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# CHRONIC HYPERCORTISOLISM AND STRUCTURAL-FUNCTIONAL PLASTICITY OF THE HIPPOCAMPUS: NEUROENDOCRINE MECHANISMS OF COGNITIVE DISORGANIZATION

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**Abstract:**
The hippocampus occupies a unique position in the architecture of the stress response: it is simultaneously a target of glucocorticoids and a key component of the negative feedback that restrains hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis.

**Keywords:** chronic hypercortisolism, hippocampus, neuroplasticity, glucocorticoid receptors, mineralocorticoid receptors, melatonin, circadian rhythms, LTP, LTD, dendritic atrophy, neurogenesis, BDNF, Cushing's disease, cognitive impairment.

## INTRODUCTION

The hippocampus occupies a unique position in the architecture of the stress response: it is simultaneously a target of glucocorticoids and a key component of the negative feedback that restrains hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis. This dual role makes it a structure of particular vulnerability. While acute fluctuations of cortisol within the physiological range support synaptic plasticity and consolidation of memory traces, sustained elevation of the hormonal background triggers a qualitatively different cascade — one that is not adaptive but disorganizing. The present work focuses on how chronic excess of glucocorticoids sequentially dismantles the plastic potential of the hippocampus — from receptor imbalance to macroscopic atrophy and cognitive deficit — and also on the role of melatonin as an endogenous antagonist of this process.

1. Receptor imbalance as the triggering neuroendocrine mechanism

The key to understanding hippocampal vulnerability lies in the coexistence of two types of corticosteroid receptors with fundamentally different affinities and functional roles. Mineralocorticoid receptors (MR) have a high affinity for cortisol and remain occupied even at basal hormone concentrations; their activation supports long-term potentiation (LTP) and enhances neuronal excitability within physiological limits. Glucocorticoid receptors (GR) have approximately tenfold lower affinity and are recruited predominantly during stress peaks of cortisol. Activation of GR, unlike MR, suppresses LTP and limits neuronal excitability.

In chronic hypercortisolism, this delicate balance shifts: sustained high GR occupancy displaces MR-mediated plastic effects, and GR expression in the hippocampus decreases through negative feedback. A vicious circle arises: weakening of hippocampal feedback leads to further HPA axis hyperactivity, which further increases the hormonal load on the hippocampus and further suppresses its plastic functions. This circuit transforms an acute adaptive reaction into a self-sustaining pathological process.

2. Melatonin–cortisol interaction: circadian control of hippocampal plasticity

A central but often overlooked component in understanding hippocampal plasticity is the circadian organization of hormonal signals. Cortisol and melatonin are in reciprocal relationships governed by the suprachiasmatic nucleus (SCN): the melatonin peak occurs during the dark phase of the day, whereas cortisol reaches its maximum in the early morning hours. This temporal separation is not accidental — it creates «windows of plasticity» in which the hippocampus finds itself either under predominantly trophic or under stress-related control.

The key mechanism of antagonism is implemented at the level of receptor crosstalk. Melatonin, acting through membrane receptors MT1 and MT2, which are widely represented in the hippocampus, including the subgranular zone, reduces the affinity of glucocorticoid receptors and, importantly, decreases their nuclear translocation. Experimentally, a similar effect is achieved without reducing the total level of GR protein or its mRNA — melatonin acts as a functional antagonist, «locking» the receptor in the cytoplasm and preventing the launch of the genomic program of glucocorticoid disorganization. In parallel, chronic exposure to glucocorticoids suppresses the expression of MT1 receptors, whereas melatonin, on the contrary, increases their level, creating conditions for restoring the hippocampus's sensitivity to its own protective signal.

At the cellular level, this confrontation unfolds at several key points. In a model of chronic dexamethasone administration (a synthetic GR agonist), melatonin prevented the suppression of neurogenesis in the dentate gyrus: the number of BrdU-positive cells and the expression of doublecortin (a marker of immature neurons) were restored to control values. In cultured hippocampal progenitor cells, melatonin blocked

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dexamethasone-induced decreases in ERK1/2 phosphorylation and in the expression of cyclins E and CDK2, returning cells to normal G1/S cell cycle transition. Moreover, melatonin protected against glucocorticoid-mediated dendritic atrophy: in chronic stress models, it prevented the reduction in expression of key synaptic plasticity proteins — NR2A/B subunits of NMDA receptors, CaMKII, synaptophysin and, crucially, BDNF. This trophic effect closes the protective circuit: melatonin not only blocks the damaging action of cortisol on existing synapses but also maintains the molecular environment necessary for the formation of new ones.

Finally, melatonin modulates the HPA axis itself. Its nocturnal rise influences the cortisol rhythm, and experimental disruption of melatonin signaling (MT1/MT2 receptor knockout) is accompanied by enhanced LTP, indicating fine-tuning rather than simple «suppression» of plasticity. Under physiological conditions, melatonin apparently restricts excessive synaptic potentiation during periods when it is not adaptive, while protecting the hippocampus from pathological glucocorticoid load. Chronic hypercortisolism disrupts this circadian architecture: loss of rhythmicity of melatonin and cortisol deprives the hippocampus of the alternation of phases «plasticity/consolidation» and «protection/restoration,» shifting the system into a mode of sustained disorganization.

3. Molecular mechanisms: from calcium overload to suppression of trophic support

At the molecular level, chronic excess of glucocorticoids implements damage through two complementary pathways — excitotoxic and trophic.

The first is related to glutamatergic transmission. Glucocorticoids increase extracellular glutamate concentration and enhance NMDA receptor expression, which increases neuronal sensitivity to calcium influx. Sustained cortisol exposure promotes the accumulation of GluA2-deficient AMPA receptors with increased calcium permeability. In pyramidal neurons of the CA1 region, this creates prerequisites for delayed calcium overload and initiation of apoptotic cascades, whereas CA3 neurons are more resistant to death itself but are subject to pronounced dendritic atrophy.

The second pathway is suppression of neurotrophic support. BDNF, which links activity-dependent plasticity to the growth and stabilization of synapses, is under direct negative control by glucocorticoids. Chronically elevated corticosterone levels reduce the expression of BDNF and its receptor TrkB in the hippocampus at the transcriptional level. Reduced BDNF signaling deprives dendritic spines of trophic support, making structural rearrangements irreversible. It is against this background that the protective action of melatonin, which restores BDNF expression, acquires particular significance.

4. Cellular plasticity: atrophy without death as a reversible but insidious target

A fundamentally important conclusion of modern research is that chronic hypercortisolism primarily causes not massive death of hippocampal neurons but atrophy of their dendritic trees and loss of spines. In chronic stress models, a decrease in dendritic complexity and spine density is observed in pyramidal neurons of CA1 and CA3 in the absence of signs of necrosis or apoptosis in a significant proportion of these cells. Under the action of chronic cortisol, the hippocampus does not «burn out» but shrinks, preserving the cellular framework while losing the fine plastic structures necessary for efficient information encoding.

In parallel, neurogenesis in the dentate gyrus suffers. Glucocorticoids are powerful inhibitors of the proliferation of neural stem/progenitor cells (NSPCs). Chronic elevation of their levels suppresses proliferation through cyclin-dependent kinase 5 and reduced BDNF support, and also enhances apoptosis of newborn cells. Dysregulation of diurnal fluctuations of glucocorticoids disrupts the epigenetic program that preserves the pool of quiescent GR-expressing stem cells; loss of rhythmicity leads to depletion of this reserve. Notably, stress does not simply «switch off» neurogenesis but shifts NSPC differentiation toward oligodendrogenesis, altering the cellular composition of the hippocampal niche.

5. Systemic correlates: from hippocampal subfields to the cognitive profile

The clinical model of Cushing's disease (CD) allows one to see how cellular events project onto the macroscopic level. In active CD, a decrease in gray matter volume of the hippocampus is observed with predominant involvement of the body and tail of the structure, as well as selective atrophy of specific subfields — presubiculum, subiculum, CA4 field and the granule cell layer of the dentate gyrus. A key observation: the volume of the left CA4 and the left complex «granule cell layer — molecular layer of the dentate gyrus» statistically mediates the relationship between cortisol levels and cognitive performance. It is the vulnerability of specific hippocampal subfields, rather than general «brain shrinkage,» that serves as the link connecting hormonal excess with memory impairment.

Functionally, chronic hypercortisolism shifts the balance of synaptic plasticity: LTP is suppressed, and long-term depression (LTD) is facilitated. At the network level, this

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is accompanied by restructuring of functional connections: hippocampal-prefrontal interactions weaken, while amygdalar circuits associated with emotional reactivity strengthen. A imbalance arises in which cognitive control gives way to emotional responding. Importantly, atrophic changes only partially regress after normalization of the hormonal background — there is a «window of reversibility,» beyond which plastic deficits become consolidated.

## CONCLUSION

Chronic hypercortisolism dismantles the plastic apparatus of the hippocampus not through a single «toxic hit» but through a sequence of interconnected shifts: MR/GR receptor imbalance deprives the hippocampus of physiological plasticity; glutamatergic excitotoxicity and suppression of BDNF signaling create a molecular environment incompatible with long-term synapse stabilization; dendritic atrophy and inhibition of neurogenesis reduce the structural substrate for encoding new experience. A circadian component is also built into this cascade: the reciprocal relationships of cortisol and melatonin normally create an alternation of phases of plasticity and protection, and in chronic hypercortisolism this architecture is destroyed. Melatonin acts as an endogenous functional antagonist of glucocorticoids — it reduces nuclear translocation of GR, restores BDNF expression, protects neurogenesis and synaptic plasticity proteins, yet its own rhythm and receptor sensitivity are suppressed under sustained cortisol excess. Understanding this multilevel cascade, including the melatonin–cortisol interaction, is fundamentally important for timely detection of cognitive risk and for developing interventions aimed at breaking the pathological circuit «hyperactive HPA axis — damaged hippocampus — weakened feedback.»

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