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Review article

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

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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.

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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.

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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,

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