Go "West," Young Man. . . The Quest for Animal Models of Infantile Spasms (West Syndrome)

Model of Infantile Spasms Induced by N-methyl-D-aspartic Acid in Prenatally Impaired Brain. Velisek L, Jehle K, Asche S, Veliskova J. *Ann Neurol* 2007;61(2):109–119. OBJECTIVE: Infantile spasms (a catastrophic epileptic syndrome of childhood) are insensitive to classic antiepileptic drugs. New therapies are limited by lack of animal models. Here we develop a new model of flexion spasms based on prenatal exposure to betamethasone combined with postnatal administration of *N*-methyl-D-aspartic acid (NMDA) and determine brain structures involved in the induction of flexion spasms. METHODS: Pregnant rats received two doses of betamethasone on day 15 of gestation. Offspring was injected with NMDA on postnatal day 15. Effects of adrenocorticotropin therapy on the development of age-specific flexion spasms were determined and electroencephalographic correlates recorded. C-fos immunohistochemistry and [^{14}C]2-deoxyglucose imaging identified brain structures involved in the development of flexion spasms. RESULTS: Prenatal betamethasone exposure sensitizes rats to development of NMDA-induced spasms and, most importantly, renders the spasms sensitive to adrenocorticotropin therapy. Ictal electroencephalogram results correspond to human infantile spasms: electrodecrement or afterdischarges were observed. Imaging studies defined three principal regions involved in NMDA spasms: limbic areas (except the dorsal hippocampus), hypothalamus, and the brainstem. INTERPRETATION: Despite certain limitations, our new model correlates well with current infantile spasm hypotheses and opens an opportunity for development and testing of new effective drugs.

COMMENTARY

One hundred sixty years after Dr. West's well-known description of his son's infantile spasms (1), over 50 years after the identification of the classical EEG pattern of this disorder, and 45 years after the term West syndrome was suggested (2), there is little more than a woefully incomplete understanding of this entity. Indeed, there is minimal consensus even about the basic characteristics of this syndrome: is it a generalized seizure disorder or do the spasms emanate from a hidden focus, such as is often seen in infantile spasms associated with tuberous sclerosis? What are the fundamental neuronal circuits supporting spasms and hypsarrhythmia? Specifically, what is the role of the brain stem? What are the relative roles of spasms and hypsarrhythmia in the derangement of normal brain function found in affected infants? Is the hypsarrhythmia interictal or does it represent status epilepticus?

Numerous genetic (3), neurophysiological, and imaging (4) methods have been employed to investigate these and related questions in infants with infantile spasms. However, an understanding of the neurobiology of this syndrome requires an animal model (5–8). The criteria for a suitable model for infantile spasms have been debated (6,7), but no consensus exists on the critical elements that render an animal model ideal or even suitable for studying infantile spasms. For example, the requirement that hypsarrhythmia be included has been questioned, and this pattern, to date, has been reported in an animal model only as an abstract (9).

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A second remarkable feature of infantile spasms, their response to adrenocorticotropic hormone (ACTH), also has been considered an element crucial to a useful animal model for infantile spasms. The pioneering work of Sorel and colleagues suggested that the neuropeptide ACTH, acting directly within the brain, might suppress infantile spasms. Early anecdotal success of ACTH therapy was confirmed by blinded controlled studies, although the rate of ACTH efficacy for infantile spasms varied widely, from ~40 to 88% (10,11). While these studies established ACTH as a robust and selective therapy for eradicating infantile spasms and hypsarrhythmia, they failed to explore underlying mechanisms. More recently, a novel mechanism of action for ACTH has been demonstrated; it involves direct action of the hormone on melanocortin receptors, resulting in reduced expression of the excitatory neuropeptide corticotropin-releasing hormone (CRH) within seizure-prone limbic regions (12). This mechanism dissociates the anti-infantile spasms effects of ACTH and its steroid-releasing actions, suggesting that analogs of ACTH that bind to melanocortin receptors (but do not release steroids) may provide effective therapy for infantile spasms, without the multiple systemic side effects of steroids (12,13).

The conceptual framework for the direct effects of ACTH on CNS neurons is built around the hypothesis that ACTH reduces the expression of CRH and that CRH is found in abnormally high levels in patients with infantile spasms. Indeed, infants with infantile spasms have abnormal levels of ACTH and cortisol in their CSF, findings consistent with elevated brain levels of CRH. The expression as well as secretion of CRH (part of the CNS–adrenal stress system) is increased by stress in several brain regions. When released during stress from hippocampal (14), amygdalar (15) and certain brainstem (16) neurons, CRH acts via a G-protein–coupled receptor to excite neurons (17), at least in part, by reducing after-hyperpolarization (18). The stress/CRH hypothesis for the pathophysiology of infantile spasms posits that myriad events that lead to infantile spasms are stressful to the developing brain, resulting in excessive expression and release of CRH in limbic and brainstem regions (8). CRH, in turn, provokes spasms and excessive neuronal synchrony (i.e., hypsarrhythmia). ACTH eliminates infantile spasms not by acting as an anticonvulsant (19), but by reducing expression and secretion of endogenous CRH (12).

The potential role of early life stress in the pathophysiology of infantile spasms is embraced by Velisek et al., in the current work. Previously, Mares et al. described flexor type movements induced by NMDA administration to immature rats (20). These movements resemble the most common variant of infantile spasms, flexion spasms. However, ACTH was not helpful in resolving NMDA-evoked seizures. Therefore, in the current work, Velisek et al. queried whether subjecting rats to prenatal stress followed by the NMDA challenge would render the NMDA-provoked seizures responsive to ACTH. The group injected pregnant rat dams with high doses of a synthetic glucocorticoid to simulate prenatal stress, then administered NMDA on postnatal day 15. This prenatal treatment allowed ACTH to increase the latency for NMDA-provoked seizures. The immediate effect of ACTH in rodents differs from its time course in humans, in whom suppression of infantile spasms and hypsarrhythmia commences after a median of 2 days (11); a finding consistent with transcriptional actions on CRH expression (12). In other immature animal models, such as kindling (21) or CRH-provoked seizures (19), ACTH also failed to demonstrate direct anticonvulsant effects.

In conclusion, the work by Velisek et al. is a valiant effort to create a model for infantile spasms by incorporating three elements: (1) drug-induced seizures that behaviorally resemble spasms; (2) simulated prior stress (although injection of glucocorticoids may not recapitulate the crucial elements by which prenatal stress excites neurons [22]); and (3) a response to ACTH that results in seizure reduction. The model falls short of ideal or suitable models, as delineated by a recent NIH workshop (7). However, because infantile spasms are a common and devastating entity and because optimal models are currently lacking, the efforts of this group offer a useful paradigm for studying certain semiological aspects of infantile spasms.

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