A Review on Underlying Causes and Therapies Related to Epilepsy

By
Name: Saima Akter Sonia
ID: 16346018

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Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing my degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material that has been accepted or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

Student's Full Name & Signature:

Saima Akter Sonia

Saima Akter Sonia
16346018

Approval

The thesis titled “A Review on Underlying Causes and Therapies Related to Epilepsy” submitted by Saima Akter Sonia (16346018) of Summer 2016 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy.

Examining Committee:

Supervisor:
(Member)

_____
Dr. Md. Aminul Haque
Assistant Professor, School of Pharmacy
Brac University

Program Coordinator:
(Member)

_____
Namara Mariam Chowdhury
Lecturer, School of Pharmacy
Brac University

Assistant Dean:
(Member)

_____
Professor Dr. Hasina Yasmin
Assistant Dean and Program Director, School of Pharmacy
Brac University

Dean:
(Chair)

_____
Professor Dr. Eva Rahman Kabir
Dean, School of Pharmacy
Brac University

Ethics Statement

The study does not involve any kind of animal and human trial.

Abstract

Epilepsy is perhaps the most well-known form of brain disorder. Action potential eruption describes a specific kind of neuronal discharge, and physiological processes are required for epileptic activities. Therefore, epileptic discharges are a replay of an overactive brain function that has been dysregulated. The causes of epilepsy are not specified; viral infections, bacterial infections, malnutrition, traumatic brain injury, cerebrovascular disease, and brain tumors are responsible for this. This study tries to find the underlying causes and therapies related to epilepsy. For this, research articles, news stories, academic publications, and government websites such as pubmed.com were used to compile this extensive literature assessment on the history of the origin of epilepsy and the gene therapies related to epilepsy**.**

Keywords: Neurodegenerative disorder, Epilepsy, Gene Therapy, Stem Cell-Based Therapy, Brain Injury, Etiology, etc.

Dedication

Dedicated to the Department of Pharmacy, Brac University.

Acknowledgement

Foremost, all the praises to Allah for His infinite blessings and compassion toward me.

First of all, I would like to thank my honorable faculty supervisor, Dr. Md. Aminul Haque, Assistant Professor, Department of Pharmacy, Brac University. for his guidance, support, and direction during my thesis period. I sincerely appreciate his assistance and patient conduct whenever I encountered difficulty throughout this stage.

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Chapter 1

1.1 Introduction

Definitions in the field of epilepsy have historically been controversial. Seizures are a defining feature of the condition; however, not all seizures are caused by epilepsy (Gastaut H, et al., 1964). For example, febrile seizures and drug-induced seizures are not the same things. Previous classifications attempted to resolve these inconsistencies by categorizing a variety of electroclinical syndromes; however, the most recent findings from imaging technology and genetics need to be added (Merlis, et al., 1970).

Epilepsy is difficult to diagnose because, in practice, the diagnostic electrical hallmark of epilepsy may be absent interictally, particularly in adults or if seizures are infrequent (Engel, 2001). Interictal epileptiform discharges may occur in nonseizure patients. This makes diagnosing epilepsy challenging. Rarely, an "epileptic EEG" is accompanied by epileptic encephalopathy. This condition has few or no overt seizures, like Landau–Kleffner syndrome and a cognitive issue may prevail (Berg AT, et al., 2010).

The ILAE recently held consultations to synthesize a consensus perspective (Scheffer IE, et al., 2016), and the results of these consultations will be published in 2017. The end product is expected to be practical and effective, taking into account the fact that the syndromes have multiple facets, with each instance being defined by a combination of clinical, electrophysiological, etiological, and concomitant aspects. It also accepts that it's not always feasible to tell whether a patient's seizures are caused by focal or generalized epilepsy and that, in certain cases, such as with tuberous sclerosis, genetic and structural causes may coexist. Certain words won't be utilized. Epilepsy in children that remits is called pharmacoresponsive, not benign. This update recognizes that children whose seizures remit may have persistent psychological problems.

The ILAE has also contemplated the question of whether or not a single seizure may be considered to be epilepsy (Fisher RS, et al., 2014), and it has come to the conclusion that it may be if there is a greater than 60% chance of another seizure; this risk is conferred by the presence of EEG spikes or a major structural etiology. After 10 years during which the individual has been seizure-free and has received no therapy for their situation, epilepsy may be deemed to have been cured. This method is pragmatic, not mechanical. It helps regulators treat patients with lower risk more leniently and decide whether to treat them medically after a single seizure (Krumholz A, et al., 2015).

Some frontal lobe epilepsies may be particularly challenging to diagnose, often with non-diagnostic ictal scalp EEGs. Additionally, some frontal lobe epilepsies were at one point thought to be movement disorders, such as "paroxysmal nocturnal dystonia," (Lugaresi E, et al., 1986) until its epileptic basis was shown later (Tinuper P, et al., 1990). The situation has become more complicated as a result of the discovery that patients with frontal lobe epilepsy may also have epileptic nocturnal wandering. This condition shares characteristics with parasomnias and also includes brief nocturnal movements that are not caused by seizure discharges but may be a release phenomenon of interictal discharges (Parrino L, et al, 2006). They might also have a higher risk of suffering from non-epileptic parasomnias than the general population does. The state will be referred to as "Sleep-related Hyper motor epilepsy (SHE)" after it is included in the new classification.

1.2 Goal of the research

This study aims to find out the underlying causes and therapies in the treatment of epilepsy.

1.3 Objectives

The following are the review's objectives:

- To gather factors about epilepsy.
- To gather details on the causes and therapies in the treatment of epilepsy.
- Find out the gene therapies for treating epilepsy.

Chapter 2

Epilepsy

Regarding brain disorders, epilepsy is perhaps the most well-known case. Epileptic activities need both the physiological mechanism of neuronal discharge, a burst of action potentials, and the style of collective activity known as neuronal synchronization. That being the case, epileptic discharges are only a rerun of the excessive brain activity that led to the dysregulation in the first place (Varela F, 2001). Individual ion channels and neurotransmitter receptors, cellular and synaptic features of single neurons, and the aggregate actions of networks of linked neurons controlled by glial cells must all be understood to explain epileptic behaviors (Cooper R, 1965).

Several types of neurological disorders like epilepsies are pretty standard. Researchers have used a broad range of artificial and natural models to recreate epileptic symptoms in animals. Clinical investigations of epilepsy in humans often begin with electrophysiological recordings. Field potentials formed by synchronous synaptic potentials in vast cortical regions (several cm3) are recorded by the Electroencephalogram (EEG), a diagnostic tool. Transmission may vary across brain areas (Ray et al., 2007). The information captured by intracranial recordings is of more excellent quality and more precise in space, and it also provides a sample of higher frequency oscillations. However, intracranial recordings frequently do not clarify the mechanisms underlying epileptic activity. Recent intracranial recordings have helped pinpoint discharges of single neurons in situ, which, according to Buzsáki et al. (2012), may help explain where epileptic synchronization first arises (Tao JX, 2007).

Using animal models, we have studied epileptogenic alterations in brain tissues leading to seizures. However, ectogenesis, the mechanism that regulates the development of seizures from an altered brain, has gotten less attention. While in vivo models may not fully replicate all

aspects of epilepsy, they have provided us with the vast bulk of the current knowledge. Research conducted in vitro, explicitly using hippocampal slices from rats, has added to our understanding of the probable mechanisms underpinning neuronal synchronization. Blocking GABA receptors or increasing neuronal excitability may generate epileptiform activity. These models give correct information on ionic conductances, synaptic events, and neuronal firing while compromising the degrees of integration in a slice and a whole brain and between healthy animal tissue and an ill human brain. Even though the models study healthy animal tissue, not an ill human brain, this is accurate (Ray A et al., 2007).

In vitro studies of human epileptic tissue provide a novel window into human epileptic activity (Kohling & Avoli, 2006). They allow for integrating imaging and genetic studies to understand cellular and neural function better. In conclusion, the extra-cellular medium of the brain may be mimicked in a tissue slice to induce certain behaviors or further pharmacological investigation.

2.1 Epilepsy Classification Based on Possible Causes

Although official epilepsy classifications have paid much attention to epilepsy semiology and electroencephalography, they have not attempted to compile a synoptical enumeration of the causes of epilepsy. There is truth to the old cliché that epilepsy is a symptom of some deeper neurological problem. The essential purpose of any such scheme is to provide a framework for therapy; hence an emphasis on etiology is a crucial aspect of any classification system. An accurate clinical diagnosis requires two pieces of information: (1) the kind of syndrome of seizures; and (2) the underlying etiology of the seizures. Epilepsy's prognosis, treatment, and progression are all profoundly impacted by its etiology, making it just as important, if not more so. In 1969, 1981, and 1989, the ILAE categorized seizure types and disorders but hardly touched on causation (Gastaut et al., 1969)

Table 1: Categorization of the causes of epilepsy (Shorvon, 2011)

Principal Group	Subcategory	Examples
Idiopathic epilepsy	Single-gene abnormalities that cause isolated cases of epilepsy.	Benign familial neonatal convulsions; Epilepsy affecting the frontal lobe that strikes mostly at night is autosomal dominant; Generalized and febrile epilepsy; Childmyoclonic epilepsy.
	Pure epilepsies with complex inheritance	Idiopathic generalized epilepsy (and its subtypes); Benign partial epilepsies of childhood
Symptomatic epilepsy	Childhood epilepsy	Lennox-Gastaut syndrome, West syndrome
Predominately genetic or developmental causation	Progressive myoclonic epilepsies	Unverricht-Lundborg disease; Dentato-rubro-pallido-luysian atrophy; Lafora body disease; Mitochondrial cytopathy; Neuronal ceroid lipofuscinosis;

		Sialidosis; Myoclonus renal failure syndrome.
	Neurocutaneous syndromes	Neurofibromatosis; Sturge-Weber syndrome.
	Neurologic single gene disorders	Lysosomal disorders.
Provoked epilepsy	Provoking factors	Fever; menstrual cycle and catamenial epilepsy; Seizures caused by alcohol and other drugs; The routine of sleeping and waking; Drug-induced seizures.

The etiology of epilepsy is discussed in a new study by the International League Against Epilepsy's (ILAE) Commission for CCE. However, the paper does not include a list of etiologic groupings. The Commission proposed a flexible and multidimensional classification scheme as the "database providing the basis of a diagnostic manual." Here, we present an etiologic framework that may help achieve this aim by serving as a repository for relevant explanations (Berg et al., 2010). This post seeks to do two things: (1) outline the framework for creating such an etiological database, and (2) argue that etiology should be a primary axis or dimension of any helpful classification scheme. Theoretically, this may act as a helpful synoptic summary of the many epilepsy causes. It is important to note that this causal dimension is only one of

the numerous multidimensional aspects of classification and does not supersede other components of the ILAE categories (Berg et al., 2010).

This paper has attempted to offer a brief historical review applicable to any research source since such a review is fundamental to the concept (Shorvon, 2011). Early ILAE classification systems emphasized electroencephalographic (EEG) features and seizure semiology. It is likely because EEG was the primary method of inquiry throughout this period. Recent neuroimaging and molecular chemistry advancements have made it possible to identify the underlying etiology of many types of epilepsy. If MRI had already been developed before electroencephalography, one can speculate how the ILAE categories of epilepsy would have altered (EEG).

2.2 Symptomatic and Idiopathic Epilepsy

Despite appearances, the theme of "symptomatic epilepsy" is rather complex. Symptomatic epilepsy, also known as organic epilepsy, was widely ignored as a "genuine epilepsy" throughout most of the nineteenth century. By the middle of the 20th century, it was generally accepted as axiomatic that all or nearly all occurrences of epilepsy were symptomatic, meaning epilepsy itself was only a symptom of an underlying cause. The antonymous term "idiopathic epilepsy" has also acquired a new meaning in recent years. This latter phrase was initially used for all types of unexplained seizures; nowadays, it is used only to designate epilepsy caused by genetics but shows no outward signs of abnormality in neuroanatomy or neuropathology (Ferrie et al., 2010).

Under the framework presented in this article, epilepsies resulting from Rett syndrome, CDKL5, & Angelman disease, along with those resulting from other genetic illnesses, are all regarded as symptoms. However, epilepsies resulting from developmental abnormalities are also included when neuropathologic alterations occur; these epilepsies are more often than not

the result of faulty development (and are, therefore, primarily heritable) than they are the result of an externally acquired cause. These congenital disorders are in the range between idiopathic epilepsy as well as obtained epilepsy (Shorvon SD, 2011).

This term may be challenged in a variety of ways, of course. Modifications to synapses, membranes, neurotransmitters, and networks, as well as possible anatomical anomalies, have been proposed as potential causes of idiopathic epilepsies. The distinction between asymptomatic and symptomatic epilepsy is somewhat arbitrary due to the lack of a "gross lesion," which is characterized as any recognizable pathophysiologic or morphological irregularity perceptible in typical clinical evaluation (which includes clinical imaging technology, histology, and neurotransmitter systems) (Wolf, 2010).

It was proposed in the most current report from the ILAE Classification Commission that genetic, structural/metabolic, and unknown be used in place of idiopathic, symptomatic, and cryptogenic. There are a lot of reasons why this recommendation was not implemented here. To begin, the word "idiopathic" has been respected throughout time and should only be changed if there are significant benefits to doing so; yet, there is a substantial dispute over the need for such a shift. Further, it is suspected that a combination of genetic and environmental variables, contributes to idiopathic epilepsies, with biological factors likely predominating but remaining primarily theoretical. 'Symptomatic epilepsy' has several genetic origins as well. As a result of these considerations, the label "idiopathic" merits continued use. Swapping the term "symptomatic" for "structural/metabolic" seems inappropriate, given that many symptom-causing illnesses are neither structurally nor metabolically in an ordinary way. It's unclear whether or not the replacement of "cryptogenic epilepsy" with "epilepsy of unknown etiology" really alters the conceptual underpinning, although it does appear to anglicize and eliminate the ancient Greek roots of the name (Guerrini, et al., 2010).

2.3 Provoked Epilepsy

This "database" has a grouping not found in the most current report from the commission. The author believes this classification to be useful and significant in any etiologic listing. As early as the 19th century, it was understood that "exciting" and "predisposing" factors contributed to the development of epilepsy in the vast majority of patients. Both may be considered "causes," and it would be naive to suggest that the inciting element (such as "stress," lack of sleep, etc.) is not a "cause." The fascinating reasons were ecological or structural, and they have been largely disregarded in recent times. In about 17 out of every 500 instances of treatment resistance, it is hypothesized that initiating variables are the primary cause of epilepsy and that addressing these factors would drastically enhance disease control in specific individuals. Seizure provocation is known to affect both inherited and acquired forms of epilepsy, as well as focal and generalized forms; it also does not fit neatly into existing seizure-type or syndromic categories, although the mechanisms by which these triggers cause seizures remain largely unknown. This subcategory exists to encompass both the more frequent seizure precipitants and reflex epilepsies (epilepsies in which a very precise provocation is the primary cause of the condition) (stress, lack of sleep, and so on) (Aird, 1985).

2.4 Focal versus Generalized Epilepsy

It is crucial to remember that etiologic categories may not consistently well delineate the threshold between focal and generalized epilepsy (complicated as it may be) does not carry over to the idiopathic vs. symptomatic classification. Generalized epilepsy is one kind of symptomatic epilepsy, whereas focal epilepsy is one type of idiopathic epilepsy. In addition, "provoked" seizures may be either inherited or acquired and can occur in either widespread or localized forms. In terms of etiologic categorization, this split is mostly useless.

2.5 Acquired Epilepsy

"Acquired" epilepsy is used to describe those cases where the symptoms may be identified but the underlying cause is not primarily hereditary or developmental. In this context, "epilepsy" refers to both environmental epilepsy and epilepsy induced by endogenous pathological conditions in which no considerable external component is known to play a role (e.g., tumor, neurodegenerative disease, autoimmune disease). By definition, systemic non-neurologic illnesses without neuropathologic indicators are not included in the category of "prompted epilepsy" (a difference centered on the exciting/predisposing causes of the dualism of the 19th century) (Shorvon, 2011).

2.6 Acute Symptomatic Epilepsy

"Acute symptomatic epilepsy" is a word that needs to be retired. In current use, the term encompasses both (1) etiological variables (such as fever, metabolic problem, and alcoholism) that are more appropriately defined as "instigating factors," and (2) symptomatic factors (such as acute brain injury) that are more correctly described as "etiological" causes. The physiological and clinical manifestations of these two types of "causes" are so different that grouping them is nonsensical. Acute brain injury (trauma, hemorrhage) seizures have a different origin and diagnosis than later-on seizures. Hence the term should be restricted to the former if it is to persist (Shorvon SD, 2011).

Chapter 3

Causes and Risk Factors

3.1 Genetic Factors

However, the assumption that a family history of epilepsy indicates an elevated risk of the illness owing to genetics is strongly constrained by the potential that a shared environmental exposure within a family can yield similar effects. Family history was present in 6–60% of cases in sub-Saharan Africa, but 5% of cases were in the United States (Ottman R et al., 1995). Family history of epilepsy cannot be explained by a single dominant gene, although there is evidence that individual polymorphisms often function in concert with environmental influences. Consanguineous marriages, which are widespread among several African ethnic groups for cultural reasons, may raise the chance of developing genetic epilepsy (Rwiza HT et al., 1992). Epilepsy was shown to be one-fourth more common in the offspring of consanguineous than in those of non-consanguineous marriages, according to a pedigree study of 23 persons with epilepsy conducted in Côte d'Ivoire. A strong genetic link has been shown between epilepsy and its development. Lennox's 1951 research on monozygotic twins noticed a significant degree of concordance between the incidence of epileptic seizures in the two sexes (Lennox et al., 1951). When comparing these results to Mali, researchers discovered that 37% of epilepsy patients had a blood relation. Patients in a case-control study in Tanzania were shown to have a higher prevalence of having a first-degree relative with epilepsy compared to controls (18%) and patients from consanguineous marriages (33%). (Matuja WB et al., 2001).

3.2 Perinatal Causes

It is estimated that anywhere from 2% to 65% of epilepsy occurrences in sub-Saharan Africa may be traced back to prenatal origins. Epilepsy may be a consequence of damage sustained during birth, frequently as a result of a challenging pregnancy or delivery. Low blood sugar and low oxygen levels are often mentioned as causes. Lacking access to neuroimaging technologies makes it challenging to link epilepsy to a fetal, neonatal, or early postnatal occurrence. The connection is often based on history, which is not always documented and might be affected by memory bias (Feksi AT, et al., 1991). Due to traditional beliefs and long travel times, many births still take place outside of a medical facility. A 2012 particular instance of research identified a substantial connection (OR 10.2, 95% CI 1.1-23.4) among both epilepsy and unfavorable prenatal outcomes, despite relying only on maternal recollection. Ngugi and coworkers found that risk factors during pregnancy and the postpartum period were most strongly linked to the onset of active convulsive epilepsy in children (population attributable fraction 0.33) (Ngugi AK, et al., 2013).

3.3 Febrile Seizures

In children, febrile seizures are often associated with epileptic seizures, and all African hospitals record these instances. Somewhere from 6-38 percent of individuals with epilepsy in sub-Saharan Africa also have a background of epilepsies. In case-control research done in Nigeria, Ogunniyi and colleagues observed an odds ratio of 11 after correcting for confounding factors such as a history of head trauma (Prischich F et al.,2008). It is unclear whether febrile or mild seizures are more common in areas where malaria is prevalent. According to a study, seventy-one percent of Tanzanian children with epilepsy also experienced seizures caused by malaria (Matuja et al., 1989).

3.4 Malnutrition

There has been less research on the probable connection between epilepsy and hunger in the world's poorest nations. A connection of this kind has been suspected for quite some time. However, epilepsy may also contribute to malnutrition due to cultural dietary taboos and stigmas in sub-Saharan Africa (Crepin S, et al., 2007). Patients in research conducted in Benin had a significantly higher prevalence of malnutrition than controls (22 vs. 9%, p = 0006).

3.5 Neurological Infections

Parasites are the most common infectious cause of generalized seizures in equatorial Africa. Malaria, 88 cysticercoses, onchocerciasis, and toxocariasis are some of the diseases in this category (Rothenberg G, et al., 1983).

In many nations in Africa, Asia, and Latin America, neurocysticercosis is the most prevalent CNS illness and a leading cause of epilepsy. Neurocysticercosis is a significant reason for partial-onset seizures in adults in locations where Taenia solium is standard. Cysticercosis is rare in Jewish and Muslim countries due to a decreased risk of infection with adult worms or environmental contamination by parasite eggs (where people have limited interaction with pigs and pork is not consumed). In endemic areas, neurocysticercosis is thought to be the cause of 30% of all cases of epilepsy (Winkler, et al., 2012). Based on this estimate, Winkler determined that there are between 1.9 and 6.1 million persons in sub-Saharan Africa who have neurocysticercosis and are at risk of getting epilepsy. Human cysticercosis or neurocysticercosis prevalence may be evaluated via serological detection of anticysticercal antibodies or cysticercal antigens in many resource-poor settings where neuroimaging is not available. Neurocysticercosis incidence varies over the continent of Africa south of the Sahara (Ibrahim N, et al., 2003). Cysticercosis was linked to an increased risk of epilepsy in a 2010 meta-analysis of data from eight African nations (overall OR 3.04, 95% CI 2.77-4.03).

With an odds ratio (OR) of 3.8, cysticercosis was considerably linked to epilepsy in Burundi (2.55–5.1). Cysticercosis is thought to affect 38 out of every 1,000 Togolese generally, but 135 out of every 1,000 Togolese who have epilepsy. Neurocysticercosis can only be diagnosed with the use of neuroimaging. It is unusual for people in sub-Saharan Africa to have access to CT. A study by Winkler and co-workers indicated that neurocysticercosis-related lesions accounted for more than half of the cases of epilepsy and CT abnormalities in rural Tanzania (Nsengiyumva G, et al., 2003). Epileptics were also more likely than controls to have CT pathology indicative of neurocysticercosis (38 of 212 [18%] versus 10 of 198 [5%]; OR 4.1%, 95% CI 2.0%-8.5%; p0.0001).

Epileptics diagnosed with neurocysticercosis in Tanzania were found to be older and to have had their initial seizure at a later age than those without the disease, according to independent studies. Neurocysticercosis should be considered in patients with delayed epilepsy (Nicoletti et al., 2002). T solium antigen prevalence was 21.6% in the Democratic Republic of Congo in 2011, with an estimated incidence rate of active epilepsy of 12.7% per 1000 individuals in the same year. The public needs to be more aware of the prevalence of neurocysticercosis so that better measures may be taken to prevent and cure the condition in endemic areas (Quet F et al., 2010).

3.6 Traumatic Brain Injury

The absence of traffic regulations and the refusal to utilize safety equipment like seat belts and helmets make road accidents the leading cause of brain damage in Africa (for motorcyclists). A person's likelihood of developing post-traumatic epilepsy after suffering brain damage as a consequence of an accident, assault, war injury, or violent sport is proportional to the severity of the initial injury and any subsequent complications. Studying epilepsy patients in Mali,

researchers discovered that 7 out of every 100 (7%) had post-traumatic seizures (Silberberg D, et al., 2006).

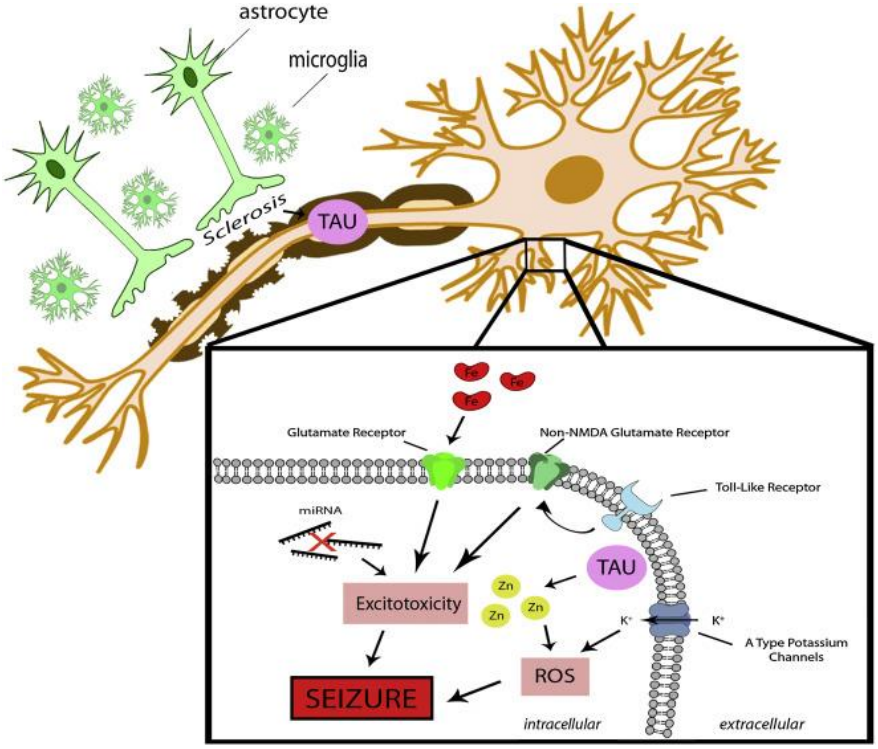

Figure 1: Initiation of Epilepsy after Stress from Traumatic Brain Injury (TBI).

3.7 Cerebrovascular Disease

Stroke is a prominent cause of epilepsy in the elderly, while it may initiate the onset of the neurological disorder suddenly or contribute to its steady progression. However, due to methodological difficulties, most studies lack high-quality research on stroke in sub-Saharan Africa. (Howitt SC et al., 1996). As a consequence, many occurrences of stroke, particularly TIAs, go undiagnosed due to a lack of specialized medical skills and imaging tools. Most research on stroke in sub-Saharan Africa comes from hospital series; however, due to selection bias, these studies may not accurately portray the population's fundamental frequency of cerebral infarction. Brain imaging is essential for classifying the many types of strokes, but it is not a service that is readily available (Sagui et al., 2010). Epilepsy is more common in people from Africa than it is in people from more developed countries; while 3–4% of patients with

epilepsy in those countries have a history of cerebral stroke, the reported prevalence of epilepsy in cerebrovascular disorders in Africa ranges from 1% to 42%, with a mean of 7% and a standard deviation of 10.

3.8 Other Infections

Meninges and cerebral parenchyma are common sites of infection for bacteria in the central nervous system. Any bacterial infection of the CNS can produce both acute symptomatic seizures and persistent acquired epilepsy. Infections of the central nervous system, such as empyemas and abscesses, are significantly associated with the later development of epilepsy, much like acute bacterial meningitis is. The blood-brain barrier, cerebrospinal fluid (CSF), the meninges, and the immunological features of the CNS all combine to make the brain and nervous system (CNS) an unfriendly habitat for infections. The risk of seizures changes with age at infection and whether or not there is a family history of epilepsy, suggesting that both genetic and brain development have a role in deciding whether or not seizures occur. Hematogenous penetration across the blood-brain barrier (BBB) or the choroid plexus is another route, as is direct infiltration through trauma or the cranial sinuses. Seizures will not happen if the infectious agent has not reached or harmed the cerebral cortex. Arteritis, ischemia, and infarction are probably involved in activating defensive mechanisms that lead to inflammatory changes that induce seizures following bacterial CNS infection.

In contrast, the precise reasons for acute symptomatic seizures and acquired epilepsy after this illness remain unknown. Like other forms of epilepsy, acquired epilepsy caused by central nervous system infections is often treated with antiepileptic drugs. Epilepsy often occurs long after an illness has been treated. Thus, at this stage, antibiotic treatment is usually unneeded. People who had seizures were less likely to develop brain tumors. Most brain tumors are found at an advanced stage because of delays in diagnosis caused by a lack of CT and MRI scanners

in many developing countries (Sander JW et al., 1996). Seizure and epilepsy are linked to almost all parasitoses (Table 1), either because of the parasite's intracerebral location or because of the accompanying widespread encephalitis or encephalopathy. Without access to neuroimaging, the best method for detecting parasites in these regions is serological testing, which, when paired with clinical and epidemiological indicators, may help to identify a diagnosis. It is challenging to demonstrate a causation relationship between parasitosis and illness when a positive serology does not indicate a current infection.

Table 2: Parasite-caused epilepsy and convulsions

Protozoans	**Helminthiases** **Nematodes**	**Angiostrongyliasis**	**Trematodoses**	**Cestodoses**
Amoebiasis Malaria Toxoplasmosis Trypanosomiasis	Filariasis Trichinellosis Toxocariasis	Strongyloidosis	Schistosomiasis Distomatosis Paragonimiasis	Hydatidosis Cysticercosis

Chapter 4

Treatment

4.1 Antiepileptic Medicines (AED)s

Epilepsy affects between 4 and 10 out of every 1,000 people at some point in their lives. If left untreated, it may lead to permanent cognitive decline, brain damage, and other neurological abnormalities. Antiepileptic medicines (AED), the backbone of epilepsy therapy, may give gratifying control or entire cessation of seizures, allowing many patients to lead normal, undisturbed lives. Despite significant advances in medication and epilepsy research and carefully adjusted AED therapy (Duncan JS, et al., 2006), around 35% of all epilepsy patients have recurring non-provoked spontaneous seizures. Patients with TLE, in which seizures start in the temporal lobe, the most epileptogenic area of the brain, have a unique challenge with drug resistance. The quality of life for people with epilepsy is drastically lowered when their seizures are not under control. Refractory epilepsy patients often have unacceptable toxicity for AEDs, cognitive impairment, and depressive symptoms, all of which are connected to their epilepsy (Luoni C, et al., 2011).

New AEDs have improved tolerance, fewer medication interactions, and simpler pharmacokinetics thanks to advances in drug discovery, but they are not more effective than earlier AEDs. As a result, an unacceptable number of patients remain refractory. Patients with drug-resistant epilepsy have few therapeutic options available. Although the ketogenic diet has shown some promise for the treatment of epilepsy, its general reactivity is low and variable. Alternatively, surgery can be an option. Resection of a defined seizure focus, such as amygdalohippocampectomy in TLE, may have good results, with around 80% of patients experiencing postoperative seizure/drug resistance-freedom. Similarly, extratemporal resections are conceivable (Engel J Jr, et al., 2003), but less often performed, and in these cases,

as much as 50% seizure independence has been observed in post-surgical patients. Surgical treatments as a high-dose therapy are hampered by the cause that only a small percentage of patients have a surgically resolvable epileptic syndrome, despite the high rate of seizure independence recorded following surgery (Thammongkol S, et al., 2012).

There is no doubt that the recent state of refractory epilepsy is a serious issue. As a consequence, researchers are devoting a great deal of time and energy to exploring various stem cell-based cell treatments and gene therapies as potential new methods of treating epilepsy. Experimental clinical trials for epilepsy have not yet been conducted using any of these methods. Many clinical studies using gene therapy have been conducted or are now underway for the treatment of numerous neurologic illnesses, including Parkinson's disease, and amyotrophic lateral sclerosis. Evidence from these studies gives hope that stem cell and gene treatments may one day provide effective treatment options for epilepsy (Sagher O, et al., 2012).

4.2 Gene Therapy in Epilepsy

Neurons (the tissue in the brain most typically targeted by gene therapy) are the target cells in this organ system. Several viral vectors, including SV, lentivirus, AAV, and herpes simplex virus, have been utilized effectively for this purpose (Kaplitt & During, 2006). Vectors may transduce nondividing cells and enable long-term gene expression without harm (Fink et al., 2011). These vectors use virus-free helper systems, ensuring that the vectors themselves are non-replicating and incapable of expressing any hazardous genes. Injection site(s), viral tropism, and promoter information may all be used to direct therapeutic gene expression to a particular set of cells or tissues (McCown, et al., 2011). These viral vectors have desirable qualities that make them promising for therapeutic usage; when used in the treatment of

epilepsy, for example, they might be directed toward possible targets by operating through several different pathways.

1. Reducing hyperexcitability by transducing native cells and producing inhibitory modulators.
2. Transduction of endogenous cells and synthesis of neurotrophic factors enhance the survival of wounded neurons and repair of partially disrupted circuits.
3. 3. Transducing endogenous cells and producing opsins to dampen neuronal activity in excitatory cells or boost firing in inhibitory cells reduces hyperexcitability.

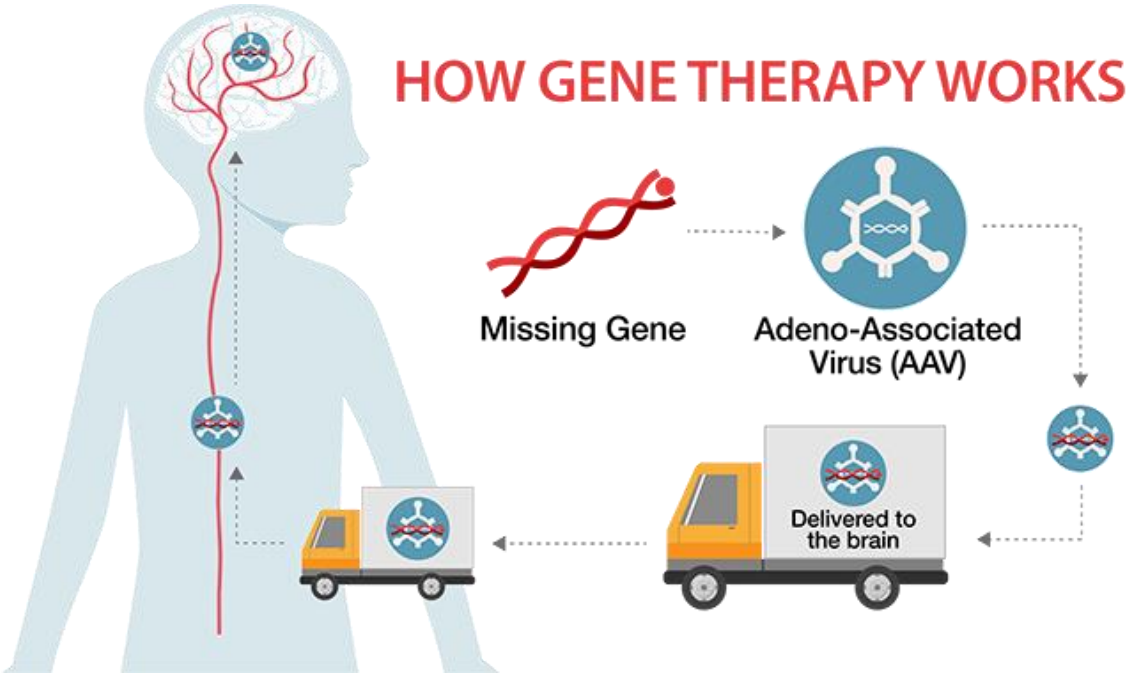

Figure 2: A healthy replacement of genes in a specialized gene delivery method.

4.2.1 Galanin Gene Therapy

The bioactive neuropeptide galanin served as the basis for one of the first therapeutic instances of employing viral vectors as a new strategy to control seizures. This technique was pioneered by researchers. Galanin is a peptide that consists of 29 or 30 amino acids and, along with its receptors, is found in a variety of locations throughout the brain. Galanin is extensively produced in the temporal lobe, such as the hippocampus, where mRNA and peptide levels are raised or expressed de novo in neurons after seizures. Exogenously given galanin may reduce excitatory glutamatergic transmission and generalized seizures. For several reasons, the galanin system is a great candidate for targeted gene therapy. (Mazarati A, et al., 2002).

After injection of an AAV vector expressing galanin under the CMV- promoter into the same area of rats, it was demonstrated in one of the first two experiments published in 2003 that the threshold for eliciting behavioral seizures was steadily raised week by week. Of note, this viral design allowed for posttranscriptional modulation of galanin levels thanks to a built-in doxycycline-off mechanism. Doxycycline, which inhibits transgene transcription, quickly reversed the effects seen and restored the baseline seizure threshold. Potentially useful in a clinical environment, such posttranscriptional regulation of virally encoded therapeutic genes would allow for finer tweaking of the peptide dose rather than being dependent on the strength of the viral promoter (Mazarati AM, et al., 1998).

It has been shown in other research that AAV-mediated local overexpression of galanin may prevent generalized seizures. Both intrahippocampal and intraperitoneal kainate (KA)-induced seizures may be prevented by overexpressing galanin in the hippocampus or piriform cortex. Nevertheless, AAV-mediated galanin overexpression does not seem to have any effect on epileptogenesis generated by electrical hippocampus kindling, and only widespread, and not localized (Haberman RP, et al., 2003), seizures induced by electrical stimulation are inhibited by such therapy. Possible explanations include the fact that transgenic galanin is not released

to any significant extent during focal seizures but may do so during generalized seizures due to the abnormally high frequency and prolonged nature of the neuronal activity. Constitutive galanin release is boosted, and acute generalized seizures are mitigated when a fibronectin release sequence is added to the viral vector. However, whether or not galanin gene therapy may prevent epileptogenesis and limit focal seizures is not yet known (Kanter-Schlifke I, et al., 2007).

4.2.2 NPY Gene Therapy

Neuropeptide Y (NPY) and its receptors are prevalent in the brain. Endogenous NPY is a key gene therapy target for epilepsy because it regulates seizures. Transgenic rats overexpressing NPY experienced fewer seizures than their wild-type littermates. However, NPY knockout mice develop spontaneous seizures and are more sensitive to chemically induced seizures (Fedele DE, et al., 2005). Animal studies and human patients with chronic TLE show that seizures raise NPY levels in interneurons that generate it and in granule cells/mossy fibers (Vezzani A, et al., 1999). These data show that NPY may operate as an endogenous seizure inhibitor by reducing glutamate release.

Richichi et al. (2004) employed a chimeric adeno-associated virus (AAV) serotype 1/2 vector to demonstrate that overexpression of transgenic NPY expressed by the neuron-specific enolase (NSE) promoter may greatly attenuate SE seizures elicited by intracerebroventricular KA injection. NPY gene therapy delayed hippocampal electrical kindling and elevated seizure threshold, suggesting it may slow epileptogenesis. Chronically epileptic rats with unprovoked spontaneous seizures demonstrated decreased frequency and delayed seizure intensity following NPY overexpression, confirming the therapeutic benefit of NPY gene therapy (Richichi C, et al., 2004). In this work, the NPY expression was encoded through the CMV chicken beta-actin (CBA) promoter. Additional study has confirmed and extended these

findings. Attenuation of KA-induced limbic seizures by AAV-mediated NPY gene transduction in rats' piriform cortex reveals potential NPY gene therapy sites besides the hippocampus. Anticonvulsive effects of NPY are mediated by Y2 receptors, not Y1 receptors, as demonstrated in Y1 or Y2 receptor null mice. NPY13-36 C-terminal overexpression for selective Y2 receptor activation suppressed KA-induced acute seizures. These latest data support the hypothesis that the Y2 receptor is the most important receptor for avoiding seizures (Foti S, 2007). It blocks voltage-gated Ca2+-channels in the hippocampus, inhibiting presynaptic glutamate release. These results have prompted a unique therapy technique in which NPY receptors are overexpressed alone or with NPY. Combinatorial gene therapy replicates and enhances the compensatory process of enhanced NPY and Y2 receptor expression after seizures. Overexpression of Y2 receptors by AAV reduced seizures in KA-induced limbic seizures and electrical rapid kindling in adult rats, and overexpression of both Y2 receptors and NPY reduced seizures even more (Woldbye et al., 2010). Both excitatory and inhibitory neurons overexpressed Y2 receptors. Y2 receptor overexpression in excitatory neurons may have led to better treatment results (Woldbye et al., 2010). Y2 receptors are a primary antiepileptic target in the hippocampus, according to virus-based receptor-ligand assays. Viral overexpression of the Y5 NPY receptor in the rat hippocampus did not affect KA-induced seizures, but co-overexpression of Y5 and NPY suppressed seizures more than NPY alone (Gotzsche et al., 2012). Y1 receptor overexpression in rat hippocampus worsened KA-induced seizures.

4.2.3 NF–Based Gene Therapies

In addition to their roles as survival factors for developing neurons, neurotrophic factors are commonly believed to enhance the survival of established adult cells and regulate synaptic plasticity. As a possible endogenous preventive mechanism against neuronal damage generated by excitotoxicity, higher protein levels of neurotrophic factors are often seen in the brain after

an epileptic episode (Simonato M, et al., 2006), possibly reducing epileptogenesis. By delaying the onset of kindling-induced generalized seizures in rats, slow and continuous administration of neurotrophic factors like GDNF, BDNF, and NT-3 has been shown to have protective effects on epileptogenesis (Xu et al., 2002). When neurotrophic factors are injected into the brain suddenly, they have more varying effects. In rats, injected BDNF into the hippocampus causes spontaneous behavioral seizures and exacerbates pilocarpine-induced seizures, although acute intraventricular treatment of GDNF may significantly inhibit KA-induced widespread limbic seizures. It is challenging to conclude studies that differ so significantly in experimental design and settings, as many factors (including duration of administration, route of administration, the concentration at the site of action, receptor expression, Etc.) may have contributed to the contradictory results (Scharfman HE et al., 2002). However, the results of these investigations lend credence to the idea that chronic (as opposed to acute) supplementation of neurotropic substances might be an effective means of halting epileptogenesis, thereby preserving healthy tissue and functioning neuronal networks. These anti-epileptogenic treatments are crucial because they can halt the chain reaction of neurobiological processes that might cause epilepsy and subsequent seizures. That they may only have a palliative impact on seizures is a major limitation of existing AEDs (Paradiso B, et al., 2009).

4.2.4 Adenosine-Based Gene Therapy

Human postictal refractoriness and seizure arrest may be mediated by adenosine release. Adenosine acts as a potent anticonvulsant by stimulating adenosine A1 receptors, which drastically reduces excitatory glutamatergic transmission. Intrahippocampal injection of adenosine reduces the incidence of uncontrolled seizures in pharmacoresistant epileptic rats, and selective adenosine A1-receptor activation in a mouse model of epilepsy prevents spontaneous seizures (Gouder N et al., 2003). The extracellular adenosine levels during spontaneous seizures in the human hippocampus appear to mirror the levels of extracellular

adenosine shown to reduce seizure activity in animals in vivo. Adverse reactions preclude the medical use of adenosine or its analogs by systemic administration. To reduce the severity of pharmacoresistant seizures, it is feasible that elevating brain levels of targeted adenosine might be a beneficial method (Van Dycke et al., 2010).

Now, adenosine-based gene therapy does not include overexpressing adenosine but focuses on the gene suppression of adenosine kinase. Since this kinase catalyzes most of the adenosine breakdown, pharmacological inhibition of this enzyme may increase endogenous adenosine levels. It is noteworthy since astrogliosis and astrocyte dysfunction has been shown in both experimental and clinical TLE. Adenosine deaminase overexpression may have a role in epileptogenesis and seizure intensity (Theofilas P et al., 2011). Adrenergic delta kinase cDNA antisense under an astrocyte-specific promoter was overexpressed using adenosine-associated virus 8 (AAV8) and entirely reversed chronic spontaneous seizures in a rat form of epilepsy. These findings demonstrate for the first time that knocking down ADK in astrocytes using a unique viral vector-based RNA interference approach may be an effective antiepileptic therapeutic target (During MJ et al., 1992).

4.2.5 SC-Based Therapy in Epilepsy

Many types of stem cells have been discovered, with the ability to develop into numerous cell types, including neurons and glial cells. These include embryonic stem (ES) cells, mesenchymal stem (MS) cells, neural stem (NS) cells, iPS cells, and, more recently, iN cells. Stem cells have the potential to differentiate into several cell types, including neurons and glial cells. After being transplanted, the neural progeny generated from stem cells may integrate into the local neural network by resorbing into the parenchyma. This results in functional improvement in a variety of neurologic conditions. Cell treatments that are based on autologous

stem cells might be effective for the treatment of epilepsy since they would provide a foundation for (Lindvall O, et al., 2012):

- Transplanted cells are utilized to restore neuronal circuits that have been damaged due to cell death or the removal of neurons.
- The transplanted cells provide trophic support, increasing the likelihood that damaged neurons would survive and repair themselves naturally.

Neurons produced from stem cells may be genetically modified for transplantation purposes and employed as a vehicle for the release of therapeutic chemicals such as neuromodulatory neurotransmitters and neurotrophic factors; this technique is known as ex vivo gene therapy.

Chapter 5

Conclusion

Epilepsy refers to a set of neurological conditions that are not contagious and are characterized by recurring epileptic seizures. The aberrant electrical activity in the brain that causes a seizure may last anywhere from a few seconds to several minutes. Accidents and direct injuries like shattered bones are also possible outcomes of these events. Epilepsy is characterized by recurrent seizures that may or may not have a clear cause. Seizures brought on by one single event, like poisoning, are not considered to be epilepsy in and of themselves. Due to the frightening nature of epilepsy symptoms, those who suffer from this condition may be stigmatized in differing degrees depending on where they live in the globe. Epilepsy and seizures have been linked to many infections, most of which may be avoided. Healthcare practitioners and doctors should benefit from knowing more about these causes, their geographic distribution, and their burden so that they can allocate resources more wisely and take more effective prevention and control measures. Seizure risk seems to be related to the pathogen, cortical involvement, brain maturation, genetics, and cytokine-mediated

inflammatory response, albeit this is not well understood. More research is needed in this area because of its obvious clinical significance. New antiepileptogenic therapies may be developed with knowledge of the processes behind seizures and epilepsy in central nervous system infections. Infectious and non-infectious sources of inflammation have analogous molecular mechanisms and procedures implicated in epilepsy. It implies that innovative anti-inflammatory medicines may be helpful to disease-modifying techniques. Further, immunization against CNS illnesses like meningitis and encephalitis and the elimination of parasitic infections via public education and sanitation improvements are the last, concrete measures toward lowering the prevalence of epilepsy. After a second seizure, epilepsy is often managed with medicine taken every day. In those who are at high risk of having further seizures, medicines may be begun after the first one. It might be beneficial to aid individuals in taking control of their health care. Alternative treatments, such as neurosurgery, neurostimulator implantation, or specialized diets, may be considered in drug-resistant instances.

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