Abstract. – Background: Mitochondria play a key role in the production of the cell energy. The final product of this process is adenosine triphosphate (ATP), used as a source of chemical energy. Besides this major role, mitochondria have been shown to be involved in other functions, such as signaling, cellular differentiation, cell death, as well as the control of the cell cycle and cell growth. The aim of this paper is to highlight the relationships between psychiatric disorders, especially schizophrenia, bipolar disorder (BD), autism, attention deficit-hyperactivity disorder (ADHD) and Alzheimer’s dementia.

Results: The review of the available literature indicate that different mitochondrial dysfunctions may accompany and/or be part of the clinical picture of some neuropsychiatric disorders.

Conclusions: Different data would indicate that mitochondrial dysfunctions may be involved in the pathophysiology of different neuropsychiatric disorders, given their key role in the cell energy metabolism. Moreover, they would greatly contribute to the process of neural apoptosis that should be at the basis of neurodegenerative disorders, such as schizophrenia, Alzheimer’s dementia and the most severe forms of BD. In addition, data are available that mitochondrial abnormalities are present also in developmental disorders, such as autism and ADHD, although the studies aiming at elucidating the role of mitochondria in the onset and pathophysiology of all these conditions should be considered preliminary. In any case, taken together, these scattered findings would suggest novel drugs targeting protecting mitochondria from oxidative stress.

Key Words: Mitochondria, ATP, Mitochondrial DNA, Nuclear DNA, Schizophrenia, Mood disorders.

Introduction

Mitochondria are rod-shaped intracellular organelles that can be considered the power generators of the cell, converting oxygen and other compounds in adenosine triphosphate (ATP), that powers the cell’s metabolic activities and exchanges with adenosine diphosphate (ADP) in the cytosol.

Mitochondria are composed by several compartments, that include the outer membrane that encloses the entire organelle and contains porin proteins that serve as diffusion channels for minute protein molecules across the membrane. Then the inner membrane that contains about 1/5 of the mitochondrial proteins, it is impermeable and ions and molecules require special membrane transporters to pass through it. Finally, the space between the outer membrane and the inner membrane that is called intermembrane space, while the matrix is the space enclosed by the inner membrane. The ATP is produced in the matrix by the ATP synthase present in the inner membrane. The matrix also contains a highly-concentrated mixture of hundreds of enzymes, special mitochondrial ribosomes, transfer ribonucleic acid (tRNA), and several copies of the mitochondrial deoxyribonucleic acid (DNA) genome.

Mitochondria possess their own DNA called mitochondrial (mtDNA), a molecule of 16.5 kb. The mitochondrial respiratory chain is associated with the inner mitochondrial membrane and consists of several protein complexes that form the mitochondrial electron transport system.

The main role of the mitochondria is the production of ATP, reduced nicotinamide adenine dinucleotide (NADH) and reduced flavin adenine dinucleotide (FADH). In addition, mitochondria are involved in a range of other processes such as the control of the cell cycle, signaling, differentia-
tion, growth and death, the regulation of the membrane potential, calcium (Ca^{2+}) signaling and steroid synthesis. Mitochondria have been implicated in several human diseases, while there are only a few data on mitochondrial dysfunctions and psychiatric symptoms and/or disorders. Therefore, the aim of this paper is to present a review on mitochondrial dysfunction in two major psychiatric disorders, in particular, schizophrenia and mood disorders.

**DNA Mutations**

Mitochondrial diseases are often caused by mutations of mtDNA, but a most of their functions are controlled by nuclear DNA (nDNA). It is possible to identify three groups of diseases: those associated with nDNA defects, those due to mtDNA defects and those related to mutations of the two genomes. The mtDNA is inherited from the mother and each mitochondria contains multiple mtDNA copies that can be both normal or mutated (heteroplasmy). The mtDNA mutation may vary from organ to organ and the phenotypic expression depends on the quantity of mutated genomes in each organ and on the dependence of each organ from oxidative metabolism: the heart, brain and skeletal muscle tissues are the most commonly organs affected by a mutation of mtDNA. As a result, there is a heterogeneous phenotypic expression of the genetic damage, even within the same family, from asymptomatic carriers to patients with multisystemic syndromes.

**Mitochondrial Diseases**

Some specific mitochondrial diseases have been identified, in particular, the Kearns Sayre syndrome (KSS), the chronic progressive external ophthalmoplegia (CPEO), the Leber’s hereditary optic neuropathy (LHON), the mitochondrial myopathy, encephalopathy, lactic acidosis, stroke-like episodes (cerebral infarction) (MELAS) and myoclonic epilepsy with ragged red fibers (MERRF). The entire mtDNA is transmitted from the mother to all children without recombination, so that they share the same sequence of mtDNA, but may have different clinical manifestations, due to the different proportion of mutated mtDNA in the case of heteroplasmy. Up-to now, more than 150 sites of mutation have been identified and a similar number of rearrangements (partial deletions and duplications) of mtDNA have been reported. For this reason, there exists significant phenotypic differences between patients with mitochondrial diseases.

**Mitochondrial Alterations in Psychiatric Disorders**

Over the past 20 years, there have been increasing observations concerning the existence of a relationship between mitochondrial dysfunctions and some psychiatric disorders. According to some Authors, psychotic, mood, anxiety and personality disorders may be part of the clinical manifestations of some mitochondrial diseases, although others are of the opinion that psychiatric disorders would represent a complication of the mitochondrial dysfunctions.

**Schizophrenia**

The pathophysiology of schizophrenia is still unclear, but there is a lot of evidence to suggest that it might result from the interaction of genetic, environmental and neurobiological factors. Recent studies hypothesize a possible role of mitochondrial dysfunctions, in particular mtDNA alterations, in the onset of schizophrenia. It is interesting to note that the few studies exploring the mRNA expression in the frontal cortex of schizophrenic patients, revealed that the altered sequences were those encoding proteins of the respiratory chain. One heteroplasmic variant of the mtDNA, encoding the ND4 subunits of the complex I, was also identified and resulted to be present at a higher frequency in male schizophrenic patients (47%) than in healthy control subjects (18%).

A reduction of the complex IV and an age-dependent increase of mtDNA deletions were observed in the frontal cortex and caudate nucleus of treated schizophrenic patients, in contrast to control subjects or patients with Alzheimer’s dementia. However, it is yet unclear whether the mitochondrial alterations are a primary or secondary phenomenon of the disease. An increased activity of the complex I was observed in platelets of schizophrenic patients with or without antipsychotic treatment, but not in those patients suffering from bipolar disorder (BD) or recurrent depression. An increased activity of the complex II and IV in the putamen and a reduction of the complex IV in the caudate nucleus have been reported in psychotic patients under treatment. A reduction of the activity of the complex IV was observed in the frontal cortex obtained postmortem from schizophrenic patients treated with neuroleptics, while the complexes I, II, and IV were altered in the temporal cortex, and complexes I and III in the basal ganglia. However, no abnormality was found in the
expression of nuclear genes encoding proteins related to mitochondrial function in the hippocampus. An increasing number of studies, carried out in peripheral central nervous system (CNS) models, would indicate that schizophrenic patients might be characterized by a dysregulation in energy production by mitochondria this would provoke increased oxidative stress that, according to the opposite hypothesis, could be also the primary event leading subsequently to mitochondrial alterations. In other words, damaged mitochondria would become less efficient producers of ATP and more efficient producers of free radicals (and the whole process would lead to a state of chronic oxidative stress). Further, mitochondria play an important role in maintaining the homeostasis of Ca²⁺ that may trigger the cascade of signals leading to cell apoptosis. Taken together, these findings would indicate that mitochondrial alterations may be involved in some processes at the basis of different neurodegenerative conditions, including schizophrenia and bipolar disorder (BD).

**Mood Disorders**

The mood disorders include different clinical pictures, such as major depression (MD), hypomania, mania and mixed states. These disorders are widespread in the general population; the prevalence of mood disorders is estimated to be 10%, up to 25% during lifetime. Several patients with mitochondrial diseases due to mtDNA mutations, including the 3243A > G mutation, may meet the criteria for a diagnosis of unipolar depression and BD, and some of them may show psychotic features and/or progressive cognitive deficits. Genetic studies have shown that MD, probably transmitted by mothers, is present in 51% of mothers of families affected by mitochondrial diseases, as compared with 12% of mothers of control subjects. Depression is also more frequent in maternal than paternal grandmothers, in uncles and nephews, but only in the group with apparent maternal transmission.

Some patients with both mitochondrial diseases and depression may show peculiar alterations in the cerebral blood flow, but data are limited and inconclusive.

**Bipolar Disorder (BD)**

Mitochondrial dysfunctions in BD might be due to altered expression of nuclear and mitochondrial genes encoding mitochondrial proteins. While using the technique of gene arrays the expression of nuclear genes was evaluated in samples of brain tissue, particularly the hippocampus of patients with BD, schizophrenia and healthy control subjects: the results showed that the expression of nuclear mRNA, encoding mitochondrial proteins, was significantly reduced in the hippocampus of BD patients, but not in those suffering from schizophrenia.

Accumulating evidence suggests that mitochondrial dysfunction, especially the impairment of the complex I, is associated with increased oxidative damage, but it is unclear if this relationship is specific to BD.

At peripheral level, leukocyte mitochondrial DNA (mtDNA) was examined in 35 patients with BD by the nested PCR method. The PCR product corresponding to the common deletion was found in 2 of 35 (5.7%) patients, and in 50% of patients with CPEO or KSS. The deletion involves a region that encodes for five tRNAs and some subunits of NADH dehydrogenase, cytochrome-c oxidase and ATP synthase. Although the correlation between this mutation and the pathophysiology of BD is unclear, deletions of mtDNA in the brain could alter energy metabolism and determine the progression of affective symptoms. Currently, it is debatable if the deletion observed in BD patients is inherited or not, or whether this mutation is associated with BD.

As already mentioned, mitochondria are involved in the regulation of intracellular Ca²⁺ concentration. The diffusion of Ca²⁺ from mitochondria to the cytosol has important consequences for the synthesis and release of neurotransmitters, receptor signalling, the action potential, and synaptic plasticity. A dysregulation of Ca²⁺ in the mitochondria might trigger the initiation of neural apoptosis.

**Autism and Attention Deficit Hyperactivity Disorder (ADHD)**

The evidence regarding these two disorders are sporadic, mostly case reports. An autistic child showed a point mutation of the mtDNA in a tRNA gene (G8363A). In a boy with a small deletion of mtDNA in mitochondrial tRNA (deletion of one of three TA nucleotide pairs in the tRNALeu (UUR) gene of the mtDNA incorporating positions 3271 to 3273) and a progressive disorder that led to the death at age 23. Hyperactivity and disciplinary problems were reported retrospectively during school years. Two subjects with ADHD were found to be carriers of a
mutation of mtDNA\textsuperscript{43}. Finally, symptoms suggestive of ADHD in adolescence, were observed in a middle-aged woman with rearrangements in mtDNA\textsuperscript{44}.

In a recent study, mitochondrial dysfunctions and mtDNA abnormalities were evaluated in lymphocytes from 10 children with autism and 10 control subjects. The results showed that the NADH oxidative and the complex I activities, evaluated in lymphocyte mitochondria was significantly lower in autistic than in healthy children. Taken together, the results of these studies would suggest that autistic children are more likely to show mitochondrial dysfunctions than normal children, although the pathophysiological role of such alterations is not yet clarified\textsuperscript{45}.

**Alzheimer’s Disease**

Alzheimer’s disease is the most common neurodegenerative disorder (about two-thirds of all dementias).

Alzheimer’s disease is clinically characterized by a progressive worsening of cognitive functions. From a macroscopic point of view the most striking feature is a marked atrophy of the brain which determines an increased width of the grooves and of cerebral ventricular volume, while the major neuropathological features are represented by intracellular gles and extracellular amyloid beta (Abeta) deposits in some brain regions.

Over the past decade, the hypothesis of the involvement of oxidative stress in the pathogenesis of Alzheimer’s disease has been progressively strengthened by a growing number of publications. It was, in fact, suggested that mitochondria may play a crucial role in the mechanisms underlying neurodegeneration. The major theory of aging suggests that alterations in mitochondrial genes, such as deletions and point mutations that accumulate progressively with age as the “common deletion”. The most frequent deletion of 4977 bp found in the mtDNA can help to reduce the functionality of one or more respiratory chain complexes, thus blocking the mechanism of electron transport and increasing the level of free radical generation with a consequent damage to mtDNA\textsuperscript{46-52}.

The mitochondrial dysfunction is probably one of the earliest events that are established in the course of Alzheimer’s disease: the appearance of metabolic abnormalities seem to precede of a decade the onset of clinical illness\textsuperscript{53,54}. Interestingly, Abeta monomers and oligomers are associated with mithocondrial membranes.

A valuable tool to determine whether any mitochondrial polymorphism may act as susceptibility or protective factor in the onset of Alzheimer’s disease has been provided by analysis of mitochondrial haplogroups: mtDNA polymorphisms may make an individual more susceptible to such a damage and start earlier the apoptosis. On the other hand, other polymorphisms may improve the activity of oxidative phosphorylation and/or reduce the production of free radicals.

Some markers of mitochondrial alterations have been observed in post-mortem brains and in blood cells from patients with Alzheimer’s disease, in particular decreased levels of cytochrome oxidase activity and pyruvate dehydrogenase\textsuperscript{55}. In addition, increased production of free radicals, lipid peroxidation, oxidative protein damage, coupled with decreased ATP production, have been reported\textsuperscript{56}. More recent studies have highlighted also changes of mitochondria structure in brain specimens\textsuperscript{57}.

**Conclusions**

Mitochondria play a key role in different cellular functions, especially those related to energy metabolism. In the last years, many evidences highlight a possible role of mtDNA and/or nDNA mutations in the pathophysiology of psychiatric disorders, such as schizophrenia, MD and BD. Schizophrenic patients may present alterations of the complex I, involved in the respiratory chain, a reduction of the complex IV and an age-dependent increase of mtDNA deletions in the frontal cortex and caudate nucleus. A common deletion of mtDNA was found in BD patients. This mutation could alter energy metabolism and intracellular Ca\textsuperscript{2+}-concentration, and it could determine neural apoptosis and the progression of affective symptoms. These data could represent the forerunner for the development of new therapeutic strategies for the treatment of some psychiatric disorders.

**References**

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