Acute and chronic animal models of epileptic seizures *in vivo* and *in vitro*

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Epilepsy is a complex brain disorder that develops as a consequence of various structural and metabolic brain changes and is associated with excessive neuronal hypersynchronous activity. Millions of people struggle with epilepsy, while antiepileptic medications successfully manage seizures in roughly 70% of patients. Clinical studies in humans provide limited insight into the complex mechanisms responsible for epileptogenesis and seizure generation, especially in temporal lobe epilepsy (TLE), which is often pharmacoresistant. The comprehension of TLE pathophysiogenesis primarily depends on status epilepticus (SE) models, such as the pilocarpine model. The use of appropriate animal models is crucial for investigating the molecular mechanisms underlying epileptogenesis and for evaluating the efficacy of new antiepileptic drugs. In this review, we summarize the most frequently used models of acute seizures induced by alterations in the extracellular ion composition, pharmacological interventions, and electrical stimulation. Chronic models of epilepsy, induced by chemoconvulsants and tetanic stimulations, were also examined. We analyzed the key advantages and distinguishing features of various in vivo and in vitro animal models, also highlighting parallels and differences between the models and the human condition.

Keywords: hippocampus, epilepsy, seizures, epilepsy models, in vitro models, in vivo models, animal models, epileptogenesis, temporal lobe epilepsy, pilocarpine

INTRODUCTION

Epilepsy is a common neurological condition that affects approximately 65 million people worldwide, of whom around 30% are resistant to treatment with antiepileptic drugs [1–3]. Such complex disorder results from various morphological and metabolic changes in the brain, characterized by a disruption of the balance between excitatory glutamatergic and inhibitory GABAergic neurotransmission, leading to hyperexcitability and the occurrence of epileptic seizures [4,5].

In recent years, numerous animal models have been developed to replicate different forms of seizures [2]. Animal models of epilepsy are important for the discovery of various molecular mechanisms of epileptogenesis and help in screening the efficacy of novel antiepileptic drugs. A lot of animal epilepsy models represent different processes that occur during seizures. Also, compounds tested for anti-seizure efficacy may display model-dependent variations in therapeutic activity [2,6]. Especially, the use of appropriate animal models is essential for studying temporal lobe epilepsy (TLE), which is the most common form of drug-resistant epilepsy in humans [7]. Development of new antiepileptic drugs to treat drug-resistant forms of epilepsy relies on the use of animal models before first trials in humans [6].

In experimental practice on animals, there are two approaches to studying seizures: in vivo and in vitro. In vivo models enable the reproduction of partial, generalized seizures, as well as status epilepticus (SE) in animals, providing the opportunity to record both EEG activity and observe behavioral seizures [8]. Models of epileptiform activity in vitro offer numerous benefits for experimental manipulation, including long and stable registration of epileptic activity on neural tissues. The use of a variety of receptor antagonists, along with manipulations in extracellular ion composition, increases neuronal activity in slices, often resulting in epileptiform activity and providing a model of symptomatic seizures [9]. In vitro models can

contribute to reducing the use of laboratory animals in demanding in vivo experiments [3].

Nowadays, no single experimental model can fully replicate all seizure phenotypes observed in human epilepsy due to the complex seizure characteristics. The choice of an appropriate model should be guided by the study's practical requirements [2]. In this review, we summarize the most frequently used models of chronic and acute epilepsy induced in vivo and in vitro.

1. Acute models of seizures

The acute phase of epileptogenesis takes place directly following initial brain injury, such as stroke or traumatic brain injury [10]. Acute seizure models reproduce different pathological conditions that lead to the development of seizure-like activity. In acute models of epilepsy, seizures can be induced by various methods: alteration of the extracellular ion composition (low Ca^{2+}, low Mg^{2+} epileptic model), pharmacological intervention (4-AP, bicuculine), and electrical stimulation [3,11–15]. Such seizure models can mimic certain aspects of human acute symptomatic seizures, especially those caused by electrolyte imbalances like hypocalcemia and hypomagnesemia [16].

1.1. GABA antagonist seizure model

A GABA antagonist seizure model can be induced by using GABAA receptor antagonists, such as gabazine, bicuculline, or picrotoxin. These substances block the GABA-mediated synaptic transmission and promote neuronal depolarization by reducing the effect of GABA and other inhibitory neurotransmitters [17]. The GABAA receptor underlies most rapid inhibition in the brain [18]. Bicuculline has convulsant properties in both adult and immature animals [14]. Raising the bicuculline concentration from 10 nM to 2 μM gradually reduced the amplitude of GABA-induced ion currents, while a concentration of 5 μM completely inhibited these currents, producing paroxysmal depolarisation shifts [19,20]. Bath application of gabazine, a GABAA receptor blocker, rapidly evokes epileptic-like activity in hippocampal slices, with the resulting CA1 hyperexcitability associated with an impaired afterhyperpolarizing potential [21].

This model is suitable for studying epilepsy in the immature brain as the GABA neuronal system in rats undergoes relatively early maturation. This enables the induction of seizure-like activity in newborn rats during the first 2 weeks after birth, a stage when many standard convulsant agents are ineffective [14,22]. According to Löscher (1981), cerebrospinal GABA concentrations are markedly lower in children experiencing febrile seizures than in controls [23].

The bicuculine model of epilepsy is conducted in vitro by superfusion with artificial cerebrospinal fluid containing bicuculine (10 μmol/l) and elevated K+ levels. Epileptiform activity begins approximately 6 ± 4 minutes after the change of perfusion solution to induce seizures and remains stable for several hours [19]. Additionally, this model can be performed in vivo by administering the convulsant and evaluating epileptic activity through EEG and behavioral assessments [22,24]. Bicuculline can induce acute focal and generalized epileptic convulsions when administered systemically [8].

1.2 Potassium channels antagonist seizure model

A potassium channels antagonist seizure model can be induced by using tetraethylammonium, 4-aminopyridin and alpha-Dendrotoxin [3,25,26]. Tetraethylammonium, a blocker of voltage-dependent potassium channels, induces both ictal-like and interictal-like epileptiform activity in hippocampal slices obtained from young (12-18-day-old) rats [25]. α-Dendrotoxin (DTX), a peptide toxin derived from snake venom, enhances neuronal excitability by inhibiting specific fast-activating, voltage-gated potassium channels [26]. 4-Aminopyridine acts as a general blocker of the voltage-gated potassium (KV) channels, effectively inhibiting KV1–KV4 channel subtypes [27]. These families include delayed rectifying

K^+ channels and A-type voltage-gated K^+ channels [28]. Specifically, 4-AP inhibits the fast transient outward potassium current in hippocampal pyramidal cells, resulting in increased depolarization and enhanced neuronal excitability [15,29].

The 4-aminopyridine model is a well-recognized in vitro model for studying acute seizures [3]. This model offers the advantage of producing stable and spontaneously occurring seizure-like events while exhibiting a lower incidence of spreading depolarizations compared to other experimental approaches, such as the low-Mg^{2+} or electrical stimulation models [3]. 4-Aminopyridine has gained significant interest as a pharmacological agent for investigating potassium channels, synaptic transmission, and the processes underlying epileptogenesis. [15].

For the induction of seizures, 4-AP (10-100 μM) is added to ACSF in the recording chamber. In the pyramidal cells of the CA3 hippocampal zone, regularly occurring epileptiform bursts have a slow deflection with superimposed faster population spikes [30]. Spontaneous epileptiform activity starts in the CA3 region of the hippocampus and spreads to the CA1 region along the Shaffer collateral pathway [15]. Ictal-like episodes consist of prolonged synchronized afterdischarges followed by a refractory period with no epileptiform activity. A delay of several seconds occurs before the CA1 region becomes involved in the ictal-like events [30]. The frequency of 4-AP–induced seizure-like events proved to be the most sensitive indicator for identifying dose-dependent antiepileptic effects of new-generation antiepileptic drugs, such as lacosamide, zonisamide, and levetiracetam [3]. In vivo studies can also reproduce ictal seizure activity using aminopyridine. [31].

1.3. Low Mg^{2+} model

The low Mg^{2+} model of epilepsy was established several decades ago and has since become a widely used tool for evaluating the efficacy of antiepileptic drugs [32]. This model has clinical relevance as hypomagnesemia may lower seizure threshold, increasing seizure susceptibility, particularly in people with a prior history of epilepsy [11]. There is evidence that epileptic patients have lower serum magnesium levels than healthy individuals, and those experiencing more frequent seizures tend to have significantly lower magnesium levels than patients with less frequent attacks [12].

Mg^{2+} ions are important for voltage-dependent block of current flow through NMDA receptors [33]. A reduction in extracellular Ca^{2+} and Mg^{2+} ions increases neuron excitability by reducing membrane charge screening near voltage-gated channels and promoting the activation of inward current. Additionally, decreased Mg^{2+} levels remove voltage-dependent Mg^{2+} block from NMDA receptors [34]. In vitro, within 20–40 minutes of perfusion with Mg^{2+}-free artificial cerebrospinal fluid, spontaneous field potentials emerge in the CA1 and CA3 hippocampal regions, but not in the dentate gyrus. Field potentials consist of repetitive deflections with superimposed population spikes [34,35]. Magnesium removal from the solution for extracellular recordings results in interictal bursting in the hippocampal CA3 zone, followed by spontaneous ictal events and the appearance of periodic clustered bursts. The ictal events consist of a tonic firing phase followed by clustered burst discharges, representing features of both tonic and clonic phases [36]. Surgical isolation of the two regions resulted in the loss of spontaneous activity in CA1, while seizure-like activity in CA3 persisted [35].

In this epileptic model, during the early stage, the first 2 hours of seizures, seizure-like activity can be reversed by restoring normal Mg^{2+} levels (2 mM) in the artificial cerebrospinal fluid or by applying NMDA receptor blockers. However, in the later phase, these interventions fail to suppress seizures [32,36,37].

1.4. Non-synaptic seizure model

The main non-synaptic epileptic models are the low Ca^{2+} and cadmium models [38,39]. The low Ca^{2+} epileptic model is beneficial for

studying nonsynaptic interactions and the role of gap junctions in the generation and spread of seizure activity [38]. In this epileptic model, the use of zero-Ca^{2+} artificial cerebrospinal fluid solution blocks chemical synaptic transmission and induces spontaneous burst-like epileptiform activity. Such hyperexcitability is associated with decreased charge screening by cations, suppression of calcium-activated hyperpolarizing currents, and reduction in GABA-mediated synaptic inhibition [40]. Hyperexcitation and hypersynchronous neuronal firing play crucial roles in the onset of low-Ca^{2+}–induced epileptiform activity [41].

Cadmium, a toxic heavy metal from industrial sources, can harm the nervous system, especially in children, and cause seizures. Cadmium is known to replace Ca^{2+} and disrupt cellular functions. In vitro application of high Cd levels (tens of μM to mM) inhibits voltage-gated Ca^{2+} channels, resulting in the blockade of synaptic transmission and seizure activity [39,42]. Cadmium can pass through the intact blood–brain barrier, impair neurogenesis, and lead to neuronal cell death [43]. Ferroptosis, a type of cell death that depends on iron, plays a critical role in seizure-induced hippocampal injury and the development of associated anxiety behaviors [39].

In non-synaptic epilepsy model, seizure-like activity is characterized by slow shifts in the extracellular field potential with superimposed fast population spikes that spread across the pyramidal cell layer in the hippocampus, and is accompanied by an elevation in extracellular potassium levels [44,45]. Electrotonic coupling via gap junctions and ephaptic transmission also contribute to synchronization of neuronal firing [38]. Perfusing hippocampal slices with zero-Ca2+ artificial cerebrospinal fluid for 30–40 minutes induces spontaneous epileptiform field bursts in the CA1 hippocampal zone [46]. Nonsynaptic epileptiform activity can persist for several hours, with single bursts lasting up to tens of seconds, resembling ictal-like activity [41].

Low Ca^{2+} epileptic model has practical implications since patients with epilepsy often have electrolyte imbalance, especially serum calcium and magnesium levels are significantly lower than in healthy people, which disrupts excitation–inhibition balance and may cause hyperexcitability [13]. Additionally, seizure activity is associated with reduced extracellular Ca^{2+} and increased K^{+} concentrations. [38]. Nonsynaptic epilepsy has been studied almost exclusively in vitro using hippocampal slices; however, Feng and Durand demonstrated that nonsynaptic activity can also be generated in vivo in the hippocampus of rats [41].

1.5 Maximal electroshock model

Maximal electroshock seizure (MES) model of acute seizures is valuable for rapidly screening numerous compounds for anticonvulsant activity, particularly for identifying agents effective against tonic–clonic generalized seizures [47]. The maximal electroshock model was developed by Putnam and Merritt (1937), who screened various compounds for anticonvulsant activity, ultimately leading to the discovery of phenytoin—the first antiseizure drug evaluated in animals before its use in humans [48]. Commonly used antiepileptic drugs, such as phenytoin, valproic acid, and carbamazepine, continue to be investigated in preclinical studies, particularly to examine their interactions within the MES model [49].

In this model, seizures are evoked by a short (0.2 s) suprathreshold electrical stimulus (50mA for mice, 150 mA for rats) applied transcorneally or transauricularly [6]. Seizures are considered maximal when additional increases in stimulus intensity fail to change the pattern or duration of their components. Such electrical stimulus is sufficiently strong to provoke maximal seizures characterized by extension of the anterior and posterior legs and body stiffness, which marks the tonic phase, lasting 10–15 seconds. After that, clonic seizures appear, which manifest as hind limb movements and body tremors, with apparent recovery to the normal state after

20–30 seconds. The test is considered positive if the animal exhibits tonic extensor seizures within 10 seconds of stimulation [47,49]. Tested antiepileptic drugs are commonly administered an hour before electrical stimulation [2].

Advantages of the MES model include its standardized protocol, the simplicity of both procedures and equipment, high reproducibility, and ability to reproduce epileptogenic features in the intact brain; nonetheless, animals are limited to a single use, and the model fails to detect anticonvulsants that increase the seizure threshold beneath the initial suprathreshold stimulus [6,7,47].

1.6. Pentylenetetrazole model

Pentylenetetrazole (PTZ) is a chemical agent that is often used to replicate the characteristics of human seizures in both acute and chronic animal epilepsy models [8,50,51]. Pentylenetetrazole acts primarily as a GABAA receptor antagonist to induce seizures, but also stimulates NMDA receptors, resulting in elevated Na+ and Ca^{2+} entry [50,52]. Moreover, PTZ promotes inflammation and glutamatergic excitotoxicity, leading to epileptic seizures and neuronal cell death [52].

In acute seizure paradigms, pentylenetetrazole can be administered by injection intraperitoneally, subcutaneously, or intravenously [2,50]. At concentrations above 60 mg/kg, PTZ triggers seizures, which progress following the Racine seizure scale from nonconvulsive absence and myoclonic seizures to generalized tonic–clonic convulsions. After injection, seizures typically occur in a 10-30 minute period [7,50,52]. The generation and propagation of PTZ-induced epilepsy occur mainly within hippocampal regions. In this model, carbamazepine, phenytoin, and pentobarbital show significant seizure-inhibiting activity [8]. The acute PTZ model provides several advantages as a seizure paradigm, such as simple administration, ability to reproduce various seizure types, and utility in drug screening [50].

2. Chronic models of epilepsy

Many people who suffer from epilepsy develop seizures during a lifetime [53]. Molecular and structural changes after traumatic brain injury, hypoxia, inflammation, stroke, and status epilepticus can lead to spontaneous recurrent seizures that progress in time and lead to chronic epilepsy [54]. During the chronic phase, spontaneous recurrent seizures emerge as the brain undergoes epileptogenic alterations sufficient to generate seizures independently of an initial epileptogenic insult [10]. Mesial temporal lobe epilepsy is the most common type of partial epilepsy in adults [55]. A lot of TLE patients have a latency period for years before chronic recurrent seizures start. Such animal models as pilocarpine, kainic acid, and kindling were developed to mimic TLE and help to study epileptogenesis. Often in these models, SE is followed by chronic spontaneous limbic seizures and hippocampal pathology [7,55,56].

2.1. Kindling

Kindling was the most widely used method in the past to model chronic temporal lobe epilepsy with complex partial seizures and study epileptogenesis [2,57]. This model is based on the observation that exhibits increased resistance to convulsions immediately following a seizure, whereas their convulsive threshold decreases over longer periods [58]. This model, developed by Goddart and colleagues (1967), is based on the concept of seizure-induced plasticity phenomenon that occurs when repetitive tetanic stimulations of the brain limbic structures gradually lead to the development of seizures with increasing severity and permanent seizure susceptibility [7,57,59]. Only after many weeks of repeated application can low-intensity subcortical stimulation trigger behavioral convulsions [59]. Early afterdischarges-related behavioral alterations resemble partial seizures, which subsequently progress to secondary generalization [7].

Kindling is generally categorized into two main types: electrical and chemical [2]. In

electrical kindling, a daily use of electric brain stimulation is used as a «chronic irritant». In this model, bipolar electrodes are implanted in the limbic structures of the brain in vivo, followed by daily single-trial stimulation, with the initial clonic convulsions appearing approximately two weeks later [59]. Whereas in chemical kindling, excitatory substances are systematically administered into the brain, leading to the induction of seizures. For example, repeated administration of subconvulsive doses of pentylenetetrazole, a GABAA receptor antagonist, is used for the induction of chemical kindling. Repetitive injections of pentylenetetrazole decrease seizure threshold and result in convulsive tonic-clonic seizures. Pentylenetetrazole-induced seizures are sensitive to compounds targeting GABAA receptors, including valproate and benzodiazepines [51]. Chemical kindling has been used to investigate neuronal damage following epileptic seizures by analyzing histological changes [51].

Kindling model elicits a stable and repeatable pattern of molecular and cellular modifications in neural networks and provides an ability to investigate the dynamics of epileptogenic processes, making it a valuable model for studying epileptogenesis. Despite its utility, the kindling procedure is time-demanding, expensive, and requires repeated stimulation sessions [7]. Since in the kindling procedure, animals develop spontaneous seizures after hundreds of stimulations, researchers now often prefer post-status epilepticus models like kainate, pilocarpine, or electrical stimulation, which induce seizures after a shorter latency [57].

2.2. Kainic acid model

The kainic acid model is a commonly used model of chronic temporal lobe epilepsy in rodents, which has significantly advanced understanding of the molecular, cellular, and pharmacological mechanisms involved in the initiation and development of epileptic seizures. Kainate (KA) is a cyclic analog of L-glutamate and an agonist of the ionotropic KA receptors. Kainate receptors are highly expressed in hippocampal pyramidal cells; also, they are found in the amygdala, entorhinal cortex, basal ganglia, and cerebellum [55,56].

The kainic acid model was first established by Ben-Ari and colleagues (1978), who demonstrated that in vivo intra-amygdaloid administration of kainic acid induces epileptiform EEG activity approximately 10 minutes after injection, which subsequently propagates to the hippocampus and cortex [60]. This model produces neuropathological lesions that resemble those observed in patients with TLE, such as neuronal loss and degenerative changes in various hippocampal fields [56,60]. KA-induced excitotoxicity appears as a result of overstimulation by excitatory neurotransmitters and cell death. The mortality rate is reduced when kainate is administered directly into brain tissue via injection, bypassing the blood–brain barrier, compared to systemic delivery [55]. When administered intraperitoneally, a single kainate dose of 6–15 mg/kg induces SE; however, delivering multiple doses of 5 mg/kg per hour until SE onset significantly reduces mortality. It is interesting that, similar to pilocarpine, KA can enhance the permeability of the blood-brain barrier [56].

Microinjection of a low dose of kainate (0.4 μg) into the CA3 zone of the posterior hippocampus induces SE, which is characterized by continuous limbic seizure activity and secondarily generalized convulsive seizures. After a latent period, more than 90% of rats develop spontaneous recurrent seizures. Epilepsy in this model is chronic and progressive, characterized by increased behavioral excitability and impaired learning and memory as a result of hippocampal pathology, which is associated with extensive neuronal loss in the CA3 zone [61].

2.3. Pilocarpine model

The pilocarpine model is well-established model in epilepsy research, recognized for

its reliable induction of status epilepticus in rodents and its close resemblance to human temporal lobe epilepsy [62]. Pilocarpine is a muscarinic acetylcholine receptor agonist and broadly used chemoconvulsant [55]. Turski and colleagues (1983) proposed the idea of generating epileptic seizures using in vivo administration of cholinergic agonist pilocarpine [63]. Pilocarpine can activate all five muscarinic receptor subtypes, with its proconvulsant effects primarily mediated through the M1 muscarinic receptor, whose activation is critical for the SE induction by systemic administration of pilocarpine [64]. Following initiation by M1 receptors, seizures are maintained by NMDA receptor activation [62,65].

In rats, pilocarpine specifically induces epileptiform activity within limbic structures, leading to motor seizures, status epilepticus, and extensive brain injury [63]. Pilocarpine model of epilepsy exhibits several pathophysiological similarities to human TLE, such as limbic system lesions, presence of a latent period preceding spontaneous recurrent seizures, and the manifestation of pharmacoresistance to conventional antiepileptic drugs [65].

Intraperitoneal administration of pilocarpine at doses of 100–400 mg/kg induces seizures that begin with automatisms and progressively develop into SE [63]. The intensity and the duration of seizures are significantly higher if rodents were treated with a single intraperitoneal dose of 300 mg/kg of pilocarpine than after injections with lower doses. However, 400 mg/kg caused high mortality rates of about 30%–40%. Administration of 300 mg/kg of pilocarpine after SE produced both ictal and interictal epileptiform activity in the EEG and predominantly generalized tonic–clonic seizures [62,63,66]. Animals on PND 15 -21 demonstrate the highest susceptibility to pilocarpine-induced status epilepticus, but have higher mortality levels than adult animals [64].

In this model, the onset and progression of seizures are usually monitored and scored using the Racine scale, which includes 5 stages [67]. During the first stage, animals exhibit minor behavioral alterations, including facial automatisms (mouth movements, mild salivation), which occurred around 10 minutes after injection of pilocarpine. The second stage displayed increased symptom severity, including enhanced motor activity and tail stiffening, but lacked clear convulsive episodes. The third stage was characterized by low-intensity tonic–clonic seizures commonly observed as rhythmic clonic movements of one forelimb. Stage four is defined by synchronous clonic movements of both forelimbs with rearing behavior, as the animal stands on its hind limbs during seizures. Stage 5 includes the most severe seizures with the additional loss of postural tone and coordination during the seizure, which potentially leads to falls. Status epilepticus is commonly defined as continuous stage 4–5 seizure activity lasting for at least one hour without interruption [67,68].

Both pilocarpine and kainic acid models induce prolonged limbic seizures that progress to status epilepticus, followed by a seizure-free latent period lasting several days to weeks, after which animals develop spontaneous recurrent seizures without remission [64,69]. However, in the pilocarpine model, in vivo neuronal damage occurs faster than in the kainic acid model, and the survival rate of the animals is lower [69].

2.4 Lithium-pilocarpine model

The lithium-pilocarpine model shares a lot of similarities with the pilocarpine model of seizures, such as similar behavioral, electrophysiological, metabolic, and neuropathological manifestations [66]. Pretreatment of rodents with low doses of lithium chloride (3 mEq/kg) administered 24 hours before the SE induction enables a substantial decrease in the pilocarpine dosage required to induce seizures, generally to 20-30 mg/kg [65,70]. Nevertheless, experimental protocols vary among studies. For instance, Antmen and colleagues (2025) repeated the injection of pilocarpine (20 mg/kg every 30 min) until the status epilepticus was achieved, with a maximum of 5 doses, and

additionally administered methylscopolamine before pilocarpine injection to minimize peripheral cholinergic effects [10]. In contrast, Glien and colleagues (2001) induced SE using 2–4 injections of pilocarpine (10 mg/kg each) administered at 30-minute intervals [71]. If pilocarpine was administered as a single dose of 30 mg/kg with SE limited to 90 minutes, the mortality rate was 45%. In contrast, administering pilocarpine in divided doses of 10 mg/kg at 30-minute intervals until the onset of status epilepticus reduced mortality levels to 7% [65].

Administration of LiCl facilitated seizure-like activity induced by low-dose pilocarpine through the activation of circulating T lymphocytes and mononuclear cells, and promoting systemic inflammation. Serum pro-inflammatory cytokine levels increase and blood-brain barrier damage occurs, which heightens theta EEG activity, before status epilepticus induced by cholinergic exposure [72]. It is interesting that patients had non-convulsive seizure activity and decreased seizure threshold after administration of lithium at the therapeutic concentrations [73].

Compared to the original pilocarpine model, the LiCl-pilocarpine model exhibits a significantly higher rate of SE induction, often reaching up to 100%; however, the pilocarpine model typically induces SE in about 60% of animals. Moreover, this approach generates more stable and prolonged seizure activity, offers high experimental reproducibility, and lowers mortality rate, thus establishing it as a robust and promising model for studying epileptogenesis [66].

CONCLUSIONS

Numerous animal models have been developed to replicate the features of human epilepsy. Animal epileptic models differ in procedures and administration of stimulus. Various models utilize chemical, electrical, or mechanical tools to induce or replicate neurological changes and behavioral symptoms in animal models that mimic human conditions. [52]. Acute models of epilepsy are effective for identifying and fast-screening for anticonvulsant agents, yet they model individual seizure episodes rather than the ongoing pathology seen in human epilepsy [47]. In vitro acute models of epilepsy are widely used due to their specific advantages. Broadly used in preclinical research, the in vitro 4-AP model is reliable and easy to reproduce model for evaluating antiepileptic drug efficiency [9]. The bicuculline model is well-suited for studying seizures in the immature brain [14]. The low Mg^{2+} model, which disinhibits NMDA receptors, is suitable for studying interictal-ictal transitions [36]. The low Ca2+ model is especially valuable for examining nonsynaptic interactions and the role of gap junctions in seizure generation [38]. The maximal electroshock model serves as a reliable approach for preclinical drug discovery and serves as an effective tool for routine screening of potential antiepileptic agents [47,49]. After investigational antiepileptic drugs show efficacy in basic screening models like maximal electroshock or pentylenetetrazole, a series of additional models is employed to characterize their anticonvulsant profile, with the most frequent use of the kindling model [6]. The kindling model has the advantage of being able to model partial and generalized seizures; however, it is time-consuming, since each animal has to go under repetitive electrical stimulation sessions [8,66]. Moreover, the kindling model is not characterized by hippocampal sclerosis, and spontaneous seizures are rarely observed, unlike after the application of chemoconvulsants, such as pilocarpine or kainic acid [7,56]. Systemic administration of kainic acid or pilocarpine is considered to reproduce the most accurately the clinical and neuropathological characteristics of human temporal lobe epilepsy in animal models [69]. Compared to the kainic acid model, the pilocarpine model is more convenient and reliable for studying epileptogenesis. In the kainic acid model, animals often need to experience a status epilepticus lasting over 3 hours to develop spontaneous seizures; however,

nearly all rats in the pilocarpine model exhibit spontaneous seizures regardless of the SE duration [56]. Seizure models in vitro detect antiepileptic effects across different mechanisms of action with efficacy similar to epileptic models in vivo [3]. However, in vitro seizure models offer benefits over in vivo systems for the ability to study the cellular mechanisms involved in epileptogenesis and minimize the number of animals used in experiments [9,30].

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ГОСТРІ ТА ХРОНІЧНІ ТВАРИННІ МОДЕЛІ ЕПІЛЕПТИЧНИХ НАПАДІВ IN VIVO ТА *IN VITRO*

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Епілепсія є комплексним розладом нервової діяльності, що розвивається внаслідок різних структурних та метаболічних змін мозку та пов'язаний з надмірною гіперсинхронною активністю нейронів. Мільйони людей страждають на епілепсію, проте лише 70% пацієнтів досягають ефективного контролю нападів за допомогою протисудомних препаратів. Клінічні дослідження лише частково дозволяють зрозуміти складні механізми, що лежать в основі епілептогенезу та розвитку судом, особливо при скроневій епілепсії, яка часто є резистентною до терапії лікарськими препаратами. Для вивчення патофізіологічних механізмів скроневої епілепсії найчастіше використовують експериментальні моделі епілептичного статусу, серед яких однією з найпоширеніших є пілокарпінова модель епілепсії. Застосування релевантних тваринних моделей є важливим для вивчення молекулярних механізмів, що лежать в основі епілептогенезу, а також для випробування ефективності нових протиепілептичних засобів. У даному огляді узагальнено інформацію про найчастіше використовувані моделі гострих нападів, що спричинені змінами позаклітинного іонного складу, впливом фармакологічних речовин та електричної стимуляції, а також наведено опис хронічних моделей епілепсії, індукованих конвульсантами та тетанічною стимуляцією. Було розглянуто основні переваги та характерні особливості різних тваринних моделей епілепсії in vivo та in vitro, а також визначено паралелі та розбіжності між моделями епілепсії та клінічними проявами захворювання у людей.

Ключові слова: гіпокамп, епілепсія, судоми, моделі епілепсії, моделі in vitro, моделі in vivo, тваринні моделі, епілептогенез, скронева епілепсія, пілокарпін

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