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Review

Pathophysiology of mitochondrial disease causing epilepsy and status epilepticus

Shamima Rahman *

Mitochondrial Research Group, Genetics and Genomic Medicine, UCL Institute of Child Health, London, UK
Metabolic Unit, Great Ormond Street Hospital, London, UK

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ABSTRACT

Epilepsy is part of the clinical phenotype in nearly 40% of children with mitochondrial disease, yet the underlying molecular mechanisms remain poorly understood. Energy depletion has been postulated as the cause of mitochondrial epilepsy, but if this were the case, then 100% of patients with mitochondrial disease would be expected to present with seizures. This review explores other potential disease mechanisms underlying mitochondrial epilepsy, including oxidative stress, impaired calcium homeostasis, immune dysfunction, and deficiency of vitamins, cofactors, reducing equivalents, and other metabolites. Different mechanisms are likely to predominate in different mitochondrial disorders, since mitochondrial function varies between neurons and astrocytes, between different types of neurons, and in different brain regions. Systematic studies in cell and animal models of mitochondrial disease are needed in order to develop effective therapies for mitochondrial epilepsy.

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1. Mitochondrial function and dysfunction

The mitochondria are subcellular organelles present inside virtually all human cells as dynamic networks. They are often described as 'powerstations', since they are responsible for producing the majority of adenosine triphosphate (ATP), the universal cellular energy currency. The mitochondria have diverse functions in addition to energy generation, including calcium homeostasis, cellular signaling via the generation of reactive oxygen species (ROS), and regulation of apoptotic cell death. Inside the mitochondria, ATP is generated through the process of oxidative phosphorylation (OXPHOS) by the concerted action of five multisubunit enzyme complexes (I–V) embedded in the mitochondrial inner membrane. Electrons are passed from NADH and $FADH_2$ to complexes I and II respectively, then sequentially to complexes III and IV via two mobile electron carriers (coenzyme Q_{10} (CoQ_{10}) and cytochrome *c*), and then from complex IV to molecular oxygen to produce water. Complexes I, III, and IV also act as proton pumps, generating an electrochemical gradient across the inner mitochondrial membrane that is ultimately harnessed by complex V (ATP synthase) to produce ATP from ADP and inorganic phosphate.

In the brain, the mitochondria are responsible for providing ATP for neurotransmission, reactive oxygen species (ROS) signaling at synapses, and regulating pre- and postsynaptic calcium concentrations [1]. Epileptogenesis is characterized by neuronal hyperexcitability that may be triggered by multiple molecular and physiological changes [2]. These changes include increased glucose utilization, reduced activity of mitochondrial respiratory chain complex I, impaired ATP production, generation of ROS, and excessive calcium fluxes [2,3]. It is, therefore, not surprising that mitochondrial dysfunction and epilepsy have been intertwined in the literature for many years [4]. However, the precise pathogenic mechanisms responsible for mitochondrial epilepsy remain enigmatic and are the subject of this review. The situation is further complicated by differences in mitochondrial function between neurons and astrocytes, between different types of neurons, and in different brain regions [5].

2. Genetic basis of primary mitochondrial disorders associated with epilepsy

Mitochondrial dysfunction leads to disease, with heterogeneous clinical presentations that can affect any tissue or organ system in the body in any combination at any age [6]. Primary mitochondrial diseases are inherited disorders that may arise from mutation of the mitochondrial DNA (mtDNA), a dedicated ~16.5 kb genome located within the mitochondria, or from mutations in hundreds of nuclear encoded genes. These nuclear genes include genes encoding subunits and assembly factors of the OXPHOS complexes and genes coding for

* UCL Institute of Child Health, 30 Guilford Street, London WC1N 1EH, UK. Tel.: +44 7905 2608; fax: +44 7404 6191.
E-mail address: shamima.rahman@ucl.ac.uk.

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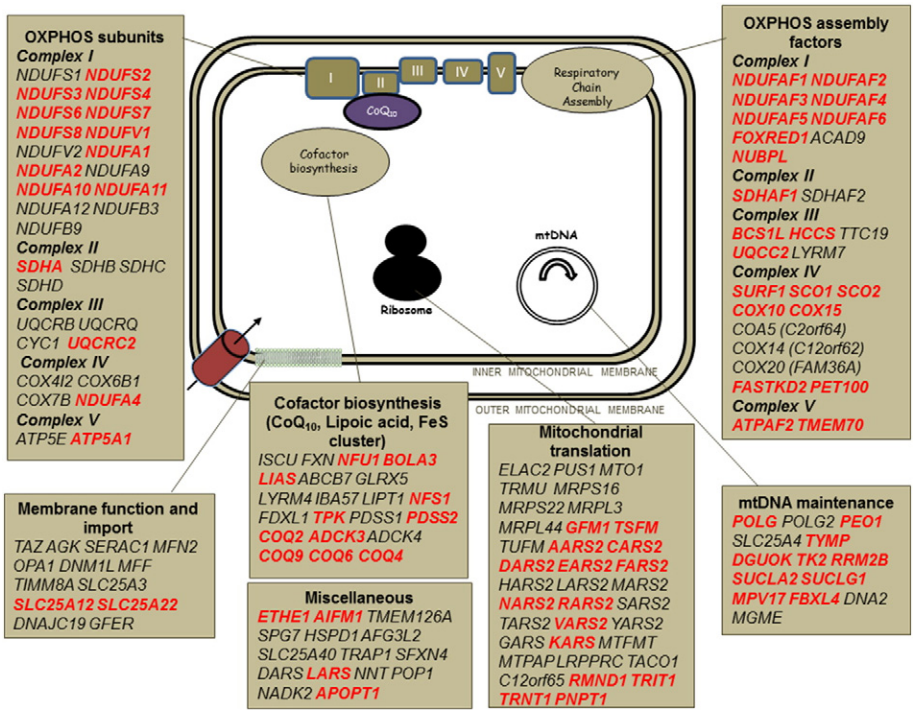

Fig. 1. Nuclear gene defects linked to mitochondrial epilepsy. Nuclear genes with mutations linked to mitochondrial disease, grouped by pathological mechanism (oxidative phosphorylation (OXPHOS) subunits; OXPHOS assembly factors; mitochondrial DNA (mtDNA) maintenance factors; mitochondrial translation factors; biosynthesis of cofactors including coenzyme CoQ_{10} (CoQ_{10}), lipoic acid and iron–sulfur (FeS) clusters; and membrane function and import). Gene defects highlighted in red have been linked to epilepsy.

mitochondrial translation factors, import proteins, and enzymes required for biosynthesis of cofactors and mitochondrial membrane lipids (Fig. 1).

The brain is frequently involved in mitochondrial disease, because of its high energy demands, and up to 40% of children with primary mitochondrial disease may experience seizures [4,7]. In 80% of cases of mitochondrial epilepsy, seizures are preceded by other clinical features [8], including feeding difficulties, faltering growth, developmental delay and/or regression, impairment of hearing and/or vision, cardiomyopathy, renal tubulopathy, anemia, hormone deficiencies, muscle weakness, and peripheral neuropathy. Epilepsy phenotypes observed in mitochondrial disease include neonatal refractory status, neonatal myoclonic epilepsy, infantile spasms, refractory or recurrent status epilepticus, epilepsia partialis continua, and myoclonic epilepsy [8]. However, frequently, it is only when multisystem features are present that clinical suspicion of mitochondrial disease is triggered [4].

3. Disease mechanisms underlying mitochondrial epilepsy

3.1. Cerebral energy deficiency and epilepsy

Since a primary function of the mitochondria is to generate the majority of cellular ATP, for decades, it has been assumed that epilepsy in mitochondrial disorders is a consequence of neuronal energy depletion. If this were the sole mechanism underlying 'mitochondrial epilepsy', then it would be logical to assume that all genetic mitochondrial disease would be associated with epilepsy. However, this is far from the case. Theoretically, each of the >250 mutations reported in the mtDNA (www.mitomap.org) should be equally likely to cause epilepsy. Yet, this is not what is observed in clinical practice; rather, there are specific 'hot spots' within the mitochondrial genome that appear to be particularly associated with epilepsy phenotypes. These hot spots include the m.3243A>G mutation present in ~80% of patients with the syndrome of mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) [9] and the m.8344A>G mutation associated with the myoclonic epilepsy, ragged red fibers (MERRF) syndrome [10]. Other hot spots include the *MTND5* gene encoding a subunit of complex I [11] and the *MTATP6* gene encoding a subunit of the ATP synthase (complex V) [12]. Mutations in both of these genes are associated with Leigh syndrome (subacute necrotizing encephalomyelopathy) presenting with infantile spasms [13]. In addition, *MTND5* mutations are another cause of MELAS [11]. Furthermore, only a fraction of the >200 nuclear gene defects linked to human disease are associated with epilepsy (Fig. 1). These observations argue against neuronal energy depletion being the unifying cause of all mitochondrial epilepsy. Other mechanisms need to be invoked.

3.2. Oxidative stress and epilepsy

It has been suggested that ROS are integral to the pathogenesis of epilepsy both in primary mitochondrial diseases and in acquired epilepsy [14]. Furthermore, production of superoxide preceded ATP depletion in an astrocyte model in which the respiratory chain was partially inhibited by nitric oxide, suggesting that ROS generation may be more important than disruption of energy metabolism in the development of mitochondrial disease [15]. Natural antioxidant defense mechanisms present inside the mitochondria include CoQ_{10}, ascorbate, and manganese superoxide dismutase (MnSOD). The group led by Manisha Patel has shown that overexpression of the *Sod2* gene encoding MnSOD can protect mice against kainic acid-induced seizures, while mice with partial knockdown of *Sod2* were more susceptible to developing seizures following kainic acid administration [16]. Recently, the same group has shown that pharmacologically scavenging ROS can attenuate seizures in mice with a forebrain specific conditional deletion of *Sod2* and that ROS production drives mitochondrial bioenergetic dysfunction in isolated hippocampal synaptosomes from a rat model treated with kainic acid [2].

Further evidence linking oxidative stress to epilepsy comes from studies of 3-hydroxyisobutyryl-CoA hydrolase (HIBCH) deficiency, a disorder of mitochondrial valine degradation. Mutations in *HIBCH* lead to a severe neurodegenerative disorder, often with prominent seizures, which may be associated with multiple OXPHOS enzyme deficiencies

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