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Mitochondrial Oxidative Stress in Temporal Lobe Epilepsy

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Abstract

Mitochondrial oxidative stress and dysfunction are contributing factors to various neurological disorders. Recently, there has been increasing evidence supporting the association between mitochondrial oxidative stress and epilepsy. Although certain inherited epilepsies are associated with mitochondrial dysfunction, little is known about its role in acquired epilepsies such as temporal lobe epilepsy. Mitochondrial oxidative stress and dysfunction are emerging as key factors that not only result from seizures, but may also contribute to epileptogenesis. The occurrence of epilepsy increases with age, and mitochondrial oxidative stress is a leading mechanism of aging and age-related degenerative disease, suggesting a further involvement of mitochondrial dysfunction in seizure generation. Mitochondria have critical cellular functions that effect neuronal excitability including production of adenosine triphosphate (ATP), fatty acid oxidation, control of apoptosis and necrosis, regulation of amino acid cycling, neurotransmitter biosynthesis, and regulation of cytosolic Ca^{2+} homeostasis. Mitochondria are the primary site of reactive oxygen species (ROS) production making them uniquely vulnerable to oxidative stress and damage which can further affect cellular macromolecule function, the ability of the electron transport chain to produce ATP, antioxidant defenses, mitochondrial DNA stability, and synaptic glutamate homeostasis. Oxidative damage to one or more of these cellular targets may affect neuronal excitability and increase seizure susceptibility.

The specific targeting of mitochondrial oxidative stress, dysfunction, and bioenergetics with pharmacological and non-pharmacological treatments may be a novel avenue for attenuating epileptogenesis and seizure initiation.

Keywords

oxidative damage; seizure; epileptogenesis; hyperexcitability; temporal lobe epilepsy

1.1 Introduction

Epilepsy is a recent addition to the neurological disorders in which mitochondrial oxidative stress and dysfunction **have** been suggested to be contributing **factors**. While a small percentage of inherited epilepsies are associated with mitochondrial dysfunction, less is known about its role in acquired epilepsies such as temporal lobe epilepsy (TLE). TLE's are a group of neurological disorders in which humans and animals experience recurrent

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epileptic seizures arising from one or both temporal lobes of the brain. Two main types of TLE are generally recognized, mesial temporal lobe epilepsy which arises in the hippocampus, parahippocampal gyrus and amygdala, and lateral temporal lobe epilepsy which arises in the neocortex. Initial trauma associated with TLE induces complex molecular, biochemical, physiological, and structural changes in the brain that contribute to epileptogenesis and the subsequent onset of spontaneous and recurrent seizures. Mitochondrial oxidative stress and dysfunction are emerging as key factors that not only result from seizures, but may also contribute to epileptogenesis. Precedence for the role of mitochondrial dysfunction in epilepsy comes from the knowledge that epilepsy frequently occurs with inherited mitochondrial disorders such as myoclonic epilepsy with ragged red fibers (MERRF) and those associated with childhood encephalopathies. A role of mitochondrial oxidative stress in lowering seizure threshold comes from studies in mice partially deficient in a critical mitochondrial antioxidant (Sod2^{-/+}) that have age-dependent spontaneous seizures. The occurrence of epilepsy in humans also increases with age, and mitochondrial oxidative stress is a leading mechanism of aging and age-related degenerative disease, suggesting a further involvement of mitochondrial dysfunction in seizure generation. Mitochondria have critical cellular functions that effect neuronal excitability including production of adenosine triphosphate (ATP), fatty acid oxidation, control of apoptosis and necrosis, regulation of amino acid cycling, neurotransmitter biosynthesis, and regulation of cytosolic Ca²⁺ homeostasis. Mitochondria are the primary site of reactive oxygen species (ROS) production and are uniquely vulnerable to oxidative damage that may play a critical role in controlling neuronal excitability. Further, mitochondria are critically involved in excitotoxicity and programmed cell death which independently contribute to seizure-induced hippocampal cell loss. As such, the targeting of mitochondrial oxidative stress and dysfunction may be a novel avenue for the development of new drugs that **are neuroprotective**, able to preserve neuronal viability and function, antiepileptic, able to attenuate seizure occurrence in epileptic patients, and antiepileptogenic, able to attenuate the development of the epileptic phenotype following an insult.

This review outlines studies supporting the emerging role of mitochondrial oxidative stress and dysfunction in epilepsy with emphasis on TLE. Evidence from a variety of animal models of TLE is discussed including the use of the chemoconvulsants kainic acid (KA), a glutamatergic agonist, and pilocarpine, a muscarinic acetylcholine agonist. Other animal models discussed include the use of pentylenetetrazole (PTZ) and electrical kindling. Evidence for the production and consequences of acute and chronic mitochondrial oxidative stress and dysfunction in various animal models of TLE **are** discussed with damage to proteins, lipids, mitochondrial DNA (mtDNA), and antioxidant defenses being considered. Mitochondrial oxidative stress and dysfunction as **causes and/or consequences** of epileptic seizures **are** given attention. Transgenic mice models of mitochondrial oxidative stress **are** discussed in relation to seizure production. The role of synaptic glutamate homeostasis in relation to glutamine synthetase and glial glutamate transporters are considered due to their known sensitivity to oxidative damage and contribution in controlling neuronal excitability. Lastly, the targeting of mitochondrial bioenergetics with pharmacological and non-pharmacological treatments as a means of attenuating epileptogenesis and seizure initiation is discussed.

2.1 Mitochondrial structure and functions

2.1.1 Mitochondrial structure

Mitochondria **are** double-membrane bound intracellular **organelles** containing their own unique genome responsible for critical cellular functions in nearly all eukaryotic cells. The outer and inner mitochondrial membranes separate the matrix and intermembrane space (Koehler, 2004). The porin containing outer membrane is permeable to molecules < 5-6 kDa

(Benz, 1994), and larger proteins must have a specific signaling sequence to be transported across the membrane. The inner membrane is highly impermeable to ions and solutes, contains specific ion channels and transport systems, and is compartmentalized into numerous cristae which expand its surface area. The inner membrane has a high protein to phospholipid ratio and contains the enzymes involved in the electron transport chain (ETC) and ATP synthesis which create the mitochondrial membrane potential. mtDNA is a unique and independent functional genome inherited maternally (Leonard and Schapira, 2000) and is made up of a 16.5 kB circular, double-stranded DNA whose 37 genes encode 13 polypeptides of the ETC, 22 tRNAs, and 2 rRNAs. However, most mitochondrial gene products are encoded by nuclear DNA (nDNA) and imported (DiMauro and Schon, 2003). Due to their high degree of mobility along cytoskeletal transport mechanisms, neuronal mitochondria can be positioned based on specific metabolic demands (Hollenbeck and Saxton, 2005) which increase during seizure activity.

2.1.2 Mitochondrial functions

The primary function of mitochondria is the production of ATP to be used as cellular energy via the metabolic processes of the tricarboxylic acid cycle (TCA) and the ETC. The mitochondria are responsible for the majority of the cells ATP supply via oxidative phosphorylation located on its inner membrane. The majority of ATP produced by the mitochondria is utilized to maintain the Na^+/K^+ ATPase which in turn maintains neuronal membrane potential and excitability. The TCA cycle's primary role is the production of the coenzymes NADH and FADH which carry electrons to the ETC. Although the ETC efficiently shuttles electrons to O_2 to phosphorylate ADP in the production of ATP, some electrons can "leak" out and react with molecular oxygen generating superoxide radical ($\text{O}_2^{\cdot-}$), particularly at complex I and III (St-Pierre et al., 2002; Muller et al., 2004) (Fig 1). Also, on the outer mitochondrial membrane the action of monoamine oxidases are associated with a two electron reduction of O_2 to hydrogen peroxide (H_2O_2) (Hauptmann et al., 1996). The steady state concentration of $\text{O}_2^{\cdot-}$ in the mitochondrial matrix, based on the rate of $\text{O}_2^{\cdot-}$ production by the ETC and concentration of the mitochondrial antioxidant manganese superoxide dismutase (MnSOD), is estimated to be $\sim 10^{-10}$ M (Tyler, 1975; Fridovich, 1978; Imlay and Fridovich, 1991; Gardner and Fridovich, 1992; Fridovich, 1995). As such, mitochondria are the major source of intracellular ROS with estimates ranging from 0.1- 4% of oxygen consumption going to $\text{O}_2^{\cdot-}$ generation in the mitochondria (Boveris, 1984).

In addition to ATP and ROS production, mitochondria play a critical role in other cellular processes illustrated in Figure 1. Mitochondria sequester free intracellular Ca^{2+} through several transport systems and are important to Ca^{2+} homeostasis (Nicholls, 1985; Duchen, 2000). Ca^{2+} can play a regulatory role by influencing mitochondrial processes such as the consumption of H_2O_2 and enzyme activity i.e. pyruvate dehydrogenase and metabolic rate. Alternatively, the mitochondrial permeability transition pore (MPT) can be stimulated to open by excessive concentrations of Ca^{2+} , and can also extrude Ca^{2+} (Zoratti and Szabo, 1995). Mitochondria play an important role in the mediation of cell death via pro-apoptotic factors (Schapira, 2002) which utilize the transition pore (Mancini et al., 1998; Susin et al., 1999). Other vital mitochondrial functions include synthesis of lipids, metabolites and amino acids including neurotransmitters, fatty acid oxidation, and control of necrotic cell death. Each of these vital inter-related mitochondrial functions is crucial for normal brain function, and a defect in one or more of these may be a likely contributor to neuronal excitability and epileptogenesis.

3.1 Mitochondrial oxidative stress and epileptic seizures

3.1.1 Mitochondrial oxidative stress

Oxidative stress results from an imbalance in oxidant and antioxidant homeostasis in favor of the production of ROS. A free radical is defined as an atom or group of atoms possessing one or more unpaired electron in their orbital, allowing them a strong propensity to react with other molecules giving or taking an electron to complete their orbital (Castagne et al., 1999; Halliwell and Gutteridge, 2007). ROS production is a normal part of aerobic respiration, and continuously occurs as electrons escape complex I and III of the mitochondrial ETC (St-Pierre et al., 2002; Muller et al., 2004). The production of $O_2^{\cdot-}$ and H_2O_2 by the ETC in close proximity to Cu^{2+} and Fe^{2+} in mitochondrial membranes can lead to the generation of the highly reactive hydroxyl radical ($OH^{\cdot-}$) through **the Fenton reaction** which readily oxidizes proteins, lipids, and DNA (Fig. 1). ROS are transient, unstable, and largely localized to cellular compartments, making their direct measurement difficult. As a result, the role of free radicals in pathologic conditions has been inferred from the measurement of indirect markers of oxidative stress such as lipid and protein oxidation and the activities of free radical scavenging enzymes (Bruce and Baudry, 1995; Patel, 2004). The brain is particularly vulnerable to oxidative stress-induced damage due to a large quantity of mitochondria, a high degree of oxidizable lipids and metals, a high oxygen consumption, and less antioxidant capacity than other tissues making oxidative stress a likely contributor to neurological disorders such as the epilepsies.

3.1.2 Mitochondrial oxidative stress: cause or consequence of epileptic seizures

There is mounting evidence for oxidative stress as an important contributing factor to seizure associated neuronal damage and death. ROS are integral to processes such as excitotoxicity and apoptosis that contribute to seizure-induced brain damage. A contributing role for ROS in seizure-induced neuronal death is supported in part by the observation that prolonged seizures result in increased oxidation of cellular macromolecules (Bruce and Baudry, 1995), while various compounds with antioxidant properties prevent excitotoxicity in vitro (Monyer et al., 1990; Lafon-Cazal et al., 1993; Puttfarcken et al., 1993; Patel, 1996) and in vivo (Schulz et al., 1995; MacGregor et al., 1996). Experimental seizures have been shown to result in impaired mitochondrial Ca^{2+} sequestering, excessive ROS production, and increased nitric oxide (NO) and peroxynitrite ($ONOO^-$) generation after prolonged seizures at timepoints preceding neuronal death in susceptible brain regions (Griffiths et al., 1984; Cheng and Sun, 1994; Bruce and Baudry, 1995; Kunz et al., 1999; Liang et al., 2000; Frantseva et al., 2000a; Milatovic et al., 2002). However, a variety of animal model studies provide evidence for a lack of oxidative damage to cellular macromolecules following seizures. For example, an initial increase in ETC complex activity and subunit expression has been demonstrated in the KA (Milatovic et al., 2001) and kindling models (Sleven et al., 2006a), and no alterations to ETC complexes or mtDNA have been reported at chronic timepoints following pilocarpine-induced SE (Nasseh et al., 2006). It should be noted that although it is often difficult to separate the effects of chemoconvulsant agents used in animal models of status epilepticus (SE) from the seizure events themselves. For example, intracortical application of iron has been used as a model of post-traumatic epilepsy (Kucukkaya et al., 1998), but also stimulates free radicals such as $OH^{\cdot-}$ (Gutteridge, 1992). Following **3-mercaptopropionic** acid-induced seizures in rats, lipid peroxidation has been shown to increase in as little as 3-6 min post-onset in susceptible brain regions. In the PTZ model, free radical production has been reported immediately following seizures (Rauca et al., 1999). (See Devi et al. (2008) for a list of the modulation to oxidant/antioxidant balance in rodents following experimental seizures (Devi et al., 2008)). Nonetheless, evidence from various animal models suggests that free radical production increases after brief and prolonged seizure episodes.

While many studies have investigated acute consequences of SE on cellular constituents, less is known about the role of oxidative stress and mitochondrial dysfunction in chronic epilepsy. Determining the role of mitochondrial dysfunction in chronic epilepsy is complicated by the difficulty in distinguishing mitochondrial oxidative stress as a cause or consequence of seizures. Nonetheless, several key studies support the idea that mitochondrial oxidative stress and dysfunction can cause epileptic seizures. For example, seizure activity can be induced by paradigms which can increase the mitochondrial free radical load, such as increased oxygen levels (Freeman et al., 1982; Yusa et al., 1987; Jenkinson, 1989; Komadina et al., 1991; Elayan et al., 2000) age-related neuronal disorders such as stroke (Velioglu et al., 2001), and brief periods of neonatal hypoxia-reoxygenation (Jensen et al., 1991; Jensen et al., 1992). Additionally, synaptic N-methyl-D-aspartate (NMDA) receptor activation resulting in increased mitochondrial $O_2^{\cdot-}$ production is a necessary component of seizures (Dugan et al., 1995; Li et al., 2001). One month following pilocarpine-induced SE, mitochondrial dysfunction 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 (Kudin et al., 2002). These abnormalities were attributed by the authors to chronic oxidative stress that decreased mtDNA copy number resulting in down regulation of ETC enzymes that they encoded. The acute increase in mitochondrial oxidative stress following SE may over time result in oxidative damage to mtDNA, as suggested by increased levels of the oxidized guanine adduct, **8-hydroxy-2-deoxyguanosine (8-OHdG)**, and decreased expression of mitochondrially encoded proteins required for proper ETC function. Seizure-induced accumulation of oxidative mtDNA lesions and resultant somatic mtDNA mutations could, over time, 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). 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). 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.

4.1 Seizure-induced oxidative damage to cellular macromolecules: relationship with neuronal excitability

Recent evidence has suggested that oxidative stress affecting a number of metabolic processes may contribute to neuronal excitability, and potentially be an active mechanism contributing to epilepsy. Mechanisms that may be active during the “latent period” as chronic epilepsy develops include a reduction in mitochondrial redox status leading to irreversible oxidation, mtDNA damage, the failure of mitochondrial repair, and decreased oxidative phosphorylation and ATP production by mitochondria. While decreased ATP production and in turn ATP-dependent Na^+/K^+ ATPase is sufficient to increase neuronal excitability (Jamme et al., 1995; Figuera et al., 2006), decreased expression and/or function of astrocytic glutamate transporters and glutamate synthetase due to oxidative stress **and redox modulation of ion channels** may be additional mechanisms of increased neuronal excitability.

4.1.1 Oxidative damage to proteins

Proteins exposed to ROS exhibit altered primary, secondary, and tertiary structures, undergo spontaneous fragmentation and manifest increased proteolytic susceptibility. The amino acid side chains of proteins are particularly susceptible to oxidation, such as irreversible damage to the ring cleavage in histidine or tryptophan, the reversible oxidation of thiol groups, and methionine oxidized to the sulfoxide and then further to the sulfone which is associated with

loss of function. Although disulfide bonds are a reversible process, these changes may significantly alter proper function changed by thiol/disulfide status. Oxidative damage to proteins can be estimated based on carbonyl content and has been found to be high in specific brain regions and to be elevated during aging and neurodegenerative disorders (Forster et al., 1996; Floor and Wetzel, 1998). In the KA model of epilepsy, an early increase in carbonyl content in the piriform cortex and hippocampus at 8 hr post-treatment has been reported which returned to control levels by 48 h (Bruce and Baudry, 1995). This early increase in protein oxidation in adult animals suggests free radical involvement in the initial phases of KA-induced pathology and fits with the hypothesis that prolonged activation of glutamate receptors leads to an increase in ROS. Four hours post-KA treatment, protein carbonyl levels have been shown to be elevated in the hippocampus, cortex, basal ganglia, and cerebellum with levels persisting up to 24 h in the hippocampus and cerebellum (Gluck et al., 2000). Elevations of oxidative stress-induced damage to proteins lasting 24 h suggests ongoing KA oxidative damage or repair mechanisms for removal of oxidized proteins requiring more than 24 h to be activated. Variation in the localization of oxidative damage suggests the cortex may have different mechanisms than the cerebellum or hippocampus for free radical scavenging or increased repair.

Mitochondrial aconitase is a TCA cycle enzyme that contains a labile iron motif in its **iron-sulfur** (Fe-S) center that is susceptible to oxidative damage by $O_2^{\cdot-}$ and related species (Fig. 1). The measurement of endogenous aconitase activity can serve both as an index of steady state $O_2^{\cdot-}$ levels and evidence of oxidative damage to proteins (Gardner and Fridovich, 1992; Fridovich, 1997). Inactivation of aconitase normalized to fumarase or citrate synthetase has been used to determine oxidative damage to mitochondrial proteins in animal models of SE and human TLE. KA-induced seizures inactivate mitochondrial aconitase but not fumarase, with maximal inactivation occurring 16 hrs post-treatment, several hours after SE and preceding neuronal death of susceptible hippocampal neurons (Liang et al., 2000). Inactivation of mitochondrial aconitase at times following the onset of behavioral seizures suggests that mitochondrial $O_2^{\cdot-}$ production may occur as a consequence of prolonged seizure activity. 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 overexpressing SOD2 mice show both are attenuated. Manganese (III) tetrakis (4-benzoic acid) porphyrin (MnTBAP), a broad spectrum antioxidant, protects rats against seizure-induced mitochondrial aconitase inactivation and hippocampal damage without decreasing behavioral seizure intensity or frequency (Liang and Patel, 2004). Pilocarpine-induced SE also showed a decrease in aconitase and alpha ketoglutarate dehydrogenase 16-44 h post-SE, which returned to normal by 8 d in the hippocampus (Cock et al., 2002). Finally, aconitase activity is decreased in the CA3 region of human cases of TLE (Vielhaber et al., 2008). One consequence of oxidative inactivation of aconitase is the release of iron and generation of H_2O_2 which can form $OH^{\cdot-}$ and thereby result in further oxidative damage. As such, SE-induced changes in hippocampal mitochondrial iron coinciding with inactivation of mitochondrial aconitase have recently been demonstrated (Liang et al., 2008).

4.1.2 Oxidative damage to the mitochondrial electron transport chain

Seizure-induced ROS production could alter critical proteins involved in controlling neuronal excitability making them more susceptible to degradation by intracellular proteolytic systems and thereby increasing seizure susceptibility. The mitochondrial ETC is critical to phosphorylation processes, regulation of membrane permeability, neurotransmitter biosynthesis, exocytosis, and the primary source of cellular ATP involved in maintaining ion pumps such as the Na^+/K^+ ATPase which contribute to neuronal excitability. When ETC enzymes are not functioning properly, as may occur in TLE, the levels of mitochondrial

ROS increases culminating in oxidative damage (Bandy and Davison, 1990). It has been demonstrated that the mitochondrial ETC can be differentially inactivated by ROS whereby $\text{OH}^\cdot$ alone and in combination with O_2 rapidly inactivates complex I and II, O_2 alone inactivates complex I, and H_2O_2 partially inactivates complex I (Zhang et al., 1990). Complex IV was largely resistant to oxidative inactivation in these studies with the exception of partial inactivation by H_2O_2 . Complex I of the mitochondrial ETC is a major producer of $\text{O}_2^\cdot$, mitochondrial ROS, redox signaling (Cadenas and Davies, 2000; Taylor et al., 2003), and has been demonstrated to be more susceptible to oxidative stress and glutathionylation compared to other ETC complexes (Taylor et al., 2003). Additionally, it has been implicated in NO physiology, induction of MPT opening, and regulation of apoptosis (Moncada and Erusalimsky, 2002). Impaired mitochondrial ETC function as a result of ROS may lead to Ca^{2+} -dependent depolarization of the mitochondrial membrane potential resulting in incomplete oxygen consumption, reduced production of ATP, and overproduction of ROS (Cadenas and Davies, 2000; Nicholls and Ward, 2000; Heinemann et al., 2002; Patel, 2002). As inhibition of the ETC produces excess ROS, which are direct inhibitors of the ETC and TCA enzymes, a vicious cycle can result leading to oxidative cell damage (Cadenas and Davies, 2000; Patel, 2004).

Evidence in support of seizure-induced oxidative damage to mitochondrial ETC complexes has been somewhat contradictory. KA-induced seizures have been shown to initially increase complex IV activity, the terminal enzyme complex of the mitochondrial ETC, and complex IV subunit mRNA 1 h post-SE in the amygdala, hippocampus, and frontal cortex which decreased by 3 d in the amygdala and hippocampus (Milatovic et al., 2001). In studies where KA was administered directly into CA3 producing seizures and ictal electroencephalogram (EEG) activity, depressed activity of nicotinamide adenine dinucleotide cytochrome c reductase (NCCR), a marker for complex I and III, was observed at 180 min post-injection in all hippocampal subfields while succinate cytochrome c reductase, a marker for complex II and III, and complex IV remained unaltered (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. However, it should be noted that the excitotoxic effects of direct injection of KA are difficult to discern from the seizures themselves. Results from the pilocarpine model have demonstrated decreased activity of complex I and IV, increased flux control of complex I and decreased respiration rates in CA1 and CA3 30 d post-treatment, with no changes detected in the dentate gyrus or parahippocampal gyrus (Kudin et al., 2002). These results suggest that seizure activity per se downregulates expression of mitochondrial encoded enzymes of oxidative phosphorylation. 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). These results suggest that mitochondria are particularly susceptible to seizure-induced oxidative damage. Alternatively, no altered expression of complex I or complex IV activity has been reported 60 d post-pilocarpine treatment (Nasseh et al., 2006). These differences, however, may be due to the fact that the Kudin et al. (2002) study used hippocampal regions for their studies while the Nasseh et al. (2006) study used whole hippocampi. Evidence from the kindling model has shown a transient decrease in complex I activity at 16 h in CA3 and an increase in complex II and III activity, which may be an attempt to upregulate mitochondrial ETC activity and compensate for a deficiency in complex I (Sleven et al., 2006a). Another study reports increased activity of complex I and increased expression of complex IV subunits in epilepsy prone EL mice (Yamada and Nakano, 1999). Disruption in the ETC and/or one or more of its ATP-dependent processes, as reported by a number of studies, could have significant effects on neuronal excitability that may contribute to seizure activity.

4.1.3 Seizure-induced damage to glutamate transporters

Neuronal and glial transporters are responsible for preventing synaptic glutamate levels from achieving neurotoxic levels (Rothstein et al., 1994a; Rothstein et al., 1996) and have been implicated in hyperexcitability and neuronal death. Glial glutamate transporters, GLAST (EAAT-1) and GLT-1 (EAAT-2), and three neuronal glutamate transporters, EAAT-3, EAAT-4, and EAAT-5, are known to be located in the plasma membrane (Kanai and Hediger, 1992; Pines et al., 1992; Storck et al., 1992; Fairman et al., 1995; Arriza et al., 1997). Although both neurons and glia contain glutamate transporters, it is believed that the majority of glutamate uptake activity is mediated by glial transporters, and in particular GLT-1, whose expression is most abundant in the hippocampus and cerebral cortex (Danbolt et al., 1990; Haugeto et al., 1996; Danbolt, 2001). GLT-1 has been demonstrated to be regulated by extracellular changes in ATP through activation of the extracellular signal-regulated protein kinase (ERK) pathway in hippocampal slices (Frizzo et al., 2007). Glutamate transporters are known to be highly sensitive to oxidative damage resulting in reduced uptake function (Trotti et al., 1998). These alterations may contribute to an increase in neurotoxic extracellular glutamate levels and increased neuronal excitability producing significant pathological consequences.

Evidence from animal studies suggests that increasing the time neurotransmitter remains in the synaptic cleft, as in the case of altered glutamate transporters, affects postsynaptic ionotropic synaptic currents (Otis et al., 1996) and may affect hippocampal neurotransmission and promote seizures. The use of the glutamate transport inhibitor, threo- β -benzyloxyaspartate, prolongs epileptiform activity (Shimamoto et al., 1998) and causes alternating periods of bursting activity and hypoactivity in young rats (Milh et al., 2007). Genetically altered mice lacking GLT-1 develop spontaneous seizures (Tanaka et al., 1997) and GLAST knockout mice display increased susceptibility to seizures (Ueda et al., 2002). Levels of EAAC-1 expression have been reported to decrease following kindling (Ghijsen et al., 1999) but increase following KA-induced SE and kindling in other studies (Miller et al., 1997; Gorter et al., 2002). An increase in GLAST mRNA and GLT-1 expression has also been reported (Nonaka et al., 1998) along with a decrease in EAAT-3 mRNA (Akbar et al., 1998). Further, decreased expression of GLT-1 and GLAST has been observed in the cortex of rats with genetic absence epilepsy (Dutuit et al., 2002) and in the hippocampus of epileptic EL mice (Ingram et al., 2001). Additionally, the expression of GLT-1, GLAST, and EAAC-1, were reported to decrease in epileptic Sod2^{-/+} and 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. The latter observations suggest that mitochondrial oxidative stress and resultant dysfunction may be sufficient to increase seizure susceptibility via alterations to glial glutamate transporters.

Alterations in the glutamatergic system have been suggested to play a role in the development of epileptogenesis in humans. Hippocampal sclerosis has been correlated with reduced hippocampal volume, elevated extracellular glutamate levels (Ronne-Engstrom et al., 1992; During and Spencer, 1993; Cavus et al., 2005), and a down regulation of glutamate transporters has been implicated in impaired glutamate uptake capacity (Meldrum et al., 1999). 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). However, **immunocytochemical** studies in patients with and without hippocampal sclerosis found no significant differences or an increase in transporter expression (Proper et al., 2002; Bjornsen et al., 2007), but have suggested excessive glutamate release or modulation of transporter function as a potential contributing factor to seizure susceptibility.

Seizure associated neuronal loss may decrease glial glutamate transporters, and a decrease in glial glutamate transporter function may increase extracellular glutamate levels and lead to further neuronal loss. It should be noted, however, that some alterations in transporters such as splice variants (Hoogland et al., 2004) may not be distinguishable by antibodies used in immunoreactive studies.

4.1.4 Seizure-induced alterations of glutamine synthetase

Extracellular glutamate is normally taken up by astroglial glutamate transporters and rapidly converted to the non-excitotoxic amino acid glutamine by glutamine synthetase (GS) in a process requiring ATP and metal ions for catalysis (Eisenberg et al., 2000). Glutamine is subsequently transported back into neurons where it can be reconverted back to glutamate, a process known as the glutamate/glutamine cycle (Hertz, 1979). A decrease in the rate of this cycle has been reported in the hippocampus of TLE patients using in vivo MR spectroscopy (Petroff et al., 2002). Results of GS expression from surgically resected TLE patients have been contradictory. Decreased levels of GS 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). However, another study failed to demonstrate alterations in GS expression in the epileptic cortex (Steffens et al., 2005).

Studies from epileptic animals have been more consistent in their results regarding levels of GS. Decreased GS expression (Laming et al., 1989; Dutuit et al., 2000), induction of seizures by inhibiting GS activity (Folbergrova et al., 1969), seizure production in rats following systemic administration of the competitive antagonist methionine sulfoximine (Szegedy et al., 1978), and a reduction in brain GS activity after antiepileptic drug therapy (Fraser et al., 1999) have all been reported. 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). Also, an acute decrease in GS activity has been reported 24 h following intrahippocampal KA injections (Waniewski and McFarland, 1990) and a decrease in GS immunoreactivity up to 3 d following i.v. injection of KA followed by an increase in GS immunoreactivity between 5-68 days (Ong et al., 1996). Inhibition of GS by methionine sulfoximine in organotypical hippocampal cultures has been demonstrated to cause a depletion of glutamine and the accumulation of glutamate in astrocytes (Laake et al., 1995). In an animal model of hippocampal GS deficiency, the majority of rats demonstrate spontaneous and recurrent seizures and a subset exhibit neuropathological features similar to TLE patients suggesting that hippocampal GS deficiency causes recurrent seizures and restoring their levels may be a novel approach to treating epilepsy (Eid et al., 2008).

It is known that GS is oxidized under conditions of oxidative stress and that GS activity is particularly sensitive to reactive nitrogen and oxygen species (Oliver et al., 1990; Smith et al., 1991; Butterfield et al., 1997). For example, it has been demonstrated that nitration of GS causes a loss of its activity without affecting its antibody detectability (Gorg et al., 2005) and that high concentrations of nitric oxide synthase are present in the piriform and entorhinal cortex (Bidmon et al., 1997). NO reversibly inhibits GS activity suggesting that a covalent modification such as nitrosylation or nitration causes its inhibition (Kosenko et al., 2003). Nitric oxide synthase (NOS) inhibition results in an increase in GS activity in cultured astrocytes and in the rat brain (Minana et al., 1997; Kosenko et al., 2003; Rose and Felipo, 2005) and reportedly protected GS from NMDA-induced inactivation in brain slices (McBean et al., 1995). The generation of ONOO⁻ from the reaction of NO with O₂⁻ may further nitrate protein tyrosine residues (Beckman and Koppenol, 1996) and has been shown to inactivate mammalian GS in vitro (Gorg et al., 2007). In PTZ-induced seizures, tyrosine

nitration and partial inhibition of GS has been reported (Bidmon et al., 2008). Further, protein tyrosine nitration has been reported in seizures induced by hyperbaric oxygen treatment (Chavko et al., 2003). Excessive oxidative stress may irreversibly damage GS structure and predispose it to proteasome degradation (Gorg et al., 2007). It has recently been hypothesized that nitration of GS may induce a neuropathological cascade which contributes to the transformation of normal tissue to become epileptogenic (Bidmon et al., 2008).

4.1.5 Redox modulation of ion channels

Ion channels can be modulated by a wide variety of factors that can alter neuronal excitability. While protein phosphorylation has been well documented as a modulator of channel function, redox alterations have begun to emerge as a significant determinant of ion channel function (DiChiara and Reinhart, 1997). A variety of ligand-gated ion channels have been shown to be regulated by redox status such as nicotinic acetylcholine receptors (Xie et al., 1992; Sorenson and Gallagher, 1993; Servent et al., 1995), glycine receptors (Ruiz-Gomez et al., 1991; Pan et al., 1995), and GABA_A receptors (Amato et al., 1999). NMDA-mediated responses can be substantially potentiated by reducing agents while oxidizing agents can diminish those responses (Majewska et al., 1990; Reynolds et al., 1990; Sucher et al., 1990; Traynelis and Cull-Candy, 1991) affecting excitotoxicity (Levy et al., 1990; Tauck and Ashbeck, 1990; Aizenman and Hartnett, 1992), long-term potentiation (Tauck and Ashbeck, 1990), and neurotransmitter release (Woodward and Blair, 1991). Hippocampal large-conductance Ca²⁺-activated K⁺ channels (BK_{Ca}) are responsible for action potential repolarization, generation of fast afterhyperpolarizations (Lancaster and Nicoll, 1987; Storm, 1987), and have been suggested to play an important role in regulating neuronal excitability at the resting membrane potential (Wann and Richards, 1994; Kang et al., 1996). The role of redox-induced alterations to BK_{Ca} channels has been investigated in various cell types (Park et al., 1995; Thuringer and Findlay, 1997; Wang et al., 1997) including central nervous system neurons (Liu et al., 1999; Gong et al., 2000). In CA1 pyramidal cells from the adult rat hippocampus the activity of BK_{Ca} channels was enhanced by intracellular exposure to the oxidizing agents 5,5'-dithio-bis(2-nitrobenzoic acid) (DNTB) and GSSG, and restored by the reducing agents dithiothreitol (DTT) and glutathione (GSH), suggesting modulation of BK_{Ca} channel function by alterations in redox status (Gong et al., 2000). In neocortical neurons from mice, however, BK_{Ca} channel function was unaffected by oxidation but changed by a reducing agent (Liu et al., 1999). BK_{Ca} channels may be differentially affected by redox agents due to the sulfhydryl group of cysteine residues they contain (DiChiara and Reinhart, 1997). Changes to BK_{Ca} channels by redox status suggests that increased levels of oxidative stress may enhance channel activity and be a contributing mechanism toward increasing neuronal excitability as occurs during epileptogenesis.

The A-type current (I_A) is a fast transient K⁺ current that plays a crucial role in the regulation of neuronal excitability based on its contribution to action potential repolarization (Storm, 1987; Riazanski et al., 2001), regulating interspike interval (Hahn et al., 2003), and increasing the latency to current injected-induced first spikes (Gustafsson et al., 1982). A-type currents are known to be modulated by second messenger cascades and phosphorylation (Martens et al., 1999). Evidence for A-type current modification by oxidation is partly based on sensitivity to oxidation demonstrated in hippocampal neurons (Muller and Bittner, 2002), oxidation-induced loss of activation for the K_v3.4 and K_v1.4 subunits (Ruppersberg et al., 1991), and the ability of arachidonic acid to inhibit postsynaptic I_A in CA1 pyramidal neurons (Angelova and Muller, 2006) and be slowed by the addition of a water soluble Vit E derivative (Angelova and Muller, 2009). Additionally, pharmacological blockade of I_A causes seizure activity (Juhng et al., 1999) and I_A has been demonstrated to be regulated by cellular redox status in control and pilocarpine-treated

epileptic rats whereby decreased GSH/GSSG caused an acceleration of recovery from inactivation which may allow neurons to reduce the cumulative inactivation of I_A during high-frequency activity and serve as a protective mechanism to limit excitability (Ruschenschmidt et al., 2006). However, epileptic activity was not found to produce chronic changes in the molecular and functional properties of the somatic I_A of dentate granule cells (Ruschenschmidt et al., 2006). The redox sensitivity of I_A may render them particularly susceptible to modulation during seizure activity and epileptogenesis suggesting their contribution to epilepsy associated neuronal excitability.

An inactivation-resistant TTX-sensitive Na^+ current ($I_{Na,p}$) has been identified in neurons (Gilly and Armstrong, 1984; Taylor, 1993; Crill, 1996) that is thought to play a role in a pacemaking current and enhancement of rhythmicity leading to repetitive action potential firing (Taylor, 1993). It has been shown that NO increases $I_{Na,p}$ which may lead to increased neuronal firing rate, neuronal excitability, disruption of normal membrane potential, and rhythmic firing of action potentials (Alonso and Llinas, 1989; Amitai, 1994; Hammarstrom and Gage, 1999). Additionally, NO deprivation by NOS inhibitors and NO scavengers caused depression of both excitatory postsynaptic currents (EPSC's) and inhibitory postsynaptic currents (IPSC's) and prevented initiation of seizure-like events in hippocampal slices from rats and mice. These results suggest that enhancement of synaptic transmission by NO under epileptic conditions may represent a positive feedback mechanism for the initiation of seizure-like events (Kovacs et al., 2009). NO may directly modulate channel protein structure by reacting with protein thiols resulting in S-nitrosylation (Stamler et al., 1992) and allowing disulfide bond formation in the channel protein (Lei et al., 1992). An increase in $I_{Na,p}$ induced by increased oxidative stress could cause membrane depolarization, increased neuronal excitability, and firing rate associated with seizures.

5.1 Seizure-induced oxidative damage to lipids

Polyunsaturated fatty acids present in phospholipids of biological membranes are highly susceptible to oxidation by ROS. Unspecific oxidation of polyunsaturated fatty acids, known as lipid peroxidation, is a free radical mediated pathway and is used as an index of irreversible neuronal damage of cell membrane phospholipids suggested as a possible mechanism of epileptic activity (Dal-Pizzol et al., 2000). Lipid peroxidation is partly caused by hydrogen abstraction from polyunsaturated fatty acids by $OH\cdot^-$ transformed from H_2O_2 and $O_2\cdot^-$ by the catalytic action of transition metals (Halliwell and Gutteridge, 1986; Coyle and Puttfarcken, 1993). The brain is particularly susceptible to injury by lipid peroxidation products and is highly sensitive to oxidative stress. Due to a high content of polyunsaturated phospholipids and a major site of ROS production, the mitochondria are also particularly sensitive to lipid peroxidation (Bindoli, 1988). Mitochondrial dysfunction resulting from lipid peroxidation may lead to compromise in a cells capability to maintain energy levels, energy failure, and the triggering of events leading to neuronal injury and death.

Marked alterations in membrane phospholipid metabolism result in the liberation of free fatty acids such as arachidonic acid, diacylglycerols, eicosanoids, lipid peroxides and free radicals (Costa, 1994). Ca^{2+} -dependent activation of phospholipase A_2 releases arachidonic acid (Erakovic et al., 1997; Mrsic et al., 1997) yielding $O_2\cdot^-$ through metabolism by lipoxygenases (Coyle and Puttfarcken, 1993). These lipid metabolites in conjunction with abnormal ion homeostasis and decreased energy generation may contribute to cell injury and death (Pellegrini-Giampietro et al., 1988; Shimizu and Wolfe, 1990; Simmet and Peskar, 1990). F(2)-isoprostanes (F_2 -IsoPs) are a novel class of prostaglandin F_2 (PGF_2)-like compound produced by a non-cyclooxygenase and free radical catalyzed mechanism involving the peroxidation of arachidonic acid. F_2 -IsoPs are often utilized as an index of lipid peroxidation in vivo because they are specific products of lipid peroxidation, detectable

in normal biological fluids, increase dramatically in models of oxidant injury, modulated by antioxidant status, and are unaffected by dietary lipids (Roberts and Morrow, 2000). F₂-IsoPs are a validated, sensitive, stable and reliable marker of free radical-induced lipid peroxidation. A large increase in prostaglandin derivatives, including prostaglandin- F₂ α a precursor of F₂-IsoP, is increased after prolonged seizures. F₂-IsoPs have been measured in microdissected dentate gyrus, CA1, and CA3 regions following KA treatment and shown to be elevated in CA3 at 16 h and correlated with neuronal loss and mitochondrial aconitase inactivation (Patel et al., 2001). Interestingly, the dentate gyrus showed a 2.5-5 fold increase between 8-24 h post-KA, even though the dentate gyrus is normally resistant to KA-induced neuronal death.

Isofurans (IsoF), a novel product of lipid peroxidation, have also shown to be elevated following KA-induced seizures with an overlapping but distinct time course as that of F₂-IsoPs in hippocampal subregions (Patel et al., 2008). The expression of IsoF's, but not F₂-IsoPs, coincided with timepoints of mitochondrial oxidative stress. Seizure-induced F₂-IsoP formation coincided with the peak hypoxia phase in affected tissues whereas IsoF formation coincide with the reoxygenation phase in this study, suggesting seizure-induced changes in tissue oxygen levels and mitochondrial dysfunction may differentially influence the formation of F₂-IsoPs and IsoFs. The combined measurement of both IsoFs and F₂-IsoPs provides a more reliable assessment of seizure-induced oxidative stress and changes in tissue oxygenation. These results suggest that oxidative damage to lipids results from seizure activity and may play an important role in seizure-induced death of vulnerable neurons.

Malondialdehyde (MDA) and 4-hydroxy-2-(E)-nonenal (4-HNE) have been used to identify oxidative damage to lipids and its association with ageing and disease (Dexter et al., 1989; Cini and Moretti, 1995). MDA levels have been reported to be increased at 8 and 16 h following KA treatment, and decreased at 48 h and 5 d in the CA3 and dentate gyrus of adult rats (Bruce and Baudry, 1995). MDA has also been reported to increase 2 h post-pilocarpine-induced SE in the cortex (Tejada et al., 2007). In an amygdala kindling model of epilepsy, MDA and 4-HNE have been reported to increase in both hemispheres 24 h following the last seizure (Frantseva et al., 2000b). Vit E and GSH prevented the rise in lipid peroxides and hippocampal neuronal death during kindling, but did not arrest the development of seizures. 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 both the KA and pilocarpine models, TBARS were reportedly increased 12-14 h post-treatment, which decreased or reached basal levels at chronic time points suggesting hypometabolism, neuronal loss, and compensatory mechanisms may be actively modulating enzymes related to ROS catabolism (Dal-Pizzol et al., 2000). In the lithium-pilocarpine 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). Hydroperoxide, another marker of lipid peroxidation, has been reported to be increased at 1 h post-pilocarpine treatment (Bellissimo et al., 2001). Lipid radicals have been detected in the extracellular space during KA-induced seizure activity using in vivo electron spin resonance microdialysis in freely moving rats (Ueda et al., 1997), suggesting a progression of lipid peroxidation during seizure activity which may lead to neuronal damage in the hippocampus following acute seizure activity.

A variety of lipid peroxidation assays have been used as evidence of free radical damage in neuropathological processes. However, the in vivo use of these assays is associated with problems such as end product instability, lack of sensitivity, and inadequate specificity for free radical mediated processes. For example, the TBARS assay is not specific for lipid peroxidation and the use of MDA as an indicator of lipid peroxidation may be problematic

due to tissue homogenization and organic solvent extraction steps (Cohen et al., 1987). Nonetheless, there is sufficient evidence to support the presence of lipid peroxidation products and mitochondrial dysfunction associated with seizure activity.

6.1 Seizure-induced oxidative damage to mtDNA

Oxidative damage to mtDNA and its consequences such as gene mutation and deletions have long been implicated in the pathogenesis of a variety of human disorders associated with mitochondrial dysfunction and ageing (Tritschler and Medori, 1993) and have recently begun to be investigated as a potential contributor to epileptogenesis. Oxidative damage to DNA can be variable, producing structural damage such as strand breaks, protein/DNA cross links, and/or modification of base pairs. mtDNA lack protective histones, is located in close proximity to the inner mitochondrial membrane where ROS are generated, lacks introns leading to genomic injury adversely affecting a coding region for the ETC or mitochondrial translational machinery, has a high transcription rate leading to an increased probability of mutations and/or deletions, and possess less efficient repair mechanisms than nDNA under certain circumstances (Yakes and Van Houten, 1997; Jarrett et al., 2008a). These characteristics result in the mitochondrial genome being particularly vulnerable to ROS-induced damage (Bohr et al., 2002). As such, levels of oxidized bases in mtDNA are 2-3 times higher than nDNA (Richter et al., 1988; Hudson et al., 1998). Increased production of ROS may cause mtDNA damage leading to decreased activities of mitochondrial ETC complexes containing mtDNA-encoded subunits and selectively diminishing the activities of complexes I, III, IV, and V (Fig. 1). A decrease in mtDNA quantity in CA1 and CA3 30 d post-pilocarpine treatment in rats has been reported (Kudin et al., 2002). However, an alternative study reported no mtDNA abnormalities 120 d post-pilocarpine-induced SE, suggesting that free radicals produced during SE do not adversely effect nuclear integrity during chronic epilepsy (Nasseh et al., 2006). Differences in the results from these studies may be based on the use of different nuclear probes during mtDNA quantification by Southern blotting.

Two commonly used markers of oxidative DNA damage are thymine glycol (TG) and 8-OHdG. TG is an adduct which can lead to cell death by blocking polymerase action (Ames, 1989; Dizdaroglu, 1993). 8-OHdG, an oxidatively modified guanine adduct, is one of the most common adducts formed from oxidation of DNA (Dizdaroglu, 1991) and has been used as an index of oxidative DNA damage with the ratio of steady state levels of 8-OHdG to 2-deoxyguanine (2-dG) (Shigenaga et al., 1990; Mecocci et al., 1993; Giulivi et al., 1995; Jarrett et al., 2008a). 8-OHdG lesions are highly mutagenic because they can mispair with adenine leading to a transversion mutation (Grollman and Moriya, 1993) and DNA polymerase will insert a wrong base opposite 8-OHdG about 27% of the time (Pinz et al., 1995). However, the accurate measurement of 8-OHdG is challenging due to the possibility of introduction of artificial oxidation during sample isolation and preparation. A time-dependent increase in mitochondrial, but not nuclear, 8-OHdG/2dG 16-48 h following KA treatment has been reported with a corresponding increase in mtDNA lesion frequency (Jarrett et al., 2008a). These changes were correlated with increased mitochondrial H₂O₂ production and decreased aconitase activity accompanied by a transient decrease in mtDNA repair.

8-OHdG can activate DNA repair systems that involve enzymatic processes including base recognition and excision to ligation of DNA strands. Short and long patch DNA base excision repair (BER) appears to be the predominant mechanism for the repair of oxidative DNA lesions in the mitochondria (Croteau and Bohr, 1997; LeDoux et al., 2007; Akbari et al., 2008; Liu et al., 2008; Szczesny et al., 2008) and its impairment and/or imbalance has been implicated in neuronal dysfunction (Audebert et al., 2002; Fishel et al., 2003; Beal,

2005; Harrison et al., 2005; Neema et al., 2005; Quach et al., 2005; Fishel et al., 2007). 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 are elevated between 24 h and 3 wk following KA-induced SE, followed by improvement in mtDNA repair (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. Although various reports have demonstrated changes in BER during several neuronal disorders such as stroke, Alzheimer's disease, and amyotrophic lateral sclerosis (Kisby et al., 1997; Copani et al., 2006; Li et al., 2006; Coppede et al., 2007), its role in epilepsy requires further exploration. The isolation of pure mitochondria is often necessary for assays aimed at determining mtDNA damage and repair, which can lead to artifactual DNA damage. To circumvent this problem, a gene- and genomic-specific quantitative extended-length polymerase chain reaction (PCR) assay has been developed that can detect oxidative mtDNA damage and repair based on relative magnitudes of gene fragment amplification (Yakes and Van Houten, 1997; Ayala-Torres et al., 2000; Santos et al., 2006).

7.1 Seizure-induced alterations in antioxidant defenses and redox status

7.1.1 Seizure-induced alterations in antioxidant defenses

Endogenous antioxidant defenses are a complex and integrated system that functions to protect cells against the deleterious effects of ROS. When antioxidants cannot breakdown ROS efficiently, oxidative damage occurs and accumulates, particularly in the mitochondria (Sies, 1993; James and Murphy, 2002). Superoxide dismutase (SOD) is an endogenous enzymatic antioxidant that has been shown to protect against programmed cell death (Rothstein et al., 1994b; Greenlund et al., 1995) and exists in three forms; CuZnSOD (SOD1) localized in the cytoplasm, MnSOD (SOD2) localized in the mitochondrial matrix, and ECSOD (SOD3), localized in the extracellular space. The dismutation of $O_2^{\cdot-}$ occurs via SOD, which produces H_2O_2 that is further broken down to O_2 and H_2O during normal conditions by catalase (CAT) and glutathione peroxidase (GPx) in a reaction that uses GSH as a co-substrate. If not adequately controlled, $O_2^{\cdot-}$ production can lead to the formation of more potent oxidants, such as $OH^{\cdot-}$, which can produce further oxidative damage and contribute to cell death (Fig. 1). Genetic inactivation of SOD1 or SOD3 results in mild phenotypes (Carlsson et al., 1995; Reaume et al., 1996) while mice completely lacking SOD2 are lethally affected by three weeks (Li et al., 1995; Huang et al., 2001), have spontaneous seizures (Lynn et al., 2005), and show no signs of compensation by increased expression of either SOD1 or SOD3 (Van Remmen et al., 1999). Hence, SOD2 is critically important as an antioxidant defense due to its proximity to the mitochondria and the primary source of $O_2^{\cdot-}$ generation.

Seizure-associated alterations to antioxidant defenses are a common finding, but whether antioxidant levels are increased or decreased remains controversial. Following KA-induced SE, increases in SOD and CAT have been measured as early as 48 h and 5 d in both piriform cortex and hippocampus (Bruce and Baudry, 1995). These changes correspond to a period of glial activation, proliferation, and degeneration of susceptible neuronal cells suggesting immediate compensation of these scavenging enzymes are not necessarily neuroprotective (Altar and Baudry, 1990). CAT activity has been reported to increase in the hippocampus, striatum, and frontal cortex but not in the cerebellum 1 hr post-pilocarpine treatment (Freitas et al., 2004), suggesting alterations in antioxidant defenses as a result of SE. Also in the pilocarpine model, CAT, GPx, and SOD were reportedly increased in the cortex 2 h post-SE (Tejada et al., 2007). SOD increased in a whole brain preparation 30 d post-amygdaloid kindling, and direct amagdaloid injection of SOD1 suppressed the production of seizures

(Mori et al., 1991). In the lithium-pilocarpine model, a decrease in GPx and no change in SOD has been reported, suggesting impaired and not increased antioxidant defense in the brain, particularly in the cortex (Erakovic et al., 2000). Using spectrophotometric methods in the pilocarpine model, hippocampal SOD has been reported to decrease at 24 h and during the chronic phase of epilepsy, while GPx increased only at 1 h post-treatment (Bellissimo et al., 2001). Twenty four hours post-pilocarpine treatment, hippocampal CAT, but not SOD, was reportedly decreased suggesting the hippocampus does not use SOD as the major free radical scavenging system, but perhaps uses CAT and/or GSH (Freitas et al., 2005). A decrease in regional brain antioxidant levels have also been reported using the electroconvulsive shock treatment in rats (Erakovic et al., 2000) lasting up to 48 h after a single seizure episode. (See Devi et al., 2008 for a list of the effects of antioxidants on experimental seizures). Considering the disparity in the evidence from a variety of animal models of epilepsy, the issue of endogenous antioxidant compensation in response to seizure activity remains unresolved.

7.1.2 Seizure-induced alterations in redox status

An alternative to the measurement of oxidized cellular targets as markers of oxidative stress has been to directly measure a subcellular redox couple as an indication of redox status. GSH is the most abundant intracellular non-enzymatic oxidant defense in the body (Meister and Anderson, 1983). The oxidation of GSH is coupled to the reduction of GPx to catalyze the removal of H₂O₂ in cells. GSH is recycled from GSSG, its disulfide redox partner, by glutathione reductase (GR) and NADPH oxidation (Fig. 1). GSH/GSSG is a commonly used biomarker of oxidative stress in biological systems (Reed and Savage, 1995). A decrease in GSH and GSSG levels suggest an alteration in GSH synthesis and/or transport. Decreased ratios of GSH/GSSG could induce structural damage to mitochondrial membranes, changes in mitochondrial enzyme activities and membrane potential, and subsequent mitochondrial dysfunction potentially affecting neuronal excitability.

A decrease in both GSH levels and GR activity has been reported in brain regions and plasma of epileptic patients (Mueller et al., 2001; Sudha et al., 2001). Animal models of epilepsy have provided inconsistent results concerning alterations in redox status. Certain studies provide evidence of a decrease in hippocampal redox status following SE (Skaper et al., 1999; Gilberti and Trombetta, 2000; Ong et al., 2000), while others report no change (Gluck et al., 2000; Gupta et al., 2002). In a study reporting no changes in GSH levels, GSSH was found to increase at 4 h post-SE in the cortex, suggesting that GSH may play a disproportionate role in the cortex but not in the hippocampus during epileptogenesis (Gluck et al., 2000). A time-dependent decrease in the GSH/GSSG ratio following KA-induced SE as measured by HPLC has been reported in mitochondrial fractions as compared to whole hippocampal homogenates (Liang and Patel, 2006). This altered redox status was accompanied by a moderate increase in GPx activity and a decrease in GR activity in hippocampal homogenates and mitochondria, respectively. Interestingly, the time course of redox changes preceded aconitase inactivation suggesting that the latter may further deplete GSH because reducing equivalents are used to reactivate aconitase. Alternately, the increased free radical load due to aconitase inactivation (i.e. H₂O₂ and iron) may further deplete GSH. This study demonstrated that mitochondrial GSH depletion occurs early after SE and is persistent even during the “latent period”. Pilocarpine-induced SE has been reported to decrease GSH in the hippocampus 24 h post-treatment (Freitas et al., 2005). In the kindling model, a persistent decrease in GSH was observed at 4 h post stimulation in CA3 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., 2006a). These observations are consistent with the notion that mitochondria contribute disproportionately to SE-induced oxidative stress.

Although GSH/GSSG measurements are an important tool in the measurement of redox status and oxidative stress, their levels may be augmented during subcellular fractionation. Alternatively, coenzyme A (CoASH) and its disulfide with GSH (CoASSG), which are primarily compartmentalized within mitochondria (Fig. 1), can be measured in whole tissue homogenates. It has been reported that CoASH/CoASSG ratios decreased in hippocampal tissue following KA-induced SE at a time course paralleling mitochondrial GSH/GSSG levels (Liang and Patel, 2006). Increases in mitochondrial $O_2^{\cdot-}$ and H_2O_2 and aconitase inactivation are likely mechanisms that may contribute to the decreased mitochondrial GSH/GSSG and CoASH/CoASSG ratios measured following seizures. Cysteine, a rate limiting precursor of GSH, was also decreased following SE in both hippocampal tissue homogenates and mitochondrial fractions (Liang and Patel, 2006). Extensive neuronal death in the CA3 subfield occurs from 2-7 days following KA treatment (Liang et al., 2000; Patel et al., 2001) after the early onset of reported redox changes, suggesting altered redox status may contribute to seizure-induced neuronal death. The decrease in mitochondrial GSH/GSSG and tissue CoASH/CoASSG as early as 8 h after KA treatment precedes the earliest inactivation of aconitase as well as increases in IsoF and 8OHdG/2DG, suggesting that mitochondrial thiol status may play a key role in mediating SE-induced oxidative damage.

8.1 Targeting mitochondrial oxidative stress in epilepsy therapy

Although significant progress has been made in the development of new antiepileptic drugs, approximately one-third of patients are refractory to currently available treatments. Epilepsy therapies are largely aimed at decreasing neuronal excitability and thereby controlling the occurrence of epileptic seizures. An alternative approach is the targeting of epileptogenesis with drugs designed towards the underlying processes that lead to the development of epilepsy. The targeting of excitotoxicity resulting from a disruption of Ca^{2+} homeostasis leading to neuronal damage and death with antiepileptic drugs has recently begun to be explored (Rho and Sankar, 1999; Trojnar et al., 2002; Sankar and Holmes, 2004). Excessive Ca^{2+} uptake during excitotoxic insults has been shown to increase mitochondrial ROS, inhibit ATP synthesis, promote cytochrome c release, and activate the MPT leading to cell death (Sullivan et al., 2005). Although it is clear that mitochondrial ROS and free radicals leading to mitochondrial oxidative stress and dysfunction are active during epileptogenesis (Fig. 2), the specificity of radicals and their origins are unclear. These findings raise the possibility that inhibition of mitochondrial dysfunction may in part underlie the successful treatment of epilepsy.

8.1.1 Antioxidant therapies

Testing antiepileptogenic therapies aimed at mitochondrial bioenergetics and oxidative stress pathways has largely been limited to animal studies. Recent studies suggest the association of seizures and SE with oxidative stress (Liang and Patel, 2006; Barros et al., 2007; Jarrett et al., 2008a). Levetiracetam, a novel antiepileptic drug, given during self-sustained SE and up to 44 h following seizure onset rescued changes to GSH, aconitase, citrate synthase, complex I, and alpha-ketoglutarate dehydrogenase (Gibbs et al., 2006). Also, it improved behavioral seizures but did not affect EEG parameters suggesting neuroprotection rather than a direct effect on seizures themselves (Gibbs et al., 2006). A current antiepileptic drug, zonisamide, which mainly acts through the inhibition of Na^+ channels, also has antioxidant properties enhancing its neuroprotective characteristics (Mori et al., 1998; Tokumaru et al., 2000). Antioxidants such as the spin trapping agent N-tert-butyl- α -phenylnitron (PBN) and vitamin E are known to accumulate in the mitochondria (Bjorneboe et al., 1991; Folbergrova et al., 1995). PBN has been shown to prevent ROS-induced damage to the ETC, maintain levels of high energy phosphates (Gupta et al., 2001), and inhibit KA-induced NO generation (Milatovic et al., 2001). Rats delivered acetylcholinesterase inhibitor-induced SE and pre-treated with PBN showed prevention of

both seizures and loss of high energy phosphates, while animals pre-treated with vitamin E showed a prevention of high energy phosphates without affecting seizures (Gupta et al., 2001). Vitamin E has been shown to have antioxidant and neuroprotective effects in pilocarpine-induced seizures and to prevent increased brain free fatty acid levels and increased CAT levels in rats (Barros et al., 2007), suggesting its protection may be mediated by antioxidant enzymatic activity. Vitamin E and GSH have been demonstrated to attenuate the rise in lipid peroxides and hippocampal cell death during kindling but not arrest the development of seizures (Frantseva et al., 2000b). However, intra-peritoneal injection of N-acetyl-L-cysteine (NAC), a GSH precursor, did not protect against diminished GSH following perforant path stimulation-induced SE and did not protect against mitochondrial dysfunction (Steven et al., 2006b). Vitamin E has been shown to slow the onset of seizures in the ferrous chloride model but have little to no effect using the PTZ-threshold, electroshock, kindling, and KA models (Levy et al., 1990; Levy et al., 1992; Xu and Stringer, 2008). A study of vitamin E in children with epilepsy demonstrated a significant decrease in seizure frequency over 3 months using a randomized double-blind experimental design (Ogunmekan and Hwang, 1989). However, clinical trials of vitamin E as an add-on therapy for refractory epilepsy have been controversial, with largely failed attempts to influence the occurrence of epileptic seizures in pediatric patients.

Vitamin C has been suggested to exert potent anticonvulsant and neuroprotective effects (Xavier et al., 2007). The neuroprotective effects of vitamin C pre-treatment in pilocarpine-treated rats have been attributed to reduced lipid peroxidation and increased CAT activity following SE (Santos et al., 2008). Vitamin C has been demonstrated to increase the latency to first seizure and decrease the mean seizure score in the pilocarpine model, reduce mortality in the PTZ model, be effective against penicillin-induced seizures (Ayyildiz et al., 2007), but be ineffective in the KA model (Xu and Stringer, 2008). D,L- α -lipoic acid is a naturally occurring cellular component which has been reported as a scavenger of ROS (Packer et al., 1995; Packer et al., 1997; Bast and Haenen, 2003). α -lipoic acid pre-treatment has been demonstrated to decrease seizure activity using ferric chloride-induced seizures (Meyerhoff et al., 2004) and increase the latency to first seizure using the pilocarpine model, but have no significant effects in the PTZ and KA models (Xu and Stringer, 2008).

Melatonin is a natural occurring compound **produced by the pineal gland that has** antioxidant properties and effects on mitochondrial oxidative stress implicated in neuronal diseases (Reiter et al., 1994; Reiter, 1998; Leon et al., 2004). The protective effects of melatonin have been reported in human epilepsy (Molina-Carballo et al., 1997) and in the PTZ model of epilepsy (Bikjdaouene et al., 2003) where its antiepileptic effects have been attributed to the regulation of GABA receptors and inhibition of glutamate mediated responses through nNOS activity and NO production (Acuna-Castroviejo et al., 1995; Leon et al., 2000; Bikjdaouene et al., 2003). However, an alternative study reported no significant effects of melatonin using the PTZ and KA models (Xu and Stringer, 2008). Melatonin has been shown to decrease iron-induced seizures (Kabuto et al., 1998), increase the latency to epileptiform activity using penicillin-induced seizures (Yildirim and Marangoz, 2006), and increase the latency to first seizure in the pilocarpine model (Xu and Stringer, 2008). Melatonin has been reported to reduce the deleterious effects of KA-induced SE on nuclear and mtDNA, lipid peroxidation, hippocampal cell loss, and seizures in rats and mice (Tan et al., 1998; Tang et al., 1998; Mohanan and Yamamoto, 2002; Yamamoto and Mohanan, 2003) as well as ROS production, decreased GSH, and complex II activity (Dabbeni-Sala et al., 2001). The ability of melatonin to act as a potent antioxidant, protect mitochondrial ROS homeostasis, and interact with mtDNA makes it a novel target therapy for use in controlling mitochondrial bioenergetics and disease. However, different mechanisms of action may occur in different models and/or epileptic syndromes complicating treatments. Additionally, activated pathways may be producing deleterious results alone, or in conjunction with other pathways. While particular antioxidants have been shown to be effective in specific

chemoconvulsant models, the same antioxidants may not be effective in alternative models, suggesting that their effects may be model specific (Xu and Stringer, 2008). Therapies aimed at mitochondrial bioenergetics and oxidative stress pathways, however, may provide a novel avenue for therapeutic intervention for the treatment of epilepsies.

8.1.2 Synthetic antioxidant therapies

The use of SOD and CAT as therapeutic agents to attenuate ROS-induced injury responses has had mixed success (Shaffer et al., 1987; Thibeault et al., 1991; Wispe et al., 1992; Lardot et al., 1996; Simonson et al., 1997) based primarily on their large size which limits cell permeability, short circulating half-life, antigenicity, and expense. An increasing number of SOD mimetics have been developed to overcome some of inherent limitations of these natural antioxidants. Oxidative stress and neuronal damage induced by SE or a deficiency in SOD2 have been demonstrated to be ameliorated by the SOD mimetics, MnTBAP, and the salen EUK compounds (Liang et al., 2000; Melov et al., 2001; Hinerfeld et al., 2004). However, acute administration of these catalytic antioxidants did not alter chemoconvulsant-induced behavioral seizure severity. MnTBAP has been shown to protect mitochondrial aconitase, 8-OHdG formation, and hippocampal neuronal loss in rats treated with KA (Liang et al., 2000) and to inhibit both necrotic and apoptotic cell death (Patel, 1996; Patel, 1998), strengthening the role of oxidative mechanisms in KA neurotoxicity. MnTBAP has also been shown to rescue the lethal phenotype and extend the lifespan of Sod2^{-/-} mice (Melov et al., 1998), prevent aconitase inactivation and cell death following NMDA application in cortical cultures (Patel, 1996), and protect mtDNA from oxidative damage in cultured fibroblasts (Milano and Day, 2000). Although the exact cellular site where MnTBAP performs its antioxidant abilities is currently unknown, a likely mechanism of action is the protection of cellular targets by scavenging intracellular reactive species such as O₂⁻, H₂O₂, ONOO⁻ and lipid peroxides (Patel and Day, 1999).

Synthetic antioxidants that protect mitochondrial targets and decrease neuronal death may be useful supplements for the clinical management of patients with SE or intractable epilepsy. The AEOL class of metalloporphyrin compounds contain a manganese center that are capable of detoxifying a wide range of ROS such as O₂⁻, H₂O₂, ONOO⁻, and lipid peroxide radicals (Patel and Day, 1999). Several water-soluble metalloporphyrin compounds have been shown to be effective in animal models of epilepsy (Liang et al., 2000), stroke (Mackensen et al., 2001) and amyotrophic lateral sclerosis (Crow et al., 2005) and may provide important tools in targeting neuroprotection and the pathogenesis of neurological disorders. Chelatable iron is an important catalyst for the initiation and propagation of free radical reactions implicated in the pathogenesis of neuronal disorders such as epilepsy. KA-induced SE has been shown to result in a time-dependent increase in chelatable iron in mitochondrial fractions of the rat hippocampus (Liang et al., 2008). *N,N'*-bis (2-hydroxybenzyl) ethylenediamine-*N,N'*-diacetic acid (HBED), a synthetic iron chelator, administered systemically ameliorated SE-induced changes in chelatable iron, mtDNA damage assessed by 8-OHdG, GSH depletion, and hippocampal cell loss, suggesting a role for mitochondrial iron in the pathogenesis of SE-induced brain damage and subcellular iron chelation as a novel therapeutic approach for its management (Liang et al., 2008). However, in studies investigating oxidative stress as a potential therapeutic target it should be noted that ROS play an important physiological role in cell signaling and their removal with antioxidants may have deleterious consequences on cellular functions during chronic administration that remain to be elucidated. 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.

8.1.3 Non-pharmacological therapy

Non-pharmacological therapies such as the ketogenic diet (KD) have been explored as a means of attenuating seizures by targeting mitochondrial bioenergetics and metabolism. The KD is often a successful treatment for children with epilepsy when pharmacological treatment is unreliable suggesting that the diet works by unique mechanisms. The KD was developed as a therapy for intractable seizures in children in the 1920's (Schwartzkroin, 1999) and is 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. Rats fed this diet have been shown to undergo ketosis, which is necessary for the diet's anticonvulsant effect and positively correlated with seizure protection (Bough et al., 1999; Stafstrom, 1999).

Currently, there is a lack of understanding regarding the precise mechanisms underlying the KD. Two theories proposed to account for the effects of the diet include the neuroprotection of ketone bodies (β -hydroxybutyrate, acetoacetate, and acetone) (Massieu et al., 2003; Mejia-Toiber et al., 2006; Noh et al., 2006; Kim do et al., 2007), and the anticonvulsant effects of **glycolysis** inhibition (Schwechter et al., 2002; Garriga-Canut et al., 2006). The application of ketone bodies to a midbrain slice preparation has been demonstrated to slow spontaneous firing of GABAergic neurons in the substantia nigra (Ma et al., 2007). However, in a hippocampal slice preparation, neither β -hydroxybutyrate or acetoacetate affected the frequency or duration of epileptiform discharges (Thio et al., 2000). A role for mitochondrial bioenergetics has also been suggested to underlie the protective effects of the KD. For example, the KD has been shown to produce mitochondrial biogenesis (Bough et al., 2006), a decrease in mitochondrial ROS (Maalouf et al., 2007) due to upregulation of the uncoupling protein UCP2 (Sullivan et al., 2004), increase the cellular antioxidant capacity (Ziegler et al., 2003; Costello and Delanty, 2004; Nazarewicz et al., 2007), and in vitro studies have demonstrated that ketosis byproducts have the ability to prevent mtDNA deletions and cell death (Yamamoto and Mohanan, 2003; Santra et al., 2004). The KD has recently been demonstrated to improve the mitochondrial redox status in rats fed the diet for 3 weeks, which may improve the ability of the brain to resist metabolic changes and oxidative stress which partly underlies the occurrence of seizures (Jarrett et al., 2008b). This study also demonstrated an increase in mitochondrial GSH levels and stimulation of its de novo biosynthesis, and an improvement in mitochondrial redox status in the hippocampus resulting in decreased mitochondrial ROS production and protection of mtDNA. These results suggest increased GSH as a possible candidate mechanism underlying the protection observed by the KD. Currently, all of the contributing mechanisms to the anticonvulsant effects of the KD remain unknown and warrant a greater understanding.

9.1 Conclusions

This review provides an overview of the role of mitochondrial oxidative stress and dysfunction in seizure-induced neuronal damage and a potential contributing factor in epileptogenesis. Mitochondria dysfunction can affect ROS production, macromolecule function, bioenergetics, glutamate excitotoxicity, neuronal death, and neuronal excitability. Each of these targets is crucial for normal brain function, and dysfunction in one or more of them may decrease seizure threshold causing the brain to be more susceptible to becoming epileptic. Targeting mitochondrial bioenergetics and oxidative stress with antioxidant and non-pharmacological treatments may prove to be useful in the management of epilepsy and attenuation of its development. Continued research in this area will provide a greater understanding of how mitochondrial oxidative stress and dysfunction contributes to the pathogenesis of TLE and how therapeutic strategies targeting mitochondrial bioenergetics can be used for patients refractory to current antiepileptic treatments.

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Index of Abbreviations

TLE	temporal lobe epilepsy
SE	status epilepticus
KA	kainic acid
Li	Pilo-lithium-pilocarpine
SOD	superoxide dismutase
GSH	glutathione
ROS	reactive oxygen species
mtDNA	mitochondrial deoxyribonucleic acid
ETC	electron transport chain
ATP	adenosine triphosphate
TCA	tricarboxylic acid cycle
MPT	mitochondrial permeability transition pore
OH[•]	hydroxyl radical
H₂O₂	hydrogen peroxide
O₂^{•-}	superoxide radical
NO	nitric oxide
ONOO⁻	peroxynitrite
8-OHdG	8-hydroxy-2-deoxyguanosine
MnSOD (SOD2)	manganese superoxide dismutase
GS	glutamine synthetase
PTZ	pentylentetrazole
NMDA	N-methyl-D-aspartic acid
F₂-IsoP	F(2)-isoprostanes
IsoF	isofurans
MDA	malondialdehyde
4-HNE	4-hydroxy-2-(E)-nonenal
TBARS	thiobarbituric acid reactive substances
Ogg1	8-oxoguanine glycosylase
Pol γ	DNA polymerase gamma
BER	base excision repair
CAT	catalase
GPx	glutathione peroxidase
GR	glutathione reductase

CoASH	coenzyme A
MnTBAP	manganese 5,10,15,20-tetrakis (4-benzoic acid) porphyrin
KD	ketogenic diet
BK_{Ca}	large conductance Ca ²⁺ -activated K ⁺ channels
DNTB	5,5'-dithio-bis(2-nitrobenzoic acid)
DTT	dithiothreitol
mitoK_{ATP}	mitochondrial ATP-sensitive K ⁺ channel
I_{Na,p}	inactivation-resistant TTX-sensitive Na ⁺ current

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Fig. 1.

Mitochondrial function and neuronal excitability. Various aspects of the mitochondria can lead to impairment of its bioenergetic capacity affecting neuronal excitability, apoptosis, and an increase in seizure susceptibility. O₂⁻ production by complex I and III of the ETC leads to the production of ONOO⁻ in a reaction with NO, and H₂O₂ through dismutation by the antioxidant MnSOD (SOD2). H₂O₂ is membrane permeable and able to diffuse out of the mitochondria causing widespread oxidative damage. Excessive O₂⁻ production also damages Fe-S containing enzymes involved in the TCA cycle such as aconitase. OH[•] can be formed from H₂O₂ through Fenton chemistry and lead to further oxidative damage of macromolecules such as ETC complexes and mtDNA. Oxidative damage to mtDNA can lead to increased mutation rates and a decrease in ETC subunit expression encoded by the mitochondrial genome. Alterations in the redox status of GSH/GSSG and CoASH/CoASSG can cause an inability to protect against the deleterious effects of ROS. Modification of neurotransmitter biosynthesis within the mitochondria can affect levels of neuronal excitability/inhibition. Oxidative damage to these targets can result in increased neuronal excitability resulting from decreased mitochondrial membrane potential and ATP levels affecting the Na⁺/K⁺ ATPase and the release of cyto C leading to apoptosis. mNa⁺C²⁺E=mitochondrial sodium calcium exchanger; mCU=mitochondrial calcium uniporter; mNICE=mitochondrial sodium independent calcium exchanger; MPT=mitochondrial permeability transition pore; GSH=glutathione; GSSG=glutathione disulfide; CoASH=coenzyme A; CoASSG=coenzyme A glutathione disulfide; GR=glutathione reductase; GPx=glutathione peroxidase; cyto C=cytochrome C; Ψ_m=mitochondrial membrane potential.