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Diverse species of animal models in epilepsy research: Progress and perspectives

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ABSTRACT

Epilepsy, a prevalent neurological disorder, is characterized by recurrent, self-sustained seizures resulting from abnormal neuronal hyperexcitability. Epilepsy encompasses a wide spectrum of etiologies, pathophysiological mechanisms, and treatment responses, resulting in considerable phenotypic heterogeneity. Over the past few decades, animal models, ranging from simple organisms to complex species, have played a pivotal role in elucidating the cellular, molecular, and circuit mechanisms underlying seizure generation and propagation, while also facilitating the development of antiseizure medication and other therapeutic interventions. This review first outlines the mechanistic basis of epilepsy and systematically summarizes existing seizure and epilepsy models across diverse taxa, including zebrafish, rodents, and non-human primates (NHPs), with a focus on model-specific features, translational relevance, and therapeutic utility. Despite substantial progress, limitations persist in recapitulating the full complexity of human epilepsy. Recent advances in genetic engineering, neuromodulation technology, and brain organoids are refining model fidelity and enhancing alignment with precision medicine approaches. Cross-species integration offers a promising avenue for bridging preclinical findings with clinical application, advancing mechanistic insight, and the development of targeted therapies.

Keywords: Epilepsy; Seizure; Animal model; Cross-species; Antiseizure medication; Precision medicine

INTRODUCTION

Epilepsy constitutes a major neurological disorder affecting over 70 million individuals globally (GBD 2021 Nervous System Disorders Collaborators, 2024). Defined as recurrent, self-sustaining paroxysmal disruptions of brain activity, epilepsy arises from aberrant neuronal discharge and manifests with a variety of symptoms contingent on the affected cerebral regions. Seizures are frequently accompanied by electroencephalographic (EEG) abnormalities and structural neuropathology. In adult populations, seizure onset is predominantly associated with structural changes in the brain, including traumatic injury, cerebrovascular insult, or hippocampal sclerosis. In contrast, congenital genetic epilepsy syndromes account for a larger proportion of cases in pediatric cohorts (Thijs et al., 2019; Walsh et al., 2017). More than half of all diagnosed cases now exhibit identifiable genetic causes, reflecting rapid progress in genomic medicine (Striano & Minassian, 2020). Parallel advancements in neuroimaging and electrophysiological diagnostics have enabled the reclassification of formerly “cryptogenic” seizures by uncovering previously undetected etiologies, while surgical techniques continue to evolve (Bernasconi et al., 2011; Frauscher et al., 2024; Wiest & Beisteiner, 2019).

Despite significant progress and development of novel antiepileptic compounds and noninvasive treatment modalities, therapeutic resistance remains a persistent challenge, particularly among those with drug-resistant epilepsy (Klein et al., 2024; Löscher et al., 2020). This treatment gap imposes a substantial burden on patients and public healthcare systems due to long-term care costs and diminished quality of life (Begley et al., 2022). Animal models have long served as an indispensable platform for elucidating epileptogenic mechanisms and testing candidate therapies.

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Ranging from simple organisms to complex species, these models have been instrumental in investigating the underlying mechanisms of epilepsy and in the development of potential treatments (Grone & Baraban, 2015; Löscher, 2017).

This review provides an overview of current mechanism knowledge on epilepsy and systematically evaluates a broad range of animal models employed in epilepsy research, with an emphasis on their defining features, experimental utility, and translational value. In contrast to earlier reviews limited to rodents or specific model categories, this work adopts a cross-species framework to capture the full diversity of experimental systems and to identify critical gaps in model development. Literature selection followed a systematic search strategy using PubMed, ScienceDirect, and Web of Science, prioritizing peer-reviewed, recent, high-impact studies published in recent years. Relevant publications were categorized by species, model type, and translational relevance to human epilepsy. Extensive cross-referencing was applied to ensure comprehensive coverage and to support an integrative, evidence-based analysis.

PATHOPHYSIOLOGY OF EPILEPSY

Epilepsy arises from disruption in the delicate balance between excitatory and inhibitory signaling within neuronal circuits. Perturbations in this balance, triggered by genetic mutations, traumatic insult, hypoxic injury, ischemia, infection, or chronic neuroinflammation, can initiate and sustain the pathophysiological cascade leading to seizure susceptibility. This excitation-inhibition disequilibrium is closely related to dysregulated neuronal ion channel activity, aberrant synaptic transmission, and altered glial cell function, all of which converge to promote neuronal hyperexcitability and network instability (Figure 1). The following section outlines key molecular and cellular contributors to epilepsy, with an

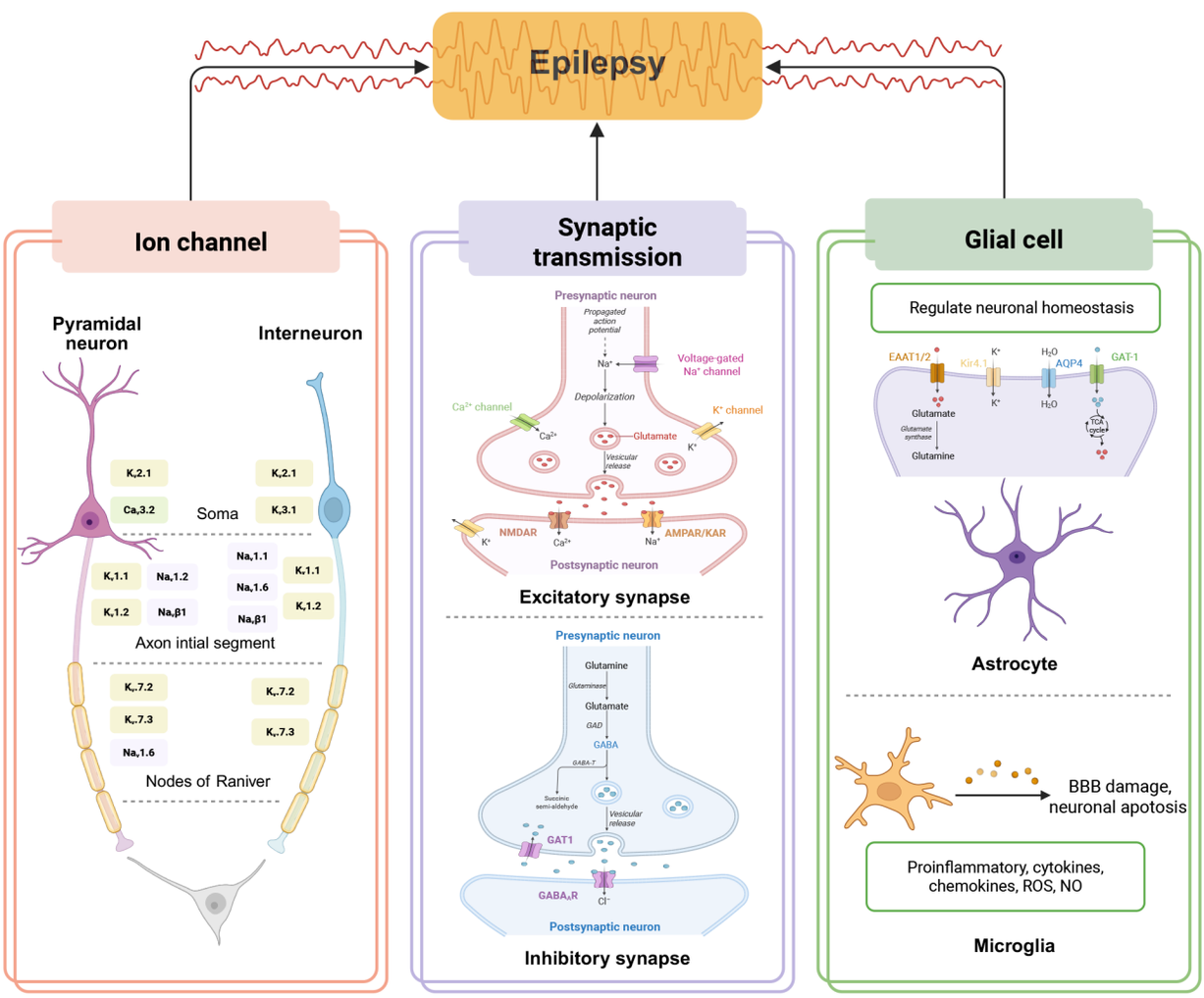

Figure 1 Pathophysiological mechanisms underlying epilepsy, including dysregulation of ion channels, synaptic transmission, and glial cell function

Schematic illustrating three key contributors to epilepsy: Ion channels, synaptic transmission, and glial cells. Ion channels: Representative Na^+, K^+, and Ca^{2+} channels are shown; their dysfunction promotes neuronal hyperexcitability. Synaptic transmission: Excitatory glutamatergic synapses activate postsynaptic NMDA and AMPA/KA receptors, while inhibitory GABAergic synapses activate GABA receptors. Imbalance between excitatory and inhibitory signaling is closely linked to seizure activity. NMDAR: N-methyl-D-aspartate receptor; AMPAR: α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor; KAR: Kainate receptor; GABA: γ-aminobutyric acid; GAD: Glutamic acid decarboxylase; GAT1: γ-aminobutyric acid transporter 1. Glial cells: Astrocytes regulate neuronal homeostasis by maintaining glutamate, potassium, and water balance. Microglial activation produces proinflammatory factors, resulting in neuronal damage. EAAT1/2: Excitatory amino acid transporters 1/2; AQP4: Aquaporin 4; TCA: Tricarboxylic acid cycle; BBB: Blood-brain barrier; ROS: Reactive oxygen species.

emphasis on the role of pathogenic gene variants, providing a mechanistic foundation for the comparative evaluation of animal models presented in subsequent sections. For a more detailed discussion of molecular pathways and emerging mechanistic insights, additional comprehensive reviews are cited.

Ion channel mechanisms

Ion channels serve as critical regulators of neuronal excitability and synaptic transmission, maintaining the electrical stability of brain networks. Dysfunction of ion channels, particularly within voltage-gated sodium, potassium, and calcium channels, represents a central mechanism in the pathogenesis of epilepsy (Chen et al., 2022; Lerche et al., 2013; Oyrer et al., 2018).

Sodium channels: Voltage-gated sodium channels (VGSCs) are essential for the generation and propagation of neuronal action potentials by mediating rapid sodium influx during depolarization (Pal et al., 2021; Watanabe, 2022). Mutations in genes encoding sodium channel subunits (e.g., *SCN1A*, *SCN2A*, *SCN8A*, *SCN1B*), which can lead to abnormal sodium channel function and persistent overexcitation of neurons, are among the most frequent genetic causes of epilepsy (Barker-Haliski & Steve White, 2020; Brunklaus et al., 2022). *SCN1A* encodes the α-subunit Nav1.1, which is predominantly expressed in inhibitory GABAergic neurons. Loss-of-function mutations in *SCN1A* reduce inhibitory tone, precipitating hyperexcitability and clinical phenotypes such as Dravet syndrome and genetic epilepsy with febrile seizures plus (GEFS+) (Steinlein, 2014; Wengert & Patel, 2021). *SCN2A*, which encodes Nav1.2 in glutamatergic neurons, modulates depolarization-driven activation followed by rapid inactivation. Mutations impairing fast inactivation of Nav1.2 are linked to a spectrum of developmental epileptic encephalopathies (DEE) (Berecki et al., 2025).

Potassium channels: Potassium channels regulate resting membrane potential, repolarization of action potentials, and neurotransmitter release, exerting broad influence over neuronal excitability (Maljevic & Lerche, 2013). With approximately 80 subtypes, this channel family contributes to various processes, including subthreshold regulation, spike repolarization, and afterhyperpolarization dynamics. Approximately 10% of potassium channel genes have been implicated in epilepsy-related disorders and syndromes (Köhling & Wolfart, 2016). Variants in genes, such as *KCNQ2*, *KCNQ3*, *KCNA1*, *KCNA2*, *KCNB1*, *KCNC1*, *KCND1*, and *KCNT1*, have been associated with diverse epileptic syndromes (Weston & Tzingounis, 2024). Notably, *KCNQ2* (Kv7.2) and *KCNQ3* (Kv7.3) mediate a slow noninactivating K^+ current known as M-current, which regulates subthreshold excitability and constrains repetitive neuronal firing. Mutations in both *KCNQ2* and *KCNQ3* can cause benign familial neonatal seizures (BFNS), a self-limited form of early-onset epilepsy (Perucca & Taglialatela, 2025).

Calcium channels: Calcium channels, widely distributed throughout the central nervous system (CNS), regulate calcium influx into neurons and are essential for neurotransmitter release, synaptic plasticity, synchronous neuronal firing, and paroxysmal depolarization drift (Nanou & Catterall, 2018; Simms & Zamponi, 2014). Among the most relevant to epilepsy are low-voltage activated T-type calcium channels—encoded by *CACNA1G* (Ca3.1), *CACNA1H* (Ca3.2), and *CACNA1I* (Ca3.3)—and high-voltage activated P/Q-type channels encoded by *CACNA1A* ($Ca_V2.1$). The $Ca_V2.1$ subtype, located predominantly at presynaptic regions, mediates vesicular exocytosis in response to calcium entry, thereby influencing neuronal excitability (Lauerer & Lerche, 2024; Powell et al., 2014). Mutations in *CACNA1A* generate aberrant rhythmic activity within the thalamocortical loop, producing spike-and-wave discharges characteristic of absence seizures (Rajakulendran & Hanna, 2016).

Synaptic transmission mechanisms

Neuronal excitability is governed not only by intrinsic membrane properties but also by dynamic synaptic interactions modulated through intracellular signaling cascades (Casillas-Espinosa et al., 2012). The glutamatergic and γ-aminobutyric acid (GABA) systems constitute the principal excitatory and inhibitory systems in the CNS, respectively. Dysregulation of these neurotransmitter systems—particularly through aberrant receptor function—has been implicated in multiple epileptogenic processes (Davletshin et al., 2023).

Glutamatergic transmission: Glutamate, the primary excitatory neurotransmitter, is released from presynaptic terminals into the synaptic cleft in a calcium-dependent manner, typically following neuronal depolarization. It acts via ionotropic glutamate receptors (iGluRs), including N-methyl-D-aspartate receptors (NMDARs), α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors (AMPARs), and kainate receptors (KARs), as well as metabotropic glutamate receptors (mGluRs). Mutations affecting these receptors have been linked to various epileptic phenotypes (Barker-Haliski & White, 2015; Chen et al., 2023b; Lemes et al., 2025).

NMDARs function as nonselective cation channels with a high calcium permeability. Rapid calcium influx through NMDARs initiates epileptiform discharges and acts as critical second messengers to trigger intracellular signaling cascades and alter neuronal function, contributing to long-term susceptibility to epilepsy (Celli & Fornai, 2021). AMPARs, which mediate fast excitatory synaptic transmission and regulate synaptic plasticity, are permeable to sodium and potassium, with calcium permeability determined by the presence or absence of the GluA2 subunit. Changes in the composition or expression of AMPARs enhance neuronal excitability and facilitate the propagation of pathological activity within epileptic networks (Hanada, 2020). KARs, tetramers composed of GluK1-5 subunits, are expressed at both presynaptic and postsynaptic sites and modulate neurotransmitter release via ionotropic and metabotropic mechanisms. Heteromeric GluK2/GluK5 KAR assemblies have been associated with recurrent seizure generation in chronic epilepsy models (Crépel & Mulle, 2015). mGluRs, belonging to the G protein-coupled receptor (GPCR) family, mediate synaptic transmission by activating intracellular signaling cascades. Their roles in epilepsy are complex and context-dependent, with both increased and decreased signaling capable of promoting seizure activity, depending on the receptor subtype and anatomical distribution within the brain (Celli et al., 2019).

GABAergic transmission: GABA, synthesized by glutamic acid decarboxylase (GAD), mediates inhibitory neurotransmission by inducing hyperpolarization upon binding to GABA receptors. This inhibitory effect counterbalances excitatory signaling and stabilizes neuronal networks. Two primary receptor classes mediate GABAergic transmission,

notably ligand-gated ionotropic $GABA_A$ receptors and G protein-coupled metabotropic $GABA_B$ receptors (Johnston & Beart, 2024).

$GABA_A$ receptors, as ligand-gated ion channels, rapidly suppress neuronal excitability by facilitating Cl^- influx. Most $GABA_A$ receptors in the brain contain a γ2 subunit encoded by *GABRG2*, with approximately 50%–60% forming α1β2γ2 complexes, and another 25%–35% comprising alternative α1,2, β1-3, and a γ2 subunit combinations (Bryson et al., 2023). Mutations in *GABRG2* were among the earliest identified in epilepsy research and remain extensively characterized, while mutations in genes encoding other subunits have also been reported (Richardson et al., 2024). $GABA_B$ receptors, belonging to the G-protein-coupled receptor family, exert both post- and pre-synaptic effects by increasing the extracellular transport of potassium and decreasing calcium influx. Dysfunctions in $GABA_B$ receptors have been implicated in the pathophysiology of generalized absence seizures and focal epileptic disorders (Avoli & Lévesque, 2022).

Other neurotransmitters: Beyond glutamate and GABA, an expanding body of evidence has highlighted the involvement of other neurotransmitters and signaling pathways in the development and progression of epilepsy, including acetylcholine, dopamine, serotonin, histamine, norepinephrine, and nitric oxide (Akyuz et al., 2021). These signaling molecules exert either pro- or antiseizure effects by interacting with glutamate and GABA to regulate neuronal excitability, synaptic plasticity, and neuroinflammation in the brain.

Glial cell mechanisms

While epilepsy research has traditionally emphasized neuronal dysfunction, accumulating evidence over the past two decades has highlighted the pivotal contribution of glial cells to the pathophysiology of epilepsy. Abnormalities involving astrocytes, microglia, glial scars, and gliomas have been consistently identified within epileptic foci in both human brain tissue and experimental models (Devinsky et al., 2013). These glial cell alterations reshape the neural microenvironment by modulating ion homeostasis, neurotransmitter clearance, and inflammatory signaling. Emerging technologies such as single-cell transcriptomics are beginning to resolve the molecular heterogeneity of glial subtypes, opening new avenues for identifying cell-type-specific therapeutic targets in epilepsy.

Astrocytes: Astrocytes surround synaptic structures and exert homeostatic control by regulating neurotransmitter levels, ion balance, and gliotransmitter release (Purnell et al., 2023). Astrocytes maintain extracellular potassium homeostasis by absorbing excess potassium ions and redistributing them through Kir4.1 channels. This buffering function ensures neurons maintain their resting membrane potential, preventing excessive neuronal firing. Disruption of Kir4.1 function in astrocytes has been shown to precipitate spontaneous seizures. Additionally, astrocytes regulate extracellular glutamate concentrations via glutamate transporters (EAATs), preventing excitotoxic accumulation within the synaptic cleft. Internalized glutamate is enzymatically converted to glutamine, which is recycled back to neurons for neurotransmitter synthesis. Impairment of this clearance mechanism enhances excitatory drive and promotes seizure susceptibility. In addition, astrocytes release gliotransmitters such as glutamate, ATP, and D-serine, which actively regulate synaptic plasticity and contribute to the network remodeling associated with epilepsy (Vezzani et al., 2022).

Microglia: Microglia function as intrinsic immune cells within the CNS, maintaining brain homeostasis and immune surveillance and responding to injury or disease (Li & Barres, 2018). Upon activation, microglia adopt a proinflammatory phenotype, releasing proinflammatory cytokines, chemokines, reactive oxygen species (ROS), and nitric oxide, factors that alter neuronal excitability, compromise synaptic function, and disrupt the blood-brain barrier (BBB) (Kinoshita & Koyama, 2021; Yu et al., 2023). Neuroinflammation mediated by reactive microglia is increasingly recognized as a driver of seizure susceptibility. In addition to their immunological role, microglia directly influence synaptic remodeling through activity-dependent mechanisms such as synaptic stripping (Wan et al., 2020) and synaptic pruning (Chen et al., 2025), both of which reshape network connectivity and modify the threshold for seizure susceptibility in epilepsy.

CROSS-SPECIES ANIMAL MODELS USED IN EPILEPSY RESEARCH

Animal models serve as indispensable platforms for dissecting the molecular, cellular, and circuit-level mechanisms underlying epilepsy. A wide spectrum of species models has been employed to recapitulate seizure phenotypes, with both naturally occurring and experimentally induced forms documented (Figure 2). While rodent models remain the most extensively utilized model organisms, other less commonly used species—ranging from complex mammals to simple invertebrates—also offer unique advantages that complement rodent-based systems and broaden the translational landscape.

Rodents

Rodent models, encompassing both acquired and genetic epilepsies, dominate preclinical epilepsy research, with mice and rats comprising the primary experimental systems (Lidster et al., 2016). Despite substantial anatomical and structural differences between rodents and humans, several conserved features underscore the utility of rodents in modeling human neurological disorders (Milior et al., 2023; Muralidharan, 2021). Genes implicated in human disease are highly conserved in rodents, with similar spatial expression patterns, neural circuitry, and network dynamics regulated by shared genetic and transcriptional programs (Huang et al., 2004; Strand et al., 2007; Chuang and Nasrallah, 2017; Graf et al., 2022; Heilbronner et al., 2016; Hodge et al., 2019). Rodent hippocampal anatomy closely parallels that of humans, making these species particularly suitable for modeling temporal lobe epilepsy (TLE) (Zhang et al., 2024b). Additionally, cortical and thalamic structures in both species contribute to the manifestation of generalized seizure phenotypes (Cao et al., 2020). Rodent models are typically classified as either induced or genetic. Induced models rely on chemoconvulsants or electrical stimulations to elicit acute or chronic seizure states, with phenotypic variability depending on induction parameters. Genetic models involve spontaneous mutations or targeted genetic lesions that produce seizure susceptibility or recapitulate specific human epileptic syndromes. Recent advances in gene-editing technologies have enabled the generation of genetic models designed to reproduce a defined human phenotype or genotype

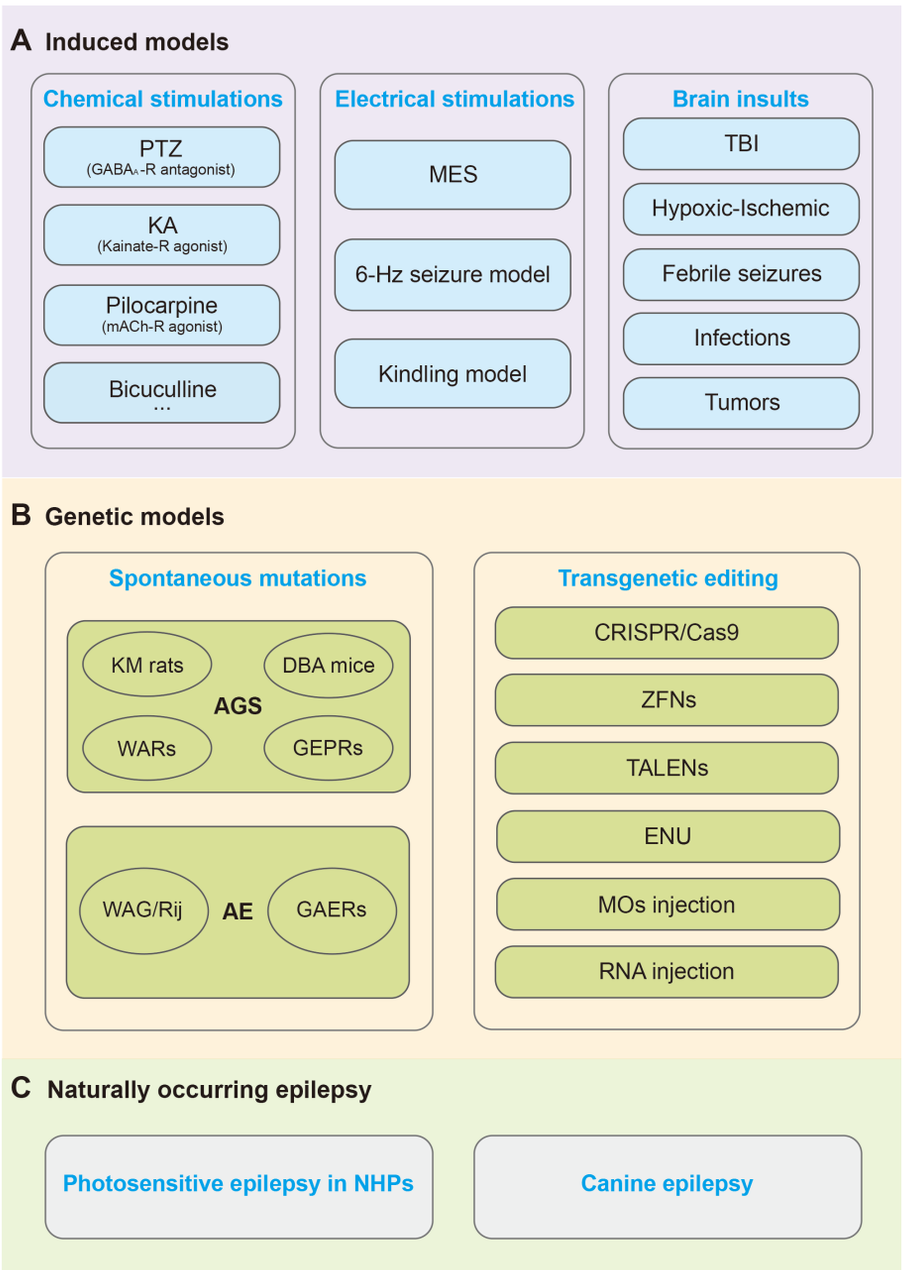

Figure 2 Schematic overview of epilepsy induction strategies in animal models

A: Induced models are generated through external interventions and include chemical stimulation, electrical stimulation, and physical brain insults. PTZ: Pentylenetetrazol; KA: Kainic acid; MES: Maximal electroshock seizure; TBI: Traumatic brain injury. B: Genetic models are based on inherited predispositions and include spontaneous mutations and transgenic editing techniques. KM rats: Krushinsky-Molodkina rats; DBA mice: Dilute Brown non-Agouti mice; WARs: Wistar Audiogenic rats; GEPRs: Genetically Epilepsy-Prone rats; WAG/Rij: Wistar Albino Glaxo rats; GAERS: Genetic Absence Epilepsy rats. CRISPR/Cas9: clustered regularly interspaced short palindromic repeats/Cas9; ZFNs: Zinc finger nucleases; TALENs: Transcription activator-like effector nucleases; ENU: N-ethyl-N-nitrosourea; MOs: Morpholinos. C: Naturally occurring epilepsy models are based on spontaneous epilepsy observed in specific species. NHPs: Non-human primates.

associated with epilepsy.

Induced models: Induced epilepsy models rely on exogenous stimuli to provoke seizures, which may be acute (short-term, single episode), status epilepticus, or chronic (long-term, recurrent). The type, severity, and progression of seizure activity depend on multiple factors, including the induction method, stimulus intensity and duration, administration route and dosage, targeted brain region, and species- or age-specific susceptibility.

Acute seizure models: Maximal electroshock seizure (MES) models involve brief, high-intensity electrical stimulation delivered via corneal, auricular, or transcranial electrodes (Browning & Nelson, 1985; Toman et al., 1946) to elicit generalized tonic-clonic seizures (GTCS), typically characterized by bilateral limb clonus and loss of posture. This model remains a cornerstone of preclinical antiseizure medication (ASM) screening due to its procedural simplicity, reproducibility, and high translational relevance (Löscher, 2017). The 6 Hz psychomotor seizure model (Brown et al., 1953; Metcalf et al., 2017), employs low-frequency (6-Hz) transcranial stimulation over a 3 s period to trigger minimal clonic seizure characterized by head nodding, forelimb clonus,

and jaw clonus. This paradigm has proven especially valuable for identifying compounds with efficacy against pharmacoresistant limbic seizures (Barton et al., 2001).

Chemoconvulsant-based models offer a pharmacological alternative for acute seizure induction. Pentylenetetrazol (PTZ), a noncompetitive $GABA_A$ antagonist, is one of the most widely employed agents in this class. Subcutaneous or intraperitoneal administration of PTZ in rodents generates a range of seizure phenotypes contingent on dosage and administration route (Monteiro et al., 2024). Acute convulsions are typically induced using a single bolus (50–100 mg/kg in mice, 60 mg/kg in adult rats), with seizure onset occurring within 30 min. Seizure severity can be immediately assessed using the modified Racine scale (Lüttjohann et al., 2009; Van Erum et al., 2019), which categorizes seizure severity from localized myoclonus to generalized clonic-tonic activity. In some cases, PTZ exposure can result in sudden unexpected death in epilepsy (SUDEP). Additional outcome metrics include latency to first generalized seizure, time to death, and post-treatment survival rate (Ciltas et al., 2023; Sadek et al., 2016; Tang et al., 2024). PTZ-induced acute seizures are frequently used to evaluate ASM efficacy, with pharmacological responses varying by endpoint (e.g., suppression of myoclonic, clonic, tonic seizures, or survival) (Löscher, 2009). This model is well-characterized for identifying potential treatments for myoclonic seizures (Löscher, 2016). Several other convulsants targeting GABAergic inhibition or alternative neurotransmitter systems have also been utilized to generate acute seizure states. These include bicuculline (Freund et al., 1987), picrotoxin (Ito et al., 1989), flurothyl (Marley et al., 1986), and allylglycine (Ashton & Wauquier, 1979), as well as compounds modulating glutamatergic, glycinergic, or mixed neurotransmission (Table 1). When applied systemically or focally, these compounds can generate different types of acute seizures, facilitating mechanistic studies, toxicological evaluation, and targeted pharmacological screening.

Status epilepticus models: Status epilepticus (SE) represents a critical neurological emergency encountered in both experimental and clinical contexts. To provide a unified framework for SE classification, the International League Against Epilepsy (ILAE) introduced a time-based operational definition: SE is a condition arising either from the failure of endogenous mechanisms responsible for seizure termination or from the initiation of pathological processes that sustain prolonged seizure activity beyond a defined threshold (time point T1), with the potential to cause long-term consequences—such as neuronal injury, cell death, and network remodeling—if seizure activity persists beyond time point T2. T1 is set at 5 min—the point at which a seizure is considered abnormally prolonged—and T2 at 30 min, marking the onset of risk for long-term neuropathological outcomes (Trinka et al., 2015).

In rodent models, SE is typically induced using prolonged electrical stimulation or chemoconvulsant agents such as pilocarpine or kainic acid (KA) (Gorter et al., 2016). Pilocarpine, a stable analog of acetylcholine and muscarinic acetylcholine receptor agonist, triggers intracellular cascades that elevate neuronal excitability and promote glutamate release. Single intraperitoneal doses ranging from 300–350 mg/kg in mice and 300–400 mg/kg in rats reliably induce SE. This model produces widespread neuropathology that closely mirrors the hippocampal and limbic damage observed in epilepsy patients with mesial temporal sclerosis (Lévesque et al., 2021). KA, a structural analog of L-glutamate and an agonist of ionotropic AMPA/KA receptors, induces neuronal death and excitotoxicity. It can be administered either intracerebrally or systemically, with intrahippocampal or intra-amygdaloid injections of 0.4–2.0 μg typically provoking seizures within 5–60 min. Systemic administration involves single bolus injections (6–15 mg/kg in rats, 20–60 mg/kg in mice), though a low-dose repeated protocol (5 mg/kg/h until SE onset) is often used to reduce mortality (Nirwan et al., 2018). Both approaches yield comparable seizure onset latencies, behavioral profiles, and EEG signatures; however, intracerebral administration leads to unilateral temporal lobe lesions, whereas systemic administration produces broader damage across hippocampal and parahippocampal regions. Species- and age-specific differences in KA sensitivity necessitate careful protocol optimization (Lévesque & Avoli, 2013).

Acute SE models, with varying times of drug administration, can be employed to evaluate the efficacy of ASMs and treatments across different dimensions. Seizure susceptibility is typically assessed using parameters such as behavioral seizure scores, stage-specific latencies, and mortality rates, providing endpoints for assessing ASM prophylaxis and seizure resistance (Do Val-da Silva et al., 2017; Liu et al., 2015). To evaluate therapeutic intervention post-SE onset, compounds are typically administered 30 min after seizure initiation—corresponding to the T2 threshold—to assess termination efficacy in pharmacoresistant SE (Shi et al., 2023; Zhao et al., 2020). Several mechanisms have been proposed to explain pharmacoresistance during SE, including the internalization of GABAergic receptors, up-regulation of AMPARs and P-glycoprotein, and overactivation of neuroinflammation (Herman, 2018; Walker, 2024).

Chronic epilepsy models: In SE-based paradigms, acquired epilepsy often occurs following the acute SE insult. Chronic spontaneous recurrent seizures (SRSs) typically emerge after a latent period spanning several weeks. The latent period reflects an active phase of epileptogenesis—the process by which a nonepileptic brain develops a chronic epileptic condition—accompanied by progressive molecular, cellular, and structural alterations. These include selective neuronal loss, dendritic retraction, mossy fiber sprouting, aberrant neurogenesis, and sustained activation of glial populations, all occurring in the absence of overt clinical seizures (Pitkänen et al., 2015). In post-SE models, this pathological remodeling is driven by histopathological changes in the hippocampus, mirroring those observed in patients with refractory TLE (Coulter et al., 2002; Löscher, 2002; Vermoesen et al., 2011). Long-term EEG and video monitoring are required to verify the emergence of SRSs. Once spontaneous seizure activity is established, the model allows for the stratification of animals into drug-responsive and drug-refractory groups for therapeutic evaluation (Wang & Chen, 2019).

Compared to acute seizure models, chronic epilepsy models have gained increasing attention. Both KA and pilocarpine-induced SE models replicate a drug-resistant state that emerges when treatment is delayed, enabling identification of compounds capable of reversing established resistance (Wang et al., 2023). These models also replicate molecular, cellular, and network alterations associated with epileptogenesis, more closely resembling the natural course of epilepsy (Williams et al., 2007), providing a suitable framework

Table 1 Common chemoconvulsants used in animal models

Chemoconvulsant	Functional target or function	Species	References
PTZ	$GABA_A$-R	Rodents	Monteiro et al., 2024
		NHPs	Pontes et al., 2016
		Zebrafish	Baraban et al., 2005
		Xenopus laevis	Bell et al., 2011; Hewapathirane et al., 2008
		C. elegans	Câmara et al., 2019; Williams et al., 2004
Bicuculline	$GABA_A$-R	Rodents	Freund et al., 1987
		NHPs	Jürgen Wenzel et al., 2000
		Zebrafish	Cassar et al., 2017
		Xenopus laevis	Hewapathirane et al., 2008
Picrotoxin	$GABA_A$-R	Rodents	Ito et al., 1989
		Zebrafish	Bandara et al., 2020; Yang et al., 2017
		Xenopus laevis	Hewapathirane et al., 2008
Flurothyl	$GABA_A$-R	Rodents	Marley et al., 1986
Penicillin	$GABA_A$-R	Rodents	Akdogan et al., 2008
		NHPs	Mayanagi & Walker, 1975
		Cat	Avoli, 1995
Allylglycine	GAD enzyme	Rodents	Ashton & Wauquier, 1979
		Zebrafish	Leclercq et al., 2015
Ginkgotoxin	GABA synthesis	Zebrafish	Lee et al., 2012
Pilocarpine	mACh-R	Rodents	Lévesque et al., 2021
		NHPs	Perez-Mendes et al., 2011
		Zebrafish	Lopes et al., 2016
		Xenopus laevis	Hewapathirane et al., 2008
Kainic acid	KA-R	Rodents	Lévesque & Avoli, 2013
		NHPs	Chen et al., 2013
		Zebrafish	Alfaro et al., 2011
		Xenopus laevis	Hewapathirane et al., 2008
Domoic acid	AMPA-R, KA-R	Rodents	Ananth et al., 2001
		NHPs	Tryphonas et al., 1990
		Zebrafish	Lefebvre et al., 2009; Tiedeken et al., 2005
4-Aminopyridine	GLUT, K-channel	Rodents	Yamaguchi & Rogawski, 1992
		Zebrafish	Winter et al., 2017
		Xenopus laevis	Hewapathirane et al., 2008

PTZ: Pentylenetetrazol; $GABA_A$-R: γ-aminobutyric acid type a receptor; GAD: Glutamic acid decarboxylase; mACh-R: Muscarinic acetylcholine receptor; KA-R: Kainate receptor; AMPA-R: α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor; GLUT-R: Glucose transporter receptor; NHPs: Non-human primates.

for evaluating disease-modifying therapies or drugs designed to prevent epilepsy onset or progression (Casillas-Espinosa et al., 2019; Clossen & Reddy, 2017; Löscher & Brandt, 2010).

Another widely used chronic model is the kindling paradigm, originally introduced in 1967, which remains a key experimental approach for studying the gradual acquisition of seizure susceptibility, although the mechanism is still not fully understood (Morimoto et al., 2004; Pitkänen and Sutula, 2002). In contrast to SE models, kindling-induced seizures are evoked rather than spontaneous. Repeated subthreshold electrical stimulations, typically targeting the hippocampus or amygdala, result in progressive increases in seizure severity and duration over time. Additionally, chemical kindling, induced by intermittent administration of low-dose PTZ similarly leads to sensitization and the eventual development of generalized seizures (Corda et al., 1991; Karler et al., 1989). Seizure progression is classically defined by the Racine scale, which describes five behavioral stages: facial clonus, head nodding, forelimb clonus, rearing, and rearing and falling accompanied by generalized clonic seizures (Racine, 1972). The transition from focal (stages 1–3) to generalized seizures (stages 4–5) involves the propagation of epileptiform activity from limbic structures to other brain regions. Once fully kindled, animals consistently exhibit stage 5 seizures and maintain long-lasting hyperexcitability in response to previously subthreshold stimuli. This progression recapitulates key aspects of epileptogenesis (Clossen & Reddy, 2017; White, 2002), including neuronal cell loss, aberrant neurogenesis, and axonal sprouting, which are relevant for neural network reorganization (Ren & Curia, 2021).

The classification of kindling as either a chronic or epileptogenesis model remains controversial. While it does not spontaneously generate seizures in the absence of ongoing stimulation, it nonetheless captures essential features of epileptogenic transformation and long-term seizure susceptibility (Bertram, 2007). Importantly, kindling has proven valuable in identifying novel ASMs, particularly those that may be ineffective in MES or PTZ (Barker-Haliski & Steve White, 2020). For example, levetiracetam, an ASM compound with a mechanism distinct from traditional agents, shows robust efficacy in kindling models, highlighting the value of this model in uncovering therapies for drug-resistant epilepsy (Klitgaard, 2001; Löscher & Hönack, 1993).

Acquired epilepsy models: Beyond SE, numerous neuropathological insults, such as traumatic brain injury (TBI), neoplasms, cerebrovascular events, CNS infections, and prolonged febrile convulsions, can initiate acquired epilepsy in humans (Becker, 2018). These injuries trigger cascades of oxidative stress, inflammation, and circuit remodeling, ultimately promoting the emergence of spontaneous recurrent seizures. Several pathologically relevant animal models have been established to mimic these clinical scenarios; three widely studied examples are summarized below.

TBI is a major precipitating factor for post-traumatic epilepsy (PTE), accounting for approximately 5% of all epilepsy cases. Post-injury seizures are classified based on their timing as immediate (<24 h), early (1–7 days), or late (>1 week) (Christensen, 2012; Frey, 2003). The initial mechanical insult triggers a rapid and sustained pathological cascade characterized by excessive production of ROS and activation of glial-driven inflammatory pathways. These processes interact synergistically to damage cellular components and disrupt mitochondrial function, while inflammation recruits immune cells and promotes the release of proinflammatory cytokines. Together, they create a persistent neuroinflammatory microenvironment that lowers seizure threshold, promotes neurodegeneration, and drives structural and functional reorganization of neural circuits, contributing to epileptogenesis.

Rodent models of TBI, particularly fluid percussion injury (FPI) and controlled cortical impact (CCI), have been extensively used to study epileptogenesis and replicate key features of human PTE (Smith, 2016). FPI is a percussive injury that mimics a closed-head-like injury in humans by rapidly injecting fluid into the intact cranial cavity through a craniotomy, which can be positioned parasagittally, centrally, or laterally to modulate injury characteristics (D'Ambrosio et al., 2004; Philips et al., 2020). In contrast, CCI enables precise control of the force, velocity, and extent of cortical tissue deformation using a pneumatic piston (Dixon et al., 1991). Both models exhibit a seizure-free latent period between acute injury and the onset of spontaneous seizures, accompanied by histopathological changes such as hippocampal neuronal death, neurogenesis, and axonal sprouting (Golub & Reddy, 2022; Pease et al., 2024). Structural magnetic resonance imaging (MRI) and EEG are increasingly applied in these models to identify biomarkers predictive of seizure onset and disease progression (Bragin et al., 2016; Perucca et al., 2019; Pitkänen & Immonen, 2014).

Hypoxic-ischemic encephalopathy represents the leading cause of neonatal seizures, exerting profound effects on the structurally and functionally immature brain (Shetty, 2015). Early-life hypoxia-induced seizures (HIS) in rats were first developed by Jensen et al. (1991) using a graded global hypoxia paradigm, in which neonatal rats are exposed to sequentially decreasing oxygen levels (7% O_2 for 8 min, 5% O_2 for 6 min, 4% O_2 for 1 min) in an airtight chamber. Acute seizures typically occur within minutes of hypoxia onset, characterized by head bobbing, wet-dog shakes, and tonic-clonic movements, accompanied by high-frequency epileptiform discharges (Rakhade & Jensen, 2009). Although this model does not produce overt neuronal loss or reactive gliosis, it induces mossy fiber sprouting in the hippocampus, which is responsible for spontaneous seizures and long-term behavioral deficits later in life (Bernard & Benke, 2015; Mikati et al., 2005; Rakhade et al., 2011). In addition to rats, mouse models have been developed to replicate the acute seizures following perinatal hypoxic injury. These rodent models mimic the age-dependent susceptibility to hypoxia and the refractory nature of seizures to conventional ASMs (Sun et al., 2016).

Febrile seizures (FS), the most prevalent seizure type in childhood, affect approximately 2%–5% of children under 5 years of age (Smith et al., 2019). Retrospective clinical analyses indicate a frequent association between early-life FS and later development of TLE (French et al., 1993). Experimental FS models in rodents involve controlled hyperthermia, either by exposing pups to a heated air stream until core body temperature reaches approximately 41°C (Baram et al., 1997) or by immersion in hot water (45.2°C) (Yang & Qin, 2004), both resulting in stereotyped convulsive behaviors including facial twitching, head nodding, and forelimb clonus. EEG analyses have implicated the amygdala and hippocampus as primary seizure initiation sites. Unlike many models of acute brain injury, FS do not induce neuronal death and trigger overt neurogenesis. Instead, they produce persistent changes in gene expression and abnormal cell morphology (Brewster et al., 2002; Dubé & Baram, 2009; Jongbloets et al., 2015), leading to long-term potentiation, increased hippocampal excitability through Hebbian plasticity, and increased suppression of GABA release (Harris et al., 2024). Additionally, FS alters the expression of hyperpolarization-activated cyclic nucleotide-gated (HCN) channels, leading to hippocampal hyperexcitability and later-onset limbic (temporal lobe) epilepsy (Chen et al., 2023a). Neuroinflammatory responses and glial cell activation also play a role in FS pathogenesis, with both deleterious and beneficial effects (Feng & Chen, 2016; Wan et al., 2020).

Acquired epilepsy models offer a powerful translational framework for investigating the mechanisms of epileptogenesis and developing preclinical strategies for anti-epileptogenic therapies. The post-insult latent period provides a unique therapeutic window for intervention, with the effects of treatments easily assessed by monitoring SRS. As in humans, not all animals subjected to brain insults will develop epilepsy. This inter-individual variability allows for identification of potential predictive biomarkers and facilitates stratification of treatment responders and nonresponders (Becker, 2018; White & Löscher, 2014).

Genetic models: Epilepsy is associated with a wide spectrum of genetic factors, with an expanding catalog of pathogenic variants now implicated in diverse epileptic phenotypes (Myers & Mefford, 2015; Noebels, 2015; Ruggiero et al., 2023; Thakran et al., 2020). Broadly, genetic models fall into two categories: those derived from spontaneous mutations and those generated via targeted genomic engineering. Both classes have yielded critical insights into seizure pathophysiology, disease progression, and pharmacological responsiveness.

Audiogenic seizure (AGS) models are reflex seizures primarily triggered by high-intensity acoustic stimulation (Faingold, 2002; Garcia-Cairasco, 2002). While rare in humans, these seizures are robustly expressed in genetically susceptible rodent strains (Stern, 2015), such as Krushinsky-Molodkina (KM) rats (Poletaeva et al., 2017), Wistar Audiogenic Rats (WARs) (Garcia-Cairasco et al., 2017), genetically epilepsy-prone rats (GEPRs) (Ribak, 2017), and Dilute Brown non-Agouti (DBA) mice (Chapman et al., 1984). AGS typically originate in the brainstem and are characterized by a wild running phase followed by tonic-clonic convulsions

(Faingold et al., 2014; Ross & Coleman, 2000). These strains are also amenable to audiogenic kindling, a process that induces changes in behavior, EEG patterns, and neuroanatomical structures involved in cortical and limbic networks (Kulikov et al., 2021; Merrill et al., 2005; Vinogradova, 2017). Audiogenic epileptic DBA/1 and DBA/2 mice may also serve as suitable models for studying mechanisms relevant to SUDEP, as they exhibit generalized seizures followed by respiratory arrest, as observed in a significant proportion of epilepsy patients (Bosco et al., 2023; Faingold et al., 2010).

Absence epilepsy (AE), which accounts for 10%–17% of all pediatric epilepsy cases (Matricardi et al., 2014), has also been successfully modeled in rodents. Wistar Albino Glaxo Rats (WAG/Rij) and Genetic Absence Epilepsy Rats (GAERS) are well-established genetic models used to replicate absence epilepsy seizures. Notably, their electrophysiological and behavioral features align with those observed in human patients, characterized by brief episodes of unresponsiveness and cessation of activity, with classical spike and slow‐wave discharges (SWDs) in EEG (van Luijtelaar & Sitnikova, 2006). In addition, their sensitivity to ASMs closely matches clinical observations, making them suitable for predicting ASM efficacy (Russo & Citraro, 2018; Russo et al., 2016). Comparative studies across epileptic and nonepileptic strains, combined with multi-site recordings from cortical and thalamic regions, have facilitated detailed investigations into the circuits and molecular mechanisms driving SWD generation and propagation (Atherton et al., 2023; Stenroos et al., 2024; van Luijtelaar and van Oijen, 2020).

Recent advances in gene-editing technologies have expanded the utility of engineered models in epilepsy research. While mice remain the most widely used system *in vivo*, rat models are also feasible due to advancements in programmable endonucleases (Ellenbroek & Youn, 2016; Guan et al., 2014). Early genetic models were obtained with spontaneous mutations in mice, providing insights into monogenic epilepsy phenotypes (Noebels, 2006). These efforts have since evolved into highly targeted strategies, including transgenesis, chemical mutagenesis, and gene targeting, which can accurately replicate human epileptic conditions (Mantegazza et al., 2010). Examples of genetically engineered models include *SCN1A* knockout mice (Barela et al., 2006), GABA-Aγ2(*R43Q*) mice (Tan et al., 2007), *Tsc1* mutant mice (Zeng et al., 2008), *Kcnq2*/*3* knock-in mice (Singh et al., 2008), and *Fmr1* knockout mice (Merlin, 2009). These mutations affect genes involved in ion channel regulation, synaptic activity, neurotransmitter release, and intracellular signaling, which are linked to a variety of epilepsy syndromes, ranging from benign familial neonatal epilepsy to severe forms such as Dravet syndrome and early infantile epileptic encephalopathy (Table 2).

Non-human primates (NHPs)

Despite their widespread utility, the translational value of rodent models is limited by substantial anatomical and physiological differences from humans. In contrast, NHPs possess a neocortical architecture, synaptic organization, and neurophysiological profile that more closely parallel those of humans. As a result, NHP models yield pathophysiological, behavioral, and electroencephalographic features that more accurately reflect human epilepsy. Many drugs that were effective in rodents have failed to reach the expected efficacy when tested in clinical trials. In this regard, NHP models provide opportunities to evaluate potential therapies (Sanabria et al., 2024). Current understanding of epilepsy in NHPs derives from both naturally occurring seizure phenotypes and experimentally induced models.

Photosensitive epilepsy model: Photosensitivity, characterized by a predisposition to trigger seizures in response to flashing lights or intermittent light stimulation (ILS), was first identified in baboons (Killam et al., 1966). Photoconvulsive episodes include myoclonic responses or sustained GTCS, often accompanied by interictal epileptic discharges (IEDs) recorded over the frontocentral cortex. Similar to humans, spontaneous seizures frequently occur during morning arousal, mirroring circadian susceptibility patterns observed in humans. Comparative studies across primate species revealed that robust photosensitivity appears to be restricted to baboons and humans, indicating a phylogenetically conserved and species-specific phenotype (Naquet et al., 1967; Stark et al., 1968). Furthermore, differences in seizure prevalence across baboon subspecies and geographic populations suggest both genetic and environmental influences (Balzamo et al., 1975; Killam, 1969).

Due to their consistent response to ASMs, epileptic baboons were among the earliest NHP models used for preclinical drug development and testing (Killam, 1976; Löscher, 1984; Meldrum et al., 1975; Wada et al., 1972). More recently, studies utilizing intracranial EEG and functional neuroimaging have expanded the characterization of this model. Seizure onset in baboons typically emerges around 5 years of age, coinciding with late adolescence (Szabó et al., 2012a). Clinical phenotypes include absence, myoclonic, and GTCS (Szabó et al., 2012b). While early studies emphasized frontothalamic networks (Naquet et al., 1975), recent investigations have implicated cortical regions in the generation and propagation of IEDs, revealing a more diffuse pathophysiology consistent with genetic generalized epilepsy. Given these features, the epileptic baboon model mirrors human genetic generalized epilepsy and serves as an optimal framework for photosensitive epilepsy, particularly juvenile myoclonic epilepsy (JME) (Salinas & Szabó, 2017; Szabó & Salinas, 2016).

Experimental models in NHPs: Multiple common convulsants used in experimental rodent models have been extensively tested in NHPs (Table 1), including aluminum hydroxide (Soper et al., 1978), bicuculline (Jürgen Wenzel et al., 2000), domoic acid (Tryphonas et al., 1990), penicillin (Mayanagi & Walker, 1975), PTZ (Pontes et al., 2016), KA (Chen et al., 2013), and pilocarpine (Perez-Mendes et al., 2011). Electrical kindling protocols have also been employed extensively to explore the mechanisms underlying epilepsy and to develop anti-seizure therapies (Wada et al., 1985). These approaches integrate the anatomical complexity and functional connectivity of NHP brains with established rodent methodologies, thereby offering enhanced translational value, particularly for TLE.

Recent advances in assisted reproductive technologies have enabled the generation of genetically modified primate models, including transgenic and gene knockout (KO) lines (Chan et al., 2001; Liu et al., 2014; Sasaki et al., 2009; Sato et al., 2016), facilitating mechanistic studies of epilepsy-associated genes. Numerous studies have modeled neurological diseases in NHPs, including Huntington's disease, autism spectrum disorders, and Parkinson's disease

Table 2 Genetic models of epilepsy

Functional target	Human gene	Associated syndrome	Species	Animal model	References
Voltage-gated sodium channel	SCN1A	GEFS+; DS	Rodents	*scn1a +/− scn1a RX/+*	Cao et al., 2012; Yu et al., 2006
			Zebrafish	*Didy^{s552} scn1lab mutant scn1lab morphant*	Baraban et al., 2013; Tiraboschi et al., 2020; Zhang et al., 2015
			Xenopus laevis	Oocyte Injection	Barela et al., 2006
			Drosophila	*Paralytic para*	Sun et al., 2012
	SCN2A	BFNS; DEE; DS	Rodents	*scn2a +/− scn2a +/RX*	Ogiwara et al., 2018
	SCN8A	DEE	Rodents	*N1768D/+ R1872W/+*	Bunton-Stasyshyn et al., 2019
	SCN1B	GEFS+; DEE; DS	Rodents	*DEE52 scn1b null mice*	Brackenbury et al., 2013
Potassium channel	KCNB1	DEE	Rodents	*G279R/+ kcnb1 −/−*	Hawkins et al., 2021; Speca et al., 2014
	KCNQ2	BFNS; DEE	Rodents	*kcnq2 +/− kcnq2 −/−*	Brun et al., 2022
			Xenopus laevis	Oocyte Injection	Hunter et al., 2006
	KCNQ3	BFNS	Rodents	*G311V/+*	Singh et al., 2008
			Zebrafish	*kcnq3 morphants*	Chege et al., 2012
	KCNT1	EIMFS; NFLE; DEE	Rodents	*kcnt1 −/− Y796H/+*	Quraishi et al., 2020; Shore et al., 2020
			Xenopus laevis	Oocyte Injection	Barcia et al., 2012
KCNH1	DEE	*Xenopus laevis*	Oocyte Injection	Simons et al., 2015	
	KCNJ10	EAST/ SeSAME	Zebrafish	*kcnj10a morphant*	Mahmood et al., 2013; Zdebik et al., 2013
			Xenopus laevis	Oocyte Injection	Bockenhauer et al., 2009
	HCN1	GEFS+; DEE; DS	Rodents	*hcn1 −/−*	Huang et al., 2009
	HCN2	AE	Rodents	*hcn2 ap/ap*	Chung et al., 2009
Voltage-gated calcium channel	CACNA1A	AE	Rodents	*cacna1a −/−*	Miao et al., 2020
			Zebrafish	*cacna1a morphants*	Gawel et al., 2020
Ionotropic γ-aminobutyric acid receptor	GABRA1	GEFS+; JME; AE; DS	Rodents	*gabra1 +/−*	Arain et al., 2012
	GABRB3	DEE; AE; DS	Rodents	*gabrb3 +/− N328D/+ D120N/+ N110D/+*	Nwosu et al., 2023; Qu et al., 2020; Qu et al., 2023; Shi et al., 2019
	GABRG2	GEFS+; JME; DS; AE	Rodents	*gabrg2 +/− Q390X/+*	Kang et al., 2015; Reid et al., 2013
			Xenopus laevis	Oocyte Injection	Baulac et al., 2001
γ-aminobutyric acid transporter/ Glucose transporter receptor	SLC6A1	MAE	Rodents	*A288V/+ S295L/+*	Shen et al., 2024
	SLC12A5	EIMFS	Rodents	*kcc2 +/−*	Puskarjov et al., 2014
			Zebrafish	*kcc2a/kcc2b mutant*	Stödberg et al., 2015
			Drosophila	*Kazachoc kcc*	Hekmat-Scafe et al., 2006
	GRIA4	AE	Rodents	*gria4 −/−*	Paz et al., 2011
Nicotinic acetylcholine receptor	CHRNA4	NFLE	Rodents	*S284L/+ S252F/+ +L264/+*	Klaassen et al., 2006; Zhu et al., 2008
			Xenopus laevis	Oocyte Injection	Weltzin et al., 2016
	CHRNB2	NFLE	Rodents	*V287L/+*	Xu et al., 2011
			Xenopus laevis	Oocyte Injection	Weltzin et al., 2016
			C. elegans	*arc-2 mutant*	Jospin et al., 2009
N-methyl-D-aspartate receptor	GRIN2A	EAS	Rodents	*grin2a +/− grin2a −/−*	Camp et al., 2023; Strehlow et al., 2019
	GRIN2B	DEE	*Xenopus laevis*	Oocyte Injection	Lemke et al., 2014
Syntaxin/Syntaxin binding protein	STX1B	GEFS+	Rodents	*stx1b +/−*	Mishima et al., 2021
			Zebrafish	*stx1b morphant*	Schubert et al., 2014
	STXBP1	DEE; DS	Rodents	*stxbp1 +/−*	Miyamoto et al., 2019
			NHPs	*STXBP1-E*	Lu et al., 2022
			Zebrafish	*stxbp1b mutant*	Grone et al., 2016
			C. elegans	*munc18-1 mutant*	Zhu et al., 2020

Continued

Functional target	Human gene	Associated syndrome	Species	Animal model	References
Synapse transmission	LGI1	ADPEAF	Zebrafish	*lgi1a/lgi1b morphant*	Teng et al., 2010; Teng et al., 2011
Neuronal migration; axonal outgrowth	PK1	PME	Rodents	*pk1 +/− pk2 +/− pk2 −/− R104Q/+*	Ban et al., 2022; Tao et al., 2011
			Zebrafish	*pk1a morphant*	Mei et al., 2013
			Drosophila	pk^{sple1}/pk^{sple1}	Tao et al., 2011
Dynein-binding protein	LIS1	Lissencephaly	*C. eleganslis-1 mutant*		Williams et al., 2004
Cyclin-dependent kinase	CDKL5	DEE	Rodents	*cdkl5 +/−*	Sampedro-Castañeda et al., 2023
Gene transcription modification	CHD2	EMA; DEE; DS	Zebrafish	*chd2 morphant*	Gawel et al., 2019
E3 ubiquitin ligase	KIAA1323	DEE	Zebrafish	*mind bomb mutant*	Hortopan et al., 2010a
Lysine catabolism	ALDH7A1	PDE	Rodent	*aldh7a1 +/− aldh7a1 −/−*	Al-Shekaili et al., 2020
			Zebrafish	*aldh7a1 mutant*	Pena et al., 2017
Tripeptidyl peptidase 1	TPP1	CLN2	Zebrafish	*tpp1 mutant*	Mahmood et al., 2013

ADPEAF: Autosomal dominant partial epilepsy with auditory features; AE: Absence epilepsy; BFNS: Benign familial neonatal seizures; CLN2: Neuronal ceroid lipofuscinosis type 2 disease; DEE: Developmental and epileptic encephalopathy; DS: Dravet syndrome; EAS: Epilepsy-aphasia spectrum; EAST/SeSAME: Epilepsy, ataxia, sensorineural deafness and renal tubulopathy; EIMFS: Epilepsy of infancy with migrating focal seizures; GEFS+: Genetic epilepsy with febrile seizures plus; JME: Juvenile myoclonic epilepsy; MAE: Myoclonic-atonic seizures; NFLE: Nocturnal frontal lobe epilepsy; PDE: Pyridoxine dependent epilepsy; PME: Progressive myoclonus epilepsy; NHPs: Non-human primates.

(Liu et al., 2016; Yang et al., 2008, 2019; Zhou et al., 2019). In a pioneering study, Murayama et al. (2020) engineered a transgenic marmoset line expressing human *GPR56* under regulation of the e1m promoter coupled to enhanced green fluorescence protein (EGFP). Loss of *GPR56* function induced cortical malformations and pharmacoresistant epilepsy, with a 15 bp deletion in a cis-regulatory element upstream of e1m identified in affected individuals. This model revealed the neuronal subtype distribution of e1m-driven *GPR56* and indicated a potential pathogenic role of GABAergic neurons in *GPR56* mutation-associated epilepsy. In a separate study, Lu et al. (2022) generated cynomolgus monkeys carrying single-nucleotide *STXBP1* mutations using cytosine base editing of one-cell embryos fertilized *in vitro*. Mutations in *STXBP1* were associated with severe early-onset epileptic encephalopathies (Table 2). Affected newborn monkeys displayed myoclonic seizures and, notably, the typical suppression-burst EEG observed in patients. These genetically modified primate models offer critical systems for elucidating the molecular and circuit-level mechanisms underlying epilepsy.

Domestic animals: Canines/felines

Domestic species such as cats and dogs have long served as translational models in epilepsy research, offering neuroanatomical and physiological advantages that bridge the gap between rodent models and human pathophysiology (Alsharafi et al., 2015). Although the use of induced seizure paradigms in these species has declined due to ethical considerations and statistical limitations imposed by smaller sample sizes, studies in such species continue to complement rodent-based approaches. Clinical reports of naturally occurring epilepsy and advances in veterinary neurology have also played a substantial role in refining diagnostic tools, informing therapeutic strategies, and supporting the development of neuromodulatory and pharmacological interventions (Charalambous et al., 2023; Hasegawa et al., 2021).

Feline epilepsy: In felines, electrical kindling of the amygdala or hippocampus has been employed to investigate the mechanistic basis of neuroplastic changes in epileptogenesis and emphasize the vital role of midbrain reticular formation (Sato, 1975; Sato & Moriwake, 1984; Shouse et al., 2004; Wada & Sata, 1974). These paradigms have also supported pharmacological screening of ASMs and neurostimulation strategies (Leviel & Naquet, 1977; Minabe et al., 1988; Wada et al., 1976, 1987). Additionally, intramuscular administration of penicillin has produced generalized SWDs in cats, enabling detailed analysis of thalamocortical circuitry involved in the pathophysiology of clinical absence seizures (Avoli, 1995). More recently, a colony of cats exhibiting familial spontaneous limbic seizures has been characterized as a genetic model of mesial temporal lobe epilepsy (MTLE) (Kuwabara et al., 2010), with EEG and MRI features closely resembling those seen in human patients, including seizure onset localized to the temporal lobe and unilateral hippocampal atrophy (Hasegawa et al., 2014; Mizoguchi et al., 2014).

Canine epilepsy: Canine epilepsy shares key clinical, etiological, and electrophysiological features with human epilepsy, making it a valuable model for translational research. Seizure episodes, including SE, occur frequently in affected dogs and may arise from structural abnormalities, metabolic disturbances, genetic variants, or unknown causes (Ekenstedt et al., 2012; Podell et al., 1995; Schwartz et al., 2011; Steinmetz et al., 2013). Seizure manifestations range from focal events—with or without impaired awareness—to GTCS (Berendt et al., 2004). EEG has enabled the identification of absence and myoclonic seizures, revealing interictal and ictal activity patterns closely resembling those observed in humans (Berendt et al., 1999; Davis et al., 2011). Since the 1970s, spontaneous epilepsy in dogs has been proposed as a useful comparative model (Frey et al., 1979; Hegreberg & Padgett, 1976), with considerable potential for research on ASM therapy, electroclinical biomarkers, and genetic mechanisms (Cui et al., 2018; Gregg et al., 2020; Patterson, 2014; Potschka et al., 2013; Varatharajah et al., 2017).

Zebrafish

Zebrafish (*Danio rerio*), a small freshwater teleost species native to South Asia, have emerged as powerful vertebrate model organisms in neurobiology due to their genetic similarity to humans, high fecundity, rapid maturation, and optical transparency (Fontana et al., 2019; Gawel et al., 2019; Kolesnikova et al., 2022; Yaksi et al., 2021). These features facilitate *in vivo* imaging, genetic manipulation, and high-

throughput screening, making zebrafish a tractable system for epilepsy research. Seizures can be reliably induced in larvae and adults using diverse chemoconvulsants or genetic perturbations, enabling the investigation of epileptogenic mechanisms and therapeutic candidates.

Pharmacologically induced acute seizure models: Acute seizure models in zebrafish were first established by Baraban et al. (2005) using PTZ, which reliably triggered seizure-like behaviors in larvae. PTZ has since become the most widely used and extensively validated pharmacological inducer, typically administered at 15–20 mmol/L for larvae and 5–15 mmol/L for adults (Afrikanova et al., 2013; Baxendale et al., 2012; Mussulini et al., 2013; Wong et al., 2010). Additional agents that elicit comparable seizure phenotypes include GABA receptor antagonists (bicuculline and picrotoxin) (Bandara et al., 2020; Cassar et al., 2017; Yang et al., 2017), glutamatergic receptor agonists (KA) (Alfaro et al., 2011; Menezes et al., 2014), cholinergic receptor agonists (pilocarpine) (Lopes et al., 2016; Vermoesen et al., 2011), cholinesterase inhibitors (physostigmine) (Kim et al., 2010), potassium channel blockers (4-aminopyridine, 4-AP) (Cassar et al., 2017; Winter et al., 2017), domoic acid (marine neurotoxin analog of KA) (Lefebvre et al., 2009; Tiedeken et al., 2005), GABA synthesis inhibitors (allylglycine) (Leclercq et al., 2015), and natural plant products (ginkgotoxin) (Lee et al., 2012). These compounds target distinct molecular pathways to induce similar epileptic phenotypes (Table 1).

Chemical convulsants offer practical advantages in zebrafish seizure modeling due to their ease of administration and rapid seizure induction. Compounds are typically delivered via immersion or direct injection, triggering stereotyped seizure behaviors characterized by initial hyperlocomotion followed by recurrent clonus-like convulsions that may lead to death (Alfaro et al., 2011; Baraban et al., 2005). Quantitative assessment of seizure phenotypes is achieved through automated locomotor tracking, electrophysiological recordings such as local field potentials or EEG, and real-time calcium imaging (Cho et al., 2017; Hunyadi et al., 2017; Meyer et al., 2016; Rosch et al., 2018; Turrini et al., 2017). Exposure to chemoconvulsants disrupts neurodevelopmental processes, leading to reduced neurogenesis and elevated expression of immediate early genes (Baraban et al., 2005; Budaszewski Pinto et al., 2021; Copmans et al., 2018; Kim et al., 2010).

Zebrafish from 2 days post-fertilization (2 dpf) through to adulthood serve distinct experimental roles across developmental stages. Zebrafish larvae are particularly valuable for *in vivo* high-throughput screening and assessment of small-molecule and natural compounds with potential anti-seizure properties (Baxendale et al., 2012; Buenafe et al., 2013; Challal et al., 2014; Copmans et al., 2018; Locubiche et al., 2024; Rosa-Falero et al., 2015). Although adult zebrafish are less amenable to large-scale screening due to anatomical constraints, they enable investigation of complex seizure-like phenotypes not readily observed in larvae (Gupta et al., 2014; Wong et al., 2010) and have shown applicability in studying the comorbidities associated with epilepsy (Canzian et al., 2019; Kundap et al., 2017; Lee et al., 2010).

Genetic epilepsy models: Genetic epilepsy models in zebrafish leverage a high degree of genomic homology, with approximately 70% of human genes represented (Howe et al., 2013) and orthologs identified for nearly 85% of epilepsy-associated loci (Hortopan et al., 2010b). These genetic similarities, combined with the ease of genetic manipulation, make zebrafish an ideal model for generating specific gene mutants that recapitulate key features of human epileptic syndromes.

Early models arose from forward-genetic screens using N-ethyl-N-nitrosourea (ENU) mutagenesis, with the *scn1lab* mutant—an ortholog of the human *SCN1A* gene implicated in Dravet syndrome—serving as a foundational example (Schoonheim et al., 2010). These mutants exhibit spontaneous electrographic abnormalities, hyperactivity, convulsive behaviors, and pharmacoresistance, closely mirroring the clinical phenotype (Baraban et al., 2013). Other genes associated with epilepsy have also been identified in ENU-generated zebrafish, including *Ube3a* (related to Angelman's syndrome) (Hortopan et al., 2010a), *ocrl1* (related to Lowe's syndrome) (Ramirez et al., 2012), and *tpp1* (related to human CLN2 disease) (Mahmood et al., 2013).

For functional studies and phenotyping, reverse genetic approaches have become dominant, with antisense morpholino (MO) knockdown strategies generating transient loss-of-function models targeting epilepsy-relevant genes such as lgi1, kcnq3, kcnj10a, chd2, stx1b, and scn1lab (Teng et al., 2010; Chege et al., 2012; Suls et al., 2013; Schubert et al., 2014; Zhang et al., 2015). Targeted genome editing using zinc finger nucleases (ZFNs) and transcription activator-like effector nucleases (TALENs) further refined mutagenesis capabilities (Hoffman et al., 2016; Stödberg et al., 2015). The advent of CRISPR/Cas9 markedly accelerated the development of efficient and specific knockout lines (Jao et al., 2013). The *stxbp1b* mutant—exhibiting spontaneous electrographic seizures—was the first model generated via CRISPR/Cas9, establishing a benchmark for precision modeling of human epileptic genotypes (Grone et al., 2016). Subsequent CRISPR-derived zebrafish models include aldh7a1$^{-/-}$ for pyridoxine-dependent epilepsy (Pena et al., 2017; Zhang et al., 2017), depdc5$^{-/-}$ for familial focal epilepsy (Swaminathan et al., 2018), and plphp$^{-/-}$ for vitamin B6-dependent epilepsy (Johnstone et al., 2019).

These genetic zebrafish lines are capable of recapitulating human phenotypes, with most models demonstrating seizure-like behavior or epileptiform discharges, offering robust platforms to dissect epileptogenic mechanisms and evaluate therapeutic candidates across a broad spectrum of epilepsy syndromes (Table 2).

Xenopus laevis

The African clawed frog (*X. laevis*) is a well-established amphibian model organism widely used in biomedical research (Karimi et al., 2018). Its ease of maintenance, high fecundity, and rapid external development enable large-scale experimental use from embryogenesis to free-swimming, optically transparent tadpoles with anatomically mature brains within 7 days. Approximately 80% of human disease-associated genes possess identifiable orthologs in this species (Hellsten et al., 2010), and the complete genome has been sequenced and annotated (Session et al., 2016). Genetic and molecular manipulation techniques, including mRNA injections (Gurdon et al., 1971) and CRISPR/Cas9 editing, have been readily applied in both oocytes and embryos (Naert et al., 2020). *Xenopus* tadpoles exhibit many advantages, including transparency for *in vivo* imaging and high BBB permeability for pharmacological manipulation,

establishing them as a powerful model for studying nervous system disorders (Pratt & Khakhalin, 2013).

Tadpole PTZ seizure model: *Xenopus* tadpoles also provide an efficient platform for studying chemically induced seizures, capitalizing on their capacity for transdermal absorption of neuroactive compounds. Immersion in chemoconvulsants elicits acute, reproducible motor seizures in freely swimming tadpoles within minutes. These episodes begin with convulsive clonus-like motor patterns, including repetitive tail bending, rapid circling, and erratic locomotion, followed by periods of behavioral arrest. With prolonged exposure, increasingly repetitive and stereotyped behaviors culminate in the loss of functional motor control. These behaviors can be elicited by seizure-induction agents with distinct mechanisms in a clear dose-dependent manner (Table 1). PTZ is frequently employed due to its wide therapeutic window and absence of lethality (Hewapathirane et al., 2008). Beyond behavioral phenotyping, seizure analysis in Xenopus tadpoles provides key insights through calcium dynamics and electrophysiological profiling, where synchronized high-amplitude calcium spikes and field-potential oscillations signal an increased neuronal firing rate and synchronicity (Bell et al., 2011; Hewapathirane et al., 2008; Xia et al., 2022).

Oocyte genetic model: *Xenopus* oocytes provide a robust heterologous expression system for functional analysis of exogenous proteins through RNA injection, a method pioneered in the 1970s (Gurdon et al., 1971). RNA extracted from tissues or synthesized based on the native or mutant protein of interest enables controlled expression of target ion channels, neurotransmitter receptors, and membrane transporters, supporting mechanistic investigation of epilepsy-linked variants. Electrophysiological recording of expressed proteins allows precise evaluation of channel and receptor function. Well before the advent of modern sequencing techniques, *Xenopus* oocytes enabled expression cloning of neuronal channels and receptors, as well as early testing of epileptogenic agents (Madeja et al., 1994; Muβhoff et al., 1994). Subsequent studies have used this platform to characterize the functional consequences of mutations identified in human epilepsy, including potassium channel genes *KCNQ2* and *KCNQ3* in benign familial neonatal convulsions (Yang et al., 1998) and the $GABA_A$ receptor gene *GABRG2* in genetic epilepsy with febrile seizures (Baulac et al., 2001; Harkin et al., 2002). This approach has since been extended to mutations affecting potassium channels (Barcia et al., 2012; Simons et al., 2015; Yang et al., 2010), sodium channels (Barela et al., 2006; Spampanato et al., 2001), $GABA_A$ receptors (Johannesen et al., 2016), N-methyl-D-aspartate (NMDA) receptors (Lemke et al., 2014), and acetylcholine receptors (Weltzin et al., 2016), reinforcing the oocyte system as a valuable platform for functional genomics in epilepsy research (Table 2).

Drosophila melanogaster

The fruit fly (*Drosophila melanogaster*), a small holometabolous insect with a short reproductive cycle of 10–12 days and a lifespan of approximately 30 days, has emerged as a powerful model for investigating neurological disorders. Despite its structurally distinct nervous system, comprising around 100 000 neurons, *Drosophila* demonstrates extensive functional conservation in key domains such as membrane excitability, ion channel regulation, and neurotransmitter signaling (Parker et al., 2011a). The complete genome has been sequenced (Adams et al., 2000), revealing approximately 75% of human disease-related genes have functional orthologs in *Drosophila* (Pandey & Nichols, 2011; Yamamoto et al., 2014), including the majority of genes linked to epilepsy in humans (Lasko & Lüthy, 2021). This conservation, combined with sophisticated genome-editing technology and rapid life cycle, has facilitated the *in vivo* investigation of genes responsible for a wide range of human diseases (Hales et al., 2015; Ugur et al., 2016). The discovery of bang-sensitive alleles in the 1970s (Benzer, 1971) established *Drosophila* as a tractable seizure model, with subsequent expansion of the genetic toolkit enabling precise recapitulation of specific mutations associated with human epilepsy (Bassett & Liu, 2014).

Seizure-sensitive mutants: *Drosophila* offers a powerful system for exploring the genetic factors related to seizure susceptibility (Table 2). The first seizure phenotype was described by Benzer (1971), who discovered a class of mutants exhibiting seizure-like behavior in response to a mechanical shock (termed bang-sensitive mutants). To date, more than 10 bang-sensitive alleles have been identified, many of which share molecular parallels with human epilepsy genes (Parker et al., 2011b; Song & Tanouye, 2008). These mutants exhibit seizure-like behaviors characterized by an initial seizure lasting several seconds, during which flies display leg-shaking, proboscis extension, and wing flapping, followed by temporary paralysis and a recovery seizure resembling the initial seizure with clonus-like activity. Similar phenotypes can be induced via electrical stimulation by inserting tungsten electrodes into immobilized flies (Marley & Baines, 2011). Other *Drosophila* mutants, referred to as temperature-sensitive paralytic mutants, exhibit behavioral paralysis when exposed to heat stress (Burg & Wu, 2012; Parker et al., 2011a).

While seizure-like activity can occur in both wild-type and mutant flies, mutants typically respond to lower stimulus thresholds and display longer seizure-like activity (Howlett & Tanouye, 2009; Kuebler & Tanouye, 2000). Conversely, certain mutants exhibit elevated seizure thresholds and function as seizure suppressors (Kuebler et al., 2001; Song & Tanouye, 2006). Similar to humans, seizures can be pharmacologically suppressed by ASMs such as valproate, phenytoin, gabapentin, and potassium bromide (Kuebler & Tanouye, 2002; Marley & Baines, 2011; Reynolds et al., 2004; Tan et al., 2004). The $para^{bss}$ mutant represents a particularly severe and pharmacoresistant model, offering utility for investigating refractory epilepsy (Kroll et al., 2015).

SCN1A-related genetic model: Seizure phenotypes have been reproduced in *Drosophila* through targeted knock-in of two human *SCN1A* gene mutations into its orthologous *Drosophila* gene, *para* (Table 2). The GEFS+ *K1270T* mutation is responsible for GEFS+ epilepsy (Abou-Khalil et al., 2001). When introduced into para, it results in temperature-dependent seizure-like activity, resembling febrile seizures in humans (Sun et al., 2012). Knock-in of the *S1231R* mutation, associated with Dravet syndrome (Fujiwara et al., 2003), is sufficient to induce both spontaneous and heat-induced seizures (Schutte et al., 2014). Electrophysiology recordings suggest an underlying mechanism related to the inhibitory reduction of GABAergic interneurons. CRISPR/Cas9 genome editing has greatly simplified the generation of additional *Drosophila* lines carrying either the *R1648H* (*R-H*) variant associated with GEFS+ or the *R1648C* (*R-C*) variant

associated with Dravet syndrome (Roemmich et al., 2021). These models exhibit comparable behavioral and cellular phenotypes, suggesting that divergent clinical outcomes in humans may arise primarily from differences in genetic background.

Caenorhabditis elegans

Caenorhabditis elegans, a nonparasitic nematode, was established as a model organism nearly five decades ago to investigate nervous system development and function (Corsi et al., 2015). Despite possessing only 302 neurons connected to approximately 7 000 synapses, *C. elegans* provides a fully mapped connectome defined through serial section electron microscopy (Cook et al., 2019; Parker et al., 2011a; White et al., 1986). Its nervous system shares conserved features of synaptic transmission, including neurotransmitters, receptors, transporters, and ion channels, though it notably lacks voltage-gated sodium channels (Hobert, 2013). The availability of single-cell RNA sequencing (scRNA-seq) data for all neuronal cell types in the adult hermaphrodite has further enhanced its utility for neurogenetic studies (Taylor et al., 2021). About 40% of C. elegans protein-coding genes have human orthologs or paralogs, and many human disease genes have counterparts in C. elegans with at least 60% sequence identity (Culetto & Sattelle, 2000; Kaletta & Hengartner, 2006). Although its application in epilepsy research is still in the early stages, the organism offers a genetically tractable, optically accessible, and experimentally versatile system to study the fundamental processes involved in seizure disorders (Cunliffe et al., 2015; Nguyen et al., 2016).

Seizure-like phenotypes in *C. elegans* (Table 2) were first described in mutants of the *lis1* ortholog, a gene associated with lissencephaly and epilepsy in humans (Williams et al., 2004), with exposure to PTZ eliciting rhythmic anterior body contractions, termed “head-bobbing”. Similar PTZ-induced convulsion phenotypes have been observed in mutants of genes involved in GABAergic synthesis and transmission (*unc-25*, *unc-46*, *unc-47*, and *unc-49*), implicating presynaptic vesicle dysfunction in convulsive motor responses (Câmara et al., 2019). Additionally, mutations in *acr-2*, which encodes a subunit of the acetylcholine receptor, have been linked to seizure-like phenotypes (Jospin et al., 2009), inducing spontaneous convulsions expressed as muscle hypercontraction behavior. Patch-clamp electrophysiological recordings and calcium imaging have revealed that these phenotypes arise from an excitation-inhibition imbalance within the locomotor circuit (Jospin et al., 2009; Qi et al., 2013; Stawicki et al., 2011).

Others

Other vertebrate systems have yielded additional insights into epilepsy. Domoic acid-exposed sea lions have been reported as a model of temporal lobe epileptogenesis, with neuropathological features such as neuron loss, mossy fiber sprouting, and hippocampal sclerosis that mirror those observed across multiple mammalian species, offering a rare opportunity to study epilepsy in a large mammalian brain (Buckmaster et al., 2014; Cook et al., 2015). Research on the Fayoumi chicken strain using brain chimera technology approaches have shown that brainstem circuits act as major generators of genetic reflex epilepsy (Batini et al., 1996; Teillet et al., 1991). In addition*, in vitro* models of turtles and guinea pigs are also capable of generating seizure-like activity, contributing to the study of the cellular basis of seizures (Uva et al., 2021; Velluti et al., 1997).

ASSESSMENT OF CURRENT ANIMAL MODELS

Epilepsy comprises a diverse spectrum of phenotypes with multifactorial etiologies and complex pathophysiological mechanisms. Despite substantial epidemiological and clinical advances, symptomatic treatment remains inadequate in many cases, largely due to limited understanding of the underlying mechanisms and biological processes. Animal models are still the most effective tools for studying epileptogenic mechanisms and evaluating therapeutic strategies. However, replicating the full phenotypic and mechanistic diversity of human epilepsy remains challenging due to interspecies differences and the heterogeneous nature of the disease.

Multidimensional comparison of experimental species: strengths and weaknesses

Each experimental species offers distinct advantages for epilepsy research, yet each also presents respective limitations (Figure 3). Mammalian systems provide the closest approximation to human brain structures and organization, offering complex neural architectures that support detailed circuit dynamics, region-specific vulnerability, and higher-order behaviors and cognitive functions. These models enable rigorous assessment of long-term neurological outcomes, such as cognitive decline, behavioral dysregulation, and gradual alterations in neural plasticity, phenomena that cannot be fully reproduced in shorter-lived species. However, the higher costs associated with mammalian models, coupled with ethical concerns and limited genetic tractability, significantly hinder the scalability of experiments. NHPs provide the most faithful replication of human neuroanatomy and behavior, conferring high translational potential for epilepsy research, yet their use is severely limited by stringent ethical oversight, high costs, and the protracted timelines required to generate genetically modified lines. Domestic animals, such as dogs and cats, also exhibit complex brain structures and naturally occurring epilepsy, but their phenotypic variability, lack of standardized protocols, and challenges in genetic manipulation limit their utility beyond observational studies. Rodents share several structural and physiological features with humans, although their brains lack sulci and gyri, making them less similar to humans than other mammals. Nevertheless, rodents strike a balance between neural complexity and experimental tractability, allowing for reproducible phenotypes, behavioral assays, and advanced genetic manipulation, all at a relatively low cost and over shorter timeframes.

Nonmammalian models offer several advantages for experimental epilepsy research, including small size, simplified neural architecture, and short lifespan, which facilitate low-cost, high-throughput screening and powerful genetic manipulation. However, their reduced network complexity restricted behavioral repertoire—primarily confined to motor responses—limit their translational potential for complex diseases like epilepsy. Zebrafish display robust, quantifiable, and reproducible seizure-like activity at both behavioral and electrographic levels, making them a preferred platform for early-stage screening of ASMs. Nonetheless, most assays are restricted to embryos and larvae, whose immature neural circuitry contributes to variable

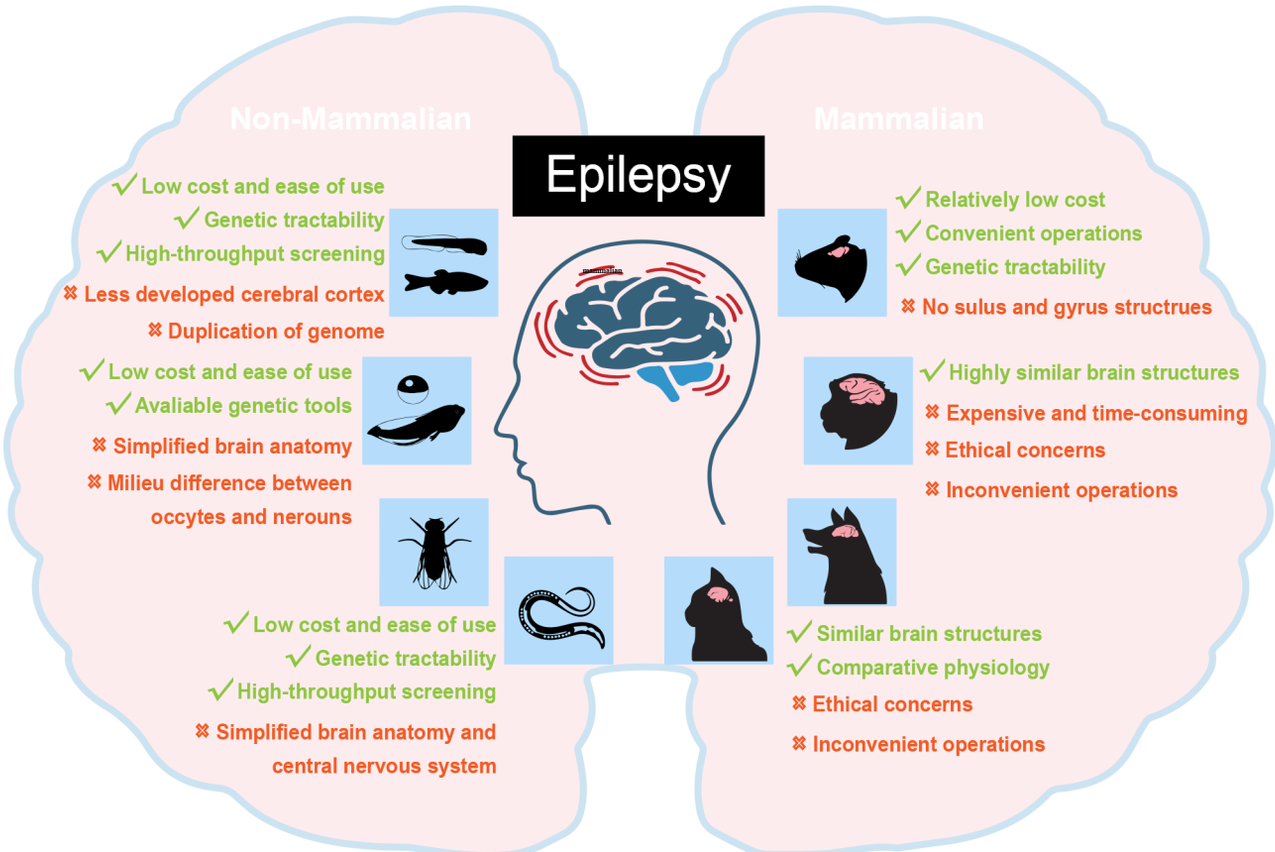

Figure 3 Summary of advantages and disadvantages of animal models of epilepsy across a wide range of species

Comparison between mammalian animal models (rodents, nonhuman primates, canines, and felines) and nonmammalian animal models (*Danio rerio*, *Xenopus laevis*, *Drosophila melanogaster*, and *Caenorhabditis elegans*). Green texts highlight advantages and red texts highlight disadvantages of each species.

pharmacological responses. Consequently, the same ASMs can produce different effects on seizure behavior in adult zebrafish (Da Silva et al., 2020; Pieróg et al., 2021). Inconsistent drug absorption when compounds are delivered via immersion—especially for hydrophobic or high-molecular-weight molecules—further complicates pharmacokinetic interpretation and may yield false negatives. Although injection or dietary delivery can overcome these limitations, such methods reduce the scalability of high-throughput screening platforms.

Similarly, *Xenopus laevis* has been widely used for electrophysiological assays, particularly in the oocyte system, yet its rudimentary brain architecture restricts relevance for modeling circuit-level pathologies. As a heterologous expression system, the oocyte milieu in *Xenopus* does not replicate the mammalian cellular environment, leading to potential structural and functional differences in proteins expressed after RNA injection. Additionally, endogenous receptors, channels, and transporters in the oocyte may affect experimental consistency when compared to human models. For example, quinidine has been shown to reverse increased potassium currents caused by *KCNT1* gain-of-function mutations in *Xenopus laevis* oocytes (Milligan et al., 2014) but has yielded variable clinical outcomes in patients with *KCNT1* mutations (Fitzgerald et al., 2019).

Invertebrate systems such as *Drosophila melanogaster* and *Caenorhabditis elegans* possess highly simplified nervous systems with relatively few neurons, constraining their capacity to replicate complex seizure phenotypes. Although targeted modeling of epilepsy-related gene variants—such as *Drosophila* mutants of human Dravet syndrome—can be introduced into nonmammalian systems, limited cellular diversity and simplified brain architecture restrict their capacity to capture the organ-level and circuit-level pathophysiology observed in human epilepsies. As a result, many of the behavioral and network changes associated with Nav1.1 cannot be accurately replicated.

Toward an "ideal" model: theoretical foundations and practical challenges

An ideal animal model for epilepsy must satisfy three primary validity criteria: construct validity, defined as the capacity to replicate the underlying etiological mechanisms of a given epilepsy syndrome; face validity, the ability to reproduce the phenotypic features of human epileptic conditions; and predictive validity, the ability to identify pharmacological or therapeutic interventions that prove effective in clinical settings (Boillot & Baulac, 2016; Mergenthaler & Meisel, 2015).

High construct validity can be achieved in some models of genetic epilepsies due to well-characterized genotype-phenotype relationships. In contrast, models of mesial TLE typically fall short in this domain. The etiology in human mesial TLE is frequently idiopathic or multifactorial, and no single experimental insult—whether chemoconvulsant exposure, electrical stimulation, or injury—adequately captures the complex, protracted pathophysiological cascade leading to chronic epilepsy in humans (Bertram, 2007; Löscher, 2011). As such, the translational relevance of many chemically or

electrically induced models remains a subject of ongoing debate.

Animal models generally exhibit either acute or chronic seizure phenotypes and abnormal electrographic discharges with high face validity, closely mimicking the symptomatology and pathology observed in human epilepsy. However, other behavioral characteristics or comorbidities may be underrepresented or neglected. Acute seizure models, while valuable for evaluating anticonvulsant efficacy, are inherently limited in their ability to capture the chronic, often lifelong nature of epilepsy. Although chronic models exist, many fail to fully represent the complexity of human epilepsy, particularly cognitive decline and network reorganization.

Predictive validity, although crucial for therapeutic development, is the most underdeveloped dimension. Most preclinical studies emphasize construct or face validity, yet few models reliably predict clinical drug responses. The MES test remains the only clinically validated preclinical assay for GTCS (Barker-Haliski et al., 2015; White & Löscher, 2014). Even models using species with high anatomical and physiological similarity to humans suffer from translational limitations due to interspecies differences in neurochemistry, receptor expression, pharmacokinetics, and BBB properties. Additionally, there is no consensus framework for defining predictive validity in epilepsy models, making it difficult to distinguish between models with poor predictive validity and phenotypes that mirror treatment-resistant epilepsy (Simonato et al., 2014).

The inherent heterogeneity of epilepsy compounds the challenge of evaluating model validity. Despite significant advances in the discovery and development of new ASMs through animal models, clinical translation remains inconsistent. Divergences in metabolism, drug distribution, and adverse effect profiles between animal systems and humans continue to undermine translational fidelity. As a result, a systematic re-evaluation of existing models, along with the development of new frameworks for assessing construct, face, and predictive validity, is essential to improve the relevance and impact of preclinical epilepsy research.

Applications of animal models: reference for model selection

Animal models represent a simplified approximation of complex human pathophysiology, designed to replicate selected features of disease rather than its clinical and mechanistic spectrum. In the context of epilepsy research, the primary goal of model development and selection is to elucidate the underlying biological mechanisms of seizures and associated comorbidities, and to evaluate the therapeutic potential of candidate compounds.

In preclinical drug development, the Epilepsy Therapy Screening Program (ETSP), an initiative funded by the National Institute of Neurological Disorders and Stroke (NINDS) and National Institutes of Health (NIH), employs a two-phase testing framework (Kehne et al., 2017). In the initial identification phase, compounds are screened across multiple well-established rodent models encompassing both acute and chronic seizure paradigms, facilitating high-throughput evaluation. Agents demonstrating efficacy are then advanced to the differentiation phase, where they are assessed in etiologically relevant models to obtain a more detailed and precise understanding of their potential efficacy (Wilcox et al., 2020). The program also maintains a publicly accessible database, Public Access to Neuroactive and Anticonvulsant Chemical Evaluations (PANAChE), which compiles detailed information on tests, procedures, and workflows.

While clinical epilepsy classification begins with etiology inferred from patient history, brain pathology, and genetic profile (Fisher et al., 2017), experimental approaches follow an inverse process. Researchers first select an epileptogenic factor and subsequently characterize the resulting phenotype within the model organism, enabling the controlled study of disease mechanisms. This phenotype is shaped by numerous factors, including the induction strategy, species-specific attributes, and the sensitivity of detection platforms. Given that each model reproduces specific aspects of human epilepsy, rigorous alignment between research objectives and model properties is critical. Models can be categorized by seizure phenotypes (Gu & Dalton, 2017; Nirwan et al., 2018; Wang et al., 2022), stages of epilepsy (e.g., ictogenesis, epileptogenesis) (Becker, 2018), specific groups (e.g., pediatric, inherited, drug-resistant epilepsy) (Auvin et al., 2012; Galanopoulou & Moshé, 2015; Löscher & White, 2023), and specific etiologies (e.g., inflammation, tumors, infections) (Golub & Reddy, 2022; Pease et al., 2024). These classification schemes provide a practical basis for selecting models that are best suited to the specific mechanistic or therapeutic questions under investigation.

RECENT PROGRESS AND PERSPECTIVES

Over the past few decades, significant advances have been made in understanding the genetics of epilepsy and in developing innovative tools for targeted therapeutic strategies (Sisodiya, 2021). The field is undergoing a paradigm shift from symptomatic seizure alleviation toward syndrome-specific treatment and disease prevention, with increasing adoption of precision medicine principles in both research and clinical contexts (Klein et al., 2024). Realizing the goals of precision medicine necessitates continuous refinement of existing animal models and the development of new systems capable of capturing the diverse pathophysiology of epilepsy. Advancements in neural circuit technology and molecular genetics are paving the way for more sophisticated animal models with enhanced translational relevance.

Optogenetic and chemogenetic tools are transforming experimental epilepsy modeling by enabling temporally and spatially precise manipulation of defined neuronal populations. Studies have successfully triggered seizures using light-based stimulation alone (Berglind et al., 2018; Krook-Magnuson et al., 2015; Osawa et al., 2013), while the optokindling model has been developed to recapitulate the hallmark properties of classical kindling, notably gradual seizure development and long-term seizure retention (Cela et al., 2019). These technologies allow targeted modulation of seizure-initiating circuits, surpassing conventional electrical or chemical methods in precision (Wang & Chen, 2019; Xiao et al., 2024). Real-time and closed-loop regulation of brain activity can now be achieved by combining simultaneous electrical recordings with optogenetic techniques (Zaaimi et al., 2023). Unlike conventional pharmacological or surgical methods, closed-loop therapies allow rapid and on-demand intervention (Zaaimi et al., 2023).

Parallel advances in next-generation sequencing have identified causative genetic variants in approximately 40% of epilepsy cases, with the expansion of epilepsy-associated genetic databases across species further facilitating research

and model development (Zhang et al., 2024a). Progress in genetic engineering has enabled the generation of mutant animal models that reproduce human pathogenic variants, leading to more disease-specific and personalized therapeutic strategies (Fischer et al., 2023; Merseburg et al., 2022; Ochenkowska et al., 2022).

Human brain organoids derived from induced pluripotent stem cells or embryonic stem cells provide a complementary platform for modeling epilepsy *in vitro*. These three-dimensional cultures recapitulate key aspects of cortical architecture and neural function (Brown et al., 2024; Sasai, 2013), and have been used to replicate cellular phenotypes, electrophysiological properties, and relevant neural circuits essential for understanding seizures (Javaid et al., 2022; Shiri et al., 2019; Weng et al., 2022). Genetic engineering applied to brain organoids enables detailed investigation of epilepsy-associated mutations by recreating the molecular and cellular abnormalities underlying genetic epilepsies (Parent & Anderson, 2015; Simkin et al., 2022; Sterlini et al., 2020). In addition to mechanistic studies, these organoids offer significant potential for personalized treatment. When derived from patient cells, organoids retain individual genetic and epigenetic features, allowing for the modeling of patient-specific epilepsies, evaluation of drug responses, and high-throughput screening to identify effective antiseizure medications and optimal dosing regimens (Chang & Chang, 2022; Hirose et al., 2020; Lybrand et al., 2020; Shcheglovitov & Peterson, 2021). Moreover, the integration of gene editing technologies into these platforms may provide a foundation for the development of targeted disease-modifying treatments.

To support the heterogeneity of epilepsy research, there remains a critical need for diversified and validated models across species. Simple organisms permit rapid genetic and molecular studies, rodents offer circuit-level and behavioral insight, and larger species provide translational relevance. Strategic integration of findings across these systems will be essential to improve mechanistic understanding and advance therapeutic discovery.

COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

Y.W., J.Z.C., and F.F. edited the manuscript. W.J.L.L., J.X., and Z.S.L. collected references, conceptualized the review, and wrote the original draft. All authors read and approved the final version of the manuscript.

REFERENCES

Abou-Khalil B, Ge Q, Desai R, et al. 2001. Partial and generalized epilepsy with febrile seizures plus and a novel *SCN1A* mutation. *Neurology*, **57**(12): 2265–2272.

Adams MD, Celniker SE, Holt RA, et al. 2000. The genome sequence of *Drosophila melanogaster*. *Science*, **287**(5461): 2185–2195.

Afrikanova T, Serruys ASK, Buenafe OEM, et al. 2013. Validation of the zebrafish pentylenetetrazol seizure model: locomotor versus electrographic responses to antiepileptic drugs. *PLoS One*, **8**(1): e54166.

Akdogan I, Adiguzel E, Yilmaz I, et al. 2008. Penicillin-induced epilepsy model in rats: dose-dependant effect on hippocampal volume and neuron number. *Brain Research Bulletin*, **77**(4): 172–177.

Akyuz E, Polat AK, Eroglu E, et al. 2021. Revisiting the role of neurotransmitters in epilepsy: an updated review. *Life Sciences*, **265**: 118826.

Alfaro JM, Ripoll-Gómez J, Burgos JS. 2011. Kainate administered to adult zebrafish causes seizures similar to those in rodent models. *European Journal of Neuroscience*, **33**(7): 1252–1255.

Alsharafi WA, Xiao B, Abuhamed MM, et al. 2015. miRNAs: biological and clinical determinants in epilepsy. *Frontiers in Molecular Neuroscience*, **8**: 59.

Al-Shekaili HH, Petkau TL, Pena I, et al. 2020. A novel mouse model for pyridoxine-dependent epilepsy due to antiquitin deficiency. *Human Molecular Genetics*, **29**(19): 3266–3284.

Ananth C, Thameem Dheen S, Gopalakrishnakone P, et al. 2001. Domoic acid-induced neuronal damage in the rat hippocampus: changes in apoptosis related genes (Bcl-2, Bax, caspase-3) and microglial response. *Journal of Neuroscience Research*, **66**(2): 177–190.

Arain FM, Boyd KL, Gallagher MJ. 2012. Decreased viability and absence-like epilepsy in mice lacking or deficient in the $GABA_A$ receptor α1 subunit. *Epilepsia*, **53**(8): e161–e165.

Ashton D, Wauquier A. 1979. Effects of some anti-epileptic, neuroleptic and gabaminergic drugs on convulsions induced by D, L-allylglycine. *Pharmacology Biochemistry and Behavior*, **11**(2): 221–226.

Atherton Z, Nagy O, Barcsai L, et al. 2023. Higher-order thalamic nuclei facilitate the generalization and maintenance of spike-and-wave discharges of absence seizures. *Neurobiology of Disease*, **178**: 106025.

Auvin S, Pineda E, Shin D, et al. 2012. Novel animal models of pediatric epilepsy. *Neurotherapeutics*, **9**(2): 245–261.

Avoli M. 1995. Feline generalized penicillin epilepsy. *The Italian Journal of Neurological Sciences*, **16**(1-2): 79–82.

Avoli M, Lévesque M. 2022. $GABA_B$ receptors: are they missing in action in focal epilepsy research?. *Current Neuropharmacology*, **20**(9): 1704–1716.

Balzamo E, Bert J, Menini C, et al. 1975. Excessive light sensitivity in *Pap_{10} papio*: its variation with age, sex, and geographic origin. *Epilepsia*, **16**(2): 269–276.

Ban Y, Yu T, Wang JY, et al. 2022. Mutation of the murine *Prickle1* (*R104Q*) causes phenotypes analogous to human symptoms of epilepsy and autism. *Experimental Neurology*, **347**: 113880.

Bandara SB, Carty DR, Singh V, et al. 2020. Susceptibility of larval zebrafish to the seizurogenic activity of GABA type A receptor antagonists. *Neurotoxicology*, **76**: 220–234.

Baraban SC, Dinday MT, Hortopan GA. 2013. Drug screening in *Scn1a* zebrafish mutant identifies clemizole as a potential Dravet syndrome treatment. *Nature Communications*, **4**: 2410.

Baraban SC, Taylor MR, Castro PA, et al. 2005. Pentylenetetrazole induced changes in zebrafish behavior, neural activity and c-fos expression. *Neuroscience*, **131**(3): 759–768.

Baram TZ, Gerth A, Schultz L. 1997. Febrile seizures: an appropriate-aged model suitable for long-term studies. *Developmental Brain Research*, **98**(2): 265–270.

Barcia G, Fleming MR, Deligniere A, et al. 2012. *De novo* gain-of-function *KCNT1* channel mutations cause malignant migrating partial seizures of infancy. *Nature Genetics*, **44**(11): 1255–1259.

Barela AJ, Waddy SP, Lickfett JG, et al. 2006. An epilepsy mutation in the sodium channel *SCN1A* that decreases channel excitability. *The Journal of Neuroscience*, **26**(10): 2714–2723.

Barker-Haliski ML, Friedman D, French JA, et al. 2015. Disease modification in epilepsy: from animal models to clinical applications. *Drugs*, **75**(7): 749–767.

Barker-Haliski M, Steve White H. 2020. Validated animal models for antiseizure drug (ASD) discovery: advantages and potential pitfalls in ASD screening. *Neuropharmacology*, **167**: 107750.

Barker-Haliski M, White HS. 2015. Glutamatergic mechanisms associated with seizures and epilepsy. *Cold Spring Harbor Perspectives in Medicine*, **5**(8): a022863.

Barton ME, Klein BD, Wolf HH, et al. 2001. Pharmacological

characterization of the 6 Hz psychomotor seizure model of partial epilepsy. *Epilepsy Research*, **47**(3): 217–227.

Bassett A, Liu JL. 2014. CRISPR/Cas9 mediated genome engineering in *Drosophila*. *Methods*, **69**(2): 128–136.

Batini C, Teillet MA, Naquet R, et al. 1996. Brain chimeras in birds: application to the study of a genetic form of reflex epilepsy. *Trends in Neurosciences*, **19**(6): 246–252.

Baulac S, Huberfeld G, Gourfinkel-An I, et al. 2001. First genetic evidence of $GABA_A$ receptor dysfunction in epilepsy: a mutation in the γ2-subunit gene. *Nature Genetics*, **28**(1): 46–48.

Baxendale S, Holdsworth CJ, Meza Santoscoy PL, et al. 2012. Identification of compounds with anti-convulsant properties in a zebrafish model of epileptic seizures. *Disease Models & Mechanisms*, **5**(6): 773–784.

Becker AJ. 2018. Review: animal models of acquired epilepsy: insights into mechanisms of human epileptogenesis. *Neuropathology and Applied Neurobiology*, **44**(1): 112–129.

Begley C, Wagner RG, Abraham A, et al. 2022. The global cost of epilepsy: a systematic review and extrapolation. *Epilepsia*, **63**(4): 892–903.

Bell MR, Belarde JA, Johnson HF, et al. 2011. A neuroprotective role for polyamines in a *Xenopus* tadpole model of epilepsy. *Nature Neuroscience*, **14**(4): 505–512.

Benzer S. 1971. From the gene to behavior. *JAMA*, **218**(7): 1015–1022.

Berecki G, Tao E, Howell KB, et al. 2025. $Na_v1.2$ channel mutations preventing fast inactivation lead to *SCN2A* encephalopathy. *Brain*, **148**(1): 212–226.

Berendt M, Gredal H, Alving J. 2004. Characteristics and phenomenology of epileptic partial seizures in dogs: similarities with human seizure semiology. *Epilepsy Research*, **61**(1-3): 167–173.

Berendt M, Høgenhaven H, Flagstad A, et al. 1999. Electroencephalography in dogs with epilepsy: similarities between human and canine findings. *Acta Neurologica Scandinavica*, **99**(5): 276–283.

Berglind F, Andersson M, Kokaia M. 2018. Dynamic interaction of local and transhemispheric networks is necessary for progressive intensification of hippocampal seizures. *Scientific Reports*, **8**(1): 5669.

Bernard PB, Benke TA. 2015. Early life seizures: evidence for chronic deficits linked to autism and intellectual disability across species and models. *Experimental Neurology*, **263**: 72–78.

Bernasconi A, Bernasconi N, Bernhardt BC, et al. 2011. Advances in MRI for 'cryptogenic' epilepsies. *Nature Reviews Neurology*, **7**(2): 99–108.

Bertram E. 2007. The relevance of kindling for human epilepsy. *Epilepsia*, **48 Suppl 2**: 65–74.

Bockenhauer D, Feather S, Stanescu HC, et al. 2009. Epilepsy, ataxia, sensorineural deafness, tubulopathy, and *KCNJ10* mutations. *The New England Journal of Medicine*, **360**(19): 1960–1970.

Boillot M, Baulac S. 2016. Genetic models of focal epilepsies. *Journal of Neuroscience Methods*, **260**: 132–143.

Bosco F, Guarnieri L, Leo A, et al. 2023. Audiogenic epileptic DBA/2 mice strain as a model of genetic reflex seizures and SUDEP. *Frontiers in Neurology*, **14**: 1223074.

Brackenbury WJ, Yuan YK, O'Malley HA, et al. 2013. Abnormal neuronal patterning occurs during early postnatal brain development of *Scn1b*-null mice and precedes hyperexcitability. *Proceedings of the National Academy of Sciences of the United States of America*, **110**(3): 1089–1094.

Bragin A, Li L, Almajano J, et al. 2016. Pathologic electrographic changes after experimental traumatic brain injury. *Epilepsia*, **57**(5): 735–745.

Brewster A, Bender RA, Chen YC, et al. 2002. Developmental febrile seizures modulate hippocampal gene expression of hyperpolarization-activated channels in an isoform- and cell-specific manner. *The Journal of Neuroscience*, **22**(11): 4591–4599.

Brown R, Rabeling A, Goolam M. 2024. Progress and potential of brain organoids in epilepsy research. *Stem Cell Research & Therapy*, **15**(1): 361.

Brown WC, Schiffman DO, Swinyard EA, et al. 1953. Comparative assay of antiepileptic drugs by “psychomotor” seizure test and minimal electroshock threshold test. *The Journal of Pharmacology and Experimental Therapeutics*, **107**(3): 273–283.

Browning RA, Nelson DK. 1985. Variation in threshold and pattern of electroshock-induced seizures in rats depending on site of stimulation. *Life Sciences*, **37**(23): 2205–2211.

Brun L, Viemari JC, Villard L. 2022. Mouse models of *Kcnq2* dysfunction. *Epilepsia*, **63**(11): 2813–2826

Brunklaus A, Feng T, Brünger T, et al. 2022. Gene variant effects across sodium channelopathies predict function and guide precision therapy. *Brain*, **145**(12): 4275–4286.

Bryson A, Reid C, Petrou S. 2023. Fundamental Neurochemistry Review: $GABA_A$ receptor neurotransmission and epilepsy: principles, disease mechanisms and pharmacotherapy. *Journal of Neurochemistry*, **165**(1): 6–28.

Buckmaster PS, Wen XL, Toyoda I, et al. 2014. Hippocampal neuropathology of domoic acid–induced epilepsy in California sea lions (*Zalophus californianus*). *Journal of Comparative Neurology*, **522**(7): 1691–1706.

Budaszewski Pinto C, de Sá Couto-Pereira N, Kawa Odorcyk F, et al. 2021. Effects of acute seizures on cell proliferation, synaptic plasticity and long-term behavior in adult zebrafish. *Brain Research*, **1756**: 147334.

Buenafe OE, Orellana-Paucar A, Maes J, et al. 2013. Tanshinone IIA exhibits anticonvulsant activity in zebrafish and mouse seizure models. *ACS Chemical Neuroscience*, **4**(11): 1479–1487.

Bunton-Stasyshyn RKA, Wagnon JL, Wengert ER, et al. 2019. Prominent role of forebrain excitatory neurons in *SCN8A* encephalopathy. *Brain*, **142**(2): 362–375.

Burg MG, Wu CF. 2012. Mechanical and temperature stressor-induced seizure-and-paralysis behaviors in *Drosophila* bang-sensitive mutants. *Journal of Neurogenetics*, **26**(2): 189–197.

Câmara DF, Machado ML, Arantes LP, et al. 2019. MPMT-OX up-regulates GABAergic transmission and protects against seizure-like behavior in *Caenorhabditis elegans*. *Neurotoxicology*, **74**: 272–281.

Camp CR, Vlachos A, Klöckner C, et al. 2023. Loss of *Grin2a* causes a transient delay in the electrophysiological maturation of hippocampal parvalbumin interneurons. *Communications Biology*, **6**(1): 952.

Canzian J, Fontana BD, Quadros VA, et al. 2019. Single pentylenetetrazole exposure increases aggression in adult zebrafish at different time intervals. *Neuroscience Letters*, **692**: 27–32.

Cao DZ, Ohtani H, Ogiwara I, et al. 2012. Efficacy of stiripentol in hyperthermia-induced seizures in a mouse model of Dravet syndrome. *Epilepsia*, **53**(7): 1140–1145.

Cao F, Liu JJ, Zhou SS, et al. 2020. Neuroligin 2 regulates absence seizures and behavioral arrests through GABAergic transmission within the thalamocortical circuitry. *Nature Communications*, **11**(1): 3744.

Casillas-Espinosa PM, Powell KL, O'Brien TJ. 2012. Regulators of synaptic transmission: roles in the pathogenesis and treatment of epilepsy. *Epilepsia*, **53 Suppl 9**: 41–58.

Casillas-Espinosa PM, Shultz SR, Braine EL, et al. 2019. Disease-modifying effects of a novel T-type calcium channel antagonist, Z944, in a model of temporal lobe epilepsy. *Progress in Neurobiology*, **182**: 101677.

Cassar S, Breidenbach L, Olson A, et al. 2017. Measuring drug absorption improves interpretation of behavioral responses in a larval zebrafish locomotor assay for predicting seizure liability. *Journal of Pharmacological and Toxicological Methods*, **88**(Pt 1): 56–63.

Cela E, McFarlan AR, Chung AJ, et al. 2019. An optogenetic kindling model of neocortical epilepsy. *Scientific Reports*, **9**(1): 5236.

Celli R, Fornai F. 2021. Targeting ionotropic glutamate receptors in the treatment of epilepsy. *Current Neuropharmacology*, **19**(6): 747–765.

Celli R, Santolini I, Van Luijtelaar G, et al. 2019. Targeting metabotropic glutamate receptors in the treatment of epilepsy: rationale and current status. *Expert Opinion on Therapeutic Targets*, **23**(4): 341–351.

Challal S, Buenafe OEM, Queiroz EF, et al. 2014. Zebrafish bioassay-guided microfractionation identifies anticonvulsant steroid glycosides from the Philippine medicinal plant *Solanum torvum*. *ACS Chemical Neuroscience*, **5**(10): 993–1004.

Chan AWS, Chong KY, Martinovich C, et al. 2001. Transgenic monkeys produced by retroviral gene transfer into mature oocytes. *Science*, **291**(5502): 309–312.

Chang BL, Chang KH. 2022. Stem cell therapy in treating epilepsy. *Frontiers in Neuroscience*, **16**: 934507.

Chapman AG, Croucher MJ, Meldrum BS. 1984. Evaluation of anticonvulsant drugs in DBA/2 mice with sound-induced seizures. *Arzneimittel-Forschung*, **34**(10): 1261–1264.

Charalambous M, Fischer A, Potschka H, et al. 2023. Translational veterinary epilepsy: a win-win situation for human and veterinary neurology. *The Veterinary Journal*, **293**: 105956.

Chege SW, Hortopan GA, Dinday MT, et al. 2012. Expression and function of KCNQ channels in larval zebrafish. *Developmental Neurobiology*, **72**(2): 186–198.

Chen KD, Garcia-Curran MM, Baram TZ. 2023a. Chapter 11 - Experimental models of febrile seizures and febrile status epilepticus. *In*: Baram TZ, Shinnar S, Stafstrom CE. Febrile Seizures. 2nd ed. San Diego: Academic Press, 195–217.

Chen N, Liu C, Yan N, et al. 2013. A macaque model of mesial temporal lobe epilepsy induced by unilateral intrahippocampal injection of kainic Acid. *PLoS One*, **8**(8): e72336.

Chen TS, Huang TH, Lai MC, et al. 2023b. The role of glutamate receptors in epilepsy. *Biomedicines*, **11**(3): 783.

Chen TS, Lai MC, Huang HYI, et al. 2022. Immunity, ion channels and epilepsy. *International Journal of Molecular Sciences*, **23**(12): 6446.

Chen ZP, Zhao XS, Wang SJ, et al. 2025. GABA-dependent microglial elimination of inhibitory synapses underlies neuronal hyperexcitability in epilepsy. *Nature Neuroscience*, **28**(7): 1404–1417.

Cho SJ, Byun D, Nam TS, et al. 2017. Zebrafish as an animal model in epilepsy studies with multichannel EEG recordings. *Scientific Reports*, **7**(1): 3099.

Christensen J. 2012. Traumatic brain injury: risks of epilepsy and implications for medicolegal assessment. *Epilepsia*, **53 Suppl 4**: 43–47.

Chuang KH, Nasrallah FA. 2017. Functional networks and network perturbations in rodents. *NeuroImage*, **163**: 419–436.

Chung WK, Shin M, Jaramillo TC, et al. 2009. Absence epilepsy in *apathetic*, a spontaneous mutant mouse lacking the h channel subunit, HCN2. *Neurobiology of Disease*, **33**(3): 499–508.

Ciltas AC, Toy CE, Güneş H, et al. 2023. Effects of probiotics on GABA/glutamate and oxidative stress in PTZ- induced acute seizure model in rats. *Epilepsy Research*, **195**: 107190.

Clossen BL, Reddy DS. 2017. Novel therapeutic approaches for disease-modification of epileptogenesis for curing epilepsy. *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease*, **1863**(6): 1519–1538.

Cook PF, Reichmuth C, Rouse AA, et al. 2015. Algal toxin impairs sea lion memory and hippocampal connectivity, with implications for strandings. *Science*, **350**(6267): 1545–1547.

Cook SJ, Jarrell TA, Brittin CA, et al. 2019. Whole-animal connectomes of both *Caenorhabditis elegans* sexes. *Nature*, **571**(7763): 63–71.

Copmans D, Orellana-Paucar AM, Steurs G, et al. 2018. Methylated flavonoids as anti-seizure agents: naringenin 4', 7-dimethyl ether attenuates epileptic seizures in zebrafish and mouse models. *Neurochemistry International*, **112**: 124–133.

Corda MG, Orlandi M, Lecca D, et al. 1991. Pentylenetetrazol-induced kindling in rats: effect of GABA function inhibitors. *Pharmacology Biochemistry and Behavior*, **40**(2): 329–333.

Corsi AK, Wightman B, Chalfie M. 2015. A transparent window into biology: a primer on *Caenorhabditis elegans*. *Genetics*, **200**(2): 387–407.

Coulter DA, McIntyre DC, Löscher W. 2002. Animal models of limbic epilepsies: what can they tell us?. *Brain Pathology*, **12**(2): 240–256.

Crépel V, Mulle C. 2015. Physiopathology of kainate receptors in epilepsy. *Current Opinion in Pharmacology*, **20**: 83–88.

Cui ZJ, Liu YM, Zhu Q, et al. 2018. Exploring the pathogenesis of canine epilepsy using a systems genetics method and implications for anti-epilepsy drug discovery. *Oncotarget*, **9**(17): 13181–13192.

Culetto E, Sattelle DB. 2000. A role for *Caenorhabditis elegans* in understanding the function and interactions of human disease genes. *Human Molecular Genetics*, **9**(6): 869–877.

Cunliffe VT, Baines RA, Giachello CNG, et al. 2015. Epilepsy research methods update: understanding the causes of epileptic seizures and identifying new treatments using non-mammalian model organisms. *Seizure*, **24**: 44–51.

Da Silva RS, Vianna MRMR, Bonan CD. 2020. Chapter 24 - Seizures and epilepsy. *In*: Gerlai RT. Behavioral and Neural Genetics of Zebrafish. London: Academic Press, 413–432.

D'Ambrosio R, Fairbanks JP, Fender JS, et al. 2004. Post-traumatic epilepsy following fluid percussion injury in the rat. *Brain*, **127**(Pt 2): 304–314.

Davis KA, Sturges BK, Vite CH, et al. 2011. A novel implanted device to wirelessly record and analyze continuous intracranial canine EEG. *Epilepsy Research*, **96**(1-2): 116–122.

Davletshin AI, Matveeva AA, Poletaeva II, et al. 2023. The role of molecular chaperones in the mechanisms of epileptogenesis. *Cell Stress and Chaperones*, **28**(6): 599–619.

Devinsky O, Vezzani A, Najjar S, et al. 2013. Glia and epilepsy: excitability and inflammation. *Trends in Neurosciences*, **36**(3): 174–184.

Dixon CE, Clifton GL, Lighthall JW, et al. 1991. A controlled cortical impact model of traumatic brain injury in the rat. *Journal of Neuroscience Methods*, **39**(3): 253–262.

Do Val-da Silva RA, Peixoto-Santos JE, Kandratavicius L, et al. 2017. Protective effects of cannabidiol against seizures and neuronal death in a rat model of mesial temporal lobe epilepsy. *Frontiers in Pharmacology*, **8**: 131.

Dubé CM, Baram TZ. 2009. Chapter 2 - Febrile seizures. *Blue Books of Neurology*, **33**: 17–26.

Ekenstedt KJ, Patterson EE, Mickelson JR. 2012. Canine epilepsy genetics. *Mammalian Genome*, **23**(1-2): 28–39.

Ellenbroek B, Youn J. 2016. Rodent models in neuroscience research: is it a rat race?. *Disease Models & Mechanisms*, **9**(10): 1079–1087.

Faingold CL. 2002. Role of GABA abnormalities in the inferior colliculus pathophysiology-audiogenic seizures. *Hearing Research*, **168**(1-2): 223–237.

Faingold CL, Raisinghani M, N'Gouemo P. 2014. Neuronal networks in epilepsy: comparative audiogenic seizure networks. *In*: Faingold CL, Blumenfeld H. Neuronal Networks in Brain Function, CNS Disorders, and Therapeutics. Amsterdam: Academic Press, 349–373.

Faingold CL, Randall M, Tupal S. 2010. DBA/1 mice exhibit chronic susceptibility to audiogenic seizures followed by sudden death associated with respiratory arrest. *Epilepsy & Behavior*, **17**(4): 436–440.

Feng B, Chen Z. 2016. Generation of febrile seizures and subsequent epileptogenesis. *Neuroscience Bulletin*, **32**(5): 481–492.

Fischer FP, Karge RA, Weber YG, et al. 2023. *Drosophila melanogaster* as a versatile model organism to study genetic epilepsies: an overview. *Frontiers in Molecular Neuroscience*, **16**: 1116000.

Fisher RS, Cross JH, French JA, et al. 2017. Operational classification of

seizure types by the international league against epilepsy: position paper of the ILAE commission for classification and terminology. *Epilepsia*, **58**(4): 522–530.

Fitzgerald MP, Fiannacca M, Smith DM, et al. 2019. Treatment responsiveness in *KCNT1*-related epilepsy. *Neurotherapeutics*, **16**(3): 848–857.

Fontana BD, Franscescon F, Rosemberg DB, et al. 2019. Zebrafish models for attention deficit hyperactivity disorder (ADHD). *Neuroscience & Biobehavioral Reviews*, **100**: 9–18.

Fontana BD, Mezzomo NJ, Kalueff AV, et al. 2018. The developing utility of zebrafish models of neurological and neuropsychiatric disorders: a critical review. *Experimental Neurology*, **299**: 157–171.

Frauscher B, Rossetti AO, Beniczky S. 2024. Recent advances in clinical electroencephalography. *Current Opinion in Neurology*, **37**(2): 134–140.

French JA, Williamson PD, Thadani VM, et al. 1993. Characteristics of medial temporal lobe epilepsy: I. Results of history and physical examination. *Annals of Neurology*, **34**(6): 774–780.

Freund RK, Marley RJ, Wehner JM. 1987. Differential sensitivity to bicuculline in three inbred mouse strains. *Brain Research Bulletin*, **18**(5): 657–662.

Frey HH, Göbel W, Löscher W. 1979. Pharmacokinetics of primidone and its active metabolites in the dog. *Archives Internationales de Pharmacodynamie et de Thérapie*, **242**(1): 14–30.

Frey LC. 2003. Epidemiology of posttraumatic epilepsy: a critical review. *Epilepsia*, **44**(s10): 11–17.

Fujiwara T, Sugawara T, Mazaki-Miyazaki E, et al. 2003. Mutations of sodium channel α subunit type 1 (SCN1A) in intractable childhood epilepsies with frequent generalized tonic-clonic seizures. *Brain*, **126**(Pt 3): 531–546.

Galanopoulou AS, Moshé SL. 2015. Neonatal and infantile epilepsy: acquired and genetic models. *Cold Spring Harbor Perspectives in Medicine*, **6**(1): a022707.

Garcia-Cairasco N. 2002. A critical review on the participation of inferior colliculus in acoustic-motor and acoustic-limbic networks involved in the expression of acute and kindled audiogenic seizures. *Hearing Research*, **168**(1-2): 208–222.

Garcia-Cairasco N, Umeoka EHL, Cortes de Oliveira JA. 2017. The Wistar Audiogenic Rat (WAR) strain and its contributions to epileptology and related comorbidities: history and perspectives. *Epilepsy & Behavior*, **71**: 250–273.

Gawel K, Banono NS, Michalak A, et al. 2019. A critical review of zebrafish schizophrenia models: time for validation?. *Neuroscience & Biobehavioral Reviews*, **107**: 6–22.

GBD 2021 Nervous System Disorders Collaborators. 2024. Global, regional, and national burden of disorders affecting the nervous system, 1990–2021: a systematic analysis for the Global Burden of Disease Study 2021. *The Lancet Neurology*, **23**(4): 344–381.

Golub VM, Reddy DS. 2022. Post-traumatic epilepsy and comorbidities: advanced models, molecular mechanisms, biomarkers, and novel therapeutic interventions. *Pharmacological Reviews*, **74**(2): 387–438.

Gorter JA, van Vliet EA, Lopes da Silva FH. 2016. Which insights have we gained from the kindling and post-status epilepticus models?. *Journal of Neuroscience Methods*, **260**: 96–108.

Graf J, Rahmati V, Majoros M, et al. 2022. Network instability dynamics drive a transient bursting period in the developing hippocampus in vivo. *eLife*, **11**: e82756.

Gregg NM, Nasseri M, Kremen V, et al. 2020. Circadian and multiday seizure periodicities, and seizure clusters in canine epilepsy. *Brain Communications*, **2**(1): fcaa008.

Grone BP, Baraban SC. 2015. Animal models in epilepsy research: legacies and new directions. *Nature Neuroscience*, **18**(3): 339–343.

Grone BP, Marchese M, Hamling KR, et al. 2016. Epilepsy, behavioral abnormalities, and physiological comorbidities in syntaxin-binding protein 1 (STXBP1) mutant zebrafish. *PLoS One*, **11**(3): e0151148.

Gu B, Katherine, Dalton KA. 2017. Models and detection of spontaneous recurrent seizures in laboratory rodents. *Zoological Research*, **38**(4): 171–179.

Guan YT, Shao YJ, Li DL, et al. 2014. Generation of site-specific mutations in the rat genome via CRISPR/Cas9. *Methods in Enzymology*, **546**: 297–317.

Gupta P, Khobragade SB, Shingatgeri VM. 2014. Effect of various antiepileptic drugs in zebrafish PTZ-seizure model. *Indian Journal of Pharmaceutical Sciences*, **76**(2): 157–163.

Gurdon JB, Lane CD, Woodland HR, et al. 1971. Use of frog eggs and oocytes for the study of messenger RNA and its translation in living cells. *Nature*, **233**(5316): 177–182.

Hales KG, Korey CA, Larracuente AM, et al. 2015. Genetics on the fly: a primer on the *Drosophila* model system. *Genetics*, **201**(3): 815–842.

Hanada T. 2020. Ionotropic glutamate receptors in epilepsy: a review focusing on AMPA and NMDA receptors. *Biomolecules*, **10**(3): 464.

Harkin LA, Bowser DN, Dibbens LM, et al. 2002. Truncation of the $GABA_A$-receptor γ2 subunit in a family with generalized epilepsy with febrile seizures plus. *American Journal of Human Genetics*, **70**(2): 530–536.

Harris SA, Gordon EE, Barrett KT, et al. 2024. Febrile seizures, ongoing epileptiform activity, and the resulting long-term consequences: lessons from animal models. *Pediatric Neurology*, **161**: 216–222.

Hasegawa D, Asada R, Hamamoto Y, et al. 2021. Focal cortical resection and hippocampectomy in a cat with drug-resistant structural epilepsy. *Frontiers in Veterinary Science*, **8**: 719455.

Hasegawa D, Mizoguchi S, Kuwabara T, et al. 2014. Electroencephalographic features of familial spontaneous epileptic cats. *Epilepsy Research*, **108**(6): 1018–1025.

Hawkins NA, Misra SN, Jurado M, et al. 2021. Epilepsy and neurobehavioral abnormalities in mice with a dominant-negative *KCNB1* pathogenic variant. *Neurobiology of Disease*, **147**: 105141.

Hegreberg GA, Padgett GA. 1976. Inherited progressive epilepsy of the dog with comparisons to Lafora's disease of man. *Federation Proceedings*, **35**(5): 1202–1205.

Heilbronner SR, Rodriguez-Romaguera J, Quirk GJ, et al. 2016. Circuit-based corticostriatal homologies between rat and primate. *Biological Psychiatry*, **80**(7): 509–521.

Hekmat-Scafe DS, Lundy MY, Ranga R, et al. 2006. Mutations in the K^+/Cl^- cotransporter gene *kazachoc (kcc)* increase seizure susceptibility in *Drosophila*. *The Journal of Neuroscience*, **26**(35): 8943–8954.

Hellsten U, Harland RM, Gilchrist MJ, et al. 2010. The genome of the western clawed frog *Xenopus tropicalis*. *Science*, **328**(5978): 633–636.

Herman ST. 2018. Chapter 10 - Acute seizures and status epilepticus. *In*: Skolnick BE, Alves WM. Handbook of Neuroemergency Clinical Trials. 2nd ed. London: Academic Press, 189–230.

Hewapathirane DS, Dunfield D, Yen W, et al. 2008. *In vivo* imaging of seizure activity in a novel developmental seizure model. *Experimental Neurology*, **211**(2): 480–488.

Hirose S, Tanaka Y, Shibata M, et al. 2020. Application of induced pluripotent stem cells in epilepsy. *Molecular and Cellular Neuroscience*, **108**: 103535.

Hobert O. 2013. The neuronal genome of *Caenorhabditis elegans*. *WormBook*, 1–106.

Hodge RD, Bakken TE, Miller JA, et al. 2019. Conserved cell types with divergent features in human versus mouse cortex. *Nature*, **573**(7772): 61–68.

Hoffman EJ, Turner KJ, Fernandez JM, et al. 2016. Estrogens suppress a behavioral phenotype in zebrafish mutants of the autism risk gene,

CNTNAP2. *Neuron*, **89**(4): 725–733.
Hortopan GA, Dinday MT, Baraban SC. 2010a. Spontaneous seizures and altered gene expression in GABA signaling pathways in a *mind bomb* mutant zebrafish. *The Journal of Neuroscience*, **30**(41): 13718–13728.
Hortopan GA, Dinday MT, Baraban SC. 2010b. Zebrafish as a model for studying genetic aspects of epilepsy. *Disease Models & Mechanisms*, **3**(3-4): 144–148.
Howe K, Clark MD, Torroja CF, et al. 2013. The zebrafish reference genome sequence and its relationship to the human genome. *Nature*, **496**(7446): 498–503.
Howlett IC, Tanouye MA. 2009. Neurocircuit assays for seizures in epilepsy mutants of *Drosophila*. *Journal of Visualized Experiments*, (26): 1121.
Huang H, Winter EE, Wang HJ, et al. 2004. Evolutionary conservation and selection of human disease gene orthologs in the rat and mouse genomes. *Genome Biology*, **5**(7): R47.
Huang Z, Walker MC, Shah MM. 2009. Loss of dendritic *HCN1* subunits enhances cortical excitability and epileptogenesis. *The Journal of Neuroscience*, **29**(35): 10979–10988.
Hunter J, Maljevic S, Shankar A, et al. 2006. Subthreshold changes of voltage-dependent activation of the K_V7.2 channel in neonatal epilepsy. *Neurobiology of Disease*, **24**(1): 194–201.
Hunyadi B, Siekierska A, Sourbron J, et al. 2017. Automated analysis of brain activity for seizure detection in zebrafish models of epilepsy. *Journal of Neuroscience Methods*, **287**: 13–24.
Ito Y, Lim DK, Nabeshima T, et al. 1989. Effects of picrotoxin treatment on $GABA_A$ receptor supramolecular complexes in rat brain. *Journal of Neurochemistry*, **52**(4): 1064–1070.
Jao LE, Wente SR, Chen WB. 2013. Efficient multiplex biallelic zebrafish genome editing using a CRISPR nuclease system. *Proceedings of the National Academy of Sciences of the United States of America*, **110**(34): 13904–13909.
Javaid MS, Tan T, Dvir N, et al. 2022. Human in vitro models of epilepsy using embryonic and induced pluripotent stem cells. *Cells*, **11**(24): 3957.
Jensen FE, Applegate CD, Holtzman D, et al. 1991. Epileptogenic effect of hypoxia in the immature rodent brain. *Annals of Neurology*, **29**(6): 629–637.
Johannesen K, Marini C, Pfeffer S, et al. 2016. Phenotypic spectrum of *GABRA1*: from generalized epilepsies to severe epileptic encephalopathies. *Neurology*, **87**(11): 1140–1151.
Johnston GAR, Beart PM. 2024. Milestone review: GABA, from chemistry, conformations, ionotropic receptors, modulators, epilepsy, flavonoids, and stress to neuro-nutraceuticals. *Journal of Neurochemistry*, **168**(7): 1179–1192.
Johnstone DL, Al-Shekaili HH, Tarailo-Graovac M, et al. 2019. PLPHP deficiency: clinical, genetic, biochemical, and mechanistic insights. *Brain*, **142**(3): 542–559.
Jongbloets BC, van Gassen KLI, Kan AA, et al. 2015. Expression profiling after prolonged experimental febrile seizures in mice suggests structural remodeling in the hippocampus. *PLoS One*, **10**(12): e0145247.
Jospin M, Qi YB, Stawicki TM, et al. 2009. A neuronal acetylcholine receptor regulates the balance of muscle excitation and inhibition in *Caenorhabditis elegans*. *PLoS Biology*, **7**(12): e1000265.
Jürgen Wenzel H, Born DE, Dubach MF, et al. 2000. Morphological plasticity in an infant monkey model of temporal lobe epilepsy. *Epilepsia*, **41 Suppl 6**: S70–S75.
Kaletta T, Hengartner MO. 2006. Finding function in novel targets: *C. elegans* as a model organism. *Nature Reviews Drug Discovery*, **5**(5): 387–399.
Kang JQ, Shen WZ, Zhou CW, et al. 2015. The human epilepsy mutation *GABRG2(Q390X)* causes chronic subunit accumulation and neurodegeneration. *Nature Neuroscience*, **18**(7): 988–996.
Karimi K, Fortriede JD, Lotay VS, et al. 2018. Xenbase: a genomic, epigenomic and transcriptomic model organism database. *Nucleic Acids Research*, **46**(D1): D861–D868.
Karler R, Murphy V, Calder LD, et al. 1989. Pentylenetetrazol kindling in mice. *Neuropharmacology*, **28**(8): 775–780.
Kehne JH, Klein BD, Raeissi S, et al. 2017. The national institute of neurological disorders and stroke (NINDS) epilepsy therapy screening program (ETSP). *Neurochemical Research*, **42**(7): 1894–1903.
Killam EK. 1976. Measurement of anticonvulsant activity in the Papio papio model of epilepsy. *Federation Proceedings*, **35**(11): 2264–2269.
Killam KF, Naquet R, Bert J. 1966. Paroxysmal responses to intermittent light stimulation in a population of baboons (*Papio papio*). *Epilepsia*, **7**(3): 215–219.
Killam KF Jr. 1969. Experimental epilepsy in primates. *Annals of the New York Academy of Sciences*, **162**(1): 610–616.
Kim YH, Lee Y, Lee K, et al. 2010. Reduced neuronal proliferation by proconvulsant drugs in the developing zebrafish brain. *Neurotoxicology and Teratology*, **32**(5): 551–557.
Kinoshita S, Koyama R. 2021. Pro- and anti-epileptic roles of microglia. *Neural Regeneration Research*, **16**(7): 1369–1371.
Klaassen A, Glykys J, Maguire J, et al. 2006. Seizures and enhanced cortical GABAergic inhibition in two mouse models of human autosomal dominant nocturnal frontal lobe epilepsy. *Proceedings of the National Academy of Sciences of the United States of America*, **103**(50): 19152–19157.
Klein P, Kaminski RM, Koepp M, et al. 2024. New epilepsy therapies in development. *Nature Reviews Drug Discovery*, **23**(9): 682–708.
Klitgaard H. 2001. Levetiracetam: the preclinical profile of a new class of antiepileptic drugs?. *Epilepsia*, **42 Suppl 4**: 13–18.
Köhling R, Wolfart J. 2016. Potassium channels in epilepsy. *Cold Spring Harbor Perspectives in Medicine*, **6**(5): a022871.
Kolesnikova TO, Demin KA, Costa FV, et al. 2022. Towards zebrafish models of CNS channelopathies. *International Journal of Molecular Sciences*, **23**(22): 13979.
Kroll JR, Saras A, Tanouye MA. 2015. *Drosophila* sodium channel mutations: contributions to seizure-susceptibility. *Experimental Neurology*, **274**: 80–87.
Krook-Magnuson E, Armstrong C, Bui A, et al. 2015. *In vivo* evaluation of the dentate gate theory in epilepsy. *The Journal of Physiology*, **593**(10): 2379–2388.
Kuebler D, Tanouye M. 2002. Anticonvulsant valproate reduces seizure-susceptibility in mutant Drosophila. *Brain Research*, **958**(1): 36–42.
Kuebler D, Tanouye MA. 2000. Modifications of seizure susceptibility in *Drosophila*. *Journal of Neurophysiology*, **83**(2): 998–1009.
Kuebler D, Zhang HG, Ren XY, et al. 2001. Genetic suppression of seizure susceptibility in *Drosophila*. *Journal of Neurophysiology*, **86**(3): 1211–1225.
Kulikov AA, Naumova AA, Aleksandrova EP, et al. 2021. Audiogenic kindling stimulates aberrant neurogenesis, synaptopodin expression, and mossy fiber sprouting in the hippocampus of rats genetically prone to audiogenic seizures. *Epilepsy & Behavior*, **125**: 108445.
Kundap UP, Kumari Y, Othman I, et al. 2017. Zebrafish as a model for epilepsy-induced cognitive dysfunction: a pharmacological, biochemical and behavioral approach. *Frontiers in Pharmacology*, **8**: 515.
Kuwabara T, Hasegawa D, Ogawa F, et al. 2010. A familial spontaneous epileptic feline strain: a novel model of idiopathic/genetic epilepsy. *Epilepsy Research*, **92**(1): 85–88.
Lasko P, Lüthy K. 2021. Investigating rare and ultrarare epilepsy syndromes with *Drosophila* models. *Faculty Reviews*, **10**: 10.
Lauerer RJ, Lerche H. 2024. Voltage-gated calcium channels in genetic epilepsies. *Journal of Neurochemistry*, **168**(12): 3853–3871.
Leclercq K, Afrikanova T, Langlois M, et al. 2015. Cross-species pharmacological characterization of the allylglycine seizure model in mice

and larval zebrafish. *Epilepsy & Behavior*, **45**: 53–63.

Lee GH, Sung SY, Chang WN, et al. 2012. Zebrafish larvae exposed to ginkgotoxin exhibit seizure-like behavior that is relieved by pyridoxal-5'-phosphate, GABA and anti-epileptic drugs. *Disease Models & Mechanisms*, **5**(6): 785–795.

Lee Y, Kim D, Kim YH, et al. 2010. Improvement of pentylenetetrazol-induced learning deficits by valproic acid in the adult zebrafish. *European Journal of Pharmacology*, **643**(2-3): 225–231.

Lefebvre KA, Tilton SC, Bammler TK, et al. 2009. Gene expression profiles in zebrafish brain after acute exposure to domoic acid at symptomatic and asymptomatic doses. *Toxicological Sciences*, **107**(1): 65–77.

Lemes JA, dos Anjos Rosário B, Rocha SMS, et al. 2025. The role of glutamate receptors and transporters in epilepsy: evidence from animal studies. *Reviews in the Neurosciences*, **36**(6): 645–660.

Lemke JR, Hendrickx R, Geider K, et al. 2014. *GRIN2B* mutations in west syndrome and intellectual disability with focal epilepsy. *Annals of Neurology*, **75**(1): 147–154.

Leppik IE, Patterson E, Hardy B, et al. 2009. Canine status epilepticus: proof of principle studies. *Epilepsia*, **50 Suppl 12**: 14–15.

Lerche H, Shah M, Beck H, et al. 2013. Ion channels in genetic and acquired forms of epilepsy. *The Journal of Physiology*, **591**(4): 753–764.

Lévesque M, Avoli M. 2013. The kainic acid model of temporal lobe epilepsy. *Neuroscience & Biobehavioral Reviews*, **37**(10 Pt 2): 2887–2899.

Lévesque M, Biagini G, de Curtis M, et al. 2021. The pilocarpine model of mesial temporal lobe epilepsy: over one decade later, with more rodent species and new investigative approaches. *Neuroscience & Biobehavioral Reviews*, **130**: 274–291.

Leviel V, Naquet R. 1977. A study of the action of valproic acid on the kindling effect. *Epilepsia*, **18**(2): 229–234.

Li QY, Barres BA. 2018. Microglia and macrophages in brain homeostasis and disease. *Nature Reviews Immunology*, **18**(4): 225–242.

Lidster K, Jefferys JG, Blümcke I, et al. 2016. Opportunities for improving animal welfare in rodent models of epilepsy and seizures. *Journal of Neuroscience Methods*, **260**: 2–25.

Liu H, Song Z, Liao DG, et al. 2015. Neuroprotective effects of trans-caryophyllene against kainic acid induced seizure activity and oxidative stress in mice. *Neurochemical Research*, **40**(1): 118–123.

Liu HL, Chen YC, Niu YY, et al. 2014. TALEN-mediated gene mutagenesis in rhesus and cynomolgus monkeys. *Cell Stem Cell*, **14**(3): 323–328.

Liu Z, Li X, Zhang JT, et al. 2016. Autism-like behaviours and germline transmission in transgenic monkeys overexpressing MeCP2. *Nature*, **530**(7588): 98–102.

Locubiche S, Ordóñez V, Abad E, et al. 2024. A zebrafish-based platform for high-throughput epilepsy modeling and drug screening in F0. *International Journal of Molecular Sciences*, **25**(5): 2991.

Lopes MW, Sapio MR, Leal RB, et al. 2016. Knockdown of carboxypeptidase A6 in zebrafish larvae reduces response to seizure-inducing drugs and causes changes in the level of mRNAs encoding signaling molecules. *PLoS One*, **11**(4): e0152905.

Löscher W. 1984. Genetic animal models of epilepsy as a unique resource for the evaluation of anticonvulsant drugs. A review. *Methods and Findings in Experimental and Clinical Pharmacology*, **6**(9): 531–547.

Löscher W. 2002. Animal models of epilepsy for the development of antiepileptogenic and disease-modifying drugs. A comparison of the pharmacology of kindling and post-status epilepticus models of temporal lobe epilepsy. *Epilepsy Research*, **50**(1-2): 105–123.

Löscher W. 2009. Preclinical assessment of proconvulsant drug activity and its relevance for predicting adverse events in humans. *European Journal of Pharmacology*, **610**(1-3): 1–11.

Löscher W. 2011. Critical review of current animal models of seizures and epilepsy used in the discovery and development of new antiepileptic drugs. *Seizure*, **20**(5): 359–368.

Löscher W. 2016. Fit for purpose application of currently existing animal models in the discovery of novel epilepsy therapies. *Epilepsy Research*, **126**: 157–184.

Löscher W. 2017. Animal models of seizures and epilepsy: past, present, and future role for the discovery of antiseizure drugs. *Neurochemical Research*, **42**(7): 1873–1888.

Löscher W, Brandt C. 2010. Prevention or modification of epileptogenesis after brain insults: experimental approaches and translational research. *Pharmacological Reviews*, **62**(4): 668–700.

Löscher W, Hönack D. 1993. Profile of ucb L059, a novel anticonvulsant drug, in models of partial and generalized epilepsy in mice and rats. *European Journal of Pharmacology*, **232**(2-3): 147–158.

Löscher W, Potschka H, Sisodiya SM, et al. 2020. Drug resistance in epilepsy: clinical impact, potential mechanisms, and new innovative treatment options. *Pharmacological Reviews*, **72**(3): 606–638.

Löscher W, White HS. 2023. Animal models of drug-resistant epilepsy as tools for deciphering the cellular and molecular mechanisms of pharmacoresistance and discovering more effective treatments. *Cells*, **12**(9): 1233.

Lu ZY, He ST, Jiang J, et al. 2022. Base-edited cynomolgus monkeys mimic core symptoms of *STXBP1* encephalopathy. *Molecular Therapy*, **30**(6): 2163–2175.

Lüttjohann A, Fabene PF, van Luijtelaar G. 2009. A revised Racine's scale for PTZ-induced seizures in rats. *Physiology & Behavior*, **98**(5): 579–586.

Lybrand ZR, Goswami S, Hsieh J. 2020. Stem cells: a path towards improved epilepsy therapies. *Neuropharmacology*, **168**: 107781.

Madeja M, Stocker M, Muβhoff U, et al. 1994. Potassium currents in epilepsy: effects of the epileptogenic agent pentylenetetrazol on a cloned potassium channel. *Brain Research*, **656**(2): 287–294.

Mahmood F, Fu S, Cooke J, et al. 2013. A zebrafish model of CLN2 disease is deficient in tripeptidyl peptidase 1 and displays progressive neurodegeneration accompanied by a reduction in proliferation. *Brain*, **136**(Pt 5): 1488–1507.

Maljevic S, Lerche H. 2013. Potassium channels: a review of broadening therapeutic possibilities for neurological diseases. *Journal of Neurology*, **260**(9): 2201–2211.

Mantegazza M, Rusconi R, Scalmani P, et al. 2010. Epileptogenic ion channel mutations: from bedside to bench and, hopefully, back again. *Epilepsy Research*, **92**(1): 1–29.

Marley R, Baines RA. 2011. Increased persistent Na^+ current contributes to seizure in the slamdance bang-sensitive *Drosophila* mutant. *Journal of Neurophysiology*, **106**(1): 18–29.

Marley RJ, Gaffney D, Wehner JM. 1986. Genetic influences on GABA-related seizures. *Pharmacology Biochemistry and Behavior*, **24**(3): 665–672.

Matricardi S, Verrotti A, Chiarelli F, et al. 2014. Current advances in childhood absence epilepsy. *Pediatric Neurology*, **50**(3): 205–212.

Mayanagi Y, Walker AE. 1975. DC potentials of temporal lobe seizures in the monkey. *Journal of Neurology*, **209**(3): 199–215.

Mei X, Wu S, Bassuk AG, et al. 2013. Mechanisms of *prickle1a* function in zebrafish epilepsy and retinal neurogenesis. *Disease Models & Mechanisms*, **6**(3): 679–688.

Meldrum BS, Anlezark G, Balzamo E, et al. 1975. Photically induced epilepsy in Papio papio as a model for drug studies. *Advances in Neurology*, **10**: 119–132.

Menezes FP, Rico EP, Da Silva RS. 2014. Tolerance to seizure induced by kainic acid is produced in a specific period of zebrafish development. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, **55**: 109–112.

Mergenthaler P, Meisel A. 2015. Chapter 2.1. 6 - Animal models: value and

translational potency. *In*: Wehling M. Principles of Translational Science in Medicine. 2nd ed. Amsterdam: Academic Press, 83–90.
Merlin LR. 2009. The fragile X mental retardation protein: a valuable partner in the battle against epileptogenesis. *Epilepsy Currents*, **9**(4): 116–118.
Merrill MA, Clough RW, Jobe PC, et al. 2005. Brainstem seizure severity regulates forebrain seizure expression in the audiogenic kindling model. *Epilepsia*, **46**(9): 1380–1388.
Merseburg A, Kasemir J, Buss EW, et al. 2022. Seizures, behavioral deficits, and adverse drug responses in two new genetic mouse models of *HCN1* epileptic encephalopathy. *eLife*, **11**: e70826.
Metcalf CS, West PJ, Thomson KE, et al. 2017. Development and pharmacologic characterization of the rat 6 Hz model of partial seizures. *Epilepsia*, **58**(6): 1073–1084.
Meyer M, Dhamne SC, LaCoursiere CM, et al. 2016. Microarray noninvasive neuronal seizure recordings from intact larval zebrafish. *PLoS One*, **11**(6): e0156498.
Miao QL, Herlitze S, Mark MD, et al. 2020. Adult loss of *Cacna1a* in mice recapitulates childhood absence epilepsy by distinct thalamic bursting mechanisms. *Brain*, **143**(1): 161–174.
Mikati MA, Zeinieh MP, Kurdi RM, et al. 2005. Long-term effects of acute and of chronic hypoxia on behavior and on hippocampal histology in the developing brain. *Developmental Brain Research*, **157**(1): 98–102.
Milior G, Morin-Brureau M, Pallud J, et al. 2023. Animal models and human tissue compared to better understand and treat the epilepsies. *Epilepsia*, **64**(5): 1175–1189.
Milligan CJ, Li M, Gazina EV, et al. 2014. *KCNT1* gain of function in 2 epilepsy phenotypes is reversed by quinidine. *Annals of Neurology*, **75**(4): 581–590.
Minabe Y, Emori K, Kurachi M. 1988. Effects of chronic lithium treatment on limbic seizure generation in the cat. *Psychopharmacology*, **96**(3): 391–394.
Mishima T, Fujiwara T, Kofuji T, et al. 2021. Syntaxin 1B regulates synaptic GABA release and extracellular GABA concentration, and is associated with temperature-dependent seizures. *Journal of Neurochemistry*, **156**(5): 604–613.
Miyamoto H, Tatsukawa T, Shimohata A, et al. 2019. Impaired cortico-striatal excitatory transmission triggers epilepsy. *Nature Communications*, **10**(1): 1917.
Mizoguchi S, Hasegawa D, Kuwabara T, et al. 2014. Magnetic resonance volumetry of the hippocampus in familial spontaneous epileptic cats. *Epilepsy Research*, **108**(10): 1940–1944.
Monteiro ÁB, Alves AF, Ribeiro Portela AC, et al. 2024. Pentylenetetrazole: a review. *Neurochemistry International*, **180**: 105841.
Morimoto K, Fahnestock M, Racine RJ. 2004. Kindling and status epilepticus models of epilepsy: rewiring the brain. *Progress in Neurobiology*, **73**(1): 1–60.
Muβhoff U, Madeja M, Bloms-Funke P, et al. 1994. Effects of the epileptogenic agent bicuculline methiodide on membrane currents induced by *N*-methyl-$_D$-aspartate and kainate (oocyte;*Xenopus laevis*). *Brain Research*, **639**(1): 135–138.
Muralidharan B. 2021. Chapter 4 - Human in vitro disease models to aid pathway and target discovery for neurological disorders. *In*: Hasija Y. Translational Biotechnology. London: Academic Press, 81–106.
Murayama AY, Kuwako KI, Okahara J, et al. 2020. The polymicrogyria-associated *GPR56* promoter preferentially drives gene expression in developing GABAergic neurons in common marmosets. *Scientific Reports*, **10**(1): 21516.
Mussulini BHM, Leite CE, Zenki KC, et al. 2013. Seizures induced by pentylenetetrazole in the adult zebrafish: a detailed behavioral characterization. *PLoS One*, **8**(1): e54515.
Myers CT, Mefford HC. 2015. Advancing epilepsy genetics in the genomic era. *Genome Medicine*, **7**(1): 91.
Naert T, Tulkens D, Edwards NA, et al. 2020. Maximizing CRISPR/Cas9 phenotype penetrance applying predictive modeling of editing outcomes in *Xenopus* and zebrafish embryos. *Scientific Reports*, **10**(1): 14662.
Nanou E, Catterall WA. 2018. Calcium channels, synaptic plasticity, and neuropsychiatric disease. *Neuron*, **98**(3): 466–481.
Naquet R, Catier J, Menini C. 1975. Neurophysiology of photically induced epilepsy in Papio papio. *Advances in Neurology*, **10**: 107–118.
Naquet R, Killam KF, Rhodes JM. 1967. Flicker stimulation with chimpanzees. *Life Sciences*, **6**(15): 1575–1578.
Nguyen JP, Shipley FB, Linder AN, et al. 2016. Whole-brain calcium imaging with cellular resolution in freely behaving *Caenorhabditis elegans*. *Proceedings of the National Academy of Sciences of the United States of America*, **113**(8): E1074–E1081.
Nirwan N, Vyas P, Vohora D. 2018. Animal models of status epilepticus and temporal lobe epilepsy: a narrative review. *Reviews in the Neurosciences*, **29**(7): 757–770.
Noebels J. 2015. Pathway-driven discovery of epilepsy genes. *Nature Neuroscience*, **18**(3): 344–350.
Noebels JL. 2006. Chapter 17 - Spontaneous epileptic mutations in the mouse. *In*: Pitkänen A, Schwartzkroin PA, Moshé SL. Models of Seizures and Epilepsy. Boston: Academic Press, 223–232.
Nwosu GI, Shen WZ, Zavalin K, et al. 2023. $GABA_A$ Receptor β3 Subunit mutation *N328D* heterozygous knock-in mice have Lennox-Gastaut syndrome. *International Journal of Molecular Sciences*, **24**(9): 8458.
Ochenkowska K, Herold A, Samarut É. 2022. Zebrafish is a powerful tool for precision medicine approaches to neurological disorders. *Frontiers in Molecular Neuroscience*, **15**: 944693.
Ogiwara I, Miyamoto H, Tatsukawa T, et al. 2018. $Na_v1.2$ haplodeficiency in excitatory neurons causes absence-like seizures in mice. *Communications Biology*, **1**: 96.
Osawa SI, Iwasaki M, Hosaka R, et al. 2013. Optogenetically induced seizure and the longitudinal hippocampal network dynamics. *PLoS One*, **8**(4): e60928.
Oyrer J, Maljevic S, Scheffer IE, et al. 2018. Ion channels in genetic epilepsy: from genes and mechanisms to disease-targeted therapies. *Pharmacological Reviews*, **70**(1): 142–173.
Pal R, Kumar B, Akhtar J, et al. 2021. Voltage gated sodium channel inhibitors as anticonvulsant drugs: a systematic review on recent developments and structure activity relationship studies. *Bioorganic Chemistry*, **115**: 105230.
Pandey UB, Nichols CD. 2011. Human disease models in *Drosophila melanogaster* and the role of the fly in therapeutic drug discovery. *Pharmacological Reviews*, **63**(2): 411–436.
Parent JM, Anderson SA. 2015. Reprogramming patient-derived cells to study the epilepsies. *Nature Neuroscience*, **18**(3): 360–366.
Parker L, Howlett IC, Rusan ZM, et al. 2011a. Seizure and epilepsy: studies of seizure disorders in *Drosophila*. *International Review of Neurobiology*, **99**: 1–21.
Parker L, Padilla M, Du YZ, et al. 2011b. Drosophila as a model for epilepsy: *bss* is a gain-of-function mutation in the para sodium channel gene that leads to seizures. *Genetics*, **187**(2): 523–534.
Patterson EE. 2014. Canine epilepsy: an underutilized model. *ILAR Journal*, **55**(1): 182–186.
Paz JT, Bryant AS, Peng K, et al. 2011. A new mode of corticothalamic transmission revealed in the *Gria4*$^{-/-}$ model of absence epilepsy. *Nature Neuroscience*, **14**(9): 1167–1173.
Pease M, Gupta K, Moshé SL, et al. 2024. Insights into epileptogenesis from post-traumatic epilepsy. *Nature Reviews Neurology*, **20**(5): 298–312.
Pena IA, Roussel Y, Daniel K, et al. 2017. Pyridoxine-dependent epilepsy in zebrafish caused by Aldh7a1 deficiency. *Genetics*, **207**(4): 1501–1518.
Perez-Mendes P, Blanco MM, Calcagnotto ME, et al. 2011. Modeling

epileptogenesis and temporal lobe epilepsy in a non-human primate. *Epilepsy Research*, **96**(1-2): 45–57.

Perucca E, Taglialatela M. 2025. Targeting Kv7 potassium channels for epilepsy. *CNS Drugs*, **39**(3): 263–288.

Perucca P, Smith G, Santana-Gomez C, et al. 2019. Electrophysiological biomarkers of epileptogenicity after traumatic brain injury. *Neurobiology of Disease*, **123**: 69–74.

Philips BH, Browne KD, Cullen DK, et al. 2020. Chapter 29 - Rat models of central nervous system injury. *In*: Suckow MA, Hankenson FC, Wilson RP, et al. The Laboratory Rat. 3rd ed. Amsterdam: Academic Press, 1023–1075.

Pieróg M, Socała K, Doboszewska U, et al. 2021. Effects of new antiseizure drugs on seizure activity and anxiety-like behavior in adult zebrafish. *Toxicology and Applied Pharmacology*, **427**: 115655.

Pitkänen A, Immonen R. 2014. Epilepsy related to traumatic brain injury. *Neurotherapeutics*, **11**(2): 286–296.

Pitkänen A, Lukasiuk K, Dudek FE, et al. 2015. Epileptogenesis. *Cold Spring Harbor Perspectives in Medicine*, **5**(10): a022822.

Pitkänen A, Sutula TP. 2002. Is epilepsy a progressive disorder? Prospects for new therapeutic approaches in temporal-lobe epilepsy. *The Lancet Neurology*, **1**(3): 173–181.

Platt SR, Haag M. 2002. Canine status epilepticus: a retrospective study of 50 cases. *Journal of Small Animal Practice*, **43**(4): 151–153.

Podell M, Fenner WR, Powers JD. 1995. Seizure classification in dogs from a nonreferral-based population. *Journal of the American Veterinary Medical Association*, **206**(11): 1721–1728.

Poletaeva II, Surina NM, Kostina ZA, et al. 2017. The Krushinsky-Molodkina rat strain: The study of audiogenic epilepsy for 65 years. *Epilepsy & Behavior*, **71**: 130–141.

Pontes JC, Lima TZ, Queiroz CM, et al. 2016. Seizures triggered by pentylenetetrazol in marmosets made chronically epileptic with pilocarpine show greater refractoriness to treatment. *Epilepsy Research*, **126**: 16–25.

Potschka H, Fischer A, von Rüden EL, et al. 2013. Canine epilepsy as a translational model?. *Epilepsia*, **54**(4): 571–579.

Powell KL, Cain SM, Snutch TP, et al. 2014. Low threshold T-type calcium channels as targets for novel epilepsy treatments. *British Journal of Clinical Pharmacology*, **77**(5): 729–739.

Pratt KG, Khakhalin AS. 2013. Modeling human neurodevelopmental disorders in the *Xenopus* tadpole: from mechanisms to therapeutic targets. *Disease Models & Mechanisms*, **6**(5): 1057–1065.

Purnell BS, Alves M, Boison D. 2023. Astrocyte-neuron circuits in epilepsy. *Neurobiology of Disease*, **179**: 106058.

Puskarjov M, Seja P, Heron SE, et al. 2014. A variant of KCC2 from patients with febrile seizures impairs neuronal Cl- extrusion and dendritic spine formation. *EMBO Reports*, **15**(6): 723–729.

Qi YB, Po MD, Mac P, et al. 2013. Hyperactivation of B-type motor neurons results in aberrant synchrony of the *Caenorhabditis elegans* motor circuit. *The Journal of Neuroscience*, **33**(12): 5319–5325.

Qu SM, Catron M, Zhou CW, et al. 2020. $GABA_A$ receptor β3 subunit mutation D120N causes Lennox-Gastaut syndrome in knock-in mice. *Brain Communications*, **2**(1): fcaa028.

Qu SM, Jackson LG, Zhou CW, et al. 2023. Heterozygous $GABA_A$ receptor β3 subunit *N110D* knock-in mice have epileptic spasms. *Epilepsia*, **64**(4): 1061–1073.

Quraishi IH, Mercier MR, McClure H, et al. 2020. Impaired motor skill learning and altered seizure susceptibility in mice with loss or gain of function of the *Kcnt1* gene encoding Slack ($K_{Na}1.1$) Na^+-activated K^+ channels. *Scientific Reports*, **10**(1): 3213.

Racine RJ. 1972. Modification of seizure activity by electrical stimulation: II. Motor seizure. *Electroencephalography and Clinical Neurophysiology*, **32**(3): 281–294.

Rajakulendran S, Hanna MG. 2016. The role of calcium channels in epilepsy. *Cold Spring Harbor Perspectives in Medicine*, **6**(1): a022723.

Rakhade SN, Jensen FE. 2009. Epileptogenesis in the immature brain: emerging mechanisms. *Nature Reviews Neurology*, **5**(7): 380–391.

Rakhade SN, Klein PM, Huynh T, et al. 2011. Development of later life spontaneous seizures in a rodent model of hypoxia-induced neonatal seizures. *Epilepsia*, **52**(4): 753–765.

Ramirez IBR, Pietka G, Jones DR, et al. 2012. Impaired neural development in a zebrafish model for Lowe syndrome. *Human Molecular Genetics*, **21**(8): 1744–1759.

Reid CA, Kim T, Phillips AM, et al. 2013. Multiple molecular mechanisms for a single $GABA_A$ mutation in epilepsy. *Neurology*, **80**(11): 1003–1008.

Ren E, Curia G. 2021. Synaptic reshaping and neuronal outcomes in the temporal lobe epilepsy. *International Journal of Molecular Sciences*, **22**(8): 3860.

Reynolds ER, Stauffer EA, Feeney L, et al. 2004. Treatment with the antiepileptic drugs phenytoin and gabapentin ameliorates seizure and paralysis of *Drosophila* bang-sensitive mutants. *Journal of Neurobiology*, **58**(4): 503–513.

Ribak CE. 2017. An abnormal GABAergic system in the inferior colliculus provides a basis for audiogenic seizures in genetically epilepsy-prone rats. *Epilepsy & Behavior*, **71**: 160–164.

Richardson RJ, Petrou S, Bryson A. 2024. Established and emerging $GABA_A$ receptor pharmacotherapy for epilepsy. *Frontiers in Pharmacology*, **15**: 1341472.

Roemmich AJ, Vu T, Lukacsovich T, et al. 2021. Seizure phenotype and underlying cellular defects in *Drosophila* knock-in models of DS (R1648C) and GEFS+ (R1648H) *SCN1A* epilepsy. *eNeuro*, **8**(5): ENEURO.0002–21.2021.

Rosa-Falero C, Torres-Rodríguez S, Jordán C, et al. 2015. *Citrus aurantium* increases seizure latency to PTZ induced seizures in zebrafish thru NMDA and mGluR's I and II. *Frontiers in Pharmacology*, **5**: 284.

Rosch RE, Hunter PR, Baldeweg T, et al. 2018. Calcium imaging and dynamic causal modelling reveal brain-wide changes in effective connectivity and synaptic dynamics during epileptic seizures. *PLoS Computational Biology*, **14**(8): e1006375.

Ross KC, Coleman JR. 2000. Developmental and genetic audiogenic seizure models: behavior and biological substrates. *Neuroscience & Biobehavioral Reviews*, **24**(6): 639–653.

Ruggiero SM, Xian JL, Helbig I. 2023. The current landscape of epilepsy genetics: where are we, and where are we going?. *Current Opinion in Neurology*, **36**(2): 86–94.

Russo E, Citraro R. 2018. Pharmacology of epileptogenesis and related comorbidities in the WAG/Rij rat model of genetic absence epilepsy. *Journal of Neuroscience Methods*, **310**: 54–62.

Russo E, Citraro R, Constanti A, et al. 2016. Upholding WAG/Rij rats as a model of absence epileptogenesis: hidden mechanisms and a new theory on seizure development. *Neuroscience & Biobehavioral Reviews*, **71**: 388–408.

Sadek B, Saad A, Subramanian D, et al. 2016. Anticonvulsant and procognitive properties of the non-imidazole histamine H3 receptor antagonist DL77 in male adult rats. *Neuropharmacology*, **106**: 46–55.

Salinas FS, Szabó CÁ. 2017. Resting-state functional connectivity changes due to acute and short-term valproic acid administration in the baboon model of GGE. *NeuroImage: Clinical*, **16**: 132–141.

Sampedro-Castañeda M, Baltussen LL, Lopes AT, et al. 2023. Epilepsy-linked kinase CDKL5 phosphorylates voltage-gated calcium channel $Ca_v2.3$, altering inactivation kinetics and neuronal excitability. *Nature Communications*, **14**(1): 7830.

Sanabria V, Romariz SAA, Braga M, et al. 2024. What we have learned from non-human primates as animal models of epilepsy. *Epilepsy & Behavior*, **154**: 109706.

Sasai Y. 2013. Next-generation regenerative medicine: organogenesis from stem cells in 3D culture. *Cell Stem Cell*, **12**(5): 520–530.

Sasaki E, Suemizu H, Shimada A, et al. 2009. Generation of transgenic non-human primates with germline transmission. *Nature*, **459**(7246): 523–527.

Sato K, Oiwa R, Kumita W, et al. 2016. Generation of a non-human primate model of severe combined immunodeficiency using highly efficient genome editing. *Cell Stem Cell*, **19**(1): 127–138.

Sato M. 1975. Hippocampal seizure and secondary epileptogenesis in the "kindled" cat preparations. *Folia Psychiatrica et Neurologica Japonica*, **29**(3): 239–250.

Sato M, Moriwake T. 1984. Postictal seizure inhibition in amygdaloid-kindled cats. *Epilepsia*, **25**(5): 545–550.

Schoonheim PJ, Arrenberg AB, Del Bene F, et al. 2010. Optogenetic localization and genetic perturbation of saccade-generating neurons in zebrafish. *The Journal of Neuroscience*, **30**(20): 7111–7120.

Schubert J, Siekierska A, Langlois M, et al. 2014. Mutations in *STX1B*, encoding a presynaptic protein, cause fever-associated epilepsy syndromes. *Nature Genetics*, **46**(12): 1327–1332.

Schutte RJ, Schutte SS, Algara J, et al. 2014. Knock-in model of Dravet syndrome reveals a constitutive and conditional reduction in sodium current. *Journal of Neurophysiology*, **112**(4): 903–912.

Schwartz M, Lamb CR, Brodbelt DC, et al. 2011. Canine intracranial neoplasia: clinical risk factors for development of epileptic seizures. *Journal of Small Animal Practice*, **52**(12): 632–637.

Session AM, Uno Y, Kwon T, et al. 2016. Genome evolution in the allotetraploid frog *Xenopus laevis*. *Nature*, **538**(7625): 336–343.

Shcheglovitov A, Peterson RT. 2021. Screening platforms for genetic epilepsies—zebrafish, iPSC-derived neurons, and organoids. *Neurotherapeutics*, **18**(3): 1478–1489.

Shen WZ, Nwosu G, Honer M, et al. 2024. γ-Aminobutyric acid transporter and $GABA_A$ receptor mechanisms in *Slc6a1*$^{+/A288V}$ and *Slc6a1*$^{+/S295L}$ mice associated with developmental and epileptic encephalopathies. *Brain Communications*, **6**(2): fcae110.

Shetty J. 2015. Neonatal seizures in hypoxic-ischaemic encephalopathy-risks and benefits of anticonvulsant therapy. *Developmental Medicine & Child Neurology*, **57 Suppl 3**: 40–43.

Shi JY, Xin HH, Shao YY, et al. 2023. CRISPR-based KCC2 upregulation attenuates drug-resistant seizure in mouse models of epilepsy. *Annals of Neurology*, **94**(1): 91–105.

Shi YW, Zhang Q, Cai KF, et al. 2019. Synaptic clustering differences due to different *GABRB3* mutations cause variable epilepsy syndromes. *Brain*, **142**(10): 3028–3044.

Shiri Z, Simorgh S, Naderi S, et al. 2019. Optogenetics in the era of cerebral organoids. *Trends in Biotechnology*, **37**(12): 1282–1294.

Shore AN, Colombo S, Tobin WF, et al. 2020. Reduced GABAergic neuron excitability, altered synaptic connectivity, and seizures in a *KCNT1* gain-of-function mouse model of childhood epilepsy. *Cell Reports*, **33**(4): 108303.

Shouse MN, Scordato JC, Farber PR. 2004. Ontogeny of feline temporal lobe epilepsy in amygdala-kindled kittens: an update. *Brain Research*, **1027**(1-2): 126–143.

Simkin D, Ambrosi C, Marshall KA, et al. 2022. 'Channeling' therapeutic discovery for epileptic encephalopathy through iPSC technologies. *Trends in Pharmacological Sciences*, **43**(5): 392–405.

Simms BA, Zamponi GW. 2014. Neuronal voltage-gated calcium channels: structure, function, and dysfunction. *Neuron*, **82**(1): 24–45.

Simonato M, Brooks-Kayal AR, Engel J Jr, et al. 2014. The challenge and promise of anti-epileptic therapy development in animal models. *The Lancet Neurology*, **13**(9): 949–960.

Simons C, Rash LD, Crawford J, et al. 2015. Mutations in the voltage-gated potassium channel gene *KCNH1* cause Temple-Baraitser syndrome and epilepsy. *Nature Genetics*, **47**(1): 73–77.

Singh NA, Otto JF, Dahle EJ, et al. 2008. Mouse models of human *KCNQ2* and *KCNQ3* mutations for benign familial neonatal convulsions show seizures and neuronal plasticity without synaptic reorganization. *The Journal of Physiology*, **586**(14): 3405–3423.

Sisodiya SM. 2021. Precision medicine and therapies of the future. *Epilepsia*, **62 Suppl 2**(Suppl 2): S90–S105.

Smith BN. 2016. How and why study posttraumatic epileptogenesis in animal models?. *Epilepsy Currents*, **16**(6): 393–396.

Smith DK, Sadler KP, Benedum M. 2019. Febrile seizures: risks, evaluation, and prognosis. *American Family Physician*, **99**(7): 445–450.

Song J, Tanouye MA. 2006. Seizure suppression by *shakB*^{2}, a gap junction mutation in *Drosophila*. *Journal of Neurophysiology*, **95**(2): 627–635.

Song J, Tanouye MA. 2008. From bench to drug: human seizure modeling using *Drosophila*. *Progress in Neurobiology*, **84**(2): 182–191.

Soper HV, Strain GM, Babb TL, et al. 1978. Chronic alumina temporal lobe seizures in monkeys. *Experimental Neurology*, **62**(1): 99–121.

Spampanato J, Escayg A, Meisler MH, et al. 2001. Functional effects of two voltage-gated sodium channel mutations that cause generalized epilepsy with febrile seizures plus type 2. *The Journal of Neuroscience*, **21**(19): 7481–7490.

Speca DJ, Ogata G, Mandikian D, et al. 2014. Deletion of the $K_v2.1$ delayed rectifier potassium channel leads to neuronal and behavioral hyperexcitability. *Genes, Brain and Behavior*, **13**(4): 394–408.

Stark LG, Joy RM, Hance AJ, et al. 1968. Further studies of photic stimulation in sub-human primates. *Life Sciences*, **7**(19): 1037–1039.

Stawicki TM, Zhou KM, Yochem J, et al. 2011. TRPM channels modulate epileptic-like convulsions via systemic ion homeostasis. *Current Biology*, **21**(10): 883–888.

Steinlein OK. 2014. Chapter 5 - Mechanisms underlying epilepsies associated with sodium channel mutations. *Progress in Brain Research*, **213**: 97–111.

Steinmetz S, Tipold A, Löscher W. 2013. Epilepsy after head injury in dogs: a natural model of posttraumatic epilepsy. *Epilepsia*, **54**(4): 580–588.

Stenroos P, Guillemain I, Tesler F, et al. 2024. EEG-fMRI in awake rat and whole-brain simulations show decreased brain responsiveness to sensory stimulations during absence seizures. *eLife*, **12**: RP90318.

Sterlini B, Fruscione F, Baldassari S, et al. 2020. Progress of induced pluripotent stem cell technologies to understand genetic epilepsy. *International Journal of Molecular Sciences*, **21**(2): 482.

Stern J. 2015. Musicogenic epilepsy. *Handbook of Clinical Neurology*, **129**: 469–477.

Stödberg T, McTague A, Ruiz AJ, et al. 2015. Mutations in *SLC12A5* in epilepsy of infancy with migrating focal seizures. *Nature Communications*, **6**: 8038.

Strand AD, Aragaki AK, Baquet ZC, et al. 2007. Conservation of regional gene expression in mouse and human brain. *PLoS Genetics*, **3**(4): e59.

Strehlow V, Heyne HO, Vlaskamp DRM, et al. 2019. *GRIN2A*-related disorders: genotype and functional consequence predict phenotype. *Brain*, **142**(1): 80–92.

Striano P, Minassian BA. 2020. From genetic testing to precision medicine in epilepsy. *Neurotherapeutics*, **17**(2): 609–615.

Suls A, Jaehn JA, Kecskés A, et al. 2013. De novo loss-of-function mutations in *CHD2* cause a fever-sensitive myoclonic epileptic encephalopathy sharing features with Dravet syndrome. *American Journal of Human Genetics*, **93**(5): 967–975.

Sun HY, Juul HM, Jensen FE. 2016. Models of hypoxia and ischemia-induced seizures. *Journal of Neuroscience Methods*, **260**: 252–260.

Sun L, Gilligan J, Staber C, et al. 2012. A knock-in model of human epilepsy in *Drosophila* reveals a novel cellular mechanism associated with heat-induced seizure. *The Journal of Neuroscience*, **32**(41): 14145–14155.

Swaminathan A, Hassan-Abdi R, Renault S, et al. 2018. Non-canonical mTOR-independent role of DEPDC5 in regulating GABAergic network development. *Current Biology*, **28**(12): 1924–1937. e5.

Szabó CÁ, Knape KD, Leland MM, et al. 2012a. Epidemiology and characterization of seizures in a pedigreed baboon colony. *Comparative Medicine*, **62**(6): 535–538.

Szabó CÁ, Salinas FS. 2016. Voxel-based morphometry in epileptic baboons: parallels to human juvenile myoclonic epilepsy. *Epilepsy Research*, **124**: 34–39.

Szabó CÁ, Salinas FS, Leland MM, et al. 2012b. Baboon model of generalized epilepsy: continuous intracranial video-EEG monitoring with subdural electrodes. *Epilepsy Research*, **101**(1-2): 46–55.

Tan HO, Reid CA, Single FN, et al. 2007. Reduced cortical inhibition in a mouse model of familial childhood absence epilepsy. *Proceedings of the National Academy of Sciences of the United States of America*, **104**(44): 17536–17541.

Tan JS, Lin F, Tanouye MA. 2004. Potassium bromide, an anticonvulsant, is effective at alleviating seizures in the *Drosophila* bang-sensitive mutant bang senseless. *Brain Research*, **1020**(1-2): 45–52.

Tang YY, Liu Y, Gong YW, et al. 2024. Caspase-1 inhibitor CZL80 protects against acute seizures via amplifying the inhibitory neural transmission. *Neurochemistry International*, **179**: 105809.

Tao H, Manak JR, Sowers L, et al. 2011. Mutations in prickle orthologs cause seizures in flies, mice, and humans. *American Journal of Human Genetics*, **88**(2): 138–149.

Taylor SR, Santpere G, Weinreb A, et al. 2021. Molecular topography of an entire nervous system. *Cell*, **184**(16): 4329–4347. e23.

Teillet MA, Naquet R, Le Gal La Salle G, et al. 1991. Transfer of genetic epilepsy by embryonic brain grafts in the chicken. *Proceedings of the National Academy of Sciences of the United States of America*, **88**(16): 6966–6970.

Teng Y, Xie XY, Walker S, et al. 2010. Knockdown of zebrafish Lgi1a results in abnormal development, brain defects and a seizure-like behavioral phenotype. *Human Molecular Genetics*, **19**(22): 4409–4420.

Teng Y, Xie XY, Walker S, et al. 2011. Loss of zebrafish *lgi1b* leads to hydrocephalus and sensitization to pentylenetetrazol induced seizure-like behavior. *PLoS One*, **6**(9): e24596.

Thakran S, Guin D, Singh P, et al. 2020. Genetic landscape of common epilepsies: advancing towards precision in treatment. *International Journal of Molecular Sciences*, **21**(20): 7784.

Thijs RD, Surges R, O'Brien TJ, et al. 2019. Epilepsy in adults. *The Lancet*, **393**(10172): 689–701.

Tiedeken JA, Ramsdell JS, Ramsdell AF. 2005. Developmental toxicity of domoic acid in zebrafish (*Danio rerio*). *Neurotoxicology and Teratology*, **27**(5): 711–717.

Tiraboschi E, Martina S, van der Ent W, et al. 2020. New insights into the early mechanisms of epileptogenesis in a zebrafish model of Dravet syndrome. *Epilepsia*, **61**(3): 549–560.

Toman JEP, Swinyard EA, Goodman LS. 1946. Properties of maximal seizures, and their alteration by anticonvulsant drugs and other agents. *Journal of Neurophysiology*, **9**(3): 231–239.

Trinka E, Cock H, Hesdorffer D, et al. 2015. A definition and classification of status epilepticus-Report of the ILAE Task Force on Classification of Status Epilepticus. *Epilepsia*, **56**(10): 1515–1523.

Tryphonas L, Truelove J, Todd E, et al. 1990. Experimental oral toxicity of domoic acid in cynomolgus monkeys (*Macaca fascicularis*) and rats. : preliminary investigations. *Food and Chemical Toxicology*, **28**(10): 707–715.

Turrini L, Fornetto C, Marchetto G, et al. 2017. Optical mapping of neuronal activity during seizures in zebrafish. *Scientific Reports*, **7**(1): 3025.

Ugur B, Chen KC, Bellen HJ. 2016. Drosophila tools and assays for the study of human diseases. *Disease Models & Mechanisms*, **9**(3): 235–244.

Uva L, Aracri P, Forcaia G, et al. 2021. Mapping region-specific seizure-like patterns in the *in vitro* isolated guinea pig brain. *Experimental Neurology*, **342**: 113727.

Van Erum J, Van Dam D, De Deyn PP. 2019. PTZ-induced seizures in mice require a revised Racine scale. *Epilepsy & Behavior*, **95**: 51–55.

van Luijtelaar G, Sitnikova E. 2006. Global and focal aspects of absence epilepsy: the contribution of genetic models. *Neuroscience & Biobehavioral Reviews*, **30**(7): 983–1003.

van Luijtelaar G, van Oijen G. 2020. Establishing drug effects on electrocorticographic activity in a genetic absence epilepsy model: advances and pitfalls. *Frontiers in Pharmacology*, **11**: 395.

Varatharajah Y, Iyer RK, Berry BM, et al. 2017. Seizure forecasting and the preictal state in canine epilepsy. *International Journal of Neural Systems*, **27**(1): 1650046.

Velluti JC, Costa da Costa J, Russo RE. 1997. The cerebral hemisphere of the turtle in vitro. An experimental model with spontaneous interictal-like spikes for the study of epilepsy. *Epilepsy Research*, **28**(1): 29–37.

Vermoesen K, Serruys ASK, Loyens E, et al. 2011. Assessment of the convulsant liability of antidepressants using zebrafish and mouse seizure models. *Epilepsy & Behavior*, **22**(3): 450–460.

Vezzani A, Ravizza T, Bedner P, et al. 2022. Astrocytes in the initiation and progression of epilepsy. *Nature Reviews Neurology*, **18**(12): 707–722.

Vinogradova LV. 2017. Audiogenic kindling and secondary subcortico-cortical epileptogenesis: behavioral correlates and electrographic features. *Epilepsy & Behavior*, **71**: 142–153.

Wada JA, Balzamo E, Meldrum BS, et al. 1972. Behavioural and electrographic effects of L-5-hydroxytryptophan and D, L-parachlorophenyl-alanine on epileptic senegalese baboon (*Papio papio*). *Electroencephalography and Clinical Neurophysiology*, **33**(5): 520–526.

Wada JA, Mizoguchi T, Komai S. 1985. Kindling epileptogenesis in orbital and mesial frontal cortical areas of subhuman primates. *Epilepsia*, **26**(5): 472–479.

Wada JA, Sata M. 1974. Generalized convulsive seizures induced by daily electrical stimulation of the amygdala in cats. Correlative electrographic and behavioral features. *Neurology*, **24**(6): 565–574.

Wada JA, Sato M, Wake A, et al. 1976. Prophylactic effects of phenytoin, phenobarbital, and carbamazepine examined in kindling cat preparations. *Archives of Neurology*, **33**(6): 426–434.

Wada Y, Okuda H, Yoshida K, et al. 1987. A new experimental model for drug studies: effects of phenobarbital and phenytoin on photosensitivity in the lateral geniculate-kindled cat. *Epilepsia*, **28**(6): 667–672.

Walker MC. 2024. Drug repurposing in status epilepticus. *Epilepsy & Behavior*, **161**: 110109.

Walsh S, Donnan J, Fortin Y, et al. 2017. A systematic review of the risks factors associated with the onset and natural progression of epilepsy. *NeuroToxicology*, **61**: 64–77.

Wan YS, Feng B, You Y, et al. 2020. Microglial displacement of GABAergic synapses is a protective event during complex febrile seizures. *Cell Reports*, **33**(5): 108346.

Wang F, Zhang QY, Wang Y, et al. 2023. Insight into drug resistance in status epilepticus: evidence from animal models. *International Journal of Molecular Sciences*, **24**(3): 2039.

Wang Y, Chen Z. 2019. An update for epilepsy research and antiepileptic drug development: toward precise circuit therapy. *Pharmacology & Therapeutics*, **201**: 77–93.

Wang YL, Wei PH, Yan F, et al. 2022. Animal models of epilepsy: a phenotype-oriented review. *Aging and Disease*, **13**(1): 215–231.

Watanabe T. 2022. Chapter 6 - Electrochemical conduction in neurons and neuronal communications. *In*: Watanabe T. Modeling Electrochemical Dynamics and Signaling Mechanisms in Excitable Cells with Pathological

Case Studies. Amsterdam: Academic Press, 117–147.
Weltzin MM, Lindstrom JM, Lukas RJ, et al. 2016. Distinctive effects of nicotinic receptor intracellular-loop mutations associated with nocturnal frontal lobe epilepsy. *Neuropharmacology*, **102**: 158–173.
Weng OY, Li Y, Wang LY. 2022. Modeling epilepsy using human induced pluripotent stem cells-derived neuronal cultures carrying mutations in ion channels and the mechanistic target of rapamycin pathway. *Frontiers in Molecular Neuroscience*, **15**: 810081.
Wengert ER, Patel MK. 2021. The role of the persistent sodium current in epilepsy. *Epilepsy Currents*, **21**(1): 40–47.
Weston MC, Tzingounis AV. 2024. Potassium channels in genetic epilepsy: a functional perspective. *In*: Noebels JL, Avoli M, Rogawski MA, et al. Jasper's Basic Mechanisms of the Epilepsies. 5th ed. New York: Oxford University Press, 921–952.
White HS. 2002. Animal models of epileptogenesis. *Neurology*, **59**(9 Suppl 5): S7–S14.
White HS, Löscher W. 2014. Searching for the ideal antiepileptogenic agent in experimental models: single treatment versus combinatorial treatment strategies. *Neurotherapeutics*, **11**(2): 373–384.
White JG, Southgate E, Thomson JN, et al. 1986. The structure of the nervous system of the nematode *Caenorhabditis elegans*. *Philosophical Transactions of the Royal Society B: Biological Sciences*, **314**(1165): 1–340.
Wiest R, Beisteiner R. 2019. Recent developments in imaging of epilepsy. *Current Opinion in Neurology*, **32**(4): 530–538.
Wilcox KS, West PJ, Metcalf CS. 2020. The current approach of the Epilepsy Therapy Screening Program contract site for identifying improved therapies for the treatment of pharmacoresistant seizures in epilepsy. *Neuropharmacology*, **166**: 107811.
Williams PA, Hellier JL, White AM, et al. 2007. Development of spontaneous seizures after experimental status epilepticus: implications for understanding epileptogenesis. *Epilepsia*, **48 Suppl 5**: 157–163.
Williams SN, Locke CJ, Braden AL, et al. 2004. Epileptic-like convulsions associated with LIS-1 in the cytoskeletal control of neurotransmitter signaling in *Caenorhabditis elegans*. *Human Molecular Genetics*, **13**(18): 2043–2059.
Winter MJ, Windell D, Metz J, et al. 2017. 4-dimensional functional profiling in the convulsant-treated larval zebrafish brain. *Scientific Reports*, **7**(1): 6581.
Wong K, Stewart A, Gilder T, et al. 2010. Modeling seizure-related behavioral and endocrine phenotypes in adult zebrafish. *Brain Research*, **1348**: 209–215.
Xia X, Vishwanath M, Zhang J, et al. 2022. Microelectrode array membranes to simultaneously assess cardiac and neurological signals of xenopus laevis under chemical exposures and environmental changes. *Biosensors and Bioelectronics*, **210**: 114292.
Xiao WJ, Li PL, Kong FJ, et al. 2024. Unraveling the neural circuits: techniques, opportunities and challenges in epilepsy research. *Cellular and Molecular Neurobiology*, **44**(1): 27.
Xu J, Cohen BN, Zhu Y, et al. 2011. Altered activity-rest patterns in mice with a human autosomal-dominant nocturnal frontal lobe epilepsy mutation in the β2 nicotinic receptor. *Molecular Psychiatry*, **16**(10): 1048–1061.
Yaksi E, Jamali A, Diaz Verdugo C, et al. 2021. Past, present and future of zebrafish in epilepsy research. *The FEBS Journal*, **288**(24): 7243–7255.
Yamaguchi SI, Rogawski MA. 1992. Effects of anticonvulsant drugs on 4-aminopyridine-induced seizures in mice. *Epilepsy Research*, **11**(1): 9–16.
Yamamoto S, Jaiswal M, Charng WL, et al. 2014. A *Drosophila* genetic resource of mutants to study mechanisms underlying human genetic diseases. *Cell*, **159**(1): 200–214.
Yang JQ, Krishnamoorthy G, Saxena A, et al. 2010. An epilepsy/dyskinesia-associated mutation enhances BK channel activation by potentiating Ca^{2+} sensing. *Neuron*, **66**(6): 871–883.
Yang SH, Cheng PH, Banta H, et al. 2008. Towards a transgenic model of Huntington's disease in a non-human primate. *Nature*, **453**(7197): 921–924.
Yang WL, Liu YB, Tu ZC, et al. 2019. CRISPR/Cas9-mediated *PINK1* deletion leads to neurodegeneration in rhesus monkeys. *Cell Research*, **29**(4): 334–336.
Yang WP, Levesque PC, Little WA, et al. 1998. Functional expression of two KvLQT1-related potassium channels responsible for an inherited idiopathic epilepsy. *Journal of Biological Chemistry*, **273**(31): 19419–19423.
Yang X, Lin J, Peng XL, et al. 2017. Effects of picrotoxin on zebrafish larvae behaviors: a comparison study with PTZ. *Epilepsy & Behavior*, **70**: 224–231.
Yang ZX, Qin J. 2004. Interaction between endogenous nitric oxide and carbon monoxide in the pathogenesis of recurrent febrile seizures. *Biochemical and Biophysical Research Communications*, **315**(2): 349–355.
Yu C, Deng XJ, Xu D. 2023. Microglia in epilepsy. *Neurobiology of Disease*, **185**: 106249.
Yu FH, Mantegazza M, Westenbroek RE, et al. 2006. Reduced sodium current in GABAergic interneurons in a mouse model of severe myoclonic epilepsy in infancy. *Nature Neuroscience*, **9**(9): 1142–1149.
Zaaimi B, Turnbull M, Hazra A, et al. 2023. Closed-loop optogenetic control of the dynamics of neural activity in non-human primates. *Nature Biomedical Engineering*, **7**(4): 559–575.
Zdebik AA, Mahmood F, Stanescu HC, et al. 2013. Epilepsy in *kcnj10* morphant zebrafish assessed with a novel method for long-term EEG recordings. *PLoS One*, **8**(11): e79765.
Zeng LH, Xu L, Gutmann DH, et al. 2008. Rapamycin prevents epilepsy in a mouse model of tuberous sclerosis complex. *Annals of Neurology*, **63**(4): 444–453.
Zhang MW, Liang XY, Wang J, et al. 2024a. Epilepsy-associated genes: an update. *Seizure: European Journal of Epilepsy*, **116**: 4–13.
Zhang S, Xie SY, Zheng Y, et al. 2024b. Current advances in rodent drug-resistant temporal lobe epilepsy models: hints from laboratory studies. *Neurochemistry International*, **174**: 105699.
Zhang YF, Kecskés A, Copmans D, et al. 2015. Pharmacological characterization of an antisense knockdown zebrafish model of dravet syndrome: inhibition of epileptic seizures by the serotonin agonist fenfluramine. *PLoS One*, **10**(5): e0125898.
Zhang YF, Vanmeert M, Siekierska A, et al. 2017. Inhibition of glutamate decarboxylase (GAD) by ethyl ketopentenoate (EKP) induces treatment-resistant epileptic seizures in zebrafish. *Scientific Reports*, **7**(1): 7195.
Zhao JL, Zheng Y, Liu KY, et al. 2020. HMGB1 is a therapeutic target and biomarker in diazepam-refractory status epilepticus with wide time window. *Neurotherapeutics*, **17**(2): 710–721.
Zhou Y, Sharma J, Ke Q, et al. 2019. Atypical behaviour and connectivity in *SHANK3*-mutant macaques. *Nature*, **570**(7761): 326–331.
Zhu BF, Mak JCH, Morris AP, et al. 2020. Functional analysis of epilepsy-associated variants in *STXBP1/Munc18–1* using humanized *Caenorhabditis elegans*. *Epilepsia*, **61**(4): 810–821.
Zhu G, Okada M, Yoshida S, et al. 2008. Rats harboring S284L *Chrna4* mutation show attenuation of synaptic and extrasynaptic GABAergic transmission and exhibit the nocturnal frontal lobe epilepsy phenotype. *The Journal of Neuroscience*, **28**(47): 12465–12476.