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MITOCHONDRIAL DYSFUNCTION, OXIDATIVE STRESS & EPILEPSY: A MYSTIFYING TRYST

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ABSTRACT

Mitochondrial dysfunction and oxidative stress are two interdependent and interconsequent underplaying phenomenon's which play a critical role in majority of disorders, irrespective of their biochemical pathways and clinical pathologies. Oxidative stress induced mitochondrial dysfunction (and vice versa) has been implicated in pathogenesis of epilepsy too. Epilepsy, a neurological disorder is characterized by the repeated occurrence of seizures due to persistent abnormality in brain circuitry/wiring, an imbalance in inhibitory and excitatory neurotransmitters or some combination of these factors. Primary epilepsy (50%) is idiopathic (unknown cause) and secondary epilepsy (50%), referred as acquired epilepsy, may result from a variety of conditions including trauma, anoxia, hypoxia, metabolic imbalances, tumors, encephalitis, viral infections, drug withdrawal and neurotoxicity. Mitochondrial dysfunction induced oxidative stress increases the cytosolic content of calcium in the cytoplasm through a combination of effects on calcium pumps and membrane integrity. Oxidative stress also affect plasma membrane Ca2+-ATPase, sarco/endoplasmic reticulum ATPase, the IP3 receptor, ryanodine receptors, store-operated calcium entry through Orai channels and voltage-gated calcium channels. In this review, the evidences suggest the role of oxidative stress and mitochondrial dysfunction as consequences of injuries to incite chronic epilepsy and resultant neuropathological changes and present work strongly advocates mitochondrial dysfunction and oxidative stress as the viable and potential therapeutic target in treatment of epileptogenic syndrome.

KEY WORDS

Epilepsy, Mitochondria, Oxidative stress.

INTRODUCTION

1. Epilepsy

Almost 50 million people worldwide have epilepsy and approximately 2.4 million people are newly diagnosed with epilepsy each year [1]. However, despite over 20 antiepileptic drugs being available, seizures remain uncontrolled in about 30% of patients [2]. Epilepsy (in Ancient Greek ἐπιλαμβάνειν, meaning literally to seize, possess, or afflict) is one of the most common serious neurological disorders. It encompasses a group of such disorders characterized by seizures or vigorous shaking that can be brief and nearly undetectable or last for long periods of time. Epileptic seizures have no immediate underlying cause, some occurring as the result of brain pathology (injury, stroke, tumors and infections), genetic mutations, or birth defects through a process known as "epileptogenesis" with a long term risk of recurrent seizures depending on the part of the brain affected and on the person's age. They are the result of excessive and abnormal nerve cell activity in the brain cortex [3].

Hugh lings Jackson defined epilepsy as a group of disorders characterized by excessive and paroxysmal neural discharges causing sudden alteration in neurological functions. Epilepsy refers to recurrent seizures and repeated occurrence of sudden, excessive and synchronous discharges in cerebral cortical neurons resulting in disruption of consciousness, sensation,

movements and impairment of mental functions or some combination of these signs. Because of their sudden nature, seizures are called ictal events, from the Latin ictus meaning 'to strike'.

The epileptogenic zone is where the seizures actually begin, and this area is usually in or near the epileptogenic lesion (trauma, injury, infection etc.). The function of nerve cells and their circuits in the epileptogenic zone are fundamentally altered, and some even destroyed. During an epileptic seizure, neurons in the epileptogenic zone begin to discharge hyper synchronous electrical signals at an excessively high rate and/or in an abnormal pattern. An epileptic seizure originate only in certain structures of the brain (e.g. the cerebral cortex and amygdala) but may then spread to other parts of CNS (e.g. the basal ganglia)[4].

The terms epilepsy, seizure and convulsion are not synonymous. A seizure always is a symptom of abnormal function in the central nervous system rather than a disease in itself. A seizure discharge is initiated in an entirely normal cerebral cortex by a variety of acute insults while epilepsy is a chronic condition in which seizures occur repeatedly due to an underlying brain abnormality which persists between seizures. A convulsion is a forceful involuntary contraction of skeletal muscles and is a physical manifestation of a seizure and the term is inappropriate as a synonym for epilepsy when epilepsy consist only of a temporary alteration of consciousness or sensation [5].

Epilepsy exists when someone has an epileptic seizure and their brain "demonstrates a pathologic and enduring tendency to have recurrent seizures" [6]. More specifically, epilepsy is diagnosed when an individual has: 1) at least two unprovoked or reflex seizures>24 h apart, 2) one unprovoked or reflex seizure and a probability of having another seizure similar to the general recurrence risk after two unprovoked seizures (≥60%) over the next 10 years, or 3) an epilepsy syndrome [6,7].

Approximately, 50 million individuals worldwide have a diagnosis of epilepsy and the prevalence is much higher in developing countries than in developed countries owing to low economic status and limited access to health care [8]. Epilepsy affects up to 1% of the population, making it second to stroke as one of the most common serious neurological disorders. About, 100 million people will have at least one epileptic seizure during their lifetime and it causes serious physical, psychological, social and economic consequences [9].

1.1 Classification

According to modern classification, two broad categories of epilepsy are recognized depending upon whether the entire brain (generalized seizure) or only a restricted part of the brain (partial seizure) is involved in the discharge at its onset. Partial seizures beginning in a discrete cortical area are categorized as simple when consciousness is preserved and complex when consciousness is altered.

Simple partial seizures may evolve into complex partial seizures or secondarily generalized tonic–clonic seizures as a result of the spread of abnormal electrical activity. Simple motor seizures result from a discharging lesion in the precentral gyrus of the frontal lobe of the cerebral hemisphere opposite the muscle contractions. Some are sustained (tonic) and others intermittent (clonic), and they involve any body part depending on the location of the abnormal brain discharge.

Complex partial seizures are the predominant seizure type affecting 20% of patients with epilepsy. The terms psychomotor, temporal lobe and limbic system seizure are older terms, all designating a form of partial seizure in which consciousness is altered but not necessarily lost. During these seizures there is a period of altered behavior for which the patient is later amnesic. The amnesia for ictal events is a key factor for the diagnosis of a complex partial seizure. Typical complex partial seizures begin with an 'aura', a sometimes complex psychic experience that may manifests in one or more of a wide variety of vivid forms: as an illusion, hallucination, dyscognitive state or emotional (affective) experience. This usually lasts a few seconds.

Primary generalized seizures (generalized seizures) involve widespread areas of the cerebral cortex while the term secondary generalized seizure, refers to a partial onset seizure that spreads to wide areas of cortex. Convulsive seizures (violent and sustained contractions of muscles) and nonconvulsive seizures (lack of prominent motor activity) are major types of generalized seizures.

Absence (petit mal) seizures occur without warning with a sudden interruption of consciousness characterized by brevity, general lack of motor activity, frequency and lack of a postictal period. The seizures usually last from 2 to 10s, occasionally longer. Patients are unaware of them and an observer may interpret an absence as a moment of daydreaming. The person stops talking

briefly in mid sentence, stares, or stops responding. As many as several hundred such seizures may occur in 1 day. Absence seizures almost always begin in childhood or adolescence. They often disappear before adulthood, presumably because of the biochemical or structural changes associated with brain maturation. When they occur with high frequency in school, they often lead to poor performance. Atonic seizures (drop attacks) are characterized by sudden loss of tone in postural muscles. In a mild variant only the head drops while in the severe form, all of the postural muscles lose tone, and the patient suddenly collapses to the ground.

2. Neuropathology of epilepsy

Action potential is the basic mechanism of neuronal excitability. A hyper excitable, pathological state result from the increased excitatory synaptic neurotransmission decreased inhibitory neurotransmission, an alteration in voltage-gated ion channels, or an alteration of intra- or extra-cellular ion concentrations in favor of membrane depolarization. This state also result when several synchronous sub threshold excitatory stimuli occur, allowing their temporal summation in the post synaptic neurons.

Action potential occurs due to depolarization of the neuronal membrane, with membrane depolarization propagating down the axon to induce neurotransmitter release at the axon terminal. The action potential occurs in an all-or-none fashion as a result of local changes in membrane potential brought about by net positive inward ion fluxes. Neurotransmitters, released by the presynaptic nerve terminal at a synapse subsequently bind to specific postsynaptic receptors for that ligand. Ligand binding results in channel activation and passage of ions into or out of the cells. The major excitatory neurotransmitter is glutamate and there are several subtypes of glutamate receptors. Glutamate receptors can be found post-synaptically on excitatory principal cells as well as on inhibitory interneuron's and have been demonstrated on certain types of glial cells. The ionotropic sub classes are the AMPA, kainate receptors and N-methyl-D-aspartate (NMDA) which allow ion influx upon activation by glutamate. They are differentiated from one another by cation permeability as well as differential sensitivity to pharmacological agonists/antagonists. All ionotropic glutamate receptors are permeable to Na^+ and K^+, and it is the influx of Na^+ and outflow of K^+ through these channels that contribute to membrane depolarization and generation of the action potential. The NMDA receptor also has a Ca^{++} channel that is blocked by Mg^{++} ions in the resting state, but under conditions of local membrane depolarization, Mg^{++} is displaced and the channel becomes permeable to Ca^{++} influx of Ca^{++}tends to further depolarize the cell, and is thought also to contribute to Ca^{++} mediated neuronal injury under conditions of excessive neuronal activation (such as status epilepticus and ischemia), potentially leading to cell death through excitotoxicity.

GABA is the major inhibitor neurotransmitter having 2 major subtypes: GABA A and GABA B. GABA A receptors are found post-synaptically, while GABA B receptors are found pre-synaptically, and can thereby modulate synaptic release. In the adult brain, GABA A receptors is permeable to Cl^- ions; upon activation Cl^- influx hyperpolarizes the membrane and inhibits action potentials. Therefore, substances which are GABA A receptor agonists, such as barbiturates and benzodiazepines, are well known to suppress seizure activity. GABA B receptors are associated with second messenger systems rather than Cl^- channels, and lead to attenuation of transmitter release due to their presynaptic location.

Normally, when a synchronous discharge begins, neurons within the focus usually possess properties which try the discharge from spreading further to adjacent neurons. This inhibitory surrounding is controlled by inhibitory neurons that use the transmitter GABA. As the abnormal discharge remains confined to the focus, it is incapable of producing any behavioral symptoms. Because pharmacological blockade of GABA mediated inhibition can trigger interictal discharges that may lead to ictal events, a convincing hypothesis emerges that epileptic seizures are the result of decreased synaptic inhibition and augmentation of the NMDA type of excitatory glutamate receptor.

Seizure propagation, the process by which a partial seizure spreads within the brain, occurs when there is sufficient activation to recruit surrounding neurons. This leads to a loss of surround inhibition and spread of seizure activity into contiguous areas via local cortical connections, and to more distant areas via long association pathways such as the corpus callosum. The propagation of bursting activity is normally prevented by intact hyper polarization and a region of surrounding inhibition created by inhibitory neurons. With sufficient activation there is a recruitment of surrounding neurons via a number of mechanisms.

Repetitive discharges lead to: 1) an increase in extracellular K^+, which blunts the extent of hyperpolarizing outward K^+ currents, tending to depolarize neighboring neurons; 2) accumulation of Ca++ in presynaptic terminals, leading to enhanced neurotransmitter release; and 3) depolarization induced activation of the NMDA subtype of the excitatory amino acid receptor, which causes more Ca^{++} influx and neuronal activation. Of equal interest, but less well understood, is the process by which seizures typically end, usually after seconds or minutes, and what underlies the failure of this spontaneous seizure termination in the life-threatening condition known as status epilepticus. The burst firing associated with prolonged epileptic discharges could lead to activation of glutamate receptors, changes in composition of glutamate and γ-amino butyric acid receptor, cytokine activation, oxidative stress, neoneurogenesis, changes in plasticity or activation of some late cell death pathways [10].

Initially there is structural, physiological and biochemical changes, such as altered cerebral blood flow and vasoregulation, disruption of the blood brain barrier, increased intracranial pressure, and disruption of fiber tracts and blood vessels.

2.1. Oxidative stress and epilepsy

Oxidative stress is a state where the balance between the oxidative reactions and the biological antioxidant potential is upset by excessive production of reactive oxygen species (ROS) and free radicals, resulting in an excessively oxidized state exerting harmful effects *in vivo* [11]. It has also been demonstrated in recent years that such enhanced oxidative stress brought about by excessive production of ROS and free radicals results not only in the acceleration of aging, but also various other diverse disorders [12,13].

ROS seem to be an important factor involved in endothelial dysfunction, diabetes, atherosclerosis and ischemia and RNS in arthritis, diabetes, degenerative neuronal diseases, cancer and atherosclerosis etc. A widely debated yet convincing concept in pathogenesis of epilepsy is involvement of oxidative stress and the two main types of free radical species are reactive oxygen species (ROS) and reactive nitrogen species (RNS) [14].

The moderate level of ROS and RNS required for maturation of cellular structures, can act as weapons for the host defense system and phagocytes release free radicals to destroy invading pathogenic microbes. ROS and RNS also have physiological roles in the regulation of intracellular signaling cascades in various types of nonphagocytic cells including fibroblasts, endothelial cells, vascular smooth muscle cells, cardiac myocytes, and thyroid tissue. Another beneficial activity of free radicals is the induction of a mitogenic response. In brief, ROS/RNS at low or moderate levels are vital to human health [15]. Oxidative stress results when the steady-state balance of prooxidants to antioxidants is shifted in the direction of the former, creating the potential for organic damage. Prooxidants are by definition free radicals, atoms, or clusters of atoms with a single unpaired electron [16].

The CNS has extraordinary metabolic rate consuming approximately 20% of all inhaled oxygen at rest and accounts for 2% of body weight [17]. This enormous metabolic demand is due to the fact that neurons are highly differentiated cells and need large amounts of ATP in order to maintain ionic gradients across cell membranes and for neurotransmission. Since most neuronal ATP is generated by oxidative metabolism, neurons depend critically on mitochondrial function and on oxygen supply [18, 19].

Mitochondria are the main site of ROS production and are therefore extremely vulnerable to oxidative damage [20]. Approximately 90% of all oxygen in a cell is consumed in the mitochondrion, especially in the inner membrane where oxidative phosphorylation occurs. Oxygen is involved in the oxidation of organic compounds and the production of energy for cell metabolism. However, only a very small amount of consumed oxygen (between 2 and 5%) is reduced, which leaves a variety of highly reactive chemicals ROS and RNS. The production of free radicals is associated with damage caused to cell structures and the pathogenesis of central nervous system (CNS) conditions, such as Parkinson's disease, stroke, dementia, and epilepsy [21].

Membrane lipids which contain unsaturated fatty acids are particularly sensitive to oxidative stress, and peroxidation of the membrane lipids leads to a disturbance of the membrane integrity. The normally damaged membranes are repaired and one important repair mechanism is reacylation of the phospholipids in the membrane. There are reports that lipid peroxidation inhibits this reacylation process [22].

The increased generation of free radicals or reduced activity of antioxidant mechanisms cause some forms of epilepsy and, in addition, increases the risk of seizure

recurrence. On the other hand, there are several experimental and clinical studies showing that seizure results in free radical production and oxidative damage to proteins, lipids and DNA. Furthermore antioxidants are found to reduce the seizure manifestations and the accompanying biochemical changes (i.e., markers of oxidative stress), further supporting the role of free radicals in seizures [23].

Cell death in epilepsy is triggered by a cascade of events with calcium overload through NMDA receptors and subsequent excess ATP consumption to restore calcium homeostasis, representing the major initial hits to cell homeostasis. Both events are linked to an increase in enzymatic ROS production, with NMDA receptor opening triggering ROS production through NADPH oxidase and ATP depletion feeding ROS production through xanthine oxidase given that breakdown of ATP in situations of high energy demand leads to increases of ATP metabolites which are substrates of xanthine oxidase [24].

ROS, disrupt Ca homeostasis, increasing its intra-cellular content, over stimulating Ca signaling pathways which causes increased ATP consumption that will produce energy depletion and increased cell death, through both necrosis and apoptosis. Furthermore, high Ca concentration in the epileptic neurons remains elevated during the chronic epilepsy phase and plays a role in the maintenance of spontaneous recurrent seizures. It can alter GABA A receptor recycling and can also increase the extracellular release of glutamate which is a major contributor to oxidative stress development. Furthermore, astroglial and neuronal glutamate transporters, which are important to maintain low levels of synaptic glutamate, are extremely sensitive to oxidative stress [25, 26].

Mitochondria are important players in maintaining cell Ca homeostasis and serve as Ca buffer. Physiological increases in mitochondrial Ca^{2+} lead to the activation of tricarboxylic acid (TCA) cycle enzymes including isocitrate dehydrogenase, α-ketoglutarate dehydrogenase, maleatedehydrogenase, as well as succinate dehydrogenase resulting in increased concentrations of reduced substrates for oxidative phosphorylation (NADH and FADH2). Therefore, physiological increase in mitochondrial Ca results in enhanced respiratory chain activity, increased proton pumping and consequently generation of ROS. The reciprocal interaction between Ca modulated ROS production and ROS modulated Ca signaling underlies the concept of ROS and Ca crosstalk. Moreover, Ca can activate nitric oxide synthase, generate nitric oxide which inhibits complex IV, which lead to ROS production at the Q 0 site of complex III. Nitric oxide has also been shown to elicit synaptic glutamate release and therefore contribute to further excitotoxicity in neighboring cells. During the injury phase of seizures, Ca concentration may reach high levels and if concentrations are moderately elevated, neurons are subjected to long lasting neuroplasticity changes. However, in case of very high Ca concentrations, cell death is induced. Ca concentration remains elevated during the latest phase. Therefore, many second messenger effects, which can produce long-lasting plasticity changes in these neurons and maintenance of the spontaneous recurrent seizures. It can alter GABA A receptor recycling which can serve as a possible mechanism for the effect of Ca on altering neuronal excitability. The increased intracellular Ca concentration also affects numerous cell physiological processes, including gene transcription, protein expression and turnover, neurogenesis, neuronal sprouting and cell signaling.

Free radicals also trigger disruption of nucleic acids, break DNA strands or directly modify purine and pyridine bases, which leads to deletions and other mutations. DNA damage activates the DNA repair enzyme poly-ADP- ribose polymerase-1 (PARP-1), which over activation depletes its substrate, nicotinamide adenine dinucleotide (NADH), slowing the rate of glycolysis, electron transport, and ATP formation, eventually leading to functional impairment or cell death[25].

2.2 Mitochondrial Dysfunction

Hypotheses link mitochondrial failure to seizure generation through changes in calcium homoeostasis, oxidation of ion channels and neurotransmitter transporters by reactive oxygen species, a decrease in neuronal plasma membrane potential, and reduced network inhibition due to interneuronal dysfunction [27].

The mitochondria have critical functions including regulation of neuronal excitability, fatty acid oxidation, excitotoxicity, apoptosis, necrosis control, amino acid cycle regulation, biosynthesis of neurotransmitters and regulation of cytosolic calcium. The best known of these functions is ATP generation by the oxidative phosphorylation system and generation of reactive oxygen species [28].

Mitochondria are unique amongst cellular organelles as they have their own genetic material, the small (16.6kb), circular mtDNA molecule. The 37 mitochondrial genes encode 13 proteins which are integral components of the mitochondrial respiratory chain and 24 RNA molecules necessary for the intra-mitochondrial synthesis of these 13 proteins. Correct coordinated expression of the 13 proteins encoded by the mitochondrial genome is essential for efficient mitochondrial energy production, and also requires the contribution of many of the nuclear-encoded proteins that constitute the mitochondrial proteome [29].

Mitochondrial proteins are modified by carbonylation, nitration, S-Glutathionylation, or S-Nitrosylation. Function of many metabolic enzymes in the mitochondrial extracellular compartment, including ATPase, cytochrome c oxidase, NADH dehydrogenase, and NADH oxidase are altered. Oxidation of adenine nucleotide translocator (ANT) impairs the influx of adenosine diphosphate (ADP) into the matrix for ATP synthesis. Oxidation of manganese superoxide dismutase (MnSOD) can further compromise antioxidant capacity and lead to further oxidative stress. Increased production of ROS directly down-regulates proteins of tight junctions and activates matrix metalloproteinase's that contribute in the opening of the blood brain barrier allowing entry of neurotoxins and inflammatory cells potentiating already existing oxidative stress. Cytochrome c released into the cytoplasm further triggers the complex intrinsic mitochondrial pathway of apoptosis. The cell death pathway may switch between apoptosis and necrosis, depending on the availability of intracellular ATP. Whereas apoptosis is the principal cell death pathway in the presence of sufficient ATP, overwhelming depletion of ATP results in necrotic cell death. In general, mitochondrial Ca^{2+} overload and consequent mitochondrial dysfunction appear to be combining factors in excitotoxicity. They are playing key roles in cell death [25].

Seizures have been reported to occur in 35 to 60% of individuals with biochemically confirmed mitochondrial disease [30] and metabolic and bioenergetic changes occur following acute seizures. Following seizures a significant increase in cellular glucose uptake and metabolism occurs, cerebral blood flow is increased to match this hyper metabolism and that results in increased lactate build up due to the increased rate of glycolysis exceeding pyruvate utilization. While hyper metabolism occurs in the human epileptic foci during seizure events, hypo metabolism is prominent between seizure episodes.

Further, mitochondria are involved in altered neurotransmitter metabolism based on the loss of mitochondrial N-acetyl aspartate in human epileptic tissue [31]. Additionally, severe metabolic dysfunction characterized by biphasic abnormal NAD (P) H fluorescence transients and changes in mitochondrial membrane potential (DSM) have been observed in ex vivo preparations from both chronically epileptic rats and human subjects [18].

Biochemical studies of brain homogenates have revealed decreased ATP concentrations after repeated seizures and seizure-induced energy failure has long been suggested as a reason for clinical sequel in prolonged seizures. However, the mechanisms that result in a failure of neurons to compensate during this period of increased energy demand are unclear. ATP production is closely linked to the mitochondrial membrane potential because the electrochemical proton gradient across the inner mitochondrial membrane is a prerequisite for ATP synthesis. Mitochondrial membrane potential depolarisation reduces the mitochondrial functional capacity for producing ATP and Ca 2+ buffering, and thus leads to mitochondrial dysfunction in various CNS pathologies [32]. Mitochondrial dysfunction during chronic epilepsy is evident by decreased ETC complex I and IV activity, increased complex II activity, and lowered mitochondrial membrane potential measured by rhodamine 123 fluorescence in the hippocampal CA1 and CA3 regions 1 month following pilocarpine-induced SE [33]. These alterations may be attributed to chronic oxidative stress decreasing mtDNA copy number resulting in down regulation of ETC enzymes that they encode. The accumulation over time of oxidative mtDNA lesions and resultant somatic mtDNA mutations resulting from seizure activity could render the brain more susceptible to subsequent epileptic seizures [34].

CONCLUSION

Mitochondrial oxidative phosphorylation being an important source of ATP for neurons influences homeostasis and has control over turnover of intracellular calcium. The dysfunction of mitochondria strongly affects neuronal excitability and synaptic transmission leading to decreased intracellular ATP

levels and changes to the calcium homeostasis which contributes to increased susceptibility to epileptic seizures. Mitochondrial dysfunction and oxidative stress both are closely interrelated to create a vicious cycle, perpetuating mitochondrial dysfunction induced epileptogenesis. ROS production resulting from mitochondrial dysfunction gradually disrupt the intracellular Ca homeostasis making neurons more vulnerable to additional stress, leading to energy failure and neuronal loss. These findings suggest that oxidative stress may be a viable target in treatment of epilepsy yet the role of antioxidants that could scavenge the excessive free radicals needs to be explored.

REFERENCES

1. WHO. Epilepsy fact sheet. http://www.who.int/mediacentre/ factsheets/fs999/en/ (accessed Oct 15, 2015).
2. Asla, P., Wolfgang, L., Annamaria, Vezzani et al., Advances in the development of biomarkers for epilepsy. Lancet Neurol., 2016; 15: 843–56.
3. Alain, LF. Epilepsy: A Review. Current Opinions in Neurological Science. 2017; 1(5): 240-254.
4. Engel J Jr (ed.) 1993. Surgical Treatment of the Epilepsies. New York: Raven Press.
5. Bowman, J., Dudek, F, E., Spitz M. Epilepsy. Encyclopedia of life sciences; 2001.
6. Fisher, R.S., Acevedo, C., Arzimanoglou, A., Bogacz, A., ILAE official report: a practical clinical definition of epilepsy. Epilepsia., 2014; 55 (4): 475–482.
7. Jessica, J., Falco, W., Ingrid, E., Schefferb, R S. Fisher; The new definition and classification of seizures and epilepsy; Epilepsy Research.,2018;139:73–79.
8. Beghi, E., Hesdorffer, D. Prevalence of epilepsy--an unknown quantity. Epilepsia., 2014; 55(7):963-967.
9. World Health Organization, Epilepsy in the WHO Africa Region, Bridging the Gap: The Global Campaign against Epilepsy Out of the Shadows. World Health Organization, Geneva, Switzerland, 2004.
10. Chuang CY. Mitochondrial Dysfunction and Oxidative Stress in Seizure-Induced Neuronal Cell Death. Acta Neurol Taiwan., 2010; 19:3-15.
11. Jones DP. Extracellular redox state: refining the definition of oxidative stress in aging. Rejuvenation Res.2006; 9(2):169-181.
12. Yoshikawa T. Free radicals and medicine. Journal of Kyoto Prefectural University of Medicine., 2011; 120(6):381-391.
13. Masahito, M., Toshiaki, H., Taisuke,K., Shojiro, Kyotani. Impact of Oxidative Stress and Newer Antiepileptic Drugs on the Albumin and Cortisol Value in Severe Motor and Intellectual Disabilities with Epilepsy. J Clin Med Res., 2018;10(2):137-145
14. Iannitti, T., PalmieriB. Antioxidant therapy effectiveness: an up to date. European Review for Medical and Pharmacological Sciences, 2014; 13: 245-278.
15. PhamHuy LA., HeH., Huy PC. Free Radicals, Antioxidants in Disease and Health. Int J Biomed Sci., 2008; 4 (2): 89-96.
16. Stamler, JS., Simon, DJ., Jaraki, O. et al. S-nitrosylation of tissue-type plasminogen activator confers vasodilatory and antiplatelet properties on the enzyme," Proceedings of the National Academy of Sciences of the United States of America., 1992;89(17):8087–8091.
17. Silver, I., Erecinska, M. Oxygen and ion concentrations in normoxic and hypoxic brain cells. Advances in Experimental Medicine and Biology. 1998; 454:7–16.
18. Kann, O., Kovacs, R., Njunting, M., Behrens, CJ., Otahal, J., Lehmann, TN., Gabriel S., Heinemann U.Metabolic dysfunction during neuronal activation in the ex vivo hippocampus from chronic epileptic rats and humans. Brain, 2005; 128:2396–2407.
19. Aguiar, TCC, Almeida, AAB, Ujo PVP, et al. Oxidative Stress and Epilepsy: Literature Review. Oxidative Medicine and Cellular Longevity.2012; article ID 795259,12 pages
20. Waldbaum, S., Liang, LP, Patel, M.Persistent impairment of mitochondrial and tissue redox status during lithium-pilocarpine-induced epileptogenesis. Journal of Neurochemistry, 2010; 115(5):1172–1182.
21. Estevez, AY, Pritchard, S., Harper,K et al. Neuroprotective mechanisms of cerium oxide nanoparticles in a mouse hippocampal brain slice model of ischemia. Free Radical Biology and Medicine, 2011; 51:1155–1163.
22. Zaleska, MM, Wilson, DF. Lipid hydroxyperoxides inhibit the reacylation of phospholipids in the neuronal membranes. J. Neurochem., 1989; 52:255-260.
23. Ercegovac, M., Neboj,J., Tatjana, S., Ljiljana, BB et al. Antiepileptic drugs affect protein, lipid and dna oxidative damage and antioxidant defense in patients with epilepsy. J med biochem, 2013; 32: 121–130.
24. Kovac, S., Albena, T., Kostova, D., Abramov, AY. The Role of Reactive Oxygen Species in Epilepsy. Reactive Oxygen Species, 2016; 1(1):38–52.
25. Martinc, B., Grabnar, I., Vovk, T. The role of reactive species in epilepto- genesis and influence of antiepileptic drug therapy on oxidative stress. Curr Neuropharmacol2012; 10:328-343.
26. Khurana, DS, Valencia, I., Michael,JG., Agustín, L. Mitochondrial Dysfunction in Epilepsy. Semin Pediatr Neurol., 2013; 20:176-187.
27. Zsurka, G et al. Mitochondrial dysfunction and seizures: the neuronal energy crisis. The Lancet Neurology., 2015; 14(9): 956 - 966
28. Rahman S., Hanna MG, Diagnosis and therapy in neuromuscular disorders: diagnosis and new treatments in mitochon-drial diseases. J Neurol Neurosurg Psychiatry., 2009; 80: 943– 53.
29. Rahman S. Mitochondrial disease and epilepsy. Developmental medicine and child neurol., 2012; 54: 397–406.
30. Debray, FG, Lambert,M., Chevalier, I., et al. Long-term out- come and clinical spectrum of 73 paediatric individuals withmitochondrial diseases. Pediatrics, 2007; 119: 722–33.
31. Vielhaber, S., Niessen, HG., Vielhaber, DG., Kudin, AP., Wellmer, J., Kaufmann, J., Schonfeld, MA., Fendrich, R., Willker, W., Leibfritz, D et al. Subfield-specific loss of

hippocampal N-acetyl aspartate in temporal lobe epilepsy. Epilepsia., 2008; 49:40–50.

32. Kovac A., Domijan MA., Matthew C., Walker 1 and Andrey Y. Abramov. Prolonged seizure activity impairs mitochondrial bioenergetics and induces cell death. Journal of Cell Science, 2012; 125(7): 1796-1805.
33. Kudin, AP., Kudina, TA, Seyfried, J., Vielhaber, S., Beck, H., Elger, CE, Kunz, WS. Seizure-dependent modulation of mitochondrial oxidative phosphorylation in rat hippocampus. Eur J Neurosci., 2002; 15:1105–1114.
34. Simon, W., and Patel M. Mitochondrial dysfunction and oxidative stress: a contributing link to acquired epilepsy? J Bioenerg Biomembr., 2010; 42(6): 449–455.

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