Internationale Pharmaceutica Sciencia

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General Overview on Anti-epileptic Screening Models for Plant Molecules/Synthesized Molecules

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Article info

Received 11 March 2020
Revised 06 April 2020
Published 13 April 2020

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Abstract

This paper reviews model advances in epilepsy in recent years. Epilepsy is the commonest serious neurological condition, with a prevalence of 0.5–1% and Epilepsy is a chronic neurological condition characterized by recurrent seizures. Use of appropriate animal models is essential because epileptogenesis and seizure generation in temporal lobe epilepsy and other forms of epilepsy cannot be fully acquired in clinical studies with humans. Seizures are a combination of electrical and behavioral events that can induce chemical, molecular, and anatomic alterations. In this review, we summarize the most frequently used models of chronic epilepsy and models of acute seizures induced by electrical and chemical kindling. Kindling is animal models of epilepsy induced by electrical stimulation of the brain. Seizures are induced with minimal neuronal damage, which could greatly enhance our ability to define the basis for the initiation and remission of spontaneous seizure. Various animal models are also critical for elucidating the mechanisms underlying neurologic dysfunctions induced by developmental alcohol exposure and for uncovering the evolutionarily conserved mechanisms of epileptogenesis.

Keywords: Epilepsy; Animal models; Anti-epileptic screening; Electrically induced

Introduction

Epilepsy is a central nervous system (neurological) disorder in which brain activity becomes abnormal, causing seizures or periods of unusual behaviour, sensations, and sometimes loss of awareness.

Focal (or partial) seizures: Occur when seizure activity is limited to a part of one brain hemisphere. There is a site, or a focus, in the brain where the seizure begins. There are two types of focal seizures [1-3]:

- Focal seizures with retained awareness: This type of focal seizure was previously known as a simple partial seizure.
- Focal seizures with a loss awareness: (previously known as complex partial seizures) this type of focal seizure may also be called a focal dyscognitive seizure [4,5].

Generalized seizures: Occur when there is widespread seizure activity in the left and right hemispheres of the brain [6]. The different types of generalized seizures are:

- Absence seizures (formerly known as petit mal)
- Tonic-clonic or convulsive seizures (formerly known as grand mal)
- Atonic seizures (also known as drop attacks)
- Clonic seizures
- Tonic seizures
- Myoclonic seizures

There are six types: Tonic-clonic (or grand mal) seizures: These are the most noticeable. When you have this type, your body stiffens, jerks, and shakes, and you lose consciousness. Sometimes you lose control of your bladder or bowels.

Epilepsy is a disorder of the brain. People are diagnosed with epilepsy when they have had two or more seizures.

Signs and symptoms that affect body movement and function may include: Weakness or paralysis. Abnormal movement, such as tremors or difficulty walking [7-9].

Symptoms that indicate a seizure is in progress include

- Losing consciousness, which is followed by confusion.
- Having uncontrollable muscle spasms.
- Drooling or frothing at the mouth.
- Falling.
- Having a strange taste in the mouth.
- Clenching in teeth.
- Biting in tongue.
- Having sudden, rapid eye movements [10-13].

Models for induced seizures or epilepsy in AED development

Electrically induced: In electrically induced induces spontaneous seizure using mild seizure induced induction condition and provide another tool understanding the mechanism of spontaneous seizure development. These spontaneous seizures are induced with minimal neuronal damage, which could greatly enhance our ability to define the basis for the initiation and remission of spontaneous seizure [14].

It is becoming increasingly clear that the genetic background of mice and rats, even in inbred strains, can have a profound influence on measures of seizure susceptibility and epilepsy [15].

a) Acute induced seizures: e.g.- MES, 6-Hz
b) Chronic induced seizure: e.g.- electrical and chemical kindling [16].

Chemically induced: Novel target for research and clinical treatment of seizure and possibly for epilepsy [17]. It is clear that while rodent seizure models have significantly contributed to our understanding of effects of developmental ethanol chemical exposure on the seizure, various animal models is also critical for elucidating the mechanisms underlying neurologic dysfunctions induced by developmental alcohol exposure and for uncovering the evolutionarily conserved mechanisms of epileptogenesis [18].

a) Acute induced seizure: e.g.-PTZ, Flurothyl
b) Chronic induced seizure: e.g. - electrical and chemical kindling (**Figure 1**) [19,20].

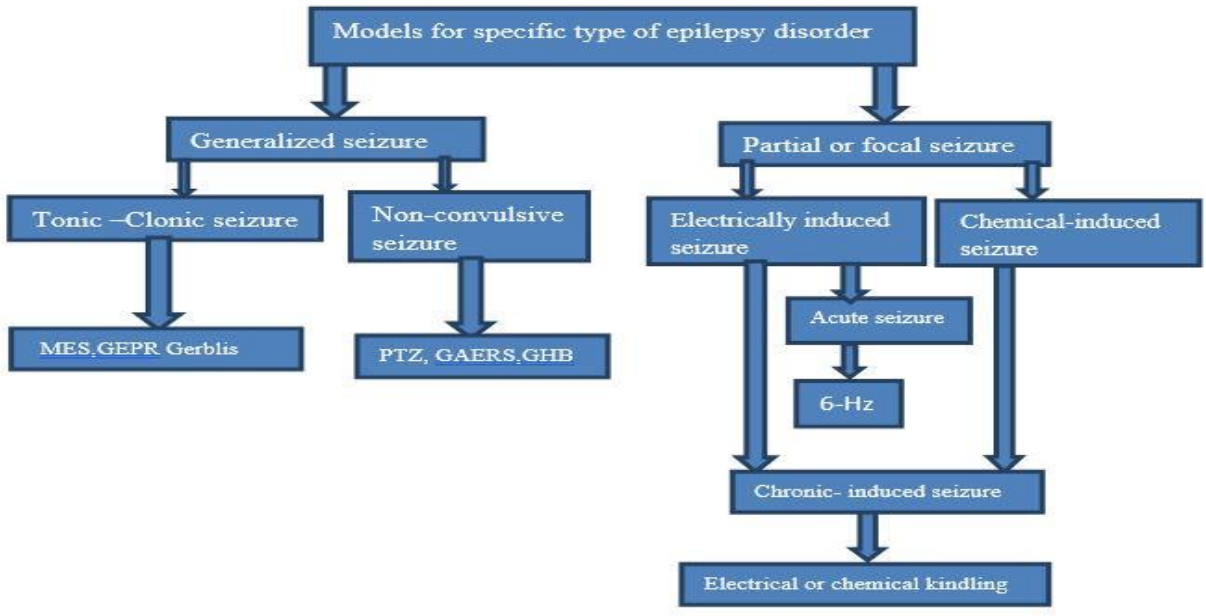

Figure 1: Flow diagram of epileptic models.

MES Model induced seizure: Maximum electroconvulsive shock (MES) is a classic experimental model for the induction of single generalized tonic-clonic seizure activity in rodents [20,21]. MES permits evaluation of the ability of a substance to prevent seizure spread through neural tissue. In the MES test, mice or rats receive an electrical stimulus of sufficient intensity to induce maximal seizures of their hind limbs, with tonic extension as the endpoint of the test. An electro-convulsion meter with corneal or ear electrodes is used to deliver the shock. Electroconvulsions induced by applying an alternating current ear clip electrode from a rodent shocker generator. The stimulus duration was 0.2 s. Tonic hind limb extension was used as the endpoint. This apparatus was used to induce seizures in two methodologically different experimental approaches: maximal electroshock seizure threshold test and MES test [22].

Animal used: Groups of 6-10 male albino Swiss mice (20-30 gm) or Wistar rats (100-150 gm) are used [23].

Phases of maximal seizure shown by normal mice typically consist of:

1. 1.Phase of tonic limb flexion.
2. Full extension of limbs.
3. Clonic interval (variable).
4. Death (in some animals)

The maximal electroshock seizure (MES) model can effectively test the potential efficacy of a compound for inhibiting tonic seizure [24-27].

Pentylenetetrazol model induced seizures: Pentylenetetrazol (PTZ) produces generalized syn-chronized clonic movements which are super ceded by tonic convulsions characterized by flexion of limbs followed by extension. The test is considered as indicative of anticonvulsant activity of drugs against Absence seizure [28-30]. Pentylenetetrazole (PTZ)-evoked seizures and the well-established rodent models of epilepsy are similar pertaining to behaviour, electrographic features [31]. Zebrafish is a small freshwater teleost that has been used as a model organism to study epilepsy. Pentylenetetrazole (PTZ)-induced seizures in zebrafish larvae [32,33] and adult [34].

Animals used: Groups of 6-10 mice (18-22 g) of either sex [35].

There are 3 distinct phases constituted the PTZ seizure sequence i.e.

1. Myoclonic jerk.
2. Clonic seizures.
3. Tonic-clonic hind limb extension.
4. Death [36-38].

Strychnine induced seizures: The convulsion action of strychnine is due to interference with post-synaptic inhibition that is mediated by Glycine [39]. Strychnine, the most abundant alkaloid of *Nux vomica*, is highly toxic to humans and most domestic animals. Strychnine is a well-known potent antagonist of glycine receptors in the vertebrate central nervous system and a strong blocker of various types of muscle and neuronal nicotinic acetylcholine receptors [40]. It acts as a selective competitive antagonist to block the inhibitory effect of glycine at all glycine receptors. The convulsions have a characteristic motor pattern. Time for onset of tonic extensor convulsions and death of animals is noted. Strychnine abolishes the flexor latency completely, leading to almost instantaneous onset of the extensor seizure [41,42].

Animal used: Albino Swiss mice of either sex (18–22 g) [43].
Dose: 2 mg/kg
Phases: Tonic extensor
Death of animals [44].

Picrotoxin-Induced convulsions: Chemical seizure models have been widely used in the preclinical evaluation of anticonvulsant properties of new drugs. Picrotoxin epileptogenesis play a role in generalised seizures [45]. Picrotoxin is a and it modifies the function of chloride ion channel of the GABA receptor complex [46-49].

Animal used: Adult albino rats of either sex (weighing 200-250 g) and mice of either sex (weighing 40-60 g) [50].
Phase: Tonic-clonic seizure [51].

Aminopyridine induced seizures in mice: 4-Aminopyridine is a powerful convulsant. The epileptiform activity is predominantly mediated by non- NMDA type excitatory amino acid receptors [52-54]. 4-Aminopyridine selectively blocks voltage-gated potassium channels, prolongs the action potential, increases calcium influx, and subsequently, enhances inter-neuronal and neuromuscular synaptic transmission [55]. Excitotoxicity is a complex process in which several mechanisms lead to intracellular Ca2+ overload and cell death observed in various neuropathological conditions [56].

Animal used: Sprague-Dawley rats (12-13 rats) [57].

Epilepsy induced by focal seizures: Topical or intracerebral application of metal and chemical can lead to simple partial seizures [58-60].

a) ***Cortical implanted metals:*** Alumina cream, cobalt, tungsten acid, applied onto or into the cerebral cortex, injection of iron in brain cortex [61].
b) ***Aluminum Hydroxide gel model:*** 4% aluminum hydroxide is injected into surgically exposed monkey neocortex, one or two months after injection spontaneous and recurrent seizures begins.
c) ***Chemical:*** Intrahippocampal-Kainic acid, tetanus toxin.

Topical application-Penicillin, picrotoxin, bicuculline [62].

Gama hydroxybutyrate model (GHB): GHB is the active ingredient in the prescription medication sodium oxybate (Xyrem). GHB 100-150 mg/kg the shows seizures, pharmacological models of absence seizure such as the GHB model are still important, the mechanistic knowledge of how targeting a single receptor can acutely bring about an absence seizure represent great advantage with respect to polygenic rat models of absence seizure, where the underlying genetic abnormalities are unknown, and monogenic mouse models of absence seizure, which have other comorbidities and where developmental changes to network excitability cannot be easily tracked [63-66].
Animal used: Wistar Albino Glaxo rats [67].

Genetic Absence Epilepsy Rat from Strasbourg (GAERS): The GAERS or Genetic Absence Epilepsy Rat from Strasbourg is a recognized animal model of absence epilepsy, a typical childhood form of epilepsy characterized by recurrent loss of contact and concomitant pattern on the electroencephalogram called "spike-and-wave" discharges.
They usually occur at a mean frequency of 1.5 per min when the animals are in a state of quiet wakefulness. Drugs effective against absence seizures in humans (Ethosuccimide, trimethadione, valproate, benzodiazepines) suppress the SWD dose-dependently, whereas drugs specific for convulsive or focal seizures (carbamazepine, phenytoin) are ineffective. Most neurotransmitters are involved in the control of SWD (dopamine, noradrenaline, NMDA, acetylcholine) [68-71].

Penicillin model of absence seizure: This study was undertaken to estimate the number of neurons in the rat hippocampus with penicillin induced epilepsy, using a stereological method, "the optical fractionator" [72-75].

Lithium-pilocarpine model: To enhance the consistency of pilocarpine, small amount of Lithium (LiCl 3 mEq/kg (i.p) is given to the animals 24 hours prior to administration of pilocarpine (20 mg/kg i.p). 1mg/kg s. c. Scopolamine is to be given 30 minutes prior to pilocarpine administration to counteract its peripheral effects. Treated animals show behavioural and electrographic evidence of status epilepticus for over 5 hours [76-78].

Kainic acid model: ICV (intracerebroventricular) injection of 0.4-0.8 µg kainic acid or systemic injection of i.p or s.c injection of 8-12 mg/kg kainic acid induces chemo-convulsion which progresses to develop into status epilepticus [32].

Conclusion

This review revealed the novel target for research and clinical treatment of seizure and possibly for epilepsy. Animal models of epilepsy include several tools including neurochemical agents, electrical protocols.in experimental options the animal model probably includes and reflect diversity of seizures type of humans. Animal models also include various features, uses and limitations. Animal model for seizures and epilepsy have played a fundamental role in advancing our understanding of basic in treatment of epilepsy. The animal model will continue to promote the progress of both neurological researches.

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