Journal of Pediatric Biochemistry 2 (2012) 213–223
DOI 10.3233/JPB-120063
IOS Press

Review Article

Mitochondrial respiratory chain defects in autism and other neurodevelopmental disorders

Abha Chauhan*, Feng Gu and Ved Chauhan
NYS Institute for Basic Research in Developmental Disabilities, Staten Island, NY, USA

Abstract. Mitochondrial respiratory electron transport chain (ETC) consists of five multi-subunit enzymes, i.e., complex I-V, which differs not only in structure but also in function, and plays an important role in adenosine triphosphate (ATP) generation by mitochondria. Each of these complexes participates in the generation of proton gradient in the mitochondrial intermembrane space, which is necessary for converting adenosine diphosphate (ADP) into ATP by ATP synthase. Brain has a high demand for energy, and neurons generate energy in the form of ATP through the respiratory chain in the mitochondria. Almost 90% of this energy is provided by mitochondrial ETC. ETC also generates most of the endogenous free radicals, i.e., reactive oxygen species (ROS) of the cell. The normal functions of ETC are essential to maintain physiological function and plasticity of neurons. Therefore, abnormalities in ETC during development, i.e., *in utero*, infancy and childhood, may be involved in the etiology of neurodevelopmental disorders. The abnormalities in mitochondrial ETC pertaining to neurodevelopmental disorders include mtDNA mutations, altered gene expression, decreased activities and protein expression levels of ETC complexes, and oxidative stress. Here, we review these mitochondrial ETC defects in autism spectrum disorders (ASDs) and other neurodevelopmental disorders, i.e., attention deficit hyperactivity disorder, schizophrenia, Down syndrome and Fragile X syndrome.

Keywords: Autism, attention deficit hyperactivity disorder, Down syndrome, electron transport chain, Fragile X syndrome, mitochondria, neurodevelopment, oxidative stress, schizophrenia

1. Introduction

Mitochondrial respiratory chain, also known as electron transport chain (ETC), is an essential and important part of mitochondria. The most important function of ETC in the cell is to generate energy in the form of adenosine triphosphate (ATP), which provides more than 90% of cellular energy to maintain its physiological activities [1,2]. ETC is closely linked to the tricarboxylic acid (TCA) cycle, also known as Krebs cycle, which produces NADH and $FADH_2$, two electron donor molecules to the ETC. Mitochondria contain inner and outer plasma membranes. The ETC is located in the inner mitochondrial membrane, and consists of five multi-subunits of enzymes, i.e., complex I (NADH dehydrogenase), complex II (succinate dehydrogenase), complex III (cytochrome bc1 complex), complex IV (cytochrome c oxidase) and ATP synthase, also known as complex V [3,4]. As shown in Fig. 1, complexes I–IV participate in the generation of proton gradient (membrane potential) in the intermembrane space of mitochondria, while complex V transports protons from intermembrane space to the mitochondrial matrix. The generated proton gradient is used by ATP synthase to catalyze the formation of ATP by the phosphorylation of adenosine diphosphate (ADP). Ubiquinone (also known as coenzyme Q10) and cy-

*Corresponding author: Abha Chauhan, NYS Institute for Basic Research in Developmental Disabilities, 1050 Forest Hill Road, Staten Island, NY 10314, USA. Tel.: +1 718 494 5258; Fax: +1 718 698 7916; E-mail: abha.chauhan@opwdd.ny.gov.

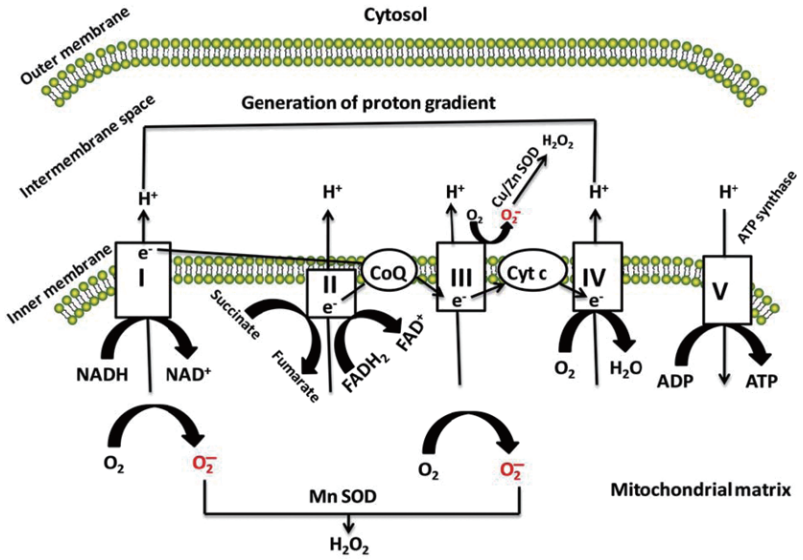

Fig. 1. Generation of ATP and superoxide (free radical) by the electron transport chain (ETC) of mitochondria. ETC is embedded in the inner mitochondrial membrane, and consists of five enzyme complexes, designated I–V, i.e., complex I (NADH dehydrogenase), complex II (succinate dehydrogenase), complex III (cytochrome bc1 complex), complex IV (cytochrome c oxidase) and complex V (ATP synthase). NADH and $FADH_2$ supply electrons to the ETC. Electrons donated from NADH and $FADH_2$ flow through the ETC complexes, passing down an electrochemical gradient to be delivered to oxygen (O_2). CoQ shuttles electrons from complexes I and II to complex III. Cytochrome c transfers electrons from ETC complex III to IV. During this process, protons are pumped through the inner mitochondrial membrane to the mitochondrial intermembrane space to establish a proton gradient, which is used by complex V to phosphorylate adenosine diphosphate (ADP) by ATP synthase, thereby generating ATP. Complex I and III are also main sites of mitochondrial free radical superoxide (O_2^-) production. Complex I-dependent O_2^- is exclusively released into mitochondrial matrix where it is converted to hydrogen peroxide (H_2O_2) by the manganese superoxide dismutase (Mn SOD). On the other hand, superoxide generated at complex III can be released to both sides of the inner mitochondrial membrane. Superoxide released into the mitochondrial intermembrane space is converted to H_2O_2 by Cu/Zn SOD. (Colours are visible in the online version of the article; http://dx.doi.org/10.3233/JPB-120063)

tochrome c are the electron carriers of the ETC, and help in the transfer of electrons between the complexes.

Mitochondrial function is under the dual genetic control of mitochondrial DNA (mtDNA) and nuclear DNA (nDNA). The mtDNA contains 37 genes that code for 13 subunits of complexes I, III, IV and V. The other subunits of the ETC complexes are coded by more than 850 nDNA genes [5]. The expression, replication, and maintenance of mtDNA also require the factors encoded by nuclear genes [6]. Furthermore, the nuclear-encoded signaling pathway genes play a role in mediating adaptive functions of mitochondria under altered conditions [6,7]. Therefore, mtDNA and/or nDNA genome mutations may lead to deficiencies of ETC complexes, and subsequently to mitochondrial dysfunctions.

Mitochondria play an important role in regulating developmental processes, including neurite outgrowth, axonal plasticity and synaptic plasticity [8]. Brain has a high demand for energy, and neurons contain a large number of mitochondria. 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 [9].

Mitochondrial ETC also produces the free radicals, i.e., reactive oxygen species (ROS), which cause oxidative stress and trigger apoptosis [2,9–11]. Oxidative stress in the cell results when generation of ROS overpowers the antioxidant defense for elimination of ROS. Under normal physiological conditions, ROS production is highly regulated by complex I [12–15]. Complexes I and III are the main sites of mitochondrial superoxide production [16,17]. The superoxide generated by complex I is exclusively released into the mitochondrial matrix, where it is converted to hydrogen peroxide (H_2O_2) by the manganese superoxide dismutase (Mn SOD). On the other hand, complex III releases superoxide to both sides of the inner mitochondrial membrane, i.e., to the mitochondrial matrix and the intermembrane space. The locus of superoxide production in complex III, the ubiquinol oxidation site, is situated immediately next to intermembrane space of mitochondria, which may explain extramitochondrial release of

superoxide. The ROS generation at complex III occurs as a result of proton cycling between ubiquinone, cytochromes b and c1, and iron-sulfur protein [18]. Superoxide generated from complex III released into the mitochondrial intermembrane space is converted to H_2O_2 by Cu/Zn SOD, which is present in the mitochondrial intermembrane space and cytosol [16]. In addition to the generation of ROS, the ETC itself is the target of ROS, which can directly and indirectly lead to impairments in activity of ETC complexes. Thus, the abnormalities of ETC will inhibit ATP synthesis, and accelerate ROS generation; resulting in impairment of energy metabolism, oxidative stress and disruption of mitochondrial functions, and subsequently affect neurons' function and plasticity, which may finally lead to neurodevelopmental disorders in children.

In this review, we discuss alterations in activities and/or protein expression of mitochondrial ETC complexes in different neurodevelopmental disorders, i.e., autism spectrum disorders (ASDs), attention deficit hyperactivity disorder (ADHD), schizophrenia (SZ), Down syndrome (DS), and Fragile X syndrome (FXS).

2. Mitochondrial respiratory chain defects in autism spectrum disorders

ASDs, which include autistic disorder, Asperger syndrome and pervasive developmental disorder-not otherwise specified, are neurodevelopmental disorders characterized by impaired social interaction, communication and social skills, as well as by repetitive and stereotypic patterns of behavior [19]. The symptoms of ASDs are typically present before the age of 3 years. According to the report from the Centers for Disease Control and Prevention (CDC), 1 in 88 children (by the age of eight years) is affected with autism, and the ratio of male to female is 5 [20]. A recent study in South Korea showed the prevalence of ASDs to be 2.64% in school-age children, with 1.89% in the general population group (from regular schools) and 0.75% in a high risk group (from special education schools and a disability registry) [21].

2.1. Human studies

A variety of biochemical, anatomical and neuroradiographical studies suggest a disturbance of brain energy metabolism in autistic individuals [22–28]. In 1998, because of frequent association of lactic acidosis and carnitine deficiency in autistic subjects, Lombard [25] presented a hypothesis that mitochondrial dysfunction and defects in neuronal oxidative phosphorylation may be involved in the etiology of autism. Since then, several lines of evidence suggest that mitochondrial energy metabolism is perturbed in autistic individuals. Based on blood analysis and/or muscle biopsy, several studies found mitochondrial dysfunction, associated with high lactate, increased lactate to pyruvate ratio, increased alanine and low carnitine levels in individuals with ASDs [28–31]. However, these individuals did not show classical features of mitochondrial disease (MD). Classical MD only occurs in few autistic individuals, and is generally accompanied by genetic abnormalities and defects in the respiratory chain. Several reviews have recently shed light on mitochondrial dysfunction in autism [32–36]. It is not yet known whether mitochondrial dysfunction in autistic children is primary etiology or secondary pathology to other causes.

Oliveira et al. [29] conducted a population-based survey of children with ASDs. They reported that 20.3% (14 of 69) children with autism had elevated levels of blood lactate. Muscle biopsies were performed in 11 of these 14 autistic children with hyperlactacidemia, and 5 of 11 subjects studied met the criteria for definite MD. This study suggested a high prevalence (5 of 69; 7.2%) of MD in autism. However, these children did not have any known mtDNA mutations and/or deletions associated with known mitochondrial disorders. In another study, plasma lactate and pyruvate levels were measured in 210 subjects with autism [30]. Hyperlactacidemia was observed in 17% (36 subjects), and elevated lactate/pyruvate ratio was found in 27% (53 of 196 subjects). MD was confirmed in 7 of the 30 fully assessed subjects who also underwent muscle biopsy.

2.1.1. Mitochondrial ETC abnormalities in autism

Several case studies have reported alterations in the activities of ETC complexes in autism. For example, deficiencies in respiratory chain enzymes, including complexes I–III and coenzyme Q were observed in two children with autism [37]. In a recent review and meta-analysis, Rossignol and Frye [32] reported deficiencies of complexes I, III, V, IV and II in 53%, 30%, 23%, 20% and 9% of children with ASDs and concomitant MD respectively.

The onset of autism is gradual in many children. In regressive autism, children first show normal social and language development but generally lose these developmental skills at 15–24 months and develop autistic

behavior [38]. This pattern may vary for some children with regressive autism. The reported incidence of regressive autism varies in different studies from 15% to 62% of cases [39–41]. Poling et al. [42] presented a singleton case of developmental regression and oxidative phosphorylation disorder in a 19-month-old girl with autism. The muscle biopsy results showed type I myofiber atrophy, increased myofiber lipid content and reduced enzymatic activities for complex I, III and IV. In a recent study, Shoffner et al. [43] reported that autistic regression occurred in 61% (17 of 28) ASD subjects with definite MD, and that fever was associated with the onset of regression in 12 of these children.

Weissman et al. [28] reviewed medical records of 25 individuals with ASDs who also had enzyme- or mutation- defined mitochondrial dysfunctions. Using mitochondrial disease criteria, 11 subjects had definite MD and 14 had probable MD. Twenty subjects had deficient activity of ETC complexes on tissue ETC or polarographic analysis. The deficiencies of complexes I, III, II and IV were observed in 64%, 20%, 5% and 4% of these subjects respectively. They reported that 40% of this group demonstrated unusual pattern of regression (multiple episodes, loss of motor skills, or regression after the age of 3), and six had mtDNA mutations [28].

Not only are the activities of ETC complexes altered in autism, but our recent study suggests that the expression levels of ETC complexes are also affected in the brain of children with autism [22]. We have reported 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 of children with autism (ages 4–10 years) as compared to age-matched control subjects, while none of the five ETC complexes was affected in the parietal and occipital cortices in subjects with autism [22]. In the cerebellum and temporal cortex, no overlap was observed in the levels of these ETC complexes between autistic and control subjects. In the frontal cortex, a lower level of ETC complexes was observed in a subset of autism cases, i.e., 60% (3/5) for complexes I, II, and V, and 40% (2/5) for complexes III and IV. These results suggest that the expression of ETC complexes is decreased in the cerebellum and the frontal and temporal regions of the brain in children with autism, which may lead to abnormal energy metabolism and oxidative stress. A striking observation was that the levels of ETC complexes were similar in adult autistic and control subjects (ages 14–39 years) [22]. A recent report on positron emission tomography (PET) of the brain of a 3-year old girl with autism also showed a partial deficiency of complexes III and IV of the respiratory chain [26]. In a retrospective case series report of individuals with co-occurrence of autism and definite or probable MD, 48% (10 of 21 children) showed abnormalities on cranial magnetic resonance imaging (MRI), and 40%, i.e. 2 of 5 children who were imaged for cranial magnetic resonance spectroscopy (MRS) showed elevated brain lactate [28]. Another ^{31}P- MRS study showed under synthesis and increased membrane degradation as well as decreased synthesis of ATP in the dorsal prefrontal cortex of brain in 11 high-functioning autistic men compared to age-matched controls subjects [24]. Previous anatomical and neuroradiographical studies of the brains of individuals with autism have also suggested a disturbance of energy metabolism [23,25].

Recent studies using lymphocytes or lymphoblasts also suggest mitochondrial ETC abnormalities in ASDs [44–47]. We reported reduced mitochondrial membrane potential and elevated free radical generation in the lymphoblasts from autistic subjects (obtained from the Autism Generic Resource Exchange) as compared to lymphoblasts from age-matched control subjects [44]. In another study, exposure to physiological concentrations of NO reduced mitochondrial membrane potential to a greater extent in the lymphoblasts from autistic subjects than from control subjects [45]. Holtzman [46] reported a 40 to 50% higher mitochondrial maximal respiratory rate in the lymphoblasts from all 9 autistic subjects studied, when compared to the lymphoblasts from their non-autistic relatives. In 7 of 9 lymphoblast pairs, they also found inhibition of complex I activity. It was suggested that the increased cellular respiratory capacity in lymphoblasts from autistic subjects was a compensatory response to the partial inhibition of ATP synthesis. In a study of lymphocytes from 10 children with autism and 10 control subjects, Giulivi et al. [47] recently reported that 6 of 10 autistic children had complex I activity below control range values, four had a lower complex V activity, and three had a lower complex IV activity. Only one child with autism fulfilled the diagnostic criteria for a definite MD.

The free radicals are generated endogenously during oxidative metabolism and energy production by mitochondria, and the ETC in mitochondria is a prime source of ROS generation [11]. Increasing evidence from our and other groups suggests a role of oxidative stress in the development and clinical manifestation of autism [48–50]. Levels of oxidative stress markers are increased in the blood [48,51–54], urine [55], and brains [22,50,56–59] of individuals with autism as compared to control subjects.

2.1.2. Association of genetic abnormalities with mitochondrial dysfunction in autism

Abnormal gene expression is one of the important etiologies of autism, which may be caused by chromosome abnormality, mtDNA mutation or deletion, or decreased levels of mRNA. Duplication of a segment of the chromosome 15q11-q13, either as an inverted duplication that is present as an extra chromosome or as an interstitial duplication constitutes one of the most frequent genetic abnormalities in autism. This abnormality occurs in 1–5% of individuals with autism [60, 61]. The risk of sudden death in individuals with autism who have inverted duplication of chromosome 15q (idic 15) is approximately 1% per year [62]. Two autistic children with a chromosome 15q11-q13 inverted duplication were reported to have motor delay, lethargy, severe hypotonia, and modest lactic acidosis [63]. The results of their muscle biopsies showed mitochondrial hyperproliferation and deficiency in complex III of ETC [63]. In another study, two autism cases associated with sudden infant death syndrome (SIDS) showed mild mitochondrial hyperproliferation and a possible complex II defect [35].

Chromosomal microarray studies in a 12-year-old boy with autism, epilepsy, and leg weakness revealed a 1-Mb deletion in the 5q14.3 region [64]. Buccal swab ETC analysis showed severe decrease in complex IV activity and mild reduction in complex I activity. These authors suggested that (a) the above deletion may be associated with complex I and IV deficits, thereby manifesting in a mitochondrial disease and autism, and (b) genes that either encode or regulate the expression and/or assembly of complex IV or I subunits may be located within the deleted region of 5q14.3 [64].

Filiano et al. [27] described 12 children who presented clinically with hypotonia, intractable epilepsy, autism, and developmental delay (HEADD syndrome). Reduced levels of mitochondrial respiratory enzymes were found in 7 of 8 children who had muscle biopsy. Five of these children exhibited increased levels of large-scale mitochondrial DNA deletions, and three children had structural mitochondrial abnormalities.

Pons et al. [65] described five subjects with autism and mtDNA mutation or mtDNA deletion. The mtDNA A3243G mutation was observed in two of these children, and in the mother of two other children. This mutation is often associated with the MELAS (mitochondrial encephalopathy with lactic acidosis and seizures) syndrome. One child had 72% mtDNA depletion in skeletal muscle and reduction in activities of complexes I, III, and IV to 34%, 23%, and 25% of control values, respectively. In another study, G8363A mutation in the mtDNA $tRNA^{lys}$ was reported in blood and skeletal muscle from an autistic boy who also showed complex IV defect [66].

In a case-control study of 235 subjects with autism and 214 controls, significant association was reported between the NADH-ubiquinone oxidoreductase 1 alpha subcomplex 5 (NDUFA5) gene and autism [67]. The product of the NDUFA5 gene is included in the mitochondrial ETC complex I. However, in another study, expression levels of the mitochondrial complex I (75-kDa subunit) mRNA in the whole blood were similar in the ASD and control groups [68].

2.1.3. Mitochondrial dysfunction in Rett syndrome

Rett syndrome is a rare ASD that affects girls almost exclusively, and it is caused by mutations in X-linked MeCP2 gene encoding methyl 1-CpG-binding protein [69]. Structural mitochondrial abnormalities have been described in muscle in individuals with Rett syndrome. Although a report on three children with Rett syndrome described normal muscle mitochondrial structure using light and electron microscopy, these children had abnormalities in mitochondrial respiratory chain enzymes, i.e., complexes I, III and IV [70]. Infantile hypotonia and a decrease in respiratory chain enzyme activity were also observed in a girl with Rett syndrome [71]. In other studies with two [72] and six girls [73] with Rett syndrome, electron microscopy of muscle biopsy samples revealed mitochondrial abnormalities and alterations, including distention, vacuolation, and membranous changes. Another report also suggested ultrastructural and biochemical alterations of muscle mitochondria in two girls with Rett syndrome [74]. In addition, the levels of very long-chain fatty acids (VLCFA) and carnitine in the serum have been reported to be decreased in Rett syndrome [75]. The administration of L-carnitine increased the levels of serum VLCFA. It was suggested that low carnitine levels may impede substrate delivery for mitochondrial beta-oxidation of long-chain fatty acids, thus increasing the use of VLCFA as substrate for beta-oxidation in the peroxisomal system [75]. Together, these studies suggest mitochondrial dysfunction and impairment of energy metabolism in Rett syndrome.

2.2. Studies with animal models

The studies in animal models of autism and related disorders have also shown mitochondrial dysfunctions. In the animal model of Angleman syndrome

having maternal ubiquitin protein ligase E3A (UBE3A) deficiency, the activity of complex III was reduced in whole brain mitochondria [76]. In Mecp2-null mouse (an animal model for Rett syndrome), the nuclear gene for ubiquinol-cytochrome c reductase core protein 1 (Uqcrc1), a subunit of the complex III, was reported to be overexpressed in the brain [77]. The brain mitochondria from these mice showed elevated respiration rates associated with respiratory complex III, and an overall reduction in coupling. These authors also reported a causal link between overexpression of Uqcrc1 gene and enhanced complex III activity in neuroblastoma cells.

3. Mitochondrial respiratory chain defects in attention deficit hyperactivity disorder

ADHD is one of the most common behavioral disorders in childhood that may persist into adulthood, and is characterized with lack of attention, impulsivity, and hyperactivity. The long-term consequences include lower educational and occupational achievement, and increased risk for developing other psychiatric disorders. It affects about 5–10% of children and 4% of adults [78]. ADHD has many biochemical abnormalities such as oxidative stress and mitochondrial dysfunction [79].

Juvenile spontaneously hypertensive rats (SHR) that are hyperactive but not hypertensive, and are defective in sustained attention were used as an animal model of ADHD by Papa et al. [80]. In a cross-talk correlation study among different regions within brain and the respiratory chain enzyme cytochrome c oxidase, altered cross-talk was observed in the anterior forebrain of the SHR rats as compared to the controls [80]. In another study, Fagundes et al. [81] studied the effects of methylphenidate (MPH), a frequently prescribed drug for the treatment of ADHD, on the ETC activities in the brain of young rats. Their results showed increased activities of mitochondrial respiratory chain enzymes by chronic administration of MPH. Particularly, complex II activity increased in the cerebellum and prefrontal cortex, and complex IV activity increased in the cerebellum, hippocampus, striatum and brain cortex [81]. These findings, to some extent, suggest reduced activities of ETC complexes in ADHD. On the contrary, MPH administration in adult rats showed inhibition of complexes I, II, III and IV in the hippocampus, prefrontal cortex, striatum and cerebral cortex [82]. These studies suggest that MPH treatment in young and old animals results in opposite effect.

4. Mitochondrial respiratory chain defects in schizophrenia

Etiology of SZ is not known but involvement of mitochondrial dysfunction due to altered oxidative phosphorylation and/or energy metabolism has been implicated in SZ [83–85]. *In vivo* imaging and postmortem studies have shown an impairment of energy metabolism in brains of patients with SZ, suggesting abnormalities in mitochondrial ETC [85,86]. Some studies have reported reduced levels of ATP in the frontal lobe, temporal lobe and basal ganglia, as detected by ^{31}P-MRS [87–89]. Abnormal mitochondrial morphology, size and density have also been reported in the brains of individuals with SZ [90,91]. Kung and Roberts [92] reported reduction of mitochondrial density by 20% in the caudate nucleus and the putamen throughout the neuropil in a mixed sample of drug-treated and off-drug SZ cases as compared to controls.

The activities and/or expression of several components of mitochondrial ETC are altered in the brains of SZ subjects. Reduced activities of complexes I, III, and IV were reported in the temporal cortex, and of complex IV in the frontal cortex in SZ [86,93]. In a recent study, Taurines et al. [68] reported inhibition of complex I (75-kDa subunit) mRNA level in SZ patients compared to the respective controls. However, Andreazza et al. [94] did not observe alteration in the activity of complex I and in the levels of complex IV subunit in the postmortem prefrontal cortex in SZ. The analysis of activities of complexex I, II, and IV in different regions of brain from SZ showed that mitochondrial function is differentially altered within the structures of the basal ganglia of chronic schizophrenics [95]. While the caudate nucleus showed reduced complex IV activity in SZ, increased activities of complexes II and IV were reported in the putamen and nucleus accumbens in SZ. Another study reported increased mRNA expression of complex IV subunit in the frontal lobe of SZ [96]. It was suggested that decrease in complex IV activity in caudate of schizophrenics is due to disease pathology, while increase in other brain regions may be attributed to the effect of medications (neuroleptics) on motor function [95]. Other studies have also suggested decreased brain energy metabolism in SZ, which can be reversed by neuroleptics [97,98].

Alterations in the mitochondrial complexes in SZ may result in oxidative stress. Several studies suggest increased oxidative stress in the brains of subjects with SZ [99,100]. In SZ, there is evidence for dysregulation of free radical metabolism, as detected by abnormal ac-

tivities of antioxidant enzymes and increased lipid peroxidation in plasma, red blood cells, and cerebrospinal fluid [101–105].

At the genetic level, cDNA microarray analysis revealed decreased expression of genes in the components of the mitochondrial ETC in postmortem brain samples from patients with SZ [106]. However, caution should be observed in the interpretation of these findings, as it has been reported that antipsychotic medications can induce differential expressions of ETC proteins including NADH dehydrogenase (ubiquinone) 1 alpha subcomplex 10 (Ndufa10), NADH dehydrogenase (ubiquinone) flavoprotein 2 (Ndufv2)) in the cerebral cortex or hippocampus of normal rats [107]. Therefore, use of prescription medications should also be considered when analyzing results of ETC in SZ.

5. Mitochondrial respiratory chain defects in Down syndrome

Several studies have suggested abnormalities in mitochondrial ETC of DS subjects. DS is a multifactorial disorder caused by trisomy of chromosome 21, and is associated with mental retardation, premature aging and neurodegeneration. Some children with ASDs also exhibit DS as a comorbid condition. The frequency of autism in subjects with DS has been reported to be 5.58% [108]. Many studies conducted with postmortem brain samples from DS patients depicted altered profile of expression of the ETC proteins, including decreased complex I (24-kDa subunit) in the occipital cortex and thalamus, complex I (75-kDa subunit) in temporal, occipital and caudate nucleus [109], and complex V beta chain in the frontal cortex [110]. An *in vitro* human fetal skin fibroblast experiment also showed a selective deficit in the catalytic efficiency of ETC complex I [111]. At the transcriptional level, Krapfenbauer et al. [112] reported that the complex I was significantly down-regulated in the cerebellum of DS subjects. Furthermore, alterations in ETC complexes were also observed in the brain of mice with trisomy 16, an animal model of DS with accelerated neuronal death. In these mice, Bambrick and Fiskum [113] reported a selective decrease in respiration with the complex I substrates (malate and glutamate) but not with the complex II substrate (succinate) in isolated cortex mitochondria, and a decrease in the 20 kDa subunit of complex I in the cortex.

6. Mitochondrial respiratory chain defects in patients with Fragile X syndrome

The Fragile X Mental Retardation (FMR) Syndrome is an inherited form of mental retardation caused by a full or partial loss of functions of the FMR1 gene on the X-chromosome [114]. Many affected individuals with FXS manifest features of autism [115]. This disorder is due to the expansion of the CGG repeats to over 200 copies within the 5' untranslated region (UTR) of the FMR1 gene on the chromosome Xq27.3. Increase in CGG repeats enhances the risk of disease. Individuals with less than 55 CGG repeats have a normal FMR1 gene. In premutation carrier, the repeat expansion is between 55 and 200 copies. The FMR protein (FMRP) is RNA-binding protein that has been shown to be involved in the expression of the mitochondrial and cytosolic Cu/Zn SOD1 [116]. Mitochondrial SOD1 functions to eliminate superoxide from the intermembrane space (Fig. 1). Therefore, abnormalities in FMRP-mediated modulation of SOD1 activity can increase mitochondrial oxidative stress, resulting in mitochondrial dysfunction [117].

Fragile X-associated tremor/ataxia syndrome (FXTAS) is a late-onset neurodegenerative disorder that affects individuals who are carriers of permutation expansions of 55–200 CGG repeats in the 5'UTR of FMR1 gene. Several studies have reported an early involvement of mitochondrial dysfunction in the pathogenesis of FXTAS [118,119]. Ross-Inta et al. [118] analysed dermal fibroblasts and brain samples from males with and without FXTAS symptoms, with a range of CGG repeats. They reported decreased NAD- and FAD-linked oxygen uptake rates, uncoupling between electron transport and ATP synthesis, lower expression of mitochondrial proteins, and increased oxidative/nitrative stress (revealed by decreased Mn SOD protein and increased mitochondrial protein nitration) in FXTAS. Interestingly, the mitochondrial abnormalities observed in FXTAS were also present, although to a lesser extent, in premutation carriers without FXTAS symptoms, which suggested that the onset of these events are earlier than the onset of clinical symptoms of FXTAS. Their results also suggested that mitochondrial dysfunction preceded the increase in oxidative stress damage by a significant period (perhaps years), and that early detection of mitochondrial dysfunction may offer early therapeutic intervention. In another study, Napoli et al. [119] reported lower oxidative phosphorylation capacity and complex IV activity in the fibroblasts from CGG premutation carriers who did not display

overt features of FXTAS. The fibroblasts from carriers who had FXTAS symptoms showed lower complex V. In addition, higher precursor-to-mature ratio of ATPB (ATPase β-subunit) from complex V was observed in the brains of patients who died with FXTAS symptoms.

7. Conclusion

Impaired mitochondrial functions, and as a consequence, impaired cellular energy state, may be one of the mechanisms underlying the pathophysiology of neurodevelopmental disorders including ASDs, ADHD, SZ, DS and FXS. Several studies have provided the evidence for deficits in the expression and/or activities of mitochondrial ETC complexes in these disorders. Since mitochondrial and nuclear genomes exert a dual genetic control on the biogenesis and maintenance of mitochondrial function, the mutations or deletions in mitochondrial or nuclear genes may also be involved in mitochondrial dysfunction in these neurodevelopmental disorders. However, it is not known whether mitochondrial dysfunction in neurodevelopmental disorders is caused by a primary genetic abnormality, or it is due to a secondary inhibition of oxidative phosphorylation by other factors. Abnormalities in mitochondrial ETC will result in impaired oxidative phosphorylation, leading to ATP depletion and disturbed brain energy metabolism, and to free radical generation and oxidative stress. Together, these defects in mitochondrial respiratory chain can lead to abnormal neurodevelopment.

Acknowledgments

This work was supported in part by funds from the New York State Office for People with Developmental Disabilities, Department of Defense Autism Spectrum Disorders Research Program AS073224P2, Autism Research Institute, Autism Speaks, and Autism Collaboration.

References

[1] Bertram R, Gram PM, Luciani DS, Sherman A. A simplified model for mitochondrial ATP production. J Theor Biol 2006; 243: 575-586.

[2] Szewczyk A, Wojtczak L. Mitochondria as a pharmacological target. Pharmacol Rev 2002; 54: 101-127.

[3] Boekema EJ, Braun HP. Supramolecular structure of the mitochondrial oxidative phosphorylation system. J Biol Chem 2007; 282: 1-4.

[4] Dudkina NV, Eubel H, Keegstra W, Boekema EJ, Braun HP. Structure of a mitochondrial supercomplex formed by respiratory-chain complexes I and III. Proc Natl Acad Sci U S A 2005; 102: 3225-3229.

[5] Cotter D, Guda P, Fahy E, Subramaniam S. MitoProteome: mitochondrial protein sequence database and annotation system. Nucleic Acids Res 2004; 32: D463-D467.

[6] Shadel GS. Expression and maintenance of mitochondrial DNA: new insights into human disease pathology. Am J Pathol 2008; 172: 1445-1456.

[7] Shadel GS, Pan Y. Multi-faceted regulation of mitochondria by TOR. Cell Cycle 2009; 8: 2143.

[8] Mattson MP, Liu D. Energetics and oxidative stress in synaptic plasticity and neurodegenerative disorders. Neuromolecular Med 2002; 2: 215-231.

[9] Polster BM, Fiskum G. Mitochondrial mechanisms of neural cell apoptosis. J Neurochem 2004; 90: 1281-1289.

[10] Cadenas E, Davies KJ. Mitochondrial free radical generation, oxidative stress, and aging. Free Radic Biol Med 2000; 29: 222-230.

[11] Lenaz G. The mitochondrial production of reactive oxygen species: mechanisms and implications in human pathology. IUBMB Life 2001; 52: 159-164.

[12] Hansen JM, Go YM, Jones DP. Nuclear and mitochondrial compartmentation of oxidative stress and redox signaling. Annu Rev Pharmacol Toxicol 2006; 46: 215-234.

[13] Jones DP. Disruption of mitochondrial redox circuitry in oxidative stress. Chem Biol Interact 2006; 163: 38-53.

[14] Kelley MR, Parsons SH. Redox regulation of the DNA repair function of the human AP endonuclease Ape1/ref-1. Antioxid Redox Signal 2001; 3: 671-683.

[15] McCord JM. The evolution of free radicals and oxidative stress. Am J Med 2000; 108: 652-659.

[16] Muller FL, Liu Y, Van Remmen H. Complex III releases superoxide to both sides of the inner mitochondrial membrane. J Biol Chem 2004; 279: 49064-49073.

[17] Barja G. Mitochondrial oxygen radical generation and leak: sites of production in states 4 and 3, organ specificity, and relation to aging and longevity. J Bioenerg Biomembr 1999; 31: 347-366.

[18] Sugioka K, Nakano M, Totsune-Nakano H, Minakami H, Tero-Kubota S, Ikegami Y. Mechanism of O2- generation in reduction and oxidation cycle of ubiquinones in a model of mitochondrial electron transport systems. Biochim Biophys Acta 1988; 936: 377-385.

[19] Lord C, Cook EH, Leventhal BL, Amaral DG. Autism spectrum disorders. Neuron 2000; 28: 355-363.

[20] Wingate, M, Mulvihill B, Kirby RS et al. Prevalence of autism spectrum disorders – Autism and Developmental Disabilities Monitoring Network, 14 sites, United States, 2008. MMWR Surveill Summ 2012; 61: 1-19.

[21] Kim YS, Leventhal BL, Koh YJ et al. Prevalence of autism spectrum disorders in a total population sample. Am J Psychiatry 2011; 168: 904-912.

[22] Chauhan A, Gu F, Essa MM et al. Brain region-specific deficit in mitochondrial electron transport chain complexes in children with autism. J Neurochem 2011; 117: 209-220.

[23] Chugani DC, Sundram BS, Behen M, Lee ML, Moore GJ. Evidence of altered energy metabolism in autistic children. Prog Neuropsychopharmacol Biol Psychiatry 1999; 23: 635-641.

[24] Minshew NJ, Goldstein G, Dombrowski SM, Panchalingam K, Pettegrew JW. A preliminary 31P MRS study of autism: evidence for undersynthesis and increased degradation of brain membranes. Biol Psychiatry 1993; 33: 762-773.
[25] Lombard J. Autism: A mitochondrial disorder? Med Hypotheses 1998; 50: 497-500.
[26] Guevara-Campos J, Gonzalez-Guevara L, Briones P et al. Autism associated to a deficiency of complexes III and IV of the mitochondrial respiratory chain. Invest Clin 2010; 51: 423-431.
[27] Filiano JJ, Goldenthal MJ, Rhodes CH, Marin-Garcia J. Mitochondrial dysfunction in patients with hypotonia, epilepsy, autism, and developmental delay: HEADD syndrome. J Child Neurol 2002; 17: 435-439.
[28] Weissman JR, Kelley RI, Bauman ML et al. Mitochondrial disease in autism spectrum disorder patients: A cohort analysis. PLoS One 2008; 3: e3815.
[29] Oliveira G, Diogo L, Grazina M et al. Mitochondrial dysfunction in autism spectrum disorders: A population-based study. Dev Med Child Neurol 2005; 47: 185-189.
[30] Correia C, Coutinho AM, Diogo L et al. Brief report: High frequency of biochemical markers for mitochondrial dysfunction in autism: No association with the mitochondrial aspartate/glutamate carrier SLC25A12 gene. J Autism Dev Disord 2006; 36: 1137-1140.
[31] Filipek PA, Juranek J, Nguyen MT, Cummings C, Gargus JJ. Relative carnitine deficiency in autism. J Autism Dev Disord 2004; 34: 615-623.
[32] Rossignol DA, Frye RE. Mitochondrial dysfunction in autism spectrum disorders: A systematic review and meta-analysis. Mol Psychiatry 2012; 17: 290-314.
[33] Palmieri L, Persico AM. Mitochondrial dysfunction in autism spectrum disorders: cause or effect? Biochim Biophys Acta 2010; 1797: 1130-1137.
[34] Rossignol DA, Bradstreet JJ. Evidence of mitochondrial dysfunction in autism and implications for treatment. Am J Biochem Biotech 2008; 4: 208-217.
[35] Gargus JJ, Imtiaz F. Mitochondrial energy-deficient endophenotype in autism. Am J Biochem Biotech 2008; 4: 198-207.
[36] Haas RH. Autism and mitochondrial disease. Dev Disabil Res Rev 2010; 16: 144-153.
[37] Tsao CY, Mendell JR. Autistic disorder in 2 children with mitochondrial disorders. J Child Neurol 2007; 22: 1121-1123.
[38] Ozonoff S, Williams BJ, Landa R. Parental report of the early development of children with regressive autism: The delays-plus-regression phenotype. Autism 2005; 9: 461-486.
[39] Goldberg WA, Osann K, Filipek PA et al. Language and other regression: Assessment and timing. J Autism Dev Disord 2003; 33: 607-616.
[40] Hansen RL, Ozonoff S, Krakowiak P et al. Regression in autism: prevalence and associated factors in the CHARGE Study. Ambul Pediatr 2008; 8: 25-31.
[41] Stefanatos GA. Regression in autistic spectrum disorders. Neuropsychol Rev 2008; 18: 305-319.
[42] Poling JS, Frye RE, Shoffner J, Zimmerman AW. Developmental regression and mitochondrial dysfunction in a child with autism. J Child Neurol 2006; 21: 170-172.
[43] Shoffner J, Hyams L, Langley GN et al. Fever plus mitochondrial disease could be risk factors for autistic regression. J Child Neurol 2010; 25: 429-434.
[44] Chauhan A, Essa, MM, Muthaitah B, Brown WT, Chauhan V. Mitochondrial abnormalities in lymphoblasts from autism. J Neurochem 2009; 109 (Suppl 1): 273.
[45] James SJ, Rose S, Melnyk S, et al. Cellular and mitochondrial glutathione redox imbalance in lymphoblastoid cells derived from children with autism. FASEB J. 2009; 23: 2374-2383.
[46] Holtzman D. Autistic spectrum disorders and mitochondrial encephalopathies. Acta Paediatr 2008; 97: 859-860.
[47] Giulivi C, Zhang YF, Omanska-Klusek A et al. Mitochondrial dysfunction in autism. JAMA 2010; 304: 2389-2396.
[48] Chauhan A, Chauhan V. Oxidative stress in autism. Pathophysiology 2006; 13: 171-181.
[49] McGinnis WR. Oxidative stress in autism. Altern Ther Health Med 2004; 10: 22-36.
[50] Chauhan A, Chauhan V. Brain oxidative stress and mitochondrial abnormalities in autism: In: Consensus paper: pathological role of the cerebellum in autism (Fatemi SH et al.). Cerebellum 2012; 11: 777-807.
[51] Chauhan A, Chauhan V, Brown WT, Cohen I. Oxidative stress in autism: Increased lipid peroxidation and reduced serum levels of ceruloplasmin and transferrin – the antioxidant proteins. Life Sci 2004; 75: 2539-2549.
[52] James SJ, Cutler P, Melnyk S et al. Metabolic biomarkers of increased oxidative stress and impaired methylation capacity in children with autism. Am J Clin Nutr 2004; 80: 1611-1617.
[53] Zoroglu SS, Armutcu F, Ozen S et al. Increased oxidative stress and altered activities of erythrocyte free radical scavenging enzymes in autism. Eur Arch Psychiatry Clin Neurosci 2004; 254: 143-147.
[54] Sogut S, Zoroglu SS, Ozyurt H et al. Changes in nitric oxide levels and antioxidant enzyme activities may have a role in the pathophysiological mechanisms involved in autism. Clin Chim Acta 2003; 331: 111-117.
[55] Ming X, Stein TP, Brimacombe M, Johnson WG, Lambert GH, Wagner GC. Increased excretion of a lipid peroxidation biomarker in autism. Prostaglandins Leukot Essent Fatty Acids 2005; 73: 379-384.
[56] Lopez-Hurtado E, Prieto JJ. A microscopic study of language-related cortex in autism. Am J Biochem Biotech 2008; 4: 130-145.
[57] Evans TA, Perry G, Smith MA et al. Evidence for oxidative damage in the autistic brain. In: Chauhan A., Chauhan V. and Brown W.T. (eds), Autism: Oxidative stress, inflammation and immune abnormalities, CRC Press, Taylor and Francis groups, Florida, 2009, pp. 35-46.
[58] Muthaiyah B, Essa MM, Chauhan V, Brown WT, Wegiel J, Chauhan A. Increased lipid peroxidation in cerebellum and temporal cortex of brain in autism. J Neurochem 2009; 108 (Suppl. 1): 73.
[59] Sajdel-Sulkowska EM, Xu M, Koibuchi N. Increase in cerebellar neurotrophin-3 and oxidative stress markers in autism. Cerebellum 2009; 8: 366-372.
[60] Schroer RJ, Phelan MC, Michaelis RC et al. Autism and maternally derived aberrations of chromosome 15q. Am J Med Genet 1998; 76: 327-336.
[61] Gillberg C. Chromosomal disorders and autism. J Autism Dev Disord 1998; 28: 415-425.
[62] Cleary N. Sudden death in chromosome 15q11-q13 duplication syndrome. http://www. idic15.org/PhysicianAdvisory_Feb2009.pdf.
[63] Filipek PA, Juranek J, Smith M et al. Mitochondrial dysfunction in autistic patients with 15q inverted duplication. Ann Neurol 2003; 53: 801-804.
[64] Ezugha H, Goldenthal M, Valencia I, Anderson CE, Legido A, Marks H. 5q14.3 deletion manifesting as mitochondrial

disease and autism: Case report. J Child Neurol 2010; 25: 1232-1235.
[65] Pons R, Andreu AL, Checcarelli N et al. Mitochondrial DNA abnormalities and autistic spectrum disorders. J Pediatr 2004; 144: 81-85.
[66] Graf WD, Marin-Garcia J, Gao HG et al. Autism associated with the mitochondrial DNA G8363A transfer RNA(Lys) mutation. J Child Neurol 2000; 15: 357-361.
[67] Marui T, Funatogawa I, Koishi S et al. The NADH-ubiquinone oxidoreductase 1 alpha subcomplex 5 (NDUFA5) gene variants are associated with autism. Acta Psychiatr Scand 2011; 123: 118-124.
[68] Taurines R, Thome J, Duvigneau JC et al. Expression analyses of the mitochondrial complex I 75-kDa subunit in early onset schizophrenia and autism spectrum disorder: increased levels as a potential biomarker for early onset schizophrenia. Eur Child Adolesc Psychiatry 2010; 19: 441-448.
[69] Amir RE, Van dV, I, Wan M, Tran CQ, Francke U, Zoghbi HY. Rett syndrome is caused by mutations in X-linked MECP2, encoding methyl-CpG-binding protein 2. Nat Genet 1999; 23: 185-188.
[70] Coker SB, Melnyk AR. Rett syndrome and mitochondrial enzyme deficiencies. J Child Neurol 1991; 6: 164-166.
[71] Heilstedt HA, Shahbazian MD, Lee B. Infantile hypotonia as a presentation of Rett syndrome. Am J Med Genet 2002; 111: 238-242.
[72] Ruch A, Kurczynski TW, Velasco ME. Mitochondrial alterations in Rett syndrome. Pediatr Neurol 1989; 5: 320-323.
[73] Eeg-Olofsson O, al Zuhair AG, Teebi AS et al. Rett syndrome: a mitochondrial disease? J Child Neurol 1990; 5: 210-214.
[74] Dotti MT, Manneschi L, Malandrini A, De Stefano N, Cazzerale F, Federico A. Mitochondrial dysfunction in Rett syndrome. An ultrastructural and biochemical study. Brain Dev 1993; 15: 103-106.
[75] Stradomska TJ, Tylki-Szymanska A, Bentkowski Z. Very long-chain fatty acids in Rett syndrome. Eur J Pediatr 1999; 158: 226-229.
[76] Su H, Fan W, Coskun PE et al. Mitochondrial dysfunction in CA1 hippocampal neurons of the UBE3A deficient mouse model for Angelman syndrome. Neurosci Lett 2011; 487: 129-133.
[77] Kriaucionis S, Paterson A, Curtis J, Guy J, Macleod N, Bird A. Gene expression analysis exposes mitochondrial abnormalities in a mouse model of Rett syndrome. Mol Cell Biol 2006; 26: 5033-5042.
[78] Faraone SV, Sergeant J, Gillberg C, Biederman J. The worldwide prevalence of ADHD: is it an American condition? World Psychiatry 2003; 2: 104-113.
[79] Bradstreet JJ, Smith S, Baral M, Rossignol DA. Biomarker-guided interventions of clinically relevant conditions associated with autism spectrum disorders and attention deficit hyperactivity disorder. Altern Med Rev 2010; 15: 15-32.
[80] Papa M, Sellitti S, Sadile AG. Remodeling of neural networks in the anterior forebrain of an animal model of hyperactivity and attention deficits as monitored by molecular imaging probes. Neurosci Biobehav Rev 2000; 24: 149-156.
[81] Fagundes AO, Rezin GT, Zanette F et al. Chronic administration of methylphenidate activates mitochondrial respiratory chain in brain of young rats. Int J Dev Neurosci 2007; 25: 47-51.
[82] Fagundes AO, Scaini G, Santos PM et al. Inhibition of mitochondrial respiratory chain in the brain of adult rats after acute and chronic administration of methylphenidate. Neurochem Res 2010; 35: 405-411.
[83] Bubber P, Tang J, Haroutunian V et al. Mitochondrial enzymes in schizophrenia. J Mol Neurosci 2004; 24: 315-321.
[84] Rezin GT, Amboni G, Zugno AI, Quevedo J, Streck EL. Mitochondrial dysfunction and psychiatric disorders. Neurochem Res 2009; 34: 1021-1029.
[85] Scaglia F. The role of mitochondrial dysfunction in psychiatric disease. Dev Disabil Res Rev 2010; 16: 136-143.
[86] Maurer I, Zierz S, Moller H. Evidence for a mitochondrial oxidative phosphorylation defect in brains from patients with schizophrenia. Schizophr Res 2001; 48: 125-136.
[87] Fujimoto T, Nakano T, Takano T, Hokazono Y, Asakura T, Tsuji T. Study of chronic schizophrenics using 31P magnetic resonance chemical shift imaging. Acta Psychiatr Scand 1992; 86: 455-462.
[88] Kegeles LS, Humaran TJ, Mann JJ. *In vivo* neurochemistry of the brain in schizophrenia as revealed by magnetic resonance spectroscopy. Biol Psychiatry 1998; 44: 382-398.
[89] Volz HR, Riehemann S, Maurer I et al. Reduced phosphodiesters and high-energy phosphates in the frontal lobe of schizophrenic patients: A (31)P chemical shift spectroscopic-imaging study. Biol Psychiatry 2000; 47: 954-961.
[90] Ben Shachar D. Mitochondrial dysfunction in schizophrenia: A possible linkage to dopamine. J Neurochem 2002; 83: 1241-1251.
[91] Uranova NA, Aganova EA. Ultrastructure of the synapses of the anterior limbic cortex in schizophrenia. Zh Nevropatol Psikhiatr Im S S Korsakova 1989; 89: 56-59 (in Russian).
[92] Kung L, Roberts RC. Mitochondrial pathology in human schizophrenic striatum: A postmortem ultrastructural study. Synapse 1999; 31: 67-75.
[93] Cavelier L, Jazin EE, Eriksson I et al. Decreased cytochrome-c oxidase activity and lack of age-related accumulation of mitochondrial DNA deletions in the brains of schizophrenics. Genomics 1995; 29: 217-224.
[94] Andreazza AC, Shao L, Wang JF, Young LT. Mitochondrial complex I activity and oxidative damage to mitochondrial proteins in the prefrontal cortex of patients with bipolar disorder. Arch Gen Psychiatry 2010; 67: 360-368.
[95] Prince JA, Blennow K, Gottfries CG, Karlsson I, Oreland L. Mitochondrial function is differentially altered in the basal ganglia of chronic schizophrenics. Neuropsychopharmacology 1999; 21: 372-379.
[96] Whatley SA, Curti D, Marchbanks RM. Mitochondrial involvement in schizophrenia and other functional psychoses. Neurochem Res 1996; 21: 995-1004.
[97] Buchsbaum MS, Haier RJ, Potkin SG, et al. Frontostriatal disorder of cerebral metabolism in never-medicated schizophrenics. Arch Gen Psychiatry. 1992; 49: 935-942
[98] Holcomb HH, Cascella NG, Thaker GK, Medoff DR, Dannals RF, Tamminga CA. Functional sites of neuroleptic drug action in the human brain: PET/FDG studies with and without haloperidol. Am J Psychiatry. 1996; 153:41-49.
[99] Reddy RD, Yao JK. Free radical pathology in schizophrenia: A review. Prostaglandins Leukot Essent Fatty Acids 1996; 55: 33-43.
[100] Yao JK, Reddy RD, van Kammen DP. Oxidative damage and schizophrenia: an overview of the evidence and its therapeutic implications. CNS Drugs 2001; 15: 287-310.
[101] Dietrich-Muszalska A, Kontek B. Lipid peroxidation in patients with schizophrenia. Psychiatry Clin Neurosci 2010; 64: 469-475.

[102] Dadheech G, Mishra S, Gautam S, Sharma P. Evaluation of antioxidant deficit in schizophrenia. Indian J Psychiatry 2008; 50: 16-20.
[103] Skinner AO, Mahadik SP, Garver DL. Thiobarbituric acid reactive substances in the cerebrospinal fluid in schizophrenia. Schizophr Res 2005; 76: 83-87.
[104] Akyol O, Herken H, Uz E et al. The indices of endogenous oxidative and antioxidative processes in plasma from schizophrenic patients. The possible role of oxidant/antioxidant imbalance. Prog Neuropsychopharmacol Biol Psychiatry 2002; 26: 995-1005.
[105] Kuloglu M, Ustundag B, Atmaca M, Canatan H, Tezcan AE, Cinkilinc N. Lipid peroxidation and antioxidant enzyme levels in patients with schizophrenia and bipolar disorder. Cell Biochem Funct 2002; 20: 171-175.
[106] Iwamoto K, Bundo M, Kato T. Altered expression of mitochondria-related genes in postmortem brains of patients with bipolar disorder or schizophrenia, as revealed by large-scale DNA microarray analysis. Hum Mol Genet 2005; 14: 241-253.
[107] Ji B, La Y, Gao L et al. A comparative proteomics analysis of rat mitochondria from the cerebral cortex and hippocampus in response to antipsychotic medications. J Proteome Res 2009; 8: 3633-3641.
[108] Lowenthal R, Paula CS, Schwartzman JS, Brunoni D, Mercadante MT. Prevalence of pervasive developmental disorder in Down's syndrome. J Autism Dev Disord 2007; 37: 1394-1395.
[109] Kim SH, Vlkolinsky R, Cairns N, Fountoulakis M, Lubec G. The reduction of NADH ubiquinone oxidoreductase 24- and 75-kDa subunits in brains of patients with Down syndrome and Alzheimer's disease. Life Sci 2001; 68: 2741-2750.
[110] Kim SH, Vlkolinsky R, Cairns N, Lubec G. Decreased levels of complex III core protein 1 and complex V beta chain in brains from patients with Alzheimer's disease and Down syndrome. Cell Mol Life Sci 2000; 57: 1810-1816.
[111] Valenti D, Manente GA, Moro L, Marra E, Vacca RA. Deficit of complex I activity in human skin fibroblasts with chromosome 21 trisomy and overproduction of reactive oxygen species by mitochondria: involvement of the cAMP/PKA signalling pathway. Biochem J 2011; 435: 679-688.
[112] Krapfenbauer K, Yoo BC, Cairns N, Lubec G. Differential display reveals deteriorated mRNA levels of NADH3 (complex I) in cerebellum of patients with Down syndrome. J Neural Transm Suppl 1999; 57: 211-220.
[113] Bambrick LL, Fiskum G. Mitochondrial dysfunction in mouse trisomy 16 brain. Brain Res 2008; 1188: 9-16.
[114] Verkerk AJ, Pieretti M, Sutcliffe JS et al. Identification of a gene (FMR-1) containing a CGG repeat coincident with a breakpoint cluster region exhibiting length variation in fragile X syndrome. Cell 1991; 65: 905-914.
[115] Hernandez RN, Feinberg RL, Vaurio R, Passanante NM, Thompson RE, Kaufmann WE. Autism spectrum disorder in fragile X syndrome: A longitudinal evaluation. Am J Med Genet A 2009; 149A: 1125-1137.
[116] Bechara EG, Didiot MC, Melko M et al. A novel function for fragile X mental retardation protein in translational activation. PLoS Biol 2009; 7: e16.
[117] Wallace DC. A mitochondrial paradigm of metabolic and degenerative diseases, aging, and cancer: A dawn for evolutionary medicine. Annu Rev Genet 2005; 39: 359-407.
[118] Ross-Inta C, Omanska-Klusek A, Wong S et al. Evidence of mitochondrial dysfunction in fragile X-associated tremor/ataxia syndrome. Biochem J 2010; 429: 545-552.
[119] Napoli E, Ross-Inta C, Wong S et al. Altered zinc transport disrupts mitochondrial protein processing/import in fragile X-associated tremor/ataxia syndrome. Hum Mol Genet 2011; 20: 3079-3092.