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Hypothalamic-pituitary-adrenocortical axis dysfunction in epilepsy

Aynara Wulsin[1,2,4], **Matia B. Solomon**[1,2], **Michael Privitera**[3], **Steve C. Danzer**[2,4], and **James P. Herman**[1,2]

[1]Department of Psychiatry and Behavioral Neuroscience, University of Cincinnati, College of Medicine, Cincinnati OH

[2]Neuroscience Program, University of Cincinnati, College of Medicine, Cincinnati OH

[3]Department of Neurology, Neuroscience Institute, University of Cincinnati, Cincinnati, OH

[4]Departments of Anesthesia and Pediatrics, University of Cincinnati, Cincinnati, OH

1. Introduction

Temporal lobe epilepsy (TLE) is the most prevalent form of epilepsy in adults, often with high rates of pharmacoresistance [1]. To date, there are no FDA-approved therapies or interventions to cure or prevent TLE. Epilepsy is a paroxysmal disorder, with the defining feature (seizures) occurring with little to no warning. Unpredictable seizures make many normal activities, like driving a car or holding down certain jobs, impossible [2]. Stress is repeatedly reported as one of the most common seizure triggers in patients with an epilepsy diagnosis, including TLE [3–9]. Understanding the molecular mechanisms underlying this association may allow clinicians to predict seizure episodes and/or mitigate their disruptive effect. A second unmet need for TLE patients is a better understanding of, and treatments for, the high incidence of comorbid stress-related psychopathologies, such as depression and anxiety [10–14].

Increased activity of the hypothalamo-pituitary-adrenocortical (HPA) axis is hypothesized to link core epilepsy symptoms and associated stress-related psychopathologies [15–17]. The relationship may be bidirectional [18,19]. Therefore, HPA axis dysfunction in TLE may be a

Corresponding: Author: Aynara, Chavez Wulsin, University of Cincinnati College of Medicine, Genome Research Institute, 2170 E. Galbraith Rd. Room 216, Cincinnati OH 45237-0506, Telephone: (513) 558-3025, Fax: (513) 558-9104, wulsinac@mail.uc.edu. James P. Herman, University of Cincinnati, Department of Psychiatry and Behavioral Neuroscience, 2170 E. Galbraith Rd. Bldg A. Room 145, Cincinnati OH 45237-0506, Telephone: (513) 558-4813, Fax: (513) 558-9104, james.herman@uc.edu

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common etiological mechanism underlying stress-evoked seizures and stress-related psychopathologies. The purpose of this review is to 1) summarize the basic functions of the HPA axis, 2) discuss the current evidence that this system is disrupted in TLE, 3) consider potential mechanisms by which the HPA axis is damaged in rodent models of TLE and 4) discuss the implications of HPA axis dysfunction in humans for seizure triggering and psychiatric comorbidities.

2. The HPA axis stress response and the importance of temporal lobe structures in its regulation

The physiological response to stress is highly conserved throughout vertebrate phylogeny. The HPA axis stress response allows individuals to adapt and cope when faced with real or perceived threats of physical or emotional significance. Upon exposure to stress, neurons in the paraventricular nucleus of the hypothalamus release corticotrophin releasing hormone (CRH), which travels through the hypophyseal portal system to cause release of adrenocorticotrophic hormone (ACTH) from the anterior pituitary. ACTH stimulates the adrenal cortex to synthesize and secrete glucocorticoids; cortisol in primates and corticosterone in rats and mice (Figure 1). Glucocorticoids act in the brain and in the periphery via binding to two major receptor types, the mineralocorticoid receptor (MR) and glucocorticoid receptor (GR). MRs bind glucocorticoids with high affinity in the brain and are thought to be largely saturated at low (non-stress) levels of circulating glucocorticoids. GRs have a lower affinity for glucocorticoids and are responsive over a wide dynamic range. Consequently, GRs are primarily responsible for the physiological effects of stress-induced glucocorticoid secretion. Together, GR/MR binding regulates gene activity to maintain energy homeostasis, control endogenous inflammatory processes and modulate cognition [20]. Glucocorticoids also act to regulate their own secretion via negative feedback pathways.

While rapid activation of the HPA axis in response to stress is essential for survival, effective termination of this response is critical to avoid potentially deleterious effects of excessive and persistent glucocorticoid secretion [20]. Thus, glucocorticoids also act via negative feedback to constrain activation of the HPA axis [21]. Feedback regulation occurs via two important GR-mediated mechanisms: 1) fast feedback inhibition of CRH-expressing neurons in the paraventricular nucleus of the hypothalamus via non-genomic mechanisms [22] and 2) long-lasting feedback inhibition mediated by genomic actions of GRs on neurons in numerous brain and body compartments, including limbic structures such as the prefrontal cortex, hippocampus and amygdala [21,23–25]. These stress-regulatory limbic structures work in parallel to process stressful stimuli. Their outputs converge into key relay structures (e.g. bed nucleus of the stria terminalis) where information is further processed for the eventual modulation of HPA axis tone and overall reactivity [26].

Prefrontal cortex

The medial prefrontal cortex plays an important role in inhibition of the HPA axis [27–30]. Stimulation of the prefrontal cortex leads to inhibition of the HPA axis response to an acute psychogenic stressor [31]. Lesions of the prefrontal cortex, on the other hand, increase

stress-induced secretion of ACTH and corticosterone [28,32,33]. Moreover, GR signaling in the medial prefrontal cortex is involved in negative feedback inhibition of acute as well as chronic stress responses [29].

Hippocampus and subiculum

Lesion studies demonstrate that the hippocampus and subiculum have a predominantly inhibitory role on HPA axis function [34–36]. For instance, surgical removal of the entire hippocampal structure results in a significant increase in expression of CRH mRNA in the paraventricular nucleus of the hypothalamus and an increase in circulating levels of corticosterone [37]. Lesions of the output fibers of the ventral hippocampus produce a similar increase in hypothalamic CRH mRNA expression and an increase in ACTH secretion [38]. Together, these studies indicate a potential role of the ventral hippocampus in regulating basal HPA axis tone. In addition, lesions to the ventral subiculum – the primary target of ventral hippocampal output – result in prolonged corticosterone secretion in response to an acute challenge as well as increased expression of hypothalamic CRH mRNA [34,39,40]. These studies indicate that the ventral subiculum is instrumental to the inhibition of HPA axis stress responses, likely as the primary cortical conduit of hippocampal outflow. Importantly, recent studies suggest that the prefrontal cortex and the ventral subiculum converge at the bed nucleus of the stria terminalis to additively inhibit HPA axis stress responses [41], suggesting interactions between the output of these two limbic HPA inhibitory structures.

Amygdala

The amygdala receives inputs from both the prefrontal cortex and the hippocampus, acting as a major hub for the integration of emotional information [42]. Unlike the latter structures, principal output nuclei of the amygdala (central and medial nuclei) are involved in HPA axis activation following exposure to stress [24,43–46]. In addition, the amygdala is important for coordinating the expression of fear and anxiety behaviors [47].

Temporal lobe structures (e.g. hippocampus, subiculum, amygdala) are implicated as the primary generators of epileptic activity in TLE [48,49] and are often damaged in the disease. HPA axis dysfunction in epilepsy, therefore, may be linked to structural and functional pathologies caused by TLE. These pathologies may result from the initial epileptogenic insult and/or persistent seizure activity.

3. HPA axis dysfunction in TLE

To date, studies examining the causal relationship between HPA axis dysfunction and epilepsy are limited. To continue exploring this relationship, it is important to consider four complexities that obscure the causal relationship between HPA axis function and epilepsy. Firstly, injuries that precipitate the development of epilepsy can also directly disrupt HPA axis function (3.1). Secondly, single seizures acutely alter HPA function (3.2). Thirdly, chronic recurrent seizures (epilepsy) may alter HPA function in a manner distinct from single seizures (3.3). Finally, chronic seizures occur in a context of brain injury and cellular

restructuring, which may alter HPA axis function independent of the seizures themselves (3.4).

3.1 Injuries associated with the development of TLE also result in HPA axis dysfunction

Although the causes of TLE are often unknown, a subset of patients develop epilepsy following a clear precipitating injury, such as head trauma or hypoxic/ischemic injury (for review on TLE pathophysiology and epidemiology [1,50]). Epilepsy can also develop following status epilepticus. Status epilepticus can lead to epilepsy when induced in rodents with chemoconvulsant drugs. It is not known, however, whether unprovoked status epilepticus in humans causes the subsequent epilepsy, or whether the underlying cause of the status epilepticus itself drives epileptogenesis. In either case, these epileptogenic brain injuries all induce rapid dysregulation of the HPA axis, which occurs prior to the clinical manifestations of epilepsy. For instance, while both single seizures and status epilepticus increase cortisol secretion, elevated levels persist for much longer following SE in humans [51]. Similar increases in cortisol following SE have been observed in monkeys [52]. In rodents, increased corticosterone levels are observed in a variety of different SE models, including intra-hippocampal kainic acid [53], systemic pilocarpine injection and systemic kainic acid injection [54]. The degree of corticosterone hyper-secretion has also been shown to correlate with the severity of epileptiform activity [54]. Furthermore, both systemic kainic-acid and pilocarpine induced seizures result in hyper-activation of CRH positive neurons in the paraventricular nucleus of the hypothalamus, leading to significantly higher levels of CRH mRNA and protein following SE among these cells [54,55]. Impairment in GABAergic inhibition of these cells has also been detected [54]. Together, these findings may account for increased ACTH and corticosterone levels evident in the acute aftermath of SE.

Clinical studies also reveal persistent hyper-secretion of cortisol following head trauma [56,57]. The severity of the injury correlates with greater levels of cortisol secretion [56,57]. Rodent studies reveal similar neuroendocrine changes following traumatic brain injury [58,59]. In a study by McCullers and colleagues, a time-course analysis of ACTH and corticosterone levels following brain injury revealed an initial surge at 1.5 hours in rats. At 6 hours post-injury, corticosterone remained elevated despite ACTH normalization. This was followed by a second peak of ACTH 18 hours post-injury [58]. Stress-induced HPA axis hyperactivity, evident as increased corticosterone and ACTH, develops one to two weeks after traumatic brain injury in rats [59]. By contrast, other groups have found depressed stress-induced activity of the HPA axis one week post-TBI, but pronounced hyperactivity 34 and 70 days post-injury [60]. Differences in the severity and type of traumatic brain injury may account for the discordant findings.

Increases in HPA axis activity are also seen acutely in stroke patients [61]. Similar to what is observed following SE, the magnitude of HPA axis hyperactivity following stroke correlates with poor post-stroke prognosis [62]. In animal models, recent evidence suggests that HPA axis dysfunction following global cerebral ischemia may be long lasting [63].This study demonstrated that although baseline corticosterone levels were normal seven days post-injury, stress-induced hyper-secretion of corticosterone was present 27 days post-injury.

Furthermore, induction of hypoxia/ischemic injury in rats results in persistent hyper-activation of the HPA axis and spontaneous seizures [64]. Reducing glucocorticoid secretion in response to the injury decreased the frequency of spontaneous seizures [64].

Taken together, these findings indicate that HPA axis dysfunction appears rapidly following epileptogenic brain injuries. Due to a lack of longitudinal data, whether HPA dysfunction results entirely from the initial injury, or whether it becomes more severe in animals that subsequently develop epilepsy, remains an open question.

3.2 Single seizures acutely increase HPA axis function

Single seizure events in humans with epilepsy (generalized tonic clonic and complex partial seizures common in TLE) result in increased activation of the HPA axis [65–70]. These studies, however, cannot dissociate the effects of single seizure events from the effects of chronic epilepsy. Studies in animals, on the other hand, consistently demonstrate that a single, evoked temporal lobe seizure in healthy (non-epileptic) rodents activates the HPA axis, leading to large increases in corticosterone levels. For example, electrical stimulation of the amygdala and dorsal hippocampus increases ACTH and corticosterone levels following both focal and generalized seizure activity [71,72]. These findings indicate that activation of the HPA axis in epilepsy is likely due in part to the direct effects of seizures.

3.3 HPA axis dysfunction in chronic TLE

TLE patients show persistent HPA axis hyperactivity even after prolonged inter-ictal (seizure free) periods. During inter-ictal periods, for example, epileptic patients have elevated morning baseline cortisol [73] and higher ACTH levels in both morning and evening samples [74,75]. TLE patients also fail to suppress cortisol release in response to dexamethasone administration and are hyper-responsive to exogenous administration of CRH. Abnormal responses are evident in patients both on and off anti-seizure medications, implying the abnormalities are not due to drug effects [73]. A recent study found that TLE patients exposed to a psychosocial stress challenge secrete cortisol at levels significantly higher than healthy controls [76]. Despite these changes in response amplitudes, circadian fluctuations of glucocorticoids – albeit with higher levels in the morning – are preserved [77]. Although HPA axis hyperactivity seems to be a consistent pathology found in patients with TLE, the number of studies is relatively small, and more work is required to fully characterize the stress response in these patients.

Studies in rodent models of TLE support the clinical evidence for HPA axis hyperactivity. In the pilocarpine-induced status epilepticus model of TLE, epileptic rats develop persistent HPA axis hyperactivity after two months. Hyperactivity is evident as increased levels of basal corticosterone, impaired glucocorticoid-mediated negative feedback (DEX challenge) and corticosterone hyper-secretion in response to CRH [78,79].

3.4 Damage to limbic structures may result in HPA axis dysfunction

Substantial cell loss and neuronal re-organization (i.e. changes to cell structure and connectivity) are observed in key stress-regulatory regions in TLE patients and rodents exhibiting TLE-like seizures. The hippocampus is primarily affected [80–85], but

abnormalities are also seen in other regions, including the subiculum [86], amygdala [84,85,87–89] and frontal cortex (i.e. anterior cingulate, medial prefrontal) [82,85,90]. In humans, mesial temporal sclerosis resulting in shrinkage of the hippocampus is the most common pathological hallmark of TLE [83,91]. Similarly, rodent studies demonstrate substantial hippocampal cell loss, neuronal dispersion, gliosis, sprouting, and aberrant neurogenesis in TLE models [92–100]. These changes occur throughout the epileptogenic process, some arising quickly after the initial precipitating injury [98,101,102], while others take time to develop [93,103,104]. As previously discussed, limbic structures such as the hippocampus, amygdala, and the pre-frontal cortex are important in the proper activation and regulation of the HPA axis [23,24,26] (Figure 1). Because the structural integrity of these key stress-regulatory regions is markedly compromised in TLE, it is possible that impaired HPA axis control may be a consequence of these injuries. Changes in the morphology and structural connectivity of the hippocampus may also contribute to the development of psychiatric comorbidities (for review see [105]).

Beyond individual structures, effective regulation of the HPA axis is most likely dependent on the coordinated activation and connectivity of a complex network involving limbic cortical and subcortical structures [26]. TLE may lead to impairments in the activation and functional connectivity of such a network [106,107]. Resting fMRI studies in TLE patients suggest substantial reductions in hippocampal, amygdala, and prefrontal cortex functional connectivity [108–111]. Others have found reductions in the functional connectivity between the hippocampus, amygdala and anterior cingulate in patients with TLE [110]. A recent fMRI study measuring BOLD reactivity in response to psychosocial acute stress (negative feedback given for both incorrect and *correct* answers on a mathematical task) demonstrated reduced activation of the hippocampus and medial prefrontal cortex [76]. It is possible that hypo-activity of these regions may result in reduced inhibitory control over the HPA axis. In the pilocarpine model of TLE, epileptic mice exhibit a substantial decrease in activity-dependent c-Fos expression in the hippocampus during interictal periods, indicative of reduced neuronal firing (~8–19h post-seizure) [112]. Hippocampal hypo-activation during inter-ictal periods may be a protective response following seizures. However, it may also compromise the ability of the hippocampus to regulate HPA axis function, especially when facing a stressful situation. Future studies should determine whether HPA axis dysfunction seen in animal models of TLE correlates with structural and functional changes in limbic activity and connectivity. Since epilepsy may be a disease of neural networks [106], it is possible that prevention or treatment of aberrant limbic networks may have a positive impact on seizure control, psychiatric comorbidities and HPA axis dysfunction.

4. Excess glucocorticoids may compromise the structural and functional integrity of limbic regions

Persistent exposure to excess levels of glucocorticoids can physically change the structure and function of neurons located in key stress-regulatory limbic regions, including the hippocampus and prefrontal cortex [113–116]. These changes have been hypothesized to increase vulnerability to injury [117], which could be particularly relevant in the context of epilepsy.

The hippocampus contains a high density of glucocorticoid receptors (GR and MR) [118] and is thought to be particularly vulnerable to the deleterious effects associated with excess glucocorticoid exposure [119,120]. Because glucocorticoid receptor binding results in the activation of genes known to modulate cellular metabolism, cellular structure and synaptic transmission [121], excess glucocorticoids may underlie structural and functional abnormalities seen following chronic exposure to stress. For instance, exposure to chronic stress and/or excess glucocorticoids induces dendritic atrophy and spine density reductions in the hippocampus [113,122–125]. Similar effects are observed on pyramidal neurons of the medial prefrontal cortex [28,114,126–129], while excess glucocorticoids increase dendritic branching in the amygdala (basolateral nucleus) [130]. Both glucocorticoid synthesis inhibitors and glutamate (NMDA)-receptor antagonists are effective in preventing some of the glucocorticoid-induced structural remodeling in the hippocampus [122]. These data suggest that glucocorticoids and glutamate receptors play an important role in mediating chronic stress-induced dendritic atrophy. In addition, prolonged exposure to excess glucocorticoids reduces hippocampal cell proliferation and adult neurogenesis [131–134]. Both adrenalectomy [135] and treatment with glucocorticoid antagonist (RU486) effectively prevent reductions in neurogenesis associated with chronic corticosterone treatment [136,137] and exposure to chronic stress [138].

Although the majority of the aforementioned glucocorticoid-induced hippocampal changes are transient and reversible, long-lasting remodeling (i.e. dendritic retraction) may increase vulnerability to neuronal damage following a “second hit” injury [117]. Several studies have shown that glucocorticoids can potentiate neuronal injury in hippocampal cells following exposure to neurotoxins [119] and kainic acid-induced seizures [139–141]. Furthermore, a history of chronic stress is sufficient to induce persistent dendritic retraction in hippocampal neurons and increases vulnerability to neurotoxic challenge [142,143]. These changes were absent in animals exposed to a single acute stressor. This suggests that chronic stress is necessary to induce persistent morphological changes in hippocampal neurons (perhaps by way of cumulative glucocorticoid exposure). Overall, excess exposure to stress hormones may further compromise the structural and functional integrity of limbic regions in TLE. These abnormalities may diminish negative feedback efficacy and/or increase excitatory drive, resulting in HPA axis hyperactivity.

5. Implications of HPA axis dysfunction in TLE

The data discussed in this review suggest that HPA axis hyperactivity is present in TLE. Although more studies are needed to understand the mechanisms by which HPA axis dysfunction develops, we hypothesize that damage to temporal lobe structures, either as a result of an initial epileptogenic injury and/or as a consequence of recurrent ictal activity, may contribute to aberrant top-down regulation of HPA axis activity. Damage would ultimately result in the hypersecretion of stress hormones (CRH, ACTH and glucocorticoids), both at baseline conditions and in response to stress. In this section, we aim to briefly discuss two potential consequences of HPA axis hyperactivity in TLE: 1) Increased seizure susceptibility and 2) Increased vulnerability to stress-related psychopathologies.

5.1 HPA axis hyperactivity may increase seizure susceptibility in TLE

Persistent exposure to excess glucocorticoid increases neuronal excitability [144–146] and decreases seizure thresholds in multiple models of TLE [147–150]. The mechanisms underlying chronic glucocorticoid effects on neuronal excitability and seizure vulnerability are not entirely known. There is some evidence suggesting that both genomic and non-genomic mechanisms following glucocorticoid binding to MR and GR are responsible for the increased neuronal excitability in the hippocampus [146,151]. In addition to glucocorticoids, increased expression of CRH in extra-hypothalamic areas, such as the dentate hilus and the hippocampal CA1 and CA3 regions, occurs acutely in animal models of TLE [152–155]. Due to its reported pro-convulsant effects [156,157], enhanced hippocampal CRH may facilitate the development of seizures in epilepsy [158,159] and/or may contribute to increased hippocampal excitotoxicity [159–161]. In support of this hypothesis, administration of CRH receptor antagonist, astressin, immediately prior to or following kainic acid-induced seizures has shown neuroprotective effects [159]. Additionally, a recent study found that environmental enrichment, which was associated with reductions in CRH and CRH receptor 1 expression in the hippocampus, inhibited kindling epileptogenesis [162].

HPA axis hyperactivity following temporal seizures may contribute to the generation of further ictal discharges. Such action may help explain the presence of seizure clusters that are commonly seen in humans and rodent models of TLE. In a similar manner, under stressful situations, hyper-secretion of glucocorticoids and other stress hormones may contribute to reductions in seizure threshold and increased neuronal excitability in TLE. Enhanced excitability may provide a potential mechanism underlying the propensity for TLE patients to identify stress as a common seizure trigger [9]. In fact, in some patients, evoking an emotional stressful response (i.e. using audio and video recordings) is sufficient to trigger spontaneous seizures [163]. These clinical findings provide evidence that abnormalities in the stress response may facilitate seizure activity in TLE.

5.2 HPA axis hyperactivity may increase susceptibility to stress-psychopathologies in TLE

HPA axis hyperactivity is a clinical feature in a subset of patients with major depression [164–167] and may contribute to the pathogenesis of the disease [168,169]. A natural experiment – Cushing's disease – provides evidence of a causal link between elevated stress hormones and psychopathology in humans. Cushing's disease is characterized by the chronic hyper-secretion of stress hormones, including ACTH and cortisol, due to excess growth of the pituitary. Although a causal relationship is not proven, the disease is associated with a high incidence of depression and anxiety [170].

GR antagonists have also shown promise in human clinical trials for the treatment of depressive symptoms [171–174]. Preclinical studies implicate excess glucocorticoid exposure as a potential mechanism for the development of stress-related psychopathologies [175–180]. We and others have shown that GR antagonists have potent anti-depressant effects in rodents [137,181,182] and can in fact reverse some of the physiological and behavioral phenotypes associated with HPA axis hyperactivity [136–138,183]. These data suggest that excess glucocorticoids may influence the development of stress-related

psychopathologies, and that glucocorticoid antagonists may be used as effective antidepressant treatment in patients with HPA axis dysfunction.

Evidence that HPA axis hyperactivity is also common to epilepsy does not prove causality. However, it does suggest that excess glucocorticoids may play a role in the expression and/or exacerbation of comorbid psychopathologies. Excess glucocorticoids may contribute to the development of psychopathologies by potentiating changes characteristic of the epileptic brain, such as reduced hippocampal neurogenesis [184,185] and/or structural rearrangements of hippocampal neurons [186]. In addition, impaired connectivity in corticolimbic mood-regulatory circuits occurring as a result of epileptic injury and/or excess glucocorticoid exposure may contribute to psychopathology [187]. Alternatively, increased CRH expression in extra-hypothalamic areas, may play a role in the development of anxiety [188]. Overall, HPA axis hyperactivity is likely one of many factors that influence the high incidence of psychopathology in TLE.

6. Conclusion

The relationship between stress, seizures and comorbid psychopathology in epilepsy is highly complex. Here, we briefly discuss some evidence that suggests that HPA axis hyperactivity may act as a common physiological mechanism underlying both stress as a precipitant of seizures and the high incidence of comorbid psychiatric illness in TLE. In our proposed model (Figure 2), the initial epileptogenic injury (i.e. the first seizure, brain trauma, hypoxia/ischemia) leads to neuronal damage (structural rearrangements and/or cell death) of limbic structures (i.e. hippocampus, amygdala and prefrontal cortex). Such neuronal damage contributes to a chain of events (i.e. epileptogenesis) that ultimately result in the development of TLE. In addition, damage to key stress-regulatory regions may impair HPA axis function, resulting in ineffective activation/termination of the stress response and overall HPA axis hyperactivity. HPA axis hyperactivity is evident from the chronic elevated secretion of glucocorticoids and other stress hormones. Excess glucocorticoids and repeated seizure activity may further exacerbate limbic damage, feeding into the epileptogenic cycle and further disrupting HPA axis function. Finally, HPA axis hyperactivity, perhaps via glucocorticoid-mediated mechanisms, may provoke seizure activity, particularly in situations of stress, while concomitantly increasing vulnerability for the development of stress-related psychopathologies. Given the widespread effects of stress hormones and their potential to influence seizure activity as well as mood, we believe that this is an important area for further study. Key goals include the development of rational therapies and non-pharmacological interventions aimed at preventing seizures and treating psychiatric comorbidities in epilepsy.

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Highlights

- Stress is one of the most commonly reported seizure-triggers, and stress-related psychopathologies are highly comorbid with TLE
- The HPA axis is hyperactive in TLE
- The functionality and structural integrity of limbic regions important in stress-regulation are compromised in TLE
- HPA axis dysfunction in epilepsy may result from aberrant connectivity of limbic structures

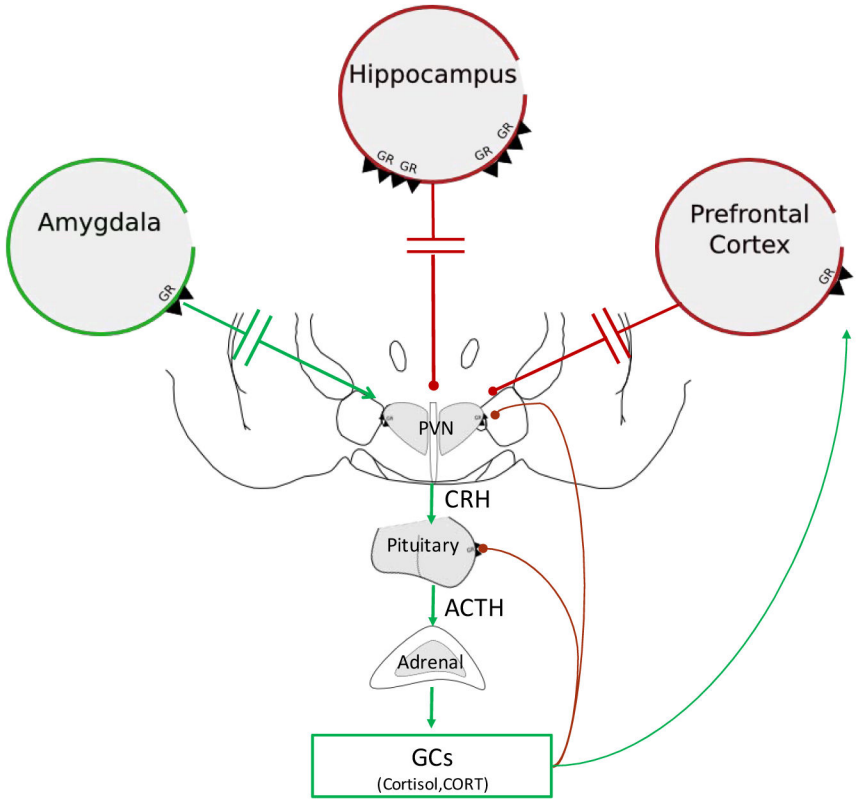

Figure 1. Hypothalamo-pituitary-adrenocortical axis

Upon a stressful event (i.e. psychogenic or physical), activation of the paraventricular nucleus of the hypothalamus (PVN) results in the release of corticotrophin releasing hormone (CRH). CRH binds to its receptors in the anterior pituitary to induce the release of adrenocorticotrophic hormone (ACTH) into the circulation. ACTH binds to receptors in the adrenal cortex that result in the synthesis and release of glucocorticoids, cortisol in humans and corticosterone (CORT) in rodents. Glucocorticoids bind to glucocorticoid receptors (GR) in the hypothalamus and pituitary to induce fast negative feedback control over the axis. In addition, glucocorticoids bind to GR located in limbic regions such as the hippocampus, prefrontal cortex, and amygdala to indirectly decrease (red lines) or increase (green lines) HPA axis activity.

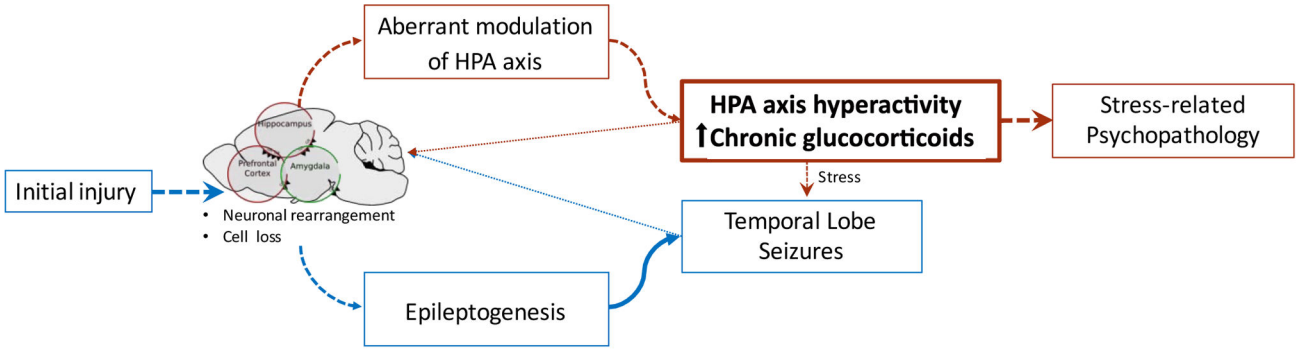

Figure 2. HPA axis dysfunction in TLE: a theoretical model

An initial precipitating injury (i.e. the first seizure, brain trauma, hypoxia/ischemia) compromises the structural integrity of limbic circuits leading to neuronal rearrangements and cell loss in stress-regulatory regions such as the hippocampus, prefrontal cortex, and amygdala. These changes give rise to epileptogenesis and the subsequent development of TLE, while simultaneously compromising the functional integrity of stress regulatory mechanisms resulting in HPA axis hyperactivity and increased vulnerability for the development of psychopathologies (depression and anxiety). Both epileptic seizures and chronic exposure to excess glucocorticoids may potentiate the neuronal damage on limbic stress-regulatory regions. Furthermore, HPA axis hyperactivity results in exaggerated responses to stress that may facilitate epileptic discharges.