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Mitochondrial Dysfunction and Refractory Epilepsy

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Editorial

Mitochondries helps on important functions, like the generation of Adenosine Triphosphate (ATP), metabolites and neurotransmitters biosynthesis, calcium homeostasis, cell death control, and they are the production site of Reactive Oxygen Species (ROS). This one, causes mitochondria to be particularly vulnerable to oxidative damage, they can play a critical role in neuronal excitability control and on susceptibility to crises associated with acquired epilepsy [1].

The ROS function is being the second messenger in signal transduction and also they are oxidative damage and inflammation mediators. There's a small group of hereditary epilepsies that present this kind of neurological disorder, such as the Myoclonic Epilepsy with Ragged Red Fibers (MERRF) and the mitochondrial encephalopathies. However, acquired epilepsies with mitochondrial dysfunction represent approximately 60% of all cases.

Temporal Lobe Epilepsy (TLE) is the greatest example of acquired epilepsy. Acquired epilepsy is often started by a brain injury (skull trauma, hypoxia, febrile crisis or epileptic status) and is continued by a "latency period" by which there are produced complex molecular cellular alterations, biochemical, physiological and structural changes in the brain, which produces a chronic epilepsy [2,3].

There are several endogenous antioxidants and overlapping to overcome the normal cell production of reactive species, however, the excessive production of ROS and Reactive Nitrogen Species (RNS), can overwhelm the antioxidant defences, change the redox state of the local cell medium and produce oxidation of the vulnerable cell objects [4].

Mitochondrial dysfunction and oxidative stress arise as probable factors that occur not only acutely, but also as factors that can contribute to epileptogenesis and chronic epilepsy. There is evidence linking oxidative stress to the initiation and progression of epilepsy in experimental models. The oxidative stress can be triggered by epileptic seizures. The intense activity of the seizures, such as those produced in animal models, can give place to cytotoxic effects mediated by oxidative stress [5].

A central oxidative stress mediator is the cellular superoxide anion (O^{2-}), which influences both physiological and pathological processes [6,7]. Increased consumption of intracellular glucose and metabolism has been found. Cerebral Blood Flow (CBF) is increased, as well as lactate, due to a higher glycolysis rate, exceeding pyruvate utilization. While this hyper-metabolism occurs on epileptic focus during the crisis, there's a prominent hypo-metabolism during interictal episodes [7].

Detailed mechanisms by which mitochondria controls the acute injuries, induced by acquired epileptic crisis as in ELTL, have not been fully elucidated. The overproduction of mitochondrial Superoxide Radicals (O^{2-}) in epileptic crisis, can cause through Fenton's reaction (advanced oxidation process in which highly reactive Hydroxyl Radicals (OH-) are produced) higher amounts of ROS, such as the Hydroxyl Radical (OH-), in the presence of Cu^{2+} and Fe^{2+}, which easily oxidizes proteins, lipids and Deoxyribonucleic Acid (DNA), potentially altering neuronal excitability and lowering the seizure threshold during epileptogenesis [8].

The brain is especially vulnerable to damage induced by oxidative stress, due to a large number of mitochondria, a high level of lipids and oxidizable metals, high oxygen consumption and a lower antioxidant capacity than other tissues. All these brain characteristics cause a greater amount of oxidative stress, which can be an important contributor in neurological diseases such as epilepsy [2].

An important and immediate consequence of oxidative stress can be neuronal death. The crisis induced by neuronal death in vulnerable brain regions is a specific model and depends on age development [9] and the genetic background of animals [10,11].

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This neuronal death can be due to three probable causes. In first place, as a result of epileptic status, which increases the oxidation of cellular macromolecules before the death of vulnerable neurons and the increase of certain compounds that possess antioxidant properties such as Superoxide Dismutase (SOD) mimetics, vitamin C and melatonin, that could prevent the crisis induced by neuronal death [8,12-15].

In second place, oxidative stress could be an important consequence of excitotoxicity, which plays a fundamental role in epileptic brain damage. Third, the neuronal death induced by epileptic crisis, involves calcium overload, as well as necrosis and apoptosis, all of which are controlled by mitochondrial function and oxidative stress [16-18].

That's how, a central oxidative stress meter is the cellular Superoxide Anion (O^{2-}) [6] and this is a main physiological resource of the mitochondria [2]. Hydrogen Peroxide (H_2O_2) is formed when oxygen is generated due to a rapid conversion of H_2O_2 by the SOD enzyme. The H_2O_2 conversion to H_2O can be accomplished by catalase and glutathione Peroxidase (GPx). The cytotoxic mechanism by which ROS induced neurological damage may involve direct oxidative damage to cellular molecules (proteins, lipids, DNA, and carbohydrates) and the chain reaction propagation of free radicals [19,20].

Lipid peroxidation is relevant in the brain due to its high content of Polyunsaturated Fatty Acids (PUFAs) and the oxidation causes them to be more hydrophilic, altering the structure of the cell membrane with resulting changes in its fluidity and permeability [21]. ROS damage to DNA through an oxidative mechanism produces 8-oxo-7,8-dihydro-2 'Deoxyguanosine (8-oxo-DG), which is a generalized cellular oxidative stress biomarker [2].

In clinical practice, in patients with chronic epilepsy (such as patients with TLE), oxidative loss has been detected with increased markers of oxidative damage and significant changes in the activity of antioxidant enzymes, even surgical resection of the epileptic focus leads to a normalization of oxidative stress markers on drug- resistant epileptic patient's serum [22].

Mitochondrial dysfunction has been proposed as an important factor in the pathogenesis of refractory or difficult-to-control epilepsy. Generally, there are several potential pathways for mitochondrial dysfunction during epilepsy, which may contribute to increased hyper excitability. The two main pathways in mitochondrial oxidative stress and increased neuronal excitability are bioenergetics failure and its full utilization [23].

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