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Oxidative Stress in Autism Spectrum Disorder

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Abstract
According to the United States Centers for Disease Control and Prevention (CDC), as of July 11, 2016, the reported average incidence of children diagnosed with an autism spectrum disorder (ASD) was 1 in 68 (1.46%) among 8-year-old children born in 2004 and living within the 11 monitoring sites' surveillance areas in the United States of America (USA) in 2012. ASD is a multifaceted neurodevelopmental disorder that is also considered a hidden disability, as, for the most part; there are no apparent morphological differences between children with ASD and typically developing children. ASD is diagnosed based upon a triad of features including impairment in socialization, impairment in language, and repetitive and stereotypic behaviors. The increasing incidence of ASD in the pediatric population and the lack of successful curative therapies make ASD one of the most challenging disorders for medicine. ASD neurobiology is thought to be associated with oxidative stress, as shown by increased levels of reactive oxygen species and increased lipid peroxidation, as well as an increase in other indicators of oxidative stress. Children with ASD diagnosis are considered more vulnerable to oxidative stress because of their imbalance in intracellular and extracellular glutathione levels and decreased glutathione reserve capacity. Several studies have suggested that the redox imbalance and oxidative stress are integral parts of ASD pathophysiology. As such, early assessment and treatment of antioxidant status may result in a better prognosis as it could decrease the oxidative stress in the brain before it can induce more irreversible brain damage. In this review, many aspects of the role of oxidative stress in ASD are discussed, taking into account that the process of oxidative stress may be a target for therapeutic interventions.

Keywords Autism · Oxidative stress · Reactive oxygen species · Inflammation · ASD

Introduction

Autism spectrum disorder (ASD) is a complex neurodevelopmental syndrome, which usually occurs before 3 years of age. In general, ASD is characterized by (1) pervasive deficits in social interaction, (2) impairments in verbal and nonverbal communication, and (3) stereotyped patterns of interests and activities. Although ASD is fundamentally diagnosed on the basis of an evaluation of clinical and behavioral criteria, which should identify alterations in social interaction, deficits in verbal and nonverbal receptive/expression, speech, and hyper-focused repetitive behaviors, individuals diagnosed with ASD may also display a range of problematic behaviors including hyperactivity, poor attention, impulsivity, aggression, self-injury, and tantrums [1–4].

According to the reports from the US Center for Disease Control and Prevention (CDC), last updated on July 11, 2016, data collected at 11 separate reporting sites in 2012 showed that the reported average incidence of children diagnosed with an autism spectrum disorder (ASD) was 1 to 68 (1.46%), among 8-year-old children born in 2004 and living within the 11 monitoring sites' surveillance areas in the USA held in 2012 (with a site ASD incidence ranging from about 1 in 122 (0.82%) to about 1 in 41 (2.46%) [5]. ASD is a multifaceted neurodevelopmental disorder that is also considered a hidden disability, as, for the most part.

Although there is no consensus today on the causes of ASD, multiple environmental and genetic risk factors have been proposed [6, 7]. The relationship between genetics and environment, which may elicit even immune and inflammatory responses in the brain, is thought to be a major key in the understanding of ASD pathophysiology and has in recent

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years become a subject of intensified research [8–11]. Diverse prenatal and perinatal environmental exposures are associated with an increased risk of ASD [12–14]. Prolonged exposure to environmental pollutants (oxidizing agents, heavy metals, herbicides, and pesticides), photosensitizers, UV light, or ionizing radiation have been studied as potential causal factors [15–18].

More recently, there is growing evidence supporting the role of oxidative stress in the pathophysiology of a number of neuropsychiatric diseases [19–21] and especially in ASD (Table 1) [43–46]. The response to oxidative stress is a keystone in neuroinflammation, in as much the latter is still considered one of the leading cause of ASD [47]. Children with ASD diagnosis are considered more vulnerable to oxidative stress because of their low plasma and cellular glutathione (L-γ-glutamyl-L-cysteinyl-glycine) levels and decreased glutathione reserve capacity [38, 48]. Several studies have suggested that the redox imbalance and oxidative stress are integral parts of ASD pathophysiology [49, 50]. There is also evidence to suggest a relationship between the oxidative stress found in subjects diagnosed with ASD and environmental exposures, particularly for heavy metals, such as mercury [17, 51–53].

Along with the host's immune system, microbiota plays an essential role in the proper functioning of the body participating in metabolic tracts and acting as a source of key nutrients. In this sense, the intestinal microbial imbalance can be a consequence of the exposure to many environmental factors, including further microorganisms, xenobiotics, and pollutants. Alterations in the microbiota and the presence of enteric pathogens may contribute to microbial dysbiosis, with possible suggestions on ASD pathogenesis [54, 55]. Many studies have reported an increased presence of gastrointestinal (GI) symptoms in children with ASD. Altered microbiome profiles, proinflammatory responses, and impaired intestinal permeability have been observed in children with ASD and co-morbid GI symptoms. Recent data would suggest that GI impairments in autistic subjects are associated with mitochondria dysfunction and the enteric microbiome [50, 56, 57]. Metabolic disorders inducing GI are related to mitochondria redox imbalance [50]. The connection between redox impairment via a mitochondria dysfunction in the enteric milieu and GI has been recently investigated in a blinded case-control study with ten children with ASD and GI complaints, ten children with Crohn's disease, and ten children with non-specific gastrointestinal complaints matched on age and gender and undergoing elective diagnostic colonoscopy [57].

Moreover, children with ASD experience significantly more GI symptoms than children without ASD [58], and their GI symptoms correlate strongly with their ASD severity [59]. Possible connections between the GI tract and mitochondrial abnormalities specific to ASD can be distinguished, such as mitochondrial dysfunction may result in GI dysfunction, exposures to environmental stressors which are associated with ASD can affect the GI tract and mitochondria, and also some substances may disrupt mitochondrial function (lipopolysaccharide or metabolites from enteric bacteria) [56].

In this review, many aspects of the role of oxidative stress in ASD are discussed, taking into account that the process of oxidative stress may be a target for therapeutic interventions. Early assessment and treatment of antioxidant status may result in a better prognosis as it may decrease the oxidative stress in the brain and the brain/gut axis before it can induce more irreversible brain damage.

The literature search was carried out using PubMed and Scopus, supplemented with Google Scholar and the reference lists of relevant papers.

Recent Insights on Oxidative Stress and Mitochondrial Dysfunction

Oxidative stress can be defined as an imbalance between prooxidants and antioxidants, resulting in a damaging action towards the cell caused by reactive oxygen species (ROS) or reactive nitrogen species (RNS) [60]. Fundamentally, ROS are signaling molecules, which may promote cell survival and tissue renewal [61, 62] or counteract cell survival gene expression, including the antioxidant enzymatic endowment, so leading cell to apoptosis [62]. The ability of cells to properly respond to oxidative stress occurs when "mild oxidative stress" is elicited, usually by a relatively low content of ROS, a condition called eustress [63]. The potentially damaging oxidative stress is called distress, and it is the major cause of neuroinflammation and impairment in the astrocyte-neuron crosstalk leading to ASD [11, 64–68]. The full comprehension of the role of ROS in ASD is still far to be elucidated. The classical overview about ROS homeostasis takes into account a balance between the antioxidant ROS scavenging system and the reactive free radicals produced during the activity of mitochondria, peroxisomes, endoplasmic reticulum, and proteasome [60]. Under normal conditions, a dynamic equilibrium exists between the production of ROS/RNS and the antioxidant capacity of the cell [69]. Fundamentally, ROS and RNS include superoxide (O_2^-), hydroxyl, peroxyl, alkoxy, hydrogen peroxide, and peroxynitrite free radicals [21, 63]. Superoxide is the first reduction product of molecular oxygen and is an important source of hydroperoxides, lipo-peroxides, and harmful free radicals [70]. These are considered main byproducts of the normal metabolism of oxygen or nitrogen and have important roles in a wide number of biological processes, such as the killing of bacteria. The excess amounts of ROS can be produced by the organism in response to pathogenic defenses or generated at normal levels but not neutralized due to the insufficient antioxidant capacity of the redox

Table 1 Oxidative stress markers in patients with autism spectrum disorder

Marker/specimen	Units	Values		*p* value	Reference
		ASD patients	Controls		
I. Oxidative stress indicators					
A. Lipid peroxidation biomarkers					
LOOH in the cerebellum	mmol/mg protein	36*	18*	$p < 0.05$	[22]
LOOH in the temporal cortex	mmol/mg protein	21*	15*	$p < 0.05$	[22]
Plasma MDA	nmol/mL (mean ± SE)	0.4969 ± 0.025	0.396 ± 0.019	$p = 0.005$	[23]
Plasma MDA	nmol/mL (mean ± SD)	7.740 ± 0.73	2.986 ± 0.36	$p < 0.0001$	[24]
Plasma MDA	nmol/mL (mean ± SD)	4.16 ± 1.67	1.49 ± 0.58	$p < 0.001$	[25]
Serum MDA	nmol/L (mean ± SD)	8.6 ± 0.5	1.76 ± 0.33	$p \leq 0.001$	[26]
RBC TBARS	mmol/g Hb (mean ± SD)	0.032 ± 0.0077	0.015 ± 0.0033	$p < 0.001$	[27]
Urine 8-iso-PGF2α	ng/mg creatinine (mean ± SE)	32.92 ± 1.98	5.71 ± 0.98	$p < 0.05$	[28]
Plasma iso[4]LGE$_2$ protein adducts	nmol/mL (mean ± SD)	16.7 ± 5.8	13.4 ± 3.4	No significance	[29]
B. Protein oxidation biomarker					
Plasma protein carbonyl	nmol/mL (mean ± SD)	4.202 ± 0.3912	2.256 ± 0.148	$p < 0.0001$	[24]
C. Protein nitration biomarker					
3-NT in the cerebellum**	pmol/g tissue (mean ± SE)	48.67 ± 9.61	28.82 ± 3.75	$p = 0.045$	[30]
D. Marker of lipid-derived oxidative protein modification					
Plasma CEP	pmol/mL (mean ± SD)	124.5 ± 57.9	110.4 ± 30.3	No significance	[29]
E. DNA oxidation biomarkers					
Serum 8OHdG	ng/mL (mean ± SD)	13.134 ± 1.33	1.46 ± 0.326	$p \leq 0.001$	[26]
II. Antioxidant enzymes					
A. Se-dependent antioxidant enzymes					
Plasma GPx	U/L (mean ± SD)	40.9 ± 11.3	24.2 ± 6.3	$p < 0.0001$	[31]
Plasma GPx	U/mL (mean ± SD)	0.27 ± 0.04	0.39 ± 0.08	$p < 0.05$	[32]
Plasma GPx	U/dL plasma (mean ± SD)	246.88 ± 99.93	143.85 ± 61.12	$p < 0.05$	[33]
RBC GPx	U/g Hb (mean ± SD)	28.72 ± 2.64	38.01 ± 5.03	$p < 0.05$	[32]
B. Other antioxidant enzymes					
Serum CAT	UAE/L (mean ± SD)	2.836 ± 0.479	0.689 ± 0.157	$p \leq 0.001$	[26]
RBC ADA	U/g Hb (mean ± SD)	0.55 ± 0.13	0.53 ± 0.15	No significance	[27]
RBC CAT	k/g Hb (mean ± SD)	209.31 ± 61.92	515.77 ± 127.9	$p < 0.001$	[27]
RBC CAT	U/g Hb (mean ± SD)	184.77 ± 52.50	72.84 ± 9.15	$p < 0.001$	[25]
GST	μmol/min/mL (mean ± SD)	0.42 ± 0.18	0.73 ± 0.37	$p = 0.002$	[34]
RBC SOD	U/g Hb (mean ± SD)	723.78 ± 90.03	993.17 ± 118.31	$p < 0.05$	[32]
RBC SOD	U/g Hb (mean ± SD)	2123.59 ± 543.53	971.31 ± 239.14	$p < 0.001$	[27]
RBC SOD	U/dL blood hemolysate (mean ± SD)	1.51 ± 0.45	1.24 ± 0.33	$p < 0.05$	[33]
RBC SOD	U/g Hb (mean ± SD)	295.06 ± 55.64	109.26 ± 38.57	$p < 0.001$	[25]
RBC XO	U/g Hb (mean ± SD)	143.94 ± 35.68	56.64 ± 17.37	$p < 0.001$	[27]
III. Glutathione					
Total plasma glutathione	μmol/L (mean ± SD)	4.1 ± 0.5	7.6 ± 1.4	$p < 0.001$	[35]
Plasma glutathione	μg/mL (mean ± SD)	22.65 ± 8.15	31.19 ± 11.56	$p < 0.05$	[33]
Total serum glutathione	mM/L (mean ± SD)	0.24 ± 0.162	0.94 ± 0.115	$p \leq 0.001$	[26]
Plasma reduced glutathione (GSH)	μmol/L (mean ± SD)	3.1 ± 0.53	4.2 ± 0.72	$p < 0.0001$	[36]
Plasma GSH	μmol/L (mean ± SD)	3.14 ± 0.56	4.2 ± 0.72	$p < 0.0001$	[37]

Table 1 (continued)

Marker/specimen	Units	Values		*p* value	Reference
		ASD patients	Controls		
Plasma oxidized glutathione (GSSG)	nmol/L (mean ± SD)	0.55 ± 0.2	0.32 ± 0.1	$p < 0.001$	[35]
Plasma GSSG	μmol/L (mean ± SD)	0.54 ± 0.17	0.32 ± 0.06	$p = 0.001$	[34]
Plasma GSSG	μmol/L (mean ± SD)	0.46 ± 0.16	0.35 ± 0.05	$p < 0.005$	[36]
Plasma GSSG	nmol/L (mean ± SD)	0.48 ± 0.16	0.35 ± 0.05	$p < 0.001$	[37]
Plasma total glutathione (GSH + GSSG)	μmol/L (mean ± SD)	4.46 ± 0.33	8.28 ± 1.03	$p = 0.001$	[34]
Plasma GSH/GSSG	– (mean ± SD)	8.6 ± 3.5	25.5 ± 8.9	$p < 0.001$	[35]
Plasma GSH/GSSG	– (mean ± SD)	14.7 ± 6.2	28.2 ± 7.0	$p < 0.0001$	[38]
Plasma GSH/GSSG	– (mean ± SD)	9.45 ± 4.08	18.3 ± 8.6	$p < 0.001$	[39]
Plasma GSH/GSSG	– (mean ± SD)	21 ± 6	47 ± 18	$p < 0.005$	[40]
Plasma GSH/GSSG	– (mean ± SD)	8.03 ± 2.46	26.07 ± 5.03	$p = 0.001$	[34]
IV. Metallothionein					
MT-1A expression in blood	–	Higher (about 14-fold) mRNA level in ASD (RTT) than in controls	No data available	$p \leq 0.001$	[41]
MT-1A expression in PBMCs	–	5-fold higher mRNA expression than in controls	No data available	$p < 0.01$	[42]
MT-1E expression in blood	–	No data available	No data available	No significance	[41]
MT-1E expression in PBMCs	–	Higher mRNA expression (about 301 folds) than in controls	No data available	$p < 0.01$	[42]
MT-2A expression in blood	–	Higher (about 1.5-fold) mRNA level in ASD (RTT) than in controls	No data available	$p \leq 0.01$	[41]
MT-2A expression in PBMCs	–	Higher mRNA expression (about 35-fold) than in controls	No data available	$p < 0.01$	[42]

SD standard deviation; *SE* standard error; *ASD* autism spectrum disorder; *RTT* Rett syndrome; *ADA* adenosine deaminase; *ASD* autism spectrum disorder; *CAT* catalase; *CEP* carboxyethyl pyrrole; *GPx* glutathione peroxidase; *GSH* reduced glutathione; *GSSG* oxidized glutathione; *GST* glutathione-S-transferase; *iso[4]LGE*$_2$ iso[4]levuglandin E$_2$; *LOOH* lipid hydroperoxide; *MDA* malondialdehyde; *mRNA* messenger ribonucleic acid; *MT-1A*, *MT-2A*, *MT-1E* metallothionein genes; *PBMCs* peripheral blood leucocytes; *RBC* red blood cell; *SOD* superoxide dismutase; *TBARS* thiobarbituric acid reactive substances; *XO* xanthine oxidase; *3-NT* 3-nitrotyrosine; *8-iso-PGF2α* 8-isoprostane-F2α; *8OHdG* 8-hydroxy-2deoxyguanosine

*Values were estimated from the graph

**Also, a significant positive correlation between cerebellar 3-NT and Hg levels ($r = 0.7961$, $p = 0.0001$) was found

homeostasis system. ROS are formed as intermediates and byproducts in the energy production cycle in mitochondrial electron transfer chain reactions [71, 72]. The ability of ROS to be scavenged by the enzymatic system of which cells are endowed depends on a huge panoply of proteins, the major of which are superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) [21, 60]. ROS are fundamentally produced by the oxidative reactions occurring during mitochondria activity, which is closely related to endoplasmic reticulum stress (ER stress) and the activity of peroxisomes and proteasomes [60]. The same mitochondria dysfunction depends on the elevated production of ROS by ER stress [73]. Recently reported data showed that the guanosine triphosphatase (GTPase) Rab32, a known regulator of the mitochondria-associated membrane (MAM) proteins, is strongly associated with ER stress, leading to both mitochondrial dysfunction and neurological disorders [74]. The cellular response to oxidative stress involves not only the full endowment of the CYP cytochrome family and many antioxidant enzymes but also complex signaling machinery leading to the expression of the transcription factor called nuclear factor (erythroid-derived 2)-like 2 (Nrf2), which is a leading factor in ROS scavenging [75–78]. Together with the Kelch-like ECH-associated protein 1, this factor plays a major role in the development of many neurodegenerative diseases [78, 79], including ASD [80–82].

Oxidative Stress in the Pathogenesis of Neurodegenerative Disorders and the Importance/Role of Selenium

Increased oxidative stress has been involved in the pathogenesis of several neurodegenerative diseases, including Alzheimer's and Parkinson's disease. In individuals with these diseases, the levels of glutathione peroxidase-4 (GPx4) and selenoprotein P (Sepp 1), as well as the expression of its regulatory genes, are usually in dyshomeostasis. In the Alzheimer's disease, the form of β-amyloid plaques that are associated with low Se concentration and oxidative stress occur [83]. Recently, it was summarized in a review that Se and selenoproteins might be closely involved in neurotransmission due to the antioxidants, inflammation, influencing protein phosphorylation and ion channels, alteration of calcium homeostasis, and brain cholesterol metabolism [84]. Therefore, numerous brain diseases can be manifested with the aid of Se and selenoproteins. For instance, in relation to Alzheimer's disease, maybe selenoproteins affect β-amyloid (Aβ) and hyperphosphorylated tau aggregation and toxicity as well as interact with redox-active metals (Cu, Fe, and Hg) in the brain. It can also be involved in antioxidant enzyme activity and to possess signaling functions via neuronal apolipoprotein E receptor-2 (ApoER2) [85].

It is known that oxidative stress plays an important role also in the pathophysiology of ASD [23, 27, 86–92]. Many studies have reported evidence of oxidative stress in individuals with ASD [24, 27, 28, 32, 33, 35, 38–40, 86, 88, 93–96]. Oxidative stress leads to a number of changes such as lipid peroxidation, protein and DNA oxidation, inflammation, altered immune response, decreased DNA methylation, and epigenetic dysregulation [97] (Fig. 1).

Blood Oxidative Stress Markers in ASD Patients

Antioxidant status in persons with ASD is diminished, suggesting pathology of ASD is associated with increased production of oxidative species and/or incorrect antioxidant metabolism. Thus, ASD can result from defects in the metabolism of cellular antioxidants which maintain intracellular redox status by quenching ROS [3]. Oxidative stress markers are highly associated with considerable cellular injury and manifest severe mitochondrial dysfunction in autistic pathology [24]. In patients with ASD, levels of various oxidative stress markers in blood were found to be increased (Table 1).

Lipid peroxidation in blood plasma is significantly increased in ASD children compared to their neurotypical siblings suggesting enhanced oxidative stress in ASD [23]. RBCs thiobarbituric acid reactive substances (TBARS) as a lipoxidation marker was found to be twice higher in ASD children than in age-matched controls [27]. Chauhan et al. [112] found the significantly increased levels of aminoglycerophospholipids (AGPs) in the blood plasma of children with ASD as compared to their neurotypical developmentally normal siblings, and proposed plasma AGP level as a potential diagnostic marker for ASD. Phospholipid composition of the erythrocyte membrane is altered in ASD. In the RBC membranes of children with ASD in comparison with their neurotypical siblings, the levels of phosphatidylethanolamine (PE) are reduced, whereas phosphatidylserine (PS) is elevated [112]. The increased oxidative stress in ASD can lead to loss of asymmetry of biological membrane and externalization of PS [113] and alteration of AGPs, i.e., PS and PE [23]. Significant depletion of total n-3 polyunsaturated fatty acids (PUFA) in RBC membranes [87] shows evidence of oxidative damage [114]. Lower erythrocyte and plasma GPx activities in ASD were also reported [32].

Selenium is an essential cofactor for GPx [115]. Increased lipid peroxidation [27] and decreased GPx in RBCs of children with ASD [32] suggest a potential deficiency of Se [116]. It was confirmed that GPx activity positively correlates with Se levels [117]. Lower GPx activity in Se deficiency is associated with peroxidative damage and mitochondrial dysfunction [118]. Pre-treatment with Se decreases lipid peroxidation and increases GPx activity [119]. In different studies of children with ASD, the activity of GPx is highly variable [120].

Also, glutathione redox imbalance is a typical event in ASD (Fig. 1, Table 1). Glutathione, an intracellular thiol tripeptide present in all mammalian tissues, plays a key role in cellular protection against oxidant damage [121]. Glutathione is an antioxidant with cellular protective functions, including ROS scavenging in the brain, and is involved in various cellular survival pathways in response to oxidative stress [122]. In ASD, genetic variations in glutathione-related pathways have been found [38, 123–125] and have been correlated with behavior in ASD individuals [126, 127]. Lower concentrations of reduced glutathione (GSH), higher levels of oxidized glutathione (GSSG), and a decrease in the GSH/GSSG redox ratio [35, 38, 93] in ASD patients compared to controls, have been reported. Also, lower GSH levels [128] and markers of increased oxidative stress [129] have been correlated with the severity of ASD. Furthermore, oxidative stress markers were also associated with the severity of gastrointestinal problems in ASD patients [130].

Moreover, the dysregulated pattern of metallothionein (MT) expression in ASD (Rett syndrome) was observed [41]. A higher level of *MT mRNA* expression in peripheral blood leucocytes (PBMCs) in ASD children compared with healthy children were reported [42] (Table 1). In humans, four main MT isoforms were described: the ubiquitous MT-1 and MT-2 [131]—from which MT-1A, MT-1E, and MT-2A are the most abundant ones [132], the brain-specific MT-3 [133], and the squamous epithelium-specific MT-4 [134]. MTs have been implied in neurodegenerative diseases [135–137], and abnormalities in their

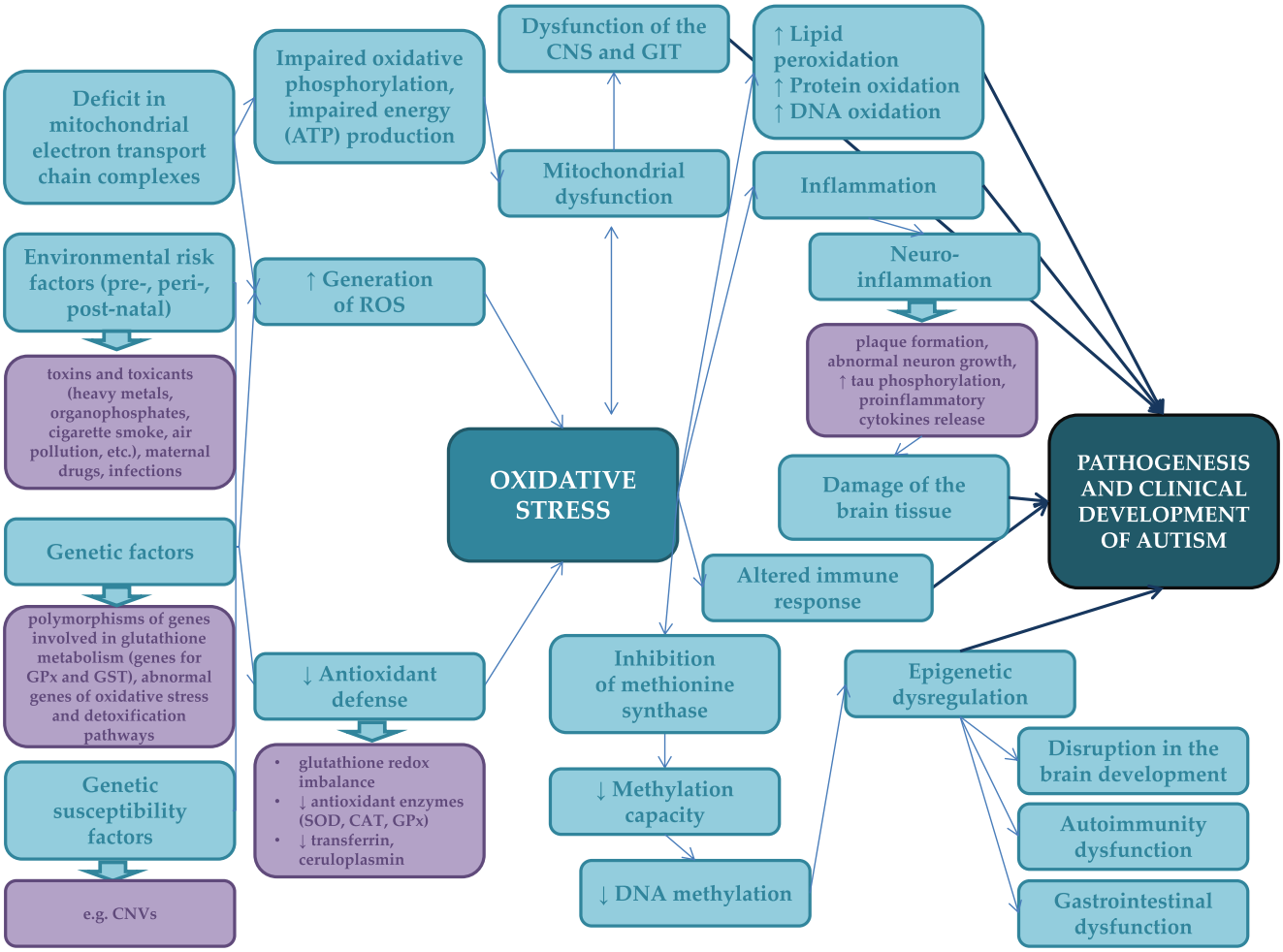


Fig. 1 The role of oxidative stress in the development and pathophysiology of ASD. Scheme of different pathways of oxidative stress in ASD adapted from [97] using literature sources [3, 38, 39, 91, 98–111]. See the text for details. ATP, adenosine triphosphate; CNS, central nervous system; CNVs, copy-number variations; GIT, gastrointestinal tract; ROS, reactive oxygen species; SOD, superoxide dismutase; CAT, catalase; GPx, glutathione peroxidase; *GPX1*, glutathione peroxidase 1 gene; GST, glutathione S-transferase; *GST*, glutathione-S-transferase gene

concentration or structure, as well as the presence of anti-MT antibodies, have been hypothesized to be associated with ASD [138].

Oxidative Stress in the Brain of ASD Patients and the Importance of Selenium as a Free Radical Scavenger

Physiological abnormalities characterizing ASD such as oxidative stress, mitochondrial dysfunction, and immune dysregulation/inflammation (Fig. 1) have been reported not only in studies examining peripheral biomarkers such as blood and urine but also in those focusing on the brain—they have found in brain tissue derived from patients with ASD. The brain regions in which these abnormalities have been found are involved in speech and auditory processing, social behavior, memory, sensory, and motor coordination [139].

The brain is extremely vulnerable to oxidative stress due to its limited antioxidant capacity, high energy demands, and high contents of unsaturated lipids and iron (Fe) [97]. The brain tissue has shown increased levels of markers of oxidative damage, coupled with decreased antioxidant status in the brain of ASD individuals compared with age-matched control persons [97]. In the brain, the levels of lipid hydroperoxide (LOOH) [22], a product of fatty acid oxidation; of malonyldialdehyde (MDA) [140], an end-product of lipid peroxidation; of 8-hydroxy-2′-deoxyguanosine (8-OH-dG) [26, 141–143], a marker of oxidative DNA damage; of protein carbonyl [97], a marker of protein oxidation; and of 3-nitrotyrosine (3-NT) [30], a marker of protein nitration, as well as the expression of carboxyethyl pyrrole (CEP), a marker of lipid-derived oxidative protein modification, were significantly increased in ASD individuals [29]. Also, a greater number of lipofuscin (a matrix of oxidized lipid and cross-linked protein)-containing brain cells was reported in

language-related cortical areas 22, 39, and 44 in ASD [144]. ASD is associated with deficits in glutathione antioxidant defense in selective regions of the brain [145]. In the brain of ASD individuals, decreased the ratio of GSH/GSSG redox/antioxidant capacity and increased oxidative stress were found [146].

Figure 2 demonstrates oxidative stress formation in the brain of ASD patients and the substantial role of Se in protecting neuronal cells against oxidative damage and death. Oxidative stress is a major underlying cause of neurodegenerative and neuroinflammatory disorders and the blood-brain barrier (BBB) injury associated with them [152]. The BBB is a highly selective semipermeable border that separates the circulating blood from the brain, and extracellular fluid in the CNS [153] and is formed by endothelial cells of the capillary wall, astrocyte end-feet ensheathing the capillary, and pericytes embedded in the capillary basement membrane [148].

In the brain of a healthy human, the BBB is due to compact proteins such as claudins, occludin, and junctional adhesion molecules (JAMs) which form together with the tight junction between neighboring endothelial cells of brain capillaries [147] (Fig. 2). The tight junction proteins are then anchored in the endothelial cells by scaffolding proteins such as the zona occludens (ZO-1, ZO-2, ZO-3) [154]. Capillaries present in the CNS are considerably different from those in the remaining parts of the body due to BBB, which creates an irreplaceable filter protecting the brain [155, 156]. In addition to these protective layers, cerebral endothelial cells are equipped with a defense system against oxidative stress including increased GSH, GPx, glutathione reductase (GR), and catalase (CAT) compared to the rest of the brain [157]. Glutathione, in particular, has been shown to play an important role in the maintenance of BBB integrity [158]. Glutathione as a thiol tripeptide is an important antioxidant in the brain. Glutathione is critical for protecting dopamine neurons in the substantia nigra pars compacta from free radical damage [159]. Glutathione is involved in both neuroprotection against oxidative stress and neuroinflammation in ASD by improving the antioxidative stress system [160].

One of the most well-known mechanisms for disruption of the BBB from oxidative stress is via matrix metalloproteinase (MMP) activation which leads to degradation of extracellular matrix (ECM) around cerebral blood vessels and neurons [161] (Fig. 2). MMPs are activated by ROS and cause loss of BBB integrity, which leads to cerebral ischemia-reperfusion injury [162].

The increased production of ROS can exert oxidative stress, and if excess ROS are not properly regulated, they can cause damage to cellular lipids, proteins, and DNA [163]. The neuronal membrane is mainly formed with polyunsaturated fatty acids (PUFAs), especially docosahexaenoic acid [164]. PUFAs are highly susceptible to lipid peroxidation [165–167], which leads to lipid hydroperoxide formation, often as a response to oxidative stress [165]. Products from lipid peroxidation such as 4-hydroxynonenal (HNE) are cytotoxic to neurons [167], and its high level has been found in a variety of neurodegenerative diseases [167–169].

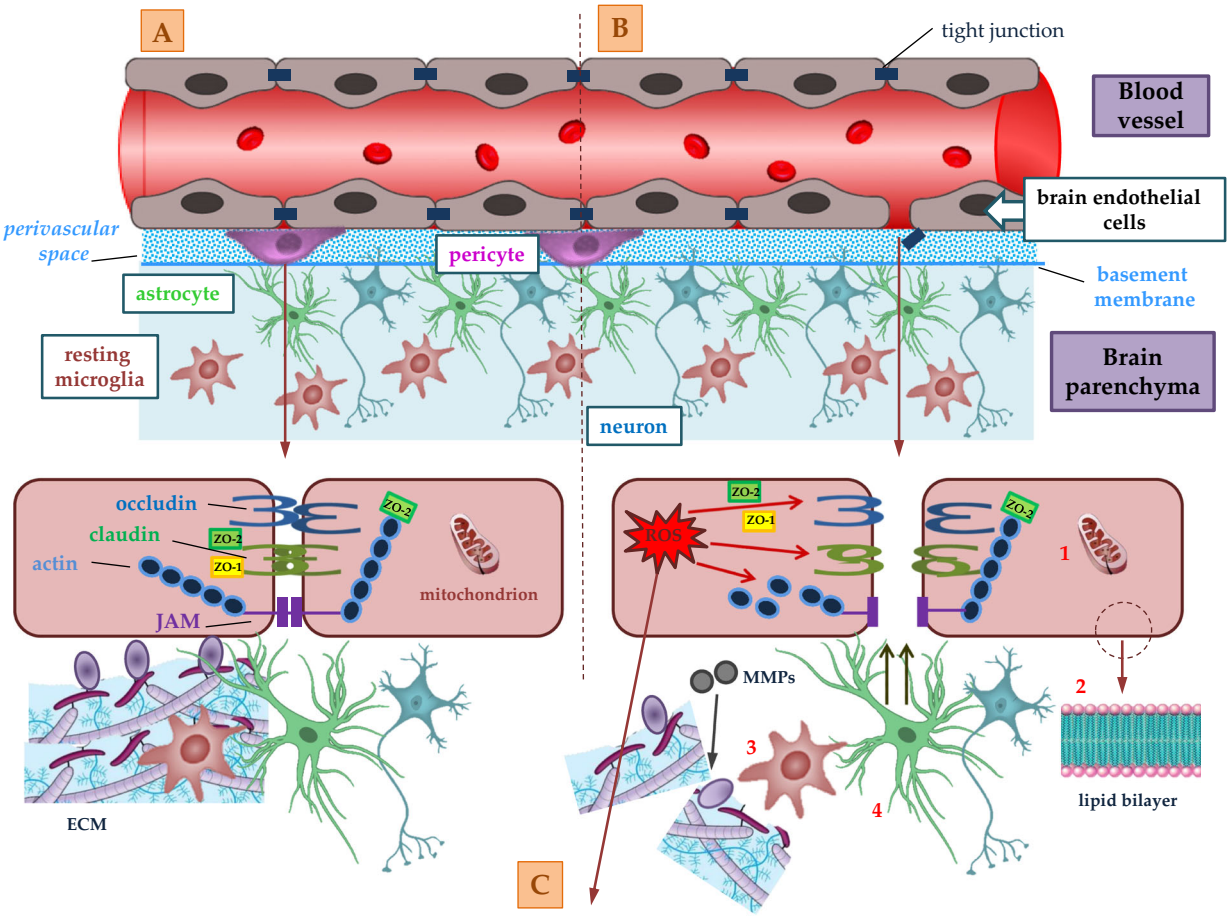
Oxidative Stress, the Central Nervous System, and Neurobehavioral Disorders

The central nervous system (CNS) is particularly vulnerable to oxidative stress because of its limited antioxidant capacity, higher energy requirements, and higher levels of lipids/ketones and iron [170]. The brain makes up about 2% of body mass but consumes 20% of the body's metabolic oxygen. Thus, neurons consume a disproportionately large share of the body's energy [171]. Because of the neurons' lack of glutathione production capacity, the CNS has a limited capacity to detoxify ROS. Therefore, neurons are the first cells to be affected by the increase in ROS and the shortage of antioxidants. In this sense, neurons are the cells most susceptible to oxidative stress [170, 172, 173]. Moreover, antioxidants are required for neuronal survival during the early critical period of CNS development [20].

As such, oxidative stress has been implicated in the pathology of several other neurobehavioral disorders, including schizophrenia, bipolar disorder, and Alzheimer's disease [174–177]. Children are more vulnerable to oxidative stress than adults because of their naturally low GSH levels from conception through infancy [178]. Altogether, these studies suggest that the brain is highly vulnerable to oxidative stress, particularly during the early stage of its development, which may result in neurodevelopmental disorders such as ASD. An increasing amount of recent evidence suggests that redox imbalance and oxidative stress may also contribute to autism pathophysiology [49, 179, 180].

Evidence of Oxidative Stress in Autism Spectrum Disorder

Children with ASD seem to be more vulnerable to oxidative stress in the form of increased lipid peroxidation due to deficient antioxidant defense mechanism, especially as young children (newborns) [181–183]. This finding suggests that early antioxidant supplementation would have a better prognosis as it may decrease the oxidative stress before that stress can induce more irreversible brain damage [49, 184]. Several lines of evidence support an association of oxidative stress with ASD. First, there is evidence of reduced endogenous antioxidant capacity. Specifically, reduced enzymatic activities of GPx, SOD, and CAT and reduced levels of total glutathione and cysteine have been reported [31, 33]. The


A
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tight junction
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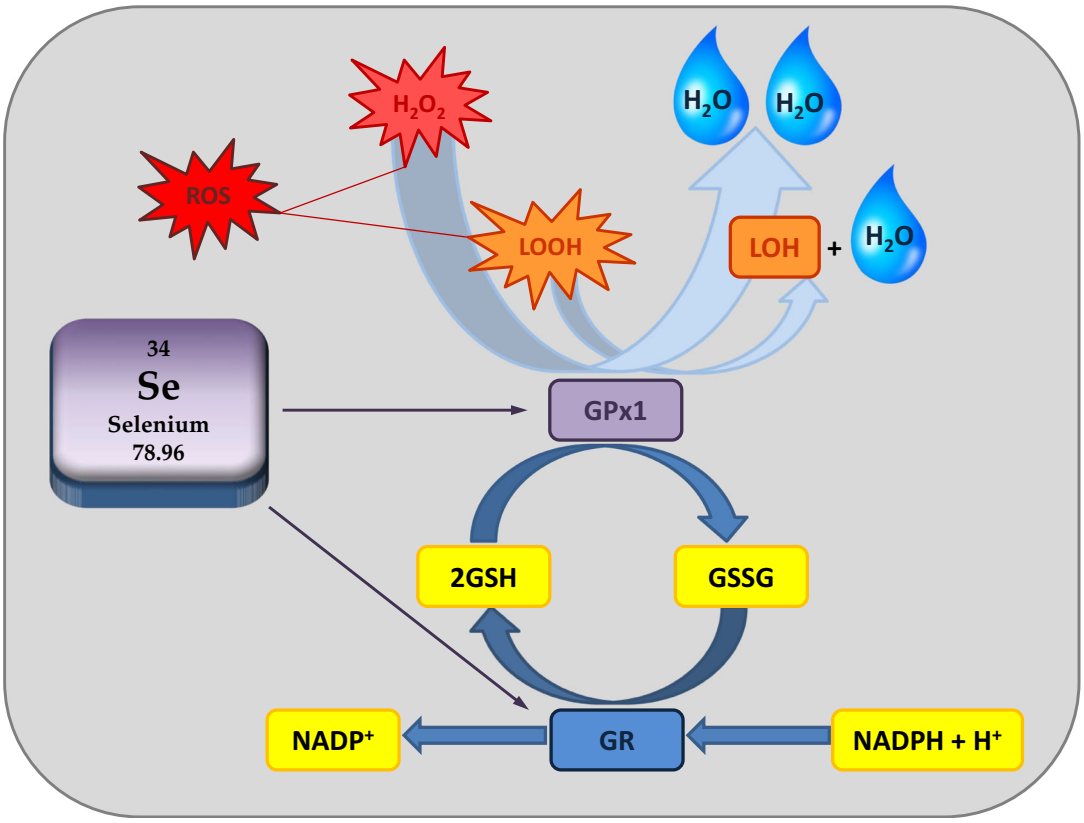
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78.96
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2GSH
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NADP+
GR
NADPH + H+

◀ **Fig. 2** Schematic representation of oxidative stress in the brain of ASD patients and the importance of selenium in its reducing. (A) Intact (undamaged) blood-brain barrier (BBB) in healthy individuals—allows normal diffusion and transport across the BBB [147]. The BBB consists of three basic parts: endothelial cells of the blood capillary, astrocyte of the brain, and pericytes embedded in the basement membrane of the capillary [148]. In the healthy brain, the BBB is intact due to claudins, occludin, and junctional adhesion molecules (JAMs) which create together the tight junction between endothelial cells. Actin and the zona occludens (ZO-1 and ZO-2, etc.) also create a scaffold for the tight junction. This construction is also supported by the extracellular matrix (ECM) [147]. (B) BBB in ADS patients—oxidative stress at brain endothelial cells. If the BBB is damaged, an altered diffusion and transport across the BBB occur. In the unhealthy brain, reactive oxygen species (ROS) accumulate from various sources, including mitochondria (1), the lipid bilayer (2), microglia (3), and astrocytes (4). An excessive formation of ROS causes altering the tight junctions, the breakdown of the ECM by enzymes matrix metalloproteinases (MMPs) and subsequent loss of BBB integrity [147]. (C) Detoxification of hydrogen peroxide (H_2O_2) and lipid hydroperoxides (LOOH) by Se-dependent glutathione peroxidase (GPx) [149]. Se reduces lipid peroxidation and enhances the activity of the selenium-dependent antioxidant enzyme GPx [119]. GPxs are considered to be key players in important biological contexts far beyond the detoxification of hydroperoxides. Se-containing GPxs are only five from eight identified (GPx1–4 and 6) [150]. The main substrate of GPx1 is H_2O_2; however, it can also degrade fatty acid hydroperoxides [151]. GPx reduces free H_2O_2 to water and degrades LOOH to their corresponding alcohols and water. GPx activity requires two molecules of the tripeptide reduced glutathione (GSH) which is converted by the enzyme glutathione reductase (GR) to oxidized glutathione (GSSG) [149], NADPH (nicotinamide adenine dinucleotide phosphate) is consumed in the reaction to form of $NADP^+$ (oxidized form of NADPH)
The figure is adapted from references [147, 149].

significant decreases in the levels of homocysteine, cystathionine, cysteine, and GSH indicate that the trans-sulfuration enzymatic pathway is most probably less efficient in children having ASD diagnosis. The reduction in the levels of these metabolites is consistent with the decrease in methionine levels [185]. Also, there is an increase in the level of GSSG and a decrease in the level of GSH. Collectively, the observed changes in the levels of all those factors are strong evidence that oxidative stress is elevated in those children who have ASD diagnosis [186].

Levels of exogenous antioxidants, including vitamin C, vitamin E, and vitamin A in plasma, and zinc and selenium in erythrocytes were also reportedly reduced in individuals diagnosed with ASD [38, 187, 188]. Moreover, altered (increased) oxidative stress in children with ASD is derived from evidence of their impaired energy metabolism [189].

Magnetic resonance spectroscopic examination of the brains of ASD individuals has found reduced synthesis of ATP. Elevated lactate and pyruvate levels have also been reported [189]. Furthermore, reports have been published showing an improvement in certain behaviors following antioxidant administration to individuals with ASD. In a double-blind, placebo-controlled trial, the authors reported that high-dose vitamin C or carnosine improved autistic behavior over baseline in those who received the test substances while the blinded controls' were essentially unchanged [190]. Likewise, children diagnosed with ASD, who had decreased blood levels of the antioxidants GSH and cysteine as well as a decreased GSH/GSSG ratio compared to the controls, had increases of these following a 3-week supplementation with betaine and folinic acid [33, 191].

Furthermore, increased excretion of oxidative stress biomarkers has been reported in children with ASD (Table 1). Specifically, the excretion of an F_2-isoprostane, 8-iso-prostaglandin $F_{2\alpha}$, is increased in children with ASD diagnosis [28]. The isoprostane is a product of non-enzymatic oxidation of arachidonic acid and is widely recognized as a reliable marker of lipid peroxidation [192]. Recent evidence supports the hypothesis that 8-isoprostane and cysteinyl-leukotrienes are possible markers for the early diagnosis of ASD [193]. Nitric oxide, a free radical that can block energy production, was found to be increased in ASD as compared to age and sex-matched controls [31]. Also, elevated nitrite concentrations have been detected in individuals with ASD diagnosis along with elevations of thiobarbituric acid reactive substances and xanthine oxidase activity in red cells [194].

Furthermore, evidence of oxidative stress in individuals with ASD diagnosis has been recently assessed by the observation that decreased serum levels of SOD might be implicated in the onset and development of ASD diagnosis in children [45]. All these reports strongly suggest that oxidative stress is of the utmost importance in ASD pathogenesis and development.

Finally, based on a recently reviewed relationship between those with ASD diagnosis and their gut microbiome, propionic acid (PPA), which is released from gut microbiome and might have toxic effects, besides some beneficial action, on the mitochondria, may play a key role in those who have ASD diagnosis and PPA has been recently related to the pathogenesis of ASD [195].

Role of Oxidative Stress in Autism Spectrum Disorder

Metallothioneins are small-molecular-weight proteins with free radical scavenging properties. MTs have important roles in metal homeostasis and detoxification. There are four MT isoforms: MT-1, MT-2, MT-3, and MT-4. The classification into classes is based on the position of cysteine residues in the MT polypeptide chain. MT-1 and MT-2 are located in all tissues (particularly the kidney and liver), MT-3 is brain tissue-specific and is known as a growth inhibitory factor which may provide a neuroprotective and antioxidative effect, and MT-4 which is expressed in squamous epithelia associated with the oral mucosa, esophagus, and upper stomach [196, 197]. Metallothionein-3 is mainly expressed in the CNS. MT-3

possesses a unique neuronal growth inhibitory activity, and the levels of this intra- and extracellularly occurring metalloprotein are markedly diminished in the brain of patients affected by a number of metal-linked neurodegenerative disorders. The list of MT-3 functions suggests that it has a role not only in the CNS but also outside this organ. MT-3 in the CNS regulates divalent heavy metal homeostasis. Owing to its antioxidant properties and modulator function not only for Zn but also for Cu in the extra- and intracellular space, MT-3 protects neuronal cells from the toxicity of various Cu(II)-bound amyloids. Earlier studies suggest that Cu dyshomeostasis may contribute to ASD [198]. It is supposed that altered Cu metabolism in ASD may be related to impaired MT system functioning and activation of free radical oxidation [199, 200]. Moreover, certain interactions between zinc and copper may also significantly contribute to ASD pathogenesis via the modulation of the MT system-mediated excitotoxicity [18].

In animal studies, because of the lower enzyme activity levels of SOD and GPx in males than in females, oxidative damage to mitochondrial DNA is 4-fold higher in males compared to females [201]. The higher GSSG level, a reliable marker of intracellular oxidative stress, found in individuals with ASD diagnosis, is supported by the previous work of James et al. [38] that recorded 72% higher GSSG in children with ASD diagnosis as compared to GSSG levels found in neurotypical children. The unexpected, non-significant change in the activity of glutathione reductase (GR) in children having ASD diagnosis, when its activity was compared to the levels in the neurotypical children used as controls, could be explained on the basis that under physiological conditions, GR activity is sufficient to maintain an expected GSH/GSSG ratio. However, excessive intracellular oxidative stress that exceeds the reducing capacity of the patient's GR efficiency will induce the export of GSSG to the plasma in an attempt to regain intracellular redox homeostasis [38, 202]. Also, there is a reported association between genetic predisposition and ASD diagnosis, suggesting that GST contributes to the risk of oxidative stress and ASD [38, 203].

In this context, a fundamental role is exerted by thioredoxin (Trx) levels. The key biological activities of Trx that apply to human diseases can be categorized as antioxidative, growth-promoting, anti-apoptotic, and inflammation-modulating. Beyond its protective role, the Trx system is involved in various cellular processes, such as cell-cell communication, transcriptional regulation, cell signaling, and DNA synthesis [204–206]. Any particular biological property of Trx is unlikely to be either "good" or "bad" in human diseases. Furthermore, the function of Trx depends on the activity of the thioredoxin reductase (TrxR). Overexpression of TrxR as a major antioxidant enzyme could support the hypothesis that oxidative stress is linked with the etiology of ASD [33].

There is mounting evidence that abnormalities of the patients' levels of ROS and NO may underlie a wide range of neuropsychiatric disorders. Abnormal methionine metabolism, high levels of homocysteine, and oxidative stress are also generally associated with neuropsychiatric disorders. NO signaling has been implicated in some physiological functions such as the release of noradrenaline and dopamine. It is thought to have neuroprotective effects at low to moderate concentrations, but excessive NO production can cause oxidative stress to neurons, thus impairing their function [90]. In children with ASD, there were higher levels of homocysteine, which was negatively correlated with GPx activity, low human paraoxonase 1 arylesterase activity, and suboptimal levels of vitamin B_{12} [207–209]. Lipid peroxidation was found to be elevated in individuals having ASD diagnosis, indicating that increased oxidative stress was causally linked to the diagnosis. Moderate to dramatic increases in isoprostane levels decreased levels of phosphatidylethanolamine, and increased levels of phosphatidylserine were observed in children with ASD diagnosis as compared to neurotypical controls. Furthermore, levels of major antioxidant proteins transferrin (iron-binding protein) and ceruloplasmin (copper-binding protein) were found to be significantly reduced in sera of those children with ASD diagnosis. A strong correlation was observed between the reduced levels of these proteins and the child's loss of previously acquired language skills [90].

Another study measured levels of metabolites in methionine pathways in children with ASD diagnosis and found that plasma methionine and the ratio of S-adenosylmethionine (SAM) to S-adenosyl-homocysteine (SAH), an indicator of methylation capacity, were significantly decreased in the children with ASD diagnosis relative to neurotypical controls [38]. Also, plasma levels of cysteine, GSH, and the ratio of GSH/GSSG, indicative of antioxidant capacity and redox homeostasis, were significantly decreased in the group with ASD diagnosis [50, 210, 211]. The same study evaluated common polymorphic variants known to modulate these metabolic pathways in 360 children diagnosed with ASD and in 205 healthy neurotypical controls. Differences in allele frequency and/or significant gene-gene interactions were studied for relevant genes encoding the reduced folate carrier polymorphism (*RFC 80G*), transcobalamin II (*TCN2 776G*), catechol-*O*-methyltransferase (*COMT 472G*), methylenetetrahydrofolate reductase (*MTHFR 677C* and *1298A*), and glutathione-S-transferase (*GST M1*) [38]. Only reduced folate carrier C1 G allele frequency is shown to be elevated in the mothers, but not in the fathers or the ASD children.

Possible Conditions Making Neurons in Pediatric Subjects' Brain Particularly Vulnerable to Oxidative Stress

The high rate of aerobic metabolism and elevated concentrations of oxidizable molecules such as polyunsaturated fatty acids and catecholamines as well iron make the nervous tissue

especially vulnerable to the oxidative stress [22]. Also, several proteins that are involved in normal brain function are vulnerable to oxidative modifications that change their activity. ROS play a critical role in both normal and pathological cell signaling pathways, including kinase activity, calcium homeostasis, and gene regulation. Also, the activities of the receptor and non-receptor types of protein kinase C, protein tyrosine kinases and transcription factors such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kappaB) are controlled by oxidative stress [26]. Membrane phospholipids are linked to most neuronal membrane proteins. Abnormalities in the metabolism of transitional metals such as copper (a pro-oxidant metal) selectively oxidized phosphatidylethanolamine in liposomes containing brain lipids cause deleterious effects in those diagnosed with autism [22, 52, 86, 212]. Excitotoxicity has been reported as a contributing factor in oxidative stress, as well as a result of oxidative stress. Glutamic acid decarboxylase (GAD), an enzyme that transforms glutamate to γ-aminobutyric acid (GABA), a glutamate transporter; glutamine synthase; and GABA receptors are susceptible to oxidative stress [90]. Reduced GABA and elevated extracellular glutamate are renowned for increasing excitotoxicity [213]. Increased levels of plasma glutamate and reduced levels of GAD and glutamine have been reported in individuals with ASD [86, 213, 214].

Oxidative Stress and Immune System Response in ASD?

Previous studies have reported a relationship between deleterious immune system response and oxidative stress. Alterations in phagocyte functions, such as chemotaxis, adherence, or tumor necrosis factor-α (TNF-α) production, have been reportedly correlated with oxidative stress in endotoxin-stimulated septic shock [45, 215]. The oxidant and antioxidant balance are fundamental for the normal functioning of the immune system's cells because these cell functions are specially linked to ROS generation [86, 215]. Serotonin, found mostly in the gut where the majority (about 70%) of the human immune system resides, is an immune system modulator among its other functions. Elevated serotonin levels have been found in the blood of patients with ASD diagnosis [216–218]. Its increased levels might also lead to gut dysfunction and immune alterations in such subjects. Decreased response to T cell mitogens, depletion of $CD4^+$ (cluster of differentiation 4) T-helper/inducer cells, reduced natural killer cell activity, and increased neopterin levels in urine and plasma are immune system abnormalities in individuals with ASD [86, 202]. The pathogenesis of a patient diagnosed with ASD includes an imbalance in serum cytokines and immunoglobulins [219, 220], and inappropriate antibody response to the combined live measles, mumps, and rubella (MMR) virus vaccine [86, 221]. ROS and oxidative stress could participate in exacerbating the neuroinflammation pattern observed in ASD [11, 222].

Conclusion

Oxidative stress-induced mechanisms are believed to be the major cause for ASD [24] along with certain other physiological abnormalities, which characterize this disease such as mitochondrial dysfunction and immune dysregulation/inflammation [139]. Figure 1 summarizes many of the knowledge addressed in this review. Interactions between genetic and environmental factors may potentiate increased oxidative stress in ASD children [3]. Among genetic factors, polymorphisms of genes involved in the metabolism of glutathione [3] such as *GPX1* [98] and *GST* [99], abnormality in genes of oxidative stress, and detoxification pathways are known [38, 100, 101]. Also, copy-number variations (CNVs) in ADS pathogenesis have been described [102]. Environmental factors include a number of influences that can threaten the individual prenatally or perinatally as well as postnatally [97]. These include the exposure of the mother or the child to heavy metals [17, 91, 223–232], infections [103], some drugs [97, 233], and other toxins from the environment such as cigarette smoke, polluted air, and organophosphate pesticides [91]. Recently, increased risk for an atypical autism diagnosis following a thimerosal-containing vaccine has been reported [234].

Moreover, the amount of Hg in the hair of children with ASD showed a significant correlation with the number of maternal dental amalgams [233]. In children with ASD, 2.5-fold higher oral antibiotic use during their first 18 months of life was observed [233]. Mitochondrial dysfunction and aberrant accumulation of transition metals may lead to the excessive generation of ROS [235]. Increased generation of ROS and decreased antioxidant defense lead to an imbalance between the production of free radicals and the ability of the body to counteract or detoxify their harmful effects — oxidative stress [97]. Oxidative stress causes a variety of undesirable processes such as oxidative degradation of lipids, proteins, and DNA [236], and inflammation changes [97, 237] which can cause damage brain tissue damage [104], modifies the immune response [97] and inhibits methionine synthase [105, 238], resulting in decreased DNA methylation [106] and epigenetic dysregulation, which all lead to the clinical symptoms of ASD [97].

The evidence indicates that *oxidative stress is an integral part of the pathophysiology (or physiopathology) of ASD* and is related to the severity of the characteristic symptoms exhibited by subjects having ASD. However, the ability to fully elucidate the mechanisms by which ROS and RNS exacerbate or induce ASD during neurodevelopment is still far to be fully accomplished and ask for further insightful evidence and clinical reports. While the current literature suggests that

improving the oxidative status of children with ASD diagnosis has the potential to reduce the affected child's symptoms, a suggestion that should be considered as a target for ameliorative therapeutic interventions, many further research studies are needed to comprehend how helping children with this pathology.

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