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Review

Early life stress in epilepsy: A seizure precipitant and risk factor for epileptogenesis

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ABSTRACT

Stress can influence epilepsy in multiple ways. A relation between stress and seizures is often experienced by patients with epilepsy. Numerous questionnaire and diary studies have shown that stress is the most often reported seizure-precipitating factor in epilepsy. Acute stress can provoke epileptic seizures, and chronic stress increases seizure frequency. In addition to its effects on seizure susceptibility in patients with epilepsy, stress might also increase the risk of epilepsy development, especially when the stressors are severe, prolonged, or experienced early in life. Although the latter has not been fully resolved in humans, various preclinical epilepsy models have shown increased seizure susceptibility in naïve rodents after prenatal and early postnatal stress exposure. In the current review, we first provide an overview of the effects of stress on the brain. Thereafter, we discuss human as well as preclinical studies evaluating the relation between stress, epileptic seizures, and epileptogenesis, focusing on the epileptogenic effects of early life stress. Increased knowledge on the interaction between early life stress, seizures, and epileptogenesis could improve patient care and provide a basis for new treatment strategies for epilepsy.

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1. Introduction

Epilepsy is a heterogeneous condition in which different underlying pathologies can cause abnormal excessive synchronous neuronal activity in the brain, resulting in epileptic seizures [1]. In the majority of patients with epilepsy, seizures can be triggered or provoked by various endogenous and exogenous factors, such as sleep deprivation, fever, light flashing, hyperventilation, or alcohol [2–17]. Some of these precipitating factors are more often found in patients with an epileptic focus localized in specific brain regions, a specific electroclinical syndrome, or certain etiology, but most seizure precipitants are reported in a wide variety of patients.

The seizure-precipitating factor most often reported by patients with epilepsy is stress; this pertains to both physical stress, like physical exercise or illness, and psychological stress. The first reports on the relation between epilepsy and stress date from over half a century ago [18–20]. In addition to its effects on seizure susceptibility, stress can also increase the risk of the *development* of epilepsy, especially when the stressors are severe, prolonged, or experienced early in life. Stressors can alter (genetic) processes important for brain morphology and function or directly affect pathways involved in epileptogenesis, here defined as the gradual changes in molecular, cellular, and network properties by which the normal brain develops the ability to generate recurrent spontaneous seizures [21–36].

In this paper, we will review the current literature on the effects of stress on epileptogenesis and epilepsy. We will discuss human as well as preclinical studies evaluating the relation between stress, epileptic seizures, and epileptogenesis, focusing on the epileptogenic effects of early life stress.

2. Stress and the brain

Stress is something we all experience every now and then, and most people have an idea what the term 'stress' means. Although there is no general consensus on its definition, from a biological perspective, stress is most often defined as the subjective experience of a threat of homeostasis (the threat itself is called a stressor) [37]. The response to stress consists of adaptive changes in the organism's physiology, resulting in a physical and psychological state optimal to reinstate homeostasis. Important in this response is the activation of the sympathetic nervous system and the hypothalamic–pituitary–adrenal (HPA) axis that jointly initiate the changes throughout the body that result in, among others, alertness and adaptation to the situation at hand.

Although stress is often very adaptive in the short term, it can potentially have long-term maladaptive consequences by changing the neuroendocrine stress response as well as brain structure and function.

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This happens especially when stress is experienced chronically or in early life. Stress-induced changes in stress responsiveness and brain function were shown to be associated with increased vulnerability to diseases, including neurological and psychiatric illnesses. In this section, we will briefly discuss the hormonal stress response and its regulation, as well as the results of acute, chronic, and early life stress on brain structure and function.

2.1. The stress response and its regulation

Exposure to a psychological or physiological stressor activates two main pathways: the autonomic nervous system and the HPA axis, leading to the secretion of catecholamines and corticosteroids, respectively (Fig. 1). The hypothalamus, which is important in regulating body homeostasis, has a key role in the control of both systems. Psychological stressors are firstly processed cortically and indirectly reach the hypothalamus via multiple nuclei in the limbic system, with an important role for the amygdala [38]. Physical stressors like pain, inflammation, and hypoglycemia activate the hypothalamus directly through monosynaptic projections from receptor cell populations located in the brain stem [38,39].

2.1.1. Sympathetic nervous system

Stress exposure activates within seconds the sympathetic part of the autonomic nervous system while suppressing the parasympathetic innervation. This is initiated by the neural control centers in the brain stem and hypothalamus, where sensory information from the thoracic and abdominal viscera is integrated with information from the cerebral cortex and the limbic system [40,41]. From the hypothalamus and brain stem, neuronal projections run to preganglionic neurons in the brain stem and the lateral horn of the thoracic and upper lumbar segments of the spinal cord [42]. Postganglionic neurons project to the viscera, resulting in the release of the catecholamines adrenaline (mostly from the adrenal medulla) and noradrenaline (mainly from sympathetic nerve terminals), together inducing a state of arousal known as the fight-or-flight response [43]. The activation of the sympathetic nervous system is short-lasting, as parasympathetic activation quickly brings the system back to baseline conditions. Indirectly (via the vagal nerve), adrenaline from the adrenal gland can increase noradrenaline levels in the brain.

2.1.2. Hypothalamic–pituitary–adrenal axis

Activation of the HPA axis is somewhat slower and induces a more long-lasting response to stress. Stress exposure stimulates the paraventricular nucleus of the hypothalamus to release corticotropin releasing hormone (CRH) and arginine vasopressin (AVP). Through the pituitary portal veins, these hormones reach the anterior pituitary where CRH stimulates the synthesis and secretion of adrenocorticotropic hormone (ACTH), a process potentiated by AVP [44]. Via the bloodstream, ACTH reaches the adrenals and stimulates the adrenal cortex to produce and

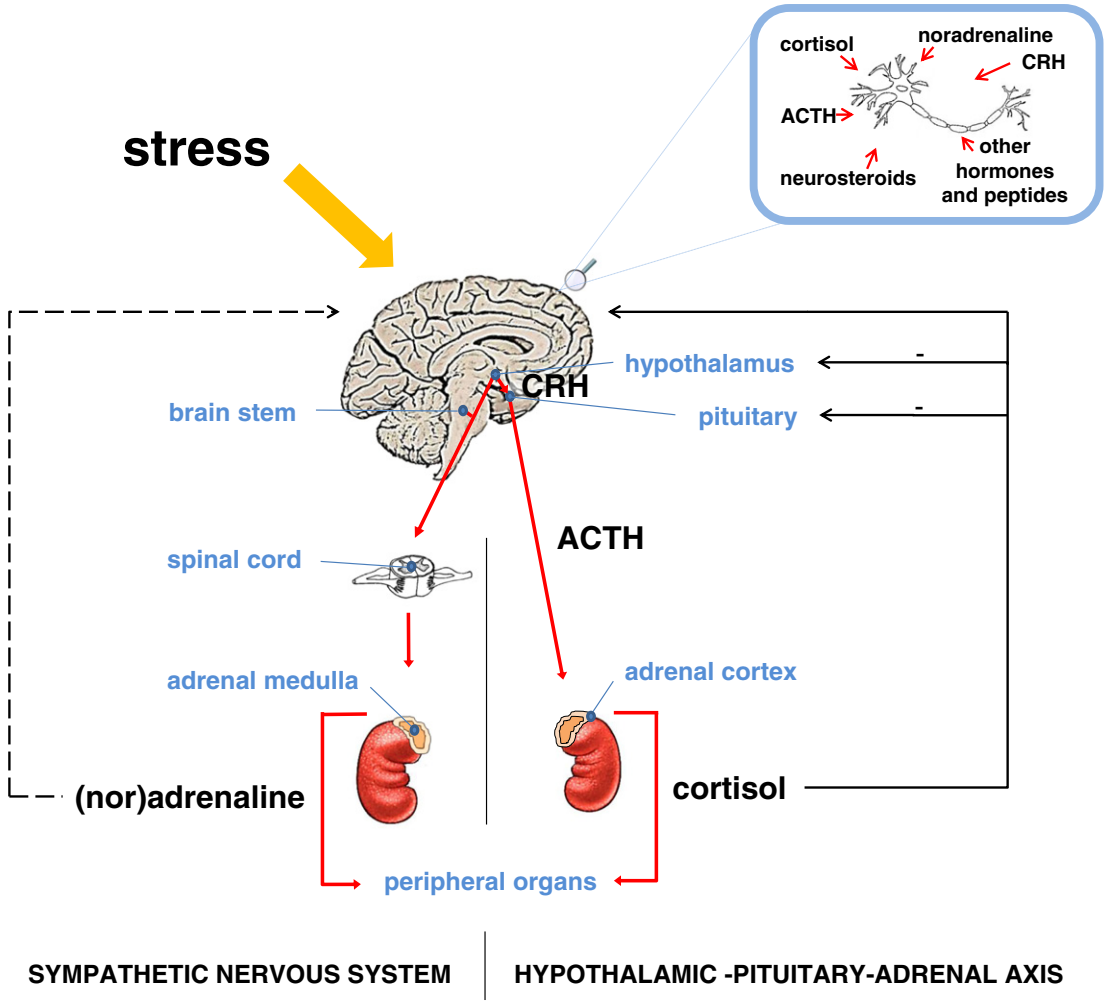

Fig. 1. Stress response. Schematic overview of the stress response mediated by the sympathetic nervous system (left) and the hypothalamic–pituitary–adrenal axis (right). Upper-right inset: all of the hormones involved in the stress response reach the brain via the bloodstream (drawn line) or indirectly via the vagal nerve (dashed line) and can therefore influence neuronal excitability. CRH—corticotropin releasing hormone, ACTH—adrenocorticotropic hormone.