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Infantile Spasms: The Role of Prenatal Stress and Altered GABA Signaling

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Abstract
Infantile spasms (IS) is a rare epileptic disorder occurring in children under the age of one that can often lead to severe developmental delays throughout life. Though over 200 etiologies have been associated with this disorder, many cases remain unexplained. Research into the etiology of IS has implicated causes such as exposure to prenatal stress or changes in GABAergic signaling. Here, we describe recent findings that draw a direct connection between prenatal stress, altered GABA signaling, and the development of IS. We also discuss how these findings can be used in the classroom to enrich discussions of nervous system physiology, development, and disease. https://doi.org/110.21692/haps.2019.017

Key words: neurophysiology, infantile spasm, epilepsy, GABA, maternal stress

Introduction
Infantile spasms (IS) is a disorder characterized by infantile epileptic spasms. IS is estimated to occur in about 2.5 – 5.0 in 10,000 live births (Paciorkowski et al. 2011; Shi et al. 2012). There are three defining features used in the diagnosis of IS. The first is the occurrence of repetitive spasms, with each spasm consisting of a short flexion, a short contraction, or both, for one to two seconds (Swann and Moshe 2012). The second defining feature is that spasm onset occurs in children one year of age or younger, most typically between three to seven months of age (Swann and Moshe 2012; Pavone et al. 2014). The third defining feature, which sets IS apart from other forms of infantile epilepsies, is hypsarrythmia (Pavone et al. 2014). Hypsarrythmia is an abnormal brain pattern on an electroencephalogram (EEG), characterized by chaotic, high-voltage, and slow waves along with asynchronous waves between each hemisphere and within each hemisphere of the cortex (Shields 2006). Several subtypes of IS have been recognized based on the particular set of symptoms present. The most common of these, West Syndrome, is defined by the appearance of all three characteristics of IS accompanied by developmental delays that become apparent as the child grows (Pavone et al. 2014).

Although the spasms associated with IS typically resolve by age five, the consequences of those early epileptic events can have repercussions throughout a patient's lifetime. IS is associated with serious developmental delays. Only seventeen percent of those affected by IS will have an IQ greater than 85, and only 15 – 25% of patients achieve a developmental outcome that would be characterized as normal (Nelson 2015). The most common developmental delays include autism, which occurs in about 15 – 33% of cases, and intellectual disability, present in about 45% of cases (Shields 2006). Since the spasms occur during a critical period of development, adverse developmental outcomes can only be prevented when treatments yield complete control of the spasms (Shields 2006). Unfortunately, there are only two currently available treatment options; neither guarantees complete spasm control, and both have significant drawbacks (Shields 2006). The first treatment option, adrenocorticotropic hormone (ACTH), has been shown to reduce spasm activity by 42 – 87% within two weeks of treatment. However, patients taking ACTH commonly experience relapse along with serious side effects such as electrolyte imbalances, delays in growth, suppression of the immune system, and cardiomyopathy (Nelson 2015). A second treatment option, the anticonvulsant drug Vigabatrin, is preferred because it has fewer side effects (Shields 2006). However, this drug also has significant limitations, including a 16 – 21% relapse rate and visual impairments in 15 – 30% of cases (Nelson 2015).

Because IS is associated with serious lifelong developmental delays there is significant interest in identifying its underlying causes, with the hope that increased understanding will aid in the development of more effective treatment approaches and preventative measures. Previous research has identified multiple conditions associated with IS, including tuberous sclerosis complex, Down syndrome, cortical malformations, and prenatal infections (Shi et al. 2012; Swann and Moshe 2012; Yuskaitis et al. 2018). However, about a third of patients are diagnosed with "cryptogenic" IS, in which no underlying cause can be identified (Shields 2006; Yuskaitis et al. 2018). There is an urgent need to elucidate the cause(s) of cryptogenic IS, as there is some evidence to suggest that IS etiology can influence treatment efficacy (Garcia-Penas and Jiminez-Legido 2017; Liang et al. 2017; Roldan 2017; Ko et al. 2018).

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A number of potential mechanisms have been proposed for cryptogenic IS. Some studies have implicated altered gamma-aminobutyric acid (GABA) signaling, because multiple patients suffering from IS have been found to be carrying mutations in GABA pathway genes (Galanopoulou 2010; Edvardson et al. 2013; Kelsom and Lu 2013; Olivetti et al. 2014; Papandreou et al. 2016). Other studies, using animal models of IS, suggest that exposure to prenatal stress might contribute to the development of IS, although the precise mechanism of action is unknown (Shi et al. 2012; Yum et al. 2012). Although these two proposed etiologies – altered GABA signaling and exposure to prenatal stress – have been studied independently, more recent research suggests they may actually be directly linked. In this review, we will describe recent findings suggesting that prenatal stress causes alterations in the GABA pathway, thereby contributing to the development of IS. We will also discuss how these findings can be used in the classroom to enrich discussions of nervous system physiology, development, and disease.

Role of the GABA pathway during normal nervous system development

GABA is a neurotransmitter that acts as an important inhibitory signal in the adult central nervous system (Li and Xu 2008). GABAergic neurons synthesize GABA from the amino acid glutamate in a reaction that is catalyzed by glutamic acid decarboxylase (GAD). When GABA is released from GABAergic neurons, it binds to receptor proteins on postsynaptic neurons (Li and Xu 2008; Wang and Kriegstein 2009). GABA's principal receptors are the $GABA_A$ receptors. $GABA_A$ receptors are ionotropic; when bound to GABA, $GABA_A$ receptors trigger the opening of Cl^- channels (Li and Xu 2008; Wang and Kriegstein 2009). In the mature brain, most cells express KCC2 (K^+ Cl^-) cotransporters, which pump Cl^- ions out of the cell, thus establishing a lower intracellular concentration of Cl^- (Wang and Kriegstein 2009). As a result, when GABA binds to $GABA_A$ receptors, Cl^- ions flow *into* the postsynaptic neuron, hyperpolarizing the neuron and leading to an *inhibitory* effect ((Li and Xu 2008; Wang and Kriegstein 2009).

While GABA is well established as an inhibitory signal throughout adulthood, its role differs during development of the nervous system. During prenatal development and into the first two weeks of infancy, most neurons express the NKCC1 cotransporter rather than the KCC2 cotransporter (Kirmse et al. 2018). NKCC1 (a Na^+ $K^+Cl^-Cl^-$ cotransporter) pumps Cl^- ions into the neuron, increasing the intracellular concentration (Li and Xu 2008; Wang and Kriegstein 2009). Therefore, when GABA binds to $GABA_A$ receptors in immature neurons, Cl^- ions flow *out* of the postsynaptic neuron, depolarizing the neuron and leading to an *excitatory* effect ((Li and Xu 2008; Wang and Kriegstein 2009; Kirmse et al. 2018).

The excitatory function of GABA is essential for many aspects of central nervous system development (Wang and Kriegstein 2009; Kirmse et al. 2018). For example, GABA directs the proliferation and migration of distinct populations of progenitor cells (Wang and Kriegstein 2009; Wu and Sun 2014). In addition, because most newly formed neurons express GABA receptors before glutamate receptors, excitatory GABA is critical in the early formation of neural networks (Wang and Kriegstein 2009). However, as the brain develops, GABA transitions from an excitatory function to the inhibitory role it will play throughout most of childhood and adulthood. This excitatory-to-inhibitory switch is driven by changes in gene expression - increased expression of KCC2 and decreased expression of NKCC1 – and normally occurs in the second week of the postnatal period (Kirmse et al. 2018). Since GABA signaling is such a prominent and critical driving force in the formation of neural circuits in the central nervous system during development, changes in prenatal and postnatal GABAergic signaling would be expected to have wide-ranging and long-lasting effects on the central nervous system.

Maternal stress can affect prenatal development

In humans, exposure to stress (both physical and emotional) stimulates the hypothalamic-pituitary-adrenal (HPA) axis, causing a variety of responses (Chrousos 2008; Brunton 2013; Goldstein et al. 2013). Part of the stress response includes the release of stress hormones, such as corticotrophin releasing hormone (CRH), catecholamines such as epinephrine, and glucocorticoids such as cortisol (Chrousos 2008; Goldstein et al. 2013). These stress hormones act on multiple body systems, including the central nervous system, cardiovascular system, and immune system, to induce a wide range of immediate effects on the body (Chrousos 2008; Goldstein et al. 2013). While the stress response is an adaptive trait, acute and chronic stress are also thought to have many adverse effects and are linked to diseases such as hypertension and metabolic disorders in adults (Chrousos 2008).

Pregnant women undergo the same physiological responses to stress, and there is evidence to suggest that the resulting hormones, particularly CRH and glucocorticoids such as cortisol, may adversely affect the developing fetus (Chrousos 2008). Although an enzyme called 11β-hydroxysteroid dehydrogenase (11βHSD2) is expressed in the placenta to prevent glucocorticoids from crossing the placental barrier, maternal stress can suppress the expression of 11βHSD2 (Huang 2014). As a result, when a pregnant woman experiences acute or chronic stress, glucocorticoids are able to cross the placental membrane and reach the fetal body. Once glucocorticoids enter the fetal body, they can potentially affect development of multiple organs and organ systems, including the central nervous system (Chrousos 2008).

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Because of the pivotal processes taking place during embryonic development, the developing fetus is especially vulnerable to changes in its environment (Sandman et al. 2011). In the central nervous system, crucial events such as neurogenesis, differentiation and proliferation of neuronal progenitor cells, synaptic formation, and the emergence of the neural circuit occur during prenatal development (Shi et al. 2012). Exposure of the fetus to gestational stress can specifically impact central nervous system development (Sandman et al. 2011). Prenatal exposure to excess glucocorticoids is thought to alter gene expression in the brain both via changes in transcription factor activity and via epigenetic modifications, such as DNA methylation and histone modifications (Fine et al. 2014; Whirledge and Cidlowski 2010). Fetal exposure to excess glucocorticoids can also interfere with neural signaling in the fetal brain, including the GABA pathway (Iacobas et al. 2013). These alterations in the developing central nervous system are hypothesized to have impacts that persist well beyond birth, increasing the risks for disorders such as anxiety, autism, schizophrenia, ADHD, and IS (Wang et al. 2017; Negrón-Oyarzo et al. 2016; Sandman et al. 2011). Indeed, a number of recent studies have shown that prenatal stress specifically alters components of the GABAergic pathway and increases susceptibility to IS in particular (Shang et al. 2010; Stevens et al. 2013; Uchida et al. 2014; Baek et al. 2016; Shi et al. 2016; Kwon et al. 2018; Vangeel et al. 2017)

Effects of prenatal stress on the GABA pathway and spasm susceptibility

A number of recent studies have shown that prenatal stress can directly alter GABAergic signaling in the fetal and neonatal brain (Stevens et al. 2013; Uchida et al. 2013; Baek et al. 2016; Shi et al. 2016; Kwon et al. 2018; Vangeel et al. 2017). These changes occur at multiple levels of the GABA pathway. Furthermore, several of these studies directly link prenatal stress and changes to GABAergic signaling with increased risk of IS (Shang et al. 2010; Baek et al. 2016; Shi et al. 2016; Kwon et al. 2018).

Prenatal stress can affect GABAergic signaling in multiple ways. First, prenatal stress has been shown to reduce the proliferation of GABAergic neurons during embryonic development (Stevens et al. 2013; Uchida et al. 2014). Prenatal stress also impairs the migration of GABAergic neurons during embryonic development, at least in part due to decreased expression of genes required for migration (Stevens et al. 2013). As a result, there is a general decrease in the number of GABAergic neurons present in the neonatal cortex of prenatally stressed offspring (Stevens et al. 2013; Uchida et al. 2014; Baek et al. 2016; Kwon et al. 2018). Prenatal stress also affects downstream components of the GABA pathway during embryonic development. A gene encoding one of the GABA receptors has been found to undergo increased DNA methylation following exposure to prenatal stress, and GABA receptor binding function is also reduced following exposure to prenatal stress (Vangeel et al. 2017; Baek et al. 2016). Collectively, these changes could significantly impair GABAergic signaling during embryonic development in prenatally stressed offspring.

In addition to changes in GABAergic neurons and GABA receptors during embryonic development, the excitatory-to-inhibitory switch that normally occurs in the neonatal period may also be affected by prenatal stress. The excitatory-to-inhibitory switch is normally driven by downregulation of NKCC1 and simultaneous upregulation of KCC2 shortly after birth (Kirmse et al. 2018). However, KCC2 expression is significantly reduced in the neonatal cortices of prenatally stressed offspring (Baek et al. 2016; Kwon et al. 2018). Thus exposure to prenatal stress might cause a delay in the excitatory-to-inhibitory switch.

These recent studies have shown that prenatal stress impairs the excitatory GABAergic signaling that occurs during embryonic development, which could potentially disrupt development of the central nervous system (Stevens et al. 2013; Uchida et al. 2014; Baek et al. 2016; Vangeel et al. 2017; Kwon et al. 2018). In addition, prenatal stress disrupts the postnatal excitatory to inhibitory switch, which could impair inhibitory GABA signaling in the neonatal brain (Baek et al. 2016; Kwon et al. 2018). These pre- and post-natal changes to GABAergic signaling could each contribute to increased IS susceptibility. Indeed, prenatal stress increases likelihood and severity of infantile spasms in rodent models of IS (Baek et al. 2016; Shi et al. 2016; Kwon et al. 2018). Human studies have also found a correlation between prenatal stress and IS (Shang et al. 2010). While future studies are needed to determine the mechanism by which prenatal stress directly alters components of the GABAergic pathway, these studies build a compelling argument supporting a model in which prenatal stress directly alters GABAergic signaling in the developing central nervous system, leading to increased susceptibility to IS.

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Conclusion

Multiple recent studies demonstrate that prenatal stress and associated changes in GABAergic pathways may present an important mechanism increasing susceptibility to the development of IS during infancy. These findings are clinically relevant as they may help in the development of more effective prevention and treatment plans for IS. Future studies should continue to elucidate the mechanisms by which prenatal stress alters GABA signaling and develop drugs that target GABA pathway components for the treatment of IS.

Classroom Implementation Guide

Because GABA serves as the primary inhibitory signal in the adult nervous system, GABAergic signaling is an important topic covered in nearly all physiology courses. This manuscript can be used to reinforce basic concepts of GABAergic signaling, incorporate current research in the field of neurophysiology into the classroom, and encourage students to discuss clinical applications of the GABA pathway. Here is a suggested outline for use of this manuscript in a physiology classroom:

1. Introduce the basic concepts of GABAergic signaling.
2. Ask students to discuss how changes in the GABA pathway might result in epilepsy. The discussion should lead to the conclusion that a decrease in GABA function could cause nervous system disinhibition or inappropriate excitation, inducing seizure.
3. Ask students to read the section of this manuscript that discusses the role of the GABA pathway during development, and use this information to predict how a delay in the excitatory-to-inhibitory switch might affect infants. Students should conclude that the delay might cause seizures.
4. More advanced students can read the rest of the paper to learn about the role of prenatal stress in altering GABAergic signaling and causing IS. Following this reading, students can be asked to discuss how these recent findings should influence maternal care guidelines and research into more effective treatments for IS. These discussions will reinforce student understanding of GABAergic signaling throughout both development and adulthood and encourage them to apply their knowledge to clinical and therapeutic applications.

About the Authors

Maria Schuck graduated from Arcadia University with a BA in Biology in May of 2019. She is currently enrolled in the Salus University Master's Program in Occupational Therapy, starting in the Fall of 2019.

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