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Association of Oxidative Stress to the Genesis of Anxiety: Implications for Possible Therapeutic Interventions

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Abstract: Oxidative stress caused by reactive species, including reactive oxygen species, reactive nitrogen species, and unbound, adventitious metal ions (e.g., iron [Fe] and copper [Cu]), is an underlying cause of various neurodegenerative diseases. These reactive species are an inevitable by-product of cellular respiration or other metabolic processes that may cause the oxidation of lipids, nucleic acids, and proteins. Oxidative stress has recently been implicated in depression and anxiety-related disorders. Furthermore, the manifestation of anxiety in numerous psychiatric disorders, such as generalized anxiety disorder, depressive disorder, panic disorder, phobia, obsessive-compulsive disorder, and posttraumatic stress disorder, highlights the importance of studying the underlying biology of these disorders to gain a better understanding of the disease and to identify common biomarkers for these disorders. Most recently, the expression of glutathione reductase 1 and glyoxalase 1, which are genes involved in antioxidative metabolism, were reported to be correlated with anxiety-related phenotypes. This review focuses on direct and indirect evidence of the potential involvement of oxidative stress in the genesis of anxiety and discusses different opinions that exist in this field. Antioxidant therapeutic strategies are also discussed, highlighting the importance of oxidative stress in the etiology, incidence, progression, and prevention of psychiatric disorders.

Keywords: Antioxidant therapy, anxiety disorders, oxidative stress, toxicity.

1. OXIDATIVE STRESS AND REACTIVE SPECIES

1.1. Reactive Oxygen Species

The human brain consumes approximately 20% of basal oxygen during metabolic processes, making the central nervous system very sensitive to oxidative stress [1]. Oxygen metabolism results in the production of oxygen ions and various free radicals. Free radicals are molecules that contain one or more unpaired electrons and are extremely reactive, with life spans of less than 10^{-11} s. The radicals derived from oxygen represent the most important class of such species generated in living systems and may damage normal cellular compartments, resulting in compromised function. Apart from detrimental effects, ROS have also been shown to be beneficial and play an important role in cell signaling, the induction of mitogenic responses, immune defense mechanisms, cellular senescence, apoptosis, and the breakdown of toxic compounds [2].

Reactive oxygen species can be produced from both endogenous and exogenous sources (Scheme **1**). Endogenous sources include mitochondria, cytochrome P450 metabolism, peroxisomes, and inflammatory cell activation. The literature has shown that isolated mitochondria can generate approximately 2-3 nmol of superoxide per minute per milligram of protein [1]. Other cellular sources of superoxide radical generation include xanthine oxidase (XO), which catalyzes the reaction of hypoxanthine to xanthine and xanthine to uric acid, consequently generating superoxide anions and hydrogen peroxide [3]. Neutrophils, eosinophils, and macrophages are other potential sources of cellular reactive species production. The role of cytochrome P450, microsomes, and peroxisomes is also well-documented [4]. Notably, superoxide anions can further interact with other molecules to generate secondary ROS either directly or through enzyme- or metal-catalyzed reactions. Similarly, the auto-oxidation of small molecules, including hemoglobin and myoglobin, mitochondrial components, and oxidative enzymes (e.g., xanthine oxidase (XO), nicotinamide adenine dinucleotide phosphate [NADP-H^+] oxidase], and cyclooxygenases), and the oxidation of unsaturated fatty acids are also reported to produce ROS [5]. Hydroxyl radicals are highly reactive, with a half-life of less than 10^{-11} s in aqueous solution [6]. They are generated by a variety of mechanisms that involve ionizing radiation that causes the decomposition of H_2O_2, resulting in the formation of hydrogen atoms (H^+) and OH•, further causing significant damage to biomolecules [6].

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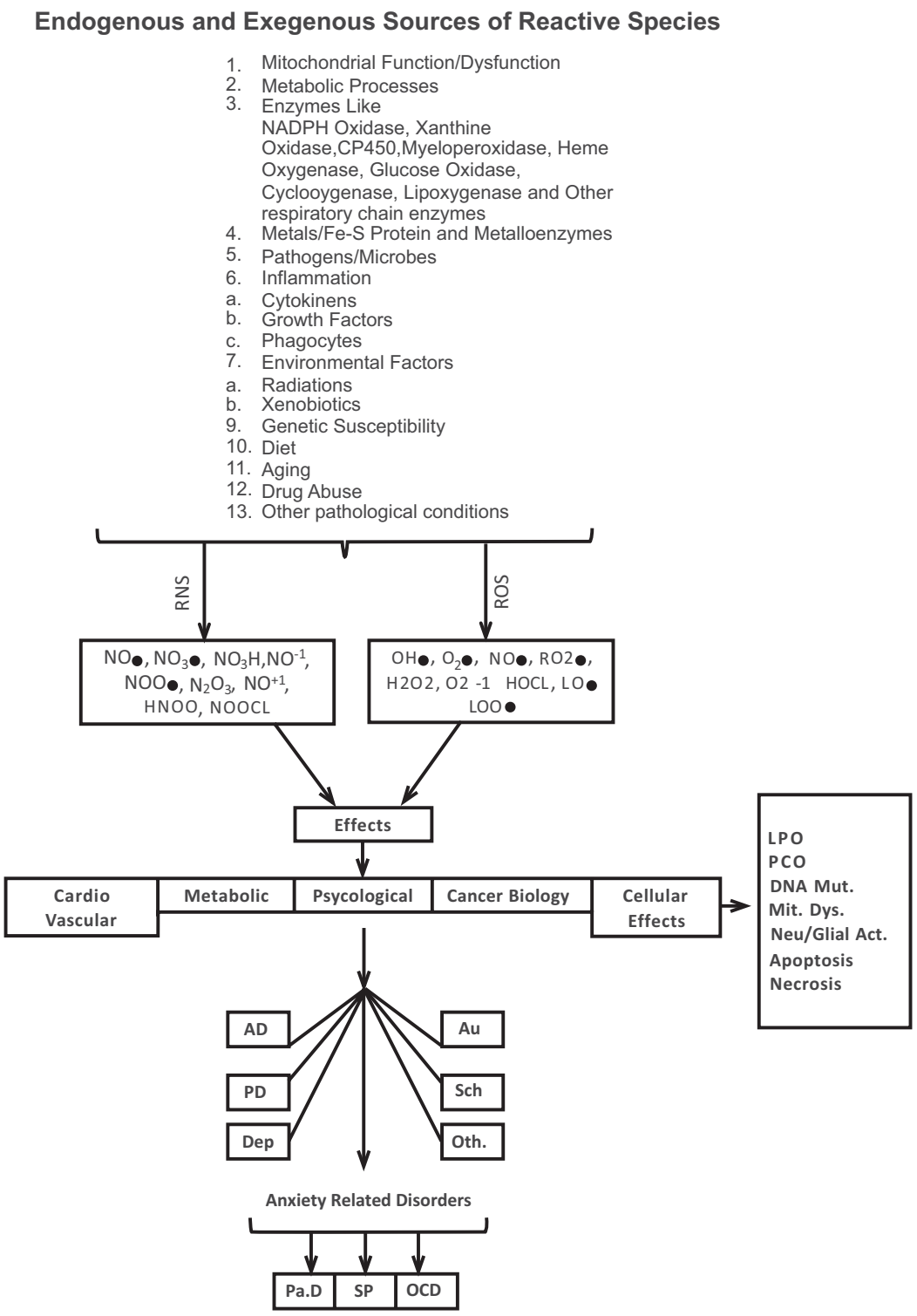


Scheme 1. Free radical production and toxic effects. AD, anxiety disorders; Au, autism; Dep, depression; DNA Mut, DNA mutation; LPO, lipid peroxidation; Mit Dys, mitochondrial dysfunction; Neu/Glia Act, neuronal or glial activation; OCD, obsessive-compulsive disorder; Oth, other disorders; Pa.D, Parkinson's disease; PCO, protein carbonylation; PD, panic disorder; RNS, reactive nitrogen species; ROS, reactive oxygen species; Sch, schizophrenia; SP, social phobia.

1.2. Reactive Nitrogen Species

Reactive nitrogen species (RNS) are also generated under normal physiological and pathological conditions (Scheme **1**). Nitric oxide (NO•) is abundant, relative to moderately reactive radicals involved in neurotransmission, blood pressure regulation, cellular defense mechanisms, smooth

muscle relaxation, and immune regulation processes [7, 8]. The nitric oxide radical (NO) is generated by specific enzymes, such as neuronal nitric oxide synthase (nNOS), inducible NOS (iNOS), and endothelial NOS (eNOS) [9]. Nitric oxide is both water- and lipid-soluble and readily diffuses through the cytoplasm and plasma membranes. It can participate in different biochemical processes to damage protein structure and function [10]. Under pathological conditions, such as inflammation, immune cells produce O^{2-} and NO, which react to produce peroxynitrite anions ($ONOO^{-1}$).

$$NO\bullet + O_2\bullet^{-1} \rightarrow ONOO^{-1} \quad [1]$$

The peroxynitrite anion ($ONOO^{-1}$) is a potent oxidizing agent that can cause DNA fragmentation and lipid peroxidation and further produce nitrosonium cations (NO^{+1}) and nitroxyl anions (NO^{-1}) [5]. Similarly, NO readily binds certain transition metal ions and may alter normal physiological functions.

$$Fe[II] + NO\bullet \rightarrow Fe[II]\text{-}NO \quad [2]$$

1.3. Free Radicals and Metals

The generation of various free radicals is closely linked to the participation of redox-active metals [11, 12], such as iron, copper, manganese, and mercury. Iron regulation has been suggested to ensure that no free intracellular iron exists. Under various conditions, however, such as excess superoxide or reduction in cellular pH, can release "free iron" from iron-containing molecules [12]. The literature has shown that the transferrin protein carries two iron ions, although it is normally only approximately one-third saturated with iron [13]. Transferrin loses its bound iron at acidic pH. The initial 10% of iron in saturated human transferrin is lost at pH 5.4, and the final 10% is lost at pH 4.3 [14]. If transferrin is bound to its receptor, then essentially all of the iron is released at pH 5.6-6.0 [15]. The released Fe[II] can participate in a chain reaction that may include the following $Fe2^{+}$-mediated basal or autoxidation reactions:

$$Fe^{2+} + O^2 \rightarrow Fe^{3+} + O_2\bullet^{-1} \quad [3]$$

The $O_2\bullet^{-1}$ that is generated can in turn react under acidic conditions to generate hydrogen peroxide and oxygen.

$$HO_2\bullet + O_2\bullet^{-1} + H^+ \rightarrow H_2O_2 + O_2 \quad [4]$$

H_2O_2 and superoxide produced in the above reactions (Schemes **3** and **4**) may react through metal catalysis (i.e., a Haber-Weiss reaction) to produce the extremely reactive hydroxyl radical, which may then extract hydrogen atoms from polyunsaturated fatty acids.

$$Fe^{2+} + O_2\bullet^{-1} + 2H^+ \rightarrow Fe^{3+} + H_2O_2 \quad [5]$$

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^{-1} + OH\bullet \quad [6]$$

Ferrous ion (Fe [II]) is the form of iron that is capable of initiating redox reactions with oxygen species. Indeed, the oxidation of Fe [II] to Fe [III] can stimulate ROS production. The possibility that Fe [III] is reduced to Fe [II] through an interaction with $O_2\bullet^{-1}$ during the early phase of lipid peroxidation under acidic conditions, perhaps *via* an intermediate, perferryl iron [10], cannot be excluded.

$$Fe^{2+} + O_2 \rightarrow Fe^{3+} + O_2\bullet^{-1} \quad [7]$$

$$Fe^{3+} + O_2\bullet^{-1} \rightarrow [Fe^{3+} — O_2\bullet^{-1} \leftrightarrow Fe^{2+} — O_2] \leftrightarrow Fe^{2+} + O_2 \quad [8]$$

In short, the majority of hydroxyl radicals generated *in vivo* are derived from the metal-catalyzed breakdown of hydrogen peroxide. We can summarize a sample Fenton reaction as the following:

$$M[n^{+}]\ [Cu^{+},\ Fe^{2+},\ Ti^{3+},\ Co^{2+}] + H_2O_2 \rightarrow M[n^{+1}] + [Cu^{2+},\ Fe^{3+},\ Ti^{4+},\ Co^{3+}] + \bullet OH + OH^{-1} \quad [9]$$

These different and diverse reactions may lead to altered physiological functions and specifically oxidative stress.

2. OXIDATIVE STRESS AND PSYCHOLOGICAL DISORDERS

The nervous system has tremendous reservoirs of polyunsaturated and saturated fatty acids that are extremely susceptible to the escalating effects of oxidative stress. The loss of membrane integrity, protein damage, neuronal dysfunction, lipid and protein oxidation, and DNA damage are some key examples of the consequences of oxidative stress. Antioxidant enzymes, such as superoxide dismutase (SOD), catalase, and glutathione peroxidase, reduce molecules or non-enzymatic antioxidants, including vitamin C, vitamin E, carotenoids, thiol antioxidants (e.g., glutathione, thioredoxin, and lipoic acid), natural flavonoids, melatonin (i.e., a hormonal product of the pineal gland), and other compounds [16, 17], constituting a defense mechanism that prevents the escalating effects of ROS. However, when ROS concentrations exceed the antioxidative capacity of an organism, the cells enter a state of oxidative stress, in which excess ROS induces oxidative damage in cellular components.

An excellent review by Andersen in 2004 [18] covered the important topic of whether oxidative stress is a primary cause or mere downstream consequence of the neuro-degenerative process. Whether molecular oxidative damage is involved in emotional neuronal circuitry is still debatable. However, the literature indicates that oxidative stress is or can be associated with different psychological disorders. The depletion of antioxidant enzymes, such as glutathione peroxidase, superoxide dismutase, catalase, glutathione reductase (*GSR1*), non-enzymatic components (e.g., free glutathione), various vitamins (e.g., vitamins A, C, and E), lipid and protein oxidation, DNA damage, and other redox alterations (e.g., selenium depletion and ceruluplasmin alterations) have been reported in various psychological disorders, including obsessive-compulsive disorder, social phobia, panic disorder, major depression, posttraumatic stress disorder, Parkinson's disease, autism, and Alzheimer's disease [19-22]. This review focuses on the possible association between oxidative stress and anxiety.

2.1. Evidence of the Link Between Anxiety and Oxidative Stress

The literature shows a link between anxiety and oxidative stress. Berry *et al.* [23] showed that pain sensitivity and emotional behavior in wildtype mice increased with age, likely because of the accumulation of oxidative damage. They demonstrated that deletion of the *p66Shc* gene resulted

in lower levels of oxidative stress, reduced pain sensitivity, and reduced anxiety-like behavior in mice. Importantly, the *p66Shc* gene is responsible for the regulation of reactive species metabolism. Desrumaux *et al*. [24] showed that vitamin E deficiency resulted in increased levels of central oxidative stress markers that in turn resulted in anxiogenic behavior without abnormalities in locomotor activity in mice. Recent studies have shown the direct involvement of oxidative stress in anxiety-like behavior in rodents [25-29].

Consistent with these findings, Salim *et al*. [27, 28] suggested the direct involvement of oxidative stress in anxiety-like behavior. Masood *et al*. [30] found that oxidative stress was induced in the hypothalamus and amygdala by L-buthionine-[*S*,*R*]-sulfoximine (BSO), an agent that produces oxidative stress by inhibiting glutathione (GSH) synthesis. These studies concluded that subchronic BSO treatment induced anxiety-like behavior in rats, which was prevented by supplementation with the antioxidant tempol. A linear relationship has also been established between peripheral blood oxidative stress markers and anxiety-like behavior in mice [25]. Rammah *et al*. [25, 31] used the elevated plus maze, a paradigm that tests anxiety-like behavior in rodents, and found that anxiety-like behavior was positively linked to oxidative status in neuronal and glial cells in the cerebellum and hippocampus, neurons in the cerebral cortex, and peripheral leucocytes (i.e., monocytes, granulocytes, and lymphocytes). Kuloglu *et al*. [32, 33] highlighted the role of oxidative stress in patients with anxiety disorders. Decreased antioxidant enzyme (i.e., SOD, GPx) levels and consequently higher lipid peroxidation were observed in subjects with obsessive-compulsive disorder and panic disorder. Similarly, Yasunari *et al*. [34] found a significant association between ROS and anxiety in hypertensive patients. Recent data have also demonstrated a positive correlation between oxidative stress markers and human aging [35] (Table **1**).

Other studies have reported the involvement of oxidative stress in bipolar disorder, schizophrenia, hypertension, and depression [19, 36-37]. Notably, although human data are more directly applicable and easily interpretable than animal data, the number of patients studied, the lack of standard controls, dietary habits, physical activity, and the possible involvement of other clinical complications may alter the overall redox status of human subjects and must be considered before any definitive conclusions can be drawn.

In 2008, we began a selective breeding program to produce two rat lines, the Carioca high-freezing (CHF) and Carioca low-freezing (CLF) lines, bred for high and low levels of defensive freezing in response to contextual cues previously associated with footshock [38]. The objective was to produce a simple and robust animal model that can be used to explore the underlying mechanisms of anxiety-related disorders. We have shown that contextual fear conditioning is a simple and accurate form of aversive learning [39] that can be used to study the mechanisms involved in pathological anxiety [40]. We obtained persuasive evidence of a clear behavioral (i.e., freezing pattern) divergence between CHF and CLF animals after only three generations [38]. We subsequently characterized these lines by examining different oxidative stress parameters. Reactive oxygen species, thiobarbituric acid reactive substance formation, GPx levels, and CAT activity were measured in different brain structures in the 12^{th} and 16^{th} generations. Consistent with our behavioral data obtained from the 3^{rd}, 7^{th}, and 9^{th} generations, CHF animals showed high levels of oxidative stress, reflected by increased ROS and lipid peroxidation and consequently decreased antioxidant enzymatic levels. Interestingly, we found that the hippocampus was the prime target of the escalating effects of ROS [41].

Our results are in strong agreement with Bonatto *et al*., Gabbita *et al*., and Serrano and Klann [42-44], who showed that the hippocampus is affected by the deleterious effects of oxidative stress. These studies are also consistent with a recent report by Allam *et al*. [45]. Butterfield *et al*. [46] showed that individuals with mild cognitive impairment exhibited increased lipid peroxidation in the hippocampus and inferior parietal lobule. The hippocampus is an important brain structure involved in contextual fear conditioning. Hippocampal lesions have been shown to disrupt freezing behavior in rats [47, 48]. Increased ROS levels and decreased antioxidant enzyme activity in the hippocampus may be expected to increase neuronal susceptibility and likely disrupt the neural circuitry involved in fear or emotional learning.

Interestingly, we also showed that gross morphological organization of the dentate gyrus, CA1, and CA3 subfields of the hippocampus in CHF rats was not different from control animals [49]. We may conclude that the observed behavioral differences, reflected by differences in freezing response and behavior in the elevated plus maze, between the high and low freezing groups cannot be explained by hippocampal injury. However, one must consider the sensitivity of the optical microscope to detect minute changes in hippocampal neuronal circuitry. Nonetheless, the involvement of hippocampal oxidative stress in CHF animals that may occur at the molecular level may play a causal role in anxiety-related disorders.

2.2. Genetic Evidence of the Association Between Oxidative Stress and Anxiety: Role of Methylglyoxal and Glyoxalase I in Anxiety

The mouse *GLO1* gene encodes the 21 kDa, 184-amino-acid enzyme glyoxalase I (*GLO1*). It is found as a dimer in the cytosol of cells. Its physiological function is to detoxify dicarbonyl metabolites, mostly methylglyoxal (MG), glyoxal and other low-molecular-weight acyclic α-oxoaldehydes. Genetic studies established the possible role of *GLO1* in various neuropsychological disorders. Depression [50], schizophrenia [51, 52], panic disorder [53], autism [54, 55], and restless legs syndrome (RLS) [56-59] have been linked to *GLO1* expression. This review focuses on the role of *GLO1* and MG in anxiety-related disorders (Table **2**).

Hovatta *et al*. [60] identified a close relationship between antioxidative defense mechanisms and anxiety-related phenotypes using genetically inbred [6] "anxious" strains of mice. These investigators found that the expression of the *GSR1* gene, which encodes *GSR1*, and *GLO1* is involved in antioxidative metabolism and highly correlated with anxiety-related phenotypes. The expression of these enzymes was

Table 1. Evidence of Involvement of Oxidative Stress in Anxiety-related Disorders

S #	Paradigm	Species	Behavioral Profile	Biochemical Profile	References
1.	OF EPM Soc Int	Mice	Anxiety	*p66Shc* gene deletion	Berry *et al*., 2006
2.	OF	Mice	Anxiety	Plasma phospholipid transfer protein (PLTP) effect on vitamin E transport	Desrumeux *et al*., 2005
3.	Light/dark test	Mice	Anxiety	Intracellular ROS in peripheral granulocytes	Bouayed *et al*., 2007
4.	Light/dark test OF	Rats	Anxiety	Intragastric vitamin A treatment	Oliveira *et al*., 2006
5.	Light/dark test OF	Rats	Anxiety	L-buthionine-(*S*,*R*)-sulfoximine (BSO)	Salim *et al*., 2010a
6.	Light/dark test OF	Rats	Anxiety	Urinary 8-isoprostane; malondialdehyde (MDA) levels in the hippocampus and amygdala	Salim *et al*., 2010b
7.	Light/dark test OF	Rats	Anxiety	Protein residues of tyrosine and tryptophan in the frontal cortex	Souza *et al*., 2007
8.	EPM OF Hole board test	Mice	Anxiety		Massod *et al*., 2008
9.	Light/dark test	Mice	Anxiety	ROS in peripheral blood lymphocytes, granulocytes, and monocytes	Rammal *et al*., 2008
10.	DSM-IV criteria	Humans	Obsessive-compulsive disorder	Venous blood levels of GSH-Px, CAT, and MDA antioxidant enzymes	Kuloglu *et al*., 2002a
11.	DSM-IV criteria	Humans	Panic disorder	Levels of GSH-Px, SOD, CAT, and MDA antioxidant enzymes	Kuloglu *et al*., 2002b
12.	DSM-IV criteria	Humans	Anxiety	plasma catecholamines and ROS	Yasunari *et al*., 2006
13.	EPM	Rats	Anxiety	ROS and MDA in cortex, hippocampus, and cerebellum in High and Low Freezing animals	Hassan *et al*., 2013
14.	Depression and alcohol use disorders	Animal models (review)	Depression and alcohol use disorders	ROS levels	Hovatta *et al*., 2010
15.	Alzheimer's disease, Parkinson's disease, and prion disease	Humans (review)	Alzheimer's disease, Parkinson's disease, and prion disease	ROS and protein aggregation levels	Gaeta and Hider, 2005
16.	Major depression and bipolar disorder	Humans	Major depression and bipolar disorder	*Glo1* mRNA in peripheral white blood cells	Fujimoto *et al*., 2008
17.	Depression	Humans	Depression	Copper levels	Salustri *et al*., 2010
18.	Alzheimer's disease	Humans	Alzheimer's disease	Oxidized purine and pyrimidine basis in nuclear DNA damage	Gabbita *et al*., 1998
19.	Aging	Humans and mice (review)	Age-related impairments in learning and memory	ROS effects in LTP of hippocampal cells (review)	Serrano and Klann, 2004
20.	Mild cognitive impairment	Humans	Mild cognitive impairment	4-Hydroxy-2-nonenal levels in the hippocampus and inferior parietal lobules	Butterfield *et al*., 2006
21.	Schizophrenia	Humans	Schizophrenia	Plasma levels of pentosidine and serum vitamin B6	Arai *et al*., 2010

BSO, L-buthionine-(*S*,*R*)-sulfoximine; CAT, catalase; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition; EPM, elevated plus maze; GSH-Px, glutathione peroxidase; LTP, long-term potentiation; MDA, malondialdehyde; OF, open field; PLTP, plasma phospholipid transfer protein; ROS, reactive oxygen species; Soc Int, social interaction; SOD, superoxide dismutase

Table 2. Genetic Evidence of Association of GLO-1 and Anxiety-related Disorders

Species	Behavioral Assessment	Genes	Reference	Observations
Humans	DSM-IV criteria for panic disorder	*GLO1*	Politi *et al*., 2006	Ala111Glu polymorphism of *GLO1* gene
Mice	OF Light/dark test	*GLO1* and *GSR1*	Hovatta *et al*., 2005	—
Mice	OF	*GLO1*	Benton *et al*., 2011	—
Mice	EPM	*GLO1**	Ditzen *et al*., 2006	HAB and LAB mice Red blood cells and amygdaloid expression measures
Mice	OF Open-arm exposure test Light/dark test USV test	*GLO1**	Kromer *et al*., 2005	HAB and LAB mice
Rats and Mice		*AVP* and *GLO1**	Landgraf *et al*., 2007	HAB and LAB mice
Mice	OF	*GLO1*	Williams *et al*., 2007	Inbred, CD1 and wildtype mice were analyzed; whole brain and amygdaloid complex were analyzed
Humans		*GLO1*	Ranganathan *et al*., 1999	—
Rats	OF Light/dark test	*GLO1* and *GSR1*	Vollert *et al*., 2011	Hippocampus, cortex, and amygdala gene expression analyzed Anxiety-like behavior provoked by sleep deprivation

AVP, arginine vasopressin; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition; EPM, elevated plus maze; HAB, High Anxiety Behavior; LAB, Low Anxiety Behavior; OF, open field; USV, ultrasonic vocalization.

higher in the most anxious mice and lower in the less anxious strains. They further confirmed that the overexpression of *GLO1* and *GSR1* induced by lentiviral vectors in the cingulate cortex increased, whereas the inhibition of *GLO1* expression induced by siRNA decreased the level of anxiety-like behavior in mice. Subsequently, Loos *et al*. [61] conducted a series of studies in which, regardless of genetic correlations, 12 different inbred mouse strains were tested in different behavioral protocols that consisted of home cage behavior, novel cage behavior, the light/dark box, and elevated plus maze. Gene expression data revealed the prominent presence of several important genes, including *GLO1* [61]. While more recently, Benton *et al*. [62] recently measured genetic markers and a diverse range of neurochemical markers (i.e., a total of 36) against the selective serotonin reuptake inhibitor fluoxetine across 30 mouse inbred strains. Consistent with the study by Hovatta *et al*., the authors found that increased *GLO1* protein expression corresponded to higher anxiety-like behavior [62].

Interestingly, Hovatta *et al*., induced the overexpression of the transgenes [*glyoxalase 1* and *glutathione reductase 1*] with a lentiviral vector and not through the direct production of toxic oxygen metabolites, which questions the mechanistic aspects of the work [60]. Similarly, several reports [50, 63-66] contradict the findings of Hovatta *et al*. [60]. Using outbred Swiss CD1 mice that exhibit high anxiety-related behavior (HAB) or low anxiety-related behavior (LAB), Kromer *et al*. [64] showed that *GLO1* is expressed to a higher extent in LAB mice than in HAB mice in several brain areas, including the hypothalamus, amygdala, and motor cortex. After subjecting the mice to extensive behavioral testing, including the elevated plus maze, dark/light box, open-arm-exposure test, ultrasonic vocalization test, tail suspension test, and forced swim test, and genetic and proteomic analyses, the authors proposed that *GLO1* might be a biological marker for trait anxiety. Importantly, the reduced expression of *GLO1* was observed not only in brain areas but also in peripheral red blood cells, suggesting that *GLO1* expression levels in the brain are highly correlated with those in peripheral blood cells.

Williams *et al*. [67] suggested that the differences in *GLO1* expression in selected lines of mice between some studies [50, 63-66] and Hovatta *et al*. [60] is most likely attributable to a combination of genetic drift and inbreeding. Genetic variability is likely partially responsible for interspecies and interindividual differences. Thornalley [66] suggested an indirect link between *GLO1* expression and oxidative stress. The depletion of GSH in oxidative stress is well known to decrease the *in situ* activity of *GLO1* and increase dicarbonyl glycation. However, this occurs regardless of whether GSH is decreased through an oxidative or non-oxidative mechanism [68]. This author further explained this point by assuming that the formation of MG and MG-H1 are both non-oxidative reactions (i.e., they can proceed in the absence of molecular oxygen). The overexpression of *GLO1* decreases dicarbonyl-dependent advanced glycation endproduct (AGE) formation [69], whereas *GLO1* inhibition increases AGE formation [70]http://www.sciencedirect.com/science/article/pii/S1471491406000621 - bib9.

Thornalley [66] suggested that the contradicting studies by Hovatta *et al*. [60] and Kromer *et al*. [44] may have had the same neuronal damage induced by MG. However, Hovatta worked with rat strains, and the other studies were conducted with bidirectional lines. Both have different genetic and neuronal vulnerability to different stressful situations and may present differential expression. Nevertheless, one should not neglect the different selection pressures with regard to neuronal damage, differences in the animal models used [71], and the use of HAB mice (i.e., a bidirectional line). Similarly, one strain from Hovatta's work, FVB/NJ, suffered complex retinal degeneration and visual impairment. Kromer *et al*. worked with a selective breeding program. Thornalley proposed that high MG exposure/concentration in the anxious strain may have caused higher *GLO1* expression. Kromer might have selected a HAB trait that may have initially low *GLO1* expression and activity compared with a random population and sustained increases in MG concentrations induced by exposure to normal fluctuations in MG formation. Clinical trials have also demonstrated the reduced expression of *GLO1* mRNA in major depression and bipolar disorder during a depressive state [50]. Insulin-responsive element, metal-responsive element, and glucocorticoid-responsive element constitute the promoter region of human *GLO1* [72]. Glucocorticoid receptors (GRs) have been shown to be associated with mood disorders, and reduced GR expression has been observed in the cerebral cortex, hippocampus, and amygdala in mood disorder patients [73-75]. However, the precise mechanism of the association between GRs and MG concentration, which may contribute to anxiety, is lacking in the literature.

The findings reported by Eser *et al*. [76] do not support a relationship between *GLO1* expression and anxiety-related behavior. The authors did not find a correlation between *GLO1* mRNA expression levels and the severity of cholecystokinin-4 (CCK-4)-induced panic. *GLO1* expression levels also did not correlate with state or trait anxiety. Cholecystokinin-4-induced panic attacks are an established and reliable model of human anxiety in healthy volunteers [75, 78-79]. The limitation of this work, however, is that behavioral and cardiovascular panic symptoms elicited by CCK-4 might be different from other anxiety-related phenotypes and cannot be extrapolated to anxious or non-anxious strains or bidirectional lines. Using another approach, Vollert *et al*. [80] induced oxidative stress by sleep deprivation. The authors observed higher *GLO1* and *GSR1*-1 protein expression levels after acute (24 h) sleep deprivation in the hippocampus, cortex, and amygdala. This effect was most likely an initial antioxidant response to combat the immediate increase in oxidative stress. Importantly, the earlier studies by Salim *et al*. [27, 28] indicate that the acute induction of oxidative stress by BSO did not cause anxiety-like behavior in rats, whereas the subchronic induction of oxidative stress by BSO or X+XO caused anxiety-like behavior in rats. Later reports from this group suggested that high anxiety corresponds to low *GSR1* and *GLO1* expression, whereas no anxiety-like behavior is correlated with high levels of *GLO1* and *GSR1* expression. This certainly suggests some sort of association between *GLO1* and *GSR1* and anxiety-like behavior in rodents [27, 28].

3. ANXIOLYTIC VS TOXIC EFFECTS OF METHYLGLYOXAL

Hambsch *et al*. [81] recently reported striking findings in which they showed that MG levels in the brain are negatively correlated with anxiety. Intracerebroventricular injections of MG were given to HAB mice in the 30th generation, inbred normal anxiety-related behavior (NAB) mice in the 4th generation, and CD1 control mice. The administration of MG in inbred HAB mice induced marked anxiolytic-like effects that reached the magnitude of "normal" CD1 controls. These findings suggest that MG concentrations more efficiently modulate anxiety-related behavior than *GLO1* expression. These are very interesting observations, and the author attempted to reconcile the discrepancies between different studies concerning *GLO1* expression and anxiety-related behavior. Higher *GLO1* expression, driven either by virus [60] or multiple copy-number variations [67], might reduce MG concentrations, thus leading to anxiety-like behavior. Increased MG concentrations followed by lower *GLO1* expression may generate low anxiety-like behavior. A recent report by Distler showed that treatment with low doses of MG reduced anxiety-like behavior, suggesting an interaction between MG and γ-aminobutyric acid (GABA) receptors. Their findings indicate that *GLO1* increases anxiety by reducing MG concentrations, thereby decreasing $GABA_A$ receptor activation. The salient feature of this work is that the authors provided baseline data in which the pharmacological inhibition of *GLO1* reduced anxiety, suggesting that *GLO1* may be a possible target for the treatment of anxiety-related disorders [82].

Considering the "anxiolytic" role of MG in anxiety or related disorders is interesting, but MG is also well-known to cause various toxic effects. The literature provides some excellent reviews [83] on this topic, which is not the focus of the present review. For simplicity, we can divide the toxic effects of MG into three main classes.

First, extensive data support the hypothesis that MG causes the production of free radicals. The exposure of rat hepatocytes, macrophage-derived cell line U937, rat mesenteric artery smooth muscle cells (VSMCs), mesothelial cells, red blood cells, Jurkat cells, and aortic smooth muscle cells to MG produces escalating levels of free radicals [84-91]. Methylglyoxal-induced ROS production in other cell lines *in vitro* and the protective effect of the antioxidant NAC further confirm the assumption that oxidative stress may contribute to MG-induced toxicity [92, 93]. Methylglyoxal has been shown to be cytotoxic, possibly involving caspase-independent channeling or the activation of mitochondria in response to oxidative cell injury [94].

Second, considerable data indicate that MG can deplete cellular GSH content. The *in vitro* treatment of human platelets, rat colonocytes, murine hepatocytes, rat lense, human umbilical veins, endothelial cells, rat VSMCs, spontaneously hypertensive rats, and Wistar-Kyoto rats with 0.5-20 mM MG, with varying incubation times (30 min to 24 h), caused 7-85% GSH depletion compared with controls [95-101]. *In vivo* treatment with MG from 0.6 mM or 1% MG to 400 mg/kg depleted GSH by 8.0-67% in mouse liver,

spleen blood, and embryos with different exposure times [102-106].

Third, MG toxicity may be induced by the inhibition of antioxidant enzymes [107]. Both *in vitro* and *in vivo* data have shown that MG exposure inhibits several antioxidant enzymes, such as *GSR1*, glutathione peroxidase, catalase, SOD, and DT-diaphorase from human, rat, mouse, and bovine tissues, including aortic VSMCs, ADF glioblastoma cells, SH-SY 5Y neuroblastoma cells, and liver, with varying degrees of inhibition that ranged from 10% to nearly 90% with different concentrations of MG (i.e., 200 μM to 100 mM) and incubation times (i.e., 0.5-24 h) [107-112].

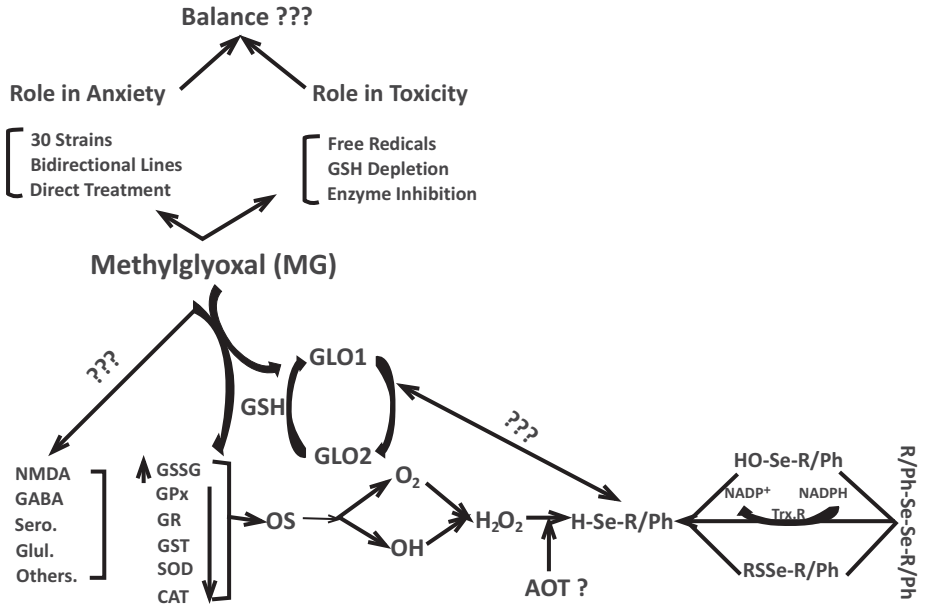
One must also consider the possible involvement of different stress-response factors (e.g., c-*Jun N*-terminal kinase [JNK], nuclear factor-κB [NF-κB], and peroxisome proliferator-activated receptors [PPARs]), the expression of which is known to be regulated by cellular redox changes [113-117]. *In vitro* MG treatment did not activate the NF-κB pathway in SH-SY 5Y cells [118], but contradictory results have also been reported [119]. In contrast, both phosphorylated JNK and PPARα were significantly increased by MG treatment. However, these channels are not activated in other kinds of cells (e.g., ADF cells). The involvement of PPARs in MG-induced cellular stress has also been reported, but its possible role in the signal transduction pathways triggered by MG in models of anxiety are unknown. Interestingly, the cell-line response to activation of various biochemical channels is different. For example, the excessive production of ROS in ADF and SH-SY 5Y cells did not trigger the same biochemical response. The role of MG-induced activation of different stress response factors in animal models of anxiety in either strains or bidirectional lines is unknown and needs to be further explored with regard to the roles of the specific channels involved so that stress-induced exacerbation or initiation can be further decoded (Scheme **2**).

Another important factor that may play a crucial role in determining the susceptibility of MG-related responses is the GSH-dependent enzymatic system. Treatment with MG has been shown to significantly reduce the concentrations of the GSH-synthesizing enzymes GS and GCS, consequently reducing intracellular GSH content (Scheme **2**) [118]. Surprisingly, MG treatment did not alter specific GPx activity, suggesting that this enzyme might not be a molecular target of MG-induced toxicity. The *GLO1* enzyme is inhibited by MG, whereas the effect on *GLO2* is not significantly different from controls in SH-SY 5Y cells. In ADF cells, MG treatment increased both *GLO1* and *GLO2* activity. These different results from two different cell lines complicate the mechanisms associated with the GSH-dependent system, worsened by the scarcity of data derived from animal models of anxiety that correlate MG with GSH-dependent enzymatic systems in rat or mice strains or bidirectional lines. Genetic variations in bidirectional lines and strains should be properly addressed because the basal level of antioxidants and detoxifying enzymes and their adaptive response to MG or any ROS might be quite different and differentially contribute to the consequences of oxidative bursts and the genesis of anxiety.

4. FUTURE DIRECTIONS

4.1. Interaction Between Methylglyoxal and other Neurotransmitter Systems

The involvement of *N*-methyl-D-aspartate (NMDA) receptors in the mediation of anxiety-related disorders is currently a hot topic in the literature. NMDA receptor



Scheme 2. Various aspects of MG interactions. AOT, antioxidant therapy; CAT, catalase; GABA, γ-aminobutyric acid; Glut, glutamate; GPx, glutathione peroxidase; GSR, glutathione reductase. GR = glucocorticoid receptor; GSH, glutathione; GSSG, oxidized glutathione; GST, glutathione *S*-transferase; MG, methylglyoxal; NADP-H, nicotinamide adenine dinucleotide phosphate; $NADP^+$, nicotinamide adenine dinucleotide phosphate, reduced; NMDA, *N*-methyl-D-aspartate; OS, oxidative stress; Sero, serotonin; SOD, superoxide dismutase; Trx-R, thioredoxin reductase.

antagonists exert anxiolytic effects [120-127]. Thus, considerable evidence indicates that NMDA receptor antagonists that act at numerous sites on the receptor can reduce anxiety. However, the precise locus and neuro-biological mechanism are still being explored. Using genetically modified mice, in which particular receptor subunits are specifically deleted from spatially restricted hippocampal subfields, some authors [128] found the involvement the NR1 and NR2B subunits of the NMDA receptor. The present challenge is to identify the MG-induced NMDA receptor-dependent synaptic and cellular mechanisms that could underlie anxiety. This will help us explore the anxiolytic effects of this compound and its possible role in the genesis of anxiety. Dysregulation of the GABA system has been suggested to play an important role in the pathophysiology of panic disorder [129, 130], but the casual role of MG that acts through GABAergic or serotonergic systems in anxious strains or lines has not been demonstrated in the literature, further complicating the relevance and understanding of the association between *GLO1* and *GSR1* and anxiety. Downregulation of the GABA system in mice has been shown to produce extreme anxiety [131-136]. Similarly, various studies have shown the involvement of serotonin in the development and regulation of anxiety [137, 138]. The modulation of neurotransmitters, such as corticotropin-releasing factor and neurokinin, has also shown an association with anxiety-like behavior [139]. However, few data explain the interaction between MG and these receptor systems in actual anxiety-related models.

4.2. Selective GLO1 Inhibition and Related Aspects

GLO1 is not an obvious participant in signal transduction associated with anxiety-related behavior, which has been demonstrated with ethanol, benzodiazepines, barbiturates, and neurosteroids [140]. Gingrich recently drew attention for his comment on the possible difference between emotional stress and oxidative stress. He attempted to explain the possible difference between emotional stress and oxidative stress and their involvement in anxiety-related disorders [140]. Although some reports have related *GLO1* to the genesis of anxiety, *GLO1* and *GSR1* are not widely acknowledged for their involvement in anxiety because they are not targets of classic anxiolytic medications. *GLO1* inhibition may be considered a novel therapeutic tool for the treatment of anxiety. However, Kim *et al.* [141] recently suggested that increased *GLO1* levels can protect against free radical-induced toxic effects and inhibit the accumulation of oxidative stress and AGR formation in high glucose-fed animal models. The interface between cytotoxic and anxiolytic effects must be established before any future therapeutic interventions are developed. Important to know is whether MG can deplete cellular GSH content, inhibit antioxidant enzymes, or generate free radicals in models of anxiety. This may involve a clearer understanding of the basal expression levels of GLO-I and *GLO2*, physiological or pathological concentrations of MG, and the cellular adaptive response to ROS.

Similarly, the role of *GLO1*, related genes, and MG in a diverse range of rat strains and bidirectional lines needs be decoded because these models are bred with different neuronal circuitries. Understanding the precise interaction between *GLO1* and MG and different neurotransmitter modulators, anxiolytics, antidepressants, and mood stabilizers either *in vitro* or more preferably *in vivo* may also be interesting. One must have accurate and sensitive methods to estimate the effects of MG *in vivo*. A recent review by Nemet *et al*. covered all of the available literature in this regard [142]. Analyzing other pathological disorders that can lead to increased MG concentrations or other clinical complications that rely on the casual role of MG, such as in diabetes mellitus [143, 144] and Alzheimer's disease, is also important. Pathological situations that involve protein glycation, the formation of protein deposits (e.g., β-amyloid), and increased protein catabolism are some biochemical examples that can be related to MG. The prevalence of anxiety in conjunction with other clinical complications and specifically the casual role of MG in a broad spectrum of psychological disorders are very important aspects that need to be explored. Palmar *et al*. recently demonstrated the role of MG in epilepsy and seizures [145]. Another aspect that deserves attention is the precise biochemical mechanism of MG-induced toxicity, ranging from its source of synthesis to the possible cascade that leads to diverse toxic effects. For example, free radicals have been shown to be a key mechanism of MG-induced toxicity. To our knowledge, however, no comprehensive or conclusive proof has been provided that can attribute the evolving toxicity to MG itself. Similarly, exploring other therapeutic interventions may be interesting, such as the following:

1. Inhibition of surplus MG production. For example, AA and Metformin have been shown to prevent the increase in MG in diabetic patients. However, to our knowledge, no studies have directly addressed the inhibition of MG in models of anxiety. Selective *GLO1* inhibition may also help in this regard.

2. Increased antioxidant capacity of cells. Antioxidant therapy could be an alternative option to combat anxiety disorders. A diverse range of natural and synthetic antioxidants and neutraceuticals approaches have been described in detail [146, 147], which may help in the design of therapeutics.

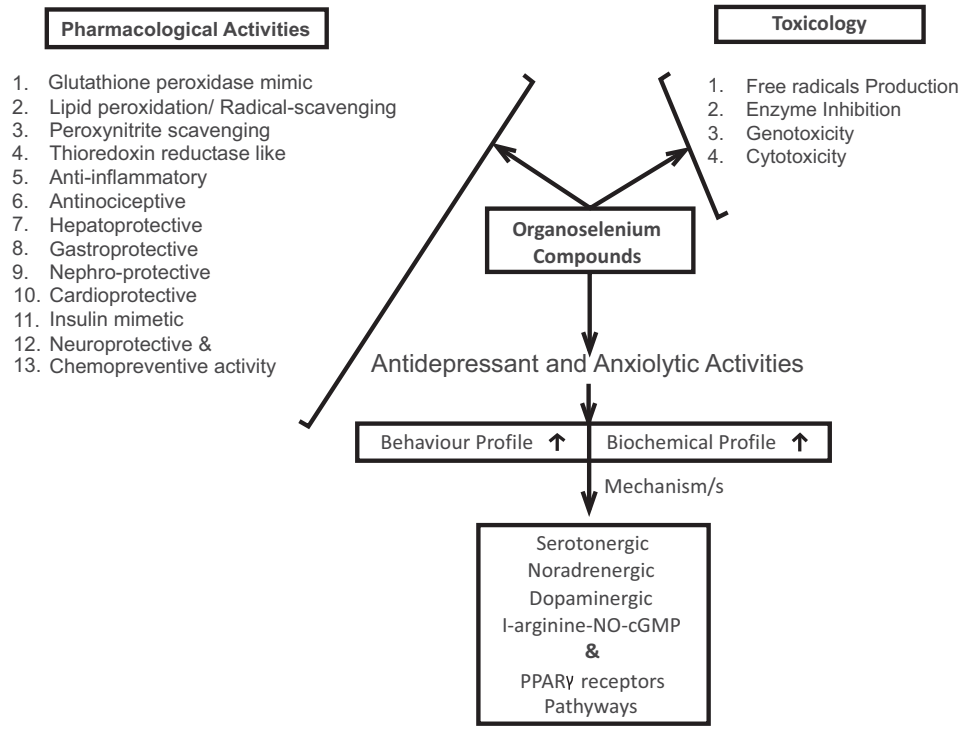
With the emerging role of MG and *GLO1* in the regulation of anxiety, both top-down and bottom-up strategies need to be developed. The selective inhibition of *GLO1* may have beneficial effects by increasing MG concentrations, which can have anxiolytic effects, but an unnecessary increase in MG concentration may trigger toxic effects. Interestingly, the MG detoxification process involves a *GLO1* and *GLO2* catalytic cycle. The conversion of *GLO2* to *GLO1* depends on GSH. Methylglyoxal can deplete cellular GSH content and consequently hinder the conversion of *GLO2* to *GLO1*, thus possibly inhibiting *GLO1*. However, one potential risk is an increase in oxidative burden in the cellular environment; therefore, the potential use of antioxidant therapy cannot be neglected. Interestingly, Masood *et al.* [30] showed that the anxiolytic diazepam did not ameliorate anxiety induced by BSO treatment. This further complements the fact that oxidative stress could be a factor in anxiety. In fact, treatment with tempol, an antioxidant, reversed the anxious phenotype [27, 28].

4.3. Possible Antioxidant Therapy

The possibility of antioxidant therapy is gaining attention in the literature, and various dietary and synthetic antioxidants have been reported [146-148]. The present review does not focus on antioxidant therapy in paradigms of anxiety, but the literature provides various studies in which natural diet supplements or components protect against anxiety-related disorders. Such antioxidants not only increase the cellular response to oxidative stress but also play an important role in signal transduction [149]. Dietary antioxidants have been reported to possess antidepressant and anxiolytic properties and exert cognitive-enhancing effects. Various natural antioxidants, such as vitamin C, rutin, caffeic acid, and rosmarinic acid, have demonstrated antidepressant activity at relatively low doses (0.1-2 mg/kg) [150].

Polyphenols (e.g., apigenin, rosmarinic acid, chlorogenic acid, and [-]epigallocatechinn gallate), flavonoids (e.g., quercetin [151]), specific foods (e.g., fresh apple [152]), and diets rich in sucrose and honey [153] have been shown to improve antioxidant status and have anxiolytic effects. Similarly, classic antidepressants, such as citalopram, have been shown to exert antioxidant activity in patients with social phobia [150]. Exogenous antioxidants obtained from natural sources may provide an interesting alternative for the treatment of anxiety-related disorders. Vitamin C, lipoic acid, vitamin E, β-carotene, and flavonoids have been shown to exert a direct action against several potent free radicals, such as hydroxyl, lipid peroxide, and super oxide radicals, and other proxidant molecules, such as hydrogen peroxide, thus inhibiting them before they can initiate a chain of oxidative reactions [154]. Various fruits, vegetables, spices, grains, and other natural food products contain important active constituents, such as quercetin, naringin, rutin, cryophyllene, eugenol, hesperetin, casein, vitamin D, oleic acid, α-linolenic acid, curcumin, gingerols, vitamins E, and other minerals. These chemical constituents protect the body against the deleterious effects of reactive species [154]. Mechanistically, antioxidants protect the organism through various diverse pathways that include but are not limited to ROS scavenging, the prevention of excitotoxicity, the dysregulation of metal homeostasis, and the reduction of secondary metabolic burden [155-158]. Closer inspection of Scheme **1** suggests two strategies that can be used to overcome the escalating effects of reactive species. The preferable option might be the upstream approach, in which one can prevent the production of free radicals or inhibit the participation of metals in catalyzing adverse reactions. This is more clinically appropriate than downstream strategies that involve inhibiting free radicals or protecting against these toxic species through the use of antioxidants.

Data on synthetic antioxidants are very diverse, and a range of different classes of compounds have been reported in the literature [148]. However, the interest in selenium chemistry has tremendously increased because of its importance in organic synthesis and biological effects. Various selenium compounds have been shown to have interesting biological effects in different animal and experimental pathological models. Several reviews from our laboratory have focused on this topic [159-161]. Briefly, organoselenium compounds have been shown to possess glutathione peroxidase-mimetic activity [162-166], lipid peroxidation/radical-scavenging/peroxynitrite-scavenging activity [167-171], thioredoxin reductase-like activity [172-176], antiinflammatory and antinociceptive activity [177-181], antinociceptive activity [182-186], hepatoprotective



Scheme 3. Toxicology and pharmacology of organoselenium compounds. PPARγ, peroxisome proliferator-activated receptor γ.

Table 3. Anxiolytic Effects of Different Organoselenium Compounds

Compound	Dose	Route	Species	Behavioral Test	Biochemical Parameters	Involved Mechanism/System	Reference
Ebselen and/or *p*-Chlorophenylalanine Nan-190 Ketanserin Prazosin Yohimbine Sch23390 Sulpiride	0-30 mg/kg	Intraperitoneal	Mice	FST TST OF	ND	Noradrenergic and dopaminergic systems	Posser *et al*., 2009
Diphenyl diselenide and/or *p*-chlorophenylalanine methyl ester WAY100635 Ketanserin Ondansetron Haloperidol SCH233390 Sulpiride Prazosin Yohimbine Propranolol	0.1-30 mg/kg	Oral	Rats	FST OF	Monoamine oxidase assay	Central monoaminergic system	Savegnago *et al*., 2007b
Diphenyl diselenide and/or Malathion	50 mg/kg	Oral	Rats	FST OF	Na^+K^+ ATPase, acetylcholinesterase, and monoamine oxidase activity TBARS, NPSH, CAT, GPx, GR, and GST activity	Na^+K^+ ATPase activity	Acker *et al*., 2009b
Diphenyl diselenide and/or L-arginine methylene blue sildenafil N^G-nitro-L-arginine ^{1}H-[1,2,4] oxadiazolo [4,3-*a*]quinoxalin-1-one Fluoxetine Imipramine	0.1-100 mg/kg	Intracerebroventricular	Mice	FST TST EPM Light/dark box Rotarod	ND	L-arginine-nitric oxide-cyclic guanosine monophosphate pathway	Savegnago *et al*., 2008b
Bis selenide and/or *p*-chlorophenylalanine methyl ester Ketanserin Ondansetron Prazosin Yohimbine Propranolol SCH23390 Sulpiride, WAY100635	0.5-5 mg/kg	Oral	Mice	FST TST	MAO-A, MAO-B, and Na^+K^+ ATPase activity	$5\text{-}HT_{2A/2C}$ and $5\text{-}HT_3$ receptors	Jesse *et al*., 2010a
Bis selenide and/or L-arginine *S*-nitroso-*N*-acetyl-penicillamine Sildenafil	0.5-5 mg/kg	Intracerebroventricular	Mice	FST TST OF	Nitrate/nitrite content	L-arginine–nitric oxide–cyclic guanosine monophosphate	Jesse *et al*., 2010b

Table 3. contd….

Compound	Dose	Route	Species	Behavioral Test	Biochemical Parameters	Involved Mechanism/System	Reference
Bis selenide and/or CCl Fluoxetine Amitriptyline Bupropion	1-5 mg/kg	Oral	Mice	FST OF	ND	Neuropathic pain model	Jesse *et al*., 2010c
Diphenyl diselenide and/or Bicuculline Ritanserin Ketanserin WAY100635	5, 25, and 50 µmol/kg	Intraperitoneal	Rats	OF EPM Footshock avoidance task	ND	$GABA_A$ and 5-HT receptors	Ghisleni *et al*., 2008a
Diphenyl diselenide	1, 10, and 50 mg/kg	Oral	Male chicks	Vocalizations, jumps, active wakefulness, time standing / sitting motionless with eyes open or closed	ND	Possibly GABA system	Prigol *et al*., 2011
Diphenyl diselenide	25 mg/kg	Maternal subcutaneous injection	28-day-old pups	EPM OF Rotarod	Selenium brain status	Selenium-induced changes	Favero *et al*., 2006
Diphenyl diselenide and/or Paroxetine Pargyline WAY100635 Ritanserin Ondansetron			Mice	OF TST FST	MAO-A and MAO-B activity	$5\text{-}HT_{2A/2C}$ and $5\text{-}HT_3$ receptors	da Rocha *et al*., 2012
p-chloro-diphenyl diselenide and/or WAY100635 Ritanserin Ondansetron	10 and 25 mg/kg	Oral	Rats	Ambulation, memory, and depression FST OF	Na^+K^+ ATPase activity and ROS levels	$5\text{-}HT_{1A}$ and $5\text{-}HT_3$ receptors	Bortolatto *et al*., 2012
m-trifluoromethyl-diphenyl diselenide and/or WAY100635 Ritanserin Ondansetron Naloxone	50 and 100 mg/kg	Oral	Mice	FST OF	ND	Serotonergic and opioid systems	Brüning *et al*., 2011
Diphenyl diselenide and/or Etraethylammonium Glibenclamide Charybdotoxin Apamin Cromakalim Minoxidil GW 9662	1-5 mg/kg	Intracerebroventricular	Mice	OFT TST	K^+ channels and PPARγ receptors	K^+ channels and PPARγ receptors	Wilhelm *et al*., 2010

AChE, acetylcholinesterase; CAT, catalase; cGMP, cyclic guanosine monophosphate; EPM, elevated plus maze; FST, forced swim test; GPx, glutathione peroxidase; GR, glucocorticoid receptor GSR; glutathione reductase; GST, glutathione *S*-transferase; MAO, monoamine oxidase; NPSH, non-protein thiol content; OF, open field; TBARS, thiobarbituric acid reactive substances; TST, tail suspension test.

activity [187-191], gastroprotective activity [192-196], nephroprotective activity [197-201], cardioprotective activity [202-206], insulin-mimetic activity [207-211], and neuroprotective activity [212-218] (Scheme **3**).

In the context of anxiety-related disorders, selenium deficiency has been related to depression, mood disorders, and anxiety [219-221]. Higher selenium intake was shown to improve depressive and anxious symptoms [222, 223]. Organoselenium compounds have been tested in various anxiety-related paradigms. Depending on the chemical structure, route of administration, and dose, various compounds have shown promising antidepressant and anxiolytic activity. Mechanistically, these compounds afford protection through interactions with serotonergic (5-HT_{1A}, 5-$HT_{2A/C}$, and 5-HT_3), noradrenergic (α_1 and α_2), and dopaminergic (D_1, D_2, and D_3) systems. The role of $GABA_A$ receptors, the possible inhibition of the L-arginine-NO-cyclic guanosine monophosphate pathway, and the modulation of PPARγ receptors has been previously reported [224-228] (Table **3**). One aspect that deserves attention is the possible toxicity (Scheme **3**) of these agents. Although organoselenium compounds offer protection against a wide range of pathological disorders, the toxicity of these compounds cannot be ignored. Free radical generation, the inhibition of thiol-containing enzymes, cytotoxicity, and mutagenicity are some of the key side effects of these compounds [159-161, 229, 230], which should be clearly monitored before any therapeutic intervention is considered.

5. CONCLUSION

Whether oxidative stress is the cause or consequence of anxiety is still an open discussion, but the oxidative stress hypothesis of anxiety has been widely proposed. Genomics, proteomics, transcriptomics, and related tools will provide diagnostic insights to help guide research to develop novel pharmacological interventions. Specifically, genetic models and animal models of anxiety using bidirectional lines provide baseline data to understand the potential molecular mechanisms associated with or directly involved in anxiety-related disorders. However, investigations of the neurobiology of anxiety at the molecular level, from neurotransmitter systems to activation of intracellular pathways that trigger anxious behavior, in these animal models are still very limited. Although suggesting antioxidant therapy for anxiety disorders in humans may be premature, reports in the literature suggest a preventive role of antioxidants in this regard. The combined use of antioxidants and classic anxiolytics may be promising. However, more intensive research using animal models of anxiety to investigate toxicological effects, dose formulations, treatment regimens, and synergistic effects between anxiolytics and antioxidants should be conducted before therapeutic applications can be considered an appropriate intervention in human anxiety disorders.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

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ABBREVIATIONS

XO = Xanthine oxidase

nadp-h^+ oxidase = Nicotinamide adenine dinucleotide phosphate

nNOS = Neuronal nitric oxide synthase

iNOS = Inducible NOS

eNOS = Endothelial NOS

$oNOO^{-1}$ = Peroxynitrite Anion

NO^{+1} = Nitrosonium Cations

NO^{-1} = Nitroxyl Anions

SOD = Superoxide Dismutase

GSR1 = Glutathione Reductase

BSO = L-Buthionine-[*s*,*r*]-Sulfoximine

CHF = Carioca high-freezing

CLF = Carioca low-freezing

CA1, and CA3

GLO1 = Glyoxalase i

MG = Methylglyoxal

HAB = High anxiety-related behavior

LAB = Low anxiety-related behavior

GRS = Glucocorticoid Receptors

CCK-4 = Cholecystokinin-4

NAB = Normal anxiety-related behavior

GABA = γ-aminobutyric Acid

GSH = Glutathione

JNK = *Jun n*-Terminal Kinase

Nf-κb = Nuclear factor-κb

pPARS = Peroxisome proliferator-activated receptors

GS = Glutathione Synthase

AGE = Advanced Glycation End Product

GPx = Glutathione Peroxidase

TBARS = Thiobarbituric Acid Reactive Substances

VSMC = Vascular Smooth Cells

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