Contribution of Oxidative Stress to the Pathophysiology of Autism Spectrum Disorders: Impact of Genetic and Environmental Factors

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Abbreviations

ADHD	Attention deficit hyperactivity disorder
ASDs	Autism spectrum disorders
BPA	Bisphenol A
CNS	Central nervous system
COX	Cyclooxygenase
DNA	Deoxyribonucleic acid
EDCs	Endocrine-disrupting chemicals
ER	Estrogen receptors
ETC	Electron transport chain
GABA	Gamma aminobutyric acid
Glo 1	Glyoxalase 1
GPx	Glutathione peroxidase
GSH	Glutathione
GSSG	Oxidized glutathione
GSTM1	Glutathione S-transferase M1
H_2O_2	Hydrogen peroxide
IFN	Interferon
IL	Interleukin
iNOS	Inducible nitric oxide synthase
LPS	Lipopolysaccharide
MAOA	Monoamine oxidase A

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MD	Mitochondrial dysfunction
MDA	Malonyldialdehyde
mGluR5	Metabotropic glutamate receptor 5
MMP	Mitochondrial membrane potential
MTHFR	Methylene tetrahydrofolate reductase
NO	Nitric oxide
$ONOO^-$	Peroxynitrite anions
PBDEs	Polybrominated diphenyl ethers
PCBs	Polychlorinated biphenyls
PDD-NOS	Pervasive developmental disorder-not otherwise specified
PDDs	Pervasive developmental disorders
PDE	Phosphodiesterase
PE	Phosphatidylethanolamine
RBC	Red blood cell
RFC	Reduced folate carrier
RNS	Reactive nitrogen species
ROS	Reactive oxygen species
SAH	*S*-adenosinehomocysteine
SAM	S-adenosylmethionine
SNPs	Single nucleotide polymorphisms
SOD	Superoxide dismutase
TBA	Thiobarbituric acid
TNF	Tumor necrosis factor
VPA	Valproic acid
XO	Xanthine oxidase

1 Autism Spectrum Disorders (ASDs)

ASDs are neurodevelopmental disorders characterized by impairments in social interactions and in verbal and nonverbal communication skills and by restricted, repetitive, and stereotyped patterns of behavior (Lord et al. 2000). ASDs include autistic disorder (also called "classical" autism), Asperger syndrome, and pervasive developmental disorder-not otherwise specified (PDD-NOS). Pervasive developmental disorders (PDDs) is a broader category, which includes the ASDs above, plus childhood disintegrative disorder and Rett syndrome. According to a recent report from the Centers for Disease Control and Prevention, the prevalence of ASDs in the USA is 1 in 68 children (Wingate et al. 2014). The symptoms of ASDs are typically present before the age of 3 years and are often accompanied by abnormalities in cognitive functioning, learning, attention, and sensory processing. Some children first show signs of normal social and language development, but these developmental skills are lost at 15–24 months and they develop autistic behavior, a condition known as regressive autism (Ozonoff et al. 2005). The reported incidence of regressive autism varies from 15 to 62 % of cases in different studies (Goldberg

et al. 2003; Hansen et al. 2008; Lord et al. 2004; Stefanatos 2008). In a few cases, regression may significantly affect language, with a lesser impact in other domains such as social interaction or imaginative play (Goldberg et al. 2003; Stefanatos et al. 1995). On the other hand, some children may regress particularly in social functions and not in language (Luyster et al. 2005).

While the cause of autism remains elusive, autism is considered a multifactorial disorder that is influenced by multiple genes and environmental factors. Some studies have suggested prenatal and perinatal onset for developmental abnormalities in autism (Kolevzon et al. 2007; Kinney et al. 2008; Miller et al. 2005). Although autism is behaviorally defined, many biochemical and immunological abnormalities have been reported in autism (Chauhan and Chauhan 2006; Chauhan et al. 2009a, 2011b, 2012, 2012a, b; Pardo-Villamizar and Zimmerman 2009; Onore et al. 2012; Rossignol and Frye 2012a, b). Extensive evidence from our and other groups suggests that oxidative stress may serve as a common link between susceptibility genes and environmental risk factors, resulting in the clinical development of autism (Chauhan and Chauhan 2006; Chauhan et al. 2009a; Deth et al. 2008; Herbert 2010).

2 Oxidative Stress

Under normal conditions, a dynamic equilibrium exists between the production of free radicals and the antioxidant capacity of the cell. Free radicals include reactive oxygen species (ROS) (such as superoxide and hydroxyl) and reactive nitrogen species (RNS) (such as peroxynitrite and nitrite) (Fig. 1). Oxidative stress occurs when ROS levels exceed the antioxidant capacity of the cell. Elevated ROS levels can be due to increased ROS generation or decreased antioxidant capacity or both.

3 Oxidative Stress in Autism: Increased Oxidative Damage Coupled with Reduced Antioxidant Defense

Numerous studies have provided evidence for elevated oxidative damage and reduced antioxidant defense in autism. Any condition that generates imbalance of free radicals will lead to oxidative stress. We hypothesized that increased vulnerability to oxidative stress by endogenous or environmental prooxidants in conjunction with genetic susceptibility factors may contribute to the development and clinical manifestations of autism (Chauhan and Chauhan 2006). In fact, the markers of lipid peroxidation, protein oxidation, and/or DNA oxidation have been reported to be increased in blood and urine and in postmortem brain samples from subjects with autism. We reported increased levels of malonyldialdehyde (MDA), a marker of lipid peroxidation in the plasma of children with autism compared to their typically developing siblings (Chauhan et al. 2004a), as well as increased lipid peroxidation (Chauhan et al. 2011b; Muthaiyah et al. 2009), DNA oxidation (Chauhan

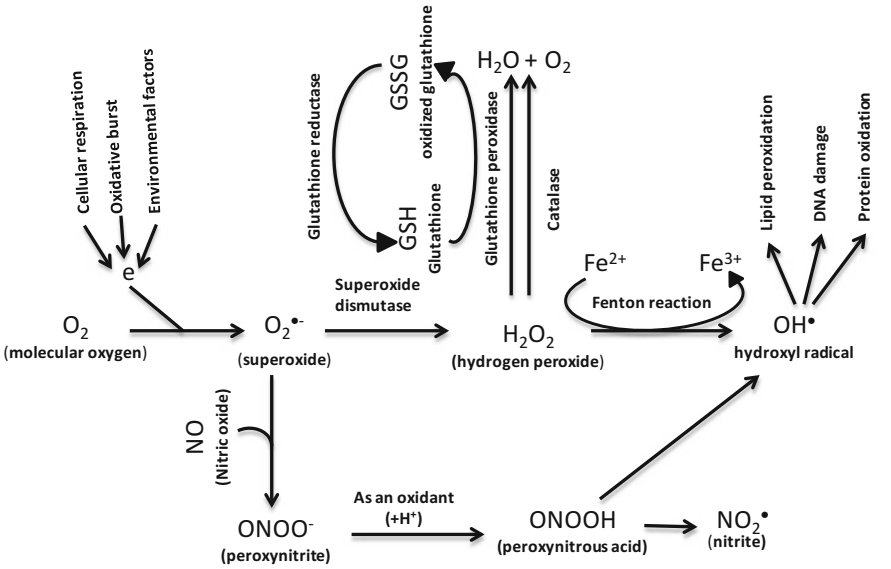

Fig. 1. The generation of free radicals (ROS and RNS) and antioxidant defense system. Molecular oxygen is reduced by an electron, which is provided by cellular respiration, oxidative burst, or environmental factors, and as a result, superoxide radicals are generated. Superoxide is converted to hydrogen peroxide (H_2O_2) by superoxide dismutase (SOD). H_2O_2 either is neutralized to H_2O and O_2 by glutathione peroxidase (GPx) and catalase, or it can produce hydroxyl radical ($OH^{\bullet}$) by Fenton reaction. During conversion of H_2O_2 into H_2O, reduced glutathione (GSH) is oxidized by GPx. Oxidized glutathione (GSSG) is then converted back to its reduced form by glutathione reductase. RNS are produced when nitric oxide (NO) reacts with superoxide to generate peroxynitrite ($ONOO^-$), a free radical. $ONOO^-$ is an oxidant and gives rise to peroxynitrous acid (ONOOH), which generates nitrite and hydroxyl free radicals. Hydroxyl radicals are the most potent free radicals that oxidize lipids, proteins, and DNA, leading to cellular damage

et al. 2011a), and protein oxidation (Chauhan et al. 2010) in the cerebellum and frontal and temporal regions of the brain in autism. Other studies also indicated increased levels of lipid peroxidation and protein oxidation markers in autism, thus confirming increased oxidative stress in autism. Zoroglu et al. (2004) reported increased thiobarbituric acid (TBA)-reactive substances in the erythrocytes of autism subjects as compared to normal controls. Ming et al. (2005) reported increased excretion of 8-isoprostane-F2α in the urine of children with autism. Isoprostanes are produced from the free radical oxidation of arachidonic acid through nonenzymatic oxidation of cell membrane lipids. Evans et al. (2008) reported increased levels of lipid-derived oxidative protein modification, i.e., carboxyethyl pyrrole and iso 4-levuglandin E2-protein adducts, in the brain, primarily in the white matter of autistic subjects. Sajdel-Sulkowska et al. (2009) reported increased levels of 3-nitrotyrosine (a specific marker for oxidative damage of protein) in the cerebellum of autistic subjects. The density of lipofuscin, a matrix of oxidized lipid and cross-linked protein, was also observed to be greater in the

cortical brain areas involved in social behavior and communication in autism (López-Hurtado and Prieto 2008).

As represented in Fig. 1, many enzymes participate in the elimination of free radicals. Alterations in the enzymes that play a vital role in the antioxidant defense mechanism against damage by ROS have also been reported in autism. For instance, compared to control subjects, individuals with autism showed decreased activity of glutathione peroxidase (GPx) in erythrocytes and plasma (Yorbik et al. 2002; Pasca et al. 2006) and decreased activities of catalase (Zoroglu et al. 2004) and superoxide dismutase (SOD) (Yorbik et al. 2002) in erythrocytes. We also reported increased oxidative damage and free radical generation, coupled with reduced activities of antioxidant enzymes, in lymphoblastoid cells from autistic subjects compared with age-matched control subjects (Essa et al. 2009).

In a study of Egyptian children, oxidative stress was found in 88.64 % of autistic children, as revealed by elevated plasma F2-isoprostane and/or reduced GPx levels (Mostafa et al. 2010). In Saudi children with autism, decreased glutathione (GSH) levels and SOD activity in red blood cells (RBCs) were observed (Al Gadani et al. 2009). Meguid et al. (2011) recently reported lower levels of SOD and GPx and increased lipid peroxidation in blood samples from autistic children as compared with control subjects.

Glutathione is the most important endogenous antioxidant for detoxification and elimination of environmental toxins and free radicals. Several clinical studies have reported lower levels of reduced glutathione (GSH), higher levels of oxidized glutathione (GSSG), and a lower redox ratio of GSH/GSSG in the plasma of individuals with autism (Adams et al. 2009, 2011; Al Gadani et al. 2009; Bertoglio et al. 2010; Geier et al. 2009; James et al. 2004, 2006). Recently, we have reported reduced levels of GSH, increased levels of GSSG, and a decrease in the ratio of GSH/GSSG in the cerebellum and temporal cortex of autistic subjects compared with age-matched control subjects (Chauhan et al. 2012a, b). In another study, James et al. (2009) reported a decreased ratio of GSH/GSSG in the lymphoblastoid cells from autistic subjects.

Ceruloplasmin (a copper-transporting protein) and transferrin (an iron-transporting protein) are major antioxidant proteins that are synthesized in several tissues, including the brain (Loeffler et al. 1995; Arnaud et al. 1988). Ceruloplasmin inhibits the peroxidation of membrane lipids catalyzed by metal ions, such as iron and copper (Gutteridge 1983). It also acts as ferroxidase and SOD, and it protects polyunsaturated fatty acids in RBC membrane from active oxygen radicals (Arnaud et al. 1988). Transferrin acts as an antioxidant by reducing the concentration of free ferrous ion (Loeffler et al. 1995). Ferrous ion contributes to oxidative stress by catalyzing the conversion of H_2O_2 to highly toxic hydroxyl radicals by the Fenton reaction (McCord and Day 1978). In addition, the Fe^{3+}-protoporphyrin (heme) group is also present in the four protein subunits of catalase enzyme (Chance and Schonbaum 1962). We have reported reduced levels of ceruloplasmin and transferrin in the serum of children with autism as compared to their developmentally normal siblings (Chauhan et al. 2004a). Interestingly, the levels of ceruloplasmin and transferrin were reduced more effectively in children with regressive autism who had lost

previously acquired language skills (Chauhan et al. 2004a). Other preliminary studies have also suggested altered serum Cu/Zn ratios in autism (McGinnis 2004).

Aberrant metabolism of the methionine cycle has also been suggested in autism. Methionine is a main amino acid in the metabolism of glutathione. Hyperhomocysteinemia can cause oxidative stress via a number of mechanisms such as auto-oxidation of homocysteine to form ROS (Heinecke et al. 1987), increased lipid peroxidation (Jones et al. 1994), and reduced production of GPx (Upchurch et al. 1997). Pasca et al. (2006) reported higher levels of total homocysteine in the plasma of children with autism compared with control subjects. In the autistic group, a strong negative correlation was observed between homocysteine levels and GPx activity, suggesting an association between high levels of homocysteine and oxidative stress in autism. Within the methionine cycle, there are redox-sensitive enzymes, i.e., methionine synthase, betaine homocysteine methyltransferase, and methionine adenosyltransferase, which are downregulated by oxidative stress. Clinical studies have reported lower concentrations of methionine, homocysteine, cystathionine, and cysteine as well as a decreased ratio of S-adenosylmethionine (SAM)/*S*-adenosinehomocysteine (SAH), an indicator of methylation capacity in the plasma of children with autism (Adams et al. 2011; Geier et al. 2009; James et al. 2004, 2006). An increased vulnerability to oxidative stress and a decreased capacity for methylation (significantly lower ratio of SAM to SAH) is, therefore, suggested in autism. According to the "redox/methylation hypothesis of autism" proposed by Deth et al. (2008), oxidative stress initiated by environmental factors in genetically vulnerable individuals leads to impaired methylation and neurological deficits secondary to reductions in the capacity for synchronizing neural networks. Interestingly, the parents of autistic children were found to share similar metabolic deficits in methylation capacity and GSH-dependent antioxidant/detoxification capacity, as observed in autistic children (James et al. 2008).

Xanthine oxidase (XO) is an endogenous prooxidant that produces superoxide radicals during conversion of xanthine to uric acid (Kellogg and Fridovich 1975). Increased XO activity has been reported in the erythrocytes of autistic subjects (Zoroglu et al. 2004).

Nitric oxide (NO) is another free radical that can react with superoxide anion and generate cytotoxic peroxynitrite anions ($ONOO^-$) (Fig. 1). NO is known to affect the development and function of the central nervous system (CNS). Its role has been implicated in neurotransmitter release (Lonart et al. 1992), neurite growth (Hindley et al. 1997), synaptogenesis (Truman et al. 1996), memory and learning (Holscher and Rose 1992), and macrophage-mediated cytotoxicity (Hibbs Jr. et al. 1988). The expression of inducible nitric oxide synthase (iNOS) and the production of NO are also known to affect inflammatory processes (Wong and Billiar 1995). The induction of iNOS is mediated by the cytokines, namely, interferon (IFN)-γ, tumor necrosis factor (TNF)-α, and interleukin (IL)-1β (Nussler et al. 1992). Sogut et al. (2003) reported increased NO levels in the RBCs of autistic subjects and suggested that NOS may be activated in autism. Elevated plasma levels of nitrite and nitrate in autism were also reported by Zoroglu et al. (2003) and Sweeten et al. (2004). A positive correlation was observed between nitrates and IFN-γ levels in the autistic

subjects, suggesting an association of elevated plasma NO with IFN-γ activity in autism (Sweeten et al. 2004).

It was reported that cholinergic receptors known to be sensitive to NO• toxicity were decreased in the cortex of subjects with autism (Perry et al. 2001). Additionally, treatment with cholinergic agonists improved behavioral abnormalities in autism (Hardan and Handen 2002). In other studies, gamma aminobutyric acid (GABA) receptors that are sensitive to oxidative stress were reduced in the hippocampus of individuals with autism (Blatt et al. 2001), and an association between a GABA(A) receptor beta 3 (GABRβ3) polymorphism with autism was suggested by Buxbaum et al. (2002). Fatemi et al. (2011) reported that upregulation of metabotropic glutamate receptor 5 (mGluR5) is associated with the underexpression of both fragile X mental retardation protein (FMRP) and GABRβ3 in autism. It has been suggested that a dysfunction of GABAergic signaling in early development may lead to a severe synaptic excitatory/inhibitory imbalance in neuronal circuit, which may be a contributing factor in the behavioral deficits observed in ASDs (Pizzarelli and Cherubini 2011).

4 Genetic Susceptibility to Oxidative/Nitrosative Stress in Autism

The cause of autism is not known, but genetic and environmental factors have been suggested to contribute to the etiology of autism. Gene mutations or deletions, copy number variations, and other genetic abnormalities are all persuasively linked to autism (Sutcliffe 2008). It has been suggested that a genetically susceptible population may be vulnerable to oxidative/nitrosative stress in autism. In addition, mutations in genes involved in oxidative/nitrosative stress may also facilitate oxidative stress in autism. Kim et al. (2009b) genotyped nine single nucleotide polymorphisms (SNPs) in the NOS-I gene and nine SNPs in the NOS-IIA gene, and conducted a transmission disequilibrium test (TDT) and haplotype analysis in 151 Korean ASD trios. They reported significant evidence for an association between NOS-IIA and ASD in the Korean population.

Glyoxalase 1 (Glo 1) plays a critical role in the detoxification of dicarboxylic compounds, thereby reducing the formation of advanced glycation end products. Glo 1 uses GSH as a cofactor to detoxify cytotoxic 2-oxoaldehydes, such as methylglyoxal, which are produced by lipid peroxidation, glycation, and degradation of glycolytic intermediates (Thornalley 2003). While two studies reported an SNP in Glo 1 in autism (Junaid et al. 2004; Sacco et al. 2007), other studies did not find an association between Glo 1 gene and autism (Rehnstrom et al. 2008; Wu et al. 2008).

Monoamine oxidase A (MAOA) catalyzes the oxidation of endogenous amine-containing neurotransmitters such as serotonin and norepinephrine (Fitzpatrick 2010). The role of MAOA in autism is of particular interest because this enzyme affects the levels of serotonin, which are known to be abnormal in some individuals with autism (Cohen 2010; Hranilovic et al. 2007). A 30-base pair (bp) repeat polymorphism

(uVNTR) within the MAOA promoter region consists of 3, 3.5, 4, or 5 copies. Expression studies have indicated that the number of repeats determines the transcriptional efficiency of the MAOA gene. In comparison to other alleles, the 3-repeat allele is associated with reduced transcription and, therefore, reduced activity of MAOA (Sabol et al. 1998; Denney et al. 1999). An association of the 3-repeat MAOA-uVNTR allele (low activity) with increased severity of autism has been reported (Cohen et al. 2003; Cohen 2010; Cohen et al. 2011). Yoo et al. (2009) also reported preferential transmission of the 3-repeat allele of an MAOA-uVNTR marker in ASDs in a Korean population. Furthermore, Davis et al. (2008) reported an association between MAOA-uVNTR polymorphism and brain growth in autism. A magnetic resonance imaging (MRI) study showed an increase in the volume of white matter in the brain of children with autism who have the low-activity, 3-repeat allele compared to those with a high-activity, 4-repeat allele.

Cyclooxygenase (COX) is an enzyme that is responsible for the formation of important biological mediators called prostanoids, including prostaglandins, prota-cyclin, and thromboxane. During inflammation, COX-2 is rapidly induced by growth factors, cytokines, and inflammatory molecules. Yoo et al. (2008) examined the relationship between ASDs and polymorphism of PTGS2 (the gene encoding COX-2) in 151 Korean family trios including children with autism. They reported a significant association of one intronic SNP (OS2745557) and the GAAA haplotypes with ASDs.

The role of the folate gene polymorphism has also been suggested in autism. Adams et al. (2007) reported that the 19-bp deletion polymorphism of dihydrofolate reductase may act independently or in concert with related folate polymorphisms as a significant risk factor for autism. James et al. (2006) reported differences in allele frequency and/or significant gene-gene interactions for genes encoding the reduced folate carrier (RFC) and methylene tetrahydrofolate reductase (MTHFR). Recently, Schmidt et al. 2012 reported association of maternal periconceptional folic acid intake with reduced ASD risk, which was strongest for mothers and children with MTHFR 677 C>T variant genotypes. Folate deficiency can increase oxidative stress by increasing the levels of homocysteine, and it can also contribute to increase in cytosolic calcium and to subsequent mitochondrial and DNA damage.

5 Role of Mitochondria in Free Radical Generation and Mitochondrial Dysfunction in Autism

Free radicals are generated endogenously during oxidative metabolism and energy production by mitochondria in the cell (Cadenas and Davies 2000; Lenaz 2001). The mitochondrial respiratory chain, also known as the electron transport chain (ETC), consisting of five enzymes, i.e., complexes I–V, is responsible for the generation of energy in the form of ATP (Bertram et al. 2006; Szewczyk and Wojtczak 2002). ETC complexes I–IV generate a proton gradient, i.e., mitochondrial membrane potential (MMP), which is needed by complex V (ATP synthase) for ATP

production. The mitochondria are also one of the main sources of free radicals, i.e., ROS and RNS, and they induce oxidative stress and trigger apoptosis (Brookes et al. 2002; Cadenas and Davies 2000; Lenaz 2001; Polster and Fiskum 2004). As shown in Fig. 1, molecular oxygen during cellular respiration is reduced to superoxide radical. Mitochondrial ETC complexes I and III are the main sites of production of superoxide radical by mitochondria (Barja 1999; Muller et al. 2004). While oxidative phosphorylation in the mitochondria generates superoxide anions, enzymatic oxidation of biogenic amines by MAO in the outer mitochondrial membrane produces H_2O_2.

Mitochondria play an important role in regulating developmental processes, including neurite outgrowth, axonal plasticity, and synaptic plasticity (Mattson and Liu 2002). The brain has a high demand for energy, and neurons contain a large number of mitochondria, especially in synapses. Therefore, neurons' function and plasticity rely on mitochondria, which are localized in synapses. Alterations of the number, morphology, or function of synaptic mitochondria can be detrimental to synaptic transmission (Polster and Fiskum 2004).

In a recent meta-analysis of data in the literature, Rossignol and Fyre (2012a) reported the strongest evidence for immune dysregulation/inflammation and oxidative stress, followed by toxicant exposures and mitochondrial dysfunction (MD) in autism. Several studies with blood, muscle biopsy, and postmortem brain tissue samples have suggested mitochondrial dysfunctions in a subset of individuals with autism (Chauhan and Chauhan 2012; Chauhan et al. 2011b, 2012b; Gargus and Imtiaz 2008; Haas 2010; Palmieri and Persico 2010; Rossignol and Frye 2012b). The review of previous reports and meta-analysis conducted by Rossignol and Frye (2012b) suggested deficiencies of complexes I, III, V, IV, and II in 53 %, 30 %, 23 %, 20 %, and 9 % of children with ASD and concomitant MD, respectively. Multiple complex deficiencies were reported in 36 % of the children with ASD/MD. In the lymphoblastoid cells from autistic subjects, we reported reduced MMP and increased free radical generation (Chauhan et al. 2009b). Recently, we also reported brain region-specific changes in the levels of mitochondrial ETC complexes, in subjects with autism. In autistic children (4–10 years of age), we observed significantly lower levels of complexes III and V in the cerebellum of complex I in the frontal cortex and of complexes II, III, and V in the temporal cortex as compared to age-matched control subjects (Chauhan et al. 2011b). These studies suggest that MD in autism may occur due to ETC abnormalities, which in turn may induce oxidative stress (Chauhan et al. 2012b).

6 Environmental Risk Factors in Autism

Genetic abnormalities alone cannot account for the majority of autism cases. Therefore, environmental factors either alone or collectively with susceptibility genes have been suggested to be involved in the etiology of ASDs (Chauhan and Chauhan 2006; Chauhan et al. 2009a; Daniels 2006; Deth et al. 2008). Both prenatal and/or postnatal exposures to certain environmental factors, such as metals, viruses, maternal

drugs, bisphenol A (BPA), organophosphate insecticides, polychlorinated biphenyls (PCBs), phthalates, etc., have been linked to the developmental problems related to autism. In a recent review, Herbert (2010) also stressed the need to explore the link between genetics, environmental factors, and oxidative stress in autism. Many of the hypotheses regarding the pathogenesis of ASDs involve a functional deficit caused by alterations in specific brain structures occurring in utero during defined temporal windows of vulnerability (Polleux and Lauder 2004). Some of the environmental factors that may contribute to the etiology of autism are discussed below.

6.1 Metals

Toxic metals have long been suspected to be involved in autism. We reported previously that levels of transferrin (an iron-transporting protein) and ceruloplasmin (a copper-transporting protein) are decreased in the serum of children with autism. Interestingly, there was a relationship between reduced levels of these proteins and regression in autism (Chauhan et al. 2004a). In another study, we reported reduced levels of phosphatidylethanolamine (PE), a membrane phospholipid in the erythrocyte membrane of children with autism (Chauhan et al. 2004b; Chauhan and Chauhan 2009). Among the various metal cations (copper, iron, calcium, cadmium, and zinc) studied, only copper was found to oxidize and decrease the levels of membrane PE. The action of copper on PE oxidation was time- and concentration-dependent (Chauhan et al. 2008). Other investigators have also reported abnormalities of copper metabolism in children with autism. Lakshmi and Geetha (2011) studied 45 autistic children with different grades of severity, i.e., low-, medium-, and high-functioning autism, and reported a correlation between copper burden and severity of disease. They also observed significantly higher levels of lead and mercury in hair and nail samples of children with autism as compared to normal control subjects. In another study, of 230 children with autistic disorder, PDD-NOS, and Asperger syndrome, Faber et al. (2009) reported increased levels of copper, decreased levels of zinc, and reduced zinc/copper ratio in the plasma of children with autism. However, Jackson and Garrod (1978) did not observe alterations in plasma levels of zinc and copper in the children with autism compared to control subjects. Similarly, in a cross-sectional case–control study and a meta-analysis, including the present and previous similar studies, De Palma et al. (2011) excluded any association of autism with concentrations of mercury, cadmium, selenium, lithium, and copper in the hair. The discrepancy in results between different studies can be attributed to the different ages of subjects studied and/or the severity of ASDs. Among all metals, the role of exposure to mercury from consumption of contaminated seafood during pregnancy, dental amalgams, and the thimerosal (mercury-based preservative) used in childhood vaccines (until recently) and flu vaccines remains a most controversial issue in autism. In particular, the measles–mumps–rubella (MMR) vaccination in children as a risk factor for the development of autism has been a subject of great debate. However, large-scale studies have not found any credible evidence for a link between vaccines and autism (Heron and Golding 2004;

Hertz-Picciotto et al. 2010; Honda et al. 2005; Kaye et al. 2001; Madsen et al. 2002; Taylor et al. 1999; Thompson et al. 2007).

6.2 Maternal Infections

There is a large body of epidemiological data suggesting an association between maternal infections (both bacterial and viral) during pregnancy and increased incidence of neuropsychiatric disorders such as autism and schizophrenia (Arndt et al. 2005; Cannon and Clarke 2005; Patterson 2011). There is also considerable epidemiological evidence for the possibility that specific gestational periods may correspond to the time window with differing vulnerability to infection-mediated disturbances in fetal brain development (Meyer et al. 2007). In autism, maternal infections in the first few weeks of gestation may lead to abnormalities in fetal brain development and a higher risk of autism in the offspring (Arndt et al. 2005; Libbey et al. 2005; Miller et al. 2005). Autism in children with congenital rubella syndrome due to maternal rubella infection during pregnancy has also been attributed to disturbance in early fetal brain development (Chess 1971; Chess and Fernandez 1980; Ueda et al. 1979).

The studies above are also supported by experiments conducted in animal models. Behavioral, cognitive, and psychopharmacological abnormalities have been detected in mice and rats following prenatal exposure to the bacterial endotoxin lipopolysaccharide (LPS) (Fortier et al. 2004; Golan et al. 2005), human influenza virus (Shi et al. 2003), and the viral mimic polyriboinosinic–polyribocytidilic acid (Meyer et al. 2006; Shi et al. 2003). Studies on prenatal exposure to rubella and other viral agents have also alluded to a possible environmental etiology of autism (Assumpcao and Kuczynski 2002; Hwang and Chen 2010; Libbey et al. 2005). In contrast, no significant correlation between prenatal viral exposure and occurrence of autism was found in other studies (Anlar et al. 1994; Chen et al. 2004; Deykin and MacMahon 1979). Nevertheless, several researchers believe that environmental insults such as maternal infections may exacerbate genetic vulnerabilities in some individuals, or they may cause alterations in genes and/or protein expression, precipitating the abnormal phenotypes observed in autistic individuals (Chauhan and Chauhan 2006; Chauhan et al. 2009a; Fatemi et al. 2008, 2009; Herbert 2010).

6.3 Maternal Drugs

6.3.1 Thalidomide

This drug was originally introduced as a sedative that was typically used to cure morning sickness in pregnant women. Later, this drug was withdrawn due to its teratogenicity and neuropathic effects. There is now growing clinical interest in thalidomide for its role as an immunomodulatory agent. In a study of 100 subjects

of embryopathy in the Swedish thalidomide registry (Miller 1991; Stromland et al. 1994), five of these individuals had autism, and they all were from a group of 15 subjects with evidence of exposure during the 20th–24th day of gestation, which implicates a 33 % rate of autism in this subpopulation. This particular period (20th–24th day of development) falls during the closure of the neural tube and also coincides with the production of the first neurons that form the motor nuclei of the cranial nerves. Injury to the motor nuclei or their projections has been reported in autistic subjects (Rodier et al. 1997). Research on thalidomide suggests that autism may be caused by a very early injury to the developing brain. It also suggests that an animal model of autism may be developed on the basis of disrupting CNS development during neural tube closure. After thalidomide treatment of rats at embryonic day 9 (E9), a dramatic shift was observed in the distribution of serotonergic neurons in the dorsal raphe nucleus on postnatal day 50. This alteration is suggested to reflect abnormalities of serotonergic neuronal differentiation and migration in autism (Miyazaki et al. 2005). In another study, Narita et al. (2002) reported an increase in levels of hippocampal serotonin, frontal cortex dopamine, and hyperserotonemia in rats exposed to thalidomide at E9, suggesting that thalidomide-induced alteration of monoamine metabolism may be associated with the pathogenesis of autism. Another mechanism proposed to explain the teratogenic effects of thalidomide is oxidative stress (Ito et al. 2011; Knobloch et al. 2011), which is one of the core characteristics of autism.

6.3.2 Valproic Acid (VPA)

VPA is an anticonvulsant and mood-stabilizing drug that is used primarily for the treatment of epilepsy and bipolar disorder and less commonly for major depression. Epidemiological studies suggest that VPA exposure during the first trimester of pregnancy may result in higher incidence of autism in the offspring. In a study on long-term prenatal exposure to several antiepileptic drugs in Aberdeen (UK), Rasalam et al. (2005) reported that VPA was most commonly associated with ASDs. In another study, Bromley et al. (2008) reported that in utero exposure to VPA resulted in a sevenfold greater incidence of ASDs in the children.

The studies above have also been reproduced in the animal models, showing that prenatal exposure to VPA can result in autistic-like behavior (Markram et al. 2008; Schneider et al. 2008), cerebral pathology (Rodier et al. 1996), and altered levels of monoamines (Narita et al. 2002). In mice, both prenatal and postnatal treatment of VPA resulted in behavioral alterations (Wagner et al. 2006; Yochum et al. 2008). Prenatal injection of VPA induced a delayed motor maturation and impairment of learning and memory (Wagner et al. 2006). Postnatal injection of VPA resulted in impaired social behavior as well as increased apoptosis in the cerebellum and hippocampus (Yochum et al. 2008). Recently, Mehta et al. (2011) reported that prenatal exposure to VPA resulted in increased repetitive and anxiety-like behaviors in mice. In rats, prenatal VPA exposure resulted in dysmorphology similar to that observed

in the brain of children with autism (Lukose et al. 2011). In another study, prenatal exposure to VPA in rats induced demethylation in the promoter regions of wnt1 and wnt2 (proteins involved in embryogenesis) in prefrontal cortex and hippocampus of offspring (Wang et al. 2010).

Several studies suggest that prenatal exposure to VPA in animals can cause biochemical abnormalities similar to those observed in human subjects with autism. Altered expression of phosphodiesterase (PDE) 4A and 4B has been reported in the brain of subjects with autism (Braun et al. 2007). Similarly, decreased expression of PDE subtypes was also observed in VPA-treated rats (Fatemi et al. 2010). Consistent with findings of hyperserotonemia in many subjects with autism (Hranilovic et al. 2007), rats exposed to VPA prenatally also showed serotonergic impairment (Dufour-Rainfray et al. 2010; Miyazaki et al. 2005). Furthermore, prenatal exposure to VPA led to reduced expression of synaptic adhesion molecules neuroligin 3 in mice, which has also been implicated in genetic studies of autism (Kolozsi et al. 2009).

One of the core biochemical features of autism is the presence of oxidative stress (Chauhan et al. 2004a; Chauhan and Chauhan 2006; Chauhan et al. 2009a; Chauhan and Chauhan 2012; Chauhan et al. 2012a). Exposure of humans, animals, and cell cultures to VPA has also been reported to induce oxidative stress. Increased oxidative stress was reported in children who were receiving VPA (Michoulas et al. 2006). In the embryonic cultures, VPA exposure increased ROS formation and induced apoptosis in postimplantation embryos (Tung and Winn 2011). VPA treatment also induced oxidative stress and inflammation in patients with epilepsy (Ounjaijean et al. 2011). Kiang et al. (2011) reported glutathione depletion after increase in oxidative stress in hepatocytes treated with VPA. Fu et al. (2010) reported that VPA induced oxidative stress and autophagy in glioma cells and that oxidative stress occurred upstream of autophagy. Glutathione S-transferase M1 (GSTM1) is a gene that codes for an enzyme involved in the management of toxicant-induced oxidative stress and is associated with increased risk of autism. When GSTM1 knockout mice and wild-type control mice were exposed to VPA, GSTM1 knockout mice showed increased behavioral abnormalities as compared to wild-type animals (Yochum et al. 2010).

6.4 Endocrine-Disrupting Chemicals (EDCs)

EDCs are the chemicals that interfere with the endocrine system (or hormone system). Humans are regularly exposed to chemicals with estrogenic effects because EDCs are found in low doses in various commonly used products. The chemicals detected in humans include BPA, pesticides such as endosulfan, PCBs, polybrominated diphenyl ethers (PBDEs), and phthalates. While most studies suggest that exposure to these chemicals poses a health risk to humans (Colborn 2004; Frye et al. 2012; Sharpe and Irvine 2004; Solomon and Schettler 2000), one study does not support such risk (Safe 2000). Nevertheless, there is a general consensus that these chemicals have the potential to cause neurodevelopmental abnormalities such as autism.

6.4.1 EDCs and Neurodevelopmental Abnormalities

Many of these EDCs are organic in nature and can mix easily with lipids. The lipid solubility of EDCs results in accumulation of these chemicals in fatty tissues such as the brain. Furthermore, these chemicals can readily transfer across the placenta prenatally and are also present in breast milk. A recent review by Frye et al. (2012) describes the effects of EDCs on behavior and the potential mechanism of their action. Many behaviors and the neuroendocrine pathways that regulate them are sexually dimorphic, i.e., different in males and females. Exposure to EDCs can alter sexually dimorphic behaviors and affect neurodevelopmental processes, leading to increased developmental, cognitive, and/or emotional disabilities (Frye et al. 2012; Schettler 2001). Hence, development of psychological disorders that are prevalent in a specific gender may be associated with the disruption of developmental trajectory and/or maturation of sexually dimorphic brain (Bale et al. 2010). Exposure to EDCs that disrupt hormone function during critical periods of life, such as intrauterine, perinatal, or juvenile periods, may influence susceptibility to sex- and/or hormonally differentiated aspects of behavior (Frye et al. 2012; Richter et al. 2007; Swan et al. 2010).

Exposure to EDCs in early life can lead to long-term changes in social and sensory function, which are commonly observed in developmental disorders. Sensory impairment is higher in children with neurodevelopmental disorders than in the general population (Carvill 2001). In individuals with ASDs, sensory abnormalities are highly prevalent (30–100 %) (Reynolds and Lane 2008). In addition to sensory abnormalities, children with developmental disabilities often manifest social problems, such as aggression (Tyrer et al. 2006).

6.4.2 Bisphenol A (BPA)

BPA (4,4'-dihydroxy-2,2-diphenylpropane) is used in the production of polycarbonated plastics (used in some food and drink containers) and epoxy resins (used in most food and beverage metal cans) (Brede et al. 2003; Carwile et al. 2011; Kang et al. 2003). It is also found in plastics used for children's toys, CDs, DVDs, dental sealants, and household electronics (Joskow et al. 2006; Suzuki et al. 2000). Global production of BPA was estimated to be more than 2.2 million tons in 2009. Several reports indicate that frequent hydrolysis of ester bonds in plastic and resins during normal use of food and drink containers and baby bottles, which is further accelerated with time, elevated temperature, and pH extremes, leads to leaching out of BPA from tin cans and plastic containers into food and beverages (Brede et al. 2003; Carwile et al. 2011; Kang et al. 2003). The primary exposure of BPA in humans occurs orally, due to leaching of BPA from incomplete polymerization of epoxy resins or degradation of the weak ester bonds that link BPA monomers.

The exposure data from several countries including the USA suggest that the human body is continually exposed to BPA (Vom Saal and Hughes 2005). The amount of BPA exposure in humans varies depending upon the consumption of food

items in plastics and metal cans. In humans, BPA has been found in biological fluids, including blood, urine, placental tissue, follicular fluid, umbilical cord blood, fetal serum, and amniotic fluid, suggesting that BPA can pass through the placenta (Ikezuki et al. 2002; Kang et al. 2006). The concentration of BPA was fivefold higher in amniotic fluid at 15–18-week gestation compared with other fluids in humans (Ikezuki et al. 2002). According to the National Toxicology Program Expert Panel Report, infants (0–12 months old fed with liquid formula) and children (1.5–6 years old) are among the most exposed and can consume up to 13 and 14.7 μg BPA/kg body weight/day, respectively (Alderson 2008). On the other hand, estimated BPA intake was much lower in breast-fed infants (0.2–1 μg/kg body weight/day) and in adults (0.008–1.50 μg/kg body weight/day).

The reports by government-sponsored panels have raised concerns for the effects of BPA on the brain, behavior, and prostate gland in fetuses, infants, and children at current environmentally relevant doses of BPA (National Toxicology Program 2007). In a randomized crossover trial of canned food consumption and urinary excretion of BPA, BPA was detected in 77 % of people who ate canned soup (Carwile et al. 2011). Several studies have reported behavior abnormalities and cognitive impairment in animals exposed to BPA and suggested that BPA exposure in humans may increase the risk for autism, schizophrenia, and attention deficit hyperactivity disorder (ADHD) (Brown 2009; Masuo et al. 2004; Wetherill et al. 2007).

BPA is a known endocrine disruptor, which binds to both estrogen receptors ERα and ERβ, and it causes disruption of cellular function during neurodevelopment (Wetherill et al. 2007). In addition, BPA exposure has been shown to enhance oxidative stress, a condition known to be involved in the etiology of autism (Chauhan and Chauhan 2006; Chauhan et al. 2009a, 2012a, b). The lipid peroxidation was increased in the brain, kidney, and testis in mice exposed to BPA during fetal life and infancy (Kabuto et al. 2004). In another study, mice injected with BPA showed increased GSSG and a decreased GSH/GSSG ratio in the brain (Kabuto et al. 2003). Other studies have shown that BPA induces oxidative stress in women (Yang et al. 2009), in zebrafish embryo (Wu et al. 2011), and in rats (Korkmaz et al. 2010; Minamiyama et al. 2010).

6.4.3 Polychlorinated Biphenyls (PCBs)

All PCBs are chlorinated biphenyl molecules. The exposure to PCBs in humans is from residual PCBs in the diet, air, water, and soil, especially by PCBs used as dispersants in pesticides and as coolants or heat transfer agents in electrical transformers (Ritchie et al. 2003; Slim et al. 2000). PCBs have also been used in microscope immersion oil and in carbonless copy paper.

PCBs are persistent pollutants with immunological and neurological effects (Crinnion 2011; Kimura-Kuroda et al. 2007). It has also been reported that PCBs increase the steady-state levels of ROS (Hennig et al. 2002), oxidative stress, and cytotoxicity that can be mitigated by antioxidants (Zhu et al. 2009). The neurological and immunological abnormalities as well as oxidative stress have been observed

in individuals with autism (Chauhan and Chauhan 2006, 2012; Chauhan et al. 2009a, 2012b; Pardo-Villamizar and Zimmerman 2009; Onore et al. 2012). In vitro studies showed that PCBs are potent inducers of apoptosis for monocytes (Shin et al. 2000) and thymocytes (Tan et al. 2003). Dietary PCB supplements in the form of contaminated whale blubber resulted in diminished mitogen response, decreased phagocytosis, and diminished numbers of CD8+ cells, indicating PCB-induced immunosuppression (Fournier et al. 2000). Animals exposed to dioxin-like PCBs also developed thymic atrophy and immunosuppression (Davis and Safe 1990). PCBs also reduced available SOD and oxidative stress and diminished the number of neutrophils and reduced cellular immunity (Narayanan et al. 1998). Both prenatal and postnatal exposures to PCBs showed a reduced number of circulating polynuclear neutrophils (Leijs et al. 2009) and increased the incidence of middle-ear disease (Chao et al. 1997), suggesting that exposure to PCBs has a lasting effect on cell-mediated immunity.

Neurological consequences of PCB exposure are more pronounced when exposure occurs in utero. The children with prenatal exposure to PCBs exhibited intellectual disabilities, impaired mental and motor neurological development, cognitive defects, and poorer gross motor function (Jacobson et al. 1985; Jacobson and Jacobson 1997; Walkowiak et al. 2001). Intelligence quotient (IQ) levels were lower in children exposed to PCBs than in children without such exposure (Chen et al. 1992, 1994; Lai et al. 2002). In mice, neonatal PCB exposure also resulted in long-term neurological problems. In utero PCB exposure adversely affected learning and memory function when exposed mice reached adulthood (Eriksson and Fredriksson 1998). In addition, postnatal exposures to PCBs can also cause neurological problems (Plusquellec et al. 2010).

6.4.4 Polybrominated Diphenyl Ethers (PBDEs)

PBDEs are widely used as flame-retardant chemicals in furniture foam, carpet pads, and the plastics surrounding electronics such as computers, cell phones, and televisions. In humans, high levels of PBDEs have been detected in breast milk, placenta, adipose tissues, and blood, including fetal blood (Frederiksen et al. 2009; Gomara et al. 2007; Mazdai et al. 2003). The levels of PBDEs in the environment and in humans are approximately tenfold higher in North America than in Europe and Asia (Frederiksen et al. 2009). Humans are exposed to PBDEs via inhalation of household dust and intake of vegetables and animal products (Frederiksen et al. 2009). Children are exposed to larger amounts of PBDEs than are adults, because of child-specific hand-to-mouth behavior and frequent ground contact (resulting in the ingestion of house dust), and their serum levels of PDBEs have been reported to be higher than adults' (Fischer et al. 2006; Toms et al. 2009). An additional source of exposure for infants is breast milk, (Frederiksen et al. 2009). Prenatal exposure to PBDEs can also occur through placental transfer (Gomara et al. 2007; Mazdai et al. 2003).

Exposure to PBDEs has been associated with neurotoxicity, especially in young children (Eriksson et al. 2001). Recent studies showed adverse effects on cognitive and neurodevelopmental parameters in humans exposed to PBDEs. In a study of Dutch children, motor, cognitive, and behavioral performance correlated with maternal serum levels of PBDEs measured in the 35th week of pregnancy (Roze et al. 2009). In another study of U.S. children (0–6 years of age), the scores of yearly tests of mental and physical development were lower among those children exposed prenatally to higher concentrations of PBDEs (Herbstman et al. 2010).

Several studies suggest that exposure to PBDEs also results in increased oxidative stress. Zhong et al. (2011) reported that PBDE metabolites, especially 6-OH-BDE85, caused cytotoxicity in human L02 cells, which was related to the degree of oxidative stress. In rodents, exposure to PBDEs also resulted in increased oxidative stress and decreased nerve conduction (Vagula et al. 2011). A study with primary neuronal cultures showed that PBDEs increased the rate of apoptosis, expression of P38 MAPK, calcium ion concentration, ROS and NO levels, and lipid peroxidation (Chen et al. 2010). Several lines of evidence have suggested abnormalities in signal transduction in autism (Chauhan and Chauhan 2009). Taken together, all of these studies implicate the deleterious effects of early childhood exposure to PBDEs and also suggest that exposure to PBDEs may contribute to elevated oxidative stress and biochemical and behavioral changes, similar to those observed in children with autism.

6.5 Phthalates

Phthalates—diesters of 1,2-benzenedicarboxylic acid (phthalic acid)—are a group of synthetic chemicals with a wide spectrum of industrial and commercial uses, e.g., as primary plasticizers for polyvinyl chloride and solvents in personal care products (such as shampoos, cosmetics, and fragrances) (Wormuth et al. 2006). Phthalate plasticizers are slowly emitted into the surrounding environment (Wormuth et al. 2006), thus constituting an indoor pollutant (Bornehag et al. 2005). Phthalates can be ingested through food or inhaled through contaminated air or dust. Dermal contact with products that contain phthalates and polymer coating in some medications are also potential sources of its exposure (Hernandez-Diaz et al. 2009).

After entering the body, phthalates undergo rapid metabolism to monoesters and can also be further oxidized to oxidative metabolites (Engel et al. 2010). The metabolites of phthalates have been detected in all biological fluids, including amniotic fluid, breast milk, semen, blood, and urine (Frederiksen et al. 2007). The maternal transmission of phthalates to offspring has been demonstrated because these compounds have been found in the amniotic fluid and fetal circulation in human (Huang et al. 2009; Wittassek et al. 2009). It has been estimated that infants may experience higher exposures to phthalates in relation to their body weight (Wormuth et al. 2006).

The exposure to phthalates (prenatal, postnatal, infancy, or childhood) has raised concerns because these chemicals have been associated with developmental and reproductive toxic effects (Borch et al. 2006; Gray et al. 2000; Engel et al. 2009, 2010). Although no study has been conducted to evaluate phthalates as a risk factor for ASDs, recent studies have reported an association of phthalate exposure with neurodevelopment. Prenatal exposure to phthalates has been associated with poor birth outcomes (Wolff et al. 2008), neurological problems in the neonate (Engel et al. 2009), behavioral abnormalities (Engel et al. 2010), reduced masculine play in boys (Swan et al. 2010), and childhood social impairment (Miodovnik et al. 2011). Phthalates also caused hyperactivity and impulsivity in rats, which resembled the clinical features observed in ADHD (Ishido et al. 2004; Masuo et al. 2004). A cross-sectional survey also reported associations between phthalate metabolites and intelligence scores (Cho et al. 2010) as well as ADHD symptoms in school-aged children (Kim et al. 2009a). Phthalates have also been suggested to interfere with the thyroid hormone system (Ghisari and Bonefeld-Jorgensen 2009; Huang et al. 2009), a system vital to normal brain development in the fetus and infant. All of these findings suggest that exposure to phthalates may cause disturbances in the normal developmental trajectory of the fetal and infant brain.

6.6 Pesticides

A large number of agricultural pesticides are known to have neurological effects (Weiss et al. 2004), which raises the possibility that gestational exposure to these compounds may be involved in the etiology of ASDs and related neurodevelopmental disorders. Although most of these compounds are used in a specific area, they are prone to drift, and detectable levels are often observed in air samples for extended periods at locations beyond the site of application (Lee et al. 2002). Elevated levels of agriculture pesticides in household dust, and their metabolites in urine, have been associated with residential proximity to treated fields (Loewenherz et al. 1997; Lu et al. 2000; Simcox et al. 1995). Accumulating evidence suggests an association of residential proximity or parental occupational exposure to pesticides with pediatric diseases, most notably for neurodevelopmental disorders (Eskenazi et al. 2007; Grandjean et al. 2006) and cancer (George and Shukla 2011).

Many environmental toxins are transferred through placenta, and the blood–brain barrier remains relatively permeable to many of these compounds until the first year of life (Andersen et al. 2000). It has been reported that prenatal exposure to organophosphate pesticides is negatively associated with cognitive development, particularly perceptual reasoning, with evidence of effects beginning at 12 months and continuing through early childhood. Paraoxonase 1 may be an important susceptibility factor for these deleterious effects (Engel et al. 2011). A study of 465 children with ASDs born in California during 1996–1998 showed a link between proximity to organochlorine pesticide applications and incidence of ASDs (Roberts et al. 2007).

Several studies suggest that pesticides are also involved in inducing elevated oxidative stress. Subchronic exposure to malathion (an organophosphate) resulted in increased levels of hepatic lipid peroxidation, protein carbonyl groups (protein oxidation marker), and 8-deoxyguanosine (DNA oxidation marker) (Mostafalou et al. 2012). Insecticides such as endosulfan are also known to cause oxidative stress (Saxena et al. 2011; Velki et al. 2011; Zervos et al. 2011).

7 Conclusions

The incidence of autism has risen dramatically in the last 20 years. While the cause of autism remains unknown, autism is considered a multifactorial disorder that is influenced by genetic and environmental factors and increased vulnerability to oxidative stress. Although genetic factors may play a role in the etiology of ASDs, not all autism cases have pathogenic mutations or copy number variants. As discussed in this review, prenatal or postnatal exposure to environmental factors such as metals, maternal drugs, infections, and endocrine disruptors, alone or in combination, is most likely to cause ASDs, at least in a subset of vulnerable individuals. Several independent studies have provided evidence of increased oxidative damage and deficient antioxidant defense mechanism in the children with autism. Emerging evidence from our and other groups has also shown mitochondrial dysfunction in autism. It is suggested that environmental factors may act as triggers for interactions of genetically susceptible alleles in autism, whereas mitochondrial dysfunction and oxidative stress may serve as common links between susceptibility genes and environmental factors, leading to behavioral abnormalities and clinical development of autism (Fig. 2).

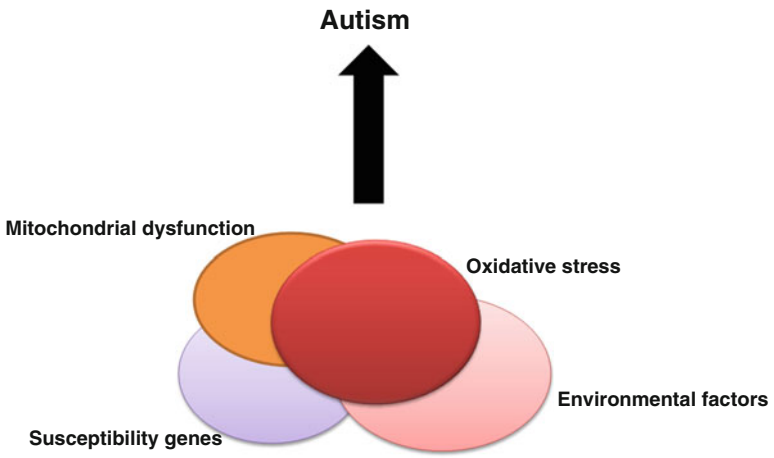

Fig. 2. Gene-environment interactions in autism. Environmental factors may interact with genetically susceptible alleles in autism, whereas oxidative stress and mitochondrial dysfunction may provide a common link between susceptibility genes and environmental factors, resulting in clinical development and behavioral symptoms of autism

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