



## Review article

## Fit for purpose application of currently existing animal models in the discovery of novel epilepsy therapies

Wolfgang Löscher<sup>a,b,\*</sup><sup>a</sup> Department of Pharmacology, Toxicology, and Pharmacy, University of Veterinary Medicine Hannover, Hannover, Germany<sup>b</sup> Center for Systems Neuroscience, Hannover, Germany

## ARTICLE INFO

## Article history:

Received 6 October 2015

Received in revised form 6 March 2016

Accepted 30 May 2016

Available online 1 August 2016

## Keywords:

Epilepsy

Antiepileptic drugs

Anti-seizure drugs

Epileptogenesis

Antiepileptogenic drugs

Pharmacoresistance

Epilepsy-associated comorbidities

Biomarkers

Adverse drug effects

## ABSTRACT

Animal seizure and epilepsy models continue to play an important role in the early discovery of new therapies for the symptomatic treatment of epilepsy. Since 1937, with the discovery of phenytoin, almost all anti-seizure drugs (ASDs) have been identified by their effects in animal models, and millions of patients world-wide have benefited from the successful translation of animal data into the clinic. However, several unmet clinical needs remain, including resistance to ASDs in about 30% of patients with epilepsy, adverse effects of ASDs that can reduce quality of life, and the lack of treatments that can prevent development of epilepsy in patients at risk following brain injury. The aim of this review is to critically discuss the translational value of currently used animal models of seizures and epilepsy, particularly what animal models can tell us about epilepsy therapies in patients and which limitations exist. Principles of translational medicine will be used for this discussion. An essential requirement for translational medicine to improve success in drug development is the availability of animal models with high predictive validity for a therapeutic drug response. For this requirement, the model, by definition, does not need to be a perfect replication of the clinical condition, but it is important that the validation provided for a given model is fit for purpose. The present review should guide researchers in both academia and industry what can and cannot be expected from animal models in preclinical development of epilepsy therapies, which models are best suited for which purpose, and for which aspects suitable models are as yet not available. Overall further development is needed to improve and validate animal models for the diverse areas in epilepsy research where suitable fit for purpose models are urgently needed in the search for more effective treatments.

© 2016 Elsevier B.V. All rights reserved.

## Contents

1. Introduction .....	158
2. Validated animal models for antiepileptic drug discovery .....	159
2.1. The maximal electroshock seizure (MES) test .....	159
2.2. The subcutaneous (sc) pentylenetetrazole (PTZ) seizure test .....	159
2.3. The kindling model of temporal lobe epilepsy .....	161
2.4. Use of validated animal models for evaluating drug combinations .....	161
2.5. Other animal models used in preclinical ASD development .....	161

**Abbreviations:** AES, American Epilepsy Society; ASD, anti-seizure drug; ASP, Anticonvulsant Screening Program; BLA, basolateral amygdala; CC, convulsant current; CD, convulsive dose; BBB, blood-brain barrier; CNS, central nervous system; ED, effective dose; ETSP, Epilepsy Therapy Screening Program; FPI, fluid percussion injury; GAD, glutamic acid decarboxylase; GAERS, genetic absence epilepsy rat from Strasbourg; ILAE, International League Against Epilepsy; iPSC, induced pluripotent stem cell; MAM, methylazoxymethanol acetate; MES, maximal electroshock seizure; NIH, National Institutes of Health; NINDS, National Institute of Neurological Disorders and Stroke; NMDA, N-methyl-D-aspartate; PET, positron emission tomography; Pgp, P-glycoprotein; PTZ, pentylenetetrazole; SE, status epilepticus; SNR, substantia nigra pars reticulata; SWD, spike-wave discharge; TBI, traumatic brain injury; TLE, temporal lobe epilepsy; TMEV, Theiler's murine encephalomyelitis virus.

\* Correspondence address: Department of Pharmacology, Toxicology and Pharmacy, University of Veterinary Medicine Hannover, Bünteweg 17, D-30559 Hannover, Germany.

E-mail address: [wolfgang.loescher@tiho-hannover.de](mailto:wolfgang.loescher@tiho-hannover.de)

<http://dx.doi.org/10.1016/j.epilepsyres.2016.05.016>

0920-1211/© 2016 Elsevier B.V. All rights reserved.

3.	Animal models of drug-resistant seizures .....	162
3.1.	Models of seizures that are difficult to control with ASDs .....	164
3.1.1.	The 6-Hz psychomotor seizure model of partial epilepsy in mice .....	164
3.1.2.	The lamotrigine-resistant kindled rat .....	164
3.1.3.	The intrahippocampal kainate mouse model of therapy-resistant mesial TLE .....	165
3.2.	Models based on selection of nonresponders .....	165
3.2.1.	The phenytoin-resistant kindled rat .....	165
3.2.2.	The phenobarbital-resistant epileptic rat .....	167
3.2.3.	ASD-resistant epileptic dogs .....	170
3.3.	Models where the resistance develops over time (e.g., multiple-hit models) .....	170
3.4.	Models for discovery of novel drugs for refractory status epilepticus .....	171
4.	Changes of efficacy during chronic drug administration .....	171
5.	Prediction of potential serious adverse reactions and their mechanisms .....	171
6.	Inclusion of pharmacokinetic analyses .....	172
6.1.	Preclinical pharmacokinetics .....	172
6.2.	Estimation of effective plasma concentrations of new ASDs for first clinical trials .....	172
6.3.	Animal models of epilepsy-associated blood-brain barrier dysfunction and its effect on drug distribution .....	172
7.	Mechanism of action and drug target engagement .....	174
8.	Stratification .....	174
9.	Identification of biomarkers in animal models .....	174
10.	Models for discovery of antiepileptogenic or disease-modifying treatments .....	175
11.	Multicenter clinical trials of novel drugs in rodent models? .....	175
12.	Emerging models .....	176
12.1.	Models of pediatric epilepsies .....	176
12.2.	Genetic animal models of epilepsy .....	176
12.3.	Models for infection-induced epilepsy .....	176
12.4.	Models for studying epilepsy-associated cognitive deficits and psychiatric comorbidities .....	176
12.5.	The zebrafish model .....	176
12.6.	Patient-derived induced pluripotent stem cells to model epilepsies .....	177
13.	Potential pitfalls of animal models in antiepileptic drug discovery .....	177
13.1.	The “old models identify old drugs” argument .....	177
13.2.	Seizure types used as endpoints for drug testing in animal models .....	177
13.3.	Lack of uniform seizure definition .....	177
13.4.	The search for broad spectrum ASDs .....	178
13.5.	Drug potency vs. efficacy .....	178
13.6.	Mechanism of action of ASDs .....	178
13.7.	Gaps and shortcomings in study design .....	178
14.	Conclusions .....	179
	Acknowledgements .....	180
	References .....	180

## 1. Introduction

Despite large investments in drug development, the overall success rate of drugs during clinical development remains low (Denayer et al., 2014). This is particularly true for CNS drugs, for which the overall success rate is below 10% (Kola and Landis, 2004; Hay et al., 2014). One prominent explanation is flawed preclinical research, in which the use and outcome of animal models is pivotal to bridge the translational gap to the clinic (Kilkenny et al., 2010; Galanopoulou et al., 2012; Landis et al., 2012; Simonato et al., 2012). Therefore, the selection of validated and predictive animal models is essential to address the clinical question. This is also pivotal for development of anti-seizure drugs (ASDs; previously termed “antiepileptic drugs”) (Galanopoulou et al., 2012; Simonato et al., 2012; Löscher et al., 2013; Simonato et al., 2014). Preclinical research has facilitated the discovery of valuable drugs for the symptomatic treatment of epilepsy. Yet, despite these therapies, seizures are not adequately controlled in about a third of all affected individuals, and comorbidities still impose a major burden on quality of life (Löscher and Schmidt, 2011; Galanopoulou et al., 2012).

More than a decade ago, translational medicine was invented both as a catchword and as a novel approach to improve success in drug development and ameliorate the low-output syndrome from collapsing pipelines (Wehling, 2011). Translational medicine describes the conditions and prerequisites for the transfer of *in*

*vitro* (e.g. cell culture) and *in vivo* (e.g. animal model) results in human applications (Wehling, 2011). Thus, it is a still-emerging attempt to define and analyze the processes governing innovative developments from ‘bench to bedside’ (Wehling, 2011). An essential requirement for translational medicine to improve success in drug development is the availability of animal models with high predictive validity for a therapeutic drug response. For this requirement, the model, by definition, needs not to be a perfect replication of the clinical condition, but it is important that the validation provided for a given model is “fit for purpose” (Denayer et al., 2014; Wartha et al., 2014; Willner and Belzung, 2015). A major concern in many disease areas, including epilepsy, is the poor reproducibility of preclinical data for compounds progressing from academic laboratories to industrial development programs and, ultimately, to clinical trials (Ioannidis, 2005; Benatar, 2007; Fisher et al., 2009; Kimmelman and London, 2011; Mullard, 2011; Philip et al., 2009; Prinz et al., 2011; Galanopoulou et al., 2012; Perrin, 2014). Thus, guidelines that improve and standardize the design, reporting, and validation of data across preclinical therapy development are important, and such guidelines are currently developed for many preclinical research areas, including preclinical ASD studies in animal models (Kilkenny et al., 2010; Philip et al., 2009; Galanopoulou et al., 2012; Landis et al., 2012; Simonato et al., 2012; Perrin, 2014).

The aim of this review is to critically discuss the translational value of currently used animal models of seizures and epilepsy,

Download English Version:

<https://daneshyari.com/en/article/6015128>

Download Persian Version:

<https://daneshyari.com/article/6015128>

[Daneshyari.com](https://daneshyari.com)