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Review Article

Mitochondrial involvement and oxidative stress in temporal lobe epilepsy

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ABSTRACT

A role for mitochondria and oxidative stress is emerging in acquired epilepsies such as temporal lobe epilepsy (TLE). TLE is characterized by chronic unprovoked seizures arising from an inciting insult with a variable seizure-free "latent period." The mechanism by which inciting injury induces chronic epilepsy, known as epileptogenesis, involves multiple cellular, molecular, and physiological changes resulting in altered hyperexcitable circuitry. Whether mitochondrial and redox mechanisms contribute to epileptogenesis remains to be fully clarified. Mitochondrial impairment is revealed in studies from human imaging and tissue analysis from TLE patients. The collective data from animal models suggest that steady-state mitochondrial reactive oxygen species and resultant oxidative damage to cellular macromolecules occur during different phases of epileptogenesis. This review discusses evidence for the role of mitochondria and redox changes occurring in human and experimental TLE. Potential mechanisms by which mitochondrial energetic and redox mechanisms contribute to increased neuronal excitability and therapeutic approaches to target TLE are delineated.

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Epilepsy is a common neurological disorder that affects approximately 0.6% of the entire population. Recurrent spontaneous convulsive or nonconvulsive seizures are the hallmark of epilepsy. A seizure is characterized by synchronized abnormal electrical discharges from a locus in the brain. Epilepsy is defined by a condition in which recurrent unprovoked seizures occur as a result of genetic disposition or acquired factors such as brain injury. Epilepsies occur throughout the life span with the highest incidence in children younger than 5 and precipitously rising in the elderly after 65 years of age [1]. Temporal lobe

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epilepsy (TLE) is the most prominent of the acquired epilepsies and is commonly preceded by an initial brain injury, such as an episode of prolonged seizures or status epilepticus (SE), complicated childhood febrile seizures, hypoxia, or trauma, which leads to chronic epilepsy or spontaneous recurrent seizures. The process whereby physiological neuronal characteristics and circuitry are altered by a precipitating event is known as epileptogenesis. Animal models of acquired epilepsy attempt to recapitulate several of the features of human TLE and usually involve an initial insult, which is followed by a variable "latent period" that results in recurrent, spontaneous seizure activity. The majority of epilepsy research is focused on ion channels and receptors with an attempt to understand and control altered network excitability. A key shift in current epilepsy research emphasis is the prevention of chronic epilepsy development and disease progression rather than the traditional focus on controlling seizures per se with antiepileptic drugs. Many different approaches have been taken in this renewed focus of research with a primary purpose of identifying antiepileptogenic or disease-modifying therapies. Toward this goal, understanding mechanisms by which injury mediates the epileptogenic process and comorbid states such as depression and memory loss that coexist with TLE is important. This review covers the major strategies employed to implicate the role of mitochondria and oxidative stress in human and experimental TLE and potential mechanisms by which altered metabolism can increase neuronal excitability.

Mitochondrial function and neuronal excitability

Mitochondria serve several key cellular functions that may have a direct and/or indirect impact on neuronal hyperexcitability such as the generation of ATP, metabolite/neurotransmitter biosynthesis, calcium homeostasis, and control of cell death and they are the primary site of reactive oxygen species (ROS) production. Given the bioenergetics of seizures themselves and injury processes that trigger epileptogenesis, the role of mitochondria and oxidative stress is gaining increased recognition in the progression of epileptogenesis [2,3]. In fact, several key events initiated by the injury process such as hippocampal cell loss, inflammation, and cell signaling suggest a role for mitochondria and redox processes in epileptogenesis. The brain's unique susceptibility to oxidative stress and bioenergetic insults probably drives or at least exacerbates neuronal excitability during epileptogenesis because of a high metabolic demand in hypersynchronous circuits. In addition, mitochondria are a critical interface between environmental factors such as diet, disease, and proper cell function. Metabolic control of neuronal excitability is evident from the broad antiepileptic efficacy of the ketogenic diet (KD), a high-fat, low-carbohydrate dietary therapy in children and adolescents [4] that is based on providing alternative mitochondrial fuels, i.e., ketones and fatty acids vs glycolytic substrates, to control intractable seizures. Metabolic control of seizures and epileptogenesis is also suggested by their regulation by epigenetic mechanisms through histone modifications as this requires high energy intermediates such as ATP, acetyl-CoA, and *S*-adenosylmethionine [5]. Altering mitochondrial functions therefore becomes a potentially important area of interest in contemporary epilepsy research.

Metabolic alterations implicating mitochondrial involvement in human TLE

The most compelling evidence for the role of mitochondria in epilepsy arises from rare inherited mitochondrial disorders associated with epileptic seizures, e.g., myoclonic epilepsy with ragged red fibers and mitochondrial encephalopathy with lactic acidosis. Mitochondrial DNA mutations and spontaneous seizure activity are evident in both disorders [6]. The role of mitochondria in acquired epilepsy is largely indirect and based on observed changes in known mitochondrial functions in human tissue and experimental models.

A major suggestion of mitochondrial involvement in human TLE comes from observations of metabolic and bioenergetic changes after acute seizures and during various phases of chronic epilepsy. Glycolytic rates, activity-matched cerebral blood flow, and lactate/pyruvate ratios are acutely increased during seizure activity [7]. This ictal hypermetabolism in the human epileptic foci is followed by interictal hypometabolism. This hypometabolism may reflect a "metabolically stressed circuit" in which mitochondrial bioenergetic capacity may be depleted. Mitochondrial involvement in epilepsy has been suggested based on the loss of mitochondrial *N*-acetylaspartate in human epileptic tissue [8,9]. Finally, severe metabolic dysfunction characterized by biphasic abnormal NAD(P)H fluorescence transients and changes in mitochondrial membrane potential have been observed in ex vivo preparations from both chronically epileptic rats and human subjects [10].

Neuronal loss in the hippocampal formation or hippocampal sclerosis is a distinct pathological finding in human TLE and thought to be important because inciting injury can result in the development and progression of TLE. Understanding the mechanisms by which seizures result in neuronal loss and contribute to TLE is important and highlights the relevance of evaluating the role of oxidative damage and mitochondrial involvement in these processes. The vulnerability of the hippocampal principal neurons in TLE is largely due to the involvement of the structure in the seizure circuit and excessive glutamatergic neurotransmission resulting in excitotoxic cell death. Neuropathological findings in human TLE provide evidence for morphological changes in mitochondria of epileptic patients. For instance, neuronal damage incurred by ischemia and seizure-related events causes mitochondrial swelling and disruption [11]. Apoptotic machinery proteins as well as excitotoxic mechanisms are also known to be activated by seizures. For example, there are increases in the antiapoptotic molecule Bcl-2 in the serum of children with TLE [12] and changes in proapoptotic molecules in epileptic brain tissue [13], highlighting the importance of mitochondrial involvement in the cell death process [14]. Additionally, ROS have been suggested in seizure-induced apoptotic cell death in the hippocampus [15]. Calcium transients associated with seizure activity represent a potential role by which mitochondria might contribute to neuronal injury in TLE [16] based on a crucial role of mitochondria in buffering cytosolic calcium.

Literature attempting to link mitochondrial (dys)function in acquired epilepsies, such as TLE, is based on measurement of mitochondrial enzyme activities, indices of mitochondrial oxidative damage, bioenergetic alterations, secondary processes such as cell death involving mitochondria, alteration of redox status [17], and inhibition of oxidative phosphorylation (OXPHOS) enzyme complexes of mitochondria in animal models and human tissue [18]. Redox status measured by reduced and oxidized forms of glutathione (GSH/GSSG) shifts to a more oxidized state in brain regions and plasma of epileptic patients [19]. Another study shows decreased copy numbers of mitochondrial DNA and decreased aconitase activity in the CA3 [20]. The hypometabolism seen in the epileptic focus in interictal phases of seizure activity may therefore be attributed more to mitochondrial dysfunction than to neuronal cell loss [21]. The impact that mitochondrial dysfunction can have in human TLE is becoming more generally accepted, and work in experimental models of TLE will continue to help elucidate mechanisms of how mitochondria are involved. In sum, evidence for alterations in metabolic functions directly and indirectly suggesting mitochondrial involvement is mounting

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