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Models for Infantile Spasms: An Arduous Journey to the Holy Grail...

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Infantile spasms (IS) is a relatively common and severe epilepsy of infants and young children. IS likely contributes to up to 10% of all mental retardation, and it evolves into further epilepsies in about 50% of cases. Although this catastrophic epilepsy was first identified more than 160 years ago, its cause and mechanism are poorly understood and treatment is unsatisfactory, particularly in preventing the postulated effects of these seizures on cognitive function.

These questions are difficult to address in human studies; thus, valid animal models for IS are needed. However, defining and characterizing suitable models for IS has been a daunting problem. Prominent among the issues facing investigators interested in developing a model for IS are the numerous causes of this disorder: IS occurs in infants with metabolic disorders, many gene mutations, brain malformations, tuberous sclerosis, congenital or postnatal infections and strokes, among other causes. This multitude of apparent “causes” has made it difficult to sort out the essential elements within any of these entities that are required and sufficient to provoke IS.

Models for IS proposed to date fit one of two general categories: those that recapitulate a specific cause of IS (eg, loss of interneurons in the ARX mouse, artificial stroke/hemispherectomy), and models that attempt to define and recreate a “final common pathway” for all of the causes that elicit IS. This latter approach has been taken by Velisek’s group, as described in this issue of Annals.

The unusual, rapid, and robust response to adrenocorticotropic hormone (ACTH), the current recommended therapy, has been considered a crucial clue for defining a common or converging mechanism for IS. Because ACTH is a component of the neuroendocrine stress response the possibility was raised that the common denominator or “final common pathway” of the many causes of IS involves stress response within the developing brain. Activation of specific components of the stress response, in turn, may promote hyperexcitability and provoke the abnormal neuronal activity (hypsarrhythmia) and seizures (spasms).

The neuropeptide corticotropin-releasing hormone (CRH) is an attractive candidate as a stress-activated convulsant that may contribute to the mechanisms of IS. It is released from hippocampal, amygdalal, and certain brainstem neurons in response to stress and promotes neuronal excitability, at least in part by reducing afterhyperpolarization. Therefore, the stress/CRH hypothesis of IS proposes that a common factor in patients with this disorder is excess secretion of CRH in limbic and brainstem regions, which triggers
the seizures. In this scenario, ACTH does not act as a direct anticonvulsant, but rather ameliorates IS by reducing the synthesis and release of endogenous CRH. In essence, ACTH functions as a true antiepileptic drug. This mechanism of action of ACTH is consistent with the time course of its efficacy in infantile spasms, where response is often all or none, requires a day or two to start, and often continues even when ACTH treatment is terminated.

Several characteristics of patients with IS support this pathophysiological model of IS. Infants with IS have low levels of ACTH in their cerebrospinal fluid. In addition, IS improves with doses of ACTH that are much greater than those required to fully activate the infant's adrenal gland to elicit secretion of maximal levels of endogenous glucocorticoids. Indeed, the efficacy of high-dose ACTH is twice that of lower doses of this hormone or of prednisone (86% vs 37–40%). This enhanced efficacy strongly supports additional mechanisms of action of this hormone, in addition to the release of glucocorticoids. The possibility that ACTH may penetrate the blood–brain barrier, enter the brain, and exert direct effects there has been demonstrated in animal models. In an immature rodent model, systemic administration of high doses of ACTH leads to its entry into the central nervous system, where it reduces the expression of the stress-activated excitatory peptide, CRH, in limbic structures. Because CRH can evoke seizures in rodents and is released during stress, this reduction of CRH levels provides a plausible mechanism for the actions of ACTH on IS. Importantly, it defines potential molecular targets for the treatment of IS, including compounds that, like ACTH, activate the melanocortin receptors or compounds that directly block CRH receptors.

In this issue of *Annals*, Velisek and colleagues present an interesting variant of the “stress-evoked” infantile spasms story. A number of years ago, the authors discovered that administration of NMDA to infant rats caused a flexion myoclonus. This was reminiscent behaviorally of flexion spasms, the most common type of seizures in infants with IS, and prompted the group to pursue this finding as a model for IS.

Whereas the NMDA-evoked movements resemble behavioral spasms, the commonality of mechanisms between NMDA-evoked seizures and IS had previously remained unexplored. A logical approach to examining whether there might be a common pathophysiology involves demonstrating a therapeutic response profile of “NMDA spasms” that mirrors IS. However, ACTH was not helpful for NMDA-evoked seizures given by the authors only immediately before NMDA. This fact should not be surprising, because ACTH does not have immediate effects on spasms in humans: the time of onset to its efficacy is measured in days (median, approximately 2 days). In this context, it may be noted that ACTH also does not block kindling or seizures induced by synthetic CRH in an infant rat model of IS. These findings are expected because ACTH likely acts by reducing the levels of endogenous CRH.

In this issue, Velisek and colleagues aim to refine their model by introducing an element of prenatal stress into the factors provoking spasmlike seizures. Rather than stressing pups in utero, they inject pregnant rats with a synthetic glucocorticoid. This approach might be criticized for several reasons. First, it is not clear that the major means by which stress influences the developing brain depends on glucocorticoids alone. In addition, the doses of steroids used are high enough to adversely influence the weight, and hence brain development, of the pups. Reduced body and brain weights are not typical in infants with IS.

This prenatal treatment rendered the NMDA-provoked seizures minimally responsive to ACTH, with modest changes in latency. Although the authors consider this an important validation of their model, this response is surprising, because it occurs within minutes of
administration of ACTH, and not hours to days, as would be expected from a putative mechanism of action via suppression of CRH expression. Therefore, the mechanisms by which ACTH administration modifies the latency to NMDA-provoked seizures are not clear and may involve direct actions within the central nervous system or peripheral effects on glucocorticoid release from the adrenal gland. Glucocorticoids can both enhance and reduce neuronal excitability.26,27

IS is a relatively common and intractable disorder, without optimal therapy. Therefore, new efforts to understand its underlying mechanisms and model it in experimental organisms deserve our attention and support. It is hoped that, among the several new suggested models for this disorder,28–30 one or more will emerge as a powerful tool that will facilitate the cure, and perhaps even the prevention, of this devastating developmental epilepsy.

Acknowledgments

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