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Animal Models of Epilepsy: An Overview

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Abstract: Epilepsy, a brain disorder characterized by recurrent seizures, affects millions worldwide. Understanding the diverse mechanisms underlying its various forms is crucial for developing effective treatments. Animal models play a vital role in this endeavor, allowing researchers to dissect the intricate neuronal networks and cellular processes involved in seizure generation and propagation. This review explores diverse animal models of epilepsy, offering comprehensive insights into their relevance and applications across different developmental stages and specific epileptic disorders. Focusing on neonatal, childhood, and adolescent disorders, the review delves into models that mimic age-specific epileptic manifestations, shedding light on the distinct mechanisms underlying these developmental phases. Additionally, the analysis extends to temporal lobe epilepsy models, elucidating their significance in understanding the complex pathophysiology associated with this prevalent form of epilepsy. Furthermore, the review delves into models simulating cortical malformations, providing a valuable platform to investigate the intricate interplay between genetic and environmental factors contributing to epileptogenesis. The discussion encompasses a thorough exploration of animal models representing partial and generalized seizures, emphasizing their role in the diverse seizure types encountered in clinical settings. By synthesizing information from various models, this overview contributes to a nuanced understanding of epilepsy pathogenesis, presenting a foundation for developing and evaluating novel therapeutic interventions.

Keywords: Animal models, Epilepsy, MES, PTZ, Seizures, Epileptogenesis

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Introduction

Epilepsy is a chronic condition caused by an imbalance of normal excitatory and inhibitory forces in the brain. Antiepileptic drug therapy is directed primarily toward reducing excitability through blockage of voltage-gated Na or Ca^{2+} channels or increasing inhibition through enhancement of -aminobutyric acid currents. Prior to clinical studies, putative antiepileptic drugs are screened in animals (usually rodents). Maximal electrical shock, pentylenetetrazol, and kindling

are typically used as non-mechanistic screens for anti-seizure seizures and epilepsy and have played a fundamental role in our understanding of the physiological and behavioural changes associated with human epilepsy. Since properties, and the rota rod test assesses acute toxicity. Animal models for the early half of the 20th century have led to the discovery of antiepileptic treatment strategies and some of those antiepileptic drugs (AEDs) are still commonly prescribed today (Löscher,2002). Animal models range in diversity from drosophila (Wei *et al*., 1990; Noebels, 1999) to non-human primates (Croll *et al*., 2019) and have proven invaluable for investigating basic mechanisms underlying epileptogenicity. Whether it is a mutated ion channel or neurotransmitter receptor, fundamental disruptions in neuronal function are consistent across the different animal models (White, 1997). Given the extraordinary diversity of animal species and modes of seizure induction how are all of the different models brought together to study the plethora of relevant human conditions associated with seizures and epilepsy? Furthermore, of the large number of existing models, how many are valid animal models that mimic clinically relevant human disorders and how many conditions are without a model? *In vivo* animal models have been categorized into models of seizures and those of epilepsy. Since human epilepsy is defined by the appearance of multiple spontaneous recurrent seizures, induction of acute seizure activity alone without chronic epileptiform behaviour is considered a model for seizures and not epilepsy (White, 1997). For example, adult rodents will have a severe, generalized seizure in response to a single exposure to the potent neurotoxin flurothyl, but will not develop spontaneous seizures; in comparison, a convulsant dose of kainic acid (KA) causes dramatic, permanent brain damage and subsequent spontaneous seizures (Stafstrom *et al*.,1992; Avanzini *et al*., 1997). These types of experiments relate to measuring seizure susceptibility using flurothyl or examining long term behavioural deficits in a permanently epileptic brain with KA. Despite tremendous advances made in the field of epilepsy research, the basic questions that can be addressed using both acute and chronic models remain the same. These questions relate to mechanisms of cellular hyperexcitability, synchronous neuronal discharge and rhythmic activity, alterations underlying the transition from an interictal to an ictal state, seizure propagation, seizure cessation, mechanisms and side effects of AEDs, and the behavioural disruptions caused by or associated with seizures (Engel *et al*., 2008).Therefore, not only are experimental models useful for investigating basic mechanisms underlying epileptogenesis and developing new preventive strategies, but these studies lead to information about normal brain function. The validity of animal models has been challenged for several reasons. First, many of the models draw mechanistic conclusions about epilepsy based on studies performed in a normal and not an epileptic brain. Second, behavioural manifestations associated with each model can differ and look nothing like a human's behaviour. For example, ictal, interictal, and postictal behaviour can vary among the different models and seizure-related behaviour(s) can range from very subtle to extremely complex. Third, data from a large range of species have been gathered to collectively inform us about the human brain. It is probably not unreasonable to suspect that certain cellular mechanisms, pathways of seizure propagation, or behavioural manifestations in the primate are more complex than in a rat or mouse. Considering the above issues, what are the criteria that a good animal model of epilepsy should meet? Given the diversity of models in use, how well do the current models themselves represent clinical conditions associated with seizures or epilepsy? The goal of this review was to establish major criteria a good animal model for a human condition should meet, followed by an overview of the current animal models of seizures and epilepsy. Even though most human conditions do not have well-characterized animal models, many of the model's available exhibit seizure phenotypes displayed by many of the diverse human epileptic conditions.

ANIMAL MODELS FOR EPILEPSY

Models for Neonatal, Childhood and Adolescent Disorders:

Only a few characterized animal models are available for the number of severe neonatal, early and late childhood, and adolescence seizure disorders. One of the most common seizure disorders observed in children is febrile seizures. A significant percentage of children experiencing prolonged febrile seizures have gone on to develop temporal lobe epilepsy (TLE) later in life; however, the relationship between febrile seizures and TLE has long been controversial. Although there is no genetic model, an experimental model using hyperthermia- induced seizures in rats has been developed that mimic febrile seizures (Puranam *et al*., 1999). Interestingly, it has been shown shown that prolonged hyperthermic seizures in the immature rat can lead to acute hippocampal injury for up to several weeks (Dube *et al*., 2000) as well as enhanced long-term hippocampal excitability on exposure to low-dose kainic acid *in vivo* or following Schaffer collateral electrical stimulation *in vitro* (Klancnik *et al*.,1992). It has also been reported that hyperthermic seizures cause a persistent enhancement of presynaptic GABA release which acts to dampen hippocampal pyramidal cell excitability. These findings will eventually require an understanding between the relationship of potentiated inhibition (Chen *et al*., 1999) and lowered seizure threshold (Klancnik *et al*., 1992) to clarify how hyperthermic seizures ultimately cause persistent excitability changes in hippocampus. Although long-term hippocampal cell loss is not observed in this model (Dube *et al*., 2000), the model is providing novel insights about the mechanisms that may underlie long term plasticity changes in hippocampus following fever-induced seizures in early childhood. Perhaps best characterized behaviourally and electrophysio-logically are rodent models for absence epilepsies: seizures commonly observed in early childhood. Examples of a few commonly studied mouse mutants include totterer (Buchhalter, 1993), stargazer (Letts *et al*., 1998), lethargic (Burgess *et al*., 1997), and slow wave epilepsy (SWE) (Cox *et al*., 1997) mice. For more detailed reviews of the gene products and functions of these single gene mutations the readers are referred to Noebels (1999), Puranam *et al*. (1999), and Prasad *et al*. (1999). However, it has recently been shown that some of these single gene mutations encode mutated 21 channels, although there has not yet been a report of a similar channelopathy in human. Most of these mutants share characteristics similar to those observed in human absence epilepsies such as brief behavioural arrest (i.e., staring or gazing); spontaneous, generalized 3- to 7-Hz discharges with seizure onset typically in the third postnatal week (corresponding to late childhood/adolescence period), and effective seizure blockade with ethosuximide. Similar phenomena are also observed in several strains of genetic mutant rats including: genetic absence epilepsy in rats from Strasbourg (GAERS) (Marescaux *et al*., 1995), the WAG/Rij rat (Coenen *et al*., 1992), and the spontaneous epileptic rat (SER) (Kanda *et al*., 1996; Noebels *et al*., 1997). Although all of these models resemble many electrographic and behavioural patterns observed in human absence epilepsies, they are not alike in that the seizures do not disappear with age (Prasad *et al*., 1999), patients do not typically exhibit ataxia (a behavioural abnormality found in most rodent models), and the EEG discharges are typically faster than 3 Hz in contrast to patients where it is rare to observe discharges greater than 4 Hz. Hypoxia is one of the most common causes of encephalopathy and a leading cause of seizures in neonates (Evans *et al*., 1998; Nordli *et al*., 2000). Jensen *et al.* (1991) and Jensen (1995) have developed a model of perinatal hypoxia in rat. Exposing the rat to global hypoxia (3-4%) between Postnatal Days (P) 7 and 15 causes acute seizure activity and spontaneous seizures several days after the hypoxic insult. In humans, hypoxic encephalopathy may be associated with an increased risk of epilepsy later in life (Jensen *et al*., 1995) and a study by the same group has shown that hypoxia-induced seizures cause both acute

and chronic increased excitability changes in hippocampal pyramidal neurons (Jensen *et al*., 1998). Rasmussen's encephalitis (RE), another severe early childhood encephalopathy associated with seizures, is an autoimmune disease caused by antibodies against the GluR3 receptor, an a-amino-3-hydroxy - 5- methylisoxazole - 4 - proprionicacid (AMPA) receptor subtype (Mantegazza *et al*., 2002). He *et al*. (1998) developed antibodies to this receptor subtype and found that it caused a similar syndrome in rabbits. Affected rabbits display spontaneous seizures and inflammatory histopathology similar to those of patients with RE and the antibodies are specific for GluR3 and no other closely related receptor subtypes such as GluR1 and GluR6 (He *et al*., 1998). A recent study has also addressed the clinical phenomenon associated with West syndrome (WS); a very common neonatal disorder characterized behaviourally by infantile spasms. Kábová *et al.* (1999) performed a study in rats that partially fulfils the requirements for WS. In their study, young rats (P12) injected with N- methyl-d-aspartate (NMDA) showed flexion seizures, on specific diffuse EEG changes, impaired performance on several behavioural tasks, refractoriness to some of the common AEDs, and mild response to valproic acid (VPA). However, these authors acknowledge that two major hallmarks of symptomatic WS, spontaneous seizures and clear pathological damage, were not observed. In addition, their model also lacks hypsarrythmia in the EEG pattern, another key feature of WS (Holmes *et al*., 1997). Clearly, more models are needed for the study of these early, catastrophic developmental disorders.

Models for Temporal Lobe Epilepsy (*TLE*):

Several well-characterized models have been described that in many ways mimic complex partial seizures observed in patients with TLE. The KA and pilocarpine (PILO) seizure models are probably the most commonly studied chemical-inductive models for TLE. The popularity of these models is attributable to the satisfaction of many of the criteria described above. KA (a glutamate analogue) (Covolan *et al*., 2000) and PILO (a cholinergic agonist) (Lemos *et al*., 1995) can be systemically or intra-cerebrally injected into an animal and reliably and rapidly produce acute seizures. In rodents, large dosages of either drug induce severe acute seizures with subsequent status epilepticus which is followed by a quiescent period of usually several weeks. This latent period is followed by the development of spontaneous recurrent seizures (Lemos *et al*., 1995). A convulsant dose of KA or PILO induces a variety of behavioural manifestations which mimic some automatisms observed in human TLE. Acute PILO injections in rodents cause facial automatisms such as eye blinking and chewing, head bobbing, and myoclonic jerks followed by motor limbic seizures, while the acute effects of KA (in rats older than P20) include similar facial automatisms but also other phenomena such as a loss of posture, scratching, and wet dog shakes followed by forelimb clonus which can lead into status epilepticus. In both models, the motor limbic seizures usually consist of forelimb clonus, profuse salivation, and rearing and falling. Pathologically, both KA and PILO generate lesions similar to those of patients with mesial temporal sclerosis. These lesions typically include loss of GABAergic interneurons in the dentate hilus and pyramidal cell death within CA3 and CAI strata of hippocampus. In addition, as reported in human epileptic hippocampus (Du *et al*., 1995), seizure-induced circuitry alterations in the form of mossy fiber sprouting in the dentate gyrus are also observed in rodents treated with KA (Wenzel *et al*., 2000) or PILO (Radley *et al*., 2003). The ge-dependent effects seen in the KA and PILO models are probably considered a major weakness of the models, since systemic KA or PILO administration to very young rodents (P20) does not lead to spontaneous recurrent seizures or produce similar pathological or long-term behavioural effects compared with older treated rats. Therefore, for rats older than P20, the characteristic development of both acute and spontaneously generated seizures in useful for developing and screening therapeutic agents that

prolong or abolish the recurrence of spontaneous seizures, Kindling, a phenomenon whereby repetitive, focal application of initially sub-convulsive electrical stimulation ultimately results in intense partial and generalized convulsive seizures (Goddard, 1967; Gv, 1969), continues to be an informative model for TLE. Although it is not routinely observed, this model strengthens its validity as an epilepsy model from observations that different species of kindled animals can develop spontaneous recurrent seizures, reinforcing the idea that brain networks become permanently hyperexcitable after repeated partial seizures (Corcoran *et al*., 1984; Shouse *et al*., 1992). To date, all animal species examined are susceptible to kindling including frogs, reptiles, rats, mice, rabbits, dogs, cats, rhesus monkeys, and baboons (McNamara *et al*., 1997). Kindling of the amygdale or other limbic regions leads to a progression through five characteristic stages of epileptic behaviour (Racine, 1972): Stage (1) facial clonus, Stage (2) head nodding, Stage (3) contralateral forelimb clonus, Stage (4) rearing, and Stage (5) rearing and falling. The increased behavioural severity also corresponds to an increase in electrographic seizure duration. Similar to the effects produced by KA or PILO, kindling also leads to sprouting of mossy fibers in the dentate gyrus of epileptic hippocampi (36) and cell death in hilus, CA3, and CA1 pyramidal neurons (Cavazos *et al.,* 1994). Therefore, the kindling model possesses some important advantages over the KA or PILO models. First, dependent on the electrode location, the investigator has control over the seizure focus, which is more complex in the KA or PILO model. Second, in a fully kindled animal, the investigator can control the long-term expression of when a Stage 5 seizure is to occur compared with the chemical models for complex partial seizures where a spontaneous seizure is almost impossible to predict. Like the chemical-inductive models, new AEDs can rapidly be screened for efficacy in preventing the progression of various kindled stages in limbic or other cortical areas. Although animals experiencing as few as 30 (Sutula, 1990; Cavazos *et al.*,1994) or as many as 150 Stage 5 seizures have been shown to display reductions in hilar, CA3, and CA1 neuronal populations, the extent of cell loss is often not as great compared with that generated by a single convulsive dose of KA or PILO. Finally, despite the popularity of the kindling model, subjects require extensive kindling stimulations before spontaneous seizures occur, and therefore it is not considered a good model for spontaneous seizures Models for Simple Reflex Epilepsies. Several genetically epilepsy-prone species have been described as models for studying photosensitive and audiogenic reflex epilepsies. The photosensitive baboon, *Papio papio*, discovered about 35 years ago (Killam *et al*., 1966; Killam *et al*., 1967) was found to be highly susceptible to intermittent photic stimulation. In response to this type of stimulus, baboons show a reflex myoclonus of facial, neck, and limbs often followed by severe tonic-clonic generalized convulsions. The seizures can be effectively blocked by AEDs used clinically for generalized convulsions such as phenobarbital, valproic acid, and other benzodiazepines (Niedermeyer, 1996). Although this is a posed genetic model for human primary generalized epilepsy (PGE), dissimilarities to human PGE include a lack of absence seizures in *P. papio* and no well-formed spike-wave bursts, and arousing stimuli do not appear to play a significant role in the seizures (Guy *et al*., 1995). Another animal displaying both photosensitive and audiogenic seizure susceptibility, albeit less commonly studied, is the Fayoumi epileptic (FEpi) strain of chickens (Buchhalter, 1993). These chickens have an autosomal recessive predisposition to epilepsy induced by light or intense auditory sound stimuli. In these animals, light produces head and neck myoclonia and a violent running fit on exposure to intense auditory stimuli. In *P. papio*, the site of seizure origin has been controversial but is suspected to be of cortical rather than subcortical origin (Guy *et al*., 1995), in contrast to FEpis, where the brainstem is believed to play a role in seizure generation (Buchhalter, 1993). Nevertheless, these models are useful for

screening new AEDs and understanding mechanisms underlying human photosensitive epilepsies. Other common rodent models for humans with audiogenic seizure susceptibility include the genetically epilepsy prone rat (GEPR) and DBA/2 mice. GEPRs have been inbred to yield two different colonies, GEPR- 3 and GEPR-9, each with differing seizure predispositions (Dailey *et al*., 1989). Rats from the GEPR-3 colony display a single running episode followed by a generalized clonus while the same stimulus in OEPR-9 rats elicits a more severe tonic-clonic convulsion sometimes preceded by a running episode. GEPRS have spontaneous seizures (although lower in incidence than in the KA model) and are therefore considered a naturally occurring epilepsy model. Although GEPRs are highly sensitive to audiogenic stimuli, the rats also display increased seizure susceptibilities to chemical convulsants, kindling, and hyperthermia (Dailey *et al*., 1989). Similar to the seizure behavioural patterns in humans, daily audiogenic seizure repetition in GEPR 9 rats results in a prolongation of the seizures with a late clonic phase following a tonic extension period (Naritoku *et al*., 1992). Neurochemical disruptions in GEPR rats include deficits in norepinephrine and serotonin activity and have recently been shown to arise from abnormalities in the locus coeruleus and its target tissues (Ryu *et al*., 1999). The DBA/2 mice are a strain of mice that are highly sensitive to intense auditory stimuli (10-20 kHz, 90-120 dB) (Naquet *et al*., 1998; Todorova *et al*., 2007). In response to intense stimuli, DBA/2 mice have seizures characterized by a violent running phase followed by clonic convulsions and then a tonic extension phase. The sensitivity to seizures begins around the second and third postnatal weeks and the severity of seizures often causes most mice to die from respiratory failure (Naquet *et al*., 1998). Studies focusing on the anatomical substrates in both GEPRS and DBA/2 mice have also suggested a subcortical origin for seizures whereby the brainstem and inferior colliculi appear to be intimately involved in seizure generation (Faingold *et al.*, 1986; La Salle *et al*., 1990). Therefore, these simple reflex models allow for the study of mechanisms of hyper-excitability in subcortical structures as targets for therapeutics in humans with these types of seizure susceptibilities.

Models for Cortical Malformations:

Genetic or environmental factors that lead to gross malformations of the cerebral cortex associated with seizures constitute an emerging field in epilepsy research and the subject of several reviews (Jacobs *et al*., 1999; Chevassus-au-Louis *et al*., 1999). Some form of cortical malformation is observed in at least 14% of all cases of epilepsy (Meencke, 1992; Walsh,1999) and in approximately 40% of severe or intractable cases (Hardiman *et al*., 1988; Farrell *et al*., 1992). Although there are few animal models that clearly mimic human malformations (Walsh, 1999), one genetic model seems to mimic subcortical band heterotopia (or double- cortex syndrome) and is termed the telencephalic internal structural heterotopia (tish) mutant rat (Lee *et al*., 1997). These rats display a bilateral band heterotopia that extends dorsally from frontal to darsoparietal neocortex. Spontaneous seizures are present in most tish mutants, are typically partial with variable secondary generalization, and appear to initiate simultaneously in normotopic and heterotopic neocortex (Chen *et al*., 2000). This finding is interesting because it is consistent with clinical studies of patients with subcortical band heterotopia in which both normotopic and heterotopic areas display epileptiform activity (Morrell, 1992). Embryologically, rats also display a second ectopic proliferative zone in addition to the normal periventricular proliferative zone, thus offering an opportunity to study developmental mechanisms involved in the proliferation, migration, and differentiation of heterotopic neurons which may offer insight into the formation of band heterotopias in A plethora of mutations have been identified that cause intrinsic neuronal excitability changes as a result of ion channelopathies or altered synaptic function (Puranam *et al*., 1999). Other genes have also been discovered that play critical roles in neurogenesis,

neuronal migration, and differentiation, and mutations in these genes are beginning to lend insight into human cortical malformations associated with epilepsy. For example, mice lacking the homeobox gene, Otx1, a transcription factor expressed in the CNS and required for normal telencephalic development, develop microcephalic brains and epilepsy (Acampora *et al*., 1996; Avanzini *et al*., 2000). Focal seizures in these mutants include automatisms such as head bobbing and teeth chattering and are followed either by a recovery or generalized seizures characterized by upper extremity clonus, rearing, and falling. These convulsions are followed by either a complete recovery or status epilepticus. A study by Di Cunto *et al*. (2000) found that mice lacking citron kinase (Citron-K), a protein regulator of cytokinesis in neural progenitors, causes severe micro-encephaly and early-onset epilepsy. Brain morphological abnormalities in these mice, like the Otx12/2 mouse, include abnormal hippocampal development, reduced cortical size, widespread cortical dysplasia, and cerebellar abnormalities. Interestingly, the flathead rat (fh/fhi) is also a mutation in the gene encoding Citron-K (unpublished results) and shows electrophysiological and behavioural manifestations strikingly similar to those of Citron-K mutant mice (Sarkisian *et al*., 1999; Roberts *et al*., 2000). The early-onset seizures and brain morphological abnormalities in Citron-K mutant mice (Di *et al*., 2000) and fh/th rats (Sarkisian *et al*., 1999) show strong similarities to human autosomic recessive lissencephalies with hypotrophic cerebellums (Walsh, 1999). Yet another example are mice lacking p35, a neuronal specific activator of cdk5, which has cortical lamination defects and seizures (Chae *et al*., 1997). In this study, the authors show that the phenotype of p352/2 mice is similar to, although milder than that of the well characterized reeler mouse (Chevassus-au-Louis *et al*., 1999), and the disrupted cortical lamination is due to defective migration of postmitotic neurons. These are only a few examples of single-gene mutations that dramatically affect normal differentiation of cortical structures (Acampora *et al*., 1996), neurogenesis (Di *et al*., 2000) and migration (Chae *et al*., 1997). Future studies will undoubtedly map out new developmental pathways stemming from these single genes, but the difficulties that lie ahead are determining how mutations in such a diverse number of genes lead to alterations in brain excitability. Novel therapeutic approaches will require an understanding of these mechanisms. The majority of metabolic disorders associated with epilepsy have no animal model. However, a study by Waymire *et al*. (1995) described a mouse that may serve as a good animal model for pyridoxine-dependent seizures. In humans, this rare condition causes seizure initiation during early infancy and persists for life. But seizures can be controlled by pyridoxine supplementation to the diet (Goutières *et al*., 1985). Mice lacking tissue nonspecific alkaline phosphatase (TNAP) have seizures caused by a defect in the metabolism of pyridoxal 59-phosphate (PLP). Because the synthesis of GAHA requires PLP as a cofactor, less GABA is subsequently made and as a result TNAP mutant mice have 50% less brain GABA. One consequence is severe, fatal seizures which initiate in the second postnatal week. Seizures in these mice can be rescued by treating animals with pyridoxine and a semisolid diet. Using a genetically epilepsy prone strain of mice (BALB/c) that also have reduced brain levels of GABA. Dolina *et al.* (1993) have also shown that supplementing the diet with pyridoxine throughout pregnancy abolishes increased susceptibility to PTZ induced and audiogenic seizures and can restore brain GABA. Therefore, these studies represent different mechanistic approaches to how a loss of pyridoxine can lead to brain hyperexcitability. The macular mutant mouse has been proposed as an animal model for Menkes' kinky hair disease (Yamano *et al*., 1987; Xu *et al*., 1994). In humans, this disease is an X-linked inherited disorder resulting from a defect in copper absorption affected infants display a progressive encephalopathy and early-onset myoclonic seizures, along with other hair, facial, and skin

abnormalities (Garcia-Alvarez *et al*., 1998). The clinical and pathological features of these mutant mice include early onset seizures accompanied by progressive degeneration of cortical neurons, severe emaciation, pigmentation changes in the fur, and curling of the whiskers (Yamano *et al*., 1987). Interestingly, while copper histidinate is the only available treatment in humans (Garcia-Alvarez *et al*.,1998), copper therapy in the macular mutant mouse can reduce the ultrastructural degeneration observed in cerebral cortex (Yamano *et al*.,1988). Collectively, these models are examples of metabolic disorders that disrupt body and cerebral metabolism, cause changes in brain excitability and neuronal damage, and lead to subsequent seizures. While advancements toward treatments have been made in these models, many of the metabolic disorders commonly associated with seizures have no therapeutic targets.

Animal Models for Partial and Generalized Seizures:

Despite a shortage of animal models that faithfully reproduce conditions, a host of models are available for the study of partial and generalized seizures. A variety of techniques can be used to induce partial (including simple and complex models) and generalized (including tonic, tonic-clonic, and absence models) seizures. Typically, the induction of partial seizures involves a focal application of chemical or electrical stimulation to a specific brain site. For example, focal application of antagonists for GABA receptors such as penicillin, bicuculline, and picrotoxin can act locally to disrupt the balance of inhibition and excitation and create an epileptogenic focus. Similarly, introduction of heavy metals such as aluminum (Ribak *et al*., 1998), cobalt (Dambinova *et al*.,1998; Craig *et al*., 2019), zinc (Pei *et al*.,1986), and iron (Kabuto *et al*., 1998; Ueda *et al*., 2000) into cortical areas can lead to the development of focal lesions and epileptogenicity. While these would be considered examples of simple partial seizures, a systemic injection of KA or PILO, and kindling of limbic regions (as described above) are reliable methods for producing a characteristic onset of complex partial seizures. These models are thus useful as rapid and easy methods for screening AEDs for efficacy against simple or complex partial seizures. Finally, genetic engineering has led to the discovery of numerous mouse mutants linked to an epileptic phenotype, some of these also display partial or complex partial seizure phenotypes (Todorova *et al*., 2007). A variety of methods are available for inducing generalized tonic-clonic or absence seizures in animals, as are some genetic models that are either highly seizure-prone or have spontaneous seizures. The following are few traditional methods of eliciting such seizure types. Convulsive seizures, characterized by tonic hind limb extension/flexion followed by clonic activity, are reliably induced by maximal electroshock which continues to be a popular method for the rapid screening of new anticonvulsant drugs (Merritt *et al*., 1938). Pentylenetetrazol (PTZ) is probably the most widely used systemically administered convulsant. Repeated injections of PTZ can be given to produce a type of chemical kindling that resembles electrical kindling. At high doses, PTZ (usually administered subcutaneously or intravenously) reliably produces tonic clonic convulsions in rats or mice and is a rapid and efficient measure of both seizure susceptibility and screening of new drugs. Given systemically at low doses, PTZ can also be used to elicit absence-like seizures (Snead,1992) which can be effectively blocked by ethosuximide, Flurothyl, a hexafluorinated ether, is a chemical inhalant used to induce a reproducible convulsive seizure pattern in rodents (Stafstrom *et al*., 1992). In this method, rats or mice are placed in an airtight chamber into which centrally administered flurothyl diffuses; after 10-20 min flurothyl initially causes myoclonic jerks followed by severe clonic-tonic convulsions. Finally, other experimental models for generalized absence seizures include thalamic stimulation (Niedermeyer, 1996), systemic penicillin administration in cat (Avoli, 1995), g-hydroxybutyrate treatment (GHB) (Snead, 1992), and intracerebroventricular opiates (Niedermeyer, 1996) as well as the number of genetic models in rats (GAERS,

WAG/R, SER) and mice (stargazer, tottering, lethargic, slow-wave epilepsy mice, mocha, and ducky) already described. Collectively, these models, both *in vivo* and *in vitro*, have been valuable in understanding basic mechanisms of partial or generalized seizure-related phenomena and are standard techniques for evaluating new therapeutics.

Conclusion

A number of reviews over the past decade or so have summarized available animal models for the study of the epilepsies (Löscher, 1997), and the addition of novel clinically relevant models has certainly not been overwhelming. In fact, the models used for exploring basic mechanisms underlying seizure generation, abnormal synaptic and neuronal networks, the long-term behavioural changes associated with seizures, and traditional screening of new AEDs have predominantly remained unchanged. However, the advancement of molecular genetics over the past decade has led to the discovery of numerous mutations (mostly in mice) associated with epileptic phenotypes. These mutations offer new insights into molecular pathways that ultimately cause seizures. In the human, several recent genes underlying febrile seizures (Wallace *et al*.,1998) and BFNC (Biervert *et al*.,1998) are associated with mutations in Na1 and K1 channels, respectively. There is thus a strong likelihood the same gene(s) in animals will be mutated and, it is hoped, will mimic in most aspects these disorders. However, despite the advancement of epilepsy genetics, especially underrepresented are the severe, early infancy and childhood disorders, where the development of new models mimicking conditions such as Ohtahara syndrome and Lennox-Gastaut syndrome will undoubtedly prove useful in understanding brain function and the control of seizures in these catastrophic disorders.

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