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Modeling new therapies for infantile spasms

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Summary

Infantile spasms are the classical seizure type of West syndrome. Infantile spasms often herald a dismal prognosis, due to the high probability to evolve into intractable forms of epilepsies with significant cognitive deficits, especially if not adequately treated. The current therapies, high doses of adrenocorticotropic hormone, steroids or the GABA transaminase inhibitor vigabatrin, are often toxic and may not always be effective. The need to identify new therapies for spasms has led to the generation of a number of rodent models of infantile spasms. These include acute and chronic models of infantile spasms, with cryptogenic or symptomatic origin, many of which are based on specific etiologies.

In this review, we will summarize the clinical experience with treating infantile spasms, the main features of the new animal models of infantile spasms and discuss their utility in the preclinical development of new therapies for infantile spasms.

Keywords

Infantile spasms; models; ACTH; vigabatrin; mTOR; rapamycin

Introduction

Infantile spasms (IS) or West syndrome manifest as a triad of clusters of flexion or extension epileptic spasms, unique interictal EEG finding called hypsarrhythmia (high amplitude EEG with multifocal epileptiform discharges on a disorganized background) and mental retardation (Hrachovy and Frost 2003; West 1841). The onset of IS is typically during infancy and usually between 4–9 months of age. Ictal EEG demonstrates generalized high amplitude mixture of slow waves and epileptiform discharges, followed by sudden voltage attenuation called *electrodecremental response* (EDR). Evolution to other types of seizures, often intractable to medical therapies, occurs in the majority of IS patients. Spasms are distinguished into symptomatic, cryptogenic and rarely idiopathic IS. Symptomatic IS occur

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in infants with defined specific underlying condition and comprise the majority of cases (60–85%). In cryptogenic IS, an underlying neurological disorder causing IS is suspected but cannot be documented. Idiopathic IS are very rare.

Although the incidence is low (1 per 2000 – 6000 live births), IS can be devastating because of associated developmental regression and subsequent evolution to intractable epilepsy syndromes. Adrenocorticotropic hormone (ACTH) and the GABA transaminase inhibitor vigabatrin are currently the recommended therapies for IS but their efficacy is not universal, and decreases in patients with symptomatic IS. Furthermore, the prolonged administration of these drugs can lead to serious side effects (Mackay, et al. 2004). The need to develop appropriate animal models to test candidate novel therapies for IS has been recognized as a benchmark for Epilepsy research during the NINDS-sponsored conference *Curing Epilepsy 2007: Translating Discoveries into Therapies* (http://www.ninds.nih.gov/research/epilepsyweb/2007_benchmarks.htm). Resolving this problem has been a great challenge and using for their effort such poetic metaphors like “Golden Fleece” quest (Baram 2003) could hardly be called a hyperbole. Nevertheless a number of promising animal models have emerged lately, based upon specific etiologies and pathologies that lead to early life epilepsies with IS. In this article, we i) will discuss what the clinical experience teaches us about the pharmacosensitivity of IS, ii) will offer you a brief overview of the current animal models of IS and iii) discuss their role in the discovery of new therapies for IS.

Treating IS: What can we learn from the clinic?

Current therapies for IS and their success

Given the chronic and evolving nature of the IS syndrome, the American Academy of Neurology (AAN) and Child Neurology Society committee that created the practice parameters for the medical management of IS utilized the following outcome measures (Mackay, et al. 2004):

a. *short-term outcome*: complete cessation of spasms, resolution of hypsarrhythmia, normalization of EEG, likelihood of relapse after the initial treatment.

b. *long-term outcome*: nonepileptiform EEG, seizure freedom, normal neurodevelopmental outcome.

The first line therapies for IS remain ACTH, and vigabatrin, which is preferred for patients with TSC(Kivity, et al. 2004) (Mackay, et al. 2004). At present, there are no standardized uniformly accepted protocols for their administration. Kossoff et al. (Kossoff, et al. 2009) have recently reported that very high doses of oral prednisolone are a less expensive alternative to ACTH. However, a number of patients may not respond to or cannot receive the first-line treatments due to concerns for adverse side effects. In such cases, compounds like clonazepam, gammaglobulin, ketogenic diet, liposteroids, nitrazepam, pyridoxine, thyrotropin-releasing hormone, topiramate, valproic acid, zonisamide have been used. However, there is insufficient evidence to recommend them as therapies for IS.

The efficacy of therapies varies, largely due to the heterogeneity of underlying pathologies and the variable treatment protocols and outcome measures. The underlying *etiology* and pathology contributing to IS (Table 1) influences their short-term response to treatment, as is best exemplified by the excellent efficacy of vigabatrin in IS patients with tuberous sclerosis complex (TSC) (Chiron, et al. 1997) and the poorer response of symptomatic IS to first-line therapies, compared to cryptogenic IS (Karvelas, et al. 2009;Mackay, et al. 2004). This creates a treatment gap, as the majority of IS patients belong into the symptomatic and therefore more refractory group. However, it emphasizes the need to consider separately the

pharmacosensitivity of cryptogenic/idiopathic IS from those occurring in patients with specific genetic abnormalities or lesions that may alter the functionality of neuronal networks involved in the control of IS.

Current therapies for IS: treating a symptom or the disease?

The dramatic appearance of IS and hypsarrhythmia and their status as the signature diagnostic elements of these catastrophic epileptic encephalopathies have absorbed the focus of treating epileptologists upon them. However, are the currently effective IS treatments disease-modifying or are we simply treating a symptom?

Effective therapies, like ACTH or vigabatrin, do not suppress IS acutely but rather gradually over the course of 2–4 weeks. Baram's studies report a median lag of two days between onset of ACTH therapy and observed suppression of IS and hypsarrhythmia, proposing that transcriptional and plastic changes are important for its therapeutic effects (Baram 2007). IS suppression improves long-term neurodevelopmental or seizure outcomes but only if effected at early stages of the disease (Kivity, et al. 2004;Lombroso 1983; Lux, et al. 2005). On the other hand, despite the initial response to therapies, at least 40% of responders eventually relapse suggesting that epileptogenesis has not been inhibited. Residual cognitive and neurological deficits and symptoms may still remain, despite the resolution of IS, probably due to independent disease processes that were not affected by the treatments. To further understand the pathogenetic mechanisms underlying IS syndromes and design better disease modifying and antiepileptogenic therapies, a number of rodent models of IS have been created and will be reviewed in the following sections.

Modeling new therapies: What can we learn from rodent models of IS?

Current rodent models of IS: an overview

The currently available models of IS include both acute and chronic models of IS, as summarized in Table 2 and have been critically reviewed recently by Stafstrom (Stafstrom 2009). Three more models have been since published, including the *aristaless-related homeobox X-linked* (ARX) knockout (Marsh, et al. 2009) and knockin (Price, et al. 2009) mouse models and the multiple-hit rat model of symptomatic IS (Scantlebury, et al. 2010).

Many of these models recapitulate specific etiopathogenic processes implicated in IS, that test the effects of stress (corticotropin-releasing hormone (CRH), betamethasone/NMDA) or specific gene mutations (ARX models). However, often such attempts produce unexpected results. The hypothesis that CRH underlies the generation of spasms has been appealing, offering a plausible explanation for the efficacy of ACTH in IS; however CRH-injected rats manifest limbic seizures and not spasms, which do not respond to ACTH. The betamethasone/NMDA model demonstrated that prenatal stressors may increase the sensitivity of spasms to ACTH. Yet emprosthotonic spasms in this model are only acutely induced by NMDA, failing to recapitulate the chronic and evolving nature of the IS syndrome. Different manipulations of the ARX gene have resulted in spasms; yet not always exhibiting their age-specificity of IS.

Spasm-like seizures have been induced by specific neuromodulatory treatments either in rats of normal genetic substrate (NMDA and tetrodotoxin (TTX) models) or in mice with specific genetic alterations predisposing to IS (γ-butyrolactone (GBL) treatment of TS65Dn mice, a Down syndrome model). Among these, only the TTX model is a chronic model; yet the spasms appear at older ages. The heterogeneity of the above models will be invaluable in deciphering how specific genetic or pathological substrates interfere with the expression and pharmacosensitivity of IS. Currently, most of the available pharmacosensitivity data are from the acute models and are not always typical of the pharmacosensitivity of the human IS

syndrome (Table 2). Moreover, most of the tested drugs have been administered prior to the induction of spasms, when it is well known that seizures per se may alter brain biology and the responsiveness of developing pups to drugs. To translate therefore such drug screening findings into clinically relevant data it will be imperative to deliver these compounds after the onset of spasms.

The multiple-hit model of symptomatic IS

The multiple-hit model of symptomatic IS (Scantlebury, et al. 2010) intentionally recreates a combination of cortical and subcortical lesions, thought to underlie human symptomatic IS syndrome. Specifically, right intracerebral injections of cytotoxic (doxorubicin) and pro-inflammatory compounds that also damage subcortical pathways (lipopolysaccharide) are performed at P3. Clusters of spasms appear between P4–P13, a developmental period equivalent to the human infantile period, in regards to motor milestones. The serotonin depleting agent p-chlorophenylalanine (injected at P5) recreates an environment of abnormal serotonin metabolism, thought to underlie many cases of IS syndrome. The multiple hit model recapitulates key features of the human IS syndrome, including age-specific expression of clusters of epileptic spasms, neurodevelopmental regression, evolution to other seizure types, as well as learning, memory and sociability deficits following the resolution of spasms.

To simulate the clinical practice, drugs were administered after the onset of spasms (P4) and continuously throughout the duration of observed spasms. In this model spasms are ACTH-refractory, consistent with the lower efficacy of ACTH in patients with symptomatic IS. However, they do respond to vigabatrin, albeit transiently. As effective therapies become available, the evolving phenotype of this model will provide an excellent setting to test efficacies in early vs late initiation of therapies, relapse rates, antiepileptogenicic actions and effects on neurodevelopment and cognition.

Future directions: can etiologies of IS offer clues for novel therapies?

The existence of treatments, like ACTH or vigabatrin, that can suppress spasms in a majority of patients with IS, regardless of their primary cause, indicates that common pathways controlling the expression of spasms may exist. Therefore, comparisons across models of IS is likely to identify these converging control mechanisms and design treatments with almost universal appeal. Choosing a candidate target for therapeutic interventions amidst the Daedalus of interacting pathways that are involved in the pathogenesis of spasms can be a challenge equivalent to the task of Theseus in the labyrinth of Minotaur. However, first glimpses at overlapping mechanisms reveal promising clues and possible “common pathways” that may potentially lead towards the discovery of more universally effective therapies for IS.

Mammalian target of rapamycin (mTOR) dysregulation and spasms

A leading cause of IS is TSC, a genetic disease linked to mutations in either hamartin (TSC1) or tuberin (TSC2). Overall, 10–30% of TSC patients develop IS in the existing cohorts, whereas 20–25% of patients with IS have TSC. This is an impressively high incidence rate for a single disease and presents a strong argument in favor of a potential causative role of the genetic deficits underlying TSC in the expression of IS. However, the incomplete penetrance of the IS phenotype in TSC patients and the lack of observed IS in animal models of TSC emphasize that IS pathogenesis, even in TSC patients, may be a multistep process, with several safety checkpoints.

Apart from TSC, the prototypic “*TORopathy*” (a spectrum of diseases linked to dysregulation of the *mammalian Target Of Rapamycin* pathway) manifest with cortical

dyslamination, cytomegaly and seizures (Crino 2009). These include sporadic causes of IS, like focal cortical dysplasias type II and hemimegalencephaly (HME) (Table 1). Mutations at either TSC1 or TSC2 genes prevent their association into a heterodimer that normally inhibits the activation of the mTOR complex TORC1. As a result of disinhibited TORC1 activity, key functions in the cellular biology are dysregulated, contributing to the formation of malformed and giant or balloon cells characteristic of tubers (Crino 2009). Interestingly, most of the known acquired pathological conditions associated with seizures, including IS, can modify the activity of mTOR pathway: hypoxia, stress, endocrine and metabolic disorders, inflammation. Inhibitors of mTOR, like rapamycin, have shown anticonvulsant actions in animal models of TSC or cortical dysplasias, improving survival and developmental outcome (Wong 2009). However, none of these models (TSC or PTEN knockouts) expresses IS, leaving the question open as to whether mTOR inhibition may be beneficial for IS. In preliminary studies, rapamycin has been shown to have beneficial effects in the multiple-hit model of IS (Raffo, et al. 2009). However, the central role of mTOR in cellular growth and differentiation renders it important to test not only its therapeutic efficacy on spasms but also its safety profile, especially if given during the sensitive infantile period.

GABA signaling and IS

The association between GABA signaling and IS has been building up from a variety of sources. Perhaps the strongest impetus to identify such a link has been the therapeutic effects of the GABA transaminase inhibitor vigabatrin, as described previously. Pathology specimens indicate decreased expression of $GABA_A$ receptor subunits conditions associated with IS (Crino 2009)and altered neurosteroid sensitivity of $GABA_A$ receptors (Jansen, et al. 2008). However, only rare associations of IS with mutations of either $GABA_A$ receptors or genes that disrupt the migration of GABAergic interneurons (i.e. ARX interneuronopathies) exist. Among the animal models of IS, vigabatrin has shown efficacy in the GBL/Ts65Dn model as well as in the multiple-hit model of spasms, suggesting that a GABA neurotransmission deficit may be a more widespread feature of a variety of conditions associated with IS. Further studies need to optimize the efficacy of GABAergic or GABA-enhancing drugs, even in the early stages of IS syndrome.

Conclusions

There is no doubt that the explosion in the availability of new models of IS promises to continue delivering new tools to combat this deleterious condition. We seem to be at a crossroads where both acute and chronic models may offer insight into new pathogenetic mechanisms for spasms and identify novel etiology-specific or universal targets for therapies. Most importantly, we can now test specific questions, like drug efficacies during the early vs late stages of the syndrome (chronic models), effects on long-term endpoints, including evolution to other seizures, development of cognitive and neurodevelopmental deficits (chronic models). Such investigations will be essential in the preclinical development of new therapies, given the known increased vulnerability of the developing brain to neuromodulatory drugs. However it is inevitable that we may be soon faced with a wealth of new data from these models on mechanisms, pharmacosensitivity and outcomes, which may not always be in agreement. To correctly interpret them and offer them to the clinicians for further clinical investigations, it will be important to generate standardized protocols and requirements for the preclinical development of novel candidate therapies for IS and similar types of early life epilepsies. Hopefully, such guidelines and advances will accelerate the progress and ensure the safe translation of these discoveries to the bedside.

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Table 1

Common etiologies of IS

Etiology of IS	Incidence	Examples
Symptomatic IS	**63–87%**	
Hypoxic-ischemic encephalopathy		
Tuberous sclerosis complex		(TSC1, TSC2 mutations)
Cortical or congenital malformations		Focal cortical dysplasias I, Focal cortical dysplasias II, Polymicrogyria, Hemimegalencephaly (i.e. pho*sphatase and tensin homolog* (PTEN) mutations), Lissencephaly (i.e. ARX mutations), Pachygyria, Corpus Callosum agenesis, Periventricular nodular heterotopia, Subcortical band heterotopia
Inborn errors of metabolism		Disorders of carbohydrate, lipid or amino acid metabolism, Storage diseases, Metallopathies Pyridoxine dependency
Post-traumatic		Birth injury
Infectious		Encephalitis, meningitis
Vascular		Strokes, hemorrhages
Chromosomal abnormalities, other Genetic causes		Trisomy 21, Cyclin D kinase like 5 (CDKL5) mutations, UBE3A mutations
Mitochondrial disorders		
Degenerative disorders		Alper’s syndrome
Neoplastic		
Toxic		
Cryptogenic IS	**13–37%**	
Idiopathic IS	rare	

Table 2

Overview of the current rodent models of infantile spasms

Model	Method	Seizure Phenotype	Age of seizures	Cognitive / behavioral deficits	Type of Model		Pharmacosensitivity	
					Course	Type of IS	Drug	Effect
Rat models								
CRH/stress [Baram and Schultz 1991]	CRH i.c.v.	Limbic seizures (jaw myoclonus, tonic extension of 1–2 limbs, leg clonus)	P5–13	Not reported	Acute	Cryptogenic	***ACTH$_{1–39}$ Pre-treatment (acute):*** 20–60min before CRH	No effect (latency, duration of seizures)
							Phenytoin Pre-treatment (acute): 45min before CRH, P5	Eliminates seizures
N-methyl-D-aspartate model (NMDA) [Kabova, et al. 1999; Kubova and Mares 2009; Mares and Velisek 1992]	NMDA i.p.	Emprosthotonus (clusters); tail twisting;	P7–25	Deficits in spatial learning (adulthood) Impaired performance in open field activity, rotarod, elevated plus maze (P21–25)	Acute	Cryptogenic	***ACTH$_{1–39}$ Pre-treatment (acute):*** 30–60 min before NMDA	No effect (latency to seizures)
							ACTH$_{1–24}$ Pre-treatment (acute): 30–60 min before NMDA	
							Pyridoxine Pre-treatment (P12, P18)	Decreases incidence of emprosthotonus; induces epileptiform activity
							Sodium valproate Pre-treatment (P18)	Decreases incidence of emprosthotonus
							Hydrocortisone Pre-treatment (P12)	Increases incidence of emprosthotonus
							Clonazepam Pre-treatment	No effect on emprosthotonus
							Vigabatrin Pre-treatment	Decreases incidence of emprosthotonus (P12)
Betamethasone/ NMDA [Velisek, et al. 2007)]	Betamethasone i.p. (G15), NMDA i.p. (P15)	Tail twisting, arching, flexor spasms	P15	Not reported	Acute	Cryptogenic	***ACTH$_{1–39}$ Pre-treatment (acute):*** 30–60 min before NMDA	Increases latency to onset of spasms
Tetrodotoxin (TTX) [Lee, et al. 2008)]	Intrahippocampal infusion of TTX, 28 days, starting on P10–12	Spasms later replaced by limbic seizures	Onset at P21	Not reported	Chronic	Cryptogenic, symptomatic	No data	
Multiple-hit model [Scantlebury, et al. 2010)]	Doxorubicin and lipopolysaccharide (P3, right intracerebral);p-chlorophenylalanine (P5, i.p.)	Spasms in clusters	P4–P13	Regression, impaired learning / sociability	Chronic	Symptomatic	***ACTH$_{1–24}$ Post-Treatment (chronic)***	No effect on frequency of spasms
		Evolution to other seizures	After P9				***Vigabatrin Post-Treatment (chronic)***	Transient decrease in spasms frequency

Model	Method	Seizure Phenotype	Age of seizures	Cognitive / behavioral deficits	Type of Model		Pharmacosensitivity	
					Course	Type of IS	Drug	Effect
Mouse models								
***ARX* knockout** [Marsh, et al. 2009]	Targeted deletion of ARX gene from cortical interneurons	Limbic seizures	P14–17	Not reported	Chronic	Genetic, symptomatic	No data	
		Spasms and limbic	Adults					
***ARX* knockin** [Price, et al. 2009]	Expansion of first polyalanine tract repeat of ARX gene	Spasm myoclonus	P7–20	Low anxiety, impaired learning, sociability	Chronic	Genetic, symptomatic	No data	
		Other seizures	3.5–10 weeks					
Down syndrome with γ-butyrolactone (GBL) [Cortez, et al. 2009)]	Ts65Dn mouse, GBL i.p.	Clusters of extensor spasms	1 week – 2 months	Not reported. Ts65Dn model: neurodevelopmental, memory, learning deficits	Acute	Symptomatic	***Vigabatrin, CGP 35348, Valproic acid, Ethosuximide***	Reduce EDR duration
							***ACTH*$_{1–24}$** 15 or 30 min before or 2min after GBL	
							ACTH*$_{1–39}$ *porcine: 30min before GBL	No effect on duration of EDR
							5-hydroxytryptophan, Baclofen	Increase in EDR duration