ANIMAL MODELS OF INFANTILE SPASMS: IS THE HOLY GRAIL FINALLY IN SIGHT?

A New Animal Model of Infantile Spasms with Unprovoked Persistent Seizures. Lee CL, Frost JD Jr, Swann JW, Hrachovy RA. *Epilepsia* 2008;49(2):298–307. PURPOSE: Infantile spasms is one of the most severe epileptic syndromes of infancy and early childhood. Progress toward understanding the pathophysiology of this disorder and the development of effective therapies has been hindered by the lack of a relevant animal model. We report here the creation of such a model. METHODS: The sodium channel blocker, tetrodotoxin (TTX), was chronically infused into the developing neocortex or hippocampus of infant rats by way of an osmotic minipump starting on postnatal day 10–12. RESULTS: After a minimum of 10 days of infusion, approximately one-third of these rats began to display very brief (1–2 s) spasms, which consisted of symmetric or asymmetric flexion or extension of the trunk and sometimes involvement of one or both forelimbs. The typical ictal EEG pattern associated with the behavioral spasms consisted of an initial generalized, high amplitude, slow wave followed by an electrodecrement with superimposed fast activity. The interictal EEG revealed multifocal spikes and sharp waves, and in most animals that had spasms a hypsarrhythmic pattern was seen, at least intermittently, during NREM sleep. Like in humans, the spasms in the rat often occurred in clusters especially during sleep–wake transitions. Comparison of the ictal and interictal EEGs recorded in this model and those from humans with infantile spasms revealed that the patterns and the frequency components of both the ictal events and hypsarrhythmia were very similar. DISCUSSION: The TTX model of infantile spasms should be of value in furthering an understanding of the pathophysiology of this seizure disorder.

COMMENTARY

Infantile spasms is a severe developmental epilepsy syndrome, with several unique clinical features (1). First, the disorder occurs during a specific window in the first year of life, commonly starting between 3 and 8 months of age. Second, infantile spasms can be caused by numerous etiologies, either acquired or congenital, which typically begin weeks-to-months prior to the onset of spasms (2). Therefore, a latent period exists prior to infantile spasms during which neural circuits become epileptogenic in an as yet unknown manner (3). Third, infantile spasms is associated with very specific and unique encephalographic findings consisting of interictal hypsarrhythmia (chaotic high-voltage slow waves, intermixed with multifocal spikes) and ictal electrodecrement (generalized attenuation of waveforms). Fourth, most anticonvulsants are not effective for infantile spasms; treatments that are sometimes effective include glucocorticoids, adrenocorticotrophic hormone (ACTH), and vigabatrin (4). Fifth, the outcome of infantile spasms is often poor, especially when the spasms do not improve with therapy and when neurological development is abnormal prior to the onset of spasms. In summary, the lack of a detailed pathophysiological explanation for many aspects of infantile spasms makes this epilepsy syndrome (sometimes referred to as a "catastrophic" epilepsy) a frustrating clinical enigma.

Progress in understanding and treating infantile spasms has been limited in part by the lack of an appropriate animal model in which to study the underlying neurobiological mechanisms. In fact, an animal model for infantile spasms has been considered to be a "holy grail" of epilepsy research (5). Ideal and minimal criteria for an animal model of infantile spasms have been discussed (6,7). Optimally, the model would mimic the human disorder, including a specific developmental window during which spasm-type seizures begin, maximal spasm occurrence in relationship to the sleep–wake cycle (especially shortly after arousal from sleep), and prevalence of spasms in clusters. The validity of an experimental model would be strengthened if EEG findings in the animal resemble interictal hypsarrhythmia and ictal electrodecrement. An ideal model also would include responsiveness to anticonvulsants that ameliorate spasms in human infants. Humans and other animal species differ markedly in the trajectory of their brain development and behavioral neurological repertoire, so it is unlikely that a single animal model will fulfill all of these criteria. Thus, a model should not necessarily be excluded if it does not meet all criteria, as long as it is relevant to understanding the pathophysiology of infantile spasms.

The developmental epilepsy model presented in the report by Lee et al. is exciting because it demonstrates a heretofore

Epilepsy Currents, Vol. 8, No. 5 (September/October) 2008 pp. 131–133
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elusive criterion: an EEG pattern that closely resembles human hypsarrhythmia. In this model, infant rats develop spasm-type seizures following chronic infusion of the sodium-channel blocker tetrodotoxin (TTX). During the infusion and long after its discontinuation, rats displayed brief spasms involving the trunk and/or limbs. EEG tracings verified an interictal pattern that closely resembles hypsarrhythmia in a human infant. Furthermore, when a spasm occurred, the EEG showed a decremental response following an initial generalized slow wave, again, similar to the human EEG pattern. To support the clinical applicability of the model, the authors present side-by-side examples of human and rat EEGs, including power spectra that exhibited convincing electrophysiological signatures. Therefore, the behavioral interictal- and ictal-EEG patterns as well as temporal features of seizures in this rodent model are reasonably comparable to human infantile spasms and hold promise for the study pathophysiological mechanisms of infantile spasms.

How does chronic infusion of TTX lead to infantile spasms in rats? By blocking neural impulses, TTX depresses neural activity at the infusion site and creates a hyperexcitable condition well beyond the focal administration site. Interestingly, despite the focal nature of the TTX infusions, EEG changes are predominantly generalized, as are the clinical seizures in these rats. Similarly, in humans, focal lesions often lead to symmetric or generalized spasms in EEG findings (8). Somehow, developmentally specific suppression of neural discharges endows the brain with an unusual pattern of hyperexcitability that produces spasms and accompanying EEG patterns (9,10). The mechanism of TTX-induced hyperexcitability requires considerable further investigation.

Given the large number of genetic and acquired etiologies of human infantile spasms, it is likely that several mechanisms interact to cause the clinical syndrome. It has been proposed that all these myriad etiologies converge at a final common pathway to result in the relatively homogeneous entity of infantile spasms (11). This hypothesis states that infantile spasms represent the response of the developing nervous system to any number of stressors that cause the neuronal release of corticotropin-releasing hormone (CRH) (12). CRH is acutely convulsant in the infant brain (but not the adult brain) and is a known endogenous cotransmitter in several brain structures sensitive to seizure generation (e.g., the hippocampus and amygdala). According to this hypothesis, ACTH acts not as an anticonvulsant but by suppressing the stress-provoked, excessive production of CRH. However, seizures following CRH injection lack some of the clinical features of infantile spasms.

Other infantile spasms models are now on the horizon, each presenting a potentially different mechanism of action. One new model involves prenatal administration of the glucocorticoid betamethasone, which causes a prenatal stress, followed by postnatal administration of NMDA, which causes spasm-like seizures in infant rats that are responsive to ACTH administration (13). Another model combines administration of doxorubicin and lipopolysaccharide to produce structural damage and reduce serotonin levels, with resultant spasm-like seizures (14). Finally, administration of a $GABA_B$-receptor agonists in a mouse model of Down syndrome results in extensor spasms and an accompanying electrodecremental EEG response (15). Together, these infantile spasms models hold the promise to increase understanding of the pathophysiology of this devastating developmental epilepsy.

Ideally, the following questions might be answered by an animal model:

- How does specific developmental sensitivity to particular insults, occurring at certain ages of brain maturation, result in such a unique syndrome?
- Can new modes of therapy be devised, based on pathophysiological mechanisms?
- Are there effective nonpharmacological methods of treatment that could be sought?
- Can approaches be developed to prevent the adverse cognitive outcomes frequently associated with infantile spasms?

Research may well be entering a new era of understanding infantile spasms and other catastrophic epilepsies of childhood. The beneficiaries of such knowledge clearly would be affected children and their families, who currently are faced with ineffective or exorbitantly expensive treatment options. In that sense, despite numerous challenges that lie ahead, the Holy Grail may actually be in sight.

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