A Minimal HPA Axis Model Linking Cortisol Dynamics, Genetics, and Temporal Lobe Epilepsy

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Abstract

Temporal lobe epilepsy (TLE) is the most common type of epilepsy due to the unique location of the hippocampus within the temporal lobe. Previous research has supported the idea that cortisol produced through the Hippocampus-Pituitary Gland-Adrenal Gland (HPA) Axis inhibits activity of the hippocampus. Current anti epileptic drugs target activity in the hippocampus to treat TLE; however, the impacts of such drugs on the HPA Axis are not studied deeply. Our minimal mathematical model of the HPA axis relates the levels of cortisol and hippocampal activity as well as adrenal gland size depending on how long an anti epileptic drug is taken. Through this model, we can understand why anti epileptic drugs need to be taken for several weeks before improvement can be seen in patient health. Moreover, we use model parameter D, a proxy for the maximum hippocampal activation when cortisol levels exceed the threshold. This parameter is determined by genetics. Nonlinear dynamical systems study through phase portraits revealed existence of 1 or 2 stable fixed points, corresponding to the epileptic and healthy states, as well as 0 or 1 unstable point depending on the genetics. The model predicts that higher values of D can be associated with an epileptic state while lower values of D can be associated with a healthy state.

Introduction

Focal, or partial, epilepsy refers to seizures that originate in one part of the brain[1]. Focal epilepsy affects around 60% of people with epilepsy. Temporal lobe epilepsy is the most common form of focal epilepsy[10, 4]. Seizures are more likely to originate in the medial temporal lobe, which is close to the hippocampus. The hippocampus is the location of neural cell development; due to the unique connections in the medial temporal lobe, the connections within the hippocampus are also weak.

The HPA axis refers to the relationship between the hypothalamus, pituitary gland, and adrenal gland. The HPA axis controls the release of cortisol, which is produced during the stress response. One of the hormones produced by the hypothalamus is corticophin-releasing hormone (CRH), which is involved in the body's stress response. CRH stimulates pituitary gland cells to divide and release adrenocorticophic hormone (ACTH). ACTH stimulates the adrenal glands to divide and produce cortisol. Cortisol serves as a regulatory hormone by inhibiting further production of CRH and ACTH.

Excess cortisol production inhibits neurogenesis, the process by which neurons form, and reduces hippocampal activity. [7, 8]. Research has found a correlation between excess cortisol and an atrophied hippocampus. High amounts of cortisol and an atrophied hippocampus are hallmarks of temporal lobe epilepsy.

Neuroimaging and previous endocrinology research have confirmed that repeated episodes of TLE are correlated with dysfunction in the HPA axis and, as a result, lead to elevated cortisol levels. Research has supported the idea that elevated cortisol levels can down regulate glucocorticoid receptors in the hippocampus, leading to neuro inflammation, neural death, and hyperexcitablity. It serves as a positive feedback loop since elevated cortisol levels lead to further atrophy and excitability of the hippocampus.

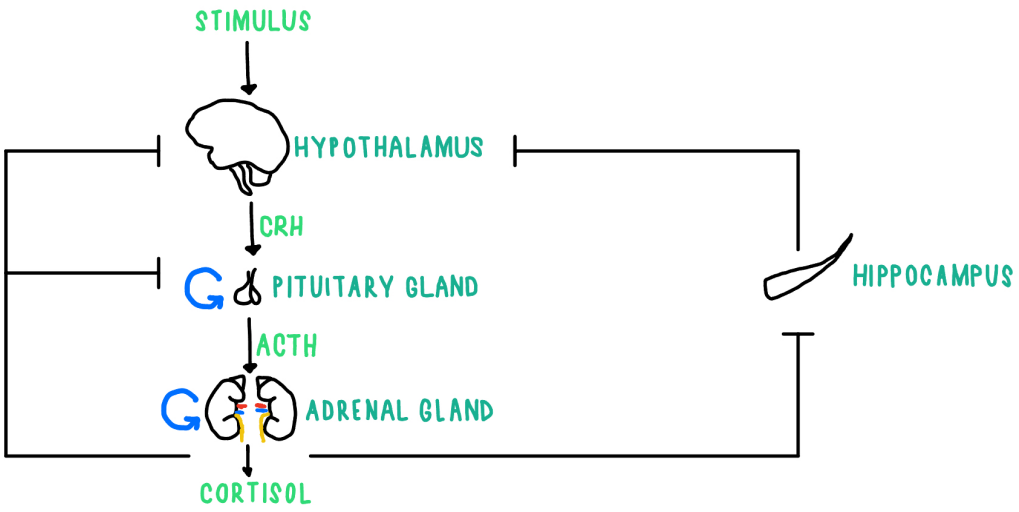

Figure 1: When a stimulus from the outside environment is perceived by the hypothalamus in the brain, the hypothalamus releases corticotrophin-releasing hormone (CRH). CRH travels to the pituitary gland where it not only stimulates the production of adrenocorticotrophic hormone (ACTH) but also causes the pituitary gland cells to replicate. ACTH travels to the adrenal glands on the top of the kidney. Like CRH, ACTH stimulates the production of cortisol and causes the replication of adrenal gland cells. Production of excess amounts of cortisol inhibits the production of CRH and ACTH. In addition, excess cortisol can inhibit neurogenesis, formation of neurons, in the hippocampus. Adapted from [3].

This paper aims to connect past research in endocrinology with neuroscience to explain the relationship between temporal lobe epilepsy and dysfunction of the HPA axis. This is done through differential equations and models. The differential equations represent the rate of production of CRH, ACTH, and cortisol, as well as the change in the size of the pituitary and adrenal glands as the cell divides. The models utilized in this paper aim to describe this relationship by relating susceptible/non susceptible populations to the high cortisol levels observed in TLE, atrophied hippocampus, and levels of CRH and ACTH.

Methods

Mathematical Model of the HPA Axis with Hippocampal Feedback

We employed a minimal mathematical model of the hypothalamic-pituitary-adrenal (HPA) axis, incorporating hippocampal modulation, adapted from previous neuroendocrine modeling frameworks, to capture the essential regulatory features of stress response and their disruption in temporal lobe epilepsy (TLE)[12]. The model consists of six coupled ordinary differential equations (ODEs) describing the temporal dynamics of corticotropin-releasing hormone (CRH, x_1), adrenocorticotropic hormone (ACTH, x_2), cortisol (x_3), pituitary tissue activity (P), adrenal tissue activity (A), and hippocampal activity (h):

$$\frac{dx_1}{dt} = q_1 \frac{Hu}{hx_3} - \alpha_1 x_1, \tag{1}$$

$$\frac{dx_2}{dt} = q_2 \frac{Px_1}{x_3} - \alpha_2 x_2, \tag{2}$$

$$\frac{dx_3}{dt} = q_3 A x_2 - \alpha_3 x_3, \tag{3}$$

$$\frac{dP}{dt} = P(b_p x_1 - a_p), \tag{4}$$

$$\frac{dA}{dt} = A(b_A x_2 - a_A), \tag{5}$$

$$\frac{dh}{dt} = a_h \frac{D}{a + b\,\mathrm{sign}(x_3 > T)} - b_h h. \tag{6}$$

Here, q_1, q_2, and q_3 denote basal production rates of CRH, ACTH, and cortisol; α_1, α_2, and α_3 represent degradation rates; a_p and b_p control pituitary homeostasis and CRH sensitivity; a_A and b_A control adrenal homeostasis and ACTH sensitivity; a_h and b_h describe hippocampal activation and decay rates; D represents the maximal hippocampal activation capacity; and T is the cortisol threshold for hippocampal activation[2].

Parameter values and their biological significance are provided in Table 1. Parameter D was varied systematically to investigate susceptibility to persistent HPA axis dysregulation.

Simulation of Acute and Chronic Suppression

To mimic the effects of anti-epileptic drugs that reduce hippocampal excitability, we introduced an exogenous suppression term to h for a finite period. Two regimes were tested:

1. **Acute suppression:** h reduced by 50% for 7 days.
2. **Chronic suppression:** h reduced by 50% for 30 days.

Numerical integration was performed using the `odeint` solver from the SciPy library (Python 3.10) with a time step of $\Delta t = 0.01$ days. Initial conditions were chosen to represent a stable baseline HPA state prior to drug administration. All simulations were run for 180 days to capture long-term post-treatment dynamics.

Results

To investigate the impact of hippocampal suppression on HPA axis dynamics, we simulated the minimal mathematical model described in Methods section under two distinct regimes of anti-epileptic intervention: *acute suppression* (1 week) and *chronic suppression* (1 month). In both cases, hippocampal activity h was transiently reduced to mimic the inhibitory effect of pharmacological treatment on hippocampal excitability, as would occur with certain anti-epileptic drugs.

Figure 2 shows the temporal evolution of cortisol (x_3), adrenal mass (A), and hippocampal activity (h) following treatment onset. In the acute suppression regime, hippocampal activity rapidly recovers after treatment cessation, with cortisol and adrenal mass returning to near-baseline values over several weeks. In contrast, chronic suppression produces a qualitatively different outcome: prolonged hippocampal inhibition leads to a sustained increase in adrenal mass and cortisol levels, along with incomplete recovery of hippocampal activity. This suggests that persistent pharmacological suppression is required to induce lasting changes in HPA axis homeostasis.

Parameter	Value	Units	Biological Significance
q_1	244.8	day^{-1}	Basal production rate of CRH by hypothalamus
q_2	50.4	day^{-1}	Basal production rate of ACTH by pituitary
q_3	12.384	day^{-1}	Basal production rate of cortisol by adrenal gland
α_1	244.8	day^{-1}	Degradation rate of CRH
α_2	50.4	day^{-1}	Degradation rate of ACTH
α_3	12.384	day^{-1}	Degradation rate of cortisol
a_p	0.05	dimensionless	Homeostatic set point for pituitary activity
b_p	0.05	dimensionless	CRH sensitivity of pituitary stimulation
a_A	0.1	dimensionless	Homeostatic set point for adrenal activity
b_A	0.1	dimensionless	ACTH sensitivity of adrenal stimulation
a_h	0.047	day^{-1}	Hippocampal activation rate due to cortisol feedback
b_h	0.047	day^{-1}	Hippocampal decay rate
D	—	day^{-1}	Maximum hippocampal activation when x_3 exceeds threshold
a	1.0	dimensionless	Saturation parameter in hippocampal feedback
b	1.0	dimensionless	Steepness of hippocampal response to cortisol threshold
T	1.5	arbitrary units	Cortisol threshold for hippocampal activation

Table 1: Parameter values, units, and biological significance in the HPA axis model.

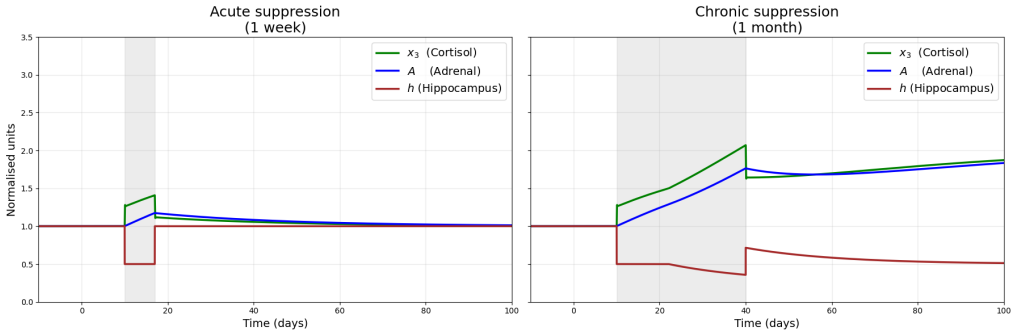

Figure 2: Temporal dynamics of cortisol (x_3, green), adrenal mass (A, blue), and hippocampal activity (h, red) under (left) acute suppression (1 week) and (right) chronic suppression (1 month) of hippocampal activity. Shaded regions indicate treatment periods. Chronic suppression produces a persistent shift in HPA axis state, whereas acute suppression effects are largely reversible.

The model can be interpreted in the context of commonly prescribed anti-epileptic drugs (AEDs) for temporal lobe epilepsy:

- **Carbamazepine**[11] acts primarily by blocking voltage-gated sodium channels, thereby reducing hippocampal excitability and limiting seizure propagation. Its enzyme-inducing properties accelerate cortisol metabolism, which can reduce circulating cortisol levels and downstream ACTH/CRH release. Experimental work in rodents has shown that carbamazepine treatment reduces corticosterone responses to stress. In the context of our model, carbamazepine's effects resemble the chronic suppression scenario, where sustained hippocampal inhibition gradually shifts the system toward lower HPA activation.

- **Levetiracetam**[5] binds to synaptic vesicle protein SV2A, directly modulating hippocampal neurotransmitter release without inducing hepatic enzymes. While its direct effects on cortisol metabolism are minimal, seizure suppression can indirectly normalize HPA activity by reducing repeated seizure-induced stress responses. In the model, this corresponds to reduced hippocampal hyperexcitability without altering cortisol degradation rates, leading to gradual stabilization of h.

- **Brivaracetam**[3], a high-affinity SV2A ligand, reduces hippocampal excitability and neurotransmitter release but has no established direct effects on the HPA axis. Its impact in the model would be similar to levetiracetam, primarily affecting the h variable without modifying cortisol clearance.
- **Phenytoin**[6] also blocks voltage-gated sodium channels but is a potent CYP3A4 enzyme inducer, increasing cortisol metabolism and thereby influencing ACTH and CRH secretion. In the model, this dual action would be represented by a reduction in h (via decreased hippocampal excitability).

We further examined the long-term dynamical consequences of hippocampal modulation by constructing phase portraits[9] of adrenal cortex mass A and mirror neuron activity m (a surrogate for hippocampal-dependent inhibitory control) for three values of the parameter D, which controls maximal hippocampal activation in the model. As shown in Figure 3, D acts as a susceptibility parameter: low D values ($D = 0.5$) yield dynamics with a single stable equilibrium associated with low adrenal mass and high hippocampal inhibition, indicative of resilience to TLE. At intermediate D ($D = 1$), trajectories become more sensitive to perturbations, and post-treatment recovery depends on initial conditions. At high D ($D = 2$), the system admits alternative stable states in which hippocampal inhibition remains low and adrenal mass is persistently elevated — a regime consistent with chronic HPA axis hyperactivity observed in TLE patients.

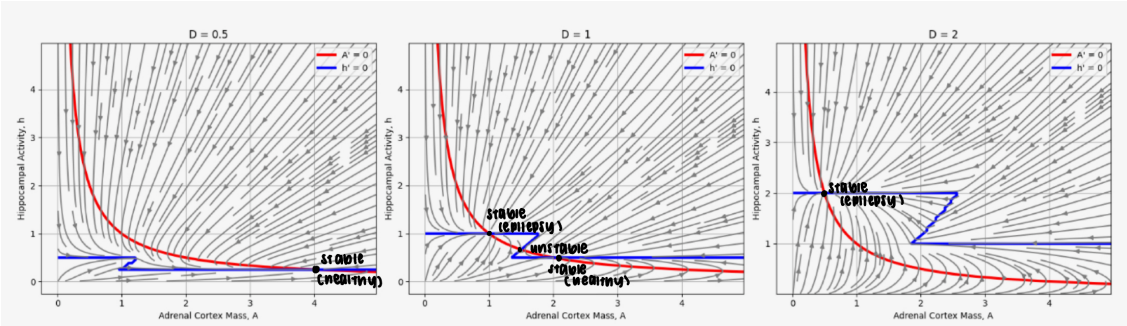

Figure 3: Phase portraits of adrenal cortex mass A versus mirror neuron activity m for three values of hippocampal activation parameter D. Red curves: $A' = 0$ nullclines; blue curves: $m' = 0$ nullclines. Arrows indicate vector field directions. Trajectories illustrate the system's response to hippocampal suppression and subsequent recovery. Larger D values correspond to increased susceptibility to chronic HPA axis dysregulation.

Taken together, these results suggest that (i) short-term hippocampal suppression has limited long-term impact on HPA axis state, (ii) prolonged suppression can shift the system into a persistently altered state with elevated cortisol and adrenal mass, and (iii) intrinsic susceptibility, captured here by the parameter D, plays a critical role in determining whether such a shift becomes permanent and whether the type of epilepsy is treatable by using drugs that shifts hippocampal activity toward the stable point representing healthy state. The model also indicates that AEDs with both hippocampal inhibitory effects and cortisol-modulating properties (e.g., carbamazepine, phenytoin) may exert more direct influence on HPA axis homeostasis, whereas drugs without enzyme-inducing effects (e.g., levetiracetam, brivaracetam) may normalize HPA function primarily through seizure control rather than direct endocrine modulation.

Conclusion

In this study, we develop and analyze a system of differential equations to model the relationship between intrinsic susceptibility, the HPA Axis, and hippocampal activity. By modeling differential equations and phase portraits, we concluded that antiepileptic drugs that serve to acutely work

against epilepsy, hippocampal activity quickly recovers after treatment before returning to baseline levels while cortisol and adrenal mass levels returning to baseline levels slowly after treatment. Anti epileptic drugs that chronically work to suppress seizure activity lead to drastic decrease in hippocampal activity, serving as a sign that seizure activity was suppressed. This was accompanied with an increase in cortisol and adrenal mass. These findings showed that persistent suppression of epilepsy using drugs are needed to induce changes in the HPA Axis.

Additionally, through analysis of phase portraits, we were able to conclude the impact of maximum hippocampal activation (modeled through parameter D) when cortisol exceeds threshold, intrinsic susceptibility, on the treatment of epilepsy. When D is smaller, the model predicts a healthy, non epileptic state. When D is higher, the model predicts a persistant epileptic state. The phase portrait constructed when the value of D is in the middle sheds light on the treatment of epilepsy. Those with epilepsy with this D value can treat the condition by using a drug that either increases adrenal cortex mass or decreases hippocampal activity. By changing any of these factors, we move away from the epileptic stable point to the healthy stable point. Current antiepileptic drugs aim to treat seizures by inducing enzymes or changing hippocampal activity.

Further research can be done on whether antiepileptic drugs increase cortisol levels to a point where it impacts day to day life. Additionally, new research suggests that decrease in hippocampal activity may be associated with a decrease, rather than increase, in cortisol levels. Further research can be done on this relationship and how it goes against the traditional understanding of cortisol inhibiting hippocampal activity.

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