Epilepsy: GABRB3 Gene and Medical Treatment

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Abstract: Epilepsy is one of the most common central nervous system disorders and chronic diseases on the existing human. By writing this essay, we summarize and combine the genetic level with the macroscopic view of the disease. In definition, epilepsy is described as repeating occurrences of sudden excessive or synchronous discharge in the cerebral cortical neuron that leading to various symptoms, depending on the brain region it affects. So, epilepsy is classified into 4 types, focal epilepsy, complex focal seizures, generalized epilepsy, and combined generalized and focal epilepsy. It is worldwide spread, affecting 50 million people, mostly kids, and elders, and the prevalence was slightly higher in males than females. At the genetic and molecular biology level, a strong association of GABRB3(Gamma-aminobutyric acid receptor subunit beta-3) gene and GABAA receptor it encodes for is shown to epilepsy because of the function of the GABAA receptor is inhibiting nerve impulses, mutation of the GABRB3 gene would psychologically lead to anxiety and restlessness, physically disorders like epilepsy. Based on looking and summarizing the macroscopic aspects of the disease, brain activities, and genetic views, we suggest therapies like CRISPR on the GABRB3 gene would likely to provide treatments for epilepsy in the future.

1 INTRODUCTION

Epilepsy is very time-honored and is with the continuous development of human civilization and development. The earliest descriptions were in texts written in 2000 BC in Akkadian and used in Mesopotamia. Descriptions related to epilepsy also appeared in the many ancient civilizations, such as ancient Egyptian, ancient Babylon, and ancient Greek. In this ancient literature, epilepsy was generally considered as evil spirits or divine punishment. This occult interpretation continued to influence what people thought about epilepsy until the appearance of Hippocrates. Hippocrates raised the first formal description of epilepsy as a kind of disease, and in his classic treatise on the Sacred Disease, he said that epilepsy was not more sacred than any other disease, and it had the same properties as other diseases and some causes of individual diseases. Complete liberation of epilepsy from superstition appeared in the 18th and 19th centuries, although the description that epilepsy is a kind of disease appeared at the Hippocrates times. And the most important progresses that appeared in the 20th century included the invention of electroencephalograph (EEG), the advance in neurosurgery, the discovery of antiepileptic drugs, and the delineation of underlying pathophysiological mechanisms. And because of these progresses, the myth about epilepsy has been shattered, and social acceptance has risen to a new level. When doing a general survey about epilepsy's history, epilepsy is so important that attract scientists and doctors from ancient times to the present constantly explore and try the solutions of the cure of epilepsy. And even now, epilepsy researching is continuing and becomes deeper into the nature of epilepsy. Science seems to be dominated by genetic research and advances in computer and information technology in the 21st century. The future of epilepsy research is researching the gene that causes epilepsy, including the Gamma-aminobutyric acid receptor subunit beta-3 gene (GABRB3 gene). This article would introduce

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epilepsy's basic information, epilepsy-related gene and discuss some new treatment means.

2 INTRODUCTION OF EPILPESY

Epilepsy is a central nervous system disorder that can affect the brain and cause frequent seizures. Epilepsy is a very common neurological and chronic disease but compared with the other similar chronic disease, the patients of epilepsy are more likely to have some physical, social, and psychological problems. By choosing one hundred patients with epilepsy from the neurological outpatient department from two hospitals in Baghdad/Iraq and doing the research, the study showed that most of the patients with epilepsy were threatened by death (88%) and felt fear from epilepsy seizure (77%). More than the half of the sample expressed feeling disappointment after the attack. Moreover, the study showed that 86% of the selected sample were severely affected by the social stigma and 64% of the selected sample thought they were a heavy burden for their family. This series of evidence shows that the psychological combat from epilepsy is very serious and can affect other aspects of life for patients. The patients of epilepsy are difficult to have marriage and children because they are afraid of their children have epilepsy and studies in many countries and cultures have shown that many families still oppose their children marrying epilepsy patients because they believed that the epilepsy patients were unable to meet their social and economic needs roles and obligations.

When a seizure happens, repeated occurrences of sudden excessive or synchronous discharge in cerebral cortical neurons result in a disruption of unconsciousness, disturbance of sensation, movement, and impairment of mental function. It is different between epilepsy and seizures, while epilepsy and seizure are often mixed. A seizure is a single occurrence; however, epilepsy is a neurological condition characterized by two or more unprovoked seizures.

2.1 Types of Epilepsy

Epilepsy has four types: focal epilepsy, complex focal seizures, generalized epilepsy, and combined generalized and focal epilepsy. These four types of epilepsy are identified by various brain positions where sudden excessive or synchronous discharges are repeated. Generalized epilepsy is the seizures happening that involve all areas of the patient's brain; nevertheless, focal epilepsy can appear to involve just the specific area of the brain. And the combined generalized and focal epilepsy is like the suggestion of the name, which is a form of epilepsy, and patients have both generalized and focal seizures. It is very important to identify the types of epilepsy because one medication may treat one specific type of epilepsy well but may worsen another type of epilepsy simultaneously.

2.2 Prevalence of Epilepsy

The prevalence of epilepsy is the proportion of any population affected by epilepsy at a specific time worldwide. The estimated proportion of the general population with active epilepsy at a given time is between 4 and 10 per one thousand people. And epilepsy affects around 50 million people in the world. Moreover, an estimated five million people are diagnosed with epilepsy each year globally. But it is worth noticing that the reported incidence of epilepsy (the rate of new cases in the population) is different between high-income and low-income economies. The incidence of epilepsy in high-income economies is obviously lower than the incidence in low-income economies. In fact, nearly 80% of people with epilepsy live in low-and middle-income countries. However, one study showed that although the incidence of epilepsy is higher in low- and middle-income countries, the lifetime prevalence appears to be roughly the same worldwide. According to a data review, lifetime epilepsy ranged from 3.2 to 30.1 per 1,000 population in high-income economies, from 4.5 to 18.6 in upper-middle-income economies, from 2.5 to 32.1 in lower-middle-income economies, and from 4.7 to 23.3 in low-income economies.

Besides regional differences in income levels, epilepsy prevalence is different by gender, which the prevalence of males with epilepsy is slightly higher than females with epilepsy. The Rochester epilepsy study found that the prevalence of epilepsy was slightly higher in males than females, and the proportion between males and females is about 6.5 to 6.0 per 1000 persons. The reason that causes this condition may be the various prevalence of the most common risk factors in gender and the concealment of the condition in women for sociocultural reasons in certain regions.

2.3 The Symptoms of Epilepsy

The symptoms of epilepsy have a great variety and exist huge differences between them. Overall, epilepsy symptoms mainly include staring at the empty space, temporary confusion, uncontrollable

jerking of limbs, losing consciousness and awareness, and psychically fear, anxiety, or deja vu. However, patients with different types of epilepsy may have some of these symptoms. And even if two patients have the same kind of epilepsy, the symptoms between them may be totally different. For example, generalized tonic-clonic seizures are the most well recognized, also called 'grand mal seizures in the past. When these seizures happen, the first symptom is a sudden loss of consciousness, and then the body would become stiff, followed by jerking of the muscles. And often, patients may turn red or blue, bite their tongue, and lose control of the bladder, but these symptoms vary with each individual. In addition, the symptoms of generalized absence seizures are much milder and briefer than generalized absence seizures, although they belong to generalized seizures. The symptoms of generalized absence seizures involve staring, loss of expression, unresponsiveness, and stopping activity. And sometimes, the patients with generalized absence seizures just show eye blinking or upward eye movements.

2.4 The Risk Factors of Epilepsy

Epilepsy is a complex disease with many causes, and seizures can be led by caused by anything that disrupts the normal electrical patterns of the brain. Epilepsy has no identifiable cause in about half the people with the condition. In the other half, the condition may be traced to various factors, including genetic influence, head trauma, brain conditions, infectious diseases, prenatal injury, and developmental disorders. First, epilepsy is considered a high genetic disease, and under many conditions, epilepsy can be heritable. For example, in idiopathic generalized epilepsy, the first-degree relatives of epilepsy patients have an 8-12% risk of developing epilepsy, which is much higher than the risk in the general genetic component. Then head trauma is related to epilepsy, and the recurrent seizure disorder because of injury to the brain following head trauma is called Posttraumatic epilepsy (PTE). Studies showed that traumatic brain injury makes up about 10-20 % of symptomatic epilepsy in the general population and 5% of all epilepsy. Third, infectious and infestations are one of the most common risk causes for seizures and acquired epilepsy and maybe the most common preventable risk factor for epilepsy worldwide, especially in resource-poor countries. Many types of infectious diseases can develop seizures, ranging from toxoplasma in the newborn, early childhood infection with human herpesvirus (HHV)-6 to Creutzfeldt-Jakob disease (CJD) in the elderly. And seizures maybe just one symptom in some infectious diseases such as neurocysticercosis (NCC). Then, prenatal injury can also result in epilepsy, which is brain damage before babies' birth that could be caused by several factors, such as poor nutrition or oxygen deficiencies. Finally, sometimes epilepsy can have linkage with developmental disorders, such as autism and neurofibromatosis.

2.5 The Brain Activity of Epilepsy

The brain activity of epilepsy is the key to a cure for epilepsy. By researching the brain activity of epilepsy, scientists can know better the mechanism of action of epilepsy, influencing factors, and so on, which provides some new ideas to find the cure methods for epilepsy. Because the brain activity of epilepsy is hard to observe and some moral and ethical barriers and so on, the research of the brain activity of epilepsy is not very rich and impeccable. It is hard to observe the brain activity directly, and scientists have to use some roundabout methods to research the brain activity of epilepsy, for example, using the method that compares with the healthy control group. The main method to detect brain activity is using a series of scientific instruments, such as electroencephalography (EEG), magnetic resonance imaging (MRI), High-density electroencephalography. EEG is used to record the brain's electrical activity, which is also the most common and basic method of detecting epileptic activity. But although EEG has high temporal resolution and sensitivity, it is less spatial resolution and is not sensitive to an activity deep in the brain. Moreover, EEG can only detect abnormal signals when the seizure happens, so EEG also has some imperfections. MRI is often used cooperatively with EEG to make the detection method more impeccable because of its better spatial resolution. To be sum, these are only short-term brain activities.

2.5.1 Short-term Brain Activity

The brain activity of epilepsy researching can be divided into short-term changes and long-term changes. The most obvious brain change for short-term brain activity is the repeated occurrences of sudden excessive or synchronous discharge in the cerebral cortical neuron. These discharges can be detected by EEG and be used to help doctors make a diagnosis of epilepsy. The EEG of epilepsy which is different from normal EEG, is called epileptiform discharge, and it occurs in up to 98% of patients with epilepsy depending on age and epileptogenicity. The

patterns of the epileptiform discharges are considered to have the following types: spikes, sharp waves, benign epileptiform discharges of childhood, spike-wave complexes, slow spike-wave complexes, 3-Hz spike-wave complexes, polypiles, hypsarrhythmia, seizure pattern, and status pattern. Although epileptiform discharge has many patterns, the epileptiform discharge has no objective definition, and even experienced electroencephalographers sometimes feel confused about the diagnosis of epileptiform.

2.5.2 Long-Term Brain Activity

For long-term brain changes of epilepsy, epilepsy can alter patients' neuromagnetic activities and brain network in the high-frequency ranges. These alterations become more pathological as the duration of epilepsy grows longer. According to new research led by the UCL Institute of Neurology and the Keck School of Medicine of USC, the team found reduced grey matter thickness in parts of the brains' outer layer and reduced volume in subcortical brain regions in all epilepsy groups when compared to the control group. And from a study of children's epilepsy, seizures alter brain functions by over activating, interrupting, or destroying vital networks of brain activity. It is clear that epilepsy has profound effects on the developing child's brain. About half of children with epilepsy experience learning difficulties, especially those involving problems with attention and memory.

3 EPILEPSY AND THE GAMMA-AMINOBUTYRIC ACID RECEPTOR SUBUNIT BETA-3 GENE (GABRB3 GENE)

In the molecular neurobiology domain, well-known disorders like autism spectrum disorder (ASD), bipolar disorder, and schizophrenia disorder are proved to have a strong relationship with mutation of genes of neurological structures like some neurotransmitters and synaptic receptors that influence not only mental aspects but also the ability to coordinate and movements. In the case of epilepsy, the most related gene is the Gamma-aminobutyric acid receptor subunit beta-3 gene.

3.1 The Gamma-Aminobutyric Acid Receptor Subunit Beta-3 Gene and the GABAA Receptor

Research and studies have shown that the mutation of the Gamma-aminobutyric acid receptor subunit beta-3 gene and the protein it codes for have a significant association with many neurodevelopmental disorders other than Epilepsy, like Angelman syndrome and autism. By analysing this particular gene and protein, more treatments and therapies could be found to aim at those common disorders that this gene involved in.

Going back to the mid-1950s, researchers and experimenters had made dozens of efforts on gamma-aminobutyric acid in both humans and animals' brains, and how some available drugs like benzodiazepines and barbiturates (function as enhancing the currents of GABAA receptor) which could affect GABAA receptor that it is one of the most common prolific targets for therapeutic.

3.2 The GABRB3 Gene

The belief that the GABRB3 gene is associate with epilepsy and childhood absence epilepsy (CAE) originated from the team of Lydia Urak, who analysed this gene's single nucleotide polymorphisms (SNPs) in particular exons. They tested 45 patients of CAE in the Medical University of Vienna, and the results showed that the strong association of CAE with 13 single nucleotide polymorphisms in the GABRB3 gene, from exon 1a promoter to the beginning of intron 3 among 45 subjects. The GABRB3 gene is located at chromosome 15, region q12 of the human genome. It has 10 exons in its coding region, and since the alternative splicing, the GABRB3 gene could code for various other protein isoforms that are subunits of the GABAA receptor.

GABRB3 gene is frequently expressed in the human brain during the proliferation and differentiation of human embryonic developments. In contrast, it is not expressed in the adult brain extensively except the hippocampus.

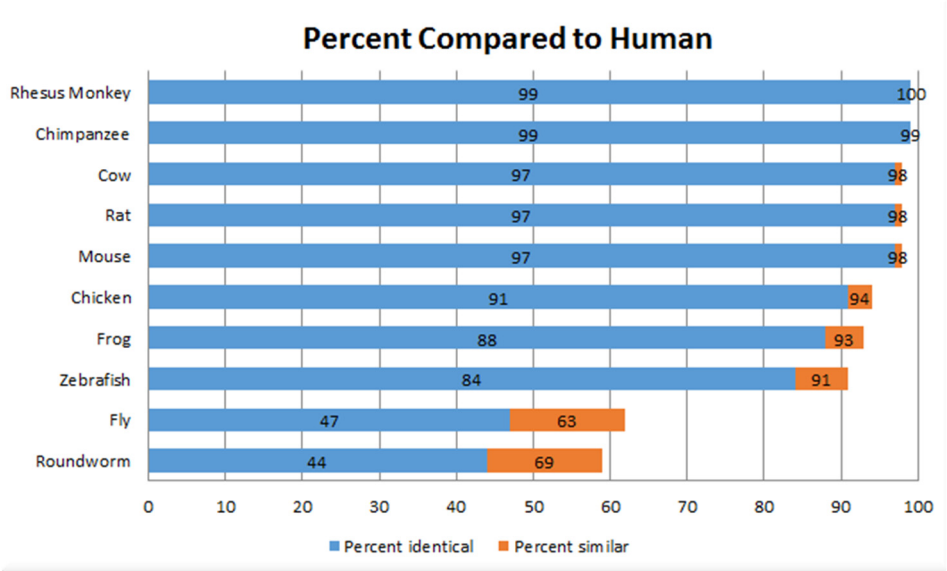

Figure 1: Conserveness of GABRB3 protein across different species and the sharing similarities.

3.3 The GABRB3 Protein

Studies have shown that the GABRB3 protein is conserved among various species. Most other mammals and vertebrates' gene models are similar to humans, k, some even have identically matched over 90%, especially the Chimpanzee and Rhesus monkeys. This illustrates the importance of this gene that the protein it encodes is necessary for the neuronal growth of the Craniata species and animals in lower classes. There are over 10 types of subunits combined to form a chloride channel (for example, GABAA receptor), and the GABRB3 protein is one of those, which will be discussed in detail in the next chapter.

3.4 The GABA and the GABAA Receptor

The Gamma (γ) -aminobutyric acid (GABA) is one of the most important inhibitory neurotransmitters involves in the central nervous system (CNS) development. As its reducing function acts on the inhibiting excitabilities of neurons, it would hyperpolarize the neurons at the resting potential of the action potential by binding to GABAA receptor or GABAAR and GABAB receptor or GABABR. The GABA controls all excitabilities areas in the human brain with another neurotransmitter. To keep a balance in the brain, those excitabilities are regulated by both the GABAergic activities and glutamatergic neurons, which produce the most common and critical excitatory neurotransmitters — glutamate that stimulates action potentials. In opposite, the inhibitory neurotransmitters GABA in GABAergic activities inhibits action potentials. When two of these neurotransmitters could not function properly depending on situations, symptoms like anxiety, restlessness, insomnia, and even disorders like schizophrenia and Parkinson's disease would occur when reducing the GABAergic activities. In addition, sedation, amnesia, and ataxia will appear when the GABAergic activities outweigh the glutamatergic activities. And the neurotransmitter GABA is manufactured by GABAergic neurons, which are neurons that use and produce GABA as their neurotransmitter that is commonly distributed in the CNS but not common outside the brain and in the spinal cord.

The GABA receptor that is significant to epilepsy is code by GABRB3, the GABAA receptor. It is wildly distributed in the human brain that it could be found in 20% to 50% of all the brain synapses. The GABAAR and GABA are most concentrated in the human limbic system that involves human emotions and memories, especially when one is under a strong feeling or challenges and traumas. And the GABAA receptor is only one of the receptors that could be activated by GABA, an ionotropic receptor and ligand-gated ion channel. By allowing the permeation of chloride ions (Cl^-) in or out of the membrane, its function is to maintain or mediate the synaptic membrane potential and inhibit action potentials.

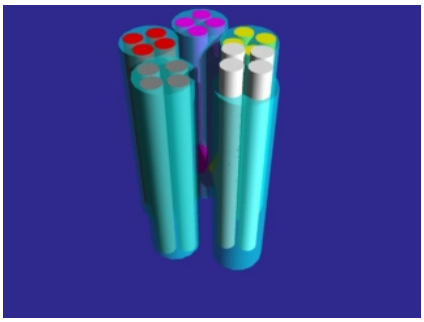

Figure 2: Structure of GABAA receptor, within 5 subunits composed a channel in the middle.

The structure of the GABAA receptor is quite normal, just like most other ligand-gated receptors, it is formed by five subunit proteins, that each of which is about 50,000 Daltons in size, and every last one of these amino acid strings goes into and out the cell membrane 4 times, leaves an N-terminal at the extracellular space, which is the end of the polypeptide that, it would function as mediating the channel's interactions. And in the middle of those amino acids, there is a large area of looping inside, with four sites where phosphorylation occurs. Those subunits that composed to this receptor have been classed into α1–α6, β1–β3, γ1–γ3, δ, ε, π, θ, and ρ1–ρ3. It seems alpha and beta are the key components of GABAA receptors since most of them are arranged by two alpha and beta subunits in the limited 5 maximums.

When GABA binds to the GABAA receptor, the ion pore in the middle will open, which facilitates the influx or efflux of chloride ions (Cl-), depending on the concentration difference of Cl- outside and inside the cell that regulates by the potassium chloride (KCC2) and sodium-potassium chloride (NKCC1) co-transporters.

3.5 Medical Treatment of Epilepsy: Benzodiazepines

Benzodiazepines (BZDs), as mentioned, are one of the most significant medical agents of epilepsy since the 1960s. They are targeted on the GABAA receptors, that they have had a strong preference towards status epilepticus and seizures. Besides, BZDs have also been used in febrile or repetitive seizures and alcohol withdrawal seizures. They became the first choice when those symptoms came since they have high efficacy, rapid onset, and less toxicity on functions like sedation, anxiety-reducing, and muscle relaxation. Each type of BZD shows different pharmacologic effects according to particular symptoms, and among all of these 35 kinds of BZDs, there are some used in epilepsy. When BZDs bind to the GABAA receptor, they are not substituting the GABA but acting as an enhancing agent to provide more chances of the channel opening to allow more Cl- get in or out to increase or decrease the current. The BZDs are sharing a structure of a benzene ring and seven-membered diazepine ring fusion.

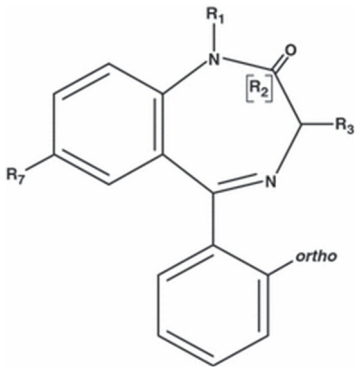

Figure 3: General chemical structure of 1,4-benzodiazepines

4 CONCLUSIONS

This dissertation resulted from an investigation into the macroscopic level, molecular biology, and genetic level of epilepsy. It concentrated on the symptoms and brain activity of epilepsy, mutation of GABAA receptor, and its gene. As an overview, the current state of knowledge we had summarized about epilepsy shows a strong association it has with the GABRB3 gene. Still, since the limitation of more recent data of how epilepsy is prevalent beyond all ages, genders, and regions and the genetic experiment of GABRB3 gene, further research needs to be conducted on those aspects.

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