INFANTILE SPASMS: A CRITICAL REVIEW OF EMERGING ANIMAL MODELS

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Infantile spasms is a developmental epilepsy syndrome with unique clinical and EEG features, a specific pattern of pharmacological responsiveness, and poor outcome in terms of cognition and epilepsy. Despite the devastating nature of infantile spasms, little is known about its pathogenesis. Until recently, there has been no animal model available to investigate the pathophysiology of the syndrome or to generate and test novel therapies. Now, several promising animal models have emerged, spanning the etiological spectrum from genetic causes (e.g., Down syndrome or Aristaless-related homeobox [ARX] mutation) to acquired causes (e.g., endogenous and exogenous toxins or stress hormones with convulsant activity or blockade of neural activity). These new models are discussed in this review, with emphasis on the insights each can provide for understanding, treating, and preventing infantile spasms.

Infantile spasms is a severe developmental epilepsy with several unique clinical features (1,2). The syndrome begins during a specific window in the first year of life, commonly between 3 and 10 months of age, and has numerous etiologies, with more than 200 already described (3). These etiologies span a wide range of acquired and congenital causes and can be categorized as symptomatic (cause known) or cryptogenic (no obvious brain disorder; cause unknown). Importantly, infantile spasms typically begins weeks to months following an initiating injury; during this latent period, neural circuits become epileptogenic. It is not known how or why the infant brain develops infantile spasms. Infantile spasms is associated with specific and unique EEG findings, consisting of interictal hypsarrhythmia (chaotic, high-voltage slow waves intermixed with multifocal spikes) and an ictal generalized slow waves, followed by generalized voltage attenuation. Unfortunately, most conventional anticonvulsants are ineffective for infantile spasms; rather, the spasms may respond to treatments such as glucocorticoids, adrenocorticotropic hormone (ACTH), and vigabatrin. The outcome of infantile spasms is usually poor, evolving into other seizure types after the first year of life; neurological development is often abnormal, especially when delay is noted prior to the onset of spasms and the spasms do not disappear with therapy.

The lack of a detailed pathophysiological explanation for many aspects of infantile spasms has been related to the frustrating absence of an animal model to investigate mechanisms (4). In fact, such a model has been considered to be a "holy grail" of epilepsy research (5). A valid animal model would not only enhance the understanding of disease pathophysiology but also encourage the development of new diagnostic approaches, permit testing of novel treatments, and help to devise strategies to reduce the cognitive and epileptic consequences. Ideal, sufficient, and minimal criteria for an animal model of infantile spasms have been proposed (6,7). Optimally, the model would mimic the human disorder, including features of: 1) the occurrence of spasm-type spontaneous seizures (flexor, extensor, or mixed flexor/extensor) in response to various etiologies and brain insults, 2) a specific developmental window during which spasm-type seizures begin, 3) a timing of spasms in relation to the sleep–wake cycle (especially during sleep–wake transitions), and 4) the presence of spasms in clusters. The validity of an experimental model would be strengthened if the interictal and ictal EEG findings resemble those in the human syndrome.

An ideal model would include an anticonvulsant response, with a pattern of efficacy that could be replicated in babies. For example, the therapeutic effect of ACTH for infantile spasms is not immediate, typically taking 1 to 3 days to occur (8). This outcome suggests that ACTH may not act directly as an anticonvulsant, but instead may act via a mechanism that obviously requires a longer time course. Furthermore, the ACTH effect on spasms and associated EEG abnormalities is usually all or none. Therefore, ACTH functions differently than conventional anticonvulsant drugs, by both suppressing the seizures and modifying the natural history of the disorder (9). Finally, a demonstration of cognitive stagnation or regression would strengthen a model's correlation with the human disorder.

Although no animal model can be expected to reproduce every aspect of the human syndrome faithfully, relevant and testable hypotheses, nonetheless, can be generated from

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experimental models. A model without ideal face validity may nevertheless provide valuable information about disease mechanism. For example, an animal model with mutation of a specific gene causative of infantile spasms in human infants or an animal model with cortical dysplpasia, such as tubers, but without spasm-type seizures, still could be informative (7).

The challenges to the development of an animal model include the interspecies differences in brain development; these differences are confounded by the lack of a developmental biomarker that can conclusively compare brains of humans and animals and by the differential expression of seizure phenotype and EEG in different species. Rather than try to mimic the human syndrome in every detail, a more productive approach is to use animal models to understand the neurobiological principles of infantile spasms, by asking specific questions on each model. This article reviews several new infantile spasms models (see Table 1) that are injecting excitement into a field that has long been stagnant.

Corticotropin-Releasing Hormone (CRH) Model—The Role of Stress in the Developing Brain

Investigations, spanning almost 20 years, have probed the role that stress plays in increasing brain excitability and provoking infantile spasms. This idea resulted from the observation that the stress hormones, ACTH and glucocorticoids, ameliorate infantile spasms (10). Acknowledgment of the diverse and multiple etiologies led to the hypothesis that stress in the developing brain is a common factor in the development of infantile spasms (10–12). Stress increases release of an endogenous hormone, corticotropin-releasing hormone (CRH). Intraperitoneal or intracerebroventricular administration of CRH, during the second week of life in rats, causes severe seizures (13). Much higher doses of exogenous CRH are required to produce seizures at older ages. Therefore, excessive release of endogenous CRH acts as an endogenous convulsant in the developing brain. The semiology of seizures induced by exogenous CRH more closely resembles limbic seizures than spasms, which is not surprising, since CRH acts on receptors located in the amygdala and hippocampus (14). Acute ACTH treatment does not influence seizures induced by exogenous CRH, which also is not unexpected, because ACTH reduces CRH expression in the same time frame (i.e., 1–2 days) as needed for ACTH to have an effect on infantile spasms in humans. These observations suggest that ACTH acts to repress infantile spasms by suppressing the level of endogenous CRH (15,16).

Stress receptors are located in areas of the brain known to be involved in seizure generation as well as in cognition and emotional function. While CRH is necessary for neuronal excitability in the normal developing brain, excess CRH, as initiated by multiple stressors, results in seizures and dendritic and neuronal structural abnormalities, as well as in long-term cognitive, learning, and memory deficits (10,17). The latter findings are intriguing in view of the cognitive deficits associated with infantile spasms. In addition, because this model involves nondamaged brain, any cognitive deficits that are found will likely be a result of the spasms themselves, offering a window into the responsible mechanisms.

EEG findings for CRH seizures differ from the hypsarrhythmia and electrodecrement seen in human infantile spasms. Instead, rhythmic sharp activity is typically recorded, as occurs with limbic seizures (13). Likewise, no spontaneous seizures have been observed after CRH administration. Nevertheless, the CRH model provides pivotal insight into the age-specific involvement of stress in seizure susceptibility and enhances the understanding of ACTH and glucocorticoid actions in brain development and infantile spasms.

NMDA Model—Cryptogenic Infantile Spasms

Intraperitoneal administration of the glutamate receptor agonist NMDA to rat pups between postnatal days (P) 12 and 18 causes a specific type of seizure, known as emprosthotonus, which consists of hyperflexion and tonic spasms of the entire body, with the loss of the righting reflex (18,19). The spasms occur in clusters, as in humans with infantile spasms. The accompanying ictal EEG shows generalized amplitude reduction, somewhat similar to electrodecremental responses in humans. Interictally, the EEG in NMDA-treated rats is variable and nonspecific, sometimes showing large-amplitude, nonsynchronous waves that could represent rat hypsarrhythmia. However, classic ictal and interictal EEG patterns, seen in other infantile spasms models, are not observed in single-channel EEG recordings from NMDA-treated rats. Cognitive deficits in the form of spatial learning and memory impairment appear in adult rats, following NMDA-induced seizures during infancy (20). NMDA-induced spasms are not sensitive to acute pretreatment with glucocorticoids (19).

In a recent modification of this model, it was hypothesized that prenatal alteration of the hypothalamic–pituitary–adrenal (HPA) axis by glucocorticoids would mimic a stressor that might predispose the immature brain to infantile spasms (21). The glucocorticoid, betamethasone, was administered to pregnant rats on gestational day 15. This treatment sensitized the fetal brain HPA axis to postnatal NMDA effects (22,23). When pups, previously exposed to prenatal betamethasone, were given NMDA on P15, they had shorter latencies to several ictal stages, including tail twisting and flexor spasms, compared with pups that did not receive prenatal betamethasone. Furthermore, spasms in betamethasone-pretreated rats were somewhat modified by acute ACTH (administered intraperitoneally 30–60 minutes prior to NMDA), with increased latencies to tail

twisting, arching, and flexor spasm seizures when NMDA was injected on P15.

The betamethasone/NMDA model satisfies some of the infantile spasms criteria for seizure semiology: age specificity, EEG changes, and cognitive deficits. Spontaneous seizures are not seen. The ACTH issue is complex, with human infantile spasms studies and animal experiments showing no acute anticonvulsant effect of ACTH (8,24,25). These data support the notion that ACTH may act through two separate mechanisms: first, by releasing glucocorticoids from the rat or human adrenal gland, with a resultant anticonvulsant effect; and second, via penetration of ACTH into the brain, where it activates melanocortin receptors and suppresses the expression of CRH (16). These latter effects require at least several hours to days. Spasms in this model are sensitive to another anticonvulsant, vigabatrin, which is often effective in infantile spasms (L. Velisek, MD, PhD, personal communication, December 2008). The model also has been used to explore brain regions involved in spasms generation, and [^{14}C]2-deoxyglucose imaging identified the limbic system, hypothalamus, and brainstem as sites activated during NMDA-induced seizures (21). Owing to the lack of brain structural damage or lesions in the betamethasone/NMDA model, these investigators proposed that the model resembles cryptogenic infantile spasms (21). The injection of two agents, betamethasone and NMDA, at different time points, raises the caveat that functional neural deficits could exist.

Tetrodotoxin (TTX) Model—Hyperexcitability Provoked by Decrease of Neuronal Activity

Chronic suppression of neural activity during specific developmental windows results in hyperexcitability and even seizures. Intrahippocampal infusion of the sodium channel blocker, tetrodotoxin (TTX), beginning on P10 to 12, caused recurrent seizures in rat pups, consisting of brief spasm-like seizures (26,27). Those seizures were associated with short epochs of fast activity on EEG.

A detailed analysis of this model was published recently using more extensive EEG recording montages (28). EEG data were analyzed from rat pups that were chronically implanted with osmotic minipumps in the neocortex or hippocampus. TTX diffused from the minipumps at a constant rate, locally blocking neuronal activity. Clinical and electrographic features were very reminiscent of human infantile spasms. When TTX was injected for 28 days, beginning on P10, there was an initial depression of neuronal activity, but later, EEG spikes developed over both hemispheres. Starting at about P21, approximately one-third of TTX-treated rats developed seizures consisting of flexor or extensor spasms. The spasms occurred singly or in clusters. The interictal EEG pattern had high-voltage, chaotic waves and multispikes, especially during non-REM sleep, which is very reminiscent of human hypsarrhythmia. The ictal EEG pattern included a generalized slow wave, followed by voltage attenuation (electrodecrement), then low-voltage fast activity, again, similar to the human ictal EEG. These EEG abnormalities continued after removal of the TTX pump. The spasms abated over time and were replaced by prolonged limbic seizures, consistent with the evolution of infantile spasms seizure semiology. Additional electrophysiological characterization, including power spectrum analysis, showed marked similarities in frequency components between rat pups and human infants. Furthermore, the latency-to-spasm onset, correlation with the sleep–wake cycle, and demonstration of focal cortical hypometabolism resemble the human condition. This model provides the first convincing evidence for hypsarrhythmia and electrodecrement in an animal model.

The TTX model emphasizes the fact that normal brain development requires normal neuronal activity and suggests that blocking neuronal activity may somehow result in infantile spasms. Obviously, there is no human disease correlate of chronic TTX infusion. Nevertheless, the exquisite EEG similarities between the TTX model in rats and infantile spasms in humans establish its credence. The TTX model, nonetheless, needs further study of age correlation, since spasms in this model occur somewhat later developmentally than in humans (12). Other aspects of the model that warrant elucidation include mechanisms governing the spontaneous remission of spasms, transition to other seizure types, treatment responsiveness, and the development of neuropathology, as well as behavioral and electrophysiological changes. All of these studies are underway (C. Lee, PhD, personal communication, December 2008). In conclusion, the TTX model, with its unique ictal and interictal EEG patterns, temporal features of seizures, and plausible mechanism, is one of the most promising developments in the study of the pathophysiology of infantile spasms (29).

Multiple-Hit Model—Cortical and Subcortical Lesions Mimicking Symptomatic Infantile Spasms

One hypothesis for infantile spasms pathogenesis is that the syndrome results from an interaction between cortical and subcortical or brainstem pathologies (30). Normal communication between these brain regions would be altered by such damage, leading to infantile spasms. Based on that hypothesis, a multiple-hit model was developed with concurrent, severe damage to cortical and subcortical structures (31). On P3, doxorubicin is injected into the cerebral ventricles and lipopolysaccharide is administered intracerebrally. These compounds create focal neuronal and white matter injuries, with inflammation in multiple brain regions. Doxorubicin is an anthracycline chemotherapeutic agent that causes neuronal damage

via oxidative stress (32). Lipopolysaccharide, a toxin released by Gram-negative bacteria, causes white matter damage accompanied by activation of inflammatory cells (33). Then, on P5, p-chlorophenylalanine is delivered intraperitoneally to deplete brain serotonin by blocking its synthetic enzyme, tryptophan hydroxylase (34); serotonin is generally known to lessen brain excitability (35). Animals receiving this triple-hit treatment developed recurrent seizures from P7 until P12, which consisted of flexor and extensor spasms in clusters (31). The EEG accompanying the spasms demonstrated electrodecremental responses. After P11, the spasms evolved into limbic seizures, with wild running behavior analogous to human infants undergoing transition from infantile spasms to other seizure types. On cognitive testing, neurodevelopmental deficits affecting several aspects of socialization and learning were found in rat pups with spasms (A. Galanopoulou, MD, PhD, personal communication, December 2008). Socialization deficits, including decreased exploration, indifference to other rats, and excessive grooming, are reminiscent of some behaviors associated with the autism spectrum disorder, which is frequently seen in children with infantile spasms (36). In addition, preliminary findings show a reduction of GABAergic neurons in the cortex and hippocampus of pups with spasms (A. Galanopoulou, MD, PhD, personal communication, December 2008).

The multiple-hit model mimics symptomatic infantile spasms that are induced by cortical and subcortical brain damage. Because the model entails injection of three toxic compounds in short succession, it raises questions about the exact mechanism(s) by which the brain damage leads to infantile spasms—are the cognitive deficits and other behavioral abnormalities a result of the seizures or of the damage caused by the toxic drugs? The model's validity depends upon the consistent appearance of the spasms, with variable pathologies induced by these agents. The multiple-hit model holds promise for understanding several aspects of infantile spasms, including the age specificity, ictal and interictal EEG findings, seizure evolution, and adverse cognitive consequences. The model also may provide information about the network of electrophysiological mechanisms that generate spasms and will allow investigation of medication responsiveness.

Aristaless-Related Homeobox (ARX) Mutation Model—Interneuronopathy

The Aristaless-related homeobox (*ARX*) gene is one of a family of homeobox genes that encode transcription factors that are necessary for normal nervous system development, including neuronal proliferation, migration, and differentiation (37). Mutations in *ARX* are associated with a variety of neurologic syndromes involving mental retardation and epilepsy, including infantile spasms (38). *ARX* knockout mice exhibit deficient proliferation of several cell types, including GABAergic interneurons (39). The hypothesis that a deficiency of cortical GABAergic inhibition is involved in developmental epilepsies gave rise to the concept of "interneuronopathy" (40). A new genetic animal model has been developed by conditional deletion of *ARX* from inhibitory interneurons of the cortex (41). These *ARX*-deficient mice exhibit a variety of seizure types during development, including brief spasm-like seizures resembling infantile spasms (E. Marsh, MD, PhD, and A. Brooks-Kayal, MD, personal communication, January 2009). On EEG, interictal spikes are seen at baseline and electrodecremental responses are recorded during spasms, again, compatible with findings in human infants with infantile spasms. The loss of subsets of interneurons within the cortex and hippocampus are the presumed pathological alterations leading to the epileptic phenotype. In addition, potential cognitive and behavioral abnormalities in *ARX*-deficient mice have been documented in pilot studies, although it is presently unclear whether this impairment is the result of the seizures or the mutation.

The importance of the *ARX* model is that it recapitulates aspects of human infantile spasms in an animal using a mutation in a known infantile spasms gene, and the *ARX* knockout mouse has the advantage of being closely related to human *ARX* mutations, allowing detailed investigation of network dysfunction. Although X-linked, with a more severe phenotype present in males, female carriers also exhibit some seizures and cognitive changes, making this model appropriate for studying sexual differences in developmental epilepsy susceptibility. Furthermore, the seizures are more spasm-like when the mutant mice reach adulthood such that the mechanisms of age-related changes in seizure phenotype are particularly amenable to investigation in this model (E. Marsh, MD, PhD, and A. Brooks-Kayal, MD, personal communication, January 2009). The technical aspects of creating this genetic model are quite challenging, with diminished survival of male *ARX* knockout mice. Further genotypic–phenotypic correlation and characterization of the spectrum of neurological abnormalities are necessary, but the prospect of an animal model of infantile spasms that involves an interneuronopathy is novel and exciting.

Down Syndrome Model—Ts65Dn Mouse

Infantile spasms occurs in up to 10% of children with Down syndrome (42). A mouse model of Down syndrome, Ts65Dn, has been used to study many aspects of this genetic disorder, including cognitive and behavioral impairment, abnormal synaptic plasticity, cortical malformation, and dendrite dysgenesis (43,44). At baseline, Ts65Dn mice, which overexpress $GABA_B$ receptors, exhibit spontaneous spike-wave discharges on EEG, but no seizures have been reported (45,46). The spike-wave discharges are similar to those induced in normal rats exposed

TABLE 1. *Animal Models of Infantile Spasms*

Model	How Model Is Created	Selected References
CRH/stress	CRH i.p.	10,12,13,16
Betamethasone/ NMDA	Betamethasone i.p. to dam on G15, followed by NMDA i.p. to offspring on P15	18,19,21
TTX	TTX i.c. infusion by osmotic pump for 28 days, beginning on P10	28
Multiple-hit	Doxorubicin i.c.v. and lipopolysaccharide i.c. on P3, followed by p-chlorophenylalanine i.p. on P5	31; A. Galanopoulou, MD, PhD, personal communication (December 2008)
ARX knockout	Targeted deletion of *ARX* gene from cortical interneurons	41; E. Marsh, MD, PhD, and A. Brooks-Kayal, MD, personal communication (January 2009)
Down syndrome	$GABA_B$ receptor agonists i.p. to Ts65Dn mice	45,46

CRH, corticotropin-releasing hormone; i.p., intraperitoneal; G, gestational day; P, postnatal day; i.c., intracerebrally; i.c.v., intracerebroventricularly; *ARX*, Aristaless-related homeobox.

to $GABA_B$ receptor agonists (47). Based on the report that a type of potassium current, mediated by the G-protein-coupled inwardly rectifying potassium channel subunit 2 (GIRK2), is increased by $GABA_B$ receptor agonists (48), it was hypothesized that $GABA_B$ receptor agonists might lead to increased susceptibility to epileptic spasms in Ts65Dn mice (46). Indeed, administration of baclofen or γ-butyrolactone (GBL; the prodrug of the $GABA_B$ agonist γ-hydroxybutyrate) caused Ts65Dn mice (1 week to 2 months old) to develop clusters of extensor spasms accompanied by polyspike-wave bursts and electrodecremental responses on EEG (resembling ictal EEG changes in humans). GBL, when injected into wild-type mice, caused spike-wave discharges and absence seizures (47). Importantly, spasms in this model decreased with medications commonly used for treatment of infantile spasms, such as ACTH, valproic acid, and vigabatrin (46,49). The model suggests that $GABA_B$ receptors may be involved in the pathogenesis of infantile spasms, at least those associated with Down syndrome, and implicates the involvement of the thalamocortical system.

The major limitation of the Ts65DN model is the requirement for the induction of spasms by a $GABA_B$ receptor agonist; that is, seizures do not occur spontaneously or chronically. The mechanism by which $GABA_B$ receptor alteration causes spasms needs to be elucidated, both in terms of potassium channel involvement and in terms of other potential mechanisms. It is curious that activating the same receptor in wild-type mice causes absence seizures with GBL and, in Ts65Dn mice, causes spasm-like seizures. The age effect must be studied further; a variation in spasms with age would be expected. Studies of cognition and physiology using this model have not yet been reported.

Conclusions

The recent proliferation of infantile spasms animal models (summarized in Table 1) is a most welcome trend! Until recently, a dearth of interest in this important area of pediatric epilepsy has kept infantile spasms and other catastrophic epilepsies in the Dark Ages. Now, the task is to evaluate, carefully and critically, these new models (and, hopefully, others to come) for the specific insights each can offer into an understanding of the disorder and then translate experimental findings into clinically useful therapies. As discussed, an ideal model that recapitulates every aspect of human infantile spasms is not expected. Rather, each model will provide a piece of the puzzle to decipher these complex, multifactorial, devastating epilepsies.

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