8

The Cross-Talk Between Mitochondria and the Nucleus in the Response to Oxidative Stress Associated with Mitochondrial Dysfunction in Mitochondrial Encephalomyopathies

Yu-Ting Wu[1], Wan-Yu Lee[1], Shi-Bei Wu[1] and Yau-Huei Wei[1,2]
[1]*Department of Biochemistry and Molecular Biology*
School of Life Sciences, National Yang-Ming University
[2]*Department of Medicine, Mackay Medical College*
Taiwan

1. Introduction

Mitochondria are responsible for the supply of the majority of ATP in human cells via respiration and oxidative phosphorylation (OXPHOS). Mitochondria also play a central role in numerous cellular processes including energy production, intracellular Ca^{2+} homeostasis, biosynthesis of pyridine nucleotides and amino acids, and β-oxidation of fatty acids. On the contrary, mitochondria are also involved in the generation of reactive oxygen species (ROS), and initiation and execution of apoptotic cell death. Accumulating evidence show that defects in one or more of these functions may contribute to mitochondrial encephalomyopathies and other neuromuscular diseases. The term "mitochondrial encephalomyopathies" was coined by pediatric neurologists to call the attention of clinicians when the brain disease was first reported in children with mitochondrial alterations in their muscle biopsies (Shapira et al., 1977). Clinically, mitochondrial encephalomyopathies are common disorders that are a result of mutations affecting genes encoding proteins of important mitochondrial function (Leonard & Schapira, 2000a). Most mitochondrial diseases, such as mitochondrial myopathy, lactic acidosis and stroke-like episodes (MELAS), are maternally inherited and frequently manifested as encephalomyopathies (Taylor et al., 2004). Furthermore, typical clinical features of mitochondrial encephalomyopathies include weakness and retardation of the heart, skeletal muscle and brain, where mitochondria are relatively abundant. Common symptoms of mitochondrial encephalomyopathies include loss of cognitive function, sensorineural deafness, optic atrophy, fluctuating encephalopathy, ataxia, seizures, dementia, migraine, stroke-like episodes, spasticity, cardiomyopathy, proximal myopathy and exercise intolerance (Stollberger & Finsterer, 2006).

Epilepsy and seizures are common features of mitochondrial dysfunction associated with mitochondrial encephalomyopathies and have been considered the most common neurological disorders. According to the electroencephalograph (EEG) and seizure procedures, epilepsy is often an important sign in the early progression of mitochondrial

encephalomyopathies (Canafoglia et al., 2001). Epilepsy is characterized by spontaneous and recurrent unprovoked seizures that may lead to numerous changes with events of cascades at the cellular level of neurons. Neuronal excitability can be affected by mitochondrial dysfunction including depletion of ATP, generation of ROS, disruption of Ca^{2+} homeostasis, defects in biosynthesis and metabolism of neurotransmitters. However, the mechanism by which mitochondrial dysfunction leads to the onset and progression of epilepsy is still unclear. In this article, we focus on the potential role of mitochondrial function in the pathophysiology of mitochondrial encephalomyopathies. Firstly, we discuss the biochemical consequences of mitochondrial dysfunction-elicited oxidative stress in affected cells of patients with mitochondrial encephalomyopathies. Secondly, we address the possible molecular mechanisms involving in the regulation of communication between defective mitochondria and the nucleus, which is termed "mitochondrial retrograde signaling" in the pathogenesis of mitochondrial encephalomyopathies. Moreover, we also explore the role of mitochondria in the regulation of Ca^{2+} homoeostasis in neuron excitability that influences the normal function of neurons and proceeds towards epileptic seizures. Finally, we discuss the role of stress responsive gene, Sirt1, in the signaling pathway of the cross-talk between mitochondria and the nucleus to be a defense mechanism against neuronal degeneration in the patients with mitochondrial encephalomyopathies. We believe that the above-mentioned information will help us gain a deeper insight into the mechanisms underlying the pathogenesis of epilepsy in patients with mitochondrial disease and guide us to develop novel therapeutic strategies for better treatment of human diseases caused by mitochondrial dysfunction.

2. Oxidative stress and mitochondrial encephalomyopathies

Typical mitochondrial myopathy and encephalomyopathies are caused by mutations in the mtDNA or nuclear DNA that affect the respiratory chain directly (Bertini & D'Amico, 2009). Since mitochondria are responsible for the supply of the majority of ATP in human cells via respiration and OXPHOS, the defective mitochondria in affected tissue cells cause not only inefficient ATP production but also increased production of ROS. The symptoms of mitochondrial encephalomyopathies and neuromuscular disorders caused by mitochondrial dysfunction-elicited oxidative stress have been proven to be similar to those documented in the patients with mitochondrial diseases (Fernández-Checa et al., 2010). Oxidative stress elicited by mitochondrial dysfunction can further increase oxidative damage to various biomolecules in mitochondria. Hence, it has been proposed that the vicious cycle is propagating in mitochondrial diseases and results in the widely observed accumulation of oxidative damage and mutation of mtDNA, which ultimately leads to a progressive decline in the bioenergetic function of mitochondria that affects tissue cells in patients with mitochondrial encephalomyopathies (Fukui & Moraes, 2008). Recently, Katayama and coworkers demonstrated that the occurrence of 8-OHdG-positive neurons was significantly increased in the peri-lesional cortices as compared with the non-lesional and control cortices in the patients with MELAS syndrome (Katayama et al., 2009). Importantly, the spread frequency of stroke-like lesions in MELAS patients was significantly reduced after treatment with the antioxidant edaravone. In addition, a key finding was that failure of adaptive responses to oxidative stress (e.g., DNA repair system) in the brain during epileptogenesis could lead to an increase in the susceptibility of mitochondria to oxidative damage (Jarrett et

al., 2008). The mitochondrial base excision repair (BER) pathway involves a highly coordinated process catalyzed by the sequential actions of the DNA repair enzymes 8-oxoguanine glycosylase (OGG1) and DNA polymerase gamma (POLG). It was reported that the RNA and protein expression levels of OGG1 and POLG were decreased during chronic epilepsy in an animal model (Lin et al., 2010). They found that spontaneous seizures coincided with an accumulation of mtDNA damage, increased mitochondrial H_2O_2, and impaired mtDNA repair, which suggest a contribution of mitochondrial defects to epileptogenesis. On the other hand, the regulation of antioxidant enzymes against oxidative stress in the cells with defective mitochondria also plays an important role in the pathophysiology of mitochondrial encephalomyopathies (Wu et al., 2010). Several animal models with the disruption of the antioxidant enzymes such as manganese superoxide dismutase (Mn-SOD) and glutathione peroxidase 1 (GPx-1) genes could lead to neuromuscular disorders that are similar to those documented in the patients with mitochondrial diseases (Li et al., 1995; Esposito et al., 2000). Taken together, the increase of oxidative stress and oxidative damage and the dysregulation of antioxidant enzymes are involved in the deterioration of bioenergetic function of the affected tissues, especially in the brain and skeletal muscle from patients with mitochondrial encephalomyopathies, which depend on mitochondrial function for supply of most of the ATP (Wei & Lee, 2003). Recent studies conducted in our own and other laboratories have provided compelling evidence to support the notion that oxidative stress elicited by impairment of the respiratory chain in the affected tissues of patients plays a role in the pathogenesis and progression of mitochondrial diseases and seizure generation (Waldbaum et al., 2010a; Wu et al., 2010).

3. Biochemical hallmarks in mitochondrial encephalomyopathies

A wide spectrum of the clinical phenotypes in the patients with mitochondrial encephalomyopathies is mostly associated with the defects in the structure or function of mitochondria. The histological and histochemical examinations of affected tissues have provided useful clues to determine the mitochondrial defects in the diagnosis of these diseases (Alhatou et al., 2004). There are well-established dye-staining methods for the assay of enzyme activities of cytochrome *c* oxidase (COX, Complex IV) and succinate dehydrogenase (SDH, Complex II) in affected muscle fibers and brain (DiMauro et al., 2002). Usually, the succinate dehydrogenase (SDH) activity staining clearly shows the subsarcolemmal accumulation of mitochondria (SDH-positive) and the activity assay of COX is particularly useful in the evaluation of mitochondrial myopathies (COX-negative fibers) because Complex IV contains subunits encoded by both the mtDNA and nuclear DNA (Taylor et al., 2004). Recently, Folbergrová et al. (2010) reported that the persistent inhibition of Complex I led to the overproduction of ROS, which could contribute to the neuronal injury in a rat model of seizures and in the patients with epileptogenesis. In a previous study, we observed a significant decrease in the copy number of mtDNA in the leukocytes of patients with mitochondrial encephalomyopathies including MERRF and MELAS syndromes, respectively (Liu et al., 2006). The amplitude of change was related to the proportion of mutant mtDNA, which may serve as a biomarker in the pathogenesis and progression of the mitochondrial diseases. Similarly, a recent study revealed that large amounts of mtDNA with a deletion were observed in hippocampal tissues of patients with epilepsy (Guo et al., 2010). Most importantly, by the establishment of cybrid cells with mitochondrial dysfunction and primary culture of

skin fibroblasts from affected tissues, we have been able to intensively study the pathogenesis of mitochondrial encephalomyopathies. Firstly, we found that the glucose metabolism was shifted to enhanced anaerobic glycolysis in the cells from patients with mitochondrial myopathy and encephalopathy. This is consistent with a previous report that glycolysis is up-regulated to compensate for the inefficient ATP production by mitochondrial OXPHOS (Pallotti et al., 2004). Although the increase in glycolysis occurred in affected cells is still equivocal, it revealed cellular adaptation for affected cells to cope with the energy crisis (Qian & van Houten, 2010). Secondly, neuronal mitochondria are important for intracellular Ca^{2+} sequestration, which suggests that mitochondria can modulate neuronal excitability and synaptic transmission which are altered in the patients with epilepsy (Tang & Zucker, 1997). Indeed, loss of Ca^{2+} buffering in hippocampal mitochondria has been demonstrated in kainate-treated chronic epileptic rats (Kunz et al. 1999). Besides, substantial alterations of mitochondrial Ca^{2+} homeostasis were also the predominant feature in cybrids harboring the mtDNA mutation associated with MERRF syndrome (Brini et al., 1999). Finally, since the oxidative damage to proteins was accumulated in the defective mitochondria from the affected tissue cells, an efficient mitochondrial protein quality control system was also essential for the survival of patients with mitochondrial encephalomyopathies (Luce et al., 2010). It has been reported that the mitochondrial Lon protease and heat-shock protein 60 (HSP60) were dysregulated in cultured skin fibroblasts established from patients with MERRF and MELAS syndromes, respectively (Wu et al., 2010). In addition, the decreased expression of mitochondrial HSP60 within the abnormal mitochondria was found in the subsarcolemmal region of muscle from the patients with mitochondrial encephalomyopathies, but HSP60 was over-expressed in the intermyofibrillar mitochondria (Carrier et al., 2000). This finding suggests that the processing and integration of imported precursor proteins are impaired in the subsarcolemmal mitochondrial aggregates of the ragged-red fibers (RRF), whereas the biosynthesis, import and assembly of proteins may still be efficient in the biogenesis of intermyofibrillar mitochondria of these muscle fibers.

4. Mitochondrial dysfunction-induced cell death and mitochondrial encephalomyopathies

Evidence showed that tissue degeneration caused by cell death has been implicated in numerous mitochondrial diseases including mitochondrial encephalomyopathies, neuromuscular disorders and neurodegenerative diseases (Sayre et al., 2008). It is important to unravel the molecular mechanism underlying decreased cell viability in the process of epileptogenesis in the mitochondrial encephalomyopathies. There are at least two mechanisms implicated in neuronal cell death, including activation of the excitotoxic cascades (mitochondrial Ca^{2+} overload; excessive stimulation of glutamate receptors, nitric oxide overproduction; elevated oxidative stress and ROS overproduction), and induction of apoptosis. In this section, we focus on the involvement of programmed cell death (apoptosis) in the mitochondrial encephalomyopathies and provoked epilepsy. Apoptosis is the best understood cell death that can could be manipulated to control the destiny of cells. Indeed, apoptotic pathway has been considered a major physiological process in triggering cell death, which is critical for morphogenesis, tissue homeostasis as well as pathogenesis of diverse diseases (Hetts, 1998). Notably, mitochondria play an important role in the initiation, execution and regulation of apoptosis since mitochondria

can release specific proteins and factors to trigger the apoptotic pathway. MtDNA mutation-elicited mitochondrial dysfunction may result in insufficient supply of ATP, excess generation of ROS, elevated oxidative stress, membrane lipids peroxidation, disruption of mitochondrial membrane potential, dysregulation of excitotoxicity, and imbalanced distribution of intracellular Ca^{2+} ions (Kann & Kovacs, 2007). All of these changes can trigger activation of the cascades of caspases and pro-apoptotic proteins, and result in apoptosis.

Clinically, many researchers tried to clarify the correlation between apoptosis-related cell death and pathogenic mechanism involved in the defects in muscle and brain of patients with mitochondrial encephalomyopathies. Many well-documented studies have revealed that apoptosis is involved in the progression of muscle myopathy (Aure et al., 2006; Umaki et al., 2002). Studies showed significant signs of apoptosis in the COX- negative muscle fibers in muscle biopsies from patients who harbored high proportions of specific point mutations in tRNA genes of mtDNA. Distinct expressions of 8-OHdG, 4-HNE, Mn-SOD, cytochrome *c* and DNase I were detected in the COX-negative muscle fibers accompanied by apoptotic markers. These results suggest the importance of apoptosis and the relationship of the oxidative stress with the severity of the muscle myopathy in mitochondrial diseases. Liu and coworkers also showed progressive cortical volume loss in patients with recurrent neocortical epilepsy (Liu et al., 2003). Accumulating evidence substantiated that apoptosis plays a role in seizure-induced neuron death as well as brain damages and also as a cause and consequence for epileptogenesis (Chuang et al., 2009b; Weise et al., 2005). It has been reported that an increase in the expression of caspases molecules was observed in temporal cortex of patients with epilepsy (Henshall et al., 2000). Increased production of ROS, NO and peroxynitrite was also reported to proceed apoptotic cell death in vulnerable brain regions (Chuang et al., 2009a, 2009b). On the other hand, inhibition of pro-apoptotic proteins and caspases activation could reduce seizure-induced neuronal cell death in experimental animal models. It has been reported that inhibition of caspase 3 was efficacious in the protection against neuronal cell loss in several models of brain injury (Liou et al., 2003). Either by short interfering RNA molecules targeting *Bim* in human cells or by knockout of *Bim* in a mouse model could reduce cell death and decrease the degeneration of hippocampal CA3 neurons following seizures (Murphy et al., 2010). In addition, the mice lacking the pro-apoptotic protein, Puma, were found to have a reduced neuronal death by 50% in the hippocampus (Engel et al., 2010). Moreover, a recent study also showed that Bcl-w was an endogenous neuroprotectant in mice and patients with temporal lobe epilepsy (Murphy et al., 2007).

The above-mentioned studies showed the potential neuroprotective effect in epilepsy by targeting apoptosis with caspase inhibitors and genetic manipulation of pro-apoptotic proteins after onset of seizures in animals. Targeting apoptosis signaling pathways to prevent mitochondrial dysfunction-induced neuronal cell death may be a potential strategy for treatment of the patients with mitochondrial encephalomyopathies. However, some researchers showed that reducing cell death by administration of apoptotic inhibitor had no improvement of epilepsy symptoms in experimental animals (Narkilahti et al., 2003). These results revealed the complex cause and consequence of epileptogenesis and epileptic seizures. Therefore, the approach of inhibiting apoptosis to improve epileptic seizures should be evaluated with caution although it is still a potential candidate to collaborate with other antiepileptic drugs.

5. Mechanism of mitochondrial dysfunction caused neuronal excitability

Abnormality of Ca^{2+} homeostasis is thought to be associated with the pathophysiology of neurodegenerative diseases (Mattson, 2007). The disease progression in patients often occurred following epileptic seizures, a cardinal and early symptom of mitochondrial diseases, especially in MERRF and MELAS syndromes (Okumura et al., 2008). Investigators also demonstrated that defects of mitochondrial respiratory chain could evoke seizures by using partial inhibition of ETC enzymes to cause deficiency of cytochrome *c* oxidase (Yamamoto & Tang, 1996). During the episode of epileptic seizures, extreme neuronal cell activity is associated with excessive cytosolic Ca^{2+} influx. It is noteworthy that dysregulation of Ca^{2+} handling in neurons might be a consequence of mtDNA mutation. The energy deficiency and ROS overproduction are the major stressors in human cells harboring disease-associated mtDNA mutations, which play an important role in the induction of the signaling cascades emitted from dysfunctional mitochondria to the nucleus. The abnormality of Ca^{2+} homeostasis induced by insufficiency of cellular ATP and oxidative damage is a potential link between mitochondrial dysfunction and epilepsy-induced hyperexcitability in neurons of patients with mitochondrial encephalomyopathies.

5.1 Redox modulation of Ca^{2+} homeostasis

Mitochondria play an important role in the regulation of Ca^{2+} homoeostasis by effective Ca^{2+} buffering (Tang & Zucker, 1997). Mitochondria can transiently accumulate substantial amounts of Ca^{2+} from the cytosol through the rapid uptake and relatively slow release of the Ca^{2+} ions. Therefore, it is possible that mitochondrial defect could have an impact on Ca^{2+} homoeostasis in cells. Abnormal Ca^{2+} homoeostasis has been reported in various cell types with defects in mitochondrial OXPHOS function (Willems et al., 2008). Many studies also proved that cells with mtDNA mutations could result in the dysregulation of mitochondrial Ca^{2+} buffering and reduction of the Ca^{2+} influx. The increase in the concentration of cytosolic Ca^{2+} was observed in the fibroblasts from patients with mitochondrial encephalomyopathies including MELAS and MERRF. The affected cells have elevated levels of Ca^{2+} ions and cannot normally induce Ca^{2+} influx in response to agonist-stimulated Ca^{2+} uptake by mitochondria (Brini et al., 1999; Moudy et al., 1995). It remains unclear as to how a pathogenic mtDNA mutation affects Ca^{2+} homeostasis. It is thought that mitochondrial Ca^{2+} uptake is dependent on the mitochondrial membrane potential, and thus mitochondrial deficiency-related decline of membrane potential plays an important role in defects of Ca^{2+} homeostasis. It has been proved that diminishment of mitochondrial membrane potential by an uncoupling agent can interfere with the uptake of Ca^{2+} by mitochondria and thus alter the transient cytosolic Ca^{2+} levels in neurons (Werth & Thayer, 1994). Indeed, defect in the mitochondrial Ca^{2+} handling was observed in the skin fibroblasts of patients with the MERRF syndrome. It was reported that cybrids harboring mtDNA mutation derived from a patient with MERRF syndrome exhibited a reduced uptake of the Ca^{2+} ions by mitochondria in response to histamine stimuli (Brini et al., 1999).

Another important factor involving in the dysregulation of cellular Ca^{2+} homeostasis is excessive ROS production induced by mitochondrial dysfunction. More and more studies have supported that ROS and cellular redox state can directly modulate Ca^{2+} signaling through regulation of ion transporters (Hool & Corry, 2007). ROS have been shown to increase the Ca^{2+} channel activity through directly oxidizing the redox-sensing thiols on the Ryanodine receptor channel, and thereby induce the Ca^{2+} uptake from plasma membrane

(Werth & Thayer, 1994), and on IP3 receptor mediating Ca^{2+} release from ER which leads to elevated cytosolic Ca^{2+} (Suzuki & Ford, 1992). On the other hand, alteration of cellular redox states such as the lower GSH/GSSG and NADH/NAD^+ ratios have been reported to modulate Ca^{2+} homeostasis by elevating the activity of Ca^{2+} channels and inhibiting the Ca^{2+} pump (Kourie, 1998; Zima et al., 2004). In general, Ca^{2+} can be re-uptake by the SR/ER Ca^{2+} ATPase following Ca^{2+} release from SR/ER Ca^{2+} stores or Ca^{2+} influx from PM to maintain the concentration of cytosolic Ca^{2+}. However, the Ca^{2+} ATPase activity is also sensitive to the redox state, but unlike activation of oxidized receptor channels, it is inhibited by oxidative modification and ROS (Kaplan et al., 2003). As described above, mtDNA mutations can elicit over-production of intracellular ROS, which not only damages cellular biomolecules but also change the redox homeostasis of affected cells. Elevated oxidative stress results in a decrease of the GSH/GSSG ratio in the skin fibroblasts and cybrids harboring mtDNA mutation established from patients with mitochondrial diseases. A decrease in the GSH levels and gluthathione reductase activity has been observed in the plasma and brain regions of epileptic patients (Mueller et al., 2001). A large amount of studies have shown that the GSH concentration and the activity of Na^+/K^+ ATPase were decreased and affected the Ca^{2+} pump in the striatum and hippocampus during pilocarpine-induced seizures. It was also demonstrated that restoration of the level of GSH by lipoic acid could abolish the seizure episodes in the rat (de Freitas, 2010). A recent study showed that the tissue levels of GSH, and GSH/GSSG ratio were persistently altered throughout the onset of epileptogenesis in experimental temporal lobe epilepsy (Waldbaum et al., 2010b). The shift of redox state to oxidation would disrupt the Ca^{2+} homeostasis through the stimulation of Ca^{2+} influx and the interference of the Ca^{2+} pump, leading to dysregulation of the cytosolic Ca^{2+} concentration and the perturbation of Ca^{2+} signaling pathways. These findings imply that redox-dependent alterations of Ca^{2+} signaling cascades may contribute to the onset and progression of epileptogenesis.

5.2 Inhibition of Ca^{2+} exchangers by energy deficiency

The defects in the respiration and OXPHOS cause a depletion of ATP, and thus compromise the removal of Ca^{2+} ions by Ca^{2+}-ATPase. Cytoplasmic Ca^{2+} concentration is also maintained by the ATP-dependent Ca^{2+} pump (Leo et al., 2005). Therefore, reduction in ATP synthesis could result in the accumulation of cytosolic Ca^{2+} (Buttgereit & Brand, 1995). A reduction in the capacity of Ca^{2+} clearance might lead to a disruption of Ca^{2+} homeostasis. Besides, lactic acidosis might be associated with an increase of cytosolic Ca^{2+} ions in patients with mitochondrial diseases. An increase in glucose uptake and the rate of glycolysis was observed in the epileptic loci during seizure episodes, which may result in elevated lactate production that is well documented in patients with mitochondrial diseases (Cornord et al., 2002). Intracellular acidification has been shown to inhibit the plasma membrane Na^+/H^+ exchanger (Anderson et al., 2003), which causes an increase in cytosolic Na^+ concentration and thus interfere with Na^+/Ca^{2+} exchange through inhibition of the exchange of cellular Ca^{2+} for extracellular Na^+, leading to cellular accumulation of Ca^{2+} ions. These findings suggest that mitochondrial dysfunction-induced insufficient supply of ATP might be another important factor contributing to elevated seizure susceptibility in human epileptic patients through alteration of ion transporters. The scenario described above can explain why an elevation of cytosolic Ca^{2+} ions is often observed in human cells harboring pathogenic mtDNA mutations, especially from MERRF and MELAS patients, respectively.

5.3 Pathological effect of defective Ca^{2+} dyshomeostasis

Proper regulation of the Ca^{2+} influx is critical to neuronal cell function, and to transduce electrochemical signals into molecular signals. Perturbed Ca^{2+} homeostasis would cause excessive amounts of Ca^{2+} within the neurons leading to dysfunction of a variety of cellular processes, followed by degeneration and cell death. When defective mitochondria alter the cellular Ca^{2+} dynamics, it might affect the specificity of Ca^{2+} signals and subsequently result in the induction of improper signaling cascades. Intriguingly, it has been reported that peripheral mitochondria accumulate more Ca^{2+} than do those in perinuclear region (Collins et al., 2002). We have observed that pathogenic mtDNA mutations can alter the distribution and movement of mitochondria, which would affect the regulation of local Ca^{2+} ions (Ma et al., 2005). Thus, the pathogenic deficit of Ca^{2+} signaling might further affect the brain function. Besides, slow elevation of cytosolic Ca^{2+} ions can lead to a corresponding increase in mitochondrial Ca^{2+} concentration. This physiological increase in mitochondrial Ca^{2+} ions could positively regulate mitochondrial metabolism through activation of TCA cycle enzymes, boosting the biosynthesis of reduced respiratory substrates, and stimulation of adenine nucleotide transporter (ANT) and Complex V to promote the production of ATP (Das & Harris, 1990; Mc Cormack & Denton, 1993). However, it has been proposed that the sustained uptake of mitochondrial Ca^{2+} results in the inhibition of Complex I and Complex III activities, which consequently increase the ROS production (Batandier et al., 2004; Jekabsone et al., 2003). When Ca^{2+} ions are overloaded to mitochondria, it temporarily provokes a pathological signal leading to the opening of the permeability transition pore (PTP) to block the intracellular Ca^{2+} homeostasis by Ca^{2+} release, and the subsequent induction of apoptosis through cytochrome *c* release (Crompton, 1999). Therefore, the great amplitude of Ca^{2+} transient in cells harboring a pathogenic mutation of mtDNA may increase the risk of inducing cell death processes. Aforementioned investigations have provided compelling evidence to support the notion that disturbed Ca^{2+} homeostasis elicited by mitochondrial dysfunction in the affected tissues, especially in the neurons of the patients, plays an important role in the epileptogenesis and disease progression of encephalomyopathies.

6. Sirtuin-mediated cellular adaptation in epileptogenesis

There are increasing evidence to reveal that sirtuins play a critical role in regulation of metabolism and the aging process through several pathways (Bordone & Guarente, 2005). Sirt1 is the most extensively studied sirtuin that mediates NAD^+-dependent deacetylation of target proteins and thereby regulates many cellular functions. Overexpression or increase of the activity of Sirt1 has been reported to be neuroprotective in several neurodegenerative diseases. The most important mechanism contributory to Sirt1-induced protective effect is related to the regulation of cell survival (de Oliveira et al., 2010). In addition to alleviating the cell death and inducing the repair system, Sirt1 can modulate cellular response to oxidative stress and promote mitochondrial function (Gerhart-Hines et al., 2007). In human cells with mitochondrial dysfunction, increase of oxidative stress and damage may trigger apoptosis, which is closely related to seizure-induced cell loss. To cope with oxidative stress, the antioxidant defense system has evolved to dispose of excess intracellular ROS. Indeed, an imbalanced expression of antioxidant enzymes has been reported in different brain regions of animals in several studies of experimental status epilepticus. Induction of Mn-SOD and catalase expression was observed in picrotoxin-induced seizures. The catalase

levels have been also reported to increase following electrically induced seizures (de Freitas, 2009). Contrary to Mn-SOD and catalase, the GPx showed a tendency to decrease in the animals with status epileptic seizures (Shin et al., 2008). Interestingly, the abnormal expression of antioxidant enzymes was commonly found in the affected tissues of patients with mitochondrial encephalomyopathies caused by pathogenic mtDNA mutations. In previous studies, we observed increased levels of intracellular ROS and imbalanced expression of antioxidant enzymes in skin fibroblasts established from patients with the MERRF syndrome (Wu et al., 2010). Increase in the expression and activity of Mn-SOD rather than other antioxidant enzymes was observed in skin fibroblasts from MERRF and CPEO patients, respectively, which suggests that the expression of antioxidant enzymes was altered and failed to cope with the increase of oxidative stress in tissue cells with mitochondrial defects. Recent studies showed that Sirt1 plays a critical role in the detoxification of ROS since it can deacetylate and activate some of the Foxo family proteins, which in turn increase the transcription of Mn-SOD and catalase genes expressions(Brunet et al., 2004). Several studies have suggested that Sirt1 is a stress responsive gene. In one of our previous studies, we showed that oxidative stress could increase Sirt1 protein expression in human skin fibroblasts upon treatment with 150-300 μM H_2O_2 (Wu et al., 2010). Increased Sirt1 protein expression was also observed in skin fibroblasts from patients with some of the mitochondrial diseases as compared to normal subjects. Therefore, it is possible that increased expression of Sirt1 in affected tissue cells of patients with mitochondrial encephalomyopathies could lead to abnormal expression of antioxidant enzymes in response to mitochondrial dysfunction, which might contribute to epileptic conditions.

On the other hand, Sirt1 may exert the calorie restriction-induced anti-aging effect by modulation of the mitochondrial function. It can promote mitochondrial respiration through deacetylation and activation of the transcription activity of PGC-1α, a master regulator of mitochondrial biogenesis (Nemoto et al., 2005). It is well known that mitochondrial biogenesis is induced in the affected tissue cells of patients with mitochondrial diseases as a compensatory adaptation to compromised bioenergetic function due to defects in OXPHOS, despite the fact that increase in the number of mitochondria might have little contribution to the bioenergetic outcome. In one of our previous studies, we demonstrated that most of the patients with mitochondrial diseases frequently display abnormal mitochondrial proliferation along with an increase in the mitochondrial mass and gene expression of mtTFA (Wu et al., 2010). In addition, we also showed that increased oxidative stress is involved in the aberrant mitochondrial proliferation. Similarly, a change in the number of mitochondria has been reported in some of the patients with seizures or epilepsy. These findings led us to conjecture that compensatory induction of Sirt1 elicited by oxidative stress may be responsible for the unusual cellular status and neurotoxicity in epileptics. This also suggests that Sirt1 may be involved in the signaling pathway of the cross-talk between defective mitochondria and the nucleus to regulate cellular adaptation to mtDNA mutation-elicited oxidative stress.

7. Therapeutic approaches to target mitochondrial bioenergetics and oxidative stress in epilepsy

Therapies for epileptic seizures have largely focused on reducing neuronal excitability and hence alleviating the frequency of occurrence of seizures and epilepsy. Recent therapeutic

approaches tend to seek for antiepileptogenic drugs that may inhibit the targets involved in the pathogenesis of epileptogenesis. Mitochondrial dysfunction triggering neuron cell death has been considered as a major contribution to the onset of seizures and is related to the resistance to epileptic therapy. Thus, therapies targeting mitochondrial bioenergetics and oxidative stress pathways could have neuroprotective effect and would be able to improve the seizure activity and attenuate the severity of epilepsy. Administration of creatine is frequently used and has been shown to protect brain injury in animal models of ALS, Huntington's disease and MPTP-induced Parkinsonism (Ferrante et al., 2000; Matthews et al., 1999). Creatine can move through blood to brain and increase the pool of phosphocreatine/creatine by mitochondrial creatine kinase to boost the neuronal energy level. Supplementation of creatine was observed to attenuate hypoxia-induced seizures in both rats and rabbits. Creatine was also found to be neuroprotective in epilepsy induced by pilocarpine (Holtzman et al., 1998). These observations suggest that creatine treatment has the potential neuroprotective effect for patients with epilepsy, although it remains to be proven by clinical trials. Additionally, diet modification by caloric restriction or ketogenic diet has been used to inhibit seizure susceptibility in epileptic EL mice through a reduction of glucose metabolism (Todorova et al., 2000). Accumulating evidence support that chronic use of ketogenic diet can alter mitochondrial function, which includes promotion of mitochondrial biogenesis, decrease of ROS production and induction of GSH biosynthesis that ultimately lead to cellular adaption and restoration of mitochondrial redox state (Jrrett et al., 2008).

On the other hand, to interfere with increased ROS during the onset of epilepsy appears to be another possible strategy for therapy. Natural antioxidant compounds such as vitamin C and E, melatonin and catalase have been shown to decrease oxidative stress and alleviate the seizure-induced brain injury (MacGrego et al., 1996; Tan et al., 1998). It has been reported that clinical trial of vitamin E as a therapy for epilepsy is controversial because it failed to improve seizure activity in pediatric patients. Similarly, although the Mn-SOD knockout mice was shown to exhibit age-dependent spontaneous and handling-induced seizures (Liang & Patel, 2004), and even more susceptible to kainate-induced seizures and neuron cell death, the SOD mimetics only reduced oxidative stress and oxidative damage but not the behavioral seizures (Rong et al., 1999). Hence, the therapeutic effect of antioxidants on epileptogenesis remains to be further investigated.

8. Conclusion

Mitochondrial dysfunction has been identified as a potential cause of epileptic seizures. Specific mtDNA mutations leading to the impairment of mitochondrial respiration and OXPHOS might be associated with epileptic phenotype. Because mitochondria supply the majority of ATP in neurons by OXPHOS and maintain the cellular Ca^{2+} homeostasis, their dysfunction can influence neuronal excitability and synaptic transmission, which may be responsible for epileptogenesis. Mitochondria play critical roles in energy metabolism, apoptosis and Ca^{2+} homeostasis, and respond to intrinsic and external stimuli through a variety of retrograde signaling pathways. Thus, mitochondrial dysfunction may trigger events involved in the cascades of the communication between mitochondria and the nucleus to mediate physiological adaptation of human cells through genetic or metabolic regulation. This may subsequently lead to alterations of the antioxidant defense system, activation of Ca^{2+} signaling, modulation of mitochondrial biogenesis and OXPHOS function.

The energy deficiency and ROS overproduction are the major stressors in human cells harboring disease-associated mtDNA mutations, which may play an important role in the induction of the retrograde signaling cascades sent from dysfunctional mitochondria to the nucleus. These events could interfere with Ca^{2+} homeostasis through decrease of the mitochondrial Ca^{2+} buffering capacity and affecting the Ca^{2+} influx and pump, which lead to the abnormal change of the cytosolic Ca^{2+} concentration and perturbation of Ca^{2+}-related signaling pathways that ultimately trigger the neuronal cell death. Therefore, it is reasonable to consider mitochondria as promising targets of neuroprotective treatment of the patients with epilepsy. In conclusion, a better understanding of the mechanisms underlying epileptics elicited by mitochondrial dysfunction will provide novel information for the design of therapeutic approaches to treat patients with epilepsies or seizures caused by or associated with mitochondrial encephalomyopathies.

9. Acknowledgment

We would like to thank the Nation Science Council of Taiwan for long-term support of the studies on mitochondrial dysfunction and mtDNA mutation in the pathophysiology of mitochondrial diseases. We also would like to express our appreciation to the technical support at National Yang-Ming University in conducting molecular and cellular biology experiments on cultured cells established from patients with various mitochondrial diseases.

10. References

Alhatou, M. I., Sladky, J. T., Bagasra, O. & Glass, J. D. (2004). Mitochondrial abnormalities in dermatomyositis: characteristic pattern of neuropathology, *Journal of Molecular Histology* 35(6): 615-619.

Anderson, S. E., Liu, H., Ho, H. S., Lewis, E. J. & Cala, P. M. (2003). Age-related differences in Na^{+}-dependent Ca^{2+} accumulation in rabbit hearts exposed to hypoxia and acidification, *American Journal of Physiology- Cell Physiology* 284: C1123-1132.

Aure, K., Fayet, G., Leroy, J. P., Lacene, E., Romero, N. B., & Lombes, A. (2006). Apoptosis in mitochondrial myopathies is linked to mitochondrial proliferation, *Brain* 129(Pt 5): 1249-1259.

Batandier, C., Leverve, X. & Fontaine, E. (2004). Opening of the mitochondrial permeability transition pore induces reactive oxygen species production at the level of the respiratory chain complex I, *The Journal of Biological Chemistry* 279(17): 17197-17204.

Bertini, E. & D'Amico, A. (2009). Mitochondrial encephalomyopathies and related syndromes: brief review, *Endocrine Development* 14: 38-52.

Blander, G. & Guarente, L. (2004). The Sir2 family of protein deacetylases, *Annual Review of Biochemistry* 73: 417-435.

Bordone, L. & Guarente, L. (2005). Calorie restriction, SIRT1 and metabolism: understanding longevity, *Nature Reviews Molecular Cell Biology* 6: 298-305.

Brini, M., Pinton, P., King, M. P., Davidson, M., Schon, E. A. & Rizzuto, R. (1999). A calcium signaling defect in the pathogenesis of a mitochondrial DNA inherited oxidative phosphorylation deficiency, *Nature Medicine* 5(8): 951-954.

Brunet, A., Sweeney, L. B., Sturgill, J. F., Chua, K. F., Greer, P. L., Lin, Y., Tran, H., Ross, S. E., Mostoslavsky, R., Cohen, H. Y., Hu, L. S., Cheng, H. L., Jedrychowski, M. P., Gygi, S. P., Sinclair, D. A., Alt, F. W. & Greenberg, M. E. (2004). Stress-dependent

regulation of FOXO transcription factors by the SIRT1 deacetylase, *Science* 303: 2011-2015.

Buttgereit, F. & Brand, M. D. (1995). A hierarchy of ATP-consuming processes in mammalian cells, *Biochemical Journal* 312: 163-167.

Canafoglia, L., Franceschetti, S., Antozzi, C., Carrara, F., Farina, L., Granata, T., Lamantea, E., Savoiardo, M., Uziel, G., Villani, F., Zeviani, M. & Avanzini, G. (2001). Epileptic phenotypes associated with mitochondrial disorders, *Neurology* 56(10): 1340-1346.

Carrier, H., Flocard, F., Tagliati, V., Arrigo, A. P. & Godinot, C. (2000). Immunolabelling of mitochondrial superoxide dismutase and of Hsp60 in muscles harbouring a respiratory chain deficiency, *Neuromuscular Disorders* 10(2): 144-149.

Chuang, Y. C., Chen, S. D., Liou, C. W., Lin, T. K., Chang, W. N., Chan, S. H. & Chang, A. Y. (2009a). Contribution of nitric oxide, superoxide anion, and peroxynitrite to activation of mitochondrial apoptotic signaling in hippocampal CA3 subfield following experimental temporal lobe status epilepticus, *Epilepsia* 50(4): 731-746.

Chuang, Y. C., Lin, J. W., Chen, S. D., Lin, T. K., Liou, C. W., Lu, C. H. & Chang, W. N. (2009b). Preservation of mitochondrial integrity and energy metabolism during experimental status epilepticus leads to neuronal apoptotic cell death in the hippocampus of the rat, *Seizure* 18(6): 420-428.

Chuang, Y. C. (2010). Mitochondrial dysfunction and oxidative stress in seizure-induced neuronal cell death, *Acta Neurologica Taiwanica* 19(1): 3-15.

Collins, T. J., Berridge, M. J., Lipp, P. & Bootman, M. D. (2002). Mitochondria are morphologically and functionally heterogeneous within the cells, *The EMBO Journal* 21: 1616-1627.

Cornord, E. M., Shamsa, K., Zeitzer, J. M., Enriquez, C. M. Wilson, C. L., Behnke, E. J., Fried, I. & Engel, J. (2002). Regional analyses of CNS microdialysate glucose and lactate in seizure patients, *Epilepsy* 43: 1360-1371.

Crompton, M. (1999). The mitochondrial permeability transition pore and its role in cell death, *Biochemical Journal* 341(2): 233-239.

Das, A. M. & Harris, D. A. (1990). Control of mitochondrial ATP synthase in heart cells: inactive to active transitions caused by beating or positive inotropic agents, *Cardiovascular Research* 24(5): 411-417.

de Freitas, R. M. (2009). The evaluation of effects of lipoic acid on the lipid peroxidation, nitrite formation and antioxidant enzymes in the hippocampus of rats after pilocarpine induced seizures, *Neuroscience Letters* 455(2): 140-144.

de Freitas, R. M. (2010). Lipoic acid alters delta-aminolevulinic dehydratase, glutathione peroxidase and Na^+,K^+-ATPase activities and glutathione-reduced levels in rat hippocampus after pilocarpine-induced seizures, *Cellular and Molecular Neurobiology* 30(3): 381-387.

de Oliveira, R. M., Pais, T. F. & Outeiro, T. F. (2010). Sirtuin: Common targets in aging and in neurodegeneration, *Current Drug Targets* 11: 1270-1280.

DiMauro, S., Hirano, M., Kaufmann, P., Tanji, K., Sano, M., Shungu, D. C., Bonilla, E. & DeVivo, D. C. (2002). Clinical features and genetics of myoclonic epilepsy with ragged red fibers, *Advanced Neurology* 89: 217-229.

Engel, T., Hatazaki, S., Tanaka, K., Prehn, J. H. & Henshall, D. C. (2010). Deletion of Puma protects hippocampal neurons in a model of severe status epilepticus, *Neuroscience* 168(2): 443-450.

Esposito, L. A., Kokoszka, J. E., Waymire, K. G., Cottrell, B., MacGregor, G. R. & Wallace, D. C. (2000). Mitochondrial oxidative stress in mice lacking the glutathione peroxidase-1 gene, *Free Radical Biology & Medicine* 28(5): 754-766.

Fernández-Checa, J. C., Fernández, A., Morales, A., Marí, M., García-Ruiz, C. & Colell, A. (2010). Oxidative stress and altered mitochondrial function in neurodegenerative diseases: lessons from mouse models, *CNS Neurol Disord Drug Targets* 9(4): 439-454.

Ferrante, R. J., Andreassen, O. A., Jenkins, B.G., Dedeoglu, A., Kuemmerle, S., Kubilus, J. K., Kaddurah-Daouk, R., Hersch, S. M. & Beal, M. F. (2000). Neuroprotective effects of creatine in a transgenic mouse model of Huntington's disease, *The Journal of Neuroscience* 20(12): 4389-4397.

Folbergrová, J., Jesina, P., Haugvicová, R., Lisý, V. & Houstek, J. (2010). Sustained deficiency of mitochondrial complex I activity during long periods of survival after seizures induced in immature rats by homocysteic acid, *Neurochemistry International* 56(3): 394-403.

Fukui, H. & Moraes, C. T. (2008). The mitochondrial impairment, oxidative stress and neurodegeneration connection: reality or just an attractive hypothesis? *Trends in Neurosciences* 31: 251-256.

Gerhart-Hines, Z., Rodgers, J. T., Bare, O., Lerin, C., Kim, S. H., Mostoslavsky, R., Alt, F. W., Wu, Z. & Puigserver, P. (2007). Metabolic control of muscle mitochondrial function and fatty acid oxidation through SIRT1/PGC-1alpha, *The EMBO Journal* 26: 1913-1923.

Guo, X., Popadin, K. Y., Markuzon, N., Orlov, Y. L., Kraytsberg, Y., Krishnan, K. J., Zsurka, G., Turnbull, D. M., Kunz, W. S. & Khrapko K. (2010). Repeats, longevity and the sources of mtDNA deletions: evidence from 'deletional spectra', *Trends in Genetics* 26(8): 340-343.

Henshall, D. C., Clark, R. S., Adelson, P. D., Chen, M., Watkins, S. C. & Simon, R. P. (2000). Alterations in bcl-2 and caspase gene family protein expression in human temporal lobe epilepsy, Neurology 55(2)*:* 250-257.

Hetts, S. W. (1998). To die or not to die: an overview of apoptosis and its role in disease, *the Journal of the American Medical Association* 279(4): 300-307.

Holtzman, D., Togliatti, A., Khait, L. & Jensen, F. (1998). Creatine increases survival and suppresses seizures in the hypoxic immature rat, *Pediatric Research* 44: 410-414.

Hool, L. C. & Corry, B. (2007). Redox control of calcium channels: from mechanisms to therapeutic opportunities, *Antioxidants & Redox Signaling* 9(4):409-435.

Jarrett, S. G., Liang, L. P., Hellier, J. L., Staley, K. J. & Patel, M. (2008). Mitochondrial DNA damage and impaired base excision repair during epileptogenesis, *Neurobiology of Disease* 30(1): 130-138.

Jekabsone, A., Ivanoviene, L., Brown, G. C. & Borutaite, V. (2003). Nitric oxide and calcium together inactivate mitochondrial complex I and induce cytochrome c release, *Journal of Molecular and Cellular Cardiology* 35(7): 803-809.

Jrrett, O., Milder, J. B., Liang, L. P. & Patel, M. (2008). The ketogenic diet increases mitochondrial glutathione, *Journal of Neurochemistry* 106: 1044-1051.

Kann, O. & Kovacs, R. (2007). Mitochondria and neuronal activity, *American Journal of Physiology - Cell Physiology* 292(2): C641-657.

Kaplan, P., Babusikova, E., Lehotsky, J. & Dobrota D. (2003). Free radical-induced protein modification and inhibition of Ca^{2+}-ATPase of cardiac sarcoplasmic reticulum, *Molecular and Cellular Biochemistry* 248(1-2): 41-47.

Katayama, Y., Maeda, K., Iizuka, T., Hayashi, M., Hashizume, Y., Sanada, M., Kawai, H. & Kashiwagi, A. (2009) Accumulation of oxidative stress around the stroke-like lesions of MELAS patients, *Mitochondrion* 9(5): 306-313.

Kourie, J. I. (1998). Interaction of reactive oxygen species with ion transport mechanisms, *American Journal of Physiology* 275(1): C1-24.

Kunz, W. S., Goussakov, I. V., Beck, H. & Elger, C. E. (1999). Altered mitochondrial oxidative phosphorylation in hippocampal slices of kainate-treated rats, *Brain Research* 826(2): 236-242.

Leo, S., Bianchi, K., Brini, M. & Rizzuto, R. (2005). Mitochondrial calcium signaling in cell death, *The FEBS Journal* 272: 4013-4022.

Leonard, J. V. & Schapira, A. H. (2000a). Mitochondrial respiratory chain disorders I: mitochondrial DNA defects, *Lancet* 355(9200): 299-304.

Li, Y., Huang, T. T., Carlson, E. J., Melov, S., Ursell, P. C., Olson, J. L., Noble, L. J., Yoshimura, M. P., Berger, C., Chan, P. H., Wallace, D. C. & Epstein, C. J. (1995). Dilated cardiomyopathy and neonatal lethality in mutant mice lacking manganese superoxide dismutase, *Nature Genetics* 11(4): 376-381.

Liang, L. P. & Patel, M. (2004). Mitochondrial oxidative stress and increased seizure susceptibility in $Sod2^{(-/+)}$ mice, *Free Radical Biology & Medicine* 36(5): 542-554.

Lin, Y., Xu, J., Cao, L., Han, Y., Gao, J., Xie, N., Zhao, X., Jiang, H. & Chi, Z. (2010). Mitochondrial base excision repair pathway failed to respond to status epilepticus induced by pilocarpine, *Neuroscience Letters* 474(1): 22-25.

Liou, A. K., Clark, R. S., Henshall, D. C., Yin, X. M. & Chen, J. (2003). To die or not to die for neurons in ischemia, traumatic brain injury and epilepsy: a review on the stress-activated signaling pathways and apoptotic pathways, *Progress in Neurobiology* 69(2): 103-142.

Liu, C. S., Cheng, W. L., Lee, C. F., Ma, Y. S., Lin, C. Y., Huang, C. C. & Wei, Y. H. (2006). Alteration in the copy number of mitochondrial DNA in leukocytes of patients with mitochondrial encephalomyopathies, *Acta Neurological Scandinavica* 113(5): 334-341.

Liu, R. S., Lemieux, L., Bell, G. S., Hammers, A., Sisodiya, S. M., Bartlett, P. A., Shorvon, S. D., Sander, J. W. & Duncan, J. S. (2003). Progressive neocortical damage in epilepsy, *Annals Neurology* 53(3): 312-324.

Luce, K., Weil, A. C. & Osiewacz, H. D. (2010). Mitochondrial protein quality control systems in aging and disease, *Advances in Experimental Medicine and Biology* 694: 108-125.

Ma, Y. S., Chen, Y. C., Lu, C. Y., Liu, C. Y. & Wei, Y. H. (2005). Upregulation of matrix metalloproteinase 1 and disruption of mitochondrial network in skin fibroblasts of patients with MERRF syndrome, *Annals of the New York Academy of Sciences* 1042: 55-63.

MacGregor, D. G., Higgins, M. J., Jones, P. A., Maxwell, W. L., Watson, M. W., Graham, D. I. & Stone, T. W. (1996). Ascorbate attenuates the systemic kainite-induced neurotoxicity in the rat hippocampus, *Brain Research* 727: 133-144.

Matthews, R. T., Ferrante, R. J., Klivenyi, P., Yang, L., Klein, A. M., Mueller, G., Kaddurah-Daouk, R. & Beal, M. F. (1999). Creatine and cyclocreatine attenuate MPTP neurotoxicity, *Experimental Neurology* 57(1): 142-149.

Mattson, M. P. (2007). Calcium and neurodegeneration, *Aging Cell* 6(3): 337-350.

Mc Cormack, J. G. & Denton, R. M. (1993). Mitochondrial Ca^{2+} transport and the role of intramitochondrial Ca^{2+} in the regulation of energy metabolism, *Developmental Neuroscience* 15(3-5): 165-173.

Moudy, A. M., Handran, S.D., Godberg, M. P., Ruffin, N., Kranz-Eble, P., Darryl, C. DeVivo. & Steven, M. Rothman. (1995). Abnormal calcium homeostasis and mitochondrial polarization in a human encephalomyopathy, *Proceedings of the National Academy of Sciences of the United States of America* 92: 729-733.

Mueller, S. G., Trabesinger, A. H., Boesiger, P. & Wieser, H. G. (2001). Brain glutathione levels in patients with epilepsy measured by in vivo H-MRS, *Neurology* 57:1422-1427.

Murphy, B., Dunleavy, M., Shinoda, S., Schindler, C., Meller, R., Bellver-Estelles, C., Hatazaki, S., Dicker, P., Yamamoto, A., Koegel, I. Chu, X., Wang, W., Xiong, Z., Prehn, J., Simon, R. & Henshall, D. (2007). Bcl-w protects hippocampus during experimental status epilepticus, *American Journal of Pathology* 171(4): 1258-1268.

Murphy, B. M., Engel, T., Paucard, A., Hatazaki, S., Mouri, G., Tanaka, K., Tuffy, L. P., Jimenez-Mateos, E. M., Woods, I., Dunleavy, M. Bonner, H. P., Meller, R., Simon, R. P., Strasser, A., Prehn, J. H. & Henshall D. C. (2010). Contrasting patterns of Bim induction and neuroprotection in Bim-deficient mice between hippocampus and neocortex after status epilepticus, *Cell Death and Differentiation* 17(3): 459-468.

Narkilahti, S., Nissinen, J. & Pitkanen, A. (2003). Administration of caspase 3 inhibitor during and after status epilepticus in rat: effect on neuronal damage and epileptogenesis, *Neuropharmacology* 44(8): 1068-1088.

Nemoto, S., Fergusson, M. M. & Finkel, T. (2005). SIRT1 functionally interacts with the metabolic regulator and transcriptional coactivator PGC-1alpha, *The Journal Biological Chemistry* 280: 16456-16460.

Qian, W. & van Houten, B. (2010). Alterations in bioenergetics due to changes in mitochondrial DNA copy number, *Methods* 51(4): 452-457.

Okumura, A., Kdikoro, H., Itomi, K., Maruyama, K., Kubota, T. & Kondo, Y. Itomi, S., Uemura, N., Natsume, J., Watanabe, K. & Morishima, T. (2008). Subacute encephalopathy: clinical features, laboratory data, neuroimaging, and outcomes, *Pediatric Neurology* 38: 111-117.

Pallotti, F., Baracca, A., Hernandez-Rosa, E., Walker, W. F., Solaini, G., Lenaz, G., Melzi D'Eril, G. V., Dimauro, S., Schon, E. A. & Davidson, M. M. (2004). Biochemical analysis of respiratory function in cybrid cell lines harbouring mitochondrial DNA mutations, *The Biochemical Journal* 384(2): 287-293.

Rong, Y., Doctrow, S. R., Tocco, G. & Baudry, M. (1999). EUK-134, a synthetic superoxide dismutase and catalase mimetic, prevents oxidative stress and attenuates kainate-induced neuropathology, *Proceedings of the National Academy of Sciences of the United States of America* 96(17): 9897-9902.

Sayre, L. M., Perry, G. & Smith, M. A. (2008). Oxidative stress and neurotoxicity, *Chemical Research in Toxicology* 21(1): 172-188.

Shapira, Y., Harel, S. & Russell, A. (1977). Mitochondrial encephalomyopathies: a group of neuromuscular disorders with defects in oxidative metabolism, *Israel Journal of Medical Sciences* 13(2): 161-164.

Shin, E. J., Ko, K. H., Kim, W. K., Chae, J. S., Yen, T. P., Kim, H. J., Wie, M. B. & Kim, H. C. (2008). Role of glutathione peroxidase in the ontogeny of hippocampal oxidative stress and kainate seizure sensitivity in the genetically epilepsy-prone rats, *Neurochemistry International* 52(6): 1134-1147.

Siegwart, R. (2001). Indirect Manipulation of a Sphere on a Flat Disk Using Force Information, *International Journal of Advanced Robotic Systems* 6(4): 12-16.

Stollberger, C. & Finsterer, J. (2006). Autonomic dysfunction in left ventricular hypertrabeculation/noncompaction, *International Journal of Cardiology* 109(2): 286-287.

Suzuki, Y. J. & Ford, G. D. (1992). Superoxide stimulates IP3-induced Ca^{2+} release from vascular smooth muscle sarcoplasmic reticulum, *American Journal of Physiology* 262(1): H114-116.

Tan, D., Manchester, L. P., Reiter, R. J., Qi, W., Kim, S. J. & El-Sokkary, G. H. (1998). Melatonin protects hippocampal neurons in vivo against kainic acid-induced damage in mice, *Journal of Neuroscience Research* 54: 382-389.

Tang, Y. G. & Zucker, R. S. (1997). Mitochondrial involvement in post-tetanic potentiation of synaptic transmission, *Neuron* 18(3): 483-491.

Taylor, R. W., Schaefer, A. M., Barron, M. J., McFarland, R. & Turnbull, D. M. (2004). The diagnosis of mitochondrial muscle disease, *Neuromuscular Disorders* 14: 237-245.

Todorova, M. T., Tandon, P., Madore, R. A., Stafstrom, C. E. & Seyfried, T. N. (2000). The ketogenic diet inhibits epileptogenesis in EL mice: a genetic model for idiopathic epilepsy, *Epilepsia* 41: 933-940.

Umaki, Y., Mitsui, T., Endo, I., Akaike, M. & Matsumoto, T. (2002). Apoptosis-related changes in skeletal muscles of patients with mitochondrial diseases, *Acta Neuropathologica* 103(2): 163-170.

Waldbaum, S. & Patel, M. (2010a). Mitochondria, oxidative stress, and temporal lobe epilepsy, *Epilepsy Research* 88(1): 23-45.

Waldbaum, S., Liang, L. P. & Patel, M. (2010b). Persistent impairment of mitochondrial and tissue redox status during lithium-pilocarpine-induced epileptogenesis, *Journal of Neurochemistry* 115(5):1172-1182.

Wei, Y. H. & Lee, H. C. (2003). Mitochondrial DNA mutations and oxidative stress in mitochondrial diseases, *Advances in Clinical Chemistry* 37: 83-128.

Weise, J., Engelhorn, T., Dorfler, A., Aker, S., Bahr, M. & Hufnagel, A. (2005). Expression time course and spatial distribution of activated caspase-3 after experimental status epilepticus: contribution of delayed neuronal cell death to seizure-induced neuronal injury, *Neurobiology of Disease* 18(3): 582-590.

Werth, J. L. & Thayer, S. A. (1994). Mitochondria buffer physiological calcium loads in cultured rat dorsal root ganglion neurons, *The Journal of Neuroscience* 14(1): 348-356.

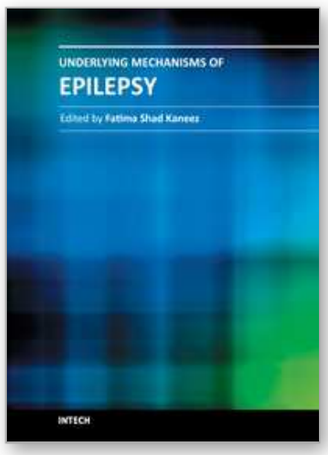
Willems, P. H., Valsecchi, F., Distelmaier, F., Verkaart, S., Visch, H. J. & Smeitink, J. A. & Koopman, W. J. (2008). Mitochondrial Ca^{2+} homeostasis in human NADH:ubiqinone oxidoreductase deficiency, *Cell Calcium* 44: 123-133.

Wu, S. B., Ma, Y. S., Wu, Y. T., Chen, Y. C. & Wei, Y. H. (2010). Mitochondrial DNA mutation-elicited oxidative stress, oxidative damage, and altered gene expression in cultured cells of patients with MERRF syndrome, *Molecular Neurobiology* 41(2-3): 256-266.

Wu, Y. T., Wu, S. B., Lee, W. Y. & Wei, Y. H. (2010). Mitochondrial respiratory dysfunction-elicited oxidative stress and posttranslational protein modification in mitochondrial diseases, *Annals of the New York Academy of Sciences* 1201: 147-156.

Yamamoto, H. & Tang, H. W. (1996). Preventive effect of melatonin against cyanide-induced seizures and lipid peroxidation in mice, *Neuroscience Letters* 207: 89-92.

Zima, A. V., Copello, J. A. & Blatter, L. A. (2004). Effects of cytosolic NADH/NAD^+ levels on sarcoplasmic reticulum Ca^{2+} release in permeabilized rat ventricular myocytes, *The Journal of Physiology* 555(3): 727-741.



Underlying Mechanisms of Epilepsy

Edited by Prof. Fatima Shad Kaneez

ISBN 978-953-307-765-9

Hard cover, 354 pages

Publisher InTech

Published online 26, September, 2011

Published in print edition September, 2011

This book is a very provocative and interesting addition to the literature on Epilepsy. It offers a lot of appealing and stimulating work to offer food of thought to the readers from different disciplines. Around 5% of the total world population have seizures but only 0.9% is diagnosed with epilepsy, so it is very important to understand the differences between seizures and epilepsy, and also to identify the factors responsible for its etiology so as to have more effective therapeutic regime. In this book we have twenty chapters ranging from causes and underlying mechanisms to the treatment and side effects of epilepsy. This book contains a variety of chapters which will stimulate the readers to think about the complex interplay of epigenetics and epilepsy.

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

IntechOpen