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ANIMAL MODELS USED IN THE SCREENING OF ANTIEPILEPTIC DRUGS

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ABSTRACT: Epilepsy is a disorder of episodic brain dysfunction characterized by recurrent unprovoked spontaneous seizures. Epilepsy is the second most common neurological disorder after stroke. Antiepileptic drug discovery in animal models starts with the assumption that the experimental seizure model mimics human seizure. The identification of potential therapeutic agents for the treatment of epilepsy requires the use of seizure models. Animal models for seizures and epilepsy have played a fundamental role in advancing our understanding of basic mechanisms underlying ictogenesis and epileptogenesis and have been instrumental in the discovery and preclinical development of novel antiepileptic drugs (AEDs). Most animal models cannot mimic all the pathophysiological, behavioural, electrophysiological, and neurochemical alterations of the spontaneous human epileptic syndrome. Therefore, while a selected few are used for routine screening of anticonvulsant compounds, some help in understanding mechanisms underlying epileptogenesis. In the case of antiepileptic drug development, once a compound appears promising, a battery of tests is carried out to characterize the clinical profile and possible mechanisms of action. A model for epilepsy is based on various criteria's, and for a model to be successful, it should have the ideal characteristics needed for the seizure model. There are many models available based on which type of epilepsy it is. This article describes the various experimental models of seizure and epilepsy.

INTRODUCTION: It is important to understand anatomy, physiology and disease mechanisms which is not completely possible on the human body; thus, an animal model of human disease is the base to develop newer therapies like preclinical screening. Epilepsy is a condition due to manifestation of paroxysmal and neuronal discharge disorder caused by abrupt. Changes in the physiology of the brain and usually characterized by seizure recurrence, which can vary depending on site, duration, and paroxysmal discharge propagation mode, reasoning the different clinical variation of epilepsy disease rather than having a single pathology [1, 2].

Epilepsy accounts for about 1% of world's burden of diseases, having 2% prevalence rate making it the most serious brain disorder that affects about 40 million people, and 100 million have chances to be affected in some time of their lifespan while in infants and children primary generalized tonic-clonic and absence seizure have increased incident rate [2, 3]. The initiation and propagation of the seizure are considered for experimental seizure

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model for discovery of new therapeutic agent and use of animal seizure model is best suited for developing new drugs for treatment of epileptic seizures. Evaluation of Phenytoin (PHT), carbamazepine (CBZ) and valproate (VPA) sodium were done with the help of a relatively simple screening procedure, and either the spread of seizure or the threshold of seizure were used as evaluation parameters which were unable to provide understanding into the mechanism of action of drugs. The clinically effective compound was used to validate the developed animal models that used simulation or chemoconvulsants.

Identification of recently marketed antiepileptic Drugs (AEDs) also the therapeutic activity and toxicity of new antiepileptic drugs can be studied utilizing various animal seizure models and species against different human epilepsy type [4]. In 19th century the major advancements in animal model led to the conclusion that, lab animals imitate the clinical symptoms of epilepsy as that of human and these models were helpful in determining the efficacy, varied aspects of neuronal function of seizure activity by anticonvulsant drugs. It was seen that separate models of animals had shown varied anticonvulsant activity revealing that not all seizures are same and their experimental screening is discussed by. In epilepsy, animal models have played a key role and has aided the development of anticonvulsants of clinical use [5, 6, 7].

Animal In Drug Discovery: The translation gap if preclinical and clinical research can be bridged by animal models. They are as follows:

Target Identification

Target Validation

Lead Identification and Optimization

Pre-Clinical testing for Safety and Efficacy

Clinical Trials

Model Validity: Animal model validation was proposed in 1984 by Wilner. Validation of the model is important because animals in the laboratory whether mice, cat, or monkeys, the disease is artificially induced in them and is not same as those which naturally arise in humans**.** The most widely accepted criteria for validation of the animal model is as follows:

Predictive Validity: It can be explained how good a model can be designed to predict freshly unknown aspects of diseases in humans, such as human-animal correlation of therapeutic outcomes, 6-OHDA rodent model for Parkinson's Disease.

Face Validity: It depicts how well a model can resemble the phenotype of disease in human for example the common disease, symptoms, signs between animal model and human for a particular disease. Example MPTP (1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine) non-human primate model for Parkinson's disease.

Construct Validity: It shows the effectiveness of mechanism used to produce the phenotype of disease in animals that mirror's the current comprehended etiology of disease in humans.

Fit To Purpose: The validation is significant for a given model to be fir-for-purpose. Out of the three categories of validation, the dissimilar animal model will give diverse outcomes as no animal model can accurately depict the same clinical condition; also, not all models can show all three validity criteria. Ex: Face validity may be more important when researching potential patho mechanisms. Ex: predictive validity has a higher priority for models to be used for benchmarking or preclinical drug discovery.

Approaches to Model Development: Available model modifications (hit and trial), Amygdala kindling along with Anti-seizure drug (Lamotrigine), After it was described by postma Epilepsy Therapy Screening Program (ETSP) adopted it. It is a part of ETSP currently. Corneal kindling in the existence of the anti-seizure drug (Lamotrigine) is described lately and is not a part of ETSP. Chemical kindling in attendance of Anti-seizure drug (Lamotrigine), At the moment, characterized in the study and is accepted in animal models and experimental medicine

Experimental Model of Epilepsy: An experimental model is applicable depending on its resemblance to human diseases, including its low cost and provides results rapidly. A model is considered ideal if it follows all the mentioned points, but to date, no model exists to satisfy all the conditions; thus, the ongoing models have some compromises.

The existing animal model can be partitioned into 2 groups as follows: The first category includes the simple, fast, and cost-efficient models useful for prime screening of new chemical entities. The second category consists of highly developed methodology needing elaborate equipment alongside slow and high-cost models for determining the specificity and deeper pharmacological profile. Numerous experimental model having their own characteristics pattern are present for the screening of anticonvulsant drug [9].

Animal Model of Seizures and the Development of Antiepileptic Drugs:

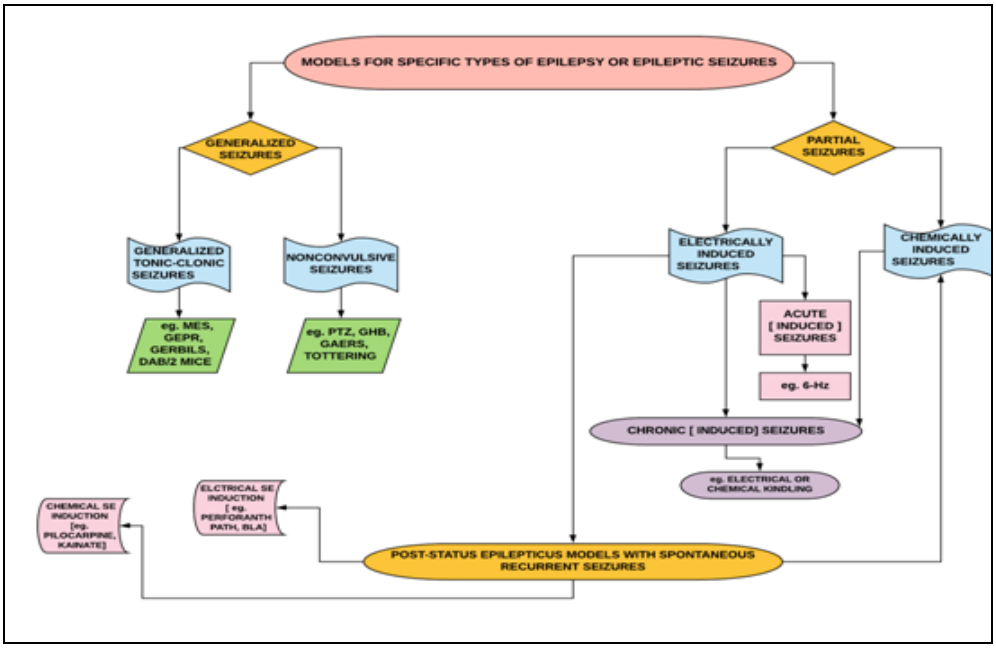

FIG. 1: ANIMAL MODELS FOR SPECIFIC TYPES OF EPILEPSY OR EPILEPTIC SEIZURES8

Criteria for Selection of Suitable Animal Model: Following considerations must be taken while selecting any model, especially animal model for research:

Suitable as an analogue, Information transferability, Organism's genetic uniformity if applicable, Proper background knowledge of biological properties, Its cost-effectiveness, and availability

Characteristics of Ideal Model of Seizures: On-the-spot development of recurrent occurring seizures. Alikeness of seizure type in clinical phenomenology compared to human epilepsy.

The onset of age-dependent epilepsy, as in the case of generalized epileptic syndromes in a person. Clinical seizures should be linked in EEG (Electroencephalogram) in epileptiform activity. Antiepileptic drugs pharmacokinetics should be compatible with those in humans. The effective plasma concentration of antiepileptic drugs should be related to those required for controlling the particular seizure type in humans [10].

Animal Models of Seizures:

Generalized Seizure Models:

The Maximal Electroshock Model (MES): It is a preferred model for generalized seizure by evaluating drug-using electroshock, which is validated clinically as well as electroencephalographically.

Description: It is very well known for the validated preclinical test to estimate the effectiveness of the drug against grand mal seizure and is also a model having gold standard in the early stage of antiepileptic drug screening. Compared to human seizure, it has an almost the same behavioural and electrographic pattern. The aim of the model is to screen the antiepileptic drugs which halts the spread of seizures. Seizures can be induced by 2 different methodologies, which tend to doffer as they activate a different part of the brain.

The first method is through transcorneal electrodes, which favourably activate the forebrain structures. The second is with the help of trans-aricular electrodes that activate the brain stem, thus being more beneficial in tonic convulsions. Trans-auricular electrode-induced seizures have a low seizure threshold making it hard for the anticonvulsant drug to inhibit it compared to corneal electrode-induced seizures. Thus it is noted that drugs more potent in MES induced by corneal electrode [11, 12, 13, 14].

Method: Adult male albino rats or mice are chosen. For per drug dose/vehicle, 6 animals are usually used. The animals chosen should have the same weight, age and all the experiments on them should be conducted on the same time of the day as a bunch of factors present such as endocrine, nutritional, temperature *etc.,* alter the seizure. All animals are given an adequate amount of food and water but are put on fasting during the test as before test starving can modify the seizure pattern induced by MES. For all convulsions induced electrically, the animal is held using hand and released just before simulation for accurate observation of seizure during the entire course. Simulations carried out by direct application of corneal electrodes causes' pain and bleeding therefore, trans-auricular electrodes (applied to the pinna with small crocodile clips covered with cotton wool & saline-moistened) are used. Saline moistening is compulsory for better contact and minimise fatal injuries resulting from MES-induced seizure. Supra maximal electroshock stimulation of 150mA (rats,) 50mA (mice), 50HZ, evoked maximal seizure for 0.2 seconds timespan [6, 7].

Two phases are included in MES profile for rodents:

Phase I: It determines tonic flexion of fore and hind limbs, terminal clonus and hind limbs tonic extension (HLTE)

Phase II: It involves stupor or unconsciousness and postictal depression.

Absence Seizure Models:

The Pentyleneterazole (PTZ) Model: The most common model employed for anticonvulsant screening is the systemic administration of pentylenetetrazole. Richard and Everett introduced Anticonvulsant seizure by PTZ as it has various advantages like easy to perform, reliable, simplified results, short time span required to produce convulsions in contrast to other models, which makes it the most preferred model [15].

Description: in this model, sub-cutaneous or intra-parenteral route of administration is used to inject PTZ and induce an epileptic seizure in rats, cats, mice, or primates. According to literature, for inducing seizures in rats, the dose varies from 70-90 mg/kg PTZ to originate generalized clonic seizures, and higher doses produce tonic seizures. The seizure is resembled by spike-wave complexes (*i.e.,* Clonic Seizures) or sharp hyper synchronizedpoly spikes (tonic seizures) in Electroencephalogram (EEG).

PTZ's mechanism of action is co-related to inhibit the inhibitory function of the GABA neurotransmitter as it antagonizes GABAergic function, and PTZ has a good affinity for the Clionophore of the postsynaptic GABA receptor complex [16].

Method: PTZ act on the entire parts of the CNS when the dose is high (100 mg/kg., sc), but the most susceptible zones are the cerebral cortex also, both types of seizures, namely tonic and clonic, are observed. The subcutaneous route is a fixed, adequate dose method because it is convenient, easy administration, as well as multiple doses and drugs can be tested with the least effort, although other methods such as slow infusion through the vein of the tail up to the endpoint of minimal seizures which is another technique mostly referred to as timed PTZ-Infusion approach.

Myoclonic jerks and clonic seizures can be triggered by a dose of 70 mg/kg., s.c (dissolved in 0.5% saline), sometimes even fatal tonic seizure might take place but 97% of animals successfully show seizures symptoms. In this model, PTZ is usually given 30 min after the test drug or depends on the peak effect of the test drug. The rats are looked after for half an hour post drug, and the response of PTZ is seen after 2.5 min after administration. The test compound is known to show anticonvulsant activity and has 100% protection and if there is negative observation of even a single episode of clonic spasm in at least 5

sec of duration. Index of anticonvulsant activity is taken in case of abolition of clonic seizure [17].

Advanced, Slow and Expensive Models: In this category, there are several models of epilepsy. A few of the models are listed below:

Acute Models:

Genetically Determined Syndromes of Reflex Epilepsy: It is primary generalized epilepsy such as: In Senegalese baboon, it is photic produced epilepsy. Seizure with secondary sensory induction may exist in few inbred strains of rodents as DBA/2 Mice and Genetically Epilepsy Prone Rats (GEPR) whereas, a genetic predisposition for seizures is seen in Gerbils, while a strain of Wistar rats has the genetic disposition for absence seizures [18].

Chemically Induced Focal or Generalized Seizure:

Bicuculline Induced Seizures: The possible GABA agonist activities mediated at GABA receptors is predicted.

Picrotoxin Induced Seizures: Picrotoxin block the GABAA receptor channel, which is associated with voltage-dependent Ca2+ channels, and also blocks presynaptic inhibition of excitatory transmitter release, which is antagonized by GABA, GABA mimetic agents along with Ca2+ channel blocker.

Strychnine: Strychnine is a glycine antagonist specifically and an activity opposite to strychnine generated seizures see activity at glycine receptor site particularly at spinal cord level.

Thiosemicarbazide (TSCZ): There is a net decrease in GABA levels in the brain with this chemical also it is the best pro-convulsant agent to test drugs with potential anticonvulsant activity. For instance, gabapentin (neuremhin), a new antiepileptic drug, has no mechanism related to GABAA or GABAB receptor. It does not interfere in GABA metabolism; some parts of the brain have shown to elevate GABA content, and in TSCZ test gabapentin, it can be actively seen. It is also moderately active in PTZ test and a lot less active in antagonizing seizures induced by Bicuculline and Picrotoxin.

G-Hydroxy Butyrate (GHB): A GABA metabolite that occurs naturally and produces a predictable sequence of EEG. It also shows behavioral events and characteristics of absence seizure when administered to different species of animals.

Penicillin: After direct administration of penicillin by injection in the cerebral cortex of monkeys, cats, dogs, men, and mice, seizures are seen within 2 min with EEG alteration and grossly observable convulsions, which are then graded accordingly to Millichap proposed scale.

Yohimbine: Yohimbine produces clonic or tonic convulsions as induced by Picrotoxin with a dose (3-12 mg/kg) administered intraperitoneally. Convulsions are induced in mice after exposing the test animals to hyperbaric oxygen, which significantly causes GABA levels reduction in the brain.

Pilocarpine: Pilocarpine develops limbic seizures, which later on progress into limbic status epileptics. This happens when it is systemically administered at high doses in rats (400 mg/kg) or mice (300-350 mg/kg) [19, 20, 21].

Lithium-Pilocarpine Model: It consists of adding a minute amount of lithium chloride (4 mEq/Kg) intraperitoneally to increase the consistency of pilocarpine. Lithium chloride is given 24 h prior to intraperitoneal administration of pilocarpine (20 mg/kg). For counteracting the peripheral effects, scopolamine is given 30 min earlier than pilocarpine administration and the animals treated show behavioral and electrographic proof of status epilepticus for 5 h [22, 23].

Other Chemicals Used For Inducing Convulsions: There are other chemicals that induce convulsions like brucine, thebaine, synthetic strychnine like agents, nicotine, caffeine, Carbon dioxideand isoniazid induced convulsion in rabbits.

Sensory Precipitated Generalized Seizure Model: For clinical manifestations like running movements, audiogenic and photogenic seizure models are useful and flexion, extension and clonus are documented clearly but the EEG evidence for such seizures are not yet established properly [17].

Chronic Models:

Primate Model: Epilepsy is a chronic disease, and a primate model would be appropriate for obtaining accurate results; with recurring focal or generalized seizures, they can be treated with antiepileptic drugs for a long period would make it easier to co-relate the drug treatment of human epilepsy. The impact of A particular drug can be contrasted with a placebo based on the type of seizure, its frequency, along with the drug's tolerance, and appearance of side effects. Furthermore, with the pharmacokinetics of the drug, it can gather details regarding the dosing intervals, t1/2 steady-state, and maintenance dosing, which are notable considerations for controlling seizures.

The primate model (alumina gel model) has given accurate results for the potentially known AEDs and is the only model that evinces that the spontaneous seizure of focal onset occurs repeatedly for months and years, making it more nearer to human epilepsy. The absence seizure primate model in preadolescent juvenile monkeys gains good anti-absence activity. Many such distinct models should be studied and researched about various forms of epilepsy that show a close resemblance to epilepsy found in man24.

Rodent Model: Rodent Model is given more preference than the primate model, although the cerebral anatomy should be just like that found in humans. Advanced chronic rat model with chronically implanted electrodes demand long-term recording of spontaneous EEG [25].

The Kindling Models:

A Pentylenetetrazole (PTZ) Induced Kindling In Rats: The most appropriate model for generalized epilepsy is the PTZ induced kindling in which kindling in the rats and mice can be performed by repeated injecting small doses of PTZ. The procedure consists of administering PTZ (30 mg/kg) by intraperitoneal route for every alternate day for about 10 weeks to develop kindled seizures instead of antiepileptic drugs like diazepam and sodium valproate.

The induced seizure is characterized by generalized spike and wave discharges shown on the EEG which is concurrent with generalized seizures such as myoclonic and tonic seizures. The basic neuronal mechanism of PTZ - kindled seizure is not much evident, but it is known to be a potent convulsant by showing its action via a particular interaction with GABA-coupled chloride ionophore [26, 27, 28, 29].

B Cobalt Induced Kindling In Rats: Clinically similar seizures as kainate-induced seizures and amygdala kindling are produced by microinjecting cobalt chloride into the lateral cerebral ventricle [30].

C Tetanus Toxin: Injecting tetanus toxin unilaterally in the hippocampus leads to neuronal loss in CA 1 pyramidal cell layer of hippocampus producing kindling model of recurrent and chronic partial seizure [31].

Alternatives to Animal Models In Epilepsy

Zebra Fish Model (DanioRerio): The wild variety of larval zebrafish is used in this model. Introducing freely swimming zebrafish to PTZ induces behavioral changes at concentrations between 2.5 – 15 mM at 7 pH.

Stage 1 can be graded by the boost in swimming activity, while in stage 2, rapid circling can be seen along the outer edge of the well, and in final stage 3, there are brief head-to-tail convulsions followed by free-floating (loss of posture). By mounting the fish on an agar plate, the electrophysiological changes can also be analyzed [32].

Execution of Epilepsy Model In Laboratory

Maximal Electroshock (MES) Induced convulsions: The experimental animals in MES model are exposed to maximal electroshock (40 mA for 0.2 sec for mice and 120 mA for rats) after their treatment using an electroconvulsive meter.

Later the duration of hind limbs extension and the protection percentage of the mice that is the abolishment of the hind limb extension before 10 seconds is noted, and then the different test groups are compared against phenytoin as a standard reference [33].

PTZ Induced Convulsions: In PTZ induced convulsant model, the experimental animals (mice preferably) are administered with PTZ (80mg/kg) intra peritoneally after their respective. Treatment and the start of convulsant and percentage of animals protected (*i.e.* the no. of animals alive after

convulsions) after 30 min of onset of convulsions is recorded. Different treatment groups are inter-compared opposite the reference standard that is Diazepam [34].

Picrotoxin - Induced Convulsion In Mice: In this model Picrotoxin 2.5 mg/kg is injected intra peritoneally to the experimental animals (rats) and later are monitored for tonic convulsions and further kept under observation to note lethality [35].

Strychnine (STR) Induced Convulsions: The experimental animals (preferably rats) in this model are given strychnine (2 mg/kg) intraperitoneally, and the tonic convulsions onset and animals protected percentage after 30 min of the start of convulsions is noted. The standard reference used was diazepam which was inter-compared between different animal test groups [36].

Isoniazid (INH) Induced Convulsions: In this model after the respective drug treatment, the experimental animals (mice) are administered with isoniazid (300 mg/kg) injection intraperitoneally and the beginning of convulsions and survival rate of animals after 24 h is recorded and compared opposite the control mice. Diazepam was used as the standard drug of treatment [37].

Lithium - Pilocarpine Induced Seizures: In this model, status epileptics are induced in experimental animals (mice) by administering pilocarpine (30 mg/kg - intraperitoneally). 24 h after lithium sulphate (3 mEq/Kg - intraperitoneally) after their particular drug treatment. At 100 mg/kg intraperitoneal dose, the effect of test compounds was studied on the severity of seizure which was observed every 15 min till 90 min and after that every 30 min till 180 min using the scoring system.

The Grading for the Response Can Be as Follows:

- Stage. No response
- Stage. Fictive Scratching
- Stage. Tremors
- Stage. Head nodding
- Stage. Fore limb clonus
- Stage. Rearing and falling back [38].

Induction of Epilepsy by Electrical Kindling: In pre-treated experimental animals, auricular electrodes are used to give a sub-convulsive shock of 21 mA for 0.1 sec twice 3 h apart. After the electroconvulsive shock, the scores are recorded after 1 h and 3 h of induction [39].

Hypoxia-Induced Convulsions: In hypoxia, induced convulsions, the experimental animals are subjected to hypoxia by producing a vacuum in the experimental jar after the respective treatment and is graded for its behavioral changes recorded [40].

CONCLUSION: In summary, the above-discussed models can be used to identify and characterize new chemical entities to treat epilepsy. Animal models of epilepsy include several tools, including electrical stimulation protocols, neuro-chemical agents, hypoxic or thermal insults, traumatic injuries, rodent strains, and optogenetics with audiogenic or idiopathic-induced seizures. An important parameter should be considered: animal models do not predict efficacy in treating human epilepsy but provide only choices for determining which compounds should be developed. The ultimate test for proof of anticonvulsant activity necessitates the use of patients to validate the conclusions obtained from animal models.

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