

# Animal Models of Epilepsy

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## EPILEPSY

Epilepsy is a brain disorder in which normal brain function is impaired. This disorder is characterized by an enduring predisposition to generate recurrent and unpredictable epileptic seizures. These seizures are triggered by neurobiological, cognitive, psychological, and social conditions. Epileptic seizures have been defined as "a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain" by International League Against Epilepsy.<sup>[2,3]</sup>

## ANIMAL MODELS

Animal models of epilepsy play an essential role in understanding the pathophysiology of epilepsy. Including in the discovery of new antiepileptic drugs.<sup>[4]</sup>

Epilepsy is not a single disease; it consists of multiple heterogeneous syndromes with various etiologies. Therefore, over 100 models of epilepsy in vitro and in vivo mimic different types of seizures.<sup>[5]</sup> Most epilepsy and antiepileptic drug studies have been conducted in chemically or electrically stimulated rat and mouse models.<sup>[6]</sup>

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## ABSTRACT

Epilepsy is one of the most common neurological disorders globally, caused by abnormal excess or synchronous neuronal activity in the brain, causing recurrent seizures. Many studies are carried out to understand the pathophysiology of this disorder and develop anti-seizure drugs. In animals, spontaneous epileptic attacks can be formed by various chemical stimuli and electrical stimulation methods, as well as genetic animal models to mimic the state of epileptic seizures. Providing animal models that are clinically similar to the model of epilepsy in humans is essential in understanding epilepsy and pharmacological studies.

**Keywords:** Animal models, epilepsy, seizure.

An Ideal model of epilepsy should show these characteristics:

- Formation of spontaneous and recurrent seizures,
- Clinically, it offers a type of seizure similar to seizures that occur in human epilepsy,
- The onset of age-related epilepsy, similar to epileptic syndromes in humans,
- Clinical seizures show epileptic EEG activity similar to that observed in humans,
- Pharmacokinetic display of Antiepileptic drugs similar to those in humans (allows the preservation of effective drug doses during chronic treatment)
- Effective plasma concentrations of antiepileptic drugs similar to those required to control the relevant type of seizure in humans.<sup>[6]</sup>

Seizure models are often produced by chemically delivering convulsant substances or electrically stimulating specific brain areas. Seizures caused by this stimulation can be observed both behaviorally and electrographically.<sup>[7]</sup>

Different animal models are used to create various forms of human epilepsy. For example, pentylenetetrazole (PTZ)-induced convulsions mimic absence epilepsy models, while maximal electroshock (MES)-induced seizures represent generalized tonic-clonic epilepsy seizures in humans.<sup>[7,8]</sup>

## CHEMICAL MODELS

### 1. Kainic Acid Model

Kainic acid is a potent amino acid agonist that activates glutamate receptors. Glutamate acts with ionotropic (NMDA, AMPA, and kainate receptors) and metabotropic receptors and plays an important role in initiating, propagating, and maintaining epileptic activity.<sup>[9,10]</sup> The Epilepsy model created by kainic acid is one of several models used to study temporal lobe epilepsy. All five subtypes of kainic acid receptors are commonly found in the hippocampus. After the injection of kainic acid, damage occurs to the hippocampus, amygdala, piriform cortex, entorhinal cortex, septum, and medial thalamus, always symmetrical.<sup>[11-13]</sup>

A depth electrode is implanted in the hippocampus while two surface electrodes are placed in the animal's cortex and cerebellum to receive continuous EEG recording. 0.4-0.8 µg kainic acid is used in intraventricular applications, 8-12 mg/kg in subcutaneous (s.c), and intraperitoneal (i.p) applications, and 1-2 µg in intraparenchymal applications used for creating epilepsy model in rats. Administration of 20-40 mg/kg (i.p. kainic acid is preferred in mice.<sup>[12,14]</sup>

Seizures usually begin to occur in the first hours of injection and can be observed for up to 6 hours. Seizures are observed according to the Racine classification. These phases are;

- (0) no seizure observed,
- (1) mouth and face movements, shaking of whiskers,
- (2) head nodding,
- (3) forelimb clonus, myoclonic jerks
- (4) rearing, tonic seizure
- (5) rearing, tonic-clonic seizure, faltering and falling,
- (6) and death.<sup>[12,15]</sup>

### 2. Pentylenetetrazole (PTZ) Model

PTZ (metrazole) is a chemical antagonist of the GABAA receptor that causes severe convulsions when

applied to animals. The most widely used animal model to study the effects of new anticonvulsant substances is the phenomenon of kindling with PTZ.<sup>[17,16]</sup>

PTZ can be used to build animal models of both acute and chronic epilepsy. For example, in the threshold dose to rodents, 60 to 100 mg/kg intraperitoneal (i.p.), or subcutaneous (s.c) acute PTZ injection causes myoclonic jerks, clonus, and tonic extension. Below the threshold dose, 20 to 40 mg/kg of PTZ i.p. repeated application, might trigger chronically self-occurring seizures (kindling phenomenon).<sup>[7]</sup>

A second dose of 20 mg/kg is administered 10 minutes after the first administration of 40 mg/kg intraperitoneal PTZ to create status epilepticus in rats. Then 10 mg/kg of PTZ is injected intraperitoneally every 10 minutes until the status model occurs. It is characterized by loss of posture and the observation of tonic-clonic seizures.<sup>[17]</sup>

### 3. Pilocarpine Model

The pilocarpine model is one of the models commonly used to study temporal lobe epilepsy. Pilocarpine, an acetylcholine receptor agonist, acts by cholinergic hyperactivation by activating muscarinic receptors.<sup>[18,19]</sup>

Usually, 1 mg/kg of scopolamine metal nitrate 30 minutes before pilocarpine administration is injected s.c. to reduce cholinergic action's peripheral effects. Then 350-385 mg/kg of pilocarpine is injected intraperitoneally. If status epilepticus is not observed in the rat, the first dose is 110 mg/kg, followed by additional doses of 60 mg/kg i.p. until it occurs.<sup>[20,21]</sup>

Rats begin to develop electrographic and behavioral seizures, lasting for several hours, approximately 45 minutes after pilocarpine injection. Behavioral seizures can be monitored according to the Racine classification.<sup>[21]</sup>

## ELECTRICAL STIMULATION MODELS

### 1. Maximal Electroshock (MES) Model

It is applied with alternating current at 50-60 Hz or lower frequency (6 Hz) with corneal, head, or ear electrodes. The current is 50 mA in the mouse and 150 mA in the rat. Electroshock seizures are loss of posture, tonic extension, and clonus following tonic flexion. The most crucial point of the model is the end seizure in the form of a tonic extension to the posterior, parallel to the body horizontal in the front and back limbs.<sup>[22]</sup> This model may not give very

accurate results, as it gives negative results in drugs with different mechanisms, such as levetiracetam, tiagabine, or vigabatrin.<sup>[23]</sup>

## 2. Kindling Model

Kindling, one of the commonly used models of chronic temporal lobe epilepsy (TLE),<sup>[24]</sup> also causes behavioral changes similar to the various emotional problems observed in patients with TLE.<sup>[25]</sup> One of the convenience shown by this model is that the epileptogenesis process is well known, easily controlled, and measured without errors. TLE's electrical kindling model is based on daily repetitive electrical stimulation of amygdaloid nuclei, piriform cortex, hippocampus, or other limbic structures.<sup>[26,27]</sup>

In this model, subjects are exposed to daily electrical stimulation, and seizure formation may develop in the amygdaloid, the region most sensitive to kindling formation, resulting from repeated arousal.<sup>[22,24]</sup> It reveals electrical stimulation in the Kindling model that initially produces short, low-frequency electrographic discharges without behavioral response. Long, high-frequency discharges occur when repeated electrical stimulation over several days has a strong convulsive reaction.<sup>[28-30]</sup> After a few days of kindling, the subject begins to experience complex seizures. The progression from simple partial seizures to complex seizures is most pronounced in the brain structure surrounding the amygdala, although it is visible with stimulation in all limbic and forebrain regions.<sup>[31]</sup>

## 3. Status Epilepticus Model

The SE model can be created in animals by chemical substances (by systemic application of kainic acid or pilocarpine) and electrical stimulation.<sup>[23]</sup> Mazarati and colleagues<sup>[33]</sup> have shown that the self-developing status epilepticus model in rats can also be stimulated by intermittent electrical stimulation. This SE induction method has a high survival rate (90-100%) if stimulation times are less than 60 Minutes. It has also been shown that SE-induced epilepsy can be improved in already kindling animals either by performing 60-minute high-frequency stimulation of the basolateral amygdala<sup>[34,35]</sup> or by pilocarpine injections.<sup>[36]</sup>

## GENETIC MODELS

Genetic absence epilepsy rats from Strasbourg (GAERS) are a genetic pattern of absence seizures

developed by Wistar rat colonies, exhibiting spontaneous spikes, and wave discharges (SWDs). They were similarly discovered when the Wistar Albino Glaxo (WAG/Rij) species was born and suffered an absence seizure.<sup>[37-39]</sup> The frequency of seizures in the GAERS strain is greater than in the WAG/Rij rats; the previous absence seizure lasts on average about 15-20 times every minute and hour. Both genetic models offer high predictability for investigating the absence and adverse effects of antiepileptic drugs. Studies on these models show that thalamocortical circuits are the critical manufacturer of absence seizures.<sup>[40]</sup>

## Conclusion

Epilepsy is a heterogeneous disorder in which various etiologies play a role, and the pathophysiology is not entirely known. Many methods can be used in experimental studies aimed at understanding this condition and preventing seizures. In creating an epilepsy model in animals, it is crucial that seizures are clinically, electrographically, and behaviorally similar to humans. Furthermore, episodes occur spontaneously, and antiepileptics can show pharmacological effects similar to that in humans. Experiments created with ideal models shed light on this disorder.

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