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Review Article

VALIDATION OF SCREENING MODELS OF EPILEPSY: A REVIEW

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ABSTRACT

Epilepsy is a severe neurological illness characterized by abnormal, recurring, and synchronized brain discharges. Long-term recurring seizure attacks can cause substantial brain function loss, as seen in people with temporal lobe epilepsy. Controlling seizure events is critical for epilepsy therapy and prognosis. The disease is more common in developing countries than in developed countries. The causes of epilepsy include chemical imbalances such as low blood sugar or sodium, head injuries, drug abuse or withdrawal, alcohol withdrawal, stroke tumor affecting the blood vessels (vascular system) in the brain, hardening of the arteries (atherosclerosis) in the brain, brain tumours, and brain infections such as meningitis or encephalitis. Given the prevalence of epilepsy and the challenges associated with currently available antiepileptic medicines, such as side effects, resistance, safety concerns, and high cost, screening models are utilized in epilepsy analysis. Screening models for seizures and epilepsy have been critical in expanding our understanding of the fundamental mechanisms underlying ictogenesis and epileptogenesis, as well as in the discovery and preclinical development of novel antiepileptic medicines (AEDs). Diverse screening models of epilepsy have been developed in recent years to imitate various seizure forms, with no clear advantages or disadvantages. In this study, we will cover the numerous screening models for epilepsy, which will aid in gaining a better understanding of the disease.

Keywords: Epilepsy, Seizures, Screening Models for Epilepsy

INTRODUCTION

Epilepsy is a central nervous system illness characterized by loss of consciousness on a regular basis, with or without convulsions, and abnormal electrical activity in the brain. Epilepsy is defined as the clinical manifestation of a set of neurons in the brain that discharge abnormally and excessively[1]. Epilepsy is a widespread neurological disorder that affects people of different ages, races, socioeconomic backgrounds, and geographic areas. Epilepsy is a brain illness marked by an enduring proclivity for seizures as well as the neurobiological, cognitive, psychological, and social implications of recurrent seizures[2-4]. Seizures are caused by abnormal body function as a result of rapid excessive nerve-cell discharges in the brain[5]. They frequently induce loss of consciousness, increased muscular activity, or an odd sensation. Neurons can fire up to 500 times per second during a seizure, which is far faster than normal . Some people experience this only once in a while, while others experience it hundreds of times per day [6] Epilepsy can be caused by a malfunction in brain circuitry, a chemical imbalance in nerve signalling called neurotransmitters, or a combination of these factors. Some patients with epilepsy have abnormally high levels of excitatory neurotransmitters, which enhance neuronal activity, while others have abnormally low levels of inhibitory neurotransmitters, which decrease neuronal activity in the brain, according to researchers. Either condition can result in excessive neural activity, which can lead to epilepsy[7-8]. GABA, or gamma-aminobutyric acid, is an inhibitory neurotransmitter that has a function in epilepsy and is one of the most studied neurotransmitters. GABA research has resulted in medications that either increase or decrease the amount of this neurotransmitter in the brain, or affect how the brain reacts to it. Glutamate and other excitatory neurotransmitters are also being studied by researchers. In the identification and development of novel medications for the treatment of epileptic seizures, animal seizure models are critical. Epilepsy is one of the most common neurological illnesses, affecting between 0.5 and 1.0 percent of the global population[9]. Seizures can present in a variety of ways, depending on the location, extent, and method of propagation of the paroxysmal discharge, and are now regarded as a spectrum of clinically distinct kinds rather than a single disorder. Epileptic seizures frequently result in a transient loss of consciousness, putting the person at danger of bodily damage and interfering with schooling and job. Treatment is symptomatic in that existing medications reduce seizures, but there is no effective prophylactic or cure. Because of the necessity for long-term therapy and the negative side effects of many medications, medication compliance is a big issue. Seizures can also be a dangerous side effect of central nervous system (CNS) stimulants and other medications. Seizures are common in heat (febrile seizures are extremely common in babies), eclampsia, uraemia, hypoglycaemia, or pyridoxine deficiency, and frequently in the abstinence syndrome of those who are physiologically addicted to CNS depressants [10-11].

Pathophysiology of epilepsy

Seizures are brief bursts of activity in the cerebral cortex. When the excitatory and inhibitory strengths of the cortical neuron organize become unbalanced, a seizure occurs. In an unsteady cell film or encompassing back / neighbouring cells, the essential physiology of a convulsive scene is discovered. Seizure root in either cortical or subcortical zone's Gray matter. At first, a tiny number of neurons focus in an aberrant way. At the local level, normal membrane conductance and breakdown of inhibitory synaptic current, as well as excessive diffusion excitability, produce a localized or more broadly attack for the formation of a generalized attack. This house is conveyed by physiological routes to reach locations in close proximity to remote areas. A potassium conductance anomaly, a deficit in voltage-dependent

ion channels, or a deficiency of membrane ATPases linked with ion transport can all produce an attack by causing an unstable neuronal membrane. Some neurotransmitters (e.g., glutamate, aspartate, acetylcholine, norepinephrine, histamine, corticotropin-releasing factor, purines, peptides, cytokines, and steroid hormones) enhance neuronal excitability and propagation, whereas butyric acid-amino (GABA) and dopamine inhibit neuronal activity and propagation. The demand for increased blood flow to the brain to bring CO2 and provide substrate for metabolic activity of neurons increases during a seizure, and as the seizure progresses, the brain suffers greater ischemia, which can lead to neuronal death and brain damage[12-13]. Certain kinds of epilepsy may be linked to mutations in distinct genes. Generalized epilepsy and seizure disorders have been linked to genes encoding protein subunits of ion channels sensitive to activated voltage ligands in children[14-15]. Mutation of genes encoding sodium channel proteins has been proposed as a mechanism for some forms of hereditary epilepsy; these channels remain open long after sodium is depleted, causing neurons to become hyper excitable as glutamate, an excitatory neurotransmitter released in large quantities, can form neurons towards glutaminergic adhere close-triggers[16]. (Figure 1)

Triggering Factors and Classification of epilepsy

Epilepsy and seizures are triggered by a variety of external and internal events. Sleep deprivation, systemic infection, fever, key stages of the menstrual cycle, intake or withdrawal of certain medicines and substances, including alcohol, and homeostatic imbalances like hyponatremia are all common seizure triggers. External sensory cues that can be used as triggers include touch, hot water, certain visual patterns, reading, and music[17].

Seizures are characterized based on whether or not consciousness is retained and whether or not motor activity is involved. "Simple partial" seizures are focal seizures with retained awareness, while "complex partial" seizures are focal seizures with diminished awareness. Tonic-clonic seizures are seizures that have a stiffening (tonic) phase followed by a muscle jerking phase, resulting in bilateral motor involvement[18-19]. (Figure 2)

Screening Models for Epilepsy

Over the years, numerous in vitro and in vivo epilepsy models have been described. Brain slices, monosynaptic systems, and neuronal cultures are among the in vitro models. These, on the other hand, are more adapted to researching epileptogenic mechanisms such as ego paroxysmal depolarizing changes, post-tetanic and long-term potentiation, suppression of GABA and glycine responses, and spontaneous repeated firing, among others.

In Vivo models, on the other hand, use a variety of animal species to induce epilepsy, such as mice, rats, guinea pigs, gerbils, cats, dogs, and monkeys, and use a variety of physical and chemical/pharmacological stimuli. Some of these epilepsy screening models are discussed.

Characteristics of Ideal Model of Epilepsy :-

- The onset of recurring seizures that occur spontaneously.
- The clinical phenomenology of these seizures is comparable to that of human epilepsy.
- In man, the onset of epilepsy is age-dependent, as in generalized epileptic disorders.
- Clinical seizures must be accompanied by epileptiform action with in EEG.
- Antiepileptic medication pharmacokinetics should be similar to those in humans.
- Antiepileptic medication plasma concentrations that are effective for managing the specific seizure type in individuals.

Anti-epileptic medication screening can be done in a variety of ways, and some of these methods are mentioned in Table 1.

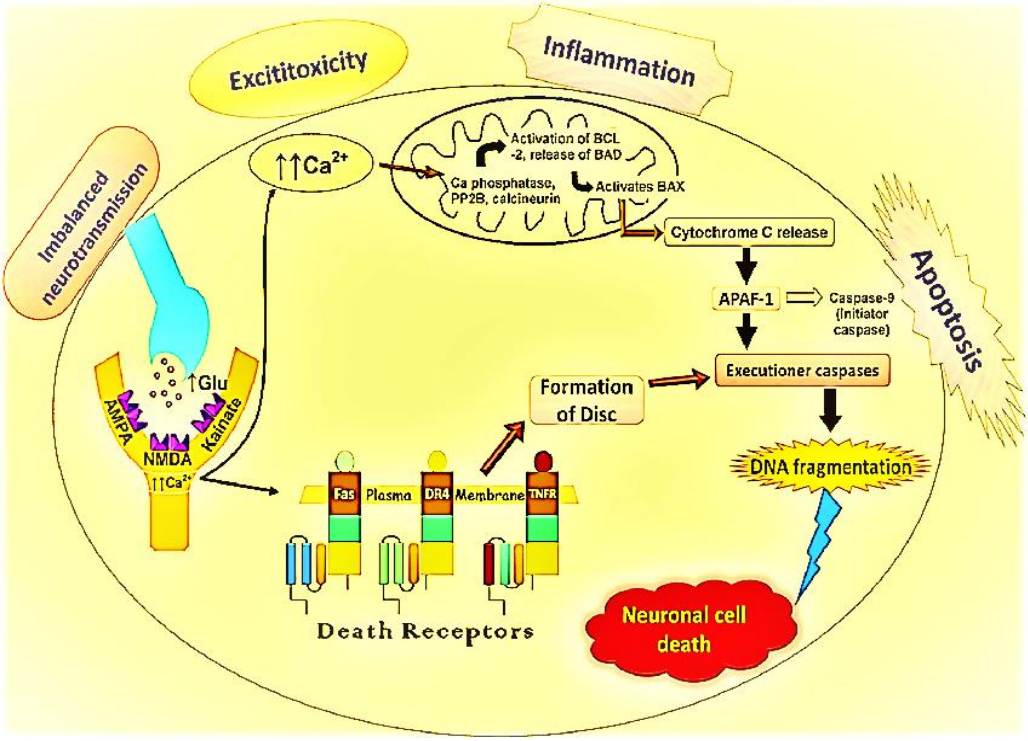

Figure 1: Pathophysiology of Epilepsy

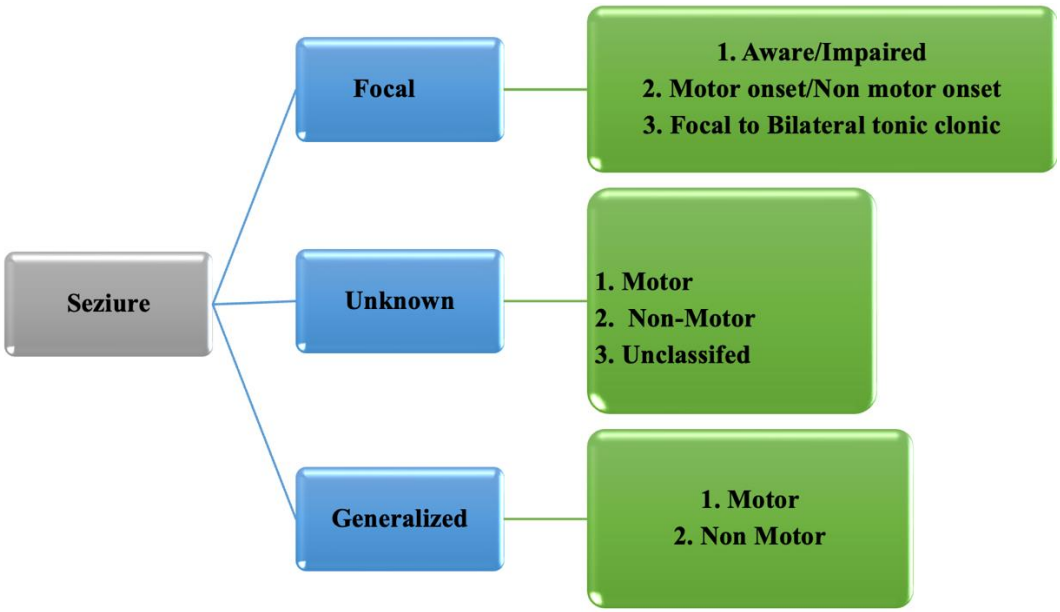

Figure 2 : Classification of Epilepsy

Table 1

Animal models	**Methods to induce convulsion**	**Types of seizures**
In- vivo model	Electrical stimulation : Maximal electroshock (MES) Kindling Chemoconvulsants: ➢ Pentylenetetrazol (PTZ) Strychnine ➢ Picrotoxin ➢ Isoniazid ➢ Lithium pilocarpine ➢ Yohimbine ➢ Bicuculline ➢ 4-aminopyridine ➢ n-methyl d-aspartate ➢ Penicillin	Generalised tonic-clonic seizures Myoclonic and absence seizures Acute simple partial seizures Clonic- tonic seizures Status epilepticus Clonic seizures Generalised tonic- clonic and absence seizures
In- vitro Model	▪ Hippocampal slices ▪ GABAA receptor binding Assay	Complex partial seizures
Genetic Models	Photosensitive baboons Audiogenic seizures mice Totterer mice and seizures -prone mouse strains Genetically epilepsy-prone rats	Generalised tonic - clonic seizures

Figure 3 : Maximal Electroshock (MES)- Induced Seizures

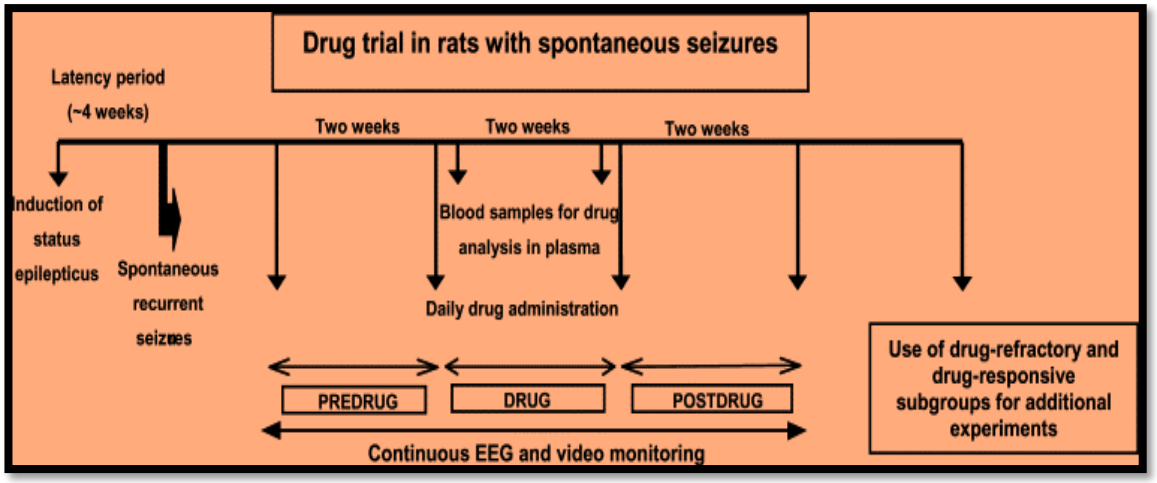

Figure 4 : Kindled Seizures Model

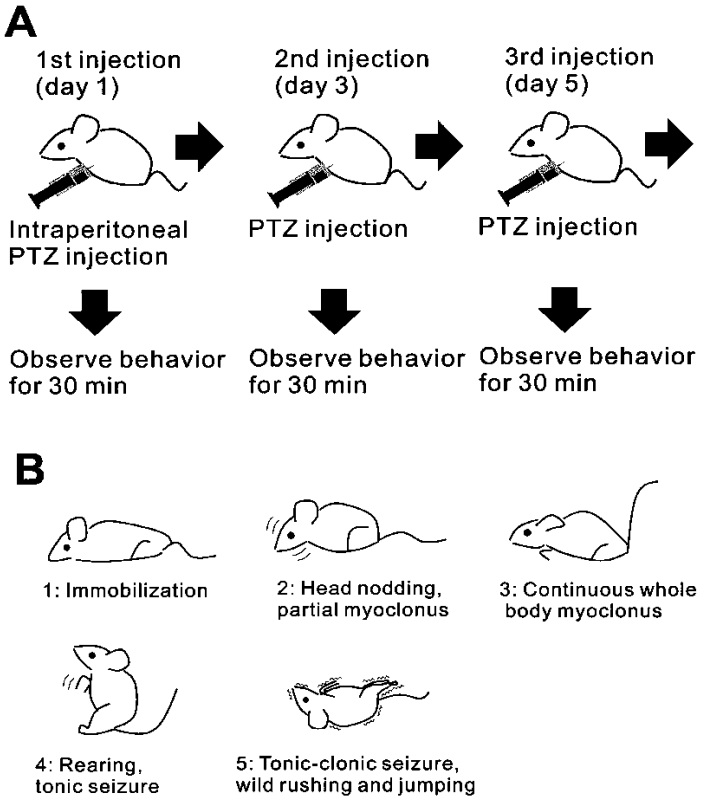

Figure 5 : Pentylenetetrazol (PTZ) Induced Model

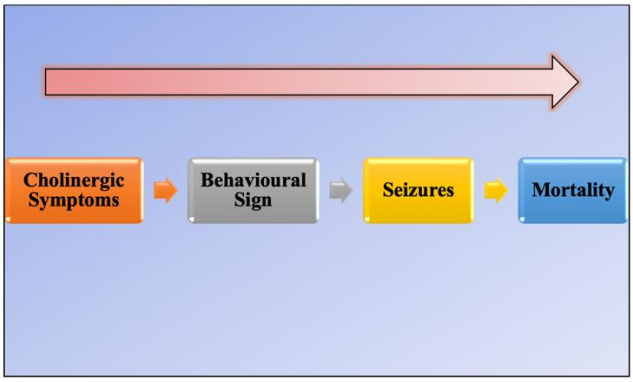

Figure 6: Development of Lithium- Pilocarpine Induced Seizures

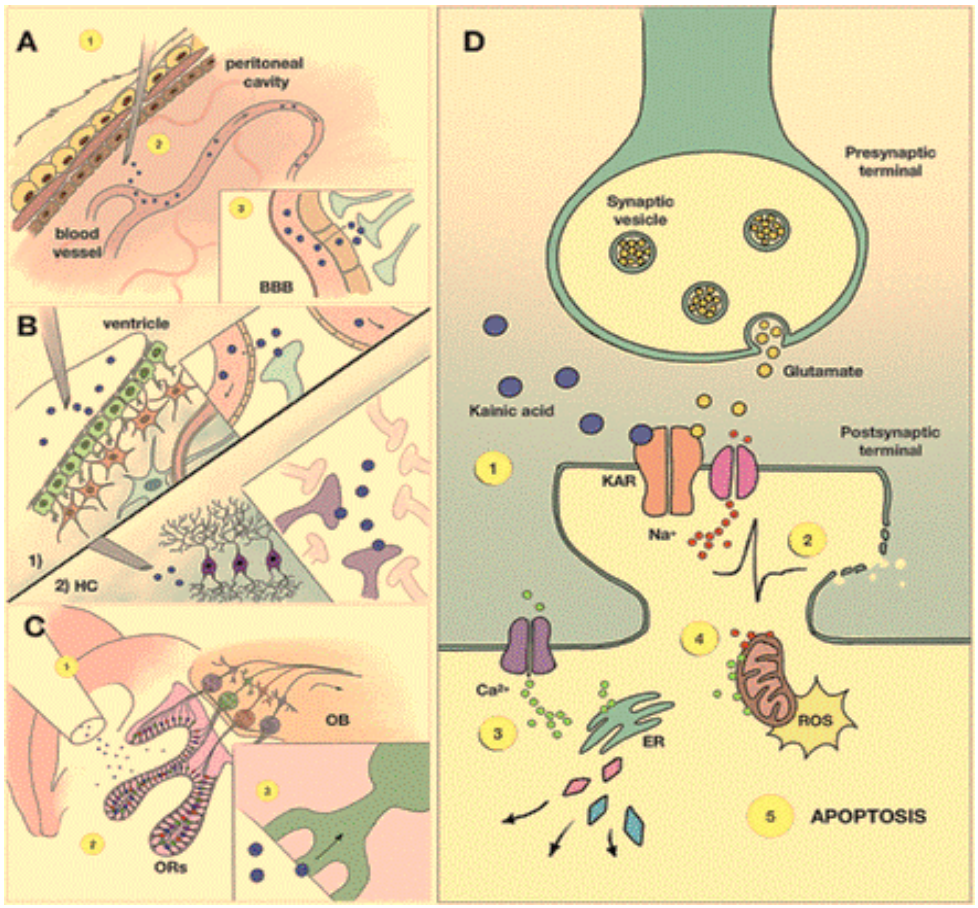

Figure 7 : Kainic acid (KA) model Mechanism

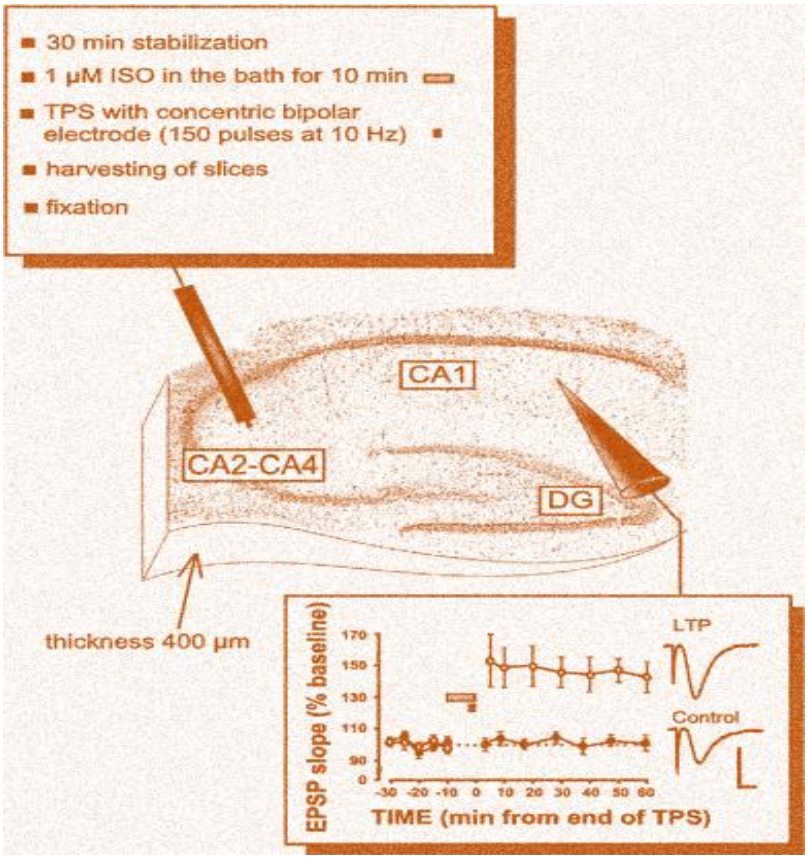

Figure 8 : Hippocampal slices Overview

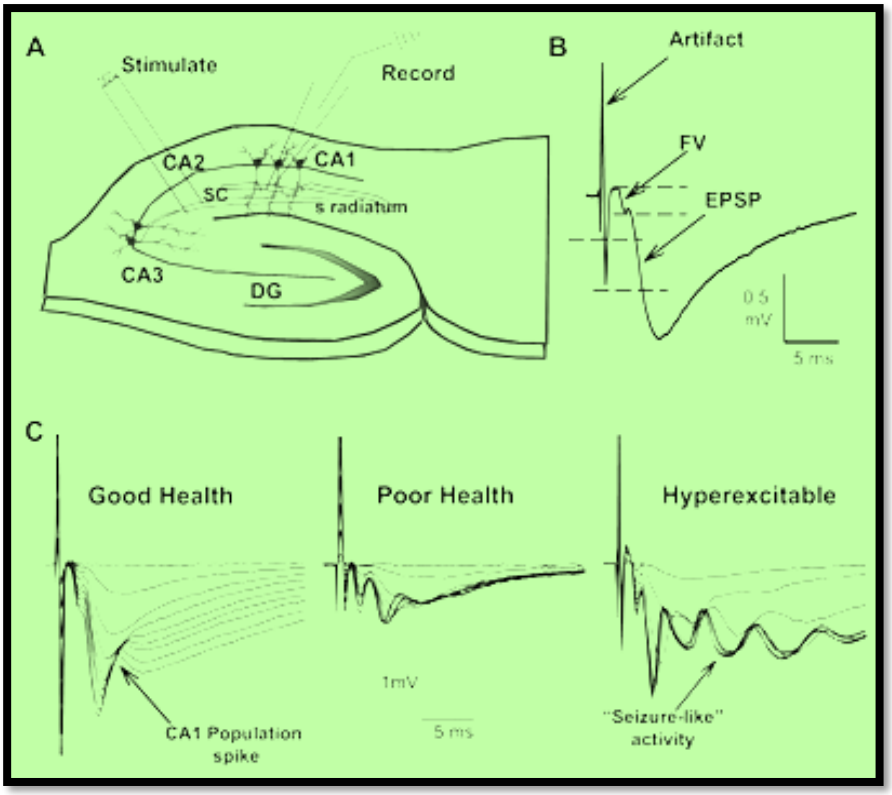

Figure 9 : Hippocampal slices Model Illustration

Maximal Electroshock (MES)- Induced Seizures

The animals employed in the maximum electroshock (MES)-induced seizures are mice or rats. An external device stimulator/convulsiometer is used to deliver an electrical stimulus strong enough to cause maximal seizures in the hind leg. The animals are given a supramaximal current strength, which is around 5- 10 times higher than their individual electrical seizure threshold (50 rnA in mice or 150 rnA in rats and for 0.25)[20-21]. Either corneal or ear clip electrodes are used to provide the stimulation. In this test, drugs like phenytoin, carbamazepine, phenobarbitone, and primidone are quite effective, whereas ethosuximide is useless. The fact that the stimulus is so intense is a major flaw in this test. As a result, certain potentially beneficial agents may be overlooked. Seizures are used to avoid this threshold. MES seizures, on the other hand, remain the gold standard for detecting antiepileptic action[22].

In addition, another study was conducted in which the rats were divided into five groups, each of which contained six rats. Different groups were given distilled water (10 mL/kg), diazepam (5 mg/kg), and ScMeOH at doses of 125, 250, and 500 mg/kg, BW, respectively. Convulsions were triggered in all groups of rats using an electro-convulsiometer thirty minutes later. Through the ear electrodes, a 60 Hz alternating current of 150 mA was supplied for 2 seconds. The presence of tonic hind limb extension was noted in the animal[23]. (Figure 3)

Threshold Model for Epilepsy

The ability of a medicine to change the seizure threshold for tonic hind limb extension is measured by the current or voltage causing hind limb extension in 50% of the animals in a threshold test. This test is substantially more sensitive to drugs than the MES test and is a better predictor of grandmal generalized seizures. Furthermore, threshold testing enable for the discovery of a drug's proconvulsant effects[22,24].

Kindled Seizures Model

Repeated application of a sub convulsive electrical stimulus causes seizure activity to gradually intensify, culminating in a generalized seizure in kindling. The resulting change is stable and long-lasting. Immobility, eye closure, vibrissae twitching, face clonus, and head nodding are the five stages of seizures. 3) contralateral forelimb clonus, 4) rearing frequently accompanied by bilateral forelimb clonus, 5) rearing and falling accompanied by generalized clonic convulsions Stages 1 and 2 are complicated partial seizures (limbic or temporal lobe), while stages 3 to 5 are limbic seizures that progress to generalized motor seizures. Kindling is a time-consuming operation that necessitates the placement of stimulation and recording electrodes on a long-term basis, as well as ongoing electrical stimulation[25-26].

The benefit of this model is that it allows the efficacy of a treatment to be tested both against the gradual process leading to epileptogenesis and against the fully ignited state. Many antiepileptic medicines are effective in preventing the development of kindled seizures, whereas others are effective in preventing the development of kindled seizures. Kindled seizures and the development of the kindling process are thus blocked by phenobarbital, diazepam, and valproate. Once kindling has occurred, phenytoin and carbamazepine inhibit seizures, but they do not reliably block kindling establishment[27-28]. (Figure 4)

Effect on leptazole -induced convulsions in rats

One hour after receiving the extracts and the usual medication diazepam (2 mg/kg, i.p.), all of the animals were injected subcutaneously with 80 mg/kg of leptazolein into the loose skin over their backs. The animals were kept under observation for another hour, and the presence or absence of convulsions was noted. The convulsion threshold was defined as the occurrence of face or forelimb clonuses lasting more than 5 seconds.

Picrotoxin-induced convulsions Model

The test chemical or the standard (e.g. 10 mg/kg diazepam i.p.) are given orally or intravenously to groups of 10 mice of either sex weighing between 18 and 22 g. The animals are injected with 3.5 mg/kg s.c. picrotoxin 30 minutes after i.p. treatment or 60 minutes after oral administration, and are observed for the following symptoms for the next 30 minutes: clonic seizures, tonic seizures, and death[29].

Isoniazid-induced convulsion

The test substance (e.g. diazepam 10 mg/kg i.p.) or the standard (e.g. diazepam 10 mg/kg i.p.) is administered orally or intraperitoneally to 10 mice of either sex weighing 18 to 22 g. Only the vehicle is sent to the controls. The animals are injected with a subcutaneous dose of 300 mg/kg isoniazid 30 minutes after i.p. or 60 minutes after p.o. treatment (isonicotinic acid hydrazide). Clonic seizures, tonic seizures, and death occur in rapid succession during the next 120 minutes[30].

Subcutaneous pentylene tetrazole (PTZ) method

Compounds that enhance the seizure threshold are identified by this model. Drugs that are effective against this seizure model could be used to treat non-convulsive seizures. The subcutaneous convulsive dose of PTZ for mice is 85 mg/kg, while for rats it is 70 mg/kg (produces clonic seizure in 97 percent of animals lasting at least 5 seconds, i.e. CD97). The animals are kept under observation for 30 minutes. The animal exhibits altered behavioural responses such as vibrissae twitching, myoclonic jerk with associated vocalization and Straub's tail, loss of righting reflex but regaining it after a few seconds, freezing movements, increased breathing, jumping and progressing to clonic seizure, and finally hind limb tonic extensor phase. The absence of clonic phase during the observation period shows that the substance under study raises the seizure threshold[31-32].

Penicillin model of absence seizure

After 1 hour of injectable administration of penicillin G (3 lac unit/kg) to a cat, epileptic activity commences, characterized by repetitive halted activity, myoclonus, staring, and occasionally escalating to GTCS. As seen in human absence seizure 13, this model depicts spike wave discharge with normal background activity on the EEG. The injection of pentylenetetrazol (85 mg/kg) subcutaneously is another means of generating absence seizures. Spike wave discharges can be seen on the EEG of the treated animals. Drugs that prevent PTZ-induced seizures are also beneficial in treating human absence seizures [24,33]

Pentylenetetrazol (PTZ) Induced Convulsions in Mice

Swiss albino mice of either sex, weighing 20–30 g, were randomly selected and marked to allow individual identification, then divided into four groups, each with six animals. Control: PTZ (80mg/kg, i.p.) + distilled water (5 ml/kg, p.o.) Diazepam (4 mg/kg, i.p.) + PTZ (80 mg/kg, i.p.) are the standard doses. PTZ (80 mg/kg, i.p.) + Ethanolic leaves extract (100 mg/kg, p.o.) Test II: PTZ (80 mg/kg, i.p.) + Ethanolic leaves extract (200 mg/kg, p.o.) For a period of seven days, the test medication was continually given. PTZ was used to cause convulsions on the seventh day. Prior to the experiment, all animal groups were given PTZ injections after receiving the appropriate therapy[34].
(Figure 5)

Lithium pilocarpine model

Pilocarpine, at a dose of 350 mg/kg i.p., was used to cause epilepticus. Atropine 1 mg/kg i.p. was given 30 minutes before pilocarpine to diminish the cholinergic effects of pilocarpine in the peripheral nervous system. The standard was diazepam (5 mg/kg). The test medication was given orally 1 hour before the pilocarpine nitrate injection[35]. 15 Every 15 minutes until 90 minutes, and then every 30 minutes until 180 minutes, the severity of status epilepticus was assessed using the following scoring system: Stage 0 - no response, Stage 1-fictive scratching, Stage 2-tremor, Stage 3-head nodding, Stage 4-Forelimb clonus, and Stage 5-Rearing and falling back. The alternate strategy of lithium pre-treatment followed by one or multiple low doses of pilocarpine causes status epilepticus (SE) and chronic epilepsy, according to the researchers.

The alternate strategy of lithium pre-treatment followed by one or multiple low doses of pilocarpine causes status epilepticus (SE) and chronic epilepsy with considerably lower fatality rates than a single dosage of pilocarpine, according to the researchers. Pre-treatment with lithium chloride (3mEq/ kg, i.p.) between 2 and 24 hours before pilocarpine injection potentiates the drug's epileptogenic effect and allows for a 10-fold reduction in the drug dose [36]. (Figure 6)

Bicuculline model

Bicuculline has been used in both a focused and systemic manner. After topical treatment in the sensorimotor cortex of rats, it was utilized to elicit acute simple focal epilepsy. Researchers established another model involving biculline and the production of chronic simple partial seizures. Systemic focal epileptogenesis is a paradigm that combines the characteristics of focal and generalized epilepsy. In this model, rats get radiation to a small portion of their cerebrum (0.25 ml). When the blood-brain barrier is injected systemically three to six months later, an epileptic focus is induced with repeated EEG spikes and focal seizures that last for several weeks following a single injection. Phenytoin, phenobarbital, chlordiazepoxide, and valproic acid all reduce the surges. Bicuculline is thought to have an epileptogenic impact via interfering with GABA ergic neurotransmission by competing for binding sites with GABA (2).

Kainic acid (KA) model

Wet dog shakes, generalized tonic-clonic convulsions, teeth chattering, and changed motor activity, including an initial hypoactivity that converts to a hyperactivity at a later stage, are all symptoms of systemic injection of the appropriate amount of KA. As early as 3 hours after injection, neurodegeneration begins in the pyramidal layer of the CA3 area of the hippocampus and in the piriform cortex. At this time, there is a positive link between the KA dose and the severity of the acute neurochemical alterations in all brain regions studied, including increases in 3, 4-dihydroxyphenylacetic acid and decreases in noradrenaline levels. Neuronal somata deteriorate and vanish in places such the olfactory cortex and sections of the amygdaloid complex, hippocampal formation, thalamus, and neocortex between 13 hours and 2 weeks[36].

In 1978, scientists discovered that KA, a cyclic analogue of L-glutamate that acts as an agonist for the ionotropic KA receptors (KARs), damages hippocampus pyramidal neurons. However, numerous researchers initially suggested the use of KA as a model for epilepsy when they performed a unilateral intra-amygdaloid injection of KA in non-anaesthetized non-paralyzed rats and observed focal seizures evolving into SE as the dosage was raised.

In addition, the CA3 field of the hippocampus showed neuronal loss and gliosis. These and other studies suggested that KA may be used to simulate TLE in animals. When KA is injected, its corresponding receptors are activated[37]. (Figure 7)

Strychnine Induced Convulsion

Strychnine is a powerful convulsant and a selective inhibitor of glycine receptors. Its convulsant action is assumed to be caused by inhibiting the motor neurons feedback inhibition. Other effects of strychnine have been discovered, including the suppression of noradrenaline and acetylcholine release from the brain. Although there is conflicting evidence, catecholamines have been linked to seizures. The noradrenergic system has been found to produce convulsant or anticonvulsant effects when stimulated or inhibited[38]. Control (0.9 percent Saline), standard (Diazepam 5 mg/kg, i.p.), group III (EERA 200 mg/kg, p.o.) and group IV (EERA 400 mg/kg, p.o.) albino mice of either sex were divided into four groups, each with six animals: control (0.9 percent Saline), standard (Diazepam 5 mg/kg, i.p.), group III (EERA 200 mg/kg, p EERA was given to groups III and IV once a day for three weeks. Strychnine nitrate (2mg/kg, i.p.) was given on the 21st day, 30 minutes after i.p. injection of Diazepam and 60 minutes after oral delivery of extract. During a one-hour period, the time between the onset of tonic extensor convulsion and death was recorded[34].

Hippocampal slices Model

Chronic animal models of epilepsy can be used to obtain hippocampal slices. Models of TLE and epileptogenesis, including as the kindling, kainite, and pilocarpine models, have benefited from the slice's technical advantages in investigating detailed cellular and synaptic events. The chronic phase of epilepsy, during which the animals exhibit spontaneous recurrent seizures (epilepsy), and the latent period, the time between the initial injury and the first spontaneous seizure, have both been studied following an epileptogenic event or stimulus (epileptogenesis). During epileptogenesis and the chronic phase of epileptogenesis, the hippocampus undergoes significant changes. (Figure 8, 9)

The fact that these animals are epileptic is an evident advantage of examining hippocampal slices from chronic animal models (rather than researching epileptiform phenomena in "normal" tissue). This fact permits the researcher to look at variables that are linked to epilepsy or may be causally related to ictogenesis. Unfortunately, as previously stated, interictal-like or ictal-like discharges have not been observed in epileptic animal slices under physiologic settings. Slices from the ventral hippocampus, which can record spontaneous waves, have yet to be tested. Another application of these slices is to look at the specifics of hippocampal circuitry abnormalities linked to epilepsy. The slice preparation enables for high data generating throughput, but it is confined to precise examination of single cells (with intracellular recordings) or the gross behaviour of small groups of neurons (with extracellular recordings). Recent technological advancements, notably in imaging approaches, have made it possible to investigate network features during slice preparation. With high-speed two-photon calcium imaging devices, for example, it is possible to concurrently record the activity of hundreds of neurons and then record from individual neurons to gain access to more microscopic features[39-41].

Photic seizures Model

In 60-80 percent of adolescent baboons, myoclonic responses to intermittent photic stimulation occur[42]. However, this reaction to antiepileptic medications is only partially comparable to human disorders. Domestic fowls are similarly susceptible to photo-induced seizures. Benzodiazepines, barbiturates, and valproic acid, which are used to treat clinical tonic-clonic and myoclonic epilepsy, can prevent these seizures.

Phenytoin, carbamazepine, and trimethadione have less beneficial therapeutic effects. These seizure models have a number of flaws, including:

a) uncertain predictive validity against a specific clinical subtype of seizures.

b) baboons' high prime and maintenance costs restrict their utility[28, 43].

Gama-hydroxybutyrate (GHB) model

GHB is a naturally occurring metabolite of gamma-aminobutyric acid (GABA) that causes electroencephalographic and behavioural abnormalities in animals that resemble generalized absence seizures[44-46]. GHB-treated animals, including monkeys and rats, show a characteristic halt in activity with gazing and bilaterally synchronous spike wave discharges. Anti-absence medications like ethosuximide specifically prevent this activity, while phenytoin makes it worse[47]. Gamma butyrolactone (GBL), a GHB prodrug that is rapidly transformed to GHB after parenteral injection, has similarly been demonstrated to cause spike and wave discharges [48] . The EEG and behavioural alterations are similar to those caused by GHB, but with a faster beginning of action and a more predictable dose response. GBL has no such impact on its own. After repeated daily injections of GBL, rats develop spontaneously occurring recurrent electroclinical seizures, according to a recent study[49]. The cause of epileptiform activity is unknown, but it is possible that it involves some type of neurotransmitter system or, more specifically, suppression of GABAergic neurotransmission[50-51].

CONCLUSION

To summarize, the pharmaceutical industry typically employs a mechanism-specific approach as a major screening tool, while mechanism-independent models are utilized to validate various mechanism-based hypotheses. Secondary examination is carried out using seizure type models. Different epilepsy models significantly advanced our understanding of epileptogenesis and ictogenesis. The models outlined above can be used to find and define new chemical entities that can be employed to treat epilepsy. Electrical stimulation regimens, neuro-chemical agents, hypoxic or thermal insults, traumatic traumas, rodent strains, and optogenetics with audiogenic or idiopathic-induced seizures are among the instruments used in animal models of epilepsy. An essential factor to consider is that Screening models do not predict efficacy in treating human epilepsy and simply present options for which drugs should be explored. The ultimate test for proving anticonvulsant activity is the use of patients to validate the findings of Screening models.

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