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Review

Pathogenesis and new candidate treatments for infantile spasms and early life epileptic encephalopathies: A view from preclinical studies

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ABSTRACT

Early onset and infantile epileptic encephalopathies (EIEEs) are usually associated with medically intractable or difficult to treat epileptic seizures and prominent cognitive, neurodevelopmental and behavioral consequences. EIEEs have numerous etiologies that contribute to the inter- and intra-syndromic phenotypic variability. Etiologies include structural and metabolic or genetic etiologies although a significant percentage is of unknown cause. The need to better understand their pathogenic mechanisms and identify better therapies has driven the development of animal models of EIEEs. Several rodent models of infantile spasms have emerged that recapitulate various aspects of the disease. The acute models manifest epileptic spasms after induction and include the NMDA rat model, the NMDA model with prior prenatal betamethasone or perinatal stress exposure, and the γ-butyrolactone induced spasms in a mouse model of Down syndrome. The chronic models include the tetrodotoxin rat model, the aristaless related homeobox X-linked (Arx) mouse models and the multiple-hit rat model of infantile spasms. We will discuss the main features and findings from these models on target mechanisms and emerging therapies. Genetic models have also provided interesting data on the pathogenesis of Dravet syndrome and proposed new therapies for testing. The genetic associations of many of the EIEEs have also been tested in rodent models as to their pathogenicity. Finally, several models have tested the impact of subclinical epileptiform discharges on brain function. The impact of these advances in animal modeling for therapy development will be discussed.

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Introduction

Epileptic encephalopathies are a spectrum of syndromes with prominent cognitive or behavioral impairments that are beyond what is expected for the underlying pathologies and to which the epileptic activity is thought to contribute significantly (Berg et al., 2010). These are particularly prevalent in the early stages of life. The poor outcomes in both epilepsy severity and neurodevelopmental and behavioral measures and the limited treatment options render these conditions a priority in epilepsy research. Clinical studies have offered insight about possible pathomechanisms. However, the inherent difficulties in human experimentation, the small numbers of patients included in studies on rare diseases, the heterogeneity of syndromes such as West syndrome and infantile spasms (IS), the limited availability of human tissue from the critical stages of early disease development, and the multiple confounders that plague the comparisons across human patients limit the power of such studies.

Over the last years, with the advances of animal modeling and discoveries into the genetics of epileptic encephalopathies, a number of animal models have emerged. These animal models were designed to recapitulate specific aspects of the phenotype of human epilepsy syndromes, recreate specific pathologies or etiologies (genetic or acquired), or test the relevance of signaling pathways on the pathogenesis or treatment response. As a result, there are several animal models of West syndrome or IS, models of Dravet syndrome or of other early onset or infantile epileptic encephalopathies (EIEEs), and animal studies attempting to decipher the contribution of epileptic spikes in the cognitive and neurodevelopmental outcomes. Because there are numerous EIEEs, here we have specifically selected those for which animal models have been created that address the phenotype or genetic causes. We will discuss how human and animal studies have contributed to our understanding on the pathophysiology of these selected epileptic encephalopathies and update on the progress in new therapies and therapeutic targets based on these animal studies.

Developmental equivalency between rodents and humans

Comparing development between rodents and humans is difficult due to the asynchronous maturation of different developmental milestones and processes that follow different tempos across species (reviewed in Akman et al., 2014, Avishai-Eliner et al., 2002, Galanopoulou and Moshe, 2011). In the endocrine literature, postnatal days (PN) 0–6 rats are considered neonatal, PN7–21 infantile, whereas juvenile rats are PN21–32 in females and PN7–35 in males. Puberty onset is around PN32–35 in females and PN35–45 in males whereas adulthood begins PN60. It is customary to consider a PN8–10 rat equivalent to a term human neonate, largely due to early studies showing that the rate of brain growth, at that age is similar to that observed in humans (Dobbing, 1974; Dobbing and Sands, 1979; Gottlieb et al., 1977). However, this presumed equivalency may not be absolute and should be used as a possible guideline. Wild type mice follow similar milestones, although trends for earlier maturation are observed compared to rats. For example, female mice reach puberty onset around PN29 and male mice around PN26–30, although differences across studies have been reported (Kumar and Boehm, 2013; Schneider, 2013). The genetic background may play a significant role in defining the developmental milestones, which therefore need to be confirmed for each rodent species, strain or genetically modified animal used (Clancy et al., 2001; Kumar and Boehm, 2013).

Although these accepted criteria have been helpful in the design of developmental studies, the correspondence is not absolute. While human neonates are born with eyes open, eye opening is usually between PN13–15 in rats and PN11 in mice. Humans learn to ambulate during the infantile stage. In contrast, rats learn to ambulate in the first two postnatal weeks, which as a result can be considered as the infantile stage of motor development in rats (Scantlebury et al., 2010). Cautionary interpretation of the developmental equivalence is therefore recommended across different developmental processes or events.

West syndrome and infantile spasms

West syndrome (Pellock et al., 2010; West, 1841) is an infantile epileptic encephalopathy characterized by at least two of the following features: (a) ictal events of flexion or extension spasms (IS) that usually appear in clusters, (b) interictal chaotic high amplitude and multifocally epileptic interictal background (hypsarrhythmia), and (c) intellectual or neurodevelopmental disabilities. Although IS often is used interchangeably with West syndrome, here we will use the term IS for the epileptic seizure and West syndrome for the clinical syndrome. Variations in presentation may occur, such as late-onset epileptic spasms or modified rather than classical hypsarrhythmia (Auvin et al., 2010; Dulac et al., 2010; Hrachovy et al., 1984). The treatment options are hormonal therapy (adrenocorticotropic hormone ACTH, glucocorticosteroids) or the GABA aminotransferase inhibitor vigabatrin (Go et al., 2012; Mackay et al., 2004; Pellock et al., 2010; Riikonen, 2014). The ketogenic diet has shown efficacy in refractory IS (Hong et al., 2010; Pires et al., 2013). Few patients may respond to certain antiepileptic drugs (valproate, topiramate, zonisamide) or vitamin B6 (Pellock et al., 2010; Riikonen, 2014).

The etiology of West syndrome is varied, with the majority (~60%) being due to structural–metabolic etiologies while the rest are either of unknown etiology or linked to genetic defects. The unknown etiology group is the infants in which no structural–metabolic or genetic etiology can be identified with the existing diagnostic tests. With the recent advances in methods for genetic diagnosis, an increasing number of associations of IS with genetic defects has been made, which is now estimated to encompass the 12% of infants with IS (EuroEPINOMICS-RES Consortium et al, 2014). The list of known genetic associations with IS is presented in Supplemental Table 1. Etiology influences treatment response. A known structural–metabolic underlying etiology diminishes significantly the chance of treatment response while the unknown etiology group bears the best prognosis (Mackay et al., 2004; Pellock et al., 2010; Riikonen, 2014). On the other hand, knowing the etiology may guide treatment selection, as is the case with tuberous sclerosis which is particularly responsive to vigabatrin (Curatolo et al., 2008; Nabbout, 2001; Pellock et al., 2010; Riikonen, 2014; Thiele, 2004).