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Treatment of Infantile Spasms: Emerging Insights From Clinical and Basic Science Perspectives

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Abstract

Infantile spasms is an epileptic encephalopathy of early infancy with specific clinical and electroencephalographic (EEG) features, limited treatment options, and a poor prognosis. Efforts to develop improved treatment options have been hindered by the lack of experimental models in which to test prospective therapies. The neuropeptide adrenocorticotrophic hormone (ACTH) is effective in many cases of infantile spasms, although its mechanism(s) of action is unknown. This review describes the emerging candidate mechanisms that can underlie the therapeutic effects of ACTH in infantile spasms. These mechanisms can ultimately help to improve understanding and treatment of the disease. An overview of current treatments of infantile spasms, novel conceptual and experimental approaches to infantile spasms treatment, and a perspective on remaining clinical challenges and current research questions are presented here. This summary derives from a meeting of specialists in infantile spasms clinical care and research held in New York City on June 14, 2010.

Keywords

infantile spasms, hypsarrhythmia, adrenocorticotrophic hormone (ACTH), vigabatrin, ganaxolone, melanocortin, corticotropin releasing hormone, animal models

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Infantile spasms or West syndrome is an epileptic encephalopathy of infancy with a number of unique features that position it among the most severe epilepsies of childhood. Many aspects of the diagnosis and treatment of infantile spasms are well described and familiar to child neurologists. The clinical presentation includes intermittent spasm-like seizures involving flexion or extension, or mixed flexion-extension movements of the arms, legs, or trunk. These seizures typically occur in clusters, often during sleep-wake transitions. The onset of infantile spasms usually occurs in the middle of the first year of life, often accompanied by stagnation or decline of developmental milestones. The appearance of infantile spasms weeks to months following a precipitating brain insult (“latent period”) implies that a period of epileptogenesis is occurring,¹ possibly with features unique to this syndrome. The existence of a latent period also raises the possibility of preventive intervention.

Infantile spasms has numerous etiologies (more than 200 already documented) but can also occur in previously healthy, normally developing children.^{2,3} Symptomatic etiologies

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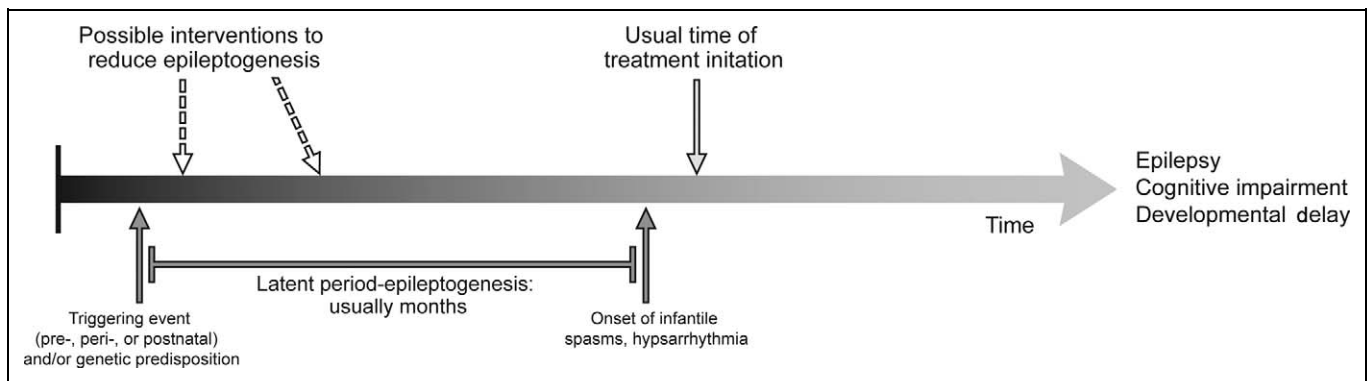


Figure 1. Schematic timeline showing precipitating neurologic insult followed by a period of epileptogenesis (latent period), which in turn is followed by onset of infantile spasms (West syndrome) and hypsarrhythmia. Although West syndrome is usually treated after the onset of spasms, it might be possible to avert some of the long-term sequelae (persistent seizures, cognitive impairment) by intervening during the latent period in cases in which the development of spasms is likely.

include genetic and acquired causes such as hypoxic ischemic encephalopathy, tuberous sclerosis complex, brain malformations, and central nervous system infections. Of note, these symptomatic etiologies overlap with those responsible for Lennox-Gastaut syndrome, which usually appears after 2 years of age, suggesting that the form of epileptic encephalopathy in a given child depends upon the stage of brain development at which the neurologic insult occurs. Alternatively, an epileptic encephalopathy such as infantile spasms can present at an earlier age, then later evolve into Lennox-Gastaut syndrome as the brain develops.⁴

Novel genetic etiologies of infantile spasms are being discovered rapidly, with an almost bewildering array of mutations affecting synapse development, gene transcription, protein phosphorylation, ion transport, and numerous other cellular functions now described.⁵⁻⁷ While each of these genetic mutations is rare, collectively they comprise an increasing proportion of infantile spasms etiologies.⁸ The fraction of infantile spasms cases with a cryptogenic or uncertain etiology is steadily decreasing over time as modern genetic testing, imaging, and biochemical diagnostic techniques improve. Based on this burgeoning information, a new nosology has been proposed for infantile spasms, with the categories of genetic, structural/metabolic, and unknown replacing the former terms cryptogenic, symptomatic, and idiopathic, respectively.⁹ (In this review, we use the former terms because they were used in the clinical studies that are discussed.) The clinical aspects of infantile spasms and its treatment have been reviewed in detail in a recent consensus report.³

The goals of infantile spasms treatment are to stop the spasms, normalize the abnormal interictal EEG pattern (hypsarrhythmia) that underlies the encephalopathy, and optimize neurodevelopmental outcome. Treatment of infantile spasms involves a unique set of therapies (discussed in further detail below). The 39-amino acid adrenocorticotrophic hormone (Highly Purified Acthar[®] Gel, hereafter referred to as ACTH) is the most commonly used treatment for infantile spasms, yet the exact mechanisms of its anticonvulsant (and possibly anti-epileptogenic) actions are unknown. ACTH therapy can be

associated with significant adverse effects and high cost, and some cases of infantile spasms do not respond to ACTH. Furthermore, emerging research suggests that some etiologies of infantile spasms respond best to other specific therapies.^{10,11} For example, vigabatrin, a γ -aminobutyric acid (GABA) transaminase inhibitor, is considered the first line of treatment for infantile spasms in children with tuberous sclerosis complex.^{12,13} In fact, it has been proposed that prophylactic antiepileptic treatment prior to the onset of infantile spasms might yield improved outcome in children with tuberous sclerosis complex, although confirmative data have not yet been reported.^{14,15} Several other treatments, discussed below, have had variable success. The prognosis of infantile spasms is generally poor, especially in symptomatic cases. For all of these reasons, optimization of treatment choice and timing of administration of infantile spasms treatment is of utmost urgency (Figure 1).

Advances in understanding the underlying mechanisms, pathophysiology, and treatment effectiveness of infantile spasms have been limited by the lack of valid animal models in which to test new hypotheses and develop new treatments. However, the recent emergence of clinically relevant animal models of infantile spasms, potential new approaches to treatment such as melanocortin receptor activation, and the continuing gap between the recognition of infantile spasms and its effective treatment, led to a summit meeting of experts in pediatric epilepsy and basic science to address how these new data might impact therapy. Although numerous unanswered questions remain about the underlying pathophysiology and treatment effectiveness, meeting participants concluded that a summary of the topics discussed would be informative to physicians treating patients with infantile spasms.

ACTH and Other Treatments of Infantile Spasms

Among the unique aspects of infantile spasms is the profile of pharmacologic responsiveness. Typically, infantile spasms respond to conventional antiepileptic drugs inconsistently, if

at all. However, as initially described in 1958, infantile spasms frequently responds dramatically to the neuropeptide ACTH.¹⁶ Since that original report, numerous studies have examined various dosage regimens and protocols of ACTH administration, as well as comparisons of ACTH with steroids such as prednisone and other agents. The most recent comprehensive review of data regarding ACTH effectiveness is found in a practice parameter published in 2004 by the American Academy of Neurology and Child Neurology Society.¹⁷ In that report, an effective treatment response in infantile spasms was defined as complete cessation of spasms plus abolition of the hypsarrhythmia. The requirement of all-or-none responsiveness differs from the usual definition of treatment effectiveness accepted for other forms of epilepsy. The all-or-none requirement reflects a consensus that unless hypsarrhythmia resolves, cognitive recovery is likely to be incomplete and disease progression (eg, to Lennox-Gastaut syndrome or other forms of epilepsy) is probable.

ACTH was deemed “probably effective” for the termination of infantile spasms and resolution of hypsarrhythmia.¹⁷ The practice parameter evaluated 14 ACTH treatment studies, 5 of which were randomized controlled trials (3 involving Highly Purified Acthar Gel). The parameter concluded that intramuscular injection of high-dose ACTH (150 IU/m² body surface area/d, divided into 2 daily doses) was more effective in the treatment of infantile spasms than oral prednisone at a dose of 2 mg/kg/d divided into 2 doses over 2 weeks of treatment.¹⁸ The practice parameter could not determine a dose response curve for ACTH by comparing low- versus high-dose treatments,¹⁹ because of methodological variability, including the rate of dose escalation of low-dose treatment, as well as the finding that the response to low-dose ACTH 20 IU/day did not differ from prednisone at 2 mg/kg/d.²⁰ It was concluded that these studies were generally underpowered to detect clinically relevant treatment differences. Therefore, according to the practice parameter, there is insufficient evidence that oral corticosteroids such as prednisone are effective in the treatment of infantile spasms, with a maximum response rate of about 30%, which was not different from placebo.¹⁷

The recent United Kingdom Infantile Spasms Study compared treatment with vigabatrin versus the synthetic, truncated ACTH analog (ACTH 1-24; tetracosactide, intramuscular depot form) or prednisolone.²¹ Patients with tuberous sclerosis complex were not included in the United Kingdom Infantile Spasms Study. The study used very low dose ACTH 1-24 (40 IU every other day—because of its long duration of action, on the order of 24-36 hours) and a very high dose of prednisolone (40 mg/d; duration of action, 18-36 hours). The primary endpoint was the clinical cessation of spasms by parental report, without requiring the abolition of hypsarrhythmia or confirmation of spasms cessation by EEG. Therefore, these data cannot be compared directly to the randomized clinical trials that used the combined endpoint of no spasms and no hypsarrhythmia confirmed by prolonged video EEG that formed the basis for the American Academy of Neurology/Child Neurology Society practice parameter. In addition, even

with its endpoint, the United Kingdom Infantile Spasms Study was underpowered to compare treatment effects of ACTH 1-24 versus prednisolone. No study to date has directly compared synthetic, truncated ACTH analogs with the natural, full-sequence form of ACTH. Also, no study has compared high-dose ACTH with high-dose corticosteroids. Thus, equivalence in dose, adrenal effects, central nervous effects, and biological activity cannot be presumed. It can be concluded that low-dose ACTH is sufficient for release of natural corticosteroids from adrenal glands, whereas high-dose ACTH is needed for a direct action on the central nervous system. In that regard, penetration of ACTH across the blood-brain barrier appears to be limited, so the central nervous system effects of this neuropeptide require a fuller explanation, as discussed below.²²

According to the cited literature, high-dose ACTH has superior efficacy compared with low-dose corticosteroids for the treatment of infantile spasms and hypsarrhythmia (87% vs 27% response rate, respectively).¹⁸ Similarly, ACTH is the only drug treatment for which long-term infantile spasms outcomes are available. Patients treated early (within 1 month of spasms onset or before the onset of developmental decline) with ACTH 1-24 show lower rates of relapse, better intellectual development and lower incidence of later epilepsy.²³⁻²⁵ This beneficial effect is particularly applicable to cryptogenic infantile spasms; efficacy in many cases of symptomatic infantile spasms is incomplete or recurrence occurs after an initial favorable response. In Finnish studies, there was no difference in response rate or relapse rate comparing low-dose (20-40 IU/day) and high-dose (120 IU/day) ACTH 1-24, and better long-term cognitive outcomes were reported with the low-dose regimen.²⁶⁻²⁸

Based on the above reports, ACTH, especially the high-dose regimen, continues to be the clinical standard of treatment of infantile spasms in the United States and several other countries.^{3,29,30} The treatment effect of ACTH has a rapid onset, with a mean time to treatment response of 2 days. The all-or-none resolution of both spasms and hypsarrhythmia suggests a disease-modifying effect of high-dose ACTH, a notion supported by clinical observations that in many instances, once spasms have ceased and ACTH is withdrawn, epileptic seizures may not recur. Approximately 40% to 60% of patients treated with ACTH 1-24 have long-term seizure freedom.^{11,31} Treatments with high-dose ACTH indicate initial efficacy rates of $\geq 87\%$ and relapse rates between 14% and 20%.¹⁸ Treatment with ACTH or ACTH 1-24 should be as short as possible (approximately 2 weeks followed by a taper) to avoid adverse effects.^{3,18,32,33} Prolonged EEG monitoring including sleep is necessary to confirm the cessation of hypsarrhythmia.

Despite the documented effectiveness of ACTH in the treatment of infantile spasms, its molecular and pathophysiological effects are not entirely known. Particularly intriguing are the observations that there is typically a lag time of approximately 48 hours before the onset of an ACTH effect, and that the clinical effect is typically all-or-none with complete cessation of the spasms and normalization of the EEG. This clinical action profile, with its very atypical for a “simple anticonvulsant”

effect, might provide clues to the mechanism by which ACTH suppresses infantile spasms. One possibility, discussed further below, is that ACTH might suppress infantile spasms via actions on melanocortin receptors.

Notably, the side-effect profile of high-dose ACTH and ACTH 1-24 (including hypertension, immune suppression, fluid retention, and central nervous system effects such as irritability), while usually reversible and not affecting every patient, can be significant. The recurrence of spasms in treated patients further supports the need for a search for alternative therapies.

Finally, it is uncertain how systemic ACTH exerts effects within the brain since the blood-brain barrier is relatively impermeable to ACTH.³⁴ Spinal fluid ACTH derives largely from ACTH released by pro-opiomelanocortin-positive neurons of the arcuate nucleus of the hypothalamus and pro-opiomelanocortin-positive neurons of the nucleus tractus solitarius of the medulla. Cerebrospinal fluid ACTH levels are low in untreated infantile spasms,³⁵⁻³⁸ suggesting deficient synthesis within the brain of ACTH and the related endogenous peptide, α -melanocyte-stimulating hormone. Cerebrospinal fluid ACTH levels do not rise, and can even fall, with ACTH treatment, suggesting feedback inhibition of ACTH release.³⁹⁻⁴¹ How ACTH achieves access to the brain or whether ACTH synthesis within the brain increases (or both) is uncertain. Both the arcuate nucleus and the nucleus tractus solitarius abut circumventricular areas where the blood-brain barrier is permeable, providing a potential site of access for systemically administered ACTH to the brain and to pro-opiomelanocortin-positive neurons. Steroid-independent melanocortin receptors are found in both nuclei.

There is no postdose spike in the cerebrospinal fluid concentration of ACTH after a systemic injection. However, as a physiological "sink," cerebrospinal fluid and the cerebrospinal fluid-blood barrier may not be the optimal compartment to study whether ACTH has direct central actions. Effects of ACTH (the parent compound or active fragments) on neurons and glia, especially considering the low concentrations needed for receptor activation, are not necessarily reflected in cerebrospinal fluid levels. An alternative hypothesis is that ACTH acts in infantile spasms, at least in part, by stimulating the production of neurosteroids in the periphery, which are able to enter the brain and exert an anticonvulsant action.²²

In addition to the well-recognized ability of ACTH to stimulate the synthesis of glucocorticoids in the zona fasciculata of the adrenal cortex, ACTH also enhances the synthesis of the mineralocorticoid precursor deoxycorticosterone in the same region of the adrenal gland. Deoxycorticosterone is not only a precursor for aldosterone but it can be converted to the neurosteroid allotetrahydrodeoxycorticosterone, which is a powerful positive modulator of GABA_A receptors and a potent anticonvulsant.⁴² Despite their steroid structures, allotetrahydrodeoxycorticosterone and related GABA_A receptor-modulating neurosteroids differ from traditional steroids in that they do not act through nuclear hormone receptors to regulate gene expression. Whereas there is a

question about the blood-brain barrier permeability of ACTH, allotetrahydrodeoxycorticosterone readily enters the brain. Therefore, allotetrahydrodeoxycorticosterone might mediate the therapeutic activity of ACTH in infantile spasms. Although the neurosteroid hypothesis is attractive, mixed results with other positive GABA_A receptor modulators such as nitrazepam (which can reduce spasm frequency but not eliminate hypsarrhythmia) and the synthetic neurosteroid analog ganaxolone (discussed below) suggest that GABA receptor modulation cannot fully explain the positive therapeutic effects of ACTH.

The possible role of neurosteroids in the action of ACTH encouraged study of the synthetic neurosteroid analog ganaxolone in infants with infantile spasms.^{43,44} In an open-label, add-on, nonblinded clinical study of children with infantile spasms refractory to other agents (including ACTH or vigabatrin), ganaxolone was well tolerated but showed only modest and nonsignificant effectiveness (spasm frequency reduced 50% in about one-third of cases); its effect on hypsarrhythmia, a requirement for antiepileptic effectiveness in infantile spasms, is unknown.⁴⁵ A recent multicenter randomized, placebo-controlled clinical trial showed no clear statistically significant treatment effect although some subjects did appear to demonstrate a treatment-related reduction in spasm clusters as assessed by 24-hour video EEG recordings.⁴⁶

Other treatments have been successful in certain etiological subtypes of infantile spasms.¹⁰ For example, children with tuberous sclerosis complex respond well to vigabatrin.^{13,47} The American Academy of Neurology/Child Neurology Society practice parameter concluded that vigabatrin is "possibly effective" in infantile spasms.¹⁷ Modest dose-dependent benefit from vigabatrin has been shown in a recent randomized trial of 221 children with infantile spasms.⁴⁸ The potential for visual field loss following vigabatrin treatment is widely reported and this side effect must be weighed against potential benefit in children with infantile spasms.⁴⁹ Recent data suggest that the risk of visual field loss in infants treated with vigabatrin for infantile spasms may not be as high as in older individuals receiving this drug.^{50,51}

A variety of alternative treatments for infantile spasms has been utilized, including zonisamide, topiramate, valproate, and the ketogenic diet; these agents have not been validated in large-scale studies, but remain options when first-line agents such as ACTH and vigabatrin fail.³ There is no convincing objective evidence for the efficacy of these alternative therapies at this time.¹⁷ Surgery can play a role in selected patients with infantile spasms secondary to cortical dysplasia.⁵²

In conclusion, clinicians choose a therapy for infantile spasms based on published evidence as well as personal experience, cost, and side-effect profile.^{29,53,54} Therapeutic choice also varies by geography—pyridoxine is a first-line treatment in Japan^{55,56} while physicians in many European countries and Canada begin with vigabatrin, irrespective of the etiology of the infantile spasms.⁵⁷ It is clear that no current therapy for infantile spasms is ideal and that novel agents are needed. As described in the next section, melanocortin receptor agonists, which share structural features with ACTH, might comprise

Table 1. Melanocortin Receptors

MCR Subtype	Ligand Affinity	Prevalent Tissue Expression	Functions
MC1R	α -MSH \geq ACTH \gg γ -MSH	Melanocytes Immune/inflammatory cells Keratinocytes Endothelial cells Glial cells	Pigmentation Antipyresis Anti-inflammation
MC2R	ACTH	Adrenal cortex	Steroidogenesis
MC3R	γ -MSH = ACTH \geq α -MSH	CNS Macrophages	Autonomic functions Anti-inflammation
MC4R	α -MSH = ACTH \gg γ -MSH	CNS	Energy homeostasis Neuroprotection
MC5R	α -MSH > ACTH > γ -MSH	Exocrine glands Lymphocytes	Exocrine secretion Immunoregulation

Abbreviations: MC, melanocortin; MCR, melanocortin receptor; MSH, melanocyte-stimulating hormone; ACTH, adrenocorticotropic hormone. Courtesy of A. Catania, MD

one such alternative. This approach is further supported by recent data attributing ACTH responsiveness to genetic polymorphisms in melanocortin receptor genes.⁵⁸

Melanocortin Receptors

ACTH and α -, β -, and γ -melanocyte-stimulating hormone comprise a family of endogenous peptides called melanocortins, derived from a common precursor, pro-opiomelanocortin. Melanocortins are critical for a variety of physiological processes, including anti-inflammation, neuroprotection, and blood pressure regulation. The cloning and characterization of 5 subtypes of melanocortin receptors, each with a different distribution and function within the body and brain, has led to increased understanding of the role of these peptides and their binding in physiological and pathophysiological processes.⁵⁹ Melanocortin receptors consist of 7 transmembrane G-protein-coupled receptors that signal via the activation of adenylyl cyclase and increase of cyclic adenosine monophosphate. Table 1 lists some of the properties of the 5 types of melanocortin receptors. Commercially available melanocortin receptor antibody assays have not been fully validated, so there is some uncertainty regarding the exact distribution of melanocortin receptors. The best evidence suggests that melanocortin receptor subtypes 3 and 4 are primarily neuronal though all melanocortin receptor subtypes have been found in the brains of various species.⁶⁰ Melanocortin receptor type 4 is distributed more widely in the brain, including cortex, thalamus, and brainstem, whereas melanocortin receptor type 3 has a more restricted localization, including such seizure-sensitive brain cortical regions as the limbic system. ACTH has been shown to act on melanocortin receptor type 4 in the amygdala to suppress endogenous convulsant molecules.⁶¹ ACTH is capable of activating all 5 melanocortin receptors, while only ACTH recognizes melanocortin receptor type 2. Melanocortin receptor type 2 is primarily localized in the adrenal cortex, where it promotes steroidogenesis.

Extra-adrenal influences of ACTH could play a role in suppressing infantile spasms. As stated above, ACTH recognizes

all 5 melanocortin receptors (Figure 2). Therefore, the peptide action is not limited to melanocortin receptor type 2-induced steroidogenesis but also includes effects mediated by other melanocortin receptors. In this regard, one of the most important properties of melanocortin receptors is that they are anti-inflammatory. When a melanocortin binds to a melanocortin receptor, the translocation of the nuclear transcription factor NF- κ B to the nucleus, a process mainly induced by cytokines and other pro-inflammatory agents, is prevented. Therefore, melanocortins inhibit the production of inflammatory mediators, an effect that occurs in both peripheral tissues and central and peripheral nervous systems. In addition, peripheral inflammatory responses are decreased by a central action of melanocortins, via descending neural pathways.^{59,62} A variety of neurodegenerative processes that involve inflammation, such as stroke, trauma, and epilepsy, could potentially be exacerbated by NF- κ B activation and lessened by NF- κ B inhibition (via melanocortins).^{63,64}

The presence of melanocortin receptors in the brain and their activation by endogenous and possibly exogenous ACTH has led to a number of hypotheses regarding the action of these compounds in infantile spasms.⁶¹ Much more work must be done to understand the neuroprotective role of ACTH and perhaps other melanocortins in infantile spasms. The availability of validated test systems, some of which are described below, offers an opportunity for translational research in the treatment of infantile spasms—testing prospective compounds in animal models and then moving promising candidate drugs from the bench to the clinic.

Animal Models of Infantile Spasms

Using animal models, hypotheses about mechanisms can be generated and tested and prospective treatment regimens for infantile spasms can be evaluated. Historically, the lack of relevant animal models has hampered the understanding of the distinctive pathophysiology of infantile spasms. Similarly, the search for a final common pathway among the diverse infantile

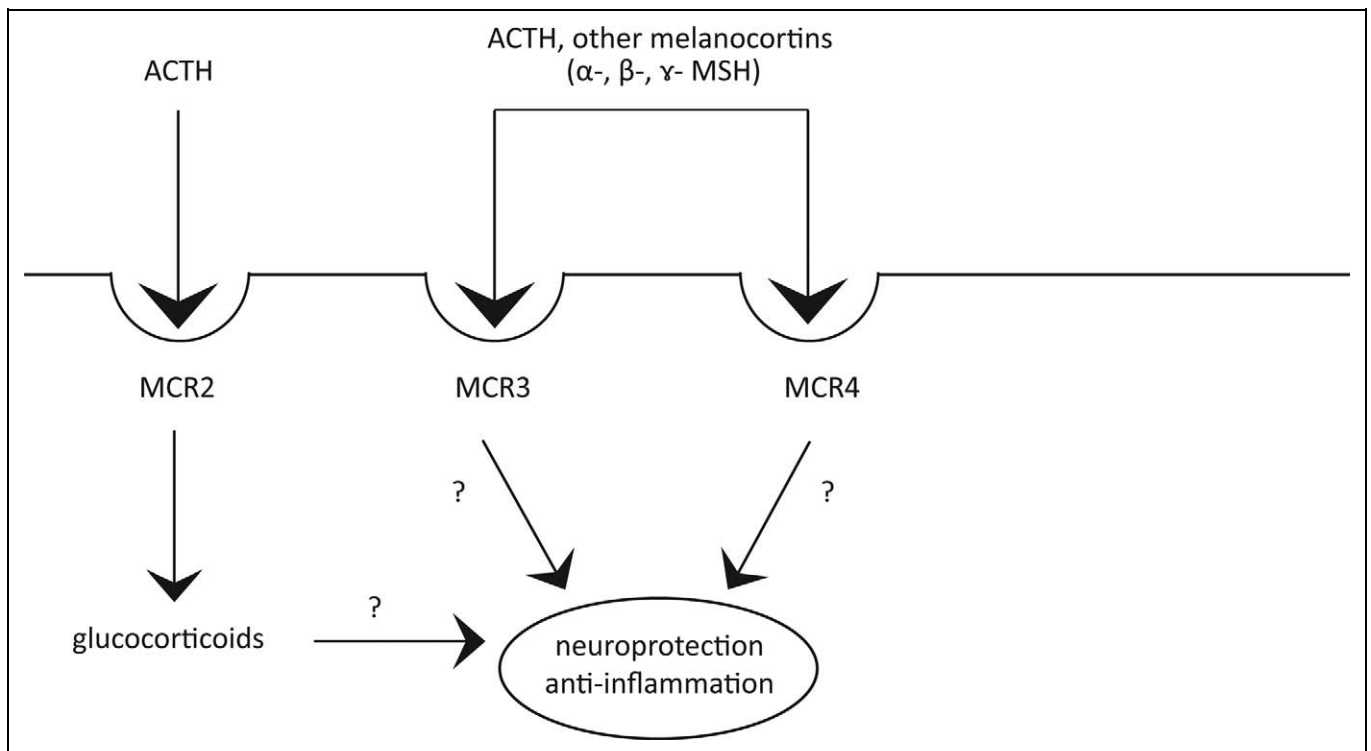


Figure 2. Schematic illustration of melanocortin receptors (MCRs) types 2, 3, and 4, their activation by ACTH or other melanocortins, and some of the possible physiological consequences of melanocortin receptor activation. It is conceivable that neuroprotection and/or anti-inflammation can be obtained in infantile spasms with novel melanocortin receptor agonists.

spasms etiologies has thus far failed to reveal a unifying neurobiological mechanism.^{65,66} However, several investigators have recently developed animal models that mimic one or more critical features of infantile spasms. These emerging infantile spasms animal models have been reviewed in detail recently^{6,67,68} and are summarized in Table 2. Criteria for an ideal model of infantile spasms would include similar seizure type, age of onset of seizures, spectrum of etiologies, EEG features, developmental cognitive deficits, and a pharmacological profile comparable with infantile spasms in humans.⁸⁷ At a minimum, a putative animal model of infantile spasms should exhibit postnatal seizures with an abnormal EEG plus cognitive impairment. Obviously, no single rodent model will replicate the human disorder exactly. Nevertheless, important pathophysiological insights can be gained if appropriate questions are posed.

In parallel with the diverse etiologies of infantile spasms in humans, a large variety of methods have been employed to induce spasm-like seizures in animals, mimicking both genetic causes (eg, Down syndrome with abnormal GABA_B-receptor/G-protein-coupled inward rectifying potassium channel subunit 2 [GIRK2] function; mutations of the Aristaless-related homeobox [*ARX*] gene causing GABAergic interneuron loss) and symptomatic/acquired etiologies (eg, toxin injections to create brain diffuse pathology; tetrodotoxin to abolish cortical neuronal activity). Despite notable differences between models, it is worth emphasizing some of their common features. Each model entails spasm-like seizures or other seizures early

in development in rodents that have been subject to a variety of genetic mutations or exogenous agents as triggers. Some seizures in these models resemble spasms; others have a semiology more closely resembling limbic or complex partial seizures (see Table 2). All models have EEG changes; some but not all models demonstrate the typical interictal EEG abnormality (hyparrhythmia) and ictal EEG changes (electrodecrement) seen in human infantile spasms—this variability is expected considering the structural differences between brains of humans and rodents, the latter having a lissencephalic cortex. In the tetrodotoxin model, in which focal intracerebral infusion of the sodium channel blocker tetrodotoxin ablates neuronal activity and results in spontaneous seizures, electrographic recordings of interictal and ictal activity are convincingly similar to human examples.⁷⁸

Seizures are seen at different postnatal ages across models, with the specific genetic or neurologic insult interacting with brain dysfunction at a particular developmental stage, resulting in varied epilepsy phenotypes. In the multiple-hit model, seizures occur at an age analogous to human infantile spasms, while in the tetrodotoxin and *ARX* mutation models, they occur somewhat later, but still within a specific age window. In some models, seizures occur secondary to genetic mutations; in others, seizures occur only in response to a provocative trigger, but each model can be informative—seizures that are spontaneous allow investigation of factors involved in epileptogenesis, while seizures occurring only in response to an exogenous trigger permit study of factors influencing network excitability.

Table 2. Animal Models of Infantile Spasms

Model	How Model Is Created	Clinical Relevance	Limitations	Selected References
CRH	CRH, ip	Stress-induced increase in CRH as common factor in multiple infantile spasms etiologies	Limbic seizures, not spontaneous	61 65 69 70 71
Chronic neonatal stress	Limiting nest material	Spontaneous spasms Appropriate age Cognitive deficits	Preliminary results (abstract only) Effects of ACTH not tested	
NMDA or betamethasone/NMDA	NMDA ip at various postnatal ages or betamethasone ip to dam on G15, followed by NMDA to offspring on P15	Model of cryptogenic IS with flexion spasms Allows testing of possible interventions Cognitive changes	No chronic, spontaneous seizures Treatments (ACTH, VGB) given prior to spasms	72 73 74 75 76 77
TTX	TTX ic infusion by osmotic pump for 28 days, beginning on P10	Chronic blockade of neuronal activity leads to hyperexcitability and seizures (spasms) Video-EEG: hypsarrhythmia and electrodecremental seizures Spasms in clusters, especially during slow wave sleep	Seizures occur at later developmental stages Treatment response unknown Cognitive changes unknown	78 79 80
Multiple-hit	Doxorubicin icv and lipopolysaccharide ic on P3; <i>p</i> -chlorophenylalanine ip on P5	Model of symptomatic IS with severe, diffuse cortical injury Appropriate age range EEG changes Cognitive changes	Need to have consistent pathologic changes and distinguish toxin effects from seizure effects ACTH ineffective, VGB transiently effective (both given after spasms onset)	81 82
ARX conditional knockout	Targeted deletion of ARX gene from cortical GABAergic interneurons	Mimics a known human mutation that causes IS Evolution of seizure type EEG abnormalities	Cognitive changes unknown Seizures occur at later developmental stages Treatment response unknown	83 84
ARX expansion	Targeted expansion of polyalanine tract in ARX gene, causing interneuronopathy	Mimics a known human mutation that causes IS Cognitive changes EEG abnormalities	Treatment response unknown	85
Down syndrome	GABA _B receptor agonists ip to Ts65Dn mice	Mimics Down syndrome, a human chromosome disorder with high incidence of IS Spasms with polyspike wave bursts and electrodecrement ACTH, VGB reduced acute spasms when given prior to GABA _B -R agonist	No chronic, spontaneous seizures Requires exogenous agent (GABA _B -R agonist) to elicit spasms	86

Abbreviations: ACTH, adrenocorticotropic hormone; CRH, corticotropin releasing hormone; NMDA, N-methyl-D-aspartate; TTX, tetrodotoxin; ip, intraperitoneal; G, gestational day; P, postnatal day; ic, intracerebral; icv, intracerebroventricular; ARX, Aristaless-related homeobox; IS, infantile spasms; VGB, vigabatrin; GABA_B-R, γ -aminobutyric acid receptor type B.

Both types of information will be useful in understanding the complexity of infantile spasms generation. In addition, a model's usefulness is enhanced if cognitive deficits can be demonstrated; most models have fulfilled this criterion to some degree. Deficits similar to those seen in children with infantile spasms have been documented, such as learning and memory impairments and autistic-like behaviors.

Regarding medication responsiveness, there is a paucity of data in most models at this time. The ACTH 1-24 fragment

is effective in the Down syndrome model⁸⁶ but ACTH is poorly effective in the multiple-hit model and modestly effective in increasing latency to onset of spasms in the betamethasone/*N*-methyl-D-aspartate model. In the corticotropin-releasing hormone model, in which limbic seizures are induced by small doses of corticotropin-releasing hormone in the immature brain,⁶⁹ ACTH would not be expected to reduce seizures since this peptide is downstream from the probable site of convulsant action.⁸⁸ Other agents have produced varied results. Vigabatrin

pretreatment prevented some extensor spasms seizures in the Down syndrome model,⁸⁶ reduced flexion seizures after *N*-methyl-D-aspartate administration,⁷² and transiently suppressed spasms in the multiple-hit model when given after seizures began.⁸¹ Preliminary data suggest that carisbamate might be beneficial in the multiple-hit model⁸² and that melanocortin receptor type 4 agonists delay the onset to spasms induced by *N*-methyl-D-aspartate.⁸⁹ While not all models respond to ACTH or other human treatments, a neuroprotective or rescue effect of a treatment would certainly increase a model's validity and point the way to testing some of the treatment protocols discussed above. Eventually, one or more model could be useful for comparing treatment efficacy prior to clinical trials.

Another way to approach the enigma of infantile spasms, rather than to create a "model" of the disorder, is to investigate whether a common final pathway can explain the pathophysiology across etiologies. If it is assumed that stress on the developing brain is a feature of many infantile spasms etiologies, then the role of the synthesis, activation, and release of endogenous stress hormones can be evaluated.^{70,90,91} A variety of stresses in the immature brain cause the release of the neuropeptide corticotropin-releasing hormone from cortical, hippocampal, amygdala, and brainstem neurons.⁹² Corticotropin-releasing hormone is highly convulsant at postnatal ages relevant to infantile spasms but not at older ages.^{65,70} In the immature brain, corticotropin-releasing hormone causes seizures, injures neurons, causes atrophy of dendritic spines, and leads to long-term learning and memory impairment.^{93,94} Preliminary data reports that chronic stress in infant rats, induced by limiting the amount of available nesting material in the cage,⁹⁵ leads to spasm-like events with electroencephalographic attenuation.⁷¹ Experimentally, ACTH has been shown to suppress release or expression of corticotropin-releasing hormone.^{61,96} The hypothesis that stress-induced corticotropin-releasing hormone dysregulation plays a role in the pathophysiology of infantile spasms can be explored in conjunction with other infantile spasms models.

All of these infantile spasms models are at an early stage and much more needs to be learned before clinical correlations can be made. Conference attendees concluded that clinically relevant insights from animal models are likely to emerge over time.

Fundamental Remaining Questions and Unresolved Issues

Infantile spasms is an epileptic encephalopathy of early infancy with severe consequences in terms of future epilepsy and cognitive impairment. The diagnosis is usually made by a pediatric neurologist, pediatrician, or other health care practitioner who treats young infants. The fundamental mechanisms and neurobiological basis of infantile spasms remain uncertain. It is doubtful that a single mechanism can account for all of the manifestations of infantile spasms; more likely, interacting pathologies lead to one or more common pathways that cause the disruption of neural circuit function in this syndrome.^{5,65} Whether the pathophysiology of infantile spasms explicitly

involves ACTH or melanocortins remains an important area of investigation.

There are multiple critical remaining questions about infantile spasms pathophysiology and treatment that will inform clinicians about where the field is headed and stimulate further research. For example, why is the presentation and treatment responsiveness of infantile spasms confined to a specific developmental window? Can we make use of this characteristic age dependence to develop a targeted treatment related to etiology or identify a final common pathway that is not critically reliant on etiology or age? What epileptogenic processes occur during the interval from neurologic insult to development of spasms/hypsarrhythmia and how can we intervene effectively during this latent period? Why does ACTH work in some patients and etiologies and not in others? Does ACTH cross the blood-brain barrier when administered peripherally, and if not, how does it cause an effect on the central nervous system? Do neurosteroids play a role? Does ACTH exert its effects on melanocortin receptors independent of the ACTH concentration? Given the associations between cytokines and other mediators of inflammation and cognitive effects, can developmental outcomes in infantile spasms be improved with further understanding of the role of inflammation? Do the anti-inflammatory effects of melanocortins provide a sufficient rationale for infantile spasms treatment?

This report should be viewed as a preliminary "status report" of new and emerging concepts from clinical data on infantile spasms and available animal models. Further scientific progress will positively impact the comprehensive care of children devastated by this severe epileptic encephalopathy.

Author Contributions

The first author (CES) wrote the article, based on discussions held at a meeting of specialists in infantile spasms clinical care and research in New York City on June 14, 2010. Drafts were reviewed by all coauthors. CES then incorporated all revisions into the final version.

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