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# Animal models of drug-resistant epilepsy*

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**ABSTRACT** – Several animal models are discussed in order to outline features of difficult-to-treat or drug-resistant epilepsy. These models can be categorised as those which show a poor response to different antiepileptic drugs and those in which subgroups of drug-resistant animals are selected, based on interindividual differences. Non-responders to antiepileptic drugs have been described in the amygdala kindling model, as well as the chronic phase of post-status epilepticus models. Epileptic dogs which do not respond to standard antiepileptic drugs may serve as a translational model to provide a more clinical environment for drug testing. Drug resistance or a poor response to several antiepileptic drugs has been reported for the 6-Hz model, lamotrigine-pretreated kindled rats, pentylentetrazole-induced seizures in rats pre-exposed to pilocarpine, as well as following intrauterine exposure of rats to methylazoxymethanol. Using models to select non-responders is highly time-consuming and elaborate, limiting their use in routine drug-screening procedures. Current efforts to identify biomarkers of drug resistance may simplify the selection process, *e.g.* replacing several weeks of seizure monitoring by a single imaging scan. Moreover, further elucidation of mechanisms of resistance may help to design a series of *ex vivo* or *in vitro* screening procedures in order to evaluate whether a test compound is affected.

**Key words:** drug resistance, drug refractoriness, pharmacoresistance, intractability, animal models, 6-Hz model, kindling, status epilepticus, epilepsy

Models of drug-resistant epilepsy are urgently needed for several reasons. First of all, implementation of models for drug screening programs may optimise selection procedures, allowing the identification of compounds that are superior to available antiepileptic drugs, regarding management of difficult-to-treat epilepsies. In addition, animal models of drug-resistant epilepsy may help to elucidate mechanisms of resistance and develop and validate novel

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strategies to overcome resistance, as well as imaging strategies to predict drug responses. In choosing a model, one must consider the validity of the model in order to mimic the clinical situation, as well as practical aspects, such as the time and effort necessary to obtain data.

As already discussed by Wolfgang Löscher in a comprehensive review (Loscher, 2011), models can be categorised as those used to select non-responders on the one hand and those in which animals exhibit a poor drug response and the model is, *per se*, resistant to antiepileptic drugs.

## Models for non-responder subgroups

### Kindling model

Regarding the response to antiepileptic drugs, the amygdala kindling model of temporal lobe epilepsy is one of the most intensely characterised chronic epilepsy models (Loscher, 2002; Loscher, 2011). Kindling is based on the repeated electrical elicitation of seizure activity *via* an implanted depth electrode. Typically, seizures evolve with ongoing stimulations in severity and length such that animals finally respond with generalised seizures in a reproducible manner. Kindled animals can then be used repeatedly for drug experiments, in which the impact of test compounds on seizure thresholds and seizure parameters at the threshold stimulation can be evaluated.

Based on the observation that the ED50 levels are substantially higher than those determined in an acute seizure model (MES test), the amygdala kindling model was suggested to be a model of drug-resistant epilepsy 25 years ago (Loscher *et al*., 1986). Some years later, Wolfgang Löscher's group described subgroups of female Wistar rats which could be selected, based on the fact that they differed in their response to the antiepileptic drug phenytoin (Rundfeldt *et al*., 1990). Whereas responders reliably exhibited an increase in the seizure threshold in response to phenytoin, non-responders showed no impact of phenytoin on seizure thresholds during repeated drug testing. Unfortunately, the vast majority of the animals could not be categorised as responders or non-responders as they showed a variable response, *i.e.* responding in one drug experiment and not in another. This fact renders the model highly time-consuming as one has to work with large animal numbers in order to select subgroups of responders (average 16%) and non-responders (average 23%) (Loscher, 1997).

In follow-up studies, subgroups of phenytoin responders and non-responders have been used to evaluate the efficacy of a series of antiepileptic drugs. Almost all antiepileptic drugs tested proved to be less efficacious in the group of phenytoin non-responders, compared to the phenytoin responder group (Loscher, 1991; Loscher *et al*., 1993; Ebert *et al*., 2000; Loscher *et al*., 2000; Reissmuller *et al*., 2000). The drug-induced increase in the focal seizure threshold was reduced in a range between 46 and 85% in phenytoin non-responders *versus* responders to carbamazepine, phenobarbital, valproate, vigabatrin, lamotrigine, felbamate, topiramate, and gabapentin. As an exception, levetiracetam was the only compound exhibiting a comparable efficacy in phenytoin responders and non-responders (Loscher *et al*., 2000).

### Post-status epilepticus models

Self-sustained status epilepticus can be experimentally induced in rodents by prolonged electrical stimulation or by administration of chemoconvulsants, such as pilocarpine or kainic acid (Loscher, 2002). As a consequence of the network, cellular, and molecular alterations occurring in response to prolonged seizure activity, animals develop recurrent spontaneous seizures following a latency period of several days to some weeks in most of the experimental setups. Epileptic animals can then be used to evaluate the anticonvulsant efficacy of test compounds. However, a thorough assessment requires very time-consuming, continuous video-EEG monitoring during vehicle control phases and drug treatment phases. As seizure frequency tends to fluctuate in chronic epilepsy models and clusters of seizures may occur in some animals, a valid conclusion needs to be based on a sufficient duration of seizure monitoring.

In general, it has been reported that the drug response in post-status epilepticus models of epileptic rats seems to be comparable to that in fully kindled rats (Loscher, 2002). As described for the kindling model, pronounced interindividual differences have been reported regarding the pharmacosensitivity of rats with spontaneous recurrent seizures. Following pilocarpine-induced status epilepticus, we demonstrated that the individual response of chronic epileptic rats to levetiracetam varied markedly from complete seizure control to no effect at all, although plasma drug levels were within the therapeutic range in all rats (Glien *et al*., 2002). Of eight rats used for final evaluation of levetiracetam efficacy, two became seizure-free in response to levetiracetam, several rats showed a relevant reduction in seizure frequency, and some rats showed no response to drug treatment at all.

Two years later, the drug response was also shown to differ in a model with electrical induction of status epilepticus using electrical stimulation of the amygdala for 25 minutes (Brandt *et al*., 2004). In this study, the authors described the selection of pheno-

barbital responders and non-responders. Of 11 rats, complete seizure control was achieved in six animals. Together with another rat that exhibited a more than 90% reduction in seizure frequency, these animals were considered responders (73%). Further rats, either showing no response at all or only moderate reduction in seizure frequency, were considered non-responders (27%). Plasma concentrations proved to be in the same range for both groups. Based on these findings, the authors suggested that drug-resistant rats selected by sub-chronic drug treatment from groups of rats with spontaneous recurrent seizures are a unique model to identify novel antiepileptic drugs for treating seizures of patients currently not controlled by available drugs (Brandt *et al*., 2004). Since this initial description, the model has been used repeatedly to analyse factors and mechanisms contributing to drug resistance. However, whether resistance extends to other antiepileptic drugs in the model has not yet been extensively tested, due to the highly time-consuming nature of drug testing in this model. To my knowledge so far, phenytoin is the only antiepileptic drug to have been evaluated in phenobarbital non-responders. Bethmann and colleagues (Bethmann *et al*., 2007) described five of six phenobarbital-resistant rats which also proved to be resistant to phenytoin, indicating that rats exhibiting an inadequate response to treatment with phenobarbital are likely to be resistant to treatment with another antiepileptic drug.

### Epileptic dogs

Canine patients with drug-resistant epilepsy may be a valuable translational model, since compounds may be evaluated under clinical conditions and there exists a variable genetic background. Dogs are relatively easy to enrol in clinical studies due to the fact that euthanasia is often already considered by owners of canine patients in which adequate seizure control cannot be achieved with available drugs.

Based on costs, efficacy, and pharmacokinetic data, phenobarbital remains to be the first choice in canine epilepsy. Considering two different reports, seizure control was achieved in 20-40% of animals treated with phenobarbital, a relevant reduction in seizure frequency by at least 50% was achieved in 40-64%, and 20-28% showed no response to phenobarbital (Schwartz-Porsche *et al*., 1985; Loscher *et al*., 2004). Depending on individual tolerability, potassium bromide add-on therapy is used in many animals, in which seizures cannot be controlled by phenobarbital monotherapy. However, a considerable subgroup of canine patients remains drug-resistant with this add-on therapy. Therefore, the efficacy of several more recent antiepileptic drugs has been evaluated in small clinical studies. These studies demonstrated that resistance can extend to levetiracetam (36% no response; only 7% seizure-free), zonisamide (18% no response; only 18% seizure-free), gabapentin (45% no response), and pregabalin (36% no response; 0% seizure-free) (Platt *et al*., 2006; von Klopmann *et al*., 2007; Volk *et al*., 2008; Dewey *et al*., 2009). However, these studies were performed in relatively small groups of canine patients and there were several limitations of the study design. Thus, the actual numbers should be considered with caution, however, overall, there is clear evidence that multidrug resistance can occur in canine epilepsy. Recently, we have used epileptic dogs with phenobarbital-resistant epilepsy in order to evaluate the efficacy of verapamil add-on therapy, based on single case reports aiming to target P-glycoprotein-mediated efflux transport (Jambroszyk *et al*., 2011).

Problems and limitations of clinical testing in epileptic dogs are related to the fact that seizure monitoring relies on reports by owners and that pharmacokinetic data of dogs tend to differ from those of humans. For many compounds, plasma elimination half-lives are rather short, rendering it difficult to obtain steady-state therapeutic concentration with feasible administration intervals. This also implies that failure to achieve seizure control in some of the clinical studies might be related to failure to maintain therapeutic plasma concentrations throughout the day, considering that not all studies carefully controlled plasma trough levels.

## Mechanisms of drug resistance in non-responder subgroups

Elucidating the factors and mechanisms that contribute to therapeutic failure is of interest for two main reasons. First, comparison with clinical data or data obtained from human tissue will further help to judge the validity of the models for drug-resistant epilepsy in human patients. Second, such knowledge may help to set up a series of simple *in vitro* screening models in order to evaluate whether a specific factor or mechanism affects a novel developmental compound.

A genetic influence on the drug response of kindled rats has been demonstrated by breeding studies with subgroups of responders and non-responders and by selection procedures in different inbred strains (Jeub *et al*., 2002). Analyses of the inhibitory impact of phenytoin on CA1 voltage-activated sodium and calcium currents indicated that kindling reduces the sensitivity of sodium channels. However, the study did not confirm any differences in the impact of phenytoin on

sodium or calcium currents between responders and non-responders.

Comparison between phenobarbital responders and non-responders, selected among rats with recurrent spontaneous seizures following an electrically-induced status epilepticus, revealed differences in neurodegeneration, $GABA_A$ receptor binding, and $GABA_A$ receptor subunit expression, thereby providing evidence that differences in the network and differences in target sensitivity may contribute to drug resistance in this model (Volk *et al*., 2006; Bethmann *et al*., 2008). Moreover, the fact that phenobarbital non-responder rats with spontaneous seizures exhibit a higher mean frequency (Loscher and Brandt, 2010) supports the concept that intrinsic severity of the disease plays a major role in the drug response (Rogawski and Johnson, 2008), in line with clinical observations suggesting that a high seizure density is one of the most important predictors of drug resistance.

Moreover, evidence exists that transporter over-expression might limit brain uptake and efficacy of antiepileptic drugs in kindled phenytoin non-responders, rats with phenobarbital-resistant spontaneous seizures in a post-status epilepticus model, as well as epileptic dogs (Potschka *et al*., 2004; Volk and Loscher, 2005; Brandt *et al*., 2006; Bartmann *et al*., 2010; Pekcec *et al*., 2009).

## Models with limited or poor drug response

### 6-Hz model

The 6-Hz model is the only acute model with seizure induction in naive animals that has been intensely discussed as a model of drug-resistant epilepsy (Barton *et al*., 2001). The model is based on electrical stimulation of mice *via* corneal electrodes with low-frequency pulses (6-Hz) for 3 seconds, which results in immobility, forelimb clonus, and behavioural automatisms, reflecting seizure characteristics of human limbic epilepsy. Following its first description about 60 years ago (Toman, 1951), the model has been neglected over many decades based on the fact that several antiepileptic drugs proved to be ineffective. However, the awareness that drug development over decades failed to deliver a major breakthrough in management of difficult-to-treat epilepsies let Steve White's group to revive the model. Further characterisation revealed that the drug responsiveness differs depending on the current intensity. At 32 mA, the sensitivity to phenytoin, lamotrigine, carbamazepine, and topiramate proved to be reduced with no efficacy at all or ED50 levels close to or even above TD50 levels (Barton *et al*., 2001). In contrast, phenobarbital, ethosuximide, valproic acid, felbamate, tiagabine, and levetiracetam displayed dose-dependent protection in a dosing range not associated with severe adverse effects (Barton *et al*., 2001). At a higher current intensity of 44 mA only, two antiepileptic drugs, levetiracetam and valproic acid, resulted in complete protection (Barton *et al*., 2001). Subsequent studies revealed efficacy of lacosamide using the 32 mA stimulation intensity, and retigabine, brivaracetam, and several test compounds at 32 and 44 mA (Loscher, 2011; Duncan and Kohn, 2005). Shannon and colleagues (Shannon *et al*., 2005) have also assessed the efficacy of several antiepileptic drugs in the 6-Hz model. However, conclusions are limited as the authors did not evaluate motor impairment, but only locomotor activity. Thus, conclusions are not directly comparable to those by Barton and colleagues (Barton *et al*., 2001).

Based on these findings, the 6-Hz seizure model has been implemented in the early phase of the NIH anticonvulsant drug screening program, such that drugs failing to demonstrate efficacy in the MES or PTZ test are tested a second time in the 6-Hz test. Considering available pharmacological data, the 6-Hz model is clearly characterised by a poor response to classic modulators of sodium channels which primarily target fast inactivation of voltage-gated sodium channels. Considering that the MES test might favour the selection of sodium channel modulators, the additional use of the 6-Hz model seems to be a good choice for early *in vivo* drug screening. However, it should be noted that as an acute model, it is unlikely to reflect chronic network, cellular, and molecular alterations that might contribute to therapeutic failure in drug-resistant epilepsy.

### Lamotrigine-resistant kindled rats

Considering the time-consuming nature of the kindling model with selection of non-responder subgroups, efforts have been made to develop alternate strategies based on the kindling paradigm. Robert Post's group (Postma *et al*., 2000) described the exposure of male Sprague Dawley rats to the antiepileptic drug lamotrigine during kindling acquisition phase which resulted in reduced drug responsiveness in fully kindled animals. These initial observations have been made using electrical kindling *via* a depth electrode in the amygdala. Later on, Steve White's group demonstrated that the same phenomenon is also observed with a chemical kindling approach, based on repeated administration of the convulsant pentylenetetrazole (Srivastava *et al*., 2004). Using this experimental approach with lamotrigine pretreatment during kindling development, reduced drug responsiveness was not only reported for lamotrigine but also for carbamazepine, phenytoin, and topiramate

(Srivastava *et al*., 2004; Srivastava and White, 2005; Srivastava and White, 2006; Srivastava *et al*., 2007). In contrast, the response of fully kindled rats to valproic acid, levetiracetam, felbamate, and retigabine was not affected by prior lamotrigine exposure (Srivastava *et al*., 2004; Srivastava and White, 2005; Srivastava and White, 2006; Srivastava *et al*., 2007). Considering that the concept of reduction in the drug response occurs in response to sub-chronic drug treatment, this might suggest that the approach is rather based on mechanisms of tolerance and cross-tolerance development than those of multidrug resistance. However, further evaluation of the cellular and molecular differences between rats, with and without lamotrigine exposure during kindling, is required to draw any conclusions.

**Post-status epilepticus model plus PTZ**

As outlined above, selection of non-responder subgroups constitutes a highly time-consuming procedure which limits the practibility of approaches for routine drug screening procedures. Even without previous selection of subgroups, drug testing in the chronic phase of post-status epilepticus models requires continuous and prolonged monitoring of spontaneous epileptic seizures. Therefore, efforts have been made to develop alternate strategies based on the use of seizure induction in post-status epilepticus models. Approaches aim to combine the advantages of a chronic model reflecting several network, cellular, and molecular alterations which characterise human epilepsy with the practibility of seizure models with electrical or chemical acute seizure induction.

Blanco and colleagues (Blanco *et al*., 2009) performed an acute maximal electroshock (MES) or acute pentylenetetrazole (PTZ) seizure test four weeks following a pilocarpine-induced status epilepticus. Whereas the efficacy of valproic acid, phenobarbital, and phenytoin in the MES test was not affected by previous status epilepticus, the response to all antiepileptic drugs was significantly reduced in the PTZ test in comparison to a control group without pilocarpine administration. Interestingly, the drug response in the PTZ test also proved to be reduced in another group of animals in which pilocarpine was administered, but it did not result in status epilepticus. Thus, the data indicate that the poor responsiveness might only partly be related to epileptogenesis-associated alterations. Therefore, further studies are necessary to evaluate the mechanisms which contribute to the poor response and address the question of whether the test situation reflects features of drug-resistant epilepsy in humans.

**Methylazoxymethanol (MAM) model**

Epilepsy associated with neuronal migration disorders in paediatric patients is often characterised by a poor drug response or mere drug refractoriness. Therefore, efforts have been made to develop animal models mimicking cortical dysplasias. In rats, treatment with methylazoxymethanol acetate (MAM) on gestational day 15 produces a neuronal migration disorder with histological features including cortical laminar disorganisation and ectopic neurons in subcortical white matter, cortical layer I and CA1 subfield of the hippocampus (Germano and Sperber, 1998).

In this model of transplacentally induced neuronal migration disorder, the efficacy of different antiepileptic drugs has been assessed (Smyth *et al*., 2002). Resistance to valproate was demonstrated in rats exposed to the convulsant kainic acid. Whereas valproate prolonged seizure latency in control animals, no such effect was observed in MAM-exposed animals. In addition to *in vivo* drug testing, the authors evaluated the response to phenobarbital, carbamazepine, valproate, ethosuximide, and lamotrigine in an *ex vivo* hippocampal slice preparation (Smyth *et al*., 2002). The compounds suppressed bursting induced by the potassium channel blocker 4-aminopyridine efficaciously in slices from control animals. However, in slices from MAM-exposed animals, bursting proved to be drug-resistant. Valproic acid, ethosuximide, and lamotrigine failed to affect the burst amplitude even at the highest concentration used.

Two years later, Serbanescu and colleagues (Serbanescu *et al*., 2004) suggested a variation of the model combining transplacental exposure to MAM with postnatal exposure to cholesterol biosynthesis inhibitor AY-9944, as a two-hit model which results in recurrent atypical absence seizures. The seizures were reported to be resistant to ethosuximide and valproate.

The models of drug-resistant epilepsy discussed are summarised in *table 1* and evidence for contributing factors is provided in *table 2*.

## Future perspectives

Decisions concerning inclusion of models in antiepileptic drug screening programs do not only have to consider the validity of the model but also its practicability as a routine screening procedure. The current state of knowledge regarding factors and mechanisms contributing to drug resistance of epilepsy strongly suggests that the most valid and important models will include chronic epilepsy models. For instance, the fact that a high seizure density is a poor prognostic factor might indicate

**Table 1.** Models of drug-resistant epilepsy.

| | | | | Selected non-responders | | |
|---|---|---|---|---|---|---|
| **Compound** | **6-Hz 32 mA/44mA** | **LTG-resistant kindled rat** | **MAM$^+$-exposed rats** | **Amygdala kindling** | **Post-SE models** | **Epileptic dogs** |
| Phenobarbital | | | | R* | R$^\#$ | R$^\#$ |
| Carbamazepine | R/R | R | R | R* | | |
| Phenytoin | R/R | R | | R$^\#$ | R* | |
| Valproate | S/S | S | R | R* | | |
| Ethosuximide | S/R | | R | | | |
| Lamotrigine | R/R | R | | R* | | |
| Topiramate | R/R | R | | R* | | |
| Felbamate | S/R | S | | R* | | R* |
| Vigabatrin | | | | R* | | |
| Tiagabine | S/R | | | | | |
| Gabapentin | | | | R* | | R* |
| Zonisamide | | | | | | R* |
| Levetiracetam | S/S | S | | S | R* | R* |
| Lacosamide | S/? | | | | | |
| Pregabalin | | | | | | R* |
| Retigabine | S/S | S | | | | |

R: resistance; S: sensitive, efficacy demonstrated; $^\#$used for selection; *resistance extends to this compound in subgroups of animals

that disease-associated alterations occurring as a consequence of repeated seizures contribute to therapeutic failure. These alterations will only be reflected by chronic models with spontaneous seizures or repeated seizure elicitation and not by models with chemical or electrical induction of acute seizures in naïve animals. Unfortunately, most of the chronic models, and in particular those with selection of responders and non-responders, are extremely elaborate and time-consuming. Therefore, the main question remains of how one can integrate more models of drug-resistant epilepsy into screening programs without letting time and costs for preclinical testing explode to unacceptable dimensions.

Further elucidation of drug-resistance mechanisms, including the role of neuroinflammation, network alterations, target alterations, efflux transporters, *etc.*, may provide the means for simple *in vitro* screening assays to study the effect of such mechanisms on the efficacy of novel test compounds. For instance, if drug resistance in a specific model is due to alterations in targets, one might evaluate binding or effects of a test compound using genetically engineered cells expressing an altered receptor or ion channel, instead of using the chronic epilepsy model. Problems in this context arise from the fact that drug resistance is considered multifactorial with various contributing factors and mechanisms. However, future increase in our knowledge of factors may guide us in implementing a battery of *in vitro* screening assays which can be integrated in early drug development. In this context, any progress in the comparison between experimental and clinical data using specimen dissected during epilepsy surgery from drug-resistant patients will also teach us further about the validity of the models used. An increased understanding of the molecular and cellular basis of drug resistance might also guide researchers and clinicians in the identification of biomarkers. Imaging tools might provide an option to predict the response in chronic epilepsy models, avoiding time-consuming selection procedures. In this context, we recently reported that a positron emission tomography (PET)

**Table 2.** Evidence for contributing factors in different models.

| | Model | | |
|---|---|---|---|
| **Mechanism or contributing factor** | **Kindling** | **Post-SE models** | **Epileptic dogs** |
| Intrinsic severity | ? | + | + |
| Network | ? | + | ? |
| Genetic | + | ? | (+) |
| Target alterations | + | + | ? |
| Pharmacokinetic (efflux transporter) | + | + | + |

?: not studied yet.

approach using a μPET scanner may help to identify responder and non-responder rats in a post-status epilepticus model (Bartmann *et al*., 2010). In this study, the impact of the P-glycoprotein modulator tariquidar on [$^{18}$F]MPPF brain penetration differed between phenobarbital responders and non-responders, reflecting enhanced efflux function of P-glycoprotein at the blood-brain barrier of the non-responder animals. PET imaging may also be an option to explore target alterations using tracers with a selected affinity for target sites with a specific subunit composition or for evaluating inflammatory reactions as a putative determinant of intrinsic severity. Provided that strategies are confirmed as reliable tools, one or two PET scans might therefore replace weeks spent in selecting responders and non-responders in the future. Moreover, as reported by Wolfgang Löscher's group, analysis of behaviour and cognition might also serve as a predictor of drug resistance (Gastens *et al*., 2008).

Considering optimisation of chronic models, acute *in vivo* screening seizure models will always be necessary for early lead selection procedures. Considering the fact that acute seizure models might preferentially select compounds with a specific mechanism of action, it may be helpful to replace early *in vivo* screening models from time to time.

In conclusion, several models of drug-resistant epilepsy have been described and characterised to a different extent. Future efforts are necessary to further explore the validity, the parallels to human drug-resistant epilepsy, the contributing factors, and mechanisms of resistance. Recent clinical studies that describe patient subgroups with epilepsy resistant to various antiepileptic drugs but responsive to selected antiepileptic drugs, further support the concept that drug resistance is not a homogenous phenomenon in different patients. The general belief that drug resistance is multifactorial (Schmidt and Loscher, 2009) also suggests that subgroups of patients are likely to exist in which different contributing factors and mechanisms predominate. Therefore, it is unlikely that a single animal model may reflect the clinical situation and also rather unlikely that a panacea exists to help overcome drug resistance in all patients. Thus, we will probably need to implement different models of drug-resistant epilepsy in drug development. These models might help to select compounds from which subgroups of patients with difficult-to-treat epilepsies might benefit. □

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