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The role of Epigenetic Mechanisms in Causing Epilepsy: A review

Shiva Raeisi Dehkordi¹, Mohammadreza Shahmohammadi², Nima Mohseni Kabir²
and Reza Jalil Khoshnod^{2*}

¹Department of Genetics, Faculty of Science, Shahrekord University, Shahrekord, Iran

²Functional Neurosurgery Research Center, Shohada Tajrish Neurosurgical Center of Excellent, Shahid Beheshti University of Medical Sciences, Tehran, Iran

*Corresponding Email: drkhoshnoud16@gmail.com

ABSTRACT

Further to genetic changes, epigenetic changes also play a major role in causing epilepsy and they are of great importance. Generally, many genomic positions associated with this disease, genetic products and cell routes that contribute to it are affected by epigenetic mechanisms that demonstrate the major and influential role of epigenetic mechanisms in causing epilepsy. It seems like many epigenetic properties have not been discovered yet. Thus, various studies are required to discover other epigenetic mechanisms, the relationship between these mechanisms and their role in causing various diseases such as epilepsy. In this research, various papers on the important and inhibitory mechanisms of epigenetic and the cases involved in pathogenicity of mechanism of various epileptic syndromes over the period of 2002 to 2016 were extracted from different resources such as PubMed and Science Direct using keywords such as epilepsy and histone. As the current therapeutic medicines are not satisfactory and we need new therapeutic methods and care for patients, thus the present research was conducted in order to discover epigenetic mechanisms with the goal of achieving new and effective medicines. Further study reveals the role of DNA methylation and other epigenetic mechanisms involved in causing epilepsy. Furthermore, epigenetic changes such as the changes following translation of histones' tails and DNA methylation are appropriate goals for new treatments as they are capable of changing compared to genetic factors like mutation. The challenges in this field have resulted in vast researches being conducted on epigenome similar to other engaged mechanisms associated with epigenetics. Epigenetic mechanisms play a major role in the development and growth of the brain. The goal in the future will be to achieve at an epigenetic and general treatment for nervous disorders such as epilepsy. Thus, manipulating epigenetic mechanisms may be the next goal of epilepsy treatment. The side effects of treatment with systematic epigenetic medicines also need to be predicted. Question about how enzymology specifically diagnoses the damaged areas in the brain and targets the selected genes associated with epilepsy is a necessary step to be taken that must be addressed in the future.

Keywords: Epileptic Syndromes, Methylation, Epigenetic.

INTRODUCTION

Epilepsy is one of the most important central nervous system complications and the person suffering from it will experience seizures and convulsions at least twice. This disease is experienced through several convulsions in the brain caused by the excessive stimulation of neurons. This disease has affected nearly 60 million people all around the world and nearly 1% of the American population. Inheriting epilepsy is mostly a multi-factorial issue pointing to

the fact that both the genetic and environmental factors work together. Epilepsy is a heterogeneous clinical disease and those suffering from it feel that their life is disrupted in terms of mental and social factors, convulsion and other side effects of treatment [1, 2]. All these factors result in epilepsy becoming a heavier burden. Losing capitals is really heavy social burden which is well over 15 billion dollars a year. Thus, a solution is required to address the sufferers, care takers and doctors [3]. The peak of the expenditures for epilepsy is in the first year following the diagnosis as the level of treatment response and the level of disease differs based on the intensity of disease [4]. The annual occurrence of epilepsy is 50 out of every 100 thousand people and its frequency is 700 out of 100 thousand. Identifying those suffering from epilepsy and providing them with affordable cares in countries with limited resources is a great challenge for both epilepsy and those providing health services [5]. Thus, we may consider epilepsy a multi-dimensional disease which requires a comprehensive approach [6]. Further to mutation of genes encoding genetic factors, genetic changes in genes encoding epigenetic factors or changes taking place in the expression of performance of these factors result in epilepsy. Changes in the performance of epigenetic factors is associated with unnatural epigenetic symptoms. These symptoms affect the genomic position associated with disease, genetic products, and cell routes [7]. As various cells of animals reach a distinguished state, the structural pattern of genome in that cell and the cells derived from it will remain unchanged. Epigenetics is the term utilized to refer to the study of such processes [8]. Generally, various epigenetic mechanisms such as chromatin changes and DNA methylation are the mechanism that program genes. Thus, the role of epigenetic mechanisms is not limited to merely expressing or turning genes off, but it gives us some information regarding where, when and how these genes are expressed. The adjusted expression of genes using epigenetic mechanisms and disruption of their molecular route may be an effective factor in causing developmental diseases [9]. Today, the genes associated with the developmental disorders of the brain which are also correlated with epilepsy have also been discovered [10]. Thus, epigenetic mechanisms have been identified in several human epilepsy syndromes. The danger of getting afflicted with epilepsy due to infection depends on many factors such as infection agents, age, genetic factors, brain damage intensity, and many other variables of which we have limited knowledge still. Many regulating key performances caused by epigenetic changes for RNA messenger molecules have been discovered recently.

MATERIALS AND METHODS

The information required for this review study was provided by the researches related to the role of epigenetic factors in epilepsy over the period of 2002 to 2016. In order to search for these studies, keywords such as epigenetics, methylation, epilepsy, and histone were used. As the current therapeutic medicines are far from being satisfactory and a need to come up with new therapeutic and caring method for these patients is felt more than any time before, this research attempted to describe the important and regulatory epigenetic mechanisms in order to achieve reliable methods by evaluating the previous researches conducted in this field. We also studied the recent discoveries made about epigenetic mechanisms and other cases involved in the pathogenicity mechanism of various epileptic syndromes, because epigenetic mechanism provide a mechanism through which the environment can reprogram the genomes in a permanent way in order to change the phenotype.

RESULTS

Epigenetic mechanisms including DNA methylation, the factors affecting histone changes and histone varieties (e.g. H2A.Z, H2A.X, and H3), factors influencing the ATP-dependent chromatin structure and non-coding RNA's performance (ncRNAs).

DNA Methylation in a biochemical manipulation of genome methylation

New results were achieved: 1- epigenetic mechanisms play an operational role in epilepsy; 2- the therapeutic reconstruction of epigenome provides us with a really powerful anti-epilepsy treatment [11]. DNA methylation is a dynamic mechanism for development especially in brain. Thus it is necessary for natural development [12]. Also, DNA methylation plays major roles in regulating gene expression which can be correlated to occurrence of epilepsy. Thus it can suppress or activate the performance of gene [13]. DNA methylation is accomplished by DNA Methyltransferase (DNMTs). An example reported for this issue is methylated lysine where S-Adenosylmethionine as a methyl group connects the methyl marked by radioactive materials to the artificial peptide tail of Histone H3 [14]. MECP2 is a protein that connects itself to DNA methyl and abounds in nervous cells. The disorders dependent upon the dominant x are associated with infants' spasm (IS) in girls and other epilepsy-related encephalopathies. Thus, DNA methylation is a major epigenetic change that plays major roles in regulating gene expression through reversible reconstruction of dynamism of chromatin [15]. Analysis of a set of genome DNA methylation patterns in

two different models of convulsion in rodents showed that following epilepsy or resistance to it, major changes take place in DNA methylation [16, 17]. ALKBH3 enzyme removes many methyl marks. This evidence was achieved by studying the adenine methylation in the first position of non-damaged mRNA's [18]. Higher activity of DNA methylating enzymes and DNA hyper-methylation are correlated with development of empirical and human epilepsy (19). It is possible to reverse DNA hyper-methylation in the brain of those suffering from epilepsy by increasing levels of Adenosine for more than 10 days. This will inhibit germination of moss-like yarns in Hippocampus and prevent epilepsy from developing for at least 3 months [20].

Histones

The changes following translation of histones include various factors such as acetylation, methylation, ubiquitination, phosphorylation, ADP - ribosylation and simulation can cause convulsion and, as a result, epilepsy [21, 22]. Due to the genetic failures that target the histone of Methyltransferase, some evidences have been gained to understand the role of histone methylation among the patients suffering from epilepsy, just like mutation in KDM5C which disrupts the activity of REST. REST is an epigenetic regulator for the genes associated with nerves which plays a major role in cases such as nervous development, irritability, and synaptic transmission. Thus the evidences indicate that KDM5C plays a major role in developing epileptic phenotypes [23]. Acetylation of histone is also involved in the process of causing temporal lobe epilepsy (TLE) [24]. Epigenetic moderators play a major role in regulating the expression of gene and determining the fate of nervous cells. One of these reformers is ubiquitin (sumo). Sumo is a short peptide. These small reformer can connect itself to the protein seeking to change performance through a Covalent bond. Thus, the post-translation simulation (PTM) of a change is necessary. It is necessary to point to the fact that both regulating enzymes of histone and the more regular factors of chromatin reconstruction are associated with epileptic disorders. For example, mutation in the second SET of type 1 in gene SETDB1 acts as a transferase histone and plays a role in epilepsy [25]. Rubinstein-Taybi syndrome (RTS) which is diagnosed by mental retardation takes place as result of mutation in the protein encoding gene connected to CREB (CBP) that is a histone acetyltransferase. Acetylases histone -2 and MECP2 are among the proteins reconstructing chromatin that play a major role in memory disorders [26].

The role of RNA's in epilepsy

Non-coding RNA's (ncRNAs) are major products of genome that play a major role in post-translation regulation, development, proliferation, and distinguishing cells [27]. Non-coding RNA's are also involved in pathogenesis of epilepsy and removing the regulations through various mechanisms [27]. Furthermore, certain evidences have confirmed the role of intervening RNA's in the pathogenicity of epilepsy. There are many achievements concerning the changes made in expression of micro RNA in tissues of those suffering from epilepsy. All these accomplishments are indicative of this fact that epigenetic regulations might be vital factors in causing epilepsy. Micro RNA's are post- gene transcription regulators. miR-146A might be involved in pathogenesis of epilepsy as an epigenetic regulators. As miR-146A is associated with interleukin level of -1B (IL), it participates in a regulating mechanism in order to prevent the inflammatory reactions from progressing too much [28]. An ongoing foundation has shown evidences of the important role of miRNA's in inflammation and safety [27]. Brain inflammation is observed so frequently among those suffering from epilepsy. The evidence of this hypothesis that inflammatory procedures might form a common and very important mechanism in the brain of those suffering from epilepsy have been strongly supported [28]. Although these molecular mechanisms that influence pathogenicity of epilepsy are still unclear, there are dozens of evidences indicating that the constant expression of inflammatory genes of the above-said regulations contribute to pathogenicity of epilepsy [28]. It is also necessary to point to the fact that inflammatory medium such as interleukin -1b (IL), pseudo-toll receptors (TLR's) and other factors are involved in development of animal empirical models of epilepsy and those patients suffering from human epilepsy [29]. High expression of TLR4 with t clear implication has been described in occurrence of laboratory and human temporal lobe epilepsy sudden attacks [29]. These TLR's are capable of diagnosing a large scope of danger signals. Thus, TLR's activate inflammatory cascade [29]. Many of the proteins associated with long ncRNA's seem to be the factors changing chromatin. Long non-coding RNA's play a role in different types of nervous disorders or other complications associated with phenotype of convulsion through the epigenetic regulation of gene [29].

Genetic disorders

MBD5 is a protein connecting with DNA methyl with an epigenetic performance in LTP, memory and learning. Mutation in the genes encoding members of MBD protein family such as MBD5 and MBD6 is similarly correlated with developmental nervous complications and epileptic phenotypes with different intensities [30]. The epigenetic performance of CDKL5 is phosphorylation of Mecp2 and DNMT1 proteins. Over the last few years, the relationship

between cyclin-dependent kinase-like 5 (CDKL5) epileptic encephalopathies have been made clear. Diagnosis of encephalopathies is based upon the early commencement of treatment-resistant epilepsy, the clinical aspects of the person suffering from autism, degree of developmental delays, and development and expansion of clinical characteristics such as Rett syndrome [31]. Another gene associated with childhood-onset epileptic encephalopathies (EEOC) is CHD2. This gene has an epigenetic performance as the transformer of chromatin (CHD family) [32]. Mutation in ATRX encodes reconstruction of chromatin of SWI/SNF family. It will finally result in alpha-thalassemia, developmental incapacities and mental disabilities. Alpha-thalassemia/mental retardation caused by mutation in ATRX are associated with epilepsy among 30% of patients [32]. SMARCA4 is another chromatin transformer of (SWI/SNF) family whose function in the central nervous system is Neurogenesis. Mutation in SMARCA2 gene which encodes the ATP-dependent chromatin reconstruction enzyme causes Nicolaides-Baraitser syndrome. This syndrome is associated with epilepsy [32]. RELN gene encodes reelin protein. Reelin is an extracellular matrix protein. This protein is involved in developing the neural communications of brain cortex during embryonic stages and post-delivery synapse formation [33]. Among the patients suffering from temporal lobe epilepsy, DNA methylation may take place in RELN gene promoter. Thus, Reelin is associated with the defect in the frequent immigration of granular layer cells and distribution of granule cells in Hippocampus [33]. The increased methylation in CPA6 gene promoter has been reported among the patients suffering from focal epilepsy and convulsions with fever [33]. On the other hand, CPA6 plays a role in biosynthesis of the internal peptides of nervous system. Reports have shown a relationship between mutations in the form of losing performance in CPA6 and occurrence of convulsion and epilepsy [33]. A cascade of cellular, molecular and nervous system such as activation of initial essential genes (IEGs) causes epilepsy. Some initial essential genes play a role in the more orderly functioning of brain under physiological and pathological conditions [34]. Epigenetic procedures might change under various chemical, physical, nutritive and even mental factors. For instance, circulation of Ketone bodies on the upper space in order to protect brain tissue against therapeutics-resistant epilepsies is well established. Ketone bodies are also really important in brain development (34). Thus, environment and life habits change the genetic expression through epigenetic mechanisms [34]. Crebbp is a transcription co-activator with intrinsic histone acetyltransferase activity. Creb1 plays a role in moderating a large array of cellular procedures such as different expression of GABA A receptor subunits. Understanding the epigenetic regulations of GABAergic nervous receptors lets us discover the therapeutic measures possible for GABA-related nervous disorders [35].

CONCLUSION

Epigenetic mechanisms play a major role in development and formation of brain. Thus our goal in the future would be the epigenetic and comprehensive treatment of nervous disorders such as epilepsy. Although there have been significant discoveries concerning the genetic basis of common epilepsies, there is still no fixed treatment for those suffering from it. Generally speaking, epigenetic regulatory mechanisms act in a coordinated course and play a key role in the development and normal performance of organisms. Thus, manipulating epigenetic mechanisms might be the new goal for epilepsy treatment. The side effects of treatment with systematic epigenetic medicines also need to be predicted. Question about how enzymology specifically diagnoses the damaged areas in the brain and targets the selected genes associated with epilepsy is a necessary step to be taken that must be addressed in the future. To achieve a fruitful life for those suffering from epilepsy, we have to overcome some obstacles. These obstacles have been known for at least 20 years, but slow steps were taken to completely resolve them. Thus, national epilepsy programs are necessary to organize full care and educational, economical support and the research aspects necessary for patients, as these patients have plenty of problems in their job, driving, socio-personal relationships, etc.

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