder, obsessive-compulsive disorder and post-traumatic stress disorder. Predominantly, pathogenesis of anxiety has focused on GABA-ergic and serotoninergic system. Several findings highlight the significance of oxidative stress to mediate the pathogenesis of anxiety disorders.

Clinical studies

Oxidative biomarkers. Clinical trials documented a raised lipid peroxidation in patients with social phobia [65], panic disorder [66] and obsessive compulsive disorder [67,68], while MDA levels in patients suffering from post-traumatic stress disorder did not differ compared to the control group [69].

Antioxidant defense biomarkers. Several clinical trials have documented elevated activities of antioxidant enzymes, such as SOD in patients with social phobia [65], panic disorder [66] and obsessive compulsive disorder [67,68], GSH-Px in patients with social phobia [65], obsessive compulsive disorder [68], and panic disorder [66], and CAT in patients with social phobia [65], *vs.* control group. In contrast to these results, the activities of CAT and GSH-Px were reduced in patients with obsessive compulsive disorder [67], what may be linked with high levels of ROS generation. A separate report showed no changes in GSH-Px, SOD, and CAT activities in post-traumatic stress disorder [69].

Modulation of oxidative balance by anxiolytic drugs. No data.

Pharmacotherapeutic strategy to reduce oxidative stress. It was indicated that N-acetylcysteine possessed anxiolytic effects in an adolescent with SSRI-resistant anxiety [70].

Conclusion. Length and heterogeneity of the anxiety disorders cause that the changes in the markers of oxidative stress in humans are inconsistent.

Animal studies

Oxidative biomarkers. A body of preclinical studies indicates a link between oxidative stress and anxiety-related behavior in mice [71] and rats [72]. The raised ROS accumulation in peripheral leucocytes and neurons was seen in anxious mice, which was selected in the light/dark choice test from the population of male Swiss albino mice [71,73]. Treatment with L-buthionine-(S,R)-sulfoximine, an inducer of oxidative stress by depleting GSH, caused anxiety-like behavioral effect and it was connected with the reduction of antioxidant defense biomarkers [72,74] (Table 1). Interestingly, it was shown that vitamin A supplementation [75] or vitamin E deficiency [76] evoked anxiogenic-like behavior, induced oxidative stress and increased lipid and protein peroxidation in the adult rat hippocampus [75]. It was also observed that accumulation of the oxidative damage in mice during development induced anxiety-like behavior, while mice with a deletion of the p66(Shc) gene showed reduced oxidative stress and decreased anxiety-related behavior [77].

Antioxidant defense biomarkers. Changes in the principal cellular enzymatic antioxidant system (increased SOD activity and decreased CAT activity) were observed in the adult rat hippocampus after vitamin A supplementation [75]. In mice, local over-expression of glyoxalase 1 and GSH-R genes in the cingulate cortex, was highly correlated with anxiety-related phenotypes, while local inhibition of glyoxalase 1 expression decreased the anxiety-like behavior [78]. Furthermore, in line with a low-anxiety-related behavioral phenotype, glyoxalase 1 protein was abundantly expressed in several brain areas and red blood cells [79].

Table 1
Oxidative and antioxidant defense biomarkers in animal studies.

Disease	Animal model	Oxidative biomarkers	Antioxidant defense biomarkers	References
Depression	Chronic mild stress	↑ lipid peroxidation (cortex, plasma)	↓ GSH (cortex) ↓ GSH-Px (cortex) ↓ vitamin C (cortex)	[45]
		↑ lipid peroxidation (brain, medulla and erythrocytes)	↓GSH (medulla) ↓GSH-Px (cortex) ↓ vitamin C (cortex)	[46]
		↑ lipid peroxidation (cerebellum, striatum) ↑ protein peroxidation (prefrontal cortex, hippocampus, cortex, striatum)	↓SOD (prefrontal cortex, hippocampus, striatum) ↑ CAT (hippocampus, cortex, striatum, cerebellum)	[40]
		↑ lipid peroxidation (cortex)	↓ SOD (prefrontal cortex, hippocampus, striatum)	[47]
		↑ lipid peroxidation (hippocampus)	↓ GSH (hippocampus) ↓ GSH-R (hippocampus) ↓ SOD (hippocampus)	[44]
		↑ lipid peroxidation (hippocampus, amygdala) ↑ protein peroxidation (prefrontal cortex)	–	[43]
		–	↓ SOD (prefrontal cortex, hippocampus, amygdala, nucleus accumbens) ↓ CAT (nucleus accumbens)	[62]
		↑ lipid peroxidation (cortex) ↑ protein peroxidation (prefrontal cortex, amygdala)	↓ SOD (prefrontal cortex, hippocampus) ↓ CAT (prefrontal cortex, hippocampus)	[41]
		↑ lipid peroxidation (cortex)	↓ vitamin A, C and E (cortex)	[42]
		↑ protein peroxidation (hippocampus, cortex)	↓ vitamin C (plasma) ↑ SOD (cortex) ↑ CAT (hippocampus, cortex)	[58]
		↑ lipid hydroperoxide (hippocampus)	↓ GSH (hippocampus) ↑ SOD (hippocampus)	[60]
	Chronic unpredictable stress	↑ lipid peroxidation (liver)	↓ GSH (liver) ↓ SOD (liver) ↓ CAT (brain)	[49]
		↑ lipid peroxidation (brain)	↓ GSH (brain) ↓ SOD (brain) ↓ CAT (brain)	[48]
	Restraint stress	↑ lipid peroxidation (plasma)	↓ GSH (plasma)	[50]
		↑ lipid peroxidation (brain, liver)	↓ GSH (brain, liver) ↓ SOD (brain, liver, serum) ↓ CAT (brain, liver, serum) ↓ GSH-S-transferase (brain, liver) ↓ GSH-R (brain, liver)	[51]
		↑ lipid peroxidation (brain, liver, heart) ↑ protein peroxidation (brain, liver, heart)	↓ GSH (brain, liver, heart) ↓ SOD (brain, liver, heart) ↓ CAT (brain, liver, heart) ↓ GSH-S-transferase (brain, liver, heart) ↓ GSH-R (brain, liver, heart)	[52]
		↑ lipid peroxidation (brain) ↑ protein peroxidation (brain)	↓ GSH (brain) ↓ SOD (brain) ↓ CAT (brain) ↓ GSH-S-transferase (brain) ↓ GSH-R (brain)	[63]
		↑ DNA damage (hippocampus)	–	[59]
	Sleep deprivation	↑ lipid peroxidation (brain)	↓ GSH (brain) ↓ CAT (brain)	[53]
	Olfactory bulbectomy	↑ lipid peroxidation (brain)	↓ GSH (brain) ↓ GSH-Px (brain) ↓ SOD (brain)	[54–57]
			↓ TAC (nucleus accumbens, cerebellum) ↑ TAC (prefrontal cortex) ↓ SOD (frontal cortex, hippocampus, dorsal striatum, cerebellum)	[61]
Anxiety	Anxious mice (Swiss albino male mice)	↑ ROS accumulation (neurons of cerebral cortex, cerebellum and hippocampus, glial cells of cerebellum and hippocampus, lymphocytes, monocytes, granulocytes)	–	[71]
	Anxious mice (Swiss albino male mice)	↑ ROS accumulation (lymphocytes, monocytes, granulocytes)	–	[73]
	L-buthionine-(S,R)-sulfoximine treatment to mice	↑ lipid peroxidation (hypothalamus) ↑ ROS (cultured neurons) ↑ superoxide (cultured neurons)	↓ TAC (hypothalamus, amygdala)	[74]
	L-buthionine-(S,R)-sulfoximine treatment to rats	↑ lipid peroxidation (hippocampus, amygdala) ↑ protein peroxidation (hippocampus, amygdala, locus coeruleus)	↓ GSH (hippocampus, amygdala)	[72]

Table 1 (*Continued*)

Disease	Animal model	Oxidative biomarkers	Antioxidant defense biomarkers	References
Schizophrenia	Perinatal phencyclidine administration to rats	↑ lipid peroxidation (hippocampus, thalamus)	↓ GSH (hippocampus, caudate nucleus, frontal cortex) ↓ GSH-Px (hippocampus) ↑ GSH-Px (frontal cortex) ↓ GSH-R (hippocampus, frontal cortex, thalamus) ↓ SOD (frontal cortex)	[124]
	Ketamine-induced schizophrenia to mice	↑ lipid peroxidation (brain)	–	[125]
	Ketamine-induced schizophrenia to mice	↑ superoxide (prefrontal cortex)	–	[127]
	Ketamine-induced schizophrenia to rats	↑ lipid peroxidation (cerebellum, prefrontal cortex, hippocampus, striatum, cortex) ↑ protein peroxidation (striatum, hippocampus)	↓SOD (cerebellum, prefrontal cortex, hippocampus) ↓CAT (cerebellum, prefrontal cortex, hippocampus)	[126]
	G72/G30 transgenic schizophrenia mice	↑ lipid peroxidation (brain)	↓GSH (brain)	[128]
	G72/G30 transgenic schizophrenia mice	–	↓CAT (cerebellum)	[131]
	Social isolation/Ppp1r2-Cre/fGluN1 knockout mice	↑ ROS production (medial prefrontal cortex, S1 cortex)	–	[129]
	Gclc knockout mice	–	↓GSH (plasma, liver, pancreas, kidney, erythrocytes)	[130]
Autism	Neuroligin-deficient mutants of Caenorhabditis elegans	↑ protein peroxidation ↑ basal oxidative stress	–	[162]
	Intraventricular infusions of propionic acid	↑ lipid peroxidation (cortex, thalamus, striatum) ↑ protein peroxidation (cortex, hippocampus, thalamus, striatum)	↓ CAT (hippocampus, striatum, cerebellum) ↓ GSH (cortex) ↓ GSH-S-transferase (cortex, thalamus, striatum, cerebellum, brain stem)	[163]
	Post-natal exposure to valproic acid in BALB/c mice	↑ lipid peroxidation (brain) ↑ nitrite levels (brain)	↓GSH (brain)	[164]
	Fragile X syndrome in mice	–	↓SOD (total brain, hippocampus, cerebellum, embryos)	[165]

CAT – catalase; GSH – glutathione; GSH-Px – glutathione peroxidase; GSH-R – glutathione reductase; ROS – reactive oxygen species; SOD – superoxide dismutase; TAC – total antioxidant capacity.

Modulation of oxidative balance by anxiolytic drugs. A reduction in nitrite concentration in the brain was characteristic for alprazolam [80,81], zolpidem [82] and buspiron [83] exposures. A decrease in the raised lipid peroxidation was seen following diazepam [84–86], alprazolam [80,81], zolpidem [82] or buspiron [83]. Some anxiolytics (diazepam, alprazolam, zolpidem, buspiron) brought a recovery of depleted GSH levels [80–83], and SOD [84] and CAT [80–83] activities, while the GSH-R activity was still reduced [86] (Table 2).

Pharmacotherapeutic strategy to reduce oxidative stress. Some reports have indicated that compounds with antioxidant activity (e.g., tempol (an antioxidant) [72], sesamol [83], N-acetylcysteine [87,88]) possess anxiolytic effects in rodents.

Conclusion. On the whole, the evidence from preclinical studies points to the increased oxidative stress as a molecular underpinning for development of anxiety.

Schizophrenia

Schizophrenia is a chronic mental disorder which affects about 1% of world population that develops progressively. Schizophrenia spectrum is defined by "abnormalities in one or more of the following five domains: delusions, hallucinations, disorganized thinking (speech), grossly disorganized or abnormal motor behavior (including catatonia), and negative symptoms" [1]. The evidence points to genetic, environmental factors and ROS as molecular basis for the development of schizophrenic diseases.

Clinical studies

Oxidative biomarkers. Clinical trials demonstrated increased total plasma peroxide [89] and serum NO levels in schizophrenic patients [90]. The increased levels of plasma MDA [89,91–94], thiobarbituric acid reactive substances (TBARS) [95] and isoprostanes in urine [95], higher levels of 3-nitrotyrosine in plasma [96] and increased DNA [97,98] and RNA damage [98] were also observed.

Postmortem studies on brains of schizophrenic patients showed oxidative damage to RNA rather than to DNA in hippocampal neurons [28], a rise in NO levels in the caudate region of brain [99] or decreased activity of XO in the occipital cortex and thalamus. The latter findings suggest a fall of local cellular defense mechanisms in schizophrenia [100].

Antioxidant defense biomarkers. In schizophrenic patients, GSH level in plasma [96], in the cerebral spinal fluid, prefrontal cortex [101] and frontal cortex [102] was found to be reduced. Some clinical trials also linked with decreased levels of vitamin E and α-tocopherol [103] with this disorder. It should be underlined that among the schizophrenic patients, the activities of the antioxidant enzymes are not always consistent. In fact, the SOD activity either increased [91,92,94,104], decreased [93,105,106] or did not change [107], the CAT levels or GSH-Px activity either increased [108] or decreased [93,109], while the GSH-Px activity either increased [108] or decreased [93]. These differences can be evoked by different severity of clinical symptoms or duration of the schizophrenia. The study using magnetic resonance spectrometry showed either a fall of GSH in the cerebrospinal fluid and medial

Table 2
Drug modulation of oxidative balance in animal studies.

Disease	Animal/Model/Procedure	Oxidative/Antioxidative biomarkers	Drug (dose, treatment, route)	Change	References
Depression	Wistar rats/chronic mild stress	- ↑ lipid peroxidation (cortex, plasma) - ↓ GSH (cortex) - ↓ GSH-Px (cortex) - ↓ vitamin C (cortex)	Escitalopram (10 mg/kg; 28 days; *po*)	Reversed except ↓ vitamin C	[45]
	Wistar rats/chronic mild stress	- ↑ lipid peroxidation (brain, medulla, erythrocytes) - ↓GSH (medulla) - ↓GSH-Px (cortex) - ↓vitamin C (cortex)	Venlafaxin (20 mg/kg; 28 days; *po*)	Reversed except ↓ vitamin C	[46]
	Swiss Albino rats/restraint stress	- ↑ lipid peroxidation (brain, liver) - ↓GSH (brain, liver) - ↓SOD (brain, liver, serum) - ↓CAT (brain, liver, serum) - ↓GSH-S-transferase (brain, liver) - ↓GSH-R (brain, liver)	Fluoxetine (20 mg/kg; 21 days; *po*)	Reversed	[51]
	Mice/sleep deprivation	- ↑ lipid peroxidation (brain) - ↑ nitrite (brain) - ↓ GSH (brain) - ↓ CAT (brain)	Desipramine (10–20 mg/kg; 5 days; *ip*) Citalopram (5–10 mg/kg; 5 days; *ip*)	Reversed ↓ GSH and CAT	[53]
	Albino mice/chronic fatigue syndrome	- ↑ lipid peroxidation (brain) - ↑ nitrite (brain) - ↓ GSH (brain) - ↓ CAT (brain)	Imipramine (10–20 mg/kg; 7 days; *ip*) Desipramine (10–20 mg/kg; 7 days; *ip*) Citalopram (5–10 mg/kg; 7 days; *ip*)	Reversed	[64]
	Swiss Albino rats/restraint stress	- ↑ lipid peroxidation (brain) - ↑ protein peroxidation (brain) - ↓GSH (brain) - ↓SOD (brain) - ↓CAT (brain) - ↓GSH-S-transferase (brain) - ↓GSH-R (brain)	Imipramine (10 mg/kg; 21 days; *po*) Fluoxetine (20 mg/kg; 21 days; *po*) Venlafaxine (10 mg/kg; 21 days; *po*)	Reversed	[63]
	Wistar rats/chronic mild stress	- ↓SOD (prefrontal cortex, hippocampus, amygdala, nucleus accumbens) - ↓CAT (nucleus accumbens)	Tianeptine (15 mg/kg; 7 days; *ip*)	Reversed – ↓ MDA levels (hippocampus) – non-stressed rats	[62]
	Wistar rats/olfactory bulbectomy	- ↓ TAC (nucleus accumbens, cerebellum) - ↑ TAC (prefrontal cortex) - ↓ SOD (frontal cortex, hippocampus, dorsal striatum, cerebellum)	Imipramine (10 mg/kg; 14 days; *ip*)	Reversed ↓ SOD - ↑ TAC (prefrontal and frontal cortex)- control rats - ↑ TAC (frontal cortex, hippocampus and nucleus accumbens) – bulbectomized rats	[61]
	Wistar rats/chronic mild stress	- ↑ lipid hydroperoxide (hippocampus) - ↓GSH (hippocampus) - ↑ SOD (hippocampus)	Imipramine (20 mg/kg; 21 days; *ip*)	Reversed except ↓ GSH - ↑ lipid hydroperoxide (hippocampus)- non-stressed rats	[60]
Anxiety	ICR mice/acute immobilization stress	- ↑ lipid peroxidation (brain)	Diazepam (0.1–0.5 mg/kg; acute; *ip*)	Reversed	[85]
	Wistar rats	No data	Diazepam (3 mg/kg; 21 days; *ip*)	- ↓ mitochondrial (cerebrum, cerebellum and brain stem) and post-mitochondrial GSH-R activity (cerebrum) - ↓ mitochondrial TBARS (cerebrum)	[86]
	Wistar rats/restraint stress	- ↑ lipid peroxidation (striatum) - ↓ SOD activity (striatum)	Diazepam (1 mg/kg; acute; *ip*)	Reversed	[84]
	Mice (Laca strain)/acute immobilization stress	- ↑ lipid peroxidation (brain) - ↑ nitrite (brain) - ↓ GSH (brain) - ↓ CAT (brain)	Alprazolam (0.25–0.5 mg/kg; acute; *ip*)	Reversed	[80]
	Mice/sleep deprivation	- ↑ lipid peroxidation (brain) - ↑ nitrite (brain) - ↓ GSH (brain) - ↓ CAT (brain)	Alprazolam (0.25–0.5 mg/kg; 5 days; *ip*)	Reversed	[81]
	Mice (Laca strain)/acute hypoxic stress	- ↑ lipid peroxidation (brain) - ↑ nitrite (brain) - ↓ GSH (brain) - ↓ CAT (brain)	Zolpidem (5–10 mg/kg; acute; *ip*)	Reversed	[82]
	Mice (Laca strain)/acute immobilization stress	- ↑ lipid peroxidation (brain) - ↑ nitrite (brain) - ↓ GSH (brain) - ↓ CAT (brain)	Buspiron (5–10 mg/kg; 5 days; *po*)	Reversed	[83]

Table 2 (*Continued*)

Disease	Animal/Model/Procedure	Oxidative/Antioxidative biomarkers	Drug (dose, treatment, route)	Change	References
Schizophrenia	Wistar rats	No data	Haloperidol (2 mg/kg; 45 and 90 days; *po*) Risperidone (2.5 mg/kg; 45 and 90 days; *po*) Clozapine (20 mg/kg; 45 and 90 days; *po*) Olanzapine (10 mg/kg; 45 and 90 days; *po*)	- *haloperidol*- ↓ SOD and CAT activity (brain) ↑ lipid peroxidation (brain) - *risperidone*- - - *clozapine*- - - *olanzapine*- -	[132]
	Wistar rats	No data	Haloperidol (2 mg/kg; 90 and 180 days; *po*) Chlorpromazine (10 mg/kg; 90 and 180 days; *po*) Ziprasidone (12 mg/kg; 90 and 180 days; *po*) Risperidone (2.5 mg/kg; 90 and 180 days; *po*) Clozapine (20 mg/kg; 90 and 180 days; *po*) Olanzapine (10 mg/kg; 90 and 180 days; *po*)	- *haloperidol* ↓ SOD and CAT, ↑ lipid peroxidation (brain) – 90 and 180 days - *chlorpromazine* ↑ lipid peroxidation (brain)- 180 days - *ziprasidone* ↑ lipid peroxidation (brain)- 180 days - *risperidone* ↑ lipid peroxidation (brain) – 180 days ↑ depleted SOD and ↓ raised lipid peroxidation (brain)- 90 days after 90 days of haloperidol treatment - *clozapine* ↑ lipid peroxidation (brain) – 180 days ↑ depleted SOD and ↓ raised lipid peroxidation (brain)- 90 days after 90 days of haloperidol treatment - *olanzapine* ↑ depleted SOD and ↓ raised lipid peroxidation (brain) – 90 days after 90 days of haloperidol treatment	[133]
	Wistar rats	No data	Haloperidol (1.5 mg/kg; 28 days; *ip*) Clozapine (25 mg/kg; 28 days; *ip*) Olanzapine (2.5, 5, 10 mg/kg; 28 days; *ip*) Aripiprazole (2, 10, 20 mg/kg; 28 days; *ip*)	- *haloperidol* ↓ lipid peroxidation (cerebral cortex) ↑ lipid peroxidation (striatum) ↑ protein peroxidation (hippocampus) - *clozapine* ↓ lipid peroxidation (cerebral cortex) ↑ protein peroxidation (hippocampus) - *olanzapine* ↓ lipid peroxidation (cerebral cortex, prefrontal cortex) - *aripiprazole* ↓ lipid peroxidation (cerebral cortex, prefrontal cortex) ↑ mitochondrial superoxide (prefrontal cortex, striatum) – (dose: 20 mg/kg)	[134]
Autism	No data	No data	No data.	No data	No data

CAT – catalase; GSH – glutathione; GSH-Px – glutathione peroxidase; GSH-R – glutathione reductase; MDA – malondialdehyde; SOD – superoxide dismutase; TAC – total antioxidant capacity; TBARS – thiobarbituric acid reactive substances; TOS – total oxidant status.

prefrontal cortex of non-treated patients with schizophrenia [101], a rise of GSH in the medial temporal lobe in the first episode of schizophrenia [110] or no changes in the posterior medial frontal cortex with a negative correlation between GSH levels and the severity of negative symptoms [111]. So, there is a compelling evidence that perturbation in the GSH levels is brain region-dependent and symptom-dependent in the course of the disorder.

According to *postmortem* studies on brains of schizophrenic patients, the levels of GSH in the prefrontal cortex [112] and striatum [113] were reduced. Such decreases were linked with

lowered activity of related enzymes, such as GSH-Px, GSH-R and GSH-S-transferase Mu isoform [112–114].

Modulation of oxidative balance by antipsychotic drugs. Literature reports on the effects of antipsychotics on the schizophrenia induced changes in oxidative status in patients undergoing long-term treatment, are inconsistent. In long-term clozapine-treated schizophrenic patients, SOD activity was higher, while GSH-Px activity was lower [115]. Another study demonstrated that in patients receiving second-generation antipsychotics (clozapine, quetiapine, amisulpride, and risperidone), the lipid peroxidation in blood was lower than in those treated with first-generation antipsychotics [116]. In contrast to the above studies, there were significant difference in SOD, GSH-Px and MDA levels in patients treated with clozapine, risperidone or typical antipsychotics [93]. The difference in oxidant/antioxidant markers depended on the drug used and the course of the schizophrenia. Among patients, serum lipid peroxidation was significantly higher in those on clozapine than in those on haloperidol treatment [94]. Another group of researchers found a rise in MDA levels in the patients treated with haloperidol, quetiapine, olanzapine and risperidone, a rise in specific SOD activity in the patients treated with haloperidol and quetiapine, and a fall of specific GSH-Px activity after treatment with haloperidol and risperidone [92]. To summarize, the exact effect induced by different typical or atypical antipsychotic drugs on antioxidant enzymes and lipid peroxidation levels is far from being established.

Pharmacotherapeutic strategy to reduce oxidative stress. Clinical trials demonstrated beneficial effects of N-acetylcysteine [117–121], omega-3 fatty acids [122,123] and vitamins E and C [123] in the treatment of schizophrenia. Furthermore, these studies seem to suggest that antioxidant treatment supports positive outcomes in the early stage of schizophrenia.

Conclusion. On the basis of clinical data it seems that several markers of oxidant/antioxidant status may be considered as a biological indicator of severity of the symptoms of schizophrenia or of its duration.

Animal studies

Oxidative biomarkers. In animal models of schizophrenia, perinatal phencyclidine (an NMDA receptor antagonist) administration increased the level of lipid peroxides in rats [124], while ketamine (an NMDA antagonist) injections to mice increased lipid [125,126] and protein [126] peroxidation and raised superoxide levels [127]. In genetic models, there were either increased levels of oxidized lipids in G72/G30 transgenic schizophrenic mice [128] or elevated cortical ROS production in γ-aminobutyric acid-ergic interneuron-specific NMDAR hypofunction mice (Ppp1r2-Cre/fGluN1 knockout [KO] mice) [129] (Table 1).

Antioxidant defense biomarkers. Perinatal phencyclidine or ketamine administration to rodents evoked depletion of the reduced GSH and several changes in enzymes activities [124,126] (see Table 1). In genetic models, there are several lines of evidence that oxidative stress plays a role in the pathogenesis of schizophrenia. For example, the glutamate cysteine ligase catalytic subunit (Gclc) gene knockout mice [130] and G72/G30 [128] transgenic mice were observed to show a fall of the GSH level. Additionally, a decreased CAT activity in the cerebellum (but not in plasma) was demonstrated in G72Tg mice [131] (Table 1).

Modulation of oxidative balance by antipsychotic drugs. Typical and atypical antipsychotic drugs by themselves changed the oxidant/antioxidant status in drug-naïve animals (Table 2). For instance, chronic haloperidol treatment decreased SOD and CAT activity and raised lipid peroxidation [132,133]. In another study, lipid peroxidation was reduced after haloperidol, clozapine, olanzapine or aripiprazole administration, while protein peroxidation was increased after haloperidol and clozapine treatment [134]. Long-term (up to 180 days) treatment with chlorpromazine, ziprasidone and risperidone evoked a rise of lipid peroxidation [133]. Post-treatment with several atypical antipsychotics after 90-days of haloperidol treatment significantly reversed the haloperidol-induced changes in oxidant/antioxidant biomarkers [133].

Pharmacotherapeutic strategy to reduce oxidative stress. Beneficial effects of early N-acetylcysteine treatment were shown in a mouse model with chronic GSH deficit [135,136]. In the ketamine model of schizophrenia, omega-3 fatty acids prevented damage of lipids and proteins in the rat brain [137].

Conclusions. Preclinical evidence indicates a dysregulation of the oxidative balance in animal models of schizophrenia, however, the exact role of oxidative stress in the pathogenesis of schizophrenia still remains not established. The action of antipsychotic drugs on oxidant and antioxidant defense biomarkers is inconclusive.

Autism

According to DSM-V classification "features of autism spectrum disorder are persistent impairment in reciprocal social communication and social interaction, and restricted, repetitive patterns of behavior, interests, or activities. These symptoms are present from early childhood and limit or impair everyday functioning" [1]. Genetic, environmental and immunological risk factors induce the oxidative damage, promote neuronal damage, and reduce methylation activity during synthesis of myelin basic protein, which is fundamental for development of the central nervous system [138].

Human studies

Oxidative biomarkers. Clinical trials revealed that autistic patients showed the increased MDA, isoprostane [139–143] and NO levels [142] in plasma and increased NO levels in red blood cells [144]. *Postmortem* studies demonstrated abnormal energy metabolism and evidence of oxidative stress. The levels of lipid hydroperoxides were increased and the levels of mitochondrial electron transport chain complexes were reduced in the cerebellum and cortical structures in the autistic children [145]. Brains of autistic patients contained the increased levels of lipid [146], protein [147,148] and DNA damage [147,149].

Antioxidant defense biomarkers. In clinical trials, the association between oxidative stress and autism has not been established and in some cases, literature reports present conflicting results. The SOD activity was either decreased in plasma [144] and erythrocytes [141,150] or increased in plasma [151] and in erythrocytes [152–154]. The CAT activity was reduced in erythrocytes [152,154], while did not change in plasma [153]. A bi-directional changes of the GSH-Px activity were also shown (a fall of the activity in plasma [144,150,151,155] and erythrocytes [141,150], or a rise of the activity in plasma [153]). In others clinical trials, it was shown that autistic children had lower levels of plasma the reduced GSH with higher levels of the oxidized GSH than typically developing children [156,157].

Modulation of oxidative balance by drugs. No data.

Pharmacotherapeutic strategy to reduce oxidative stress. N-acetylcysteine [158], coenzyme Q10 [159] or ascorbic acid [160] treatment

ameliorates symptoms in the autistic patients. Co-administration of N-acetylcysteine and risperidone decreased irritability in autistic patients but did not change the core symptoms of autism (hyperactivity and noncompliance, lethargy and social withdrawal, stereotypic behavior, inappropriate speech) [161].

Conclusions. It seems that antioxidant status is changed in autism what further may induce several changes in the brain. Higher levels of antioxidant enzyme activities may be evoked by a prior higher oxidative stress as a compensatory mechanism.

Animal studies

Oxidative biomarkers. In preclinical studies, various animal models of autism showed the effect of oxidative stress on the central nervous system. Neuroligin-deficient mutants of *Caenorhabditis elegans*, as a genetic model of autism, showed an increased basal level of oxidative stress with a higher level of oxidized proteins [162]. In another preclinical model of autism, induced by intraventricular infusions of propionic acid (dietary and gut bacterial fatty acid) increased lipid and protein oxidation in several brain structures [163]. Postnatal exposure to valproic acid (an anticonvulsant and mood-stabilizing drug) in BALB/c mice evoked an increase in MDA and nitrite levels [164] (Table 1).

Antioxidant defense biomarkers. It was also demonstrated that mice lacking the fragile X mental retardation protein showed a reduced SOD expression and these mice were more sensitive to oxidative stress and demonstrated behavioral characteristics of autism [165]. GSH-S-transferase M1 (a gene associated with the high risk of autism) knockout mice are sensitive to toxicants, like the valproic acid which generates oxidative stress and it is known to cause autism-like behavioral deficits [166]. Studies in an animal model of autism induced by intraventricular infusions of propionic acid demonstrated reduced antioxidant enzymatic activity [163]. Postnatal exposure to valproic acid in BALB/c mice evoked a decrease in GSH [164] (Table 1).

Modulation of oxidative balance by drugs. No data.

Pharmacotherapeutic strategy to reduce oxidative stress. No data.

Conclusions. There are several pieces of evidence from preclinical studies indicating that apart from genetic factors, chronic inflammation, mitochondrial dysfunction or metal intoxication, the oxidative stress is involved in the pathogenesis of autism. However, the exact contribution of this pathological state still awaits full elucidation.

Summary

In the last time, extensive efforts in clinical and preclinical research have provided compelling evidence demonstrating the involvement of the oxidative stress in both etiology and course of the psychiatric diseases according clinical and preclinical researches. Pharmacological interventions using antidepressant, anxiolytic or antipsychotic drugs can efficiently normalize biomarkers of the oxidant/antioxidant balance during psychiatric disorders. Additionally, consistent data underline the importance of substances with antioxidant activity (by themselves or in combined therapy) provoked positive outcomes in these diseases and could be promising therapy for the treatment many disturbances in the brain. Nevertheless, several important issues still await full elucidation and additional preclinical and clinical studies are needed to assess the exact contribution of the oxidative stress in psychiatric disorders

Conflicts of interest

The authors declare no conflicts of interest.

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