Mitochondrial Dysfunction and Psychiatric Disorders

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Mitochondria are intracellular organelles crucial in the production of cellular energy. Mitochondrial diseases may result from malfunctions in this biochemical cascade. Several investigators have proposed that mitochondrial dysfunction is related to the pathophysiology of bipolar disorder (BD), major depressive disorder (MDD) and schizophrenia (SZ). The authors reviewed recent study findings and tried to delineate the current understanding of the correlation between mitochondrial dysfunction and psychiatric disorders. A growing body of evidence suggests that mitochondrial dysfunction is important in patients with psychiatric disorders. The evidence include impaired energy metabolism in the brain detected using results of magnetic resonance spectroscopy, electron microscopy, co-morbidity with mitochondrial diseases, the effects of psychotropics on mitochondria, increased mitochondrial DNA (mtDNA) deletion in the brain, and association with mtDNA mutations/polymorphisms or nuclear-encoded mitochondrial genes. It is possible that the new information will lead to a focus on psychiatric disorder as a metabolic disease. Treatment with psychotropics might ultimately enhance energy metabolism and reduce the damage of oxidative stress. The next step in the study of mitochondrial dysfunction in patients with psychiatric disorders should be clarification of how mitochondrial dysfunction, a nonspecific risk factor, causes specific symptoms. Further study of mitochondrial dysfunction in patients with psychiatric disorder is expected to be useful for the development of cellular disease markers and new psychotropics. *(Chang Gung Med J 2009;32:370-9)*

Key words: mitochondria, mtDNA, bipolar disorder, major depressive disorder, schizophrenia

Mitochondria are intracellular organelles containing DNA (mtDNA) inherited solely from the mother. Mitochondria play a crucial role in adenosine 5'-triphosphat triphosphate (ATP) production through oxidative phosphorylation (OXPHOS), a process carried out by the respiratory chain complexes I, II, III, and V.[1-3] They are also involved in amino acid, lipid, and steroid metabolism and serve as Ca^{2+} buffers, sources of free radicals and regulators of apoptosis. Mitochondrial dysfunction or disease represents a malfunction in the biochemical process of energy production, resulting from disruption of either mtDNA or nuclear DNA.[1-3]

Mitochondrial dysfunction has been studied in patients with brain diseases, including neurodegenerative diseases and, to some extent, psychiatric disorders.[4,5] Several brain illnesses result from mutations in the mtDNA, such as mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS), or in genes coding for complex I and II proteins, such as fatal Leigh syndrome which is X-linked.[6] Friedreich's ataxia is a disorder with trinucleotide repeat expansions in several polypeptides in complexes I through III.[7] There is also good evi-

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dence of mitochondrial dysfunction in patients with other neurodegenerative disorders (Alzheimer's disease, Huntington's disease, Parkinson's disease) that have mutations or defects in other proteins and energy metabolism pathways.[8] In general, mitochondrial dysfunction contributes to neurodegeneration either by apoptosis or generation of reactive oxygen species (ROS). There have been discussions about oxidative stress contributing to the pathophysiology of mood disorders.[9-11] A recent focus was made on the mutations in the enzyme glutamate cystein ligase modifier that would result in a decreased antioxidant response in patients with this illness.[12] The purpose of this review is to describe the current understanding of variations in mtDNA or mitochondrial function that impact the pathophysiology reported in patients with bipolar disorder (BD), major depressive disorder (MDD), and schizophrenia (SZ).

Comorbid mitochondrial disease and psychiatric disorders

Psychiatric symptoms have been noted in subjects with mitochondrial diseases. Fattal et al.,[13] identified 19 confirmed case reports of mitochondrial diseases with comorbid psychiatric problems, including BD, MDD, psychosis, anxiety disorders, and personality changes. Depression is one of the symptoms of the mitochondrial disease, chronic progressive external ophthalmoplegia (CPEO).[14] A high comorbidity of mitochondrial MELAS in SZ and bipolar affective disorder has also been documented.[15-17] In addition, a case report of MELAS that was preceded by mania prior to diagnosis, further supports the role of mtDNA mutations in the etiology of psychiatric disorders.[18] Transgenic mice with mitochondrial DNA deletions that related to a mutation in the nuclear-encoded POLG gene also displayed abnormal behaviors including decreased cued and contextual fear conditioning, increased startle response, and decreased and distorted day-night rhythm of wheel-running activity compared with normal mice.[19]

Acute confused state and SZ-like hallucination syndrome are sometimes observed in patients with MELAS, a typical mitochondrial encephalopathy.[20] Cases of mitochondrial encephalopathies presenting MDD or BD have also been reported (Table 1).[20] It cannot be concluded that these psychiatric symptoms have a causal relationship with mitochondrial encephalopathies. Suzuki et al.[21] performed psychiatric evaluations of patients with mitochondrial diabetes with the 3243 mtDNA mutation, based on their clinical impression that the compliance of patients with mitochondrial diabetes was worse than that of patients with common diabetes mellitus. They suggested that comorbidity of mental disorder in patients with diabetes mellitus with the 3243 mutation may be higher than that in diabetes mellitus in general (8-15%). In addition, comorbidity of diabetes mellitus was reported to be higher in patients with BD.[22] To date, there is no report on the prevalence of psychiatric disorders in patients with mtDNA mutations.

Psychiatrists should consider mitochondrial diseases as possible diagnoses in their patients particularly when they are accompanied by multiple comorbid physical symptoms. The reports we reviewed all alluded to a possible relationship between some psychiatric diseases (or subtypes of psychiatric diseases) with mitochondrial disease. The question remains whether the occurrence of psychiatric symptoms in these patients is just a coincidence or is more directly related to the mitochondrial diseases. Additional reports and further research in this area are clearly needed, with emphasis on diagnostic assessments and true risks and benefits of evidence-based treatments.

Neuroimaging studies

Both structural and functional MRI (fMRI) studies have identified alterations of size and function in the prefrontal cortex and limbic regions in BD patients.[23] fMRI studies have also revealed decreased pH, phosphocreatine and ATP levels and increased lactate levels in these brain regions, all of which are hallmarks of decreased energy metabolism.[24] Dager et al.[25] used two-dimentional proton echo-plannar spectroscopic imaging to quantify regional brain chemistry in cingulate gyrus of both medication-free BD patients and age-and sex-matched healthy subjects. They found that patients with BD exhibited elevated gray matter lactate and γ-aminobutyric acid levels; other gray and white matter chemical measures were not significantly different between the diagnostic groups. They concluded that there was a shift in the energy metabolism from oxidative phosporylation toward glycolysis in the medication-free BD patient, and suggested the possibility of mitochondrial alterations underlying these

Table 1. Cases of Mitochondrial Disorders with Comorbid Affective Disorder

Author	Disease or symptoms	mtDNA mutation	Psychiatric disorder	Note
Wallace[34]	Leber's disease	–	Depressive state	
Nakamura et al.[32]	Mitochondrial encephalopathy	–	Depression followed by dementia	
Stewart & Naylor[37]	KSS	–	Bipolar illness	
Ciafaloni et al.[35]	Familial CPEO	Multiple deletions	Affective disorder	The mother and her daughter both had CPEO and mood disorder.
Suomalainen et al.[38]	Familial CPEO	Multiple deletions	Recurrent severe depression	Other affected members of the pedigree also had comorbid depression.
Sweeney et al.[39]	Muscle weakness,	A3251G	Recurrent psychotic depression	Another patient in the pedigree had agoraphobia
Shanske et al.[36]	Bronchial asthma	A3243G	Depression	9-year-old boy.
Kato et al.[31]	Drug-induced ptosis	4977-bp deletion	Bipolar disorder	
Suzuki et al.[21]	Diabetes mellitus	A3243G	Depression, dysthymia	Four of 15 had mood disorders.
Onishi et al.[40]	Diabetes mellitus, hearing loss	A3243G	Major depression	
Miyaoka et al.[30]	Diabetes mellitus	A3243G	Recurrent depression	Cases of panic disorder or phobia were also reported
Inagaki et al.[33]	Diabetes mellitus	A3243G	Reversible frontal lobe syndrome	After recurrent catatonic symptoms, loss of drive emerged. Blunted effect appeared, and was improved by idebenone.

Data adapted from Kato T and Kato N. (2000)

Abbreviations: CPEO: chronic progressive external ophthalmoplegia; KSS: Kearns–Sayre syndrome.

findings. Imaging studies taking together highlight that it was unlikely that bipolar disorder was localized to abnormalities within a single neuroanatomic structure.[26] There may be relatively diminished prefrontal modulation of subcortical and medial temporal structures within the anterior limbic network (e.g., amygdala, anterior striatum and thalamus), which may result in dysregulation of mood. These considerations are portrayed schematically in Fig. 1.[27,28] In their review of proton (^{1}H) magnetic resonance spectroscopy (MRS) and phosphorus (^{31}P) MRS in bipolar subjects compared with healthy control subjects, Strok and Renshaw[29] proposed a hypothesis of mitochondrial dysfunction in bipolar disorder that involves impaired oxidative phosphorylation, a resultant shift toward glycolytic energy production, a decrease in total energy production and/or substrate availability, and altered phospholipid metabolism (Fig. 2).

Electron microscopy studies

Electron microscopy studies have revealed mitochondrial abnormalities in SZ. No researchers have examined morphological or morphometric abnormalities in BPD or MDD lymphocytes. A significant decrease in mitochondria number and density in the prefrontal cortex and caudate nucleus of postmortem brains of subjects with SZ was observed compared with control subjects.[30] A lower number of mitochondria in patients who were not taking antipsychotic medications was found compared with those taking antipsychotics or control medications, suggesting drug treatment normalized the number of mitochondria.[31] Two strong schizophrenia candidate

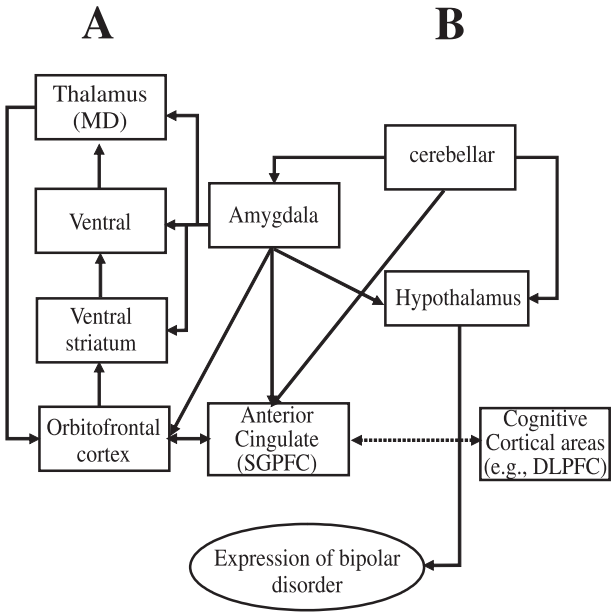

Fig. 1 Diagram adopted from Ketter et al. (2002). Schematic of the anterior limbic network as a model of the expression of bipolar symptoms. (A) 'Iterative' prefrontal subcortical network that shows inputs from other brain regions to modulate appropriate behavioral responses. (B) Limbic areas that modulate (e.g., amygdala) or express the responses (e.g., hypothalamus).

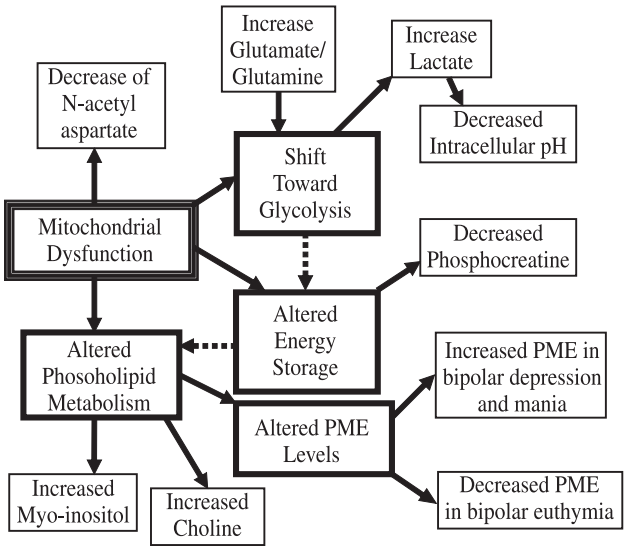

Fig. 2 MRS indications of mitochondrial dysfunction in bipolar disorder. Summary of recent MRS research on metabolite alterations in bipolar subjects and how these results may be integrated into a hypothesis of mitochondrial dysfunction. Abbreviations used: MRS: magnetic resonance spectroscopy, PME: phosphomonoester.

genes, Disrupted in Schizophrenia 1 (DISC1) and G72, have splicing isoforms that are targeted to mitochondria although the exact functions of these proteins in the mitochondria remain unknown.[32,33]

Animal studies and cellular models

Findings from animal studies and cellular models on the molecular pharmacology of mood stabilizing drugs implicated mitochondrial energy metabolism as a target for these drugs. A series of investigations showed that lithium and other mood stabilizers increased the expression of the antiapoptic gene *Bcl-2*.[34] These were among the first studies to use a mitochondrial target for mood stabilizers. cDNA microarray studies in animals examining targets of mood stabilizers, at least lithium and valproate, strongly suggested that these drugs increased energy metabolism and decreased oxidative damage and that these effects may be important for their efficacy in BD.[35] Some of the most recent studies demonstrated that such effects were also observed under pathological conditions such as excitotoxicity and oxidative stress.[36]

Einet et al.[37] explored the significance of Bcl-2 in the association between mitochondrial function and BD. They tested Bcl-2 heterozygote mice in models of BD and anxiety disorders. Mutant mice had reduced mitochondrial Bcl-2 levels, and although they had no gross behavioral abnormalities, they demonstrated a significant increase of anxiety-like behaviors. Mutant mice did not differ from wild types in the measures of locomotion or in the forced swim test for depression-like behavior suggesting a specific effect on anxiety-like behaviors. This study demonstrated that Bcl-2 may be a key factor in anxiety disorders and that its effects may possibly originate from its role in the mitochondria.

Glycogen synthase kinase-3 (GSK3) has been recently linked to BD, MDD and SZ, and the neurotransmitter systems and therapeutic treatments associated with these diseases.[38] GSK3 inhibition may be a common component of the mechanism of action of lithium and valproate.[39] Several intracellular signaling cascades converge on GSK3 to modulate its activity, and several neurotransmitter systems also regulate GSK3, including serotonergic, dopaminer-

gic, cholinergic, and glutamatergic systems. A neuron-specific GSK3 beta transgenic mice have been reported to show Alzhiemer's disease-like phenotypes.[40]

cDNA microarray studies

Studies using cDNA microarray techniques have demonstrated decreased expression of a cluster of genes in components of the mitochondrial electron transport chain (ETC) in postmortem BD and SZ samples, even after the effects of sample pH was controlled.[41] It was shown that antidepressants, valproate and antipsychotics had inhibitory effects on mitochondrial functions and expression of mitochonria-related genes in the brain.[42-45] Medication-free BD patients showed up-regulation of *CASQ1* (gene product: calsequestrin 1) when compared with control subjects at the critical pH thresholds.[41] Most medicated patients were treated with more than two classes of drugs. It is unclear whether the inhibitory effects of the drugs on mitochondria reflected their side effects or some efficacies. The inhibitory effects of the drugs may have partially normalizing effects in these patients.

Down-regulation of NADH-ubiquinone oxidoreductase 20-kDa subunit (Complex I), cytochrome *c* oxidase polypeptide VIC (Complex IV) and ATP synthase (Complex V) lipid-binding protein were further verified using real-time PCR in samples from patients with BD.[46] The expression of the NADH-ubiquinone oxidoreductase 20-kDa subunit was increased in subjects with BD who were receiving lithium at the time of death, when compared with subjects with BD who were not being treated with lithium.[46] Because the mitochondrial ETC is a major source for the generation of reactive oxygen species, these findings suggest that oxidative damage may play an important role in the pathophysiology of BD and SZ. The effect of lithium treatment may be involved in neuroprotection against this damage.

The expression of nuclear messenger RNA coding for mitochondrial proteins was significantly decreased in the hippocampus in subjects with BD but not with SZ.[47] Subjects with BD were characterized by a pronounced and extensive decrease in the expression of genes regulating oxidative phosphorylation and the ATP-dependent process of proteasome degradation. The molecular evidence strengthens the hypothesis that decreased pH and high-energy phosphate levels in BD were the result of mitochondrial dysfunction. Neuroleptic medications have been reported to have supportive and inhibitory effects on mitochondrial function.[48-50] Antipsychotic treatments may up-regulate genes for mitochondrial respiration, and this could explain why the SZ group had levels more comparable with control subjects. Lithium and valproic acid did not seem to be responsible for the down-regulation of genes because they did not cluster together in hierarchical clustering (Fig. 3), and lithium had no such effects in an animal study.[51] This provides evidence that the decreased gene expression in these bipolar disorder samples was not due to neuroleptic medication, lithium, or valproic acid. Again, factors inherent in postmortem studies, which were beyond the investigators' control, may have contributed to the reduced RNA quality.

In a series of experiments, Kato and Kato[20] identified mtDNA abnormalities and several amino acid substitutions in specific candidate genes in samples from BD patient. Further, mtDNA polymorphisms (5178C and 10398A) were found to be associated with BD. The 5178C genotype was associated with lower brain intracellular pH.

Mitochondrial DNA copy number variation and common deletion

Vawter et al.[52] reported a strong association of prolonged death (presumably longer intervals of hypoxia) with increased mtDNA copy number in dorsolateral prefrontal cortex (DLPFC). After controlling for the strong effects of agonal duration, there was a trend towards decreased mtDNA copy number in BD compared with the control subjects. Vawter et al. reported about 50-500 copies of mtDNA per copy of nuclear DNA in DLPFC homogenate depending on agonal-pH state of individual subjects. Frahm et al.[53] reported a 10-fold higher range of mtDNA copy number of 1259-4617 varying widely among brain regions, agonal factors, and methodology.[54] The copy number of mtDNA can be induced in hypoxic states[54] resulting in mitochondrial proliferation and/or mtDNA replication.

The most frequent mtDNA deletion is a 4977 base pair 'common deletion', and several researchers have investigated this deletion in patients with psychiatric disorders. Shao et al.[55] studied the expression of the 13 mtDNA-encoded genes and D-loop to compare levels of common deletion in brain tissue

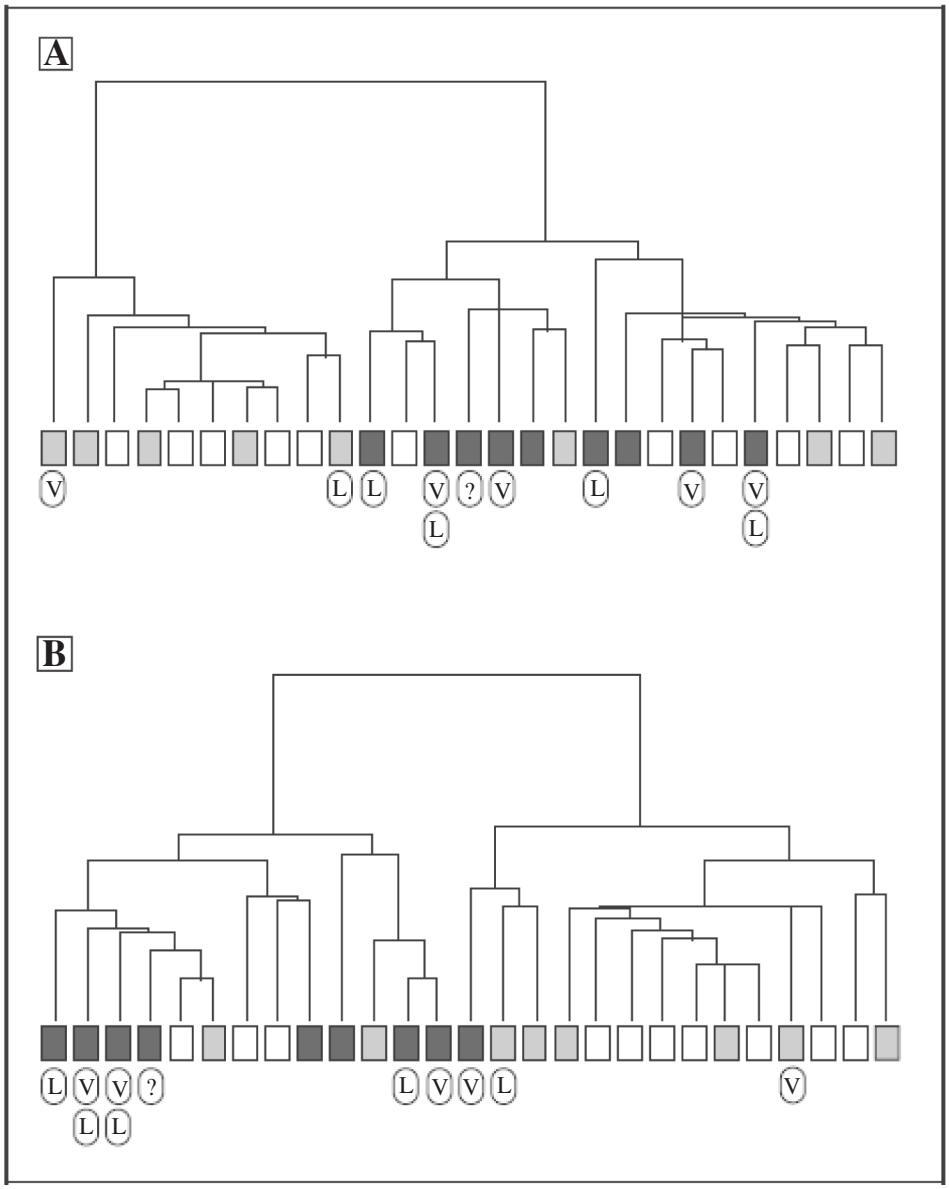

Fig. 3 Diagram adopted from Konradi et al. (2004). Hierarchical clustering of samples. (A) All genes with a standard deviation higher than 4% of the mean of their expression value and that are present in at least 20% of the samples were used for clustering (n = 216). Significant clustering of bipolar disorder samples was observed (p = .005). (B) Genes known to be involved in complexes I through V of the mitochondrial respiratory chain and present in at least 20% of the samples were used for clustering (n = 72). Significant clustering of samples from patients with bipolar disorder (p = .004) and control subjects (p = .02) was observed. Redundant probe sets were excluded from clustering analysis. Dark-shaded rectangles indicate bipolar disorder; light-shaded rectangles, schizophrenia; open rectangles, controls; Abbreviations used: L: lithium carbonate; V: valproic acid; ?: treatment not known.

from patients with BD, MDD and SZ, respectively. There were significant decreases in expression of 10/13 and 6/13 mitochondrial transcripts for SZ and MDD respectively compared with the control subjects, after adjustment for age, gender, pH and agonal factors. In BD an increase of mtDNA common deletion was found, and insignificant increases were seen for SZ or MDD. The findings of the alterations in the

mitochondrial transcript expression appeared to be independent of the common deletion as there were no significant correlations between the mitochondrial gene expressions for the 13 transcripts with the levels of the common mtDNA deletion. However, the trend of the data suggests that an increase of common deletion is associated with decreased mitochondrial gene expression. The observation requires confirmation with a larger cohort and suggests that accumulation of the common mtDNA deletion and decrease in transcription overall may include susceptibility factors for neuropsychiatric disorders. However, the effects of medications in the study cannot be excluded.

Summary

Multiple lines of evidence suggest mitochondrial dysfunction may play a role in patients with psychiatric disorders. The growing body of evidence, including morphological, genetic, comorbidity with mitochondrial disorders, and imaging data, supports the role of mitochondrial dysfunction in BD, MDD and SZ.

Researchers have proposed that altered intracellular calcium regulation and defective energy metabolism of mitochondrial dysfunction contribute to the pathophysiology of psychiatric disorders. This theory was based on the findings in psychiatric patients with regional alterations of brain pH, white matter hyperintensities, low phosphocreatine and ATP, or increased mtDNA deletions. Altered mitochondrial genome expression has also been suggested, particularly on the gene encoding complex I. Searching for candidate mtDNA single nucleotide polymorphisms associated with SZ, BPD and MDD has yielded a number of positive findings, although these results tend not to be replicated, possibly due to low sample sizes or an association of multiple nuclear and mitochondrial genomic variants in combination that lead to respiratory chain dysfunction and predisposition to these disorders. Nevertheless, the results of these studies suggest a role of mitochondrial dysfunction in the etiology of psychiatric disorders.

It is possible that the new data will lead to a focus on psychiatric disorder as a metabolic disease – one in which energy metabolism becomes decreased, leading to subtle neuronal damage and cell death, which may be more evident in patients with chronic illnesses with lasting cognitive impairments. Treatment with psychotropics might ultimately enhance energy metabolism and reduce the damage of oxidative stress. The future study of mitochondrial dysfunction in psychiatric disorders should bring clarification as to how nonspecific mitochondrial dysfunction can cause specific symptoms of psychiatric disorders. Further study of mitochondrial dysfunction in psychiatric disorder is expected to be useful for the development of cellular disease markers and new psychotropics.

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粒線體功能障礙和精神疾病

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粒線體是細胞內生產能量的重要胞器。粒線體疾病常導因於能量代謝反應過程的異常。若干研究者認爲，粒線體功能障礙與躁鬱症、重鬱症及精神分裂症的病理有關。本篇作者們檢視目前的研究報告，並討論線粒體功能障礙和精神疾病的相關性。越來越多的研究證據指向粒線體功能障礙，是精神疾病病理重要的一部分。如以磁共振波譜分析大腦能量代謝，電子顯微鏡檢查腦細胞粒線體數目，與粒線體疾病的共病現象，精神藥物對粒線體的影響，大腦中粒線體 DNA 斷裂的增加，以及粒線體 DNA 突變／多形性或細胞核編碼粒線體基因的相關性，都在精神疾病患者的檢查中有重要的發現。這些新的證據可能將精神疾病的焦點轉向代謝性疾病，即因能量代謝降低，導致隱微的神經元損傷和細胞死亡，這些情形在慢性疾病併持久認知缺損的病人可能更爲明顯。精神藥物治療最終可能會提高能量代謝及減少氧化壓力的損傷。接下來在研究粒線體功能障礙和精神疾病的關係中，應澄清如此非特異性的粒線體功能障礙，如何能導致特異的精神疾病症狀。進一步研究精神疾病患者的粒線體功能障礙，預計對於開發疾病的細胞標記和新的精神藥物能有幫助。(長庚醫誌 2009;32:370-9)

關鍵詞：粒線體，粒線體去氧核糖核酸，躁鬱症，重鬱症，精神分裂症

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