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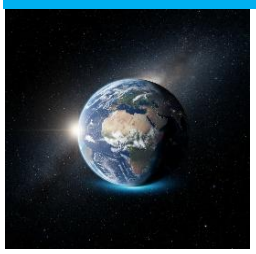

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Physical activity and pharmacological interventions in reversing stress-induced hippocampal atrophy: An analysis of molecular mechanisms

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Abstract

Background: Chronic stress, unlike its acute adaptive form, leads to a persistent disruption of homeostasis and an increasing allostatic load. A central component of the biological response to stress is the activation of the hypothalamic-pituitary-adrenal (HPA) axis, which leads to the release of glucocorticoids, particularly cortisol. The hippocampus, due to its high density of glucocorticoid receptors, becomes one of the main target structures for cortisol action. Its chronic excess becomes neurotoxic to the hippocampal structure and leads to its atrophy.

Aim: The aim of this study is to analyze the mechanisms leading to hippocampal damage and to evaluate the clinical evidence regarding the reversibility of these changes through pharmacological and non-pharmacological interventions.

Material and methods: The literature review was conducted by searching the electronic databases PubMed and Google Scholar. The search process utilized a combination of the logical operators AND/OR and the following keywords: chronic stress, cortisol, hippocampal atrophy, neuroplasticity, HPA axis, BDNF, physical exercise.

Results: Chronic exposure to cortisol leads to dendritic atrophy, loss of synaptic spines, and inhibition of neurogenesis within the hippocampus. Recent reports, however, highlight the key role of the mTORC1 signaling pathway and BDNF expression in reversing these deficits. While psychoplastogens such as ketamine promote rapid synaptic remodeling, regular physical activity facilitates sustained structural adaptations.

Conclusions: Hippocampal damage caused by chronic stress is not a completely irreversible process. The transition from a neurotoxic state to structural regeneration is possible through multi-track molecular pathways activated by both modern pharmacotherapy and systematic physical activity. This synergy opens new perspectives in education and sports medicine, aiming at the biological reconstruction of brain structures and improvement of the quality of life.

Key words: chronic stress; cortisol; hippocampus; dendritic atrophy; neuroplasticity; HPA axis; brain-derived neurotrophic factor (BDNF); ketamine; psychoplastogens; physical exercise; lifestyle interventions.

1. Introduction

Stress is a physiological, evolutionarily determined response of the body to external stimuli. While acute (short-term) stress serves an adaptive function by mobilizing cognitive resources in situations of immediate danger, chronic stress is defined as a state of persistent disruption of homeostasis that exceeds the capacity of the body's compensatory mechanisms. This phenomenon leads to a growing allostatic load, in which persistent hypercortisolemia causes adverse neurostructural changes (1). The hippocampus, which serves as the center for memory consolidation and emotional regulation, is a structure exceptionally sensitive to the effects of stress. Activation of the hypothalamic-pituitary-adrenal axis constitutes a central component of the stress response, leading to the release of glucocorticoids. Owing to its high density of glucocorticoid receptors, the hippocampus is particularly vulnerable to their prolonged elevation, which is associated with neurotoxic effects (2).

It has been demonstrated that prolonged exposure to glucocorticoids initiates a cascade of molecular events: from impaired BDNF (brain-derived neurotrophic factor) signaling, through dendritic tree atrophy, to a reduction in the density of hippocampal synaptic spines (3,4).
A significant advancement in understanding these mechanisms came with the discovery of the antidepressant properties of ketamine - an NMDA receptor antagonist. Unlike traditional psychotropic drugs, ketamine induces an almost immediate effect in the form of synaptic remodeling. This phenomenon laid the foundation for the identification of psychoplastogens - a new class of substances capable of rapidly improving neuronal integrity (5).

Contemporary neurobiology indicates, however, that pharmacotherapy is not the only path to rebuilding brain structures. An equally important role in promoting neuroplasticity is attributed to non-pharmacological interventions, particularly regular physical activity and lifestyle modifications. Physical activity, by stimulating endogenous BDNF production and optimizing HPA axis function, serves as a natural mechanism counteracting atrophy, which is of fundamental importance for the quality of educational processes and the preservation of cognitive reserves.

This paper represents an attempt to synthesize current knowledge on the molecular basis of hippocampal atrophy and the mechanisms that reverse it. This analysis is particularly important in the era of the search for targeted therapies and health-promoting strategies that would allow

not only for the alleviation of clinical symptoms, but above all for the biological repair of brain structures affected by the destructive impact of stress, thereby improving overall quality of life.

2. Research materials and methods

The literature review was conducted by searching the electronic databases PubMed and Google Scholar. The search process utilized a combination of the logical operators AND/OR and the following keywords: chronic stress, cortisol, hippocampal atrophy, neuroplasticity, HPA axis, BDNF, physical exercise, lifestyle interventions. The analysis included original articles, systematic reviews, and meta-analyses published in peer-reviewed scientific journals, with particular emphasis on classic studies (the foundations of neurotoxicity theory) and the most recent meta-analyses from the past 10 years.

3. Literature review

3.1. The Hippocampus and the HPA Axis (The Hypothalamic-Pituitary-Adrenal axis)

Understanding the pathomechanism of hippocampal atrophy requires a prior analysis of its structure and role in the physiological regulation of the hormonal axis. The hippocampus is located in the central part of the temporal lobe and forms part of the limbic system. Anatomically, it comprises the subiculum, CA1-CA4 fields, and the dentate gyrus. The structural foundation of the hippocampus is the so-called trisynaptic circuit. The information processing begins in the dentate gyrus, passes through the pyramidal neurons of the CA3 and CA1 fields, and ends with the transmission of a signal to cortical structures (2). The hippocampus's primary role in regulating the stress response is to modulate the activity of the hypothalamic-pituitary-adrenal (HPA) axis through negative feedback. This cascade begins with the release of corticotropin-releasing hormone (CRH) by the hypothalamus. These hormones stimulate the anterior pituitary lobe to release adrenocorticotropic hormone (ACTH), which stimulates the adrenal cortex to produce glucocorticoids, primarily cortisol. Under physiological conditions, the hippocampus, which has a high density of type I and II glucocorticoid receptors (MR and GR), detects an increase in cortisol concentration and sends an inhibitory signal to the hypothalamus, which suppresses the stress response. MR receptors

have an affinity for cortisol that is 10 times higher than that of GR receptors. They are almost completely saturated even at baseline hormone levels, whereas GR (type II) receptors are activated mainly during severe stress (6).

However, in a situation of chronic hypercortisolism, this regulatory mechanism begins to function as a "vicious cycle." In a fundamental paper describing this mechanism, it was termed the "glucocorticoid cascade hypothesis" (7). Excess cortisol exhibits direct neurotoxic effects, causing atrophy of hippocampal cells. As a result of this process, this structure loses its ability to effectively suppress the HPA axis, leading to the secretion of even greater, uncontrolled amounts of cortisol, which further damages neural tissue.

As demonstrated in one of the key studies, the mechanism perpetuating HPA axis dysfunction is hypermethylation of the promoter region (1F promoter) of the NR3C1 gene. This process leads to a permanent reduction in the expression of glucocorticoid receptors in the hippocampus, which impairs the effectiveness of the negative feedback mechanism. As a result, the structure loses its ability to inhibit cortisol secretion. Methylation of the NR3C1 gene may be a potential biomarker of stress exposure (8).

3.2. Molecular mechanisms

Sources indicate that in the presence of excess glucocorticoids, hippocampal neurons become more susceptible to damage. With increased exposure to cortisol, nerve cells may be damaged even under conditions of mild hypoxia or transient hypoglycemia, which under normal conditions would not be harmful to them (9). Glucocorticoids inhibit glucose transport into neurons by suppressing GLUT transporters (specifically GLUT3), thereby causing the energy reserves necessary for activating defense mechanisms to be depleted more rapidly (2,10).

Under conditions of chronic stress, pathological accumulation of glutamate in the synaptic cleft also occurs. Glucocorticoids stimulate glutamate release and inhibit glial transporters (GLT-1), which facilitate the uptake of excess glutamate (11,12). This results in excessive stimulation of NMDA receptors, which, under conditions of neuronal energy deficit, induces a massive influx of calcium ions into the cytoplasm. This process activates intracellular catabolic processes, leading to the activation of proteases, lipases, and nucleases that degrade the cytoskeleton and

cell membranes. Neurons with impaired glucose metabolism exhibit dysfunction of ATP-dependent ion pumps, making them unable to efficiently remove excess calcium, which ultimately leads to cell apoptosis (13). This mechanism also depends on the efficiency of mitochondrial function, which, under conditions of hypercortisolemia, may be subject to structural and functional damage. This phenomenon, defined in the literature as mitochondrial allostatic load, represents the metabolic cost of cellular adaptation to chronic stress (14). It manifests as a disruption of organelle dynamics (a predominance of fragmentation over fusion) and impaired mitochondrial transport to synapses, which makes regions with high energy demands, such as the hippocampus, particularly susceptible to structural regression. Mitochondria, when functioning inefficiently, become the primary source of intracellular oxidative stress and begin to produce reactive oxygen species (ROS), thereby leading to damage to mitochondrial DNA (mtDNA). This creates a self-perpetuating mechanism of organelle dysfunction and further cellular energy deficit.

3.3. Dendritic atrophy

Hippocampal atrophy results not only from neuronal loss but also from structural remodeling. As a result of excess cortisol, pyramidal neurons in the CA3 region lose their dendritic branches (15, 16). A reduced number of synaptic connections primarily contributes to cognitive impairment. Recent studies suggest that under conditions of hypercortisolism, microglia surrounding neurons trigger pro-inflammatory activation by secreting inflammatory cytokines such as IL-1β, IL-6, and TNF-α. Inflammatory mediators induce oxidative stress and lead to neuronal structural damage and dendritic degradation. Chronic inflammation impairs the microglia's ability to perform neuroprotective functions, which further exacerbates atrophic processes (17).

3.4. Decrease in BDNF

Under conditions of chronic stress, there is a reduction in BDNF (Brain-Derived Neurotrophic Factor), which is essential for the growth, differentiation, and survival of neurons (18). A recent analysis of the pathomechanism of hippocampal atrophy further points to the significant role of the microbiota-gut-brain axis. It has been demonstrated that intestinal homeostasis is

essential for maintaining normal BDNF levels (19). Microbiota dysbiosis induced by chronic stress may correlate with reduced hippocampal volume (20).

In addition, the influence of epigenetic changes has also been noted, explaining the failure of BDNF levels to return to physiological values despite the resolution of the stressor. Chronic hypercortisolism causes methylation of the BDNF gene's promoter IV, which permanently inhibits the production of this protein (21).

Furthermore, it has been demonstrated that traumatic experiences during early infancy or even the prenatal period induce changes in DNA methylation within the promoter regions of the BDNF gene. As demonstrated in studies, this mechanism leads to long-term silencing of BDNF transcription. This results in impaired neurogenesis and a reduction in dendritic architecture in the hippocampus (22, 23).

3.5. Inhibition of neurogenesis

The hippocampus is one of the few areas in the brain where new neurons are generated throughout life. This process occurs primarily in the granule cell zone of the dentate gyrus, where new granule cells are constantly being generated. Cortisol, however, significantly impairs this process and also reduces the survival and proper differentiation of already formed cells (24). Stress-activated microglia release the cytokine interleukin-1β (IL-1β), which is a key mediator of neurogenesis inhibition. IL-1β activates the kynurenine pathway in progenitor cells, which, through the production of neurotoxic metabolites, directly limits the cells' ability to differentiate (25). Interferon-gamma (IFN-γ) has also been identified as a factor harmful to neurogenesis; its excess impairs neurogenesis in the hippocampus (26).

The kynurenine pathway is a significant modulator of hypercortisolism-induced neurotoxicity. It exerts a significant influence on NMDA receptors through the production of two opposing metabolites - quinolinic acid (QUIN), an NMDA receptor agonist, and kynurenic acid (KYNA), its antagonist. Under conditions of chronic stress, a pathological shift in the balance occurs toward the production of neurotoxic quinolinic acid (QUIN), which is driven by the stimulation of the enzyme tryptophan dioxygenase (TDO). This metabolite not only enhances glutamatergic

excitotoxicity but also generates oxidative stress. It constitutes a direct molecular mechanism leading to synaptic degradation (27,28).

3.6. MRI evidence of hippocampal atrophy

Imaging studies provide macroscopic confirmation of the molecular mechanisms occurring within cells that lead to hippocampal atrophy. According to the sources analyzed, the percentage changes in hippocampal volume vary depending on the specific disorder, the duration of stress, or brain lateralization. The overall range of measurable atrophy in neuropsychiatric disorders ranges from 5% to as high as 26% in pioneering studies on this topic (2). Contemporary meta-analyses approach these data with greater caution, indicating an average range of atrophy oscillating around 8-10%, which, however, still constitutes a clinically relevant structural change (29). In contrast, a study by the ENIGMA (Enhancing Neuro Imaging Genetics Through Meta-Analysis) consortium - the world's largest neuroimaging database - demonstrated a difference in hippocampal volume of approximately 1.5% in the group of patients with PTSD (Posttraumatic Stress Disorder), with this reduction being more pronounced in women at 2.42% (30). The lower percentage values in this study may reflect the large sample size, which mitigates selection biases typical of small clinical groups and makes these results highly statistically significant and more representative of the general population.

Additionally, deformities within the anterior segment of the hippocampus - which is more responsible for the stress response and emotion regulation - constitute an early biomarker of glucocorticoid neurotoxicity, preceding the global volumetric decline of the structure or the atrophy of the posterior segment (31,32).

3.7. Pharmacological reversal of neurostructural change

Ketamine may contribute to the reversal of stress-related structural changes in the hippocampus and restoring neuroplasticity. In addition to its use as an anesthetic or analgesic, it has been shown to be highly effective as an antidepressant (33). Its antidepressant effect is closely associated to the process of synaptic reconstitution. The mechanism of this action begins with the blockade of NMDA receptors on GABAergic interneurons. This leads to a rapid release of glutamate in the prefrontal cortex. The excess glutamate strongly stimulates AMPA receptors (34,35). This, in turn, opens voltage-gated calcium channels, which stimulates the release of stored BDNF. This then activates a signaling cascade leading to the stimulation of the mTORC1 complex (mechanistic target of rapamycin complex 1). This complex stimulates the synthesis of synaptic proteins (such as PSD-95 or GluA1), leading to dendritic spine regrowth within as little as 2-24 hours (36).

Additionally, ketamine not only builds new connections but also protects existing ones from the neurotoxic quinolinic acid (QUIN) (35). Ketamine, acting as a non-competitive antagonist, blocks the receptor's ion channel, which effectively inhibits the excitotoxic influx of calcium ions induced by QUIN and interrupts the cascade of molecular damage typical of chronic hypercortisolism (27).

Ketamine's clinical success in reversing hippocampal atrophy has laid the foundation for the identification of a new class of compounds known as psychoplastogens (35). Recent reports indicate the existence of a number of substances - including ketamine metabolites (e.g., (2S,6S;2R,6R)-hydroxynorketamine) and selective AMPA receptor modulators - that exhibit analogous neuroregenerative potential (36). This opens up prospects for the development of a new generation of therapies that - following the example of ketamine - will enable the biological repair of brain structures affected by the destructive impact of chronic stress.

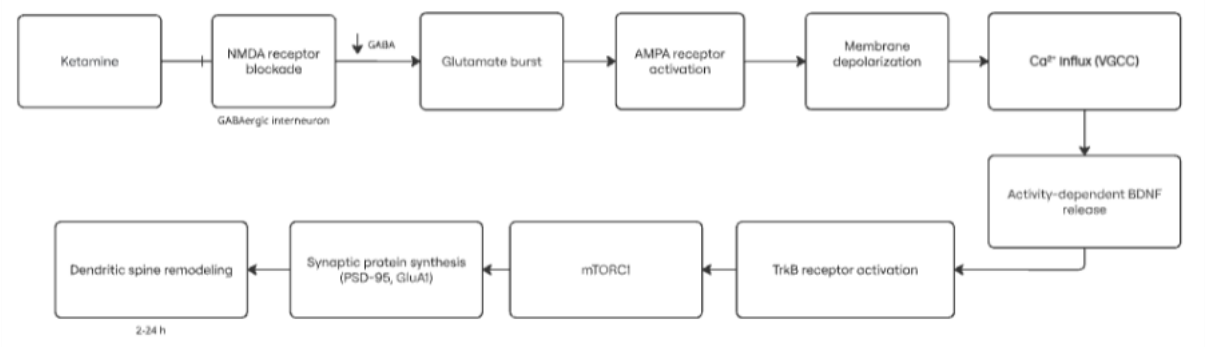

Figure 1. A ketamine-induced signaling cascade leading to synaptogenesis.

3.8. Physical activity as a driver of long-term neuroplasticity

Although pharmacological interventions, such as ketamine administration, offer rapid structural recovery, lifestyle-based strategies - particularly physical activity - provide a lasting foundation for building hippocampal resilience. Studies show that aerobic exercise can increase hippocampal volume by approximately 2%, which in practice means reversing the atrophy associated with chronic stress and aging (37). A key mediator of these changes is BDNF, whose serum levels increase proportionally to exercise intensity (38). Importantly, in the context of prevention, physical exercise not only promotes neurogenesis but also protects existing neurons

from the cytotoxic effects of cortisol by regulating negative feedback in the HPA axis (39). Significant evidence has been provided for the existence of a so-called exercise intensity threshold, above which a transient increase in cortisol levels occurs; however - and most importantly from a long-term perspective - regular physical activity leads to the body's adaptation to this factor. This mechanism involves improving the negative feedback of the HPA axis, which allows the body to extinguish the stress response more quickly and effectively by stimulating cortisol secretion. Physical activity exhibits strong pro-plastic potential, which has been repeatedly confirmed in both animal models and human studies (40). Preclinical studies have shown that physical exercise promotes neuroplasticity by enhancing cellular signaling and stimulating neuronal growth and differentiation. In humans, these effects are reflected in structural changes in the brain; increased density of white and gray matter has been observed in various areas of the cortex and the hippocampus in response to various training protocols. This translates directly into improved cognitive function, particularly in the areas of learning and memory. As the researchers emphasize, physical activity not only promotes neurogenesis itself but, above all, creates an optimal physiological environment for plastic changes (41). According to their analysis, the synergy between physical exertion and mental stimulation (education) is crucial for the survival of new nerve cells and their functional integration into existing neural networks. Enhancing neuroplasticity thus forms the foundation for improving the quality of cognitive processes and protecting brain structures from degradation caused by chronic stress. Consequently, incorporating physical activity into educational and therapeutic programs is a key strategy for maintaining full hippocampal function and improving the overall quality of life for populations exposed to chronic allostatic load.

4. Discussion

This study represents an attempt to synthesize current knowledge regarding the impact of chronic hypercortisolism on hippocampal architecture and the potential reversibility of these changes. The accumulated literature strongly suggests that chronic stress exerts a destructive effect on the body, primarily affecting the negative feedback mechanisms of the hypothalamic-pituitary-adrenal axis. This leads to the emergence of a vicious cycle in which the dysfunction of regulatory structures exacerbates pathological cortisol production. The key finding is that these processes - though initially subclinical and subtle in daily functioning - manifest as

measurable structural changes in imaging studies. A significant issue addressed in this work is the dual-track approach to modulating synaptic plasticity. On one hand, pharmacological interventions using subanesthetic doses of ketamine show promising potential for the rapid reversal of morphological effects of stress. Such an immediate structural response represents a significant advancement in our understanding of neuroplasticity, opening prospects for new generations of psychoplastogens. On the other hand, recent evidence highlights that the reversibility of hippocampal damage is equally achievable through non-pharmacological means. Regular physical activity acts as a powerful driver of endogenous neurogenesis, primarily by upregulating BDNF expression and optimizing HPA axis reactivity. While ketamine facilitates "rapid" synaptic remodeling, systematic exercise ensures "sustained" neuroprotection and long-term biological reconstruction of brain structures. Integrating these two modalities offers a comprehensive strategy for improving the quality of life and cognitive performance.

5. Conclusions

Hippocampal damage caused by chronic stress is not an irreversible process. Reversibility of atrophy can be achieved through both pharmacological and lifestyle-based interventions. While rapid-acting compounds like ketamine offer immediate synaptic restoration, regular physical activity provides a necessary, sustainable foundation for long-term brain health and volume recovery. Understanding these synergistic mechanisms opens new perspectives in sports medicine and education. Promoting physical culture should be considered a fundamental neuroprotective strategy, essential for maintaining neurobiological quality of life and protecting brain structures from the destructive impact of chronic stress.

Disclosure

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The authors declare no conflict of interest - there are no financial or personal relationships with people or organisations which could influence the work presented in this review.

During the preparation of this work, the author(s) used Google's Chat Generative Pre-trained Transformer (Gemini 3) to support the editing process, including grammar, spelling, punctuation, and stylistic refinement. All content generated with AI assistance was carefully reviewed and revised by the author(s), who accept full responsibility for the accuracy, interpretation, and integrity of the final manuscript.

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