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Mitochondrial dysfunction and oxidative stress: a contributing link to acquired epilepsy?

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Abstract Mitochondrial dysfunction and oxidative stress contribute to several neurologic disorders and have recently been implicated in acquired epilepsies such as temporal lobe epilepsy (TLE). Acquired epilepsy is typically initiated by a brain injury followed by a "latent period" whereby molecular, biochemical and other cellular alterations occur in the brain leading to chronic epilepsy. Mitochondrial dysfunction and oxidative stress are emerging as factors that not only occur acutely as a result of precipitating injuries such as status epilepticus (SE), but may also contribute to epileptogenesis and chronic epilepsy. Mitochondria are the primary site of reactive oxygen species (ROS) making them uniquely vulnerable to oxidative damage that may affect neuronal excitability and seizure susceptibility. This mini-review provides an overview of evidence suggesting the role of mitochondrial dysfunction and oxidative stress as acute consequences of injuries that are known to incite chronic epilepsy and their involvement in the chronic stages of acquired epilepsy.

Keywords Epilepsy · Mitochondria · Oxidative stress

Introduction

Mitochondrial dysfunction and oxidative stress are recognized as playing a contributing role in several neurological disorders, and most recently have been implicated in acquired epilepsies. Mitochondrial dysfunction has been directly associated with a small percentage of inherited epilepsies such as myoclonic epilepsy with ragged red fibers (MERRF) and mitochondrial encephalopathies but its role in acquired epilepsies, which accounts for approximately 60% of all epilepsy cases, remains to be fully explored. Temporal lobe epilepsy (TLE) is the most prominent example of acquired epilepsy which is commonly preceded by an initial brain injury such as an episode of prolonged seizures or status epilepticus (SE), childhood febrile seizures, hypoxia or trauma. These preceding events induce a series of complex molecular, biochemical, physiological, and structural changes in the brain that contribute to the subsequent onset of spontaneous seizures, or "epileptogenesis." Compelling evidence for mitochondrial dysfunction in acquired epilepsy comes from the observation that metabolic and bioenergetic changes occur following acute seizures and during different phases of chronic epilepsy. For example, acutely following seizures associated with SE a significant increase in cellular glucose uptake and metabolism occurs. Cerebral blood flow is increased to match this hypermetabolism and there is an increased lactate build up due to the increased rate of glycolysis exceeding pyruvate utilization. While hypermetabolism occurs in the human epileptic foci during seizure events, hypometabolism is prominent between seizure episodes. Mitochondria are suggested to be involved in altered neurotransmitter metabolism based on the loss of mitochondrial N-acetyl aspartate in human epileptic tissue (Savic et al. 2000; Vielhaber et al. 2008). Additionally, severe metabolic dysfunction characterized by biphasic abnormal NAD(P)H fluorescence transients and changes in mitochondrial membrane potential (dsm) have been observed in ex vivo preparations from both chronically epileptic rats and human subjects (Kann et al. 2005).

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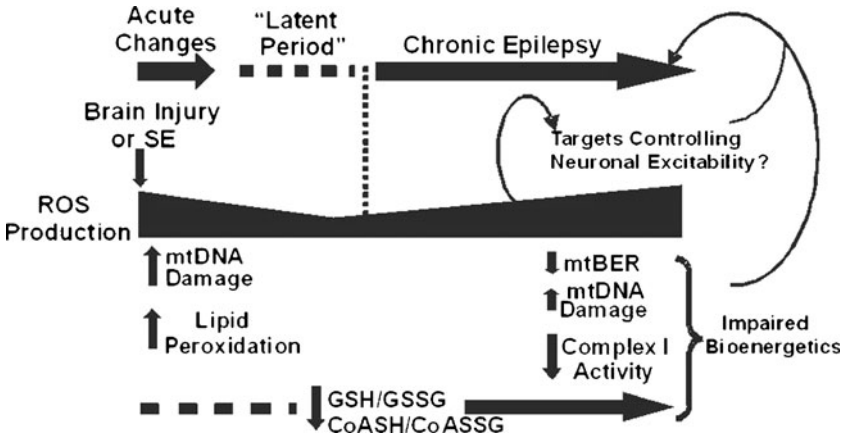

Fig. 1 Time-course of mitochondrial oxidative stress and subsequent damage during epileptogenesis. Note the initial and persistent decrease in mitochondrial and tissue redox status (CoASH/CoASSG, GSH/GSSG) throughout epileptogenesis which may serve an ongoing link to chronic epilepsy

Mitochondria subserve important functions such as the generation of ATP, metabolite/neurotransmitter biosynthesis, calcium homeostasis, control of cell death and are the primary site of reactive oxygen species (ROS) production. The latter renders mitochondria particularly vulnerable to oxidative damage that may play a critical role in controlling neuronal excitability and subsequent seizure susceptibility associated with acquired epilepsy. ROS function as second messengers in signal transduction but are also mediators of oxidative damage and inflammation. The detailed mechanisms by which mitochondria control acute seizure-induced neuronal injury and/or chronic seizure activity associated with acquired epilepsies such as TLE have not been fully elucidated. Seizure-induced overproduction of mitochondrial superoxide radicals ($O_2^{\cdot-}$) (Liang et al. 2000) can, through the Fenton reaction, produce more highly reactive species such as hydroxyl radical ($OH^{\cdot-}$) in the presence of Cu^{2+} and Fe^{2+} which readily oxidize proteins, lipids, and DNA potentially altering neuronal excitability and thereby decreasing seizure threshold during epileptogenesis. The brain is uniquely vulnerable to oxidative stress-induced damage due to a large quantity of mitochondria, a high degree of oxidizable lipids and metals, high oxygen consumption, and less antioxidant capacity than other tissues making oxidative stress a likely contributor to neurological disorders such as the epilepsies. In this mini-review we provide a brief overview of the evidence suggesting the role of oxidative stress and mitochondrial dysfunction as acute consequences of injuries that are known to incite chronic epilepsy and their involvement in the chronic stages of acquired epilepsy.

Mitochondrial dysfunction and oxidative stress: acute consequences of injuries inciting acquired epilepsies

Acute increases in mitochondrial oxidative stress and subsequent damage to cellular macromolecules have been demonstrated following repeated seizures i.e. SE (Bruce and Baudry 1995; Gluck et al. 2000; Liang et al. 2000; Patel et al. 2001; Tejada et al. 2007; Jarrett et al. 2008a; Waldbaum et al. 2010). In addition to SE, other injuries that are capable of leading to chronic acquired epilepsies such as hypoxic-ischemic insults, traumatic brain injury, viral infection and hyperthermia can individually produce mitochondrial dysfunction and oxidative stress (Ozawa et al. 2002; Gil et al. 2003; Xu et al. 2004; Chang et al. 2007; Bhargava et al. 2010; Mustafa et al. 2010; Schwarzbold et al. 2010). This suggests that mitochondrial dysfunction may be at least one final common factor that contributes to epileptogenesis. One important and immediate consequence of injury-induced oxidative stress may be neuronal death. Seizure-induced neuronal death in vulnerable brain regions is model-specific and dependent on the developmental age (Rakhade and Jensen 2009) and genetic background of animals (Schauwecker and Steward 1997; Mohajeri et al. 2004). Several key studies suggest a mechanistic role for mitochondrial dysfunction and ROS in SE-induced neuronal death. First, SE results in increased oxidation of cellular macromolecules prior to the death of vulnerable neurons and certain compounds that possess antioxidant properties (superoxide dismutase (SOD) mimetics, vitamin C, spin traps and melatonin) prevent seizure-induced neuronal death (Tan et al. 1998; Tang et al. 1998; Liang et al. 2000; Mohanan and Yamamoto 2002; Yamamoto and Mohanan 2003; Barros et al. 2007; Xavier et al. 2007). Secondly, oxidative stress has been suggested to be a significant consequence of excitotoxicity, which plays a critical role in epileptic brain damage. Thirdly, seizure-induced neuronal death involves calcium overload (Ding et al. 2007; Weiergraber et al. 2007; Deshpande et al. 2008) as well as both necrosis and apoptosis, which are all partly controlled by mitochondrial function and oxidative stress. Finally, the occurrence of seizure-induced oxidative stress is dependent on the developmental age of animals much like seizure-induced neuronal death (Patel and Li 2003).

Numerous studies demonstrate acute increases in subcellular ROS production and oxidative damage following SE. Increased ROS production has been demonstrated from

isolated mitochondria or with the use of surrogate markers for protein and DNA oxidation (Bruce and Baudry 1995; Gluck et al. 2000; Liang et al. 2000; Patel et al. 2001; Tejada et al. 2007; Jarrett et al. 2008a; Waldbaum et al. 2010). The latter include protein, lipids, and DNA that are modified by ROS and are stable enough to be analyzed by reliable quantitative methods assessed following chemoconvulsant-induced SE. Notably, maximal inactivation of mitochondrial aconitase has been demonstrated 16 h post-SE in the kainate model (KA) and at times preceding the death of susceptible hippocampal neurons (Liang et al. 2000). Recent work from our laboratory has demonstrated an acute increase in mitochondrial hydrogen peroxide (H_2O_2) production, an index of mitochondrial oxidative stress, and oxidative damage to mitochondrial DNA (mtDNA) up to 96 h following KA- and lithium-pilocarpine (Li-Pilo)-induced epileptogenesis (Jarrett et al. 2008a; Waldbaum et al. 2010). Lipid peroxidation, the unspecific oxidation of polyunsaturated fatty acids, is a pathway mediated by free radicals that can be used as an index of irreversible neuronal damage of cell membrane phospholipids suggested as a mechanism of epileptic activity (Dal-Pizzol et al. 2000). Malondialdehyde (MDA) has been used to identify oxidative damage to lipids acutely following seizure events (Dexter et al. 1989; Cini and Moretti 1995) and their levels have been reported to be increased up to 16 h following KA treatment in the hippocampus (Bruce and Baudry 1995), up to 24 h in an amygdala kindling model of epilepsy (Frantseva et al. 2000), and 2 h post-pilocarpine-induced SE in the cortex (Tejada et al. 2007). The thiobarbituric acid reactive substances (TBARS) assay revealed increased lipid oxidation following KA-induced seizures as early as 4 h in the cortex, hippocampus, basal ganglia, and cerebellum, which remained elevated at 24 h in the hippocampus and cerebellum (Gluck et al. 2000). In the Li-Pilo model, increased whole brain free fatty acids (FFA), a marker of membrane phospholipid metabolism, have been reported 1 and 2.5 h post-treatment (Erakovic et al. 2000) and hydroperoxide has been reported to be increased at 1 h post-pilocarpine treatment (Bellissimo et al. 2001). A large increase in stable arachidonic acid derived prostaglandin products of lipid oxidation, including F2-isoprostanes (F_2-IsoP) and isofurans (IsoFs) has been shown early after SE in hippocampal subregions (Patel et al. 2001). Cellular dysfunction resulting from lipid peroxidation may lead to a compromise in a cells capability to maintain energy levels, energy failure, and the triggering of events leading to neuronal injury and death. Interestingly, the highest levels of SE-induced formation of F2-IsoPs and IsoFs occur in the dentate gyrus in which injury-resistant granule neurons reside (Patel et al. 2001; Patel et al. 2008) which suggests alternate roles besides neuronal death of these lipid peroxidation end products.

In studies where KA was administered directly into the CA3 hippocampal subregion producing seizures, depressed activity of nicotinamide adenine dinucleotide cytochrome c reductase (NCCR), a marker for electron transport chain (ETC) complex I and III, was observed at 180 min post-injection in all hippocampal subfields (Chuang et al. 2004). These changes were accompanied by swelling of mitochondrial spaces and membrane disruption, suggesting that complex I enzyme dysfunction and mitochondrial ultrastructural damage in the hippocampus were associated with prolonged seizures. An acute increase in mitochondrial but not nuclear 8-OHdG/2dG, an oxidatively modified guanine adduct, has been demonstrated 16–48 h following KA-induced SE which coincided with increased mtDNA lesion frequency, mitochondrial H_2O_2 production and decreased aconitase activity and a transient decrease in mtDNA repair (Jarrett et al. 2008a). A decrease in the intracellular antioxidant, glutathione (GSH), and increased H_2O_2 production and mtDNA damage was observed 24–96 h in the hippocampus after Li-Pilo treatment (Waldbaum et al. 2010). In the kindling model, a persistent decrease in GSH was observed as early as 4 h post stimulation in the hippocampus which preceded a transient decrease in mitochondrial ETC complex I activity and aconitase levels, suggesting GSH as an early and critical determinant of later neuronal death and dysfunction (Sleven et al. 2006). Following KA-induced SE, our laboratory has shown an acute decrease in mitochondrial GSH/GSSG and tissue CoASH/CoASSG as early as 8 h and up to 7 d from the hippocampus (Liang and Patel 2006). Finally, pilocarpine-induced SE has been reported to decrease GSH in the hippocampus 24 h post-treatment (Freitas et al. 2005).

In summary, SE and other epileptogenic injuries result in increased ROS formation and oxidative damage to proteins, lipids and DNA. Furthermore, although plasma membrane/extracellular sources contribute to SE-induced ROS formation (Patel et al. 2005), the predominant source is the mitochondrial compartment. Thus, current studies have established mitochondrial dysfunction and oxidative stress as an acute consequence of seizure activity but the question remains whether these alterations can further contribute to chronic epilepsy.

Mitochondrial dysfunction and oxidative stress in chronic acquired epilepsy

Evidence of mitochondrial dysfunction and oxidative stress during chronic epilepsy has recently emerged from animal studies (Kudin et al. 2002; Chuang et al. 2004; Gao et al. 2007; Jarrett et al. 2008a; Waldbaum et al. 2010) and human TLE specimens (Kunz et al. 2000; Mueller et al. 2001; Sudha et al. 2001; Vielhaber et al. 2008). Work from our laboratory has demonstrated a time-dependent increase

in mitochondrial H_2O_2 production, oxidative damage to mtDNA, and decreased mtDNA repair capacity prior to and during recurrent epilepsy following KA-induced epileptogenesis (Jarrett et al. 2008a). An increase in mitochondrial oxidative stress and mtDNA damage prior to and during recurrent epilepsy has also been shown in the Li-Pilo model of SE (Waldbaum et al. 2010). A key finding of the Jarrett et al. (2008a) study was that failure of adaptive responses to ongoing oxidative stress in the brain during epileptogenesis, such as mtDNA repair, could lead to an increase in seizure susceptibility. The mitochondrial base excision repair pathway (mtBER) involves a highly coordinated process catalyzed by the sequential actions of the DNA repair enzymes 8-oxoguanine glycosylase (Ogg1) and DNA polymerase gamma (Pol γ). Ogg1 and Pol γ mRNA and protein levels have been shown to be elevated following KA-induced SE but decreased during chronic epilepsy (Jarrett et al. 2008a). Spontaneous seizures coincided with accumulation of mtDNA damage, increased mitochondrial H_2O_2, decreased Ogg1 and Pol γ, and impaired mtDNA repair in this study, suggesting a role for the contribution of mitochondrial injury to epileptogenesis.

Mitochondrial dysfunction during chronic epilepsy is evident by decreased ETC complex I and IV activity, increased complex II activity, and lowered mitochondrial membrane potential measured by rhodamine 123 fluorescence in the hippocampal CA1 and CA3 regions 1 month following pilocarpine-induced SE (Kudin et al. 2002). These alterations may be attributed to chronic oxidative stress decreasing mtDNA copy number resulting in down regulation of ETC enzymes that they encode. The accumulation over time of oxidative mtDNA lesions and resultant somatic mtDNA mutations resulting from seizure activity could render the brain more susceptible to subsequent epileptic seizures. Further, ultrastructural damage to mitochondria has been observed in the hippocampus of chemoconvulsant-treated epileptic rats (Chuang et al. 2004). Forty five days post-pilocarpine-induced SE, mitochondrial encoded complex IV subunit III decreased while nuclear encoded subunit IV remained unchanged along with nuclear encoded complex II in the hippocampus (Gao et al. 2007). The link between mitochondrial dysfunction and epilepsy is further supported by the finding that certain patients with TLE show mitochondrial complex I deficiency in the seizure foci (Kunz et al. 2000) and aconitase activity is decreased in the CA3 hippocampal subregion of human cases of TLE (Vielhaber et al. 2008). Mice that are partially deficient in MnSOD (SOD2) ($Sod2^{-/+}$) show evidence of exacerbated KA-induced mitochondrial aconitase inactivation and hippocampal neuronal loss (Liang and Patel 2004), while over expressing SOD2 mice showing both are attenuated (Liang et al. 2000). Additionally, the expression of the glutamate transporters, GLT-1, GLAST, and EAAC-1 were reported to decrease in epileptic $Sod2^{-/+}$ mice at increasing ages (Liang and Patel 2004). The decrease in hippocampal GLT-1 and GLAST in $Sod2^{-/+}$ mice coincided with decreased aconitase activity as well as increased mitochondrial oxidative stress and seizure susceptibility which may explain the age-related vulnerability of a subset of these mice to epileptic seizures. Additionally, the levels of GLAST protein was reportedly lower in samples from epileptic patients than controls (Tessler et al. 1999) and a decrease in GLT-1 expression was reported in the hippocampus of sclerotic tissue obtained from resected TLE patients (Mathern et al. 1999). Decreased levels of glutamine synthetase (GS), the enzyme responsible for converting glutamate to glutamine, have been reported following hippocampal sclerosis (Petroff et al. 2002; Eid et al. 2004; van der Hel et al. 2005) and an increase in glutamine and glutamate in the thalamus in epileptic patients has been reported (Helms et al. 2006). In the KA model, a transient increase in GS expression was reported during the "latent period" which was reduced during the transition to the chronic phase of epilepsy suggesting a decreased capacity for glutamate metabolism as spontaneous and recurrent seizures became evident (Hammer et al. 2008). Thus, recent evidence supports the role of mitochondrial oxidative stress not merely as a consequence of seizures, but an active contributor to seizures and epileptogenesis.

Can redox alterations during the "latent period" provide a link between acute and chronic oxidative events?

An important question that emerges from these studies is, does acute injury-induced ROS formation contribute mechanistically to chronic epilepsy? Furthermore, which mitochondrial and cellular alterations may be occurring during the "latent period" between initial brain injury and the onset of spontaneous and recurrent seizures so as to facilitate the progression of chronic epilepsy? Could a widespread cellular and sub-cellular oxidized environment be present that has the potential to induce structural damage to mitochondrial membranes, changes in mitochondrial enzyme activities and membrane potential, and subsequent mitochondrial dysfunction potentially affecting neuronal excitability? As noted above, increased mitochondrial H_2O_2 production during epileptogenesis occurs in a bi-phasic manner. Early SE-induced ROS is accompanied by adaptive mtDNA repair and chronic ROS production is accompanied by a failure of mtDNA repair induction (Jarrett et al. 2008a). Although the production of mitochondrial H_2O_2 returns to control levels during the "latent period", measurement of more sensitive indices of oxidative stress e.g. mitochondrial and tissue redox status suggest the occurrence of ongoing oxidative stress particularly in the

mitochondrial compartment during the "latent period" (Waldbaum et al. 2010) (Fig. 1). Redox couples such as GSH and its disulfide (GSSG) serve as biomarkers of oxidative stress (Reed and Savage 1995; Liang and Patel 2006) and coenzyme A (CoASH) and its disulfide with GSH (CoASSG), which are primarily compartmentalized within mitochondria, can be measured as a marker of mitochondrial specific redox status (Liang and Patel 2006). Hippocampal GSH/GSSG and CoASH/CoASSG following Li-Pilo-induced SE have been recently demonstrated to decrease by 24 h and remain permanently impaired throughout epileptogenesis and chronic epilepsy even when measurements of H_2O_2 production and mtDNA damage returned to control levels (Waldbaum et al. 2010). These changes in redox state during epileptogenesis began prior to the reported occurrence of neuronal death in the hippocampus (Liang et al. 2000) and may contribute to it as well as causing significant mitochondrial dysfunction (Jain et al. 1991; Werner and Cohen 1993) potentially affecting neuronal excitability through ETC dysfunction and decreased ATP production (Fig. 1). A decrease in both GSH levels and glutathione reductase (GR) activity has been reported in brain regions and plasma of epileptic patients (Mueller et al. 2001; Sudha et al. 2001). A profound and persistent oxidation of GSH to GSSG and depletion of total GSH during epileptogenesis, including the "latent period," would favor post-translational modifications such as S-glutathionylation and/or S-nitrosylation of sensitive targets e.g. ion channels and energy-dependent transporters that could ultimately alter neuronal excitability. Therefore, altered cellular and mitochondrial redox status may play an important mechanistic link between acute and chronic stages of epilepsy.

Therapies targeting mitochondrial bioenergetics

Novel therapies targeting mitochondrial bioenergetics and oxidative stress that are neuroprotective and ameliorate consequences of SE may be useful in the management of epilepsy and attenuation of its development. An increasing number of SOD mimetics have been developed to overcome the inherent limitations of natural antioxidant compounds such as catalase and vitamins C and E. MnTBAP and the salen EUK compounds have been shown to attenuate oxidative stress and neuronal damage induced by SE or a deficiency in SOD2 (Liang et al. 2000; Melov et al. 2001; Hinerfeld et al. 2004). The metalloporphyrin catalytic antioxidants contain a manganese center that are capable of detoxifying a wide range of ROS (Patel and Day 1999) and several water-soluble compounds have been shown to be effective in animal models of epilepsy (Liang et al. 2000). *N,N′*-bis (2-hydroxybenzyl) ethylenediamine-*N,N′*-diacetic acid (HBED), a synthetic iron chelator, administered systemically ameliorated SE-induced alterations, mtDNA damage, GSH depletion, and hippocampal cell loss, suggesting subcellular iron chelation as a novel therapeutic approach for seizure management (Liang et al. 2008). The ketogenic diet (KD), based on the intake of high-fat/low-carbohydrate/low-protein leading to a switch from glucose metabolism to the generation and metabolism of ketones, has been administered as a means of attenuating seizures. Recent evidence suggests that chronic consumption of a KD may alter mitochondrial function by chronically decreasing production of ROS, increasing the expression of uncoupling proteins, promoting mitochondrial biogenesis, stimulating GSH biosynthesis, and activating the NF E2-related factor 2 (Nrf2) pathway via redox signaling leading to cellular adaptation, induction of protective proteins, and improvement of mitochondrial redox state (Sullivan et al. 2004; Bough et al. 2006; Jarrett et al. 2008b; Milder et al. 2010). These findings raise the possibility that targeting mitochondrial dysfunction may in the future provide therapeutic avenues for the successful treatment of epilepsies.

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