Endocrine Adaptation in Addiction: HPA Axis Plasticity as a Target for Treatment

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Abstract

Addictive drugs often feel pleasurable at first, but over time the body develops tolerance and withdrawal symptoms through built-in "anti-reward" systems called opponent processes. These systems play a key role in addiction, yet their biological basis is not fully understood. Here, we propose that one such opponent process involves the body's stress hormone system, known as the hypothalamic-pituitary-adrenal (HPA) axis. We focus on alcohol addiction, where the HPA axis releases β-endorphin, which produces feelings of pleasure and pain relief. Using a mathematical model, we show that slow changes in the size and function of the HPA glands act as an internal balancing mechanism that reduces β-endorphin secretion over time. This mechanism works through fold-change detection (FCD), meaning the body responds to relative changes in hormone levels rather than absolute ones. While this process can make the system more vulnerable to addiction, it may also play an adaptive role in learning and adjustment. Our model highlights changes in gland size as potential new targets for addiction treatment.

Introduction

Addictive disorders to psychoactive substances is a profound challenge in public health, social welfare and economic stability. The economic burden of addiction is multifaceted: in the United States, the annual cost of substance abuse, from health care, loss of productivity, criminal justice and social services, has been estimated to be greater than $740 billion [1]. Recently, alcohol misuse alone costs society over $249 billion [2]. These figures underscore the scale of this issue. Millions of individuals worldwide are affected by substance use disorders, exerting sustained pressure on families, workplaces, health-systems, and governments.

Beyond solely the economic impact, the human toll of addiction is extensive. While global estimates differ, substance abuse remains widespread as a significant portion of individuals transition from casual use to clinical dependence. According to recent United Nations Office on Drugs and Crime (UNODC) assessments, tens of millions of people worldwide are currently living with substance use disorders [4]. The scale of this population combined with the associated societal burden emphasizes the importance of urgent support to understand biological mechanisms underlying addiction and the necessity of new therapeutic targets.

Biologically, addiction is a disorder of both reward and stress regulation. Initially, psychoactive substances often produce intense pleasure, but with repeated use, the body mounts counter-regulatory responses leading to tolerance, withdrawal and craving [5]. These processes reflect adaptations in neural circuits and stress systems. The transition from intermittent use to compulsive dependence is marked not only by enhanced craving for positive reinforcement but also by the emergence of negative reinforcement.

Within this biological framework, attention has largely been placed on the hypothalamic –pituitary – adrenal (HPA) axis as a central regulatory system that links reward, stress and adaptation. The HPA axis not only participates in the acute pleasurable effects of substance but also undergoes long-term functional changes that can contribute to tolerance, persistent craving, and relapse vulnerability. Seen especially in alcohol use disorders, acute ingestion of alcohol activates the HPA

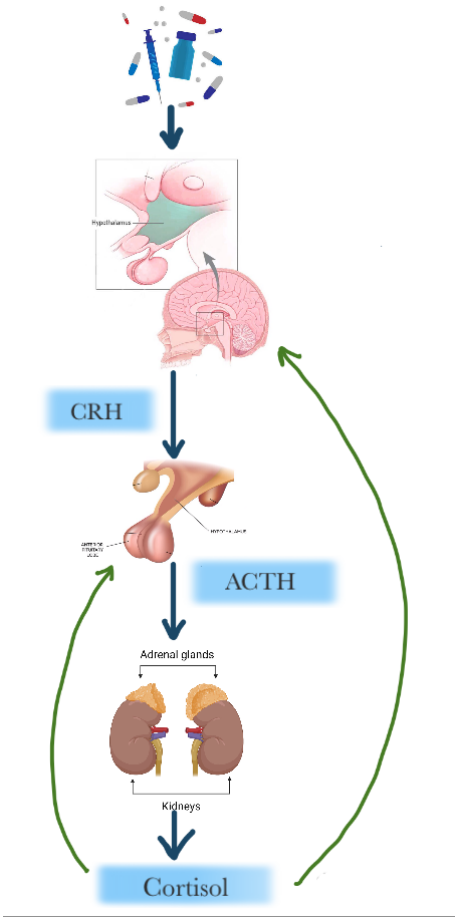

Figure 1: A simplified diagram of the HPA axis. Addictive substances activate the hypothalamus, which releases CRH. CRH stimulates the pituitary gland to release ACTH, which then triggers the adrenal glands to produce cortisol. Cortisol feeds back to the brain to regulate the system.

axis, elevating levels of adrenocorticotropic hormone (ACTH) and cortisol, and engages endogenous opioid peptides such as β-endorphin, contributing to pleasurable and pain-relieving effects [6]. Over chronic use, the dysregulation of the HPA axis is seen in individuals with alcohol dependence. Numerous studies report altered cortisol responses, blunted HPA reactivity during abstinence, and linkage of such dysregulation to relapse risk and craving [3]. These findings strongly support that the HPA axis is not only a mediator of initial drug reward regulation but also a major component of the opponent-process adaptations that drive tolerance, withdrawal, and relapse.

In this paper, we propose a novel model of an opponent process in which slow adaptive changes in the size and functional capacity of the HPA glands operate as an internal balancing mechanism, implementing a form of fold-change detection (FCD). Here, the body's endocrine system responds to relative changes rather than absolute levels of hormone secretion, gradually reducing β-endorphin output in response to repeated alcohol exposure, therefore diminishing the reward signal and increasing tolerance while concurrently enhancing the negative affective backdrop to propel further use.

Methods

The HPA axis is activated by external stress or addictive substances, denoted by the input u, which stimulates hypothalamic secretion of corticotropin-releasing hormone (CRH, x_1). CRH in

turn stimulates the pituitary gland (P) to release adrenocorticotropic hormone (ACTH, x_2), which acts on the adrenal gland (A) to produce cortisol (x_3). Cortisol provides negative feedback on both hypothalamus and pituitary, closing the regulatory loop. In addition, both the pituitary and adrenal glands adapt their effective size on a slower timescale of weeks, producing the long-lasting phenomena of tolerance and withdrawal observed in addiction.

The model equations are given by:

$$\frac{dx_1}{dt} = q_1 \frac{u}{x_3} - \alpha_1 x_1, \tag{1}$$

$$\frac{dx_2}{dt} = q_2 \frac{P x_1}{x_3} - \alpha_2 x_2, \tag{2}$$

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

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

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

$$\frac{dx_4}{dt} = q_4 \frac{P x_1}{x_3} - \alpha_4 x_4. \tag{6}$$

Here, x_1, x_2, and x_3 denote the concentrations of CRH, ACTH, and cortisol, respectively. Parameters q_i represent production rates, while α_i represent degradation rates. The slow gland variables P and A capture the size or capacity of the pituitary and adrenal glands, respectively. Their dynamics are governed by net growth terms proportional to hormonal drive ($b_p x_1$, $b_A x_2$) and basal decay (a_p, a_A). This slow growth introduces a timescale separation between hormone fluctuations (minutes to hours) and gland adaptation (weeks).

This system exhibits exact adaptation, in which steady-state levels of x_1 and x_2 return to baseline despite chronic elevation of the input u. Physiologically, this corresponds to the phenomenon of tolerance: although addictive substances initially increase CRH, ACTH, and β-endorphins, x_4 (co-secreted with ACTH), these levels adapt back to baseline within weeks, leading to diminished reward despite continued substance use. Similarly, during withdrawal, the slow decay of gland sizes results in blunted ACTH and endorphin responses, consistent with hedonic dysregulation and relapse vulnerability.

Results

To understand how repeated exposure to an addictive substance changes the HPA axis over time, we simulated the full model under different patterns of input. The goal was to observe both the fast hormone responses (CRH, ACTH, cortisol, and β-endorphin) and the slow structural changes in the pituitary and adrenal glands.

Figure 2 shows the short-term response of the system when the input $u(t)$ is increased for a period of time and then returned to baseline. When the input rises, cortisol (x_3), adrenal gland size (A), and β-endorphin (x_4) all increase. However, even though the stimulus stays high, the hormone levels gradually return toward their original values. This illustrates the exact adaptation property of the system: after a temporary rise, the hormones settle back near baseline despite continued stimulation. When the stimulus is removed, the hormone levels briefly drop below baseline before slowly recovering, capturing the withdrawal-like dip in endocrine activity.

To study the dynamics over longer timescales, Figure 3 shows how all four hormone variables respond when the input increases stepwise at two different time points. Each increase in $u(t)$ produces an immediate spike in CRH (x_1), ACTH (x_2), cortisol (x_3), and β-endorphin (x_4). But in every case, the response slowly decays back toward baseline even though the elevated input is maintained. This pattern reflects fold-change detection (FCD): the system responds strongly to a change in input, not to the absolute level.

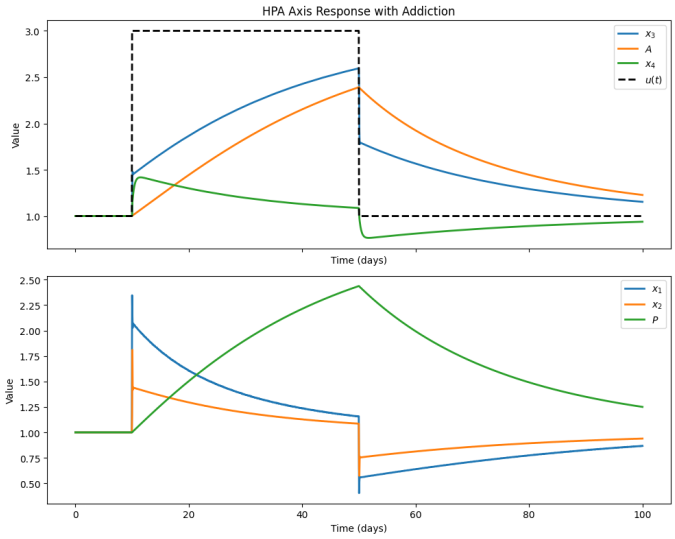

Figure 2: Short-term response of the HPA axis to an addictive stimulus. When the input $u(t)$ increases, cortisol (x_3), adrenal gland size (A), and β-endorphin (x_4) rise quickly. Even though the stimulus remains high, the hormone levels slowly return toward baseline, showing exact adaptation. After the stimulus is removed, the hormones briefly fall below baseline before gradually recovering, resembling withdrawal dynamics.

Finally, Figure 4 shows the corresponding slow changes in pituitary size (P) and adrenal size (A). These glands grow gradually in response to sustained hormone drive, but return toward baseline very slowly after the stimulus drops. This long-term growth and shrinkage creates the internal opponent process: the more the system is stimulated, the more the glands expand, and the less responsive the hormone output becomes. As a result, the rewarding effects of endocrine opioids such as β-endorphin diminish over time, helping explain the development of tolerance and the reduced pleasure seen in chronic addiction.

Together, these simulations show how fast hormonal adaptation and slow gland remodeling interact to produce the familiar cycle of initial reward, tolerance, withdrawal, and craving seen in addiction. The model suggests that long-lasting changes in gland size may serve as a key biological mechanism underlying opponent processes.

Conclusion

We showed how slow structural changes in the glands of the HPA axis can act as an internal opponent process that shapes the body's response to addictive substances. Using a mathematical model, we demonstrated that although addictive inputs cause immediate increases in CRH, ACTH, cortisol, and β-endorphin, these hormone levels gradually return to baseline even when the stimulus remains high. This exact adaptation arises from fold-change detection (FCD), meaning the system is sensitive to relative changes rather than absolute levels.

Over longer timescales, the pituitary and adrenal glands slowly grow in response to repeated stimulation, which reduces the hormonal response to future inputs. This provides a natural explanation for why the pleasurable effects of substances such as alcohol diminish over time and why withdrawal produces a prolonged and uncomfortable drop in endocrine activity. The model therefore highlights gland size and long-term endocrine remodeling as potentially important biological contributors to tolerance, dependence, and relapse risk.

The results suggest that the HPA axis is not only a fast-acting stress system but also a slow-learning adaptive system whose structural changes may be central to addictive behavior. Understanding these slow opponent processes may open new directions for treatment strategies that

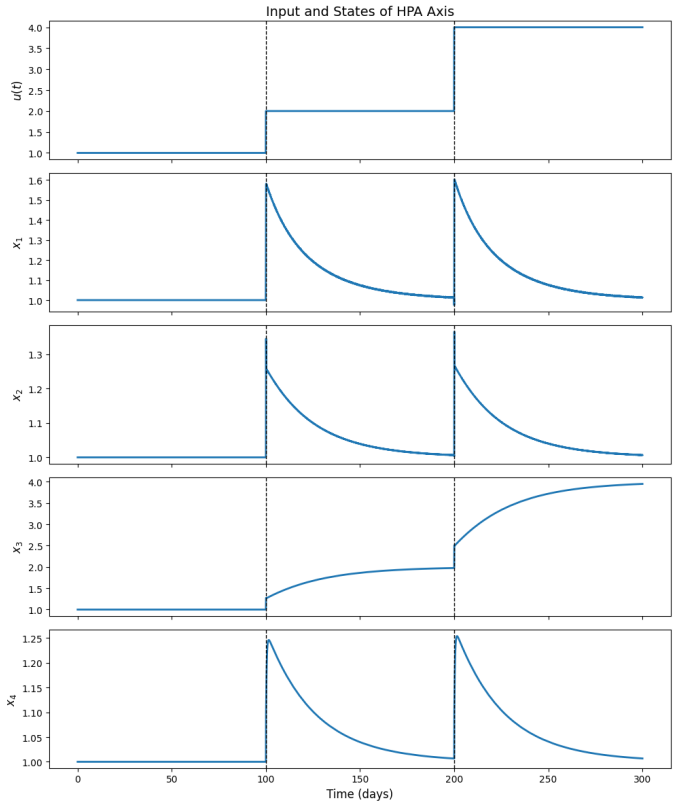

Figure 3: Stepwise increases in the addictive input show the fold-change detection (FCD) property of the HPA axis model. Each jump in $u(t)$ triggers a sharp rise in CRH (x_1), ACTH (x_2), cortisol (x_3), and β-endorphin (x_4), followed by a slow return toward baseline even though the input stays elevated. This pattern demonstrates that the system responds to changes in input rather than to absolute levels.

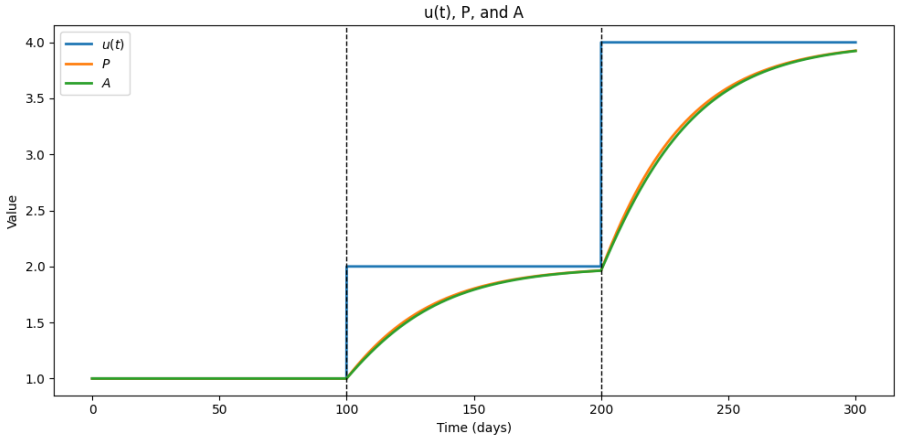

Figure 4: Slow changes in pituitary size (P) and adrenal size (A) during long-term stimulation. Repeated increases in the addictive input cause the glands to grow gradually, reducing hormone responsiveness over time. When the input decreases, the glands shrink slowly, producing prolonged withdrawal-like effects. These structural changes act as an internal opponent process that contributes to tolerance and dependence.

focus on restoring healthy gland function and improving long-term recovery.

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