Animal Models for the Development of New Neuropharmacological Therapeutics in the *Status Epilepticus*

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Abstract: *Status epilepticus* (SE) is a major medical emergency associated with significant morbidity and mortality. SE is best defined as a continuous, generalized, convulsive seizure lasting > 5 min, or two or more seizures during which the patient does not return to baseline consciousness. The relative efficacy and safety of different drugs in the treatment of human SE should be determined in a prospective, randomized, blinded study. However, complementary animal models of SE are required to answer important questions concerning the treatment of SE because of the obvious difficulties of setting up such studies in clinical emergency conditions. This review offers an overview of the implementation and characteristics of some of the most prevalent animal models of SE currently in use. A description is also provided about how animal models of SE may facilitate the use of neurobiological techniques to successfully address critical questions in the drug treatment of SE. In particular, the experience with recently introduced drugs such as intravenous valproate will be addressed. Finally, the importance of some animal models and pharmacological approaches is explained and we discuss their impact in the development of therapeutic strategies to improve pharmacological treatment for SE is discussed.

Key Words: Epilepsy, *status epilepticus*; animal models, antiepileptic drugs, valproate.

INTRODUCTION

Seizures are usually brief and self-terminating. Occasionally, seizures can persist unstoped, or repeated seizures can occur without recovery; this situation is termed *status epilepticus* (SE). The definition of SE is based on the clinical manifestation, a prolonged seizure or a series of seizures during which the patient has incomplete recovery of consciousness, and the duration. It is important to note that practically all seizure types may become prolonged, thereby fulfilling the definition of SE [103]. The duration parameter is contentious and has shaped a change in current definition of SE. Because experimental studies revealed significant damage to the brain after 30 minutes of seizure activity, even when blood pressure, respiration, and body temperature are monitored [64, 65, 71], some authors have defined SE epilepticus as seizures that persist for 20 to 30 minutes [12, 18, 20, 76]. However, it has been documented that most seizures terminate spontaneously within a few minutes [99], and seizures lasting longer than five to ten minutes were unlikely to stop spontaneously and should be treated [85]. Therefore, an operational definition of SE has been proposed: continuous, generalized, convulsive seizure lasting longer than five minutes (in an adult or child older than five years), or two or more seizures during which the patient does not return to baseline consciousness [49]. These definitions can be applied to any type of seizure, and, for treatment purposes, it is more practical to conceptualize SE using these narrower time windows. While generalized convulsive *status epilepticus* (GCSE) may be the most frequently considered form of SE, nonconvulsive *status epilepticus* (NCSE) is

probably an under-recognized and under-treated condition. NCSE is difficult to diagnose clinically and it may be confused with other neurological and psychiatric syndromes. NCSE includes three clinical situations: complex partial SE, absence SE, and obtundation in the presence of electrographic SE. Animal models that provide information helpful to clinical management exist for both complex partial SE and absence SE.

More than half of the patients with SE have no history of seizures. Patients who have a first episode of SE are at substantial risk for future episodes and the development of chronic epilepsy [19]. On the other hand, the overall mortality rate among adults with SE is approximately 20 percent, and classic animal models of SE have clearly demonstrated that "epileptic" brain damage does not result from complicating peripheral factors, but from excessive neuronal activity during SE [65, 87]. Findings from animal studies show that following the acute episode of SE, many of the animals develop spontaneous seizures after a latent period lasting days to weeks [9, 47, 107] that are more likely to occur in adult than in young animals [91]. Animal studies have also demonstrated that there are important differences between the type and degree of seizure-induced brain damage in young and adult animals. For example, in the adult animal, status epilepticus causes neuronal loss in CA1 and CA3 hippocampal regions, the dentate granule cell layer, and the dentate hilus [69, 74, 88]. Young animals are less vulnerable to cell loss in the hippocampus following prolonged seizures than are mature animals [1, 10, 33]. In addition to the cell loss, prolonged seizures can cause synaptic reorganization, sprouting and formation of new synapses in different brain regions. In the hippocampus, prolonged seizures induce sprouting of mossy fibers in the fascia dentate and the pyramidal CA3 region [97, 79]. Mossy fiber changes after SE are age-related, indeed younger animals

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development less sprouting than older animals after prolonged seizures of similar characteristics [89]. Deficits in learning, memory, and behavior are also related to age of the animals at the time of SE-induction [90].

According to these findings, the main objective of the treatment of SE is the rapid and effective cessation of clinical and electrical seizure activity. The prospective and randomized investigation of different drugs in the treatment of SE is problematic in clinical emergency conditions. Therefore, the development of animal models of SE leads to a much more systematic way of evaluating potential drugs. In addition, animal models constitute one of the most valuable tools to better understand the pathophysiology of SE so a better understanding of these seizure-initiating mechanisms should facilitate progress in new therapeutic strategies to improve treatment. The present review provides an overview of some of the strategies utilized in the development of SE animal models, describes the most prevalent pharmacological therapeutic in SE, and discusses the utility of the models in addressing several crucial issues in the development of new drugs in the treatment of human SE.

CLASSICAL ANIMAL MODELS OF SE

Animal seizure models were first used successfully by Merritt and Putnam in 1938 [67]. They screened compounds using electrically induced seizures in cats and discovered the anti-convulsant properties of phenytoin [68]. At present, a wide variety of animal models of epileptic seizures and SE exist; and the diversity of available animal models offers a opportunity to discover and develop better antiepileptic drugs. SE can be induced in animal models using either convulsant chemicals or electrical stimulation. Furthermore, it is has been possible to induce non-convulsive SE in animals, thus avoiding confusing factors, such as hypoxia, hyperthermia and acidosis that occur during convulsive SE. The animal models that have received the greatest attention have been those that have used systemic administration of pilocarpine (a muscarinic receptor agonist) [16, 66, 106, 107], systemic or local administration of kainic acid (a potent glutamate receptor agonist and inhibitor of glutamate uptake) [9], or protocols using electrical stimulation of specific brain areas, for example within the limbic system [29, 46, 47, 87].

SE Induced by Convulsant Chemicals

Induction of SE can be achieved by systemic or local (intracerebroventricular, intracerebral) drug administration. In these models, morphological changes in the hippocampus produced by the cytotoxic agents used to induce SE are often similar to those appearing in human mesial temporal lobe epilepsy. However, the damage in the animal model can be more severe and widespread.

1) Systemic Convulsant Administration

Pilocarpine is among the most commonly used drugs to induce SE in animals models. Pilocarpine-induced SE can be achieved by high doses of intraperitoneal injections on the order of 300 mg/kg; however, relatively high mortality rates are generally associated with this method. Methylscopolamine

(1 mg/kg i.p. or s.c.) may be administered 30 min before or together with pilocarpine to attenuate the peripheral cholinergic activity of pilocarpine. Alternatively, lithium pre-treatment, followed by one or several low doses of pilocarpine, produces SE and chronic epilepsy with much lower mortality rates than a single dose of pilocarpine [26]. Pre-treatment with lithium chloride (3 mEq/kg, i.p.) between 2-24 hours prior to pilocarpine injection potentiates the epileptogenic action of pilocarpine and allows a 10-fold reduction in the drug dose [4]. Systemic administration of multiple low doses (5 mg/kg, i.p.) of kainic acid is associated with a relatively low mortality rate and a high percentage of rats becoming epileptic when compared to induction protocols using single high doses (15-30 mg/kg, i.p.) of kainic acid [30]. Systemic administration of bicuculline (a potent GABA_A receptor antagonist that produces convulsive seizures through inhibition of inhibitory neurotransmission) may also induce SE [64, 65].

2) Local Convulsant Administration

The application of drugs, intracerebrally or in specific brain sites such as the amygdala [96] or the hippocampus [58], were used to induce SE. Intrahippocampal injection of pilocarpine (2.4 mg/ μ l; injected volume 1.0 μ l) has been reported to induce SE and spontaneous recurrent seizures with near zero mortality [40]. Kainic acid at doses of 0.1-3.0 μ g/kg may also be administered intracerebrally, with the lower doses producing minimal mortality but generally low seizure rates requiring relatively long latent periods [40]. Cobalt lesions in motor cortex induce focal motor seizures, which may be converted to secondarily generalized convulsive SE by intraperitoneal administration of homocysteine thiolactone [113, 114]. Intrahippocampal administration of pertussis toxin (5 μ g/hippocampus bilaterally) increases the severity of SE induced by electrical stimulation delivered to perforant path for 30 min [61]. In addition, combination of an ineffective perforant path stimulation (that did not lead to the development of self-sustaining seizures) with pertussis toxin administration, induces self-sustaining SE [61]. Potassium-channel blockers such as 4-aminopyridine, that enhance the release of neurotransmitter from nerve terminals, have been commonly used for experimental seizure induction both *in vivo* and *in vitro* animal models [54, 55, 56, 95, 110]. Intrahippocampal injection of 4-aminopyridine *in vivo* (100 mM; injected volume 5.0 μ l) induced a continued epileptic activity, with near zero mortality that lasted $\geq$ 60 minutes and which resembled an SE [55]. These prolonged seizures generate electrophysiological changes, but the animals did not exhibit secondarily generalized SE. Therefore, this model could represent a excellent experimental approach of NCSE and is suitable for the studying the possible treatment of prolonged nonconvulsive seizures.

SE Induced by Electrical Stimulation

Sustained electrical stimulation of the perforant path (i.e. the pathway from the entorhinal cortex to the dentate gyrus) in anesthetized animals resulted in SE [87]. Usually, a bipolar stimulating electrode is implanted into the angular bundle of the perforant path. The position of electrodes is optimized by the maximal amplitude recording (typically $\geq$ 2 mV) of the population spike evoked from the dentate gyrus

by the stimulation of the perforant path. To induce self-sustaining SE, animals are stimulated in the awake state for 30 min with 10 s, 20 Hz trains (1 ms square wave; 20 V) delivered every minute, together with 2 Hz continuous stimulation [59]. However, it should be possible to induce prolonged seizure states from numerous limbic sites including parts of hippocampal formation, olfactory/limbic cortical areas, and caudate putamen [29]. For example, a model of SE may be elicited in the limbic system by a continuous electrical stimulation of the hippocampus [46, 47]. Under appropriate conditions such as length of stimulation, the side (left vs. right) of stimulation or kindling before stimulation, this self-sustaining limbic SE persisted for many hours after discontinuing the electrical stimulus [46, 47]. For the induction of self-sustaining limbic SE, a pair of bipolar stimulating electrodes is implanted in the left posterior ventral hippocampus. After 1 week of recovery, stimulus trains (50 Hz of 1 ms, 400 μ A biphasic square wave pulses for 10 s) are delivered every 13 s for 90 min to induce SE [46, 47]. In this model, only animals displaying self-sustaining limbic SE for 2 h are employed for experimental purpose, because these animals are more likely to develop spontaneous recurrent seizures than animals with shorter SE [11]. Focal stimulation of the amygdala also induces the development of spontaneous seizures in rats, and this model mimics different aspects of human temporal lobe epilepsy [72]. Self-sustained status epilepticus lasting for 6–20 h may be induced by a 20–30 min stimulation of the lateral nucleus of the amygdala (100 ms train of 1 ms, 60 Hz bipolar pulses, 400 μ A, every 0.5 s) [72].

Genetic and Transgenic Seizures Models

The ability to manipulate the genome of mice has led to identification of a diversity of genes whose absence or modification may cause epileptic seizures. Alternatively, transfection strategies or transgenic gene targeting techniques may be used to selectively identify genes encoding voltage- and ligand-gated ion channels. This manipulation suggests that these targeted genes can play an important role in regulating excitability, and facilitate assessment of circuit function during seizures. In gene studies, once a given protein is determined to potentially play a role in a presumed epileptogenic mechanism, the expression of this gene can be manipulated, and effects on epilepsy assessed. In transgenic strategies, the expression levels of a gene are manipulated by constructing animals with transgenic overexpression of certain mRNA species or targeted gene deletions [73] that result in an epileptic phenotype [5]. Other techniques include transfection using antisense oligonucleotide manipulation of mRNA levels [112] or various expression vectors [35]. These advancements in molecular genetics are contributing to understand the mechanisms underlying genetic control of neuronal excitability, and to point out feasible genes underlying genetic forms of human epilepsy. These techniques also provide a valuable model to elucidate how the genotype produces the phenotype form of different human epilepsy, including SE condition.

Models of SE in Immature Animals

The consequences of prolonged seizures in the developing brain are an important issue that is not readily

answered by human studies. Therefore, experimental animals models are required to understand the pathophysiology of age seizure-induced vulnerability. The most commonly used models of SE in immature brain are systemic administration of kainic acid [33, 90, 91], lithium-pilocarpine [82], and protocols using electrical stimulation, such as continuous hippocampal stimulation [100] or perforant path stimulation [101]. Pentylenetetrazol (PTZ) given systemically at postnatal day 10 or 21 also lead a SE [70]. In this model, seizures are induced by repetitive subconvulsive injections of PTZ given as a first dose of 40 mg/kg followed 10 min later by 20 mg/kg. Thereafter, rats received every 10 min additional injections of PTZ 10 mg/kg until the onset of SE [70]. Furthermore, Corticotropin-releasing hormone has been employed as potent convulsant that induces limbic seizures at picomolar doses in infant rats at postnatal day 10 to 13 [80]. This model of SE causes neuronal damage in the CA3 subfield of the hippocampus and mossy fiber reorganization in these rats [80]. Additional animal models for prolonged seizures in the immature brain, include early life hyperthermic seizures [21], perinatal hypoxia [36], and early-life flurothyl-induced status [32].

PHARMACOLOGICAL THERAPIES IN SE

The goal of treatment for SE is the prompt cessation of seizure activity. The ideal pharmacological agent in the management of SE should be easy to administer, have an immediate and long-lasting antiseizure effect, and have no major adverse effects on cardiorespiratory function and the level of consciousness. Unfortunately, none of the agents currently employed in SE therapies meet all the criteria mentioned above. For example, benzodiazepines and barbiturates depress consciousness and respiratory function, phenytoin and fosphenytoin cause hypotension and cardiac dysrhythmias, and the maximal antiseizure effect of phenytoin, fosphenytoin, and phenobarbital is delayed by limits on the rate of intravenous administration.

The standard treatment for GCSE should be the application of a fast-acting benzodiazepine, followed, if necessary, by phenytoin to initiate maintenance therapy [18]. Thereafter, in SE that is refractory to a sufficient dose of a benzodiazepine and phenytoin, phenobarbital, and later an anesthetic, barbiturate (pentobarbital or thiopental), were usually given. Infants and neonates frequently received phenobarbital initially. A major disadvantage of phenobarbital is the marked and prolonged sedative effect it produces. Respiratory depression and hypotension are also potential hazards. If SE remains refractory after subanesthetic doses of other agents, then general anesthesia is indicated as a last resort. This control convulsive movements and reduces cerebral seizure activity and metabolic needs, and can be achieved with barbiturate or nonbarbiturate anaesthetics.

Benzodiazepines (diazepam, lorazepam, midazolam, and clonazepam) are potent, fast-acting antiseizure drugs, and they exert their antiepileptic effect by preventing the spread of seizure rather than suppressing the seizure focus [102]. Their primary pharmacological actions are probably related to an enhancement of GABAergic transmission mediated by a benzodiazepine-receptor [93, 94]. At higher concentrations, benzodiazepines limit sustained repetitive neuronal firing,

and this effect may be important to their mechanism of action in SE [52]. Diazepam and lorazepam are preferred as initial therapy. In clinical testing, lorazepam was more effective than phenytoin to control brief overt convulsive SE [104]. Midazolam is a fast-acting benzodiazepine that is associated with a very favorable hemodynamic and pharmacokinetic profile and has the advantage of rapid absorption with IM administration [6]. Midazolam effectively controlled convulsive seizure activity and is also used for the treatment of refractory SE [39, 75], but tolerance and rebound seizures can be problematic. It is important to note that all benzodiazepines carry the risk of respiratory depression and hypotension, and therefore the clinician should be prepared to intubate or give pressors if necessary.

Phenytoin is structurally related to phenobarbital [105], and is useful when benzodiazepines fail. In rat models of self-sustaining SE induced by brief intermittent perforant path stimulation, both diazepam (10 mg/kg i. v.) and phenytoin (50 mg/kg i.v.) prevented the establishment of SE when administered 10 min prior to perforant path stimulation [59]. Phenytoin was effective in aborting SE when injected 10 min after 30 min of perforant path stimulation, while diazepam was significantly less effective than pretreatment in attenuating SE. Therefore, these drugs were highly effective in blocking the induction of self-sustaining SE in the rat model but failed to affect its maintenance [59]. Phenytoin exerts its anticonvulsant effect by stabilizing the inactivated state of sodium channels, thereby limiting sustained repetitive firing of neurons [51]. Its use in GCSE is limited by side effects at high infusion rates. At maximal infusion rates, it induces hypotension and cardiac arrhythmias such as bradycardia and ectopic beats [48]. It does not, however, depress either respiration or the functioning of the central nervous system in comparison with the benzodiazepines. Fosphenytoin is a water-soluble prodrug of phenytoin, which is rapidly and completely converted to phenytoin (conversion half-life 8-15 min) by nonspecific phosphatases. Because infusion-site reactions (phlebitis and soft-tissue damage) are less common with fosphenytoin, it can be applied at a higher rate infusion than phenytoin. In comparative studies of phenytoin and fosphenytoin, no significant differences in efficacy, adverse effects, or pharmacokinetics have been demonstrated [77]. Systemic side effects appear to depend on the free phenytoin levels and do not differ markedly between fosphenytoin and phenytoin [41, 78].

Barbiturates were initially the drug group of choice before the advent of benzodiazepines and exert their anticonvulsant effects by enhancing activation of GABA_A receptors [50, 93]. Phenobarbital penetrates to the CNS rapidly and was as effective as the combination of diazepam and phenytoin for the treatment of SE [84]. Pentobarbital and thiopental are potent antiseizure drugs and, in adequate doses, will almost always control SE, but severe hypotension requiring pressor therapy limits their safety [116]. Since side effects such as respiratory depression, coma, and hypotension are quite pronounced, their use is only recommended when combination therapy with benzodiazepines and phenytoin fails.

Propofol is a short-acting IV anesthetic that can be administered by bolus or infusion. Several studies and case reports document the efficacy of propofol in the treatment of refractory GCSE, NCSE, and complex partial SE [8, 53, 92]. Propofol is extremely lipid-soluble, and its induction characteristics are similar to those of thiopental, with dose-related depression of conscious level, cardiovascular and respiratory function. Propofol has the advantage of a very rapid onset of action and recovery, with only minor haemodynamic side effects.

SE AND UTILITY OF ANIMAL MODELS TO DRUGS DEVELOPMENT

A new drug would be recommended for first line use if it showed equivalent efficacy to a standard drug, and was better tolerated. If a new drug had similar efficacy and tolerability to the standard antiepileptic drug, it would be seen as second line. It is clear that although several new antiepileptic drugs such as Gabapentin, Lamotrigine, Oxcarbazepine, Levetiracetam, Topiramate, Vigabatrin or Zonisamide, have become available in the last decade, these have not had a great impact on the treatment of SE. Furthermore, the literature demonstrating new drug's efficacy in animal models is limited to a few experiments and drugs. For example, felbamate or fluorofelbamate, a felbamate analog, displayed an anticonvulsant effect in an animal model of SE induced by sustained electrical stimulation [60, 62]. Tiagabine, a GABA uptake inhibitor, was also effective in reduce generalized tonic-clonic seizures in cobalt-lesioned rats in which SE was induced by injection of homocysteine thiolactone [113]. Due to limitations of the information to date, the efficacy of these drugs for control of SE in humans was not evaluated in experimental clinical trials.

There are currently a number of potential antiepileptic compounds undergoing clinical evaluation. For example, pregabalin, a structural GABA analog, which increases GABA content in neuronal tissues and binds to a subunit of Ca²⁺ channels [98]; retigabine, which increases K⁺ conductance in neuronal cells [81], rufinamide, losigamone, remacemide, ganaxolone, harkoseride, talampanel, valro-cemide, carabersat and benzopyran. To date, none of these potential agents was tested in animal models of SE.

As mentioned in the preceding section, current antiepileptic drugs for the treatment of SE carry the risk of respiratory depression, hypotension and cardiac arrhythmias. Furthermore, the use of general anesthetics is a common treatment of refractory SE, but it carries the risk of hypotension and infection. Therefore, new contributions to therapeutic antiepileptic drugs are needed for the treatment of SE. Among current existing drugs, the role of intravenous VPA in SE looks promising. Use of VPA would be advantageous for several reasons if shown to be safe and effective in the treatment of SE. Intravenous VPA has not been shown to cause sedation and respiratory depression associated with benzodiazepines and barbiturates, or the hypotension associated with barbiturates and phenytoin [31]. Valproic acid (VPA) is an anticonvulsant agent that has been used widely in the therapy of primary and generalized and

partial-onset seizures. The pharmacological effects of VPA involve a variety of mechanisms, including modulation of GABAergic systems [27, 44, 45], reduction of aspartate concentration and its release [17, 83], and induction of inositol depletion [115]. VPA mechanisms also involve direct action on membrane electrical properties that tend to reduce neuronal excitability. Indeed, it has been suggested that VPA may act by decreasing repetitive cell firing [63], increasing potassium conductance [86], blocking both sodium and potassium ion channels [109], and regulating both sodium and potassium channel gating [23]. It has been shown that VPA may interfere with excitatory synaptic transmission [3, 28, 57], possibly due to the postsynaptic modulation of the non-NMDA receptor-mediated excitatory postsynaptic currents [57]. As a result of its wide spectrum of anticonvulsant activity against different seizure types, it is believed that valproate acts through several mechanisms.

For several years, VPA was only available in oral formulations. Starting in the 1980s, the use of the intravenous form of VPA has been reported in an increasing number of case series, indicating relatively easy use, relatively good tolerability and suggesting that it may be efficacious in SE treatment [2, 25, 37, 42, 108]. Experience with intravenous VPA in the treatment of SE is too limited to recommend its use as a first-line agent. Prospective investigation will be required to confirm the efficacy and safety of intravenous VPA in SE, and animal models are a good complementary tool to answer some questions concerning the treatment of SE by VPA. Intravenous administration of VPA was as rapid as benzodiazepines to suppress generalized tonic-clonic seizures in a mouse model of GCSE induced by repeated transauricular electrical stimulation [34]. In a rat-model with cortical cobalt lesions that were injected with homocysteine thiolactone to induce GCSE, VPA was effective at high plasmatic levels [114]. In addition, intravenous VPA suppresses at relative high doses, whereas minor doses prevent the SE induced by intra-hippocampal application of 4-aminopyridine [55]. According to these animal model findings, VPA may be a useful alternative as a nonsedative drug for the treatment of SE.

ADVANTAGES AND LIMITATIONS OF SE ANIMAL MODELS

For the effective and efficient discovery and development of new drugs, it is necessary to know the mechanisms of SE, possess reliable preclinical animal models of SE that are representative of human pathology, and have reference compounds after which new drugs can be modeled and assessed. Information gained from animal studies includes a broad understanding of the chemical, molecular and anatomic consequences of SE. One of the main advantages of animal models of SE consist in the wide array of techniques available to the researcher to understanding the etiology and pathophysiology of the SE. Recent advances in neurophysiological techniques, molecular biology, optical imaging of neuronal activity, and *in vivo* recording techniques provide different levels of insight into the basic pathophysiology of the SE. Many of these issues are not possible to study in humans, due to ethical concerns. For example, at cellular levels, patch clamp techniques provide a

method to assess alterations in ion channel function [7, 54, 111] as well as alterations in synaptic function of neurons from an epileptic animal [15, 24]. With the development of single cell mRNA expression profiling, it has become possible to combine patch recordings of ion channel function with gene expression profiling of the mRNAs encoding the relevant proteins [22]. This technique gives an important tool to understand the molecular mechanisms underlying alterations in neuronal function in epilepsy [13, 14]. On the other hand, the circuit analysis is important for the study of epileptogenic mechanisms, where little bridging has been possible between whole animal, *in vivo* recordings and patch clamp recording studies *in vitro*. Recent advances in optical imaging techniques and positron emission tomography (PET) imaging have facilitated this type of transitional study. High resolution CCD cameras combined with lipophilic voltage sensitive dyes and brain slice techniques, represent a useful tools to investigate circuit function with a high spatial and temporal resolution, which can resolve individual action potentials [43]. PET scanner developed for small animals can be used to assess the metabolic brain changes during the seizures in conscious rodent [38].

Numerous animal models have been used in research studies to understand the mechanisms underlying the physiopathology of SE. Without this information, it will be difficult to design a novel therapy by using a mechanistic approach. Furthermore, animal models are necessary to identify new pharmacological therapies for the treatment of SE. A number of models have been suggested as appropriate for these studies, but at the moment, there is no general agreement about which models may be most suitable and relevant to the human condition. In addition, better models for therapy discovery may be different from those models suited to study the basic mechanisms of SE. More important, none of the available models have been clinically validated. For a model to be considered valid, it should be highly predictive of clinical response to any new therapy. It is not clear how any new model for SE therapy should be validated, but it is clear that the current models are not fully adequate.

Animal models will continue to be useful, especially when whole-animal preparations are used to generate material for detailed *in vitro* examination. These models share the property that *in vivo* and *in vitro* techniques are combined to allow experiments that could not be conducted in either environment exclusively. Choice of a model system depends upon several factors, the type of SE to be modeled, familiarity and convenience. Interpretation of findings from each of these models can be difficult. Thus, at present, it is not possible to judge which SE model is best suited for developing new strategies in the search for anticonvulsant drugs.

CONCLUSION

The goal of SE treatment is to control seizures completely without unacceptable side effects. None of the currently available treatments accomplishes that; many of the drugs employed in SE have unwelcome side effects or fail to completely control seizures. With only a few exceptions, these drugs were discovered by screening in animal models,

and the underlying mechanisms are only now coming into clear focus. The need remains for further research in appropriate animal models to develop new antiepileptic drugs for treating the processes of SE.

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